Medicinrådet

Bilag til Medicinrådets anbefaling vedr. pralsetinib til behandling af RET-fusionspositiv, fremskreden ikke-småcellet lungekræft

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. pralsetinib til RET-fusionspositiv, fremskreden ikke-småcellet lungekræft
2. Forhandlingsnotat fra Amgros vedr. pralsetinib til RET-fusionspositiv, fremskreden ikke-småcellet lungekræft
3. Ansøgers endelige ansøgning vedr. pralsetinib til RET-fusionspositiv, fremskreden ikke-småcellet lungekræft

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Til Medicinrådet

Høringssvar fra Roche Pharmaceuticals vedrørende Medicinrådets udkast til vurdering af Gavreto (pralsetinib) til behandling af patienter med RET-fusionspositiv NSCLC.

Roche Pharmaceuticals har en række bemærkninger til udkastet til vurderingsrapporten, som vi modtog d. 17. februar 2023. Overordnet finder Roche ikke, at Medicinrådets vurdering af klinisk spørgsmål 1 og 2 er i overensstemmelse med den ansøgte population. Roche stiller sig desuden kritisk overfor valget om at se bort fra en sundhedsøkonomisk analyse og derved simplificere beslutningen om omkostningseffektivet til den årlige lægemiddelomkostning. I øvrigt en sundhedsøkonomisk analyse der blev efterspurgt af Medicinrådet, og som har været den primære årsag til at behandlingen af denne ansøgning har taget over et år at validere.

I nedenstående afsnit forholder Roche sig til følgende emner enkeltvis:

- Håndtering af data, valg og fravalg af analyser (PICO- spørgsmål 1 og 2).
- Sundhedsøkonomisk analyse af førstelinjebehandling (PICO- spørgsmål 1 og 2).

Håndtering af data, valg og fravalg af analyser

Det nævnes gentagne gange i vurderingsrapporten (side 5, 6, 14, 19, 36 og 52), at baselinekarakteristika fra ARROW-studiet gør, at effekten af pralsetinib overestimeres i forhold til effekten af pembrolizumab monoterapi eller i kombination med kemoterapi [1]. Roche vil gerne påpege, at populationen der ansøges på, er RET-fusionspositive NSCLC patienter. Effekten og sikkerheden af pralsetinib er undersøgt i netop denne population i ARROW-studiet, og vi mener derfor, at det er forkert at sige, at effekten af pralsetinib overestimeres i en RET-fusionspositiv population [2]. Roche anerkender, at der er forskelle i baselinekarakteristika mellem ARROW- og KEYNOTE-studierne samt at disse forskelle må forventes at skyldes, at der er tale om to forskellige patientgrupper af NSCLC. Medicinrådet skriver selv på side 36, at der er tale om to molekylærbiologisk forskellige patientgrupper [1]. Sammenligningen af pralsetinib og pembrolizumab monoterapi eller i kombination med kemoterapi kompliceres yderligere af at forskellen i baselinekarakteristika også påvirker de enkelte lægemidlers effekt forskelligt. F.eks. nævner medicinrådet på side 41 i vurderingsrapporten, at rygning er negativ prognostisk, men at det samtidigt ses at checkpoint inhibitors (såsom pembrolizumab) virker bedre hos rygere [1,3]. Det kan ikke på samme måde forventes at rygehistorik, skulle have samme påvirkning på RET-fusionspositive NSCLC patienter og behandling med pralsetinib.

Som Roche allerede har redegjort for i vores ansøgning, er der på nuværende tidspunkt begrænset og sparsom evidens for effekten og sikkerheden af immunterapi til RET-fusionspositive NSCLC patienter. Der er også begrænset evidens omkring sammenhængen mellem RET-fusioner og PD-L1 status, og hvordan man bedst behandler ud fra disse biomarkører. Dette øger usikkerheden omkring den reelle effekt af immunterapi til RET-fusionspositive NSCLC patienter, samt om effekten er korrekt estimeret, overestimeret eller underestimeret.

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Artiklen af Hess et al omkring RET-fusionspositive NSCLC patienter bliver inkonsistent brugt igennem vurderingsrapporten [4]. På side 5, 19, 41 og 52 skriver Medicinrådet, at patienter med RET-fusioner ser ud til at være associeret med en favorabel prognose, set i forhold til patienter uden RET-fusioner med henvisning til Hess et al [1,4]. På side 14 beskriver Medicinrådet konklusionen fra studiet i en mere nuanceret og retvisende gengivelse, hvor Medicinrådet blandt andet skriver, at forskellen var statistisk insignifikant efter justering for forskelle i baseline[1,4]. Roche er ikke enig i, at studiet kan bruges som kilde til at underbygge at RET-fusionspositivitet er associeret med en favorable prognose (som den bliver brugt på side 5, 19 ,41 og 52), da studiet netop konkluderer, at der ikke er forskel, hvis man justerer for baseline forskelle, og der er derfor sparsom evidens for, at RET-fusion alene skulle drive den forskel (som medicinrådet rigtig nok har skrevet på side 14) [4]. Ydermere afslutter studiets forfattere konklusionen med at skrive, at studiet har en lille patientpopulation, at der kan være potentielle konfunders som studiet ikke tager højde for samt at studiet ikke specifikt er designet til at vurdere den prognostiske effekt af RET-fusioner[4].

Samlet set vil det i vurderingsrapporten være mere relevant at diskutere usikkerheden af effekten af pembrolizumab monoterapi eller i kombination med kemo til RET-fusionspositive patienter, fremfor om effekten af pralsetinib overestimeres relativt. Pralsetinib er undersøgt i RET-fusionspositive NSCLC patienter og afspejler derfor den reelle effekt i denne patient gruppe, mens der omvendt er evidensmæsssigt usikkerhed omkring effekten af immunterapi. Herunder specifikt pembrolizumab, til RET-fusionspositive NSCLC patienter som ikke alene kan tilskrives forskelle i baselinekarateristika mellem ARROW og KEYNOTE-studierne.

I forhold til præsentation af data til sammenligning i vurderingsrapporten, vil Roche gerne henlede til at den primære analyse i den kliniske del af ansøgningen er foretaget i forhold til de registerstudier med RET-fusionspositive patienter som er behandlet med checkpoint inhibitor og at KEYNOTE-studier er inkluderet som en supplerende analyse af ovenstående grunde.

Sundhedsøkonomisk analyse

Roche stiller sig kritisk overfor, at der ikke kan laves en sundhedsøkonomisk analyse af førstelinjebehandlingen. Den sundhedsøkonomiske analyse er valideret af sekretariatet, og før det har sekretariatet af flere omgange stillet uddybende spørgsmål til den sundhedsøkonomiske analyse. En proces der har gjort, at det har taget størstedelen af et år at validere ansøgningen, og som har skabt betydelig forsinkelse i den endelige vurdering af pralsetinib - men som sekretariatet alligevel vælger at se bort fra. Den nuværende vurderingsrapport kunne være færdiggjort allerede i midten 2022.

Roche anerkender, at der er visse usikkerheder ved analysen, men at det er bedre at foretage en sundhedsøkonomisk analyse og beskrive usikkerhederne. En sundhedsøkonomisk analyse kan give en indikation om retningen på omkostningseffektiviteten (under visse antagelser), men Medicinrådet vælger at se bort fra denne, og i stedet reduceres Medicinrådets vurdering til et simpelt spørgsmål om pakkeprisen på lægemidlerne. Det er et unuanceret grundlag at basere

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en beslutning om omkostningseffektivetet på - og det er ikke en tilgang, der er anvendt i andre lignende sager i Medicinrådet (fx. selpercatinib til RET-fusionspositive NSCLC og entrectinib til NTRK-fusionspositive patienter). Det betyder desværre også, at Medicinrådet ikke bliver præsenteret for de relativt få omkostninger, som det vil udgøre, såfremt de nuværende behandlingslinjer byttes rundt, så de RET-fusionspositive patienter kan tilbydes en targeteret behandling i første linje - ligesom ved andre lignende mutationer/fusioner (ALK, ROS1 og EGFR).

Mvh
Andreas Fanø
Christian Graves Beck

1. Medicinrådet. Udkast: Medicinrådets anbefaling vedr. pralsetinib til behandling af RET-fusionspositiv, fremskreden ikke-småcellet lungekræft version 1.0. 2023 Mar 29;
2. Clinicaltrials.gov. Phase 1/2 Study of the Highly-selective RET Inhibitor, Pralsetinib (BLU-667), in Patients With Thyroid Cancer, Non-Small Cell Lung Cancer, and Other Advanced Solid Tumors (ARROW), https://clinicaltrials.gov/ct2/show/NCT03037385. 2021;
3. Zhao W, Jiang W, Wang H, He J, Su C, Yu Q. Impact of Smoking History on Response to Immunotherapy in Non-Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis. Frontiers Oncol. 2021;11:703143.
4. Hess LM, Han Y, Zhu YE, Bhandari NR, Sireci A. Characteristics and outcomes of patients with RET-fusion positive non-small lung cancer in real-world practice in the United States. BMC cancer [Internet]. 2021;21(1):28. Available from: https://doi.org/10.1186/s12885-020-07714-3

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28.02.2023

DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.03.2023
Leverandør	Roche
Lægemiddel	Gavreto (pralsetinib)
Ansøgt indikation	Gavreto (pralsetinib) til behandling af RET-fusionspositiv, fremskreden ikke-småcellet lungekræft
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Gavreto (pralsetinib):

Tabel 1: Forhandlingsresultat Gavreto 2. linje

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Gavreto	100 mg	60 stk.	27.137,47	[redacted]	[redacted]

[redacted]

Tabel 2: Forhandlingsresultat Gavreto 1. linje

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Gavreto	100 mg	60 stk.	27.137,47	[redacted]	[redacted]

[redacted]

Aftaleforhold

[redacted]

Retsevmo (selpercatinib) blev anbefalet til ibrugtagning til samme population (2. linje behandling) i februar 2022. Der er i dag ingen behandlingsvejledning til behandling af denne patientpopulation.

[redacted]

Konkurrencesituationen

[redacted]

Tabel 2: Sammenligning af lægemiddeludgifter

Lægemiddel	Styrke	Pakningsstørrelse	Dosering dagligt	Pris pr. pakning (SAIP, DKK)	Antal pakninger pr. år	Lægemiddeludgift pr. år (SAIP, DKK)
Gavreto	100 mg	60 stk.	400 mg	[redacted]	24,35	[redacted]
Retsevmo	80 mg	112 stk.	320 mg	[redacted]	13,05	[redacted]

*Pris udregnet på niveau 1.

Status fra andre lande

Land	Status	Kommentar	Link
Norge	Ikke anbefalet	Legemiddelverket har ikke estimert relativ effekt eller kostnadseffektivitet for bruk av Gavreto (pralsetinib) i RET-fusjonspositiv NSCLC.	https://nyemetoder.no/metoder/pralsetinib-gavreto
Sverige	Anbefalet	Gavreto har subvention for NSCLC og inngår i högkostnadsskyddet. «Baserat på nuvarande kunskap om Gavreto bedöms kostnaden för behandling vara rimlig i förhållande till effekten. Mot denna bakgrund beslutar TLV att Gavreto ska vara subventionerat och ingå i högkostnadsskyddet. Besluttet 22.04.2022	https://www.tlv.se/beslut/beslut-lakemedel/generell-subvention/arkiv/2022-04-25-gavreto-ingar-i-hogkostnadsskyddet.html
England	Ikke anbefalet		https://www.nice.org.uk/guidance/ta812/chapter/1-Recommendations

Konklusion

[redacted]

Application for the assessment of pralsetinib for first line treatment of RET fusion-positive patients with non-small cell lung cancer

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Gavreto
Generic name	Pralsetinib
Marketing authorization holder in Denmark	Roche Registration GmbH Emil-Barrell-Strasse1 79639 Grenzach-Wyhlen, Germany
ATC code	L01EX23
Pharmacotherapeutic group	Antineoplastic agent
Active substance(s)	Pralsetinib
Pharmaceutical form(s)	Capsules
Mechanism of action	Pralsetinib is an oral precision therapy designed to selectively target rearranged during transfection (RET) tyrosine kinase alterations, including fusions and mutations.
Dosage regimen	400 mg of pralsetinib once daily.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Gavreto is indicated as monotherapy for the treatment of adult patients with rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor.
Other approved therapeutic indications	N/A
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	N/A
Packaging – types, sizes/number of units, and concentrations	100 mg capsules of 60
Orphan drug designation	No

2. Abbreviation

AE	Adverse Event
AIC	Akaike Information Criterion
AIP	Apotekets Indkøbspris
ALK	Anaplastic lymphoma kinase

ATT	Average Treatment effect on the Treated
BIC	Bayesian Information Criterion
BSA	Body Surface Area
CBR	Clinical benefit rate
CGDB	Clinico-Genomics database
CNS	Central nervous system
DCR	Disease control rate
DMC	Danish Medicines Council
EDM	Enhanced Data Mart
EGFR	Epidermal growth factor receptor
EKG	Electrocardiogram
EMA	European Medicines Agency
EPAR	European public assessment report
ESCAT	ESMO Scale for Clinical Actionability of molecular Targets
ESMO	European Society of Medical Oncology
GHD	Guardant Health database
HR	Hazard Ratio
HRQoL	Health-Related Quality of Life
HSUV	Health State Utility Values
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
ICI	Immune checkpoint inhibitors
IPD	Individual patient data
IPTW	Inverse Probability of Treatment Weighting
IV	Intravenous
KM	Kaplan-meier
KN-024	KEYNOTE-024
KN-042	KEYNOTE-042
KN-189	KEYNOTE-189
N/A	Not applicable
NICE	National Institute for Health and Care Excellence
NR	Not reached
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PH	Proportional Hazards
PSA	Probabilistic Sensitivity Analysis
PS	Performance Status
QALY	Quality-adjusted life year
RECIST	Response Evaluation Criteria in Solid Tumours
RET	Rearranged during transfection
RKKP	The Danish Clinical Quality Program – National Clinical Registries
RMSTD	Restricted Mean Survival Time Difference
ROS1	ROS proto-oncogene 1 receptor tyrosine kinase
RWD	Real-world data

SAR	Serious adverse reaction
SCLC	Small cell lung cancer
SD	Stable disease
SLR	Systematic Literature Review
SQ	Squamous
TKI	Tyrosine kinase inhibitor
TMB	tumour mutational burden
TTOT	Total Time On Treatment
TPS	Tumor proportion score
TRAE	Treatment related adverse events
QALY	Quality-Adjusted Life Years
QLQ-C30	Quality-of-Life Questionnaire-Core 30
QLQ-LC13	Quality-of-Life Questionnaire-Lung Cancer 13
WT	Wild-type

3. Tables and Figures

4. Summary

4.1 Introduction

On November 19, 2021, the European Commission (EC) approved Gavreto (pralsetinib) as monotherapy for first-line treatment of adult patients with rearranged during transfection (RET)-fusion positive non-small cell lung cancer (NSCLC). The approval is based on results from ARROW, a multicentre, single-arm, open-label study investigating the safety, tolerability, and efficacy of pralsetinib in RET fusion-positive NSCLC patients. This application, submitted to the Danish Medicines Council on January 28, 2022, provides the basis for the assessment of pralsetinib in comparison with Danish standard of care.

During the course of the last two decades, the development of genetic testing has resulted in the identification of genetic alterations that play key roles as oncogenic drivers and predictors of responses to therapy in lung cancer. The RET fusion gene is an oncogene, which has been identified in 1-2% of patients with NSCLC. RET fusions are more frequent in 'younger' (<60 years of age) non-smoking patients with lung adenocarcinomas. As with anaplastic lymphoma kinase (ALK) and c-ros oncogene 1 receptor tyrosine kinase (ROS1) rearrangements, RET fusions are associated with specific pathological features, and tumours often tend to be more poorly differentiated in a high prevalence of central nervous system (CNS) metastases. Patients with RET fusion-positive NSCLC are at a different stage of life, with different expectations and different psychosocial needs from the lung cancer population as a whole.

Currently, there is no specific treatment pathway for RET fusion-positive patients and therefore patients go into the standard NSCLC treatment pathway according to Danish guidelines. In Denmark, first-line treatment for patients with

locally advanced or metastatic NSCLC, is, depending on PD-L1 status, either pembrolizumab monotherapy or a combination of pembrolizumab and platinum-based chemotherapy. However, there is accumulating evidence that the current treatment options for RET fusion-positive NSCLC patients do not offer the same level of efficacy typically achieved with targeted therapies for oncogenic drivers.

4.2 Clinical assessment

METHODS: The assessment presented in the following are based on two PICOs: the efficacy and safety of pralsetinib for treatment of RET fusion-positive NSCLC patients was evaluated in comparison to either pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy. As no direct evidence comparing pralsetinib with the comparators of interest are available, two systematic literature reviews were conducted to identify relevant studies for the comparisons. The first approach was to search for literature in the specific population of interest, patients with RET fusion-positive NSCLC. It was already suspected that limited evidence would be available, and therefore, no strict restrictions were applied to the study design. Because limited evidence for the comparators of interest were expected, the scope of the review was broadened to include NSCLC patients with unknown RET fusion status as well.

Electronic searches were carried out in PubMed and in CENTRAL (via Cochrane Library) on October 21 and 22, 2021. For the search in RET fusion-positive NSCLC, a total of seven references from seven studies were found eligible for inclusion. These include the clinical study ARROW (NCT03037385) that assesses the efficacy and safety of pralsetinib, and six retrospective studies that evaluate the effect of immune checkpoint inhibitors (ICIs) in first and later treatment lines. For the search for comparative data in NSCLC with unknown RET fusion status, 14 additional references from four studies were found eligible for inclusion. Three were found relevant for the comparison with pembrolizumab monotherapy. These include the clinical studies KEYNOTE-024 (NCT02142738) and KEYNOTE-042 (NCT02220894) that assess the efficacy and safety of pembrolizumab monotherapy in populations with stage IV NSCLC and PD-L1 expression ≥50%, and a real-world study that evaluate the effect of pembrolizumab in Danish NSCLC patients. One study was found relevant for the comparison with pembrolizumab in combination with chemotherapy; the clinical study KEYNOTE-189 (NCT02578680) that assesses the efficacy and safety of pembrolizumab and platinum-based chemotherapy in a population with stage IV NSCLC and PD-L1 expression ≤49%.

In order to compare the efficacy of the treatments, a series of comparisons were conducted using the studies included in the systematic literature reviews (SLRs). Data for pralsetinib was compared in a narrative manner to data for ICI-based therapy from the retrospective studies, which included RET fusion-positive patients. Comparisons were made for overall survival (OS), progression-free survival (PFS) and overall response rate (ORR). In the absence of data in patients with RET fusion-positive NSCLC for pembrolizumab monotherapy and pembrolizumab in combination with chemotherapy, additional comparisons based on comparator data in NSCLC populations with unknown RET fusion status were conducted. This approach was based on the assumption that there is no difference in prognosis between patients with RET fusion-positive and RET wild-type NSCLC. For the wild-type comparison between pralsetinib and pembrolizumab monotherapy, naïve indirect treatment comparisons (ITCs) were conducted for OS and PFS using individual patient data (IPD) from the population that had received no prior systemic therapy from ARROW, and comparative data from the populations with previously untreated NSCLC and PD-L1 expression ≥50 from KEYNOTE-024 and KEYNOTE-042. In addition, the treatment-effect of pralsetinib was compared to real-world NSCLC patients receiving first-line pembrolizumab from the Flatiron Enhanced Data Mart (EDM) database. The analyses were conducted for OS and PFS. Lastly, the efficacy (OS, PFS and ORR) and safety of pralsetinib was compared in narrative manner to that reported for pembrolizumab in KEYNOTE-024 and KEYNOTE-042, and to OS and PFS reported in a real-world Danish cohort receiving ICI treatment. Similar analyses were carried out to compare pralsetinib with pembrolizumab in combination with chemotherapy. For the naïve ITCs and narrative comparisons data from

KEYNOTE-189 was used, and for the Flatiron analysis, data from NSCLC patients receiving first-line pembrolizumab in combination with chemotherapy from the EDM database were included.

In addition to the two clinical questions that address the efficacy and safety of pralsetinib in first-line, Roche have by request from the scientific committe, also included a third clinical question, which address the efficacy and safety of pralsetinib compared to selpercatinib for patients with RET fusion-positive NSCLC, who require systemic therapy following prior treatment with platinum-based chemotherapy (see appendix L). A SLR identified 2 comparator studies eligible for inclusion; the clinical study LIBRETTO-001 and the retrospective study SIREN, which both evaluates the efficacy and safety of selpercatinib in second-line. Narrative comparisons were conducted for OS, PFS, ORR, intracranial-ORR and safety.

RESULTS: Efficacy results from ARROW were reported at for the overall efficacy population and the population that had received no prior systemic treatment. At a recent CCOD of March 4, 2022, the median OS was 44.3 months in the overall population, while the median OS was still immature in the treatment naïve population. At the CCOD of November 6, 2020 the OS rate was 76.0% (95% CI, 69.9-82.0) and 82.3% (95% CI, 71.9-92.8) at 12 months and 66.0% (95% CI, 57.9-74.1) and 74.0% (95% CI, 59.3-88.6) at 24 months in the overall efficacy population and the treatment naive population, respectively. The median OS and the OS-rates reported in ARROW were notably higher than those reported for pembrolizumab monotherapy and pembrolizumab in combination with chemotherapy in RET fusion-positive or RET wild-type NSCLC populations. To mitigate evidence gaps, naïve ITCs using comparative data from KEYNOTE-024, KEYNOTE-042 and KEYNOTE-189 were conducted. Despite immature data for pralsetinib, results from all analyses showed statistically significant treatment-effects, favouring pralsetinib over pembrolizumab with or without chemotherapy. Results from the real-world Flatiron EDM analyses showed similar trends. In terms of PFS, treatment with pralsetinib at the CCOD of March 4, 2022 resulted in a median PFS of 13.2 months (95% CI, 11.4-16.8) in the overall efficacy population and 12.6 months (95% CI, 9.2-16.6) in the population that received no prior systemic treatment. At the CCOD of November 6, 2020 the PFS rate was 56% (95% CI, 48.9-63.1) and 52.6% (95% CI, 37.7-67.5) at 12 months and 42.1% (95% CI, 33.2-51.0) and 47.8% (95% CI, 31.6-64.1) at 24 months in the overall efficacy population and the treatment naive population, respectively. Pralsetinib demonstrated the longest median PFS in comparison to those reported in RET fusion-positive and RET wild-type NSCLC patients. In addition, the results from the naïve ITC analyses showed statistically significant treatment-effects, favouring pralsetinib over pembrolizumab with or without chemotherapy. Similar trends were seen from the Flatiron EDM analyses. ORR was the primary endpoint in ARROW. At the CCOD of November 6, 2020, ORR was 64.4% (95% CI, 57.9-70.5) in the overall efficacy population and 72.0% (95% CI, 60.4-81.8) in the population that had received no prior systemic treatment. Results from the recent CCOD showed similar results. An analysis that assessed the association between tumour response at landmark times and survival, indicated that ORR may be a predictor of longer OS in RET fusion-positive NSCLC, pointing to the high response rates observed being clinically meaningful. The reported ORRs in ARROW were vastly higher than those observed in the comparative studies except for the two retrospective studies assessing ICI in combination with chemotherapy in small groups of RET fusion-positive patients. Furthermore, treatment with pralsetinib, which penetrates the blood-brain barrier, resulted in a high intercranial ORR in evaluable patients with measurable CNS metastases at baseline. All patients had target brain lesion shrinkage with treatment.

For the comparison with selpercatinib efficacy results were reported for the overall population in ARROW, the population previously treated with platinum-based chemotherapy in ARROW and LIBRETTO-001, and pretreated patients in SIREN. Median OS was 44.3 months in both populations in ARROW, but not reached in LIBRETTO-001. OS was not reported in SIREN. At 12 months the reported OS rates were 72.4% in ARROW and 88.3% in LIBRETTO-001, and at 24 months the OS rates were 61.9% and 68.9%, respectively, indicating that the initial difference in OS survival at 1 year are levelled out after 2 years. However, as median OS is immature in LIBRETTO-001 it is not possible to conclude if there are relevant difference between pralsetinib and selpercatinib. In terms of PFS, the comparison

between ARROW and LIBRETTO-001 showed a numerical difference in favour of selpercatinib, however the confidence intervals were overlapping. The median PFS for selpercatinib reported in SIREN was markedly lower than the one reported in LIBRETTO-001. Importantly, differences in baseline characteristics with a higher number of baseline CNS metastases in ARROW and SIREN than in LIBRETTO-001, and a higher number of patients with EOCG PS 0 in LIBRETTO-001 and SIREN than in ARROW, could contribute to a poorer prognosis in ARROW, which is likely to affect the results. The ORRs and intracranical-ORRs reported for pralsetinib and selpercatinib were comparable with overlapping confidence intervals. Thus, based on the available evidence it is not possible to conclude if there are relevant differences between pralsetinib and selpercatinib.

In ARROW, safety results were reported for the overall safety population with all tumour types and for the safety population of patients with RET fusion-positive NSCLC. Pralsetinib was found to be well tolerated with a predictable and manageable safety profile in both populations. The safety profiles of pralsetinib and pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy are difficult to compare due to study differences. Overall, the rate of grade ≥3 adverse events (AEs) for pralsetinib in ARROW is numerically higher than what has been reported for pembrolizumab in both KEYNOTE-024 and KEYNOTE-042, but comparable to what has been reported in KEYNOTE-189. In terms of discontinuation rates, the proportion of patients discontinuing treatment in the pralsetinib arm is numerically higher than that reported in the pembrolizumab arm in KEYNOTE-024, but slightly lower compared to KEYNOTE-42, and much lower compared to the pembrolizumab plus chemotherapy arm in KEYNOTE-189. Furthermore, the Danish real-world study, which reported the rate of discontinuations due to immune-related AEs, suggests a rate of discontinuations in Danish patients receiving immunotherapy comparable to the rate reported in KEYNOTE-189.

For the comparison with selpercatinib safety results were reported for the overall safety population and the NSCLC safety population in ARROW and LIBRETTO-001 as well as the safety population in SIREN. The rate of discontinuation due to AEs and grade ≥3 AEs were numerically higher for pralsetinib than selpercatinib. However, safety outcomes across studies are difficult to compare due to differences in baseline characteristics, data maturity and reporting. Overall, the safety profiles of both pralsetinib and selpercatinib were found to be manageable.

Data on quality of life (QoL) was collected via the EORTC QLQ-C30 questionnaire in ARROW but no analysis has yet been carried out for the CCOD of November 6, 2020 nor the CCOD of March 4, 2022. Thus, data is not presented in this assessment, and no comparisons with the comparators of interest have been performed.

CONCLUSION: The efficacy results observed with pralsetinib appear aligned with other selective targeted therapies in biomarker-defined NSCLC subsets, such as ALK and ROS1 at a similar stage in their development – and in line with the overall superiority of dedicated targeted therapy versus conventional options across the field of oncology. In terms of safety, pralsetinib was generally well tolerated, with a low rate of treatment discontinuation. Considering all the analyses conducted, pralsetinib tends to show superiority when compared with the current Danish treatment options for patients with RET fusion-positive NSCLC in first -line, and reinforces the clinical trial results and supports the use of pralsetinib in the indication under primary assessment. Due to the limitations associated with the methods used and the limited data available, the results presented are associated with significant uncertainty and should be carefully assessed. However, the consistency observed for the comparators where both non-adjusted naïve ITCs and adjusted RWE ITCs methods are used, are encouraging and validate, to an extent, the use of the evidence generated.
In addition, the available evidence in second-line further supports the use of selective targeted therapy. Considering the narrative comparison conducted, it is not possible to conclude if there are relevant differences between pralsetinib and selpercatinib for patients with RET fusion-positive NSCLC following prior treatment with platinum-based chemotherapy.

While associated with some limitations, the ITC strategy presents an alternative to mitigate important gaps identified that are crucial for decision-making. In addition, the evidence generation activities associated with this assessment show the importance of considering RWE as a valid information source, especially in an environment of rare disease where the observed prevalence does not allow a randomized controlled trial without compromising access to treatment. Going forward, Roche is committed to generate additional evidence via ongoing clinical randomized controlled trials (AcceleRET Lung), high-quality real-world data (RWD) collection and other ITCs.

4.3 Health economic assessment

METHODS: The purpose of the health economic analysis was to estimate the cost-effectiveness of treating RET fusion-positive NSCLC patients with pralsetinib versus pembrolizumab monotherapy and pembrolizumab in combination with chemotherapy. The analysis was based on a global cost-utility (CU) model, which was adjusted to a Danish setting. A partitioned survival model was developed to determine the cost-effectiveness of pralsetinib versus relevant comparators. The model uses a time horizon of 20 years, a cycle length of 1 month and a discount rate of 3.5% for cost and quality-adjusted life years (QALYs). The efficacy data sources used for pralsetinib were Kaplan-Meier plots for OS and PFS for the treatment naive population from ARROW and the comparative efficacy data sources were based on estimates derived from the naïve ITC analyses with KEYNOTE-042 and KEYNOTE-189. In terms of safety, data from ARROW, KEYNOTE-042 and KEYNOTE-189 was used. The cost sources used were drug costs, hospital costs, cross-sectional costs, AE costs, end-of-life costs and patient and transportation costs. The overall approach to the CU model was to estimate the cost per QALY and the ICERs for pralsetinib relative to the relevant comparators. In addition to the base case analyses, uncertainty in the input parameters in the model were explored through extensive sensitivity and scenario analyses.

All applied extrapolations were validated by clinical experts in an international advisory board. Country-specific inputs in the model were validated by a Danish expert to ensure alignment with Danish clinical practice. Previous HTA submissions served as the basis for identification of utility values used in the health economic model, but aside from that, cost-effectiveness studies have not been identified and used in the development of the model.

The budget impact is estimated per year in the first 5 years after the recommendation of pralsetinib.
The budget impact analysis compares the costs for the Danish regions in the scenario where pralsetinib is recommended as a possible standard treatment for RET fusion-positive NSCLC and the scenario where pralsetinib is not recommended. The total budget impact per year is the difference between the two scenarios.

RESULTS: Base case results from the CU analyses showed that the QALYs associated with pralsetinib are [redacted] and the total cost of patients treated with first-line pralsetinib is [redacted]. The QALYs associated with pembrolizumab monotherapy are [redacted] and the total cost of patients treated with first-line pembrolizumab monotherapy is [redacted] The QALYs associated with pembrolizumab in combination with chemotherapy are [redacted] and the total cost of patients treated with first-line pembrolizumab in combination with chemotherapy is [redacted] The ICER of pralsetinib compared to pembrolizumab monotherapy is [redacted] and the ICER of pralsetinib compared to pembrolizumab in combination with chemotherapy is [redacted].

The budget impact analysis assumes that ~26 RET fusion-positive NSCLC patients are eligible for treatment with pralsetinib a year. It is expected that implementation of testing in all oncology departments in Denmark will take 2-3 years. The budget impact of recommending pralsetinib as first-line treatment in patients with RET fusion-positive NSCLC is [redacted] the first year and [redacted] in year 5.

Roche has also provided a health economic analysis of pralsetinib as a second-line treatment compared to selpercatinib. In this analysis equal effect is assumed and the analysis is conducted as a cost minimization analysis (see appendix L).

CONCLUSION: Considering the information gathered, in terms of clinical efficacy, safety, costs and resources used, pralsetinib presents as a valuable treatment option for patients with RET fusion-positive NSCLC, when compared with current treatment options in Denmark. Pralsetinib may be a cost-effective treatment depending on the willingness-to-pay threshold of the Medicines Council. The model results are sensitive to changes in the drug costs and in the relative efficacy estimates. The added costs for pralsetinib versus the comparators were primarily driven by a longer treatment duration for pralsetinib.

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

Non-small cell lung cancer (NSCLC) is a well-known disease with a poor prognosis and relatively short survival from the time of diagnosis. The newest Danish cancer survival data shows that 49.9% of patients are alive after one year, 32.9% are alive after two years and 16.5% are alive after five years [1].

In recent years an increasing number of molecular alterations and biomarkers have been studied and described. Some of these alterations have been identified as oncogenic drivers e.g. epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) and ROS proto-oncogene 1 receptor tyrosine kinase (ROS1). In NSCLC, rearranged during transfection (RET) fusions is one of these oncogenic drivers. The frequency of the RET fusion has been reported in between 1-2% of NSCLCs, representing a similar frequency to other known rare oncogenic drivers in NSCLC such as ALK and ROS1 [2–4]. Similar to what is described for ALK- and ROS1-positive NSCLC patients, RET fusion-positive NSCLC patients are more likely to have lung adenocarcinoma, be younger, female and never or light smokers [5–7]. Most common RET fusion partners in NSCLC are KIF5B and CCDC6, other less common partners are NCOA4, TRIM33, ZNF477P, ERCC1, HTR4 and CLIP1 [8,9].

In 2020, 4817 patients were diagnosed with lung cancer in Denmark. Of the total number of annual cases, approximately 55% will have stage IIIb-IV disease (n=2650) [1,10], around 85% of these will be diagnosed with NSCLC (n=2253) [1], and around 75% of these will have non-squamous disease (n=1690) [1]. Assuming a prevalence of RET fusions of 1-2% and a test frequency of 100%, this equals between 17-34 RET fusions-positive NSCLC patients. However, feedback from clinicians reveal that although some NSCLC patients in Denmark are currently being tested for RET fusions, only few RET fusion-positive patients are found each year. This, together with the experience of the frequency of ALK- and ROS1-positive NSCLC patients being slightly lower in Denmark compared to the literature, could indicate a relatively lower incidence of RET fusions of around 1.5% among NSCLC patients in Denmark compared to the incidence reported in peer-reviewed literature.

RET fusion testing is not currently included in the standard testing for NSCLC and this influences the incidence and prevalence observed in the past 5 years. A project with The Danish Clinical Quality Program - National Clinical Registries (RKKP) aimed to identify the number of NSCLC patients in Denmark, who had been tested for EGFR, ALK, ROS1 and RET from 2018-2020. In the 3-year period, a total of 13 patients with RET fusions were identified across sites. The project also found that a relatively small proportion of NSCLC patients were tested for RET fusions (6%), and that the majority of testing took place at Vejle Hospital [10]. However, this does not correlate with the number of RET fusion-positive patients identified at the different sites, indicating a lack of reporting. Uncertainty in the numbers due to missing data in the RKKP report alongside the fact that RET fusions are not included in the annual report from the

Danish Lung Cancer Group (DLCG) [1] should be considered when estimating patient numbers. Given these uncertainties, Roche estimates that 5 or less RET fusion-positive NSCLC patients are identified per year in Denmark (Table 1).

As RET fusion testing becomes routine in all oncology departments in Denmark, the patient numbers are expected to rise. Based on the aforementioned annual NSCLC patient numbers, Roche estimates that there will be approximately 26 RET fusion-positive NSCLC patients in Denmark a year when testing is fully implemented. The estimated number of patients eligible for treatment, which takes the above mentioned uncertainties into account, can be seen in Table 2.

Table 1: Incidence and prevalence in the past 5 years

Year	2016	2017	2018	2019	2020
Incidence in Denmark	<5	<5	<5	<5	<5
Prevalence in Denmark	1.5%	1.5%	1.5%	1.5%	1.5%
Global prevalence*	1-2%	1-2%	1-2%	1-2%	1-2%

* Based on peer-review literature [2–4].

Table 2: Estimated number of patients eligible for treatment

Year	**2022**	**2023**	**2024**	**2025**	**2026**
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	<5	5-15	20-30	~26	~26

Testing for RET fusions in NSCLC

The European Society of Medical Oncology (ESMO) precision medicine working group recommends the use of multigene next-generation sequencing (NGS) in NSCLC [11]. This recommendation covers that tumours (or plasma) from NSCLC patients with advanced disease are profiled using a NGS technology that can detect level 1 alterations. RET fusions in NSCLC are classified as level IC in the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT), and should therefore be covered in the recommendation [11]. ESMO has, in 2021, also published a recommendation on the standard methods to detect RET fusions, which is aligned with the earlier NGS recommendations [12]. Because the application is covering a fusion, it is also important to use RNA-based NGS, or DNA-based NGS designed to capture such fusions [11]. Therefore, the recommended testing strategy would be as presented in Figure 1 below (adapted after Belli et al [12]). It should be noted that there are strengths and limitations with the different testing methods and to be certain, the results should be confirmed with a NGS method that is specified for fusions.

Currently, RET fusions are not included in the Danish guidelines for molecular testing in NSCLC. Despite this, some NSCLC patients are already being tested for RET fusions today. Some oncology departments in Denmark are using DNA or RNA NGS panels (including RET fusions) as part of their routine testing. The recommendations from the Danish NSCLC guideline do not yet reflect the approvals of RET fusion specific TKIs.

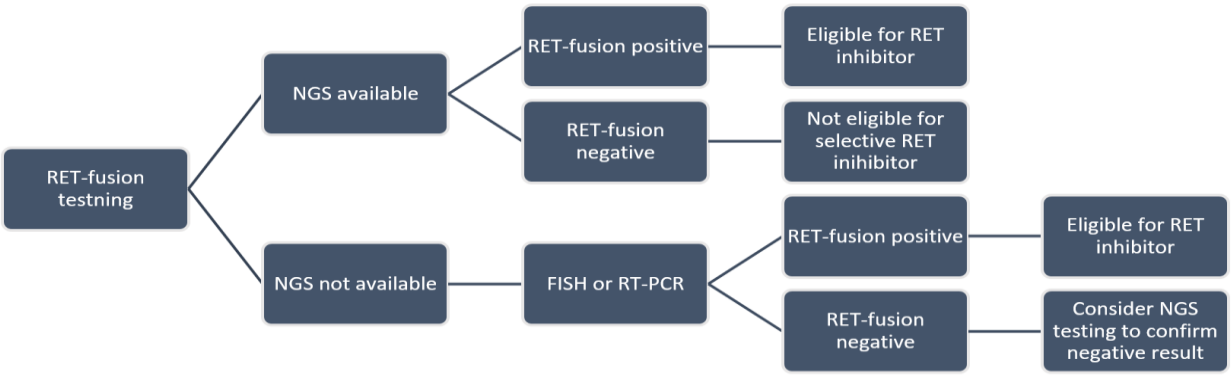


Figure 1: RET fusion-testing algorithm adapted after Belli et al [12]. Abbreviations: RET - rearranged during transfection; NGS - next generation sequencing; FISH - fluorescence in situ hybridization; RT-PCR - Reverse Transcription-Polymerase Chain Reaction.

Prognosis of RET fusions-positive NSCLC patients

As testing and treatment of RET fusions in NSCLC is not yet standard of care, there is limited knowledge on the prognostic value of RET fusions in NSCLC. As of today, there is no clear evidence that patients with RET fusion-positive NSCLC have a different prognosis than those that are RET fusion-negative.

An independent analysis of the Flatiron-Foundation Medicine Clinico-Genomics database (CGDB) has investigated the association between RET fusion status and clinical outcome in a real-world setting. A study by Hess et al. (2021) compared baseline characteristics and clinical outcomes by RET fusion status among patients with metastatic or advanced NSCLC treated with standard therapies. The study included 5807 eligible patients with follow-up data until June 2019 (RET fusion-positive cohort, n=46; RET fusion-negative cohort, n=5761) [6]. In the study, an unadjusted analysis showed that NSCLC patients with RET fusions have different baseline characteristics that contribute to a favourable overall survival (OS). However, when baseline characteristics were adjusted for baseline covariates, no significant differences were seen. The results from this study should be interpreted with caution due to the small size of the RET fusion-positive cohort and potential biases not accounted for.

Similar to patients with oncogene driver-positive NSCLC such as ALK and ROS1, RET fusion-positive NSCLC patients are more likely to have lung adenocarcinoma, be younger, female and never or light smokers compared to the NSCLC population as a whole [5–7]. Because of these similarities in patient demographics and disease characteristics, RET fusions-positive patients are expected to have a similar prognosis.

5.1.1 Patient populations relevant for this application

The relevant patient population for this application is RET fusion-positive NSCLC patients, which reflects the approved EMA indication for pralsetinib. However, due to the limited evidence on clinical outcomes in RET fusion-positive NSCLC patients treated with the comparators of interest, comparative data in NSCLC populations with unknown RET fusion status is also included in the application.

5.2 Current treatment options and choice of comparators

5.2.1 Current treatment options

Current treatment guidelines for NSCLC states that NSCLC patients should be treated with either immunotherapy and/or chemotherapy, or targeted therapy depending on their molecular profile e.g. PD-L1 expression, activated EGFR-mutations, ALK-translocation and ROS1 (Figure 2).

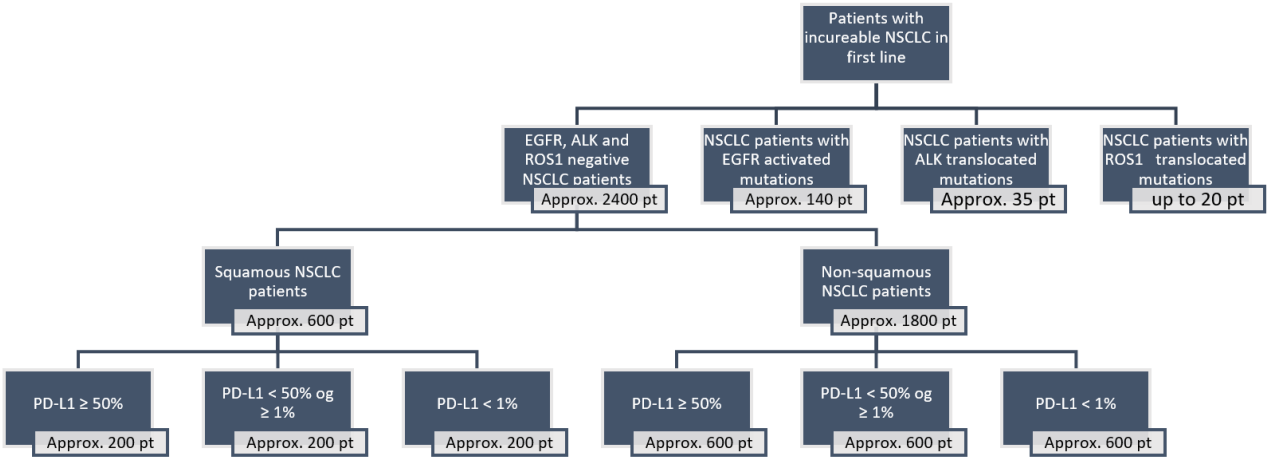


Figure 2: The Medicines Council recommended treatment in first-line NSCLC, adapted after the Medicines Council treatment guideline in first-line NSCLC. Abbreviations: NSCLC - non-small cell lung cancer; EGFR – epidermal growth factor receptor; ALK – Anaplastic lymphoma kinase; RET – Rearranged during transfection; pt – patients; PD-L1 – programmed death-ligand 1.

Recently another targeted therapy, selpercatinib, was approved by EMA for monotherapy treatment of adults with advanced RET fusion-positive NSCLC who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy [13]. On the 23rd of March 2022 the Medicines Council recommended the use of selpercatinib for RET fusion-positive NSCLC, if the patient has experienced disease progression after previous treatment with platinum-based chemotherapy. The Medicines Council finds, despite the uncertainty in the data set, that patients are likely to live longer with selpercatinib treatment than with docetaxel, which is the current standard of care for this patient group. The recommendation includes patients who are in good general condition (performance status 0-1) because the effect of selpercatinib has only been studied in these patients [14].

Currently there is no specific treatment pathway for RET fusion-positive patients. Patients without EGFR, ALK or ROS1 are currently treated depending on their PD-L1 expression and it is expected that RET fusions-positive patients are treated in this group. Because the majority of RET fusion-positive patients have non-squamous histology, the relevant treatment for these patients in first-line according to the Danish guidelines is therefore [15,16]:

- Patients with non-squamous NSCLC and PD-L1-expression ≥50%
    - Pembrolizumab
- Patients with non-squamous NSCLC and PD-L1-expression ≤49%
    - Pembrolizumab in combination with platinum based chemotherapy

Because the current standard of care is dependent on PD-L1 status, it is relevant to understand the relationship between PD-L1 status and RET fusions as well as the clinical outcomes in RET fusion-positive NSCLC patients when treated with ICI with or without chemotherapy. However, only limited evidence is available.

The pivotal studies of pembrolizumab (included in the assessment) have only excluded EGFR- or ALK-positive patients, and have not reported on clinical outcomes in patients with specific driver mutations like RET fusions. Identified retrospective studies (included in the assessment) describe the relation between RET fusions and clinical outcomes when treated with ICI monotherapy or ICI in combination with chemotherapy [6,17–21]. In these studies there was no clear pattern in PD-L1 expression, and varying distributions between negative and positive PD-L1 status were reported in the RET fusion-positive cohorts [6,17–21]. Thus, RET fusions cannot be excluded based on PD-L1 status. In terms of efficacy, the majority of these studies found that most of the RET fusion-positive NSCLC patients had limited benefit of treatment with ICI. In addition, a case study by Offin et al described response across treatment lines for 14 patients. In the study, no responses were observed, and the best objective response to therapy in most patients was progressive disease. Furthermore, median PFS was short [5]. Due to the limited evidence on clinical outcomes in RET fusion-positive patients treated with ICI with or without chemotherapy, and especially in relation to pembrolizumab, it is also important to understand how NSCLC patients in general respond to ICI with or without chemotherapy in relation to their PD-L1 expression. To describe this relationship we have included the relevant clinical studies of pembrolizumab as well as a real-world study that describes the nationwide survival benefit after implementation of first-line immunotherapy (primarily pembrolizumab) for patients with advanced NSCLC in Denmark.

5.2.2 Choice of comparators

As previously described, the majority of Danish RET fusion-positive patients are currently unidentified. As it stands, there is no specific treatment pathway for RET fusion-positive patients and therefore patients go into the standard NSCLC treatment pathway according to Danish guidelines. As the majority of RET fusion-positive patients have non-squamous histology, the most appropriate comparators for pralsetinib in first-line treatment is [15,16]:

- Pembrolizumab for patients with non-squamous NSCLC and PD-L1-expression ≥50%.
- Pembrolizumab in combination with platinum based chemotherapy for patients with non-squamous NSCLC and PD-L1-expression ≤49%.

5.2.3 Description of the comparators

Pembrolizumab is a monoclonal anti-programmed cell death-1 (PD-1) antibody [22]. Depending on the patients PD-L1 expression levels, pembrolizumab is either given as a monotherapy or in combination with pemetrexed and platinum chemotherapy [22]. Patients should be treated with pembrolizumab until disease progression or unacceptable toxicity [22]. In order to initiate treatment with immunotherapy, NSCLC patients must be tested for their tumour PD-L1 expression.

Pembrolizumab is packaged as 50 mg powder for concentrate for solution for infusion. The recommended dose for adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. From a clinical expert we know that most oncology departments in Denmark are dosing pembrolizumab monotherapy every 6 weeks [23].

5.3 The intervention

Pralsetinib is the first approved first-line treatment for RET fusion-positive NSCLC patients, and hence it will offer a new treatment option. It is an oral, selective inhibitor of RET tyrosine kinase. Gene rearrangements (fusions) in each of the genes encoding these target kinases can result in fusion proteins that constitutively activate downstream signalling and drive oncogenesis in different tumour types.

Pralsetinib has been studied in the phase 1/2 ARROW trial with RET fusion-positive NSCLC patients. This showed a treatment effect, which led to a regulatory approval from EMA. Targeting treatment to specific mutations is generally considered effective, and is well known in lung cancer, where treatments targeting EGFR, ALK and ROS1 have been proven to be effective. As described in section 5.1 it is necessary to test and identify NSCLC patients with RET fusions. The relevant test flow for detection of RET fusions in NSCLC can be seen in Figure 1.

Dosage of pralsetinib is 400 mg once daily. Pralsetinib is formulated as capsules containing 100 mg.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

In order to assess the clinical evidence available for treatment of patients with locally advanced or metastatic RET fusion-positive NSCLC and assess the feasibility of conducting indirect treatment comparisons (ITCs) of pralsetinib with relevant comparators used in Danish clinical practice, two systematic literature reviews (SLRs) were conducted. The first approach was to search in the specific population of interest, patients with RET fusion-positive NSCLC. It was already suspected that limited evidence would be available, and therefore, no strict restrictions were applied to the study design; this included interventional and observational studies. Because of the sparse evidence for the comparators of interest, there was a need to broaden the scope of the review and include RET wild-type NSCLC patients. Considering the lack of clear evidence showing a different prognosis in patients who were RET fusion-positive and RET wild-type, this appeared as an option to overcome the lack of comparative data.

The Medicines Council methods guide for assessing new pharmaceuticals version 1.2 has provided guidance for the literature search. The search for peer-reviewed published full-text articles has been set up using the search strings provided in appendix A. As described, searches were set up in both RET fusion-positive NSCLC and NSCLC with unknown RET fusion status. Electronic searches were carried out in PubMed and in CENTRAL (via Cochrane Library) on October 21 and 22, 2021, giving a total of 4 searches. The searches contain terms descriptive of the area as described in the search strings. The Search Builder for each search is available in appendix A.

For the search in RET fusion-positive NSCLC, 247 and 12 references were identified in PubMed and CENTRAL, respectively. For the search in NSCLC with unknown RET fusion status, 154 and 22 references were identified in PubMed and CENTRAL, respectively.

Two reviewers independently screened the references by title and abstract according to the defined in- and exclusion criteria (Table 61 and Table 62 in appendix A) using a reference management tool. Of the 259 references in the RET fusion-positive NSCLC search, 15 were included for full-text review. No duplicates were identified. In the search in NSCLC with unknown RET fusion status, 15 out of 176 were included for full-text review. For this search, duplicates were excluded via the search string. Following full-text review of the included references, 7 and 10 references from the search in RET fusion-positive NSCLC and the search in NSCLC with unknown RET fusion status, respectively, were deemed relevant for the assessment. There was no overlap between the two searches in terms of included references.

In addition, four hand-searched abstracts were identified and included in the assessment. These references present data with longer follow-up from some of the clinical trials identified in the search in NSCLC with unknown RET fusion status. They are as follows:

- Nationwide Survival Benefit after Implementation of First-Line Immunotherapy for Patients with Advanced NSCLC—Real World Efficacy; Mouritzen et al; Cancers; 2021
- Final analysis of the phase III KEYNOTE-042 study: Pembrolizumab (Pembro) versus platinum-based chemotherapy (Chemo) as first-line therapy for patients (Pts) with PD-L1–positive locally advanced/ metastatic NSCLC. Mok, T. et al, Ann Oncol. 2019;30 (suppl 2; abstr 1020).
- KEYNOTE-042 3-Year Survival Update: 1L Pembrolizumab vs Chemotherapy for PD-L1-Positive Locally Advanced or Metastatic NSCLC. B.C., Cho et al., World Conference on Lung Cancer (WCLC) 2020
- Pembrolizumab + Pemetrexed-Platinum for Metastatic NSCLC: 4-Year Follow-up From KEYNOTE-189, Gray et al., WCLC 2020

Thus, from all searches, 7 references were included for RET fusion-positive NSCLC (7 from PubMed, 0 from CENTRAL) and 14 referenes were included for NSCLC with unknown RET fusion status (10 from PubMed, 0 from CENTRAL and 4 hand-searched). PRISMA flow charts and a list of excluded references are available in appendix A. Lastly, EMA's European public assessment report (EPAR) for both pralsetinib (AR0000) and its comparator pembrolizumab (AR0011, AR0043 and AR0057) have been consulted.

6.2 List of relevant studies

For the search in RET fusion-positive NSCLC, a total of 7 references from 7 studies were found eligible for inclusion. These include ARROW (NCT03037385) that assesses the efficacy and safety of pralsetinib monotherapy and 6 retrospective studies that evaluate the effect of ICIs in first and later treatment lines. The studies were used to address both clinical questions.

For the search for comparative data in NSCLC with unknown RET fusion status, a total of 14 references from 4 studies were found eligible for inclusion. Three were found relevant for clinical question 1. These include the clinical studies KEYNOTE-024 (NCT02142738) and KEYNOTE-042 (NCT02220894) that assess the efficacy and safety of pembrolizumab monotherapy in populations with stage IV NSCLC and PD-L1 expression ≥50%, and the real-world study by Mouritzen et al that evaluate the effect of pembrolizumab monotherapy in Danish NSCLC patients. One study was found relevant for clinical question 2, and include the clinical study KEYNOTE-189 (NCT02578680) that assesses the efficacy and safety of pembrolizumab in combination with chemotherapy in a population with stage IV NSCLC and PD-L1 expression ≤49%.

In addition, Roche has conducted a real-world study using the Flatiron Health-Foundation Medicine Enhanced Data Mart (EDM) database in order to compare pralsetinib with pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy for treatment of NSCLC patients with unknown RET fusion status in a real-world setting [24].

The included studies from the SLR are listed in Appendix A. This list further includes an ongoing study of the pralsetinib clinical development programme, the AcceleRET Lung trial**.** Results from this study are expected to be available in 2026-2027. For more detailed information about study characteristics of the included clinical studies, refer to appendix B.

7. Efficacy and safety

7.1 Efficacy and safety of pralsetinib compared to pembrolizumab for patients with NSCLC and PD-L1 ≥50%

7.1.1 Relevant studies

In the following section, we provide a brief description of each study included in the assessment, and address any relevant differences between the studies in terms of study and patient characteristics. For detailed study characteristics refer to appendix B. For baseline characteristics of patients included in each study refer to appendix C.

7.1.1.1 Studies in RET fusion-positive NSCLC

7.1.1.1.1 Pralsetinib

ARROW (NCT03037385)

ARROW is a multicentre, phase 1/2, non-randomised, open-label, multi-cohort study evaluating the safety, tolerability and efficacy of pralsetinib in patients with RET fusion-positive NSCLC, RET-mutant medullary thyroid cancer (MTC), RET fusion-positive thyroid cancer and other RET-altered solid tumours. The study consists of a dose escalation part (phase 1, completed) and an expansion part in patients treated with 400 mg of pralsetinib once daily (phase 2, ongoing).

The primary endpoints were overall response rate (ORR) evaluated by blinded independent central review (BICR) according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) and safety. Secondary endpoints were progression free survival (PFS) and overall survival (OS).

Efficacy and safety data for RET fusion-positive NSCLC patients are derived from the clinical cut-off date (CCOD) November 6, 2020. The efficacy population includes 233 NSCLC-patients who began treatment on or before May 22, 2019, to allow sufficient follow-up time from initial response among responders. In addition data was reported for efficacy subpopulations either including patients that received prior systemic therapy (n=158) or patients that received no prior systemic therapy (n=75). Safety assessment was based on the overall safety population including all patients who were initiated with 400 mg of pralsetinib (n=281).

In Gainor et al. the RET fusion-positive NSCLC patient population from ARROW is described [25]. This publication presents data from an earlier data cut-off (CCOD: May 22, 2022), than the one presented in the EPAR (CCOD: November 6, 2020) [26].

New data from ARROW (CCOD: March 4, 2022) was presented at ESMO 2022. Efficacy was assessed in 281 patients with fusion-positive NSCLC who have received pralesetinib. Additionally, data was reported for efficacy subpopulations including treatment naïve patients (n=116), which has further been devided into pre-aligibility revision (n=47) and post eligibility revision (n=69) and for patients with prior platinum treatment (n=141). These data have not been peer-reviewed and, thus, only included in the following as supplemental data. The difference between the pre-eligibility and the post eligibility subpopulations are amendment 9 to the ARROW study protocol that allowed 200 treatment naïve patients to be included in ARROW. The new criteria was: Any RET fusion-positive NSCLC patient NOT previously treated with platinum chemotherapy, instead of previously either: progressed following standard systemic therapy; any RET fusion-positive NSCLC patient NOT previously treated with platinum chemotherapy; have not adequately responded to standard systemic therapy; Intolerant of standard therapy; or Investigator has determined that treatment with standard therapy is not appropriate. Where possible we will present the treatment naïve

population as a whole, otherwise we will present data from the post-eligibility subgroup as this is closest to the indication and PICO [27].

7.1.1.1.2 ICI-based therapy for RET fusion-positive NSCLC patients

Besides Gainor et al that presents data from ARROW, which is described above, a total of six articles were included in the SLR on RET fusion-positive NSCLC patients treated with ICI. These will be described in the following section. For additional information, refer to Table 73 in appendix A. Data from these studies will not be included in appendix D, but only in the outcome tables in section 7.1.2 and 7.2.2.

In Bhandari et al, they described RET fusion patients captured in either Flatiron Health-Foundation Medicine Clinical-genomic Database (CGDB) (n=29) or Guardant Health (GHD) (n=40) that were treated with ICI [17]. Of these databases, CGDB has the most detailed baseline characteristics. CGDB presents data for three patients groups: 1). Patients receiving ICI-based therapy in first-line (n=17), 2) patients receiving ICI-based therapy in second-line (n=11) and 3) a subgroup of patients receiving carboplatin, pemetrexed and pembrolizumab in first-line (n=12). OS, rwPFS and response are presented for the first group. Response and duration of treatment is reported for the third group.

From the IMMUNOTARGET registry a publication by Mazieres et al described the 16 RET fusion-positive NSCLC patients that were treated with ICI [18]. OS, PFS and response was described for the cohort, however it was not specified for the RET fusion-positive cohort in what treatment line the patient received ICI and what kind of ICI treatment the patient received. Response was measured with RECIST 1.1.

Guisier et al presents data from the IMAD2 study, which was conducted in the French Lung Cancer Group Centers [19]. It included a total of 9 RET-translocations that all received ICI treatment in second or later lines. OS, PFS and response measured with RECIST 1.1 was presented. This study had the same limitations as Mazieres et al. It was not specified for the RET fusion-positive cohort in what treatment line the patient received ICI and what kind of ICI treatment the patient received.

Hedge et al is a retrospective review of RET fusion-positive patients referred to the phase 1 clinical trials program at MD Anderson [21]. In total 27 NSCLC patients had RET fusions and of these patients 14 received ICI. In addition, two NSCLC patients had RET point mutations. Time to discontinuation was presented for the 29 NSCLC RET fusion-positive patients and compared for the patients that received ICI and non-ICI treatment.

Hess et al, like Bhandari et al, also uses the Flatiron Health-Foundation Medicine CGDB, where patient characteristics are described for 46 RET fusion-positive NSCLC patients [17]. Of these, 15 patients have positive PD-L1 expression, 7 patients have negative PD-L1 expression and for 24 patients PD-L1 is missing or unknown. Of the 46 patients, 9 received first-line pembrolizumab with chemotherapy like in KEYNOTE-189. We must expect some overlap in the reported populations in this article and the one by Bhandari et al, however we cannot be sure who and how many.

Rozenblum et al is a retrospective study performed at Davidoff cancer in Israel between 2011 and 2015 [20]. A total of 9 RET fusion-positive NSCLC patients were found and 4 of these were treated with ICI. Median treatment duration and response were reported for the 4 patients.

7.1.1.1.3 Comparability between studies

NSCLC patients in ARROW were required to have pathologically documented, definitively diagnosed locally advanced or metastatic disease with a RET fusion. Patients were either not previously or previously treated with platinum-based chemotherapy. The retrospective studies included RET fusion-positive patients treated in first, second or later lines,

but the specific treatment lines were not reported in all studies. All patients were treated with ICI-based therapy or pembrolizumab in combination with pemetrexed and cisplatin like in KEYNOTE-189. Patients treated with ICI monotherapy received either nivolumab, pembrolizumab, atezolizumab or durvalumab. However, in four out of the six studies it was not specified what kind of ICI the patients received (appendix C). As mentioned above Bhandari et al and Hess et al both reported data from FMIs CGDB on RET fusion-positive patients.

Available baseline characteristics and comparability of patients across studies is presented in appendix C. However, only two out of the six retrospective studies reported baseline characteristics for the RET fusion-positive patients specifically, making it difficult to compare.

Overall, the uncertainties in terms of specific ICIs and treatment lines are limitations that should be taken into consideration when comparing the available data with the data from ARROW. Moreover, the limited information on baseline characteristics alongside the small sample size in the retrospective studies makes it difficult to assess the degree of comparability, which is largely unclear. However, all patients are RET fusion-positive, and are considered representative of Danish patients eligible for RET inhibitor treatment. Despite the limited data from the retrospective studies, we therefore find it relevant to present the available first-line data from Bhandari et al and the available line-agnostic data from the other studies.

7.1.1.2 Studies in NSCLC with unknown RET fusion status

In the absence of data in patients with RET fusion-positive NSCLC for pembrolizumab monotherapy, a series of comparisons based on comparator data in NSCLC populations with unknown RET fusion status have been conducted. The comparisons are based on the assumption that RET fusion positivity versus wild-type is not prognostic, which is supported by the literature, suggesting no strong evidence for a prognostic value of RET fusions (see previous description). The included clinical studies and real-world studies are described in the following.

7.1.1.2.1 Pembrolizumab monotherapy

KEYNOTE-024 (NCT02142738)

KEYNOTE-024 was a multicentre, phase 3, open-label, randomised controlled study evaluating the efficacy and safety of pembrolizumab monotherapy compared to standard of care (SOC) platinum-based chemotherapies in the treatment of participants with previously untreated stage IV, NSCLC with PD-L1≥50% of TCs and no sensitizing EGFR mutations or ALK translocations.

The study included 305 patients that were randomly assigned in a 1:1 ratio to receive treatment with either pembrolizumab administered intravenously at a dose of 200 mg every 3 weeks for 35 cycles or the investigator's choice of platinum-based chemotherapy for 4 to 6 cycles every 3 weeks. Crossover from the chemotherapy group to the pembrolizumab group was permitted in the event of disease progression. Randomisation was stratified by ECOG performance status (PS) (0 vs. 1), histology (non-squamous vs. squamous), and region of enrolment (East Asia vs. non-East Asia).

The primary efficacy endpoint was PFS per RECIST 1.1 as assessed by blinded independent central radiologic review. Key secondary endpoints included OS and safety. Safety assessment was based on the safety analysis set including all patients who received at least one dose of trial treatment (n=304). Clinical cut-off dates and median time of follow-up for the analyses conducted are listed in appendix B.

KEYNOTE-042 (NCT02220894)

KEYNOTE-042 was a multicentre, phase 3, open-label, randomised controlled study evaluating the efficacy and safety of pembrolizumab monotherapy compared to SOC platinum-based chemotherapies in the treatment of participants with previously untreated locally advanced or metastatic NSCLC without a sensitising EGFR mutation or ALK translocation and with an ECOG PS score of 0 or 1, life expectancy 3 months or longer, and a PD-L1 Tumour Proportion Score (TPS) of 1% or greater.

The study included 1274 patients that were randomly assigned in a 1:1 ratio to receive treatment with either pembrolizumab administered intravenously at a dose of 200 mg every 3 weeks for up to 35 cycles or the investigator's choice of platinum-based chemotherapy for 4 to 6 cycles every 3 weeks. Randomisation was stratified by region of enrolment (East Asia vs. rest of world), ECOG PS status (0 vs. 1), histology (non-squamous vs. squamous) and PD-L1 TPS status (≥50% vs. 1%-49%).

The primary efficacy endpoint was OS for each PD-L1 subgroup: TPS≥50%; TPS≥20%; and TPS≥1%. Key secondary endpoints included PFS per RECIST 1.1 as assessed by blinded independent central review. Safety assessment was based on the safety analysis set including all patients who received at least one dose of trial treatment (n=1251). Clinical cut-off dates and median time of follow-up for the analyses conducted are listed in appendix B.

Danish nationwide RW study of first-line ICI (Mouritzen et al)

The RW study by Mouritzen et al. assessed OS and PFS in Danish NSCLC patients before and after the implementation of first-line ICIs in Denmark as well as possible prognostic factors for OS. ICI was defined as per the Danish guidelines at the time with a fixed pembrolizumab dose at 200 mg or 2 mg/kg every 3 weeks for a maximum of 2 years. 12 patients (12%) in the cohort received nivolumab (3 mg/kg) every 2 weeks. As the vast majority of the patient population received pembrolizumab, the study can be viewed as an assessment of real-life efficacy and safety of pembrolizumab in a Danish patient population.

Baseline demographics and clinical data from the Danish NSCLC population without EGFR and ALK alterations treated with first-line ICI was extracted from the Danish Lung Cancer Register (DLCR) from January 1, 2013 to October 1, 2018 (n=6890). The cohort was separated into a DLCR pre-approval cohort of patients who initiated treatment before the approval of ICIs in any treatment line (March 1, 2013 to August 1, 2014; n=1658) as well as a post-approval cohort of patients initiating treatment after the approval of 1L ICI in Denmark (1 March 2017 to 1 October 2018, n=2055). Patients who initiated first-line treatment between August 2, 2014 and February 28, 2017 (n=3177) were excluded from the analysis to minimize the impact of second-line ICI, which was implemented in Denmark in September 2015. As data on PS, detailed outcome data, and treatment details are lacking in DLCR, electronic health record (EHR) data was consulted to identify patients treated with first-line ICI. Matching of the two datasets was performed and 482 patients receiving first-line ICI were found across DLCR and EHR data.

Flatiron EDM RWD study (data on file)

See description in appendix F.

7.1.1.2.2 Comparability between studies

As mentioned previously, NSCLC patients in ARROW were required to have pathologically documented, definitively diagnosed locally advanced or metastatic disease with a RET fusion. Patients were either not previously or previously treated with platinum-based chemotherapy. In KEYNOTE-024, patients were required to have stage IV or recurrent disease. Patients in KEYNOTE-042 were required to have locally advanced or metastatic disease, but more than 80% of the enrolled patients had stage IV disease. In both KEYNOTE studies patients were required to have received no prior chemotherapy for metastatic disease. All three trials had similar eligibility requirements in terms of age and performance status. KEYNOTE-024 and KEYNOTE-042 also had similar requirements in terms of biomarker status

availability. All three trials enrolled patients regardless of histology. However most RET fusions are detected in non-squamous NSCLC patients, and hence, only 1.3% of the trial population in ARROW had squamous histology. Both real-world studies included NSCLC patients regardless of histology who received ICI in a first-line setting.

Comparability of baseline characteristics of patients in ARROW, KEYNOTE-024 and KEYNOTE-042 and the real-world studies is described in detail in appendix C. Overall, factors which may be considered the most imbalanced between ARROW and the comparator studies include gender, histological features and smoking status. The proportion of patients with brain metastasis was only reported in ARROW and in the Danish population receiving ICI as reported by Mouritzen et al, and can therefore not be compared across all studies. Most of the differences observed in baseline characteristics are to be expected, and inherent uncertainties are unavoidable when comparing a population consisting exclusively of RET fusion-positive patients in ARROW with populations with unknown RET fusion status. However, the populations are considered comparable to an extent that allows narrative and naïve comparisons. The cross-study differences should be taken into consideration when interpreting the results from the comparative analyses. Lastly, the comparison versus an external control cohort from the Flatiron EDM database achieved excellent balance after adjustment.

7.1.2 Efficacy and safety – results per study

In the following section, we provide a summary of the key efficacy and safety findings for each included study. Data on the following outcomes have been extracted if available:

- Overall survival
- Progression-free survival
- Overall response rate
- Grade ≥3 adverse events
- Discontinuation due to adverse events
- Quality of life

For each outcome, we present data for the RET fusion-positive population following the population with unknown RET fusion status. For ARROW, data from the CCOD of November 6, 2020 are presented. In addition, updated data from the CCOD of March 4, 2022 recently presented at ESMO 2022 have been included. These data have not been peer-reviewed and are therefore only included as supplemental data. For the other studies included, data from the most recent clinical cut-off date are presented unless otherwise specified.

For detailed efficacy and safety results, refer to appendices D and E.

7.1.2.1 Overall survival

7.1.2.1.1 RET fusion-positive NSCLC

The clinical trial evaluating pralsetinib, ARROW, reports data for OS defined as the time from randomisation to death of any cause. Data is presented for the total study populations and the population that has received no prior systemic therapy (Table 3).

OS is evaluated in four out of the six included retrospective studies, but OS is not reached in two of the four studies. Bhandari et al. presents OS data for patients treated with ICI-based therapy in first-line from the CGDB database (CGDB subgroup, n=17) as well as patients treated with carboplatin, pemetrexed and pembrolizumab, referred to as the KEYNOTE-189 regime, in first-line (CGDB post-hoc subgroup, n=12). Data is presented in Table 3**.**

Table 3: Overall survival in RET fusion-positive populations

Trial name	Intervention	Median follow-up	N	Overall survival			
				Median, mo. (95% CI)	12 mo rate, % (95% CI)	24 mo rate, % (95% CI)	HR (95% CI)
Clinical trials							
ARROW (total efficacy population) [26] CCOD: Nov 6, 2020	Pralsetinib	17.1 mo.	233	NR	76.0 (69.9-82.0)	66.0 (57.9-74.1)	N/A
ARROW (no prior systemic treatment) [26] CCOD: Nov 6, 2020	Pralsetinib	12.8 mo.	75	NR	82.3 (71.9-92.8)	74.0 (59.3-88.6)	N/A
ARROW (updated total efficacy population) [27] CCOD: Mar 4, 2022	Pralsetinib	26.8 mo.	281	44.3 (31.9-NR)	N/A	N/A	N/A
ARROW (updated treatment naïve population) [27] CCOD: Mar 4, 2022	Pralsetinib	22.1 mo.	116	NR (31.9-NR)	N/A	N/A	N/A
Retrospective studies							
Bhandari et al (CGDB subgroup) [17]	ICI-based therapy*	-	17	19.1 (6.9-NR)	-	-	N/A
Bhandari et al (CGDB post-hoc subgroup) [17]	KN-189 regime	-	12	19.0 (6.9-NR)	-	-	N/A
Mazieres et al § [18]	ICI-based therapy*	16.1 mo.	16	21.3 (3.8-28.0)	-	-	N/A
Guisier et al ¤ [19]	ICI-based therapy*	9.2 mo.	9	NR (26.8-NR)	88.9 (70.6-100)	-	N/A
Hess et al [6]	KN-189 regime	-	9	NR	-	-	N/A
Hegde et al [21]	ICI-based therapy	-	16	-	-	-	N/A
Rozenblum et al [20]	ICI-based therapy	-	4	-	-	-	N/A

§ Outcome measured as time from first administration of ICI therapy to death due to any cause. ¤ Outcome measured as time from introduction of ICI to death. *Available information on the distribution of ICI-based therapies can be found in Table 86.

Abbreviations: CI – confidence interval; HR – hazard ratio; ICI – immune checkpoint inhibitors; N/A – not applicable; NR – not reached; mo – months; CGDB – clinical-genomic database; kn-189 – Keynote-189.

7.1.2.1.2 NSCLC with unknown RET fusion status

The clinical trials, KEYNOTE-024 and KEYNOTE-042, report data for OS defined as the time from randomisation to death of any cause. Data is presented for the total study populations with PD-L1 ≥50% and the non-squamous subpopulations with PD-L1 ≥50% (Table 4). Data with the the longest possible follow-up have been extracted for both KEYNOTE-studies. As OS-rates are not available at the latest data cut-off date for either of the studies, results based on the final protocol-defined OS analysis from both have also been extracted. The results for the total study population showed trends aligned with the results for the non-squamous populations. For the non-squamous subgroups, only hazard ratios (HRs) without Kaplan Meier (KM) plots are available. Moreover, OS data is not reported separately for the non-squamous subgroup at the most recent cut-off. For these reasons data for the total study populations will inform the comparative analyses presented in section 7.1.3.

The real-world study by Mouritzen et al assessed OS in Danish NSCLC patients receiving treatment with first-line ICI-based therapy. Data is presented for a population of 482 patients found across DLCR and EHR data, referred to as the ICI-cohort (Table 4).

Table 4: Overall survival in populations with unknown RET fusion status

Trial name	Intervention	Median follow-up	N	Overall survival			
				Median, mo (95% CI)	12 mo. rate, % (95% CI)	24 mo. rate, % (95% CI)	HR (95% CI)
Clinical trials							
KEYNOTE-024 Reck 2021 [28]	PEMB	60 mo.	154	26.3 (18.3-40.4)	-	-	0.62 (0.48-0.81)
	Chemotherapy		151	13.4 (9.4-18.3)	-	-	
KEYNOTE-024 Reck 2019 [29]	PEMB	25.2 mo.*	154	30.0 (18.3-NR)	70.3 (62.3-76.9)	51.5 (43.0-59.3	0.63 (0.47-0.86
	Chemotherapy		151	14.2 (9.8-19.0)	54.8 (46.4-62.4	34.5 (26.7-42.4)	
KEYNOTE-024 (non-sq subgroup) Reck 2019 [29]	PEMB	25.2 mo.*	125	-	-	-	0.58 (0.41-0.83)
	Chemotherapy		124	-	-	-	
KEYNOTE-042 Cho 2021 [30]	PEMB	46.9 mo.	299	20.0 (15.9-24.2)	-	-	0.68 (0.57-0.82)
	Chemotherapy		300	12.2 (10.4-	-	-	

				14.6)			
KEYNOTE-042 Mok 2019 [31]	PEMB	12.8 mo.*	299	20.0 (15.4-24.9)	-	45%	0.69 (0.56-0.85)
	Chemotherapy		300	12.2 (10.4-14.2)	-	30%	
KEYNOTE-042 (non-sq subgroup) Mok 2019 [31]	PEMB	12.8 mo.*	192	-	-	-	0.82 (0.63-1.07)
	Chemotherapy		186	-	-	-	
Real-world evidence							
Mouritzen et al. [32]	ICI cohort	-	482	19.0 (16.0-22.0)	64	42	N/A

*Denotes that follow up is for the ITT and not the specified subgroup. Abbreviations: CI – confidence interval; EDM – enhanced data mart; HR – hazard ratio; ICI – immune checkpoint inhibitors; non-sq – non-squamous; NR - not reached; PEMB – pembrolizumab; mo – months; N/A – not applicable.

7.1.2.2 Progression-free survival

7.1.2.2.1 RET fusion-positive NSCLC

ARROW reports data for PFS for the total study populations and the population that has received no prior systemic therapy (Table 5). PFS is defined as the time from randomization to disease progression or death. Progression is assessed by blinded independent central review according to RECIST version 1.1.

PFS is evaluated in four out of the six included retrospective studies. Hegde et al. does not report data on PFS, but reports on time-to-treatment discontinuation (TTD) and Rozenblum et al presents median treatment duration. Data is presented in Table 5**.**

Table 5: Progression-free survival in RET fusion-positive populations

Trial name	Intervention	Median follow-up	N	Progression-free survival			
				Median, mo (95% CI)	12 mo. rate, % (95% CI)	24 mo. rate, % (95% CI)	HR (95% CI)
Clinical trials							
ARROW (total efficacy population) [26] CCOD: Nov 6, 2020	Pralsetinib	17.1 mo.	233	16.4 (11.0-24.1)	56.0 (48.9-63.1)	42.1 (33.2-51.0)	N/A
ARROW (no prior systemic treatment) [26]	Pralsetinib	12.8 mo.	75	13.0 (9.1-NR)	52.6 (37.8-67.5)	47.8 (31.6-64.1)	N/A

CCOD: Nov 6, 2020							
ARROW (updated total efficacy population) [27] CCOD: Mar 4, 2022	Pralsetinib	25.8 mo.	281	13.2 (11.4-16.8)	N/A	N/A	N/A
ARROW (updated treatment naïve population) [27] CCOD: Mar 4, 2022	Pralsetinib	**	116	12.6 (9.2-16.6)	N/A	N/A	N/A
Retrospective studies							
Bhandari et al (CGDB subgroup) [17]	ICI-based therapy*	-	17	4.2 (1.4-8.4)	-	-	N/A
Bhandari et al (CGDB post-hoc subgroup) [17]	KN-189 regime	-	12	5.4 (1.4-14.2)	-	-	N/A
Mazieres et al. [18]	ICI-based therapy*	16.1 mo.	16	2.1 (1.3-4.7)	7 (0.4-27.1)	-	N/A
Guisier et al. [19]	ICI-based therapy*	9.2 mo.	9	7.6 (2.3-NR)	26.7 (8.3-85.8)	-	N/A
Hess et al [6]	KN-189 regime	-	9	6.6 (0.4-NR)	-	-	N/A
Hegde et al [21]	ICI-based therapy	-	16^	3.4 §	-	-	N/A
Rozenblum et al [20]	ICI-based therapy	-	4	11 (1-26) ¤	-	-	N/A

^ 14 had RET fusions and 2 had RET point mutations; § reported as time-to-treatment discontinuation (TTD). ¤ reported as median treatment duration in weeks (range). *Available information on the distribution of ICI-based therapies can be found in Table 86. Abbreviations: CI – confidence interval; HR – hazard ratio; ICI - immune checkpoint inhibitors; N/A - Not applicable; NR - not reached; mo. – months; CGDB – clinical-genomic database, KN-189 – Keynote-189; ** not reported for this patient group.

7.1.2.2.2 NSCLC with unknown RET fusion status

Both KEYNOTE-024 and KEYNOTE-042 report data for PFS in the total study population with PD-L1 ≥50%, but only KEYNOTE-024 report PFS data for the non-squamous subpopulation with PD-L1 ≥50% (Table 6). In both trials, PFS is defined as the time from randomization to disease progression or death. Progression is assessed by blinded independent central review according to RECIST version 1.1. The results for the total study population showed trends aligned with the results for the non-squamous population. For the non-squamous subgroup from KEYNOTE-024, only a HR without KM is available. Moreover PFS data is not reported separately for the non-squamous subgroup at the most recent cut-off. For these reasons data for the total study populations will inform the comparative analyses presented in section 7.1.3.

The real-world study by Mouritzen et al assessed PFS in Danish NSCLC patients receiving treatment with first-line ICI. Data is presented for a population of 579 patients found in the EHR-ICI cohort (Table 6).

Table 6: Progression-free survival in populations with unknown RET fusion status

Trial name	Intervention	Median follow-up	N	Progression-free survival			
				Median, mo (95% CI)	12 mo rate, % (95% CI)	24 mo rate, % (95% CI)	HR (95% CI)
Clinical trials							
KEYNOTE-024 Reck 2021 [28]	PEMB	60 mo.	154	7.7 (6.1-10.2)	-	-	0.50 (0.39-0.65)
	Chemotherapy		151	5.5 (4.2-6.2)	-	-	
KEYNOTE-024 (non-sq subgroup) Reck 2016 [33]	PEMB	11.2 mo.*	125	-	-	-	0.55 (0.39-0.76)
	Chemotherapy		124	-	-	-	
KEYNOTE-042 Cho 2021 [30]	PEMB	46.9 mo.	299	6.5 (5.9-8.6)	-	-	0.85 (0.72-1.02)
	Chemotherapy		300	6.5 (6.2-7.6)	-	-	
Real-world evidence							
Mouritzen et al. [32]	EHR-ICI cohort	-	579	8.2 (7.2-9.3)	-	-	N/A

*Denotes that follow up is for the ITT and not the specified subgroup. Abbreviations: CI – confidence interval; EDM – enhanced data mart; HR – hazard ratio; ICI – immune checkpoint inhibitors; non-sq – non-squamous; NR – not reported; PEMB – pembrolizumab; mo. – months; N/A – not applicable; EHR-ICI – electronic health record immune checkpoint inhibitor.

7.1.2.3 Overall response rate

7.1.2.3.1 RET fusion-positive NSCLC

ARROW reports data for ORR for the total study populations and the population that has received no prior systemic therapy (Table 7). ORR is defined as the proportion of patients who have a partial or complete response to treatment. ORR is assessed by blinded independent central review according to RECIST version 1.1. In addition, intercranial ORR was assessed by BICR in ten patients with measureable CNS metastasis at baseline in the response-evaluable population (Table 8). There were no patients with measurable baseline CNS metastases in the treatment-naïve subgroup.

ORR is evaluated in five out of the six included retrospective studies. Data is presented in Table 7**.** Intercranial ORR was not assessed in the included studies.

Table 7: Overall response rate in RET fusion-positive populations

Trial name	Intervention	Median follow-up	N	ORR		
				ORR, n (%) (95% CI)	CR, n (%)	PR, n (%)
Clinical trials						
ARROW (total efficacy population) [26] CCOD: Nov 6, 2020	Pralsetinib	17.1 mo.	233	150 (64.4) (57.9-70.5)	11 (4.7)	139 (59.7)
ARROW (no prior systemic treatment) [26] CCOD: Nov 6, 2020	Pralsetinib	12.8 mo.	75	54 (72.0) (60.4-81.8)	4 (5.3)	50 (66.7)
ARROW (updated total efficacy population) [27] CCOD: Mar 4, 2022	Pralsetinib	-	281	185 (65.8) (60.0-71.4)	18 (6.4)	167 (59.4)
ARROW (updated treatment naïve population, post eligibility revision) [27] CCOD: Mar 4, 2022	Pralsetinib	-	69	52 (75.4) (63.5-84.9)	4 (5.8)	48 (69.6)
Retrospective studies						
Bhandari et al (CGDB subgroup) [17]	ICI-based therapy*	-	13	7 (53.8)	1 (7.7)	6 (46.2)
Bhandari et al (CGDB post-hoc subgroup) [17]	KN-189 regime	-	10	7 (70)	1 (10)	6 (60)
Mazieres et al. [18]	ICI-based therapy*	16.1 mo.	16	1 (6.3)	1 (6.3) §	-
Guisier et al. [19]	ICI-based therapy*	9.2 mo.	8	3 (37.5)	0 (0)	3 (37.5)
Hess et al. [6]	KN-189 regime	-	9	6 (75)	1 (12.5)	5 (62.5)
Hegde et al. [21]	ICI-based therapy	-	16	-	-	-
Rozenblum et al. [20]	ICI-based therapy	-	4	0 (0)	0 (0)	0 (0)

*Available information on the distribution of ICI-based therapies can be found in Table 86. § Reported as CR/PR. Abbreviations: CR – complete response; ICI - immune checkpoint inhibitor; ORR – overall response rate; PR – partial response; mo. – months; CGDB – clinical-genomic database, KN-189 – Keynote-189; CI – confidence interval.

Table 8: CNS response in the response-evaluable population

	ORR, n (%) (95% CI)	CR, n (%)	PR, n (%)	SD, n (%)	CBR, n (%) (95% CI)	DCR, n (%) (95% CI)
ARROW [26] Overall population, n=10 CCOD: Nov 6, 2020	7 (70.0) (34.8-93.3)	3 (30.0)	4 (40.0)	3 (30.0)	8 (80.0) (44.4-97.5)	10 (100) (69.2-100)
ARROW [27] Updated overall population, n=15 CCOD: Mar 4, 2022	8 (53.3) (26.6-78.7)	2 (20.0)	5 (33.3)	N/A	N/A	N/A

Abbreviations: CBR – clinical benefit rate; CI – confidence interval; CNS – central nervous system; CR – complete response, DCR – disease control rate; ORR – overall response rate; PD – progressive disease; PR – partial response; SD – stable disease.

7.1.2.3.2 NSCLC with unknown RET fusion status

KEYNOTE-024 and KEYNOTE-042 report data for ORR in the total study population with PD-L1 ≥50%. None of the studies report ORR data for the non-squamous subgroup with PD-L1 ≥50% (Table 9). ORR is defined as the proportion of patients who have a partial or complete response to treatment. ORR was assessed by blinded independent central review according to RECIST version 1.1. Intercranial ORR was not assessed in the studies.

Table 9: Objective response rate in populations with unknown RET fusion status

Trial name	Intervention	Median follow-up	N	ORR		
				ORR, n (%) (95% CI)	CR, n (%)	PR, n (%)
Clinical trials						
KEYNOTE-024 Reck 2021 [28]	PEMB	60 mo.	154	71 (46.1) (38.1-54.3)	7 (4.5)	64 (41.5)
	Chemotherapy		151	47 (31.1) (23.8-39.2)	0 (0)	47 (31.1)
KEYNOTE-042 Cho 2021 [30]	PEMB	46.9 mo.	299	39.1% (33.6-44.9)	-	-
	Chemotherapy		300	32.3% (27.1-37.9)	-	-

Abbreviations: CR – complete response; ORR – overall response rate; PEMB – pembrolizumab; PR – partial response; CI – confidence interval; mo. – months.

7.1.2.4 Discontinuations due to adverse events

7.1.2.4.1 RET fusion-positive NSCLC

ARROW reports data for discontinuation due to AEs in both the NSCLC population, including 281 patients (median exposure of 9.5 months) and the total safety population, consisting of 528 patients (median exposure of 7.9 months). Data is presented in Table 10. The result for the NSCLC population showed a trend aligned with the result for the total safety population.

None of the six included retrospective studies reported outcomes related to discontinuation due to AEs.

Table 10: Discontinuation due to AEs in the RET fusion-positive safety populations

Trial name	Intervention	Median exposure (min, max), months	N	Discontinuation due to AEs, n (%)
ARROW (NSCLC population) EPAR (AR0000) [26] CCOD: Nov 6, 2020	Pralsetinib	7.89 (0.3,28.4)	281	55 (19.6)
ARROW (Total safety population) EPAR (AR0000) [26] CCOD: Nov 6, 2020	Pralsetinib	9.46 (0.1,33.9)	528	91 (17.2)
ARROW (Updated NSCLC safety population) [27] CCOD: Mar 4, 2022	Pralsetinib	15.0	281	28 (10)*

Abbreviations: AEs - adverse events; * reported as TRAEs.

7.1.2.4.2 NSCLC with unknown RET fusion status

KEYNOTE-024 and KEYNOTE-042 report data for discontinuation due to AEs only in the total safety population. Neither histology or PD-L1 expression status are expected to affect the proportion of patients that experience AEs leading to discontinuation of treatment, and therefore, in line with the approach in the current Medicines Council guideline [34], AE data for the safety population from the two trials are included in the assessment. Data is presented in Table 11. It should be noted that the data reported from KEYNOTE-024 and KEYNOTE-042 are from earlier cut-off dates as data is not available from the latest cut-off dates.

Mouritzen et al reports data for discontinuation due to AEs in the population of 579 patients found in the EHR-ICI cohort (Table 11).

Table 11: Discontinuation due to AEs in the safety populations with unknown RET fusion status

Trial name	Intervention	Median exposure, months	N	Discontinuation due to AEs, n (%)
KEYNOTE-024 EPAR (AR0011) [35]	PEMB	7.03 ¤	154	14 (9.1)
	Chemotherapy	3.48 ¤	150	21 (14.0)

KEYNOTE-042 EPAR (AR0057) [36]	PEMB	5.55 (0.03-27.3)	636	130 (20.4)
	Chemotherapy	- §	615	91 (14.8)
Mouritzen et al [32]	EHR-ICI cohort	-	579	170 (31)*

* Reported as immune related AEs only. § Not reported for the chemotherapy arm. ¤ reported as days, calculated based on 30.4 days/months. Abbreviations: AEs – adverse events; PEMB – pembrolizumab, EHR-ICI – electronic health record immune checkpoint inhibitor.

7.1.2.5 Grade ≥3 adverse events

7.1.2.5.1 RET fusion-positive NSCLC

ARROW reports data for grade ≥3 AEs in both the NSCLC population and the total safety population. Data is presented in Table 12. The safety result for the NSCLC population showed a trend aligned with the result for the total safety population.

None of the six included retrospective studies reported outcomes related to AEs.

Table 12: Grade ≥3 AEs in the RET fusion-positive safety populations

Trial name	Intervention	Median exposure (min, max), months	N	Grade ≥3 AEs, n (%)
ARROW (NSCLC population) EPAR (AR0000) [26] CCOD: Nov 6, 2020	Pralsetinib	7.89 (0.3, 28.4)	281	212 (75.4) *incl. deaths due to AE: 35 (12.5)*
ARROW (Total safety population) EPAR (AR0000) [26] CCOD: Nov 6, 2020	Pralsetinib	9.46 (0.1, 33.9)	528	406 (76.9) *Deaths due to AE: 66 (12.5)*
ARROW (Updated NSCLC safety population) [27] CCOD: Mar 4, 2022	Pralsetinib	15.0	281	231 (82.2)

Abbreviations: AEs - adverse events; EPAR – European public assessment report.

7.1.2.5.2 NSCLC with unknown RET fusion status

KEYNOTE-024 and KEYNOTE-042 report data for grade ≥3 AEs only in the total safety population. As previously stated neither histology nor PD-L1 expression status are expected to affect the proportion of patients that experience grade ≥3 AEs [34], and therefore AE data for the total safety populations from the trials are included. Data is presented in Table 13. Again, data reported from KEYNOTE-024 and KEYNOTE-042 is from early cut-off dates.

Table 13: Grade ≥3 AEs in the safety populations with unknown RET fusion status

Trial name	Intervention	Median exposure	N	Grade ≥3 AEs, n (%)

		(min, max)		
KEYNOTE-024 EPAR (AR0011) [35]	PEMB	7.03	154	82 (53.2) *incl. grade 5: 9 (5.8)*
	Chemotherapy	3.48	150	109 (72.7) *incl. grade 5: 7 (4.7)*
KEYNOTE-042 EPAR (AR0057) [36]	PEMB	5.55 (0.03-27.3)	636	326 (51.3) *incl. grade 5: 68 (10.7)*
	Chemotherapy	- §	615	350 (56.9) *incl. grade 5: 47 (7.6)*

§Not reported for the chemotherapy arm. Abbreviations: AEs - adverse events; PEMB – pembrolizumab; EPAR – European public assessment report.

7.1.2.6 Quality of life

7.1.2.6.1 RET fusion-positive NSCLC

Data on quality of life (QoL) was collected in ARROW but no analysis has been carried out for the November 6, 2020 or the March 4, 2022 data cut.

7.1.2.6.2 NSCLC with unknown RET fusion status

KEYNOTE-024, but not KEYNOTE-042, reports data on quality of life in the total population. In KEYNOTE-024, QoL was assessed using the instruments EORTC QLQ-C30, EORTC QLQ-LC13 and EQ-5D-3L, which provides a measure of non-cancer-specific health status. The questionnaire completion rates were over 90% at baseline and over 80% for most study visits up to Week 24. The mean global health status/quality of life (GHS/QoL) score at baseline were similar between patients in the pembrolizumab and chemotherapy groups. At Week 15, an improvement from baseline of 6.9 points (95% CI, 3.3-10.6) for pembrolizumab and a decrease of 0.9 points (95% CI, -4.8-3.0) for chemotherapy were observed [37]. Deterioration in the QLQ-LC13 composite of cough, chest pain, and dyspnoea was observed in fewer patients in the pembrolizumab group than in the chemotherapy group (46 (31%)) vs 58 (39%)). Among the 46 patients in the pembrolizumab group, deterioration was due to chest pain for six (13%), cough in 13 (28%), and dyspnoea in 27 (59%). Among the 58 patients in the chemotherapy group, deterioration was due to chest pain in 13 (22%), cough in 13 (22%), and dyspnoea in 32 (55%). Time to deterioration was longer with pembrolizumab than with chemotherapy (median not reached (95% CI, 8.5-NR) vs 5.0 months (95% CI, 3.6-NR); HR: 0.66, (95% CI, 0.44-0.97; two-sided nominal p=0.029)).

7.1.3 Comparative analyses of efficacy and safety

7.1.3.1 Method of synthesis

Considering the sparse data available for patients with RET fusion-positive NSCLC, additional comparisons were conducted using NSCLC patients with unknown RET fusion status based on the assumption that there is no difference in prognosis between patients with RET fusion-positive and RET wild-type NSCLC. Table 14 provides an overview of the performed comparisons. The methods used are described in the following section and in appendix F (Flatiron analysis)

Table 14: Overview of the performed comparisons

Population	Comparator	Analyses	Study, population	Outcome
RET fusion-positive NSCLC				

1L	ICI	Narrative synthesis	RET fusion-positive patients	OS, PFS, ORR
NSCLC with unknown RET fusion status				
1L PD-L1 ≥ 50%	Pembrolizumab	Naïve indirect treatment comparison	KEYNOTE-024, NSCLC PD-L1 ≥ 50% (non-sq and sq), N=154	OS, PFS
			KEYNOTE-042, NSCLC PD-L1 ≥ 50% (non-sq and sq), N=299	
		Flatiron (EDM database)	RET fusion-negative patients	OS, PFS
		Narrative synthesis	KEYNOTE-024, NSCLC PD-L1 ≥ 50% (non-sq and sq) KEYNOTE-042, NSCLC PD-L1 ≥ 50% (non-sq and sq) Mouritzen et al. 2021, RWD, NSCLC, first-line treatment with ICI	OS, PFS, ORR, safety

Abbreviations: EDM - extended data mart; ICI - immune checkpoint inhibitor; NSCLC – non-small cell lung cancer; ORR - overall response rate; OS – overall survival; PD-L1 – programmed death ligand 1; sq – squamous; PFS – progression-free survival, RET – rearranged during transfection.

7.1.3.1.1 RET fusion-positive NSCLC

Narrative comparison with RET fusion-positive NSCLC patient treated with ICI

As described previously, we have examined the available literature for studies with RET fusion-positive NSCLC patients receiving ICI, preferably pembrolizumab with or without chemotherapy. From the SLR, we identified six retrospective studies that include RET fusion-positive patients receiving ICI. The reported median OS, median PFS and ORR was extracted from each study when available.

In earlier applications to the Medicines Council on tyrosine kinase inhibitors (TKIs) with similar indications e.g. EFGR, ALK and ROS1, it is standard to present the overall data including responses in both first and later lines together. When possible we will present data in first-line and in the overall populations.

The narrative comparisons should be seen as supplementary comparisons. Presenting available data on RET fusion-positive NSCLC patients treated with ICI in different treatment lines will help provide an overview of how RET fusion-positive NSCLC patients respond to ICI in general.

7.1.3.1.2 NSCLC with unknown RET fusion status

Naïve indirect comparison

Naïve indirect treatment comparisons (ITCs) were conducted to compare outcomes and to estimate trends around the treatment-effect between pralsetinib and pembrolizumab monotherapy. Since evidence for pralsetinib arises from a single-arm trial, only unanchored comparisons were possible. Two relevant comparator studies, KEYNOTE-024 and KEYNOTE-042, were included through the performed SLR (refer to section 6 and appendix A). The comparability between these studies and ARROW are described in detail in appendix C.

Individual patient data (IPD) for the pembrolizumab monotherapy were not available, and therefore naïve ITCs were conducted (without performing any adjustment) using aggregate-level data reported for the comparator studies. The

MAIC methodology was considered, but not found relevant due to differences in key treatment effect modifiers between the RET fusion-positive NSCLC population in ARROW and the RET wild-type population in KEYNOTE-024 and KEYNOTE-042. The RET fusion-positive population is younger, more likely to have non-squamous disease, and less likely to be smokers versus patients with RET wild-type disease [6]. Matching to the comparator population may be considered an improvement in an attempt to overcome study differences prior to estimating a treatment-effect. However, the MAIC approach is limited in that the comparator study population is not the target population of interest, and the MAIC methodology by design matches IPD onto the comparator study population. Therefore, attempting to account for the distributions of prognostic factors and effect modifiers in the studies, would adjust away the characteristics typical of RET fusion-positive patients. This would result in an analysis that in addition of being in non-RET fusion-positive patients, would be adjusted to a population different from the one expected to receive pralsetinib. In such case the results from the MAIC would be difficult to assess and would be meaningless in the context of pralsetinib. Moreover, the lack of overlap in the patient populations means that any adjustments would likely result in a very small effective sample size (ESS). As the naïve ITCs do not allow for any adjustments, these comparisons must be interpreted in the light of differences in patient characteristics, including potential key prognostic factors or treatment-effect modifiers.

Naïve ITCs analyses were performed for OS and PFS. Considering that OS and PFS are time-to-event endpoints that can be considered for any follow-up time, it was deemed appropriate to consider patients enrolled in ARROW at any time for these endpoints. This population, referred to as the unrestricted efficacy population, is a broader RET fusion-positive NSCLC population than the efficacy population, which was limited to patients who enrolled on or prior to May 22, 2020 to ensure enough follow-up time to measure ORR. In order to include all patients who initiated treatment with pralsetinib, the unrestricted efficacy population (n=116) was used in analyses of OS and PFS. Considering that OS and PFS are time-to-event endpoints that can be considered for any follow-up time, it was deemed appropriate to consider patients enrolled at any time for these endpoints. Results for the unrestricted population were identical to the overall efficacy population.

Data for OS and PFS were recreated from published KM curves using an algorithm developed by Guyot (2012) [38]. Virtual-IPD were then estimated by generating survival data for the comparator. A Cox regression model was fitted to the IPD from ARROW and the recreated IPD from the comparator study to estimate a naïve HR between pralsetinib versus pembrolizumab, with uncertainty around the treatment-effect presented as a 95% confidence interval (CI).

No adjustment was made for any differences between study populations. Bias may be introduced into the comparison where differences between study populations exist and have not been accounted for in the analysis. There is a number of observed differences between the studies (Appendix C). A higher proportion of patients in ARROW had adenocarcinoma compared to the comparators, ARROW also included a higher proportion of patients with CNS metastases (only reported in KEYNOTE-189) and a higher proportion of non-smoking patients. All of these factors are considered to be potential treatment-effect modifiers or prognostic factors, which have not been accounted for in the naïve comparisons. This could result in a biased treatment-effect if no attempt is made to overcome observed cross-trial differences. Additionally, some factors (including race, presence of CNS metastases and RET fusion status) were not well-reported in the comparator studies, and therefore, in the absence of available comparator data, it is unclear regarding the extent of population differences for these characteristics. The potential direction of the bias is unclear; however, patients from ARROW might be considered healthier with a higher proportion of non-smokers compared with the comparator studies. Additionally, the median age of ARROW patients (prior systemic therapy cohort) was slightly lower than all comparator studies, suggesting that the ARROW trial included a younger cohort of patients. However, the ARROW trial included a higher proportion of patients with CNS metastases present compared with patients in the KEYNOTE-189 trial.

This ITC approach may be considered naïve, as there was no attempt to overcome potential imbalances in trial populations. This form of comparison has been criticised for leading to over-precise estimates [39], and literature suggests that, where possible, naive comparisons of arms from different trials should be avoided where an alternative approach might otherwise be feasible. However, the approach taken was the only option available to permit the necessary comparison of pralsetinib with the relevant comparators.

7.1.3.2 Narrative comparison vs. RET wild-type patients (KN-024, KN-042 and Mouritzen et al)

A narrative comparison were conducted to compare OS, PFS, ORR and safety outcomes between pralsetinib and pembrolizumab monotherapy, Two relevant comparator studies, KEYNOTE-024 and KEYNOTE-042, were included through the performed SLR. In addition to this, a real-world study on Danish patients receiving immunotherapy by Mouritzen et al. was identified. All three studies were deemed relevant for the comparison with pralsetinib. The reported data was extracted from each study and compared to data from ARROW in a narrative manner. The study by Mouritzen et al only reports on OS and PFS, and is therefore only included in the narrative comparison for these endpoints.

7.1.3.3 Results from the comparative analysis

In the following section, we provide a summary of the results from the comparative analysis. Data are presented for the following outcome:

- Overall survival
- Progression-free survival
- Overall response rate
- Safety
    - Discontinuation due to adverse events
    - Grade ≥3 adverse events
    - Safety profiles

For each outcome, we present data for the RET fusion-positive population following the population with unknown RET fusion status. Results for the Flatiron analysis arepresented in appendix F**.** Furthermore, an overview of all results from the comparative analyses are available in appendix F.

Data on quality of life (QoL) for patients treated with pralsetinib in ARROW has not yet been analysed for the CCOD of November 6, 2020 nor the CCOD of March 4, 2022, and thus no comparative analysis have been conducted for this outcome. Data on quality of life for patients treated with pembrolizumab monotherapy is presented in section 7.1.2. Only QoL data from KEYNOTE-024 was available.

7.1.3.3.1 Overall survival

The following comparative analyses will be presented for OS:

- Narrative comparison vs. RET fusion-positive patients treated with ICI
- Naïve ITC vs. RET wild-type patients (KN-024, KN-042)
- Flatiron comparison using the EDM database (RET wild-type patients) (see section in appendix F)
- Narrative comparison vs. RET wild-type patients (KN-024, KN-042, Mouritzen et al) (see section in appendix F)

RET fusion-positive NSCLC

Narrative comparison vs. RET fusion-positive patients treated with ICI

At the CCOD of November 6, 2020, OS for pralsetinib was assessed in ARROW in both the overall efficacy population (17.1 months of median follow-up) and the population that received no prior systemic treatment (12.8 months of median follow-up). Median OS was not reached in either the overall efficacy population or the subgroup that had received no prior systemic treatment. In the overall efficacy population, the OS rate was 76.0% (95% CI, 69.9-82.0) at 12 months and 66.0% (95% CI, 57.9-74.1) at 24 months. In the population with no prior systemic treatment, the OS rate was 82.3% (95% CI, 71.9-92.8) at 12 months and 74.0% (95% CI, 59.3-88.6) at 24 months. Likewise at the CCOD of March 4, 2022, OS was reported in both the overall population (26.8 months of median follow-up) and in the treatment naïve population (22.1 months of median follow-up). The median OS in the overall population was 44.3 months (95% CI, 31.9-NR), while the median OS was not reached in the treatment naïve population.

Median OS for RET fusion-positive NSCLC patients treated with ICI was only reported by Bhandari et al, Mazieres et al and Guisier et al. For the overall populations the studies reported medians of 19.1 months (95% CI, 6.9-NR), 21.3 months (95% CI, 3.8-28.0) and NR (95% CI, 26.8-NR), respectively. It should be noted that 12 of the 17 patients in Bhandari et al received the KEYNOTE-189-like regime and that this group therefore is reflecting this. The result for this subpopulation is presented as part of clinical question 2. Guisier et al reported an OS rate at 12 months of 88.9% (95% CI, 70.6-100).

Overall, a median OS of 44.3 months was reported for patients treated with pralsetinib in the overall population compared to a median OS of 19.1 months and 21.3 months in the studies with RET fusion-positive NSCLC patients treated with ICI.

NSCLC with unknown RET fusion status

Naïve indirect treatment comparisons

Naïve ITC analysis for OS was informed by IPD from the subpopulation that had received no prior systemic therapy from ARROW, including a cohort of 116 patients and by aggregate data for 154 and 299 previously untreated patients with PD-L1 TPS ≥50% from KEYNOTE-024 and KEYNOTE-042, respectively. The presented results are derived using data from ARROW (CCOD: November 6, 2020), and data from the final protocol-defined OS analysis from KEYNOTE-024 (CCOD: July 10, 2017) [29] and KEYNOTE-042 (CCOD: February 26, 2018) [31]

At the CCOD of November 6, 2020 in ARROW, 16 out of 116 patients treated with pralsetinib had experienced an event. In KEYNOTE-024, 73 out of 154 patients receiving pembrolizumab experienced an event at the data cut-off, while the number of events in the pembrolizumab arm in KEYNOTE-042 were not reported. A summary of the KM curves are presented in Figure 3 and Figure 4. Median OS for pralsetinib was not reached (NR) at the time of follow-up, whereas median OS for pembrolizumab based on KEYNOTE-024 and KEYNOTE-042, respectively, was [redacted]. The estimated unadjusted HRs were [redacted] and [redacted] respectively (Table 15).

Overall, despite immature data for pralsetinib, the results from the analyses showed a significant treatment effect, favouring pralsetinib over pembrolizumab (HR <1). However, because no adjustments have been made for cross-trial differences, it is likely that the degree of uncertainty has been underestimated. Moreover, bias may be introduced into the comparisons where differences between study populations exist and have not been accounted for in the analyses. However, the results from the naïve ITC analyses show that pralsetinib is at least numerically superior to pembrolizumab despite the methodological challenges.

Table 15: Naïve ITC for OS – pralsetinib versus pembrolizumab

Comparison	Analysis	Pralsetinib	N	Pembrolizumab	N	HR (95% CI) Unadjusted
Pralsetinib (ARROW) vs pembrolizumab (KN-024)	Base case	No prior therapy, unrestricted efficacy population	116	Previously untreated, PD-L1 TPS ≥50% [29]	154	[redacted]
Pralsetinib (ARROW) vs pembrolizumab (KN-042)	Base case	No prior therapy, unrestricted efficacy population	116	Previously untreated, PD-L1 TPS ≥50% [31]	299	[redacted]

Abbreviations: HR - hazard ratio; OS - overall survival; PD-L1 – programmed death ligand 1; TPS – tumour proportion score; KN-024 – Keynote-024; KN-042 – Keynote-042; CI – confidence interval.

[redacted]

[redacted]

Narrative comparison vs. RET wild-type patients (KN-024, KN-042 and Mouritzen et al)

OS has been reported for pembrolizumab monotherapy for patients with previously untreated NSCLC and PD-L1 expression ≥50 in both KEYNOTE-024 and KEYNOTE-042. In KEYNOTE-024, OS is available at 60 months of median follow-up (CCOD: June 1, 2020) [28]. At the data cut-off, 103 patients (66.9%) in the pembrolizumab group and 123 patients (81.5%) in the chemotherapy group had died. Median OS was 26.3 months (95% CI, 18.3-40.4) in the pembrolizumab group and 13.4 months (95% CI, 9.4-18.3) in the chemotherapy group with a HR of 0.62 (95% CI, 0.48-0.81). OS-rates at 12 and 24 months were not presented at the latest data cut-off date, but results based on the final protocol-defined OS analysis from KEYNOTE-024 (CCOD: July 10, 2017) [29] are available. At 12 months, the estimated percentages of patients alive were 70.3 (95% CI, 62.3 to 76.9) and 54.8% (95% CI, 46.4 to 62.4) in the pembrolizumab and chemotherapy group, respectively. The estimated 24-month rates were 51.5% (95% CI, 43.0 to 59.3) and 34.5% (95% CI, 26.7 to 42.4). In KEYNOTE-042, the median follow-up was 46.9 months (range: 35.8-62.1) (CCOD: February 21, 2020) [30]. The number of events were not reported at the date of data cut-off. Median OS was 20.0 months (95% CI, 15.9-24.2) for pembrolizumab and 12.2 months (95% CI, 10.4-14.6) for chemotherapy with a HR of 0.68 (95% CI, 0.57-0.82). Like for KEYNOTE-024, OS-rates at 12 and 24 months were not presented at the latest data cut-off date, but an OS-rate at 24 months based on the final protocol-defined OS analysis from KEYNOTE-042 (CCOD: February 26, 2018) [31] is available. At 24 months, the estimated percentages of patients alive were 45% and 30% (95% CIs were not reported) in the pembrolizumab and chemotherapy group, respectively.

The study by Mouritzen et al assessed the real-world efficacy of ICI treatment in Denmark [32]. Median OS was 19.0 (95% CI, 16.0-22.0).

Overall, the reported OS for the comparator range from 19.0 months in the study by Mouritzen et al. to 20.0 months and 26.3 months in KEYNOTE-042 and KEYNOTE-024, respectively. At the CCOD of March 4, 2022, median OS for patients treated with pralsetinib in ARROW was 44.3 months (95% CI, 31.9-NR) in the overall efficacy population and stil immature in the population with no prior systemic treatment. In ARROW, the reported OS-rates were 76.0% at 12 months and 66.0% at 24 months in the overall efficacy population, and 82.3% at 12 months and 74.0% at 24 months in the population that had received no prior systemic treatment. The 12- and 24-months rates reported in ARROW were notably higher than the rates reported in the pembrolizumab arms in KEYNOTE-024 (54.8% at 12 months and 34.5% at 24 months) and KEYNOTE-042 (30% at 24 months). Thus data show a numerical trend in favour of pralsetinib, indicating a clinically meaningful benefit.

Conclusion

At the CCOD of November 6, 2020, median OS for patients treated with pralsetinib in ARROW was not reached in either the overall efficacy population or the population that had received no prior systemic treatment. The OS rate was 76.0% at 12 months and 66.0% at 24 months in the overall efficacy population, while it was 82.3% at 12 months and 74.0% at 24 months in the population that had received no prior systemic treatment. At the CCOD of March 4, 2022, the median OS was 44.3 months in the overall population, while the median OS was still immature in the treatment naïve population. Based on the available comparative evidence, the following conclusions can be made:

- Median OS data from the two retrospective studies including RET fusion-positive NSCLC treated with ICI was comparable with the median OS data reported in the pembrolizumab arm of KEYNOTE-042 and the Danish real-world study, which all included patients with unknown RET fusion status. The median OS in the pembrolizumab arm of KEYNOTE-024 was slightly longer than was reported in the other comparative studies. The 12-month OS-rates reported in ARROW were slightly lower than the one reported in the retrospective study by Guisier et al, and higher than the one reported in KEYNOTE-024, and the 24-month rates in ARROW

were notably higher than the rates reported in the KEYNOTE-studies. The median OS of 44.3 months reported at the CCOD of March 4, 2022 in ARROW was much longer than the median OS between 19.0-30.0 months reported in the comparator studies, indicating a clinically meaningful benefit of pralsetinib.

- The results from the naïve ITC analyses, comparing pralsetinib to pembrolizumab showed statistically significant treatment-effects, favouring pralsetinib over pembrolizumab. Despite methodological challenges, the results showed that pralsetinib is at least numerically superior to pembrolizumab.

- Results from the real-world Flatiron EDM analysis showed a trend similar to the naïve ITC analyses. The estimated treatment-effect was statistically significant, favouring pralsetinib over pembrolizumab.

A full overview of the reported OS data used in the comparative analysis can be found in Appendix F.

7.1.3.3.2 Progression-free survival

The following comparative analyses will be presented for PFS:

- Narrative comparison vs. RET fusion-positive patients treated with ICI
- Naïve ITC vs. RET wild-type patients (KN-024, KN-042)
- Flatiron comparison using the EDM database (RET wild-type patients) (see section in appendix F)
- Narrative comparison vs. RET wild-type patients (KN-024, KN-042, Mouritzen et al) (see section in appendix F)

RET fusion-positive NSCLC

Narrative comparison vs. RET fusion-positive patients treated with ICI

At the CCOD of November 6, 2020, PFS for pralsetinib was assessed in ARROW in both the overall efficacy population (17.1 months of median follow-up) and the population with no prior systemic treatment (12.8 months of median follow-up). Median PFS was 16.4 (95% CI, 11.0-24.1) months in the overall efficacy population and 13.0 (95% CI, 9.1-NR) months in the population that had received no prior systemic treatment. In the overall efficacy population, the PFS rate was 56.0% (95% CI, 48.9-63.1) at 12 months and 42.1% (95% CI, 33.2-51.0) at 24 months. In the population with no prior systemic treatment, the PFS rate was 52.6% (95% CI, 37.8-67.5) at 12 months and 47.8% (95% CI, 31.6-64.1) at 24 months. Likewise at the CCOD of March 4, 2022, PFS was reported in both the overall population (25.8 months of median follow-up) and in the treatment naïve population (median follow-up not reported). The median PFS was 13.2 months (95% CI, 11.4-16.8) in the overall population and 12.6 months (95% CI, 9.2-16.6) in the treatment naïve population.

Median PFS were reported by Bhandari et al, Mazieres et al and Guisier et al. The studies reported medians of 4.2 months (95% CI, 1.4-8.4), 2.1 months (95% CI, 1.3-4.7) and 7.6 months (95% CI, 2.3-NR), respectively. It should be noted that 12 of the 17 patients in Bhandari et al received the KEYNOTE-189-like regime and that this group therefore is reflecting this. As mentioned, Hegde et al reported TTD and Rozenblum et al reported median treatment duration. These have been included to provide additional information. Hedge et al reported a median TTD of 3.4 months and Rozenblum et al reported a median treatment duration of 11 weeks (range: 1-26). In addition to the median PFS reported, Mazieres et al and Guisier et al reported a PFS rate at 12 months of 7% (95% CI, 0.4-27.1) and 26.7% (95% CI, 8.3-85.8), respectively.

Overall, the reported median PFS for RET fusion-positive NSCLC patients treated with ICI ranged from 2.1 to 7.6 months. At the CCOD of November 6, 2020, median PFS for patients treated with pralsetinib in ARROW was 16.4 months for the overall efficacy population and and 13.0 months for the population with no prior systemic treatment.

At the CCOD of March 4, 2022, median PFS was 13.2 months and 12.6 months, respectively. When comparing the median PFS from Guisier et al, which reported the longest median of the retrospective studies, to the median reported in the overall population in ARROW, there is a difference of 8.8 months at the first CCOD and 5.6 months at the ladder CCOD. The difference in comparison to the population that has received no prior systemic treatment in ARROW is 5.4 months and 5.0 months, respectively. The greatest difference is observed between the median PFS reported in Mazieres et al, which is the shortest of the retrospective studies, and the median reported in the two populations in ARROW. In terms of PFS rate at 12 months, there is a difference of 29.3% and 25.9% between the rates reported in ARROW and that seen in Guisier et al, which reported the highest rate observed in the comparator studies. The differences in comparison to the rate reported in Mazieres et al are 49.0% and 45.6%. Thus, despite the difference in data collection - prospective versus retrospective - the results indicate that there is a clinically meaningful difference between pralsetinib and ICI in RET fusion-positive NSCLC patients.

NSCLC with unknown RET fusion status

Naïve indirect treatment comparisons

Similar to the analysis for OS, naïve ITC analyses for PFS was informed by IPD from the subpopulation that had received no prior systemic therapy from ARROW and aggregate data for 154 and 299 previously untreated patients with PD-L1 TPS ≥50% from KEYNOTE-024 and KEYNOTE-042, respectively. The presented results are derived using data from ARROW (CCOD: November 6, 2020), and data from the final protocol-defined PFS analysis from KEYNOTE-024 (CCOD: May 9, 2016) [33] and KEYNOTE-042 (CCOD: February 26, 2018) [31]

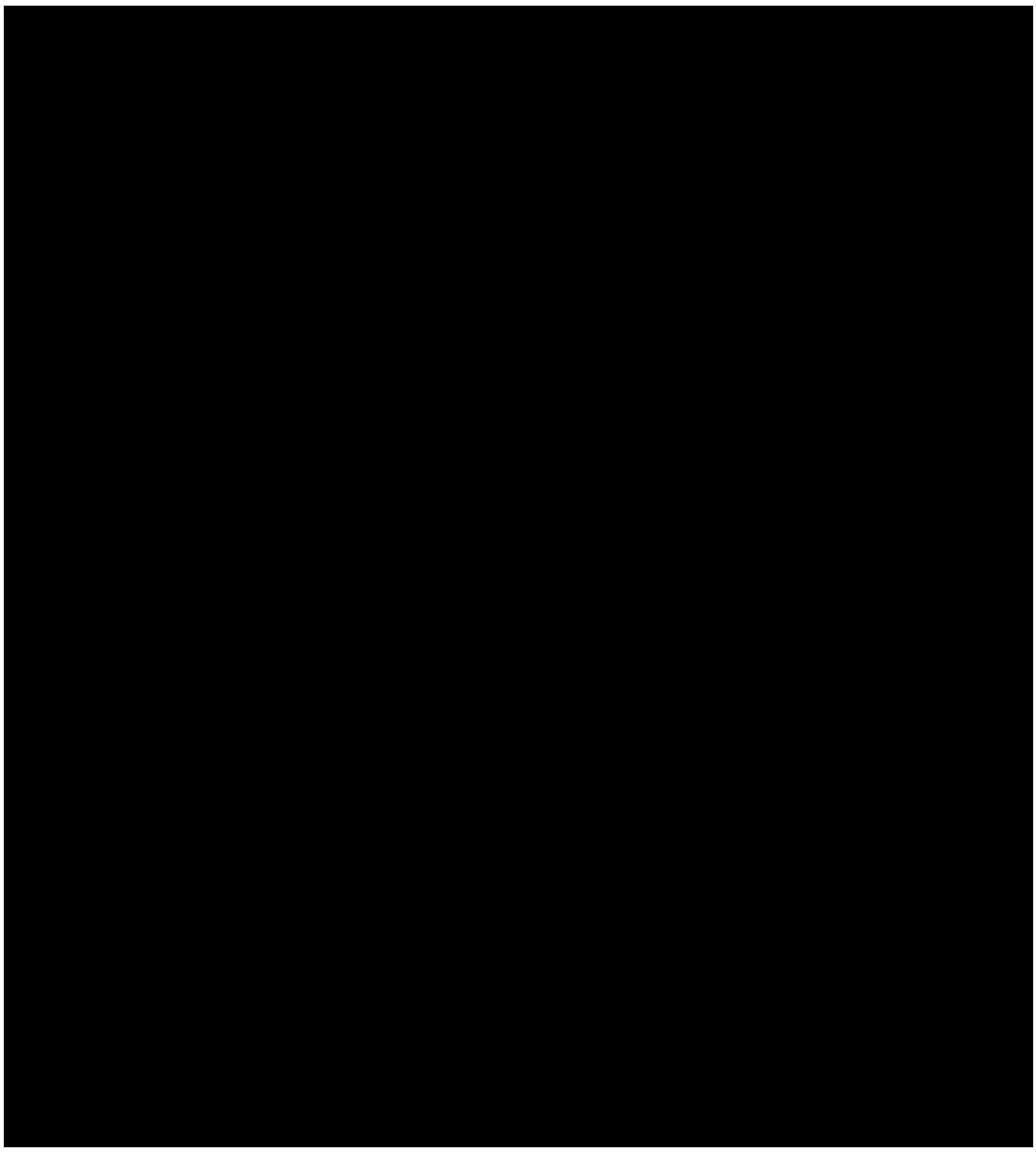
At the CCOD of November 6, 2020 in ARROW, 31 out of 116 patients treated with pralsetinib had experienced an event. The number of events in the pembrolizumab arm in KEYNOTE-024 and KEYNOTE-042 were not reported. A summary of the KM curves are presented in Figure 5 and Figure 6. Median PFS for pralsetinib was [redacted], and median PFS for pembrolizumab based on KEYNOTE-024 and KEYNOTE-042, respectively, was [redacted]. The estimated unadjusted HRs compared to pembrolizumab were [redacted] and [redacted] respectively (Table 16).

Overall, results showed a significant treatment effect in terms of PFS, favouring pralsetinib over pembrolizumab (HR <1). Because no adjustments have been made for cross-trial differences, it is however likely that the degree of uncertainty has been underestimated. Moreover, bias may be introduced into the comparisons where differences between study populations exist and have not been accounted for in the analyses. Despite the methodological challenges, the results show that pralsetinib is at least numerically superior to pembrolizumab.

Table 16: Naïve ITC for PFS – pralsetinib versus pembrolizumab

Comparison	Analysis	Pralsetinib	N	Pembrolizumab	N	HR (95% CI) Unadjusted
Pralsetinib (ARROW) vs pembrolizumab (KN-024)	Base case analysis	No prior therapy, unrestricted efficacy population	116	Previously untreated, PD-L1 TPS ≥50% [33]	154	[redacted]
Pralsetinib (ARROW) vs pembrolizumab (KN-042)	Base case analysis	No prior therapy, unrestricted efficacy population	116	Previously untreated, PD-L1 TPS ≥50% [31]	299	[redacted]

Abbreviations: HR – hazard ratio; PD-L1 – programmed death ligand 1; PFS – progression-free survival; TPS – tumour proportion score; KN-024 – KEYNOTE-024; KN-042 – KEYNOTE-042; CI – confidence interval.



Narrative comparison vs. RET wild-type patients (KN-024, KN-042 and Mouritzen et al)

At the CCOD of November 6, PFS for pralsetinib was reported for the overall efficacy population (17.1 months of median follow-up) and for the subgroup with no prior systemic treatment (12.8 months of median follow-up). The PFS rates for the overall efficacy population were 56.0% (95% CI, 48.9-63.1) at 12 months and 42.1% (95% CI, 33.2-51.0) at 24 months. For the population with no prior systemic treatment the 12-month PFS rate was 52.6% (95% CI, 37.7-67.5), while the 24-month PFS rate was 47.8% (95% CI, 31.6-64.1). Median PFS was 16.4 months (95% CI, 11.0, 24.1) in the overall population and 13.0 (95% CI, 9.1, NR) in the subgroup with no prior systemic treatment. At the CCOD of March 4, 2022, median PFS was 13.2 months (95% CI, 11.4-16.8) in the overall population (25.8 months of median follow-up) and 12.6 months (95% CI, 9.2-16.6) in the treatment naïve population (median follow-up not reported).

Pembrolizumab monotherapy in patients with NSCLC and PD-L1 ≥50% has been assessed in KEYNOTE-024 and KEYNOTE-042. In KEYNOTE-024, PFS data is available at 60 months of median follow-up [28]. At data cut-off, 126 (81.8%) in the pembrolizumab arm and 141 (93.4%) in the chemotherapy arm had progressed or died. Median PFS was 7.7 months (95% CI, 6.1-10.2) in the pembrolizumab arm and 5.5 months (95% CI, 4.2- 6.2) in the chemotherapy group. In KEYNOTE-042, the median follow-up for PFS was 46.9 months (range: 35.8-62.1) [30]. The median PFS was

6.5 months (95% CI, 5.9-8.6) for pembrolizumab and 6.5 months (95% CI, 6.2-7.6) for chemotherapy with a hazard rate of 0.85 (95% CI, 0.72-1.02).

The study by Mouritzen et al assessed the real-world efficacy of ICI treatment in Denmark [32]. Median PFS was 8.2 months (95% CI, 7.2-9.3).

Overall, the reported median PFS estimates are relatively consistent across the three studies, ranging from 6.5-7.7 months in the KEYNOTE trials and 8.2 months in the first-line ICI study by Mouritzen et al. This is despite the study design in Mouritzen et al. being a real-world register study. Median PFS estimates for pralsetinib in the ARROW trial are longer than what has been reported in all three pembrolizumab studies. Thus, despite study difference, the results indicate that there is a clinically meaningful difference between pralsetinib and pembrolizumab in NSCLC patients with unknown RET fusion status.

Conclusion

At the CCOD of November 6, 2020, treatment with pralsetinib resulted in a median PFS of 16.4 months (95% CI, 11.0-24.1) in the overall efficacy population and 13.0 (95% CI, 9.1-NR) in the subgroup that had received no prior systemic treatment. The PFS rates for the overall efficacy population were 56.0% (95% CI, 48.9-63.1) at 12 months and 42.1% (95% CI, 33.2-51.0) at 24 months. For the population with no prior systemic treatment the PFS rate was 52.6% (95% CI, 37.7-67.5) at 12 months and 47.8% (95% CI, 31.6-64.1) at 24 months. The analysis from the CCOD of March 4, 2022 showed comparable median PFSs with those previously reported. Based on the available comparative evidence, the following conclusions can be made:

- The median PFS reported for pralsetinib in both the overall efficacy population and in the population that received no prior systemic therapy is vastly higher compared to those reported for ICI in RET fusion-positive NSCLC patients in the retrospective studies. The same trend in terms of median PFS was observed when comparing with the KEYNOTE studies and the Danish real-world study by Mouritzen et al, which all included NSCLC patients with unknown RET fusion status.
- The results from the naïve ITC analyses, comparing pralsetinib to pembrolizumab showed a statistically significant treatment-effect, favouring pralsetinib over pembrolizumab. Despite methodological challenges, the results showed that pralsetinib is at least numerically superior to pembrolizumab.
- The same trend was seen in the Flatiron analysis, comparing data from ARROW with data from real-world patients treated with pembrolizumab included in the EDM database. The estimated treatment-effect was statistically significant, favouring pralsetinib over pembrolizumab.

A full overview of the reported PFS data used in the comparative analysis can be found in Appendix F.

7.1.3.3.3 Overall response rate

The following comparative analyses will be presented for ORR:

- Narrative comparison vs. RET fusion-positive patients treated with ICI
- Narrative comparison vs. RET wild-type patients (KN-024, KN-042)

In addition, a supplementary landmark analysis, which assess the association of tumour response with survival is presented in appendix F.

RET fusion-positive NSCLC

Narrative comparison vs. RET fusion-positive patients treated with ICI

ORR was the primary efficacy endpoint in ARROW and is reported for both the overall efficacy population and the population that had received no prior systemic treatment. In the overall efficacy population at the CCOD of November 6, 2020, the ORR was 150 of 233 (64.4%, 95% CI 57.9-70.5) with 11 patients (4.7%) experiencing a CR and 139 patients (59.7%) experiencing a PR. In the population that received no prior systemic treatment, the ORR was 54 of 75 (72.0%, 95% CI 60.4-81.8) with 4 patients (5.3%) experiencing a CR and 50 patients (66.7%) experiencing a PR [26]. Likewise at the CCOD of March 4, 2022, ORR was reported in both the overall population and in the treatment naive population (post-eligibility). ORR in the overall population was 185 of 281 (65.8%, 95% CI 60.0-71.4) with 18 patients (6.4%) experiencing a CR and 167 patients (59.4%) experiencing a PR. In the treatment naive population post-eligibility revision, the ORR was 52 of 69 (75.4%, 95% CI 63.5-84.9) with 4 patients (5.8%) experiencing a CR and 48 patients (69.6%) experiencing a PR [27].

Response to ICI was reported in five of the six retrospective studies [6,17–20]. In Bhandari et al, 7 of 13 patients (53.8%) had a confirmed response and 4 patients had a missing response. In Guisier et al, 3 of 8 patients (37.5%) had a confirmed response and 1 patient was not evaluable. In Mazieres et al, 1 of 16 patients (6.3%) had a confirmed response. Rozenblum et al reported an ORR of 0% based on an evaluation of 4 patients. It should be noted that the majority of the patients in Bhandari et al (12 out of 17) received the KEYNOTE-189-like treatment regime. Hess et al only reported ORR in patients treated with the KEYNOTE-189 regime. Response was measured with RECIST 1.1 in Mazieres et al and Guisier et al. None of the retrospective studies reported more than 1 patient with a complete response (CR).

There is a large difference between the reported ORRs in the retrospective studies, ranging from 0% to 53.8%. When comparing the ORR from Bhandari et al, which reports the highest ORR of the retrospective studies, to the ORR reported in the overall population in ARROW, there is a difference of 10.6% at the CCOD of November 6, 2020 and 12.0% at the CCOD of March 4, 2022. The difference in comparison to the population that has received no prior systemic treatment in ARROW is 18.2% and 21.6%, respectively. The greatest difference is observed between the ORR reported in Rozenblum et al, which is the lowest ORR of the retrospective studies, and the ORRs reported in the two populations in ARROW. As mentioned, a large proportion of patients in Bhandari et al received the KEYNOTE-189 regime, which is expected to influence the result. It should also be noted that only two of the retrospective studies base the assessment on RECIST 1.1, giving rise to possible bias in what is reported. Despite study differences, the results indicate that there is a clinically meaningful difference between pralsetinib and ICI in RET fusion-positive NSCLC patients.

NSCLC with unknown RET fusion status

Narrative comparison vs. RET wild-type patients (KN-024 and KN-042)

As described, in ARROW at the CCOD of November 6, 2020 an objective response was recorded in 150 of 233 patients (64.4%, 95% CI 57.9-70.5) in the overall efficacy population, and in 54 of 75 patients (72.0%, 95% CI 60.4-81.8) in the population that has received no prior systemic treatment. The recorded number of patients with CR was 11 (5.7%) and 4 (5.3%), respectively [26]. At the CCOD of March 4, 2022, ORR in the overall population was 185 of 281 (65.8%, 95% CI 60.0-71.4). In the treatment naive population post-eligibility revision, ORR was 52 of 69 (75.4%, 95% CI 63.5-84-9). 18 patients (6.4%) in the overall population and 4 patients (5.8%) in the treatment naïve population experienced a CR [27].

In KEYNOTE-024, the ORR at 60 months of follow-up was 46.1% (95% CI, 38.1-54.3) with 71 of 154 patients responding to pembrolizumab. 7 patients (4.5%) experienced a CR while 64 patients (41.5%) experienced PR [28]. In KEYNOTE-042, the ORR at 46.9 months follow-up was 39.1% (95% CI, 33.6-44.9). The recorded number of patients with CR and PR is not reported for the most recent data cut [30].

Overall, the response rate recorded for pralsetinib in ARROW are vastly higher in both the overall efficacy population and the population that had received no prior systemic treatment (64.4% and 72.0%, respectively (CCOD: November 6, 2020) and 65.8% and 75.4%, respectively (CCOD: March 4, 2022)), when comparing to the results for pembrolizumab (39.1% and 46.1%). Thus, despite study differences, the results indicate that there is a clinically meaningful difference between pralsetinib and pembrolizumab in NSCLC patients with unknown RET fusion status.

Conclusion

Overall, pralsetinib shows a clinically relevant response rate of 64.4% (95% CI, 57.9-70.5) in the overall efficacy population and 72.0% (95% CI, 60.4-81.8) in the population with no prior systemic treatment at the CCOD of November 6, 2020. ORR at the CCOD of March 4, 2022 was 65.8% (95% Cl, 60.0-71.4) in the overall population and 75.4% (95% CI, 63.5-84-9) in the treatment naive population post-eligibility revision. The landmark analysis suggested that ORR may be a predictor for longer overall survival in RET fusion-positive NSCLC. This points to the high response rate presented in ARROW being important and clinically meaningful. Treatment with pralsetinib also seems to result in higher response rates compared to pembrolizumab within NSCLC based on the following results:

- The ORR reported for pralsetinib is vastly higher than that observed in the retrospective studies where patients received ICI. These results were consistent in both the overall efficacy population and in the population that received no prior systemic therapy at both CCODs.
- The ORR reported for pralsetinib is vastly higher than that observed for pembrolizumab in both KEYNOTE-024 and KEYNOTE-042. These results were consistent in both the overall efficacy population and in the population that received no prior systemic therapy at both CCODs.

A full overview of the reported ORR data used in the comparative analysis and the supplementary landmark analysis can be found in appendix F.

7.1.3.3.4 Safety

The safety results will be presented in three parts as follows:

- Narrative comparison of discontinuation due to AEs in RET fusion-positive patients in ARROW and RET wild-type patients in KEYNOTE-024 and KEYNOTE-042
- Narrative comparison of grade ≥3 AEs in RET fusion-positive patients in ARROW and RET wild-type patients in KEYNOTE-024, KEYNOTE-042 and Mouritzen et al.
- Review of the safety profiles of pralsetinib and pembrolizumab monotherapy

Safety data from ARROW was reported for the total safety population, which includes patients with RET-altered NSCLC, MTC, and other solid tumours, and for the RET fusion-positive NSCLC population. Median (min, max) exposure to pralsetinib were 7.9 months (0.1, 33.9) and 9.5 months (0.3, 28.4), respectively (CCOD: November 6, 2020). In addition, data on the NSCLC safety population (n=281) with a median treatment duration of 15.0 months was reported (CCOD: March 4, 2022). In KEYNOTE-024 safety was assessed in the as-treated population, which included all patients who received at least one dose of the assigned trial treatment. Relevant safety data for pembrolizumab are derived from either the primary safety analysis (CCOD: May 9, 2016) or the latest updated safety analysis (CCOD: June 1, 2020) depending on data availability. Median exposure to pembrolizumab treatment was 214.0 days (mean 205.7, SD 144.9) at the first data cutoff and median treatment duration was 7.9 months (range, 1 day-30.2 months) at the final data cutoff. In KEYNOTE-042, safety was also assessed in the as-treated population. Relevant safety data for pembrolizumab are derived from either the second interim analysis (CCOD: September 4, 2018) or the final analysis (CCOD: February 21, 2020). Median cycles of pembrolizumab was 9 (range, 1 to 36) at both data cutoffs.

Discontinuation due to adverse events

Narrative comparison vs. RET wild-type patients (KN-024, KN-042 and Mouritzen et al)

In the total safety population, 91 of 528 patients (17.2%) discontinued treatment due to an AE at the CCOD of November 6, 2020. A similar proportion was observed in the RET fusion-positive NSCLC population, where 55 of 281 patients (19.6%) discontinued treatment due to an AE [26]. In the NSCLC safety population, 28 of 281 patients (10%) discontinued treatment due to TRAEs at the CCOD of March 4, 2022 [27].

Data on discontinuation due to AEs for pembrolizumab is available from the early safety analyses from both KEYNOTE-studies. In KEYNOTE-024 and KEYNOTE-042, 14 of 154 patients (9.1%) and 130 of 636 patients (20.4%) treated with pembrolizumab discontinued treatment due to an AE [35,36].

The real-world study by Mouritzen et al. reported discontinuations due to immune-related AEs. It was reported that 31% of patients discontinued ICI treatment due to immune-related AEs [32]. Although this rate is exclusive to immune-related AEs, it is overall higher than the rate of discontinuations reported in KEYNOTE-024 and KEYNOTE-042, which could suggest a higher rate of discontinuation is a real-life setting or for Danish NSCLC patients specifically.

The differences in discontinuations due to AEs between pralsetinib and pembrolizumab are overall difficult to compare due to differences in reporting, study design, stratification factors, patient population and data maturity. The two rates of discontinuations reported in KEYNOTE-024 and KEYNOTE-042 are very different, making it difficult to establish a baseline for pembrolizumab. The rate of discontinuations due to AEs in the ARROW study is lower when compared to pembrolizumab in KEYNOTE-042 but higher than the rate reported in the KEYNOTE-024 study. The rate reported for Danish patients in the study by Mouritzen et al. could suggest an even higher rate of AEs leading to discontinuations in real-life patients.

Grade ≥3 adverse events

Narrative comparison vs. RET wild-type patients (KN-024 and KN-042)

In the total safety population, 406 of 528 patients (76.9%) experienced a grade ≥3 AE and in the RET fusion-positive NSCLC population 212 of 281 patients (75.4%) experienced a grade ≥3 AE at the CCOD of November 6, 2020 [26]. In the NSCLC safety population, 231 of 281 patients (82.2%) experienced grade ≥3 AEs at the CCOD of March 4, 2022 [27].

Data on grade ≥3 AEs for pembrolizumab is available from the early safety analyses from both KEYNOTE-studies. In KEYNOTE-024 and KEYNOTE-042, 82 of 154 patients (53.2%) and 326 of 636 patients (51.3%) experienced a grade ≥3 AE, respectively [35,36].

The rate of grade ≥3 AEs for pralsetinib in ARROW is numerically higher than what has been recorded for pembrolizumab in both KEYNOTE-024 and KEYNOTE-042. The differences in rates between pralsetinib and pembrolizumab are overall difficult to compare due to differences in reporting, study design, stratification factors, patient population and data maturity.

Safety profiles

Narrative comparison of the safety profiles of pralsetinib vs pembrolizumab

The narrative comparison of safety profiles will compare data from ARROW to the most recent reported data from KEYNOTE-024 and KEYNOTE-042. Refer to appendix E for an overview of the safety data.

Pralsetinib in ARROW

At the CCOD of November 6, 2020, the safety profiles presented for patients with RET fusion-positive NSCLC was similar to that of patients in the overall safety population. In the NSCLC RET fusion-positive population, 99.3% of patients experienced an AE. The most common AEs were anaemia (45.9%), AST increased (44.8%), constipation (42.0%), and hypertension (34.2%). Treatment-related AEs occurred in 94.0% of patients. At the CCOD of March 4, 2022, 99.6% of patients in the NSCLC safety population experienced at least one AE. The most common AEs where comparable with the ones previously reported: anaemia (53.7%), AST increased (48.8%), constipation (44.5%), and hypertension (36.7%). TRAEs of any grade occurred in 94.2% of patients [27].

At the CCOD of November 6, 2020, grade ≥3 AEs were reported in 212 of 281 patients in the RET fusion-positive NSCLC population treated with pralsetinib (75.4%). The most common grade ≥3 AEs were anaemia (16.4%), hypertension (16.0%), neutropenia (10.7%), and neutrophil count decreased (12.8%). 155 of 281 patients (55.2%) experienced a treatment-related grade ≥3 AE. Deaths due to an AE occurred in 35 patients (12.5%) in the RET fusion-positive NSCLC population and 2 deaths (<1%) were considered related to pralsetinib. In the overall safety population, 6 patients died due to a treatment-related AE (investigator assessed). These included rhabdomyolysis, pneumonia, pneumocystis jirovecii pneumonia, pneumonitis, and death (unknown cause of death in 1 patient and multifactorial cause in 1 patient). At the CCOD of March 4, 2022, 82.2% of patients in the NSCLC safety population experienced grade ≥3 AEs. The most common grade ≥3 AEs were comparable with the ones previously reported: anaemia (23.1%), hypertension (17.8%), neutropenia (10.7%), and neutrophil count decreased (14.2%). Treatment-related grade ≥3 AEs occurred in 62.6% of patients [27].

In the RET fusion-positive NSCLC population, at the CCOD of November 6, 2020, 166 of 281 patients (59.1%) experienced a serious adverse event (SAE). The most common SAEs were pneumonia (11.7%), disease progression (7.5%), pneumonitis (4.6%), and anaemia (3.2%). Treatment-related SAEs occurred in 69 patients (24.6%). AEs leading to discontinuation of pralsetinib occurred in 55 of 281 patients (19.6%), while interruption of treatment due to an AE was seen in 67.6% of patients. At the CCOD of March 4, 2022, 28 of 281 patients (10%) in the NSCLC safety population discontinued treatment due to TRAEs [27].

AEs of special interest (AESIs) were identified as transaminase elevations, pneumonitis, hypertension and haemorrhagic events. Their rates and information on reversibility and manageability has been described in the EPAR for the overall safety population (CCOD: November 6, 2020):

- Increased AST and ALT of grade 3-4 occurred in 5.7% and 4.2% of patients respectively. Median time to onset for AST was 2.1 weeks while it was 3.1 weeks for ALT. Serious adverse reactions (SARs) for increased AST and ALT were reported for 0.6% of patients. No patients required permanent dose discontinuations but dose interruption due to AST or ALT occurred in 4.4% and 3.4% of patients, respectively, while dose reductions were carried out in 1.3% for both events. Median time to resolution was 3.7 weeks.

- Pneumonitis/ILD occurred with a median time to onset of 15.6 weeks. SARs were reported for 5.3% of patients, with 2.5% grade 3 events, 0.6% grade 4, and 1 grade 5 event (0.2%). The majority of patients with grade 1 or grade 2 pneumonitis were able to continue treatment without recurrent pneumonitis/ILD following dose interruption and dose reduction. Dose interruptions occurred in 8.9%, dose interruptions in 5.3% and permanent dose discontinuations in 1.9% due to pneumonitis/ILD. Median time to resolution was 3.7 weeks.

- Hypertension grade ≤2 events occurred in 16.9% of patients and grade 3 events in 16.1% of patients. No grade 4 or grade 5 events were reported. Median time to onset was 2.1 weeks. SAEs of grade 3 were reported in 1.3% of all patients. Dose interruptions occurred in 7.4% of patients, dose reductions in 4.0% and 1 patient (0.2%) required permanent dose discontinuation. Median time to resolution was 3.1 weeks.

- Haemorrhagic events occurred in 18.8% of patients, including grade 3 events in 2.8% of patients and with grade 4 and 5 events each occurring in 1 patient (0.2%). SARs of haemorrhage were reported for 3.2% of patients, including grade 3 and 4 events (0.6%) and one grade 5 event (0.2%). 14 patients (2.7%) required dose interruption and dose reduction or permanent dose discontinuations each occurred in 1 patient.

Pembrolizumab in KEYNOTE-024

Data from the primary analysis of KEYNOTE-024 was published in New England Journal of Medicine (NEJM) in 2016 and the EPAR (AR0011) (CCOD: May 9, 2016) [33,35] Reck et al. 2016). 5-year updated OS data including safety was published by Reck et al (2021) (CCOD: June 1, 2020) [28].

In the primary analysis, 53.2% of the patients had grade ≥3 AEs. 26.6% of the patients had treatment-related grade ≥3 AEs [35]. In the updated analysis, no grade ≥3 AE rates were reported. Related grade ≥3 AEs occurred in 31.2% of the patients treated with pembrolizumab. 7 additional patients in the pembrolizumab group had experienced grade ≥3 treatment-related AEs since the initial data publication in NEJM 2016. There were two treatment-related deaths in the pembrolizumab arm; sudden death of unknown cause and pneumonitis. AEs were reported as treatment-related AEs occurring in ≥10% of patients in either arm (pembrolizumab vs chemotherapy). The most common (≥2%) grade ≥3 treatment-related AE in the pembrolizumab arm was diarrhea (3.9%). Treatment-related SAEs occurred in 22.7% of patients treated with pembrolizumab. AE leading to discontinuation had occurred in 9.1% at the first data cut-off [35], and treatment-related AEs leading to discontinuation had occurred in 13.6% at the last data cut-off [28].

Pembrolizumab in KEYNOTE-042

Safety data from the second Interim analysis from KEYNOTE-042 was published in the the EPAR (AR0057) (CCOD: September 4, 2018) and a final analysis was presented at ELCC in 2019. A 3-year updated OS was reported for KEYNOTE-042 at WCLC 2020, cut-off February 2020 [30].

At the first data cut any AE grade ≥3 were reported in 326 patients (51.3%). Of these 68 events were of grade 5 [36]. When the updated OS data was presented only treatment-related AEs were reported. Grade ≥3 treatment-related AEs occurred in 120 patients (18.9%) treated with pembrolizumab; the most common (≥2%) being pneumonitis (3.1%) [36]. Of these events, 13 were of grade 5. Any SAEs occurred in 257 of the patients (40.4%), and treatment-related SAEs occurred in 88 of the patients (13.8%). Again pneumonitis was the main treatment-related SAE and occurred in 3.9 % of the patients. This was followed by pleural effusion which occurred in 0.9% of the patients [36]. AEs leading to discontinuation of pembrolizumab occurred in 20.4% at the first data cut-off. Treatment-related AEs leading to discontinuation of pembrolizumab occurred in 9.1% reported at the latest data cut-off [30].

Conclusion on safety profiles

For discontinuations due to AE, the rates reported for pembrolizumab were vastly different with 9.1% in KEYNOTE-024 and 20.4% in KEYNOTE-042. The rate of discontinuations for pralsetinib was 19.6% (CCOD: November 6, 2020), which is higher than the reported rate for pembrolizumab in KEYNOTE-024, but slightly lower than the rate in KEYNOTE-042. In ARROW, 10.0% of patiens discontinued pralsetinib due to TRAEs (CCOD: March 4, 2022) which is lower than pembrolizumab in KEYNOTE-024 (13.6%) and slightly higher than pembrolizumab in KEYNOTE-042 (9.1%).

The number of patients experiencing a grade ≥3 AE was numerically higher for pralsetinib (75.4% at the CCOD of November 6, 2020, and 82.2% at the CCOD of March 4, 2022) than for pembrolizumab in KEYNOTE-024 (53.2%) and KEYNOTE-042 (51.3%). Similarly, the number of treatment-related grade ≥3 AEs was also higher for pralsetinib (55.2% at the CCOD of November 6, 2020, and 62.6% at the CCOD of March 4, 2022) compared to pembrolizumab in KEYNOTE-024 (31.2%) and KEYNOTE-042 (18.9%).

Overall, it is difficult to compare the safety profile of pralsetinib to the one for pembrolizumab. The rate of grade ≥3 AEs seems to be higher for pralsetinib for both all causality AEs and treatment-related AEs, while the rate of discontinuations is slightly lower than pembrolizumab in KEYNOTE-042, but higher than the rate reported in KEYNOTE-024. Differences in reporting, study design, stratification factors, patient population and data maturity could be contributing to bias when comparing results of the three trials directly.

Conclusion

Overall, the safety profiles of pralsetinib and pembrolizumab are difficult to compare in a narrative manner due to differences between the studies and the results presented for pembrolizumab in KEYNOTE-024, KEYNOTE-042 and the study by Mouritzen et al.

- The rate of discontinuations for pralsetinib is higher when compared to the rate observed for pembrolizumab in KEYNOTE-024 but slightly lower than the observed rate in KEYNOTE-042. The reported rate of discontinuations due to immune-related AEs in Mouritzen could suggest an even higher rate of discontinuations in Danish patients receiving immunotherapy.
- The rate of grade ≥3 AEs seems to be higher in pralsetinib when compared to pembrolizumab in KEYNOTE-024 and KEYNOTE-042.

A full overview of the reported safety data used in the comparative analysis can be found in Appendix F.

7.2 Efficacy and safety of pralsetinib compared to pembrolizumab in combination with chemotherapy for patients with NSCLC and PD-L1 expression ≤49%

7.2.1 Relevant studies

In the following section, we provide a brief description of each study included in the assessment and address any relevant differences between the studies in terms of study and patient characteristics. For detailed study characteristics refer to appendix B. For baseline characteristics of patients included in each study refer to appendix C.

7.2.1.1 RET fusion-positive NSCLC

Relevant studies in RET fusion-positive NSCLC populations including ARROW are presented in section 7.1.1. For this clinical question data from the subpopulation treated with the KEYNOTE-189 regime from Bhandari et al and data from Hess et al will be used.

7.2.1.2 NSCLC with unknown RET fusion status

7.2.1.2.1 Pembrolizumab in combination with platinum-based chemotherapy

KEYNOTE-189 (NCT02578680)

KEYNOTE-189 was a multicentre, phase 3, open-label, randomised controlled study evaluating the efficacy and safety of pembrolizumab in combination with chemotherapy compared to placebo in combination with chemotherapy in the treatment of participants with metastatic non-squamous NSCLC without sensitizing EGFR or ALK mutations who had received no previous treatment for metastatic disease.

The study included 616 patients that were randomly assigned 2:1 to receive pemetrexed and a platinum-based drug plus either 200 mg of pembrolizumab or placebo every 3 weeks for 4 cycles, followed by pembrolizumab or placebo

for up to a total of 35 cycles plus pemetrexed maintenance therapy. Randomization was stratified according to PD-L1 expression (tumour proportion score, ≥1% vs. <1%), choice of platinum-based drug (cisplatin vs. carboplatin), and smoking history (never vs. former or current). Treatment was continued until radiographic progression, unacceptable toxic effects, investigator decision, or patient withdrawal of consent. If toxicity was clearly attributed to one agent, that drug alone could be discontinued. Patients in the placebo-combination group in whom disease progression was verified by blinded, independent central radiologic review were eligible to cross over to receive pembrolizumab monotherapy.

The primary efficacy endpoint was PFS as assessed by Blinded Central Imaging according to RECIST version 1.1 and OS. Key secondary endpoints included confirmed objective response as assessed by Blinded Central Imaging according to RECIST version 1.1, and safety. Key exploratory endpoints were quality of life assessed by the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 (QLQ-C30) and Lung Cancer 13 (QLQ-LC13).

Efficacy was assessed in the intention-to-treat population, which included all the patients who had undergone randomization. Safety was assessed in the as-treated population, which included all patients who had undergone randomization and received at least one dose of the assigned combination therapy (n=607). Clinical cut-off dates and median time of follow-up for the analyses conducted are listed in appendix B.

Flatiron EDM RWD study (data on file)

See description in appendix F.

7.2.1.2.2 Comparability between studies

Patients in KEYNOTE-189 were required to have previously untreated locally advanced or metastatic disease, while NSCLC patients in ARROW were required to have pathologically documented, definitively diagnosed locally advanced or metastatic disease with a RET fusion either not previously or previously treated with platinum-based chemotherapy. Both trials had similar eligibility requirements in terms of age and performance status. PD-L1 status was not determined in ARROW. ARROW enrolled patients regardless of histology, however most RET fusions are detected in non-squamous NSCLC cancer patients, and hence, only 1.3% of the trial population in the study had squamous disease. KEYNOTE-189 mainly included patients with non-squamous histology. In KEYNOTE-189, PD-L1 status, but no other biomarker status, were available, while PD-L1 status was not determined in ARROW. The Flatiron EDM study included NSCLC patients regardless of histology, receiving ICI in combination with chemotherapy in a first-line setting

Comparability of baseline characteristics of patients in ARROW and KEYNOTE-189 and the real-world study is described in detail in appendix C. Overall, there were differences in the populations when comparing ARROW and KEYNOTE-189, such as in the proportion of patients with smoking history, CNS metastases, and race of the included patients. The populations are however deemed similar enough to perform narrative and naïve comparisons, although cross-trial differences and uncertainties should be taken into account when interpreting the results. The comparison versus the adjusted external control cohort from the Flatiron EDM database achieved excellent balance.

7.2.2 Efficacy and safety – results per study

In the following section, we provide a summary of the key efficacy and safety findings for each included study.
Data on the following outcomes have been extracted if available:

- Overall survival

- Progression-free survival
- Overall response rate
- Discontinuation due to adverse events
- Grade ≥3 adverse events
- Quality of life

Data for the RET fusion-positive population is presented in section 7.1.2 and data for the population with unknown RET fusion status is presented in the following. Results from ARROW from the CCOD of November 6, 2020, and the CCOD of March 4, 2022 are presented in section 7.1.2. Results from the other studies included are from the most recent CCOD unless otherwise stated. For detailed efficacy and safety results, refer to appendices D and E.

7.2.2.1 Overall survival

7.2.2.1.1 RET fusion-positive NSCLC

Relevant studies in RET fusion-positive NSCLC populations including ARROW, Bhandari et al and Hess et al are presented in section 7.1.2. For this clinical question, data from the subpopulation treated with the KEYNOTE-189 regime from Bhandari et al and Hess et al will be used.

7.2.2.1.2 NSCLC with unknown RET fusion status

The clinical trial, KEYNOTE-189, reported data for OS defined as the time from randomisation to death of any cause. Subjects without documented death at the time of analysis were censored at the date of last known contact. Data is presented for the total study population, the subpopulation with PD-L1 1-49% and subpopulation with PD-L1 <1% (Table 17). Data with the the longest possible follow-up have been extracted for all populations. As OS-rates are not available at the latest data cut-off date for either population, results based on the final protocol-defined analysis have also been extracted. Data for all populations will inform the comparative analyses presented in section 7.2.3.

Table 17: Overall survival in NSCLC population with unknown RET fusion status

Trial name	Intervention	Median follow-up	N	Overall survival			
				Median, mo. (95% CI)	12 mo rate, % (95% CI)	24 mo rate, % (95% CI)	HR (95% CI)
Clinical trials							
KEYNOTE-189 Total study population Gray 2021 [40]	PEMB + chemotherapy	46.3 mo. (range, 41.8-54.1)	410	22.0 (19.5-24.5)	-	45.7%	0.60 (0.50-0.72)
	Chemotherapy		206	10.6 (8.7-13.6)	-	27.3%	
KEYNOTE-189 Total study population Rodríguez Abreu 2021 [41]	PEMB + chemotherapy	31 mo	410	22.0 (19.5-24.5)	69.8%	45.7%	0.56 (0.46-0.69)
	Chemotherapy		206	10.6 (8.7-13.6)	48.0%	27.3%	
KEYNOTE-189	PEMB +	46.3 mo.	128	21.8 (17.7-	-	-	0.66 (0.47-0.93)

PD-L1 TPS 1-49% Gray 2021 [40]	chemotherapy	(range, 41.8-54.1)		25.6)			
	Chemotherapy		58	12.1 (8.7-19.4)	-	-	
KEYNOTE-189 PD-L1 TPS 1-49% Rodríguez Abreu 2021 [41]	PEMB + chemotherapy	31 mo	128	21.8 (17.7-25.6)	71.1%	44.3%	0.66 (0.46-0.96)
	Chemotherapy		58	12.1 (8.7-19.4)	50.0%	31.0%	
KEYNOTE-189 PD-L1 TPS <1% Gray 2021 [40]	PEMB + chemotherapy	46.3 mo. (range, 41.8-54.1)	127	17.2 (13.8-22.8)	-	-	0.51 (0.36-0.71)
	Chemotherapy		63	10.2 (7.0-13.5)	-	-	
KEYNOTE-189 PD-L1 TPS <1% Rodríguez Abreu 2021 [41]	PEMB + chemotherapy	31 mo	127	17.2 (13.8-22.8)	63.4%	39.3%	0.51 (0.36-0.71)
	Chemotherapy		63	10.2 (7.0-13.5)	47.5%	14.2%	

Abbreviations: CI – confidence interval; EDM – enhanced data mart; HR – hazard ratio; N/A – not applicable; NR – not reached; PEMB – pembrolizumab; TPS – tumour proportion score; mo. - months.

7.2.2.2 Progression-free survival

7.2.2.2.1 RET fusion-positive NSCLC

Relevant studies in RET fusion-positive NSCLC populations including ARROW, Bhandari et al and Hess et al are presented in section 7.1.2. For this clinical question, data from the subpopulation treated with the KEYNOTE-189 regime from Bhandari et al and data from Hess et al will be used.

7.2.2.2.2 NSCLC with unknown RET fusion status

KEYNOTE-189 reported data for PFS for the total study population, the subpopulation with PD-L1 1-49% and subpopulation with PD-L1 <1% (Table 18). PFS was defined as the time from randomization to disease progression or death. Progression was assessed by blinded central imaging vendor review according to RECIST version 1.1. Data with the the longest possible follow-up have been extracted for all populations. As PFS-rates are not available at the latest data cut-off date for either population, results based on the final protocol-defined analysis have also been extracted. Data for all populations will inform the comparative analyses presented in section 7.2.3.

Table 18: Progression-free survival in NSCLC population with unknown RET fusion status

Trial name	Intervention	Median follow-up	N	Progression-free survival			
				Median, mo. (95% CI)	12 mo rate, % (95% CI)	24 mo rate, % (95% CI)	HR (95% CI)

Clinical trials							
KEYNOTE-189 Total study population Gray 2021 [40]	PEMB + chemotherapy	46.3 mo. (range, 41.8-54.1)	410	9.0 (8.1-10.4)	-	22.6%	0.50 (0.41-0.59)
	Chemotherapy		206	4.9 (4.7-5.5)	-	4.4%	
KEYNOTE-189 Total study population Rodríguez Abreu 2021 [41]	PEMB + chemotherapy	31 mo	410	9.0 (8.1-10.4)	39.4%	22.0%	0.49 (0.41-0.59)
	Chemotherapy		206	4.9 (4.7-5.5)	17.6%	3.4%	
KEYNOTE-189 PD-L1 TPS 1-49% Gray 2021 [40]	PEMB + chemotherapy	46.3 mo. (range, 41.8-54.1)	128	9.4 (8.1-13.8)	-	-	0.54 (0.39-0.76)
	Chemotherapy		58	4.9 (4.7-8.6)	-	-	
KEYNOTE-189 PD-L1 TPS 1-49% Rodríguez Abreu 2021 [41]	PEMB + chemotherapy	31 mo	128	9.4 (8.1-13.8)	43.8%	22.3%	0.53 (0.38-0.74)
	Chemotherapy		58	4.9 (4.7-8.6)	20.5%	4.1%	
KEYNOTE-189 PD-L1 TPS <1% Gray 2021 [40]	PEMB + chemotherapy	46.3 mo. (range, 41.8-54.1)	127	6.2 (4.9-8.1)	-	-	0.67 (0.49-0.93)
	Chemotherapy		63	5.1 (4.5-6.8)	-	-	
KEYNOTE-189 PD-L1 TPS <1% Rodríguez Abreu 2021 [41]	PEMB + chemotherapy	31 mo	127	6.2 (4.9-8.1)	26.0%	13.3%	0.67 (0.49-0.93)
	Chemotherapy		63	5.1 (4.5-6.8)	15.5%	3.4%	

Abbreviations: CI – confidence interval; EDM – enhanced data mart; HR – hazard ratio; N/A – not applicable; NR – not reached; PEMB – pembrolizumab; TPS – tumour proportion score; mo. - months.

7.2.2.3 Overall response rate

7.2.2.3.1 RET fusion-positive NSCLC

Relevant studies in RET fusion-positive NSCLC populations including ARROW, Bhandari et al and Hess et al are presented in section 7.1.2. For this clinical question, data from the subpopulation treated with the KEYNOTE-189 regime from Bhandari et al and data from Hess et al will be used.

7.2.2.3.2 NSCLC with unknown RET fusion status

KEYNOTE-189 reported data for ORR for the total study population, the subpopulation with PD-L1 1-49% and subpopulation with PD-L1 <1% (Table 19**).** ORR is defined as the proportion of patients who have a partial or complete

response to treatment. ORR was assessed by blinded central imaging vendor review according to RECIST version 1.1. Intercranial ORR was not assessed in the study.

Table 19: Overall response rate in NSCLC population with unknown RET fusion status

Trial name	Intervention	Median follow-up	N	ORR		
				ORR, n (%) (95% CI)	CR, n (%)	PR, n (%)
KEYNOTE-189 Total study population Rodríguez-Abreu 2021 and Gray 2021 [40,41]	PEMB + chemotherapy	46.3 mo. (range, 41.8-54.1)	410	48.3% (-)	5 (1.2%)	193 (47.1%)
	Chemotherapy		206	19.9% (-)	1 (0.5%)	40 (19.4%)
KEYNOTE-189 PD-L1 TPS 1-49% Gray 2021 [40]	PEMB + chemotherapy	46.3 mo. (range, 41.8-54.1)	128	50.0% (-)	3 (2.3%)	61 (47.7%)
	Chemotherapy		58	20.7% (-)	1 (1.7%)	11 (19.0%)
KEYNOTE-189 PD-L1 TPS <1% Gray 2021 [40]	PEMB + chemotherapy	46.3 mo. (range, 41.8-54.1)	127	33.1% (-)	0 (0%)	42 (33.1%)
	Chemotherapy		63	14.3% (-)	0 (0%)	9 (14.3%)

Abbreviations: CI – confidence interval; CR – complete response; ORR – objective response rate; PEMB – pembrolizumab; PD-L1 – programmed death ligand 1; PR – partial response; TPS – tumour proportion score; mo. - months.

7.2.2.4 Discontinuations due to adverse events

7.2.2.4.1 RET fusion-positive NSCLC

Data for ARROW is presented in section 7.1.2.

7.2.2.4.2 NSCLC with unknown RET fusion status

KEYNOTE-189 reported data for discontinuation due to AEs only in the total safety population. According to the guideline from the Medicines Council neither histology nor PD-L1 expression status are expected to affect the proportion of patients that discontinue treatment due to AEs [34], and therefore AE data for the safety population is included. Data is presented in Table 20.

Table 20: Discontinuations due to adverse events in NSCLC population with unknown RET fusion status

Trial name	Intervention	Median follow-up	N	Discontinuation due to AEs, n (%)
KEYNOTE-189 (Safety population) Rodriguez-Abreu 2021 [41]	PEMB + chemotherapy	31 mo.	405	146 (36.0%)
	Chemotherapy		202	35 (17.3%)

Abbreviations: AEs - adverse events; PEMB – pembrolizumab

7.2.2.5 Grade ≥3 adverse events

7.2.2.5.1 RET fusion-positive NSCLC

Data for ARROW is presented in section 7.1.2.

7.2.2.5.2 NSCLC with unknown RET fusion status

KEYNOTE-189 reports data for grade ≥3 AEs only in the total safety population. Data is presented in Table 21.

Table 21: Grade ≥3 adverse events in NSCLC population with unknown RET fusion status

Trial name	Intervention	Median exposure (min, max)	N	Grade ≥3 AEs, n (%)
KEYNOTE-189 (Safety population) Rodriguez-Abreu 2021 [41]	PEMB + chemotherapy	31 mo.	405	292 (72.1%) *incl. grade 5: 29 (7.2%)*
	Chemotherapy		202	135 (66.8) *incl. grade 5: 14 (6.9%)*

Abbreviations: AEs - adverse events; PEMB – pembrolizumab

7.2.2.6 Quality of life

7.2.2.6.1 RET fusion-positive NSCLC

Data on QoL was collected in ARROW but no analysis has been carried out for the CCOD of November 6, 2020 nor the CCOD of March 4, 2022.

7.2.2.6.2 NSCLC with unknown RET fusion status

KEYNOTE-189 reported data on patient-reported outcomes (PROs) using the instruments EORTC QLQ-C30 and EORTC QLQ-LC13. Both were administered at cycles 1-5, every three cycles thereafter during year 1, and every four cycles during years 2-3. Key PRO endpoints were change from baseline to week 12 (during chemotherapy) and week 21 (following chemotherapy) in QLQ-C30 GHS/QOL score, and time to deterioration in cough, chest pain, or dyspnoea. PROs were analysed in all randomly assigned patients who received at least one dose of study medication and who completed at least one PRO assessment. At the CCOD (November 8, 2017), the median follow-up was 10.5 months (range 0.2–20.4) [42].

At baseline, 359 (89%) of 402 patients in the pembrolizumab plus pemetrexed-platinum group and 180 (90%) of 200 patients in the placebo plus pemetrexed–platinum group were com-pliant with QLQ-C30; at week 12, 319 (90%) of 354 and 149 (89%) of 167 patients, respectively, were compliant; and at week 21, 249 (76%) of 326 and 91 (64%) of 143 patients, respectively, were compliant. Compliance with the QLQ-LC13 was similar.

From baseline to week 12, GHS/QOL scores were maintained in both treatment arms. The least-squares (LS) mean change was 1.0 point (95% CI, -1.3-3.2) in the pembrolizumab plus pemetrexed-platinum arm and -2.6 points (95% CI, -5.8-0.5) in the placebo plus pemetrexed-platinum arm, resulting in a difference between the groups of 3.6 points (95% CI, -0.1-7.2); two-sided, nominal p=0·053). From baseline to week 21, GHS/QOL scores were better maintained with pembrolizumab plus pemetrexed–platinum with a LS mean change of 1.3 points (95% CI, -1.2-3.6) than with

placebo plus pemetrexed–platinum with a change of -4.0 points (95% CI, -7.7; -0.3). The difference between the groups was 5.3 points [1.1 to 9.5]; p=0·014).

Median time to deterioration in cough, chest pain, or dyspnoea was not reached (95% CI, 10.2-NR) with pembrolizumab plus pemetrexed–platinum, and was 7.0 months (95% CI, 4·8-NR) with placebo plus pemetrexed–platinum (HR: 0.81 (95% CI, 0.60–1.099), two-sided, nominal p=0.16).

7.2.3 Comparative analyses of efficacy and safety

7.2.3.1 Method of synthesis

As for clinical question 1, comparative analyses were performed using data for both patients with RET fusion-positive NSCLC and NSCLC patients with unknown RET fusion status.

An overview of the performed analyses is presented in Table 22. The methods used are described in detail in section 7.1.3.1 and appendix F (Flatiron analysis).

Table 22: Overview of the performed comparisons

Population	Comparator	Analyses	Study, population	Outcome
RET fusion-positive NSCLC				
1L	ICI	Narrative synthesis	RET fusion-positive patients	OS, PFS, ORR
NSCLC with unknown RET fusion status				
1L PD-L1 ≤49%	Pembrolizumab in combination with platinum-based chemotherapy	Naïve indirect treatment comparison	KEYNOTE-189, NSCLC PD-L1 >1% (non-sq), N=410	OS, PFS
		Flatiron (EDM database)	RET fusion-negative patients	OS, PFS
		Narrative synthesis	KEYNOTE-189, NSCLC PD-L1 ≤49% (non-sq)	OS, PFS, ORR, safety

Abbreviations: EDM - extended data mart; ICI - immune checkpoint inhibitor; NSCLC – non-small cell lung cancer; ORR - overall response rate; OS – overall survival; PD-L1 – programmed death ligand 1; sq – squamous; PFS – progression-free survival.

7.2.3.1.1 RET fusion-positive NSCLC

Narrative comparison with ICI

Of the six studies identified in the SLR, two studies were found to describe outcomes for RET fusion-positive NSCLC patients treated with pembrolizumab, pemetrexed and carboplatin (KEYNOTE-189-like regime) [6,17]. Data was extracted for OS and PFS. Refer to section 7.1.3.1 for further details.

Bhandari et al. defined a subgroup of RET fusion-positive NSCLC patients receiving pembrolizumab, pemetrexed and carboplatin in a first-line setting (KEYNOTE-189 regime) based on data from the Flatiron-FMI CGDB database. The subgroup included 12 patients. Hess et al also presented data on patients treated with the KEYNOTE-189 regime from the Flatiron-FMI CGDB database. The study included 9 patients. As previously noted, there may be an overlap between the patients included in each study as both are based on the Flatiron CGDB database.

7.2.3.1.2 NSCLC with unknown RET fusion status

Naïve indirect treatment comparison

Naïve ITCs were conducted to compare outcomes and to estimate a treatment-effect between pralsetinib and pembrolizumab, pemetrexed and carboplatin. One relevant comparator study, KEYNOTE-189, was included through the performed SLR. The differences between this study and ARROW are described in detail in section 7.2.1. Naïve ITCs analyses were performed for OS and PFS. The method applied is similar to the one applied for clinical question 1. Refer to section 7.1.3.1 for a description of the method.

Narrative comparison with KEYNOTE-189

A narrative comparison were conducted to compare OS, PFS, ORR and safety outcomes between pralsetinib and pembrolizumab in combination with platinum-based chemotherapy, Data from ARROW and KEYNOTE-189 informed the comparison. Data was extracted from each study and compared in a narrative manner.

7.2.3.2 Results from the comparative analysis

In the following section, we provide a summary of the results from the comparative analysis. Data are presented for the following outcome:

- Overall survival
- Progression-free survival
- Overall response rate
- Safety
    - Discontinuation due to adverse events
    - Grade ≥3 adverse events
    - Safety profiles

For each outcome, we present data for the RET fusion-positive population following the population with unknown RET fusion status. Data for the RET fusion-positive population already presented in section 7.1.3.2, will not be described in detail in the following, but will be summarized in the conclusion per outcome. Results for the Flatiron analysis are presented in appendix F**.** Furthermore, an overview of all results from the comparative analyses are available in appendix F.

As previously described, data on QoL for patients treated with pralsetinib in ARROW has not yet been analysed for the CCOD of November 6, 2020 nor the CCOD of March 4, 2022, and thus no comparative analysis have been conducted for this outcome. Data on quality of life for patients treated with pembrolizumab in combination with chemotherapy is presented in section 7.2.2.

7.2.3.2.1 Overall survival

For OS, the following comparative analyses will be presented:

- Narrative comparison vs. RET fusion-positive patients treated with ICI in combination with chemotherapy
- Naïve ITC vs. RET wild-type patients (KN-189)
- Flatiron comparison using the EDM database (RET wild-type patients) (see section in appendix F)
- Narrative comparison vs. RET wild-type patients (KN-189) (see section in appendix F)

RET fusion-positive NSCLC

Narrative comparison vs. RET fusion-positive patients treated with pembrolizumab, pemetrexed, and carboplatin

OS for pralsetinib was assessed in ARROW in both the overall efficacy population and the population with no prior systemic treatment at the CCOD of November 6, 2020. Median follow-up was 17.1 months and 12.8 months, respectively. Median OS was not reached in either population. In the overall efficacy population, the OS rate was 76.0% (69.9-82.0) at 12 months and 66.0% (57.9-74.1) at 24 months, and in the population with no prior systemic treatment, it was 82.3% (71.9-92.8) at 12 months and 74.0% (59.3-88.6) at 24 months. At the CCOD of March 4, 2022, the median follow-up was 26.8 months in the overall population and 22.1 months in the treatment naïve population. The median OS was 44.3 (95% CI, 31.9-NR) in the overall population while the median OS was not reached in the treatment naïve population [27].

Median OS was not reached in the RET fusion-positive cohort in Hess et al. and a confidence interval could not be evaluated. In Bhandari et al a median OS of 19 months (6.9-NR) was reported for the 12 patients receiving pembrolizumab, pemetrexed and carboplatin.

Overall, a median OS of 44.3 months was reported for patients treated with pralsetinib in the overall population compared to a median OS of 19.1 months in the study by Bhandari et al. However, median OS was not reached in the other comparator study by Hess et al. The difference in outcome between comparator studies, makes it difficult to compare OS for pralsetinib versus pembrolizumab, pemetrexed and carboplatin in RET fusion-positive patients. Furthermore, the results from the comparator studies are subject to uncertainty due to the small sample sizes.

NSCLC with unknown RET fusion status

Naïve indirect treatment comparison

Naïve ITC analysis for OS was informed by IPD from the subpopulation that had received no prior systemic therapy from ARROW, including a cohort of 116 patients and by aggregate data for 410 previously untreated patients with PD-L1 TPS >1% from KEYNOTE-189. The presented result is derived using data from from ARROW (CCOD: November 6, 2020) and data from the final protocol-defined OS analysis from KEYNOTE-189 (CCOD: September 21, 2018) [43]

At the CCOD of November 6, 2020 in ARROW, 16 out of 116 patients treated with pralsetinib had experienced an event. The number of events in the arm receiving pembrolizumab in combination with chemotherapy in KEYNOTE-189 were not reported. A summary of the KM curves are presented in Figure 7. Median survival for pralsetinib is not reached at the time of follow-up, whereas median survival for pembrolizumab in combination with chemotherapy is [redacted] The estimated unadjusted HR was [redacted](Table 23).

Overall, the result favours pralsetinib over pembrolizumab in combination with chemotherapy (HR <1), and the estimated treatment-effect derived is statistically significant. As no adjustments have been made for differences between the two trials, it is likely that the degree of uncertainty has been underestimated. Bias may also be introduced into the comparison where differences between study populations exist and have not been accounted for in the analysis. Despite the methodological challenges, the results from analysis shows that pralsetinib is at least numerically superior to pembrolizumab.

Table 23: Naïve ITC for OS – pralsetinib versus pembrolizumab in combination with chemotherapy

Comparison	Analysis	Pralsetinib	N	Pembrolizumab	N	HR (95% CI) Unadjusted

Pralsetinib (ARROW) vs pembrolizumab + chemotherapy (KN-189)	Base case	No prior therapy, unrestricted efficacy population	116	Previously untreated, PD-L1 TPS >1% [43]	410	[redacted]

Abbreviations: HR - hazard ratio; OS – overall survival; PEMB – pembrolizumab; PD-L1 – programmed death ligand 1; TPS – tumor proportion score.

[redacted]

Narrative comparison vs. RET wild-type patients (KN-189)

The population relevant for clinical question 2 is NSCLC with PD-L1 ≤49%. In KEYNOTE-189, pembrolizumab in combination with pemetrexed and platinum-based chemotherapy was assessed separately for treatment of NSCLC with PD-L1 TPS 1-49% and PD-L1 TPS <1%. For both populations, the median follow-up was 46.3 months. In the PD-L1 TPS 1-49% population, median OS was 21.8 months (95% CI, 17.7-25.6) for pembrolizumab in combination with chemotherapy, while it was 17.2 months (95% CI, 13.8-22.8) in the PD-L1 TPS <1% population. The OS rate reported at 24 months for the total study population was 45.7% for pembrolizumab in combination with chemotherapy. OS-rates at 12 and 24 months for the PD-L1 TPS 1-49% and PD-L1 TPS <1% populations were not presented at the latest data cut-off date, but results based on the final protocol-defined analysis (CCOD: May 20, 2019) [41] are available. For the population with PD-L1 TPS 1-49%, the estimated OS-rates at 12 months were 71.1% (95% CI, not reported) and 50.0% (95% CI, not reported) in the pembrolizumab plus chemotherapy and chemotherapy group, respectively. The estimated 24-month rates were 44.3% (95% CI, not reported) and 31.0% (95% CI, not reported). For the population with PD-L1 TPS <1%, the estimated OS-rates at 12 months were 63.4% (95% CI, not reported) in the pembrolizumab plus chemotherapy group and 47.5% (95% CI, not reported) in the chemotherapy group. The estimated 24-month rates were 39.3% (95% CI, not reported) and 14.2% (95% CI, not reported).

In ARROW, at the CCOD of March 4, 2022, median OS for patients treated with pralsetinib was 44.3 months in the overall efficacy population and stil immature in the population with no prior systemic treatment. The reported median was notably higher than the medians reported in KEYNOTE-189. At the CCOD of November 6, 2020 in ARROW, the reported OS-rates were 76.0% at 12 months and 66.0% at 24 months in the overall efficacy population, and 82.3% at 12 months and 74.0% at 24 months in the population that had received no prior systemic treatment. The 12- and 24-months rates reported in ARROW were notably higher than the rates reported in the pembrolizumab plus chemotherapy arms in both the population with PD-L1 TPS 1-49% (71.1% at 12 months and 44.3% at 24 months) and

population with PD-L1 TPS <1% (63.4% at 12 months and 39.3% at 24 months). Thus, data show a numerical trend in favour of pralsetinib, indicating a clinically meaningful benefit.

Conclusion

At the CCOD of November 6, 2022, median OS for patients treated with pralsetinib in ARROW was not reached in either the overall efficacy population or the population that had received no prior systemic treatment. The OS rate was 76.0% at 12 months and 66.0% at 24 months in the overall efficacy population, while it was 82.3% at 12 months and 74.0% at 24 months in the population that had received no prior systemic treatment. At the CCOD of March 4, 2022, the median OS was 44.3 months in the overall population while the median OS was not reached in the treatment naïve population. Based on the available comparative evidence, the following conclusions can be made:

- Median OS from the retrospective study by Bhandari et al including RET fusion-positive NSCLC patients treated with pembrolizumab in combination with chemotherapy was comparable with the medians reported in the population with unknown RET fusion status in KEYNOTE-189. The 12- and 24-month OS-rates reported in ARROW (CCOD: November 6, 2020) were notably higher than the ones reported in both the population with PD-L1 TPS 1-49% and PD-L1 TPS <1% from KEYNOTE-189. The median OS of 44.3 months (CCOD: March 4, 2022) is much longer than the median OS between 17.2-22.0 months reported in the comparator studies, indicating a clinically meaningful benefit of pralsetinib.
- The result from the naïve ITC analysis, comparing pralsetinib to pembrolizumab in combination with chemotherapy showed a statistically significant treatment-effect, favouring pralsetinib over pembrolizumab in combination with chemotherapy. Despite methodological challenges, the result showed that pralsetinib is at least numerically superior to pembrolizumab in combination with chemotherapy.
- Results from the real-world Flatiron EDM analysis showed a trend similar to the naïve ITC analyses. The estimated treatment-effect was statistically significant, favouring pralsetinib over pembrolizumab in combination with chemotherapy.

A full overview of the reported OS data used in the comparative analysis can be found in Appendix F.

7.2.3.2.2 Progression-free survival (PFS)

The following comparative analyses will be presented for PFS:

- Narrative comparison vs. RET fusion-positive patients treated with ICI in combination with chemotherapy
- Naïve ITC vs. RET wild-type patients (KN-189)
- Flatiron comparison using the EDM database (RET wild-type patients) (see section in appendix F)
- Narrative comparison vs. RET wild-type patients (KN-189) (see section in appendix F)

RET fusion-positive NSCLC

Narrative comparison vs. RET fusion-positive patients treated with pembrolizumab, pemetrexed, and carboplatin

For pralsetinib at the CCOC of November 6, 2022, PFS has been reported for the overall efficacy population (17.1 months of median follow-up) and for the subgroup with no prior systemic treatment (12.8 months of median follow-up). The PFS rates for the overall efficacy population were 56.0% (95% CI, 48.9-63.1) at 12 months and 42.1% (95% CI, 33.2-51.0) at 24 months. For the population with no prior systemic treatment the 12-month PFS rate was 52.6% (95% CI, 37.7-67.5) and the 24-month PFS rate was 47.8% (95% CI, 31.6-64.1). Median PFS was 16.4 months (95% CI, 11.0-24.1) in the overall population and 13.0 (95% CI. 9.1-NR) in the subgroup with no prior systemic treatment. At the CCOD of March 4, 2022, PFS was reported in the overall population with a median follow-up of 25.8 months and in the

treatment naïve population (median follow-up was not reported). The median PFS in the overall population was 13.2 months (95% Cl, 11.4-16.8) and 12.6 months (95% CI, 9.2-16.6) in the treatment naïve population [27].

In Bhandari et al, median PFS was reported as 5.4 months (95% CI, 1.4-14.2) for the patients receiving pembrolizumab, pemetrexed and carboplatin, while it was 6.6 months (95% CI, 0.4-NR) in the 9 patients in Hess et al.

The median PFS was longer for pralsetinib in both the overall efficacy population and the subgroup with no prior systemic treatment when compared to the median PFS presented in the studies by Bhandari et al and Hess et al. The comparative results are however uncertain due to the small sample sizes presented for pembrolizumab, pemetrexed and carboplatin in RET fusion-positive patients.

NSCLC with unknown RET fusion status

Naïve indirect comparison

Similar to the analysis for OS, naïve ITC analysis for PFS was informed by IPD from the subpopulation that had received no prior systemic therapy from ARROW and aggregate data for 410 previously untreated patients with PD-L1 TPS >1% from KEYNOTE-189. The presented result is derived using data from ARROW (CCOD: November 6, 2020), and data from the final protocol-defined PFS analysis from KEYNOTE-189 (CCOD: September 21, 2018) [43]

At the CCOD of November 6, 2020 in ARROW, 31 out of 116 patients treated with pralsetinib had experienced an event. The number of events in the arm receiving pembrolizumab in combination with chemotherapy in KEYNOTE-189 were not reported. A summary of the KM curves are presented in Figure 8. Median PFS for pralsetinib was [redacted], and median PFS for pembrolizumab in combination with chemotherapy was [redacted] The estimated unadjusted HRs was [redacted] compared to pembrolizumab in combination with chemotherapy (Table 24).

Overall, the result favours pralsetinib over pembrolizumab (HR <1), and the estimated treatment-effect is statistically significant. As no adjustments have been made for differences between the two trials, it is likely that the degree of uncertainty has been underestimated. Bias may also be introduced into the comparison where differences between study populations exist and have not been accounted for in the analysis. Despite the methodological challenges, the result from analysis shows that pralsetinib is at least numerically superior to pembrolizumab.

Table 24: Naïve ITC for PFS – pralsetinib versus pembrolizumab in combination with chemotherapy

Comparison	Analysis	Pralsetinib	N	Pembrolizumab	N	HR (95% CI) Unadjusted
Pralsetinib (ARROW) vs pembrolizumab + chemotherapy (KN-189)	Base case	No prior therapy, unrestricted efficacy population	116	Previously untreated, PD-L1 TPS >1% [43]	410	[redacted]

Abbreviations: HR - hazard ratio; PEMB – pembrolizumab; PD-L1 – programmed death ligand 1; PFS – progression-free survival; TPS – tumor proportion score; CI – confidence interval; KN-189 – KEYNOTE-189.

Narrative comparison vs. RET wild-type patients (KN-189)

In KEYNOTE-189, pembrolizumab in combination with pemetrexed and platinum-based chemotherapy was assessed separately for treatment of NSCLC with PD-L1 TPS 1-49% and PD-L1 TPS <1%. For both populations, the median follow-up was 46.3 months.

In the population with PD-L1 TPS 1-49%, the median PFS for pembrolizumab in combination with chemotherapy was 9.4 months (8.1-13.8). In the population with PD-L1 TPS <1%, the median PFS for pembrolizumab in combination with chemotherapy was 6.2 months (4.9-8.1). PFS-rates at 12 and 24 months for the PD-L1 TPS 1-49% and PD-L1 TPS <1% populations were not presented at the latest data cut-off date, but results from an ealier data cut-off (CCOD: May 20, 2019) [41] are available. For the population with PD-L1 TPS 1-49%, the estimated PFS-rates at 12 months were 43.8% (95% CI, not reported) and 20.5% (95% CI, not reported) in the pembrolizumab plus chemotherapy and chemotherapy group, respectively. The estimated 24-month rates were 22.3% (95% CI, not reported) and 4.1% (95% CI, not reported). For the population with PD-L1 TPS <1%, the estimated PFS-rates at 12 months were 26.0% (95% CI, not reported) in the pembrolizumab plus chemotherapy group and 15.5% (95% CI, not reported) in the chemotherapy group. The estimated 24-month rates were 13.3% (95% CI, not reported) and 3.4% (95% CI, not reported).

The median PFS estimates for pembrolizumab in combination with chemotherapy are slightly higher for the PD-L1 TPS 1-49% population than for the population with PD-L1 TPS <1% (9.4 months vs. 6.2 months). Pralsetinib has demonstrated a longer PFS in both the overall efficacy population (16.4 months at the CCOD of November 6, 2020 and 13.2 months at the CCOD of March 4, 2022) and the population with no prior systemic treatment (13.0 months at the CCOD of November 6, 2020 and 12.6 months at the CCOD of March 4, 2022). In ARROW, the reported PFS-rates were 56.0% at 12 months and 42.1% at 24 months in the overall efficacy population, and 52.6% at 12 months and 47.8% at 24 months in the population that had received no prior systemic treatment. The 12- and 24-months rates reported in ARROW were notably higher than the rates reported in the pembrolizumab plus chemotherapy arms in both the population with PD-L1 TPS 1-49% (43.8% at 12 months and 22.3% at 24 months) and population with PD-L1 TPS <1% (26.0% at 12 months and 13.3% at 24 months). Thus data indicates a numerical trend in favour of pralsetinib. Thus, despite study difference, the results indicate that there is a clinically meaningful difference between pralsetinib and pembrolizumab in combination with chemotherapy in NSCLC patients with unknown RET fusion status.

Conclusion

At the CCOD of November 6, 2020, pralsetinib demonstrated 16.4 months (95% CI, 11.0-24.1) of median PFS in the overall efficacy population and 13.0 months (95% CI, 9.1-NR) in the population with no prior systemic treatment. The PFS rate was 56% (95% CI, 48.9-63.1) at 12 months and 42.1% (95% CI, 33.2-51.0) at 24 months in the overall efficacy population, and it was 52.6% (95% CI, 37.7-67.5) at 12 months and 47.8% (95% CI, 31.6-64.1) at 24 months in the population with no prior systemic treatment. The median PFSs reported at the CCOD of March 4, 2022 were comparable with previously reported PFSs. When reviewing the available comparative evidence the following conclusions can be made:

- Pralsetinib demonstrated the longest median PFS presented in the narrative comparisons for both RET fusion-positive patients in the retrospective studies and RET wild-type patients in KEYNOTE-189. The 12- and 24-month PFS-rates reported in ARROW were notably higher than the ones reported in both the population with PD-L1 TPS 1-49% and PD-L1 TPS <1% from KEYNOTE-189.

- The result from the naïve ITC analysis showed a statistically significant treatment-effect, favouring pralsetinib over pembrolizumab in combination with chemotherapy. Despite methodological challenges, the result showed that pralsetinib is at least numerically superior to pembrolizumab in combination with chemotherapy.

- The same trend was seen in the comparison of data from ARROW to real-world patients treated with pembrolizumab in combination with chemotherapy in the Flatiron EDM database. The risk of progression was halved in patients treated with pralsetinib and the difference in months using RMSTD was nearly 5 months.

A full overview of the reported PFS data used in the comparative analysis can be found in Appendix F.

7.2.3.2.3 Overall response rate

The following comparative analyses will be presented for ORR:

- Narrative comparison vs. RET fusion-positive patients treated with ICI in combination with chemotherapy
- Narrative comparison vs. RET wild-type patients (KN-024, KN-042)

In addition, a supplementary landmark analysis, which assess the association of tumour response with survival is presented in appendix F.

RET fusion-positive NSCLC

Narrative comparison vs. RET fusion-positive patients treated with pembrolizumab, pemetrexed, and carboplatin

ORR was the primary efficacy endpoint in the ARROW trial and is reported for both the overall efficacy population as well as the population with no prior systemic treatment at the CCOD of November 6, 2020. In the overall efficacy population, the ORR was 150 of 233 (64.4%, 95% CI 57.9-70.5) with 11 patients (4.7%) experiencing a CR and 139 patients (59.7%) experiencing a PR. In the population that received no prior systemic treatment, the ORR was 54 of 75 (72.0%, 95% CI 60.4-81.8) with 4 patients (5.3%) experiencing a CR and 50 patients (66.7%) experiencing a PR [26]. At the CCOD of March 4, 2022, ORR was 185 of 281 (65.8%, 95% CI 60.0-71.4) with 18 patients (6.4%) experiencing a CR and 167 patients (59.4%) experiencing a PR in the overall population. ORR was 52 of 69 (75.4%, 95% CI 63.5-84-9) with 4 patients (5.8%) experiencing a CR and 48 patients (69.6%) experiencing a PR in the treatment naïve population post-eligibility revision [27].

ORR was measured in the study by Bhandari et al. for the subgroup of 12 patients receiving pembrolizumab, pemetrexed and carboplatin. Response data was missing for 2 patients. 7 patients (70%) achieved a response. 1 patient (10%) achieved a complete response, while 6 patients (60%) achieved a partial response.

Response data was also available for the RET fusion-positive patient population (n=9) in the study by Hess et al. Response data was missing for 1 patient. A response was reported for 6 patients (75.0%); complete response was achieved in 1 patient (12.5%), while a PR was achieved in 5 patients (62.5%).

The ORR was slightly higher for the two RWD studies on pembrolizumab, pemetrexed and carboplatin in RET fusion-positive patients. The response data presented in Bhandari et al. and Hess et al. is however limited with both samples consisting of 10 patients or fewer, making comparisons difficult.

NSCLC with unknown RET fusion status

Narrative comparison vs. RET wild-type patients (KN-189)

In KEYNOTE-189, ORR for pembrolizumab in combination with chemotherapy is reported separately for the population with PD-L1 TPS 1-49% and PD-L1 TPS <1%. In the population with PD-L1 TPS 1-49% (n=128), 50.0% of patients achieved a response with 3 patients (2.3%) experiencing a CR and 61 patients (47.7%) achieving a PR. In the population with PD-L1 TPS <1% (n=127), the ORR was 33.1% with 0 patients achieving a CR and 42 patients (33.1%) experiencing a PR.

The ORR data for pembrolizumab in combination with chemotherapy suggests a lower response rate in the population with PD-L1 TPS <1% as well as a lower number of patients achieving CR. When comparing data from ARROW to the response data for pembrolizumab in combination with chemotherapy, the ORRs are markedly higher in patients receiving pralsetinib with the majority of patients in both populations achieving an objective response and several patients achieving CR.

Conclusion

Overall, at the CCOD of November 6, 2020, pralsetinib showed a clinically relevant response rate of 64.4% in the overall efficacy population and 72.0% in the population with no prior systemic treatment. Comparably, at the CCOD of March 4, 2022, ORR was 65.8% in the overall population and 75.4% in the treatment naive population post-eligibility revision. The landmark analysis presented in section 7.1.3.2 suggested that the ORRs could be a predictor for longer overall survival. As discussed, there are limitations when performing narrative comparisons and when comparing data for population consisting exclusively for RET fusion-positive patients with populations where the proportion of RET fusion-positive patients is unknown.

- In general, the evidence for pembrolizumab in combination with chemotherapy in RET fusion-positive patients is still very limited with data derived from small patient groups in the studies by Bhandari et al. and Hess et al. This makes it difficult to conclude on the level of response that can be expected for this treatment regimen in RET fusion-positive patients.

- In the comparison to the larger datasets on RET wild-type NSCLC patients treated with pembrolizumab in combination with chemotherapy from KEYNOTE-189, the ORRs for pralsetinib are markedly higher.

A full overview of the reported ORR data used in the comparative analysis can be found in Appendix F.

7.2.3.2.4 Safety

The safety results will be presented in three parts as follows:

- Narrative comparison of discontinuation due to AEs in RET fusion-positive patients in ARROW and RET wild-type patients in KEYNOTE-189
- Narrative comparison of grade ≥3 AEs in RET fusion-positive patients in ARROW and RET wild-type patients in KEYNOTE-189
- Review of the safety profiles of pralsetinib and pembrolizumab and chemotherapy

Safety data from ARROW was reported for the total safety population (n=528), which includes patients with RET-altered NSCLC, MTC, and other solid tumours, and for the RET fusion-positive NSCLC population (n=281). Median (min, max) exposure to pralsetinib were 7.9 months (0.1, 33.9) and 9.5 months (0.3, 28.4), respectively (CCOD: November 6, 2020). In addition, data on the NSCLC safety population (n=281) with a median treatment duration of 15.0 months was reported (CCOD: March 4, 2022). In KEYNOTE-189 safety was assessed in the as-treated population, which included all patients who had undergone randomization and received at least one dose of the assigned combination therapy [44]. Relevant safety data for pembrolizumab in combination with chemotherapy are derived from either the primary safety analysis (CCOD: November 8, 2017), second safety analysis (CCOD: May 20, 2019) or the latest updated safety analysis (CCOD: August 28, 2020) depending on data availability.

Discontinuation due to adverse events

Narrative comparison vs. RET wild-type patients (KN-189)

In ARROW, 91 of 528 patients (17.2%) in the total safety population and 55 of 281 patients (19.6%) in the RET fusion-positive NSCLC population discontinued treatment due to an adverse event. The two rates are relatively stable across both populations. At the CCOD of March 4, 2022, 28 of 281 patients (10%) in the NSCLC safety population discontinued treatment due to TRAEs [27].
In KEYNOTE-189, 146 of 405 patients (36.0%) in the group treated with pembrolizumab in combination with chemotherapy discontinued treatment due to AEs and 111 patients (27.4%) discontinued due to TRAEs.

The recorded rate of discontinuations due to adverse events is overall lower for pralsetinib in ARROW than for pembrolizumab in combination with chemotherapy in KEYNOTE-189. The difference is 16.4% in favour of pralsetinib when comparing to the highest recorded rate in the RET fusion-positive NSCLC population. However, it can be difficult to compare the results for discontinuations due to differences in reporting, study design, stratification factors, patient population and data maturity.

Grade ≥3 adverse events

Narrative comparison vs. RET wild-type patients (KN-189)

For pralsetinib in the ARROW trial, 406 of 528 patients (76.9%) experienced a grade ≥3 event in the total safety population, while it was 212 of 281 patients (75.4%) in the RET fusion-positive NSCLC population at the CCOD of November 6, 2020. In the NSCLC safety population, 231 of 281 patients (82.2%) experienced grade ≥3 AEs at the CCOC of March 4, 2022 [27].
In KEYNOTE-189, 292 of 405 patients (72.1%) in the group treated with pembrolizumab in combination with chemotherapy experienced a grade ≥3 adverse event.

Overall, the rate of grade ≥3 AEs for pralsetinib in ARROW is slightly higher than what has been reported for pembrolizumab in combination with chemotherapy in KEYNOTE-189. As previously mentioned, it can be difficult to

compare the results for grade ≥3 AEs due to differences in reporting, study design, stratification factors, patient population and data maturity.

Safety profiles

Narrative comparison vs. RET wild-type patients (KN-189)

A description of the safety profile for pralsetinib can be found in section 7.1.3.2.4.

At the CCOD of May 20, 2019, 292 patients (72.1%) in the pembrolizumab plus chemotherapy arm had experienced a grade ≥3 AE, and of those, 29 incidents were of grade 5 (see Table 99). Treatment-related grade ≥3 AEs were reported from the most recent data cut-off and occurred in 211 patients (52.1%) in the pembrolizumab plus chemotherapy arm. Of these, 8 of the incidents were of grade 5 (2%) [40]. The causes of deaths were reported from an earlier data cut-off and these were acute kidney injury (n = 2), pneumonitis (n = 2), death (unknown cause), encephalopathy, neutropenic sepsis, and pneumonia (n = 1 each) [41].

The most common treatment-related grade 3-4 AEs were reported in the EPAR-0043. These were neutropenia (14.6%), anaemia (13.6%) and thrombocytopenia (7.7%). Discontinuations due to AEs occurred in 27.7% of patients while treatment-related AEs leading to discontinuation of treatment occurred in 21.0% of patients in the pembrolizumab plus chemotherapy arm. Treatment-related SAEs occurred in 106 patients (26.2%) in the pembrolizumab plus chemotherapy arm and the most common were febrile neutropenia (5.2%), thrombocytopenia (3.2%) and diarrhea (3.0%) [45].

Conclusion on safety profiles

Discontinuations due to AEs were less frequent for pralsetinib in ARROW (19.6%) (CCOD: November 6, 2020) when compared to pembrolizumab plus chemotherapy in KEYNOTE-189 (36.0%). Similarly, the rate of discontinations due to TRAEs were lower for pralsetinib (10.0%, CCOD: March 4, 2022) than for pembrolizumab plus chemotherapy (27.4%). Treatment-related grade 5 AEs were observed for both pralsetinib and pembrolizumab combined with chemotherapy but in both cases with a low incidence of <1-2%.

Overall, the rate of grade ≥3 AEs for pralsetinib at the CCOD of November 6, 2020 (75.4%) was similar to the rate for pembrolizumab plus chemotherapy (72.1%). However, the rate for pralsetinib at the CCOD of March 4, 2022 (82.2%) was higher. The same was the case when comparing the number of grade ≥3 TRAEs.

Conclusion

Overall, the safety profiles of pralsetinib and pembrolizumab combined with chemotherapies are difficult to compare due to differences between the studies. However, based on the available evidence, pralsetinib seems to have a similar rate of grade ≥3 events but a much lower rate of discontinuations due to AEs and TRAEs.

A full overview of the reported safety data used in the comparative analysis can be found in Appendix F.

8. Health economic analysis

The health economic analysis conducted in the present application is a cost-utility (CU) analysis. The purpose of the health economic analysis was to estimate the cost-effectiveness of treating RET fusion-positive NSCLC patients with pralsetinib versus pembrolizumab monotherapy and pembrolizumab in combination with chemotherapy. The analysis was based on a global CU model adjusted to a Danish setting.

8.1 Model

The CU model compares pralsetinib to relevant comparators in a population of treatment-naïve patients with RET fusion-positive NSCLC and estimates the incremental cost-effectiveness ratios (ICERs). A budget impact model is also included. Both models were developed in Excel.

The CU model was designed to accommodate as much of the available evidence as possible and accurately reflect the condition of patients with RET fusion-positive NSCLC. A partitioned survival model was developed to determine the cost-effectiveness of pralsetinib versus relevant comparators. The advantages of this approach in NSCLC are as follows:

- OS, PFS and total time on treatment (TTOT) data from the clinical trial can be used directly in the model.
- Time dependencies and treatment effects are reflected within the survival curves, whereas a Markov model would have required cumbersome tunnel states.
- Parametric models allow time-varying hazards to be modelled, whereas a Markov structure would have required several sets of transition matrices to have this functionality.
- Hazard ratios from network meta-analyses or SLRs can be applied to OS, PFS and time-to-treatment-discontinuation (TTD) curves directly.

Table 25 outlines the specifications of the CU model.

Table 25: Model specifications

Model aspect	Details/assumptions
Structure	Partitioned survival model
Time horizon	20 years
Cycle length	1 month (30.428 days)
Discount rates	3.5% for costs and outcomes
Comparators	Pembrolizumab Pembrolizumab + pemetrexed + platinum-based chemotherapy
Efficacy data source	- ARROW Kaplan-Meier plots for OS and PFS (basis for all comparisons) - Comparative efficacy was estimated from a naïve ITC based on an SLR in wild-type NSCLC
Safety data source	Pralsetinib: ARROW Pembrolizumab: KEYNOTE-042 Pembrolizumab in combination with chemotherapy: KEYNOTE-189 (See appendix E)
Cost sources	Drug costs Hospital costs Cross-sectional costs AE costs End-of-life costs Patient and transportation costs

Abbreviations: AE – adverse events; SLR – systematic literature review; OS – overall survival; PFS – progression-free survival; ITC – indirect treatment comparison; NSCLC – non-small cell lung cancer.

All applied extrapolations were validated by clinical experts on an international advisory board. Country-specific inputs in the model were validated by the Danish clinical expert to ensure alignment with Danish clinical practice. The health

economic model was reviewed and quality checked by an in-house team member experienced in quality assurance who was not directly involved in the development of the model.

Previous HTA submissions served as the basis for identification of utility values used in the health economic model (see section 8.4), but aside from that, cost-effectiveness studies have not been identified and used in the development of the model.

8.1.1 Model structure

The model consists of three mutually exclusive health states: pre-progression or progression-free survival (PFS), post-progression survival (PPS) and death. Figure 1 illustrates the model structure of the CU analysis.

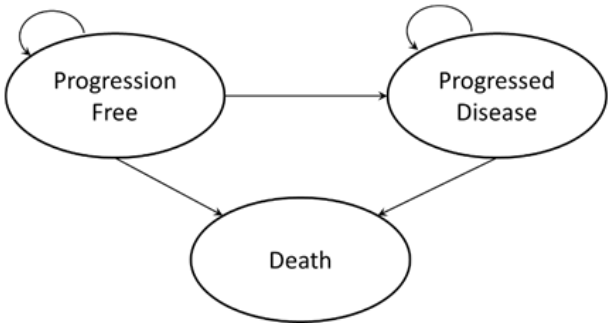


Figure 9: Model structure

8.1.2 Patient flow in the model

The patient cohort enters the model in the pre-progression health state. After each model cycle, patients can either stay in the same state or progress to PPS or die. Once patients reach PPS they can stay in that state or die, but they cannot transition back to the PFS health state.

Any transitions to post-progression and death are defined by the PFS and OS curves. The proportion of the cohort remaining in the pre-progression health state over time is derived directly from the PFS curve (see Appendix G). State membership for the death state is calculated as 1 minus the OS curve, and state membership for the post-progression health state is calculated as the difference between the OS curve and the PFS curve (the proportion of patients who are still alive but are no longer pre-progression).

The model also considers TTOT and TTD, which are modelled independently of OS and PFS and are not used to inform health state occupancy. In accordance with clinical practice, TTOT implies that patients be treated until disease progression, treatment discontinuation due to intolerable adverse events or death.

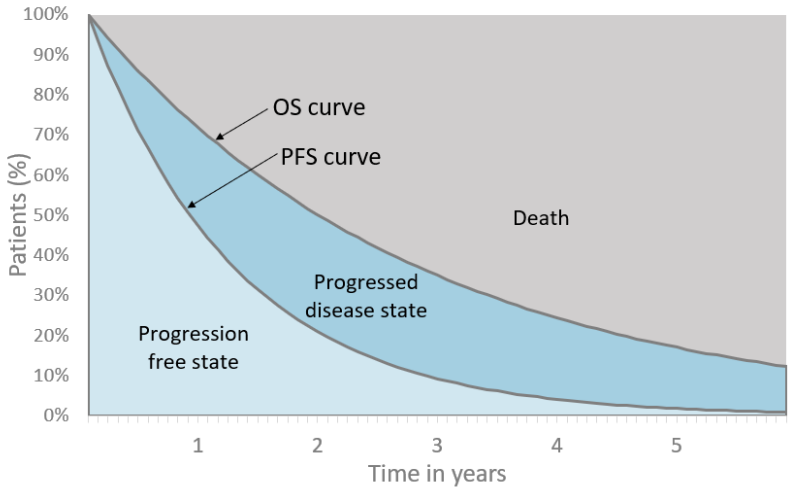


Figure 10: Mutually exclusive survival curves. Please note that this is purely illustrative and is not based on any efficacy data reported elsewhere in this document. Abbreviations: OS – overall survival; PFS – progression-free survival.

8.1.3 Applied perspective

The base case model has a restricted societal perspective in accordance with the Danish Medicines Council (DMC) guidelines [46]

8.1.4 Time horizon

The health economic model utilises the base case time horizon of 20 years. This was based on the proportion of patients alive for pralsetinib according to OS (i.e., the highest possible survival curve used in the model) to demonstrate the ceiling of the survival estimates used by the model. In addition, it should be noted that the mean age of the included patients in cycle 0 is 63 years.

8.1.5 Cycle length and half-cycle correction

The model has a cycle length of one month (365.25 days/12 months = 30.44 days per month), which was deemed a sufficient length of time to account for changes in PFS and OS. The monthly cycle length allows for ease of interpretation of model engine outputs and allows for accurate modelling of outcomes without impairing computational efficiency by having many cycles in the model engines.

Since trial endpoints are included based on the observation of patients at the end of each month, half-cycle correction was used. The need for half-cycle correction decreases as cycles become shorter (e.g., a one-week cycle would not require half-cycle correction); however, a one-month cycle length still benefits from half-cycle correction. The half-cycle correction was implemented by default.

The cycle length allows alignment with chemotherapy treatment regimens, which are applied in cycles measured in weeks.

8.1.6 Discounting

Both costs and quality-adjusted life years (QALYs) were discounted at a rate of 3.5%, in line with the Danish Ministry of Finance [47]and the DMC guidelines [46] By default, the discount rates were not included in the deterministic sensitivity analysis (DSA) or probabilistic sensitivity analysis (PSA), as the outputs were unlikely to be informative. For the purposes of calculating life years in each health state, the undiscounted values were used. In the fully incremental results, discounted life years were considered.

8.1.7 General mortality

General population background mortality was implemented using the most recent National Life Tables for Denmark [48]. General population mortality was only used in the model engine if the predicted death rate per cycle for OS and PFS dropped below that of the risk of all-cause death.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

In Table 26, we present input data on clinical efficacy, adverse reactions, and health state utility values (HSUVs) applied in the model and describe how these input data were obtained.

Table 26: Input data used in the model

Name of estimates*	Results from study or indirect treatment comparison (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How input value was obtained/estimated**
Progression-free survival	Pralsetinib: median progression-free survival of [redacted] in patients with no prior treatment. Pembrolizumab: median progression-free survival of [redacted] The HR was estimated to be [redacted] compared to pralsetinib in an indirect comparison. Pembrolizumab + pemetrexed + chemotherapy: median progression-free survival of [redacted] The HR was estimated to be [redacted] compared to pralsetinib in an indirect comparison. See sections 7.1.3.2 and 7.2.3.2.	[redacted]	The input value is estimated in the naïve indirect comparison presented in sections 7.1.3 and 7.2.3. The model is a partitioned survival model, and the number of people in any state at any point is estimated based on parametric survival equations.
Overall survival	Pralsetinib: median overall survival was not reached by the end of the study period. Pembrolizumab: median survival was [redacted] in KEYNOTE-042. From the naïve indirect comparison, the HR was [redacted] compared to pralsetinib. See section 7.1.3.2. Pembrolizumab + pemetrexed + chemotherapy: median survival was [redacted] in KEYNOTE-189. From the naïve indirect comparison, the HR was [redacted] compared to pralsetinib. See section 7.2.3.2.	[redacted]	The input value is estimated in the naïve indirect comparison presented in sections 7.1.3 and 7.2.3. The model is a partitioned survival model, and the number of people in any state at any point is estimated based on parametric survival equations.
Total time on treatment	N/A	[redacted]	The input value is estimated in the naïve indirect comparison presented in sections 7.1.3 and 7.2.3.

Adverse reaction 1* (measured in costs)	N/A	Pralsetinib: DKK 10,908.79. Pembrolizumab: DKK 2,698.38. Pembrolizumab + pemetrexed + chemotherapy: DKK 6,285.11.	Cost estimates are based on Danish DRG tariffs, further described in section 8.5.
Adverse reaction 2* (measured as occurrence)	Pralsetinib: 75.4% in the NSCLC RET fusion-positive population and 76.9% in the total safety population of the ARROW trial experienced grade 3-5 AEs. Pembrolizumab: 53.2% and 51.3% experienced grade 3-5 AEs in the as-treated populations in KEYNOTE-024 and KEYNOTE-042, respectively. Pembrolizumab + pemetrexed + chemotherapy: safety population in KEYNOTE-189. 72.1% experienced grade 3-5 AEs. See sections 7.1.3.2 and 7.2.3.2.	Overall rates for AEs are not applied in the model. Instead, rates are applied for specified relevant AEs. See section 8.2.2.5.	Occurrences of AEs used in the model for pralsetinib were sourced from the ARROW trial [26]. For patients receiving pembrolizumab the AE rates were sourced from the KEYNOTE-042 trial (Appendix E), and for patients receiving pembrolizumab in combination with chemotherapy, the AE rates were sourced from the KEYNOTE-189 trial (Appendix E).
Adverse reaction 3* (measured as utility loss)	Utility decrements associated with any AE were identified through an SLR or assumption-based. See section 8.4.	Utility losses associated with AEs as used in the model are presented in section 8.4.2.	Utility losses associated with any AE were identified through an SLR or assumption-based. See section 8.4.
Progression-free disease* (measured as utility)	Nafees et al. (2008) [49] 0.6532	0.6532	The HSUV is obtained from an SLR. See section 8.4.
Progressed disease* (measured as utility)	Nafees et al. (2008) [49] 0.4734	0.4734	The HSUV is obtained from an SLR. See section 8.4.

[a]In the model, the HR is the reciprocal of that found in the indirect comparison. Abbreviations: ITT – intention to treat; PP – per-protocol; N/A – not applicable; HSUV - health state utility values; AE – Adverse event; SLR – systematic literature review; HR – Hazard Ratio; DRG – diagnose related groups.

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

Patient population in the health economic analysis submitted

The Danish patient population with RET fusion-positive NSCLC has been described in detail in Section 5.

The clinical documentation for pralsetinib was based on the ARROW trial and the unrestricted efficacy population consisting of 116 patients. The baseline characteristics of patients in the ARROW trial are presented in Appendix C.

To ensure comparability in the health economic model, which assesses pralsetinib as first-line therapy in RET fusion-positive NSCLC patients, the patient population of relevance is the treatment-naïve group from the ARROW study, with key demographic information shown in Table 27. No sources were found to describe demographics for the

Danish population with RET fusion-positive NSCLC. However, there is nothing to suggest significant differences between demographics for patients in ARROW and the Danish population. For more information, see Appendix C. The base case utilises the naïve comparisons, which are based on the 'unrestricted efficacy population' (described in Section 7.1.3.1).

Table 27: Patient population

Patient population Important baseline characteristics	No prior systemic treatment (n=75)	Unrestricted efficacy population (n=116)	Danish clinical practice (including source)
Mean age (median)	[redacted]	[redacted]	N/A
% males	[redacted]	[redacted]	N/A
Mean BSA, m²	[redacted]	[redacted]	N/A
Weight	[redacted]	[redacted]	N/A

Source: [a][50]; Abbreviations: BSA – body surface area; N/A – not applicable.

8.2.2.2 Intervention

Pralsetinib in the health economic model

Pralsetinib is the first first-line treatment to be approved for RET fusion-positive NSCLC patients and will offer a new treatment option in Denmark. A description of how pralsetinib is expected to be used in Danish clinical practice can be found in section 5.3 and is summarised in Table 28.

In the health economic model, the posology of pralsetinib follows that of the ARROW trial, as this trial was used to inform the model. The total dose applied in the model for pralsetinib was 400 mg daily. It is not expected that use of pralsetinib in Danish clinical practice will differ from the ARROW trial.

Table 28: Intervention

Intervention	Clinical documentation (including source)	Used in the model (number/value, including source)	Expected Danish clinical practice (including source, if known)
Posology	400 mg daily[a]	400 mg daily	400 mg daily
Length of treatment (time on treatment) (mean/median)	Median time on treatment: 12.78 months.	Median time on treatment: 14 months.	N/A
Criteria for discontinuation	All patients received pralsetinib until disease progression, intolerance, withdrawal of consent or investigator decision[a].	All patients received pralsetinib until disease progression or discontinuation.	All patients are expected to receive pralsetinib until disease progression or intolerance.
The pharmaceutical's position in Danish clinical practice	First-line (treatment-naïve)[a]	First-line	First-line

Source: [a] [26]; Abbreviations: N/A – Not applicable.

8.2.2.3 Comparators

The CUA is carried out as two separate analyses vs pembrolizumab monotherapy and pembrolizumab in combination with chemotherapy.

To inform elements regarding the relevant comparators, a systematic literature search was conducted as described in Section 6. Clinical expert opinion and guidelines [16] were used to identify the clinical practice for first-line treatment with immunotherapies in Denmark.

For pembrolizumab as monotherapy, the KEYNOTE-042 trial (see section 7.1.1) was applied to inform the model. Pembrolizumab was administered intravenously at a dose of 200 mg every 3 weeks for 35 treatment cycles.
In the health economic model, we assumed that the posology of monotherapy pembrolizumab (Table 29) follows the posology described by the clinical expert. Patients receiving pembrolizumab as monotherapy are dosed at 2 mg/kg every third week during the first four treatment cycles and thereafter at 4 mg/kg every sixth week. Patients receive treatment with pembrolizumab for a maximum of two years [15].

For pembrolizumab plus pemetrexed plus chemotherapy, the KEYNOTE-189 trial (see section 7.2.1) was applied to inform the model. As for monotherapy, we assumed in the health economic model that the posology of pembrolizumab in combination with pemetrexed and platinum-based chemotherapy (Table 30) follows the posology described by the clinical expert. Patients receiving pembrolizumab in combination with chemotherapy were assumed to receive four treatment cycles of pembrolizumab dosed at 2 mg/kg in combination with pemetrexed and cisplatin (40%) or carboplatin (60%). Following the first four treatment cycles, patients were assumed to continue treatment with either pembrolizumab as monotherapy dosed at 4 mg/kg every six weeks for up to 17.5 treatment cycles (30%), or pembrolizumab in combination with pemetrexed dosed at 2 mg/kg every three weeks (70%) for up to 35 treatment cycles.

To match Danish clinical practice, we included treatment discontinuation after two years for monotherapy pembrolizumab. In cases where the treatment regimens in the clinical trials differed from the Danish guidelines and clinical expert opinion, the Danish clinical practice was preferred.

Table 29: Monotherapy pembrolizumab

	KEYNOTE-042	Used in the model	Danish clinical practice
Posology	200 mg every third week administered as an intravenous (IV) infusion.	Initial four treatment cycles are dosed at 2 mg/kg every third week. Thereafter, 4 mg/kg is infused every sixth week.	Initial four treatment cycles are dosed at 2 mg/kg every third week. Thereafter, 4 mg/kg is infused every sixth week. Pembrolizumab is administered as an IV infusion over 30 minutes. The first treatment is infused over 30 minutes[a].
Length of treatment	35 treatment cycles	17.4 treatment cycles (corresponding to 2 years)	Patients should be treated with pembrolizumab until disease progression or unacceptable toxicity[b].
The comparator's position in Danish clinical practice	N/A	First-line	First-line

Sources: [a] [23], [b] [22] .Abbreviations: N/A – Not applicable; IV - intravenous.

Table 30: Pembrolizumab in combination with pemetrexed and platinum-based chemotherapy

	KEYNOTE-189	Used in the model	Danish clinical practice)
Posology	Treatment with pemetrexed and a platinum-based chemotherapy together with pembrolizumab	Pembrolizumab is dosed at 2 mg/kg every third week. Pemetrexed is dosed at 500 mg/m^2 BSA every third week, plus	Pembrolizumab is dosed at 500 mg/m^2 BSA administered the first day in 21-day cycles. Pembrolizumab is administered as an IV

	dosed at 200 mg every third week.	either 75 mg/m^2 BSA of cisplatin chemotherapy or 400 mg/m^2 BSA of carboplatin chemotherapy.	infusion for 60 minutes at the first visit and 30 minutes at the following visits. Cisplatin chemotherapy in combination with pemetrexed is dosed at 75 mg/m^2 BSA infused for 1 hour. However, cisplatin is administered together with one litre of NaCl both before and after cisplatin, resulting in a total infusion time of 4 hours. Pemetrexed is dosed at 500 mg/m^2 BSA administered as an IV infusion for 10 minutes. Carboplatin in combination with pembrolizumab and pemetrexed is dosed at 400 mg/m^2 BSA and administered as 30-minute IV infusions, and pemetrexed is dosed at 500 mg/m^2 BSA administered as an IV infusion for 10 minutes[a].
Length of treatment	Initial four treatment cycles followed by maintenance therapy for up to 35 treatment cycles.	Initial four treatment cycles of pembrolizumab + pemetrexed + platinum-based chemotherapy followed by either 35 treatment cycles of pembrolizumab and pemetrexed every third week or 17.5 treatment cycles of pembrolizumab monotherapy every sixth week.	Patients should be treated with pembrolizumab in combination with pemetrexed and platinum-based chemotherapy until disease progression or unacceptable toxicity[b].
The comparator's position in the Danish clinical practice	N/A	First-line	First-line

Source: [a] [23], [b] [22]. Abbreviations: N/A – Not applicable, BSA – body surface area; IV - intravenous.

8.2.2.4 Relative efficacy outcomes

The relative efficacy estimates produced in the naïve comparisons vs KEYNOTE-042 and KEYNOTE-189 (see section 7.1.3) were chosen as the base cases for the CUAs vs pembrolizumab and pembrolizumab in combination with chemotherapy. The Flatiron EDM comparisons and the naïve comparison vs KEYNOTE-024 have been included as sensitivity analyses.

Both the naïve comparisons and the Flatiron EDM comparisons were deemed feasible to include in the economic analysis, since they produce relative efficacy estimates. The naïve comparison was chosen as the base case, as it allows for a comparison of the clinical trial ARROW vs the available clinical trials for pembrolizumab. Since KEYNOTE-042 provides the largest dataset on patients receiving pembrolizumab monotherapy and did not allow for cross-over between treatment arms, this comparison was chosen as base case ahead of KEYNOTE-024. The comparison vs real-life patients in the Flatiron EDM database are however also relevant, due to both the size of the included populations and the fact that it can provide evidence of the real-life efficacy of both comparator regimens. TTD HRs were not reported in the naïve comparisons, and were therefore set equal to PFS HRs.

The HRs from the naïve comparisons as well as the Flatiron EDM analysis for OS, PFS and TTD are presented in Table 31. The proportional hazards assumption is applied to all HRs obtained. Please note that in the model, the direction of the comparisons is changed: the reciprocals of the values presented below are applied in the cost-effectiveness model as the reference treatment in the model is pralsetinib for all comparisons rather than the comparators as the

reference treatment.

For further information on the comparability of KEYNOTE-042, KEYNOTE-024 and KEYNOTE-189, see section 7.1.1 and 7.2.1. For further information of the methodology and limitations of the naïve and the Flatiron EDM comparisons, see section 7.1.3.1.

The relative efficacy estimates from the indirect comparisons are presented in appendix F.

Table 31: Summary of the values of the relative efficacy outcomes

Analysis	Clinical efficacy outcome	Clinical documentation			Used in the model (value)		
		OS [95% CI]	PFS [95% CI]	TTOT [95% CI]	OS [95% CI]	PFS [95% CI]	TTOT [95% CI]
Base case Naïve comparisons	Pralsetinib vs pembrolizumab monotherapy						
	Pralsetinib vs pembrolizumab + pemetrexed + chemotherapy						
Sensitivity analysis Flatiron EDM comparison	Pralsetinib vs pembrolizumab monotherapy						
	Pralsetinib vs pembrolizumab + pemetrexed + chemotherapy						
Sensitivity analysis Naïve comparison KEYNOTE-024	Pralsetinib vs pembrolizumab monotherapy						

Note: HR estimate <1 favours pralsetinib over comparator. Abbreviations: N/A – Not applicable; OS – overall survival; PFS – Progression-free survival; TTOT - Total Time On Treatment; EDM - Enhanced Datamart.

8.2.2.5 Adverse reaction outcomes

The AE rates applied in the health economic model for pralsetinib were sourced from the ARROW trial. For patients receiving pembrolizumab, the AE rates were sourced from the KEYNOTE-042 trial, and for patients receiving pembrolizumab in combination with chemotherapy, AE rates were sourced from the KEYNOTE-189 trial. For each study included for the comparators, AE rates were assessed in the full study population. AEs were included if they were of grade 3 severity or worse and occurred in at least 2% of any arm in the source study.

The adverse events observed in the clinical documentation are presented in Appendix F.

Table 32: Grade 3 serious or severe AEs occurring in ≥2% of patients in the arm of interest

Adverse reaction outcome	Clinical documentation	Used in the model (numerical value)		
		Pralsetinib	PEMB	PEMB + pemetrexed + chemotherapy

Anaemia	**Pralsetinib** AE rates were sourced from the population of treatment-naïve patients in the ARROW trial. **Pembrolizumab** AE rates were sourced from the full population of patients receiving pembrolizumab in the KEYNOTE-042 trial. **Pembrolizumab + pemetrexed + chemotherapy** AE rates were sourced from the full population of patients receiving pembrolizumab in the KEYNOTE-189 trial. (See Appendix E.)	7.76%	0.00%	18.27%
Asthenia		0.00%	0.00%	6.67%
Blood creatine phosphokinase increased		12.93%	0.00%	0.00%
Decreased appetite		0.00%	0.00%	0.00%
Diarrhoea		0.00%	0.00%	5.19%
Dyspnoea		0.00%	0.00%	4.20%
Fatigue		0.00%	0.00%	6.91%
Hypertension		12.07%	0.00%	0.00%
Hyponatraemia		2.59%	0.00%	0.00%
Lymphocyte count decreased		5.17%	0.00%	0.00%
Lymphopenia		5.17%	0.00%	0.00%
Nausea		0.00%	0.00%	3.46%
Neutropenia		7.76%	0.00%	16.05%
Pneumonia		5.17%	7.39%	0.00%
Pneumonitis		5.17%	0.00%	2.96%
Rash		0.00%	0.00%	1.98%
Severe skin reactions		0.00%	0.00%	2.22%
Thrombocytopenia		0.00%	0.00%	8.40%
Vomiting		0.00%	0.00%	3.95%
Neutrophil count decreased		18.97%	0.00%	0.00%
White blood cell count decreased		6.90%	0.00%	0.00%
Acidosis		2.59%	0.00%	0.00%
Lung infection		4.31%	0.00%	0.00%

Abbreviations: PEMB – pembrolizumab; AE – adverse event.

8.3 Extrapolation of relative efficacy

8.3.1 Time-to-event data – summarised

PFS and OS Kaplan–Meier data for pralsetinib were obtained from the ARROW trial IPD (see Appendix E). OS and PFS Kaplan–Meier curves were generated from the time-to-event datasets. Survival estimates for other comparators were generated using HRs. A summary of the steps taken to generate OS and PFS curves for each treatment in the model is shown below:

- Pralsetinib OS and PFS estimates were generated by fitting parametric models to the Kaplan–Meier curves from ARROW.

- For all other treatments, the appropriate HRs from the naïve ITC analysis were applied to the OS and PFS curves for pralsetinib to generate OS and PFS curves for each comparator.

To determine the parametric models to be used for extrapolation of survival estimates for the standard parametric models, the Akaike information criterion (AIC) and Bayesian information criterion (BIC) were considered.

A summary of the AIC and BIC statistics for each parametric model across each treatment in ARROW is presented in Table 33.

Table 33: AIC and BIC for standard parametric models fit to ARROW IPD

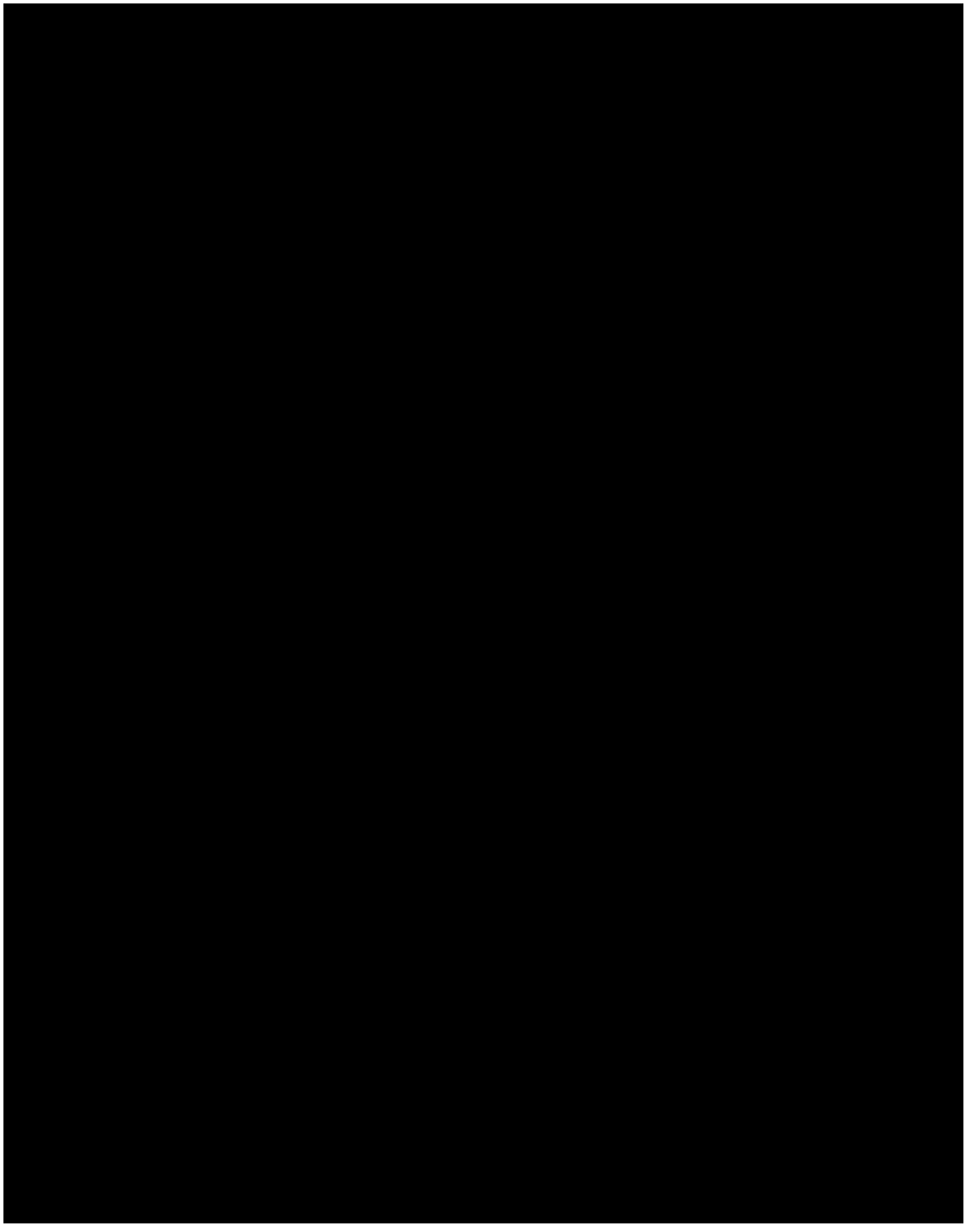
Model	OS		PFS		TTOT	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	[redacted]					
Generalised gamma						
Gompertz						
Log-logistic						
Lognormal						
Weibull						
Gamma						

Abbreviations: AIC - Akaike information criterion; BIC - Bayesian information criterion; OS – overall survival; PFS – progression-free survival; TTOT – total time on treatment.

The exponential model was best-fitting for OS and TTOT according to AIC and BIC, the Log-normal model was best-fitting according to AIC for PFS, and the exponential model was best-fitting according to BIC for PFS.

All parametric models for OS, PFS and TTOT along with the Kaplan–Meier data are presented in Figure 11, Figure 12 and Figure 13.

[redacted]



proportion of transitions across the model time horizon are measured by the extrapolated part of the curves. Given the importance of the extrapolated period to model survival, progression and treatment discontinuation, as well as the large disparity in long-term predictions from the different parametric curves, a key factor in curve selection was long-term clinical plausibility in the extrapolated period.

To inform long-term clinical plausibility of parametric models and to determine the OS, PFS and TTOT curve selections used in the model base case, an advisory board was convened. Clinical experts were asked to predict plausible ranges

for OS, PFS and TTOT for pralsetinib and comparators at landmark periods. Following this, clinicians were shown extrapolations and asked to confirm which were and were not plausible [51]

Pembrolizumab + pemetrexed + chemotherapy and pembrolizumab monotherapy were modelled by applying a hazard ratio from the indirect treatment comparison to the modelled pralsetinib OS. This approach was justified by investigation of the Schoenfeld residuals, which are presented in Appendix G in Figure 46, Figure 47, Figure 48, Figure 48, Figure 49, Figure 50 and Figure 51.

For OS, the exponential and Weibull distributions were deemed the most clinically plausible by the clinical experts. These two distributions represented the most conservative extrapolations and best represented the clinical experts' plausible landmark survival predictions for pralsetinib. The Weibull curve demonstrated a decreasing hazard function over time, which clinical experts suggested is a characteristic that is observed in this patient population [51]
Therefore, Weibull curves were selected as the most clinically plausible curves to represent both pralsetinib and comparator untreated OS and were therefore used in the economic model base case.
The exponential distribution was deemed by the clinical experts to be the most realistic distribution to model long-term PFS for pralsetinib and comparators. Therefore, the exponential curves were selected as the most clinically plausible curves to represent both pralsetinib and comparator untreated PFS and were used in the economic model base case. The hazard function for the Weibull distribution is presented in Figure 41 of Appendix G. In addition, the appendix presents a summary of the process for the clinical validation of the chosen extrapolations.
TTOT is likely to follow similar trends to PFS. The exponential curve accurately predicts TTOT in the ARROW trial at 2 years (28.3% vs 28.5%). Therefore, exponential curves were selected as the most clinically plausible curves to represent both pralsetinib and comparator untreated TTOT in clinical practice and were used in the economic model base case.

Figure 14, Figure 15 and Figure 16 provide a graphical representation of the time-to-event data curves, including both the Kaplan–Meier data and the parametric distributions applied in the base case analysis for both pralsetinib and the two comparators. In addition, Table 34, Table 35 and Table 36 present health state occupancy at relevant time points for patients receiving treatment with pralsetinib, pembrolizumab monotherapy, and pembrolizumab in combination with chemotherapy. From the figures presented below, it becomes evident that the methodology of extrapolating survival estimates for the comparators by applying the estimated HRs provides a reasonably good fit to the observed data from KEYNOTE 042 and KEYNOTE 189, although the observed data deviate slightly beyond 20 months. This was addressed in a sensitivity analysis where the extrapolations with the overall best fit where chosen. Overall best fit was measured by the mean absolute error from the Kaplan-Meier estimates to the extrapolations.
Specifically, this implied choosing the Log-normal distribution for OS and Gompertz distribution for PFS (and TTOT) in the comparison of pralsetinib and pembrolizumab monotherapy and the exponential distribution for OS and the gamma distribution for PFS for the comparison of pralsetinib and pembrolizumab in combination with chemotherapy.

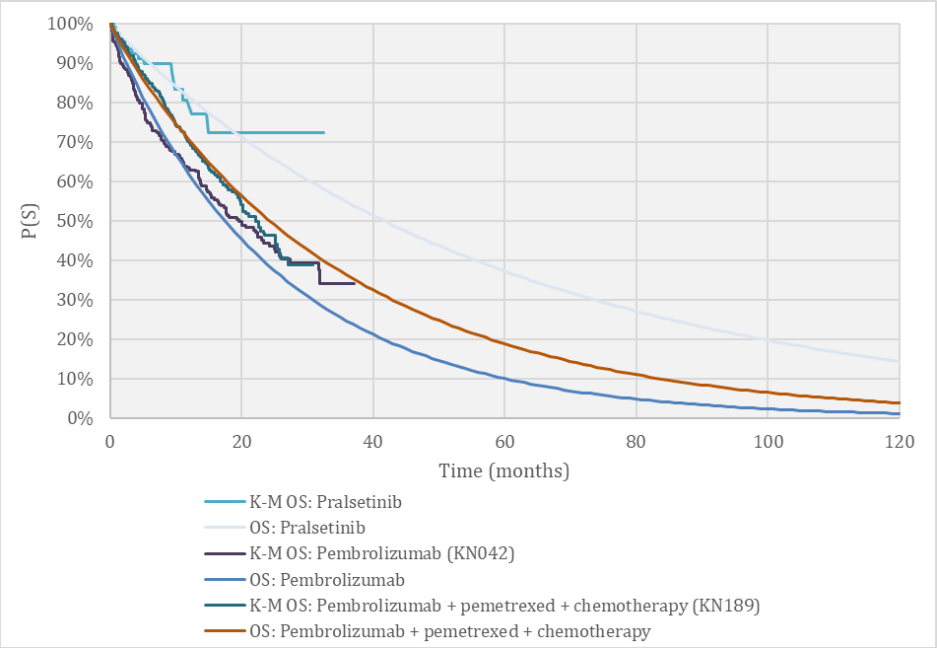


Figure 14: Weibull distribution to model untreated OS for pralsetinib and comparators. Abbreviations: TTOT – total time on treatment; K-M – Kaplan meyer; LCI – lower confidence interval; UCI – upper confidence interval.

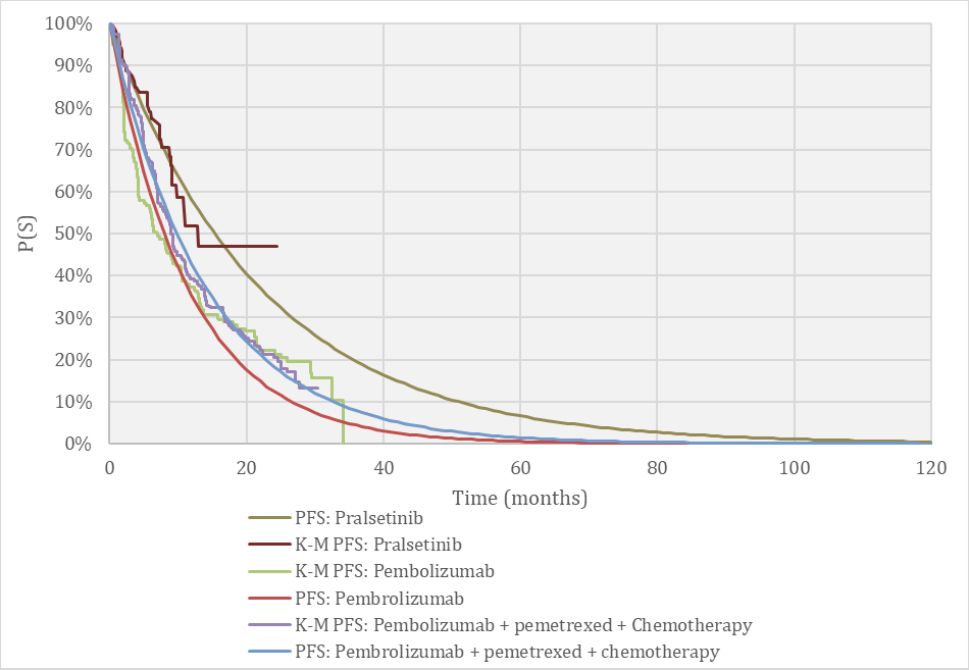
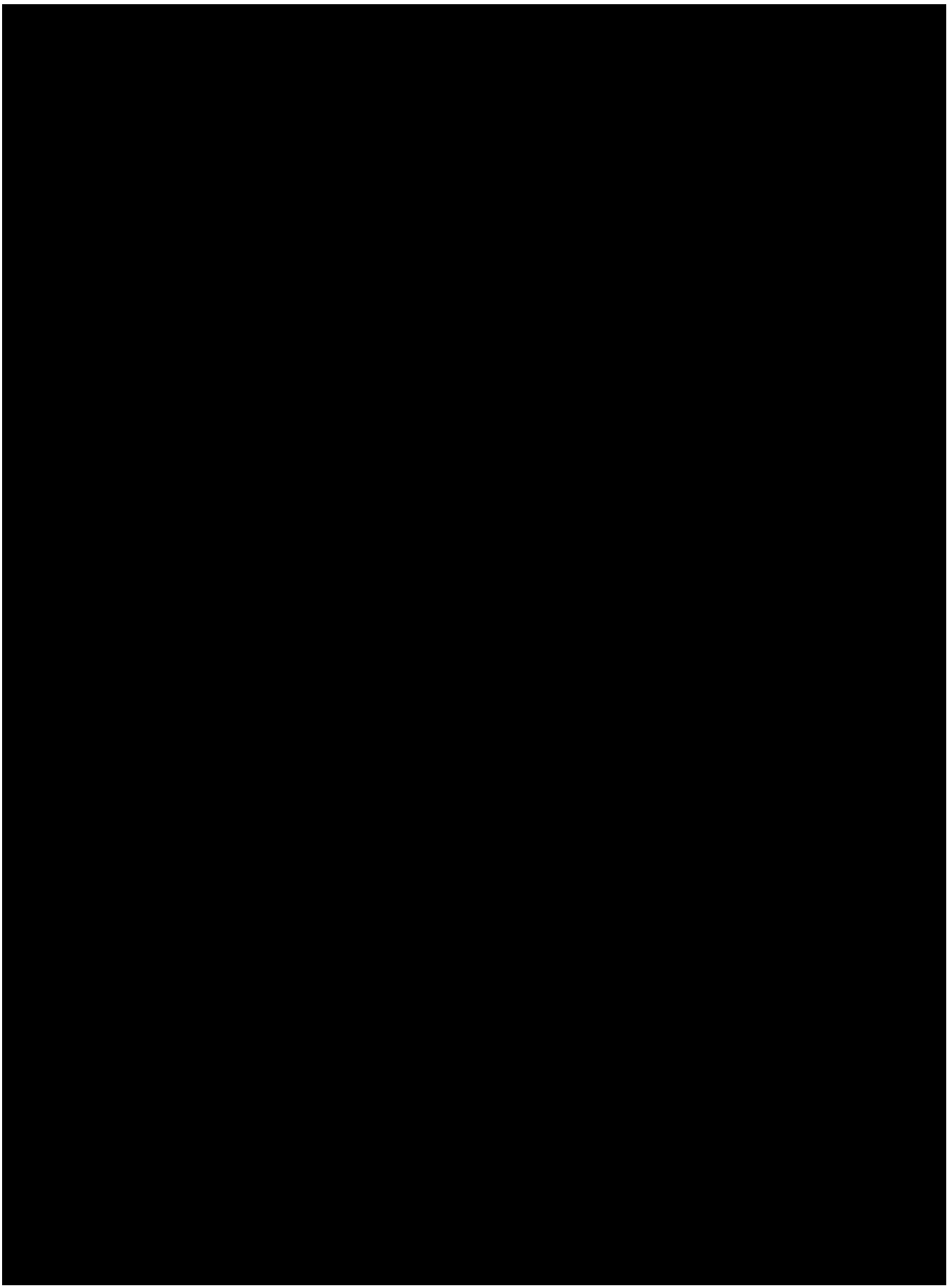


Figure 15: Exponential distribution to model untreated PFS for pralsetinib and comparators. Abbreviations: TTOT – total time on treatment; K-M – Kaplan meyer; LCI – lower confidence interval; UCI – upper confidence interval



[redacted]

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUVs)

In the ARROW trial, the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) was used to obtain HRQoL data, collected directly from RET fusion-positive NSCLC subjects. Patients completed the EORTC QLQ-C30 on day 1 of cycles 1 through 12. If the patient did not complete the questionnaire at cycle 1, day 1 (i.e., for a baseline), they were asked not to complete the questionnaire at subsequent cycles. In total, 74.7% (210/281) of subjects in the unrestricted efficacy population returned an EORTC QLQ-C30 response at baseline, and 69.0% (194/281) returned a response at baseline and had at least one further post-baseline assessment available. [redacted]. However, given the large amount of missing data, utilities were not viewed as robust enough to inform decision-making. Instead, HSUVs were identified in the literature. To identify HSUVs for relevant health states and adverse events, a series of health technology assessment (HTA) -compatible SLRs was performed. The SLRs can be accessed in Appendix H.

No studies were identified in the SLR which reported utility data associated specifically with patients with RET fusion-positive NSCLC. In the absence of RET fusion-positive health state utility data, it was assumed that RET fusion-positive patients do not demonstrate different HRQoL data from advanced NSCLC patients; therefore, advanced NSCLC health state utility values can be used. This assumption has been validated by clinical experts. Due to the anticipated paucity of HSUV data in the population of interest, a search of previous submissions to NICE for treatments of NSCLC in the first and second lines was conducted to investigate potential alternative sources of utility data for the economic model. The population of interest for this search was patients with locally advanced or metastatic NSCLC regardless of mutation status. A total of 14 previous submissions were identified for first-line, and a total of 16 previous submissions were identified for second-line.

For the purpose of documenting HSUVs for the health economic model, it was decided that previous submissions had to be within first-line therapy, given that the utility in patients treated with second-line therapy is likely lower, as their disease might be more progressed. Additionally, previous submissions were of relevance only if the following three criteria were met: I) HSUV data were accessible, II) the source of the HSUV data could be identified and III) HSUV data were accessible for the health states PFS and PD. For the purpose of informing AEs with utility decrements, we first considered previous submissions in first-line therapy and included information from previous submissions in second-line therapy if information was not accessible for first-line. Previous submissions with AE utility decrements data were considered in the assessment if I) utility decrements for AEs were present in the application and II) the source of the utility values could be identified.

A summary of all identified utility values is presented in Appendix K.

8.4.2 Health state utility values used in the health economic model

HSUV were identified in four previous submissions to NICE for the first-line treatments of NSCLC (see Appendix K). Nafees et al. (2008) [49] was the most commonly cited published source of HSUVs in the previous submissions. Additionally, it was preferred that the utilities for both health states be derived from the same source. Thus, in the base case, HSUVs were sourced from Nafees et al. (2008) [49].

The HSUVs used in the model were derived from Nafees et al. (2008), a study in which societal preferences in utility values in the UK for health states related to metastatic NSCLC patients on second-line treatment were reported. The methodology used in Nafees et al. (2008) [49] allowed an estimation of utility scores for varied combinations of disease stage and toxicity. This presents a more realistic approach to patients' experience, as it is likely that patients will experience more than one toxicity at a time and also move between stages of disease. The study adapted existing health state descriptions of metastatic breast cancer developed in a previous study to describe patients receiving second-line treatment for NSCLC. The methodology included a rapid literature review, exploratory interviews with expert physicians and content validation interviews. After development and validation of health states, members of the general public in the UK were recruited for interviews. The interview included two tasks, the visual analogue scale and standard gamble utility methods, which sought to establish people's preferences for different health states of NSCLC. As Nafees et al. 2008 only reported average HSUVs, it was not possible to apply Danish preference weights to the health states. Likewise, it was not possible to generate EQ-5D-5L utilities. No EQ-5D-5L data was identified in the literature nor data that could be mapped to EQ-5D-5L in the literature.

The utility values of all toxicities were supported by some of the qualitative responses from participants.
For several of the AEs, utility decrements were only identified in one previous submission, and this value was applied in the health economic model. For seven of the AEs, more than one submission informed utility values. For six of the AEs for which more than one previous submission stated a utility decrement, the submissions sourced the same study, namely Nafees et al. (2008) [49], and this was applied in the health economic model. For anaemia, data on utility decrements were identified from two different sources. In the health economic model, utility decrements from Nafees et al. (2008) [49] were applied to give the best possible consistency across sources for utility values. For some identified AEs, utility decrements were not identified in the literature. These were recorded as 'no data available'. Additionally, some utility decrements were based on assumptions.

The applied HSUV and utility values associated with relevant AEs are summarised in Table 37.

Table 37: Summary of the HSUVs used in the model

	HSUV	95% CI	Duration (days)	Source (literature search, study, ITC, etc.)
Health states				
Progression-free disease	0.6532	0.6096, 0.6968	N/A	Nafees et al. (2008) [49]
Progressed disease	0.4734	0.3873, 0.5595	N/A	Nafees et al. (2008) [49]
Adverse reaction				
Anaemia	-0.073	-	23.800	Nafees et al. (2008) [49], Duration: Assumption (same as fatigue)
Asthenia	-0.0740	-	23.800	Nafees et al. (2008) [49], Duration: Assumption (same as fatigue)

Blood creatine phosphokinase increased	0.00	N/A	0.000	No data available
Diarrhoea	-0.0470	-0.0772, -0.0164	5.500	Nafees et al. (2008) [49], Duration:
Dyspnoea	-0.07346	-0.1097, -0.03722	15.000	Nafees et al. (2008) [49], Duration: Assumption
Fatigue	-0.0740	-	23.800	Nafees et al. (2008) [49], Duration:
Hypertension	-0.07346	-0.1097, -0.0722	15.000	Nafees et al. (2008) [49], Duration: Assumption
Hyponatremia	-0.0850	-	15.000	KEYNOTE-010 trial, Duration: Assumption
Lymphocyte count decreased	0.00	N/A	0.000	No data available
Lymphopenia	-0.0500	-	15.000	CheckMate 057 trial, Duration: Assumption
Nausea	-0.0850	-	15.000	KEYNOTE-010 trial, Duration: Assumption
Neutropenia	-0.0900	-	15.000	Nafees et al. 2008 [49], Duration: Assumption
Pneumonia	-0.0080	-	15.000	Marti et al. (2013), Duration: Assumption
Pneumonitis	-0.0850	-	15.000	KEYNOTE-010 trial, Duration: Assumption
Rash	0.00	N/A	0.000	No data available
Severe skin reactions	0.00	N/A	0.000	Assumption
Thrombocytopenia	0.00	N/A	0.000	Assumption
Vomiting	-0.0480	-	15.000	Nafees et al. (2008) [49], Duration: Assumption
Neutrophil count decreased	0.00	N/A	0.000	Assumption
White blood cell count decreased	0.00	N/A	0.000	No data available
Acidosis	0.00	N/A	0.000	No data available
Lung infection	0.00	N/A	0.000	No data available

Abbreviations: HSUV - Health state utility values; N/A - not applicable; CI – confidence interval; ITC – indirect treatment comparison.

Although this application concerns a 1L treatment for NSCLC, the utility values from Nafees et al. (2008) [49] have been accepted in previous NICE technical appraisals in first-line treatments for NSCLC. It is therefore deemed acceptable for use in this submission. In order to account for uncertainties regarding the HSUVs, sensitivity analyses were conducted by including the HSUVs reported by Chouaid et al. 2013 [52] in the DSA (see section 8.7.1). Chouaid et al. 2013 has been used as the reference for HSUVs in multiple previous NICE submissions on NSCLC. In addition, we have presented the results from sensitivity analyses where we have applied HSUV from the ARROW trial and used the same utility values that were applied in the assessment of selpercatinib for the treatment of RET fusion-positive NSCLC

[redacted]

Age adjustments

As the time horizon of the model is measured in years, it was important to consider the impact of age- and sex-related disutility. The regression algorithm from Ara and Brazier 2010 was used to generate utility multipliers to decrease baseline utility as patient's age within the model. The general population utility for the modelled population as they entered the model (0.813, assuming a mean population age of 63 years, 47.7% of which were male) was used to generate utility multipliers using the utilities recorded in the trial, which were applied back to the general population utility for each cycle of the model as shown below in Table 38.

Table 38: Implementation of Ara and Brazier general population utility algorithm using utility values from Nafees et al. (2008)

Data	Pre-progression	Post-progression
Utility from Nafees et al. (2008) [49]	0.653	0.473
General population utility on model entry	0.813	0.813
Calculated utility multiplier	0.803	0.582

8.5 Resource use and costs

In this section, we present the identified use of resources and the applied unit costs. Overall, the resource use and the estimated costs included in this analysis can be categorised as:

- Drug costs
- Hospital costs
- Patient and transportation costs

Furthermore, the hospital costs include the following elements:

- Drug administration costs
- Health state costs
- Adverse event costs
- Test costs for RET fusion-positive NSCLC
- End-of-life costs

In the CU model, drug costs and drug administration costs in total are denoted as treatment costs. In this section, drug costs are presented for first-line therapies and for subsequent therapies. Since subsequent treatments are not included in the model base case, drug administration costs are only presented for first-line treatments. Administration costs associated with subsequent therapies can be found in the 'Subsequent treatments' sheet of the model.

Patients with NSCLC are treated entirely in the hospital sector. Thus, the analysis does not include healthcare costs in the primary care sector. Municipal costs are not included in the analysis. Patients with NSCLC will most likely incur municipal costs (e.g., home care). However, we have not identified data documenting differences in municipal costs between treatments. Hence, municipal costs are ignored, as the incremental costs between treatments are assumed to be very low.

8.5.1 Drug costs

First-line

First-line treatments include pralsetinib, pembrolizumab (monotherapy), and pembrolizumab in combination with pemetrexed and platinum-based chemotherapy.

- Pralsetinib 100 mg capsules are administered orally once daily (400 mg/day). A treatment cycle is defined as 30 days for patients treated with pralsetinib. This is based on an expected Danish clinical practice of handing out two packages of pralsetinib at a time (amounting to 30 days treatment supply).
- Pembrolizumab as monotherapy is administered intravenously every three weeks (2 mg/kg) for the first four treatment cycles and thereafter every sixth week (4 mg/kg). In the model, pembrolizumab monotherapy is administered every sixth week (4 mg/kg) for all treatment cycles. This represents a conservative approach, since this assumption implies fewer consultations and thereby lower costs for patients treated with pembrolizumab as monotherapy.
- Pembrolizumab (2 mg/kg) given in combination with pemetrexed (500 mg/m^2 BSA) and platinum-based chemotherapy is administered every three weeks. Platinum-based chemotherapy is cisplatin (75 mg/m^2) or carboplatin (500 mg/m^2). In the model, a 40/60 distribution is assumed.

Following the current treatment guidelines, patients with NSCLC and PD-L1-expression ≥50% should receive treatment with pembrolizumab (monotherapy) until disease progression or experiencing toxic adverse events, for a maximum treatment length of two years [1,15]. Similarly, patients with NSCLC and PD-L1 expression of <50% should receive treatment with pembrolizumab in combination with pemetrexed and cisplatin or carboplatin for the first four treatment cycles (i.e., 12 weeks) [1,15]. Based on clinical expert opinion, 70% of the patients continue treatment with pembrolizumab and pemetrexed following the first four treatment cycles, whereas the remaining 30% continue treatment with pembrolizumab monotherapy [23].

Table 39 provides an overview of the applied medicine prices and dosing regimens for each individual medication included. Pralsetinib is not yet registered in "Taksten" so the model applies a placeholder list price. Table 40 presents the cost per model cycle for patients treated with pralsetinib and for patients receiving one of the comparison treatments. Treatment costs were calculated based on a mean body weight of 65.5 kg and a mean BSA of 1.75 m2 reported in the ARROW trial. In addition, in the base case scenario, no vial sharing is assumed (i.e., waste is included).

Table 39: Unit costs and dosing regimens applied in the model

Treatment	Strength	Pack size	Dose	Price (AIP), DKK
Pralsetinib	[redacted]			
Pembrolizumab	100 mg/vial	1 vial	4 mg/kg Q6W 2 mg/kg Q3W	23,204.61
Pemetrexed	500 mg/vial	1 vial	500 mg/m^2 Q3W	4,724.06
Cisplatin	100 mg/vial	1 vial	75 mg/m^2 Q3W	200.00
Carboplatin	450 mg/vial	1 vial	400 mg/m^2 Q3W	203.00

Sources: [54] and Roche (Placeholder AIP for pralsetinib). Abbreviations: Q3W - once every 3 weeks.

Table 40: Drug cost per model cycle applied in the model

Treatment	Cost per model cycle, DKK
Pralsetinib	[redacted]
Pembrolizumab	47,329
Pembrolizumab + pemetrexed + platinum-based chemotherapy	
Including platinum-based chemotherapy (first four series)	59,628
Pembrolizumab monotherapy (subsequent model cycles, 30%)	59,205
Pembrolizumab + pemetrexed (subsequent model cycles, 70%)	55,642

Subsequent therapy costs

Costs related to subsequent therapies are not included in the base case but are instead explored in a sensitivity analysis. Following Danish treatment guidelines, patients receiving pembrolizumab as first-line therapy should be initiated on treatment with platinum-based chemotherapy after disease progression. Similarly, the recent DMC recommendation of selpercatinib states that patients who have received pembrolizumab in combination with platinum-based chemotherapy as first-line treatment should be initiated on selpercatinib after disease progression. The clinical expert assessed that patients who receive pralsetinib as first-line therapy will most likely be initiated on subsequent treatment based on their performance status (PS). Patients with PS 0-1 will receive immunotherapy (atezolizumab) as second-line therapy, whereas patients with PS > 1 will receive platinum-based chemotherapy. It was assessed by the clinical expert that patients would be equally distributed across PS 0-1 and PS >1 following disease progression [16,23].

Finally, the clinical expert assessed that 40-45% of patients who experienced disease progression would not receive any subsequent treatment [23]. 42.5% are allocated to "No treatment" for each first-line treatment.
Table 41 provides an overview of the included therapies conditioned on the first-line treatment.

Table 41: Subsequent therapies, distribution

		Subsequent therapy				
First-line treatment	**Docetaxel**	**Platinum-based chemotherapy**	**Pembrolizumab**	**Atezolizumab**	**Selpercatinib**	**No treatment**
Pralsetinib	0%	28.75%	0%	28.75%	0%	42.5%
Pembrolizumab	0%	57.5%	0%	0%	0%	42.5%
Pembrolizumab, pemetrexed & cisplatin/carboplatin	0%	0%	0%	0%	57.5%	42.5%

Sources: [16,23].

For cisplatin and carboplatin, the dosing is equivalent to the dosing for first-line treatment.. Atezolizumab (1,200 mg) is administered intravenously every third week. The price (AIP) of atezolizumab is DKK 21,799.09 for 840 mg [54]. Selpercatinib 160 mg is administered orally twice daily (320 mg/day). A treatment cycle is defined as 28 days, cf. the

Danish selpercatinib HTA submission [55]. The price (AIP) is DKK 72,618 for 112 capsules of 80 mg (collected in April 2022).

Table 42 provides an overview of the treatment duration and cost per cycle of the subsequent therapies. Treatment duration for docetaxel and atezolizumab was based on the findings from the OAK trial [56], who found a median treatment duration of 2.1 months for second-line treatment with docetaxel and 3.4 months for second-line treatment with atezolizumab. As no source could be identified for second-line use of platinum-based chemotherapy, the treatment length of docetaxel was used as a proxy for chemo-based regimens. Treatment duration for selpercatinib was based on data from the LIBRETTO-001 study, who found a median time on treatment of 10.12 months [57]

The costs of the cycles of subsequent therapies were incurred as a one-time cost at the time of progression.

Table 42: Treatment duration and cost, subsequent therapies

Therapy	Treatment duration (number of model cycles)*	Drug cost per model cycle, DKK	Total administration cost, DKK	Total cost of patient time, DKK	Total transportation cost, DKK
Platinum-based chemotherapy	2.1	585	69,514	2,601	809
Atezolizumab	3.4	47,394	82,486	2,586	939
Selpercatinib	10.12	78,940	73,072	5,632	2,400

*Sources: Clinical expert; and Rittmeyer, 2019; and EMA, Retsevmo, INN-selpercatinib, Assessment report, 2020.

8.5.2 Hospital costs

Administration and monitoring costs

For the assessment of drug administration costs including consultations and monitoring visits, a distinction was made in the model between the first three treatment cycles and the consecutive treatment cycles [23].

Table 43 presents patients' healthcare resource use associated with treatment and monitoring, by treatment cycles. The applied resource use and unit costs associated with drug administration for the subsequent therapies can be seen in the 'Subsequent Treatments' sheet in the model.

8.5.2.1 Pralsetinib

First treatment cycle: Days 0-30

Based on clinical expert opinion, patients receiving pralsetinib undergo an electrocardiogram (EKG), blood test, bronchoscopy and PET-CT scan to establish baseline values and status prior to treatment initiation. Following this, patients have a first consultation with an oncologist where the patient is informed about the procedure for the offered treatment.

Patients treated with pralsetinib undergo a blood test which is followed by a consultation at the oncology department two weeks after treatment initiation [23].

Second treatment cycle: Days 31-60

Six weeks after treatment initiation, patients treated with pralsetinib undergo a blood test which is followed by a consultation at the oncology department [23].

Third treatment cycle: Days 61-90

Two months after treatment initiation, patients treated with pralsetinib undergo a CT scan to monitor disease progression. In addition, during treatment cycle three, patients treated with pralsetinib undergo yet another blood test which is followed by a consultation at the oncology department [23].

Subsequent treatment cycles: Days >90

In all subsequent treatment cycles, patients undergo a blood test at the same time as they collect their treatment in the clinic. In addition to this, patients have one consultation with an oncologist and one CT scan for monitoring disease progression every third month [23].

8.5.2.2 Pembrolizumab monotherapy

First treatment cycle: Days 0-42

Similar to patients treated with pralsetinib, patients receiving pembrolizumab as monotherapy undergo an EKG, blood test, bronchoscopy and PET-CT scan to establish baseline values and status prior to treatment initiation. Following this, patients have a first consultation with an oncologist where the patient is informed about the procedure for the offered treatment.

Patients treated with pembrolizumab undergo a blood test which is followed by a consultation at the oncology department and treatment administration [23].

Second treatment cycle: Days 43-84

In the second treatment cycle, patients treated with pembrolizumab undergo a blood test which is followed by a consultation at the oncology department and treatment administration.

Two months after treatment initiation, patients undergo a CT scan to monitor disease progression [23].

Third treatment cycle: Days 85-126

In the third treatment cycle, patients undergo a blood test which is followed by a consultation at the oncology department and treatment administration [23].

Subsequent treatment cycles: Days >126

In all subsequent treatment cycles, patients treated with pembrolizumab undergo a blood test which is followed by a consultation at the oncology department and treatment administration. In addition to this, patients undergo one CT scan for monitoring disease progression every third month (0.47 times per treatment cycle) [23].

8.5.2.3 Pembrolizumab in combination with platinum-based chemotherapy

First treatment cycle: Days 0-21

Patients receiving pembrolizumab in combination with platinum-based chemotherapy undergo an EKG, blood test, bronchoscopy and PET-CT scan to establish baseline values and status prior to treatment initiation. Following this, patients have a first consultation with an oncologist where the patient is informed about the procedure for the offered treatment.

Hereafter, patients receiving pembrolizumab in combination with platinum-based chemotherapy undergo a blood test which is followed by a consultation at the oncology department and treatment administration [23].

Second treatment cycle: Days 22-42

In the second treatment cycle, patients undergo a blood test which is followed by a consultation at the oncology department and treatment administration [23].

Third treatment cycle: Days 43-63

In the third treatment cycle, patients undergo a blood test which is followed by a consultation at the oncology department and treatment administration.

Two months after treatment initiation, patients treated with pembrolizumab in combination with platinum-based chemotherapy undergo a CT scan to monitor disease progression [23].

Subsequent treatment cycles: Days >63

In all subsequent treatment cycles, patients treated with pembrolizumab in combination with platinum-based chemotherapy undergo a blood test, which is followed by a consultation at the oncology department and treatment administration. In addition to this, patients undergo one CT scan for monitoring disease progression every third month (0.23 times per treatment cycle) [23].

Table 43: Drug administration: resource use and unit costs (first-line)

Treatment	Treatment cycle	Activity	Resource use per treatment cycle	Unit cost, DKK*	Source (unit costs)*
Pralsetinib	1	EKG/blood test	1	1,482	DRG 23MA04
		PET-CT scan	1	3,081	DRG 36PR06
		Bronchoscopy	1	6,322	DRG 04MP09
		First consultation	1	3,203	DRG 17MA98
		Consultation	1	3,203	DRG 17MA98
		Blood test	1	1,482	DRG 23MA04
	2	Blood test	1	1,482	DRG 23MA04
		Consultation	1	3,203	DRG 17MA98
	3	Blood test	1	1,482	DRG 23MA04
		Consultation	1	3,203	DRG 17MA98
		CT scan	1	2,007	DRG 30PR06
	Subsequent cycles	Blood test	1	1,482	DRG 23MA04
		Consultation	0.33	3,203	DRG 17MA98
		CT scan	0.33	2,007	DRG 30PR06
Pembrolizumab	1	EKG/blood test	1	1,482	DRG 23MA04
		PET-CT scan	1	3,081	DRG 36PR06
		Bronchoscopy	1	6,322	DRG 04MP09
		First consultation	1	3,203	DRG 17MA98

		Consultation/ administration	1	17,556	DRG 27MP21
		Blood test	1	1,482	DRG 23MA04
	2	Blood test	1	1,482	DRG 23MA04
		Consultation/ administration	1	17,556	DRG 27MP21
		CT scan	1	2,007	DRG 30PR06
	3	Blood test	1	1,482	DRG 23MA04
		Consultation/ administration	1	17,556	DRG 27MP21
	Subsequent cycles	Blood test	1	1,482	DRG 23MA04
		Consultation/ administration	1	17,556	DRG 27MP21
		CT scan	0.47	2,007	DRG 30PR06
Pembrolizumab, pemetrexed & platinum-based chemotherapy	1	EKG/blood test	1	1,482	DRG 23MA04
		PET-CT scan	1	3,081	DRG 36PR06
		Bronchoscopy	1	6,322	DRG 04MP09
		First consultation	1	3,203	DRG 17MA98
		Consultation/ administration	1	17,556	DRG 27MP21
		Blood test	1	1,482	DRG 23MA04
	2	Blood test	1	1,482	DRG 23MA04
		Consultation/ administration	1	17,556	DRG 27MP21
	3	Blood test	1	1,482	DRG 23MA04
		Consultation/ administration	1	17,556	DRG 27MP21
		CT scan	1	2,007	DRG 30PR06
	Subsequent cycles	Blood test	1	1,482	DRG 23MA04
		Consultation/ administration	1	17,556	DRG 27MP21
		CT scan	0.23	2,007	DRG 30PR06

*Source: 2021 DRG tariffs [58] CT - computed tomography; EKG – Electrocardiogram; PET - Positron emission tomography.

Health state costs

In addition to treatment-specific administration and monitoring costs, the model allows the user to insert costs related to general best supportive care and healthcare resource utilisation within the progression-free and progressed disease states and upon entrance into the death state. Based on input from the clinical expert, we assume that all

relevant costs are captured in the treatment-specific administration and monitoring costs, hence no additional health state costs are applied. Table 44 and Table 45 summarises the health state costs from the model.

Table 44: Health state costs, progression-free disease state

	Share of patients	Annual resource use	Unit per cycle	Unit cost, DKK*	Source (unit cost)*	Total cost per cycle, DKK
Oncology visit	0%	0	0	3,203	DRG 17MA98	0
Nurse visit	0%	0	0	3,203	DRG 17MA98	0
Blood test	0%	0	0	1,482	DRG 23MA04	0
CT scan	0%	0	0	2,007	DRG 30PR06	0
PET scan	0%	0	0	3,081	DRG 36PR06	0

*Source: 2021 DRG tariffs [58]

Table 45: Health state costs, progressed disease state

	Share of patients	Annual resource use	Unit per cycle	Unit cost, DKK*	Source (unit cost)*	Total cost per cycle, DKK
Oncology visit	0%	0	0	3,203	DRG 17MA98	0
Nurse visit	0%	0	0	3,203	DRG 17MA98	0
Blood test	0%	0	0	1,482	DRG 23MA04	0
CT scan	0%	0	0	2,007	DRG 30PR06	0
PET scan	0%	0	0	3,081	DRG 36PR06	0

*Source: 2021 DRG tariffs [58]

Adverse event costs

An overview of the observed and included AEs for pralsetinib, pembrolizumab (monotherapy), and pembrolizumab in combination with pemetrexed and platinum-based chemotherapy is presented in Table 46. In addition, the table presents the applied unit cost for each AE. The AE costs are considered for the first model cycle only; this is because AEs would manifest rapidly after treatment initiation and would either resolve rapidly (i.e., within a single model cycle) or be cause for discontinuation. Thus, given the AE rates and the unit cost per AE, a weighted AE cost per comparator is estimated (see Table 47).

Table 46: Adverse event rates and costs

Event	Unit cost, DKK*	Source*	Rate (pralsetinib)	Rate (pembrolizumab)	Rate (pembrolizumab, pemetrexed & cisplatin/ carboplatin)	Patient time, hours (see section 8.5.4)**
Anaemia	3,114	DRG 16MA98	7.8%	0.0%	18.3%	2
Asthenia	3,987	DRG 23MA03	0.0%	0.0%	6.7%	2

Blood creatine phosphokinase increased	0		12.9%	0.0%	0.0%	0
Diarrhoea	5,130	DRG 06MA11	0.0%	0.0%	5.2%	2
Dyspnoea	1,732	DRG 04MA98	0.0%	0.0%	4.2%	2
Fatigue	3,987	DRG 23MA03	0.0%	0.0%	6.9%	2
Hypertension	1,518	DRG 10MA98	12.1%	0.0%	0.0%	2
Hyponatraemia	1,518	DRG 10MA98	2.6%	0.0%	0.0%	2
Lymphocyte count decreased	3,114	DRG 16MA98	5.2%	0.0%	0.0%	2
Lymphopenia	3,114	DRG 16MA98	5.2%	0.0%	0.0%	2
Nausea	0		0.0%	0.0%	3.5%	0
Neutropenia	3,114	DRG 16MA98	7.8%	0.0%	16.0%	2
Pneumonia	36,514	DRG 04MA13	5.2%	7.4%	0.0%	288
Pneumonitis	36,514	DRG 04MA13	5.2%	0.0%	3.0%	288
Rash	1,735	DRG 09MA98	0.0%	0.0%	2.0%	2
Severe skin reactions	1,735	DRG 09MA98	0.0%	0.0%	2.2%	2
Thrombocytopenia	35,483	DRG 16MA03	0.0%	0.0%	8.4%	288
Vomiting	5,130	DRG 06MA11	0.0%	0.0%	4.0%	2
Neutrophil count decreased	22,545	DRG 16MA10	19.0%	0.0%	0.0%	216
White blood cell count decreased	3,114	DRG 16MA98	6.9%	0.0%	0.0%	2
Acidosis	1,518	DRG 10MA98	2.6%	0.0%	0.0%	2
Lung infection	36,514	DRG 04MA13	4.3%	0.0%	0.0%	288

Table 47: Weighted adverse event costs

Sector	Pralsetinib, DKK	Pembrolizumab, DKK	Pembrolizumab pemetrexed & cisplatin/carboplatin, DKK

Hospital	10,909	2,698	6,285

Testing costs for RET fusions

The implementation of NGS testing in NSCLC has been ongoing for several years, with a larger and larger proportion of patients undergoing NGS testing as a standard diagnostic tool when diagnosed with metastatic NSCLC. This is in line with current ESMO guidelines, which recommend NGS testing for metastatic NSCLC [12]. The scientific committee provided an estimate of the degree of implementation in the recent assessment of selpercatinib in 2L NSCLC, with NGS being used for 75% of the NSCLC patient population [14].

Overall, the use of NGS testing will likely continue to increase within lung cancer over the coming years until reaching full coverage. This implementation has so far happened independently of pralsetinib, and it is not deemed realistic that a DMC approval of pralsetinib in itself will be the main driver for full NGS coverage. For this reason, assigning the cost of NGS to the pralsetinib arm alone would likely result in an overestimation of the incremental costs. Based on this rationale, testing costs are not included in the base case, but the impact of these costs has been explored in a sensitivity analysis.

The sensitivity analysis uses the approach taken by the DMC in the assessment of selpercatinib [14] in order to assess the scenario with the full impact of test costs. In this analysis, the costs of NGS are applied to the remaining 25% not yet being tested with NGS. An NGS test is assumed to cost approximately DKK 5,000 with a yearly incidence for RET fusions being 1.5%. Test costs are applied as a one-time cost. Table 48 presents the applied test costs.

Table 48: Test costs for RET fusion-positive NSCLC in sensitivity analysis

Cost component	Costs, DKK
Cost per test	5,000
Proportion who are RET fusion-positive	1.5%
RET fusion genetic test cost per RET fusion-positive patient	333,333
Proportion of RET fusion test costs assigned to pralsetinib	25.0%
RET fusion genetic test cost per pralsetinib patient	83,333

Sources: [14,23] Rearranged during transfection.

End-of-life costs

In the model, end-of-life costs in terms of palliative care (e.g., at a hospice) are not included. However, terminal patients typically receive palliative radiation therapy. We have included the cost of palliative radiation therapy of DKK 93,155 (DRG 27MP05) as an end-of-life cost when entering the PPS state [58]

8.5.3 Patient and transportation costs

According to the DMC guidelines, patient time cost and transportation cost are included. The applied unit cost for patient time is DKK 179 per hour and for transportation is DKK 100 for transportation (round trip) for each hospital contact [59] and DKK 35.2 per primary sector contact (assuming a distance of 5 km to the GP at a cost of DKK 3.52 per

km) [59]. In Table 62, the estimated patient time spent for different activities is presented. Hence, the cost of every hour spent is DKK 179. All time estimates include 30 minutes of transportation time unless otherwise stated.

The applied patient time associated with drug administration for the subsequent therapies can be seen in the 'Subsequent Treatments' sheet in the model.

Patient time associated with the treatment of adverse events is presented in Table 46. For adverse events treated in an outpatient setting (corresponding to a resource use of one outpatient contact), the patient time spent is assumed to be 2 hours. For adverse events leading to an admission (i.e., pneumonia, pneumonitis, thrombocytopenia, neutrophil count decreased and lung infection), the patient time spent is estimated as the expected length of admission in days multiplied by 24 hours. The expected length of admission is assumed to be the 'trimpunkt' (the maximum length of stay included in the DRG tariff) minus 1 day.

Table 49: Estimates for patient time

	Patient time (minutes)*
Drug administration	
Pralsetinib	
EKG/blood test	75
PET-CT scan	60**
Bronchoscopy	60**
First consultation/administration	90
Consultation	75
Blood test	45
Consultation/administration	75
CT scan	60**
Pembrolizumab	
EKG/blood test	75
PET-CT scan	60**
Bronchoscopy	60**
First consultation	150
Consultation/administration	75
Blood test	45
CT scan	60**
Pembrolizumab, pemetrexed and platinum-based chemotherapy	
EKG/blood test	75
PET-CT scan	60**
Bronchoscopy	60**

First consultation	150
Consultation/administration	75
Blood test	45
CT scan	60**
Adverse events	
Patient time estimates are presented in Table 46.	

*Sources: Clinical expert [23] and assumptions. **Estimate does NOT include 30 minutes of transportation time. Abbreviations: CT - computed tomography; EKG – Electrocardiogram; PET - Positron emission tomography.

8.6 Results

In this section, we present the results of the CU analysis for pralsetinib compared to pembrolizumab as monotherapy and pembrolizumab in combination with platinum-based chemotherapy. The overall approach to the model is to estimate the cost per QALY. We have estimated the ICERs for pralsetinib relative to the relevant comparators.

8.6.1 Base case overview

Table 50 provides an overview of the base case used in the health economic model.

Table 50: Base case overview

Model setting	Base case input
Comparators	Pembrolizumab Pembrolizumab in combination with chemotherapy
Type of model	Partitioned survival model
Time horizon	20 years (lifetime)
Treatment line	First-line. Subsequent treatment lines not included.
Relative efficacy estimates	A naïve indirect treatment comparison was conducted (without performing any adjustment) using aggregate-level data from KEYNOTE-042 and KEYNOTE-189. Comparator / OS HR / PFS HR / TTOT HR Pembrolizumab Pembrolizumab + pemetrexed + chemotherapy [redacted]
Health related quality of life	Health state utility values were identified from a literature search of previous submissions to NICE for treatments of NSCLC in the first and second lines to investigate potential alternative sources of utility data for the economic model. The following HSUVs were applied: ***Progression-free disease:*** 0.6532 ***Progressed disease:*** 0.4734
Included costs	We have included the following cost components in the model: Drug costs Hospital costs

<table>
<tr><td></td><td>Administration and monitoring costs
Costs of adverse events
Terminal care costs
Patient and transportation costs</td></tr>
<tr><td>Dosage of pharmaceuticals</td><td>The following dosages were applied in the model base case<table><tr><th>Treatment</th><th>Dosage</th><th>Frequency</th></tr><tr><td>Pralsetinib</td><td>400 mg</td><td>QD</td></tr><tr><td>Pembrolizumab</td><td>4 mg/kg</td><td>Q6W</td></tr><tr><td>Pembrolizumab + pemetrexed + chemotherapy</td><td>Pembrolizumab: 2 mg/kg
Pemetrexed: 500 mg/m^2
Cisplatin: 75 mg/m^2
Carboplatin: 500 mg/m^2</td><td>Q3W</td></tr></table></td></tr>
<tr><td>Median time on treatment</td><td>Total time on treatment was extrapolated using the exponential parametric distribution.<table><tr><th>Treatment</th><th>Median time on treatment</th></tr><tr><td>Pralsetinib
Pembrolizumab
Pembrolizumab + pemetrexed + chemotherapy</td><td>[redacted]</td></tr></table></td></tr>
<tr><td>Parametric function for PFS</td><td>Intervention: Exponential
Comparator: Exponential</td></tr>
<tr><td>Parametric function for OS</td><td>Intervention: Weibull
Comparator: Weibull</td></tr>
</table>

Abbreviations: HSUV - Health State Utility Values; NICE - The National Institute for Health and Care Excellence; NSCLC - Non-small cell lung cancer; OS – overall survival; PFS – progression-free survival; QD - once a day; Q6W – once every 6 weeks; TTOT - Total Time On Treatment.

8.1.1 Base case results

In this section, we present the results from the CU analysis on pralsetinib compared to pembrolizumab monotherapy (presented in Table 51) and pembrolizumab combined with platinum-based chemotherapy and pemetrexed (presented inTable 52) in patients with RET fusion-positive NSCLC.

The QALYs associated with pralsetinib are [redacted] and the total cost of patients treated with first-line pralsetinib is DKK [redacted]. The QALYs associated with pembrolizumab monotherapy are [redacted] and the total cost of patients treated with first-line pembrolizumab monotherapy is DKK [redacted] The QALYs associated with pembrolizumab in combination with chemotherapy are [redacted] and the total cost of patients treated with first-line pembrolizumab in combination with chemotherapy is DKK [redacted]

The ICER of pralsetinib compared to pembrolizumab monotherapy is [redacted] and the ICER of pralsetinib compared to pembrolizumab in combination with chemotherapy is [redacted] which indicates that treatment with pralsetinib is dominant against pembrolizumab in combination with chemotherapy.

Table 51: Base case results on pralsetinib compared to pembrolizumab monotherapy

Per patient	Pralsetinib	Pembrolizumab monotherapy	Difference
Mean life years gained			
Total life years gained (discounted)	[redacted]		
Life years gained in progression-free health state (undiscounted)			
Life years gained in progressed health state (undiscounted)			
QALYs			
Total QALYs (discounted)			
QALYs in progression-free health state (discounted)			
QALYs in progressed health state (discounted)			
Costs (DKK)			
Total costs			
Drug costs			
Hospital sector costs			
Patient time and transport costs			
Adverse reaction costs			
ICER			
Incremental results	**Intervention vs comparator**		
ICER (per QALY)	[redacted]		

Abbreviations: ICER - Incremental Cost Effectiveness Ratio; QALY – Quality-adjusted life year.

Table 52: Base case results on pralsetinib compared to pembrolizumab combined with chemotherapy

Per patient	Pralsetinib	Pembrolizumab + pemetrexed + chemotherapy	Difference
Mean life years gained			
Total life years gained (discounted)	[redacted]		
Total life years gained (undiscounted)			
Life years gained in progression-free health state (undiscounted)			

Life years gained in progressed health state (undiscounted)	[redacted]
QALYs	
Total QALYs (discounted)	
QALYs in progression-free health state (undiscounted)	
QALYs in progressed health state (undiscounted)	
Costs (DKK)	
Total costs	
Drug costs	
Hospital sector costs	
Patient time and transport costs	
Adverse reaction costs	
ICER	
Incremental results	**Intervention vs comparator**
ICER (per QALY)	[redacted]

Abbreviations: ICER - Incremental Cost Effectiveness Ratio; QALY – Quality-adjusted life year.

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

Uncertainty in the input parameters in the health economic model has been explored through extensive sensitivity and scenario analyses. Functionality is included in the model to enable input parameters to be varied systematically in order to evaluate their influence on the ICER. Depending on the type of parameter or assumption tested, the options are set differently (one-way sensitivity analyses or scenario analyses).

In the deterministic sensitivity analyses, all input parameters were adjusted by +/- 10% except for vial wastage, testing costs, utilities, HR sources for pembrolizumab and pembrolizumab + pemetrexed + chemotherapy and subsequent treatments, which were adjusted based on assumption of wastage, inclusion of testing costs, sourced study, applied indirect comparison and inclusion of subsequent treatments, respectively.
Furthermore, as presented in section 8.3 the Kaplan-Meier estimates from KN189 and KN042 were compared to the extrapolations of PFS and OS. In scenario analyses, the extrapolations for PFS and OS with the best fit to the KM data for both pembrolizumab monotherapy and pembrolizumab in combination with platinum-based chemotherapy was tested.

In Table 53, we present the results from the deterministic sensitivity analyses for the comparison between pralsetinib and pembrolizumab monotherapy, and inTable 54, we present the results from the deterministic sensitivity analyses for the comparison between pralsetinib and pembrolizumab in combination with chemotherapy.

In addition to this, Figure 17 and Figure 18 present the tornado diagram for the 10 parameters from the DSA that affect the estimate of the ICER the most for the comparison of pralsetinib and pembrolizumab monotherapy and for the comparison between pralsetinib and pembrolizumab in combination with chemotherapy.

Finally, Figure 19 presents the ICER estimated with different values for the price of pralsetinib, varying from 100% (maximum AIP) to as low as to a point where the ICER becomes dominant.

Table 53: One-way sensitivity and scenario analyses results for the comparison between pralsetinib and pembrolizumab monotherapy

	Change	Reason/ rationale/ source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	[redacted]		
Vial wastage	Vial sharing	N/A			
Utilities	Chouaid	N/A			
	Selpercatinib submission	N/A			
	ARROW trial	N/A			
HR source pembrolizumab	Wild-type EDM flatiron	N/A			
	Naïve comparison KEYNOTE-024	N/A			
Test costs	Including cost of testing	N/A			
Subsequent therapies	Including cost of subsequent therapies	N/A			
Extrapolations best fitting KM curves from KN-042*	OS: Generalised gamma PFS/TTNT: Exponential	N/A			
RET fusion additional HR	[redacted]	Minus 10%			
		Plus 10%			

HR pembrolizumab OS: Naïve treatment comparison	[redacted]
HR pembrolizumab PFS: Naïve treatment comparison	
HR pembrolizumab TTOT: Naïve treatment comparison	
Pralsetinib: Weibull distribution, OS, parameter 1	
Pralsetinib: Exponential distribution, PFS, parameter 1	
Pralsetinib: Exponential distribution, TTOT, parameter 1	
Pralsetinib AE N	
Pembrolizumab AE N	
Progression-free health state: Nafees et al. (2008) utility	
Progressed health state: Nafees et al. (2008) utility	

*Scenario analyses. Results not included in tornado diagram. Abbreviations: AE – adverse event; EDM - Enhanced Data Mart; HR – hazard ratio; ICER - Incremental Cost Effectiveness Ratio; KM – Kaplan-meier; KN-042 – KEYNOTE-042; OS – overall survival; PFS – progression-free survival; QALY – Quality-adjusted life year; RET - Rearranged during transfection; TTOT - Total Time On Treatment.

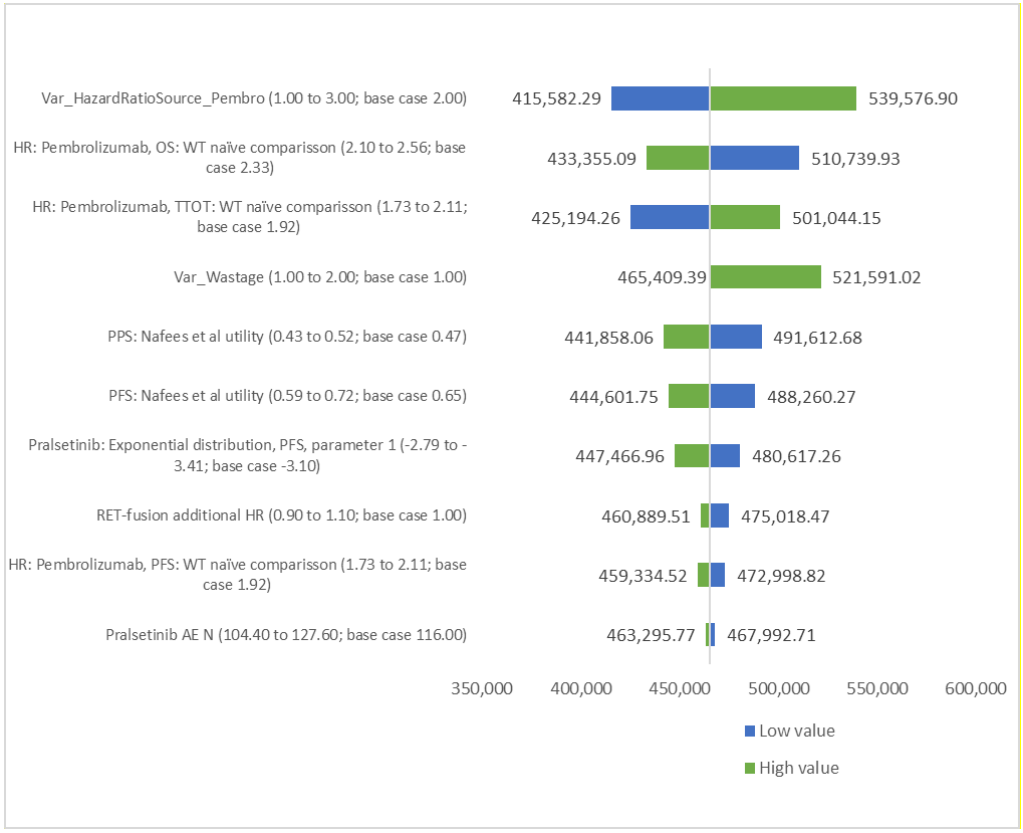


Figure 17: Tornado diagram: ICER results, pralsetinib compared to pembrolizumab monotherapy

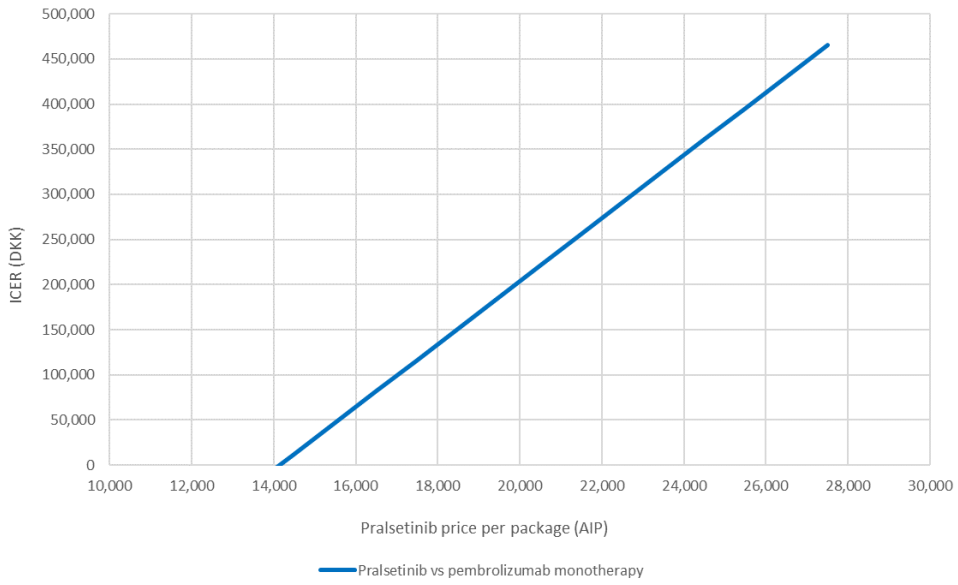


Figure 18: ICERs estimated with different values for the drug price of pralsetinib

Table 54: One-way sensitivity and scenario analyses results for the comparison between pralsetinib and pembrolizumab in combination with chemotherapy

	Change	Reason/ rationale/ source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	[redacted]				
Vial wastage					
Utilities					
HR source pembrolizumab + pemetrexed + chemotherapy					
Test costs					
Subsequent therapies					
Extrapolations best fitting KM curves from KN-189*					
HR pembrolizumab in combination with chemotherapy OS: Naïve treatment comparison					
HR pembrolizumab in combination with chemotherapy PFS: Naïve treatment comparison					
HR pembrolizumab in combination with chemotherapy TTOT: Naïve treatment comparison					
Pralsetinib: Weibull distribution, OS, parameter 1					
Pralsetinib: Exponential distribution, PFS, parameter 1					

	[redacted]
Pralsetinib: Exponential distribution, TTOT, parameter 1	
Pralsetinib AE N	
Pembrolizumab + pemetrexed + chemotherapy AE N	
Platinum-based chemotherapy weighting first line: Carboplatin	
Platinum-based chemotherapy weighting first line: Pemetrexed (first cycles)	
Platinum-based chemotherapy weighting first line: Pemetrexed (subsequent cycles)	
Progression-free health state: Nafees et al. (2008) utility	
Progressed health state: Nafees et al. (2008) utility	

*Scenario analyses. Results not included in tornado diagram. Abbreviations: AE – adverse event; EDM - Enhanced Data Mart; HR – hazard ratio; ICER - Incremental Cost Effectiveness Ratio; KM – Kaplan-meier; KN-189 – KEYNOTE-189; OS – overall survival; PFS – progression-free survival; QALY – Quality-adjusted life year; RET - Rearranged during transfection; TTOT - Total Time On Treatment.

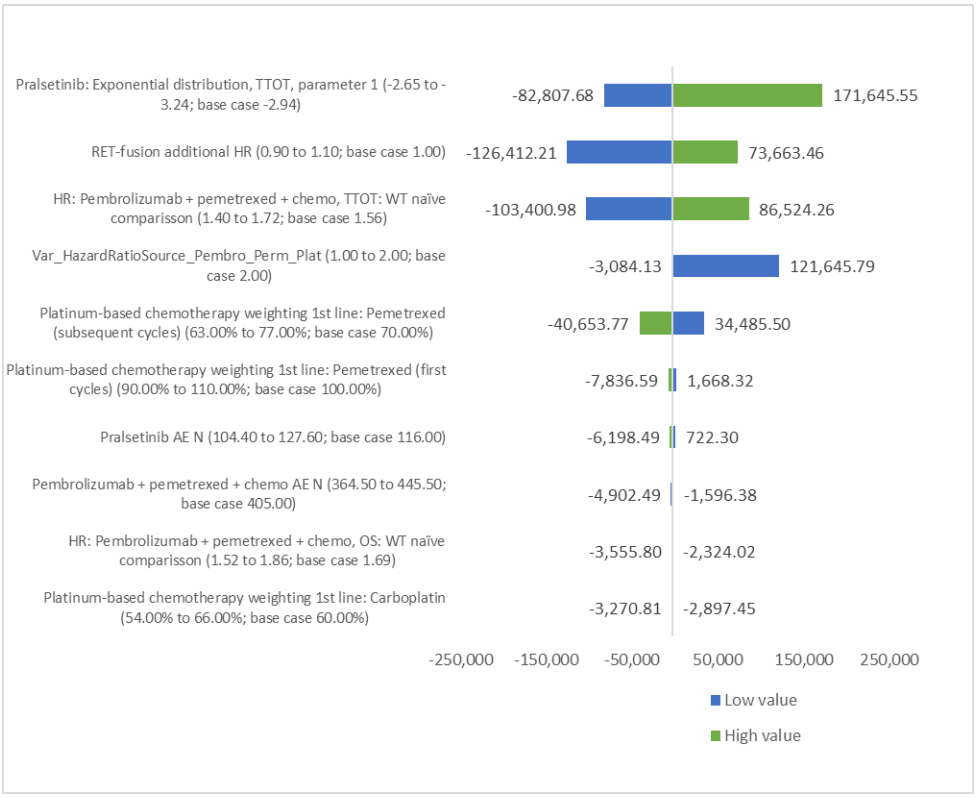


Figure 19: Tornado diagram: ICER results, pralsetinib compared to pembrolizumab in combination with chemotherapy

8.7.2 Probabilistic sensitivity analyses

To assess the uncertainty surrounding the variables included in the CU model, a PSA was undertaken using 1,000 iterations. Several parameters in the model are not necessarily fixed values but possess certain variability. This variability can be due to variations in the population with respect to the outcome, heterogeneity of the population and/or incomplete knowledge of the model parameters. The latter variability can be approximated through a PSA. This allows the CU model not only to evaluate the deterministic base case but also to see how the economic results might vary if parameters of the models varied simultaneously.

Table 55 presents the average along with the 95% confidence intervals for total cost of life years gained and QALYs gained from the PSA pralsetinib, pembrolizumab, and pembrolizumab + pemetrexed + chemotherapy, respectively. In addition to this, Table 56 presents the average ICER along with 95% confidence intervals from the PSA.

Finally, Figure 20, Figure 21, Figure 22 and Figure 23 present the cost-effectiveness planes and acceptability curves for pralsetinib compared to pembrolizumab (monotherapy) and pralsetinib compared to pembrolizumab in combination with chemotherapy.

Table 55: Results from the PSA analysis: total costs, life years gained and QALYs gained

	Pralsetinib	Pembrolizumab	Pembrolizumab + pemetrexed + chemotherapy
Total cost, DKK			

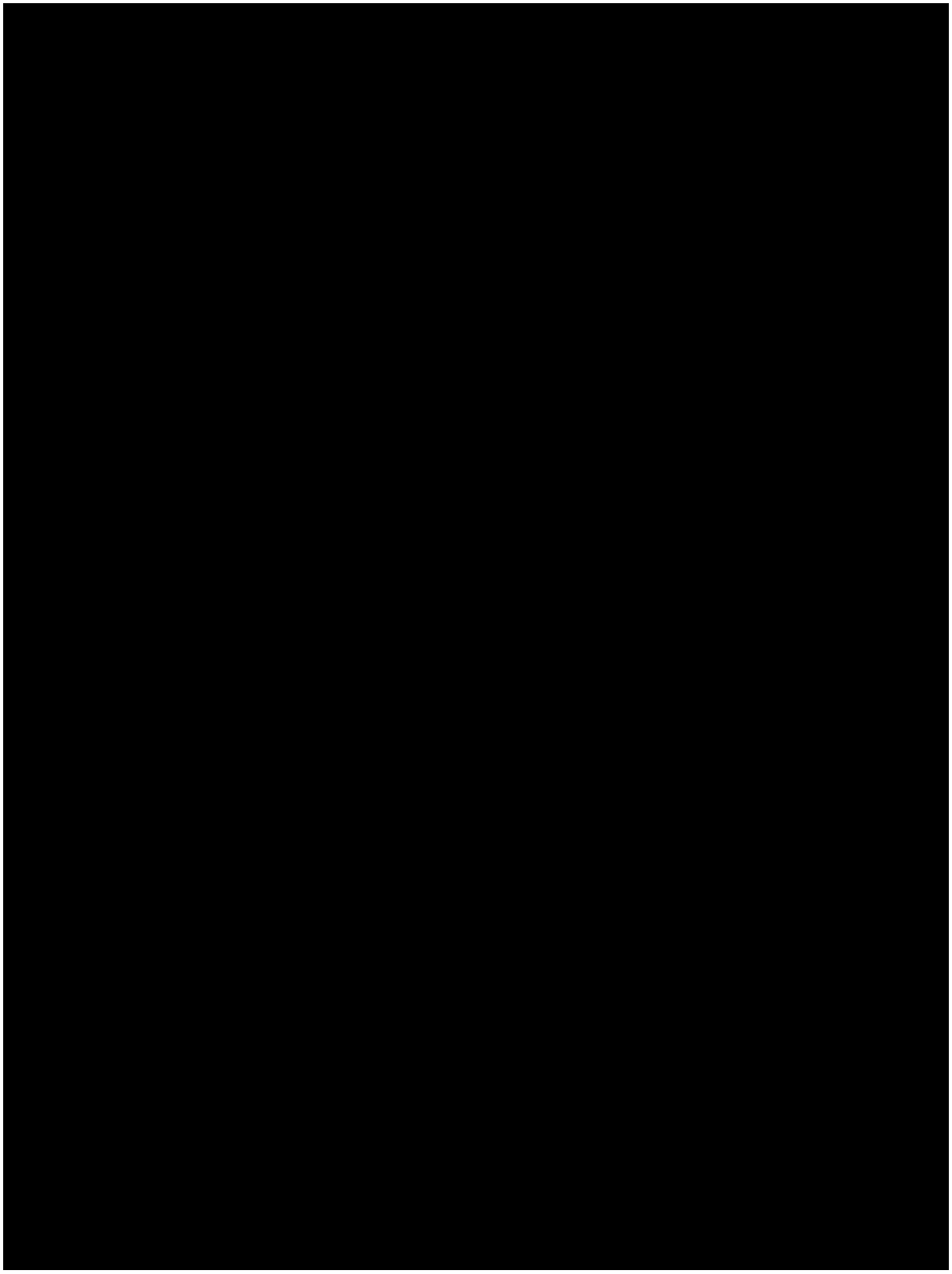
Deterministic results	[redacted]
PSA average	
PSA 95% confidence interval	
Life years	
Deterministic results	
PSA average	
PSA 95% confidence interval	
QALYs	
Deterministic results	
PSA average	
PSA 95% confidence interval	

Abbreviations: PSA - Probabilistic Sensitivity Analysis; QALY – Quality-adjusted life year.

Table 56: Results from the PSA analysis: incremental cost-effectiveness, DKK

	Pralsetinib vs pembrolizumab	Pralsetinib vs pembrolizumab + pemetrexed + chemotherapy
Incremental cost-effectiveness ratio (cost per QALY), DKK		
Deterministic results	[redacted]	
PSA average		
PSA 95% confidence interval		

Abbreviations: PSA - Probabilistic Sensitivity Analysis; QALY – Quality-adjusted life year.



9. Budget impact analysis

The purpose of the budget impact analysis was to estimate the budgetary impact of recommending pralsetinib as the standard treatment of RET fusion-positive NSCLC at Danish hospitals. The budget impact is estimated per year in the first five years after the recommendation of pralsetinib.
The budget impact analysis compares the costs for the Danish regions in the scenario where pralsetinib is recommended as a possible standard treatment of RET fusion-positive NSCLC and the scenario where pralsetinib is not recommended. The total budget impact per year is the difference between the two scenarios.

Number of patients

As mentioned in section 5.1, the expected number of RET fusion-positive NSCLC patients is based on a prevalence of 1.5% and around 2,253 NSCLC patients yearly in Denmark and without taking performance status and other factors into consideration. For that reason, we assume a yearly incidence of ~26 treatment-eligible patients with NSCLC who are RET fusion-positive.

Currently, few patients among all Danish NSCLC cases are tested for RET. We expect that implementation of RET fusion testing in all oncology departments in Denmark will take two to three years if pralsetinib is recommended by the Danish Medicines Council. Therefore, the estimated number of patients who will be offered treatment with pralsetinib, presented in Table 57, increases over time with the expectation that all patients will be identified, and therefore offered treatment with pralsetinib, after four years.

In case pralsetinib is not recommended as first-line therapy in patients with RET fusion-positive NSCLC, we assume that patients will be equally distributed between receiving pembrolizumab as monotherapy and pembrolizumab in combination with chemotherapy as first-line therapy. The resulting treatment distribution of patients if pralsetinib does not receive recommendation is presented in Table 58.

Table 57: Number of incident patients expected to be treated over the next five-year period if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Pralsetinib	1	4	12	20	26
Pembrolizumab	12.5	11	7	3	0
Pembrolizumab + pemetrexed + chemotherapy	12.5	11	7	3	0
Total number of patients	26	26	26	26	26

Table 58: Number of incident patients expected to be treated over the next five-year period if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Pralsetinib	0	0	0	0	0
Pembrolizumab	13	13	13	13	13
Pembrolizumab + pemetrexed + chemotherapy	13	13	13	13	13
Total number of patients	26	26	26	26	26

Expenditure per patient

The cost-per-patient estimates applied in the budget impact analysis were based on the undiscounted cost estimates from the cost-per-patient analysis, excluding patient and transportation costs. These are presented separately for patients receiving pralsetinib, pembrolizumab (monotherapy) and pembrolizumab in combination with chemotherapy in Table 59.

Table 59: Costs per patient per year applied in the budget impact model, DKK

	Year 1	Year 2	Year 3	Year 4	Year 5

Pralsetinib					
Drug costs	[redacted]				
Hospital sector costs	63,234	30,328	20,004	13,845	10,007
AE costs	10,909	0	0	0	0
Primary sector costs	0	0	0	0	0
Pembrolizumab					
Drug costs	[redacted]				
Hospital sector costs	153,306	54,271	14,092	8,844	5,592
AE costs	2,698	0	0	0	0
Primary sector costs	0	0	0	0	0
Pembrolizumab + pemetrexed + chemotherapy					
Drug costs	[redacted]				
Hospital sector costs	248,083	93,677	23,178	9,835	7,039
AE costs	6,285	0	0	0	0
Primary sector costs	0	0	0	0	0

Abbreviations: AE – adverse event.

Budget impact

Below, we present the results of the budget impact analysis in the first five years with and without a recommendation of pralsetinib. The result of the budget impact can be found in the 'Budget impact' sheet in the Excel model.

The budget impact of recommending pralsetinib as first-line treatment in patients with RET fusion-positive NSCLC is DKK [redacted] in the first year and DKK [redacted] in year 5. In Table 60, the budget impact in each year is presented.

Table 60: Expected budget impact of recommending the pharmaceutical for the current indication, DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
Pralsetinib is recommended	[redacted]				
Of which: Drug costs	[redacted]				
Of which: Hospital costs	5,080,588	6,547,881	5,803,143	4,605,730	3,624,160
Of which: Primary sector costs	0	0	0	0	0
Of which: Adverse reaction costs	123,202	142,453	193,790	245,126	283,629
Pralsetinib is NOT recommended	[redacted]				
Of which: Drug costs	[redacted]				
Of which: Hospital costs	5,218,049	7,141,370	7,625,885	7,868,712	8,032,915
Of which: Primary sector costs	0	0	0	0	0
Of which: Adverse reaction costs	116,785	116,785	116,785	116,785	116,785

Budget impact of the recommendation	[redacted]				

10. Discussion on the submitted documentation

A discussion of the submitted documentation can be found in the summary (section 4).

11. List of experts

[redacted]

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13. Appendix A – Literature search for efficacy and safety of intervention and comparators

No direct evidence comparing pralsetinib with pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy are available. In order to identify relevant studies for the comparisons two systematic literature reviews were conducted. The first approach was to search for literature in patients with RET fusion-positive NSCLC. Because it was suspected that limited evidence for the comparators of interest would be available, the scope of the review was broadened to include NSCLC patients with unknown RET fusion status as well.

The Medicines Council methods guide for assessing new pharmaceuticals version 1.2 has provided guidance for the literature search. Electronic searches were carried out in PubMed and in CENTRAL (via Cochrane Library) on October 21 and 22, 2021. The searches were based on the defined PICOs described in Table 61 and Table 62. In addition, the searches contain terms descriptive of the area as described in the search strings.

Table 61: Inclusion and exclusion criteria for the search in RET fusion-positive NSCLC

	Inclusion criteria	Exclusion criteria
Population	Adult patients with RET fusion-positive advanced, non-small cell lung cancer (NSCLC)	Populations irrelevant to scope
Intervention	Pralsetinib (400 mg once daily)	Intervention irrelevant to scope
Comparators	• Pembrolizumab • Pembrolizumab + platinum-based chemotherapy • Immunotherapies	Comparator irrelevant to scope
Outcomes	At least one effect measure relevant for scope: • Overall survival (OS) • Progression free survival (PFS) • Overall Response Rate (ORR) • Safety • Quality of life	Outcome(s) out of PICO scope, i.e. studies that do not report at least one of the relevant effect measures.
Design	Phase II, III or IV RCTs Retrospective, observational studies Full text only	Case Reports, Comments, Editorials, Guidelines, Letters, News, Review articles Conference abstracts In vitro studies
Language	English, Scandinavian	Other language
Publication data (date limits)	No date limits	Not applicable
Human/animal	Human only	Veterinary (not human)

Table 62: Inclusion and exclusion criteria for the search in NSCLC with unknown RET fusion status

	Inclusion criteria	Exclusion criteria
Population	Adult patients with advanced non-small cell lung cancer (NSCLC)	Populations irrelevant to scope
Intervention	Pralsetinib (400 mg once daily)	Intervention irrelevant to scope
Comparators	• Pembrolizumab • Pembrolizumab + platinum-based chemotherapy	Comparators irrelevant to scope
Outcomes	At least one effect measure relevant for scope: • Overall survival (OS) • Progression free survival (PFS) • Overall Response Rate (ORR) • CNS progression • Safety • Quality of life	Outcome(s) out of PICO scope, i.e. studies that do not report at least one of the relevant effect measures.
Design	Phase II, III or IV RCTs Full text only	Case Reports, Comments, Editorials, Guidelines, Letters, News, Review articles Retrospective, observational studies Conference abstracts In vitro studies
Language	English, Scandinavian	Other language
Publication data (date limits)	No date limits	Not applicable
Human/animal	Human only	Veterinary (not human)

Table 63: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
PubMed	MEDLINE	No date limits No date limits	RET fusion-positive NSCLC: 22-Oct-2021 NSCLC with unknown RET fusion status: 22-Oct-2021
CENTRAL	Cochrane Library	No date limits No date limits	RET fusion-positive NSCLC: 21-Oct-2021

			NSCLC with unknown RET fusion status: 22-Oct-2021

Table 64: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched
Annals of Oncology, EMSO 2019	www.annalsofoncology.org/	Manual search by individual words in congress material	Pembrolizumab, NSCLC, KEYNOTE-042
World Conference on Lung Cancer (WCLC) 2020	wclc2020.iaslc.org/	Manual search by individual words in congress material	Pembrolizumab, NSCLC, KEYNOTE-042
WCLC 2020	wclc2020.iaslc.org/	Manual search by individual words in congress material	Pembrolizumab, NSCLC, KEYNOTE-189

Supplementary manual searches

The EPARs listed below were manually searched via EMA's website https://www.ema.europa.eu/en. The date of search for the EPARs for pembrolizumab was October 22, 2021, while the date of access for the EPAR for pralsetinib was December 9, 2021.

- EPAR (AR0000) – Gavreto (pralsetinib)
- EPAR (AR0011) – Keytruda (pembrolizumab)
- EPAR (AR0043) – Keytruda (pembrolizumab)
- EPAR (AR0057) – Keytruda (pembrolizumab)

13.1 Search strategy

The search strategy and search strings have been developed based on the PICOs. The inclusion and exclusion criteria for the searches are presented in Table 61 and Table 62. The search strings and results for each database are presented below (

Table 65**,** Table 66**,** Table 67**,** Table 68 and screen shots). In the comment field of the tables it is stated, which search term applies to what part of the PICO.

Search strategy for RET fusion-positive NSCLC

Table 65: Search strategy, PubMed - October 22, 2021

#	Search term	Comment
1	nsclc[tiab]	Search terms for population

2	(non-small-cell-lung[tiab] OR nonsmall-cell-lung[tiab]) AND (cancer[tiab] OR cancers[tiab] OR carcinoma[tiab] OR adenocarcinoma[tiab])	
3	Carcinoma, Non-Small-Cell Lung[mh] AND drug therapy[sh]	
4	(nonsquamous[tiab] OR non-squamous[tiab]) AND lung[tiab] AND (cancer[tiab] OR carcinoma[tiab])	
5	lung[tiab] AND adenocarcinoma[tiab]	
6	Adenocarcinoma of Lung[mh] AND drug therapy[sh]	
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	
8	pralsetinib[nm] OR pralsetinib[tiab] OR Gavreto*[tiab]	Search terms for interventions
9	pembrolizumab[nm] OR pembrolizumab[tiab] OR Keytruda*[tiab] OR MK-3475*[tiab] OR MK3475*[tiab]	
10	immunotherapy[tiab] OR immunotherap*[tiab]	
11	#8 OR #9 OR #10	
12	Proto-Oncogene Proteins c-ret[mh]	Search terms for RET changes
13	(RET[tiab] OR "rearranged during transfection"[tiab]) AND (alteration*[tiab] OR altered[tiab] OR aberration*[tiab] OR aberrant[tiab] OR rearrange*[tiab] OR re-arrange*[tiab] OR fusion*[tiab] OR fused[tiab] OR mutant*[tiab] OR mutat*[tiab])	
14	#12 OR #13	
15	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR News[pt] OR case report[ti]	Publication types for exclusion
16	#14 NOT #15	
17	#7 AND #11 AND #16	Combination of population, drugs and RET

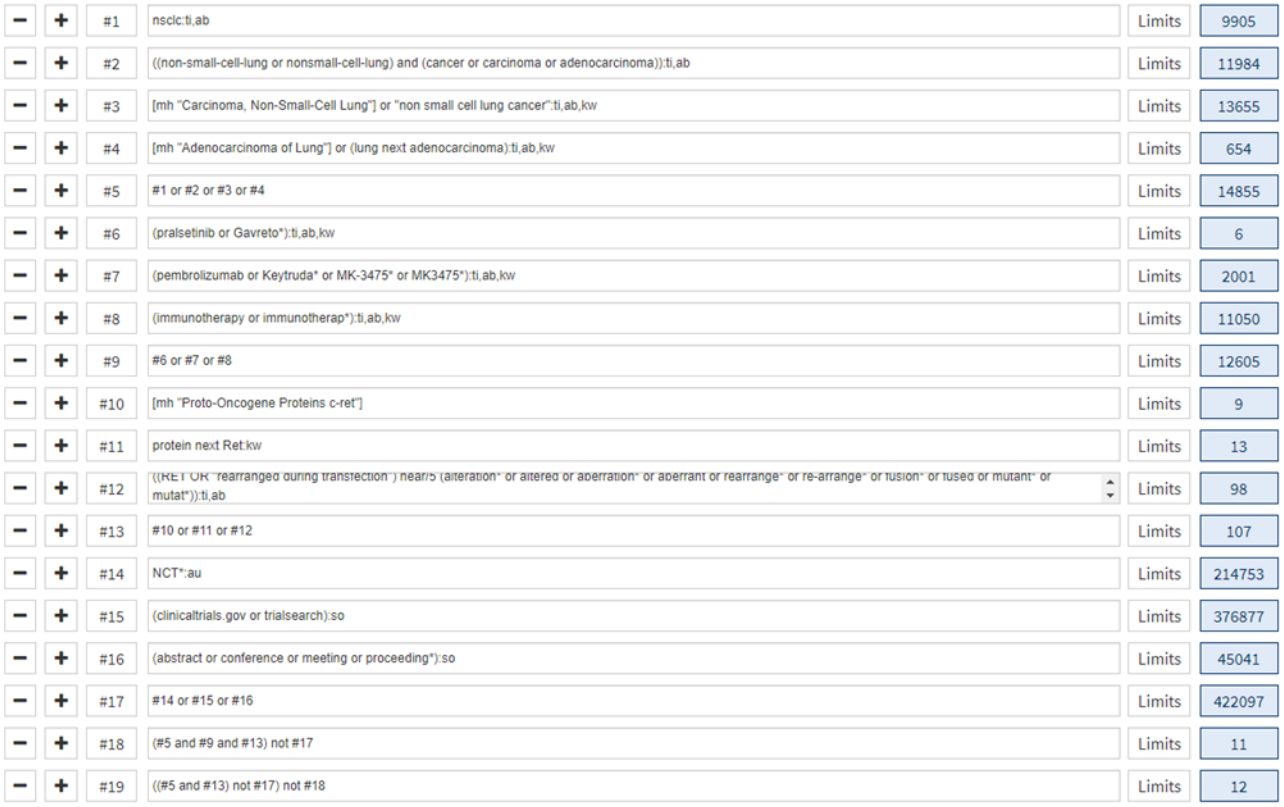
18	Clinical Trial[pt] OR Comparative Study[pt] OR Multicenter Study[pt] OR Observational Study[pt]	Search filter for identification of other studies in the population (without drugs) with RET change
19	Cohort Studies[mh] OR Prospective Studies[mh] OR Retrospective Studies[mh]	
20	clinical trial[tiab] OR controlled trial[tiab]	
21	randomized[tiab] OR randomised[tiab] OR randomly[tiab] OR controlled[tiab] OR placebo[tiab]	
22	(phase 1[tiab] OR phase I[tiab] OR phase 2[tiab] OR phase II[tiab] OR phase 3[tiab] OR phase III[tiab]) AND (trial*[tiab] OR study[tiab])	
23	(comparative[tiab] OR multicent*[tiab] OR multi-cent* OR single-cent*[tiab] OR single-arm[tiab]) AND (trial*[tiab] OR study[tiab])	
24	(observational[tiab] OR cohort[tiab] OR prospective[tiab] OR retrospective*[tiab]) AND (study[tiab] OR analy*[tiab])	
25	Registries[mh] OR registry[tiab] OR nation-wide[tiab] OR nationwide[tiab] OR real-worl[tiab] OR real-life[tiab]	
26	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	
27	#7 AND #16 AND #26	
28	#17 OR #27	Complete search, RET changes

Search	Actions	Details	Query	Results	Time
#28	•••	>	Search: **#17 OR #27**	247	07:10:21
#27	•••	>	Search: **#7 AND #16 AND #26**	198	07:09:53
#26	•••	>	Search: **#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25**	6,097,109	07:09:41
#25	•••	>	Search: **Registries[mh] OR registry[tiab] OR nation-wide[tiab] OR nationwide[tiab] OR real-worl[tiab] OR real-life[tiab]**	261,968	07:09:29
#24	•••	>	Search: **(observational[tiab] OR cohort[tiab] OR prospective[tiab] OR retrospective*[tiab]) AND (study[tiab] OR analy*[tiab])**	1,635,920	07:09:17
#23	•••	>	Search: **(comparative[tiab] OR multicent*[tiab] OR multi-cent* OR single-cent*[tiab] OR single-arm[tiab]) AND (trial*[tiab] OR study[tiab])**	463,182	07:09:05
#22	•••	>	Search: **(phase 1[tiab] OR phase I[tiab] OR phase 2[tiab] OR phase II[tiab] OR phase 3[tiab] OR phase III[tiab]) AND (trial*[tiab] OR study[tiab])**	136,612	07:08:54
#21	•••	>	Search: **randomized[tiab] OR randomised[tiab] OR randomly[tiab] OR controlled[tiab] OR placebo[tiab]**	1,539,917	07:08:41
#20	•••	>	Search: **clinical trial[tiab] OR controlled trial[tiab]**	304,502	07:08:30
#19	•••	>	Search: **Cohort Studies[mh] OR Prospective Studies[mh] OR Retrospective Studies[mh]**	2,229,461	07:08:20
#18	•••	>	Search: **Clinical Trial[pt] OR Comparative Study[pt] OR Multicenter Study[pt] OR Observational Study[pt]**	2,837,583	07:08:09
#17	•••	>	Search: **#7 AND #11 AND #16**	77	07:07:58
#16	•••	>	Search: **#14 NOT #15**	5,698	07:07:48
#15	•••	>	Search: **Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR News[pt] OR case report[ti]**	4,234,821	07:07:36
#14	•••	>	Search: **#12 OR #13**	6,539	07:07:22
#13	•••	>	Search: **(RET[tiab] OR "rearranged during transfection"[tiab]) AND (alteration*[tiab] OR altered[tiab] OR aberration*[tiab] OR aberrant[tiab] OR rearrange*[tiab] OR re-arrange*[tiab] OR fusion*[tiab] OR fused[tiab] OR mutant*[tiab] OR mutat*[tiab])**	5,221	07:07:10
#12	•••	>	Search: **Proto-Oncogene Proteins c-ret[mh]**	3,698	07:06:57
#11	•••	>	Search: **#8 OR #9 OR #10**	113,021	07:06:45
#10	•••	>	Search: **immunotherapy[tiab] OR immunotherap*[tiab]**	109,625	07:06:35
#9	•••	>	Search: **pembrolizumab[nm] OR pembrolizumab[tiab] OR Keytruda*[tiab] OR MK-3475*[tiab] OR MK3475*[tiab]**	6,216	07:06:23
#8	•••	>	Search: **pralsetinib[nm] OR pralsetinib[tiab] OR Gavreto*[tiab]**	62	07:06:13
#7	•••	>	Search: **#1 OR #2 OR #3 OR #4 OR #5 OR #6**	107,324	07:06:02
#6	•••	>	Search: **Adenocarcinoma of Lung[mh] AND drug therapy[sh]**	2,383	07:05:52
#5	•••	>	Search: **lung[tiab] AND adenocarcinoma[tiab]**	36,320	07:05:38
#4	•••	>	Search: **(nonsquamous[tiab] OR non-squamous[tiab]) AND lung[tiab] AND (cancer[tiab] OR carcinoma[tiab])**	1,834	07:05:26
#3	•••	>	Search: **Carcinoma, Non-Small-Cell Lung[mh] AND drug therapy[sh]**	23,766	07:05:14
#2	•••	>	Search: **(non-small-cell-lung[tiab] OR nonsmall-cell-lung[tiab]) AND (cancer[tiab] OR cancers[tiab] OR carcinoma[tiab] OR adenocarcinoma[tiab])**	73,902	07:05:03
#1	•••	>	Search: **nsclc[tiab]**	50,484	07:04:40

Table 66: Search strategy, Central via Cochrane Library - October 21, 2021

#	Search term	Comment
1	nsclc:ti,ab	Search terms for population
2	((non-small-cell-lung or nonsmall-cell-lung) and (cancer or carcinoma or adenocarcinoma)):ti,ab	
3	[mh "Carcinoma, Non-Small-Cell Lung"] or "non small cell lung cancer":ti,ab,kw	
4	[mh "Adenocarcinoma of Lung"] or (lung next adenocarcinoma):ti,ab,kw	
5	#1 or #2 or #3 or #4	
6	(pralsetinib or Gavreto*):ti,ab,kw	Search terms for interventions
7	(pembrolizumab or Keytruda* or MK-3475* or MK3475*):ti,ab,kw	
8	(immunotherapy or immunotherap*):ti,ab,kw	
9	#6 or #7 or #8	
10	[mh "Proto-Oncogene Proteins c-ret"]	Search terms for RET changes
11	protein next Ret:kw	
12	((RET OR "rearranged during transfection") near/5 (alteration* or altered or aberration* or aberrant or rearrange* or re-arrange* or fusion* or fused or mutant* or mutat*)):ti,ab	
13	#10 or #11 or #12	
14	NCT*:au	Publication types for exclusion
15	(clinicaltrials.gov or trialsearch):so	
16	(abstract or conference or meeting or proceeding*):so	
17	#14 or #15 or #16	
18	(#5 and #9 and #13) not #17	Combination of population, drugs and RET

19	((#5 and #13) not #17) not #18	Combination of population and RET



#1	nsclc:ti,ab	Limits	9905
#2	((non-small-cell-lung or nonsmall-cell-lung) and (cancer or carcinoma or adenocarcinoma)):ti,ab	Limits	11984
#3	[mh "Carcinoma, Non-Small-Cell Lung"] or "non small cell lung cancer":ti,ab,kw	Limits	13655
#4	[mh "Adenocarcinoma of Lung"] or (lung next adenocarcinoma):ti,ab,kw	Limits	654
#5	#1 or #2 or #3 or #4	Limits	14855
#6	(pralsetinib or Gavreto*):ti,ab,kw	Limits	6
#7	(pembrolizumab or Keytruda* or MK-3475* or MK3475*):ti,ab,kw	Limits	2001
#8	(immunotherapy or immunotherap*):ti,ab,kw	Limits	11050
#9	#6 or #7 or #8	Limits	12605
#10	[mh "Proto-Oncogene Proteins c-ret"]	Limits	9
#11	protein next Ret:kw	Limits	13
#12	((RET OR "rearranged during transfection") near/5 (alteration* or altered or aberration* or aberrant or rearrange* or re-arrange* or fusion* or fused or mutant* or mutat*)):ti,ab	Limits	98
#13	#10 or #11 or #12	Limits	107
#14	NCT*:au	Limits	214753
#15	(clinicaltrials.gov or trialsearch):so	Limits	376877
#16	(abstract or conference or meeting or proceeding*):so	Limits	45041
#17	#14 or #15 or #16	Limits	422097
#18	(#5 and #9 and #13) not #17	Limits	11
#19	((#5 and #13) not #17) not #18	Limits	12

Search strategy for NSCLC with unknown RET fusion status

Table 67: Search strategy, PubMed - October 22, 2021

#	Search term	Comment
1	(Carcinoma, Non-Small-Cell Lung[mh] OR Adenocarcinoma of Lung[mh]) AND Drug Therapy[sh]	Search terms for population
2	nsclc[tiab]	
3	(non-small cell[tiab] OR nonsmall cell[tiab] OR squamous cell[tiab] OR nonsquamous cell[tiab] OR large cell[tiab]) AND lung[tiab] AND (cancer[tiab] OR carcinoma[tiab] OR adenocarcinoma[tiab])	
4	lung[tiab] AND adenocarcinoma[tiab]	
5	#1 OR #2 OR #3 OR #4	

6	pembrolizumab[nm] OR pembrolizumab[tiab] OR Keytruda*[tiab] OR MK-3475*[tiab] OR MK3475*[tiab]	Search terms for interventions
7	pralsetinib[nm] OR pralsetinib[tiab] OR Gavreto*[tiab]	
8	#6 OR #7	
9	#5 AND #8	
10	("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh])	Publication types for exclusion
11	#9 and #10	
12	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti]	
13	#11 NOT #12	
14	english[la] AND hasabstract	
15	#13 AND #14	Complete search

Search	Actions	Details	Query	Results	Time
#15	•••	>	Search: **#13 AND #14**	154	06:57:28
#14	•••	>	Search: **english[la] AND hasabstract**	20,889,715	06:57:17
#13	•••	>	Search: **#11 NOT #12**	164	06:57:05
#12	•••	>	Search: **Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Guideline[pt] OR Letter[pt] OR News[pt] OR Review[pt] OR Systematic Review[pt] OR case report[ti]**	7,049,894	06:56:54
#11	•••	>	Search: **#9 and #10**	251	06:56:41
#10	•••	>	Search: **("Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "Clinical Trials as Topic"[mh:noexp] OR randomly[tiab] OR trial[ti]) NOT ("Animals"[mh] NOT "Humans"[mh])**	1,341,813	06:56:28
#9	•••	>	Search: **#5 AND #8**	1,647	06:56:10
#8	•••	>	Search: **#6 OR #7**	6,277	06:55:59
#7	•••	>	Search: **pralsetinib[nm] OR pralsetinib[tiab] OR Gavreto*[tiab]**	62	06:55:48
#6	•••	>	Search: **pembrolizumab[nm] OR pembrolizumab[tiab] OR Keytruda*[tiab] OR MK-3475*[tiab] OR MK3475*[tiab]**	6,216	06:55:37
#5	•••	>	Search: **#1 OR #2 OR #3 OR #4**	115,632	06:55:26
#4	•••	>	Search: **lung[tiab] AND adenocarcinoma[tiab]**	36,320	06:55:15
#3	•••	>	Search: **(non-small cell[tiab] OR nonsmall cell[tiab] OR squamous cell[tiab] OR nonsquamous cell[tiab] OR large cell[tiab]) AND lung[tiab] AND (cancer[tiab] OR carcinoma[tiab] OR adenocarcinoma[tiab])**	86,637	06:55:05
#2	•••	>	Search: **nsclc[tiab]**	50,484	06:54:52
#1	•••	>	Search: **(Carcinoma, Non-Small-Cell Lung[mh] OR Adenocarcinoma of Lung[mh]) AND Drug Therapy[sh]**	25,630	06:54:37

Table 68: Search strategy, Central via Cochrane Library - October 22, 2021

#	Search term	Comment
1	("non small cell lung cancer" or "large cell lung carcinoma" or "lung adenocarcinoma" or "squamous cell lung carcinoma"):kw	Search terms for population
2	nsclc:ti,ab	
3	(("non small cell" or "nonsmall cell" or "squamous cell" or "nonsquamous cell" or "large cell") near/4 lung near/4 (cancer or carconima*)):ti,ab	
4	(lung near/4 adenocarcinoma):ti,ab	

5	#1 or #2 or #3 or #4	
6	(pralsetinib or Gavreto*):ti,ab,kw	Search terms for interventions
7	(pembrolizumab or Keytruda* or MK-3475* or MK3475*):ti,ab,kw	
8	#6 or #7	
9	#5 and #8	
10	("conference abstract" or review):pt,ti	Search terms for publications types
11	NCT*:au	
12	("clinicaltrials gov" or trialsearch):so	
13	(meeting or conference or proceedings):so	
14	#10 or #11 or #12 or #13	
15	#9 not #14	Publication types for exclusion
16	#15 not pubmed:an	Complete search

#1	("non small cell lung cancer" or "large cell lung carcinoma" or "lung adenocarcinoma" or "squamous cell lung carcinoma"):kw	Limits	5428
#2	nsclc:ti,ab	Limits	9905
#3	(("non small cell" or "nonsmall cell" or "squamous cell" or "nonsquamous cell" or "large cell") near/4 lung near/4 (cancer or carconima*)):ti,ab	Limits	11869
#4	(lung near/4 adenocarcinoma):ti,ab	Limits	529
#5	#1 or #2 or #3 or #4	Limits	14617
#6	(pralsetinib or Gavreto*):ti,ab,kw	Limits	6
#7	(pembrolizumab or Keytruda* or MK-3475* or MK3475*):ti,ab,kw	Limits	2001
#8	#6 or #7	Limits	2003
#9	#5 and #8	Limits	581
#10	("conference abstract" or review):pt,ti	Limits	204990
#11	NCT*:au	Limits	214753
#12	("clinicaltrials gov" or trialsearch):so	Limits	376877
#13	(meeting or conference or proceedings):so	Limits	44737
#14	#10 or #11 or #12 or #13	Limits	611454
#15	#9 not #14	Limits	108
#16	#15 not pubmed,an	Limits	22

13.2 Systematic selection of studies

PRISMA flow diagrams for the four literature searches are presented below.

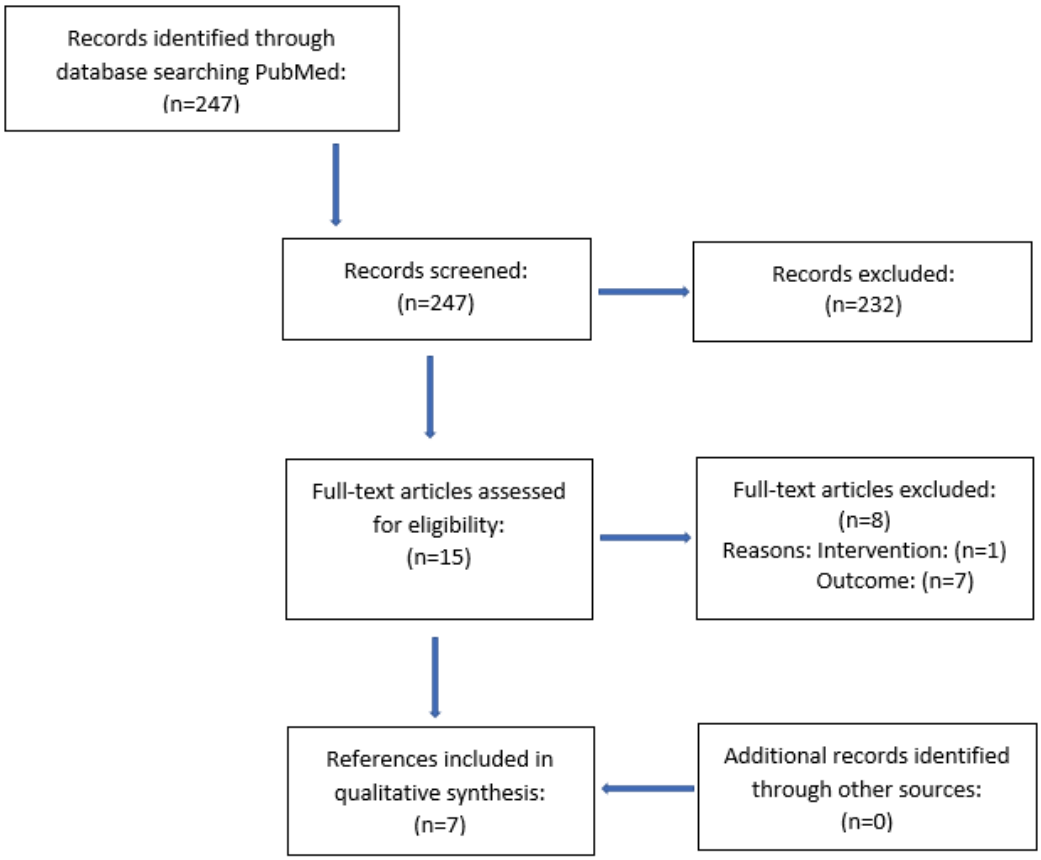


Figure 24: PRISMA flow diagram, PubMed search - RET fusion-positive NSCLC

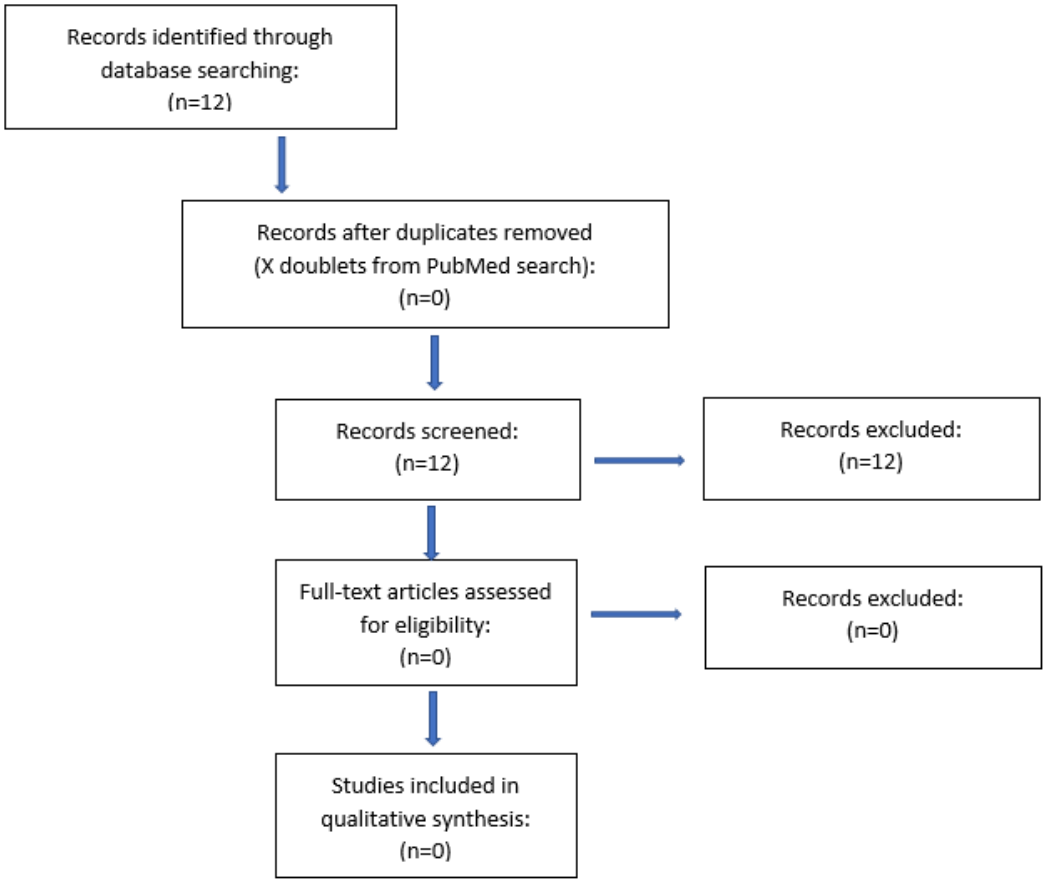


Figure 25: PRISMA flow diagram, CENTRAL search - RET fusion-positive NSCLC

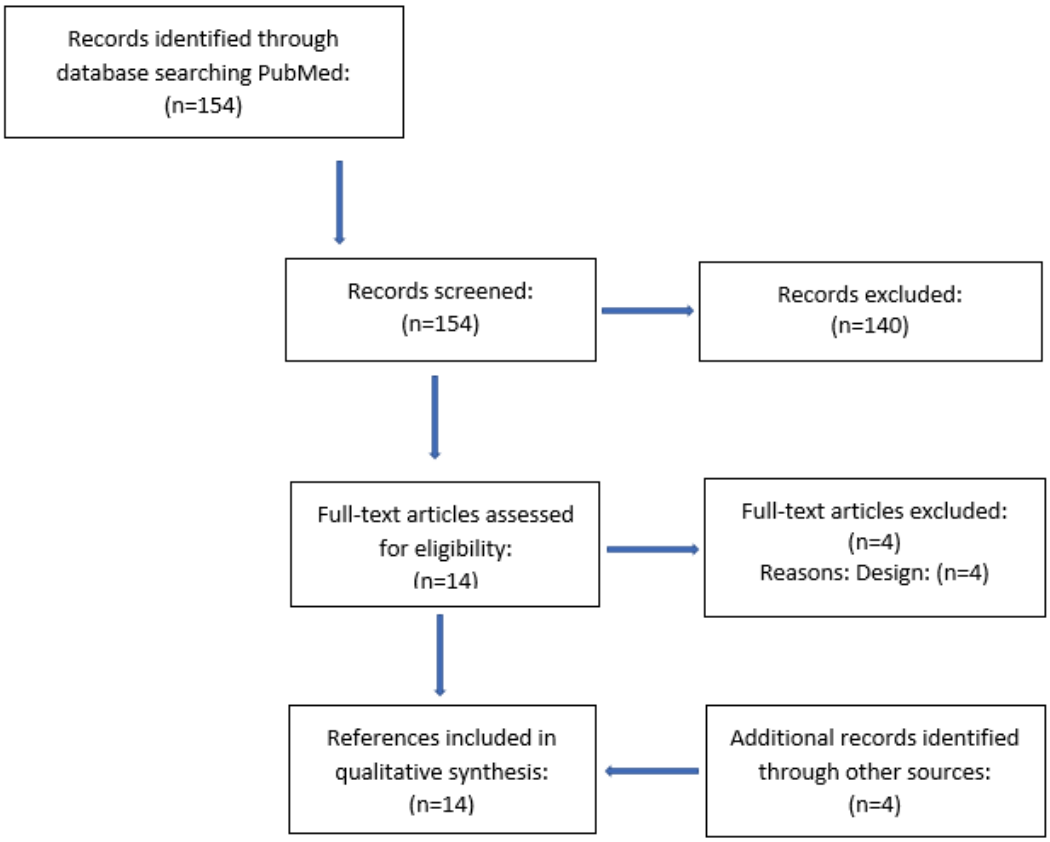


Figure 26: PRISMA flow diagram, PubMed search - NSCLC with unknown RET fusion status

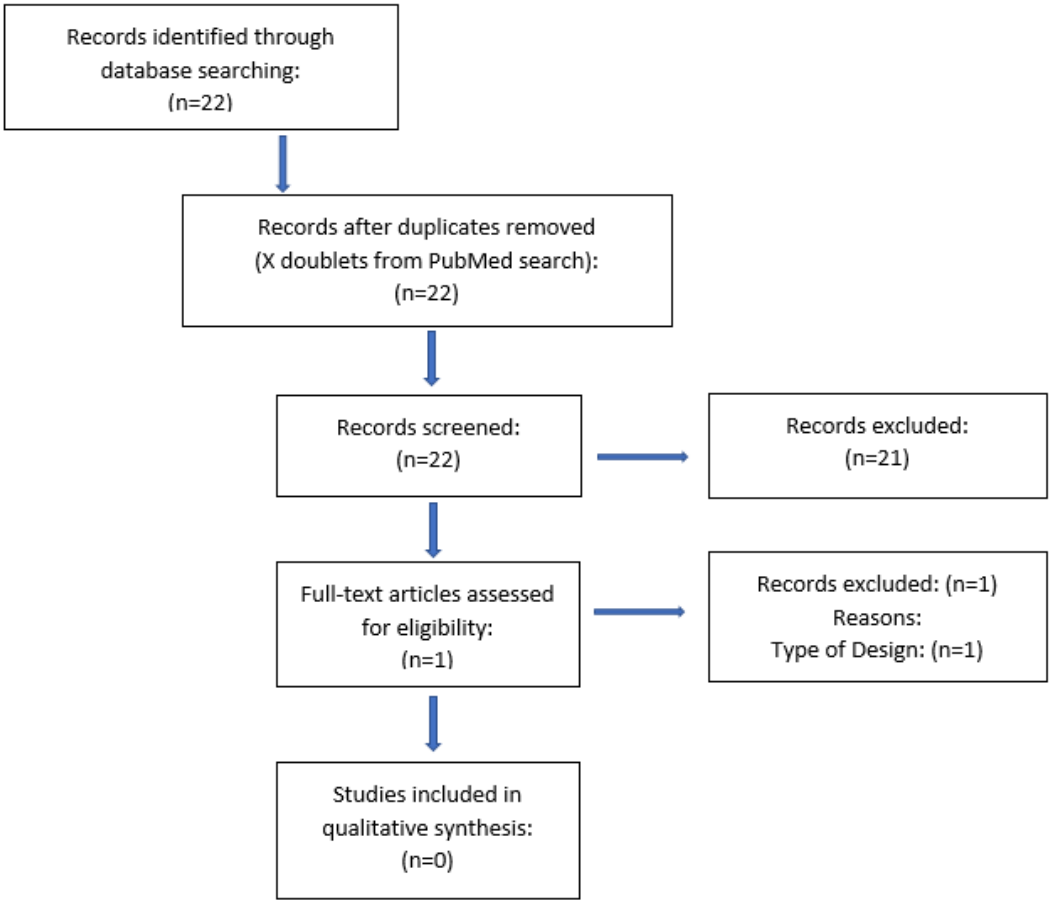


Figure 27: PRISMA flow diagram, Central search - NSCLC with unknown RET fusion status

List of excluded full-text papers

Search in RET fusion-positive NSCLC

Based on the title and abstract screening a total of 15 references were selected for full-text review. Following review, 8 references were excluded due to the reasons stated in

Table 69.

Table 69: List of excluded full text papers

Reference	Reason for exclusion
Oncogene-specific differences in tumor mutational burden, PD-L1 expression, and outcomes from immunotherapy in non-small cell lung cancer. Negrao MV, Skoulidis F, Montesion M, Schulze K, Bara I, Shen V, et al. Journal for immunotherapy of cancer, 2021	Outcome - fusions are grouped
Outcomes to first-line pembrolizumab in patients with PD-L1-high (≥50%) non-small cell lung cancer and a poor performance status. Alessi JV, Ricciuti B, Jiménez-Aguilar E, Hong F, Wei Z, Nishino M, et al. Journal for immunotherapy of cancer, 2020	Outcome - outcomes not presented RET+ specific

Benefit of Targeted DNA Sequencing in Advanced Non-Small-Cell Lung Cancer Patients Without EGFR and ALK Alterations on Conventional Tests. Byeon S, Lee B, Park WY, Choi YL, Jung HA, Sun JM, et al. Clinical lung cancer, 2020	Intervention - Non-targeted therapy not specified
Association of genetic and immuno-characteristics with clinical outcomes in patients with RET-rearranged non-small cell lung cancer: a retrospective multicenter study. Lu C, Dong XR, Zhao J, Zhang XC, Chen HJ, Zhou Q, et al. Journal of hematology & oncology, 2020	Outcome - reported on grouped in all lines or by individual data
Association of Patient Characteristics and Tumor Genomics With Clinical Outcomes Among Patients With Non-Small Cell Lung Cancer Using a Clinicogenomic Database. Singal G, Miller PG, Agarwala V, Li G, Kaushik G, Backenroth D, et al. Jama, 2019	Outcome
The Impact of Smoking and TP53 Mutations in Lung Adenocarcinoma Patients with Targetable Mutations-The Lung Cancer Mutation Consortium (LCMC2). Aisner DL, Sholl LM, Berry LD, Rossi MR, Chen H, Fujimoto J, et al. Clinical cancer research : an official journal of the American Association for Cancer Research, 2018	Outcome
Clinical application of amplicon-based next-generation sequencing to therapeutic decision making in lung cancer. Takeda M, Sakai K, Terashima M, Kaneda H, Hayashi H, Tanaka K, et al. Annals of oncology : official journal of the European Society for Medical Oncology, 2015	Outcome
High Discrepancy of Driver Mutations in Patients with NSCLC and Synchronous Multiple Lung Ground-Glass Nodules. Wu C, Zhao C, Yang Y, He Y, Hou L, Li X, et al. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer, 2015	Outcome

Search in NSCLC with unknown RET fusion status

Based on the title and abstract screening, a total of 15 studies were selected for full-text review. Following review, 5 studies were excluded due to the reasons stated in Table 70**.**

Table 70: List of excluded full text papers

Reference	Reason for exclusion
Long-Term Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin With or Without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous NSCLC Awad MM, Gadgeel SM, Borghaei H, Patnaik A, Yang JC, Powell SF, et al. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer, 2021	Design - Phase II
Pembrolizumab in patients with non-small-cell lung cancer of performance status 2 (PePS2): a single arm, phase 2 trial. Middleton G, Brock K, Savage J, Mant R, Summers Y, Connibear J, et al. The Lancet Respiratory medicine, 2020	Design - Phase II, single arm
24-Month Overall Survival from KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin with or without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous Non-Small Cell Lung Cancer. Borghaei H, Langer CJ, Gadgeel S, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer, 2019	Design - Phase II
Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. The Lancet Oncology, 2016	Design - KN-021, Phase II

Randomized, phase 2 study of carboplatin and pemetrexed with or without pembrolizumab as first-line therapy for advanced NSCLC: KEYNOTE-021 cohort G. Langer C, Gaddgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell S, et al. Annals of oncology, 2016	Design - Phase II

Table 71: Studies included in the assessment

Reference (title, author, journal, year)	Trial name NCT number	Dates of study (start and expected completion date)	Used in comparison of
RET fusion-positive NSCLC			
Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study; Gainor et al; Lancet oncology; 2021[25].	ARROW NCT03037385	Study start date: March 2017 Estimated study completion date: February 2024	Clinical question 1 and 2 Pralsetinib in RET fusion-positive NSCLC
Efficacy of immune checkpoint inhibitor therapy in patients with RET fusion-positive non-small-cell lung cancer; Bhandari et al; Immunotherapy; 2021 [17].	-	-	Clinical question 1 and 2 ICI and KN-189 regime in RET fusion-positive NSCLC
Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry; Mazieres et al; Annals of Oncology; 2019 [18].	IMMUNO-TARGET	-	Clinical question 1 ICI in RET fusion-positive NSCLC
Efficacy and Safety of Anti-PD-1 Immunotherapy in Patients With Advanced NSCLC With BRAF, HER2, or MET Mutations or RET Translocation:GFPC 01-2018; Guisier et al; Journal of thoracic Oncology; 2020 [19].	IMAD2 study	-	Clinical question 1 ICI in RET fusion-positive NSCLC
Characteristics and outcomes of patients with RET-fusion positive non-small lung cancer in real-world practice in the United States; Hess et al; BMC cancer; 2021 [6].	-	-	Clinical question 2 KN-189 regime in RET fusion-positive NSCLC
Responsiveness to immune checkpoint inhibitors versus other systemic therapies in RET-aberrant malignancies; Hegde et al; ESMO open; 2020 [21]	-	-	Clinical question 1 ICI in RET fusion-positive NSCLC
Clinical Impact of Hybrid Capture-Based Next-Generation Sequencing on Changes in Treatment Decisions in Lung Cancer; Rozenblum et al; Journal of thoracic oncology; 2017 [20]	-	-	Clinical question 1 ICI in RET fusion-positive NSCLC
WT NSCLC			

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. Reck M et al. N Engl J Med 2016; 375:1823-1833 plus Suppl. doi: 10.1056/NEJMoa1606774 [33]. Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial, Brahmer, J. et al. Lancet Oncol 2017 [37]. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. Reck, M. et al, J Clin Oncol 2019, DOI: 10.1200/JCO.18.00149 Journal of Clinical Oncology 37, no. 7 (March 01, 2019) 537-546 [29] Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%. Reck, M. et al. J Clin Oncol 2021. DOI: 10.1200/JCO.21.00174 [28].	KEYNOTE-024 NCT02142738	August 2014 to May 2021	Clinical question 1 Pralsetinib vs pembrolizumab for patients with NSCLC and PD-L1 expression ≥50%
Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Mok, T. et al. Lancet 2019 May 4;393(10183): 1819-1830. doi: 10.1016/S0140-6736(18)32409-7 [31] Final analysis of the phase III KEYNOTE-042 study: Pembrolizumab (Pembro) versus platinum-based chemotherapy (Chemo) as first-line therapy for patients (Pts) with PD-L1–positive locally advanced/ metastatic NSCLC. Mok, T. et al, Ann Oncol. 2019;30(suppl 2; abstr 1020). doi: 10.1093/annonc/mdz063 [60]. KEYNOTE-042 3-Year Survival Update: 1L Pembrolizumab vs Chemotherapy for PD-L1-Positive Locally Advanced or Metastatic NSCLC. B.C., Cho et al., WCLC 2020 [30].	KEYNOTE-042 NCT02220894	October 2014 to March 2022	Clinical question 1 Pralsetinib vs pembrolizumab for patients with NSCLC and PD-L1 expression ≥50%
Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. Gandhi L. et al. N Engl J Med 2018;378:2078-92. DOI: 10.1056/NEJMoa1801005 [44] Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. Gadgeel S. et al. J Clin Oncol. 2020 May 10;38(14):1505-1517. doi: 10.1200/JCO.19.03136. Epub 2020 Mar 9. PMID: 32150489 [43] Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3	KEYNOTE-189 NCT02578680		Clinical question 2 Pralsetinib vs pembrolizumab in combination with chemotherapy for patients with NSCLC and PD-L1 expression ≤49%

trial. Garassino et al. Lancet Oncol 2020. Doi: 10.1016/s1470-2045(19)30801-0 [42] Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. Rodríguez-Abreu D. et al. Ann Oncol. 2021 Jul;32(7):881-895. doi: 10.1016/j.annonc.2021.04.008. Epub 2021 Apr 22. PMID: 33894335 [41]. Safety of pemetrexed plus platinum in combination with pembrolizumab for metastatic nonsquamous non-small cell lung cancer: A post hoc analysis of KEYNOTE-189. Garon et al. Lung Cancer. 2021. doi: 10.1016/j.lungcan.2021.02.021 [61] Pembrolizumab + Pemetrexed-Platinum for Metastatic NSCLC: 4-Year Follow-up From KEYNOTE-189, Gray et al., WCLC 2020 [40].			
Nationwide Survival Benefit after Implementation of First-Line Immunotherapy for Patients with Advanced NSCLC—Real World Efficacy; Mouritzen et al; Cancers; 2021 [32].	-	-	Clinical question 1 Pralsetinib vs ICI in a Danish first-line RW setting
Flatiron EDM RWD study [24]	-	-	Clinical question 1 and 2 Pralsetinib vs pembrolizumab for patients with NSCLC and PD-L1 expression ≥50% Pralsetinib vs pembrolizumab in combination with chemotherapy for patients with NSCLC and PD-L1 expression ≤49%

Table 72: Ongoing studies not included in the assessment

Trial name	NCT number	Aim	Dates of study
RET fusion-positive NSCLC			
AcceleRET Lung	NCT04222972	AcceleRET Lung was initiated to complement ARROW. It is a phase 3 multicentre trial that will evaluate pralsetinib at 400 mg QD against platinum-based chemotherapy in patients with RET fusion-positive NSCLC. The primary objective is PFS and the secondary and exploratory objectives are to assess efficacy, CNS activity, QoL, lung cancer symptoms and health status.	Study start date: June 2020 Estimated study completion date: December 31, 2024 Status: recruiting

Table 73: Overview of study design for studies included in the technology assessment

Study NCT	Aim	Study design	Patient population (included in the application)	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period (included in the application)
Clinical trials						
ARROW NCT03037385	To evaluate the safety, tolerability and efficacy of pralsetinib in patients with RET fusion-positive NSCLC, RET-mutant MTC, RET fusion-positive thyroid cancer and other RET-altered solid tumours.	Single-arm, open-label, fase I/II	Patients with RET fusion-positive NSCLC.	I: Pralsetinib once daily Total efficacy population (n=233) No prior systemic treatment (n=75)	ORR evaluated by BICR according to RECIST 1.1 and safety. Median follow-up: Total efficacy population: 17.1 mo. No prior systemic treatment: 12.8 mo.	PFS and OS. Median follow-up: Total efficacy population: 17.1 mo. No prior systemic treatment: 12.8 mo.
KEYNOTE-024 NCT02142738	To evaluate the efficacy and safety of pembrolizumab compared to SOC platinum-based chemotherapies in the treatment of patients with previously untreated stage IV NSCLC and PD-L1 expression ≥50%.	RCT, open-label, fase III	Patients with previously untreated stage IV NSCLC and PD-L1 ≥50%.	I: Pembrolizumab (n=154) C: Investigator's choice of chemotherapy (n=151)	PFS assessed by BICR according to RECIST 1.1. Median follow-up: 60 mo.	OS, ORR assessed according to RECIST 1.1 and safety. Median follow-up: 60 mo.
KEYNOTE-042 NCT02220894	To evaluate the efficacy and safety of pembrolizumab compared to platinum-based chemotherapy in the treatment of patients with previously untreated, PD-L1-expressing, locally advanced or metastatic NSCLC.	RCT, open-label, fase III	Patients with previously untreated, locally advanced or metastatic NSCLC and PD-L1 ≥50%.	I: Pembrolizumab (n=299) C: Chemotherapy (n=300)	OS in patients with PD-L1 TPS ≥50%, ≥20%, and ≥1%. Median follow-up: 46.9 mo.	PFS assessed by BICR according to RECIST 1.1 in patients with PD-L1 TPS ≥50%, ≥20%, and ≥1%. ORR assessed by BICR according to RECIST 1.1 in patients

						with PD-L1 TPS ≥50%, ≥20%, and ≥1%. Number of Patients who experienced at least one AE and number of patients who discontinued study treatment due to an AE. Median follow-up: 46.9 mo.
KEYNOTE-189 NCT02578680	To evaluate the efficacy and safety of pembrolizumab in combination with chemotherapy compared to placebo in combination with chemotherapy in the treatment of patients with metastatic nonsquamous NSCLC without sensitizing EGFR or ALK mutations who had received no previous treatment for metastatic disease.	RCT, double-blind, fase III	Patients with metastatic non-squamous NSCLC without sensitizing EGFR or ALK mutations who had received no previous treatment for metastatic disease.	I: Pembrolizumab plus chemotherapy (N=410) C: Chemotherapy (N=206)	PFS assessed by Blinded Central Imaging, according to RECIST 1.1, and OS. Median follow-up: 46.3 mo. (range, 41.8-54.1)	Confirmed objective response assessed by Blinded Central Imaging according to RECIST 1.1, and safety. Median follow-up, ORR: 46.3 mo. (range, 41.8-54.1) Median follow-up, safety: 31 mo.
Real-World Evidence						
Bhandari 2021 **[17]**	To describe outcomes of patients with RET fusion-positive NSCLC who received ICI-based treatments in the US.	Retrospective study using Flatiron-FMI GCDB and GHD.	Patients with RET fusion-positive NSCLC treated in first- and second-line.	CGDB, 1L: ICI (n=17) CGDB, 1L: KN-189 like Regimen (n=12) CGDB, 2L: ICI (n=11)	OS, rwPFS and response are presented for patients in first-line treated with ICI. Additionally a subgroup consisting of patients treated in first-line with KN-189-like regimen also with OS, rwPFS and response.	

					Response and duration of treatment is reported for patients in second-line treated with ICI. Median follow-up: N/A
IMMUNOTARGET Mazieres 2019 **[18]**	To address the efficacy of ICI in the context of oncogenic addiction.	Retrospective study using IMMUNOTARGET registry.	Patients with RET fusion-positive NSCLC treated in first- or second-line (not specified).	Intervention: ICI (n=16) Specific ICI not specified.	OS, PFS and response Median follow-up: 16.1 mo.
IMAD2 study Guisier 2020 **[19]**	To determine ICI efficacy against BRAF-, HER2-, MET-, and RET-NSCLC in a real-world setting.	Retrospective conducted in French Lung Cancer Group (GFPC) centers.	Patients with RET fusion-positive NSCLC treated in second-line or later (not specified).	Intervention: ICI (n=9) Specific ICI not specified.	OS, PFS and response Median follow-up: 9.2 mo.
Hegde 2020 **[21]**	To determine whether there is a benefit of ICIs in RET fusion-positive malignancies.	Retrospective review of all patients with RET fusion-positive malignancies who were referred to the Department of Investigational Cancer Therapeutics, the phase I clinical trials programme at The University of Texas MD Anderson Cancer Center.	Patients with RET fusion-positive NSCLC.	Intervention: ICI (n=14) 27 patients had RET fusions	Time to discontinuation.
Hess 2021 **[6]**	To compare the baseline characteristics and clinical outcomes among patients with metastatic NSCLC by RET fusion status treated in standard practice settings prior to the approval of selective RET inhibitors.	Retrospective study using Flatiron-FMI GCDB.	Patients with RET fusion-positive NSCLC.	Intervention: KN-189-like regimen (n=9) 46 patients had RET fusions	OS, PFS and response.

Rozenblum 2017 **[20]**	To assess the contribution of hybrid-capture (HC)-based NGS to clinical decision making and clinical outcomes in real-life clinical practice.	Retrospective study performed at Davidoff Cancer Center in Israel between 2011 and 2015.	Patients with RET fusion-positive NSCLC.	Intervention: ICI (n=4) 9 patients had RET fusions	Median treatment duration and response.
Mouritzen 2021	To assess OS and PFS for Danish NSCLC patients before and after the implementation of first-line ICIs in Denmark as well as possible prognostic factors for OS.	Retrospective study using the Danish Lung Cancer Register (DLCR) from January 1, 2013 to October 1, 2018.	Patients with NSCLC treated in first-line.	Intervention: ICI cohort (n=482) / EHR-ICI cohort (n=579)	OS and PFS.

13.3 Quality assessment

The described literature searches have been performed based on the fact that no direct evidence comparing pralsetinib with pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy are available. Therefore we have set up searches to identify literature within the following two topics:

- RET fusion-positive NSCLC
- NSCLC with unknown RET fusion status

As it appears from the search strategies, the literature searches have been narrowed by terms for population and interventions. In addition, we have included terms that ensure the searches are focused on RET fusions in the 'RET fusion positive NSCLC' search. Likewise, focused on RET wild-type in the 'NSCLC with unknown RET fusion status' search. To narrow the search results further we have inserted a filter for publication types that we wanted to exclude. Furthermore, we have chosen not to include any outcome search terms to ensure that the searches within the two described search topics reflect a broad search.

To ensure that every literature article in the search result is assessed with a first and second opinion, two reviewers independently screened the references by title and abstract according to the defined in- and exclusion criteria using a reference management tool.

With the above-mentioned search parameters and strategies in mind - and looking at the output of the searches where we can see that the articles we would expect to find actually are included - we find it reasonable to conclude that the search strings are strong.

13.4 Unpublished data

Currently there is no available publication plan for the unpublished data presented in the assessment.

14. Appendix B – Main characteristics of included studies

Table 74: Main characteristics of ARROW

Trial name: ARROW	NCT number: 03037385
Objective	To evaluate the safety, tolerability and efficacy of pralsetinib in patients with RET fusion-positive NSCLC, RET-mutant medullary thyroid cancer (MTC), RET fusion-positive thyroid cancer and other RET-altered solid tumours.
Publications – title, author, journal, year	Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study; Gainor et al; Lancet oncology; 2021
Study type and design	Open-label, single arm, phase 1/2 study, consisting of a dose escalation part (phase 1, completed) and an expansion part in patients treated with 400 mg of pralsetinib once daily (phase 2, ongoing).

Sample size (n)	Efficacy population, RET fusion-positive NSCLC, n: 233 Safety population, RET fusion-positive NSCLC, n: 281
Main inclusion and exclusion criteria	Insert the inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov **Inclusion criteria** ● Diagnosis during dose escalation (Phase 1) - Pathologically documented, definitively diagnosed non-resectable advanced solid tumor. ● All patients treated at doses > 120 mg per day must have medullary thyroid cancer (MTC), or a RET-altered solid tumor per local assessment of tumor tissue and/or blood. ● Diagnosis during dose expansion (Phase 2) - All patients (with the exception of patients with MTC enrolled in Groups 3, 4, and 9) must have an oncogenic RET-rearrangement/fusion or mutation (excluding synonymous, frameshift, and nonsense mutations) solid tumor, as determined by local or central testing of tumor or circulating tumor nucleic acid in blood; as detailed below. ○ Group 1 - patients must have pathologically documented, definitively diagnosed locally advanced or metastatic NSCLC with a RET fusion previously treated with a platinum-based chemotherapy. ○ Group 2 - patients must have pathologically documented, definitively diagnosed locally advanced or metastatic NSCLC with a RET fusion not previously treated with a platinum-based chemotherapy, including those who have not had any systemic therapy. Prior platinum chemotherapy in the neoadjuvant and adjuvant setting is permitted if the last dose of platinum was 4 months or more before the first dose of study drug. ○ Group 3 - patients must have pathologically documented, definitively diagnosed advanced MTC that has progressed within 14 months prior to the Screening Visit and was previously treated with cabozantinib and/or vandetanib. ○ Group 4 - patient must have pathologically documented, definitively diagnosed advanced MTC that has progressed within 14 months prior to the Screening Visit and was not previously treated with cabozantinib and/or vandetanib. ○ Group 5 -patients must have a pathologically documented, definitively diagnosed advanced solid tumor with an oncogenic RET fusion, have previously received SOC appropriate for their tumor type (unless there is no accepted standard therapy for the tumor type or the Investigator has determined that treatment with standard therapy is not appropriate), and must not be eligible for any of the other groups. ○ Group 6 - patients must have a pathologically documented, definitively diagnosed advanced solid tumor with an oncogenic RET fusion or mutation that was previously treated with a selective TKI that inhibits RET. ○ Group 7 - patients must have a pathologically documented, definitively diagnosed advanced solid tumor with an oncogenic RET mutation previously treated with SOC appropriate for the tumor type and not eligible for any of the other groups. ○ Group 8 - patients must have pathologically documented, definitively diagnosed locally advanced or metastatic NSCLC with a RET fusion that was previously treated with a platinum based chemotherapy (China only). ○ Group 9 - patients must have pathologically documented, definitively diagnosed advanced MTC that has progressed within 14 months prior to the Screening Visit, and was not previously treated with systemic therapy (except prior cytotoxic chemotherapy is allowed) for advanced or metastatic disease (China only). ● Patients must have non-resectable disease.

	● Patient agrees to provide tumor tissue (archived, if available or a fresh biopsy) for RET status confirmation and is willing to consider an on-treatment tumor biopsy, if considered safe and medically feasible by the treating Investigator. For Phase 2, Group 6, patients are required to undergo a pretreatment biopsy to define baseline RET status in tumor tissue. ● Patient has Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-1. **Exclusion criteria** ● Patient's cancer has a known primary driver alteration other than RET. For example, NSCLC with a targetable mutation in EGFR, ALK, ROS1 or BRAF; colorectal with an oncogenic KRAS, NRAS, or BRAF mutation. ● Patient has any of the following within 14 days prior to the first dose of study drug: ○ Platelet count < 75 × 10^9/L. ○ Absolute neutrophil count <1.0 × 10^9/L. ○ Hemoglobin < 9.0 g/dL (red blood cell transfusion and erythropoietin may be used to reach at least 9.0 g/dL, but must have been administered at least 2 weeks prior to the first dose of study drug. ○ Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × the upper limit of normal (ULN) if no hepatic metastases are present; >5 × ULN if hepatic metastases are present. ○ Total bilirubin > 1.5 × ULN; > 3 × ULN with direct bilirubin > 1.5 × ULN in presence of Gilbert's disease. ○ Estimated (Cockcroft-Gault formula) or measured creatinine clearance <40 mL/min. ○ Total serum phosphorus >5.5 mg/dL. ● QT interval corrected using Fridericia's formula (QTcF) >470 msec or history of prolonged QT syndrome or Torsades de pointes, or familial history of prolonged QT syndrome. ● Clinically significant, uncontrolled, cardiovascular disease. ● Central nervous system (CNS) metastases or a primary CNS tumor that is associated with progressive neurological symptoms. ● Clinically symptomatic interstitial lung disease or interstitial pneumonitis including radiation pneumonitis. ● Patients in Groups 1-5 and 7 (Phase 2) previously treated with a selective RET inhibitor.
Intervention	400 mg of pralsetinib once daily Efficacy population, n: 233 Safety population, n: 281
Comparator(s)	No comparator
Follow-up time	Primary analysis, CCOD May 22, 2020: Median follow-up of 17.1 mo. (IQR 14·6–20.3) for the total efficacy population and 13·6 mo. (IQR 13·0–17·6) for the population that has received no prior systemic treatment. Updated analysis, CCOD November 6, 2020: Median follow-up of 17.1 mo. (95% CI, 13.7-19.6) for the total efficacy population and 12.8 mo. (95% CI, 11.1-15.9) for the population that has received no prior systemic treatment.
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Primary endpoints were response rate (ORR) evaluated by blinded independent central review (BICR) according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) and safety. Secondary endpoints were progression free survival (PFS) and overall survival (OS). **Other endpoints:** Other secondary endpoints were duration of response (DOR), clinical benefit rate (CBR) defined as complete or partial response or stable disease of ≥ 16 weeks, disease control rate (DCR), but results are not included in this application.
Method of analysis	ORR, PFS, OS were assessed in the full efficacy populations, defined as all patients who initiated pralsetinib 400 mg once daily by July 11, 2019 (n=233). ORR and its two-sided 95% CIs were based on exact binomial distributions by means of the Clopper-Pearson method. PFS and OS were determined by means of the Kaplan-Meier method. Estimates of duration of follow-up for PFS and OS were based on the inverse Kaplan-Meier method, with 95% CIs based on the Greenwood formula. For median PFS, the CI calculation was based on identity (i.e., linear) transformation. OS and PFS at specific time-points were computed, along with the standard errors using Greenwood's formula. Safety assessment was based on the overall safety population including all patients who were initiated with 400 mg of pralsetinib (n=281).
Subgroup analyses	Separate efficacy analyses were done for patients who had received previous platinum-based chemotherapy and for patients who were treatment naive. Characteristics of the treatment naive population, which is included in this application, are presented in appendix C. The analyses were pre-specified. The same methods of analysis were applied as for the total NSCLC efficacy population (see above). A sample size of 170 patients with treatment-naive RET fusion-positive NSCLC not previously treated with a platinum-based chemotherapy (enrolment ongoing) was predicted to provide more than 90% power at the two-sided significance level of 0.05 for testing the null hypothesis overall response rate of 48% versus the alternative rate of 61%.

Table 75: Main characteristics of Bhandari et al.

Trial name: Not applicable	**NCT number:** N/A
Objective	To describe outcomes of patients with rearranged during transfection (RET) fusion-positive non-small-cell lung cancer (NSCLC) who received immune checkpoint inhibitor (ICI)-based treatments in the US.
Publications – title, author, journal, year	Efficacy of immune checkpoint inhibitor therapy in patients with RET fusion-positive non-small-cell lung cancer; Bhandari et al; Immunotherapy; 2021 (Bhandari et al. 2021)
Study type and design	A retrospective observational cohort study, using two de-identified datasets: the nationwide (US-based) Flatiron Health-Foundation Medicine, Inc. (FMI) NSCLC Clinico-Genomic database (CGDB) and the Guardant Health database (GuardantINFORM™, GHD).
Sample size (n)	In the Flatiron Health-Foundation Medicine clinico-Genomic database (CGDB) a total of n=9439 patients was available. Of these n=8321 was advanced/metastatic NSCLC and n=72 of

	these had confirmed RET-fusion. N=65 RET-fusion positive NSCLC patients had no co-occurring EGFR mutation and of these n=29 had evidence of immune checkpoint inhibitor therapy. In the Guardant Health Database (GHD) n=193 was RET-fusion positive advanced/metastatic NSCLC patients. Of these 192 had a confirmed RET-fusion and n=141 had no co-occurring EFGR-mutation. There are evidence that n=40 of these patients received immune checkpoint inhibitor therapy. A total of 69 RET-fusion positive patients was included in the study
Main inclusion and exclusion criteria	***Inclusion criteria*** [17] ● Patients aged 18 years or older ● patients were those who had a confirmed diagnosis of advanced/metastatic NSCLC between 1 January 2011 and 31 March 2019 (CGDB) and 1 January 2016 and 1 March 2019 (GHD) ● activating RET fusion ● evidence of receiving ICI therapies (i.e., nivolumab, pembrolizumab, atezolizumab or ipilumumab) with or without other agents in the regimen for NSCLC regardless of the line of therapy (LOT) ***Exclusion criteria*** [17] ● Patients with co-occurring EGFR mutations
Intervention	Immune checkpoint inhibitors (i.e., nivolumab, pembrolizumab, atezolizumab or ipilumumab) or carboplatin, pemetrexed and prembrolizumab
Comparator(s)	N/A
Follow-up time	Not available
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Real-world response Real-world median progression free survival Real-world median overall survival **Other endpoints:** No
Method of analysis	The index date was defined as the date of diagnosis of advanced/metastatic NSCLC. Patients' baseline demographic and clinical characteristics recorded closest to the index date available in each database were described. Treatment regimens that included an ICI were recorded by line of therapy (LOT) and the median (95% CI) duration of treatment, by LOT, was estimated using Kaplan–Meier approach. Treatment discontinuation was defined as one of the following: if the current LOT was followed by another LOT; if patients died within 30 days after their last LOT; or if the gap between the final administration or noncancelled order of treatment and the end of

	follow-up time period was >60 days. The patients were censored if they did not meet the definition for treatment discontinuation. Patterns of treatment (i.e., LOT, drug regimens [combination or monotherapy] by LOT) and sequencing of treatments were also reported descriptively. In the CGDB, real-world response, specific to a LOT, was reported as change in disease burden (progressive disease, stable disease, partial response or complete response) as assessed by the physician following radiographic imaging. All patients without response variables recorded within the LOT were considered to have missing response values; no imputation of missing values was conducted. Information on real-world response was not available in the GHD. Real-world PFS was only available in the CGDB; however, OS was available in both databases. These outcomes were summarized using Kaplan–Meier method from the initiation of the LOT in which ICI-based therapies were used. The patients were censored at the database cut-off date for both real-world PFS and OS analysis if no event had occurred.
Subgroup analyses	There was performed a post hoc subgroup analysis on patients receiving carboplatin, pemetrexed and pembrolizumab
Other relevant information	N/A

Table 76: Main characteristics of IMMUNOTARGET registry

Trial name: IMMUNOTARGET registry	**NCT number: N/A**
Objective	The primary objective of our study was to describe the progression-free survival (PFS) of patients treated with PD1/PD-L1 checkpoint inhibitors (ICI) in each subgroup carrying an oncogenic driver. The secondary objectives were both the best overall response (that was not confirmed by a second measurement) and the OS for each molecular subgroup. We also analyzed the outcome of patients according to smoking status, line of treatment, and PD-L1 expression.
Publications – title, author, journal, year	Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry; Mazieres et al; Annals of Oncology; 2019 [18]
Study type and design	Registry Retrospective study
Sample size (n)	The registry included 551 patients from 24 centers in 10 countries. The molecular alterations involved KRAS (n = 271), EGFR (n = 125), BRAF (n = 43, V600E n = 17, other n = 18), MET (n = 36, MET amplification n = 13, exon 14 skipping mutation n = 23), HER2 (n = 29), ALK (n = 23), RET (n = 16), and ROS1 (n = 7).
Main inclusion and exclusion criteria	***Inclusion criteria*** [18] • a pathologic diagnosis of lung cancer • local testing positive (either direct sequencing or NGS on validated platforms) for at least one oncogenic driver mutation: EGFR (exon 18–21) activating mutation, HER2 (exon 20) activating mutation, KRAS mutation, BRAF (exon 15) mutation, MET

	amplification or exon 14 mutation, ALK rearrangement, ROS1 rearrangement or RET rearrangement • single agent ICI therapy with commercial anti-PD1/PD-L1-antibodies; (iv) local response assessment according to RECIST1.1 criteria • follow-up with survival status. • Optionally, investigators were asked to record immunotherapy-related adverse events (irAE) and PD-L1 expression in tumor cells. ***Exclusion criteria*** [18] ● Not reported
Intervention	Most of the overall (94%) patients received anti-PD1-antibodies (nivolumab n = 466, pembrolizumab n = 48, other n = 6), fewer patients (6%) had anti-PD-L1-antibodies (atezolizumab n = 19, durvalumab n = 11, other n = 1)
Comparator(s)	N/A
Follow-up time	In the entire cohort, median follow-up was 16.1 months.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Response rate Overall survival Progression free-survival **Other endpoints:** N/A
Method of analysis	Anonymized clinical data were recorded by local investigators using electronic case report forms (eCRF) in a password-protected secure online portal from the University of Toulouse (https://ec.claudiusregaud.fr/CSOnline/). Data were centrally collected at the University of Toulouse (France). The registry was open for enrolment from May 2017 until April 2018. Best response to systemic therapies, defined as a complete or partial response achieved at least once during the course of therapy, was assessed locally using RECIST v1.1 criteria. All statistical evaluations were carried out according to the predefined plan as stated in the protocol. Data were summarized according to frequency and percentage for qualitative variables, and by median and range for quantitative variables. The 95% confidence interval for response rate was calculated using the exact binomial distribution. PFS was measured as the time from the first administration of ICI therapy to progression defined by RECIST1.1, or death due to any cause. Patients alive without progression at the time of analysis were censored at the initiation of a new therapy or last follow-up. OS was measured as the time from the first administration of ICI therapy to death due to any cause. Patients alive at the time of analysis were censored at the last follow-up. Survival data were estimated using the Kaplan–Meier method and compared using the log-rank test in overall cohort and oncogenic driver subgroups. Statistical analyses were carried out using STATA 13.1 software (StataCorp, TX).

Subgroup analyses	In the publication a Molecular subgroup analyses was performed which included KRAS, BRAF, MET and HER2. Due to a low number of patients, ALK, ROS1, and RET were analyzed together in a subgroup termed 'rearrangements'.
Other relevant information	PD-L1 analysis was carried out in each center according to local procedures. Antibodies used were E1L3N (32.8%), SP142 (31.7%), 22C3 (22.2%), SP263 (6.7%), 28-8 (5.6%), and others (1.1%). Results were provided in percentage of staining of tumor cells with three cut-off levels: 1%, 10%, and 50%

Table 77: Main characteristics of IMAD2

Trial name: IMAD2	**NCT number:** N/A
Objective	The study was undertaken to determine immune checkpoint inhibitor (ICI) efficacy against BRAF-, HER2-, MET-, and RET-NSCLC in a real-world setting
Publications – title, author, journal, year	Efficacy and Safety of Anti-PD-1 Immunotherapy in Patients With Advanced NSCLC With BRAF, HER2, or MET Mutations or RET Translocation:GFPC 01-2018; Guisier et al; Journal of thoracic Oncology; 2020 [19]
Study type and design	Retrospective multicentre study
Sample size (n)	A total of 109 patients was included, of these 9 patients was RET-translocated and received ICI.
Main inclusion and exclusion criteria	***Inclusion criteria*** [19] • Adult patients with metastatic NSCLC with BRAF-, HER2- or MET-activating mutations or RET-translocations • Treatment single agent anti–PD1 or PD-L1 ICI ***Exclusion criteria*** [19] • Patients included in a clinical immunotherapy trial were excluded
Intervention	Nivolumab Pembrolizumab
Comparator(s)	N/A
Follow-up time	Median follow-up lasted 9.2 months
Is the study used in the health economic model?	No

Primary, secondary and exploratory endpoints	**Endpoints included in this application:** ICI-treatment duration, progression-free survival (PFS), objective response rate, duration of response, and overall survival (OS). **Other endpoints:** Safety
Method of analysis	PFS was defined as the time from initiation of ICI to progression on ICI. Progression was defined as Response Evaluation Criteria in Solid Tumors version 1.1 criteria (RECIST 1.1) radiological or clinical progression (deteriorated clinical status preventing systemic treatment) or death. Assessments were done in each participating center without centralized imaging review. OS was calculated as the time from the introduction of ICI to death and the ORR to ICI as the best response according to RECIST 1.1 (radiological assessment was performed every 6 weeks). AEs were reported according to Common Terminology Criteria for Adverse Events version 4. The Kaplan-Meier method was used to estimate PFS and OS for the entire cohort and according to the molecular genotypes. All statistical analyses were computed with the RStudio statistical software (version 1.1.383)
Subgroup analyses	N/A
Other relevant information	PD-L1 status is reported

Table 78: Main characteristics of Hess et al 2021

Trial name: not applicable	**NCT number:** N/A
Objective	This observational study utilizing a linked electronic health records (EHR) database to genomics testing results was designed to compare characteristics, tumor response, progression-free (PFS) and overall survival (OS) outcomes by RET fusion status among patients with metastatic NSCLC treated with standard therapies.
Publications – title, author, journal, year	Characteristics and outcomes of patients with RET-fusion positive non-small lung cancer in real-world practice in the United States; Hess et al; BMC cancer; 2021 [6]
Study type and design	This retrospective observational study utilized the Flatiron-Foundation Medicine Clinico-Genomics database (CGDB).
Sample size (n)	A total of 5807 patients were identified that met the eligibility criteria (RET+ cohort, N = 46; RET- cohort, N = 5761).
Main inclusion and exclusion criteria	***Inclusion criteria*** [6] ● Patients with metastatic NSCLC identified in the CGDB were eligible for this study if they were age 18 years or older at the time of diagnosis who received their initial systemic anti-cancer therapy within 180 days of metastatic diagnosis.

	• All patients in the CGDB had results of next-generation sequencing (NGS) reported in the database from FMI • Patients were required to have initiated the systemic therapy on or after January 1, 2011 • No minimum follow-up time was required after initiation of first-line therapy. ***Exclusion criteria*** [6] • Patients only treated with adjuvant or neoadjuvant systemic therapy were excluded to avoid the inclusion of patients with early stage disease with missing stage data, but patients who were diagnosed with earlier stage disease who progressed were included if they received systemic therapy within 180 days after progression.
Intervention	The most common regimens used in the first-line setting for the RET+ (n = 46) and RET- cohorts (n = 4392). The most common first-line regimens used for patients with non-squamous NSCLC were bevacizumab + carboplatin + pemetrexed (23.9% for the RET+ and 9.8% for the RET- cohort), pembrolizumab + carboplatin + pemetrexed (19.6%, RET+; 14.1% RET-), pemetrexed + carboplatin (13.0% RET+; 16.1% RET-). All other regimens were each used in less than 5% of the RET+ cohort (other than clinical trial participation, which was 6.5% for RET+ and 3.3% of the RETcohort); these other regimens comprised 37.0% of all RET+ first-line therapies. Among patients with RET- cancers, carboplatin + paclitaxel was used among 8.7%, pembrolizumab among 7.6%, and erlotinib among 7.1%. The other regimens were each used by less than 5% of the RET- cohort and comprised 36.6% of first-line therapies. Overall, 14 patients (30.4%) in the RET+ cohort and 1702 (29.5%) in the RET- cohort received checkpoint inhibitors in the first line setting. Pembro + PC was used by 9 (19.6%) patients in the RET+ cohort and 665 (11.5%) in the RETcohort.
Comparator(s)	N/A
Follow-up time	Not reported
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Response rate Overall survival Progression free-survival **Other endpoints:** No other endpoints reported
Method of analysis	Baseline characteristics, defined at start of first-line therapy, were compared between the RET+ and RET- cohorts using student's t-test for continuous measures and Chi-squared/Fisher's exact test for categorical measures. Missing values were reported descriptively and included as a categorical variable in the comparative analyses to avoid losing cases due to missing data. Descriptive analyses were conducted to characterize testing and treatment patterns of both cohorts. Duration of treatment was defined from the start of the line of therapy until the last infusion/administration of any drug within that regimen. Due to the high number of treatment regimens used in NSCLC, multiplicity is a concern and pairwise comparisons of individual treatment patterns were not made but all regimens were reported

	descriptively. Analyses were conducted to compare tumor response, PFS and OS between the RET+ and RET- cohorts. Tumor response outcomes were analysed using Fisher's exact test, and best response during the line of therapy was categorized as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) as recorded by the oncologist in the patient record. Additionally, odds ratios were calculated for objective response rate (ORR), which combined both CR and PR, and were analysed among patients with response data recorded using multivariable logistic regression by RET status. Time-to-event analyses (PFS and OS) were conducted using Kaplan-Meier method and Cox proportional hazards regression from the start of the line of therapy. Baseline covariates in the multivariable regression for the adjusted analysis of PFS and OS included age, sex, race, practice type (academic or community), body weight, body mass index (BMI), stage at initial diagnosis, tumor histology, smoking status, microsatellite instability (MSI) status, genomic alterations, Eastern Cooperative Oncology Group (ECOG) performance status, PD-L1 expression (positive = > 1% staining versus negative), initial treatment regimen (checkpoint inhibitor use yes/no), and reported metastatic sites. Secondary analyses compared tumor response and evaluated adjusted and unadjusted PFS and OS from the start of first-line therapy among the subgroup of patients in both cohorts who received first-line pembrolizumab + pemetrexed + platinum (pembro + PC, the regimen evaluated in Keynote [KN]-189), which has recently become a standard of care for patients with NSCLC [34]. For the KN-189 regimen analyses, carboplatin and cisplatin were considered interchangeable.
Subgroup analyses	N/A
Other relevant information	N/A

Table 79: Main characteristics of Hedge et al 2020

Trial name: not applicable	**NCT number:** N/A
Objective	This is a large retrospective study comparing the efficacy of ICIs with non-immune checkpoint inhibitor therapy in RET-aberrant malignancies as measured by time to treatment discontinuation for disease progression
Publications – title, author, journal, year	Responsiveness to immune checkpoint inhibitors versus other systemic therapies in RET-aberrant malignancies; Hegde et al; ESMO open; 2020 [21]
Study type and design	This study was conducted as a retrospective review of all patients with RET+ malignancies who were referred to the Department of Investigational Cancer Therapeutics, the phase I clinical trials programme at The University of Texas MD Anderson Cancer Center.
Sample size (n)	Ninety-five patients with RET+ malignancies were referred to the MD Anderson phase I clinical trials programme between September 2014 and August 2018. A total of 29 had RET positive NSCLC, 13 patients received non-ICI treatment and 16 ICI treatment. Of the 16 RET-postive NSCLC receiving ICI, 14 was RET-fusion positive.
Main inclusion and exclusion criteria	***Inclusion criteria*** [21] • RET+ malignancy was defined as a tumour harbouring a known activating RET aberration (RET rearrangement or RET point mutations)

	Exclusion criteria [21] • patients who had not received any systemic therapy prior to referral were excluded from this analysis • receiving selective RET kinase inhibitors
Intervention	One of the following: Chemotherapy, multikinase inhibitor (MKI), Arginase inhibitor, chemotherapy and MKI, Osimertinib, Anti-CTLA-4, Anti-PD-1, Antio-PD-L1, Anti-PD-1 and chemotherapy, or Anti-PD-1 and MKI.
Comparator(s)	N/A
Follow-up time	Not reported
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Time to treatment discontinuation (TTD) **Other endpoints:** Not applicable
Method of analysis	TTD was analysed using the Kaplan-Meier method. The R software packages 'survival' and 'survminer' were used for statistical analysis. Patients who discontinued treatment for reasons other than disease progression were censored. To identify independent predictors of TTD, multivariate analysis was performed using the Cox proportional hazard model.
Subgroup analyses	N/A
Other relevant information	N/A

Table 80: Main characteristics of Rozenblum et al 2017

Trial name: N/A	**NCT number:** N/A
Objective	Targeted therapy significantly prolongs survival in lung adenocarcinoma. Current diagnostic guidelines include only EGFR and anaplastic lymphoma receptor tyrosine kinase gene (ALK) testing. Next-generation sequencing (NGS) reveals more actionable genomic alterations than do standard diagnostic methods. Data on the influence of hybrid capture (HC)-based NGS on treatment are limited, and we investigated its impact on treatment decisions and clinical outcomes.
Publications – title, author, journal, year	Clinical Impact of Hybrid Capture-Based NextGeneration Sequencing on Changes in Treatment Decisions in Lung Cancer; Rozenblum et al; Journal of thoracic oncology; 2017 [20]

Study type and design	Retrospective study included patients with advanced lung cancer on whom HC-based NGS was performed between November 2011 and October 2015. Demographic and clinicopathologic characteristics, treatments, and outcome data were collected.
Sample size (n)	This retrospective cohort study included 101 sequential patients with advanced lung cancer who were treated at the Davidoff Cancer Center at Rabin Medical Center (Petah Tikva, Israel) between November 2011 and October 2015. Of these a total of 9 patients had RET-fusion positive NSCLC.
Main inclusion and exclusion criteria	Not reported
Intervention	Targeted therapies (not specified) or immunotherapy. 33 patients received immunotherapy (either nivolumab [n = 20] or pembrolizumab [n = 13]) from these 4 RET-fusion positive NSCLC received ICI.
Comparator(s)	N/A
Follow-up time	Not reported
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Objective response rate **Other endpoints:** Disease control rate; Median treatment duration
Method of analysis	Not reported
Subgroup analyses	N/A
Other relevant information	N/A

Table 81: Main characteristics of KEYNOTE-024

Trial name: KEYNOTE-024	**NCT number: 02142738**
Objective	To assess the efficacy and safety of pembrolizumab (MK-3475/SCH 900475) compared to standard of care (SOC) platinum-based chemotherapies in the treatment of participants with

	previously untreated stage IV, programmed cell death ligand 1 (PD-L1) strong expressing Non-Small Cell Lung Cancer (NSCLC).
Publications – title, author, journal, year	Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. Reck, M et al. N Engl J Med 2016; 375:1823-1833 plus Suppl Appendix. doi: 10.1056/NEJMoa1606774 Health-related quality of life results for pembrolizumab versus chemotherapy in advanced, PD-L1 positive NSCLC (KEYNOTE-024): a multicenter, international, randomised, open label phase 3 trial. Brahmer, JR et al. Lancet Oncology 2017 Dec;18 (12)1600-1609. doi: 10.1016/S1470-2045(17)30690-3. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater. Reck, M et al. J Clin Oncol 2019, 37:537-546. DOI: 10.1200/JCO.18.00149 Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. Reck, M et al. J Clin Oncol. 2021 Apr 19;JCO2100174. doi: 10.1200/JCO.21.00174
Study type and design	Randomized, open label, phase III trial. Patients were randomly assigned in a 1:1 ratio to receive treatment with either pembrolizumab or the investigator's choice of chemotherapy. Randomization was stratified by ECOG performance-status score (0 vs. 1), tumor histologic type (squamous vs. nonsquamous), and region of enrollment (East Asia vs. non–East Asia) and did not include any provisions regarding equal distribution of enrollment across participating sites or stratification by site. Treatment was continued for the specified number of cycles or until the patient had radiologic disease progression (defined according to RECIST); had treatment-related adverse events of unacceptable severity, or withdrew consent or until the investigator decided to withdraw the patient, whichever occurred first. Patients in the chemotherapy group who had disease progression, which was verified by means of blinded, independent, central radiologic review, could cross over to receive pembrolizumab, if safety criteria were met. Trial status: Active, not recruiting
Sample size (n)	305
Main inclusion and exclusion criteria	Inclusion Criteria: ● Aged ≥18 years ● Histological or cytological diagnosis of Stage IV NSCLC lacking epidermal growth factor receptor (EGFR)-sensitizing mutation and/or anaplastic lymphoma kinase (ALK) translocation, and received no prior systemic chemotherapy treatment for their metastatic NSCLC ● At least one radiographically measurable lesion per RECIST 1.1 ● Life expectancy of at least 3 months ● Performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status ● Adequate organ function ● No history of prior malignancy, with the exception of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, or in situ cervical

	cancer, or has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy ● Provided newly obtained formalin fixed tumor tissue from a biopsy of a tumor at the time of or AFTER the diagnosis of metastatic disease has been made AND from a site not previously irradiated ● PD-L1 strong expressing tumor as determined by immunohistochemistry (IHC) at a central laboratory ● Female participants must have a negative pregnancy test at screening if of childbearing potential or be of non-childbearing potential ● Female participants of childbearing potential and male partners with female partners of childbearing potential must agree to use 2 adequate barrier methods of contraception during the study and for 120 days after last dose of study drug and up to 180 days after last dose of chemotherapy Exclusion Criteria: ● EGFR sensitizing mutation and/or ALK translocation ● Has received systemic therapy for the treatment of their stage IV NSCLC. Completion of treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as therapy was completed at least 6 months prior to the diagnosis of metastatic disease. ● Currently participating or has participated in a study of an investigational agent or using an investigational device within 30 days of first dose of study drug ● Tumor specimen is not evaluable for PD-L1 expression by the central laboratory ● Receiving systemic steroid therapy <= 3 days prior to first dose of study drug or receiving any other form of immunosuppressive medication ● Expected to require any other form of systemic or localized antineoplastic therapy during the study ● Received prior systemic cytotoxic chemotherapy, biological therapy, major surgery within 3 weeks of first dose of study drug; received thoracic radiation therapy of > 30 gray (Gy) within 6 months of first dose of study drug ● Received prior therapy with an anti-programmed cell death protein 1 (anti-PD-1), anti-PD-L1, anti-programmed cell death-ligand 2 (anti-PD-L2), anti-CD137 (4-1BB ligand, a member of the Tumor Necrosis Factor Receptor [TNFR] family), or anti-Cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) ● Has untreated central nervous system (CNS) metastases and/or carcinomatous meningitis ● Active autoimmune disease that has required systemic treatment in past 2 years ● Allogenic tissue/solid organ transplant ● Interstitial lung disease or pneumonitis that has required oral or IV steroids ● Received or will receive a live vaccine within 30 days prior to first dose of study drug ● Active infection requiring IV systemic therapy ● Known history of human immunodeficiency virus (HIV) ● Known active tuberculosis, or hepatitis B or C ● Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study ● Is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol) ● Pregnant or breastfeeding, or expecting to conceive or father children during the study and through 120 days after last dose of pembrolizumab or 180 days after last dose of SOC chemotherapy

	• Immediate family member who is investigational site or sponsor staff directly involved with this study
Intervention	Pembrolizumab 200 mg every 3 weeks administered as intravenous (IV) infusion for up to 35 cycles. n=154
Comparator(s)	Chemotherapy 4-6 cycles every 3 weeks, n=151: Carboplatin AUC 5-6 + Paclitaxel 200 mg/m² with optional Pemetrexed maintenance Carboplatin AUC 5-6 **OR** Cisplatin 75 mg/m² + Pemetrexed 500 mg/m² with optional Pemetrexed maintenance Carboplatin AUC 5-6 + Paclitaxel 200 mg/m² Carboplatin AUC 5-6 **OR** Cisplatin 75 mg/m² + Gemcitabine 1250 mg/m².
Follow-up time	Primary analysis, CCOD May 9, 2016: median follow-up of 11.2 mo. (range, 6.3 to 19.7). Updated analysis, CCOD July 10, 2017: median follow-up of 25.2 mo. (range, 20.4 to 33.7). Five year analysis, CCOD June 1, 2020: median follow-up of 59.9 mo. (range 55.1-68.4).
Is the study used in the health economic model?	Yes (sensitivity analysis)
Primary, secondary and exploratory endpoints	Primary endpoint: Progression Free Survival (PFS) per RECIST 1.1 as assessed by blinded independent central radiologists' review in subjects with PD-L1 strong, 1L metastatic NSCLC treated with pembrolizumab compared to standard of care (SOC) chemotherapies. Secondary endpoints: Overall Survival (OS), ORR (objective response rate) as assessed by RECIST 1.1. and to evaluate the safety and tolerability profile. Exploratory endpoints: To evaluate PFS per immune-related response criteria (irRC), PFS assessed by RECIST 1.1 by investigator review in the next line of therapy (PFS2), ORR per irRC, response duration per RECIST 1.1 by blinded independent central radiologists' review.
Method of analysis	The Kaplan–Meier method was used to estimate progression-free and overall survival. For the analysis of progression-free survival, data for patients who were alive and had no disease progression or who were lost to follow-up were censored at the time of the last tumor assessment. For the analysis of overall survival, data for patients who were alive or who were lost to follow-up were censored at the time of the last contact. Between-group differences in progression-free and overall survival were assessed with the use of a stratified log-rank test. Hazard ratios and associated 95% confidence intervals were assessed with the use of a stratified Cox proportional-hazards model with Efron's method of handling ties. The same stratification factors used for randomization were applied to the

	stratified log-rank and Cox models. Differences in response rate were assessed with the use of the stratified method of Miettinen and Nurminen.
Subgroup analyses	Analysis of progression-free survival in key subgroups was performed according to RECIST, version 1.1, by blinded, independent, central review. The subgroups were age, sex, region of enrollment, ECOG persormance status, histologic type, smoking status, brain metastases at baseline and platinum- based chemotherapy regime.
Other relevant information	Test used for PD-L1 expression testing: PD-L1 IHC 22C3 pharmaDx assay (Dako North America)

Table 82: Main characteristics of KEYNOTE-042

Trial name: KEYNOTE-042	**NCT number: 02220894**
Objective	The primary study hypothesis is that pembrolizumab prolongs overall survival (OS) compared to SOC chemotherapy in PD-L1 positive NSCLC patients
Publications – title, author, journal, year	Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Mok T et al. Lancet 2019 May 4;393(10183): 1819-1830. doi: 10.1016/S0140-6736(18)32409-7
Study type and design	Randomized, open label, phase III trial. Patients were assigned 1:1 to receive pembrolizumab 200 mg alone or the investigators choice of chemotherapy. Randomisation was stratified by region of enrollment (East Asia vs rest of world), ECOG performance score (0-1), histology (squamous vs non-squamous), and PD-L1 TPS expression (≥50% vs 1%-49 %). Treatment was continued until radiographic progression, the patient developed intolerable toxic effects, the investigator decided to stop treatment or the patient withdrew consent, up to maximum of 35 cycles in the pembrolizumab group and 4-6 cycles in the chemotherapy group. Maintenance therapy with pemetrexed was optional. No cross over from chemotherapy group to pembrolizumab was allowed as part of study. Trial status: Active, not recruiting
Sample size (n)	1274
Main inclusion and exclusion criteria	Inclusion criteria: ● Histologically- or cytologically-confirmed diagnosis of advanced or metastatic NSCLC ● PD-L1 positive tumor ● Measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 ● Life expectancy of at least 3 months

	• No prior systemic chemotherapy for the treatment of the participant's advanced or metastatic disease (treatment with chemotherapy and/or radiation as part of neoadjuvant/adjuvant therapy is allowed as long as completed at least 6 months prior to diagnosis of advanced or metastatic disease) • Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 • Adequate organ function • No prior malignancy, with the exception of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, or in situ cancer, or has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy • Submission of formalin-fixed diagnostic tumor tissue (in the case of participants having received adjuvant systemic therapy, the tissue should be taken after completion of this therapy) • Female participants of childbearing potential must have a negative urine or serum pregnancy test and must be willing to use two adequate barrier methods of contraception or a barrier method plus a hormonal method starting with the screening visit through 120 days after the last dose of pembrolizumab or 180 days after the last dose of chemotherapeutic agents used in the study • Male participants with a female partner(s) of child-bearing potential must be willing to use two adequate barrier methods of contraception from screening through 120 days after the last dose of pembrolizumab or 180 days after the last dose of chemotherapeutic agents used in the study. Exclusion criteria: • Epidermal growth factor receptor (EGFR)-sensitizing mutation and/or is echinoderm microtubule-associated protein-like 4(EML4) gene/anaplastic lymphoma kinase (ALK) gene fusion positive • Currently participating or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of study therapy • No tumor specimen evaluable for PD-L1 expression by the central study laboratory • Squamous histology and received carboplatin in combination with paclitaxel in the adjuvant setting • Is receiving systemic steroid therapy ≤3 days prior to the first dose of study therapy or receiving any other form of immunosuppressive medication with the exception of daily steroid replacement therapy • The NSCLC can be treated with curative intent with either surgical resection and/or chemoradiation • Expected to require any other form of systemic or localized antineoplastic therapy while on study • Any prior systemic cytotoxic chemotherapy, biological therapy or major surgery within 3 weeks of the first dose of study therapy; received lung radiation therapy >30 Gy within 6 months of the first dose of study therapy • Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) • Known central nervous system metastases and/or carcinomatous meningitis • Active autoimmune disease that has required systemic treatment in the past 2 years • Had allogeneic tissue/solid organ transplantation • Interstitial lung disease or history of pneumonitis that has required oral or IV steroids • Has received or will receive a live vaccine within 30 days prior to the first study therapy (seasonal flu vaccines that do not contain live vaccine are permitted) • Active infection requiring intravenous systemic therapy • Known history of human immunodeficiency virus (HIV)

	• Known active Hepatitis B or C • Regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol) • Pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the study
Intervention	Pembrolizumab 200 mg every 3 weeks administered as intravenous (IV) infusion for up to 35 cycles. n=637
Comparator(s)	Chemotherapy: 4-6 cycles every 3 weeks, n=637 Carboplatin AUC 5-6 + Paclitaxel 200 mg/m² (with optional Pemetrexed maintenance for non-squamous histology) **OR** Carboplatin AUC 5-6 + Pemetrexed 500 mg/m² (with optional Pemetrexed maintenance for non-squamous histology).
Follow-up time	Primary analysis, CCOD February 26, 2018: median follow-up of 12.8 mo. (range 0.1-38.3). Updated analysis, CCOD September 4, 2018: median follow-up of 14.0 mo (range, 0.1–43.7). 3 year survival update, CCOD February 21, 2020: median follow-up of 46.9 mo. (range, 35.8-62.1).
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary endpoints: Overall Survival (OS) in Participants With a Tumor Proportion Score (TPS) of ≥50%, Overall Survival (OS) in Participants With a Tumor Proportion Score (TPS) of ≥20%, and Overall Survival (OS) in Participants With a Tumor Proportion Score (TPS) of ≥1%. Secondary endpoints: Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants With a Tumor Proportion Score (TPS) of ≥50%, TPS of ≥20%,and TPS of ≥1%. Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by Blinded Independent Central Review (BICR) in Participants With a Tumor Proportion Score (TPS) of ≥50%, TPS of ≥20% and TPS of ≥1%. Number of Participants Who Experienced At Least One Adverse Event (AE) and Number of Participants Who Discontinued Study Treatment Due to an Adverse Event (AE). Exploratory endpoints: PFS per investigator-assessed RECIST 1.1 response criteria in subjects with TPS≥50%, TPS≥20%, and TPS≥1%, ORR per investigator-assessed RECIST 1.1 response criteria in subjects with TPS≥50%, TPS≥20%, and TPS≥1%. Response duration per RECIST 1.1 by central independent radiologists' review in subjects with TPS≥50%, TPS≥20%, and TPS≥1% respectively. PFS as assessed by RECIST 1.1 by investigator review in the next line of therapy (PFS2). OS in TPS 1-49 % population, genomic signatures that predict response in subjects treated with pembrolizumab. Evaluate relationship between pembrolizumab treatment and

	biomarkers predicting response (e.g., PD-L1, genetic variation, serum sPDL1) utilizing newly obtained or archival FFPE tumor tissue and blood, including serum and plasma.
Method of analysis	The Kaplan-Meier method was used to estimate overall survival, progression-free survival, and duration of response. Data for patients who were alive or lost to follow-up were censored at the time of last contact for estimation of overall survival. The stratified log-rank test was used to assess between-group differences in overall and progression-free survival. A stratified Cox regression model with Efron's method of tie handling was used to estimate hazard ratios (HRs) and associated 95% CIs. The stratified Miettinen and Nurminen method was used to assess between-group differences in response rate. All randomisation stratification factors were applied to all stratified analyses.
Subgroup analyses	Prespecified analysis of overall survival in key subgroups was performed for PD-L1 TPS≥50%, TPS≥20%, and TPS≥1% groups with regards to age, sex, geographic region, ECOG performance status, histologic type, smoking status, chemotherapy regime and disease status. Exploratory analysis of outcome in patients with PD-L1 TPS 1-49 % and of time to progression on next-line therapy (PFS2)
Other relevant information	Test used for PD-L1 expression testing: PD-L1 IHC 22C3 pharmaDx assay (Agilent Technologies, Carpinteria, CA, USA)

Table 83: Main characteristics of KEYNOTE-189

Trial name: KEYNOTE-189	**NCT number: 02578680**
Objective	To assess the efficacy and safety of pembrolizumab in combination with chemotherapy compared to placebo in combination with chemotherapy in the treatment of participants with metastatic nonsquamous Non-Small Cell Lung Cancer (NSCLC) without sensitizing EGFR or ALK mutations who had received no previous treatment for metastatic disease.
Publications – title, author, journal, year	Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. Gandhi L. et al. N Engl J Med 2018;378:2078-92. DOI: 10.1056/NEJMoa1801005 [44] Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. Gadgeel S. et al. J Clin Oncol. 2020 May 10;38(14):1505-1517. doi: 10.1200/JCO.19.03136. Epub 2020 Mar 9. PMID: 32150489 [43] Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Garassino et al. Lancet Oncol 2020. Doi: 10.1016/s1470-2045(19)30801-0 [42]. Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. Rodríguez-Abreu D. et al. Ann Oncol. 2021 Jul;32(7):881-895. doi: 10.1016/j.annonc.2021.04.008. Epub 2021 Apr 22. PMID: 33894335 [41]. Safety of pemetrexed plus platinum in combination with pembrolizumab for metastatic nonsquamous non-small cell lung cancer: A post hoc analysis of KEYNOTE-189. Garon et al. Lung Cancer. 2021. doi: 10.1016/j.lungcan.2021.02.021 [61].

Study type and design	Randomized, double-blind, phase III trial. Patients were assigned 2:1 to receive pemetrexed and a platinum-based drug plus either 200 mg of pembrolizumab or placebo every 3 weeks for 4 cycles, followed by pembrolizumab or placebo for up to a total of 35 cycles plus pemetrexed maintenance therapy. Randomization was stratified according to PD-L1 expression (tumor proportion score, ≥1% vs. <1%), choice of platinum-based drug (cisplatin vs. carboplatin), and smoking history (never vs. former or current). Treatment was continued until radiographic progression, unacceptable toxic effects, investigator decision, or patient withdrawal of consent. If toxicity was clearly attributed to one agent, that drug alone could be discontinued. Patients in the placebo-combination group in whom disease progression was verified by blinded, independent central radiologic review were eligible to cross over to receive pembrolizumab monotherapy. Trial status: Active, not recruiting
Sample size (n)	616 participants
Main inclusion and exclusion criteria	***Inclusion criteria (source: clinicaltrials.gov)*** ● Has a histologically-confirmed or cytologically confirmed diagnosis of stage IV nonsquamous NSCLC. ● Has confirmation that epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK)-directed therapy is not indicated. ● Has measurable disease. ● Has not received prior systemic treatment for their advanced/metastatic NSCLC. ● Can provide tumor tissue. ● Has a life expectancy of at least 3 months. ● Has a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status. ● Has adequate organ function ● If female of childbearing potential, is willing to use adequate contraception for the course of the study through 120 days after the last dose of study medication or through 180 days after last dose of chemotherapeutic agents. ● If male with a female partner(s) of child-bearing potential, must agree to use adequate contraception starting with the first dose of study medication through 120 days after the last dose of study medication or through 180 days after last dose of chemotherapeutic agents. ***Exclusion criteria (source: clinicaltrials.gov)*** ● Has predominantly squamous cell histology NSCLC. ● Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks prior to administration of pembrolizumab. ● Before the first dose of study medication: a) Has received prior systemic cytotoxic chemotherapy for metastatic disease, b) Has received antineoplastic biological therapy (e.g., erlotinib, crizotinib, cetuximab), c) Had major surgery (<3 weeks prior to first dose) ● Received radiation therapy to the lung that is >30 Gray (Gy) within 6 months of the first dose of study medication. ● Completed palliative radiotherapy within 7 days of the first dose of study medication. ● Is expected to require any other form of antineoplastic therapy while on study. ● Received a live-virus vaccination within 30 days of planned start of study medication. ● Has clinically active diverticulitis, intra-abdominal abscess, gastrointestinal obstruction, peritoneal carcinomatosis.

	● Known history of prior malignancy except if participant has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy, except for successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers. ● Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. ● Previously had a severe hypersensitivity reaction to treatment with another monoclonal antibody (mAb). ● Known sensitivity to any component of cisplatin, carboplatin or pemetrexed. ● Has active autoimmune disease that has required systemic treatment in the past 2 years. ● Is on chronic systemic steroids. ● Is unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), other than an aspirin dose ≤1.3 g per day, for a 5-day period (8-day period for long-acting agents, such as piroxicam). ● Is unable or unwilling to take folic acid or vitamin B12 supplementation. ● Had prior treatment with any other anti-programmed cell death-1 (PD-1), or PD-ligand 1 (PD-L1) or PD-L2 agent or an antibody targeting other immuno-regulatory receptors or mechanisms. Has participated in any other pembrolizumab study and has been treated with pembrolizumab. ● Has an active infection requiring therapy. ● Has known history of Human Immunodeficiency Virus (HIV). ● Has known active Hepatitis B or C. ● Has known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial. ● Is a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol). ● Has symptomatic ascites or pleural effusion. ● Has interstitial lung disease or a history of pneumonitis that required oral of IV glucocorticoids to assist with management. ● Is pregnant or breastfeeding, or expecting to conceive or father children prior to 120 days after the last dose of study medication or through 180 days after last dose of chemotherapeutic agents.
Intervention	410 participants received pembrolizumab 200 mg intravenously (IV) PLUS pemetrexed 500 mg/m^2 IV (with vitamin supplementation) PLUS cisplatin 75 mg/m^2 IV **OR** carboplatin Area Under the Curve (AUC) 5 IV on Day 1 of every 3-week cycle (Q3W) for 4 cycles followed by pembrolizumab 200 mg IV PLUS pemetrexed 500 mg/m^2 IV Q3W until progression.
Comparator(s)	206 participants received saline placebo IV PLUS pemetrexed 500 mg/m^2 IV (with vitamin supplementation) PLUS cisplatin 75 mg/m^2 IV **OR** carboplatin AUC 5 IV on Day 1 of every 3-week cycle (Q3W) for 4 cycles followed by saline placebo IV PLUS pemetrexed 500 mg/m^2 IV Q3W until progression. With Amendment 10 (effective date: 23-Dec-2019), all participants discontinued saline placebo. If documented progression occurs, participants could be able to receive pembrolizumab Q3W for the remainder of the study or until documented further progression.
Follow-up time	Primary analysis, CCOD November 8, 2017: median follow-up of 10.5 mo. (range, 0.2-20.4). Interim analysis, CCOD September 21, 2018: median follow-up of 23.1 mo. (range, 18.6-30.9) Final analysis, CCOD May 20, 2019: median follow-up of 31.0 mo. (range, 26.5-38.8).

Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was progression-free survival as assessed by Blinded Central Imaging, according to RECIST version 1.1 and overall survival. Secondary endpoints were confirmed objective response as assessed by Blinded Central Imaging according to RECIST version 1.1, and safety. Exploratory endpoints were QoL assessed by EORTC QLQ-C30 and EORTC QLQ-LC13. **Other endpoints:** Duration of response as assessed by Blinded Central Imaging according to RECIST version 1.1, progression-free survival as assessed by Investigator Immune-related RECIST (irRECIST) Response Criteria.
Method of analysis	Efficacy was assessed in the intention-to-treat population, which included all the patients who had undergone randomization. Safety was assessed in the as-treated population, which included all patients who had undergone randomization and received at least one dose of the assigned combination therapy. The Kaplan–Meier method was used to estimate overall and progression-free survival. Data for patients who were alive or lost to follow-up were censored for overall survival at the time they were last known to be alive; data for patients who crossed over were not censored at the time of crossover. Data for patients who were alive and did not have disease progression or who were lost to follow-up were censored for the analysis of progression-free survival at the time of the last imaging assessment. The stratified log-rank test was used to assess between-group differences in overall and progression-free survival. Hazard ratios and associated 95% confidence intervals were calculated with the use of a stratified Cox proportional-hazards model and Efron's method for handling tied events to assess the magnitude of the treatment difference. Differences in response rate were assessed with the stratified method of Miettinen and Nurminen. The randomization stratification factors were applied to all stratified efficacy analyses.
Subgroup analyses	Between-group treatment effect for OS, PFS and ORR (with a nominal 95% CI) were estimated and plotted within each category of the following classification variables: Age (≤65, >65 years), ECOG Performance Scale (0, 1), sex (female, male), race (white, non-white), smoking status (never, former/ current), brain metastasis status at baseline (yes, no), disease stage (IVA, IVB), PD-L1 expression (unknown, TPS <1%, or TPS ≥1% (including 1–49% and TPS≥50%) and platinum chemotherapy (cisplatin, carboplatin). The analyses were specified in the study protocol.
Other relevant information	PD-L1 expression was assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA).

Table 84: Main characteristics of Mouritzen et al 2021

Trial name: No name	**NCT number: N/A**
Objective	The selection of patients with non-small cell lung cancer (NSCLC) for immune checkpoint inhibitor (ICI) treatment remains challenging. This real-world study aimed to compare the overall survival (OS) before and after the implementation of ICIs, to identify OS prognostic

	factors, and to assess treatment data in first-line (1L) ICI-treated patients without epidermal growth factor receptor mutation or anaplastic lymphoma kinase translocation.
Publications – title, author, journal, year	Nationwide Survival Benefit after Implementation of First-Line Immunotherapy for Patients with Advanced NSCLC—Real World Efficacy; Mouritzen et al; Cancers; 2021 [32]
Study type and design	Data from the Danish NSCLC population initiated with 1L palliative antineoplastic treatment from 1 January 2013 to 1 October 2018, were extracted from the Danish Lung Cancer Registry (DLCR). Long-term survival and median OS pre- and post-approval of 1L ICI were compared. From electronic health records, additional clinical and treatment data were obtained for ICI-treated patients from 1 March 2017 to 1 October 2018
Sample size (n)	There are the following cohorts included: the DLCR pre-approval (n = 1658) cohort; post-approval (n = 2055) cohort and DLCR-ICI cohort (n = 482).
Main inclusion and exclusion criteria	***Inclusion criteria*** [32] ● Patients with NSCLC ● Initiation of 1L palliative antineoplastic treatment fro 1 March 2013 to October 2018 ***Exclusion criteria*** [32] ● EGFR and ALK alterations ● Initiation of 1L treatment between 2 August 2014 and 28 February 2017
Intervention	Immune checkpoint inhibitor – primarily pembrolizumab and only nivolumab in 2%
Comparator(s)	Not applicable
Follow-up time	For the ICI cohort the median followup period was 27.2 months (95% CI 26.7–28.2).
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Median Overall survival, median progression free-survival **Other endpoints:** Overall survival rates 1-, 2- and 3-year.
Method of analysis	For the DLCR Cohorts, a chi-square test was used to test for differences in categorical baseline characteristics between the pre- and post-approval cohorts, similarly to the DLCR-CTx and DLCR-ICI cohorts. The TNM stage was not considered due to the large proportion of missing values in the DLCR. Kaplan–Meier (KM) estimates were used to assess OS, and the log-rank test was used to compare the estimated survival curves. 2.3.2. The EHR-Identified ICI Cohort KM estimates were used to assess OS, PFS, and TTD, and log-rank tests were used to test for differences according to baseline characteristics. In the survival analyses, the Charlson

	Comorbidity Index Score (CCIS) was categorized as 0–1 and ≥2. Smoking status was excluded from the analyses due to a limited number of "never smokers" and the heterogenous smoking patterns in the "former smoking" group. TNM stage was excluded as a covariate from the survival analyses because of its interaction with metastatic sites. The remaining baseline characteristics were included as covariates and, for each of them, the assumption of proportional hazard function was assessed. Since the ECOG PS violated the assumption, weighted univariable and multivariable Cox regressions were used. Multivariable Cox regression analysis was extended with an interaction between sex and histopathology. Survival analyses were not adjusted for age-related background mortality. The median follow-up was calculated using the reverse KM estimate. All analyses were performed using R version 4.0.2 (R Core Team, Vienna, Austria). The survival- and ggsurvplot-packages were used to construct the KM estimates, and the coxphw package was used to perform the weighted Cox regressions.
Subgroup analyses	N/A
Other relevant information	N/A

Table 85: Main characteristics of Flatiron RWD study

Trial name: Effectiveness comparison between Flatiron EDM patients on three different regimes and ARROW RET-fusion positive patients given pralsetinib	**NCT number: N/A**
Objective	**The objectives of this study were:** 1. To compare the time-to-treatment discontinuation (TTD) between RET-fusion positive advanced NSCLC patients treated with pralsetinib versus all-comers in the Flatiron Health NSCLC EDM treated with pembrolizumab, carboplatin, and pemetrexed in the 1L, pembrolizumab alone in the 1L, and docetaxel in the 2L settings 2. To compare overall survival (OS) between RET-fusion positive advanced NSCLC patients treated with pralsetinib versus all-comers in the Flatiron Health NSCLC EDM treated with pembrolizumab, carboplatin, and pemetrexed in the 1L, pembrolizumab alone in the 1L, and docetaxel in the 2L settings 3. To compare progression-free survival (PFS) between RET-fusion positive advanced NSCLC patients treated with pralsetinib versus all-comers in the Flatiron Health NSCLC EDM treated with pembrolizumab, carboplatin, and pemetrexed in the 1L, pembrolizumab alone in the 1L, and docetaxel in the 2L settings
Publications – title, author, journal, year	Flatiron RWD study
Study type and design	A synthetic control from the Flatiron EDM database was compared with RET-fusion positive (RET+) patients from the ARROW trial after applying a set of harmonised eligibility criteria. Three separate comparisons were performed in total, each with three endpoints. The RET+ patients from the ARROW trial were treated with pralsetinib, whereas those in the EDM

	database were administered pembrolizumab, carboplatin, and pemetrexed (pembro+chemo) as the 1L therapy, pembrolizumab alone as the 1L therapy, or docetaxel as the 2L therapy.
Sample size (n)	71 RET-fusion positive NSCLC treated with pralsetinib; 1270 wt NSCLC patients treated with pembrolizumab, carboplatin, pemetrexed 1L ; 686 wt NSCLC patients treated with pembrolizumab mono-therapy 1L; and 52 wt NSCLC patients treated with docetaxel in 2L mono-therapy
Main inclusion and exclusion criteria	Inclusion criteria ● Patients must have unresectable locally advanced or metastatic NSCLC ○ ARROW patients must have a RET-fusion positive tissue sample ● Patient has an ECOG of 0 or 1 ○ The ARROW data has at most one subject with ECOG > 1. Thus, if EDM patients with ECOG > 1 are included, the non-overlap between the two datasets becomes an issue that cannot be solved by statistical weighting methods since we can only adjust for ECOG values common in both arms ● Subjects in the EDM database must have a line start date that falls between 2017 and 2019 (to be in line with the time frame of the ARROW trial) ● Histology must be non-squamous ○ For each comparison, the ARROW data has at most two patients with squamous histology Exclusion criteria ● For EDM, patients with > 90-day gap between advanced diagnosis and first visit or medication administration were excluded in accordance with best practices ● Patients in the EDM must not have had pralsetinib or selpercatinib or clinical study drugs in any line ● Patient has another known driver mutation (EGFR, ALK, ROS1 or BRAF) at index date ● Index date less than 6 months prior to the EDM cut-off date ○ Patients that die within 6 months are included ● For Stage at initial diagnosis and Smoking status, patients must not have either missing entries or have entries labelled Not reported.
Intervention	Pralsetinib
Comparator(s)	Pembrolizumab, carboplatin, and pemetrexed in the 1L, pembrolizumab alone in the 1L, and docetaxel in the 2L settings
Follow-up time	Not reported
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** 1. Time-to-treatment discontinunation 2. Overall survival 3. Progression-free survival

Method of analysis	**Descriptive statistics** All analyses are presented by the EDM comparative treatment group, of which there are three: (1) pembrolizumab in 1L, (2) pembrolizumab, carboplatin, and pemetrexed in 1L, and (3) docetaxel in 2L. Continuous variables were summarised using descriptive statistics (n, median, and interquartile range). The standardised mean difference (SMD) was used to assess imbalances between the ARROW trial patients and external controls. Categorical variables were summarised showing the number and percentage (n,%) of patients overall and by disease subtypes. To assess imbalance between cohorts, the SMD for both continuous and categorical variables were used. The SMD is preferred over p-values because of its robustness to sample size [62]. For covariates with more than three levels, a Mahalanobis distance-based method was used to generalise the SMD metric [63]. If a variable has an SMD exceeding 0.1, it is considered to be imbalanced between the two cohorts [62]. **Synthetic control** For all three outcomes (TTD, OS, PFS), several time-to-event models were fit. The results presented are those that have performed well in terms of balancing the most number of the variables deemed prognostically important. Later sections provide brief descriptions of the two main methods used to balance the ARROW and EDM cohorts: inverse probability of treatment weighting (IPTW), and matching. For all IPTW and matching analyses, the average treatment effect on the treated (ATT) was estimated. The overall goal was to achieve covariate balance between the ARROW pralsetinib arm and synthetic control arm, by matching the external data from the EDM to the ARROW patient characteristics. After balancing, the variables included in the outcome model for both IPTW and matching are those noted to be included in the set of adjustment variables in section 7.1.3.1.2 (Flatiron EDM comparison), that are found to still be slightly imbalanced post-adjustment, which was set to be those variables with SMD values between 0.1 and 0.12. Variables with SMD above 0.12 were not included in the outcome models. Note that by including covariates in the Cox model, the computed ATT is conditional on patient covariates. That is, the effect of treatment vs no treatment in the treated population is conditional on covariates (e.g. covariate-matched treated). **Inverse probability treatment weighting (IPTW)** IPTW is a well-established method for mitigating bias due to measured confounders when estimating treatment effects in non-randomized settings [64]. The data for the ARROW pralsetinib arm and EDM comparator arm were pooled. A logistic regression propensity score model was estimated by regressing a pralsetinib treatment indicator on baseline covariates. Propensity scores were calculated for each patient using the fitted values from the propensity score model. IPTW weights for the ATT estimand were computed by assigning each patient in the pralsetinib arm a weight of 1 and each patient in the comparator arm a weight of [propensity score] / (1 – [propensity score]). The effective sample size was calculated by taking the square of the sum of all weights divided by the summation of each of the weights squared [65]. All tables and figures presented for the IPTW analysis were produced after trimming subjects with large weights [66,67]. Next, IPTW-weighted Cox proportional hazards (PH) regression models were used to estimate hazard ratios (HR) between the pralsetinib and comparator arms and 95% confidence intervals (95% CIs) were computed using robust standard errors. For each model, the PH assumption was checked using a combination of Schoenfield tests and visual inspection of the Kaplan-Meier (KM) curves and log-negative-log (LNL) survival plots [68]. The weighted restricted mean survival time difference (RMSTD) estimated via weighted Kaplan-Meier curves was presented to cross-check instances where the PH assumption may be violated. The 95% CIs were computed via bootstrapping with 10000 iterations [69]. The weighted KM plots were also generated to visually assess time to event between comparator groups for each endpoint.

	Matching Matching was performed among the cohort comparison groups conditioned on the potential confounder set [70–72]. Matching was used to estimate the ATT through a nearest-neighbor approach based on propensity scores to account for small sample sizes. Several matching options were explored: 1:1, 2:1, and 4:1 matching with and without replacement. The option that was assessed as yielding the best results in terms of balance is presented in the results. A measure resulting from the matching analysis is the sample size of the matched pseudo-population. For example for settings where sampling is done with replacement, the same patient or subset of patients may be re-sampled multiple times. Thus, this measure of sample size is not the same measure as the effective sample size described in the previous section. For each outcome, doubly-robust estimation (DRE) was implemented in the weighted Cox PH model. Those variables that remain imbalanced were included in the outcome model. Finally, for each outcome the weighted RMSTD was estimated using the matched dataset as another way to cross-check for any violations of the PH assumption from the DRE estimates. Bootstrapping was used to estimate the 95% CI for both the weighted HR and RMSTD in the matched datasets. Weighted KM plots were also generated on the matched datasets to visually assess time to event between comparator groups for each endpoint.
Subgroup analyses	N/A
Other relevant information	N/A

15. Appendix C – Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

In the following, we provide tables of baseline characteristics of patients included in the studies used for each comparison of efficacy and safety. Table 86 presents all studies, including ARROW and the retrospective studies, used in the narrative comparison of patients with RET fusion-positive NSCLC that are used to inform both clinical question 1 and 2. Table 87 and Table 88 include the clinical studies used in the comparison of RET fusion-positive patients from ARROW and patients with unknown RET fusion status from KEYNOTE-024 and KEYNOTE-042 (clinical question 1) and KEYNOTE-189 (clinical question 2). Below is a description of the comparability of the baseline characteristics across the studies and how well the study populations align with patients treated in Danish clinical practice.

15.1 Comparability of patients across studies

RET fusion-positive NSCLC

Comparability of patients in ARROW and included retrospective studies

NSCLC patients in ARROW were required to have pathologically documented, definitively diagnosed locally advanced or metastatic disease with a RET fusion. Patients were either not previously or previously treated with platinum-based chemotherapy. The retrospective studies included RET fusion-positive patients treated in first, second or later lines, but the specific treatment lines were not reported in all studies. All patients were treated with ICI-based therapy or pembrolizumab in combination with pemetrexed and cisplatin like in KEYNOTE-189. Patients treated with ICI monotherapy received either nivolumab, pembrolizumab, atezolizumab or durvalumab. However, in four out of the six studies it was not specified what kind of ICI the patients received.

Only two out of the six retrospective studies report baseline characteristics for the RET fusion-positive patients specifically, making it difficult to compare across trials. ARROW enrolled patients regardless of histology, but as most RET fusions are detected in non-squamous NSCLC patients, only 1.3% of the trial population in ARROW had squamous disease. As expected, similar proportions were observed in the RET fusion-positive patients in the retrospective studies from which data was available. The proportion of males and females as well as non-smokers were somewhat balanced between the studies from which data was available. The limited information on other characteristics makes it difficult to assess the degree of comparability.

Overall, the uncertainties in terms of specific ICIs and treatment lines are limitations that should be taken into consideration when comparing the available data with the data from ARROW. Moreover, the limited information on baseline characteristics alongside the small sample size in the retrospective studies makes it difficult to assess the degree of comparability, which is largely unclear.

Based on the data available, it is deemed most informative to use the comparator data from the Flatiron analysis in a first-line setting by Bhandari et al (2021) and the line-agnostic ICI data from the other retrospective studies.

NSCLC with unknown RET fusion status

Comparability of patients in ARROW, KEYNOTE-024, KEYNOTE-042, Mouritzen et al and Flatiron EDM study

In ARROW, NSCLC patients were required to have pathologically documented, definitively diagnosed locally advanced or metastatic disease with a RET fusion. Patients were either not previously or previously treated with platinum-based chemotherapy. In KEYNOTE-024, patients were required to have stage IV or recurrent disease. Patients in KEYNOTE-042 were required to have locally advanced or metastatic disease, but more than 80% of the enrolled patients had stage IV disease. In both KEYNOTE studies patients were required to have received no prior chemotherapy for metastatic disease.

All three trials had similar eligibility requirements in terms of age and performance status. KEYNOTE-024 and KEYNOTE-042 also had similar requirements in terms of biomarker status availability. In the KEYNOTE studies, PD-L1 status, but no other biomarker status, were available. KEYNOTE-042 required patients to have PD-L1≥ 1% at enrolment and KEYNOTE-024 required patients to have PD-L1≥50%. PD-L1 status was not determined in ARROW. All three trials enrolled patients regardless of histology. However most RET fusions are detected in non-squamous NSCLC patients, and hence, only 1.3% of the trial population in ARROW had squamous histology. The proportion of patients with squamous histology was 18.4% in KEYNOTE-024 and 37% in the population with PD-L1 expression ≥50% in KEYNOTE-042. The ratio of non-squamous/squamous histology can have an impact on survival outcomes.

Across the three clinical trials the median age of patients is similar, ranging from 60 to 66 years. ECOG PS was well-balanced across all studies, with 30-35% of patients having ECOG PS 0 and 97-100% of patients in all studies with either ECOG PS 0 or 1. Smoking status is balanced between the KEYNOTE studies, but differs from the ARROW study that includes far less former and current smokers (34% and 3%) compared to the KEYNOTE studies (59-71% and 20-22%). For this reason patients from ARROW might be considered healthier. Lastly, there is a difference in the proportion of males across the trials, ranging from 50% in ARROW to 70% in KEYNOTE-042.

Overall, the KEYNOTE trials are found to be comparable in regard to baseline characteristics. The comparability has previously been described in the Medicines Council treatment guideline for first-line NSCLC [34]. As described in the introduction of this submission, RET fusion-positive NSCLC patients are more likely to be younger, to have non-squamous disease and to be non-smokers. This is also reflected in the RET fusion-positive population in ARROW when comparing to the populations with unknown RET fusion status in the KEYNOTE studies. These factors are considered to be potential treatment-effect modifiers or prognostic factors, which can result in a biased treatment-effect. Other

factors including presence of brain metastasis, RET fusion status and PD-L1 status were not reported in all studies, and therefore the extent of population differences for these characteristics is unclear.

The study by Mouritzen examined real-world cohorts of Danish patients receiving ICI and should therefore serve as a strong indicator for the characteristics of the assessed population receiving ICI as well as the efficacy of ICI in Danish patients. Some of the reported characteristics in the ARROW trial and the KEYNOTE studies (race, smoking history, etc.) are not reported in the study by Mouritzen et al. When comparing the population presented in Mouritzen et al to that of ARROW, the populations are overall comparable based on the baseline characteristics reported for both the EHR-based ICI cohort and the ICI cohort matched across EHR and the DLCR database. Some differences should however be noted: a) as the population in Mouritzen et al is Danish, it is likely more homogenous when compared to the population in ARROW; b) the study by Mouritzen included a slightly higher proportion of patients with ECOG PS 2 and above, whereas ARROW only included patients with PS 1; c) due to the low incidence of RET fusions in squamous NSCLC, ARROW included a smaller proportion (1.3%) when compared to the population i Mouritzen (23%). When compared to the KEYNOTE studies, the study by Mouritzen et al included patients with ECOG PS 2 and above (not included in the KEYNOTE studies). The proportion (16%) is however fairly small, and the studies should overall be comparable to the Danish population treated with ICI.

The RWD study in the Flatiron EDM database was used to perform an adjusted comparison of ARROW patients versus real-life patients receiving pembrolizumab monotherapy in first-line NSCLC. Several baseline characteristics were used for matching the two populations, and the standardised mean difference (SMD) was used to assess imbalances between the ARROW trial patients and external controls from the Flatiron EDM database. A variable was considered imbalanced, if the SMD between the two cohorts exceeded 0.1. Multiple variables required balancing with smoking history and variables relating to the sum of metastases being particularly imbalanced. After adjustments had been performed, balancing was excellent for all variables that were explicitly adjusted for. The two variables with SMD exceeding 0.1 are still close, with ECOG and time from initial diagnosis having SMD values of 0.146 and 0.129, respectively. Although the sum of total metastases is highly imbalanced, the variable itself is suspected to be lacking in reliability and sensitivity analyses were carried out, showing that explicitly adjusting for this variable does not change the overall conclusion.

Overall, factors which may be considered the most imbalanced between ARROW and the comparator studies include gender, histological features and smoking status. The proportion of patients with brain metastasis was only reported in ARROW and in the Danish population receiving ICI as reported by Mouritzen et al, and can therefore not be compared across all studies. Most of the differences observed in baseline characteristics are to be expected, and inherent uncertainties are unavoidable when comparing a population consisting exclusively of RET fusion-positive patients in ARROW with populations with unknown RET fusion status. However, the populations are considered comparable to an extent that allows narrative and naïve comparisons. The cross-study differences should be taken into consideration when interpreting results from the comparative analyses. Lastly, the comparison versus an external control cohort from the Flatiron EDM database achieved excellent balance.

Comparability of patients in ARROW, KEYNOTE-189 and Flatiron EDM study

Patients in KEYNOTE-189 were required to have previously untreated locally advanced or metastatic disease, while NSCLC patients in ARROW were required to have pathologically documented, definitively diagnosed locally advanced or metastatic disease with a RET fusion either not previously or previously treated with platinum-based chemotherapy.

Both trials had similar eligibility requirements in terms of age and performance status. In the KEYNOTE-189, PD-L1 status, but no other biomarker status, were available. Patients were required to have PD-L1≥ 1% at enrolment. In

ARROW, PD-L1 status was not determined. ARROW enrolled patients regardless of histology, however most RET fusions are detected in non-squamous NSCLC cancer patients, and hence, only 1.3% of the trial population in the study had squamous histology. KEYNOTE-189 mainly included patients with non-squamous histology (96.1%). Thus, the populations in the two trials are comparable in terms of histological features.

Median age of patients is similar between trials, ranging from 60 to 65 years. ECOG PS was also well-balanced between the two trials, with 34-42% of patients having ECOG PS 0 and 97-100% of patients in both studies with either ECOG PS 0 or 1. There is a substantial difference in the smoking status with ARROW including a notably higher proportion of non-smoking patients compared to KEYNOTE-189. Moreover, the proportion of patients with brain metastases was notably higher in ARROW than in KEYNOTE-189 (37% vs. 17%).

The RWD study in the Flatiron EDM database was used to perform an adjusted comparison of ARROW patients versus real-life patients receiving pembrolizumab, carboplatin, and pemetrexed in first-line NSCLC. Several baseline characteristics were used for matching the two populations, and the standardised mean difference (SMD) was used to assess imbalances between the ARROW trial patients and external controls from the Flatiron EDM database. A variable was considered imbalanced, if the SMD between the two cohorts exceeded 0.1. Several variables required balancing; in particular smoking history and variables related to metastases. Following adjustments, all variables were excellently balanced, although the sum of metastases remained imbalanced. A lack of reliability was suspected for this variable and sensitivity analyses were carried out, showing that explicitly adjusting for this variable does not change the overall conclusion.

Overall, there were differences in the populations when comparing ARROW and KEYNOTE-189, such as in the proportion of patients with smoking history and brain metastases of the included patients. The populations are however deemed similar enough to perform narrative and naïve comparisons, although cross-trial differences and uncertainties should be taken into account when interpreting the results.

15.2 Comparability of the study populations with Danish patients eligible for treatment

As described previously, RET fusion-positive NSCLC patients are expected to have similar characteristics as patients with ALK and ROS1 positive NSCLC. Thus, patients are more likely to have lung adenocarcinoma and to be younger than wildtype NSCLC patients. Also, a higher proportion of RET fusion-positive patients are expected to be female and/or never or light smokers compared to wildtype NSCLC patients.

ARROW enrolled patients regardless of histology, however as most RET fusions are detected in non-squamous NSCLC cancer patients, only 1.3% of the trial population in the study had squamous disease. In comparison to the populations in the comparative studies, patients in ARROW were slightly younger, a higher proportion were female and the majority of patients had never smoked. Furthermore, the majority of patients in ARROW have ECOG PS 0-1, which is transferable to current Danish clinical practice.

Overall, the study population from ARROW is considered representative of Danish patients eligible for RET fusion inhibitor treatment.

Table 86: Baseline characteristics of patients in ARROW and retrospective studies (clinical question 1 and 2)

	ARROW		Bhandari 2021* [17]	Mazieres 2019 [18]	Guisier 2020* [19]	Hess 2021* [6]	Hedge 2020* [21]	Rozenblum 2017* [20]
	Total efficacy population	No prior systemic treatment						
Intervention	Pralsetinib	Pralsetinib	ICI-based therapy	ICI-based therapy	ICI-based therapy	KN-189 regimen	ICI-based therapy	ICI-based therapy
RET fusion-positive - no.	233	75	17	16	9	9	16	4
Age								
Median (range) — yr	60.0 (26-87)	63.0 (30-87)	-	54.5 (29-73)	-	-	-	-
Mean (± SD) — yr	-	-	-	-	57.8 ±6.4	-	-	-
Gender — no. (%)								
Male sex	111 (47.6)	39 (52.0)	-	7 (43.7)	5 (56)	-	-	-
Female sex	122 (52.4)	36 (48.0)	-	9 (56.3)	4 (44)	-	-	-
ECOG performance status — no. (%)								

0	78 (33.5)	31 (41.3)	-	-	-	-	-	-
1	149 (63.9)	43 (57.3)	-	-	-	-	-	-
0-1	-	-	-	-	8 (89)	-	-	-
2	6 (2.6)	1 (1.3)	-	-	-	-	-	-
≥2	-	-	-	-	1 (11)	-	-	-
Missing	-	-	-	-	0 (0)	-	-	-
Histologic features — no. (%)								
Non-squamous	224 (96.1)	74 (98.7)	-	14 (87.5)	8 (89)	-	-	-
Squamous	3 (1.3)	1 (1.3)	-	0 (0)	1 (11)	-	-	-
Large cell carcinoma	-	-	-	1 (6.3)	0 (0)	-	-	-
Undifferentiated	1 (<1)	0	-	-	-	-	-	-
Other	5 (2.1)	0	-	-	-	-	-	-
Not specified	-	-	-	1 (6.3)	0 (0)	-	-	-

Administered ICI — no. (%)								
Pembrolizumab	-	-	2 (11.8)	-	2 (9)	-	-	-
Pembrolizumab + platinum-based chemotherapy	-	-	12 (70.6)	-	0 (0)	-	-	-
Atezolizumab	-	-	2 (11.8)	-	0 (0)	-	-	-
Nivolumab	-	-	-	-	7 (30)	-	-	-
Other	-	-	1 (5.9)	-	0 (0)	-	-	-
Line of ICI therapy — no. (%)								
1	-	-	-	-	0 (0)	-	-	-
2	-	-	-	-	6 (26)	-	-	-
3	-	-	-	-	2 (9)	-	-	-
≥4	-	-	-	-	1 (4)	-	-	-
Smoking history — no. (%)								
Yes	-	-	-	5 (31.3)	5 (56)	-	-	-

Former	78 (33.5)	28 (37.3)	-	-	-	-	-	-
Current	6 (2.6)	4 (5.3)	-	-	-	-	-	-
No	145 (62.2)	41 (54.7)	-	10 (66.7)	4 (44)	-	-	-
Unknown	4 (1.7)	2 (2.7)	-	1 (6.3)	0 (0)	-	-	-

* Baseline characteristics are not presented for the studies as the available baseline characteristics are from an overall population and not for the RET fusion specific population.

Table 87: Baseline characteristics of patients in ARROW, KEYNOTE-024, KEYNOTE-042, Mouritzen et.al, and Flatiron EDM (clinical question 1)

	ARROW		**KEYNOTE-024**		**KEYNOTE-042**		**Mouritzen et al.**		**Flatiron EDM**
	Total efficacy population	No prior systemic treatment	Total efficacy population		Total efficacy population		ICI cohort	ICI cohort (EHR-based)	Pembrolizumab monotherapy (unadjusted)
Intervention	Pralsetinib (n=233)	Pralsetinib (n=75)	PEMB (n=154)	Chemo (n=151)	PEMB (n=299)	Chemo (n=300)	ICI (n=482)	ICI (n=579)	PEMB (n=686)
Age									
Median (range) — yr	60.0 (26-87)	63.0 (30-87)	64.6 (33-90)	66.0 (38-85)	63.0 (56-68)	64.0 (57-69)	70 (45-88)	-	-
≥65 yr — no. (%)	88 (37.8)	34 (45.3)	-	-	56	54	-	-	489 (71.3)

Gender — no. (%)									
Male sex	111 (47.6)	39 (52.0)	59.7	62.9	69	70	41.7	246 (42)	311 (45.3)
Female sex	122 (52.4)	36 (48.0)	40.3	37.1	31	30	58.3	333 (58)	375 (54.7)
Race — no. (%)									
White	121 (51.9)	52 (69.3)	-	-	-	-	-	-	493 (71.9)
Asian	92 (39.5)	17 (22.7)	-	-	-	-	-	-	-
Native Hawaiian or other	2 (0.9)	1 (1.3)	-	-	-	-	-	-	-
Other	2 (0.9)	0	-	-	-	-	-	-	123 (17.9)
Unknown	16 (6.9)	5 (6.7)	-	-			-	-	70 (10.2)
Region of enrollment — no. (%)									
European	-	-	-	-	71 (24)	66 (22)	482 (100)	579 (100)	-
Non–East Asia	-	-	133 (86.4)	132 (87.4)	-	-	-		-
East Asia	-	-	21 (13.6)	19 (12.6)	92 (31)	94 (31)	-		-

Latin America	-	-	-	-	53 (18)	63 (21)	-		-
Other	-	-	-	-	83 (28)	77 (26)	-		-
ECOG performance status — no. (%)									
0	78 (33.5)	31 (41.3)	54 (35.1)	53 (35.1)	96 (32)	91 (30)	-	194 (34)	230 (33.5)
1	149 (63.9)	43 (57.3)	99 (64.3)	98 (64.9)	203 (68)	209 (70)	-	295 (51)	456 (66.5)
2	6 (2.6)	1 (1.3)	-	-	0 (0)	0 (0)	-	-	-
≥2	-	-	-	-	-	-	-	90 (16)	0 (0)
Smoking status — no. (%)									
Never	145 (62.2)	41 (54.7)	5 (3.2)	19 (12.6)	64 (21)	67 (22)	-	-	58 (8.5)
Former	78 (33.5)	28 (37.3)	115 (74.7)	101 (66.9)	178 (60)	174 (58)	-	-	-
Current	6 (2.6)	4 (5.3)	34 (22.1)	31 (20.5)	57 (19)	59 (20)	-	-	-
Unknown	4 (1.7)	2 (2.7)	-	-	0 (0)	0 (0)	-	-	0 (0)
Histologic features — no. (%)									

Adenocarcinoma	224 (96.1)	74 (98.7)	125 (81.2)	124 (82.1)	192 (64)	186 (62)	291 (60.4)	409 (71)	‡
Squamous	3 (1.3)	1 (1.3)	29 (18.8)	27 (17.9)	107 (36)	114 (38)	92 (19.1)	135 (23)	-
Undifferentiated	1 (<1.0)	0	-	-	0 (0)	0 (0)	-	-	-
Other	5 (2.1)	0	-	-	0 (0)	0 (0)	99 (20.5)	35 (6)	-
History of CNS/brain metastases — no. (%)	87 (37.3)	25 (33.3)	-	-	-	-		38 (7)	89 (13.0)
PD-L1 tumor proportion score — no. (%)							-		
≥1%	-	-	-	-	-	-	-	-	-
≥20%	-	-	-	-	-	-	-	-	-
≥50%	-	-	154 (100)	151 (100)	299 (100)	300 (100)		552 (95)	-
Previous therapy for nonmetastatic disease — no. (%)									
Radiotherapy	-	-	-	-	40 (13)	39 (13)	-	-	-
Neoadjuvant therapy	-	-	3 (1.9)	1 (0.7)	1 (<1)	5 (2)	-	-	-
Adjuvant therapy	-	-	6 (3.9)	3 (2.0)	8 (3)	4 (1)	-	-	-

Previous therapy — no. (%)									
Chemotherapy	138 (59.2)	0	-	-	-	-	-	-	-
Platinum chemotherapy	136 (58.4)	0	-	-	-	-	-	-	-
PD-(L)1 inhibitors	69 (29.6)	0	-	-	-	-	-	-	-
Multi-kinase inhibitors	44 (18.9)	0	-	-	-	-	-	-	-
Prior radiation therapy	90 (38.6)	16 (21.3)	-	-	-	-	-	-	-
Prior cancer related surgeries / procedures	116 (49.8)	34 (45.3)	-	-	-	-	-	-	-

‡ Due to data sparsity, all NSCLC patients in Flatiron were assumed to be non-squamous.

Table 88: Baseline characteristics of patients in ARROW and KEYNOTE-189 (clinical question 2)

	ARROW		KEYNOTE-189		Flatiron EDM
	Total efficacy population	No prior systemic treatment	Total efficacy population		Pembrolizumab and chemotherapy
Intervention	Pralsetinib (n=233)	Pralsetinib (n=75)	PEMB + chemo (n=410)	Placebo + chemo (n=206)	PEMB + chemo (n=1270)

Age					
Median (range) — yr	60.0 (26-87)	63.0 (30-87)	65.0 (34.0–84.0)	63.5 (34.0–84.0)	-
<65 yr — no. (%)	88 (37.8)	34 (45.3)	197 (48.0)	115 (55.8)	508 (40.0)
Gender — no. (%)					
Male sex	111 (47.6)	39 (52.0)	254 (62.0)	109 (52.9)	701 (55.2)
Female sex	122 (52.4)	36 (48.0)	156 (38.0)	97 (47.1)	569 (44.8)
Race — no. (%)					
White	121 (51.9)	52 (69.3)	-	-	883 (69.5)
Asian	92 (39.5)	17 (22.7)	-	-	-
Native Hawaiian or other	2 (0.9)	1 (1.3)	-	-	-
Other	2 (0.9)	0	-	-	248 (19.5)
Unknown	16 (6.9)	5 (6.7)	-	-	139 (10.9)
Region of enrollment — no. (%)					

Europe	-	-	243 (59.3)	131 (63.6)	-
North America	-	-	111 (27.1)	46 (22.3)	-
East Asia	-	-	4 (1.0)	6 (2.9)	-
Other regions	-	-	52 (12.7)	23 (11.2)	-
ECOG performance status — no. (%)					
0	78 (33.5)	31 (41.3)	186 (45.4)	80 (38.8)	512 (40.3)
1	149 (63.9)	43 (57.3)	221 (53.9)	125 (60.7)	758 (59.7)
2	6 (2.6)	1 (1.3)	1 (0.2)	0	0 (0)
Smoking status — no. (%)					
Never	145 (62.2)	41 (54.7)	8 (11.7)	25 (12.1)	126 (9.9)
Current or former	-	-	362 (88.3)	181 (87.9)	1144 (90.1)
Former	78 (33.5)	28 (37.3)	-	-	-
Current	6 (2.6)	4 (5.3)	-	-	-

Unknown	4 (1.7)	2 (2.7)	-	-	0 (0)
Histologic features — no. (%)					
Adenocarcinoma	224 (96.1)	74 (98.7)	394 (96.1)	198 (96.1)	-
Squamous	3 (1.3)	1 (1.3)	-	-	-
NSCLC not otherwise specified	-	-	10 (2.4)	4 (1.9)	-
Undifferentiated	1 (<1.0)	0	-	-	-
Other	5 (2.1)	0	6 (1.5)	4 (1.9)	-
History of CNS/brain metastases — no. (%)	87 (37.3)	25 (33.3)	73 (17.8)	35 (17.0)	-
PD-L1 tumor proportion score — no. (%)					
<1%	-	-	127 (31.0)	63 (30.6)	-
1–49%	-	-	128 (31.2)	58 (28.2)	-
≥50%	-	-	132 (32.2)	70 (34.0)	-
Could not be evaluated	-	-	23 (5.6)	15 (7.3)	-

Previous therapy for nonmetastatic disease — no. (%)					
Thoracic radiotherapy	-	-	28 (6.8)	20 (9.7)	-
Neoadjuvant therapy	-	-	5 (1.2)	6 (2.9)	-
Adjuvant therapy	-	-	25 (6.1)	14 (6.8)	-
Previous treatment — no. (%)					-
Chemotherapy	138 (59.2)	0	-	-	-
Platinum Chemotherapy	136 (58.4)	0	-	-	-
PD-(L)1 Inhibitors	69 (29.6)	0	-	-	-
Multi-kinase inhibitors	44 (18.9)	0	-	-	-
Prior Radiation Therapy	90 (38.6)	16 (21.3)	-	-	-
Prior Cancer Related Surgeries/ Procedures	116 (49.8)	34 (45.3)	-	-	-

16. Appendix D – Efficacy and safety results per study

16.1 Definition, validity and clinical relevance of included outcome measures

Table 89: Included outcome measures across the included clinical trials (ARROW, KEYNOTE-024, KEYNOTE-042, KEYNOTE-189, LIBRETTO-001, SIREN)

Outcome measure	**Definition**	**Validity**	**Clinical relevance**
OS	OS is defined as the time from randomisation to death of any cause.	OS is considered an important clinical endpoint in clinical trials within oncology. For many years it has been considered the gold-standard endpoint for establishing clinical benefit. However, using OS can be associated with certain limitations as it may be affected by subsequent therapy or patient crossover between treatment arms in studies of early treatment. In previous Medicines Council assessments within NSCLC, OS has been defined as one of the most important clinical endpoints.	To our knowledge, published information on minimal important differences is not available. In previous Medicines Council assessments within NSCLC, the lung cancer expert committee has found a difference in median OS of 3 months and an absolute risk reduction of 5% after 12, 18 and 24 months clinically relevant.
PFS	PFS is defined as the time from randomization to disease progression or death. In ARROW and KEYNOTE-042 progression was assessed by blinded independent central review according to RECIST version 1.1. In KEYNOTE-024, progression was assessed by blinded independent central radiologists review according to RECIST version 1.1 and in KEYNOTE-189, progression was assessed by blinded central imaging vendor review per RECIST 1.1.	PFS is a widely used endpoint within oncology trials. It is used to assess the time during which patients are alive without progressive disease. PFS is not affected by the impact of subsequent treatment and patient crossover between trial arms in the same manner as OS, and therefore serves as a relevant supplement to OS. In previous Medicines Council assessments within NSCLC, PFS has been defined as an important clinical endpoint.	To our knowledge, published information on minimal important differences is not available. In previous Medicines Council assessments within NSCLC, the lung cancer expert committee has found a difference in median PFS of 3 months and an absolute risk reduction of 5% after 12 and 18 months clinically relevant.

ORR	ORR is defined as the proportion of patients who have a partial or complete response to treatment. In ARROW and KEYNOTE-042, response was assessed by blinded independent central review according to RECIST version 1.1. In KEYNOTE-024, response was assessed by blinded independent central radiologists review according to RECIST version 1.1, and in KEYNOTE-189, response was assessed by blinded central imaging vendor review per RECIST 1.1.	ORR is an important endpoint to demonstrate the response to treatment. In previous Medicines Council assessments, ORR has been defined as an important clinical endpoint.	To our knowledge, published information on minimal important differences is not available. In a previous Medicines Council assessment, the tumor agnostic expert committee has found a difference in the proportion of patients that obtain complete or partial response of 15% clinically relevant.
Discontinuation due to AEs	Proportion of patients that discontinue study treatment due to any adverse event. AEs are coded using the standard MedDRA and grouped system organ class.	In previous Medicines Council assessments within NSCLC, discontinuation due to AEs has been defined as one of the most important clinical endpoints.	To our knowledge, published information on minimal important differences is not available. In previous Medicines Council assessments within NSCLC, the lung cancer expert committee has found a difference in the proportion of patients that discontinued treatment due to AEs or treatment related AEs of 5% clinically relevant.
Grade ≥3 AEs	Proportion of patients that experience any grade ≥3 adverse event. AEs are coded using the standard MedDRA and grouped system organ class. Grading (severity of the AE) is defined according to Common Terminology Criteria for Adverse Events (CTCAE).	The proportion of patients that experience grade ≥3 adverse events is an expression of possible severe toxicity. Adverse events are not necessarily related to treatment. In previous Medicines Council assessments within NSCLC, grade 3-4 AEs has been defined as an important clinical endpoint.	To our knowledge, published information on minimal important differences is not available. In previous Medicines Council assessments within NSCLC, the lung cancer expert committee has found a difference in the proportion of patients that experienced a grade 3-4 AE of 5% clinically relevant.
HRQoL	In ARROW, QoL was assessed by EORTC QLQ-C30, but no analysis has been carried out for the November 6, 2020 data cut.	In previous Medicines Council assessments within NSCLC, HRQoL has been defined as an important clinical endpoint.	To our knowledge, published information on minimal important differences is not available.

	In KEYNOTE-024, QoL was assessed by EORTC QLQ-C30, EORTC QLQ-LC13 and EuroQoL EQ-5D. KEYNOTE-042 does not report data on QoL. In KEYNOTE-189, QoL was assessed by EORTC QLQ-C30 and EORTC QLQ-LC13.		

16.2 Results per study

Table 90: Results of ARROW (NCT03037385)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS Total efficacy population	Pralsetinib	233	NR	N/A	N/A	N/A	N/A	N/A	N/A	OS was determined by means of the Kaplan-Meier method. Estimates of duration of follow-up was based on the inverse Kaplan-Meier method, with 95% CIs based on the Greenwood formula. Patients who were still alive or lost to follow-up were censored at the last known alive date.	CCOD Nov 6, 2020 [26]
Median OS	Pralsetinib	75	NR	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the total efficacy population.	CCOD Nov 6, 2020 [26]

No prior systemic treatment, efficacy population											
[redacted]											
12 mo. OS Total efficacy population	Pralsetinib	233	76.0 (69.9-82.0)	N/A	N/A	N/A	N/A	N/A	N/A	OS was determined by means of the Kaplan-Meier method. Estimates of duration of follow-up was based on the inverse Kaplan-Meier method, with 95% CIs based on the Greenwood formula. OS at specific time-points were computed, along with the standard errors using Greenwood's formula. Patients who were still alive or lost to follow-up were censored at the last known alive date.	CCOD Nov 6, 2020 [26]
12 mo. OS No prior systemic	Pralsetinib	75	82.3 (71.9-92.8)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the total efficacy population.	CCOD Nov 6, 2020 [26]

treatment, efficacy population											
24 mo. OS Total efficacy population	Pralsetinib	233	66.0 (57.9-74.1)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the total efficacy population at 12 months.	CCOD Nov 6, 2020 [26]
24 mo. OS No prior systemic treatment, efficacy population	Pralsetinib	75	74.0 (59.3-88.6)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the total efficacy population at 12 months.	CCOD Nov 6, 2020 [26]
Median OS Updated total efficacy population	Pralsetinib	281	44.3 (31.9-NR)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the initial total efficacy population.	CCOD Mar 4, 2022 [27]
Median OS Updated treatment naïve population	Pralsetinib	116	NR (31.9-NR)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the initial total efficacy population.	CCOD Mar 4, 2022 [27]

Median PFS Total efficacy population	Pralsetinib	233	16.4 mo. (11.0-24.1)	N/A	N/A	N/A	N/A	N/A	N/A	PFS was determined by means of the Kaplan-Meier method. Estimates of duration of follow-up was based on the inverse Kaplan-Meier method, with 95% CIs based on the Greenwood formula. CI calculation was based on identity (i.e., linear) transformation.	CCOD Nov 6, 2020 [26]
Median PFS No prior systemic treatment, efficacy population	Pralsetinib	75	13.0 mo. (9.1-NR)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the total efficacy population.	CCOD Nov 6, 2020 [26]
[redacted]											
12 mo. PFS Total efficacy population	Pralsetinib	233	56.0 (48.9-63.1)	N/A	N/A	N/A	N/A	N/A	N/A	PFS was determined by means of the Kaplan-Meier method. Estimates of duration of follow-up was based on the inverse Kaplan-Meier method, with 95% CIs based on the	CCOD Nov 6, 2020 [26]

										Greenwood formula. PFS at specific time-points was computed, along with the standard errors using Greenwood's formula.	
12 mo. PFS No prior systemic treatment, efficacy population	Pralsetinib	75	52.6 (37.8-67.5)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the total efficacy population.	CCOD Nov 6, 2020 [26]
24 mo. PFS Total efficacy population	Pralsetinib	233	42.1 (33.2-51.0)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the total efficacy population at 12 months.	CCOD Nov 6, 2020 [26]
24 mo. PFS No prior systemic treatment, efficacy population	Pralsetinib	75	47.8 (31.6-64.1)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the total efficacy population at 12 months.	CCOD Nov 6, 2020 [26]
Median PFS	Pralsetinib	281	13.2 (11.4-16.8)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the initial total efficacy population.	CCOD Mar 4, 2022 [27]

Updated total efficacy population											
Median PFS Updated treatment naïve population	Pralsetinib	116	12.6 (9.2-16.6)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the initial total efficacy population.	CCOD Mar 4, 2022 [27]
ORR Total efficacy population	Pralsetinib	233	150 (64.4%) (57.9-70.5)	N/A	N/A	N/A	N/A	N/A	N/A	ORR and its two-sided 95% CI were based on the exact binomial distribution by means of the Clopper-Pearson method.	CCOD Nov 6, 2020 [26]
ORR No prior systemic treatment, efficacy population	Pralsetinib	75	54 (72.0%) (60.4-81.8)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the total efficacy population.	CCOD Nov 6, 2020 [26]
ORR Updated total efficacy population	Pralsetinib	281	185 (65.8) (60.0-71.4)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the initial total efficacy population.	CCOD Mar 4, 2022 [27]

ORR Updated treatment naïve population, post eligibility revision	Pralsetinib	69	52 (75.4) (63.5-84.9)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the initial total efficacy population.	CCOD Mar 4, 2022 [27]
Overall efficacy population	Pralsetinib	10	7 (70) (34.8-93)	N/A	N/A	N/A	N/A	N/A	N/A	ORR and its two-sided 95% CI were based on the exact binomial distribution by means of the Clopper-Pearson method.	CCOD Nov 6, 2020 [26]
Updated overall population	Pralsetinib	15	8 (53.3) (26.6-78.7)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for the initial overall efficacy population.	CCOD Mar 4, 2022 [27]
Discontinuations due to AEs Total safety population	Pralsetinib	528	91 (17.2%)	N/A	N/A	N/A	N/A	N/A	N/A	Proportion of patients that discontinued study treatment due to any AE.	CCOD Nov 6, 2020 [26]

Discontinuations due to AEs RET fusion-positive NSCLC population	Pralsetinib	281	55 (19.6%)	N/A	N/A	N/A	N/A	N/A	N/A	Proportion of patients that discontinued study treatment due to any AE.	CCOD Nov 6, 2020 [26]
Discontinuations due to AEs Updated NSCLC safety population	Pralsetinib	281	28 (10%)*	N/A	N/A	N/A	N/A	N/A	N/A	Proportion of patients that discontinued study treatment due to any TRAE.	CCOD Mar 4, 2022 [27]
Grade ≥3 AEs Total safety population	Pralsetinib	528	406 (76.6%)	N/A	N/A	N/A	N/A	N/A	N/A	Proportion of patients that experienced any grade 3-5 AE.	CCOD Nov 6, 2020 [26]
Grade ≥3 AEs RET fusion-positive NSCLC population	Pralsetinib	281	212 (75.4%)	N/A	N/A	N/A	N/A	N/A	N/A	Proportion of patients that experienced any grade 3-5 AE.	CCOD Nov 6, 2020 [26]

Grade ≥3 AEs Updated NSCLC safety population	Pralsetinib	281	231 (82.2)	N/A	N/A	N/A	N/A	N/A	N/A	Proportion of patients that experienced any grade 3-5 AE.	CCOD Mar 4, 2022 [27]
HRQoL	Pralsetinib	Data on QoL was collected in ARROW but no analysis has yet been carried out for the November 6, 2020 data cut nor for the March 4, 2022.									

* reported as TRAEs

Table 91: Results of KEYNOTE-024 (NCT02142738)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS Total efficacy population	PEMB	154	26.3 mo. (18.3-40.4)	12.9 mo.	N/A	N/A	HR: 0.62	0.48–0.81	NR	The description of the method used is not available from the data cutoff in question. The description is derived from the primary study publication. The Kaplan-Meier method was used to estimate OS, with censoring of data for patients alive or lost to follow-up at time of last contact. Between-group difference in OS was assessed using a stratified log-rank test. HRs and associated	CCOD Jun 1 2020. Median follow-up 60 months [28].
	Chemo	151	13.4 mo. (9.4-18.3)								

										95% CIs were assessed using a stratified Cox proportional hazards model with Efron's method of handling ties. The same stratification factors used for randomization were applied to the stratified log-rank and Cox models.	
12 mo. OS Total efficacy population	PEMB	154	70.3% (62.3-76.9)	15.5%	N/A	N/A	HR: 0.63	0.47-0.86	0.002	Same as for the total efficacy population at 60 months follow-up.	CCOD Jul 10 2017. Median follow-up 25.2 months [29]
	Chemo	151	54.8% (46.4-62.4								
24 mo. OS Total efficacy population	PEMB	154	51.5 (43.0-59.3	17.0%	N/A	N/A	HR: 0.63	0.47-0.86	0.002	Same as for the total efficacy population at 60 months follow-up.	CCOD Jul 10 2017. Median follow-up 25.2 months [29]
	Chemo	151	34.5 (26.7-42.4)								
Median OS Non-SQ	PEMB	125	-	N/A	N/A	N/A	HR: 0.58	0.41-0.83	-	HR and associated 95% CI were assessed using a Cox proportional hazard model.	CCOD Jul 10 2017. Median follow-up 25.2 months [29]
	Chemo	124	-								

Median PFS Total efficacy population	PEMB	154	7.7 mo. (6.1-10.2)	2.2 mo.	N/A	N/A	HR: 0.50	0.39-0.65	NR	The description of the method used is not available from the data cutoff in question. The description is derived from the primary study publication. The Kaplan-Meier method was used to estimate PFS. Data for patients who were alive and had no disease progression or who were lost to follow-up were censored at the time of the last tumor assessment. Between-group difference in PFS was assessed using a stratified log-rank test. HRs and associated 95% CIs were assessed using a stratified Cox proportional hazards model with Efron's method of handling ties. The same stratification factors used for randomization were applied to the stratified log-rank and Cox models.	CCOD Jun 1 2020. Median follow-up 60 months [28].
	Chemo	151	5.5 mo. (4.2-6.2)								
Median PFS Non-SQ	PEMB	125	-	N/A	N/A	N/A	HR: 0.55	0.39-0.76	NR	HR and associated 95% CI were assessed using a Cox proportional hazard model.	CCOD May 9 2016. Median follow-up 11.2 months [33].
	Chemo	124	-								
ORR	PEMB	154	71 (46.1%) (38.1-54.3)	15.0%	N/A	N/A	N/A	N/A	N/A	The description of the method used is not available from the	CCOD Jun 1 2020. Median

	Chemo	150	47 (31.1%) (23.8-39.2)							data cutoff in question. The description is derived from the primary study publication. Differences in response rate were assessed with the use of the stratified method of Miettinen and Nurminen.	follow-up 60 months [28].
Discontinuations due to AEs As treated population	PEMB	154	14 (9.1%)	-4.9%	-9.2; 3.2	N/A	RR: 0.65	0.34-1.23	0.185	The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR in the comparator group.	CCOD May 9 2016. Median follow-up 11.2 months [35].
	Chemo	150	21 (14.0%)								
Grade ≥3 AEs As treated population	PEMB	154	82 (53.2%)	-19.6%	-28.4;-8.7	N/A	RR: 0.73	0.61-0.88	0.0006	The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR in the comparator group.	CCOD May 9 2016. Median follow-up 11.2 months [35].
	Chemo	150	109 (72.7%)								
HRQoL	PEMB	See qualitative description in section 7.1.2									
	Chemo										

Table 92: Results of KEYNOTE-042 (NCT02220894)

	Estimated absolute difference in effect	Estimated relative difference in effect	Description of methods used for estimation	References

Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS Total efficacy population	PEMB	299	20.0 mo. (15.9-24.2)	7.8 mo.	N/A	N/A	HR: 0.68	0.57-0.82	NR	The description of the method used is not available from the data cutoff in question. The description is derived from the primary study publication. The Kaplan–Meier method was used to estimate OS. Data for patients who were alive or lost to follow-up were censored at the time of last contact for estimation of OS. The stratified log-rank test was used to assess between-group differences in OS. A stratified Cox regression model with Efron's method of tie handling was used to estimate HR and associated 95% CI.	CCOD Feb 21 2021. Median follow-up, ITT 49.6 months [30].
	Chemo	300	12.2 mo. (10.4-14.6)								
24 mo. OS	PEMB	299	45 (CI not reported)	15%	N/A	N/A	HR: 0.69	0.56-0.85	0.0003	Same as for the total efficacy population at 49.6 months follow-up.	CCOD Feb 26 2018. Median follow-up, ITT 12.8 months [31]
	Chemo	300	30 (CI not reported)								
Median OS	PEMB	192	-	N/A	N/A	N/A	HR: 0.82	0.63-1.07	NR		

Non-SQ	Chemo	186	-							HR and associated 95% CI were assessed using a Cox proportional hazard model.	CCOD Feb 26 2018. Median follow-up, ITT 12.8 months [31]
Median PFS Total efficacy population	PEMB	299	6.5 mo. (5.9-8.6)	0.0 mo.	N/A	N/A	HR: 0..85	0.72-1.02	NR	The description of the method used is not available from the data cutoff in question. The description is derived from the primary study publication. The Kaplan–Meier method was used to estimate PFS. Data for patients without disease progression or who were lost to follow-up were censored at the time of last tumour imaging for estimation of PFS. For PFS data for patients who started new anticancer therapy without radiographic evidence of progression were censored at the time of the last tumour assessment before new anticancer therapy was initiated. The stratified log-rank test was used to assess between-group differences in OS. A stratified Cox regression model with Efron's method of tie handling was used to estimate HR and associated 95% CI.	CCOD Feb 21 2021 Median follow-up, ITT 49.6 months [30].
	Chemo	300	6.5 mo. (6.2-7.6)								

ORR Total efficacy population	PEMB	299	39.1% (33.6-44.9)	6.8%	N/A	N/A	N/A	N/A	N/A	The description of the method used is not available from the data cutoff in question. The description is derived from the primary study publication. Differences in response rate were assessed with the use of the stratified method of Miettinen and Nurminen.	CCOD Feb 21 2021 Median follow-up, ITT 49.6 months [30].
	Chemo	300	32.3% (27.1-37.9)								
Discontinuations due to AEs	PEMB	636	130 (20.4%)	5.6%	1.18-11.24	N/A	RR: 1.38	1.08-1.76	0.0094	The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR in the comparator group.	CCOD Sep 4 2018. Median follow-up, ITT 14.0 months [36].
	Chemo	615	91 (14.8%)								
Grade ≥3 AEs	PEMB	636	326 (51.3%)	-5.7%	-10.8;-0.13	N/A	RR: 0.90	0.81-1.00	0.045	The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR in the comparator group.	CCOD Sep 4 2018. Median follow-up, ITT 14.0 months [36].
	Chemo	615	350 (56.9%)								
HRQoL	PEMB	See narrative description in section 7.1.2									
	Chemo										

Table 93: Results of KEYNOTE-189 (NCT02578680)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS Total efficacy population	PEMB + Chemo	410	22.0 mo. (19.5-24.5)	11.4 mo.	N/A	N/A	0.60	0.50-0.72	-	The description of the method used is not available from the data cutoff in question. The description is derived from the primary study publication. The Kaplan-Meier method was used to estimate the OS curve in each treatment group. Difference in OS was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to estimate HR and associated 95% CI. The stratification factors used for randomization were applied to both the stratified log-rank test and the stratified Cox model.	CCOD Aug 28, 2020. Median follow-up 46.3 mo [40].
	Chemo	206	10.6 mo. (8.7-13.6)								
Median OS PD-L1 TPS 1%-49%	PEMB + Chemo	128	21.8 mo. (17.7-25.6)	9.7 mo.	N/A	N/A	0.66	0.47-0.93	-	Same as for the total efficacy population	CCOD Aug 28, 2020. Median follow-up 46.3 mo [40].
	Chemo	58	12.1 mo. (8.7-19.4)								

Median OS PD-L1 TPS > 1%	PEMB + Chemo	127	17.2 mo. (13.8-22.8)	7.0 mo.	N/A	N/A	0.51	0.36-0.71	-	Same as for the total efficacy population	CCOD Aug 28, 2020. Median follow-up 46.3 mo [40].
	Chemo	63	10.2 mo. (7.0-13.5)								
12 mo OS Total efficacy population	PEMB + Chemo	410	69.8%	21.8%	N/A	N/A	0.56	0.46-0.69	-	The description of the method used is not available from the data cutoff in question. The description is derived from the primary study publication. The Kaplan-Meier method was used to estimate the OS curve in each treatment group. Difference in OS was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to estimate HR and associated 95% CI. The stratification factors used for randomization were applied to both the stratified log-rank test and the stratified Cox model.	CCOD May 20, 2019. Median follow-up 31 mo [41].
	Chemo	206	48.0%								
24 mo OS Total efficacy population	PEMB + Chemo	410	45.7%	18.4%	N/A	N/A	0.60	0.50-0.72	-	Same as for the total efficacy population at 31 months follow-up.	CCOD Aug 28, 2020. Median follow-up 46.3 mo [40].

	Chemo	206	27.3%								
12 mo OS PD-L1 TPS 1-49%	PEMB + Chemo	128	71.1%	21.1%	N/A	N/A	0.66	0.46-0.96	-	Same as for the total efficacy population	CCOD May 20, 2019. Median follow-up 31 mo [41].
	Chemo	58	50.0%								
24 mo OS PD-L1 TPS 1-49%	PEMB + Chemo	128	44.3%	13.3%	N/A	N/A	0.66	0.46-0.96	-	Same as for the total efficacy population	CCOD May 20, 2019. Median follow-up 31 mo [41].
	Chemo	58	31.0%								
12 mo OS PD-L1 TPS <1%	PEMB + Chemo	127	63.4%	15.9%	N/A	N/A	0.51	0.36-0.71	-	Same as for the total efficacy population	CCOD May 20, 2019. Median follow-up 31 mo [41].
	Chemo	63	47.5%								
24 mo OS PD-L1 TPS <1%	PEMB + Chemo	127	39.3%	25.1%	N/A	N/A	0.51	0.36-0.71	-	Same as for the total efficacy population	CCOD May 20, 2019. Median follow-up 31 mo [41].
	Chemo	63	14.2%								

Median PFS Total efficacy population	PEMB + Chemo	410	9.0 (8.1-10.4)	4.1 mo.	N/A	N/A	0.50	0.41-0.59	-	The description of the method used is not available from the data cutoff in question. The description is derived from the primary study publication. The Kaplan-Meier method was used to estimate the PFS curve in each treatment group. Difference in PFS was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to estimate HR and associated 95% CI. The stratification factors used for randomization were applied to both the stratified log-rank test and the stratified Cox model.	CCOD Aug 28, 2020. Median follow-up 46.3 mo [40].
	Chemo	206	4.9 (4.7-5.5)								
Median PFS PD-L1 TPS 1%-49%	PEMB + Chemo	128	9.4 mo. (8.1-13.8)	4.5 mo.	N/A	N/A	0.54	0.39-0.76	-	Same as for the total efficacy population	CCOD Aug 28, 2020. Median follow-up 46.3 mo [40].
	Chemo	58	4.9 mo. (4.7-8.6)								
Median PFS PD-L1 TPS > 1%	PEMB + Chemo	127	6.2 mo. (4.9-8.1)	1.1 mo.	N/A	N/A	0.67	0.49-0.93	-	Same as for the total efficacy population	CCOD Aug 28, 2020. Median follow-up 46.3 mo [40].
	Chemo	63	5.1 mo. (4.5-6.8)								

12 mo. PFS Total efficacy population	PEMB + Chemo	410	39.4%	21.8%	N/A	N/A	0.49	0.41-0.59	-	The description of the method used is not available from the data cutoff in question. The description is derived from the primary study publication. The Kaplan-Meier method was used to estimate the PFS curve in each treatment group. Difference in PFS was assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling was used to estimate HR and associated 95% CI. The stratification factors used for randomization were applied to both the stratified log-rank test and the stratified Cox model.	CCOD May 20, 2019. Median follow-up 31 mo [41].
	Chemo	206	17.6%								
24 mo. PFS Total efficacy population	PEMB + Chemo	410	22.6%	18.2%	N/A	N/A	0.50	0.41-0.59	-		CCOD Aug 28, 2020. Median follow-up 46.3 mo [40].
	Chemo	206	4.4%								

12 mo. PFS PD-L1 TPS 1%-49%	PEMB + Chemo	128	43.8%	23.3%	N/A	N/A	0.53	0.38-0.74	-	Same as for the total efficacy population at 31 months follow-up.	CCOD May 20, 2019. Median follow-up 31 mo [41].
	Chemo	58	20.5%								
24 mo. PFS PD-L1 TPS 1%-49%	PEMB + Chemo	128	22.3%	18.2%	N/A	N/A	0.53	0.38-0.74	-	Same as for the total efficacy population	CCOD May 20, 2019. Median follow-up 31 mo [41].
	Chemo	58	4.1%								
12 mo. PFS PD-L1 TPS > 1%	PEMB + Chemo	127	26.0%	10.5%	N/A	N/A	0.67	0.49-0.93	-	Same as for the total efficacy population	CCOD May 20, 2019. Median follow-up 31 mo [41].
	Chemo	63	15.5%								
24 mo. PFS PD-L1 TPS > 1%	PEMB + Chemo	127	13.3%	9.9%	N/A	N/A	0.67	0.49-0.93	-	Same as for the total efficacy population	CCOD May 20, 2019. Median follow-up 31 mo [41].
	Chemo	63	3.4%								
ORR	PEMB + Chemo	410	48.3% (CI is not reported)	28.4%	N/A	N/A	N/A	N/A	N/A	The description of the method used is not available from the data cutoff in question. The	CCOD Aug 28, 2020. Median

Total efficacy population	Chemo	206	19.9% (CI is not reported)							description is derived from the primary study publication. Stratified Miettinen and Nurminen's method was used for comparison of the ORR between two treatment groups.	follow-up 46.3 mo [40].
ORR PD-L1 TPS 1%-49%	PEMB + Chemo	128	50.0%	29.3%	N/A	N/A	N/A	N/A	N/A	Same as for the total efficacy population	CCOD Aug 28, 2020. Median follow-up 46.3 mo [40].
	Chemo	58	20.7%								
ORR PD-L1 TPS > 1%	PEMB + Chemo	127	33.1%	18.8%	N/A	N/A	N/A	N/A	N/A	Same as for the total efficacy population	CCOD Aug 28, 2020. Median follow-up 46.3 mo [40].
	Chemo	63	14.3%								
Discontinuations due to AEs Safety population	PEMB + Chemo	405	146 (36.0%)	18.7%	8.7-32.7	N/A	RR: 2.08	1.50-2.89	<0.0001	The absolute difference and 95% confidence interval were estimated by applying the resulting RR and the ACR in the comparator group.	CCOD May 20, 2019. Median follow-up 31 mo [41].
	Chemo	202	35 (17.3%)								
Grade ≥3 AEs	PEMB + Chemo	405	292 (72.1%)	5.3%	-2.7-14.0	N/A	RR: 1.08	0.96-1.21	0.19	The absolute difference and 95% confidence interval were estimated by applying the	CCOD May 20, 2019. Median

	Chemo	202	135 (66.8%)							resulting RR and the ACR in the comparator group.	follow-up 31 mo [41].
HRQoL	PEMB + Chemo	See narrative description in section 7.2.2									
	Chemo										

17. Appendix E – Safety data for intervention and comparators

17.1 Pralsetinib

Safety data on the intervention, pralsetinib, is derived from ARROW from the CCOD November 6, 2020.

Table 94 95: Safety data from ARROW (CCOD: November 6, 2020)

	RET fusion-positive NSCLC patients (N=281)			Overall safety population (N=528)		
Safety parameter	**Pralsetinib, n (%)**	**Drug exposure (mo.)** Median (min, max)	**CCOD Reference**	**Pralsetinib, n (%)**	**Drug exposure (mo.)** Median (min, max)	**CCOD Reference**
Any AE, n (%)	279 (99.3)	7.89 (0.3, 28.4)	Nov 6, 2020 EPAR (AR0000) [26]	525 (99.4)	9.46 (0.1, 33.9)	Nov 6, 2020 EPAR (AR0000) [26]
Grade ≥3 AE Grade 5	212 (75.4) 35 (12.5)		Nov 6, 2020 EPAR (AR0000) [26]	406 (76.9) 66 (12.5)		Nov 6, 2020 EPAR (AR0000) [26]

Treatment-related AE	264 (94.0)		Nov 6, 2020 EPAR (AR0000) [26]	493 (93.4)		Nov 6, 2020 EPAR (AR0000) [26]
Grade ≥ 3 treatment-related AE (grade 5)	155 (55.2) 2 (<1)		Nov 6, 2020 EPAR (AR0000) [26]	291 (55.1) 6 (1.1)		Nov 6, 2020 EPAR (AR0000) [26]
Any SAE	166 (59.1)		Nov 6, 2020 EPAR (AR0000) [26]	288 (54.5)		Nov 6, 2020 EPAR (AR0000) [26]
Treatment-related SAE	69 (24.6)		Nov 6, 2020 EPAR (AR0000) [26]	108 (20.5)		Nov 6, 2020 EPAR (AR0000) [26]
Discontinuation of treatment due to AEs	55 (19.6)		Nov 6, 2020 EPAR (AR0000) [26]	91 (17.2)		Nov 6, 2020 EPAR (AR0000) [26]

Abbreviations: AE - adverse event; TRAE - treatment-related adverse event; SAE - serious adverse event; TR-SAE - treatment-related serious adverse event

Supplemental safety data on the intervention, pralsetinib, is derived from ARROW from the CCOD March 4, 2022.

Table 96: Safety data from ARROW (CCOD: March 4, 2022)

	RET fusion-positive NSCLC patients (N=281)		
Safety parameter	**Pralsetinib, n (%)**	**Drug exposure (mo.)** Median	**CCOD** **Reference**
Any AE, n (%)	280 (99.6)	15.0	Mar 4, 2022 [27]
Grade ≥3 AE Grade 5	231 (82.2) -		Mar 4, 2022 [27]
Treatment-related AE	265 (94.3)		Mar 4, 2022 [27]
Grade ≥ 3 treatment-related AE (grade 5)	176 (62.6)		Mar 4, 2022 [27]

Any SAE	-		Mar 4, 2022 [27]
Treatment-related SAE	-		Mar 4, 2022 [27]
Discontinuation of treatment due to TRAEs	28 (10)		Mar 4, 2022 [27]

Abbreviations: AE - adverse event; TRAE - treatment-related adverse event; SAE - serious adverse event.

17.2 Pembrolizumab

Both KEYNOTE-024 and KEYNOTE-042 report safety data for the mixed safety population. However, neither histology or PD-L1 expression status are expected to affect the proportion of patients that experience AEs. Data is reported from the latest CCOD available. Mouritzen et al only reports data on discontinuation due to immune-related AEs. These are described in the main text of the application.

Table 97: Safety data from KEYNOTE-024

Safety parameter	PEMB (N=154)	PEMB + platinum-based chemotherapy (N=150)	Median follow up (mo.)	CCOD Reference
Any AE, n (%)	148 (96.1)	145 (96.7)	11.2	May 9, 2016 EPAR (AR0011) [35]
Grade ≥3 AE Grade 5	82 (53.2) 9 (5.8)	109 (72.7) 7 (4.7)	11.2	May 9, 2016 EPAR (AR0011) [35]
Treatment-related AE	118 (76.7)	135 (90.0)	60.0	June 1, 2020 Reck 2021 [28]
Grade ≥3 treatment-related AE Grade 5	48 (31.2) 2 (1.3)	80 (53.3) 3 (2.0)	60.0	June 1 2020 Reck 2021 [28]
Any SAE	68 (44.2)	66 (44.0)	11.2	May 9, 2016 EPAR (AR0011) [35]

Treatment-related SAE	35 (22.7)	31 (20.7)	60.0	June 1 2020 Reck 2021 [28]
Discontinuation of treatment irrespective of reason	N/A	N/A	N/A	N/A
Discontinuation of treatment due to AEs	14 (9.1)	21 (14.0)	11.2	May 9, 2016 EPAR (AR0011) [35]
Discontinuation of treatment due to treatment related AE	21 (13.6)	16 (10.7)	60	June 1, 2020 Reck 2021 [28]

Abbreviations: AE - adverse event; TRAE - treatment-related adverse event; SAE - serious adverse event; TR-SAE - treatment-related serious adverse event

Table 98: Safety data from KEYNOTE-042

Safety parameter	PEMB N=636	Chemotherapy N=615	Median follow up (months)	CCOD Reference
Any AE, n (%)	608 (95.6)	605 (98.4)	14	September 4, 2018 EPAR (AR0057) [36]
Grade ≥3 AE Grade 5	326 (51.3) 68 (10.7)	350 (56.9) 47 (7.6)	14	September 4, 2018 EPAR (AR0057) [36]
Treatment-related AE	406 (63.8)	554 (90.1)	46.9	February 21, 2020 Cho 2021 [30]
Grade ≥3 treatment-related AE Grade 5	120 (18.9) 13 (2.0)	256 (41.6) 14 (2.3)	46.9	February 21, 2020 Cho 2021 [30]
Any SAE	257 (40.4)	187 (30.4)	14	September 4, 2018 EPAR (AR0057) [36]
Treatment-related SAE	88 (13.8)	91 (14.8)	14	September 4, 2018 EPAR (AR0057) [36]

Discontinuation of treatment irrespective of reason	N/A	N/A	N/A	N/A
Discontinuation of treatment due to AEs	130 (20.4)	91 (14.8)	14.0	September 4, 2018 EPAR (AR0057) [36]
Discontinuation of treatment due to treatment related AE	58 (9.1)	59 (9.6)	46.9	February 21, 2020 Cho 2021 [30]

Abbreviations: AE - adverse event; TRAE - treatment-related adverse event; SAE - serious adverse event; TR-SAE - treatment-related serious adverse event

17.3 Pembrolizumab in combination with platinum-based chemotherapy

Table 99: Safety data from KEYNOTE-189

Safety parameter	Placebo + chemotherapy N=202	PEMB + chemotherapy N=405	Median follow up (months)	CCOD Reference
Any AE, n (%)	200 (99.0)	404 (99.8)	31	May 20, 2019 Rodriguez-Abreuet 2021 [41]
Grade ≥3 AE Grade 5	135 (66.8) 14 (6.9)	292 (72.1) 29 (7.2)	31	May 20, 2019 Rodriguez-Abreuet 2021 [41]
Treatment-related AE	183 (90.6)	376 (92.8)	46.3	August 28, 2020 Gray 2020 [40]
Grade ≥3 treatment-related AE Grade 5	85 (42.1) 2 (1.0)	211 (52.1) 8 (2.0)	46.3	August 28, 2020 Gray 2020 [40]
Any SAE	95 (47)	202 (49.9)	10.5	November 8, 2017 EPAR (0043) [45]

Treatment-related SAE	42 (20.8)	106 (26.2)	10.5	November 8, 2017 EPAR (0043) [45]
Discontinuation of treatment irrespective of reason	N/A	N/A	N/A	N/A
Discontinuation of treatment due to AEs*	35 (17.3)	146 (36.0)	31	May 20, 2019 Rodriguez-Abreuet 2021 [41]
Discontinuation of treatment due to treatment related AE	20 (9.9)	111 (27.4)	46.3	August 28, 2020 Gray 2020 [40]

*Refers to discontinuation of any treatment. Abbreviations: AE - adverse event; TRAE - treatment-related adverse event; SAE - serious adverse event; TR-SAE - treatment-related serious adverse event

18. Appendix F – Comparative analysis of efficacy and safety

18.1 Clinical question 1 - Efficacy and safety of pralsetinib compared to pembrolizumab for patients with NSCLC and PD-L1 ≥50%

18.1.1 Relevant studies

18.1.1.1 Flatiron EDM RWD study (data on file)

A synthetic control arm from the Flatiron EDM database was compared with RET fusion-positive patients receiving pralsetinib from the ARROW trial. The synthetic control arm included comparative treatment groups with pembrolizumab in first-line and pembrolizumab, carboplatin, and pemetrexed. Patients receiving pralsetinib were sourced from the ARROW trial (cut-off date November 6, 2020). The analysis focused on ARROW patients with no prior systemic therapy and with: 1) recorded smoking history, 2) reported stage 3) ECOG 0-1 and 4) non-squamous histology. This narrowed the ARROW population down to 71 patients. 686 patients receiving first-line pembrolizumab and 1270 patients receiving first-line pembrolizumab, carboplatin, and pemetrexed were identified in the Flatiron database.

The Flatiron Health database is a US-based national wide, demographically and geographically diverse longitudinal observational database derived from EHR data. The database includes data from over 280 cancer clinics, representing more than 2.2 million active U.S cancer patients available for analysis. The records of patients diagnosed with NSCLC were extracted from the Flatiron EHR-derived de-identified database. The source population was the overall population reported in the EHR and managed in at least one of the U.S. oncology clinics included in the Flatiron Health network from January 2011 and onwards with at least two visits in the Flatiron system.

Patients were eligible for inclusion if they were included in the EDM database, diagnosed with locally advanced or metastatic NSCLC between January 1, 2011 and March 1, 2020 and had initiated first-line or second-line therapy at a Flatiron Health clinic. The patient baseline period/index date is defined as the start of the patient's first-line therapy for the first-line group. All patients were followed from index date until death or censoring. Patients with >90-day gap between date of diagnosis and first visit/administration were excluded. To account for the Covid-19 pandemic, patients were censored on March 1, 2020. All eligible patients were required to have at least 6 months of potential follow-up (i.e. treatment initiation date no later than September 1, 2019). A full list of inclusion and exclusion criteria can be found in section 18.1.2.2.

The analysis included three endpoints of interest: time-to-treatment discontinuation (TTD), OS, and PFS. TTD was defined as the time from initiation of the line of therapy until the end of a given line of therapy, or death. If neither occurred, censoring was applied at the date of the last follow-up (last EHR activity - last available visit, lab, treatment or administration). OS was defined as the time from initiation of line of therapy until death. Censoring occurs at the last day of follow-up if no death date is recorded. PFS was defined as time from initiation of line of therapy to disease progression or death from any cause. Time of progression was determined based on clinical assessment as well as pathologic or radiographic evidence where available or mixed progression [24].

18.1.2 Method of synthesis

18.1.2.1 Flatiron comparison using the EDM database

The dataset for the Flatiron EDM comparison included patients receiving first-line pembrolizumab and patients receiving first-line pembrolizumab, carboplatin, and pemetrexed. For all three outcomes (OS, PFS, and TTD), several time-to-event models were fit. The results presented are those that have performed well in terms of balancing the most number of variables deemed prognostically important. The main two methods used to balance the ARROW and EDM cohorts are inverse probability of treatment weighting (IPTW) and matching. For both analyses, the average treatment effect on the treated (ATT) was estimated. The overall goal was to achieve covariate balance between the ARROW and EDM cohort by matching data from the EDM to the ARROW patient characteristics. After balancing, variables included in the outcome models and adjusted for were:

- Age (<65; ≥65)
- Sex (female; Male)
- Smoking status (history of smoking; no history of smoking)
- ECOG (0; 1)
- Time from initial diagnosis to first dose (month)
- Stage at initial diagnosis (stage I, II, or III; stage IV)
- Race (white; unknown; other)

The following variables are also presented in baseline characteristic tables:

- Metastases (isolated brain/CNS site; none; other)
- Sum of total metastases
- Brian/CNS metastasis only
- Liver metastasis only

For the variables involving metastases, an under-recording of these variables is a suspected limitation of the EDM database. This is a limitation in terms of balancing, and achieving balance in respect to these variables were therefore not deemed a primary goal.

The results presented in this application will be for the IPTW analysis, as it was found to result in the best overall balance across outcomes. The outcome model for IPTW was established by pooling data for the ARROW pralsetinib arm with the EDM comparator group. A logistic regression propensity score model was estimated by regressing a pralsetinib treatment indicator on baseline covariates. For each patient, propensity scores were calculated using the fitted values from the propensity score model. IPTW weights for the ATT estimates were computed by assigning each patient in the pralsetinib arm a weight of 1 and each patient in the comparator arm a weight of [propensity score] /(1 - [propensity score]). The effective sample size was calculated by taking the square of the sum of all weights divided by the summation of each of the weights squared. Tables and figures presented for the IPTW analysis were produced after trimming subjects with large weights. After this, IPTW-weighted Cox proportional hazards (PH) regression models were used to estimate HRs between pralsetinib and the comparators. 95% CIs were calculated using robust standard errors. Baseline characteristics before and after matching as well as the results can be found in appendix K.

For each model, the PH assumption was assessed using a combination of Schoenfield tests and visual inspection of KM curves and log-negative-log survival plots. Weighted restricted mean survival time difference (RMSTD) was estimated via weighted KM curves and used to cross-check instances where the PH assumption may be violated. 95% CIs were calculated via bootstrapping with 10000 iterations.

18.1.2.2 Supplementary information from the Flatiron EDM analysis

Descriptive statistics – flowchart and baseline tables

Figure 28 shows the impact of the elibiligity criteria on the EDM database patients.

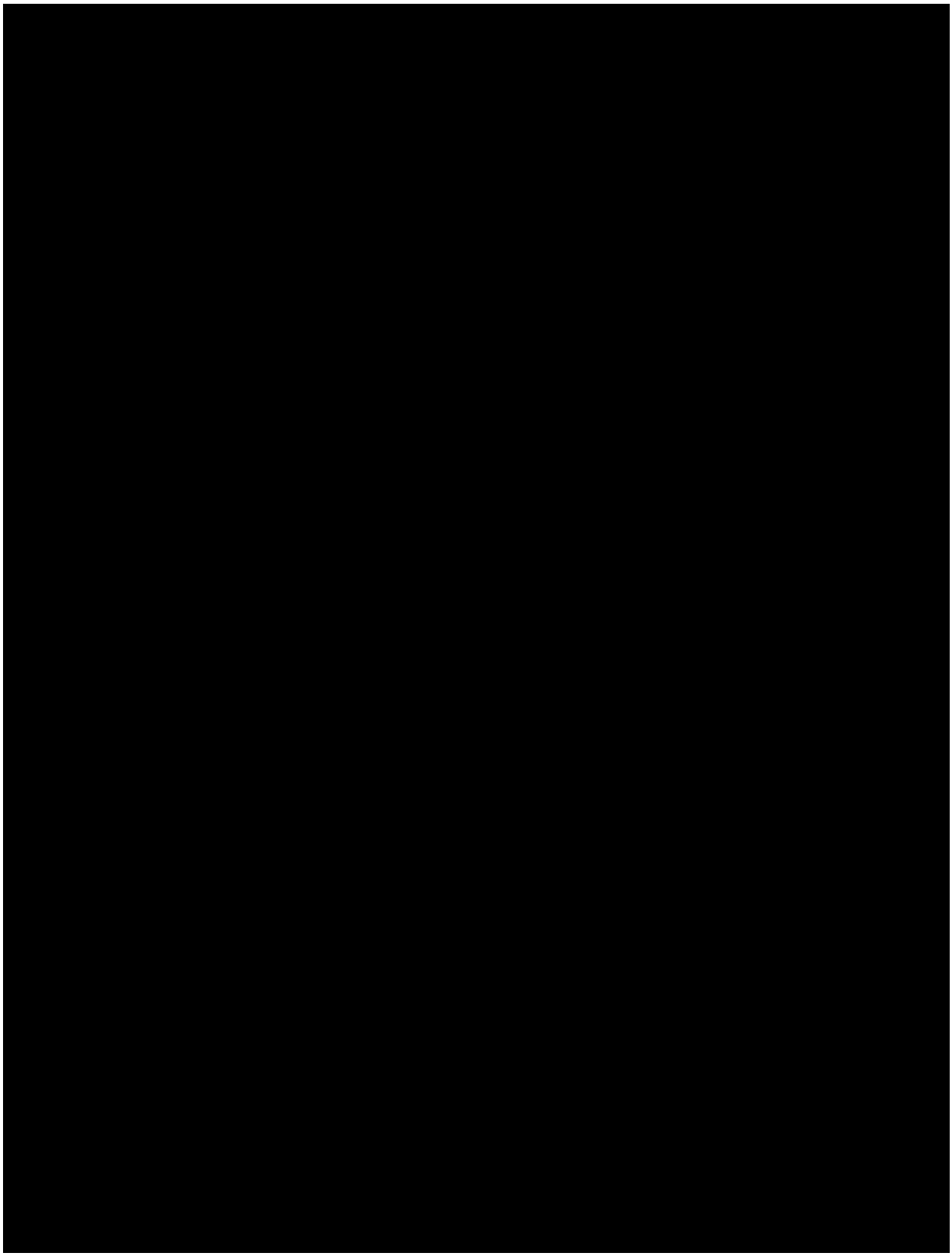
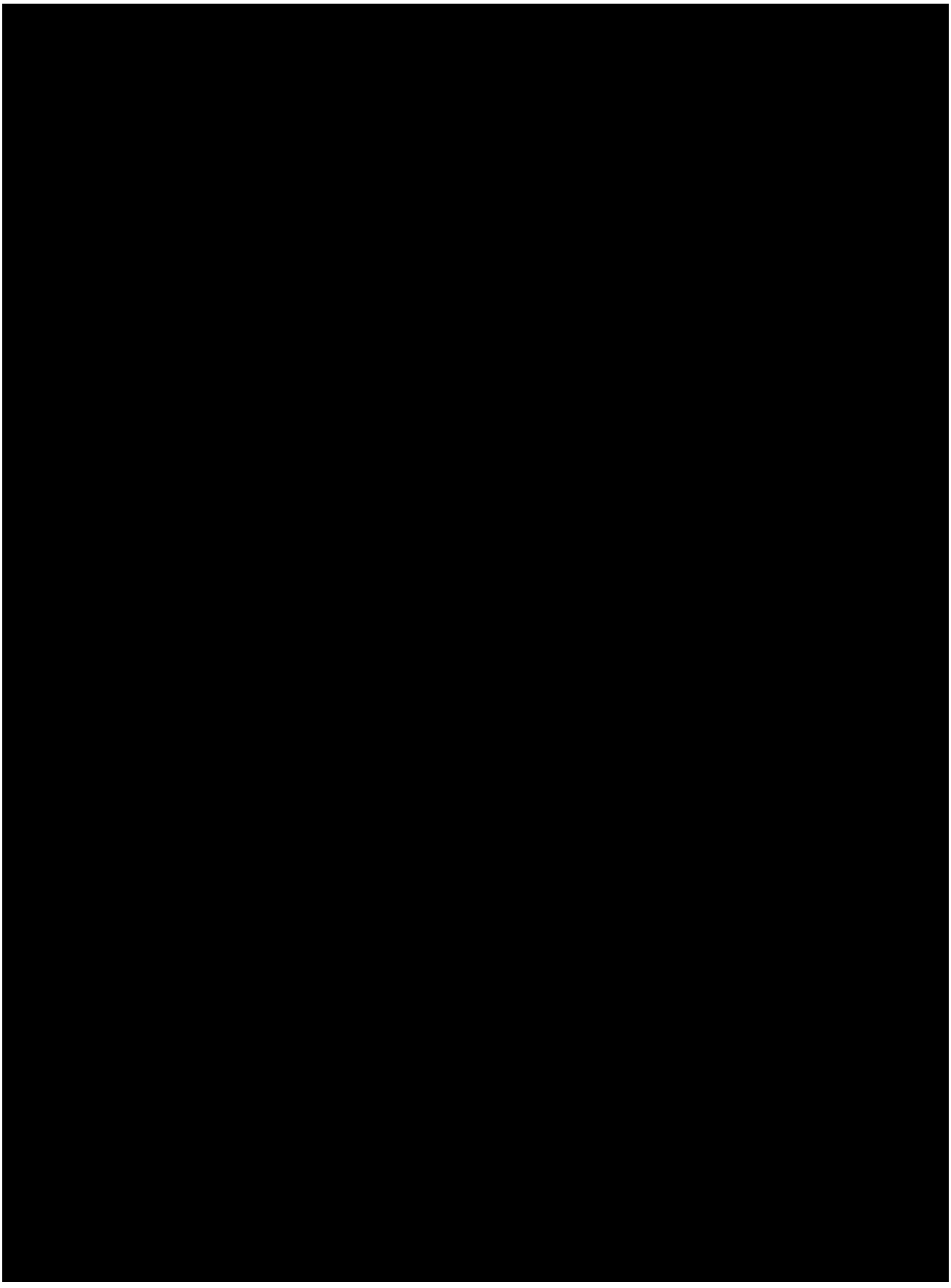
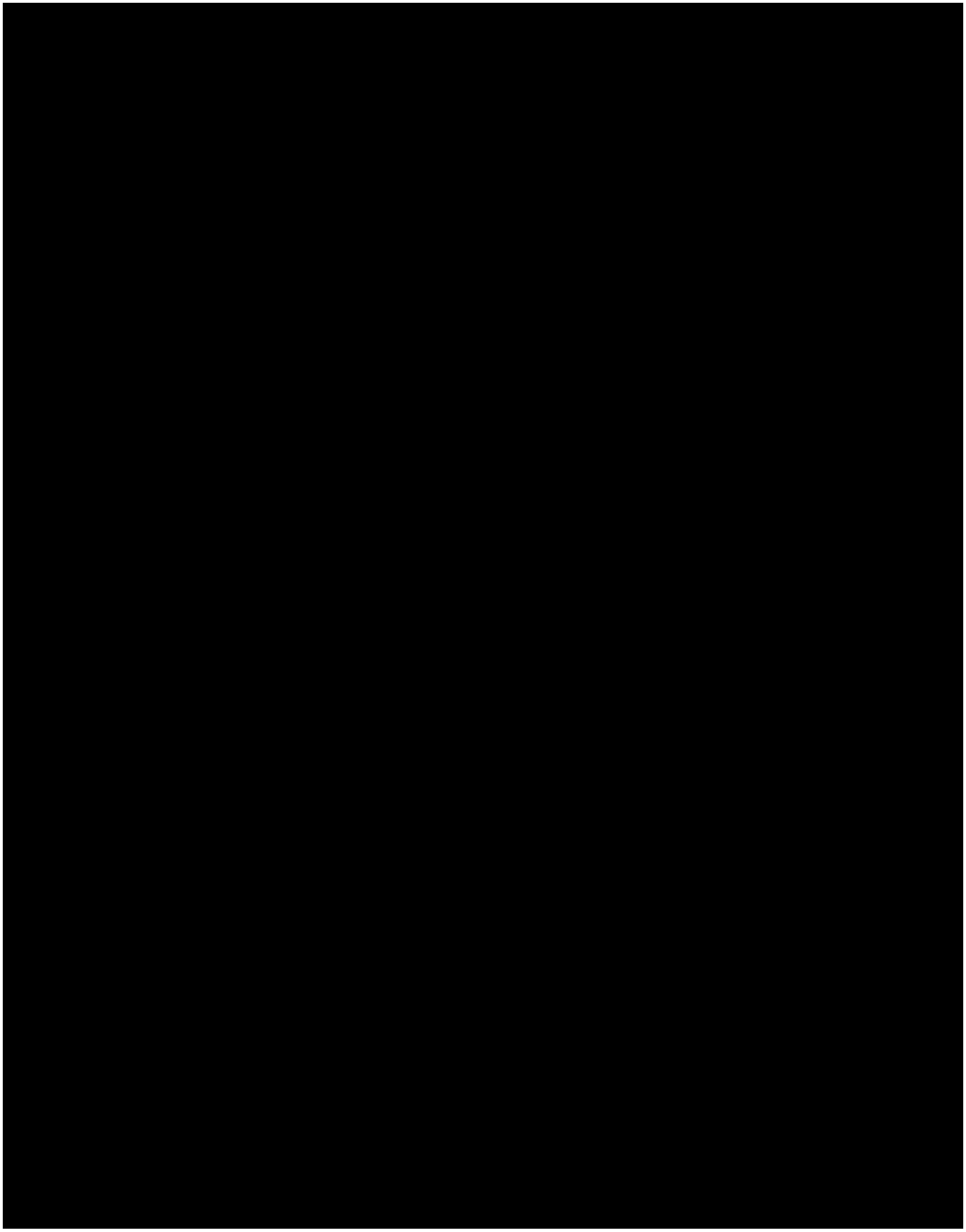


Table 100, Table 101, Table 102 and Table 103 show the key baseline characteristics prior to any adjustment or weighting. The tables also include an “Adjusted” column that indicates whether the covariate is one that is being explicitly

balanced (“Y”) or not (“N”). All baseline characteristics tables following matching have a row labelled “n”, which is the sample size of the matched pseudo-population, and not the effective sample size.





Distribution of weights

Distribution of weights for the comparisons of pralsetinib vs. Pembrolizumab and Pembrolizumab, carboplatin, and pemetrexed can be found in Figure 44 and 45 respectively. For both comparisons, trimming was unnecessary as all subjects had weights less than three. The use of a fixed threshold was motivated by the observation that there were no scenarios where a large number of patients had large weights.

[redacted]

18.1.3 Results from the comparative analyses

18.1.3.1 Overall survival

Flatiron EDM comparison

The weighted KM curve based on IPTW for OS can be seen in Figure 31**.** HR estimated from Cox regression was [redacted] which is statistically significant. The [redacted]. Overall, pralsetinib is statistically significantly favoured over pembrolizumab.

[redacted]

Overview of all reported OS data

Table 105: Overview of the reported OS data relevant for the assessment

Analyses	Treatment Study, population, n	Median, mo. (95%CI)	Rate at 12 mo. (95%CI)	Rate at 24 mo. (95%CI)	HR (95%CI)	RMSTD (95% CI)
Narrative comparison						
Pralsetinib in RET fusion-positive NSCLC	**Pralsetinib** ARROW, overall efficacy, n=233	NR (NR-NR)	76.0 (69.9-82.0)	66.0 (57.9-74.1)	N/A	N/A
	Pralsetinib ARROW, no prior systemic treatment, n=75	NR (NR-NR)	82.3 (71.9-92.8)	74.0 (59.3-88.6)	N/A	N/A
	Pralsetinib ARROW, updated total efficacy n=281	44.3 (31.9-NR)	N/A	N/A	N/A	N/A
	Pralsetinib ARROW, updated treatment naïve, n=116	NR (31.9-NR)	N/A	N/A	N/A	N/A
ICI in RET fusion-positive NSCLC	**ICI** Bhandari et al, n=17	19.1 (6.9-NR)	-	-	N/A	N/A
	ICI Mazieres et al, n=16	21.3 (3.8-28.0)	-	-	N/A	N/A
	ICI Guisier et al, n=9	NR (26.8-NR)	88.9 (70.6-100)	-	N/A	N/A
Pembrolizumab in RET wt NSCLC	**Pembrolizumab** KEYNOTE-024, previously untreated, PD-L1 ≥50%, n=154	26.3 (18.3-40.4)	70.3 (62.3-76.9)	51.5 (43.0-59.3	N/A	N/A
	Pembrolizumab KEYNOTE-042, previously untreated, PD-L1 ≥50%, n=299	20.0 (15.9-24.2)	-	45 (CI not reported)	N/A	N/A
	ICI Mouritzen et al., ICI cohort, n=482	19.0 (16.0-22.0)	64	42	N/A	N/A
Naïve ITC						
Pralsetinib vs. pembrolizumab in RET wt NSCLC	**Pralsetinib** ARROW, no prior therapy, unrestricted, n=116	[redacted]				
	Pembrolizumab KEYNOTE-024, previously untreated, PD-L1 ≥50%, n= 154					
	Pralsetinib					

Pralsetinib vs. pembrolizumab in RET wt NSCLC	ARROW, no prior therapy, unrestricted, n=116					
	Pembrolizumab KN-042, previously untreated, PD-L1 ≥50%, n=299	[redacted]				
Flatiron real-world comparison						
Flatiron EDM, IPTW Pralsetinib vs. pembrolizumab in RET wt NSCLC	**Pralsetinib** ARROW, no prior therapy, n=71	[redacted]				
	Pembrolizumab EDM, previously untreated, n=[redacted]					

Abbreviations: CI – confidence interval; EDM – Enhanced Data Mart; ICI - immune checkpoint inhibitors; N/A - not applicable; NR - not reached; NSCLC – non-small cell lung cancer; PD-L1 – programmed death ligand 1; wt – wild-type; IPTW - Inverse probability of treatment weighting; KN-024 – KEYNOTE-024; KN-042 – KEYNOTE-042; mo. - months.

18.1.3.2 Progression-free survival

Flatiron EDM comparison

The weighted KM curve based on IPTW for PFS can be seen in Figure 32**.** The HR estimated from Cox regression was [redacted] which is statistically significant. The 24.3 month RMSTD was [redacted] Overall, pralsetinib is statistically significantly favoured over pembrolizumab.

Note, that for the IPTW PH model, the Schoenfeld test found that the PH assumption was violated. Based on the LNL plot, however, the PH assumption was deemed to be satisfied.

[redacted]

Overview of all reported PFS data

Table 106: Overview of the reported PFS data relevant for the assessment

Analyses	Treatment Study, population, n	Median, mo. (95%CI)	Rate at 12 mo. (95%CI)	Rate at 24 mo. (95%CI)	HR (95%CI)	RMSTD (95% CI)
Narrative comparison						
Pralsetinib in RET fusion-positive NSCLC	**Pralsetinib** ARROW, overall efficacy, n=233	16.4 (11.0-24.1)	56.0 (48.9-63.1)	42.1 (33.2-51.0)	N/A	N/A
	Pralsetinib ARROW, no prior systemic treatment, n=75	13.0 (9.1-NR)	52.6 (37.7-67.5)	47.8 (31.6-64.1)	N/A	N/A
	Pralsetinib ARROW, updated total efficacy n=281	13.2 (11.4-16.8)	N/A	N/A	N/A	N/A
	Pralsetinib ARROW, updated treatment naïve, n=116	12.6 (9.2-16.6)	N/A	N/A	N/A	N/A
ICI in RET fusion-positive NSCLC	**ICI** Bhandari et al, n=17	4.2 (1.4-8.4)	-	-	N/A	N/A
	ICI Mazieres et al, n=16	2.1 (1.3-4.7)	7 (0.4-27.1)	-	N/A	N/A
	ICI Guisier et al, n=9	7.6 (2.3-NR)	26.7 (8.3-85.8)	-	N/A	N/A
	ICI Hedge et al, n=16 ^	3.4*	-	-	N/A	N/A
	ICI Rozenblum et al, n=4	2.75**	-	-	N/A	N/A
Pembrolizumab in RET wt NSCLC	**Pembrolizumab** KN-024, previously untreated, PD-L1 ≥50%, n=154	7.7 (6.1-10.2)	-	-	N/A	N/A
	Pembrolizumab KN-042, previously untreated, PD-L1 ≥50%, n=299	6.5 (5.9-8.6)	-	-	N/A	N/A
	ICI Mouritzen et al., ICI RW cohort, n=579	8.2 (7.2-9.3)	-	-	N/A	N/A
Naïve ITC						
Pralsetinib vs. pembrolizumab in RET wt NSCLC	**Pralsetinib** ARROW, no prior therapy, unrestricted, n=116	[redacted]				
	Pembrolizumab KN-024, previously untreated, PD-L1 ≥50%, n=154					
Pralsetinib vs. pembrolizumab in RET wt NSCLC	**Pralsetinib** ARROW, no prior therapy, unrestricted, n=116					
	Pembrolizumab					

	KN-042, previously untreated, PD-L1 ≥50%, n=299					
Flatiron RW comparison						
Flatiron EDM, IPTW Pralsetinib vs. pembrolizumab in RET wt NSCLC	**Pralsetinib** ARROW, no prior therapy, n=71	[redacted]				
	Pembrolizumab EDM, previously untreated, n[redacted]					

^ 14 had RET fusions and 2 had RET point mutations; * reported as Time-to-treatment discontinuation (TTD); ** reported as median treatment duration and converted from weeks to months. Abbreviations: CI – confidence interval; EDM – Enhanced Data Mart; ICI - immune checkpoint inhibitors; N/A - not applicable; NR - not reached; NSCLC – non-small cell lung cancer; PFS – progression free survival; PD-L1 – programmed death ligand 1; wt – wild-type; IPTW - Inverse probability of treatment weighting; KN-024 – KEYNOTE-024; KN-042 – KEYNOTE-042; RET- rearranged during transfection.

18.1.3.3 Objective response

Overview of all reported ORR data

Table 107: Overview of the reported ORR data relevant for the assessment

Analyses	Treatment Study, population, n	ORR, n (%) (95% CI)	CR, n (%)	PR, n (%)
Narrative comparison				
Pralsetinib in RET fusion-positive NSCLC	**Pralsetinib** ARROW, overall efficacy, n=233	150 (64.4%) (57.9-70.5)	11 (4.7%)	139 (59.7%)
	Pralsetinib ARROW, no prior systemic treatment, n=75	54 (72.0%) (60.4-81.8)	4 (5.3%)	50 (66.7%)
	Pralsetinib ARROW, updated total efficacy n=281	185 (65.8) (60.0-71.4)	18 (6.4)	167 (59.4)
	Pralsetinib ARROW, updated treatment naïve, post eligibility revision, n=69	52 (75.4) (63.5-84.9)	4 (5.8)	48 (69.6)
ICI in RET fusion-positive NSCLC	**ICI** Bhandari et al, n=13	7 (53.8%)	1 (7.7%)	6 (46.2%)
	ICI Mazieres et al, n=16	1 (6.3%)	1 (6.3%)*	-
	ICI Guisier et al, n=8	3 (37.5%)	0 (0)	3 (37.5%)
	ICI Rozenblum et al, n=4	0 (0)	0 (0)	0 (0)
Pembrolizumab in RET wt NSCLC	**Pembrolizumab** KN-024, previously untreated, PD-L1 ≥50%, n=154	71 (46.1%) (38.1-54.3)	7 (4.5%)	64 (41.5%)

	Pembrolizumab KN-042, previously untreated, PD-L1 ≥50%, n=299	39.1% (33.6-44.9)	-	-

* reported as CR/PR. Abbreviations: CR – complete response; ICI – immune checkpoint inhibitor; ORR – overall response rate; PR – partial response; wt – wild-type; KN-024 – KEYNOTE-024; KN-042 – KEYNOTE-042; RET – rearranged during transfection; NSCLC – non-small cell lung cancer; CI – confidence interval.

18.1.3.4 Safety

Overview of the reported safety data

Table 108: Overview of the reported safety data

Analyses	Treatment Study, population, n	Discontinuations due to AEs	Grade ≥3 AEs
Narrative comparison			
Pralsetinib in RET fusion-positive NSCLC	**Pralsetinib** ARROW, overall safety population, n=528	17.2%	76.9%
	Pralsetinib ARROW, RET fusion-positive NSCLC safety population, n=281	19.6%	75.4%
	Pralsetinib ARROW, updated RET fusion-positive NSCLC safety population, n=281	10.0% §	231 (82.2)
Pembrolizumab in RET wt NSCLC	**Pembrolizumab** KN-024, overall safety population, n=154	9.1%	53.2%
	Pembrolizumab KN-042, overall safety population, n=636	20.4%	51.3%
	Pembrolizumab Mouritzen et al., n=579	31%*	-

***** Discontinuation due to immune-related AEs. Abbreviations: AEs - Adverse Events; RET – rearranged during transfection, KN-024 – KEYNOTE-024; KN-042 – KEYNOTE-042; NSCLC – non-small cell lung cancer. § reported as TRAEs.

18.2 Clinical question 2 - Efficacy and safety of pralsetinib compared to pembrolizumab in combination with chemotherapy for patients with NSCLC and PD-L1 expression ≤49%

18.2.1 Relevant studies

18.2.1.1 Flatiron EDM RWD study (data on file)

Se description in section 18.1.1.1

18.2.2 Method of synthesis

18.2.2.1 Flatiron comparison using the EDM database

The methodology in the Flatiron comparison using the EDM database has been described in section 18.1.2.1.

18.2.3 Results from the comparative analyses

18.2.3.1 Overall survival

Flatiron EDM comparison

The weighted KM curve for pralsetinib versus pembrolizumab, carboplatin, and pemetrexed for OS based on IPTW can be seen in Figure 33**.** The HR estimated from Cox regression was [redacted] which is statistically significant. The 32.5 month RMSTD was [redacted] Overall, pralsetinib is statistically significantly favoured over pembrolizumab in combination with chemotherapy.

[redacted]

Overview of all reported OS data

Table 109: Overview of the reported OS data relevant for the assessment

Analyses	Treatment Study, population, n	Median, mo. (95%CI)	Rate at 12 mo. (95%CI)	Rate at 24 mo. (95%CI)	HR (95%CI)	RMSTD (95% CI)
Narrative comparison						
Pralsetinib in RET fusion-positive NSCLC	**Pralsetinib** ARROW, overall efficacy, n=233	NR (NR-NR)	76.0 (69.9-82.0)	66.0 (57.9-74.1)	N/A	N/A
	Pralsetinib ARROW, no prior systemic treatment, n=75	NR (NR-NR)	82.3 (71.9-92.8)	74.0 (59.3-88.6)	N/A	N/A

	Pralsetinib ARROW, updated total efficacy n=281	44.3 (31.9-NR)	N/A	N/A	N/A	N/A
	Pralsetinib ARROW, updated treatment naïve, n=116	NR (31.9-NR)	N/A	N/A	N/A	N/A
Pembrolizumab + chemo in RET fusion-positive NSCLC	**Pembrolizumab + chemo** Bhandari et al, n=12	19.1 (6.9-NR)	-	-	N/A	N/A
	Pembrolizumab + chemo Hess et al, n=9	NR	-	-	N/A	N/A
Pembrolizumab + chemo in RET wt NSCLC	**Pembrolizumab + chemo** KN-189, previously untreated, PD-L1 1-49%, n=128	21.8 (17.7-25.6)	71.1%	44.3%	N/A	N/A
	Pembrolizumab + chemo KN-189, previously untreated, PD-L1 <1%, n=127	17.2 (13.8-22.8)	63.4%	39.3%	N/A	N/A
Naïve ITC						
Base case Pralsetinib vs. pembrolizumab + chemo in RET wt NSCLC	**Pralsetinib** ARROW, no prior therapy, unrestricted, n=116	[redacted]				
	Pembrolizumab + chemo KN-189, previously untreated, PD-L1 >1%, n=410					
Flatiron RW comparison						
Flatiron EDM, IPTW Pralsetinib vs. pembrolizumab + chemo in RET wt NSCLC	**Pralsetinib** ARROW, no prior therapy, n=71					
	Pembrolizumab + chemo EDM, previously untreated, n=[redacted]					

Abbreviations: CI – confidence interval; EDM – Enhanced Data Mart; ICI - immune checkpoint inhibitors; N/A - not applicable; NR - not reached; NSCLC – non-small cell lung cancer; PD-L1 – programmed death ligand 1; wt – wild-type, IPTW - Inverse probability of treatment weighting, RMSTD - root mean square (total) deviation; RET – rearranged during transfection; KN-189 – KEYNOTE-189.

18.2.3.2 Progression-free survival

Flatiron EDM comparison

The weighted KM curve for pralsetinib vs. pembrolizumab, carboplatin, and pemetrexed for PFS based on IPTW can be seen inFigure 34. The HR estimated from Cox regression was[redacted] which is statistically significant. The 24.3 month RMSTD was [redacted]. Overall, pralsetinib is statistically significantly favoured over pembrolizumab.

[redacted]

Overview of all reported PFS data

Table 110: Overview of the reported PFS data relevant for the assessment

Analyses	Treatment Study, population, n	Median, mo. (95%CI)	Rate at 12 mo. (95%CI)	Rate at 24 mo. (95%CI)	HR (95%CI)	RMSTD (95% CI)
Narrative comparison						
Pralsetinib in RET fusion-positive NSCLC	**Pralsetinib** ARROW, overall efficacy, n=233	16.4 (11.0-24.1)	56.0 (48.9-63.1)	42.1 (33.2-51.0)	N/A	N/A
	Pralsetinib ARROW, no prior systemic treatment, n=75	13.0 (9.1-NR)	52.6 (37.7-67.5)	47.8 (31.6-64.1)	N/A	N/A
	Pralsetinib ARROW, updated total efficacy n=281	13.2 (11.4-16.8)	N/A	N/A	N/A	N/A
	Pralsetinib ARROW, updated treatment naïve, n=116	12.6 (9.2-16.6)	N/A	N/A	N/A	N/A

Pembrolizumab + chemo in RET fusion-positive NSCLC	**Pembrolizumab + chemo** Bhandari et al, n=12	5.4 (1.4-14.2)	-	-	N/A	N/A
	Pembrolizumab + chemo Hess et al, n=9	6.6 (0.4-NR)	-	-	N/A	N/A
Pembrolizumab + chemo in RET wt NSCLC	**Pembrolizumab + chemo** KN-189, previously untreated, PD-L1 1-49%, n=128	9.4 (8.1-13.8)	43.8%	22.3%	N/A	N/A
	Pembrolizumab + chemo KN-189, previously untreated, PD-L1 <1%, n=127	6.2 (4.9-8.1)	26.0%	13.3%	N/A	N/A
Naïve ITC						
Base case Pralsetinib vs. pembrolizumab + chemo in RET wt NSCLC	**Pralsetinib** ARROW, no prior therapy, unrestricted, n=116	[redacted]				
	Pembrolizumab + chemo KN-189, previously untreated, PD-L1 >1%, n=410					
Flatiron RW comparison						
Flatiron EDM, IPTW Pralsetinib vs. pembrolizumab + chemo in RET wt NSCLC	**Pralsetinib** ARROW, no prior therapy, n=71					
	Pembrolizumab + chemo EDM, previously untreated, n=[redacted]					

Abbreviations: CI – confidence interval; EDM – Enhanced Data Mart; ICI - immune checkpoint inhibitors; N/A - not applicable; NR - not reached; NSCLC – non-small cell lung cancer; PD-L1 – programmed death ligand 1; wt – wild-type; mo. – Months; IPTW - Inverse probability of treatment weighting, RMSTD - root mean square (total) deviation; RET – rearranged during transfection; KN-189 – KEYNOTE-189.

18.2.3.3 Objective response

Overview of all reported ORR data

Table 111: Overview of the reported ORR data relevant for the assessment

Analyses	Treatment Study, population, n	ORR, n (%) (95% CI)	CR, n (%)	PR, n (%)
Narrative comparison				
Pralsetinib in RET fusion-positive NSCLC	**Pralsetinib** ARROW, overall efficacy, n=233	150 (64.4%) (57.9-70.5)	11 (4.7%)	139 (59.7%)
	Pralsetinib ARROW, no prior systemic treatment, n=75	54 (72.0%) (60.4-81.8)	4 (5.3%)	50 (66.7%)

	Pralsetinib ARROW, updated total efficacy n=281	185 (65.8) (60.0-71.4)	18 (6.4)	167 (59.4)
	Pralsetinib ARROW, updated treatment naïve, post eligibility revision, n=69	52 (75.4) (63.5-84.9)	4 (5.8)	48 (69.6)
Pembrolizumab + chemo in RET fusion-positive NSCLC	**Pembrolizumab + chemo** Bhandari et al, n=10	70%	10%	60%
	Pembrolizumab + chemo Hess et al, n=8	75%	12.5%	62.5%
Pembrolizumab + chemo in RET wt NSCLC	**Pembrolizumab + chemo** KN-189, previously untreated, PD-L1 1-49%, n=128	50%	2.3%	47.7%
	Pembrolizumab + chemo KN-189, previously untreated, PD-L1 <1%, n=127	33.1%	0.0%	33.1%

Abbreviations: CR – complete response; ICI – immune checkpoint inhibitor; ORR – overall response rate; PR – partial response; wt – wild-type; NSCLC – non-small cell lung cancer; RET – rearranged during transfection; KN-189 – KEYNOTE-189; CI – confidence interval; PD-L1 – programmed cell death ligand-1.

18.2.3.4 Safety

Overview of all reported safety data

Table 112: Overview of the reported safety data

Analyses	Treatment Study, population, n	Grade ≥3 AEs	Discontinuations due to AEs
Narrative comparison			
Pralsetinib in RET fusion-positive NSCLC	**Pralsetinib** ARROW, overall safety population, n=528	76.9%	17.2%
	Pralsetinib ARROW, RET fusion-positive NSCLC safety population, n=281	75.4%	19.6%
	Pralsetinib ARROW, updated RET fusion-positive NSCLC safety population, n=281	10.0% §	231 (82.2)
Pembrolizumab + chemo in RET wt NSCLC	**Pembrolizumab + chemo** KN-189, safety population, n=405	72.1%	36.0%

Abbreviations: AE – adverse event; wt – wild-type; RET – rearranged during transfection; NSCLC – non-small cell lung cancer. § reported as TRAEs.

18.3 Supplementary analysis

18.3.1 Analysis of survival by tumour response

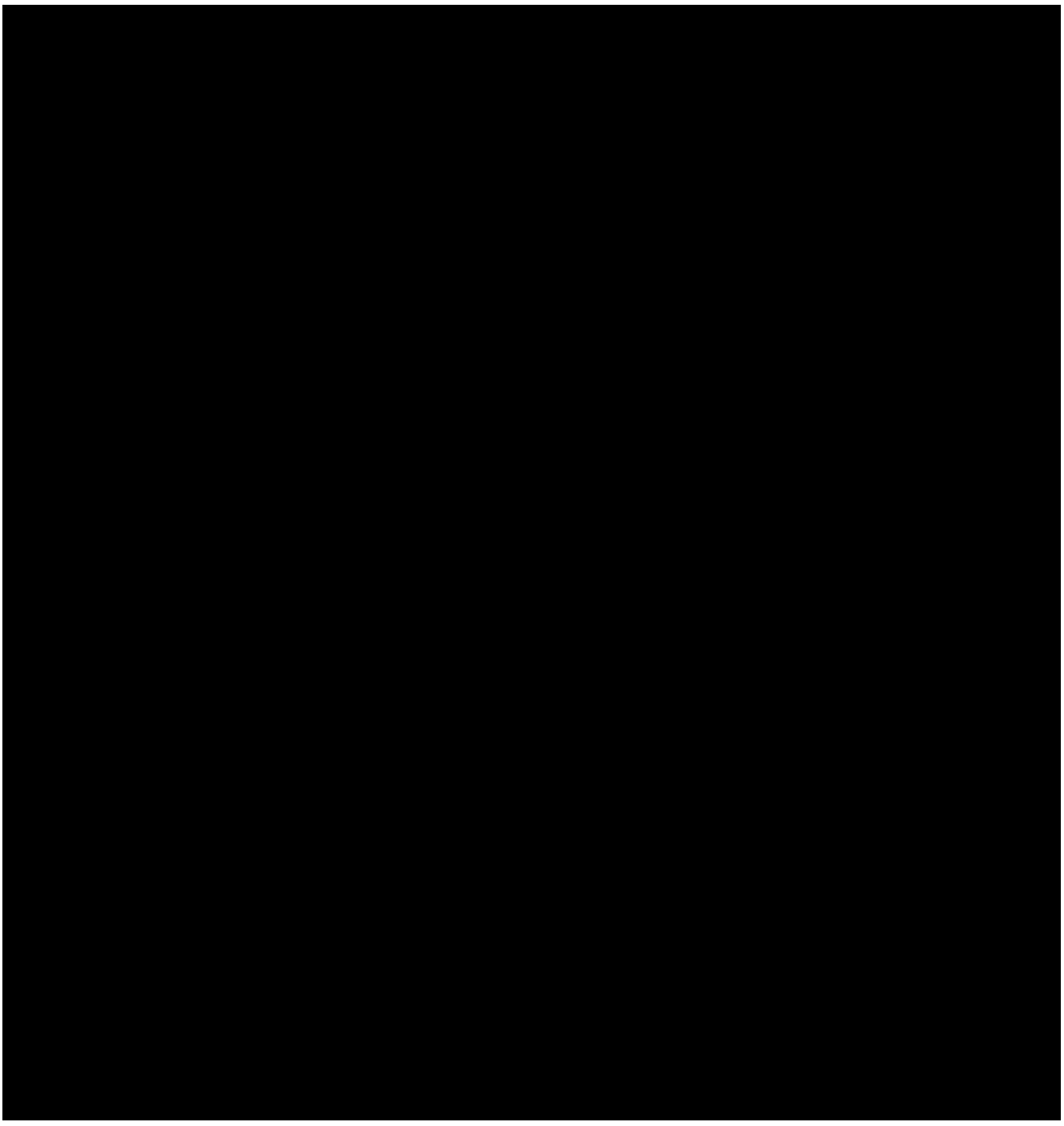
Although ARROW included OS as an endpoint, median OS was not yet reached at the CCOD of November 6, 2020. In order to assess the association of tumour response with survival, a landmark analysis will be presented in the following.

The landmark analysis was based on a population that includes 216 NSCLC patients in the efficacy population with documented evidence of a targetable RET fusion by either local or central testing,and measurable (target) disease at baseline per BICR (CCOD: November 6, 2020). The analysis included landmarks at 2, 3, and 4 months from the first dose. Each analysis included the patients who were alive and under the study follow-up at each of the time points. Summary statistics were used to describe patient demographics and baseline disease characteristics among responders and non-responders. Unadjusted and adjusted Cox proportional hazards models were used to assess association between tumour response at the landmark time and survival.

[redacted]

The results suggest an association of tumour response with survival although it should be noted, that tumour response may act as a surrogate marker for patients with a favourable prognosis [75] and that responders may have a longer survival due to pre-treatment characteristics that could favour a longer survival. Cox proportional hazards models adjusted for basic demographics were carried out to address this concern. The data suggests an association of tumour response with overall survival and supports the use of ORR as an endpoint.

[redacted]

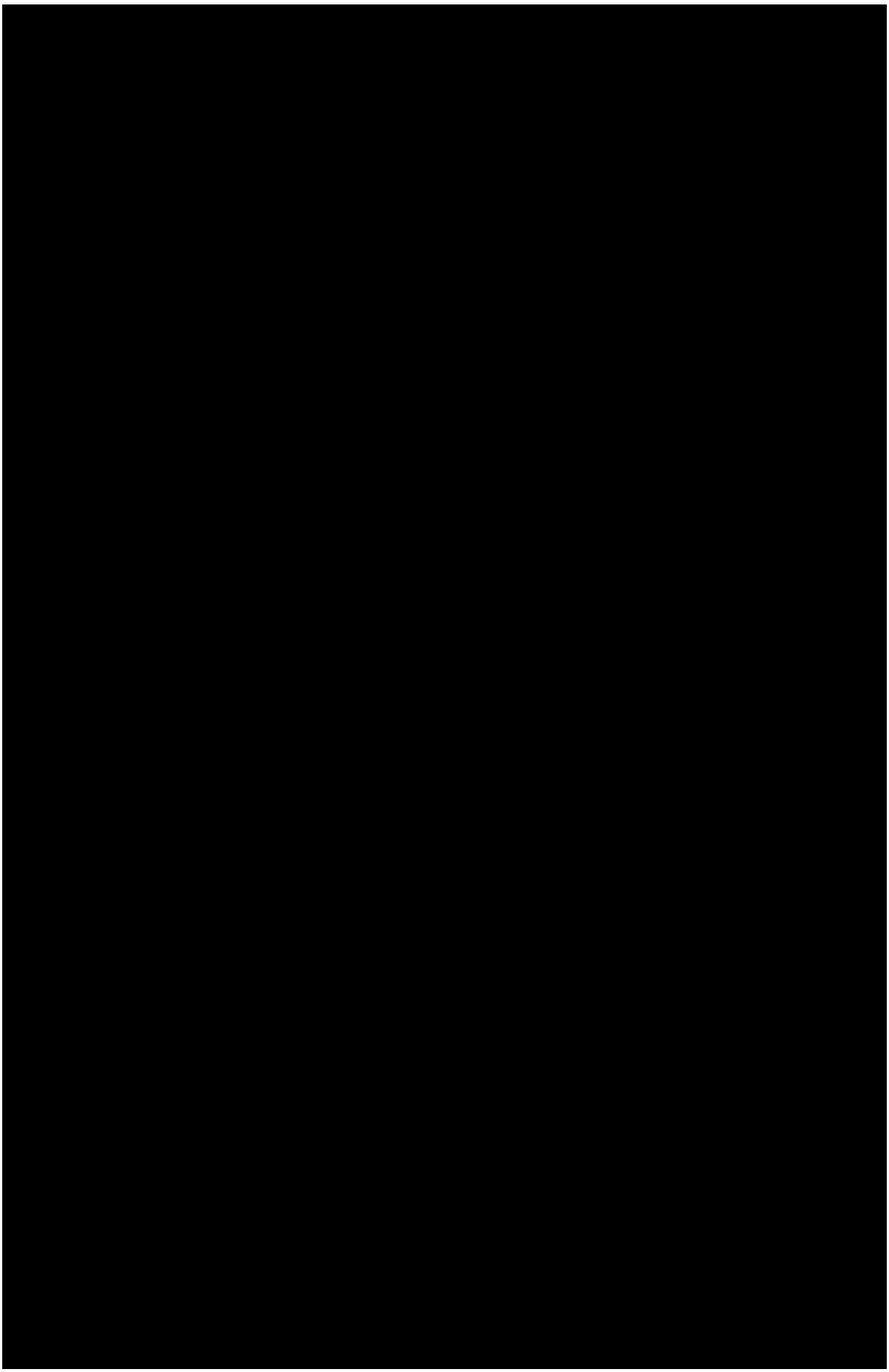


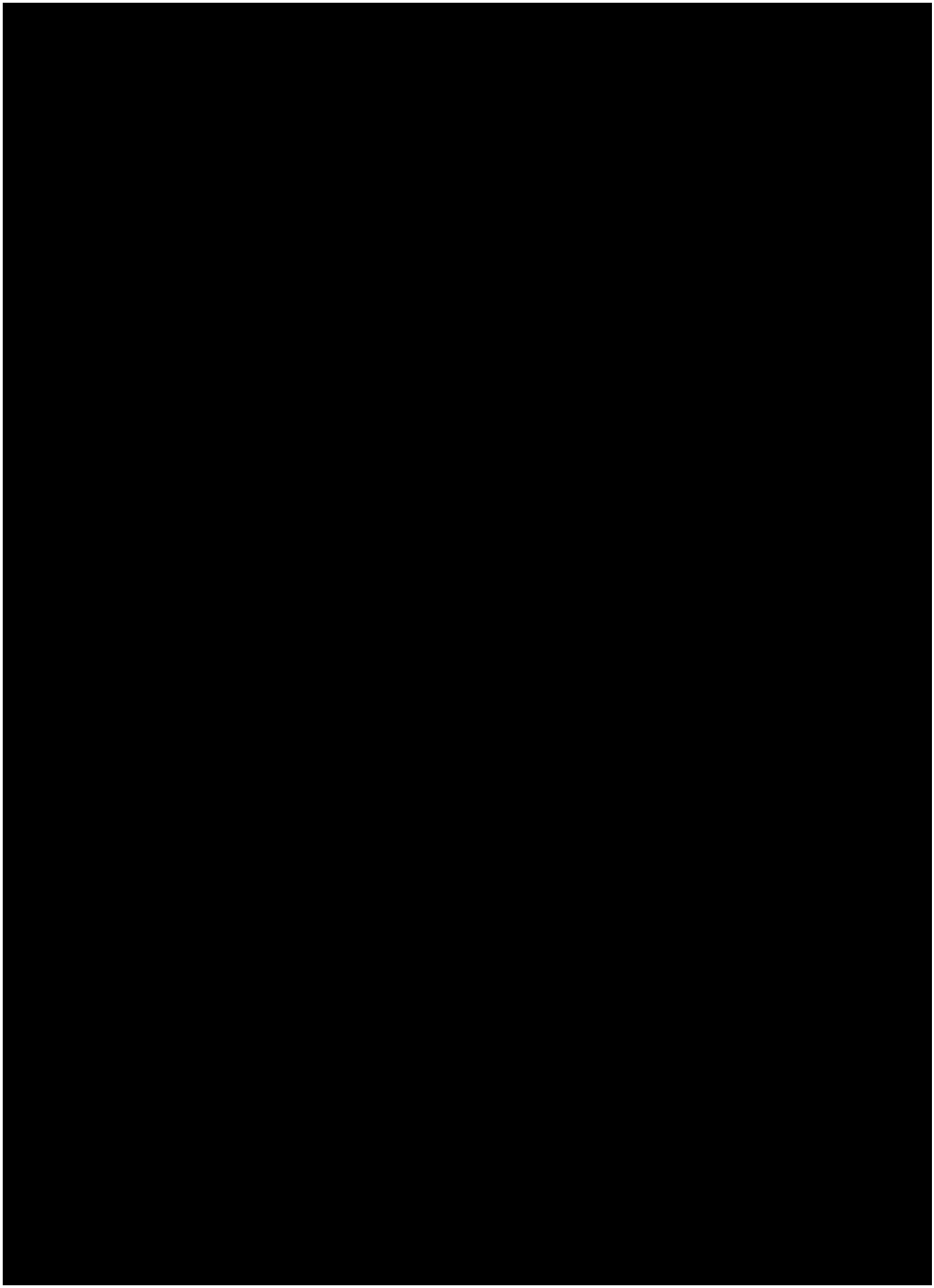
Abbreviations: CI – confidence interval; HR – Hazard ratio.

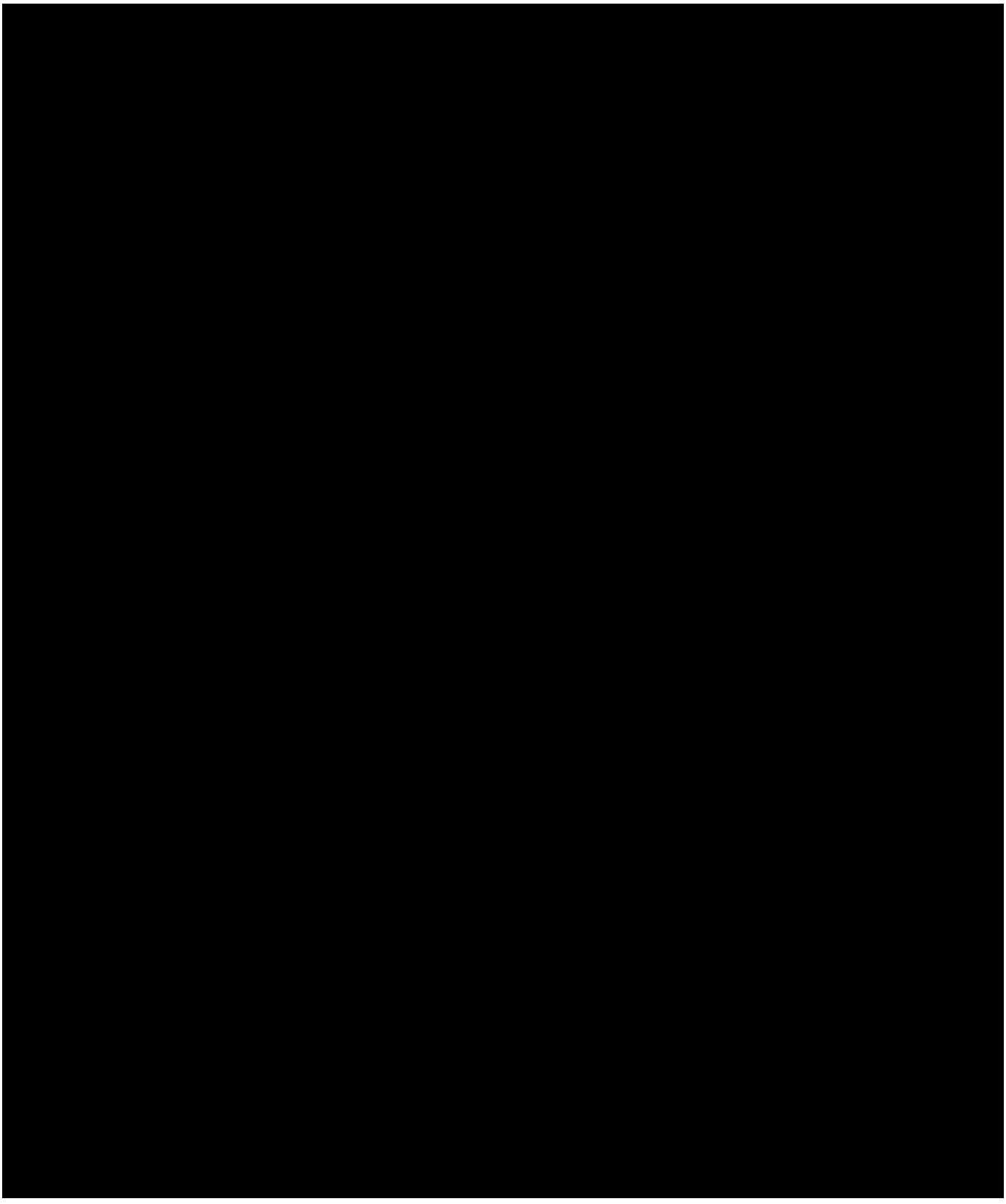
19. Appendix G – Extrapolation

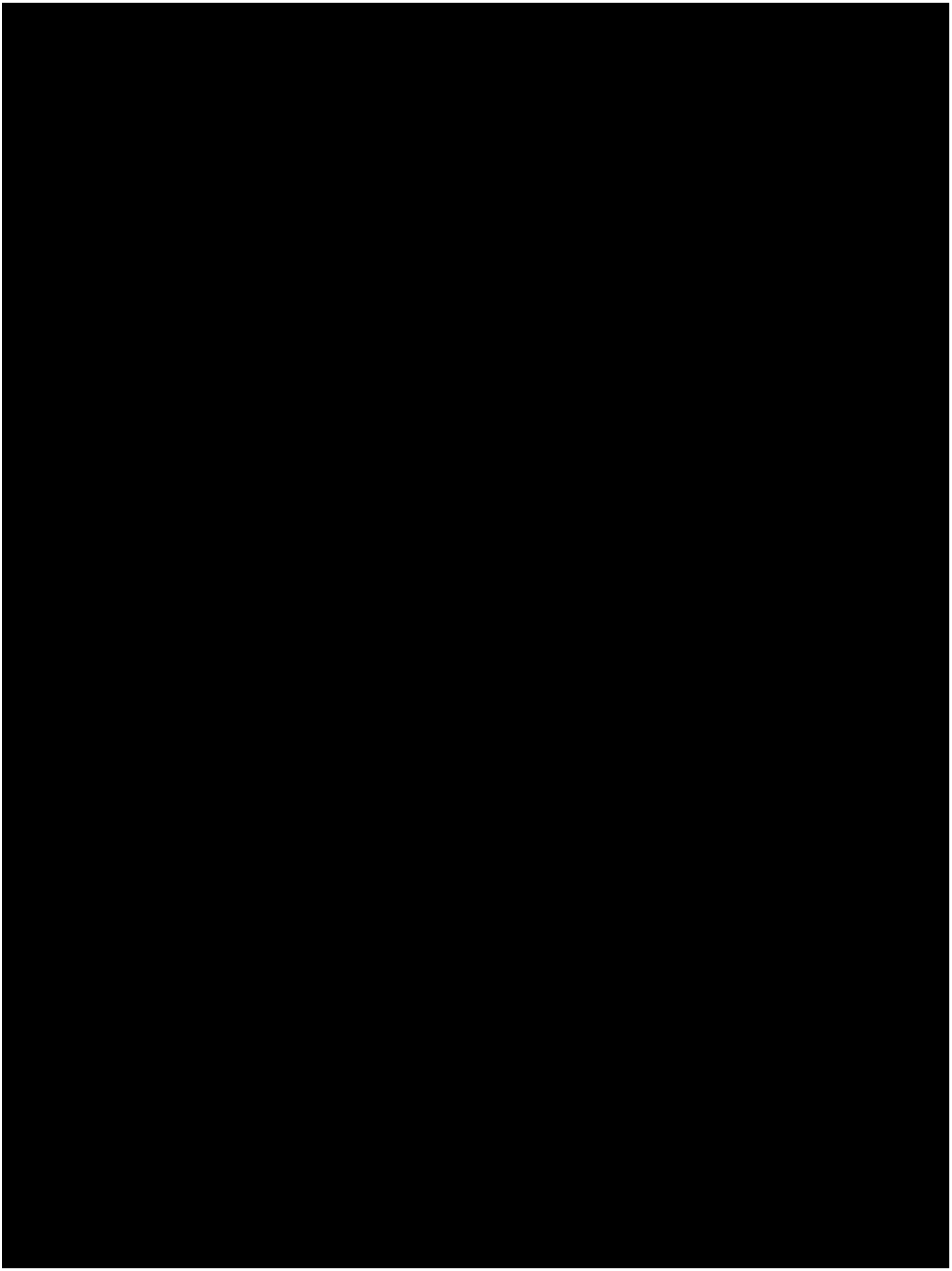
PFS and OS Kaplan–Meier data for pralsetinib were obtained from the ARROW trial individual patient data (IPD) (Roche, 2020). OS and PFS Kaplan–Meier curves were generated from the time to event datasets. Survival estimates for other comparators were generated using HRs. A summary of the steps taken to generate OS and PFS curves for each treatment in the model is shown below:

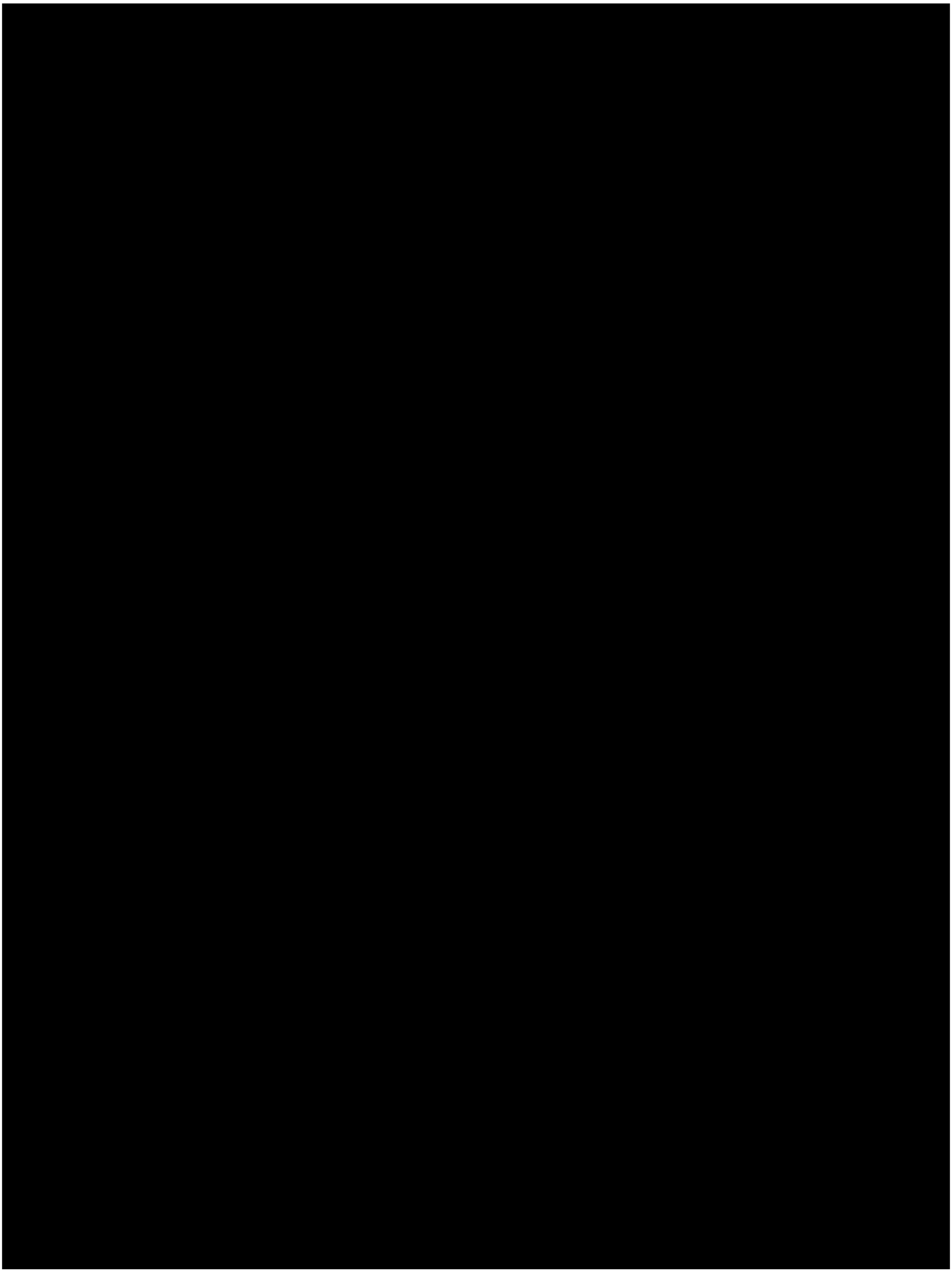
- Pralsetinib OS and PFS estimates were generated by fitting parametric models to the Kaplan–Meier curves from ARROW.
- For all other treatments, the appropriate HRs from the multiple sources were applied to the OS and PFS curves for pralsetinib to generate OS and PFS curves for each comparator.

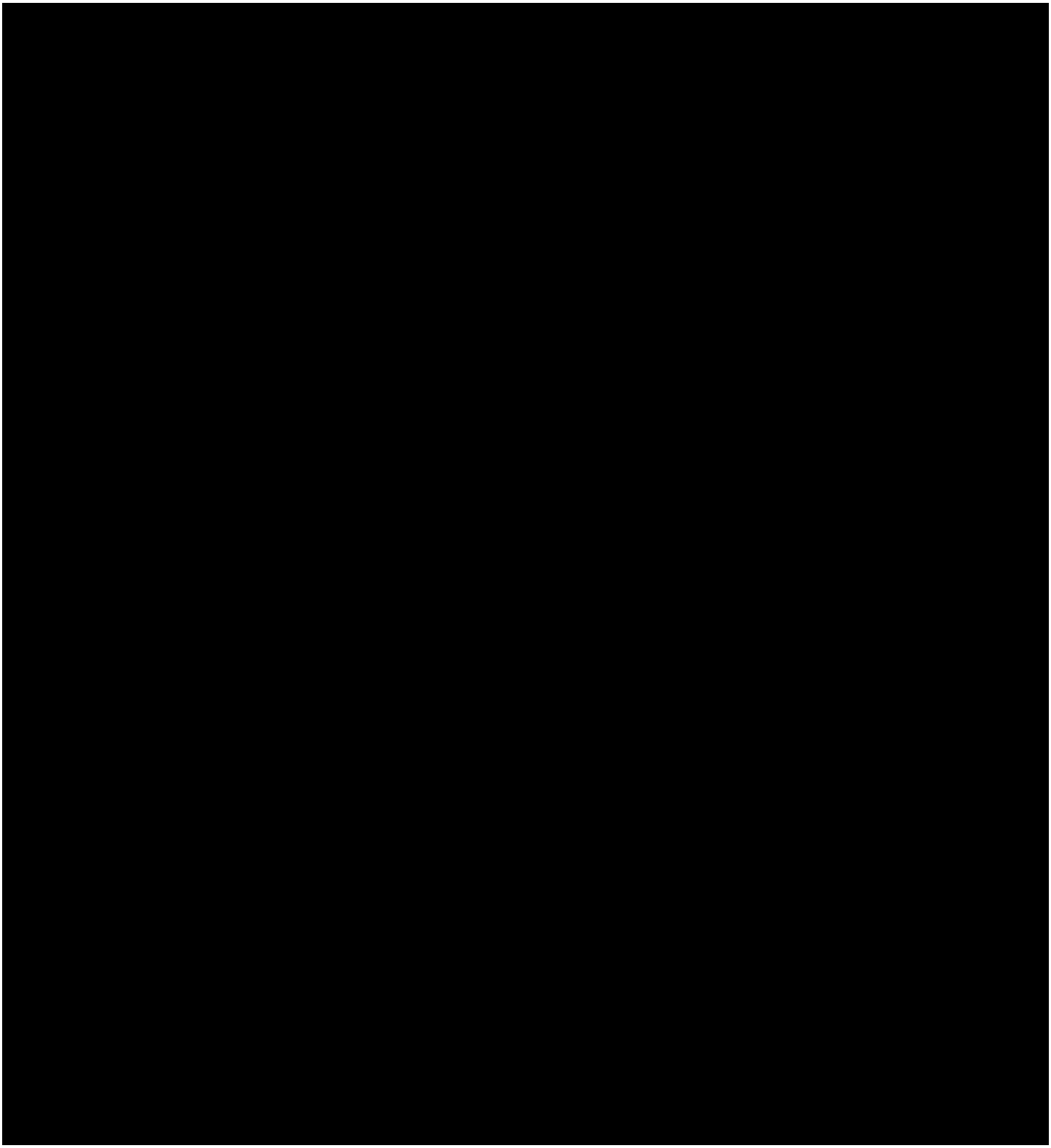


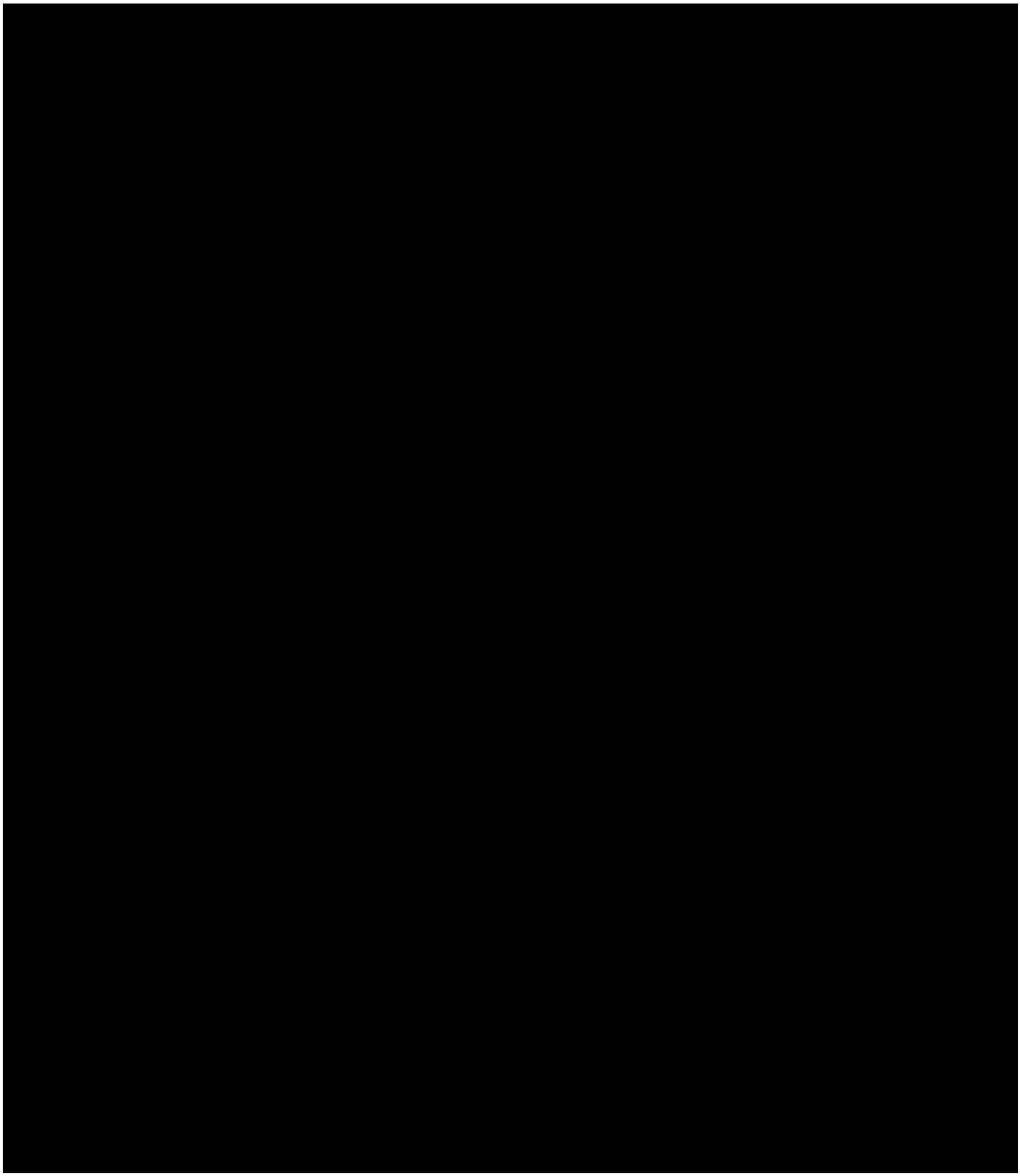


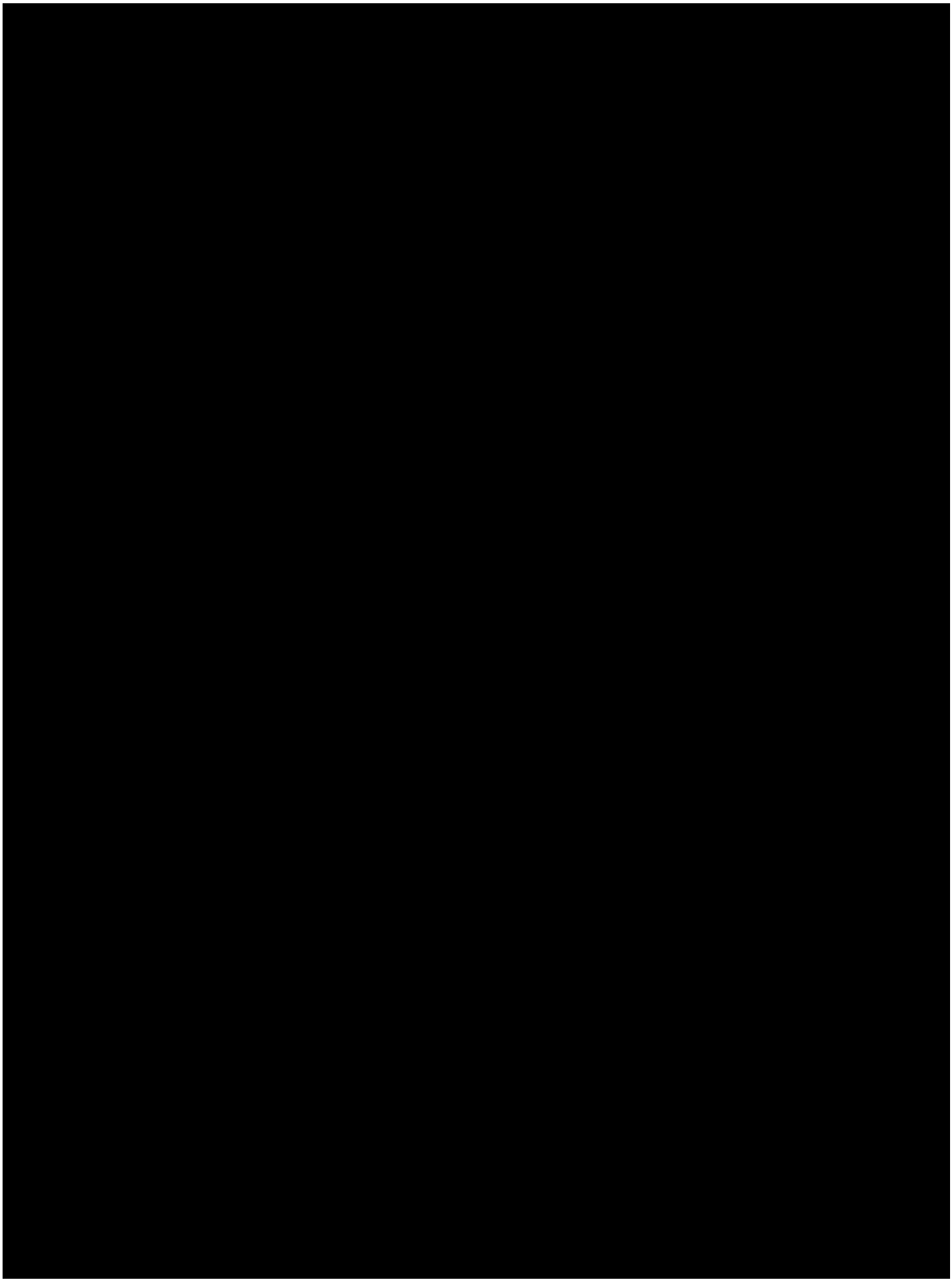


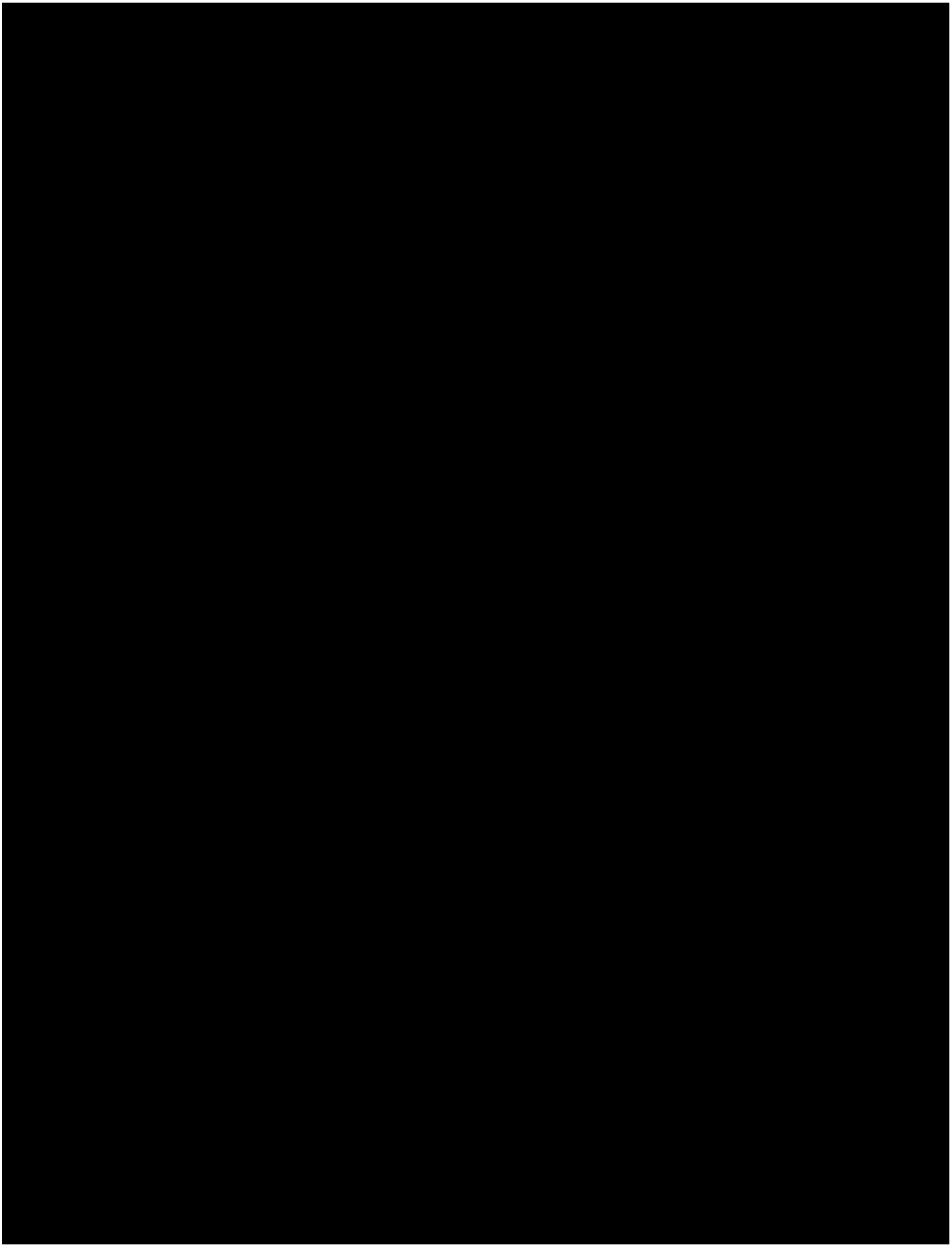


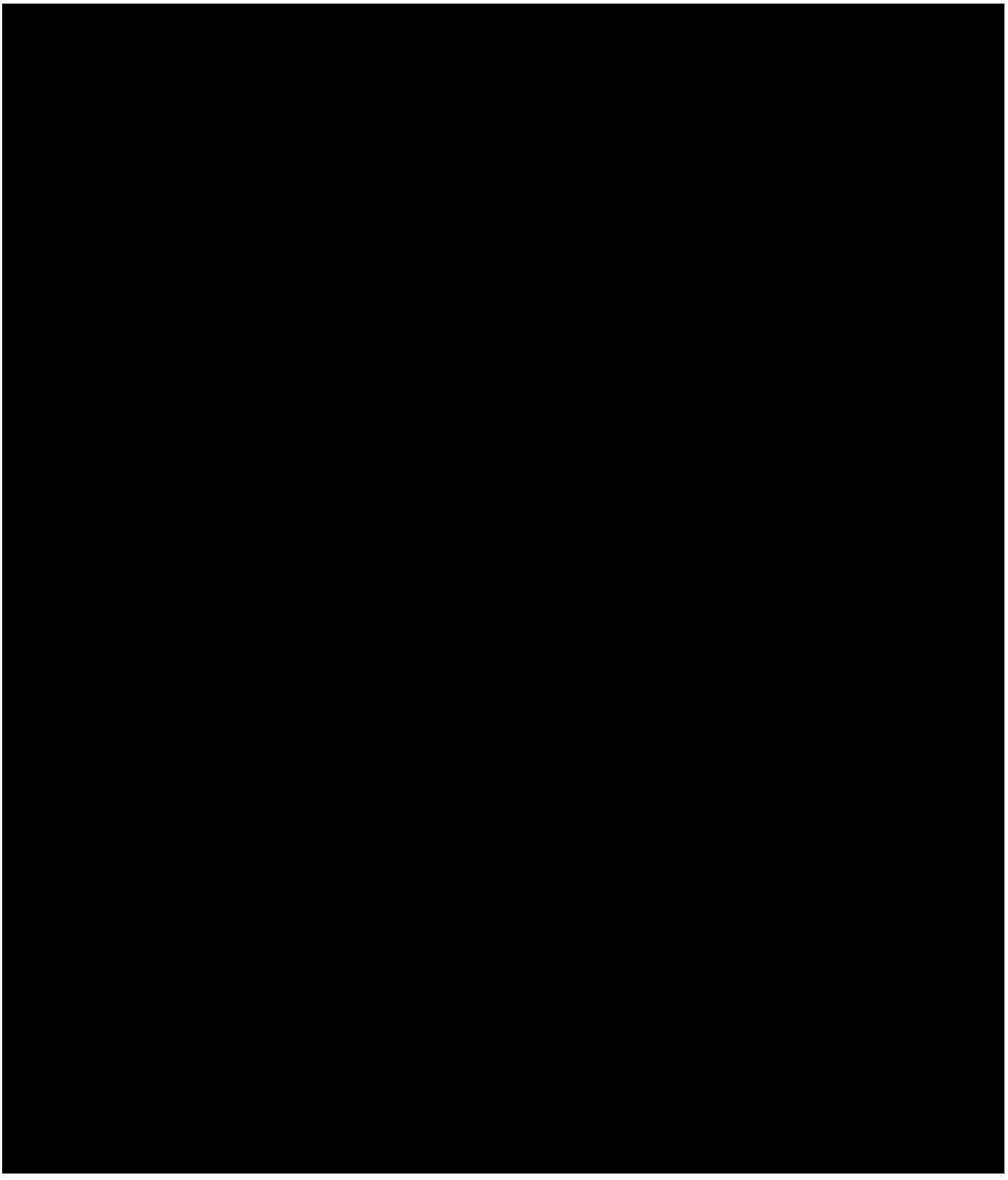


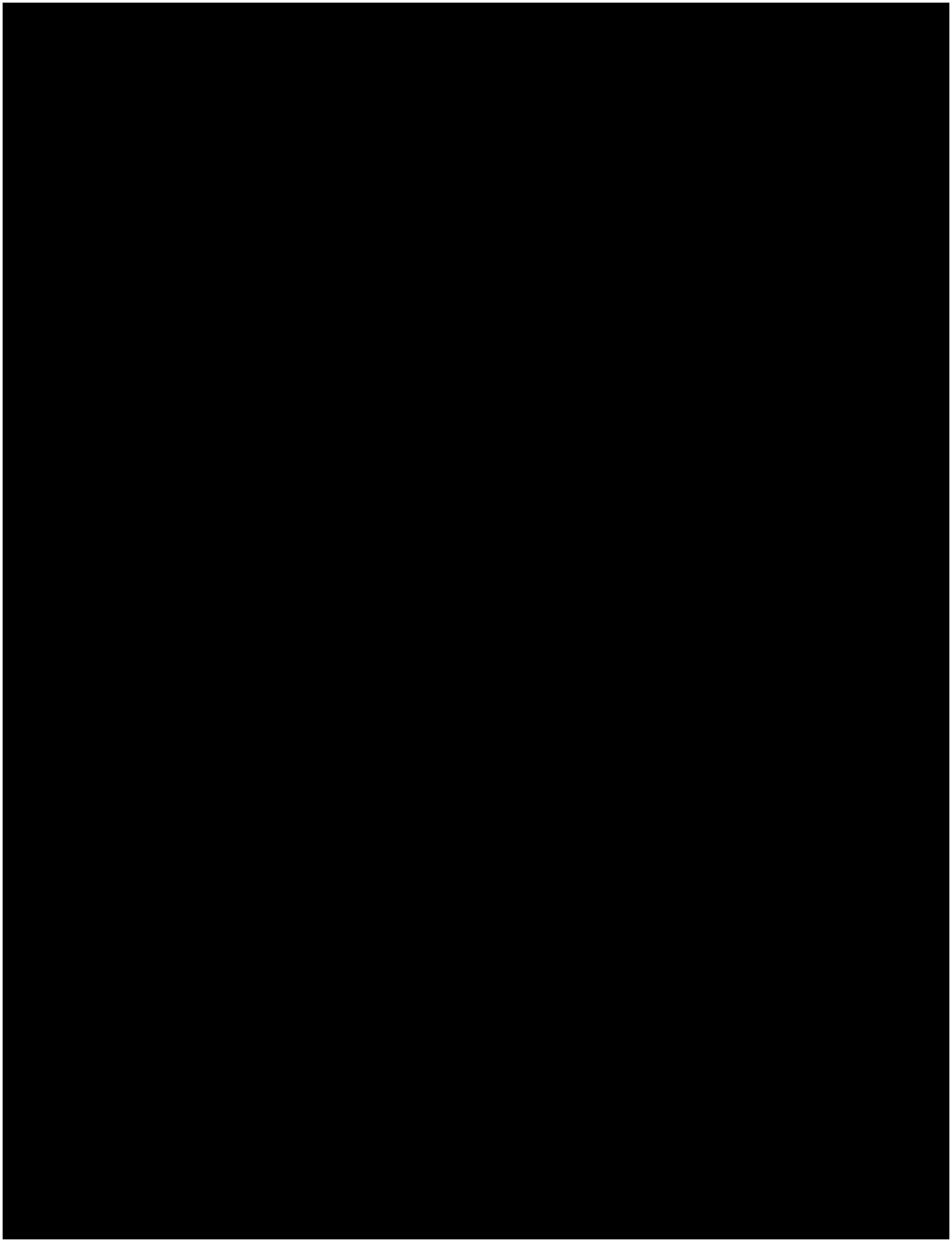


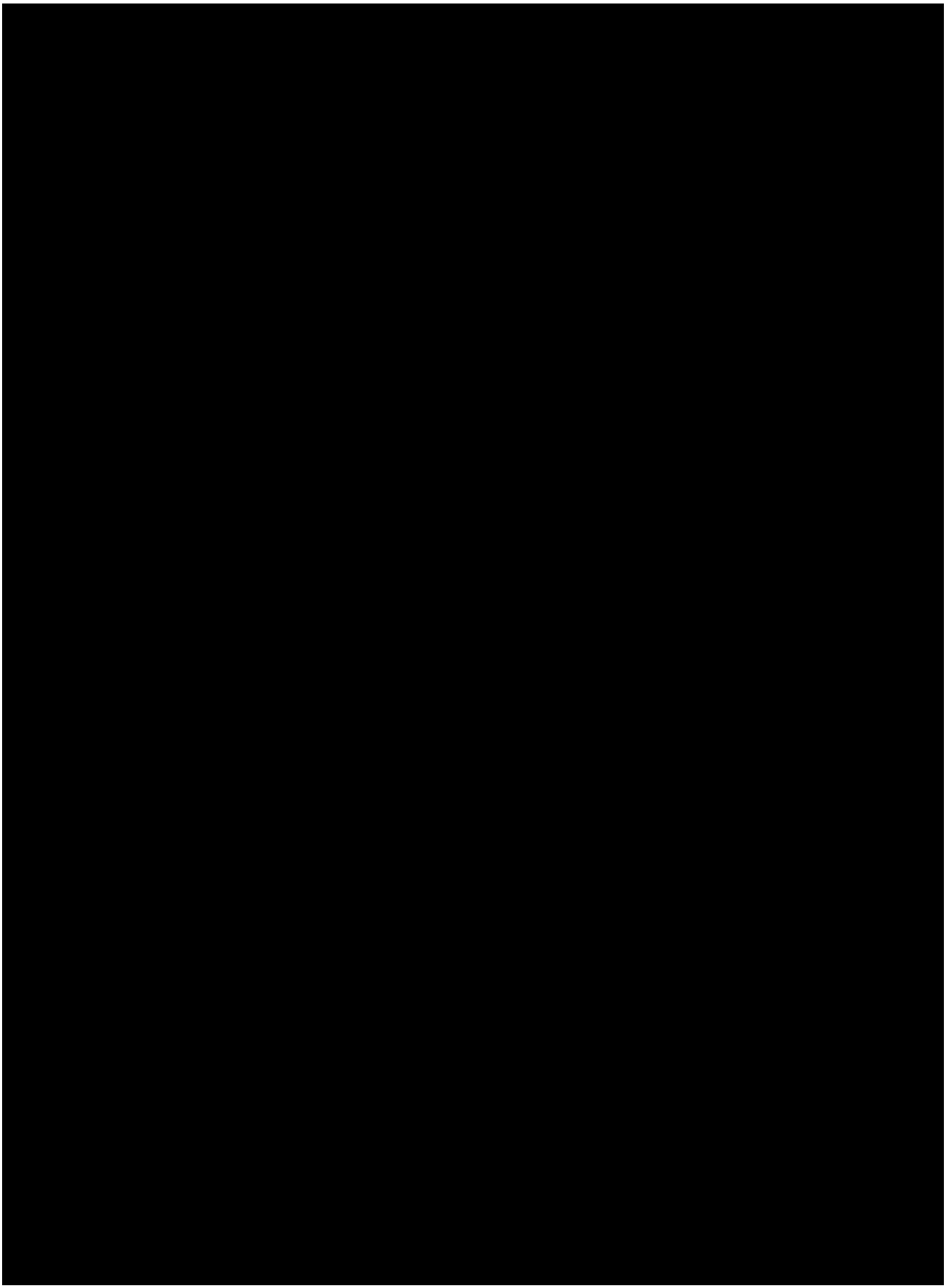


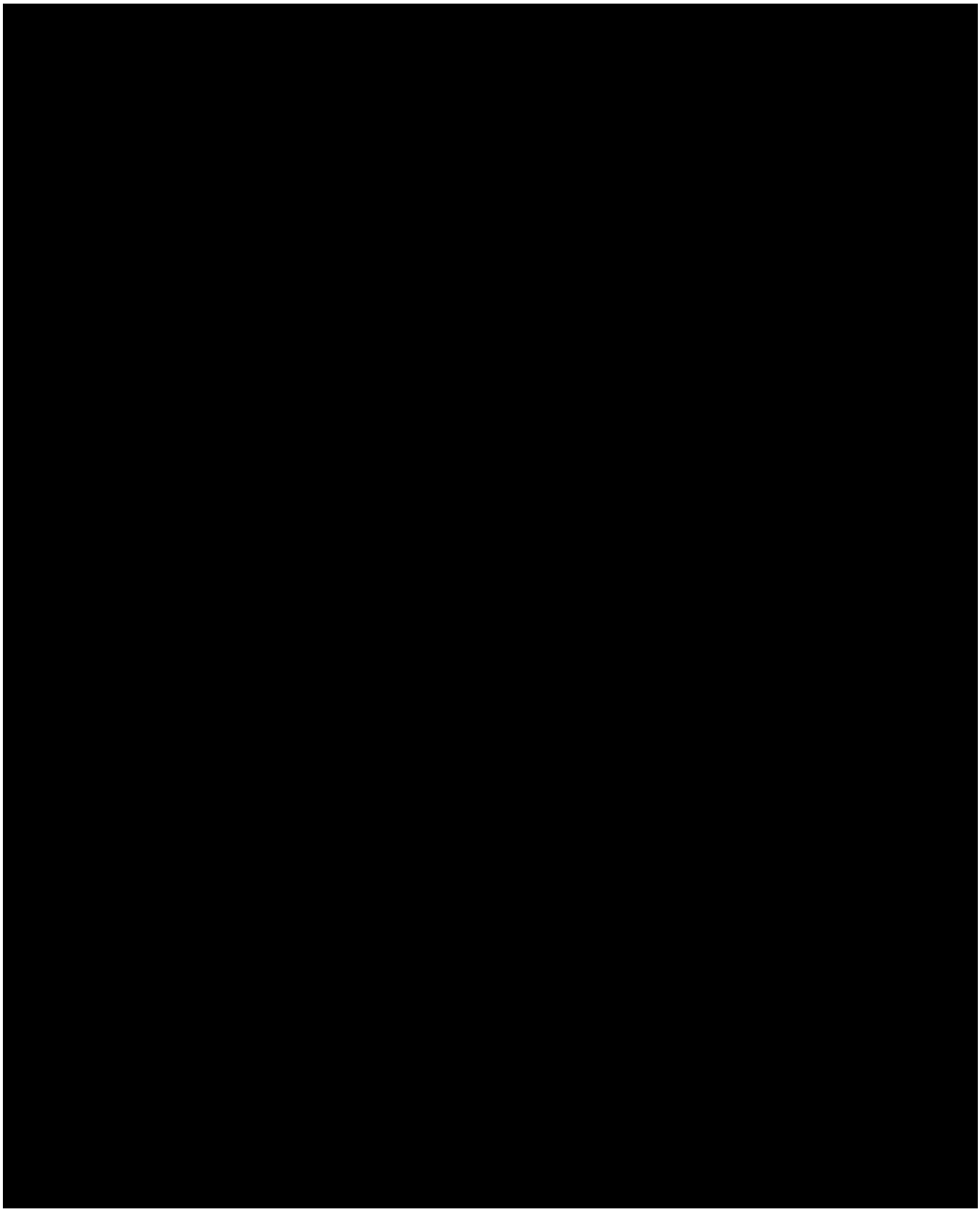


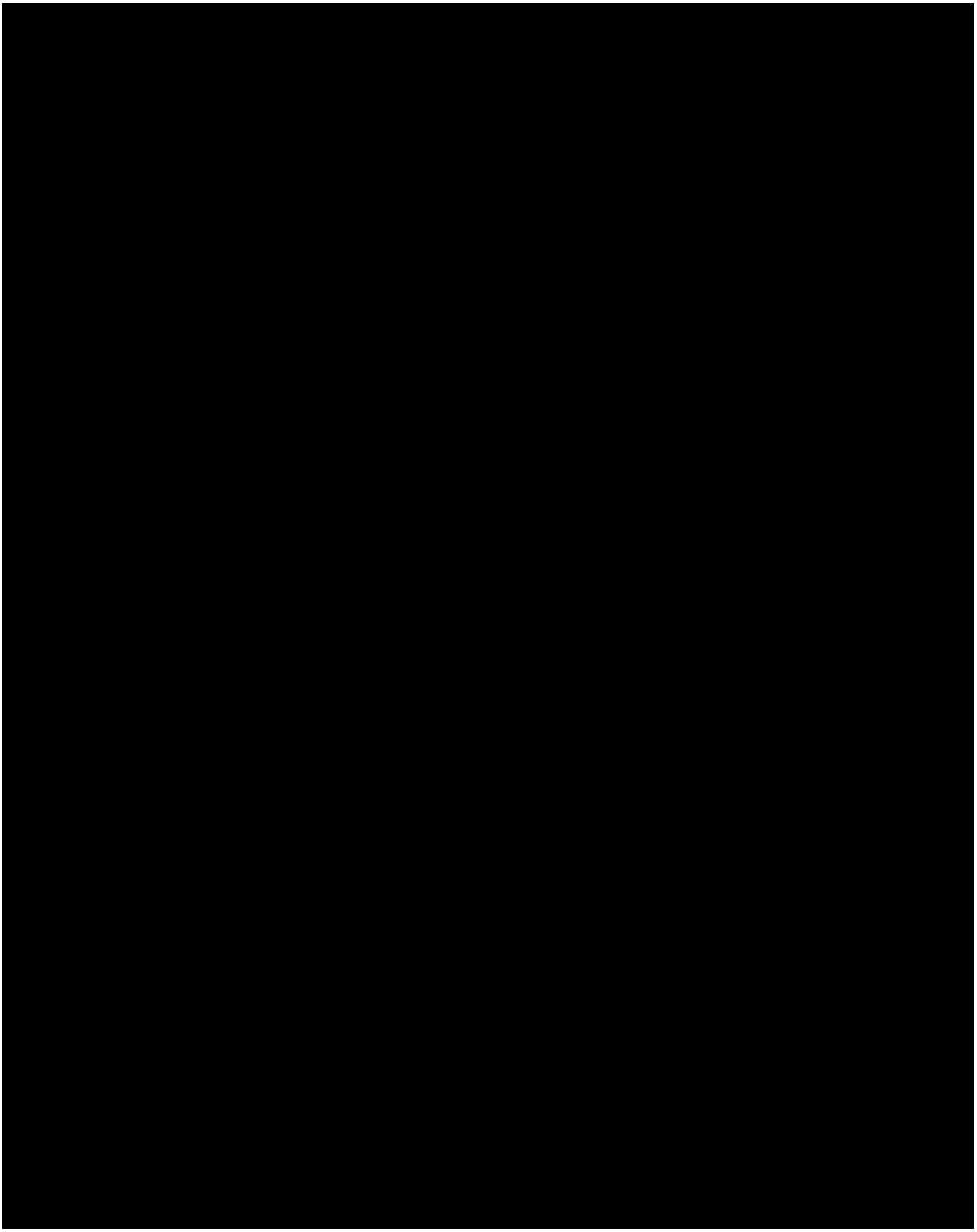


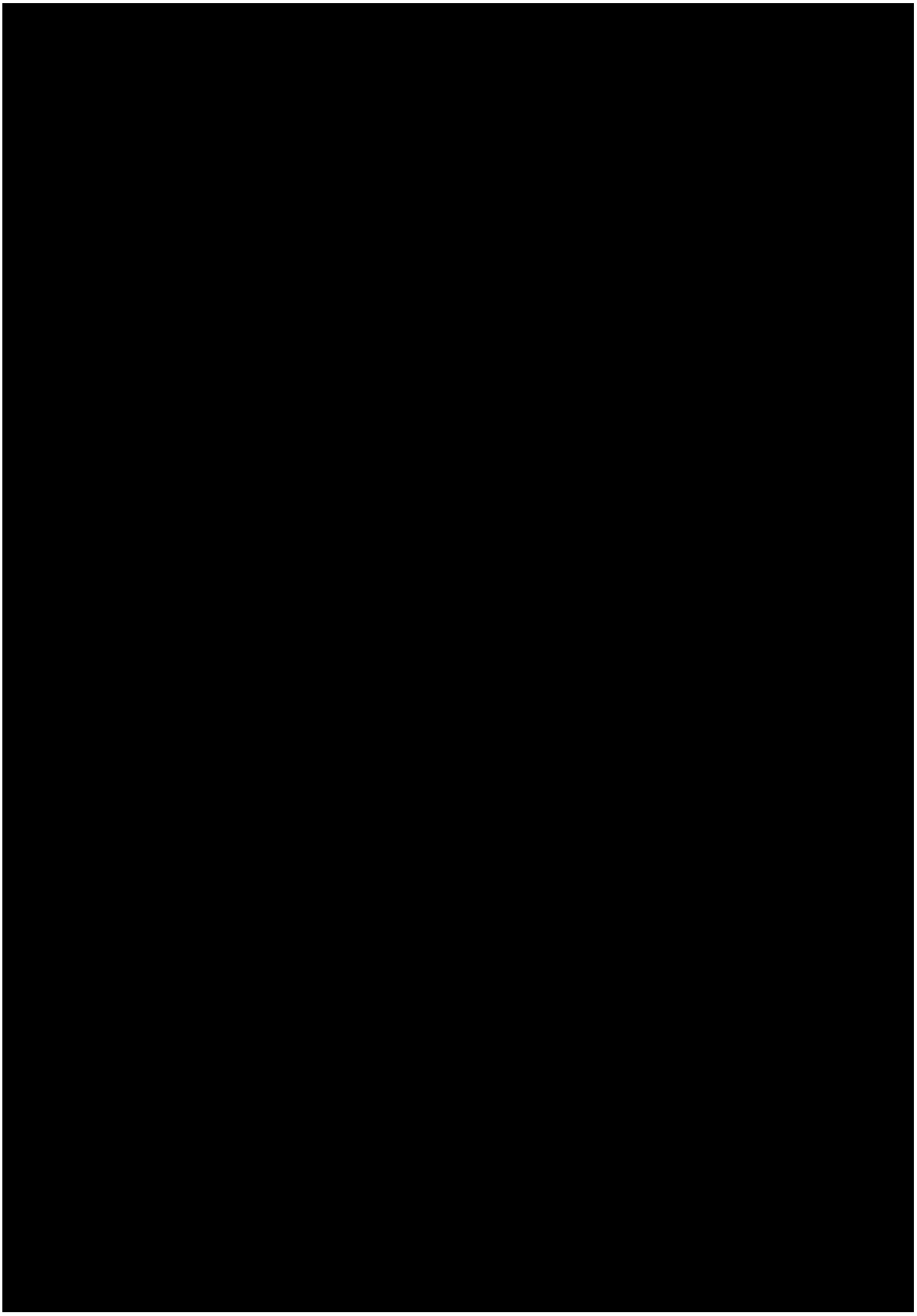












20. Appendix H - Literature search for HRQoL data

To identify utility values for the two health states and relevant AEs a series of health technology assessment (HTA)-compatible systematic literature reviews (SLRs) have been performed with the objective to identify the following evidence in patients with RET fusion-positive NSCLC:

- Clinical;
- Economic evaluations for relevant treatments;
- Health state utility values (HSUVs) for relevant health states;
- Cost/resource use data.

20.1.1 Data sources

The SLR was performed in the following electronic databases via the Ovid platform: Embase from 1974 to 2020 October 8 (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily), Medline from 1946 to 2020 October 6, EconLit from 1886 to 2020 October 1 and EBM Reviews from 2005 to October 7, 2020 (incorporating; Cochrane Database of Systematic Reviews), ACP Journal Club from 1991 to September 2020, Database of Abstracts of Reviews of Effects (DARE) 1st Quarter 2016, Cochrane Clinical Answers September 2020, Cochrane Central Register of Controlled Trials (CENTRAL) September 2020, Cochrane Methodology Register 3rd Quarter 2012, HTA Database 4th Quarter 2016 and NHS EED 1st Quarter 2016.

Any databases which were not updated to the present day (e.g. DARE, HTA, NHS EED), were also searched via the University of York Centre for Reviews and Dissemination (CRD) website.

20.1.2 Search strategy

Systematic literature search

The search strategies for the SLR of HSUVs and a summary of the resulting hits are provided below. Due to the narrow population of interest, a single search strategy was developed to identify studies across all four component SLRs (clinical, economic evaluation, HSUV, and cost/resource use).

Embase 1974 to 2020 October 08
Accessed 9th October 2020

	Searches	Results
1	protein Ret/	4836
2	("ret?" or "ret-fusion" or "ret-fusion-positive" or "ret-positive" or "ret-altered" or "ret-mutated").mp.	26693
3	1 or 2	26693
4	exp non small cell lung cancer/	100441
5	(nsclc or mnsclc or ansclc or msqnsclc or sqclc or nsnsclc or lansclc or cpnpc).ti,ab.	83283
6	(lac adj3 (lung or adenocarcinoma)).ti,ab.	261
7	((scc adj3 squamous cell carcinoma) and lung).ti,ab.	2253
8	(non adj3 small adj3 cell adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	100362
9	(('non small' or nonsmall) adj3 lung adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	104193
10	(('non small' or nonsmall) adj3 cell adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	104277
11	(bronchial adj3 ('non small' or nonsmall) adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	225
12	('non small cell' adj3 (lung or bronchial or pulmonary or bronchopulmonary or bronchus) adj3 (cancer* or carcinoma*)).ti,ab.	100411
13	('non small' adj3 cell adj3 (cancer* or carcinoma*) adj3 lung*).ti,ab.	100562
14	(pulmonary adj3 'non small cell' adj3 (cancer* or carcinoma*)).ti,ab.	257
15	(large adj3 cell adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	1007

16	((squamous or nonsquamous or 'non squamous') adj5 (cell or 'non small cell') adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	8082
17	(bronchus adj3 squamous adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	16
18	(lung adj3 epidermoid adj3 (cancer* or carcinoma*)).ti,ab.	211
19	(lung adj3 squamous adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	5590
20	(lung and (nsclc* or cpnpc* or 'non small' or nonsmall or large or squamous or 'non squamous' or nonsquamous) and (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcinogenesis or tumo?r* or metasta*)).ti,ab.	153934
21	((adenocancer or adenocarcinoma) adj3 (lung or pulmonary)).ti,ab.	29980
22	or/4-21	200393
23	3 and 22	1734

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to October 06, 2020

Accessed 9th October 2020

	Searches	Results
1	Proto-Oncogene Proteins c-ret/	3499
2	("ret?" or "ret-fusion" or "ret-fusion-positive" or "ret-positive" or "ret-altered" or "ret-mutated").mp.	18972
3	1 or 2	18972
4	exp Carcinoma, Non-Small-Cell Lung/	54031
5	(nsclc or mnsclc or ansclc or msqnsclc or sqclc or nsnsclc or lansclc or cpnpc).ti,ab.	48243
6	(lac adj3 (lung or adenocarcinoma)).ti,ab.	218
7	((scc adj3 squamous cell carcinoma) and lung).ti,ab.	1478
8	(non adj3 small adj3 cell adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	68729
9	(('non small' or nonsmall) adj3 lung adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	71399
10	(('non small' or nonsmall) adj3 cell adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	71445
11	(bronchial adj3 ('non small' or nonsmall) adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	272
12	('non small cell' adj3 (lung or bronchial or pulmonary or bronchopulmonary or bronchus) adj3 (cancer* or carcinoma*)).ti,ab.	68842
13	('non small' adj3 cell adj3 (cancer* or carcinoma*) adj3 lung*).ti,ab.	68921
14	(pulmonary adj3 'non small cell' adj3 (cancer* or carcinoma*)).ti,ab.	190
15	(large adj3 cell adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	742
16	((squamous or nonsquamous or 'non squamous') adj5 (cell or 'non small cell') adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	5274
17	(bronchus adj3 squamous adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	10
18	(lung adj3 epidermoid adj3 (cancer* or carcinoma*)).ti,ab.	167
19	(lung adj3 squamous adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	3945
20	(lung and (nsclc* or cpnpc* or 'non small' or nonsmall or large or squamous or 'non squamous' or nonsquamous) and (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or angiosarcoma* or	101211

	chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcinogenesis or tumo?r* or metasta*)).ti,ab.	
21	((adenocancer or adenocarcinoma) adj3 (lung or pulmonary)).ti,ab.	21974
22	or/4-21	126510
23	3 and 22	598

EBM Reviews, incorporating: EBM Reviews - Cochrane Database of Systematic Reviews 2005 to October 7, 2020, EBM Reviews - ACP Journal Club 1991 to September 2020, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016, EBM Reviews - Cochrane Clinical Answers September 2020, EBM Reviews - Cochrane Central Register of Controlled Trials September 2020, EBM Reviews - Cochrane Methodology Register 3rd Quarter 2012, EBM Reviews - Health Technology Assessment 4th Quarter 2016, EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2016
Accessed 9th October 2020

	Searches	Results
1	Proto-Oncogene Proteins c-ret/	13
2	("ret?" or "ret-fusion" or "ret-fusion-positive" or "ret-positive" or "ret-altered" or "ret-mutated").mp.	750
3	1 or 2	750
4	exp Carcinoma, Non-Small-Cell Lung/	4575
5	(nsclc or mnsclc or ansclc or msqnsclc or sqclc or nsnsclc or lansclc or cpnpc).ti,ab.	9678
6	(lac adj3 (lung or adenocarcinoma)).ti,ab.	5
7	((scc adj3 squamous cell carcinoma) and lung).ti,ab.	66
8	(non adj3 small adj3 cell adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	12225
9	(('non small' or nonsmall) adj3 lung adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	12507
10	(('non small' or nonsmall) adj3 cell adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	12513
11	(bronchial adj3 ('non small' or nonsmall) adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	38
12	('non small cell' adj3 (lung or bronchial or pulmonary or bronchopulmonary or bronchus) adj3 (cancer* or carcinoma*)).ti,ab.	12241
13	('non small' adj3 cell adj3 (cancer* or carcinoma*) adj3 lung*).ti,ab.	12215
14	(pulmonary adj3 'non small cell' adj3 (cancer* or carcinoma*)).ti,ab.	18
15	(large adj3 cell adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	45
16	((squamous or nonsquamous or 'non squamous') adj5 (cell or 'non small cell') adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	1367
17	(bronchus adj3 squamous adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	7
18	(lung adj3 epidermoid adj3 (cancer* or carcinoma*)).ti,ab.	18
19	(lung adj3 squamous adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	385
20	(lung and (nsclc* or cpnpc* or 'non small' or nonsmall or large or squamous or 'non squamous' or nonsquamous) and (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcinogenesis or tumo?r* or metasta*)).ti,ab.	14361
21	((adenocancer or adenocarcinoma) adj3 (lung or pulmonary)).ti,ab.	571
22	or/4-21	16188
23	3 and 22	65

EconLit 1886 to October 01, 2020
Accessed 9th October 2020

	Searches	Results
1	("ret?" or "ret-fusion" or "ret-fusion-positive" or "ret-positive" or "ret-altered" or "ret-mutated").mp.	280
2	(nsclc or mnsclc or ansclc or msqnsclc or sqclc or nsnsclc or lansclc or cpnpc).ti,ab.	8
3	(lac adj3 (lung or adenocarcinoma)).ti,ab.	0
4	((scc adj3 squamous cell carcinoma) and lung).ti,ab.	0
5	(non adj3 small adj3 cell adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	18
6	(('non small' or nonsmall) adj3 lung adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	18
7	(('non small' or nonsmall) adj3 cell adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	18
8	(bronchial adj3 ('non small' or nonsmall) adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	0
9	('non small cell' adj3 (lung or bronchial or pulmonary or bronchopulmonary or bronchus) adj3 (cancer* or carcinoma*)).ti,ab.	18
10	('non small' adj3 cell adj3 (cancer* or carcinoma*) adj3 lung*).ti,ab.	18

11	(pulmonary adj3 'non small cell' adj3 (cancer* or carcinoma*)).ti,ab.	0
12	(large adj3 cell adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	0
13	((squamous or nonsquamous or 'non squamous') adj5 (cell or 'non small cell') adj3 lung adj3 (cancer* or carcinoma*)).ti,ab.	2
14	(bronchus adj3 squamous adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	0
15	(lung adj3 epidermoid adj3 (cancer* or carcinoma*)).ti,ab.	0
16	(lung adj3 squamous adj3 cell adj3 (cancer* or carcinoma*)).ti,ab.	1
17	(lung and (nsclc* or cpnpc* or 'non small' or nonsmall or large or squamous or 'non squamous' or nonsquamous) and (neoplasm* or cancer* or carcinoma* or adenocarcinoma* or angiosarcoma* or chondrosarcoma* or sarcoma* or teratoma* or lymphoma* or blastoma* or microcytic* or carcinogenesis or tumo?r* or metasta*)).ti,ab.	46
18	((adenocancer or adenocarcinoma) adj3 (lung or pulmonary)).ti,ab.	1
19	or/2-18	46
20	1 and 19	0

Hand search

The electronic searches were supplemented by hand searching reference lists of included studies, relevant conference proceedings (last three years availability), and HTA body websites. Additional websites recommended by NICE, including the EuroQoL website, were also hand searched. A summary of the hand searching methods and results relevant for the SLR of HSUVs is provided below.

Source	Date	Search details	Search terms	No. hits	Downloaded
Conferences					
ASCO Annual Meeting 2020	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
ASCO Annual Meeting 2019	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer" AND "ret"	31	0
			"Non-small cell lung cancer" AND "ret"	31	0
			"NSCLC" AND "ret"	24	0
ASCO Annual Meeting 2018	21/10/2020	ASCO Meeting Library (advanced search): https://meetinglibrary.asco.org/ Searched by keyword, filtered by meeting and year	"Non small cell lung cancer" AND "ret"	44	0
			"Non-small cell lung cancer" AND "ret"	44	0
			"NSCLC" AND "ret"	42	0
ELCC 2020	21/10/2020	Cancelled	N/A	N/A	N/A
ELCC 2019, Geneva	21/10/2020	https://oncologypro.esmo.org/meeting-resources/european-lung-cancer-congress-2019 Searched using online search bar, basic search	RET	1	0
ELCC 2018, Geneva	21/10/2020	Abstract book (Journal of Thoracic Oncology 13(4):S1-S149): https://www.jto.org/issue/S1556-0864(18)X0004-5 searched using CTRL + F	RET	6	0
52nd ESHG Conference 2019	22/10/2020	https://www.nature.com/collections/afhijbfgib Searched oral presentations PDF using CTRL + F	RET(space)	3	0
			RET+	0	0
			RET-	0	0
			Lung	22	0
51st ESHG Conference 2018	22/10/2020	https://www.nature.com/collections/dcbjhfbdad/ Searched oral presentations PDF using CTRL + F	RET(space)	4	0
			RET+	0	0
			RET-	0	0
			lung	9	0
50th ESHG Conference 2017	22/10/2020	https://www.nature.com/collections/ygctjrwfhb	RET(space)	7	0
			RET+	0	0
			RET-	0	0
			Lung	4	0
ESMO Virtual Congress 2020	21/20/2020	Abstracts not yet available	N/A	N/A	N/A

ESMO Congress 2019, Barcelona	21/20/2020	Abstract book (Annals of Oncology 30(Suppl 5)): https://www.annalsofoncology.org/issue/S0923-7534(19)X9100-0) searched using CTRL + F	RET	1	0
ESMO Congress 2018	21/20/2020	https://oncologypro.esmo.org/meeting-resources/esmo-2018-congress Searched using search bar, basic search	RET	17	0
ESP Annual Congress 2019	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	N/A	N/A	N/A
ESP Annual Congress 2018	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	N/A	N/A	N/A
ESP Annual Congress 2017	21/20/2020	Abstracts not yet available: https://www.esp-pathology.org/publications/esp-annual-meeting-abstracts.html	N/A	N/A	N/A
ISPOR US 2020, Orlando	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	2	0
			“Non-small cell lung cancer” AND “ret”	2	0
			“NSCLC” AND “ret”	2	0
ISPOR US 2019, New Orleans	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	0	0
			“Non-small cell lung cancer” AND “ret”	0	0
			“NSCLC” AND “ret”	0	0
ISPOR US 2018, Baltimore	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	0	0
			“Non-small cell lung cancer” AND “ret”	0	0
			“NSCLC” AND “ret”	0	0
ISPOR Europe 2019, Copenhagen	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	0	0
			“Non-small cell lung cancer” AND “ret”	0	0
			“NSCLC” AND “ret”	0	0
ISPOR Europe 2018, Barcelona	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	0	0
			“Non-small cell lung cancer” AND “ret”	0	0
			“NSCLC” AND “ret”	0	0
ISPOR Europe 2017, Glasgow	22/10/2020	ISPOR Presentations Database, keyword search filtered by conference: https://www.ispor.org/heor-resources/presentations-database/search	“Non small cell lung cancer” AND “ret”	0	0
			“Non-small cell lung cancer” AND “ret”	0	0
			“NSCLC” AND “ret”	0	0
	22/10/2020		RET(space)	6	0

HTAi 2019, Cologne		Abstract booklet: https://htai.org/annual-meetings/htai-2019-cologne/abstract-book/ searched using CTRL + F	RET+	0	0
			RET-	0	0
			Lung cancer	50	0
HTAi 2018, Vancouver	22/10/2020	Abstract booklet: https://htai.org/annual-meetings/htai-2018-vancouver/abstract-book/ searched using CTRL + F	RET(space)	11	0
			RET+	0	0
			RET-	0	0
			Lung cancer	15	0
HTAi 2017, Rome	22/10/2020	Abstract booklet: https://htai.org/wp-content/uploads/2018/09/AM17_Rome_Abstractbook_Final-1.pdf searched using CTRL + F	RET(space)	6	0
			RET+	0	0
			RET-	0	0
			Lung cancer	31	0
NCRI Cancer Conference 2019	22/10/2020	https://abstracts.ncri.org.uk/year_published/2019/ Searched using search online search feature	Non small cell lung cancer	18	0
			Non-small cell lung cancer	17	0
			NSCLC	13	0
NCRI Cancer Conference 2018	22/10/2020	https://abstracts.ncri.org.uk/ Searched using online search feature, filtered by year	Non small cell lung cancer	28	0
			Non-small cell lung cancer	25	0
			NSCLC	24	0
NCRI Cancer Conference 2017	22/10/2020	https://abstracts.ncri.org.uk/ Searched using online search feature, filtered by year	Non small cell lung cancer	19	0
			Non-small cell lung cancer	17	0
			NSCLC	20	0
SMDM 17th Biennial European Conference 2018	22/10/2020	Scientific program: https://smdm.confex.com/smdm/17bec/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1&searchterm=NSCLC	“Non small cell lung cancer”	2	0
			“Non-small cell lung cancer”	2	0
			“NSCLC”	2	0
SMDM 41st North American Meeting 2019	22/10/2020	Scientific program search: https://smdm.confex.com/smdm/2019/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1	“Non small cell lung cancer”	4	0
			“Non-small cell lung cancer”	4	0
			“NSCLC”	3	0
SMDM 40th North American Meeting 2018	22/10/2020	Scientific program search: https://smdm.confex.com/smdm/2018/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1	“Non small cell lung cancer”	3	0
			“Non-small cell lung cancer”	3	0
			“NSCLC”	3	0
SMDM 39th North American Meeting 2017	22/10/2020	Scientific program search: https://smdm.confex.com/smdm/2017/meetingapp.cgi/Search/0?sort=Relevance&size=10&page=1	“Non small cell lung cancer”	1	0
			“Non-small cell lung cancer”	1	0
			“NSCLC”	0	0

USCAP Annual Meeting 2020	22/10/2020	Abstracts from USCAP 2020: Pulmonary, Mediastinum, Pleura, and Peritoneum Pathology (1869-1980): https://www.nature.com/articles/s41379-020-0485-4 Searched PDF using CTRL + F	RET(space)	12	0
			RET+	0	0
			RET-	0	0
USCAP Annual Meeting 2019	22/10/2020	Abstracts from USCAP 2019: Pulmonary Pathology (1803-1896), searched PDF using CTRL + F: https://www.nature.com/articles/s41379-019-0244-6	RET(space)	18	0
			RET+	0	0
			RET-	1	0
USCAP Annual Meeting 2018	22/10/2020	USCAP 2018 Abstracts: Pulmonary Pathology (2011–2128), searched PDF using CTRL + F: https://www.nature.com/articles/modpathol201822	RET(space)	9	0
			RET+	0	0
			RET-	0	0
HTA agencies					
CADTH (pCODR)	20/10/2020	https://cadth.ca/pcodr/find-a-review. Searched using main search tool bar	Non small cell lung cancer	28	0
G-BA	20/10/2020	https://www.g-ba.de/beschluesse/ Searched terms within decision section, filtered for final reports	Non small cell lung cancer AND ret	80	0
HAS	20/10/2020	https://www.has-sante.fr/jcms/fc_2875208/en/search-for-a-guideline-an-assesment All publications by topic, filtered for respiratory tract diseases -> Respiratory tract cancers	N/A	12	0
Institute for Clinical and Economic Review	20/10/2020	https://icer-review.org/ Searched terms in main search bar	Non small cell lung cancer	1	0
IQWiG	20/10/2020	https://www.iqwig.de/en/projects-results/publications/iqwig-reports.1071.html Searched IQWiG reports by keyword	Non small cell lung cancer	228	0
NICE	20/10/2020	https://www.nice.org.uk/ Searched terms in search bar; filtered on “Guidance” and published “Technology Appraisal Guidance”	Non small cell lung cancer	41	0†
PBAC	22/10/2020	Public Summary documents, searched by product (CTRL + F): http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/public-summary-documents-by-product	Pralsetinib	0	0
			Selpercatinib	0	0
			Pembrolizumab	28	0
			Pemetrexed	9	0
			Atezolizumab	8	0
			Bevacizumab	12	0

			Carboplatin	0	0
			Cisplatin	0	0
			Paclitaxel	7	0
			Docetaxel	9	0
			Gemcitabine	0	0
			Vinorelbine	3	0
			Nintedanib	5	0
			Nivolumab	28	0
SMC	20/10/2020	https://www.scottishmedicines.org.uk/. Searched terms in search bar	Non small cell lung cancer	62	0
Other sources					
University of York CRD website	21/10/2020	https://www.crd.york.ac.uk/CRDWeb/ Searched terms in any field, combined with AND, in DARE, NHS EED, and HTA	"RET" AND "non-small cell lung cancer"	1	0
			"RET" AND "non-small cell lung cancer"	1	0
			"RET" AND "NSCLC"	0	0
EuroQoL website	21/10/2020	https://euroqol.org/search-for-eq-5d-publications/ Advanced search in all fields	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
University of Sheffield ScHARRHUD	21/10/2020	https://www.scharrhud.org/index.php?recordsN1&m=search Searched terms in any field	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
INAHTA	21/10/2020	https://database.inahta.org/ Advanced search, terms searched in all field and combined with AND	"Non small cell lung cancer" AND "ret"	0	0
			"Non-small cell lung cancer" AND "ret"	0	0
			"NSCLC" AND "ret"	0	0
National Institute for Health Research (NIHR)	21/10/2020	https://www.nihr.ac.uk/	Non small cell lung cancer	4	0
			Non-small cell lung cancer	4	0
			NSCLC	2	0
			RET	2	0
Reference checking	31/10/2020	Reference checking reviews/included studies	N/A	N/A	0
Ad hoc	31/10/2020	Google Scholar	N/A	N/A	0

Abbreviations: ASCO, American Society of Clinical Oncology; CADTH, Canadian Agency for Drugs and Technologies in Health; CRD, Centre for Reviews and Dissemination; DARE, Database of Abstracts of Reviews of Effects; ELCC, European Lung Cancer Conference; ESHG, European Society of Human Genetics; ESMO, European Society for Medical Oncology; ESP, European Society of Pathology; G-BA, Federal Joint Committee; HAS, Haute Autorité de Santé; HTA, health technology assessment; HTAi, Health Technology Assessment International; INAHTA, International Network of Agencies for Health Technology Assessment; IQWiG, Institute for Quality and Efficiency in Health Care; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; N/A, not applicable; NCRI, National

Cancer Research Institute; NHS EED, National Health Service Economic Evaluation Database; NICE, National Institute for Health and Care Excellence; NSCLC, non-small cell lung cancer; PBAC, Pharmaceutical Benefits Advisory Committee; pCODR, pan-Canadian Oncology Drugs Review; SMC, Scottish Medicines Consortium; SMDM, Society for Medical Decision Making; USCAP, United States and Canadian Academy of Pathology.

† ID3743 Selpercatinib for RET fusion-positive advanced NSCLC: expected publication June 2021

Eligibility criteria

The eligibility criteria for the SLR of HSUVs follow the PICO elements and are detailed in Table 122. The criteria were developed to support the overall objective of the SLR, to identify utility values for the two health states and relevant AEs for patients with stage III/IV RET positive NSCLC.

The inclusion/exclusion of citations (both at the title/abstract phase and full publication review) was conducted by two independent analysts. Any disputes were referred to the project manager and resolved by consensus.

Relevant data were extracted into pre-approved summary tables by a reviewer. A second reviewer checked the data extraction and any inconsistencies were resolved through discussion.

Table 122: Eligibility criteria

CRITERIA	INCLUDE	EXCLUDE
POPULATION	Adult patients with stage III/IV RET+ NSCLC, regardless of treatment line	● Paediatric patients ● Patients with NSCLC who are not RET+ ● Mixed populations (where a breakdown of data for patients with RET+ disease is not provided)
INTERVENTION & COMPARATORS	No restriction	-
OUTCOMES	● HSUVs (and disutilities [e.g. associated with progression or AEs]) for relevant health states (individual [patient or caregiver]) derived using the following techniques: ○ Generic, preference-based instruments (e.g. EQ-5D [3L/5L], SF-6D, HUI2, HUI3, AQoL, 15D, QWB, MAUI) ○ Direct methods (e.g. TTO, SG, VAS) ○ Mapping algorithms allowing data from disease-specific/generic measures to be mapped to preference-based HSUVs ● Disease-specific/generic (non-utility) HRQOL data (e.g. EORTC-QLQ-C30)	Outcomes not listed in "include" column
STUDY DESIGN	● Studies reporting original HSUV data	● Reviews/editorials ● BIMs ● Case reports ● Pharmacokinetic studies ● Animal/*in vitro* studies
GEOGRAPHY	No restriction	-
PUBLICATION DATE	No restriction	-
LANGUAGE	English language publications or non-English language publications with an English abstract	Non-English language publications without an English abstract

Abbreviations: 15D, 15 Dimensions; AE, adverse event; AQoL, Assessment of Quality of Life; BIM, budget impact model; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D (3L/5L), European Quality of Life-5 Dimensions (3 Level/5 Level version); HRQOL, health-related quality of life; HSUV, health state utility value; HUI2/3, Health Utilities Index Mark 2/3; MAUI, multi-attribute utility instrument; NSCLC, non-small cell lung cancer; QWB, Quality of Well Being; SF-6D, Short Form-6 Dimensions; SG, standard gamble; TTO, time trade off; VAS, visual analogue scale.

Study selection

The electronic database searches identified a total of 2,397 citations. Following removal of 518 duplicates, 1,879 citations were screened on the basis of title and abstract. A total of three citations were considered to be potentially relevant and were obtained for full text review. At this stage, a further two citations were excluded. The single remaining study reported disease-specific health-related quality of life (HRQOL) data (i.e. non-utility data) for patients with RET fusion-positive NSCLC in the LIBRETTO-001 trial (Kilde: Minchom, 2020).
Hand searching yielded no additional relevant articles.

The flow of studies through the review is summarised in the PRISMA flow diagram in Figure 52. A list of studies excluded on the basis of full text review is provided in Table 47, along with the rationale for exclusion.

No studies were identified which reported utility data associated specifically with patients with RET fusion-positive NSCLC. Therefore, a search of previous submissions to NICE for treatments of NSCLC in the first-line and second-line setting and beyond was conducted to investigate potential alternative sources of utility data for the economic model. The population of interest for this search was patients with locally advanced or metastatic NSCLC regardless of mutations status, receiving treatment in the first-line or second-line+ settings. A total of 30 previous submissions were identified (first-line N=14; second-line+ N=16). The previous submissions with utility data considered for the health economic analysis are listed in Table 14.

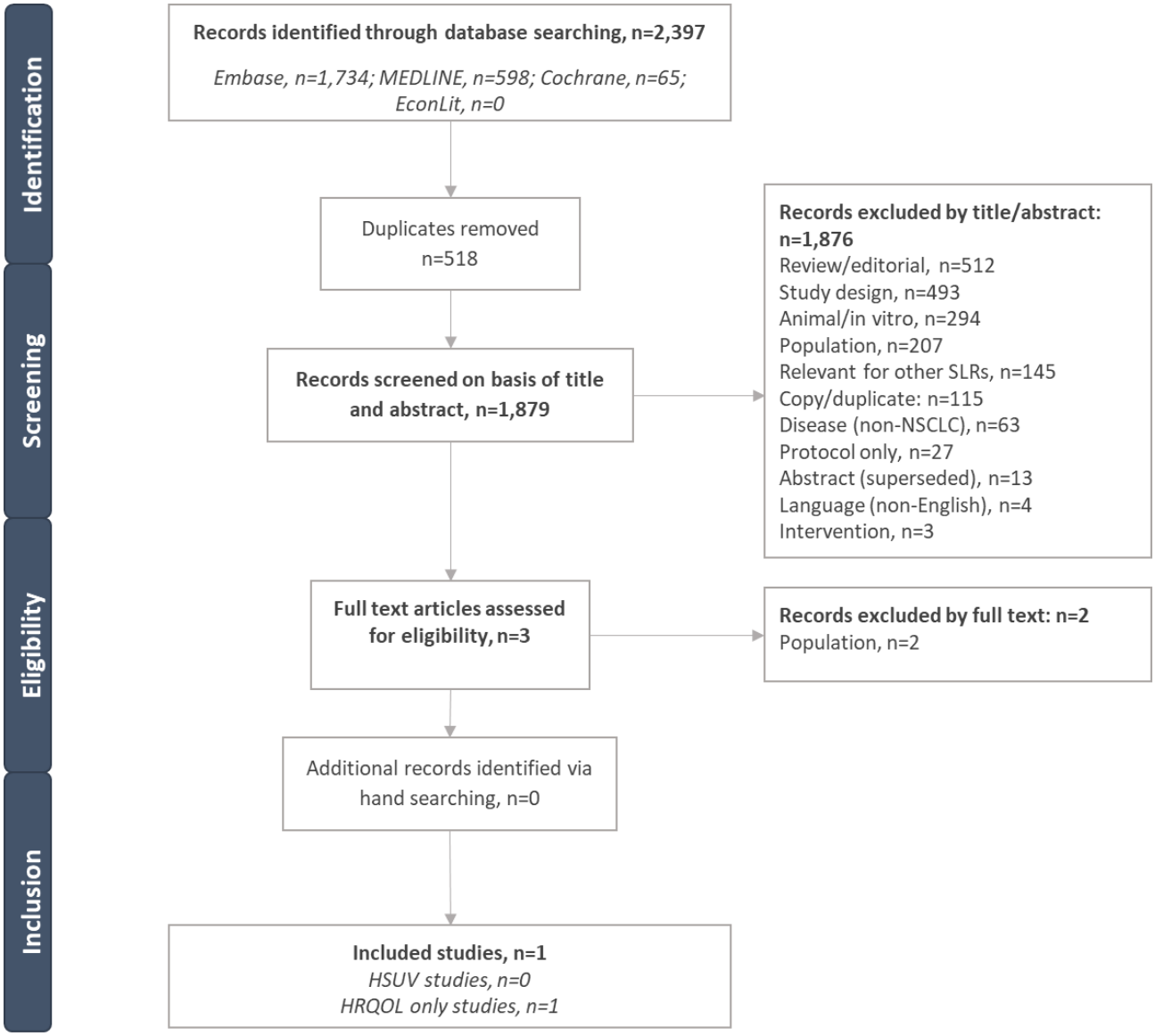


Figure 52: PRISMA flow diagram for the HSUV SLR

Abbreviations: HRQOL, health-related quality of life; HSUV, health state utility value; NSCLC, non-small cell lung cancer; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review.

Table 123: List of studies excluded on full text review (N=2)

	Reference	Rationale for exclusion
1	Novello, S. et al. Administration of sunitinib to patients with non-small cell lung cancer and irradiated brain metastases: A phase II trial. Journal of Clinical oncology 2009; 1):8077.	Population; NSCLC but early/non-RET+ etc.
2	Page, R. et al. Health-related quality of life (HRQOL) with sunitinib (SU) as maintenance therapy following carboplatin (C) and paclitaxel (P) treatment for locally advanced or metastatic non-small cell lung cancer (NSCLC). European Journal of Cancer 2009; 7(2-3):548.	Population; NSCLC but early/non-RET+ etc.

20.1.3 Quality assessment and generalizability of estimates

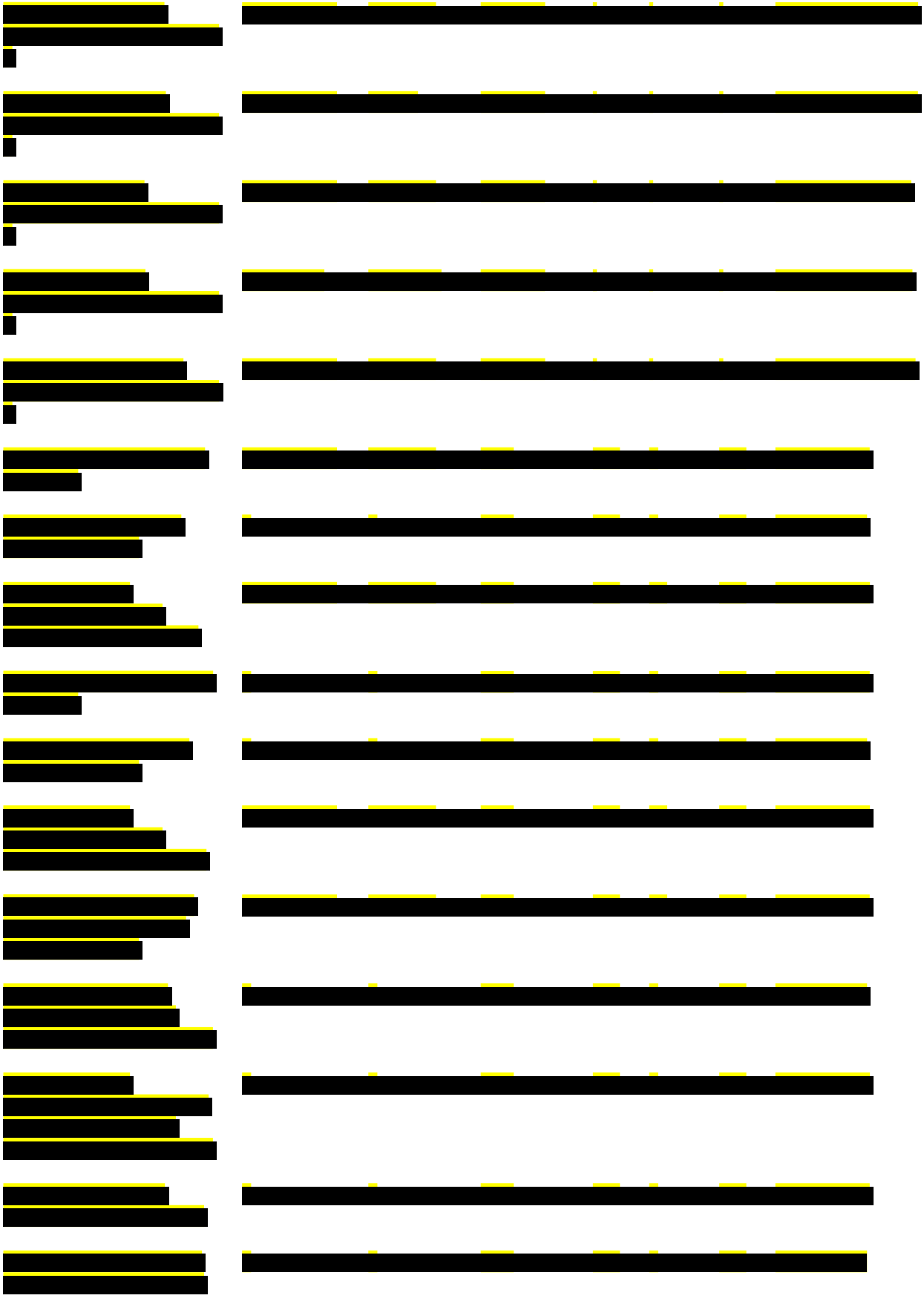
During data extraction, the relevance of any identified utilities and the quality of the studies generating them was assessed and recorded, and the quality of any mapping algorithms examined. This process enables justification of the use/non-use of different utility values or mapping algorithms in an economic model.

21. Appendix I – Mapping of HRQoL data

Mapping of HRQoL data was not carried out for this assessment.

22. Appendix J – Probabilistic sensitivity analyses

[redacted]



[redacted]

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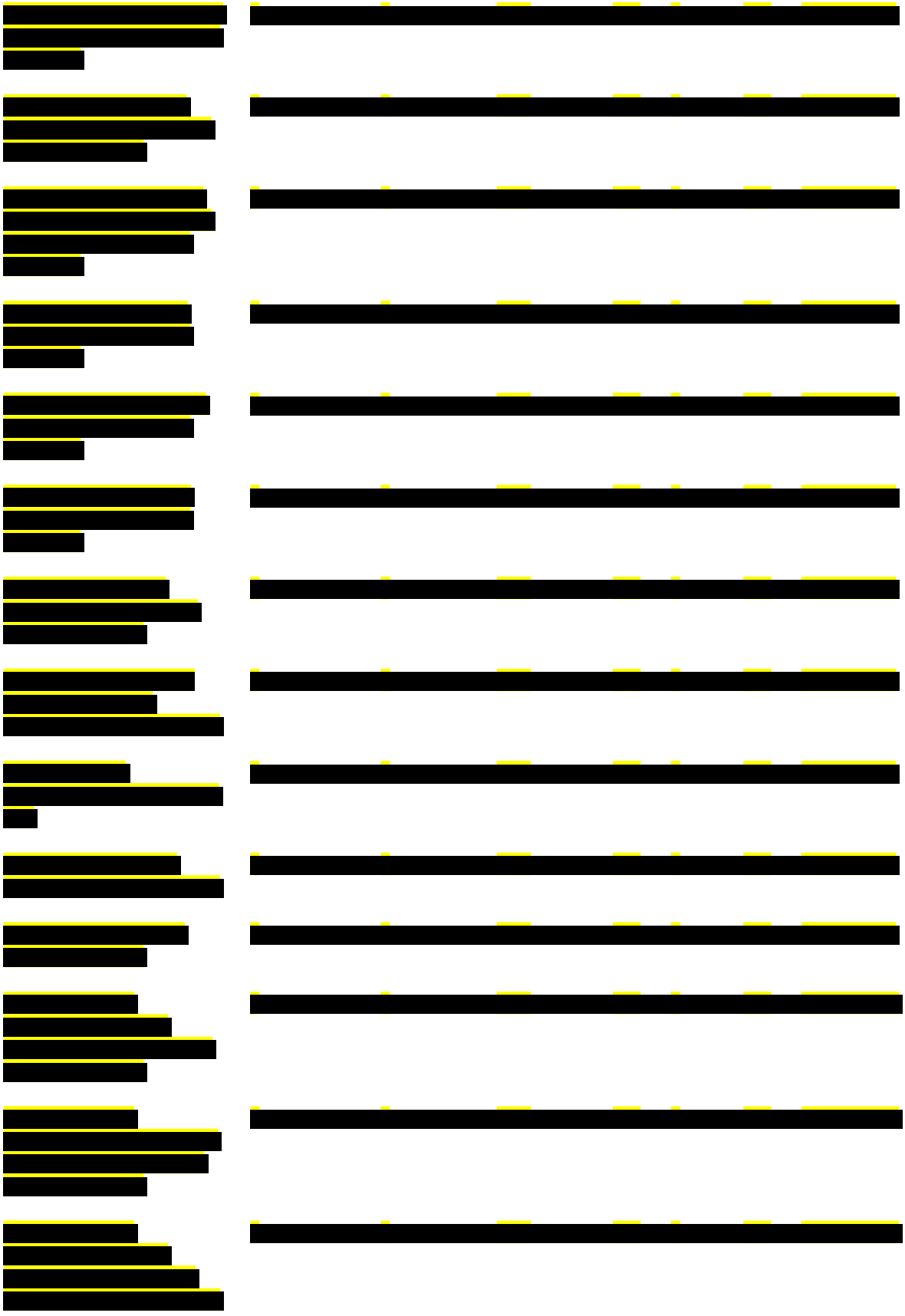
[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

23. Appendix K – Overview of utility values derived from the health economic literature search

	Results [95% CI]	Instrument/ source	Tariff (value set) used	Comments
Progression-free				
TA500 Ceritinib for untreated ALK-positive non-small-cell lung cancer, January 2018 [76]	0.810 [-]	PFS: Ceritinib: ASCEND-4 trial Crizotinib: PROFILE-1014 trial	N/A	Patients with untreated ALK-positive advanced NSCLC
TA258 Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer, June 2012 [77]	0.6532 [0.6096, 0.6968]	Nafees et al. (2008) [49]	N/A	Patients with previously untreated EGFR mutation-positive locally advanced or metastatic NSCLC
TA192 Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer, July 2010 [78]	0.6532 [-]	Nafees et al. (2008) [49]	N/A	Patients with previously untreated EGFR-TK mutation-positive locally advanced or metastatic NSCLC
TA181 Pemetrexed for the first-line treatment of non-small-cell lung cancer, September 2009 [online] [79]	0.65 [-]	Nafees et al. (2008) [49]	N/A	Patients with chemotherapy-naïve locally advanced or metastatic NSCLC who are unsuitable for surgery
Progressed				
TA500 Ceritinib for untreated ALK-positive non-small-cell lung cancer, January 2018 [76]	0.641 [-]	Chouaid et al. (2013) [52]	N/A	Patients with untreated ALK-positive advanced NSCLC
TA258 Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer, June 2012 [77]	0.4734 [0.3873, 0.5595]	Nafees et al. (2008) [49]	N/A	Patients with previously untreated EGFR mutation-positive locally advanced or metastatic NSCLC

TA192 Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer, July 2010 [online] [78]	0.4734 [-]	Nafees et al. (2008) [49]	N/A	Patients with previously untreated EGFR-TK mutation-positive locally advanced or metastatic NSCLC
TA181 Pemetrexed for the first-line treatment of non-small-cell lung cancer, September 2009 [online] [79]	0.47 [-]	Nafees et al. (2008) [49]	N/A	Patients with chemotherapy-naïve locally advanced or metastatic NSCLC who are unsuitable for surgery
Anaemia				
TA192 Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer, July 2010 [online] [78]	-0.0735 [-]	Eli Lilly (2009) [80]	N/A	Patients with previously untreated EGFR-TK mutation-positive locally advanced or metastatic NSCLC
TA181 Pemetrexed for the first-line treatment of non-small-cell lung cancer, September 2009 [online] [79]	-0.073 [-]	Nafees et al. (2008) [49]	N/A	Patients with chemotherapy-naïve locally advanced or metastatic NSCLC who are unsuitable for surgery
Asthenia				
TA192 Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer, July 2010 [online] [78]	-0.0735 [-]	Nafees et al. (2008) [49]	N/A	Patients with previously untreated EGFR-TK mutation-positive locally advanced or metastatic NSCLC Assumed to be that of fatigue
TA181 Pemetrexed for the first-line treatment of non-small-cell lung cancer, September 2009 [online] [79]	-0.073 [-]	Nafees et al. (2008) [49]	N/A	Patients with chemotherapy-naïve locally advanced or metastatic NSCLC who are unsuitable for surgery Assumed to be that of fatigue
Diarrhoea				
TA258 Erlotinib for the first-line treatment of locally advanced or metastatic EGFR-TK mutation-positive non-small-cell lung cancer, June 2012 [77]	-0.0468 [-0.0772, -0.0164]	Nafees et al. (2008) [49]	N/A	Patients with previously untreated EGFR mutation-positive locally advanced or metastatic NSCLC
TA192 Gefitinib for the first-line treatment of locally advanced or	-0.0468	Nafees et al. (2008) [49]	N/A	Patients with previously untreated EGFR-TK mutation-

metastatic non-small-cell lung cancer, July 2010 [online] [78]	[-]			positive locally advanced or metastatic NSCLC
TA181 Pemetrexed for the first-line treatment of non-small-cell lung cancer, September 2009 [online] [79]	-0.047 [-]	Nafees et al. (2008) [49]	N/A	Patients with chemotherapy-naïve locally advanced or metastatic NSCLC who are unsuitable for surgery
Dyspnoea				
TA403 Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer, August 2016 [online] [81]	-0.07346 [-0.1097, -0.03722]	Nafees et al. (2008) [49]	N/A	Patients with locally advanced or metastatic NSCLC that has progressed after platinum-based chemotherapy
Fatigue				
TA192 Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer, July 2010 [online] [78]	-0.0735 [-]	Nafees et al. (2008) [49]	N/A	Patients with previously untreated EGFR-TK mutation-positive locally advanced or metastatic NSCLC
TA181 Pemetrexed for the first-line treatment of non-small-cell lung cancer, September 2009 [online] [79]	-0.073 [-]	Nafees et al. (2008) [49]	N/A	Patients with chemotherapy-naïve locally advanced or metastatic NSCLC who are unsuitable for surgery
Hypertension				
TA403 Ramucirumab for previously treated locally advanced or metastatic non-small-cell lung cancer, August 2016 [online] [81]	0.07346 [-0.1097, -0.0722]	Nafees et al. (2008) [49]	N/A	Patients with locally advanced or metastatic NSCLC that has progressed after platinum-based chemotherapy
Hyponatraemia				
TA428 Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy, January 2017 [online] [82]	-0.085 [-]	KEYNOTE-010 trial	N/A	Patients with advanced PD-L1 positive NSCLC whose disease has progressed after platinum-based doublet chemotherapy
Lymphopenia				

TA484 Nivolumab for previously treated non-squamous non-small-cell lung cancer, November 2017 [online] [83]	-0.05 [-]	CheckMate 057 trial	N/A	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy
Nausea				
TA192 Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer, July 2010 [online] [78]	-0.0480 [-]	Nafees et al. (2008) [49]	N/A	Patients with previously untreated EGFR-TK mutation-positive locally advanced or metastatic NSCLC
TA181 Pemetrexed for the first-line treatment of non-small-cell lung cancer, September 2009 [79]	-0.0480 [-]	Nafees et al. (2008) [49]	N/A	Patients with chemotherapy-naïve locally advanced or metastatic NSCLC who are unsuitable for surgery
Neutropenia				
TA192 Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer, July 2010 [online] [78]	-0.0897 [-]	Nafees et al. (2008) [49]	N/A	Patients with previously untreated EGFR-TK mutation-positive locally advanced or metastatic NSCLC
TA181 Pemetrexed for the first-line treatment of non-small-cell lung cancer, September 2009 [online] [79]	-0.089 [-]	Nafees et al. (2008) [49]	N/A	Patients with chemotherapy-naïve locally advanced or metastatic NSCLC who are unsuitable for surgery
Pneumonia				
TA484 Nivolumab for previously treated non-squamous non-small-cell lung cancer, November 2017 [online] [83]	-0.008 [-]	Marti et al. (2013)	N/A	Adult patients with locally advanced or metastatic NSCLC after prior chemotherapy
Pneumonitis				
TA428 Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy, January 2017 [online] [82]	-0.085 [-]	KEYNOTE-010 trial	N/A	Patients with advanced PD-L1 positive NSCLC whose disease has progressed after platinum-based doublet chemotherapy
Vomiting				

TA192 Gefitinib for the first-line treatment of locally advanced or metastatic non-small-cell lung cancer, July 2010 [online] [78]	-0.0480 [-]	Nafees et al. (2008) [49]	N/A	Patients with previously untreated EGFR-TK mutation-positive locally advanced or metastatic NSCLC
TA181 Pemetrexed for the first-line treatment of non-small-cell lung cancer, September 2009 [online] [79]	-0.048 [-]	Nafees et al. (2008) [49]	N/A	Patients with chemotherapy-naïve locally advanced or metastatic NSCLC who are unsuitable for surgery

24. Appendix L – Clinical question 3

24.1 Introduction to clinical question 3

In addition to the application for pralsetinib for RET fusion-positive NSCLC patients in first-line, Roche have by request from the scientific committe, also included clinical question 3 in the application. Clinical question 3 covers: Efficacy and safety of pralsetinib compared to selpercatinib for patients with RET fusion-positive NSCLC, who require systemic therapy following prior treatment with platinum-based chemotherapy.

The patient population, testing and prognosis for RET fusion-positive NSCLC is described in section 5.1.

As mentioned in section 5.2.1 selpercatinib is recommended by the Medicines Council for RET fusion-positive NSCLC, if the patient has experienced disease progression after previous treatment with immunotherapy and platinum-based chemotherapy. The relevant comparator in second-line treatment (first-line RET fusion inhibitor) in Denmark is therefore selpercatinib.

Both pralsetinib and selpercatinib are only approved as first-line RET-fusion TKIs [84] [13].

Comparator
Selpercatinib is a RET fusion TKI. Selpercatinib is packaged as either 40 mg or 80 mg hard capsules and the recommended dose is based on the patient's body weight (less than 50kg: 120 mg twice daily or 50 kg or greater: 160 mg twice daily). Treatment should be continued until disease progression or unacceptable toxicity [13].

24.2 Literature search and identification of efficacy and safety studies

This literature search have been performed in accordance with the method previously described in section 6.1.

Table 124: Inclusion and exclusion criteria for the search in RET fusion-positive NSCLC

	Inclusion criteria	Exclusion criteria

Population	Adult patients with RET fusion-positive advanced, non-small cell lung cancer (NSCLC)	Populations irrelevant to scope
Intervention	Pralsetinib (400 mg once daily)	Intervention irrelevant to scope
Comparators	● Selpercatinib	Comparator irrelevant to scope
Outcomes	At least one effect measure relevant for scope: ● Overall survival (OS) ● Progression free survival (PFS) ● Overall Response Rate (ORR) ● Safety ● Quality of life	Outcome(s) out of PICO scope, i.e. studies that do not report at least one of the relevant effect measures.
Design	Phase II, III or IV RCTs Retrospective, observational studies Full text only	Case Reports, Comments, Editorials, Guidelines, Letters, News, Review articles Conference abstracts In vitro studies
Language	English, Scandinavian	Other language
Publication data (date limits)	No date limits	Not applicable
Human/animal	Human only	Veterinary (not human)

Search strategy for RET fusion-positive NSCLC (2L)

No direct evidence comparing pralsetinib with selpercatinib is available. In order to identify relevant studies for the comparator – selpercatinib – a systematic literature review was conducted with the aim to perform an indirect comparison.

The Medicines Council methods guide for assessing new pharmaceuticals version 1.2 has provided guidance for the literature search. Electronic searches were carried out in PubMed and in CENTRAL (via Cochrane Library) on September 14, 2022. The searches were based on the defined PICOs described in Table 124**.** In addition, the searches contain terms descriptive of the area as described in the search strings.

The result of the selection process appear from the PRISMA flow charts (see section 25.3).

Hand-searched literature has been included too, in total one reference:

- Selpercatinib in Patients With RET Fusion–Positive Non–Small-Cell Lung Cancer: Updated Safety and Efficacy From the Registrational LIBRETTO-001 Phase I/II Trial; Drilon et al; J Clin Oncol; 2022

This reference has been added in the PRISMA flow diagram (see section 24.3).

Table 125: Search strategy, PubMed - September 14, 2022

#	Search term	Comment
1	nsclc[tiab]	Search terms for population
2	(non-small-cell-lung[tiab] OR nonsmall-cell-lung[tiab]) AND (cancer[tiab] OR cancers[tiab] OR carcinoma[tiab] OR adenocarcinoma[tiab])	
3	Carcinoma, Non-Small-Cell Lung[mh] AND drug therapy[sh]	
4	(nonsquamous[tiab] OR non-squamous[tiab]) AND lung[tiab] AND (cancer[tiab] OR carcinoma[tiab])	
5	lung[tiab] AND adenocarcinoma[tiab]	
6	Adenocarcinoma of Lung[mh] AND drug therapy[sh]	
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	
8	Proto-Oncogene Proteins c-ret[mh]	Search terms for RET changes
9	(RET[tiab] OR "rearranged during transfection"[tiab]) AND (alteration*[tiab] OR altered[tiab] OR aberration*[tiab] OR aberrant[tiab] OR rearrange*[tiab] OR re-arrange*[tiab] OR fusion*[tiab] OR fused[tiab] OR mutant*[tiab] OR mutat*[tiab])	
10	#8 OR #9	
11	selpercatinib[nm] OR selpercatinib[tiab] OR Retevmo*[tiab] OR Retsevmo*[tiab] OR LOXO-292*[tiab] OR LOXO292*[tiab]	Search terms for interventions
12	#7 AND #10 AND #11	Combination of population, RET, and drugs
13	Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR News[pt] OR case report[ti]	Publication types for exclusion
14	#12 NOT #13	Complete search

Search Builder PubMed:

Search	Actions	Details	Query	Results	Time
#14	•••	›	Search: **#12 NOT #13**	56	06:52:58
#13	•••	›	Search: **Case Reports[pt] OR Comment[pt] OR Editorial[pt] OR Letter[pt] OR News[pt] OR case report[ti]**	4,397,128	06:52:46
#12	•••	›	Search: **#7 AND #10 AND #11**	70	06:52:34
#11	•••	›	Search: **selpercatinib[nm] OR selpercatinib[tiab] OR Retevmo*[tiab] OR Retsevmo*[tiab] OR LOXO-292*[tiab] OR LOXO292*[tiab]**	152	06:52:22
#10	•••	›	Search: **#8 OR #9**	6,891	06:52:08
#9	•••	›	Search: **(RET[tiab] OR "rearranged during transfection"[tiab]) AND (alteration*[tiab] OR altered[tiab] OR aberration*[tiab] OR aberrant[tiab] OR rearrange*[tiab] OR re-arrange*[tiab] OR fusion*[tiab] OR fused[tiab] OR mutant*[tiab] OR mutat*[tiab])**	5,539	06:51:53
#8	•••	›	Search: **Proto-Oncogene Proteins c-ret[mh]**	3,876	06:51:39
#7	•••	›	Search: **#1 OR #2 OR #3 OR #4 OR #5 OR #6**	117,248	06:51:26
#6	•••	›	Search: **Adenocarcinoma of Lung[mh] AND drug therapy[sh]**	2,800	06:51:12
#5	•••	›	Search: **lung[tiab] AND adenocarcinoma[tiab]**	39,857	06:50:57
#4	•••	›	Search: **(nonsquamous[tiab] OR non-squamous[tiab]) AND lung[tiab] AND (cancer[tiab] OR carcinoma[tiab])**	2,013	06:50:45
#3	•••	›	Search: **Carcinoma, Non-Small-Cell Lung[mh] AND drug therapy[sh]**	26,746	06:50:30
#2	•••	›	Search: **(non-small-cell-lung[tiab] OR nonsmall-cell-lung[tiab]) AND (cancer[tiab] OR cancers[tiab] OR carcinoma[tiab] OR adenocarcinoma[tiab])**	80,625	06:49:01
#1	•••	›	Search: **nsclc[tiab]**	55,823	06:48:46

Showing 1 to 14 of 14 entries

Table 126: Search strategy, Central via Cochrane Library - September 14, 2022

#	Search term	Comment
1	nsclc:ti,ab	Search terms for population
2	((non-small-cell-lung or nonsmall-cell-lung) and (cancer or carcinoma or adenocarcinoma)):ti,ab	
3	[mh "Carcinoma, Non-Small-Cell Lung"] or "non small cell lung cancer":ti,ab,kw	
4	[mh "Adenocarcinoma of Lung"] or (lung next adenocarcinoma):ti,ab,kw	
5	#1 or #2 or #3 or #4	

6	(selpercatinib or Retevmo* or Retsevmo* or LOXO-292* or LOXO292*):ti,ab,kw	Search for interventions
7	#5 or #6	
8	[mh "Proto-Oncogene Proteins c-ret"]	Search terms for RET changes
9	protein next Ret:kw	
10	((RET OR "rearranged during transfection") near/5 (alteration* or altered or aberration* or aberrant or rearrange* or re-arrange* or fusion* or fused or mutant* or mutat*)):ti,ab	
11	#8 or #9 or #10	
12	NCT*:au	Publication types for exclusion
13	(clinicaltrials.gov or trialsearch):so	
14	(abstract or conference or meeting or proceeding*):so	
15	#12 or #13 or #14	
16	(#5 and #7 and #11) not #15	Combination of population, drugs and RET

Search Builder Central via Cochrane Library:

#1	nsclc:ti,ab	Limits	10500
#2	((non-small-cell-lung or nonsmall-cell-lung) and (cancer or carcinoma or adenocarcinoma)):ti,ab	Limits	12538
#3	[mh "Carcinoma, Non-Small-Cell Lung"] or "non small cell lung cancer":ti,ab,kw	Limits	14371
#4	[mh "Adenocarcinoma of Lung"] or (lung next adenocarcinoma):ti,ab,kw	Limits	714
#5	#1 or #2 or #3 or #4	Limits	15660
#6	(selpercatinib or Retevmo* or Retsevmo* or LOXO-292* or LOXO292*):ti,ab,kw	Limits	21
#7	#5 or #6	Limits	15670
#8	[mh "Proto-Oncogene Proteins c-ret"]	Limits	11
#9	protein next Ret:kw	Limits	11
#10	((RET OR "rearranged during transfection") near/5 (alteration* or altered or aberration* or aberrant or rearrange* or re-arrange* or fusion* or fused or mutant* or mutat*)):ti,ab	Limits	104
#11	#8 or #9 or #10	Limits	113
#12	NCT*:au	Limits	231950
#13	(clinicaltrials.gov or trialsearch):so	Limits	430113
#14	(abstract or conference or meeting or proceeding*):so	Limits	46829
#15	#12 or #13 or #14	Limits	477325
#16	(#5 and #7 and #11) not #15	Limits	26

24.3 Systematic selection of studies

PRISMA flow diagrams for the literature searches in PubMed and Cochrane respectively are presented below.

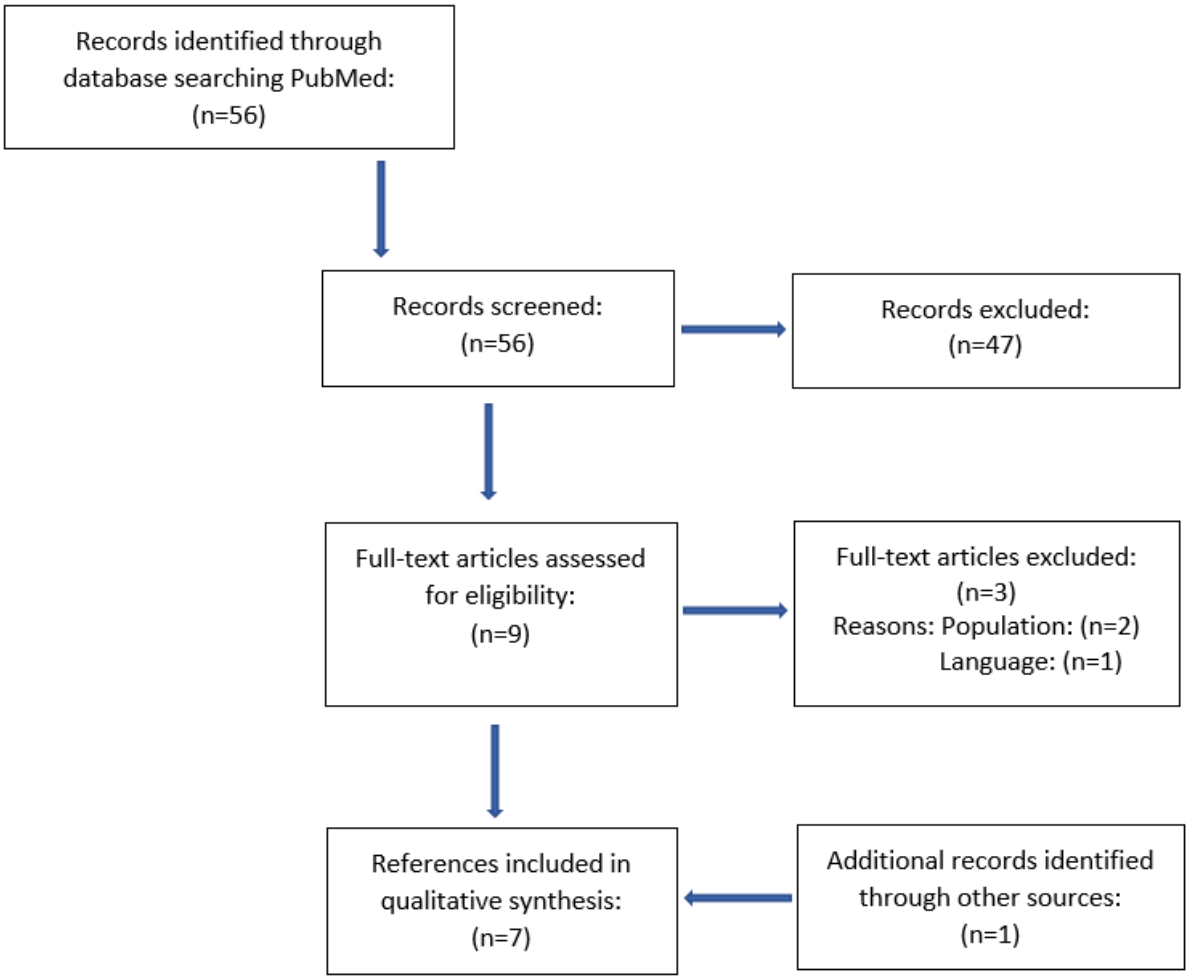


Figure 53: PRISMA flow diagram, PubMed search - RET fusion-positive NSCLC

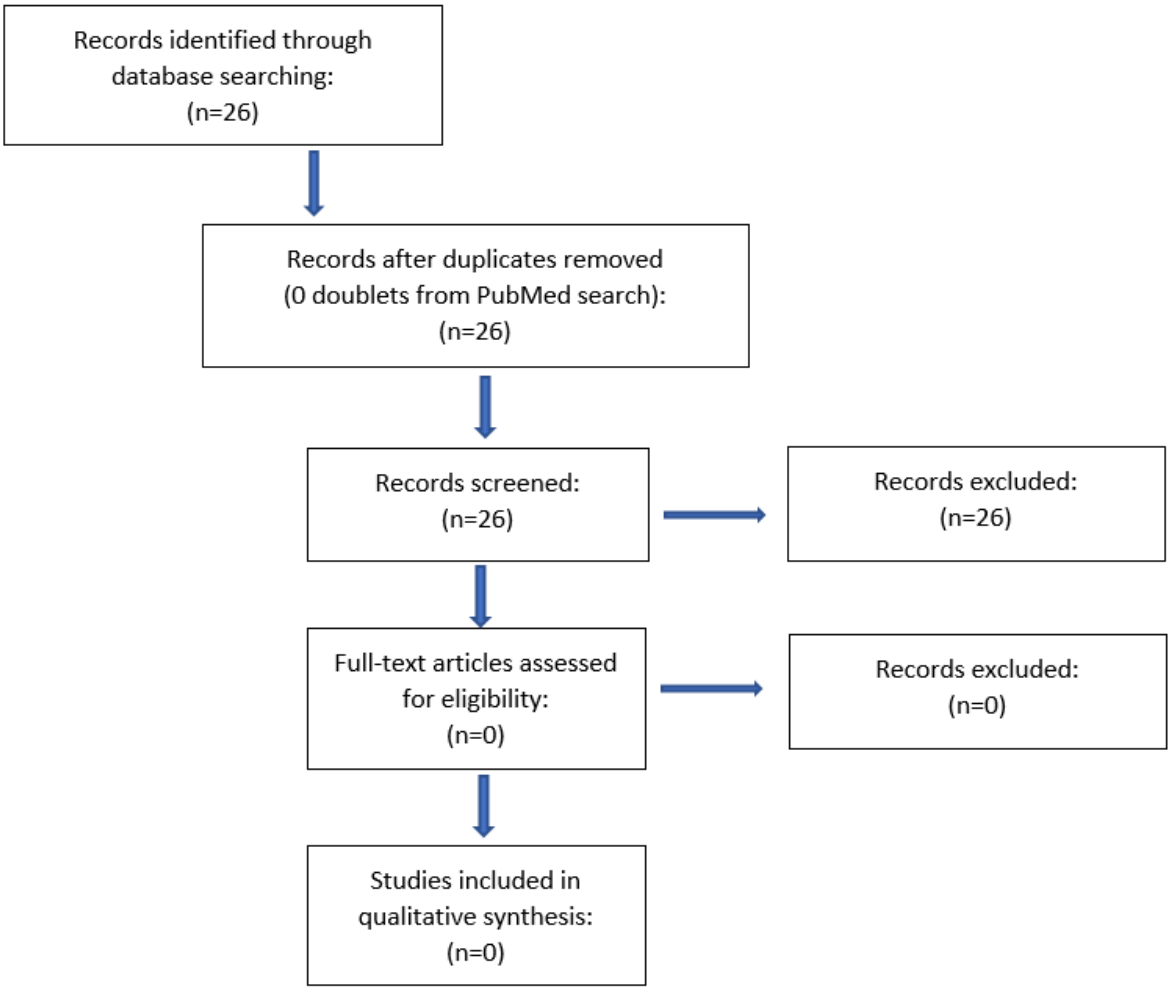


Figure 54: PRISMA flow diagram, Cochrane search - RET fusion-positive NSCLC

A total of 7 references from 2 studies were found eligible for inclusion. Six were indentifiend in the Pubmed-search and one was hand searched after the database searches had been performed. Two references were found relevant for clinical question 3. These include the clinical study LIBRETTO-001 and the retrospective study SIREN which both evaluates the efficacy and safety of selpercatinib. Five references based on the LIBRETTO-001 study have been excluded due to older CCODs as compared to the hand-searched LIBRETTO-001 reference, which is included in the following.

24.4 Efficacy and safety of pralsetinib compared to selpercatinib for patients with RET fusion-positive NSCLC, who require systemic therapy following prior treatment with platinum-based chemotherapy

24.4.1 Relevant studies

Study characteristics of ARROW is presented in section 7.1.1. In addition to the previously described populations in that section, we will also present a treatment-naive population from the ARROW study.

In the following section, we provide a brief description of LIBRETTO-001 [73] and SIREN [74] which evaluates the efficacy and safety of selpercatinib, and address any relevant differences between ARROW and LIBRETTO-001 and SIREN in terms of study and patient characteristics.

24.4.1.1 LIBRETTO-011

LIBRETTO-001 is an open-label, multi-center phase 1/2 study evaluating the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of selpercatinib in participants with advanced solid tumors, including RET fusion-positive solid tumors, MTC and other tumors with RET activation. The study consist of a dose escalation part (phase 1, completed) and an expansion part in patients treated with the recommended dose of 160 mg of selpercatinib twice daily (phase 2, ongoing) [73].

The primary endpoint was an ORR (a complete or partial response) as evaluated by an independent review committee according to RECIST 1.1. Secondary endpoints were among others ORR (by investigator), DOR, PFS, OS, and safety [73].

Efficacy and safety data for RET fusion-positive NSCLC patients are derived from the CCOD June 15, 2021. The total population includes 356 patients with RET fusion-positive advanced NSCLC who had received selpercatinib by or before December 15, 2020 to allow ≥6 months of follow-up. Of these efficacy-evaluable patients were either treatment naïve (n=69) or previously treated with platinum-based chemotherapy (n=247). The safety assessment was based on the overall safety population including all patients who had received at least one dose of selpercatinib as of June 15, 2021 (n=796) and on the NSCLC safety population including all patients with RET fusion-positive NSCLC who had received at least one dose of selpercatinib as of June 15, 2021 (n=356) [73].

For detailed study characteristics please refer to Table 127 below.

Table 127: Main characteristics of LIBRETTO-001

Trial name: LIBRETTO-001	NCT number: 03157128
Objective	To evaluate the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of selpercatinib (also known as LOXO-292) administered orally to participants with advanced solid tumors, including RET-fusion positive solid tumors, MTC and other tumors with RET activation.
Publications – title, author, journal, year	Selpercatinib in Patients With RET Fusion–Positive Non–Small-Cell Lung Cancer: Updated Safety and Efficacy From the Registrational LIBRETTO-001 Phase I/II Trial; Drilon A, Subbiah V, Gautschi V, Tomasini P, de Braud P, Solomon BJ, Tan DSW, Alonso G, Wolf J, Park K, Goto K, Soldatenkova V, Szymczak S, Barker SS, Puri T, Lin AB, Loong H, Besse B; J Clin Oncol; 2022 Patient-Reported Outcomes with Selpercatinib Among Patients with RET Fusion-Positive Non-Small Cell Lung Cancer in the Phase I/II LIBRETTO-001 Trial; Minchom A, Tan AC, Massarelli E, Subbiah V, Boni V, Robinson B, Wirth LJ, Hess LM, Jen MH, Kherani J, Olek E, McCoach CE; Oncologist; 2022 Efficacy of Selpercatinib in RET Fusion-Positive Non-Small-Cell Lung Cancer; Drilon A, Oxnard GR, Tan DSW, Loong HHF, Johnson M, Gainor J, et al; New England Journal of Medicine; 2020 Efficacy and safety with selpercatinib by last prior systemic therapy received in patients (Pts) with RET fusion + non-small cell lung cancer (NSCLC); Gautschi O, Drilon A, Tan DSW, Oxnard GR, McCoach C, Goto K, et al; Annals of Oncology; 2020 Hypersensitivity reactions (HR) to selpercatinib in RET fusion+ non-small cell lung cancer (NSCLC) patients (pts) following immune checkpoint inhibition (CPI). Annals of Oncology; McCoach C, Tan DSW, Besse B, Goto K, Zhu VW, Rolfo CD, et al; 2020

	Intracranial activity of selpercatinib (LOXO-292) in RET fusion-positive non-small cell lung cancer (NSCLC) patients on the LIBRETTO-001 trial.; Subbiah V, et al; Journal of clinical oncology; 2020 Overcoming MET-dependent resistance to selective RET inhibition in patients with RET fusion-positive lung cancer by combining selpercatinib with crizotinib; Rosen EY, Johnson ML, Clifford SE, Somwar R, Kherani JF, Son J, et al; Clin Cancer Res. 2020
Study type and design	Open-label, multi-center phase 1/2 study in participants with advanced solid tumors, including RET fusion-positive solid tumors, MTC, and other tumors with RET activation. The trial will be conducted in 2 parts: Phase 1 (dose escalation - completed) and phase 2 (dose expansion).
Sample size (n)	Efficacy population (previously treated with platinum-based chemptherapy), CCOD June 15, 2021, n=247 Overall safety population, CCOD June 15, 2021, n= 796 NSCLC safety population, CCOD June 15, 2021, n= 353

Main inclusion and exclusion criteria	Insert the inclusion and exclusion criteria related to NCT number from www.clinicaltrials.gov
	
	Inclusion criteria
	
	For Phase 1
	
	• Participants with a locally advanced or metastatic solid tumor that:
	• Has progressed on or is intolerant to standard therapy, or
	• For which no standard therapy exists, or in the opinion of the Investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or
	• Decline standard therapy
	• Prior multikinase inhibitors (MKIs) with anti-RET activity are allowed
	• A RET gene alteration is not required initially. Once adequate PK exposure is achieved, evidence of RET gene alteration in tumor and/or blood is required as identified through molecular assays, as performed for clinical evaluation
	• Measurable or non-measurable disease as determined by RECIST 1.1 or RANO as appropriate to tumor type
	• Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2 or Lansky Performance Score (LPS) greater than or equal to (≥) 40 percent (%) (age less than [<] 16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment
	• Adequate hematologic, hepatic and renal function
	• Life expectancy of at least 3 months
	
	For Phase 2: As for phase 1 with the following modifications:
	
	• For Cohort 1: Participants must have received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinical benefit from appropriate standard of care therapy
	• Cohorts 1 and 2:
	  o Enrollment will be restricted to participants with evidence of a RET gene alteration in tumor
	  o At least one measurable lesion as defined by RECIST 1.1 or RANO, as appropriate to tumor type and not previously irradiated
	• Cohorts 3 and 4: Enrollment closed
	• Cohort 5:

	○ Cohorts 1-4 without measurable disease ○ MCT not meeting the requirements for Cohorts 3 or 4 ○ MTC syndrome spectrum cancers (e.g., MTC, pheochromocytoma), cancers with neuroendocrine features/differentiation, or poorly differentiated thyroid cancers with other RET alteration/activation may be allowed with prior Sponsor approval ○ cfDNA positive for a RET gene alteration not known to be present in a tumor sample • Cohort 6: Participants who otherwise are eligible for Cohorts 1, 2 or 5 who discontinued another RET inhibitor may be eligible with prior Sponsor approval • Cohort 7: Participants with a histologically confirmed stage IB-IIIA NSCLC and a RET fusion; determined to be medically operable and tumor deemed resectable by a thoracic surgical oncologist, without prior systemic treatment for NSCLC ***Key Exclusion Criteria (Phase 1 and Phase 2)*** • Phase 2 Cohorts 1 and 2: an additional known oncogenic driver • Cohorts 3 and 4: Enrollment closed • Cohorts 1, 2 and 5: prior treatment with a selective RET inhibitor Notes: Participants otherwise eligible for Cohorts 1, 2, and 5 who discontinued another selective RET inhibitor may be eligible for Phase 2 Cohort 6 with prior Sponsor approval • Investigational agent or anticancer therapy (including chemotherapy, biologic therapy, immunotherapy, anticancer Chinese medicine or other anticancer herbal remedy) within 5 half-lives or 2 weeks (whichever is shorter) prior to planned start of LOXO-292 (selpercatinib). In addition, no concurrent investigational anti-cancer therapy is permitted Note: Potential exception for this exclusion criterion will require a valid scientific justification and approval from the Sponsor • Major surgery (excluding placement of vascular access) within 2 weeks prior to planned start of LOXO-292 (selpercatinib) • Radiotherapy with a limited field of radiation for palliation within 1 week of planned start of LOXO-292 (selpercatinib), with the exception of participants receiving radiation to more than 30% of the bone marrow or with a wide field of radiation, which must be completed at least 4 weeks prior to the first dose of study treatment • Any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy • Symptomatic primary CNS tumor, metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. Participants are eligible if neurological symptoms and CNS imaging are stable and steroid dose is stable for 14 days prior to the first dose of LOXO-292 (selpercatinib) and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery (SRS) • Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of LOXO-292 (selpercatinib) or prolongation of the QT interval corrected (QTcF) greater than (>) 470 milliseconds (msec) ○ Participants with implanted pacemakers may enter the study without meeting QTc criteria due to nonevaluable measurement if it is possible to monitor for QT changes. ○ Participants with bundle branch block may be considered for study entry if QTc is appropriate by a formula other than Fridericia's and if it is possible to monitor for QT changes. • Required treatment with certain strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers and certain prohibited concomitant medications Phase 2 Cohort 7 (neoadjuvant treatment): Participant must not have received prior systemic therapy for NSCLC.
Intervention	Selpercatinib

Comparator(s)	N/A
Follow-up time	Median follow-up time (DoR), prior platinum population: 21.2 mo. Median follow-up time (PFS), prior platinum population: 24.7 mo.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Primary endpoints in phase 2** • ORR assessed by Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) or Response Assessment in Neuro-Oncology (RANO), as appropriate per tumor type. Time Frame: Approximately every 8 weeks or 16 weeks based on the treatment cycle. **Secondary endpoints (phase 2):** • ORR by Investigator. Time Frame: Approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in participants who have not progressed. • Best Change in Tumor Size from Baseline (by IRC and Investigator). Time Frame: Approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in participants who have not progressed • DOR by IRC and Investigator. Time Frame: Approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in participants who have not progressed. • CNS ORR (by IRC). Time Frame: Approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in participants who have not progressed • Time to Any and Best Response (by IRC and Investigator). Time Frame: every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in participants who have not progressed • Time to Any and Best Response (by IRC and Investigator) • CBR (by IRC and Investigator). Time Frame: Approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in participants who have not progressed • PFS (by IRC and Investigator). Time Frame: Approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in participants who have not progressed • OS. Time Frame: Approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in participants who have not progressed • Percentage of Participants with any SAE[s]. Time Frame: From the time of informed consent, for approximately 24 months (or earlier if the participant discontinues from the study), and through Safety Follow-up (28 days after the last dose) • Pharmacokinetics (PK): Area Under the Plasma Concentration-Time Curve of LOXO-292 (Selpercatinib). Time Frame: Cycle 1 Day 1 through Cycle 5 Day 1 (Cycle = 28 days) • PK: Maximum Concentration (Cmax) of LOXO-292 (Selpercatinib). Time Frame: Cycle 1 Day 1 through Cycle 5 Day 1 (Cycle = 28 days)
Method of analysis	ORR were calculated based on the maximum likelihood estimator and accompanied by a 2-sided 95% exact binomial CI using the Clopper-Pearson method. The effectiveness of

	selpercatinib were demonstrated if the lower limit of the 2-sided 95% CI exceeds 20%. OS, DOR, and PFS is estimated with the Kaplan– Meier method. The Kaplan-Meier estimate with 95% CI calculated using Brookmeyer and Crowley method were provided for median. The event-free rate with 95% CI calculated using Greenwood's formula were provided for selected time points. Median follow-up for OS, DOR and PFS were estimated according to the Kaplan-Meier estimate of potential follow-up. Data on QoL was collected in LIBRETTO-001 but no analysis has yet been carried out for the June 15, 2021 data cut.
Subgroup analyses	Separate efficacy analyses were done for patients who had received previous platinum-based chemotherapy, for a subset of the first 105 patients enrolled who had received previous platinum-based chemotherapy and for patients who were treatment naive. Characteristics of the populations previously treated with platinum-based chemotherapy, which is included in this application, are presented in Table 129. The safety assessment was based on the overall safety population and on the NSCLC safety population.

24.4.1.2 SIREN

In addition to LIBRETTO-001 another publication was included: Selpercatinib in RET fusion-positive non-small-cell lung cancer (SIREN): a retrospective analysis of patients treated through an access program.

SIREN (selpercatinib in RET fusion-positive NSCLC) is a retrospective, non-interventional, international, multicenter study evaluating the efficacy and safety of selpercatinib in RET fusion-positive NSCLC patients within a Named Patient Protocol (NPP) under real-world conditions [74].

The primary endpoint was the systemic ORR according to RECIST v1.1 criteria. The secondary outcomes were among others PFS, intracranial ORR, DOR, and safety [74].

SIREN retrospectively documented patients with locally advanced or metastatic RET fusion-positive NSCLC who were treated with selpercatinib through an access program between August 2019 and January 2021. The CCOD was January 27, 2021. Efficacy was assessed in the overall population (n=50) as well as in two subgroups: Treatment naïve (n=13) and pretreated patients (n=37). Safety was assessed in all patients who had received at least one dose of selpercatinib as of the CCOD (n=50) [74].

For detailed study characteristics please refer to Table 128 below.

Table 128: Main characteristics of SIREN

Trial name: SIREN	NTC number: NA
Objective	To evaluate the efficacy and safety of selpercatinib in participants with RET fusion-positive advanced NSCLC under real-world conditions
Publications – title, author, journal, year	Selpercatinib in RET fusion-positive non-small-cell lung cancer (SIREN): a retrospective analysis of patients treated through an access program; Illini O, Hochmair MJ, Fabikan H, Weinlinger C, Tufman A, Swalduz A, Lamberg K, Hashemi SMS, Huemer F, Vikström A,

	Wermke M, Absenger G, Addeo A, Banerji S, Calles A, Clarke S, Maio MD, Durand A, Duruisseaux M, Itchins M, Kääränien OS, Krenn F, Laack E, de Langen AJ, Mohorcic K, Pall G, Passaro A, Prager G, Rittmeyer A, Rothenstein J, Schumacher M, Wöll E, Valipour A; Ther Adv Med Oncol; 2021
Study type and design	A retrospective, non-interventional, international, multicenter study.
Sample size (n)	Efficacy population, CCOD January 27, 2021, n=50 Pretreated efficacy population, CCOD January 27, 2021, n=37 Eafety population, CCOD January 27, 2021, n= 50
Main inclusion and exclusion criteria	*Inclusion criteria:* • Patients with NSCLC with RET activation, who: • Are not eligible for an ongoing selpercatinib clinical trial and are medically-suitable for treatment with selpercatinib • Have progressed or are intolerant to standard therapy, or no standard therapy option exists, or in the opinion of the investigator, are unlikely to derive significant clinical benefit from standard therapy • Have adequate organ function • Have received at least one follow-up assessment of treatment response (CT scan)
Intervention	Selpercatinib
Comparator(s)	N/A
Follow-up time	Median follow-up time (PFS), pretreated population: 9.2 months
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Primary endpoint:** • Systemic ORR defined according to RECIST v1.1 criteria **Secondary endpoints:** • TRAEs determined by the treating physician • Disease control rate (DCR) defined as the proportion of patients with complete response, partial response, or stable disease • Intracranial ORR • Duration of treatment defined as the time between selpercatinib start to last dose received • DOR assessed as the time between the initial response to therapy and subsequent disease progression or death due to any cause

	• PFS measured as the time from first dose of selpercatinib to first progression event according to RECIST v1.1 criteria.
Method of analysis	DOR, duration of treatment, and PFS were analyzed using the Kaplan– Meier methodology with median presented along with 95% CIs. CIs for ORR and DCR were calculated using the Clopper–Pearson method. Data on QoL was not collected in SIREN.
Subgroup analyses	-

24.4.1.3 Comparability between studies

Please see Table 129 for baseline charateristics for the included study populations in ARROW, LIBRETTO-001 and SIREN.

All three studies ARROW, LIBRETTO-001 and SIREN included RET fusionpositive NSCLC patients. In all studies patients were presented as the overall populations, not previously or previously treated. Age, gender, race and smoking status are comparable acorss the studies. The propotion of patients with ECOG PS 0 were larger in both LIBRETTO-001 (36.4%) and SIREN (38%) compared to ARROW (26.2 %) while the propotion of patients with ECOG PS 1 was larger in ARROW (69.5%) compared to both LIBRETTO-001 (60.7%) and SIREN (35%). Proportions of patients with ECOG PS 2 was comparable between ARROW (3.5%) and LIBRETTO-001 (2.8%). In SIREN ECOG PS was reported as > 2 with 27%.

It should be noted that 31.2% had CNS metastases at baseline in the population who had previously been treated with platinum-based chemotherapy in LIBRETTO-011 while 39 % had CNS metastases at baseline in the population who had received prior platinum-based chemotherapy in ARROW. In SIREN 13 of 37 pretreated patients had CNS metastases. In SIREN the population is a bit broader than the populations with prior platinum-based treatment.

Distribution of RET-fusion partners are also comparable between the studies.

Table 129: Baseline characteristics of patients in ARROW, LIBRETTO-001 and SIREN (clinical question 3)

	ARROW				LIBRETTO-001	SIREN
	Total efficacy population CCOD: Nov 6, 2020 [26]	Prior platinum treatment CCOD: Nov 6, 2020 [26]	Updated total efficacy population CCOD: Mar 4, 2022 [27]	Updated prior platinum treatment CCOD: Mar 4, 2022 [27]	Prior platinum treatment CCOD: Jun 15, 2022 [73]	Pretreated population CCOD: Jan 27, 2021 [74]
Intervention	Pralsetinib (n=233)	Pralsetinib (n=136)	Pralsetinib (n=281)	Pralsetinib (n=141)	Selpercatinib (n=247)	Selpercatinib (n=37)
Age						
Median (range) — yr	60.0 (26-87)	59.0 (26-85)	-	-	61.0 (23-81)	58 (38-80)

≥ 65 yr — no. (%)	88 (37.8)	46 (33.8)	-	-	-	17 (46)
< 65 yr – no. (%)	145 (62.2)	90 (66.2)	176 (62.6)	93 (66.0)	-	20 (54)
Gender – no. (%)						
Male	111 (47.6)	65 (47.8)	129 (45.9)	67 (47.5)	107 (43.3)	15 (41)
Female	122 (52.4)	71 (52.2)	-	-	140 (56.7)	22 (60)
Race – no. (%)						
White	121 (51.9)	55 (40.4)	130 (46.3)	57 (40.4)	108 (43.7)	-
Black	0	0	-	-	12 (4.9)	-
Asian	92 (39.5)	70 (51.5)	128 (45.6)	71 (50.4)	118 (47.8)	3 (8)
Other/Unknown/ Missing	20 (8.7)*	11 (8.1)*	2 (0.7)	2 (1.4)	9 (3.6)*	34 (92)
ECOG performance status — no. (%)						
0	78 (33.5)	37 (27.2)	83 (29.5)	37 (26.2)	90 (36.4)	14 (38)
1	149 (63.9)	94 (69.1)	191 (68.0)	98 (69.5)	150 (60.7)	13 (35)
2	6 (2.6)	5 (3.7)	6 (2.1)	5 (3.5)	7 (2.8)	
≥ 2	-	-	-	-	-	10 (27)
Smoking status — no. (%)						
Never	145 (62.2)	86 (63.2)	176 (62.6)	89 (63.1)	165 (66.8)	28 (76)
Former	78 (33.5)	47 (34.6)	-	-	78 (31.6)	9 (24)
Current	6 (2.6)	1 (<1)	-	-	4 (1.6)	0
Former/Current	-	-	100 (35.6)	50 (35.5)	-	-

Unknown/Missing	4 (1.7)	2 (1.5)	5 (1.8)	2 (1.4)	-	-
Histologic features — no. (%)						
Adenocarcinoma	224 (96.1)	131 (96.3)	-	-	221 (89.5)	33 (90)
Squamous	3 (1.3)	1 (<1)	-	-	1 (0.4)	-
NSCLC not otherwise specified	-	-	-	-	22 (8.9)	2 (5)
Undifferentiated	1 (<1.0)	1 (<1)	-	-	-	-
Other	5 (2.1)	3 (2.2)	-	-	-	2 (5)
Baseline CNS/brain metastases — no. (%)	87 (37.3)	54 (39.7)	97 (34.5)	55 (39.0)	77 (31.2)	N=13 (35*)
Previous treatment — no. (%)						
Chemotherapy	138 (59.2)	136 (100)	-	-	-	-
Platinum Chemotherapy	136 (58.4)	136 (100)	141 (50.2)	141 (100)	247 (100)	30 (81)
PD-(L)1 Inhibitors	69 (29.6)	55 (40.4)	73 (26.0)	57 (40.4)	144 (58.3)	25 (68)
Multi-kinase inhibitors	44 (18.9)	38 (27.9)	45 (16.0)	39 (27.7)	85 (34.4)	-
Tyrosine-kinase inhibitor	-	-	-	-	-	12 (32)
Prior Radiation Therapy	90 (38.6)	65 (47.8)	-	-	-	-
Prior Cancer Related Surgeries/ Procedures	116 (49.8)	70 (51.5)	-	-	-	-
Others	-	-	-	-	97 (39.3)	-
RET fusion – no. (%)						

KIF5B	164 (70.4)	98 (72.1)	197 (70.1)	98 (69.5)	153 (61.9)	23 (62)
CCDC6	41 (17.6)	24 (17.6)	50 (17.8)	27 (19.1)	53 (21.5)	8 (22)
NCOA4	1 (<1)	0	2 (<1)	1 (<1)	5 (2.0)	0
TRIM27	-	-	-	-	-	1 (3)
Others	27 (11.6)	14 (10.3)	32 (11.4)	15 (10.6)	38 (15.4)	-
Not determined	-	-	-	-	-	5 (14)

*Calculated based on what was reported in the publication.

24.4.2 Efficacy and safety – results per study

In the following section, we provide a summary of the key efficacy and safety findings for each included study.
Data on the following outcomes have been extracted if available:

- Overall survival
- Progression-free survival
- Overall response rate
    - Intracranial-ORR
- Discontinuation due to adverse events
- Grade ≥3 adverse events

OS, PFS, ORR and intracranial-ORR for pralsetinib is reported for the total efficacy population and for the population who had received prior platinum-based chemotherapy in ARROW (CCOD: November 6, 2020 and CCOD: March 4, 2022). OS, PFS, ORR and intracranial-ORR for selpercatinib is reported for the population who had previously been treated with platinum-based chemotherapy in LIBRETTO-001 (CCOD: June 15, 2021). Further, PFS, ORR and intracranial-ORR for selpercatinib is reported for the pretreated population in SIREN (CCOD: January 27, 2021).

Discontinuation due to AEs and grade ≥3 AEs for pralsetinib are reported for the total safety population and the NSCLC safety population (CCOD: November 6, 2020), please refer to Table 10 and Table 12. Furhermore, discontinuation due to TRAEs and grade ≥3 AEs are reported for pralsetinib in the updated NSCLC safety population (CCOD: March 4, 2022) (Table 10 and Table 12).Discontinuation due to AEs and grade ≥3 AEs for selpercatinib is reported for total safety population and the NSCLC population in LIBRETTO-011 (CCOD: June 15, 2021). For selpercatinib in SIREN, discontinuation due to TRAEs and grade ≥3 TRAEs are reported for the pretreated population (CCOD: January 27, 2021).

24.4.2.1 Overall survival

OS is evaluated in both ARROW and LIBRETTO-001 and defined as:

- ARROW: the time from randomisation to death of any cause

- LIBRETTO-001: number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause)

OS is not reported in SIREN. The analysis method used in ARROW were the same for all populations (see appendix D for description). In LIBRETTO-001, OS was estimated with the Kaplan–Meier method. The Kaplan-Meier estimate with 95% CI calculated using Brookmeyer and Crowley method were provided for the median. The event-free rate with 95% CI at 12 and 24 months were calculated using Greenwood's formula.

Median OS was 44.3 months in ARROW while not reached in LIBRETTO-001. Data is presented in Table 130.

Table 130: Overall survival in RET fusion-positive populations in second-line

Trial name	Intervention	Median follow-up	N	Overall survival			
				Median, mo. (95% CI)	12 mo rate, % (95% CI)	24 mo rate, % (95% CI)	HR (95% CI)
Clinical trials							
ARROW (Total efficacy population) [26]	Pralsetinib	17.1 mo.	233	NR	76.0 (69.9-82.0)	66.0 (57.9-74.1)	N/A
ARROW (Prior platinum treatment) [26]	Pralsetinib	20.1 mo.	136	NR	72.4 (64.3-80.5)	61.9 (51.9-71.9)	N/A
ARROW (Updated total efficacy population) [27]	Pralsetinib	26.8 mo.	281	44.3 (31.9-NR)	N/A	N/A	N/A
ARROW (Updated prior platinum treatment population) [27]	Pralsetinib	29.4 mo.	141	44.3 (26.9-44.3)	N/A	N/A	N/A
LIBRETTO-001 (Prior platinum treatment) [73]	Selpercatinib	26.4 mo.	247	NR	87.9 (83.0-91.4)	68.9 (62.2-74.7)	N/A
SIREN (Pretreated patients) [74]	Selpercatinib	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: CI – confidence interval; HR – hazard ratio; N/A – not applicable; NR – not reached; mo – months.

24.4.2.2 Progression-free survival

PFS is evaluated in both ARROW, LIBRETTO-001 and SIREN and defined as:

- ARROW: time from randomization to disease progression or death as assessed by BICR according to RECIST version 1.1
- LIBRETTO-001: number of months elapsed between the date of the first dose of LOXO-292and the earliest date of documented disease progression or death (whatever the cause)
- SIREN: the time from first dose of selpercatinib to first progression event

The analysis method used in ARROW were the same for all populations (see appendix D for description). In LIBRETTO-001, PFS is estimated with the Kaplan-Meier method. The Kaplan-Meier estimate with 95% CI calculated using Brookmeyer and Crowley method were provided for median. The event-free rate with 95% CI at 12 and 24 months were calculated using Greenwood's formula. In SIREN, PFS were analyzed using the Kaplan-Meier method with median presented along with 95% CI.

Data is presented in Table 131.

Table 131: Progression-free survival in RET fusion-positive populations in second-line

Trial name	Intervention	Median follow-up	N	Progression-free survival			
				Median, mo. (95% CI)	12 mo. rate, % (95% CI)	24 mo. rate, % (95% CI)	HR (95% CI)
Clinical trials							
ARROW (Total efficacy population) [26]	Pralsetinib	12.9 mo.	233	16.4 (11.0-24.1)	56.0 (48.9-63.1)	42.1 (33.2-51.0)	N/A
ARROW (Prior platinum treatment) [26]	Pralsetinib	18.4 mo.	136	16.5 (10.5-24.1)	56.7 (47.9-65.6)	41.0 (30.3-51.6)	N/A
ARROW (Updated total efficacy population) [27]	Pralsetinib	25.8 mo.	281	13.2 (11.4-16.8)	N/A	N/A	N/A
ARROW (Updated prior platinum treatment population) [27]	Pralsetinib	28.1 mo.	141	16.4 (11.4-22.3)	N/A	N/A	N/A
LIBRETTO-001 (Prior platinum treatment) [73]	Selpercatinib	24.7 mo.	247	24.9 (19.3-NE)	70.5 (64.1-76.0)	51.4 (44.3-58.1)	N/A
SIREN (Pretreated patients) [74]	Selpercatinib	9.2 mo.	37	12.2 (NR)	N/A	N/A	N/A

Abbreviations: CI – confidence interval; HR – hazard ratio; N/A - Not applicable; NR - not reached; mo. – months.

24.4.2.3 Overall response rate

ORR is evaluated in both ARROW, LIBRETTO-001, and SIREN and defind as:

- ARROW: proportion of patients who have a partial or complete response to treatment as assessed by BICR according to RECIST version 1.1
- LIBRETTO-001: proportion of patients who have a partial or complete response to treatment as assessed by an independent review committee (IRC) per RECIST version 1.1.
- SIREN: proportion of patients with complete or partial response to treatment per RECIST version 1.1.

The analysis method used in ARROW were the same for all populations (see appendix D for description). In LIBRETTO, ORR were calculated based on the maximum likelihood estimator and accompanied by a 2-sided 95% exact binomial CI using the Clopper-Pearson method. The effectiveness of selpercatinib were demonstrated if the lower limit of the 2-sided 95% CI exceeds 20%. In SIREN, CIs for ORR were calculated using the Clopper-Pearson method.

Data is presented in Table 132.

Table 132: Overall response rate in RET fusion-positive populations in second-line

Trial name	Intervention	Median follow-up	N	ORR		
				ORR, n (%) (95% CI)	CR, n (%)	PR, n (%)
Clinical trials						
ARROW (Total efficacy population) [26]	Pralsetinib	-	233	150 (64.4) (57.9-70.5)	11 (4.7)	139 (59.7)
ARROW (Prior platinum treatment) [26]	Pralsetinib	-	136	80 (58.8) (50.1-67.2)	7 (5.1)	73 (53.7)
ARROW (Updated total efficacy population) [27]	Pralsetinib	-	281	185 (65.8) (60.0-71.4)	18 (6.4)	167 (59.4)
ARROW (Updated prior platinum treatment population) [27]	Pralsetinib	-	141	84 (59.6) (51.0-67.7)	10 (7.1)	74 (52.5)
LIBRETTO-001 (Prior platinum treatment) [73]	Selpercatinib	-	247	151 (61) (55-67)	18 (7)	133 (54)
SIREN (Pretreated patients) [74]	Selpercatinib	-	37	25 (68) (50-82)	4 (11)	21 (58)

Abbreviations: CR – complete response; ORR – overall response rate; PR – partial response; mo. – months; CI – confidence interval.

Additionally intracranial-ORR is reported in both ARROW, LIBRETTO-001 and SIREN. Data is presented in Table 133.

Table 133: Intracranial overall response rate in RET fusion-positive populations in second-line

Trial name	Intervention	N	Baseline brain metastases, N (%)	Measureable CNS metastasis at baseline, N	Intracranial-ORR		
					ORR, n (%) (95% CI)	CR, n (%)	PR, n (%)

ARROW (Total efficacy population) [26]	Pralsetinib	233	87 (37.3)	10	7 (70) (34.8-93)	3 (30.0)	4 (40.0)
ARROW (Prior platinum treatment) [26]	Pralsetinib	136	54 (39.7)	9	6 (66.7) (29.9-92.5)	2 (22.2)	4 (44.4)
ARROW (Updated total efficacy population)§ [27]	Pralsetinib	281	97 (34.5)	15	8 (53.3) (26.6-78.7)	2 (20.0)	5 (33.3)
LIBRETTO-001 (Prior platinum treatment)* [73]	Selpercatinib	247	77 (31.2)	26	22 (84.6) (65.1-95.6)	7 (26.9)	15 (57.7)
SIREN (Pretreated patients) [74]	Selpercatinib	37	13 (35)	7	7 (100)	0 (0)	7 (100)

Abbreviations: CR – complete response; ORR – overall response rate; PR – partial response; mo. – months; CI – confidence interval; § 14 out of 15 had prior platinum treatment and one was treatment naive; *from supplemental table 5.

24.4.2.4 Discontinuation due to adverse events

Discontinuation of treatment due to AEs for pralsetinib have been reported in section 7.1.2.4 in Table 10.

Discontinuation of treatment due to AEs for selpercatinib in LIBRETTO-001 (CCOD: June 15, 2021) and SIREN (CCOD: January 27, 2021) is described below in Table 134.

Table 134: Discontinuation due to AEs in the RET fusion-positive safety populations in second-line

Trial name	Intervention	Median exposure, months	N	Discontinuation due to AEs, n (%)
LIBRETTO-001 (Overall safety popualtion) [73]	Selpercatinib	36.1	796	64 (8)
LIBRETTO-001 (NSCLC safety popualtion) [73]	Selpercatinib	36.1	356	N/A
SIREN (Safety population) [74]	Selpercatinib	16.9	50	0 (0)*

Abbreviations: AEs - adverse events; *reported as TRAEs.

24.4.2.5 Grade ≥3 adverse events

Grade ≥3 AEs for pralsetinib have already been reported in section 7.1.2.5 in Table 12.

Grade ≥3 AEs for selpercatinib in LIBRETTO-001 (CCOD: June 15, 2021) and SIREN (CCOD: January 27, 2021) is reported in Table 135 below.

Table 135: Grade ≥3 AEs in the RET fusion-positive safety populations

Trial name	Intervention	Median exposure, months	N	Grade ≥3 AEs, n (%)
LIBRETTO-001 (Overall safety population) [73]	Selpercatinib	36.1	796	572 (71.9)
LIBRETTO-001 (NSCLC safety population) [73]	Selpercatinib	36.1	356	263 (73.9)*
SIREN (Safety population) [74]	Selpercatinib	16.9	50	12 (24)**

Abbreviations: AEs - adverse events; * supplemental table 6; **reported as TRAEs.

24.4.3 Comparative analyses of efficacy and safety

24.4.3.1 Method of synthesis

Considering the recent recommendation of selpercatinib in 2L after platinum-based treatment from the Danish Medicines Council, the following analysis comparing pralsetinib and selpercatinib was performed:

- Narrative comparison of RET fusion-positive NSCLC patients in second-line

Below is an overview of the performed comparison and a description of the used methods.

Table 136: Overview of the performed comparison for clinical question 3

Population	Comparator	Analyses	Study, population	Outcome
RET fusion-positive NSCLC				
2L	Selpercatinib	Narrative comparison	RET fusion-positive NSCLC patients	OS, PFS, ORR

Abbreviations: NSCLC – non-small cell lung cancer; ORR - overall response rate; OS – overall survival; PFS – progression-free survival; OS – overall survival; RET – rearranged during transfection.

Narrative comparison

As described in the litteratur section 24.2 in appendix L, we have examined the available literature for studies with RET fusion-positive NSCLC patients treated with selpercatinib in second-line. From the SLR we identified 2 relevant studies of selpercatinib and median OS, median PFS, median ORR, intracranial-ORR and safety including discontinuation due to AEs, grade ≥3 adverse events and safety profiles was extracted [73], [74].

24.4.3.2 Results from the comparative analysis

In the following section, we provide a summary of the results from the comparative analysis. Data are presented for the following outcome:

- Overall survival
- Progression-free survival
- Overall response rate
    - Intracranial-ORR
- Safety
    - Discontinuation due to adverse events
    - Grade ≥3 adverse events
    - Safety profiles

As previously described, data on QoL for patients treated with pralsetinib in ARROW has not yet been analysed for the CCOD of November 6, 2020 nor the CCOD of March 4, 2022, and thus no comparative analysis have been conducted for this outcome.

24.4.3.2.1 Overall survival

Narrative comparison

The median OS was 44.3 months in both the overall population and the population previously treated with platinum-based chemotherapy for the CCOD of March 4, 2022 from ARROW [27]. The median OS was not reached in the LIBRETTO-001 study. For pralsetinib in ARROW, 12- and 24-months survival rates were reported from the CCOD of November 6, 2020. In the total efficacy population, the survival rates were 76.0% (69.9-82.0) at 12 months and 66.0% (57.9-74.1) at 24 months. In the population who had received prior platinum-based chemotherapy, OS at 12 and 24 months were 72.4% (64.3-80.5) and 61.9% (51.9-71.9), respectively [26]. For Selpercatinib in LIBRETTO-001, survival rates of 87.9% (83.0-91.4) and 68.9% (62.2-74.7) were observed for 12 months and 24 months, respectively [73].

At 12 months the reported OS rates are between 72.4-88.3% and at 24 months the OS rates reported are between 61.9-68.9%. This could indicate that the initial difference in OS survival at 1 year are levelled out after 2 years. However, as median OS is immature in LIBRETTO-001 it is currently difficult to deem one treatment better than the other.

Conclusion

Based on the data presented above:

- Pralsetinib showed a median OS of 44.3 months in both populations.
- Based on the immature median OS for selpercatinib and the reported OS rates at 12- and 24-months, it is not possible to conclude if there is a relevant difference between pralsetinib and selpercatinib.

24.4.3.2.2 Progression-free survival (PFS)

Narrative comparison

Median PFS was reported for both pralsetinib and selpercatinib.

For pralsetinib in ARROW, the median PFS was reported for both CCODs. At the CCOD of November 6, 2020, the median follow-up was 12.9 months and median PFS 16.4 months (11.0-24.1) in the total efficacy population, and medium follow-up was 18.4 months and median PFS 16.5 months (10.5-24.1) in the population previously treated with platinum-based chemotherapy [26]. At the CCOD of March 4, 2022, the total efficacy population had had 25.8 months of follow-up and a median PFS of 13.2 months (11.4-16.8). In the population previously treated with platinum-based chemotherapy, the median follow-up was 28.1 months and the median PFS was 16.4 months (11.4-22.3) [27].

For selpercatinib median PFS was reported in both LIBRETTO-001 and in SIREN. In LIBRETTO- 001, the median follow-up was 24.7 months and the median PFS was 24.9 (19.3-NE) months [73]. In SIREN, the median follow-up time was 9.2 months and the median PFS was 12.2 months. The confidence intervals were not reached [74].

It should be noted that there are 31.2% CNS metastases at baseline in the population who had received prior platinum-based chemotherapy in the LIBRETTO-011 study and 39.0% in the population previously treated with platinum-based chemotherapy in ARROW (CCOD: March 4, 2022). In addition, there are also a larger propotion of patients with ECOG PS 0 in LIBRETTO-001 (36.4%) compared to ARROW (26.2%) (CCOD: March 4, 2022) [73], [26]). Both of these difference could contribute to a poorer prognosis and the difference could contribute to the numerical difference between selpercatinib and pralsetinib.

In SIREN there are also a relative high number of ECOG PS 0 (38%), but an equal amount of brain metastases (35%) as the one seen in ARROW [74], [26].

Conclusion

Based on the data presented above:

- The median PFS reported for pralsetinib and selpercatinib are comparable with overlapping confidence intervals for the reported median PFS. The RWE median PFS for selpercatinib reported in SIREN was markedly lower than the one reported in LIBRETTO-001.
- There are differences in baseline characteristics with a higher number of baseline CNS metastases in ARROW and SIREN than in LIBRETTO-001. In addition there is a higher number of patients with EOCG PS 0 in LIBRETTO-001 and SIREN than in ARROW. Both of these differences should be taken into consideration when compairing the two studies.

24.4.3.2.3 Overall response rate and intracranial-ORR

Narrative comparison

Both ORR and intracranial-ORR was reported for pralsetinib in ARROW and selpercatinib in LIBRETTO-001 and SIREN.

For pralsetinib ORR was reported for both CCODs. At the CCOD of November 6, 2020, ORR was 64.4% (57.9-70.5) in the total efficacy population with 11 patients (4.7%) showing a CR and 139 patients (59.7%) experiencing a PR. In the population who had received prior platinum-based chemotherapy, ORR was 58.8% (50.1-67.2) with 7 patients (5.1%) and 73 patients (53.7%) experiencing a CR and PR, respectively [26]. At the CCOD of March 4, 2022, the updated total efficacy population had an ORR of 65.8% (60.0-71.4) with 18 patients (6.4%) experiencing a CR and 167 patients (59.4%) experiencing a PR. In the updated population previously treated with platinum-based chemotherapy, ORR was 59.6% (51.0-67.7) with 10 patients (7.1%) and 74 patients (52.5%) showing a CR and PR, respectively [27].

In ARROW at the CCOD of November 6, 2020, the intracranial-ORR was 70% (34.8-93) in the total efficacy population with 3 patients (30.0%) experiencing a CR and 4 patients (40.0%) experiencing a PR in the total efficacy population. In the population who had received prior platinum-based chemotherapy, intracranial-ORR was 66.7% (29.9-92.5) with 2 patients (22.2%) and 4 patients (44.4%) showing a CR and PR, respectively [26]. At the CCOD of March 4, 2022, the updated total efficacy population had an intracranial-ORR of 53.3% (26.6-78.7) with 2 patients (20%) experiencing a CR and 5 patients (33.3%) experiencing a PR. 14 out of the 15 patients had prior platinum-based treatment and one patient was treatment naïve [27].

For selpercatinib ORR was reported in LIBRETTO-001 and SIREN. In LIBRETTO-001, ORR was 61% (55-67) with 18 patients (7%) and 133 patients (54.0%) experiencing a CR and PR, respectively [73]. In SIREN, ORR was 68% (50-82) with 4 patients (11%) showing a CR and 21 patients (58.0%) experiencing a PR [74].

In LIBRETTO-001 the intracranial-ORR was 84.6% (65.1-95.6) with 7 (26.9%) CRs and 15 (57.7 %) PRs [73]. In SIREN the Intracranial-ORR was 100% with 0 CRs and 7 (100%) PRs [74].

In general both pralsetinib and selpercatinib shows clinically relevant intracranial-ORR with comparable responses seen in all studies. It should also be noted that the populations in general are small and that the confidence intervals are wide and overlapping.

Conclusion

Based on the data presented above

- The ORRs reported for pralsetinib and selpercatinib are comparable with overlapping confidence intervals.
- Intracranial-ORRs for pralsetinib and selpercatinib are comparable with overlapping confidence intervals.

24.4.3.2.4 Safety

Discontinuation due to adverse events

Discontinuation due to adverse events was reported for both pralsetinib in ARROW and selpercatinib in LIBRETTO-001 and SIREN.

As reported in section 7.1.2.4.1, 55 (19.6%) patients in the NSCLC safety population and 91 (17.2%) patients in the total safety population discontinued treatment due to AEs at the CCOD of November 6, 2020. At the CCOD of March 4, 2022, 10% discontinued treatment due to TRAEs.

In LIBRETTO-001, 64 (8%) patients discontinued treatment due to AEs and in SIREN none of the 37 patients discontinued due to TRAEs.

Grade ≥3 adverse events

Grade ≥3 AEs was reported for both pralsetinib in ARROW and selpercatinib in LIBRETTO-001 and SIREN.

As reported in section 7.1.2.5.1, 212 (75.4%) patients treated with pralsetinib experienced grade ≥3 AEs (including 35 (12.5%) grade 5 AEs) in the NSCLC population, and 406 (76.9%) patients experienced grade ≥3 AEs (including 66 (12.5%) grade 5 AEs) in the total safety population (CCOD: November 6, 2020). In the updated safety population (CCOD: March 4, 2022), 231 (82.2%) patients experienced grade ≥3 AEs and 176 (62.2%) patients had TRAEs [27].
In LIBRETTO-001 for selpercatinib, 572 (71.9 %) patients experienced grade ≥3 AEs and 307 (38.6 %) experienced grade ≥3 TRAEs in the overall safety population. In the NSCLC population, 73.9% patients had grade ≥3 AEs and 40.2% experienced TRAEs [73]. In SIREN grade ≥3 TRAEs was reported for 12 (24%) patients including deaths due to AEs in 3 patients [74].

Safety profiles

A description of the safety profile for pralsetinib can be found in section 7.1.3.2.

In LIBRETTO-001 (CCOD: June 15, 2021), 99.9% had at least one AE of any grade in the overall safety population with the most common being edema (48.5%), diarrhea (47.0%) and fatigue (45.9%). 45 patients experienced grade 5 treatment-emergent AEs, eg. respiratory failure (in seven), sepsis and cardiac arrest (in five each), pneumonia and acute respiratory failure (in three each). 95.0% of patients had at least one TRAE of any grade. Treatment-related grade ≥3 AEs occurred in 38.6% patients including one grade 5 TRAE (pneumonitis). The most common grade ≥3 TRAEs included hypertension (13.2%), increased ALT (9.0%) and increased AST (6.3%). Further, 44% of patients experienced treatment-emergent SAE of which 11% was treatment-related. The most common SAE was pneumonia (4%) and the most common treatment-related SAE was drug hypersensitivity (1%). Dose reduction was warranted in 41% of patients while 8% discontinued treatment as a consequense AEs. Of these, 3% was considered by the investigator to be treatment-related. One fatal AE (acute respiratory failure) was considered treatment-related by the investigator. This occurred in a patient with RET-mutant medullary thyroid cancer [73].

The safety profile observed in patients with NSCLC was consistent with that of the overall safety population. In this subpulation all patients had at least one AE of any grade with the most common being diarrhea (51.7%), dry mounth (45.8%) and fatique (43.0%). 24 (6.7%) patients experienced grade 5 treatment-emergent AEs, including respiratory failure (in 6 each), cardiac arrest (in 4 each), pneumonia, sepsis, cerebral hemorrhage (in 2 each), multiple organ dysfunction syndrome, sudden death, somnolence, dyspnea, hypoxia, corona virus infection, acute respiratory failure, and cardiorespiratory arrest (in 1 each). 95.8% of patients had at least one TRAE of any grade.Treatment-related grade ≥3 AEs occurred in 40.2% patients. No grade 5 TRAE were observed. The most common grade ≥3 TRAEs included hypertension (13.8%), increased ALT (11.5%) and increased AST (6.7%) [73].

Table 137: Safety data from LIBRETTO-001 (CCOD: June 15, 2021)

	Overall safety population (n=796)			NSCLC safety population (n=356)		
Safety parameter	**Selpercatinib, n (%)**	**Drug exposure (mo.)** Median	**CCOD Reference**	**Selpercatinib, n (%)**	**Drug exposure (mo.)** Median	**CCOD Reference**
Any AE, n (%)	795 (99.9)	36.1	Jun 15, 2021 [73]	356 (100.0)	36.1	Jun 15, 2021 [73]
Grade ≥3 Grade 5	572 (71.9) 45 (-)			263 (73.9) 24 (6.7)		
Treatment-related AE	756 (95.0)			341 (95.8)		
Grade ≥3 Grade 5	307 (38.6) 1 (-)			143 (40.2) 0 (0)		
Any SAE	- (44)			N/A		
Treatment-related SAE	- (11)			N/A		
Discontinuation of treatment due to AEs	- (8)			N/A		

Abbreviations: AE - adverse event; TRAE - treatment-related adverse event; SAE - serious adverse event; TR-SAE - treatment-related serious adverse event

SIREN (CCOD: January 27, 2021) reports only on TRAEs. 88% of the safety population experienced TRAEs of any grade with the most common being fatigue/asthenia (40%), increased liver enzyme levels (34%), dry mouth (26%), hypertension (26%), and peripheral edema (20%). Most TRAEs were of grade 1 or 2. Treatment-related grade ≥3 AEs occurred in 24% of patients and included increased liver enzyme levels (10%), prolonged QTc time (4%), abdominal pain (4%), hypertension (4%), and fatigue/asthenia (4%). TRAEs lead to dose reduction in 40% with fatigue/asthenia (14%) and increased liver enzyme levels (12%) being the main course. Dose interruption was carried out in 13 patients (26%) and no patients discontinued treatment due to TRAEs. Three patients had died at the CCOD; two from myocardial infarction and on from oncologic progression. However, the treating physicians evaluated the fatal event to be treatment-emergent [74].

Table 138: Safety data from SIREN (CCOD: January 27, 2021)

	SIREN Pretreated population (n=50)		
Safety parameter	**Selpercatinib, n (%)**	**Drug exposure (mo.)** Median	**CCOD** **Reference**
Any AE, n (%)	N/A	16.9	Jan 27, 2021 [74]
Grade ≥3 Grade 5	N/A		
Treatment-related AE	43 (88)		
Grade ≥ 3 (grade 5)	12 (24)		
Any SAE	N/A		
Treatment-related SAE	N/A		
Discontinuation of treatment due to AEs	0 (0)		

Conclusion

- Conclusion is based on the above sections: discontunation due to AEs, grade ≥3 AEs and safety profiles.There are observed higher discontinuation rates for pralsetinib than selpercatinib.
- The proportion of patients experiencing grade ≥3 AEs was slightly lower in the safety populations in LIBRETTO-001 compared to the safety populations in ARROW at the first CCOD, and lower compared to the last CCOD.
- The proportion of patients experiencing grade ≥3 TRAEs was lower in the safety populations in LIBRETTO-001 compared to the safety populations in ARROW at both CCODs. The RWE from SIREN show a lower rate of grade ≥3 TRAEs.

The differences in baseline characteristics between study populations, which have not been adjusted for, may make patients more or less susceptible to experiencing AEs and discontinuing due to AEs. These differences along with differences in data maturity and reporting makes it difficult to do an overall comparison between pralsetinib and selpercatinib in terms of safety.

24.5 Health economic analysis

As addition to the health economic analysis of pralsetinib as first line treatment, Roche have by request from the DMC also included a health economic analysis of pralsetinib as second line treatment.

This supplement health economic analysis is based on the studies and comparison presented in section 24.4. This comparison shows the median PFS reported for pralsetinib and selpercatinib is comparable with overlapping confidence intervals for the reported median PFS as well as the 12- and 24 month PFS rates. Based on the immature median OS for selpercatinib and the reported OS rates at 12- and 24-months, it is not possible to conclude if there are relevant difference between pralsetinib and selpercatinib (see section 24.4 for further details).

Likewise for ORR and intracranical-ORR it is not possible to conclude if there are relevant differences between pralsetinib and selpercatinib (see section 24.4 for details).

As it is not possible to conclude relevant differences in the efficacy of pralsetinib and selpercatinib in any of the endpoints, the efficacy of selpercatinib in the second line treatment is assumed to be identical to the efficacy of pralsetinib.

The safety of pralsetinib is described in section 7.1.3.2, and the safety of selpercatinib is described in section 24.4. In this supplement second line health economic analysis the AE rates applied for pralsetinib is identical to the health economic analysis of pralsetinib as first line treatment. AE rates of selpercatinib is extracted from the LIBRETTO-001 [73]. Only AE of grade ≥3 and an incidence > 2 % is included.

24.5.1 Model

The model used in the health economic analysis of pralsetinib as second line treatment is identical to health economics analysis of pralsetinib as first line treatment (described in section 8.1).

Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice.

The relationship between data for relative efficacy and the parameters used to model pralsetinib as second line treatment is the same as applied in the analysis of first line treatment (described in section 8.2). The efficacy of selpercatinib is describes in section 25.4. As described earlier, it is not possible to conclude any relevant differences between pralsetinib and selpercatinib the parameters applied for selpercatinib is assumed to be identical to the parameters applied to pralsetinib.

The efficacy of the overall (ITT) population is used to model the efficacy of pralsetinib as second line treatment. This is done for several reasons. Pretreated patients account for the majority of patients in the ITT-population (58%). OS, PFS and ORR (both medians and rates) is very similar between the group of pretreated patients and the overall population, and it is impossible to conclude differences between the two groups. By using the ITT-population the number of patients is not reduced – thus statistical power is not reduced. For these reasons the second line treatment of pralsetinib is modelled based on the ITT-population, and not on only pretreated. A variety of extrapolated curves is included in the model for the DMC to use, and all possible alternative assumptions about OS, PFS etc. that the DMC could choose to make as well within these – both small and large changes.

Extrapolation of relative efficacy

The extrapolation of pralsetinib as second line treatment is identical to the extrapolation of pralsetinib as first line treatment (described in section 8.3), and expanded above.

Documentation of health-related quality of life (HRQoL)

Health-related quality of life (HRQoL) applied in the analysis of pralsetinib as second line treatment is identical to the HRQoL applied in the analysis of first line treatment (described in section 8.4), and it is assumed that the HRQoL of selpercatinib is the same as pralsetinib.

Resource use and costs

The frequency and unit costs applied in the analysis of pralsetinib as second line treatment is identical to the analysis of first line treatment (described in section 8.5). For selpercatinib it is assumed that resources and costs is the same as pralsetinib in terms of monitoring, administration etc. However, for selpercatinib the AE rates are taken from the LIBRETTO-001 [73] and only AE grade ≥3 with a rate > 2 % is included.

Results

The results of the supplement analysis of pralsetinib as a second line treatment is presented below. As the effect of pralsetinib is assumed to be similar to selpercatinib there is no differences in life years or QALY, but if pralsetinib is recommend as second line treatment it will generate a saving of [redacted] DKK per patient compared to selpercatinib. The analysis is based on AIP.

Table 139: Base case results on pralsetinib compared to selpercatinib as second line treatment

Per patient	Pralsetinib	Selpercatinib	Difference
Mean life years gained	[redacted]		
Total life years gained (discounted)			
Life years gained in progression-free health state (undiscounted)			
Life years gained in progressed health state (undiscounted)			
QALYs			
Total QALYs (discounted)			
QALYs in progression-free health state (discounted)			
QALYs in progressed health state (discounted)			
Costs (DKK)			
Total costs			
Drug costs			
Hospital sector costs			
Patient time and transport costs			
Adverse reaction costs			
ICER			
Incremental results	**Intervention vs comparator**		
ICER (per QALY)	[redacted]		

Budget impacts analysis

The cost per patient analysis also serves as the engine in the budget impact model, and thus costs (expect patient and transportation, which is not included) is the same. It is assumed that 8 new patients every year will be candidates for pralsetinib as second line treatment. This assumption is based on the DMC evaluation of selpercatinib. If pralsetinib is recommended as second line treatment it is assumed that pralsetinib will have a market uptake of 100 %. If pralsetinib is not recommended it is assumed that pralsetinib will not have any market uptake. Future market shares depend on multiple factors such as developments in the treatment landscape, and available physical and economic resources. The estimate is an assumption and is associated with uncertainty. Market share and number of patients is fully adjustable for the DMC.

In Table 140 the costs per patient applied in the budget impact model is presented, and the results of the budget impact model is presented in Table 141. The analysis shows that the recommendation of pralsetinib will generate a total savings of [redacted] DKK compared to selpercatinib at year 5. The analysis is based on AIP.

Table 140: Costs per patient per year applied in the budget impact model, DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
Pralsetinib					
Drug costs	[redacted]				
Hospital sector costs	63,234	30,328	20,004	13,845	10,007
AE costs	10,909	0	0	0	0
Primary sector costs	0	0	0	0	0
Selpercatinib					
Drug costs	[redacted]				
Hospital sector costs	63.234	30.328	20.004	13.845	10.007
AE costs	3.717	0	0	0	0
Primary sector costs	0	0	0	0	0

Table 141: Expected budget impact of recommending the pharmaceutical for the current indication, DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
Pralsetinib is recommended	[redacted]				
Of which: Drug costs	[redacted]				
Of which: Hospital costs	*505.868*	*748.494*	*908.524*	*1.019.282*	*1.099.338*
Of which: Primary sector costs	*0*	*0*	*0*	*0*	*0*
Of which: Adverse reaction costs	*87.270*	*87.270*	*87.270*	*87.270*	*87.270*
Pralsetinib is NOT recommended	[redacted]				
Of which: Drug costs	[redacted]				
Of which: Hospital costs	*505.868*	*748.494*	*908.524*	*1.019.282*	*1.099.338*
Of which: Primary sector costs	*0*	*0*	*0*	*0*	*0*
Of which: Adverse reaction costs	*29.733*	*29.733*	*29.733*	*29.733*	*29.733*
Budget impact of the recommendation	[redacted]				