Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende nivolumab i kombination med ipilimumab og begrænset kemoterapi til førstelinje-behandling af uhelbredelig ikke-småcellet lungekræft

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet, oktober 2021
2. Ansøgers notat til Rådet, maj 2022
3. Forhandlingsnotat fra Amgros vedr. nivolumab i kombination med ipilimumab og begrænset kemoterapi til ikke-småcellet lungekræft
4. Ansøgers endelige ansøgning vedr. nivolumab i kombination med ipilimumab og begrænset kemoterapi til ikke-småcellet lungekræft

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To the Medicines Council,

Consultation reply regarding nivolumab + ipilimumab + limited chemotherapy for 1L NSCLC.

Bristol Myers Squibb assumes the conclusion outlined in the draft assessment report to be relying on a stark misconception of how one would otherwise have expected the employment of the updated methodological approach to unfold in this first case processing. In this context, conclusions are suggested to be hinging on past methods, triggering conclusions unfit for purpose and, hence, solid and informed decision making. As is, the Medicines Council motivate current decision by claiming that BMS hasn't provided evidence that nivolumab + ipilimumab + limited chemotherapy is neither as good as, nor better than, the standard of care. This is incorrect.

In the context of the above, BMS is requesting an immediate clock-stop of the assessment to secure a solid, fair and compliant evaluation.

The overall survival (OS) benefit is usually named a critical outcome measure in NSCLC, and the OS benefit of nivolumab + ipilimumab + limited chemotherapy observed in the squamous (SQ) and PD-L1 expression level <1% is very comparable to recently approved immunotherapy + chemotherapy combinations in 1L NSCLC:

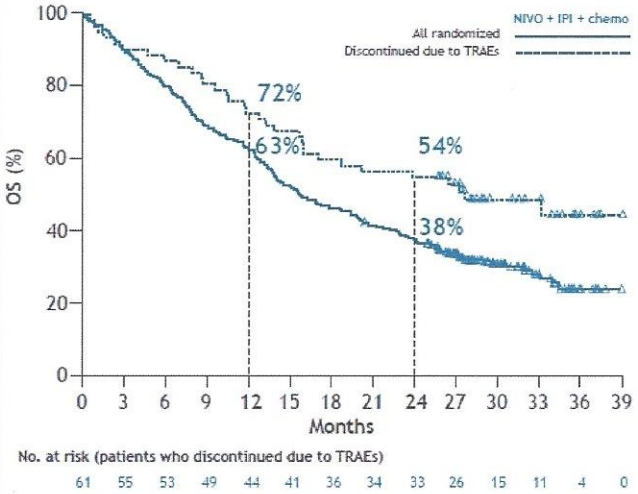
Subgroup Histology PD-L1 exp.	Follow-up median [range]	Overall Survival HR (95% CI) ARR at XX months	Grade 3-5 AEs RR (95% CI) ARR	Discontinuation due to AEs RR (95% CI) ARR
Nivolumab + ipilimumab + limited chemotherapy				
SQ <1%	30.7 [24.4 - NR]	0.48 (0.28 - 0.81) 24month Δ: 22%-point	RR 1.22 (1.03 - 1.45)* ARR: 8.5%-point	2.59 (1.69 - 3.96)** ARR: 11.8%
Pembrolizumab + chemotherapy				
NSQ ≥ 1% to <50%;	10.5 [0.2 - 20.4]	0.55 (0.34 - 0.90) 12month Δ: 19.8%-point	1.02 (0.91 - 1.16) ARR 1.4%-point	1.86 (1.30 - 2.70) ARR 12.8%-point
NSQ; <1%	18.7 [0.2 - 30.9]	0.52 (0.36 - 0.74) 18month Δ: 24%-point	1.08 (0.95 - 1.24) ARR 4.8%-point	2.06 (1.46 - 2.89) ARR 17.3%-point
SQ; ≥ 1% to <50%	14.3 [0.1-31.3]	0.59 (0.42- 0.84) 18month Δ: 17%-point	1.00 (0.88 - 1.14) ARR 0.1%-point	2.07 (1.45 - 2.95) ARR 14.1%-point

PLEASE NOTE: THE MEDICINES COUNCIL REPORTS ODDS RATIOS (ORS), AND ORS SHOULD NOT BE INTERPRETED AS RELATIVE RISKS (RRS)
* THE REPORTED OR WAS 1.42 (95% CI: 1.05 - 1.91).
** THE REPORTED OR WAS 2.97 (95% CI: 1.84 - 4.78).

The Danish Medicines Council stress in the conclusion for SQ<1% that patients with SQ NSCLC usually present with comorbidities and poor performance status (PS) and therefore argue the intervention would only be relevant for a limited number of patients. The DMC may recall the source of BMS's estimated number of patients; it comes from a DMC decision document from January 2021 which estimates 120 patients with SQ<1% NSCLC in PS 0-1 and without significant comorbidities could be eligible for pembrolizumab + chemotherapy combination. While patient numbers may be small, surely this shouldn't impact the *relevance* of the OS benefit for this subgroup.

In the 1L treatment of NSCLC of SQ histology and PD-L1 expression level <1%, nivolumab + ipilimumab + limited chemotherapy has demonstrated a statistically significant, clinically meaningful, OS benefit versus the current standard of care: chemotherapy. The 24 months survival rate is quadrupled from 11% to 33%.

It is true, that the RR of both Grade 3/4 adverse events (AEs) and treatment discontinuation due to AEs is in disfavor of nivolumab + ipilimumab + limited chemotherapy. However, it is important to note that the absolute risk differences are not very different from recently approved immunotherapy + chemotherapy combinations in 1L NSCLC. In addition the patients who discontinue treatment with nivolumab + ipilimumab due to adverse events are not subject to worse outcomes than the overall intention to treat (ITT) population:



Patients who discontinued all components of NIVO + IPI + chemo due to TRAEs

	NIVO + IPI + chemo (n = 61)
Median OS,[b] mo	27.5
2-year OS rate, %	54
ORR, n (%)	31 (51)
Median DOR after discontinuation,[c] mo	14.5
Ongoing response for ≥ 1 year after discontinuation,[c] %	56

Among patients who discontinued all components of NIVO + IPI + chemo due to TRAEs:
- Median (range) number of doses was 7 (1–33) for NIVO and 3 (1–17) for IPI
- Median (range) duration of treatment was 4.4 (0–23.3) months

Continued OS benefit despite discontinuation of dual immunotherapy has also been shown in 1L unresectable pleural mesothelioma (CM-743), 1L renal cell carcinoma (CM-214), 1L metastatic melanoma (CM-067) and 1L NSCLC (CM-227). Importantly, the 4 year minimum follow-up from the CM227 phase III trial in 1L NSCLC also supports the sustained OS benefit of dual immunotherapy in SQ<1% patients with a HR of 0.53 (95% CI: 0.34 - 0.84) and a 4 year survival rate of 22% versus 5% for chemotherapy.

BMS is disillusioned by the fact that CM227 phase III trial data, highly relevant to the assessment of the long-term durability of a clinical benefit of dual immunotherapy in NSCLC, is disregarded. The fundamental mechanics of cost / QALY assessments are being rendered obsolete, if 4 years follow-up from a relevant phase III trial is being disregarded as per the assessment report. BMS argues, that a benefit of dual immunotherapy at 4 years cannot be disregarded simply because the CM227 design did not include 2 cycles of chemotherapy to further complement the dual immunotherapies mode of action. How will the Medicines Council in the future rely on RWE in its cost/QALY assessments if 4 years minimum follow-up from a phase III trial is simply disregarded?

Sincerely,

Anders Thelborg
General Manager
Bristol Myers Squibb, Denmark

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Virum, 20. maj 2022.

Til Medicinrådet

Hermed Bristol Myers Squibbs (BMS) tilbagemelding på udkast til vurderingsrapport for Nivolumab (Nivo) i kombination med Ipilimumab (Ipi) og to serier dobbelt platinbaseret kemoterapi (PDC) til førstelinjebehandling af ikke-småcellet lungekræft (1L NSCLC)

BMS imødeser Medicinrådets anbefaling vedr. behandling med Nivo+Ipi+PDC til 1L NSCLC planlagt til 15. juni 2022. Denne første ansøgning under de nye metoder blev indsendt 24. februar 2021, og således er der gået lige knap 16 måneder med sagsbehandlingen af en vigtig behandlingsmulighed med dobbelt immunterapi. Behandlingen adskiller sig fra eksisterende immunterapeutisk behandling med PD-1/PD-L1 checkpointhæmmere i NSCLC ved, udover at bryde tumorens resistens overfor T-celledrab i tumor, *også* at fremme selve aktiveringen af patientens immunsystem. Det betyder, at antallet af aktiverede T-celler øges og at flere forskellige typer af T-celler aktiveres samt at antallet af hukommelses-T-celler også øges[1-4]. Klinisk har dette vist sig afgørende for at generere dybe og langvarige responser på tværs af histologi og PD-L1-ekspression i NSCLC.

BMS benytter lejligheden til at gøre opmærksom på to principielle forhold samt to sagsspecifikke forhold.

Kommentarer af principiel karakter

Omkostninger bør beregnes ud fra den dosering, som anvendes i klinisk praksis

Medicinrådets beslutningsgrundlag bør i videst mulig udstrækning afspejle den virkelighed som forventes i klinisk praksis, både ift. lægemidlernes relative effekt, sikkerhed og omkostninger.

Ift. beregning af omkostninger er Nivo regulatorisk godkendt til dosering i fast dosis, men har hidtil været anvendt med en vægtbaseret dosering i andre indikationer i Danmark. I de seneste tre vurderingsrapporter fra Medicinrådet har Nivo-omkostningen været baseret på en fast dosering, hvilket overestimerer omkostningerne ved behandlingen, såfremt nuværende kliniske praksis med vægtbaseret dosering fortsættes. Hvis den sundhedsøkonomiske analyse i stedet foretages med vægtbaseret dosering, reduceres ICER'en med ca. ni procent på listeprisniveau, og dermed øges sandsynligheden for, at Nivo+Ipi+PDC er omkostningseffektiv.

Medicinrådet præsenterer ikke resultaterne fra ansøgers hovedanalyse

Medicinrådets sekretariat fortsætter tilsyneladende den ændrede praksis, hvor rådet ikke længere præsenteres for resultaterne af ansøgers sundhedsøkonomiske analyse. Dette er ikke blot et brud med tidligere praksis, men også en politik, som skiller sig ud ift. andre HTA-institutioner i lande, vi normalt sammenligner os med. Normen er, at beslutningstagere præsenteres for resultater af begge parters hovedanalyser, og dette vil også bidrage til rådets forståelse af usikkerheden forbundet med de sundhedsøkonomiske analyser - selv når de to analyser giver relativt ens resultater.

I dette konkrete tilfælde giver BMS' analyse en QALY-gevinst på 1,17 mod Medicinrådets 0,83 (forskel på 29%) og en ICER på ca. 624 000 kr. pr. QALY mod Medicinrådets ICER på ca. 720 000 kr. (forskel på 15%).

Kommentarer af sagsspecifik karakter

Bivirkninger ved Nivo+Ipi+PDC som leder til behandlingsophør

Medicinrådet fremhæver, at behandling med Nivo+Ipi+PDC har flere bivirkninger, som leder til behandlingsophør, end behandling med kemoterapi alene har. I denne sammenhæng er det afgørende også at nævne, at det i CM9LA-studiet ikke blev observeret, at det påvirker overlevelsen negativt, hvis patienter

behandlet med interventionen ophørte med behandling pga. behandlingsrelaterede bivirkninger, se Bilag 1[5]. Dette fænomen er også observeret i fase III-studier med Nivo+Ipi i andre EMA-godkendte indikationer; herunder metastatisk melanom (CM067), renalcellecarcinom (CM214) og lungehindekræft (CM743), samt i FDA godkendt NSCLC (CM227), og er med al sandsynlighed en afledt konsekvens af den biologiske effekt af Ipilimumab på patientens immunsystem[5].

Overlevelse blandt patienter behandlet med kemoterapi

Medicinrådet vurderer, i en følsomhedsanalyse, at overlevelsen i kemoterapiarmen i CM9LA hos patienter med planocellulær histologi og PD-L1-ekspression <1 % er lavere, end hvad man vil forvente i dansk klinisk praksis. I følsomhedsanalysen antages overlevelsen ved behandling med kemoterapi for denne patientgruppe at være på niveau med overlevelsen for ITT-populationen i studiet. Konkret forskydes overlevelsen blandt planocellulære PD-L1 <1% patienter, behandlet med kemoterapi, spekulativt i MR's følsomhedsanalyse fra de 11% observeret ved to år i CM9LA-studiet til 26%. Givet at overlevelsen for Nivo+Ipi+PDC ikke samtidigt justeres, reduceres den estimerede relative effektforskel fra den effektforskel, der blev observeret i CM9LA-studiet. Derved frembringes et meget lavt QALY-estimat for sundhedsgevinsten ved Nivo+Ipi+PDC, som altså kan føre til et underestimat af omkostningseffektiviteten af Nivo+Ipi+PDC.

Sammenlignet med OS i kemoterapi-armen blandt planocellulære PD-L1 <1%-patienter, efter to år på 11%, synes dette estimat ikke væsentligt afvigende fra DLCG og DLCRs Årsrapport 2019-20[6], som MR refererer til. Årsrapporten inkluderer OS for planocellulære patienter i henhold til stadie (figur 8.1.1.4)[6]. OS for stadie IV A+B aflæses til ca. 7-15% efter to år. I en nylig Real-World-publikation aflæses OS for planocellulære stadie IV-patienter ligeledes til ca. 8% efter to år[7]. I CM227-studiet sås overlevelsesrater i kemoterapiarmen på 16%, 9% og 5% efter hhv. 24, 36 og 48 mdr. i studiets planocellulære PD-L1 <1% population (n=46)[8]. Overlevelsen for planocellulære stadie IV-patienter præsenteres ikke i Real-World-publikationen, som MR også henviser til[9].

Ift. den relative effektforskel blev der i CM9LA-studiet stratificeret for henholdsvis histologi og PD-L1-ekspression, og studiet viste en relativ effektforskel for OS på HR 0,48 med et snævert konfidensinterval (95% CI: 0,28 – 0,81) samt en forøgelse af overlevelsen ved 24 måneder fra 11% til 33%, altså 22%-point[5]. En relativ effektforskel der ligeledes er set i CM227-studiet (Nivo+Ipi vs PDC) blandt planocellulære PD-L1 <1% patienter, hvor der blev estimeret en OS HR 0,53 (95% CI: 0,34 – 0,84)[8].

Tilbage står, at denne følsomhedsanalyse:

- Sammenligner OS fra ITT-populationens kemoterapi-arm med OS blandt planocellulære PD-L1 <1% patienter behandlet med Nivo+Ipi+PDC.
- Blander OS på tværs af histologi og PD-L1-ekspression ind i en analyse af planocellulære PD-L1 <1% patienter. Her vil forhold som f.eks. brugen af pemetrexed i 1L blandt ikke-planocellulære patienter og effekten af 2L immunterapi ved højere PD-L1-ekspression influere på kemoterapi-armens OS.
- Ignorerer den relative effektforskel fra randomiserede, stratificerede data, hvor relevante patientkarakteristika netop ér balancerede til formålet, fordi Nivo+Ipi+PDC-armen ikke justeres.

Pga. ovenstående forhold bør Rådet lægge meget lille vægt på resultaterne i denne følsomhedsanalyse.

Med disse fire pointer in mente ser vi frem til, at en alt for lang sagsbehandlingsproces endelig kan nå frem til en afgørelse d. 15. juni, så vi sammen kan sikre, at der også kan tilbydes immunterapi til førstelinje metastatiske NSCLC patienter med planocellulær PD-L1 <1% i Danmark.

Med venlig hilsen,

Anders Thelborg
Adm. direktør
Bristol Myers Squibb, Danmark

Referencer

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Bilag 1

Overlevelse for ITT-populationen samt patienter som afbrød behandlingen på grund af behandlingsrelaterede bivirkninger i CheckMate-9LA studiet. [5]

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23.05.2022
DBS/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	15.06.2022
Leverandør	Bristol Meyer Squibb (BMS)
Lægemiddel	Opdivo (nivolumab) + Yervoy (ipilimumab)
Ansøgt indikation	Nivolumab i kombination med ipilimumab og to cykler platinbaseret kemoterapi til førstelinjebehandling af metastatisk ikke-småcellet lungekræft uden sensibiliserende EGFR-mutation eller ALK-translokation.

Forhandlingsresultat

Amgros har opnået følgende pris på Opdivo (nivolumab) og Yervoy (ipilimumab):

Tabel 1: Forhandlingsresultat Opdivo (nivolumab)

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Opdivo (nivolumab)	240 mg/24 ml	1 stk.	22.003,74	[redacted]	[redacted]
Opdivo (nivolumab)	100 mg/10 ml	1 stk.	9.168,23	[redacted]	[redacted]
Opdivo (nivolumab)	40 mg/4 ml	1 stk.	3.690,68	[redacted]	[redacted]

Leverandøren tilbød en yderligere rabat i forbindelse med igangsættelse af prisregulering af alle immunterapierne i februar 2022. Prisen vil være gældende indtil 31.12 2023. Amgros har mulighed for at aktivere prisreguleringen igen, hvis der kommer øget konkurrence og dermed mulighed for at få bedre priser på alle immunterapier.

Tabel 2: Forhandlingsresultat Yervoy (ipilimumab)

Lægemiddel	Styrke/dosis	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	SAIP (DKK) 01.07.2022	Rabatprocent ift. AIP
Yervoy (ipilimumab)	5 mg/ml	10 ml.	25.653,53	[redacted]	[redacted]	[redacted]
Yervoy (ipilimumab)	5 mg/ml	40 ml.	102.385,5	[redacted]	[redacted]	[redacted]

Leverandøren har valgt at øge rabatten på Yervoy (ipilimumab) dels da der er kommet konkurrence fra parallelimportører, og dels da Amgros har publiceret et udbud med fortrolige priser. Prisen vil være gældende fra d. 01.07.2022 og indtil 31.12.2023.

Konkurrencesituationen

Der er ingen andre godkendte immunterapier til patienter med planocellulær NSCLC og PD-L1-ekpression <1.

Nedenstående tabel viser prisen for behandling med Opdivo (nivolumab) i kombination med Yervoy (ipilimumab) for et års behandling. Amgros er opmærksom på, at den gennemsnitlige behandlingslængde kan variere mellem de to behandlinger, men for overskuelighedens skyld er tabellen opgjort for 12 måneder.

Tabel 3: Sammenligning af lægemiddelpriser

Lægemiddel	Dosis	Frekvens	Antal behandlinger i 12 måneder	Pris for behandling i 12 måneders SAIP (DKK)
Opdivo (Nivolumab)*	360 mg	Hver 3. uge	[redacted]	[redacted]
Yervoy (ipilimumab)	1 mg/kg	Hver 6. uge	[redacted]	[redacted]
Total pris for 12 måneders behandling med fast dosis Opdivo (nivolumab)				[redacted]
Opdivo (nivolumab)**	4,5 mg/kg	Hver 3. uge	[redacted]	[redacted]
Yervoy (ipilimumab)	1 mg/kg	Hver 6. uge	[redacted]	[redacted]
Total pris for 12 måneders behandling med vægtbaseret dosis Opdivo (nivolumab)				[redacted]

*Fast dosis

**Vægtbaseret dosis 4,5mg/kg hver 3 uge. Den gennemsnitlige vægt er 70,36 kg jf. Medicinrådets vurderingsrapport

Status fra andre lande

Norge: Ikke anbefalet[1]
Sverige: Anbefalet
England: Ikke anbefalet[2]

Konklusion

[redacted]

[1] https://nyemetoder.no/metoder/ipilimumab-yervoy-nivolumab-opdivo-indikasjon-iii
[2] https://www.nice.org.uk/guidance/ta724/chapter/1-Recommendations

Medicinrådet

Application for the assessment of nivolumab (Opdivo®) in combination with ipilimumab (Yervoy®) and 2 cycles of platinum-doublet chemotherapy for the first-line treatment of metastatic non-small cell lung cancer in adults

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk
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1. Basic information

Contact information	
Name	**Lars Oddershede**
Title	Market Access Manager | Market Access
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Overview of the pharmaceutical	
Proprietary name	OPDIVO YERVOY
Generic name	Nivolumab Ipilimumab
Marketing authorization holder in Denmark	Bristol-Myers Squibb
ATC code	L01XC17 L01XC11
Pharmacotherapeutic group	Nivolumab: programmed death receptor 1 (PD-1) blocking antibody Ipilimumab: human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking Antibody
Active substance(s)	Nivolumab ipilimumab
Pharmaceutical form(s)	Concentrate for solution for infusion
Mechanism of action	Nivolumab: human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2 Ipilimumab: human immunoglobulin G1κ (IgG1κ) monoclonal antibody (HuMAb), which binds to the cytotoxic T-lymphocyte antigen 4 (CTLA-4) an immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway
Dosage regimen	Metastatic NSCLC: 360 mg every 3 weeks (30-minute IV infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute IV infusion) and histology-based platinum-doublet chemotherapy every 3 weeks
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	OPDIVO, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC, regardless of PD-L1 status, with no EGFR or ALK genomic tumour aberrations

Overview of the pharmaceutical	
Other approved therapeutic indications	**Nivolumab and ipilimumab combination therapy** **Melanoma** OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults Relative to nivolumab monotherapy, an increase in progression-free survival and overall survival for the combination of nivolumab with ipilimumab is established only in patients with low tumor PD-L1 expression **Renal cell carcinoma** OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma **Nivolumab monotherapy** **Non-small cell lung cancer** OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults (second-line) **Adjuvant treatment of melanoma** OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection **Renal cell carcinoma** OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults **Classical Hodgkin lymphoma** OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and treatment with brentuximab vedotin **Squamous cell cancer of the head and neck** OPDIVO as monotherapy is indicated for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy **Urothelial carcinoma** OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy **Esophageal squamous cell carcinoma** OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Overview of the pharmaceutical	
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	Nivolumab and ipilimumab in combination with histology-based platinum-doublet chemotherapy Q3W for up to 2 cycles
Packaging – types, sizes/number of units, and concentrations	Nivolumab (10.0 mg/mL): Single-use vials 40 mg/4 mL 240 mg/24 mL 100 mg/10 mL Ipilimumab (5.0 mg/mL): Single-use vials 50 mg/mL 200 mg/mL
Orphan drug designation	No

Abbreviations: ALK, anaplastic lymphoma kinase; CTLA-4, human cytotoxic T-lymphocyte antigen 4; EGFR, epidermal growth factor receptor; HuMAb, monoclonal antibody; IgG4, human immunoglobulin G4; IV, intravenous; NSCLC, non-small cell lung cancer; PD-, programmed death receptor; Q#W, every # week.

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2. Abbrevations

Abbreviation	Description
3-IGI	3-Item Global Index
5-FU	5-fluorouracil
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
ASBI	Average symptom burden index
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
AUC	Area under the concentration curve
BEV	Bevacizumab
BIC	Bayesian Information Criteria
BICR	Blinded independent central review
BMS	Bristol Myers Squibb
BSC	Best supportive care
BV	Brentuximab vedotin
Carb	Carboplatin
CBC	Complete blood count
CEM	Cost-effectiveness model
CENTRAL	Central Register of Controlled Trials
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CM	CheckMate
CNS	Central nervous system
CPS	Combined positive score
CRC	Colorectal cancer
CTLA-4	Cytotoxic T-lymphocyte antigen-4
DBL	Data base lock
DC	Discontinuation
DCR	Disease control rate
DKK	Danish krone
DLT	Dose limiting toxicities
DMC	Danish Medicines Council
DOR	Duration of response

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DoT	Duration of treatment
ECOG PS	Eastern Cooperative Oncology Group performance status
EGFR	Epidermal growth factor receptor
EGP	Economic guidance panel
EMA	European Medicines Agency
EQ-5D	EuroQol-5D
ERG	Evidence Review Group
ESMO	European Society for Medical Oncology
EU	Europe
FDA	Food and Drug Administration
GI	Gastrointestinal
HCC	Hepatocellular carcinoma
HR	Hazard Ratio
HRQOL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
IHC	immunohistochemistry
IMDC	International Metastatic RCC Database Consortium
IMM	Immune-modulating medication
IgG4	Immunoglobulin G4
IO	Immuno-oncology
IPI	Ipilimumab
IRRC	Immune related response criteria
IRT	Interactive response technologies
ITC	Indirect treatment comparison
ITT	Intent to treat
IV	Intravenous
KN	KEYNOTE
KM	Kaplan-Meier
KOL	Key opinion leader
LCSS	Lung Cancer Symptom Scale
LY	Life years
mAB	Monoclonal antibody
MHC	Major histocompatibility complex
MID	Minimal important difference
MSI-H	Microsatellite instability-high
NA	Not applicable
NE	Not estimable

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NIVO	Nivolumab
NIVO+IPI+PDC	Nivolumab + ipilimumab combined with limited platinum doublet chemotherapy
NMA	Network meta-analysis
NR	Not reached
NSCLC	Non-small cell lung cancer
NSQ	Non-squamous
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
Pac	Paclitaxel
PD	Progressed disease
PD-L1	Programmed death ligand 1
PDC	Platinum doublet chemotherapy
Pembro	Pembrolizumab
PF	Progression free
PFS	Progression-free survival
PLAT-PEMX	Platinum plus pemetrexed
PP	Purchase price
PRO	Patient reported outcome
PS	Performance status
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
QALY	Quality adjusted life year
RCC	Renal cell carcinoma
RCT	Randomized control trial
RECIST	Response Evaluation Criteria in Solid Tumors
SCAN-LEAF	Long-term Epidemiological Follow-up of Non-small Cell Lung Cancer in Scandinavia
SCC	Squamous cell carcinoma
SD	Standard deviation
SE	Standard Error
SLR	Systematic literature review
SOC	Standard of care
SQ	Squamous
TCR	T-cell receptor
TMB	Tumour mutational burden
TPS	Tumour proportional score

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TRAE	Treatment related adverse event
UI	Utility index
UK	United Kingdom
US	United States of America
VAS	Visual analogue scale
VAT	Value added tax
VEGF	Vascular endothelial growth factor

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3. Tables and Figures

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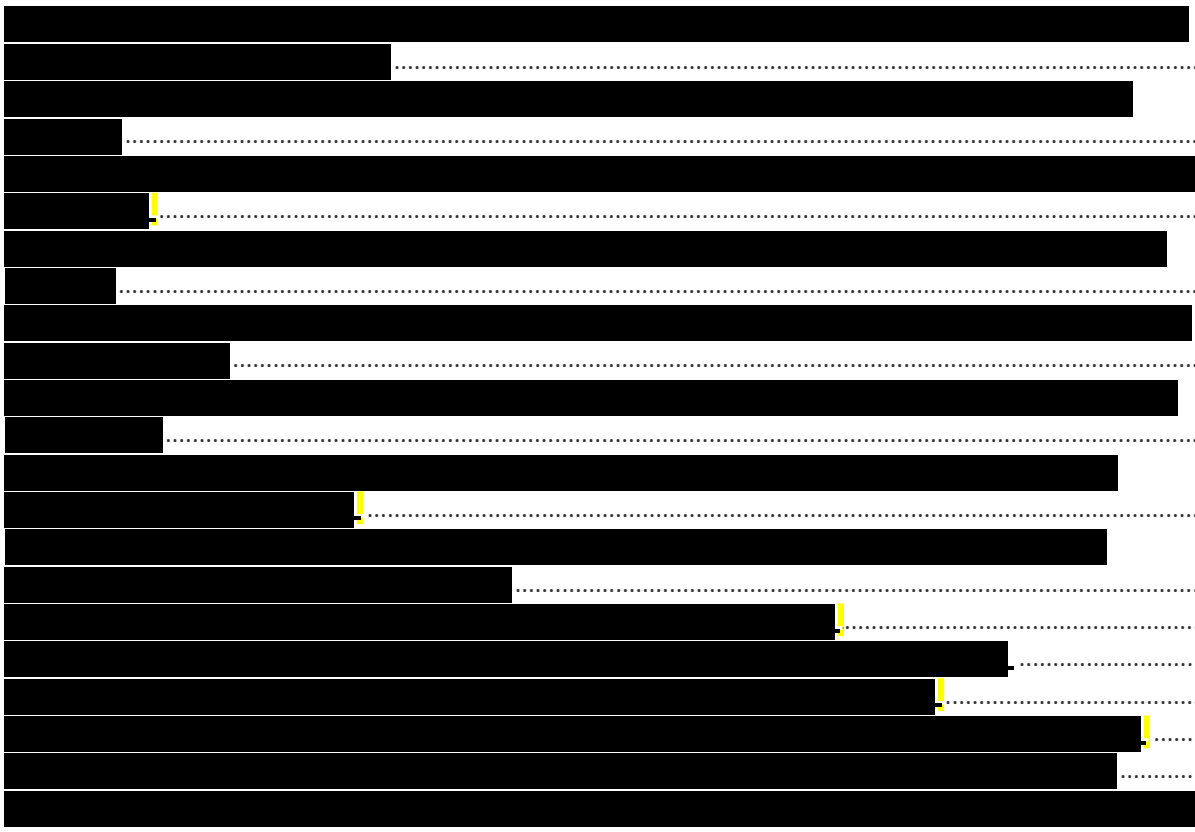

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4. Summary

Lung cancer is one of the most common causes of death related to cancer. Most lung cancers do not cause any symptoms until they have spread and as a result, almost half of patients with lung cancer are diagnosed at an advanced stage, when the probability of long-term survival is low. Patients with non-small cell lung cancer (NSCLC) experience a substantial loss of healthy years compared with the general population.

On 06 November 2020, the European Commission approved nivolumab (NIVO) in combination with ipilimumab (IPI) and two cycles of platinum-based chemotherapy (PDC) (NIVO+IPI+PDC): Indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation.

Combining the two checkpoint inhibitors NIVO+IPI with distinct but complementary mechanisms have proven to be effective, with long-term survival benefit observed in melanoma (CheckMate 067), renal cell cancer (RCC) (CheckMate 214), NSCLC (CheckMate 227 and CheckMate 9LA) and unresectable malignant pleural mesothelioma (CheckMate 743).

CheckMate 9LA compares NIVO+ low-dose IPI (1 mg/kg every 6 weeks) and 2 cycles of PDC to PDC alone as a first-line treatment option in patients with advanced NSCLC, regardless of programmed death-ligand 1 (PD-L1) expression and histology. Two database locks (DBLs) are presented: 1-year (minimum follow-up time 12.7 months) and 2-year (minimum follow-up time 24.4 months for OS). At a minumum follow-up of 24.4 months, the median OS was 15.8 months for NIVO+IPI+PDC and 11.0 months for PDC alone (HR: 0.72, 95% CI: 0.61–0.86). The 2-year survival rate was 38% vs. 26%, respectively.

In CheckMate 9LA, sex, histology [nonsquamous (NSQ) and squamous (SQ)] and PD-L1 expression (<1% vs ≥1%), were stratification factors, and efficacy by PD-L1 expression was a secondary endpoint. Data from NSCLC studies have shown PD-L1 to be a predictive biomarker for anti-PD-(L)1 monotherapy efficacy. In CheckMate 9LA, benefit with NIVO+IPI+PDC was also similar in patients across PD-L1 expression. For the 2-year DBL, OS HRs have been reported as follows: PD-L1 expression <1%: 0.67 (95% CI 0.51–0.88), and ≥1%: 0.70 (95% CI 0.65–0.89). Respective progression free survival (PFS) HRs have been reported as follows: PD-L1 expression <1%: 0.68 (95% CI 0.51–0.89), and ≥1%: 0.67 (95% CI 0.53–0.84).

CheckMate 9LA is the second phase III trial in first-line NSCLC to show benefit of a NIVO+IPI-based regimen in patients with PD-L1 expression <1%, following the CheckMate 227 trial. In CheckMate 227, the 2-year survival rate was 40% vs. 23%, the 3-year survival rate was 34% and 15%, and the 4-year survival rate was 24% and 10% for NSCLC patients with PD-L1 expression <1% treated with NIVO+IPI versus PDC, respectively (Paz-Ares 2021b).

The long term results from Checkmate 227 can be interpreted in relation to an IO treatment stop at two-years, which also corresponds to the current clinical practice according to the most recent guidelines for NSCLC in Denmark.

In an indirect treatment comparison (ITC) including randomized clinical trials (KEYNOTE 407, KEYNOTE 189 and KEYNOTE 024/042) comparing immunotherapy (alone or in combination) vs. PDC, the intervention; NIVO+IPI+PDC was compared vs. other regimens available in first-line treatment of NSCLC. HRs for OS for the comparator vs NIVO+IPI+PDC ranged from 0.93 to 1.18, with the 95% confidence intervals overlapping . The comparison of relatively immature data from CheckMate 9LA to more mature data from other comparator trials should be interpreted with caution, given the different patient populations, treatment regimens, study follow-up as well as the dynamic between dual-IO, mono-IO, and PDC: specifically, the short-term benefit conferred by PDC compared with the longer-term benefit of dual-IO therapy. This also causes differences in usage of subsequent treatment across the trials. There is also a difference in maintenance treatment, where a large share of patients treated with pembrolizumab + PDC (KEYNOTE 189) is treated

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with pemetrexed for as long as five cycles. Also, when comparingthe safety of CheckMate 9LA across the comparator trials, it should be noted that the CheckMate 9LA study includes the reporting of treatment related adverse events (TRAEs) whereas the KEYNOTE trials report all cause adverse events.

In this submission, the core analysis is therefore comparing NIVO+IPI+PDC vs PDC in line with previous economic evaluations of treatment in advanced NSCLC in the literature and from other countries, a three health-state cohort model was developed to evaluate the cost-effectiveness of NIVO+IPI+PDC. The model was developed using a partitioned survival (also known as area under the curve) modelling technique. The Partitioned Survival Model (PSM) consists of the following three health states:

- Progression-free (PF)
- Progressed disease (PD)
- Death

All patients enter the model in the PF state. Patients may remain PF when their disease remains stable or move into the PD or death health states when it progresses. Patients who enter the PD state have experienced disease progression as defined by RECIST 1.1 criteria. State occupancy is estimated using parametric survival models based on the CheckMate 9LA and CheckMate 227 data for PFS and OS. Costs and outcomes were calculated by combining the state occupancy with cost, medical resource use, and quality of life assigned to each health state (PF and PD). Health care costs include the cost of drug acquisition, drug administration, drug monitoring, disease management (PF, PD), end of life care, management of adverse events (AEs), and subsequent treatments. In the base case analysis, treatment duration for NIVO+IPI+PDC and PDC are modelled based on the duration of treatment (DoT) curves observed in CheckMate 9LA. For NIVO+IPI, a 2-year stopping rule is applied consistent with the design of the CheckMate 9LA, the summary of product characteristics and common clinical practice (European Medicines Agency 2020c). Health outcomes include life years (LYs) and quality adjusted life years (QALYs) gained. The quality of life aspect was modelled using utilities derived from the EQ-5D data collected in the CheckMate 9LA trial using Danish weights.

In the base case, a cost-effectiveness analysis is conducted for the intention to treat (ITT) population which includes both the NSQ and SQ histology patients and not stratified by PD-L1 expression. In addition to this base case, a cost-effectiveness analysis was conducted for a SQ population with PD-L1<1% expression. Top line results of these analyses are presented in Table 1. They suggest that NIVO+IPI+PDC is associated with substantial health benefits (in terms of LYs and QALY gains), but also with higher total costs compared with PDC. Table 2 presents the incremental results. NIVO+IPI+PDC results in an incremental cost of 476 747 DKK per LYG and 586 906 per QALY gained vs. PDC in the ITT population, and an incremental cost of 501 608 DKK per LYG and 623 662 per QALY gained vs. PDC in the SQ PDL1<1% subgroup.

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Table 1: Base case cost-effectiveness results (total)

Treatment	Total costs, DKK	Total LYs	Total QALYs
ITT population			
NIVO+IPI+PDC	1 035 589	3.25	2.41
PDC	408 589	1.93	1.35
SQ DPL1<1% subgroup			
NIVO+IPI+PDC	996 705	2.54	1.95
PDC	267 931	1.09	0.78

..LY: Life year; NIVO+IPI+PDC : nivolumab + ipilimumab combined with limited chemotherapy; PDC: Platinum doublet chemotherapy; QALY: Quality adjusted life years;DKK: Danish krone

Table 2: Base case cost-effectiveness results (incremental)

NIVO+IPI+PDC vs.	Inc. costs, DKK	Inc. LY	Inc. QALYs	Inc. cost per LYG, DKK	Inc. cost per QALY, DKK
ITT population					
PDC	627 000	1.32	1.07	476 747	586 906
SQ PDL1<1% subgroup					
PDC	728 774	1.45	1.17	501 608	623 662

..Inc: Incremental; LY: Life year; LYG: Life years gained; ; NIVO+IPI+PDC : nivolumab + ipilimumab combined with limited chemotherapy; PDC: Platinum doublet chemotherapy; QALY: Quality adjusted life years; Vs: VersusVs.; DKK: Danish krone

NIVO+IPI+PDC is a new treatment option that will provide attainable OS benefit across PD-L1 expressions levels and histology, and should be considered one of the accepted standards of care for the initial treatment of advanced and metastatic NSCLC without EGFR mutations or ALK translocations. NIVO+IPI+PDC will also address the remaining unmet need of an IO based treatment option for SQ NSCLC patients with PD-L1 expression <1%. The results show a total budget impact of 82 805 994 DKK over a 5 year timeframe for SQ NSCLC patients with PD-L1 expression <1%.

There are no clinical trials with direct comparisons of NIVO+IPI+PDC versus the other immunotherapies that can confirm whether one of them offers superior efficacy in this setting. The existing alternatives were evaluated under the "old" Medicines Council system without evaluation of cost-effectiveness.

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

5.1 The medical condition and patient population

In Denmark, lung cancer is one of the most frequent cancer types (Cancer.dk 2020). Further, it is the second most leading site for cancer incidence in both men and women. While the rate of lung cancer has been decreasing over time in men, recently men have seen an increase in lung cancer incidences, due to the ageing population. On the other hand, lung cancer in women has seen an increase until recent years, at which point the risk and incidence of lung cancer in women has remained unchanged. The 1-year relative survival rate across all disease stages for 2012 – 2016 for men and women is 44% and 53%, respectively, with a 5-year relative survival rates at 14% and 20%, respectively (NORDCAN 2016).

Lung cancer has been associated with a high prevalence of somatic mutations, primarily as a result of chronic exposure to tobacco, a known mutagen (Alexandrov 2013). Molecular tumour markers (mutations) that have a predictive value for targeted therapy in NSCLC include epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) gene rearrangements. It is recommended to include tests for these mutations in the evaluation of all patients with NSCLC (Medicinrådet 2020b). Programmed death ligand 1 (PD-L1) expression on tumour cells is a predictive biomarker for immunotherapy, and immunohistochemical testing of PD-L1 expression is currently recommended during diagnosis (Medicinrådet 2020b). Although PD-L1 expression on tumour cells is an established predictive biomarker, patients with low or no PD-L1 expression still benefit. Hence, additional biomarkers are urgently needed to better identify patients for treatment with immunotherapy.

The updated guidelines from American Society of Clinical Oncology (ASCO), applicable to patients without driver alterations in EGFR or ALK, suggests that patients with high PD-L1 expression (tumour proportion score [TPS] ≥ 50%) and NSQ NSCLC, is treated with single-agent IO (Hanna 2020). For most patients with NSQ NSCLC and either negative (0%) or low positive (1% to 49%) PD-L1, the Expert Panel recommends pembrolizumab/carboplatin/ pemetrexed. For patients with high PD-L1 expression (TPS ≥ 50%) and SQ NSCLC, the Expert Panel recommends single-agent pembrolizumab. For most patients with SQ disease and either negative (0%) or low positive PD-L1 (TPS 1% to 49%), the Expert Panel recommends pembrolizumab/carboplatin/(paclitaxel or nab-paclitaxel) or PDC (Hanna 2020). Recommendations are conditional on the basis of histology, PD-L1 status, and/or the presence or absence of contraindications (Hanna 2020).

The recent years' progress in therapies with IO as first- and second-line treatment options for advanced NSCLC are exciting but is still not an available option for all patients and longterm survival is only obtained by limited share of the patients diagnosed with advanced NSCLC. According to the yearly report from Danish Lung Cander Group (DLCG) and Danish Lung cancer registry the 1-year survival rate for patients with SQ NSCLC is 57.3% and 59.3% for patients with NSQ (Adenocarcinoma) regardless of disease stage (Dansk Lunge Cancer Gruppe & Dansk Lunge Cancer Register 2019).

5.1.1 Patient populations relevant for this application

Nivolumab in combination with ipilimumab and two cycles of platinum-based chemotherapy (NIVO+IPI+PDC) is EC approved for the first-line treatment of metastatic NSCLC in adults whose tumours have no sensitising EGFR mutation or ALK translocation. In Denmark 4 886 patients were diagnosed with lung cancer in 2018 (Cancer.dk 2020). Of the diagnosed, 85-90% are NSCLC patients (Novello 2016). Almost the same numbers of men and women suffer from lung cancer (Dansk Lunge Cancer Gruppe 2017). When considering patients in Denmark (regardless of histology), most commonly, people are diagnosed between the ages of 71 and 75 (Dansk Lunge Cancer Gruppe & Dansk Lunge Cancer Register 2019). In the SCAN-LEAF study, the mean age in Cohort 1 (Ekman 2017) was 69 years and in and Cohort 2 68.4 years (Sandelin 2017).

The NSCLC two main histological subtypes, SQ carcinoma and NSQ carcinoma, are estimated to constitute approximately 25% and 75% of NSCLC patients in Denmark, respectively (Medicinrådet 2020b). Patients with NSCLC

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are typically only presented with symptoms at an advanced stage of the disease (stage IIIB and IV). In a study by Ekman et al. of NSCLC in Scandinavia (Norway, Sweden, and Denmark), 59% of were diagnosed with advanced disease (Ekman 2017).

The number of patients with incurable lung cancer was 2 529 in Denmark 2017 (Dansk Lunge Cancer Gruppe 2017). The choice of treatment dependents on the tumour pathology including biomarkers and the performance status of the patient (Medicinrådet 2020b).

In Denmark, NSCLC patients are routinely tested for EGFR mutations and ALK translocations (Dansk Lunge Cancer Gruppe & Dansk Lunge Cancer Register 2016). In 2016 the share of patients with activating EGFR mutations equalled 6.9%, while the share of patients with ALK translocation equalled 1.7%; which then in total accounts for approximately 175 patients with non-squamous histology (Dansk Lunge Cancer Gruppe 2017). First-line treatment of NSCLC patients with EGFR or ALK alterations is targeted treatment with tyrosine kinase inhibitors (Medicinrådet 2020b).

The NSCLC patients without EGFR or ALK gene alterations are divided dependent on the tumour expression of PD-L1. The PD-L1 status together with performance status (PS) predict if a patient is recommended a first-line treatment of either monotherapy blockade of PD-1, or such treatment combined with PDC (Medicinrådet 2020b).

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

PDCs have for long been the standard of care (SOC) for advanced NSCLC (without EGFR-mutations and ALK-, ROS1-rearrangements). Currently available first-line PDC treatment options for NSCLC have similar and modest efficacy (median overall survival (OS): 10-14 months; median progression free survival (PFS): 5 – 6 months, objective response rate (ORR): 30 – 35%, with median duration of response (DOR) of only 6 months) (Gridelli 2008). This shows that with PDC treatment, most patients die within the first year of receiving a lung cancer diagnosis.

In recent years, immunotherapies have become available as first- and second-line treatment options for advanced NSCLC. In Denmark, immunotherapies are available treatments for patients with PD-L1 expression ≥50% (with absence of EGFR or ALK aberrations); combination immunotherapy with PDC are also available for patients with NSQ, PD-L1 expression <50% (with absence of of EGFR or ALK aberrations) (Dansk Lunge Cancer Gruppe 2017, Medicinrådet 2020b). Patients with SQ, PD-L1 expression ≥ 1 % and < 50 % (with absence of of EGFR or ALK aberrations) is also offered combination IO with PDC based on re-evaluation and recommendation on 27th of January 2021 by the DMC. There are currently no 1L IO options for NSCLC patients with SQ and PD-L1 <1% (Medicinrådet 2021c).

Therapeutic choices in first-line treatments of NSQ and SQ NSCLC in Denmark, the Medicines Council drug recommendation and treatment guidance concerning medicinal products for first-line treatment of incurable NSCLC, have recently been updated to 20 Jan 2022 (version 1.7), which will be in effect from 1 May 2022 (Medicinrådet 2022) (version 1.6; in effect since 1 Nov 2020). The guideline version 1.7 includes changes in relation to treatment of NSCLC patients with *EGFR* mutations and ALK translocation, as well as an addition of atezolizumab and cemipimab to the existing SOC pembrolizumab as treatment options for NSCLC patients with PD-L1 expression ≥50%. The sections below describe the current treatment recommendations as of November 2020 (Dansk Lunge Cancer Gruppe 2020).

First-line treatment of advanced non-small cell lung cancer- non squamous

For patients with NSQ NSCLC with PD-L1 ≥50% and PS 0-1, the current standard treatment is pembrolizumab based on a randomized phase III study (KEYNOTE 024) in which pembrolizumab 200mg flat dose every 3 weeks is examined vs. PDC for metastatic NSCLC and high PD-L1 expression (≥50%) (Reck 2016). In June 2017, a guideline was prepared by the Interregional Forum for Coordination of Medicine, which has been established by the Danish Regions' Directorate of Health. In Denmark, weight-adjusted dosing of pembrolizumab with 2 mg / kg was also required in the first-line NSCLC instead of a flat dose of 200 mg, as this reduces the costs (Dansk Lunge Cancer Gruppe 2017).

For patients with NSQ NSCLC with PD-L1 ≥ 1 % and < 50 % and PD-L1 <1% and PS 0-1, the standard treatment is immunotherapy with pembrolizumab in combination with platinum based chemotherapy and pemetrexed, based on a randomized phase III study (KEYNOTE 189) (Gadgeel 2020, Medicinrådet 2020a).

First-line treatment of advanced non-small cell lung cancer- squamous

As for NSQ NSCLC patients, patients with SQ NSCLC PD-L1 ≥ 50% and PS 0-1, the current standard treatment for suitable patients is with pembrolizumab. As well, weight-adjusted dosing of pembrolizumab with 2 mg / kg is also required in the first-line NSCLC instead of a flat dose of 200 mg, as this reduces the costs (Dansk Lunge Cancer Gruppe 2017).

For SQ NSCLC patients with PD-L1 ≥ 1 % and < 50% and PS 0-1, the standard treatment is pembrolizumab in combination with platinum-based chemotherapy and (nab)-taxanes, based on the results of the KEYNOTE 407 trial (Medicinrådet 2021a).

For patients with SQ with PD-L1 < 1 % and PS 0-2, standard treatment is 4 (to 6) cycles of carboplatin in combination with either vinorelbine, gemcitabine, or a taxane (paclitaxel). The most frequently used combination in Denmark is carboplatin intravenously and vinorelbine, orally. The median survival on PDC is about 10 months. Patients in PS 3-4 do not benefit from treatment (Dansk Lunge Cancer Gruppe 2017). No immunotherapy treatment is currently available for 1/3 of the SQ first-line NSCLC patient population.

Current treatment algorithm Denmark

The current NSCLC first-line treatment algorithm, PS < 2, is illustrated in the table below and is based on the Medicines Council guideline for treatment of first-line NSCLC version 1.6 (Medicinrådet 2020b) and the recent recommendation from the Medicines Council of pembrolizumab in combination with PDC in NSQ patients with PD-L1 expression <1% (Gadgeel 2020, Medicinrådet 2020b) and of pembrolozumab in combination with platinum and (nab)-taxanes in SQ patients with PD-L1 ≥ 1 % and < 50% (Medicinrådet 2021a):

Table 3: Current first-line NSCLC treatment algorithm per PD-L1 expression level and histology

PD-L1 expression level	Squamous histology	Non-squamous histology
≥ 50 %	Pembrolizumab monotherapy	
≥ 1% and < 50%	Pembrolizumab in combination with platinum + (nab)-taxanes	Pembrolizumab in combination with platinum and pemetrexed
< 1%	PDC	

The expected number of patients eligible for pembrolizumab in combination with PDC has recently been shared by the Medicines Council in the protocols for the re-assessment in NSQ NSCLC with a PD-L1 expression <1% (Gadgeel 2020, Medicinrådet 2020b) and in SQ NSCLC with a PD-L1 expression ≥ 1% and < 50% (Medicinrådet 2021a). It would be a reasonable assumption that the number of patients eligible for NIVO+IPI+PDC would not differ significantly from the number of patients expected to be eligible for pembrolizumab in combination with PDC.

The protocol for the re-assessment of pembrolizumab in combination with PDC for NSQ NSCLC with a PD-L1 expression < 1% estimated a total of 250 patients (Gadgeel 2020, Medicinrådet 2020b). When extrapolating that estimate to the other PD-L1 expression levels, a relevant estimate of patients with NSQ histology that could be considered eligible for NIVO+IPI+PDC would be 750 patients (3x250) (Medicinrådet 2020b).

The protocol for the re-assessment of pembrolizumab in combination with PDC for SQ NSCLC with a PD-L1 expression ≥ 1 % and <50% (Medicinrådet 2021a) estimated a total of 120 patients. When extrapolating that estimate to the other

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PD-L1 expression levels, a relevant estimate of patients with SQ histology that could be considered eligible for NIVO+IPI+PDC would be 360 patients (3x120) (Medicinrådet 2020b).

The number eligible for NIVO+IPI+PDC, divided by current comparator, is presented below.

Table 4: Firstline NSCLC Patient numbers per PD-L1 expression level and histology

PD-L1 expression level	Squamous histology	Non-squamous histology
≥ 50 %	Pembrolizumab monotherapy, n=370	
≥ 1% and < 50%	Pembrolizumab in combination with platinum + (nab)-taxanes, n=120	Pembrolizumab in combination platinum and pemetrexed, n=500
< 1%	PDC, n=120	

Second line treatment of advanced non-small cell lung cancer

For NSQ patients with PD-L1 ≥ 50% who have received first-line pembrolizumab, preferred second-line treatment is PDC, combined with vinorelbine or pemetrexed. NSQ patients with PD-L1 <50% who have received first-line pembrolizumab combined with PDC and pemetrexed, preferred second-line treatment is docetaxel. For suitable patients with PD-L1 > 1% and immunotherapy naïve; pembrolizumab, nivolumab and atezolizumab are approved for second-line therapy. Patients who are assessed as unfit for immunotherapy in second-line treatment are assessed with a view to second-line PDC and the choice of regimen depends on what has been used in first-line including maintenance. Pemetrexed, vinorelbine, docetaxel and erlotinib may be effective and may be used in patients with PS 0-2 (Dansk Lunge Cancer Gruppe 2017, Medicinrådet 2020b).

Patients with SQ carcinoma with PD-L1 ≥ 50% who have received first-line pembrolizumab, preferred second-line treatment is PDC, typically including carboplatin and vinorelbine. SQ patients with PD-L1 ≥ 1 % and <50 % who have received first-line pembrolizumab combined with PDC, preferred second-line treatment is docetaxel (Dansk Lunge Cancer Gruppe 2017, Medicinrådet 2020b). For patients who have received first-line PDC and who are not suitable for immunotherapy, second-line treatment is standard docetaxel. For SQ patients with PD-L1 <1%, who received PDC, immunotherapy (NIVO, atezolizumab) should be considered (Dansk Lunge Cancer Gruppe 2020).

Second-line treatment for disease progression after first-line treatment will vary depending on the patient's condition and first-line treatment (Dansk Lunge Cancer Gruppe 2020). Patients who progress after first-line treatment generally have a poor prognosis for effects of second-line treatments.

5.2.2 Choice of comparator

The choice of main comparator is PDC, based on the comparator arm in the CheckMate 9LA clinical trial which included patients across histology and PD-L1 expression level.

In the CheckMate 9LA trial, the PDC regimen received by patients with NSQ NSCLC consisted of carboplatin or cisplatin plus pemetrexed, while patients with SQ NSCLC received carboplatin plus paclitaxel. Pemetrexed maintenance therapy was offered to NSQ patients who had not progressed after the initial 4 treatment cycles of PDC.

Other key comparators in Denmark are pembrolizumab monotherapy or pembrolizumab in combination with the PDC agents: carboplatin and pemetrexed (Dansk Lunge Cancer Gruppe 2019, Medicinrådet 2019, Medicinrådet 2020b, Medicinrådet 2021c). There are no direct comparisons of any of these regimens to confirm whether one of them offers superior efficacy in this setting and the cost-effectiveness of these treatments have not been assessed through the new

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DMC process (as of February 21st, 2021). Therefore, NIVO+IPI+PDC should be considered one of the accepted standards of care for the initial treatment of advanced and metastatic NSCLC without EGFR mutations or ALK translocations.

5.2.3 Description of the comparators

5.2.3.1 Description of platinum doublet chemotherapy- main comparator

An overview of relevant PDCs are presented in Table 5.

Table 5: Description platinum doublet chemotherapy

Name of preparation/pharmaceutical	PDC
Active ingredient	Carboplatin (ATC: L01XA02) Cisplatin (ATC: L01XA01) Gemcitabine (ATC: L01BC05) Pemetrexed (ATC: L01BA05)
Mode of action	Please see SmPC for each product*
Pharmaceutical form	Concentrate for solution for infusion
Strength and packaging	Carboplatin 10 mg/ml Cisplatin 1 mg/ml Gemcitabine 1000 mg/vial Pemetrexed 500 mg/vial
Posology, dosing, and method of administration	**PDC:** • q3w x 4 followed by optional maintenance pemetrexed for non-squamous histology **Gemcitabine/Cisplatin** • Gemcitabine 1000 or 1250 mg/m2 for a 30-minute IV infusion on days 1 and 8 with cisplatin at a dose of 75 mg/m2 as a 30 to 120-minute IV infusion on Day 1 of a 3-week treatment cycle for up to 4 cycles. **Gemcitabine/Carboplatin** • Gemcitabine 1000 mg/m2 as a 30-minute IV infusion on Days 1 and 8 with carboplatin at a dose of AUC 5 as a 30-minute IV infusion, on Day 1 of a 3-week cycle, for up to 4 cycles. Carboplatin should be given following gemcitabine on Day 1 of each cycle, carboplatin dose (mg) = Target AUC x [(CrCl (ml/min) + 25] **Pemetrexed/Cisplatin** • Pemetrexed 500 mg/m2 as a 10-minute IV infusion on Day 1 with cisplatin at a dose of 75 mg/m² as a 120-minute IV infusion on Day 1 of a 3-week treatment cycle, • for up to 4 cycles. Pemetrexed additionally 500 mg/m2 **Pemetrexed/Carboplatin**

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	• Pemetrexed at 500 mg/m2 as a 10-minute IV infusion on Day 1, followed by carboplatin at a dose of AUC 5 or 6 as a 30-minute IV infusion, on Day 1 of a 3-week treatment cycle, for up to 4 cycles. Carboplatin should be given following gemcitabine on Day 1 of each cycle, carboplatin dose (mg) = Target AUC x [(CrCl (ml/min) + 25]. Pemetrexed additionally 500 mg/m2
Should the intervention be used with other drugs?	No
Treatment length/criteria for termination of treatment	Until disease progression, unacceptable toxicity or completion of the 4 cycles, whichever came first. Subjects with NSQ histology who had stable disease or response after 4 cycles, could continue pemetrexed maintenance after 4 cycles of PDC (if selected at randomization) until disease progression or unacceptable toxicity.
Required monitoring, under administration or during treatment period	Please see SmPC for each product*
Requirements of diagnostics or other tests	No
Medically approved indication /-s	Please see SmPC for each product*

Reference: *SmPC available at EMA (European Medicines Agency 2020c)

5.2.3.2 Description of pembrolizumab monotherapy and combination therapy- comparators in scenario analyses

An overview of pembrolizumab monotherapy and combination therapies are provided in Table 6 below.

Table 6: Description of pembrolizumab monotherapy and combination therapy

Name of preparation/pharmaceutical	Pembrolizumab monotherapy Pembrolizumab in combination with pemetrexed and PDC Pembrolizumab in combination with nab/tax and PDC
Active ingredient	Pembrolizumab
Pharmaceutical form	Concentrate for solution for infusion. Testing for PD-L1 tumour expression using a validated test is recommended to select patients with NSCLC.
Strength and packaging	One vial of powder contains 50 mg of pembrolizumab. After reconstitution, 1 mL of concentrate contains 25 mg of pembrolizumab.
Posology, dosing, and method of administration	Pembrolizumab monotherapy: 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes Pembrolizumab combination therapy:

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	200 mg every 3 weeks administered as an intravenous infusion over 30 minutes
Treatment length/criteria for termination of treatment	Until disease progression or unacceptable toxicity. Atypical responses (i.e. an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.
Medically approved indication /-s	• As monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults. • As monotherapy for the adjuvant treatment of adults with Stage III, melanoma and lymph node involvement who have undergone complete resection • As monotherapy for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumors express PD-L1 with a ≥ 50% tumor TPS with no EGFR or ALK positive tumor mutations. • In combination with pemetrexed and PDC, for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations. • In combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults. • As monotherapy for the treatment of locally advanced or metastatic non-small cell lung carcinoma in adults whose tumors express PD-L1 with a ≥ 1% TPS and who have received at least one prior PDC regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA. • As monotherapy for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed ASCT and BV, or who are transplant-ineligible and have failed BV. • As monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing PDC • As monotherapy for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing PDC and whose tumours express PD-L1 with a CPS ≥ 10 • As monotherapy or in combination with platinum and 5-FU PDC, is indicated for the first-line treatment of metastatic or unresectable

	recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 • As monotherapy for the treatment of recurrent or metastatic head and neck • In combination with axitinib, for the first-line treatment of advanced renal cell carcinoma in adults squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after PDC
Required monitoring, under administration or during treatment period	Monitoring for signs of adverse reactions
Requirements of diagnostics or other tests	Histology: PD-L1, ALK, EGFR

Abbreviations: PD-L1: programmed death ligand 1; NSCLC: non-small cell lung cancer; TPS: tumour proportion score; EGFR: Epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; ASCT: autologous stem cell transplant; BV: brentuximab vedotin; CPS: combined positive score; 5-FU: 5-fluorouracil
Reference: SmPC available at EMA (European Medicines Agency 2020b)

5.3 The intervention

On 18th of September 2020, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) recommended approval of NIVO+IPI+PDC for the first-line treatment of metastatic NSCLC in adults whose tumours have no sensitizing EGFR mutation or ALK translocation, and final approval was given by the European Commission on 9th of November 2020 (European Medicines Agency 2020a). NIVO+IPI+PDC is the first dual immuno-oncology therapy that has shown significant overall survival in first-line NSCLC patients, regardless of histology or PD-L1 expression.

The Food and Drug Administration (FDA) approved the combination of NIVO+IPI as first-line treatment for patients with metastatic NSCLC whose tumours express PD-L1 (≥1%) (based on CheckMate 227) (FDA 2020) as well as NIVO+IPI+PDC (based on CheckMate 9LA), as first-line treatment for patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumour aberrations (FDA 2020).

Please see the following sections and Table 7 for an overview of NIVO+IPI+PDC.

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Table 7: Overview of the treatment

Proprietary name	NIVO+IPI+PDC
Generic name	Nivolumab Ipilimumab
Method of administration	IV infusion
Dosing	Metastatic NSCLC: 360 mg every 3 weeks (30-minute IV infusion) with ipilimumab 1 mg/kg every 6 weeks (30-minute IV infusion) and histology-based PDC every 3 weeks with a treatment cap of two years
Treatment duration	Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient or up to two years
Administration with other medicines	Nivolumab and ipilimumab in combination at start of treatment with histology-based PDC Q3W for up to 2 cycles
Monitoring	Monitored continuously (at least up to 5 months after the last dose) for adverse reaction
Diagnostic testing	Histology: ALK, EGFR

Abbreviations: PD-L1: programmed death ligand 1; NSCLC: non-small cell lung cancer; TPS: tumour proportion score; EGFR: Epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; ASCT: autologous stem cell transplant; BV: brentuximab vedotin; CPS: combined positive score; 5-FU: 5-fluorouracil
Reference: SmPC available at EMA (European Medicines Agency 2020c)

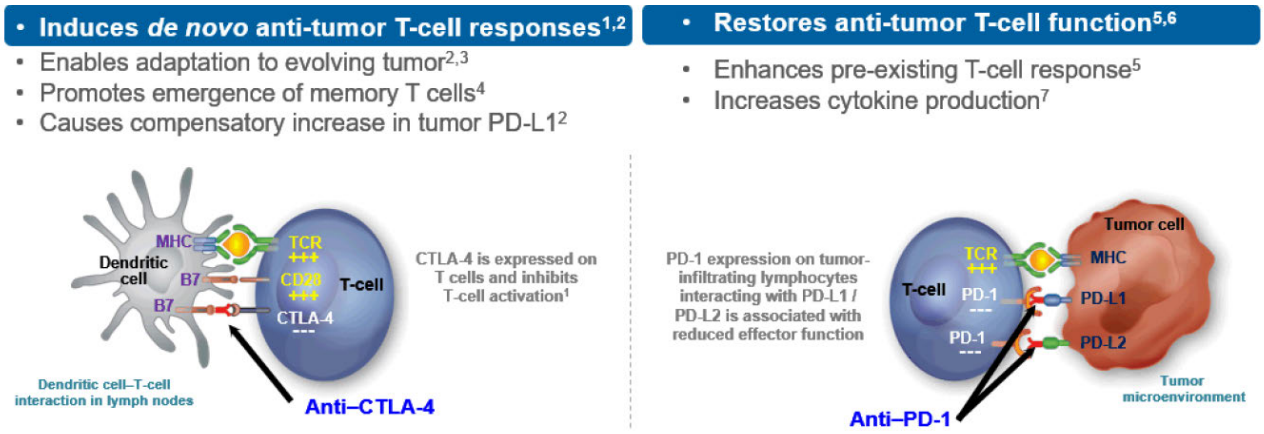
5.3.1 Mechanism of action

Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (mAb), which binds to the checkpoint inhibitor;programmed cell death receptor-1 (PD-1) and blocks its interaction with programmed cell death ligand-1 (PD-L1) and PD-L2. PD-1 is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion (Bristol-Myers Squibb 2020d). Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth (Bristol-Myers Squibb 2020d).

Cytotoxic T-lymphocyte-associated protein (CTLA-4) is a negative regulator of T-cell activity. Ipilimumab is a human immunoglobulin G1κ (IgG1κ) mAb that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumour infiltrating T-effector cells (Bristol-Myers Squibb 2020d). Inhibition of CTLA-4 signalling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumour immune response.

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumour responses in metastatic melanoma and advanced RCC (Bristol-Myers Squibb 2020d). In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in increased anti-tumour activity (Bristol-Myers Squibb 2020d) (see Figure 1).

Figure 1: Mechanisms of action of ipilimumab and nivolumab



Reference: (European Medicines Agency 2020c)

5.3.2 Proof of concept: nivolumab plus ipilimumab with limited platinum doublet chemotherapy

Nivolumab and ipilimumab are immune checkpoint inhibitors designed to target separate, distinct, and complementary checkpoint pathways (PD-1 and CTLA-4), activating the body's natural immune response to recognize and attack cancer cells (Table 8) (Weber 2009, Pardoll 2012, Das 2015, Wei 2018, Wei 2019). Ipilimumab (anti-CTLA-4) induces de novo anti-tumour T-cell responses by enabling adaptation to the evolving tumour, promotes the emergence of memory T-cells and induces a compensatory increase in tumour PD-L1 (Pardoll 2012, Das 2015, Wei 2018, Wei 2019), while nivolumab (anti-PD-1) restores anti-tumour T-cell function by enhancing pre-existing T-cell response and increasing cytokine production (Hamanishi 2007, Brahmer 2010, Wang 2014).

Table 8: Nivolumab and ipilimumab: mechanism of action for dual immune checkpoint blockade

Ipilimumab (anti-CTLA-4)	Nivolumab (anti-PD-1)
Induces de novo anti-tumour T-cell responses	Restores anti-tumour T-cell function (Brahmer 2010, Wang 2014)
Enables adaptation to evolve tumour Promotes emergence of memory T-cells Causes compensatory increase in tumour PD-L1	Enhances pre-existing T-cell response (Wang 2014) Increase cytokine production (Hamanishi 2007)

Source: (Hamanishi 2007, Weber 2009, Brahmer 2010, Pardoll 2012, Wang 2014, Das 2015, Wei 2018, Wei 2019)

Nivolumab and ipilimumab have a history of demonstrating durable benefit in other tumours. Dual checkpoint blockade with nivolumab and ipilimumab met its primary end points in Phase 3 clinical trials in previously untreated metastatic melanoma (CheckMate067) and previously untreated advanced RCC (CheckMate214), as well as most recently unresectable malignant pleural mesothelioma (CheckMate743), resulting in approvals for both indications by the US FDA and the EMA (Larkin 2015, Motzer 2018, Bristol-Myers Squibb 2020d, European Medicines Agency 2020c, Baas 2021).

In metastatic melanoma (CheckMate 067), nivolumab plus ipilimumab demonstrated durable responses and long-term survival benefits over IO monotherapy (Larkin 2019). The median duration of response (mDOR) had not been reached in the nivolumab plus ipilimumab and nivolumab groups and was 14.4 months in the ipilimumab group (Larkin 2019). Median overall survival (mOS) and median progression free survival (mPFS) at 5-year follow-up in both nivolumab groups demonstrated statistically significantly improvements compared to the ipilimumab group (P<0.001): a mOS of

over 60.0 (95% CI, 38.2-NR) and a mPFS of 11.5 (95% CI, 8.7-19.3) months in the nivolumab plus ipilimumab group, 36.9 (95% CI, 28.2-58.7) and 6.9 (95% CI, 5.1-10.2) months in the nivolumab only group, and 19.9 (95% CI, 16.8-24.6) and 2.9 (95% CI, 2.8-3.2) months in the ipilimumab only group (Larkin 2019). Although the trial was not designed for a formal statistical comparison between both nivolumab groups, a pre-specified descriptive analyses showed clear numerical trends favouring OS (hazard ratio (HR): 0.83, 95% CI, 0.67-1.03) and PFS (HR: 0.79, 95% CI, 0.64-0.96) in the combination group as compared to nivolumab alone, which demonstrates the contribution of components (Figure 2) (Larkin 2019). In addition, nivolumab plus ipilimumab treatment lead to a median treatment-free interval (time from end of first-line to start of second-line therapy) 9 times longer than both nivolumab and ipilimumab monotherapies (18.1 months vs. 1.8 months and 1.9 months, respectively), and was well-tolerated, as patients maintained the same level of health-related quality of life (HRQoL) at 5-year follow-up relative to that at baseline (Larkin 2019). The superior efficacy observed with nivolumab plus ipilimumab as compared with nivolumab alone in CheckMate 067 was accompanied with a higher incidence of Grade 3/4 treatment-related adverse events (TRAEs) in the combination arm; however, these typically resolved in under 4 weeks and patients' HR-QoL was maintained over the 5-year follow-up period, even after treatment discontinuation (Figure 2) (Larkin 2019).

In addition, a four year update of CheckMate 067 by Hodi et al. 2018 included a separate post-hoc analysis in the NIV + IPI treated patient group, both progression-free survival and overall survival outcomes were similar at 4 years regardless of whether patients discontinued treatment early because of treatment-related adverse events. In the NIV + IPI treated patient group, median progression-free survival was 11·1 months (95% CI 6·9–26·7; 43 events in 74 patients) and median overall survival was not reached (95% CI 30·5–not reached; 35 events in 74 patients) in patients who discontinued because of treatment-related adverse events during the induction phase, and 8·6 months (95% CI 5·3–13·2; 120 events in 187 patients) and 37·1 months (25·1–not reached; 98 events in 187 patients), respectively, in patients who did not discontinue treatment because of a treatment-related adverse event. 4-year progression-free survival was 35% (95% CI23−47) in patients who discontinued NIVO+IPI+PDC early because of treatment-related adverse events during the induction phase, and 30% (23−37) in those who did not discontinue treatment because of a treatment-related adverse event, and 4-year overall survival was 54% (95% CI 42−64) vs. 46% (39−54),respectively (Hodi 2018).

[redacted]

[redacted]

Similarly, at a median follow-up of 25.2 months in CheckMate 214, nivolumab plus ipilimumab significantly reduced the risk of death by 37% when compared to sunitinib in patients with in intermediate/poor risk RCC (mOS: NR and 26.0 months, respectively; HR:0.63, p<0.001) (Motzer 2018). Patients also experienced better HRQoL and symptom control compared to sunitinib. HR-QoL benefits of nivolumab plus ipilimumab over sunitinib were observed early during the nivolumab plus ipilimumab induction and generally maintained throughout the treatment period, including during maintenance with nivolumab monotherapy (Motzer 2018).

In recent landmark analysis of CheckMate 214 at follow-up greater than 42 months, the association of AEs at 6 months with long-term survival was assessed in the NIVO+IPI arm among 493 ITT patients at risk. OS outcomes were similar between patients with immune-related AEs (n=422) vs. those without (n=71) and were similar between patients who discontinued therapy due to any-grade treatment-related AEs (n=85) vs. those who did not (n=408) , indicating that these AEs did not negatively affect long-term OS (Motzer 2020).

In CheckMate 227, at the 3-year DBL, nivolumab plus ipilimumab demonstrated a 21% reduction in the risk of death, compared to PDC alone, in NSCLC patients with PD-L1 expression ≥1% (HR: 0.79, 95% CI: 0.67–0.93) (Figure 3) (Ramalingam 2020). The median OS was 17.1 months in the NIVO+IPI group and 15.7 months in the NIVO monotherapy group compared to 14.9 months in the PDC group; 3-year OS rates were 33% (NIVO+IPI), 29% (NIVO), and 22%, respectively (Figure 3) (Ramalingam 2020). At the 4-year DBL, the OS rates were similar to the rates at the 3-year DBL; 4-year OS rates were 29% (NIVO+IPI), 21% (NIVO), and 18% (PDC) (Paz-Ares 2021a). Although the trial was not designed for a formal statistical comparison between both nivolumab groups, exploratory analyses indicated that the nivolumab plus ipilimumab combination was associated with numerical benefit across key efficacy metrics (OS, PFS, ORR, and DOR) compared with nivolumab monotherapy in PD-L1 ≥1% patients (Hellmann 2019b).

In summary, nivolumab plus ipilimumab is the first dual immunotherapy approved in NSCLC and one out of four tumours where dual checkpoint blockade with nivolumab plus ipilimumab has demonstrated significantly increased OS, durable benefit and improved HRQoL in a phase III trial, while offering a predictable and tolerable safety profile

(Hellmann 2019b, Larkin 2019, Tannir 2020). Combining nivolumab and ipilimumab in NSCLC, malignant pleural mesothelioma (MPM), RCC, and melanoma produces durable responses and survival benefits, establishing a robust body of evidence for the durability of this regimen.

Building on the benefits of nivolumab plus ipilimumab in NSCLC seen in CheckMate 227, it was hypothesized that adding limited cycles of PDC (two cycles) would provide rapid initial disease control, complementing the durability. NIVO, IPI, and PDC each have non-overlapping anti-cancer mechanisms and may have synergistic and/or added activity as combination therapy. Two cycles of PDC added during induction may be sufficient to provide a synergistic effect with NIVO+IPI by increasing tumour antigen and reducing inhibitory signal with a net effect of activating the host immune system. Furthermore, other IO plus PDC combinations that have been launched as first-line NSCLC treatments or are in late-stage development trials use four cycles of PDC, with the potential for much higher levels of PDC -related toxicities compared to limited PDC with two cycles.

5.3.3 Pack size and price

The strength, pack size, and pharmacy purchase prices (PPP) (Apotekets indkøbspris, AIP) per pack for nivolumab and ipilimumab are included in Table 9 below.

Table 9 : Strength, pack size, and pharmacy purchasing price per pack for nivolumab and ipilimumab

Treatment	Strength	Pack size	Price per pack (PPP, DKK)
Nivolumab	10 mg/ml	4 ml	3 690.69
	10 mg/ml	10 ml	9 168.23
	10 mg/ml	24 ml	22 003.74
Ipilimumab	5 mg/ml	10 ml	25 653.53
	5 mg/ml	40 ml	102 385.55

Abbreviations: DKK, Danish Krona; PPP, pharmacy purchasing price.
Source: (Danish Medicines Agency)

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6. Literature search and identification of efficacy and safety studies

To populate the scenario analyses where NIVO+IPI+PDC is compared against all relevant comparators according to Danish clinical practice, a systematic literature review (SLR) was conducted to identify all randomized-controlled trials (RCT) involving NIVO (with or without IPI) and relevant comparators in the first-line treatment of metastatic NSCLC. The SLR was conducted in March 2020 and a total of 11,697 records were screened by two reviewers and 225 full-texts were assessed for inclusion. In the end, 67 unique RCTs were included in the core SLR.

Additional insight into the SLR is presented in Appendix A Literature search for efficacy and safety of intervention and comparator(s) . For a comprehensive overview of the SLR, please the separate Appendix O Systematic literature review report.

6.1 Identification and selection of relevant studies

The search terms comprised disease terms, a study design filter and intervention terms. All identified studies were evaluated against predefined eligibility criteria. For RCTs deemed eligible, data relating to the study design, enrolled patients, and study outcomes were extracted. Each RCT was rated according to published criteria examining its internal and external validity.

6.1.1 Population

The target population of the SLR broadly aligns with the CheckMate 227 trial, as the trial form the key evidence base for nivolumab (with and without ipilimumab) in first-line treatment setting for NSCLC.

6.1.2 Eligibility criteria

Eligible studies for the SLR were: RCTs involving nivolumab monotherapy, nivolumab plus ipilimumab combination therapy, or relevant comparators, that enrolled subjects with advanced, metastatic (stage IV) or recurrent NSCLC with no prior systemic anticancer therapy (including PDC, targeted therapy, and IOs) for advanced, metastatic or recurrent NSCLC.

To determine the most appropriate interventions and comparators to include in the SLR, a review of treatment guidelines was conducted. Based on this review of treatment guidelines, all therapies currently recommended for first-line NSCLC for patients with good PS (0-1 or 0-2), as well as emerging IO therapies, were included in the SLR.

Eligibility criteria were specified in terms of population, intervention and comparators, outcomes and study design (PICOS).

6.1.3 Data sources

Searches were run in the databases using the OVID SP portal: Epub ahead of print, MEDLINE® and MEDLINE® in process; EMBASE; and The Cochrane Central Register of Controlled Trials (CENTRAL)

The initial search was conducted on June 2nd 2016. The search was rerun on: January 12th, 2017, October 27th, 2017 and March 15th 2018. On March 22nd, 2018 a parallel search was conducted to include S-1, atezolizumab, and pembrolizumab when combined with PDCs, including pemetrexed-based platinum combinations. Additional refreshes, to capture the full scope of comparators, were conducted in November 2018 and October 2019. On March 14th 2020, the final refresh was run. On April 1st 2020 a search for the additional comparators camrelizumab and tislelizumab was conducted. A tabular summary of these searches is as well as the seach string details are provided in the separate document Appendix O Systematic literature review report.

With regards to conference abstracts, a summary of the conferences for inclusion is provided in the Appendix O Systematic literature review report. To complement the search of published trials, an electronic search of conference

proceedings (and hand search for those conferences that were not indexed in EMBASE) was conducted to identify conference abstracts for the last three years.

In order to identify any on-going trials expected to report in the next year, searches were run in ClinicalTrials.gov and World Health Organization (WHO) International Clinical Trials Registry Platform Search Portal. By limiting the search to studies last updated from October 2019, it is assumed that studies completed before this date would have published their results by now, and if they have not, it is likely that no results will ever be published. It was anticipated that a proportion of completed studies would have been published and will be retrieved in the review of full papers.

Where data on treatment-related adverse events (TRAEs) were not available in the published literature, the European Public Assessment Reports (EPAR) were used as a source of information.

Further, an updated manual search was conducted in 2020, to capture any additional recently updated data for the identified comparators.

6.1.4 Study selection

All abstracts, and thereafter selected full text articles, were reviewed according to the eligibility criteria, by two experienced systematic reviewers, with any studies that were queried were referred to a third reviewer for a consensus.

A preferred reporting of items for systematic reviews and meta-analyses (PRISMA) flow diagram indicating the number of studies included and excluded at each stage of the review process was generated (Hutton) (Figure 4)

All studies that meet the inclusion criteria underwent data extraction, which were also validated by a second extractor.

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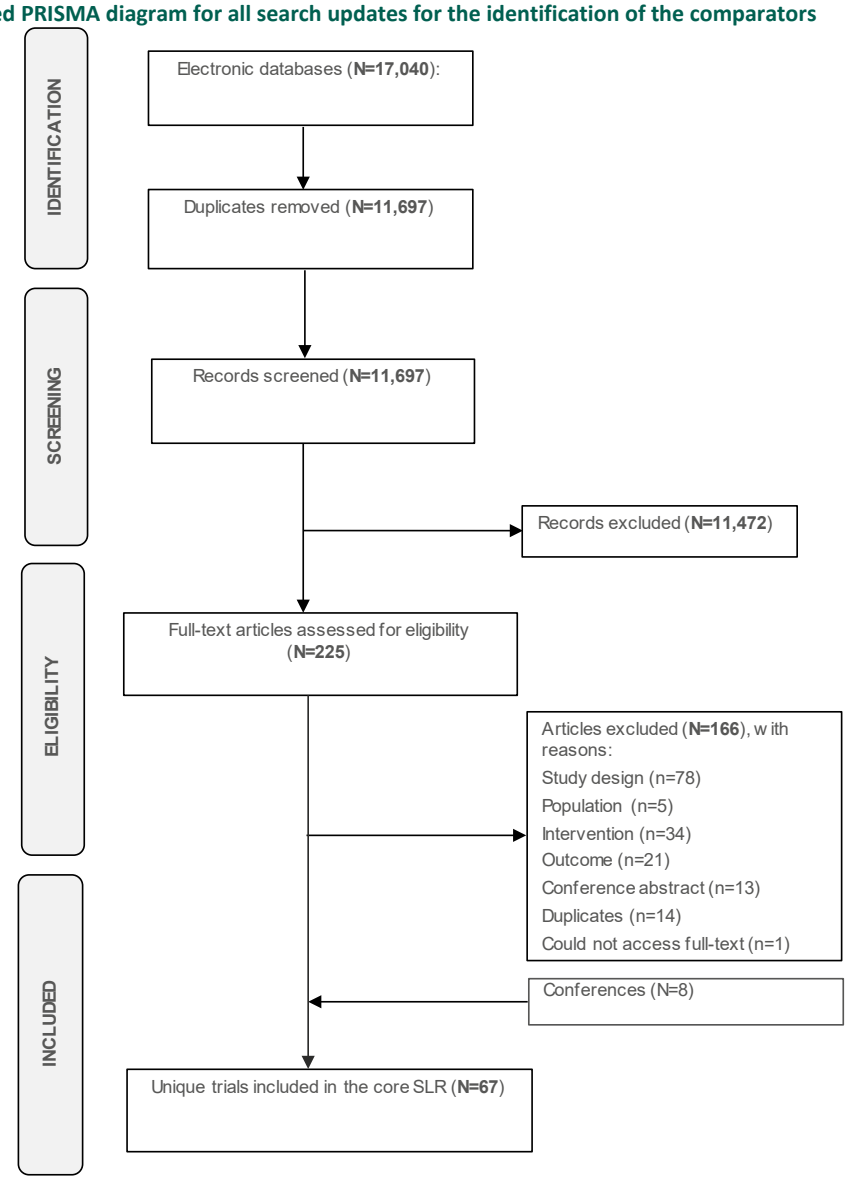
Figure 4: Consolidated PRISMA diagram for all search updates for the identification of the comparators



Abbreviations: SLR = systematic literature review; WHO = World Health Organisation

6.1.5 Strengths and limitations of SLR

The strength of this SLR lies in the extremely large body of evidence identified (total number of randomized advanced NSCLC patients, over 25,000 patients). This SLR had no language restrictions and no time limits. Evidence from conferences and registers was also sought in addition to peer-reviewed publications to capture the breadth of all new up and coming research in advanced NSCLC. However, the SLR did not capture grey literature, such as EPAR and SmPC documents; these documents were, thus, identified through hand searches.

A potential limitation of this SLR is the fact that the patients included all originated from clinical trials, and are thus not entirely representative of the real-world population of metastatic NSCLC. Patients had less comorbidities (such as other cancer, autoimmune disease, etc) and also less involvement of untreated or uncontrolled brain metastases (most studies allowed brain metastases only if they were treated and under control).

6.2 List of relevant studies

Out of the 67 included studies, six trials were identified to be relevant to as they include treatment regimens that had regulatory approval in Denmark, and for which the control arm of the trial involved a PLAT-based PDC.

- CheckMate 9LA
- CheckMate 227
- KEYNOTE 024
- KEYNOTE 042
- KEYNOTE 407
- KEYNOTE 189

As there has been updated data cuts presented for CheckMate 9LA, CheckMate 227, KEYNOTE 189, KEYNOTE 407, since the time the SLR was conducted, later data cuts of the identified trials have been sourced through hand searches. Table 10 below presents the details of the studies that have been included in the ITC, using the most up-to-date data available for each given endpoint. See Appendix B Main characteristics of included studies for detailed information about included studies.

Table 10: Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of studies (start and expected completion date)	Used in comparison of*
Paz-Ares et al. Lancet Oncol 2021 Reck et al. ESMO Open 2021	CheckMate 9LA	03215706	July 20, 2017-November 20, 2020	• PDC • pembrolizumab+platinum+pemetrexed • pembrolizumab monotherapy • pembrolizumab+ carboplatin+(nab) paclitaxel
Hellmann (2019b) Paz-Ares et al. J Thor Oncol 2021	CheckMate 227	02477826	August 5, 2015 – August 23, 2022	• PDC (extrapolations)
Brahmer et al. WCLC 2017	KEYNOTE 024	02142738	August 25, 2014-May 31, 2021	CheckMate 9LA vs pembrolizumab monotherapy
Mok et al. ELCC 2019	KEYNOTE 042	02220894	October 30, 2014-March 7, 2022	CheckMate 9LA vs pembrolizumab monotherapy
Rodriguez-Abreu et al. ASCO 2020	KEYNOTE 189	02578680	January 15, 2016-March 7, 2022	CheckMate 9LA vs pembrolizumab+platinum+pemetrexed
Paz-Ares et al. JTO 2020	KEYNOTE 407	02775435	June 9, 2016-February 15, 2022	CheckMate 9LA vs pembrolizumab+ carboplatin+(nab) paclitaxel

References: (Brahmer 2017, Hellmann 2019b, Mok 2019b, Reck 2020c, Rodriguez-Abreu 2020, Paz-Ares 2021a)

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7. Efficacy and safety

7.1 Efficacy and safety of nivolumab plus ipilimumab in combination with two cycles of platinum doublet chemotherapy vs. chemotherapy alone for patients with non-small cell lung cancer

The efficacy of NIVO+IPI+PDC vs. PDC alone as first-line treatment in patients with advanced NSCLC regardless of PD-L1 expression and histology has recently been investigated in the open-label, multicenter, randomized phase 3 trial, CheckMate 9LA (European Medicines Agency 2020a, Paz-Ares 2021a).

CheckMate-227 is an open-label, multi-part, randomized phase 3 trial conducted to evaluate different NIVO-based regimens vs. PDC in subjects with stage IV or recurrent NSCLC who had not received previous systemic anticancer therapy for advanced or metastatic disease (Hellmann 2019b).

The above clinical trials are described below and the details of the main characteristics are found in Appendix B Main characteristics of included studies.

7.1.1 Relevant studies

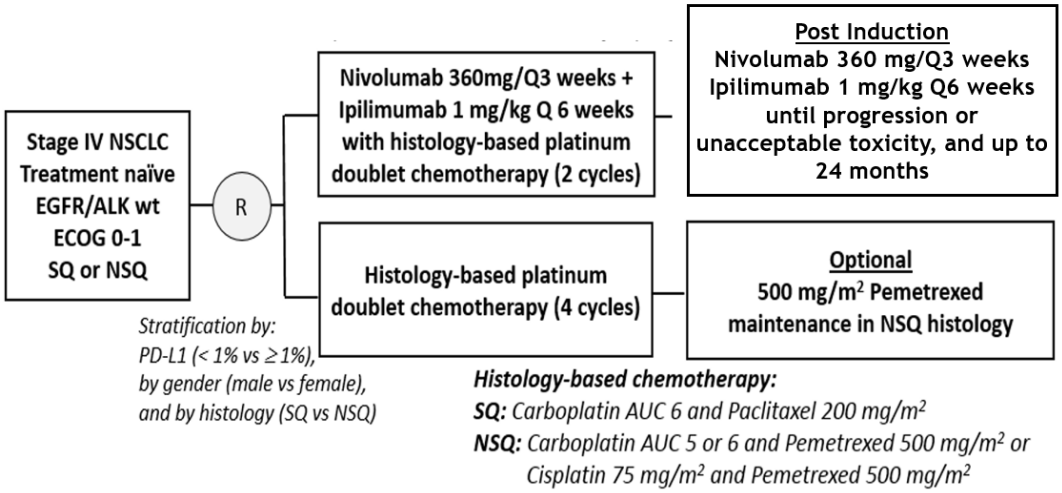
7.1.1.1 Study CheckMate-9LA

CheckMate-9LA (CheckMate9LA) is an open-label, multicentre, randomized phase 3 trial conducted to evaluate NIVO+IPI+PDC vs. PDC alone as a first-line treatment in patients with advanced NSCLC regardless of PD-L1 expression and histology (Reck 2020a). Baseline demographics and disease characteristics for all randomized subjects were balanced across the treatment groups (see Appendix B Main characteristics of included studies).

7.1.1.1.1 Study design

The study design diagram for CheckMate-9LA is provided in Figure 5 (European Medicines Agency 2020a).

Figure 5: CheckMate 9LA study design



Abbreviations: ALK: anaplastic lymphoma kinase; BICR: blinded independent central review; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; IHC: immunohistochemistry; NSCLC: non-small cell lung cancer; NSQ: non-squamous; ORR: overall response rate; PD-L1: programmed cell death ligand-1; PFS: progression-free survival; PS: performance status; Q3: every three; Q6: every six; SQ: squamous; TMB: tumor mutational burden.Source: (European Medicines Agency 2020a)

In CheckMate 9LA, patients were randomized (1:1) to one of the following arms:

- NIVO 360 mg Q3W plus IPI 1 mg/kg Q6W plus histology-based PDC Q3W for up to 2 cycles
- Histology-based PDC Q3W for up to 4 cycles

In both arms of the trial, patients were stratified according to tumour histologic features (SQ vs. NSQ) as well as PD-L1 expression (<1% vs. ≥ 1%) and sex.

Histology-based PDC consisted of the following:

- NSQ: pemetrexed (500 mg/m2) + cisplatin (75 mg/m2) or carboplatin (AUC 5 or 6), Q3W
    - Patients in the control arm with stable disease or who had a response after 4 cycles of PDC could continue with maintenance pemetrexed
- SQ: carboplatin (AUC6) + paclitaxel (200 mg/m2), Q3W

All treatments continued until disease progression, unacceptable toxicity, or completion of study as per protocol (defined as treatment for up to 2 years for immunotherapy). Crossover between treatment arms within the study was not permitted (European Medicines Agency 2020a).

7.1.1.1.2 Study population and patient characteristics

Key eligibility criteria for CheckMate 9LA are listed below (European Medicines Agency 2020a):

- Age ≥18 with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–1
- Histologically confirmed SQ or NSQ stage IV/recurrent NSCLC
- No prior systemic anticancer therapy as primary therapy for advanced or metastatic disease
- No known EGFR mutations or ALK translocations sensitive to targeted therapy
- No central nervous system (CNS) metastases, unless treated and neurologically returned to baseline for ≥2 weeks before randomization
    - Prior palliative radiotherapy to non-CNS lesions must have been completed ≥2 weeks before randomization
- Prior adjuvant or neoadjuvant PDC or prior definitive chemoradiation for locally advanced disease was allowed for up to 6 months before enrolment

7.1.1.1.3 Study endpoints

The primary endpoint of CheckMate 9LA was OS in the ITT population (European Medicines Agency 2020a, Paz-Ares 2021a).

Hierarchical secondary endpoints were PFS and ORR for NIVO+IPI+PDC vs. PDC alone. Other secondary endpoints were OS, PFS, and ORR in patients based on PD-L1 expression levels and tumour mutational burden (European Medicines Agency 2020a, Paz-Ares 2021a).

Exploratory endpoints were safety, tolerability, patient-reported outcomes (PRO), and progression-free survival until next line of treatment (PFS2) (European Medicines Agency 2020a).

7.1.1.2 Study CheckMate-227, Part 1

CheckMate-227 (CA209-227) is an open-label, two-part, randomized phase 3 trial conducted to evaluate different NIVO-based regimens vs. PDC in subjects with stage IV or recurrent NSCLC who had not received previous systemic anticancer therapy for advanced or metastatic disease (Hellmann 2019b). For additional details, see Appendix B Main characteristics of included studies. Baseline demographics and disease characteristics for all randomized subjects were balanced across the treatment groups (Appendix L Baseline characteristics and study design CheckMate 227).

7.1.1.2.1 Study design

In Part 1A, patients with ≥1% PD-L1 expression were randomized (1:1:1) to one of the following (Hellmann 2019b) (Figure 6):

- NIVO 3 mg/kg Q2W plus IPI 1 mg/kg Q6W
- NIVO monotherapy 240 mg Q2W
- Histology-based PDC Q3W for up to 4 cycles

In Part 1B, patients with <1% PD-L1 expression were randomized (1:1:1) to one of the following (Hellmann 2019b):

- NIVO 3 mg/kg Q2W plus IPI 1 mg/kg Q6W
- NIVO 360 mg Q3W plus PDC Q3W for up to 4 cycles
- Histology-based PDC Q3W for up to 4 cycles

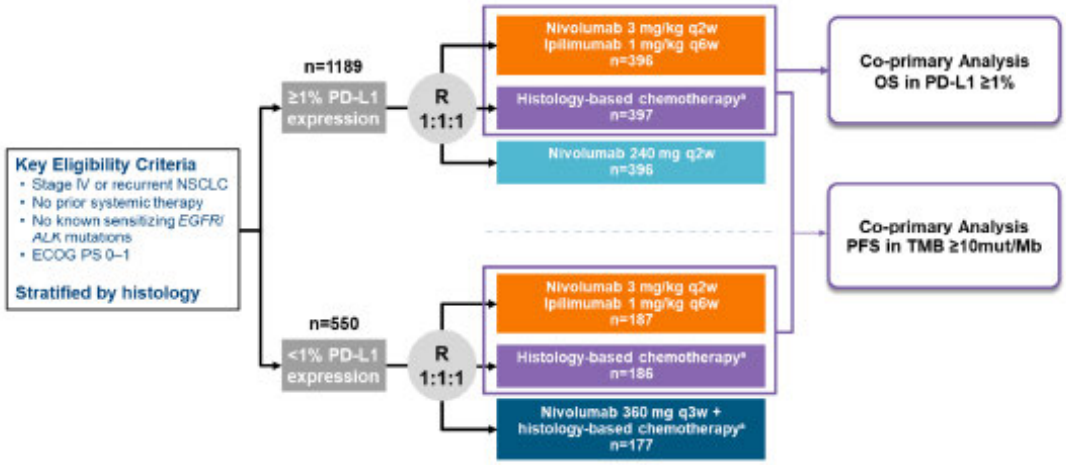
In both portions of the trial, patients were stratified according to tumour histologic features (SQ vs. NSQ) (Hellmann 2019b).

Histology-based PDC consisted of the following (Hellmann 2019b):

- NSQ: pemetrexed (500 mg/m2) + cisplatin (75 mg/m2) or carboplatin (AUC 5 or 6), Q3W for up to 4 cycles
    - Patients with stable disease or who had a response after 4 cycles of PDC or NIVO+IPI could continue with maintenance pemetrexed or pemetrexed + NIVO, respectively
- SQ: gemcitabine (1000 or 1250 mg/m2) + cisplatin (75 mg/m2), or gemcitabine (1000 mg/m2) plus carboplatin (AUC 5), Q3W for up to 4 cycles

All treatments continued until disease progression, unacceptable toxicity, or completion of study as per protocol (defined as treatment for up to 2 years for immunotherapy). Crossover between treatment arms within the study was not permitted (Hellmann 2019b).

Figure 6: CheckMate 227 Part 1 study design



[a] Squamous (SQ) histology: gemcitabine with cisplatin or gemcitabine with carboplatin
Non-squamous (NSQ) histology: pemetrexed with cisplatin or pemetrexed with carboplatin. Subjects with stable disease or response after cycle 4 could have continued pemetrexed alone as maintenance therapy until disease progression or unacceptable toxicity.

Abbreviations: ALK - anaplastic lymphoma kinase, ECOG - Eastern Cooperative Oncology Group, EGFR - epidermal growth factor receptor, IV - intravenous, mut/Mb - mutations per megabase, NSCLC - non-small cell lung cancer, OS - overall survival, PD-L1 - programmed cell death ligand 1, PFS - progression-free survival, PS - performance status, qXw - every X weeks, TMB - tumor mutational burden

Source: (European Medicines Agency 2020a)

7.1.1.2.2 Study population

Checkmate 227 included adult patients with stage IV or recurrent NSCLC. Of the 2876 subjects in Part 1, 1739 underwent randomisation where 1189 subjects were enrolled in Part 1A (PD-L1 ≥1%) and 550 in Part 1B (PD-L1 <1%) (Hellmann 2019b).

The key eligibility criteria were the following:

- Age ≥18
- ECOG PS 0–1
- Histologically confirmed SQ or NSQ stage IV/recurrent NSCLC
- No prior systemic anticancer therapy as primary therapy for advanced or metastatic disease
- No known EGFR mutations or ALK translocations sensitive to targeted therapy
- No autoimmune disease
- No CNS metastases, unless treated and neurologically returned to baseline for ≥2 weeks before randomization
    - Prior palliative radiotherapy to non-CNS lesions must have been completed ≥2 weeks before randomization
- Prior adjuvant or neoadjuvant PDC or prior definitive chemoradiation for locally advanced disease was allowed for up to 6 months before enrolment

7.1.1.2.3 Study endpoints

The co-primary endpoints in Part 1 included (Hellmann 2019b):

- OS with NIVO+IPI compared with PDC in patients with PD-L1 ≥1%
- PFS for NIVO+IPI compared with PDC in patients with TMB ≥10 mut/Mb

Secondary endpoints in the tumour PD-L1 hierarchy were (Hellmann 2019b):

- PFS for NIVO+IPI compared with PDC in patients with PD-L1 <1%
- OS with NIVO+PDC compared with PDC in patients with PD-L1 <1%
- OS with NIVO monotherapy compared with PDC in patients with PD-L1 ≥50%

Secondary endpoints in the TMB statistical hierarchy were (Hellmann 2019b):

- PFS for nivolumab compared with chemotherapy in patients with TMB ≥13 mut/Mb and PD-L1 ≥1%
- OS for NIVO+IPI compared with PDC in patients with TMB ≥10 mut/Mb

Exploratory outcomes, such as health-related quality of life (HRQOL), ORR in all randomised patients irrespective of PD-L1 expression, duration of response (DoR), safety, and OS and PFS in other subgroups, were also investigated and are listed below (Hellmann 2019b):

- HRQOL
- ORR in all randomised patients and those with PD-L1 ≥1% and <1%
- OS and ORR in patients with PD-L1 <1%
- OS in patients with PD-L1 <1%
- OS, ORR, and PFS in patients with PD-L1 ≥1% and ≥50%

7.1.2 Efficacy and safety- results by study

7.1.2.1 Results of CheckMate 9LA

For the market authorization study, CheckMate 9LA, two database locks (DBLs) are presented: 1-year (minimum follow-up time 12.7 months) and 2-year (minimum follow-up time 24.4 months for OS; 23.3 months for other outcomes). An overview of the efficacy and safety results of CheckMate 9LA is provided below. Additional details around outcomes and results are found in Appendix D Efficacy and safety results per study.

7.1.2.1.1 Overall survival in all randomized patients

7.1.2.1.1.1 1-year database lock

At the 1-year DBL, with a minimum follow-up of 12.7 months, NIVO+IPI+PDC demonstrated a 34% reduction in the risk of death compared with PDC alone (HR: 0.66, 95% CI: 0.55–0.80) (Paz-Ares 2021a). The median OS was 15.6 months (95% CI 13.9–20.0) for NIVO+IPI+PDC and 10.9 months (95% CI (9.5–12.6) for in the control group (stratified HR 0.66, 95% CI 0.55-0.80) (Paz-Ares 2021a). Separation of the Kaplan-Meier curves for OS for NIVO+IPI+PDC and PDC occurred early and the difference grew rapidly, such that OS rates at 6 months were 81% vs. 73% and at 1 year were 63% vs. 47%, respectively Figure 7 (Paz-Ares 2021a). No crossing of the overall survival curves was observed in CheckMate-9LA, showing the rapid initial disease control resulting from the use of nivolumab plus ipilimumab with limited

chemotherapy (Paz-Ares 2021a). As a result, a greater difference in overall survival between the experimental group and control group was observed in CheckMate 9LA (HR of 0·66 at a minimum follow-up of 12·7 months) than in CheckMate 227 (HR of 0·73 at a minimum follow-up of 29·3 months) (Paz-Ares 2021a).

Subsequent systemic therapy was received by 111 (31%) patients in the NIVO+IPI+PDC and 144 (40%) patients in the PDC arm. Subsequent immunotherapy was received by 19 (5%) of 361 patients in the experimental group and 108 (30%) of 358 patients in the control group, and subsequent PDC by 105 (29%) of 361 patients and 80 (22%) of 358 patients, respectively (Paz-Ares 2021a).

7.1.2.1.1.2 2-year database lock

At the 2-year DBL, with a minimum follow-up of 24.4 months, the median OS was 15.8 months (95% CI 13.9–19.7) for NIVO+IPI+PDC and 11.0 months (95% CI 9.5–12.7) for the PDC alone group (HR 0.72, 95% CI 0.61-0.86); see Figure 8 (Reck 2021). The 2-year OS was 38% versus 26% for NIVO+IPI+PDC versus PDC alone, respectively (Reck 2021).

Subsequent systemic therapy was received by 122 (34%) patients in the NIVO+IPI+PDC and 163 (46%) patients in the PDC arm, all randomized patients. Subsequent immunotherapy was received by 26 (7%) of 361 patients in the NIVO+IPI+PDC group and 127 (36%) of 358 patients in the PDC group, and subsequent PDC by 114 (32%) of 361 patients and 85 (24%) of 358 patients, respectively (Reck 2021).

7.1.2.1.2 Overall survival in pre-defined subgroups in all randomized patients

7.1.2.1.2.1 1-year database lock

At the 1-year DBL, the OS benefit demonstrated by NIVO+IPI+PDC compared to PDC in CheckMate 9LA was consistent across most subgroups, including histology (SQ/NSQ) and PD-L1 status (PD-L1 ≥1%, ≥50%, 1-49%, <1%) (Table 11) (Paz-Ares 2021a).

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Patients with SQ and NSQ histology who received NIVO+IPI+PDC showed, respectively, 38% (HR: 0.62, 95% CI: 0.45–0.86) and 31% (HR: 0.69, 95% CI: 0.55–0.87) reductions in the risk of death compared with PDC alone (Figure 9) (European Medicines Agency 2020a, Paz-Ares 2021a). Median OS for SQ and NSQ patients were 14.5 (95% CI 13.1-19.4) and 17.0 months (95% CI 14·0–NR) for NIVO+IPI+PDC vs. 9.1 (95% CI 7.2-11.6) and 11.9 months (95% CI 9.9-14.1) for PDC, respectively (Figure 9) (Paz-Ares 2021a).

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Patients who received NIVO+IPI+PDC showed reductions in the risk of death compared with PDC alone regardless of PD-L1 status, with reductions of 38%, 36%, 39%, and 34% for patient subgroups of <1%, ≥1%, 1-49%, and ≥50% tumour PD-L1 expression, respectively please see Figure 10 and Figure 11 below (European Medicines Agency 2020a, Paz-Ares 2021a). and Figure 4A,B in Paz-Ares et al (Paz-Ares 2021a). 1-year OS rates for patients who received NIVO+IPI+PDC vs. PDC were 63% vs. 45% for PD-L1 <1%, 66% vs. 47% for PD-L1 ≥1%, 63% vs. 43% for PD-L1 1-49%, and 70% vs. 51% for PD-L1 ≥50%, see Figure 10 (Paz-Ares 2021a) and Figure 11 below (European Medicines Agency 2020a).

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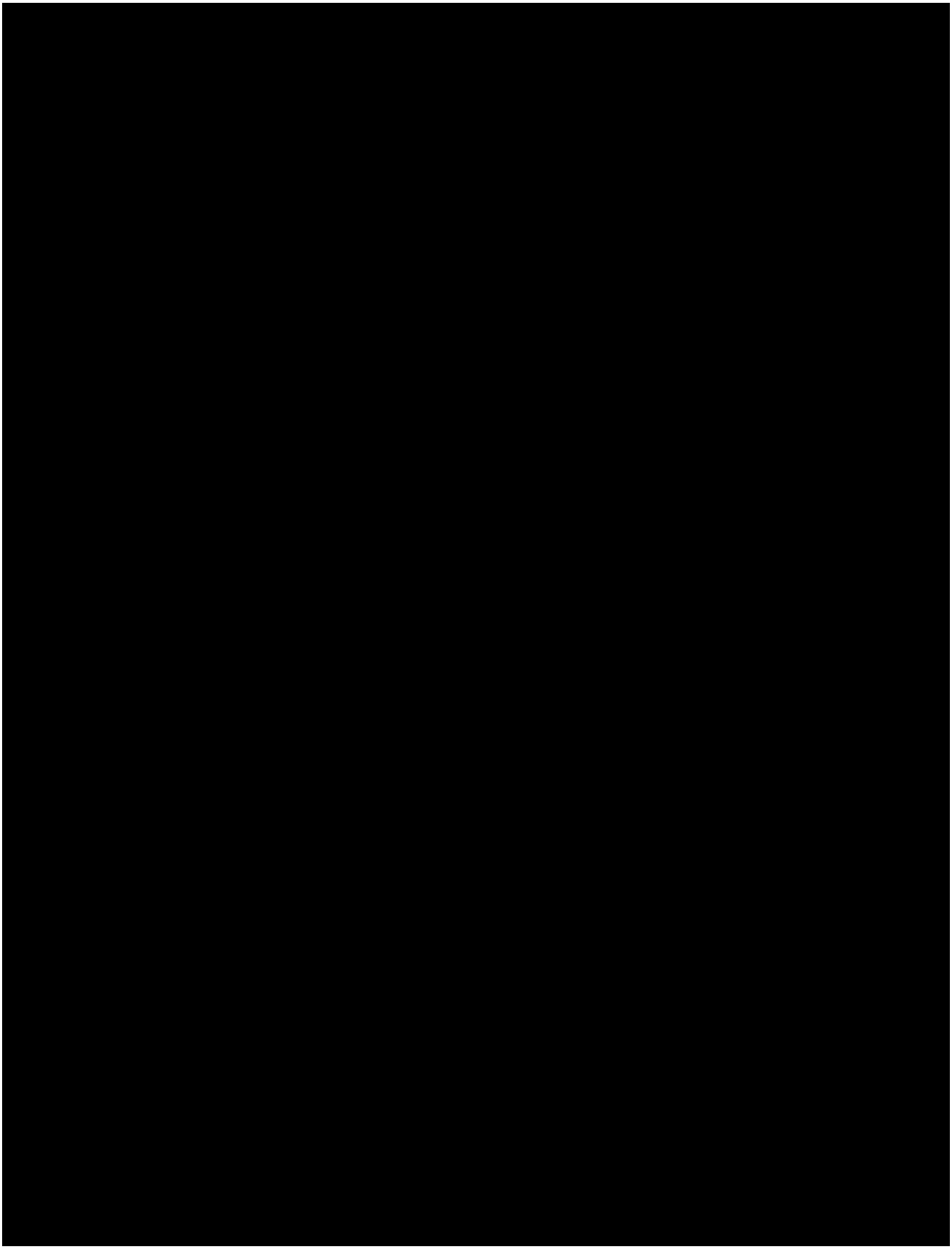

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7.1.2.1.2.2 2-year database lock

At the 2-year DBL, the OS benefit demonstrated by NIVO+IPI+PDC compared to PDC in CheckMate 9LA was consistent across most subgroups, including histology (SQ/NSQ) and PD-L1 status (PD-L1 ≥1%, ≥50%, 1-49%, <1%) (Table 12) (Reck 2021).

[redacted]

Patients with NSQ histology showed a median OS of 17.8 months (95% CI 14.1–20.7) and 12.0 months (95% CI 9.9–13.9) for NIVO+IPI+PDC and PDC alone, respectively (HR 0.78, 95% CI 0.63–0.96). Patients with SQ histology showed a median OS of 14.5 months (95% CI 13.1–19.3) and 9.1 months (95% CI 7.2–11.6) for NIVO+IPI+PDC and PDC alone, respectively (HR 0.63, 95% CI 0.47–0.85); see Figure 12 (Reck 2021).

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[redacted]

Patients who received NIVO+IPI+PDC showed reductions in the risk of death compared with PDC alone regardless of PD-L1 status. In patients with PD-L1 <1%, median OS was 17.7 months versus 9.8 months for NIVO+IPI+PDC versus PDC alone, respectively (HR 0.67, 95% CI 0.51–0.88); 2-year OS rates were 37% versus 22%, respectively (Figure 13)(Reck 2021). In patients with PD-L1 ≥1%, efficacy results were consistent with those with PD-L1 expression <1% and with all randomized patients. Median OS with PD-L1 ≥1% was 15.8 months versus 10.9 months for NIVO+IPI+PDC versus PDC alone, respectively (HR 0.70, 95% CI 0.56-0.89); 2-year OS rates were 41% versus 28%, respectively (Figure 14)(Reck 2021).

[redacted]

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Efficacy improvements in the NIVO+IPI+PDC versus the PDC alone arm both in patients with PD-L1 <1% and ≥1% were observed across non-squamous and squamous histologies. For patients with PD-L1 <1% OS HRs were 0.75 (95% CI 0.54–1.04) (Figure 15A) and 0.48 (95% CI 0.28–0.81) (Figure 15C) for the non-squamous and squamous histologies, respectively. For patients with PD-L1 ≥1%, OS HRs were 0.71 (95% CI 0.53-0.95) (Figure 15B) and 0.70 (95% CI 0.48-1.01) (Figure 15D) for the non-squamous and squamous histologies, respectively.

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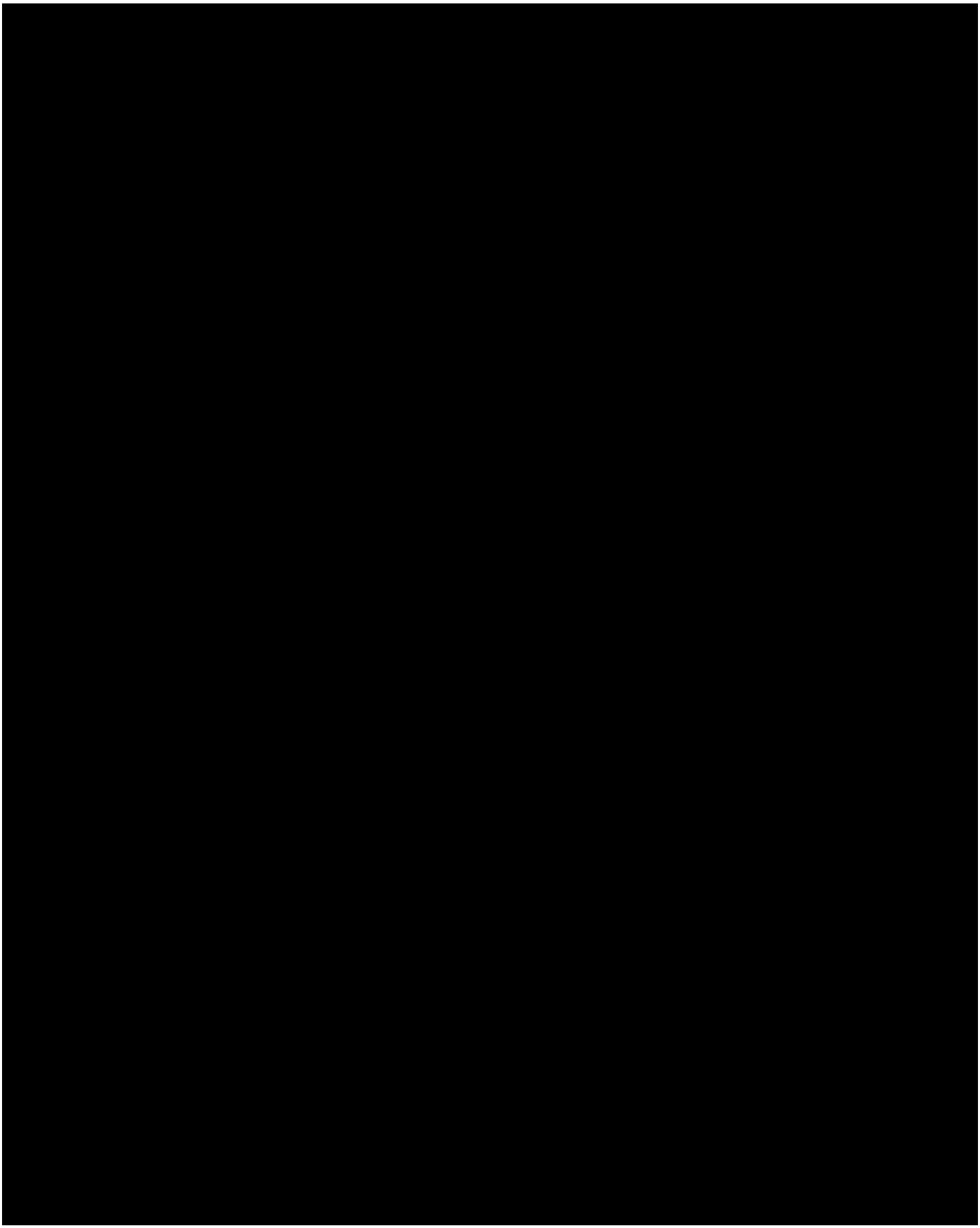

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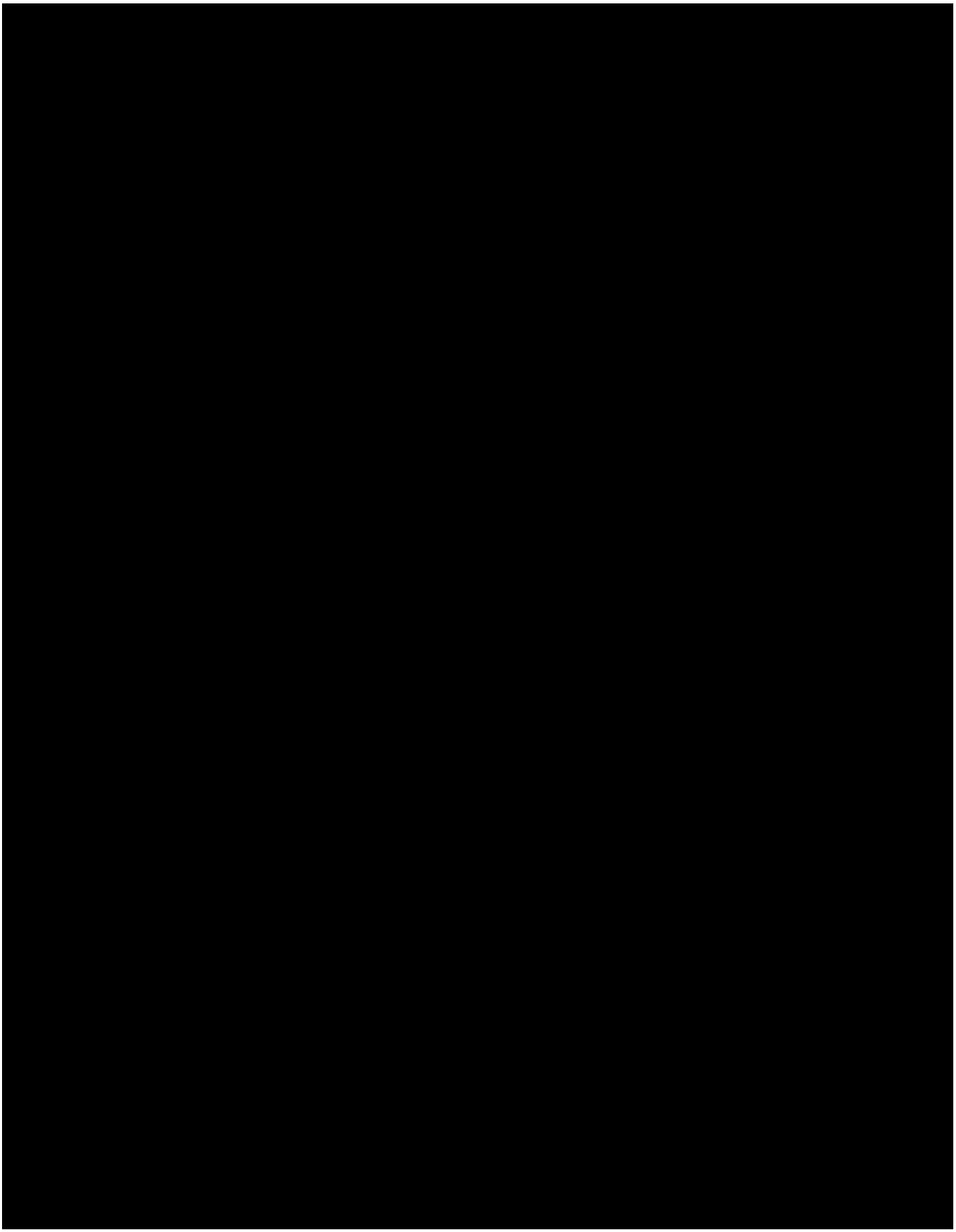

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7.1.2.1.3 Response rates and durability of response in all randomized patients

7.1.2.1.3.1 1-year database lock

At the 1-year DBL, the objective response rate (ORR) was 38.2% (95% CI 33.2-43.5) for NIVO+IPI+PDC and 24.9% (95%CI 20.5-29.7) for PDC after a minimum follow-up of 12.2 months (Table 13 below) (Paz-Ares 2021a). The percentage of patients with a complete response (CR), the disappearance of all target lesions, was 2% with NIVO+IPI+PDC vs. 1% with PDC (Table 13) (Paz-Ares 2021a).

Median duration of response (DOR) for NIVO+IPI+PDC (11.3 months, 95% CI 8.5,NR) was more than double that for PDC alone (5.6 months, 95% CI 4.4,7.5)(Table 13) (Table 2 in (Paz-Ares 2021a). However, follow-up time for DOR begins at time of response and not time from randomization, so follow-up time for responses are shorter than other outcomes, with extensive censoring after 9 months (Paz-Ares 2021a), which caused the DOR to evolve with further 2-year follow-up (see data for 2-year DBL below) (Reck 2021). At 1 year, 49% (95% CI 40-58) vs. 24% (95% CI, 14–34) of patients had an ongoing response in the experimental vs. control group, respectively. Differences between experimental and control groups in objective response rates and median durations of response were consistent across PD-L1 and histology subgroups) (Paz-Ares 2021a).

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Table 13: CheckMate 9LA; Objective response rate, time to response, and duration of response in all randomized patients (1-year database lock)

Outcome	NIVO+IPI+PDC (n=361)	PDC (n=358)
Objective responses (% [95% CI])	138 (38.2%; 33.2-43.5)	89 (24.9%; 20.5-29.7)
Best overall response, no. (%)		
Complete response	8 (2%)	4 (1%)
Partial response	130 (36%)	85 (24%)
Stable disease	164 (45%)	185 (52%)
Progressive disease	32 (9%)	45 (13%)
Could not be determined/not reported	27 (8%)	39 (11%)
Median time to response (ICR), months	2.6 (1.4-3.1)	1.5 (1.4-2.8)
Median duration of response (95%, CI), months	11.3 (8.5-NR)	5.6 (4.4-7.5)
Patients with a response who had ongoing responses		
Rate (95% CI) t 6 months	73%(65-80)	45%(34-55)
Rate (95% CI) t 12 months	49% (40-58)	24% (14-34)

Abbreviations: Chemo: chemotherapy; CI: confidence interval; DCR: disease control rate; Ipi: ipilimumab; Nivo: nivolumab; ORR: overall response rate.
Source: (Adapted from (Paz-Ares 2021a))

For duration of response, follow-up time begins at the time of response, rather than the time of randomization, which further affects the maturity of the data; as there is extensive censoring after 9 months, the DOR evolve with further 2-year follow-up (see data for 2-year DBL below) (Reck 2021). Specifically, the immature duration of response data from the NIVO+IPI+PDC arm of CheckMate 9LA may be capturing the earlier yet less durable PDC -based responses, and provide evidence to support the conjecture that more durable dual IO-based responses (via complementary mechanisms of action of anti-PD1 and CTLA-4 inhibition) may be captured after a longer duration of follow-up. Overlays of CheckMate 9LA KM curves against the three-year data from CheckMate 227 are presented in Figure 16.

7.1.2.1.3.2 2-year database lock

At the 2-year DBL, the ORR was 38.0% (95% CI 32.9–43.2) for NIVO+IPI+PDC and 25.4% (95% CI 21.0–30.3) for PDC (Table 14)(Reck 2021). The percentage of patients with CR was 3.3% with NIVO+IPI+PDC versus. 1.1% with PDC (Table 14)(Reck 2021). Four patients who had partial responses in the NIVO+IPI+PDC arm at the 1-year DBL improved to complete responses at the 2-year DBL. Median DOR was improved from the 1-year DBL for the NIVO+IPI+PDC arm and remained longer versus the PDC arm (13.0 months versus 5.6 months, respectively); 34% versus 12% of responses were ongoing at the 2-year DBL (Table 14)(Reck 2021).

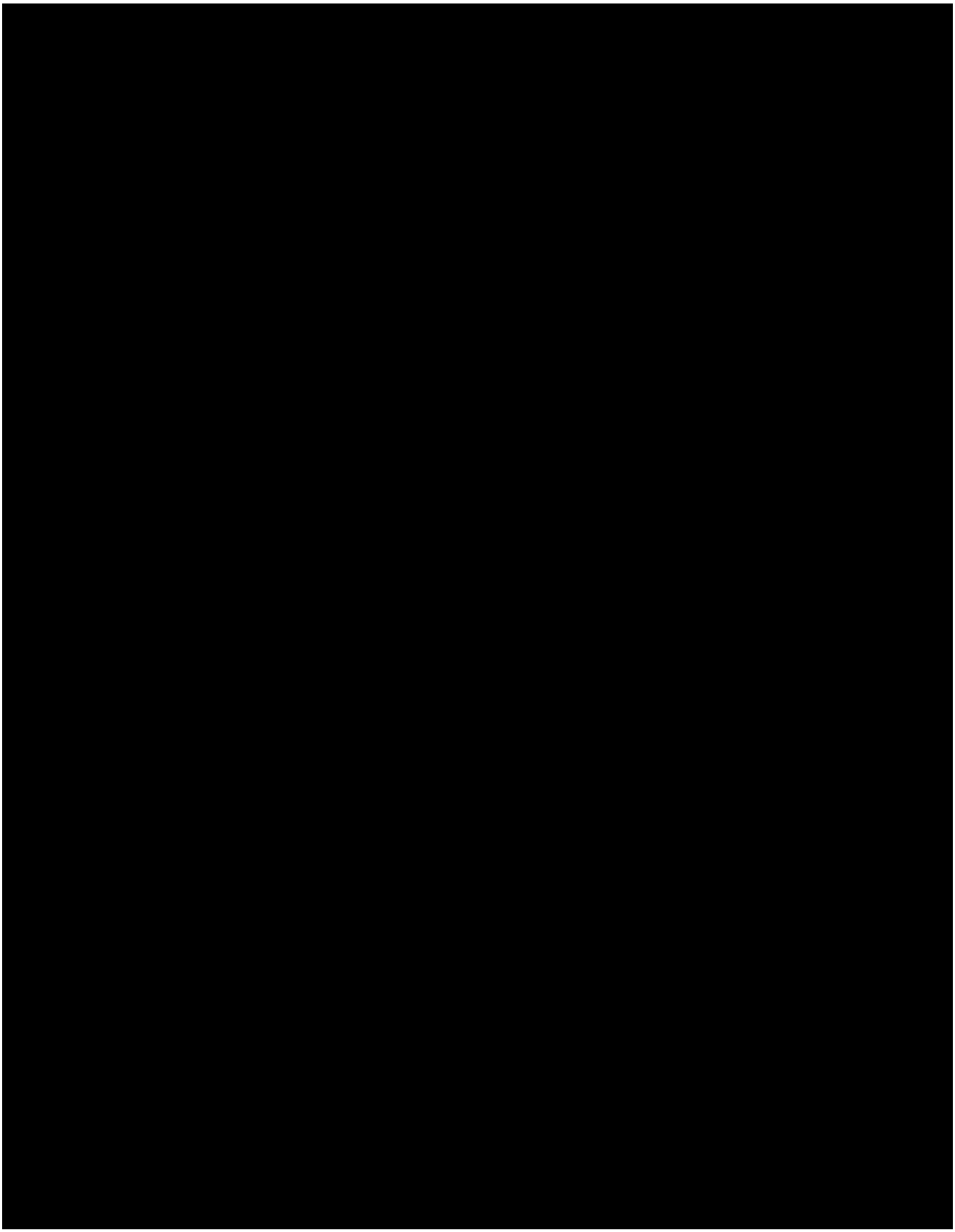
The ORR and DOR remained higher in the NIVO+IPI+PDC versus the PDC alone arm in patients with non-squamous and squamous histologies (Table 14)(Reck 2021). Simular results were observed for both PD-L1 <1% and PD-L1 ≥1% histology across the non-squamous and squamous subgroups. In patients with PD-L1 <1%, ORR was 31% versus and 20% with NIVO+IPI+PDC versus PDC alone, respectively; median DOR was 17.5 months versus 4.3 months, respectively, with 45% versus 0% of responses ongoing at the 2-year DBL (Reck 2021). In patients with PD-L1 ≥1%, ORR was 43% versus and 28% with NIVO+IPI+PDC versus PDC alone, respectively; median DOR was 11.8 months versus 5.6 months, respectively, with 33% versus 13% of responses ongoing at the 2-year DBL (Reck 2021).

Table 14: CheckMate 9LA; Objective response rate, time to response, and duration of response in all randomized patients (2-year database lock)

Outcome	NIVO+IPI+PDC (n=361)			PDC (n=358)		
Objective responses (%; 95% CI)	Overall	NSQ	SQ	Overall	NSQ	SQ
Objective responses (%; 95% CI)	137 (38.0; 32.9-43.2)	81 (32.9; 27.1–39.2)	56 (48.7; 39.3–58.2)	91 (25.4; 21.0–30.3)	56 (22.8; 17.7–28.5)	35 (31.3; 22.8–40.7)
Best overall response, no. (%)						
Complete response	12 (3.3)[a]	5 (2.0)	7 (6.1)	4 (1.1)	3 (1.2)	1 (0.9)
Partial response	125 (34.6)	76 (30.9)	49 (42.6)	87 (24.3)	53 (21.5)	34 (30.4)
Stable disease	165 (45.7)	125 (50.8)	40 (34.8)	184 (51.4)	134 (54.5)	50 (44.6)
Progressive disease	33 (9.1)	125 (50.8)	9 (7.8)	44 (12.3)	30 (12.2)	14 (12.5)
Could not be determined/not reported	26 (7.2)	16 (6.5)	10 (8.7)	39 (10.9)	26 (10.5)	13 (11.6)

Abbreviations: Chemo: chemotherapy; CI: confidence interval; DCR: disease control rate; Ipi: ipilimumab; Nivo: nivolumab; NSQ: non-squamous; ORR: overall response rate; SQ: squamous.
Note: a4 patients who had a partial response as best response at a previous 1-year DBL (12.2 months minimum follow-up for response) improved to complete responses.
Source: (Reck 2021)

[redacted] presents the DOR for the NIVO+IPI+PDC versus the PDC alone arm both in patients with PD-L1 <1% and ≥1% across non-squamous and squamous histologies. For patients with PD-L1 <1%, the median DOR was 17.5 months and 7.1 months for NIVO+IPI+PDC and PDC, respectively, for non-squamous histology ([redacted]), and 18.7 months and 2.8 months for NIVO+IPI+PDC and PDC, respectively, for squamous histology ([redacted] (Reck 2021). For patients with PD-L1 ≥1%, the median DOR was 20.1 months and 14.5 months for NIVO+IPI+PDC and PDC, respectively, for non-squamous histology ([redacted]), and 10.4 months and 4.4 months for NIVO+IPI+PDC and PDC, respectively, for squamous histology ([redacted]) (Reck 2021).



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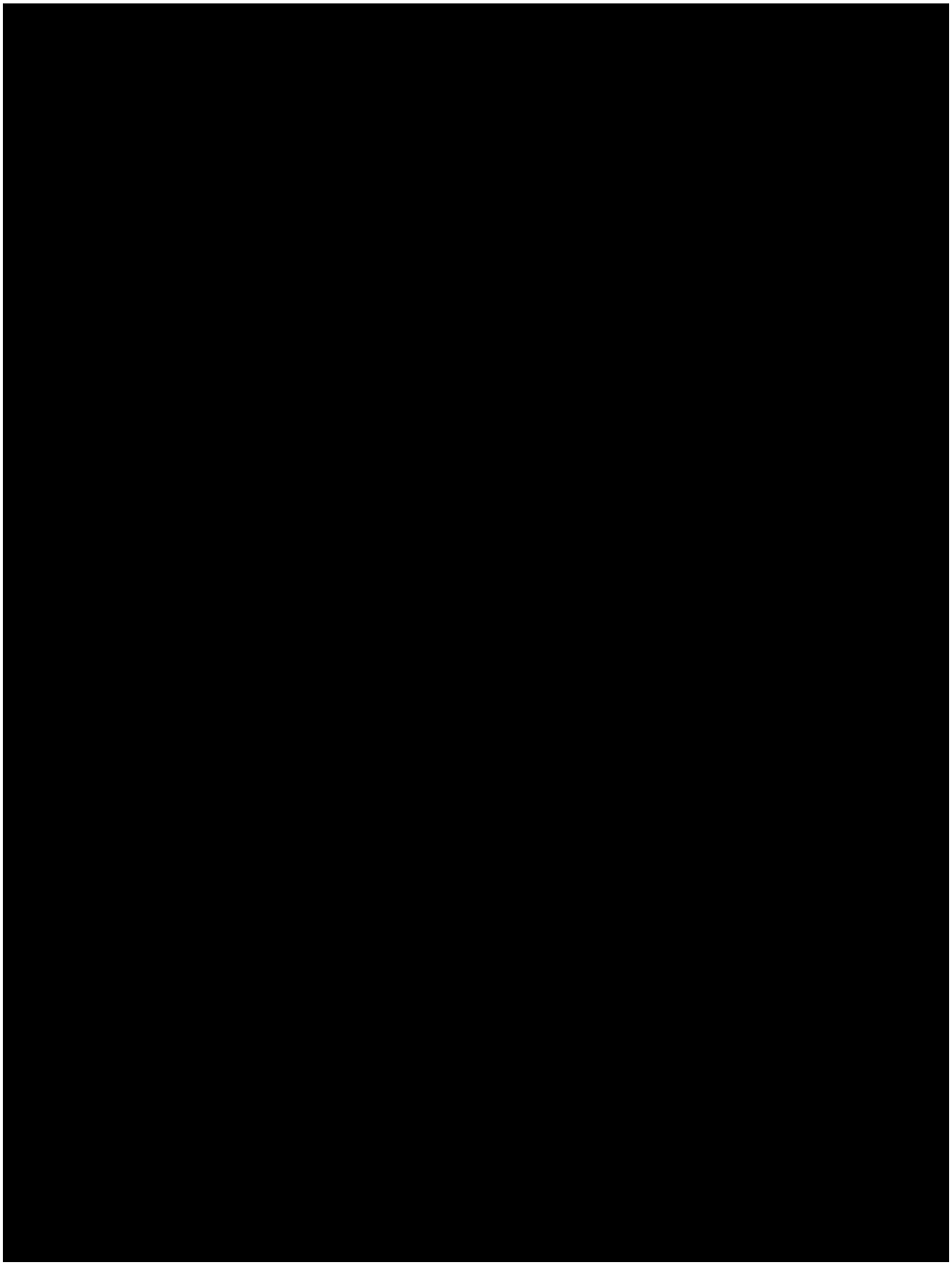

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7.1.2.1.4 Progression free survival in all randomized patients

7.1.2.1.4.1 1-year database lock

At the 1-year DBL, a reduction in the risk of disease progression or death by 32% was seen, compared to PDC (PFS HR: 0.68, 95% CI 0.57,0.82) (Paz-Ares 2021a). The median PFS was 6.7 months (95% CI 5.6,7.8) for NIVO+IPI+PDC and 5.0 months (95% CI 4.3,5.6) for PDC (Figure 18) (Paz-Ares 2021a). Separation of the Kaplan-Meier curves for PFS for NIVO+IPI+PDC over PDC occurred early, grew rapidly, and was maintained thereafter such that the PFS rates for NIVO+IPI+PDC vs. PDC at 6 months and 1 year were 51% vs. 36% and 33% vs. 18%, respectively (Paz-Ares 2021a).

The median PFS in patients with PD-L1 <1% was 5.8 months (95% CI 4.4, 7.6) for NIVO+IPI+PDC and 4.6 months (95% CI 4.2,5.6) for PDC (HR: 0.71, 95% CI 0.53,0.94) and in the PD-L1≥1% patient group the median PFS was 7.5 months (95% CI 5.6, 9.0) for NIVO+IPI+PDC and 4.7 months (95% CI 4.2, 5.6) (HR: 0.67, 95% CI 0.53,0.84) (Figure 19) (Paz-Ares 2021a).

The median PFS in patients with PD-L1 1-49% was 6.9 months (95% CI 5.6-8.0) for NIVO+IPI+PDC and 5.3 months PDC (95% CI 4.2,5.7) (HR: 0.69, 95% CI 0.51-0.94) and in the PD-L1 ≥50% patient group median PFS was 7.5 months (95% CI 4.4,13.8) for NIVO+IPI+PDC and 4.4 months (95% CI 4.1,5.4) for PDC (HR: 0.61, 95% CI 0.42, 0.89) (Figure 20) (Paz-Ares 2021a).

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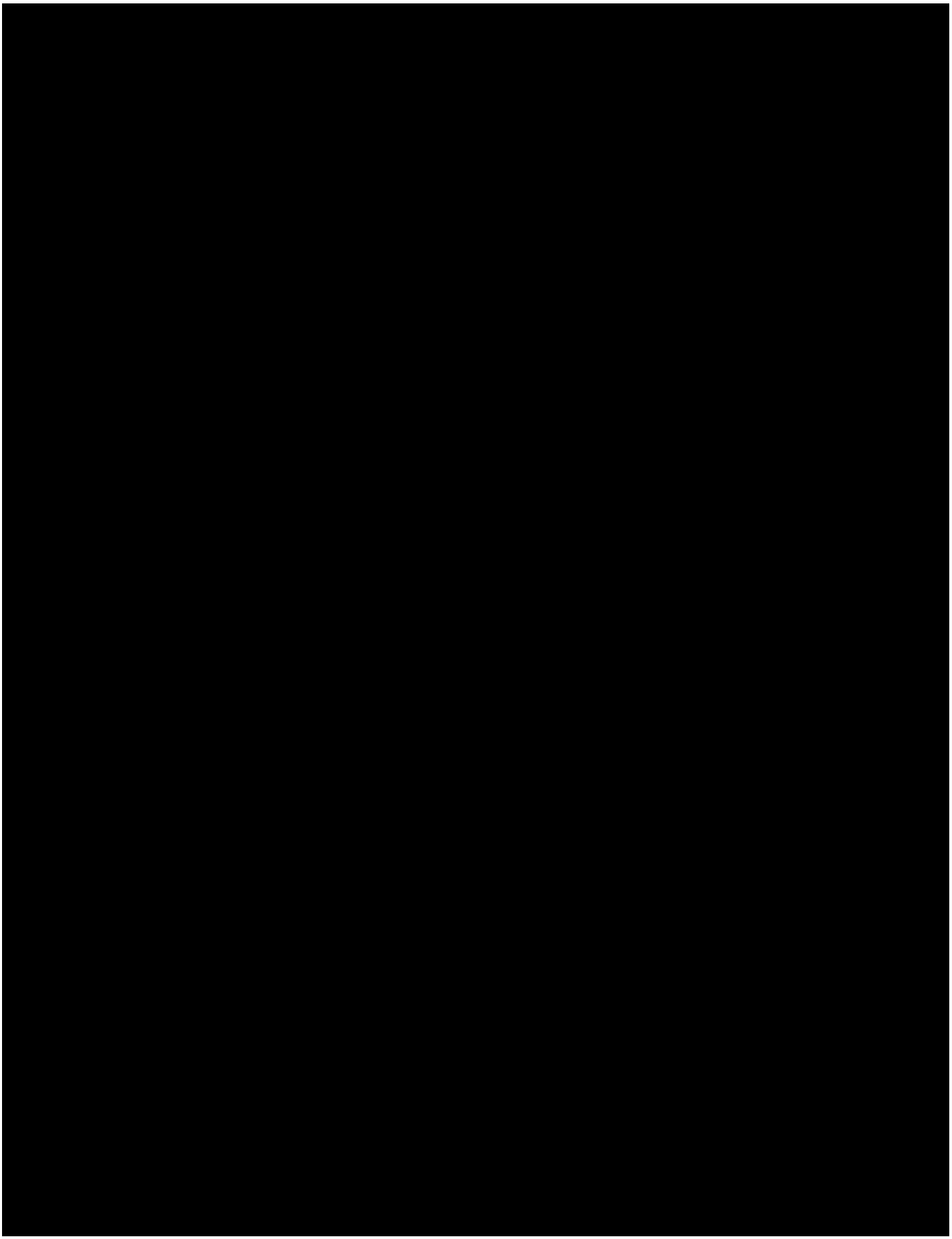

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7.1.2.1.4.2 2-year database lock

At the 2-year DBL, PFS continues to be prolonged in the NIVO+IPI+PDC versus PDC alone arm. The median PFS was 6.7 months (95% CI 5.6–7.8) for NIVO+IPI+PDC and 5.3 months (95% CI 5.6–7.8) for PDC alone, with an HR of 0.67 (95% CI 0.56-0.79); see Figure 21 (Reck 2021). The 2-year PFS rates were 20% and 8% for NIVO+IPI+PDC and PDC alone, respectively (Reck 2021).

Figure 22 presents the DOR for the NIVO+IPI+PDC versus the PDC alone arm both in patients with PD-L1 <1% and ≥1% across non-squamous and squamous histologies. For patients with PD-L1 <1%, the median PFS was 6.4 months and 5.6 months for NIVO+IPI+PDC and PDC, respectively, for non-squamous histology (HR 0.70, 95% CI 0.51–0.97)(Figure 22A), and 5.3 months and 4.2 months for NIVO+IPI+PDC and PDC, respectively, for squamous histology (HR 0.65, 95% CI 0.37–1.12) (Figure 22C) (Reck 2021).

The PFS HRs have been reported as 0.68 (95% CI 0.51–0.89) for PD-L1 expression <1% and 0.67 (95% CI 0.53–0.84) for PD-L1 expression ≥1%. For patients with PD-L1 ≥1%, the median PFS was 7.5 months and 5.4 months for NIVO+IPI+PDC and PDC, respectively, for non-squamous histology (HR 0.69, 95% CI 0.52–0.92)(Figure 22B), and 5.7 months and 4.4 months for NIVO+IPI+PDC and PDC, respectively, for squamous histology (HR 0.60, 95% CI 0.41–0.86)(Figure 22D) (Reck 2021).

7.1.2.1.5 Patient reported outcomes in all randomized patients

7.1.2.1.5.1 1-year database lock

At the 1-year DBL in CheckMate 9LA, a combination of NIVO+IPI+PDC maintained or improved on-treatment symptom burden and overall health status compared with baseline, similar to PDC alone (Reck 2020c). Both arms showed a trend for improvement over time in lung cancer symptom scale (LCSS), average symptom burden index (ASBI), LCSS 3-Item Global Index (3-IGI), and EQ-5D-3L visual analogue scale (VAS), though respective MIDs were not reached. There was a decreased risk and delayed time to definitive deterioration in health-related quality of life with NIVO+IPI+PDC alone (Reck 2020c).

7.1.2.1.6 Treatment duration

7.1.2.1.6.1 1-year database lock

At the 1-year DBL, the median duration of therapy was 6.1 months (IQR, 2.7 to 13.5) with NIVO+IPI+PDC and 2.4 months (IQR, 2.0 to 5.3.) with PDC. The median number of doses of nivolumab and received as combination therapy was 9.0 (IQR, 4.0 to 19.0) and 4.0 (IQR, 2.0 to 10.0), respectively (Paz-Ares 2021a). The most common reason for treatment

discontinuation was disease progression (175 [49%] of 358 patients in the experimental group vs. 160 [46%] of 349 in the control group (Paz-Ares 2021a).

7.1.2.1.6.2 2-year database lock

At the 2-year DBL, the median duration of therapy was 6.1 months (range, 0–24.4) with NIVO+IPI+PDC and 2.5 months (range, 0–34.5) with ipilimumab. The median number of doses was 9.0 (range, 1-36) for nivolumab and 4.0 (range, 1-18) for ipilimumab (Reck 2021). In the PDC alone arm, 75% of patients received four cycles of chemotherapy, where a total of 100 (29%) patients in the PDC arm had completed the full four cycles of chemotherapy without optional pemetrexed maintenance therapy. Further, 159 of 238 (67%) patients with non squamous tumor histology receiving pemetrexed maintenance (Reck 2021).

7.1.2.1.7 Safety

7.1.2.1.7.1 1-year database lock

At the 1-year DBL, NIVO+IPI+PDC was received by 358 patients with a minimum follow-up of 12.7 months. The incidence of grade 3 and 4 treatment-related adverse events was numerically higher in the experimental vs. control group (Paz-Ares 2021a). A summary of TRAEs reported in CheckMate9LA is presented in Table 15 below (Paz-Ares 2021a).

It is important to note that in this safety analysis, patients were exposed to NIVO+IPI+PDC over a median duration of therapy (DOT) that was 2.5-times higher compared to PDC (6.1 months vs. 2.4 months, respectively) (Paz-Ares 2021a).

Treatment-related adverse events (TRAE) of any grade leading to treatment discontinuation were reported in 69 (19%) patients in the experimental group (due to any of the components of the regimen; IPI alone, NIVO+IPI, or the PDC regimen) vs. 26 (7%) patients in the control group. Treatment-related adverse events of grade 3–4 leading to treatment discontinuation were reported in 58 (16%) patients in the experimental group and 16 (5%) patients in the control group (Paz-Ares 2021a).

Table 15: CheckMate 9LA; Overview of TRAEs reported (1-year database lock)

TRAE,[a] %	NIVO+IPI+PDC (n=358)		PDC (n=349)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
TRAEs leading to discontinuation of any component of the regimen	69 (19%)	58 (16%)	26 (7%)	16 (5%)
Serious TRAEs	106 (30%)	91 (25%)	62 (18%)	51 (15%)
Treatment-related deaths[b]	7 (2%)		6 (2%)	

Note: [a]Includes events reported between first dose and 30 days after last dose of study drug; [b]Treatment-related deaths in the NIVO+IPI+PDC arm (n = 7; 1 for each event) were due to acute renal failure due to chemotherapy, thrombocytopenia, pneumonitis, hepatic toxicity, hepatitis, diarrhea, sepsis, and acute renal insufficiency; treatment-related deaths in the chemo arm (n = 6; 1 for each event) were due to sepsis, anemia, pancytopenia, respiratory failure, pulmonary sepsis, and febrile neutropenia (1 grade 5 AE was reported [sudden death due to fall] as potentially treatment-related but cause of death was recorded as unknown).
Abbreviations: AE: adverse event; Chemo: chemotherapy; Ipi: ipilimumab; Nivo: nivolumab; TRAE: treatment-related adverse event.
Source: (Adapted from (Paz-Ares 2021a))

Among all patients, the most common TRAEs of any grade (present in ≥15% of patients) were nausea, anaemia, asthenia and diarrhoea (Paz-Ares 2021a). The most common types of TRAEs associated with NIVO+IPI+PDC were those involving the skin, endocrine and gastrointestinal systems, with the majority being Grade 1 or 2 (Paz-Ares 2021a).

7.1.2.1.7.2 2-year database lock

At the 2-year DBL, safety data were consistent with reports from the 1-year DBL. The incidence of TRAE and grade 3 and 4 TRAE was numerically higher in the NIVO+IPI+PDC vs. PDC alone group (Reck 2021). A summary of TRAEs reported in CheckMate9LA is presented in Table 16 below (Reck 2021).

As patients were exposed to NIVO+IPI+PDC at a higher rate than PDC alone, when adjusted for the different treatment exposure in each arm, the incidence of TRAEs per 100 patient-years was 714.8 versus 880.0, respectively. In a post-hoc analysis of the onset of TRAEs, The onset of the majority of grade 3/4 TRAEs in the NIVO+IPI+PDC arm occurred during the first 2 cycles, corresponding to the duration of the limited course of PDC in this arm; the majority of grade 3/4 TRAEs in the PDC alone arm occurred until cycles 7-8 (Reck 2021).

TRAE of any grade leading to treatment discontinuation of all components of the regimen were reported in 61 (17%) patients in the NIVO+IPI+PDC group versus 21 (6%) patients in the PDC alone group; treatment-related death occurred in 8 (2%) versus 6 (2%) patients, respectively (Reck 2021).

The most common TREAs of any grade (frequency of ≥ 10%) reported were: nausea, anemia, pruritus, diarrhea, asthenia, rash, fatigue, decreased appetite, hypothyroidism, vomiting, neutropenia, and constipation. The most commonly reported immune-mediated AE (IMAEs) of any grade were rash (17%), hypothyroidism/thyroiditis (16%), and hyperthyroidism (8%); the most common grade 3/4 IMAEs were hepatitis, rash, and colitis (each 4%) (Reck 2021).

Table 16: CheckMate 9LA; Overview of TRAEs reported (2-year database lock)

TRAE,[a] n %	NIVO+IPI+PDC (n=358)		PDC (n=349)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
TRAEs leading to discontinuation of any component of the regimen	79 (22)	65 (18)	29 (8)	17 (5)
Serious TRAEs	109 (30)	93 (26)	62 (18)	51 (15)
Treatment-related deaths[b]	8 (2)		6 (2)	

Note: [a]Includes events reported between first dose and 30 days after last dose of study drug; [b]Treatment-related deaths in the NIVO+IPI+PDC arm (n = 7; 1 for each event) were due to acute renal failure due to chemotherapy, thrombocytopenia, pneumonitis, hepatic toxicity, hepatitis, diarrhea, sepsis, and acute renal insufficiency; treatment-related deaths in the chemo arm (n = 6; 1 for each event) were due to sepsis, anemia, pancytopenia, respiratory failure, pulmonary sepsis, and febrile neutropenia (1 grade 5 AE was reported [sudden death due to fall] as potentially treatment-related but cause of death was recorded as unknown).
Abbreviations: AE: adverse event; Chemo: chemotherapy; Ipi: ipilimumab; Nivo: nivolumab; TRAE: treatment-related adverse event.
Source: (Reck 2021)

7.1.2.2 Results of CheckMate 227 Part 1

For the supporting study, CheckMate 227 (Part 1), the 4-year DBL (minimum follow-up time 49.4 months) is presented. An overview of the efficacy and safety results of CheckMate 227 is provided below based on the 2 year DBL (minimum follow-up 29.3 months).

7.1.2.2.1 Overall survival in PD-L1 ≥1% patients

In the 4-year DBL updated analysis with a minimum follow-up time 49.4 months, nivolumab plus ipilimumab demonstrated a median OS of 17.1 months compared to 14.9 months as shown by chemotherapy in patients with PD-L1 ≥1% (HR 0.76, 95% CI 0.65–0.90)(Paz-Ares 2021b); for patients receiving nivolumab monotherapy, the median OS was 15.7 months (vs chemotherapy HR 0.91, 95% CI 0.78–1.06)(Figure 23)(Paz-Ares 2021b). The 4-year OS rates were 29%, 21%, and 18% for nivolumab plus ipilimumab, nivolumab alone, and chemotherapy, respectively (Paz-Ares 2021b).

Efficacy improvements in the nivolumab plus ipilimumab versus the chemotherapy arm in patients with ≥1% were observed across non-squamous and squamous histologies. For PD-L1 ≥1% patients with nonsquamous histology, median OS was 19.4 months (95% CI 15.6–24.3) and 17.2 months (95% CI 14.3–19.6) for nivolumab and ipilimumab versus chemotherapy, respectively (HR 0.81, 95% CI 0.67–0.99)(Figure 24A)(Paz-Ares 2021b). For PD-L1 ≥1% patients with squamous histology, median OS was 14.8 months (95% CI 12.1–18.7) and 9.2 months (95% CI 7.6–13.9) for nivolumab and ipilimumab versus chemotherapy, respectively (HR 0.68, 95% CI 0.51–0.89)(Figure 24B)(Paz-Ares 2021b).

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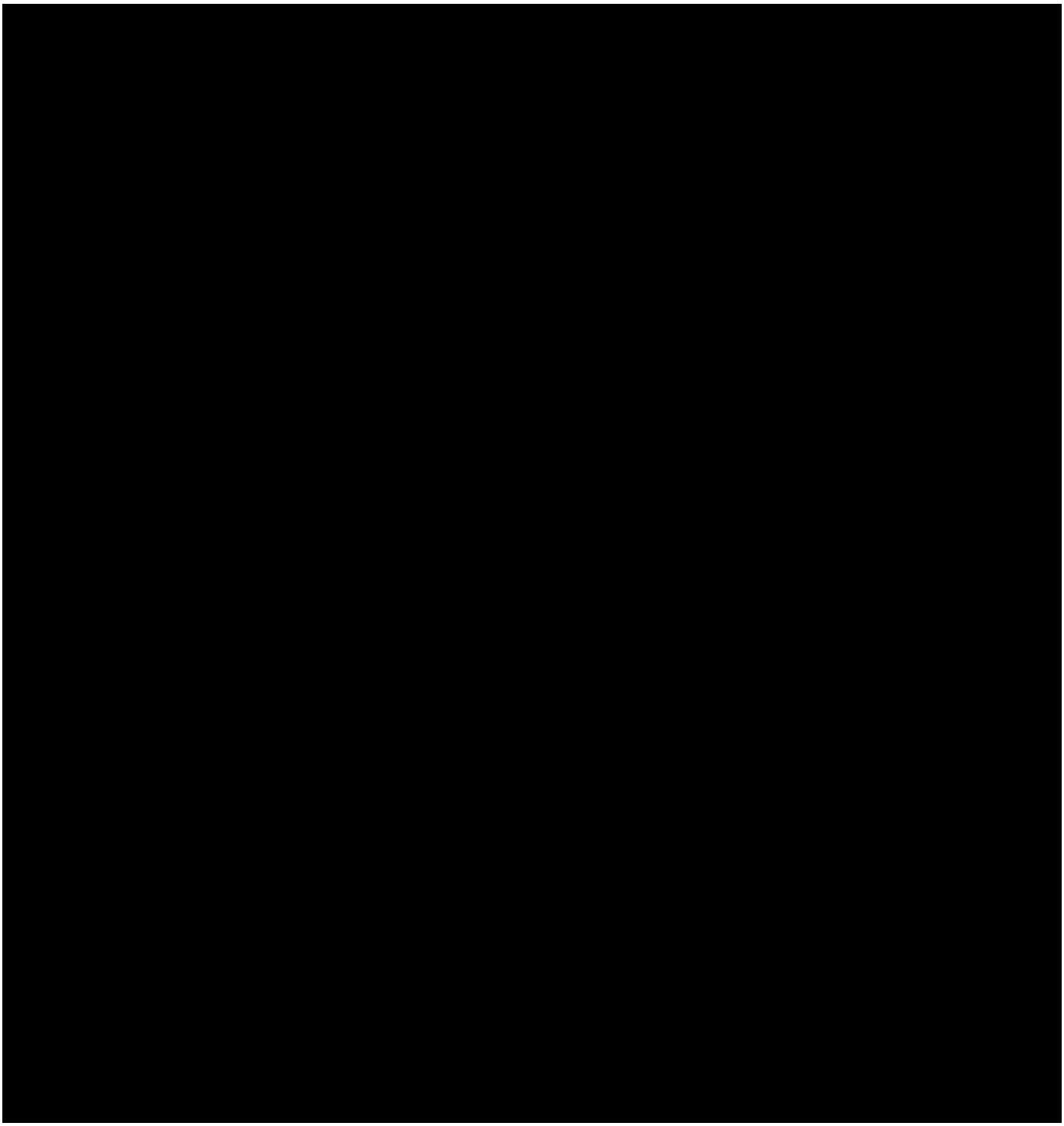

For PFS, patients treated with nivolumab plus ipilimumab, 14% were progression-free at 4 years versus 4% with chemotherapy. Among the patients who experienced a PFS event, subsequent systemic therapy was administered in 33.7% of the patients who had received nivolumab plus ipilimumab and in 48.8% of those who had received chemotherapy; immunotherapy was administered in 39.9% of those in the chemotherapy group (Paz-Ares 2021b).

ORR was consistent with those previously reported. Median DOR was 23.2 months versus 6.7 months for nivolumab plus ipilimumab versus chemotherapy, respectively; 34% and 7%, respectively, of confirmed responders had ongoing responses for at least 4 years since their first response (Paz-Ares 2021b).

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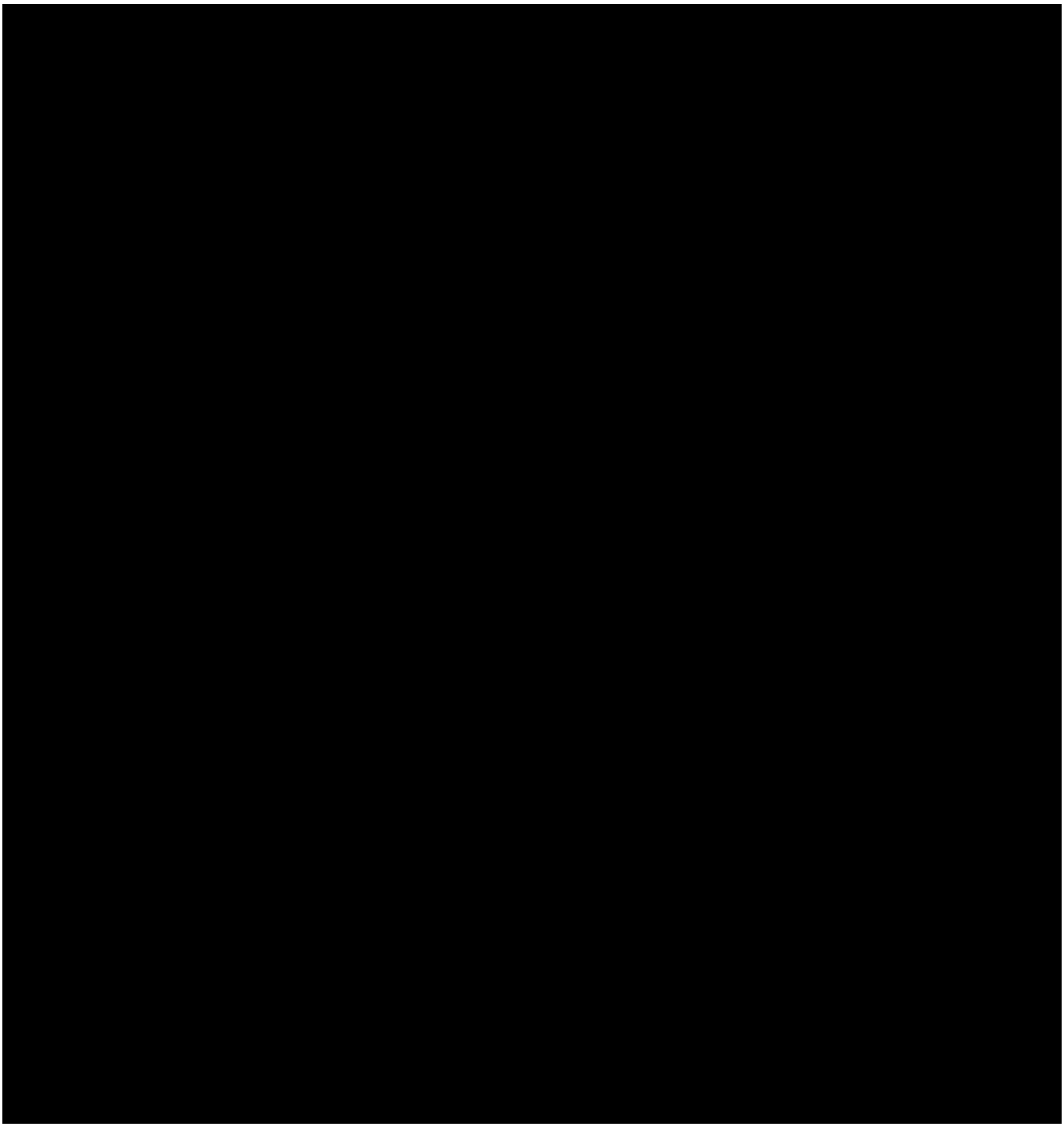
7.1.2.2.2 Overall survival in PD-L1 <1% patients

In the 4-year DBL updated analysis with a minimum follow-up time 49.4 months, nivolumab plus ipilimumab demonstrated a median OS of 17.2 months compared to 12.7 months as shown by chemotherapy in patients with PD-L1 <1% (HR 0.64, 95% CI 0.51–0.81); for patients receiving nivolumab plus chemotherapy treatment, the median OS was 15.2 months (vs chemotherapy alone: HR 0.82, 95% CI 0.65–1.02) (Figure 25) (Paz-Ares 2021b). The 4-year OS rates were 29%, 21%, and 18% for nivolumab plus ipilimumab, nivolumab alone, and chemotherapy, respectively (Paz-Ares 2021b).

Efficacy improvements in the nivolumab plus ipilimumab versus the chemotherapy arm in patients with <1% were observed across non-squamous and squamous histologies. For PD-L1 <1% patients with nonsquamous histology, median OS was 17.5 months (95% CI 12.3–23.9) and 13.1 months (95% CI 9.8–15.3) for nivolumab and ipilimumab versus chemotherapy, respectively (HR 0.69, 95% CI 0.53–0.89) (Figure 26A) (Paz-Ares 2021b). For PD-L1 <1% patients with squamous histology, median OS was 15.9 months (95% CI 9.0–33.9) and 8.5 months (95% CI 6.4–13.0) for nivolumab and ipilimumab versus chemotherapy, respectively (HR 0.53, 95% CI 0.34–0.84) (Figure 26B) (Paz-Ares 2021b).



For PFS, patients treated with nivolumab plus ipilimumab, 14% were progression-free at 4 years, while no patients remained progression-free with chemotherapy alone (Paz-Ares 2021b). ORR was consistent with those previously reported. Median DOR was 18.0 months versus 4.8 months for nivolumab plus ipilimumab versus chemotherapy, respectively; 31% of nivolumab plus ipilimumab confirmed responders had ongoing responses for at least 4 years since their first response, while no patients who received chemotherapy had an ongoing reponse (Paz-Ares 2021b).

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7.1.2.2.3 Safety

7.1.2.2.3.1 2-year database lock

At the 2-year DBL in Part 1, 576 patients received nivolumab plus ipilimumab with a minimum follow-up of 29.3 months. Safety findings for nivolumab plus ipilimumab were manageable and consistent with previous findings for nivolumab plus ipilimumab; no new safety concerns were identified. A summary of TRAEs reported in CheckMate 227 is presented in Table 17 (Hellmann 2019b).

Overall, the frequency of grade 3 and 4 TRAEs was similar in the group that received nivolumab plus ipilimumab and in the chemotherapy group (32.8% vs. 36.0%) (Hellmann 2019b). It is important to note that nivolumab plus ipilimumab demonstrated comparable all cause TRAEs, despite the longer DOT compared to chemotherapy (mDOT; 4.2 months vs 2.6 months respectively) (Hellmann 2019b).

Treatment-related adverse events leading to discontinuation for any grade were more common with nivolumab plus ipilimumab than with chemotherapy (18.1% vs. 9.1%), as well as for grade 3-4 (12.3% vs. 4.9%). Among the 391 patients who had a PD-L1 expression level of 1% or more who were treated with nivolumab monotherapy, treatment-related adverse events of any grade resulted in discontinuation in 48 patients (12.3%). Treatment-related deaths occurred in 8 patients who received NIVO+IPI and in 6 patients who received PDC (Hellmann 2019b).

Table 17:. Overview of treatment-related adverse events reported in CheckMate 227 Part 1 (2-year database lock)

TRAE, n (%)	Nivo+ipi (n=576)		Chemotherapy (n=570)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
All events, no. (%)	442 (76.7)	189 (32.8)	467 (81.9)	205 (36.0)
Serious event, no. (%)	141 (24.5)	106 (18.4)	79 (13.9)	61 (10.7)
Treatment-related deaths, no. (%)	8 (1.4)	-	6 (1.1)	-
Any event leading to discontinuation*	104 (18.1)	71 (12.3)	52 (9.1)	28 (4.9)
Reported in ≥15% of patients				
Diarrhea	98 (17.0)	10 (1.7)	55 (9.6)	4 (0.7)
Rash	98 (17.0)	9 (1.6)	30 (5.3)	0
Fatigue	83 (14.4)	10 (1.7)	108 (18.9)	8 (1.4)
Decreased appetite	76 (13.2)	4 (0.7)	112 (19.6)	7 (1.2)
Nausea	57 (9.9)	3 (0.5)	206 (36.1)	12 (2.1)
Anemia	22 (3.8)	8 (1.4)	188 (33.0)	66 (11.6)
Neutropenia	1 (0.2)	0	98 (17.2)	54 (9.5)

Note: For nivolumab plus ipilimumab, these events included treatment-related adverse events leading to the discontinuation of ipilimumab alone or the discontinuation of both nivolumab and ipilimumab; the discontinuation of nivolumab alone was not permitted. Adverse events leading to the discontinuation of ipilimumab earlier than the discontinuation of nivolumab occurred in 18 patients (3.1%).
Abbreviations: Ipi: ipilimumab; Nivo: nivolumab; TRAE: treatment-related adverse event.
Source: (Hellmann 2019b)

7.1.2.2.3.2 4-year database lock

As at the 4-year DBL all patients had been off immunotherapy treatment for 2 years or longer, no new TREAs data was reported in the nivolumab plus ipilimumab arm since the previous DBLs; otherwise, the the incidence of any-grade and grade 3 or 4 TRAEs, serious TRAEs, and TRAEs leading to discontinuation in all treatment arms, was largely unchanged

from previous reports (Paz-Ares 2021b). Overall, the incidence rates of TRAEs per 100 patient-years were: 607.7 for nivolumab plus ipilimumab, 1059.8 for chemotherapy alone, 351.8 for nivolumab monotherapy, and 933.7 for nivolumab plus chemotherapy (Paz-Ares 2021b).

7.1.2.3 Supporting evidence of safety for NIVO+IPI +/- PDC

CheckMate 568 is a two-part, phase 2, single-arm study of immunotherapy combinations for first-line treatment of patients with advanced NSCLC where Part 1 evaluated NIVO+IPI and Part 2 evaluated NIVO+IPI combined with 2 cycles of PDC. The primary end points were dose-limiting toxicity, safety and tolerability. Results from minimum follow-up of 26 months showed that the addition of 2 cycles of chemotherapy to NIVO+IPI was tolerable, with no new safety signals in patients with untreated advanced NSCLC. A DLT of transient, asymptomatic grade 3 AST and ALT elevation was observed during the 9-week DLT assessment window but the regimen was considered safe based on pre-specified criteria (DLT incidence of ≤ 25%) (Barlesi 2019, Ready 2019, Gainor 2020).

Furthermore, the latest results of CheckMate 817, a single arm study of NIVO+IPI in first-line NSCLC, the OS observed in a general population (ECOG PS 0–1, cohort A (n=391)) was consistent with CheckMate 227 Part 1 and despite poor performance status or comorbidities, special populations (ECOG PS 2 or ECOG PS 0–1 and one of the following: asymptomatic untreated brain metastases, hepatic or renal impairment, HIV, cohort A1 (n=198)) had promising efficacy outcomes with 1-year OS rate of 47% (clinicaltrials.gov 2021). Importantly, the treatment-related select AE profile of flat-dose NIVO + weight-based IPI was consistent across Cohorts A and A1, select AEs occurred early after treatment initiation and resolved quickly with guidelines-based management (Barlesi 2019, Ready 2019, Gainor 2020).

7.2 Comparison dual-IO (CheckMate 9LA) vs. other immunotherapies

7.2.1 Efficacy of immunotherapies

7.2.1.1 Efficacy and safety of nivolumab plus ipilimumab in combination with chemotherapy vs. pembrolizumab monotherapy (NSCLC PD-L1 ≥50%)

In this section, the results of the predefined subgroup analyses of CheckMate 9LA are compared against relevant immunotherapy treatment options in Denmark.

7.2.1.1.1 Relevant studies- KEYNOTE 042 and KEYNOTE 024

7.2.1.1.1.1 KEYNOTE 042

An overview of the KEYNOTE 042 trial, including patients with advanced NSCLC and PD-L1≥1% is presented below. Additional details are found in Appendix B Main characteristics of included studies.

7.2.1.1.1.1.1 Study design

KEYNOTE 042 is a randomised, open-label, phase III trial of pembrolizumab monotherapy vs. platinum-based chemotherapy as first-line therapy for patients with locally advanced or metastatic non-small-cell lung cancer and PD-L1 ≥1% (Mok 2019b).

7.2.1.1.1.1.2 Study population and patient characteristics

3428 patients across all study sites were screened for enrolment. 3019 had samples that were evaluable for PD-L1 expression, of whom 1978 (66%) had a TPS of 1% or greater, including 922 (31%) who had a TPS of 50% or greater. From Dec 19, 2014, to March 6, 2017, 1275 patients were randomly allocated to receive pembrolizumab (n=638) or chemotherapy (n=637). One patient in the pembrolizumab group was randomly assigned treatment after death and, therefore, the intention-to-treat population included 1274 patients (637 in each group, figure 1). Important protocol deviations, defined as those that could substantially affect the quality or integrity of key study data or a patient's rights, safety, or wellbeing, were reported in 17 (1%) of 1274 patients, but only one patient discontinued study treatment

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because of a study violation. The patient demographics and disease characteristics were similar between groups and across the TPS populations at baseline (see Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety) (Mok 2019b).

Patients were assigned 1:1 to receive pembrolizumab 200 mg alone or the investigator's choice of carboplatin to achieve an area under the curve of 5–6 mg/mL per min plus paclitaxel 200 mg/m² or pemetrexed 500 mg/m². All drugs were administered intravenously every 3 weeks. Randomisation was stratified by region of enrolment (east Asia vs rest of world), ECOG performance status score (0 vs 1), histology (SQ vs NSQ), and PD-L1 TPS (≥50% vs 1–49%), and treatment was allocated in blocks of four in each stratum. Treatment was open label because the differences in infusion durations, administration schedules, and requirements for premedication would have made masking difficult. Thus, patients, investigators, members of the external data monitoring committee, and select representatives of the sponsor were not masked, but the central radiological reviewers were unaware of treatment assignment (Mok 2019b).

7.2.1.1.1.3 Study endpoints

In the original protocol, written in 2014, the primary endpoint was overall survival in patients with a PD-L1 TPS of 50% or greater and secondary endpoints were overall survival in patients with a PD-L1 TPS of 1% or greater and progression-free survival in patients with a TPS of 50% or greater and of 1% or greater. Exploratory endpoints were overall and progression-free survival in patients with a TPS of 1–49% and objective response among those with a TPS of 50% or greater, 1–49%, and 1% or greater. In 2015, after the enrolment of 662 patients, a significant overall survival benefit was reported in patients with previously treated advanced NSCLC and a PD-L1 TPS of 1% or greater in the KEYNOTE-010 study of pembrolizumab vs. docetaxel. Consequently, the primary endpoints in the KEYNOTE 042 study protocol were amended to overall survival in patients with a PD-L1 TPS of 50% or greater and of 1% or greater, and the secondary and exploratory endpoints were amended to include progression-free survival and objective response, respectively, in these populations. In April 2017, after enrolment was complete, an intermediate TPS cut-off point of ≥20% was also introduced (Mok 2019b).

7.2.1.1.1.2 KEYNOTE 024

An overview of the KEYNOTE 024 trial including patients with advanced NSQ NSCLC and PD-L1 ≥50% is presented below. Additional details are found in Appendix B Main characteristics of included studies.

7.2.1.1.1.2.1 Study design

KEYNOTE 024 is a randomized open-label phase III trial of pembrolizumab vs platinum-based chemotherapy in first-line patients with PD-L1 strong metastatic NSCLC (Reck 2016).

7.2.1.1.1.2.2 Study population and patient characteristics

A total of 1934 patients at 142 sites in 16 countries were screened for enrolment, including 1729 who submitted samples for PD-L1 assessment (Reck 2016).. Of the 1653 patients whose samples could be evaluated for PD-L1, 500 (30.2%) had a PD-L1 tumour proportion score of 50% or greater. Between September 19, 2014, and October 29, 2015, a total of 305 patients at 102 sites who met inclusion criteria were randomly assigned to either the pembrolizumab group (154 patients) or the chemotherapy group (151 patients). In the chemotherapy group, the most common regimen was carboplatin plus pemetrexed (in 67 patients). All the patients in the pembrolizumab group received the trial treatment. In the chemotherapy group, 1 patient withdrew consent before receiving the planned trial treatment, and 46 patients received pemetrexed maintenance therapy after completion of combination chemotherapy. The demographic characteristics of the patients and the disease characteristics at baseline were generally well balanced between treatment groups (Reck 2016), although more patients in the chemotherapy group than in the pembrolizumab group had never smoked (12.6% vs. 3.2%) and more patients in the pembrolizumab group than in the chemotherapy group had brain metastases (11.7% vs. 6.6%). These differences were not statistically significant (Reck 2016). For

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details, see Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

7.2.1.1.2.3 Study endpoints

The primary end point was progression-free survival, which was defined as the time from randomization to disease progression or death from any cause. Secondary end points included overall survival, which was defined as the time from randomization to death from any cause; objective response rate, which was defined as the percentage of patients with a confirmed complete or partial response; and safety. An exploratory end point was duration of response, which was defined as the time from the first documentation of a complete or partial response to disease progression (Reck 2016).

7.2.1.1.2 Efficacy and safety results

7.2.1.1.2.1 KEYNOTE 042

7.2.1.1.2.1.1 Overall survival

At a median follow up of 12.8 months, OS differed significantly between groups (Figure 27) (Mok 2019b)). The median survival duration was 20.0 months (95% CI 15.4–24.9) in the pembrolizumab group compared with 12.2 months (95% CI 10.4–14.2) in the chemotherapy group. 496 patients in the TPS 20% or greater population died, with the difference in overall survival remaining significant. Median survival was 17.7 months (95% CI 15·3–22·1) in the pembrolizumab group compared with 13.0 months (11.6–15.3) in the chemotherapy group. In the TPS 1% or greater population, 809 patients died and overall survival was again significantly different. Median survival was 16.7 months (95% CI 13·9–19·7) in the pembrolizumab group compared with 12.1 months (11.3–13.3) in the chemotherapy group. The estimated percentages of patients alive at 24 months in the pembrolizumab and the chemotherapy groups were 45% and 30%, respectively, in the TPS 50% or greater population, 41% and 30% in the TPS 20% or greater population, and 39% and 28% in the TPS 1% or greater population.

At the final protocol-specified analysis, with a median follow-up of 14 months (Figure 28), the OS benefit with pembrolizumab vs chemotherapy was maintained, mOS was 20.0 months (95% CI 15.9-24.2) in the TPS 50% pembrolizumab group compared with 12.2 (95% CI 10.4,14.6) in the chemotherapy group (HR: 0.70 (95% CI 0.58,0.86) (Figure 28) (Mok 2019a).

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7.2.1.1.2.1.2 Progression free survival

At a median follow-up of 12.8 months, mPFS was 7.1 months (95% CI 5·9–9·0) in the pembrolizumab group and 6.4 months (6.1–6.9) in the chemotherapy group in the TPS 50% or greater population, 6.2 months (5.1–7.8) and 6.6 months (6.2–7.3) in the 20% or greater population, and 5.4 months (4.3–6.2) and 6.5 months (6.3–7.0) in the TPS 1% or greater population (Figure 29) (Mok 2019b). Significance in the TPS 50% or greater population did not reach the prespecified superiority boundary and, therefore, was not tested in the TPS 20% or greater and 1% or greater populations.

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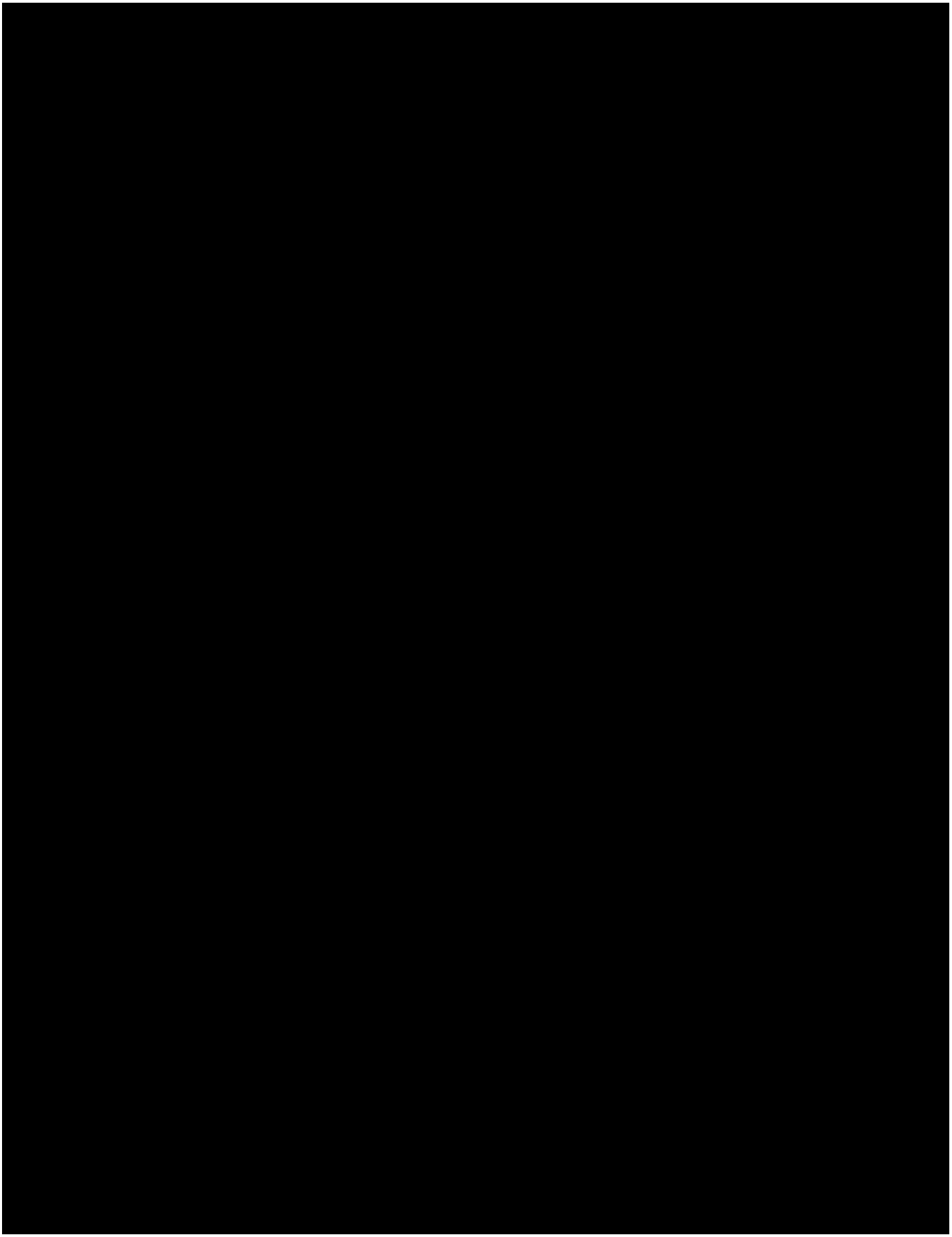

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At the final protocol-specified analysis, with a median follow-up of 14 months mPFS was not significantly improved with pembrolizumab (6.5 months (95% CI 5.9 - 8.5) vs chemotherapy (6.4 months (95% CI 6.2 - 7.2) in patients with TPS 50%, therefore secondary efficacy hypotheses were not formally tested beyond TPS 50% (Figure 30) (Mok 2019a).

7.2.1.1.2.1.3 Duration of response

At a median follow-up of 12.8 months, the mDOR was 20.2 months in the pembrolizumab group in all TPS populations and was 10.8 months, 8.3 months, and 8.3 months, respectively, in the TPS 50% or greater, 20% or greater, and 1% or greater populations in the chemotherapy group (see appendix of Mok 2019) (Mok 2019b).

At the final protocol-specified analysis, with a median follow-up of 14 months, DOR was longer with pembrolizumab vs chemotherapy, 22.0 months (95% CI 2.1+ - 36.5+) and 10.8 months (95%CI 1.8+ - 30.4+) respectively (Figure 30) (Mok 2019a).

7.2.1.1.2.1.4 Objective response rate

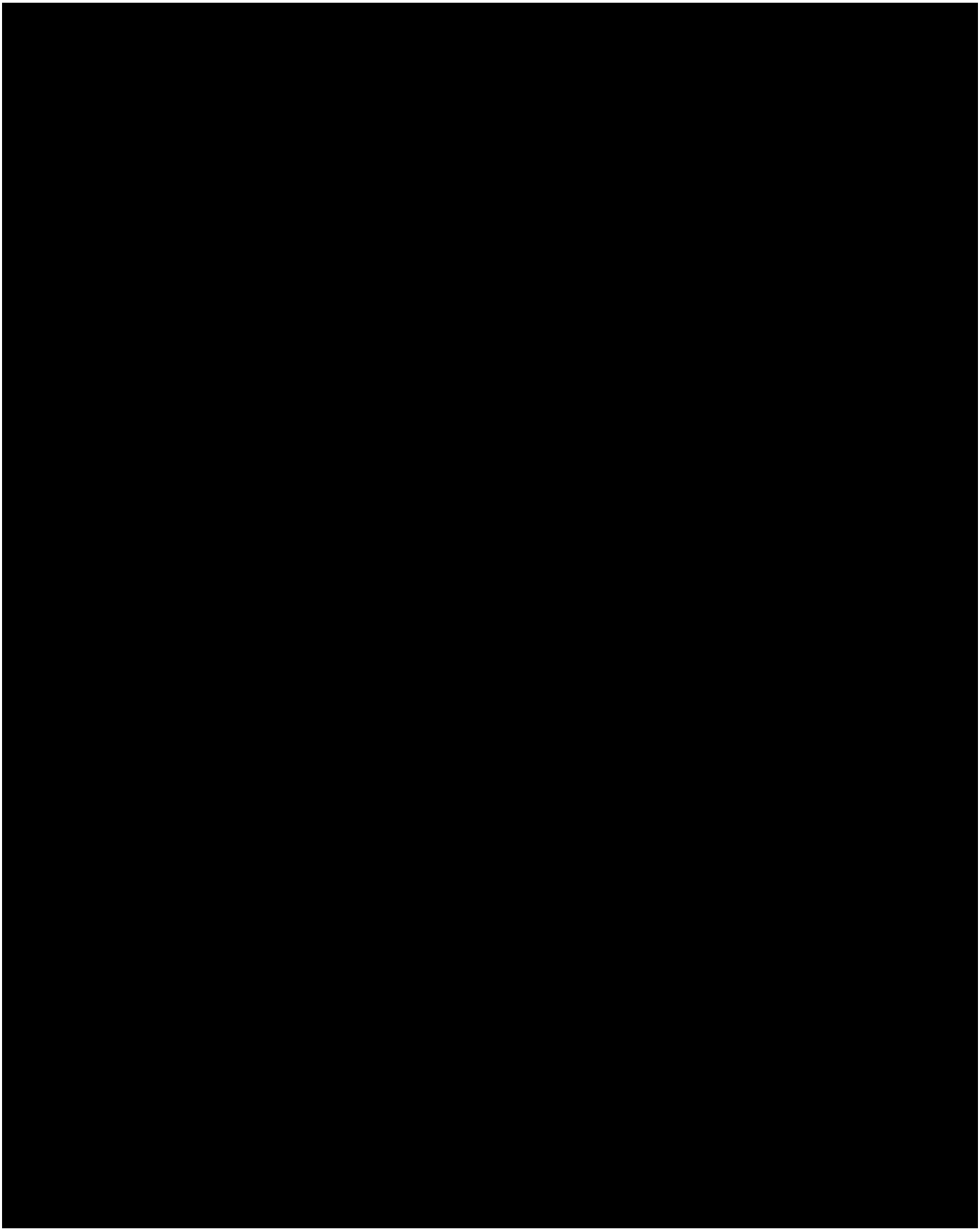
At a median follow-up of 12.8 months, the objective response to treatment in the PD-L1 TPS 50% or greater population was 118 (39%, 95% CI 34–45) of 299 patients in the pembrolizumab group and 96 (32%, 27–38) of 300 patients in the chemotherapy group. The values in the TPS 20% or greater and 1% or greater populations were 138 (33%, 29–38) of 413 vs. 117 (29%, 25–34) of 405 and 174 (27%, 24–31) of 637 vs. 169 (27%, 23–30) of 637, respectively, see appendix of Mok et al (Mok 2019b).

At the final protocol-specified analysis, with a median follow-up of 14 months, the ORR was 39.1% in the pembrolizumab group and 32% in the chemotherapy group (Mok 2019a).

7.2.1.1.2.1.5 Safety results

At a median follow-up of 12.8 months, the TRAEs of any grade occurred in 399 (63%) of 636 patients in the pembrolizumab group and 553 (90%) of 615 patients in the chemotherapy group (see Table 2 in (Mok 2019b)). Treatment-related adverse events of grade 3 or worse severity occurred in 113 (18%) of 636 patients in the pembrolizumab group and 252 (41%) of 615 patients in the chemotherapy group. Treatment-related adverse events led to death in 13 (2%) and 14 (2%) patients in the pembrolizumab and chemotherapy groups, respectively, and treatment discontinuation in 57 (9%) and 58 (9%), respectively. The most common treatment-related adverse event was hypothyroidism (69 [11%] of 636) in the pembrolizumab group and anaemia (229 [37%] of 615) in the chemotherapy group (see Table 2, in the appendix of (Mok 2019b)). Treatment-related adverse events of grade 3 or worse severity that occurred in 20 or more patients were pneumonitis in the pembrolizumab group and anaemia, decreased neutrophil count, neutropenia, decreased white blood cell count, and decreased platelet count in the chemotherapy group (see Table 2, in the appendix of (Mok 2019b)). Adverse events of interest (events judged likely to be immune mediated and infusion reactions) occurred in 177 (28%) of 636 patients (51 [8%] grade ≥3) in the pembrolizumab group and 44 (7%) of 615 patients (9 [1%] grade ≥3) in the chemotherapy group (Figure 30) (Mok 2019b). The only grade 3 or worse immune-mediated events that occurred in five or more patients in the pembrolizumab group were pneumonitis, severe skin reactions, and hepatitis (Figure 31) (Mok 2019b). One patient in the pembrolizumab group died because of pneumonitis that occurred concurrently with disease progression.

At the final protocol-specified analysis, with a median follow-up of 14 months, the grade 3–5 TRAEs were less frequent in the pembrolizumab group (18%) vs the chemotherapy group (41%) (Mok 2019a).



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7.2.1.1.2.2 KEYNOTE 024

7.2.1.1.2.2.1 Overall survival

In the intention-to-treat population, at the time of the second interim analysis with median duration of follow-up of 11.2 months, 108 deaths had occurred. The estimated percentage of patients who were alive at 6 months was 80.2% (95% CI, 72.9 to 85.7) in the pembrolizumab group and 72.4% (95% CI, 64.5 to 78.9) in the chemotherapy group (Figure 32); median overall survival was not reached in either group. Overall survival was significantly longer in the pembrolizumab group than in the chemotherapy group (hazard ratio for death, 0.60; 95% CI, 0.41 to 0.89; P=0.005) (Reck 2016).

The median duration of treatment was 7.0 months (range, 1 day to 18.7 months) in the pembrolizumab group and 3.5 months (range, 1 day to 16.8 months) in the chemotherapy group. The median number of treatment cycles in the pembrolizumab group was 10.5 (range, 1 to 26); the median number in the chemotherapy group was 4 (range, 1 to 6), both for patients who had squamous tumours and for those who had NSQ tumours (Reck 2016).

7.2.1.1.2.2.2 Progression free survival

In the intention-to-treat population, on the basis of 189 total events of progression or death, median progression-free survival was 10.3 months (95% CI, 6.7, NR) in the pembrolizumab group and 6.0 months (95% CI 4.2, 6.2) in the chemotherapy group (Figure 33) (European Medicines Agency 2016, Reck 2016). The estimated percentage of patients who were alive and had no disease progression at 6 months was 62.1% (95% CI, 53.8 to 69.4) in the pembrolizumab group and 50.3% (95% CI 41.9, 58.2) in the chemotherapy group. Progression-free survival was significantly longer in the pembrolizumab group than in the chemotherapy group (HR for disease progression or death: 0.50; 95% CI 0.37,0.68; P<0.001).

7.2.1.1.2.2.3 Safety results

During treatment with the initially assigned therapy at a median duration of follow-up of 11.2 months, TRAEs occurred in 73.4% of the patients in the pembrolizumab group and in 90.0% of the patients in the chemotherapy group (Table 18). Grade 3, 4, or 5 treatment-related adverse events occurred in twice as many patients in the chemotherapy group as in the pembrolizumab group (53.3% vs. 26.6%). Serious treatment-related adverse events occurred in a similar percentage of patients in the pembrolizumab group and the chemotherapy group (21.4% and 20.7%, respectively). Discontinuation of treatment because of treatment-related adverse events occurred in 7.1% of patients in the pembrolizumab group and in 10.7% of patients in the chemotherapy group. Treatment-related adverse events that led to death occurred in one patient in the pembrolizumab group (sudden death of unknown cause on day 2) and three patients in the chemotherapy group (one death due to pulmonary sepsis on day 25, one death due to pulmonary alveolar haemorrhage on day 112, and one death of unknown cause on day 8) (Reck 2016).

Table 18: KEYNOTE 024; Adverse events in the as treated population (median follow-up of 11.2 months)

Adverse events, n (%)	Pembrolizumab (N=154)		Chemotherapy (N=150)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
Treatment-related†				
Any	113 (73.4)	41 (26.6)	135 (90.0)	80 (53.3)
Serious	33 (21.4)	29 (18.8)	31 (20.7)	29 (19.3)
Led to discontinuation	11 (7.1)	8 (5.2)	16 (10.7)	9 (6.0)
Led to death	1 (0.6)	1 (0.6)	3 (2.0)	3 (2.0)
Occurred in ≥10% of patients in either group‡				

Nausea	15 (9.7)	0	65 (43.3)	3 (2.0)
Anaemia	8 (5.2)	3 (1.9)	66 (44.0)	29 (19.3)
Fatigue	16 (10.4)	2 (1.3)	43 (28.7)	5 (3.3)
Decreased appetite	14 (9.1)	0	39 (26.0)	4 (2.7)
Diarrhoea	22 (14.3)	6 (3.9)	20 (13.3)	2 (1.3)
Neutropenia	1 (0.6)	0	34 (22.7)	20 (13.3)
Vomiting	4 (2.6)	1 (0.6)	30 (20.0)	1 (0.7)
Pyrexia	16 (10.4)	0	8 (5.3)	0
Constipation	6 (3.9)	0	17 (11.3)	0
Stomatitis	4 (2.6)	0	18 (12.0)	2 (1.3)
Decrease neutrophil count	0	0	20 (13.3)	6 (4.0)
Increase blood creatinine level	3 (1.9)	0	15 (10.0)	1 (0.7)
Decrease platelet count	0	0	18 (12.0)	9 (6.0)
Thrombocytopenia	0	0	17 (11.3)	8 (5.3)
Decreased white-cell count	1 (0.6)	0	16 (10.7)	3 (2.0)
Dysgeusia	1 (0.6)	0	15 (10.0)	0
Immune-mediated				
Any	45 (29.2)	15 (9.7)	7 (4.7)	1 (0.7)
Hypothyroidism	14 (9.1)	0	2 (1.3)	0
Hyperthyroidism	12 (7.8)	0	2 (1.3)	0
Pneumonitis	9 (5.8)	4 (2.6)	1 (0.7)	1 (0.7)
Infusion reaction	7 (4.5)	0	2 (1.3)	0
Severe skin reaction	6 (3.9)	6 (3.9)	0	0
Thyroiditis	4 (2.6)	0	0	0
Colitis	3 (1.9)	2 (1.3)	0	0
Myositis	3 (1.9)	0	0	0
Hypophysis	1 (0.6)	1 (0.6)	0	0
Nephritis	1 (0.6)	1 (0.6)	0	0
Pancreatitis	1 (0.6)	1 (0.6)	0	0
Type 1 diabetes mellitus	1 (0.6)	1 (0.6)	0	0

* The as-treated population included all patients who received at least one dose of a trial treatment. For the patients in the chemotherapy group who crossed over to the pembrolizumab group after disease progression, only events that occurred during treatment with the assigned chemotherapy regimen are included.† Events were attributed to treatment by the investigator and are listed as indicated by the investigator on the case-report form. Although decreased neutrophil count and neutropenia may reflect the same condition, they were listed by the investigators as two distinct events; this is also the case for decreased platelet count and thrombocytopenia.‡ Events are listed in descending order of frequency in the total population.§ The immune-mediated events, both those that were and those that were not attributed to study treatment by the investigator, are listed in descending order of frequency in the pembrolizumab group. In addition to specific preferred terms, related terms are also included

Source: (Adapted from (Reck 2016))

Efficacy and safety of nivolumab plus ipilimumab in combination with chemotherapy vs. pembrolizumab + platinum+pemetrexed for first-line treatment in a population with NSQ NSCLC

7.2.1.1.2.3 Relevant study- KEYNOTE 189

An overview of the KEYNOTE 189 trial including patients with advanced NSQ NSCLC regardless of PD-L1 expression is presented below. Additional details are presented in Appendix B Main characteristics of included studies.

7.2.1.1.2.3.1 Study design

Randomized, double blinded, placebo-controlled, multicentre phase 3 trial conducted to evaluate pembrolizumab in combination with pemetrexed and carboplatin as a first-line treatment in patients with advanced NSQ NSCLC regardless of PD-L1 expression (Gandhi 2018).

7.2.1.1.2.3.2 Study population and patient characteristics

A total of 965 patients were screened for enrolment at 126 sites in 16 countries. Between February 26, 2016, and March 6, 2017, a total of 616 patients from 118 sites who had met all the eligibility criteria were randomly assigned to the pembrolizumab-combination group (410 patients) or the placebo-combination group (206 patients) (Gandhi 2018). The baseline demographic and disease characteristics were generally well balanced between the groups, although the percentage of men was higher in the pembrolizumab-combination group than in the placebo-combination group (62.0% vs. 52.9%, P=0.04) (Gandhi 2018). A PD-L1 tumour proportion score of 1% or greater was reported in 63.0% of the patients, carboplatin was the chosen platinum-based drug in 72.2% of the patients, and 88.1% of the patients were current or former smokers (Gandhi 2018). Additional details are found in Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

7.2.1.1.2.3.3 Study endpoints

The two primary end points were overall survival (time from randomization to death from any cause) and progression-free survival (time from randomization to disease progression, as assessed by blinded, independent central radiologic review, or death from any cause, whichever occurred first). The secondary end points were the response rate (the percentage of patients with a confirmed complete or partial response), the duration of response (time from first documented complete or partial response to disease progression or death), and safety. Both the response rate and the duration of response were assessed by blinded, independent central radiologic review. Exploratory end points included the effect of PD-L1 expression on efficacy and patient-reported outcomes.

7.2.1.1.2.4 Efficacy and safety results of KEYNOTE 189

7.2.1.1.2.4.1 Overall survival

Interim results at median follow-up of 10.5 months has previously been published by Gandhi et al (Gandhi 2018).

In the updated analysis with a median follow-up of 23.1 months, 213 patients (52.0%) in the pembrolizumab-combination group and 144 patients (69.9%) in the placebo-combination group had died (Gadgeel 2020). Median (95% CI) OS was 22.0 (19.5 to 25.2) months in the pembrolizumab-combination group and 10.7 (8.7 to 13.6) months in the placebo-combination group (HR, 0.56; 95% CI 0.45, 0.70); estimated 24-month OS rates were 45.5% and 29.9%, respectively (Gadgeel 2020).

In the latest follow-up at the time of the SLR, the protocol specified final analysis, with a median follow-up of 31.0 months, the mOS was 22.0 months (95% CI 19.5, 24.5) in the pembrolizumab combination group and 10.6 months (95% CI 8.7,13.6) in the placebo-combination group (HR: 0.56 (95% CI 0.46,0.69) (Figure 34) (Rodriguez-Abreu 2020).

7.2.1.1.2.4.2 Progression free survival

Interim results at median follow-up of 10.5 months has previously been published by Gandhi et al (Gandhi 2018). At 23.1 months median (95% CI) PFS was 9.0 (8.1 to 9.9) months and 4.9 (4.7 to 5.5) months in the pembrolizumab-combination and placebo-combination groups, respectively (HR, 0.48; 95% CI 0.40, 0.58); estimated 24-month PFS rates were 20.5% and 1.5%. As with OS, PFS benefit with the addition of pembrolizumab was observed irrespective of PD-L1 expression (Gadgeel 2020).

In the latest follow-up at the time of the SLR, the protocol specified final analysis, with a median follow-up of 31.0 months, the mPFS was 9.0 months (95% CI 8.1,10.4) in the pembrolizumab combination group and 4.9 months (95% CI 4.7,5.5) in the placebo combination group (HR: 0.49 (95% CI 0.41,0.59) (Figure 35) (Rodriguez-Abreu 2020).

7.2.1.1.2.4.3 Duration of response

Interim results at median follow-up of 10.5 months has previously been published by Gandhi et al (Gandhi 2018). In the 23.1 month follow-up analysis the median DOR was 12.4 months (1.1+ to 29.0+) and 7.1 months (2.4 to 22.0+) months in the pembrolizumab-combination and placebo-combination groups, respectively (see Table 2 in (Gadgeel 2020)). Ninety patients (52.3%) in the pembrolizumab-combination group and 8 (26.9%) in the placebo-combination group had estimated DOR ≥ 12 months (Gadgeel 2020).

In the latest follow-up at the time of the SLR, the protocol specified final analysis, with a median follow-up of 31.0 months, the duration of response was 12.4 months (95%CI 1.1- 29.0+) for the pembrolizumab combination group and 7.1 months (95%CI 2.4- 22.0+) in the placebo combination group (Rodriguez-Abreu 2020).

7.2.1.1.2.4.4 Objective response rate

Interim results at median follow-up of 10.5 months has previously been published by Gandhi et al (Gandhi 2018). In the 23.1 month follow-up analysis, the confirmed objective response occurred in 197 (48.0%) patients in the pembrolizumab-combination group (complete response [CR], n = 4; partial response [PR], n = 193) and 40 patients (19.4%) in the placebo-combination group (CR, n = 1; PR, n = 39) (Gandhi 2018).

In the latest follow-up at the time of the SLR, the protocol specified final analysis, with a median follow-up of 31.0 months, the ORR was 48.3% in the pembrolizumab combination group and 19.9% in the placebo combination group (Gandhi 2018, Rodriguez-Abreu 2020).

7.2.1.1.2.4.5 Safety

Interim results at median follow-up of 10.5 months has previously been published by Gandhi et al (Gandhi 2018). In the 23.1 months follow-up analysis, all-cause adverse events had occurred in 404 patients (99.8%) in the pembrolizumab-combination group and 200 (99.0%) in the placebo-combination group. Grade 3-5 AEs occurred in 291 (71.9%) and 135 patients (66.8%), respectively. Compared with initial analysis, 2 additional patients in each group had all-cause AEs leading to death; 8 patients (2.0%) in the pembrolizumab-combination group died of AEs attributed to study treatment. AEs of acute kidney injury occurred in 25 patients (6.2%) in the pembrolizumab-combination group and occurred in 1 patient (0.5%) in the placebo-combination group. Since the prior analysis, no new patients who died as a result of the AE of acute kidney injury occurred in the pembrolizumab-combination group. The most frequently occurring AEs in both treatment groups were nausea, anaemia, and fatigue (Gadgeel 2020).

In the latest follow-up at the time of the SLR, the protocol specified final analysis, with a median follow-up of 31.0 months, one additional Grade 3-5 AE had occurred in the pembrolizumab-combination group (n=292 (72.1%)).

7.2.1.1.2.4.6 Updated results from the WCLC2020 conference

During the application finalization in Feb 2021, a new KEYNOTE 189 data-cut with a median follow-up of 46.3 months (range, 41.8-54.1) was presented at the WCLC 2020 (Gray 2020). This data-cut was not included in the SLR, the ITCs, nor the cost-effectiveness modelling. It is, however, of relevance to the application and therefore described briefly below.

Since the latest data-cut, tailends of OS curves continued to convergence and the OS HR decreased with more follow-up from HR 0.56 (95% CI 0.46,0.69) with a median follow-up of 31.0 months to HR 0.60 (95% CI, 0.50, 0.72) with a median follow-up of 46.3 months, see Figure 36 and Figure 37 below (Gray 2020).

With respect to the ITT population, the PFS results remained stable with more follow-up from HR 0.49 (95% CI 0.41,0.59) with a median follow-up of 31.0 months to HR 0.50 (95% CI, 0.41, 0.59) with a median follow-up of 46.3 months, see Figure 38 and Figure 39 below (Gray 2020). With respect to the subgroup analyses, the PD-L1 TPS<1% has now converged with the chemo-arm and a sustained PFS benefit cannot observed.

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Efficacy and safety of nivolumab plus ipilimumab in combination with chemotherapy vs. pembrolizumab + chemotherapy for first-line treatment in a population with SQ NSCLC

7.2.1.1.2.5 Relevant study- KEYNOTE 407

An overview of the KEYNOTE 407 trial including patients with advanced SQ NSCLC regardless of PD-L1 expression is presented below. For additional details, seeAppendix B Main characteristics of included studies.

7.2.1.1.2.5.1 Study design

KEYNOTE 407 is a randomized, double-blind, phase 3 study of carboplatin-paclitaxel/nab-paclitaxel chemotherapy with or without pembrolizumab (MK-3475) in first-line metastatic SQ NSCLC (Paz-Ares 2018).

7.2.1.1.2.5.2 Study population and patient characteristics

A total of 779 patients from 137 sites in 17 countries were screened for randomization. Of the 561 patients who met all eligibility criteria, 2 were excluded from randomization because of a physician's decision (Paz-Ares 2018). Between August 19, 2016, and December 28, 2017, the remaining 559 patients from 125 sites underwent randomization; 278 patients were assigned to the pembrolizumab-combination group and 281 to the placebo-combination group. With respect to the stratification factors, a PD-L1 tumour proportion score of 1% or greater was observed for 63.1% of patients, paclitaxel was the choice of taxane for 60.1% of patients, and East Asia was the region of enrolment for 19.0% of patients. Baseline demographic and disease characteristics were as expected for a trial involving patients with metastatic, squamous NSCLC and were well balanced between groups (Paz-Ares 2018). For more details, see Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

7.2.1.1.2.5.3 Study endpoints

The trial had dual primary end points of overall survival and progression-free survival, which was assessed by means of blinded, independent central review of radiologic images. The secondary end points were response rate and duration of response, which were assessed by means of blinded, independent central radiologic review, and safety. The effects of PD-L1 expression on overall survival, progression-free survival, and response rate were prespecified exploratory end points (Paz-Ares 2018).

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7.2.1.1.2.6 Efficacy and safety results KEYNOTE 407

7.2.1.1.2.6.1 Overall survival

Interim results at median follow-up of 7.8 months has previously been published by Paz-Ares et al (Paz-Ares 2018).

At the time of data cut-off of the updated analysis with a median follow-up of 14.3 months, 365 deaths had occurred in the intention-to-treat population, representing an additional 160 deaths across both treatment arms since the primary analysis (Reck 2020c). A clinically meaningful improvement in OS was observed among patients in the pembrolizumab plus chemotherapy group compared with those in the placebo plus chemotherapy group. Median (95% CI) OS was 17.1 (14.4–19.9) months in the pembrolizumab plus chemotherapy group and 11.6 (10.1–13.7) months in the placebo plus chemotherapy group (HR, 0.71 [95% CI: 0.58,0.88]) (Figure 40) (Reck 2020c). The OS rates at 12 months, 18 months, and 24 months were 64.7%, 48.0%, and 37.5% in the pembrolizumab plus chemotherapy group, respectively, and 49.6%, 36.5%, and 30.6% in the placebo plus chemotherapy group, respectively. HR (95% CI) for OS was 0.67 (0.51–0.87) in patients with PD-L1 ≥1% and 0.79 (0.56–1.11) in patients with PD-L1 < 1%. Among patients with PD-L1≥50% , the HR (95% CI) for OS was 0.79 (0.52–1.21) and the HR (95% CI) for OS was 0.59 (0.42–0.84) among those with PD-L1 TPS 1% to 49% (Reck 2020c).

7.2.1.1.2.6.2 Progression free survival

Interim results at median follow-up of 7.8 months has previously been published by Paz-Ares et al (Paz-Ares 2018).

At the time of data cut-off for the updated analysis at a median follow-up of 14.3 months, 217 patients (78.1%) in the pembrolizumab plus chemotherapy group and 252 patients (89.7%) in the placebo plus chemotherapy group had experienced PFS events (Reck 2020c). Median (95% CI) PFS was 8.0 (6.3–8.4) months in the pembrolizumab plus chemotherapy group and 5.1 (4.3–6.0) months in the placebo plus chemotherapy group (HR, 0.57 [95% CI: 0.47–0.69]) (Figure 41) (Reck 2020c). The PFS rates at 12 months and 24 months were 35.8% and 18.6% for patients in the pembrolizumab plus chemotherapy group, respectively, and 17.7% and 6.3% for patients in the placebo plus chemotherapy group, respectively. The HR (95% CI) for PFS was 0.50 (0.39–0.63) in patients with PD-L1 ≥1% and 0.67 (0.49–0.91) in patients with PD-L1 < 1% (Figure 41) (Reck 2020c).

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7.2.1.1.2.6.3 Duration of response

At the time of data cut-off for the updated analysis at a median follow-up of 14.3 months, the duration of response was 8.8 months (range 1.3 + to 28.4 +) for the pembrolizumab plus chemotherapy group and 4.9 months (range 1.3 + to 28.3 +) in the placebo plus chemotherapy group (Reck 2020c).

7.2.1.1.2.6.4 Objective response rate

At the median follow-up of 14.3 months, the ORR was 62.6% (95% CI 56.6–68.3) in the pembrolizumab plus chemotherapy group and 38.4% (95% CI 32.7–44.4) in the placebo plus chemotherapy group (Reck 2020c).

7.2.1.1.2.6.5 Safety

Overall, 274 of 278 patients (98.6%) treated with pembrolizumab plus chemotherapy and 275 of 280 patients (98.2%) treated with placebo plus chemotherapy experienced one or more AEs, at median follow-up of 14.4 months (Reck 2020c). Consistent with the previous analysis, the most frequently occurring AEs in either treatment group were anemia, alopecia, neutropenia, and nausea. AEs leading to discontinuation of any treatment occurred more frequently in the pembrolizumab plus chemotherapy group (n = 76; 27.3%) than in the placebo plus chemotherapy group (n = 37; 13.2%); only 45 patients (16.2%) and 20 patients (7.1%) discontinued all treatments owing to an AE, respectively. All-cause grade 3 to 5 AEs occurred in 206 patients (74.1%) and 195 patients (69.6%) in the pembrolizumab plus chemotherapy and placebo plus chemotherapy groups, respectively. Treatment-related grade 3 to 5 AEs occurred in 157 patients (56.5%) in the pembrolizumab plus chemotherapy group and 156 patients (55.7%) in the placebo plus chemotherapy group. A total of 12 patients (4.3%) in the pembrolizumab plus chemotherapy group had treatment-related AEs leading to death; the AEs included sepsis (n = 3), death (cause not specified) (n = 2), cardiac arrest, cardiac failure, hepatic failure, necrotizing fasciitis, pneumonitis, pulmonary haemorrhage, and respiratory failure (n = 1 each). In the placebo plus chemotherapy group, a total of five patients (1.8%) had treatment-related AEs leading to death, which included septic shock (n = 2), pneumonia, acute kidney injury, and pulmonary haemorrhage (n = 1 each) (Reck 2020c).

7.2.1.1.2.6.6 Comparative analyses

7.2.1.1.2.6.6.1 Method of synthesis

Indirect treatment comparison structure

This section focus on the ITC of NIVO+IPI+PDC against key IO-based comparators in the first-line advanced NSCLC population using a frequentist approach.

Three-node ITC networks were constructed for each relevant comparison, provided there was a common comparator between the pivotal randomized controlled trial (RCT) that evaluated NIVO+IPI+PDC (CheckMate 9LA) and the RCT(s) involving the other IO-based regimens. Nodes were connected using direct evidence from CheckMate 9LA and from the RCT(s) involving the relevant IO-based regimen; the third connection in the network was informed by indirect evidence alone (Figure 42).

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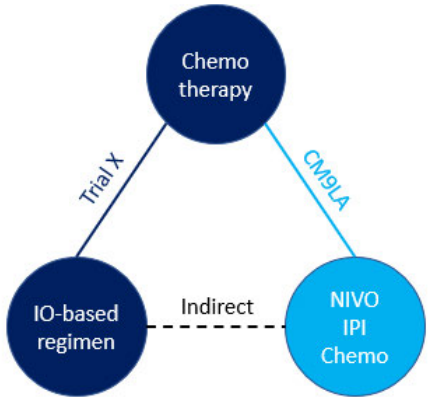
Figure 42: Example indirect treatment diagram



Abbreviations: Chemo, chemotherapy; CM, CheckMate; IO, immunotherapy; IPI, ipilimumab; NIVO, nivolumab
Notes: Solid lines represent direct head-to-head evidence; dashed line represents indirect evidence. Circles represent treatment regimens being compared

7.2.1.1.2.6.6.2 Evidence base and eligibility criteria

Efficacy data for NIVO+IPI+PDC was drawn from the CheckMate 9LA trial, an ongoing phase 3 randomized study that evaluated NIVO+IPI+PDC compared to CHEMO alone as first-line of therapy in NSCLC. All data relevant to treatment comparators were identified and collected from a previously conducted SLR (see section 6 and Appendix A Literature search for efficacy and safety of intervention and comparator(s) and Appendix O Systematic literature review report). A summary of the eligibility criteria applied for the SLR can be seen in the separate Appendix O Systematic literature review report.

The eligibility criteria for the ITC was restricted to RCTs involving regimens that had regulatory approval in Denmark, and for which the control arm of the trial involved a PLAT-based chemotherapy doublet.. As such, relevant comparisons were against the following interventions:

- PEMBRO-PLAT-PEMX (KEYNOTE 189)
- PEMBRO-PLAT-(Nab)TAX (KEYNOTE 407)
- PEMBRO monotherapy (KEYNOTE 024)
- PEMBRO monotherapy (KEYNOTE 042)

The Bucher ITC results allow the following comparisons to be made:

- The CheckMate 9LA all-comers population with pembrolizumab monotherapy in a population with ≥50% PD-L1
- The CheckMate 9LA all-comers population with pembrolizumab + platinum + pemetrexed in a population with NSQ NSCLC
- The CheckMate 9LA all-comers population with pembrolizumab + platinum + (nab)-paclitaxel in a population with SQ NSCLC

7.2.1.1.2.6.6.3 Target population

The overall target population is treatment-naïve individuals with advanced or recurrent NSCLC, without sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocations, who have good performance status (PS) (Eastern Cooperative Oncology Group [ECOG] 0 or 1).

For each of the ITCs, the target population varied depending on the approved or aspirational indications of the treatments in the comparison, primarily considering histology and programmed death ligand 1 (PD-L1) expression level. The main ITCs were designed to target PD-L1 all-comers for IO-chemo combinations, and to target PD-L1 ≥ 50% for IO monotherapy.

7.2.1.1.2.6.6.4 Histology-specific considerations

The trials involving IO-based regimens were conducted in histology all-comer populations, SQ-only populations, and NSQ only populations. The CheckMate 9LA RCT involved all histologies, which aligned with some of the comparator RCTs. In comparisons between CheckMate 9LA and RCTs that were limited to SQ-only or NSQ only RCT populations, we assumed that the effect size for NIVO+IPI+PDC relative to the chemotherapy combination of either CARB-TAX or PLAT-PEMX was the same within the SQ and NSQ subgroups. This assumption was based on the findings that the relative effect sizes did not differ substantially, as well as due to practical reasons relating to sample size.

7.2.1.1.2.6.6.4.1 PD-L1-related considerations

In the main analyses, the comparator RCTs were restricted to the relevant target populations: PD-L1 all-comers for IO plus chemo combinations, and PD-L1 ≥ 50% for IO monotherapies. In CheckMate 9LA, the relative effect sizes were similar across PD-L1 defined categories; hence, in order to preserve the RCT design and maximize sample size, the PD-L1 all-comer population was used in the indirect comparisons with IO monotherapies, under the assumption that PD-L1 expression levels do not modify treatment effect for dual-IO (specifically, the combination of PD-1 inhibitors plus CTLA-4 inhibitors).

7.2.1.1.2.6.6.4.2 Lumping vs. splitting PDs

In the ITC, PLAT-based chemotherapy doublets were lumped into a common CHEMO node, where necessary (including NabTAX-based PDs, PEMX-based PDs, as well as GEM/VNB/TAX/TXT-based PDs), to enable indirect comparisons. Given the available evidence showing potentially better efficacy associated with NabTAX-based PDs and PEMX-based PDs relative to GEM/VNB/TAX/TXT-based PDs, ITCs requiring such lumping were interpreted with caution.

7.2.1.1.2.6.6.5 Subgroup and sensitivity analyses

Sensitivity analyses involving histology-matched populations were conducted, as were analyses involving PD-L1-matched populations. ITCs for alternate target populations were also conducted for KEYNOTE 189 and KEYNOTE 407-based comparisons, using PD-L1 thresholds of <1%, <50%, ≥1%, and ≥50% (for full report, see Appendix P Bucher ITC across histology and PD-L1 expression levels)

7.2.1.1.2.6.6.6 Statistical Considerations

To prepare the raw extracted data for analysis, several steps were taken:

- HRs were converted to log HRs by taking the natural logarithm of the HR;
- Standard errors (SE) of log HRs were calculated in two steps:
    - First, the upper and lower 95% CIs were converted to the natural log scale;
    - Second, the SE on the natural log scale was calculated according to the equation:
        - SE= (UCL-LCL)/(2*1.96)
    - where UCL is the upper confidence limit and LCL is the lower confidence limit.

For estimates reported with other confidence interval widths (e.g. 97.72%, 90%), the appropriate Z-score was used in lieu of 1.96.

For binary endpoints, missing numerators (i.e. # subjects with the endpoint of interest) were calculated by multiplying the reported denominator by the reported proportion of subjects who experienced the endpoint.

In addition:

- Kaplan-Meier (KM) curves were digitized and individual patient-level data were generated using the method described by Guyot et al.3
- Medians, landmark survival, and HRs were calculated when not reported by study authors, using the R package 'survival'.

7.2.1.1.2.6.6.7 Assessment of proportional hazards assumption

The proportional hazards assessment was conducted using various tests:

- A visual inspection of the KM curve (ensuring the recreated curve accurately matches the original);
- Examining a log-cumulative hazard plot of the patient-level data for each pair of curves, examining to see if lines are close to parallel; and,
- Assessing Schoenfeld residual plots with Schoenfeld residuals global test, to assess slope in generalized linear regression of Schoenfeld residuals.

Even in the presence of proportional hazards violations, an overall HR can be useful, and can be interpreted as the overall hazard ratio over a given duration of follow-up. As such, HRs were reported for all intended comparisons even if there was evidence of proportionality assumption violations.

7.2.1.1.2.6.6.8 Pairwise meta-analytic approach

For each endpoint of interest, if there were multiple trials with same comparators in the same population, we conducted a pairwise meta-analysis of competing trials using a frequentist approach. We used the R package 'meta' to conduct this analysis, using the inverse variance approach for pooling and the DerSimonian-Laird method for estimating between studies variance. We grouped comparisons according to the network structure of the ITC: RCTs were meta-analyzed if they compared the same regimens within the ITC.

Fixed effect models were used when the number of RCTs in any given meta-analysis (i.e. at most two) was insufficient for estimating a value for the between studies standard deviation.

7.2.1.1.2.6.6.9 Indirect treatment comparison approach

The ITC was based on the frequentist approach using the Bucher method:

$$\hat{d}_{BC} = \hat{d}_{AC} - \hat{d}_{AB} \text{ , and}$$

$$Var(\hat{d}_{BC}) = Var(\hat{d}_{AC}) + Var(\hat{d}_{AB}),$$

where dBC represents the estimated treatment effect size between regimens B and C, and Var is the associated variance. Inputs were based on a pooled pairwise meta-analysis estimate when there was more than one RCT comparing any two regimens, and based on a single RCT when only one was available.

7.2.1.1.2.6.6.10 Statistical heterogeneity

Due to small number of trials (at most 2) in any direct pairwise meta-analysis, heterogeneity statistics were not calculated.

Tabular summaries were prepared of the median and landmark OS and PFS, as well as KM curve overlays, across the RCTs. We evaluated the range of estimates from a clinical perspective, considering the prevalence of subsequent IO use, delays in receipt of subsequent IOs, characteristics of the enrolled patient population, duration of follow-up, and maturity of the data for each trial.

Patient characteristics across the RCTs in any given ITC were reviewed using a tabular format. Specific focus was placed on differences in patient characteristics that might modify the treatment effect (i.e. treatment effect modifiers).

Such treatment effect modifiers were identified by reviewing endpoint-specific plots showing treatment effect size by subgroup, as presented by the RCT study authors; subgroup estimates were summarized in a tabular format and p-values were calculated.5 Given the immaturity of the Checkmate 9LA data, an initial analysis of effect modification was conducted but not presented within the current report, as it will be updated with more mature data as it becomes available.

7.2.1.1.2.6.6.11 Limitations of the Bucher ITC

The Bucher-based ITC is a simple frequentist-based method, which has a number of very important limitations that need to be considered when interpretation its results. These limitations include but are not limited to:

- There was considerable heterogeneity in terms of trial design, sample sizes, and populations, threatening the assumptions of similarity and transitivity on which all indirect treatment comparisons rely
- There were also important differences in population mixes included in the various studies, due to the large number of possible histology (all-comer, NSQ, SQ) and PD-L1 (all-comers, <1%, >=1%, 1-49%, >=50%) subgroup combinations
- Patient follow-up time was often limited and varied considerably between the studies
- There were multiple violations of the proportional hazards assumption within and between studies, making the use of a constant HR in the economic model very questionable and a Fractional Polynomial Network Meta Analysis approach has been applied.
- There was varied use and protocol-defined differences for cross-over and subsequent use of immunotherapies in the PDC arm which means that the 'common comparator' may not have been sufficiently similar to permit indirect comparisons within the set of immunotherapy trials.
- The studies may have been conducted in the pre-IO and post-IO era, leading to differences in second-line treatments that have been used and their efficacy

7.2.1.1.2.6.7 Results from the comparative analysis

Comparison of efficacy and safety of nivolumab plus ipilimumab in combination with chemotherapy vs. to pembrolizumab monotherapy (NSQ NSCLC PD-L1 ≥50%)

In Table 19 the efficacy results of the frequentist-based indirect comparisons (using Bucher method) of CheckMate 9LA against the latest follow-up of the KEYNOTE 042 trial using the PD-L1 ≥50% subgroup data is presented. The ITC provides an OS HR of 0.94 (95% CI 0.72, 1.24), a PFS HR of 0.82 (95% CI 0.63, 1.06). The HR for DoR is 1.19 (95% CI 0.71, 2.00) and the HR for ORR is 1.37 (95% CI 0.86, 2.18). All ITC estimates were non-significant and relatively close to the null value of 1. Additional details can be found in Appendix P Bucher ITC across histology and PD-L1 expression levels.

Table 19: CheckMate 9LA ITT population vs. KN042 PD-L1 ≥50% population

Study	CheckMate 9LA (Paz-Ares 2021a)		KEYNOTE 042 (Mok 2019a)	
Intervention	**Nivo+ipi+Chemo**	**Chemo**	**Pembro**	**Chemo**
N	361	358	299	300
Overall Survival (OS)				
Data cut	9 March, 2020		Sept 4, 2018	
Median follow-up: randomization to data cut-off, months (range)	NR (IQR: 12.7-NR)		NR	
Median follow-up: randomization to data cut-off or death, months (range)	13.2 (IQR: 6.4 - 17.0)		14.0 (IQR: 0.1 – 43.7)	
Median OS, months (95% KI)	15.6 (13.9 - 20.0)	10.9 (9.5 - 12.6)	20.0 (15.9 - 24.2)	12.2 (10.4 - 14.6)
Hazard Ratio HR (95% CI)	0.66 (0.55 - 0.80)		0.70 (0.58 – 0.86)	
Data source	(Paz-Ares 2021a)		(Mok 2019a)	
ITC HR (95 % CI)[a]	0.94 (0.72 – 1.24)			
Progression-Free Survival (PFS)				
Definition	Committee assessed RECIST 1.1		Committee assessed RECIST 1.1	
Data cut	9 March, 2020		Sept 4, 2018	
Median follow-up: randomization to data cut-off, months (range)	NR (IQR: 12.2-NR)		NR	
Median follow-up: randomization to data cut-off or death, months (range)	13.2 (IQR: 6.4 - 17.0)		14.0 (IQR: 0.1 – 43.7)	
Median PFS, months (95% CI)	6.7 (5.6 - 7.8)	5.0 (4.3 - 5.6)	6.5 (5.9 - 8.5)	6.4 (6.2 - 7.2)
HR (95% CI)	0.68 (0.57 - 0.82)		0.83 (0.69 - 1.00)	
Data source	(Paz-Ares 2021a)		(Mok 2019a)	
ITC HR (95 % CI)[a]	0.82 (0.63 – 1.06)			
Duration of response (DoR)				
Definition	Committee assessed RECIST 1.1		Committee assessed RECIST 1.1	
Data cut	9 March, 2020		Sept 4, 2018	
Median follow-up: randomization to data cut-off, months (range)	NR (IQR: 12.2- NR)		NR	
Median follow-up: randomization to data cut-off or death, months (range)	13.2 (IQR: 6.4 - 17.0)		14.0 (IQR: 0.1 – 43.7)	

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Median DoR, months (95% CI)	11.3 (8.5 - NA)	5.6 (4.4 - 7.5)	22.0 (2.1+ - 36.5+)	10.8 (1.8+ - 30.4+)
Hazard Ratio HR (95% CI)	[redacted]		0.42 (0.28 – 0.61)[b]	
Data source	HR calculated from CheckMate 9LA raw data; Medians reported by (Paz-Ares 2021a)		Medians reported by (Mok 2019a); HR calculated from KM curve presented by (Mok 2019a)	
ITC HR (95 % CI)[a]	[redacted]			
Objective response rate (ORR)				
Definition (complete response + partial response)	Committee assessed RECIST 1.1		Committee assessed RECIST 1.1	
Data cut	9 March, 2020		Sept 4, 2018	
Median follow-up: randomization to data cut-off, months (range)	NR (IQR: 12.2-NR)		NR	
Median follow-up: randomization to data cut-off or death, months (range)	13.2 (IQR: 6.4 - 17.0)		14.0 (IQR: 0.1 – 43.7)	
Complete + partial response, n (%)	8 (2) + 130 (36)	4(1) + (85 (24)	2 (0.7) + 115 (38.5)	1 (0.3) + 95 (31.7)
ORR (%)	38.2	24.9	39.1	32.0
Data source	(Paz-Ares 2021a)		(Mok 2019a)	
ITC ORR odds ratio	1.37 (0.86 – 2.18)			

[a] HR<1 favours NIVO+IPI + chemo, [b] calculated from Kaplan-Meier curve reconstructions, [c] Odds ratio >1 favours NIVO+IPI+PDC

The main difference in the control arm between CheckMate 9LA and KEYNOTE 042 was that KEYNOTE 042 was restricted to CARB-based regimens, whereas about 20% of patients in CheckMate 9LA received a CIS-based regimen. As noted above, CIS- and CARB-based regimens have been shown to have different toxicity profiles. Overall, the combination of NIVO+IPI+PDC led to a higher frequency of adverse events than PEMBRO monotherapy, both in the KEYNOTE 024 and the KEYNOTE 042 indirect comparisons. For ITCs involving KEYNOTE 042, Table 20, Table 21, Table 22, and Table 23 capture the arm-specific, trial-specific and indirect treatment comparisons with CheckMate 9LA.

Table 20: Indirect treatment comparisons for Grade 3/4/5 treatment-related AEs: CheckMate 9LA vs. KEYNOTE 042

Study	Intervention n / N (%)	Comparator n / N (%)	Odds ratio (95% CI)
CheckMate 9LA (ITT population)	169 / 358 (47.2%)	135 / 349 (38.7%)	1.42 (1.05, 1.91)
KEYNOTE 042 (PD-L1 ≥ 1% population)	117 / 636 (18.4%)	253 / 615 (41.1%)	0.32 (0.25, 0.42)
Indirect comparison: NIVO+IPI+PDC vs. PEMBRO	N/A	N/A	4.39 (2.96, 6.52)

Abbreviations: CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab; PEMBRO = pembrolizumab
For A vs. B comparisons, odds ratios greater than 1 represents more AEs for treatment A
KEYNOTE 042 data source: Mok et al. ELCC 2019 (Mok 2019a); CheckMate 9LA data source: (Bristol-Myers Squibb 2021a)

Table 21: Indirect treatment comparisons for Grade 1-5 treatment-related AEs: CheckMate 9LA vs. KEYNOTE 042

Study	Intervention n / N (%)	Comparator n / N (%)	Odds ratio (95% CI)
CheckMate 9LA (ITT population)	328 / 358 (91.6%)	306 / 349 (87.7%)	1.54 (0.94, 2.51)
KEYNOTE 042 (PD-L1 ≥ 1% population)	405 / 636 (63.7%)	553 / 615 (89.9%)	0.20 (0.14, 0.27)
Indirect comparison: NIVO+IPI+PDC vs. PEMBRO	N/A	N/A	7.82 (4.38, 13.96)

Abbreviations: CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab; PEMBRO = pembrolizumab
For A vs. B comparisons, odds ratios greater than 1 represents more AEs for treatment A
KEYNOTE 042 data source: Mok et al. ELCC 2019 (Mok 2019a); CheckMate 9LA data source: (Bristol-Myers Squibb 2021a)

Table 22: Indirect treatment comparisons for Grade 3/4/5 treatment-related AEs leading to discontinuation: CheckMate 9LA vs. KEYNOTE 042

Study	Intervention n / N (%)	Comparator n / N (%)	Odds ratio (95% CI)
CheckMate 9LA (ITT population)	58 / 358 (16.2%)	16 / 349 (4.6%)	4.02 (2.26, 7.15)
KEYNOTE 042 (PD-L1 ≥ 1% population)	48 / 636 (7.5%)	43 / 615 (7.0%)	1.09 (0.71, 1.66)
Indirect comparison: NIVO+IPIPDC vs. PEMBRO	N/A	N/A	3.71 (1.81, 7.59)

Abbreviations: CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab; PEMBRO = pembrolizumab
For A vs. B comparisons, odds ratios greater than 1 represents more AEs for treatment A
KEYNOTE 042 data source: Mok et al. Lancet 2019.(Mok 2019b) CheckMate 9LA data source: (Bristol-Myers Squibb 2021a)

Table 23: Indirect treatment comparisons for Grade 1-5 treatment-related AEs leading to discontinuation: CheckMate 9LA vs. KEYNOTE 042

Study	Intervention n / N (%)	Comparator n / N (%)	Odds ratio (95% CI)
CheckMate 9LA (ITT population)	69 / 358 (19.3%)	26 / 349 (7.4%)	2.97 (1.84, 4.78)
KEYNOTE 042 (PD-L1 ≥ 1% population)	62 / 636 (9.7%)	59 / 615 (9.6%)	1.02 (0.70, 1.48)
Indirect comparison: NIVO+IPI+PDC vs. PEMBRO	N/A	N/A	2.91 (1.59, 5.35)

Abbreviations: CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab; PEMBRO = pembrolizumab
For A vs. B comparisons, odds ratios greater than 1 represents more AEs for treatment A
KEYNOTE 042 data source: Mok et al. ELCC 2019 (Mok 2019a); CheckMate 9LA data source: (Paz-Ares 2021a) (Table S12)

7.2.1.1.2.6.8 Comparison of efficacy and safety of nivolumab plus ipilimumab in combination with chemotherapy vs. pembrolizumab + platinum+ pemetrexed for first-line treatment in a population with NSQ NSCLC

In Table 24 the efficacy results of the ITC of CheckMate 9LA against the latest follow-up of the KEYNOTE 189 trial (ITT) is presented. The ITC provides an OS HR of 1.18 (95% CI 0.89-1.55), a DoR HR of 1.02 (95% CI 0.60-1.73) which both were non-significant. The PFS ITC estimate (HR: 1.39, 95% CI 1.07, 1.79) is favourable for pembrolizumab+platinum+ pemetrexed whereas the HR: 0.50, 95% CI 0.30, 0.83 for ORR shows a small advantage for NIVO+IPI+PDC. Additional details can be found in Appendix P Bucher ITC across histology and PD-L1 expression levels.

Table 24: CheckMate 9LA ITT population vs. KN189 ITT population

Study	CheckMate 9LA (Paz-Ares 2021a)		KEYNOTE 189 (Gadgeel 2019, Gadgeel 2020, Rodriguez-Abreu 2020)	
Intervention	**Nivo+ipi+Chemo**	**Chemo**	**Pembro+plat+pem**	**Plat+pem**
N	361	358	410	206
Overall Survival (OS)				
Data cut	9 March, 2020		20 May, 2019	
Median follow-up: randomization to data cut-off, months (range)	NR (12.7- NR)		31.0 (IQR: 26.5 to 38.8)	
Median follow-up: randomization to data cut-off or death, months (range)	13.2 (IQR: 6.4 - 17.0)		18.8 (IQR: 0.2 – 38.8)	
Median OS, months (95% KI)	15.6 (13.9 - 20.0)	10.9 (9.5 - 12.6)	22.0 (19.5 - 24.5)	10.6 (8.7 - 13.6)
Hazard Ratio HR (95% CI)	0.66 (0.55 - 0.80)		0.56 (0.46 - 0.69)	
Data source	(Paz-Ares 2021a)		(Rodriguez-Abreu 2020)	
ITC HR (95 % CI)[a]	1.18 (0.89, 1.55)			
Progression-Free Survival (PFS)				
Definition	Committee assessed RECIST 1.1		Committee assessed RECIST 1.1	

Data cut	9 March, 2020		20 May, 2019	
Median follow-up: randomization to data cut-off, months (range)	NR (12.2 - NR)		31.0 (IQR: 26.5 - 38.8)	
Median follow-up: randomization to data cut-off or death, months (range)	13.2 (IQR: 6.4 - 17.0)		18.8 (IQR: 0.2 – 38.8)	
Median PFS, months (95% CI)	6.7 (5.6 - 7.8)	5.0 (4.3 - 5.6)	9.0 (8.1 - 10.4)	4.9 (4.7 - 5.5)
HR (95% CI)	0.68 (0.57 - 0.82)		0.49 (0.41 - 0.59)	
Data source	(Paz-Ares 2021a)		(Rodriguez-Abreu 2020)	
ITC HR (95 % CI)[a]	1.39 (1.07, 1.79)			
Duration of response (DoR)				
Definition	Committee assessed RECIST 1.1		Committee assessed RECIST 1.1	
Data cut	9 March, 2020		21 Sept, 2018	
Median follow-up: randomization to data cut-off, months (range)	NR (IQR: 12.2 – NR)		23.1 (IQR: 18.6 - 30.9)	
Median follow-up: randomization to data cut-off or death, months (range)	13.2 (IQR: 6.4 - 17.0)		18.7 (IQR: 0.2 to 30.9)	
Median DoR, months (95% CI)	11.3 (8.5 - NA)	5.6 (4.4 - 7.5)	12.4 (1.1- 29.0+)[d]	7.1 (2.4- 22.0+)[d]
Hazard Ratio HR (95% CI)	[redacted]		0.49 (0.33 - 0.73)[b]	
Data source	HR calculated from CheckMate 9LA raw data; Medians reported by (Paz-Ares 2021a)		(Gadgeel 2020); HR calculated from KM curve presented by (Gadgeel 2019, Gadgeel 2020, Rodriguez-Abreu 2020) (supplemental slide presentation; same data cut and duration of follow-up)	
ITC HR (95 % CI)[a]	[redacted]			
Objective response rate (ORR)				
Definition (complete response + partial response)	Committee assessed RECIST 1.1		Committee assessed RECIST 1.1	
Data cut	9 March, 2020		20 May, 2019	
Median follow-up: randomization to data cut-off, months (range)	NR (IQR: 12.2 – NR)		31.0 (IQR: 26.5 - 38.8)	
Median follow-up: randomization to data cut-off or death, months (range)	13.2 (IQR: 6.4 - 17.0)		18.8 (IQR: 0.2 - 38.8)	

Complete + partial response, n (%)	8 (2) + 130 (36)	4(1) + 85 (24)	198 (48.3)[e]	41 (19.9)[e]
ORR (%)	38.2	24.9	48.3	19.9
Data source	(Paz-Ares 2021a)		(Rodriguez-Abreu 2020); (Gadgeel 2020)[e]	
ITC ORR odds ratio	0.50 (0.30, 0.83)			

[a] HR<1 favours NIVO+IPI+PDC, [b] calculated from Kaplan-Meier curve reconstructions, [c] Odds ratio >1 favours NIVO+IPI+PDC, [d] Presented as median (range); + indicates no progressive disease by last time of assessment. [e] ORR is based on Rodriguez-Abreu however, the n (%) not provided for CR and PR separately; these were reported as CR=4(1) + PR=193 (47.1) for Pembro+plat+pem, and 1 (0.5) + 39 (18,9) for Plat+pem in an earlier publication by (Gadgeel 2020).

In the safety analysis the ITT population from CheckMate 9LA have been used. A known limitation of this approach is the lack of alignment in common comparator, as CARB-TAX is expected to have a different toxicity profile from CARB-PEMX and CIS-PEMX.

Using the ITT data from CheckMate 9LA, the ITC estimates are OR (95% CI):

- 0.99 (0.63, 1.56) for grade 3/4/5 treatment-related AEs;
- 1.31 (0.61, 2.83) for grade 1-5 treatment-related AEs, and
- 1.03 (0.49, 2.13) for grade 1-5 treatment-related AEs leading to discontinuation.

Irrespective of which population was used from CheckMate 9LA, all ITC estimates were non-significant and relatively close to the null value of 1 (Table 25, Table 26 and Table 27).

Table 25: Indirect treatment comparisons for Grade 3/4/5 treatment-related AEs: CheckMate 9LA vs. KEYNOTE 189

Study	Intervention n / N (%)	Comparator n / N (%)	Odds ratio (95% CI)
CheckMate 9LA (ITT population)	169 / 358 (47.2)	135 / 349 (38.7)	1.42 (1.05, 1.91)
KEYNOTE 189	196 / 405 (48.4%)	80 / 202 (39.6%)	1.43 (1.02, 2.01)
Indirect comparison: **NIVO+IPI+PDC vs. PEMBRO-PLAT-PEMX**	N/A	N/A	0.99 (0.63, 1.56)

Abbreviations: AE = adverse event; CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab; PEMBRO = pembrolizumab; PEMX = pemetrexed; PLAT = platinum
For A vs. B comparisons, odds ratios greater than 1 represent more AEs for treatment A
Data source: KEYNOTE 189 reported as treatment-related grade 3-5 AEs in the 2018 EPAR;(European Medicines Agency 2018) CheckMate 9LA: treatment-related grade 3/4 and grade 5 AEs reported separately in Paz-Ares; raw data were obtained to avoid double counting.(Paz-Ares 2021a)

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Table 26: Indirect treatment comparisons for Grade 1-5 treatment-related AEs: CheckMate 9LA vs. KEYNOTE 189

Study	Intervention n / N (%)	Comparator n / N (%)	Odds ratio (95% CI)
CheckMate 9LA (ITT population)	328 / 358 (91.6%)	306 / 349 (87.7%)	1.54 (0.94, 2.51)
KEYNOTE 189	372 / 405 (91.9%)	183 / 202 (90.6%)	1.17 (0.65, 2.11)
Indirect comparison: **NIVO+IPI+PDC vs. PEMBRO-PLAT-PEMX**	N/A	N/A	1.31 (0.61, 2.83)

Abbreviations: AE = adverse event; CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab; PEMBRO = pembrolizumab; PEMX = pemetrexed; PLAT = platinum
For A vs. B comparisons, odds ratios greater than 1 represent more AEs for treatment A
KEYNOTE 189 data source: (European Medicines Agency 2018)

Table 27: Indirect treatment comparisons for Grade 1-5 treatment-related AEs leading to discontinuation: CheckMate 9LA vs. KEYNOTE 189

Study	Intervention n / N (%)	Comparator n / N (%)	Odds ratio (95% CI)
CheckMate 9LA (ITT population)	69 / 358 (19.3%)	26 / 349 (7.4%)	2.97 (1.84, 4.78)
KEYNOTE 189	85 / 405 (21.0%)	17 / 202 (8.4%)	2.89 (1.67, 5.02)
Indirect comparison: **NIVO+IPI+PDC vs. PEMBRO-PLAT-PEMX**	N/A	N/A	1.03 (0.49, 2.13)

Abbreviations: AE = adverse event; CI = confidence interval; IPI = ipilimumab; NIVO = nivolumab; PEMBRO = pembrolizumab; PEMX = pemetrexed; PLAT = platinum
For A vs. B comparisons, odds ratios greater than 1 represent more AEs for treatment A
KEYNOTE 189 data source: (European Medicines Agency 2018)

7.2.1.1.2.6.9 Comparison of efficacy and safety of nivolumab plus ipilimumab in combination with chemotherapy vs. pembrolizumab + chemotherapy for first-line treatment in a population with SQ NSCLC

In Table 28 the efficacy results of the ITC of CheckMate 9LA against the latest follow-up of the KEYNOTE 407 trial (ITT) is presented. The ITC HR estimate for OS is 0.93 (95% CI 0.70,1.23) and for PFS 1.19 (95% CI 0.92,1.55) which both are non-significant. Also the HRs for DoR and ORR were non-significant (HR: 0.79, 95% CI 0.50,1.25 and HR: 0.70, 95% CI 0.44,1.11, respectively). Additional details can be found in Appendix P Bucher ITC across histology and PD-L1 expression levels.

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Table 28. CheckMate 9LA ITT population vs. KN407 ITT population

Study	CheckMate 9LA (Paz-Ares 2021a)		KEYNOTE 407 (Paz-Ares 2019, Paz-Ares 2020)	
Intervention	**Nivo+ipi+Chemo**	**Chemo**	**PEMBRO-CARB-(NAB)TAX**	**Placebo-CARB-(NAB)TAX**
N	361	358	278	281
Overall Survival (OS)				
Data cut	9 March, 2020		9 May, 2019	
Median follow-up: randomization to data cut-off, months (range)	NR (IQR: 12.7 – NR)		NR	
Median follow-up: randomization to data cut-off or death, months (range)	13.2 (IQR: 6.4 - 17.0)		14.3 (IQR: 0.1 - 31.3)	
Median OS, months (95% KI)	15.6 (13.9 - 20.0)	10.9 (9.5 - 12.6)	17.1 (14.4 - 19.9)	11.6 (10.1 - 13.7)
Hazard Ratio HR (95% CI)	0.66 (0.55 - 0.80)		0.71 (0.58 - 0.88)	
Data source	(Paz-Ares 2021a)		(Paz-Ares 2019, Paz-Ares 2020)	
ITC HR (95 % CI)a	0.93 (0.70, 1.23)			
Progression-Free Survival (PFS)				
Definition	Committee assessed RECIST 1.1		Committee assessed RECIST 1.1	
Data cut	9 March 2020		9 May, 2019	
Median follow-up: randomization to data cut-off, months (range)	NR (IQR: 12.2 – NR)		NR	
Median follow-up: randomization to data cut-off or death, months (range)	13.2 (IQR: 6.4 - 17.0)		14.3 (IQR: 0.1 – 31.3)	
Median PFS, months (95% CI)	6.7 (5.6 - 7.8)	5.0 (4.3 - 5.6)	8.0 (6.3 – 8.4)	5.1 (4.3 – 6.0)
HR (95% CI)	0.68 (0.57 - 0.82)		0.57 (0.47 - 0.69)	
Data source	(Paz-Ares 2021a)		(Paz-Ares 2019, Paz-Ares 2020)	
ITC HR (95 % CI)[a]	1.19 (0.92, 1.55)			
Duration of response (DoR)				
Definition	Committee assessed RECIST 1.1		Committee assessed RECIST 1.1	
Data cut	9 March, 2020		9 May, 2019	
Median follow-up: randomization to data cut-off, months (range)	NR (IQR: 12.2 – NR)		NR	

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Median follow-up: randomization to data cut-off or death, months (range)	13.2 (IQR: 6.4 - 17.0)		14.3 (IQR: 0.1 – 31.3)	
Median DoR, months (95% CI)	11.3 (8.5 - NA)	5.6 (4.4 - 7.5)	8.8 (1.3+ - 28.4+)	4.9 (1.3+ - 28.3+)
Hazard Ratio HR (95% CI)	[redacted]		0.63 (0.47 - 0.85)[b]	
Data source	HR calculated from CheckMate 9LA raw data; Medians reported by (Paz-Ares 2021a)		Medians reported in (Paz-Ares 2019, Paz-Ares 2020); HR calculated from KM curve presented by (Paz-Ares 2019, Paz-Ares 2020)	
ITC HR (95 % CI)[a]	[redacted]			
Objective response rate (ORR)				
Definition (complete response + partial response)	Committee assessed RECIST 1.1		Committee assessed RECIST 1.1	
Data cut	9 March, 2020		9 May, 2019	
Median follow-up: randomization to data cut-off, months (range)	NR (IQR: 12.2 – NR)		NR	
Median follow-up: randomization to data cut-off or death, months (range)	13.2 (IQR: 6.4 - 17.0)		14.3 (IQR: 0.1 – 31.3)	
Complete + partial response, n (%)	8 (2) + 130 (36)	4(1) + 85 (24)	6 (2.2) + 168 (60.4)	9 (3.2) + 99 (35.2)
ORR (%)	38.2	24.9	62.6	38.4
Data source	(Paz-Ares 2021a)		(Paz-Ares 2019, Paz-Ares 2020)	
ITC ORR odds ratio	0.70 (0.44 – 1.11)			

[a] HR<1 favours NIVO+IPI+PDC, [b] calculated from Kaplan-Meier curve reconstructions, [c] Odds ratio >1 favours NIVO+IPI+PDC,

In Table 29, Table 30 and Table 31 the safety ITC estimates are presented. A known limitation of this approach is the lack of alignment in common comparator, as CARB-PEMX and CIS-PEMX are expected to have a different toxicity profile from CARB-TAX and CARB-NabTAX.

Using ITT data from CheckMate 9LA, the ITC estimates are (OR 95% CI):

- 1.44 (0.92, 2.25) for grade 3/4/5 treatment-related AEs;
- 0.61 (0.26, 1.39) for grade 1-5 treatment-related AEs, and
- 1.04 (0.50, 2.15) for grade 1-5 treatment-related AEs leading to discontinuation.

Irrespective of which population was used from CheckMate 9LA, all ITC estimates were non-significant.

Table 29: Indirect treatment comparisons for Grade 3/4/5 treatment-related AEs: CheckMate 9LA vs. KEYNOTE 407

Study	Intervention n / N (%)	Comparator n / N (%)	Odds ratio (95% CI)
CheckMate 9LA (ITT population)	169 / 358 (47.2)	135 / 349 (38.7)	1.42 (1.05, 1.91)
KEYNOTE 407	152 / 278 (54.7%)	154 / 280 (55.0%)	0.99 (0.71, 1.38)
Indirect comparison: **NIVO+IPI+PDC vs. PEMBRO-CARB-(Nab)TAX**	N/A	N/A	1.44 (0.92, 2.25)

Abbreviations: CARB = carboplatin; CI = confidence interval; IPI = ipilimumab; (Nab)TAX = albumin-bound or standard paclitaxel; NIVO = nivolumab; PEMBRO = pembrolizumab; TAX = paclitaxel
For A vs. B comparisons, odds ratios greater than 1 represents more AEs for treatment A
KEYNOTE 407 data source: (European Medicines Agency 2019)

Table 30: Indirect treatment comparisons for Grade 1-5 treatment-related AEs: CheckMate 9LA vs. KEYNOTE 407

Study	Intervention n / N (%)	Comparator n / N (%)	Odds ratio (95% CI)
CheckMate 9LA (ITT population)	328 / 358 (91.6%)	306 / 349 (87.7%)	1.54 (0.94, 2.51)
KEYNOTE 407	265 / 278 (95.3%)	249 / 280 (88.9%)	2.54 (1.30, 4.96)
Indirect comparison: **NIVO+IPI+PDC vs. PEMBRO-CARB-(Nab)TAX**	N/A	N/A	0.61 (0.26, 1.39)

Abbreviations: CARB = carboplatin; CI = confidence interval; IPI = ipilimumab; (Nab)TAX = albumin-bound or standard paclitaxel; NIVO = nivolumab; PEMBRO = pembrolizumab; TAX = paclitaxel
For A vs. B comparisons, odds ratios greater than 1 represents more AEs for treatment A
KEYNOTE 407 data source: (European Medicines Agency 2019)

Table 31: Indirect treatment comparisons for Grade 1-5 treatment-related AEs leading to discontinuation: CheckMate 9LA vs. KEYNOTE 407

Study	Intervention n / N (%)	Comparator n / N (%)	Odds ratio (95% CI)
CheckMate 9LA (ITT population)	69 / 358 (19.3%)	26 / 349 (7.4%)	2.97 (1.84, 4.78)
KEYNOTE 407	50 / 278 (18.0)	20 / 280 (7.1)	2.85 (1.65, 4.93)
Indirect comparison: **NIVO+IPI+PDC vs. PEMBRO-CARB-(Nab)TAX**	N/A	N/A	1.04 (0.50, 2.15)

Abbreviations: CARB = carboplatin; CI = confidence interval; IPI = ipilimumab; (Nab)TAX = albumin-bound or standard paclitaxel; NIVO = nivolumab; PEMBRO = pembrolizumab; TAX = paclitaxel
For A vs. B comparisons, odds ratios greater than 1 represents more AEs for treatment A
KEYNOTE 407 data source: (European Medicines Agency 2019)

7.2.1.1.2.6.9.1 Forest plots for all comparisons

Figure 43 to Figure 47 below presents forest plots for all of the results based on the Bucher ITC and illustrates the main outcomes of results, namely that the confidence intervals for individual study results overlap in the majority of cases,

spporting equal efficacy across the immunotherapies. In addition forest plots per outcome also for the meta-anlayzed estimates for KeyNote 024 + KeyNote 042 are presented, in Figure 48 to Figure 50.

Figure 43: Summary forest plot across all comparisons and populations – overall survival

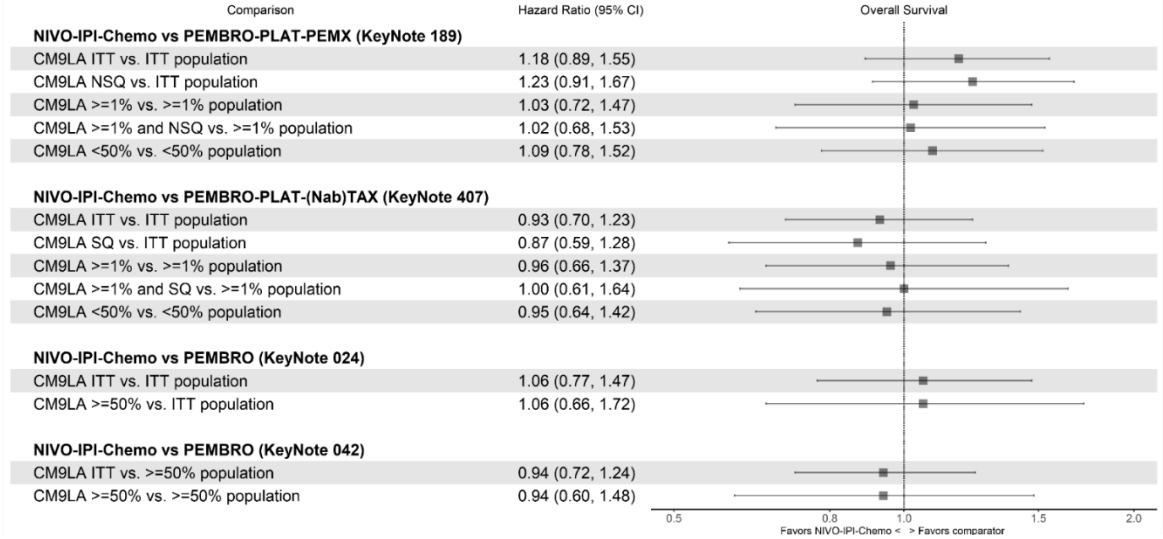
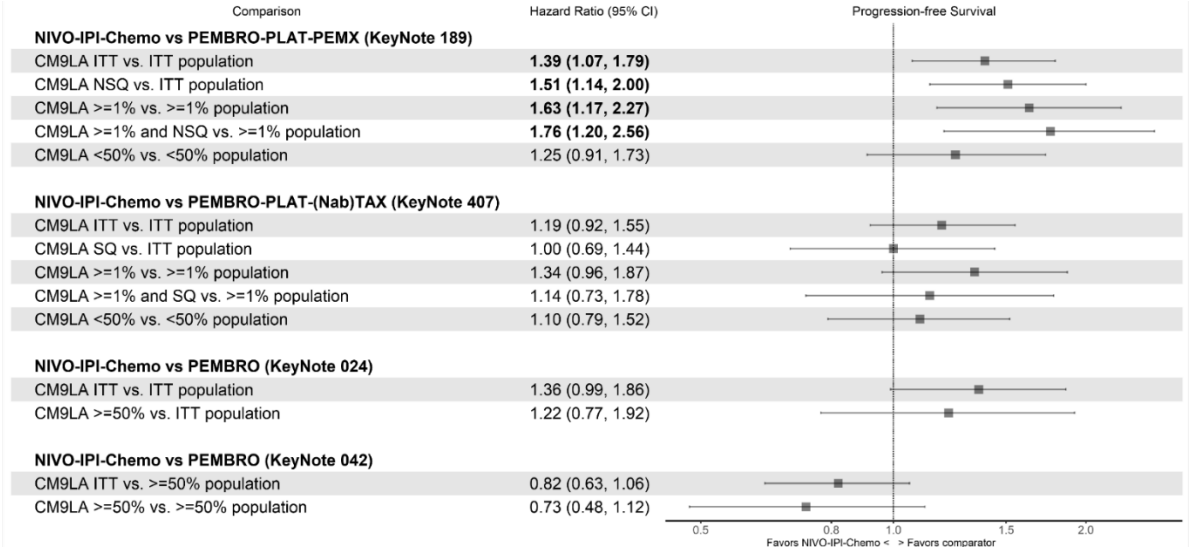


Figure 44: Summary forest plot across all comparisons and populations – progression-free survival



[redacted]

Figure 46: Summary forest plot across all comparisons and populations – objective response

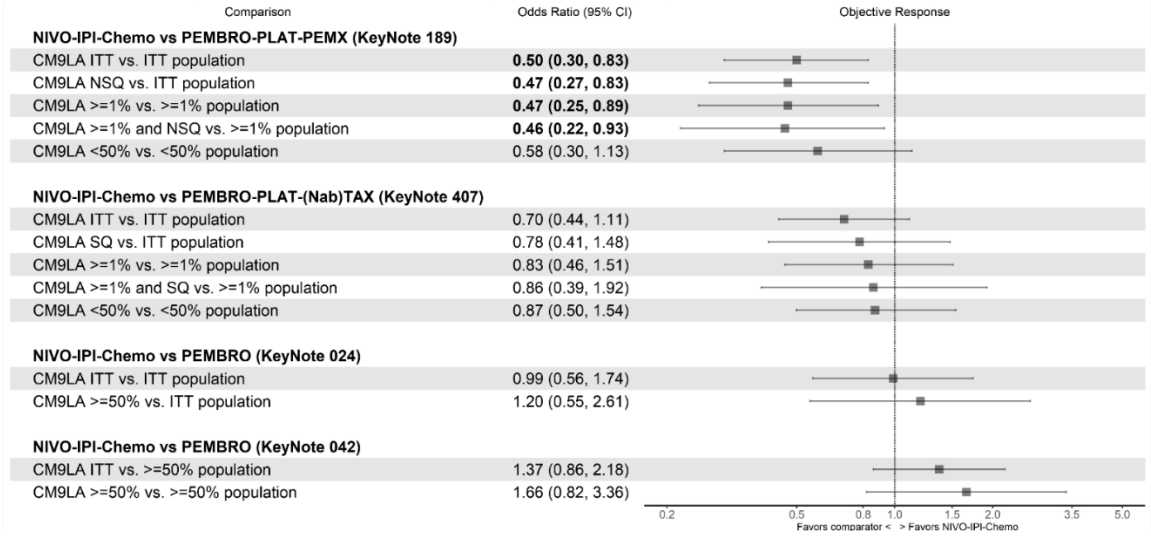
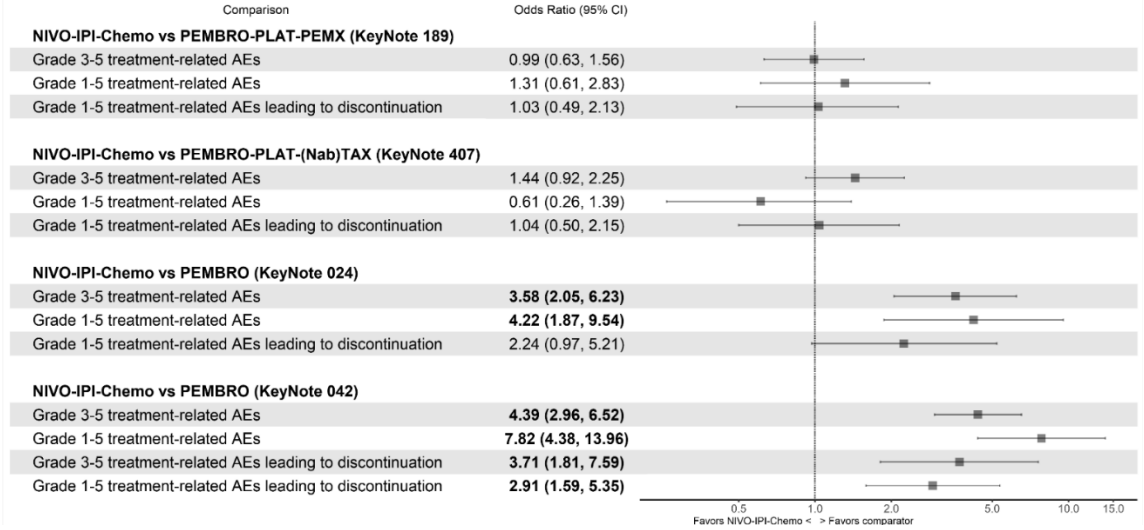
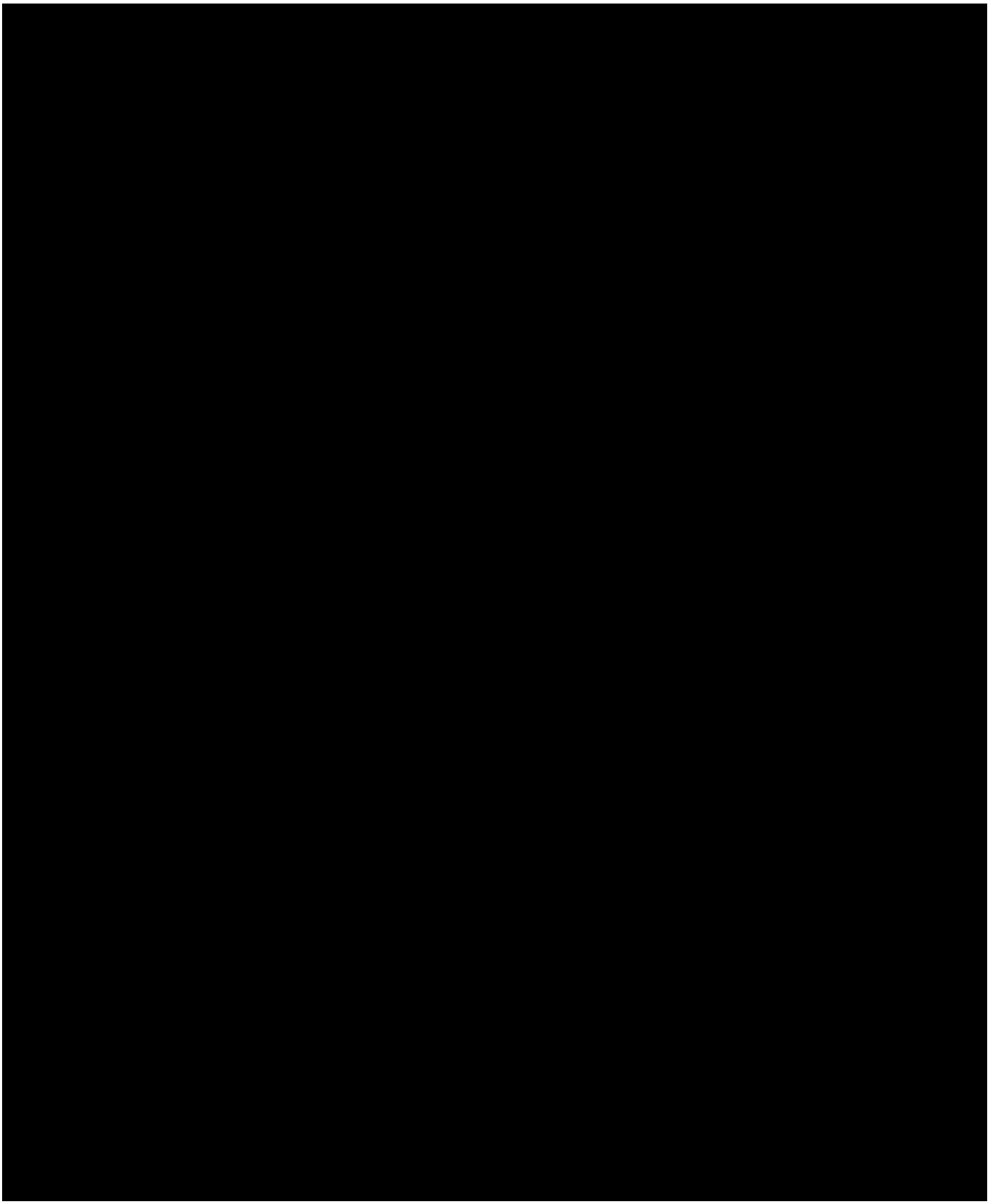


Figure 47: Summary forest plot across all comparisons and populations – AEs





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7.2.1.1.2.6.10 Discussion on the comparative analysis

For every comparison, there were only one or two suitable randomized trials. The main finding is that nivo+ipi+chemo had comparable OS efficacy compared with pembrolizumab monotherapy where the 95% CIs contain 1 for PFS and OS for all comparators.

The outcomes of the subgroup analysis across all relevant histology based and PD-L1 expression levels shows that the relative effect size between nivo+ipi+chemo and chemotherapy alone is not influenced by PD-L1 expression level or histology; i.e. the treatment effect in the overall population is the same as in histology-specific or PD-L1-specific sub-populations, and that subgroup-level differences in treatment effect estimates are due to chance alone. However, it should be noted that CheckMate 9LA was not powered to detect treatment effects within PD-L1-based subgroups or PD-L1-based subgroups by histology. The population with PD-L1 ≥50% is not protected by randomization or stratification; imbalances in known or unknown baseline factors may exist. An analysis of this patient population may result in small patients' numbers results in wide confidence intervals.

HRs for OS for the comparator vs nivo+ipi+chemo ranged from 0.93 to 1.18. Nivo+ipi+chemo also had comparable efficacy for PFS except when compared with pembrolizumab + platinum + pemetrexed which had improved PFS compared with the NIVO-containing regimen. PFS is a surrogate outcome typically not predictive of similar gains in OS for IO therapies because of weak correlations between endpoints and the mechanism of action where IO therapies have a delayed response compared with cytotoxic agents (Petrelli 2019). Therefore, the OS hazard ratios were used as the primary focus for comparison of agents.

The comparison of relatively immature data from Checkmate 9LA relative to more mature data from other comparator trials should be interpreted with caution, given the different dynamic between dual-IO, mono-IO, and chemo: specifically, the short-term benefit conferred by chemotherapy compared with the longer-term benefit of dual-IO therapy. The overlays of the OS Kaplan-Meier curves from CheckMate 227 Part 1, CheckMate 9LA, and the most recent data available for KEYNOTE 189 show differences in temporal trends associated with the different treatment regimens (Rodriguez-Abreu 2020). While the combination of pembrolizumab + PDC resulted in an early OS benefit, longer term data from KEYNOTE 189, through approximately 24 months where the censoring begins, do not demonstrate any plateauing effect as seen with CheckMate 227 Part 1. As a consequence, the proportion of patients alive by 2.5 to 3 years was similar for nivo+ipi and pembrolizumab + PDC, based on a naïve comparison. As the long-term OS trajectory of the NIVO+IPI+PDC regimen in CheckMate 9LA is expected to be similar to the NIVO+IPI regimen from CheckMate 227, a similar crossing of the KEYNOTE 189 OS curves by 2.5 to 3 years and potentially beyond is expected.

The proportional hazard assumption across the trials was assessed and disclosed that the HRs cannot be assumed to be constant over time for OS in CheckMate 9LA vs KEYNOTE 189 in the PD-L1 all comers and the PD-L1≥50% subgroups as well as for PFS in CheckMate 9LA vs KEYNOTE 024 in the PD-L1≥ 50% subgroup as well as for PFS vs KEYNOTE 042 in the PD-L1 ≥1% and PD-L1 ≥ 50% subgroups. Finally, there was evidence of proportional hazards violation in the comparisons of OS for CheckMate 9LA vs KEYNOTE 042 in the PD-L1 ≥1, PD-L1 1-49% and PD-L1 ≥ 50% subgroups.

Because of the violation of proportional hazards assumption mentioned above analyses were expanded beyond simple reported HR models to time-varying models that are better suited for dealing with survival evidence where the proportional hazards assumption is not met. Fractional polynomial models address this issue, however, they are more complex than Bayesian NMAs involving constant HRs, so their application should be limited to instances where such methods are not appropriate. The results of this NMA disclose that while the projected HRs for NIVO+IPI+PDC gradually increase beyond the null value (HR of 1) by 24 months and beyond, it should be noted that these are projections beyond the observed time horizon of the CheckMate 9LA trial; it may be more clinically plausible that the HRs stabilize to an HR of 1.

Differences in study design and conduct may have influenced the validity of the indirect treatment comparisons between Checkmate 9LA and other comparator RCTs. The complexity of interpreting the impact of these differences on the ITC estimates formed the basis of choosing to conduct a series of ITCs, rather than an integrated network of the full evidence base. The first consideration was reflected in the OS performance of the chemotherapy regimens, which was heterogeneous across the evidence base. This is thought to have been influenced by a number of factors, including: study period, region(s), blinding, specific chemo regimens and dosing, timing and extent of use of subsequent immunotherapies, as well as differences in prognostic factors (which may also have modified treatment effect estimates). Such differences challenge the validity of assuming a common chemotherapy comparator in the ITCs, highlighting the need to consider the quantitative estimates of relative effect with caution. The difference in subsequent treatments is illustrated in Table 32 below.

Table 32: Differences in subsequent treatments across trials

CheckMate 9LA	KEYNOTE 189	KEYNOTE 407	KEYNOTE 024	KEYNOTE 042
Cross-over / subsequent therapy:	Cross-over / subsequent therapy:	Cross-over / subsequent therapy:	Cross-over / subsequent therapy:	Cross-over / subsequent therapy:
Subsequent **systemic therapy**: 34% in NIVO+IPI+PDC arm; 46% in chemotherapy arm. Subsequent **immunotherapy:** 7% in NIVO+IPI+PDC arm; 36% in chemotherapy arm. (Reck 2021)	Cross-over to pembrolizumab monotherapy permitted at progression (following blinded radiological review) (40.8%). Overall use of subsequent IO (within or outside of trial): 53.9%. [source: (Gadgeel 2020)] The most frequent second-line IO was pembrolizumab (33.5%) and nivolumab (6.8%) [source: (Gandhi 2018)].	Cross-over to pembrolizumab monotherapy permitted at progression (following blinded radiological review) (40.1%). Overall use of subsequent IO (within or outside of trial): 49.1%. [source:(Barlesi 2019)] The most frequent second-line IO was not reported.	The effective cross-over rate was 65% (55% while on-study). 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.	Crossover not permitted. 20% of patients in the chemotherapy arm received subsequent immunotherapy (13% received nivolumab). Patients with radiographic disease progression who were clinically stable could continue study treatment until progression was confirmed on a scan obtained at least 4 weeks later.

A second difference was that CheckMate 9LA was open-label, as opposed to the double-blinded design of KEYNOTE 189 and KEYNOTE 407. In the open-label CheckMate 9LA study, knowledge of treatment allocation for first-line therapy may have influenced decisions regarding subsequent treatment and the possibility of switch prior to confirmed progression for patients randomized to the chemotherapy arm.

A third difference is the difference in duration of treatment across the trials (Table 33). NIVO+IPI+PDC had a median duration of treatment of 6.1 months whereas the treatment duration of pembrolizumab ranged between 6.3 months (Paz-Ares 2018) to 7.4 months (Gandhi 2018).

Table 33: Comparison of duration of treatment across trials

9LA (months)		CM 227 (months)		KEYNOTE 024 (months)		KEYNOTE 189 (months)		KEYNOTE 407 (months)			
NIVO+IPI+PDC	PDC	NIVO+IPI	PDC	pembrolizumab	PDC	pembro combination	placebo-combination	pembro combination	placebo-combination	Pembro combination	placebo-combination
6.1 (0-24.4)	2.5 (0.0-34.5)	4.2 (0.03-24)	2.6 (0.03-22.1)	7.0 (0.0-18.7)	3.5 (1-16.8)	7.4 (2.7-12.1)	5.4 (1.1-9.7)	6.3 (2.2-10.4)	4.7 (1.2-8.2)	7.1 (0.03-26.3)	4.6 (0.03-24.1)
Reck 2021		Ramalingam 2020		Reck 2016		Gandhi 2018		Paz-Ares 2018		Paz-Ares 2020	

Reference(Reck 2021); (Ramalingam 2020); (Reck 2016); (Gandhi 2018); (Paz-Ares 2018); (Reck 2020c).

The share of patients receiving 5 or more cycles of pemetrexed in the PDC arm is approx. 67% (135/202) in KEYNOTE 189 (Gadgeel 2020) which is understood to be similar to what is seen in Danish clinical practice (Clinical expert interview 2020). This is comparable to CM-9LA where 159 of 238 (67%) patients with nonsquamous tumor histology received pemetrexed maintenance and at the 2 year database lock, 11 patients were still receiving pemetrexed maintenance therapy (Reck 2021).

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8. Health economic analysis

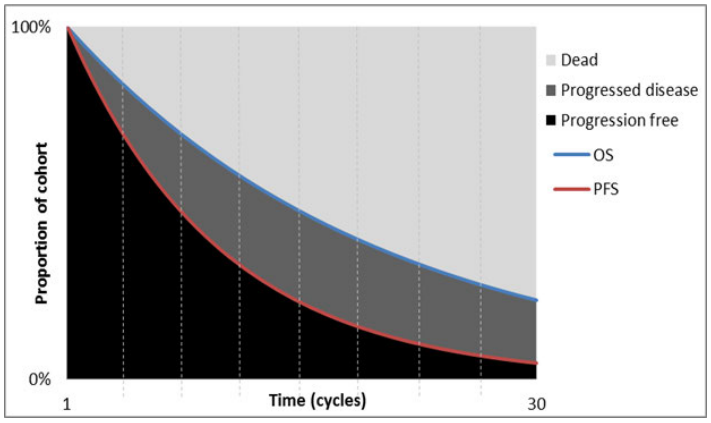
8.1 Model

A cohort model was developed to evaluate the incremental cost-effectiveness of NIVO+IPI+PDC vs. alternative therapy options in patients with previously untreated Stage IV or recurrent NSCLC.

The structure of the model comprises of three health states: progression-free (PF), progressed disease (PD), and death. These health states correspond to the primary and secondary endpoints of the CheckMate 9LA trial and other key trials for nivolumab. A partitioned survival model (PSM) modelling technique was used, as is common in oncology indications and consistent with previous IO therapy HTA submissions. This means that health state occupancy was calculated directly from the areas under the PFS curve, between the PFS and OS curves and above the OS curve observed in CheckMate 9LA for PF, PD and death, respectively. Figure 51 presents a visual description of the PSM for illustrational purposes. In the PF health state, CheckMate 9LA DoT data was used to inform duration (and hence cost) of treatment. A two-year stopping rule was applied to NIVO+IPI+PDC and other IO therapies in the base case analysis, consistent with CheckMate 9LA clinical trial design and common clinical practice in many countries.

The model was developed in Microsoft Excel (Office 365) and programmed using standard Excel functions wherever possible. Visual basic was used sparingly and was limited to running Monte-Carlo simulations in the probabilistic sensitivity analysis (PSA), for generating survival estimates, and for navigation purposes. All model references and assumptions are clearly described within the Excel file.

Figure 51: Overview of the partitioned survival method (illustrational)



..OS: Overall survival; PFS: Progression-free survival

A one-week cycle length was used for the first 28 weeks of the model to accommodate the administration cycles of the included therapies. From week 28 onwards, four-weekly model cycles are used.

The costs and health outcomes (in terms of QALYs) associated with treatments are calculated by combining the estimated time spent in the PF and PD states with the costs and health utilities assigned to those states. The healthcare costs considered in the evaluation included the cost of drug acquisition, drug administration, monitoring, disease management, end-of-life care, management of AEs, subsequent (second-line) treatments, and (optional) biomarker testing costs.

In the base case analysis, the health effects associated with the different treatment strategies were modelled in terms of QALYs. The quality of life aspect of treatment was modelled using data derived from the CheckMate 9LA clinical trial.

A summary of the core elements of the economic model is shown in Table 34.

Table 34: Technical description of the economic model

Aspect	Details	Comment
Analytical method	Cohort-based partitioned survival model	Analytical technique that is applied very commonly in oncology and has been used in various technology appraisals for anti-cancer treatments in NSCLC
Time horizon	Lifetime (25 years)	To capture the costs and outcomes over the patient's lifetime. The model shows approximately 1% and 0.2% of patients survive at year 25 in the NIVO+IPI+PDC and the PDC arm, respectively, therefore the time horizon selected was 25 years.
Cycle length	Weekly (week 1 to 28) Four-week (week 28 onwards)	Weekly cycles until week 28 to accommodate differing administration cycles for chemotherapies
Half-cycle correction	Yes	The model calculated mid-cycle estimates in each health state by taking the average of patients present at the beginning and at the end of each cycle.
Discounting options	Costs and health outcomes	Both costs and outcomes are subject to annual discounting in the evaluation
Treatment arms	NIVO+IPI+PDC PDC	In line with CheckMate 9LA, NIVO+IPI+PDC and PDC are considered to be the most relevant comparators for the main analysis.
Software used	Microsoft Excel (Office 365)	Excel is an accessible and widely available platform
Inputs		
Clinical efficacy and safety	ITT: • CheckMate 9LA trial – based on the 2- year DBL for direct comparison • CheckMate 227 (Part 1) trial – based on the 4- year DBL is used for extrapolation of NIVO+IPI+PDC and PDC PFS and OS data SQ PD-L1<1% • CheckMate 9LA trial – based on SQ PD-L1<1% data and the 2-year DBL for direct comparison • CheckMate 227 (Part 1b) trial – based on the 4- year DBL is used for extrapolation of NIVO+IPI+PDC and PDC PFS and OS data	The CheckMate 9LA and 227 trials are the key registrational trials for nivolumab regimens in the first-line treatment of Stage IV or recurrent NSCLC. Dataset used for external validation were SEER, Nordic registry data, and previous Checkmate trials
Treatment duration	NIVO+IPI+PDC : CheckMate 9LA DoT KM PDC: CheckMate 9LA DoT KM	CheckMate 9LA DoT KM are relatively mature, therefore there is no need for extrapolation The model allows the user to work with alternative assumptions around DoT (e.g. use PFS as a proxy for DoT)
Costs	A review of published studies and previous HTA submissions reporting the	Costs are sourced from official Danish sources as per guidance (Medicinrådet 2021b)

	economic burden in patients with advanced NSCLC	
Utilities	CheckMate 9LA EQ-5D data (treatment specific utilities for PF and PD, or utilities based on TTD) A review of previous HTA submissions within advanced NSCLC (disutility of AEs for scenario analyses)	Utility values derived with EQ-5D-5L Danish utility weights
Outputs		
Cost-effectiveness ratios	Incremental cost effectiveness ratio (ICER)	ICER: Incremental cost per effect (e.g. life years gained)
Costs	Disaggregated, total and incremental	-
QALYs	Disaggregated, total and incremental	-
Life years (LY)	Disaggregated, total and incremental	-
Cost-efficiency frontier	Yes	-
Incremental cost-effectiveness plane	Yes	-
Cost-effectiveness acceptability curve and frontiers	Yes	-
Automated PSA and DSA	Yes	-

..first-line: First-line; AE: Adverse events; DBL: Database lock; DoT: Duration of treatment; DSA: Deterministic sensitivity analysis; EQ-5D: EuroQol-5 dimensions; HTA: Health technology assessment; ICER: Incremental cost-effectiveness ratio; IO: Immuno-oncology; KM: Kaplan-Meier; NIVO+IPI+PDC : nivolumab + ipilimumab combined with limited chemotherapy; NSCLC: Non-small cell lung cancer; OS: Overall survival; PD: Progressed disease; PDC: Platinum doublet chemotherapy; PF: Progression-free; PFS: Progression-free survival; PSA: Probabilistic sensitivity analysis; QALY: Quality adjusted life year; SEER: Surveillance, Epidemiology, and End Results program; TTD: Time to death; US: United States

8.1.1 Key assumptions for Danish adaptation

8.1.1.1 Perspective

As recommended in the "Medicinrådets metodevejledning for vurdering af nye lægemidler" (Medicinrådet 2020) from DMC an "restricted health-care perspective" is applied where the indirect costs of carers accompanying patients at every physician visits (excluding infusions) in terms of loss of leisure time, and transportation costs of the patients will be included. Productivity changes as a result of the intervention will not be considered.

8.1.1.2 Time horizon, cycle length and discounting

A time horizon of 25 years was used in the model, which was assumed to be a lifetime horizon for patients with advanced NSCLC. Approximately 1% of the patients in the nivolumab plus ipilimumab plus chemotherapy arm and 0.2% of the patients in the chemotherapy arm are estimated to be alive after 25 years.

A one-week cycle length was used for the first 28 weeks of the model to accommodate the administration cycles of the included therapies. From week 28 onwards, four-weekly model cycles are used.

The model applies a discount rate of 3.5% for costs and health effects in the base case (Medicinrådet 2021b).

8.1.1.3 Wastage and dose intensity

In the base case analysis, flat dosing, vial sharing and a two-year stopping rule is applied to the nivolumab and ipilimumab therapies in the base case analysis, consistent with Checkmate 9LA clinical trial design and summary of product caractheristics (European Medicines Agency 2020c).

There is a possibility to explore the following options in the model as scenario analyses:

- Treatment cap: treatment caps by year for nivolumab and ipilimumab
- Wastage: there is also a possibility to explore scenarios without vial sharing in the model
- Posology: Weight-based dosing for nivolumab
- Discount: discount levels for nivolumab and/or ipilimumab

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

Table 35 summarizes and presents in a coherent manner the estimates that inform the base case health economic model. The input data that informs the model include clinical effect, state occupancy, disease management, monitoring, administration, QALY, AEs, subsequent treatments, and costs.

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Table 35: Input data used in the base case health economic model (ITT and SQ PDL1<1% respectively)

Name of inputs	Source	Value used in model	How is the value used in the model/Comments
Clinical effect - ITT			
OS NIVO+IPI+PDC	Parametric model	2-knot spline normal distribution	CheckMate 9LA KM data up to 2424 months and independent log-normal OS curve fitted to CheckMate 227 Part 1 complete data set, from month 24 and onwards
OS PDC	Parametric model	2-knot spline odds distribution	CheckMate 9LA KM data up to 24 months and independent log-logistic OS curve fitted to CheckMate 227 Part 1 complete data set, from month 24 and onwards
PFS NIVO+IPI+PDC	Parametric model	2-knot spline hazards distribution	CheckMate 9LA KM data up to 24 months and independent 2 knot spline odds PFS curve fitted CheckMate 227 Part 1 complete data set, from month 24 and onwards
PFS PDC	Parametric model	2-knot spline normal distribution	CheckMate 9LA KM data up to 24 months and independent 2 knot spline normal PFS curve fitted to CheckMate 227 Part 1 complete data set, from month 24 and onwards
DoT NIVO+IPI+PDC	Parametric model	KM curves	CheckMate 9LA KM DoT data
DoT PDC	Parametric model	KM curves	CheckMate 9LA KM DoT data
Clinical effect – SQ PDL1<1%			
OS NIVO+IPI+PDC	Parametric model	Generalized gamma distribution	CheckMate 9LA KM data up to 2424 months and independent log-normal OS curve fitted to CheckMate 227 Part 1 complete data set, from month 24 and onwards
OS PDC	Parametric model	Log-logistic distribution	CheckMate 9LA KM data up to 24 months and independent log-logistic OS curve fitted to CheckMate 227 Part 1 complete data set, from month 24 and onwards
PFS NIVO+IPI+PDC	Parametric model	1-knot spline normal distribution	CheckMate 9LA KM data up to 24 months and independent 2 knot spline odds PFS curve fitted CheckMate 227 Part 1 complete data set, from month 24 and onwards
PFS PDC	Parametric model	Log-logistic distribution	CheckMate 9LA KM data up to 24 months and independent 2 knot spline normal PFS curve fitted to CheckMate 227 Part 1 complete data set, from month 24 and onwards
DoT NIVO+IPI+PDC	Parametric model	KM curves	CheckMate 9LA KM DoT data
DoT PDC	Parametric model	KM curves	CheckMate 9LA KM DoT data
State occupancy – ITT and SQ PDL1<1%			
Progression free	Partitioned survival model	Progression free survival curve	PF=P(PFS)
Death	Partitioned survival model	1-P(OS)	Death=1-P(OS)
Progressed disease	Partitioned survival model	P(OS)-P(PFS)	PD=P(OS)-P(PFS)

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[redacted]			
Anaemia occurrence	CheckMate 9LA trial	[redacted]	Any treatment-emergent grade 3 or above events occurring in at least 5% of patients in either treatment arm
Neutropenia occurrence	CheckMate 9LA trial	[redacted]	Any treatment-emergent grade 3 or above events occurring in at least 5% of patients in either treatment arm
Fatigue occurrence	CheckMate 9LA trial	[redacted]	Any treatment-emergent grade 3 or above events occurring in at least 5% of patients in either treatment arm
Lipase increase occurrence	CheckMate 9LA trial	[redacted]	Any treatment-emergent grade 3 or above events occurring in at least 5% of patients in either treatment arm
Thrombocytopenia occurrence	CheckMate 9LA trial	[redacted]	Any treatment-emergent grade 3 or above events occurring in at least 5% of patients in either treatment arm
Neutrophil count decreased occurrence	CheckMate 9LA trial	[redacted]	Any treatment-emergent grade 3 or above events occurring in at least 5% of patients in either treatment arm
Platelet count decreased occurrence	CheckMate 9LA trial	[redacted]	Any treatment-emergent grade 3 or above events occurring in at least 5% of patients in either treatment arm
White blood cell count decreased occurrence	CheckMate 9LA trial	[redacted]	Any treatment-emergent grade 3 or above events occurring in at least 5% of patients in either treatment arm
Febrile neutropenia occurrence	CheckMate 9LA trial	[redacted]	Any treatment-emergent grade 3 or above events occurring in at least 5% of patients in either treatment arm
Hypertension occurrence	CheckMate 9LA trial	[redacted]	Any treatment-emergent grade 3 or above events occurring in at least 5% of patients in either treatment arm
Anaemia disutility	(Lloyd 2008b)	-0.125	One week mean duration
Neutropenia disutility	(Nafees 2017)	-0.460	One week mean duration
Fatigue disutility	(Nafees 2017)	-0.410	One week mean duration
Lipase increase disutility	Assumed zero*	0.000	One week mean duration
Thrombocytopenia disutility	(Attard 2014a)	-0.184	One week mean duration
Neutrophil count decreased disutility	(Nafees 2017), assumed the same as neutropenia: (Huang 2017)	-0.460	One week mean duration
Platelet count decreased disutility	Assumed zero*	0.000	One week mean duration

White blood cell count decreased disutility	(Nafees 2017), assumed the same as neutropenia: (Huang 2017)	-0.460	One week mean duration
Febrile neutropenia disutility	(Nafees 2017)	-0.500	One week mean duration
Hypertension disutility	(Nafees 2017)	-0.050	One week mean duration
Anaemia cost	(Sundhedsdatastyrelsen 2022) + (Clinical expert interview 2020).	2 180 DKK	Sundhedsdatastyrelsen (2022). Interactive DRG: 04MA98 (BOQA) Treatment with blood transfusion (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption)
Neutropenia cost	(Sundhedsdatastyrelsen 2022) + (Clinical expert interview 2020).	2 180 DKK	Sundhedsdatastyrelsen (2022). Hospitalization on average for 5 days for 20% of patients: Interactive DRG: 04MA98 (ZZ0149A) Somatic examination (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption
Fatigue cost	Assumed zero according to Danish KOL (Clinical expert interview 2020)	0 DKK	Would be handled in a monitoring related visit, no extra cost
Lipase increase cost	Assumed zero according to Danish KOL (Clinical expert interview 2020)	0 DKK	Would be handled in a monitoring related visit, no extra cost
Thrombocytopenia cost	Assumed zero according to Danish KOL (Clinical expert interview 2020)	0 DKK	Would be handled in a monitoring related visit, no extra cost
Neutrophil count decrease cost	Assumed zero according to Danish KOL (Clinical expert interview 2020)	0 DKK	Would be handled in a monitoring related visit, no extra cost
Platelet count decreased cost	Assumed zero according to Danish KOL (Clinical expert interview 2020)	0 DKK	Would be handled in a monitoring related visit, no extra cost
White blood cell count cost	(Helsedirektoratet 2017)	0 DKK	Would be handled in a monitoring related visit, no extra cost
Febrile neutropenia cost	(Sundhedsdatastyrelsen 2022) + (Clinical expert interview 2020)	2 180 DKK	Sundhedsdatastyrelsen (2022). Hospitalization on average for 5 days for 20% of patients: Interactive DRG: 04MA98 (ZZ0149A) Somatic examination (DC349M) Kræft i bronkier eller

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			lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption
Hypertension cost	(Clinical expert interview 2020)	0 DKK	Would be handled in a monitoring related visit, no extra cost
Health state utility values – ITT and SQ PDL1<1%			
NIVO+IPI+PDC PF	CheckMate 9LA trial	[redacted]	Treatment specific utilities during PFS (for NIVO+IPI+PDC and PDC) from CheckMate 9LA are used
PDC PF	CheckMate 9LA trial	[redacted]	
Health state - overall PF	CheckMate 9LA trial	[redacted]	Used in scenario analysis
NIVO+IPI+PDC PD	CheckMate 9LA trial	[redacted]	Treatment specific utilities during PD (for NIVO+IPI+PDC and PDC) from CheckMate 9LA are used
PDC PD	CheckMate 9LA trial	[redacted]	
Health state specific PD	CheckMate 9LA trial	[redacted]	
Death	CheckMate 9LA trial	[redacted]	
Disease management – ITT and SQ PDL1<1%			
Specialist visit resource use per 4 weeks in PD state	(Clinical expert interview 2020)	1	Resource use is multiplied with the costs
Palliative radiotherapy (brain) resource use per 4 weeks in PD state	(Clinical expert interview 2020)	0.039	Resource use is multiplied with the costs
Palliative radiotherapy (bone) resource use per 4 weeks in PD state	(Clinical expert interview 2020)	0.039	Resource use is multiplied with the costs
Blood transfusion per 4 weeks in PD state	(Clinical expert interview 2020)	0.08	Resource use is multiplied with the costs
CT scan per 4 weeks in PD state	(Clinical expert interview 2020)	0.31	Resource use is multiplied with the costs
X-ray per 4 weeks in PD state	(Clinical expert interview 2020)	0.15	Resource use is multiplied with the costs
MRI per 4 weeks in PD state	(Clinical expert interview 2020)	0.08	Resource use is multiplied with the costs
Hospitalization inpatient oncology ward resource use per 4 weeks in PD state	(Clinical expert interview 2020)	0.43	Resource use is multiplied with the costs
99Tc node scintigraphy scan	(Clinical expert interview 2020)	0.15	Resource use is multiplied with the costs

per 4 weeks in PD state			
Specialist visit resource use per 4 weeks in PF state	(Clinical expert interview 2020)	1	Resource use is multiplied with the costs
Palliative radiotherapy (brain) resource use per 4 weeks in PF state	(Clinical expert interview 2020)	0	Not relevant in the PF state according to Danish KOL
Palliative radiotherapy (bone) resource use per 4 weeks in PF state	(Clinical expert interview 2020)	0	Not relevant in the PF state according to Danish KOL
Blood transfusion per 4 weeks in PF state	(Clinical expert interview 2020)	0.08	Resource use is multiplied with the costs
CT scan per 4 weeks in PF state	(Clinical expert interview 2020)	0.31	Resource use is multiplied with the costs
X-ray per 4 weeks in PF state	(Clinical expert interview 2020)	0.15	Resource use is multiplied with the costs
MRI per 4 weeks in PF state	(Clinical expert interview 2020)	0.08	Resource use is multiplied with the costs
Hospitalization inpatient oncology ward resource use per 4 weeks in PF state	(Clinical expert interview 2020)	0	Not relevant in the PF state
99Tc node scintigraphy scan per 4 weeks in PF state	(Clinical expert interview 2020)	0.08	Resource use is multiplied with the costs
Outpatient visit unit cost	Kommunernes og Regionernes Løndatakontor 2022, Medicines council 2020	1 467 DKK	Kommunernes og Regionernes Løndatakontor 2022, Specialeansvarlige overlæger (Overlæger, lægelige chefer m.v.). bruttolön Okt 2021. available from: https://krl.dk/#/sirka Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.
Radiotherapy (brain) unit cost	Sundhedsdatastyrelsen (2022)	2 180 DKK	Sundhedsdatastyrelsen (2022). Interactive DRG: 04MA98 (BWGC) External radiation therapy (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption)
Radiotherapy (bone) unit cost	Sundhedsdatastyrelsen (2022)	2 180 DKK	Sundhedsdatastyrelsen (2022). Interactive DRG: 04MA98 (BWGC) External radiation therapy (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption)

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Blood transfusion unit cost	Sundhedsdatastyrelsen (2022)	4 223 DKK	Sundhedsdatastyrelsen (2022). Interactive DRG: 16PR02 (BOQA0) Blood transfusion (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption)
CT scan unit cost	Sundhedsdatastyrelsen (2022)	2 411 DKK	Sundhedsdatastyrelsen (2022). Interactive DRG: 16PR02 (BOQA0) Blood transfusion (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption)
X-ray unit cost	Sundhedsdatastyrelsen (2022)	1 640 DKK	Sundhedsdatastyrelsen (2022). Interactive DRG: 30PR18 (UXRC00) X-ray examination of the thorax (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption)
MRI unit cost	Sundhedsdatastyrelsen (2022)	2 416 DKK	Sundhedsdatastyrelsen (2022). Interactive DRG: 30PR02 UXMH00) MRI scan of the whole body (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption)
Hospitalization inpatient oncology ward unit cost per day	Sundhedsdatastyrelsen (2022)	2 180 DKK	Sundhedsdatastyrelsen (2022). Interactive DRG: 04MA98 (BXXB0) Interdisciplinary assessment and treatment (DC349M) Kræft i bronkier eller lunge med metastaser . Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption).
99Tc node scintigraphy scan unit cost	Sundhedsdatastyrelsen (2022)	4 808 DKK	Sundhedsdatastyrelsen (2022). Interactive DRG: 36PR06 (WKBGD19XX) Bone scintigraphy, multiphase, Tc-99m-XPD (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption)
Administration costs – ITT and SQ PDL1<1%			
NIVO+IPI+PDC	Sundhedsdatastyrelsen (2022)	2 180 DKK	Sundhedsdatastyrelsen (2022). Interactive DRG: (BWAA60) Medicingivning ved intravenøs injektion
Monitoring costs – ITT and SQ PDL1<1%			
NIVO+IPI+PDC: office visit per 4 weeks	(Clinical expert interview 2020)	1	Resource use is multiplied with the costs
NIVO+IPI+PDC: hepatic function test per 4 weeks	(Clinical expert interview 2020)	1	Resource use is multiplied with the costs
NIVO+IPI+PDC: renal function test per 4 weeks	(Clinical expert interview 2020)	1	Resource use is multiplied with the costs

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NIVO+IPI+PDC: thyroid test per 4 weeks	(Clinical expert interview 2020)	1	Resource use is multiplied with the costs
NIVO+IPI+PDC: comprehensive metabolic panel + ACTH per 4 weeks	(Clinical expert interview 2020)	1	Resource use is multiplied with the costs
NIVO+IPI+PDC: complete blood count test per 4 weeks	(Clinical expert interview 2020)	0	Resource use is multiplied with the costs
PDC: office visit per 4 weeks	(Clinical expert interview 2020)	1	Resource use is multiplied with the costs
PDC: hepatic function test per 4 weeks	(Clinical expert interview 2020)	1	Resource use is multiplied with the costs
PDC: renal function test per 4 weeks	(Clinical expert interview 2020)	1	Resource use is multiplied with the costs
PDC: thyroid test per 4 weeks	(Clinical expert interview 2020)	0	Resource use is multiplied with the costs
PDC: comprehensive metabolic panel + ACTH per 4 weeks	(Clinical expert interview 2020)	0	Resource use is multiplied with the costs
PDC: complete blood count test per 4 weeks	(Clinical expert interview 2020)	1.33	Resource use is multiplied with the costs
Office visit unit cost	Kommunernes og Regionernes Løndatakontor 2022, Medicines council 2020.	1 467 DKK	Kommunernes og Regionernes Løndatakontor 2022, Specialeansvarlige overlæger (Overlæger, lægelige chefer m.v.). bruttolön Okt 2021. available from: https://krl.dk/#/sirka Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.
Hepatic function test unit cost	(Rigshospitalets Labportal 2022)	144 DKK	Rigshospitalets Labportal (2022). Test code for hepatic tests included (codes): NPU19651, NPU19654, NPU27783, NPU19673, NPU01370, NPU03278. https://labportal.rh.dk/Labportal.asp
Renal function test unit cost	(Rigshospitalets Labportal 2022)	264 DKK	Rigshospitalets Labportal (2022). Test code for renal tests included (codes): NPU01459, NPU01472, NPU03429, NPU03230, NPU01536, NPU23745, NPU02192, NPU04998, NPU19673. https://labportal.rh.dk/Labportal.asp
Thyroid test unit cost	(Rigshospitalets Labportal 2022)	79 DKK	Rigshospitalets Labportal (2022). Test code included: (NPU03577) Thyrotropin. https://labportal.rh.dk/Labportal.asp
Comprehensive metabolic panel + ACTH unit cost	(Rigshospitalets Labportal 2022)	520 DKK	Assumed same cost as complete blood count

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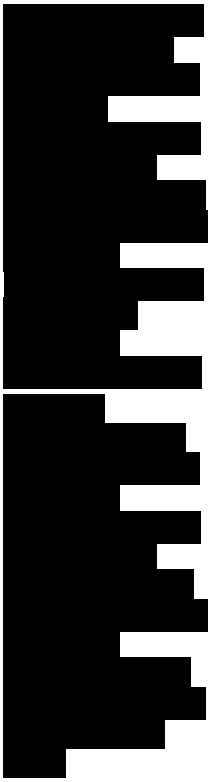
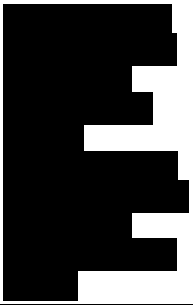
Complete blood count unit cost	(Rigshospitalets Labportal 2022)	520 DKK	Rigshospitalets Labportal (2022). Test code for CBC tests included (codes): NPU02902 (cost for test assumed as proxy for codes: NPU01960, NPU01961, NPU02593), NPU01473 (cost for test assumed as proxy for codes: B-Hb (Hemoglobin), Erc(B)-MCV, Erc(B)-MCH, Erc(B)-MCHC), and RGH00982. https://labportal.rh.dk/Labportal.asp
Subsequent treatments – ITT			
Proportion received ST	DMC clinical feedback	After NIVO+IPI+PDC: 70% After PDC: 70%	Proportion received ST is multiplied by the proportion of patients receiving each subsequent treatment
Proportion of patients receiving each subsequent treatment	CheckMate 9LA		Proportion received ST is multiplied by the proportion of patients receiving each subsequent treatment
Average time on ST treatment duration (months)	CheckMate 9LA		Nivolumab 2 year restricted mean duration of treatment from the cost effectiveness model for nivolumab in pre-treated stage IV or recurrent NSCLC populated with the 5-year DBL of the pooled CM057/017 trials.
Average time on ST treatment duration (months)	KOL feedback		Based on expert opinion from the virtual advisory board (Bristol-Myers Squibb 2020b)
Subsequent treatments –SQ PDL1<1%			

Proportion received ST	DMC clinical feedback	After NIVO+IPI+PDC: 70% After PDC: 70%	Proportion received ST is multiplied by the proportion of patients receiving each subsequent treatment
Proportion of patients receiving each subsequent treatment	CheckMate 9LA	[redacted]	Proportion received ST is multiplied by the proportion of patients receiving each subsequent treatment. Note that the distributions of 2L treatments in each arm were re-calculated to exclude pemetrexed, which is a NSQ specific treatment.
Average time on ST treatment duration (months)	CheckMate 9LA	[redacted]	Nivolumab 2 year restricted mean duration of treatment from the cost effectiveness model for nivolumab in pre-treated stage IV or recurrent NSCLC populated with the 5-year DBL of the pooled CM057/017 trials.
Average time on ST treatment duration (months)	KOL feedback	[redacted]	Based on expert opinion from the virtual advisory board (Bristol-Myers Squibb 2020b)

Abbreviations:KOL=Key opinion leader; AE=Adverse events, OS=overall survival, PFS=Progression free survival, PD=Progressed disease, Nivo=nivolumab;Suni=sunitinib, ST=subsequent; TX=treatment; N+I=nivolumab in combination with ipilimumab
Source: (Den norske legeforening 2017, Helsedirektoratet 2017, Oslo Universitetssykehus 2017, Aleris Røntgen 2018, Metoder 2018)

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

8.2.2.1 Patient population

The Danish patient population: The average age at diagnosis in the Danish Cancer registry was 72 years (Dansk Lunge Cancer Gruppe 2017) which also was validated by the Danish KOL (Clinical expert interview 2020).

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The patient weight is assumed to be 70.35 kg (Dansk Lunge Cancer Gruppe 2017). This weight was supported by the Danish KOL. The male to female percentage of patients in the Danish cancer registry is 49% which was also validated by the Danish KOL (Clinical expert interview 2020).

Patient population in the clinical documentation submitted: The pivotal clinical trial is CheckMate 9LA. The median age is 63.7 years. Mean weight of the population equals to 72.33 kg. The proportion of female patients is 29.9%.

Patient population in the health economic analysis submitted: The health economic model utilitised two patient populations in the analysis and presents separate results for each. The two populations are; an all comers population (referred herein as the ITT population) and a SQ PD-L1<1% population. The ITT results are presented as the base case analysis, with the SQ PD-L1<1% providing an alternative analysis. This sub-population was included upon request to BMS from the DMC. It was identified because the clinical benefits of treatment with PDC alone is known to be poorer among this group, with higher unmet needs. This increases the need for effective treatment options.

For each population, the health economic model utilised the same patient population characteristics from the clinical documentation and the Danish clinical practice:

The median age in the model is 72 years. The Danish clinical input and the clinical documentation correspond to the age used in the model.

The mean weight of 70.35 kg used in the model matches the Danish clinical practice

The proportion of female patient in the model originates from the Danish clinical practice (49% females).

Table 36: Patient population

Patient population	Clinical documentation	Used in the model	Danish clinical practice
Age	63.7 years from the CheckMate 9LA cohort	72 years	72 years
Mean weight of the population	72.33 kg from the CheckMate 9LA cohort	70.35 kg	70.35 kg
Proportion of female patients	29.9% females from the CheckMate 9LA cohort	49%	49%
Body surface area	Calculated from the average weight and height	1.802	1.802

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice (as defined in section 2.2): The expected dosing in CheckMate 9LA, the pivotal Phase 3 trial of the NIVO+IPI+PDC combination, NIVO (360 mg) every 3 weeks, low-dose IPI (1 mg/kg) is given every 6 weeks and PDC (cisplatin, paclitaxel, pemetrexed, carboplatin) is given every 3 weeks for up to 2 cycles. Treatment with NIVO+IPI should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient, to a maximum of 2 years.

Intervention in the clinical documentation submitted: NIVO (360 mg Q3W) was administered with IPI (1 mg/kg Q6W), plus 2 cycles of histology based PDC. After 2 cycles, NIVO+IPI treatment could continue for up to 24 months, or until Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 defined disease progression, unacceptable toxicity or other reasons specified in the protocol.

- SQ histology: carboplatin area under the concentration time curve (AUC) 6 + paclitaxel 200 mg/m2 (or 175 mg/m2 as per local institutional practice)
- NSQ histology: carboplatin AUC 5 or 6 + pemetrexed 500 mg/m2 or cisplatin 75 mg/m2 + pemetrexed 500 mg/m2.

Intervention as in the health economic analysis submitted: The health economic model followed the official label and the treatment duration was based on DoT as observed in CheckMate 9LA.

For the ITT population analysis, the combination of NIVO+IPI+PDC combination from the pivotal Phase 3 trial is utilised. For the SQ PD-L1<1% population, only the SQ histology PDC component is utilised (i.e. carboplatin AUC 6 + paclitaxel 200mg/m2 (or 175 mg/m2 as per local institutional practice))

Table 37: Intervention, nivolumab and ipilimumab in combination with two cycles of platinum doublet chemotherapy

Intervention	Clinical documentation /indirect comparison (including source)	Used in model (number/value incl. source)	Expected Danish clinical practice (incl. source, if known)
Posology	ITT: In CheckMate 9LA, the pivotal Phase 3 trial of the NIVO+IPI+PDC combination, NIVO (360 mg) every 3 weeks, low-dose IPI (1 mg/kg) is given every 6 weeks and PDC (cisplatin, paclitaxel, pemetrexed, carboplatin) is given every 3 weeks for up to 2 cycles. SQ PD-L1<1%: In CheckMate 9LA, the pivotal Phase 3 trial of the NIVO+IPI+PDC combination, NIVO (360 mg) every 3 weeks, low-dose IPI (1 mg/kg) is given every 6 weeks and PDC (paclitaxel, carboplatin) is given every 3 weeks for up to 2 cycles	ITT: In CheckMate 9LA, the pivotal Phase 3 trial of the NIVO+IPI+PDC combination, NIVO (360 mg) every 3 weeks, low-dose IPI (1 mg/kg) is given every 6 weeks and PDC (cisplatin, paclitaxel, pemetrexed, carboplatin) is given every 3 weeks for up to 2 cycles SQ PD-L1<1%: In CheckMate 9LA, the pivotal Phase 3 trial of the NIVO+IPI+PDC combination, NIVO (360 mg) every 3 weeks, low-dose IPI (1 mg/kg) is given every 6 weeks and PDC (paclitaxel, carboplatin) is given every 3 weeks for up to 2 cycles	ITT: In CheckMate 9LA, the pivotal Phase 3 trial of the NIVO+IPI+PDC combination, NIVO (360 mg) every 3 weeks, low-dose IPI (1 mg/kg) is given every 6 weeks and PDC (cisplatin, paclitaxel, pemetrexed, carboplatin) is given every 3 weeks for up to 2 cycles SQ PD-L1<1%: In CheckMate 9LA, the pivotal Phase 3 trial of the NIVO+IPI+PDC combination, NIVO (360 mg) every 3 weeks, low-dose IPI (1 mg/kg) is given every 6 weeks and PDC (paclitaxel, carboplatin) is given every 3 weeks for up to 2 cycles
Length of treatment	Up to 2 years or until disease progression or unacceptable toxicity	Up to 2 years	Up to 2 years or until disease progression or unacceptable toxicity

Abbreviations: NIVO+IPI+PDC=nivolumab in combination with ipilimumab and platinum doublet chemotherapy

8.2.2.3 Comparator

The current Danish clinical practice (as described in section 5): Key comparators in Denmark are pembrolizumab monotherapy or in pembrolizumab in combination with the chemotherapy agents, pemetrexed and carboplatin (Dansk Lunge Cancer Gruppe 2019, Medicinrådet 2019, Medicinrådet 2020b). However, there are no direct comparisons of any of these regimens to confirm whether one of them offers superior efficacy in this setting and the cost-effectiveness of these treatments have not yet been assessed through the new DMC process (as of February 21st, 2020). Therefore, NIVO+IPI+PDC can be considered one of the accepted standards of care for the initial treatment of advanced and metastatic NSCLC without EGFR mutations or ALK translocations. According to the product description of the various PDC treatments the recommended doses are the following:

- Cisplatin 75 mg/m2 Q3W for 4 trt cycles
- Paclitaxel 200 mg/m2 Q3W for 4 trt cycles
- Pemetrexed 500 mg/m2 Q3W for 4 trt cycles
- Carboplatin 685 mg Q3W for 4 trt cycles

Comparators in the clinical documentation submitted: Histology dependent, platinum-based doublet chemotherapy was selected by the investigator and administered on Day 1 Q3W for 4 cycles. After 4 cycles, subjects with NSQ histology

could continue to receive optional maintenance therapy with 500 mg/m2 pemetrexed alone on Day 1 of each 3 weeks until disease progression or unacceptable toxicity. Histology based platinum-based doublet chemotherapy was one of the following:

- SQ histology: carboplatin AUC 6 + paclitaxel 200 mg/m2 (or 175 mg/m2 as per local institutional practice)
- NSQ histology: carboplatin AUC 5 or 6 + pemetrexed 500 mg/m2 or cisplatin 75 mg/m2 + pemetrexed 500 mg/m2

Comparator in the health economic analysis submitted: The health economic model followed the official label and provides a comparison with PDC. The treatment duration was based on DoT as observed in CheckMate 9LA. As a supplement, scenario analyses for cost-effectiveness has also been run against the other relevant immunotherapy based treatment regimes.

Table 38: Comparator, platinum doublet chemotherapy

Comparator	Clinical documentation /indirect comparison (including source)	Used in model (number/value incl. source)	Danish clinical practice (incl. source, if known)
Posology	**PDC:** • q3w x 4 followed by optional maintenance pemetrexed for non-squamous histology **Gemcitabine/Cisplatin** • Gemcitabine 1000 or 1250 mg/m2 for a 30-minute IV infusion on days 1 and 8 with cisplatin at a dose of 75 mg/m2 as a 30 to 120-minute IV infusion on Day 1 **Gemcitabine/Carboplatin** • Gemcitabine 1000 mg/m2 as a 30-minute IV infusion on Days 1 and 8 with carboplatin at a dose of AUC 5 as a 30-minute IV infusion, on Day 1. Carboplatin should be given following gemcitabine on Day 1 **Pemetrexed/Cisplatin** • Pemetrexed 500 mg/m2 as a 10-minute IV infusion on Day 1 with cisplatin at a dose of 75 mg/m² as a 120-minute IV infusion on Day 1 **Pemetrexed/Carboplatin**	Cisplatin 75 mg/m2 Q3W for 4 trt cycles Paclitaxel 200 mg/m2 Q3W for 4 trt cycles Pemetrexed 500 mg/m2 Q3W for 4 trt cycles Carboplatin 685 mg Q3W for 4 trt cycles	

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	• Pemetrexed at 500 mg/m2 as a 10-minute IV infusion on Day 1, followed by carboplatin at a dose of AUC 5 or 6 as a 30-minute IV infusion, on Day 1. Carboplatin should be given following gemcitabine on Day 1 of each cycle, carboplatin dose (mg) = Target AUC x [(CrCl (ml/min) + 25]. Pemetrexed additionally 500 mg/m2Gemcitabine 1000 or 1250 mg/m2 for a 30-minute IV infusion on days 1 and 8 with cisplatin at a dose of 75 mg/m2 as a 30 to 120-minute IV infusion on Day 1.		
Length of treatment	• Gemcitabine or cisplatin for a 3-week treatment cycle for up to 4 cycles • Gemcitabine and carboplatin for a 3-week cycle, for up to 4 cycles. • Pemetrexed with cisplatin for a 3-week treatment cycle, for up to 4 cycles • Pemetrexed followed by carboplatin for a 3-week treatment cycle, for up to 4 cycles	3 week treatment cycles up to 4 cycles.	

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted documentation: As CheckMate 9LA is a head-to-head study including a comparison with PDC, which is the relevant comparator across histology and PD-L1 expression levels in Danish clinical practice, the efficacy results from CheckMate 9LA are presented in the base case.

- At the 2-year DBL, median overall survival was 15.8 months (95% CI 13.9, 19.7) in the NIVO+IPI+PDC group versus 11.0 months (95% CI 9.5–12.7) in the PDC group (HR 0.72 [95% CI 0.61, 0.86]).
- The median PFS was 6.7 months (95% CI 5.6–7.8) for NIVO+IPI+PDC versus 5.3 months (4.4–5.6) in the PDC group (HR 0.67 [95% CI 0.67, 0.79]).
- The safety profile of NIVO+IPI+PDC was manageable and consistent with findings from previous studies, where high-grade (≥ Grade 3) TRAEs where numerically higher than PDC (48% vs 38%, respectively)

Relevance of the documentation for Danish clinical practice As CheckMate 9LA is a head-to-head study including a comparison with PDC, which is the relevant comparator in the Danish clinical practice, the clinical documentation from CheckMate 9LA is highly relevant for the Danish clinical practice.

The relative efficacy outcomes in the submitted health economic analysis: the submitted health economics model utilises the parametrisations of the KM curves presented in the CheckMate 9LA up to 24 months and then independent extrapolations fitted to CheckMate 227 from month 24 and onwards.

Table 39: Summary of relative efficacy - ITT

Clinical efficacy outcome	Used in the model (value)	Clinical documentation
OS NIVO+IPI+PDC	2-knot spline normal distribution	CheckMate 9LA KM data up to 24 months and independent log-normal OS curve fitted to CheckMate 227 Part 1 complete data set, from month 24 and onwards
OD PDC	2-knot spline odds distribution	CheckMate 9LA KM data up to 24 months and independent log-logistic OS curve fitted to CheckMate 227 Part 1 complete data set, from month 24 and onwards
PFS NIVO+IPI+PDC	2-knot spline hazrads distribution	CheckMate 9LA KM data up to 24 months and independent 2 knot spline odds PFS curve fitted CheckMate 227 Part 1 complete data set, from month 24 and onwards
OS PDC	2-knot spline normal distribution	CheckMate 9LA KM data up to 24 months and independent 2 knot spline normal PFS curve fitted to CheckMate 227 Part 1 complete data set, from month 24 and onwards
DoT NIVO+IPI+PDC	KM curves	CheckMate 9LA KM DoT data
DoT PDC	KM curves	CheckMate 9LA KM DoT data

Abbreviations: N+I=nivolumab in combination with ipilimumab ; suni=sunitinib; PFS=progression-free survival, OS=Overall survival, DoT=Duration of treatment

Table 40: Summary of relative efficacy – SQ PD-L1<1%

Clinical efficacy outcome	Used in the model (value)	Clinical documentation
OS NIVO+IPI+PDC	Generalized gamma distribution	CheckMate 9LA KM data up to 24 months and independent log-normal OS curve fitted to CheckMate 227 Part 1b , the SQ<1 subset, from month 24 and onwards
OD PDC	Log-logistic distribution	CheckMate 9LA KM data up to 24 months and independent log-logistic OS curve fitted to CheckMate 227 Part 1b, the SQ<1 subset, from month 24 and onwards
PFS NIVO+IPI+PDC	1-knot spline normal distribution	CheckMate 9LA KM data up to 24 months and independent 2 knot spline odds PFS curve fitted CheckMate 227 Part 1b, the SQ<1 subset, from month 24 and onwards
OS PDC	Log-logistic distribution	CheckMate 9LA KM data up to 24 months and independent 2 knot spline normal PFS curve fitted to CheckMate 227 Part 1b, the SQ<1 subset, from month 24 and onwards
DoT NIVO+IPI+PDC	KM curves	CheckMate 9LA KM DoT data, the SQ<1 subset
DoT PDC	KM curves	CheckMate 9LA KM DoT data, the SQ<1 subset

Abbreviations: N+I=nivolumab in combination with ipilimumab ; suni=sunitinib; PFS=progression-free survival, OS=Overall survival, DoT=Duration of treatment

8.2.2.5 Adverse reaction outcomes

Adverse reaction outcomes in the clinical documentation submitted: The safety profile of NIVO+IPI+PDC was manageable and consistent with findings from previous studies. There were more high grade (Grade ≥3) TRAEs observed in the NIVO+IPI+PDC treatment arm compared to patients on PDC alone (48% vs 38%, respectively). Serious treatment related adverse events of any grade occurred in 109 (30%) patients in the NIVO+IPI+PDC arm and 62 (18%) in the PDC arm. Seven (2%) deaths occurred in the NIVO+IPI+PDC arm (acute kidney failure, diarrhoea, hepatotoxicity, hepatitis, pneumonitis, sepsis with acute renal insufficiency, and thrombocytopenia; one patient each) and six (2%) deaths in the PDC arm (anaemia, febrile neutropenia, pancytopenia, pulmonary sepsis, respiratory failure, and sepsis; one patient each) were treatment related.

Adverse reaction outcomes in the health economic analysis submitted: In the base case, AEs with >5% incidences in either arm are included, for both the ITT and SQ PDL1<1% populations. AEs have a marginal impact on the ICER. Narrowing the scope of AEs included may be a conservative approach as N+I have a better toxicity profile in comparison with PDC. The cost of AEs is applied as a one-off cost in the first cycle of the model. For AEs that are not incurred within the first year or are ongoing, applying costs in the first cycle of the model may over-estimate costs due to discounting.

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8.3 Extrapolation of relative efficacy

8.3.1 Time to event data

This section provides a brief description of the piecewise extrapolation approach using in this cost-effectiveness assessment of NIVO+IPI+PDC. A more comprehensive description is presented in Appendix G.

A key challenge to the long term extrapolation of OS from CheckMate 9LA is the limited follow-up time. The hazard (risk of death) of cancer patients has been shown to follow a pattern of first increasing hazard followed by a long term decreasing hazard (Decision Support Unit 2020, Gray 2021). When extrapolating based on short term follow-up data, before the long-term decrease in hazard has been adequitly reflected in the data, standard parametric extrapolations put weight on the initial increasing hazard and does not capture the expected long-term decline. This leads to overestimating the hazard, which is turn underestimates the long-term OS. This is what we observed when comparing standard parametric extrapolation based on CheckMate 9LA to the OS observed for NIVO+IPI in first-line NSCLC in the CheckMate 227 study (see Figure 52).

It is important to consider the external validation of survival extrapolations, especially when there is limited follow-up like in 9LA (Decision Support Unit 2013, Decision Support Unit 2020, Gray 2021). CheckMate 227 provides a natural source of validation of OS extrapolation from 9LA since similar patients was treated with NIVO+IPI in first-line NSCLC, please see Appendix L Baseline characteristics and study design CheckMate 227 for a comparison of CheckMate 9LA and CheckMate 227. Clinical experts has confirmed that patients treated with NIVO+IPI+PDC are expected to have similar outcomes to those treated with NIVO+IPI in CheckMate 227. The large underestimation of OS based on

extrapolation of the 9LA data, when comparing to CheckMate 227 therefore demonstrate that an alternative extrapolation approach was needed to estimate the long term survival of patients treated with NIVO+IPI+PDC.

In this case it was found that a piecewise approach, as proposed by Bagust and Beale (Bagust 2014a), which is also discussed in the NICE TDS 21, using data from 227 was the best approach to estimate long term OS and PFS from 9LA. Given the similarity between the CheckMate9LA and CheckMate227 Part 1 trials, survival data from CheckMate 227 Part 1 (3 years DBL) was used to extrapolate CheckMate9LA survival. To this end, KM data obtained from CheckMate 9LA was used directly (up to 13 months; week 60 in the model) and CheckMate 227 Part 1 data was subsequently used to project long-term outcomes (from month 13 onwards). The so-called 'Piecewise approach A' using the complete 3-year dataset from CheckMate 227 part 1, in combination with the Kaplan-Meier estimates from 9LA was used to generate long-term estimates for CheckMate 9LA in the cost-effectiveness assessment of Nivo+IPI+PDC.

A detailed description and rationale for the piecewise approach as well as the curve selections per outcome are outlined in Appendix G Extrapolation and a summary is presented in section 8.3.2 below. Because the piecewise extrapolations rely on extrapolating CheckMate 227, the section outline the curve selection based on the CheckMate 227 data.

An alternative to the piecewise survival extrapolation approach was also explored where survival extrapolations were solely based upon data from CheckMate 9LA. This alternative approach was included as a means of providing survival extrapolation based only upon CheckMate 9LA. The benefits of the 'parametric only' approach is that it is technically simpler, and only uses data for patients who received the exact intervention evaluated in this analysis, i.e. NIVO+IPI plus two rounds of PDC. However, the main drawback is that the still limited available follow-up from CheckMate 9LA means that the variance of long-term extrapolations increases, and that data from a highly similar patient group from CheckMate 227 is not leveraged. Particularly, the 'parametric only' approach fails to account for the expected decrease to OS hazard beyond two years. For this reason, the piecewise approach was used as the base case in this analysis. Results using extrapolations solely based upon CheckMate 9LA are included as scenario analysis.

8.3.2 Summary

Table 42 provides a summary of all the parametric survival modelling options recommended in the previous sections. For the base case analysis, the piecewise approach A using CheckMate 9LA KM data up to 13 months followed by parametric curves fit to the complete CheckMate 227 dataset was used for modelling OS and PFS. DoT was modelled using the KM data from CheckMate 9LA.

In addition to the recommended parametric curves, outlined in Table 42, the cost-effectiveness model is structurally built to model a number of other parametric distributions outlined in the AIC/BIC goodness-of-fit tables.

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Table 42: Summary of the survival analyses for OS, PFS and DoT

Endpoint	Approach in base case
OS	ITT - Piecewise approach A • NIVO+IPI+PDC: CheckMate 9LA OS KM data + CheckMate 227 Part 1 (complete data set) 2 knot spline normal curve • PDC:CheckMate 9LA OS KM data + CheckMate 227 Part 1 (complete data set) 2 knot spline odds curve SQ-PD-L1<1% - Piecewise approach A • NIVO+IPI+PDC: CheckMate 9LA OS SQ PD-L1<1% KM data + CheckMate 227 Part 1b Generalised gamma cruve • PDC:CheckMate 9LA OS SQ PD-L1<1% KM data + CheckMate 227 Part 1b Log-logistic curve
PFS	ITT - Piecewise approach A • NIVO+IPI+PDC:CheckMate 9LA PFS KM data + CheckMate 227 Part 1 (complete data set) 2 knot spline hazard curve • PDC CheckMate 9LA PFS KM data + CheckMate 227 Part 1 (complete data set) 2 knot spline normal curve SQ-PD-L1<1% - Piecewise approach A • NIVO+IPI+PDC:CheckMate 9LA PFS SQ PD-L1<1% KM data + CheckMate 227 Part 1b (complete data set) 1 knot spline normal curve • PDC CheckMate 9LA PFS SQ PD-L1<1% KM data + CheckMate 227 Part 1b (complete data set) log-logistic
DoT	ITT • NIVO+IPI+PDC: CheckMate 9LA DoT KM data • PDC: CheckMate 9LA DoT KM data SQ PD-L1<1% • NIVO+IPI+PDC: CheckMate 9LA SQ PD-L1<1% DoT KM data • PDC: CheckMate 9LA SQ PD-L1<1% DoT KM data

CM: CheckMate; DoT: Duration of treatment; KM: Kaplan-Meier; NIVO+IPI+PDC : nivolumab + ipilimumab combined with limited chemotherapy; OS: Overall survival; PDC: Platinum doublet chemotherapy; PFS: Progression-free survival

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

The CheckMate 9LA trial collected patient reported outcomes (PRO), one of which was the EuroQol Five Dimension Three Level (EQ-5D-3L) questionnaire. The EQ-5D-3L is a weighted preference based questionnaire which comprises of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety) each of which are assigned 3 levels (no problems, some problems, extreme problems). The EQ-5D-3L is a descriptive system used to compute a utility index with scores ranging from -0.109 (worst imaginable health state) to 1 (best imaginable health state) in the Danish general population. The EQ-5D-3L assessment schedule within the trial is outlined in Table 43.

Table 43: EQ-5D-3L assessment schedule in CheckMate 9LA

EQ-5D-3L assessment schedule	On-treatment assessment		Post-treatment Follow-up	
	Every 3 weeks for the first 6 months	Every 6 weeks after the initial 6 months up to 2 years	2 follow ups (FU): 35 and 115 days from last dose	Survival follow-up: Every 3 months from FU visit 2
NIVO+IPI+PDC	✓	✓	✓	✓
PDC	✓	✓	✓	✓

SOURCE: CheckMate 9LA (Bristol-Myers Squibb 2020b)
EQ-5D: EuroQol 5 dimensions; EQ-5D-3L: EuroQol 5 dimensions 3 levels; FU: Follow up; NIVO+IPI+PDC: nivolumab + ipilimumab combined with limited chemotherapy; PDC: Platinum doublet chemotherapy

Health state utility values reported in trial data

Patients' disease-related symptoms and overall health status were measured in the CheckMate 9LA trial using validated patient-reported instruments for NSCLC: Lung Cancer Symptom Scale Average Symptom Burden Index (LCSS ASBI) and LCSS 3-item global index (LCSS 3-IGI), and EuroQol-5 dimension questionnaire (EQ-5D-3L VAS) and EQ-5D-3L utility index (EQ-5D-3L UI) (Quality of Life Research Associates 2013, EuroQoL 2017, Gadgeel 2020).

The LCSS is a validated instrument designed to assess the impact of treatment on disease-related symptoms (Quality of Life Research Associates 2013). It consists of six symptom-specific questions related to dyspnea, cough, fatigue, pain, hemoptysis, and anorexia, plus three summary items: symptom distress, interference with activity, and global HRQoL (Quality of Life Research Associates 2013). For the six individual symptom measures, the degree of impairment is recorded on a 100 mm visual analogue scale with scores from 0 to 100 with zero representing the best score (Quality of Life Research Associates 2013). The LCSS ASBI can be derived as the average of scores for the six symptom-related items (Quality of Life Research Associates 2013, Gadgeel 2020). The LCSS 3-IGI can be calculated as the the sum of the scores for the three global items, with higher scores indicating reduced symptom burden (Gadgeel 2020).

The EQ-5D VAS is a standardized instrument for use as a measure of self-reported health status and includes a 5-dimension descriptive system as well as a visual analog rating scale (EuroQoL 2017). The EQ-5D descriptive system is comprised of the following 5-dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (EuroQoL 2017). The EQ-5D VAS records the participant's self-rated health status on a 100-point vertical VAS (0 = worst imaginable health state, 100 = best imaginable health state) (EuroQoL 2017). The EQ-5D UI scores are calculated by mapping the EQ-5D descriptive index responses into a single dimension health UI ranging from death (0) to full health (1), by using utility weights for the UK population (Pickard 2007).

Overall health status: change from baseline (on treatment) in EQ-5D-3L VAS (minimum follow-up 12.2 months)

A trend towards on-treatment improvement in overall health status was observed with NIVO+IPI+PDC, as measured by EQ-5D-3L VAS, compared to baseline in the descriptive analyses (see Figure 25 in (Gadgeel 2020). The mean EQ-5D-3L VAS scores for both treatments arms improved and were maintained over time, trending towards overall health status scores of the normal population (see Figure (Gadgeel 2020). MID in EQ-5D-3L VAS change from baseline was reached by NIVO+IPI with limited PDC at Week 72 and Week 90 (see Figure 25 in (Gadgeel 2020). Completion rates were mostly comparable between treatment arms and above 80% (Gadgeel 2020).

8.4.1 Overview of health state utility values (HSUV)

Three-level EQ-5D (EQ-5D-3L) utility data were collected in CheckMate 9LA clinical studies in line with the clinical study protocols. As per protocol, patients were randomized to treatment (NIV+IPI+PDC vs. PDC) and completed a baseline and then regular on-treatment assessments until radiological disease progression. After stopping treatment, patients completed EQ-5D-3L assessments at two follow-up visits and then regularly (every three months for the first 12 months, then every sixth months) in the survival follow-up phase. The data cut-off date was March 9, 2020. Danish utility weights were applied to the EQ-5D-3L data.

A systematic literature review of published health state utility studies was performed to identify utility values associated with adverse events (Appendix H Literature search for HRQoL data). The review targeted subjects relating to advanced or metastatic NSCLC. A separate review was carried out of submissions to international health technology agencies (HTA). 25 studies related to first-line NSCLC treatment were identified. The most common source of utility values was publications reporting results of a cost-utility study. Some of these obtained utilities from a clinical trial but most cited previous literature. Preference were given to utility values from studies where data was presented separately for pre- and post-progression health states. Almost all studies were based in either the US or the UK; in the

absence of a suitable mapping algorithm or sufficiently granular data, these were incorporated into the model without any conversions.

8.4.2 Health state utility values used in the health economic model

[redacted] Treatment-specific utilities by health state derived directly from CheckMate 9LA are selected for the model base case analysis' progression free health state; an approach that was considered appropriate by the experts from the virtual advisory board (Bristol-Myers Squibb 2020b). Using treatment specific utilities will capture benefits and side-effects of each treatment using the desired metric: (mapped) EQ-5D-5L DK values.

The disutility from adverse are implicitly been captured in the treatment-specific utility values from CheckMate 9LA and were not added to the treatment specific utilities, to avoid double counting. In addition, the disutility values associated with adverse events were identified through literature searches and had not been valued using the preferred value set (DK EQ-5D-5L), rather EQ-5D-3L UK values. For this reason, it was hard to establish their magnitude if applied alongside utility values that had been derived using Danish population preferences. Adding such utility decrements on a different 'scale' to the progression-based utility values which had been developed specifically using a Danish value set would raise questions about how well the resulting utility in the model really reflected the preferences of the Danish population.

[redacted]

	HSUV	95% C.I.	Source (literature search, study, ITC, etc.)
Pre-progression			
Health state - overall †	[redacted]	[redacted]	CheckMate 9LA utility analysis. Mapped Danish EQ-5D-5L value set applied to EQ-5D-3L responses.
Treatment specific for Nivo+Ipi+PDC	[redacted]	[redacted]	
Treatment specific for PDC	[redacted]	[redacted]	
Post-progression			
Health state - overall †	[redacted]	[redacted]	CheckMate 9LA utility analysis. Mapped Danish EQ-5D-5L value set applied to EQ-5D-3L responses.
Treatment specific for Nivo+Ipi+PDC	[redacted]	[redacted]	
Treatment specific for PDC	[redacted]	[redacted]	
Adverse events †			
Anaemia	-0.125	0.01	(Lloyd 2008a)
Neutropenia	-0.46	0.05	(Nafees 2017)
Fatigue	-0.41	0.04	(Nafees 2017)
Thrombocytopenia	-0.184	0.02	(Attard 2014b)
Neutrophil count decreased	-0.46	0.05	(Nafees 2017) (assumed equal to neutropenia based on (Huang 2017))
White blood cell count decreased	-0.46	0.05	(Nafees 2017) (assumed equal to neutropenia based on (Huang 2017))
Febrile Neutropenia	-0.5	0.05	(Nafees 2017)
Hypertension	-0.05	0.00	(Nafees 2017)

† Not applied in the base case analysis

Danish utility weights were applied to convert the EQ-5D-3L data to utility values in the model and age adjustment of utility values was applied to account for the increased morbidity and decreased function linked to increasing age. The age adjustment was calculated using the multiplicative method as described in NICE DSU Technical Support Document 12 (Ara 2011). The general population utility values used in the age adjustment calculations are listed in Table 45 below (Wittrup-Jensen 2009, Nordjylland 2021). The new Danish EQ-5D-5L preference weights and related DMC methods guidance was recently published (Jensen 2021, Medicinrådet 2021b). Although EQ-5D-5L was not a requirement from the DMC for this submission, the EQ-5D-5L value set (Jensen 2021) was applied to the EQ-5D-3L responses by the means of a validated mapping method (van Hout 2021). The mapping was done according to the preferred method which was an ordinal logistic regression that disregarded age and gender and accounted for unobserved heterogeneity using a latent factor.**Table 45: General Danish population utility values**

Age group (years)	Mean utility
50-69	0.818

70-79	0.813
80+	0.721

SOURCE: (Wittrup-Jensen 2009, Nordjylland 2021)

For indirect treatment comparators vs. other immunotherapies no treatment-specific utility values could be obtained through direct comparison. For this reason it was assumed that all immunotherapies would have the same pre-progression and post-progression utility values as NIVO+IPI+PDC.

8.4.2.1 Time to death utilities

In the model, there is also the possibility of selecting time-to-death utilities. The utilities are based on analyses of the patient-level utilities in relation to proximity of death, typically with decreasing utilities as death approaches. TTD-based utilities enable the model to capture the variation in health-related quality of life of a patient between the time of progression and death (Table 46).

[redacted]

	HSUV	95% C.I.	Source (literature search, study, ITC, etc.)
Nivo+Ipi+PDC			
>52 Weeks	[redacted]	[redacted]	CheckMate 9LA utility analysis. Mapped Danish EQ-5D-5L value set applied to EQ-5D-3L responses
27-52 Weeks	[redacted]	[redacted]	CheckMate 9LA utility analysis. Mapped Danish EQ-5D-5L value set applied to EQ-5D-3L responses
5-26 Weeks	[redacted]	[redacted]	CheckMate 9LA utility analysis. Mapped Danish EQ-5D-5L value set applied to EQ-5D-3L responses
<=4 Weeks	[redacted]	[redacted]	CheckMate 9LA utility analysis. Mapped Danish EQ-5D-5L value set applied to EQ-5D-3L responses
PDC			
>52 Weeks	[redacted]	[redacted]	CheckMate 9LA utility analysis. Mapped Danish EQ-5D-5L value set applied to EQ-5D-3L responses
27-52 Weeks	[redacted]	[redacted]	CheckMate 9LA utility analysis. Mapped Danish EQ-5D-5L value set applied to EQ-5D-3L responses
5-26 Weeks	[redacted]	[redacted]	CheckMate 9LA utility analysis. Mapped Danish EQ-5D-5L value set applied to EQ-5D-3L responses
<=4 Weeks	[redacted]	[redacted]	CheckMate 9LA utility analysis. Mapped Danish EQ-5D-5L value set applied to EQ-5D-3L responses
Overall			

>52 Weeks	[redacted]	[redacted]	CheckMate 9LA utility analysis. Mapped Danish EQ-5D-5L value set applied to EQ-5D-3L responses
27-52 Weeks	[redacted]	[redacted]	CheckMate 9LA utility analysis. Mapped Danish EQ-5D-5L value set applied to EQ-5D-3L responses
5-26 Weeks	[redacted]	[redacted]	CheckMate 9LA utility analysis. Mapped Danish EQ-5D-5L value set applied to EQ-5D-3L responses
<=4 Weeks	[redacted]	[redacted]	CheckMate 9LA utility analysis. Mapped Danish EQ-5D-5L value set applied to EQ-5D-3L responses

8.5 Resource use and costs

8.5.1 Disease management costs

The disease management costs represent the resource use required every four weeks to provide care to Stage IV or recurrent NSCLC patients regardless of treatment. As the model cycle is one week for the first 28 weeks, the disease management cost is divided by four for the first 28 weeks. After 28 weeks, the cycle length is 4 weeks.

Resource use estimates for disease management were based on input from a Danish clinical expert (Clinical expert interview 2020) and are the same for both the ITT and SQ PD-L1<1% populations. This expert specified disease management costs associated with patients in the PF and PD health states as described in Table 47. Unit costs were sourced from section 8 of the guidelines “Værdisætning af enhedsomkostninger” (Medicinrådet 2020c).

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Table 47: Disease management costs in the progression free and progressed disease health states, per 4 weeks

Resource name	No required PF health state) per 4 weeks	No required PD health state) per 4 weeks	Unit cost (DKK)	Reference for unit costs (and resource use)
Outpatient visit unit cost	1	1	1 467	Kommunernes og Regionernes Løndatakontor 2022, Specialeansvarlige overlæger (Overlæger, lægelige chefer m.v.). bruttolön Okt 2021. available from: https://krl.dk/#/sirka Calculated: salary/hours per month and multiplied by two according to Medicine council 2020. (KOL assumption)
Radiotherapy (brain) unit cost	0	0. 039	2 180	Sundhedsdatastyrelsen (2022). Interactive DRG: 04MA98 (BWGC) External radiation therapy (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/. (KOL assumption)
Radiotherapy (bone) unit cost	0	0.039	2 180	Sundhedsdatastyrelsen (2022). Interactive DRG: 04MA98 (BWGC) External radiation therapy (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/. (KOL assumption)
Blood transfusion unit cost	0.08	0.08	4 223	Sundhedsdatastyrelsen (2022). Interactive DRG: 16PR02 (BOQA0) Blood transfusion (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption)
CT scan unit cost	0.31	0.31	2 411	Sundhedsdatastyrelsen (2022). Interactive DRG: 36PR07 (UXCC75) CT scan of lungs (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption)
X-ray unit cost	0.15	0.15	1 640	Sundhedsdatastyrelsen (2022). Interactive DRG: 30PR18 (UXRC00) X-ray examination of the thorax (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/. (KOL assumption)
MRI unit cost	0.08	0.08	2 416	Sundhedsdatastyrelsen (2022). Interactive DRG: 30PR02 UXMH00) MRI scan of the whole body (DC349M) Kræft i bronkier eller lunge med metastaser. Available at:

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				http://interaktivdrg.sundhedsdata.dk/ (KOL assumption)
Hospitalization inpatient oncology ward unit cost per day	0	0.43	2 180	Sundhedsdatastyrelsen (2022). Interactive DRG: 04MA98 (BXXB0) Interdisciplinary assessment and treatment (DC349M) Kræft i bronkier eller lunge med metastaser . Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption).
99Tc bone scintigraphy scan unit cost	0.08	0.15	4 808	Sundhedsdatastyrelsen (2022). Interactive DRG: 36PR06 (WKBGD19XX) Bone scintigraphy, multiphase, Tc-99m-XPD (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption)

Abbreviations: CT: Computed tomography; DRG: Diagnosis-related group; MRI: Magnetic resonance imaging; NOK: Norwegian Krone; PD: Progressive disease; PF: Progression free

The end of life/terminal care costs are applied as a one-off cost to all patients which are newly entering the death state over the time horizon of the model. The one-off costs is estimated to 41 473 DKK based on 30 days palliative treatment for breast cancer patients (DRG 04MA07) (Medicinrådet 2020c).

8.5.2 Drug acquisition costs

ITT population

Three PDC treatment options are available for the two treatment arms of the CheckMate 9LA. Table 48 provide patient distributions for PDC treatments for NIVO+IPI+PDC and PDC, respectively. The distributions are based on the number of patients receiving each regimen as reported in the CheckMate 9LA CSR (Bristol-Myers Squibb 2020e).

Table 48: Distribution of patients receiving each PDC regimen - ITT

	NIVO+IPI+PDC		PDC	
PDC regimen	**Percentage**	**Calculation**	**Percentage**	**Calculation**
Carboplatin + paclitaxel	32%	115/358	32%	111/349
Carboplatin + pemetrexed	47%	169/358	47%	164/349
Cisplatin + pemetrexed	21%	74/358	21%	75/349

SOURCE: CheckMate 9LA (Bristol-Myers Squibb 2020e)
NIVO+IPI+PDC: nivolumab + ipilimumab combined with limited chemotherapy; PDC: Platinum doublet chemotherapy

For the SQ PD-L1<1% population, and in line with the CheckMate 9LA CSR (Bristol-Myers Squibb 2020e), the PDC treatment option used is 100% of patients on carboplatin + paclitaxel.

Three PDC treatment options are available for the two treatment arms of the CheckMate 9LA. Table 49 provides patient distributions for PDC treatments for NIVO+IPI+PDC and PDC, respectively. The distributions are based on the number of patients receiving each regimen as reported in the CheckMate 9LA CSR (Bristol-Myers Squibb 2020e).

Table 49: Distribution of patients receiving each PDC regimen - SQ PDL1<1%

	NIVO+IPI+PDC	PDC
PDC regimen	Percentage	Percentage
Carboplatin + paclitaxel	100%	100%

SOURCE: CheckMate 9LA (Bristol-Myers Squibb 2020e)
NIVO+IPI+PDC: nivolumab + ipilimumab combined with limited chemotherapy; PDC: Platinum doublet chemotherapy

Table 50 provides a summary of the drug acquisition costs used for both the ITT and PD-L1<1% population, however, the PDL1<1% population does not include pemetrexed as a PDC agent and therefore the PDC agent given to this subpopulation is carboplatin + paclitaxel. In the base case analysis, the cost per dose for each treatment is calculated by assuming vial sharing (i.e. if the full vial is not used the remaining content will be given to another patient).

Table 50: Dosing details of included treatments

	Drug	Tablet dose/ vial concentration	Cost per vial/pack, DKK	Dose	Cost per dose, DKK	Source
NIVO+IPI+PDC	Nivolumab	240 mg	22 003.74	360 mg Q3W up to 2 years	33 005.61	www.medicinpriser.dk
		100 mg	9 168.23			
		40 mg	3 690.69			
	Ipilimumab	200 ml	102 385.55	1 mg/kg Q6W	36 013.45	
		50 ml	25 653.53			
	Cisplatin	100 mg	200	75 mg/m^2 Q3W for 4 trt cycles	7 802.28	
		50 mg	100			
	Paclitaxel	300 mg	201.50	200 mg/m^2 Q3W for 4 trt cycles		
		100 mg	110.50			
	Pemetrexed	500 mg	6 068	500 mg/m^2 Q3W for 4 trt cycles		
		100 mg	1 456			
	Carboplatin	450 mg	203	685 mg Q3W for 4 trt cycles		
		150 mg	84			
PDC	Cisplatin	100 mg	200	75 mg/m^2 Q3W for 4 trt cycles	7 868.17	www.medicinpriser.dk
		50 mg	100			
	Paclitaxel	300 mg	201.50	200 mg/m^2 Q3W for 4 trt cycles		
		100 mg	110.50			
	Pemetrexed	500 mg	6 068	500 mg/m^2 Q3W for 4 trt cycles		
		100 mg	1 456			
	Carboplatin	450 mg	203	685 mg Q3W for 4 trt cycles		
		150 mg	84			

SOURCE: (Danish Medicines Agency 2022), CheckMate 9LA (Bristol-Myers Squibb 2020e)
G: Gram; Mg: Milligram; M2: Square meter; NIVO+IPI+PDC: nivolumab + ipilimumab + chemotherapy; PDC: Platinum-doublet chemotherapy; Q1W: Every week; Q2W: Every two weeks; Q3W: Every three weeks; Q6W; Every 6 weeks; Trt: treatment

8.5.3 Pemetrexed maintenance costs

In Checkmate 9LA and for the ITT population only 45% of the NSQ NSCLC patients in the PDC arm received pemetrexed maintenance therapy consisting of 500 mg/m2 administered intravenously once every 3 weeks until for a maximum of 1.25 years (Clinical expert interview 2020) (Table 51). In CheckMate 9LA the median number of doses received was 6.0 (IQR: 4.0-12.0) (Paz-Ares 2021a).

Table 51: Pemetrexed maintenance therapy for patients with NSQ NSCLC

Pemetrexed maintenance	Input	Reference
Proportion of patients with NSQ receiving maintenance is reflected in the DoT KM data	100.0%	CheckMate 9LA CSR (Bristol-Myers Squibb 2020e)
3-weekly cost of pemetrexed, DKK	10 936.55	Model calculation
Administration unit cost, DKK	2 180	Sundhedsdatastyrelsen (2022). Interactive DRG: 04MA98 (BWAA60) Medication by intravenous injection (DC349M) Cancer of the bronchi or lung with metastases. Available at: http://interaktivdrg.sundhedsdata.dk/
Monitoring unit cost, DKK	2 566.60	Assumed to be same as chemotherapy

…first-line: First-line; CSR: Clinical study report; DoT: Duration of treatment; KM: Kaplan-Meier; N/A: Not applicable; NHS: National health services; NSCLC: Non-small Cell Lung Cancer; NSQ: Non-squamous;

8.5.4 Administration costs

All treatments are administered in an outpatient setting. The costs associated with the administration (infusion) are 2180 DKK (code BWAA60) (Sundhedsdatastyrelsen 2022). In the base-case it is assumed that the administration cost per infusion is the same independent of treatment combination and is the same for both the ITT and SQ PD-L1<1% populations.

8.5.5 Monitoring costs

The need of monitoring associated with each treatment combination/arm have been estimated by a Danish KOL (Clinical expert interview 2020). Frequency estimates and unit costs for both the ITT and SQ PD-L1<1% populations, are outlined in Table 52, below.

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Table 52: Monitoring costs associated with each treatment regimen

Resource item	NIVO+IPI+PDC	PDC	Unit cost (DKK)	Reference for costs
Office visit	1	1	1 467	Kommunernes og Regionernes Løndatakontor 2022, Specialeansvarlige overlæger (Overlæger, lægelige chefer m.v.). bruttolön Okt 2021. available from: https://krl.dk/#/sirka Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.
Hepatic function test	1	1	144	Rigshospitalets Labportal (2022). Test code for hepatic tests included (codes): NPU19651, NPU19654, NPU27783, NPU19673, NPU01370, NPU03278. https://labportal.rh.dk/Labportal.asp
Renal function test	1	1	264	Rigshospitalets Labportal (2022). Test code for renal tests included (codes): NPU01459, NPU01472, NPU03429, NPU03230, NPU01536, NPU23745, NPU02192, NPU04998, NPU19673. https://labportal.rh.dk/Labportal.asp
Thyroid test	1	0	79	Rigshospitalets Labportal (2022). Test code included: (NPU03577) Thyrotropin. https://labportal.rh.dk/Labportal.asp
Comprehensive metabolic panel + ACTH	1	0	520	Assumed same cost as complete blood count
Complete blood count	0	1.33	520	Rigshospitalets Labportal (2022). Test code for CBC tests included (codes): NPU02902 (cost for test assumed as proxy for codes: NPU01960, NPU01961, NPU02593), NPU01473 (cost for test assumed as proxy for codes: B-Hb (Hemoglobin), Erc(B)-MCV, Erc(B)-MCH, Erc(B)-MCHC), and RGH00982. https://labportal.rh.dk/Labportal.asp

Abbreviations: CT: Computerized tomography; NOK, Norwegian Krone; PDC, platinum doublet chemotherapy

The monitoring costs for pemetrexed maintenance treatment are assumed to consist of an office visit, hepatic function test and complete blood count every 3 weeks for a maximum of 1.25 years (Clinical expert interview 2020).

8.5.6 Adverse events and adverse-event costs

The AEs considered in the model include grade 3, 4 or 5 TRAEs experienced by ≥5% of patients in the NIVO+IPI+PDC or PDC arm of CheckMate9LA or in any of the comparator arms (based on the individual trial results). This cut-off value is in line with previous IO submissions (Latimer 2013, Attard 2014b, Insinga 2019). The included AEs are presented in Table 53, and are the same for both the ITT and SQ PD-L1<1% populations.

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[redacted]

AE Type	CheckMate 9LA	
	NIVO+IPI+PDC	PDC
Anaemia	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Lipase Increased	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Febrile Neutropenia	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]

SOURCE: CheckMate 9LA (Bristol-Myers Squibb 2020e)
AE: Adverse event: NIVO+IPI+PDC: Nivolumab + ipilimumab combined with limited chemotherapy; PDC: Platinum doublet-chemotherapy

The dis-utilities assigned to AEs in the model are summarized in Table 54. Dis-utility values are only applied when the overall health state and overall TTD utility approaches are selected. When treatment specific heath state utilities are applied, it is assumed that these already account for the disutility of AEs, wherefore the separate AE dis-utilities are set to 0 to avoid double counting.

Table 54: Disutility by adverse event (cut-off 5%, grade 3-4)

Adverse event	Dis-utility	Reference
Anemia	-0.125	(Lloyd 2008a)
Neutropenia	-0.460	(Nafees 2017)
Fatigue	-0.410	(Nafees 2017)
Lipase Increased	0.000	Assumed zero*
Thrombocytopenia	-0.184	(Attard 2014b)
Neutrophil count decreased	-0.460	(Nafees 2017), assumed the same as neutropenia: (Huang 2017)
Platelet count decreased	0.000	Assumed zero*
White blood cell count decreased	-0.460	(Nafees 2017), assumed the same as neutropenia: (Huang 2017)
Febrile Neutropenia	-0.500	(Nafees 2017)
Hypertension	-0.050	(Nafees 2017)

SOURCE:
NOTE: Utility decrements estimated for the United Kingdom were used from the Nafees et al. (Nafees 2017) publication
*Utility decrement for lipase increased and platelet count decreased was unavailable, therefore the associated dis-utility is assumed to be zero

The need of additional monitoring due to the occurrence of adverse events was also estimated in the KOL interviews. For several adverse events the KOLs assumed no additional monitoring would be needed, i.e.: alanine aminotransferase increased, aspartate aminotransferase increased, decreased appetite, fatigue, lymphocyte count decreased, neutrophil count decreased, platelet count decreased, thrombocytopenia, and white blood cell count decrease.

However, for the adverse events listed below, in Table 55, the KOLs anticipated that additional visits and/or procedures would be required.

It was assumed that the costs due to AE-related mortality were already captured by the terminal care costs in the model, since all mortality events are reflected in the OS curve. AE events grade 3, 4 or 5 reported to have been observed in ≥ 5% of patients across all treatments regimens (including external comparators) were selected and included in the model. The cost associated with each individual AE is outlined in Table 55. The total cost of all AEs is based on the cost of each AE weighted by the proportion of patients incurring each AE. The total cost of AEs is applied as a one-off cost in the first model cycle.

Table 55: Adverse event related monitoring (in addition to the ordinary monitoring)

Adverse events	Unit Cost (DKK)	Reference for costs
Anaemia	2 180	Sundhedsdatastyrelsen (2022). Interactive DRG: 04MA98 (BOQA) Treatment with blood transfusion (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption)
Neutropenia	2 180	Sundhedsdatastyrelsen (2022). Hospitalization on average for 5 days for 20% of patients: Interactive DRG: 04MA98 (ZZ0149A) Somatic examination (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption)
Fatigue	0	Would be handled in a monitoring related visit, no extra cost
Lipase Increased	0	Would be handled in a monitoring related visit, no extra cost
Thrombocytopenia	0	Would be handled in a monitoring related visit, no extra cost
Neutrophil count decreased	0	Would be handled in a monitoring related visit, no extra cost
Platelet count decreased	0	Would be handled in a monitoring related visit, no extra cost
White blood cell count decreased	0	Would be handled in a monitoring related visit, no extra cost
Febrile neutropenia	2 180	Sundhedsdatastyrelsen (2022). Hospitalization on average for 5 days for 20% of patients: Interactive DRG: 04MA98 (ZZ0149A) Somatic examination (DC349M) Kræft i bronkier eller lunge med metastaser. Available at: http://interaktivdrg.sundhedsdata.dk/ (KOL assumption)
Hypertension	0	Would be handled in a monitoring related visit, no extra cost

Abbreviations: DkK: Danish Krone

The cost and disutility of AEs are applied as a one-off in the first model cycle. That is, the total treatment cost and disutility per episode of each AE is multiplied by the proportion of each AE outlined in Table 53 and included in week one. It is assumed that both the treatment cost per episode and disutility per episode accounts for the duration of the AE. The application of AE costs and disutility in week one is potentially a conservative assumption for two reasons:

AEs which are incurred after one year on treatment would be discounted in terms of costs and QALYs; therefore, applying these costs in week one will overestimate the impact of AEs. Week one has the maximum number of patients on treatment (patients in PFS at risk of experiencing AEs); therefore, applying the cost and disutility of AEs in week one will overestimate the impact of AE Nevertheless, it should be noted that the total impact of AEs on the ICER is marginal,

it is estimated that on average AEs have an impact lower than 1% on the ICER of NIVO+IPI+PDC in comparison with PDC.

8.5.7 Subsequent treatment costs

It is assumed that 70% of patients who received PDC and NIVO+IPI+PDC went on to receive subsequent threapy. This is the same proportion for both the ITT and SQ-PD-L1<1% populations. In Danish clinical practice, it is assumed that about 70% of the patients continue to 2nd line treamtment and this proportion was assumed in the DMC draft assessment report of 9LA.

Table 56 presents the distribution of patients who receive one or more of the top nine most common subsequent treatments by initial treatment for the ITT population. Table 57 presents the distribution of patients for the SQ PD-L1<1% population.

[redacted]

	NIVO+IPI+PDC	PDC
Nivolumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]

[redacted]

	NIVO+IPI+PDC*	PDC*
Nivolumab	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]
Atezolizumab	[redacted]	[redacted]
Carboplatin	[redacted]	[redacted]
Cisplatin	[redacted]	[redacted]
Docetaxel	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]
Paclitaxel	[redacted]	[redacted]
Pemetrexed	[redacted]	[redacted]

* The distributions of 2L treatments in each arm were re-calculated to exclude pemetrexed, which is a NSQ specific treatment

The average treatment duration for each subsequent therapy was based on estimates from the previously developed health-economic model for pre-treated stage IV or recurrent NSCLC. [redacted]

[redacted]

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Table 58 presents the acquisition cost of each subsequent treatment included for both the ITT and SQ PD-L1<1% population, however, pemetrexed is not included as as PDC agent in the SQ PD-L1<1% population. The administration cost is 2 180 DKK.

Table 58: Acquisition cost of subsequent treatments

Drug	Tablet dose/vial concentration (mg)	Cost per vial/pack, DKK	Dose	Cost per dose (weighted), DKK	Source
Nivolumab	240	22 003.74	3 mg/kg Q2W	20 240.30	www.medicinpriser.dk
	100	9 168.23			
	40	3 690.69			
Pembrolizumab	100	23 204.61	200 mg Q3W	46 409.22	www.medicinpriser.dk
Atezolizumab	1200	31 141.55	1200 mg Q3W	31 141.55	www.medicinpriser.dk
	840	21 799.09			
Carboplatin	450	203	685 mg Q3W	371.00	www.medicinpriser.dk
	150	84			
Cisplatin	100	200	75 mg/m^2 Q3W	300.00	www.medicinpriser.dk
	50	100			
Docetaxel	80	150	75 mg/m^2 Q3W	363.00	www.medicinpriser.dk
	20	71			
Gemcitabine	2000	1 200	1250 mg/m2	2 200.00	www.medicinpriser.dk
	1000	1 000			
Paclitaxel	300	201.50	200 mg/m^2 Q3W	312.00	www.medicinpriser.dk
	100	110.50			
Pemetrexed	500	6 068	500 mg/m^2 Q3W	12 136.00	www.medicinpriser.dk
	100	1 456			

SOURCE: (Danish Medicines Agency 2022); CheckMate 9LA (Bristol-Myers Squibb 2020d)
first-line: First-line; CheckMate 9LA: CheckMate 9LA; FDA: U.S. Food and Drug Administration; g: Gram; mg: Milligram; m2: Square meter; Q2W: Every two weeks; Q3W: Every three weeks; Q6W; Every 6 weeks; Trt: treatment

Table 59 presents the monitoring cost for each subsequent treatment included in the analysis for both the ITT and SQ PD-L1<1% population, however, pemetrexed is not included as as PDC agent in the SQ PD-L1<1% population.

Table 59: Monitoring cost of subsequent treatments

Treatment	Total cost of monitoring, DKK	Monitoring component (per month)	Source
Nivolumab	1 954.00	1x office visit 1x hepatic enzyme test 1x renal function test 1x thyroid test	KOL Assumption
Pembrolizumab	1 954.00	1x office visit 1x hepatic enzyme test 1x renal function test 1x thyroid test	KOL Assumption
Atezolizumab	1 690.00	1x office visit 1x hepatic enzyme test 1x thyroid test	KOL Assumption
Carboplatin	1 987.00	1x office visit 1x CBC	KOL Assumption
Cisplatin	1 987.00	1x office visit 1x CBC	KOL Assumption
Docetaxel	1 987.00	1x office visit 1x CBC	KOL Assumption
Gemcitabine	2 566.60	1x hepatic enzyme test 1x renal function test 1x office visit 1.33x CBC	KOL Assumption
Paclitaxel	1 987.00	1x office visit 1x CBC	KOL Assumption
Pemetrexed	2 566.60	1x hepatic enzyme test 1x renal function test 1x office visit 1.33x CBC	KOL assumption

8.5.8 Patient costs

For the total patient costs, the cost of transportation and the cost of patient and relative time (i.e. 'Patientomkostninger') (Medicinrådet 2020c) were summed and inputted in the model. No direct estimate for transportation costs could be obtained, for this reason, transportation costs were obtained by multiplying the estimated frequency of transport for medical services with the unit cost of the average transportation. The unit cost for the average transportation including return trip was calculated to ~100 DKK (assuming a cost of 3.52 DKK/km and an average travel distance of 14 km), in line with guidance from the DMC (Medicinrådet 2020c). The cost of patients' time was valued to 208 DKK per hour (Statistics Denmark 2022), and it was assumed that the average treatment would require two hours. This result in a total unit cost per event of 416 DKK.

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8.6 Results

8.6.1 ITT

8.6.1.1 Base case overview

Table 60: Base case settings overview, trial based analysis (ITT)

Comparator	Standard care, PDC (ITT population)
Base case comparator, trial based	PDC
Type of model	Partitioned survival model
Perspective	Restricted societal perspective (patient costs included)
Time horizon	25 years (life time)
Discounting	3.5% for costs and effects
Starting age, weight and proportion female	72 years; 70.35 kg; 49% female
Treatment line	First-line. Subsequent treatment lines based on CheckMate 9LA.
Measurement and valuation of health effects	Treatment specific health-related quality of life measured with EQ-5D-3L in CheckMate 9LA mapped to Danish EQ-5D-5L. Danish age-adjusted population weights were used to estimate health-state utility values.
Included costs	Pharmaceutical costs, hospital costs, costs of adverse events, patient costs
Dosage of pharmaceutical	Flat dosing, vial sharing
Average time on treatment	Based on duration of treatment (DoT) in CheckMate 9LA, treatment cap at 2 years
Pemetrexed maintenance treatment	1.25 years
Parametric function for OS	CheckMate 9LA KM + parametric - CheckMate 227 part 1, (complete data set, 4 years data cut)
Parametric function for PFS	CheckMate 9LA KM + parametric - CheckMate 227 part 1 (complete data set, 4 years data cut)
Parametric function for DoT	CheckMate 9LA DoT KM data
Extrapolation assumptions NIVO+IPI+PDC vs PDC	OS NIVO+IPI+PDC: 2-knots spline normal curve OS PDC: 2-knots spline odds curve PFS NIVO+IPI+PDC: 2-knots spline hazard curve PFS PDC: 2-knots spline normal curve DoT NIVO+IPI+PDC: KM curves DoT PDC: KM curves

8.6.1.2 Base case results- nivolumab plus ipilimumab in combination with two cycles of platinum doublet chemotherapy vs. chemotherapy alone for patients with NSCLC, ITT population

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Results of the trial-based analysis show that treatment with NIVO+IPI+PDC is associated with better survival than treatment with only PDC. This results in an expected gain in life years (1.32 years) and quality-adjusted life years (1.07 QALYs). This comes at an expected additional cost of 627 000 DKK, mostly due to the higher drug acquisition costs. Treatment with NIVO+IPI+PDC is associated with fewer adverse events. The total incremental cost-effectiveness ratio (ICER) per QALY for NIVO+IPI+PDC vs. PDC is estimated to be 586 906 DKK.

The Table 61 below present results for NIVO+IPI+PDC compared to PDC.

Table 61: Base case results: nivolumab + ipilimumab combined with platinum doublet chemotherapy vs. platinum doublet chemotherapy – ITT population

Per patient	NIVO+IPI+PDC	PDC	Difference
Life years gained			
Total life years gained	3.25	1.93	1.32
QALYs			
Total QALYs	2.41	1.35	1.07
QALYs (Health states)	2.41	1.35	1.07
QALYs (adverse events)	N/A	N/A	N/A
Costs			
Total costs	1 035 589	408 589	627 000
Disease management	192 824	134 166	58 658
Drug costs	703 537	78 027	625 510
Administrative costs	48 303	17 576	30 727
Monitoring costs	25 035	14 798	10 237
Adverse event costs	365	600	-235
Subsequent treatment costs	45 420	153 909	-108 489
Patient costs	20 104	9 513	10 592
Incremental results	NIVO+IPI+PDC vs. PDC		
ICER per life year	476 747		
ICER per QALY	586 906		

PDC: Platinum doublet chemo

8.6.2 SQ PD-L1<1%

8.6.2.1 Base case overview

Table 62: Base case settings overview, trial based analysis

Comparator	Standard care, PDC (SQ PDL1<1% population)
Base case comparator, trial based	PDC
Type of model	Partitioned survival model
Perspective	Restricted societal perspective (patient costs included)
Time horizon	25 years (life time)
Discounting	3.5% for costs and effects
Starting age, weight and proportion female	72 years; 70.35 kg; 49% female
Treatment line	First-line. Subsequent treatment lines based on CheckMate 9LA.
Measurement and valuation of health effects	Treatment specific health-related quality of life measured with EQ-5D-3L in CheckMate 9LA mapped to Danish EQ-5D-5L. Danish age-adjusted population weights were used to estimate health-state utility values.
Included costs	Pharmaceutical costs, hospital costs, costs of adverse events, patient costs
Dosage of pharmaceutical	Flat dosing, vial sharing
Average time on treatment	Based on duration of treatment (DoT) in CheckMate 9LA, treatment cap at 2 years
Pemetrexed maintenance treatment	N/A – pemetrexed not included in the squamous population
Parametric function for OS	CheckMate 9LA SQ PD-L1<1% KM + parametric - CheckMate 227 part 1b, (complete data set, 4 years data cut)
Parametric function for PFS	CheckMate 9LA SQ PD-L1<1% KM + parametric - CheckMate 227 part 1b (complete data set, 4 years data cut)
Parametric function for DoT	CheckMate 9LA SQ PD-L1<1% DoT KM data
Extrapolation assumptions NIVO+IPI+PDC vs PDC	OS NIVO+IPI+PDC: Generalized gamma curve OS PDC: Log-logistic curve PFS NIVO+IPI+PDC: 1-knot spline normal curve PFS PDC: Log-logistic curve DoT NIVO+IPI+PDC: KM curves DoT PDC: KM curves

8.6.2.2 Base case results- nivolumab plus ipilimumab in combination with two cycles of platinum doublet chemotherapy vs. chemotherapy alone for patients with NSCLC, SQ PDL1<1% population

Results of the trial-based analysis show that treatment with NIVO+IPI+PDC is associated with better survival than treatment with only PDC. This results in an expected gain in life years (1.45 years) and quality-adjusted life years (1.17

QALYs). This comes at an expected additional cost of 728 774 DKK, mostly due to the higher drug acquisition costs. Treatment with NIVO+IPI+PDC is associated with fewer adverse events. The total incremental cost-effectiveness ratio (ICER) per QALY for NIVO+IPI+PDC vs. PDC is estimated to be 623 662 DKK.

Table 63 below present results for NIVO+IPI+PDC compared to PDC in the SQ PDL1<1% subgroup.

Table 63: Base case results: nivolumab + ipilimumab combined with chemotherapy vs. chemotherapy – SQ PDL1<1% population

Per patient	NIVO+IPI+PDC	PDC	Difference
Life years gained			
Total life years gained	2.54	1.09	1.45
QALYs			
Total QALYs	1.95	0.78	1.17
QALYs (Health states)	1.95	0.78	1.17
QALYs (adverse events)	N/A	N/A	N/A
Costs			
Total costs	996 705	267 931	728 774
Disease management	154 239	92 631	61 608
Drug costs	710 731	1 577	709 154
Administrative costs	49 611	6 328	43 283
Monitoring costs	25 825	4 830	20 995
Adverse event costs	365	600	-235
Subsequent treatment costs	38 402	157 013	-118 610
Patient costs	17 531	4 952	12 579
Incremental results	NIVO+IPI+PDC vs. PDC		
ICER per life year	501 608		
ICER per QALY	623 662		

PDC: Platinum doublet chemo

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyse, ITT and SQ PDL<1%

One-way sensitivity analysis was undertaken by varying key parameters by their standard error, 95% CI or +/- 20% of the expected values (base case) based on data availability. The following parameters were included as part of the one-way sensitivity analysis:

- Discount rate – varied from 0% to 6% (Sanders 2016)

- Body weight and body surface area – varied by +/- 20%
- Costs: included disease management, treatment acquisition, administration, and monitoring; and – varied by +/- 20%
- Utilities: PF and PD health states (treatment specific) – varied by 95% CI

Table 64 summarizes the deterministic sensitivity analyses for NIVO+IPI+PDC vs. PDC for the ITT population, while Table 65 summarizes the deterministic sensitivity analyses for NIVO+IPI+PDC vs. PDC for the SQ PDL1<1% population. Figure 53 and Figure 54 show the tornado diagram for the ITT and SQ PDL1<1% respectively. Figure 53 and Figure 54 indicate that changes to most of the input parameters included in the analysis do not have a large impact on the ICER for both the ITT and SQ PDL1<1% populations. In the ITT population, the parameters with the largest impact on the incremental cost per QALY gained are the average body weight (effects the cost of treatment), the discount rate applied to QALYs, and the utility values applied to PD and PF for NIVO+IPI+PDC. Similarly, the parameters with the largest impact on the ICER for the SQ PDL1<1% subgroup is the average body weight, discount rate applied to QALYs, the utility values applied to PF for NIVO+IPI+PDC, and the PF disease management costs.

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Table 64: Deterministic sensitivity analysis of NIVO+IPI+PDC vs. PDC - ITT

Parameter	Base case value	Analysis	Values for DSA	Inc. Costs DKK	Inc. QALYs	Inc. cost per QALY DKK	Difference ICER %
Base Case Analysis				627 000	1.068	586 906	N/A
Discount rate costs	3.5%	Lower	2.8%	631 793	1.068	591 393	0.76%
		Higher	4.2%	622 516	1.068	582 709	-0.72%
Discount rate QALY	3.5%	Lower	2.8%	627 000	1.116	561 829	-4.27%
		Higher	4.2%	627 000	1.024	612 139	4.30%
Average body weight	70.349	Lower	56.279	587 113	1.068	549 570	-6.36%
		Higher	84.418	666 886	1.068	624 242	6.36%
Average body surface area	1.802	Lower	1.442	639 291	1.068	598 412	1.96%
		Higher	2.163	617 875	1.068	578 365	-1.46%
Costs							
Disease management costs - PF	3 376.17	Lower	2 700.94	618 351	1.068	578 811	-1.38%
		Higher	4 051.40	635 648	1.068	595 001	1.38%
Disease management costs - PD	4 057.17	Lower	3 245.74	623 519	1.068	583 648	-0.56%
		Higher	4 868.60	630 480	1.068	590 164	0.56%
Costs disease management - terminal care	41 473	Lower	33 178.40	627 397	1.068	587 278	0.06%
		Higher	49 767.60	626 602	1.068	586 534	-0.06%
Admin cost nivolumab	2 180	Lower	1 744.00	621 187	1.068	581 466	-0.93%
		Higher	2 616.00	632 812	1.068	592 347	0.93%
Admin cost ipilimumab	2 180	Lower	1 744.00	623 991	1.068	584 090	-0.48%
		Higher	2 616.00	630 008	1.068	589 723	0.48%
Admin costs Platinum doublet chemo	2 186.24	Lower	1749.00	628 431	1.068	588 246	0.23%
		Higher	2 623.50	625 568	1.068	585 566	-0.23%
Monitor costs NIVO+IPI+ PDC	2 474	Lower	1 979.20	622 187	1.068	582 401	-0.77%
		Higher	2 968.80	631 812	1.068	591 411	0.77%
Monitor costs PDC	2 566.60	Lower	2 053.28	628 184	1.068	588 015	0.19%
		Higher	3 079.92	625 815	1.068	585 798	-0.19%
Outcomes							
TS utilities PF NIVO+IPI+ PDC	[redacted]	Lower	[redacted]	627 000	1.034	606 191	3.29%
		Higher	[redacted]	627 000	1.102	568 810	-3.08%
TS utilities PD NIVO+IPI+ PDC	[redacted]	Lower	[redacted]	627 000	1.035	605 965	3.25%
		Higher	[redacted]	627 000	1.102	569 010	-3.05%
TS utilities PF PDC	[redacted]	Lower	[redacted]	627 000	1.085	577 767	-1.56%
		Higher	[redacted]	627 000	1.051	596 340	1.61%
TS utilities PD PDC	[redacted]	Lower	[redacted]	627 000	1.095	572 782	-2.41%
		Higher	[redacted]	627 000	1.042	601 744	2.53%

.BSA: body surface area; Chemo: chemotherapy: DSA: deterministic sensitivity analysis: Inc: Incremental; LY: life year; NIVO+IPI+PDC; nivolumab + ipilimumab combined with limited chemotherapy; PD: progressed disease; PDC: Platinum doublet chemotherapy; PF: progression free; PFS: progression free survival QALY: quality adjusted life year: TS: Treatment specific

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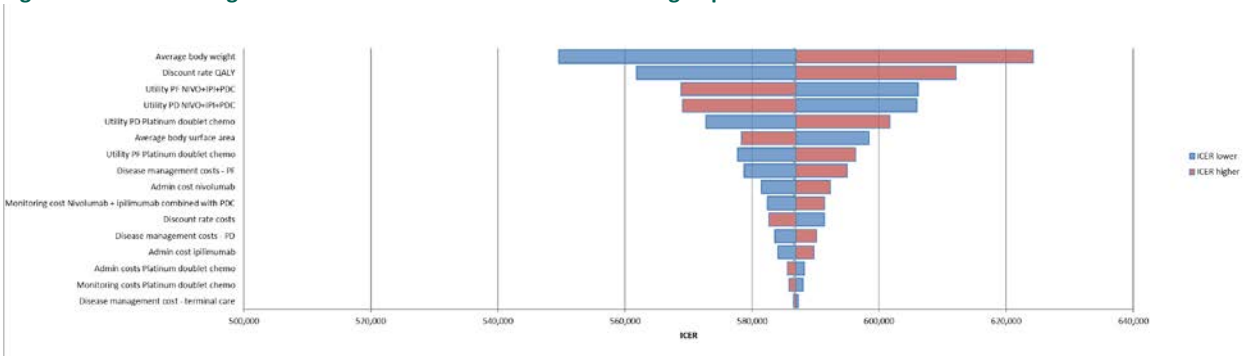
Figure 53: Tornado diagram for DSA NIVO+IPI+PDC vs. PDC showing impact on the ICER - ITT



Admin: administration; DSA: deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; PD: progressed disease; PDC: Platinum doublet chemotherapy; PF: progression free; PFS: progression free survival; QALY: quality adjusted life year;

Table 65: Deterministic sensitivity analysis of NIVO+IPI+PDC vs. PDC - SQ PD-L1<1%

Parameter	Base case value	Analysis	Values for DSA	Inc. Costs DKK	Inc. QALYs	Inc. cost per QALY DKK	Difference ICER %
Base Case Analysis				728 774	1.169	623 662	N/A
Discount rate costs	3.5%	Lower	2.8%	733 420	1.169	627 638	0.64%
		Higher	4.2%	724 395	1.169	619 915	-0.60%
Discount rate QALY	3.5%	Lower	2.8%	728 774	1.212	601 128	-3.61%
		Higher	4.2%	728 774	1.128	646 143	3.60%
Average body weight	70.349	Lower	56.279	687 872	1.169	588 660	-5.61%
		Higher	84.418	769 676	1.169	658 664	5.61%
Average body surface area	1.802	Lower	1.442	728 501	1.169	623 429	-0.04%
		Higher	2.163	728 769	1.169	623 658	0.00%
Costs							
Disease management costs - PF	3 376.17	Lower	2 700.94	716 070	1.169	612 791	-1.74%
		Higher	4 051.40	741 478	1.169	634 533	1.74%
Disease management costs - PD	4 057.17	Lower	3 245.74	728 714	1.169	623 611	-0.01%
		Higher	4 868.60	728 834	1.169	623 713	0.01%
Costs disease management - terminal care	41 473	Lower	33 178.40	729 216	1.169	624 040	0.06%
		Higher	49 767.60	728 332	1.169	623 284	-0.06%
Admin cost nivolumab	2 180	Lower	1 744.00	722 765	1.169	618 520	-0.82%
		Higher	2 616.00	734 783	1.169	628 804	0.82%
Admin cost ipilimumab	2 180	Lower	1 744.00	725 689	1.169	621 022	-0.42%
		Higher	2 616.00	731 859	1.169	626 302	0.42%
Admin costs Platinum doublet chemo	2 186.24	Lower	1749.00	730 022	1.169	624 730	0.17%
		Higher	2 623.50	727 527	1.169	622 594	-0.17%
Monitor costs NIVO+IPI+ PDC	2 474	Lower	1 979.20	723 799	1.169	619 405	-0.68%
		Higher	2 968.80	733 749	1.169	627 919	0.68%
Monitor costs PDC	2 566.60	Lower	2 053.28	729 731	1.169	624 481	0.13%
		Higher	3 079.92	727 817	1.169	622 843	-0.13%
Outcomes							
TS utilities PF NIVO+IPI+ PDC	[redacted]	Lower	[redacted]	728 774	1.129	645 417	3.49%
		Higher	[redacted]	728 774	1.208	603 326	-3.26%
TS utilities PD NIVO+IPI+ PDC	[redacted]	Lower	[redacted]	728 774	1.157	629 776	0.98%
		Higher	[redacted]	728 774	1.180	617 665	-0.96%
TS utilities PF PDC	[redacted]	Lower	[redacted]	728 774	1.182	616 677	-1.12%
		Higher	[redacted]	728 774	1.155	630 807	1.15%
TS utilities PD PDC	[redacted]	Lower	[redacted]	728 774	1.180	617 796	-0.94%
		Higher	[redacted]	728 774	1.157	629 640	0.96%

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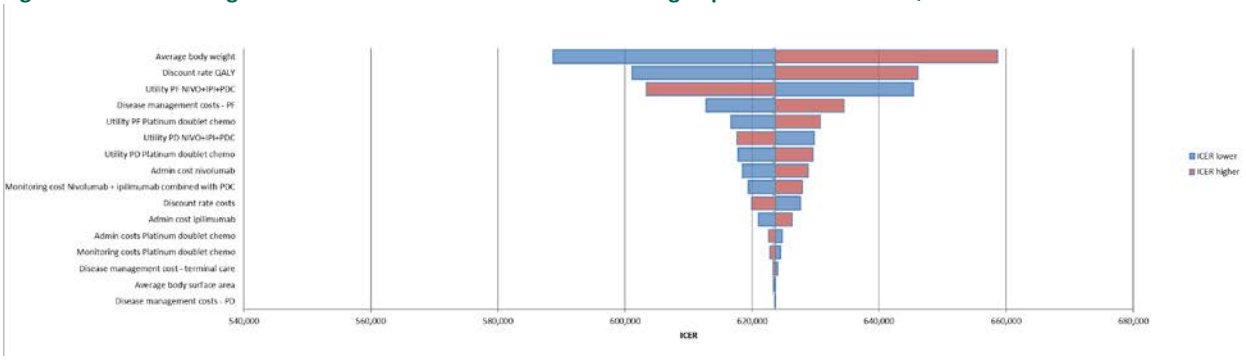
Figure 54: Tornado diagram for DSA NIVO+IPI+PDC vs. PDC showing impact on the ICER - SQ PDL1<1



Admin: administration; DSA: deterministic sensitivity analysis; ICER: incremental cost-effectiveness ratio; PD: progressed disease; PDC: Platinum doublet chemotherapy; PF: progression free; PFS: progression free survival; QALY: quality adjusted life year;

8.7.2 Probabilistic sensitivity analyses ITT and SQ PDL<1%

Probabilistic sensitivity analysis (PSA) was conducted for NIVO+IPI+PDC compared to relevant treatment options for both the ITT and SQ PDL1<1% populations. For each analysis, parameter values were sampled from their respective distributions, and the cost-effectiveness of the intervention compared to that of the comparator and 1000 iterations were used. The results show the uncertainty of the ICER per QALY as a function of the uncertainty of the exact values of the parameters included in the analysis. For additional details, see Appendix J Probabilistic sensitivity analyses. Results are presented below in scatterplots against a cost-effectiveness plane.

The results of the PSA (for 1 000 iterations) are presented in Table 66 for the ITT population, and in Table 67 for the SQ PDL1<1% subpopulation. The tables also present results from the deterministic analysis for comparison. The probabilistic incremental cost per QALY gained is 587 562 DKK versus PDC for the ITT population, and 618 509 DKK versus PDC for the SQ PDL1<1% subgroup. The small difference between the probabilistic and deterministic results in the comparison with PDC indicates that the results of the analyses are robust. The cost-effectiveness acceptability curve (CEAC) is shown in Figure 55 for the ITT population, and in Figure 56 for the SQ PDL1<1% subpopulation.

Table 66: Probabilisitc sensitivity analysis - ITT

NIVO+IPI+PDC	Incremental cost per QALY (DKK)	
	Deterministic	Probabilistic
PDC	586 906	587 562

NIVO+IPI+PDC: nivolumab + ipilimumab combined with limited chemotherapy; PDC: Platinum doublet chemotherapy, QALY: Quality adjusted life year

Figure 55: Incremental costs (DKK) and QALYs shown on cost-effectiveness plane, nivolumab + ipilimumab combined with chemotherapy vs. chemotherapy - ITT

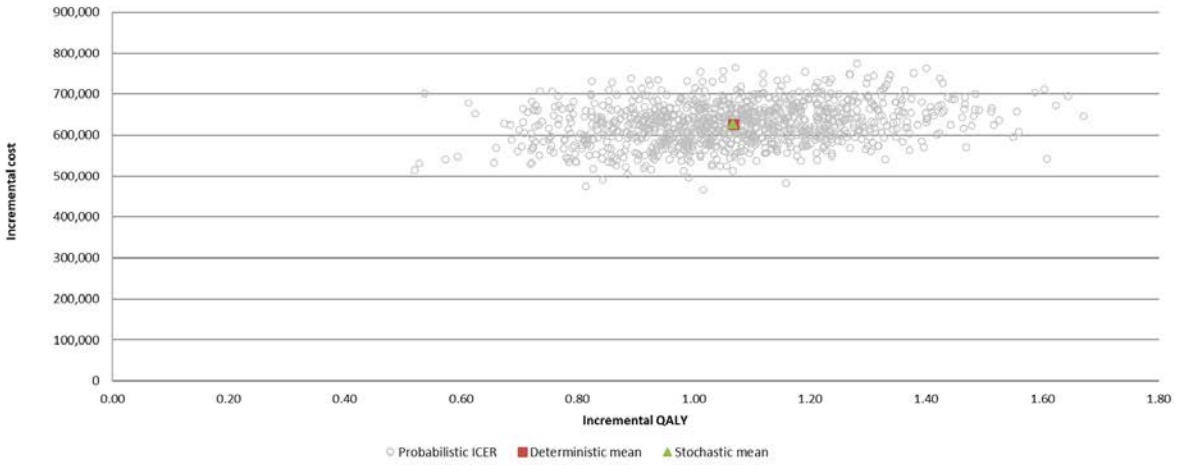
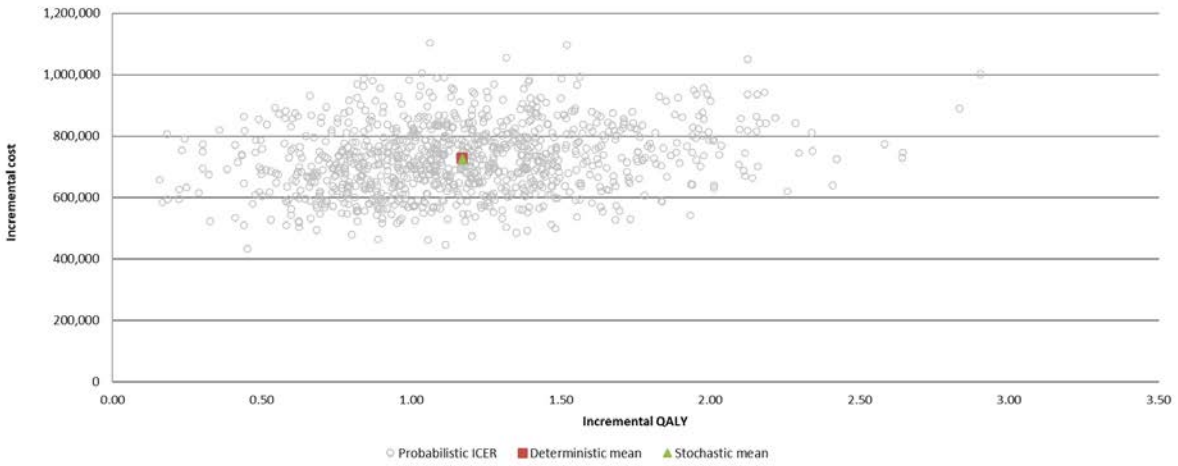


Table 67: Probabilisitc sensitivity analysis – SQ PDL1<1%

NIVO+IPI+PDC	Incremental cost per QALY (DKK)	
	Deterministic	Probabilistic
PDC	623 662	618 509

NIVO+IPI+PDC: nivolumab + ipilimumab combined with limited chemotherapy; PDC: Platinum doublet chemotherapy, QALY: Quality adjusted life year

Figure 56: Incremental costs (DKK) and QALYs shown on cost-effectiveness plane, nivolumab + ipilimumab combined with chemotherapy vs. chemotherapy – SQ PDL1<1%



8.7.3 Scenario analyses, ITT and SQ PDL<1%

Scenario analyses were undertaken to investigate the effect of certain model inputs on costs and outcomes. Table 68 provides a descriptions of the scenarios and an interpretation of the results for the ITT population, while Table 70 provides a description of the scenario analysis undertaken in the SQ PDL1<1% population. Table 69 and Table 71 summarizes the results of the scenario analyses for the ITT and SQ PDL1<1% populations respectively.

Table 68: List of scenario analyses - ITT

Scenario	Base case setting	Scenario setting
Time horizon	25 years	15 years, 20 years
Payer perspective	Patient costs included	Patient costs excluded
Starting age of cohort	72 years	63.7 years as in CheckMate 9LA
Proportion female	49%	29.9 % as in CheckMate 9LA
Dosing regiment	Flat dosing	Weight-based dosing for nivolumab and pembrolizumab
Utilities	Treatment-specific	Overall utilities by health state (not treatment specific and including AEs dis-utilities)
Wastage	Exclude wastage (vial sharing)	Include wastage (no vial sharing)
9LA only curve selection – loglogistic curves for nivo+ipi+PDC and PDC OS	OS Nivo+ipi+PDC: 2-knot spline normal OS PDC: 2-knot spline odds PFS Nivo+ipi+PDC: 2-knot spline hazards PFS PDC: 2-knot spline normal	OS Nivo+ipi+PDC: Loglogistic OS PDC: Loglogistic PFS Nivo+ipi+PDC: 2-knot spline hazards PFS PDC: 2-knot spline normal

Table 69: Results for scenario analyses – ITT

Scenario	Nivolumab + ipilimumab combined with PDC		Platinum doublet chemotherapy		Incremental		ICER per QALY (DKK)
	Total costs (DKK)	Total QALYs	Total costs (DKK)	Total QALYs	Costs (DKK)	QALYs	
Base case	1 035 589	2.41	408 589	1.35	627 000	1.07	586 906
20 year time horizon	1 032 438	2.38	407 559	1.34	624 879	1.05	597 814
15 year time horizon	1 022 596	2.27	404 220	1.31	618 376	0.97	638 949
Starting age of cohort: 63.7 years	1 041 879	2.54	410 117	1.38	631 762	1.16	542 384
Proportion female: 29.9%	1 042 036	2.41	408 433	1.34	633 603	1.06	596 150
Weight-based dosing	982 508	2.41	408 589	1.35	573 919	1.07	537 219
Overall utilities	1 035 589	2.25	408 589	1.29	627 000	0.96	654 209
Patient costs excluded	1 015 485	2.41	399 077	1.35	616 408	1.07	576 992
Include wastage (no vial sharing)	1 143 780	2.41	417 264	1.35	726 515	1.07	680 058
9LA only curve selection	1 001 918	1.94	402 218	1.27	599 701	0.67	894 781

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Table 70: List of scenario analyses - SQ PDL1<1%

Scenario	Base case setting	Scenario setting
Time horizon	25 years	15 years, 20 years
Payer perspective	Patient costs included	Patient costs excluded
Starting age of cohort	72 years	63.7 years as in CheckMate 9LA
Proportion female	49%	29.9 % as in CheckMate 9LA
Dosing regiment	Flat dosing	Weight-based dosing for nivolumab and pembrolizumab
Utilities	Treatment-specific	Overall utilities by health state (not treatment specific and including AEs dis-utilities)
Wastage	Exclude wastage (vial sharing)	Include wastage (no vial sharing)
9LA only curve selection – loglogistic curves for nivo+ipi+PDC and PDC OS	OS Nivo+ipi+PDC: Generalized gamma OS PDC: Loglogistic PFS Nivo+ipi+PDC: 1-knot spline normal PFS PDC: Loglogistic	OS Nivo+ipi+PDC: Loglogistic OS PDC: Loglogistic PFS Nivo+ipi+PDC: 1-knot spline normal PFS PDC: Loglogistic

Table 71: Results for scenario analyses- SQ PD-L1<1%

Scenario	Nivolumab + ipilimumab combined with PDC		Platinum doublet chemotherapy		Incremental		ICER per QALY (DKK)
	Total costs (DKK)	Total QALYs	Total costs (DKK)	Total QALYs	Costs (DKK)	QALYs	
Base case	996 705	1.95	267 931	0.78	728 774	1.17	623 662
20 year time horizon	994 662	1.93	267 707	0.78	726 954	1.15	631 912
15 year time horizon	988 565	1.86	266 980	0.77	721 584	1.09	664 252
Starting age of cohort: 63.7 years	1 000 457	2.05	268 489	0.79	731 968	1.26	582 315
Proportion female: 29.9%	1 003 435	1.94	267 856	0.78	735 579	1.16	632 853
Weight-based dosing	941 828	1.95	267 931	0.78	673 897	1.17	576 700
Overall utilities	996 705	1.81	267 931	0.71	728 774	1.10	663 131
Patient costs excluded	979 174	1.95	262 979	0.78	716 195	1.17	612 897
Include wastage (no vial sharing)	1 106 129	1.95	268 308	0.78	837 821	1.17	716 981
9LA only curve selection	1 024 213	2.19	267 630	0.75	756 582	1.44	525 895

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9. Budget impact analysis

The budget impact analysis focusing on the SQ PDL1<1% subgroup uses a yearly cohort of 120 patients over a five year period and is comparing the budget impact of introducing NIVO+IPI+PDC vs current SOC in SQ with PD-L1 expression<1%, PDC-. The analysis was carried out from a restricted health-care perspective and in the analyses the following costs were included: disease management, acquisition, administration, monitoring, adverse events, other costs, subsequent treatment and, transportation. All these costs are sourced from the cost-effectiveness model. Consequently, the patient initiating the treatment in the cost and budget impact model will incur the same cost in the same rate as in the cost-effectiveness model.

9.1 Number of patients

The assumptions around market shares rest on market research conducted, as well as the amount of data available to support the added value of NIVO+IPI+PDC. The number of expected patients to be treated with NIVO+IPI+PDC vs the other comparators if NIVO+IPI+PDC over the next five years is introduced is presented in Table 72 and the number of expected patients per comparator in the scenario if NIVO+IPI+PDC is not introduced is captured in Table 73 the number of expected patients. There is currently an unmet need of an immunotherapy in the segment of patients with SQ disease and PD-L1 expression <1%. Therefore, the expectations are that treatment with NIVO+IPI+PDC will become standard of care in this segment.

Table 72: Number of 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
For the pharmaceutical under consideration					
NIVO+IPI+PDC	60	120	120	120	120
PDC	60	0	0	0	0
Total number of patients	**120**	**120**	**120**	**120**	**120**

Table 73: Number of 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
For the pharmaceutical under consideration					
NIVO+IPI+PDC	-	-	-	-	-
PDC	120	120	120	120	120
Total number of patients	**120**	**120**	**120**	**120**	**120**

9.2 Expenditure per patient

The costs per patient per year for NIVO+IPI+PDC if the combination are presented in Table 74. These per patient costs are used to calculate the budget impact shown in **Table 75** below.

Table 74: Costs per patient per year (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5	Total per patient over 5 years
For the pharmaceutical under consideration costs per patient						
NIVO+IPI+PDC	690 778	219 319	17 657	12 451	9 517	949 772
PDC	210 310	24 891	13 806	5 907	3 317	258 230

9.3 Budget impact

The results show a total budget impact of 82 805 994 DKK over a 5 year timeframe (Table 75), based on the number of patients expected to be treated per year and market penetration in Table 72. The key cost drivers for the budget impact analysis are the differences in costs for disease management, drug acquisition, monitoring and subsequent treatment, between the two scenarios (with and without the introduction of NIVO+IPI+PDC).

Table 75: Expected budget impact of recommending the pharmlaceutical for the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	**54 065 274**	**97 546 003**	**111 099 513**	**112 432 021**	**113 395 652**
Of which: Disease management costs	6 680 566	9 271 974	11 431 773	12 945 953	13 969 392
Of which: Acquisition costs	33 172 347	76 129 866	86 104 290	86 104 290	86 104 290
Of which: Administration costs	2 743 426	5 366 537	6 005 589	6 005 589	6 005 589
Of which: Monitoring costs	1 484 555	2 758 467	3 127 446	3 127 446	3 127 446
Of which: Adverse event costs	57 918	43 844	43 844	43 844	43 844
Of which: Other costs	-	-	-	-	-
Of which: Subsequent treatment costs	9 926 461	3 975 315	4 386 571	4 204 899	4 145 091
Minus: **The pharmaceutical under consideration is NOT recommended**	**25 237 146**	**28 224 063**	**29 880 839**	**30 589 657**	**30 589 657**
Of which: Disease management costs	7 102 427	9 253 550	9 919 437	10 307 570	10 307 570

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	Year 1	Year 2	Year 3	Year 4	Year 5
Of which: Acquisition costs	189 253	189 253	189 253	189 253	189 253
Of which: Administration costs	759 367	759 367	759 367	759 367	759 367
Of which: Monitoring costs	579 624	579 624	579 624	579 624	579 624
Of which: Adverse event costs	71 992	71 992	71 992	71 992	71 992
Of which: Other costs	-	-	-	-	-
Of which: Subsequent treatment costs	16 534 484	17 370 277	18 361 166	18 681 852	18 681 852
Budget impact of the recommendation	**28 828 128**	**69 321 939**	**81 218 674**	**81 842 363**	**82 805 994**

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10. Discussion on the submitted documentation

NIVO+IPI+PDC is a new treatment option that will provide attainable OS benefit across histology and PD-L1 expressions levels and should be considered one of the accepted standards of care for the first-line treatment of advanced and metastatic NSCLC without EGFR mutations or ALK translocations. The base case analysis of cost-effectiveness of NIVO+IPI+PDC vs PDC for the ITT and SQ PD-L1<1% population and scenario analyses vs. existing IO therapies demonstrates that NIVO+IPI+PDC overall is a cost-effective alternative for this population.

NIVO+IPI+PDC treatment has demonstrated increased levels of durable response that translate into survival benefits over PDC alone. In CheckMate 9LA, ITT patients experienced median OS of 15.7 months with NIVO+IPI+PDC compared to 10.2 months with PDC alone. This survival benefit was maintained when exploring NIVO+IPI+PDC treatment vs PDC alone in the SQ PD-L1<1% population (median OS for NIVO+IPI+PDC was 13.8 months vs 7.4 months for PDC). Whilst total LYs and total QALYs were lower in both arms, due to SQ patients spending slightly longer on treatment [redacted] the incremental difference between the intervention and comparator increased for both LYs (ITT incremental LYs were 1.32 vs 1.45 incremental LYs for SQ PD-L1<1%) and QALYs (ITT incremental QALYs were 1.07 vs 1.17 incremental QALYs for SQ PD-L1<1%, see section 8.6 for detailed results).

The CheckMate 9LA trial was also able to demonstrate early disease control through the addition of limited PDC (two cycles of PDC) during the first 3 months of treatment vs. PDC alone compared to CheckMate 227, where an early crossing of the survival curve of was observed of NIVO+IPI vs PDC. This supports the hypothesis that adding limited cycles of PDC (2 cycles) would provide rapid initial disease control while building on the potential durable benefit of NIVO+IPI seen in NSCLC and other tumours.

Strengths and limitations of the economic evaluation

The key strengths of the economic evaluation include:

- The three-health state structure (partitioned survival model) has been extensively validated and applied in numerous previous technology appraisals
- The key value of NIVO+IPI+PDC is the potential for long-term durable survival benefits. Within the economic model, the long-term OS extrapolations were validated using both real world datasets (SEER, and Swedish and Norwegian registry data) data from CheckMate 227 and the pooled CheckMate 017 and 057 data.
- Health state utility weights were derived from EQ-5D data collected in the CheckMate 9LA trial. The values used in the model are considered representative of the target population. EQ-5D values were mapped with a peer reviewed algorithm to reflect the new Danish EQ-5D-5L value tariff.

The key limitations of the economic evaluation include:

- With a minimum follow-up 24.4 months (OS), CheckMate 9LA data is still relatively immature. However, given the similarities between CheckMate 9LA and CheckMate 227, it was possible to extrapolate OS using mature survival data from CheckMate 227 by applying the piecewise approach A. The utilization of the long term follow-up of dual IO from CheckMate 227 received widespread support by HTA agencies, in advisory boards and KOL interviews conducted as part of the submission planning.
- Long-term extrapolation of OS using data from short-term clinical trials will always be subject to uncertainty. This study reports significant efforts to validate long-term OS extrapolations against long-term data from external sources. However, long-term validation reflecting availability of IO therapy is difficult as real-world evidence mainly reflect PDC long-term

- The three-health state modelling approach may underestimate the durable response of the NIVO+IPI+PDC regimen in the long-term. Treatment response is not explicitly modelled as prognostic of survival and it is assumed that treatment response from a first-line therapy will not alter future disease progression on subsequent therapies

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11. List of experts

[redacted]

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13. Appendix A Literature search for efficacy and safety of intervention and comparator(s)

A systematic literature review (SLR) was conducted to identify all randomized-controlled trials (RCT) involving NIVO (with or without IPI) and relevant comparators, i.e., immunotherapies (IO), targeted therapies, PDC, non-PDC, monotherapies and best supportive care (BSC), in the first-line treatment of metastatic (stage IIIB and IV) non-small cell lung cancer (NSCLC). The specific objectives of the systematic review were:

- To systematically identify RCTs comparing two or more relevant first-line regimens used in treating advanced NSCLC;
- To extract data that describe the study design, patient characteristics, and endpoints measured in the included RCTs; and
- To summarize and characterize these data in order to gain an understanding of the evidence base that will inform a quantitative synthesis.

Search strategy

Literature was identified via electronic search of MEDLINE, EMBASE, and the Central Register of Controlled Trials (CENTRAL) was conducted in March 2020 via the OVIDSP portal. Then, conferences and registers were searched for unpublished RCTs.

Eligible studies for the SLR were: RCTs involving NIVO monotherapy, NIVO+IPI combination therapy, or relevant comparators, that enrolled subjects with advanced, metastatic (stage IV) or recurrent NSCLC with no prior systemic anticancer therapy (including PDC, targeted therapy, and IOs) for advanced, metastatic or recurrent NSCLC.

Eligibility criteria were specified in terms of population, intervention and comparators, outcomes and study design (PICOS) (Higgins).

For descriptions of the search strategy, seach string and eligibility criteria, see sectiontion 4.1-2, Section 5.4 and Section 8.1 in Appendix O Systematic literature review report.

Systematic selection of studies

The study flow diagram is provided below (Figure 57). A total of 11,697 records were screened by two reviewers and 225 full-texts were assessed for inclusion. In the end, 67 unique RCTs, i.e. 59 published articles and 8 conference abstracts, were included in the core SLR. In addition, 6 RCTs involving monotherapies or BSC in patient with good performance status (PS) and 21 RCTs carried out in an elderly or PS 2 population were identified.

A total of 53 RCTs out of 67 compared any of the following therapy to PDC: (1) a targeted therapy (i.e. bevacizumab) in combination with PDC, or (2) another anticancer therapy, i.e. S-1 in combination with platinum, necitumumab in combination with cisplatin-gemcitabine, pemetrexed in combination with platinum, platinum in combination with nanoparticle albumin bound (nab) paclitaxel, or a non-PDC. These 53 RCT constituted the totality of the evidence for the treatment of first-line metastatic NSCLC as recommended by international and national guidelines prior to the era of IOs.

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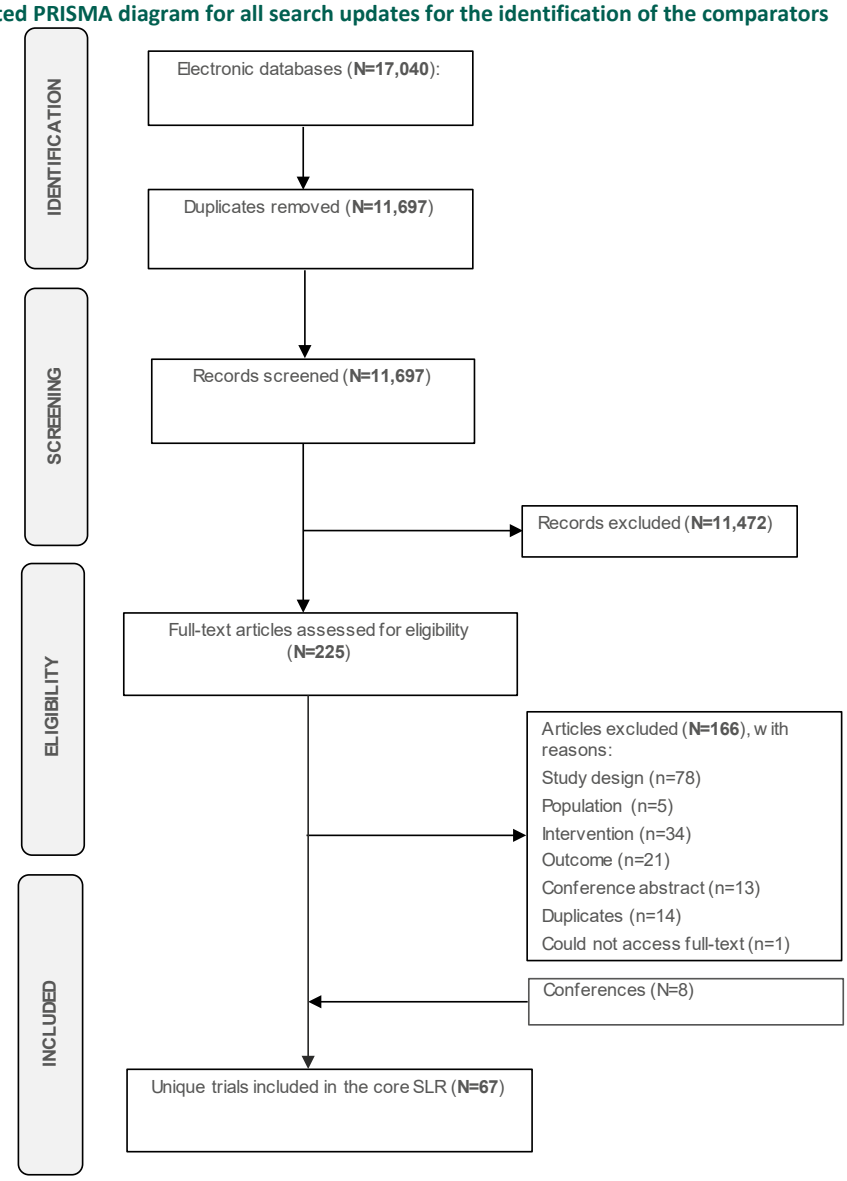
Figure 57: Consolidated PRISMA diagram for all search updates for the identification of the comparators



Abbreviations: SLR = systematic literature review; WHO = World Health Organisation

Among the 67 studies, 14 involved an an IO in one of the arms, either as an: IO monotherapy (i.e., NIVO, pembrolizumab, atezolizumab, or durvalumab), IO combination with another IO (i.e., NIVO+IPI, durvalumab+tremelimumab), IO combination with a targeted agent (i.e. bevacizumab), or IO combination with PDC (i.e. pembrolizumab+PDC, atezolizumab+PDC, or camrelizumab+PDC). Twelve out of 14 IO studies were large international phase III trials (i.e. CheckMate 026 and 227; KEYNOTE 024, 042, 189 and 407; Impower 110, 130, 131, 132 and 150; and MYSTIC). KEYNOTE 021 was a phase II trial conducted in the US and Taiwan. The trial of camrelizumab was a phase III trial carried out in a single country, i.e. China. Six IO trials were conducted in a population of non-squamous histology, i.e. KEYNOTE 021 and 189, Impower 130, 132 and 150, and the trial of camrelizumab. Two IO trials included a population of squamous histology, i.e. KEYNOTE 407 and Impower 131. The remainders were carried out in a population of mixed histology, but reported efficacy endpoints by non-squamous and squamous histology. With respect to PD-L1 expression, one IO trial included patients with PD-L1 ≥50% (i.e. KEYNOTE 024) and three included

patients with PD-L1 ≥1% (CheckMate 026, KEYNOTE 042 and Impower 110). The remainders were conducted in an "all comers" population.

For a comperhensive overview of the SLR, please see Section 4.3, Section 5.3, and Section 5.4, with elibility of studies described in Section 8.2 in the separate document Appendix O Systematic literature review report (Bristol-Myers Squibb 2020f).

Quality assessment

The strength of this SLR lies in the extremely large body of evidence identified (total number of randomized advanced NSCLC patients, over 25,000 patients). This SLR had no language restrictions and no time limits. Evidence from conferences and registers was also sought in addition to peer-reviewed publications to capture the breadth of all new up and coming research in advanced NSCLC.

A potential limitation of this SLR is the fact that the patients included all originated from clinical trials, and are thus not entirely representative of the real-world population of metastatic NSCLC. Patients had less comorbidities (such as other cancer, autoimmune disease, etc.) and also less involvement of untreated or uncontrolled brain metastases (most studies allowed brain metastases only if they were treated and under control).

Further, the supplement to the literature search was based on a manual desk search, to identify additional and updated outcomes for the immunotherapy trials. The manual search was able to capture studies to complete the indirect treatment comparison, even though this type of search may not capture the extend of data an electronic search on data bases via a structures search string may.

For more details on quality and limitations of the SLR, please see Section 6 in the Appendix O Systematic literature review report (Bristol-Myers Squibb 2020f).

Unpublished data

The unpublished data used in this submission (grade 3-5 adverse events by 5% cut-off, utilities, subsequent treatments and duration of treatment) are all sourced from the CheckMate 9LA trial. Landmark survival information is also marked as confidential where appropriate for analyses that utilize a mix of sources including Checkmate 227, pooled Checkmate 057/17 analyses, SEER and Norwegian and Swedish registry data in addition to data from the CheckMate 9LA trial.

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14. Appendix B Main characteristics of included studies

Table 76: Overview of CheckMate 9LA

Trial name: CheckMate 9LA	NCT number: NCT03215706
Objective	To determine whether NIVO+IPI+PDC is more effective than PDC by itself when treating stage IV NSCLC as the first treatment given for the disease
Publications – title, author, journal, year	EMA SmPC Reck M, et al. First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in advanced non-small-cell lung cancer: CheckMate 9LA 2-year update. ESMO Open. 2021;6(5):1-13.
Study type and design	Open-label, multicentre, randomized phase 3 trial conducted to evaluate NIVO+IPI+PDC vs. PDC alone as a first-line treatment in patients with advanced NSCLC regardless of PD-L1 expression and histology In CheckMate9LA, patients were randomized (1:1) to one of the following arms: • NIVO 360 mg Q3W plus IPI 1 mg/kg Q6W plus histology-based PDC Q3W for up to 2 cycles • Histology-based PDC Q3W for up to 4 cycles In both arms of the trial, patients were stratified according to tumor histologic features (SQ vs. NSQ) as well as PD-L1 expression (<1% vs. ≥1%) and sex. Histology-based PDC consisted of the following: • NSQ: pemetrexed (500 mg/m2) + cisplatin (75 mg/m2) or carboplatin (AUC 5 or 6), Q3W • Patients in the control arm with stable disease or who had a response after 4 cycles of PDC could continue with maintenance pemetrexed • SQ: carboplatin (AUC6) + paclitaxel (200 mg/m2), Q3W All treatments continued until disease progression, unacceptable toxicity, or completion of study as per protocol (defined as treatment for up to 2 years for immunotherapy). Crossover between treatment arms within the study was not permitted.
Sample size (n)	1150 enrolled, 719 randomized, and 707 treated

Trial name: CheckMate 9LA	NCT number: NCT03215706
Main inclusion and exclusion criteria	**Inclusion Criteria:** • Participants with histologically confirmed Stage IV or recurrent NSCLC squamous or non-squamous histology, with no prior systemic anticancer therapy • Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1 • Measurable disease by CT or MRI per response evaluation criteria in solid tumors version 1.1 (RECIST 1.1) criteria • Participants must have PD-L1 IHC testing with results performed by a central laboratory during the screening period **Exclusion Criteria:** • Participants with known epidermal growth factor receptor (EGFR) mutations which are sensitive to available targeted inhibitor therapy (including, but not limited to, deletions in exon 19 and exon 21 [L858R] substitution mutations) are excluded • Participants with known anaplastic lymphoma kinase (ALK) translocations which are sensitive to available targeted inhibitor therapy are excluded • Participants with untreated CNS metastases are excluded. Participants are eligible if CNS metastases are adequately treated and participants are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to first treatment
Intervention	NIVO (360 mg every 3 weeks [Q3W]) was administered with IPI (1 mg/kg every 6 weeks [Q6W]), plus 2 cycles of histology based PDC as follows: • SQ histology: carboplatin area under the plasma drug concentration-time curve (AUC) 6 + paclitaxel 200 mg/m2 (or 175 mg/m2 as per local institutional practice) NSQ histology: carboplatin AUC 5 or 6 + pemetrexed 500 mg/m2 or cisplatin 75 mg/m2 + pemetrexed 500 mg/m2
Comparator(s)	Histology dependent, PDC was selected by the investigator and administered on Day 1 Q3W for 4 cycles. After 4 cycles, subjects with NSQ histology could continue to receive optional maintenance therapy with 500 mg/m2 pemetrexed alone on Day 1 of each 3 weeks until disease progression or unacceptable toxicity. Histology based PDC was one of the following: • SQ histology: carboplatin AUC 6 + paclitaxel 200 mg/m2 (or 175 mg/m2 as per local institutional practice) • NSQ histology: carboplatin AUC 5 or 6 + pemetrexed 500 mg/m2 or cisplatin 75 mg/m2 + pemetrexed 500 mg/m2 In both arms, on-study tumour assessments began at Week 6 post first dose date (+/- 7 days) and were performed every 6 weeks (+/- 7 days) until Week 48. After Week 48, tumour assessments were performed every 12 weeks (+/- 7 days) until BICR assessed progression.
Follow-up time	1-year database lock March 2020 follow-up: minimum 12.7 months 2-year database lock February 2021 follow-up: minimum 24.4 months (OS), minimum follow-up for all other analyses was 23.3 months.
Is the study used in the health economic model?	Yes

Trial name: CheckMate 9LA	NCT number: NCT03215706
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was overall survival in the intention to treat population Hierarchical secondary endpoints • PFS and ORR for NIVO+IPI+PDC vs. PDC alone Other secondary endpoints • OS, PFS, and ORR in patients based on PD-L1 expression levels and tumour cell somatic mutations Exploratory endpoints • Safety, tolerability, PRO, and progression-free survival until next line of treatment (PFS2)
Method of analysis	All efficacy analyses were intention-to-treat analyses. We used the Kaplan–Meier method to estimate rates of progression-free survival and overall survival, and a stratified log-rank test for treatment comparisons.
Subgroup analyses	Subgroup analysis included by histology (squamous and non-squamous) and PD-L1 status
Other relevant information	n/a

Abbreviations: NSCLC: non-small cell lung canceer; PD-L1: programmed death ligand 1; SQ: squamous; NSQ: non-squamous; EGFR: Epidermal growth factor receptor; ALK: anaplastic lymphoma kinase; ASCT: autologous stem cell transplant; BV: brentuximab vedotin; CPS: combined positive score; 5-FU: 5-fluorouracil; AUC: area under the curve; BICR: blinded independent central review; OS: overall survival, PFS: progression free survival; ORR: objective response rate; PRO: patient reported outcomes; Q#W, every # of weeks
Reference: SmPC available at EMA (European Medicines Agency 2020c); (Reck 2020a).

Table 77: Overview of CheckMate 227 Part 1

Trial name: CheckMate 227 Part 1	NCT number: NCT03215706
Objective	To show that NIVO, or NIVO+IPI, or NIVO+PDC improves progression free survival and/or overall survival compared with PDC in patients with advanced lung cancer
Publications – title, author, journal, year	Hellmann MD, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2019 Nov 21;381(21):2020-2031. Reck M, Schenker M, et al. Nivolumab plus ipilimumab vs. chemotherapy as first-line treatment in advanced non-small-cell lung cancer with high tumour mutational burden: patient-reported outcomes results from the randomised, open-label, phase III CheckMate 227 trial. Eur J Cancer. 2019 Jul;116:137-147. Hellmann MD, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N Engl J Med. 2018 May 31;378(22):2093-2104. Paz-Ares LG, et al. First-Line Nivolumab Plus Ipilimumab in Advanced NSCLC: 4-Year Outcomes From the Randomized, Open-Label, Phase 3 CheckMate 227 Part 1 Trial. J Thorac Oncol. 2021; in press.
Study type and design	Open-label, randomised, multi-part, phase 3 trial, comparing NIVO-based regimens vs. PDC in biomarker-selected patients with PDC-naïve stage IV or recurrent NSCLC. Part 1a: (PD-L1 ≥1%): NIVO, NIVO+IPI, or PDC (SQ vs. NSQ stratification) Part 1b: (PD-L1 <1%): NIVO+IPI, NIVO+PDC, or PDC (SQ vs. NSQ stratification) Patients were stratified according to tumour histologic features (SQ vs. NSQ), where:

Trial name: CheckMate 227 Part 1	NCT number: NCT03215706
	○ NSQ: pemetrexed + cisplatin or carboplatin ○ Patients with stable disease or who had a response after 4 cycles of PDC or NIVO+PDC could continue with maintenance pemetrexed or pemetrexed + NIVO, respectively ○ SQ: gemcitabine + cisplatin, or gemcitabine + carboplatin Treatments continued until disease progression, unacceptable toxicity, or completion of study as per protocol (defined as treatment for up to 2 years for immunotherapy). Crossover between treatment arms within the study was not permitted.
Sample size (n)	A total of 2876 where enrolled in Part 1, of which 1739 underwent randomisation, with 1189 PD-L1 ≥1% subjects and 550 PD-L1 <1% subjects randomised into the respective treatment arms in a 1:1:1 fashion
Main inclusion and exclusion criteria	**Inclusion Criteria:** • Subjects with histologically confirmed Stage IV or recurrent NSCLC squamous or non-squamous histology, with no prior systemic anticancer therapy • Subjects must have programmed death-ligand 1 (PD -L1) immunohistochemical (IHC) testing, with results, performed by the central lab during the Screening period • Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 1 • Measurable disease by CT or MRI per RECIST 1.1 criteria **Exclusion Criteria:** • Subjects with untreated Central nervous system (CNS) metastases are excluded • Subjects with an active, known or suspected autoimmune disease are excluded • Any positive test for hepatitis B virus or hepatitis C virus or human immunodeficiency virus (HIV) indicating acute or chronic infection
Intervention	Part 1a: NIVO 3 mg/kg Q2W + ipilimumab 1 mg/kg Q6W or NIVO monotherapy 240 mg Q2W Part 1b: NIVO 3 mg/kg Q2W + ipilimumab 1mg/kg Q6W, or NIVO 360 mg Q3W plus PDC
Comparator(s)	PDCin 3-week cycles for a maximum of 4 cycles +/- pemetrexed maintenance
Follow-up time	Part 1 2-year database lock July 2019: minimum follow-up time 29.3 months 3-year database lock February 2020 follow-up: minimum 37.7 months 4-year database lock February 2021 follow-up: minimum 49.4 months Part 2 Ongoing
Is the study used in the health economic model?	For the extrapolation
Primary, secondary and exploratory endpoints	**Primary** PFS in patients with TMB ≥10 mut/Mb: 7.2 months vs. 5.5 months, for NIVO+IPI vs. PDC (HR = 0.58), OS in PD-L1–selected population (part 1a): 17.1 months vs. 14.9, NIVO+IPI vs. PDC (HR = 0.79) **Other**

Trial name: CheckMate 227 Part 1	NCT number: NCT03215706
	HRQL, exploratory OS, and PFS in other subgroups, ORR (described in further detail below)
Method of analysis	Kaplan–Meier analysis was peformed to estimate the duration of overall survival and progression-free survival, along with the duration of response. Nonparametric log-rank test used to assess the primary and secondary hierarchical end points and a stratified Cox proportional-hazards model, with the treatment group as a single covariate, to calculate hazard ratios for death with associated two-sided confidence intervals. If the proportional assumption was not met, hazard ratios were still reported to provide a conventional estimate of overall average effect and supplemented by median and landmark estimates. For objective response rates, Clopper–Pearson used method to calculate 95% exact two-sided confidence intervals..
Subgroup analyses	n/a
Other relevant information	n/a

Abbreviations: ALK, anaplastic lymphocyte kinase; EGFR, epidermal growth factor receptor; HR, hazard ration; HRQL, Health related quality of life; NSCLC, non-small cell lung cancer; NSQ, non-squamous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PD, platinum-doublet; PFS, progressive free survival; SQ, squamous; TMB, tumour mutation burden Source: www.clinicaltrials.gov

Table 78: Overview of KEYNOTE 024

Trial name: KEYNOTE 024	NCT number: NCT02142738
Objective	This is a study to assess the efficacy and safety of pembrolizumab compared to standard of care (SOC) PDC in the treatment of participants with previously untreated stage IV, programmed cell death ligand 1 (PD-L1) strong expressing NSCLC. The primary hypothesis of this study is that participants with PD-L1 strong NSCLC will have a longer PFS, as assessed by RECIST 1.1 when treated with pembrolizumab than when treated with SOC PDC. With Amendment 09 (20 December 2017), once participants have achieved the study objective or the study has ended, participants will be discontinued from this study and enrolled in an extension study to continue protocol-defined assessments and treatment.
Publications – title, author, journal, year	Reck M, et al. Pembrolizumab vs. Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016 Nov 10;375(19):1823-1833. Satouchi M, et al. First-line pembrolizumab vs chemotherapy in metastatic non-small-cell lung cancer: KEYNOTE-024 Japan subset. Cancer Sci. 2020 Sep 14. Lala M, et al. A six-weekly dosing schedule for pembrolizumab in patients with cancer based on evaluation using modelling and simulation. Eur J Cancer. 2020 May;131:68-75. Bhadhuri A, et al. Cost effectiveness of pembrolizumab vs chemotherapy as first-line treatment for metastatic NSCLC that expresses high levels of PD-L1 in Switzerland. Swiss Med Wkly. 2019 Dec 27;149:w20170. van Vugt MJH, et al. Immunogenicity of pembrolizumab in patients with advanced tumors. J Immunother Cancer. 2019 Aug 8;7(1):212. Brahmer JR, et al. Health-related quality-of-life results for pembrolizumab vs. chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial. Lancet Oncol. 2017 Dec;18(12):1600-1609.
Study type and design	Randomized open-label phase III trial of pembrolizumab vs PDC chemotherapy in first-line patients with PD-L1 strong metastatic NSCLC Treatment Phase: Participants randomized to pembrolizumab will be treated for up to 35 cycles or until documented progressive disease (PD) occurs. Participants randomized to SOC PDCs will be treated with their randomized study drug for up to 4-6 cycles. After this, participants with non-squamous histologies may choose to be treated with maintenance pemetrexed for the remainder of the study or until disease progression, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw the participant, noncompliance with study treatment or procedures requirements, the participant receives 35 treatments of study treatment (pembrolizumab arm only), or administrative reasons. Participants receiving pembrolizumab who stop drug administration after receiving 35 study treatments for reasons other than disease progression or intolerability, or participants who attain a complete response and stop study treatment may be eligible for retreatment with pembrolizumab upon experiencing disease progression. The decision to retreat with a second course of pembrolizumab will be at the discretion of the Investigator only if participants meet the criteria for retreatment and the study is ongoing. Retreatment (second course) is limited to 17 cycles. Participants randomized to receive SOC PDC may be eligible to receive pembrolizumab if crossover criteria are met. Cross-Over Phase: This is only applicable for participants randomized to receive SOC. Eligible participants will be treated with pembrolizumab for the remainder of the study or until disease progression, unacceptable AEs, intercurrent illness that prevents further administration of

Trial name: KEYNOTE 024	NCT number: NCT02142738
	treatment, investigator's decision to withdraw the participant, noncompliance with study treatment or procedures requirements, the participant receives 35 treatments of study treatment (pembrolizumab arm only), or administrative reasons.
Sample size (n)	N= 305 patients (randomized 1:1 between intervention and comparator)
Main inclusion and exclusion criteria	**Inclusion Criteria:** • 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 PDC 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 PDC **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 PDC 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 PDC, 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)

Trial name: KEYNOTE 024	NCT number: NCT02142738
	• 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 cPDC • Immediate family member who is investigational site or sponsor staff directly involved with this study
Intervention	Participants receive pembrolizumab 200 mg, administered as intravenous (IV) infusion on Day 1 of each 21-day cycle for up to 35 cycles.
Comparator(s)	Paclitaxel + carboplatin: Participants receive paclitaxel 200 mg/m^2 and carboplatin AUC 5 or 6, administered as IV infusion on Day 1 of each 21-day cycle for 4-6 cycles followed by optional pemetrexed 500 mg/m^2 Q3W maintenance for participants with non-squamous histologies for the remainder of the study or until documented PD or participant discontinuation. If PD occurs, participants may be able to receive pembrolizumab Q3W in a second course of treatment Pemetrexed + carboplatin: Participants receive pemetrexed 500 mg/m^2 and carboplatin AUC 5 or 6, IV infusion on Day 1 of each 21-day cycle for 4-6 cycles; participants with non-squamous histologies may then receive pemetrexed 500 mg/m^2 on Day 1 of each 21-day cycle as maintenance therapy for the remainder of the study or until documented PD or participant discontinuation. If PD occurs, participants may be able to receive pembrolizumab Q3W in a second course of treatment. Pemetrexed + cisplatin: Participants receive pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2, administered as IV infusion on Day 1 of each 21-day cycle for 4-6 cycles followed by optional pemetrexed 500 mg/m^2 Q3W maintenance for the remainder of the study or until documented PD or participant discontinuation. If PD occurs, participants may be able to receive pembrolizumab Q3W in a second course of treatment. Gemcitabine + carboplatin: Participants receive gemcitabine 1250 mg/m^2, administered as IV infusion on Days 1 and 8 of each 21-day cycle and carboplatin AUC 5 or 6, administered as IV infusion on Day 1 of a 21-day cycle, for 4-6 cycles or until documented PD or participant discontinuation. If PD occurs, participants may be able to receive pembrolizumab Q3W in a second course of treatment. Gemcitabine + cisplatin: Participants receive gemcitabine 1250 mg/m^2, administered as IV infusion on Days 1 and 8 of each 21-day cycle and cisplatin 75 mg/m^2, administered as IV infusion on Day 1 of each 21-day cycle for 4-6 cycles or until documented PD or participant discontinuation. If PD occurs, participants may be able to receive pembrolizumab Q3W in a second course of treatment.

Trial name: KEYNOTE 024	NCT number: NCT02142738
Follow-up time	Median follow-up 59.9 months
Is the study used in the health economic model?	Yes, in a scenario analysis
Primary, secondary and exploratory endpoints	**Primary** PFS **Secondary** OS ORR
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	
Other relevant information	n/a

Abbreviations: PD: progressed disease; AUC: area under the curve; PFS: progression free survival; OS: overall survival; ORR: objective response rate; Q#W: every # weeks; PD: progressed disease
Reference: www.clinicaltrials.gov

Table 79 Overview of KEYNOTE 042

Trial name: KEYNOTE 042	NCT number: NCT02220894
Objective	Study of Pembrolizumab (MK-3475) Vs. Platinum-Based Chemotherapy for Participants With Programmed Cell Death-Ligand 1 (PD-L1)-Positive Advanced or Metastatic Non-Small Cell Lung Cancer
Publications – title, author, journal, year	Wu YL, et al. Randomized clinical trial of pembrolizumab vs chemotherapy for previously untreated Chinese patients with PD-L1-positive locally advanced or metastatic non-small-cell lung cancer: KEYNOTE-042 China Study. Int J Cancer. 2020 Nov 24. Weng X, et al. Cost-Utility Analysis of Pembrolizumab Vs. Chemotherapy as First-Line Treatment for Metastatic Non-Small Cell Lung Cancer With Different PD-L1 Expression Levels. Oncol Res. 2020 Mar 27;28(2):117-125. Mok TSK, et al. Pembrolizumab vs. 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. Lancet. 2019 May 4;393(10183):1819-1830.
Study type and design	A Randomized, Open Label, Phase III Study of Overall Survival Comparing Pembrolizumab (MK-3475) Vs. Platinum Based Chemotherapy in Treatment Naïve Subjects With PD-L1 Positive Advanced or Metastatic Non-Small Cell Lung Cancer (Keynote 042)

Trial name: KEYNOTE 042	NCT number: NCT02220894
	In this study, participants with programmed cell death ligand 1 (PD-L1)-positive non-small cell lung cancer (NSCLC) will be randomized to receive single agent pembrolizumab for up to 35 treatments or standard of care (SOC) PDC (carboplatin + paclitaxel or carboplatin + pemetrexed for 4 to 6 21-day cycles). Participants in the PDC arms with non-squamous tumor histologies may receive pemetrexed maintenance therapy after the 4 to 6 cycles of PDC. The primary study hypothesis is that pembrolizumab prolongs overall survival (OS) compared to SOC PDC.
Sample size (n)	Enrolled: 1274
Main inclusion and exclusion criteria	**Inclusion Criteria:** • Histologically- or cytologically-confirmed diagnosis of advanced or metastatic NSCLC • PD-L1 positive tumor • Measureable 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

Trial name: KEYNOTE 042	NCT number: NCT02220894
	• 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	Participants receive pembrolizumab 200 mg intravenous (IV) on Day 1 of every 21-day cycle (every 3 weeks, or Q3W) for up to 35 treatments.
Comparator(s)	Participants receive carboplatin target dose Area Under Curve (AUC) 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + paclitaxel 200 mg/m^2 IV on Day 1 of every 21-day cycle (Q3W) for a maximum of 6 cycles OR carboplatin target dose AUC 5 (maximum dose 750 mg) or AUC 6 (maximum dose 900 mg) + pemetrexed 500 mg/m^2 IV on Day 1 Q3W for a maximum of 6 cycles; participants with non-squamous histologies may go on to receive optional treatment with pemetrexed 500 mg/m^2 IV on Day 1 Q3W.
Follow-up time	Median follow-up: 33.0 months
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary** • OS in Participants With a TPS of ≥50% [Through Database Cutoff Date of 26-Feb-2018 (up to approximately 38 months)] • OS in Participants With a TPS of ≥20% [Through Database Cutoff Date of 26-Feb-2018 (up to approximately 38 months)] • OS in Participants With a TPS of ≥1% [Through Database Cutoff Date of 26-Feb-2018 (up to approximately 38 months)] **Secondary** • PFS Per RECIST 1.1 as Assessed by Blinded Independent Central Review (BICR) in Participants With a TPS of ≥50% [Through Database Cutoff Date of 26-Feb-2018 (up to approximately 38 months)] • PFS Per RECIST 1.1 as Assessed by Blinded Independent Central Review in Participants With a TPS of ≥20% [Through Database Cutoff Date of 26-Feb-2018 (up to approximately 38 months)]

Trial name: KEYNOTE 042	NCT number: NCT02220894
	• PFS Per RECIST 1.1 as Assessed by Blinded Independent Central Review in Participants With a TPS of ≥1% [Through Database Cutoff Date of 26-Feb-2018 (up to approximately 38 months)] • ORR Per RECIST 1.1 as Assessed by Blinded Independent Central Review in Participants With a TPS of ≥50% [Through Database Cutoff Date of 26-Feb-2018 (up to approximately 38 months)] • ORR Per RECIST 1.1 as Assessed by Blinded Independent Central Review in Participants With a TPS of ≥20% [Through Database Cutoff Date of 26-Feb-2018 (up to approximately 38 months)] • ORR Per RECIST 1.1 as Assessed by Blinded Independent Central Review in Participants With a TPS of ≥1% [Through Database Cutoff Date of 26-Feb-2018 (up to approximately 38 months)] • Number of Participants Who Experienced At Least One AE [Through Database Cutoff Date of 26-Feb-2018 (up to approximately 38 months)] • Number of Participants Who Discontinued Study Treatment Due to an AE [Through Database Cutoff Date of 26-Feb-2018 (up to approximately 38 months)]
Method of analysis	Overall survival, progression-free survival, and objective response were assessed in the intention-to-treat population, defined as all patients alive at the time of random allocation to a treatment group. Duration of response was assessed in all patients who had complete or partial response. Safety was assessed in the as-treated population, defined as all randomly allocated patients who received at least one dose of study treatment. 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. 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 progression-free survival. Data for patients who were alive without evidence of disease progression but who discontinued the study without radiographical evidence of progression were censored at the time of the last radiographical assessment showing response. For progression-free survival and duration of response, 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 overall and progression-free survival. A stratified Cox regression model with Efron's method of tie handling14 was used to estimate hazard ratios and associated 95% CIs. The stratified Miettinen and Nurminen method15 was used to assess between-group differences in response rate. All randomisation stratification factors were applied to all stratified analyses.
Subgroup analyses	PD-L1 status
Other relevant information	n/a

Abbreviations: CI, confidence intevral; SQ: squamous; NSCLC: non-small cell lung cancer; AUC; area under the curve; PFS: progression free survival; OS: overall survival; ORR: objective response rate; AE: adverse events; PD-L, programmed death ligase; RECIST, Response Evaluation Criteria in Solid Tumors; TPS, Tumour Proportion Score.
Reference: www.clinicaltrials.gov (Mok 2019b, Wu 2020)

Table 80: Overview of KEYNOTE 189

Trial name: KEYNOTE 189	NCT number: NCT02578680
Objective	This is an efficacy and safety study of pembrolizumab combined with pemetrexed/platinum PDC vs. pemetrexed/platinum PDC alone in participants with advanced or metastatic NSCLC who have not previously received systemic therapy for advanced disease. Participants will be randomly assigned to receive pembrolizumab combined with pemetrexed/platinum (Investigators choice of cisplatin or carboplatin), OR pemetrexed/platinum (Investigators choice of cisplatin or carboplatin).
Publications – title, author, journal, year	Gadgeel S, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol. 2020 May 10;38(14):1505-1517. Garassino MC, et al. 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. Lancet Oncol. 2020 Mar;21(3):387-397. Gandhi L, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018 May 31;378(22):2078-2092.
Study type and design	Randomized, double blinded, placebo-controlled, multicentre phase 3 trial conducted to evaluate pembrolizumab in combination with pemetrexed and carboplatin as a first-line treatment in patients with advanced NSCLC regardless of PD-L1 expression.
Sample size (n)	N= 616 (randomized 2:1 between intervention and comparator)
Main inclusion and exclusion criteria	**Inclusion Criteria:** • 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:** • Has predominantly squamous cell histology NSCLC.

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Trial name: KEYNOTE 189	NCT number: NCT02578680
	• 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 PDC 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 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	Pembrolizumab 200 mg in combination with pemetrexed 500 mg/m2 and carboplatin/cisplatin Q3W for four cycles, followed by pembrolizumab and pemetrexed Q3W up to 31 cycles.
Comparator(s)	Placebo mg in combination with pemetrexed 500 mg/m2 and carboplatin/cisplatin Q3W for four cycles, followed by placebo and pemetrexed Q3W up to 31 cycles.

Trial name: KEYNOTE 189	NCT number: NCT02578680
Follow-up time	Median of 23.1 months
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary** PFS OS **Secondary** ORR Duration of response Number of Participants Who Experienced an AE Number of Participants Who Discontinued Any Study Drug Due to an AE **Other** PFS as Assessed by Investigator Immune-related RECIST
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	n/a
Other relevant information	n/a

Abbreviations: Q3W: every third week; PD: progressed disease; PFS: progression free survival; OS: overall survival; ORR: objective response rate; AE: adverse event
Reference: ..www.clinicaltrials.gov..

Table 81: Overview of KEYNOTE 407

Trial name: KEYNOTE 407	NCT number: NCT02775435
Objective	To determine whether the addition of the PD-1 inhibitor pembrolizumab (Keytruda, Merck) to PDC improves outcomes in patients with squamous NSCLC of any level of PD-L1 expression
Publications – title, author, journal, year	Paz-Ares L, et al. A Randomized, Placebo-Controlled Trial of Pembrolizumab Plus Chemotherapy in Patients With Metastatic Squamous NSCLC: Protocol-Specified Final Analysis of KEYNOTE-407. J Thorac Oncol. 2020 Oct;15(10):1657-1669. Mazieres J, et al. Health-Related Quality of Life With Carboplatin-Paclitaxel or nab-Paclitaxel With or Without Pembrolizumab in Patients With Metastatic Squamous Non-Small-Cell Lung Cancer. J Clin Oncol. 2020 Jan 20;38(3):271-280. Paz-Ares L, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med. 2018 Nov 22;379(21):2040-2051.
Study type and design	A randomized, double-Blind, phase 3 study of carboplatin-paclitaxel/nab-paclitaxel PDC with or without pembrolizumab (MK-3475) in first-line metastatic SQ NSCLC Patients were randomly assigned, in a 1:1 ratio, to receive 200 mg of pembrolizumab or saline placebo on day 1 for up to 35 cycles. For the first 4 cycles, all the patients also received carboplatin (at a dose calculated to produce an area under the concentration–time curve of 6 mg per milliliter per minute) on day 1 and either paclitaxel (200 mg per square meter of body-surface area) on day 1 or nab-paclitaxel (100 mg per square meter) on days 1, 8, and 15. All treatments were administered intravenously in 3-week cycles. The patients who received paclitaxel also received premedication with a glucocorticoid, a type 1 antihistamine, and a type 2 antihistamine according to local guidelines; premedication with a glucocorticoid and antihistamines was not required for patients who received nab-paclitaxel.
Sample size (n)	N= 559
Main inclusion and exclusion criteria	**Inclusion Criteria:** • Has a histologically or cytologically confirmed diagnosis of stage IV (M1a or M1b-American Joint Committee on Cancer [AJCC] 7th edition) squamous NSCLC. • Has measurable disease based on RECIST 1.1 as determined by the local site investigator/radiology assessment. • Has not received prior systemic treatment for metastatic NSCLC. • Has provided tumor tissue from locations not radiated prior to biopsy. • 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 an adequate method of contraception for the course of the study through 120 days after the last dose of study drug. • If male with a female partner(s) of child-bearing potential, must agree to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of study drug. Males with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner. **Exclusion Criteria:** • Has non-squamous histology NSCLC.

Trial name: KEYNOTE 407	NCT number: NCT02775435
	• 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 drug: a) Has received prior systemic cytotoxic chemotherapy for metastatic disease; b) Has received other targeted or biological antineoplastic therapy (e.g., erlotinib, crizotinib, cetuximab) for metastatic disease; c) Has had major surgery (<3 weeks prior to first dose). • Received radiation therapy to the lung that is > 30 Gy within 6 months of the first dose of study drug. • Completed palliative radiotherapy within 7 days of the first dose of study drug. • Is expected to require any other form of antineoplastic therapy while on study. • Has received a live-virus vaccination within 30 days of planned treatment start. • Has a known history of prior malignancy except if the participant has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy. • Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. • Has pre-existing peripheral neuropathy that is ≥ Grade 2 by Common Terminology Criteria for Adverse Events (CTCAE) version 4 criteria. • Previously had a severe hypersensitivity reaction to treatment with another monoclonal antibody. • Has a known sensitivity to any component of carboplatin or paclitaxel or nab-paclitaxel. • Has active autoimmune disease that has required systemic treatment in past 2 years. • Is on chronic systemic steroids. • Had prior treatment with any other anti-programmed cell death 1 (anti-PD-1), or programmed cell death ligand 1 (PD-L1) or PD-L2 agent or an antibody or a small molecule targeting other immuno-regulatory receptors or mechanisms. • Has participated in any other pembrolizumab trial 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. Active Hepatitis B. • Is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs or has a recent history (within the last year) of substance abuse (including alcohol). • Has interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoids to assist with management. • Is pregnant or breastfeeding, or expecting to conceive or father children while on study drug and for the required duration of contraception after the last dose of study drug.
Intervention	Pembrolizumab + PDC: Participants receive pembrolizumab 200 mg by intravenous (IV) infusion prior to PDC on Day 1 of each 21-day cycle for up to 35 cycles PLUS Investigator's choice of paclitaxel (200 mg/m^2 by IV infusion on Day 1 of each 21-day cycle for 4 cycles) or nab-paclitaxel (100 mg/m^2 by IV infusion on Days 1, 8, 15 of each 21-day cycle for 4 cycles) PLUS carboplatin AUC 6 by IV infusion on Day 1 of each 21-day cycle for 4 cycles.
Comparator(s)	PDC Participants receive normal saline by IV infusion prior to PDC on Day 1 of each 21-day cycle for up to 35 cycles PLUS Investigator's choice of paclitaxel (200 mg/m^2 by IV infusion on Day 1 of each 21-day cycle for 4 cycles) or nab-paclitaxel (100 mg/m^2 by IV infusion on Days 1, 8, 15 of each 21-day cycle for 4 cycles) PLUS carboplatin AUC 6 by IV infusion on Day 1 of each 21-day cycle for 4 cycles.

Trial name: KEYNOTE 407	NCT number: NCT02775435
Follow-up time	Median of 14.3 months
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary** PFS OS **Secondary** ORR Duration of response Number of Participants Who Experienced an AE Number of Participants Who Discontinued Study Treatment Due to an AE
Method of analysis	The Kaplan–Meier method was used to estimate overall survival, progression-free survival, and duration of response. The stratified log-rank test was used to assess between-group differences in overall and progression-free survival. A stratified Cox proportional-hazards model and Efron's method of tie handling were used to assess the magnitude of the difference between the trial groups. There was no violation of the proportional-hazards model in the intention-to-treat population. In some subgroups, there was a delayed separation of the survival curves, suggesting a possible deviation from the proportional-hazards assumption. The stratified method of Miettinen and Nurminen was used to assess differences in response rate. The randomization stratification factors were applied to all stratified analyses.
Subgroup analyses	
Other relevant information	n/a

Abbreviations: SQ: squamous; NSCLC: non-small cell lung cancer; AUC; area under the curve; PFS: progression free survival; OS: overall survival; ORR: objective response rate; AE: adverse events
Reference: www.clinicaltrials.gov.

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

Table 82: Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	CheckMate-9LA (Reck 2020a)		CheckMate-227* (Hellmann 2019b)		KEYNOTE 407 (Paz-Ares 2018)		KEYNOTE 189 (Gandhi 2018)			KEYNOTE 024 (Reck 2016)		KEYNOTE 042 (Mok 2019b)	
	NIVO+IPI+ PDC (n=361)	PDC (n=358)	NIVO+IPI (n=396)	NIVO (n=396)	Pembro combo (n=278)	Placebo combo (n=281)	PDC (n=151)	Pembro combo (n=410)	Placebo combo (n=206)	PDC (n=397)	Pembro (n=154)	Pembro PD-L1 ≥50% (n=299)	PDC PD-L1 ≥50% (n=300)
Age, median (range), years	65 (35–81)	65 (26–86)	64 (26–87)	64 (27–85)	65 (29–87)	65 (36–88)	66.0 (38–85)	65.0 (34.0–84.0)	63.5 (34.0–84.0)	64 (29–87)	64.5 (33–90)	63.0 (56.0–68.0)	64.0 (57.0–69.0)
Female, %	30	30	35.6	31.3	80.9	16.4	37.1	38.0	47.1	34.5	40.3	31	30
ECOG PS, %[a]													
0	31	31	34.1	35.9	26.3	32.0	35.1	45.4	38.8	33.8	35.1	32	30
1	68	68	`65.7	63.6	73.7	68.0	64.9	53.9	60.7	65.2	64.3	68	70
2	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0.2	0	n/a	n/a	n/a	n/a
Missing data	n/a	n/a	0.3	0.5	n/a	n/a	n/a	n/a	n/a	1.0	n/a	n/a	n/a
Smoking status, %													
Never smoker	13	14	14.1	12.6	7.9	6.8	12.6	11.7	12.1	12.8	3.2	21	22
Current/former smoker	87	86	84.3	86.5	92.1	93.2	87.4	88.3	87.9	85.6	96.8	79	78
Missing data	n/a	n/a	1.5	1.0	n/a	n/a	n/a	n/a	n/a	1.5	n/a	n/a	n/a
Histology, %													
Squamous	31	31	29.5	29.5	97.8	97.5	17.9	n/a	n/a	29.2	18.8	36	36
Non-squamous	69	69	70.5	70.5	2.2	2.5	82.1	96.1	96.1	70.8	81.2	64	64

NSCLC not otherwise specified	n/a	n/a	n/a	n/a	n/a	n/a	n/a	2.4	1.9	n/a	n/a	n/a	n/a
other	n/a	n/a	n/a	n/a	n/a	n/a	n/a	1.5	1.9	n/a	n/a	n/a	n/a
Metastases, %													
Bone	27	31	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Liver	19	24	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
CNS	18	16	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Brain	n/a	n/a	n/a	n/a	7.2	8.5	6.6	17.8	17.0	n/a	11.7	n/a	n/a
Tumor PD-L1 expression,[b] %													
<1%[c]	40	39	n/a	n/a	34.2	35.2	n/a	31.0	30.6	n/a	n/a	n/a	n/a
≥1% [c]	60	61	100.0	100.0	63.3	63.0	n/a	63.4	62.1	100.0	n/a	n/a	n/a
1–49% [c]	38	32	48.2	46.0	37.1	37.0	n/a	31.2	28.2	51.6	n/a	n/a	n/a
≥50% [c]	22	29	51.8	54.0	26.3	26.0	n/a	32.2	34.0	48.4	n/a	100	100
Could not be evaluated	n/a	n/a	n/a	n/a	n/a	n/a	n/a	5.6	7.3	n/a	n/a	n/a	n/a

Note: [a]ECOG PS was not reported for 1 patient (0.3%) in each of the NIVO+IPI+PDC and chemo arms; [b]6% and 7% of patients in the NIVO+IPI+PDC and chemo arms, respectively, were unevaluable for PD-L1; [c]Calculated as a percentage of quantifiable patients.
* Data for Part 1A only presented: all patients with PD-L1 ≥1% status.
Abbreviations: Chemo: chemotherapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; Ipi: ipilimumab; Nivo: nivolumab; Pembro, prembrolizumab; PD-L1: programmed cell death ligand-1.

Comparability of patients across studies

The comparability of patients across studies are discussed in section 7.2.1.1.2.6.10.

Comparability of the study populations with Danish patients eligible for treatment

Differences between the study populations and the Danish patient population and how this affects transferability of results to Danish clinical practice are described in section 8 above.

16. Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

The outcomes measures in focus of the current application are the state of the art measures for oncology trials, OS, PFS, DoR and ORR.

Results per study

Overall survival (OS) is the gold standard primary end point to evaluate the outcome of any drug, biologic, intervention, or procedure that is assessed in oncologic clinical trials. OS is universally recognized as being unambiguous, unbiased, with a defined end point of paramount clinical relevance, and positive results provide confirmatory evidence that a given treatment extends the life of a patient.

Progression-free survival (PFS), the time from treatment initiation until disease progression or worsening, may be used as a direct or surrogate measure of clinical benefit for drug approvals, depending on the disease and response observed, while overall survival (OS), the duration of patient survival from the time of treatment initiation, is a universally-accepted direct measure of clinical benefit.

While improvements in OS clearly demonstrate clinical benefits that are meaningful to patients, PFS, depending on the magnitude, may have high value as well. By design, PFS and OS will be related, as OS is comprised of PFS plus post-progression survival.

The tables below presents the estimated relative difference in effect of the trial included in the comparative analyses. P-value is included where available.

Table 83: Results of CheckMate 9LA (NCT03215706)

CheckMate 9LA (NCT03215706)											
				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**	If superiority with respect to overall survival was shown, formal statistical testing was done hierarchically on progression-free survival and objective response rate at the significance level adjusted for the primary endpoint and interim analysis to preserve the overall type 1 error rate (0·0252 for progression-free survival and 0·025 for objective response rate). Survival curves and rates were estimated using the Kaplan-Meier method. HRs and CIs were estimated with a stratified Cox proportional-hazards model with treatment group as a single covariate. Safety analyses, including a prespecified assessment of the incidence	
Median OS (1-year DBL)	NIVO+IPI+PDC	361	15.6 (13.9 - 20.0) months	5.62	1.92-8.92	-	HR: 0.66	0.55–0.85	-		Paz-Ares et al. Lancet Oncol 2021 (Paz-Ares 2021a)
	PDC	358	10.9 (9.5 - 12.6) months								
Median OS (2-year DBL)	NIVO+IPI+PDC	361	15.8 (13.9–19.7) months	4.28	1.79-7.03	-	HR: 0.72	0.61–0.86	-		Reck et al. ESMO Open 2021 (Reck 2021)
	PDC	358	11.0 (9.5–12.7) months								
Median PFS (1-year DBL)	NIVO+IPI+PDC	361	6.7 (5.6 - 7.8) months	2.35	1.10-3.77	-	HR: 0.68	0.57 - 0.82	-		Paz-Ares et al. Lancet Oncol 2021 (Paz-Ares 2021a)
	PDC	358	5.0 (4.3 - 5.6) months								
Median PFS (2-year DBL)	NIVO+IPI+PDC	361	6.7 (5.6–7.8) months	2.61	1.41-4.16	-	HR: 0.67	0.56–0.79	-		Reck et al. ESMO Open 2021

CheckMate 9LA (NCT03215706)											
	PDC	358	5.3 (5.6–7.8) months							of treatment-related adverse events per 100 patient-years, assessed all randomly assigned patients who received at least one dose of study drug.	(Reck 2021)
Median duration of response (1-year DBL)	NIVO+IPI+PDC	361	11.3 (8.5 - NR)	5.60	2.40-10.40	-	[redacted]	[redacted]	-		Paz-Ares et al. Lancet Oncol 2021 (Paz-Ares 2021a) HR calculated from CheckMate 9LA raw data
	PDC	358	5.6 (4.4 - 7.5)								
Median duration of response (2-year DBL)	NIVO+IPI+PDC	361	13.0 (8.7–20.2) months	-	-	-	-	-	-		Reck et al. ESMO Open 2021 (Reck 2021)
	PDC	358	5.6 (4.4–7.2) months								
% objective response rate (1-year DBL)	NIVO+IPI+PDC	361	38.2 (33·2–43·5)	-	-	-	-	-	-		Paz-Ares et al. Lancet Oncol 2021 (Paz-Ares 2021a)
	PDC	358	24.9 (20·5–29·7)								
	NIVO+IPI+PDC	361	38.0 (32.9–43.2)	-	-	-	-	-	-		

CheckMate 9LA (NCT03215706)											
% objective response rate (2-year DBL)	PDC	358	25.4 (21.0–30.3)								Reck et al. ESMO Open 2021 (Reck 2021)
TRAE grade 3/4/5, n (%) (1-year DBL)	NIVO+IPI+PDC	358	169 (47.2)	-	-	-	OR:1.42	1.05 -- 1.91	-		BMS data on file
	PDC	349	135 (38.7)								
TRAE grade 3/4, n (%) (2-year DBL)	NIVO+IPI+PDC	358	173 (48)	-	-	-	-	-	-		Reck et al. ESMO Open 2021 (Reck 2021)
	PDC	349	132 (38)								

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Table 84: Results of CheckMate 227 (NCT03215706)

CheckMate 277 (NCT03215706)											
				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**	Kaplan–Meier analysis was performed to estimate the duration of overall survival. Nonparametric log-rank test used to assess the primary and secondary hierarchical end points and a stratified Cox proportional-hazards model, with the treatment group as a single covariate, to calculate HRs for death with associated two-sided CI. If the proportional assumption was not met, HRs were still reported to provide a conventional estimate of overall average effect and supplemented by median and landmark estimates.	
Median OS PD-L1 ≥1% (4-year DBL)	NIVO+IPI	396	17.1 (15.0-20.1) months	8.38	3.5-14.32	-	HR: 0.64	0.51-0.81	-		(Paz-Ares 2021b)
	PDC	397	14.9 (12.7-16.7) months								
Median OS PD-L1 <1% (4-year DBL)	NIVO+IPI	187	17.2 (12.8-22.0) months	6.86	2.86-11.72	-	HR: 0.64	0.51-0.81	-		(Paz-Ares 2021b)
	PDC	186	12.2 (9.2-14.3) months								
TRAE grade 3/4/5, n (%) (2-year DBL)	NIVO+IPI	576	189 (32.8)	-	-	-	-	-	-		(Hellmann 2019b)
	PDC	570	205 (36.0)								

Table 85: Results of KEYNOTE 189 (NCT02578680]

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**	Efficacy analyses were performed in the intention-to-treat (ITT) population, which included all randomly assigned patients; safety analyses were performed in the as-treated population, which included all randomly assigned patients who received greater than 1 dose of therapy. The Kaplan-Meier method was used to estimate OS, PFS, and PFS-2. A stratified Cox proportional hazards model with Efron's method of tie handling was used to determine HRs and 95% CIs. Stratification factors used for randomization were applied. Analyses were not controlled for multiplicity; no alpha was assigned to this updated analysis.	
Median overall survival	Pembro+plat+pem	410	22.0 (19.5 - 24.5) months	8.33	4.76-12.44	-	HR: 0.56	0.46–0.69	-		Rodriguez-Abreu et al. ASCO 2020 (Rodriguez-Abreu 2020)
	Plat+pem	206	10.6 (8.7 - 13.6) months								
Median PFS	Pembro+plat+pem	410	9.0 (8.1 - 10.4) months	5.10	3.41-7.05	-	HR: 0.49	0.41 - 0.59	-		Rodriguez-Abreu et al. ASCO 2020 (Rodriguez-Abreu 2020)
	Plat+pem	206	4.9 (4.7 - 5.5) months								
Median duration of response	Pembro+plat+pem	410	12.4 (1.1-29.0+)[a]	7.39	2.63-14.42	-	HR: 0.49	0.33 – 0.73	-		Gadgeel et al. JCO 2020; Gadgeel et al. ASCO 2019 (suppl. slide presentation)(Gadgeel 2020)
	Plat+pem	206	7.1 (2.4-22.0+)[a]								

Results of KEYNOTE 189 (NCT02578680]											
% objective response rate	Pembro+plat+pem	410	48.3 (43.4 – 53.2)	-	-	-	-	-	-		Rodriguez-Abreu 2020; Gadgeel et al 2020[b] (Gadgeel 2020, Rodriguez-Abreu 2020)
	Plat+pem	206	19.9 (14.7 – 26.0)								
TRAE grade 3/4/5, n (%)	Pembro+plat+pem	405	196 (48.4)	-	-	-	OR: 1.43	1.02 – 2.01	-		(European Medicines Agency 2018)
	Plat+pem	202	80 (39.6)								

Note: [a] Presented as median (range); + indicates no progressive disease by last time of assessment. [b] ORR is based on Rodriguez-Abreu however, the n (%) not provided for CR and PR separately; these were reported as CR=4(1) + PR=193 (47.1) for Pembro+plat+pem, and 1 (0.5) + 39 (18,9) for Plat+pem in an earlier publication by Gadgeel et al 2020.

Table 86: Results of KEYNOTE 407 (NCT02775435]

Results of KEYNOTE 407 (NCT02775435]											
				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 overall survival	PEMBRO-CARB-(NAB)TAX	278	17.1 (14.4 - 19.9) months	4.74	1.58-8.40	-	HR: 0.71	0.58 – 0.88	-	OS, PFS, and DOR were estimated using the nonparametric Kaplan-Meier method. The magnitude of treatment differences (HR and 95% CI) was assessed with a stratified Cox proportional hazards model and the Efron method of tie handling. Safety analyses included all randomized patients who received at least one dose of study treatment. AEs that occurred during crossover pembrolizumab treatment were excluded from the primary safety comparison between treatment arms.	Paz-Ares et al. JTO 2020 (Reck 2020c)
	Placebo-CARB-(NAB)TAX	281	11.6 (10.1 - 13.7) months								
Median PFS	PEMBRO-CARB-(NAB)TAX	278	8.0 (6.3 – 8.4) months	3.85	2.29-5.75	-	HR: 0.57	0.47 - 0.69	-		Paz-Ares et al. JTO 2020 (Reck 2020c)
	Placebo-CARB-(NAB)TAX	281	5.1 (4.3 – 6.0) months								
Median duration of response	PEMBRO-CARB-(NAB)TAX	278	8.8 (1.3+ - 28.4+) months	2.88	0.86-5.53	-	HR: 0.63	0.47 - 0.85[a]	-		Paz-Ares JTO 2020; Paz-Ares ESMO 2019 (Barlesi 2019, Reck 2020c)
	Placebo-CARB-(NAB)TAX	281	4.9 (1.3+ - 28.3+)								

Results of KEYNOTE 407 (NCT02775435]											
% objective response rate	PEMBRO-CARB-(NAB)TAX	278	62.6 (56.6 – 68.3)	-	-	-	-	-	-	For median duration of response, HR calculated from KM curve presented by Paz-Ares ESMO 2019	Paz-Ares JTO 2020 (Reck 2020c)
	Placebo-CARB-(NAB)TAX	281	38.4 (32.7 – 44.4)								
TRAE grade 3/4/5, n (%)	PEMBRO-CARB-(NAB)TAX	278	152 (54.7)	-	-	-	OR: 0.99	0.71 – 1.38	-		(European Medicines Agency 2019)
	Placebo-CARB-(NAB)TAX	280	154 (55.0)								

Notes: [a] calculated from Kaplan-Meier curve reconstructions

Table 87: Results of KEYNOTE 024 (NCT 02142738]

Results of KEYNOTE 024 (NCT 02142738]											
				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 overall survival	PEMBRO	154	26.3 (18.3 – 40.4) months	8.21	3.14-14.52	-	HR: 0.62	0.48 – 0.81	-	HR calculated from KM curves presented by Brahmer et al WCLC 2017(based on data cut-off of July 10, 2017 with median follow-up 25.2 mo)	Brahmer et al. ESMO 2020 (Brahmer 2020)
	PDC	151	13.4 (9.4- 18.3) months								
Median PFS	PEMBRO	154	7.7 (6.1 – 10.2) months	5.50	2.96-8.60	-	HR: 0.50	0.39 – 0.65	-		Brahmer et al. ESMO 2020 (Brahmer 2020)
	PDC	151	5.5 (4.2 – 6.2) months								
Median duration of response	PEMBRO	154	29.1 (2.2 – 60.8+)	18.90	7.70-38.70	-	HR: 0.25	0.14 - 0.45[a]	-		Brahmer et al. ESMO 2020; Brahmer et al WCLC 2017 (Brahmer 2017, Brahmer 2020)
	PDC	151	6.3 (3.1 – 52.4)								
% objective	PEMBRO	154	46.1	-	-	-	-	-	-		Brahmer et al. ESMO 2020
	PDC	151	31.1								

Results of KEYNOTE 024 (NCT 02142738]											
response rate											(Brahmer 2020)
TRAE grade 3/4/5, n (%)	PEMBRO	154	48 (31.2)	-	-	-	OR: 0.40	0.25 – 0.63	-		Brahmer et al. ESMO 2020; (Brahmer 2020)
	PDC	150	80 (53.3)								

Notes: [a] calculated from Kaplan-Meier curve reconstructions

Table 88: Results of KEYNOTE 042 (NCT02220894], subgroup PD-L1 ≥50%

Results of KEYNOTE 042 (NCT02220894], subgroup PD-L1 ≥50%											
				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 overall survival	PEMBRO	299	20.0 (15.9 - 24.2) months	5.23	1.99-8.83	-	HR: 0.70	0.58 – 0.86	-	Info not provided in abstract	Mok et al. ELCC 2019 (Mok 2019a)
	PDC	300	12.2 (10.4 - 14.6) months								
Median PFS	PEMBRO	299	6.5 (5.9 - 8.5) months	1.31	0.00-2.88	-	HR: 0.83	0.69 – 1.00	0.0260	Info not provided in abstract	Mok et al. ELCC 2019 (Mok 2019a)
	PDC	300	6.4 (6.2 - 7.2) months								
Median duration of response	PEMBRO	299	22.0 (2.1+ - 36.5+) months	14.91	6.90	27.77	HR: 0.42	0.28 – 0.61[a]	-	For duration of response, HR calculated from KM curve presented by Mok et al. ELCC 2019.	Mok et al. ELCC 2019 (Mok 2019a)
	PDC	300	10.8 (1.8+ - 30.4+) months								
% objective response rate	PEMBRO	299	39.1	-	-	-	-	-	-	Info not provided in abstract	Mok et al. ELCC 2019 (Mok 2019a)
	PDC	300	32.0								
TRAE grade 3/4/5, n (%)*	PEMBRO	636	117 (18)	-	-	-	OR: 0.32	0.25 -- 0.42	-	Info not provided in abstract	Mok et al. ELCC 2019 (Mok 2019a)
	PDC	615	253 (41)								

Note: *based on ITT population; [a] calculated from Kaplan-Meier curve reconstructions

17. Appendix E Safety data for intervention and comparator

The safety data for the intervention and the comparators are described in section 7 above.

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18. Appendix F Comparative analysis of efficacy and safety

The comparative analyses of efficacy and safety are presented in section 7 above.

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19. Appendix G Extrapolation

19.1 Survival Extrapolation

19.1.1 Theoretical background

Data sources

DoT, PFS and OS data were projected using parametric survival models based on the April, 2021 DBL of CheckMate 9LA (i.e. after a minimum follow-up of 24.64 months for all endpoints) and April, 2021 4-year DBL of CheckMate 227.

All survival modelling was conducted using the FlexSurv package in R and modelled using the FlexSurvReg function. Standard parametric and spline-based survival models were fitted to individual patient level data from the CheckMate 9LA trial and CheckMate 227 trials.

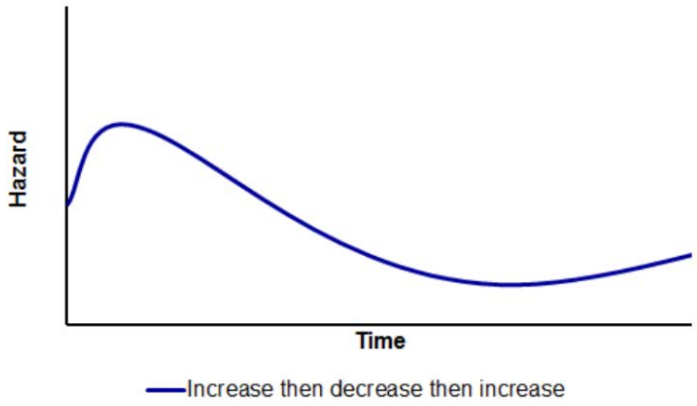
Methodologies

Economic models in oncology typically need to consider a lifetime horizon but patient follow-up in clinical trials is generally limited, thus survival and duration of treatment data needs to be extrapolated beyond the observed trial data.

The standard approach to extrapolation of OS and PFS in HTA's has been to use standard parametric modelles (SPM), guided by the technical support document (TSD) 14 from the NICE decision support unit (Decision Support Unit 2013). However, a number of recent studies has shown that this approach does not seen to estimate and model long term survival of IO well, including studies on NIVO in second-line NSCLC and second-line RCC (Ouwens 2019, Chaudhary 2020, Klijn 2021) . The limits of the SPM in modelling long term OS for IO treatments is also outlined in the recent guidance on flexible survival extrapolations in the TSD 21 from the NICE DSU that was recently published:

"The advent of immuno-therapy treatments for oncology has resulted in an increase in the use of complex survival models, because delayed responses to treatment and the existence of long-term survivors have been hypothesised to result in complex hazard functions (Othus 2017, Bullement 2019, Ouwens 2019). However, complex hazard functions are not only conceivable in immuno-oncology. For instance, in most cancer trials the mortality (hazard) rate upon entry to the trial may be relatively low, due to trial eligibility criteria meaning that recruited patients must be fit enough to receive treatment with a potentially toxic (new) therapy. However, due to the nature of the disease, the mortality rate is likely to rise in the short-term. Then, over time, as the case-mix of the cohort changes because the sicker patients die, healthier patients and treatment responders survive and so the mortality rate decreases. In the longer term the effectiveness of the treatment might wane, or disease progression might occur, resulting in an increase in the hazard. Even if the treatment represented a cure for a small proportion of patients, in the very long-term hazards would be expected to rise, reflecting age-related mortality", see (Figure 58).

Figure 58: More complex hazard function



Source: Adapted from Figure 4 in (Decision Support Unit 2013).

"Longer-term changes in the hazard may not be observed within the trial period, but - given a realistic expectation that they will be observed beyond the trial period - these are relevant for inclusion in a model used for economic evaluation, where a lifetime time horizon is typically used. None of the standard parametric models could adequately represent the hazard functionillustrated in Figure 4. It may be useful to consider survival models that can capture such hazard functions. Hazard functions are not routinely presented in NICE Technology Appraisals, but their inclusion may add to an understanding of the longer-term assumptions that are being made." [TSD 21 page 14-15, emphasis added to the later paragraph](Decision Support Unit 2020).

This initial increase followed by a decreasing hazard function as outlined in the example (Figure 58) of the TSD 21, has been observed across a number of NIVO studies (for an overview of hazard functions, see section 19.3). This is also what we see for CheckMate 9LA where there is an increasing hazard from the start of the trial followed by a decreasing hazard. For CheckMate 9LA the key challenge is that the decreasing trend occurs around the time of minimum follow-up whereby there is less patients in the trial informing this decreasing trend. Hence, when SPM are fitted to the 9LA data, the increasing trend in the start of the study gets more weight than the long term decrease. This leads to extrapolations that does not capture the long term decrease in hazard, which results in underestimation of long term OS, as discussed in a recent paper by Gray et al. (Gray 2021).

This issue is seen when we compare SPM extrapoaltion of 9LA with the observed OS for 227. As seen from Figure 59, the extrapolations of 9LA lies significantly below the OS observed toward the end of 227, which is not clinically plausible. CheckMate 227 provides a natural source of validation of OS extrapolation from 9LA since similar patients was treated with NIVO+IPI in first-line NSCLC, please see Appendix L Baseline characteristics and study design CheckMate 227 for a comparison of 9LA and 227. As outlined in the TSD 14, it is important to assess the clinical plausibility of extrapolation, especially when there is limited follow-up and data are immature.

For this reason we investigate alternative approaches to extrapolate long term outcomes from 9LA that are more clinically plausible. In this case it was found that a piece wise approach, as proposed by Bagust and Beale and also discussed in the TDS 21, using data from 227 was the best approach to estimate long term OS and PFS from 9LA.

Latimer's Method

Considering that routine parametric curves generated from CheckMate 9LA patient-level data only (as per Latimer's method) underestimate long-term survival of patients treated with NIVO+IPI+PDC, the methods proposed by Jackson et al. (Jackson 2017) were incorporated.

Jackson et al. (Jackson 2017) present and describe a framework illustrating the decisions that need to be made to inform the appropriate selection of methods for the extrapolation of long-term survival using external data. Based on this framework, if the population in the external data has the same mortality at all times (at least in the long-term) as that of the disease population receiving the control and the disease population receiving the intervention, then hazard ratios can be estimated and used directly without adjustment. However, if mortality at all times cannot be assumed to be the same then the long-term mortality must be adjusted. Given the similarity between the CheckMate9LA and CheckMate 227 Part 1 trials, they are expected to have comparable long-term outcomes; an opinion that was agreed with by experts in the virtual advisory board (Bristol-Myers Squibb 2020b). Therefore, survival data from CheckMate 227 Part 1 (4- years DBL) was used to extrapolate CheckMate 9LA survival. To this end, KM data obtained from CheckMate 9LA (up to 24 months; week 104 in the model) was used directly and CheckMate 227 Part 1 data was subsequently used to project long-term outcomes (after month 24).

For the extrapolated parts of the curves, parametric curves were derived from CheckMate 227 Part 1 patient-level data (as per Latimer) and 'per cycle conditional survival' rates were subsequently applied to the proportion of patients having survived to that particular point in time. For example, if 38.76% of patients have survived until week

104 (based on CM9LA KM data), and 5% of remaining patients are expected to die in the subsequent 4-week cycle (e.g., 1 out of 20 remaining CheckMate 227 Part 1 patients die between week 104 and 108), the resulting survival rate at the end of the cycle would become 36.82% [i.e., 38.76% x (1-0.05)]. Considering the similarity of the two studies, in terms of design and OS/PFS outcomes, both at 24 months and across the observed study period (see section 0), we believe this approach is justified.

For the generation of the CheckMate 227 parametric curves, a 'Piecewise approach' using the complete 4-year dataset from CheckMate 227 part 1 was used to derive parametric curves for OS and PFS using data starting from baseline until the end of patient follow up.

A cut-off point of 24 months to switch from CheckMate 9LA KM data to the CheckMate 227 Part 1 parametric curves was selected for the base case analysis. Although minimum patient follow up was 24.64 months at the DBL of CheckMate 9LA (Bristol-Myers Squibb 2021b), the primary reason for selecting this specific timepoint was because a lot of censoring occurred after around 24 months in the OS data in both CM9LA treatment arms ( ). Bagust and Beale warn for the risk of bias that can be introduced by censoring patients (often visually evident as sudden downward movements in the KM plot at the end of the observed data) (Bagust 2014b). Latimer highlights that the selection of a timepoint for switching from KM curve to extrapolation becomes increasingly arbitrary as the effective sample size decreases (Latimer 2014). Therefore selecting a timepoint before large censoring occurs, maintains a suitable sample size from which to apply the extrapolation. Different switching time points are included in scenario analyses.

The piecewise approach with a cut-off point of 24 months was applied to both the OS and (the more mature) PFS data for both the NIVO+IPI+PDC and PDC groups in the economic model.

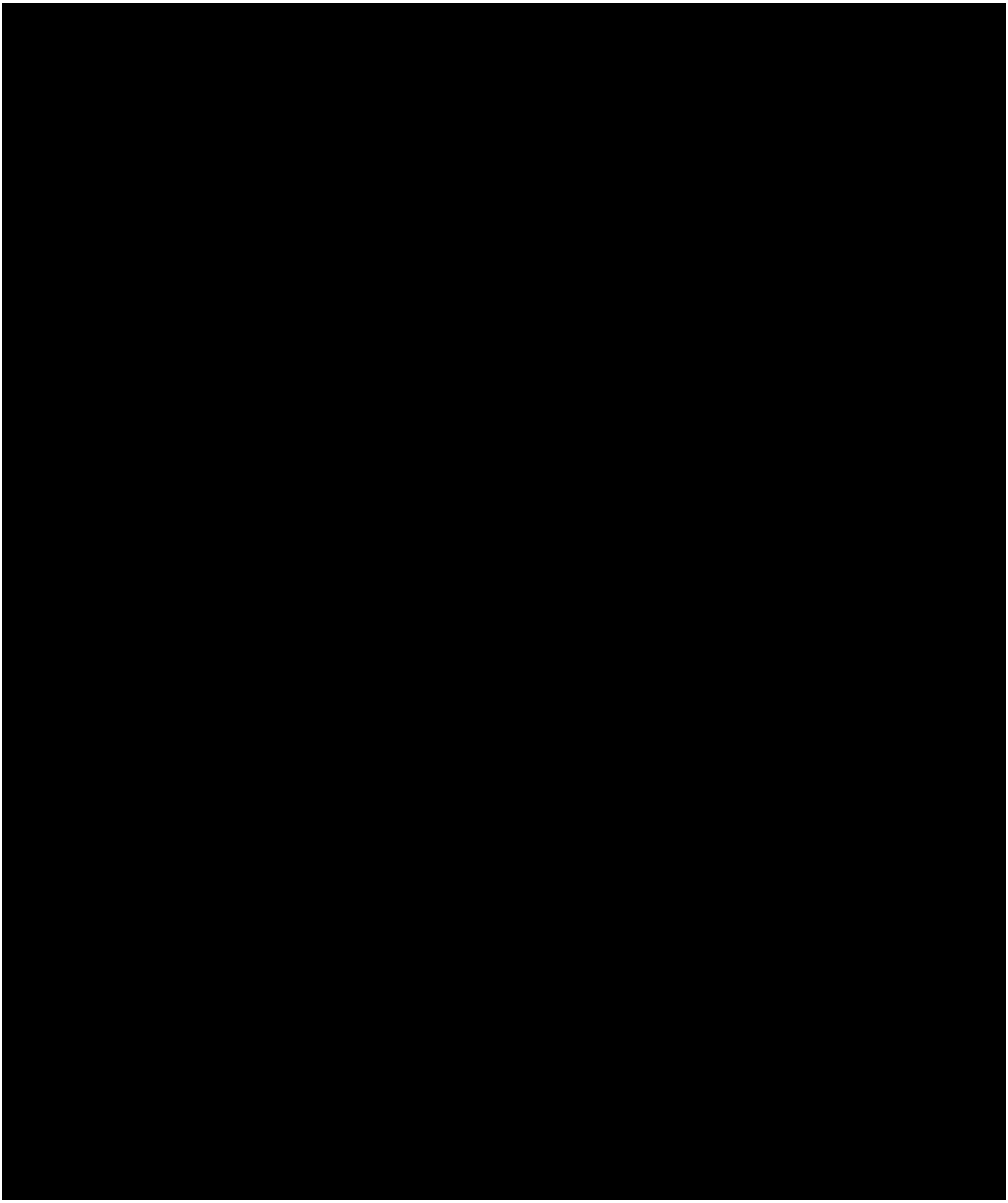
In summary, the piecewise approach was selected to extrapolate long-term OS and PFS outcomes for NIVO+IPI+PDC and PDC using 24 months as the timepoint for the switch from KM to extrapolation.

19.2 ITT

19.2.1 Overall Survival

19.2.1.1 Proportional hazards assumptions

The proportional hazards assumption was tested for the CheckMate 227 Part 1 OS using log-cumulative hazard plots (see Figure 62) the Grambsch-Therneau test and Schoenfield residuals plot (see Figure 63). The log-cumulative hazard plots are not parallel and cross at two points, once very early on and a second time at around 5 months. The Grambsch-Therneau test also clearly rejects the proportional hazards assumption ($p < 0.01$). In addition, the Schoenfeld residual plots show that the proportional hazards assumption does not hold. Therefore, only independent models were fitted using the CheckMate 227 data.



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19.2.1.2 Nivolumab plus ipilimumab plus 2 cycles chemotherapy

19.2.1.2.1 Statistical tests

Goodness of fit statistics for the parametric curves based on CheckMate 227 part 1 data are presented in Table 89. The lognormal and generalized gamma are statistically the best fitting distributions, followed by spline models. For the AIC values that differ by more than 3, there is a significantly different model fit to the data; this suggests that not all models would be reasonable fit to the data as the range of AIC values observed is much larger. [redacted] shows the curves with the best statistical fit resulting from piecewise approach.

Table 89: Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to OS data for NIVO+IPI for CheckMate 227 Part 1

Independent distributions	AIC	BIC
Lognormal	3736.822	3745.558
Generalised gamma	3738.211	3751.315
Spline on normal 2 knots	3738.510	3755.983
Spline on normal 1 knot	3738.613	3751.717
Spline on odds 1 knot	3739.272	3752.376
Spline on hazards 2 knots	3740.698	3758.171
Spline on odds 2 knots	3740.858	3758.331
Spline on hazards 1 knot	3740.942	3754.046
Gompertz	3740.956	3749.693
Log-logistic	3742.834	3751.57
Weibull	3776.439	3785.176
Gamma	3787.164	3795.901
Exponential	3810.617	3814.985

„AIC: Akaike information criterion; BIC: Bayesian information criterion; CM: CheckMate; NIVO+IPI: nivolumab + ipilimumab; OS: Overall survival

[redacted]

Clinical plausibility / external validation

The piecewise approach parametric survival models for OS in the NIVO+IPI+PDC arm (section 19.1.1) were validated through consistency with the selected PFS curves and using:

- CheckMate 017 and 057 pooled data
- Swedish and Norwegian registry data (primarily chemotherapy)
- SEER data

The conditional survival, defined as the percentage of patients alive in year X who will survive to year Y, for each of the sources mentioned above are presented in [redacted]

The conditional survival presented in [redacted] was used to construct a curve to predict long-term OS for 1L NSCLC patients receiving NIVO+IPI+PDC. This curve was constructed using a step-wise approach with each successive step adopting data that most closely related to CheckMate 9LA, see Figure 65 and Figure 66. The constructed curve was produced in 5 steps:

1. The absolute survival at year 1 was derived from the NIVO+IPI+PDC arm in CheckMate 9LA 2 year DBL.

2. The absolute survival at year 2 was also derived from the NIVO+IPI+PDC arm in CheckMate 9LA 2 year DBL. The minimum follow-up of the CheckMate 9LA data used was 24.64 months.

3. To predict OS at 3 and 4 years, the conditional survival from year 2 to 3 and from year 3 to 4, as observed in CheckMate 227 4 year DBL, was applied. As discussed in section 7, CheckMate 227 Part 1 is considered the best source of evidence to predict survival for CheckMate 9LA patients receiving NIVO+IPI(+PDC).

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4. As there are no trials involving NSCLC patients taking NIVO+IPI as 1L treatment, conditional survival from year 4 to 5 was derived from the pooled analysis of CheckMate 017 and 057 (data reflecting long-term OS in NSCLC patients treated with IO in 2L) to predict OS at 5-years.

5. Given that no relevant trial data for this patient population with a follow-up longer than 5 years is available, registry data were used to predict survival at 10 years. A Nordic patient population was considered an appropriate proxy for the patient population of interest. Norwegian registry data were available for up to 10 years wherefore it was utilized to estimate OS at 10 years using the conditional survival between 5 and 10 years.

6. The registry with the longest follow-up data available to us, at the time of developing the constructed OS curve, was the SEER registry. SEER registry data were leveraged to predict OS at 15 years using the conditional survival between 10 and 15 years. Using this approach, a survival of 7.7% is predicted at 15 years.

7. SEER registry data were also leveraged to predict OS at 17 years using the conditional survival between 15 and 17 years. Using this approach, a survival of 6.0% is predicted at 17 years.

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The constructed curve was derived using data from pre-treated trials and registries which to a large extent represent chemotherapy during the time before IO therapies were available. Therefore, long-term OS rates predicted with these constructed curves can be considered a conservative estimate; experts from the virtual advisory board agreed with this (Bristol-Myers Squibb 2020b).

Using the conditional survival allows us to use the shape of the curve from previous trials or registry data as an indication of the long-term shape of the OS curve for NIVO+IPI+PDC. Although, it can be expected that survival curves for IO therapies are flatter compared with those from data reflecting mainly chemotherapy. Therefore, the tail of the constructed survival curve could be seen as conservative and the 10-year OS for NIVO+IPI+PDC will likely be above the estimated 12.5%. While the constructed curve has been developed using data from various sources (e.g. clinical trials for different treatment lines and registry data), experts from the virtual advisory board agreed that, given limited external data, it is the best available estimate from which to validate the NIVO+IPI+PDC OS curve (Bristol-Myers Squibb 2020b).

Overall survival estimates based on various functional forms are presented in Table 91.

At 5 years, OS predictions for all models underestimate OS compared with the constructed curve. At 17 years, all curves except for lognormal and spline on hazard 1 knot slightly overestimate OS; this is acceptable, given the constructed curve is based on SEER data which captures a period of time where IO therapies were not available. Therefore, using SEER data as a lower bound together with the expectation that OS survival plateaus when patients are treated with IO therapies, the spline on normal 2 knots functional form was selected. The functional form selected (spline on normal 2 knots) is also the same as that used in the previous analysis (CheckMate 9LA 12-month datacut).

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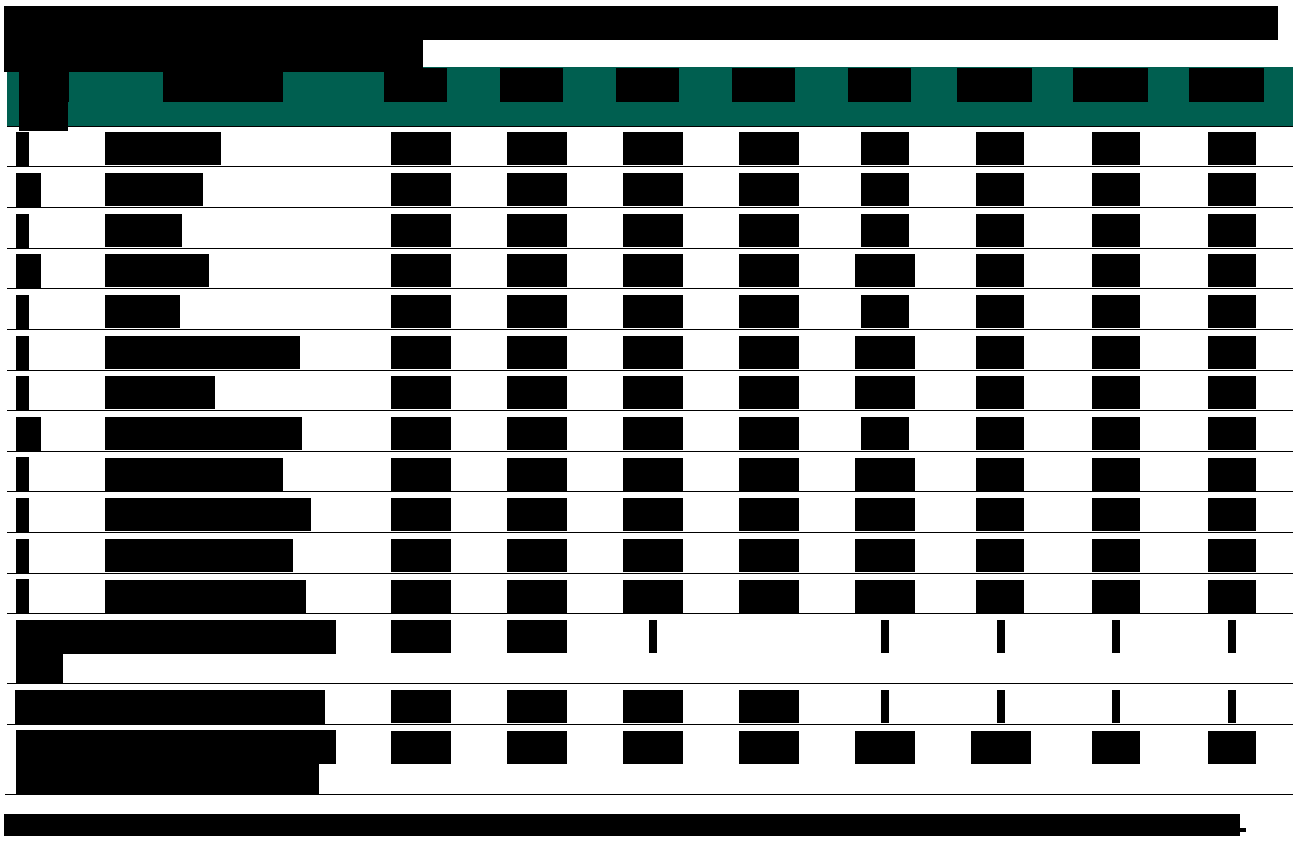
An alternative to the piecewise survival extrapolation approached was also explored. In this alternative approach, survival was extrapolated using parametric extrapolation only, based solely upon data from CheckMate 9LA, i.e. the piecewise approach using data from CheckMate 227 was disregarded. This alternative approach was included as a means of providing survival extrapolation based only upon CheckMate 9LA. The benefits of the 'parametric only' approach is that it is technically simpler, and only uses data for patients who received the exact intervention evaluated in this analysis, i.e. NIVO+IPI plus two rounds of PDC. However, the main drawback is that the still limited available follow-up from CheckMate 9LA means that the variance of long-term extrapolations increases, and that data from a highly similar patient group from CheckMate 227 is not leveraged. Particularly, the 'parametric only' approach fails to account for the expected decrease to OS hazard beyond two years (see section 19.1.1).

Just as for the piecewise approach, the choice of survival model for the 'parametric only' approach was based upon a combination of landmark survival analysis, statistical fit, and clinical plausibility. Table 92 presents the survival and statistical fit among alternative extrapolation models. Unlike the curves fitted using the 'piecewise approach' (i.e. including data from CheckMate 227 in the extrapolations), all 'parametric only' extrapolations predicted a substantially lower overall survival than the constructed curve using the best available reference data. This constituted another reason why the piecewise approach was considered a better base-case then the 'parametric only' approach. Among the estimated survival curves, the log-logistic model predicted the least pessimistic overall long-term survival and the best fit against the constructed survival curve. Another benefit of the log-logistic model is that it also provided one of the best fits for the comparator arm (see below in section 19.2.1.3.1), which made it an attractive choice in case it was desirable to use the same distribution for both treatment arms. For this reason, log-logistic was chosen as the model for the alternative scenario using 'parametric only' survival extrapolations (i.e. solely based upon CheckMate 9LA).

[redacted]



19.2.1.3 PDC

19.2.1.3.1 Statistical tests

The goodness of fit statistics are presented in Table 93. The loglogistic was the best fitting distribution by AIC and BIC criteria. Figure 67 shows the curves with the best statistical fit resulting from piecewise approach. Long term survival for the different distributions is consistent.

Table 93: Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to OS data for PDC from CheckMate 227 Part 1

Independent distributions	AIC	BIC
Loglogistic	4015.383	4024.120
Spline on odds 1 knot	4015.702	4028.807
Spline on odds 2 knots	4017.539	4035.012
Spline on hazards 2 knots	4017.965	4035.438
Spline on normal 2 knots	4018.031	4035.504
Spline on hazards 1 knot	4018.637	4031.742
Spline on hazards 3 knots	4019.253	4041.094
Lognormal	4020.976	4029.712
Spline on normal 1 knot	4022.030	4035.134
Generalised gamma	4022.196	4035.300
Gompertz	4046.691	4055.427
Exponential	4063.597	4067.966
Weibull	4064.960	4073.697
Gamma	4065.362	4074.098

AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: Overall survival; PDC: Platinum-doublet chemotherapy

[redacted]

Clinical plausibility / external validation

In 2013, the National Lung Cancer Audit (NLCA) reported the 5-year survival rates for stage IV lung cancer to be 5% (Audit 2013, National Lung Cancer Audit 2018). However, since IO therapy has recently become standard of care in the 2L setting, survival rates are expected to have improved. Therefore, the survival estimates for standard of care in a previous NICE submissions (TA447, TA557) were utilized to validate the long-term survival in the PDC arm (National Institute for Health and Care Excellence 2017, National Institute for Health and Care Excellence 2019). In TA 447, the ERG preferred survival curves that resulted in a survival of 9.6% and 1.5% at 5 and 10 years, respectively, in a PD-L1 positive population. It is expected that an all-comers population, such as those in CM9LA, would have lower survival compared with a PD-L1 positive population as it includes PD-L1 non-expressing patients. In TA557, the NICE committee stated that a 5-year survival of 5-11% for standard of care was considered realistic.

The conditional survival presented in Table 94 was used to construct a curve to predict long-term OS for 1L NSCLC patients receiving PDC. This curve was constructed using a step-wise approach with each successive step adopting data that most closely related to CheckMate 9LA, see [redacted] and [redacted] The constructed curve was produced in 4 steps:

1. The absolute survival at year 1 was derived from the PDC arm in CheckMate 9LA 2 year DBL.

2. The absolute survival at year 2 was also derived from the PDC arm in CheckMate 9LA 2 year DBL. The minimum follow-up of the CheckMate 9LA data used was 24.64 months (Bristol-Myers Squibb 2021b)

3. To predict OS at 3 and 4 years, the conditional survival from year 2 to 3 and from year 3 to 4 as observed in CheckMate 227 4 year DBL was applied.

4. The registry with the longest follow-up data available to us, at the time of developing the constructed OS curve, was the SEER registry. SEER registry data were leveraged to predict OS at 5, 10 and 15 years using the conditional survival between 4-5 years, 5-10 years, 10-15 years and 15 - 17 years, repsectively.

[redacted]

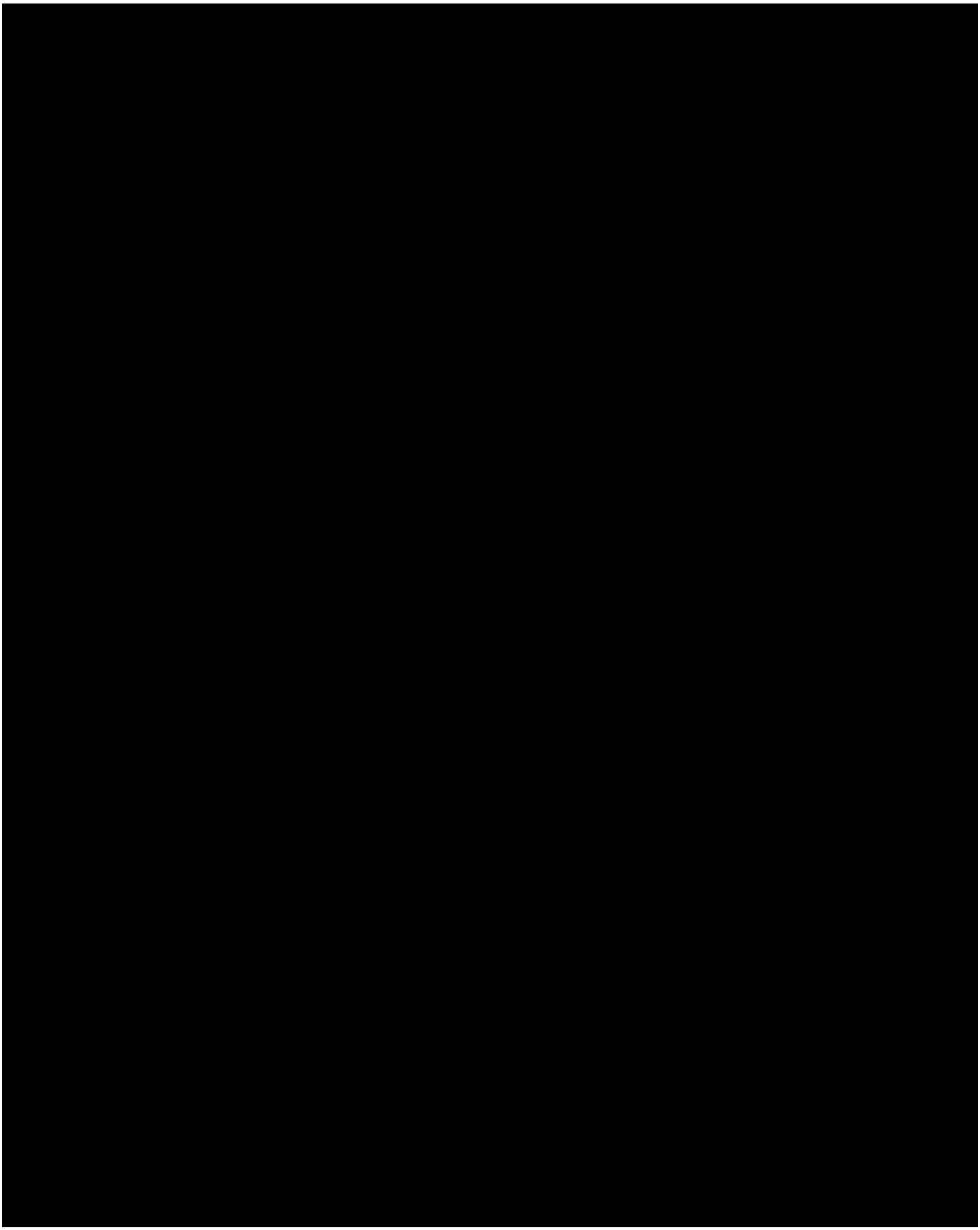


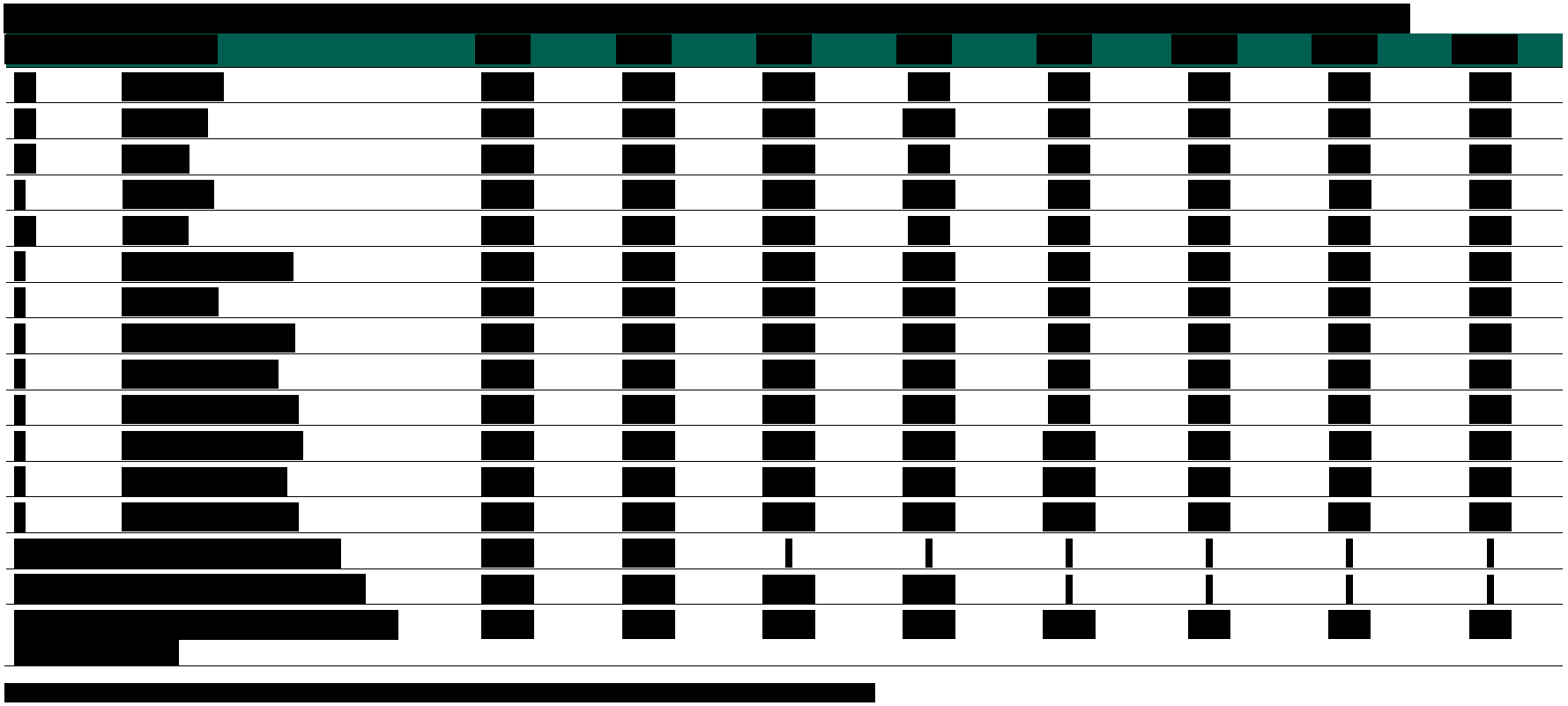
Table 95 presents the survival estimates at different landmark points for the eight best fitting distributions (based on AIC criteria) for OS in the PDC arm. All of the best fitting distributions are within the range 5-11% at 5 years.

At 5 and 17 years, OS predictions for all models underestimate OS compared with the constructed curve. Therefore, the curve with the closest estimations at years 5-17 to constructed curve was selected, i.e. spline on odds 2 knots.

[redacted]

Just as for the NIVO+IPI+PDC arm, an alternative approach was explored where survival was extrapolated using only data from CheckMate 9LA, i.e. a parametric only approach that did not include comparable data from CheckMate 227. This parametric only approach was methodologically simpler since it only extrapolated survival based upon one data source. However, in doing so, it also disregarded highly comparable data from CheckMate 227 which had a longer follow-up (4 years) than what is currently available for the CheckMate 9LA study (2 years). Considering the similarity of the comparison arms in CheckMate 9LA and CheckMate 227, the piecewise approach which uses data from both studies is expected to provide a better estimate of survival than the 'parametric only' approach (i.e. using only data from CheckMate 9LA.

Just as for the piecewise approach, the choice of survival model for the 'parametric only' approach was based upon a combination of landmark survival analysis, statistical fit, and clinical plausibility. Table 96 presents the survival and statistical fit among alternative extrapolation models. The best-fitting curves were the 2-knots spline models, with the log-logistic model having the best fit among parametric models. Most models estimated a lower long-term survival than the constructed curve which also relied upon data from CheckMate 227, which was expected considering that the 'parametric only' approach did not factor in survival data from CheckMate 227. The log-logistic model was chosen as the preferred model for the 'parametric only' scenario based upon its alignment with its expected survival, statistical fit and also the fact that this model offered the best fit for the NIVO+IPI+PDC arm in the comparable scenario, thereby reducing uncertainty caused by using different models for the two arms.



19.2.2 Progression-free survival

The April 2021 database lock for CheckMate 9LA had a minimum follow-up of 24.64 months for all data (Bristol-Myers Squibb 2021b). The piecewise approach (combining CheckMate 9LA KM data up to 24 months with CheckMate 227 Part 1 extrapolations based on the full data set) was used, which is consistent with the modelling approach for OS. Given that PFS data is inherently more mature than OS data, the extrapolated portion of the curves will be shorter.

19.2.2.1 Proportional hazards assumptions

The proportional hazards assumption was tested for the CheckMate 227 Part 1 PFS using log-cumulative hazard plots (see Figure 70) the Grambsch-Therneau test and Schoenfield residuals plot (see Figure 71). The log cumulative hazards plot shows the curves crossover at approximately 5 months. The Grambsch-Therneau test also clearly rejects the proportional hazards assumption (p = 0.000). In addition, the visual inspection of the Schoenfeld residuals plot demonstrates that the proportional hazards do not hold. Therefore, only independent models were fitted using the CheckMate227 data.

19.2.2.2 Nivolumab plus ipilimumab plus 2 cycles chemotherapy

19.2.2.2.1 Statistical tests

The goodness of fit statistics are presented in Table 97. Figure 72 shows the piecewise approach curves with the best statistical fit.

Table 97: Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to PFS data for NIVO+IPI for CheckMate 227 part 1

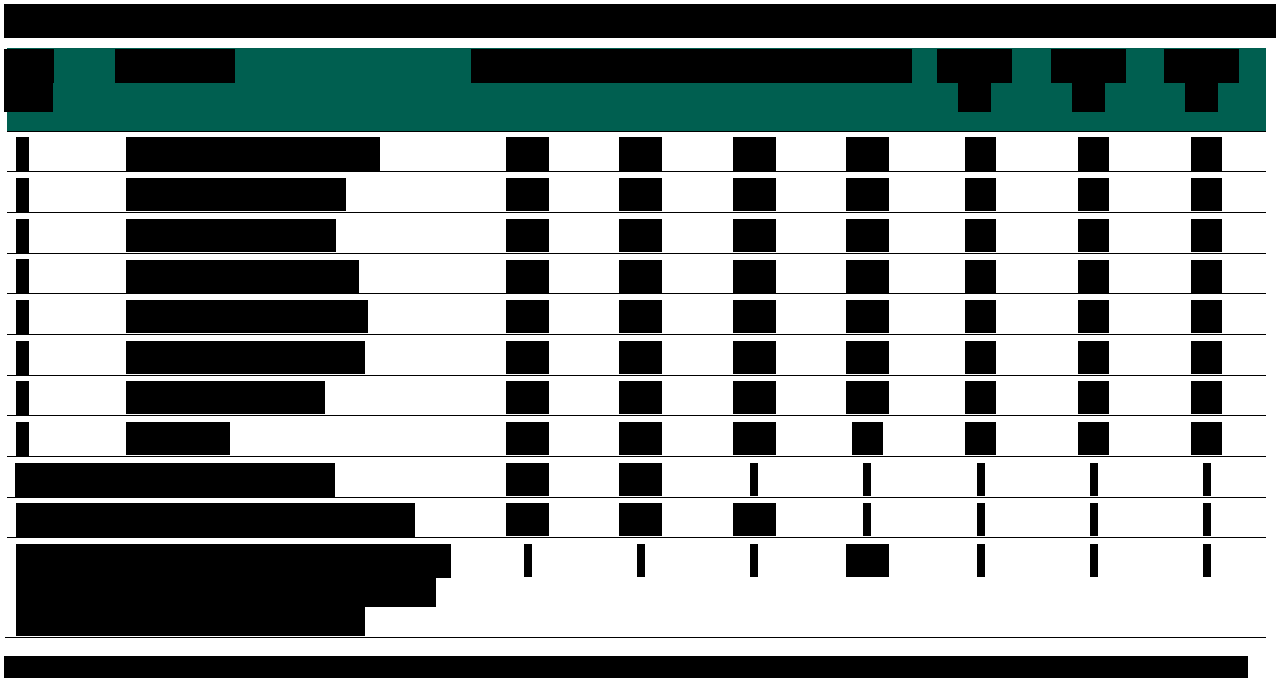
Independent distributions	AIC	BIC
2 spline hazard	2954.95	2972.42
2 spline odds	2955.28	2972.75
1 spline odds	2964.92	2978.03
1 spline normal	2965.11	2978.21
2 spline normal	2967.69	2985.16
1 spline hazard	2969.09	2982.20
Generalized gamma	2973.54	2986.65
Lognormal	3001.77	3010.51
Loglogistic	3014.50	3023.24
Gompertz	3028.38	3037.12
Weibull	3110.05	3118.78
Gamma	3150.96	3159.70
Exponential	3240.59	3244.96

AIC: Akaike information criterion; BIC: Bayesian information criterion; NIVO+IPI: nivolumab + ipilimumab; PFS: Progression-free survival

Clinical plausibility / external validation

Table 98 presents PFS at different landmark points using the eight best fitting distributions taken from piecewise approach (based on AIC/BIC) in the NIVO+IPI+PDC arm. The three best fitting distributions were the spline on hazard 2 knots, the spline on odds 2 knots, and the spline on odds 1 knot. To validate the PFS extrapolations, PFS at 5 years was predicted by deriving the conditional survival (defined as the percentage of patients in PFS at year X who will be in PFS at year Y) from years 4 to 5 from the pooled analysis of CheckMate 017 and 057 (Gettinger 2019) (87.9%) and applying it to the 4-year PFS from CheckMate 227 Part 1 (the pooled CheckMate 017 and 057 data were the longest follow-up for PFS at the time of the validation). Since the data reflect 2L IO therapy, it can be considered a conservative estimate for the 1L population evaluated in this analysis. Using this approach, the predicted 5-year PFS was 11.87%.

In order to be conservative and consistent with the analysis based on the previous DBL, the best fitting distribution (spline on hazard 2 knots) which has a 5-year estimate of 10.4% was selected for the base case.



19.2.2.3 PDC

19.2.2.3.1 Statistical tests

The goodness of fit statistics are presented in Table 99. Figure 73 shows the piecewise curves with the best statistical fit.

Table 99: Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to PFS data for PDC from CheckMate 227 part 1

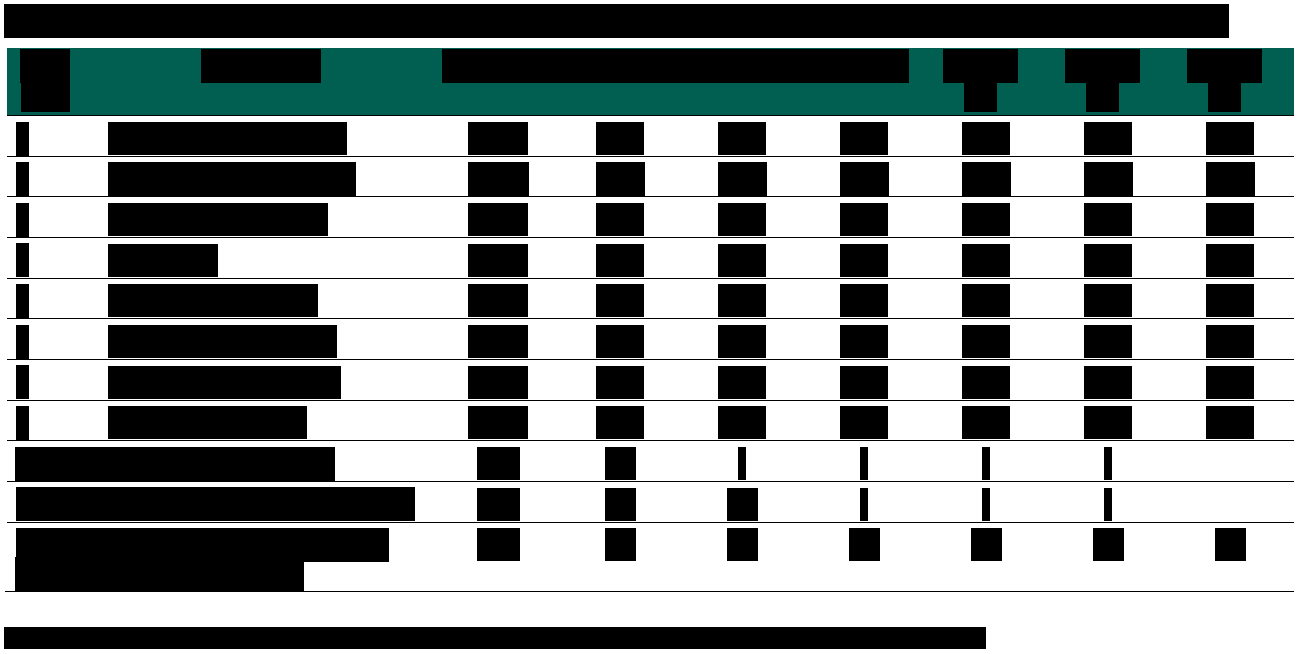
Independent distributions	AIC	BIC
2 spline hazard	2651.76	2669.24
2 spline normal	2654.85	2672.32
2 spline odds	2655.17	2672.64
Loglogistic	2658.38	2667.12
1 spline odds	2660.05	2673.16
1 spline hazard	2673.20	2686.30
1 spline normal	2682.80	2695.90
Generalized gamma	2685.39	2698.49
Lognormal	2687.14	2695.87
Gamma	2740.41	2749.15
Gompertz	2745.65	2754.38
Weibull	2754.77	2763.51
Exponential	2757.37	2761.74

AIC: Akaike information criterion; BIC: Bayesian information criterion; PDC: Platinum-doublet chemotherapy; PFS Progression-free survival

[redacted]

Clinical plausibility / external validation

[redacted] presents the PFS at different landmark points for the eight best fitting distributions in the PDC arm. Given the maturity of PFS for PDC, the extrapolated curves result in only marginal differences in long-term PFS. Therefore, it was considered appropriate to select the second best-fitting distribution (spline on normal 2 knots) based on goodness of fit statistics and that it provides more conservative conditional survival estimates at years 2-3 and 3-5.

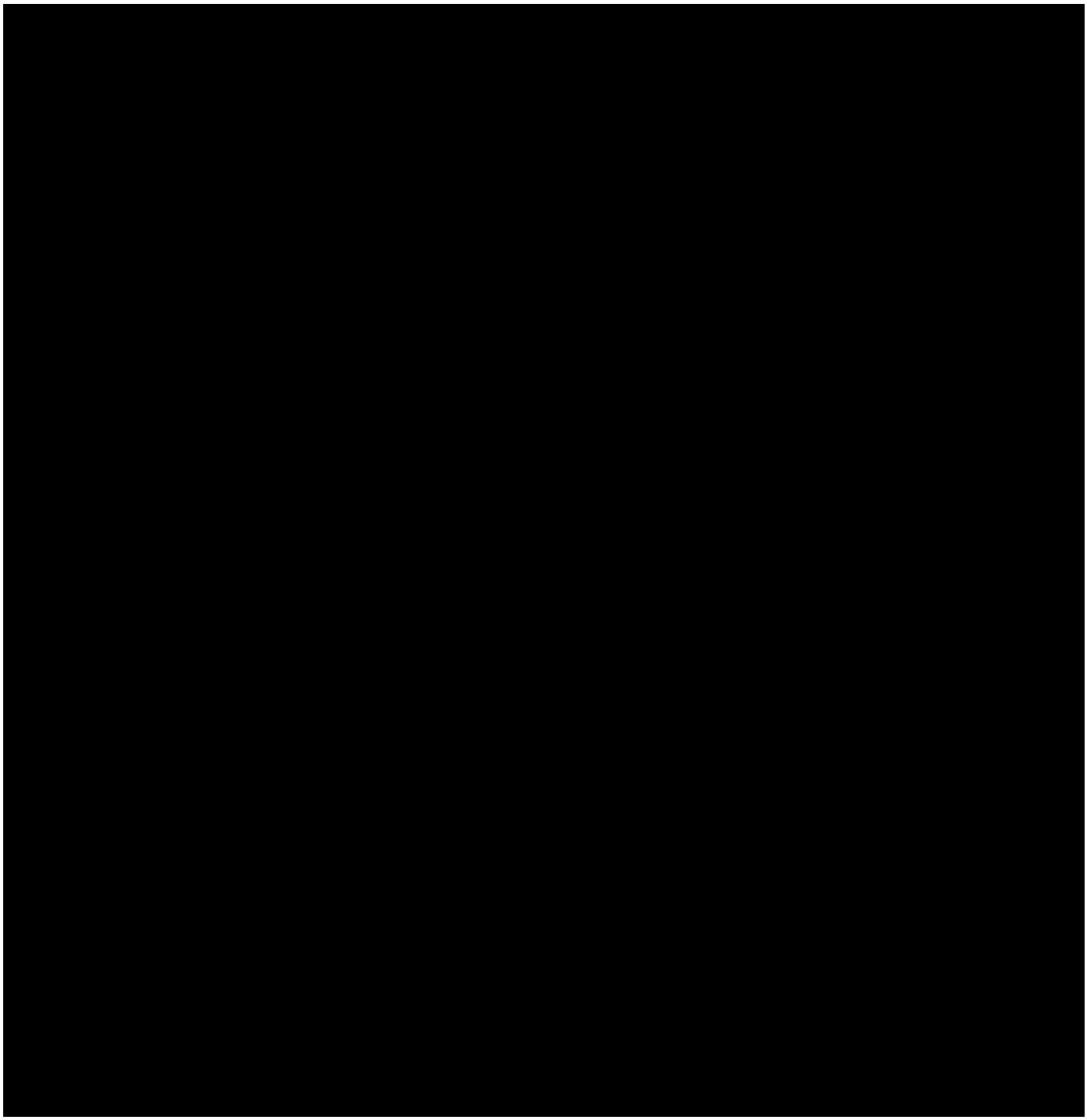


19.2.2.4 Duration of treatment

Various assumptions can be made about the duration of treatment (DoT) in the economic model. In oncology models, it is often assumed that PFS can be used as a proxy for DoT. Nevertheless, patients may stop treatment before progression (e.g. due to intolerability or adverse events) or continue treatment beyond disease progression. In CheckMate 9LA both PFS and DoT were measured directly and KM curves are available for both endpoints. At least for NIVO+IPI+PDC and PDC, DoT KM data can thus be directly used to inform treatment duration in the model.

Figure 74 shows the PFS and DoT KM curves for NIVO+IPI+PDC from CheckMate 9LA. The PFS KM curve for NIVO+IPI+PDC lies above the KM DoT curve, indicating that a proportion of patients may have discontinued treatment before disease progression. A steep drop in the DoT curve can also be seen at 24 months which reflects the two-year stopping rule included in the study protocol.

Figure 75 shows that the DoT KM curve for PDC is also below the PFS KM curve. This mainly reflects that patients with SQ histology discontinue treatment following 4 cycles of chemotherapy, but could also reflect early discontinuation due to toxicity. Only subjects with NSQ histology were allowed pemetrexed maintenance until disease progression or unacceptable toxicity.



Due to the dynamics between PFS and DoT, the economic model thus allows users to use either PFS or DoT to inform treatment cost calculations for patients on NIVO+IPI+PDC or PDC. In the base case analysis, the model uses the DoT KM curve for NIVO+IPI+PDC to more accurately reflect treatment use in the clinical trial. For PDC, treatment costs are also modelled according to the DoT curve in the base case analysis, to reflect that chemotherapy is discontinued after 4 cycles of treatment after which NSQ patients who have not progressed can continue on pemetrexed maintenance therapy. Furthermore both NIVO+IPI+PDC and PDC KM curves for DoT are very close to 0 at end of follow-up. Hence it was considered appropriate to use the DoT KM curve (rather than a parametric extrapolation) for treatment cost calculations for both arms in the base case analysis. Experts stated that the best available evidence to inform treatment

duration/discontinuation for NIVO+IPI+PDC and PDC is the CheckMate 9LA DoT KM curves and therefore agreed DoT KM curves should be used in the base case analysis.(Bristol-Myers Squibb 2020b).

19.2.2.5 IO treatment stopping rules

Depending on local clinical practice, different options to model the maximum treatment duration for IO therapies (NIVO+IPI) are included on the "Costs" worksheet. These are separate for each IO therapy and can be categorized as either "financial" or "medical" and include:

Financial

- **Full reimbursement:** the treatment is administered until progression or treatment discontinuation (due to AEs or other reasons) and the full cost is incurred by health care payers
- **Economic dose cap:** in this scenario, it is assumed that any patients on treatment beyond the user-defined dose cap are provided with treatment at zero cost. For NIVO+IPI, BMS is assumed to incur the treatment acquisition cost and healthcare payers are assumed to incur the administration and monitoring costs. This strategy reflects a risk sharing agreement between manufacturers and healthcare payers

Medical

- **Cap reimbursement by year:** in this scenario any patients on treatment are assumed to receive therapy up until the year selected by the user, i.e. healthcare payers do not incur any treatment costs beyond the user-defined maximum treatment duration (acquisition, monitoring, and administration). For example, if the cap is "2" years – any patients on treatment at this point in time will receive treatment for a maximum of 2 years and healthcare payers would not incur treatment costs after that point.
- **Cap reimbursement by dose:** in this scenario any patients on treatment are assumed to receive treatment until the number of doses selected by the user, i.e. healthcare payers do not incur treatment costs (acquisition, monitoring, and administration) after the selected number of doses have been administered. For example, if the dose cap for NIVO is "10" doses – any patients on treatment would have a maximum treatment duration of 20 weeks and would not incur NIVO treatment costs after that time (10 doses, 2-week periodicity). The cap by dose provides further granularity in treatment capping compared to the cap by year

It should be noted that the "medical" cap reimbursement options currently used in the base case analysis of the economic model are reflective of the CheckMate 9LA clinical trial design (as well as that of various other IO regimens). Of note, should the user want to select a different stopping rule than the 2-year treatment cap considered in the study, the model assumes there is no impact on efficacy (PFS and OS).

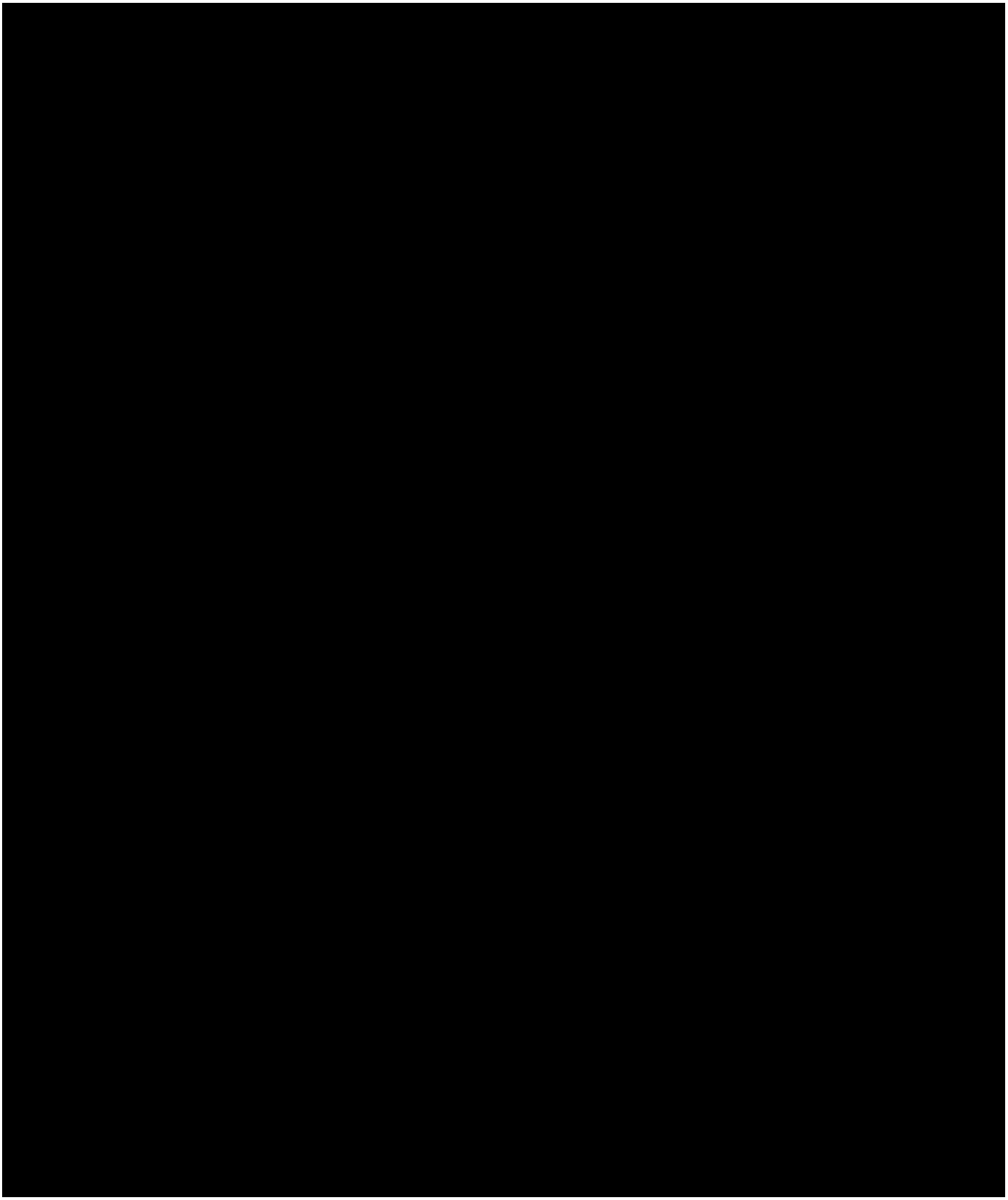
19.2.3 Smoothed hazard estimates for CheckMate 9LA and CheckMate 227 part 1

The below figure (Figure 89) includes an overview of the hazard over time for a number of nivolumab studies including CheckMate 9LA and CheckMate 227 in 1st line NSCLC. These smoothed hazard estimates comes from different sources which is why the methodology varies.

As outlined above the hazard in CheckMate 9LA increases up until the time point of minimum follow-up (around 13 months). Hence, the decrease in hazard seen after that minimum follow-up get little weight in extrapolations based solely on 9LA.

The smoothed hazard from CheckMate 227, clearly shows that the long term hazard of treatment with Nivo+ipi in 1st line NSCLC goes down over time. Similar is seen for nivo in 2nd line NSCLC, as observed in CheckMate 017 and CheckMate

057. The smoothed hazard from CheckMate 057 clearly shows the issue of fitting extrapolations to immature data that has not yet captured the long term decrease in hazard. The data on smoothed hazard from nivolumab in 2nd line renal cell carcinoma, which was presented part of a recent study on survival extrapolations within immuno oncology, show the same long term decrease, and that this was not apparent from the initial short term data.



19.3 SQ PDL1<1%

19.3.1 Overall Survival

19.3.1.1 Proportional hazards assumptions

The proportional hazards assumption was tested for the CheckMate 227 Part 1 OS using log-cumulative hazard plots (see Figure 77) the Grambsch-Therneau test and Schoenfield residuals plot (see Figure 78). As the log-cumulative hazard plot shows that the two curves are relatively parallel, the proportional hazards assumption could not be rejected. The Grambsch-Therneau test also failed to reject the proportional hazards assumption ($p < 0.68$). In addition, the Schoenfeld residual plots shows that the proportional hazards assumption cannot be rejected. For this reason, both dependent and independent models were fitted for the squamous, PD-L1 negative subgroup using the CheckMate 227 data.

19.3.1.2 Nivolumab plus ipilimumab plus 2 cycles chemotherapy

19.3.1.2.1 Statistical tests

Goodness of fit statistics for the parametric curves based on CheckMate 227 part 1 data are presented in Table 101. The lognormal and generalized gamma are statistically the best fitting distributions, followed by spline models. For the AIC values that differ by more than 3, there is a significantly different model fit to the data; this suggests that not all models would be reasonable fit to the data as the range of AIC values observed is much larger. Figure 79 shows the curves with the best statistical fit resulting from piecewise approach A. The spline on odds 2 knots was the least conservative estimation of long term survival, however most curves showed the plateau typically observed with IO therapies.

Table 101: Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to OS data for NIVO+IPI for CheckMate 227 Part 1

Independent distributions	AIC	BIC
Lognormal	324.69	328.35
1 spline normal	325.38	330.87
Generalized gamma	325.42	330.91
1 spline hazard	326.00	331.49
1 spline odds	326.27	331.76
Loglogistic	326.39	330.04
2 spline normal	327.28	334.59
2 spline hazard	327.28	334.60
2 spline odds	327.75	335.06
Exponential	328.19	330.02
Gompertz	328.99	332.65
Weibull	330.13	333.79
Gamma	330.18	333.84

AIC: Akaike information criterion; BIC: Bayesian information criterion; NIVO+IPI: nivolumab + ipilimumab; OS: Overall survival

Clinical plausibility / external validation

The piecewise approach parametric survival models for OS in the NIVO+IPI+PDC arm (section 19.1.1) were validated through consistency with the selected PFS curves and using:

- CheckMate 017 and 057 pooled data (Gettinger 2019)
- Swedish and Norwegian registry data (primarily chemotherapy)
- SEER data

The conditional survival, defined as the percentage of patients alive in year X who will survive to year Y, for each of the sources mentioned above are presented in [redacted]

The conditional survival presented in [redacted] was used to construct a curve to predict long-term OS for 1L NSCLC patients receiving NIVO+IPI+PDC. This curve was constructed using a step-wise approach with each successive step adopting data that most closely related to CheckMate 9LA, see Figure 65 and Figure 66. The constructed curve was produced in 5 steps:

8. The absolute survival at year 1 was derived from the NIVO+IPI+PDC arm in CheckMate 9LA 2 year DBL.

9. The absolute survival at year 2 was also derived from the NIVO+IPI+PDC arm in CheckMate 9LA 2 year DBL. The minimum follow-up of the CheckMate 9LA data used was 24.64 months.

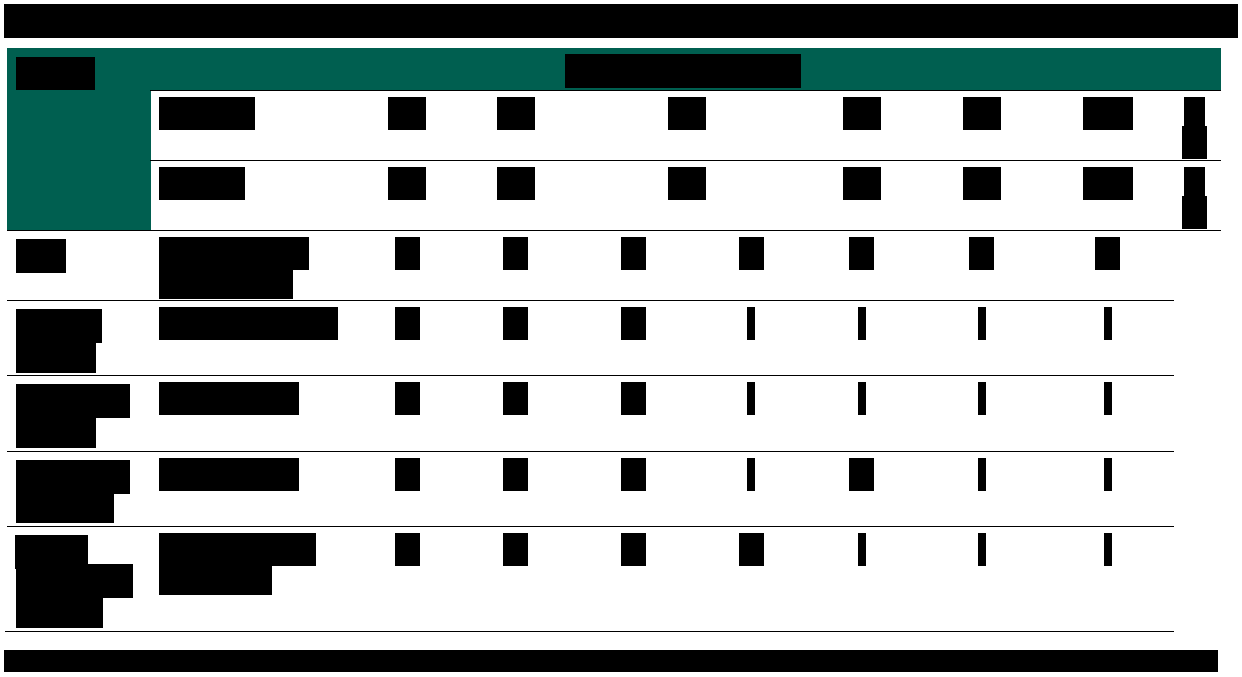
10. To predict OS at 3 and 4 years, the conditional survival from year 2 to 3 and from year 3 to 4, as observed in CheckMate 227 4 year DBL, was applied. As discussed in section 0, CheckMate 227 Part 1 is considered the best source of evidence to predict survival for CheckMate 9LA patients receiving NIVO+IPI(+PDC).

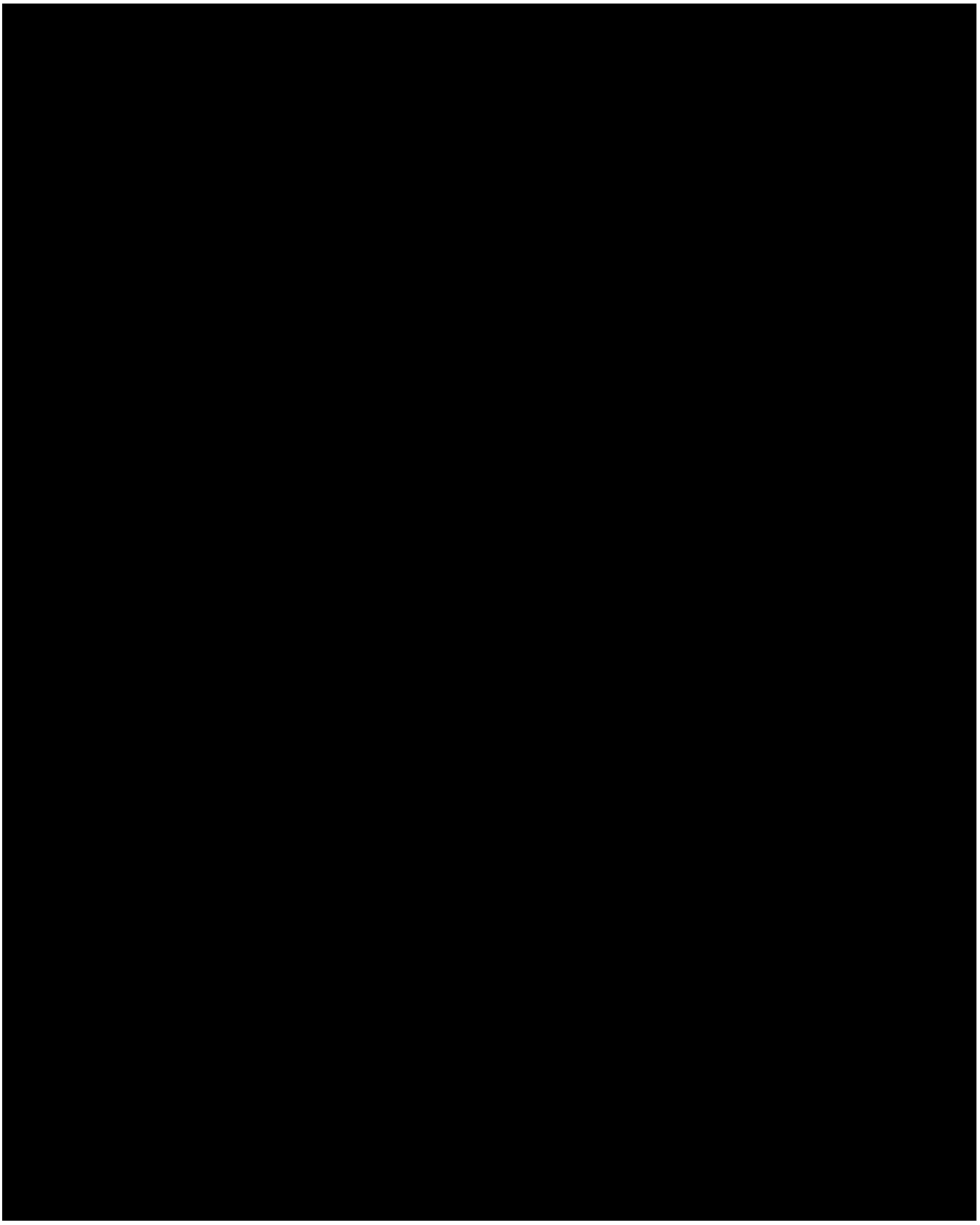
11. As there are no trials involving NSCLC patients taking NIVO+IPI as 1L treatment, conditional survival from year 4 to 5 was derived from the pooled analysis of CheckMate 017 and 057 (data reflecting long-term OS in NSCLC patients treated with IO in 2L) to predict OS at 5-years.

12. Given that no relevant trial data for this patient population with a follow-up longer than 5 years is available, registry data were used to predict survival at 10 years. A Nordic patient population was considered an appropriate proxy for the patient population of interest. Norwegian registry data were available for up to 10 years wherefore it was utilized to estimate OS at 10 years using the conditional survival between 5 and 10 years.

13. The registry with the longest follow-up data available to us, at the time of developing the constructed OS curve, was the SEER registry. SEER registry data were leveraged to predict OS at 15 years using the conditional survival between 10 and 15 years. Using this approach, a survival of 7.7% is predicted at 15 years.

14. SEER registry data were also leveraged to predict OS at 17 years using the conditional survival between 15 and 17 years. Using this approach, a survival of 6.0% is predicted at 17 years.

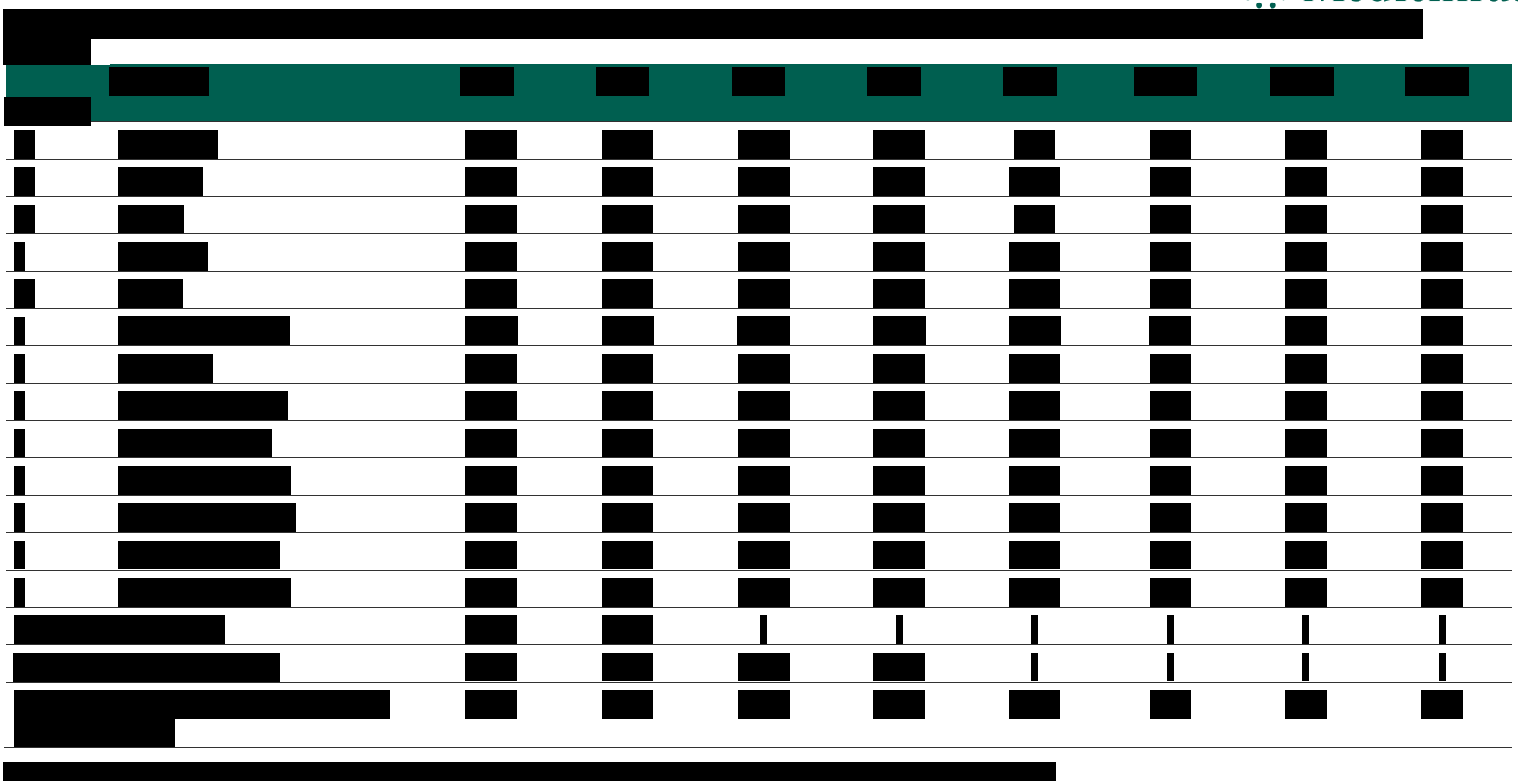




The constructed curve was derived using data from pre-treated trials and registries which to a large extent represent chemotherapy during the time before IO therapies were available. Therefore, long-term OS rates predicted with these constructed curves can be considered a conservative estimate; experts from the virtual advisory board agreed with this (Bristol-Myers Squibb 2020b).

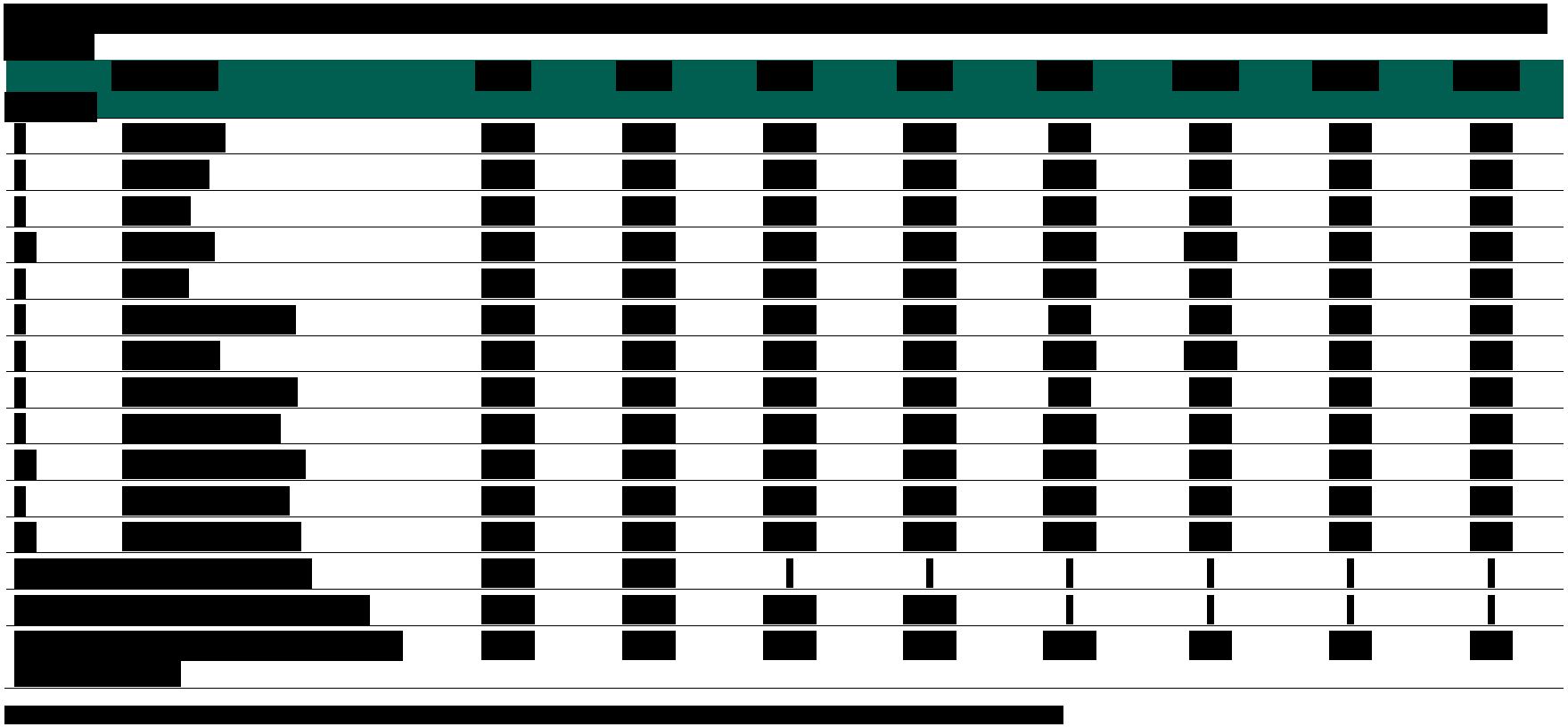
Using the conditional survival allows us to use the shape of the curve from previous trials or registry data as an indication of the long-term shape of the OS curve for NIVO+IPI+PDC. Although, it can be expected that survival curves for IO therapies are flatter compared with those from data reflecting mainly chemotherapy. Therefore, the tail of the constructed survival curve could be seen as conservative and the 10-year OS for NIVO+IPI+PDC will likely be above the estimated 12.5%. While the constructed curve has been developed using data from various sources (e.g., clinical trials for different treatment lines and registry data), experts from the virtual advisory board agreed that, given limited external data, it is the best available estimate from which to validate the NIVO+IPI+PDC OS curve (Bristol-Myers Squibb 2020b).

Overall survival estimates based on various functional forms are presented in [redacted]. At 5 years, OS predictions for all models underestimate OS compared with the constructed curve. At 17 years, all curves except for lognormal and spline on hazard 1 knot slightly overestimate OS; this is acceptable, given the constructed curve is based on SEER data which captures a period of time where IO therapies were not available. Therefore, using SEER data as a lower bound together with the expectation that OS survival plateaus when patients are treated with IO therapies. The generalized gamma functional form was selected as it is a conservative estimate compared to the constructed curve when looking at the conditional survival.



An alternative to the piecewise survival extrapolation approached was also explored. In this alternative approach, survival was extrapolated using parametric extrapolation only, based solely upon data from CheckMate 9LA, i.e. the piecewise approach using data from CheckMate 227 was disregarded. This alternative approach was included as a means of providing survival extrapolation based only upon CheckMate 9LA. The benefits of the 'parametric only' approach is that it is technically simpler, and only uses data for patients who received the exact intervention evaluated in this analysis, i.e. NIVO+IPI plus two rounds of PDC. However, the main drawback is that the still limited available follow-up from CheckMate 9LA means that the variance of long-term extrapolations increases, and that data from a highly similar patient group from CheckMate 227 is not leveraged. Particularly, the 'parametric only' approach fails to account for the expected decrease to OS hazard beyond two years (see section 19.1.1).

Just as for the piecewise approach, the choice of survival model for the 'parametric only' approach was based upon a combination of landmark survival analysis, statistical fit, and clinical plausibility. Table 104 presents the survival and statistical fit among alternative extrapolation models among SQ, PD-L1<1% patients. For most models, the long-term survival (15-17 years) was unfeasibly low, and amongst the others the long-term survival was estimated higher than for the constructed curve. The curve which predicted long-term survival most in line with the constructed curve was the 1-knot spline odds model, however,r this mocdel clearly underestimated mid-term survival compared to the constructed curve. The log-logistic model was deemed the most plausible curve and chosen for the scenario with the 'extrapolations only' approach. Another benefit of choosing the log-logisitc model was that it also offered a reasonable fit for the PDC curve for the same 'extrapolations only' settings, thereby reducing methodological uncertainty through keeping distribution consistent across the treatment arms.



19.3.1.3 PDC

19.3.1.3.1 Statistical tests

The goodness of fit statistics are presented in Table 105. The loglogistic was the best fitting distribution by AIC and BIC criteria. Figure 82 shows the curves with the best statistical fit resulting from piecewise approach A. Long term survival for the different distributions is consistent.

Table 105: Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to OS data for PDC from CheckMate 227 Part 1

Independent distributions	AIC	BIC
Lognormal	318.28	321.94
Loglogistic	318.84	322.50
Exponential	319.31	321.14
1 spline normal	319.96	325.45
Generalized gamma	320.07	325.56
1 spline hazard	320.51	325.99
Gompertz	320.55	324.21
1 spline odds	320.73	326.22
Gamma	321.16	324.82
Weibull	321.31	324.97
2 spline normal	321.93	329.24
2 spline odds	322.16	329.47
2 spline hazard	322.50	329.81

AIC: Akaike information criterion; BIC: Bayesian information criterion; OS: Overall survival; PDC: Platinum-doublet chemotherapy

Clinical plausibility / external validation

In 2013 the National Lung Cancer Audit (NLCA) reported the 5-year survival rates for stage IV lung cancer to be 5% (National Lung Cancer Audit 2018). However, since IO therapy has recently become standard of care in the second-line setting, survival rates are expected to have improved. Therefore, the survival estimates for standard of care in a previous NICE submissions (TA447, TA557) were utilized to validate the long-term survival in the PDC arm (NICE 2017, NICE 2019). In TA 447, the ERG preferred survival curves that resulted in a survival of 9.6% and 1.5% at 5 and 10 years, respectively,

in a PD-L1 positive population. It is expected that an all-comers population, such as those in CheckMate 9LA, would have lower survival compared with a PD-L1 positive population as it includes PD-L1 non-expressing patients. In TA557, the NICE committee stated that a 5-year survival of 5-11% for standard of care was considered realistic.

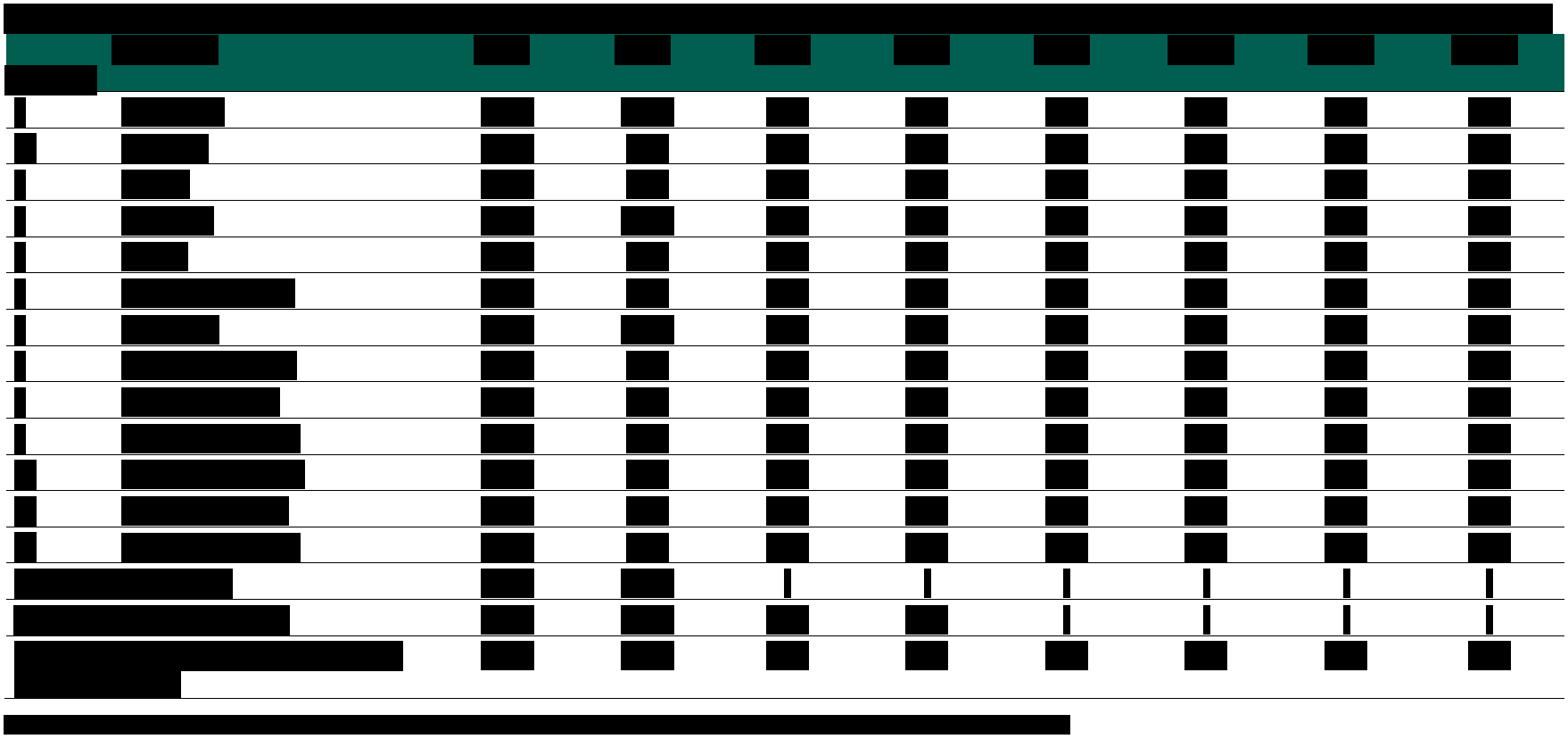
Table 106 presents the survival estimates at different landmark points for the six best fitting distributions (based on AIC criteria) for OS in the PDC arm. Considering that the all-comers population would have lower survival compared with a PD-L1 positive population, the 5-year survival should likely be below 9.6%. The log-logistic curve was chosen as it provides the best fit compared to the constructed curve in years 3 and 5, as well as providing the best long-term estimates when compared to the constructed curve.

[redacted]

Just as for the NIVO+IPI+PDC arm, an alternative approach was explored where survival was extrapolated using only data from CheckMate 9LA, i.e. a parametric only approach that did not include comparable data from CheckMate 227. This parametric only approach was methodologically simpler since it only extrapolated survival based upon one data source. However, in doing so, it also disregarded data highly comparable data from CheckMate 227 which had a longer follow-up (4 years) than what is currently available for the CheckMate 9LA study (2 years). Considering the similarity of the comparison arms in CheckMate 9LA and CheckMate 227, the piecewise approach which uses data from both studies is expected to provide a better estimate of survival than the 'parametric only' approach (i.e. using only data from CheckMate 9LA.

The choice of survival model for the 'parametric only' approach was based upon a combination of landmark survival analysis, statistical fit, and clinical plausibility. Table 107 presents the survival and statistical fit among alternative extrapolation models. Compared to the constructed survival curve, all extrapolations based upon only data from CheckMate 9LA estimated a considerably lower survival for the PDC arm. The Log-logisitc model predicted the highest

survival, and since this model also showed on of the best statistical fits, it was chosen as the model for the scenario based upon the ‘parametric only’ approach (i.e. extrapolations solely based upon CheckMate 577).



19.3.2 Progression-free survival

The March 2020 database lock for CheckMate 9LA had a minimum follow-up of 12.7 months for OS and 12.2 months for all other data. Piecewise approach A (combining CheckMate 9LA KM data up to 13 months with CheckMate 227 Part 1 extrapolations based on the full data set) was again used for the base case analysis, which is consistent with the modelling approach for OS. Given that PFS data is inherently more mature than OS data, the extrapolated portion of the curves will be shorter.

19.3.2.1 Proportional hazards assumptions

A Grambsch and Therneau's correlation test between Schoenfeld residuals and log of time failed to reject the proportional hazards assumption at a 5% significance level (p=0.133). The log cumulative hazards plot (Figure 83) also shows early crossover of the curves at three time points, indicating that the proportional hazards assumption cannot be rejected. However, the visual inspection of the Schoenfeld residuals plot (Figure 84) demonstrates that the proportional hazards may not hold. Therefore, both dependent and independent models were fitted for the squamous, PD-L1 negative subgroup using the CheckMate 227 data.

19.3.2.2 Nivolumab plus ipilimumab plus 2 cycles chemotherapy

19.3.2.2.1 Statistical tests

The goodness of fit statistics are presented in Table 108. Figure 85 shows the piecewise approach curves with the best statistical fit. The lognormal and generalized gamma distributions produced a conservative PFS in comparison to the spline models.

Table 108: Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to PFS data for NIVO+IPI for CheckMate 227 part 1

Independent distributions	AIC	BIC
Generalized gamma	234.56	240.05
1 spline normal	240.58	246.07
2 spline normal	241.54	248.85
1 spline odds	242.44	247.93
2 spline odds	242.98	250.29
1 spline hazard	243.38	248.87
2 spline hazard	243.47	250.79
Lognormal	248.11	251.77
Gompertz	248.18	251.84
Loglogistic	249.11	252.77
Weibull	259.92	263.58
Gamma	263.19	266.85
Exponential	265.56	267.39

AIC: Akaike information criterion; BIC: Bayesian information criterion; NIVO+IPI: nivolumab + ipilimumab; PFS: Progression-free survival

Clinical plausibility / external validation

Table 109 presents PFS at different landmark points using the five best fitting distributions taken from piecewise approach A (based on AIC/BIC) in the NIVO+IPI+PDC arm. The three best fitting distributions were the generalised gamma, 1 knot spline normal, and 2 knot spline normal.

To validate the PFS extrapolations, PFS at 5 years was predicted by deriving the conditional survival (defined as the percentage of patients in PFS at year X who will be in PFS at year Y) from years 2 to 5 from the pooled analysis of

CheckMate 017 and 057 (59.7%) and apply it to the 2-year PFS from CheckMate 227 Part 1 (20.2%). The pooled CheckMate 017 and 057 data were the longest follow-up for PFS at the time of the validation. Since the data reflect second-line IO therapy, it can be considered a conservative estimate for the first-line population evaluated in this analysis.

Using this approach, the predicted 5-year PFS was 12.9%. Both the second and third best fitting distributions were close to the 5 year predicted estimate (less than 1.5% difference). In order to be conservative, the second rank (spline on normal 1 knot) curve was chosen as it is more conservative than the generalised gamma at year 10, but still has a good fit to the CM9LA data.

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]

19.3.2.3 PDC

19.3.2.3.1 Statistical tests

The goodness of fit statistics are presented in Table 110. Figure 86 shows the piecewise curves with the best statistical fit. The long term progression free survival for the different distributions is consistent with the spline on hazards 2 knots and spline on normal 2 knots being the most optimistic curves for PDC.

Table 110: Statistical goodness-of-fit indicators (AIC/BIC) values for independent parametric models fitted to PFS data for PDC from CheckMate 227 part 1

Independent distributions	AIC	BIC
Loglogistic	219.64	223.29
2 spline hazard	220.75	228.06
1 spline odds	221.05	226.54
2 spline odds	222.46	229.77
Lognormal	222.99	226.65
2 spline normal	223.01	230.33
1 spline normal	224.81	230.30
Generalized gamma	224.95	230.44
1 spline hazard	224.98	230.46
Gamma	231.81	235.47
Gompertz	232.85	236.51
Exponential	233.40	235.23
Weibull	234.58	238.23

AIC: Akaike information criterion; BIC: Bayesian information criterion; PDC: Platinum-doublet chemotherapy; PFS: Progression-free survival

[redacted]

Clinical plausibility / external validation

[redacted] presents the PFS at different landmark points for the five best fitting distributions in the PDC arm. Given the maturity of PFS for PDC, the extrapolated curves result in only marginal differences in long-term PFS. Therefore, it was considered appropriate to select the best-fitting distribution (log-logistic) based on goodness of fit statistics in the base case analysis.

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]

19.3.2.4 Duration of treatment

Various assumptions can be made about the duration of treatment (DoT) in the economic model. In oncology models, it is often assumed that PFS can be used as a proxy for DoT. Nevertheless, patients may stop treatment before progression (e.g., due to intolerability or adverse events) or continue treatment beyond disease progression. In CheckMate 9LA both PFs and DoT were measured directly and KM curves are available for both endpoints. At least for NIVO+IPI+PDC and PDC, DOT KM data can thus be directly used to inform treatment duration in the model.

Figure 87 shows the PFS and DoT KM curves from CheckMate 9LA. The PFS KM curve for NIVO+IPI+PDC lies below the KM DoT curve, indicating that most patients continued treatment before and after disease progression. Similar to the ITT population, aA steep drop in the DoT curve can also be seen at 24 months which reflects the two-year stopping rule included in the study protocol.

Figure 88 shows that the DoT KM curve for PDC is also below the PFS KM curve. This mainly reflects that patients with SQ histology discontinue treatment following 4 cycles of PDC, but could also reflect early discontinuation due to toxicity.

[redacted]

CM: CheckMate; DoT: Duration of treatment; KM: Kaplan-Meier; PDC: Platinum-doublet chemotherapy; PFS: Progression-free survival

Due to the dynamics between PFS and DoT, the economic model thus allows users to use either PFS or DoT to inform treatment cost calculations for patients on NIVO+IPI+PDC or PDC. In the base case analysis, the model uses the DoT KM curve for NIVO+IPI+PDC to more accurately reflect treatment use in the clinical trial. For PDC, treatment costs are also modelled according to the DoT curve in the base case analysis, to reflect that PDC is discontinued after 4 cycles of treatment. Furthermore both NIVO+IPI+PDC and PDC KM curves for DoT are very close to 0 at end of follow-up. Hence it was considered appropriate to use the DoT KM curve (rather than a parametric extrapolation) for treatment cost calculations for both arms in the base case analysis. Experts stated that the best available evidence to inform treatment duration/discontinuation for NIVO+IPI+PDC and PDC is the CheckMate 9LA DoT KM curves and therefore agreed DoT KM curves should be used in the base case analysis (Bristol-Myers Squibb 2020b).

The model also has the option to model DoT on the basis of parametric curves generated from CheckMate 9LA individual patient level data .

19.3.2.5 IO treatment stopping rules

Depending on local clinical practice, different options to model the maximum treatment duration for IO therapies (NIVO+IPI) are included on the "Costs" worksheet. These are separate for each IO therapy and can be categorized as either "financial" or "medical" and include:

Financial

- **Full reimbursement:** the treatment is administered until progression or treatment discontinuation (due to AEs or other reasons) and the full cost is incurred by health care payers
- **Economic dose cap:** in this scenario, it is assumed that any patients on treatment beyond the user-defined dose cap are provided with treatment at zero cost. For NIVO+IPI, BMS is assumed to incur the treatment acquisition cost and healthcare payers are assumed to incur the administration and monitoring costs. This strategy reflects a risk sharing agreement between manufacturers and healthcare payers

Medical

- **Cap reimbursement by year:** in this scenario any patients on treatment are assumed to receive therapy up until the year selected by the user, i.e., healthcare payers do not incur any treatment costs beyond the user-defined maximum treatment duration (acquisition, monitoring, and administration). For example, if the cap is "2" years – any patients on treatment at this point in time will receive treatment for a maximum of 2 years and healthcare payers would not incur treatment costs after that point.
- **Cap reimbursement by dose:** in this scenario any patients on treatment are assumed to receive treatment until the number of doses selected by the user, i.e. healthcare payers do not incur treatment costs (acquisition, monitoring, and administration) after the selected number of doses have been administered. For example, if the dose cap for NIVO is "10" doses – any patients on treatment would have a maximum treatment duration of 20 weeks and would not incur NIVO treatment costs after that time (10 doses, 2-week periodicity). The cap by dose provides further granularity in treatment capping compared to the cap by year

It should be noted that the "medical" cap reimbursement options currently used in the base case analysis of the economic model are reflective of the CheckMate 9LA clinical trial design (as well as that of various other IO regimens). Of note, should the user want to select a different stopping rule than the 2-year treatment cap considered in the study, the model assumes there is no impact on efficacy (PFS and OS).

19.3.2.6 ITT validation of the piecewise approach A

19.3.2.6.1 External validation of OS extrapolation

19.3.2.6.1.1 Independent extrapolation models for OS

Nivolumab plus Ipilimumab plus 2 Cycles Chemotherapy

The landmark survival analysis in Table 112 shows that the most optimistic curve with the best statistical fit using only the CheckMate 9LA parameterizations, the log-logistic curve, is still underestimating the CheckMate 227 OS KM data. Furthermore when compared to the constructed OS curves, the tail would be expected to have a greater prediction of OS due to the validation curves being a conservative estimate as they are to a large extent representative of PDC data in the long term.

[redacted]

[redacted]	[redacted]	[redacted]							
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[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

The conditional OS is shown in [redacted]

[redacted]

[redacted]	[redacted]	[redacted]				
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Based on the validation exercise presented above, it is shown that the OS for NIVO+IPI+PDC is heavily underestimated using only the CheckMate 9LA parameterizations. Due to the immaturity of the CheckMate 9LA data, it is not yet possible to observe the expected long-term plateau of the OS rate that is typical of IO therapies (CheckMate 227, CheckMate 017 and CheckMate 057). Therefore, the piecewise approach was investigated for the base case.

PDC

The landmark survival analysis for PDC is presented in [redacted] and conditional survival in [redacted].

[redacted]

[redacted]	[redacted]	[redacted]							
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[redacted]

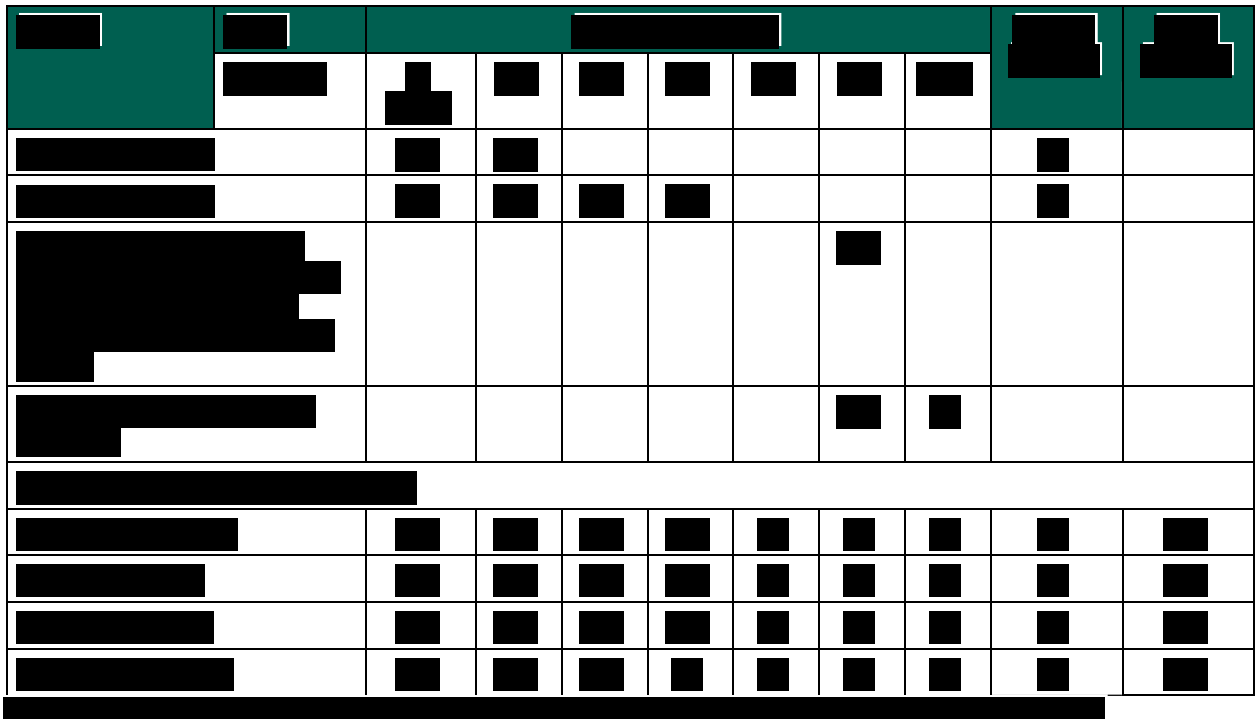
In line with NIVO+IPI+PDC the piecewise approach was investigated for PDC as well to be consistent between the intervention and comparator arms OS extrapolation methods.

19.3.2.6.2 External validation of PFS

19.3.2.6.2.1 Independent extrapolation models for PFS

External validation in [redacted] shows that the extrapolated portion of the curve is underestimating the potential for long-term progression free survival compared with CheckMate 227 because of the shorter follow-up for CheckMate 9LA and the subsequent immaturity of the data.

[redacted]

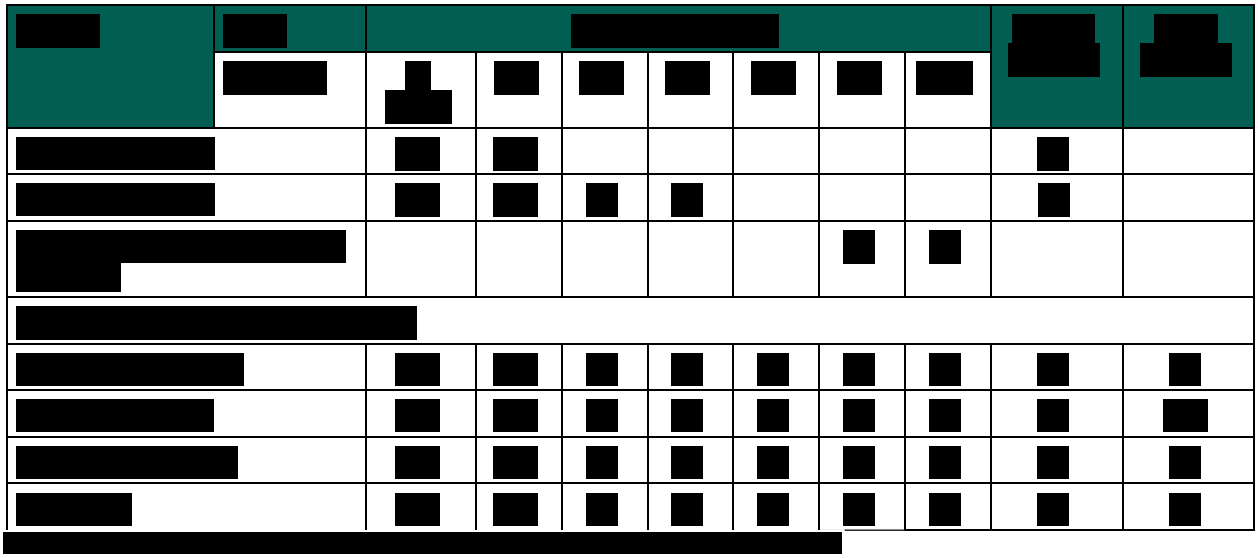


Based on the validation exercise presented above, it is shown that the PFS for NIVO+IPI+PDC is underestimated using only the CheckMate 9LA parameterizations. Therefore, the piecewise approach was investigated for the base case analysis would also be consistent with the modelling approach investigated for OS.

PDC

External validation in [redacted] shows the spline on hazards 2 knots and spline on normal 2 knots is the closest estimate to predicted CheckMate 227 long-term survival.

[redacted]



19.3.3 Smoothed hazard estimates for CheckMate 9LA and CheckMate 227 part 1

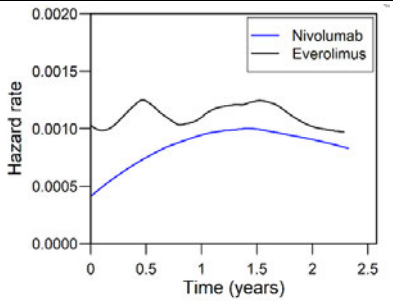
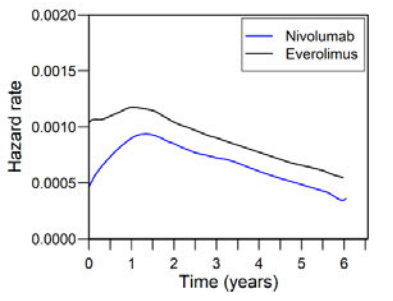
The below figure (Figure 89) includes an overview of the hazard over time for a number of nivolumab studies including CheckMate 9LA and CheckMate 227 in 1st line NSCLC. These smoothed hazard estimates comes from different sources which is why the methodology varies.

As outlined above the hazard in 9LA increases up until the time point of minimum follow-up (around 13 months). Hence, the decrease in hazard seen after that minimum follow-up get little weight in extrapolations based solely on 9LA.

The smoothed hazard from CheckMate 227, clearly shows that the long term hazard of treatment with Nivo+ipi in 1st line NSCLC goes down over time. Similar is seen for nivo in 2nd line NSCLC, as observed in CheckMate 017 and CheckMate 057. The smoothed hazard from 057 clearly shows the issue of fitting extrapolations to immature data that has not yet captured the long term decrease in hazard. The data on smoothed hazard from nivolumab in 2nd line renal cell carcinoma, which was presented part of a recent study on survival extrapolations within immuno oncology, show the same long term decrease, and that this was not apparent from the initial short term data.

Figure 89: Smoothed hazard over time in a number of CheckMate trials of nivolumab

[redacted]

CheckMate 025 **Treatment:** Nivo **Indication:** 2st line advanced renal cell carcinoma **Estimation:** muhaz function in R **Source:** Presented as supplementary material (file 1) in recently published study by klijn et al. (2021)		

20. Appendix H Literature search for HRQoL data

Objective of the literature search

Identifying data of HRQoL of NSCLC treatment, including IOs, was part of the objective of the core efficacy and safety SLR, as presented in Section 13 in the Appendix O Systematic literature review report. For a comprehensive description of the SLR, please see the attached SLR document in Appendix A Literature search for efficacy and safety of intervention and comparator(s) (Bristol-Myers Squibb 2020f). For information specific to HRQoL data availability, please see Section 5.10 in the separate document Appendix O Systematic literature review report (Bristol-Myers Squibb 2020f).

Overall, A total of 20 studies reported HRQoL data, with most commonly used ones including LCSS, FACT, and EORTC-QLQ. Among IO RCTs, EORTC QLQ-C30 and EORTC QLQ-LC13 were used in KEYNOTE trials, IMpower 150, and MYSTIC. EQ-5D/EQ-5D-3L was used in 4 studies, i.e. CheckMate 227, KEYNOTE 024, SQUIRE, and ERACLE.

Search strategy

For descriptions of the search strategy and string, please see Section 4.2 and Section 8.1 in Appendix O Systematic literature review report. For key eligibility criteria, please see Section 4.1 in the Appendix A Literature search for efficacy and safety of intervention and comparator(s) (Bristol-Myers Squibb 2020f).

Six IO RCTs reported health-related quality of life (HRQoL) data, i.e. KEYNOTE 024, 189 and 407, IMpower 150, CheckMate 227 and MYSTIC. Overall, a significant improvement in the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) global health status (GHS)/QoL score was observed between pembrolizumab and PDC group in the KEYNOTE trials. In contrast, no clinically meaningful worsening of EORTC QLQ-C30 or Quality of Life Questionnaire-Lung Cancer Module 13 (QLQ-LC13) was identified in the atezolizumab arms compared to bevacizumab combination PDC. In MYSTIC, a significant reduction in some symptoms was observed over 12 months post-baseline in the durvalumab arms compared to the PDC arm. Finally in CheckMate 227, clinically meaningful improvements in the Lung Cancer Symptom Scale (LCSS) average symptom burden index (ASBI) and LCSS three-item global index (3-IGI) at week 12 were observed in the NIVO+IPI arm compared to the PDC arm in a population with high tumor mutation burden (TMB).

Results from the HRQoL SRL results, are presented in Section 5.10 in the Appendix O Systematic literature review report, as well as during the Executive summary in Section 1 in the Appendix A Literature search for efficacy and safety of intervention and comparator(s).

For a comperhensive overview of the SLR, please see the attached SLR document in in the separate document Appendix O Systematic literature review report (Bristol-Myers Squibb 2020f).

Quality assessment and generalizibility of estimates

The different available measurement and time trade off tools used for the HRQoL affect the generalizability and transferability of results.

21. Appendix I Mapping of HRQoL data

HRQoL data was derived from the individual trials. Although EQ-5D-5L was not a requirement from the DMC for this submission, the EQ-5D-5L value set (Jensen 2021) was applied to the EQ-5D-3L responses by the means of a validated mapping method (van Hout 2021). The mapping was done according to the preferred method which was an ordinal logistic regression that disregarded age and gender and accounted for unobserved heterogeneity using a latent factor.

22. Appendix J Probabilistic sensitivity analyses

The objective of the PSA is to assess the variation in model results stemming from uncertainty in each individual parameter used in the model. To conduct a PSA, probabilistic distributions are assigned to each input in the model and used to randomly select new plausible values. Each new sampled value is applied in the model, with the results of the model under each new value being recorded. This process is then repeated for a large number of iterations. The series of results recorded in the PSA can be used to quantify the overall variation in results.

The key parameters in the PSA included:

- Clinical data
- Cost data
- Utility data

A summary of the distributions applied in the PSA is provided in Table 118. The distributions selected follow the recommendations by Briggs (2006). The complete PSA can be found in sheet the CUA Excel file “HE model for NIVO+IPI+2cycles PDC in SQ negative 1L NSCLC_v5.0” and sheet “Model parameters”.

Table 118 : Summary of probabilistic distributions applied in the PSA

Parameter cluster	Parameters	Distribution
Clinical data	Survival distribution parameters for PFS and OS	Multivariate normal distribution, with correlation between shape, and scale parameter
Cost data	Disease management costs – PF, PD Acquisition cost Administration cost Monitoring cost AE cost Other costs	Gamma distribution*
Utility data	Utility weights assigned to PF and PD states Disutility of AE’s	Beta distribution* Gamma distribution*

AE: Adverse event; DoT: Duration of treatment; OS: Overall survival; PD: Progressed disease; PF: Progression-free; PFS: Progression free survival; PSA: Probabilistic sensitivity analysis;
*For each variable the deterministic value and the standard error (SE) were used to generate the alpha and beta values to construct the gamma and beta distributions in Microsoft Excel (Office 365).

23. Appendix L Baseline characteristics and study design CheckMate 227

CheckMate 227 Part 1

CheckMate 227 is a phase III trial that examined PFS with NIVO+IPI versus PDC among patients with untreated, advanced NSCLC Table 119. CheckMate 9LA and 227 Part 1 have very similar study designs. Thus, CheckMate 227 Part 1 could be used to validate or inform the long-term extrapolations of CheckMate 9LA.

The key population for this trial included patients with Stage IV or recurrent NSCLC, with no prior systemic therapy, no known sensitizing *EGFR/ALK* alterations, and an ECOG PS of 0 or 1.

Table 119: Design of the CheckMate 227 study

CheckMate 227 Study aspect	Description
Trial	CheckMate 227
Phase	Phase III
Efficacy measures	Primary: OS in patients whose tumors express PD-L1 ≥1%, and PFS in patients with high TMB (≥10 mut/Mb) across the PD-L1 spectrum Secondary: PFS with nivolumab monotherapy versus chemotherapy, OS with NIVO+IPI versus chemotherapy
Intervention	Nivolumab 3 mg/kg Q2W plus ipilimumab 1 mg/kg Q6W
Comparator	Pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 Q3W for up to four cycles, followed by pemetrexed maintenance therapy Gemcitabine 1000 mg/m^2 plus cisplatin 75 mg/m^2 Q3W for up to four cycles
Population	Adult patients with Stage IV or recurrent NSCLC, with no prior systemic therapy, no known sensitizing EGFR/ALK alterations, and an ECOG PS 0-1
Use for the economic models	Key patient level data for CheckMate 227 Part 1 to be used in the economic model

ALK: Anaplastic lymphoma kinase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: Epidermal growth factor receptor; Kg: Kilogram; m: meter; mut/Mb: Mutations per megabase; mg: Milligram; NIVO+IPI: nivolumab +ipilimumab; NSCLC: Non-small cell lung cancer; OS: Overall survival; PD-L1: Programmed cell death ligand 1; PFS: Progression-free survival; Q2W/Q3W: Every 2 weeks/Every 3 weeks; TMB: Tumor mutational burden;

Table 120 provides an overview of the key characteristics of patients enrolled in Part 1 of the CheckMate 227 trial (Bristol-Myers Squibb 2019).

Table 120: Baseline characteristics in all patients randomised to nivolumab and ipilimumab, chemotherapy, or nivolumab in CheckMate 227

	All randomised (PD-L1 <1% + PD-L1 ≥ 1%)	
	NIVO+IPI (n=583)	**PDC (n=583)**
Median age, years (range)	64 (26 – 87)	64 (29 – 87)
Female, %	33	34
ECOG PS,% 0 / 1	35 / 65	33 / 66
Smoking status, % (Current +former/Never)	85/14	86/13
Histology, % (Squamous / non-squamous)	28 / 72	28 / 72
Metastases, % (Bone/Liver/CNS)	28/21/11	26/22/9
Tumour PD-L1 expression, %		
<1%	32	32
≥1%	68	68
1 – 49%	33	35
≥50%	35	33
Tissue TMB, %		
Evaluable	57	59
≥10 mut/Mb	42	46
<10 mut/Mb	58	54

Abbreviations: CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance-status; mut/Mb, mutations per megabase PD-L1, programmed death-ligand 1; TMB, tumour mutational burden

In Part 1 of CheckMate 227, subjects were first assessed for PD-L1 expression, using a 1% cut-off, and categorized into 2 separate groups. Patients who had PD-L1 expression in 1% or more of tumor cells were enrolled in Part 1a of the trial, and those with a PD-L1 expression level of less than 1% were enrolled in Part 1b. Subjects within each group were stratified by histology (SQ vs. NSQ). A number of treatment arms have been included in the trial (Arms A through G), however for the purpose of the economic evaluation described herein, the treatment arms of interest are B+D for NIVO+IPI and C+F for PDC.

Subjects with PD-L1 ≥1% NSCLC (Part 1a)

- Arm B: nivolumab 3 mg/kg IV over 30 minutes Q2W + ipilimumab 1 mg/kg IV over 30 minutes every 6 weeks (Q6W) given for up to 24 months in the absence of disease progression or unacceptable toxicity. Treatment beyond initial investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST) 1.1-defined progression was permitted if the subject had investigator assessed clinical benefit and was tolerating nivolumab plus ipilimumab.
- Arm C: histology-based PDC IV in 3-week cycles for a maximum of 4 cycles or until disease progression or unacceptable toxicity (whichever came first). For subjects with NSQ histology, pemetrexed maintenance was allowed until disease progression or unacceptable toxicity after 4 cycles of chemotherapy

Subjects with PD-L1 negative (<1%) NSCLC (Part 1b)

- Arm D: nivolumab 3 mg/kg IV over 30 minutes Q2W + ipilimumab 1 mg/kg IV over 30 minutes Q6W given for up to 24 months in the absence of disease progression or unacceptable toxicity. Treatment beyond initial

investigator-assessed RECIST 1.1-defined progression was permitted if the subject had investigator assessed clinical benefit and was tolerating NIVO+IPI.

- Arm F: histology-based PDC IV in 3-week cycles for a maximum of 4 cycles or until disease progression or unacceptable toxicity (whichever comes first). For subjects with NSQ histology, pemetrexed maintenance was allowed until disease progression or unacceptable toxicity after 4 cycles of chemotherapy.

Similarities and differences between CheckMate 9LA and CheckMate 227 Part 1

Given the immaturity of CheckMate 9LA, CheckMate 227 can be considered the best available evidence available to validate or estimate long-term outcome for 1L NSCLC patients treated with NIVO+IPI. To highlight the value of CheckMate 227 part 1 as an external data source, a comparison with CheckMate 9LA is presented. The trials are comparable in terms of their design, clinical setting (1L NSCLC), patient baseline characteristics, stratification factors, and disease progression and survival (PFS and OS) outcomes.

Both studies recruited subjects with treatment-naïve stage IV or recurrent NSCLC. As shown in Table 121, the patient population in both studies were very similar in terms of key baseline characteristics (e.g. age, gender, smoking status, ECOG performance status, histology and PD-L1 expression mix).

The treatment regimens administered in both studies were also largely similar, albeit there were a number of differences. A comparison of the CheckMate 227 and CheckMate 9LA treatment regimens is presented in Table 122. Patients in the intervention arm of CheckMate 9LA were treated with 360 mg NIVO every three weeks (Q3W), whereas patients in CheckMate 227 received a dose of 3 mg NIVO per kilogram body weight every 2 weeks (Q2W). There were also minor differences in what constituted PDC between the two studies. In addition to platinum, for example, patients with SQ disease received gemcitabine and paclitaxel in CheckMate 227 and 9LA, respectively. The most marked difference in treatment regimens between the two trials, however, was the addition of 2 cycles of PDC to NIVO+IPI in the CheckMate 9LA study. This addition of 2 cycles of PDC did not lead to higher treatment discontinuation or a lower exposure to IO therapy. [redacted]

Given the similarities, it can be expected that the long-term clinical outcomes of both studies would be comparable. This assumption was also validated through the virtual advisory board.(Bristol-Myers Squibb 2020b) Also, overlays of available OS (Figure 91) and PFS KM curves (Figure 92 and Figure 93) from CheckMate 9LA and CheckMate 227 part 1 indeed reveal very similar trajectories. The addition of two cycles of PDC did not affect exposure to IO treatment and the longer time survival benefit for dual IO therapy was still observed. Small variation in PD-L1 status at baseline does not seem to have an effect, since PD-L1 status is not an effect modifier in CheckMate 9LA (nivo+ipi+PDC vs PDC unstratified OS HRs similar between the PD-L1 subgroups; PD-L1 < 1%: 0.62, PD-L1 ≥ 1%: 0.64, PD-L1 1–49%: 0.61, PD-L1 ≥ 50%: 0.66) (Reck 2020b).

Table 121: Patient baseline characteristics for CheckMate 227 Part 1 and CheckMate 9LA

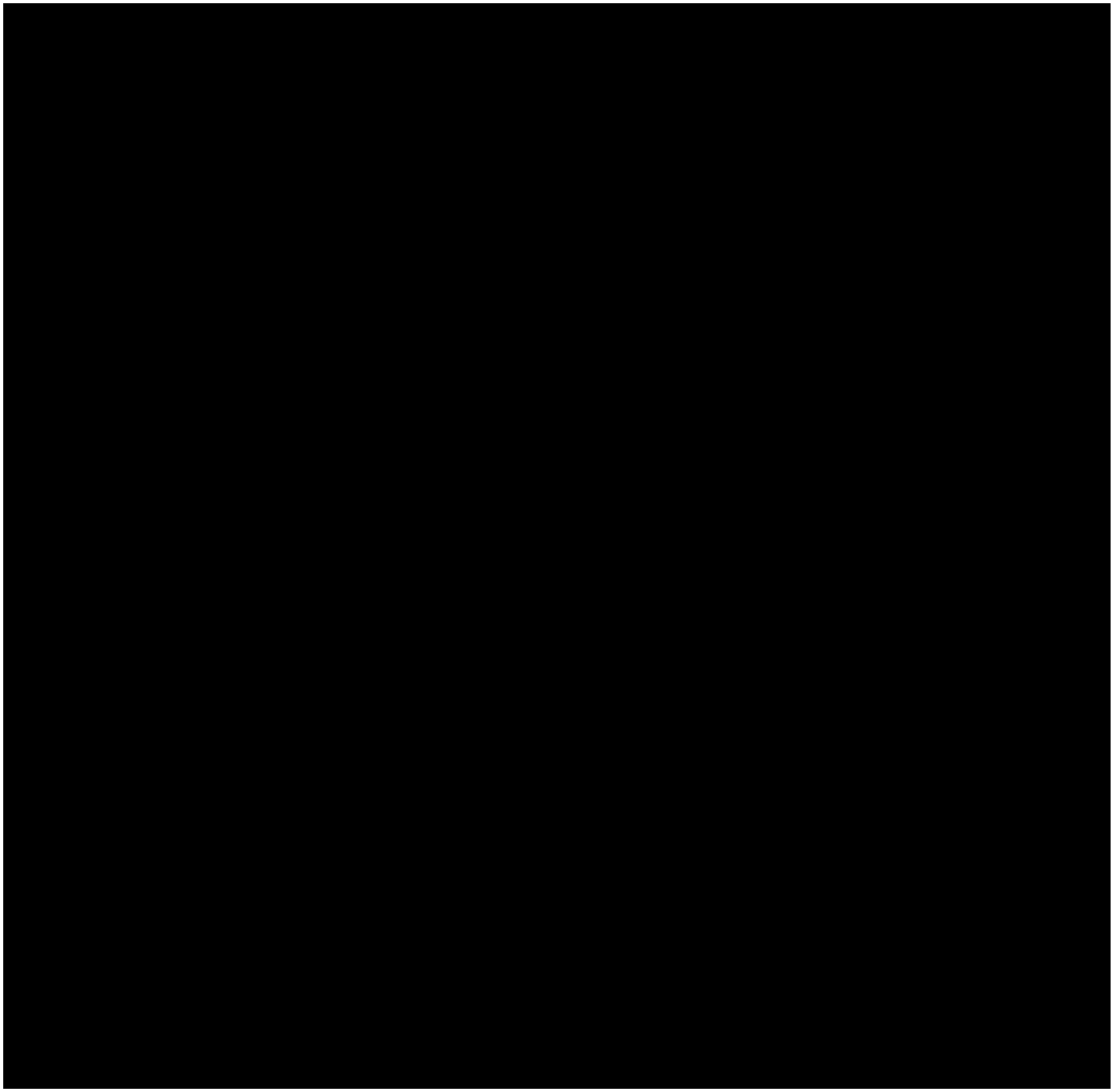
Characteristics	CheckMate 227 Part 1		CheckMate 9LA	
Treatment arm	NIVO+IPI (N = 583)	PDC (N = 583)	NIVO+IPI+PDC (N = 361)	PDC (N = 358)
Median age, years	64.0	64.0	65.0	65.0
< 65, %	52.5	52.3	48.8	49.7
≥ 75, %	9.9	9.4	10.2	9.2
Gender, % male	67.4	66.0	69.8	70.4
Smoking Status, %				
Current/former	85.2	85.6	87.3	85.2
Never smoked	13.6	13.4	12.7	14.8
ECOG PS, %				
0	35.0	32.8	31.3	31.3
1	64.7	66.2	68.4	68.4
Tumor histologic type, %				
Squamous	28.1	28.1	31.3	31.0
Non-squamous	71.9	71.9	68.7	69.0
PD-L1 expression level, %				
<1%	32.1	31.9	37.4	36.0
≥1%	67.9	68.1	56.2	57.0
*** Based on CheckMate 227 CSR (July 2019 data lock) (Bristol-Myers Squibb 2019)– Part 1a and Part 1b (arms B+D for NIVO+IPI, arms C+F for PDC)**				
**** Based on CheckMate 9LA CSR 12 months DBL (Bristol-Myers Squibb 2020e)– All-comers**				

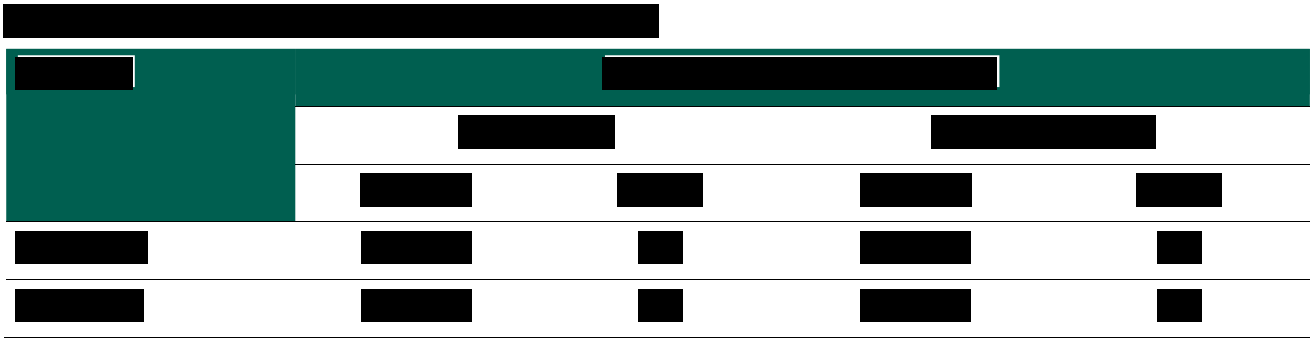
CM: CheckMate; CSR: Clinical study report; DBL: Database lock; ECOG PS: Eastern cooperative oncology group performance status; NIVO+IPI: Nivolumab + ipilimumab; NIVO+IPI+PDC : Nivolumab + ipilimumab combined with limited chemotherapy; PD-L1: Programmed cell death-ligand 1

Table 122: Treatment regimens for CheckMate 227 Part 1 and CheckMate 9LA

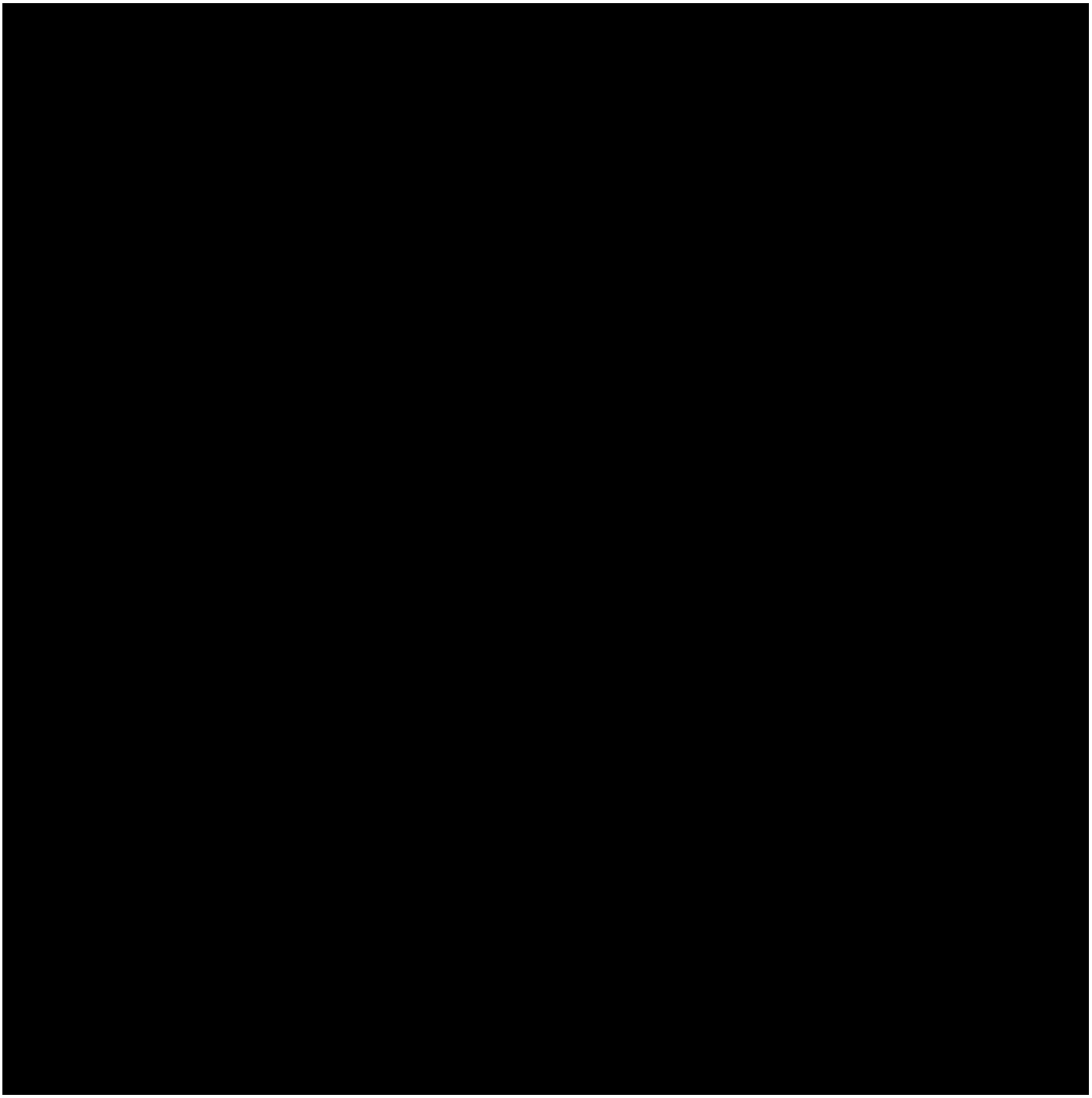
	CheckMate 227 Part 1	CheckMate 9LA
Intervention treatment	Nivolumab 3 mg/kg IV Q2W + Ipilimumab 1 mg/kg Q6W a	Nivolumab 360 mg Q3W + Ipilimumab 1 mg/kg Q6W + 2 cycles PDC (by histology)
		PDC for SQ: – Carboplatin AUC 6 + paclitaxel 200 mg/m^2 or 175 mg/m^2 [b]
		PDC for NSQ: – Carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2 – Cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2
Continuation of intervention treatment	Arms B and D, Treatment continue for up to 24 months or; – until disease progression – unacceptable toxicity	After 2 cycles PDC, Nivolumab and Ipilimumab continue for up to 24 months or; – until disease progression – unacceptable toxicity – other reasons specified in the protocol
Comparator treatment	PDC Q3W for maximum 4 cycles[a] (by histology)	PDC Q3W for maximum 4 cycles (by histology)
	SQ: – Carboplatin AUC 5 + gemcitabine 1000 mg/m^2 [c] – Cisplatin 75 mg/m2 + gemcitabine 1000 or 1250mg/m^2 [c]	SQ: – Carboplatin AUC 6 + paclitaxel 200 mg/m^2 or 175 mg/m^2 [b]
	NSQ: – Carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2 [c] – Cisplatin 75 mg/m2 + pemetrexed 500 mg/m^2 [c]	NSQ: – Carboplatin AUC 5 or 6 + pemetrexed 500 mg/m^2 – Cisplatin 75 mg/m^2 + pemetrexed 500 mg/m^2
Continuation of comparator treatment	After 4 cycles, NSQ: pemetrexed 500mg/m^2 Q3W maintenance therapy until; – disease progression, or – unacceptable toxicity	After 4 cycles, NSQ: pemetrexed 500mg/m^2 Q3W maintenance therapy until; – disease progression – unacceptable toxicity
[a] **Treatment the same for both arms B and D** [b] **As per local institutional practice** [c] **Treatment the same for both arms C and F**		

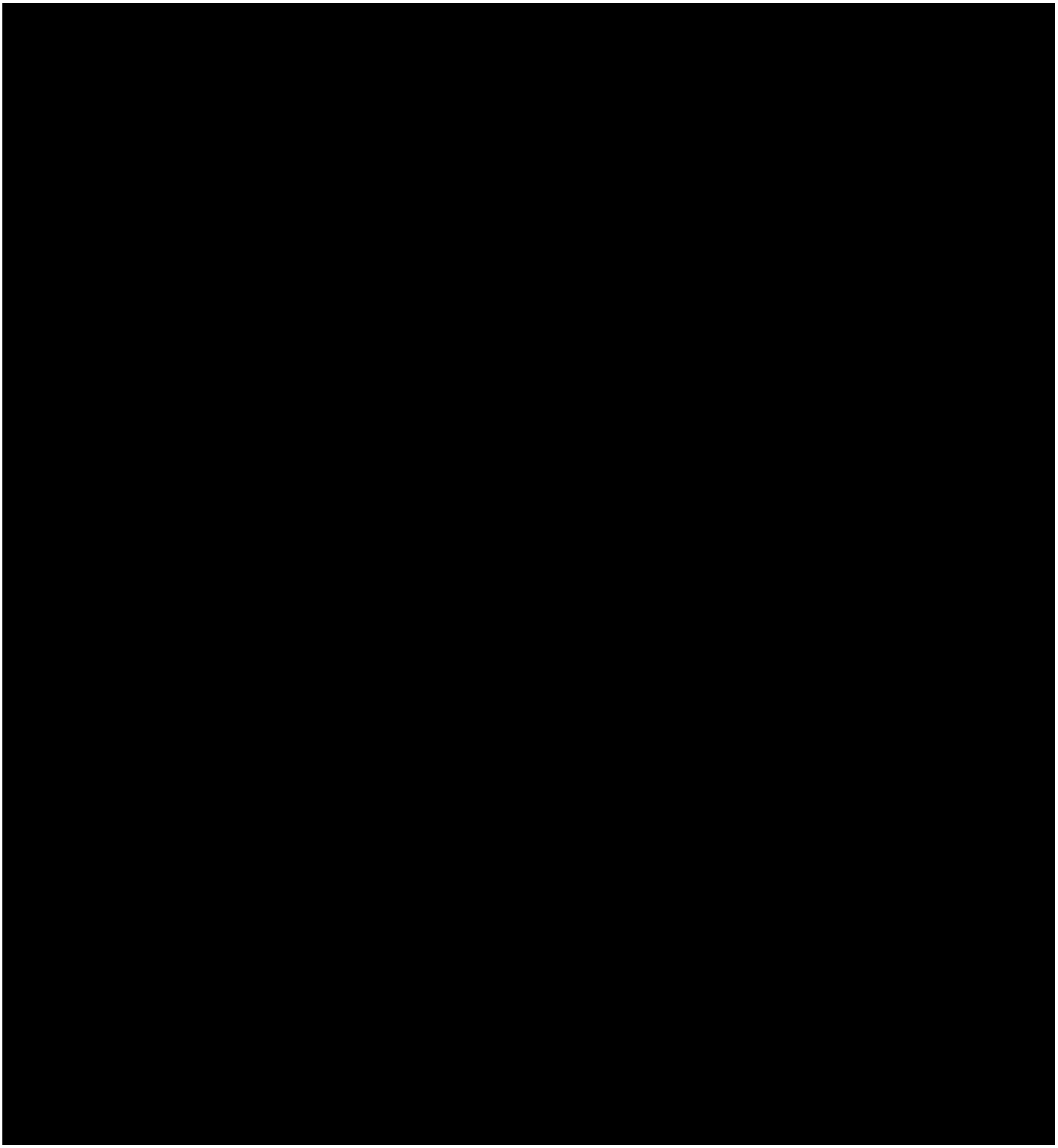
AUC: Area under the concentration-time curve; CM: CheckMate; IV: Intravenous; kg: Kilogram; m: meter; mg: Milligram; NSQ: Non-squamous; PDC: Platinum-doublet chemotherapy; Q2W: Every two weeks; Q3W: Every three weeks; SQ: Squamous;

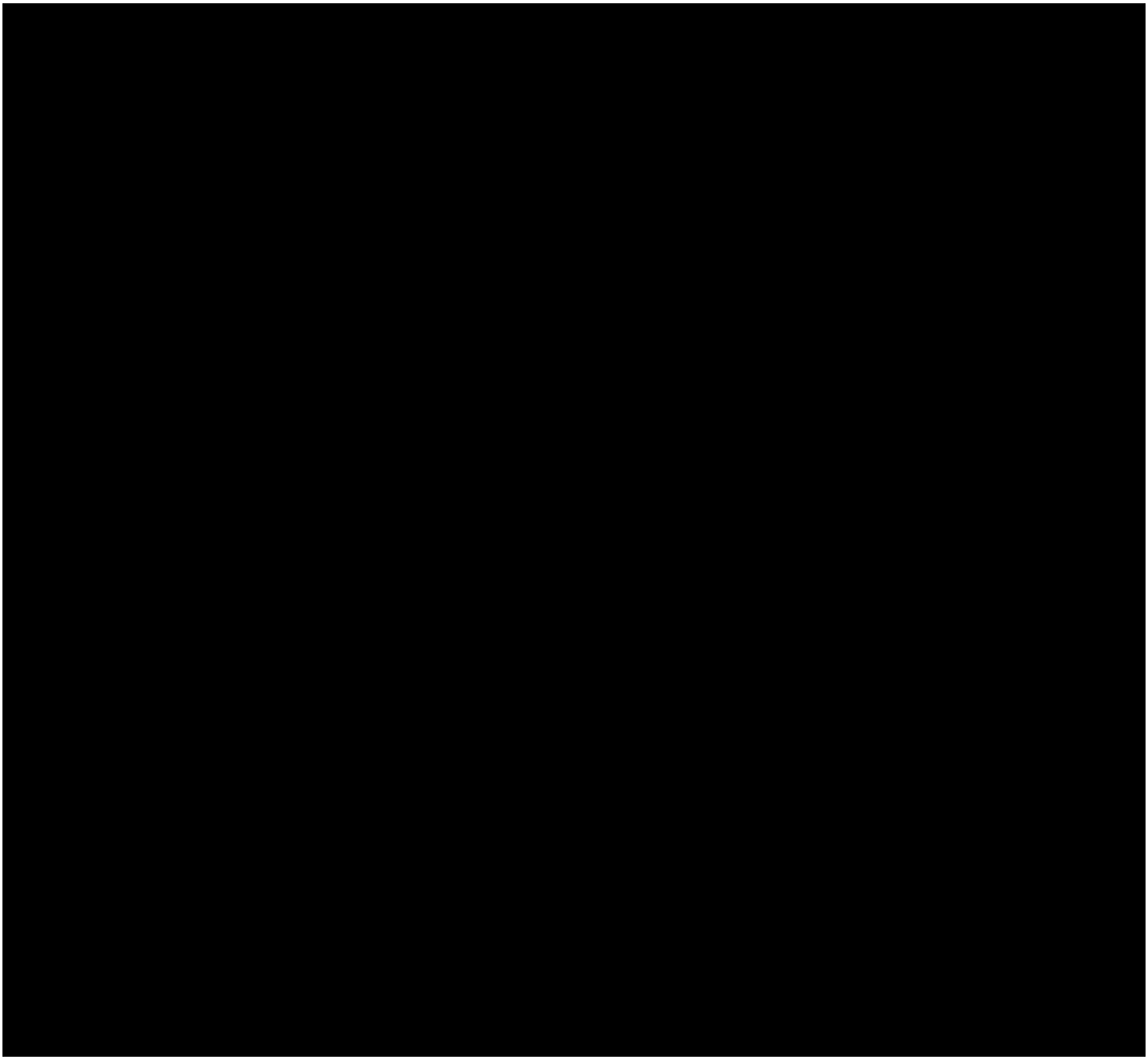




2Y DBL: 2-year database lock; 4Y DBL: 4-year database lock; CM: CheckMate; DoT: Duration of treatment; SE: Standard error







24. Appendix M Ongoing studies for the intervention

This submission focuses on NIVO+IPI+PDC for the first-line treatment of patients with metastatic NSCLC. The efficacy and safety data are mainly based on the phase 3 trial, Checkmate 9LA. In addition, supporting evidence from other clinical trials involving patients with metastatic NSCLC and treated with NIVO+IPI+PDC is also included when relevant (e.g., CheckMate 227 and 568).

Table 124: Ongoing studies of nivolumab-based therapy in NSCLC

Title of the study and RCT	Objective of the study	Intervention	Comparator	End-points	Start date	Expected end date
CheckMate 227 **Part 1 completed** **DBL 24 January 2018; 15 March 2018 for descriptive OS** **Part 2 ongoing**	To show that NIVO, NIVO+IPI, or NIVO+PDC improves PFS or OS compared with PDC in patients with advanced lung cancer	Part 2 NIVO 360 mg + PDC Q3W, up to 4 doses, followed by NIVO 360 mg Q3W +/ pemetrexed maintenance	Part 2: PDC in 3-week cycles for a maximum of 4 cycles +/- pemetrexed maintenance	Part 2 Primary: OS NIVO+PDC vs. PDC; Secondary: PFS, ORR, efficacy by PD-L1	August 2015	Estimated Primary Completion Date: January 2019 Estimated Study Completion Date: December 2020
CheckMate 568 **Part 1 completed** **DBL 25 August 2017** **Part 2 ongoing**	Part 1 Determine the ORR in stage IV NSCLC subjects treated with NIVO+IPI as first-line therapy Part 2 Determine the safety and tolerability of NIVO+IPI+PDC in first-line stage IV NSCLC	Part 1 NIVO+IPI (regardless of PD-L1 expression) Part 2 NIVO+IPI+PDC (regardless of PD-L1 expression)	N/A	Part 1 Primary: ORR in subjects with PDL1 ≥1%; ORR in subjects with PD-L1 <1% Part 2 Primary: DLT within 9 weeks; after first dose, safety and tolerability	10 February 2016	Estimated Primary Completion Date: 9 June 2019 Estimated Study Completion Date: 24 January 2022
CheckMate 012 (completed)	Evaluating the safety and tolerability of NIVO combined with three chemotherapy regimens (cisplatin/ gemcitabine; cisplatin/	Cohorts with various regimens of NIVO+IPI (Cohorts G-J, N-Q) Cohort P: NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q12W	N/A	Primary: safety and tolerability Secondary: ORR and PFS rate at 24 weeks (Cohorts P and Q were based on IRRC assessment)	9 December 2011	Actual Primary Completion Date: 20 July 2016 Estimated Study Completion Date:

	pemetrexed; and carboplatin/ paclitaxel) in subjects with NSCLC	Cohort Q: NIVO 3 mg/kg Q2W + IPI 1 mg/kg Q6W				29 December 2018
CheckMate 817	Evaluate the safety of NIVO+IPI in patients with advanced (stage 4 or recurrent) NSCLC	NIVO 240 mg + IPI 1 mg/kg Q6W	N/A	Primary: safety (Cohort A), ORR in high TMB (Cohort C)	14 September 2016	Estimated Primary Completion Date: 16 June 2020 Estimated Study Completion Date: 17 November 2021
CheckMate 026	Show that NIVI will improve PFS in subjects with strong stage IV or recurrent PD-L1+ NSCLC compared to PDC	NIVO	Investigator's choice of NIVO+IPI+PDC +/-pemetrexed maintenance	Primary: PFS in PD-L1 >5%	25 March 2014	Actual Primary Completion Date: 1 July 2016 Estimated Study Completion Date: 1 October 2018

Reference: (https://clinicaltrials.gov/)

25. Appendix O Systematic literature review report

Please see separate document “Appendix O Systematic literature review of 1st line therapy for advanced non-small cell lung cancer (NSCLC)”

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26. Appendix P Bucher ITC across histology and PD-L1 expression levels

Please see separate document " Appendix P Bucher ITC across histology and PD-L1 expression levels".

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27. Appendix Q CHECKMATE 9LA EQ-5D UTILITIES ANALYSIS RESULTS

Please see separate document " Appendix Q - CHECKMATE 9LA EQ-5D UTILITIES ANALYSIS RESULTS".

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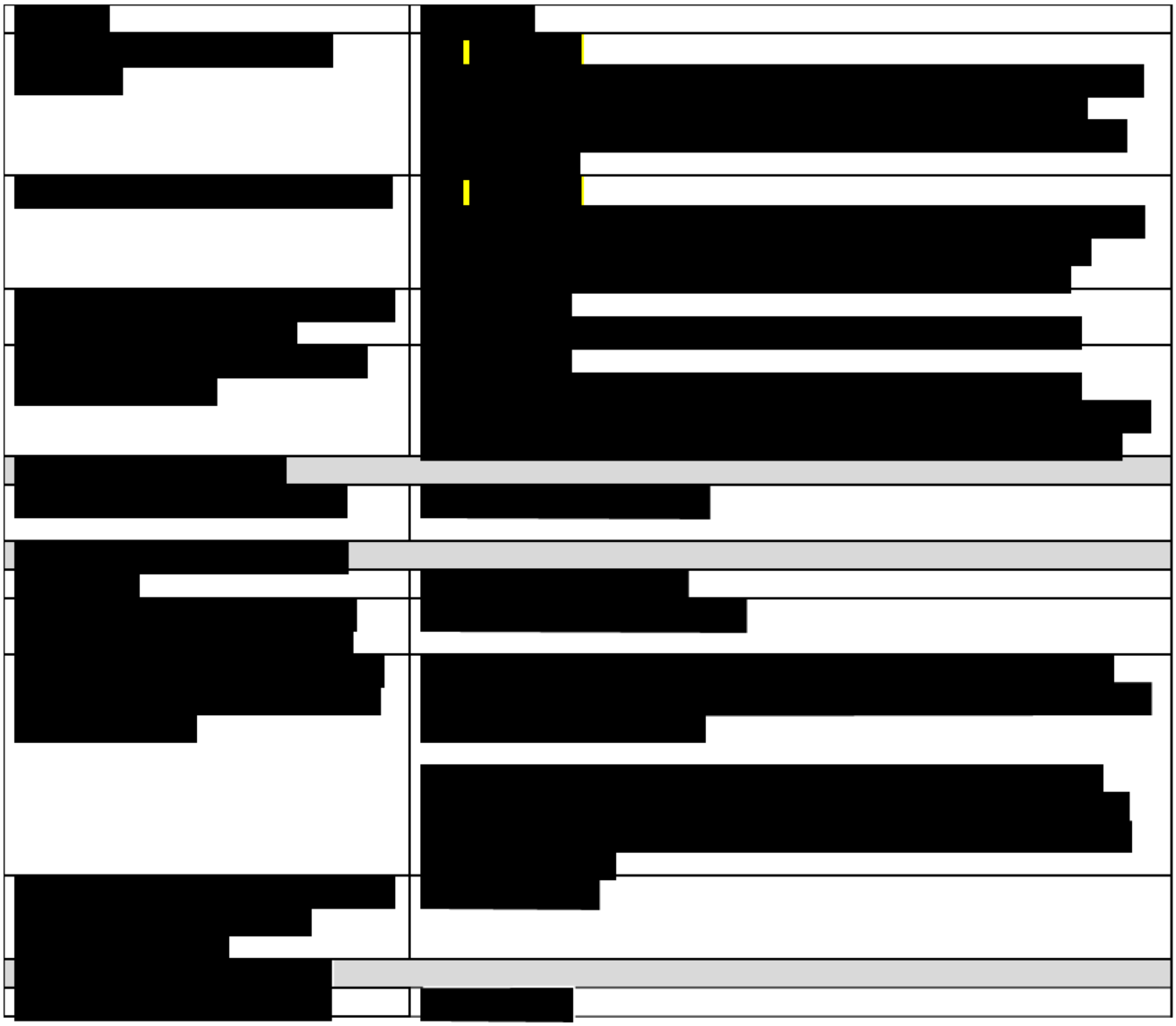

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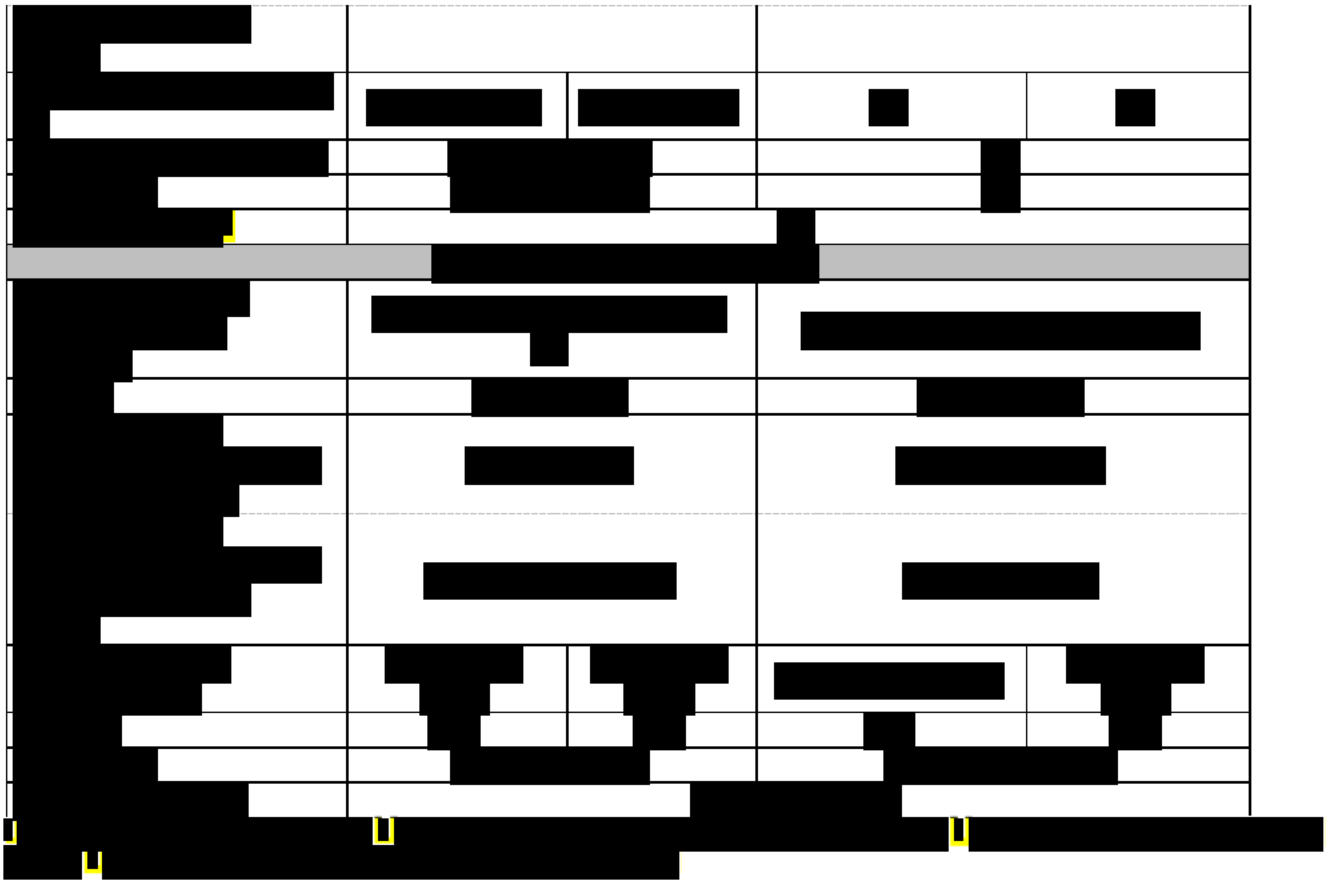

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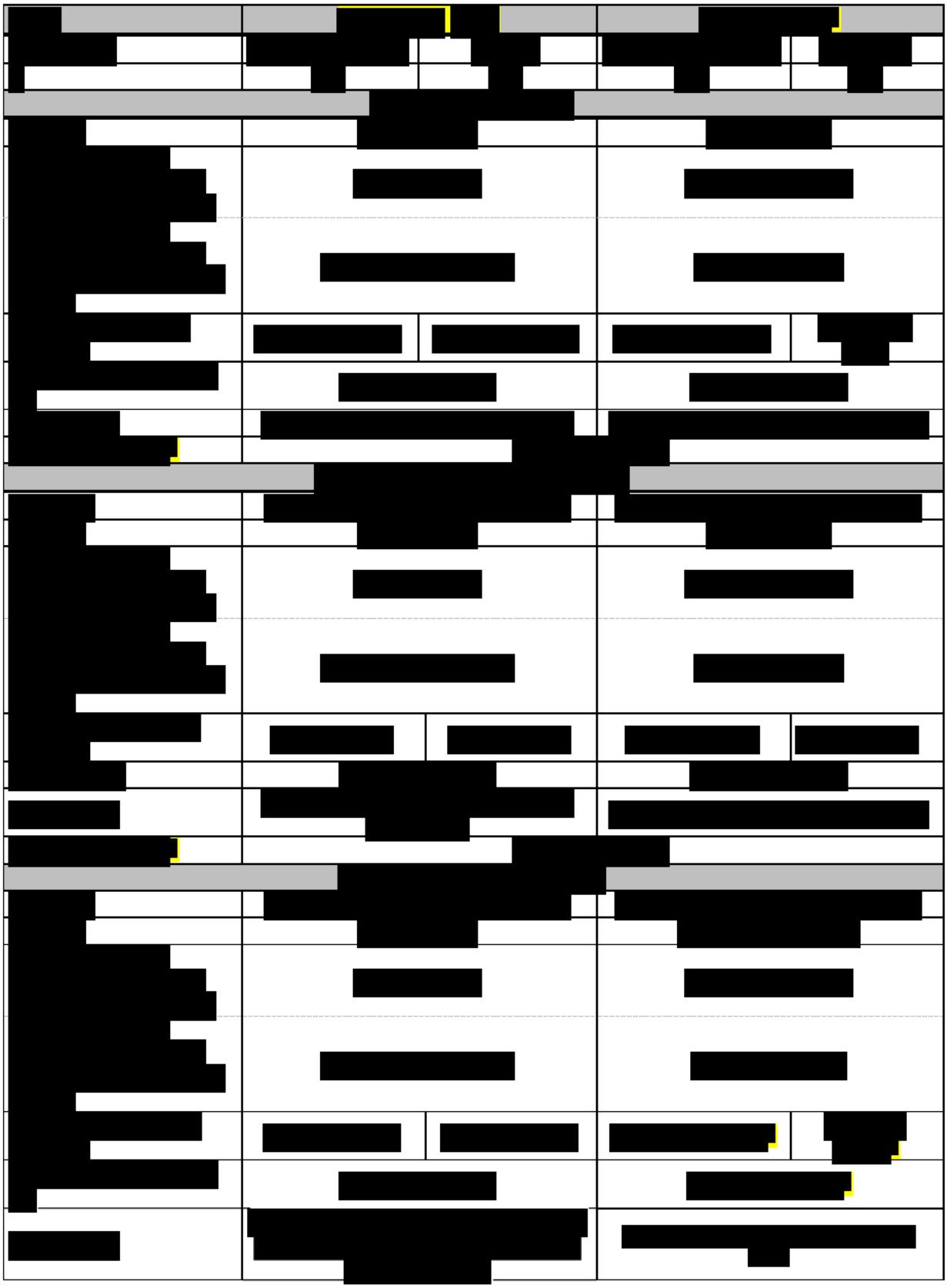

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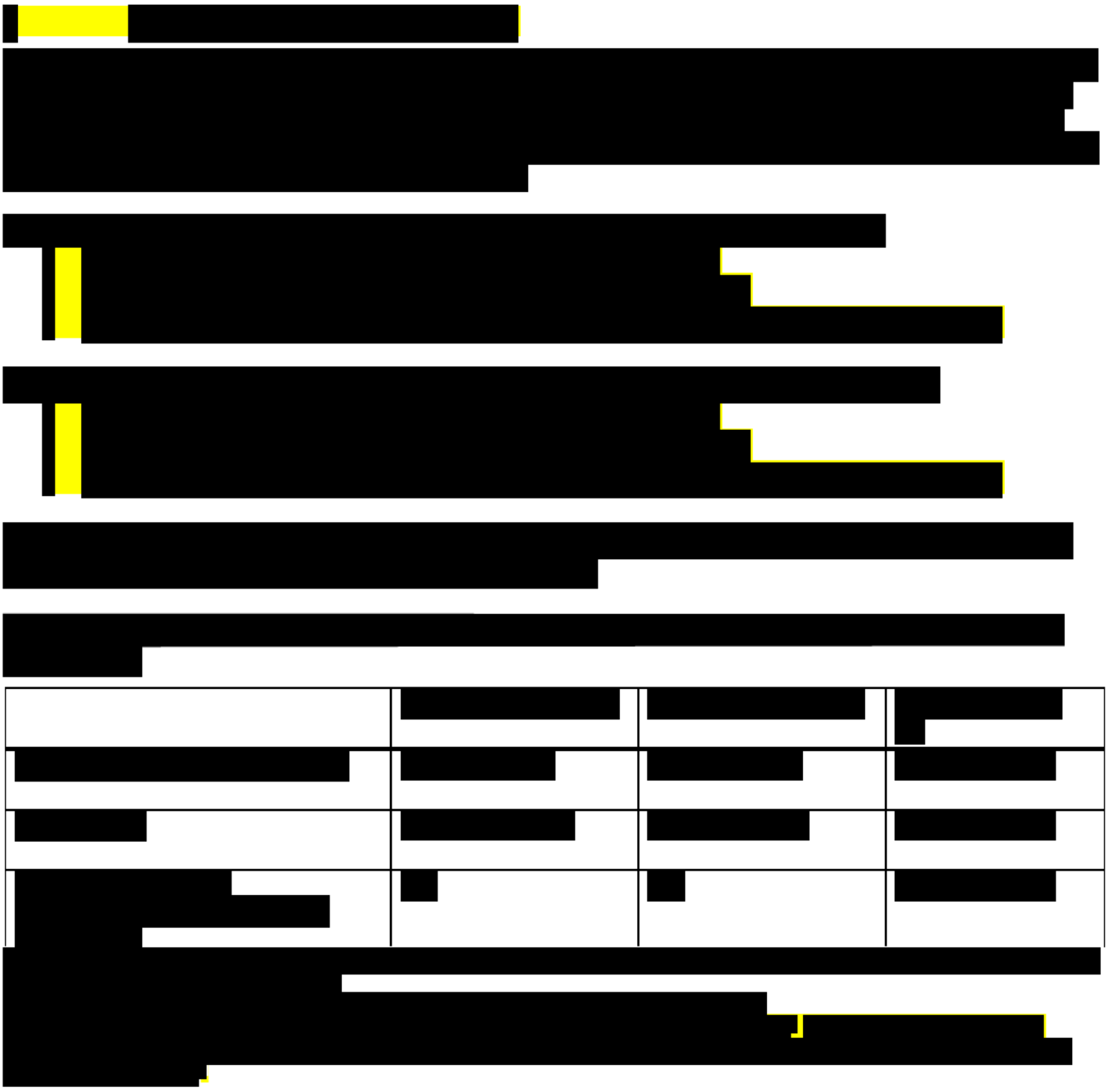

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[redacted] *kMate 9LA data source: Paz-Ares 2021 Supplemental Table S12; percentages also reported by Reck et al. ASCO 2020.*[6]

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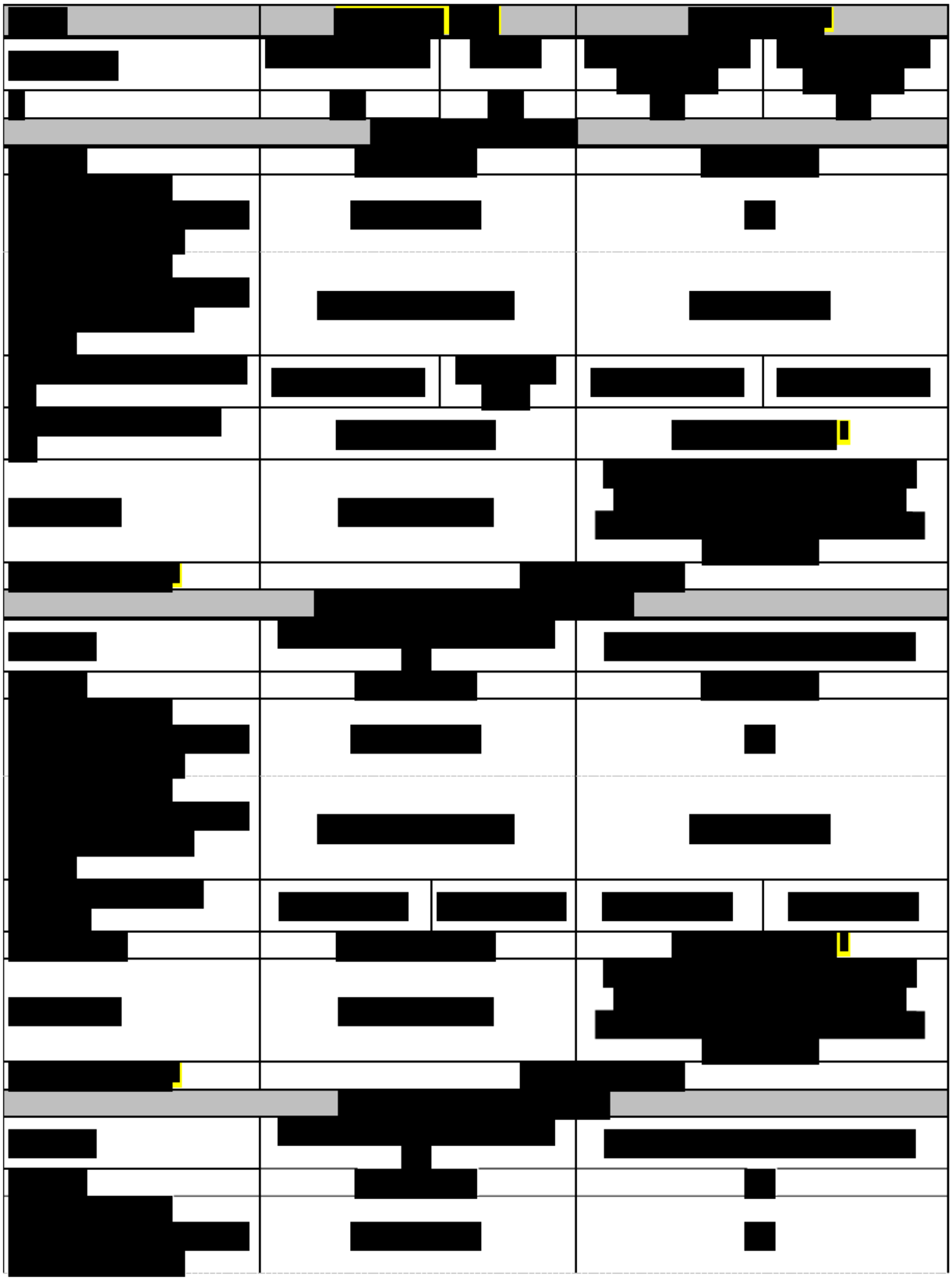

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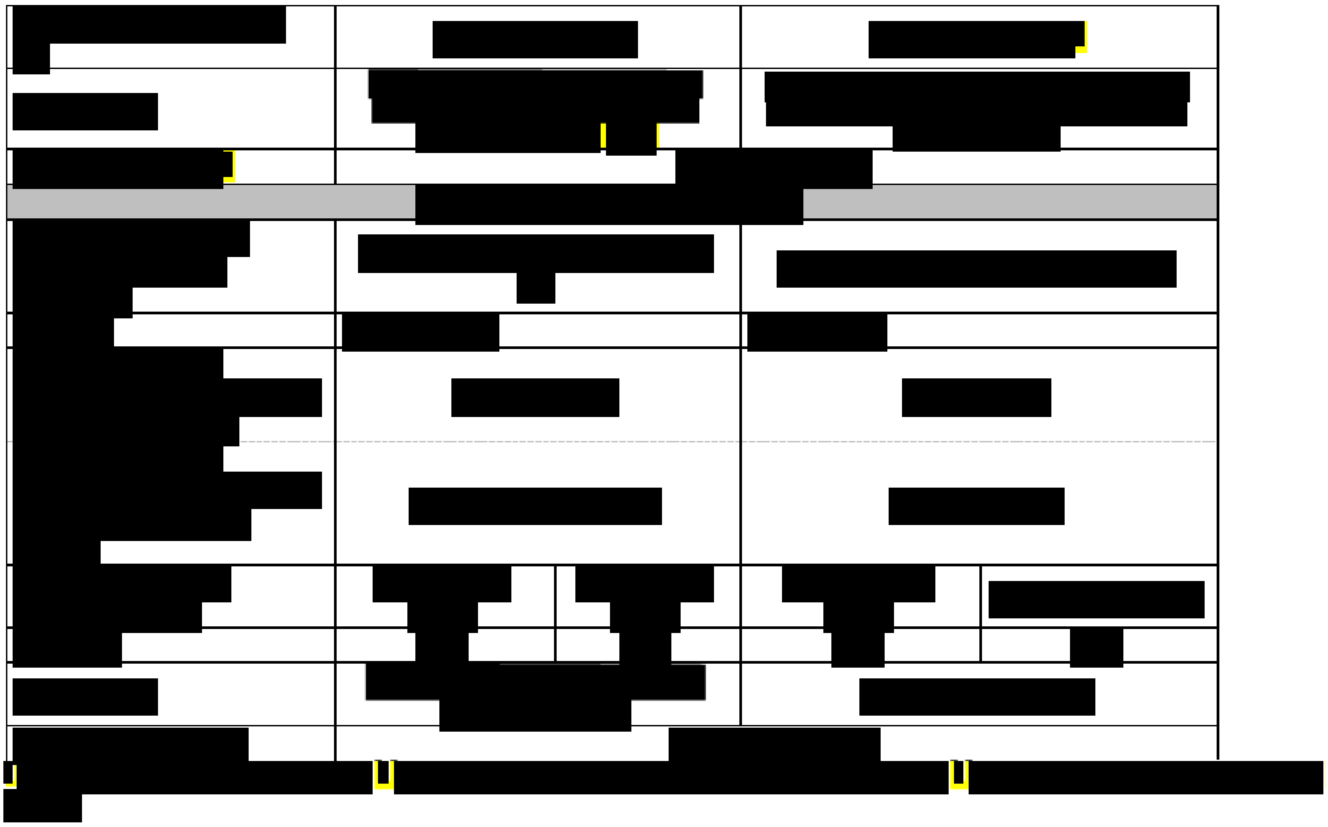

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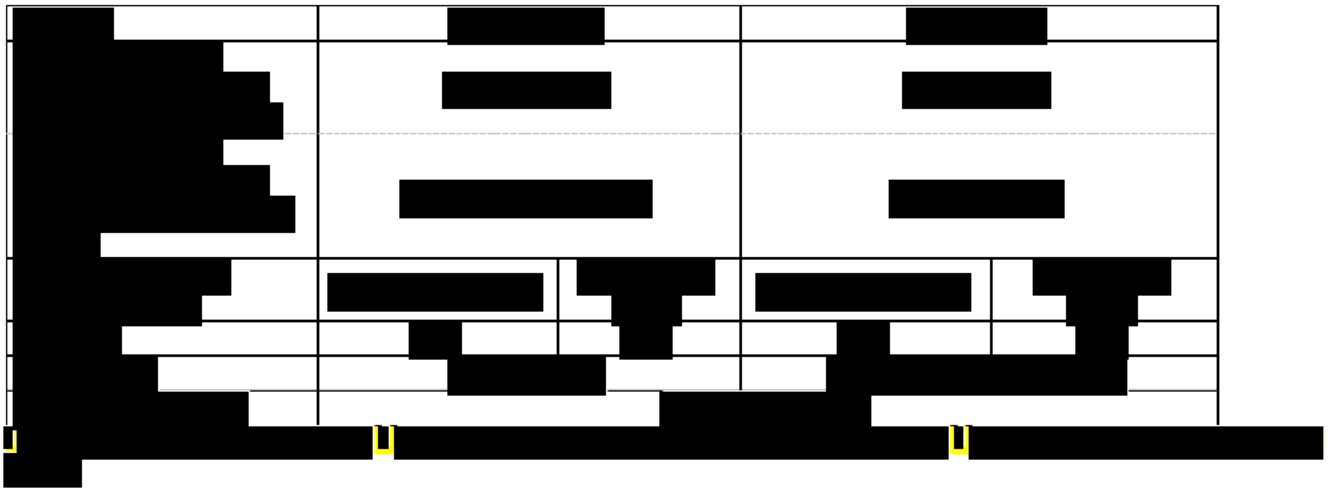

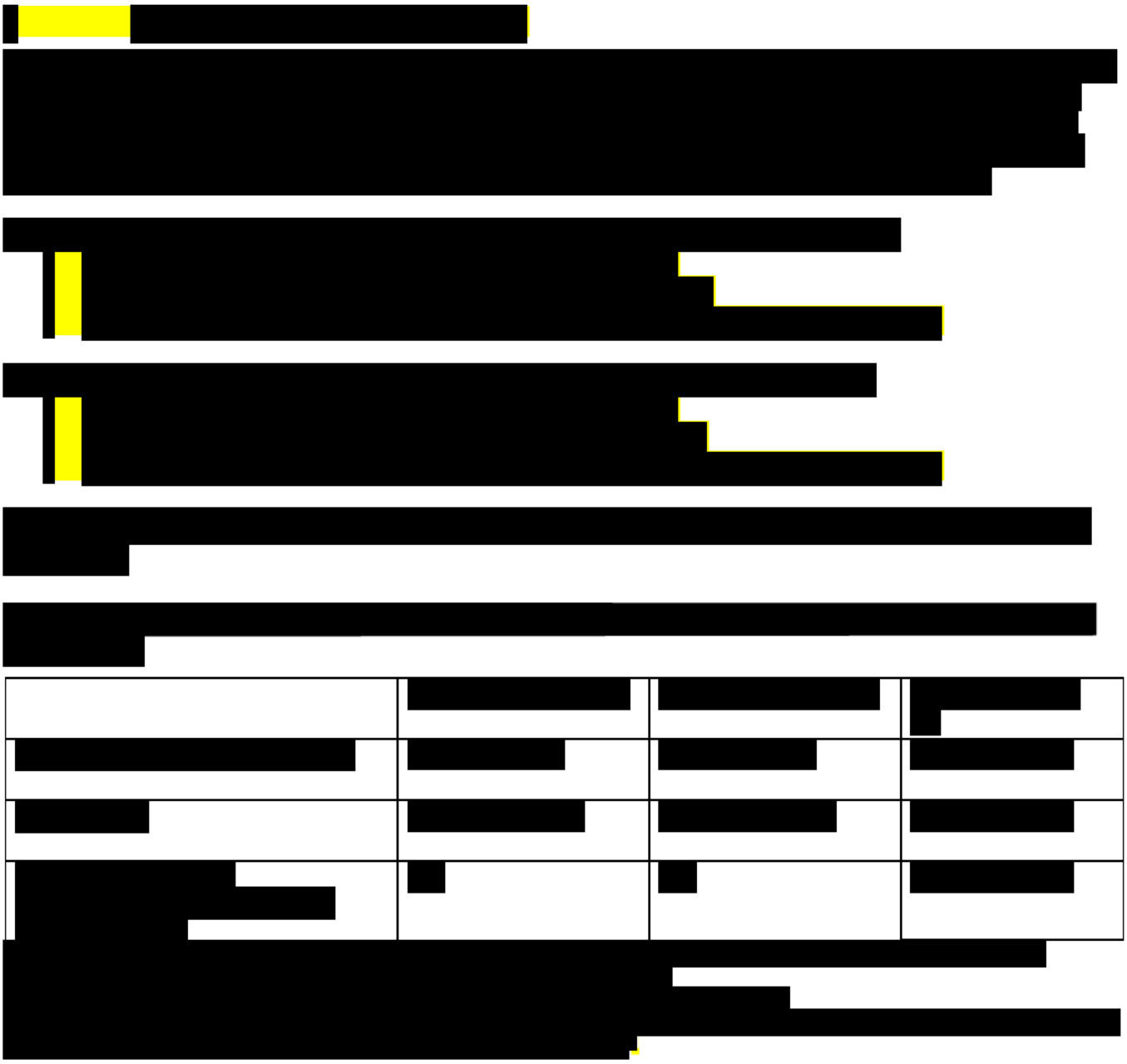

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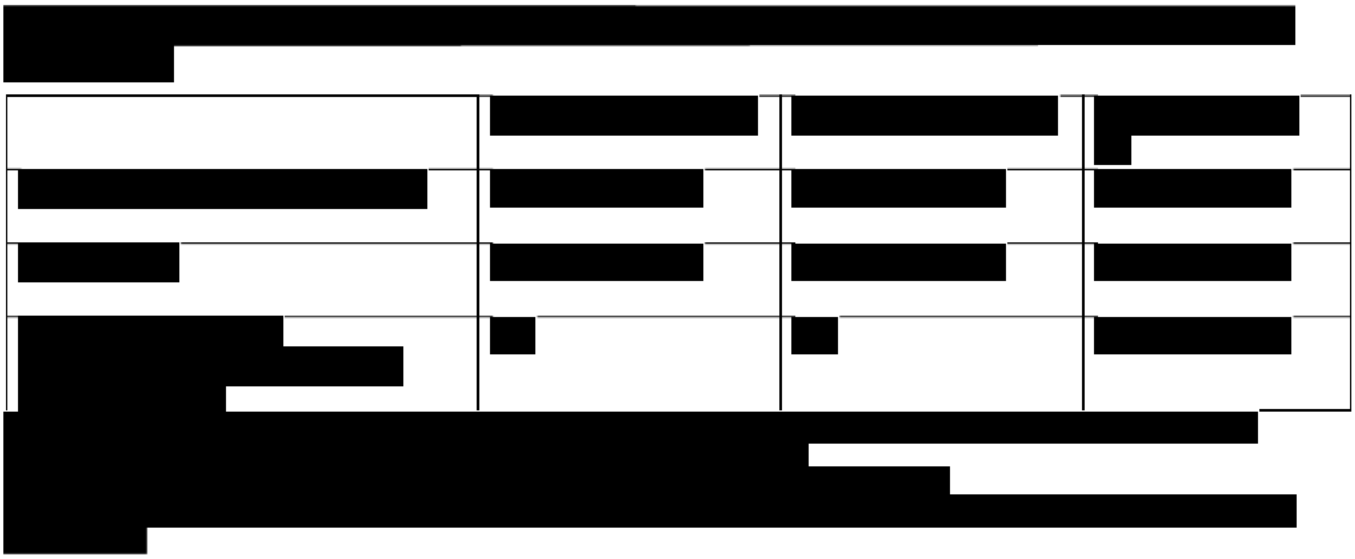

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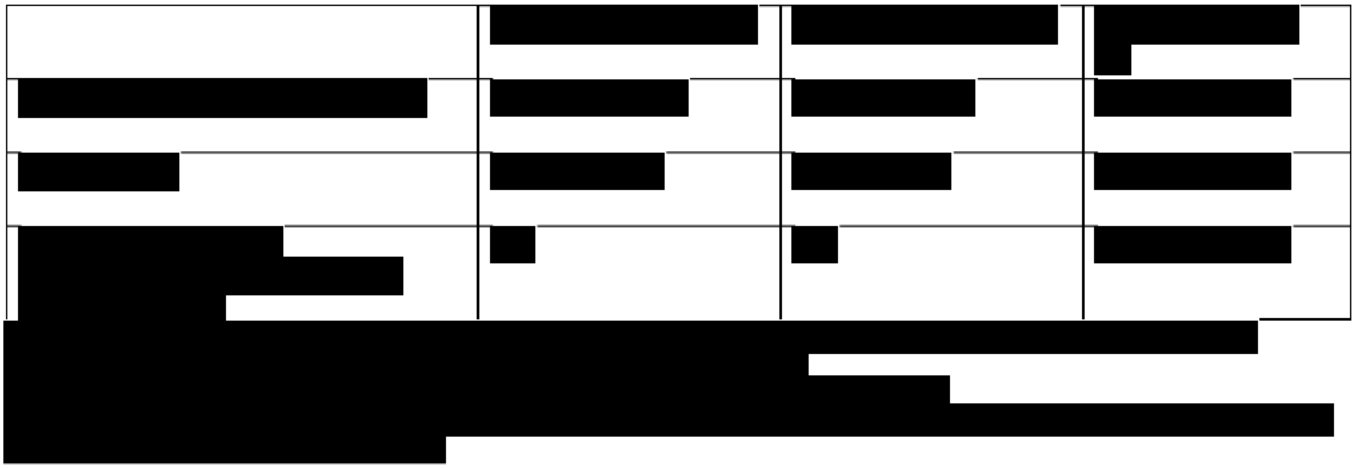

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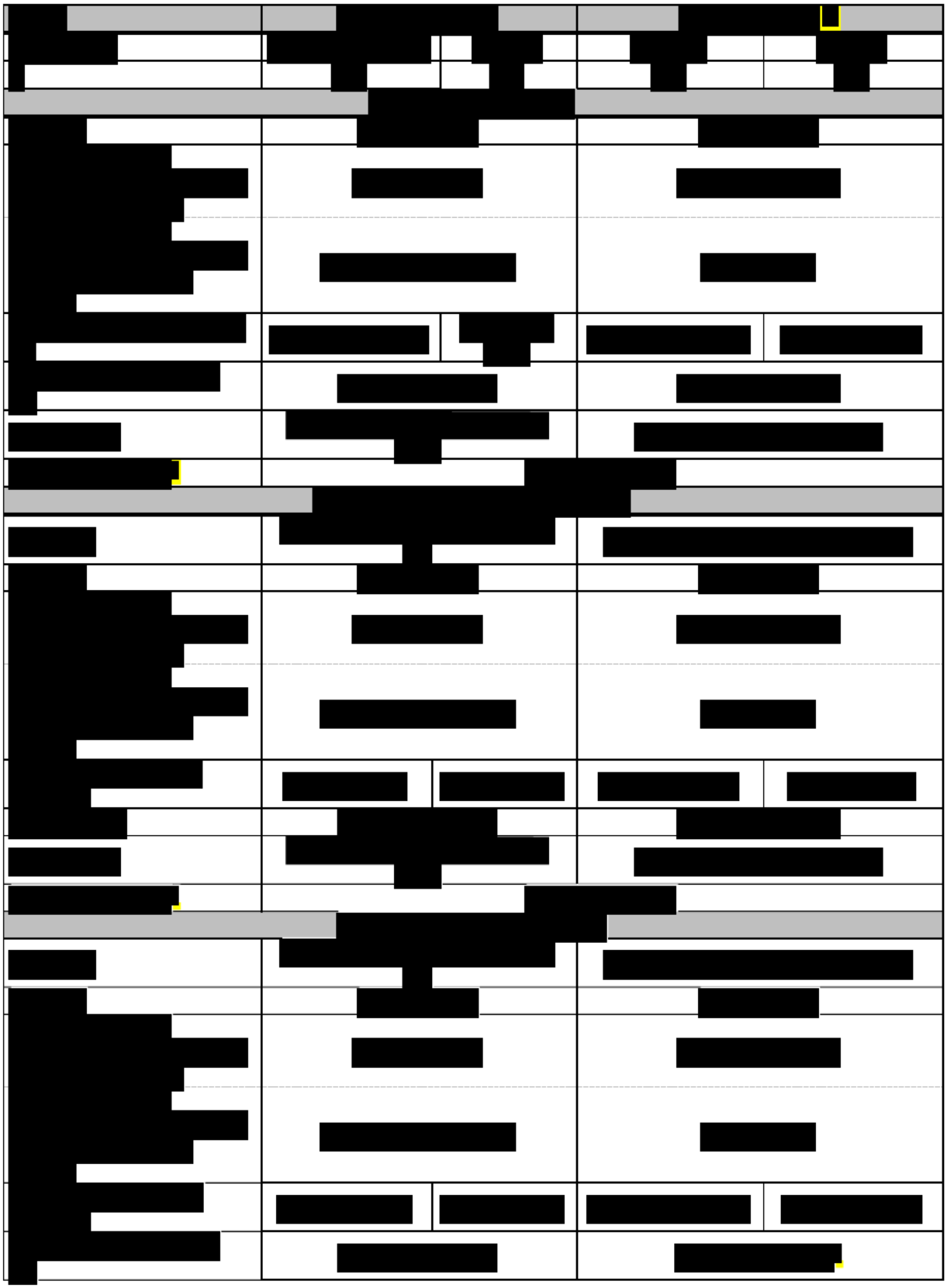

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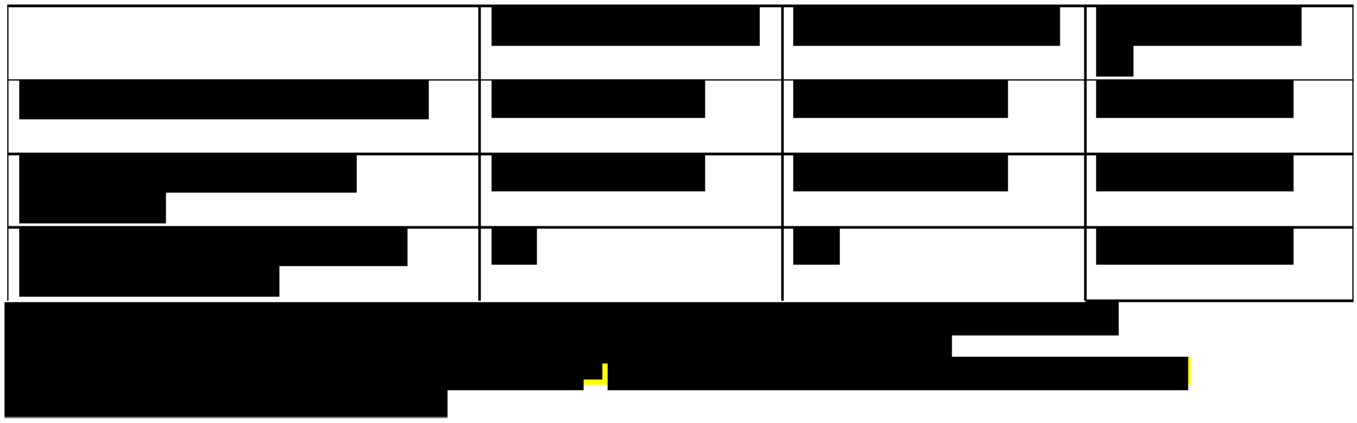

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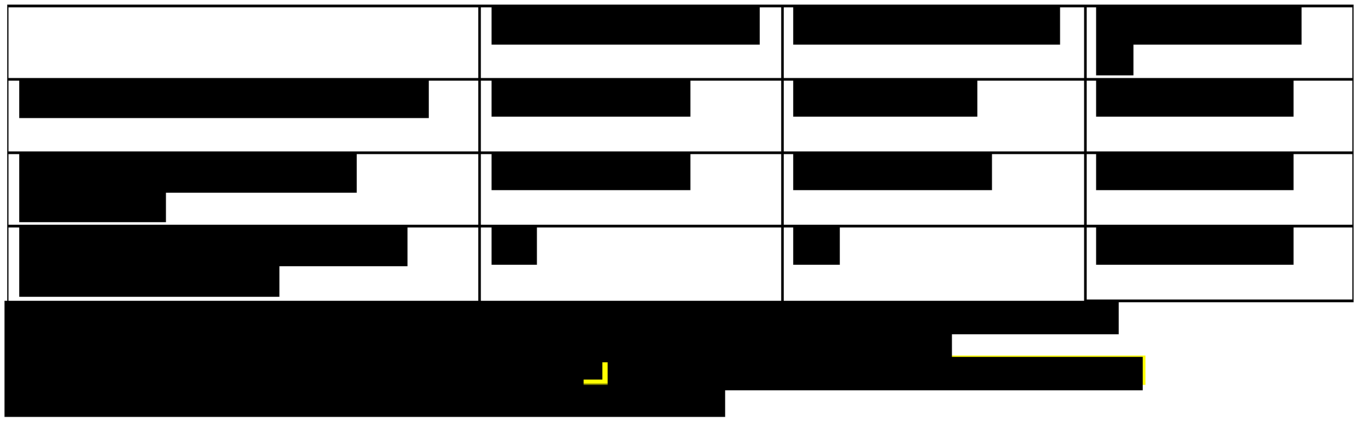

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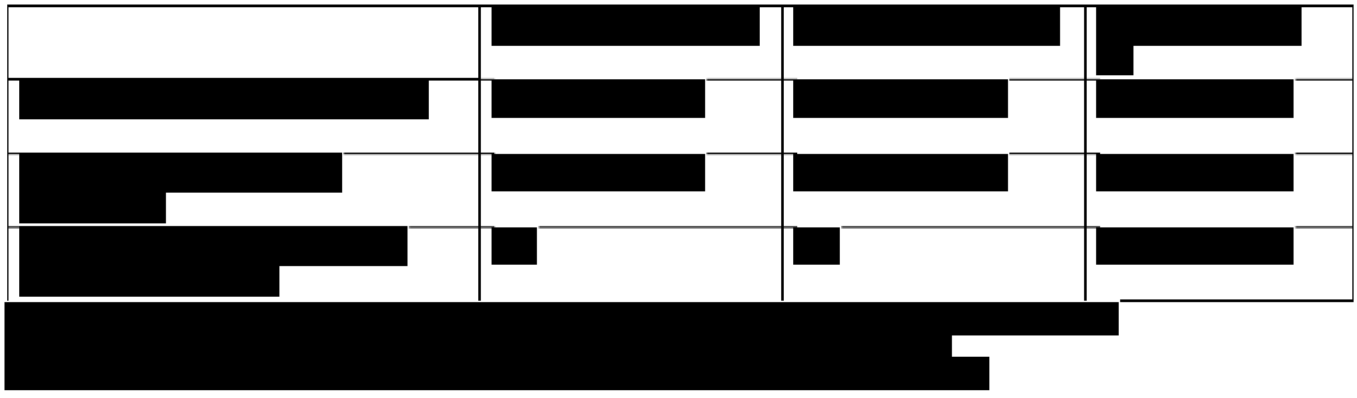

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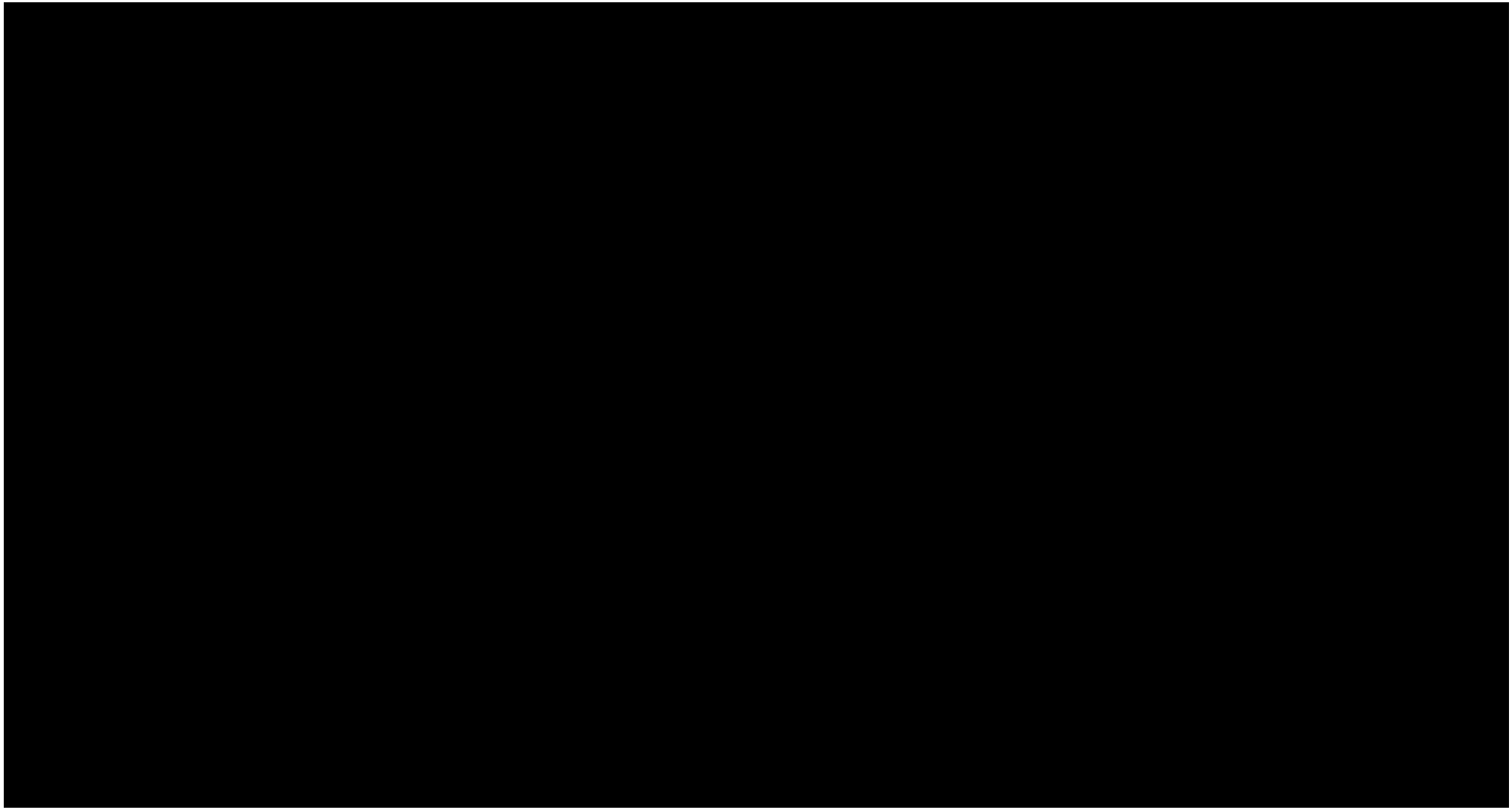

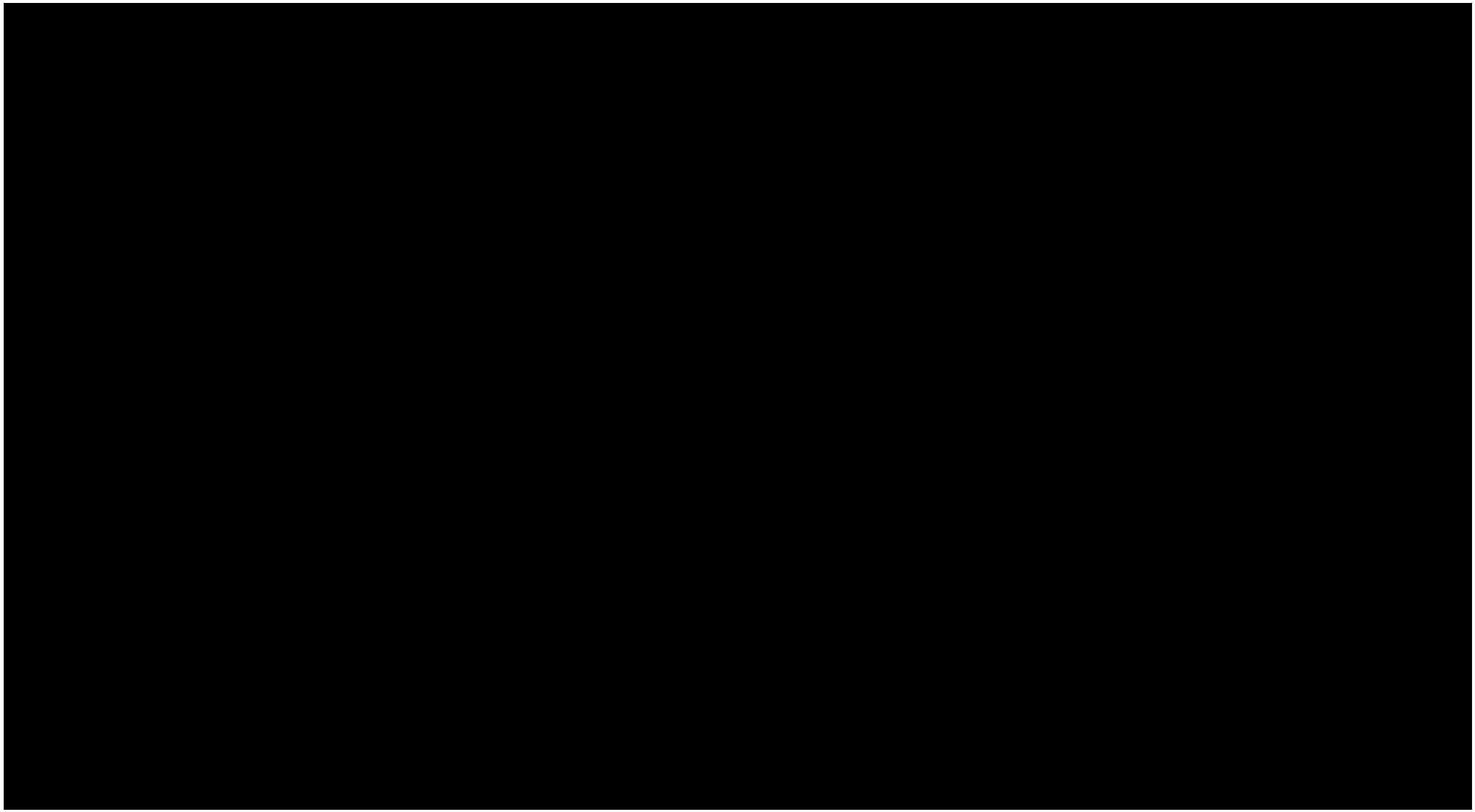

CHECKMATE 9LA
EQ-5D UTILITIES ANALYSIS RESULTS

2-YEAR DBL (MARCH 2021) - DENMARK SUBMISSION

VERSION 1_0
8 MARCH 2022

TABLE OF CONTENTS

1 SYNOPSIS

In the CheckMate 9LA clinical trial, extensive EQ-5D-3L data were collected for patients on-treatment every 3 weeks until week 24 then every 6 weeks whilst on treatment. After treatment patients completed EQ-5D-3L assessments at two follow-up visits (+30 days and +80 days after stopping treatment) and then regularly (every three months for the first 12 months, then every sixth months) in the survival follow-up phase. For estimate of utility within health states the following approaches were taken:

All EQ-5D-3L assessments were converted into a 3L index score (e.g. 11111, 33333). These 3L index scores were mapped to 5L utility values and the Denmark 5L value set was used to assign Denmark 5L utility index scores (vanHout 2021 Jenssen 2021).

Estimated mean utility values per health state were obtained by use if LSmean estimated from a repeated measures mixed model analysis (MMRM), accounting for multiple EQ-5D assessments within a subject. All EQ-5D assessments collected in the study (including baseline, on treatment and survival follow up visits) were included in the model for estimation and no imputation for missing data was applied which implies an underlying assumption of missing data being "missing completely at random (MCAR)".

2 INTRODUCTION

Three-level EQ-5D (EQ-5D-3L) utility data were collected in CheckMate 9LA clinical study in line with the clinical study protocol. As per protocol, patients were randomized to treatment (nivolumab + ipilimumab + platinum-based doublet chemotherapy versus platinum-based doublet chemotherapy) and completed a baseline and then regular on-treatment assessments until radiological disease progression. After stopping treatment, patients completed EQ-5D-3L assessments at two follow-up visits and then regularly (every three months for the first 12 months, then every sixth months) in the survival follow-up phase.

Key outcomes of the clinical study are overall survival, as well as progression-free survival assessed by blinded independent central review (BICR).

The utility analyses described in this report relate to the 2-Year database lock (DBL [March 2021]).

This report focuses on key utility estimates:

1) Progression-based health state utility value estimates
2) Time-to-death state utility value estimates

Appendix documents contain information on other health state models.

In the text of this report utility estimates for Denmark are presented, using EQ-5D-3L mapping to 5L methodology as detailed in Section 3.2 (i.e., mapped Danish EQ-5D-5L value set applied to EQ-5D-3L responses).

3 METHODS

3.1 Study Population

The data cutoff date for the 2-year data was 18 February 2021.

The patient population is all randomized patients in the global study.

The utility analysis used the EQ-5D-3L index score (utility index [UI]) at all timepoints in the study.

As per protocol, EQ-5D-3L data were collected at baseline and follow-up visits (every three weeks for the first six months, then every six weeks until disease progression or discontinuation of treatment). The EQ-5D-3L questionnaire was administered at follow-up visits, which occurred 35 days (follow-up visit 1) and 115 days (follow-up visit 2) after the last dose, and then at survival follow-up visits which occurred every three months after follow-up visit 2 until death. Any EQ-5D-3L data from any unscheduled visits with a known assessment data (unscheduled) were also included.

The dates of the EQ-5D-3L assessments were used in assignment of EQ-5D-3L assessments to health states (days were calculated relative to the date of randomization + 1).

3.2 Denmark Weights

EQ-5D-3L mapping to 5L was applied for the Danish utility index values using the van Hout method. The ordered logistic regression (including adjacent dimensions and a latent factor) approach using the van Hout and Shaw 2021 algorithm was used to predict 5L responses from 3L responses for each individual assessment as collected in the study (as per the preferred model in Table 2 in van Hout and Shaw 2021[1]).

The Danish 5L value set was used to obtain the predicted 5L utility score for each individual assessment (relating to the preferred model in Table 2 in Jensen 2021[2]). The predicted 5L index value obtained for each individual assessment was used to estimate the mean utility values within the population-based health states of interest (using methodology as described below).

[1] van Hout BA, Shaw JW. Mapping EQ-5D-3L to EQ-5D-5L. Value in Health. 2021;24(9):1285-1293.

[2] Jensen CE, Sørensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. *Applied Health Economics and Health Policy.* 2021:1-13.

3.3 Health State Models

3.3.1 Progression-based Health State Model

The date of progression used matches the primary analysis method in the clinical study (i.e., date of progression was assigned based on the BICR).

The dates of the EQ-5D-3L assessments were compared to date of progression; EQ-5D-3L assessments prior to the date of progression (i.e., including baseline) are considered to be prior to progression, while EQ-5D-3L assessments on the same date or afterwards are considered to be post-progression.

3.3.2 Time-to-Death Health State Model

For patients who died, EQ-5D-3L assessments were grouped by the date of the EQ-5D-3L assessment relative to date of death into four categories: 0–28 days (≤4 weeks), 29–182 days (5–26 weeks), 183–364 days (27–52 weeks), or ≥365 days (>52 weeks).

EQ-5D-3L assessments from patients who have not died (and are ongoing in the study) and EQ-5D-3L assessments ≥365 days prior to last known alive date are included in the category ≥365 days.

EQ-5D-3L observations within 364 days of last-known alive date from patients who have not died (and are ongoing in the study) are excluded.

Note that the choice of cut-off applied was as per the 1-year DBL (and these categories were selected based on prior health technology assessment [HTA] submissions for CheckMate 227).

3.3.3 Estimating Utility Value for Health State

In order to estimate mean values of EQ-5D-3L for each health state, a mixed model approach was used to account for repeated EQ-5D-3L measurements per patient within a health state (mixed model for repeated measures [MMRM]). For each health state model, two statistical models were fit: one with and one without treatment. [redacted]

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4 RESULTS (2-YEAR DATABASE LOCK [DBL])

The were 719 patients in the all-randomized global population in the 9LA study.

There were 705 patients in the 9LA study with at least one observed UI value.

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4.1.1 Baseline Utility (2-year DBL)

[redacted]

4.2 Overall Utilities (2-year DBL)

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[redacted]	[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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4.3 Progression-based Utilities (2-year DBL)

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4.4 Time-to-Death Utilities: 2-year

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