Medicinrådet

Bilag til Medicinrådets anbefaling vedr. durvalumab til behandling af ikke-resektabel eller metastatisk kræft i galdevejene

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. durvalumab
2. Forhandlingsnotat fra Amgros vedr. durvalumab
3. Ansøgers endelige ansøgning vedr. durvalumab

Att: Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø

AstraZeneca A/S
Johanne Møllers Passage 1, 4.
1799 København V
T: +45 4366 6462
astrazeneca.com · astrazeneca.dk

København, 26.04.2024

RE: Assessment report of Imfinzi (duravalumab) in combination with gemcitabine and cisplatin for first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC).

AstraZeneca appreciates the opportunity to comment on the drafted version of the assessment report. Overall, AstraZeneca acknowledges the assessment and finds most of the comments and conclusion to be a fair summary of the available data with only a few comments.

Survival rates
For the last ten years, there has been no major advance for the broad population of first-line unresectable or metastatic BTC, with current treatment options limited to gemcitabine-cisplatin chemotherapies. The median overall survival for patients receiving systemic treatment is less than one year, illustrating the poor prognosis for this patient population. (1) With the recent release of the long-term survival follow-up, it's shown that Imfinzi in combination with standard-of-care (SoC) chemotherapy demonstrated a clinically meaningful long-term overall survival (OS) benefit at three years for patients with advanced BTC. At more than three years (median follow-up of 41.3 months), results showed Imfinzi plus chemotherapy reduced the risk of death by 26% versus chemotherapy alone (based on a hazard ratio [HR] of 0.74; 95% confidence interval [CI], 0.63-0.87). At the 3-year data cut, the 12- and 24-months overall survival rates were higher for the Imfinzi-based regimen versus SoC chemotherapy and more than twice as many patients on the Imfinzi-based regimen were alive at three years versus chemotherapy alone (14.6% versus 6.9%). (2)

Long term survival and plateau development
AstraZeneca's analysis of the cost per QALY used external data from previous immuno-oncology (IO) trials and registry studies to support long-term survival predictions. Medicinrådet did not chose to use the external data from previous IO studies in their base case analysis, as these were based on other indications up to 5 years (3) and epidemiological data on intrahepatic cholangiocarcinoma from the Surveillance, Epidemiology, and End Results (SEER) database in the United States for the mortality risks beyond 5 years (4). The main critique from Medicinrådet regarding the use of previous IO data is that it is uncertain because the diseases and patient populations are fundamentally different and have different prognoses. We do not agree with this as we still see a common pattern of plateau development across indications even for quite severe diseases, such as metastatic lung-cancer. The main critiques from Medicinrådet regarding the use of the SEER data are that it is a patient population differing in some aspects from the clinical trial and also that it is based on American mortality risks that are not necessarily relevant for Danish patients. We do not agree with the choice of not using the external data to support the overall survival extrapolations, as the long-term survival data from previous trials provide plausible evidence for predicting long-term survival also for durvalumab in this setting. For example, we can see a common pattern of long-term plateau development across IO indications even for quite severe diseases, such as metastatic lung cancer. As regards the SEER data from the US, we agree that there are differences in the populations in the TOPAZ-1 trial and the epidemiological data, but the SEER data are probably still the best available source regarding long-term risks beyond 5 years for this type of disease. Extrapolations that are just based on the clinical trial data are not necessarily better at predicting the overall survival in the long run than the previous IO data and the epidemiological evidence we used in our base case.

While the Medicinrådets base case analysis is more conservative, we still think that it is good that Medicinrådet acknowledges that some plateau development can be expected also in advanced biliary tract cancer and takes that into account in the analysis.

Down-staging patients
AstraZeneca acknowledge Medicinrådets statement regarding down-staging for potential curative treatment. Currently, 10-15% of patients are assessed to be eligible for resection when responding (both complete and partial response is a relevant outcome) on systemic treatment with curative intend. These patients are being reassessed after three months of systemic treatment. Based on the higher response rate for the Imfinzi-based regimen the potential of increasing the proportion of patient eligible for resection and thereby potential for curative treatment will be highly relevant in a clinical setting.

Given data is very mature and efficacy has reached a plateau, there is very little uncertainty in this assessment, and we therefore look forward to the final decision, so that patients with this poor prognosis can have a new treatment option.

Best regards,
Malene Krag Kjeldsen, Medical Advisor
Mattias Ekman, Health Economics Scientific Lead
Sara Vinther, Market Access Manager

AstraZeneca AS

References:
1: https://www.cancer.dk/galdeblaere-og-galdegangskraeft-galdevejscancer/fakta/statistik/
2: https://www.astrazeneca.com/media-centre/press-releases/2024/imfinzi-plus-chemotherapy-doubled-overall-survival-rate-at-three-years-for-patients-with-advanced-biliary-tract-cancer-in-topaz-1-phase-iii-trial.html
3: Lin EP-Y, Hsu C-Y, Berry L, Bunn P, Shyr Y. Analysis of Cancer Survival Associated With Immune Checkpoint Inhibitors After Statistical Adjustment. JAMA Netw Open. 2022 ;5(8) :e2227211.
4: Elgenidy A, Afifi AM, Jalal PK. Survival and Causes of Death among Patients with Intrahepatic Cholangiocarcinoma in the United States from 2000 to 2018. Cancer Epidemiology, Biomarkers & Prevention. 2022;31(12):2169–76.

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

25.04.2024
CAF/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	22.05.2024
Leverandør	AstraZeneca
Lægemiddel	Imfinzi (durvalumab)
Ansøgt indikation	Behandling af ikke-resektabel eller metastatisk kræft i galdegangen
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende pris på Imfinzi (durvalumab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Imfinzi	50 mg/ml	2,4 ml	4.278,62	[redacted]	[redacted]	[redacted]
Imfinzi	50 mg/ml	10 ml	17.672,28	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling af Imfinzi.

Aftaleforhold

[redacted]

Konkurrencesituationen

Imfinzi er den første immunterapi til behandling af ikke-resektabel eller metastatisk kræft i galdegangen.
[redacted]

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Paknings-størrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Imfinzi	50 mg/ml	10 ml	1500 mg hver 3. uge de første 8 cykler. Derefter 1500 mg hver 4 uge*	[redacted]	[redacted]
Imfinzi	50 mg/ml	10 ml	1500 mg hver 4. uge**	[redacted]	[redacted]

* Første års behandling med opstart og vedligeholdelsesbehandling.
** Andet års behandling med vedligeholdelsesbehandling.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Under evaluering	Link til vurdering
Sverige	Under evaluering	Link til vurdering
England	Anbefalet	Link til anbefaling

Konklusion

[redacted]

Medicinrådet

Application for the assessment of Imfinzi (durvalumab) in combination with gemcitabine and cisplatin for first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC).

Version 1.3

Submission date: June 26, 2023
1st validation received from DMC: 01.12.2023
Updated application submitted by AstraZeneca: 20.12.2023
2nd validation received from DMC: 05.01.2024
Updated application submitted by AstraZeneca: 15.01.2024
Modelling questions received from DMC: 20.02.2024
Updated application submitted by AstraZeneca: 01.03.2024
Complement to the update submitted by AstraZeneca: 18.03.2024

Table of contents

1. Basic information

Contact information	
Company	AstraZeneca A/S, Johanne Møllers Passage 1. 4 sal. 1799 København V
Name	Sara Vinther
Title	Market Access Manager
Responsibility	Reimbursement
Phone number	+45 26463260
E-mail	sara.vinther@astrazeneca.com
Name	Malene Krag Kjeldsen
Title	Medical Advisor
Responsibility	Medical
Phone number	+45 61 28 73 67
E-mail	malenekrag.kjeldsen@astrazeneca.com
Name	Mattias Ekman
Title	Health Economics Scientific Lead
Responsibility	Health Economics
Phone number	+46 767-98 86 67
E-mail	mattias.ekman@astrazeneca.com

Overview of the pharmaceutical	
Proprietary name	Imfinzi
Generic name	Durvalumab
MA holder in Denmark	AstraZeneca AB SE-151 85 Södertälje Sverige
ATC code	L01FF03
Pharmacotherapeutic group	PD-1/PDL-1 (Programmed cell death protein 1/death ligand 1) inhibitors
Active substance(s)	Durvalumab
Pharmaceutical form(s)	Intravenous injection
Mechanism of action	Durvalumab is an ICI (immune checkpoint inhibitor) that selectively blocks the interaction of PD-L1 with PD-1 and cluster of differentiation 80 (CD80). The blockade of PD-L1/PD-1 and PD-L1/CD80 communication prevents the inhibition of immune responses caused by overexpressed PD-L1, allowing the immune system to exert a cytotoxic T cell-driven response against PD-L1-expressing tumour cells.
Dosage regimen	1500 mg every 4th week
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	IMFINZI in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC). The indication was approved by EMA 21st December 2022

Overview of the pharmaceutical	
Other approved therapeutic indications	**Hepatocellular carcinoma** IMFINZI in combination with tremelimumab is indicated for the first-line treatment of adults with advanced or unresectable hepatocellular carcinoma (HCC). **Non-Small Cell Lung Cancer (NSCLC)** Imfinzi as monotherapy is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. IMFINZI in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations. **Small Cell Lung Cancer (SCLC)** Imfinzi in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).
Will dispensing be restricted to hospitals?	Yes. Labeled BEGR
Combination therapy and/or co-medication	IMFINZI in combination with gemcitabine and cisplatin
Packaging – types, sizes/number of units, and concentrations	Vial of 2,4 ml and 10 ml. 50 mg/ml
Orphan drug designation	No

2. Abbreviations

[Include a list of abbreviations used in this application.]

Abbreviation / term	Definition
ADA	Antidrug antibody
AE	Adverse event
AIC	Akaike information criterion
AoV	Ampulla of Vater
APC	Antigen-presenting cell
BIC	Bayesian information criterion
BIRC	Blinded central independent review
BTC	Biliary Tract Cancer
CCA	Cholangiocarcinoma
CEM	Cost-effectiveness model
CI	Confidence interval
CR	Complete response
CTCAE	Common terminology criteria for AEs
CUA	Cost-utility analysis

DCO	Data cut-off
DCR	Disease control rate
DMC	Danish Medicines Council
DNA	Deoxyribonucleic Acid
DoR	Duration of response
eCCA	Extrahepatic cholangiocarcinoma
ECOG	Eastern Cooperative Oncology Group
ES-SCLC	Extensive-stage small cell lung cancer
ESMO	European Society of Medical Oncology
FAS	Full analysis set
GemCis	Gemcitabine + Cisplatin
GBC	Gallbladder cancer
GHS	Global health status
IVRS	Interactive Voice Response System
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HE	Health economics
HR	Hazard ratio
HRQoL	Health-related quality of life
HSVU	Health-state utility values
IA	Interim analysis
intrahepatic CCA	Intrahepatic cholangiocarcinoma
ICER	Incremental cost-effectiveness ratio
ICI	Immune checkpoint inhibitor
IO	Immuno oncology
ITT	Intention to treat
IVRS/IWRS	Interactive voice-response system/interactive web response system
IQR	Interquartile range
KEE	Key external expert
KM	Kaplan-Meier
MoA	Mechanism of Action
MMRM	Mixed model repeated measures
NSCLC	Non-small cell lung cancer
NR	Not Reported
ORR	Objective response rate
OS	Overall survival
PD	Progressed disease
PD-1	Programmed cell death 1
PD-L1	Programmed death ligand 1
PHA	Proportional hazard assumption
PFS	Progression-free survival
PK	pharmakokinetics
PPS	Post-progression survival
PR	Partial response
PRO	Patient reported outcome
PS	Performance status
QALY	Quality-adjusted life-year
Q4W	Every four weeks

RECIST 1.1	Response Evaluation Criteria in Solid Tumours version 1.1;
RMST	Restricted mean survival time
SAS	Safety analysis set
SD	Stable disease
SmPC	Summary of product characteristics
SoC	Standard of Care
TAP	Tumour area positivity
TEAE	Treatment emergent adverse event
TTD	Time to treatment discontinuation
ULN	Upper limit of normal
WHO	World Health Organisation

3. Tables and Figures

List of tables

List of figures

4. Summary

There have been no new therapies offered for the broad population of first-line unresectable or metastatic biliary tract cancer (BTC) in the last ten years, with current treatment options limited to gemcitabine-based chemotherapies. There is a consensus across treatment guidelines positioning gemcitabine plus cisplatin (GemCis) as the preferred chemo backbone in first-line treatment for unresectable BTC. However, GemCis only offers limited survival benefit to unresectable BTC patients, with median OS in clinical trials generally being <12 months, highlighting the critical need for additional treatment options that extend survival (1-3).

AstraZeneca is applying for durvalumab in combination with GemCis in first-line treatment of adults with unresectable BTC. This application is based on the Phase III, randomised, double-blind, placebo controlled, multicentre and international TOPAZ-1 clinical trial that assessed the efficacy and safety of durvalumab in combination with GemCis chemotherapy in previously untreated unresectable or metastatic BTC patient population (ClinicalTrials.gov identifier: NCT03875235) (4). In December 2022 EMA approved IMFINZI (durvalumab) in combination with gemcitabine and cisplatin as first-line treatment for adults with unresectable or metastatic BTC (5). Durvalumab is a high-affinity, human, recombinant IgG1κ monoclonal antibody, which acts as a potent inhibitor of human PD-L1(6), and is known as an immune checkpoint inhibitors (ICI). The TOPAZ-1 trial enrolled 685 previously untreated BTC patients who were randomized 1:1 to receive 1500 mg durvalumab or placebo every three weeks for the first eight cycles in combination with gemcitabine (1000 mg/m^2) plus cisplatin (25 mg/m^2), followed by durvalumab or placebo monotherapy every 4 weeks until disease progression or unacceptable toxicity . Results presented are mainly from the primary data cut-off (DCO: February 2021) (7, 8) as well as the most recent data cut-off with 6.5 month updated analysis (DCO: September 2022) (9) which was carried out to further characterise long-term survivorship of durvalumab + GemCis.

DCO(September 2022) demonstrated a significant improvement in median OS of 1.6-month with the durvalumab regimen compared to the placebo regimen (12.9 months vs. 11.3 months, HR: 0.76; 95% CI: 0.64–0.91; p=0.021), representing a >10% improvement in mOS, corresponding to a 24% reduction in the overall risk

of death. Since the initial DCO analysis, the benefit of durvalumab + GemCis was further demonstrated, with the OS HR improving from 0.8 to 0.76 between the primary analysis (61.9% OS maturity) to the most recent DCO (76.9% OS maturity). DMC asked if at later DCO was available. We have been able to get OS update from 23rd Oct 2023. These data further confirmed earlier results and HR improved slightly reaching HR= 0.74 (0.63, 0.87). Median OS (12.9 m vs 11.3 m) were largely unchanged compared to prior DCOs (durvalumab vs placebo, all comparisons).

A statistically significant, clinically meaningful, and sustained improvement in PFS was observed in the durvalumab + GemCis treatment arm with 7.2 months when compared with the placebo + GemCis treatment arm with 5.7 months. (HR: 0.75; 95% CI: 0.63–0.89; p=0.001), shown by an early and sustained separation from forth month in the Kaplain Meier curves. This corresponds to a 25% lower risk of progression overall. The sustained difference of PFS is reflected at 12 months, with a 12-month PFS of 16.0% with durvalumab + GemCis compared to 6.6% for placebo + GemCis (10).

The safety of durvalumab in the durvalumab + GemCis regimen was observed to have a manageable profile without additional toxicity compared to placebo + GemCis regimen. At the most recent DCO, overall rates of grade 3/4 AEs were comparable between the treatment arms (74% vs. 75.1%) and fewer AEs led to discontinuations vs. placebo + GemCis (8.9% vs. 11.4%). No new safety signals were identified from the known safety profiles of each individual treatment (10).

Patients relevant for this application

In alignment with TOPAZ-1 and the EMA indication, the patients relevant for this application is those who have biliary tract cancer including gallbladder cancer. While this application focuses on Danish patients who have unresectable or metastatic biliary tract cancer including gallbladder cancer as well as intrahepatic and extrahepatic cholangiocarcinoma, it excludes patients with ampulla of Vater cancer disease.

Cancer of the biliary tract and gallbladder is rare in Denmark. It is estimated that in 2021, 380 men and women were diagnosed with BTC (11). The median age of first time locally treated cholangiocarcinoma is around 70 years in Denmark (12). BTC is mainly a cancer of elderly population, with increased incidence >65 years (13).

Although no treatment guideline has been constructed by the Danish Medicines Council for BTC, the Danish Liver and Biliary Cancer Group (DLCGC) has published guidelines on cholangiocarcinoma that were last updated on October 2020 (14). Patients with unresectable BTC who are fit (ECOG 0-1) with bilirubin <50 and adequate liver- and kidney function should be considered for palliative/life prolonging chemotherapy. Obstructed bile ducts in icteric patients must be relieved before chemotherapy (14).

The recommendation for first-line (1L) treatment for all subgroups of BTC is platinum-based combination chemotherapy, namely gemcitabine and cisplatin (GemCis), for patients with good performance status (PS) 0-1.

Costs and QALY

The economic evaluation suggests that the first-line use of durvalumab + GemCis for treating locally advanced or metastatic BTC is associated with longer survival and QALY gains. A QALY gain of 0.80 and an incremental cost of DKK 855 468 were estimated over a lifetime horizon in the health economic model. The deterministic ICER of durvalumab + GemCis versus GemCis for the management of first-line BTC was estimated to be DKK 1 072 206 per QALY gained.

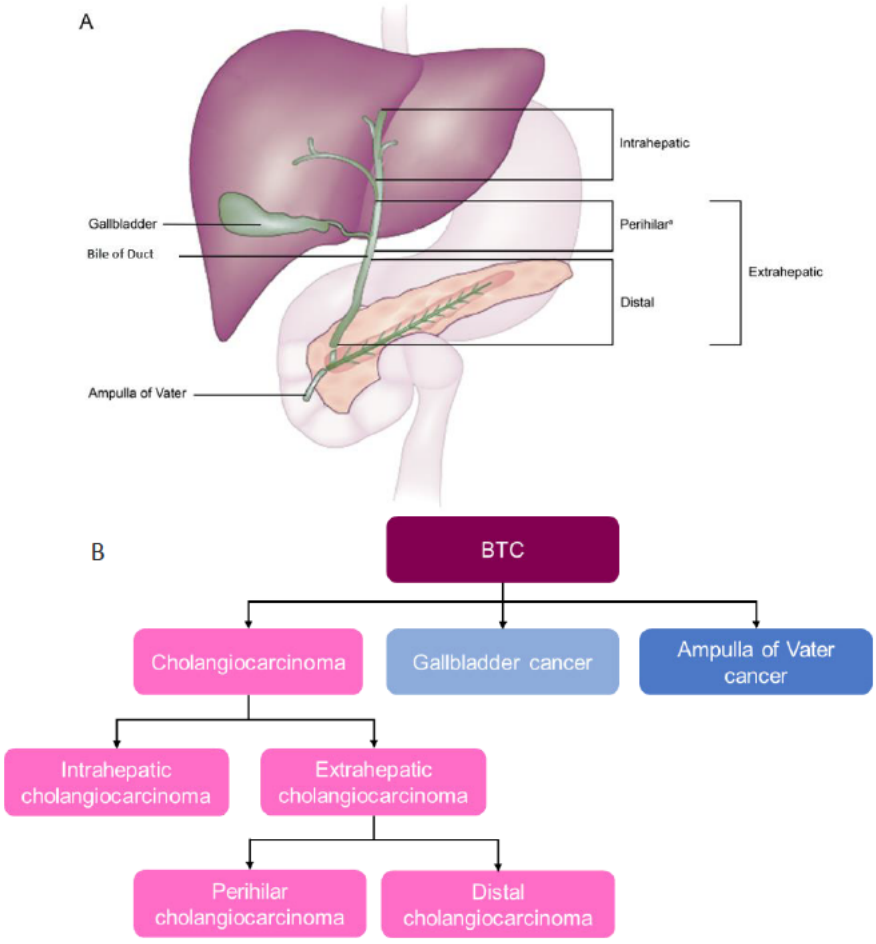
The budget impact of introducing durvalumab + GemCis is estimated to increase from MDKK 27.6 in year 1 (2024) to MDKK 78.0 in year 5 (2028), with the difference in first-line pharmaceutical costs as the main driver.

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

5.1 The medical condition and patient population

BTC is the collective term given to gallbladder cancer and cholangiocarcinoma (CCA) – cancer originating in the bile ducts. Sometimes the ampulla of Vater (where the bile duct and pancreatic duct meet) (Figure 1 A and B) is also included in the definition of BTC (15-17). BTC is a highly aggressive and rare disease, representing ~3% of all gastrointestinal malignancies and <1% of all cancers overall (18-20). As such, BTC is considered an orphan disease across the UK, Europe, the US and Asia with very limited therapeutic options (21). Overall, BTC is slightly more common in men than women (incidence ratio of 1.2–1.5:1.0) and in older adults, with average age at diagnosis ranging from 60–70 years across Europe, the US and Asia (18, 22, 23).

Figure 1: Anatomy of biliary tract with subcategorization of BTC.



Footnotes: *[a]Perihilar cholangiocarcinoma can also be referred to as hilar or Klatskin* ***Source:*** *Adapted from ESMO*

Risk factors comprise various reasons for chronic inflammation of the biliary system such as primary sclerosing cholangitis or cholelithiasis and globally also parasitic infection by liver flukes (15, 24). Comorbidities associated to metabolic syndrome constitute an increasing disease burden predisposing also to development of BTC (25). In its early stages, BTC is generally asymptomatic or presents with non-specific symptoms, such as fatigue and loss of appetite (26, 27). As the disease progresses, more specific symptoms develop, such as jaundice (yellowing of the skin), excessively dark urine and pale stools, weight loss and abdominal pain, nausea, and fever (26). As a result, patients seek medical care late, delaying the diagnosis and resulting in up to 80% of BTC patients being

diagnosed at an advanced stage of disease, which precludes potentially curative surgical interventions (28, 29). As with the majority of solid tumours, surgery is the only curative treatment for these cancers (30). However, since only a minor proportion (20%) of patients are diagnosed with resectable cancer with a high recurrence rate, the majority of patients eventually develop a metastatic disease with poor prognosis (17, 25). In addition to the poor prognosis of advanced BTC, patients experience a substantial clinical and humanistic burden due to signs and symptoms of disease, as well as treatment-related toxicity (1, 27, 31).
There have been no major advances for the broad population of first-line treatment of unresectable or metastatic BTC in the last ten years, with current treatment options being limited to combinations of chemotherapy. There is a consensus across treatment guidelines positioning gemcitabine in combination with cisplatin (GemCis) as the preferred first-line treatment for advanced BTC (18, 32, 33). However, GemCis offers only limited survival benefit to advanced BTC patients with a median OS in clinical trials generally being <12 months highlighting the critical need for additional treatment options that can prolong survival (1-3, 34).

Danish landscape

Cancer of the biliary tract and gallbladder is rare in Denmark. In 2021, 380 men and women were diagnosed with BTC (11). After a minor increase in the incidence during the previous 50 years, the incidence has slightly decreased within the last decade without major fluctuations (13). In 2021 the median age of first time locally treated cholangiocarcinoma is around 70 years in Denmark (12). BTC is mainly a cancer of elderly population, with increased incidence >65 years (13).

Cholangiocarcinoma (CCA) is one of the most common malignant tumours of the biliary tract. The epidemiology of CCA is highly variable across geographical regions (30), and the median survival with palliative chemotherapy is approximately 12 months(35). BTC is mainly a cancer of elderly population, with increased incidence >65 years, but as mentioned before, affecting also young adults (36).

CCA can be further subcategorised as follows (14, 37):

- **Intrahepatic CCA** originates in the bile ducts within the liver and accounts for 20% of CCA cases. The incidence is increasing.
- **Extrahepatic CCA** refers to both perihilar and distal CCA
  - **Perihilar CCA** originates where the left and right hepatic ducts join together, and accounts for 50% of CCA cases
  - **Distal CCA** originates in bile ducts further away from the liver, including those running through the pancreas to the small intestine and accounts for 25% of CCA cases. 5% occurs in multiple sites of the bile ducts.

Gallbladder cancer has a lower incidence with 1-2 new cases per 100.000 person per year. Gallbladder cancer is 2-4 times more prevalent in women compared to men (14).

Ampullary cancers arising from the ampulla of Vater (the junction of the pancreatic and distal common bile ducts) are sometimes included under the term BTC; histologically, they can be pancreaticobiliary or intestinal, arising from the biliary or pancreatic epithelium, or small bowel epithelium, respectively (25).

5.1.1 Patient populations relevant for this application

Based on data from TOPAZ-1, EMA has on December 16th 2022, approved the following indication: *durvalumab in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC) (5).*

The labelled indication based on TOPAZ-1 data covers ITT population irrespective of PD-L1 expression. PD-L1 expression was a secondary endpoint, but the analyses showed efficacy across all subgroups (TAP [tumour area positivity]). Thus, PD-L1 expression cannot be considered as a biomarker for overall survival (OS), which is in accordance with previous results in other IO trials in BTC (38-41). As the clinical trial only included patients with cancer in gallbladder and CCA, Ampulla Vater is excluded in this application as well in this section of presenting the incidence and prevalence of BTC patients in Denmark. The eligible population for durvalumab + GemCis consists of patients fit enough to tolerate chemotherapy (gemcitabine + platinum-compound) treatment (ECOG <2 with adequate liver- and kidney function) and the addition of immunotherapy. Safety of durvalumab + GemCis treatment is described in section 7.3. The estimated number of eligible patients for durvalumab + GemCis is described in section 5.1.1.1.

AstraZeneca has for this application therefore provided documentation of efficacy and safety for the ITT population of TOPAZ-1 without focusing on the subgroups. How these patients fit into current clinical practice in Denmark is described in section 5.2.

5.1.1.1 Incidence and prevalence of unresectable and metastatic biliary tract cancer and numbers of patients eligible for durvalumab + GemCis

During the last decade, advances in diagnostics and surgical techniques have improved the overall survival in early stages of BTC. However, as mentioned in chapter 5.1, the prognosis remains poor for patients with unresectable or metastatic disease.

The stage at diagnosis is the greatest determinant for prognosis in solid tumours (36). The 1-year survival rate for all cases is 50% and 5-year survival less than 20% (13). Nevertheless, the 5-year survival rate in metastatic disease remains dismal with 1.1-1.6% of patients being alive after 5 years from diagnosis highlighting the unmet need for new treatment options (36). This means that the prevalence of unresectable or metastatic BTC is relatively not much greater than the incidence.

The total incidence of resectable and unresectable BTC has been stable the last decade with an age-standardized incidence around 4.9 per 100 000 inhabitants (13), comprising the incidence of gallbladder cancer, biliary tract cancer and 20% of the liver cancer incidence representing intrahepatic cholangiocarcinoma (42, 43).

Determining patient numbers diagnosed with BTC is challenging due to the registry entities. According to the yearly cancer report from the Danish National Cancer Registry 267 patients were diagnosed with BTC in 2021, with 114 males and 153 females (44). However, the 267 BTC patients does not include intrahepatic CCA as these are registered within liver cancer patients (45) (). In the 10th edition of International Classification of Disease (ICD) BTC patients covers several ICD-codes (46); Intrahepatic CCA is classified in the category C22 (Malignant neoplasm of liver and intrahepatic bile ducts) with C22:1 (intrahepatic bile duct carcinoma), Gall bladder is C23 (Malignant neoplasm of gallbladder) and extrahepatic cholangiocarcinoma within C24 (Malignant neoplasm of other and unspecified parts of biliary tract). While it was possible to find the yearly incidence of patients within ICD C22, the number of patients within C22.1 was lacking in the Danish registry. AstraZeneca therefore chooses to use data from the Swedish Cancer registry (42) and NordCan (13) to estimate number of patients with intrahepatic CCA. It is estimated that this proportion of patients accounts for 20% of C22, resulting in 113 patients diagnosed with intrahepatic cholangiocarcinoma in 2021. Hence, with extracting the number of intrahepatic CCA patients from the C22 ICD-10 category, and adding the number of patients from C23 and C24 a total of 380 patients are estimated to have been diagnosed with BTC in 2021. Incidence from 2017-2021 is presented in Table 1.

Table 1: BTC Incidence in 2016-2021

	2017	2018	2019	2020	2021
C22	452	550	518	494	568
C22.1*	90 (20%)	110 (20%)	104 (20%)	99 (20%)	114 (20%)
C23+C24**	235	202	248	231	267
Incidence in Denmark C22.1+C23+C24	325	312	352	330	381

** C22.1 is 20% of C22 Estimated based on data from NordCan(13) and the Swedish Cancer Register(42)*
***C23+C24 data from Sundhedsdatastyrelsen (47)*

According to Danish National guidelines only approximately 1/3 of cholangiocarcinomas are respectable (14). AstraZeneca assumes that the incidence of unresectable and metastatic BTC in total is 70% of the yearly incidence. This estimation is confirmed by market research and interviews. In addition, the total number of 380 patients in 2021 also includes patients with ampullary cancers of hepatobiliary origin. Patients with initially resectable, but relapsed unresectable and/or metastatic cancer are also candidates for GemCis with durvalumab. However, there is no registry data to capture these patients. Yet, the lack of these patients is estimated to even out the number of patients with ampullary cancers. According to ESMO guidelines (25), chemotherapy is the current standard of care for 1L advanced BTC for fit patients. According to clinicians treating BTC, most of the patients that they evaluate for chemotherapy have a good performance status (PS 0-1). Patients with a performance status of 0-1 are eligible for platinum-based treatment. Gemcitabine monotherapy may be considered for patient with PS 2. Patients with a PS more than 2 are directly referred to palliative care unit. The GemCis combination is the recommended drug of first choice, but oxaliplatin may be used instead of cisplatin when there is concern about renal function (25). Based on market research and interviews, it is assumed that 65% of 1L BTC patients have ECOG 0-1 and therefore eligible for platinum-based therapy, and that 77% of these patients again are eligible for GemCis treatment. Comorbidities are considered when selecting the platinum-agent. The contraindications towards PD-(L)1 inhibitors are commonly similar for all available ICIs and usually cover trial exclusion criteria: active or prior documented autoimmune disease within 2 years of initiation of the study; a history of immunodeficiency; a history of severe immune-mediated adverse reactions; medical conditions that required systemic immunosuppression, except physiological dose of systemic corticosteroids (≤ 10 mg/day prednisone or equivalent); uncontrolled intercurrent illnesses; active tuberculosis or hepatitis B or C or HIV infection or patients receiving live attenuated vaccine within 30 days before or after the start of PD-(L)1 therapy (48). ICIs should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis. Based on AstraZeneca's estimations and interviews, it is assumed that 75% of the GemCis population will be eligible for addition of durvalumab therapy (Table 2).

The remaining 25% of the unresectable and metastatic BTC population is estimated to have a PS ≥2, and these patients are either treated with less toxic single agent chemotherapy, for instance gemcitabine monotherapy (PS 2), or BSC (PS ≥3). BTC is a group of rapidly progressive cancers in the biliary tract and the response to first-line therapy is relatively short with current treatment options (median PFS 8 months for GemCis, see chapter 5.2.4). For this reason, only the incident population is included in the estimated patient population.

It is furthermore assumed that not all eligible patients will receive durvalumab in combination with GemCis during the first year after reimbursement, but that there will be a gradual uptake. The number of patients eligible (ITT population) for receiving treatment with PD-(L)1 inhibitors in combination with GemCis in 1L treatment of unresectable or metastatic BTC is presented in Table 2 and the patient uptake in for the next five years, if reimbursed, in Table 3.

Table 2: Estimated patient number eligible for Imfinzi + Gem/Cis, patient numbers from 2021.

Incidence BTC[1,2]	Incidence of Locally advanced, unresectable, metastatic[3]	Patients with unresectable or metastatic BTC, ECOG 0-1 at 1L (eligible for platinum-based chemotherapy)[4]	Patients eligible for GemCis[4]	PD-L(1) + Gem/Cis[5]
380	266 (70%)	173 (65%)	133 (77%)	100 (75%)

Source:[1]*Danish Cancer Registry(47),(11)* [2]*fraction of intrahepatic CCA of liver cancer estimated from Swedish Cancer registry(42),* [3] *DLGCG national guidelines(14) confirmed by market research and expert interviews,* [4] *Market research and expert interview,* [5] *AstraZeneca assumption aligned with expert interviews*

Table 3: Estimated number of patients eligible for durvalumab+GemCis

Year	2024	2025	2026	2027	2028
Patients eligible for PD-(L)1i + GemCis	100	100	100	101	101
Expected uptake of new patients	50%	60%	80%	100%	100%
Number of PD-(L)1i + GemCis patients	50	60	80	101	101

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

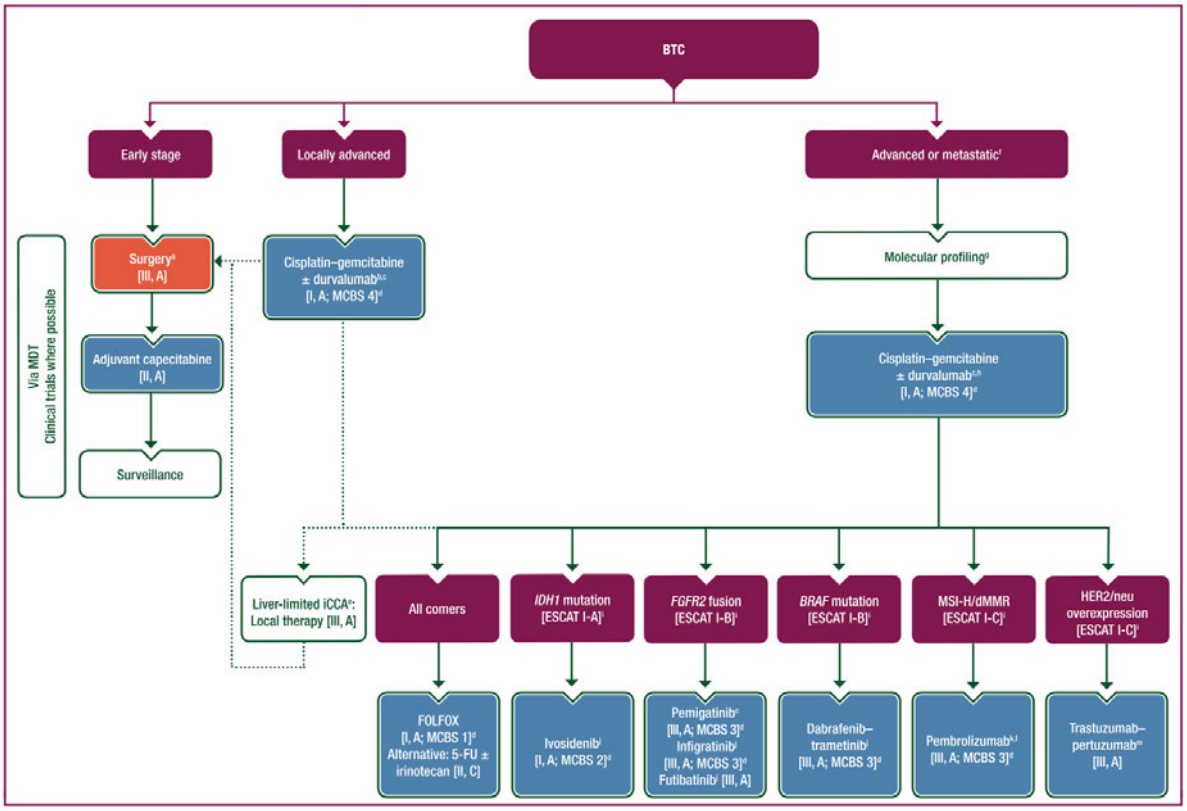
Although no treatment guideline has been constructed by the Danish Medicines Council for BTC, the Danish Liver and Biliary Cancer Group (DLCGC) has published guidelines on cholangiocarcinoma that were latest updated on October 2020 (14). Patients with unresectable BTC who are fit (ECOG 0-1) with bilirubin <50 and adequate liver- and kidney function should be considered for palliative/life prolonging chemotherapy. Obstructed bile ducts in icteric patients must be relieved before chemotherapy (14). The recommendation for first-line treatment for all subgroups of BTC is platinum-based combination chemotherapy, namely gemcitabine and cisplatin (GemCis), for patients with good performance status (PS) 0-1. Median OS with GemCis was 13.0 months among relatively fit patients (PS 0-1) in an international randomised controlled trial (RCT) setting (25). There is currently insufficient evidence to recommend continuous treatment beyond 6 months and decisions should be based upon individual patient toxicity, tolerability and tumour response (25). For 1L treatment also other combinations may be considered if the patient's condition requires it. ESMO guidelines on BTC recommends that oxaliplatin may be substituted for cisplatin when there is concern about renal function (25). For frail patients (PS 2), gemcitabine monotherapy may be considered.

According to the Danish clinician AstraZeneca consulted, GemCis is the first choice of combination in eligible patients, which is in accordance with ESMO guidelines (49). Oxaliplatin may be substituted for cisplatin if renal function is a concern. Carboplatin in combination with gemcitabine may also be considered in isolated cases. Thus, according to the same clinician, the majority of patients with advanced BTC are treated with GemCis in 1L setting in Denmark. The recommendation for second line (2L) treatment depends on the choice of first-line therapy and patient's performance status. Commonly, chemotherapy regimens with different mechanism of action (MoA) should be chosen for subsequent treatment lines. Targeted therapies may be applicable, if the presence of driver mutations can be shown with validated next genome sequencing panels. According to DLCGC guidelines, 2L treatment is only recommended in clinical trials, however patients with a good performance can be offered genomic profiling for biologically targeted therapy such as FGFR2 mutations or microsatellite stability evaluation (14). Based on individual patient evaluation, Danish clinicians assess that BTC patients with good performance status can be offered treatment such as irinotecan-based combinations, capecitabine or oxaliplatin. In addition, pemigatinib was recommended by the Danish Medicines Council for patients with intrahepatic cholangiocarcinoma with performance status 1-0 and with FGFR2 fusion or other rearrangements.

However, the Council did not assess when in the treatment algorithm pemigatinib should be ordinated. Third line therapies are rare, and clinicians estimate that around 80-90% of patients will receive BSC. No immunotherapies are marketed or reimbursed for BTC at present.

Given BTC's severity and rapid progression, and that a relatively high proportion of patients will never receive treatment in 2L, there is a high unmet need for new treatments with new MoA in 1L. ESMO guidelines (updated 10 November, 2022) recommend, based on data from TOPAZ-1, that durvalumab in combination with GemCis should be considered for the 1L treatment of advanced BTC (25). The current treatment recommendation for the management of BTC is shown in Figure 2.

Figure 2: Summary of the ESMO recommendation and treatment algorithm for BTC



Sources: *ESMO (2022)(18)*

5.2.2 Choice of comparator(s)

There have been no major advances in the first-line treatment of unresectable or metastatic BTC during the last ten years. The available chemotherapy treatment options for unresectable or metastatic BTC patients in Denmark include combinations of platinum-based therapies (cisplatin, carboplatin or oxaliplatin), pyrimidine analogues (gemcitabine, capecitabine or fluorouracil) and irinotecan (30). Thus, there are no approved indications for treatment with immune checkpoint inhibitors or targeted therapies in first-line to compare. As outlined and summarised in chapter 5, gemcitabine + cisplatin (GemCis), or other platinum-based chemotherapy based on patient characteristics, is established in first-line for unresectable or metastatic BTC, and GemCis is currently used for most patients in this line. The clinician consulted by AstraZeneca, have stated that patients with contraindication will receive oxaliplatin, however, oxaliplatin-based chemotherapy is mainly used in 2L. The clinicians consulted by AstraZeneca, have stated that carboplatin or preferably oxaliplatin is chosen for patients with reduced kidney function, whilst the majority of patients will receive cisplatin. Furthermore, they state that irinotecan-based chemotherapy is mainly used in 2L. Thus, the majority of patients with ECOG 0-1 are currently treated with GemCis in 1L for BTC, and since durvalumab is indicated in combination with GemCis, the comparator for this assessment is GemCis.

AstraZeneca does not expect that durvalumab + GemCis will replace gemcitabine in combination with other platinum therapies, because patients that receive oxaliplatin or carboplatin have contraindications towards cisplatin. Since these patients are not eligible for GemCis, they will not be eligible for durvalumab + GemCis.

5.2.3 Description of the comparator GemCis(50)

Generic name(s) (ATC-code)

Gemcitabine (L01BC05) **Cisplatin** (L01XA01)

Mode of action

Gemcitabine is a nucleoside analogue antimetabolite which inhibits DNA synthesis, whereas cisplatin is an alkylating agent which binds to DNA preventing transcription and leading to apoptosis

Pharmaceutical form(51)

Gemcitabine Accord 10 mg/ml solution for injection **Cisplatin** 1 mg/ml is a solution for injection

Posology

Chapter 5.2.4 below describes posology for GemCis and BTC.

Method of administration

Gemcitabine: Intravenous use **Cisplatin**: Intravenous use

Dosing

Gemcitabine: 1000 mg/m^2 **Cisplatin**: 25 mg/m^2

Should the pharmaceutical be administered with other medicines?

Chapter 5.2.4 below describes the combination of gemcitabine and cisplatin for BTC

Treatment duration/criteria for end of treatment

Gemcitabine and **cisplatin** administered on Days one and eight, every third week for eight cycles

Necessary monitoring, both during administration and during the treatment period

Renal toxicity, which is above all cumulative, is serious and requires special precautions during administration. Nausea and vomiting can be intense and require treatment with suitable antiemetics. Careful monitoring must also be carried out for ototoxicity, myelosuppression and anaphylactic reactions

Need for diagnostics or other tests (i.e. companion diagnostics)

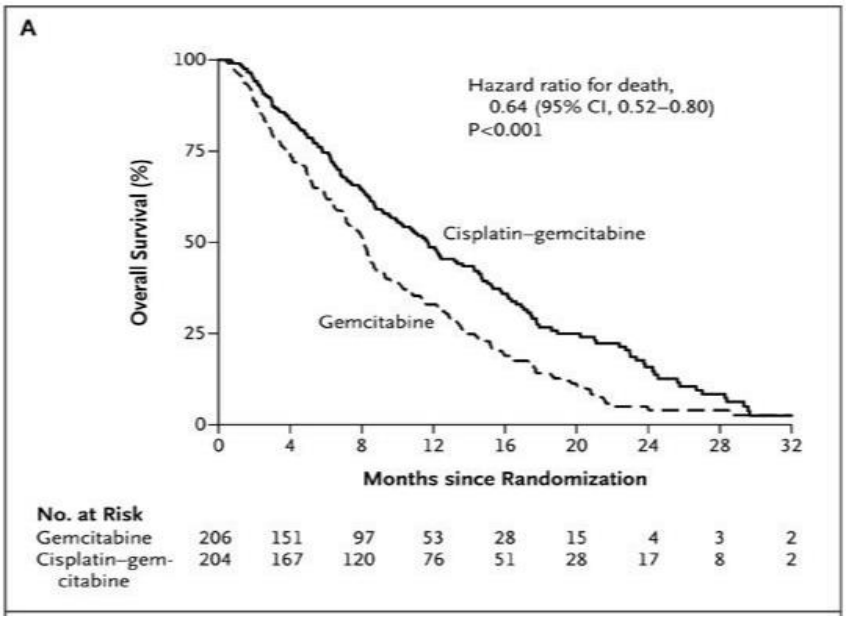
No

5.2.4 Efficacy studies – Documentation for the comparator's clinical efficacy

Treatment with comparator GemCis for BTC was introduced to clinical practice based on the ABC-02 study (3, 25). This was a phase III RCT where 410 patients with unresectable, locally advanced or metastatic BTC (cholangiocarcinoma, gallbladder cancer, or ampullary cancer) received either cisplatin (25 mg per square meter of body-surface area) followed by gemcitabine (1000 mg per square meter), each administered on days 1 and 8, every 3 weeks for eight cycles, or gemcitabine alone (1000 mg per square meter on days 1, 8, and 15, every 4

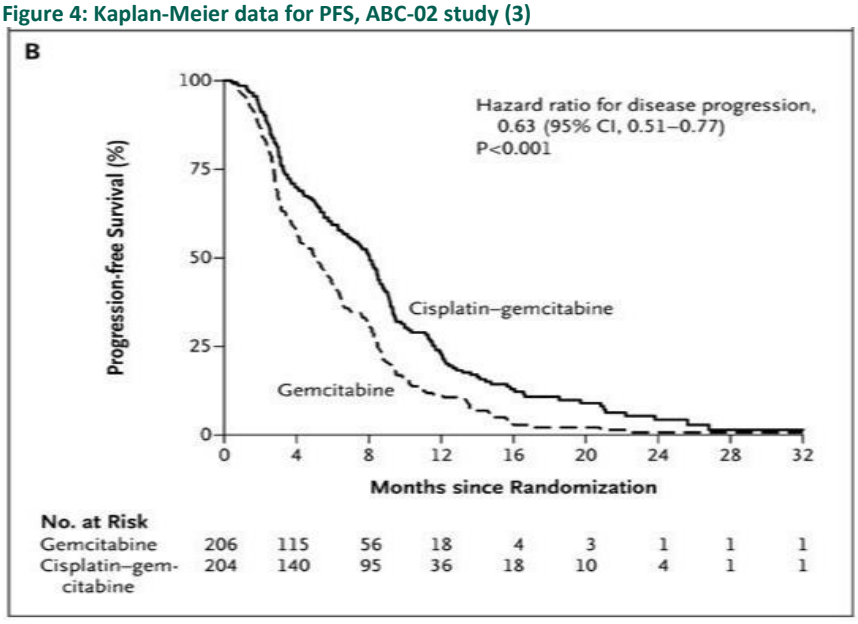
weeks for six cycles) for up to 24 weeks. Treatment duration and chemotherapy dosing in this study was in line with ESMO treatment guidelines; treatment up to maximum 6 months or shorter duration based on patient toxicity, tolerability and tumour response (25). Patients had ECOG 0-2 and an expected life expectancy > 3 months. Thus, also patients with ECOG 2 were included in contrast to Norwegian clinical practice and TOPAZ-1 trial criteria. Patients were included from the UK (3). As this study was performed before the introduction of immunotherapy for BTC, none of the patient's received immunotherapy in 2L. The primary end point was overall survival. After a median follow-up of 8.2 months and 327 deaths, the median overall survival was 11.7 months among the 204 patients in the cisplatin–gemcitabine group and 8.1 months among the 206 patients in the gemcitabine group (hazard ratio, 0.64; 95% confidence interval, 0.52 to 0.80; P<0.001) (Figure 3) (3).

Figure 3: Kaplan-Meier data for OS, ABC-02 study (3)



The median progression-free survival was 8.0 months in the GemCis group and 5.0 months in the gemcitabine-only group (P<0.001). In addition, the rate of tumour control among patients in the GemCis group was significantly increased (81.4% vs. 71.8%, P=0.049) (Figure 4) (3).

Figure 4: Kaplan-Meier data for PFS, ABC-02 study (3)



5.3 The intervention Durvalumab + GemCis

Generic name(s) (ATC-code)

Durvalumab (Imfinzi) (L01FF03)

Mode of action

Mode of action is described in section

Pharmaceutical form(51)

Concentrate for solution for infusion 50mg/ml

Posology

Durvalumab (1500mg) administered on day 1 of each cycle, in combination with gemcitabine (1000mg/m2) and cisplatin (25mg/m2) administered on days 1 and 8 of each cycle up to eight cycles. After completion of gemcitabine and cisplatin, 1500mg of durvalumab is to be administered once every 4 weeks

Method of administration

Administered as an intravenous infusion over 1 hour

Dosing

1500mg every 4 weeks

Should the pharmaceutical be administered with other medicines?

Yes, in combination with GemCis (ref posology)

Treatment duration/criteria for end of treatment

Until disease progression or unacceptable toxicity

Necessary monitoring, both during administration and during the treatment period

The SmPC lists several precautions for immune-mediated adverse events, signs for these should be monitored. Patients should be monitored for signs and symptoms of infusion-related reactions. For BTC specifically signs and symptoms of cholangitis and biliary tract infections should be monitored.

Need for diagnostics or other tests (i.e. companion diagnostics)

No

5.3.1 Durvalumab mode of action

Durvalumab is a high-affinity, human, recombinant IgG1κ monoclonal antibody which acts as a potent inhibitor of human PD-L1 (5). PD-L1 binds to either the PD-1 or CD80 (B7.1) receptors expressed on activated T cells and antigen-presenting cells (APCs) (52). By binding to its receptors, PD-L1 blocks T-cell function which leads to a reduction in cellular activity, proliferation, and cytokine production (53). Therefore, the interaction of PD-L1 with PD-1 is a so-called 'immune checkpoint,' and durvalumab belongs to the class of immunotherapies termed immune checkpoint inhibitors (ICI). BTC exhibits immunogenic features, including upregulated expression of PD-L1, translating into a significant immune resistance mechanism within the tumour microenvironment (8, 54-56).

In addition, tissue studies have demonstrated that the presence of tumour infiltrating lymphocytes (TILs) in BTC tissues, which is indicative of an active host immune response, is associated with better outcomes for patients (57, 58). Therefore, BTC represents a promising candidate to target with PD-L1 inhibitors. For the treatment of BTC, durvalumab is administered in combination with GemCis, which is considered the currently established standard of care (SOC) for first-line treatment. Gemcitabine is a nucleoside analogue antimetabolite which inhibits DNA synthesis, whereas cisplatin is an alkylating agent, which binds to DNA thus preventing transcription and leading to apoptosis (59). Accumulating evidence suggests that ICIs (such as PD-L1 inhibitors) combined with cytotoxic chemotherapy may provide a complementary benefit in mounting effective antitumour immunity by promoting antigen presentation, increasing the production of protective T cells, and overcoming immunosuppression in the tumour bed (60, 61). An immunotherapy agent that aids in the recognition of cancer cells by T cells may lead to long-lived tumour destruction, helping to prolong the tumour responses seen with cytotoxic agents (62). Therefore, combining a PD-L1 antagonist such as durvalumab with cytotoxic agents may result in enhanced efficacy and improved outcomes via different but synergistic mode of actions.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

AstraZeneca argues for not including a systematic literature search for this application as it include the head-to-head clinical trial of TOPAZ-1 to document for the efficacy and safety of durvalumab in combination with GemCis comparing GemCis alone. GemCis is already implemented in the Danish clinical practice as a 1L treatment for adults with unresectable or metastatic BTC, and there is no clinical practice for using ICI in combination with chemotherapy in BTC. However, in 2021 AstraZeneca had performed a systematic literature review (SLR) to identify published clinical efficacy and safety data of durvalumab and relevant comparators for the adjuvant treatment of BTC patients including disease subtypes. Searches we performed in electronic databases (Ovid, MEDLINE) along with handsearching of conference proceedings, clinical trial registries (clinicaltrial.gov), and regulatory sources (FDA and EMA). The electronic database searches identified 8663 articles. A total of 78 publications met inclusion criteria describing 38 unique randomised clinical trials (RCTs) (reported in 39 publications). Of the 38 included trials, the majority (n = 27, 71%) were phase II RCTs mainly conducted in Europe (n = 17, 45%) and Asia (n = 14, 37%). The current standard of care, gemcitabine plus cisplatin (GemCis), was the most commonly evaluated comparator in the included RCTs (n= 17). Other commonly evaluated therapies were gemcitabine (n= 7), gemcitabine plus oxaliplatin (n=6) and gemcitabine plus S-1 (n=4). These chemotherapy regimens were combined with various targeted therapies including panitumumab, cetuximab, cediranib, and durvalumab. However, according to a Danish clinician interviewed for this application, these chemotherapies and the combination therapies are not of preference in Danish clinical practise, hence these data are argued not relevant to emphasise the efficacy and safety of durvalumab with GemCis compared to GemCis, an already established treatment for Danish patients in advanced BTC in first-line. Hence, only one trial was identified in the SLR that provides clinical evidence that is directly relevant for this application; the phase III clinical trial TOPAZ-1.

6.2 List of relevant studies

Table 4: Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. Do-Youn Oh, M.D. et al., NEJM Evid, 2022; DOI:https://doi.org/10.1056/EVIDoa2200015; (8)	**TOPAZ-1**	**NCT03875235**	Actual Study Start Date: April 16, 2019 Actual Primary Completion Date: August 11, 2021 (Final data collection date for primary outcome measure)	Overall Survival, Progression Free Survival, Safety(AE and AE grade 3 or more) and HRQoL

7. Efficacy and safety

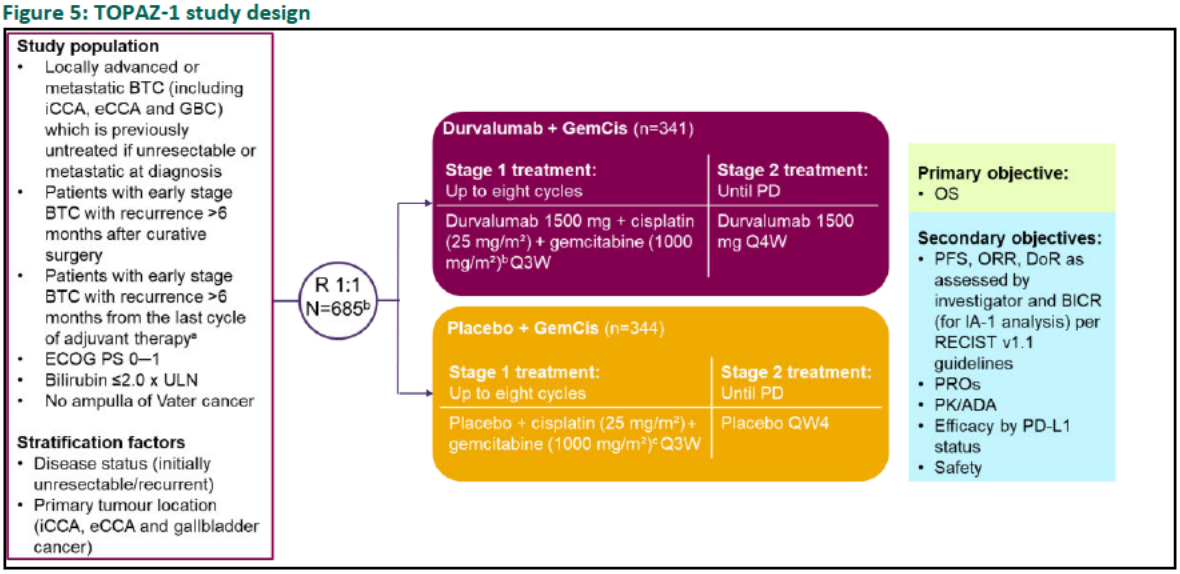
7.1 TOPAZ-1: durvalumab in combination with Gemcis compared to Gemcis for the first-line treatment of adults with unresectable or metastatic biliary tract cancer (BTC).

AstraZeneca presents efficacy and safety data from the phase III clinical trial, TOPAZ-1, a head-to-head study, as this study is found to be most applicable to show the efficacy and safety of durvalumab in combination with Gemcis vs. GemCis. GemCis is the comparator and is currently the preferred first-line treatment option for BTC patients with unresectable and metastatic disease according to the Danish guideline, DLCGC in line with international guidelines.

7.1.1 Study overview

TOPAZ-1 (NCT03875235) is an ongoing randomised, double-blind, multicentre, phase III clinical trial that assessing the efficacy and safety of durvalumab in combination with GemCis vs. placebo in combination with GemCis for the first-line treatment of unresectable or metastatic BTC, including intrahepatic or extrahepatic CCA and gallbladder cancer. Cross over was not allowed. TOPAZ-1 study design is presented in Figure 5.

Figure 5: TOPAZ-1 study design



Footnotes: *[a]Patients with recurrence >6 months after curative surgery without adjuvant therapy or >6 months after adjuvant therapy were included. [c] Corresponds to the global cohort. [c]Cisplatin (25 mg/m²) and gemcitabine (1000 mg/m²), each administered on Days 1 and 8, Q3W for 8 cycles.* ***Source:*** *Oh et al. (2022)a.(8) AstraZeneca Data on File (10)*

Treatment naïve BTC patients with unresectable and metastatic disease were randomised into treatment arms in 1:1 ratio using IVRS/IWRS (interactive voice-response system/interactive web response system) and treated until they experienced confirmed disease progression (PD), unacceptable toxicity, or met any of the trial discontinuation criteria. In certain cases, patients with confirmed PD could continue to receive their assigned intervention if the study investigator deemed that they were continuing to receive benefit from the treatment. From April 2019 to December 2020, 914 patients were enrolled at 105 sites in 17 countries. In total, 685 patients were randomly assigned to receive either treatments: 341 to the durvalumab plus GemCis group and 344 to the placebo plus GemCis group. Of these, 3 and 2 patients discontinued, respectively. Patients with HBV infections received antiviral therapy prior to randomisation to ensure adequate viral suppression. The study design of TOPAZ-1 including inclusion and exclusion criteria arms are described in Appendix B *Main characteristics of included studies*

Table 5: Dosing information for the investigational product and comparator in TOPAZ-1 .

Treatment arms	Formulation and dosing
Study arm	Cisplatin (25 mg/m2) and gemcitabine (1000 mg/m2), each administered on day one and eight of each Q3W cycle in combination with durvalumab (1500 mg) via infusion on day one of each Q3W cycle, for up to eight cycles. After completion of GemCis, durvalumab monotherapy (1500 mg) administered via infusion Q4W
Control arm	Cisplatin (25 mg/m2) and gemcitabine (1000 mg/m2), each administered on day one and eight of each Q3W cycle in combination with placebo via infusion on day one of each Q3W cycle, for up to eight cycles. After completion of GemCis, placebo administered via infusion Q4W

Source: *AstraZeneca Data on File TOPAZ-1 (10)*

The primary objective was to evaluate OS with investigator assessment of unresectable BTC patients receiving durvalumab + GemCis as first-line treatment compared with patients receiving placebo + GemCis. The primary endpoint was formally analysed at two planned data cuts (first data cut-off [DCO1; interim analysis (IA-1)] and second data cut-off [DCO2; final formal analysis (IA-2)]. Approximately 6.5 months after the IA-2 DCO, an additional analysis was carried out to further characterise long-term survivorship of durvalumab + GemCis, given that the difference between treatment groups for OS was increasingly apparent over time in IA-2. Table 6 shows the planned and updated table for TOPAZ-1. The secondary objectives were to evaluate progression-free survival (PFS), objective response rate (ORR) and duration of response (DoR) for patients receiving durvalumab + GemCis compared with patients receiving placebo + GemCis. These endpoints were investigator assessed along with BICR assessments according to RECIST 1.1. Although it is to be noted that BICR sensitivity analysis was only conducted for the first interim analysis, and will not be included in this application as it will only focus on the latest updated interim analysis from DCO3.

Other secondary endpoints included:

- To assess disease-related symptoms, impacts, and HRQoL e.g. time to deterioration using EORTC-QLQ-C30, EORTC-QLQ-BIL21
- To assess the efficacy of durvalumab + GemCis compared with placebo + GemCis by PD-L1 expression according to RECIST 1.1 using Investigator assessments
- To assess the PK of durvalumab when used in combination with GemCis
- To investigate the immunogenicity of durvalumab

Table 6. Planned and updated data cuts for TOPAZ-1

Data cut	Analysis
DCO1	**Interim analysis (IA-1) OS** **DCO1** (IA-1, December 18, 2020): Included 685 patients and was performed after 369 patients had undergone ≥32 weeks of follow-up.
DCO2	**Final analysis (IA-2) OS** **DCO2** (IA-2, Final formal analysis, August 11, 2021): Was performed when 424 deaths had occurred in the two treatment arms. The median duration of follow-up was 13.7 months in the durvalumab + GemCis arm vs. 12.6 months in the placebo + GemCis arm with 61.9% overall maturity for OS in the global cohort
DCO3	**Updated final (+ 6.5 months IA-2) OS** **DCO3** (IA-2+ 6.5 months, February 25, 2022): The update occurred at approximately the same OS maturity that was prespecified for the final analysis in the original protocol with 76.9% overall maturity for OS in the global cohort

In addition to the above we have also included updated OS data from 23rd Oct 2023. This DCO is named 3 years OS DCO All efficacy analyses were carried out on the full analysis set (FAS), which includes all randomised patients. *In general, assessment was carried out by the trial investigator, and tumour status was assessed according to the RECIST 1.1 guidelines (63).* A summary of the key analysis sets from TOPAZ-1 are presented in Table 7.

Table 7: Key analysis sets in TOPAZ-1.

Population	Definition
Full analysis set (FAS)	ITT population: all patients randomised to a treatment arm (including those who do not subsequently receive treatment)
Safety analysis set (SAS)	All patients who received at least one dose of study treatment

If nothing else is stated, all results presented in this application refers to the full analysis set (FAS). Efficacy results from TOPAZ-1 can be found in section 7.2, and safety data in section 7.3.

7.2 Efficacy

7.2.1 Primary endpoint: Overall survival (IA-2 + 6.5 months and 3 years DCO

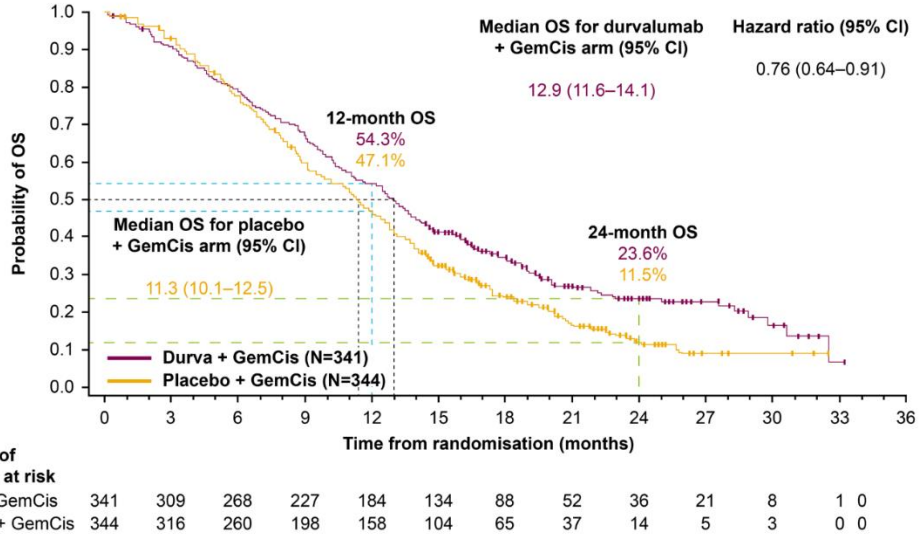
At the final analysis (IA-2) TOPAZ-1 met its primary endpoint, demonstrating a statistically significant, clinically meaningful and sustained improvement in OS for the durvalumab + GemCis treatment arm compared with the placebo + GemCis treatment arm (HR: 0.80, 95% CI: 0.66–0.97; *p*=0.021), corresponding to a 20% reduction in the overall risk of death. The reported median OS was 12.8 months (95% CI: 11.1–14.0) and 11.5 months (95% CI: 10.1–12.5) for durvalumab + GemCis and placebo + GemCis, respectively. The improvement of OS benefit was sustained with 24% reduction in the overall risk of death (HR: 0.76, 95% CI: 0.64–0.91), when an additional 6.5 months of follow-up was conducted for the primary disclosure of OS (IA-2)(67). The median OS continued to be longer with durvalumab + GemCis (12.9 months (95% CI: 11.6–14.1)) compared to placebo + GemCis (11.3 months (95% CI: 10.1–12.5)), with the median OS benefit of durvalumab + GemCis increasing from 1.3 to 1.6 months compared to IA-2 (12.8 and 11.5 months, respectively) representing a >10% improvement in median OS at the 6.5 month update (64). These OS results were presented at ESMO 2022 (IA-2 + 6.5 months) (62), and this analysis included a total of 103 new OS events (76.9% overall maturity; 527/685). As seen at IA-2, a greater proportion of patients remained on durvalumab + GemCis (9.5% patients; 32/341) than on placebo + GemCis (2.0% patients; 7/344) (61). As the data matured in longer follow-up, the OS benefit improved (HR 0.76; 95% CI 0.64, 0.91; p<NR) vs the OS in DCO2 for AI-2 (HR 0.80; 95% CI 0.66, 0.97; p<0.021).

DMC has asked when next DCO is planned. For this application we have just been granted access to 3 years DCO from 23rd Oct 2023. The primary analysis of OS (Aug 2021 DCO), which showed a statistically significant improvement with the addition of durvalumab to gem-cis, remains the most appropriate and important data demonstrating the survival benefit of durva + gem/cis.
OS results for durva + gem/cis improved from the primary analysis (61.9% maturity) to the pre-specified final analysis (Feb 2022 DCO, 76.9% maturity). With the additional 6 months of OS follow-up, the OS HR improved from 0.80 to 0.76 and the median OS benefit increased from 1.3 to 1.6 months. With more mature data, the IO-tail seen at the primary analysis was maintained, with 1- and 2-year landmark OS values consistent across DCOs, showing double the number of patients alive at 2 years with durva + gem-cis vs. gem-cis.

The latest exploratory OS data (Oct 2023 DCO) confirm the survival benefit of durvalumab + gem-cis with even longer-term follow-up, with a slight improvement in the HR (0.74), consistent median OS benefit and OS landmarks versus the prior DCOs, and a clear separation of the OS curves in the long-term. The summary of the OS results is presented in Table 8.

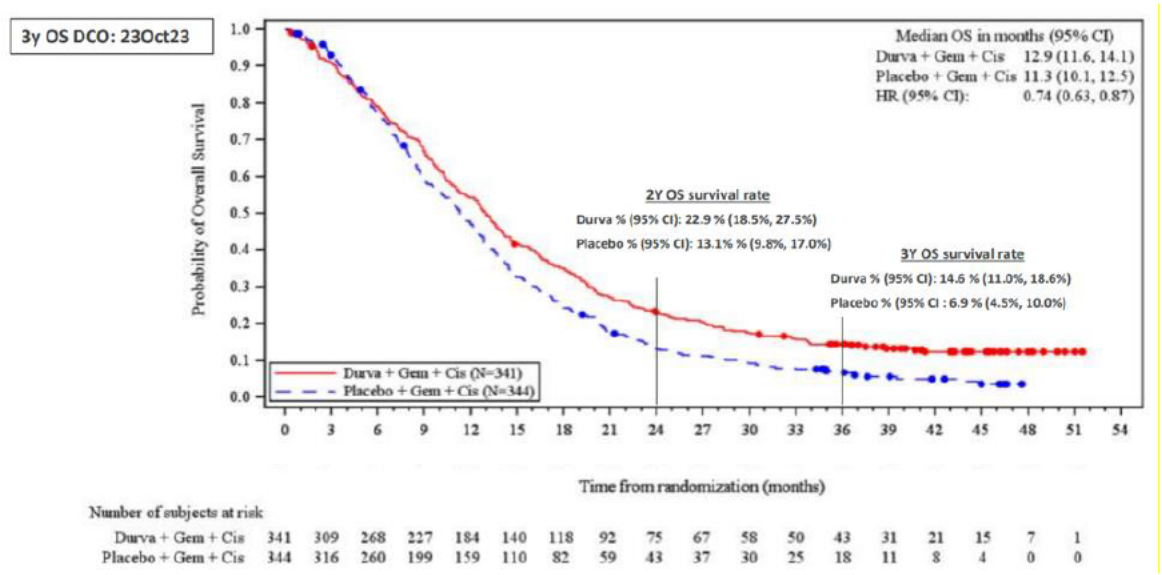
The KM plot for OS was captured in both IA-2 and in the updated analysis of IA-2, but for this application the latest KM plot from the updated analysis is shown in Figure 6. And the most updated KM plot from October 2023 is shown in Figure 7. Approximately at six months the survival curves separated between the treatment arms which was clear and sustained favouring the durvalumab + GemCis arm. The difference in OS between treatment arms became increasingly apparent over time reflecting the long-term benefit (10).

Figure 6: KM plot of OS in TOPAZ-1 (6.5 month update; FAS)



Source: *AstraZeneca Data on File – TOPAZ-1 – 6.5 month update.(9, 65)*

Figure 7: KM plot of OS in TOPAZ-1 (3 years update)



Source: Oh et al. 2024 (66)

The separation of the survival curves can be attributed to the mechanism of action of immunotherapy. Thus, when the chemotherapy part of the treatment ended, the added benefit from durvalumab was clearly seen as higher number of patients alive along the landmarks 12, 18 and 24 months (Figure 6). Furthermore, twice as many patients were alive at two years in the durvalumab + GemCis arm compared to placebo + GemCis arm (23.6% vs. 11.5%). These trends are similar to other studies with immune checkpoint inhibitors + chemotherapy vs. chemotherapy alone that have been conducted in multiple solid tumour types (67, 68). For these patients with metastatic cancer where median expected survival is usually shorter than 1 year, an OS gain of approximately doubling the patients alive at two years is considered to be of clinical importance. The 3 years OS update show a clear and maintained separation of OS tail (IO effect)

The convergence of the KM curves at ~32 months should not be considered a robust or meaningful observation; this is in part due to the fact the OS data is still not fully mature (76.9%) and only few patients have passed the follow-up of 24 months. It should also be noted that the curves do not cross until the point where the last patient in the placebo + GemCis arm was censored (61, 62).

Table 8: Summary of TOPAZ-1 OS results (IA-2,6.5 month update and 3 years; FAS)

		Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
		IA-2; FAS		*6.5 month updated analysis; FAS (3 years in blue)*	
Number of deaths, n (%)		198 (58.1)	226 (65.7)	248 (72.7)	279 (81.1)
Number of censored patients, n (%)		143 (41.9)	118 (34.3)	93 (27.3)	65 (18.9)
Hazard ratio[a, b]		0.80		0.76 (0.74)	
95% CI for hazard ratio[a, b]		0.66–0.97		0.64–0.91 (0.63, 0.87)	
97% CI for hazard ratio[c]		0.64–0.99		N/R	
Log-rank test: 2-sided p-value[c]		0.021		N/R	
Median OS, months (95% CI)[d]		12.8 (11.1–14.0)	11.5 (10.1–12.5)	12.9 (11.6–14.1) 12.9(11.6_14.1)	11.3 (10.1–12.5) 11.3(10.1-12.5)
OS rate, % (95% CI)[d]	12 months	54.1 (48.4–59.4)	48.0 (42.4–53.4)	54.3 (48.8–59.4)	47.1 (41.7–52.3)
	18 months	35.1 (29.1–41.2)	25.6 (19.9–31.7)	34.8 (29.6–40.0)	24.1 (19.6–28.9)
	24 months	24.9 (17.9–32.5)	10.4 (4.7–18.8)	23.6 (18.7–28.9)	11.5 (7.6–16.2)
Median (95% CI) duration of follow-up in censored patients, months		13.7 (0.4–27.2)	12.6 (0.7–26.0)	19.9 (0.4–33.2)	18.7 (0.7–32.5)

Footnotes: *[a]Analysis performed using stratified Cox proportional hazards model (ties = Efron), adjusting for disease status and primary tumour location. CI calculated using a profile likelihood approach. Hazard ratio <1 favours durvalumab, associated with a longer overall survival than placebo. [b]At pre-planned interim analysis, study met its primary objective by demonstrating OS superiority for durvalumab + GemCis vs placebo + GemCis. [c]Overall survival was analysed using a log-rank test stratified by disease status and primary tumour location. [d]Calculated using Kaplan-Meier technique. CI for median overall survival derived based on Brookmeyer-Crowley method.*
Source: *Oh et al. (2024) (66). ; Oh et al. (2022)c.(9)*

The ratio of restricted mean survival time (RMST) can also be used to quantify the OS benefit of treatment. This refers to a measure of average survival from time zero to a specified time point as the area under the survival curve up to that point (69). The RMST of OS difference between durvalumab + GemCis and placebo + GemCis increased from 1.68 to 2.17 months, between IA-2 and the 6.5 month update. Additionally, the piecewise HR at 6 months dropped from 0.74 to 0.71, between IA-2 and the 6.5 month update (Table 9). This 0.6 month difference increase in RMST between the two arms and drop in piecewise HR, further highlights the benefit that durvalumab + GemCis treatment has on OS (65, 70).

Table 9: TOPAZ-1 OS RMST and piecewise HR results (IA-2 and 6.5 month update; FAS)

	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
	IA-2; FAS		*6.5 month updated analysis; FAS*	
RSMT, months (SE)	14.1 (0.5)	12.5 (0.5)	15.3 (0.6)	13.1 (0.5)
95% CI for RMST	13.1–15.1	11.6–13.3	14.1–16.4	12.1–14.1
RMST difference (SE)	1.68 (0.68)		2.17 (0.77)	
95% CI for difference	0.35–3.02		0.66–3.67	
p-value	0.014		0.005	
Piecewise HR at 0–6 months	0.91		0.91	
Piecewise HR at 6+ months	0.74		0.71	
95% CI for piecewise HR at 6 months	0.58–0.94		0.58–0.88	

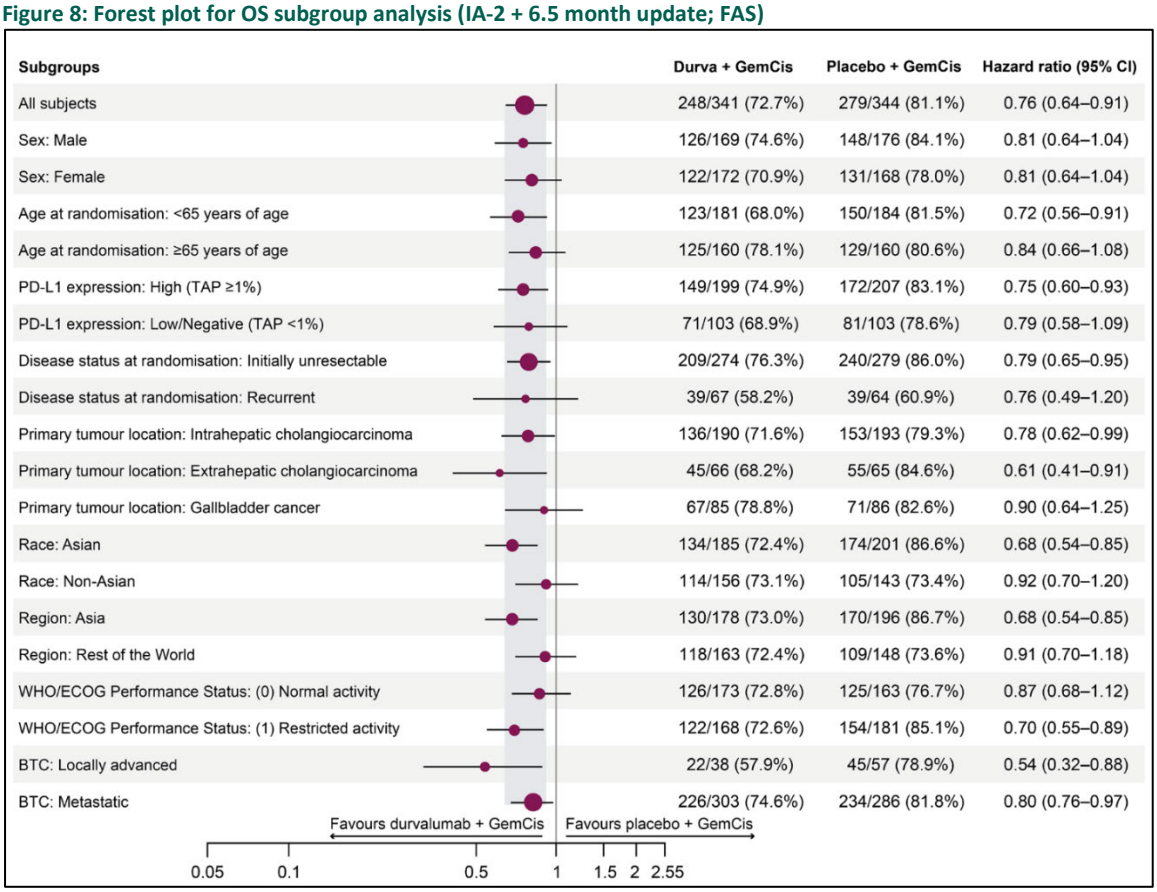
Footnote: *restricted mean survival was estimated up to the last time point (rounded down to the nearest integer) on which each treatment arm has an observed event in the study.* **Source:** AstraZeneca Data on File – TOPAZ-1 Restricted Mean Survival Time Analysis.(70)

The aim of using the piecewise HR is to show that the relative efficacy improved over time. Unlike most conventional cancer treatments, immunotherapy has an indirect mechanism of action, which causes a delayed treatment effect. This leads to delayed separation of survival curves between the treatment groups, but also a durable response. As these characteristics of the treatment effect typically violates the proportional hazards assumption., it is important to study how the HR develops over time.

7.2.2 Exploratory subgroup analysis of OS

Prespecified subgroup analyses were undertaken in both the IA-2 and the 6.5 month updated analysis to assess the consistency of treatment effect across expected prognostic and/or predictive factors. At IA-2, no statistically significant (p=0.292) interaction with the treatment effect from stratification factors was identified, including disease status and primary tumour location (10). Furthermore, at the 6.5 month updated analysis, the OS benefit favouring durvalumab + GemCis treatment vs. placebo + GemCis treatment was consistent across the prespecified subgroups, with all HR point estimates continuing to favour durvalumab + GemCis. Importantly, this included patients with a PD-L1 negative/low status, which is defined as PD-L1 tumour area positivity (TAP) score <1% (Figure 8). TAP refers to the percentage of viable tumour cells showing partial or complete membrane staining relative to all viable tumour cells present in the sample. In alignment with the prespecified analysis at the TAP 1% cut-off, post-hoc analyses using additional TAP cut-offs (5% and 10%) indicated a consistency of treatment effect for OS across PD-L1 subgroups in both the 6.5 month updated analysis and the IA-2 analysis. Additionally, a post hoc interaction test of durvalumab by PD-L1 status for OS suggested that PD-L1 status did not have a substantial impact on OS (p-value for TAP <1%, ≥1%: 0.7264, p-value for TAP <5%, ≥5%: 0.2612), suggesting that PD-L1 expression may not be a useful predictive biomarker to guide durvalumab use in BTC. It's important to note that the study was not sized for any of the individual subgroup evaluations and no adjustments were made for multiplicity.

Figure 8: Forest plot for OS subgroup analysis (IA-2 + 6.5 month update; FAS)

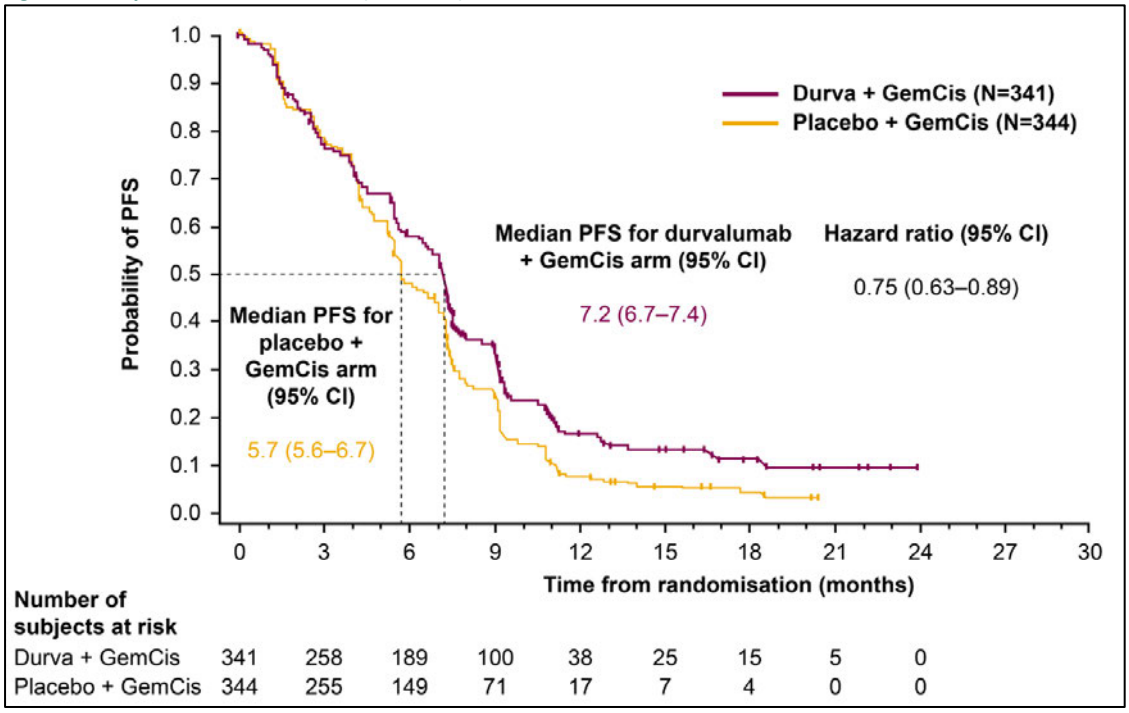


Footnotes: *The overall analysis was performed using a stratified Cox proportional hazards model, adjusting for disease status (initially unresectable or recurrent) and primary tumour location (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma or gallbladder cancer) from IVRS. Profile likelihood methods were used to calculate CIs. Estimates for all subgroup categories were from an unstratified Cox proportional hazards model with treatment as the only covariate. Stratification subgroups are from the electronic case report form (eCRF). Size of circle is proportional to the number of events. Grey band represents the 95% CI for the overall (all patients) hazard ratio. Hazard ratio (durvalumab + GemCis vs. Placebo + GemCis) and 95% CI. A hazard ratio < 1 favours durvalumab + GemCis.*
Source: *AstraZeneca Data on File – TOPAZ-1 Clinical Study Report – 6.5 month update.(70)*

7.2.3 Key secondary endpoint: Progression-free Survival (IA-2)

PFS was included in the multiple testing procedure and could therefore be formally tested, as OS met statistical significance at IA-2. At the final DCO for IA-2, 573 PFS events had occurred across the durvalumab + GemCis and placebo + GemCis treatment arms (83.6% overall maturity; 573/685). Overall, 80.9% (276/341) had progressed or died in the durvalumab + GemCis group compared to 86.3% (297/344) in the placebo + GemCis group. Treatment with durvalumab + GemCis resulted in a statistically significant, clinically meaningful, and sustained improvement in PFS compared with placebo (HR: 0.75; 95% CI: 0.63–0.89; p=0.001), with the median PFS of 7.2 months (95% CI: 6.7–7.4) for the durvalumab + GemCis treatment arm and 5.7 months (95% CI: 5.6–6.7) for the placebo treatment arm (Figure 9 and Table 10). For patients with BTC, a cancer with a very rapid progression and associated decline in HRQoL, a median increase in progression free survival of 1.5 months is of clinical importance. This corresponds to a **25% reduction in the overall risk of progression or death** with the addition of durvalumab to GemCis compared with placebo + GemCis (8, 10).

Figure 9: KM plot of PFS in TOPAZ-1 (IA-2; FAS)



Footnotes: *[a]Only includes progression events that occurred within 2 missed visits of the last evaluable assessment; [b]Calculated using the KM technique; [c]The hazard ratio and its CI was estimated using a stratified Cox proportional hazards model (ties = Efron) adjusting for disease status and primary tumour location; [d] The p-value is based on a stratified log-rank test and tested at 0.0481 significance level. A hazard ratio < 1 favours durvalumab + GemCis, to be associated with a longer progression-free survival than Placebo + GemCis.*
Source: *Oh et al.(2022)a.(8); AstraZeneca Data on File – TOPAZ-1 (10)*

The KM plot for PFS separated at approximately four months of treatment, in favour of the durvalumab + GemCis treatment arm, which remained consistent through to the tail. The sustained separation of PFS curves is reflected in PFS rates at 6, 9, and 12 months (Table 10), with a 12-month PFS of 16.0% in the durvalumab + GemCis group compared to 6.6% in the placebo + GemCis group. The PFS separation occurred earlier than the

OS separation, supporting the early positive effect of durvalumab to patients. This is further supported by the median times to response occurring earlier in the durvalumab + GemCis group compared to the placebo + GemCis group (section 7.2.6) (10). The durvalumab + GemCis PFS curve also suggests a subset of patients with enduring PFS, as reflected in the tail of the PFS curve after 12 months. In contrast to the durvalumab + GemCis group, the placebo + GemCis PFS curve showed the expected continuing decline that is typical with chemotherapies, with no evidence of a subgroup of individuals with long-term PFS (10).

Table 10: Summary of TOPAZ-1 PFS results (IA-2; FAS)

		Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
Total events, n (%)[a]		276 (80.9)	297 (86.3)
Median PFS, months (95% CI)[b]		7.2 (6.7–7.4)	5.7 (5.6–6.7)
Hazard ratio[c]		0.75	
95% CI for hazard ratio[c]		0.63–0.89	
2–sided p-value[d]		0.001	
Progression-free at DCO, n (%)		56 (16.4)	28 (8.1)
PFS rate, % (95% CI)[b]	6 months	58.3 (52.8–63.4)	47.2 (41.6–52.5)
	9 months	34.8 (29.6–40.0)	24.6 (20.0–29.5)
	12 months	16.0 (12.0–20.6)	6.6 (4.1–9.9)

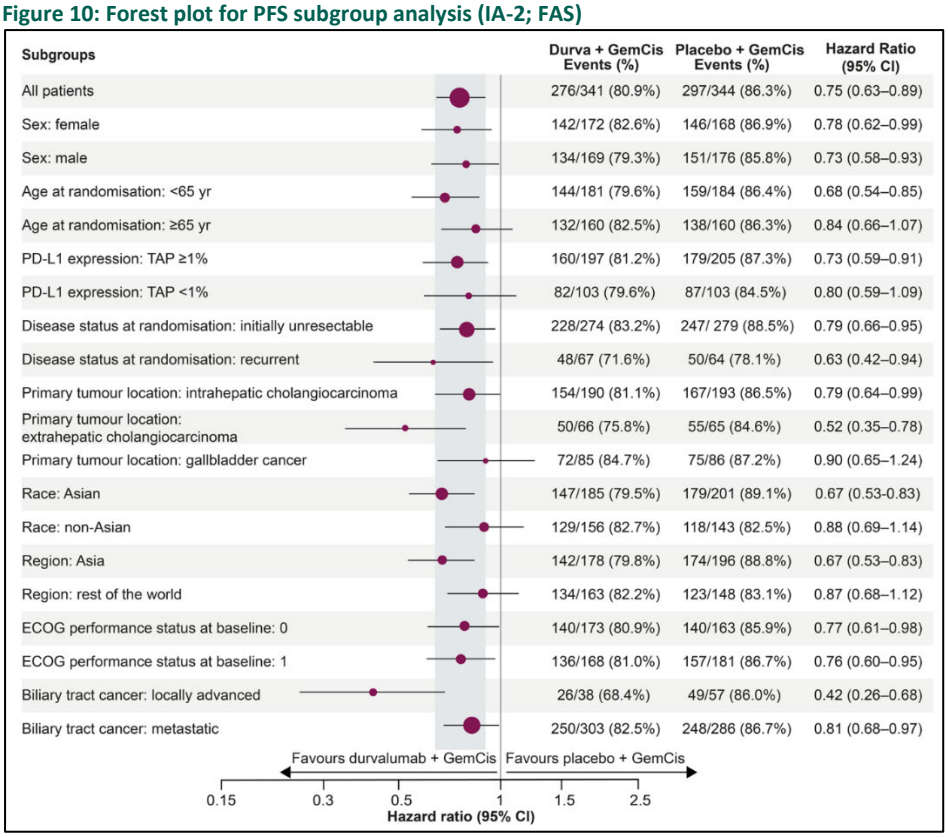
Footnotes: *[a]Only includes progression events that occurred within two missed visits of the last evaluable assessment; [b]Calculated using the KM technique; [c]The hazard ratio and its CI was estimated using a stratified Cox proportional hazards model (ties = Efron) adjusting for disease status and primary tumour location; [d] The p-value is based on a stratified log-rank test and tested at 0.0481 significance level. A hazard ratio <1 favours durvalumab + GemCis, to be associated with a longer progression-free survival than Placebo + GemCis.*

EMA have concluded in the EPAR for the Imfinzi BTC indication that "Overall PFS data support survival results, showing an advantage for the durvalumab + Gem/Cis arm (median PFS 7.2 months) over the placebo + Gem/Cis arm (median PFS 5.7 months), with a HR for PFS of 0.75 (95.19% CI 0.63, 0.89), and p-value of 0.001. The KM curves separate as of month 4, with landmark analysis at 6, 9 and 12 months supporting the PFS benefit from added durvalumab" (71).

7.2.4 Exploratory subgroup analysis of PFS

Prespecified subgroup analyses were performed to assess the consistency of treatment effect across expected prognostic and/or predictive factors. No statistically significant (p=0.157) interaction with the treatment effect from stratification factors was identified. Improvements in PFS in favour of patients receiving durvalumab + GemCis compared to those receiving placebo + GemCis were consistently observed across the prespecified subgroups as shown in Figure 10, and all estimated HRs favoured durvalumab + GemCis. As with the OS prespecified analyses, it's important to note that the study was not sized for any of the individual subgroup evaluations and no adjustments were made for multiplicity. The lower number of patients and events across individual subgroups means there is greater uncertainty in the point estimates which results in wider CIs. Furthermore, imbalance in other baseline covariates may have contributed to differences in HR across any subgroups (10).

Figure 10: Forest plot for PFS subgroup analysis (IA-2; FAS)



Footnotes: *The overall analysis was performed using a stratified Cox proportional hazards model, adjusting for disease status (initially unresectable or recurrent) and primary tumour location (intrahepatic CCA, eCCA or gallbladder cancer) from IVRS. Profile likelihood methods were used to calculate CIs. Estimates for all subgroup categories were from an unstratified Cox proportional hazards model with treatment as the only covariate. Stratification subgroups are from the eCRF. Size of circle is proportional to the number of events. Grey band represents the 95% CI for the overall (all patients) HR. Hazard group ratio (durvalumab + GemCis vs. Placebo + GemCis) and 95% CI. A hazard ratio < 1 favours durvalumab + GemCis.* ***Source:*** *AstraZeneca Data on File – TOPAZ-1 Clinical Study Report.(65)*

7.2.5 Objective response rate and best objective response (BOR) at IA-2

The ORR was 26.7% (91/341) for the durvalumab + GemCis treatment arm, and 18.7% (64/343) for the placebo + GemCis treatment arm. There was a higher frequency of complete responses (CR) (2.1%; 7/341) and partial responses (PR) (24.6%; 84/341) in the durvalumab + GemCis group compared to the placebo + GemCis group (0.6%; 2/343 and 18.1%; 62/343, respectively)(10). The higher likelihood of response to treatment with durvalumab + GemCis was found to be clinically meaningful (OR: 1.60; 95% CI: 1.11–2.31; nominal p=0.011) (8, 10). The ORR benefit of durvalumab + GemCis was consistently observed across all prespecified subgroups. The summary of the ORR results are presented in Table 11.

Table 11: Best objective response, TOPAZ-1 (IA-2; FAS) (62)

	Durvalumab + GemCis (N=341)	Placebo + GemCis (N=343)
Responders,[1,*] n (%)	91 (26.7)	64 (18.7)
Complete response,[1] n (%)	7 (2.1)	2 (0.6)
Partial response,[1] n (%)	84 (24.6)	62 (18.1)
Non-responders, n (%)	250 (73.3)	279 (81.3)
Stable disease, n (%)	200 (58.7)	220 (64.1)
Progressive disease,[†] n (%)	47 (13.8)	51 (14.9)
Not evaluable	3 (0.9)	8 (2.3)

*Confirmed response; †Death recorded within 13 weeks after randomisation is considered progression
GemCis, gemcitabine and cisplatin

7.2.6 Duration of response (DoR) at IA-2

Duration of response (DoR) was defined as the time from the first response (either complete or partial) until the date of progression, death, or the last evaluable RECIST assessment (for patients that have not progressed) (10). At the IA-2 analysis, the median DoR from onset for patients with an objective response was 6.4 months in the durvalumab + GemCis treatment arm and 6.2 months in the placebo + GemCis treatment arm. A greater percentage of patients in the durvalumab + GemCis treatment arm remained in response at 9 months following onset response (32.6% vs. 25.3% respectively) and 12 months (26.1% vs. 15.0%). Summary of the DoR results is presented in Table 12.

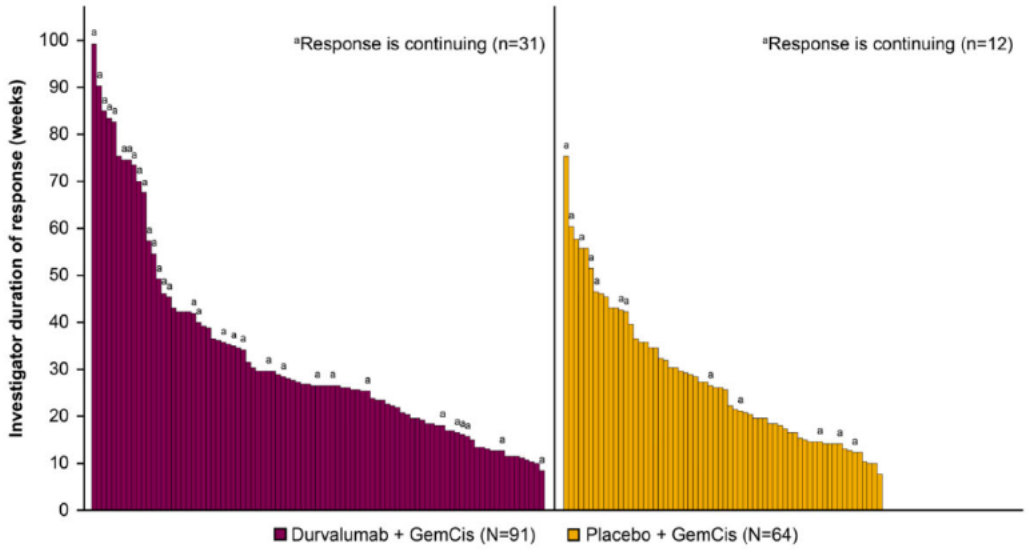
Table 12: TOPAZ-1 DoR results (IA-2; FAS; patients with objective response and measurable disease at baseline)

		Durvalumab + GemCis (n=91)[a]	Placebo + GemCis (n=64)[a]
Number of patients who subsequently progressed or died, n (%)		60 (65.9)	51 (79.7)
Median time to onset of response from randomisation, months, n (IQR)		1.6 (1.3–3.0)	2.7 (1.4–4.1)
Median DoR from onset of response, months (95% CI)[a,b]		6.4 (5.9–8.1)	6.2 (4.4–7.3)
Percentage remaining in response, %[b]	**≥3 months**	88.9	89.0
	≥6 months	59.3	54.2
	≥9 months	32.6	25.3
	≥12 months	26.1	15.0

Footnotes: *[a]Duration of response is the time from the first documentation of CR/PR until the date of progression, death, or the last evaluable RECIST assessment for patients that do not progress. The DoR was calculated following the PFS methodology; [b]Calculated using the Kaplan-Meier technique;* ***Sources:*** *Oh et al.(2022)a;(8) AstraZeneca Data on File – TOPAZ-1 (10)*

There were also substantially more responders in the durvalumab + GemCis group who had ongoing responses (34.1%; 31/91; of whom, more were still receiving study treatment) than in the placebo + GemCis group (18.8%; 12/64; Figure 11). Responses of at least 15.5 months' duration were reported for 10 patients for durvalumab + GemCis vs. one patient for placebo + GemCis, all of which were ongoing at DCO.

Figure 11: DoR by-treatment group waterfall plots (post-hoc analysis; IA-2; FAS; patients with objective response and measurable disease at baseline)



Footnotes: *[a]denotes ongoing responses. Response was continuing if Investigator duration of response was censored, and the patient does not have a censored progressive disease/death.* ***Sources:*** *AstraZeneca Data on File – TOPAZ-1 (10)*

Overall, these results show that the addition of durvalumab increased the number of confirmed responses as well as durable responses. Furthermore, patients also responded faster to durvalumab + GemCis compared to placebo + GemCis, with median time to response being 1.6 months vs. 2.7 months, respectively, further supporting the early effect of durvalumab on tumour growth (7, 10).

7.2.7 Summary of efficacy data from TOPAZ-1

TOPAZ-1 met its primary endpoint for the ITT population, a statistically significant improvement for overall survival (OS) for durvalumab + GemCis vs. placebo + GemCis. The median OS gain was modest at IA-2 + 6.5 months and 3 years OS, increasing mOS with 1.3 months (median OS were 12.8 months and 11.5 months respectively in the intervention and the control arm). EMA have concluded that results from secondary endpoints (investigator-assessed PFS, ORR, DOR) supports the primary end point, and that sensitivity and subgroup analyses were consistent with the main analysis, suggesting that the benefits are observed across the predefined subgroups (71). When analysing OS data from the TOPAZ-1 trial it is important to evaluate the full KM data and landmark analyses, since these identify the long-term survivors. The full benefit of durvalumab add-on therapy was seen at later landmark analyses and 3 year OS DCO. The Kaplan-Meier (KM) plot for OS separated at approximately six months of treatment, after which there was a clear and sustained separation of the survival curves in favour of the durvalumab + GemCis arm. The KM curve for 3 years OS show a clear tail and maintained separation of the curves

Twice as many patients in the durvalumab + GemCis arm compared to placebo + GemCis arm were alive (23.9% vs. 11.5%) after 24 months. Considering that BTC is an aggressive disease where most of the patients progress very rapidly, these results are of clinical significance showing that some patients do have a relatively great benefit of the treatment. In chapter 8.1.2 data from TOPAZ-1 is contextualised further with data from the literature presenting that a proportion of long term-survivors are observed in immunotherapy (IO) trials, and that these patients may be seen forming a plateau on Kaplan-Meyer OS curves. This is important background information that should be taken into account when estimating how the TOPAZ-1 patients will perform after trial follow-up.

7.3 Safety and tolerability of durvalumab in TOPAZ-1

Almost all patients in both treatment arms experienced one or more adverse events (AEs), regardless of causality. However, the nature and frequency of these events was consistent with that expected for the selected study population and the known safety profile of the study treatments (10). Importantly, durvalumab did not significantly increase toxicity to that observed with chemotherapy in this trial, and the rates of CTCAE Grade 3 or 4 causally related AEs were very similar between groups. The toxicity was mainly driven by chemotherapy and the distribution of AEs reflects the toxicity profile of gemcitabine and cisplatin. A summary of AEs and treatment-related AEs (TRAEs) is presented in Table 13.

Table 13: Summary of safety data (IA-2; SAS)

Parameter, n (%)	Durvalumab + GemCis (n=338)	Placebo + GemCis (n=342)
Any grade	336 (99.4)	338 (98.8)
Any serious AE	160 (47.3)	149 (43.6)
Any grade 3/4 AE	256 (75.7)	266 (77.8)
Any AE leading to discontinuation	44 (13.0)	52 (15.2)
Any AE leading to death	12 (3.6)	14 (4.1)
Any immune-mediated AE	43 (12.7)	16 (4.7)
Any TRAE	314 (92.9)	308 (90.1)
Any serious TRAE	53 (15.7)	59 (17.3)
Any grade 3/4 TRAE	212 (62.7)	222 (64.9)
Any TRAE leading to discontinuation	30 (8.9)	39 (11.4)
Any TRAE leading to death[a]	2 (0.6)	1 (0.3)

Footnote: *Includes AEs with onset date on or after the date of the first dose or AEs that worsened after the first dose. Includes AEs occurring up to 90 days following the date of the last dose or up to the first subsequent therapy. [a]TRAEs leading to death were ischemic stroke and hepatic failure in the durvalumab treatment group and polymyositis in the placebo treatment group.* ***Sources:*** *Oh et al. (2022)a;(7) Oh et al. (2022)b.(72)*

The vast majority of patients in TOPAZ-1 experienced at least one AE. Furthermore, the majority of the AEs were either haematological (following chemotherapy) or were consistent with the underlying disease condition in this patient population (e.g. cholangitis). A summary of the most common AEs (experienced by ≥10% of patients in either the durvalumab or placebo treatment arms or of Grade 3 or 4 with an incidence of ≥2% in either treatment group) in TOPAZ-1 is presented in Table 14 (7).

Table 14: Common TRAEs (occurring in ≥10% of patients in the durvalumab or placebo treatment arms or of Grade 3 or 4 with an incidence of ≥2% in either treatment arm; IA-2; SAS)

Preferred term, n (%)	Durvalumab + GemCis (n=338)		Placebo + GemCis (n=342)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Anaemia	163 (48.2)	80 (23.7)	153 (44.7)	77 (22.5)
Nausea	136 (40.2)	5 (1.5)	117 (34.2)	6 (1.8)
Constipation	108 (32.0)	2 (0.6)	99 (28.9)	1 (0.3)
Neutropoenia	107 (31.7)	68 (20.1)	102 (29.8)	72 (21.1)
Neutrophil count decreased	91 (26.9)	71 (21.0)	106 (31.0)	88 (25.7)
Fatigue	91 (26.9)	11 (3.3)	90 (26.3)	12 (3.5)
Decreased appetite	87 (25.7)	7 (2.1)	79 (23.1)	3 (0.9)
Platelet count decreased	70 (20.7)	33 (9.8)	79 (23.1)	29 (8.5)
Pyrexia	68 (20.1)	5 (1.5)	56 (16.4)	2 (0.6)

Preferred term, n (%)	Durvalumab + GemCis (n=338)		Placebo + GemCis (n=342)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Vomiting	62 (18.3)	5 (1.5)	62 (18.1)	7 (2.0)
Diarrhoea	57 (16.9)	4 (1.2)	51 (14.9)	6 (1.8)
Asthenia	48 (14.2)	10 (3.0)	48 (14.0)	8 (2.3)
Abdominal pain	47 (13.9)	2 (0.6)	58 (17.0)	9 (2.6)
Thrombocytopaenia	43 (12.7)	16 (4.7)	45 (13.2)	18 (5.3)
Pruritis	38 (11.2)	NR	28 (8.2)	NR
Rash	38 (11.2)	3 (0.9)	27 (7.9)	0
White blood cell count decreased	37 (10.9)	15 (4.4)	46 (13.5)	20 (5.8)
Abdominal pain (upper)	35 (10.4)	0	30 (8.8)	1 (0.3)
Insomnia	32 (9.5)	NR	36 (10.5)	NR
Cholangitis	29 (8.6)	22 (6.5)	18 (5.3)	11 (3.2)
Alanine aminotransferase increased	29 (8.6)	4 (1.2)	35 (10.2)	2 (0.6)
Hypokalaemia	28 (8.3)	10 (3.0)	17 (5.0)	4 (1.2)
Hyponatraemia	22 (6.5)	7 (2.1)	22 (6.4)	8 (2.3)
Leukopenia	20 (5.9)	8 (2.4)	17 (5.0)	3 (0.9)
Hypertension	20 (5.9)	6 (1.8)	20 (5.8)	7 (2.0)
Pulmonary embolism	16 (4.7)	8 (2.4)	13 (3.8)	7 (2.0)
Sepsis	15 (4.4)	12 (3.6)	9 (2.6)	8 (2.3)
Biliary tract infection	14 (4.1)	11 (3.3)	7 (2.0)	7 (2.0)
Pneumonia	14 (4.1)	9 (2.7)	10 (2.9)	6 (1.8)
Acute kidney injury	13 (3.8)	11 (3.3)	7 (2.0)	5 (1.5)
Biliary obstruction	11 (3.3)	7 (2.1)	10 (2.9)	8 (2.3)
Blood bilirubin increased	10 (3.0)	4 (1.2)	23 (6.7)	10 (2.9)

Footnote: *Number (%) of patients with any AE, sorted in decreasing frequency for PT in the durvalumab + GemCis group. Patients with multiple events in the same PT are counted only once in that PT. Patients with events in more than one PT are counted once in each of those PTs* ***Source:*** Oh et al. (2022)a.(7)

The distribution of grade 3 or 4 AEs reflects the toxicity profile of gemcitabine and cisplatin. Cholangitis is a common AE in patients with BTC due to obstruction of the biliary tract and stents. Generally, cholangitis is an AE occuring irrespective of the given treatment. However, neutropenia due to chemotherapy increases the risk for systemic infection and hospitalization.

Immune-mediated adverse events and association with efficacy

A higher proportion in the durvalumab + GemCis arm (12.7%) experienced immune mediated AEs (imAEs) compared to the placebo + GemCis arm (4.7%), since only a minor proportion received immunotherapy in 2L in

the placebo + GemCis arm (4.7%). Most imAEs were grade 1 or 2 and manageable. The most common imAEs by category (1% of participants in either arm) were hypothyroid events, dermatitis/rash, hepatic events and adrenal insuficiency (73). The distribution of imAEs was similar to other trials combining ICIs with chemotherapy (CM648, CM649, KN189, KN407) (74-78). No new safety signals were observed. Overall, 20 out of 43 (46.5%) participants with an imAE in the durvalumab arm and 8 out of 16 (50%) participants with an imAE in the placebo arm had an imAE that resolved (73). The most common imAEs by category (>1% of participants in either arm) were hypothyroid events, dermatitis / rash, hepatic events and adrenal insufficiency. Incidence of immune-mediated adverse events in presented in Table 15.

Table 15: Incidence of immune-mediated adverse events, TOPAZ-1, SAS (56)

	Durvalumab + GemCis (N=338)	Placebo + GemCis (N=342)
Any AE, n (%)	336 (99.4)	338 (98.8)
Grade 3 or 4 AE	250 (74.0)	257 (75.1)
AE leading to death	13 (3.8)	14 (4.1)
AE leading to discontinuation	43 (12.7)	52 (15.2)
Any TRAE, n (%)	314 (92.9)	308 (90.1)
Grade 3 or 4 TRAE	206 (60.9)	217 (63.5)
TRAE leading to death	2 (0.6)	1 (0.3)
TRAE leading to discontinuation	30 (8.9)	39 (11.4)

Footnote: *Number (%) of patients with any AE, sorted in decreasing frequency for PT in the durvalumab + GemCis group. Patients with multiple events in the same PT are counted only once in that PT. Patients with events in more than one PT are counted once in each of those PTs* ***Source:*** Antonuzzo et al. ESMO 2022 Poster (73)

Table 16: Summary of safety data (IA-2; SAS)

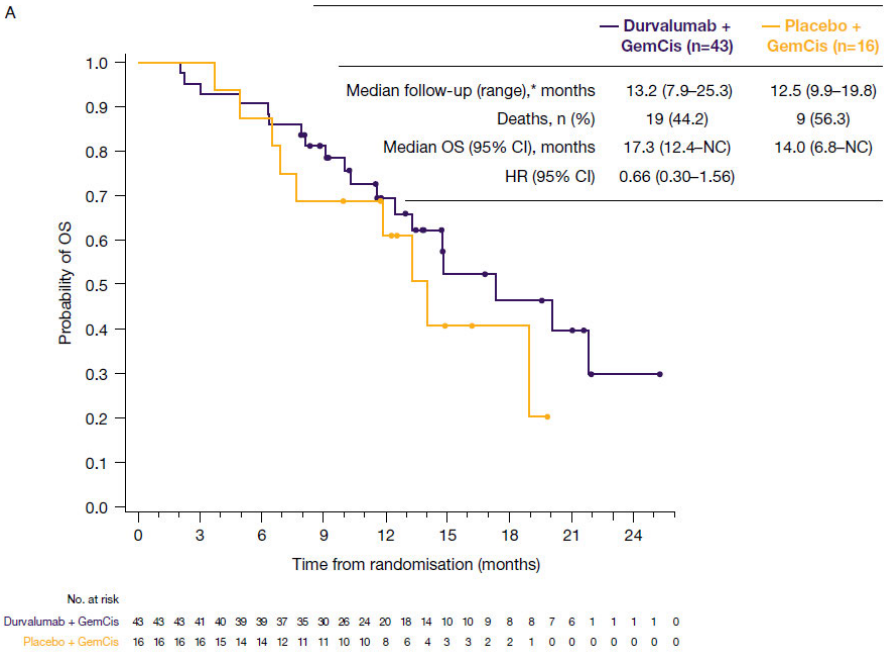
Parameter, n (%)	Durvalumab + GemCis (n=338)	Placebo + GemCis (n=342)
Adverse events		
Any grade	336 (99.4)	338 (98.8)
Any serious AE	160 (47.3)	149 (43.6)
Any grade 3/4 AE	256 (75.7)	266 (77.8)
Any AE leading to discontinuation	44 (13.0)	52 (15.2)
Any AE leading to death	12 (3.6)	14 (4.1)
Any immune-mediated AE	43 (12.7)	16 (4.7)
Treatment-related AEs		
Any TRAE	314 (92.9)	308 (90.1)
Any serious TRAE	53 (15.7)	59 (17.3)
Any grade 3/4 TRAE	212 (62.7)	222 (64.9)
Any TRAE leading to discontinuation	30 (8.9)	39 (11.4)
Any TRAE leading to death[a]	2 (0.6)	1 (0.3)

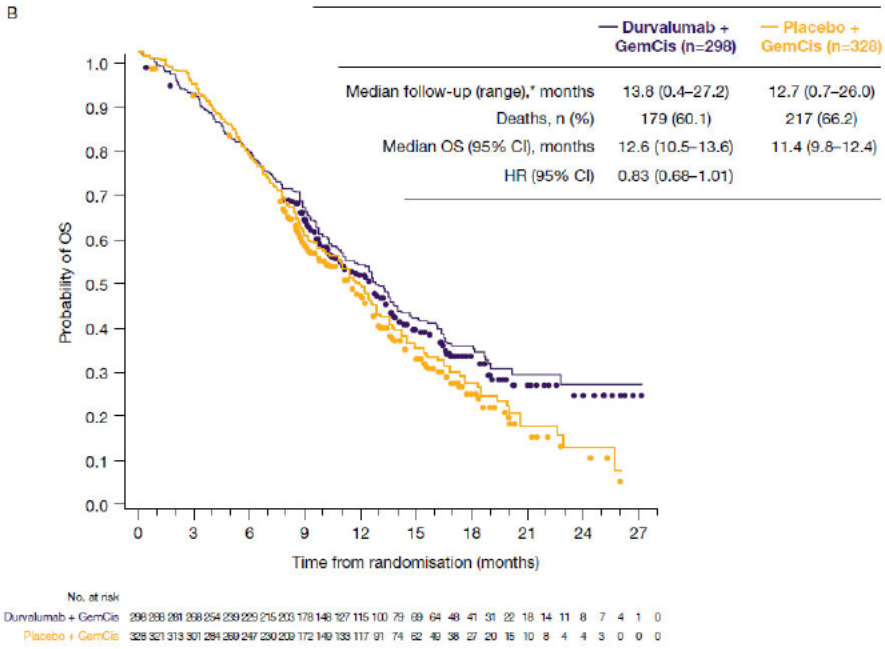
Footnotes: *Includes AEs with onset date on or after the date of the first dose or AEs that worsened after the first dose. Includes AEs occurring up to 90 days following the date of the last dose or up to the first subsequent therapy. [a]TRAEs leading to death were ischemic*

stroke and hepatic failure in the durvalumab treatment group and polymyositis in the placebo treatment group. ***Sources:*** *AstraZeneca Data on File – TOPAZ-1 Clinical Study Report (2022);[10] Oh et al. (2022)b.*

The impact of imAEs on efficacy was further analyzed. Consistent with previous studies, imAEs may be associated with greater OS benefit. The development of imAEs reflects the activation of the immune system, which is the desired response. However, also patients not developing imAEs were shown to benefit from ICIs in TOPAZ-1. imAEs occurred most frequently within 3 months, but could occur at any time during the study, with median time to onset that varied according to imAE type (73). The wide range of the on-set has been observed in previous studies with ICIs. Previously, the early detection and management of imAEs has been a concern among physicians. However, during the recent years, the knowledge and experience has increased significantly. Thus, imAEs are mainly detected early and treatment with high-dose corticosteroids initiated promtly, since data has confirmed that the use of high-dose corticosteroids after the response has developed does not diminish or jeopardize the long-term response to ICIs. Patients with similar imAEs as in TOPAZ-1 are mainly treated in outpatient clinics and they are rarely in need of hospital care due to imAEs. The major reason for hospitalisation remains to be chemotherapy-related toxicity and cholangitis due to biliary tract procedures and stents. Overall survival for durvalumab versus placebo for participants (A) with or (B) without an immune-mediated adverse event is presented in Figure 12.

Figure 12: Overall survival for durvalumab versus placebo for participants (A) with or (B) without an immune-mediated adverse event (ESMO 2022)





Footnotes: **For censored participants* ***Source:*** *Antonuzzo et al. ESMO 2022 Poster ((73))*

7.3.1 Treatment exposure in the safety analysis set

The median relative dose intensity of gemcitabine and cisplatin was comparable in the two treatment arms durvalumab + GemCis and placebo + GemCis (8), showing that durvalumab in practice did not have any dose limiting effects on chemotherapy (Table 17).

Table 17: Treatment exposure in the safety analysis set (36)

Treatment exposure	Durvalumab + GemCis (n=338)	Placebo + GemCis (n=342)
Median actual treatment duration,[a] months (range)		
Durvalumab/placebo	7.3 (0.1–24.5)	5.8 (0.2–21.5)
Gemcitabine	5.2 (0.1–8.3)	5.0 (0.2–8.6)
Cisplatin	5.1 (0.1–8.3)	4.9 (0.2–8.5)
Durvalumab/placebo	10.0 (1–29)	8.0 (1–26)
Gemcitabine	8.0 (0–8)	8.0 (1–8)
Cisplatin	8.0 (0–8)	7.5 (1–8)
Median relative dose intensity (IQR)		
Durvalumab/placebo	100 (93.8–100)	100 (95.0–100)
Gemcitabine	93.8 (82.5–100)	93.8 (82.2–100)
Cisplatin	93.8 (83.3–100)	93.8 (81.3–100)

Footnotes: *[a]Actual treatment exposure = intended exposure – total duration of dose delays, where intended exposure was calculated as min(last dose date where dose >0 + [20 if last dose in period one or 27 if last dose in period two], date of death, date of DCO) - first dose date +1) / (365.25/12), and a dose delay is defined as any length of time where the patient has not taken any of the planned dose.*

7.4 Patient reported outcomes in TOPAZ-1(updated/added section but does not shown on tracked changes)

TOPAZ-1 evaluated PROs via validated HRQoL questionnaires and other measures, which were completed before treatment dosing and before any other study procedures were conducted at the visit. Several instruments were used to measure HRQoL in TOPAZ-1: the EORTC-QLQ-C30, the EORTC-QLQ-BIL21 and EQ-5D-5L. These were collected at the start of each cycle for the first 8 cycles (every third week). From the 9th cycle until progression these were collected every 4th week. After Cycle 16 Day 1, QoL questionnaires were administered every other cycle. The QoL questionnaires were also administered monthly for the first three months after treatment discontinuation.

7.4.1 Secondary PROs: EORTC-QLQ-C30 and EORTC-QLQ-BIL21

A secondary objective of the TOPAZ-1 study was to assess disease-related symptoms, impacts and HRQoL of durvalumab + GemCis vs. placebo + GemCis. Two PRO instruments were used to measure HRQoL: the EORTC-QLQ-C30 and the EORTC-QLQ-BIL21 (Table 18). PRO endpoints assessed included time-to-deterioration (TTD), symptom improvement rate, and adjusted mean change from baseline score, definitions of these can be found in Table 19.

Table 18: HRQoL assessment

Outcome	Description	Items of interest	PRO analysis set (N)
EORTC QLQ-C30	30-item self-administered questionnaire comprising five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), and a global health status/QoL scale. Results in each outcome variable consisted of a score from 0 to 100. A high score on GHS/functional scales represented a high functionating level, whilst a high score on symptom scales represented a high level of symptom burden.	GHS/QoL and impacts (e.g., physical function); multi-term symptoms (e.g., fatigue); and single items (e.g., appetite loss, insomnia)	Durvalumab + GemCis, N=318 Placebo + GemCis, N=328
EORTC-QLQ-BIL21	21-item self-administered questionnaire comprising three single-item functional assessments (side effects, difficulties draining bags/tubes and concerns regarding weight loss) and five symptom scales (eating, jaundice, tiredness, pain, anxiety). Results in each outcome variable consisted of a score from 0 to 100. A high score on GHS/functional scales represented a high functionating level, whilst a high score on symptom scales represented a high level of symptom burden.	Single-item symptoms (e.g., abdominal pain, pruritus, jaundice)	Durvalumab + GemCis, N=305 Placebo + GemCis, N=322

Source: *AstraZeneca Data on File – TOPAZ-1 Clinical Study Report (2022);(10) Kaupp-Roberts et al. (2016).*

Table 19: Key HRQoL endpoints measured in TOPAZ-1

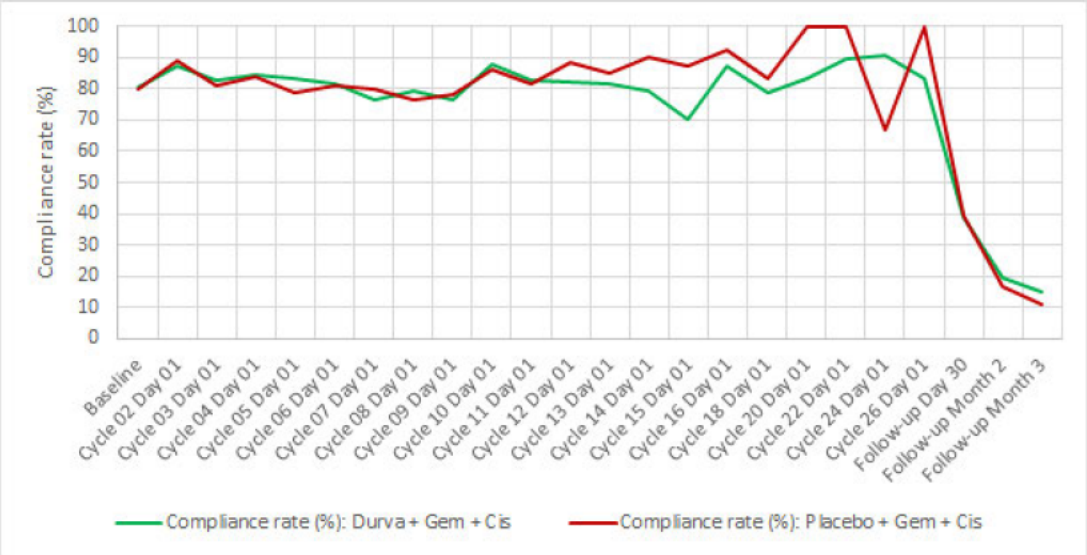
Endpoint	Description
TTD	Defined as the time from the date of randomisation until the date of the first clinically meaningful deterioration. A clinically meaningful change was defined as absolute change in score from baseline of ≥10 points (higher for improvement, lower for deterioration).
Symptom improvement rate	The proportion of subjects with a best overall score response of "improved" in symptoms or GHS/QoL or function; and a clinically meaningful change, defined as absolute change in score from baseline of ≥10 points (higher for improvement, lower for deterioration).
Adjusted mean change from baseline	Performed using a MMRM of all the post-baseline scores for each visit. The model included treatment, visit, and treatment-by-visit interaction as explanatory variables and the baseline score and the baseline score by visit interaction as covariates. Mean scores were calculated for all post-baseline visits up to the latest scheduled visit where ≥20 subjects on each treatment have available PRO scores.

Source: *AstraZeneca Data on File – TOPAZ-1 Clinical Study Report (2022).*

7.4.1.1 Compliance rates

Compliance rates (defined as at least one subscale able to be determined) for PROs were high (>80%) at baseline for both treatment groups for both questionnaires. Compliance rates remained high (>70%) for the majority of timepoints for PROs in both treatment groups over 28 cycles of treatment. However, the compliance rate dropped after the discontinuation of treatment in both groups. The compliance rate over time for EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-BIL21 are shown in Figure 13 - Figure 15.

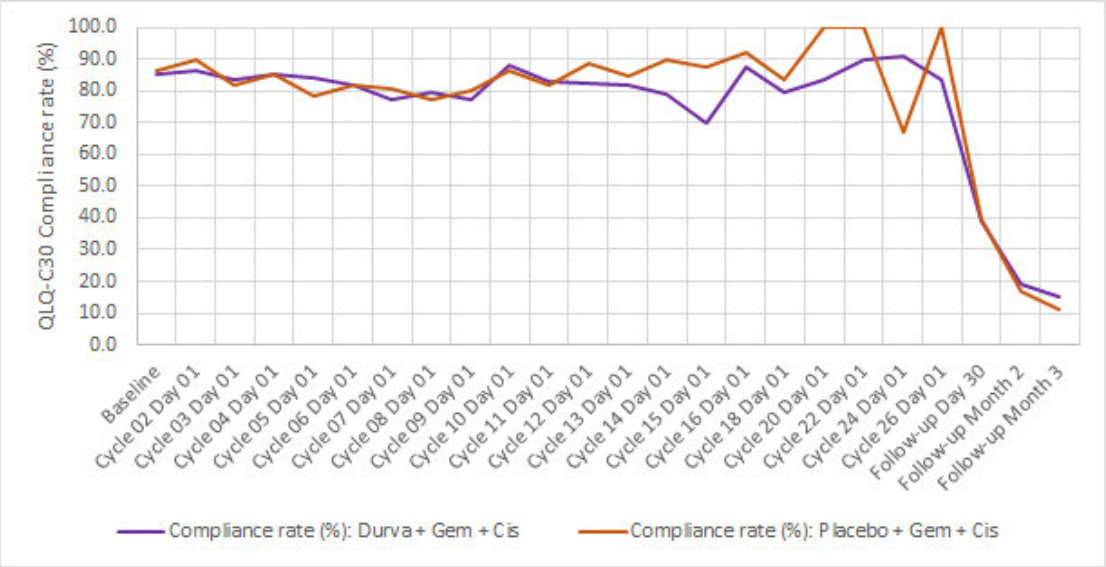
Figure 13: Compliance with EQ-5D-5L by visit (PRO analysis set).



Note: Compliance Rate = Evaluable/Expected * 100, with Expected forms = number of subjects still under QoL follow-up (still on treatment) at given timepoint, and Evaluable forms = forms where at least one subscale can be determined.

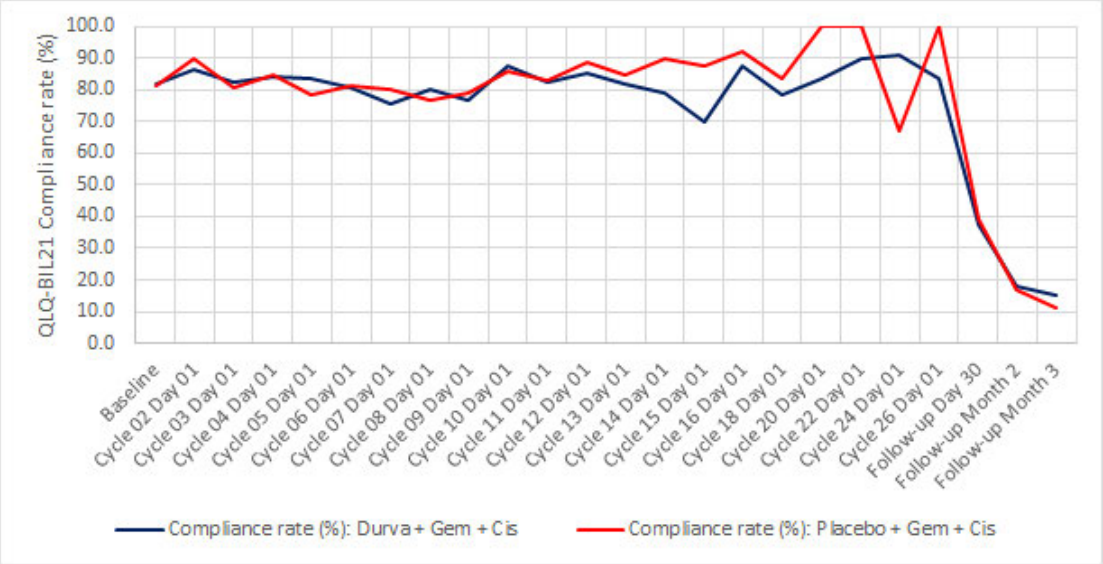
Source: AstraZeneca Data on File – TOPAZ-1 CSR (2022).

Figure 14: Compliance rate for EORTC QLQ-C30 by visit



Source: AstraZeneca Data on File – TOPAZ-1 CSR (2022).

Figure 15: Compliance rate for EORTC QLQ-BIL21 by visit



Source: AstraZeneca Data on File – TOPAZ-1 CSR (2022).

7.4.1.2 Missing data

According to the study plan, the information from patients with missing data was to be reviewed in order to determine whether data analytic procedures were likely to be biased. Patients with missing data were to be reviewed for imbalances in factors such as study arm, treatment adherence, institution, and reason for non-adherence. When QoL data were missing at a particular time point, data from prior time points were to be reviewed in order to investigate whether missing status was preceded by a significant change in QoL scores. Missing item status was relative to other scores on the same questionnaire would also be investigated. If there was no evidence from this review for dependence of the missingness mechanism on covariates or prior QoL scores, the data would be analysed assuming the data were MAR.

For each subscale in EORTC QLQ-C30, if <50% of the subscale items are missing, then the subscale score was divided by the number of non-missing items and multiplied by the total number of items on the subscales (79).

If at least 50% of the items were missing, then that subscale was treated as missing. Missing single items are treated as missing.
Health state utility values were derived from each completed EQ-5D-5L questionnaire with responses to all 5 domains, hence no adjustment for missing data in the EQ-5D-5L questionnaires. However, mixed models for repeated measures (MMRM) were used to estimate the statistical relationship between utilities and health state (e.g. defined by progression or treatment status). This method accounts for the autocorrelation in utility score within each patient and are appropriate when handling data that are missing at random.

7.4.1.3 Baseline status

Baseline scores were generally comparable across both treatment arms for all EORTC QLQ-C30 and EORTC QLQ-BIL21 scales. Both treatment groups presented with a slightly lowered health status (GHS/QoL per EORTC QLQ-C30; Table 20) and mild symptoms at baseline (mild per EORTC QLQ-C30 for fatigue, pain, insomnia, and appetite loss; with low-to-mild baseline symptomatology per EORTC QLQ-BIL21 for abdominal pain, weight loss, pain, anxiety, and tiredness). A full summary of baseline EORTC QLQ-C30 and EORTC QLQ-BIL21 scores can be found in Tables 14.2.5.2 and 14.2.5.8 of the TOPAZ-1 CSR.

Table 20: Summary of baseline EORTC QLQ-C30 GHS score

	Durvalumab + GemCis (N=318)	Placebo + GemCis (N=328)
n[a]	269	282
Mean (SD)	63.0 (18.95)	65.7 (20.64)
Median (95% CI)	66.7 (60.70–65.26)	66.7 (63.27–68.11)

Footnotes: *[a]Number of patients with EORTC QLQ-C30 GHS response data.* ***Source:*** *AstraZeneca Data on File TOPAZ-1 CSR (2022).*

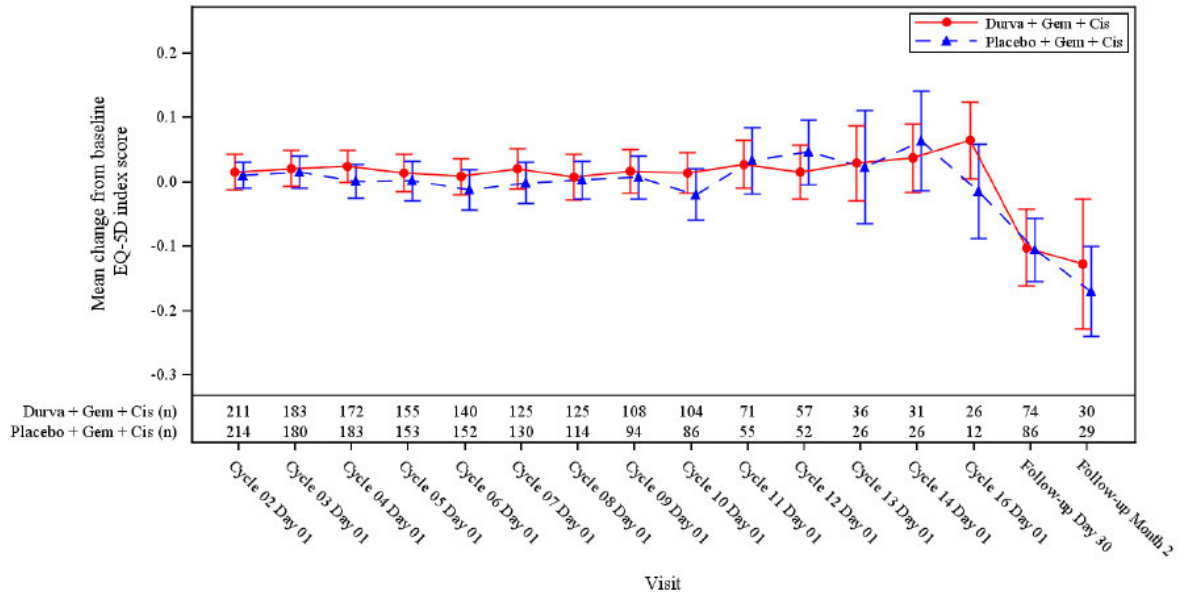
Baseline EQ-5D-5L baseline index scores are presented in Table 21. The change from baseline in EQ-5D-5L index score over time is presented in Figure 16.

Table 21: Summary of baseline EQ-5D-5L index score and VAS score

	Durvalumab + GemCis (N=318)	Placebo + GemCis (N=328)
n[a]	254	261
Mean (95% CI) index score[b]	0.7676 (0.7452–0.7898)	0.7815 (0.7570–0.8060)
Median	0.7680	0.8370
Mean (95% CI) VAS score	70.0 (67.2–73.4)	71.4 (69.3–73.5)
Median	74.5	74.0

Footnotes: [a]Number of patients with EQ-5D-5L response data. [b]Based on UK tariff ***Source:*** *AstraZeneca Data on File – TOPAZ-1 CSR (2022).*

Figure 16: EQ-5D-5L Change from baseline in EQ-5D index score over time (PRO analysis set).



Footnotes: Baseline is defined as last evaluable assessment on or prior to first dose start timeOnly subjects who have a baseline EQ-5D-5L assessment are included. Timepoints are reported by visit for each treatment arm, provided at least one treatment arm has >= 20 subjects with data at a given visit. Mean changes from baseline with 95% CIs are shown. An upward trend is favorable.

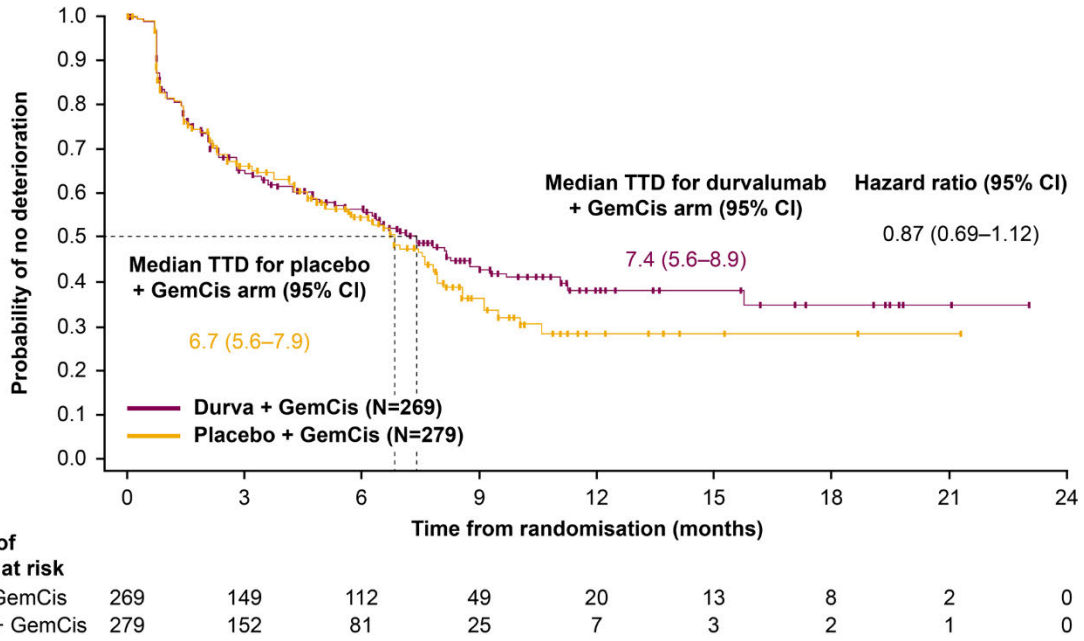
Overall, change from baseline analyses were consistent with no detriment in QoL per EQ-5D-5L in the durvalumab + Gem/Cis group compared with the placebo + Gem/Cis group.

7.4.1.4 Time-to-deterioration

TTD measured by EORTC QLQ-C30 showed that no detriment in QoL was observed in the durvalumab + GemCis treatment arm compared to the placebo + GemCis treatment arm (**Figure 17**, **Figure 18**). There was a trend towards slight improvement in TTD for GHS, emotional and social functioning, fatigue, pain, nausea/vomiting, dyspnoea, insomnia, and diarrhoea in the durvalumab + GemCis group compared to the placebo + GemCis treatment arm. The trend for the remaining scale/items favoured placebo (**Figure 18**) **(7, 80)**. Median TTD of GHS/QoL was numerically longer for patients treated with durvalumab + GemCis, compared to those treated with placebo (7.4 months and 6.7 months, respectively (**Figure 17**);. Separation of the TTD curves occurred at around seven months in favour of durvalumab, which is consistent with the timing of the separation of the OS curves (**Figure 17**, **Figure 18**) (7, 80, 81).

Similarly, TTD measured via EORTC QLQ-BIL21 also demonstrated that there was no detriment in QoL for patients receiving durvalumab + GemCis, and results showed a trend towards slight improvement in TTD for abdominal pain, jaundice, pain, and anxiety for patients in the durvalumab + GemCis treatment arm compared to the placebo + GemCis treatment arm. The trend for the remaining scale/items favoured placebo (Figure 18B).

Figure 17: KM plot of TTD for EORTC QLQ-C30 GHS in TOPAZ-1 (IA-2; PRO analysis set[a])



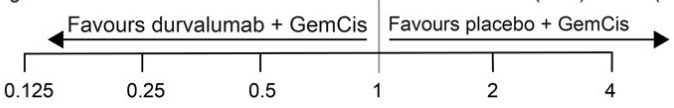
Number of subjects at risk									
Durva + GemCis	269	149	112	49	20	13	8	2	0
Placebo + GemCis	279	152	81	25	7	3	2	1	0

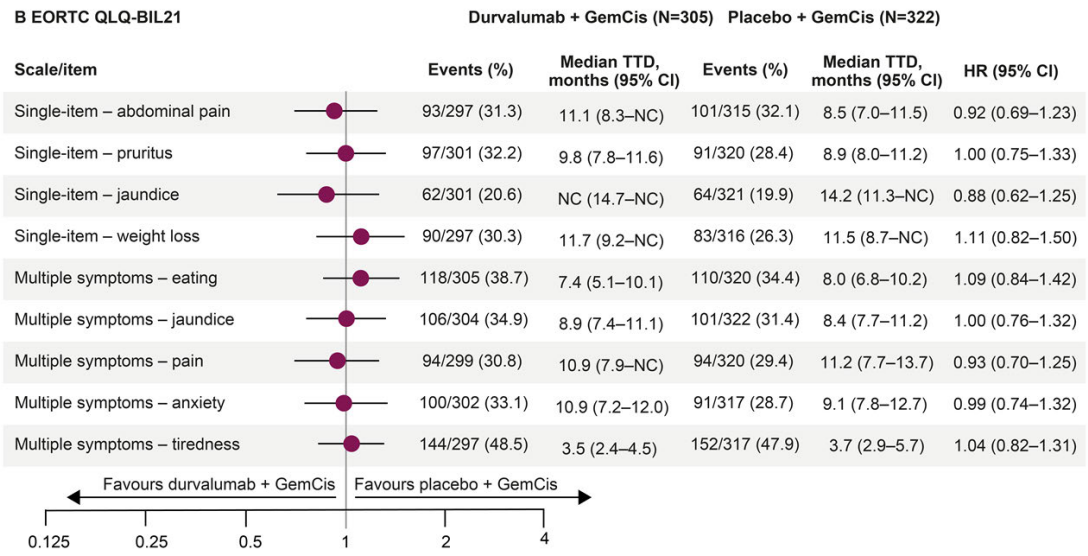
***Footnotes**: [a]Subset of the FAS consisting of patients with baseline EORTC QLQ-C30 scores of ≥10*

***Source:** AstraZeneca Data on File – TOPAZ-1 Clinical Study Report (2022)(80); Burris et al. (2022) (81).*

Figure 18: TTD in EORTC QLQ-C30 and EORTC QLQ-BIL21, forest plot of HRs in TOPAZ-1 (IA-2; PRO analysis set[a])

A EORTC QLQ-C30	Durvalumab + GemCis (N=318)		Placebo + GemCis (N=328)		
Scale/item	Events (%)	Median TTD, months (95% CI)	Events (%)	Median TTD, months (95% CI)	HR (95% CI)
GHS/QoL	132/269 (49.1)	7.4 (5.6–8.9)	135/279 (48.4)	6.7 (5.6–7.9)	0.87 (0.69–1.12)
Functional – physical	138/271 (50.9)	6.6 (4.9–8.6)	125/280 (44.6)	7.7 (6.4–9.2)	1.05 (0.83–1.35)
Functional – role	144/264 (54.5)	5.6 (3.7–6.7)	142/278 (51.1)	6.5 (4.7–7.8)	1.08 (0.85–1.36)
Functional – cognitive	137/271 (50.6)	6.0 (4.8–8.9)	126/282 (44.7)	7.7 (6.6–9.0)	1.09 (0.86–1.39)
Functional – emotional	110/269 (40.9)	10.1 (7.9–12.2)	95/280 (33.9)	10.0 (8.0–NC)	0.98 (0.75–1.30)
Functional – social	138/271 (50.9)	6.0 (4.0–9.6)	130/281 (46.3)	6.8 (4.8–8.4)	0.98 (0.77–1.25)
Multiple symptoms – fatigue	163/311 (52.4)	3.0 (2.4–4.5)	163/326 (50.0)	3.5 (2.8–4.4)	0.97 (0.78–1.20)
Multiple symptoms – pain	137/316 (43.4)	6.5 (5.1–8.9)	132/325 (40.6)	7.0 (5.7–8.3)	0.98 (0.77–1.25)
Multiple symptoms – nausea / vomiting	137/318 (43.1)	6.6 (4.3–9.3)	134/325 (41.2)	6.6 (4.2–8.0)	0.95 (0.74–1.21)
Single-item – dyspnea	109/314 (34.7)	8.8 (7.2–NC)	110/322 (34.2)	8.1 (7.2–10.7)	0.93 (0.71–1.22)
Single-item – insomnia	110/305 (36.1)	8.8 (6.9–14.1)	117/320 (36.6)	7.2 (6.5–9.3)	0.87 (0.67–1.14)
Single-item – appetite loss	138/307 (45.0)	6.0 (4.3–8.8)	111/315 (35.2)	8.5 (6.8–10.2)	1.24 (0.96–1.60)
Single-item – constipation	135/306 (44.1)	5.7 (3.5–7.9)	127/318 (39.9)	7.2 (5.1–8.1)	1.09 (0.86–1.39)
Single-item – diarrhea	84/317 (26.5)	18.2 (11.1–NC)	88/328 (26.8)	11.0 (9.0–12.7)	0.86 (0.63–1.16)



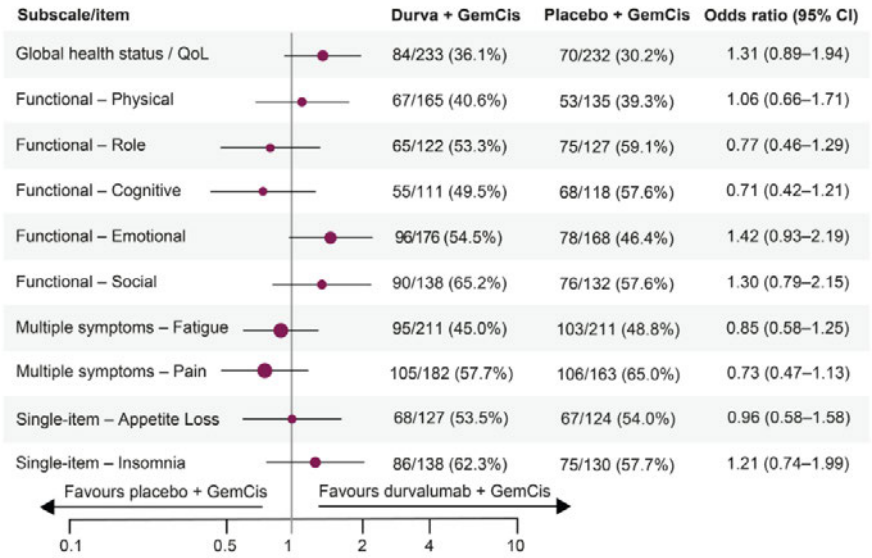


Footnotes: [a]*Subset of the FAS consisting of patients with baseline EORTC QLQ-C30 and/or EORTC QLQ-BIL21 scores of ≥10.*
Source: *AstraZeneca Data on File – TOPAZ-1 Clinical Study Report (2022)(80); Burris et al. (2022)(81).*

7.4.1.5 Improvement rates

Improvement rates as measured by **EORTC QLQ-C30 demonstrated that no detriment in QoL was observed in the durvalumab + GemCis** treatment arm compared to the placebo + GemCis treatment arm (Figure 19). Furthermore, a trend towards a slight increase in OR of clinically meaningful improvement for global health status/QoL, functioning [physical, emotional, social] and insomnia was observed for patients in the durvalumab + GemCis treatment arm. The trend for the remaining scales/items favoured placebo + GemCis.

Figure 19: Improvements based on best objective response for EORTC QLQ-C30, forest plot of odds ratio in TOPAZ-1 (IA-2; PRO analysis set[a])

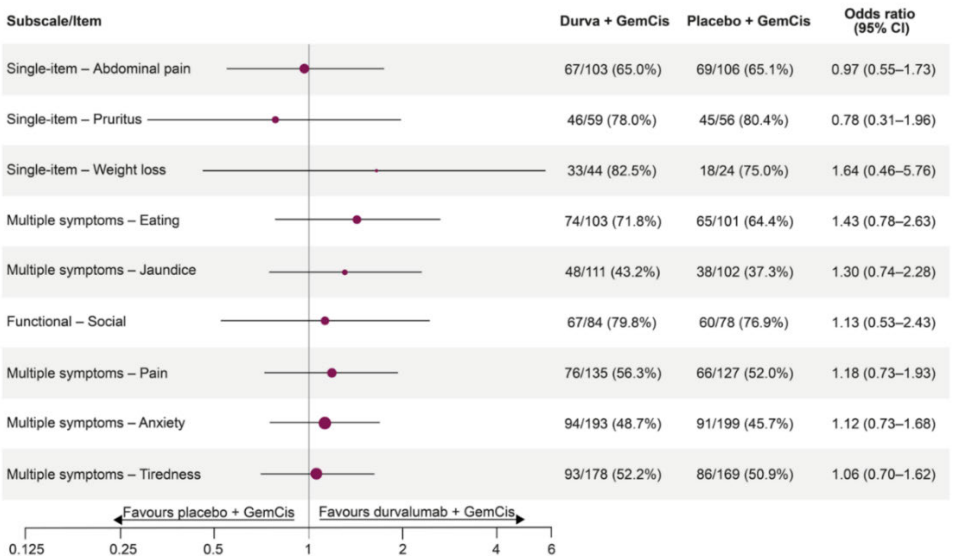


Footnotes: [a]*Subset of the FAS consisting of patients with baseline EORTC QLQ-C30 scores of ≥10.* ***Source:*** *AstraZeneca Data on File – TOPAZ-1 Clinical Study Report (2022).*

Similarly, **improvement rates as measured by EORTC QLQ-BIL21 also demonstrated that no detriment in QoL was observed in the durvalumab + GemCis treatment arm** compared to the placebo + GemCis treatment arm (Figure 20). A trend towards a slight increase in OR of clinically meaningful improvement for jaundice and weight loss (single item), as well as eating, jaundice, pain, anxiety, and tiredness (multiple symptoms) was

demonstrated for the durvalumab + GemCis treatment arm. The trend for the remaining scales/items favoured placebo + GemCis.

Figure 20: Improvements based on best objective response for EORTC QLQ-BIL21, forest plot of odds ratio in TOPAZ-1 (IA-2; PRO analysis set[a])

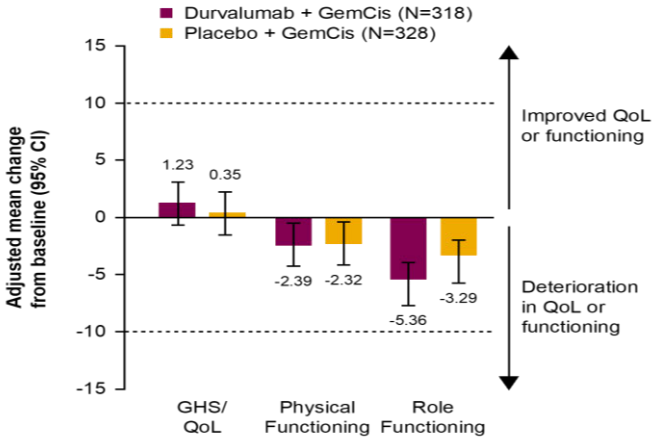


***Footnotes**: [a]Subset of the FAS consisting of patients with baseline EORTC QLQ-BIL21 scores of ≥10. **Source:** TOPAZ-1 CSR (2022).*

7.4.1.6 Adjusted mean change from baseline

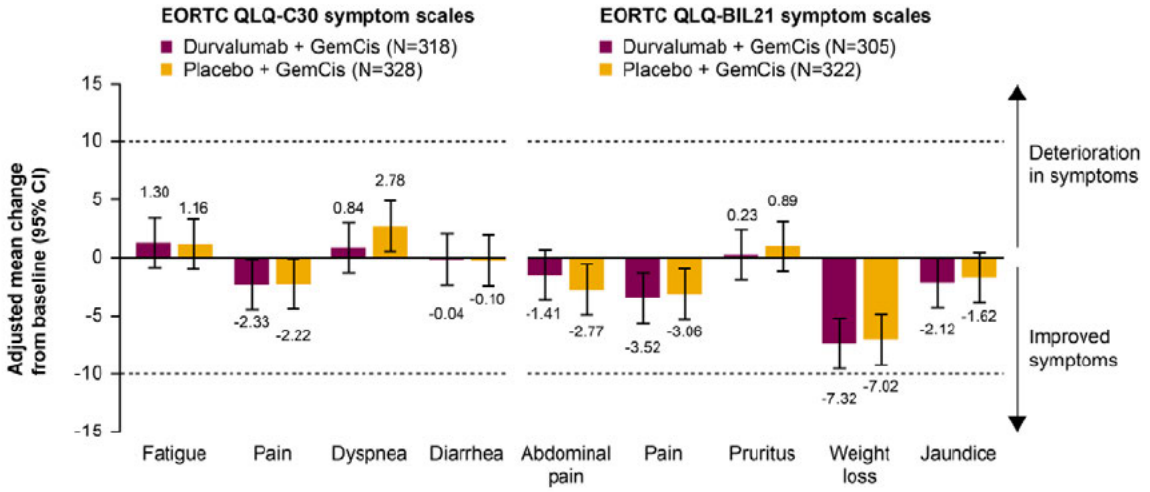
The adjusted mean change from baseline analyses were consistent with no clinically meaningful detriment in QoL for the durvalumab + GemCis treatment arm compared with the placebo + GemCis treatment arm in either the EORTC QLQ-C30 and EORTC QLQ-BIL21 measures. Furthermore, adjusted mean change from baseline in EORTC QLQ-C30 GHS/QoL averaged over all visits was higher with durvalumab + GemCis than with placebo + GemCis, indicating a trend towards improved QoL in patients receiving durvalumab + GemCis
The adjusted mean change from baseline scores for EORTC QLQ-C30 functional domains was below the threshold for a clinically meaningful deterioration for patients receiving durvalumab + GemCis, indicating patients maintained functioning (Figure 21). Adjusted mean change from baseline in symptom scores (EORTC QLQ-C30 and EORTC QLQ-BIL21) indicates that patients treated with durvalumab + GemCis maintained symptom control with no detriment (Figure 22).

Figure 21: Adjusted mean change from baseline scores (95% CI) averaged over all visits for EORTC QLQ-C30 GHS/QoL and functioning (IA-2; PRO analysis set[a])



Footnotes: *Subset of the FAS consisting of patients with baseline EORTC QLQ-C30 scores of ≥10. Adjusted mean change from baseline analysis was performed for all post-baseline scores for each visit. The data reported here are the adjusted mean change from baseline averaged over all visits. Dotted lines represent the threshold for clinically meaningful change.* ***Source:*** *Burris et al. (2022).*

Figure 22: Adjusted mean change from baseline scores (95% CI) averaged over all visits for symptom scales (IA-2; PRO



Footnotes: *Subset of the FAS consisting of patients with baseline EORTC QLQ-C30 and/or EORTC QLQ-BIL21 scores of ≥10. [a]Adjusted mean change from baseline analysis was performed for all post-baseline scores for each visit. The data reported here are the adjusted mean change from baseline averaged over all visits. Dotted lines represent the threshold for clinically meaningful change.* ***Source:*** *Adapted from Burris et al. (2022).*

7.4.2 Exploratory PROs

Additional PRO assessments were included in TOPAZ-1 as exploratory outcomes (Table 22).

Table 22: Overview of exploratory PRO outcomes collected in TOPAZ-1

Outcome (type)	Description of PRO instrument
EQ-5D-5L	Assesses HRQoL and consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS): • The five dimensions of the descriptive system are: mobility, self-care, usual activities, pain/discomfort and, anxiety/depression. The five levels of each dimension are: no problems, slight problems, moderate problems, severe problems, and extreme problems • The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled "The best health you can imagine" (100) and "The worst health you can imagine" (0)
PRO-CTCAE	Assesses symptomatic toxicities and is a self-reported measure in which patients report their experiences if specific symptoms as: none, mind, moderate, severe, very severe. The AEs included in the PRO-CTCAE for the TOPAZ-1 trial included mouth and throat sores, shortness of breath, cough, rash, hair loss, numbness or tingling in hands or feet.
PGIS	Patient self-report global index to assess the severity of a specific condition. In TOPAZ-1, patients rated the severity of their BTC symptoms using a single state scale (from 'no symptoms' to 'very severe').

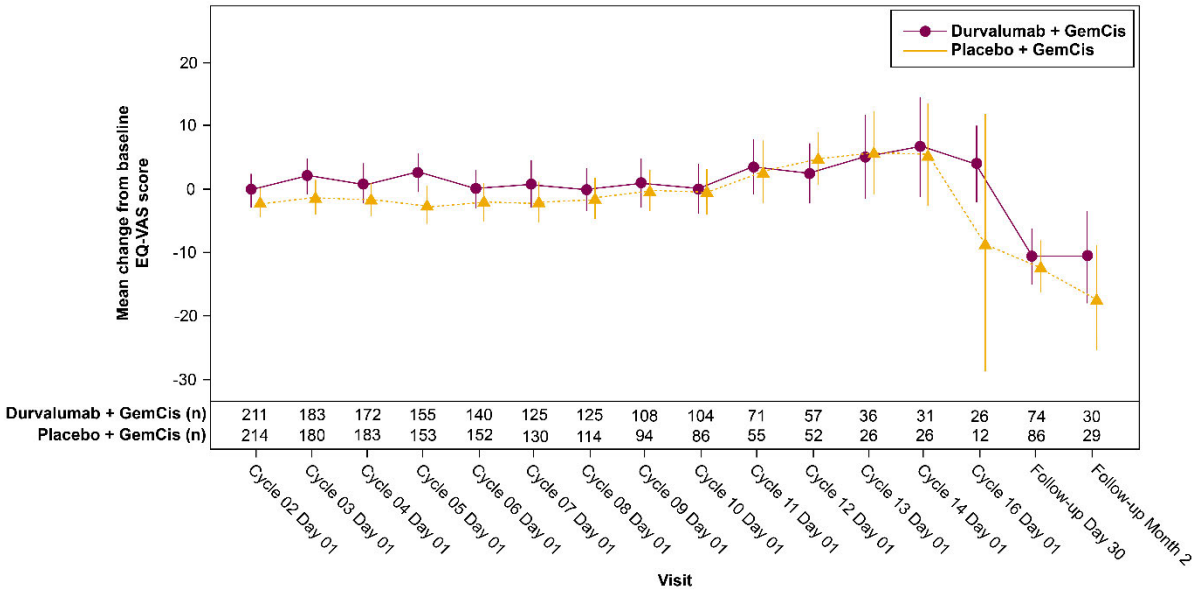
Source: *AstraZeneca Data on File – TOPAZ-1 Clinical Study Report (2022).*

7.4.2.1 EQ-5D-5L

Mean absolute EQ-VAS scores at baseline were comparable for durvalumab + GemCis and placebo + GemCis (70.0 and 71.4, respectively). The change from baseline in ED-5D-5L VAS score was similar over time for

durvalumab + GemCis and placebo + GemCis treatment arms (Figure 23, indicating that durvalumab + GemCis demonstrated no detriment in QoL vs. placebo + GemCis.

Figure 23: EQ-5D-5L change from baseline in EQ-VAS score over time (IA-2; PRO analysis seta)



***Footnotes**: [a]Subset of the FAS consisting of patients with baseline EQ-5D-5L assessments. Timepoints are reported by visit for each treatment arm, provided at least one treatment arm has ≥20 subjects with data at a given visit. An upwards trend is favourable.*
***Source:** AstraZeneca Data on File – TOPAZ-1 Clinical Study Report (2022).*

7.4.2.2 PRO-CTCAE

Patient-reported treatment tolerability was explored using PRO-CTCAE (pre-selected items based on treatment groups, i.e., mouth and throat sores, shortness of breath, cough, rash, hair loss, numbness or tingling in hands or feet) and global assessment of treatment tolerability (EORTC QLQ-BIL21 item 49). From the patients' perspective, durvalumab + GemCis and placebo + GemCis were similarly well-tolerated over the treatment period, in terms of the frequency and burden of patient-reported treatment symptoms and in terms of the perceived interference with daily activities. Overall, results were supportive of the tolerability of durvalumab + GemCis (80).

7.4.2.3 PGIS

Patients' global impression of the severity of cancer symptoms was explored using the PGIS. At baseline, the majority of patients who reported 'no symptoms' and 'very mild' symptoms were similar between both treatment groups. This was also true for the number of patients who reported 'severe' and 'very severe' symptoms. At cycle 16, no considerable differences were observed between the treatment arms (80).

7.4.3 Summary of safety data from TOPAZ-1

In the EPAR for the Imfinzi BTC indication, EMA concludes that "overall, the incidence of any AEs, high-grade AEs, SAEs, AEs with outcome of death and AEs leading to discontinuation is comparable across both arms. It does not seem that durvalumab exacerbates the known adverse reactions of chemotherapy and, reassuringly, it does not seem that durvalumab has an impact on patients' tolerability to chemotherapy. The incidence of imAEs is higher in the durvalumab + chemotherapy arm, but most of these were of low grade and manageable".

EMA further describes that "The incidence of imAEs is noticeable, but most of them correspond to hypothyroidism or rash/dermatitis and can be managed following toxicity guidelines" (71). Thus, the overall safety profile of durvalumab plus GemCis was manageable, and the toxicity was driven by the well-known AEs from gemcitabine and cisplatin. Since BTC is an aggressive cancer with a significant symptom burden, durvalumab plus GemCis with durvalumab maintenance after the chemotherapy part of the treatment provides an acceptable safety profile for progression-free time in the cancer trajectory with a possibility for long-term OS benefit.

Overall, change from baseline analyses (including MMRM) were consistent with no detriment in QoL per EORTC QLQ-C30 and EORTC QLQ-BIL21 in the Durvalumab + Gem/Cis group compared with the placebo + Gem/Cis group. Trends towards slight improvement were detected for durvalumab + Gem/Cis compared with placebo + Gem/Cis were seen for global health status/QoL, emotional functioning, and symptoms pain and dyspnea (EORTC QLQ-C30) and pruritus, weight loss, jaundice, and pain (EORTC QLQ-BIL21 symptoms).

7.5 Ongoing and completed studies of durvalumab in BTC

Durvalumab has been investigated as a treatment for BTC through the key Phase III trial, TOPAZ-1, which was supplemented by the supportive Phase II trial, Study MEDITREME. Details on these two studies are presented in Table 23.

Table 23. Overview of key trials for Durvalumab in BTC

Study (Phase; Indication; NCT number)	Study Aim	Study Type	Population	N	Intervention	Comparator	Primary outcome	Estimated Completion
TOPAZ-1 (Phase III; advanced BTC; NCT03875235)	To assess safety & efficacy of durvalumab + GemCis in unresectable BTC	Randomised Double-Blind Multi-centre Global	Previously untreated patients with recurrent, unresectable or metastatic BTC	685	• Durvalumab (IV) + GemCis (IV)	• Placebo (IV) + GemCis (IV)	OS	March 2025[a]
Study MEDITREME (Phase II; advanced BTC; NCT03046862)	To assess the efficacy of durvalumab/ tremelimumab + GemCis in advanced BTC	Open Label Single-centre	Chemotherapy naïve patients with unresectable or recurrent BTC	124	• Durvalumab (IV) + tremelimumab (IV) + GemCis (IV)	NA	Response rate	December 2021

Footnotes: *[a]Follow-up of TOPAZ-1 is continuing to capture long-term OS data.*

8. Health economic analysis

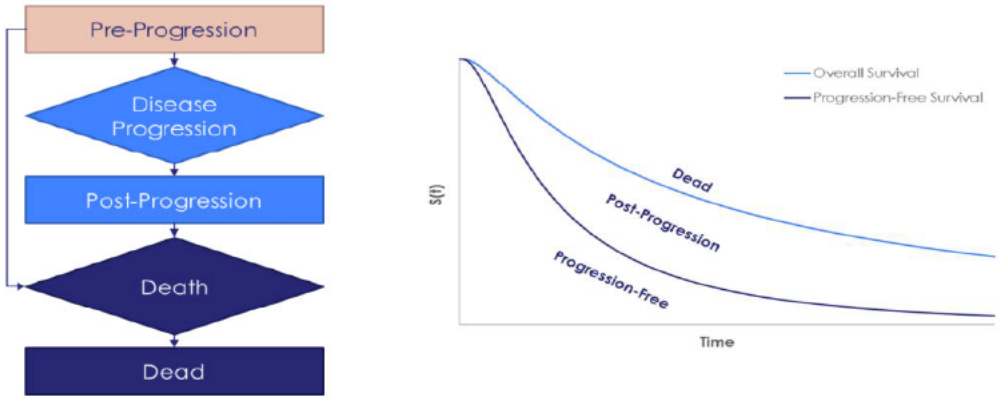
8.1 Model

8.1.1 Cost-utility model design

The cost-utility analysis used in this submission contains a three health states partitioned survival model (Figure 24). All patients start in the pre-progression state where they can remain progression free, move to the post-progression state and then to the death state or move directly from the pre-progression state to the death state. The proportion of patients in the post-progression state (PPS) health state is calculated by subtracting the percentage of patients in the PFS state from the percentage of patients that are alive as per the OS curve. This approach also allows for modelling of OS and PFS based on study-observed events, which facilitates the

replication of within-trial data and means that the model is expected to accurately reflect disease progression and the observed survival profile of patients treated with durvalumab + GemCis.

Figure 24: Structure of the partitioned survival model



In the model, health state transitions are based on survival curves fitted to OS, PFS and TTD data from TOPAZ-1. Parametric survival models are used to extrapolate outcomes beyond the observed data for a lifetime horizon. Data on relative survival from previous IO trials were used for extrapolations in the durvalumab + GemCis arm for OS extrapolations beyond 43 months.

8.1.2 Base case model assumptions

A summary of the base case inputs has been summarised in Table 24 below. The impact of these inputs on the ICER was tested in sensitivity and scenario analyses. AstraZeneca proposes a time horizon of 30 years for the base-case analysis. The 30-year time horizon is long enough to capture the consequences of the treatment both in terms of costs and QALYs over a lifetime horizon. A 5-year time horizon is used for the total budget impact, based on Medicinrådet guidelines.

A discount rate of 3.5% was used in cost per QALY analysis according to the latest recommendations from the Ministry of Finance (82). No discounting was used for the 5-year budget impact analysis.

Table 24: Assumptions and parameter values for base case analysis

Assumption/Parameter	Value in base case analysis	Comments
Comparator	**GemCis**	**SoC/TOPAZ-1**
Type of model	Partitioned survival model with three health states	Standard model in oncology
Treatment lines	First and subsequent treatment lines included	TOPAZ-1
Included costs	Pharmaceutical costs Hospital costs Cost of adverse events Patient costs End of life costs	Standard costs from limited societal perspective
Age (mean)	62.4	TOPAZ-1

Assumption/Parameter	Value in base case analysis	Comments
Male proportion	50.4%	TOPAZ-1
Weight (kg)*	77.3	Danish medical expert input
Height (m)*	1.71	Danish medical expert input
Body surface area (kg/m²)	1.92	Estimated (Mosteller formula)
Wastage assumption	Yes	Vial sharing could be possible but including wastage is more conservative
Discount rate, costs	3.5%	Finance ministry recommendation
Discount rate, outcomes	3.5%	Finance ministry recommendation
Time horizon	30 years	Long enough to capture lifetime horizon
Utility approach	Health state utilities (progression free, progressed) based on the Danish EQ-5D-5L tariff	Health-related quality of life measured with EQ-5D-5L in study TOPAZ-1. Danish tariff by Jensen et al. used
OS distribution – durvalumab + GemCis	Log-logistic up to 43 months	Most plausible extrapolation based on goodness-of-fit of the different curves up to 43 months
Long-term OS for durvalumab + GemCis	Long-term modelling of OS tail development beyond 43 months based on a systematic review of previous IO trials	Straight extrapolations too conservative as they do not take IO tail development into account
OS distribution – GemCis	Log-logistic	Most plausible extrapolation based on long-term survival rates (ENSCCA) and the goodness-of-fit of the different curves
PFS distribution – durvalumab + GemCis	Spline hazards 3 knots	Based on the AIC/BIC goodness-of-fit to the, as well as the plausibility of long-term extrapolations
PFS distribution – GemCis	Spline hazards 3 knots	Based on the AIC/BIC goodness-of-fit to the, as well as the plausibility of long-term extrapolations
TTD distribution – durvalumab + GemCis	Log-logistic	Based on consistency with PFS, as the treatment is indicated to be continued until progression or unacceptable toxicity
TTD distribution – GemCis	Spline odds 3 knots	Based on the AIC/BIC goodness-of-fit to the, as well as the plausibility of long-term extrapolations

*Based on expert input rather than TOPAZ-1 data to make the estimates relevant for Denmark

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

Key take aways:

- *Standard parametric models are used for the comparator arm (GemCis).*
- *Standard parametric model are combined with landmark OS data (24, 36, 48 and 60 months) from previous IO trials for the durvalumab + GemCis arm*
- *The rationale for the overall approach is that standard parametric models can predict 5-year survival for the GemCis arm well compared with real-world data, while standard parametric modelling seem too pessimistic compared with previous IO trials regarding long-term OS and plateau development.*
- *The landmark OS data from previous IO trials are used for estimating the relative mortality in IO studies compared with the normal population beyond 24 months, with a separate relative mortality risk for each time period: 24-36, 36-48 and 48-60 months.*
- *Beyond 60 months, a relative risk (standardized mortality ratio, SMR) was used based on long-term real-world evidence.*
- *The modelling approach is flexible and it is possible to start using the approach with relative mortality risks based on previous IO studies (between 24-60 months) and a standardized mortality ratio based on real-world data (beyond 60 months) at any time between 24 and 120 months. See the box for "Long-term modelling" next to the "Results" section on the dashboard in the HE model.*
- *The approach based on using relative risks (started at some point between 24 and 120 months) can also potentially be used in both arms or parametric modelling can be used throughout in both arms.*

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

8.2.1.1 Rationale for the modelling approach

The concept of long-term survivors established across IO-trials is where a subpopulation benefitting from the treatment could be identified as separation of the survival curves and formation of the "tail". This subpopulation of long-term survivors is rarely captured in the more robust median OS, which merely reflects the first survival estimates of OS benefit. Landmark survival rates have shown to identify the long-term responders most accurately between the study arms. Additionally, based on our external discussions landmark analyses have been concluded to reflect long-term responses seen in real-world by oncologists with experience in using ICIs for GI cancers. A long-term survival plateau for the immunotherapy treatment arm has been observed across several cancer types. The effect is usually delayed in the sense that there is not always a clear separation between the OS curves from the beginning and the plateauing of the Kaplan-Meier survival curves is typically evident from around 3 years (83-85). The delayed but durable effects can be explained by the indirect mechanism of action, with the therapy acting on the patient's immune cells rather than on the tumour itself (86-88). Traditionally, the focus in oncology has been on endpoints such as median survival and single hazard ratios, which are typically calculated using Cox models. In IO trials, the assumption of proportional hazards which normally underpins this analysis is not always met, which means that standard approaches to survival analysis may not fully capture the survival benefits (89-91). Medians, by definition, do not capture the dynamics in the second half of the survival curve where the majority of the benefits of IOs are realised. Several more complex modelling approaches have been proposed and may have advantages compared with standard parametric modelling for overall survival extrapolation of IO treatments (92-94). There is increasing awareness of the challenges surrounding quantification of IO survival benefits, and some increasing acceptance of alternative endpoints such as landmark survival rates which have already been incorporated into ASCO and ESMO value frameworks (95).

Although the era of immunotherapy has lasted more than a decade, in majority of the approved indications with ICIs with or without combining with other drugs, long-term data can still not be found. The longest follow-up data available is for malignant melanoma (CM067) (96, 97) and non-small cell lung cancer (KN024, KN042) (98, 99). With regards to BTC, TOPAZ-1 is the first positive study to show the benefit of adding a PD-(L)1 inhibitor durvalumab to standard chemotherapy and has therefore also the longest follow-up of almost two years. In general, the follow-up of IO trials is still rather short in GI cancers, which would be comparable to some extent with BTC since the patient characteristics and tumour profiles show similarities. Of the IO trials in a similar first-line setting combining a PD-(L)1 inhibitor with chemotherapy, advanced oesophageal squamous cell carcinoma with 29 months of follow-up (CM648) (74, 76) and advanced gastric cancer, gastroesophageal junction cancer and oesophageal adenocarcinoma with 36 months of follow-up (CM649) (75) have the longest follow-up.
However, despite the differences in the tumour biology, patient characteristics and prognosis between various solid tumours, the separation of the KM survival curves, and development of the plateau appear show similarities across studies and tumour types which is aligned with the known mode of action of ICIs.

Data from KeyNote-966 was recently published (100). KN-966 is a randomised, double-blind, placebo-controlled, phase 3 trial, where pembrolizumab (PD-L1i) in combination with gemcitabine and cisplatin were compared with gemcitabine and cisplatin alone for patients with advanced BTC. KN-966 has a similar design to TOPAZ-1, but gemcitabine could be administered until progression in both treatment arms in KN-966. Gemcitabine was administered for a maximum of 8 cycles in TOPAZ-1, mirroring Danish clinical practice. KN-966 also had a positive read out on OS. The data from KN-966 was mature with a median follow up of 25.6 months at the final data cut. Landmark analyses of KM-data from the IO-arms of both KN-966 and TOPAZ-1 shows comparable results, with estimated 24-month OS rates of 25% in the pembrolizumab group, and 23.9% in the durvalumab group. KN-966 thus supports the effect of IO shown in TOPAZ-1.

8.2.1.2 Method for extracting long-term mortality rates from IO trials

Reviews of OS extrapolation in HTAs of immunotherapies suggests that both the manufacturers and the agencies initial best-case estimates with traditional parametric extrapolation on average appeared to underestimate OS when compared to more mature data (101, 102). This implies that traditional methods do not capture immunotherapies delayed effect on OS precise enough. Challenges with immature KM-data may be handled by awaiting more mature data, but this is problematic for the BTC patients with high mortality rates who have a great need for new therapies with novel modes of actions right now. With the increasing amount of external data that can be used when assuming long-term IO effect, it is no longer necessary to await updated data and thus novel methods should be used when extrapolating long-term effect.

A key motivation for the long-term modelling approach AstraZeneca has taken is that the follow-up so far in the TOPAZ-1 trial is too short to capture the plateauing effect by statistical fitting to the available OS data. Many novel modelling techniques, such as spline modelling or cure rate modelling can therefore not be applied, as these approaches require the development of a more mature plateau.

The data clearly suggest an increasing benefit over time in TOPAZ-1, with the difference in landmark OS increasing from 7.2% at 12 months, to 10.7% at 18 months and to 12.1% and 24 months. The piecewise HR is also improving from 0.91 for the time period up to 6 months to 0.71 beyond 6 months (Table 25).

Table 25: Median OS, landmark OS and overall and piecewise OS HR

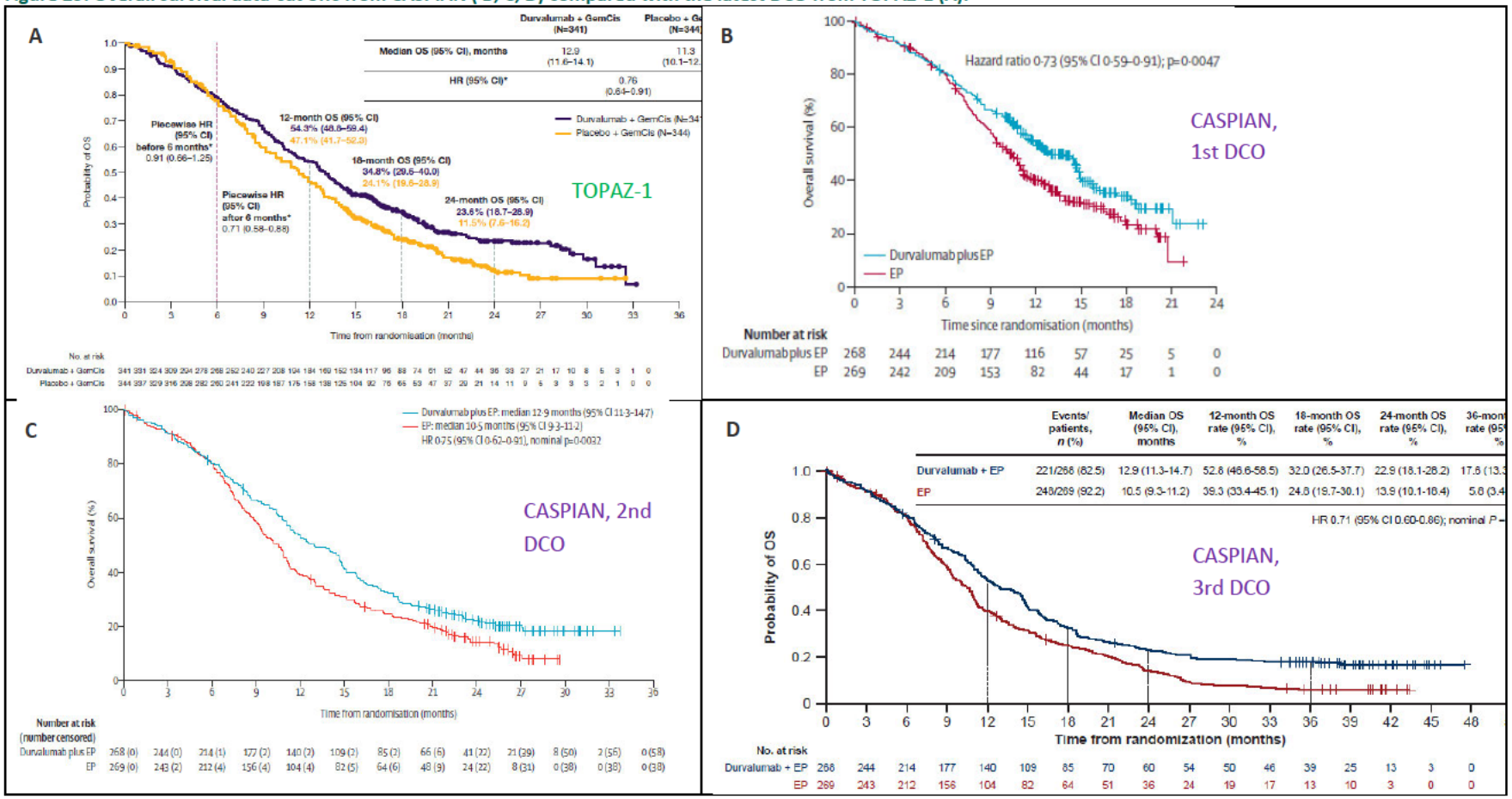
Endpoint	Durvalumab + chemotherapy	Placebo + chemotherapy
mOS (months), [95% CI]	12.9 [11.6, 14.1]	11.3 [10.1, 12.5]
12 month OS [95% CI] (%) **18 month OS [95% CI] (%)** **24 month OS [95% CI] (%)**	54.3 [48.8, 59.4] 34.8 [29.6, 40] 23.6 [18.7, 28.9]	47.1 [41.7, 52.3] 24.1 [19.6, 28.9] 11.5 [7.6, 16.2]
Overall HR [95% CI] **Piecewise HR: 0-6 months** **Piecewise HR: 6 months+**	0.76 [0.64-0.91] 0.91 [0.66, 1.26] 0.71 [0.58, 0.88]	

Source: *Oh et al. 2022 ESMO poster (9)*

The aim of using the piecewise HR is to show that the relative efficacy improved over time. Unlike most conventional cancer treatments, immunotherapy has an indirect mechanism of action, which causes a delayed treatment effect. This leads to delayed separation of survival curves between the treatment groups, but also a durable response. As these characteristics of the treatment effect typically violates the proportional hazards assumption, it is important to study how the HR develops over time.

Recently, a trial combining durvalumab with chemotherapy in extensive-stage small-cell lung cancer, a 3-year update was disclosed showing the formation of the tail (CASPIAN) (103, 104). The latest data cut-off from TOPAZ-1 (Figure 25, A) could be compared with the OS results from the CASPIAN trial including durvalumab vs. chemotherapy in the treatment of extensive-stage small-cell lung cancer (ES-SCLC). At the first data cut-off from CASPIAN, no tail-development was yet visible (Figure 25, B). An intermediate data cut-off from CASPIAN with a similar follow-up time to the latest data cut-off from TOPAZ-1 is also shown (Figure 25, C). With 3-year follow up, a tail of long-term survivors has developed in the durvalumab arm (Figure 25, D). Just as BTC, ES-SCLC is also a very severe disease with rapid progression, which has a long-term survival similar to BTC if treated only with chemotherapy (104, 105). With the 3-year OS update of TOPAZ-1 (Figure 7), the situation is now similar to the intermediate DCO from CASPIAN in panel C.

Figure 25: Overall survival data-cut offs from CASPIAN (B, C, D) compared with the latest DCO from TOPAZ-1 (A).



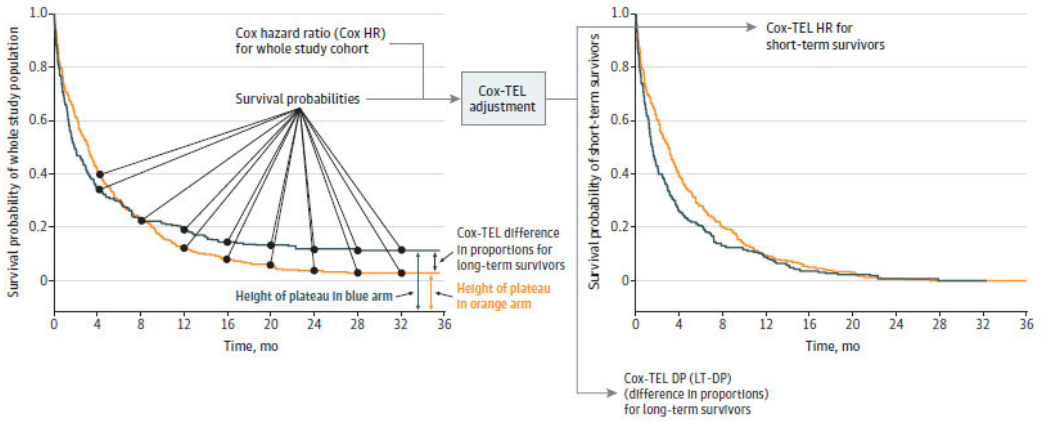
A:TOPAZ-1 with 22.9 months median OS follow-up (8), B: CASPIAN with 14.2 months median OS follow-up (104)A:TOPAZ-1 with 22.9 months median OS follow-up (8), B: CASPIAN with 14.2 months median OS follow-up (104), C: CASPIAN with 25.1 months median OS follow-up (105), D: CASPIAN with 39.4 months median OS follow-up (103). (105), D: CASPIAN with 39.4 months median OS follow-up (103). DCO: Data cut-off

CASPIAN is just one study, but as mentioned previously there is a growing body of evidence indicating that traditional parametric modelling does not fully capture the plateauing of the long-term survival in IO trials. For example, Chaudhary et al. (2023) showed that models that incorporate external data sources performed better than standard parametric models in predicting 5-year OS based on 2- and 3-year data (92). In the absence of specific data on the long-term survival in TOPAZ-1, we modelled the tail development based on data from previous IO trials. The study most useful for our purposes was a systematic review and meta-analysis by Lin et al. (2022) (106), which had the aim of comparing outcomes with immune checkpoint inhibitors treatments (ICI or ICI plus chemotherapy) versus chemotherapy-alone outcomes. In particular, the selection criteria in the study limited the eligibility of the included studies to:

1. Randomised phase III studies
2. Reporting primary or secondary survival outcomes, including OS results
3. Advanced or metastatic setting
4. Reporting HRs and OS KM curves

The study by Lin et al. (106) was limited to three cancer types, i.e. NSCLC, melanoma and urothelial cancer, but these cancer types have the advantage that a reasonable number of phase III studies are available. This makes it possible to use these results for a meta-analysis. The overall results in study by Lin et al. (106) suggest that the mean long-term difference in the proportion of survivors between the IO arm and the control was 8% (95% CI 6% - 10%). In the study, the overall Cox proportional hazards ratios were transformed to a hazard ratio for patients with short-term treatment response (ie, short-term survivor) and a difference in proportions in long-term survival for patients with long-term survival by a statistical method (Cox-TEL (106),(Figure 26). However, we did not use these results directly in the modelling, as the data are still too immature for a similar modelling approach. Instead, we decided to use the landmark overall survival rates from the studies identified in Lin et al. to investigate how the overall survival rates develop over time for IO therapies, based on landmark overall survival probabilities. Hence, we use the extrapolated OS curves up to a certain point (which can be varied in the model) and then assume that the long-term mortality will develop as the average in previous IO studies to capture the plateau effect. The mortality is defined as relative mortality compared with the normal population. We looked at yearly mortalities rather than monthly mortalities, as the latter would add complexity without having a major impact on the results

Figure 26: Cox Proportional Hazards–Taylor Expansion Adjustment for Long-term Survival Data Adjustment Method Schema.



Cox hazard ratios (HRs) are transformed to Cox-TEL HRs (ST-HRs, for patients with short-term treatment response) and difference in proportions (LT-DPs, for responders with long-term survival) by Cox-TEL. The only data required to perform the adjustment are Cox HRs with 95% CIs and survival probabilities excerpted from Kaplan-Meier survival curves.

***Source**: Figure 1 in Lin et al. (106)*

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

According to medical expert feedback, the clinical results in TOPAZ-1 should be transferable to Danish clinical practice. Median OS for GemCis in TOPAZ-1 was similar to median OS in the publication by Markussen et al. (107), with 11.3 month median OS for GemCis in TOPAZ-1 and 12.0 months in Markussen et al. (107).

8.2.2.1 Patient population

Patient population in the health economic analysis is as in TOPAZ-1 with the exception of weight and height, where Danish patients are estimated to be taller and heavier than in the clinical trial
). There might also be differences in mean age and gender distribution between the Danish patient population and the TOPAZ-1 population. However, changing age and gender distribution in the model would affect the normal population mortality used in the model, but would not affect the survival and time to treatment discontinuation curves from the trial. Hence, we prioritize the internal validity of the model and use the age and gender distribution from TOPAZ-1. Survival expectancy would be reduced with higher age, but the treatment duration and the costs might then be reduced as well.

Table 26: Patient population

Patient population Important baseline characteristics	Clinical documentation / indirect comparison etc. (including source)	Used in the model (number/value including source)	Danish clinical practice (including source)
Age (mean)	62.4 in TOPAZ-1	62.4 in model as in TOPAZ-1	Typically a few years older in clinical practice (66-67) according to medical expert, but trial followed for internal validity
Male proportion	50.4% in TOPAZ-1	50.4% in model	40-45% male according to medical expert, but trial followed for internal validity
Mean weight (kg)	66.5 in TOPAZ-1	77.3 in model based on expert input	At start of treatment, the patients are similar to average Danish person of the same age and gender
Mean height (m)	1.637 in TOPAZ-1	1.71 in model based on expert input	At start of treatment, the patients are similar to average Danish person of the same age and gender
Creatinine Clearance (mL/min)	85.3 in TOPAZ-1	85.3 in model as in TOPAZ-1	Transferable to Denmark according to medical expert

8.2.2.2 Intervention

The intervention and the comparator in TOPAZ-1 are well aligned with current and expected clinical practice in Denmark. The intervention and the comparator are described with regard to posology, dosing, time on treatment, criteria for discontinuation and clinical practice in Table 27 and Table 28.

Table 27: Intervention: Durvalumab + GemCis

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	Durvalumab 1500 mg (or placebo) via IV infusion Q3W, starting on Day 1, Cycle 1 in combination with cisplatin 25 mg/m2 and gemcitabine 1000 mg/m2 (each administered on Days 1 and 8 Q3W) up to 8 cycles, followed by durvalumab or placebo 1500 mg as monotherapy Q4W until clinical progression or RECIST 1.1 defined radiological PD, unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met (EMA 2023 (5))	The same dose as in the EPAR product information (EMA 2023 (5))	Expected to follow the EPAR product information.
Length of treatment (time on treatment) (mean/median)	The indication is treatment to progression or unacceptable toxicity. Time to treatment discontinuation (TTD) was also reported.	The model uses curves fitted to TTD KM data from TOPAZ-1	Expected to be similar to TOPAZ-1 PFS and TTD curves
Criteria for discontinuation	Patient can continue with durvalumab+ GemCis until clinical progression or RECIST 1.1 defined radiological PD, or unacceptable toxicity, or withdrawal of consent, or another discontinuation criterion (e.g. low weight)	Based on trial criteria	Discontinuation criteria in TOPAZ-1 expected to be in line with Danish clinical practice
The pharmaceutical's position in Danish clinical practice	The comparator arm GemCis is standard therapy. Durvalumab is a new treatment modality not previously used in Denmark	The model uses the clinical trial medications both for treatment and comparator. No need for any indirect treatment comparison.	The comparator arm GemCis is standard therapy for those patients who can tolerate doublet platinum-based chemotherapy. Durvalumab + GemCis is a new treatment modality not previously used in Denmark.

8.2.2.3 Comparators

As discussed in section 5.2.2, the majority of patients with ECOG 0-1 are currently treated with GemCis in 1L for BTC, and since durvalumab is indicated in combination with GemCis, the comparator for this assessment is GemCis.

Table 28: Comparator: GemCis

Comparator	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
Posology	Cisplatin 25 mg/m2 and gemcitabine 1000 mg/m2 (each administered on Days 1 and 8 Q3W) up to 8 cycles	The same dose as in the EPAR product information (EMA 2023 (5))	Expected to follow the EPAR product information.
Length of treatment	Treatment up to 8 cycles	As in TOPAZ-1 trial	
The comparator's position in the Danish clinical practice	The TOPAZ-1 trial used GemCis because it is standard therapy: "The combination of gemcitabine and cisplatin is a widely recognized treatment regimen and has remained as first-line SoC in patients with unresectable and advanced BTC" (EPAR EMA 2023 (71))	The model uses GemCis as in the TOPAZ-1 trial	The comparator arm GemCis is standard therapy for those patients who can tolerate doublet platinum-based chemotherapy.

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation included OS and PFS (Table 29). The relevance of the documentation for Danish clinical practice regarding OS and PFS is covered in Table 30. The relative efficacy outcomes in the submitted health economic analysis include parametric OS and PFS curves fitted from the TOPAZ-1 KM data + OS tail development from previous clinical trials, as described in section 8.2.1.

Table 29: Relative efficacy outcomes

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Primary endpoint in the study: **Overall survival (OS)**	OS curves from the TOPAZ-1 study	Fitted and extrapolated OS curves from the TOPAZ-1 study used in combination with tail development from previous IO clinical trials
Secondary endpoint: **Progression-free survival (PFS)**	PFS curves from the TOPAZ-1 study	Fitted and extrapolated PFS curves from the TOPAZ-1

Table 30: Relevance of clinical efficacy outcomes

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Primary endpoint in the study: **Overall survival (OS)**	OS curves from the TOPAZ-1 study	Relevant endpoint for patients in Denmark	OS highly relevant for Danish clinical practice. Extrapolation is necessary to capture full clinical value and tail development important to consider from clinical viewpoint
Secondary endpoint: **Progression-free survival (PFS)**	PFS curves from the TOPAZ-1 study	Relevant endpoint for patients in Denmark	PFS relevant for Danish clinical practice. Extrapolation necessary to capture the full clinical value of delaying progression.

8.2.2.5 Adverse reaction outcomes

Adverse reaction outcomes were based on the TOPAZ-1 study and are covered in section 7.3 and in Appendix D Efficacy and safety results per study and E. Costs and disutilities of adverse events were included in the health economic model (see sections 8.4.2 and 8.5.4).

8.3 Extrapolation of relative efficacy

8.3.1 Overall survival

8.3.1.1 Survival extrapolations for OS

Parametric distributions were fit to individual patient data for OS for each treatment arm separately, as the proportional hazards assumption does not hold (crossing curves), see Appendix G. AIC and BIC criterion were computed to assess the goodness-of-fit of the extrapolations to trial data. Based on long-term survival rates from the ENSCCA registry data (5-year survival of 1.8%) and the goodness-of-fit of the different curves, the log-logistic distribution was selected for both treatment arms. It estimates 5-year survival at 2.83% for GemCis, which reflects the long-term survival of patients in European RWE as described above. This distribution is also one of the best fitting curves according to AIC and BIC for both treatment arms, as the AIC is within the 5 points of the best fitting curve for each treatment arm (a 5 points difference is commonly not considered as significant). For scenario analysis, the Gamma (best-fitting distribution with regards solely to AIC/BIC statistics) was selected for both treatment arms to explore the impact of selecting the best distribution based on AIC/BIC results.

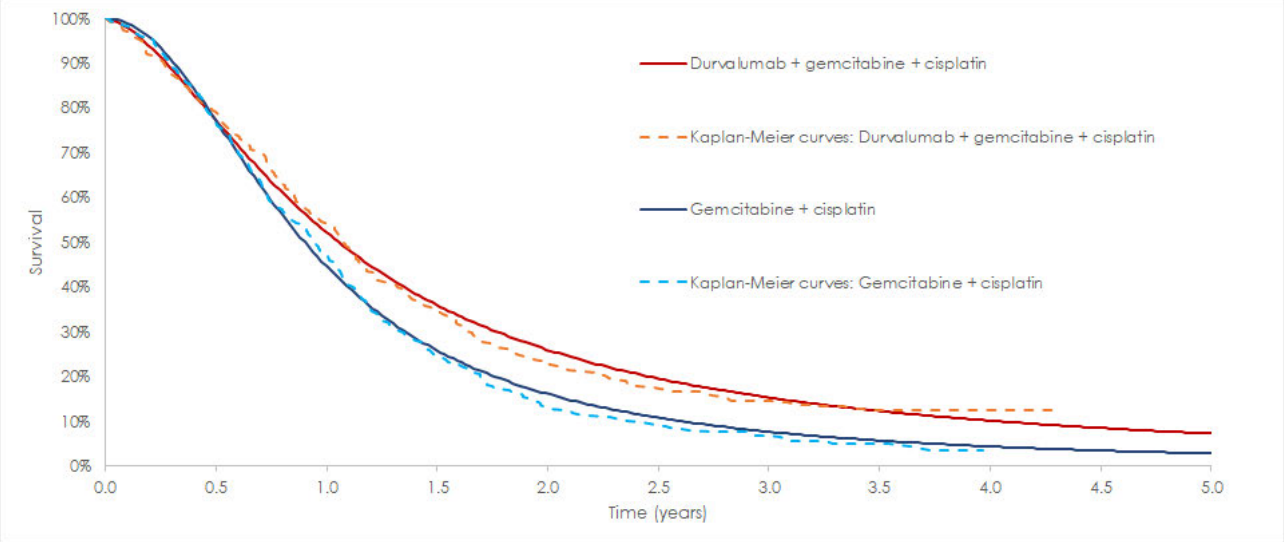
Based on these results, the following distributions, presented in Figure 27, were selected:

- For GemCis, log-logistic was selected for base case analysis, and Gamma for scenario analysis
- For durvalumab + GemCis, log-logistic was selected for reference analysis, and Gamma for scenario analysis

For the long-term OS extrapolation in the durvalumab arm, the parametric extrapolation is used up to 43 months, and the approach used beyond that is described in the sections below.

In the model, the user can select any extrapolation for OS for either treatment arm. There is also an option to apply a piecewise approach to OS, to explore the impact of using the Kaplan Meier curve until a cut-off timepoint selected by the user, and the extrapolation after the cut-off. Switching directly to the extrapolation from the cut-off time point onwards may result in jumps or sudden drops in OS curve, which would be implausible. To avoid this, after the cut-off the *risk (hazard) of death* of the survival extrapolation is applied to the Kaplan-Meier survival. The maximum time until which the Kaplan-Meier curve can be used is the end of trial follow-up for the endpoint.

Figure 27: OS selected distributions for each treatment arm from TOPAZ-1 trial (before the application of long-term)



8.3.1.2 Long-term extrapolation of effect in the durvalumab + GemCis arm

Based on the recent systematic review by Lin et al. (106), 23 randomised controlled phase 3 trials (see Table 1, Lin et al. 2022) comparing immune checkpoint inhibitors treatment versus chemotherapy across three cancer types (non–small cell lung cancer, urothelial carcinoma and melanoma) were selected to inform on long-term (>24 months) survival probabilities from IO trials. The Embase database was searched for complementary full-text publications and conference abstracts on the included trials published between 22 May 2022 and 20 February 2023 to ensure the inclusion of latest publicly available data. Overall survival rates at 24, 36, 48 and 60 months from the experimental and control arms were extracted, when available based on length of follow-up. If landmark values for overall survival rates were not provided in text of the publications, the values were estimated by manual inspection of the curves in figures. For more detail and data, see Appendix K. The data are also included in the Excel model ('IO OS data' worksheet).

The conditional mortality rate was estimated as the difference between landmark OS at time t + 12 month minus OS at time t, divided by OS at time t. For example, the conditional survival for the time period between 24 and 36 months is estimated as:

(landmark OS at 36 months - landmark OS at 24 months)/landmark OS at 24 months).

These values were estimated for each trial and then the average for all included trials was estimated for the time periods 24 – 36 months, 36 – 48 months, and 48 – 60 months. There were too few relevant studies with follow-up longer than 60 months to obtain reliable estimates for the survival development beyond 60 months. Based on the extracted landmark overall survival rates, the mean conditional survival decreases from 26.3% between 24 and 36 months to 12.1% between 48 and 60 months in the experimental (IO) arm. In terms of relative mortality risk between the

experimental arm and the control arm, it decreases from 0.86 between 24 and 36 months to 0.56 between 48 and 60 months (Table 31). This suggests that the plateau effect increases over time. In the model, the starting age is 62. The conditional mortality was therefore compared with the age-related mortality rates for the time periods of interest, i.e. the general age related mortality at age 64 (start age + 24 months) for the time period between 24-36 months etc. The relative mortality compared with the normal population is estimated by dividing the conditional mortality with the age-related mortality. In the experimental arm, the mortality relative to the normal population decreases from 27.24 between 24-36 months to 9.19 between 48-60 months (Table 31).

The mean of the median ages in the studies included in the systematic review by Lin et al. (106) was 63.7 years (median 64; range 57 – 69). Hence the median age in these IO trials was well aligned to the median age in the TOPAZ-1 study, which was 64 (mean age 62.4).

Table 31: Mean conditional mortality, relative risk and mortality relative to the normal population from 24-60 months in IO

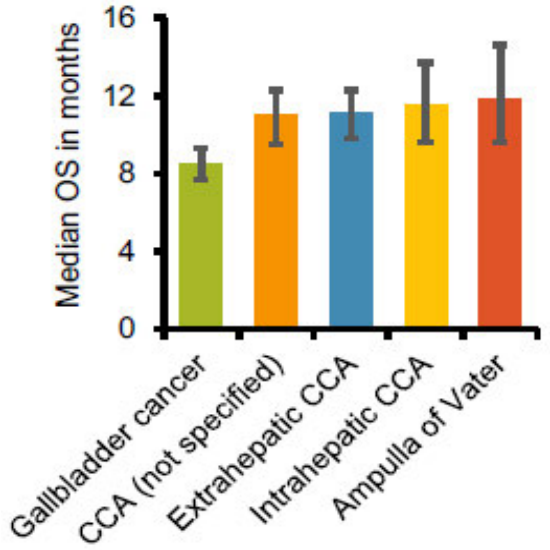
Outcome (mean)	Time period		
	24-36 m	***36-48 m***	***48-60 m***
Conditional mortality, experimental arm	26.3%	19.4%	12.1%
Conditional mortality, control arm	30.7%	23.0%	21.6%
Relative mortality risk for experimental vs. control	0.86	0.84	0.56
Age-related mortality (by age)*	0.97% (64)	1.12% (65)	1.32% (66)
Relative mortality, experimental arm**	27.24	17.24	9.19
Relative mortality, control arm**	31.77	20.47	16.34

**Estimated from Danish life tables (Statistics Denmark) **Mortality relative to normal Danish population with age 64 (24-36m), 65 (36-48m) and 66 (48-60m).*

For the time horizon beyond 5 years, it is difficult to find reliable data on conditional survival and relative mortality in the IO trials in the systematic review by Lin et al. (106). In general, there is more data for the earlier time periods, while the data between 48-60 months builds on fewer studies. Instead, we based the relative mortality on real-world evidence for the period after 60 months. A targeted literature review was performed to identify long-terms survival in studies of BTC as well. The literature search included both studies based on clinical trials and real-world studies based on registry data. Although a few studies fulfilled the inclusion criteria, the only one that contained useful data for our purposes was a study by Elgenidy et al. (108) based on the SEER database in the US. The main advantage of this study is that it has very long follow-up with data from 2000-2018 and hence results that stretch both beyond 5 and 10 years. A limitation is that the study only includes patients with intrahepatic CCA, i.e., a subpopulation of BTC, rather than all types of BTC patients. The study presents standardized mortality ratios (SMRs) with their 95% confidence intervals for each cause of death using the SEER*Stat software version 8.3.9.2. The SMR represents the ratio of the number of deaths observed in patients with intrahepatic CCA over a given period to the number that would be expected to die in age-adjusted and demographically similar patients over the same period. Between 5-10 years, the SMR for all-cause mortality was 4.65 (95% CI 3.91 – 5.49) and beyond 10 years it was 1.44 (95% CI 0.9 – 2.18). It is notable that the SMR beyond 10 years is not significantly above 1, i.e., the mortality might not be higher than in an age-adjusted and demographically similar sample from the normal population.

The mortality for intrahepatic CCA is in line with other types of CCA, but is lower than for gallbladder cancer (Figure 28). Hence, it is plausible to assume that the SMRs for intrahepatic CCA should be representative for CCA in general, but gallbladder has a somewhat higher disease severity. In the absence of gallbladder-specific data, we have assumed that it will be similar to intrahepatic CCA with regard to long-term relative risks.

Figure 28: Median OS by primary BTC site



Source: McNamara et al. (2020) (109)

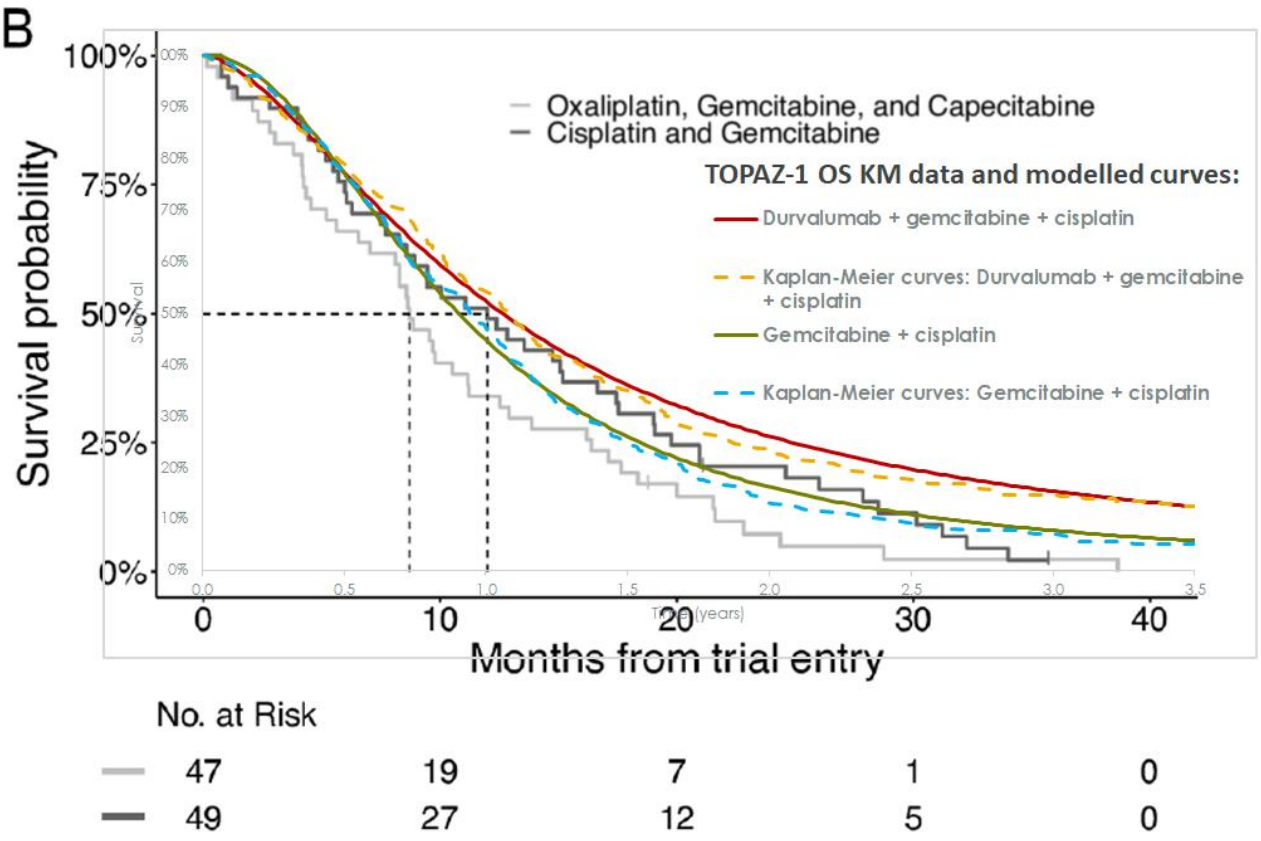
Over time, the incidence of gallbladder cancer has decreased in western countries, while the incidence of intrahepatic CCA has been on the rise. A recent Swedish study indicates that intrahepatic CCA was the largest BTC subtype during the period 2011-2019, representing 28.2% of all cases (110). Gallbladder cancer was the second most common representing 25.8% of all cases. Hence, cholangiocarcinoma, including intrahepatic and extrahepatic (distal and perihilar), represents the majority of cases (68%). This means that the SEER data on intrahepatic CCA are probably fairly representative for the whole BTC population.

A survival adjustment was applied to the extrapolated OS function to ensure that at each cycle, the probability of survival in the target population did not exceed that of the Danish general population. If at any timepoint the survival was higher than in the general population, the model took the value from the latter. However, in the base case, this adjustment was not necessary.

8.3.1.3 External validation of OS extrapolation

In an investigator-initiated randomized phase II trial conducted in Denmark, patients with advanced biliary tract cancer were treated with either oxaliplatin 50 mg/m2 and gemcitabine 1000 mg/m2 on day 1 in a two-week cycle with capecitabine 650 mg/m2 twice-daily continuously or cisplatin 25 mg/m2 and gemcitabine 1000 mg/m2 on day 1 and day 8 in a three-week cycle (107). The modelling of the GemCis arm can be compared with the OS results from this trial. The median PFS (mPFS) was 7.3 months (95% CI 6.0–8.7) and the mOS was 12.0 months (95% CI 8.3–16.7) in the GemCis arm. This is slightly better than in TOPAZ-1, where mPFS was 5.7 months (95% CI 5.6–6.7) and mOS was 11.3 months (95% CI 10.1–12.5) in the GemCis arm, but still on about the same level. The base-case modelling is compared with the OS data presented by Markussen et al. (107) in Figure 29. The visual comparison shows that the extrapolation for the GemCis arm is well aligned with the data from Markussen et al. up to 30 months. After that, there is too much censoring and no patients at risk in the Danish trial data to make an adequate comparison. In any case, the results show that the modelling is in line with a Nordic patient group treated with GemCis up to 30 months.

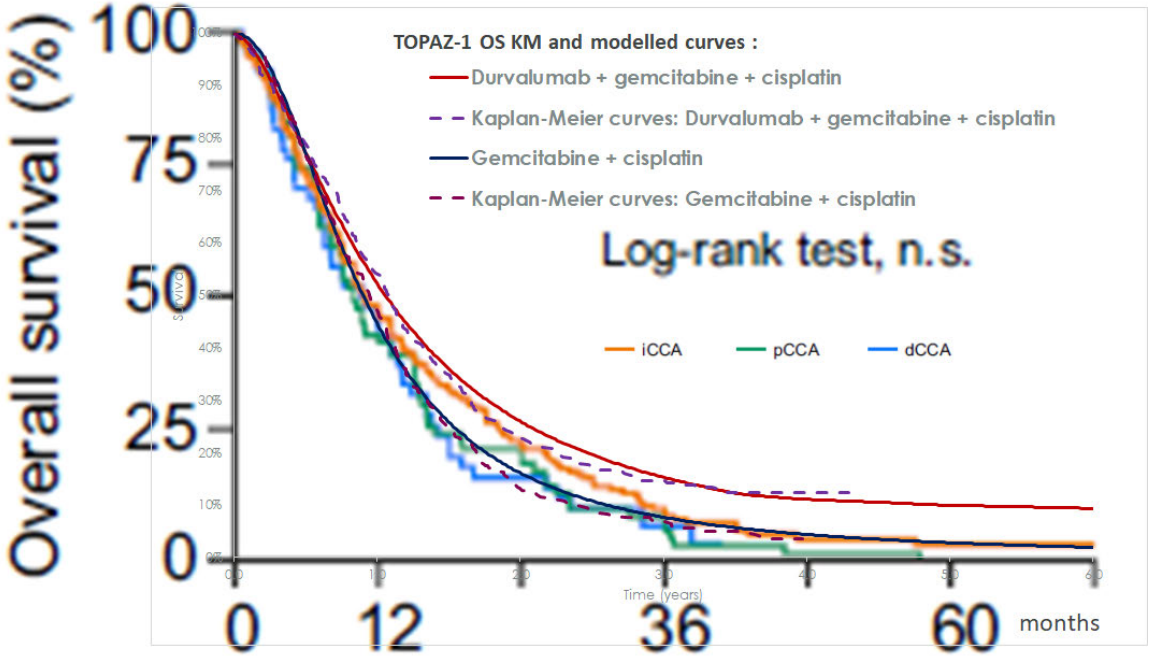
Figure 29: Base-case OS extrapolations compared with the OS outcome from a Danish study



On the European level, data on cholangiocarcinoma are available for more than 5 years from the ENSCCA registry that enrolled 2234 patients from 26 hospitals in 11 countries (111). Out of the total sample, 477 (29.0%) received active palliative therapy, i.e. chemotherapy (26.2% of whole cohort), locoregional therapy (1.5%) and combined chemo- and locoregional therapies (1.3%). The mOS for patients receiving active palliative therapy was 10.6 months (95% CI 9.2-12.0 months) from time of treatment initiation. This is slightly below the point estimate for mOS in TOPAZ-1 (11.3 months as mentioned above), but still on a comparable level. The 1-, 3-, and 5-year survival rates were 45.2%, 8.4%, and 1.8% respectively. The 1-year survival rate is comparable with the GemCis arm in TOPAZ-1 (45.2% in ENSCCA vs. 47.1% for GemCis in TOPAZ-1).

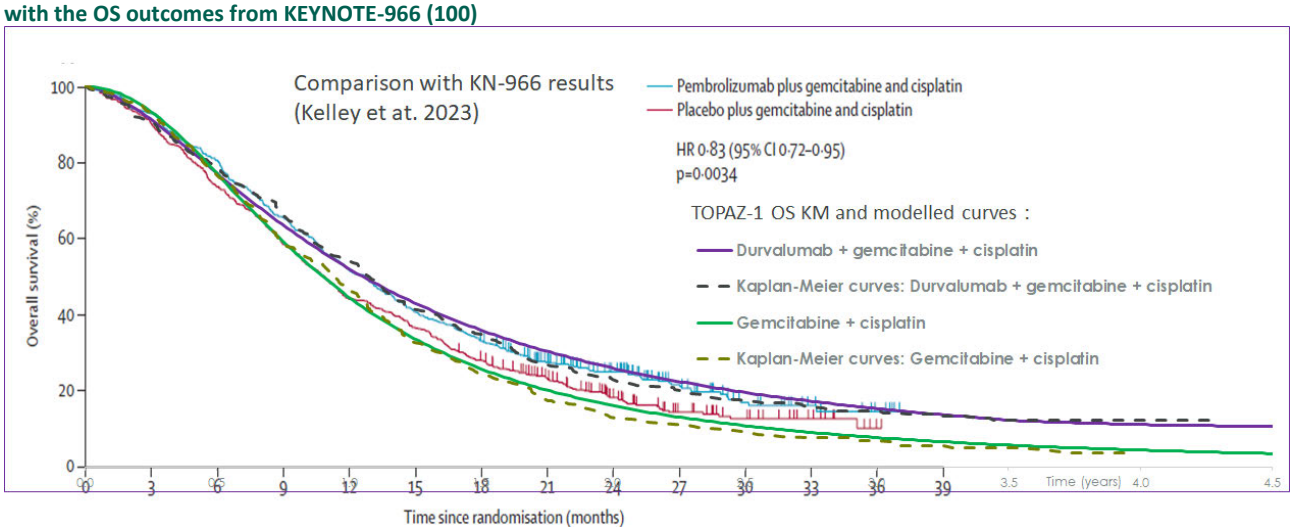
The base-case modelling is compared with the OS data presented by Izquierdo-Sanchez et al. (111) in Figure 30. The visual comparison shows that the extrapolation for the GemCis arm is well aligned with the data from the ENSCCA registry.

Figure 30: Base-case OS extrapolations compared with the OS outcome from unresectable patients with palliative treatment in European ENSCCA registry



Recently, data from the KEYNOTE-966 study was published (100). It has slightly longer follow-up and slightly more patients per randomized group. In Figure 31 below, OS KM data and modelling from TOPAZ-1 are compared with KEYNOTE-966. We are aware that directly comparing clinical trials may not be appropriate due to differences in patient population and design, but it can nevertheless be interesting as starting point for discussions.

Figure 31: OS extrapolations with external IO data starting to be used beyond 43 months for durvalumab + GemCis compared with the OS outcomes from KEYNOTE-966 (100)



For long-term comparison of OS even beyond 5 years there is a study based on SEER data from the US available. As previously mentioned, it is limited to a subgroup of BTC (intrahepatic CCA), but this is now the largest BTC subgroup in the Nordics. In the study by Markussen et al. (107), for example, 56% of the patients belonged to the intrahepatic CCA subgroup. In the TOPAZ-1 trial, intrahepatic CCA also represented 56%.

The SEER data from Elgenidy et al. (108) indicate a good alignment between the extrapolation for the GemCis arm and the chemotherapy treatment group in the SEER data up to around 6 years (Figure 32). After that, there is increasing underprediction of the chemotherapy arm. The extrapolation for the durvalumab + GemCis arm cannot necessarily be validated through the SEER data, but is notable that the OS curves is below those for treatments involving surgery (Surgery/ Radiotherapy, Cancer-directed surgery, etc) but above chemotherapy or chemo-radiotherapy. It is also notable that the long-term plateauing of the durvalumab + GemCis extrapolation appears to be realistic given the behaviour of the other OS curves in the figure, which are all flattening out over time. The model has flexibility to align to the OS outcome for chemotherapy with the SEER data. If the SMRs between 5 and 10 years and beyond 10 years from the Elgenidy study (108) are applied to the GemCis OS extrapolation beyond 5 years (discussed in section 8.2.1), the alignment becomes closer, but may overestimate OS slightly in the long run compared with the SEER data for chemotherapy alone (Figure 33). The results of this scenario is included as the last of the OS scenario analyses in Table 55 below, but we are keeping the unadjusted OS extrapolation as base case for the GemCis arm.

Figure 32: Base-case OS extrapolations compared with long-term SEER data on intrahepatic CCA

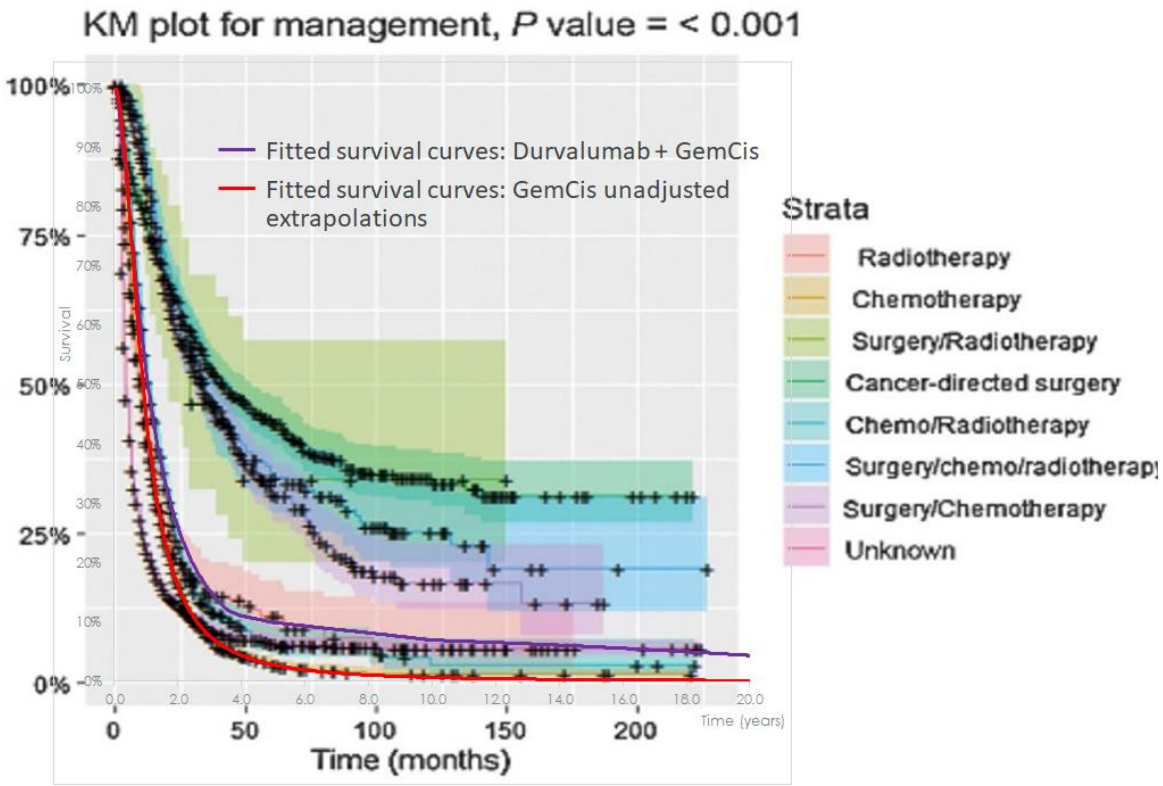
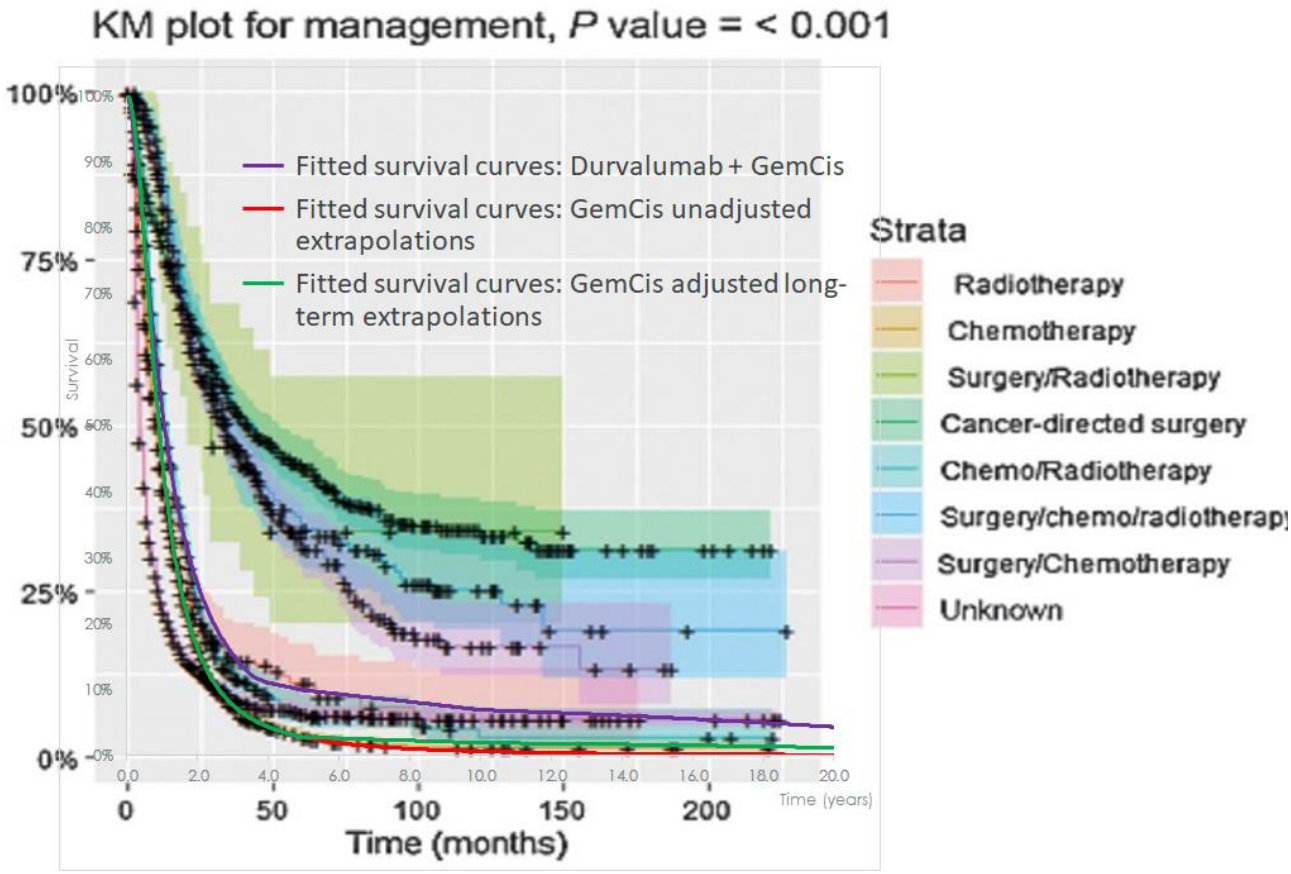


Figure 33: OS extrapolations with long-term adjustment to both durvalumab + GemCis and GemCis alone



8.3.2 Progression-free survival

8.3.2.1 Survival extrapolations for PFS

PFS was modelled independently of OS as is standard in partitioned survival models. Based on the AIC/BIC goodness-of-fit to the mature TOPAZ-1 PFS data, as well as the plausibility of long-term extrapolations, the Spline hazards 3 knots distribution for durvalumab + GemCis and for GemCis was selected (see Appendix G for further details). This distribution minimizes AIC/BIC statistics and leads to more conservative long-term PFS rates compared to several standard parametric functions.

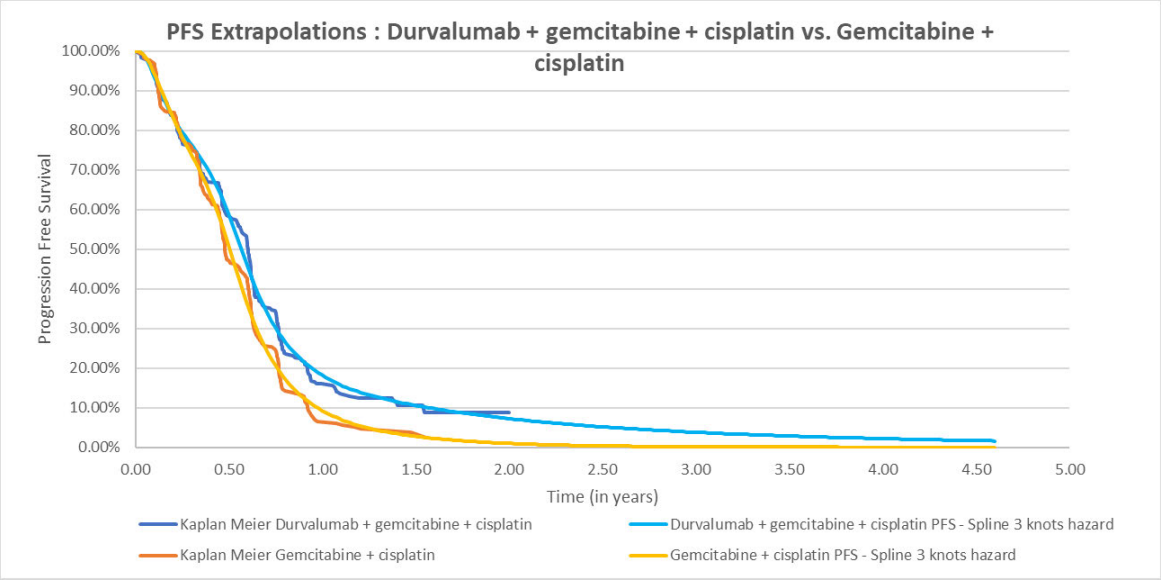
For scenario analyses, the best-fitting standard parametric distribution for durvalumab + GemCis and the second-best for GemCis (Gamma) was selected for both treatment arms.

In summary:

- For GemCis, the Spline hazards 3 knots distribution was selected for the base case analysis, and the Gamma distribution as scenario analysis
- For durvalumab + GemCis, the Spline hazards 3 knots was selected for base case analysis, and Gamma for scenario analysis

In the model, the user can select any distribution for PFS for either treatment arm. There is also an option to apply a piecewise approach to PFS, to explore the impact of using the Kaplan Meier curve until cut-off and the extrapolation after cut-off. The method applied is the same as for the OS piecewise option.

Figure 34: PFS selected distributions for both treatment arms (TOPAZ-1 trial – August 2021)



8.3.3 Time to treatment discontinuation

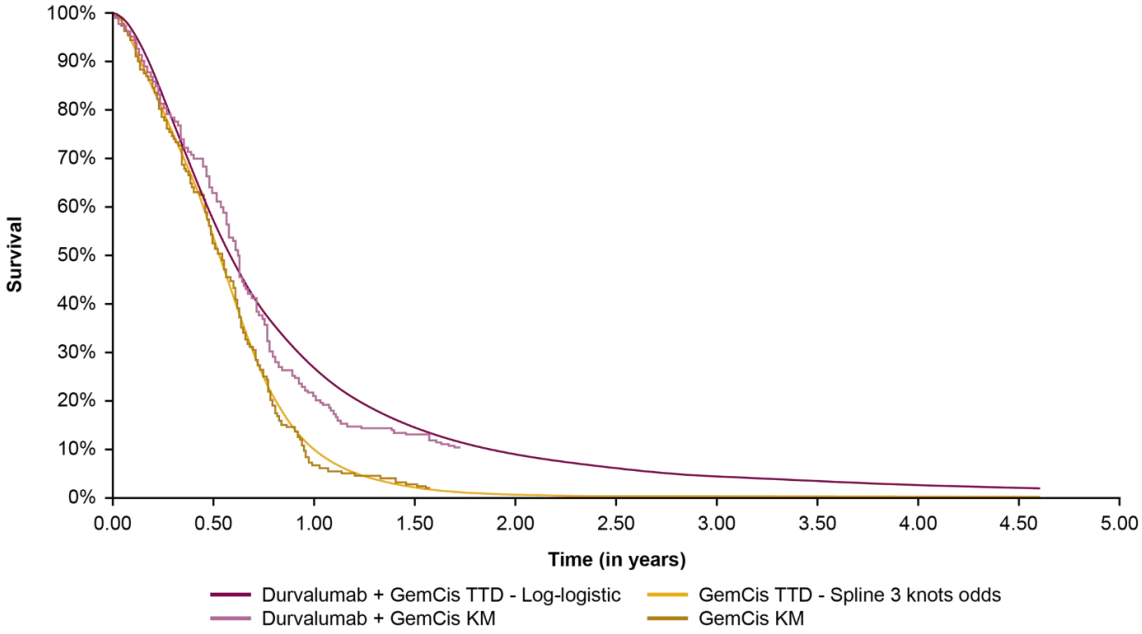
The curve selection was based on AIC/BIC goodness-of-fit and consistency with PFS, the log-logistic distribution was selected for durvalumab + GemCis and the spline odds 3-knots for the GemCis.

The Gamma distribution was tested in a scenario analysis for GemCis. A piecewise approach was applied for durvalumab + GemCis as scenario analysis to evaluate the impact of using the Kaplan Meier curve until the cut-off point, and the log-logistic extrapolation after cut-off. This approach allows the direct use of Kaplan Meier data, and therefore reduces uncertainty associated with the extrapolation. A cut-off of 15 months was chosen because 15 months corresponds to the appearance of a plateau in the TTD KM curve. The method applied is the same as for the OS piecewise option.

The reason for choosing different distributions for TTD for the two arms is primarily to achieve consistency with PFS, as the treatment is indicated to be continued until progression or unacceptable toxicity. The Spline hazards 3 knots PFS extrapolation for durvalumab + GemCis predicts 7.25% of patients as progression-free at 24-months; this aligns most closely with the 24-month predictions for patients remaining on treatment using the exponential (8.17%) and log-logistic (8.90%) curves, of which the log-logistic showed better fit to the Kaplan-Meier data as per AIC/BIC. In addition, the Spline hazards 3 knots PFS extrapolation for durvalumab + GemCis predicts 1.3% of patients as progression-free at 60-months, compared with 1.7% for the TTD using a log-logistic distribution. In contrast, the best-fitting spline odds 3 knots distribution for TTD predicts 9.44% and 3.1% of patients remaining on treatment at 24 and 60 months, respectively, predictions which are less plausible based on the PFS estimates compared to the log-logistic.

The selected base case TTD extrapolations are summarized in Figure 35. For durvalumab + GemCis, the log-logistic distribution was selected, whilst for GemCis the Spline odds 3 knots distribution was selected (10).

Figure 35: Summary of selected TTD distributions



Source: *AstraZeneca Data on File (10)*

The TTD curve for durvalumab lies slightly above the PFS curve from month 12 and onwards (Figure 35). In terms of costs, it would be more favorable for the model results with treatment to progression based on PFS. Modelled TTD thus may therefore be slightly overestimated, but the choice of TTD curve is chosen based on consistency with PFS.

8.3.4 Summary of curve selection for OS, PFS and TTD

The proportion of patients alive at different time points in the model is presented for each treatment arm in Table 32. These proportions were derived from the base case extrapolations of the TOPAZ-1 OS and PFS curves, see sections above.

- OS: the log-logistic distribution for both treatment arms, with long-term extrapolation from month 43 in the durvalumab + GemCis arm
- PFS: the spline hazards 3 knots for both treatment arms
- TTD: For GemCis, the Spline odds 3 knots distribution was selected and for durvalumab + GemCis, the log-logistic was selected

Table 32: Proportion of patients alive, progression-free or on treatment at different time points (pure parametric extrapolations modelled by treatment arm)

Endpoint	Time Horizon	Durvalumab + GemCis	Placebo + GemCis
OS	2 years	26.1%	16.22%
	5 years*	7.25%	2.83%
	10 years*	2.45%	0.68%
	15 years*	1.28%	0.30%
	20 years*	0.80%	0.16%
	25 years*	0.56%	0.10%
	30 years*	0.42%	0.07%
PFS	6 months	59.02%	51.05%
	12 months	18.22%	9.32%
	18 months	10.60%	2.81%
	2 years	7.25%	0.98%
	5 years	1.32%	0.00%
	10 years	0.18%	0.00%
TTD**	6 months	57.48%	54.58%
	12 months	26.65%	10.03%
	18 months	14.42%	2.06%
	2 years	8.90%	0.62%
	5 years	1.68%	0.01%
	10 years	0.46%	0.00%

**This is with parametric extrapolations used throughout. With adjusted OS beyond 2 years (at 43 months), these proportions will be different for OS in the durvalumab + GemCis arm. **Treatment costs for GemCis are limited to 8 cycles, i.e. to around 5 months.*

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

Key takeaways:

- *Utilities were derived from EQ-5D-5L responses collected in TOPAZ-1 trial using the value set from Jensen et al. (112).*
- *Disutility values and durations for adverse events were sourced from the literature*

8.4.1 Overview of health state utility values (HSUV)

In the TOPAZ-1 trial, health-related quality of life (HRQoL) was captured using EQ-5D-5L. For this economic evaluation, utilities were calculated from TOPAZ-1 through mixed model for repeated measures approach, including univariate and multivariate analyses with covariates such treatment received, treatment status and progression status.

Utilities were derived from EQ-5D-5L responses collected in TOPAZ-1 trial using the value set from Jensen et al. (112).

A univariate model of utility by progression status was selected for the base case as progression status was found to be the strongest predictor of patient utility, second only to and very similar to treatment discontinuation status. Given that treatment discontinuation status refers to cessation of placebo treatment in the GemCis arm, progression status is a more clinically meaningful covariate and was selected for the base case. The utilities are presented in Table 33 below.

Table 33: Base case health-state utility values used in the health economic model

Health state	HSUV (95% confidence interval)
Pre-progression	0.873 (0.862–0.884)
Post-progression	0.756 (0.714–0.798)

Footnotes: *HSUVs were sourced from the TOPAZ-1 interim analysis.* ***Source:*** *AstraZeneca Data on File (53) ; Jensen et al. (112)*

8.4.2 Disutilities due to adverse events

The impact of AEs on QoL could not be directly estimated from the TOPAZ-1 trial data as AEs can occur at any time and may not be captured by the QoL questionnaires collected during the trial based on a regular-interval assessment schedule (at every cycle until treatment discontinuation and monthly afterwards). As such, disutility values and durations were sourced from the literature. In the absence of BTC-specific values, values previously used in a NICE evaluation of a treatment for advanced CCA were applied. QALY decrements, defined at the disutility multiplied by the duration, were applied as a one-off decrement in the first model cycle. A limitation of this approach is that the model doesn't account for the possibility of recurrence of any given adverse event. A summary of disutilities per Grade 3 or 4 AEs is presented in Table 34 (10).

Table 34: Base case health-state Grade 3-4 AE disutility values

AE	Disutility	Duration (days)	Source – disease area
Neutropenia	-0.0607	7	TA722 - Relapsed or refractory advanced cholangiocarcinoma(113)
Anaemia	-0.085	9.9	
Thrombocytopenia	-0.085	14	
Cholangitisa	-0.085	4.7	
Neutrophil count decrease	-0.0607	7	Assumed same as Neutropenia(113)
White blood cell count decreased	-0.0607	7	
Platelet count decreased	-0.085	14	Assumed same as thrombocytopenia(113)

Footnotes: *[a]Cholangitis disutility assumed the same as anaemia.*

8.4.3 Age-adjusted utilities

Age-adjusted utilities were incorporated into the model to account for the decrease in quality of life as patients get older.

This functionality can be selected by the user to apply a decrement, a multiplier or a cap to utility values based on patients' age, which is applied as explained below. In the base case, a multiplier effect was used based on data from Medicinrådet (114).

- Utility multiplier: based on the patient's age in the model, an adjustment is made to utility so that the patient's utility decreases at the same rate as the general population utility. This follows the formula below:
  - Utility at age "entry age + X years" = Utility in the model*(Utility in the general population at age "entry age + X years"/"Utility in the general population at age "entry age")

Further options:

- Utility decrement: based on the patient's age in the model, an adjustment is made to utility so that the patient's utility decreases by the same absolute number as the general population utility. This follows the formula below:
  - Utility at age "entry age + X years" = Utility in the model + (Utility in the general population at age "entry age + X years" - "Utility in the general population at age "entry age")
- Utility cap: assumes that the utility of patients can never be above the age-adjusted utility of the global population

Age-specific utilities were extracted from Danish utility data compiled by Medicinrådet. Table 35 presents mean utility values by age group.

Table 35: Age-adjusted utilities

Age group	Mean utility value
50-69	0.818
70-79	0.813
≥80	0.721

***Source**: Appendiks til Medicinrådets metodevejledning: Aldersjustering for sundhedsrelateret livskvalitet (114)*

8.5 Resource use and costs

Key takeaways:

- *Pharmaceutical costs were based on prices from medicinpriser.dk*
- *Health care utilization for routine care and adverse event handling was based on input from a medical expert*
- *Unit cost were mainly based on prices from DRG-takster 2023*

8.5.1 Pharmaceutical costs

The pharmaceutical costs for durvalumab, gemcitabine/cisplatin and for subsequent therapies were based on prices from medicinpriser.dk (AIP) (Table 36).

Table 36: Drug acquisition costs

Drug	Form	Strength	Pack Size	Costs per pack (DKK)
Durvalumab	IV	50mg/ml	10ml	18 069.82
Durvalumab	IV	50mg/ml	2ml	4 374.87
Gemcitabine	IV	10 mg/ml	180ml	370.00
Gemcitabine	IV	10 mg/ml	200ml	385.00
Gemcitabine	IV	10 mg/ml	220ml	420.00
Cisplatin	IV	1mg/ml	50ml	100.00
Cisplatin	IV	1mg/ml	100ml	200.00
Oxaliplatin	IV	5 mg/ml	10ml	41.18
Oxaliplatin	IV	5 mg/ml	20ml	68.80
Oxaliplatin	IV	5 mg/ml	40ml	127.82
Carboplatin	IV	10 mg/ml	15 ml	84.00
Carboplatin	IV	10 mg/ml	45 ml	203.00
Leucovorin	IV	10 mg/ml	10 ml	111.00
Fluorouracil	IV	50mg/ml	100 ml	300.00
Irinotecan	IV	20 mg / mL	5 ml	125.00
Irinotecan	IV	20 mg / mL	15ml	3 050.00
Irinotecan	IV	20 mg / mL	25ml	350.00
Teysuno (Gimeracil/Oteracil/Tegafur)	Oral	15mg/4.35mg/11.8mg	126	965.00
Teysuno (Gimeracil/Oteracil/Tegafur)	Oral	20mg/5.8mg/15.8mg	84	1 265.00
Capecitabine	Oral	150mg	60	671.00
Capecitabine	Oral	500mg	120	580.00
Nivolumab	IV	10mg/ml	4ml	3 508.46

Drug	Form	Strength	Pack Size	Costs per pack (DKK)
Nivolumab	IV	10mg/ml	10ml	8 715.54
Pembrolizumab	IV	25mg/ml	2ml	11 029.44
Pembrolizumab	IV	25mg/ml	4ml	22 058.88

Source: www.medicinpriser.dk 01.06.2023

The drug dosing regimens are described in Table 38 for first-line treatments and in Table 39 for subsequent treatments. Drug acquisition costs were calculated based on patient mean weight/body surface area (BSA). Accounting for wastage is important to accurately calculate the number of vials required per administration for an average patient. All treatments using a weighted dosage, i.e. dependent on patient's weight or BSA, are subject to wastage and/or vial sharing. In the base case, wastage is assumed. The Mosteller formula (115) was used for calculating BSA:

$$\textit{Mosteller formula: BSA } (m^2) = (\textit{height (cm) x weight (kg)}/3600)^{½}$$

The method of moments approach was used to account for patients' variability in weight and BSA. For treatments that are administered based on the weight or the BSA, the weight and BSA distribution was estimated using a normal distribution informed by the mean weight and height estimated by expert opinion (as patients' weight and height in TOPAZ-1 were seen as not representative of the Danish patient population). The standard deviations for height and weight were obtained from TOPAZ-1 as these values could be difficult for experts to estimate without access to patient-level registry data. For every weight and/or BSA value, the corresponding dose was calculated. A weighted average of all the individual costs was then applied in the model. The cost per cycle (inclusive of wastage) is based upon the weighted-average number of vials used per patient. If vial wastage is removed, a cost per mg approach is utilized.
Table 37 below shows the patient characteristics used in the modelling, based on expert opinions and data from the TOPAZ trial. Those are only used for non-fixed dose treatments (gemcitabine and cisplatin for example). As durvalumab is given at a fixed dose for all patients, patients characteristics do not affect durvalumab treatment acquisition costs.

Table 37: Patient characteristics from the TOPAZ-1 trial

Patient characteristic	Value	Standard deviation	Source
Mean weight (kg)	77.3	15.85	Expert opinion*, TOPAZ-1
Mean height (cm)	171	9.57	Expert opinion*, TOPAZ-1
Mean body surface area (kg/m^2)	1.92	0.38	Mosteller formula (115)
Creatine clearance (mL/min)	85.3	NA	TOPAZ-1

*According to a Danish clinical expert, patients are of mean height and weight for their age at diagnosis. For a 60-69-year old, this would mean 77.3 kg and 171 cm based on data presented by the expert. (Mean weight was 66.5 kg and mean height 163.7 cm in TOPAZ-1).

Table 38: Dosing Regimens – First-line

Treatment Regimen	Drug	Dosage	Form	Loading phase (first 8 treatment cycles)		Maintenance phase (treatment cycles 9+)		Source
				Cycle length	Frequency of dosing	Cycle length	Frequency of Dosing	
First-line treatments								
Durvalumab + GemCis	Durvalumab	1500mg	IV	21 days	Day 1	28 days	Day 1	TOPAZ-1 trial
	Gemcitabine	1000 mg/m²	IV		Days 1 and 8		No dose	
	Cisplatin	25 mg/m²	IV				No dose	
GemCis	Gemcitabine	1000 mg/m²	IV	21 days	Days 1 and 8	N/A	No dose	TOPAZ-1 trial
	Cisplatin	25 mg/m²	IV				No dose	

Abbreviations: IV: intravenous

Table 39: Dosing Regimens – Subsequent therapies

Treatment Regimen	Drug	Dosage	Form	Treatment cycle length	Frequency of dosing	Source
Subsequent treatment						
FOLFOX	Oxaliplatin	85 mg /m²	IV	14 days	Day 1	Lamarca et al. 2021 (116)
	Leucovorin	400 mg /m²	IV			
	Fluorouracil	400 mg /m² Then 2400 mg /m²	IV			
FOLFIRI	Irinotecan	180 mg /m²	IV	14 days	Day 1	
	Leucovorin	400 mg /m²	IV			
	Fluorouracil	400 mg /m² Then 2400 mg /m²	IV			

Treatment Regimen	Drug	Dosage	Form	Treatment cycle length	Frequency of dosing	Source
Xelox (capecitabine + oxaliplatin)	Capecitabine	1000 mg /m²	Oral	21 days	PO twice a day for 14 days	
	Oxaliplatin	130 mg /m²	IV	21 days	Day 1	
Teysuno	Tegafur, gimeracil and oteracil	60mg twice daily	Oral	42 days	PO twice a day for 28 days	European medicine agency (48) Inoue et al 2021. (117)
Nivolumab monotherapy	Nivolumab	3 mg/kg	IV	14 days	Day 1	DaBlaCa (2023) (118)
Pembrolizumab monotherapy	Pembrolizumab	2 mg/kg	IV	21 days	Day 1	Medicinrådet recommendation 2023 (119)

*. * expressed as tegafur content ** this dosing regimen is not incorporated into the model because the mean duration of treatment (see Table 38 and Table 39) is less than 4 full cycles.*

A summary of the drug acquisition costs is presented in Table 40 and Table 41. A relative dosing intensity (RDI) was applied for the first-line treatments, from the TOPAZ-1 data on file. First-line treatment cycle costs are applied in the model in the first week of the treatment cycle. GemCis treatment acquisition costs were not applied to either treatment arm after 8 treatment cycles. For subsequent treatments, the treatment cycle costs were converted into a weekly cycle cost. Costs and vial sizes for each comparator are linked with the costs input sheet and data parameters sheet so care is needed if altering these values.

Table 40: Drug acquisition cost summary: first-line treatments

Regimen	Drug	Relative dosing intensity	Total dose per treatment cycle	Drug cost per treatment cycle (DKK)	Total cost per treatment cycle (cycles 1-8) (DKK)	Total cost per treatment cycle (after cycle 8) (DKK)
First-line treatments						
Durvalumab + GemCis	Durvalumab	96.3%	1445 mg	53 639.12	54 670.42 (Cycle length: 3 weeks)	53 639.12 (Cycle length: 4 weeks)
	Gemcitabine	89.9%	3127 mg	769.96		
	Cisplatin	90.5%	78.7 mg	261.33		
GemCis	Gemcitabine	89.1%	3099 mg	764.36	1 025.69	0

In the absence of information on the RDI for all subsequent therapies, a 100% RDI was assumed for all subsequent therapies. This is because the RDI is not always available in the literature and in the absence of data for all, we wished to use the same assumption for all treatments.

Table 41: Drug acquisition cost summary: subsequent treatments

Regimen	Drug	Total dose per treatment cycle	Drug cost per treatment cycle (DKK)	Total cost per treatment cycle (DKK)	Weekly treatment cost (DKK)
FOLFOX	Oxaliplatin	148 mg	122.17	945.32	472.66
	Leucovorin	696 mg	336.63		
	Florouracil	4,869 mg	486.52		
FOLFIRI	Irinotecan	313 mg	346.53	1 169.68	584.84
	Leucovorin	696 mg	336.63		
	Florouracil	4,869 mg	486.52		
Platinum based chemotherapies	Assumed to be the same as GemCis				341.90
Teysuno	Teysuno	3,360 mg		5 319.64	886.61
Capecitabine + oxaliplatin	Capecitabine	48690 mg	1 118.23	1 293.21	431.07
	Oxaliplatin	226 mg	174.98		
Nivolumab monotherapy	Nivolumab	232 mg	20 211.34	20 211.34	10 105.67

Regimen	Drug	Total dose per treatment cycle	Drug cost per treatment cycle (DKK)	Total cost per treatment cycle (DKK)	Weekly treatment cost (DKK)
Pembrolizumab monotherapy	Pembrolizumab	155 mg	34 103.03	34 103.03	11 367.68
Pemazyre	Pemigatinib	13.5 mg	54 854.02	54 854.02	18 284.67

8.5.2 Administration costs

With the exception of Teysuno (an oral treatment) and capecitabine, durvalumab and all the other treatments are administered via IV infusion. Administration costs are based on a DRG cost (DRG takster 2024 (120), 07MA98; DKK 1947). The model makes a difference between simple and more complex infusions, but the DRG costs do not make this distinction and we have assumed the same cost for both categories. In addition, it assumed that the administration cost is DRG-based and independent of the administration time.

The duration of IV infusions is still included as a basis for time costs and was estimated based on various literature sources, primarily the TOPAZ-1 protocol, the EMA Summary of Product Characteristics and Cancer Research UK. IV infusion times are described in Table 42. Leucovorin can be administered simultaneously in separate IV bags with oxaliplatin or irinotecan in the second-and third-line regimens FOLFOX and FOLFIRI. Fluorouracil is administered as a 44 to 46 hour continuous IV infusion in the home environment, with no need for nursing monitoring after discharge from the hospital, apart from the disconnection of the IV drip.

Table 42: IV infusion times

Regimen	Duration of infusion	Comment	Source
First-line comparators			
Durvalumab + GemCis	5 hrs	GemCis is a 4-hour infusion time. According to TOPAZ protocol, durvalumab is administered during 1h and no other drug can be co-administered. The administration time is reduced to 1 hour after 8 treatment cycles when the maintenance phase switches to durvalumab monotherapy.	TOPAZ protocol 7.0 (121)
GemCis	4 hrs	GemCis is a 4-hour infusion time according to the TOPAZ protocol.	TOPAZ protocol 7.0
Second-line comparators			
FOLFOX	2.5 hrs	Fluorouracil (5-FU) I.V. push is usually given over 3 to 5 minutes on Day 1, after the end of the leucovorin infusion and continuous I.V. infusion (via home-infusion pump) over 44 - 46 hours. Leucovorin and oxaliplatin can be given together and would take over 2h. A total of 2.5h of administration time is estimated by Kreftlex.no.	Kreftlex.no; Cancer Research UK

Regimen	Duration of infusion	Comment	Source
FOLFIRI	3 hrs	Fluorouracil (5-FU) I.V. push is usually given over 3 to 5 minutes on Day 1, after the end of the leucovorin infusion and continuous I.V. infusion (via home-infusion pump) over 44 - 46 hours. Leucovorin and Irinotecan can be given together and would take over 2h. A total of 2.5h of administration time is estimated by Kreftlex.no.	Kreftlex.no; Cancer Research UK
Capecitabine + oxaliplatin	2 hrs	Oxaliplatin administration only. A total of 2h of administration time is estimated by Kreftlex.no. Outpatient prescription for home administration (capecitabine)	Kreftlex.no; Cancer Research UK
Nivolumab monotherapy	30 mins	Nivolumab is administered as intravenous infusion over 30 mins	EMA, Summary of Product Characteristics
Pembrolizumab monotherapy	30 mins	Pembrolizumab is administered as intravenous infusion over 30 mins	EMA, Summary of Product Characteristics

Table 43 provides a summary of the administration costs. Total costs were calculated by adding the one-off cost from the schedule of benefits and hourly cost of chemotherapy multiplied by the time for infusion for the relevant treatment regimen. GemCis treatment administration costs were not applied to either treatment arm after 8 treatment cycles. For first-line treatments, administration costs for the full treatment cycle are applied in the model in the first week of the treatment cycle. For subsequent treatments, administration costs for the full treatment cycle were converted into a weekly cycle cost.

Table 43: Administration cost summary

Comparator	Total cost per treatment cycle (Initial phase: cycles 1-8) (DKK)	Total cost per treatment cycle (Maintenance phase: After cycle 8) (DKK)
First-line treatments		
Durvalumab + GemCis	3 894.00 (3-week cycle)	1 947 (4-week cycle)
GemCis	3 894.00 (3-week cycle)	0
Treatment	**Cost per treatment cycle (DKK)**	**Weekly cost (DKK)**
Subsequent treatments		
FOLFOX	1 947.00	649.00
FOLFIRI	1 947.00	649.00
Platinum based chemotherapies	Assumed to be the same as GemCis	0
Capecitabine + oxaliplatin	1 947.00	649.00
TS-ONE	0	0

8.5.3 Health care utilization for routine care and monitoring

The health state costs were based on unit costs and healthcare utilization frequencies for routine care (Table 44 and Table 45). The healthcare utilization items were derived from clinical management of BTC in Denmark and were, together with the estimated frequencies, validated by a clinical expert. Frequencies were estimated based on the model's cycle length. The unit costs were taken from DRG-takster 2024 (120), DMC (122), Rigshospitalets Labportal and Lægeforeningen (123, 124). The office visit and nurse are assumed to have half an hour duration.

Table 44: Health care utilization costs

Resource item	Unit cost (DKK)	Source/Comment
Oncology consultation (office visit)	1 947	DRG-takster 2024: 07MA98: MDC09 1-dagsgruppe, pat. mindst 7 år
Nurse visit	1 947	DRG-takster 2024: 07MA98: MDC09 1-dagsgruppe, pat. mindst 7 år
Emergency room visit	1 947	DRG-takster 2024: 07MA98: MDC09 1-dagsgruppe, pat. mindst 7 år
Biliary stent or catheter replacement	10 416	DRG-takster 2024: 06PRO1: Indsættelse af endoskopiske stents
CT scan	2 021	DRG-takster 2024: 30PR07: CT-scanning, ukompliceret
MRI	2 142	DRG-takster 2024: 30PRO3: MR-scanning, ukompliceret
Liver function test	78	Laboratorieundersøgelser (ALAT + ASAT + ALP + Bilirubin + GT), Rigshospitalets Labportal (https://labportal.rh.dk/Metodeliste.asp)
Renal function test	80	Laboratorieundersøgelser (P-kreatinin + P-glucose + C-reaktivt protein (CRP) + B-hæmoglobin + Urea), Rigshospitalets Labportal
Complete blood count	54	Laboratorieundersøgelser Blod (MCV, MCH, MCHC) Rigshospitalets Labportal
Biochemistry tests	220.95	Laboratorieundersøgelser (Electrolytes, Coagulation, CA19-9), Rigshospitalets Labportal
Patient time cost, per hour	203	Værdisætning af enhedsomkostninger, vers 1.7
Patient transport cost	140	Værdisætning af enhedsomkostninger, vers 1.7

Table 45: Healthcare resources use per month

Resource item	Treatment line/Health state				
	First-line treatment (PF)	Second-line treatment (PD)	Third-line treatment (PD)	No treatment (PD)	Beyond 5 years
Oncology consultation (office vistit)	3.00 (day 1 and 8 each cycle, 2 per 3 weeks)	2.00 (every two weeks)	2.00 (every two weeks)	0.33 (every third month)	0.08 (once per year)

Resource item	Treatment line/Health state				
	First-line treatment (PF)	Second-line treatment (PD)	Third-line treatment (PD)	No treatment (PD)	Beyond 5 years
Nurse visit	3.00 (day 1 and 8 each cycle, 2 per 3 weeks)	2.00 (every two weeks)	2.00 (every two weeks)	0.33 (every third month)	0.08 (once per year)
Emergency room visit	0.04 (0.5 per year)	0.06 (0.7 per year)	0.06 (0.7 per year)	0.15 (0.15 per year)	0.00
Biliary stent or catheter replacement	0.25 (every 4 months)	0.25 (every 4 months)	0.25 (every 4 months)	0.17 (every 6 months)	0.00
CT scan	0.33 (every third month)	0.33 (every third month)	0.33 (every third month)	0.00 (every third month)	0.08 (once per year)
MRI	0.00	0.00	0.00	0.00	0.00
Liver function test	1.75 (1.5-2 times per month)	2.00 (every two weeks)	2.00 (every two weeks)	0.00	0.00
Renal function test	1.75 (1.5-2 times per month)	2.00 (every two weeks)	2.00 (every two weeks)	0.00	0.00
Complete blood count	4.00 (every week)	2.00 (every two weeks)	2.00 (every two weeks)	0.00	0.00
Biochemisty test	1.75 (1.5-2 times per month)	2.00 (every two weeks)	2.00 (every two weeks)	0.00	0.00

8.5.4 Adverse event costs

Grade 3–4 AEs that occurred in at least 5% in either treatment arm in the TOPAZ-1 trial were included in the model. Seven grade 3-4 AEs were eligible for inclusion. Adverse event costs were applied as a one-off total cost in the first cycle. This cost was calculated by multiplying the percentage of patients experiencing each AE by the cost per event (Table 46) and summing all the AEs per treatment arm.

Table 46: Health care utilization and costs for adverse event management

Adverse event	Cost per AE (DKK)	Source	Comment
Neutropenia	1 947	DRG-takster 2024	Assumed one outpatient visit: 07MA98: MDC09 1-dagsgruppe, pat. mindst 7 år
Anaemia	6 165	DRG-takster 2024	Medical visit + blood transfusion: 07MA98: MDC09 1-dagsgruppe, pat. mindst 7 år + 16PR02: Transfusion af blod, övrig
Thrombocytopenia	1 947	DRG-takster 2024	Assumed one outpatient visit: 07MA98: MDC09 1-dagsgruppe, pat. mindst 7 år
Cholangitis	43 630	DRG-takster 2024	Usually requires inpatient care: 07MA08: Ondartede sygdomme i lever, galdeveje og bugspytkirtel, pat. mindst 18 år

Adverse event	Cost per AE (DKK)	Source	Comment
Neutrophil count decrease	1 947	DRG-takster 2024	Assumed one outpatient visit: 07MA98: MDC09 1-dagsgruppe, pat. mindst 7 år
Platelet count decreased	1 947	DRG-takster 2024	Assumed one outpatient visit: 07MA98: MDC09 1-dagsgruppe, pat. mindst 7 år
White blood cell count decreased	1	DRG-takster 2024	Assumed one outpatient visit: 07MA98: MDC09 1-dagsgruppe, pat. mindst 7 år

Source: *DRG-takster 2024 (120)*

8.5.5 Subsequent treatment costs

Patients were assumed to become eligible for subsequent treatment upon first-line treatment discontinuation, based on the TOPAZ-1 TTD curves. This means that patients who receive the full 8 treatment cycles of GemCis in the GemCis arm may not receive active treatment for a period of time (because the corresponding TTD curve from the TOPAZ-1 trial corresponds to placebo). There is an option in the model to use the PFS curves rather than the TTD curves to estimate first-line treatment costs and model initiation of subsequent lines of treatment.

The cost of subsequent lines of treatment after first-line treatment discontinuation was incorporated in the economic evaluation. Subsequent treatments were accounted for in terms of drug acquisition and administration costs only, with costs applied per weekly model cycle. The model base case reflects the mix of subsequent treatments received by patients in the TOPAZ-1 trial, and the TOPAZ-1 OS data incorporate the effect of these subsequent treatments on survival. Costs were calculated based on the proportion of patients receiving subsequent therapies, the distribution of treatments used at each line and the mean time on treatment per line of treatment. There is no standard 2nd line therapy in advanced BTC. Following progression on GemCis, patients with good performance status may be considered for 5-FU/capecitabine or taxane-based treatment, and patients may go on to receive later line of treatments.

The subsequent treatment distribution used in the base-case analysis in the model was obtained from TOPAZ-1 data on file and the distributions assumed are shown in Table 47 and Table 48. The 2nd- and 3rd-line regimens were categorized into subgroups in order to determine distributions in the model. The subgroups consist of FOL combinations, platinum-based combinations (PBC), TS-ONE, Capecitabine + PBC and Immunotherapies. The cost and durations of these subgroups were based the assumptions and sources in Table 49. The model calculates a weighted average of the mean duration of 2L treatments and assumes that patients progress to 3L after this weighted average mean duration spent on 2L treatment and the 3-week wash-out period. The same approach is taken to determine discontinuation from 3L treatment.

Table 47: Subsequent active treatments in second line

	Durvalumab+ GemCis	GemCis
Proportion receiving 2nd line therapy	50.7%	53.8%
Fluorouracil combinations	47%	43%

		Durvalumab+ GemCis	GemCis
2nd line treatment distribution	Platinum based chemotherapies	28%	22%
	Teysuno	11%	13.5%
	Capecitabine + PBC	14%	15%
	Pemigatinib	0%	0%
	Immunotherapies	1%	7%
Duration of treatment	Fluorouracil combinations	1.9 months	1.9 months
	Platinum based chemotherapies	4.67 months	4.67 months
	Teysuno	2.5 months	2.5 months
	Capecitabine + PBC	4.67 months	4.67 months
	Pemigatinib	5.66 months	5.66 months
	Immunotherapies	3.72 months	3.72 months

Table 48: Subsequent active treatments in third line

		Durvalumab + GemCis	GemCis
Proportion receiving 3rd+ line + therapy among those who were treated in 2nd line		19.6%	24.4%
3rd+ line treatment distribution	Fluorouracil combinations	50%	38%
	Platinum based chemotherapies	22%	18%
	Taysuno	8%	15%
	Capecitabine + PBC	12%	19%
	Pemigatinib	0%	0%
	Immunotherapies	8%	11%
Duration of treatment	Fluorouracil combinations	1.9 months	1.9 months
	Platinum based chemotherapies	4.67 months	4.67 months
	Teysuno	2.5 months	2.5 months
	Capecitabine + PBC	4.67 months	4.67 months
	Pemigatinib	5.66 months	5.66 months
	Immunotherapies	1.77 months	1.77 months

Table 49: Sources for costs and duration of subsequent treatment in 2nd and 3rd+ line

	Cost	Duration
Fluorouracil combinations	Average of FOLFOX and FOLFIRI	Average sourced from ABC-06 (FOLFOX) and Caprica et al 2019 (FOLFORI) (116) (125)
Platinum based chemotherapies	Assumed to be same cost as GemCis	Conservatively, assumed to be the same as the mean duration of placebo treatment in the placebo + GemCis arm from TOPAZ-1 clinical trial (80)
TS-ONE	Cost of TS-ONE	Inoue et al 2021 (117)
Capecitabine + PBC	Cost of capecitabine + oxaliplatin	Assumed same as platinum chemotherapies
Immunotherapies	Average of nivolumab monotherapy and pembrolizumab monotherapy	For 2nd line, average of duration of pembrolizumab mono used in 2nd line in TOPAZ-1 trial and nivolumab median number of doses received over a 2 week cycle (3.22 months) from Kim et al 2020 (126) For 3rd+ line, average duration of nivolumab mono and pembrolizumab mono used in 3rd+ line in TOPAZ-1 trial

The model accounts for a treatment-free period between the end of the prior line of treatment and initiation of subsequent treatment. In the ABC-06 trial, which evaluated FOLFOX as a second-line treatment, a maximum of 6 weeks was allowed between disease progression on first-line treatment and the initiation of second-line chemotherapy. In the base case a conservative approach was applied and it is assumed that there is a 3-week treatment free period between first and second line treatment, and second and third line treatment (116). During these treatment-free periods, disease management costs for with patients who are not on treatment are incurred.

8.5.6 Patient time and transport cost

The assumption is that each oncologist visit and nurse visit will have a 30 minute duration and that an emergency room visit and biliary stent or catheter replacement will take around one hour. It is also assumed that these types of visits require transport back and forth to the hospital. It is assumed that diagnostics and tests (CT scan, liver, renal, blood and biochemistry tests) are performed in conjunction with other visits and do not lead to additional time and travel costs. At least with regard to CT scans this might potentially be an underestimate as a CT scan could be scheduled separately and take approximately 30 minutes. The chemotherapy administration was assumed to occur on the same days as medical visits based on input from the medical expert. Hence, only the time cost of the infusions were included based on Table 42, but not separate transport cost. The unit costs for patient time and transport costs were obtained from Værdisætning af enhedsomkostninger (Medicinrådet)

8.5.7 End of life costs

A one-off cost of DKK 77 651 is applied at the transition to the death health state to represent the cost of palliative care. This cost was obtained by using the end of life cost from the DMC assessment of Tucatinib and Kadcyla, but has been adjusted to the current price level (CPI Dec 2023). No other costs are associated with the death health state.

8.6 Results

Key takeaways:

- *The base-case ICER for durvalumab + GemCis compared with GemCis was estimated to be DKK 1 072 206 per QALY gained*
- *The incremental cost and incremental QALYs were DKK 855 468 and 0.80 respectively*
- *The analysis suggests that the first-line use of durvalumab + GemCis for treating locally advanced or metastatic biliary tract cancer is associated with longer survival and potentially substantial QALY gains, in a disease area where no advances have been seen in the last 10 years.*

8.6.1 Base case overview

The key assumptions for the base case analysis are presented in section 8.1.2, Table 24.

8.6.2 Base case results

An ICER of DKK 1 072 206 per QALY gained is estimated for durvalumab + GemCis versus GemCis. The incremental cost and incremental QALYs are DKK 855 468 and 0.80 respectively (Table 50).

Table 50: Base-case results

Results	Total Costs	Total QALYs	Total LYs
Durvalumab + GemCis	1 186 583 DKK	1.84	2.33
GemCis	331 115 DKK	1.04	1.29
Incremental results	855 468 DKK	0.80	1.04
ICER per QALY and per LY		*1 072 206 DKK*	*822 240 DKK*

Breakdown of costs and QALYs by health state are shown in Table 51 and Table 52.

Table 51: Cost breakdown by health state

Costs	Pre-progression	Post-progression	Total
Durvalumab + GemCis	1 012 458 DKK	174 125 DKK	1 186 583 DKK
GemCis	159 084 DKK	172 030 DKK	331 115 DKK

Table 52: QALY breakdown by health state

QALYs	Pre-progression	Post-progression	AE disutility	Total
Durvalumab + GemCis	0.692	1.146	-0.002	1.836
GemCis	0.480	0.560	-0.002	1.038

Breakdown by cost category is shown in Table 53.

Table 53: Breakdown by cost category

Cost category	Durvalumab + GemCis	GemCis	Difference
Drug acquisition: 1st line	764 845 DKK	6 899 DKK	757 945 DKK
Drug acquisition: subsequent therapies	10 873 DKK	20 679 DKK	-9 806 DKK
Drug administration: 1st line	40 942 DKK	26 194 DKK	14 748 DKK

Cost category	Durvalumab + GemCis	GemCis	Difference
Drug administration: subsequent therapies	11 084 DKK	11 985 DKK	-901 DKK
Disease management	235 704 DKK	164 953 DKK	70 751 DKK
AEs	5 465 DKK	4 076 DKK	1 389 DKK
Terminal care	72 449 DKK	75 534 DKK	-3 085 DKK
Patient time and transportation costs	45 221 DKK	20 795 DKK	24 426 DKK
Total	**1 186 583 DKK**	**331 115 DKK**	**855 468 DKK**

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

A DSA was conducted, assuming a standard error of 10% of the mean value when no standard error is available. Table 54 presents the twenty parameters leading to the greatest variation of ICER.

Table 54: DSA parameters with the most influence on the ICER

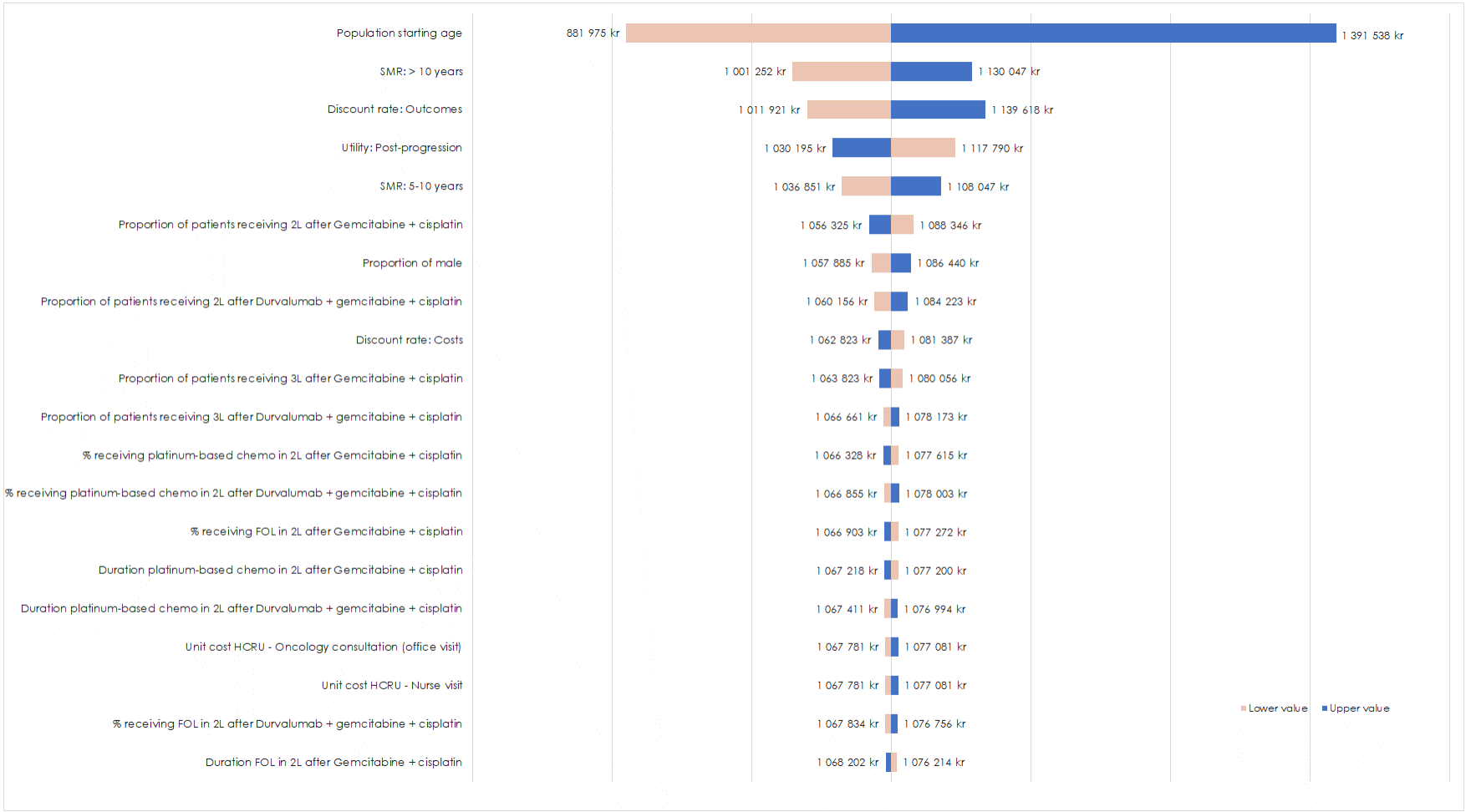
Parameters	Base case value	Lower bound value	Upper bound value	ICER with lower bound	ICER with upper bound
Population starting age	62.40	56.16	68.64	750 177 kr	1 197 153 kr
SMR: > 10 years	1.44	0.80	2.08	1 001 252 kr	1 130 047 kr
Discount rate: Outcomes	3.5%	2.8%	4.2%	1 011 921 kr	1 139 618 kr
Utility: Post-progression	0.76	0.71	0.80	1 117 790 kr	1 030 195 kr
SMR: 5-10 years	4.65	3.86	5.44	1 036 851 kr	1 108 047 kr
Proportion of patients receiving 2L after Gemcitabine + cisplatin	0.54	0.43	0.64	1 088 346 kr	1 056 325 kr
Proportion of male	0.50	0.41	0.60	1 057 885 kr	1 086 440 kr
Proportion of patients receiving 2L after Durvalumab + gemcitabine + cisplatin	0.51	0.41	0.61	1 060 156 kr	1 084 223 kr

Parameters	Base case value	Lower bound value	Upper bound value	ICER with lower bound	ICER with upper bound
Discount rate: Costs	3.5%	2.8%	4.2%	1 081 387 kr	1 062 823 kr
Proportion of patients receiving 3L after Gemcitabine + cisplatin	0.24	0.20	0.29	1 080 056 kr	1 063 823 kr
Proportion of patients receiving 3L after Durvalumab + gemcitabine + cisplatin	0.20	0.16	0.24	1 066 661 kr	1 078 173 kr
% receiving platinum-based chemo in 2L after Gemcitabine + cisplatin	0.22	0.18	0.26	1 077 615 kr	1 066 328 kr
% receiving platinum-based chemo in 2L after Durvalumab + gemcitabine + cisplatin	0.28	0.23	0.34	1 066 855 kr	1 078 003 kr
% receiving FOL in 2L after Gemcitabine + cisplatin	0.43	0.35	0.51	1 077 272 kr	1 066 903 kr
Duration platinum-based chemo in 2L after Gemcitabine + cisplatin	4.67	3.75	5.59	1 077 200 kr	1 067 218 kr
Duration platinum-based chemo in 2L after Durvalumab + gemcitabine + cisplatin	4.67	3.75	5.59	1 067 411 kr	1 076 994 kr
Unit cost HCRU - Oncology consultation (office visit)	1947.00	1584.16	2346.70	1 067 781 kr	1 077 081 kr
Unit cost HCRU - Nurse visit	1947.00	1584.16	2346.70	1 067 781 kr	1 077 081 kr
% receiving FOL in 2L after Durvalumab + gemcitabine + cisplatin	0.47	0.38	0.56	1 067 834 kr	1 076 756 kr
Duration FOL in 2L after Gemcitabine + cisplatin	1.90	1.53	2.27	1 076 214 kr	1 068 202 kr

The tornado diagram of DSA for durvalumab + GemCis versus GemCis alone is available in Figure 36.

The tornado diagram presents the twenty parameters which had the largest effect on the ICER. The parameters associated with the greatest impact on results were the starting age, the SMRs for OS between 5-10 years and beyond 10 years, the discount rate for outcomes (discounted QALYs), the post-progression utility, and the proportion of patients receiving 2L treatment after GemCis. For all other parameters, the ICER increased or decreased with 2% or less when the input parameters were increased or decreased with 10%.

Figure 36: Tornado diagram



8.7.2 Scenario analysis

A series of further scenario and one-way sensitivity analyses were conducted to assess the impact of using alternative parameter estimates. The variables tested in scenario analyses are summarized in Table 55.

Table 55: Results of scenario analyses (discounted)

Scenario	Incremental cost	Incremental QALYs	ICER (DKK/QALY)
Base case	**855 468 DKK**	**0.80**	**1 072 206 DKK**
Time horizon			
Time horizon 10 years	825 460 DKK	0.47	1 741 683 DKK
Time horizon 20 years	848 105 DKK	0.72	1 172 979 DKK
PFS			
Spline Odds (3 knots) in both arms	855 468 DKK	0.80	1 071 863 DKK
Spline Normal (3 knots) in both arms	855 468 DKK	0.79	1 076 782 DKK
Gamma in both arms	855 468 DKK	0.78	1 090 095 DKK
TTD			
Treatment duration limited to 2 years	735 358 DKK	0.80	922 400 DKK
Gamma in both arms	706 585 DKK	0.80	885 603 DKK
Spline Hazard (3 knots) in both arms	949 692 DKK	0.80	1 190 302 DKK
PFS as basis for first-line treatment costs	749 289 DKK	0.80	939 126 DKK
OS			
Gamma in both arms (see section 8.3.1.1) + long-term OS adjustment in the durvalumab + GemCis arm beyond 43 months	839 486 DKK	0.72	1 152 398 DKK
Spline hazard (3 knots) in both arms (see section 8.3.1.1) + long-term OS adjustment in the durvalumab + GemCis arm beyond 43 months	859 324 DKK	0.90	958 526 DKK
Long-term OS adjustment in both arms (see section 8.3.1.2). Switch at 43 months in both arms	848 027 DKK	0.60	1 404 275 DKK
Long-term OS adjustment in both arms (see section 8.3.1.2). Switch at 43 months in the durvalumab + chemotherapy arm and at 60 months in the chemotherapy arm	851 410 DKK	0.69	1 233 525 DKK
Long-term OS adjustment in only the durvalumab + GemCis arm beyond 48 months	853 249 DKK	0.74	1 149 852 DKK

Scenario	Incremental cost	Incremental QALYs	ICER (DKK/QALY)
No long-term adjustment in any arm (pure parametric OS extrapolations)	840 019 DKK	0.40	2 123 515 DKK
Utility approach			
No age adjustment for utilities	855 468 DKK	0.81	1 049 657 DKK
Age-based decrement for utilities	855 468 DKK	0.80	1 074 082 DKK
Costs			
Exclusion of end-of-life care costs	858 553 DKK	0.80	1 076 073 DKK
Cost of AEs excluded	854 079 DKK	0.80	1 070 465 DKK
Exclude wastage costs	835 158 DKK	0.80	1 046 750 DKK
Subsequent treatment costs excluded	871 718 DKK	0.80	1 092 574 DKK

In the scenario analyses, the incremental cost-effectiveness ratios ranged from 885 603 DKK to 2 123 515 DKK. The results were most sensitive to a scenario assuming standard parametric extrapolations in both arms with no plateauing (the ICER increased to 2 123 515 DKK) and assuming a shorter time horizon for the extrapolation (the ICER increased to 1 741 683 DKK with 10-year time horizon). The ICER was also sensitive to different TTD distributions (down to 885 603 DKK with parametric gamma in both arms), but not very sensitive to utility assumptions or exclusion of certain cost types. A lower ICER was obtained when the treatment duration was limited to 2 years (922 400 DKK). This is a plausible scenario, as a Nordic clinical expert we have been in touch with mentioned that it was unlikely that patients would be treated with an immune checkpoint inhibitor therapy for more than 2 years in clinical practice.

8.7.3 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis was conducted to account for the joint uncertainty associated to parameter estimates. Probability distributions and parameter values in the PSA are available in Appendix J. We have as far as possible used study data to inform the SE estimates in the PSA. For efficacy parameters, SMRs or the utilities, the standard errors were estimated based on study data. For AE disutilities, resource use, landmark rates or duration of subsequent therapy, the SE was estimated based on the assumption that the SE was 10% of the parameter value. These groups of parameters have minimal impact on the model outcomes. We consider that 10% variation for these parameters gives quite realistic estimates for informing the PSA. Regarding the subsequent treatment durations, for example, many of the treatments used have fixed treatment durations (e.g. chemotherapies used for 6 cycles) so not large variations are expected. In addition, the patient monitoring approach is not expected to vary substantially, since it is already adjusted by health state. Usually, patient monitoring is dependent on the patient status (progression free or progressed), and it is expected to be quite standard over time. For the efficacy parameters, covariance matrices were used for modelling the correlation between the parameters. A technique known as Cholesky decomposition was used in order to provide correlated draws from a multivariate normal distribution. For other parameters, such as resource use or utilities, we assumed independent probability distributions. Probabilistic results are shown in Table 56. Durvalumab + GemCis has an ICER of DKK 1 052 803 per QALY gained versus GemCis. This is fairly similar to the deterministic base case ICER, which

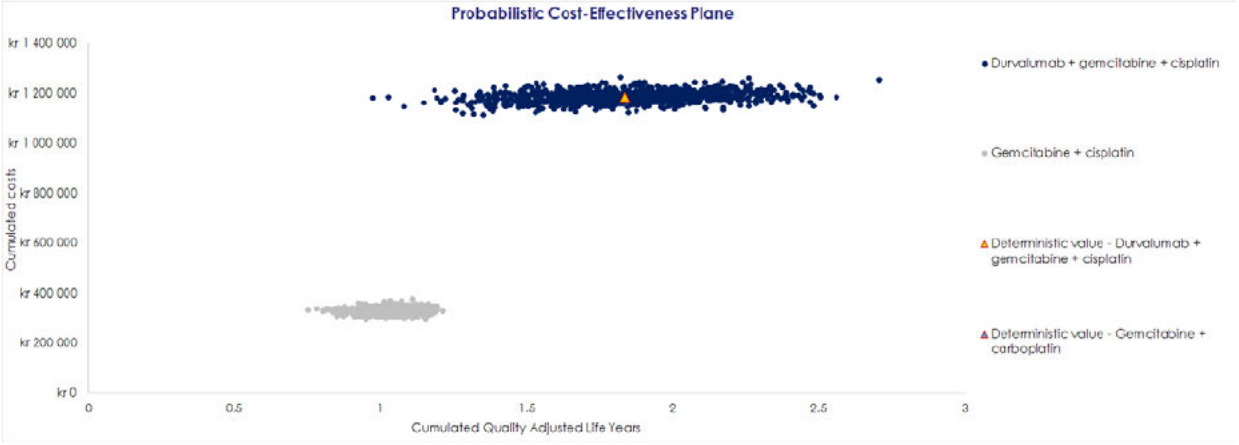
was DKK 1 072 206 per QALY gained. Durvalumab + GemCis is associated with greater QALYs at additional cost (incremental QALYs and costs of 0.81 and DKK 856 373 respectively).

Table 56: Probabilistic results

Treatment	Total costs	Total QALYs	Incremental cost	Incremental QALYs	Fully incremental ICER
GemCis	331 559 DKK	1.04	-	-	-
Durvalumab + GemCis	1 187 931 DKK	1.85	856 373 DKK	0.81	1 052 803 DKK

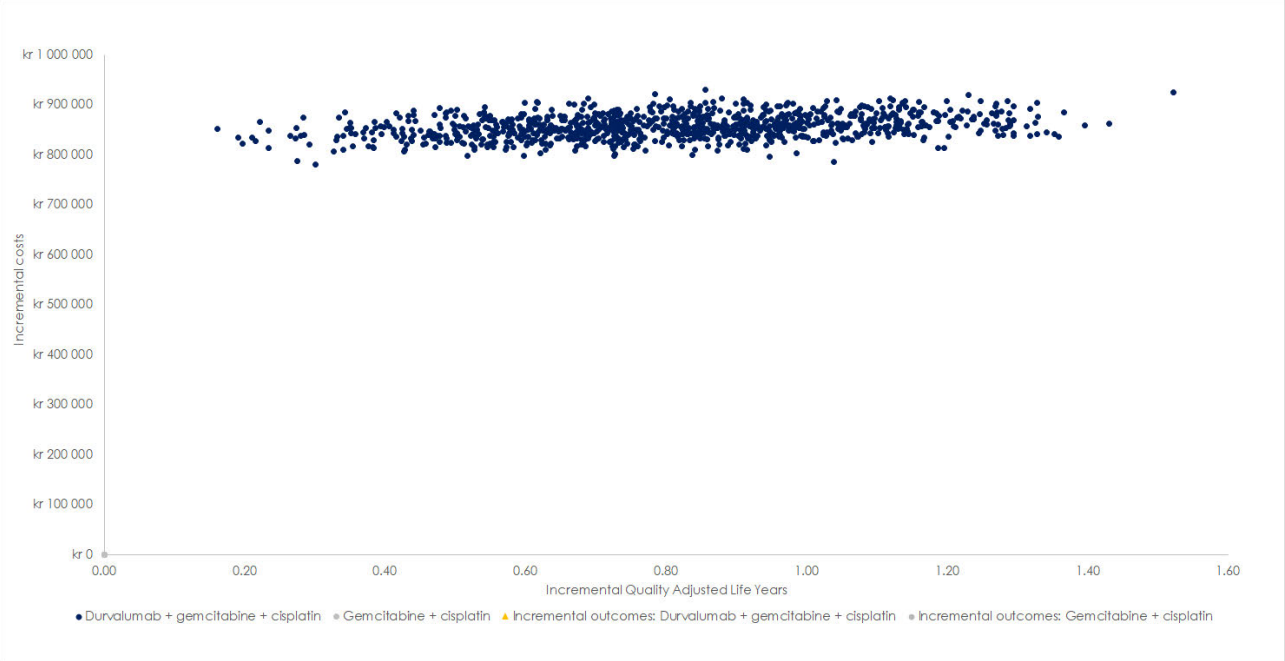
The incremental cost-effectiveness scatter plot for 1,000 iterations of the PSA is shown in Figure 37. Each iteration is presented in terms of incremental costs and QALYs between durvalumab in combination with gemcitabine and cisplatin and gemcitabine and cisplatin.

Figure 37: Incremental results - probabilistic results



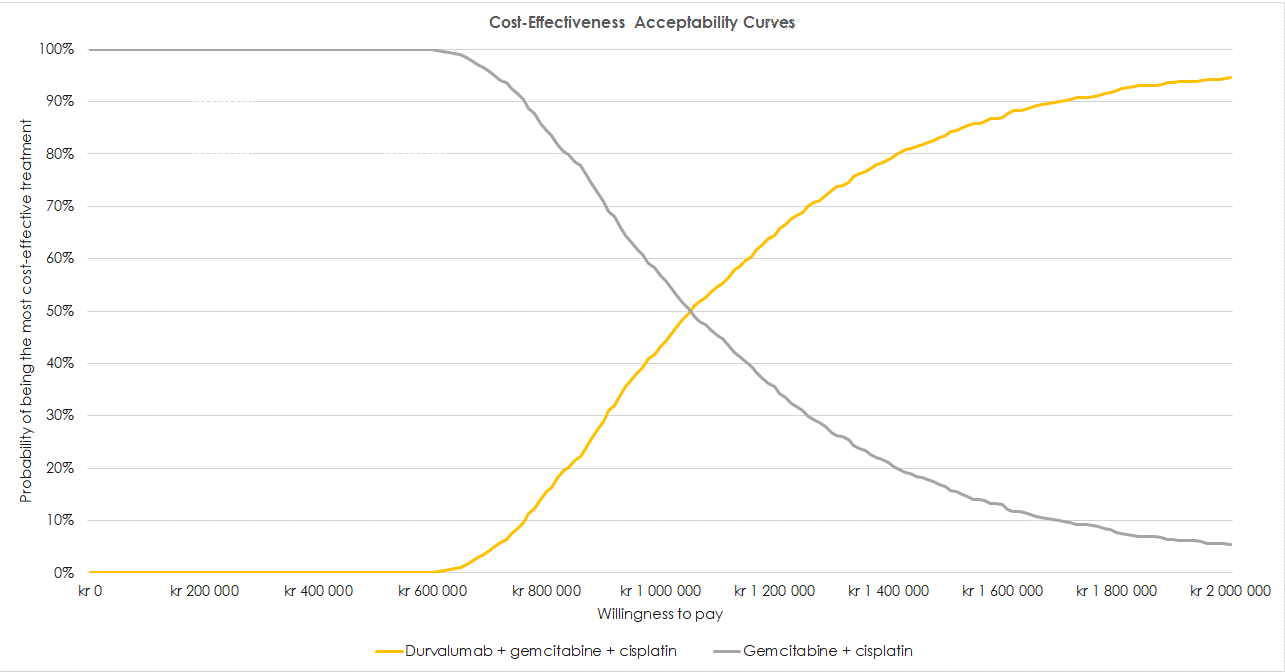
The PSA results for durvalumab + GemCis and GemCis are presented in Figure 38.

Figure 38: Probabilistic incremental cost-effectiveness plane for durvalumab + GemCis versus GemCis



The CEAC describes for each strategy the probability of being cost-effective across a range of willingness to pay (WTP) thresholds (Figure 39). Durvalumab + GemCis (with list prices) is more likely to be a cost-effective option beyond a WTP of around DKK 1 050 000 – 1 070 000 per QALY gained.

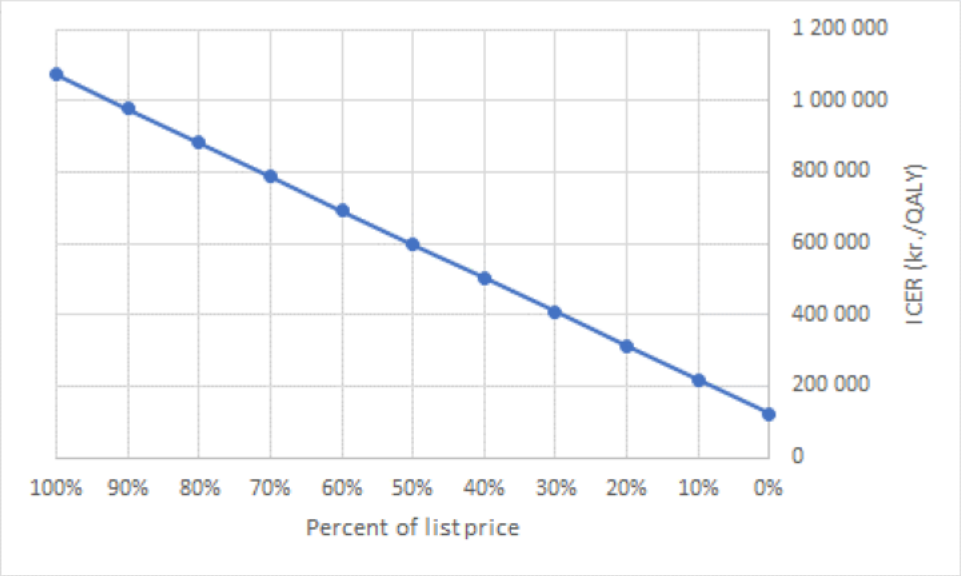
Figure 39: Cost-effectiveness acceptability curves



8.7.4 Price-ICER diagram

The price-ICER diagram in shown in Figure 40. The fact that the ICER is not zero at zero price is because the treatment is also associated with increased costs for administration of pharmaceuticals and disease management. The latter is primarily due to patients being expected to live longer with their disease with durvalumab + GemCis, which also leads to increased costs for disease management and follow-up.

Figure 40: Cost per QALY at different price levels (as percent of list price)



9. Budget impact analysis

The budget impact calculations build on the cost component of the cost per QALY analysis described in previous section in combination with the epidemiology and patient number estimates in section 5.1.1.1.

9.1 Number of patients

As indicated by the expected patient numbers in section 5.1.1.1, we are expecting a gradual market uptake going from 50% in year 1 to 100% in year 4 and 5.

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

	Year 1	Year 2	Year 3	Year 4	Year 5
Durvalumab + GemCis	50	60	80	101	101
GemCis	50	40	20	0	0
Total number of patients	100	100	100	101	101

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

	Year 1	Year 2	Year 3	Year 4	Year 5
Durvalumab + GemCis	0	0	0	0	0
GemCis	100	100	100	101	101
Total number of patients	100	100	100	101	101

9.2 Expenditure per patient

The cost per patient for durvalumab + GemCis is shown in Table 59 and the cost per patient for GemCis is shown in Table 60. The cost per patient tables show how the costs develop over time and by cost category. For durvalumab + GemCis, for example, the majority of the cost will be in year one (66%). The same is true for the comparator GemCis, but with an even higher proportion of the total cost in the first year (72%). The pattern is different regarding the first-line pharmaceutical costs, where the durvalumab + GemCis acquisition costs represent 64% of the total accumulated costs, while the GemCis pharmaceutical acquisition costs only represents 2% of the total costs.

The difference in the cost per patient is shown in Table 61. However, as indicted by the number of patients in Table 57 above, it is expected that it will take a few years before all eligible patients have switched to PD-L1 durvalumab + GemCis.

Table 59: Cost per patient (DKK) – Intervention: Durvalumab + GemCis

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6+	Total costs
Drug acquisition first-line	541 159	114 182	39 283	20 498	12 426	37 296	764 845
Drug acquisition subsequent lines	4 635	4 557	1 070	310	126	175	10 873
Drug administration first-line	32 822	4 145	1 426	744	451	1 354	40 942
Drug administration subsequent lines	5 221	4 292	984	294	121	173	11 084
Disease management first-line	115 826	28 836	10 874	5 652	3 419	1 378	165 985
Disease management subsequent lines	18 017	17 861	7 228	3 979	3 184	19 451	69 719
Adverse events	5 465	0	0	0	0	0	5 465
Patient time and transportation first-line	23 362	5 813	2 184	1 133	684	2 045	35 221
Patient time and transportation subsequent lines	2 203	2 281	909	493	391	3 722	10 000
Terminal care	36 716	20 120	7 701	2 956	758	4 198	72 449
All costs	785 426	202 088	71 659	36 058	21 560	69 792	1 186 583

Table 60: Cost per patient (DKK) – Comparator: GemCis

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6+	Total costs
Drug acquisition first-line	6 899	0	0	0	0	0	6 899
Drug acquisition subsequent lines	10 670	9 072	856	68	9	4	20 679
Drug administration first-line	26 194	0	0	0	0	0	26 194
Drug administration subsequent lines	6 461	5 026	454	36	5	2	11 985
Disease management first-line	102 184	5 581	488	108	35	4	108 400
Disease management subsequent lines	24 295	21 705	5 107	2 133	1 215	2 098	56 553
Adverse events	4 076	0	0	0	0	0	4 076
Patient time and transportation first-line	13 515	0	0	0	0	0	13 515
Patient time and transportation subsequent lines	2 986	2 837	649	262	149	397	7 280
Terminal care	42 476	21 943	6 095	2 300	1 066	1 654	75 534
All costs	239 757	66 164	13 649	4 907	2 480	4 159	331 115

Table 61: Cost difference (DKK) - Durvalumab + GemCis vs. GemCis

Cost category	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6+	Total costs
Drug acquisition first-line	534 259	114 182	39 283	20 498	12 426	37 296	757 945
Drug acquisition subsequent lines	-6 035	-4 514	213	243	116	171	-9 806
Drug administration first-line	6 629	4 145	1 426	744	451	1 354	14 748
Drug administration subsequent lines	-1 240	-734	529	257	116	170	-901
Disease management first-line	13 642	23 255	10 387	5 544	3 383	1 374	57 585
Disease management subsequent lines	-6 279	-3 844	2 121	1 847	1 969	17 353	13 166
Adverse events	1 389	0	0	0	0	0	1 389
Patient time and transportation first-line	9 847	5 813	2 184	1 133	684	2 045	21 706
Patient time and transportation subsequent lines	-783	-556	260	230	243	3 325	2 720
Terminal care	-5 760	-1 823	1 606	655	-308	2 544	-3 085
All costs	545 670	135 924	58 010	31 151	19 081	65 633	855 468

9.3 Budget impact

The budget scenarios with and without durvalumab + GemCis recommended are shown in Table 62 and Table 63. The budget impact (Table 64) is obtained by combining the patient numbers with the cost per patient estimates. The budget impact estimations are also taking costs overlapping over several years into account (i.e., patients starting the treatment in year one will, on average, be associated with some costs also in subsequent years).

The budget impact is summarized in Table 65. The budget impact increases from MDKK 27.6 in year 1 (2024) to MDKK 78.0 in year 5 (2028). The main driver is the difference in first-line pharmaceutical costs.

Table 62: Budget scenario with durvalumab + GemCis recommended (DKK)

Cost category	2024	2025	2026	2027	2028
Drug acquisition first-line	27 361 747	38 661 033	52 773 891	67 594 595	71 933 744
Drug acquisition subsequent lines	764 076	1 409 134	1 348 136	1 159 868	1 084 127
Drug administration first-line	2 946 362	3 234 064	3 495 059	3 780 357	3 941 498
Drug administration subsequent lines	583 199	1 053 272	1 100 569	1 087 341	1 096 559
Disease management first-line	10 884 142	12 826 632	13 984 138	15 210 258	16 219 005
Disease management subsequent lines	2 112 412	4 097 601	4 602 671	4 770 196	5 021 459
Adverse events	476 351	491 565	520 807	550 205	551 714
Terminal care	1 841 096	2 244 768	2 625 603	3 037 866	3 265 947
All costs	46 969 385	64 018 069	80 450 875	97 190 686	103 114 053

Table 63: Budget scenario with durvalumab + GemCis NOT recommended (DKK)

Cost category	2024	2025	2026	2027	2028
Drug acquisition first-line	688 912	690 801	692 695	694 594	696 499
Drug acquisition subsequent lines	1 065 354	2 004 569	2 101 671	2 114 933	2 121 802
Drug administration first-line	2 615 425	2 622 595	2 629 786	2 636 996	2 644 226
Drug administration subsequent lines	645 125	1 165 596	1 217 373	1 224 725	1 228 671
Disease management first-line	10 203 084	10 806 536	10 888 310	10 930 119	10 964 151
Disease management subsequent lines	2 425 870	4 673 025	5 232 064	5 482 505	5 636 771
Adverse events	406 997	408 113	409 232	410 354	411 479
Terminal care	1 349 464	1 353 164	1 356 874	1 360 594	1 364 325
All costs	19 400 231	23 724 399	24 528 004	24 854 821	25 067 923

Table 64: Budget impact of introducing durvalumab + GemCis (DKK)

Cost category	2024	2025	2026	2027	2028
Drug acquisition first-line	26 672 834	37 970 232	52 081 196	66 900 001	71 237 245
Drug acquisition subsequent lines	-301 278	-595 435	-753 535	-955 066	-1 037 675
Drug administration first-line	330 938	611 468	865 274	1 143 361	1 297 272
Drug administration subsequent lines	-61 926	-112 324	-116 803	-137 385	-132 112
Disease management first-line	681 058	2 020 096	3 095 828	4 280 139	5 254 854

Cost category	2024	2025	2026	2027	2028
Disease management subsequent lines	-313 458	-575 424	-629 393	-712 309	-615 312
Adverse events	69 354	83 453	111 575	139 852	140 235
Terminal care	491 632	891 604	1 268 728	1 677 272	1 901 622
All costs	27 569 154	40 293 670	55 922 871	72 335 865	78 046 130

Table 65: Summary of the budget impact of introducing durvalumab + GemCis (DKK)

Scenarios	2024	2025	2026	2027	2028
Scenario with durvalumab + GemCis	46 969 385	64 018 069	80 450 875	97 190 686	103 114 053
Scenario without durvalumab + GemCis	19 400 231	23 724 399	24 528 004	24 854 821	25 067 923
Budget impact	27 569 154	40 293 670	55 922 871	72 335 865	78 046 130

Except for uncertainties explored already for the cost analysis, there is some uncertainty regarding the market uptake for the budget impact analysis. We have assumed a gradual uptake, starting at 50% in year 1 and reaching 100 after 4 years. If the market uptake is quicker, it could lead to increased budget impact in the early years. However, it might not be realistic that 100% of the eligible patients would be treated with durvalumab + GemCis even after 4 to 5 years. A more realistic estimate could be 90-95% and hence the 5 year budget impact could be slightly lower than indicated here.

10. Discussion on the submitted documentation

10.1 The TOPAZ-1 trial and its relevance

TOPAZ-1 is a randomised, double-blind, placebo-controlled, phase III trial investigating the efficacy and safety of durvalumab plus GemCis in comparison to placebo plus GemCis, for up to eight cycles, followed by durvalumab or placebo monotherapy until disease progression or unacceptable toxicity, in patients with advanced BTC.

A main strength of the clinical documentation is that the trial included the most relevant comparator as GemCis is the current standard of care for these patients in Denmark. OS was also the primary endpoint in the TOPAZ-1 trial and is the most relevant endpoint (together with HRQoL) as a major building block for the QALY analysis.

When analysing OS data from the TOPAZ-1 trial it is important to evaluate the full KM data and landmark analyses. TOPAZ-1 met its primary endpoint for the ITT population, a statistically significant improvement for overall survival (OS) in favour of the durvalumab arm. The median OS gain was modest, increasing mOS with 1.3 months. The full benefit of durvalumab add-on therapy was however seen at later landmark analyses. The Kaplan-Meier (KM) plot for OS separated at approximately six months of treatment, after which there was a clear and sustained separation of the survival curves in favour of the durvalumab + GemCis arm. Twice as many patients in the durvalumab + GemCis arm compared to placebo + GemCis arm were alive (23.9% vs. 11.5%) after 24 months. In the latest data cut-off (Oct 23, 2023), landmark OS rates were 22.9% vs. 13.1% at 24 months and 14.6% vs. 6.9% at 36 months for durvalumab + GemCis vs. GemCis (Oh et al. 2024 (66)).

10.2 Long-term survival modelling

A long-term survival plateau for the immunotherapy arm have been observed across several cancer types. Hence, standard parametric models carry the risk of underestimating the long-term survival for immunotherapy. To model the long-term OS for durvalumab in combination with GemCis data from a systematic review investigating long-term survival in a fairly large sample of major IO trials with long-term data was used. In the latest data-cut off from TOPAZ-1, the follow-up time did not yet fully capture the time period when the tail is expected to develop. The assumption in the base case therefore is that in the absence of mature clinical trial data, the most likely prediction is that the OS tail will develop in the same way (in terms of relative mortality) as the average of the IO arms in the trials included in the systematic review. In the base case, standard parametric modelling was used throughout for the control arm (GemCis).

10.3 Results and uncertainties

The economic evaluation suggests that the first-line use of durvalumab + GemCis for treating locally advanced or metastatic biliary tract cancer is associated with longer survival and potentially substantial QALY gains. A QALY gain of 0.80 and an incremental cost of DKK 855 468 were estimated over a lifetime horizon. In the base case analysis, the deterministic ICER of durvalumab + GemCis versus GemCis for the management of first-line BTC was DKK 1 072 206 per QALY gained. The QALY gain is especially due to an increase in time spent in the post-progression states vs. GemCis alone. With the delayed efficacy of IO therapy, a proportional correlation between PFS and OS improvement is not established. In particular, a larger proportion of long-term survivors was expected to contribute to the long-term QALY gain for durvalumab + GemCis. Scenario analyses indicate that the main inputs that influence the ICER are selection of OS extrapolation methods (including time point for the long-term OS adjustment) and the time horizon.

The main uncertainty of the analysis is in the long-term extrapolations, where we used data from a number of previous IO trials to inform the development of the plateau in overall survival over time. The underlying assumption is that this type of modelling has the potential to better predict the development of the immunotherapy arm than standard parametric modelling, as there is a growing body of evidence indicating that traditional model based on immature data are less suited for long-term IO extrapolations than novel approaches.

10.4 Concluding remarks

BTC is an aggressive disease with short survival. Patients seek medical care overdue due to late developing symptoms, delaying the diagnosis and resulting in up to 80% of BTC patients being diagnosed at an advanced stage of disease. At this stage patients have often developed symptoms such as jaundice, excessively dark urine and pale stools, weight loss and abdominal pain, nausea, and fever. The 5-year survival rate remains dismal, especially for patients with distant metastasis being only ~2% with current treatment. Thus, there is a substantial unmet need for effective treatments with the opportunity for long-term responses that are available early in the metastatic setting.

No advances have been seen in the last 10 years for BTC patients and durvalumab would fill a significant unmet need for this patient group. In a therapeutic area with only few treatment options and relatively small long-term benefits for patients, the results from TOPAZ-1 shows that durvalumab, if recommended in Denmark for BTC, has the potential to significantly improve outcomes for patients that today have a very poor prognosis.

11. List of experts

[redacted]

12. References

1. Ghidini M, Pizzo C, Botticelli A, Hahne JC, Passalacqua R, Tomasello G, et al. Biliary tract cancer: current challenges and future prospects. Cancer Manag Res. 2019;11:379-88.
2. Okusaka T, Nakachi K, Fukutomi A, Mizuno N, Ohkawa S, Funakoshi A, et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: a comparative multicentre study in Japan. Br J Cancer. 2010;103(4):469-74.
3. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273-81.
4. ClinicalTrials.gov. Durvalumab or Placebo in Combination With Gemcitabine/Cisplatin in Patients With 1st Line Advanced Biliary Tract Cancer (TOPAZ-1) (NCT03875235). Available at: https://clinicaltrials.gov/ct2/show/NCT03875235. Last updated: July 2022.

Accessed: June 2022 2019 [
5. EMA. Imfinzi Summary of Product Characteristics. 2023.
6. Al-Salama ZT. Durvalumab: A Review in Extensive-Stage SCLC. Target Oncol. 2021;16(6):857-64.
7. Oh D-Y, He AR, Qin S, Chen L-T, Okusaka T, Vogel A, et al. A phase 3 randomized, double-blind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin (GemCis) in patients (pts) with advanced biliary tract cancer (BTC): TOPAZ-1. Journal of Clinical Oncology. 2022;40(4_suppl):378-.
8. Oh D-Y, Ruth He A, Qin S, Chen L-T, Okusaka T, Vogel A, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evidence. 2022:EVIDoa2200015.
9. Oh D, He, AR., Qin, S., Chen, L., et al. 56P - Updated overall survival from the Phase 3 TOPAZ-1 study of durvalumab or placebo plus gemcitabine and cisplatin in patients with advanced biliary tract cancer. ESMO Annual Congress 2022. 2022.
10. AstraZeneca Data on File. TOPAZ-1 Clinical Study Report. 2022.
11. Authority TDHD. Nye kræfttilfælde i Danmark 2021. 2023 27-01-2023.
12. RKKP. Dansk lever-galdevejscancer Database - Årsrapport 1. januar 2021 til 31. december 2021. https://www.rkkp.dk/kvalitetsdatabaser/databaser/dansk_lever_og_galdevejscancer/om-databasen/; 2022.
13. (IARC) IAfRoC. NORDCAN Association of the Nordic Cancer Registries 1965-2023 [Available from: https://nordcan.iarc.fr/en.
14. Dansk Lever-galdevejs Cancer Gruppe D. Nationale kliniske retningslinjer for udredning og behandling af Cholangiocarcinom. 2020 [updated October 27th 2020. 1.0:[Available from: https://dlgcg.dk/wp-content/uploads/2021/11/dlgcg_cc_admgodk271020.pdf.
15. Bridgewater JA, Goodman KA, Kalyan A, Mulcahy MF. Biliary tract cancer: epidemiology, radiotherapy, and molecular profiling. American Society of Clinical Oncology Educational Book. 2016;36:e194-e203.
16. Valle JW, Lamarca A, Goyal L, Barriuso J, Zhu AX. New Horizons for Precision Medicine in Biliary Tract Cancers. Cancer Discov. 2017;7(9):943-62.
17. ESMO. Biliary tract cancer: a guide for patients. Available at: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3181994. Accessed: June 2022 2019 [
18. Valle JW, Borbath I, Khan SA, Huguet F, Gruenberger T, Arnold D. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v28-v37.
19. Baria K, De Toni EN, Yu B, Jiang Z, Kabadi SM, Malvezzi M. World-Wide Incidence and Mortality of Biliary Tract Cancer. Gastro Hep Advances. 2022.
20. Charbel H, Al-Kawas FH. Cholangiocarcinoma: epidemiology, risk factors, pathogenesis, and diagnosis. Curr Gastroenterol Rep. 2011;13(2):182-7.
21. Ciardiello D, Maiorano BA, Parente P, Rodriquenz MG, Latiano TP, Chiarazzo C, et al. Immunotherapy for Biliary Tract Cancer in the Era of Precision Medicine: Current Knowledge and Future Perspectives. International Journal of Molecular Sciences. 2022;23(2):820.

22. American Cancer Society. Key Statistics for Bile Duct Cancer. Available at: https://www.cancer.org/cancer/bile-duct-cancer/about/key-statistics.html#:~:text=Bile%20duct%20cancer%20can%20occur,extrahepatic%20bile%20ducts%20it's%2072. [Last accessed: August 2022]. 2022.
23. American Society of Clinical Oncology (ASCO). Bile Duct Cancer (Cholangiocarcinoma): Statistics. Available at: https://www.cancer.net/cancer-types/bile-duct-cancer-cholangiocarcinoma/statistics#:~:text=For%20extrahepatic%20bile%20duct%20cancer,this%20part%20of%20the%20world. [Last accessed: August 2022]. 2022.
24. Marcano-Bonilla L, Mohamed EA, Mounajjed T, Roberts LR. Biliary tract cancers: epidemiology, molecular pathogenesis and genetic risk associations. Chin Clin Oncol. 2016;5(5):61.
25. ESMO. Billiary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up,. Annals of Oncology2022.
26. British Liver Trust. Bile duct cancer. Available at: https://britishlivertrust.org.uk/information-and-support/living-with-a-liver-condition/liver-conditions/bile-duct-cancer/#symptoms. Accessed: June 2022 2022 [
27. Hunter LA, Soares HP. Quality of Life and Symptom Management in Advanced Biliary Tract Cancers. Cancers (Basel). 2021;13(20):5074.
28. Lamarca A, Hubner RA, David Ryder W, Valle JW. Second-line chemotherapy in advanced biliary cancer: a systematic review. Ann Oncol. 2014;25(12):2328-38.
29. Shroff RT, Kennedy EB, Bachini M, Bekaii-Saab T, Crane C, Edeline J, et al. Adjuvant Therapy for Resected Biliary Tract Cancer: ASCO Clinical Practice Guideline. Journal of Clinical Oncology. 2019;37(12):1015-27.
30. Norsk Gastrointestinal Cancer Gruppe. Cholangiocarcinom. Retningslinjer NGICG-HPB,2021.
31. Oneda E, Abu Hilal M, Zaniboni A. Biliary Tract Cancer: Current Medical Treatment Strategies. Cancers (Basel). 2020;12(5).
32. NCCN. NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers - Version 2 2022.
33. Nagino M, Hirano S, Yoshitomi H, Aoki T, Uesaka K, Unno M, et al. Clinical practice guidelines for the management of biliary tract cancers 2019: The 3rd English edition. J Hepatobiliary Pancreat Sci. 2021;28(1):26-54.
34. Valle JW, Furuse J, Jitlal M, Beare S, Mizuno N, Wasan H, et al. Cisplatin and gemcitabine for advanced biliary tract cancer: a meta-analysis of two randomised trials. Ann Oncol. 2014;25(2):391-8.
35. Sundhed.dk. Kolangiokarcinom 2022 [updated December 5th 2022 Available from: https://www.sundhed.dk/sundhedsfaglig/laegehaandbogen/mave-tarm/tilstande-og-sygdomme/galdeveje/kolangiokarcinom/.
36. Kreftregisteret. Cancer in Norway 2021,. Cancer incidence, mortality, survival and prevalence in Norway2022.
37. cancer.dk. Galdeblærekræft og galdegangskræft 2022 [updated 28.06.2022. Available from: https://www.cancer.dk/galdeblaere-og-galdegangskraeft-galdevejscancer/.
38. Piha-Paul SA, Oh DY, Ueno M, Malka D, Chung HC, Nagrial A, et al. Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: Results from the KEYNOTE-158 and KEYNOTE-028 studies. Int J Cancer. 2020;147(8):2190-8.
39. Ueno M, Ikeda M, Morizane C, Kobayashi S, Ohno I, Kondo S, et al. Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: a non-randomised, multicentre, open-label, phase 1 study. Lancet Gastroenterol Hepatol. 2019;4(8):611-21.
40. Kim RD, Chung V, Alese OB, El-Rayes BF, Li D, Al-Toubah TE, et al. A Phase 2 Multi-institutional Study of Nivolumab for Patients With Advanced Refractory Biliary Tract Cancer. JAMA Oncol. 2020;6(6):888-94.
41. Chen X, Wu X, Wu H, Gu Y, Shao Y, Shao Q, et al. Camrelizumab plus gemcitabine and oxaliplatin (GEMOX) in patients with advanced biliary tract cancer: a single-arm, open-label, phase II trial. J Immunother Cancer. 2020;8(2).
42. Samverkan RCI. Cancer i lever och gallvägar, SweLiv. Årsrapport nationellt kvalitetsregister, 2022. Diagnosår: 2009-2021. 2022.
43. Kreftregisterert. Cancer in Norway 2021,. Cancer incidence, mortality, survival and prevalence in Norway2022.
44. Cancerregistret. Nye kræfttilfælde i Danmark 2021. 2023 27-01-2023.

45. Authority TDHD. Bilag 1. Grupperinger anvendt i Cancerregisteret 2022 [updated January 2022. Available from: https://sundhedsdatastyrelsen.dk/-/media/sds/filer/find-tal-og-analyser/sygdomme-og-behandlinger/kraeft/kraeft_nye_tilfaelde_aarsrapporter/grupperinger_cancerregisteret.pdf.
46. Organisation WH. ICD-10 version:2019 2019 [updated February 1st 2020. Available from: https://icd.who.int/browse10/2019/en.
47. Sundhedsdatastyrelsen. Nye kræfttilfælde i Danmark 2021. sunhetsdata.dk: Sundhedsdatastyrelsen; 2023.
48. (EMA) EMA. Teysuno SUMMARY OF PRODUCT CHARACTERISTICS [Available from: https://www.ema.europa.eu/en/documents/product-information/teysuno-epar-product-information_en.pdf.
49. A He JV, C Lee, M Ikeda, P Potemski, C Morizane et al.,. Outcomes by primary tumour location in patients with advanced biliary tract cancer treated with durvalumab or placebo plus gemcitabine and cisplatin in the Phase 3 TOPAZ-1 study. ESMO 29 June 2022. 2022.
50. Agency TDM. Lægemiddelstyrelsen Produktresuméer 2023 [updated May 29th 2023. Available from: https://produktresume.dk/AppBuilder/search.
51. Agency DM. Medicinpriser 2023 [updated May 31st 2023. Available from: https://www.medicinpriser.dk/default.aspx.
52. Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev. 2010;236:219-42.
53. European Medicines Agency. IMFINZI (durvalumab) SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf. Last Accessed: April 2022. [
54. Macek Jilkova Z, Aspord C, Decaens T. Predictive Factors for Response to PD-1/PD-L1 Checkpoint Inhibition in the Field of Hepatocellular Carcinoma: Current Status and Challenges. Cancers (Basel). 2019;11(10).
55. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252-64.
56. Qin W, Hu L, Zhang X, Jiang S, Li J, Zhang Z, et al. The Diverse Function of PD-1/PD-L Pathway Beyond Cancer. Front Immunol. 2019;10:2298.
57. Fluxá P, Rojas-Sepúlveda D, Gleisner MA, Tittarelli A, Villegas P, Tapia L, et al. High CD8+ and absence of Foxp3+ T lymphocytes infiltration in gallbladder tumors correlate with prolonged patients survival. BMC Cancer. 2018;18(1):243.
58. Kim R, Coppola D, Wang E, Chang YD, Kim Y, Anaya D, et al. Prognostic value of CD8CD45RO tumor infiltrating lymphocytes in patients with extrahepatic cholangiocarcinoma. Oncotarget. 2018;9(34).
59. Mirallas O, López-Valbuena D, García-Illescas D, Fabregat-Franco C, Verdaguer H, Tabernero J, et al. Advances in the systemic treatment of therapeutic approaches in biliary tract cancer. ESMO Open. 2022;7(3):100503.
60. Bracci L, Schiavoni G, Sistigu A, Belardelli F. Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer. Cell Death & Differentiation. 2014;21(1):15-25.
61. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature. 2011;480(7378):480-9.
62. Vanneman M, Dranoff G. Combining immunotherapy and targeted therapies in cancer treatment. Nature reviews cancer. 2012;12(4):237-51.
63. RECIST 1.1 Guidelines. New response evaluation criteria in solid tumours:

Revised RECIST guideline (version 1.1). Available at: https://project.eortc.org/recist/wp-content/uploads/sites/4/2015/03/RECISTGuidelines.pdf. Accessed: July 2022 2008 [Available from: https://recist.eortc.org/recist-1-1-2/.
64. ESMO. ESMO-MCBS scorecard durvalumab for adult patients with locally advanced or metastatic biliary tract cancer. Avaliable at: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-350-1 Last Accessed: 26/10/2022 2022 [
65. AstraZeneca Data on File. Unprecedented time for IMFINZI in 2022 and 2023. 2022.
66. Oh DY, He AR, Qin S, Chen LT, Okusaka T, Vogel A, et al., editors. Three-year survival and safety update from the Phase 3 TOPAZ-1 study of durvalumab plus chemotherapy in biliary tract cancer. Poster presented at the Cholangiocarcinoma Foundation 2024 Annual Conference, April 18; 2024; Salt Lake City, UT, USA.

67. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2018;378(22):2078-92.
68. Zhou F, Zhao W, Gong X, Ren S, Su C, Jiang T, et al. Immune-checkpoint inhibitors plus chemotherapy versus chemotherapy as first-line treatment for patients with extensive-stage small cell lung cancer. Journal for immunotherapy of cancer. 2020;8(2).
69. Liang F, Zhang S, Wang Q, Li W. Treatment effects measured by restricted mean survival time in trials of immune checkpoint inhibitors for cancer. Ann Oncol. 2018;29(5):1320-4.
70. AstraZeneca Data on File. TOPAZ-1 Restricted Mean Survival Time Analysis 2022.
71. EMA. EPAR. CHMP extension of indication variation assessment report. Procedure No EMEA/H/C/004771/II/00462023.
72. Oh D-Y, He AR, Qin S, Chen L-T, Okusaka T, Vogel A, et al. A phase 3 randomized, double-blind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin (GemCis) in patients (pts) with advanced biliary tract cancer (BTC): TOPAZ-1. In: #GI22. AGCS, editor.: American Society of Clinical Oncology; 2022.
73. Antonuzzo L, Takahashi, H., Park, JO, Sookprasert, A., et al. 57P - Immune-mediated adverse event incidence, timing and association with efficacy in the Phase 3 TOPAZ-1 study of durvalumab or placebo plus gemcitabine and cisplatin in advanced biliary tract cancer. ESMO Annual Congress 2022. 2022.
74. Kato K, Doki Y, Ogata T, Motoyama S, Kawakami H, Ueno M, et al. First-line nivolumab plus ipilimumab or chemotherapy versus chemotherapy alone in advanced esophageal squamous cell carcinoma: a Japanese subgroup analysis of open-label, phase 3 trial (CheckMate 648/ONO-4538-50). Esophagus. 2023;20(2):291-301.
75. Janjigian YY, Shitara K, Moehler M, Garrido M, Salman P, Shen L, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet. 2021;398(10294):27-40.
76. Doki Y, Ajani JA, Kato K, Xu J, Wyrwicz L, Motoyama S, et al. Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. N Engl J Med. 2022;386(5):449-62.
77. Novello S, Kowalski DM, Luft A, Gümüş M, Vicente D, Mazières J, et al. Pembrolizumab Plus Chemotherapy in Squamous Non–Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study. Journal of Clinical Oncology. 2023:JCO.22.01990.
78. Garassino MC, Gadgeel S, Speranza G, Felip E, Esteban E, Dómine M, et al. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non–Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. Journal of Clinical Oncology. 2023:JCO.22.01989.
79. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Brussels: European Organisation for Research and Treatment of Cancer; 2001 [Available from: https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf.
80. AstraZeneca. TOPAZ-1 Clinical study report (CSR). 2022.
81. Burris HA, Okusaka T, Vogel A, Lee MA, Takahashi H, Breder VV, et al. Patient-reported outcomes for the phase 3 TOPAZ-1 study of durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. ESMO Annual Congress 2022. 2022;40(16_suppl):4070-.
82. Finansministeriet. Dokumentationsnotat – den samfundsøkonomiske diskonteringsrente fm.dk: Finansministeriet; 2021.
83. Ascierto PA, Del Vecchio M, Mackiewicz A, Robert C, Chiarion-Sileni V, Arance A, et al. Overall survival at 5 years of follow-up in a phase III trial comparing ipilimumab 10 mg/kg with 3 mg/kg in patients with advanced melanoma. J Immunother Cancer. 2020;8(1).
84. Michielin O, Lalani AK, Robert C, Sharma P, Peters S. Defining unique clinical hallmarks for immune checkpoint inhibitor-based therapies. J Immunother Cancer. 2022;10(1).
85. Wada S, Kobayashi S, Tsunoda T. Future prospects for cancer immunotherapy - Strategies for ineffective cancers. Hum Vaccin Immunother. 2022;18(1):2031699.
86. Kaufman HL, Atkins MB, Subedi P, Wu J, Chambers J, Joseph Mattingly T, 2nd, et al. The promise of Immuno-oncology: implications for defining the value of cancer treatment. J Immunother Cancer. 2019;7(1):129.
87. Kim H, Kim DW, Kim M, Lee Y, Ahn HK, Cho JH, et al. Long-term outcomes in patients with advanced and/or metastatic non-small cell lung cancer who completed 2 years of immune checkpoint inhibitors or achieved a durable response after discontinuation without disease progression: Multicenter, real-world data (KCSG LU20-11). Cancer. 2022;128(4):778-87.

88. Michielin O, Atkins MB, Koon HB, Dummer R, Ascierto PA. Evolving impact of long-term survival results on metastatic melanoma treatment. J Immunother Cancer. 2020;8(2).
89. Castanon E, Sanchez-Arraez A, Alvarez-Mancenido F, Jimenez-Fonseca P, Carmona-Bayonas A. Critical reappraisal of phase III trials with immune checkpoint inhibitors in non-proportional hazards settings. Eur J Cancer. 2020;136:159-68.
90. Damuzzo V, Agnoletto L, Leonardi L, Chiumente M, Mengato D, Messori A. Analysis of Survival Curves: Statistical Methods Accounting for the Presence of Long-Term Survivors. Front Oncol. 2019;9:453.
91. Quinn C, Garrison LP, Pownell AK, Atkins MB, de Pouvourville G, Harrington K, et al. Current challenges for assessing the long-term clinical benefit of cancer immunotherapy: a multi-stakeholder perspective. J Immunother Cancer. 2020;8(2).
92. Chaudhary MA, Edmondson-Jones M, Baio G, Mackay E, Penrod JR, Sharpe DJ, et al. Use of Advanced Flexible Modeling Approaches for Survival Extrapolation from Early Follow-up Data in two Nivolumab Trials in Advanced NSCLC with Extended Follow-up. Med Decis Making. 2023;43(1):91-109.
93. Federico Paly V, Kurt M, Zhang L, Butler MO, Michielin O, Amadi A, et al. Heterogeneity in Survival with Immune Checkpoint Inhibitors and Its Implications for Survival Extrapolations: A Case Study in Advanced Melanoma. MDM Policy Pract. 2022;7(1):23814683221089659.
94. Ouwens M, Mukhopadhyay P, Zhang Y, Huang M, Latimer N, Briggs A. Estimating Lifetime Benefits Associated with Immuno-Oncology Therapies: Challenges and Approaches for Overall Survival Extrapolations. Pharmacoeconomics. 2019;37(9):1129-38.
95. Everest L, Shah M, Chan KKW. Comparison of Long-term Survival Benefits in Trials of Immune Checkpoint Inhibitor vs Non-Immune Checkpoint Inhibitor Anticancer Agents Using ASCO Value Framework and ESMO Magnitude of Clinical Benefit Scale. JAMA Netw Open. 2019;2(7):e196803.
96. Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Cowey CL, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19(11):1480-92.
97. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Long-Term Outcomes With Nivolumab Plus Ipilimumab or Nivolumab Alone Versus Ipilimumab in Patients With Advanced Melanoma. J Clin Oncol. 2022;40(2):127-37.
98. Borghaei H, Gettinger S, Vokes EE, Chow LQM, Burgio MA, de Castro Carpeno J, et al. Five-Year Outcomes From the Randomized, Phase III Trials CheckMate 017 and 057: Nivolumab Versus Docetaxel in Previously Treated Non-Small-Cell Lung Cancer. J Clin Oncol. 2021;39(7):723-33.
99. Paz-Ares L, Ciuleanu TE, Cobo M, Schenker M, Zurawski B, Menezes J, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(2):198-211.
100. Kelley RK, Ueno M, Yoo C, Finn RS, Furuse J, Ren Z, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2023.
101. Bullement A, Willis A, Amin A, Schlichting M, Hatswell AJ, Bharmal M. Evaluation of survival extrapolation in immuno-oncology using multiple pre-planned data cuts: learnings to aid in model selection. BMC Med Res Methodol. 2020;20(1):103.
102. Johannesen KH, C.; Huetson, P.; Torkilseng, E.B.; Thybo, S.H. Comparing and validating the overall survival extrapolations for immuno-oncology treatments applied in the HTA's by NoMA and TLV. ISPOR Europe 2019. 2019;November 2-6, 2019.
103. Paz-Ares L, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer: 3-year overall survival update from CASPIAN[☆]. ESMO Open. 2022;7(2).
104. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019;394(10212):1929-39.
105. Goldman JW, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2021;22(1):51-65.

106. Lin EP, Hsu CY, Berry L, Bunn P, Shyr Y. Analysis of Cancer Survival Associated With Immune Checkpoint Inhibitors After Statistical Adjustment: A Systematic Review and Meta-analyses. JAMA Netw Open. 2022;5(8):e2227211.
107. Markussen A, Jensen LH, Diness LV, Larsen FO. Treatment of Patients with Advanced Biliary Tract Cancer with Either Oxaliplatin, Gemcitabine, and Capecitabine or Cisplatin and Gemcitabine-A Randomized Phase II Trial. Cancers (Basel). 2020;12(7).
108. Elgenidy A, Afifi AM, Jalal PK. Survival and Causes of Death among Patients with Intrahepatic Cholangiocarcinoma in the United States from 2000 to 2018. Cancer Epidemiol Biomarkers Prev. 2022;31(12):2169-76.
109. McNamara MG, Lopes A, Wasan H, Malka D, Goldstein D, Shannon J, et al. Landmark survival analysis and impact of anatomic site of origin in prospective clinical trials of biliary tract cancer. J Hepatol. 2020;73(5):1109-17.
110. Rahman R, Ludvigsson JF, von Seth E, Lagergren J, Bergquist A, Radkiewicz C. Age trends in biliary tract cancer incidence by anatomical subtype: A Swedish cohort study. Eur J Cancer. 2022;175:291-8.
111. Izquierdo-Sanchez L, Lamarca A, La Casta A, Buettner S, Utpatel K, Klümpen H-J, et al. Cholangiocarcinoma landscape in Europe: Diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. Journal of Hepatology. 2022;76(5):1109-21.
112. Jensen CE, Sorensen SS, Gudex C, Jensen MB, Pedersen KM, Ehlers LH. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. Appl Health Econ Health Policy. 2021;19(4):579-91.
113. NICE. Single Technology Appraisal: Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 alterations [ID3740]

Committee Papers 2021 [Available from: https://www.nice.org.uk/guidance/ta722/documents/committee-papers.
114. Medicinrådet. Appendiks: Aldersjustering for sundhedsrelateret livskvalitet. www.medicinraadet.dk Medicinrådet.
115. Fancher KM, Sacco AJ, Gwin RC, Gormley LK, Mitchell CB. Comparison of two different formulas for body surface area in adults at extremes of height and weight. Journal of Oncology Pharmacy Practice. 2016;22(5):690-5.
116. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. The Lancet Oncology. 2021;22(5):690-701.
117. Inoue H, Todaka A, Yamazaki K, Fushiki K, Shirasu H, Kawakami T, et al. Efficacy and safety of S-1 following gemcitabine with cisplatin for advanced biliary tract cancer. Investigational New Drugs. 2021;39(5):1399-404.
118. DaBlaCa. Dansk BlæreCancer Gruppe. Behandling og opfølgning af muskelinvasiv blærekræft. Version 1.4. Klinisk Retningslinje - Kræft Aarhus2023 [Available from: https://www.dmcg.dk/siteassets/kliniske-retningslinjer---skabeloner-og-vejledninger/kliniske-retningslinjer-opdelt-pa-dmcg/blarecancer/dablaca_beh_opfolgn_muskelinvasiv_v1.4_admgodk010823.pdf.
119. Medicinrådet. Medicinrådets anbefaling vedr. pembrolizumab i kombination med kemoterapi med eller uden bevacizumab til levetids-forlængende behandling af livmoderhalskræft, hvis tumorer udtrykker PD-L1 CPS ≥ 1 Copenhagen2023 [Available from: https://medicinraadet.dk/media/4xjmx1x2/medicinr%C3%A5dets-anbefaling-vedr-pembrolizumab-i-komb-med-kemoterapi-med-eller-uden-bevacizumab-vers-1-0x.pdf.
120. Sundhedsdatastyrelsen. DRG-takster 2024. sundhedsdatastyrelsen.dk: Sundhetsdatastyrelsen; 2024.
121. AstraZeneca. A Phase III Randomized, Double-Blind, Placebo-Controlled, Multi-Regional, International Study of Durvalumab in Combination with Gemcitabine plus Cisplatin versus Placebo in Combination with Gemcitabine plus Cisplatin for Patients with First-Line Advanced Biliary Tract Cancers (TOPAZ-1) - Protoocol 7.0. 2020.
122. Medicinrådet. Værdisætning af enhedsomkostninger. medicinraadet.dk: Medicinrådet,; 2023.
123. Lægeforeningen. Takstkort 29A, Laboratorieundersøgelser. laeger.dk: Lægeforeningen; 2023.
124. Lægeforeningen. Honorartabell. laeger.dk: Lægeforeningen; 2023.
125. Caparica R, Lengelé A, Bekolo W, Hendlisz A. FOLFIRI as second-line treatment of metastatic biliary tract cancer patients. Autopsy & Case Reports. 2019;9(2).
126. Kim RD, Chung V, Alese OB, El-Rayes BF, Li D, Al-Toubah TE, et al. A phase 2 multi-institutional study of nivolumab for patients with advanced refractory biliary tract cancer. JAMA oncology. 2020;6(6):888-94.

127. Izquierdo-Sanchez L, Lamarca A, La Casta A, Buettner S, Utpatel K, Klümpen H-J, et al. Cholangiocarcinoma landscape in Europe: Diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. Journal of hepatology. 2022.
128. Mazieres J, Rittmeyer A, Gadgeel S, Hida T, Gandara DR, Cortinovis DL, et al. Atezolizumab Versus Docetaxel in Pretreated Patients With NSCLC: Final Results From the Randomized Phase 2 POPLAR and Phase 3 OAK Clinical Trials. J Thorac Oncol. 2021;16(1):140-50.
129. Herbst RS, Garon EB, Kim DW, Cho BC, Gervais R, Perez-Gracia JL, et al. Five Year Survival Update From KEYNOTE-010: Pembrolizumab Versus Docetaxel for Previously Treated, Programmed Death-Ligand 1-Positive Advanced NSCLC. J Thorac Oncol. 2021;16(10):1718-32.
130. Castro Gd, Kudaba I, Wu Y-L, Lopes G, Kowalski DM, Turna HZ, et al. 363 KEYNOTE-042 5-year survival update: pembrolizumab versus chemotherapy in patients with previously untreated, PD-L1–positive, locally advanced or metastatic non–small-cell lung cancer. Journal for ImmunoTherapy of Cancer. 2021;9(Suppl 2):A390-A.
131. Jassem J, de Marinis F, Giaccone G, Vergnenegre A, Barrios CH, Morise M, et al. Updated Overall Survival Analysis From IMpower110: Atezolizumab Versus Platinum-Based Chemotherapy in Treatment-Naive Programmed Death-Ligand 1-Selected NSCLC. J Thorac Oncol. 2021;16(11):1872-82.
132. Brahmer JR, Lee JS, Ciuleanu TE, Bernabe Caro R, Nishio M, Urban L, et al. Five-Year Survival Outcomes With Nivolumab Plus Ipilimumab Versus Chemotherapy as First-Line Treatment for Metastatic Non-Small-Cell Lung Cancer in CheckMate 227. J Clin Oncol. 2023;41(6):1200-12.
133. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2019;381(21):2020-31.
134. Nishio M, Barlesi F, West H, Ball S, Bordoni R, Cobo M, et al. Atezolizumab Plus Chemotherapy for First-Line Treatment of Nonsquamous NSCLC: Results From the Randomized Phase 3 IMpower132 Trial. J Thorac Oncol. 2021;16(4):653-64.
135. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50. J Clin Oncol. 2021;39(21):2339-49.
136. West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(7):924-37.
137. Jotte R, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Rodríguez-Abreu D, Hussein M, et al. Atezolizumab in Combination With Carboplatin and Nab-Paclitaxel in Advanced Squamous NSCLC (IMpower131): Results From a Randomized Phase III Trial. J Thorac Oncol. 2020;15(8):1351-60.
138. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. First-Line Nivolumab in Stage IV or Recurrent Non-Small-Cell Lung Cancer. N Engl J Med. 2017;376(25):2415-26.
139. Garassino MC, Kilickap S, Özgüroğlu M, Sezer A, Gumus M, Bondarenko I, et al. OA01.05 Three-year Outcomes per PD-L1 Status and Continued Cemiplimab Beyond Progression + Chemotherapy: EMPOWER-Lung 1. Journal of Thoracic Oncology. 2023;18(3):e2-e3.
140. Govindan R, Szczesna A, Ahn MJ, Schneider CP, Gonzalez Mella PF, Barlesi F, et al. Phase III Trial of Ipilimumab Combined With Paclitaxel and Carboplatin in Advanced Squamous Non-Small-Cell Lung Cancer. J Clin Oncol. 2017;35(30):3449-57.
141. Maio M, Grob JJ, Aamdal S, Bondarenko I, Robert C, Thomas L, et al. Five-year survival rates for treatment-naive patients with advanced melanoma who received ipilimumab plus dacarbazine in a phase III trial. J Clin Oncol. 2015;33(10):1191-6.
142. Robert C, Long GV, Brady B, Dutriaux C, Di Giacomo AM, Mortier L, et al. Five-Year Outcomes With Nivolumab in Patients With Wild-Type BRAF Advanced Melanoma. J Clin Oncol. 2020;38(33):3937-46.
143. Larkin J, Minor D, D'Angelo S, Neyns B, Smylie M, Miller WH, Jr., et al. Overall Survival in Patients With Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial. J Clin Oncol. 2018;36(4):383-90.
144. Balar AV, Castellano DE, Grivas P, Vaughn DJ, Powles T, Vuky J, et al. Efficacy and safety of pembrolizumab in metastatic urothelial carcinoma: results from KEYNOTE-045 and KEYNOTE-052 after up to 5 years of follow-up. Ann Oncol. 2023;34(3):289-99.

145. Fradet Y, Bellmunt J, Vaughn DJ, Lee JL, Fong L, Vogelzang NJ, et al. Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of >2 years of follow-up. Ann Oncol. 2019;30(6):970-6.
146. van der Heijden MS, Loriot Y, Duran I, Ravaud A, Retz M, Vogelzang NJ, et al. Atezolizumab Versus Chemotherapy in Patients with Platinum-treated Locally Advanced or Metastatic Urothelial Carcinoma: A Long-term Overall Survival and Safety Update from the Phase 3 IMvigor211 Clinical Trial. Eur Urol. 2021;80(1):7-11.
147. Powles T, Csoszi T, Ozguroglu M, Matsubara N, Geczi L, Cheng SY, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(7):931-45.
148. Galsky MD, Arija JÁ A, Bamias A, Davis ID, De Santis M, Kikuchi E, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet. 2020;395(10236):1547-57.

Version log

Version	Date	Change
1.0	27 November 2020	Application form for assessment made available on the website of the Danish Medicines Council.
1.1	9 February 2022	Appendix K and onwards have been deleted (company specific appendices) Color scheme for text highlighting table added after table of contents Section 6: Specified requirements for literature search Section 7: Stated it explicitly that statistical methods used need to be described Section 8.3.1: Listed the standard parametric models Section 8.4.1: Added the need for description of quality of life mapping Appendix A: Specified that the literature search needs to be specific for the Danish context and the application Appendices B and D: Stated it explicitly that statistical methods need to be described in the tables in the appendices
1.2	20 June 2022	Clarification of the introduction, including instructions on how to complete the form.
1.3	6 December 2022	Clarification regarding new IT security requirements concerning macros in excel files has been added, see page 1.

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

A systematic literature review is not included in this application, as the head-to-head study of TOPAZ-1 is mainly used to demonstrate the efficacy and safety of durvalumab in combination with GemCis compared to GemCis alone. As GemCis is the only available treatment for BTC patients with metastatic or resectable disease in Denmark, AstraZeneca have neither included a comparative analysis, as there are no other relevant comparators for the treatment in Denmark. If Medicinraadet still find it useful, AstraZeneca will provide this per request.

Example of table: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase			
Medline			
The Cochrane Library			
Clinicaltrial.gov			

Abbreviations:

Example of table: Registers included in the search

Database	Platform	Search strategy	Date of search
US NIH registry & results database			
WHO ICTRP registry			
EU Clinical Trials Register			

Example of table: Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched
N/A			
N/A			

Conference	Source of abstracts	Search strategy	Words/terms searched
N/A			

Search strategy

Search strings are not included in this application, as the head-to-head study of TOPAZ-1 is mainly used to demonstrate the efficacy and safety of durvalumab in combination with GemCis compared to GemCis alone. As GemCis is the only available treatment for BTS patients with metastatic or resectable disease in Denmark, AstraZeneca argues that a systematic literature search is not necessary. If Medicinraadet still find it useful, AstraZeneca will provide this per request.

Example of search strategy table:

No.	Query	Results
#1		
#2		
#3		
#4		

Unpublished data

This application mentions unpublished data in the form of data on file from AstraZeneca.

Appendix B Main characteristics of included studies

Trial name: Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer(TOPAZ)	NCT number: NCT03875235
Objective	Patients with previously untreated unresectable or metastatic biliary tract cancer or with recurrent disease 1:1 to receive durvalumab or placebo in combination with gemcitabine plus cisplatin for up to eight cycles, followed by durvalumab or placebo monotherapy until disease progression or unacceptable toxicity. The primary objective was to assess overall survival. Secondary end points included progression-free survival, objective response rate and safety
Publications – title, author, journal, year	Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. Do-Youn Oh, M.D. et al. NEJM Evid 2022; 1 (8); DOI:https://doi.org/10.1056/EVIDoa2200015; June 1, 2022.
Study type and design	A Phase III Randomized, Double-Blind Placebo Controlled, Multi-Regional, International Study of Durvalumab in Combination with Gemcitabine Plus Cisplatin Versus Placebo in Combination with Gemcitabine Plus Cisplatin for Patients With First-Line Advanced Biliary Tract Cancer
Sample size (n)	Intervention: n=341 Comparator: n=344
Main inclusion and exclusion criteria	**Inclusion criteria:** 1. Histologically confirmed, unresectable advanced or metastatic biliary tract, including cholangiocarcinoma (intrahepatic or extrahepatic) and gallbladder carcinoma. 2. Patients with preciously untreated disease if unresectable or metastatic at initial diagnosis will be eligible. 3. Patient with recurrent disease >6 months after curative surgery or >6 months after the completion of adjuvant therapy (chemotherapy and/or radiation) will be eligible. 4. WHO/ECOG PS of 0 or 1 [36] **Exclusion criteria:** 1. History of another primary malignancy 2. Brain metastases or spinal cord compression 3. Uncontrolled intercurrent illness 4. Major surgical procedure within 28 days prior to the first dose of IP. 5. Prior locoregional therapy such as radioembolization [36]
Intervention	Durvalumab + GemCis: n=341 Durvalumab in combination with IV infusion every 3 weeks with gemcitabine plus cisplatin up to 8 cycles followed by durvalumab monotherapy every 4 weeks until disease progression or other discontinuation criteria.

Trial name: Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer(TOPAZ)	NCT number: NCT03875235
Comparator(s)	Placebo + GemCis n=344 Placebo in combination with IV infusion every 3 weeks with gemcitabine plus cisplatin up to 8 cycles followed by placebo monotherapy every 4 weeks until disease progression or other discontinuation criteria.
Follow-up time	Actual Study Start Date :April 16, 2019 Actual Primary Completion Date : August 11, 2021 Follow-up time:
Is the study used in the health economic model?	Yes

Primary, secondary and exploratory endpoints	***Primary Outcome Measures:***
	
	• Overall survival
	
	Secondary Outcome Measures:
	
	• PFS according to RECIST 1.1 using investigator assessment
	• ORR according to RECIST 1.1 using investigator assessment
	• DoR according to RECIST 1.1 using investigator assessment
	• EORTC QLQ-C30 and EORTC QLQ-BIL21
	• PFS, ORR, DoR, and DCR according to RECIST 1.1 using Investigator assessments and OS by PD-L1 expression
	• Serum concentration of durvalumab (peak and trough concentration)
	• Tiered results of ADAs for durvalumab
	• To assess the safety and tolerability profile of durvalumab + GemCis vs. placebo + GemCis
	  • *AEs*
	  • *physical examinations*
	  • *laboratory findings*
	  • *WHO/ECOG PS*
	  • *ECG and vital signs*

Method of analysis	The primary objective at IA-2 was to evaluate the superiority of durvalumab + GemCis compared with placebo + GemCis in terms of OS, as analyzed using a stratified log-rank test (stratified by disease status and primary tumor location) to assess statistical inference. The treatment effect was estimated by HR and its 95% CI based on a Cox proportional hazards model (stratified by disease status and primary tumor location). Kaplan-Meier plots of OS were presented by treatment, and median OS and estimated OS rates at 12, 18, and 24 months were presented. As a lack of proportionality was evident, the variation in treatment effect was also described by piecewise HR (using Cox modelling). Progression-free survival, the key secondary endpoint, was analyzed using the same methodology as for OS.

Trial name: Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer(TOPAZ)	NCT number: NCT03875235

Subgroup analyses

Prespecified

- Gender
- Age
- PD-L1 expression
- Disease status
- Tumor location
- Race
- ECOG performance

BTC stage (locally advanced vs metastatic) [36]

Other relevant information

Summary of baseline patient demographics and disease characteristics in TOPAZ-1 (IA-2; FAS)

Patient Characteristics	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
Age (years)		
Median (range)	64 (20–84)	64 (31–85)
Sex, n (%)		
Female	172 (50.4)	168 (48.8)
Race, n (%)		
Asian	185 (54.3)	201 (58.4)
Region, n (%)		
Asia	178 (52.2)	196 (57.0)
Rest of world	163 (47.8)	148 (43.0)
ECOG-PS, n (%)		
0	173 (50.7)	163 (47.4)
1	168 (49.3)	181 (52.6)
Primary tumour type, n (%)		
intrahepatic CCA	190 (55.7)	193 (56.1)
eCCA	66 (19.4)	65 (18.9)
Gallbladder cancer	85 (24.9)	86 (25.0)

Patient Characteristics	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
Disease status, n (%)		
Initially unresectable	274 (80.4)	279 (81.1)
Recurrent	67 (19.6)	64 (18.6)
Disease classification, n (%)		
Locally advanced[a]	38 (11.1)	57 (16.6)
Metastatic	303 (88.9)	286 (83.1)
Missing	1 (0.3)	1 (0.1)
MSI status, n (%)		
High	3 (0.9)	2 (0.6)
Stable	160 (46.9)	168 (48.8)
Missing[b]	178 (52.2)	174 (50.6)
Virology status, n (%)		
No viral hepatitis	187 (54.8)	174 (50.6)
Any viral hepatitis B	69 (20.2)	81 (23.5)
Active viral hepatitis B	8 (2.3)	14 (4.1)
Prior hepatitis C	8 (2.3)	10 (2.9)
Missing	82 (24.0)	83 (24.1)
PD-L1 expression, n (%)		
High (TAP ≥1%)	197 (57.8)	205 (59.6)
Low/negative (TAP <1%)	103 (30.2)	103 (29.9)
Missing	41 (12.0)	36 (10.5)

Footnotes: *[a]Patient has only unresectable sites of disease; [b] MSI status missing includes MSI-unknown and not tested..*

Source: *Oh et al.(2022)a;(72)* AstraZeneca Data on File – TOPAZ-1 Clinical Study Report.*(65)*

Appendix C Baseline characteristics of patients in TOPAZ-1 of efficacy and safety

Since this application only include a head-to-head study of TOPAZ-1 comparing durvalumab in combination with GemCis versus GemCis only, a comparative study was performed as GemCis is an implemented comparator in Danish clinical practice. The following include baseline characteristics of TOPAZ-1, which were generally well balanced between treatment arms in TOPAZ-1 in terms of age, sex, and race, as well as in terms of disease characteristics such as ECOG-PS and primary tumour type. Enrolled patients included those with gallbladder cancer and cholangiocarcinoma both intrinsic and extrinsic with performance status 0-1. Furthermore, these patients were stratified with according to tumor area positivity (TAP) for the purpose of subgroup analysis, with 57.8% of patients being treated with durvalumab in combination with GemCis having High TAP (≥1%) vs higher proportion of patients in the control arm (59.8 %). 30.2% of the patients in durvalumab arm had low/negative TAP(<1%) vs 29.9% in the control arm. However it is important to note that the study was not sized for any of the individual subgroup evaluations and no adjustments were made for multiplicity.

Patient Characteristics	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
	TOPAZ-1	
Age (years)		
Median (range)	64 (20–84)	64 (31–85)
Sex, n (%)		
Female	172 (50.4)	168 (48.8)
Race, n (%)		
Asian	185 (54.3)	201 (58.4)
Region, n (%)		
Asia	178 (52.2)	196 (57.0)
Rest of world	163 (47.8)	148 (43.0)
ECOG-PS, n (%)		
0	173 (50.7)	163 (47.4)
1	168 (49.3)	181 (52.6)
Primary tumour type, n (%)		
intrahepatic CCA	190 (55.7)	193 (56.1)
eCCA	66 (19.4)	65 (18.9)
Gallbladder cancer	85 (24.9)	86 (25.0)
Disease status, n (%)		
Initially unresectable	274 (80.4)	279 (81.1)

Patient Characteristics	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
	TOPAZ-1	
Recurrent	67 (19.6)	64 (18.6)
Disease classification, n (%)		
Locally advanced[a]	38 (11.1)	57 (16.6)
Metastatic	303 (88.9)	286 (83.1)
MSI status, n (%)		
High	3 (0.9)	2 (0.6)
Stable	160 (46.9)	168 (48.8)
Missing[b]	178 (52.2)	174 (50.6)
Virology status, n (%)		
No viral hepatitis	187 (54.8)	174 (50.6)
Any viral hepatitis B	69 (20.2)	81 (23.5)
Active viral hepatitis B	8 (2.3)	14 (4.1)
Prior hepatitis C	8 (2.3)	10 (2.9)
Missing	82 (24.0)	83 (24.1)
PD-L1 expression, n (%)		
High (TAP ≥1%)	197 (57.8)	205 (59.6)
Low/negative (TAP <1%)	103 (30.2)	103 (29.9)
Missing	41 (12.0)	36 (10.5)

Age Characteristics	D + Gem/Cis (N = 341)	Placebo + Gem/Cis (N = 344)	Total (N = 685)
	TOPAZ-1		
Age (years)			
Mean (standard deviation)	62.2 (10.49)	62.6 (10.66)	62.4 (10.57)
Median (min, max)	64 (20, 84)	64 (31, 85)	64 (20, 85)
Category (n%)			
< 65 years	181 (53.1)	184 (53.5)	365 (53.3)
⩾ 65 to < 75 years	122 (35.8)	114 (33.1)	236 (34.5)

⩾ 65 years	160 (46.9)	160 (46.5)	320 (46.7)
⩾ 75 years	38 (11.1)	46 (13.4)	84 (12.3)

Comparability of patients across studies

As application uses head-to-head study of TOPAZ-1, no patients characteristics from other studies are used to

Comparability of the study populations with Danish patients eligible for treatment

The patient population in Denmark is expected to be aligned with the labelled population in Europe, and this label was derived from the perceived risks and benefits in patients included in the registrational TOPAZ-1 trial, it is therefore assumed that the population in the clinical evidence is largely aligned with patients in Danish clinical practice.

Appendix D Efficacy and safety results per study

Definition and analysis of included outcome measures

As the analysis was based on standard outcomes in oncology such as OS and PFS, we find it less relevant to discuss the validity and clinical relevance of the outcome measures and focus on the definition and statistical analysis. Some further secondary endpoints are included as supporting information although they are not directly used in the cost per QALY analysis. These secondary endpoints include ORR (Objective Response Rate), DoR (Duration of Response), and DCR (Disease Control Rate)

Outcome measure	Definition	Statistical analysis (as described in the Study Protocol and SAP)
Primary Endpoints		
OS	From date of randomization until death due to any cause	Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive. Median OS was calculated using the Kaplan-Meier technique. The second interim analysis (IA-2) was pre-specified after approximately 397 OS events occurred in both arms (59% maturity). IA-2: Stratified log-rank analysis test adjusting for disease status and primary tumor location for primary comparison of survival between randomized treatment groups providing a p-value and stratified Cox proportional hazard model providing hazard ratio (HR) (95% CI) and ([1-adjusted alpha] x 100%)
OS Rate at 12 Months	From date of randomization until death due to any cause	Calculated at 12 months using the Kaplan-Meier technique
OS Rate at 18 Months	From date of randomization until death due to any cause	Calculated at 18 months using the Kaplan-Meier technique

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Outcome measure	Definition	Statistical analysis (as described in the Study Protocol and SAP)
OS Rate at 24 Months	From date of randomization until death due to any cause	Calculated at 24 months using the Kaplan-Meier technique
Secondary Endpoints		
PFS	PFS based on investigator assessments according to RECIST version 1.1 was defined as time from date of randomization until date of objective disease progression or death (by any cause in the absence of progression), regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy prior to progression. Progression (i.e., PD) was defined as at least a 20% increase in the sum of diameters of target lesions (TLs) and an absolute increase of ≥5mm, taking as reference the smallest sum of diameters since treatment started including the baseline sum of diameters, or a measurable increase in a non-target lesion, or the appearance of new lesions.	The analysis was performed using a stratified log-rank test, adjusting for disease status and primary tumor location. The effect of Arm A versus Arm B was estimated by the HR together with its corresponding 95% CI and p-value. Median PFS was calculated using the Kaplan-Meier technique. Kaplan-Meier plots of PFS were presented by treatment arm.
ORR	Disease assessments based on investigator assessments were determined by using RECIST version 1.1 guidelines. The ORR was defined as the percentage of patients with confirmed complete response (CR) or confirmed partial response (PR). The CR was defined as disappearance of all target and non-target lesions and no new lesions. The PR was defined as >= 30% decrease in the sum of diameters of target lesions (compared to baseline) and no new non-target lesion. A confirmed CR or PR was defined as 2 CRs or 2 PRs with no evidence of progression in-between. Patients who discontinued randomized treatment without progression, received	Primary interim analysis, IA-1: Exact Clopper-Pearson confidence intervals and a p-value from a stratified CMH test adjusting for disease status and primary tumor location Primary analysis with tumor data according to RECIST 1.1 based on BICR in FAS-32w with a measurable disease at baseline per BICR. Secondary interim analysis: IA-2 and FA: Odds ratio and p-value from a CMH test adjusted for disease status and primary tumor location, using tumor data according to RECIST 1.1 by Investigator assessment

Outcome measure	Definition	Statistical analysis (as described in the Study Protocol and SAP)
	a subsequent anti-cancer therapy and then responded were not included as responders for ORR.	
DoR	The DoR was defined as the time from the date of first documented OR (confirmed CR or confirmed PR) until date of documented progression (PD) based on investigator assessments by using RECIST version 1.1 or death in absence of disease progression (i.e. date of PFS event or censoring - date of first response + 1) . A confirmed CR was defined in above outcome measures. The PD was defined at least 20% increase in sum of diameters of target lesions (compared with nadir at 2 consecutive visits with an absolute increase of 5 mm), unequivocal progression of existing non-target lesions or new lesion. For participants who were alive and no documented PD at the time of data cutoff for analysis, DoR was censored at the last evaluable disease assessment date. Median DoR was calculated using Kaplan-Meier method.	KM plot and Swimmer plot of DoR according to RECIST 1.1 based on Investigator assessments. Median DoR calculated from the KM curve. At IA-1, KM plot and Swimmer plot of DoR according to RECIST 1.1 as assessed by BICR
DCR	Disease control rate based on investigator assessments according to RECIST version 1.1 was defined as the rate of best objective response of complete response (CR) or partial response (PR) by week 48 or who have stable disease (SD) at least 48 weeks following start of treatment.	Summary statistics using DCR, DCR-24w, DCR-32w and DCR-48w as assessed by the Investigator according to RECIST 1.1 At IA-1, summary statistics using DCR, DCR-24w, DCR-32w and DCR-48w as assessed by BICR
Safety and tolerability	Safety and tolerability were assessed in terms of AEs, physical examinations, laboratory findings, WHO/ECOG PS, ECG and vital signs	Safety data were not formally analyzed but summarized descriptively using the safety analysis set, according to the treatment received. All AEs, both in terms of current MedDRA preferred term and CTCAE grade, were summarized descriptively by count (n) and percentage (%) for each treatment group.

Results per study

Summary of absolute and relative effects from TOPAZ-1

Table A3a Results of TOPAZ-1 (NCT03875235)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median OS (DCO 25 Feb 2022)	Durvalumab + GemCis	341	12.9 (11.6, 14.1) months	1.6 months	NA	NA	HR: 0.76	0.64–0.91	NA	*Median calculated using the Kaplan-Meier technique. The analysis was performed using a stratified Cox proportional hazards model (ties = Efron), adjusting for disease status and primary tumor location. The CI being calculated using a profile likelihood approach.*	TOPAZ-1 CSR Addendum
	GemCis	344	11.3 (10.1, 12.5) months								
12-month OS rate (DCO 25 Feb 2022)	Durvalumab + GemCis	341	54.3% (48.8, 59.4)	7.2%	NA	NA	NA	NA	NA	*The survival rates are based on the Kaplan–Meier estimator.*	Data-on-file, TOPAZ-1 CSR Addendum
	GemCis	344	47.1% (41.7, 52.3)								

Table A3a Results of TOPAZ-1 (NCT03875235)											
18-month OS rate (DCO 25 Feb 2022)	Durvalumab + GemCis	341	34.8% (29.6, 40.0)	10.7%	NA	NA	NA	NA	NA	*The survival rates are based on the Kaplan–Meier estimator.*	Data-on-file, TOPAZ-1 CSR Addendum
	GemCis	344	24.1% (19.6, 28.9)								
24-month OS rate (DCO 25 Feb 2022)	Durvalumab + GemCis	341	23.6% (18.7, 28.9)	12.1%	NA	NA	NA	NA	NA	*The survival rates are based on the Kaplan–Meier estimator.*	Data-on-file, TOPAZ-1 CSR Addendum
	GemCis	344	11.5% (7.6, 16.2)								
Median OS 3 years DCO	Durvalumab + GemCis	341	12.9% (11.6, 14.1)				HR=0.74	(0.63, 0.87)	NA		3 years OS(Oct 23 (66))
	GemCis	344	11.3 (10.1, 12.5)								
Median PFS *(IA-2, DCO 11 Aug 2021)*	Durvalumab + GemCis	341	7.2 (6.7, 7.4) months	1.5 months	NA	NA	HR: 0.75	0.63, 0.89	0.001	*Median calculated using the Kaplan-Meier technique. The hazard ratio and its CI were estimated using a stratified Cox proportional hazards model (ties = Efron) adjusting for disease status and primary tumor location.*	Data-on-file, TOPAZ-1 CSR
	GemCis	344	5.7 (5.6, 6.7) months								
ORR	Durvalumab + GemCis	341	26.7% (22.1, 31.7)	8.0%	1.8%, 14.3%*	NA	OR: 1.60	1.11, 2.31	0.011	*Odds ratio and p-value from a CMH test adjusted for disease*	Data-on-file, TOPAZ-1 CSR

Table A3a Results of TOPAZ-1 (NCT03875235)										
(IA-2, DCO 11 Aug 2021)	GemCis	343	18.7% (14.7, 23.2)						*status and primary tumor location, using tumor data according to RECIST 1.1 by Investigator assessment*	
DoR (IA-2, DCO 11 Aug 2021)	Durvalumab + GemCis	91	6.4 (5.9, 8.1) months	0.2 months	NA	NA	NA	NA	*The DoR was calculated following the PFS methodology. Descriptive analysis without any formal comparison or p value attached (not including relative efficacy).*	Data-on-file, TOPAZ-1 CSR
	GemCis	64	6.2 (4.4, 7.3) months							
DCR (IA-2, DCO 11 Aug 2021)	Durvalumab + GemCis	341	85.3% (81.1, 88.9)	2.7%	-2.7%, 8.3%*	NA	NA	NA	*Disease control rate is the rate of best objective response of CR, PR, or SD. Descriptive analysis without any formal comparison or p value attached (not including relative efficacy).*	Data-on-file, TOPAZ-1 CSR
	GemCis	344	82.6% (78.1, 86.4)							
Any AE (IA-2, DCO 11 Aug 2021)	Durvalumab + GemCis	338	99.4% (97.9, 99.9)	0.6%	-0.8%, 2.0%*	RR: 1.01	0.99, 1.02	0.4198	*Descriptive analysis of proportions*	Data-on-file, TOPAZ-1 CSR
	GemCis	342	98.8% (97.0, 99.7)							
Any AE of any CTCAE	Durvalumab + GemCis	338	75.7% (70.8, 80.2)	-2.0%	-8.4%, 4.3%*	RR: 1.00	0.92, 1.09	0.9534	*Descriptive analysis of proportions*	Data-on-file, TOPAZ-1 CSR

Table A3a Results of TOPAZ-1 (NCT03875235)			
Grade ≥3 (IA-2, DCO 11 Aug 2021)	GemCis	342	77.8% (73.0, 82.1)

*95% CIs for differences not directly available in TOPAZ-1 CSR or EPAR. Estimated by AZ Nordics based on formula for confidence interval for the difference in proportions.

Confidence interval = $(p_1 – p_2) +/- z*\sqrt{(p_1(1-p_1)/n_1 + p_2(1-p_2)/n_2)}$, where p_1, p_2: sample 1 proportion, sample 2 proportion; z: the z-critical value based on the confidence level; and n_1, n_2: sample 1 size, sample 2 size. Relative risks for AE proportions also estimated with formulas.

Appendix E Safety data for intervention and comparator(s)

Data on adverse events were obtained from the TOPAZ-1 Clinical Study Report. See also section 7.3.

Category of adverse event	Durvalumb + GemCis (n = 338)	Placebo + GemCis (n = 342)
Any AE	336 (99.4)	338 (98.8)
Any AE possibly related to any study medication	314 (85.2)	308 (70.5)
Any AE of CTCAE Grade 3 or higher	256 (75.7)	266 (77.8)
Any AE of CTCAE Grade 3 or higher, possibly related to any study medication	212 (62.7)	222 (64.9)
Any AE of maximum CTCAE Grade 3 or 4	249 (73.7)	257 (75.1)
Any AE of maximum CTCAE Grade 3 or 4, possibly related to any study medication	211 (62.4)	221 (64.6)
Any AE with outcome of death	12 (3.6)	14 (4.1)
Any AE with outcome of death, possibly related to any study medication	2 (0.6)	1 (0.3)
Any SAE (including events with outcome of death)	160 (47.3)	149 (43.6)
Any SAE (including events with outcome of death), possibly related to any study medication	53 (15.7)	59 (17.3)
Any AE leading to discontinuation of study treatment	44 (13.0)	52 (15.2)
Any AE leading to discontinuation of durvalumab or placebo	21 (6.2)	18 (5.3)
Any AE leading to discontinuation of Gem and/or Cis	43 (12.7)	47 (13.7)
Any AE leading to discontinuation of study treatment, possibly related to any study medication	30 (8.9)	39 (11.4)
Any imAE	43 (12.7)	16 (4.7)
Any imAE, possibly related to any study medication	38 (11.2)	14 (4.1)

imAE: Immune-mediated adverse event
Note: Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted in each of those categories.

Appendix F Comparative analysis of efficacy and safety

Given that a single head-to-head study formed the basis of the application, no meta-analysis or indirect treatment comparisons were used in the submission.

Appendix G Extrapolation

This appendix describes how extrapolation and parameterization was performed. We are starting with the primary endpoint OS and will then move on to parametrizations and extrapolations for PFS and TTD.

12.1.1 Overall survival

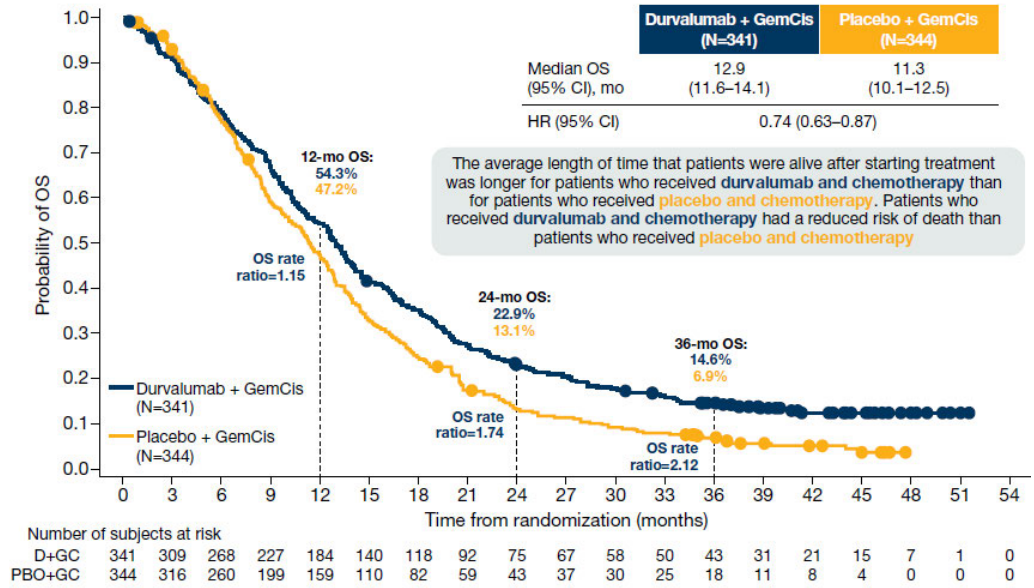
12.1.1.1 Proportional hazard

The proportional hazards assumption was tested for the standard parametric modelling. Schoenfeld residuals results do not show a clear trend over time [redacted] and the associated statistical test for proportionality shows a p-value that is not significant (p=0.069); this means that the hypothesis that the proportional hazard assumptions (PHA) hold cannot be rejected based on p-value alone. While the PHA cannot be refuted by the p-value of Schoenfeld' residuals, the log-cumulative hazards plots and Kaplan Meier curves in [redacted] and Figure 43 show that the curves cross each other at 6 months, which indicates that proportional hazard does not hold, and PHA was deemed to be violated, and independent models were used. Parametric distributions were fit to individual patient data for OS for each treatment arm separately.

[redacted]

[redacted]

Figure 43: OS Kaplan Meier curve of durvalumab + GemCis versus GemCis (23rd October 2023 cut-off (66))



CI, confidence interval; GemCis, gemcitabine+cisplatin; HR, hazard ratio; mo, months; OS, overall survival; PBO, placebo

12.1.1.2 Survival extrapolations for OS

Parametric distributions were fit to individual patient data for OS for each treatment arm separately, as the proportional hazards assumption does not hold (crossing curves).

AIC and BIC criterion were computed to assess the goodness-of-fit of the extrapolations to trial data. The values are reported in Table 66.

Table 66: AIC/BIC for each treatment arm (OS Oct 2023 cut-off from TOPAZ-1 trial)

	GemCis		Durvalumab + GemCis	
Model	AIC	BIC	AIC	BIC
Weibull	2347.7	2318.2	2317.0	2322.0
Generalized gamma	2299.1	2310.6	2302.4	2313.9
Gamma	2301.1	2308.8	2310.4	2318.0
Log-logistic	2293.4	2301.1	2292.0	2299.7
Gompertz	2339.1	2346.7	2318.4	2326.1
Log-normal	2314.5	2322.2	2309.3	2316.9
Exponential	2347.7	2351.5	2317.0	2320.8
Spline 1 knots, scale = hazard	2299.0	2310.5	2304.0	2315.4
Spline 2 knots, scale = hazard	2293.1	2308.5	2291.0	2306.3
Spline 3 knots, scale = hazard	2294.1	2313.3	2288.5	2307.6
Spline 1 knots, scale = odds	2290.1	2301.6	2292.1	2303.6
Spline 2 knots, scale = odds	2292.1	2307.4	2291.9	2307.2
Spline 3 knots, scale = odds	2293.7	2312.9	2288.5	2307.6
Spline 1 knots, scale = normal	2295.1	2306.7	2298.5	2310.0
Spline 2 knots, scale = normal	2293.0	2308.3	2293.7	2309.0
Spline 3 knots, scale = normal	2293.6	2312.8	2288.6	2307.7

Abbreviations: AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion, GemCis: gemcitabine + cisplatin
Highlighted row indicates model with lowest AIC/BIC

The loglogistic distribution appears to be the best fitting distribution for each treatment arm. Nevertheless, the AIC and BIC statistics are close (difference <5 points AIC) for most of the distributions. Therefore, assessing long-term survival plausibility was important for the selection of the most appropriate distribution for OS, as selecting the best distribution based on AIC/BIC might lead to underestimation of 5-year survival rates (see below).

Figure 44 and Figure 45 present the standard parametric distributions obtained for each treatment arm, as well as the two best fitting spline distributions for each treatment arm.

Figure 44: OS extrapolations: GemCis (comparator) from TOPAZ-1 trial

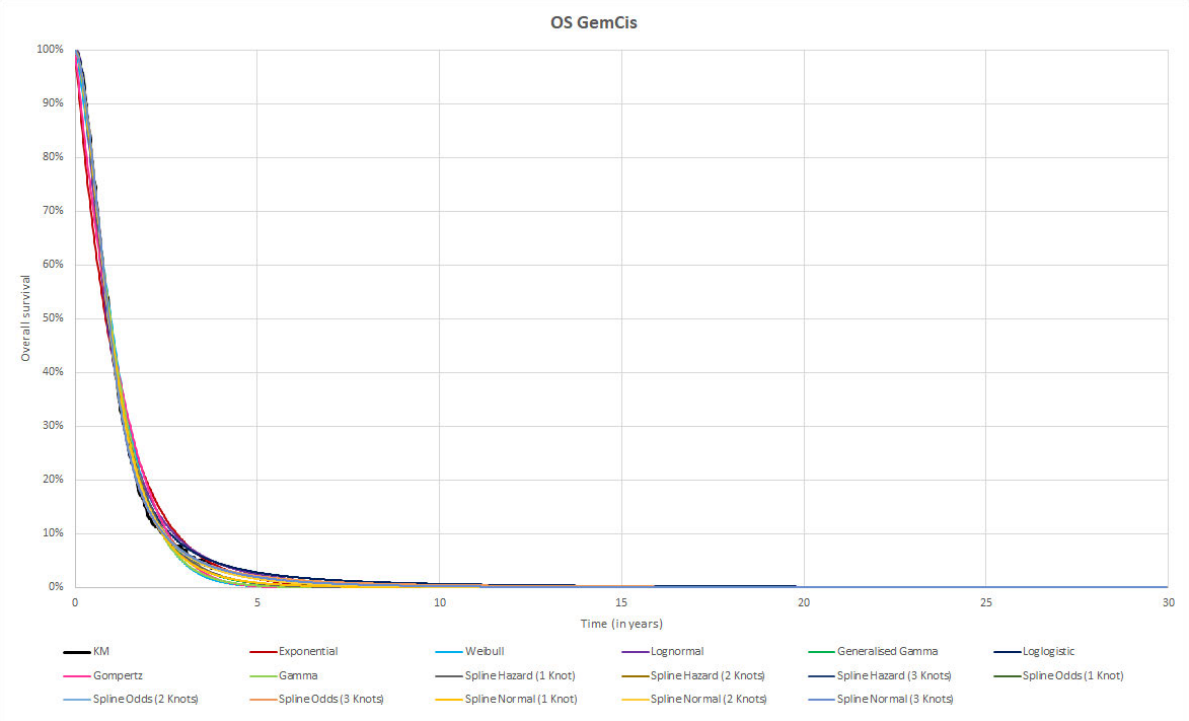


Figure 45: OS extrapolations: durvalumab + GemCis (intervention) from TOPAZ-1 trial

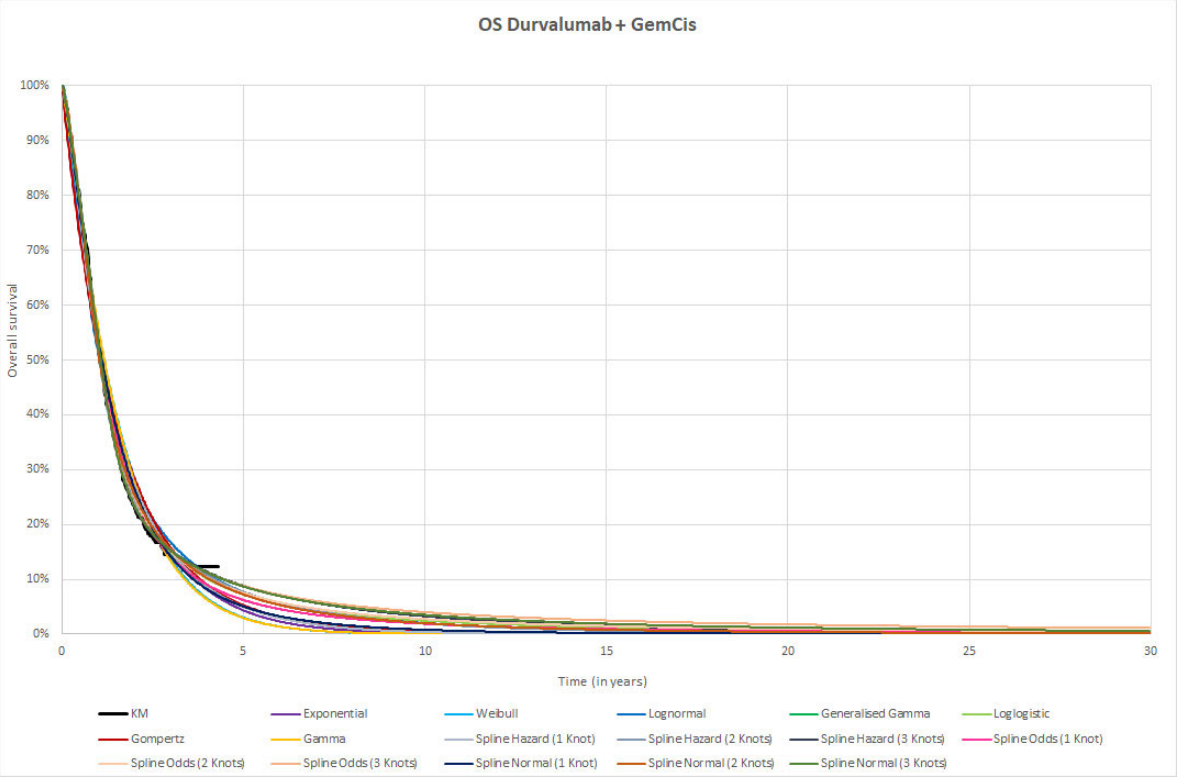


Table 67 summarizes survival rates by distribution for each treatment arm, with comparison to RWE.

Table 67: Overall survival rates (survival extrapolations from TOPAZ-1 and external RWE data)

Distribution	GemCis			Durvalumab + GemCis		
	2-year survival rate	3-year survival rate	5-year survival rate	2-year survival rate	3-year survival rate	5-year survival rate
Exponential	19.29%	8.47%	1.63%	28.62%	15.31%	4.38%
Log-normal	17.56%	8.24%	2.47%	27.54%	16.80%	7.75%
Log-logistic	16.22%	7.72%	2.83%	26.08%	15.37%	7.29%
Weibull	16.68%	4.58%	0.22%	28.38%	13.85%	3.06%
Gompertz	18.66%	5.84%	0.22%	28.46%	15.86%	5.34%
Generalized gamma	16.17%	5.65%	0.77%	27.18%	14.83%	5.14%
Gamma	16.03%	4.73%	0.36%	27.90%	13.44%	2.99%
Spline 1 knot odds	14.79%	6.17%	1.88%	25.44%	14.25%	6.26%
Spline 1 knot normal	15.49%	5.39%	0.90%	26.64%	14.25%	5.09%
ENSCCA Registry data (127)	-	8.4%	1.8%	-	-	-
SEER Registry data (iCCA) (108)	-	-	3%	-	-	-

Abbreviations: ENSCCA: European network for the Study of Cholangiocarcinoma, iCCA: Intrahepatic cholangiocarcinoma, RWE: Real world evidence

There is variability in the long-term survival rates obtained with the different distributions, especially for GemCis in the long-term. 5-year survival rates are estimated as high as 2.83% with the log-logistic (best statistical fit), and as low as 0.22% with the Gompertz and the Weibull distribution. Therefore, the long-term survival estimates from GemCis was compared to real-world evidence.

5-year survival rates from among patients receiving treatment for unresectable cholangio-carcinoma were 1.8% in the ENSCCA database and 3% in the SEER data for iCCA. These rates highlight that there are advanced BTC patients who can experience long-term survival, and the distributions with the best fit to the Kaplan-Meier data may underestimate or overestimate long-term survival. Real-world survival rates from ENSCCA Registry data are comparable to 3 and 5-year rates obtained with the log-logistic, log-normal, and spline 1 knot odds distributions, justifying the use of distributions such as these that reflect higher long-term survival. The SEER iCCA 5-year data are closest to the lognormal and log-logistic distributions. According to AIC/BIC criteria, the log-loglogistic was the best fitting parametric distribution and spline odds 1 knot the best fitting spline function. For the durvalumab + GemCis arm, the log-logistic model is best according to BIC while the spline odds 3 knots is best to according to AIC. Generalized gamma or gamma are the second best parametric distributions, but have less good correspondence to the ENSCCA and SEER iCCA data.

12.1.1.3 Curve selection

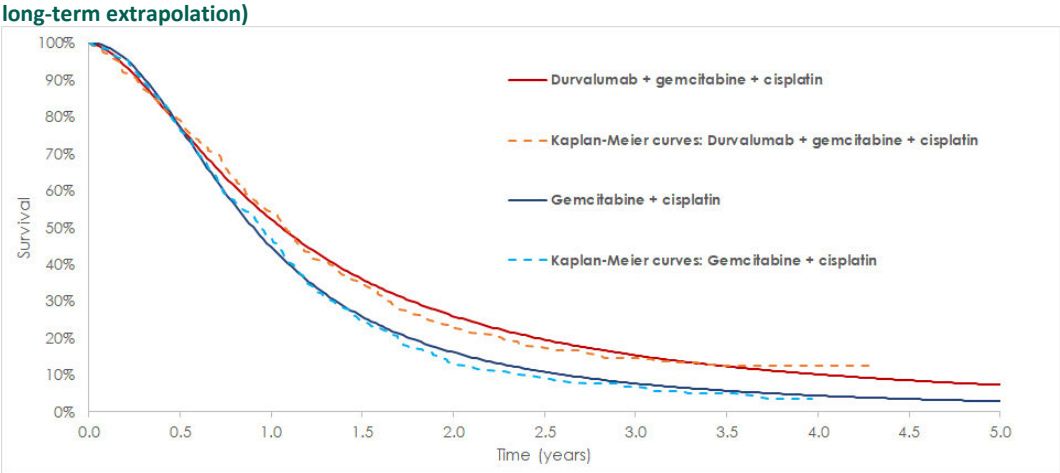
Based on long-term survival rates (ENSCCA) and the goodness-of-fit of the different curves, the log-logistic distribution was selected for both treatment arms. It estimates 5-year survival at 2.83% for GemCis, which reflects the long-term survival of patients in European RWE in in the US SEER data reasonably well as described above. This distribution is also one of the best fitting curves according to AIC and BIC for both treatment arms, as the AIC is within the 5 points of the best fitting curve for each treatment arm (a 5 points difference is commonly not considered as significant). For scenario analysis, the Gamma and spline hazard 3 knots were selected for both treatment arms to explore the impact of selecting alternative distributions with good fit according to AIC and BIC. Most of the spline distributions have AIC and BIC values within 5 points of each other, so the choice between different spine functions has a limited impact on the results.

Based on these results, the following distributions, presented in Figure 27, were selected:

- For GemCis, log-logistic was selected for base case analysis, and Gamma and spline hazard 3 knots for scenario analysis
- For durvalumab + GemCis, log-logistic was selected for reference analysis, and Gamma and spline hazard 3 knots for scenario analysis
    - For the long-term OS extrapolation in the durvalumab arm, the parametric extrapolation is used up to 43 months based on median follow-up, and the approach used beyond that is described above in sections 8.3.1.2 and 8.3.1.3.

In the model, the user can select any extrapolation for OS for either treatment arm. There is also an option to apply a piecewise approach to OS, to explore the impact of using the Kaplan Meier curve until a cut-off timepoint selected by the user, and the extrapolation after the cut-off. Switching directly to the extrapolation from the cut-off time point onwards may result in jumps or sudden drops in OS curve, which would be implausible. To avoid this, after the cut-off the *risk (hazard) of death* of the survival extrapolation is applied to the Kaplan-Meier survival. The maximum time until which the Kaplan-Meier curve can be used is the end of trial follow-up for the endpoint.

Figure 46: OS selected distributions for each treatment arm from TOPAZ-1 trial (before the application of long-term extrapolation)



Abbreviations: OS: Overall Survival

12.1.2 Progression-free survival

12.1.2.1 Proportional hazard

PFS was modelled independently of OS as is standard in partitioned survival models. Table 68 provides descriptive statistics of PFS data from TOPAZ-1 and shows that a higher proportion of patients in GemCis treatment arm experienced a PFS event over the trial follow-up (86% versus 81% for durvalumab + GemCis). Given the high event rate in both arms, the PFS data can be considered mature. Figure 49 shows the PFS Kaplan Meier for each treatment arm.

Table 68: PFS time to event data (October 2021 cut-off from TOPAZ-1 trial)

	Total number of events N - %	Median time to event (Months)
Durvalumab + GemCis (n = 341)	276 (81%)	7.23 CI = (6.74 ; 7.43)
GemCis (n=344)	297 (86%)	5.75 CI = (5.55 ; 6.74)

Although the results from the Schoenfeld residuals do not show a clear trend over time, and the associated statistical test for proportionality shows a p-value that is not significant (p=0.108) (Figure 47); this means that the hypothesis that the assumptions hold cannot be rejected based on p-value alone. However, Figure 48 and Figure 49 show that the log-cumulative hazard curves and PFS curves and cross each other and the PFS curves are overlapping up until 4.5 months, which indicates that proportional hazard does not hold, and PHA was deemed to be violated, and independent models were used.

Figure 47: Schoenfeld's residuals plot (p-value: 0.108 > 0.05)

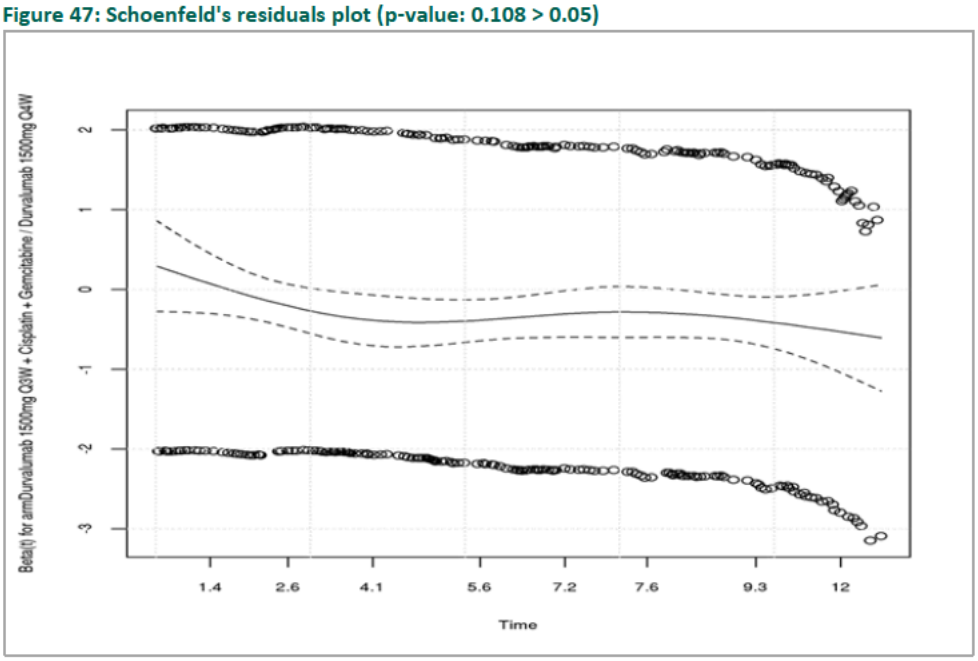


Figure 48: Log-cumulative hazard plot PFS

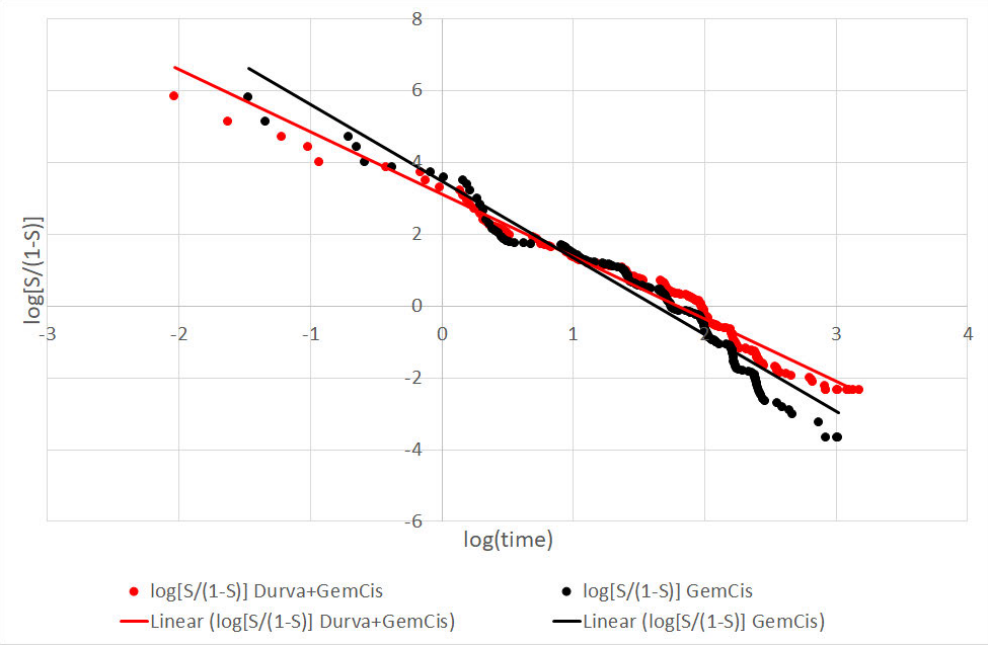
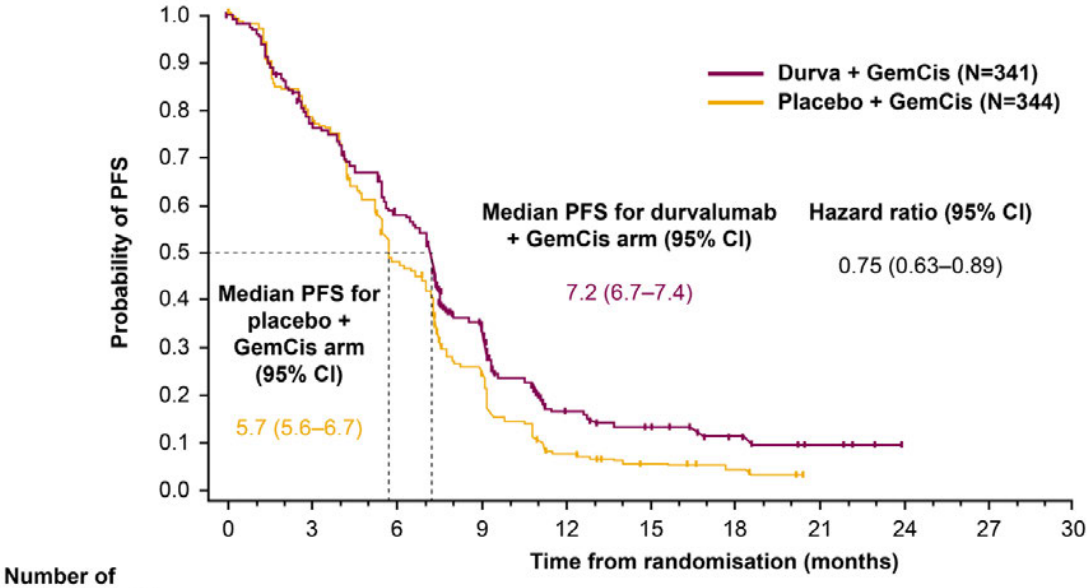


Figure 49: PFS Kaplan Meier curve of durvalumab + GemCis versus GemCis (August 2021 cut-off



Number of subjects at risk									
Durva + GemCis	341	258	189	100	38	25	15	5	0
Placebo + GemCis	344	255	149	71	17	7	4	0	0

12.1.2.2 Survival extrapolations for PFS

The AIC and BIC criteria were calculated to assess the goodness-of-fit of the extrapolations to the trial data. The values are reported in Table 69.

Table 69: AIC and BIC for each treatment arm (PFS)

	GemCis		Durvalumab +GemCis	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Weibull	1,650	1,658	1,712	1,719
Generalized gamma	1,652	1,663	1,710	1,722
Gamma	1,652	1,660	1,708	1,716
Log-logistic	1,673	1,680	1,713	1,720
Gompertz	1,681	1,689	1,734	1,740
Log-normal	1,687	1,694	1,729	1,736
Exponential	1,738	1,742	1,744	1,748
Spline 1 knots, scale = hazard	1,652	1,664	1,712	1,724
Spline 2 knots, scale = hazard	1,653	1,668	1,711	1,726
Spline 3 knots, scale = hazard	1,638	1,658	1,679	1,698
Spline 1 knots, scale = odds	1,653	1,665	1,704	1,715
Spline 2 knots, scale = odds	1,643	1,657	1,701	1,716
Spline 3 knots, scale = odds	1,637	1,657	1,684	1,703
Spline 1 knots, scale = normal	1,651	1,662	1,706	1,717
Spline 2 knots, scale = normal	1,649	1,664	1,707	1,723
Spline 3 knots, scale = normal	1,639	1,658	1,689	1,708

Abbreviations: AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion
Highlighted row indicates model with lowest AIC/BIC

Compared to standard parametric models, spline models enable hazard and survival functions with complex shapes to be more accurately modelled. Figure 48 shows that the log-cumulative hazard plots are not straight lines for either treatment. In line with this, in general the spline models showed better statistical fit than standard parametric models.

Results shows that the Spline hazards 3 knots distribution appears to be the best fitting for durvalumab + GemCis and second-best fitting for GemCis.

Regarding standard parametric distributions, the lowest AIC/BIC were obtained with the Gamma for durvalumab + GemCis; this distribution had the second lowest AIC/BIC among standard parametric distributions for GemCis. Figure 50 and Figure 51 show the extrapolations obtained for each treatment arm and includes all parametric distributions and the best spline-based distribution based on AIC and BIC and visual adequacy.

Figure 50: PFS extrapolations - GemCis (TOPAZ-1 trial – August 2021)

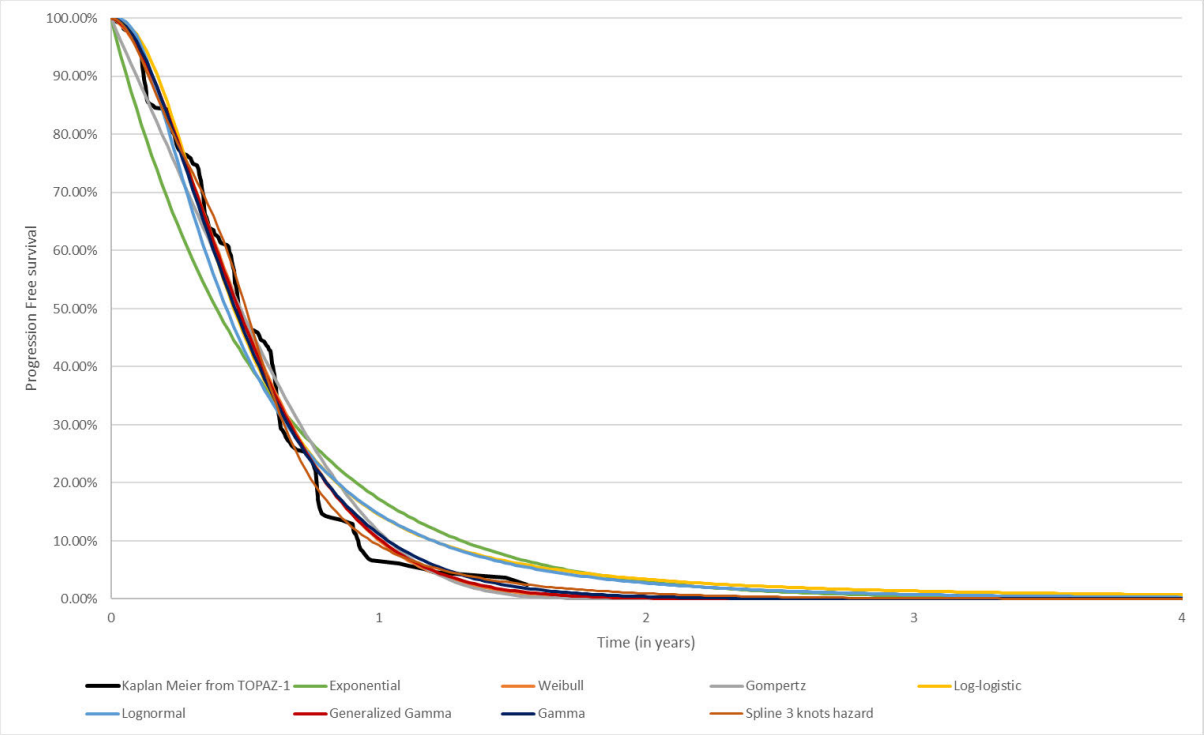


Figure 51: PFS extrapolations - durvalumab + GemCis (TOPAZ-1 trial – August 2021)

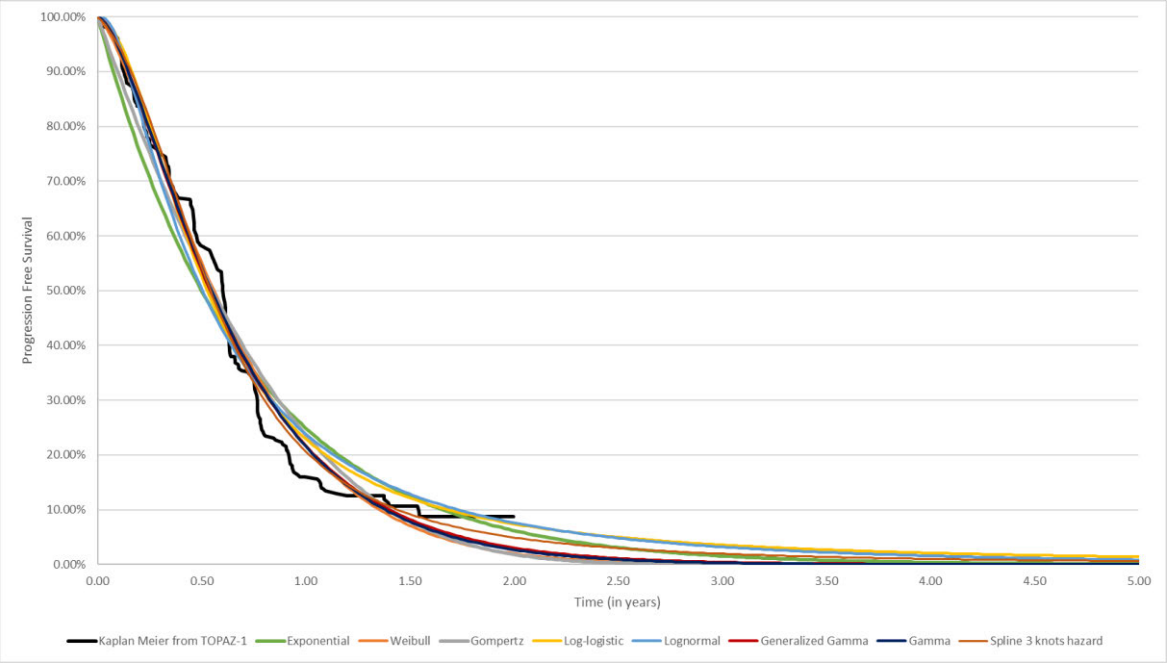


Table 70 summarizes survival rates at 6, 12 and 24 months by distribution for each treatment arm.

Table 70: Progression Free survival rates (survival extrapolations from TOPAZ-1 – August 2021)

Distribution	GemCis			Durvalumab + GemCis		
	6-months PFS rate	12-months PFS rate	24-months PFS rate	6-months PFS rate	12-months PFS rate	24-months PFS rate
Exponential	41.71%	17.40%	3.03%	50.03%	25.03%	6.26%
Log-normal	42.92%	14.65%	3.41%	50.46%	23.95%	7.67%
Log-logistic	45.50%	14.79%	2.79%	52.72%	23.06%	7.46%
Weibull	48.05%	10.33%	0.09%	55.28%	21.89%	2.04%
Gompertz	48.63%	11.79%	0.00%	54.00%	23.81%	1.89%
Generalized gamma	47.46%	10.51%	0.15%	53.91%	21.82%	3.11%
Gamma	46.07%	11.31%	0.41%	54.37%	21.71%	2.73%
Spline hazards 3 knots	51.05%	9.32%	0.98%	59.02%	18.22%	7.25%
TOPAZ-1	47.2%	6.6%	-	58.3%	16.0%	-

In line with the good fit to the Kaplan-Meier data based on the AIC/BIC criterion, the spline hazards 3 knots model shows the closest alignment of all distributions in Table 70 with PFS landmark data from TOPAZ-1, in both arms.

Considering longer-term PFS predictions for GemCis, the log-normal distribution predicted the most optimistic PFS (24-months PFS rate of 3.41%), and the Gompertz the least optimistic (0%). The Spline hazards 3 knots distribution (second best statistical fit) also estimated a conservative 24-month PFS rate of 0.98%. For durvalumab + GemCis, the log-normal distribution predicted the most optimistic PFS (24-months PFS rate of 7.67%), and again the best fitting Spline hazard 3 knots distribution estimated slightly lower 24-month PFS of 7.25%.

12.1.2.3 Curve selection

Based on the AIC/BIC goodness-of-fit to the mature TOPAZ-1 PFS data, as well as the plausibility of long-term extrapolations, the Spline hazards 3 knots distribution for durvalumab + GemCis and for GemCis was selected (Figure 52). This distribution minimizes AIC/BIC statistics and leads to more conservative long-term PFS rates compared to several standard parametric functions.

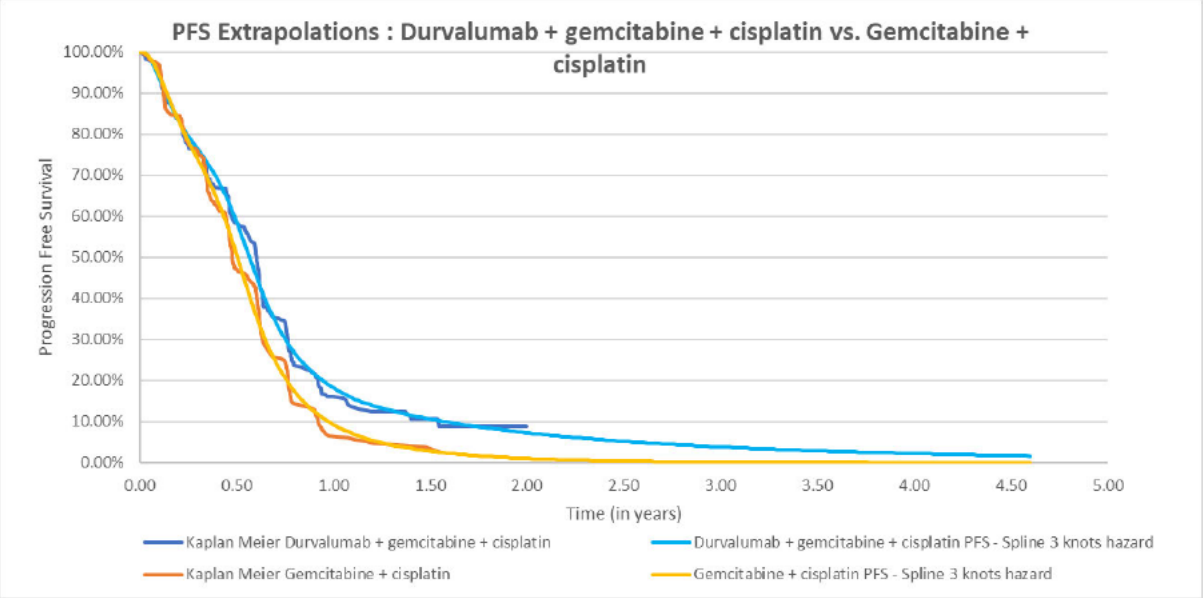
For scenario analyses, the best-fitting standard parametric distribution for durvalumab + GemCis and the second-best for GemCis (Gamma) was selected for both treatment arms.

In summary:

- For GemCis, the Spline hazards 3 knots distribution was selected for the base case analysis, and the Gamma distribution as scenario analysis
- For durvalumab + GemCis, the Spline hazards 3 knots was selected for base case analysis, and Gamma for scenario analysis

In the model, the user can select any distribution for PFS for either treatment arm. There is also an option to apply a piecewise approach to PFS, to explore the impact of using the Kaplan Meier curve until cut-off and the extrapolation after cut-off. The method applied is the same as for the OS piecewise option.

Figure 52: PFS selected distributions for both treatment arms (TOPAZ-1 trial – August 2021)



Abbreviations: PFS : Progression-Free Survival

12.1.2.4 Time to treatment discontinuation

A larger proportion of patients discontinued placebo in the GemCis treatment arm compared to durvalumab in the durvalumab + GemCis arm (94% versus 80%). In line with this, median TTD was longer in the durvalumab + GemCis treatment arm (7.52 months versus 6.51 months in GemCis arm). Table 71 provides descriptive statistics of TTD data from TOPAZ-1 clinical trial.

Table 71: TTD time-to-event data (August 2021 cut-off from TOPAZ-1 trial)

	Total number of events N - %	Median time to event (Months)
durvalumab (from durvalumab + GemCis arm) (n = 341)	275 (80%)	7.52 CI = (6.97 ; 7.75)
Placebo (from placebo + GemCis arm) (n=344)	322 (94%)	6.51 CI = (5.88 ; 7.16)

Abbreviations: CI: Confidence Interval, TTD: Time to treatment discontinuation

AIC and BIC criterion values were calculated to assess the goodness-of-fit of the TTD extrapolations to the trial data. The values are reported in Table 72.

Table 72: AIC and BIC for each treatment arm (TTD)

	GemCis		Durvalumab + GemCis	
Model	**AIC**	**BIC**	**AIC**	**BIC**
Weibull	1,809	1,816	1,762	1,769
Generalized gamma	1,810	1,822	1,761	1,773
Gamma	1,818	1,825	1,759	1,767
Log-logistic	1,848	1,856	1,761	1,769
Log-normal	1,884	1,892	1,791	1,798
Exponential	1,899	1,903	1,793	1,797
Gompertz	1,833	1,840	N/A	N/A
Spline 1 knots, scale = hazard	1,809	1,821	1,763	1,774
Spline 2 knots, scale = hazard	1,810	1,825	1,754	1,769
Spline 3 knots, scale = hazard	1,797	1,816	1,727	1,747
Spline 1 knots, scale = odds	1,815	1,827	1,749	1,760
Spline 2 knots, scale = odds	1,796	1,811	1,751	1,766
Spline 3 knots, scale = odds	1,796	1,815	1,730	1749
Spline 1 knot, scale = normal*	N/A	N/A	N/A	N/A
Spline 2 knots, scale = normal	1,804	1,820	1,757	1,772
Spline 3 knots, scale = normal	1,798	1,818	1,731	1,750

Abbreviations: AIC: Akaike Information Criterion – BIC: Bayesian Information Criterion. Highlighted row indicates model with lowest AIC/BIC.

**It was not possible to fit a spline 1 knot normal scale model due to convergence issues*

The curve selection was based on AIC/BIC goodness-of-fit and consistency with PFS, the log-logistic distribution was selected for durvalumab + GemCis and the spline odds 3-knots for the GemCis.

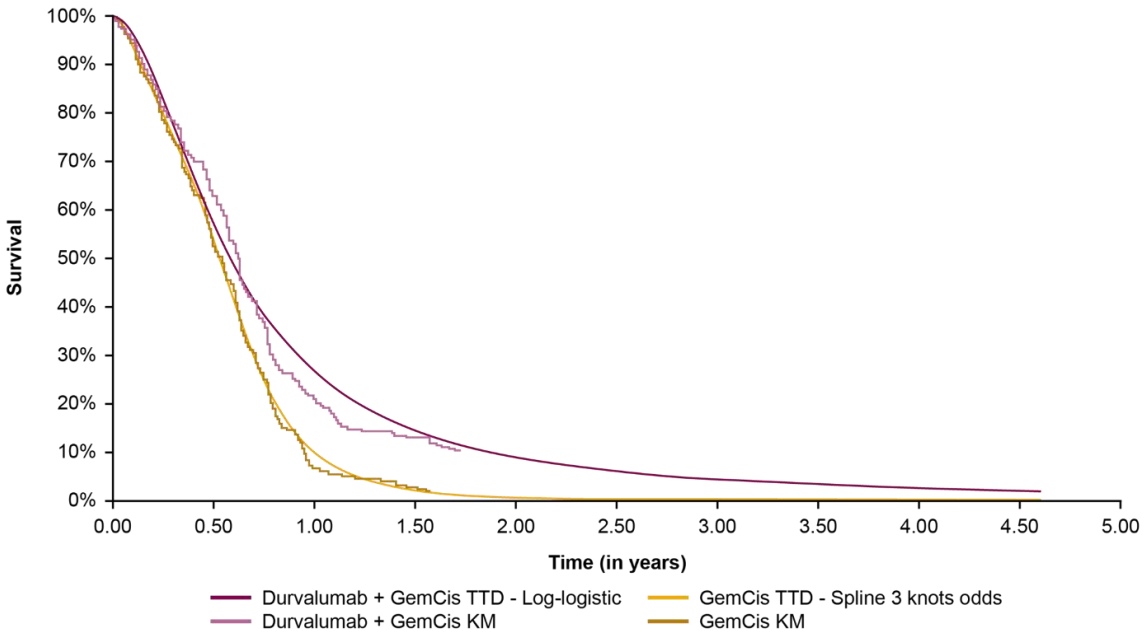
The Gamma distribution was tested in a scenario analysis for GemCis. A piecewise approach was applied for durvalumab + GemCis as scenario analysis to evaluate the impact of using the Kaplan Meier curve until the cut-off point, and the log-logistic extrapolation after cut-off. This approach allows the direct use of Kaplan Meier data, and therefore reduces uncertainty associated with the extrapolation. A cut-off of 15 months was chosen because 15 months corresponds to the appearance of a plateau in the TTD KM curve. The method applied is the same as for the OS piecewise option.

The reason for choosing different distributions for TTD for the two arms is primarily to achieve consistency with PFS, as the treatment is indicated to be continued until progression or unacceptable toxicity. The Spline hazards 3 knots PFS extrapolation for durvalumab + GemCis predicts 7.25% of patients as progression-free at 24-months; this aligns most closely with the 24-month predictions for patients remaining on treatment using the exponential (8.17%) and log-logistic (8.90%) curves, of which the log-logistic showed better fit to the Kaplan-Meier data as per

AIC/BIC. In addition, the Spline hazards 3 knots PFS extrapolation for durvalumab + GemCis predicts 1.3% of patients as progression-free at 60-months, compared with 1.7% for the TTD using a log-logistic distribution. In contrast, the best-fitting spline odds 3 knots distribution for TTD predicts 9.44% and 3.1% of patients remaining on treatment at 24 and 60 months, respectively, predictions which are less plausible based on the PFS estimates compared to the log-logistic.

The selected base case TTD extrapolations are summarised in Figure 53. For durvalumab + GemCis, the log-logistic distribution was selected, whilst for GemCis the Spline odds 3 knots distribution was selected (10).

Figure 53: Summary of selected TTD distributions



***Abbreviations**: TTD: time to treatment discontinuation.*
***Source:** AstraZeneca Data on File (10)*

Appendix H Literature search for HRQoL data

As clinical trial data from TOPAZ-1 were used for the HRQoL data and health state values, no literature search was performed.

Appendix I Mapping of HRQoL data

Introduction

This appendix summarises the background, methods and results of the descriptive summary and regression analysis of EQ-5D-5L health state utility data as assessed in the TOPAZ study.

The results of this analysis are intended to provide evidence for use in cost-effectiveness models to support health technology assessment appraisal and reimbursement submissions.

The utility values used for analysis were mapped from EQ5D-5L profiles to the Danish value set, applying the algorithm detailed in Jensen et al. (112).

This report is based on data from the following data cut-off: DCO 1 Aug 2021. The analysis was performed on the ITT analysis set of TOPAZ, consisting of all completed EQ5D measures (non-missing responses across all 5 domains). However, EQ5D responses recorded subsequent to being censored for progression were not included in the model.

Patients with missing baseline data were included; the frequencies of those patients are detailed below.

Subjects with missing baseline measurement

Treatment	Missing Baseline
Durva + Gem + Cis	56
Placebo + Gem + Cis	60

Background

The EQ-5D is a standardised measure of self-reported health, developed by the EuroQol Group. There are 5 dimensions or domains: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. In the 5-level ('5L') version of the questionnaire, there are 5 possible levels of response that a subject can give for each dimension: no, mild, moderate, severe, and severe / unable to.

An EQ-5D profile consists of a 5 digit value, with each digit representing a subject's response for each domain. The EQ-5D profiles can be converted to a health state utility using a country-specific value set. The value set assigns weights to each level in each dimension that represent the society's preference towards different states of health. The EQ-5D health state utility is constructed such that 1 is the maximum value and it represents 'full health'. A value of 0 corresponds to a quality of life equivalent to being dead, and negative values are possible which represent a quality of life worse than death.

In TOPAZ, the EQ-5D-5L was administered according to the following schedule of assessments:
"Insert text describing assessment schedule from CSP/CSR"

Methods

A descriptive summary of the EQ-5D health state utilities by arm and study visit, and by arm and progression status is provided in the appendix.

A mixed model for repeated measures (MMRM) was used to model EQ-5D health state utilities. Models were fitted using the restricted maximum likelihood method (REML) with the following covariates included as fixed effects:

- (Randomised) Treatment
- Progression status (pre-progression, post-progression)
- Treatment + Progression status
- Treatment * Progression status (Both terms and their interaction included)

To allow for the correlation over time of the repeated utility measurements within subjects, covariance structures were specified.

The hierarchy of covariance structures proceeds from most to least flexible:

1. Unstructured – each visit is allowed to have a different variance, and each combination of visits is allowed to have a different covariance.
2. Toeplitz with heterogeneity – each visit is allowed to have a different variance, covariances between measurements depend on how many visits apart they are.
3. Autoregressive, order 1 (AR(1)) with heterogeneity – each visit is allowed to have a different variance, and covariances decrease based on how many visits apart they are. Covariances decrease towards zero as the number of visits between observations increases.
4. Toeplitz – as above for number 2, but each visit shares the same variance.
5. Autoregression, order 1 (AR(1)) – as above for number 3, but each visit shares the same variance.

This report presents the results from the models using the first covariance structure in the sequence that successfully converges for all models (i.e. for each of the 4 covariate options). If for a particular set of covariates none of the models converged, then no results are presented for that model, and the remaining model results are based on the most flexible covariance structure for which the models converged.

For each model, parameter estimates, and marginal ('least square') means are presented including 95% confidence intervals. This information is also saved as a spreadsheet file including covariance matrices for the parameters. Confidence intervals are based on robust standard error estimates.

Analysis was performed in R 4.1.0 using the mmrm package 0.2.2 for model fitting.

Results

The results presented in this section are from models including a Autoregressive - order 1 with Heterogeneity covariance structure.

Goodness of fit

Description	Covariates	converges	AIC	BIC
Progression status	pffl	TRUE	**-5297.8**	-5182.2

Description	Covariates	converges	AIC	BIC
Treatment + Progression status	TRT01P+pffl	TRUE	-5291.2	-5175.6
Treatment + Progression status	TRT01P*pffl	TRUE	-5286.8	-5171.2
Treatment	TRT01P	TRUE	-5270.3	-5154.6

The best fitting model in terms of AIC was the model including a term for pffl.

Model terms: TRT01P

Parameter Estimates

Parameter	Estimate	SE	DF	p_value	95% LCL	95% UCL
(Intercept)	0.864	0.008	718.1	<0.001	0.847	0.880
Durva + Gem + Cis	0.010	0.011	677.4	0.380	-0.012	0.032

Marginal means

TRT01P	Estimate	SE	DF	95% LCL	95% UCL
Placebo + Gem + Cis	0.864	0.008	718.1	0.847	0.880
Durva + Gem + Cis	0.873	0.007	613.4	0.859	0.888

Model terms: pffl

Parameter Estimates

Parameter	Estimate	SE	DF	p_value	95% LCL	95% UCL
(Intercept)	0.873	0.006	647.4	<0.001	0.862	0.884
Post prog	-0.117	0.021	263.7	<0.001	-0.158	-0.077

Marginal means

pffl	Estimate	SE	DF	95% LCL	95% UCL
Pre prog	0.873	0.006	647.4	0.862	0.884
Post prog	0.756	0.021	244.5	0.714	0.798

Model terms: TRT01P+pffl

Parameter Estimates

Parameter	Estimate	SE	DF	p_value	95% LCL	95% UCL
(Intercept)	0.869	0.008	706.8	<0.001	0.852	0.885
Durva + Gem + Cis	0.009	0.011	685.2	0.424	-0.013	0.031
Post prog	-0.117	0.021	264.6	<0.001	-0.158	-0.076

Marginal means

TRT01P	pffl	Estimate	SE	DF	95% LCL	95% UCL
Placebo + Gem + Cis	Pre prog	0.869	0.008	706.8	0.852	0.885
Durva + Gem + Cis	Pre prog	0.877	0.007	604.9	0.863	0.892
Placebo + Gem + Cis	Post prog	0.752	0.022	262.7	0.709	0.795
Durva + Gem + Cis	Post prog	0.761	0.022	263.5	0.717	0.804

Model terms: TRT01P*pffl

Parameter Estimates

Parameter	Estimate	SE	DF	p_value	95% LCL	95% UCL
(Intercept)	0.869	0.008	688.2	<0.001	0.852	0.885
Durva + Gem + Cis	0.009	0.011	651.7	0.422	-0.013	0.031
Post prog	-0.117	0.028	279.7	<0.001	-0.172	-0.062
Durva + Gem + Cis: Post prog	0.000	0.042	261.7	0.991	-0.081	0.082

Marginal means

TRT01P	pffl	Estimate	SE	DF	95% LCL	95% UCL
Placebo + Gem + Cis	Pre prog	0.869	0.008	688.2	0.852	0.885
Durva + Gem + Cis	Pre prog	0.877	0.007	589.8	0.863	0.892
Placebo + Gem + Cis	Post prog	0.751	0.028	257.1	0.695	0.807
Durva + Gem + Cis	Post prog	0.761	0.032	228.1	0.698	0.824

Appendix J Probabilistic sensitivity analyses

To account for the joint uncertainty associated to parameter estimates, a probabilistic analysis was conducted, randomly sampling model inputs from specified probability distributions. Standard deviations, standard errors and 95% confidence intervals were included when available. When these values were not reported, the standard error was introduced as 10% variation of the default value, this variation being assumed as reasonable for uncertainty. In the Excel model, the PSA parameters can be found on the worksheet *data_parameters*, columns S to X.

We have as far as possible used study data to inform the SE estimates in the PSA. For efficacy parameters or the utilities, the standard errors were estimated based on study data. For AE dis-utilities, resource use or duration of subsequent therapy, the SE was estimated based on the assumption that the SE was 10% of the parameter value. These three groups of parameters have minimal impact on the model outcomes. We consider that 10% variation for these parameters gives quite realistic estimates for informing the PSA. Regarding the subsequent treatment durations, for example, many of the treatments used have fixed treatment durations (e.g. chemotherapies used for 6 cycles) so not large variations are expected. In addition, the patient monitoring approach is not expected to vary substantially, since it is already adjusted by health state. Usually, patient monitoring is dependent on the patient status (progression free or progressed), and it is expected to be quite standard over time.

A technique known as Cholesky decomposition was used in order to provide correlated draws from a multivariate normal distribution. The Cholesky decomposition technique is for example described in the textbook by Briggs et al. (2006), chapter 4.4.2. For other parameters, such as resource use or utilities, we assumed independent probability distributions.

Parameters included in the PSA are presented in the table below.

Detailed table of parameters included in the PSA

Parameter	Probability distribution	Parameter value	Rational
Survival curve PFS Durvalumab + GemCis	Inclusion in PSA based on Cholesky decomposition		AZ TOPAZ Interim analysis
Survival curve OS Durvalumab + GemCis			AZ TOPAZ DCO3
Survival curve TTD Durvalumab + GemCis			AZ TOPAZ Interim analysis
Survival curve PFS GemCis			AZ TOPAZ Interim analysis
Survival curve OS GemCis			AZ TOPAZ DCO3
Survival curve TTD GemCis			AZ TOPAZ Interim analysis
Age	Normal	$\alpha = 62.4$ $\beta = 6.24$	TOPAZ-1 trial
Discount rate costs	Beta	$\alpha = 96.47$ $\beta = 2659.68$	Finance ministry guidelines for base case discount rate

Parameter	Probability distribution	Parameter value	Rational
Discount rate outcomes	Beta	α = 96.47 β = 2659.68	Finance ministry guidelines for base case discount rate
Male proportion	Beta	α = 49.10 β = 48.32	TOPAZ-1 trial
Height	Normal	α = 1.71 β = 0.171	Danish expert input
Weight	Normal	α = 77.30 β = 7.73	Danish expert input
Creatinine	Normal	α = 85.3 β = 8.53	TOPAZ-1 trial
Body surface area	Normal	α = 1.92 β = 0.192	Mosteller's formula
Utility: PFS	Beta	α = 11.83 β = 1.72	TOPAZ EQ5D-5L Danish utilities
Utility: PPS	Beta	α = 23.64 β = 7.63	TOPAZ EQ5D-5L Danish utilities
OS SMR: 5-10 years	Normal	α = 4.64 β = 0.40	Elgenidy et al. (2022)
OS SMR: > 10 years	Normal	α = 1.44 β = 0.33	Elgenidy et al. (2022)
OS landmark rates	Normal	Alfa and beta based on mean landmark and standard deviation	
Frequency of adverse events	Beta	Alfa and beta based on mean frequency and standard deviation	
AE frequency durva + GemCis: Neutropenia	Beta	α = 79.70 β = 316.81	TOPAZ-1 trial
AE frequency durva + GemCis: Anaemia	Beta	α = 76.06 β = 244.88	TOPAZ-1 trial
AE frequency durva + GemCis: Thrombocytopenia	Beta	α = 95.25 β = 1931.40	TOPAZ-1 trial
AE frequency durva + GemCis: Cholangitis	Beta	α = 93.44 β = 1344.03	TOPAZ-1 trial
AE frequency durva + GemCis: Neutrophil count decrease	Beta	α = 78.79 β = 296.40	TOPAZ-1 trial
AE frequency durva + GemCis: Platelet count decrease	Beta	α = 90.10 β = 829.31	TOPAZ-1 trial
AE frequency durva + GemCis: White blood cell count decrease	Beta	α = 95.56 β = 2076.17	TOPAZ-1 trial

Parameter	Probability distribution	Parameter value	Rational
AE frequency GemCis: Neutropenia	Beta	α = 78.69 β = 294.24	TOPAZ-1 trial
AE frequency GemCis: Anaemia	Beta	α = 77.28 β = 266.17	TOPAZ-1 trial
AE frequency GemCis: Thrombocytopenia	Beta	α = 94.65 β = 1691.15	TOPAZ-1 trial
AE frequency GemCis: Cholangitis	Beta	α = 96.77 β = 2927.23	TOPAZ-1 trial
AE frequency GemCis: Neutrophil count decrease	Beta	α = 74.04 β = 214.06	TOPAZ-1 trial
AE frequency GemCis: Platelet count decrease	Beta	α = 91.42 β = 984.06	TOPAZ-1 trial
AE frequency GemCis: White blood cell count decrease	Beta	α = 94.14 β = 1529.00	TOPAZ-1 trial
Disutility: Neutropenia	Beta	α = 1.60 β = 24.70	TA439
Disutility: Anaemia	Beta	α = 0.14 β = 1.55	TA439
Disutility: Thrombocytopenia	Beta	α = 0.14 β = 1.55	TA571
Disutility: Cholangitis	Beta	α = 0.14 β = 1.55	TA722
Disutility: Neutrophil count decrease	Beta	α = 1.60 β = 24.70	Assumed same as neutropenia
Disutility: Platelet count decrease	Beta	α = 0.14 β = 1.55	Assumed same as thrombocytopenia
Disutility: White blood cell count decreased	Beta	α = 1.60 β = 24.70	Assumed same as neutropenia
RDI - Durvalumab (in GemCis combo)	Beta	α = 1890.72 β = 72.64	TOPAZ-1 trial
RDI - Gemcitabine (in durvalumab combo)	Beta	α = 1512.98 β = 169.98	TOPAZ-1 trial
RDI - Cisplatin (in durvalumab combo)	Beta	α = 1508.55 β = 158.36	TOPAZ-1 trial
RDI - Gemcitabine (CisGem)	Beta	α = 1573.57 β = 192.50	TOPAZ-1 trial

Parameter	Probability distribution	Parameter value	Rational
RDI - Cisplatin (CisGem)	Beta	α = 1580.48 β = 193.35	TOPAZ-1 trial
Healthcare resource use 1L: Oncol. visit	Gamma	α = 100 β = 0.03	Expert input
Healthcare resource use 1L: Nurse visit	Gamma	α = 100 β = 0.03	Expert input
Healthcare resource use 1L: Emergency visit	Gamma	α = 100 β = 0.005	Expert input
Healthcare resource use 1L: Biliary stent or replacement	Gamma	α = 100 β = 0.0025	Expert input
Healthcare resource use 1L: CT scan	Gamma	α = 100 β = 0.0033	Expert input
Healthcare resource use 1L: MRI scan	Gamma	α = 0 β = 0	Expert input
Healthcare resource use 1L: Liver function test	Gamma	α = 100 β = 0.0175	Expert input
Healthcare resource use 1L: Renal function test	Gamma	α = 100 β = 0.0175	Expert input
Healthcare resource use 1L: Complete blood count	Gamma	α = 100 β = 0.04	Expert input
Healthcare resource use 1L: Biochemistry tests	Gamma	α = 100 β = 0.0175	Expert input
Healthcare resource use 2L: Oncol. visit	Gamma	α = 100 β = 0.02	Expert input
Healthcare resource use 2L: Nurse visit	Gamma	α = 100 β = 0.02	Expert input
Healthcare resource use 2L: Emergency visit	Gamma	α = 100 β = 0.007	Expert input
Healthcare resource use 2L: Biliary stent or replacement	Gamma	α = 100 β = 0.0025	Expert input
Healthcare resource use 2L: CT scan	Gamma	α = 100 β = 0.0033	Expert input

Parameter	Probability distribution	Parameter value	Rational
Healthcare resource use 2L: MRI scan	Gamma	α = 0 β = 0	Expert input
Healthcare resource use 2L: Liver function test	Gamma	α = 100 β = 0.02	Expert input
Healthcare resource use 2L: Renal function test	Gamma	α = 100 β = 0.02	Expert input
Healthcare resource use 2L: Complete blood count	Gamma	α = 100 β = 0.02	Expert input
Healthcare resource use 2L: Biochemistry tests	Gamma	α = 100 β = 0.02	Expert input
Healthcare resource use 3L: Oncol. visit	Gamma	α = 100 β = 0.02	Expert input
Healthcare resource use 3L: Nurse visit	Gamma	α = 100 β = 0.02	Expert input
Healthcare resource use 3L: Emergency visit	Gamma	α = 100 β = 0.007	Expert input
Healthcare resource use 3L: Biliary stent or replacement	Gamma	α = 100 β = 0.0025	Expert input
Healthcare resource use 3L: CT scan	Gamma	α = 100 β = 0.0033	Expert input
Healthcare resource use 3L: MRI scan	Gamma	α = 0 β = 0	Expert input
Healthcare resource use 3L: Liver function test	Gamma	α = 100 β = 0.02	Expert input
Healthcare resource use 3L: Renal function test	Gamma	α = 100 β = 0.02	Expert input
Healthcare resource use 3L: Complete blood count	Gamma	α = 100 β = 0.02	Expert input
Healthcare resource use 3L: Biochemistry tests	Gamma	α = 100 β = 0.02	Expert input
HCRU No treatment: Oncol. visit	Gamma	α = 100 β = 0.0033	Expert input

Parameter	Probability distribution	Parameter value	Rational
HCRU No treatment: Nurse visit	Gamma	α = 100 β = 0.0033	Expert input
HCRU No treatment: Emergency visit	Gamma	α = 100 β = 0.0015	Expert input
HCRU No treatment: Biliary stent or replacement	Gamma	α = 100 β = 0.0017	Expert input
Proportion of patients receiving 2L subsequent therapy after Durvalumab + GemCis	Beta	α = 48.79 β = 47.45	TOPAZ-1 trial
Proportion of patients receiving 2L subsequent therapy after GemCis	Beta	α = 45.66 β = 39.21	TOPAZ-1 trial
Proportion of patients receiving 3L subsequent therapy after Durvalumab + GemCis	Beta	α = 80.20 β = 329.00	TOPAZ-1 trial
Proportion of patients receiving 3L subsequent therapy after GemCis	Beta	α = 75.36 β = 233.48	TOPAZ-1 trial
% receiving FOL in 2L after Durvalumab + GemCis	Beta	α = 52.78 β = 60.11	TOPAZ-1 trial
% receiving FOL in 2L after GemCis	Beta	α = 56.63 β = 75.25	TOPAZ-1 trial
% receiving Pt-based chemo in 2L after Durvalumab + GemCis	Beta	α = 71.80 β = 185.34	TOPAZ-1 trial
% receiving Pt-based chemo in 2L after GemCis	Beta	α = 78.02 β = 280.44	TOPAZ-1 trial
% receiving Teysuno (TS One) in 2L after Durvalumab + GemCis	Beta	α = 88.85 β = 716.03	TOPAZ-1 trial
% receiving Teysuno (TS One) in 2L after GemCis	Beta	α = 86.34 β = 551.80	TOPAZ-1 trial

Parameter	Probability distribution	Parameter value	Rational
% receiving capecitabine in 2L after Durvalumab + GemCis	Beta	α = 86.23 β = 546.11	TOPAZ-1 trial
% receiving capecitabine in 2L after GemCis	Beta	α = 85.15 β = 493.85	TOPAZ-1 trial
% receiving immunotherapy in 2L after Durvalumab + GemCis	Beta	α = 99.34 β = 15199.66	TOPAZ-1 trial
% receiving immunotherapy in 2L after GemCis	Beta	α = 92.87 β = 1222.80	TOPAZ-1 trial
Duration FOL in 2L after Durvalumab + GemCis	Normal	α = 1.90 β = 0.19	Caparica (2019), Lamarca (2021)
Duration FOL in 2L after GemCis	Normal	α = 1.90 β = 0.19	Caparica (2019), Lamarca (2021)
Duration Pt-based chemo in 2L after Durvalumab + GemCis	Normal	α = 4.67 β = 0.47	TOPAZ-1 trial
Duration Pt-based chemo in 2L after GemCis	Normal	α = 4.67 β = 0.47	TOPAZ-1 trial
Duration Teysuno (TS-One) in 2L after Durvalumab + GemCis	Normal	α = 2.50 β = 0.25	Inoue (2021)
Duration Teysuno (TS-One) in 2L after GemCis	Normal	α = 2.50 β = 0.25	Inoue (2021)
Duration capecitabine in 2L after Durvalumab + GemCis	Normal	α = 4.67 β = 0.47	TOPAZ-1 trial
Duration capecitabine in 2L after GemCis	Normal	α = 4.67 β = 0.47	TOPAZ-1 trial
Duration immunotherapy in 2L after Durvalumab + GemCis	Normal	α = 3.72 β = 0.37	TOPAZ-1 trial, Kim (2020)
Duration immunotherapy in 2L after GemCis	Normal	α = 3.72 β = 0.37	TOPAZ-1 trial, Kim (2020)
% receiving FOL in 3L after	Beta	α = 49.50 β = 49.50	TOPAZ-1 trial

Parameter	Probability distribution	Parameter value	Rational
Durvalumab + GemCis			
% receiving FOL in 3L after GemCis	Beta	α = 62.00 β = 102.79	TOPAZ-1 trial
% receiving Pt-based chemo in 3L after Durvalumab + GemCis	Beta	α = 78.16 β = 283.34	TOPAZ-1 trial
% receiving Pt-based chemo in 3L after GemCis	Beta	α = 82.00 β = 378.11	TOPAZ-1 trial
% receiving Teysuno (TS One) in 3L after Durvalumab + GemCis	Beta	α = 91.81 β = 1040.52	TOPAZ-1 trial
% receiving Teysuno (TS One) in 3L after GemCis	Beta	α = 85.00 β = 487.33	TOPAZ-1 trial
% receiving capecitabine in 3L after Durvalumab + GemCis	Beta	α = 87.72 β = 633.51	TOPAZ-1 trial
% receiving capecitabine in 3L after GemCis	Beta	α = 81.00 β = 349.58	TOPAZ-1 trial
% receiving immunotherapy in 3L after Durvalumab + GemCis	Beta	α = 91.81 β = 1040.52	TOPAZ-1 trial
% receiving immunotherapy in 3L after GemCis	Beta	α = 89.00 β = 728.18	TOPAZ-1 trial
Duration FOL in 3L after Durvalumab + GemCis	Normal	α = 1.90 β = 0.19	Caparica (2019), Lamarca (2021)
Duration FOL in 3L after GemCis	Normal	α = 1.90 β = 0.19	Caparica (2019), Lamarca (2021)
Duration Pt-based chemo in 3L after Durvalumab + GemCis	Normal	α = 4.67 β = 0.47	TOPAZ-1 trial
Duration Pt-based chemo in 3L after GemCis	Normal	α = 4.67 β = 0.47	TOPAZ-1 trial
Duration Teysuno (TS-One) in 3L after Durvalumab + GemCis	Normal	α = 2.50 β = 0.25	Inoue (2021)

Parameter	Probability distribution	Parameter value	Rational
Duration Teysuno (TS-One) in 3L after GemCis	Normal	α = 2.50 β = 0.25	Inoue (2021)
Duration capecitabine in 3L after Durvalumab + GemCis	Normal	α = 4.67 β = 0.47	TOPAZ-1 trial
Duration capecitabine in 3L after GemCis	Normal	α = 4.67 β = 0.47	TOPAZ-1 trial
Duration immunotherapy in 3L after Durvalumab + GemCis	Normal	α = 1.77 β = 0.18	TOPAZ-1 trial
Duration immunotherapy in 3L after GemCis	Normal	α = 1.77 β = 0.18	TOPAZ-1 trial

Appendix K Studies and data for analysis of tail development

Landmark OS for the studies included in the data for the long-term OS development described in section 8.3.1.2. Only studies with OS landmark data available for 36 months or more were included in the calculations of the relative risks.

IO studies and data for analysis of tail development

Study	Arm	OS24	OS36	OS48	OS60	Reference
NSCLC trials:						
CheckMate 017/057	E	26.9%	17.1%	14.2%	13.4%	Borghaei et al. 2021 (98)
CheckMate 017/057	C	13.5%	8.2%	4.6%	2.6%	Borghaei et al. 2021 (98)
OAK	E	29.8%	21.0%	15.5%		Mazieres et al. 2020 (128)
OAK	C	21.5%	12.4%	8.7%		Mazieres et al. 2020 (128)
KEYNOTE-010	E	35.0%	22.9%	17.5%	15.6%	Herbst et al. 2021 (129)
KEYNOTE-010	C	15.7%	11.0%	8.8%	6.5%	Herbst et al. 2022 (129)
KEYNOTE-042	E	38.9%	25.3%	20.2%	16.6%	de Castro et al. 2022 (130)
KEYNOTE-042	C	28.6%	16.7%	12.3%	8.5%	de Castro et al. 2022 (130)
Impower 110	E	42.2%	29.2%	24.0%		Jassem et al. 2021 (131)
Impower 110	C	31.0%	26.0%	21.5%		Jassem et al. 2021 (131)
CheckMate 227	E	40.0%	33.0%	28.0%	24.0%	Hellman et al. 2019, Brahmer et al. 2023 (132, 133)
CheckMate 227	C	33.0%	22.0%	18.0%	14.0%	Hellman et al. 2019, Brahmer et al. 2023 (132, 133)
Impower 132	E	39.6%	27.1%			Nishio et al. 2021 (134)
Impower 132	C	35.3%	26.4%			Nishio et al. 2021 (134)
KEYNOTE-024	E	51.0%	43.7%	35.8%	31.9%	Reck et al. 2021 (135)
KEYNOTE-024	C	33.0%	24.7%	19.8%	16.3%	Reck et al. 2021 (135)
KEYNOTE-189	E	45.7%	31.3%	23.6%	19.4%	Garassino et al. 2023 (78)
KEYNOTE-189	C	27.3%	17.4%	13.8%	11.3%	Garassino et al. 2023 (78)
KEYNOTE-407	E	36.0%	29.9%	21.9%	18.4%	Novello et al. 2023 (77)
KEYNOTE-407	C	30.8%	18.6%	12.3%	9.7%	Novello et al. 2023 (77)
Impower 130	E	39.6%				West et al. 2019 (136)
Impower 130	C	30.3%				West et al. 2019 (136)
Impower 131	E	32.5%				Jotte et al. 2020 (137)
Impower 131	C	26.6%				Jotte et al. 2020 (137)
CheckMate 026	*No rates presented*					Carbone et al. 2017 (138)
CheckMate 9LA	E	38.0%	27.0%			Paz-Ares et al. 2022 (99)
CheckMate 9LA	C	26.0%	19.0%			Paz-Ares et al. 2022 (99)
EMPOWER-Lung 1	*No rates presented*					Garassino et al. 2023 (139)
NCT01285609	E	24.0%				Govindan 2017 (140)
NCT01285609	C	18.0%				Govindan 2017 (140)
Melanoma trials:						
CA184-024	E	28.9%	21.3%	19.1%	18.2%	Maio et al. 2015 (141)
CA184-024	C	18.8%	12.1%	9.7%	8.8%	Maio et al. 2015 (141)
CheckMate 066	E	58.0%	51.0%	44.0%	39.0%	Robert et al. 2020 (142)
CheckMate 066	C	26.0%	22.0%	18.0%	17.0%	Robert et al. 2020 (142)

Study	Arm	OS24	OS36	OS48	OS60	Reference
CheckMate 037	E	38.7%				Larkin et al. 2018 (143)
CheckMate 037	C	33.9%				Larkin et al. 2018 (143)
UC trials:						
KEYNOTE-045	E	26.9%	20.7%	16.7%		Fradet et al., Balar at al. 2022 (144, 145)
KEYNOTE-045	C	14.3%	11.0%	10.1%		Fradet et al., Balar at al. 2022 (144, 145)
Imvigor 211	E	22.4%	14.8%			Van der Heijden et al. 2021 (146)
Imvigor 211	C	13.1%	7.6%			Van der Heijden et al. 2021 (146)
KEYNOTE-361	E	37.1%	26.1%			Powles et al. 2021 (147)
KEYNOTE-361	C	32.1%	22.0%			Powles et al. 2021 (147)
Imvigor 130	*Indication withdrawn*					Galsky et al. 2020 (148)

C: Control; E: Experimental; OS24: Landmark OS at 24 months; OS36: Landmark OS at 36 months, etc.