Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission** from AstraZeneca:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. AMMF – The Cholangiocarcinoma Charity
   b. British Liver Trust
   c. Cholangiocarcinoma UK

4. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group

5. **External Assessment Report – factual accuracy check**

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Dr Mairéad McNamara – clinical expert, nominated by AstraZeneca
   b. Andrea Sheardown – patient expert, nominated by AMMF – The Cholangiocarcinoma Charity
   c. Helen Morement – patient expert, nominated by AMMF – The Cholangiocarcinoma Charity (see document 3a.)

8. **Technical engagement responses from stakeholders:**
   a. Cholangiocarcinoma UK

9. **External Assessment Group critique of company response to technical engagement** prepared by Liverpool Reviews and Implementation Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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Document B

Company evidence submission

February 2023

File name	Version	Contains confidential information	Date
ID4031_DurvalumabaBTC_NICE_DocB_Final fully redacted	1.0	Yes (AiC/CiC)	13th February 2023

Contents

Tables and figures

Abbreviations

AE	Adverse event
AIC	Akaike Information Criterion
AoV	Ampulla of Vater
AQS	Absolute QALY shortfall
BIC	Bayesian Information Criterion
BNF	British National Formulary
BOR	Best objective response
BSA	Body surface area
BSG	British Society of Gastroenterology
BTC	Biliary tract cancer
CA	Carbohydrate antigen
CC	Cholangiocarcinoma
CD	Cluster of differentiation
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CR	Complete response
CSP	Clinical study protocol
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
D	Durvalumab 1,500 mg
DCO	Data cut-off
DCR	Disease control rate
DoR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EHCC	Extrahepatic cholangiocarcinoma
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-3L/5L	EuroQol-5 Dimensions-3 Levels /5 Levels
ESMO	European Society for Medical Oncology
FA	Final analysis
FAS	Full analysis set
GBC	Gallbladder cancer
Gem/Cis	Gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2
GHS	Global Health Status
GP	General practitioner
HCRU	Healthcare resource use
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQoL	Health-related quality of life
HSUV	Health state utility value
HTA	Health Technology Assessment
IA	Interim analysis
ICER	Incremental cost-effectiveness ratio
IDMC	Independent Data Monitoring Committee
IHCC	Intrahepatic cholangiocarcinoma
ILAP	Innovative Licensing and Access Pathway
imAE	Immune-mediated adverse event
IO	Immuno-oncology
IP	Investigational product
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
KM	Kaplan–Meier
LCHP	Log-cumulative hazard plots
LY	Life year
LYG	Life years gained
MCBS	Magnitude of Clinical Benefit Scale
MHRA	Medicines and Healthcare products Regulatory Agency

MMRM	Mixed model repeated measures
MoA	Mode of action
MRI	Magnetic resonance imaging
NA	Not applicable
NHB	Net health benefit
NHS	National Health Service
NMB	Net monetary benefit
ONS	Office for National Statistics
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressed disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PF	Progression-free
PFS	Progression-free survival
PGIS	Patient Global Impression of Severity
PHA	Proportional hazards assumption
PPS	Post-progression survival
PR	Partial response
PRO	Patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PS	Performance status

PQS	Proportional QALY shortfall
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QLQ-BIL21	21-Item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire
QLQ-C30	30-Item Core Quality of Life Questionnaire
QoL	Quality of life
QxW	Every x weeks
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RoW	Rest of the world
SAE	Serious adverse event
SAS	Safety analysis set
SLR	Systematic literature review
SoC	Standard of care
TAP	Tumour area positivity
TNM	Tumour-node-metastasis
TSD	Technical Support Document
TTD	Time to treatment discontinuation
VAS	Visual Analogue Scale
WHO	World Health Organization
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

- **This appraisal compares durvalumab with gemcitabine and cisplatin (D + Gem/Cis) with the current standard of care, gemcitabine and cisplatin (Gem/Cis) for the first-line treatment of patients with locally advanced, unresectable, or metastatic biliary tract cancer (BTC), including patients with recurrent disease after treatment with curative intent**
  - Durvalumab is a high-affinity, human, recombinant IgG1κ mAb that selectively blocks the interaction of programmed cell death ligand 1 (PD-L1), with receptors programmed cell death protein 1 (PD-1) and cluster of differentiation (CD)80[1]
  - Durvalumab (in combination with Gem/Cis) is the first immunotherapy to be approved for first-line locally advanced, unresectable, or metastatic BTC[2]
- **BTC is a collective term for a group of rare and aggressive cancers that form in the cells of the bile ducts which in the majority (up to 80%) of cases are not diagnosed until an advanced stage when curative treatment is unfeasible[3-5]**
- **Patients with locally advanced, unresectable, or metastatic BTC have limited treatment options and a very poor prognosis[6-8]**
  - Current first-line standard of care (SoC) for locally advanced, unresectable, or metastatic BTC is Gem/Cis[6]
  - Median overall survival (OS) with current SoC is <1 year; [7, 8] although there are limited UK-wide 5 year survival rates reported for locally advanced, unresectable, or metastatic BTC,[9, 10] it is expected that only a small proportion of patients survive for 5 years after diagnosis
  - There have been no new treatments approved for first line use in locally advanced, unresectable, or metastatic BTC in over 10 years
  - There is an unmet need for new therapies that are able to extend median and longer-term survival without substantial additional toxicity

- **D + Gem/Cis is the only licenced treatment for first line locally advanced, unresectable, or metastatic BTC in over a decade to demonstrate a statistically significant and clinically meaningful survival benefit versus SoC (placebo + Gem/Cis) (HR 0.80 [95% CI 0.66, 0.97] p=0.021 at the pre-specified IA-2 DCO [final formal analysis])[11, 12]**
  - The HR decreased to 0.76 (95% CI 0.64, 0.91) (a 24% reduction in the risk of death) with an additional 6.5 months of follow-up data, at which time overall maturity for OS was 76.9%[13, 14]
  - An OS treatment benefit with D + Gem/Cis was observed across all pre-defined subgroups (based on demographics, geographical region, primary tumour location, disease status, World Health Organization (WHO)/ Eastern Cooperative Oncology Group (ECOG) performance status (PS), and PD-L1 status)
  - Addition of D to Gem/Cis resulted in no detriment in QoL and a manageable safety profile consistent with the established safety profile of Gem/Cis
- **Treatment with D + Gem/Cis led to a doubling in the OS rate at 2 years compared with placebo + Gem/Cis (23.6% vs 11.5%), with a clear and sustained separation in OS Kaplan–Meier (KM) curves from 6 months at the most recent additional 6.5-month data cut-off (25 February 2022)[13, 14]**
  - Due to the magnitude of the clinical benefit seen in the TOPAZ-1 trial, D + Gem/Cis has been awarded an innovation passport and reviewed by the Medicines and Healthcare products Regulatory Agency (MHRA) as part of Project Orbis
  - D + Gem/Cis was included in the recently updated ESMO BTC guidelines, which recommend the combination should be considered for first-line advanced BTC patients, with a grade 4 Magnitude of Clinical Benefit Scale (MCBS) score, which is classified as a substantial clinical benefit
- **D + Gem/Cis is anticipated to replace Gem/Cis as the first-line treatment of choice for the broad licensed population of patients with locally advanced, unresectable, or metastatic BTC due to the substantial improvement in OS demonstrated in the TOPAZ-1 trial**

- Durvalumab is the first immunotherapy to be approved for first-line locally advanced, unresectable, or metastatic BTC treatment and is available for the broad licensed population immediately after diagnosis due to the lack of requirement for molecular testing

B.1.1 Decision problem

The objective of this single technology appraisal is to evaluate the clinical- and cost-effectiveness of durvalumab with gemcitabine and cisplatin (D + Gem/Cis) for the first-line treatment of locally advanced, unresectable, or metastatic (BTC).

The submission covers the technology's full marketing authorisation for this indication and, with the exception of the comparators, is in line with the scope issued by the National Institute for Health and Care Excellence (NICE). The comparator considered in the company submission is gemcitabine and cisplatin only (further details and rationale are provided in Table 1).

Table 1 summarises the decision problem addressed by the company submission.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with unresectable advanced or metastatic biliary tract cancer, including people with recurrent disease after treatment with curative intent	As per NICE scope	NA
Intervention	Durvalumab with gemcitabine and cisplatin	As per NICE scope	NA
Comparator(s)	Established clinical management without durvalumab including: • Gemcitabine with cisplatin • For people with poor kidney function: – Gemcitabine with oxaliplatin • For frailer people: – Gemcitabine alone – Fluorouracil (5-FU) alone – Capecitabine alone	Gemcitabine with cisplatin	**Patients with poor kidney function:** This population has not been considered in the submission as patients with poor kidney function are unable to tolerate cisplatin. ESMO guidelines for the management of BTC recommend that oxaliplatin is substituted for cisplatin where renal function is a concern[6]. Patients who are not able to receive cisplatin would therefore not be considered suitable candidates for D + Gem/Cis. In addition, the TOPAZ-1 study enrolled patients with a minimum CrCl >50 mL/min (Appendix M, Table 51) and therefore the data presented in this submission do not represent a population with poor kidney function. **Frail patients**: This patient population has not been considered in the submission. Frail patents are considered to be those with a PS >1. Frail patients are not expected to tolerate cisplatin and current ESMO guidelines recommend gemcitabine monotherapy for patients with a PS of 2.[6] Patients only considered eligible for Gem monotherapy would not therefore be considered suitable for D + Gem/Cis. Furthermore, the TOPAZ-1 study excluded patients with PS >1 (Appendix M, Table 51) and therefore the data presented in this submission do not represent a frail population.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			Based on the above, the only appropriate comparator for this submission is gemcitabine with cisplatin.
Outcomes	• Overall survival • Progression-free survival • Response rates (including overall response rates) • Time to treatment discontinuation • Adverse effects of treatment • Health-related quality of life	As per NICE scope	NA
Subgroups to be considered	• If evidence allows results by type of biliary tract cancer and level of PD-L1 expression will be considered	As per NICE scope	NA

Abbreviations: BTC, biliary tract cancer; CrCl, creatinine clearance; D, durvalumab 1,500 mg; ESMO, European Society for Medical Oncology; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; PD-L1, programmed cell death ligand-1; PS, performance status.

B.1.2 Description of the technology being evaluated

Details of the technology being appraised in the submission are provided in Table 2. The summary of product characteristics (SmPC) for durvalumab is provided in Appendix C.[2]

Table 2: Technology being evaluated

UK approved name and brand name	Durvalumab (IMFINZI®) in combination with gemcitabine and cisplatin
Mechanism of action	Durvalumab is a high-affinity, human, recombinant IgG1κ mAb that selectively blocks the interaction of PD-L1, with receptors, PD-1 and CD80.[1] In doing so, it releases the inhibition of immune responses in the tumour microenvironment, resulting in prolonged T-cell activation and anti-tumour activity.
Marketing authorisation/CE mark status	A marketing authorisation application (national procedure within Project Orbis) was submitted with the MHRA on 31 May 2022, with marketing authorisation in Great Britain granted on 25 January 2023.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	***Indication covered in this submission:*** IMFINZI in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with locally advanced, unresectable, or metastatic biliary tract cancer (BTC). ***Existing indications:*** • Durvalumab 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. • Durvalumab 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).
Method of administration and dosage	• Durvalumab 1,500 mg is administered as an intravenous infusion over 1 hour on Day 1 every 3 weeks for up to 8 cycles in combination with Gem/Cis, followed by 1,500 mg every 4 weeks as monotherapy[2] • Gemcitabine 1,000 mg/m^2 is administered as an intravenous infusion over 30 minutes on Day 1 and Day 8 every 21 days for 8 cycles[8, 15] • Cisplatin 25 mg/m^2 is administered as an intravenous infusion over 60 minutes on Day 1 and Day 8 every 21 days for 8 cycles[8, 15]
Additional tests or investigations	None
Acquisition cost (including VAT)	• Durvalumab is anticipated to be commercially available as a 120 mg vial at a list price of £592 per vial and as a 500 mg vial at a list price of £2,466 • Gemcitabine list price: £9.82 per 1000mg • Cisplatin list price: £15.62 per 100mg
Patient access scheme (if applicable)	There is a simple PAS agreed with NHS England which provides a [redacted] discount on the list price of durvalumab, and this is reflected in the submission. There is no PAS in place for gemcitabine or cisplatin.

Abbreviations: CD, cluster of differentiation; IgG1κ, immunoglobulin G1 kappa; mAb, monoclonal antibody; MHRA, Medicines and Healthcare Products Regulatory Agency; PAS, Patient Access Scheme; PD-1, programmed cell death protein 1, PD-L1, programmed cell death ligand 1.

B.1.3 Health condition and position of the technology in the treatment pathway

- Biliary tract cancer (BTC) is a collective term for a group of rare and aggressive cancers that form in the cells of the bile ducts[3]
- **Up to 80% of patients with BTC are diagnosed with locally advanced, unresectable, or metastatic disease, for which curative intent treatment is unfeasible[4, 5]**
  - In addition, up to 80% of patients who receive initial treatment with curative intent experience disease recurrence within two years[16, 17]
- In 2022 there were an estimated 2,307 incident cases of BTC in England,[18] of which 1,846 patients were estimated to have locally advanced, unresectable or metastatic disease[19]
- **Current first-line SoC for locally advanced, unresectable, or metastatic BTC is chemotherapy (Gem/Cis)[6] and there has been no licenced innovation in treatments for this population in >10 years**
  - Gem/Cis was recommended as the first-line treatment option for locally advanced, unresectable, or metastatic BTC in British Society of Gastroenterology (BSG) and European Society for Medical Oncology (ESMO) guidelines prior to the recent ESMO guideline update,[20, 21] which now also states **D + Gem/Cis should be considered for first-line locally advanced, unresectable, or metastatic BTC patients[6]**
  - Gem/Cis is the first-line treatment for the majority of patients in UK clinical practice as confirmed by clinical experts[19]
- **Patients with locally advanced, unresectable, or metastatic BTC have a poor prognosis, with median overall survival of <1 year[7, 8]**
  - Few patients survive for 5 years after their diagnosis, and, although there are limited UK-wide 5-year survival rates reported for locally advanced, unresectable, or metastatic BTC,[9, 10] it is expected that only a small proportion of patients survive for 5 years after diagnosis even on current standard of care (Gem/Cis)[22]

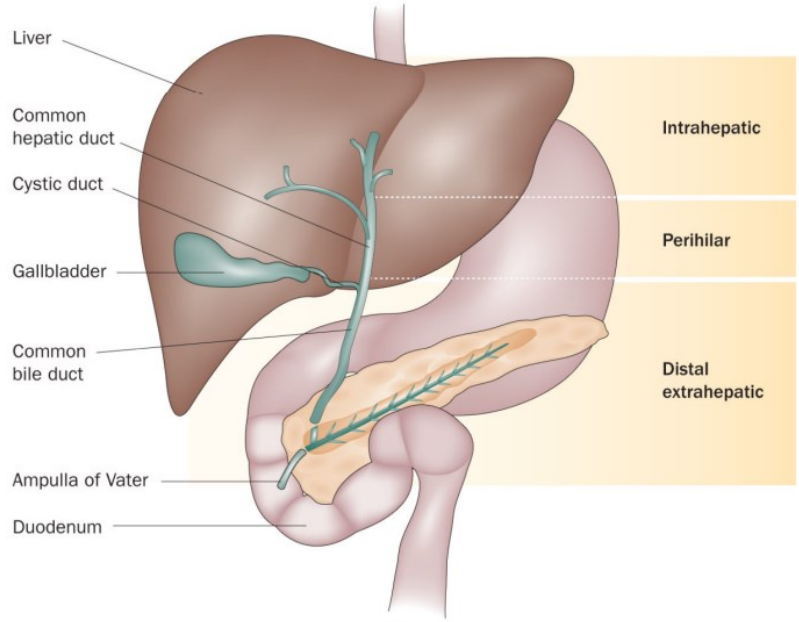
- **With no meaningful innovation in the last decade, there is a clear unmet need for additional treatment options that can improve survival without impacting on QoL and AE burden**
- **It is anticipated that D+ Gem/Cis will replace Gem/Cis as the first-line treatment of choice for locally advanced, unresectable, or metastatic BTC as recommended by ESMO[6]**
  - Eligible patients will be the broad locally advanced, unresectable, or metastatic BTC population who are eligible for Gem/Cis treatment and do not have a contraindication to immunotherapy
  - Treatment can be initiated immediately after diagnosis; there is no requirement for molecular testing

B.1.3.1 Disease overview

Biliary tract cancer (BTC) is a collective term for cancers that form in the cells of the bile ducts (cholangiocarcinoma [CC]), gallbladder, or ampulla of Vater (AoV, where the bile duct and pancreatic duct meet) (Figure 1). CC is one of the most common malignant tumours of the biliary tract and can be further subcategorised as follows:

- Intrahepatic CC (IHCC), originating in the bile ducts within the liver
- Extrahepatic CC (EHCC), which refers to both perihilar (originated where the left and right hepatic ducts join) and distal CC (originates in the bile ducts further away from the liver, including those running through the pancreas to the small intestine).

Figure 1: Anatomy of the biliary tract



Source: Blechacz et al. (2011).[23]

The strongest risk factors for BTC are drivers of chronic inflammation within the biliary system, including primary sclerosing cholangitis or cholelithiasis.[24] However, there are differences in risk factors between the BTC subtypes. For example, cirrhosis, parasitic fluke infection, hepatitis B and hepatitis C infection are associated with CC, while the development of gallstones and gallbladder polyps are risk factors associated with gall bladder cancer (GBC).[24]

Epidemiology

BTC is a rare condition. In England in 2022, there were an estimated 2,307 incident cases of BTC (incidence rate of 0.0043%),[18] of which 1,846 patients (80%) were estimated to have locally advanced, unresectable or metastatic disease.[19] Overall, in the UK, advanced BTC affects a similar proportion of men and women. [25] [25] Most cases of CC occur in patients aged >65 years,[26] while GBC is more common in patients aged 85–89 years of age.[27]

Burden of disease

Patients with locally advanced, unresectable, or metastatic BTC have a poor prognosis, with RCTs reporting median overall survival of <1 year with current standard of care (SoC),[7, 8] and although there are no UK-wide 5-year survival rates reported for locally advanced, unresectable, or metastatic BTC,[9, 10] it is expected that only a small proportion of patients survive for 5 years after diagnosis. A UK observational study in advanced BTC reported that the median survival for patients who received a gemcitabine-based chemotherapy was 12.5 months.[28]

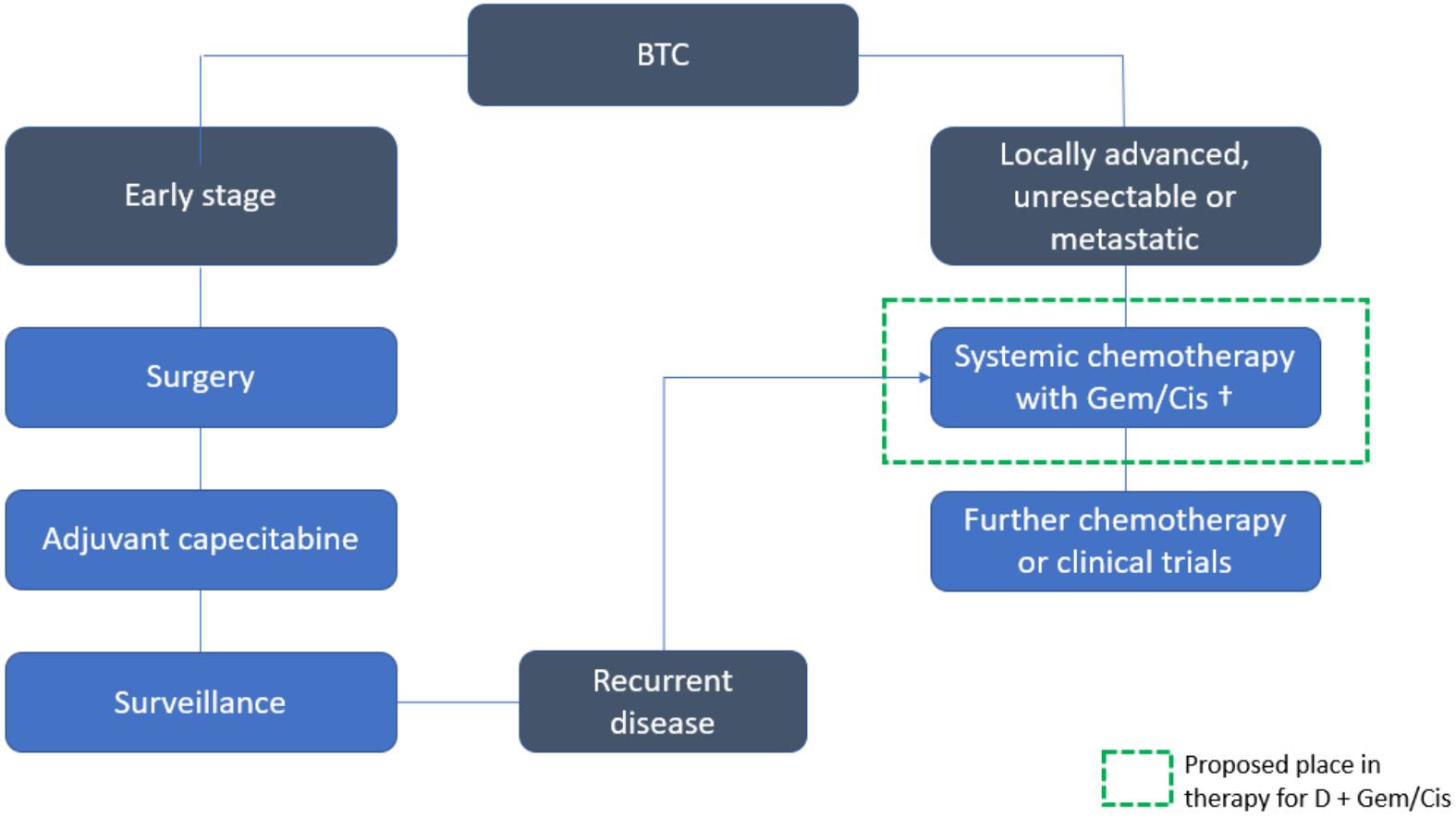
Patients also experience a substantial clinical and humanistic burden due to a rapid deterioration in their condition and an increase in associated signs and symptoms of disease, as well as treatment-related toxicity. [28-30] [28-30] As BTC progresses to an advanced stage, patients may experience symptoms such as jaundice (yellowing of the skin and eyes), cholangitis (inflammation of the bile duct system), itchy skin, dark urine and pale stools[31] which are associated with blockage of the bile duct.[32] Metastatic spread is also associated with additional symptoms depending on the site of metastasis. [33-35] [33-35] The high symptom burden can impact on physical functioning and emotional wellbeing. [28, 36-38] [28, 36-38]

Locally advanced, unresectable, or metastatic BTC patients may require informal caregiving to manage daily living, with caregivers often providing physical, practical, and emotional support to the patient.[39] Caregiving is associated with psychological and economic strains, resulting in diminishing wellbeing and increased stress on carers.[40] In addition, caring for a BTC patient may impact the ability to go to work, leading to financial strain and indirect economic costs. Evidence shows that caregiver burden is closely correlated to patient symptom burden, indicating treatments that improve or relieve patient symptoms would likely reduce caregiver burden, in addition to improving patient HRQoL.[41]

B.1.3.2 Current clinical pathway of care

The current clinical pathway of care is illustrated in Figure 2.

Figure 2: Current pathway of care for BTC with proposed durvalumab + Gem/Cis place in therapy



†Oxaliplatin may be given instead of cisplatin, particularly if there are concerns regarding kidney function. For patients in poor health (PS >1), single agent chemotherapy with gemcitabine is typically offered.
Abbreviations: BTC, biliary tract cancer; PS, performance status.
Source: Adapted from Vogel et al. (2022)[6] and verified with expert clinical opinion.[19]

Diagnosis and staging

Diagnosis of BTC at an early stage is challenging. Due to its anatomical location it is often not detected in routine physical exams, and symptoms may be absent or non-specific and initially attributed to other, more common causes.[32, 42] The diagnosis of BTC may consist of both imaging and pathological components including liver function testing, tumour marker testing (carbohydrate antigen 19–9 [CA 19–9], endoscopic retrograde cholangiopancreatography with or without biopsy.[43] Non-invasive imaging with ultrasound, computerised tomography (CT) scans and magnetic resonance imaging (MRI) combined with magnetic resonance cholangiopancreatography may also be performed.[43]

Disease staging aims to establish the extent of the cancer. It is usually based on MRI of the biliary tract and CT scans of the chest, given that the lungs and regional lymph nodes are the most common sites of distant metastasis.[33, 34, 44] BTC is staged using the American Joint Committee on Cancer tumour-node-metastasis (TNM) staging system or the number system.[44] The TNM system is subcategorised into the tumour (T)-stage, lymph node (N)-stage, and metastases (M)-stage, with lower stages reflecting early stage BTC and higher stages reflecting later stage disease.[45] For locally advanced or metastatic disease, treatment is limited to symptom management and prevention of further spread (i.e. disease is unresectable).

Molecular testing may occur at diagnosis with a view to establishing which later line treatments will be the most suitable, however molecular testing is not required for initiation of first-line treatment.

The vast majority of patients (up to 80%) are diagnosed with unresectable or metastatic disease, for which curative intent treatment is unfeasible.[4, 5] In addition, up to 80% of patients who receive initial treatment with curative intent experience disease recurrence within two years.[16, 17] There is therefore a need for effective and tolerable therapies for the vast majority of patients who will require treatment for advanced stage disease.

Guidelines

There are currently no NICE guideline recommendations for the first-line management of locally advanced, unresectable, or metastatic BTC. Current guidelines of relevance to UK clinical practice include those issued by the British Society of Gastroenterology (last updated in 2012) and European Society for Medical Oncology (ESMO) (updated in 2022) (see Table 3). This was confirmed by UK clinicians (n=5) in a series of one-to-one interviews, who when asked which guidelines are used in practice generally referenced the ESMO BTC guidelines[6] and also referenced the ABC-02 trial (the pivotal Phase 3 study that compared Gem/Cis versus Gem alone for the first-line treatment of locally advanced or metastatic BTC)[8] as the basis of evidence for the current standard of care.[19]

Table 3: Guidelines on the management of advanced BTC

	British Society of Gastroenterology (2012)[20]	**ESMO (2022)[6]**
BTC subtype	CC	BTC
Preferred first-line regimen	Gem/Cis	Gem/Cis D+Gem/Cis (Grade 4, ESMO-MCBS)
Alternative first-line regimens	Further data on specific subsets of CC are warranted to identify the best treatment combination for different subcategories of CC	Oxaliplatin may be substituted for cisplatin when renal function is of concern Gemcitabine monotherapy may be used for patients with a PS of 2
Second line	No recommendations	FOLFOX is the SoC; other therapies may be considered based on molecular profile

Abbreviations: CC, cholangiocarcinoma; D, durvalumab; ESMO, European Society for Molecular Oncology; Gem/Cis, gemcitabine/cisplatin; MCBS, Magnitude of Clinical Benefit Scale; SoC, standard of care.
Sources: Kahn et al. (2012);[20] Vogel et al. (2022).[6]

Current pathway of care

The current pathway of care for the management of BTC is outlined in Figure 2. The management of BTC is dependent on its resectability status and the stage at which it is diagnosed. Patients with early stage BTC that is deemed resectable (around 20% of BTC patients) can be treated surgically with curative intent, which is considered the optimal intervention for long-term survival.[4, 5, 46, 47]

In patients with disease recurrence (around 80% who receive resection),[16, 17] and in those diagnosed with locally advanced, unresectable, or metastatic BTC at first

diagnosis, there are currently no curative options. Treatment is limited to chemotherapy, and there have been no innovations in the management of first line locally advanced, unresectable, or metastatic BTC for over a decade.

Patients with locally advanced, unresectable, or metastatic BTC are generally offered chemotherapy.[6] SoC for patients who are in good health (performance status [PS] 0–1) is typically a combination of gemcitabine and cisplatin for up to 8 cycles.[6] Oxaliplatin may be given instead of cisplatin, particularly if there are concerns regarding kidney function. For patients in poor health (PS >1), single agent chemotherapy with gemcitabine is typically offered.[6] This was generally supported by UK clinical experts, who stated that approximately 80% of locally advanced, unresectable, or metastatic BTC patients are considered fit enough for chemotherapy treatment.[19] They confirmed Gem/Cis is considered to be the SoC for these patients based on the outcomes of the ABC-02 trial.[8] Clinicians most frequently reported use of gemcitabine monotherapy for patients who are unsuitable for Gem/Cis, which is usually due to performance status of 2 or more. However, UK clinician consensus was that oxaliplatin is not used for first-line treatment of locally advanced, unresectable, or metastatic BTC.[19] Current ESMO guidelines suggest molecular profiling to determine appropriate second-line therapy.[6]

Clinicians indicated that patients who experience disease recurrence after initial curative therapy would be managed in a similar manner to those who present with locally advanced or metastatic disease.

B.1.3.3 Limitations of the current treatment pathway

Locally advanced, unresectable, or metastatic BTC represents an extremely challenging condition to treat, with very limited options for patients. There has been no licenced innovation in first line locally advanced, unresectable, or metastatic BTC treatment in over a decade and current options are limited to gemcitabine-based chemotherapies that offer a minimal survival benefit (median <1 year).[7, 8]

There remains a major unmet need for new therapies to treat locally advanced, unresectable, or metastatic BTC that can be initiated without delay, that extend

median and longer-term survival and maintain QoL of patients, without the addition of further substantial toxicity.[21]

B.1.3.4 Durvalumab and gemcitabine/cisplatin place in therapy

Durvalumab is a high-affinity, human, recombinant IgG1κ mAb that selectively blocks the interaction of PD-L1, with receptors, PD-1 and CD80.[1] In doing so, it releases the inhibition of immune responses in the tumour microenvironment, resulting in prolonged T-cell activation and anti-tumour activity.[1] The current consensus on the mode of action (MoA) and associated efficacy of durvalumab involves binding to PD-L1 on the surface of tumour cells, and thus preventing interaction with PD-1.[48]

For the treatment of locally advanced, unresectable, or metastatic BTC, durvalumab is administered in combination with Gem/Cis, which is the current SoC for first-line treatment.[6] Durvalumab in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with locally advanced, unresectable, or metastatic biliary tract cancer.[2]

The efficacy and safety of D + Gem/Cis has been investigated in the TOPAZ-1 trial, which is the first positive global Phase III trial for a broad first-line population of locally advanced, unresectable, or metastatic BTC in over a decade.[11] D + Gem/Cis demonstrated a statistically significant and clinically meaningful improvement in overall survival (OS) versus placebo + Gem/Cis with a doubling in OS at 2 years.[13, 14] Furthermore, an OS treatment benefit was observed with D + Gem/Cis across all pre-defined subgroups (based on demographics, geographical region, primary tumour location, disease status, World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status (PS), and PD-L1 status). Furthermore, addition of D to Gem/Cis resulted in no detriment in QoL and a manageable safety profile consistent with the established safety profile of Gem/Cis.

The clear benefits offered by D + Gem/Cis in comparison to SoC chemotherapy have been recognised through the award of an innovation passport via the UK Innovative Licensing and Access Pathway (ILAP) programme, which aims to accelerate development and access to innovative medicines, for durvalumab + Gem/Cis in the treatment of locally advanced, unresectable, or metastatic BTC. D + Gem/Cis has

also been reviewed by the Medicines and Healthcare products Regulatory Agency (MHRA) through Project Orbis,[49] highlighting the innovative nature of this treatment. D + Gem/Cis for treatment of locally advanced, unresectable, or metastatic BTC has also been awarded an ESMO Magnitude of Clinical Benefit Scale (MCBS) score of 4, which is classified as a substantial magnitude of benefit. This grading was awarded due to the ≥10% increase in overall survival at 2 years demonstrated in the TOPAZ-1 trial.[6] Durvalumab is the only immunotherapy licensed for the first-line treatment of locally advanced, unresectable, or metastatic BTC and, in combination with Gem/Cis, is the first licenced treatment in over a decade to improve outcomes for this underserved population. It is anticipated that D + Gem/Cis will replace Gem/Cis as the first-line treatment option for the broad population of patients with locally advanced, unresectable, or metastatic BTC (Figure 2, green dotted boxes). The majority of patients who are suitable candidates for Gem/Cis therapy can be considered for D + Gem/Cis therapy – no evaluation for PD-L1 status is required[2] and treatment can be initiated without delay, which is crucial in a patient population with such a poor prognosis. The only patients eligible for Gem/Cis who would not be eligible to receive D + Gem/Cis are patients who have a contraindication to immunotherapy agents. This was confirmed by UK clinicians, who estimate approximately 20% of locally advanced, unresectable, or metastatic BTC patients eligible for Gem/Cis would have a contraindication to receiving immunotherapy.[19] ESMO guidelines on the management of BTC that were published in 2022 already recommends that D + Gem/Cis be considered for use in this position of the treatment pathway.

B.1.4 Equality considerations

Use of D + Gem/Cis is not expected to raise any equality issues.

B.2 Clinical effectiveness

- **The clinical evidence for D + Gem/Cis is derived from TOPAZ-1, a Phase 3, international, double-blind randomised controlled trial (RCT)**
  - TOPAZ-1 compared the efficacy and safety of D + Gem/Cis with placebo + Gem/Cis (current SoC, as confirmed by UK clinicians) in patients with previously untreated unresectable advanced or metastatic BTC, or patients with recurrent disease >6 months after surgery
- **In TOPAZ-1, D + Gem/Cis demonstrated a statistically significant and clinically meaningful improvement in OS versus placebo + Gem/Cis (HR 0.80 [95% CI 0.66, 0.97] at the pre-specified IA-2 DCO (final formal analysis)**
  - The HR decreased to 0.76 (95% CI 0.64, 0.91) (a 24% reduction in the risk of death) with an additional 6.5 months of follow-up data, at which time overall maturity for OS was 76.9%
  - An OS treatment benefit with D + Gem/Cis was observed across all pre-defined subgroups (based on demographics, geographical region, primary tumour location, disease status, WHO/ECOG PS, and PD-L1 status)
  - UK clinicians confirmed the TOPAZ-1 trial outcomes were generalisable to UK clinical practice and considered the OS subgroup analysis outcomes generalisable to the FAS outcomes.
- **Treatment with D + Gem/Cis led to a doubling in the OS rate at 2 years compared with placebo + Gem/Cis (23.6% vs 11.5%), with a clear and sustained separation in OS Kaplan–Meier (KM) curves from 6 months at the most recent additional 6.5-month data cut-off (25 February 2022)**
  - Due to the non-conventional survival dynamics associated with immuno-oncology therapy (e.g., delayed curve separation), it is important to consider the OS rate at 2 years which clearly demonstrates the durable OS benefit offered by D + Gem/Cis over the current SoC (Gem/Cis)
- A statistically significant and clinically meaningful improvement in progression-free survival (PFS) was observed for the D + Gem/Cis group compared with the placebo + Gem/Cis group (HR 0.75; 95% CI: 0.63, 0.89; p=0.001 at IA-2), with separation of KM curves seen at 4 months, indicating an early treatment effect of this regimen
  - This early treatment effect was further supported by a faster median time to response in the D + Gem/Cis group compared with the placebo + Gem/Cis group

- Addition of D to Gem/Cis resulted in no detriment in QoL and a manageable safety profile consistent with the established safety profile of Gem/Cis
- **TOPAZ-1 is the first Phase 3 trial in over a decade to demonstrate statistically significantly improved OS and PFS versus standard of care for patients with previously untreated, locally advanced, unresectable, or metastatic BTC and represents an important advancement in treatment options for these patients**
  - Recently updated ESMO BTC guidelines recommend that D + Gem/Cis be considered for all first line locally advanced, unresectable, or metastatic BTC patients, with a grade 4 MCBS score, indicating a substantial clinical benefit
  - Durvalumab is the first immunotherapy licenced for the treatment of unresectable locally advanced, or metastatic BTC, to be used in combination with gemcitabine and cisplatin, and is expected to replace Gem/Cis as the SoC in this setting
  - UK clinicians have advocated for use of D + Gem/Cis in all patients who would otherwise be eligible for Gem/Cis and have no contraindications to immunotherapy
- **The clinical evidence demonstrated by the TOPAZ-1 trial and the subsequent ESMO guidance and clinical advocacy for use of D + Gem/Cis in first line locally advanced, unresectable, or metastatic BTC confirms the importance of enabling access to this combination therapy which offers potential for a longer-term, durable survival benefit compared to currently available treatment options**

B.2.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify evidence from randomised controlled trials (RCTs) on the efficacy and safety of systemic treatments for locally advanced, unresectable, or metastatic or recurrent BTC, including D + Gem/Cis.

The SLR study question was specified using the PICOS framework (Population, Intervention, Comparator, Outcome and Study type). Full details of the methodology, including search strategy, PRISMA flow diagram, list of included studies and list of excluded studies at full text review is provided in Appendix D.

B.2.2 List of relevant clinical effectiveness evidence

The SLR identified three RCTs reporting on the efficacy and safety of D + Gem/Cis in patients with previously untreated locally advanced, unresectable, or metastatic or recurrent BTC.

Of the three identified studies, one is considered of relevance to the submission. TOPAZ-1 was a pivotal Phase 3 randomised, double-blind, placebo-controlled, parallel-group, multi-regional international study to compare the efficacy and safety of D + Gem/Cis with placebo + Gem/Cis.[11-13] Data from TOPAZ-1 has been included in the economic model presented in this submission. An overview of this study is presented in Table 4.

IMMUCHEC was a Phase 2, open-label study consisting of five treatment arms (tremelimumab in combination with D + Gem/Cis, tremelimumab with D + Gem, tremelimumab with Gem/Cis, Gem/Cis and D + Gem/Cis).[50] MEDITREME was a Phase 2, open-label, single-centre study to compare the efficacy and safety of tremelimumab in combination with D + Gem/Cis versus D + Gem/Cis. [51] [51] These studies are not considered further in the submission due to the nature of the design (Phase 2, open-label) and the small patient populations enrolled, meaning that the studies were not sufficiently powered to detect significant differences between treatment groups. Furthermore, MEDITREME used a durvalumab dose of 1,120 mg, which is outside of the licensed dose and neither study followed the licensed dosing schedule of durvalumab treatment administered Q4W as monotherapy after 8 cycles of D + Gem/Cis therapy. However, for completeness, a brief overview of the methodology and results of these studies is presented in Appendix N.

Table 4: List of relevant clinical effectiveness evidence

Study	TOPAZ 1
Study design	Phase 3, randomised, double-blind, placebo-controlled, parallel-group, multiregional international study
Population	Patients previously untreated for unresectable advanced or metastatic BTC, or patients who developed recurrent disease >6 months after surgery
Intervention(s)	D + Gem/Cis
Comparator(s)	Placebo + Gem/Cis

Study	TOPAZ 1
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	NA
Reported outcomes specified in the decision problem	**OS** **PFS** ORR **TTD†** **AEs** **HRQoL**

† TTD was not included in the pre-specified trial outcomes however have been calculated for the purpose of the economic model.
Abbreviations: AE, adverse event; BTC, biliary tract cancer; D, durvalumab 1,500 mg; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Summary of trial methodology – TOPAZ-1 (Study D933AC00001)

TOPAZ-1 is an ongoing Phase 3, randomised, double-blind, placebo-controlled, international, multi-centre study to assess the efficacy and safety of first-line treatment with D + Gem/Cis versus placebo + Gem/Cis in patients with unresectable advanced or metastatic BTC.

The methodology for and data from TOPAZ-1 is drawn from a number of sources. These include the clinical study report (CSR),[12] CSR addendum,[13] clinical study protocol (CSP),[52] one primary publication (Oh et al. (2022a);[11] and two supporting poster/abstract presentations (Oh et al. (2022b),[14] Burris et al. (2022).[53]

B.2.3.2 Study objectives

The primary objective of the study was to confirm the superiority of D + Gem/Cis compared with placebo + Gem/Cis in terms of OS.

B.2.3.2.1 Study locations

The study included 105 sites in 17 countries across Europe, North America, South America, and Asia-Pacific. The study included 47 patients randomised across 8 sites in the UK.

B.2.3.2.2 Trial design

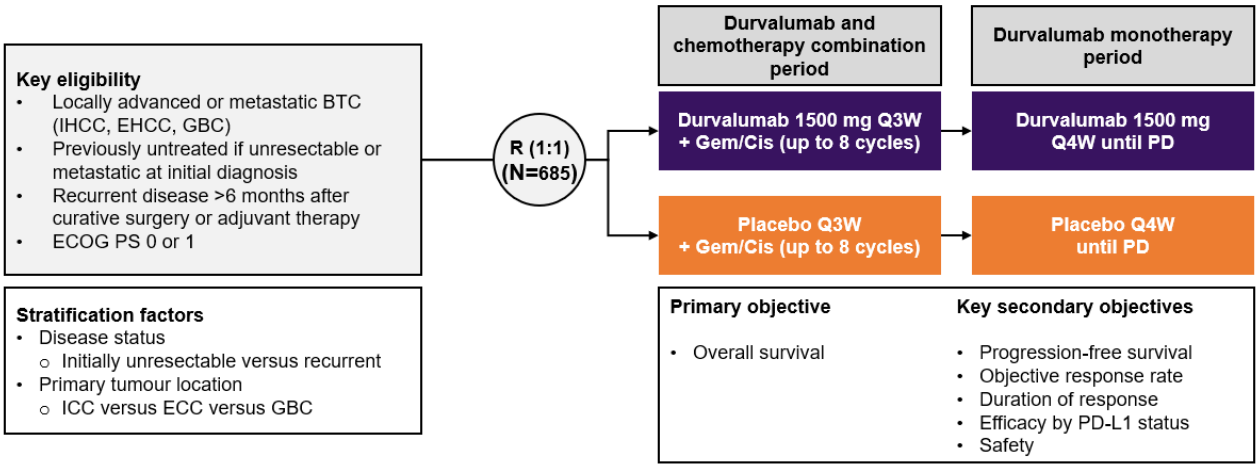
Patients who fulfilled the study eligibility criteria (see Table 5) were randomised in a 1:1 ratio to receive either durvalumab in combination with gemcitabine and cisplatin (D+ Gem/Cis) or placebo in combination with Gem/Cis.

Durvalumab and chemotherapy combination period: Patients received either durvalumab 1,500 mg or placebo (administered on Day 1) in combination with gemcitabine and cisplatin (administered on Day 1 and Day 8) in 3-weekly cycles for up to 8 cycles.

Durvalumab monotherapy period: After completing the chemotherapy period, patients received 1,500 mg durvalumab or placebo as monotherapy every 4 weeks until clinical progression (or Response Evaluation Criteria in Solid Tumours version 1.1 [RECIST 1.1]-defined radiological PD), unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

An overview of the trial design is presented in Figure 3.

Figure 3: TOPAZ-1 study design



Abbreviations: ADA, antidrug antibody; AoV, ampulla of Vater; Bili, bilirubin; BTC, biliary tract cancer; DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; EHCC, extrahepatic cholangiocarcinoma; GB, gallbladder; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; IHCC, intrahepatic cholangiocarcinoma; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed cell death ligand-1; PFS, progression-free survival; PK, pharmacokinetic; PRO, patient-reported outcomes; PS, performance status; QxW, every x weeks; R, randomisation; ULN, upper limit of normal.
Source: Oh et al. (2022b).[14]

B.2.3.2.3 Data cut-offs

Three data cut-offs were planned. A first interim analysis (IA-1, to assess clinical activity, no formal statistical analysis), a second interim analysis (IA-2) and a final analysis (FA). At the time of IA-2, the primary study objective was met: a statistically significant improvement in OS was observed for D +Gem/Cis versus placebo + Gem/Cis and confirmed by the Independent Data Monitoring Committee (IDMC), therefore IA-2 was considered the final, formal statistical analysis for OS and the sponsor was unblinded. A further analysis was conducted, providing an approximately 6.5 months of additional follow-up since IA-2. The analysis periods in the study were therefore as follows:

- ***IA-1 (DCO 18 December 2020):*** The objective of IA-1 was to evaluate the efficacy of D + Gem/Cis in terms of clinical activity (as measured by objective response rate [ORR] and duration of response [DoR], per blinded independent central review assessment). Results from IA-1 are not presented in this submission.
- ***IA-2 (final formal analysis; DCO 11 August 2021):*** The primary objective was to evaluate the superiority of D + Gem/Cis compared with placebo + Gem/Cis in

terms of OS, as analysed using a stratified log-rank test (stratified by disease status and primary tumour location) to assess statistical inference.

- ***6.5-month update (DCO 25 February 2022):*** Presented updated exposure, OS, and safety data based on approximately 6.5 months of additional follow-up since the IA-2 DCO.

B.2.3.2.4 Method of randomisation and blinding

All patients were centrally assigned to randomised study treatment using an IVRS/IWRS. Each patient was assigned a unique randomisation number in a sequential manner. Randomisation was stratified by disease status (initially unresectable versus recurrent) and primary tumour site (IHCC versus EHCC versus GBC). No member of the extended study team at AstraZeneca, at the investigational centres, or any blinded Contract Research Organisation handling data has access to the randomisation scheme until the time of the final data analysis (i.e., the primary OS analysis).

The study was conducted in a double-blind fashion. Patients, Investigators, and study centre staff were blinded to the durvalumab/placebo treatment allocation and remained blinded to each patient's assigned study treatment throughout the course of the study. To maintain this blinding, an unblinded pharmacist who was otherwise uninvolved in the study prepared the intravenous (IV) durvalumab or placebo solutions for administration for each patient as specified by the randomisation scheme and IVRS. The IV bag was then covered with a translucent coloured or opaque sleeve which was secured (stapling or heat sealing) after preparation by the unblinded pharmacist prior to dispensing to other study personnel. Once the infusion was completed, the infusion bag was discarded with the sleeve covering in place to ensure that the blind was maintained. The interactive voice response system (IVRS)/interactive web response system (IWRS) provided the unblinded pharmacists the kit identification number to be allocated to the patient at the dispensing visit.

An individual patient's study treatment could be unblinded for medical/safety reasons. Additionally, after stopping study treatment, the CSP permitted unblinding if required to inform decisions regarding subsequent anti-cancer treatment (e.g., clinical study participation or immunotherapy options outside of clinical trial). Under

all circumstances of unblinding, to maintain the treatment blind during the study, information was not shared with AstraZeneca personnel and other site staff members.

B.2.3.2.5 Eligibility criteria

Details of key inclusion and exclusion criteria for TOPAZ-1 are presented in Table 5. A full list of inclusion and exclusion criteria is presented in Appendix M.

Table 5: Eligibility criteria – TOPAZ-1

Inclusion	Exclusion
• Males and females aged ≥18 years at the time of screening[†] • Histologically confirmed, unresectable advanced or metastatic adenocarcinoma of biliary tract, including cholangiocarcinoma (intrahepatic or extrahepatic) and gallbladder carcinoma • Patients with previously untreated disease if unresectable or metastatic at initial diagnosis • Patients who developed recurrent disease >6 months after surgery with curative intent and, if given, >6 months after the completion of adjuvant therapy (chemotherapy and/or radiation) • WHO/ECOG PS of 0 or 1 at enrolment • ≥1 lesion that qualified as a RECIST 1.1 TL at baseline • No prior exposure to immune-mediated therapy, including, but not limited to, other anti CTLA-4, anti PD-1, anti-PD-L1, and anti-PD-L2 antibodies, excluding therapeutic anti-cancer vaccines • Adequate organ and marrow function (see Appendix M for criteria) – Including CrCl >50mL/min • Life expectancy ≥12 weeks at screening • Body weight >30 kg • Provision of a recent tumour biopsy or an available unstained archived tumour tissue sample in a quantity sufficient to allow for analysis (taken ≤ 3 years prior to screening (not to be those used as RECIST TLs unless there were no other lesions suitable for biopsy) • Patients with HBV infection (as characterised by positive HBsAg and/or anti-HBc with detectable HBV DNA [≥10 IU/mL or above the limit of detection per local laboratory]) had to receive antiviral therapy prior to randomisation per institutional practice and remain on antiviral therapy for the study duration and for 6 months after the last dose of study treatment	• Ampullary carcinoma • History of allogeneic organ transplantation • Active or prior documented autoimmune or inflammatory disorders (see Appendix M for further details) • Uncontrolled intercurrent illness, including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active ILD, serious chronic gastrointestinal conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase the risk of incurring AEs, or compromise the ability of the patient to give written informed consent • History of another primary malignancy, except: – Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence – Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease – Adequately treated carcinoma in situ without evidence of disease • History of leptomeningeal carcinomatosis • History of active primary immunodeficiency • Active infection, including tuberculosis • Any unresolved toxicity NCI-CTCAE Grade ≥2 from a previous anti-cancer therapy, with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria • Brain metastases or spinal cord compression (including asymptomatic an adequately treated disease) • Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment (concurrent use of hormonal therapy for non-cancer-related conditions, e.g., HRT was acceptable) • Active HCV infection

† For patients aged <20 years and enrolled in Japan, a written informed consent was to be obtained from the patient and his/her legally acceptable representative.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CrCl, creatinine clearance; CTCAE, Common Terminology Criteria for Adverse Event; CTLA-4, Cytotoxic T-lymphocyte-associated antigen-4; ECOG, Eastern Cooperative Oncology Group, HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HRT, hormone replacement therapy; IBD, inflammatory bowel disease; ILD, interstitial lung disease; IP, investigational product; NCI, National Cancer Institute; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand-1; PD-L2, programmed cell death ligand-2; PS, performance status; RA, rheumatoid arthritis; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1 ; TL, target lesion; ULN, upper limit of normal; WHO, World Health Organization.
Source: CSR.[12]

B.2.3.2.6 Trial drugs

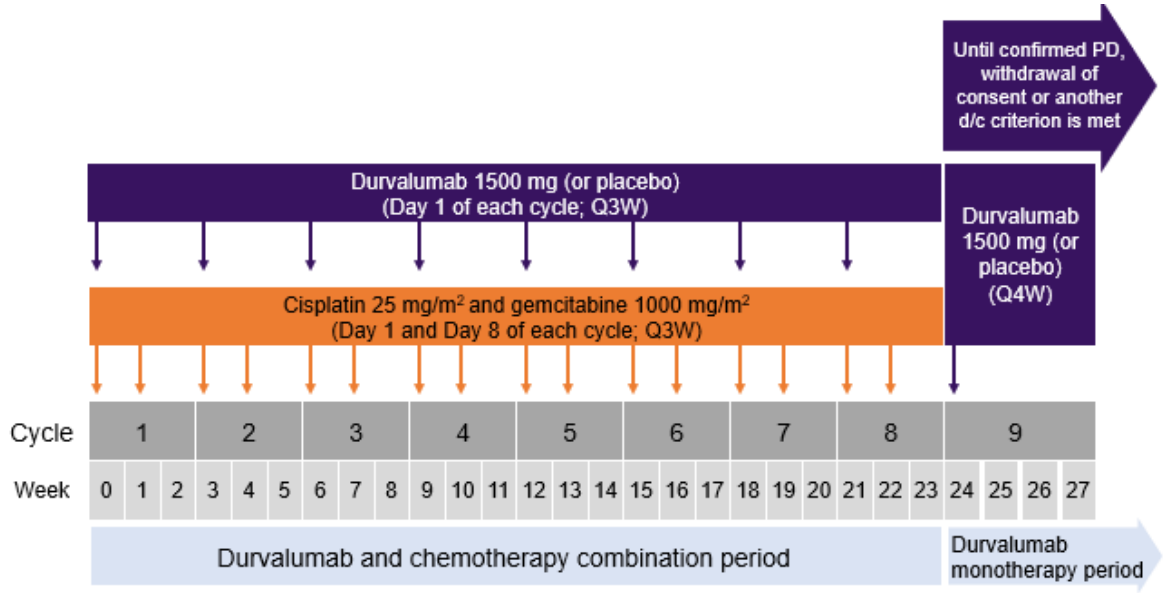
Details of the dosing schedule for the trial drugs are presented in Figure 4.

Intervention – D + Gem/Cis (N=341): In the chemotherapy period, durvalumab 1,500 mg IV was administered on Day 1 every 3 weeks (Q3W), while gemcitabine 1,000 mg/m^2 IV and cisplatin 25 mg/m^2 IV were each administered on Days 1 and 8 Q3W starting on Cycle 1 for up to 8 cycles. After completing the chemotherapy period, patients received 1,500 mg durvalumab as monotherapy via IV infusion Q4W in the monotherapy period until clinical progression (or RECIST 1.1-defined radiological PD), unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Note: If a patient's weight fell to ≤30 kg, the patient received weight-based dosing equivalent to 20 mg/kg of durvalumab (or placebo) Q3W (i.e., with chemotherapy) or Q4W (i.e., during monotherapy) after consultation between the Investigator and the study physician, until the weight improved to >30 kg, at which point the patient was to start receiving the fixed dosing of durvalumab 1,500 mg (or placebo) Q3W or Q4W.

Comparator – placebo + Gem/Cis (N=344): Placebo IV was administered on Day 1 Q3W, while gemcitabine 1,000 mg/m^2 IV and cisplatin 25 mg/m^2 IV were each administered on Days 1 and 8 Q3W starting on Cycle 1 for up to 8 cycles. After completing the chemotherapy period, patients received placebo as monotherapy via IV infusion Q4W in the monotherapy period until clinical progression (or RECIST 1.1-defined radiological PD), unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met.

Figure 4: Dosing schedule for D+ Gem/Cis and placebo + Gem/Cis – TOPAZ-1



For patients who have discontinued gemcitabine/cisplatin due to treatment-related toxicity before completion of Cycle 8, treatment with durvalumab/placebo may continue at the Investigator's discretion when toxicity resolves to Grade 2 or less; in that case, durvalumab/placebo monotherapy will be administered Q4W. During the initial chemotherapy period, durvalumab or placebo were given on Day 1 of each cycle (Q3W). For durvalumab treatment schedules, if there was a dosing delay while on the Q3W schedule, all future dosing days were to be delayed ensuring that the intervals between dosing study treatment were always at least 21 days. For Gem/Cis, dosing delays were to be managed according to local prescribing guidelines. If any cycle was delayed, the cycle number and week number were also delayed.
Abbreviations: d/c, discontinuation; PD, progressive disease; QxW, every x weeks.

B.2.3.2.7 Permitted and disallowed concomitant medications

Concomitant medications that were permitted or disallowed during TOPAZ-1 were as follows:

- ***Permitted medications:*** Concomitant medications deemed necessary to provide adequate prophylactic or supportive care (e.g., acetaminophen or diphenhydramine, and other than those identified as disallowed below); best support care including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy to non-target lesions; inactivated virus (e.g., the influenza vaccine). Other medication considered necessary for a patient's safety and well-being was also allowed at the discretion of the Investigator.
- ***Disallowed medications:*** Other investigational anti-cancer therapies (other than those under investigation in TOPAZ-1); mAbs against cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), PD-1 or PD-L1 (other than those

under investigation in TOPAZ-1); any concurrent chemotherapy, radiotherapy, immunotherapy or biologic or hormonal therapy for cancer treatment (other than those under investigation in the TOPAZ-1 trial); live attenuated vaccines; immunosuppressive medications (including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers); epidermal growth factor receptor-tyrosine kinase inhibitors; herbal an natural remedies which may have immune-modulating effects.

B.2.3.2.8 Primary outcome

The primary outcome was OS, which was defined as the time between randomisation and death due to any cause. Patients who discontinued treatment and were in long-term follow-up were assessed for survival every 3 months and following each DCO. 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.

B.2.3.2.9 Other outcomes used in the economic model and/or specified in the scope

B.2.3.2.9.1 Secondary efficacy assessments

All secondary efficacy endpoints were Investigator assessed according to RECIST 1.1. Definitions were as follows:

- **Progression-free survival (PFS):** The time from randomisation until radiological tumour progression or death from any cause, regardless of whether the patient withdrew from therapy or received another anticancer therapy prior to progression (i.e., date of event or censoring – date of randomisation + 1). Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. However, if the patient progressed or died after 2 or more missed visits, the patient was censored at the time of the latest evaluable RECIST 1.1 assessment prior to the 2 missed visits.
- **ORR:** The number (%) of patients with at least one visit response of complete response (CR) or partial response (PR). Data obtained up until progression, or the last evaluable assessment in the absence of progression, were included in

the assessment of ORR. Patients who went off treatment without progression, received a subsequent therapy, and then responded were not included as responders.

- **DoR:** Time from first documented response (CR or PR) until date of documented progression or death in the absence of disease progression (i.e., date of PFS event or censoring – date of first response + 1). The time of the initial response was defined as the latest of the dates contributing toward the first visit response of CR or PR.

Tumour assessments were performed every 6 weeks (± 1 week) for the first 24 weeks (relative to the date of randomisation) and then every 8 weeks (± 1 week) thereafter until RECIST 1.1-defined radiological disease progression (relative to the date of randomisation) plus at least 1 additional follow-up scan.

B.2.3.2.9.2 Patient-reported outcomes

Patient-reported outcomes (PROs) included as secondary endpoints comprised the European Organisation for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire (EORTC-QLQ-C30) and the European Organisation for Research and Treatment of Cancer 21-Item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire (EORTC-QLQ-BIL21). A description of these measures is provided in Appendix M.

Key outcomes assessed using the EORTC-QLQ-C30 and the EORTC-QLQ-BIL21 were as follows:

Time to deterioration: 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 Global Health Status (GHS)/Quality of life (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 mixed model repeated measures (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.

Additional exploratory analyses were conducted using Patient Global Impression of Severity (PGIS), Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) and EuroQol-5 Dimensions-5 Levels (EQ-5D-5L). As PGIS and PRO-CTCAE were exploratory analyses and are not included in the economic model, results of these are not presented in this submission.

Patients completed PRO assessments using electronic patient-reported outcome (ePRO) tablet devices at study sites. The PRO questionnaires were completed before treatment dosing and before any other study procedures were conducted in the following order: EORTC QLQ-C30, EORTC QLQ-BIL21, PGIS, EuroQol-5 Dimensions 5 Levels (EQ-5D-5L), and PRO-CTCAE. The assessment schedule included baseline followed by Q3W for the first eight treatment cycles relative to the date of randomisation, then every cycle (4 weeks) thereafter until progression or death. After Cycle 16 Day 1, assessments were made every other cycle. Patients who discontinued durvalumab treatment were assessed at 30 (±3) days since the last dose of treatment and then at month 2 and 3 since the last dose.

B.2.3.2.9.3 Adverse events

For AEs, on treatment (or treatment-emergent AEs) were defined as any AEs that started after dosing or prior to dosing and which worsens following exposure to the treatment. AEs observed up until 90 days following discontinuation of the investigational product (IP) or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurred first) were used for the reporting of AE summary tables. AEs and serious adverse events (SAEs) were collected from the time of the patient signing the informed consent form until the follow-up period is completed (90 days after the last dose of IP).

B.2.3.2.10 Pre-planned subgroups

Prespecified subgroup analyses for OS, PFS, and ORR included disease status at randomisation, primary tumour location, sex, age, race (Asian, Non-Asian ethnicity), region (Asia, rest of the world [RoW]), WHO/ECOG PS (0, 1), extent of disease (unresectable, metastatic), and PD-L1 status (tumour area positivity [TAP] ≥1% versus <1%).

B.2.3.3 Baseline characteristics and demographics

Patient characteristics at baseline are summarised in Table 6. The median age was 64 years (range: 20 to 85 years), with 46.7% of patients aged 65 years or older. Approximately half of patients were male (50.4%), and 56.4% of patients were of Asian ethnicity. Demographic characteristics were well balanced between the treatment groups in terms of age, sex, and race. Baseline disease characteristics are presented in Table 7. Disease characteristics such as ECOG-PS and primary tumour type were also well balanced between the two treatment groups. Prior anti-cancer treatments included adjuvant cytotoxic chemotherapy (7.6% of patients) and radiotherapy (2.8% of patients), and the frequency and number of prior regimens was well-balanced between the two treatment groups (data not shown). Overall, 186 (27.2%) patients had undergone prior surgical procedures for BTC (curative for 19.1% patients and non-curative for 8.0% patients), and the treatment groups were balanced in terms of the type and frequency of specific procedures (data not shown).

Table 6: Demographic characteristics of participants in TOPAZ-1 at baseline across treatment groups - FAS

TOPAZ-1 Baseline characteristics	D + Gem/Cis (N=341)	Placebo + Gem/Cis (N=344)	Total (N=685)
Age (years)			
Median (min, max)	64 (20, 84)	64 (31, 85)	64 (20, 85)
Sex, n (%)			
Female	172 (50.4)	168 (48.8)	340 (49.6)
Race n (%)			
Asian	185 (54.3)	201 (58.4)	386 (56.4)
White	131 (38.4)	124 (36)	255 (37.2)
Black or African American	8 (2.3)	6 (1.7)	14 (2.0)
American Indian or Alaskan Native	0	1 (0.3)	1 (0.1)

TOPAZ-1 Baseline characteristics	D + Gem/Cis (N=341)	Placebo + Gem/Cis (N=344)	Total (N=685)
Other	17 (5.0)	12 (3.5)	29 (4.2)
Region			
Asia	178 (52.2)	196 (57.0)	374 (54.6)
Europe	108 (31.7)	107 (31.1)	215 (31.4)
North America	37 (10.9)	28 (8.1)	65 (9.5)
South America	18 (5.3)	13 (3.8)	31 (4.5
Weight (kg)			
Mean (SD)	[redacted]	[redacted]	[redacted]

Abbreviations: BMI, body mass index; D, durvalumab 1,500 mg; FAS, full analysis set; Gem/Cis, gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2; SD, standard deviation.
Source: Oh et al. (2022a);[11] CSR.[12]

Table 7: Disease characteristics at baseline – FAS

	Number (%) of patients		
	D + Gem/Cis (N = 341)	Placebo + Gem/Cis (N = 344)	Total (N = 685)
Primary tumour location			
IHCC	190 (55.7)	193 (56.1)	383 (55.9)
EHCC	66 (19.4)	65 (18.9)	131 (19.1)
GBC	85 (24.9)	86 (25.0)	171 (25.0)
Overall disease classification			
Locally advanced only	38 (11.1)	57 (16.6)	95 (13.9)
Metastatic	303 (88.9)	286 (83.1)	589 (86.0)
WHO/ECOG PS			
(0) Normal activity	173 (50.7)	163 (47.4)	336 (49.1)
(1) Restricted activity	168 (49.3)	181 (52.6)	349 (50.9)
PD-L1 expression			
High (TAP ≥1%)	197 (57.8)	205 (59.6)	402 (58.7)
Low/negative (TAP <1%)	103 (30.2)	103 (29.9)	206 (30.1)
Missing	41 (12.0)	36 (10.5)	77 (11.2)
MSI status			
High	3 (0.9)	2 (0.6)	5 (0.7)
Stable	160 (46.9)	168 (48.8)	328 (47.9)
Missing†	178 (52.2)	174 (50.6)	352 (51.4)
Virology status			
No viral hepatitis	187 (54.8)	174 (50.6)	361 (52.7)
Any viral hepatitis B	69 (20.2)	81 (23.5)	150 (21.9)

	Number (%) of patients		
	D + Gem/Cis (N = 341)	**Placebo + Gem/Cis (N = 344)**	**Total (N = 685)**
Prior hepatitis C	8 (2.3)	10 (2.9)	18 (2.6)
Missing	82 (24.0)	83 (24.1)	165 (24.1)

† Includes MSI-unknown and not tested. Overall, 5 of 333 (1.5%) patients with an MSI result were MSI high.
Abbreviations: D, durvalumab 1,500 mg; ECOG, Eastern Cooperative Oncology Group; EHCC, extrahepatic cholangiocarcinoma; FAS, full analysis set; GBC, gallbladder cancer; Gem/Cis, gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2; IHCC, intrahepatic cholangiocarcinoma; MSI, microsatellite instability; PD-L1, programmed cell death ligand-1; PS, performance status; TAP, tumour area positivity; WHO, World Health Organization.
Source: Oh et al. (2022a).[11]

B.2.3.4 Expert elicitation/opinion

A series of one-to-one virtual interviews with oncologists based in the UK were conducted in December 2022. The aim of the interviews was to elicit expert insights on the current BTC treatment landscape and understand the clinical perception of the TOPAZ-1 trial. Interviews were conducted with 5 oncologists, 3 based in England and 2 based in Scotland. While the identities of clinicians remain anonymous, all interviewees had extensive experience in the treatment of BTC and were familiar with the TOPAZ-1 trial.

An interview guide was developed and used in all 5 interviews. The guide contained questions on BTC disease background and epidemiology and the treatment pathway. Efficacy results and extrapolations for the PFS and OS endpoints were also presented as well as a table of proposed healthcare resources use for clinicians to provide comment on.

Insights from the clinicians are included throughout the dossier. The full report, which is qualitative in nature and includes details of the discussion guide, is provided as a 'Data on File' reference.[19]

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Populations analysed

Details of the population analysis sets defined in TOPAZ-1 along with their use in the study are presented in Table 8.

Table 8: Population analysis sets – TOPAZ-1

Analysis set (based on the global cohort†	Definition	Purpose
FAS	All randomised patients (as randomised, regardless of actual treatment). For ORR and BOR, the main analysis was conducted among the subset of patients with measurable disease at baseline (per Investigator).	Baseline characteristics, efficacy analyses
PRO analysis set	For each PRO questionnaire, a separate analysis set was defined. The PRO sets include all patients from the FAS, except for patients with no questionnaire translation available or who did not complete questionnaires due to physical limitations (e.g., blindness), illiteracy, or other language reasons.	PRO analyses
SAS	All patients who received ≥1 dose of study treatment (as treated; a patient who received any amount of durvalumab was reported in the D + Gem/Cis group. Erroneously treated patients (e.g., those randomised to durvalumab but actually given placebo) were summarised according to the treatment they received. If a patient only received therapy from the placebo arm, they were to be summarised in the placebo treatment group. If a patient received any amount of durvalumab, they were summarised in the durvalumab treatment group.	Exposure and safety analyses

† The global cohort represents the population reported in the CSR. Recruitment of patients in China continued until a total of approximately 130 Chinese patients were randomised.
Abbreviations: BOR, best objective response; CSR, clinical study report; D, durvalumab 1500 mg; FAS, full analysis set; Gem/Cis, gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2; ORR, objective response rate; PRO patient reported outcome; SAS, safety analysis set.

B.2.4.2 Hypothesis objective

The objective of TOPAZ-1 was to demonstrate superiority of the OS benefit of D + Gem/Cis versus placebo + Gem/Cis in patients with previously untreated, unresectable, locally advanced, or metastatic BTC.

The hypothesis of improved OS could be tested using the global cohort when:

- Approximately 397 OS events across D + Gem/Cis and placebo + Gem/Cis treatment groups had occurred (59% maturity) (IA-2)
- Approximately 496 OS events across D + Gem/Cis and placebo + Gem/Cis treatment groups had occurred (74% maturity) (FA).

Note: At the time of the IA-2, 424 death events had occurred (representing 61.9% overall maturity for OS). The interim analysis of OS met the prespecified O'Brien-

Fleming type boundary for declaring statistical significance between the treatment groups, based on the Lan-DeMets α spending function to ensure strong control of the Type 1 error (with a 2-sided interim p-value of <0.0300 for the treatment comparison), and therefore IA-2 became the final formal analysis.

B.2.4.3 Statistical analysis

Statistical analyses were conducted for each endpoint as follows:

- ***OS:*** Analysed using a stratified log-rank test (stratified by disease status and primary tumour location) to assess statistical inference. The treatment effect was estimated by hazard ratio (HR) and its 95% confidence interval (CI) based on a Cox proportional hazards model (stratified by disease status and primary tumour location). KM 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).
- ***PFS:*** Analysed using the same methodology as for OS.
- **ORR:** Analysed using a stratified Cochran-Mantel-Haenszel (CMH) test adjusting for the same factors as the primary endpoint OS. The treatment effect was estimated by odds ratio, 95% CI, and p-value.
- Remaining secondary endpoints were summarised descriptively.

B.2.4.4 Sample size and power calculation

Approximately 672 patients (336 patients per treatment group) were planned to be randomised into the global cohort (1:1) to D + Gem/Cis or placebo + Gem/Cis.

The study was powered to demonstrate the superiority of the OS benefit of D + Gem/Cis versus placebo + Gem/Cis. For the planned OS analyses, strong control of the familywise error rate at the remaining 4.9% level (2-sided) across the testing of OS and PFS endpoints was achieved through a combined approach of alpha allocation to the planned OS analyses (IA-2; whilst making provision for the potential for a subsequent, planned FA) via alpha spending function and a hierarchical testing procedure; that is, PFS was to be tested only if OS met statistical significance (either) at IA-2 or FA.

The IA-2 OS analysis was conducted when 424 of the 496 expected OS events at FA (61.9% overall maturity for OS) had occurred, using the Lan-DeMets spending function approximating O'Brien-Fleming boundaries to ensure strong control of the Type 1 error (with a 2-sided interim p value of < 0.0300 for the treatment comparison). As OS met statistical significance at IA-2, significance levels for PFS at IA-2 for the log-rank test were derived based on the Lan-DeMets alpha spending function approximating Pocock boundaries, which strongly controls the Type I error at the 0.049 level (2-sided).

B.2.4.5 Data management and patient withdrawals

Discontinuation from study treatment, for any reason, did not impact patients' participation in the study. Patients were to continue attending subsequent study visits, and data collection was to continue according to the CSP. If the patient did not agree to continue in-person study visits, a modified follow-up was arranged to ensure the collection of endpoints and safety information. Patients who permanently discontinued study treatment for reasons other than RECIST 1.1-defined radiological PD were to continue to have RECIST scans performed every 6 weeks ± 1 week for the first 24 weeks (relative to the date of randomisation) and then every 8 weeks ± 1 week thereafter (relative to the date of randomisation) until RECIST 1.1-defined radiological PD plus at least 1 additional follow-up scan or death (whichever came first).

If a patient was discontinued for RECIST 1.1-defined radiological PD, the patient should have had 1 additional follow-up scan performed, preferably at the next (and no later than the next) scheduled imaging visit and no less than 4 weeks after the prior assessment of PD. All patients were followed up for survival until the end of the study.

Patients were free to withdraw from the study at any time. Patients who withdrew consent for further participation in the study did not receive any further IP or undergo further study observation, with the exception of follow-up for survival, which will continue until the end of the study, unless the patient had expressly withdrawn consent to survival follow-up.

Patients will be considered lost to follow-up only if no contact has been established by the time the study has completed, such that there is insufficient information to determine the patient's status at this time.

B.2.4.6 Participant flow in the relevant randomised controlled trials

From April 2019 to December 2020, 914 patients were enrolled at 105 sites in 17 countries, including 8 sites in the UK. In total, 685 patients were randomly assigned to treatment. Of these, 341 patients were assigned to the D + Gem/Cis group and 338 patients received treatment. The remaining 344 patients were assigned to the placebo + Gem/Cis group and 342 of these patients received treatment. At the IA-2 DCO, 63 (18.6%) patients in the D + Gem/Cis group and 20 (5.8%) patients in the placebo + Gem/Cis group were receiving ongoing study treatment. At the 6.5-month update DCO, 32 (9.5%) patients in the D + Gem/Cis group and 7 (2.0%) patients in the placebo + Gem/Cis group were receiving ongoing study treatment. Full details of participant flow are presented in Appendix D.

B.2.5 Critical appraisal of the relevant clinical effectiveness evidence

A summary of the quality assessment of TOPAZ-1 is provided in Table 9.

Table 9: Quality assessment results for TOPAZ-1

Trial number (acronym)	Grade	Details
Was randomisation carried out appropriately?	Yes	Randomisation was carried out in a 1:1 fashion by IVRS/IWRS.
Was the concealment of treatment allocation adequate?	Yes	Study was double-blind; the patients, Investigator and study centre staff were blinded to the durvalumab/ placebo allocation. For durvalumab and placebo, the IV bag was covered with a translucent colour or opaque secured sleeve after preparation by an unblinded third party pharmacist. Following infusion, the infusion bag was discarded with the sleeve in place.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Baseline patient characteristics were generally well balanced between treatment groups, including ECOG PS, primary tumour type, disease status and PD-L1 expression
Were the care providers, participants, and outcome assessors blind to treatment allocation?	Yes	The study was double-blind; the patients, Investigator and study centre staff were blinded to the durvalumab/ placebo allocation. To maintain the blind, an otherwise uninvolved third-party pharmacist unblinded to the durvalumab/placebo prepared the durvalumab/placebo infusion as specified by the randomisation and IVRS. The IVRS/IWRS provided the kit identification number to the unblinded pharmacist. Kit

Trial number (acronym)	Grade	Details
		numbers of durvalumab dispensed were recorded by the pharmacist and monitored by an unblinded monitor. Other study centre staff and monitors were not given access to kit number identification. No member of the extended study team at AstraZeneca, the investigational centres or any blinded Contract Research Organisation handling data had access to the randomisation scheme.
Were there any unexpected imbalances in dropouts between groups?	No	At the time of IA-2 (11 Aug 21 DCO) 275 patients in the durvalumab plus Gem/Cis arm had discontinued durvalumab and 201 patients had terminated the study. In the placebo plus Gem/Cis arm, 322 patients had discontinued placebo and 233 patients had terminated the study.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	The primary and key secondary outcomes listed in the methodology section are consistent with those reported in the results section.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Analyses in the overall population were conducted on the FAS (i.e., ITT), comprising all patients randomised to treatment. The analysis included patients who were randomised but did not go on to receive treatment. Patients were considered lost to follow-up if no contact has been established by the time the study was complete. Investigators documented all attempts to re-establish contact with missing patients. Procedures for accounting for missing, unused, and spurious data are described in the SAP.

Adapted from Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination).
Abbreviations: DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; IA-2, interim analysis 2; ITT, intent-to-treat; IV, intravenous; IVRS; interactive voice response system; IWRS; interactive web response system; PD-L1, programmed cell death ligand-1; PS, performance status; SAP, statistical analysis plan.

B.2.6 Clinical effectiveness results of the relevant studies

B.2.6.1 TOPAZ-1

At the pre-planned second interim analysis (IA-2, DCO 11 Aug 21), a statistically significant improvement in overall survival in the D + Gem/Cis arm compared with the placebo + Gem/Cis arm was observed. Therefore, the key secondary endpoint of progression-free survival was formally evaluated at IA-2 and a statistically significant improvement was also observed in the D + Gem/Cis arm compared with the placebo + Gem/Cis arm. The results of this analysis were reviewed by an independent data monitoring committee, which concluded that the data met the prespecified criteria for a statistically significant difference in overall survival. The sponsor was unblinded and the overall survival results from IA-2 are to be considered the final, formal statistical analysis for overall survival.[11]

A further OS and safety analysis was conducted after 6.5 months of additional follow-up (DCO 25 Feb 2022). At the time of this analysis, the OS benefit in the D + Gem/Cis arm numerically improved compared with IA-2 and the overall OS event maturity at this DCO was 76.9%.[14]

The TOPAZ-1 study is ongoing, allowing for further, exploratory follow-up analyses of overall survival.[11]

The results presented for TOPAZ-1 within this submission are from the second interim analysis (IA-2, DCO 11 Aug 21) and, where available, the 6.5-month updated analysis (DCO 25 Feb 22).

B.2.6.1.1 Primary efficacy outcome: Overall survival

IA-2 (DCO 11 Aug 21): There were 424 OS events (61.9% overall maturity for OS). Treatment with D + Gem/Cis resulted in a statistically significantly and clinically meaningful improvement in OS versus placebo + Gem/Cis, (HR: 0.80; 95% CI: 0.66, 0.97; p=0.021) corresponding to a 20% reduction in the risk of death. Median OS was longer with D + Gem/Cis than placebo + Gem/Cis (12.8 months [95% CI: 11.1, 14.0] versus 11.5 months [95% CI: 10.1, 12.5]). The OS KM curves separated after approximately 6 months, and demonstrated a clear and sustained separation, which increased over time (Appendix M, Figure 10). The survival rate at 2 years was 24.9% in the D + Gem/Cis group and 10.4% in the placebo + Gem/Cis group.[11]

6.5-month update (DCO 25 Feb 2022): This update included 103 new OS events (527 OS events in total) and overall maturity for OS increased to 76.9%. The median duration of follow-up in censored patients was 19.9 months in the D + Gem/Cis group and 18.7 months in the placebo + Gem/Cis group.

With 6.5 months of additional follow-up, the OS benefit in the D + Gem/Cis arm numerically improved versus IA-2. The HR improved to 0.76 (95% CI: 0.64, 0.91) (Table 10) and demonstrated consistency with the OS benefit of D +Gem/Cis observed in IA-2 with more mature data. Median OS for patients treated with D + Gem/Cis also improved (12.9 months vs 12.8 months at IA-2) whereas median OS in the placebo + Gem/Cis group fell to 11.3 months (versus 11.5 months at IA-2). The OS KM curves (Figure 5) demonstrated continuing separation compared with IA-2

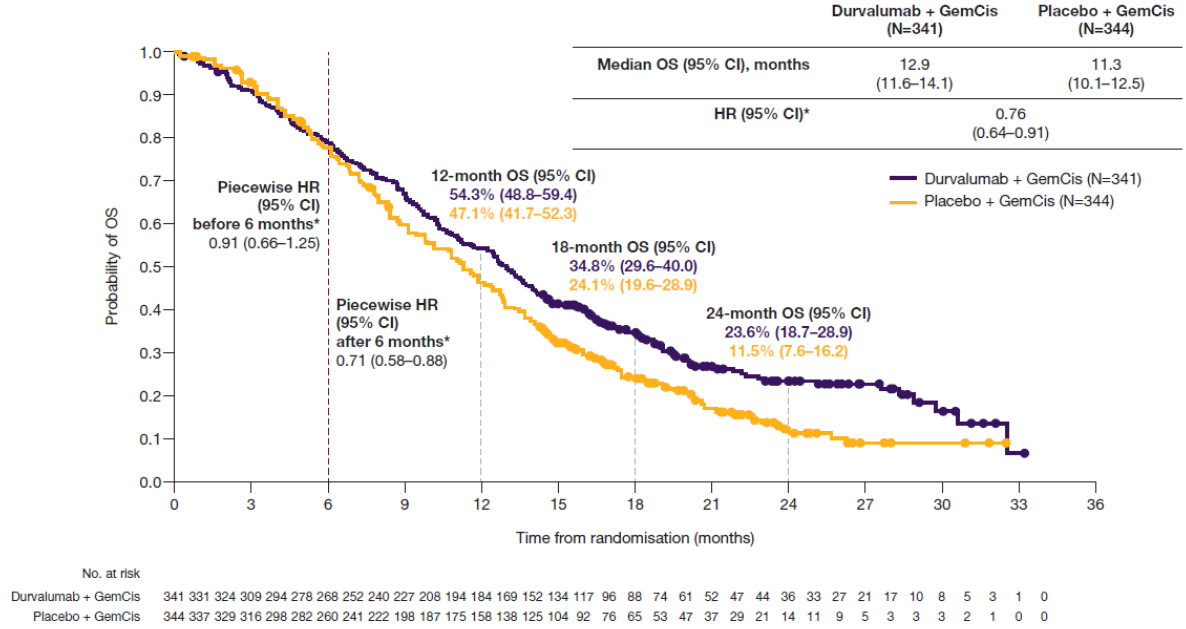
and showed a subset of patients with a sustained OS benefit. Furthermore, twice as many patients were alive at two years in the D + Gem/Cis arm compared with the placebo + Gem/Cis arm (23.6% vs. 11.5%), demonstrating that the survival benefit observed with D +Gem/Cis is sustained with further follow-up (Table 10).

Table 10: Overall survival – FAS (6.5-month update [DCO 25 February 2022])

Analysis (DCO)	**6.5-month update (25 Feb 2022)**	
	D + Gem/Cis (N = 341)	**Placebo + Gem/Cis (N = 344)**
Death, n (%)	248 (72.7)	279 (81.1)
Censored patients, n (%)	93 (27.3)	65 (18.9)
Still in survival follow-up†	89 (26.1)	59 (17.2)
Terminated prior to death‡	4 (1.2)	6 (1.7) ‡‡
Lost to follow-up	0	0
Withdrawn consent	4 (1.2)	6 (1.7) ‡‡
Median OS (months)§	12.9	11.3
95% CI for median overall survival§	11.6, 14.1	10.1, 12.5
OS at 12 months, % (95% CI) §	54.3 (48.8, 59.4)	47.1 (41.7, 52.3)
OS at 18 months, % (95% CI) §	34.8 (29.6, 40.0)	24.1 (19.6, 28.9)
OS at 24 months, % (95% CI) §	23.6 (18.7, 28.9)	11.5 (7.6, 16.2)
Median (range) duration of follow-up in censored patients (months)	19.9 (0.4-33.2)	18.7 (0.7-32.5)
Hazard ratio (95% CI) ¶, ††	0.76 (0.64, 0.91)	

† Includes patients known to be alive at DCO; ‡Includes patients with unknown survival status or patients who were lost to follow-up or patients with 'other' recorded on case report form; § Calculated using the Kaplan–Meier technique. CI for median overall survival derived based on Brookmeyer-Crowley method; ¶ The analysis was performed using a stratified Cox proportional hazards model (ties = Efron), adjusting for disease status and primary tumour location. The CI being calculated using a profile likelihood approach. A hazard ratio <1 favours durvalumab, to be associated with a longer overall survival than placebo; ††At the pre-planned interim analysis (IA-2; DCO: 11 August 2021, with 61.9% overall maturity for OS in the global cohort), the study met its primary objective by demonstrating OS superiority for D + Gem/Cis vs placebo + Gem/Cis (per the prespecified O'Brien Fleming type boundary for declaring statistical significance between the treatment groups (with a 2-sided interim p value of < 0.0300): HR of 0.80 (97% CI: 0.64, 0.99), p=0.021; ‡‡ At IA2, the investigator made a transcription error that was clarified at the 6.5 month update analysis. At IA2, the last known date that patient was known to be alive was erroneously reported as 29 June 2021. The last-known date that the patient was known to be alive is 24 July 2020.
Abbreviations: CI, confidence interval; D, durvalumab 1,500 mg; DCO, data cut-off; FAS, full analysis set; Gem/Cis, gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2; HR, hazard ratio; IA-2, interim analysis 2; OS, overall survival.
Source: CSR[12], Oh et al. (2022a).[11]

Figure 5: KM plot of overall survival – FAS (6.5 Month Update [DCO 25 February 2022])



Patients not known to have died at the time of analysis were censored at the last recorded date on which the patient was last known to be alive. Dots indicate a censored observation.
Abbreviations: Abbreviations: CI, confidence interval; D, durvalumab 1,500 mg; DCO, data cut-off; FAS, full analysis set; Gem/Cis, gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2; HR, hazard ratio; KM, Kaplan–Meier.
Source: CSR addendum[13] and Oh et al. (2022b).[14]

B.2.6.1.2 Assumptions of proportional hazards and piecewise analyses

Delayed separation of KM curves is commonly seen in clinical trials with immunotherapy in combination with chemotherapy. As such, the time-to-event endpoints for immunotherapy vs treatments with a different MoA typically violate the proportional hazards assumption. [54] [54] A kernel-smoothed estimate of the OS hazard function and the associated log-log (event times) versus log (time) plot confirmed a departure from the assumption of proportional hazards both at IA-2 and the 6.5-month update DCOs (data not shown). Given the lack of proportionality, the variation in treatment effect on OS was described by piecewise HR (Cox modelling) calculated over distinct time-periods, based on before and after separation of the OS curves at six months.

IA-2 (DCO 11 Aug 21): The HR from 0–6 months was 0.91 (95% CI: 0.66, 1.26) and the HR from six months onwards was 0.74 (95% CI: 0.58, 0.94) (i.e., before and after separation of the OS curves).

6.5-month update (DCO 25 Feb 2022): Given limited censoring before 6 months at IA-2, the piecewise HR remained 0.91 for 6 months (from randomisation). With 6.5 months of additional follow-up, the HR after separation of the curves was 0.71 (95% CI: 0.58, 0.88).

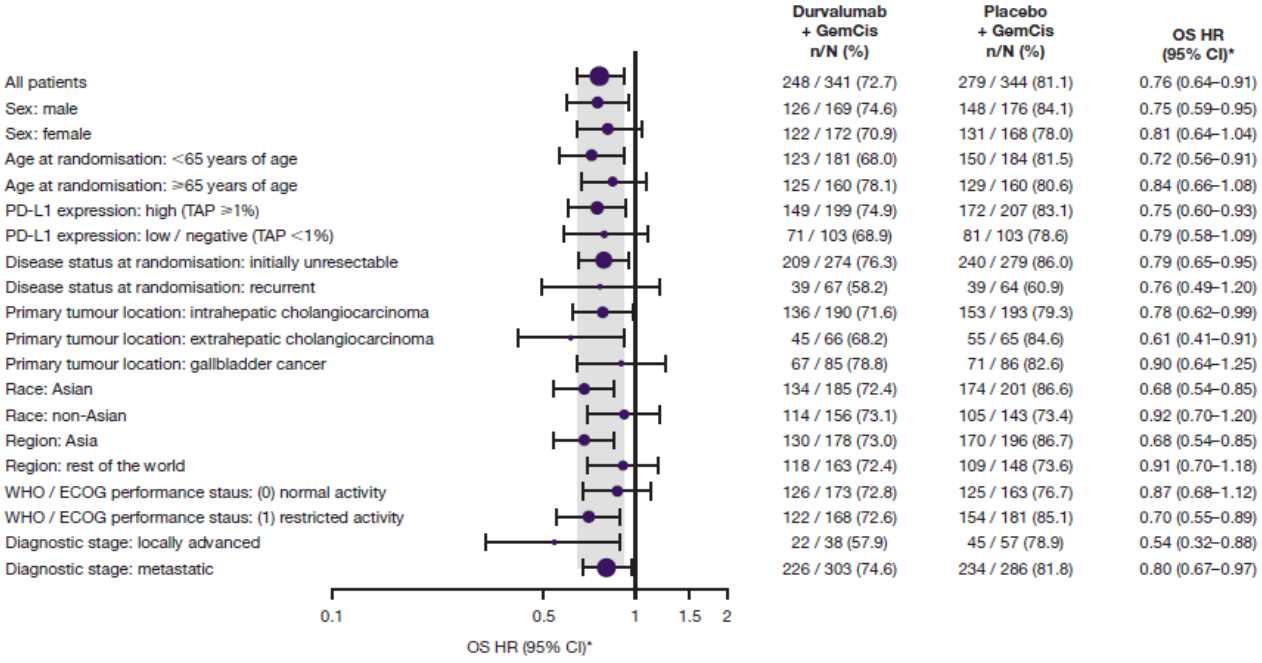
B.2.6.1.3 Subgroup analyses

A pre-planned subgroup analysis was carried out for OS. Details of the methodology are provided in Section B.2.7. It should be noted that TOPAZ-1 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 the individual subgroups may lead to greater uncertainty in their point estimates and wider CIs. Imbalances in other baseline covariates may have contributed to differences in HR across subgroups.

Additionally, UK clinicians reviewed the OS subgroup data and considered it generalisable to the FAS data. Based on a holistic review of all available OS data, they advocated for broad use of D + Gem/Cis in all patients who would otherwise be eligible for gemcitabine with cisplatin and have no contraindications to immunotherapy.[19]

6.5-month update (DCO 25 Feb 2022): An OS benefit for D + Gem/Cis versus placebo + Gem/Cis was consistently observed across all pre-defined subgroups, based on demographics, geographical region, primary tumour location, disease status, WHO/ECOG PS, and PD-L1 status (Figure 6). Improvements in OS in favour of D + Gem/Cis were consistent between IA-2 and the 6.5-month update with all estimated HRs favouring D + Gem/Cis at both DCOs.

Figure 6: Forest plot of overall survival by subgroup – FAS (6.5-month update [DCO 25 Feb 2022])



The overall analysis was performed using a stratified Cox proportional hazards model, adjusting for disease status (initially unresectable or recurrent) and primary tumour location (IHCC, EHCC or GBC) from IVRS. Profile likelihood methods were used to calculate CIs. Estimates for all subgroup categories were from an unstratified Cox 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) hazard ratio. Hazard ratio (D + Gem/Cis vs placebo + Gem/Cis) and 95% CI. A hazard ratio < 1 favours D + Gem/Cis.
Abbreviations: CI, confidence interval; D, durvalumab 1,500 mg; DCO; data cut-off; ECOG, Eastern Cooperative Oncology Group; EHCC, extrahepatic cholangiocarcinoma; FAS, full analysis set; Gem/Cis, gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2; IA-2, interim analysis 2; IHCC, intrahepatic cholangiocarcinoma; IVRS, interactive voice response system; PD-L1, programmed cell death ligand 1; TAP, tumour area positivity; WHO, World Health Organization.
Source: CSR[12] and Oh et al. (2022b).[14]

B.2.6.1.4 Secondary efficacy outcome – progression-free survival

IA-2 (DCO 11 Aug 21): Investigator-assessed PFS was formally tested for statistical significance following observation of statistical significance for OS. At the time of IA-2, 573 PFS events had occurred (83.6% data maturity).

A statistically significant and clinically meaningful improvement in PFS was observed for the D + Gem/Cis group compared with the placebo + Gem/Cis group (HR 0.75; 95% CI: 0.63, 0.89; p=0.001), corresponding to a 25% reduction in the overall risk of progression or death with D + Gem/Cis (Table 11). Median PFS was longer with D + Gem/Cis than placebo + Gem/Cis (7.2 months [95% CI: 6.7, 7.4] vs 5.7 months [95% CI: 5.6, 6.7]).

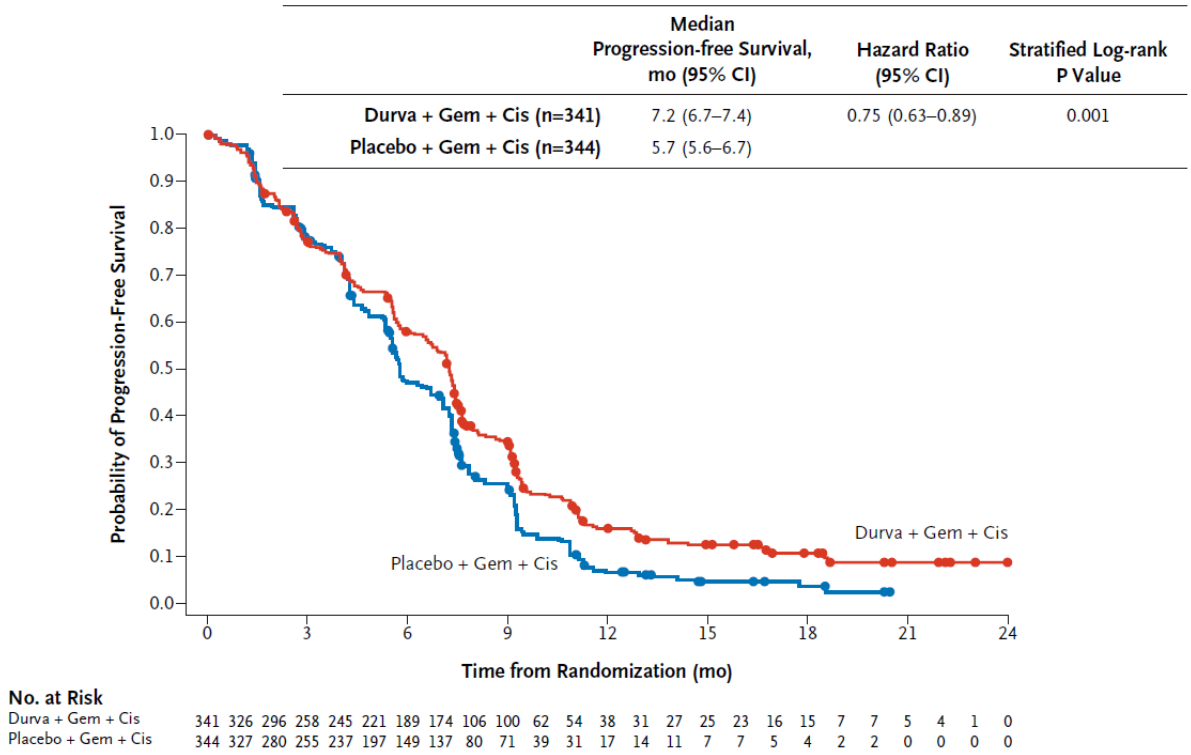
A sustained separation in the KM curves in favour of the D + Gem/Cis treated group was observed from approximately 4 months, extending up to the end of follow-up (24 months) (Figure 7).

Table 11: Progression free survival – FAS (IA-2 [DCO 11 Aug 21])

RECIST 1.1	D + Gem/Cis (N=341)	Placebo + Gem/Cis (N=344)
Total events†, n (%)	276 (80.9)	297 (86.3)
Censored patients, n (%)	65 (19.1)	47 (13.7)
Median PFS‡, months (95% CI)	7.2 (6.7, 7.4)	5.7 (5.6, 6.7)
PFS at 6 months‡, % (95% CI)	58.3 (52.8, 63.4)	47.2 (41.6, 52.5)
PFS at 9 months‡, % (95% CI)	34.8 (29.6, 40.0)	24.6 (20.0, 29.5)
PFS at 12 months‡, % (95% CI)	16.0 (12.0, 20.6)	6.6 (4.1, 9.9)
HR for PFS§ (95.19% CI; 2-sided p-value¶)	0.75 (0.63, 0.89; p=0.001)	
Median (range) duration of follow-up in censored patients (months)	9.2 (0, 24)	6.9 (0, 20.4)

† Only includes progression events that occurred within 2 missed visits of the last evaluable assessment; ‡e Calculated using the Kaplan–Meier technique; § 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; ¶ The p-value is based on a stratified log-rank test and tested at 0.0481 significance level. A hazard ratio < 1 favours D + Gem/Cis, to be associated with a longer PFS than placebo + Gem/Cis.
Abbreviations: CI, confidence interval; D, durvalumab 1,500 mg; DCO, data cut-off; FAS, full analysis set; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; HR, hazard ratio; IA-2, interim analysis 2; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1.
Source: CSR.[12]

Figure 7: KM plot of progression-free survival – FAS (IA-2 [DCO 11 Aug 21])



Dot indicates a censored observation. PFS based on Investigator assessments according to RECIST 1.1. Patients who had not progressed or died at the time of analysis were censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment prior to the 2 missed visits and therefore excluded from the number of events.
Abbreviations: CI, confidence interval; D, durvalumab 1,500 mg; DCO, data cut-off; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; HR, hazard ratio; IA-2, interim analysis 2; KM, Kaplan–Meier; PFS, progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1.
Source: CSR[12] and Oh et al. (2022a).[11]

B.2.6.1.5 Secondary efficacy outcome - objective response rate

IA-2 (DCO 11 Aug 21): Among patients with measurable disease at baseline, the ORR was 26.7% (91/341 patients) in the D + Gem/Cis group versus 18.7% (64/343 patients) in the placebo + Gem/Cis group. The higher likelihood of response to treatment with D + Gem/Cis was found to be clinically meaningful (odds ratio [OR] 1.60 [95% CI: 1.11, 2.31]; nominal p=0.011) (Table 12). This included confirmed CR in 7 (2.1%) of patients treated with D + Gem/Cis versus 2 (0.6%) patients treated with placebo + Gem/Cis.

Table 12: Objective response rate (investigator confirmed) using stratified CMH test – FAS patient with measurable disease at baseline (IA-2 [DCO 11 Aug 21])

RECIST 1.1	Number (%) patients	
	D + Gem/Cis (N = 341)	Placebo + Gem/Cis (N = 343)
Complete response	7 (2.1)	2 (0.6)
Partial response	84 (24.6)	62 (18.1)
Number (%) of patients with response†	91 (26.7)	64 (18.7)
Odds ratio‡	1.60	
95% CI	1.11, 2.31	
Nominal 2-sided p-value	0.011	

† Responses included confirmed complete or partial response per Investigator according to RECIST 1.1. Does not include patients who discontinued randomised treatment without progression or received a subsequent anti-cancer therapy and then responded; ‡ An odds ratio >1 favours D + Gem/Cis.
Note: The analysis was performed using a stratified CMH test with factors for disease status and tumour location (per IVRS).
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; D, durvalumab 1,500 mg; DCO, data cut-off; FAS, full analysis set; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; IA-2, interim analysis 2; IVRS, interactive voice response system; RECIST 1.1, Response Evaluation criteria in Solid Tumours version 1.1.
Source: CSR.[12]

B.2.6.1.5.1 Best objective response

A higher frequency of CR was reported for D + Gem/Cis (7 [2.1%] patients) compared with placebo + Gem/Cis (2 [0.6%] patients). Partial responses were, also, more frequent with D + Gem/Cis (84 [24.6%] patients) than with placebo + Gem/Cis (62 [18.1%] patients).[11] The first post-baseline tumour assessment was scheduled for 6 ± 1 weeks after randomisation, and a best objective response (BOR) of stable disease of at least 5 weeks' duration was reported for [redacted] patients and [redacted] patients, by respective treatment group. A BOR of PD was reported at a similar frequency in both treatment groups ([redacted], by respective treatment group).[12]

B.2.6.1.6 Secondary efficacy outcome – duration of response

IA-2 (DCO 11 Aug 21): The response to treatment with D + Gem/Cis was more durable compared with the response to placebo + Gem/Cis as reflected in the higher rate estimates for patients remaining in response at 9 months (32.6% patients in the D + Gem/Cis group vs 25.3% patients in the placebo + Gem/Cis group) and at 12 months (26.1% patients in the D + Gem/Cis group vs 15.0% patients in the placebo + Gem/Cis group) (Table 13). At the IA-2 DCO, there were also

[redacted] in the D + Gem/Cis group who had ongoing responses ([redacted]; of whom, [redacted] were still receiving study treatment) than in the placebo + Gem/Cis group ([redacted], of whom [redacted] were still receiving treatment). Overall, responses occurred earlier for D + Gem/Cis compared to placebo + Gem/Cis (median 1.6 months compared to 2.7 months, respectively).[11]

Table 13: Duration of response (Investigator confirmed) – FAS; patients with objective response and measurable disease at baseline (IA-2 [DCO 11 Aug 21])

	D + Gem/Cis (N = 91)	Placebo + Gem/Cis (N = 64)
Number of responders who subsequently progressed or died	[redacted]	[redacted]
Number of censored responders, n (%)	[redacted]	[redacted]
Number of ongoing responses	[redacted]	[redacted]
Censored death	[redacted]	[redacted]
Duration of response from onset of response (months)†, ††		
Median (95% CI)	6.4 (5.9, 8.1)	6.2 (4.4, 7.3)
25th percentile, 75th percentile	4.6, 17.2	3.8, 9.0
Percentage remaining in response††		
≥ 3 months	88.9	89.0
≥ 6 months	59.3	54.2
≥ 9 months	32.6	25.3
≥ 12 months	26.1	15.0

† 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 (including rules for censoring; ‡ One patient received surgical resection for BTC and remained on study treatment after surgery. The site continued scans (each resulting in RECIST not evaluable). Per the SAP, DoR was censored at patient's last evaluable RECIST 1.1 assessment; § For two patients the ongoing responses were apparently maintained with subsequent anti-cancer therapy. Both patients discontinued treatment due to subjective disease progression. Per PFS censoring methodology, DoR was censored at patient's last evaluable RECIST 1.1 assessment for both cases; ¶ One patient responded to treatment but then withdrew consent for study participation, without RECIST progressive disease, and later died. Due to withdrawal of consent, follow-up scans were not performed. In the absence of at least 2 or more missed visits, the patient was censored at the time of the latest evaluable RECIST 1.1 assessment; †† Calculated using the Kaplan–Meier technique.
Percentages were calculated based on the number of confirmed responders. One month is calculated as 30.4375 days. Note: When considering the similar median values, the reader should consider the impact of the IA-2 DCO, as longer durability of response is evident for D + Gem/Cis in the number of ongoing responses, 95% CI of the median, the interquartile range, and in the percentage of patients remaining in response at 6, 9, and 12 months.
Abbreviations: BTC, biliary tract cancer; CI, confidence interval; CR, complete response; D, durvalumab 1,500 mg; DCO, data cut-off; FAS, full analysis set; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; IA-2, interim analysis 2; PR, partial response.
Source: CSR.[12]

B.2.6.1.7 Secondary outcome – disease control rate

The disease control rate (DCR) was 85.3% in the D + Gem/Cis group and 82.6% in the placebo + Gem/Cis group. DCR favoured the D + Gem/Cis group compared with the placebo + Gem/Cis group at all timepoints: 57.5% vs 48.3%, respectively at 24 weeks, 41.9% vs 36.3, respectively at 32 weeks and 35.2% vs 27.0%, respectively at 48 weeks, suggesting that sustained disease control was more likely with D + Gem/Cis treatment.

B.2.6.1.8 Secondary outcome – patient reported outcomes/quality of life

IA-2 (DCO 11 Aug 21): PROs were assessed using the EORTC QLQ-C30 and EORTC QLQ-BIL21 questionnaires. A description of these measures is provided in Appendix M.1.2 (Table 52). A high score on a functional or global health status/QoL scale represents a high level of functioning or global QoL, while a high score on a symptom scale/item represents a high level of symptom burden. A clinically meaningful change/difference is defined as an absolute change in the score from baseline of ≥10 points. All PRO analyses were performed on the PRO analysis set (see Table 8 for definition).

B.2.6.1.8.1 Compliance

Compliance rates with the EORTC QLQ-30 were high (≥85%) at baseline and were similar between treatment groups up to Cycle 16 (≥80% at the majority of timepoints). Compliance rates with the EORTC QLQ-BIL21 were also high (≥85%) at baseline and were similar between treatment groups up to Cycle 16 (>80% at the majority of timepoints).

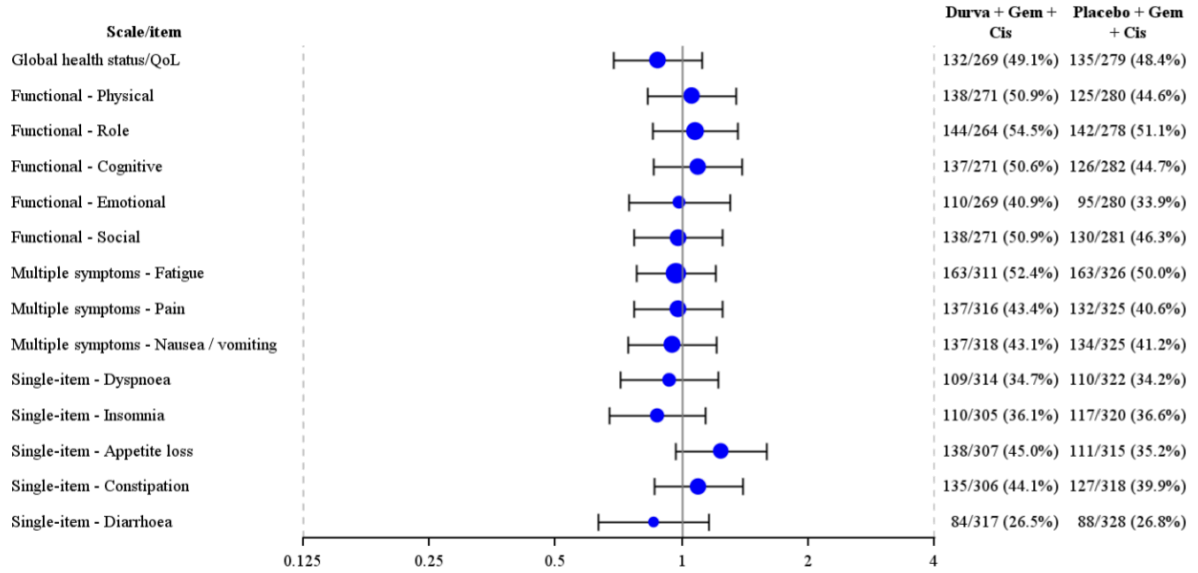
B.2.6.1.8.2 Baseline scores

Baseline scores were comparable across treatment groups for all EORTC QLQ-C30 and EORTC QLQ-BIL21 scales/items. In both treatment groups, patients presented with slightly lowered health status (global health status/QoL per EORTC QLQ-C30) and mild symptomatology at baseline (i.e., 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).

B.2.6.1.8.3 Time to deterioration

No detriment in QoL as measured using the EORTC QLQ-C30 was observed in the D + Gem/Cis treatment group compared with the placebo + Gem/Cis group (Figure 8). There was a trend towards an improvement in global health status functioning (emotional and social), fatigue, pain, nausea/vomiting, dyspnoea, insomnia, and diarrhoea with D + Gem/Cis treatment.

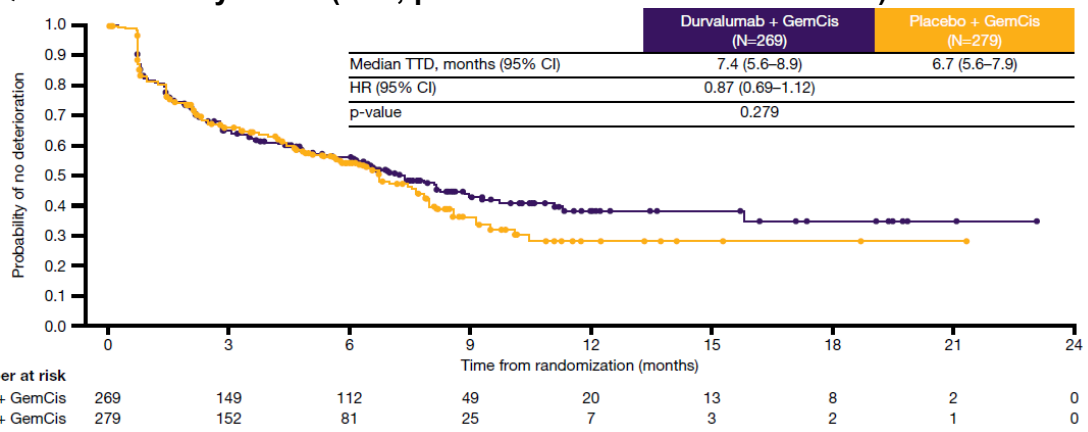
Figure 8: Forest plot of hazard ratios for time to deterioration (months) for EORTC QLQ-C30 items – PRO analysis set (IA-2; patients with baseline scores for each symptom ≤ 90 [≥ 10])



Estimates for each scale/item were from a stratified Cox proportional hazard model, adjusting for disease status initially unresectable or recurrent) and primary tumour location (IHCC, EHCC or GBC) providing the HR and 95% CI. Stratification factors were from IVRS. A hazard ratio < 1 favours D + Gem/Cis. The size of the circle is proportional to the number of events. Time to deterioration was defined as the time from randomisation until the date of first clinically meaningful deterioration confirmed by a subsequent visit (increase from baseline of ≥10 for symptom scales and a decrease of ≥ 10 for Global Health Status/QoL and functional domains), or patient too sick to complete questionnaire, or death (by any cause).
Abbreviations: CI confidence interval; D, durvalumab 1,500 mg; EORTC, European Organisation for Research and Treatment of Cancer; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; HR, hazard ratio; IA-2, interim analysis 2; IHCC, intrahepatic cholangiocarcinoma; IVRS, interactive voice response system; PRO, patient-reported outcome; QLQ-C30, 30-Item Core Quality-of-Life Questionnaire' QoL quality of life.
Source: CSR [12] and Burris et al. (2022).[53]

Separation of the D + Gem/Cis and placebo + Gem/Cis curves for time to deterioration of GHS/QoL occurred at around 7 months in favour of durvalumab (Figure 9), which is consistent with the OS curves for D + Gem/Cis and placebo + Gem/Cis (see Section B.2.6.1.1).

Figure 9: KM plot for time to deterioration (months) for EORTC QLQ-C30 Global Health Status/QoL – PRO analysis set (IA-2; patients with baseline scores ≥10)



Dots represent censored observations. Time to deterioration was defined as the time from randomisation until the date of first clinically meaningful deterioration that was confirmed at a subsequent visit (decrease from baseline of ≥10 for Global Health Status/QoL), or patient too sick to complete questionnaire, or death (by any cause). All data (scheduled or not) during treatment or follow-up was considered for determination of deterioration. Patients were censored at their last evaluable PRO assessment. Hazard ratio and CI were calculated using a stratified Cox proportional hazards model adjusted for disease status of primary tumour location. An HR <1 favours D + Gem/Cis.

Abbreviations: CI, confidence interval; CSR, clinical study report; D, durvalumab 1,500 mg; EORTC, European Organisation for Research and Treatment of Cancer; Gem/Cis, gemcitabine 1,000 mg/m^2 cisplatin 25 mg/m^2; HR, hazard ratio; IA-2, interim analysis 2; KM, Kaplan–Meier; PRO, patient-reported outcome; QLQ-C30, 30-Item Core Quality-of-Life Questionnaire; QoL, quality of life.
Source: CSR[12] and Burris et al. (2022).[53]

No detriment in QoL as measured using the EORTC QLQ-BIL21 was observed in the D + Gem/Cis treatment group compared with the placebo + Gem/Cis group (Figure 10). There was a trend towards a slight improvement in abdominal pain, jaundice (single item), pain, and anxiety with D + Gem/Cis treatment.

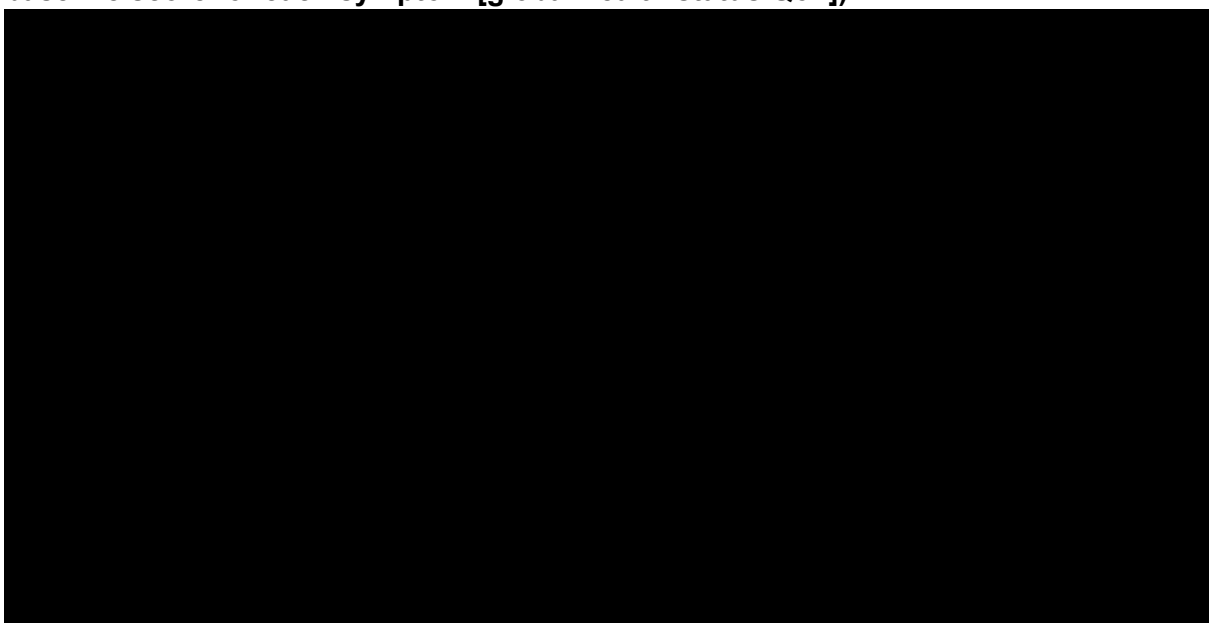
Figure 10: Forest plot of hazard ratios for time to deterioration (months) for EORTC QLQ-BIL21 items – PRO analysis set (IA-2; patients with baseline scores for each symptom ≤90)

Estimates for each scale/item were from a stratified Cox proportional hazard model, adjusting for disease status (initially unresectable or recurrent) and primary tumour location (IHCC, EHCC or GBC) providing the HR and 95% CI. Stratification factors were from IVRS. A hazard ratio < 1 favours D + Gem/Cis. The size of the circle is proportional to the number of events. Time to deterioration was defined as the time from randomisation until the date of first clinically meaningful deterioration confirmed or death (by any cause).
Abbreviations: CI confidence interval; D, durvalumab 1,500 mg; EORTC, European Organisation for Research and Treatment of Cancer; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; HR, hazard ratio; IA-2, interim analysis 2; IHCC, intrahepatic cholangiocarcinoma; IVRS, interactive voice response system; PRO, patient-reported outcome; QLQ-BIL21, 21-Item Cholangiocarcinoma and Gallbladder Cancer Quality-of-Life Questionnaire; QoL quality of life.
Source: CSR.[12]

B.2.6.1.8.4 Improvement rates

No detriment in QoL as measured using the EORTC QLQ-C30 was observed in the D + Gem/Cis treatment group compared with the placebo + Gem/Cis group. A trend in the OR of clinically meaningful improvement for global health status/QoL, functioning (physical, emotional, social) and insomnia was observed in favour of the D + Gem/Cis treatment group (Figure 11).

Figure 11: Forest plot of odds ratios for improvements based on best objective response for EORTC QLQ-C30 items – PRO analysis set (IA-2; patients with ≥1-0 [≤90] baseline score for each symptom [global health status/QoL])



The analysis was performed using logistic regression adjusted for disease status (initially unresectable or recurrent) and primary tumour location (IHCC, EHCC, or GBC) with 95% CI calculated by profile likelihood. Stratification factors were from IVRS. Odds ratio (D + Gem/Cis vs placebo + Gem/Cis) and 95% CI. An odds ratio >1 favours D + Gem/Cis. Size of circle is proportional to the number of patients with improvement.
Abbreviations: CI confidence interval; D, durvalumab 1,500 mg; EORTC, European Organisation for Research and Treatment of Cancer; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; IA-2, interim analysis 2; IHCC, intrahepatic cholangiocarcinoma; IVRS, interactive voice response system; PRO, patient-reported outcome; QLQ-C30, 30-Item Core Quality-of-Life Questionnaire' QoL quality of life.
Source: CSR.[12]

No detriment in QoL as measured using the EORTC QLQ-BIL21 was observed in the D + Gem/Cis treatment group compared with the placebo + Gem/Cis group. A trend in the OR of clinically meaningful improvement for jaundice and weight loss [single item] and eating, jaundice, pain, anxiety, and tiredness [multiple symptoms]) was observed in favour of the D + Gem/Cis treatment group (Figure 12).

Figure 12: Forest plot of odds ratios for improvements based on best objective response for EORTC QLQ-BIL21 items – PRO analysis set (patients with baseline scores ≥10)

The analysis was performed using logistic regression adjusted for disease status (initially unresectable or recurrent) and primary tumour location (IHCC, EHCC or GBC) with 95% CI calculated by profile likelihood. Stratification factors were from IVRS. Odds ratio (D + Gem/Cis vs placebo + Gem/Cis) and 95% CI. An odds ratio >1 favours D + Gem/Cis. Size of circle is proportional to the number of patients with improvement.
Abbreviations: CI confidence interval; D, durvalumab 1,500 mg; EORTC, European Organisation for Research and Treatment of Cancer; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; IA-2, interim analysis 2; IHCC, intrahepatic cholangiocarcinoma; IVRS, interactive voice response system; PRO, patient-reported outcome; QLQ-BIL21, 21-Item Cholangiocarcinoma and Gallbladder Cancer Quality-of-Life Questionnaire; QoL quality of life.
Source: CSR.[12]

B.2.6.1.8.5 Change from baseline

Overall, change from baseline analyses (including MMRM) were consistent with no detriment in QoL per EORTC QLQ-C30 and EORTC QLQ-BIL21 in the D + Gem/Cis group compared with the placebo + Gem/Cis group. Improvements were observed for D + Gem/Cis compared with placebo + Gem/Cis for global health status/QoL, emotional functioning, and symptoms pain and dyspnoea (EORTC QLQ-C30) and pruritus, weight loss, jaundice, and pain (EORTC QLQ-BIL21 symptoms).

B.2.6.1.9 Exploratory endpoint - EQ-5D-5L

Mean absolute EQ-Visual Analogue Scale (VAS) scores at baseline were [redacted]). The change from baseline in EQ-5D-5L VAS score was [redacted] (Figure 13), indicating [redacted] with the addition of durvalumab to Gem/Cis.

Figure 13: EQ-5D-5L change from baseline in EQ-VAS score over time – PRO analysis set (IA-2)

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.

Abbreviations: EQ-5D-5L: EuroQol-5 Dimension 5 component scale; EQ-VAS: EuroQol-5 Dimension Visual Analogue Scale; FAS: full analysis set; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; PRO: patient reported outcome.
Source: CSR.[12]

Data for other exploratory PRO endpoints (PRO-CTCAE and PGIS) are not presented in this submission and can be found in the CSR.

B.2.6.1.10 Efficacy conclusions

TOPAZ-1 met its primary endpoint, demonstrating a statistically significant and clinically meaningful improvement in OS with D + Gem/Cis versus placebo + Gem/Cis with a clear and sustained separation of OS curves from 6 months. The difference in OS between treatment groups was increasingly apparent over time as

demonstrated with the additional 6.5-month data cut, and twice as many patients were alive at two years in the D + Gem/Cis arm compared with the placebo + Gem/Cis arm. Treatment with D + Gem/Cis also resulted in a significant improvement in PFS (HR 0.75 [95% CI 0.63, 0.89]; p=0.001) with separation of curves seen from 4 months indicating the early treatment effect of this regimen. Furthermore, treatment with D + Gem/Cis also resulted in a clinically meaningful improvement in ORR (26.7% versus 18.7% with placebo + Gem/Cis) and a faster median time to response (1.6 months) compared with placebo + Gem/Cis (2.7 months). PRO endpoints demonstrated that the addition of durvalumab to Gem/Cis resulted in no detriment in QoL and a trend towards a longer time to deterioration with D + Gem/Cis treatment. The results of TOPAZ-1 therefore demonstrate that the addition of durvalumab to Gem/Cis is associated with a significant and clinically meaningful extension to OS and PFS, with no detrimental effect on QoL, for a patient population who currently have very poor OS and limited treatment options that have not evolved in more than 10 years. D + Gem/Cis for treatment for locally advanced, unresectable, or metastatic BTC has also been awarded an ESMO MCBS score of 4, which is classified as a substantial magnitude of benefit. This grading was awarded due to the ≥10% increase in overall survival at 2 years demonstrated in the TOPAZ-1 trial.[6]

B.2.7 Subgroup analysis

Pre-planned subgroup analyses of OS, PFS and ORR included disease status, primary tumour location, sex, age, race (Asian, non-Asian ethnicity), region (Asia, RoW), WHO/ECOG PS (0, 1), extent of disease (locally advanced, metastatic), and PD-L1 status (TAP ≥1% versus <1%;).

For each subgroup level of a factor, the HR (for the treatment comparisons of interest) and 95% CI was calculated from a Cox proportional hazards model that only contained a term for treatment. These were presented on a forest plot including the HR and 95% profile likelihood CI, along with the results of the overall primary analysis. To assess the consistency of treatment effect between subgroups for plausible subgroups, the presence of quantitative interactions between treatment and stratification factors was checked using an overall global interaction test (at the

2-sided 10% significance level). Where statistically significant, an attempt to determine the cause and type of interaction was to be made using stepwise backwards selection on the saturated model until a final model was reached where all included interactions were significant, and all excluded interactions were non-significant.

Please see section B.2.6.1.3 for the pre-defined subgroup analyses for OS. Results for the PFS and ORR endpoints are presented in Appendix E. A treatment effect in favour of D + Gem/Cis was observed for all endpoints cross all subgroups analysed.

B.2.8 Meta-analysis

TOPAZ-1 is the only Phase 3 RCT reporting on the efficacy and safety of durvalumab in combination with Gem/Cis in patients with locally advanced, unresectable, or metastatic BTC. Therefore, a meta-analysis was not required.

B.2.9 Indirect and mixed treatment comparisons

As head-to-head clinical trial data were available for durvalumab in combination with Gem/Cis versus Gem/Cis only (the only relevant comparator for the submission (Table 1)) and no further studies that were deemed relevant to the decision problem were identified in the SLR, an indirect or mixed-treatment comparison was not required.

B.2.10 Adverse reactions

B.2.10.1 TOPAZ-1

AE data were recorded in the TOPAZ-1 trial at IA-2 and the 6.5-month update DCOs. In this section, AE data are presented from the 6-5-month update, which represents the most recent DCO. Data for the safety analysis set (SAS) (see Table 8 for population definition) which included 338 D + Gem/Cis-treated patients and 342 placebo + Gem/Cis-treated patients is presented in this section.

B.2.10.1.1 Exposure

6.5-month update (DCO 25 Feb 2022): In total, [redacted] patients in the D + Gem/Cis group continued with treatment compared with [redacted] patients in the

placebo + Gem/Cis group. The median actual duration of exposure was [redacted] months in the D + Gem/Cis group and [redacted] months in the placebo + Gem/Cis group (Table 14) (and was consistent with the median duration in the IA-2 analysis [data not shown]). This difference was due to a longer duration of durvalumab monotherapy as the administration of study treatments was similar between treatment groups during the chemotherapy period (data not shown). There was no meaningful difference between treatment groups in exposure to gemcitabine or cisplatin (Table 15).

Table 14: Duration of durvalumab or placebo exposure – SAS (6.5 Month Update [DCO 25 February 2022])

	Number (%) of patients	
	D + Gem/Cis (N = 338)	**Placebo + Gem/Cis (N = 342)**
Total (intended) treatment duration (months)†		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Total treatment years	[redacted]	[redacted]
Actual treatment duration (months)‡		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Total treatment years	[redacted]	[redacted]

† Total treatment duration = (min (last dose date where dose > 0 + [20 if last dose in period 1 (combination) or 27 if last dose in period 2 (maintenance)], date of death, date of DCO) - first dose date +1) / (365.25/12); ‡Actual treatment duration = total treatment duration minus the total duration of delays.
Abbreviations: D, durvalumab 1,500 mg; DCO, data cut-off; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; SAS, safety analysis set; SD, standard deviation.
Source: CSR addendum.[13]

Table 15: Duration of gemcitabine or cisplatin exposure – SAS (6.5 Month Update [DCO 25 February 2022])

	Number (%) of patients	
	D + Gem/Cis (N = 338)	**Placebo + Gem/Cis (N = 342)**
Gemcitabine		
Total (intended) treatment duration (months)†		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Total treatment years	[redacted]	[redacted]
Actual treatment duration (months)‡		
Mean (SD)	[redacted]	[redacted]

	Number (%) of patients	
	D + Gem/Cis (N = 338)	Placebo + Gem/Cis (N = 342)
Median (min, max)	[redacted]	[redacted]
Total treatment years	[redacted]	[redacted]
Cisplatin		
Total (intended) treatment duration (months)†		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Total treatment years	[redacted]	[redacted]
Actual treatment duration (months)‡		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Total treatment years	[redacted]	[redacted]

† Total treatment exposure = (min (last dose date where dose > 0 + W, date of death, date of DCO) - first dose date + 1) / 365.25/12). Where W = 6 if the last dose was scheduled on Day 1 and W = 13 if the last dose scheduled on Day 8; ‡ treatment duration = total treatment duration minus the total duration of dose delays.

Abbreviations: D, durvalumab 1,500 mg; DCO, data cut-off; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; SAS, safety analysis set; SD, standard deviation.
Source: CSR addendum.[13]

B.2.10.1.2 AE overview

6.5-month update (DCO 25 Feb 2022): Nearly all patients in both treatment arms had experienced an AE by the 6-5-month DCO (99.4% of patients in the D + Gem/Cis group and 98.8% of patients in the placebo + Gem/Cis group) (Table 16). The proportion of patients who experienced an AE that was possibly related to study medication was similar between treatment groups (92.9% with D + Gem/Cis and 90.1% with placebo + Gem/Cis). SAEs were reported by [redacted] of the D + Gem/Cis group and [redacted] of the placebo + Gem/Cis group. AEs leading to discontinuation of study treatment were reported for 12.7% of the D + Gem/Cis group and 15.2% of the placebo + Gem/Cis group. ImAEs were [redacted] in the D + Gem/Cis group than the placebo + Gem/Cis group ([redacted] vs [redacted]), however most imAEs were [redacted], and the proportion of Grade 3 or 4 immune-mediates adverse events (imAEs) was [redacted] between the treatment groups ([redacted] in the D + Gem/Cis group and [redacted] in the placebo + Gem/Cis group). [redacted] imAEs led to death in either treatment group (Table 16).

Table 16: Overview of adverse events – SAS (6.5 Month Update [DCO 25 February 2022])

AE category	Number (%) of patients†	
	D + Gem/Cis (N=338)	Placebo + Gem/Cis (N=342)
Any AE	336 (99.4)	338 (98.8)
Possibly related to any study medication‡	314 (92.9)	308 (90.1)
Any AE of max CTCAE Grade 3 or 4	250 (74.0)	257 (75.1)
Possibly related to any study medication‡, §	206 (60.9)	217 (63.5)
Any AE leading to death	13 (3.8)	14 (4.1)
Possibly related to any study medication‡	2 (0.6)	1 (0.3)
Any SAE (including AEs leading to death)	[redacted]	[redacted]
SAE possibly related to any study medication‡	[redacted]	[redacted]
Any AE leading to discontinuation of study treatment	43 (12.7)	52 (15.2)
Durvalumab or placebo	[redacted]	[redacted]
Gem and/or Cis	[redacted]	[redacted]
Possibly related to any study medication‡	30 (8.9)	39 (11.4)
Any AE leading to dose interruption/delay or reduction	[redacted]	[redacted]
Durvalumab or placebo	[redacted]	[redacted]
Gem and/or Cis	[redacted]	[redacted]
Any infusion reaction AEs¶	[redacted]	[redacted]
Any imAE	[redacted]	[redacted]
Any imAE possibly related††	[redacted]	[redacted]
imAEs of maximum CTCAE Grade 3 or 4‡‡	[redacted]	[redacted]
imAEs of maximum CTCAE Grade 3 or 4 possibly related††	[redacted]	[redacted]
Any imSAE (including AEs leading to death)	[redacted]	[redacted]
Any imSAE (including AEs leading to death) possibly related††	[redacted]	[redacted]
Any imAE with outcome of death	[redacted]	[redacted]

† 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; ‡ As assessed by the Investigator; § The maximum CTCAE grade per patient/event is considered (i.e., does not include patients with subsequent Grade 5 events); ¶ Infusion reaction, as assessed by the Investigator; †† As assessed by the Investigator. Missing responses are counted as related; ‡‡ All CTCAE grades per patient, not just the maximum, were considered when identifying whether there was a Grade 3 or 4 event (i.e., includes patients with subsequent Grade 5 events).
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; DCO, data cut-off D, durvalumab 1,500 mg; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; IA-2, interim analysis-2;

imAE, immune mediated AE; SAE, serious adverse event; SAS, safety analysis set.
Source: CSR addendum.[13]

B.2.10.1.3 Most common AEs by preferred term

6.5-month update (DCO 25 Feb 2022): The most common AEs occurring in the D + Gem/Cis group were [redacted] (Table 17). In the placebo + Gem/Cis group, the most common AEs were [redacted] (Table 17). [redacted].

Table 17: Most common adverse events occurring in ≥10% of patients in either treatment group – SAS (6.5 Month Update [DCO 25 February 2022])

Preferred term	Number (%) of patients†	
	D + Gem/Cis (N = 338)	Placebo + Gem/Cis (N = 342)
Patients with any AE	336 (99.4)	338 (98.8)
Anaemia	[redacted]	[redacted]
Nausea	[redacted]	[redacted]
Constipation	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Pruritis	[redacted]	[redacted]
Rash	[redacted]	[redacted]
Abdominal pain upper	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]
Alanine aminotransferase increased	[redacted]	[redacted]

† Number (%) of patients with any AE, sorted in decreasing frequency for preferred term in the D + Gem/Cis group. Patients with multiple events in the same preferred term are counted only once in that preferred term. Patients with events in more than one preferred term are counted once in each preferred term.
Table includes AEs with an onset date or pre-treatment AEs that increased in severity on or after the date of first dose and up to and including 90 days following the date of last dose of study treatment or up to the date of initiation of the first subsequent anticancer therapy (whichever occurred first).
Percentages were based on the total numbers of patients in the treatment group.
MedDRA version 24.0.
Abbreviations: AE, adverse event; DCO, data cut-off; D, durvalumab 1,500 mg; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; IA-2, interim analysis 2; SAS, safety analysis set.
Source: CSR addendum.[13]

B.2.10.1.4 Grade 3 or 4 AEs by preferred term

6.5-month update (DCO 25 Feb 2022): A similar proportion of patients experienced Grade 3 or 4 AEs in the D + Gem/Cis and placebo + Gem/Cis treatment groups (74.0% vs 75.1%) (Table 16). The most common Grade 3 or 4 AEs in the D +

Gem/Cis group were [redacted]. In the placebo + Gem/Cis group, the most common Grade 3 or 4 AEs were [redacted] (see Table 16).

Table 18: CTCAE Grade 3 or 4 AEs reported for ≥5% of patients in either treatment group – SAS (6.5 Month Update [DCO 25 February 2022])

Preferred term	Number (%) of patients†	
	D + Gem/Cis (N = 338)	Placebo + Gem/Cis (N = 342)
Patients with any maximum CTCAE Grade 3 or 4 AE	250 (74.0)	257 (75.1)
Anaemia	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
Cholangitis	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]

† Number (%) of patients with any AE of maximum CTCAE Grade 3 or 4, sorted in decreasing frequency for preferred term in the D + Gem/Cis group at the 6.5-month analysis.
Abbreviations: AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; D, durvalumab 1,500 mg; Gem/Cis, gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2; IA-2, interim analysis 2; SAS, safety analysis set.
Source: CSR addendum.[13]

B.2.10.2 Additional studies

Two Phase 2 studies (IMMUCHEC and MEDITREME) were identified in the SLR. These studies have not been considered in the submission due to the nature of the design (Phase 2, open label) and the small patient populations enrolled, meaning that the studies were not sufficiently powered to detect significant differences between treatment groups. Furthermore, MEDITREME used a durvalumab dose of 1,120 mg, which is outside of the anticipated licensed dose.[2] For completeness, a summary of these studies including safety data is presented in Appendix N.

B.2.10.3 Safety overview

The addition of durvalumab to Gem/Cis demonstrated a manageable safety profile consistent with the established safety profiles of the single agents.[11] The most commonly reported AEs were reflective of the known toxicities of Gem/Cis and were balanced between both treatment groups (either overall or assessed as possibly related to study treatment) (Table 16).
[redacted] (see Table 17), which is consistent with the known safety profile of durvalumab. Overall, AEs of maximum CTCAE Grade 3 or 4 either overall or possibly related to study treatment were reported at a similar frequency between both treatment groups. Rates of study treatment discontinuation due to AEs were low and similar between treatment arms (Table 16).

Immuno-oncology (IO) based regimens are associated with imAEs, which typically resolve following initiation of appropriate medical treatment or withdrawal of therapy. Overall, imAEs in the D + Gem/Cis arm were consistent with the known safety profile of durvalumab and Gem/Cis and were manageable according to treatment guidelines with the majority of patients continuing on study therapy.[12]
[redacted],
and [redacted] (Table 16).

B.2.11 Ongoing studies

Follow-up of TOPAZ-1 is continuing to capture long term OS data. Final data are expected to be available in [redacted].

IMMUCHEC is an investigator-led study, and the availability of further readouts is unknown. MEDITREME is complete.

There are no additional studies reporting adverse reactions to D + Gem/Cis when used for the treatment of locally advanced, unresectable, or metastatic BTC.

B.2.12 Interpretation of clinical effectiveness and safety evidence

B.2.12.1 Principal (interim) findings from the clinical evidence highlighting the clinical benefits and harms of the technology

Summary of efficacy evidence

TOPAZ-1 is the first Phase 3 trial in over a decade to demonstrate statistically significantly improved outcomes versus standard of care for the first-line treatment of unresectable, locally advanced, or metastatic BTC by combining durvalumab (immunotherapy) with gemcitabine and cisplatin (chemotherapy).

Current treatment options for patients with previously untreated, unresectable, locally advanced, or metastatic BTC are limited to gemcitabine-based chemotherapies that offer a limited survival benefit.[7, 8] There have been no new therapies approved for the broad BTC population in over a decade.

TOPAZ-1 was the first positive global Phase 3 study to compare the efficacy and safety of an immunotherapy (durvalumab) in combination with SoC chemotherapy (gemcitabine and cisplatin) versus placebo plus chemotherapy for previously untreated, unresectable, locally advanced, or metastatic BTC.

TOPAZ-1 met its primary objective of demonstrating the superiority of the OS benefit of D + Gem/Cis versus placebo + Gem/Cis. At the time of IA-2 (DCO: 11 August 2021) treatment with D + Gem/Cis resulted in a statistically significant, clinically meaningful, and sustained improvement in OS versus placebo + Gem/Cis, with a HR of 0.80 (97% CI: 0.64, 0.99, p = 0.021); With a further 6.5 months of additional follow-up (DCO: 25 February 2022), the improvement in OS derived from the addition of durvalumab to Gem/Cis increased (HR: 0.76; 95% CI: 0.64, 0.91), corresponding to a 24% reduction in the overall risk of death. The clear and sustained separation in the OS KM curves from 6 months observed at IA-2 was maintained with the additional follow-up. Median OS at the 6.5-month follow-up was 12.9 months for the durvalumab + Gem/Cis treatment arm and 11.3 in the placebo + Gem/Cis treatment arm. Furthermore, twice as many patients were alive at two years in the D + Gem/Cis arm compared with the placebo + Gem/Cis arm (23.6% vs.

11.5%). Improvements in OS for D + Gem/Cis over placebo + Gem/Cis were consistently observed across prespecified subgroups (based on demographics, geographical region, primary tumour location, disease status, WHO/ECOG PS, and PD-L1 status). However, it is important to note that the study was not sized for any of the individual subgroup evaluations and the lower number of patients and events across the individual subgroups may lead to greater uncertainty in the point estimates, and wider CIs.

Treatment with D + Gem/Cis also resulted in a statistically significant, clinically meaningful, and sustained improvement in PFS compared to placebo + Gem/Cis (HR 0.75 [95% CI 0.63, 0.89] p = 0.001) corresponding to a 25% reduction in the overall risk of progression or death. A sustained separation of KM curves was seen from 4 months post-treatment initiation.

Patients receiving D + Gem/Cis also experienced a clinically meaningful improvement in investigator confirmed ORR (26.7%) compared placebo + Gem/Cis-treated patients (18.7% [OR 2.60; 95%; CI: 1.11–2.31; nominal p=0.011).

Summary of QoL and safety evidence

PRO secondary endpoints (EORTC QLQ-C30 and EORTC QLQ-BIL21) demonstrated that the addition of durvalumab to Gem/Cis resulted in no detriment in QoL and a trend towards a longer time to deterioration (as measures using the EORTC QLQ-C30 questionnaire) with D + Gem/Cis treatment. The change from baseline in EQ-5D-5L VAS score was similar over time for the D + Gem/Cis and placebo + Gem/Cis treatment groups.

The overall safety profile of durvalumab + Gem/Cis was generally manageable, and addition of durvalumab did not add additional toxicity to that observed with Gem/Cis. Almost all patients across both treatment groups in TOPAZ-1 experienced AEs during the study. Importantly, durvalumab did not add additional toxicity to that observed with chemotherapy in this trial, and the rates of CTCAE Grade 3 or 4 AEs were very similar between the treatment groups. No new safety signals were identified beyond the known safety profiles of each individual treatment.[11]

Discussion on clinical evidence

Approximately 80% of patients with BTC are diagnosed at an advanced stage, when patients experience substantial disease-related symptoms and QoL burden, and when treatment with curative intent is unfeasible.[4, 5] Furthermore, 80% of patients who receive initial treatment with curative intent will experience disease recurrence within two years.[16, 17] Current treatment for these patients is limited to chemotherapy and there have been no innovations in the management of first-line unresectable advanced or metastatic BTC for over a decade. Patients with locally advanced, unresectable, or metastatic BTC have a poor prognosis, with median overall survival of <1 year with current chemotherapy SoC,[7, 8] and there is therefore a substantial unmet need in this patient population. This was supported by UK clinicians, who confirmed the Gem/Cis arm from the TOPAZ-1 trial (i.e. current SoC), which achieved a median OS of 11.5 months,[14] was generalisable to UK clinical practice.[19] Clinicians also alluded that the greatest unmet need for locally advanced, unresectable, or metastatic BTC patients is the requirement for more effective treatments which can improve overall survival and long-term control of the disease.[19]

D + Gem/Cis has demonstrated a statistically significant and clinically meaningful improvement in OS versus placebo + Gem/Cis with a clear and sustained separation in OS KM curves from 6 months and an important improvement in median OS, which should be considered in the context of the current life expectancy for these locally advanced, unresectable, or metastatic BTC patients of less than 1 year.[7, 8] It should be noted that median OS and OS HRs do not always fully capture the non-conventional survival dynamics such as delayed curve separation. This may result in a substantial loss of statistical power and lack of survival difference reported by treatment arms. As outlined in section B.2.6.1.2, there was a delayed separation in the KM curves and the proportional hazard assumptions was violated. The delayed separation of the survival curves can be attributed to the mechanism of action of immunotherapy. Unlike chemotherapy or radiation, where tumour cells are killed directly, immunotherapy requires time to mount an effective immune response, and for that response to be translated into an observable clinical response.[12, 55, 56] As demonstrated by the piecewise HR, the HR improved after 6 months at the time of

IA-2 and further improved with the additional 6.5 months follow-up data. Hence, is it important to look beyond the median OS and consider the clinical value captured by the long-term OS data, which better demonstrate the potential for a long-term survival benefit. The importance of considering these types of data is reflected in the ESMO MCBS scoring system, which includes % increase in survival at landmark timepoint analyses. In the case of the TOPAZ-1 trial, the OS rate at two years for the D + Gem/Cis arm is double that of the Gem/Cis arm (23.6% vs. 11.5%, respectively at 6.5-month follow-up DCO). This clearly demonstrates the improved potential for a long-term survival benefit and durable OS benefit offered by D + Gem/Cis over the current SoC. A statistically significant and clinically meaningful improvement in PFS was also observed for the D + Gem/Cis group compared with the placebo + Gem/Cis group, with separation of KM curves seen at 4 months, indicating that there is an early treatment effect of this regimen. This was further supported by a faster median time to response in the D + Gem/Cis group compared with the placebo + Gem/Cis group. Furthermore, addition of D to Gem/Cis resulted in no detriment in QoL and a manageable safety profile consistent with the established safety profile of Gem/Cis.

The clear benefits offered by D + Gem/Cis in comparison to SoC chemotherapy have been recognised by ESMO, who have recommended D + Gem/Cis as the preferred regimen for the first-line treatment of locally advanced, unresectable, or metastatic BTC. The combination has been awarded an ESMO-MCBS score of 4, which corresponds to a substantial magnitude of benefit, due to the ≥10% increase in two-year survival in a non-curative setting where the median OS with current SoC is <12 months[6] Durvalumab has also been awarded an innovation passport via the UK ILAP programme, which aims to accelerate development and access to innovative medicines, for D + Gem/Cis in the treatment of locally advanced, unresectable, or metastatic BTC, further highlighting the innovative nature of this treatment.

The licensed indication for D + Gem/Cis is for the first-line treatment of adults with locally advanced, unresectable, or metastatic biliary tract cancer. D + Gem/Cis is a suitable therapy option for all immunotherapy-eligible first-line locally advanced, unresectable, or metastatic BTC patients who would otherwise be eligible to receive Gem/Cis. There is no requirement for PD-L1 testing among this patient group. UK

clinicians confirmed that the outcomes of the TOPAZ-1 trial are generalisable to UK clinical practice and advocate for the use of D + Gem/Cis in all patients who would otherwise be eligible for gemcitabine with cisplatin and have no contraindications to immunotherapy.[19] This highlights the importance of ensuring patient access to this first innovative treatment option in a decade which provides the opportunity of extended survival for this underserved population with aggressive disease and poor survival rates.

B.2.12.2 Strengths and limitations of the clinical evidence base for the technology

Internal validity

TOPAZ-1 is a large, multinational, well controlled and well conducted study. The study employed a randomised, double-blind, placebo-controlled, parallel group design to minimise bias. All study personnel and the sponsor remained blinded to treatment allocation throughout the trial as described in Section B.2.3.2.4. Randomisation was stratified by disease status (initially unresectable versus recurrent) and primary tumour site (IHCC versus EHCC versus GBC) as these represent important prognostic factors in BTC.[12]

Permitted concomitant medications were limited to those deemed necessary for prophylaxis, supportive care, safety, or well-being; no other therapies for BTC were permitted, this reducing any possibility of distorting the perceived effects of durvalumab, gemcitabine and cisplatin.

Eligibility criteria were selected to ensure enrolment of a wide range of patients with BTC in the study, including patients with IHCC, EHCC and GBC. The use of Gem/Cis as the standard of care is consistent with current European treatment guidelines on the management of BTC.[6]

Baseline characteristics were well balanced between treatment groups with no notable differences in terms of demographics (e.g., age, sex), baseline disease characteristics (ECOG PS, tumour type) or prior treatments received.

OS, which was the primary endpoint of TOPAZ-1, is considered the most appropriate and reliable endpoint in randomised controlled oncology clinical studies as it is not subject to investigator bias.[57]

PFS and ORR which were assessed as secondary outcomes also represent important endpoints in cancer trials as they are assessed prior to survival and are therefore not subject to any potential confounding effect of subsequent therapy. As the study adopted a rigorous double-blind design, measurement of these endpoints was not subject to assessment bias.

An IDMC composed of independent experts was convened to meet approximately every 6 months to review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. At IA-2, the IDMC was also responsible for reviewing unblinded efficacy data and providing their opinion as to minimum efficacy criteria being met.

The dropout rate for reasons other than radiologic or clinical progression or toxicity was low and balanced between the 2 treatment arms (Appendix D.2). Compliance with study treatments was assured as durvalumab, placebo, gemcitabine, and cisplatin were given as IV infusions administered by staff at the study centres.

External validity

The TOPAZ-1 study reflects the proposed indication and anticipated use of D + Gem/Cis in clinical practice in England. The trial dosing for D + Gem/Cis matches that used in UK clinical practice.[15, 19]

Gem/Cis is the international standard of care for the first-line treatment of patients with locally advanced, unresectable, or metastatic BTC who have good performance status, [25] [25] is the recommended regimen in ESMO guidelines (alongside D + Gem/Cis, which was included in the 2022 update)[6] and is the most commonly used regimen in the UK for the treatment of first-line locally advanced, unresectable, or metastatic BTC. Gem/Cis is considered to be the only appropriate comparator, as any patients who are ineligible to receive Gem/Cis would also be ineligible for D + Gem/Cis. This was validated by UK clinicians who confirmed that Gem/Cis is

considered the first-line SoC for locally advanced, unresectable, or metastatic BTC patients and is received by approximately 80% of BTC patients who are able to receive chemotherapy.[19] The enrolment criteria for TOPAZ-1 were consistent with the expected population that will use D + Gem/Cis in UK clinical practice, i.e. those with good performance status. This was also confirmed by UK clinicians who advocate for the use of D + Gem/Cis in all patients who would otherwise be eligible for Gem/Cis and have no contraindications to immunotherapy.[19]

In TOPAZ-1, patients received durvalumab or placebo in combination with Gem/Cis chemotherapy for up to 8 cycles, after which chemotherapy was discontinued and patients continued to receive durvalumab or placebo monotherapy until clinical progression, or unless there was unacceptable toxicity, consent was withdrawn, or the patient discontinued for another reason. The use of Gem/Cis for up to 8 cycles is in line with previous trials investigating the efficacy and safety of Gem/Cis[8] and is consistent with UK clinical practice.[19]

In addition to OS being considered the most appropriate and reliable endpoint in randomised controlled oncology clinical studies,[57] OS was considered the most appropriate endpoint for TOPAZ-1 given that median OS in patients with locally advanced, unresectable, or metastatic BTC is less than 1 year.[7, 8] At the prespecified IA-2 analysis (with 61.9% overall maturity for OS), the D + Gem/Cis group performed similarly to other studies of immune checkpoint inhibitors + chemotherapy vs chemotherapy alone (conducted in multiple solid tumour types), [58-60] [58-60] including delayed separation of the OS curves and a subset of patients with enduring OS, as reflected in the relatively flat tail of the OS curve (seen from around 18 months in TOPAZ-1; see Figure 5). In comparison, the placebo + Gem/Cis group experienced a median OS that was consistent with the historical median OS associated with this treatment regimen of less than 1 year.[7, 8]

PFS and ORR which were assessed as secondary outcomes also represent important endpoints in cancer trials as previously described. All secondary efficacy endpoints were Investigator-assessed using RECIST version 1.1, which is a well-recognised international standard for measuring tumour burden.[61]

The impact of treatment on various aspects of health-related quality of life (HRQoL was assessed using a number of recognised, reliable, and validated tools, including the BTC-specific EORTC QLQ-C30/BIL21 and the cancer-specific EORTC-QLQ-C30. The EORTC scales include many of the key BTC symptoms and impacts, such as abdominal pain, fatigue, pruritus, jaundice, lack of appetite, physical functioning, and insomnia and are therefore considered relevant to patients' experience of the disease.

B.3 Cost effectiveness

B.3.1 Summary of the economic analysis

- The Phase III TOPAZ-1 met its primary endpoint, demonstrating a **statistically significant**, **clinically meaningful**, and **sustained improvement** in OS for the D + Gem/Cis treatment arm compared with the placebo + Gem/Cis treatment arm (12.9 months [95% CI: 11.6, 14.1] versus 11.3 months [95% CI: 10.1, 12.5])
- The economic analysis focuses on establishing the cost effectiveness of D + Gem/Cis against **one key active comparator**, Gem/Cis, which is currently recommended by NICE and represents standard of care in the NHS for patients with previously untreated, unresectable locally advanced or metastatic BTC
- The economic **analysis uses data from the TOPAZ-1 study**, which is the most relevant and representative dataset for this submission
- A **three-state partitioned survival model** was implemented. The health states include progression-free (PF), progressed disease (PD) and death. The model is populated with data (time-to-event outcomes, health state utilities, and AEs) from the TOPAZ-1 study
- A **1.2x QALY weight is appropriate for decision making in this appraisal** based on the proportional QALY shortfall associated with Gem/Cis relative to the general population. Note that the proportional QALY shortfall is very high (almost within range for a 1.7x QALY weight) reflecting the severity of this disease
- **The probabilistic analysis predicted that D + Gem/Cis provided [redacted] additional quality-adjusted life years (QALYs) using a 1.2x QALY weight and an incremental cost of [redacted] when compared to Gem/Cis, giving an incremental cost per QALY gained (ICER) of [redacted]**
- **The deterministic analyses were consistent with the probabilistic analyses, with a corresponding cost per QALY of [redacted]**
- ICERs ranged between [redacted] and [redacted] in scenario analyses (Section B.3.12.2)

B.3.2 Published cost-effectiveness studies

An SLR was conducted to identify relevant economic evaluations of treatments for patients with previously untreated, unresectable, locally advanced, or metastatic BTC. Detailed descriptions of the review methodology and results are reported in Appendix G. All database searches were conducted between 14 and 23 October 2022. In total, five cost-effectiveness studies were identified, none of which were conducted from a UK perspective. A summary of these studies is presented in Table 19.

Table 19: Summary list of published cost-effectiveness studies

Study	Study design summary	Population	Currency (year) Total costs	QALYs	Cost per QALY
Sangchan et al. (2014) [62] [62] Thailand	• Markov model comparing palliative plastic stent with palliative metal stent • Lifetime horizon • Perspective: healthcare system • 6 health states: EBD, post-EBD, PTBD, post-PTBD, no drainage, death	Unresectable perihilar/hilar CC	Thai Baht (2011) Plastic stent: 62,981 Metal stent: 98,841	Plastic stent: 0.1 Metal stent: 0.29	Metal stent vs plastic stent: 192,650
Suttichaimongkol et al. (2018)[63] Thailand	• Markov model comparing palliative EDD and palliative PTBD with palliative care • Time horizon: NR • Perspective: public healthcare providers • 6 health states: EBD, post-EBD, PTBD, post-PTBD, palliative care, post palliative care, death	Unresectable perihilar/hilar CC Bismuth type I–IV	Thai Baht (NR) EBD: 99,582 PTBD: 29,758 Palliative care: 6,287	EBD: 0.21 PTBD: 0.07 Palliative care: 0.07	EBD vs palliative care: 655,520 PTBD vs palliative care: 6,548,398
Roth and Carrelson (2012) [64] [64] USA	• Decision-analytic model comparing 1L Gem/Cis with 1L Gem mono • Lifetime horizon • Perspective: societal • 4 health states: pre-progression, post-progression, pre-progression with AE, death	Unresectable locally advanced or metastatic CC, BTC or AoV	US Dollar (2010) Gem/Cis: 33,654 Gem mono: 44,886	Gem/Cis: 0.561 Gem mono: 0.75	Gem/Cis vs Gem mono: 59,480
Tsukiyama et al. (2017) [65] [65] Japan	• Markov model comparing 1L Gem/Cis with 1L Gem mono • Time horizon: 36 months • Perspective: healthcare payers • 3 health states: progression-free, progressed, death	Unresectable locally advanced or metastatic BTC	Japanese Yen (NR) Gem/Cis: 15,446,575 Gem mono: 12,328,228	QALYs Gem/Cis: 10.04 Gem mono: 7.61	Gem/Cis vs Gem mono (cost/QALY): 13,707,020

Study	Study design summary	Population	Currency (year) Total costs	QALYs	Cost per QALY
Chen et al. (2022) [66] [66] China	• Markov model comparing 1L Cap/Oxa with 1L Gem/Oxa • Lifetime horizon • Perspective: healthcare payers • 3 health states: PFS with responsive/stable disease, progression survival, death	Unresectable or metastatic IHCC, EHCC and GBC	US Dollar (NR) Cap/Oxa: 12,275.51 Gem/Oxa: 13,649.62	Cap/Oxa: 0.66 Gem/Oxa: 0.54	Cap/Oxa vs Gem/Oxa: -12,070.42

Abbreviations: 1L, first line; AE, adverse event; AoV, ampulla of Vater; BTC, biliary tract cancer; Cap, capecitabine; CC, cholangiocarcinoma; Cis, cisplatin; EBD, endoscopic biliary drainage; EHCC, extrahepatic cholangiocarcinoma; GBC, gallbladder cancer; Gem (mono), gemcitabine (monotherapy); ICER, incremental cost-effectiveness ratio; IHCC, intrahepatic cholangiocarcinoma; NR, not reported; Oxa, oxaliplatin; PFS, progression-free survival; PTBD, percutaneous transhepatic biliary drainage; QALYs, quality-adjusted life year; QALM, quality-adjusted life month.

B.3.3 Economic analysis

No published economic evaluations of D + Gem/Cis were identified in the cost-effectiveness SLR (see section B.3.2). Therefore, a *de novo* model was developed to assess the cost effectiveness of D + Gem/Cis versus Gem/Cis in patients with untreated, unresectable, locally advanced, or metastatic BTC.

B.3.3.1 Patient population

The relevant population for the cost-effectiveness analysis is adults with previously untreated, unresectable locally advanced or metastatic BTC, including people with recurrent disease after treatment with curative intent. This population is consistent with the FAS of the TOPAZ-1 study, the primary source of clinical data in the economic analysis, and the final scope issued by NICE. The baseline characteristics of the TOPAZ-1 population are summarised in Table 6 of the submission. In brief, across both study arms in TOPAZ-1 [DCO 25 Feb 2022], the mean age was [redacted], the mean weight was [redacted] and 50.4% were male. These characteristics were balanced between treatment arms.

B.3.3.2 Model structure

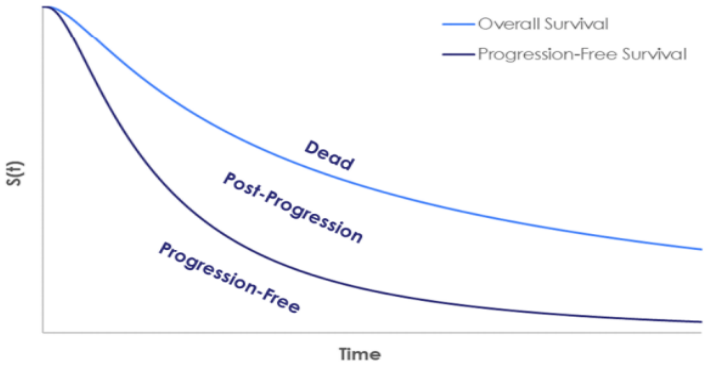
A three-state area under the curve (AUC) model, also known as a partitioned survival model, was developed in Microsoft Excel® to assess the cost effectiveness of D + Gem/Cis versus Gem/Cis. The three distinct and mutually exclusive health

states are PF, progressed disease (PD) and death. The model structure was selected based on the following:

- The structure directly leverages the time-to-event endpoints collected in the TOPAZ-1 study, namely OS and PFS, demonstrating the model accurately reflects disease progression and the observed survival profile of patients treated with D + Gem/Cis and Gem/Cis.
- The structure is consistent with approaches adopted in the majority of economic evaluations submitted to HTA bodies for treatments in advanced and/or metastatic cancer settings, [67-70] [67-70] and was accepted in the only previous NICE appraisal in BTC (TA722).[71]
- Progression-based models are suitable in oncology indications where patients are expected to unilaterally progress, and no cure or spontaneous remission are considered clinically plausible with current therapies.
- As noted in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19,[72] partitioned survival modelling is well understood, intuitive and easy to communicate.

An illustration of the model state structure is provided in Figure 14.

Figure 14: Model schematic



All patients enter the model in the PF health state and receive first-line treatment for locally advanced/metastatic BTC with either D + Gem/Cis or Gem/Cis. Within this health state patients are at risk of disease progression (moving into post-progression) or death. Patients in the 'progressed disease' health state are also at

risk of transitioning to ‘death’, which is an absorbing state. The three states are mutually exclusive and fully exhaustive, meaning that patients must occupy one of the states at any given time.

As outlined in the DSU review of partitioned survival analysis (TSD19),[72] the model estimates the proportion of the cohort in each state based upon parametric or non-parametric survival models fit separately to the PFS and OS curves. The proportion occupying PF state is estimated directly from the cumulative survival probabilities for PFS, while the proportion occupying the PD state is estimated from the cumulative survival of OS minus the cumulative survival of PFS. The numbers occupying the death state are calculated as one minus the OS curve. Individual transition probabilities are not modelled within a partitioned survival model. See calculations below:

- Progression-free: PF
- Progressed disease: OS – PF
- Death: 1 – OS

Extrapolated OS curves were adjusted for general population mortality informed by life tables for the UK to ensure that the disease-specific probability of death never falls below that of the general population.[73]

D + Gem/Cis time on treatment was derived from the PFS curve as this is considered most reflective of how disease progression is assessed in clinical practice, i.e., by the treating physician, and is consistent with the UK marketing authorisation. Furthermore, the TOPAZ-1 trial protocol specified that after completing the chemotherapy treatment period, patients would be treated with durvalumab until clinical progression, unless there was unacceptable toxicity, withdrawal of consent, or another discontinuation criterion was met. Therefore, PFS curves were deemed most appropriate to estimate treatment-related costs. Gem/Cis time on treatment was derived from the PFS curve, although this was capped at a maximum of 8 cycles of treatment. A more detailed summary of costs is provided in Section B.3.6.

Consistent with the NICE reference case, the health benefits of treatment were measured in terms of quality-adjusted life years (QALYs) using EQ-5D-based health-

state utility values (HSUVs) evaluated using UK general population preference weights. EQ-5D-5L data routinely collected in TOPAZ-1 were mapped to EQ-5D-3L HSUVs using the Hernández Alava et al., 2017 algorithm,[74] in line with the updated 2022 NICE Methods Guide.[75]

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) and in the base case progression status was selected to model utilities (i.e., HSUVs were assigned the PF and PD states) because it was a strong predictor of patient utility, and because treatment discontinuation status refers to cessation of placebo treatment in the Gem/Cis arm, making progression status a more clinically meaningful covariate. Over the lifetime time horizon, PF and PD HSUVs were adjusted for the gradual decline in quality of life expected to occur with age, using the regression analysis of general population EQ-5D-3L HSUVs from Ara and Brazier (2010).[76] The effect of AEs on quality of life was captured as a one-off QALY loss applied at the start of the model. Only AEs associated with first-line treatment were included in the model. See Section B.3.5 for a detailed summary of the measurement and valuation of health effects.

PFS was used in the base case to model treatment duration, treatment costs and on/off first-line treatment utilities. In a scenario analysis, TTD curves for the D + Gem/Cis and Gem/Cis arms were used to model discontinuation of all treatment components (Appendix O).

B.3.3.3 Features of the economic analysis

In the base case analysis, costs and health outcomes were modelled over a lifetime horizon which was assumed to be 20 years (i.e., until <1% of the patient population remains alive) and discounted at an annual rate of 3.5%, as per the NICE reference case.

A weekly cycle length was applied to capture the costs and events associated with the rapid progression of BTC and to account for different treatment schedules (Q3W, Q4W). A half-cycle correction was applied to account for events occurring at any point during each cycle. This half-cycle correction was not applied to the calculation

of first-line drug acquisition and administration costs in the first cycle to ensure the full cost of treatment initiation was captured.

A complete overview of the features of the economic analysis and a comparison with a previous NICE evaluation in advanced cholangiocarcinoma (TA722)[71] is presented in Table 20. TA722 was considered the only comparable NICE submission, therefore was used to validate model inputs where appropriate.

Table 20: Features of the economic analysis

	Previous appraisal	Current appraisal	
Factor	**Pemigatinib in TA722[71]**	**Chosen values**	**Justification**
Model structure	PartSA	PartSA	This approach is consistent with previous models in BTC and in the advanced/metastatic setting of other oncology indications. Makes direct use of the PFS and OS data collected for D + Gem/Cis and placebo + Gem/Cis in the TOPAZ-1 study.
Perspective on costs	NHS and PSS	NHS and PSS	As per NICE reference case
Perspective on outcomes	All health effects for patients	All health effects for patients	As per NICE reference case
Time horizon	40 years	20 years	As per NICE reference case: lifetime horizon for the patient population. <1% of the patient population in the durvalumab arm remain alive at 20 years in the analysis.
Cycle length	1-week	1-week	Considered short enough to capture changes in health and captures the dosing schedules
Discount rate	3.5%	3.5%	As per NICE reference case

	Previous appraisal	Current appraisal	
Factor	**Pemigatinib in TA722[71]**	**Chosen values**	**Justification**
Outcome measure	• QALYs by health states (PF and PD) • LYs by health states (PF, PD) • Mean and median PFS, TTD and OS	• QALYs by health states (PF and PD) • LYs by health states (PF, PD) • Mean and median PFS, TTD and OS	As per NICE reference case
Treatment waning effect	No	No	D + Gem/Cis is treat to progression and TOPAZ-1 data are mature
Source of utilities	EQ-5D data from FIGHT-202	EQ-5D data from TOPAZ-1	EQ-5D data collected from relevant population within the clinical study, as per the NICE reference case
Source of resource use	ESMO BTC guidelines	• ESMO BTC guidelines • TA722 • Clinical opinion	Resource use is consistent with TA722 and was validated with clinical experts
Source of costs	• NHS reference costs • eMIT	• NHS reference costs • eMIT • BNF • PSSRU	As per NICE reference case

Abbreviations: BNF, British National Formulary; BTC, biliary tract cancer; eMIT, electronic market information tool; EQ-5D, EuroQol 5 dimensions; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PartSA, partitioned survival analysis; PFS, progression-free survival; PPS, post-progression survival; PSS, Personal Social Services; PSSRU, Personal Social Services Research Unit; TTD, time to discontinuation; QALY, quality-adjusted life year; LY, life year.

B.3.3.4 Intervention technology and comparators

The TOPAZ-1 trial is the key data source of this cost-effectiveness analysis, in which durvalumab in combination with Gem/Cis (intervention arm) is compared with placebo + Gem/Cis (comparator arm) in patients with previously untreated, unresectable, locally advanced, or metastatic BTC.

Durvalumab is administered at a dose of 1,500 mg by IV infusion (on Day 1 of a 3-weekly cycle) in combination with gemcitabine at a dose of 1,000 mg and cisplatin at a dose of 25 mg (on Days 1 and 8 of a 3-weekly cycle) for up to 8 cycles followed by durvalumab (1,500 mg) monotherapy Q4W until disease progression or other

discontinuation criteria. In line with the TOPAZ-1 trial, the comparator for this analysis is Gem/Cis administered by IV infusion Q3W up to 8 cycles.

Based on ESMO and BSG guidelines, Gem/Cis is considered the first-line SoC for the treatment of unresectable, locally advanced, or metastatic BTC.[6, 20] Other chemotherapy options, such as gemcitabine monotherapy, are available for the first-line treatment of advanced or metastatic BTC for patients who are not able to receive Gem/Cis, e.g. if they are in poor health or have poor renal function. However, patients that are unable to receive Gem/Cis would also be considered ineligible for durvalumab in addition to Gem/Cis. Therefore, other first-line chemotherapy options are not considered to be relevant comparators. Gem/Cis was also validated as the SoC in this setting and the only relevant comparator for D + Gem/Cis by UK clinical experts in a series of interviews.[19]

An overview of the current clinical pathway of care is provided in Section B.1.3.2 and Figure 2.

B.3.4 Clinical parameters and variable

The baseline characteristics, efficacy and AE data used in the economic analysis were taken from the TOPAZ-1 trial and are outlined in sections B.3.4.1, B.3.4.2 and 0, respectively.

B.3.4.1 Baseline characteristics

The baseline characteristics from TOPAZ-1 used to inform the economic analysis are presented in Table 21. Baseline characteristics were considered generalisable to the UK BTC population by UK clinical experts.[19] A more detailed summary is provided in section B.3.3.1.

Table 21: Baseline patient characteristics informing the economic analysis

	Value	Source	Use in model
Mean age (years)	[redacted]	TOPAZ-1[12]	Used to inform estimation of background mortality and adjustment of HRQoL over time
Proportion female (%)	49.6%		
Body surface area (m²)	[redacted]		Used to inform estimation of drug costs

† BSA is calculated based on mean height and weight using the Du Bois method.[77]
Abbreviations: HRQoL, health-related quality of life; m, metre.
Source: CSR.[12]

B.3.4.2 Efficacy

Two data cut-offs from the TOPAZ-1 trial were available.

- ***IA-2 (final formal analysis; DCO 11 August 2021):*** The primary objective was to evaluate the superiority of D + Gem/Cis compared with placebo + Gem/Cis in terms of OS, as analysed using a stratified log-rank test (stratified by disease status and primary tumour location) to assess statistical inference.
- ***6.5-month update (DCO 25 February 2022):*** Presented updated exposure, OS, and safety data based on approximately 6.5 months of additional follow-up since the IA-2 DCO.

Data from both data cut-offs were used in the analysis. PFS, TTD, and utility values were sourced from the IA-2 DCO, with median patient follow-up of ~16 months. OS, safety, and subsequent treatment inputs were sourced from the 6.5-month follow up (note: PFS, TTD and QoL data were not recorded at the 6.5-month follow-up).

In line with NICE DSU TSD 14,[78] it was necessary to assess the cost effectiveness of D + Gem/Cis over a lifetime horizon. Therefore, parametric survival analysis was undertaken to extrapolate OS (Section B.3.4.2.2), PFS (Section B.3.4.2.3), and TTD (Appendix O) to inform the cost-effectiveness model beyond the trial period.

B.3.4.2.1 Survival analyses and extrapolations

Survival analyses were conducted through four main steps, which are aligned with the survival model selection process algorithm described in NICE DSU TSD 14[78] and NICE DSU TSD 21[79]:

- Assessment of the proportional hazards assumption (PHA)
  - The PHA was primarily assessed based on log-cumulative hazard plots (LCHP), with additional formal statistical methods (such as Schoenfeld residual test) considered to further confirm the validity of proportional hazards. If the PHA holds (LCHP curves are parallel and do not cross, or Schoenfeld's residuals p-value is >0.05 indicating no autocorrelation among residuals at 95% confidence interval) dependent models should be selected. In this case, parametric models are fitted for one treatment and a

proportional treatment effect is used to generate the other treatment curve. If the PHA does not hold (LCHP curves cross or are not considered parallel, or Schoenfeld's residuals p-value is significant), then independent models or more flexible models, such spline-based models, should be selected, which permit capturing different shapes of the hazards.

- Statistical goodness of fit (Akaike Information Criterion [AIC]/ Bayesian Information Criterion [BIC])
  - The statistical fit of each curve was assessed by considering the ranking of AIC and BIC values.
- Visual fit to KM plots
  - The goodness of fit of the parametric curves to the KM data for D + Gem/Cis and placebo + Gem/Cis was visually assessed, with consideration given to the entire trial period for which data were available.
- Assessment of hazard functions
  - The hazards (rates of events) within the trial period and hazards beyond the trial using a 20-year time horizon for each distribution were assessed. For the within-trial period, the trial hazard was visually compared to the model-predicted hazards. Hazards over a 20-year timeframe were also considered to confirm that the extrapolated hazards for the chosen base case curve is clinically plausible. Consideration of the extrapolated hazards was important as due to small patient numbers at the end of follow-up in the TOPAZ-1 trial, some hazard predictions were overly influenced by the events occurring at the end of follow-up.
- External validation is desirable in understanding the suitability of the extrapolated curves.
  - Although TOPAZ-1 trial data are very mature, clinical plausibility in the long-term remains an important consideration. UK clinical expert opinion was sought to understand outcomes that could be expected under the current SoC (Gem/Cis), and to validate the survival extrapolations for D + Gem/Cis and Gem/Cis. RWE was also considered and used where appropriate to validate the model extrapolations.[22]

The following sections outline the approach taken to inform OS and PFS. TTD details can be found in Appendix O.

B.3.4.2.2 Overall survival

Survival curves were fitted to the time-to-event OS data from the TOPAZ-1 FAS (6.5-month DCO: 25 February 2022). The TOPAZ-1 OS data are mature (76.9% for overall maturity for OS); 73% and 81% maturity for D + Gem/Cis and placebo plus Gem/Cis, respectively (Table 22).

Table 22: OS time to event data (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])

	Total number of events, N (%)	Median time to event, months (95% CI)
D + Gem/Cis (n = 341)	248 (73%)	12.94 (11.56; 14.06)
Placebo + Gem/Cis (n=344)	279 (81%)	11.33 (10.12; 12.45)

Abbreviations: CI, confidence interval; D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; OS, overall survival.

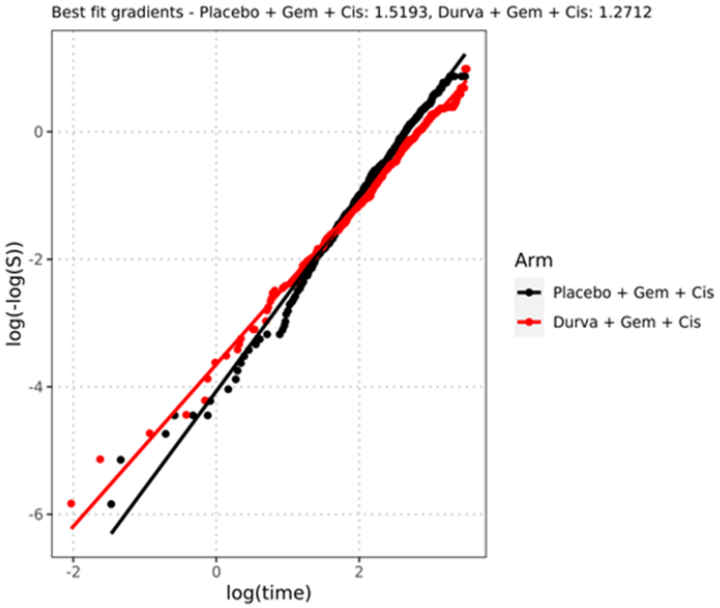
The OS data for D + Gem/Cis and placebo + Gem/Cis are presented in Figure 5. Based on observed data, D + Gem/Cis was associated with a statistically significant reduction in overall risk of death of 24% versus placebo + Gem/Cis (HR: 0.76, 95% CI: 0.64, 0.91). The HR was an improvement from IA-2 (DCO 11 Aug 2021), which also gave a statistically significant, clinically meaningful, and sustained improvement in OS versus placebo + Gem/Cis (HR 0.80 [97% CI: 0.64, 0.99]; p = 0.021).

As can be seen in Figure 5, the KM curves for OS separated at approximately 6 months of treatment followed by a sustained separation of the curves in favour of the D + Gem/Cis arm. The convergence of the KM curves at ~32 months is not considered to be a robust or meaningful observation since there is a very small number of patients at risk in the tails of both curves, particularly in the placebo + Gem/Cis arm. The curves do not cross until the point where the last patient in the placebo + Gem/Cis arm was censored.

The first step in selecting the choice of parametric survival model for OS was to assess whether the PHA holds for the TOPAZ-1 OS data. The global p-value for Schoenfeld residuals test was non-significant (p=0.097), meaning the PHA cannot be rejected. However, the LCHP curves are not parallel and cross at 6 months,

indicating the treatment effect varies over time (Figure 15). On this basis there is clear violation of the PHA.

Figure 15: Log-cumulative hazard plot of OS (TOPAZ-1 trial, 6.5-month DCO [25 Feb 2022])



Abbreviations: DCO, data cut-off; durva, durvalumab; OS, overall survival.

As the PHA was considered to be violated, parametric models (including spline-based models) were fitted separately to both arms. In accordance with NICE DSU TSD 14[78] and NICE DSU TSD 21[79], seven standard parametric distributions (exponential, gamma, generalised gamma, log-normal, log-logistic, Weibull, Gompertz), along with flexible spline-based models (up to 3 knots), were fitted to the observed OS data from the TOPAZ-1 study.

Flexible parametric models were considered due to their ability to accommodate hazard functions with complex shapes (NICE DSU TSD 21, Section 2.1.2,[79]), and the assessment of hazard functions supported the consideration of such models. For the spline-based approach, Royston-Parmer models were used and fitted with up to 3 knots. Spline knot locations were chosen as equally spaced quantiles of the uncensored survival times, for example, at the median with one knot or at the 33.3% and 66.7% quantiles for two knots. Boundary knots are chosen as the minimum and maximum event times.

B.3.4.2.2.1 D + Gem/Cis

Statistical goodness of fit

The survival models for the D + Gem/Cis arm were ranked according to their AIC values (Table 23). Based on the AIC and BIC statistics, the gamma distribution was the best fit. However, all models with a difference of <4 compared to the model with the lowest AIC were judged to also represent a good relative statistical fit to the data.

Table 23: AIC/BIC for D + Gem/Cis (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])

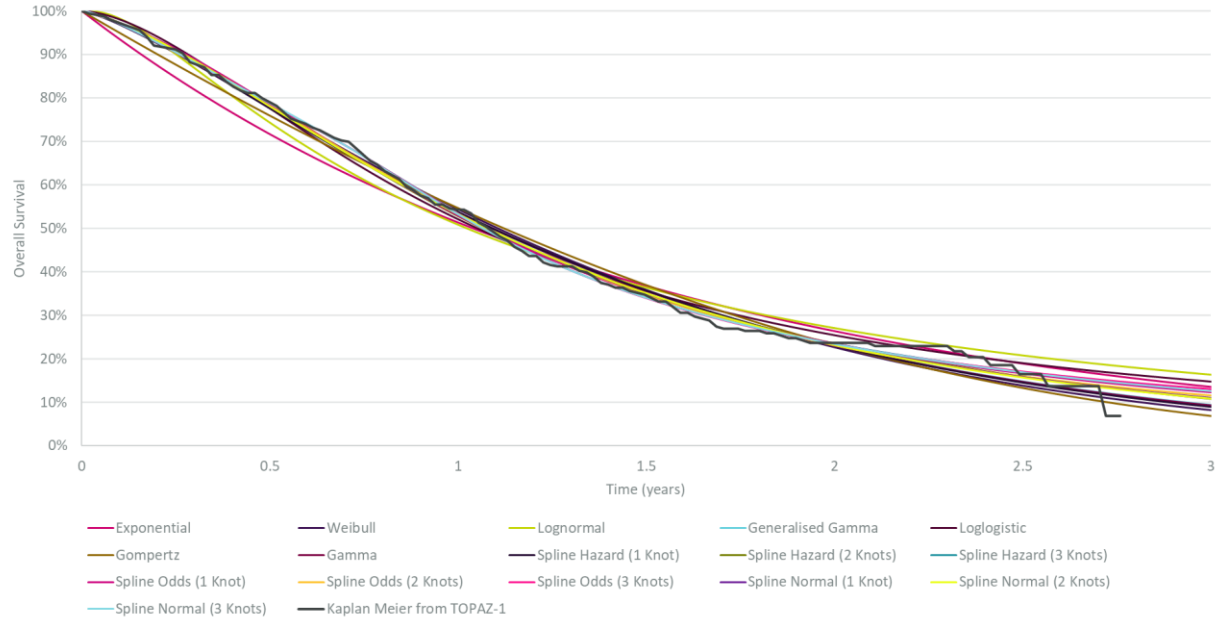
	D + Gem/Cis	
Model	**AIC (rank)**	**BIC (rank)**
Gamma	1,913.54 (1)	1,921.21 (1)
Spline 1 knot, scale = odds	1,914.00 (2)	1,925.00 (4)
Spline 1 knot, scale = normal	1,914.28 (3)	1,925.78 (5)
Weibull	1,914.41 (4)	1,922.08 (2)
Generalised gamma	1,915.53 (5)	1,927.03 (6)
Spline 3 knots, scale = hazard	1,915.60 (6)	1,934.76 (12)
Spline 3 knots, scale = normal	1,915.73 (7)	1,934.89 (13)
Spline 3 knots, scale = odds	1,915.87 (8)	1,935.03 (14)
Spline 1 knot, scale = hazard	1,915.90 (9)	1,927.40 (7)
Spline 2 knots, scale = odds	1,916.10 (10)	1,931.43 (9)
Spline 2 knots, scale = hazard	1,916.16 (11)	1,931.49(10)
Spline 2 knots, scale = normal	1,916.43 (12)	1,931.76 (11)
Log-logistic	1,917.07 (13)	1,924.73 (3)
Gompertz	1923.31 (14)	1930.97 (8)
Exponential	1,931.69 (15)	1,935.52 (15)
Log-normal	1,933.49 (16)	1,941.15 (16)

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion, D, Durvalumab 1500mg; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg.

Visual fit to KM plot

Visual inspection of the extrapolated survival curves indicates that all distributions provided a reasonable fit to the observed KM data for the D + Gem/Cis arm (Figure 16).

Figure 16: OS extrapolations - D + Gem/Cis (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])



Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; OS, overall survival.

Based on the good visual fit and similar statistical fit based on AIC for all distributions, as well as the fact that TOPAZ-1 data are very mature, selection of the OS extrapolation for the base case was informed by 1) assessment of the hazard function shape to determine whether standard parametric models can suitably model survival, 2) clinical expert opinion to ensure clinical plausibility of extrapolations in the long-term.

Assessment of hazard function

Figure 17 presents the raw hazard plot for D + Gem/Cis OS, which shows that the hazard changes over the course of the trial. It also shows that there is [redacted], but this is driven by the very low numbers of patients at risk at the end of the trial. The smoothed hazards are presented in Figure 18 which shows that the trial hazard changes over time ([redacted]). As specified in NICE DSU TSD 21,[79] complex hazard functions cannot be represented well by standard parametric models, and flexible models (such as spline-based models) that allow hazard functions with complex shapes should also be considered.

Figure 17: OS hazard plot (raw) - D + Gem/Cis (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])

Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; ITT, intent-to-treat; OS, overall survival.

Figure 18: OS smoothed hazard plot (kernel method) - D + Gem/Cis (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])

Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; ITT, intent-to-treat; OS, overall survival.

Hazards over a 20-year timeframe have also been considered to confirm that the extrapolated hazard for the chosen base case curve is clinically plausible, which is

particularly important due to small patient numbers at the end of the TOPAZ-1 trial which has influenced some hazard predictions.

Figure 19 presents the hazard plots for the standard parametric curves extrapolated over a 20-year time horizon. The exponential, Gompertz, Weibull, generalised gamma and gamma distributions did not capture the turning point in the trial hazard, and therefore were not considered appropriate. The log-normal and log-logistic parametric distributions were able to capture the overall change in the trial hazard. Clinical expert opinion on long-term survival was required to justify their use (see section External validation for D + Gem/Cis OS).

Figure 19: OS extrapolated hazard plots (standard parametric models) – D + Gem/Cis (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])

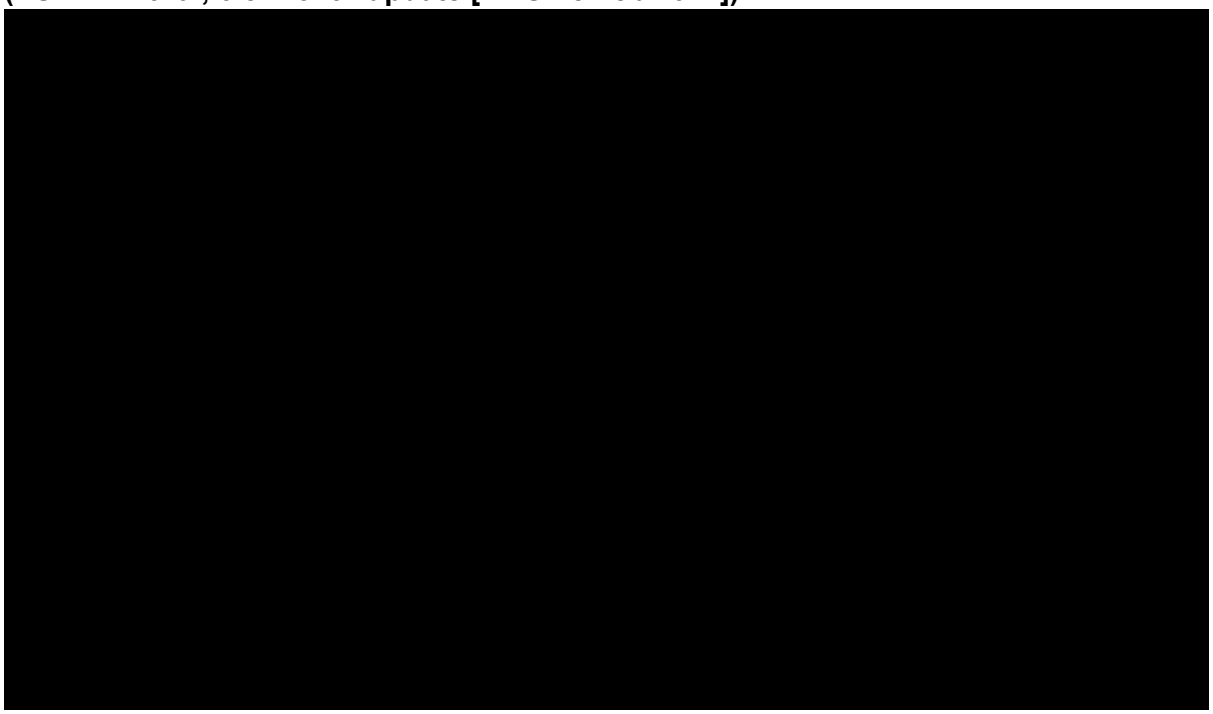


Figure 20, Figure 21 and Figure 22 present the hazard plots for spline models on the hazard scale (1 to 3 knots), odds scale (1 to 3 knots) and normal scale (1 to 3 knots), respectively.

The hazard plot for the spline models using the hazard scale (Figure 20) shows that only the 3-knot model captured the overall change in trial hazard. The models

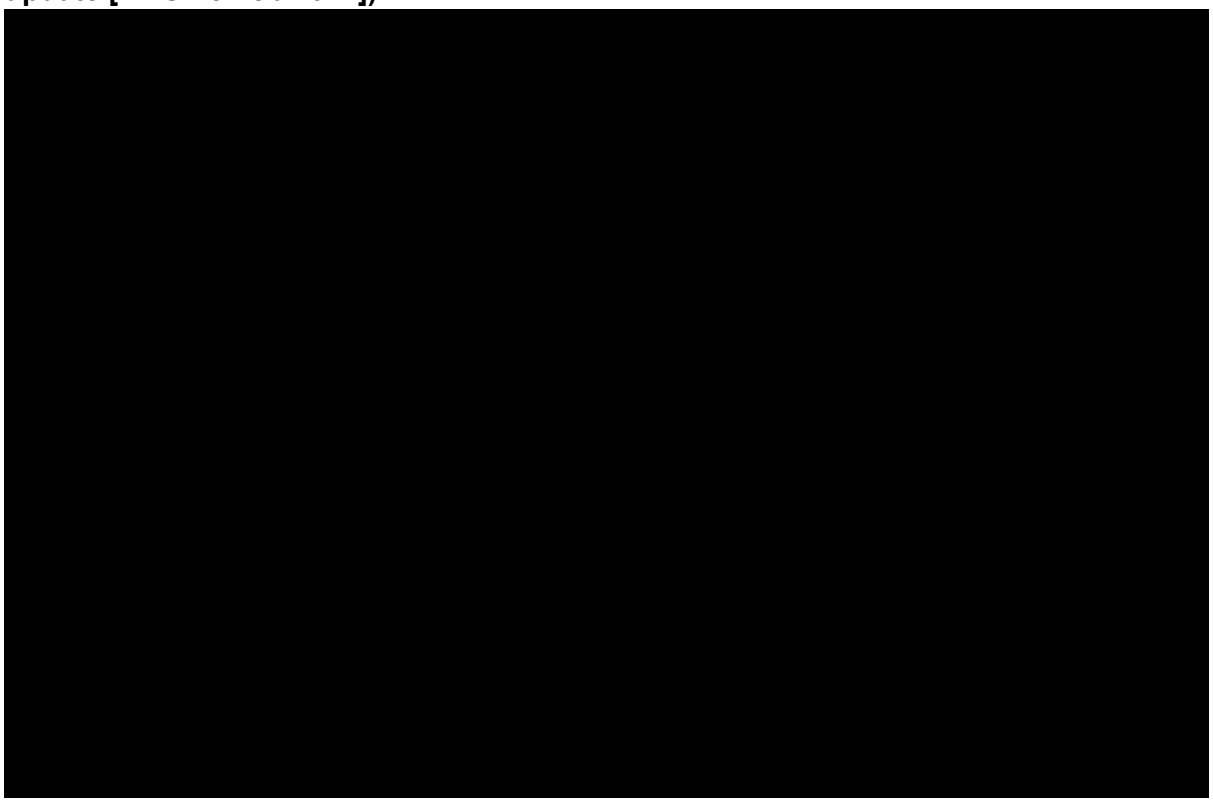
utilising 1 or 2 knots did not accurately fit the trial hazard, and therefore were not considered appropriate to model survival.

Other spline models were considered to accurately capture the shape of the trial hazard regardless of the number of knots applied, and the extrapolations for the spline models on the odds scale and normal scale were similar (Figure 21 and Figure 22). However, for both odds and normal scales, applying 3 knots overestimated the initial increase in the trial hazard, therefore 1- and 2 knot models were preferred. AIC statistics favour both spline models with 1 knot on the odds (rank: 2nd) and normal (rank: 3rd) scales (see Table 23). Based on visual inspection, the 1 and 2 knot spline models on the odds scale provided a closer fit to the trial hazard compared to those on the normal scale, however in order to select the most plausible extrapolation, clinical expert opinion was sought on long term survival predictions (see Section External validation for D + Gem/Cis OS).

Figure 20: OS: D + Gem/Cis, scale=hazard, 1-3 spline knots (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])

Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; OS overall survival.

Figure 21: OS: D + Gem/Cis, scale=odds, 1-3 spline knots (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])



Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; OS overall survival.

Figure 22: OS: D + Gem/Cis, scale=normal, 1-3 spline knots (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])

Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; OS overall survival.

External validation for D + Gem/Cis OS

Clinical expert opinion was sought to ensure that the best-fitting model provides a clinically plausible extrapolation beyond the trial data (Table 24 presents 2- 3- and 5-year survival predictions from all models explored). Clinical expert opinion was sought in a validation meeting, where clinicians were presented with spline odds (1-knot), log-logistic and gamma distributions.[19] The majority of clinical experts agreed that the extrapolation provided by the spline odds (1 knot) has clinical plausibility in this patient population based on 12.37% of patients alive at 3 years.

The clinical experts found it challenging to comment on the 5-year OS estimates due to their lack of long-term clinical experience with D + Gem/Cis. For the Gem/Cis arm, the 5-year OS estimate for the base case curve was 0.52% (see Section External validation for Gem/Cis OS) which was considered clinically plausible. Based on this and given both the observation in the trial that twice as many patients remain alive at

the 2-year landmark analysis in the D + Gem/Cis arm compared to the placebo + Gem/Cis arm (24.9% versus 10.4%) and the increasing separation of the survival curves, it was considered plausible for 4.99% of patients to be alive at 5-years in the D + Gem/Cis arm using the spline odds (1 knot).

Gamma, Weibull, generalised gamma and Gompertz were considered by clinical experts to underestimate the proportion of patients expected to be alive at 3 years in the UK. This is consistent with these distributions not capturing the turning point in the trial hazard (see section External validation for Gem/Cis OS). In addition, the log-logistic, exponential, and log-normal were considered by clinical experts to overestimate the proportion of patients expected to be alive at 3 years.

The flexible spline odds (1 knot) was selected to inform OS in the base case. Limiting the model to 1 knot reduces the risk of overfitting the data and means that the extrapolation is less heavily influenced by trends observed towards the end of the follow-up period which is informed by a smaller number of patients and fewer events compared to 2 and 3 knot models. Among the spline-based models, the spline odds (1 knot) provided the best statistical fit based on AIC and BIC scores and best visual fit, as well as the most plausible OS estimate at 3 years based on clinical expert opinion. In addition, the shape of the extrapolated hazard function is in line with clinical expert expectations i.e., increasing hazards in the short-term followed by decreasing hazards over time, which is reported for other immunotherapies. [80] [80]

Table 24: OS rates for D + Gem/Cis (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])

Distribution	D + Gem/Cis		
	2-year survival rate	3-year survival rate	5-year survival rate
TOPAZ-1	23.65%	-	-
Gamma	23.20%	9.37%	1.40%
Spline 1 knot, scale = odds	**23.60%**	**12.37%**	**4.99%**
Spline 1 knot, scale = normal	23.39%	11.08%	3.23%
Weibull	22.80%	8.29%	0.82%
Generalized gamma	23.25%	9.50%	1.48%

Distribution	D + Gem/Cis		
	2-year survival rate	3-year survival rate	5-year survival rate
Spline 3 knots, scale = hazard	23.57%	12.52%	3.87%
Spline 3 knots, scale = normal	23.50%	12.64%	4.75%
Spline 3 knots, scale = odds	23.45%	13.09%	5.82%
Spline 1 knot, scale = hazard	23.18%	9.03%	1.11%
Spline 2 knots, scale = odds	23.19%	11.62%	4.39%
Spline 2 knots, scale = hazard	23.62%	10.87%	2.23%
Spline 2 knots, scale = normal	23.34%	10.93%	3.11%
Log-logistic	25.53%	15.10%	6.89%
Gompertz	23.33%	6.95%	0.11%
Exponential	26.49%	13.63%	3.61%
Log-normal	27.17%	16.42%	7.45%

Note: distributions are ranked according to their AIC statistic.

Abbreviations: AIC, Akaike Information Criterion; D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; OS, overall survival.

B.3.4.2.2.2 Placebo + Gem/Cis

Statistical goodness of fit

The survival models for the Gem/Cis arm were ranked according to their AIC values (Table 25). Based on the AIC statistics, the spline normal (1 knot) distribution was the best fit. All models with a difference of <4 compared to the model with the lowest AIC were judged to also represent a good relative statistical fit to the data.

Table 25: AIC/BIC for placebo + Gem/Cis (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])

	Gem/Cis	
Model	**AIC (rank)**	**BIC (rank)**
Spline 1 knot, scale = normal	1,990.76 (1)	2,002.23 (3)
Gamma	1,990.99 (2)	1,998.67 (1)
Spline 1 knot, scale = odds	1,991.36 (3)	2,002.91 (4)
Spline 2 knots, scale = odds	1,992.60 (4)	2,007.96 (8)

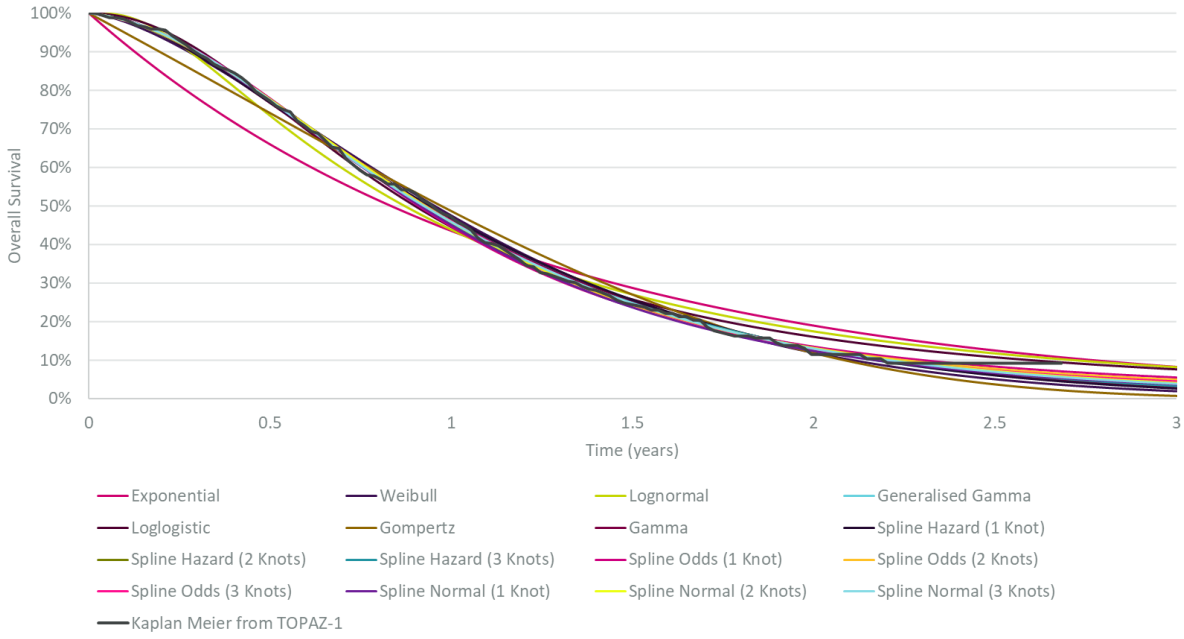
	Gem/Cis	
Spline 2 knots, scale = normal	1,992.68 (5)	2,008.04 (9)
Weibull	1,992.75 (6)	2,000.44 (2)
Generalised gamma	1,992.90 (7)	2,004.42 (6)
Spline 1 knot, scale = hazard	1,993.50 (8)	2,005.02 (7)
Spline 2 knots, scale = hazard	1,994.03 (9)	2,009.39 (10)
Spline 3 knots, scale = odds	1,994.12 (10)	2,013.32 (11)
Spline 3 knots, scale = normal	1,994.52 (11)	2,013.72 (12)
Spline 3 knots, scale = hazard	1,995.65 (12)	2,014.85 (13)
Log-logistic	1,995.74 (13)	2,003.42 (5)
Gompertz	2,014.61 (14)	2,022.29 (14)
Log-normal	2,017.01 (15)	2,024.69 (15)
Exponential	2,049.55 (16)	2,053.40 (16)

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg.

Visual fit to KM plot

Similar to the D + Gem/Cis arm, visual inspection of the extrapolated survival curves indicated that all distributions, with the exception of the exponential, provided a good fit to the observed KM data for the placebo + GemCis arm (Figure 23).

Figure 23: OS extrapolations – placebo + Gem/Cis (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])



Abbreviations: DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; OS, overall survival.

Based on the good visual fit and similar statistical fit based on AIC for all distributions, as well as the fact that TOPAZ-1 data are very mature, selection of the OS extrapolation in the base case analysis was informed by 1) assessment of the hazard function shape to determine whether standard parametric models can suitably model survival, 2) clinical expert opinion to ensure clinical plausibility of extrapolations in the long-term.

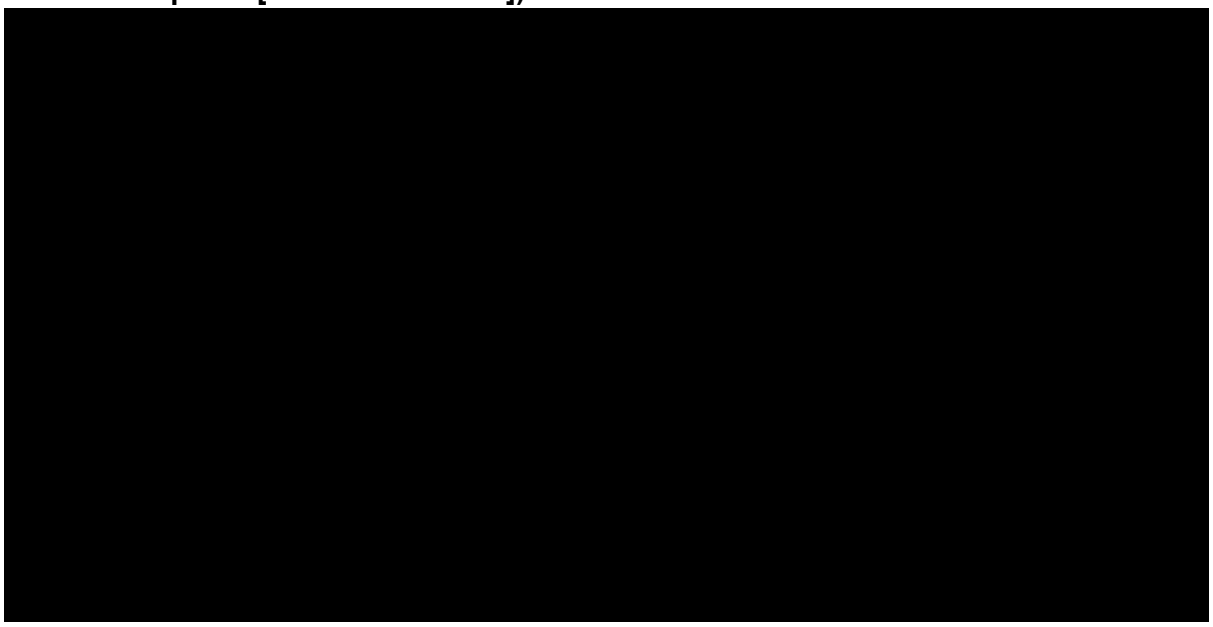
Assessment of hazard function

Figure 24 presents the raw hazard plot for placebo + Gem/Cis OS, which shows that the hazard changes over the course of the trial. Similar to D + Gem/Cis, [redacted], which is driven by the very low numbers of patients at risk at the end of the trial. The smoothed hazards are presented in Figure 25, which supports the observation that the trial hazard changes over time (e.g., [redacted]). Standard parametric models may not accurately model these changes in survival, and flexible models (such as spline-based models) that allow hazard functions with complex shapes were also considered potentially appropriate. This was consistent with the selection process used in the D + Gem/Cis arm.

Figure 24: OS hazard plot (raw) – Placebo + Gem/Cis (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])

Abbreviations: DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; ITT, intent-to-treat; OS, overall survival.

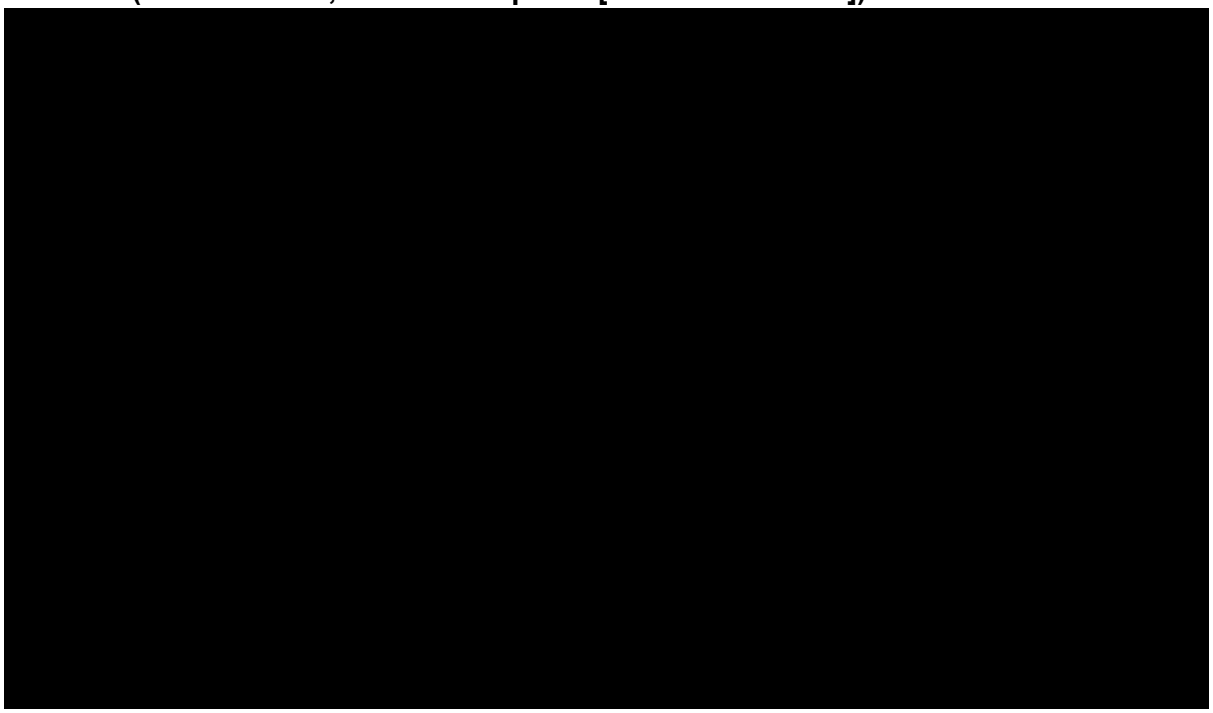
Figure 25: OS smoothed hazards (kernel method) – placebo + Gem/Cis (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])



Abbreviations: DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; ITT, intent-to-treat; OS, overall survival.

Extrapolated hazards over a 20-year timeframe were also considered (Figure 26). The hazard plot for placebo + Gem/Cis [redacted] as D + Gem/Cis does. The models predicting increasing hazards (Gompertz, Weibull, generalised gamma, and gamma) were also considered, based on visual inspection, but could be over-influenced by the small sample size at the tail of the survival curve from TOPAZ-1. This highlighted the requirement for clinical expert opinion on long-term survival to justify the choice of model (see Section External validation for Gem/Cis OS).

Figure 26 OS extrapolated hazard plots (standard parametric models) – placebo + Gem/Cis (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])

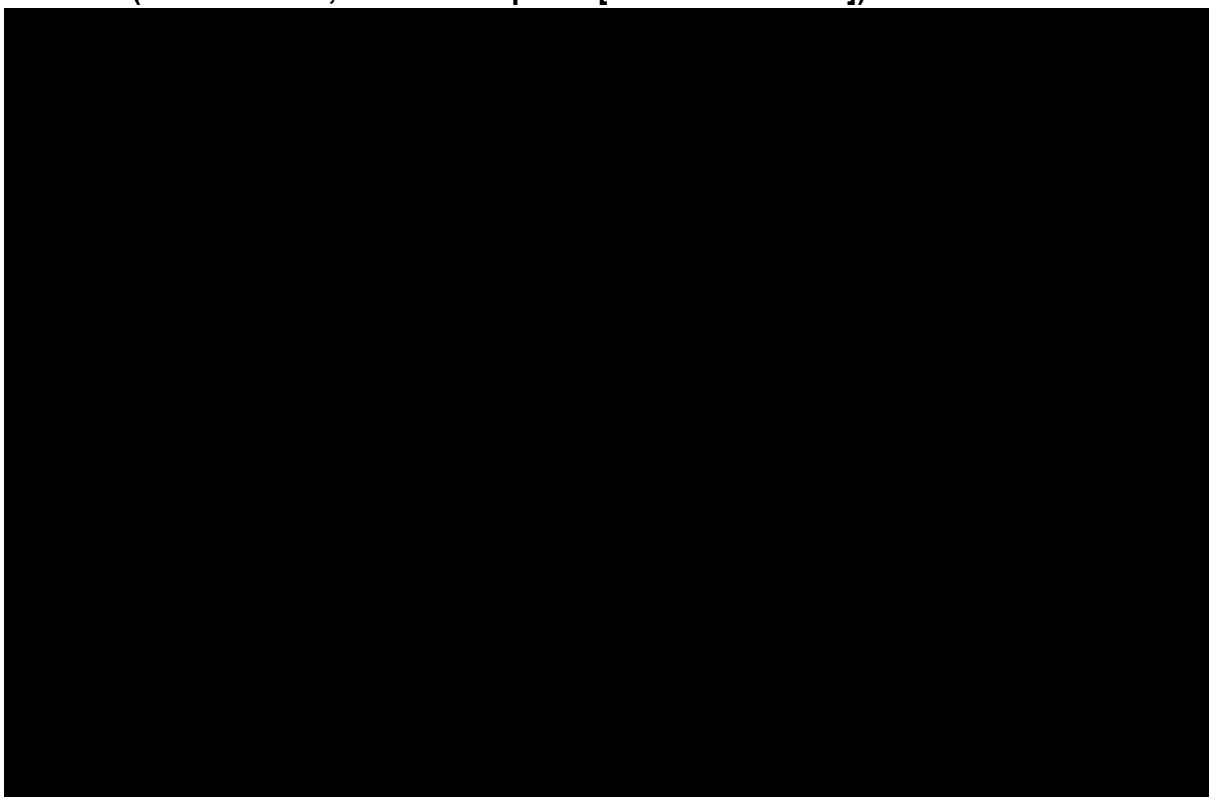


Abbreviations: DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; OS, overall survival.

Figure 27, Figure 28 and Figure 29 present the hazard plots for spline models on the hazard scale (1 to 3 knots), odds scale (1 to 3 knots) and normal scale (1 to 3 knots), respectively.

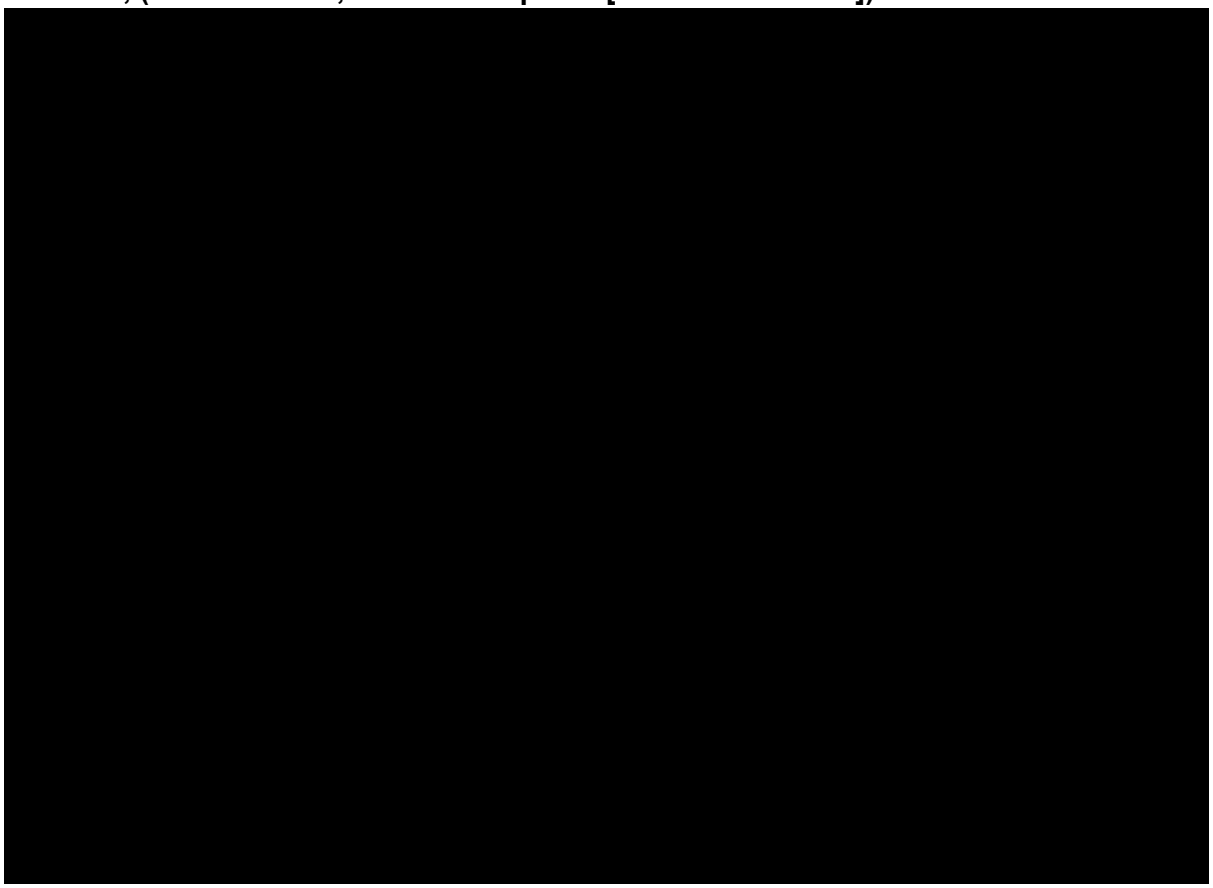
The hazard plot for the spline models using the hazard scale (Figure 27) shows all models predicted increasing hazards. All other spline models (on the odds scale and normal scale) model the hazards changing over time, with AIC statistics favouring 1 knot in both cases (normal rank: 1st; odds rank: 3rd). Clinical expert opinion was elicited to select the most plausible extrapolation.

Figure 27: OS extrapolated hazard plot, scale=hazard, 1-3 spline knots – placebo + Gem/Cis (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])



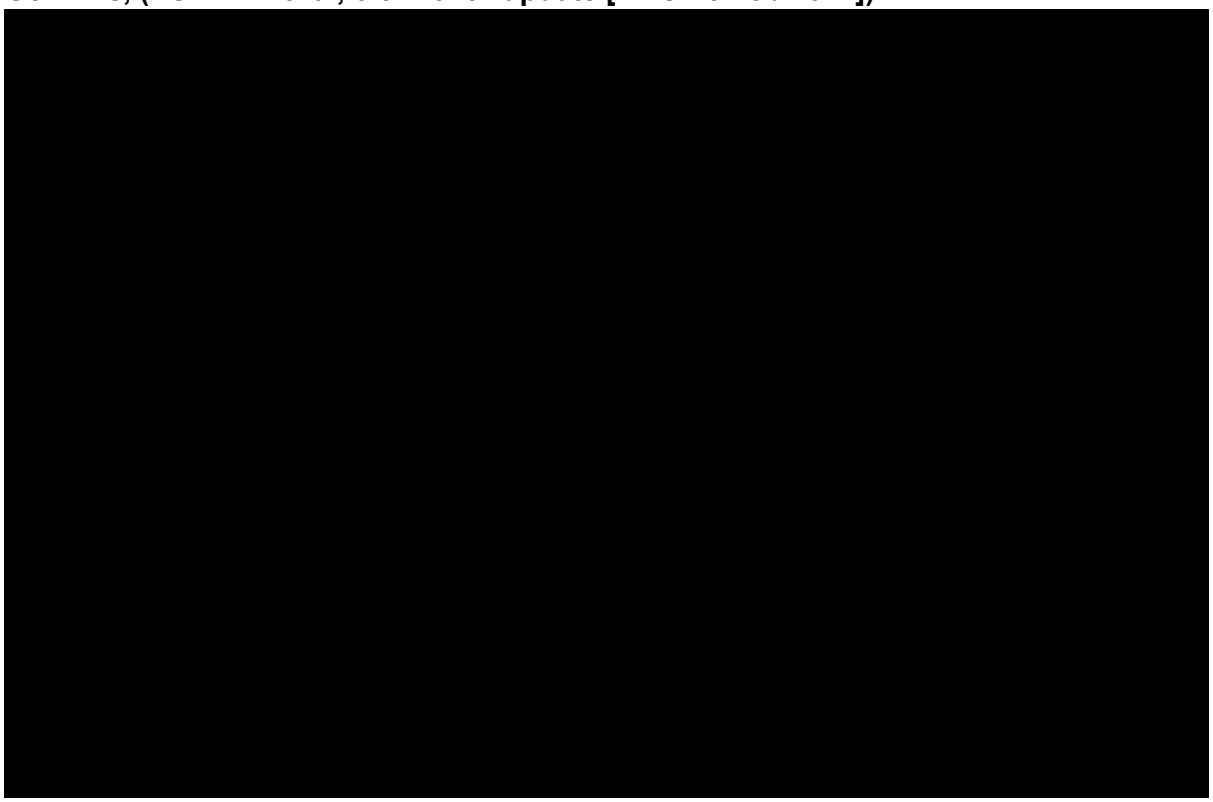
Abbreviations: DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; OS, overall survival.

Figure 28: OS extrapolated hazard plot, scale=odds, 1-3 spline knots - placebo + Gem/Cis, (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])



Abbreviations: DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; OS, overall survival.

Figure 29: OS extrapolated hazard plot, scale=normal, 1-3 spline knots - placebo + Gem/Cis, (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])



Abbreviations: DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; OS, overall survival.

External validation for Gem/Cis OS

Table 26 presents 2-, 3- and 5-year survival predictions from all models explored. Clinical opinion was sought to ensure that the best-fitting model was selected. All models fit the mature data well; therefore, clinical plausibility was key for resolving uncertainty in the long-term extrapolation choice.

In a clinical expert validation meeting, the majority of experts stated that in current UK clinical practice, 4% of patients are expected to be alive at 3 years.[19] This estimate is supported by the McNamara 2020 study which presents pooled data from a prospective first-line advanced BTC trial which found the proportion of patients alive and at risk at 3 years post-randomisation was 4%.[2222] The 4% estimate aligns

with the 3-year OS rate estimated by spline normal (1 knot), spline normal (2 knots), and spline normal (3 knots).

The clinical experts found it challenging to comment on 5-year OS estimates. Based on the clinical input on the expected 3-year OS rate for patients treated with Gem/Cis, the following distributions were not considered further because they either overestimated (spline odd (1 knot), spline odd (2 knots), spline odd (3 knots), log-logistic, log-normal and exponential) or underestimated (Weibull, generalised gamma, spline hazard (1 knot) and Gompertz) the proportion of patients alive at 3 years.

In a previous NICE technology appraisal in second-line patients with advanced cholangiocarcinoma treated with active symptom control (ASC) + mFOLFOX (TA722), clinical advisors to NICE estimated that survival at 3 years would be 3%, and 0.1% at 5 years.[71] In the first-line setting, it was considered that survival estimates are higher, aligning with the 3-year OS estimate of 4% advised in the clinical expert validation meeting.[19] The 5-year OS rates estimated by the spline normal (1 knot), spline normal (2 knots), and spline normal (3 knots) were all higher than 0.1%, therefore were assumed to be clinically plausible at 5 years.

The spline normal (1 knot) was considered most appropriate for the base case based on having the closest survival estimates to what was cited by expert opinion and external studies (McNamara 2020 and TA722, i.e., 4% at 3 years and >0.1% at 5 years), having the highest ranked AIC score and good visual fit. In addition, utilising 1 knot in the model reduces the risk of overfitting the data compared to spline-based models utilising 2 or more knots. The 3- and 5- year survival estimates for the spline normal (1 knot) were validated by an internal AstraZeneca physician.

Table 26: OS rates for placebo + Gem/Cis (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])

Distribution	Placebo + Gem/Cis		
	2-year survival rate	3-year survival rate	5-year survival rate
TOPAZ-1	11.51%	-	-
Spline 1 knot, scale = normal	**12.48%**	**3.78%**	**0.52%**
Gamma	13.06%	3.15%	0.15%
Spline 1 knot, scale = odds	13.60%	5.56%	1.67%

Distribution	Placebo + Gem/Cis		
	2-year survival rate	3-year survival rate	5-year survival rate
Spline 2 knots, scale = odds	13.56%	4.92%	1.35%
Spline 2 knots, scale = normal	13.18%	4.14%	0.60%
Weibull	12.03%	1.99%	0.02%
Generalised gamma	12.81%	2.90%	0.11%
Spline 1 knot, scale = hazard	13.04%	2.62%	0.06%
Spline 2 knots, scale = hazard	13.30%	3.33%	0.15%
Spline 3 knots, scale = odds	12.97%	4.54%	1.10%
Spline 3 knots, scale = normal	13.10%	3.93%	0.51%
Spline 3 knots, scale = hazard	13.30%	3.37%	0.14%
Log-logistic	16.15%	7.68%	2.81%
Gompertz	11.98%	0.76%	0.00%
Log-normal	17.56%	8.24%	2.47%
Exponential	19.07%	8.33%	1.59%

Note: distributions are ranked according to their AIC statistic

Abbreviations: AIC, Akaike Information Criterion; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; OS, overall survival.

B.3.4.2.2.3 Selection of OS distributions for base case

The OS base case for D + Gem/Cis was informed by the spline odds (1 knot). Since the hazard function for D + Gem/Cis has a complex shape over time, a flexible model was required to accommodate the change in hazard rate as recommended by NICE DSU TSD 21.[79] Therefore, standard parametric models were not considered appropriate. Considering all spline-based models, the spline odds (1 knot) was considered to provide a plausible 3-year survival rate of 12.64% based on UK clinical expert opinion. In addition, the spline odds (1 knot) provided the best AIC score compared to other spline-based models and most closely aligned with landmark survival estimates at 2 years compared to all spline-based and standard parametric models.

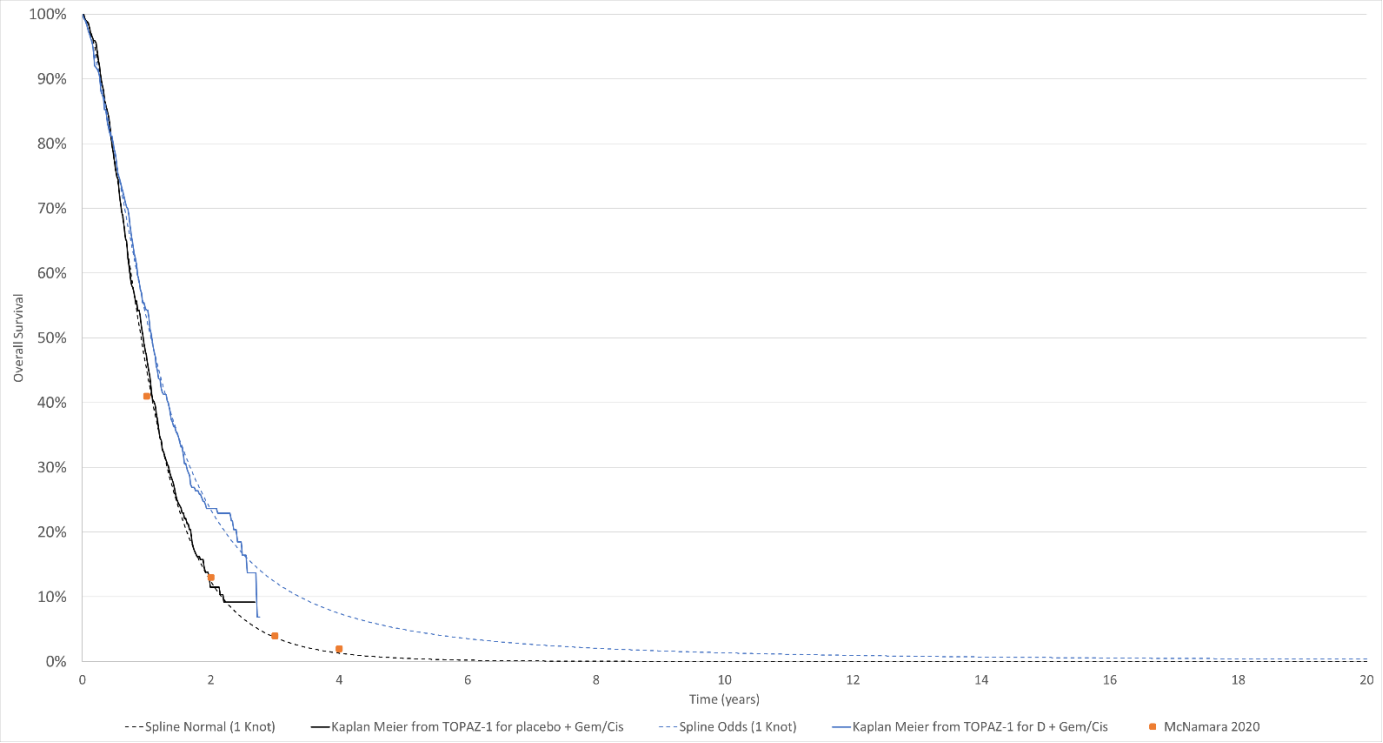
The OS base case for Gem/Cis was informed by the spline normal (1 knot). Similar to the D + Gem/Cis hazard function, the Gem/Cis hazard function changes over time and it was important to capture the survival trajectory. Clinical experts advised a 3-year OS rate of 4% for patients receiving Gem/Cis in UK clinical practice which was supported by an external study in BTC. [22] [22] The spline normal (1 knot) was selected for the base case as aligned with clinical expectations and avoided overfitting the

data with multiple knots; it also had a better visual and statistical fit, according to AIC, in comparison to all other distributions.

To ensure uncertainty is fully explored and in line with NICE guidance, the alternative plausible models were investigated in sensitivity analyses (see Section B.3.12.1).

For comparative purposes, Figure 30 is a plot of OS KM and selected base case extrapolations for D + Gem/Cis and placebo + Gem/Cis over the entire model time horizon. Survival points as reported in McNamara 2020[2222] at 1-, 2-, 3-, and 4-year post-randomisation in a study in BTC have been included to demonstrate consistency with the placebo + Gem/Cis arm.

Figure 30 Overall survival, selected base case distributions over 20 years



Abbreviations: D, durvalumab; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; ITT, intent-to-treat; OS, overall survival.

B.3.4.2.3 Progression free survival

PFS data were derived from extrapolated survival curves fitted to the time-to-event data from the TOPAZ-1 full analysis set (DCO: 11 August 2021). TOPAZ-1 PFS data are mature, with 81% and 86% events occurring by DCO in the D + Gem/Cis and placebo + Gem/Cis arms, respectively (Table 27).

Table 27: PFS time to event data (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])

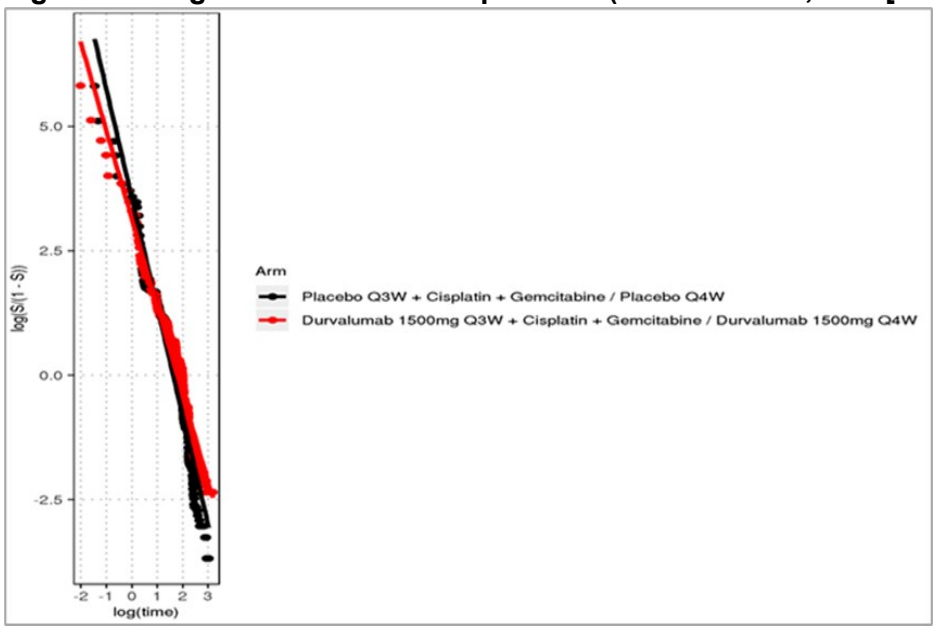
	Total number of events, N (%)	Median time to event, Months (95% CI)
D + Gem/Cis (n = 341)	276 (81)	7.23 (6.74; 7.43)
Placebo + Gem/Cis (n=344)	297 (86)	5.75 (5.55; 6.74)

Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; PFS, progression-free survival.

The PFS data for D + Gem/Cis and placebo + Gem/Cis are presented in Figure 7. D + Gem/Cis was associated with a statistically significant reduction in the overall risk of progression or death of 25% compared with placebo + Gem/Cis (HR: 0.75; 95% CI: 0.63, 0.89; p=0.001).

Using a consistent approach with the selection of OS extrapolations, the PHA was assessed. The global p-value for Schoenfeld's residual was non-significant (p=0.108), however the LCHP curves show a clear crossing, indicating that the relative treatment effect is likely to vary over time (Figure 31). On this basis there is clear violation of the PHA.

Figure 31: Log-cumulative hazard plot PFS (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])



Abbreviations: DCO, data cut-off; PFS, progression-free survival; QxW, every x weeks.

Given that the PHA was considered to be violated, parametric models (including flexible spline-based models) were fitted separately for both arms to the observed PFS data from TOPAZ-1.

Consistent with OS, for the spline-based approach, Royston-Parmer models were used and fitted with up to 3 knots. Spline knot locations were chosen as equally spaced quantiles of the uncensored survival times, for example, at the median with one knot or at the 33.3% and 66.7% quantiles for two knots. Boundary knots were chosen as the minimum and maximum event times.

B.3.4.2.3.1 D + Gem/Cis

Statistical goodness of fit

The survival models were ranked for the PFS D + Gem/Cis arm according to their AIC values (Table 28). Based on the AIC values, the spline hazard (3 knots) was the best fit. Overall, the spline-based models showed better statistical fit than standard parametric models.

Table 28: PFS AIC/BIC for D + Gem/Cis (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])

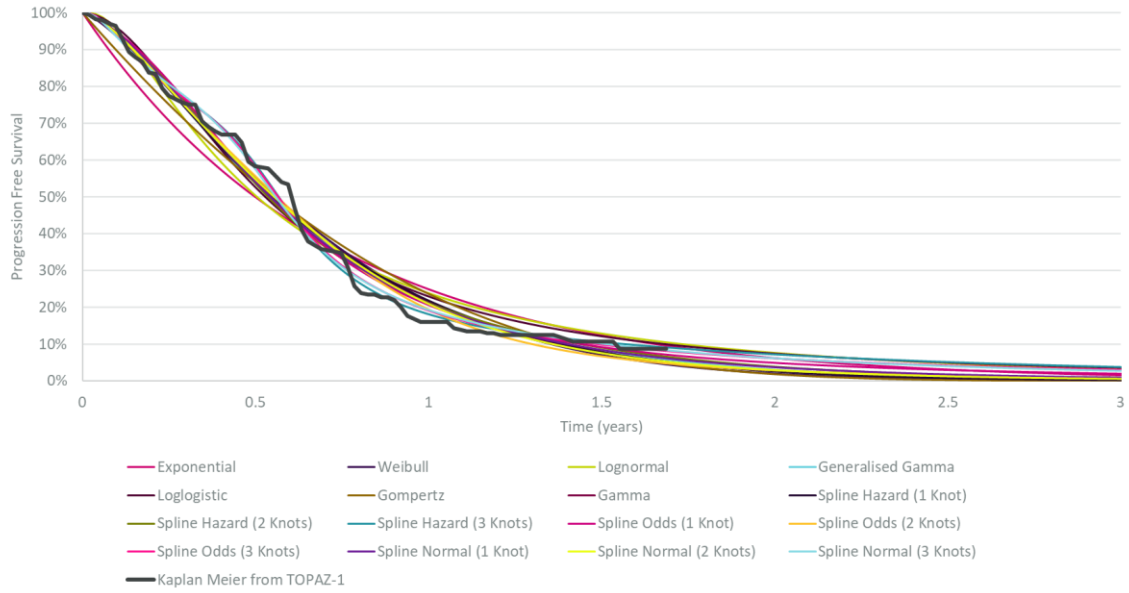
	D + Gem/Cis	
Model	**AIC (Rank)**	**BIC (Rank)**
Spline 3 knots, scale = hazard	1,679.09 (1)	1,698.25 (1)
Spline 3 knots, scale = odds	1,683.94 (2)	1,703.10 (2)
Spline 3 knots, scale = normal	1,688.78 (3)	1,707.94 (3)
Spline 2 knots, scale = odds	1,700.90 (4)	1,716.22 (6)
Spline 1 knot, scale = odds	1,704.05 (5)	1,715.55 (4)
Spline 1 knot, scale = normal	1,705.68 (6)	1,717.17 (7)
Spline 2 knots, scale = normal	1,707.26 (7)	1,722.59 (11)
Gamma	1,708.47 (8)	1,716.13 (5)
Generalised gamma	1,710.22 (9)	1,721.71 (10)
Spline 2 knots, scale = hazard	1,710.89 (10)	1,726.21 (13)
Weibull	1,711.74 (11)	1,719.40 (8)
Spline 1 knot, scale = hazard	1,712.19 (12)	1,723.68 (12)
Log-logistic	1,712.56 (13)	1,720.22 (9)
Log-normal	1,728.69 (14)	1,736.35 (14)
Gompertz	1,732.73 (15)	1,740.40 (15)
Exponential	1,743.92 (16)	1,747.75 (16)

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; PFS, progression-free survival.

Visual fit to KM plot

Visual inspection of the extrapolated survival curves indicated that all distributions provide a good visual fit to the observed KM data for D + Gem/Cis (Figure 32).

Figure 32: PFS extrapolations - D + Gem/Cis (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])



Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; PFS, progression-free survival.

All distributions had a good visual fit to the mature trial data, therefore the PFS extrapolation curve for the base case was informed by 1) statistical goodness-of-fit 2) assessment of the hazard function shape to determine whether standard parametric models can suitably model survival, 3) clinical expert opinion to ensure clinical plausibility of the extrapolations in the long-term.

Assessment of hazard function

Figure 33 shows the raw hazard plot for D + Gem/Cis PFS, which shows that the hazard changes over the course of the trial. The smoothed hazards are presented in Figure 34. The slope shows that the trial hazard changes over time, [redacted]. In line with NICE DSU TSD 21[79] guidance, flexible models (such as spline-based models) that enable hazard functions with complex shapes were considered because changing trial hazards may not be captured well by standard parametric models.

Figure 33: PFS hazard plot (raw) - D + Gem/Cis (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])

Abbreviations: D(urva), durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; ITT, intent-to-treat; PFS, progression-free survival.

Figure 34: PFS smoothed hazards (kernel method) - D + Gem/Cis (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])

Abbreviations: D(urva), durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; ITT, intent-to-treat; PFS, progression-free survival.

Similar to OS, the hazard plots for all parametric curves were extrapolated over a 20-year time horizon to confirm clinical plausibility of the base case curve in the long-term.

Figure 35 shows the hazard plots for the standard parametric curves. The exponential, Gompertz, Weibull, generalised gamma and gamma distributions did not capture the turning point in the trial hazard, and therefore were not considered appropriate. The log-normal and log-logistic parametric distributions were able to capture the overall change in the trial hazard. Clinical expert opinion on long-term survival was required to justify their use in the base case analysis (see Section External validation for D + Gem/Cis PFS).

Figure 35: PFS extrapolated hazard plots (standard parametric models) – D + Gem/Cis (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])

Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; PFS, progression-free survival.

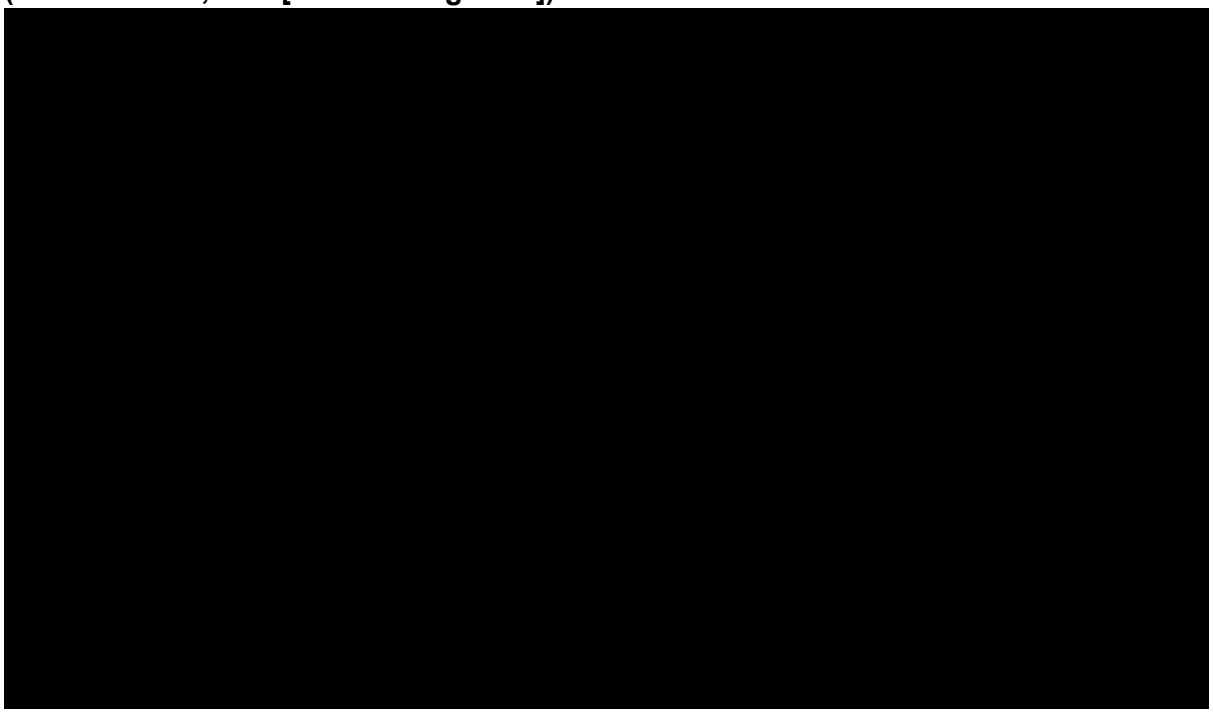
Figure 36, Figure 37 and Figure 38 present the hazard plots for spline models on the hazard scale (1 to 3 knots), odds scale (1 to 3 knots) and normal scale (1 to 3 knots), respectively.

The hazard plot for the spline models using the hazard scale (Figure 36) shows that only the 3-knot model captured the overall change in trial hazard. The models utilising 1 and 2 knots did not accurately fit the trial hazard, and therefore were not considered appropriate to model PFS. The spline hazard (3 knots) was considered to overestimate the initial increase in the trial hazard.

Spline models on the odds scale and normal scale were considered to accurately capture the trial hazard regardless of the number of knots applied, and all extrapolations were considered similar (Figure 37 and Figure 38). However, for both distributions applying 3 knots overestimated the initial increase in the trial hazard, whereas applying 1 or 2 knots underestimated the decrease in the trial hazard.

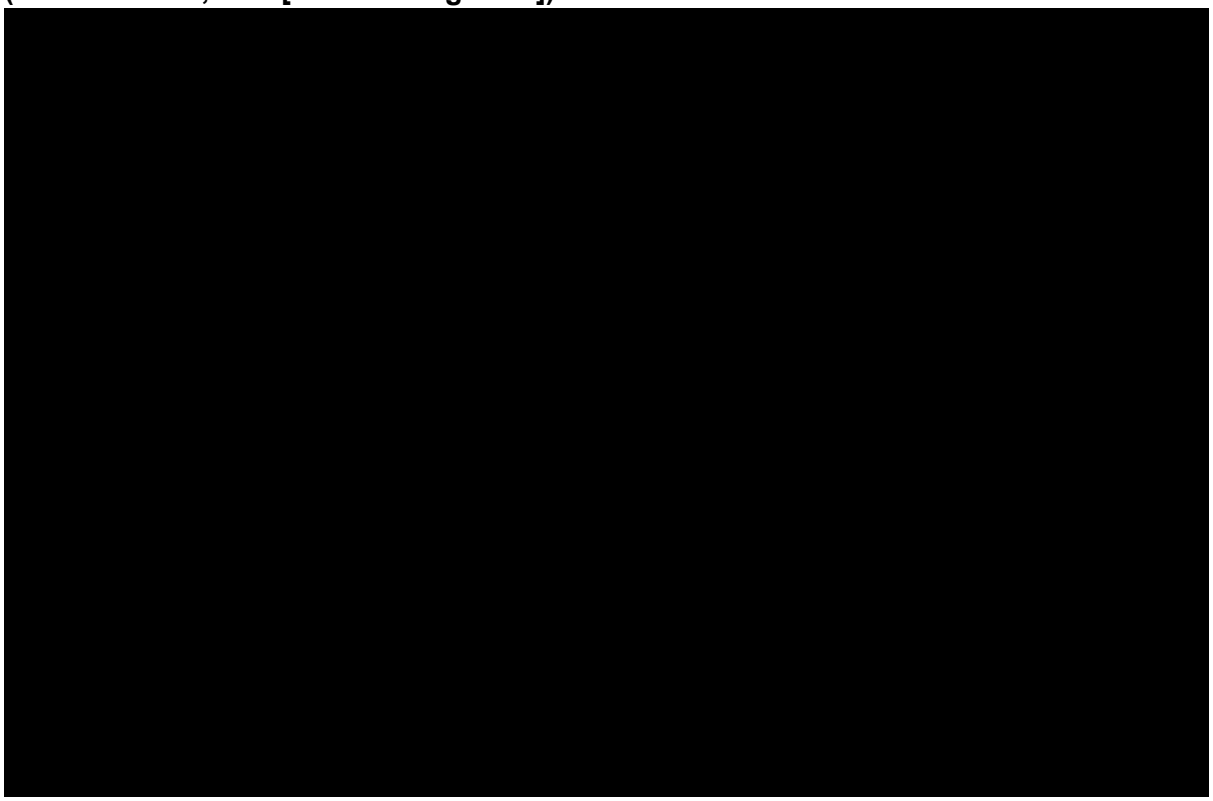
AIC statistics favoured the spline models with 3 knots on the hazard (rank: 1st), odds (rank: 2nd) and normal (rank: 3rd) scale (see Table 28). Based on visual inspection, it was not clear which curves fit the trial hazard best; however, the spline models utilising 3 knots and the spline odds (1 knot) were considered to provide the closest fit. In order to select the most plausible extrapolation, clinical expert opinion was key to predict long-term survival[19] (see Section External validation for D + Gem/Cis PFS).

Figure 36: PFS extrapolated hazard plot, scale=hazard, 1-3 spline knots - D + Gem/Cis, (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])



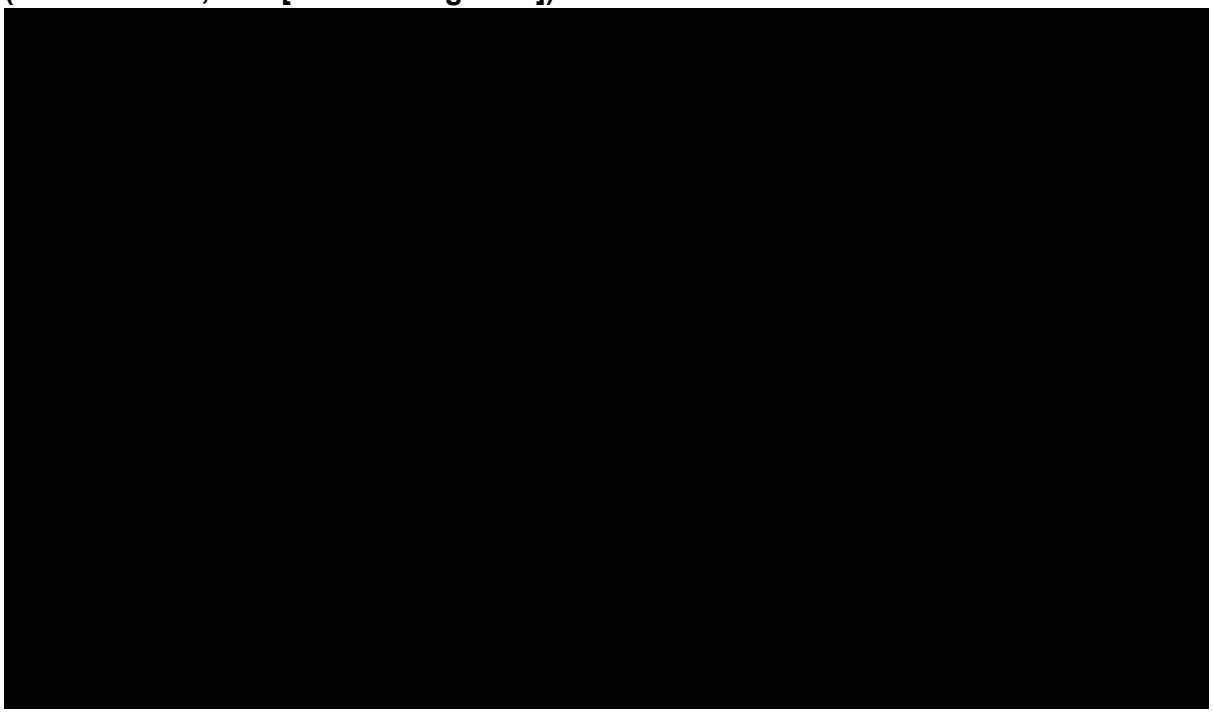
Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; PFS, progression-free survival.

Figure 37: PFS extrapolated hazard plot, scale=odds, 1-3 spline knots - D + Gem/Cis, (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])



Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; PFS, progression-free survival.

Figure 38: PFS extrapolated hazard plot, scale=normal, 1-3 spline knots - D + Gem/Cis, (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])



Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; PFS, progression-free survival.

External validation for D + Gem/Cis PFS

Similar to OS, the clinical experts stated perceptions of PFS for patients treated with D + Gem/Cis was challenging to comment on due to their lack of long-term clinical experience. Clinicians were presented with the predicted proportion of progression-free patients at various timepoints (from 6 months to 10 years) for three distributions: spline 3-knot hazards, gamma, and spline 1-knot odds.[19] The majority of clinical experts expected 5% of patients to be progression free at the 24-month landmark analysis, indicating that the spline odds (1 knot) distribution provided the most clinically plausible estimate at 24 months (4.96%) (see Table 29).

Gamma, Weibull, generalised gamma and Gompertz were considered by clinical experts to underestimate the proportion of patients expected to be progression free at 24 months in the UK, as well as overestimate the proportion of patient's progression free at 12 months based on the observed data. In addition, the log-logistic, exponential, and log-normal were considered by clinical experts and the

observed data to overestimate the proportion of patients expected to be progression free at 24 and 12 months, respectively. This supports the observation from the D + Gem/Cis PFS hazards plot that the standard parametric models were not considered suitable due to the complex shape of the curve.

The flexible spline odds (1 knot) was selected to inform PFS in the base case. Although the distribution was ranked 5th based on AIC score, it had a similar visual fit to the best fitting spline-based models and was considered the most plausible across all spline-based models according to clinical experts. In addition, the spline odds (1 knot) was the best statistical (based on AIC) and visual fitting spline-based model with only 1 knot. As highlighted for OS, 1 knot diminishes the risk of overfitting the data and ensures the extrapolation is not based upon trends observed towards the end of the follow-up period informed by fewer events.

Table 29: PFS rates for D + Gem/Cis (survival extrapolations from TOPAZ-1 trial, IA-2 [DCO 11 August 2021])

Distribution	D + Gem/Cis		
	6-months PFS rate	12-months PFS rate	24-months PFS rate
TOPAZ-1	58.30%	16.00%	-
Spline 3 knots, scale = hazard	59.02%	18.22%	7.25%
Spline 3 knots, scale = odds	58.2%	19.20%	6.20%
Spline 3 knots, scale = normal	57.65%	19.39%	6.21%
Spline 2 knots, scale = odds	55.72%	19.55%	2.92%
Spline 1 knot, scale = odds	**54.43%**	**20.76%**	**4.96%**
Spline 1 knot, scale = normal	54.15%	21.14%	3.76%
Spline 2 knots, scale = normal	54.92%	21.06%	2.99%
Gamma	54.37%	21.71%	2.73%
Generalised gamma	53.91%	21.82%	3.11%
Spline 2 knots, scale = hazard	53.76%	21.30%	3.91%
Weibull	55.28%	21.89%	2.04%
Spline 1 knot, scale = hazard	54.19%	21.97%	2.62%
Log-logistic	52.72%	23.06%	7.46%
Log-normal	50.46%	23.95%	7.67%
Gompertz	54.00%	23.81%	1.89%
Exponential	50.03%	25.03%	6.26%

Note: distributions are ranked according to their AIC statistic.

Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; PFS, progression-free survival.

B.3.4.2.3.2 Placebo + Gem/Cis

Statistical goodness of fit

The PFS extrapolations were ranked for the placebo + Gem/Cis arm according to their AIC values (Table 30). Based on the AIC values, the spline odds (3 knots) was the best fit. Similar to the D + Gem/Cis arm, the spline-based models showed better statistical fit than standard parametric models.

Table 30: PFS AIC/BIC for placebo + Gem/Cis (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])

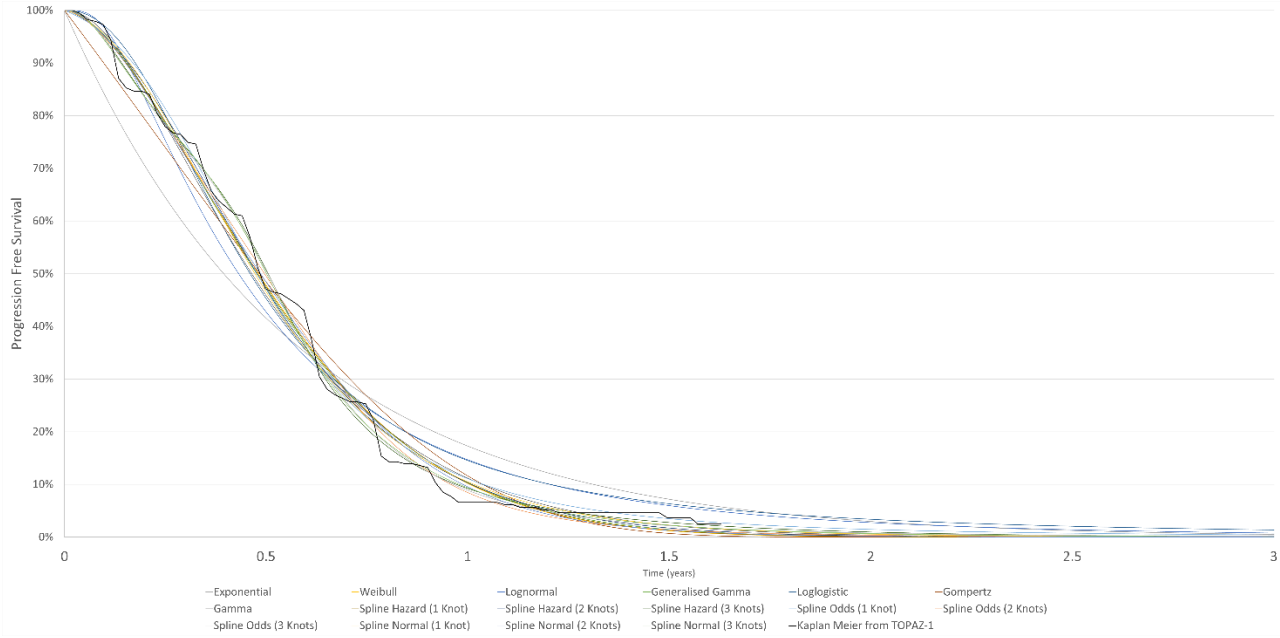
	Placebo + Gem/Cis	
Model	**AIC (Rank)**	**BIC (rank)**
Spline 3 knots, scale = odds	1,637.37 (1)	1,656.57 (1)
Spline 3 knots, scale = hazard	1,638.52 (2)	1,657.72 (2)
Spline 3 knots, scale = normal	1,639.11 (3)	1,658.31 (4)
Spline 2 knots, scale = odds	1,643.31 (4)	1,658.68 (5)
Spline 2 knots, scale = normal	1,648.98 (5)	1,664.35 (10)
Weibull	1,650.30 (6)	1,657.98 (3)
Spline 1 knot, scale = normal	1,650.59 (7)	1,662.11 (7)
Gamma	1,652.06 (8)	1,659.74 (6)
Spline 1 knot, scale = hazard	1,652.21 (9)	1,663.73 (9)
Spline 2 knots, scale = hazard	1,652.74 (10)	1,668.10 (12)
Spline 1 knot, scale = odds	1,653.58 (11)	1,665.11 (11)
Generalised gamma	1,654.76 (12)	1,663.28 (8)
Log-logistic	1,672.61 (13)	1,680.29 (13)
Gompertz	1,681.58 (14)	1,689.26 (14)
Log-normal	1,686.64 (15)	1,694.32 (15)
Exponential	1,737.96 (16)	1,741.80 (16)

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; PFS, progression-free survival.

Visual fit to KM plot

Visual inspection of the extrapolated survival curves indicated that most distributions, with the exception of exponential, log-logistic and log normal, provided a good visual fit to the observed KM data for placebo + Gem/Cis (Figure 39).

Figure 39: PFS extrapolations – placebo + Gem/Cis (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])



Abbreviations: DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; PFS, progression-free survival.

Similar to the D + Gem/Cis arm and based on the good visual fit to the mature trial data, selection of the PFS extrapolation for the base case required 1) assessment of the hazard function shape to determine whether standard parametric models can suitably model survival, 2) clinical expert opinion to ensure clinical plausibility of the selected model in the long-term.

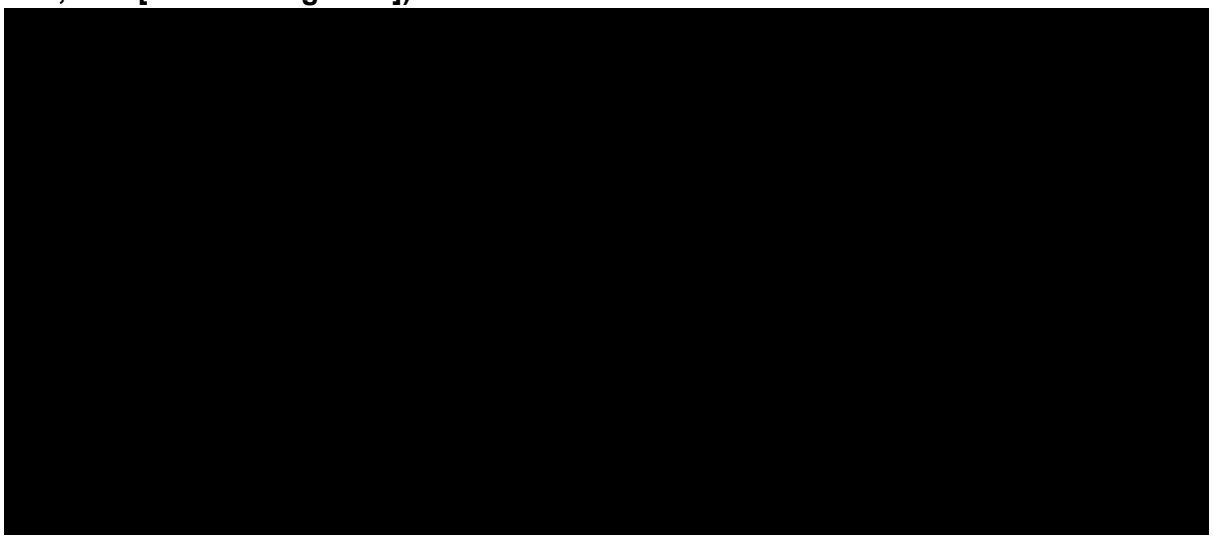
Assessment of hazard function

Figure 40 shows the raw hazard plot for placebo + Gem/Cis PFS, which illustrates that the hazards change over the course of the trial. The smoothed trial hazards are presented in Figure 41. Similar to D + Gem/Cis PFS, [redacted]. In line with NICE DSU TSD 21[79] and consistent with the selection process used for the D + Gem/Cis arm, spline-based models with complex shapes were considered.

Figure 40: PFS hazard plot (raw) - placebo + Gem/Cis (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])

Abbreviations: DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; ITT, intent-to-treat; PFS, progression-free survival.

Figure 41: PFS smoothed hazards (kernel method) - placebo + Gem/Cis (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])

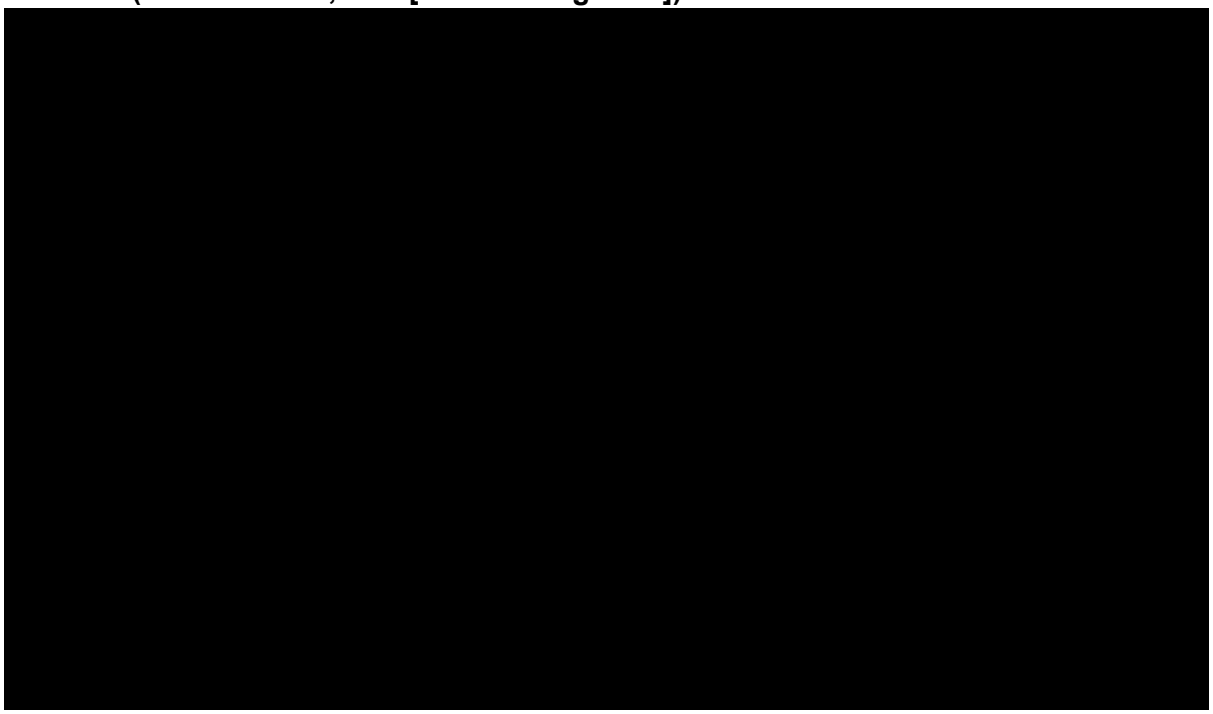


Abbreviations: DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; ITT, intent-to-treat; PFS, progression-free survival.

Extrapolated hazards over a 20-year time horizon were considered for standard parametric models (Figure 42). Also observed for D + Gem/Cis PFS, the exponential, Gompertz, Weibull, generalised gamma and gamma did not capture the turning point in the trial hazard, whereas the log-normal and log-logistic do. Again, clinical expert

opinion was required to confirm plausibility of the long-term estimates (see Section External validation for Gem/Cis PFS).

Figure 42: PFS extrapolated hazard plots (standard parametric models) – placebo + Gem/Cis (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])



Abbreviations: DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; PFS, progression-free survival.

Figure 43, Figure 44 and Figure 45 present the hazard plots for spline models on the hazard scale (1 to 3 knots), odds scale (1 to 3 knots) and normal scale (1 to 3 knots), respectively.

From visual inspection, the only spline hazard model capturing the overall change in trial hazard was the model utilising 3 knots (Figure 43). All spline models on the odds and normal scales were considered to capture the shape of the trial hazard, however the models applying 2 knots were not considered to accurately estimate the decrease in hazard when extrapolated. Overall, the models with 3 knots were considered to have the observed best fit to the trial hazard which is consistent with them scoring the lowest AIC statistics (odds rank: 1st, hazard rank: 2nd, normal rank: 3rd). However, the spline odds and spline normal models utilising 1 knot were also considered able to capture the increase and decrease in hazards. Therefore, clinical

expert opinion on the extrapolations was key to selecting the most appropriate PFS curve.

Figure 43: PFS extrapolated hazard plot, scale=hazard, 1-3 spline knots - placebo + Gem/Cis, (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])

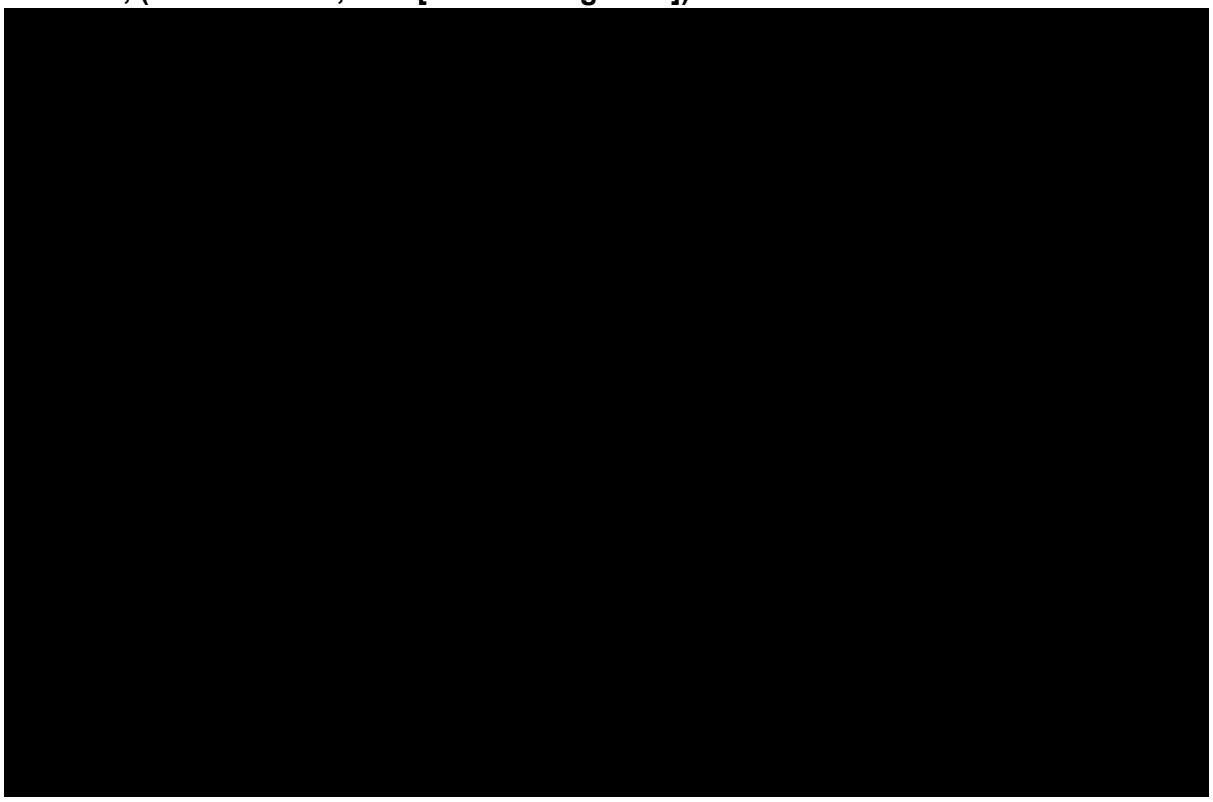


Figure 44: PFS extrapolated hazard plot, scale=odds, 1-3 spline knots - placebo + Gem/Cis, (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])

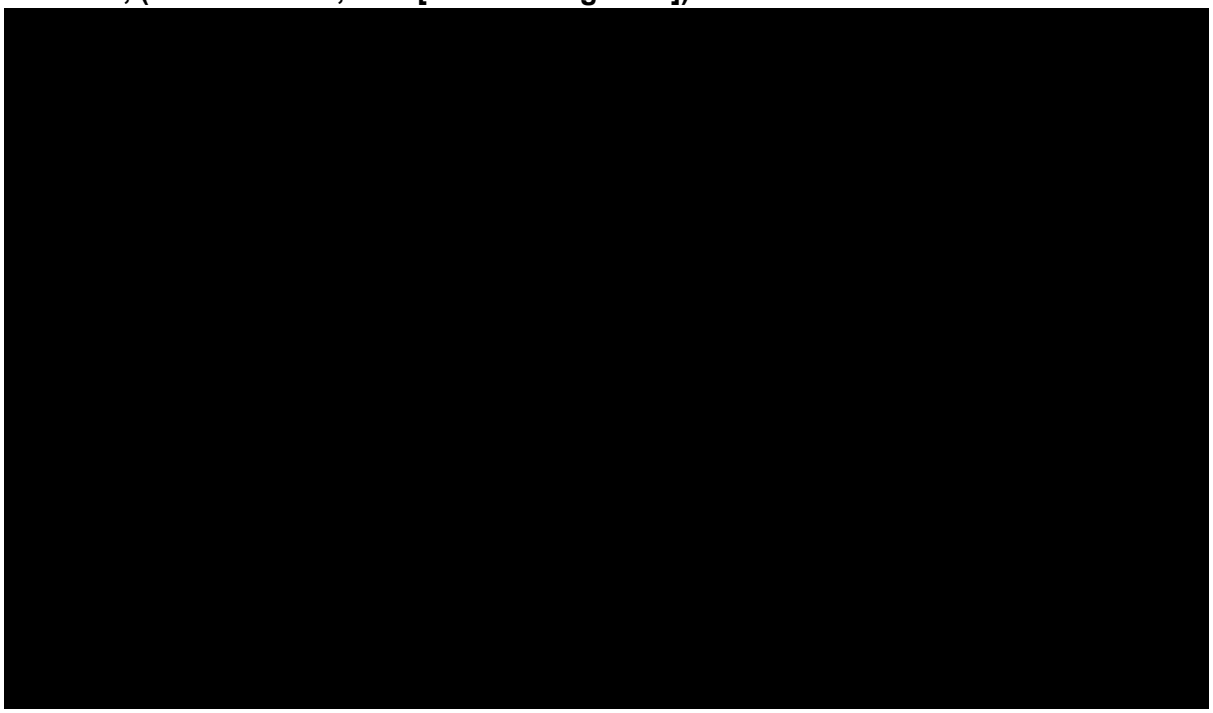
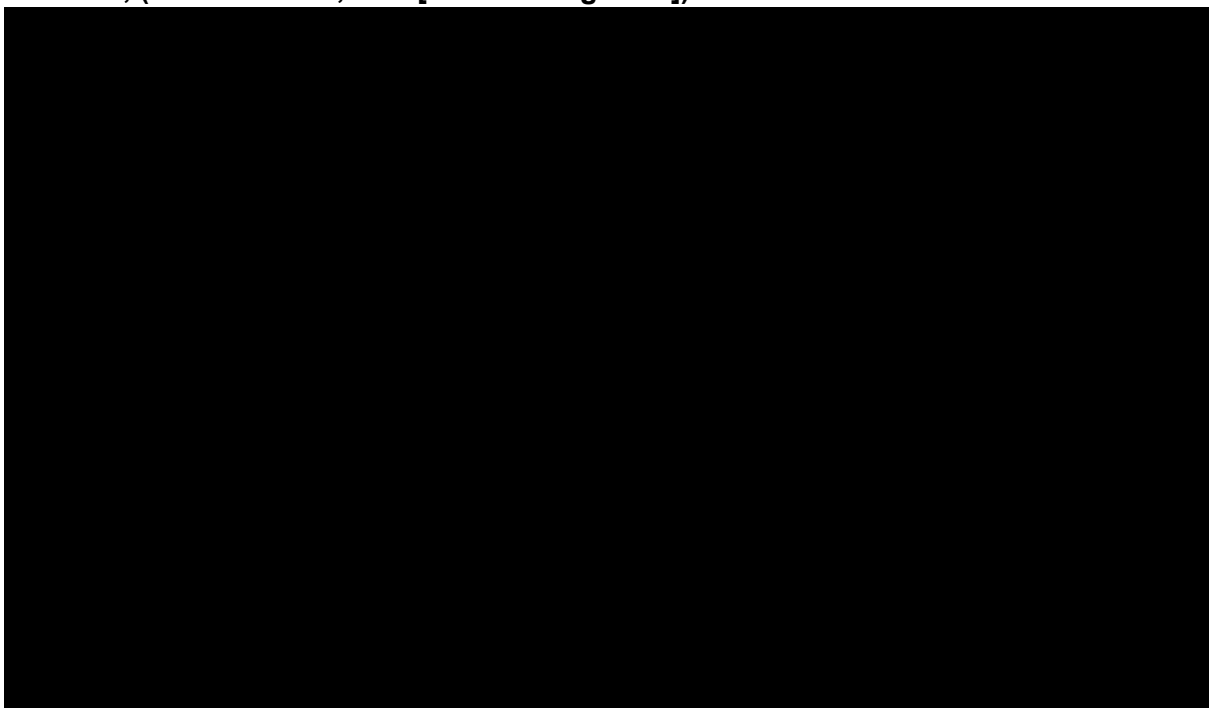


Figure 45: PFS extrapolated hazard plot, scale=normal, 1-3 spline knots - placebo + Gem/Cis, (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])



External validation for Gem/Cis PFS

Based on good visual fit to the mature trial data and in line with the PFS extrapolation selection process for D + Gem/Cis, clinical expert opinion was important in ensuring the chosen model provides a plausible extrapolation beyond the observed trial data. Clinicians were shown the predicted proportion of progression-free patients at various timepoints (from 6 months to 10 years) for three distributions: spline 3-knot odds, log-logistic and Weibull. These three distributions represent a range of extrapolated estimates (e.g., log-logistic predicts an initially lower estimate but very long tail, and Weibull predicts a pessimistic estimate). Clinical expert consensus was that the spline model odds was the most clinically plausible model from the distributions shown.[19] This consensus was largely driven by the 24-month PFS estimate of 0.8% for patients treated with Gem/Cis since diagnosis of advanced and/or metastatic disease (see Table 31).

Determined from UK clinical opinion, the Weibull, gamma, generalised gamma and Gompertz were considered to underestimate the proportion of patients who are progression free at 24 months. Whereas the log-logistic, log-normal and exponential were considered to overestimate the proportion of patients who are progression free at 12 and 24 months. This supports the initial finding that the standard parametric models were not considered suitable to model survival in this patient population based on the NICE DSU TSD 21[79] recommended assessment of the PFS hazard function.

The spline normal (1 knot) was selected to inform the PFS base case for placebo + Gem/Cis. This distribution was considered to predict a clinically plausible 24-month PFS rate since 0.58% is closely aligned to the clinical experts' opinion (see Table 31). Three knot models were not selected in the base case because of the concern that this would overfit the data and be overinfluenced by observations at the end of the trial period where few patients remained at risk. Two knot models appeared to overestimate the observed hazard and provided the worst visual fit (Figure 43, Figure 44 and Figure 45). Spline normal (1 knot) was the best statistically fitting (based on AIC) spline-based model with 1 knot. In addition, the spline normal (1

knot) more closely aligned to the 6 month observed data in comparison to the higher AIC-ranked spline-based models.

Table 31: PFS rates for placebo + Gem/Cis (survival extrapolations from TOPAZ-1 trial, IA-2 [DCO 11 August 2021])

Distribution	Gem/Cis		
	6-months PFS rate	12-months PFS rate	24-months PFS rate
TOPAZ-1	47.2%	6.60%	-
Spline 3 knots, scale = odds	50.90%	9.00%	0.80%
Spline hazards 3 knots, scale = hazard	51.05%	8.99%	0.98%
Spline 3 knots, scale = normal	50.44%	9.47%	0.68%
Spline 2 knots, scale = odds	55.72%	19.55%	2.92%
Spline 2 knots, scale = normal	48.63%	9.68%	0.20%
Weibull	48.05%	10.33%	0.09%
Spline 1 knot, scale = normal	**46.79%**	**10.62%**	**0.58%**
Gamma	46.07%	11.31%	0.41%
Spline 1 knot, scale = hazard	47.78%	10.43%	0.10%
Spline 2 knots, scale = hazard	47.37%	10.44%	0.24%
Spline 1 knot, scale = odds	47.31%	11.21%	1.48%
Generalised gamma	47.46%	10.51%	0.15%
Log-logistic	45.50%	14.79%	2.79%
Gompertz	48.63%	11.79%	0.00%
Log-normal	42.92%	14.65%	3.41%
Exponential	41.71%	17.40%	3.03%

Note: distributions are ranked according to their AIC statistic.

Abbreviations: DCO, data cut-off; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; PFS, progression-free survival.

B.3.4.2.3.3 Selection of PFS distributions for base case and scenario analyses

The spline odds (1 knot) distribution was used to inform PFS in the base case for D + Gem/Cis. In line with NICE DSU TSD 21[79], flexible models were considered more appropriate than standard parametric models in this patient population due to the complex shape of the hazard plot for D + Gem/Cis (Figure 34). In comparison to all spline-based models assessed, the spline odds (1 knot) had the most clinically plausible PFS rate of 4.96% at 24 months, determined by UK clinical experts.

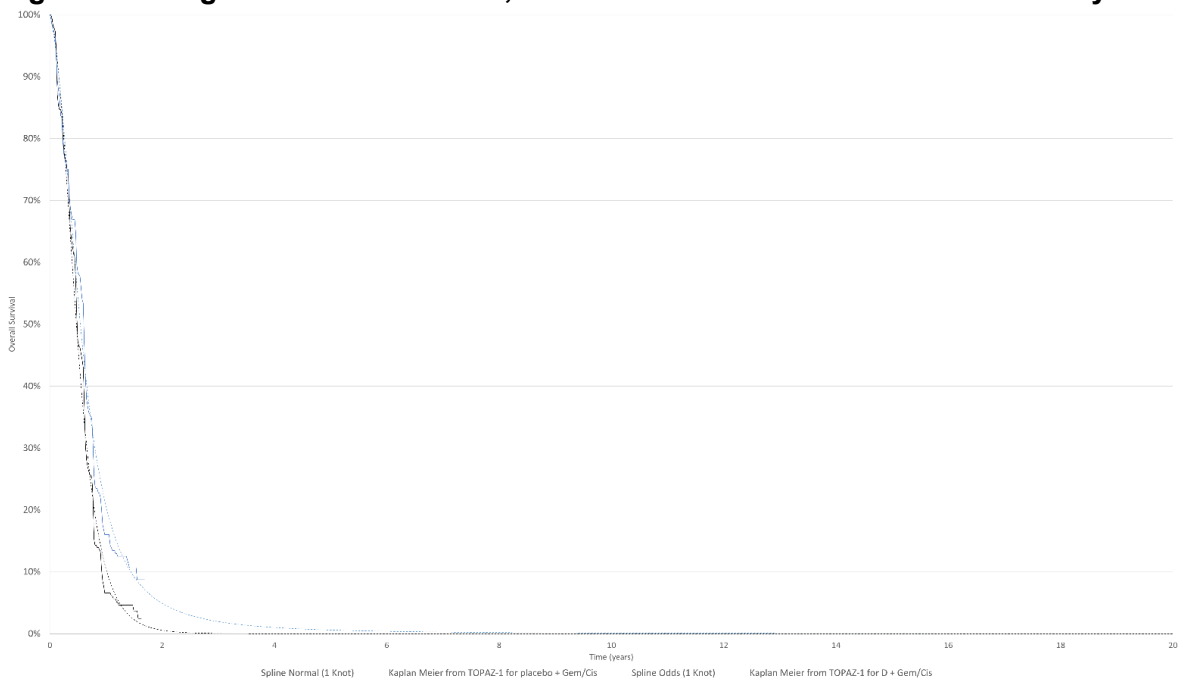
Furthermore, this distribution applies 1 knot, reducing the risk of overfitting the data versus spline-based models utilising 2 or more knots.

The spline normal (1 knot) distribution was used to inform PFS in the base case for placebo + Gem/Cis. Comparable to D + Gem/Cis, the hazard plot for placebo + Gem/Cis has a complex shape meaning standard parametric models were not considered appropriate to model PFS in this patient population. Although spline models utilising 3 knots were considered to fit the trial hazards best, as discussed above, utilising 1 knot avoids risk of overfitting the data. Therefore, spline normal (1 knot) was deemed more suitable to model PFS than spline-based models with better statistical fit but utilising 2 or 3 knots. The spline normal (1 knot) was the best statistically fitting (according to AIC) spline-based distribution applying 1 knot.

In line with NICE guidance, other plausible curves were explored in scenario analysis to measure uncertainty (see Section B.3.12.1).

For comparative purposes, Figure 46 shows a plot of PFS KM and selected base case extrapolations for D + Gem/Cis and placebo + Gem/Cis over the entire model time horizon.

Figure 46: Progression-free survival, selected base case distributions over 20 years



B.3.4.3 Adverse events

AEs that occurred in the TOPAZ-1 trial are reported in Section B.2.10. Grade ≥3 AEs with an incidence of greater than 5% in either treatment arm of the TOPAZ-1 trial were included as one-off events in the first cycle of the model.

Table 32 presents the AEs from TOPAZ-1 (February 2022 DCO)[13] included within the cost-effectiveness analysis.

Table 32: Treatment-related adverse events (Grade 3+, 6.5-month update [DCO 25 Feb 22])

Adverse event	D + Gem/Cis	Gem/Cis
Neutropenia	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]
Thrombocytopenia	[redacted]	[redacted]
Cholangitis	[redacted]	[redacted]
Neutrophil count decrease	[redacted]	[redacted]
Platelet count decreased	[redacted]	[redacted]
White blood cell count decreased	[redacted]	[redacted]

Abbreviations: D, durvalumab; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg.
Source: CSR addendum.[13]

B.3.4.4 Base case summary

A summary of the main clinical parameters and variables applied in the base case analysis is presented in Table 33.

Table 33: Summary of clinical model parameters and variables used in the economic model base case

Parameter	Value	Rationale	Section
Baseline characteristics	As presented in Table 21 informed by TOPAZ-1	Aligned to the observed efficacy in TOPAZ-1 and considered generalisable to UK practice	B.3.4.1
OS models	Independent models: • D + Gem/Cis: spline odds (1 knot) • Gem/Cis: spline normal (1 knot)	Good visual and statistical (based on AIC) fit to KM, good extrapolation of longer-term OS and considered most clinically plausible	B.3.4.2.2

Parameter	Value	Rationale	Section
PFS models	Independent models: • D + Gem/Cis: spline odds (1 knot) • Gem/Cis: spline normal (1 knot)	Good visual and statistical (based on AIC) fit to KM, good extrapolation of longer-term PFS and considered clinically plausible	B.3.4.2.3
TTD models	Independent models: • Gem/Cis: spline hazard (3 knots) • D + Gem/Cis: spline odds (1 knot)	Good visual and statistical (based on AIC) fit to KM	Appendix O
Adverse events	Grade ≥3 AEs occurring in ≥5% of patients in either treatment arm (any Grade)	Considered to reflect the main AEs experienced by patients and those that could impact the economic analysis	B.3.4.3

Abbreviations: AE, adverse event; AIC, Akaike Information Criterion; D, durvalumab; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival.

B.3.5 Measurement and valuation of health effects

B.3.5.1 Health-related quality-of-life data from clinical trials

In TOPAZ-1, HRQoL for both treatment arms was measured using the EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-BIL21 questionnaires. The assessment schedule for the EQ-5D-5L included baseline followed by Q3W for the first eight treatment cycles relative to the date of randomisation, then every cycle (4 weeks) thereafter until progression or death. After Cycle 16 Day 1, EQ-5D-5L assessments were made every other cycle.

All patients from the FAS were included in the PRO analysis, except for patients with no questionnaire translation available or who did not complete the questionnaire due to other physical or language reasons. For EQ-5D-5L, the PRO analysis set comprised n=317 patients receiving D + Gem/Cis and n=328 patients receiving placebo + Gem/Cis, totalling n=645 patients.

For the model, HSUVs were derived from a subset of 633 patients from the PRO analysis set where EQ-5D-5L questionnaires with responses to all 5 domains were completed and patients had at least 1 follow-up visit.

B.3.5.2 Mapping

In line with NICE guidance,[75] the EQ-5D-5L responses collected in TOPAZ-1 responses were 'cross walked' to produce EQ-5D-3L derived UK utility values[75] using the Hernández Alava et al., 2017 algorithm.[82]

In total, 633 patients completed an EQ-5D-5L questionnaire (i.e., all 5 domains completed) at ≥1 follow-up visit, and 81.4% completed one at baseline. All completed questionnaires were used to derive health state utilities, including those from the small proportion of patients without an EQ-5D-5L measurement at baseline.

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 is appropriate when handling data that are missing at random. Specifically, a random intercept model assuming independent within-subject errors was fitted to account for the subject variability. Estimation was based on restricted maximum likelihood method. Kenward-Roger approximation was used to estimate the degrees of freedom.[83]

Univariate and multivariate analyses were conducted by fitting models including each of the covariates listed below (i) separately, (ii) together with treatment received, and (iii) their interaction

- Treatment received
- Progression status (progression-free, progressed)
- Treatment received + progression status (progression-free, progressed)
- Treatment received × treatment status (on/off treatment)

Model performance for the different univariate and multivariate analyses was compared using AIC and BIC scores (Table 34). A univariate model of utility by progression status was selected for the base case as progression status was the strongest predictor of patient utility (lowest AIC and BIC), second to and similar to treatment discontinuation status. Given that treatment discontinuation status refers to

cessation of placebo treatment in the Gem/Cis arm, progression status is a more clinically meaningful covariate.

Table 34: UK utilities Hernández Alava et al. (2017) crosswalk algorithm: AIC and BIC for univariate and multivariate models

Model	Parameters	AIC	BIC
1	Utility = treatment	-4871.4	-4691.1
2	Utility = progression state	-4901.5	-4721.2
3	Utility = treatment and progression state	-4892.3	-4705.6
4	Utility = treatment × time progression state and treatment and progression state	-4885.9	-4692.8
5	Utility = treatment discontinuation state	-4905.9	-4725.6
6	Utility = treatment and treatment discontinuation state	-4896.7	-4710.0
7	Utility = treatment × treatment discontinuation state and treatment and treatment discontinuation state	-4890.2	-4697.0

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

A total of 4,385 observations were recorded for patients whilst progression-free and 238 were recorded post-progression. A tabulated summary of the EQ-5D-5L 'cross walked' to EQ-5D-3L utility values by progression status is presented in Table 35.

Table 35: Summary of utility values by progression state

Health state	Number of patients	Number of observations	Mean (95% CI)
Progression-free	633	4385	0.797 (0.787; 0.807)
Progressed disease	173	238	0.679 (0.638; 0.720)

Abbreviations: CI, confidence interval.
Source: post-hoc analyses TOPAZ-1.

In scenario analysis, utility was estimated based on scores by treatment status (pre- and post- discontinuation of study treatment [i.e., durvalumab or placebo]). A tabulated summary of the EQ-5D-5L 'cross walked' to EQ-5D-3L utility values by treatment discontinuation is provided in Table 36.

Table 36: Summary of utility values by treatment discontinuation status

Health state	Number of patients	Number of observations	Mean (95% CI)
Pre-treatment discontinuation	633	4383	0.798 (0.788; 0.808)
Post-treatment discontinuation	172	240	0.680 (0.642; 0.719)

Abbreviations: CI, confidence interval.

Source: Post-hoc analyses TOPAZ-1.

B.3.5.3 Health-related quality-of-life studies

An SLR was conducted to identify relevant studies reporting HRQoL or utility data for patients with unresectable locally advanced or metastatic BTC. All database searches were conducted between 14 and 23 October 2022. A total of 22 relevant HRQoL studies were identified. Detailed descriptions of the review methodology and results are reported in Appendix H. Only one study identified in the review reported EQ-5D utilities.[84] This study was not used in the economic analysis as it only reported utility at trial baseline and after 4-months of follow-up on treatment in the ABC-06 trial, rather than by progression-status.

B.3.5.4 Adverse reactions

AE-related QALY decrements, defined as the disutility adjusted for the duration of the AE, were applied as a one off-decrement in the first model cycle, based on the frequency reported in Section B.3.4.3.

AEs can occur at any point in time; therefore, disutilities could not be estimated by the HRQoL questionnaires completed on specific days during the TOPAZ-1 trial. A summary of AE disutilities, durations and sources are presented in Table 37.

Table 37: Disutility per adverse events (Grade 3 and 4)

AE	Disutility	Source – disease area	Duration (days)	Source – disease area
Neutropenia	-0.0607	TA722 - Relapsed or refractory advanced cholangiocarcinoma[71]	7	TA722 - Relapsed or refractory advanced cholangiocarcinoma[71]
Anaemia	-0.085		9.9	
Thrombocytopenia	-0.085		14	
Cholangitis	-0.085		4.7	
Neutrophil count decrease	-0.0607	Assumed same as neutropenia	7	Assumed same as neutropenia
Platelet count decreased	-0.085	Assumed same as thrombocytopenia	14	Assumed same as thrombocytopenia
White blood cell count decreased	-0.0607	Assumed same as neutropenia	7	Assumed same as neutropenia

Abbreviations: AE, adverse event.

B.3.5.5 Health-related quality-of-life data used in the cost-effectiveness analysis

HRQoL data are scarce for patients with previously untreated, unresectable locally advanced or metastatic BTC. This is due to the rarity of the condition and lack of previously approved treatment options and corresponding clinical trial data.

Therefore, the base case utility values were derived from TOPAZ-1 (Section B.3.5.2). This was considered the most robust and applicable source of utility data for this population, as data were directly collected from patients with previously untreated, unresectable locally advanced or metastatic BTC. The values measure the health states using EQ-5D-5L cross-walked to EQ-5D-3L which is the preferred method outlined in the NICE reference case.

HSUVs were applied consistently across treatment arms by progression status since progression status was the strongest predictor of patient utility (Section B.3.5.2). When a patient moves from a pre-progression to a post-progression state, their utility decreases.

HSUVs were adjusted over the lifetime time horizon by applying age-related decrements to reflect the aging of the cohort. Age-related utility decrements were included in the model base case to account for the natural decline in quality of life associated with age. Utility values from the general population at each age were calculated using the OLS regression model published by Ara and Brazier (2010) (see Equation 1).[76] The utility multiplier was calculated per increase in age and applied in each cycle throughout the model time horizon. The mean age ([redacted] years) and proportion male (50.4%) from TOPAZ-1 was used in this equation.

Equation 1: OLS regression used to estimate the mean HSUVs for individuals in the general population[76]

$$EQ-5D = 0.9508566 + 0.0212126 * male - 0.0002587 * age - 0.0000332 * age^2$$

Table 38 summarises the utility values included within the cost-effectiveness analysis base case and scenarios. In addition, treatment specific AE disutility was included, as described in Section B.3.5.4.

Table 38: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean	95% CI	Reference in submission (section and page number)	Justification
Base case				
Progression-free	[redacted]	[redacted]	Section B.3.5.2	Derived from TOPAZ-1 trial
Progressed disease	[redacted]	[redacted]	Section B.3.5.2	

Abbreviations: CI, confidence interval.

B.3.6 Cost and healthcare resource use identification, measurement, and valuation

An SLR was undertaken to identify cost and HCRU studies for the treatment of BTC. All database searches were conducted between 14 and 23 October 2022. A total of 10 cost studies (incl. 5 reporting HCRU as well) were identified, none of which were conducted in the UK. It was therefore considered most appropriate to derive unit costs for the base case economic analysis from the most recent NHS reference costs, British National Formulary (BNF)[85] and the drugs and pharmaceutical electronic market information tool (eMIT).[86] HCRU was sourced from previous NICE technology appraisals and validated with clinical experts and ESMO guidelines. Detailed descriptions of the review methodology and results are reported in Appendix I.

B.3.6.1 Intervention and comparators' costs and resource use

This section provides a summary of the intervention and comparator treatment costs used in the analysis.

B.3.6.1.1 Drug acquisition costs

The drug unit costs for each treatment included were sourced from the British National Formulary (BNF) and the drugs and pharmaceutical electronic market information tool (eMIT), presented in Table 39. The durvalumab list price has an approved confidential simple discount Patient Access Scheme (PAS) of [redacted], resulting in a fixed net price of [redacted] per 500 mg vial.

Table 39: Unit drug costs

Drug	Strength (mg) per vial	List price (with PAS)	Price per mg	Source
Durvalumab	120 mg	£592.00 [redacted]	£4.93 ([redacted])	BNF 2022 (confidential PAS price)
	500 mg	£2,466.00 [redacted]	£4.93 ([redacted])	BNF 2022 (confidential PAS price)
Gemcitabine	1,000 mg	£9.82	£0.01	eMIT June 2022
Cisplatin	100 mg	£15.62	£0.16	eMIT June 2022

Abbreviations: BNF, British National Formulary; eMIT, electronic market information tool; PAS, patient access scheme.

B.3.6.1.2 Dosing schedules

The dosing schedule for each treatment was taken from TOPAZ-1 which is in line with the marketing authorisation for D + Gem/Cis.[2]

Durvalumab is administered at a dose of 1,500 mg in combination with Gem/Cis once every 3 weeks (21 days) for 8 cycles, followed by 1,500 mg every 4 weeks as monotherapy.[2]

In both treatment arms, gemcitabine is given at a dose of 1,000 mg/m^2 administered on Days 1 and 8 of each 3-week cycle. Cisplatin is given at a dose of 25 mg/m^2 administered on Days 1 and 8 of each 3-week cycle.[8, 15] A maximum of 8 cycles is implemented.

Gemcitabine and cisplatin are administered based on patient body surface area (BSA). The Du Bois formula[87] was used for calculating BSA:

Equation 2: BSA calculation

$$BSA = (Weight^{0.425} * Height^{0.725}) * 0.007184$$

The method of moments approach was used to account for variability in patient BSA. A BSA distribution was estimated using a normal distribution for the patient weight based on the mean and standard deviation measured at baseline from TOPAZ-1 (Table 40). For every BSA value, the corresponding dose was calculated and a weighted average of all the individual costs was applied in the model.

Table 40: Patient characteristics from the TOPAZ-1 trial

Patient characteristic	Value	Standard deviation	Source
Mean weight (kg)	[redacted]	[redacted]	TOPAZ-1
Mean height (cm)	[redacted]	[redacted]	TOPAZ-1
Mean body surface area (kg/m^2)	[redacted]	[redacted]	Du Bois formula[87]

Abbreviations: NA, not applicable.

No vial wastage was assumed in the base case, therefore a cost per mg approach was utilised. This is because, gemcitabine in combination with cisplatin is routinely used in the NHS at chemotherapy clinics where vial sharing occurs. Regardless, the acquisition costs for Gem/Cis are minimal; therefore, the effect of any wastage assumptions is negligible on modelled outcomes and is explored in a scenario analysis. In addition, durvalumab is associated with no wastage given the dosage is fixed at 1,500 mg and there is a 500 mg vial available.

To account for dose reductions, missed doses and treatment interruptions, the relative dose intensity (RDI) from TOPAZ-1 was applied for first-line treatments in the base case (see Table 41). RDI is calculated as the percentage of the actual dose intensity delivered relative to the intended dose intensity through treatment discontinuation. The frequency of any dose delays for durvalumab (44.7% of patients) and placebo (47.1% of patients) were similar, with greater than 3 delays to durvalumab, or placebo therapy reported for 8.3% and 6.7% patients, respectively. AEs were the most common reason for treatment delay and there was no difference between treatment groups for duration of delay. Infusion interruptions were reported for 3 (0.9%) patients in each treatment group (each case was a single interruption due to AEs).

Table 41 presents the dosing schedules, dose intensity and final cost per treatment cycle used in the model base case. A weekly cycle length was applied to capture the costs and events associated with the rapid progression of BTC and to account for different treatment schedules (Q3W, Q4W). A half-cycle correction was applied to account for events occurring at any point during each cycle. This half-cycle correction was not applied to the calculation of first-line drug acquisition and administration costs in the first cycle to ensure the full cost of treatment initiation was

captured. Gem/Cis treatment acquisition costs were not applied to either treatment arm after 8 treatment cycles.

Table 41. Dosing schedules and cost per treatment cycle (using durvalumab PAS price)

Regimen	Drug	First dose	Second dose	Relative dosing intensity	Flat dose, weight-based (BSA), surface-based	Administration frequency	Total dose per treatment cycle	Drug cost per treatment cycle	Total cost per treatment cycle
First-line treatments									
D + Gem/Cis for cycles 1-8	Durvalumab	1,500mg	NA	[redacted]	Fixed	Day 1 of a 3-week cycle	[redacted]	[redacted]	[redacted] (Cycle length: 3 weeks)
	Gemcitabine	1,000 mg/m^2	1,000 mg/m^2	[redacted]	BSA-based	Days 1 and 8 of a 3-week cycle	[redacted]	[redacted]	
	Cisplatin	25 mg/m^2	25 mg/m^2	[redacted]	BSA-based	Days 1 and 8 of a 3-week cycle	[redacted]	[redacted]	
D + Gem/Cis after 8 cycles	Durvalumab	1,500mg	NA	[redacted]	Fixed	Day 1 of a 4-week cycle	[redacted]	[redacted]	[redacted] (Cycle length: 4 weeks)
Gem/Cis for cycles 1-8	Gemcitabine	1,000 mg/m^2	1,000 mg/m^2	[redacted]	BSA-based	Days 1 and 8 of a 3-week cycle	[redacted]	[redacted]	[redacted] (Cycle length: 3 weeks)
	Cisplatin	25 mg/m^2	25 mg/m^2	[redacted]	BSA-based	Days 1 and 8 of a 3-week cycle	[redacted]	[redacted]	

Abbreviations: BSA, body surface area; D, durvalumab 1,500 mg; Gem/Cis, gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2; NA, not applicable.

B.3.6.1.3 Administration costs

The cost of delivering IV infusion therapy was sourced from the National Schedule of NHS costs 2020/21, as presented in Table 42, and was applied as a fixed cost to all treatments administered IV. Pemigatinib has no administration costs due to oral administration.

Table 42. Drug administration unit costs

Treatment setting	Code	Description	Cost	Source
IV infusion	SB12Z	Deliver simple parenteral chemotherapy	£281.11	National Schedule of NHS costs 2020/21[88]

Abbreviations: IV, intravenous.

B.3.6.2 Health-state unit costs and resource use

The model base case assumes that HCRU utilisation and costs are dependent on a patient's health state (progression-free and progressed disease) given that patients who have not progressed and are on treatment will require more monitoring and blood tests[19].

Unit costs for monitoring and disease management are included in Table 43 and were sourced from the NHS Cost Collection costs 2020/2021 and the PSSRU Unit Costs of Health and Social Care report for 2021.[89]

Three sources were used to validate expected HCRU utilisation for BTC patients: the ESMO BTC guidelines,[44] TA722[71] (pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma) and clinical expert opinion solicited from 5 medical oncologists practicing in the UK.[19]

The ESMO BTC guidelines state during treatment for advanced disease follow-up should be conducted at a frequency of 8-12 weeks and imaging may be used to monitor the course of disease.[44]

While HCRU in TA722[71] (pemigatinib appraisal) was referred to, the generalisability of values for this appraisal is considered limited due to both the difference in treatment setting and administration compared with D + Gem/Cis; pemigatinib is an

oral monotherapy used for relapsed or refractory BTC patients whereas D + Gem/Cis is delivered intravenously and is used in the first-line setting.

Feedback elicited from UK medical oncologists treating BTC patients confirmed that CT scans are conducted every 12 weeks for all BTC patients, in line with the ESMO guidelines[44] and TA722[71] for the PF setting. It was concluded that quarterly CT scans would continue in the PD state following D + Gem/Cis in line with ESMO guidelines and clinician opinion. Clinicians stated that blood tests would be conducted with every round of chemotherapy, which is assumed to be once every 3 weeks in line with the dosing schedule for D + Gem/Cis. It is also assumed this frequency would continue in the PD state for all patients who receive subsequent treatment (approximately 50% of patients). This is more frequent than the quarterly intervals applied in TA722,[71] which is likely to be due to differences in administration, as described above.

Clinicians also concluded that BTC patients would be examined by their medical oncologist at every treatment cycle but less frequently when off treatment, approximately once every 3 months. Similar to blood tests, it is assumed oncologist examinations would occur once every 3 weeks in line with the dosing schedule for D + Gem/Cis. It is also assumed this frequency would continue in the PD state for all patients who receive subsequent treatment (approximately 50% of patients). Again, this is more frequent than the quarterly intervals applied in TA722,[71] which is likely to be due to differences in administration, as described above. Clinicians were also asked to comment on frequency of GP visits, inpatient administrations/hospitalisation, and MacMillan nurse visits. They concluded these are highly variable depending on the clinical status of the patients and therefore have not been included in the base case, in line with TA722.[71] While clinicians did acknowledge that BTC patients are seen by a nurse at every treatment appointment, this is assumed to be included in the overall cost of treatment administration and has not been included in the base case, which is consistent with TA722.[71]

For simplicity, the PF cost is not modelled to change in the Gem/Cis arm after the maximum treatment duration (8 cycles). Furthermore, the PD state cost is not

modelled to change in either arm after post discontinuation of subsequent treatment costs.

Values used in the base case are presented in Table 44.

Table 43: Healthcare resource use costs

Resource	Unit cost
CT scan	£143.73
Blood tests	£3.63
Oncologist/ clinical examination (outpatient oncology visit)	£185.20

Abbreviations: CT, computed tomography.
Source: National Schedule of NHS costs 2020/21.[88]

Table 44: Summary of health state resource use and cost

Resource	Progression free			Progressed disease		
	Patients per month	Frequency per month	Cost per month†	Patients per month	Frequency per month	Cost per month†
CT scan	100%	0.33	£47.43	100%	0.33	£47.43
Blood tests	100%	1.44	£5.23	50%	1.44	£2.61
Oncologist/clinical examination (outpatient oncology visit)	100%	1.44	£332.87	50%	1.44	£166.44
Total cost	£385.53			£216.48		

† Monthly values were elicited from clinicians, a weekly cost is calculated and applied in the model by dividing the monthly values by 4.358.
Abbreviations: CT, computed tomography.

B.3.6.3 Adverse reaction unit costs and resource use

Unit costs associated with the management of AEs are presented in Table 45 and were sourced from the National Schedule of NHS costs 2020/21[88] and PSSRU 2021.[89] AE 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 (outlined in Section B.3.4.3) by the cost per event and summing all the AE-related costs per treatment arm.

Table 45: List of adverse reactions and summary of costs in the economic model

AE	Value	Description and code
Neutropenia	£679.39	Non-elective short stay weighted average SA08G-SA08J, Other haematological or splenic disorders
Anaemia	£1,961.94	Non-elective short stay weighted average SA04G-SA04L, Iron deficiency anaemia
Thrombocytopenia	£881.88	Non-elective short stay weighted average SA12G-SA12JK Thrombocytopenia
Cholangitis	£680.49	Non-elective short stay weighted average FD04C-FD04E, Nutritional Disorders without Interventions
Neutrophil count decrease	£679.39	Assume same as neutropenia
Platelet count decreased	£881.88	Assume the same as thrombocytopenia
White blood cell count decreased	£679.39	Assume the same as neutropenia

Abbreviations: AE, adverse event.
Source: National Schedule of NHS costs 2020/21.[88]

B.3.6.4 Miscellaneous unit costs and resource use

B.3.6.4.1 Subsequent treatments

In the base case, patients were assumed to become eligible for subsequent treatment upon disease progression as per the TOPAZ-1 study protocol and following UK clinical practice. Patients who received the full 8 treatment cycles of Gem/Cis in SoC arm do not receive further active treatment until disease progression.

The list of subsequent treatments included in the analysis was derived from 5 UK clinical experts to reflect UK clinical practice. Subsequent treatment costs were accounted for in terms of drug acquisition and administration costs only, with costs applied per weekly model cycle. Consistent with first-line treatment costs, no wastage was assumed.

Costs were calculated based on 1) the proportion of patients receiving second-line treatment derived from TOPAZ-1 and aligned with clinical expert opinion (50.70% for patients receiving D + Gem/Cis and 53.80% for patients receiving Gem/Cis), 2) the mean duration on each treatment, as obtained from relevant RCTs (Table 46). It is assumed that the OS data from TOPAZ-1 used in the model captures the efficacy of

these subsequent treatments. Those patients receiving one of the subsequent treatments included in Table 46 were assumed to receive best supportive care following the subsequent therapy, which is not associated with a treatment-related cost. The distribution of subsequent treatments was equivalent between D + Gem/Cis and Gem/Cis.

Eligibility for subsequent treatment based upon treatment discontinuation was assessed using the TTD curve in scenario analyses. This approach was not considered reflective of how disease progression is assessed in UK clinical practice, i.e., by investigator, and is not consistent with the marketing authorisation.

Table 46: Subsequent active treatments

Treatment	Proportion of patients		Duration in months	
	Proportion	Source	Months	Source
FOLFOX	75%	Clinical expert opinion	6	ABC-06 trial[90]
Gem/Cis retreatment	10%	Clinical expert opinion	6	ABC-06 trial[90]
Pemigatinib	5%	Clinical expert opinion	7.20	FIGHT-202 trial[71]
Clinical trials*	10%	Clinical expert opinion	N/A	N/A

*No cost associated with clinical trials therefore duration on treatment (months) is not included in the model
Abbreviations: FOLFOX, folinic acid, fluorouracil, oxaliplatin; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg.

The dosing schedule and cost per treatment cycle for subsequent treatment costs is provided in Table 47.

Table 47. Dosing schedules and cost per treatment cycle

Regimen	Drug	First dose	Second dose	Relative dosing intensity	Flat dose, weight-based (BSA), surface-based	Administration frequency	Total dose per treatment cycle	Drug cost per treatment cycle	Total acquisition cost per treatment cycle
First-line treatments									
FOLFOX	Oxaliplatin	85 mg/m^2	85 mg/m^2	100%	BSA-based	2 weeks	148 mg	£45.12	£112.67
	Leucovorin	350 mg/m^2	350 mg/m^2	100%	BSA-based	2 weeks	609 mg	£50.50	
	Fluorouracil	2800 mg/m^2	2800 mg/m^2	100%	BSA-based	2 weeks	4869 mg	£17.06	
Gem/ Cis retreatment	Gemcitabine	1000 mg/m^2	1000 mg/m^2	89.1%	BSA-based	Days 1 and 8 of a 3-week cycle	3,099 mg	£30.81	£43.06
	Cisplatin	25 mg/m^2	25 mg/m^2	89.1%	BSA-based	Days 1 and 8 of a 3-week cycle	77.5 mg	£12.25	
Pemigatinib	Pemigatinib	14 mg	14 mg	100%	Fixed	Daily for 14 days and break for 7 days	14 mg	£7,159.00	£7,159.00

Abbreviations: BSA, body surface area; D, durvalumab 1,500 mg; Gem/Cis, gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2; NA, not applicable.

B.3.6.4.2 End-of-life costs

End-of-life costs were included in the base case, based on the healthcare and social care costs reported by Round et al. (2015)[91] and in line with TA722.[71] Of the cancer types included in the study (breast, lung, prostate and colorectal), colorectal is the most clinically comparable to BTC. Costs were inflated to the latest price year using the Personal Social Services Research Unit inflation indices[92] and were applied as a one-off cost at the point of death. The total estimated end of life cost per person is £6,977.30, presented in Table 48.

Table 48: Cost of terminal care

Cost component	Per person total cost	Reference	2021 uplifted cost
Healthcare	£4,854	Round et al. (2015)[91]	£5,339.40
Social care	£1,489		£1,637.90
Total	**£6,343**		**£6,977.30**

B.3.7 Severity

The current SoC in the UK for first-line unresectable BTC is Gem/Cis. Clinical experts in the UK highlighted that the prognosis for these patients is extremely poor (median OS <1 year). [28, 30] [28, 30] Thus, there remains a critical unmet need for new treatment options which can be accessed immediately after diagnosis (i.e., no molecular testing), and improve efficacy, without significantly impacting toxicity and QoL.

TOPAZ-1 is the first positive global Phase III trial for the broad first-line advanced unresectable or metastatic BTC population in over a decade. In the trial, D + Gem/Cis demonstrated a statistically significant and clinically meaningful improvement in OS compared with placebo + Gem/Cis (HR: 0.76 [95% CI: 0.64, 0.91]) and a doubling in OS at 2 years (23.6% vs 11.5%).

In line with the updated NICE process and methods,[75] the severity of unresectable BTC, measured by the absolute QALY shortfall (AQS) or the proportional QALY shortfall (PQS) associated with SoC (gemcitabine in combination with cisplatin)

relative to the general population without BTC was calculated. Within the framework, differential QALY weights are applied if the AQS or PQS estimates lie within given cut-off ranges (Table 49).

Table 49. QALY weight referenced within the new NICE process and methods manual

QALY weight	Absolute shortfall	Proportional shortfall
1x	Less than 12	Less than 0.85
1.2x	12–18	0.85–0.95
1.7x	At least 18	At least 0.95

Abbreviations: NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year.

To inform the total expected QALYs for patients treated with SoC, the total discounted QALYs for the Gem/Cis arm in the base case were used. Total expected QALYs for patients without BTC, but otherwise identical in characteristics, were then calculated. This calculation used population utility norms informed by Ara and Brazier (2010),[76] mortality estimates informed by the most recent Office of National Statistics (ONS) life tables[73] and a discount rate of 3.5% per annum, to align with parameters used in the cost-effectiveness analysis. The expected QALYs for the general population were compared with those in the SoC arm in order to evaluate QALY shortfall.

AQS is estimated to be 10.32 with a PQS of 92.8% (Table 51). The methods explored provide clear rationale that a 1.2x QALY weight is appropriate for decision making in this appraisal since the PQS is almost in the cut-off range for a 1.7x QALY weight. Scenario analysis consistently demonstrates that a 1.2x QALY weight should be applied (Section B.3.12.2).

The discounted QALYs from NICE TA722 were redacted from the submission therefore it was not possible to calculate the QALY shortfall for the comparator arm. Since TA722 is considered the only relevant NICE submission, it was not possible to validate the severity modifier results in this submission.

Table 50: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution	49.6	Section B.3.4.1
Starting age	[redacted]	Section B.3.4.1

Abbreviations: QALY, quality-adjusted life year.

Table 51: Summary of QALY shortfall analysis

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	QALY shortfall
11.13	0.81	Absolute:10.32 Proportional: 92.8%

Abbreviations: QALY, quality-adjusted life year.

B.3.8 Uncertainty

The OS KM for D + Gem/Cis has a long tail, which is a common feature of immunotherapies, and reflects the potential long-term responders. Although there is convergence of the KM curves at ~32 months, this was not considered to be a robust or meaningful observation since there are very small number of patients in the tail of both curves, especially in the placebo + Gem/Cis arm. The curves do not cross until the point where the last patient in the placebo + Gem/Cis arm was censored. The long tail may lead to some uncertainty about the long-term survival in the real world, despite the OS curves being relatively complete. There is no real-world evidence with patients receiving D + Gem/Cis that can support extrapolations beyond the trial and clinical expert opinion was sought to validate the extrapolations selected in the base case (Section B.3.4.4).

B.3.9 Managed access proposal

As outlined in Section B.2.6.1.1, at the time of the 6.5-month follow-up (DCO: 25 Feb 2022), OS data maturity was 76.9%. The TOPAZ-1 trial is ongoing, [redacted]. These further analyses are not expected to materially impact the assessment of cost effectiveness or reduce any potential uncertainties in cost effectiveness given the OS data is already highly mature and is

a key driver of the model. Therefore, D + Gem/Cis is not considered an appropriate candidate for a Managed Access Agreement.

B.3.10 Summary of base-case analysis inputs and assumptions

B.3.10.1 Summary of base-case analysis inputs

A summary of the key variables included in the model are provided in Table 52.

Table 52 Summary of key variables applied in the economic model

Variable	Value	Lower, Upper bound and (distribution)	Reference to section in submission
General settings			
Cycle length	1 week	None	B.3.3.3
Time horizon	20 years	None	B.3.3.3
Discount rate	3.5%	None	B.3.3.3
Population			
Starting age	[redacted]	[redacted]	B.3.3.1
Proportion male	50.4%	40.5%, 60.2% (Beta)	B.3.3.1
Weight	[redacted]	[redacted]	B.3.3.1
Height	[redacted]	[redacted]	B.3.3.1
Creatinine Clearance (mL/min)	[redacted]	[redacted]	B.3.3.1
Efficacy (survival distributions)			
Overall Survival (D + Gem/Cis)	Spline Odds (1 knot)	Variance-covariance matrices	B.3.4.2.2.1
Progression Free Survival (D + Gem/Cis)	Spline Odds (1 knot)	Variance-covariance matrices	B.3.4.2.2.2
Overall Survival (Placebo + Gem/Cis)	Spline Normal (1 knot)	Variance-covariance matrices	B.3.4.2.3.1
Progression Free Survival (Placebo + Gem/Cis)	Spline Normal (1 knot)	Variance-covariance matrices	B.3.4.2.3.2
Safety (proportion experiencing)			
Neutropenia (D + Gem/Cis)	[redacted]	[redacted]	B.3.4.3
Anaemia (D + Gem/Cis)	[redacted]	[redacted]	B.3.4.3
Thrombocytopenia (D + Gem/Cis)	[redacted]	[redacted]	B.3.4.3
Cholangitis (D + Gem/Cis)	[redacted]	[redacted]	B.3.4.3
Neutrophil count decrease (D + Gem/Cis)	[redacted]	[redacted]	B.3.4.3
Platelet count decreased (D + Gem/Cis)	[redacted]	[redacted]	B.3.4.3

Variable	Value	Lower, Upper bound and (distribution)	Reference to section in submission
White blood cell count decreased (D + Gem/Cis)	[redacted]	[redacted]	B.3.4.3
Neutropenia (Placebo + Gem/Cis)	[redacted]	[redacted]	B.3.4.3
Anaemia (Placebo + Gem/Cis)	[redacted]	[redacted]	B.3.4.3
Thrombocytopenia (Placebo + Gem/Cis)	[redacted]	[redacted]	B.3.4.3
Cholangitis (Placebo + Gem/Cis)	[redacted]	[redacted]	B.3.4.3
Neutrophil count decrease (Placebo + Gem/Cis)	[redacted]	[redacted]	B.3.4.3
Platelet count decreased (Placebo + Gem/Cis)	[redacted]	[redacted]	B.3.4.3
White blood cell count decreased (Placebo + Gem/Cis)	[redacted]	[redacted]	B.3.4.3
Utility			
Progression-free	[redacted]	[redacted]	B.3.5.5
Post-progression	[redacted]	[redacted]	B.3.5.5
Disutility			
Neutropenia	-0.0607	-0.05, -0.07 (Beta)	B.3.5.4
Anaemia	-0.0850	-0.07, -0.10 (Beta)	B.3.5.4
Thrombocytopenia	-0.0850	-0.07, -0.10 (Beta)	B.3.5.4
Cholangitis	-0.0850	-0.07, -0.10 (Beta)	B.3.5.4
Neutrophil count decrease	-0.6070	-0.49, -0.72 (Beta)	B.3.5.4
Platelet count decreased	-0.0850	-0.07, -0.10 (Beta)	B.3.5.4
White blood cell count decreased	-0.0607	-0.05, -0.07 (Beta)	B.3.5.4
Costs			
Durvalumab 500mg/10mL	[redacted]	None	B.3.6.1.1
Gemcitabine 1000mg/26.3mL	£9.82	None	B.3.6.1.1
Cisplatin 100mg/100mL	£15.62	None	B.3.6.1.1
Oxaliplatin 200mg/40mL	£60.29	None	B.3.6.4.1
Leucovorin 500mg/50mL	£21.51	None	B.3.6.4.1
Fluorouracil 5000mg/100mL	£3.46	None	B.3.6.4.1
Pemigatinib 13.5mg	£7,159.00	None	B.3.6.4.1
Drug administration	£281.11	£228.72, £338.82 (Gamma)	B.3.6.1.3

Variable	Value	Lower, Upper bound and (distribution)	Reference to section in submission
CT scan	£143.73	£116.94, £173.24 (Gamma)	B.3.6.2
Oncologist/ clinical examination (outpatient oncology visit)	£231.16	£188.08, £278.61 (Gamma)	B.3.6.2
Blood tests	£3.63	£2.95, £4.38 (Gamma)	B.3.6.2
Neutropenia	£697.39	£567.42, £840. 56 (Gamma)	B.3.6.3
Anaemia	£1,961.94	£1,596.31, £2,364.71 (Gamma)	B.3.6.3
Thrombocytopenia	£881.88	£717.53, £1,062.92 (Gamma)	B.3.6.3
Cholangitis	£680.49	£553.67, £820.19 (Gamma)	B.3.6.3
Neutrophil count decrease	£679.39	£552.78, £818.86 (Gamma)	B.3.6.3
Platelet count decreased	£881.88	£717.53, £1,062.92 (Gamma)	B.3.6.3
White blood cell count decreased	£679.39	£552.78, £818.86 (Gamma)	B.3.6.3
Terminal care	£6977.3	£5,677.01, £8,409.67 (Gamma)	B.3.6.4.2
Resource use			
CT scan (PFS)	0.33/month	0.27, 0.40 (Gamma)	B.3.6.2
Oncologist/ clinical examination (outpatient oncology visit) (PFS)	1.44/month	1.17, 1.74 (Gamma)	B.3.6.2
Blood tests (PFS)	1.44/month	1.17, 1.74 (Gamma)	B.3.6.2
CT scan (PD)	0.33/month	0.27, 0.40 (Gamma)	B.3.6.2
Oncologist/ clinical examination (outpatient oncology visit) (PD)	0.72/month	0.59, 0.87 (Gamma)	B.3.6.2
Blood tests (PD)	0.72/month	0.59, 0.87 (Gamma)	B.3.6.2
Subsequent therapy (proportion receiving)			
Second-line therapy after D + Gem/Cis	51%	41%, 61% (Beta)	B.3.6.4.1
Second line therapy after Placebo + Gem/Cis	54%	43%, 64% (Beta)	B.3.6.4.1
FOLFIRI in second line	75%	59%, 88% (Beta)	B.3.6.4.1
Platinum-based chemo in second line	10%	8%, 12% (Beta)	B.3.6.4.1
Pemigatinib in second line	5%	4%, 6% (Beta)	B.3.6.4.1
Clinical trial in second line	10%	8%, 12% (Beta)	B.3.6.4.1

Probabilistic analysis was performed for the base case as this accounts for joint uncertainty across most input parameters in the model. The probabilistic analysis is

also the preferred NICE reference case.[93] All parameters were included in the probabilistic analysis, with the exception of time horizon, discount rates and drug costs as these are not subject to parameter uncertainty. Parameters were assigned probability distributions and point estimates were drawn using Monte Carlo simulation techniques, run with 10,000 iterations for the base case. Where available, known correlation between parameters was preserved.

Parametric distributions were varied using the means and variance-covariance matrices of the parameters in Cholesky decomposition. The beta distribution was used for utility values, gender distribution, adverse event rates, proportion receiving second line therapies and second line therapy distribution; the normal distribution was used for other population parameters (e.g., age) and duration on second line therapy; the gamma distribution was used for costs and resource use, and dosing and administration parameters. In the absence of data on the variability around the sampling distribution of mean values, the standard error was assumed equal to 10% of the mean.

Scenario analysis was conducted using the probabilistic analysis and 1,000 iterations.

Deterministic analysis was also performed. One-way deterministic sensitivity analysis (DSA) was performed to identify key model drivers. Parameters presented were varied one at a time between their upper and lower 95% confidence intervals, which were determined using standard errors when available (e.g., for utilities), or using standard errors estimated based on ±10% variation around the mean where measures of variance around the base case values were not available. All parameters were included in the DSA except for time-horizon and drug costs which were not subject to parameter uncertainty.

B.3.10.2 Assumptions

A summary of all the model assumptions and justifications is provided in Table 53.

Table 53. Main model assumptions

Model input	Assumption	Rationale/ Justification
Perspective	NHS and PSS	NICE reference case

Model input	Assumption	Rationale/ Justification
Discounting	3.5% per annum for costs and health outcomes	NICE reference case
Time horizon	20 years	A lifetime horizon consistent with NICE reference case. Fewer than 0.36% of patients are alive in the D + Gem/Cis arm after this time horizon.
Cycle length	1 week	The cycle length is 1 week to capture the costs and events associated with the rapid progression of disease and to account for different treatment schedules (Q3W, Q4W, etc).
Efficacy	Direct extrapolation of TOPAZ-1 efficacy endpoints (OS and PFS) for the base case.	Uses available data from a head-to-head randomised control trial vs the relevant comparator. Validated by clinical experts as the preferred approach.
	Independent models are fitted for OS, PFS and TTD.	Inspection of the Schoenfeld residual and log-cumulative hazards plots indicate the proportional hazards assumption was systematically violated between the two treatment arms. Independent models capture different shapes of the hazards between the two arms.
Utilities	Utility values are assumed to differ by health state, but not by treatment arm.	A univariate model of utility by progression status was selected because progression status was the strongest predictor of patient utility, second to and similar to treatment discontinuation status. Given that treatment discontinuation status refers to cessation of placebo treatment in the Gem/Cis arm, progression status is considered a more clinically meaningful covariate.
Costs	Intervention (D + Gem/Cis) is aligned to the existing PAS for durvalumab.	Reflects cost of durvalumab in current UK clinical practice.
	Health state costs are based on time to treatment discontinuation derived from PFS parametric extrapolations.	The UK marketing authorisation for durvalumab is treat to progression, therefore no patients are expected to be on treatment after progression.
Vial sharing	No vial wastage was assumed.	Acquisition costs for Gem/Cis are minimal; therefore, the effect of any wastage assumptions is negligible. Gem/Cis is routinely used in the NHS at chemotherapy clinics where vial sharing occurs. Durvalumab is associated with no wastage given the dosage is fixed at 1,500mg, and the vial size for 1 pack is 500mg. To be consistent with first-line treatment, all subsequent treatments were assumed to have no vial wastage.
Subsequent treatment	50.7% and 53.8% of patients who progress on D + Gem/Cis and Gem/Cis respectively, will receive subsequent treatments.	The proportions are aligned with the clinical trial and UK clinical opinion. Note that oncologists at an expert validation meeting indicated that 50% of patients who progress will receive subsequent treatments in UK practice.

Model input	Assumption	Rationale/ Justification
	Patients were assumed to become eligible for subsequent treatment upon progression as per the TOPAZ-1 PFS curves, with subsequent treatment costs applied per weekly model cycle.	The marketing authorisation for durvalumab is treat to progression.
	The duration of subsequent treatment was dependent on the specific treatment.	The duration of each subsequent treatment was taken from relevant clinical trials.
End-of-life care costs	Inclusion of end-of-life care cost.	Inclusion of these costs reflects the additional care required in the months prior to death, borne by the NHS/PSS. End-of-life costs were applied as a one-off cost at the point of death.

Abbreviations: D, durvalumab; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; NICE, National Institute for Health and Care Excellence; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; PSS, Personal Social Services; QxW, every x weeks; TTD, time to treatment discontinuation.

B.3.11 Base-case results

B.3.11.1 Base-case incremental cost-effectiveness analysis results

Probabilistic results including total costs, life years gained (LYG), QALYs, and incremental cost per QALY gained for D + Gem/Cis versus placebo + Gem/Cis are presented in Table 54. These results are based on the current PAS price for durvalumab as presented in Table 39. As discussed in section B.3.7, based on the calculated QALY shortfall, this appraisal meets criteria for the severity modifier with a QALY weighting of 1.2. Tabulated base case results are presented in Appendix J.

The net health benefit (NHB) base case results are presented in Table 55.

[redacted]

The cost-effectiveness plane showing the incremental costs and QALYs from the simulations for D + Gem/Cis versus Gem/Cis is presented in Figure 47. The cost-effectiveness acceptability curves (CEAC) are presented in Figure 48.

Table 54: Base-case results: probabilistic (fully incremental CE results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (x1.2 modifier)	ICER vs. baseline (x1.2 modifier)
D + Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gem/Cis	£19,352.24	1.11	0.81				

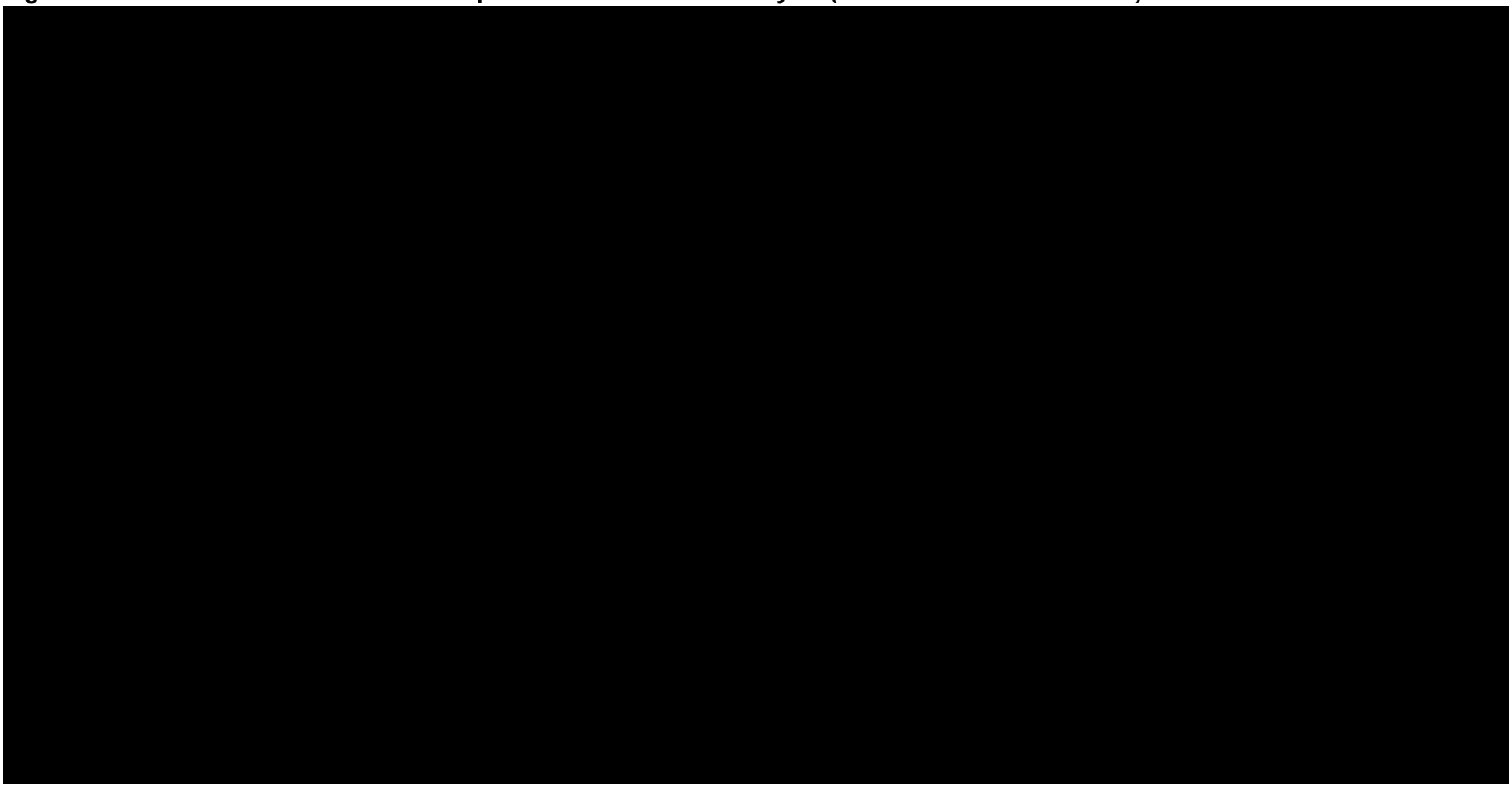
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Table 55: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.2 modifier)	Net health benefit (x1.2 modifier)	
D + Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gem/Cis	£19,352.24	0.81				

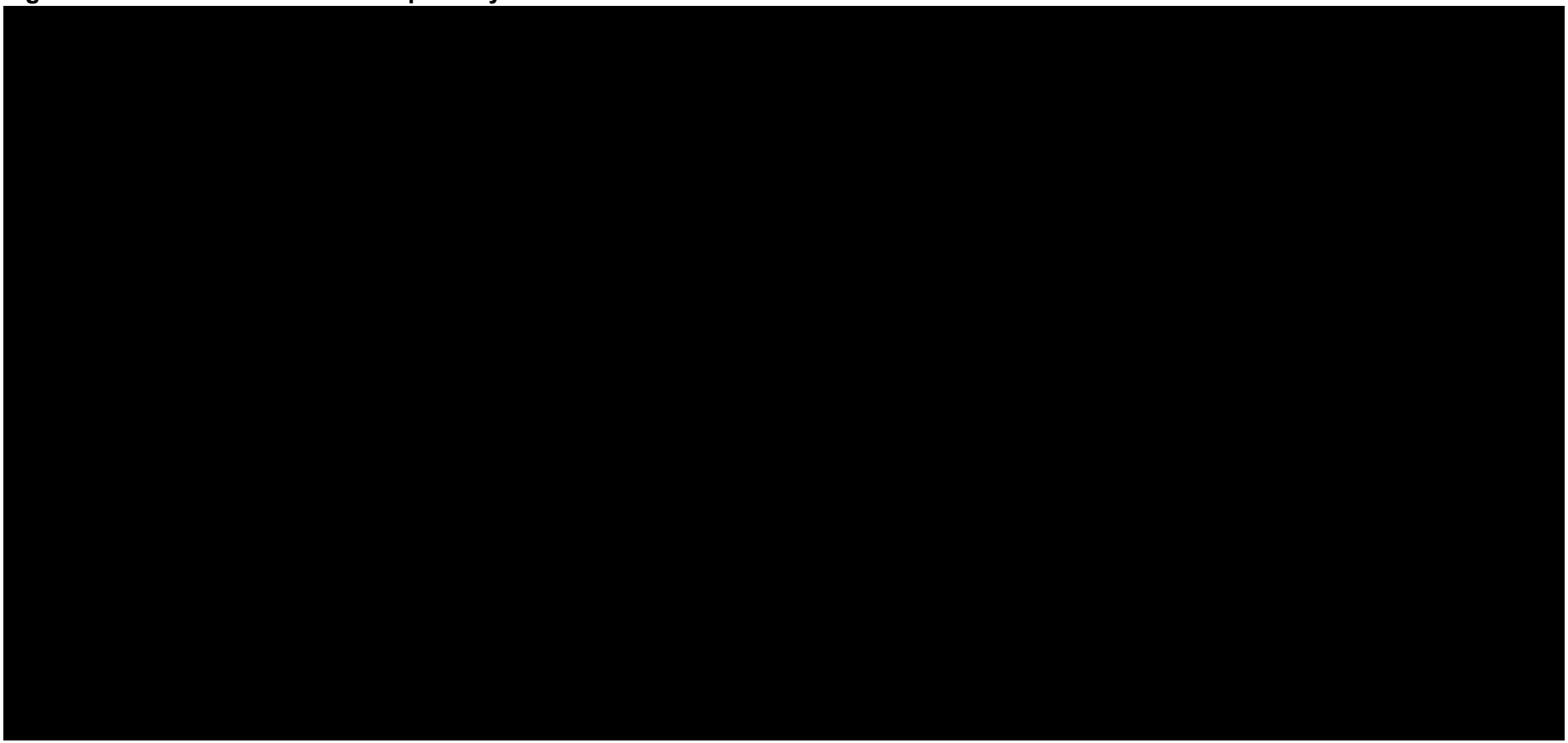
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; NHB, net health benefit.

Figure 47: Incremental cost-effectiveness plane for the scenario analysis (based on results with PAS)



Abbreviations: PAS, patient access scheme.

Figure 48: Cost-effectiveness acceptability curves



The deterministic results using base case settings are presented in Table 56. Application of the 1.2x QALY weight results in an incremental QALY gain of [redacted] and an ICER of [redacted]

Table 56: Base-case results: deterministic (fully incremental CE results)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (x1.2 modifier)	ICER (£/QALY) (x1.2 modifier)
D + Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gem/Cis	£19,417.47	1.10	0.81				

Abbreviations: D, durvalumab; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.12 Exploring uncertainty

B.3.12.1 Deterministic sensitivity analysis

Table 57 presents the ICERs for all parameters included in the DSA and Figure 49 presents the tornado plot showing the 10 parameters which had the largest impact on the ICER. Overall, the results show the outcomes of the cost-effectiveness analysis are most sensitive to utility values for PD health state followed by the discount rate on outcomes and proportion of patients receiving subsequent treatments.

Across the DSA the deterministic ICER changes at most by 3.4% compared to the base case, which further demonstrates that the ICER is robust to changes in individual parameters.

Table 57: One-way deterministic sensitivity analysis (with PAS)

Parameter	ICER at lower bound (% change vs. base case)	ICER at upper bound (% change vs. base case)
Utility: Post-progression	[redacted]	[redacted]
Discount rate: Outcomes	[redacted]	[redacted]
% receiving FOLFOX in 2L after Gem/Cis	[redacted]	[redacted]
% receiving FOLFOX in 2L after D + Gem/Cis	[redacted]	[redacted]
Proportion of patients receiving 2L after Gem/Cis	[redacted]	[redacted]
Proportion of patients receiving 2L after D + Gem/Cis	[redacted]	[redacted]
Duration FOLFOX in 2L after Gem/Cis	[redacted]	[redacted]
Duration FOLFOX in 2L after D + Gem/Cis	[redacted]	[redacted]
Utility: Progression-free	[redacted]	[redacted]
% receiving pemigatinib in 2L after Gem/Cis	[redacted]	[redacted]

Abbreviations: 2L, second line; D, durvalumab; Gem/Cis, gemcitabine 1,500 mg and cisplatin 25 mg; ICER, incremental cost-effectiveness ratio; FOLFOX, folinic acid, fluorouracil, oxaliplatin; PAS, patient access scheme.

Figure 49: Tornado showing one-way sensitivity analysis results on the ICER (with PAS)

Abbreviations: ICER, incremental cost-effectiveness ratio; PAS, patient access scheme.

B.3.12.2 Scenario analysis

Scenario analysis was conducted by running the probabilistic analysis for 1,000 iterations. The results are presented in Table 58. ICERs ranged between [redacted] (using log-logistic distribution for D + Gem/Cis OS) and [redacted] (using Spline normal [1-knot] distribution for D + Gem/Cis OS).

The analysis indicated that the OS distribution for D + Gem/Cis was the largest driver of the model results.

Table 58: Probabilistic scenario analysis results (discounted)

Parameter	Base case	Scenario	Rationale	ICER (£/QALY) (x1.2 modifier)
D + Gem/Cis OS distribution	Spline odds (1 knot)	Log-logistic	• The log-logistic fits the observed trial data well. • Immunotherapies are understood to be associated with prolongation of survival.	[redacted]

Parameter	Base case	Scenario	Rationale	ICER (£/QALY) (x1.2 modifier)
			• Log-logistic 5-year survival = 6.89%.	
		Spline normal (1 knot)	Considered plausible by clinical experts based on 3-year survival (12.64%)	[redacted]
Gem/Cis OS distribution	Spline normal (1 knot)	Spline normal (2 knot)	Considered plausible by clinical experts based on 3-year survival estimate (4.14%)	[redacted]
D + Gem/Cis PFS distribution	Spline odds (1 knot)	Spline hazard (2 knot)	Considered plausible by clinical experts based on 2-year PFS rate (3.91%)	[redacted]
Gem/Cis PFS distribution	Spline normal (1 knot)	Spine hazard (3 knot)	Considered plausible by clinical experts based on 2-year PFS rate (0.80%)	[redacted]
Costs and utilities	Costs and utilities based on PFS parametric extrapolations	Time on treatment costs based on TTD parametric extrapolations Utility values: Pre-treatment discontinuation: 0.798 (0.788; 0.808) Post-treatment discontinuation: 0.680 (0.642; 0.719)	• TTD extrapolation estimates the exact number of patients on or off treatment at a given time. • Treatment discontinuation was considered second strongest predictor of patient utility based on AIC and BIC statistics.	[redacted]
Vial wastage	No vial wastage assumed	100% vial wastage assumed	Treatments using a weighted dosage (Gem/Cis) are subject to wastage and/or vial sharing.	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

B.3.13 Subgroup analysis

No relevant subgroup analyses have been carried out.

B.3.14 Benefits not captured in the QALY calculation

As patients with BTC are often diagnosed at an advanced stage, it is likely that they will require informal care. The QALY is a generic measure of disease burden for the patient only. Therefore, does not capture the quality-of-life effects for specific populations, such as caregivers. Caregiving is associated with psychological and economic strains, resulting in diminishing wellbeing and increased stress.[40] In addition, caring for a BTC patient may impact the ability to go to work, leading to financial strain and indirect economic costs. Evidence shows that caregiver burden is closely correlated to patient symptom burden, indicating treatments that improve or relieve patient symptoms would likely reduce caregiver burden, in addition to improving patient HRQoL.[41] D + Gem/Cis improves response rates and reduces progression rates, potentially reducing the time and effort required from a caregiver, ultimately improving the caregiver's HRQoL and productivity.

B.3.15 Validation

B.3.15.1 Validation of cost-effectiveness analysis

As described in section B.3.3.2 the modelling approach and structure was selected and developed considering a range of factors, including (1) accurately reflecting the primary (OS) and key secondary outcomes (PFS) in TOPAZ-1, (2) consistency with approaches accepted in previous appraisals in disease areas comparable to BTC (e.g., NICE TA722), (3) the ability to capture the important aspects of the clinical and treatment pathway (e.g., patients are expected to unilaterally progress, and cure is not considered clinically plausible with current therapies), and (4) being intuitive and easy to communicate.

Unit costs were sourced from the most recent eMIT database, BNF, National Schedule of NHS reference costs and the PSSRU Unit Costs of Health and Social Care report to ensure that the results of the analysis are appropriate for decision making in the UK. Where possible, the model has been populated with clinical input data from the TOPAZ-1 trial which, as discussed in section B.3.3.1, is considered generalisable to the UK population and clinical practice.

Clinical validation was sought for the analysis consisting of a series of UK expert interviews held in December 2022 and involving 5 clinical experts. The clinical experts were practicing oncologists based in the UK (3 based in England and 2 based in Scotland) and provided clinical input into the modelling assumptions and inputs.

The model was subject to review and quality control before finalization. Two external health economists not involved in the model development reviewed the model for coding errors, inconsistencies, and plausibility of inputs and outputs. A range of extreme value and logic tests were conducted to examine the behavior of the model and ensure that the results were logical.

B.3.16 Interpretation and conclusions of economic evidence

A *de novo* economic model was developed to assess the cost effectiveness of D + Gem/Cis versus Gem/Cis. The TOPAZ-1 trial directly compares the treatments in the relevant population and is considered generalisable to UK clinical practice.

PFS data from TOPAZ-1 were assessed using IA-2 (DCO: 11 Aug 2022), with median patient follow-up of ~16 months and OS data from TOPAZ-1 was derived from 6.5-month follow-up (DCO: 25 Feb 2022). The results show that D + Gem/Cis significantly increases both progression-free survival and overall survival versus Gem/Cis, highlighting the clinical benefit of an immunotherapy-based regimen for these patients:

- TOPAZ-1 is the first Phase 3 trial in over a decade to demonstrate statistically significant improved outcomes for patients with previously untreated, locally advanced, unresectable, or metastatic BTC by combining durvalumab (immunotherapy) with Gem/Cis (chemotherapy). Current treatment options for these patients are limited to gemcitabine-based chemotherapies that offer a limited survival benefit.[7, 8] With no meaningful innovation in the last decade, there is a clear unmet need for additional treatment options that can improve survival without impacting on QoL and AE burden.

- The KM plot for OS separated at approximately 6 months of treatment, after which there was a clear and sustained separation of the survival curves in favour of the D + Gem/Cis arm, with the difference in OS between treatment arms becoming increasingly apparent over time. With 6.5 months of additional follow-up, the HR decreased from 0.80 at IA-2 (95% CI: 0.66, 0.97) to 0.76 (95% CI: 0.58, 0.88). In addition, given limited censoring before 6 months at IA-2, the piecewise HR remained 0.91 for 6 months (from randomisation). This is in line with survival dynamics of immunotherapy-based regimens.[7, 8] The convergence of the KM curves at ~32 months should not be considered a robust or meaningful observation since the curves do not cross until the point where the last patient in the placebo + Gem/Cis arm was censored.

- TOPAZ-1 met its primary endpoint, demonstrating a statistically significant, clinically meaningful, and sustained improvement in OS for the D + Gem/Cis treatment arm compared with the placebo + Gem/Cis treatment arm (12.9 months [95% CI: 11.6, 14.1] versus 11.3 months [95% CI: 10.1, 12.5]).

- Treatment with D + Gem/Cis 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 D + Gem/Cis treatment arm and 5.7 months (95% CI: 5.6–6.7) for the placebo treatment arm. A sustained separation in the KM curves in favour of the D + Gem/Cis treated group was observed from approximately 4 months, indicating early benefit of D + Gem/Cis.

- In line with the new NICE manual, the severity of the condition was assessed by calculating the absolute and proportional QALY shortfall. As detailed in Section B.3.7, D + Gem/Cis qualifies for a severity modifier based on the proportional QALY shortfall in the base case and all scenarios. Note that the QALY shortfall is very high (almost within range for a 1.7x QALY weight) reflecting the severity of BTC.

- Base case results demonstrate that treatment with D + Gem/Cis is associated with an ICER (including the 1.2x modifier) of [redacted] per QALY gained

when compared with Gem/Cis. This is consistent with the deterministic analysis.

- In line with the guidance from the NICE methods manual, structural and parameter uncertainty was explored. Running the analysis under a range of key scenarios yielded ICERs between [redacted] and [redacted]

The main strengths of the evaluation are:

- The economic analysis was based on a simple, transparent, and well-accepted partitioned survival model structure which is widely used in advanced oncology.

- Where possible, UK-specific evidence has been used to inform the economic model, including clinical effectiveness and QoL (EQ-5D) data from TOPAZ-1, and costs and resource use taken from well-established UK sources and previous NICE appraisals in comparable disease areas.

- The TOPAZ-1 data and model inputs, including (but not limited to) survival extrapolations, HCRU and subsequent treatments, were reviewed in a series of one-to-one interviews with UK clinical experts, who confirmed the data are generalisable to the UK setting.

- The model input review process in addition to the highly mature OS data ensures both clinical plausibility and reduced uncertainty in the overall analysis. However, extrapolation was necessary due to the lifetime horizon of the trial.

- The economic evaluation undertaken demonstrates that the QALY gains are substantial, supporting the first line use of D + Gem/Cis for treating locally advanced, unresectable, or metastatic BTC.

The main limitation of the evaluation is the lack of real-world data to validate long-term survival projections (>5 years) for D + Gem/Cis in patients with locally advanced or metastatic BTC.

B.3.16.1 Conclusions

Durvalumab in combination with Gem/Cis has been awarded an innovation passport via ILAP demonstrating the ability of this combination to fulfil a significant unmet patient need for further treatment options for BTC. In addition, durvalumab with Gem/Cis represents an important new therapeutic option for advanced and metastatic BTC patients, offering the potential for long-term survival in the first-line population without additional AE burden.

The clinical importance of D + Gem/Cis is evident from the receipt of a grade 4 score on the ESMO MCBS, indicating substantial clinical benefit, due to the >10% improvement in OS at 2 years. The combination was subsequently included in the updated ESMO BTC guidelines, which state D + Gem/Cis should be considered for the first-line treatment of advanced BTC. In line with the ESMO guidelines, UK clinicians have advocated for use of D + Gem/Cis in all BTC patients who would otherwise be eligible for Gem/Cis and have no contraindications to immunotherapy

[redacted]

In summary, the economic evaluation undertaken demonstrates that QALY gains are substantial supporting the first line use of D + Gem/Cis for treating locally advanced, unresectable, or metastatic BTC. D + Gem/Cis is also associated with better quality of life, as well as clinically meaningful and statistically significant longer survival in a patient population with a high unmet need.

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Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analyses

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement, and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]

Summary of Information for Patients (SIP)

February 2023

File name	Version	Contains confidential information	Date
ID4031_DurvalumabaBTC_NICE_SIP_FinalnoACIC	1.0	No	13th February 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

RESPONSE
Durvalumab (IMFINZI®) (in combination with gemcitabine and cisplatin)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

RESPONSE
This treatment will be used by adult patients with unresectable advanced or metastatic biliary tract cancer, including people with recurrent disease after treatment with curative intent.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

RESPONSE
Marketing authorisation for this indication was granted by the Medicines and Healthcare Products Regulatory Agency (MHRA) on 25 January 2023. This approval was achieved under Project Orbis, an innovative regulatory assessment pathway. The UK MHRA Summary of Product Characteristics can be found here https://www.medicines.org.uk/emc/product/9495/smpc.[1] The approved indication is: 'IMFINZI in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with locally advanced, unresectable, or metastatic biliary tract cancer (BTC)'.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

RESPONSE

AMMF

- AMMF is a UK-wide patient advisory group (PAG) focused on supporting people with biliary tract cancer. AstraZeneca global part-sponsored the AMMF conference in 2022 and will do the same in 2023. Conference sponsorship amounts from global AZ to AMMF are as follows: 2022, £45,000; 2023, £45,000
- In 2022, AstraZeneca global supported an AMMF project to establish a global connection between PAGs in order to build cholangiocarcinoma community collaborations, provide reliable, unbiased and credible information and education for patients, healthcare professionals, patient advocacy etc. The Global Cholangiocarcinoma Alliance – General Support Program 2022: €80,000
- In 2022, AstraZeneca global supported an AMMF project to help create a dedicated European group to support the very specific needs of patients and carers who are living with CCA. This grant supported educational materials 2022: £40,000
- The AstraZeneca UK medical team have not sponsored any activities or carried out any collaborative project work with AMMF although we do meet occasionally via virtual calls to discuss the priorities of AMMF

CCA-UK

- CCA UK is a UK multi-disciplinary special interest group in cholangiocarcinoma. The AstraZeneca UK medical team have part sponsored the CCA-UK conference, last year (2022) and this year (2023). Sponsorship amounts: 2022: £5000+VAT, 2023: £5000+VAT

All patient group contributions are published annually on AstraZeneca UK's website: https://www.astrazeneca.co.uk/about-us/working-with-patient-groups.html

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

RESPONSE

Durvalumab in combination with gemcitabine and cisplatin will be used to treat patients with BTC. BTC is a collective term for cancers which occur in the gall bladder and the bile ducts (the tubes that connect the liver and the gall bladder to the small bowel).

Durvalumab will be used in combination with gemcitabine and cisplatin by adults with BTC when:

- The cancer has spread into nearby tissues or lymph nodes (locally advanced disease) or to other organs in the body (metastatic disease) and can't be surgically removed

  or

- The cancer has initially been surgically removed, but has returned (recurrent disease)

Approximately 2,296 people in England have BTC (0.0043% of the population).[2] Most patients who receive a BTC diagnosis (around 80%) will have cancer that has spread and cannot be removed by surgery.[3, 4] In addition, of those patients whose cancer can be surgically removed, up to 80% will see a return of their cancer within 2 years.[5, 6]

Patients with BTC experience a substantial impact on their quality of life as a result of the symptoms of their disease. Symptoms can occur if the bile ducts become blocked by the cancer and may include jaundice (yellowing of the skin and eyes), cholangitis (inflammation of the bile duct system), itchy skin, dark urine and pale stools. Patients whose cancer has spread to other parts of the body may also experience other symptoms, which depend on where the cancer has spread. Treatments for BTC, such as chemotherapy, can be associated with side effects which can further negatively affect the quality of life of people with BTC.

People whose cancer has spread beyond the bile ducts and cannot be surgically removed, or whose cancer has returned after surgery, have poor survival expectations. On average, patients with BTC live less than one year when treated with the currently available SoC.[7, 8] Few patients survive for 5 years after diagnosis, however there are limited UK 5-year survival rates reported for BTC.[9, 10]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

RESPONSE

BTC is hard to diagnose in its early stages as there may be no symptoms, or symptoms may be general, and attributed to other (more typically common) causes, BTC is also hard to spot in routine physical examinations due to its location deep inside the body.[11, 12] BTC may be diagnosed with imaging procedures, such as endoscopy (a detailed look at the bile duct using a camera), tissue biopsies (taking a small sample of body tissue for examination), ultrasound, magnetic resonance imaging (MRI) or computed tomography (CT) scans. Blood tests may also be conducted (e.g. to measure function of the liver and/or the presence of tumour markers).

Beyond receiving a diagnosis of BTC, no additional tests are required to determine whether a person is eligible to receive treatment with durvalumab plus Gem/Cis and treatment can be initiated.

Molecular testing (looking at specific components of the cancer) may be performed at diagnosis; this is typically done to decide which further treatments may be of most benefit if the person's cancer starts to get worse while they are receiving first-line treatment and does not affect whether a person can start treatment with durvalumab plus Gem/Cis.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

RESPONSE

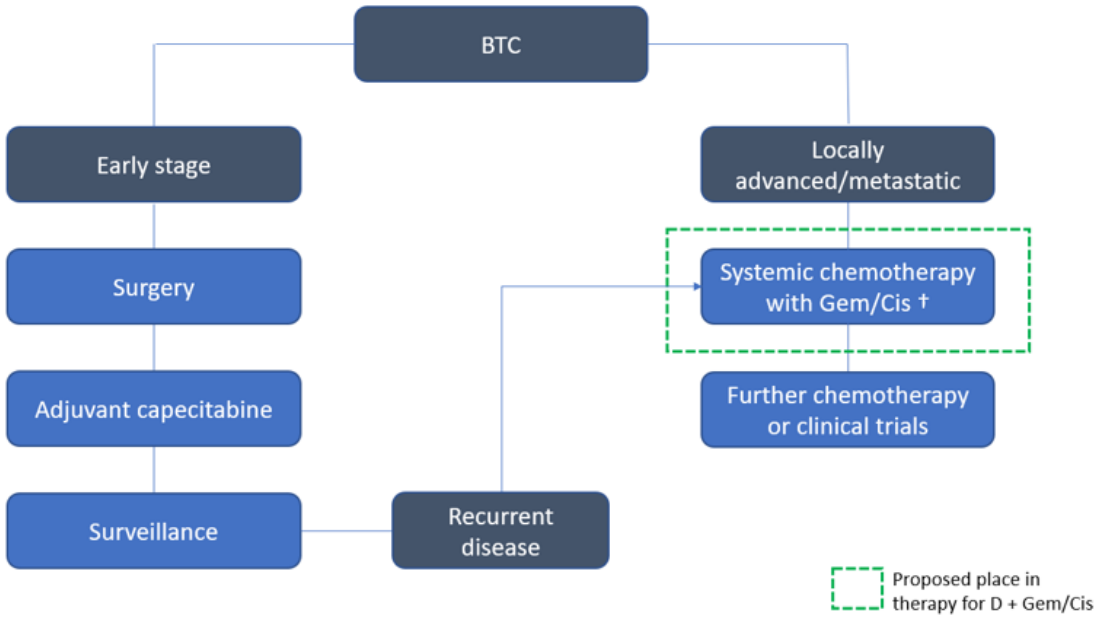
Figure 1 presents an overview of the current treatment pathway for BTC.

People who are diagnosed with BTC at an early stage (before the cancer has spread) will typically undergo surgery to remove the cancer, followed by chemotherapy to remove any remaining cancer cells. They will then be monitored to check for signs that the cancer has returned.

People whose cancer has spread beyond the bile ducts and cannot be surgically removed, or whose cancer has returned after surgery (locally advanced/metastatic or recurred disease in Figure 1), are usually treated with chemotherapy. Most people currently receive a combination of two chemotherapies called gemcitabine and cisplatin (Gem/Cis) as their first-line treatment. Gem/Cis can cause damage to normal cells as well as destroying cancer cells.[13] Because of this, patients need to be in good general health to receive Gem/Cis treatment.[14] Other treatment options are available for those people for whom Gem/Cis is not a suitable treatment. If a person's cancer continues to grow following first-line treatment, they may be offered further chemotherapy, or encouraged to participate in a clinical trial.[14] For certain patients (those whose have a type of BTC called cholangiocarcinoma, and whose cancer is shown to have a fibroblast growth factor receptor 2 [FGFR2] fusion or rearrangement in molecular testing), NICE recommends a treatment called pemigatinib for people whose cancer has started to progress on chemotherapy.[15]

Approximately 30% of people will receive best supportive care (BSC) only, i.e. they will not receive chemotherapy as they are unlikely to benefit/be able to tolerate the treatment.[16]

Figure 1: Current pathway of care for BTC with proposed durvalumab + Gem/Cis place in therapy



† Oxaliplatin may be given instead of cisplatin, particularly if there are concerns regarding kidney function. For patients in poor health (PS >1), single agent chemotherapy with gemcitabine is typically offered.
Abbreviations: BTC, biliary tract cancer; PS, performance status.
Source: Adapted from Vogel et al. (2022)[17] and verified with doctors who specialise in the treatment of BTC.

Durvalumab in combination with gemcitabine and cisplatin for the treatment of advanced/metastatic BTC

Durvalumab in combination with gemcitabine and cisplatin can provide a novel treatment option (the first in >10 years) in UK clinical practice for people with locally advanced, unresectable, or metastatic BTC.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

RESPONSE

A series of interviews were conducted with BTC patients in the USA to identify symptoms and impacts of living with BTC.[18] In total, 23 patients were interviewed, of whom 20 had locally advanced or metastatic disease. The most commonly reported signs and symptoms of BTC were fatigue/lack of energy (100% of patients), abdominal pain (83%), lack of appetite (78%), difficulty eating/feeling full (78%), insomnia (78%), diarrhoea (74%), abdominal bloating (70%), muscle loss (70%) and nausea/queasiness (65%). However a range of other symptoms affecting multiple different areas of the body were

also reported by different patients (for example, itchy skin, hair loss, sensitivity to cold, insomnia). On a disturbance scale of 1-10, where 0 was rated as “not disturbing” and 10 was “very disturbing”, patients found fatigue (average rating 7.9) and abdominal pain (average rating 7.6) the most disturbing symptoms of BTC. In total, 96% of patients reported physical impacts associated with BTC (e.g. difficulty walking), 74% of patients reported emotional impacts such as depression and 61% of patients report cognitive impacts (e.g. memory loss, fuzzy brain).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

RESPONSE

Durvalumab is a type of treatment called an immunotherapy. Durvalumab is designed to specifically recognise and attach to a protein called ‘programmed cell death ligand 1’ (PD-L1), which is present on the surface of many cancer cells. PD-L1 switches off the body’s immune cells that would otherwise attack the cancer cells. By attaching to PD-L1, durvalumab blocks its effects, allowing the immune system to attack the cancer cells and slow down or stop the growth of the cancer.

Durvalumab in combination with gemcitabine and cisplatin (Gem/Cis) is the first treatment in more than 10 years to have shown an improvement in survival for patients with BTC compared with the current standard of care treatment (Gem/Cis).

Durvalumab + Gem/Cis has been included in recent guidelines for the treatment of BTC that have been developed by the European Society of Medical Oncology. These guidelines recommend that durvalumab + Gem/Cis replace Gem/Cis as the first-line treatment of choice for people with BTC.[17]

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- **Yes** / ~~No~~

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

RESPONSE

For the treatment of BTC, durvalumab will be used in addition to Gem/Cis. While durvalumab is an immunotherapy which is designed to recognise a specific type of protein

that is found in tumour cells, gemcitabine and cisplatin are chemotherapies which work by destroying cells which are growing and dividing.[14] Gem/Cis are commonly available treatments which are used to treat a number of different types of cancer. While Gem/Cis treatment helps to slow down the growth of the cancer, it can also damage normal, non-cancerous cells which are growing and dividing.[13] Because of this, patients need to be in good general health to receive Gem/Cis treatment.[14] As Gem/Cis can affect normal cells, people receiving these medicines can experience side effects. Some of the most common side effects that people taking Gem/Cis may experience include an increased risk of infection (due the impact of chemotherapy on white blood cells), anaemia (due to an effect on the number of red blood cells), increased bruising and bleeding (due to chemotherapy effects on platelets which help blood to clot), flu-like symptoms, nausea, fatigue and kidney damage.[13]

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

RESPONSE

Durvalumab, gemcitabine and cisplatin are all given by intravenous infusion (i.e. via a drip) by a nurse. Each chemotherapy period may last several hours.[13] Treatment is given over periods of three weeks, and each three week period is called a cycle.

For up to eight cycles, treatment is given as follows:

- Day 1: Durvalumab (1,500 mg) infusion followed by gemcitabine (1,000 mg/m^2) infusion and cisplatin (25 mg/m^2) infusion
- Day 8: Gemcitabine (1,000 mg/m^2) infusion and cisplatin (25 mg/m^2) infusion

No further treatment is needed until day 1 of the next cycle. Once the eight cycles have been completed, gemcitabine and cisplatin treatment is stopped. Treatment with durvalumab (1,500 mg) alone can continue, once every 4 weeks, until the cancer starts getting worse.

The administration method of durvalumab has minimal impact on patients and caregivers. This administration method (intravenous) is the same as the existing standard of care (gemcitabine with cisplatin) but additional time will be required to administer durvalumab before chemotherapy once every 3 weeks for up to 8 cycles (total of 24 weeks, maximum). Additional time for administration will then be required for patients remaining on durvalumab in the maintenance phase, when administration will be once every 4 weeks, which will continue until disease progression or unacceptable toxicity.[1]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

RESPONSE

There is only one relevant clinical trial providing evidence for use of durvalumab with gemcitabine and cisplatin for the treatment of unresectable, locally advanced or metastatic BTC. This clinical trial, called TOPAZ-1, has compared the efficacy and safety of

durvalumab in combination with Gem/Cis versus placebo (a dummy treatment with no active substance) in combination with Gem/Cis.[19, 20] TOPAZ-1 is a large, international trial which included patients in the UK, and is still ongoing.

TOPAZ-1 included adults (aged ≥18 years) with BTC whose cancer had spread into nearby tissues or lymph nodes (locally advanced disease) or to other organs in the body (metastatic disease) and could not be surgically removed, or patients whose cancer had returned after previous surgery. To be included in the trial, participants had to be in good general health, and have good kidney function.

In total, 341 participants were given durvalumab + Gem/Cis and 344 participants were given placebo + Gem/Cis.

The outcomes measured in the trial included survival (how long participants remained alive after starting treatment), how long patients remained alive without their cancer getting worse, and how many participants experienced a shrinkage or disappearance of their cancer. Quality of life was also measured using a number of different questionnaires that were completed by participants at a range of points over the trial. Side effects of treatment were also measured.

Further details about the study design (including criteria for participant selection) are available from the following sources:

- Oh et al (2022) Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evidence. 2022;1(8):EVIDoa2200015 [20]
- Oh et al (2022) Updated overall survival (OS) from the phase III TOPAZ-1 study of durvalumab (D) or placebo (PBO) plus gemcitabine and cisplatin (+ GC) in patients (pts) with advanced biliary tract cancer (BTC). Annals of Oncology. 2022;33((suppl_7)):S19-S26 [19]

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

RESPONSE

In the TOPAZ-1 trial, overall survival was significantly greater in the group of participants who received durvalumab + Gem/Cis compared with the group of participants who received placebo + Gem/Cis. At two years, the number of trial participants who remained alive in the durvalumab + Gem/Cis group was double that of the placebo + Gem/Cis group (23.6% vs 11.5%). Participants who received durvalumab + Gem/Cis also lived longer on average without their disease getting worse (7.2 months) than participants who received placebo + Gem/Cis (5.7 months). In addition, more participants who were treated with durvalumab + Gem/Cis (26.7% of participants) experienced either a decrease in the size of their tumour or the tumour shrank so much that it could not be detected by tests and scans than participants who were treated with placebo + Gem/Cis (18.7% of participants).

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D)

was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

RESPONSE

Quality of life was assessed in TOPAZ 1 using a number of different questionnaires that were completed by the participants until they stopped taking the study treatment. These included questionnaires on general health (EQ-5D), the impact of having cancer (EORTC-QLQ-C30), and on specific issues that are known to affect people with BTC (EORTC-QLQ-BIL21). The results of the questionnaires showed that adding durvalumab to Gem/Cis for the treatment of BTC did not have a negative impact on participants' general health, physical and emotional wellbeing or symptoms associated with BTC.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

RESPONSE

Like all medicines, durvalumab is associated with side effects; however, not everybody gets them.

During the clinical trial (TOPAZ-1) the most commonly reported side effects experienced by participants receiving durvalumab in combination with Gem/Cis were those already known to occur with Gem/Cis treatment, such as effects on the blood cells, anaemia, nausea and fatigue. A full list of side effects has been included in the patient information leaflet (PIL).[21]

Immunotherapies such as durvalumab can be associated with immune-mediated side effects, inflammation in different organs of the body including the lungs, liver, intestines or glands.[21] Immune-mediated side effects are typically treated with corticosteroids, however, the treating doctor may decide to delay the next dose of durvalumab or stop durvalumab treatment altogether if these side effects occur.[21] In TOPAZ-1, immune-mediated side effects with durvalumab treatment were manageable with appropriate medical intervention, and most patients were able to continue with the treatment.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

RESPONSE

Treatment with durvalumab (+ Gem/Cis) slows down disease progression, leading to people with BTC living longer. Durvalumab + Gem/Cis resulted in no detriment in quality of life compared with Gem/Cis treatment and keeps patients in better health for a longer period, potentially reducing the time and effort required from a caregiver, ultimately improving the caregiver's quality of life and productivity.

Durvalumab is initially given at the same time and has the same mode of administration as Gem/Cis, meaning that patients do not require additional hospital trips.

The benefits offered by durvalumab + Gem/Cis have been recognised by ESMO, a leading professional society for medical oncology, who have recommended durvalumab + Gem/Cis as the preferred regimen for the first-line treatment of advanced BTC. Durvalumab has received the highest potential score for the patient population considered in this appraisal, representing a substantial magnitude of benefit. [17]

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

RESPONSE

Durvalumab treatment is longer than standard of care (Gem/Cis). Patients receiving Gem/Cis alone receive a maximum of 8 cycles of treatment whereas patients receiving durvalumab in combination with Gem/Cis continue to receive durvalumab every 4 weeks following the initial 8 cycles of combination therapy and until disease progression.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

RESPONSE

How the model reflects the condition

- The model simulates BTC by modelling different stages of the disease called 'health states'. In the model, hypothetical patients occupy a health state and can move between over time. The health states that this model uses are:
  - 'Progression-free' (the cancer is not getting worse)
  - 'Progressed disease' (the cancer is getting worse)
  - 'Death'
- Patients experience different quality of life and accrue different costs depending on the health state they are in, with those in 'Progression-free' experiencing the best quality of life and lowest costs, and those in the 'Progressed disease' health state experiencing the worst quality of life and higher costs. The model works by simulating how patients move between the health states when they are given different treatments; the more effective the treatment, the more time patients will spend in the 'Progression-free' health state.

Clinical trial outcomes used in the model

- The TOPAZ-1 clinical trial studied the efficacy (looking at the overall survival and the time until the disease progressed) as well as quality of life for those receiving durvalumab (+ Gem/Cis) and the side effect associated with treatment. All of these data were included in the model.
- Participants of the TOPAZ-1 clinical trial were followed for 2 years after starting treatment. In the model, trial data were extrapolated to model efficacy outcomes over a total of 20 years. Statistical prediction models were used to estimate future outcomes based on the data available. The predictions selected were based on how well the models could replicate the observed data, and how realistic the predictions were from a clinical perspective, based on input from oncologists.

Modelling how much a treatment extends life

- Treatment with durvalumab (+ Gem/Cis) extends life by delaying cancer progression. In the TOPAZ-1 clinical trial, people lived longer without their disease progressing and the number of trial participants who remained alive in the durvalumab + Gem/Cis group was double that of the placebo + Gem/Cis group (23.6% vs 11.5%) at 2 years after starting the treatment.

Modelling how much a treatment improves quality of life

- The model considers quality of life to be mainly driven by the health state patients are in (whether their cancer is getting worse) rather than the treatment they are on. Adding durvalumab to Gem/Cis for the treatment of BTC did not have a negative impact on participants' general health, physical and emotional wellbeing or symptoms associated with BTC.
- The model also considers that patients may experience side effects which may negatively impact quality of life; data from the TOPAZ-1 clinical trial informed the types

of side effects experienced on both treatments, and how many patients experienced each side effect.

- Quality of life was captured via the use of questionnaires on general health (EQ-5D), the impact of having cancer (EORTC-QLQ-C30), and on specific issues that are known to affect people with BTC (EORTC-QLQ-BIL21). NICE prefer the use of EQ-5D, so this was used in the model.

Modelling how the costs of treatment differ with the introduction of durvalumab

- Durvalumab is given in addition to the current treatment (Gem/Cis), it is administered in the same way (intravenously in a hospital) on the same day as Gem/Cis and requires ~1 extra hour. Additionally, after a maximum of 8 treatment cycles, Gem/Cis treatments stop but durvalumab treatments continue, with one treatment every 4 weeks.

Uncertainty

- As previously mentioned, the model is based on predictions of long-term outcomes informed by the two years of data collected in the TOPAZ-1 study. This is common practice in economic evaluations of new drugs but is a source of uncertainty in the analysis. Clinicians were consulted in selecting the models used in the analysis and alternative models were also tested.

Health economic model results

D + Gem/Cis is associated with an improvement in survival, a gain in QALYs and greater costs than Gem/Cis. The exact results are considered to be commercially confidential and are presented in Section B.3.11 of the company submission (Document B)

Additional factors

- A severity modifier is applicable to this condition. BTC has a significant impact on the quality and duration of life. The way that the model expresses this is in 'quality-adjusted life years (QALY)', one QALY is equal to 1 year of life in perfect health. Comparing the QALYs of the BTC population with those of a comparable UK population (age, gender) without BTC showed that a 1.2x severity modifier should be applied.
- As patients with BTC are often diagnosed at an advanced stage, it is likely that they will require informal care. The analysis does not capture the impact that improved treatment might have on the quality of life of carers. Some patients with BTC and/or their caregivers are still of working age, therefore treatment that enables patients or their caregivers to continue working with have benefits for the economy.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

RESPONSE

Durvalumab in combination with gemcitabine and cisplatin (Gem/Cis) is the first treatment in more than 10 years to have shown an improvement in survival for patients with BTC compared with the current standard of care treatment (Gem/Cis).

Durvalumab + Gem/Cis was awarded an innovation passport via the UK Innovative Licensing and Access Pathway (ILAP) programme, which aims to accelerate development

and access to innovative medicines. Durvalumab + Gem/Cis has also been included in recent guidelines for the treatment of BTC that have been developed by the European Society of Medical Oncology. These guidelines recommend that durvalumab + Gem/Cis are considered as the first-line treatment of choice for people with BTC.[17]

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.
Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme
Find more general information about the Equality Act and equalities issues here

RESPONSE

Use of durvalumab (+ Gem/Cis) is not expected to raise any equality issues.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

RESPONSE

Further information on BTC:

- https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/

- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

RESPONSE

Locally advanced disease: the cancer has spread into nearby tissues or lymph nodes.

Metastatic disease: The cancer has spread to other organs in the body.

QALY: one QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale).

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. AstraZeneca. IMFINZI 50 mg/mL concentrate for solution for infusion. Summary of Product Characteristics. https://www.medicines.org.uk/emc/product/9495/smpc. 2023.
2. Genus T, Tataru D, Morement H, Khan SA, Toledano MB. Incidence and Mortality Rates of Cholangiocarcinoma in England. 2019.
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4. 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 : official journal of the American Society of Clinical Oncology. 2019;37(12):1015-27.
5. Doussot A, Gonen M, Wiggers JK, Groot-Koerkamp B, DeMatteo RP, Fuks D, et al. Recurrence Patterns and Disease-Free Survival after Resection of Intrahepatic Cholangiocarcinoma: Preoperative and Postoperative Prognostic Models. Journal of the American College of Surgeons. 2016;223(3):493-505.e2.
6. Zhang XF, Beal EW, Bagante F, Chakedis J, Weiss M, Popescu I, et al. Early versus late recurrence of intrahepatic cholangiocarcinoma after resection with curative intent. The British journal of surgery. 2018;105(7):848-56.
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8. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. The New England journal of medicine. 2010;362(14):1273-81.
9. Marcano-Bonilla L, Mohamed EA, Mounajjed T, Roberts LR. Biliary tract cancers: epidemiology, molecular pathogenesis and genetic risk associations. Chinese clinical oncology. 2016;5(5):61.

10. Cancer Research UK. Survival for bile duct cancer. 2021. Available from: https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/survival. Accessed on: 12th December 2022.
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14. European Society for Medical Oncology. Biliary tract cancer*: An ESMO guide for patients. 2019.
15. National Institute for Health and Care Excellence. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [TA722]. 2021.
16. AstraZeneca. UK MC: KEE input on advanced biliary tract cancer (BTC) UK Questionnaire (durvalumab). Data on file. 2023.
17. Vogel A, Bridgewater J, Edeline J, Kelley RK, Klümpen HJ, Malka D, et al. Biliary tract cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Annals of oncology : official journal of the European Society for Medical Oncology. 2022.
18. Patel N, Lie X, Gwaltney C, Rokutanda N, Barzi A, Melisi D, et al. Understanding Patient Experience in Biliary Tract Cancer: A Qualitative Patient Interview Study. Oncol Ther. 2021;9(2):557-73.
19. Oh D, He AR, Qin S, Chen L, Okusaka T, Vogel a, et al. Updated overall survival (OS) from the phase III TOPAZ-1 study of durvalumab (D) or placebo (PBO) plus gemcitabine and cisplatin (+ GC) in patients (pts) with advanced biliary tract cancer (BTC). Annals of Oncology. 2022;33((suppl_7)):S19-S26.
20. Oh D-Y, He AR, Qin S, Chen L-T, Okusaka T, Vogel A, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evidence. 2022;1(8):EVIDoa2200015.
21. AstraZeneca. IMFINZI 50 mg/mL concentrate for solution for infusion. Patient Information Leaflet. https://www.medicines.org.uk/emc/product/9495/pil. 2023.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]

Clarification questions

March 2023

File name	Version	Contains confidential information	Date
ID4031 durvalumab clarification letter_Company response_[redacted]_v1_22Mar23	1.0	Yes	22 March 2023

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

The TOPAZ-1 trial

A1. In the TOPAZ-1 trial clinical study report, it is stated that [redacted] and in the protocol (page 135) under the heading '9.5.1.2 Progression-free survival' that '[redacted]. Please provide the results of piecewise analyses for PFS.

Response: A piecewise analysis was conducted for PFS at IA-2 (DCO: 11 Aug 21). The timepoint chosen for the piecewise analysis was [redacted], as this is when a separation in the KM curves is observed (see company submission, figure 7). The HR from [redacted] was [redacted] and the HR from [redacted] onwards was [redacted] (Table 1).

Table 1: Progression-free survival based on Investigator assessments according to RECIST 1.1, piecewise hazard ratio analysis - FAS (IA-2 [DCO: 11 Aug 21])

Progression-free survival status	D + Gem/Cis (N=341)	Placebo + Gem/Cis (N=344)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	

Notes: [a] Only includes progression events that occur within 2 missed visits of the last evaluable assessment; [b] The analysis was performed using a stratified Cox model adjusting for disease status and primary tumour location
Abbreviations: CI, confidence interval; D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1000 mg/m2 and cisplatin 25 mg/m2; n, number; RECIST, Response Evaluation Criteria in Solid Tumors version
Source: AstraZeneca. IEMT009. TOPAZ-1 clinical trial. Data on File. 2021[1]

A2. In the TOPAZ-1 trial clinical study report, PD-L1 status is described using [redacted]. In the TOPAZ-1 study publication, and in the company submission, PD-L1 status is described using tumour area positivity scores (TAP). Please explain i) the reason(s) for the differences in terminology and ii) the rationale for using TAP/[redacted] scores to describe PD-L1 status rather than 'combined positive score' or 'tumour proportion score'.

Response:

While PD-L1 testing was implemented in the TOPAZ-1 trial, the results demonstrated that the addition of durvalumab to chemotherapy benefited patients with PD-L1 TAP of both ≥1% and <1%, indicating PD-L1 status may have limited value in predicting

clinical benefit with D + Gem/Cis for first line treatment of advanced or metastatic BTC.[2]

i) The abbreviations '[redacted]' and 'TAP' both refer to the 'tumour area positivity' score, which assesses PD-L1 expression on tumour and immune cells. The abbreviation '[redacted]' was used in the CSR and as described in the CSP, the Ventana SP263 assay was used to measure PD-L1 expression in TOPAZ-1 trial.[3,4] However, the scoring methodology for this assay was subsequently re-named the to 'TAP' by the owner of the assay. Hence 'TAP' was used in the NEJM publication and the company submission and is also used in the SmPC.[5,6]

ii) PD-L1 assays require a combination of staining with a particular antibody and a method of generating a score. Different assays are associated with different scoring methodologies for different tumour types. Some methodologies measure PD-L1 expression on tumour cells and immune cells and some on tumour cells only. Variations in PD-L1 assays and scoring are outlined in Table 2.

Table 2: PD-L1 assays and scoring algorithms

Name of scoring algorithm	Measures TCs	Measures ICs	Associated assay	Associated tumour type
Tumour area positivity score (TAP/ [redacted])	Yes	Yes	Ventana SP263	GI
PD-L1 expression on tumour cells (TC)	Yes	No	Ventana SP263	Lung
Tumour proportion score (TPS)	Yes	No	Dako 22C3	Lung
Combined positive score (CPS)	Yes	Yes	Dako 22C3	GI

The Ventana PD-L1 (SP263) Assay was developed alongside durvalumab and was used to assess PD-L1 expression in the PACIFIC study, which compared durvalumab with placebo in patients with unresectable, stage III NSCLC with no disease progression after concurrent chemoradiotherapy. In this trial, PD-L1 scoring was conducted according to the TC methodology, as described in Table 2. The Ventana PD-L1 (SP623) Assay was used in the TOPAZ-1 trial. This assay is optimised per indication and

it was optimised to TAP for use in BTC. In BTC, the immune system plays a key role in the aetiology of disease. The strongest risk factor for developing BTC are drivers of chronic inflammation within the biliary system, including primary sclerosing cholangitis or cholelithiasis. Hence, immune cells as well as tumour cells were included in the PD-L1 scoring methodology for BTC (TAP). Although the CPS algorithm includes immune cells as well as tumour cells, this algorithm is associated with the Dako 22C2 assay, not the Ventana PD-L1 (SP263) Assay.

It should be noted that, as per the MHRA marketing authorisation, no evaluation for PD-L1 status is required before initiation of treatment with D + Gem/Cis for the first-line treatment of locally advanced, unresectable, or metastatic BTC. As outlined in the company submission, the treatment benefit of this regimen is consistent across all pre-defined subgroups, including PD-L1 status. Additionally, the CSR addendum suggests PD-L1 expression may not be a useful predictive biomarker to guide the use of D + Gem/Cis in BTC due to the consistency in treatment effect for OS across PD-L1 subgroups.[4] PD-L1 testing for BTC is not expected to be required in clinical practice and is not expected to guide treatment decisions for BTC patients being treated with D + Gem/Cis. This is reflected in the company submission, which utilises the ITT data from the TOPAZ-1 to evaluate the cost-effectiveness of D + Gem/Cis in advanced or metastatic BTC. Therefore, the PD-L1 testing methodology employed in the TOPAZ-1 clinical trial is considered immaterial.

A3. The TOPAZ-1 trial clinical study report includes a summary of the subsequent anti-cancer therapies given to patients in both arms of the trial (Table 16). Please provide a breakdown of the different cytotoxic regimens given to patients with progressed disease.

Response:

Subsequent anti-cancer therapies reported in the TOPAZ-1 trial

While Table 16 in the clinical study report contains a summary of subsequent anti-cancer therapies given to patients in the TOPAZ-1 trial at the time of IA-1 (DCO: 11 Aug 21), an updated summary at the time of 6.5 month update (DCO: 25 Feb 2022) is provided in Table 2 in the clinical study report addendum. We would like to clarify

this subsequent therapy analysis was summarised into the [redacted][4]

An additional analysis of post-progression subsequent therapies was conducted which reports individual agents received by patients. An analysis of second line subsequent therapy agents received upon experiencing disease progression in the TOPAZ-1 trial has been provided in Appendix A, Table 1. Please note, this table reports all individual agents received by patients in the second line setting and some patients may receive overlapping categories of agents in the same line of therapy. This table has not been categorised according to the type of therapy and is separate to the summary analysis reported in Table 2 of the CSR addendum.

Subsequent therapies included in the company submission

Subsequent therapies were re-distributed in the company submission compared with the treatments reported in the TOPAZ-1 study as some of the subsequent treatments in the study are not routinely used in UK clinical practice:

- As stated in Table 3 of the company submission, the ESMO guidelines recommend FOLFOX is the standard of care of care treatment in the second line setting and other therapies may be considered based on molecular profile.[7]

- A recent NICE technology appraisal for second-line treatment of cholangiocarcinoma (TA722: Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement), the committee concluded modified folinic acid, 5-fluorouracil and oxaliplatin, plus active symptom control (mFOLFOX+ASC) and ASC alone also were the most appropriate comparators for the appraisal.[8]

- The TOPAZ-1 trial was initiated prior to the regulatory approval and subsequent NICE recommendation for the use of pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement (TA722).[8]

- There are no immunotherapies or antiangiogenic therapies approved for use in BTC in the UK and the use of these therapies as subsequent treatments is generally considered to be associated with clinical trials.

- Feedback on second line therapy options for BTC patients was also elicited from 5 UK clinical experts who advised[9]:

    - If a patient has an FGFR2 mutation, they are eligible for pemigatinib. Approximately 5% of 2L BTC patients receive pemigatinib
    - For patients without an actionable mutation, the majority of clinicians reported using FOLFOX
    - Clinicians also reported re-treating with Gem/Cis if patients had had a good initial response and not experienced disease progression within 6-12 months of initial treatment
    - Two clinicians reported using FOLFIRI as subsequent treatments, either as an alternative to FOLFOX in 2L or in 3L if patients are fit enough
    - Some clinicians also reported enrolling patients in clinical trials for access to subsequent therapies

- Use of taxane chemotherapies is not included in the ESMO guidelines and was not mentioned by UK clinical experts

- The ESMO guidelines do not specify use of any particular agents in the third-line setting[7]

Further rationale for the distribution of cytotoxic chemotherapies as subsequent therapies in the company submission is as follows:

- While table 1 in Appendix A reports a range of alternative cytotoxic agents used as second-line subsequent therapies, this is likely to be due to the global nature of the TOPAZ-1 trial and is not considered reflective of UK clinical practice, as confirmed in TA722 and by UK expert clinicians

- Some of these therapies (tegafur, oteracil, gimeracil) do not have a marketing authorisation for use in the UK

During interviews with UK clinical experts, feedback on the generalisability of the OS outcomes from the TOPAZ-1 to the UK was also sought. While clinicians considered their ability to comment on performance of the D + Gem/Cis arm was limited due to lack of clinical experience with this regimen, they concluded the OS outcomes from the TOPAZ-1 trial were in line with their expectations for UK BTC patients. Therefore, it was not considered necessary to adjust overall survival outcomes to account for the redistribution of subsequent therapies.

In summary, the distribution of subsequent treatments as described in the company submission combined with the OS outcomes from the TOPAZ-1 clinical trial is considered to be the best representation of UK clinical practice and clinical outcomes.

Section B: Clarification on cost-effectiveness data

The EAG does not have any cost-effectiveness clarification questions.

Section C: Textual clarification and additional points

C1. Please confirm whether the headings for Figures 11 and 12 in the company submission should refer to ‘best overall response’ rather than ‘best objective response’.

We confirm the headings for Figures 11 and 12 in the company submission should refer to ‘best overall response’. We apologise for this typographical error.

C2. Please provide details of the price sources used to estimate the subsequent treatment costs presented in Table 47 of the company submission.

Price sources used to estimate the subsequent treatment costs presented in the company submission (Table 47) are provided in

Table 3.

Table 3: Treatment costs for subsequent therapies

Drug	Strength (mg) per vial/ tablet	Pack size	Formulation	Cost per pack	Cost per vial/ tablet	Cost/mg	Min cost/ mg	Source
Gemcitabine	200 mg	1	vial	£8.55	£8.55	£0.04	£0.01	eMIT November 2022; DYC036
Gemcitabine	1,000 mg	1	vial	£9.82	£9.82	£0.01		eMIT November 2022; DYC035
Gemcitabine	2,000 mg	1	vial	£21.00	£21.00	£0.01		eMIT November 2022; DYC037
Cisplatin	50 mg	1	vial	£18.21	£18.21	£0.36	£0.16	eMIT November 2022; DHA011
Cisplatin	100 mg	1	vial	£15.62	£15.62	£0.16		eMIT November 2022; DHA010
Oxaliplatin	50 mg	1	vial	£20.45	£20.45	£0.41	£0.30	eMIT November 2022; DHA354
Oxaliplatin	100 mg	1	vial	£46.78	£46.78	£0.47		eMIT November 2022; DHA355
Oxaliplatin	200 mg	1	vial	£60.29	£60.29	£0.30		eMIT November 2022; DHC072
Leucovorin	300 mg	1	vial	£21.51	£21.51	£0.07	£0.07	eMIT November 2022; DHA027
Florouracil	1,000 mg	1	vial	£3.46	£3.46	£0.00	£0.00	eMIT November 2022; DHA265
Pemigatinib	13.5 mg	14	tablet	£7,159.00	£511.36	£37.88	£37.88	BNF https://bnf.nice.org.uk/drugs/pemigatinib/medicinal-forms/

References

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2. Oh D-Y, He AR, Qin S, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evidence 2022;1(8):EVIDoa2200015. DOI: doi:10.1056/EVIDoa2200015.
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4. 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) (6.5 Month Update). Clinical Study Report Addendum (65 month update) 2022.
5. Oh DY, Lee KH, Lee DW, et al. Gemcitabine and cisplatin plus durvalumab with or without tremelimumab in chemotherapy-naive patients with advanced biliary tract cancer: an open-label, single-centre, phase 2 study. Lancet Gastroenterol Hepatol 2022;7(6):522-532. DOI: 10.1016/S2468-1253(22)00043-7.
6. AstraZeneca. IMFINZI 50 mg/mL concentrate for solution for infusion. Summary of Product Characteristics. https://www.medicines.org.uk/emc/product/9495/smpc. 2023.
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8. National Institute for H, Care E. Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement [TA722]. 2021 (https://www.nice.org.uk/guidance/ta722/chapter/1-Recommendations).
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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	**Helen Morement**
2. Name of organisation	AMMF – The Cholangiocarcinoma Charity
3. Job title or position	CEO
4a. Brief description of the organisation (including who funds it). How many members does it have?	AMMF is a charity, registered with the Charity Commission for England and Wales, registration no 1091915. It is the UK's only charity dedicated solely to cholangiocarcinoma (CCA). Funding is received via donations from members of the public, and some industry funding is received by way of sponsorship for projects such as AMMF's annual CCA conference. The charity does not have members.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	AMMF has received the following sponsorship from AstraZeneca: £45,000 received May 2022 to help support AMMF's 2022 Hybrid European Cholangiocarcinoma Conference. £40,000 received December 2022 to help support AMMF's Cholangiocarcinoma Education project (preparing and providing educational information on cholangiocarcinoma to pan-cancer organisations, and advocacy groups, across Europe).

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	AMMF supports patients with cholangiocarcinoma and their caregivers, providing them with information on treatments and clinical trials. We communicate with patients and their loved ones on a one to one basis by email and telephone, and face to face at our annual conference, and many patients and carers use AMMF's private online discussion forums to discuss their treatments and participation in clinical trials. www.ammf.org.uk

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The symptoms of cholangiocarcinoma (CCA) can be vague and easily attributed to a number of other causes and because of this, together with a lack of awareness at primary care level, this cancer is frequently diagnosed late. For the majority of patients, this late diagnosis will mean their cancer is inoperable and for them, this is a terminal diagnosis. For many patients this diagnosis and the prognosis can be truly shocking and they find it very difficult to assimilate the details. Patients struggle to accept that there really is so little treatment available to them, and that a diagnosis of inoperable CCA means their life will end soon – they have very little time left. Currently a resection is the only potentially curative treatment there is for CCA, so inoperable patients are left with very limited options. The standard first line treatment for those with inoperable CCA is the chemotherapy combination, Gemcitabine and Cisplatin. Undergoing this chemotherapy, which might or might not extend their life for a few months[1], is often at the expense of the quality of their life, and that of their families. For loved ones and carers, understanding the diagnosis and its implications can be as difficult for them as for the patient. Many struggle to comprehend that there is no effective treatment for their loved one, and ask AMMF for advice on, 'treatments not available under the NHS'. Seeing loved ones enduring the side effects of chemotherapy, including repeated infections requiring hospitalisation which takes them away from their families when their life expectancy is so short, is very difficult. As is, of course, trying to come to terms to what is happening, not only to their loved one, but to their lives in general – especially as so many are in what should be the 'prime of their life'. Although CCA is considered a cancer affecting older people, at AMMF we hear from many in their 30s, 40s and up with this diagnosis. When the survival rates are improving and more effective treatments are being discovered for many other cancers, a diagnosis of cholangiocarcinoma, and learning that there is so little in the treatment armoury, leaves people – patients, their loved ones and carers - feeling confused, isolated and helpless. Many of the comments we receive at AMMF are, sadly, similar: "After my diagnosis I felt so alone and afraid, I had no one to turn to for help." "I was shell shocked. I didn't know who to turn to for help. I was alone."

	"I went through endless tests; the doctors didn't know what was wrong with me. I lost valuable time." "They told me surgery was my only chance of survival, but it might already be too late." *[1]ABC-02 trial 2010: "The median survival in the cisplatin–gemcitabine group was 11.7 months (95% confidence interval [CI], 9.5 to 14.3), as compared with 8.1 months (95% CI, 7.1 to 8.7) for the gemcitabine-only group (P<0.001)."*

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients see a number of therapies, for example targeted therapies, immunotherapies, and SIRT, available to CCA patients in other countries, and they find it very difficult to understand why these effective treatments (not curative, but life extending) are not available for cholangiocarcinoma patients within the NHS. Many will search for treatments available privately or internationally.

8. Is there an unmet need for patients with this condition?	There are a number of unmet needs for cholangiocarcinoma patients: Effective treatments for CCA are desperately needed. The incidence of this disease is increasing year on year, with mortality mirroring incidence[2], and many younger adults being diagnosed. Currently resection is the only potentially curative treatment, but few are eligible for this. Standard of care 1st line chemotherapy for inoperable CCA patients hasn't changed in years and offers modest, if any, benefit. Currently there is one approved targeted therapy. New and more effective treatments for CCA are desperately needed. The addition of the immunotherapy, durvalumab to the standard first line Gemcitabine/Cisplatin chemotherapy has been shown to improve survival. Centres of Expertise for CCA patients are needed There seems to be no set pathway/guidance for the care of cholangiocarcinoma patients, many are never seen by those with specialist knowledge, and many are not considered for surgery nor for clinical trials. AMMF strongly believes that all CCA patients should be seen in 'centres of expertise' for confirmation of their diagnosis (operable/inoperable), and where their treatment pathway should be endorsed by an HPB multidisciplinary team, experienced in the care of CCA patients. Molecular profiling is needed for all CCA patients Molecular profiling should now be available for all those diagnosed with CCA – at diagnosis or during 1st line treatment. With the advent of targeted therapies, this is essential so that all those eligible for such treatments can be considered in a timely manner. Currently it seems molecular profiling under the NHS is available to only very few CCA patients in the UK, with many seeking this privately. [2]*Incidence and Mortality rates of cholangiocarcinoma in England* *https://www.annalsofoncology.org/article/S0923-7534(19)30962-7/fulltext*

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	Patients and carers look to new technologies and therapies with the hope these will offer extended survival over the more standard chemotherapies and/or best supportive care that might be offered. Although the addition of durvalumab to the current first line standard treatment, the combination chemotherapy Gemcitabine and Cisplatin, is not curative, for them this treatment is something they know could be effective in extending survival. For those for whom the treatment is effective, the trial results have shown the response to be more durable than the chemotherapy combination alone, which might or might not be effective for them, or indeed best supportive care.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients and carers see new technologies heralding new hope – the only disadvantages expressed by patients and carers that AMMF is aware of is that clinical trials are available to so few, and similarly that new technology and therapies are not adopted in a timely and uniform manner.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The benefit of durvalumab given with gemcitabine and cisplatin was seen in patients regardless of the primary origin of their cancer, including patients with intrahepatic or extrahepatic cholangiocarcinoma or gallbladder cancer.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that AMMF is aware of.

Other issues

13. Are there any other issues that you would like the committee to consider?	The first line treatment for those with inoperable cholangiocarcinoma has not changed in over a decade. The addition of durvalumab offers a small, but realistic improvement for a group of patients for whom there is so little in terms of effective treatment.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Incidence of CCA in increasing, with mortality that parallels incidence. • Currently there is very little effective treatment for CCA patients. • Many CCA patients are not considered for surgery nor for clinical trials – 'centres of expertise' are needed for confirmation of diagnosis and treatment pathway, and for molecular profiling. • All CCA patients should receive molecular profiling at diagnosis or during 1st line treatment in order to benefit in a timely manner from available targeted therapies. • Adding the immunotherapy durvalumab to the chemotherapy combination, gemcitabine and cisplatin, offers an improved first line treatment, extending survival with good quality of life.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]

Patient Organisation Submission

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	British Liver Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The British Liver Trust is the UK's leading liver health charity, working to improve liver health for all and supporting all adults affected by liver disease or liver cancer. We are funded by voluntary donations, including community and event fundraising, individual donors, gifts in wills, corporate supporters and trust and foundation grants. We operate throughout the UK, reaching more than two million people each year. Our website has over 1.5 million unique visitors annually, our online forum has over 32,000 members, our nurse-led Helpline handles approximately 400 enquiries a month, regular newsletter goes to circa 17,000 people with liver disease and liver cancer, we run around 250 support groups each year (currently virtual but moving to a mix of virtual and face to face post Covid); and connect with around 20,000 people via social media.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	AstraZeneca £5,000 August 2nd 2022. Purpose- For liver cancer patient resources and patient support. This was an arm's length grant and the company had no input into any content.

the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	The British Liver Trust have collated information for this submission via a variety of different sources and channels; 1. Direct feedback and communication from patient and carers via our nurse-led specialist helpline 2. Feedback and comments via threads on our liver community forum (32K members) 3. Insight gained from patients attending support groups 4. Interview with a liver palliative clinical nurse specialist on her experiences of caring for patients with biliary tract cancers 5. Literature search and review of current guidelines

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A diagnosis of biliary tract cancer comes as a huge shock. Often the diagnostic process has been protracted. Patients and carers are fearful of the future and they often express frustration that they have been diagnosed too late for curative options. Patients and carers worry about whether there will be any treatment options, whether those options will be available in their area, how will family life/finances be impacted by the diagnosis and treatment. What will their quality of life be like and how long are they likely to live for. Examples: 1) a patient posted on the British Liver Trust online forum and called the helpline. She was a distressed lady who had a late diagnosis of bile duct cancer, no curative options. She was only offered chemotherapy but was unsure about it, she had recently lost her partner and did not know how she was going to cope with side effects, and would it be worth it from the survival perspective? 2) a gentleman was diagnosed with a large intrahepatic cholangiocarcinoma two years ago after much investigation. He was not suitable for surgery but was suitable for a trial. He and his partner are grateful for the trial, but quality of life has been significantly affected for both of them due to side effects and the ongoing fear of 'when will the cancer start to grow again, what happens then?' 3) A palliative care and liver clinical nurse specialist told us about one of her patients, a lady who was diagnosed abroad with late-stage cholangiocarcinoma. She returned to the UK to be with family and was very symptomatic. As there were no curative options, she was offered chemotherapy with Gemcitabine and Cisplatin. She experienced significant side effects and unfortunately her cancer progressed through treatment. Palliative care was continued to manage her symptoms, she died shortly after stopping the chemotherapy. After diagnosis the patient was grieved for her lost life, career and the thought of leaving her family. The whole process had a devastating, traumatic effect on both her and her family.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Some patients/carers think that there are no options other than surgery, callers to the nurse led helpline ask whether transplant is an option. Others have researched on the internet and are more aware of potential treatment options and trials. There is disappointment and frustration at the lack of treatment options available and the strict entry criteria for trials. It is also true to say that when presented with the statistics of survival on various treatments they wonder whether there is any point proceeding. Some feel they are just being used as a 'guinea pig' others feel that participation in a trial or new treatment will help others further down the line. Most are complementary about the care they receive from medical and nursing staff but fear delays in treatment due to the current state of the NHS – staff shortages, expense of drugs etc
8. Is there an unmet need for patients with this condition?	Yes. Earlier diagnosis would enable more patents to get potentially curative treatment. For those who are not suitable for this then personalised medicine with the use of 'liquid biopsies 'for example would enable treatments to be targeted at the individuals most likely to respond to a particular treatment such as the one in this submission. The rates of cholangiocarcinoma are increasing, survival rates are still poor therefore there needs to be a focus on providing effective treatments. From our literature search the consensus seems to be that the TOPAZ trial demonstrates a modest improvement in survival. Any improvement in survival is encouraging and may help to focus the direction of future treatments.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	They hope that it will prolong survival without having a significant effect on their quality of life.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Patients have not provided any feedback on disadvantages.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	The patients who would gain most from the technology are those for whom there are no potentially curative treatment options.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Liver cancer disproportionally affects people from disadvantaged backgrounds. There needs to be equality of access to this treatment rather than a postcode lottery. How will the technology be funded? Are there enough clinicians/CNS's to enable safe management of treatment/side effects etc

Other issues

13. Are there any other issues that you would like the committee to consider?	Please see below for our key messages.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• Patients who have biliary tract cancers that are unresectable or advanced will have low survival rates. • Patients currently have limited treatment choices and have a very poor quality of life • There is a lack of options to treat these patents and the proposed treatment will provide much needed hope and possibly more time with loved ones.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

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About you

1. Your name	[redacted]
2. Name of organisation	Cholangiocarcinoma-UK (British Association for the Study of the Liver)
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes or No A specialist in the treatment of people with this condition? Yes or No A specialist in the clinical evidence base for this condition or technology? Yes or No Other (please specify):
5a. Brief description of the organisation (including who funds it).	Cholangiocarcinoma-UK is a special interest group of the British Association for the Study of the Liver, a Charity
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	n/a
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	no

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	improved median overall survival (OS)
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	- improved median overall survival (OS) - progression-free survival improved - no significant increase in toxicity
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	yes

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Chemotherapy combo: Gem Cis
9a. Are any clinical guidelines used in the	BSG guidelines but these are a decade old and in the process of revision, which will not be published for at least a year, but the treatment is FDA approved

treatment of the condition, and if so, which?	
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Well defined
9c. What impact would the technology have on the current pathway of care?	Adding durvalumab (Imfinzi) in combination with current standard dual chemotherapy combo of gemcitabine and cisplatin
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Not currently used
10a. How does healthcare resource use differ between the technology and current care?	Is an addition
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Senidary care (Med Oncology)
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	The drug

11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	yes
11a. Do you expect the technology to increase length of life more than current care?	yes
11b. Do you expect the technology to increase health-related quality of life more than current care?	yes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	unclear

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	No difference

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional trsting
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Don't know
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	yes
16a. Is the technology a 'step-change' in the management of the condition?	Yes, for this conidtion

16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – poor survival
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Does not seem to according to the data

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	yes
18a. If not, how could the results be extrapolated to the UK setting?	By adding the new drug Durvulamab
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival and toxicity and yes these were assessed
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a
18d. Are there any adverse effects that were not apparent in clinical	n/a

trials but have come to light subsequently?	
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
20. How do data on real-world experience compare with the trial data?	

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	no
21b. Consider whether these issues are different from issues with current care and why.	

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Advanced Cholangiocarcinoma has a very poor overall survival (OS) • Current standard of care is combination chemo with Gem-Cis • Durvulamab addition improves OS • Without an increase in toxicity •

Thank you for your time.

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EAG STA REPORT ID4031

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]

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UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]

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LIST OF ABBREVIATIONS

AE	Adverse event
AIC	Akaike Information Criterion
AZ	Astra Zeneca
BIC	Bayesian Information Criterion
BNF	British National Formulary
BTC	Biliary tract cancer
CCA	Cholangiocarcinoma
CI	Confidence interval
CS	Company submission
CSP	Clinical study protocol
CSR	Clinical study report
D+Gem/Cis	Durvalumab with gemcitabine and cisplatin
DCO	Data cut-off
DCR	Disease control rate
dMMR	Mismatch protein repair deficiency
DoR	Duration of response
DSU	Decision Support Unit
EAG	External Assessment Group
eCCA	Extrahepatic cholangiocarcinoma
ECOG	Eastern Cooperative Oncology Group
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D-3L/5L	EuroQol-5 Dimensions-3 Levels /5 Levels
ESMO	European Society for Medical Oncology
FAS	Full analysis set
FGFR2	Fibroblast growth factor receptor 2
FOLFOX	Folinic acid, fluorouracil, oxaliplatin
Gem/Cis	Gemcitabine (1,000mg/m^2) and cisplatin (25mg/m^2)
HR	Hazard ratio
HRQoL	Health-related quality of life
IA	Interim analysis
iCCA	Intrahepatic cholangiocarcinoma
ICER	Incremental cost effectiveness ratio
imAE	Immune-mediated adverse event
IV	Intravenous
KM	Kaplan–Meier
LY	Life year
LYG	Life years gained
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed model repeated measures

NICE	National Institute for Health and Care Excellence
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
P	Placebo
P+Gem/Cis	Placebo with gemcitabine and cisplatin
PAS	Patient Access Scheme
PD	Progressed disease
PD-L1	Programmed cell death-ligand 1
PFS	Progression-free survival
PGIS	Patient Global Impression of Severity
PPS	Post-progression survival
PR	Partial response
PRO	Patient-reported outcome
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality adjusted life year
QLQ-BIL21	21-Item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire
QLQ-C30	30-Item Core Quality of Life Questionnaire
Q3W/Q4W	Every 3 weeks/every 4 weeks
RCT	Randomised controlled trial
RDI	Relative dose intensity
RWE	Real world evidence
SAE	Serious adverse event
SAS	Safety analysis set
SoC	Standard of care
TAP	Tumour area positivity
TOPAZ-1	The main trial discussed in the company submission
TSAP	Trial statistical analysis plan
TSD	Technical Support Document
TTD	Time to treatment discontinuation
VAS	Visual analogue scale
WTP	Willingness to pay

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making.

Section 1.1 provides an overview of the key issues identified by the EAG. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the incremental cost effectiveness ratio (ICER) per quality adjusted life year (QALY) gained. Sections 1.3 to 1.5 explain the key issues identified by the EAG in more detail. Section 1.6 outlines the key cost effectiveness issues identified by the EAG.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table A Summary of key issues

ID	Summary of issue	Report sections
Issue 1	Generalisability of TOPAZ-1 trial results to NHS patients	3.2.3
Issue 2	Modelling overall survival for patients treated with D+Gem/Cis	6.2
Issue 3	Modelling progression-free survival for patients treated with D+Gem/Cis	6.3
Issue 4	Modelling treatment costs based on time to treatment discontinuation	6.4

D=durvalumab; Gem/Cis=gemcitabine+cisplatin

The key differences between the company's preferred assumptions and the EAG's preferred assumptions relate to the independent parametric distributions used to model overall survival, progression-free survival and time to treatment discontinuation.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a QALY. An ICER is the ratio of the extra cost for every QALY gained.

The company model generates cost effectiveness results for the comparison of durvalumab with gemcitabine and cisplatin (D+Gem/Cis) versus Gem/Cis. The assumptions that have the biggest effects on costs and QALYs are:

- choice of parametric distribution used to model overall survival for patients treated with D+Gem/Cis

- choice of parametric distribution used to model progression-free survival for patients treated with D+Gem/Cis
- choice of parametric distribution used to estimate treatment costs for patients treated with D+Gem/Cis
- choice of parametric distribution used to estimate treatment costs for patients treated with Gem/Cis

1.3 The decision problem: summary of the EAG's key issues

Issue 1 Generalisability of TOPAZ-1 trial results to NHS patients

Report section	Section 3.2.3
Description of issue and why the EAG has identified it as important	• Evidence provided relates to the final scope issued by NICE except that no evidence is presented for the subgroup of patients with ampullary carcinoma • Approximately half (54.6%) of TOPAZ-1 trial patients were recruited from treatment centres in Asia. The EAG notes that the treatment effect of D+Gem/Cis versus P+Gem/Cis was numerically greater for patients in the 'Asian race' and in the 'Asian region' subgroups than for patients in the 'non-Asian race' and in the 'rest of the world' subgroups, respectively. Clinical advice to the EAG is that this benefit may be due to the relatively high incidence of hepatitis B in Asia, which may be linked to better patient responses to D+Gem/Cis. However, these subgroup analyses should be interpreted with caution, as they were not powered to demonstrate significant differences within subgroups
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	None

D=durvalumab; EAG=External Assessment Group; Gem/Cis=gemcitabine+cisplatin; P=placebo; NICE=National Institute for Health and Care Excellence; OS=overall survival

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Not applicable

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 2 Modelling overall survival for patients treated with D+Gem/Cis

Report section	Section 6.2
Description of issue and why the EAG has identified it as important	Clinical experts found it challenging to comment on the clinical plausibility of OS extrapolations due to their limited experience of treating patients with D+Gem/Cis. The choice of distribution used to model OS has a large influence on the size of the ICER per QALY gained. The EAG considers that, in addition to the distribution chosen by the company to model OS for patients treated with D+Gem/Cis (spline 1 knot odds), the Gamma distribution is as statistically and clinically plausible
What alternative approach has the EAG suggested?	The EAG carried out analyses using the Gamma distribution to model OS for patients treated with D+Gem/Cis
What is the expected effect on the cost effectiveness estimates?	The ICER for the comparison of D+Gem/Cis versus P+Gem/Cis increased to [redacted] per QALY gained
What additional evidence or analyses might help to resolve this key issue?	Seek further expert clinical advice to help determine the most plausible distribution to use to model OS for patients treated with D+Gem/Cis

D=durvalumab; EAG=External Assessment Group; Gem/Cis=gemcitabine+cisplatin; ICER=incremental cost effectiveness ratio; OS=overall survival; QALY=quality adjusted life year

Issue 3 Modelling progression-free survival for patients treated with D+Gem/Cis

Report section	Section 6.3
Description of issue and why the EAG has identified it as important	Clinical experts found it challenging to comment on the clinical plausibility of PFS extrapolations due to their limited experience of treating patients with D+Gem/Cis. Given this uncertainty, the EAG considered that it would be more appropriate to use a PFS distribution that had a better statistical fit to TOPAZ trial data than the distribution used by the company
What alternative approach has the EAG suggested?	The EAG carried out an analysis using the spline 3 knot hazard distribution (AIC rank: 1; BIC rank: 1) to model PFS for patients treated with D+Gem/Cis
What is the expected effect on the cost-effectiveness estimates?	Using the spline 3 knot hazard distribution to model PFS for patients treated with D+Gem/Cis increased the ICER for the comparison of D+Gem/Cis versus P+Gem/Cis to [redacted] per QALY gained
What additional evidence or analyses might help to resolve this key issue?	Seek further expert clinical advice to help determine the most plausible distribution to use to model PFS for patients treated with D+Gem/Cis

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; D=durvalumab; EAG=External Assessment Group; Gem/Cis=gemcitabine+cisplatin; ICER=incremental cost effectiveness ratio; PFS=progression-free survival; QALY=quality adjusted life year

Issue 4 Modelling treatment costs based on time to treatment discontinuation

Report section	Section 6.4
Description of issue and why the EAG has identified it as important	In the base case, the company modelled treatment costs using PFS as a proxy for TTD. More accurate costs of treatment can be generated by fitting distributions to TOPAZ-1 TTD trial data
What alternative approach has the EAG suggested?	The EAG carried out the following analyses: • use of the spline 3 knot hazard distribution (AIC rank: 1; BIC rank: 1) to model TTD for patients treated with D+Gem/Cis • use of the spline 2 knot odds distribution (AIC rank: 2; BIC rank: 1) to model TTD for patients treated with Gem/Cis
What is the expected effect on the cost-effectiveness estimates?	• Using the spline 3 knot hazard distribution to model TTD for patients treated with D+Gem/Cis increased the ICER for the comparison of D+Gem/Cis versus Gem/Cis to [redacted] per QALY gained • Using the spline 2 knot odds distribution to model TTD for patients treated with Gem/Cis increased the ICER for the comparison of D+Gem/Cis versus Gem/Cis to [redacted] per QALY gained
What additional evidence or analyses might help to resolve this key issue?	None

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; D=durvalumab; Gem/Cis=gemcitabine+cisplatin; ICER=incremental cost effectiveness ratio; PFS=progression-free survival; QALY=quality adjusted life year; TTD=time to treatment discontinuation

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table B Deterministic results: EAG revisions to company base case (durvalumab PAS price)

Scenario/EAG revisions	Incremental		ICER	
	Costs	**QALYs (x1.2 modifier)***	**£/QALY (x1.2 modifier)**	**Change from company base case**
A. Company CS base case	[redacted]	[redacted]	[redacted]	
R1) Minor cost amendments (AE-related QALY decrement removed, neutropenia AE cost corrected and IV administration costs corrected)	[redacted]	[redacted]	[redacted]	[redacted]
R2) Gamma distribution used to model OS for patients treated with D+Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]
R3) Spline 3 knot hazard distribution used to model PFS for patients treated with D+Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]
R4) Spline 3 knot odds distribution used to model PFS for patients treated with Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]
R5) Spline 3 knot hazard distribution (fitted to TOPAZ-1 TTD data) used to estimate treatment costs for patients treated with D+Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]
R6) Spline 2 knot odds distribution (fitted to TOPAZ-1 TTD data) used to estimate treatment costs for patients treated with Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]
B. EAG preferred scenario (R1, R3-R6)	[redacted]	[redacted]	[redacted]	[redacted]
C. EAG scenario (R1-R6)	[redacted]	[redacted]	[redacted]	[redacted]

* The EAG considers that the methods used to estimate the company severity modifier were appropriate

AE=adverse event; CS=company base case; D=durvalumab; EAG=External Assessment Group; Gem/Cis=gemcitabine+cisplatin; ICER=incremental cost effectiveness ratio; IV=intravenous; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival; QALYs=quality adjusted life years; TTD=time to treatment discontinuation

Table C Probabilistic results: EAG revisions to company base case (durvalumab PAS price)

Scenario/EAG revisions	Incremental		ICER	
	Costs	QALYs (x1.2 modifier)	£/QALY (x1.2 modifier)	Change from company base case
A. Company CS base case	[redacted]	[redacted]	[redacted]	
B. EAG preferred scenario (R1, R3-R6)	[redacted]	[redacted]	[redacted]	[redacted]
B. EAG scenario (R1-R6)	[redacted]	[redacted]	[redacted]	[redacted]

EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years

Modelling errors identified and corrected by the EAG are described in Section 6.1. For further details of the exploratory and sensitivity analyses carried out by the EAG, see Section 6.1 to Section 6.6.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This appraisal focuses on the use of durvalumab with gemcitabine and cisplatin (D+Gem/Cis) for treating unresectable or advanced biliary tract cancer (BTC). In this External Assessment Group (EAG) report, the term 'company submission' (CS) refers to the company's document B, which is the company's full submission.

2.2 Biliary tract cancer

Biliary tract cancer is the collective term for three cancers, cancer of the bile duct, cancer of the gallbladder and cancer of the ampulla of Vater (ampullary cancer). Biliary tract cancer accounts for about 1% of all cancers in humans.[1] Clinical advice to the company and the EAG is that, in the NHS, approximately 80% of BTC tumours are diagnosed at an advanced stage.

Cancer of the bile duct is termed cholangiocarcinoma (CCA). Subtypes of CCA are classified according to site of origin, i.e., intrahepatic or extrahepatic (Table 1). Clinical advice to the EAG is that identifying CCA tumour subtypes is complex and, in clinical practice, CCA tumours are often misclassified.[2] In particular, perihilar tumours (a subtype of extrahepatic tumours) are routinely misclassified as being intrahepatic (iCCA).

Table 1 CCA classifications

CCA classification	Site of origin
Intrahepatic (iCCA)	Bile ducts in the liver
Extrahepatic (eCCA) includes perihilar and distal	Perihilar CCA starts just outside the liver, including where the left and right hepatic ducts join Distal CCA starts in the bile ducts below the perihilar region near the bowel

CCA=cholangiocarcinoma
Source: Cancer Research UK[3]

Annually, in England, approximately 2800 people are diagnosed with cancer of the bile duct[4] (including ampullary cancer) and approximately 1000 people are diagnosed with cancer of the gallbladder.[5] UK wide statistics are not available by disease stage for bile duct cancer or for gallbladder cancer.[6,7] Survival estimates from the National Cancer Intelligence Network (2015),[7] indicate that the 5 year survival rate (all stages of BTC) is approximately 5%. Clinical advice to the EAG is that survival for patients with Stage 4 BTC is usually no more than 12 months.

2.3 Durvalumab

Durvalumab is a monoclonal antibody that selectively blocks the interaction of programmed death-ligand 1 (PD-L1) with receptors PD-1 and CD80 (CS, Table 2). The Medicines and

Healthcare products Regulatory Agency (MHRA) marketing authorisation[8] for durvalumab was issued on 25th January 2023. D+Gem/Cis is indicated for the first-line treatment of adults with locally advanced, unresectable, or metastatic BTC.[8] Durvalumab (1500mg) is administered as an intravenous (IV) infusion over 1 hour on Day 1, every 3 weeks for up to 8 cycles in combination with Gem/Cis and then as a monotherapy (1500mg) every 4 weeks as maintenance until disease progression or unacceptable toxicity.[9]

Gemcitabine and cisplatin are administered as intravenous (IV) infusions on day 1 and day 8 every 3 weeks. Gemcitabine is given at a dose of 1000mg/m^2 over 30 minutes. Cisplatin is given at a dose of 25mg/m^2 over 60 minutes.

2.4 Company's overview of current service provision

2.4.1 Clinical guidelines

The EAG agrees with the company (CS, p22) that there are no NICE guidelines for the first-line treatment of patients with unresectable or advanced BTC. Clinical advice to the company (CS, p22) and the EAG is that NHS clinical practice is informed by the 2022 European Society for Medical Oncology (ESMO) guidelines and the ABC-02[10] trial.

2.4.2 Treatments in the pathway

The company's overview of the treatment pathway for patients with unresectable or advanced BTC is shown in Figure 1.

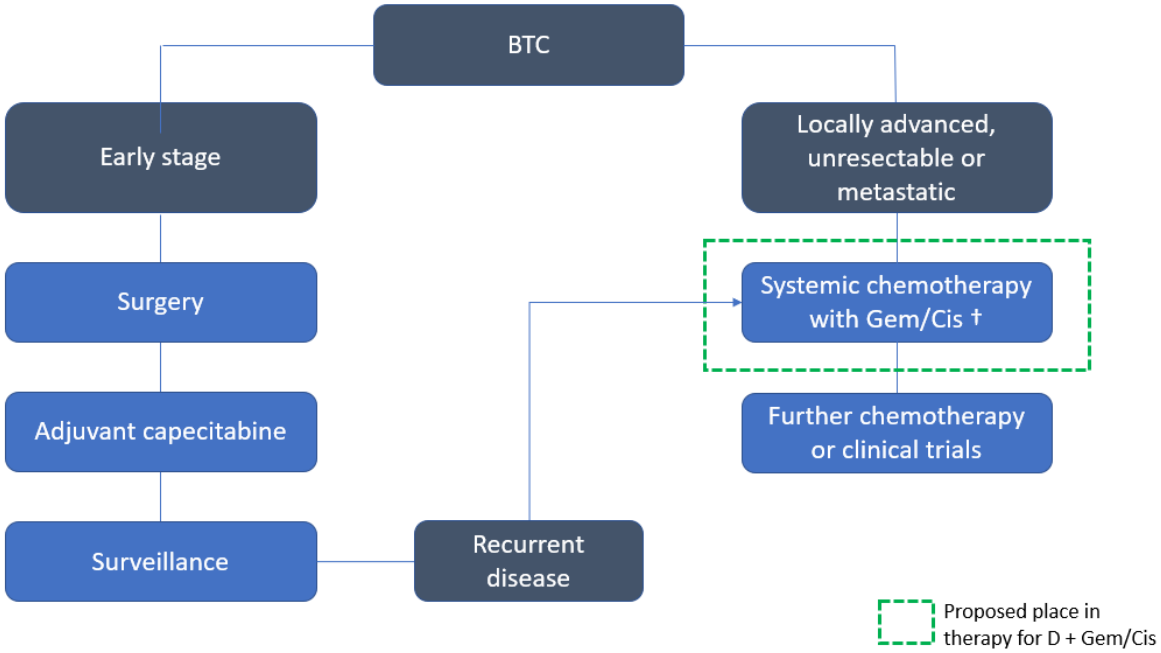


Figure 1 Company's overview of treatment pathway for NHS patients with unresectable or advanced biliary tract cancer

†Oxaliplatin may be given instead of cisplatin, particularly if there are concerns regarding kidney function. For patients in poor health (PS>1), single agent chemotherapy with gemcitabine is typically offered.
BTC=biliary tract cancer; Gem/Cis=gemcitabine+cisplatin
Source: CS, Figure 2

The company's proposed positioning of D+Gem/Cis is to replace Gem/Cis as the NHS standard of care (SoC) for first-line treatment.

Clinical advice to the EAG is that:

i. Figure 1 reflects the NHS pathway for patients with unresectable or advanced BTC
ii. treatment with Gem/Cis is the SoC for NHS patients who are fit enough to tolerate treatment, including patients with performance status (PS) 2. Treatment with Gem/Cis is based on the 2010 ABC-02[10] trial results (Gem/Cis versus gemcitabine)
iii. immunohistochemistry is increasingly used in the NHS to identify patients whose tumours show mismatch protein repair deficiency (dMMR) as evidenced by loss of mismatch repair proteins MLH1, MSH2, MSH6 and PMS2. This small (~1%) subgroup of patients might be treated with nivolumab via the Cancer Drugs Fund.[11]
iv. patients with poor kidney function who cannot tolerate treatment with cisplatin are offered treatment with gemcitabine+oxaliplatin, gemcitabine+carboplatin or gemcitabine monotherapy
v. patients who are considered frail, may be treated with gemcitabine monotherapy

vi. following treatment with Gem/Cis NHS treatment options are FOLFOX or capecitabine. Patients with fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement positive CCA are offered pemigatinib (in line with NICE TA722[12] guidance).

2.5 Critique of company's definition of decision problem

A summary of the final scope[13] issued by NICE, the decision problem addressed by the company, and EAG comments are presented in Table 2. Each parameter is discussed in more detail in the text following Table 2 (Section 2.5.1 to Section 2.5.7).

Table 2 Summary of decision problem

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
Population	Adults with unresectable advanced or metastatic biliary tract cancer, including people with recurrent disease after treatment with curative intent	As per scope	As per scope, except that no evidence is presented for: • patients with ampullary carcinoma • patients with PS=2 who are fit enough to tolerate treatment with cisplatin. See Section 2.5.2 for discussion.
Intervention	Durvalumab with gemcitabine+cisplatin	As per scope	As per scope. In the TOPAZ-1 trial, patients received treatment with D+Gem/Cis or P+Gem/Cis.
Comparator(s)	Established clinical management without durvalumab including: • Gemcitabine+cisplatin For people with poor kidney function: • Gemcitabine+oxaliplatin For frailer people: • Gemcitabine alone • Fluorouracil alone • Capecitabine alone	• Gemcitabine with cisplatin Patients with poor kidney function and frailer patients are not considered in the CS for the following reasons: • Patients with poor kidney function are unable to tolerate cisplatin and are not suitable for treatment with D+Gem/Cis. In addition, patients recruited to the key trial discussed in the CS (TOPAZ-1), had a minimum creatinine clearance of >50mL/min and do not represent a population of patients with poor kidney function. • Frail patients (patients with an ECOG PS>1) are not expected to tolerate treatment with cisplatin and are therefore not suitable for treatment with D+Gem/Cis. ESMO guidelines[1] recommend treatment with gemcitabine monotherapy for patients with PS=2. In addition, patients recruited to the TOPAZ-1 trial were of PS≥1 and are not	The company has presented clinical effectiveness evidence from the TOPAZ-1 trial (D+Gem/Cis versus P+Gem/Cis). Clinical advice to the EAG is that NHS patients with poor kidney function are not offered treatment with cisplatin and therefore will not receive D+Gem/Cis or Gem/Cis. The EAG notes that the ESMO[1] guidelines (p7) state that 'gemcitabine monotherapy may be preferred in patients with PS=2 or other factors of fragility.' Clinical advice to the EAG is that some NHS patients with PS=2 who are at the fitter end of the scale are suitable for treatment with cisplatin and are currently

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
		representative of a frail population.	treated with Gem/Cis.
Outcomes	• Overall survival • Progression-free survival • Response rates (inc. overall response rates) • Time to treatment discontinuation • Adverse effects of treatment • Health-related quality of life	As per scope	The company has presented clinical effectiveness evidence from the TOPAZ-1 trial for all outcomes listed in the final scope issued by NICE.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life-year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any	As per scope	The company has provided cost effectiveness results in terms of the incremental cost per quality adjusted life year gained. Outcomes were assessed over a lifetime time horizon and costs were considered from an NHS and PSS perspective.

Parameter	Final scope issued by NICE	Decision problem addressed in the company submission with rationale	EAG comment
	commercial arrangements for the intervention, comparator, and subsequent treatment technologies will be taken into account The availability and cost of biosimilar and generic products should be taken into account		
Subgroups	If the evidence allows, results by type of biliary tract cancer and level of PD-L1 expression will be considered	As per scope	The company has provided OS, PFS and ORR TOPAZ-1 trial subgroup results by primary tumour location and PD-L1 status. These subgroup analyses were pre-planned. In the CS, PD-L1 expression is described as TAP score. The TAP scores are presented as high (TAP≥1%) or low/negative (TAP<1%). Section 2.5.7 explains why the company chose to use TAP scores in the TOPAZ-1 trial. The company cautions (CS, Section B.2.6.1.3) that the TOPAZ-1 trial subgroups were not powered to detect statistically significant effects and no adjustments were made for multiple testing.

Abbreviations: D=durvalumab; Gem/Cis=gemcitabine+cisplatin; ECOG=Eastern Co-operative Oncology Group; ESMO=European Society for Medical Oncology; PD-L1=programmed death-ligand 1; OS=overall survival; P=placebo; PFS=progression-free survival; ORR=objective response rate; PSS=personal and social services; TAP=tumour area positivity
Source: Final scope issued by NICE and CS, Table 1

2.5.1 Source of direct clinical effectiveness data

The company identified one phase III, international, double-blind, placebo-controlled randomised controlled trial (RCT) that provides data demonstrating the efficacy and safety of D+Gem/Cis. This trial, the TOPAZ-1[14,15] trial, compares the clinical effectiveness of D+Gem/Cis (n=341) with P+Gem/Cis (n=344). Patients receive durvalumab or placebo in combination with gemcitabine and cisplatin in 3-weekly cycles for up to 8 cycles. At the end of the chemotherapy treatment, patients receive durvalumab monotherapy or placebo every 4 weeks until clinical progression or unacceptable toxicity.

2.5.2 Population

The population discussed in the CS largely matches the population specified in the final scope issued by NICE.

Ampullary cancer is one of three BTC subtypes, however, patients with ampullary carcinoma were excluded from the TOPAZ-1 trial. The company's rationale (TOPAZ-1 trial protocol, p11) is that the genetic profile of ampullary cancer differs from the genetic profiles of other BTC subtypes and that, by excluding patients with ampullary cancer from the TOPAZ-1 trial, the heterogeneity of the population is reduced. Clinical advice to the EAG is that it was appropriate to exclude patients with ampullary cancer from the TOPAZ-1 trial. Ampullary carcinoma is a heterogenous disease because it is located at the junction between the pancreas, the intestinal tract and the biliary tract. Clinical advice to the EAG is that treatment for NHS patients with ampullary cancer is variable across treatment centres and includes either the FOLFIRINOX chemotherapy regimen (folinic acid, fluorouracil, irinotecan and oxaliplatin) or Gem/Cis.

There is no evidence presented in the CS for the use of D+Gem/Cis in patients with PS=2. Clinical advice to the EAG is that NHS patients with PS=2, who are fit enough to tolerate cisplatin are routinely treated with Gem/Cis, although modifications in the dose of cisplatin may be needed. The EAG notes that the marketing authorisation for D+Gem/Cis does not limit treatment by PS. Clinical advice to the EAG is that clinicians would be cautious about using D+Gem/Cis in patients with PS=2 due to patient frailty and lack of data from the TOPAZ-1 trial.

2.5.3 Intervention

The intervention is D+Gem/Cis. See Section 2.3 for details of the marketing authorisation and treatment protocols for durvalumab, gemcitabine and cisplatin.

2.5.4 Comparators

The company has presented clinical effectiveness evidence for the comparison of D+Gem/Cis versus Gem/Cis. Clinical advice to the EAG is that the regimen of Gem/Cis used in the TOPAZ-1 trial matches the regimen used to treat NHS patients. Further, clinical advice to the EAG is that Gem/Cis is the SoC for NHS patients with no contra-indications who are well enough to tolerate the regimen.

There is no clinical effectiveness evidence for the use of D+Gem/Cis versus the other comparators listed in the final scope issued by NICE:

i) Gemcitabine+oxaliplatin (for patients with poor kidney function). The company states (CS, Table 1) that patients with poor kidney function would be unable to tolerate treatment with cisplatin and would therefore not be suitable for treatment with the D+Gem/Cis. Clinical advice to the EAG is that NHS patients with poor kidney function may be treated with gemcitabine+oxaliplatin, gemcitabine+carboplatin or gemcitabine monotherapy. The company highlights that patients with poor kidney function (defined as CrCl <50 mL/min) were not recruited to the TOPAZ-1 trial.

ii) Gemcitabine, fluorouracil, capecitabine monotherapies (for frail patients). Frail patients are defined in the CS (Table 1) as patients with PS>1. The company states that frail patients would not be expected to tolerate treatment with cisplatin and are therefore not suitable for treatment with D+Gem/Cis. The company cites the ESMO guidelines[1] recommendation for the use of gemcitabine monotherapy in patients with PS=2. The company highlights that, as the TOPAZ-1 trial recruited only patients with PS=0 or 1, the trial does not provide evidence for the use of D+Gem/Cis in patients of PS=2.

   Clinical advice to the EAG is that some NHS patients with PS=2, who are at the fitter end of the scale, are treated with Gem/Cis. Treating patients with PS=2 using Gem/Cis is in line with the protocol of the pivotal ABC-02[10] trial.

2.5.5 Outcomes

Direct evidence from the TOPAZ-1 trial is available for D+Gem/Cis versus Gem/Cis for all the outcomes listed in the final scope issued by NICE, i.e., OS, progression-free survival (PFS), objective response rate (ORR), time to treatment discontinuation (TTD), adverse effects of treatment (AE) and health-related quality of life (HRQoL). The company notes (CS, Table 4)

that although TTD was not a pre-specified outcome in the TOPAZ-1 trial, TTD data could be used in the company model.

2.5.6 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a 20-year time period (which the company considered was equivalent to a lifetime horizon) and costs were considered from an NHS perspective.

2.5.7 Subgroups

As listed in the final scope issued by NICE, evidence is available from the CS for OS, PFS and ORR by type of BTC and level of PD-L1 expression. The company highlights (CS, p51) that these subgroup analyses were pre-planned, but that the trial was not powered to detect statistically significant treatment effects within subgroups and no adjustments were made for multiple testing.

The company describes PD-L1 status using 'tumour area positivity scores' (TAP). The TAP scores are categorised as high (TAP≥1%) or low/negative (TAP<1%). In response to Clarification Question A2, the company explained that the Ventana PD-L1 SP263 assay used to assess PD-L1 status in the TOPAZ-1 trial was developed specifically for use with durvalumab and that the TAP score is a combination of tumour and immune cell count. The company further explained that the Combined Positive Score (CPS), which also includes measures of tumour and immune cells, is used to describe PD-L1 status in other cancers, however, the CPS is a measure derived from a different assay (Dako 22C3).

The company highlights that the MHRA[8] marketing authorisation for durvalumab does not stipulate that PD-L1 status must be established before treatment and that PD-L1 status will not be used to drive NHS treatment decisions for patients with BTC. Clinical advice to the EAG is that PD-L1 testing is not routinely carried out on BTC tumours and that there is currently no evidence that PD-L1 is a prognostic or predictive factor for treatment outcomes.

The other pre-planned subgroup analysis results presented in the CS are disease status, sex, age, race (Asia versus non-Asian ethnicity), region (Asia versus the rest of the world), Eastern Co-operative Oncology Group (ECOG) PS and extent of disease.

2.5.8 Other considerations

Durvalumab is available to the NHS at a confidential discounted Patient Access Scheme (PAS) price. There is no PAS in place for gemcitabine or cisplatin. The cost effectiveness results presented in the CS were generated using the PAS price for durvalumab and publicly

available prices for gemcitabine and cisplatin. Pemigatinib is available to the NHS at a confidential discounted PAS price. Cost effectiveness results generated using confidential prices are available in an EAG confidential appendix.

Clinical need

Despite trials evaluating several targeted therapies, including cediranib,[16] erlotinib,[17] cetuximab,[18] panitumumab,[19] ramucirumab,[20] and merestinib[20] as first-line treatments for advanced BTC, Gem/Cis chemotherapy has remained the SoC for the past decade. Durvalumab is the first immunotherapy licensed for patients with advanced, unresectable or metastatic BTC (CS, p10); NICE expects to publish guidance for the use of D+Gem/Cis in October 2023.[21] NICE has also started an appraisal of pembrolizumab with Gem/Cis in patients with advanced BTC and expects to publish this guidance in March 2024.[22] Pembrolizumab with Gem/Cis is not currently licensed for use in the UK.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used by the company to identify and select clinically relevant evidence of the effectiveness of D+Gem/Cis are presented in the CS (Appendix D). An assessment of the extent to which the review was conducted in accordance with the EAG in-house systematic review checklist is summarised in Table 3. The EAG considers that the company conducted the review to a good standard. The EAG did not find any relevant studies in addition to those identified by the company.

Table 3 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes	See CS, Appendix D1, Table 6
Were appropriate sources searched?	Yes	See CS, Appendix 1, Section D.1.1.1
Was the timespan of the searches appropriate?	Yes	See CS, Appendix 1, Section D.1.1.1
Were appropriate search terms used?	Yes	See CS, Appendix 1, Section D.1.1.1 and Section D.1.1.2
Were the eligibility criteria appropriate to the decision problem?	Yes	See CS, Appendix D.1.2
Was study selection applied by two or more reviewers independently?	Yes	See CS, Appendix D.1.2
Were data extracted by two or more reviewers independently?	Yes	See Company Factual Accuracy Check, Issue 3
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	The company used the quality assessment checklist for clinical trials devised by the Centre for Reviews and Dissemination at the University of York[23]
Was the quality assessment conducted by two or more reviewers independently?	Yes	See Company Factual Accuracy Check, Issue 3
Were attempts to synthesise evidence appropriate?	Not applicable	The TOPAZ-1 trial directly compares the intervention (D+Gem/Cis) versus the main comparator listed in the final scope issued by NICE (Gem/Cis). Indirect treatment comparisons were, therefore, not required

D=durvalumab; Gem/Cis=gemcitabine+cisplatin
Source: EAG in-house checklist

3.2 EAG summary and critique of clinical effectiveness evidence

3.2.1 Trials included in the company systematic literature review

The company identified one relevant phase III RCT (TOPAZ-1) that provides clinical effectiveness evidence for the comparison of D+Gem/Cis versus Gem/Cis for patients with previously untreated locally advanced, unresectable, or metastatic or recurrent BTC.

The company also identified two potentially relevant phase II RCTs (the MEDITREME[24] trial and the IMMUCHEC[25] trial); these trials investigated the use of D+Gem/Cis as a treatment for patients with previously untreated locally advanced, unresectable, or metastatic or recurrent BTC. The MEDITREME[24] trial was a single centre trial comparing D+Gem/Cis with or without tremelimumab versus Gem/Cis followed by durvalumab plus tremelimumab with Gem/Cis. This trial was conducted in South Korea and 49 patients were treated with D+Gem/Cis. Durvalumab was administered at a dose of 1120mg (the licensed dose in the UK is 1500mg) The authors of the published paper[24] describing the MEDITREME trial reported that patients were not initially randomised to treatments and the study was not designed to compare results between treatment arms. The results for patients treated with D+Cis/Gem in the MEDITREME trial are presented in the CS (Appendix N) and show that, at a median follow-up of 26.6 months (IQR 19 to 27.9), 21% of patients remained on treatment. Median OS was 20.2 months (95% CI: 12.8 to 27.6) and median PFS was 11.8 months (95% CI: 6.9 to 16.6). The company reported (CS, p72) that the MEDITREME trial was complete.

The IMMUCHEC[25] trial was designed to assess the clinical effectiveness of tremelimumab in combination with D+Cis/Gem. The trial was conducted in treatment centres in Germany and comprised five treatment arms, including one for patients treated with D+Gem/Cis (n=29) and one for patients treated with Gem/Cis (n=35). The three remaining arms were different treatment combinations of durvalumab with tremelimumab. The details of the IMMUCHEC trial reported in the CS (Appendix N) are derived from a conference abstract. Median OS in the D+Cis/Gem arm of the trial was lower than in the Gem/Cis arm (12.87 months versus 16.93 months). Median PFS was also lower in the D+Cis/Gem arm than in the Gem/Cis arm (5.97 months versus 8.97 months).The company does not know (CS, p72) when further updates from the IMMUCHEC[25] trial will become available as it is an investigator-led study.

The EAG agrees with the company that the MEDITREME[5] and IMMUCHEC[25] and trials are not relevant to this appraisal due to their design and the small numbers of recruited patients.

3.2.2 Characteristics of the TOPAZ-1 trial

The TOPAZ-1 trial is an ongoing, double-blind, placebo-controlled RCT that compares D+Gem/Cis versus Gem/Cis as treatments for patients with unresectable, locally advanced, or metastatic BTC. Randomisation was stratified by disease status (initially unresectable versus recurrent), primary tumour location (intra versus extra versus gall bladder). The treatment regimens used in the TOPAZ-1 trial are described in.

Table 4.

The TOPAZ-1 trial is being conducted in 105 sites in 17 countries across Europe, North America, South America and Asia-Pacific (CS, p30) and includes eight UK treatment centres (n=47 patients).

The TOPAZ-1 trial is ongoing; however, the independent data monitoring committee concluded that data from the second interim analysis (IA-2, data cut-off date 11th August 21) met the pre-specified criteria for a statistically significant difference in OS. Therefore, no further formal statistical testing of OS was to be performed. At IA-2, 63 (18.6%) patients in the D+Gem/Cis arm and 20 (5.8%) patients in the P+Gem/Cis arm remained on study treatment (CS, p46).

Additional analyses of OS and safety outcomes are presented from a 6.5-month update. At this point, 32 (9.5%) patients in the D+Gem/Cis arm and 7 (2.0%) patients in the P+ Gem/Cis arm remained on study treatment.

Table 4 TOPAZ-1 trial treatment regimens

Treatment arm	Chemotherapy regimen	Maintenance regimen
Durvalumab	Durvalumab 1500mg (Day 1) Gem/Cis (Day 1 and Day 8) 3-weekly cycles	Durvalumab 1500mg Q4W
Placebo	Gem/Cis (Day 1 and Day 8) 3-weekly cycles	Placebo Q4W

Gem/Cis=gemcitabine+cisplatin; Q4W=every 4 weeks
Source: text from CS, p34

Clinical advice to the EAG is that treatment with Gem/Cis is the SoC in NHS treatment centres for patients who are fit enough to tolerate treatment with cisplatin and that the Gem/Cis treatment regimen in the TOPAZ-1 trial matches the regimen used in NHS clinical practice.

3.2.3 Demographic and disease characteristics of the patients in the TOPAZ-1 trial

The baseline patient demographic characteristics and disease characteristics are provided in the CS (Table 6 and Table 7). The EAG agrees with the company (CS, p40) that the characteristics are well-balanced across the two treatment arms of the TOPAZ-1 trial.

Clinical advice to the EAG is that patients in the TOPAZ-1 trial are typical of a clinical trial population i.e., they are younger and fitter than NHS patients with BTC. TOPAZ-1 trial patients have a median age of 64 years, whereas patients in the NHS are, on average, around 70 years old. The patients in the TOPAZ-1 trial have a PS of 0 or 1; NHS patients with PS=2 who are fit enough for treatment are offered treatment with Gem/Cis.

The proportions of patients in the TOPAZ-1 trial with iCCA and eCCA are 55.9% and 19.1%, respectively. Clinical advice to the EAG is that compared with the NHS, patients with iCCA are overrepresented and patients with eCCA are underrepresented. However, clinical advice to the EAG is that there are problems with the diagnosis of subtypes of CCA. (See Section 2.2 of this EAG report). Clinical advice to the EAG is that any difference in CCA subtypes between the TOPAZ-1 trial and an NHS population is likely of minor importance.

In the TOPAZ-1 trial, approximately 50% of tumours were tested for (high or stable) microsatellite instability status (MSI), a measure of dMMR. The remaining 50% of tumours were either not tested for MSI due to insufficient tissue sample, or the test results were missing.[15] As noted in Section 2.4.2 of this EAG report, clinical advice to the EAG is that tumours with dMMR might respond optimally to treatment with an immunotherapy. However, the company was unable to conduct any subgroup analyses relevant to MSI as there were too few patients (n=5, 1.5%) with tumours classified as 'high' (CSR, p8). It is noted in the TOPAZ-1 trial publication[15] that the prevalence of MSI in the 333 patients with evaluable MSI status (1.5%) is consistent with the prevalence reported in the literature.

Approximately half (54.6%) of patients in the TOPAZ-1 trial were recruited from treatment centres in Asia. Clinical advice to the EAG is that systemic BTC treatment in Asia is similar to NHS treatment, although there may be greater use of locoregional treatments in Asian centres than in the NHS. Clinical advice to the EAG is that the inclusion of 54.6% of patients from Asia does not limit the generalisability of TOPAZ-1 trial results to NHS patients. However, clinical advice to the EAG is that it is biologically plausible that patients with BTC who also have viral hepatitis B will have a more favourable response to treatment with immunotherapy than to other treatment. Clinical advice to the EAG is that any additional treatment benefit associated with viral hepatitis B is likely to be modest.[26] The EAG notes from the CSR (Table 17) that in

the TOPAZ-1 trial, viral hepatitis B was more prevalent amongst patients from Asian treatment centres compared with patients from the rest of the world ([redacted] versus [redacted]).

3.2.4 Quality assessment of the TOPAZ-1 trial

The company conducted a quality assessment of the TOPAZ-1 trial (CS, Table 9) using the quality assessment checklist for clinical trials devised by the Centre for Reviews and Dissemination at the University of York.[23] The EAG agrees with the company's assessment and considers that the TOPAZ-1 trial is of good methodological quality.

3.2.5 Statistical approach adopted for the analysis of the TOPAZ-1 trial

Information relevant to the statistical approach taken by the company to analyse TOPAZ-1 trial data has been extracted from the Clinical Study Report (CSR),[14] the CSR addendum,[27] the final version of the trial statistical analysis plan (TSAP) (which is available in the supplementary materials to the published trial report[24]), the trial protocol,[28] and the CS. A summary of the EAG checks of the pre-planned statistical approach used by the company to analyse data from TOPAZ-1 trial is provided in Table 5.

The company planned to conduct three analyses of TOPAZ-1 trial data: a first interim analysis (IA-1, no formal statistical analysis), a second interim analysis (IA-2) and a final analysis. However, the independent data monitoring committee concluded that data from IA-2 (data cut-off date 11 August 21) met the pre-specified criteria for a statistically significant difference in OS (CS, p31). The sponsor was therefore unblinded at this time, and formal statistical analysis of OS was conducted using data collected up to the cut-off date. No further formal statistical testing of OS was to be performed. Safety data and additional OS data are available from an updated analysis conducted 6.5 months after IA-2 (data cut-off date 25 February 2022).

The company analysed OS and PFS data using Cox proportional hazards (PH) models. However, the company concluded that there was a lack of proportionality for OS data (CS, p50) [redacted]. Therefore, the EAG considers that the hazard ratio (HR) should not be used to summarise the treatment effect of D+Gem/Cis versus P+Gem/Cis for OS [redacted]. To address the lack of proportionality of the OS data, the company provided piecewise HRs for distinct time periods. [redacted] in the CS; therefore, the EAG requested these analyses as part of the clarification letter to the company (see Section 3.2.8 of this EAG report).

Table 5 EAG assessment of statistical approaches used in the TOPAZ-1 trial

Item	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Partial	OS, PFS and DCR analyses were carried out using data from patients in the FAS (all randomised patients). Analyses of ORR were carried out using data from patients in the FAS who had measurable disease at baseline, and analyses of DoR were carried out using data from patients in the FAS who achieved objective response. PRO analyses were carried out using data from the PRO analysis set (all patients from the FAS, except for patients with no questionnaire translation available or who did not complete questionnaires due to other physical or language reasons). Safety analyses were carried out using data from the safety analysis set (all patients who received any study drug). The EAG is satisfied that these populations were clearly defined and pre-specified in the trial protocol (pp118-119), except for the PRO analysis set. PRO analyses were originally specified to be carried out using data from the FAS, but an amendment to the TSAP specified that PRO analyses would be carried out using data from the PRO analysis set (TSAP, p40). The EAG considers this amendment to the TSAP to be reasonable.
Was an appropriate sample size calculation pre-specified?	Yes	A sample size calculation was pre-specified in the trial protocol (pp116-117). With a log-rank test at IA-2 and a Fleming-Harrington (0, 1) test at the final analysis, the overall power would be at least 86% based on an assumed average HR of 0.745 under the assumption of PH or up to a 6-month delayed effect (i.e., delayed separation of the OS curves by up to 6 months). The EAG is satisfied that the sample size calculation was appropriate.
Were all protocol amendments made prior to analysis?	Partial	Changes in the conduct of the study or planned analyses are listed in the CSR (pp98-104) and the CSR addendum (p15). Most protocol amendments were made prior to the date of data cut-off for IA-2 (11 August 21). Version 8 of the protocol is dated 17th Jan 2022 and was released to address long-term follow-up of patients beyond the 6.5 month updated analysis. Only minor amendments were made to the TSAP after the IA-2 data cut-off date. Some post-hoc analyses were conducted, but these are clearly listed in the CSR (p104) and labelled as post-hoc analyses where results are presented. The EAG considers that all changes to the protocol and TSAP following the data cut-off date for IA-2 were reasonable and well justified.
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	The company's multiple testing procedure was pre-specified in the TSAP (pp92-95). A small alpha expenditure of 0.001 was allocated to testing ORR at IA-1. The company planned to strongly protect the family-wise error rate at the remaining 4.9% level (2-sided) across the testing of OS and PFS endpoints. This was achieved through a combined approach of alpha allocation to the planned OS analyses via alpha spending function and a hierarchical testing procedure; that is, PFS was to be tested only if OS

Item	EAG assessment	Statistical approach with EAG comments
		met statistical significance (either) at IA-2 or the final analysis. The EAG considers that the multiple testing procedure was appropriate. The company analysed OS and PFS data using Cox PH models. See Section 3.2.5 of this EAG report.
Was the analysis approach for PROs appropriate and pre-specified?	Yes	PROs were assessed as a secondary efficacy endpoint using the EORTC QLQ-C30 and EORTC QLQ-BIL21. Additional exploratory analyses were conducted using PGIS, PRO-CTCAE and EQ-5D-5L. The EAG is satisfied that the analysis approaches pre-specified in the trial protocol (pp136-138) were appropriate.
Was the analysis approach for AEs appropriate and pre-specified?	Yes	Safety data presented in the CS included an overview of AEs, AEs reported for ≥10% of patients in either treatment arm and G3 or G4 AEs reported for ≥5% of patients in either treatment arm (CS, Table 16 to Table 18). Safety analyses were descriptive only and were pre-specified in the TSAP (pp108-116).
Was a suitable approach employed for handling missing data?	Yes	The company's approach to handling missing data is outlined in the TSAP (efficacy outcomes, pp52-57; PROs, pp57-70; safety, pp109-110). The EAG is satisfied that the approach described was appropriate.
Were all subgroup and sensitivity analyses pre-specified?	Yes	Subgroup analyses for OS, PFS and ORR are presented in the CS (OS, Figure 6; PFS, Appendix E, Figure 4; ORR, Appendix E, Figure 5). All the subgroup analyses presented in the CS were pre-specified in the TSAP (pp97, 101, 102). No sensitivity analyses were presented in the CS.

AE=adverse event; CS=company submission; CSR=clinical study report; D=durvalumab; DCR=disease control rate; DoR=duration of response; EAG=External Assessment Group; EORTC QLQ-BIL21=European Organisation for Research and Treatment of Cancer 21-Item Cholangiocarcinoma and Gallbladder Cancer Quality of Life Questionnaire; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer 30-Item Core Quality of Life Questionnaire; EQ-5D-5L=EuroQol-5 Dimensions-5 Levels; FAS=full analysis set; G=grade; Gem/Cis=gemcitabine+cisplatin; HR=hazard ratio; IA-1=first interim analysis; IA-2=second interim analysis; ORR=objective response rate; OS=overall survival; P=placebo; PFS=progression-free survival; PGIS=Patient Global Impression of Severity; PH=proportional hazards; PRO=patient-reported outcome; PRO-CTCAE=Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events; TSAP=trial statistical analysis plan
Source: CS, CSR, CSR addendum, trial protocol, TSAP, and EAG comment

3.2.6 Efficacy results from the TOPAZ-1 trial

The results presented in the CS are from the IA-2 (OS maturity=61.9%) and, where available, from the 6.5-month updated analysis (OS maturity=76.9%).

A summary of the results for the primary and key secondary efficacy endpoints from the TOPAZ-1 trial is provided in

Table 6.

Table 6 Summary of efficacy results from the TOPAZ-1 trial

Outcome	D+Gem/Cis	P+Gem/Cis
OS (6.5 month updated analysis), FAS	(N=341)	(N=344)
Deaths, n (%)	248 (72.7)	279 (81.1)
Median OS, months (95% CI)	12.9 (11.6 to 14.1)	11.3 (10.1 to 12.5)
HR (95% CI)	0.76 (0.64 to 0.91)[a]	
PFS (IA-2), FAS	(N=341)	(N=344)
PFS events, n (%)	276 (80.9)	297 (86.3)
Median PFS, months (95% CI)	7.2 (6.7 to 7.4)	5.7 (5.6 to 6.7)
HR for PFS (95.19% CI; p-value [b])	0.75 (0.63 to 0.89; p=0.001)	
ORR (IA-2), FAS patients with measurable disease at baseline	(N=341)	(N=343)
Number (%) of patients with response	91 (26.7)	64 (18.7)
OR (95% CI; nominal p-value)	1.60 (1.11 to 2.31; p=0.011)	
Complete response, n (%)	7 (2.1)	2 (0.6)
Partial response, n (%)	84 (24.6)	62 (18.1)
Stable disease ≥5 weeks, n (%) [c]	[redacted]	[redacted]
Progressive disease, n (%)	[redacted]	[redacted]
Not evaluable, n (%)	[redacted]	[redacted]
DoR (IA-2), FAS patients with measurable disease at baseline and objective response	(N=91)	(N=64)
Median DoR (95% CI)	6.4 (5.9 to 8.1)	6.2 (4.4 to 7.3)
% remaining in response at 12 months	26.1	15.0
DCR, FAS		
DCR, n (%)	[redacted] (85.3)	[redacted] (82.6)

[a] No p-value reported as formal statistical testing was not performed at the 6.5 month updated analysis of OS (see Section 3.2.5 of this EAG report)
[b] The p-value is based on a stratified log-rank test and tested at 0.0481 significance level
[c] The first post-baseline tumour assessment was scheduled for 6±1 weeks after randomisation
CI=confidence interval; D=durvalumab; DCR=disease control rate; DoR=duration of response; FAS=full analysis set; Gem/Cis=gemcitabine+cisplatin; HR=hazard ratio; IA-2, interim analysis 2; ORR=objective response rate; OR=odds ratio; OS=overall survival; P=placebo; PFS=progression-free survival
Source: CS, Table 10 to Table 13; CSR, Table 14.2.3.2.1 and Table 14.2.3.6.1

3.2.7 Overall survival

Median OS was improved by 1.6 months for patients in the D+Gem/Cis arm in comparison to patients in the P+Gem/Cis arm, and the HR favoured D+Gem/Cis. However, the company (and EAG) concluded that the OS PH assumption does not hold (CS, p50), and therefore the EAG considers that the HR is not an appropriate measure of treatment effect for this outcome.

To address the lack of proportionality of the OS data, the company provided piecewise HRs for distinct time periods. The Kaplan-Meier (K-M) curves (CS, Figure 5) do not separate until

approximately 6 months, and for this reason, the company calculated piecewise HRs for the period of the trial up to 6 months follow-up (HR=0.91, 95% CI: [redacted]; confidence intervals extracted by the EAG from the CSR addendum[27]), and the period of the trial after 6 months follow-up (HR=0.71, 95% CI: 0.58 to 0.88).

The piecewise HRs suggest that D+Gem/Cis and P+Gem/Cis are of similar efficacy for the first 6 months, and after this point, patients in the D+Gem/Cis arm experience treatment benefit in comparison to patients in the P+Gem/Cis arm. The EAG concurs with Freeman et al[29] that piecewise HRs can 'lack biological plausibility, due to the assumption of an instantaneous change in the hazard rate between time intervals'. However, clinical advice to the EAG is that the discontinuation of chemotherapy in both arms of the trial may have prompted a change in treatment effect, and therefore here, the instant change in HR may be plausible. The EAG considers that the piecewise HRs are more informative than the HR provided for the whole trial period.

The company conducted OS subgroup analyses (6.5 month updated analysis) by various baseline characteristics, including geographical region, primary tumour location, disease status, PS, and PD-L1 status. The (favourable) treatment effect of D+Gem/Cis versus P+Gem/Cis was generally consistent across all subgroups (CS, Figure 6), including by PD-L1 status. The EAG notes that the treatment effect of D+Gem/Cis versus P+Gem/Cis was numerically greater for patients in the 'Asian race' and in the 'Asian region' subgroups than for patients in the 'non-Asian race' and in the 'rest of the world' subgroups, respectively. Clinical advice to the EAG is that these subgroup differences could be due to the fact that patients with BTC who also have viral hepatitis B may have a more favourable response to treatment with immunotherapy, and in the TOPAZ-1 trial, viral hepatitis B was more prevalent amongst patients from Asian treatment centres compared with patients from the rest of the world ([redacted] versus [redacted]) (see Section 3.2.3 of this EAG report). However, these subgroup analyses should be interpreted with caution, as they were not powered to demonstrate statistically significant differences within subgroups.

3.2.8 Progression-free survival

Median PFS was improved by 1.5 months for patients in the D+Gem/Cis arm in comparison to patients in the P+Gem/Cis arm, and the HR demonstrated a statistically significant benefit favouring D+Gem/Cis. However, in the TOPAZ-1 trial CSR (p132), it is stated that '[redacted]. The EAG agrees with the company that the K-M curves for PFS (CS, Figure 7) separate at approximately 4 months (CS, p53), and that

[redacted]

In the TOPAZ-1 trial protocol, it is stated under the heading '9.5.1.2 Progression-free survival' that 'if a lack of proportionality is evident, the variation in treatment effect will be described by presenting piecewise HR calculated over distinct time-periods'. Therefore, as part of the clarification letter to the company, the EAG asked the company to provide results of a piecewise analysis for PFS. The company confirmed (clarification question A1) that a piecewise analysis was conducted for PFS at IA-2. The K-M curves (CS, Figure 7) separate at approximately [redacted], and for this reason, the company calculated piecewise HRs for the period of the trial up to [redacted] follow-up ([redacted]), and the period of the trial after [redacted] follow-up ([redacted]). The piecewise PFS HRs suggest that D+Gem/Cis and P+Gem/Cis are of similar efficacy for the first 4 months, and after this point, patients in the D+Gem/Cis arm experience treatment benefit in comparison to patients in the P+Gem/Cis arm. Once again, the EAG considers the that the piecewise HRs are more informative than the HR provided for the whole trial period.

For PFS, the favourable treatment effect of D+Gem/Cis versus P+Gem/Cis was generally consistent across all subgroups (CS, Appendix E, Figure 4)

3.2.9 Objective response rate

Among patients with measurable disease at baseline, the ORR was higher for patients in the D+Gem/Cis arm than for patients in the P+Gem/Cis arm. The relative effect (odds ratio [OR]) favoured D+Gem/Cis (p=0.011). The statistical testing of ORR was not accounted for in the hierarchical testing procedure, and so the reported p-value is only nominal.

The EAG notes that the number of patients with a confirmed complete response was low in both arms (D+Gem/Cis, n=7, 2.1%; P+Gem/Cis, n=2, 0.6%).

For ORR, the treatment effect of D+Gem/Cis versus P+Gem/Cis was [redacted] (CS, Appendix E, Figure 5).

3.2.10 Duration of response

Full results for DoR are provided in the CS (Table 13). Median DoR was similar between treatment arms. However, the results for the percentage of patients remaining in response at different time points suggest that there may be a subset of patients who achieve longer response times when treated with D+Gem/Cis rather than P+Gem/Cis. In particular, the

percentage of patients remaining in response at 12 months was higher for those treated with D+Gem/Cis than for those treated with P+Gem/Cis (26.1% versus 15.0%, respectively). Overall, responses also occurred earlier for patients treated with D+Gem/Cis compared to patients treated with P+Gem/Cis (median 1.6 months compared to 2.7 months, respectively).

3.2.11 Disease control rate

The overall disease control rates (DCR) were similar across treatment arms (

Table 6). When DCR was examined at different time points (24 weeks, 32 weeks and 48 weeks), DCR was consistently higher for patients in the D+Gem/Cis arm than for patients in the P+Gem/Cis arm (57.5% versus 48.3%, respectively at 24 weeks, 41.9% versus 36.3%, respectively at 32 weeks and 35.2% versus 27.0%, respectively at 48 weeks).

3.2.12 Post-progression treatment

The company reported (CSR, Table 14.1.18) that, at the time of the 6.5 month updated analysis, 52.3% of patients in the TOPAZ-1 trial had received post-progression anti-cancer treatments. Clinical advice to the EAG is that in the NHS, approximately 33% of patients receive second-line treatment, however, patients in the TOPAZ-1 trial are younger and fitter (on average) than patients treated in the NHS.

In response to Clarification Question A3, the company provided a breakdown of the post-progression treatments administered to patients in the TOPAZ-1 trial. Clinical advice to the EAG is that, on progression, most NHS patients are treated with FOLFOX. Re-treatment with Gem/Cis is an option for patients who had a good initial response and did not experience progression within 6 months. Patients with an FGFR2 mutation are treated with pemigatinib in line with TA722.[12] Clinical advice to the EAG is that the post-progression treatments available in the TOPAZ-1 trial are similar to the treatments offered to NHS patients.

3.3 Patient reported outcomes from the TOPAZ-1 trial

HRQoL data from the TOPAZ-1 trial patients were provided in the CS (Section B.2.6.1.8). Data were collected from randomised patients during the TOPAZ-1 trial using the EORTC QLQ-C30[30] and EORTC QLQ-BIL21[31] questionnaires. Patient responses to the EQ-5D-5L[32] and the

EQ-5D Visual Analogue[32] Scale (VAS) were assessed as exploratory endpoints. HRQoL data reported in the CS were derived from IA2 (DCO 11th August 2021).

HRQoL data were also collected using the Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events[33] (PRO-CTCAE) and the Patient Global Impression of Severity[34] (PGIS) questionnaires. The results from patient responses to the PRO-CTCAE and the PGIS questionnaires were assessed as exploratory endpoints and the results are available in the TOPAZ-1 CSR.

HRQoL was assessed at baseline (prior to drug administration on day 1 of the first treatment cycle), on day 1 of each chemotherapy treatment cycle and at each of the 4-weekly monotherapy visits. After 16 cycles of monotherapy, questionnaires were administered at alternate visits (i.e., every 8 weeks). Post-treatment follow-up was conducted monthly.

3.3.1 Summary of EQ-5D data

The TOPAZ-1 trial EQ-5D VAS results are summarised in the CS (CS, Figure 13). The graph shows that the mean absolute VAS scores at baseline were [redacted] in the D+Gem/Cis arm and the Gem/Cis arm [redacted]); the change from baseline was also [redacted] in both treatment arms. The EAG agrees with the company's assessment (CS, p63) that HRQoL [redacted] for patients treated with D+Gem/Cis compared with patients treated with Gem/Cis.

The EQ-5D-5L questionnaire results are not reported in the CS.

3.3.2 Summary of EORTC QLQ-C30 and QLQ- BIL21

The results from the EORTC QLQ-C30 and QLQ-BIL21 questionnaires are reported in sections B.2.6.1.8 to B.2.6.1.10 of the CS. The EAG summary of the results is presented in Table 7.

Table 7 EAG summary of EORTC questionnaire results

Compliance rates	Baseline scores comparable?	Time to deterioration	Improvement rates	Change from baseline
EORTC QLQ-C30				
Compliance rates in both arms were ≥85% at baseline and ≥80% at most time points up to Cycle 16 (CS, p57)	Yes (CS, p57)	No statistically significant difference in HRQoL as measured by the EORTC QLQ-C30 in the D+Gem/Cis arm relative to patients in the P+Gem/Cis arm was observed (CS, p58) A trend favouring the D+Gem/Cis arm was observed for: global health status/QoL, functioning (emotional and social), fatigue, pain, nausea/vomiting, dyspnoea, insomnia, diarrhoea (CS, p58) The curves in the K-M plot for Global Health Status (CS, Fig 9) separate at 7 months in favour of treatment with D+Gem/Cis The timing of the separation of the curves is in keeping with the OS data reported in the TOPAZ-1 trial (CS, p59). EAG comment A trend favouring the P+Cis/Gem arm is apparent for: physical, role, and cognitive functioning, appetite loss, constipation (CS, Fig 8).	No statistically significant difference in HRQoL as measured using the EORTC QLQ-C30 was observed in the D+Gem/Cis arm compared with the P+ Gem/Cis arm (CS, p60). A trend favouring the D+Gem/Cis arm was observed for: Global Health Status/QoL, functioning (physical, emotional, and social) and insomnia (CS, p60 and CS, Fig 11) EAG comment A trend favouring the P+Gem/Cis arm is apparent for: functioning (role and cognitive) fatigue, pain (CS, Fig 11).	Overall, change from baseline analyses (including MMRM) were consistent with no detriment in QoL (CS, p62) Improvements were noted in D+Gem/Cis arm for: global health status/QoL, emotional functioning, pain, and dyspnoea (CS, p62).
EORTC QLQ-BIL21				

Compliance rates in both trial arms were ≥85% at baseline and ≥80% at most time points up to Cycle 16 (CS, p57)	Yes (CS, p57)	No statistically significant difference in QoL as measured using the EORTC QLQ-BIL21 was observed in the D + Gem/Cis treatment group compared with the placebo + Gem/Cis group (CS, p59 and CS, Fig 10) A trend favouring the D+Gem/Cis arm is apparent for abdominal pain, jaundice (single item), pain and anxiety (CS, p59) A trend favouring the P+Gem/Cis arm for weight loss and eating is apparent (EAG comment, CS, Fig 10).	No statistically significant difference in HRQoL as measured by EORTC QLQ-C30 for patients in the D+Gem/Cis arm relative to patients in the P+Gem/Cis arm (CS, p61) A trend in favour of the D+Gem/Cis arm noted for: jaundice and weight loss (single item), eating, jaundice, pain, anxiety, and tiredness (multiple symptoms) [CS, p61, CS, Fig 12]. <u>EAG comment</u> A trend in favour of the D+Gem/Cis arm is apparent for abdominal pain and pruritus.	Overall, change from baseline analyses (including MMRM) were consistent with no detriment in QoL (CS, p62) (CS, p62) There were improvements reported in the D+Gem/Cis arm for pruritus, weight loss, jaundice and pain (CS, p62).

CS=company submission; D=durvalumab; EORTC=European Organisation for Research and Treatment of Cancer; Gem/Cis=gemcitabine+cisplatin; HRQoL=health-related quality of life; K-M=Kaplan-Meier; MMRM=mixed models for repeated measures; P=placebo

3.4 EAG conclusions: HRQoL

The company states (CS, p74) that the EORTC QLQ-C30 and EORTC QLQ-BIL21 questionnaire results demonstrate that the addition of durvalumab to Gem/Cis did not result in any detriment to patient HRQoL. The EAG agrees that HRQoL for patients treated with D+Gem/Cis appears to be comparable with the HRQoL reported by patients treated with P+Gem/Cis.

3.5 Safety and tolerability results from the TOPAZ-1 trial

The safety and tolerability data presented in the CS were derived from the 6.5 month updated TOPAZ-1 trial results (DCO 25th Feb 2022). The safety analysis set (SAS) is defined in the CS (Table 8) and includes 338 patients from the D+Gem/Cis arm and 342 patients from the P+Gem/Cis arm of the TOPAZ-1 trial (CS, p65).

The AE data presented in the CS are:

- duration of treatment with durvalumab or placebo (CS, Table 14)
- duration of treatment with gemcitabine or cisplatin (CS, Table 15)
- overview of AEs (CS, Table 16)
- most common AEs occurring in ≥10% of patients (CS, Table 17)
- grade 3 (G3) or Grade 4 (G4) AEs occurring in ≥5% of patients (CS, Table 18)

3.5.1 Overview of adverse events

The mean duration of treatment (CS, Table 14) was longer in the D+Gem/Cis arm than in the P+Gem/Cis arm ([redacted] months versus [redacted] months). The EAG agrees with the company (CS, p66) that the difference in treatment duration between the trial arms can be attributed to treatment with durvalumab as the duration of treatment with gemcitabine and cisplatin (CS, Table 15) was similar between trial arms and was not longer than 5 months in either arm.

The overview of AEs (CS, Table 16) shows that most patients experienced any category of AE (D+Gem/Cis: 99.4%; P+Gem/Cis: 98.8%) and the proportions of patients who reported an AE related to study treatment were similar (D+Gem/Cis: 92.9%; P+Gem/Cis: 90.1%). Except for immune-related AEs (imAE), similar proportions of patients reported events across all categories. [redacted] deaths in the D+Gem/Cis arm and [redacted] death in the P+Gem/Cis arm were considered as possibly related to study treatment. Similar proportions of patients in the D/Cis+Gem and P+Cis/Gem arm discontinued treatment due to AEs (12.7% versus 15.2%, respectively).

Patients treated with durvalumab reported more imAE than patients in the placebo arm. The company highlights (CS, p67) that most imAEs were of G1 or G2 and, that similar proportions

of patients experienced G3 or G4 events (D+Gem/Cis: [redacted]; P+Gem/Cis: [redacted]%). The company also highlights (CS, p67) that [redacted] imAEs led to deaths.

3.5.2 Adverse events

Common adverse events

The most common AEs reported in ≥10% of patients (CS, Table 17) in the D+Gem/Cis arm were anaemia ([redacted]), nausea ([redacted]), constipation ([redacted]) and neutropenia ([redacted]). The most common AEs reported in the P+Gem/Cis arm were anaemia ([redacted]), nausea ([redacted]), neutrophil count decrease ([redacted]) and neutropenia ([redacted]). The company highlights (CS, p67) that [redacted] was the only AE reported with a [redacted] between trial arms.

Grade 3 and Grade 4 adverse events

The data presented (CS, Table 18) show that similar proportions of patients in the D+Gem/Cis and P+Gem/Cis arms experienced G3 and G4 AEs (74% and 75.1%, respectively). The most common events in both the D+Gem/Cis arm and in the P+Gem/Cis arm were [redacted] ([redacted] and [redacted]), [redacted] ([redacted] and [redacted]) and [redacted] ([redacted] and [redacted]). The company highlights (CS, p71) that G3 and G4 imAEs were reported in [redacted] of patients in either arm of the TOPAZ-1 trial.

3.5.3 EAG conclusions: safety and tolerability

The company states (CS, p72) that, consistent with the known safety profiles of durvalumab, gemcitabine and cisplatin, treatment with D+Gem/Cis has a manageable toxicity profile, with no new safety concerns identified. Clinical advice to the EAG is that no unexpected safety concerns associated with the use of D+Gem/Cis arose during the TOPAZ-1 trial.

3.6 EAG clinical effectiveness conclusions

The company has presented evidence from the TOPAZ-1 trial, a mature, high quality RCT. In line with the final scope issued by NICE, this trial compared the clinical effectiveness of D+Gem/Cis versus P+Gem/Cis. P+Gem/Cis is SoC in the NHS for patients with unresectable advanced or metastatic BTC (including patients with recurrent disease after treatment with curative intent). The EAG is satisfied that the methods used to analyse TOPAZ-1 trial results were appropriate. Trial results demonstrated a statistically significant OS benefit for patients treated with D+Gem/Cis compared to patients treated with P+Gem/Cis. There were no differences in HRQoL between trial arms. Further, D+Gem/Cis was shown to have a manageable toxicity profile and no new safety concerns were identified.

4 COST EFFECTIVENESS EVIDENCE

This section provides a structured critique of the economic evidence submitted by the company in support of the use of D+Gem/Cis as an option for treating unresectable or advanced BTC. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company has provided an electronic copy of their economic model, which was developed in Microsoft Excel.

4.1 Company review of published cost effectiveness evidence

The company undertook a systematic review to identify published cost effectiveness models that generated results for patients with locally advanced, unresectable or metastatic BTC that could potentially inform the development of an economic model.

The database searches were designed to retrieve articles published between 2011 and 2022. The company also searched conference proceedings (2019-2022), the NICE website and Institute for Clinical and Economic Review (2010-2022), and bibliographies of recent systematic reviews and HTA guidance. Full details of the company's systematic review are provided in the CS, Appendix G. The company's search identified five non-UK studies;[35-39] none of the studies included D+Gem/Cis as a treatment option.

4.1.1 EAG critique of the company's literature review

A summary of the EAG's critique of the company's literature review methods is provided in Table 8.

Table 8 EAG appraisal of systematic review methods (cost effectiveness)

Review process	EAG response
Was the review question clearly defined in terms of population, interventions, comparators, outcomes and study designs?	Yes
Were appropriate sources searched?	Yes
Was the timespan of the searches appropriate?	Yes
Were appropriate search terms used?	Yes
Were the eligibility criteria appropriate to the decision problem?	Yes
Was study selection applied by two or more reviewers independently?	Yes
Were data extracted by two or more reviewers independently?	Data were extracted by a single reviewer and checked by a second reviewer
Were appropriate criteria used to assess the quality of the primary studies?	Yes
Was the quality assessment conducted by two or more reviewers independently?	Undertaken by one reviewer and checked by a second reviewer
Were any relevant studies identified?	Five unique cost effectiveness analyses were identified; however, none of the studies included durvalumab as a treatment option and none were carried out in the UK

EAG=External Assessment Group
Source: EAG in-house checklist

4.1.2 EAG conclusions

The EAG has no concerns about the methods used by the company to identify cost effectiveness studies.

4.2 EAG summary and critique of the company's submitted economic evaluation

4.2.1 NICE Reference Case checklist and Drummond checklist

Table 9 NICE Reference Case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	The scope developed by NICE	Yes
Comparator(s)	As listed in the scope developed by NICE	Yes
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Yes
Perspective on costs	NHS and PSS	Yes
Type of economic evaluation	Cost utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Yes
Synthesis of evidence on health effects	Based on systematic review	NA. Direct evidence was available from the TOPAZ-1 trial
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults	Yes
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	Yes
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	Yes
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Yes

EQ-5D=EuroQol-5 Dimension; PSS=Personal Social Services; QALY=quality adjusted life year
Source: EAG assessment of Reference Case using NICE checklist

Table 10 Critical appraisal checklist for the economic analysis completed by the EAG

Question	Critical appraisal	EAG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	
Were all the important and relevant costs and consequences for each alternative identified?	Yes	
Were costs and consequences measured accurately in appropriate physical units?	Mostly	The EAG removed the AE-related QALY decrement to avoid double counting
Were the cost and consequences valued credibly?	Mostly	The EAG corrected the cost of treating neutropenia and corrected IV administration costs
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	
Did the presentation and discussion of study results include all issues of concern to users?	Yes	

AE=adverse event; EAG=External Assessment Group; IV=intravenous; QALY=quality adjusted life year
Source: Drummond and Jefferson (1996)[40]

4.3 Model structure

The company developed a partitioned survival model. This structure was used to inform the previous NICE BTC appraisal (TA722[12]).

The three mutually exclusive health states modelled were progression-free (PF), progressed disease (PD) and death. All patients enter the model in the PF health state and are then at risk of moving to the PD or death health states. Patients in the PD health state are only at risk of moving to the death health state. Patients do not move out of the death health state. An illustration of the company model structure is shown in Figure 2.

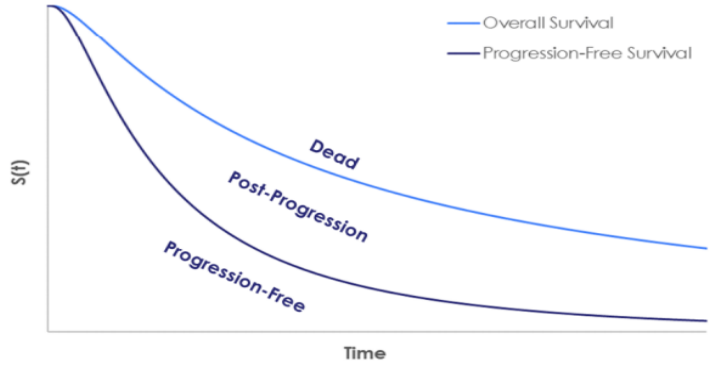


Figure 2 Company model schematic

Source: CS, Figure 14

4.3.1 Population

The modelled population is adults with previously untreated, unresectable, locally advanced or metastatic BTC, including people with recurrent disease after treatment with curative intent. Company model baseline characteristics reflect the TOPAZ-1 trial population (Table 11).

Table 11 Model baseline population characteristics (TOPAZ-1 trial, FAS population)

Baseline characteristic	Value
Mean age	[redacted]
Mean weight	[redacted]
Proportion female	49.6%
Body surface area	[redacted]

FAS=full analysis set
Source: CS, Section B.3.3.1 and CS, Table 21

4.3.2 Interventions and comparators

The modelled intervention and comparator reflect the TOPAZ-1 trial, i.e., D+Gem/Cis and P+Gem/Cis respectively. First-line drug doses are shown in Table 12. Following completion of eight cycles of Gem/Cis, patients receive durvalumab (1,500mg) monotherapy every 4 weeks until disease progression or discontinuation criteria are met.

Table 12 Model first-line drug doses

Trial first-line drugs	Dose
Durvalumab	1,500mg by intravenous infusion (on Day 1 of a 3-weekly cycle)
Gemcitabine*	1,000mg on Days 1 and 8 of a 3-weekly cycle for up to eight cycles
Cisplatin*	25mg on Days 1 and 8 of a 3-weekly cycle for up to eight cycles

*Intervention and comparator doses
Source: CS, Section B.3.3.4

4.3.3 Perspective, time horizon and discounting

The model perspective was reported to be that of the NHS and Personal Social Services (PSS) and the cycle length was 1 week. The time horizon was 20 years (<1% of population alive at this time), and costs and outcomes were discounted at a rate of 3.5% per annum. A half-cycle correction was applied to all costs and outcomes, except first-line drug and administration costs during the first cycle.

4.4 Treatment effectiveness and extrapolation

In accordance with the guidance outlined in NICE DSU TSD 14[41] and TSD 21[42], the company firstly assessed whether the PH assumption held for OS, PFS and time to treatment discontinuation (TTD) data from the TOPAZ-1 trial, using a log-cumulative hazard plot and the Schoenfeld residuals test. Alongside standard parametric distributions, more flexible Royston-Parmer spline models were considered due to their ability to accommodate hazard functions with complex shapes. Curve selection was carried out by:

- considering Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC)
- visual inspection of fit to K-M data
- assessing plausibility of hazards within and beyond the trial period
- clinical opinion
- comparison with real world evidence (RWE) where available.

4.4.1 Overall survival

The DCO February 2022 TOPAZ-1 trial OS data are mature (D+Gem/Cis: 73%; P+Gem/Cis: 81%). Results from company statistical tests indicated that the PH assumption was violated and therefore separate parametric curves were fitted to TOPAZ-1 trial D+Gem/Cis and P+Gem/Cis data. The base case parametric curves chosen by the company are shown in Table 13.

Table 13 Parametric curves fitted to TOPAZ-1 overall survival data

Model arms	Base case parametric curves
Durvalumab+Gem/Cis	Spline 1 knot, scale=odds
Gem/Cis	Spline 1 knot, scale=normal

Gem/Cis=gemcitabine+cisplatin
Source: CS, Section B.3.4.2.2

4.4.2 Progression-free survival

The DCO August 2021 PFS data are mature (D+Gem/Cis: 81%; P+Gem/Cis: 86%). Results from company statistical tests indicated that the PH assumption was violated and therefore separate parametric curves were fitted to TOPAZ-1 trial D+Gem/Cis and P+Gem/Cis data. The base case parametric curves chosen by the company are shown in Table 14.

Table 14 Parametric curves fitted to TOPAZ-1 progression-free survival data

Model arms	Base case parametric curves
Durvalumab+Gem/Cis	Spline 1 knot, scale=odds
Gem/Cis	Spline 1 knot, scale=normal

Gem/Cis=gemcitabine+cisplatin
Source: CS, Section B.3.4.2.3

4.5 Adverse events

The company included ≥Grade 3 AEs with an incidence of >5% in either treatment arm of the TOPAZ-1 trial in the model (DCO February 2022). These AEs, which were similar between treatment arms, were included as one-off events that occurred during the first model cycle.

4.6 Health-related quality of life

EQ-5D-5L data were collected during the TOPAZ-1 trial. These data were collected at baseline and then every 3 weeks for the first eight treatment cycles and then every 4 weeks until progression or death. After Cycle 16, assessments were carried out every other cycle. Utility values were derived from 633 patients who provided responses to all five domains of the EQ-5D-5L questionnaires and had at least one follow-up visit. Responses were 'cross walked' to produced EQ-5D-3L utility values using the Hernández Alava algorithm.[43] Mixed models for repeated measures (MMRM) were used to estimate the statistical relationship between utilities and health state. The utility values used in the company model are presented in Table 15.

Table 15 Model utility values (derived from post-hoc analyses of TOPAZ-1 trial data)

Health state	Number of patients (observations)	Mean (95% CI)
Progression-free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]

CI=confidence interval
Source: CS, Section B.3.5.2

The company also applied Grade 3 and Grade 4 AE-related QALY decrements. These disutilities were applied during the first cycle only. The values used by the company were either assumptions or values used in the TA722[12] model. Details are provided in CS, Table 37.

In addition, the company applied age-related utility decrements to account for the natural decline in HRQoL that is associated with age. These values were calculated using the Ara and Brazier[44] Ordinary Least Squares regression model.

4.6.1 Resources and costs

4.6.2 Drug costs

Drug acquisition costs

Modelled dosing schedules were those used in the TOPAZ-1 trial (Table 12). Durvalumab is available to the NHS at a discounted confidential PAS price. In the base case, it was assumed that there was no drug wastage. Costs for gemcitabine and cisplatin were sourced from the online pharmaceutical electronic market information tool (eMIT).[45] Unit costs are presented in Table 16.

Table 16 Unit drug costs

Drug	Strength (mg) per vial	Price per mg	Source
Durvalumab	120mg	[redacted]	Confidential PAS price
	500mg	[redacted]	Confidential PAS price
Gemcitabine	1,000mg	£0.01	eMIT[45] June 2022
Cisplatin	100mg	£0.16	eMIT[45] June 2022

eMIT=electronic Market Information Tool; PAS=Patient Access Scheme
Source: CS, Table 39

Relative dose intensity (RDI) multipliers, derived from TOPAZ-1 trial data, were applied (Table 17).

Table 17 Relative dose intensity multipliers

Regimen	Drug	First dose	Relative dose intensity
Durvalumab+Gem/Cis	Durvalumab	1500mg	[redacted]
	Gemcitabine	1000mg/m^2	[redacted]
	Cisplatin	25mg/m^2	[redacted]
Durvalumab+Gem/Cis after eight cycles	Durvalumab	1500mg	[redacted]
Gem/Cis for 1-8 cycles	Gemcitabine	1000mg/m^2	[redacted]
	Cisplatin	25mg/m^2	[redacted]

Source: CS, Table 41

Drug administration costs

Durvalumab, gemcitabine and cisplatin are administered via IV infusion. The cost of administering a drug via IV infusion (£281.11) was sourced from National Schedule of NHS costs 2021/22 (SB12Z Deliver simple parenteral chemotherapy).

Treatment duration

The company used PFS as a proxy for treatment duration in the base case. The company considered that it was not appropriate to model eligibility for subsequent treatment based on TTD data as such an approach does not reflect how disease progression is assessed in UK clinical practice, i.e., by investigator, and is not reflective of the marketing authorisation.

Subsequent treatment costs

Patients were modelled to be eligible for subsequent treatment on disease progression. The proportion of patients initiating subsequent treatment was derived from the TOPAZ-1 trial (50.70% for patients receiving D+Gem/Cis and 53.80% for patients receiving Gem/Cis). Relevant NHS subsequent treatments were identified by consulting five clinical experts and costs were estimated based the proportion of patients who would receive each drug (based on clinical opinion) and mean duration of treatment (Table 18). The distribution of subsequent treatments was assumed equivalent between D+Gem/Cis and Gem/Cis.

Table 18 Subsequent treatments

Treatment	Proportion of patients		Duration in months		Total acquisition cost per cycle
	Proportion	Source	Months	Source	
FOLFOX	75%	Clinical expert opinion	6	ABC-06 trial[46]	£112.67
Gem/Cis retreatment	10%	Clinical expert opinion	6	ABC-06 trial[46]	£43.06
Pemigatinib	5%	Clinical expert opinion	7.20	FIGHT-202 trial[12]	£7,159
Clinical trials*	10%	Clinical expert opinion	N/A	N/A	-

*No cost associated with clinical trials therefore duration on treatment (months) is not included in the model
FOLFOX=folinic acid, fluorouracil, oxaliplatin; Gem/Cis=gemcitabine1500mg and cisplatin 25mg
Source: CS, Table 46 and Table 47

Subsequent treatment costs included drug acquisition and administration costs only, with costs applied per weekly model cycle. Consistent with first-line treatment costs, no wastage was assumed. Dosing schedules were sourced from the relevant clinical trials outlined in Table 18 (CS, Table 47). Drug prices for all subsequent treatments were sourced from the eMIT[45] except pemigatinib whose price was sourced from the British National Formulary (BNF).[47] Following second-line therapy, patients were assumed to receive best supportive care, which was not associated with any treatment-related cost.

4.6.3 Health state unit costs and resource use

Resource use estimates were derived from ESMO guidelines[48], NICE TA722[12], and clinical opinion (five medical oncologists practising in the UK)[49]. Costs were sourced from NHS Cost Collection 2020/2021[50] and the 2021 Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care report[51]. Three categories of resource use were included in the model: CT scans, blood tests and outpatient oncology visits. The health state resource use and costs used in the company model are presented in Table 19.

Table 19 Company model health state resources and costs

Resource	Progression free			Progressed disease		
	Patients per month	Frequency per month	Cost per month†	Patients per month	Frequency per month	Cost per month†
CT scan	100%	0.33	£47.43	100%	0.33	£47.43
Blood tests	100%	1.44	£5.23	50%	1.44	£2.61
Oncologist/clinical examination (outpatient oncology visit)	100%	1.44	£332.87	50%	1.44	£166.44
Total cost	£385.53			£216.48		

†Monthly values were elicited from clinicians, a weekly cost is calculated and applied in the model by dividing the monthly values by 4.358
CT=computed tomography
Source: CS, Table 44

4.6.4 Adverse event costs

Adverse event costs were sourced from NHS Cost Collection 2020/21[50] or were assumptions based on the similarity of the treatment of that AE with other AEs that was associated with an NHS cost code. AE costs were applied as one-off costs during the first model cycle. Costs were estimated by multiplying the percentage of patients in the TOPAZ-1 trial who experienced an AE by the cost associated with that AE. The AE costs used in the company model are presented in CS, Table 45.

4.6.5 End-of-life costs

In line with TA722,[12] end-of-life costs were based on Round et al[52] (2015) estimates for patients with colorectal cancer. Costs were inflated to 2021 prices using the PSSRU inflation indices[51] and applied as a one-off cost at the point of death. The total estimated end-of-life (health and social care components) cost used in the company model was £6,977.30.

4.6.6 Severity modifier

Expected general population QALYs were estimated using Ara and Brazier[44] population norms (start age [redacted] years; 49.6% female) and Office for National Statistics life tables.[53] These QALYs were discounted at a rate of 3.5% per annum. Results from the company QALY shortfall calculations are presented in Table 20.

Table 20 Company QALY shortfall calculation results

Outcome	Total QALYs	Shortfall	
		Absolute	Proportional
Expected total for the general population	11.13		
Disease specific	0.81	10.32	0.928
QALY multiplier		1.2	1.2
WTP threshold		£36,000	

CS=company submission; QALY=quality adjusted life year; WTP=willingness to pay
Source: CS, Section B.3.7

5 COST EFFECTIVENESS RESULTS

The company base case deterministic results are presented in Table 21. These results were generated using the PAS price for durvalumab, BNF price for pemigatinib and eMIT prices for all other drugs. The EAG is aware that pemigatinib is available to the NHS at a confidential PAS price.

Table 21 Company deterministic base case cost effectiveness results (durvalumab PAS price)

Technologies	Total		Incremental		ICER (£/QALY, x1.2 modifier)
	Costs	QALYs	Costs	QALYs (x1.2 modifier)	
D+Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gem/Cis	£19,417	0.81			

CS=company submission; D=durvalumab; Gem/Cis=gemcitabine+cisplatin; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: CS, Table 56

The company probabilistic base cost effectiveness results (10,000 model iterations) are presented in Table 22. These results are very similar to the company deterministic results.

Table 22 Company probabilistic base case cost effectiveness results (durvalumab PAS price)

Technologies	Total		Incremental		ICER (£/QALY, x1.2 modifier)
	Costs	QALYs	Costs	QALYs (x1.2 modifier)	
D+Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gem/Cis	£19,352	0.81			

CS=company submission; D=durvalumab; Gem/Cis=gemcitabine+cisplatin; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: CS, Table 54

5.1.1 Deterministic sensitivity analyses

The company carried out a range of deterministic sensitivity analyses. Results from these analyses showed that the key cost effectiveness drivers were the utility value for the PD health state, discount rate applied to outcomes and the proportions of patients receiving subsequent treatment with FOLFOX following previous treatment with Gem/Cis (Table 23).

Table 23 Company key deterministic sensitivity analysis results (durvalumab PAS price)

Input name	Base case input	Lower bound input	Upper bound input	Lower bound ICER/QALY (x1.2 modifier)	Change with lower bound (%)	Upper bound ICER/QALY (x1.2 modifier)	Change with upper bound (%)
Utility: post-progression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate: outcomes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage receiving FOLFOX second-line after prior treatment with Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage receiving FOLFOX second-line after prior treatment with D+Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

D=durvalumab; ICER=incremental cost effectiveness ratio; FOLFOX=folinic acid, fluorouracil, oxaliplatin; Gem/Cis= gemcitabine+cisplatin; PAS=Patient Access Scheme; QALY=quality adjusted life year
Source: Company model

5.1.2 Probabilistic scenario analyses

The company carried out nine probabilistic scenario analyses (CS, Table 58), exploring the effect of changing seven different model input parameters:

- D+Gem/Cis OS distribution (log-logistic; spline 1 knot, normal)
- Gem/Cis OS distribution (spline 2 knot, normal)
- D+Gem/Cis PFS distribution (spline 2 knot, hazard)
- Gem/Cis PFS distribution (spline 3 knot, hazard)
- Costs (TTD)
- utility pre-treatment discontinuation (0.798 [0.788 to 0.808])
- utility post-treatment discontinuation (0.680 [0.642 to 0.719])
- vial wastage (100%).

The resulting ICERs per QALY gained ranged from [redacted] (D+Gem/Cis PFS distribution, spline 2 knot hazard) to [redacted] (D+Gem/Cis OS distribution, spline 1 knot normal) (using x1.2 modifier).

5.1.3 Subgroup analyses

No subgroup analyses were carried out.

5.2 Validation

The company sought clinical validation of modelling assumptions and inputs from five oncologists practising in the UK. In addition, two external health economists (not involved in model development) reviewed the model to identify any coding errors or inconsistencies. They also assessed the plausibility of inputs and outputs and carried out a range of extreme value and logic tests.

6 EAG CRITIQUE OF COMPANY ECONOMIC MODEL

6.1 Introduction

The EAG is satisfied that the company model algorithms are accurate and that the parameter values used in the company's cost effectiveness model match those presented in the CS. The EAG considers that the company's use of a partitioned survival model structure and the modelled pathway, including the choice of comparator, are appropriate.

A summary of the modelling issues considered by the EAG is shown in Table 24.

Table 24 Summary of EAG company model critique

Aspect considered	EAG comment	Section of EAG report
Model structure	• The model structure (partitioned survival model approach) is appropriate for addressing the decision problem	6.1
Population	• The company modelled population largely matches the population defined in the NICE scope. However, patients in the TOPAZ-1 trial are younger and fitter than would likely be treated in the NHS	Table 2
Comparators	• The comparator included in the model represents SoC for NHS patients	Table 2
Modelling OS and PFS	• The methods and evidence used by the company to assess the goodness of fit of distributions to model OS and PFS were appropriate. In addition to the distributions used in the company base case, the EAG identified other distributions (also considered by the company) that were as statistically and clinically plausible • The EAG carried out an analysis using the Gamma (rather than the spline 1 knot) distribution to model OS for patients treated with D+Gem/Cis • The EAG also carried out analyses using a spline 3 knot hazard (D+Gem/Cis) distribution and a spline 3 knot odds (Gem/Cis) distribution to model PFS	6.2, 6.3
TTD	• D+Gem/Cis treatment costs should have been estimated using a parametric distribution fitted to TTD data rather than by using a parametric distribution fitted to PFS data • The spline 3 knot hazard distribution was a better fit to the TOPAZ-1 trial TTD K-M data than the spline 1 knot odds distribution (used in a company scenario analysis) to model TTD for patients treated with D+Gem/Cis • The spline 3 knot hazard distribution (company's choice) and the spline 2 knot odds (EAG choice) distributions are statistically indistinguishable. However, the spline 2 knot odds distribution generates a TTD rate that more closely matches the TOPAZ-1 trial 6-month P+Gem/Cis TTD rate than the spline 3 knot hazard distribution	6.4
Treatment costs	• The RDI values and their implementation within the model were appropriate. However, there were minor technical errors in calculations of costs of treatments that were dosed based on BSA (effect not considered in EAG revisions due limited impact on cost effectiveness results)	NA

Resource use	• The administration cost relating to the second dose of Gem/Cis and the subsequent FOLFOX* treatment cost were incorrect	NA
Subsequent treatments	• The subsequent treatments included in the model and the proportions of patients receiving each treatment were appropriate	NA
Utility values	• The utility values used in the company base case conform to the NICE Reference Case[13] • The PFS utility value used in the company base case is close to the UK general population norm; this seems optimistic given the HRQoL burden experienced by patients	6.5
Adverse events	• The AE-related QALY decrements should not have been applied as the health impact of AEs is likely to have been captured by patients in their EQ-5D responses*	NA
Company severity modifier	• The methods used to estimate the company severity modifier were appropriate • The EAG re-calculated the severity modifier based on EAG preferred scenario results; the modifier remained at x1.2	6.6.1
PSA	• The deterministic model is set up so that patients only receive one line of subsequent treatment. When running the PSA, the proportions of patients receiving each subsequent treatment do not always add up to 100% (effect not considered in EAG revisions due limited impact on cost effectiveness results)	NA

*Errors were corrected in revision R1
AE=adverse event; EAG=External Assessment Group; NA=not applicable; OS=overall survival; PSA=probabilistic sensitivity analysis; PFS=progression-free survival; RDI=relative dose intensity; SoC=standard of care; TTD=time to discontinuation

6.2 Overall survival

The company followed NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14[41] guidance when assessing the goodness of fit of standard parametric distributions and flexible spline based models (up to three knots) to TOPAZ-1 trial OS K-M data.

The company and the EAG agree that there are several distributions that, statistically, fit the TOPAZ-1 trial data equally well (i.e., AICs are all within 4 points of the lowest AIC) and are clinically plausible (expert advice and RWE [where available]). To illustrate the impact of distribution choice on cost effectiveness results, see Appendix 8.1, Table 33.

6.2.1 Overall survival: D+Gem/Cis

In the company base case, the spline 1 knot odds distribution was used to model OS for patients treated with D+Gem/Cis. The company clinical experts found it challenging to comment on projected 5-year OS rates due to their lack of experience of treating patients with D+Gem/Cis (CS, p100); nevertheless, three of the five clinical experts consulted by the company agreed that the spline 1 knot odds distribution provided the most clinically plausible survival rate at 3 years (AZ data on file, p6).

The EAG considers that the methods used by the company to select a distribution to model OS for patients treated with D+Gem/Cis were appropriate; however, other distributions may be equally statistically and clinically plausible. Specifically, the EAG considers that the Gamma distribution is as plausible as the spline 1 knot odds distribution; it has comparable AIC/BIC scores (ranking first on both) and generates a 2-year survival rate that is close to the TOPAZ-1 trial 2-year survival rate (Table 25). Furthermore, of the five clinical experts that were consulted, one considered that the Gamma distribution provided the best overall fit to TOPAZ-1 trial OS K-M data and another considered that the Gamma distribution may provide plausible survival rates at 5 years (AZ data on file, p6). The EAG therefore considers that the Gamma distribution is as plausible as the spline 1 knot odds distribution.

Table 25 Comparison of statistical fit and estimated survival for selected distributions (D+Gem/Cis)

Distribution		AIC (rank)	BIC (rank)	Overall survival rates		
				2-year	3-year	5-year
Company base case	Spline 1 knot odds	1914.00 (2)	1925.00 (4)	23.60%	12.37%	4.99%
A clinically and statistically plausible alternative	Gamma	1913.54 (1)	1921.21 (1)	23.20%	9.37%	1.40%
TOPAZ-1				23.65%	-	-

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; D=durvalumab; Gem/Cis=gemcitabine+cisplatin
Source: CS, Table 23 and Table 24

6.2.2 Overall survival: Gem/Cis

In the base case, the company used a spline 1 knot normal distribution to model OS for patients treated with Gem/Cis; this distribution ranked first on AIC and third on BIC scores and resulted in a survival rate of 3.78% at 3 years. This level of survival is comparable to 3-year survival (4%) reported by McNamara et al[54] in a prospective study of first-line advanced BTC. Three of the five clinical experts consulted by the company agreed that the spline 1 knot normal distribution provided the most clinically plausible 3-year survival rate for patients treated with Gem/Cis (AZ data on file, p6). Use of the spline 1 knot normal distribution resulted in a survival rate of 0.52% at 5 years (Table 26). This is lower than the survival rate reported at 4 years (2%) by McNamara et al,[54] and higher than the 5-year survival rate (0.1%) estimated by clinical advisors during a NICE appraisal of a second-line treatment for advanced cholangiocarcinoma (TA722[12]). Clinical experts consulted by the company considered that the 5-year survival rate generated using the spline 1 knot normal distribution was plausible as survival in the first-line setting is likely to be higher than survival in the second-line setting (CS, p110).

Given the clinical advice to the company and the real world evidence provided by McNamara et al,[54] the company's use of the spline 1 knot normal distribution to model OS for patients treated with Gem/Cis was appropriate.

Table 26 Comparison of statistical fit and estimated survival rates for selected distributions (Gem/Cis)

Distribution		AIC (rank)	BIC (rank)	Overall survival rate			
				2-year	3-year	4-year	5-year
Company base case	Spline 1 knot normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOPAZ-1				[redacted]	-	-	-
McNamara et al[54]				13%	4%	2%	-
TA722[12] clinical experts				-	-	-	0.1%

EAG=External Assessment Group; AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; Gem/Cis=gemcitabine+cisplatin
Source: CS, Table 25 and Table 26

6.3 Progression-free survival

The company followed NICE DSU TSD 14[41] guidance when assessing the goodness of fit of standard parametric distributions and flexible spline based models (up to three knots) to TOPAZ-1 trial PFS K-M data. When assessing parametric distributions based on statistical fit to trial data, a difference of <4 compared to the distribution with the lowest AIC means that the distributions all represent a good relative statistical fit to the data.

6.3.1 Progression-free survival: D+Gem/Cis

In the company base case, the spline 1 knot odds distribution (AIC rank: 5; BIC rank 4) was used to model PFS for patients treated with D+Gem/Cis. This distribution generates a 2-year PFS rate of [redacted]%. The company selected this distribution as three of the five clinical experts consulted supported this choice (AZ data on file, p7). The EAG highlights that the distribution used by the company is 24.69 points higher than the highest ranked AIC distribution and so is a relatively poor statistical fit compared to other distributions considered by the company.

The company reported that clinicians found it challenging to comment on the clinical plausibility of PFS extrapolations due to their lack of experience of treating patients with D+Gem/Cis (AZ data on file, p7). Given this uncertainty, the EAG considers that it would have been more appropriate to model PFS using distributions that provided a better statistical fit to the TOPAZ-1 trial PFS K-M data. The spline 3 knot hazard distribution was associated with the lowest AIC/BIC scores and matched TOPAZ-1 trial PFS data most closely at 6 and 12-months (Table 27). Compared with TOPAZ-1 trial data, the EAG considers that all parametric models considered by the company overestimate the proportion of patients who are progression-free at 12-months (magnitude of error ranging from 2.22% points to 9.03% points)

(CS, Table 29); the spline 3 knot hazard distribution generated the lowest overestimate. Thus, use of the spline 3 knot hazard distribution to model PFS for patients treated with D+Gem/Cis is the EAG's preferred approach.

Table 27 Comparison of statistical fit and estimated PFS for selected distributions (D+Gem/Cis)

Distribution		AIC (rank)	BIC (rank)	Progression-free survival rate		
				6-month	12-month	24-month
Company base case	Spline 1 knot odds	1704.05 (5)	1715.55 (4)	[redacted]	[redacted]	[redacted]
EAG alternative	Spline 3 knot hazard	1679.09 (1)	1698.25 (1)	[redacted]	[redacted]	[redacted]
TOPAZ-1				[redacted]	[redacted]	[redacted]

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; D=durvalumab; EAG=External Assessment Group; Gem/Cis=gemcitabine+cisplatin
Source: CS, Table 28 and Table 29

6.3.2 Progression-free survival: Gem/Cis

Despite not having the best statistical fit (AIC rank: 7; BIC rank 7), the company used the spline 1 knot normal distribution to model PFS for patients treated with Gem/Cis. The company considered that this distribution generated a clinically plausible 24-month PFS rate (CS, p129) and, relative to higher AIC-ranked spline distributions, a more accurate 6-month PFS rate (Table 28). The EAG highlights that the distribution used by the company is 13.22 points higher than the highest ranked AIC distribution.

Compared with TOPAZ-1 trial data, all the parametric distribution 12-month PFS rates were overestimates (magnitude of error ranging from 2.40% points to 10.80% points) (CS, Table 31). The EAG considers that the spline 3 knot odds distribution should have been chosen to model PFS for patients treated with Gem/Cis as, statistically, it is the best fit to TOPAZ-1 trial data (AIC rank: 1; BIC rank 1), generates PFS estimates that most closely matched TOPAZ-1 trial data at 12 months (Table 28) and produces a 24-month PFS rate that is consistent with the opinions of three clinical experts (AZ data on file, p6).

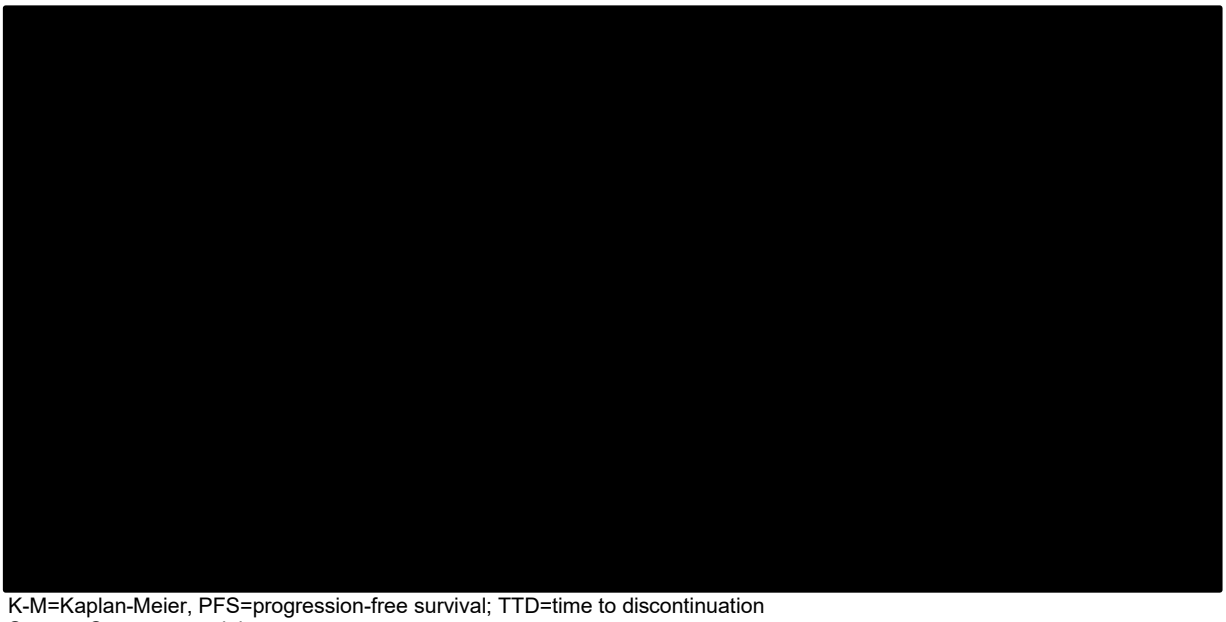
Table 28 Comparison of statistical fit and estimated PFS for selected distributions (Gem/Cis)

Distribution		AIC (rank)	BIC (rank)	Progression-free survival rate		
				6-month	12-month	24-month
Company base case	Spline 1 knot normal	1650.59 (7)	1662.11 (7)	46.79%	10.62%	0.58%
EAG preferred	Spline 3 knot odds	1637.37 (1)	1656.57 (1)	50.90%	9.00%	0.80%
TOPAZ-1				47.20%	6.60%	-

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; EAG=External Assessment Group; Gem/Cis=gemcitabine+cisplatin
Source: CS, Table 30 and Table 31

6.4 Treatment duration

Company clinical experts advised (CS, Appendix O, p139) that in the UK, patients with BTC are typically prescribed Gem/Cis for a maximum duration of 6 months (Q3W for up to 8 cycles). In the company base case, PFS was used as a proxy for TTD. PFS is a reasonable proxy for TTD for patients treated with Gem/Cis as TOPAZ-1 trial PFS and TTD K-M data closely match up to 6 months; however, PFS is not a good proxy for TTD for patients receiving D+Gem/Cis as TTD is always higher than PFS (Figure 3). Use of PFS to model treatment duration will therefore underestimate the true costs of D+Gem/Cis.



K-M=Kaplan-Meier, PFS=progression-free survival; TTD=time to discontinuation
Source: Company model

Figure 3 TOPAZ-1 trial D+Gem/Cis: PFS and TTD K-M data

The company model is structured so that different parametric distributions may be used to model TTD. The EAG considers that when assessing parametric distributions based on statistical fit to trial data, a difference of <4 compared to the distribution with the lowest AIC means that the distributions all represent a good relative statistical fit to the data.

The EAG notes that, in the CS, the company states that independent parametric models fitted to TOPAZ-1 trial TTD data were used to cost treatment in the base case (Table 33, p133). For information, this is an error; in the company base case parametric models fitted to PFS were used to cost treatment.

6.4.1 Treatment duration: D+Gem/Cis

In the company scenario analysis that used TTD to cost time on treatment, the company selected the spline 1 knot odds distribution to model TTD for patients treated with D+Gem/Cis. This model was a good statistical fit to TOPAZ-1 trial TTD data (AIC rank: 4; BIC rank: 4). The company justified selecting this distribution by highlighting that the estimated proportion of

patients still on treatment at 24 months (Table 29) approximated the company modelled 24-month PFS rate for patients treated with D+Gem/Cis ([redacted]%). The EAG highlights that the distribution used by the company is 21.44 points higher than the highest ranked AIC distribution and as TTD was always higher than PFS there is no justification for choosing a distribution that ensures TTD equals PFS at a specific time point.

Relative to the spline 1 knot odds distribution, the spline 3 knot hazard distribution provides a more accurate estimate of the proportion of patients still receiving durvalumab at 6 and 12 months in the D+Gem/Cis arm of the TOPAZ-1 trial and is ranked higher for both AIC and BIC (and is statistically indistinguishable from the spline 3 knot odds and the spline 3 knot normal distributions, Table 29). The EAG therefore considers that, without any additional external information, the spline 3 knot hazard distribution should be used to model TTD for patients in the D+Gem/Cis arm.

Table 29 Comparison of statistical fit and estimated TTD for selected distributions (D+Gem/Cis)

Distribution		AIC (rank)	BIC (rank)	Proportion of patients remaining on treatment		
				6-months	12-months	24-months
Company base case	Spline 1 knot odds	1748.93 (4)	1760.42 (4)	[redacted]	[redacted]	[redacted]
EAG preferred	Spline 3 knot hazard	1727.49 (1)	1746.65 (1)	[redacted]	[redacted]	[redacted]
Statistically plausible alternatives	Spline 3 knot odds	1729.95 (2)	1749.11 (2)	[redacted]	[redacted]	[redacted]
	Spline 3 knot normal	1730.90 (3)	1750.06 (3)	[redacted]	[redacted]	[redacted]
TOPAZ-1 trial				[redacted]	[redacted]	-

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; D=durvalumab; EAG=External Assessment Group; Gem/Cis=gemcitabine+cisplatin
Source: CS, Appendix O, Table 57 and Table 58

6.4.2 Treatment duration: Gem/Cis

In the company base case, the spline 3 knot hazard distribution (AIC rank: 3; BIC rank 3) was used to model TTD for patients treated with Gem/Cis; this distribution is only 1.14 points higher than the highest ranked AIC distribution i.e., it represents a good relative statistical fit to the data. In addition, this distribution generates a 24-month TTD rate of [redacted]%. The consensus of the clinical experts consulted by the company was that approximately 0.8% of patients treated with Gem/Cis are likely to be progression-free at 24 months; the company highlights that, of all distributions considered, the spline 3 knot hazard 24-month TTD rate most closely aligns with the company's modelled PFS rate.

The EAG considers that it is important that the distribution used to model TTD for patients treated with Gem/Cis has a good statistical fit and aligns with the TOPAZ-1 trial TTD rate at 6 months. The EAG has carried out an analysis using the spline 2 knot odds distribution (AIC rank: 2; BIC rank 1) as, of all distributions considered, the 6-month TTD rate generated by this distribution most closely matches the TOPAZ-1 trial 6-month TTD rate ([redacted]% difference) (Table 30); after 6 months of treatment, patients are no longer treated with Gem/Cis. At 6 months, the difference between the TOPAZ-1 trial TTD rate and the TTD rate generated by the company's chosen distribution is ([redacted]%).

Table 30 Comparison of statistical fit and estimated TTD rates for selected distributions (Gem/Cis)

Distribution		AIC (rank)	BIC (rank)	Time to treatment discontinuation rate		
				6-month	12-month	24-month
Company base case	Spline 3 knot hazard	1796.72 (3)	1815.93 (3)	[redacted]	[redacted]	[redacted]
EAG alternative	Spline 2 knot odds	1795.97 (2)	1811.33 (1)	[redacted]	[redacted]	[redacted]
Statistically plausible alternatives	Spline 3 knot odds	1795.58 (1)	1814.78 (2)	[redacted]	[redacted]	[redacted]
	Spline 3 knot normal	1798.37 (4)	1817.58 (5)	[redacted]	[redacted]	[redacted]
TOPAZ-1 trial				[redacted]	[redacted]	-

AIC=Akaike Information Criterion; BIC=Bayesian Information Criterion; EAG=External Assessment Group; Gem/Cis=gemcitabine+cisplatin
Source: CS, Appendix O, Table 59 and Table 60

6.5 Utility values

The company has described the HRQoL burden experienced by patients with locally advanced, unresectable or metastatic BTC due to rapid disease progression and treatment-related toxicity (CS, p19). This description, however, is inconsistent with the mean PFS health state utility value ([redacted]) used in the company model. The value used in the company model was estimated using EQ-5D data collected as part of the TOPAZ-1 trial and is only slightly lower than the average utility value for a 62-year-old (weighted by the TOPAZ-1 trial gender distribution) in the UK general population (0.818[44]). As patients treated with D+Gem/Cis remain in the PFS state longer than patients treated with Gem/Cis, a lower PFS utility value reduces the QALYs associated with treatment with D+Gem/Cis more than it reduces the QALYs associated with treatment with Gem/Cis. Therefore, the net effect is to increase the ICER per QALY gained for the comparison of D+Gem/Cis versus Gem/Cis.

Company deterministic sensitivity analyses show that the ICER per QALY gained is sensitive to the utility value used to represent HRQoL in the model PD health state (CS, Table 57). This parameter is characterised by greater uncertainty than the PFS health state utility value as it

was estimated based on fewer observations from fewer patients (PF health state: 4385 observations [633 patients]; PD health state: 238 observations [173 patients]) (CS, Table 35).

The EAG was unable to identify appropriate alternative PFS and PD health state utility values. However, even if these values had been available, the EAG considers that time to death utilities (also not available) would have more accurately captured the deterioration in HRQoL experienced by patients as disease progresses than PD health state utility values. In the absence of alternative utility values, the EAG considers that as the utility values used in the company model were estimated using TOPAZ-1 trial data and their derivation conforms to the NICE Reference Case[13] it is appropriate to use them to assess the cost effectiveness of D+Gem/Cis versus Gem/Cis, although their use may favour D+Gem/Cis.

6.6 Impact on the company base case results of EAG amendments

The following EAG revisions have been made to the company base case:

- minor cost revisions (removal of AE-related QALY decrement, corrected neutropenia AE cost and corrected IV administration costs) (R1)
- Gamma distribution used to model OS for patients treated with D+Gem/Cis (R2)
- spline 3 knot hazard distribution used to model PFS for patients treated with D+Gem/Cis (R3)
- spline 3 knot odds distribution used to model PFS for patients treated with Gem/Cis (R4)
- spline 3 knot hazard distribution used to estimate treatment costs for patients treated with D+Gem/Cis (R5)
- spline 2 knot odds distribution used to estimate treatment costs for patients treated with Gem/Cis (R6)

Details of how the EAG revised the company model are presented in Appendix 8.2 of this EAG report. The EAG cost effectiveness results are provided in Table 31 (deterministic results) and in Table 32 (probabilistic results). These results have been generated using list prices for all drugs except for durvalumab (PAS price).

6.6.1 Severity modifier

The EAG re-calculated the severity modifier based on EAG preferred scenario results; the modifier remained at 1.2.

Table 31 Deterministic results: EAG revisions to company base case (durvalumab PAS price)

Scenario/EAG revisions	D+Gem/Cis		Gem/Cis		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs (x1.2 modifier)	£/QALY (x1.2 modifier)	Change from base case
A. Company CS base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
R1) Minor cost amendments (AE-related QALY decrement removed, neutropenia AE cost corrected and IV administration costs corrected)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R2) Gamma distribution used to model OS for patients treated with D+Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R3) Spline 3 knot hazard distribution used to model PFS for patients treated with D+Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R4) Spline 3 knot odds distribution used to model PFS for patients treated with Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R5) Spline 3 knot hazard distribution (fitted to TOPAZ-1 TTD data) used to estimate treatment costs for patients treated with D+Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
R6) Spline 2 knot odds distribution (fitted to TOPAZ-1 TTD data) used to estimate treatment costs for patients treated with Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B. EAG preferred scenario (R1, R3-R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C. EAG scenario (R1-R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE=adverse event; CS=company base case; D=durvalumab; EAG=External Assessment Group; Gem/Cis=gemcitabine+cisplatin; ICER=incremental cost effectiveness ratio; IV=intravenous; OS=overall survival; PAS=Patient Access Scheme; PFS=progression-free survival; QALYs=quality adjusted life years; TTD=time to treatment discontinuation

Table 32 Probabilistic results: EAG revisions to company base case (durvalumab PAS price)

Scenario/EAG revisions	D+Gem/Cis		Gem/Cis		Incremental		ICER	
	Cost	QALYs	Cost	QALYs	Cost	QALYs (x1.2 modifier)	£/QALY (x1.2 modifier)	Change from base case
A. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
B. EAG preferred scenario (R1, R3-R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C. EAG scenario (R1-R6)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

D=durvalumab; EAG=External Assessment Group; Gem/Cis=gemcitabine+cisplatin; ICER=incremental cost effectiveness ratio; PAS=Patient Access Scheme; QALYs=quality adjusted life years

6.7 Cost effectiveness conclusions

The clinical effectiveness results presented by the company have been estimated based on direct evidence from a mature, high quality RCT (TOPAZ-1 trial). In the TOPAZ-1 trial, the comparator was P+Gem/Cis; Gem/Cis represents standard of care for NHS patients with BTC.

Based on the parametric distributions that are considered statistically plausible, the deterministic ICER per QALY could lie between [redacted] and [redacted]. Clinical uncertainty around the duration of survival for patients treated with D+Gem/Cis who are still alive at the end of the trial period means that an assessment of clinical plausibility for each distribution considered is challenging. This was acknowledged by the company and was demonstrated by the differing opinions offered by the five clinical experts consulted by the company. In addition, the EAG has some concerns about the choices made by the company to model PFS and TTD.

The EAG considers that as the utility values used in the company model were estimated using TOPAZ-1 trial data and their derivation conforms to the NICE Reference Case,[13] it is appropriate to use them to assess the cost effectiveness of D+Gem/Cis versus Gem/Cis. However, the utility values are high, and the PD value is based on very few observations (less than two per person).

EAG revisions have increased the company base case ICERs per QALY gained for the comparison of D+Gem/Cis versus Gem/Cis; the company and the EAG deterministic and probabilistic ICERs per QALY gained are higher than [redacted].

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8 APPENDICES

8.1 Exploratory cost effectiveness results

Table 33 Cost effectiveness results using different parametric distributions to represent overall survival rates for patients treated with D+Gem/Cis

Model	AIC (rank)	2-year survival rate	3-year survival rate	5-year survival rate	ICER per QALY gained (x1.2 modifier)
TOPAZ-1		[redacted]			
Gamma	1,913.54 (1)	[redacted]	[redacted]	[redacted]	[redacted]
Spline 1 knot, scale = odds	1,914.00 (2)	[redacted]	[redacted]	[redacted]	[redacted]
Spline 1 knot, scale = normal	1,914.28 (3)	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	1,914.41 (4)	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	1,915.53 (5)	[redacted]	[redacted]	[redacted]	[redacted]
Spline 3 knots, scale = hazard	1,915.60 (6)	[redacted]	[redacted]	[redacted]	[redacted]
Spline 3 knots, scale = normal	1,915.73 (7)	[redacted]	[redacted]	[redacted]	[redacted]
Spline 3 knots, scale = odds	1,915.87 (8)	[redacted]	[redacted]	[redacted]	[redacted]
Spline 1 knot, scale = hazard	1,915.90 (9)	[redacted]	[redacted]	[redacted]	[redacted]
Spline 2 knots, scale = odds	1,916.10 (10)	[redacted]	[redacted]	[redacted]	[redacted]
Spline 2 knots, scale = hazard	1,916.16 (11)	[redacted]	[redacted]	[redacted]	[redacted]
Spline 2 knots, scale = normal	1,916.43 (12)	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	1,917.07 (13)	[redacted]	[redacted]	[redacted]	[redacted]

AIC=Akaike Information Criterion; ICER=incremental cost effectiveness ratio; QALY=quality adjusted life year
Source: Company model

8.2 EAG revisions to company model

Table 34 Microsoft Excel revisions made by the EAG to the company model

EAG revision number and description (see Section 6.10)	Revision instructions
R1) Minor cost revisions	**Insert sheet named "EAG Revisions"** In cell C3 enter text "R1" Set value in cell D3=1
IV administration costs corrected	In Sheet 'Unit Costs' Set value in cell I55=438.38 Name cell I55 "administration_cost_IV_subs2" Copy cell H55 Paste values in range H56:H62 Set value in cell H60=IF('EAG Revisions'!D3=1,375.66,281.11) Set value in cell H62=0 Change "administration_cost_IV_subs" range to H55:H62 In Sheet 'Dosing & Admin' Set value in cell H34 {=IF(F34:F44=Control!Q11,IF('EAG Revisions'!D3=1, administration_cost_IV_subs2, administration_cost_IV_subs),0)}
AE-related QALY decrement removed	In Sheet 'Utility' Set value in cell K60={IF('EAG Revisions'!D3=1,0,active_u.aes*(inputs_AE_duration/365.25))}
Neutropenia cost value corrected	In Sheet 'Unit Costs' Set value in cell E94=IF('EAG Revisions'!D3=1,679.39,697.39)
R2) Gamma used to model D+Gem/Cis OS	In Sheet 'EAG Revisions' In cell C4 enter text "R2" Set value in cell D4=1 In Sheet 'Control'

EAG revision number and description (see Section 6.10)	Revision instructions
	Set value in cell I36=IF('EAG Revisions'!D4=1,7,11)
R3) Spline 3 knot hazard used to model PFS for patients treated with D+Gem/Cis	In Sheet 'EAG Revisions' In cell C5 enter text "R3" Set value in cell D5=1 In Sheet 'Control' Set value in cell I37=IF('EAG Revisions'!D5=1,10,11)
R4) Spline 3 knot odds used to model PFS for patients treated with Gem/Cis	In Sheet 'EAG Revisions' In cell C6 enter text "R4" Set value in cell D6=1 In Sheet 'Control' Set value in cell I42=IF('EAG Revisions'!D6=1,13,14)
R5) Time on treatment costs estimated using TTD data; spline 3 knot hazard distribution used to extrapolate TTD for patients treated with D+Gem/Cis	In Sheet 'EAG Revisions' In cell C7 enter text "R5" Set value in cell D7=1 In Sheet 'Control' Set value in cell I25=IF(OR('EAG Revisions'!D7=1,'EAG Revisions'!D8=1),1,2) Set value in cell I38=IF('EAG Revisions'!D7=1,10,11)
R6) Time on treatment costs estimated using TTD data; spline 2 knot odds distribution used to extrapolate TTD for patients treated with Gem/Cis	In Sheet 'EAG Revisions' In cell C8 enter text "R6" Set value in cell D8=1 In Sheet 'Control' Set value in cell I43=IF('EAG Revisions'!D8=1,12,10)

Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Thursday 4 May 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Summary

The Company would like the thank NICE and the EAG for the opportunity to review the EAG report. Factual inaccuracies identified by the Company are presented in this document.

An overview of the inaccuracies and proposed changes are summarised in Table 1 and further detailed in the following pages. Updated ICERs are presented in Table 2. For simplicity, we have aligned scenario lettering and numbering with the EAR. Please note:

- A revised company base case (scenario A1) has been provided, which updates the CS base case with the minor cost amendments identified by the EAG
- In line with the EAG comments regarding PFS extrapolations, an additional company scenario (scenario A2) has been provided, which updates the CS base case with the minor cost amendments identified by the EAG and applies the alternative parametric distributions for PFS deemed as plausible by the EAG
- A company updated EAG preferred scenario has been provided (scenario B1) which updates the EAG preferred scenario to incorporate the use of TTD data to derive outcomes as well as treatment costs, rendering the PFS data obsolete in this scenario. This scenario is equivalent to the CS base case, updated with the minor cost amendments identified by the EAG and incorporating the use of TTD data to model costs and utility values

Table 1: Summary of Company issues in response to the EAR

Issue	Details of inaccuracy	Proposed change
Issue 1: Lack of evidence that patients with viral hepatitis B may experience greater treatment benefit with D + Gem/Cis	No robust clinical evidence has been provided to support the suggestion that patients with BTC who also have viral hepatitis B may have a more favourable response to treatment with immunotherapy	Text suggesting patients with hepatitis B may have a more favourable response to treatment with immunotherapy should be removed
Issue 2: Use of nivolumab for dMMR patients is not routine clinical practice	Nivolumab is currently funded via the CDF and therefore is not considered part of routine clinical practice for these patients with dMMR	Supplementary text to clarify that this use of nivolumab is not part of routine practice should be added
Issue 3: Number of SLR reviewers	Data was extracted by two or more reviewers independently and the quality assessment was conducted by two or more reviewers independently	Update Table 3, column 2 (EAG response) rows 7 (Were data extracted by two or more reviewers independently?) and 9 (Was the quality assessment conducted by two or more reviewers independently?) to state 'Yes' We apologise for the lack of clarity
Issue 4: Suggestion that discontinuation of chemotherapy in both arms of the trial may have prompted a change in treatment effect	The statement that the "*discontinuation of chemotherapy in both arms of the trial may have prompted a change in treatment effect*" is not considered accurate	Removal of this text and/or inclusion of additional text stating the company position, which is that the delayed separation of the survival curves can be attributed to the mechanism of action of immunotherapy, which requires time to mount an effective immune response

Issue 5: EAG scenario using the gamma distribution to model OS for patients treated with D + Gem/Cis is not appropriate	The spline 1 knot odds parametric distribution is the most appropriate with regards to modelling long-term survival for the D+Gem/Cis arm	We suggest scenario R2 (use of the Gamma parametric distribution) is removed as an alternative approach for modelling OS for patients treated with D+Gem/Cis
Issue 6: Use of TTD data to estimate treatment costs for patients treated with D+Gem/Cis and Gem/Cis	Use of TTD data to model treatment costs is not as reflective of real-world clinical practice compared with PFS assessed by investigator If TTD data is used to model treatment costs, utility values should also be modelled by treatment status (pre-treatment discontinuation and post-treatment discontinuation) using the TTD data	We suggest scenarios using TTD to model treatment costs (R5 and R6) are removed or updated to incorporate use of TTD for HSUVs (R5a and R6a, Table 2)
Issue 7: Cost effectiveness conclusions are not reflective of plausible scenarios	The ICER range presented in section 6.2 appears to correspond to the cost-effectiveness results using a range of parametric distributions presented in the appendices, which are not all considered plausible	Suggest ICERs are removed from text in section 6.2 or ICERs and text are updated to reflect plausible scenarios considered by EAG

Table 2: Deterministic results for Company base case, EAG revisions and Company revisions

Scenario/EAG/ Company revisions	Incremental		ICER	
	Costs	**QALYs (x1.2 modifier)***	**£/QALY (x1.2 modifier)**	**Change from company base case[a]**
A. Original company CS base case	[redacted]	[redacted]	[redacted]	[redacted]
R1) Minor cost amendments (AE-related QALY decrement removed, neutropenia AE cost corrected and IV administration costs corrected)	[redacted]	[redacted]	[redacted]	[redacted]
R3) Spline 3 knot hazard distribution used to model PFS for patients treated with D+Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]
R4) Spline 3 knot odds distribution used to model PFS for patients treated with Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]
R5a) Spline 3 knot hazard distribution (fitted to TOPAZ-1 TTD data) used to estimate treatment costs and utility values for patients treated with D+Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]
R6a) Spline 2 knot odds distribution (fitted to TOPAZ-1 TTD data) used to estimate treatment costs and utility values for patients treated with Gem/Cis	[redacted]	[redacted]	[redacted]	[redacted]
A.1 Revised company CS base case (aligns to EAR R1 scenario)	[redacted]	[redacted]	[redacted]	[redacted]
A.2 Company scenario (R1 + R3 + R4)	[redacted]	[redacted]	[redacted]	[redacted]
B.1 Company updated EAG preferred scenario (R1 + R3-R6a)	[redacted]	[redacted]	[redacted]	[redacted]

Notes: [a] Indicates change from original Company base case, as presented in the Company Submission

Issue 1 Lack of evidence that patients with viral hepatitis B may experience greater treatment benefit with D + Gem/Cis

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 1.3, pg 10 *"Pre-planned OS subgroup analysis results showed that the treatment effect of D+Gem/Cis versus P+Gem/Cis favoured patients in the 'Asian race' and the 'Asian region' subgroups compared to patients in the 'non-Asian race' and 'rest of the world' subgroups, respectively. Clinical advice to the EAG is that this benefit may be due to the relatively high incidence of hepatitis B in Asia, which may be linked to better patient responses to D+Gem/Cis"* **Section 3.2.3, pg 29** *"However, clinical advice to the EAG is that it is biologically plausible that patients with BTC who also*	The Company propose this text is removed or supplementary text is added as follows: "*It should be noted that the pre-planned subgroup analyses were exploratory in nature as the TOPAZ-1 trial was not powered or sized to demonstrate significant differences for any of the individual subgroup evaluations. Differences in HR across subgroups may be due to imbalances in other baseline covariates. Therefore, the results of the subgroup analyses should be viewed cautiously and in the context of the statistically significant results in the FAS population".*	No robust clinical evidence has been provided to support the suggestion that patients with BTC who also have viral hepatitis B may have a more favourable response to treatment with immunotherapy. The pre-planned subgroup analyses were exploratory in nature as the TOPAZ-1 trial was not powered or sized to demonstrate significant differences for any of the individual subgroup evaluations and no adjustments were made for multiplicity. While there are some differences in the HR across subgroups, this may be due to imbalances in other baseline covariates. Results of the subgroups analyses should therefore be viewed cautiously and in the context	The text in Section 1.3 (p10) has been changed to "The EAG notes that the treatment effect of D+Gem/Cis versus P+Gem/Cis was numerically greater for patients in the 'Asian race' and in the 'Asian region' subgroups than for patients in the 'non-Asian race' and in the 'rest of the world' subgroups, respectively". This is not a factual inaccuracy but for clarity, the following text has been added to Section 1.3 (p10) and Section 3.2.7 (p34): "However, these subgroup analyses

have viral hepatitis B will have a more favourable response to treatment with immunotherapy than to other treatment. Clinical advice to the EAG is that any additional treatment benefit associated with viral hepatitis B is likely to be modest. The EAG notes from the CSR (Table 17) that in the TOPAZ-1 trial, viral hepatitis B was more prevalent amongst patients from Asian treatment centres compared with patients from the rest of the world ([redacted] versus [redacted]).” **Section 3.2.7, pg 33** “*The EAG notes that the treatment effect of D+Gem/Cis versus P+Gem/Cis was numerically greater for patients in the ‘Asian race’ and the ‘Asian region’ subgroups than for patients in the ‘non-Asian race’ and ‘rest of the world’ subgroups, respectively.*		of the statistically significant results in the FAS population. The reference provided in the EAG report (Dong 2023) includes a speculative argument that it is biologically plausible that favourable treatment benefit of D+Gem/Cis is driven by overexpression of PD-1 in patients with hepatitis B expression, which is considered a biomarker for predicting efficacy of ICIs. However, in the TOPAZ-1 trial, the favourable treatment benefit of D+Gem/Cis compared with Gem/Cis was demonstrated to be independent of the level of PD-L1 expression (as outlined in the CS, section B.1.3.4). Statements suggesting differences in the treatment effect between subgroups, which are not statistically significant, are considered inaccurate and potentially misleading due to exploratory	should be interpreted with caution as they were not powered to demonstrate statistically significant differences within subgroups”.

Clinical advice to the EAG is that these subgroup differences could be due to the fact that patients with BTC who also have viral hepatitis B may have a more favourable response to treatment with immunotherapy, and in the TOPAZ-1 trial, viral hepatitis B was more prevalent amongst patients from Asian treatment centres compared with patients from the rest of the world ([redacted] versus [redacted]) (see Section 3.2.3 of this EAG report)."		nature of the analyses and lack of robust evidence to support the suggestions.	

Issue 2 Use of nivolumab for dMMR patients is not routine clinical practice

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 2.4.2, pg17 "*This small (~1%) subgroup of patients might be treated with nivolumab via the Cancer Drugs Fund"*	"*This small (~1%) subgroup of patients might be treated with nivolumab via the Cancer Drugs Fund, and therefore is not considered routine clinical practice".*	As nivolumab is currently funded via the CDF, it is not considered part of routine clinical practice for these patients with dMMR. As such, there should be no suggestion that it may be	This is not a factual inaccuracy. The statement describes current clinical practice. No change required.

		appropriate to compare the efficacy of D+Gem/Cis with nivolumab in the small subpopulation of BTC patients.	

Issue 3 Number of SLR reviewers

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Table 3, pg 26, row 7 and 9	Update Table 3, column 2 (EAG response) rows 7 (Were data extracted by two or more reviewers independently?) and 9 (Was the quality assessment conducted by two or more reviewers independently?) to state 'Yes'.	We confirm this was conducted by 2 reviewers and apologise for the lack of clarity in the CS.	Thank you for the clarification. We have updated the report to reflect this information.

Issue 4 Suggestion that discontinuation of chemotherapy in both arms of the trial may have prompted a change in treatment effect

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 3.2.7, pg 34 "*However, clinical advice to the EAG is that the discontinuation of*	The company propose: • Removal of the text "*However, clinical advice to the EAG is that the discontinuation of*	The Company agree that piecewise HRs are potentially more informative than the HR provided for the entire trial period, as outlined in section	This is not a factual inaccuracy. The EAG's statement that discontinuation of chemotherapy in both

chemotherapy in both arms of the trial may have prompted a change in treatment effect, and therefore here, the instant change in HR may be plausible. The EAG considers that the piecewise HRs are more informative than the HR provided for the whole trial period."	*chemotherapy in both arms of the trial may have prompted a change in treatment effect, and therefore here, the instant change in HR may be plausible.",* and/or • Addition of the text "*The CS notes that the delayed separation in survival curves can be attributed to the mechanism of action of immunotherapy, as it requires time to mount an effective immune response, and for that response to be translated into an observable clinical response. The CS also states that median OS and OS HRs do not always fully capture the non-conventional survival dynamics such as delayed curve separation"*	B.2.12.1, pg, 75 of the CS. However, the CS also states the delayed separation of the survival curves can be attributed to the mechanism of action of immunotherapy, which requires time to mount an effective immune response, and for that response to be translated into an observable clinical response. The statement in the EAR regarding discontinuation of chemotherapy is inaccurate, as while patients in the D+Gem/Cis and Gem/Cis arms are limited to a maximum of 8 x 3-weekly cycles of Gem/Cis (approximately 5.5 months), not all patients are able to complete the maximum number of administrations and therefore chemotherapy discontinuation will occur at multiple treatment cycles. This is inferred by the separation in PFS curves at 4 months (CS, figure 7).	arms may have prompted a change in treatment effect is based on clinical opinion. No change required.

		Therefore, it is illogical that the discontinuation of chemotherapy in both arms of the trial would prompt an instantaneous change in treatment effect at 4 months.	

Issue 5 EAG scenario using the spline 1 knot odds parametric distribution to model OS for patients treated with D + Gem/Cis is the most appropriate

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Section 1.5, pg 11 Issue 2: Modelling overall survival for patients treatment with D+Gem/Cis **Section 1.6, pg 13** Scenario R2 **Table 24, pg 56, row 4** **Section 6.2.1 pg 58** *"The EAG considers that the methods used by the company to select a distribution to model OS for patients treated with D+Gem/Cis were*	Suggest scenario R2 is removed as an alternative approach for modelling OS for patients treated with D+Gem/Cis Suggest the text on pg 58 is amended to "*The EAG considers that the methods used by the company to select a distribution to model OS for patients treated with D+Gem/Cis were appropriate; however, other distributions may be equally statistically and clinically plausible. Specifically, the EAG considers that the Gamma distribution is as plausible as the spline 1 knot odds distribution; it has comparable AIC/BIC scores (ranking first on both) and generates a*	The Company agrees that the spline 1 knot odds is the most appropriate parametric distribution to model OS for the D+Gem/Cis arm. The Gamma distribution may be considered as statistically plausible as the spline 1 knot odds model when considering within trial fit only. However, the Company maintains that the spline 1 knot odds model provides a more statistically and	This is not a factual inaccuracy. The EAG's statement that the Gamma distribution is clinically plausible is based on the opinion of two of the five clinical experts consulted by the company. The disagreement among clinical experts about the most plausible extrapolation reflects the clinical uncertainty around the survival benefit for patients treated with

appropriate; however, other distributions may be equally statistically and clinically plausible. Specifically, the EAG considers that the Gamma distribution is as plausible as the spline 1 knot odds distribution; it has comparable AIC/BIC scores (ranking first on both) and generates a 2-year survival rate that is close to the TOPAZ-1 trial 2-year survival rate (Table 25). Furthermore, of the five clinical experts that were consulted, one considered that the Gamma distribution provided the best overall fit to TOPAZ-1 trial OS K-M data and another considered that the Gamma distribution may provide plausible survival rates at 5 years (AZ data on file, p6). The EAG therefore considers that the Gamma distribution is	*2-year survival rate that is close to the TOPAZ-1 trial 2-year survival rate (Table 25). However, it is recognized that the Gamma distribution may underestimate longer-term survival, and does not capture the long-term OS benefits associated with immunotherapies. Therefore, whilst providing a statistically good fit it may not provide a clinically plausible extrapolation and so the spline 1 knot odds model should be retained in the base case."*	clinically plausible extrapolated fit: • The majority of the clinical experts agreed that the spline 1 knot odds model is preferred over the Gamma[1] • Gamma was considered by clinical experts to underestimate the proportion of patients expected to be alive at 3 years in the UK • When using the Gamma distribution for D + Gem/Cis and the spline 1 knot normal distribution for placebo + Gem/Cis, long-term OS is predicted to be similar, which is not clinically plausible given the known mechanism of actions for IOs which leads to a durable, adaptive response, and a sustained separation in OS Kaplan Meier tails	D+Gem/Cis. The company has not presented any evidence of a sustained survival benefit in this indication for patients who have received immunotherapy. No change required.

as plausible as the spline 1 knot odds distribution" **Section 6.6, pg 64** *"Gamma distribution used to model OS for patients treated with D+Gem/Cis (R2)"* **Table 31, row 4 (R2), pg 65** **Table 33, row 3, pg 72** **Table 34, row 3 (R2), pg73**		compared with chemotherapy.[2] The spline 1 knot odds model captures this recognised tail of the IO OS curve. Given this, the Gamma distribution should not be considered as clinically plausible as the spline knot 1 odds model.	

Issue 6 Use of TTD data to estimate treatment costs for patients treated with D+Gem/Cis and Gem/Cis

Description of problem	Description of proposed amendment	Justification for amendment	EAG Response
Issue 3a Use of PFS to model treatment costs is more reflective of likely real-world treatment costs			
Section 1.6, Table B, row 7 (R5) and row 8 (R6), pg 13	The company proposed scenarios R5 and R6 and associated commentary are removed, or commentary is added to note that PFS is likely a more accurate reflection of treatment costs	Patients in the TOPAZ-1 trial may be treated at Investigator discretion beyond disease progression, which is not expected in clinical practice due	This is not a factual inaccuracy. The TOPAZ-1 trial efficacy data and subsequent modelled outcomes reflect treatment

Section 1.6, Table B, row 7 (R5) and row 8 (R6), pg 13 **Section 6.1, Table 24, row 5 and 6, pg 56** **Table 31, row 7 and row 8, pg 65**	in real world clinical practice as the TOPAZ-1 trial allowed treatment beyond progression at the investigator's discretion	to Blueteq prescribing control. PFS is therefore a more accurate reflection of likely treatment costs in real world clinical practice. Use of TTD data results in treatment costs that do not reflect the likely treatment costs in a real-world setting.	received during the trial. If modelled time on treatment is modified to be different from trial time on treatment, then trial patient outcomes should also be modified to reflect the modelled time on treatment. No change required.
Issue 3b Use of TTD to model treatment costs but not utilities			
Section 1.5, Issue 4, pg 12 **Section 1.6, Table B, row 7 (R5) and row 8 (R6), pg 13** **Section 6.1, Table 24, row 5 and 6, pg 56** **Section 6.4, pg 61-63** **Table 31, row 7 and row 8, pg 65** **Section 8.2, row 6 (R5) and row 7 (R6), pg 74**	If the EAG do not agree with the removal of scenarios R5 and R6, it is proposed to update these scenarios to model utility values by treatment status (pre-treatment discontinuation and post-treatment discontinuation) using the TTD data. We proposed scenario R5 is updated to Scenario R5a: • Using the spline 3 knot hazard distribution to model TTD for patients treated with D+Gem/Cis increased the ICER for the comparison of	To be consistent, costs and utilities should be modelled using the same curve (i.e., PFS or TTD). Therefore, if the EAG prefer to model costs using the TTD curve, utility values should also be modelled using the TTD curve (pre-treatment discontinuation and post-treatment discontinuation).	This is not a factual inaccuracy. The EAG considers that costs and utility estimates do not always need to be based on the same underlying curve. No change required.

	D+Gem/Cis versus Gem/Cis to [redacted] per QALY gained We propose scenario R6 is updated to scenario R6a: • Using the spline 2 knot odds distribution to model TTD for patients treated with Gem/Cis increased the ICER for the comparison of D+Gem/Cis versus Gem/Cis to [redacted] per QALY gained See below the company updated EAR scenarios i.e., R5 updated to R5a and R6 updated to R6a		

	Scenario	**Incremental cost**	**Incremental QALYs (x1.2 modifier)**	**ICER (x1.2 modifier)**	**Change from company base case[a]**		
	R5a)	[redacted]	[redacted]	[redacted]	[redacted]		
	R6a)	[redacted]	[redacted]	[redacted]	[redacted]		
	Notes: [a] Indicates change from original Company base case, as presented in the Company Submission						

Issue 7 Cost effectiveness conclusions are not reflective of plausible scenarios

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG Response**
Section 6.7, pg 67 **"***Uncertainty around OS beyond the TOPAZ-1 trial period means that the deterministic ICER per QALY gained could lie between [redacted] and [redacted]"*	Suggest this is either: a. Amended to remove reference to ICERs and text added to note that uncertainty in ICERs has been explored and presented in Section 1.6, Table B and section 6.6 Table 31, or	The ICER range presented on page 67 in the EAG report [redacted]) appears to correspond to the cost-effectiveness results using different parametric distributions	This is not a factual inaccuracy. However, for clarity, the text in Section 6.7 p67 has been updated to: "Based on the parametric distributions that are considered statistically plausible, the deterministic

	b. Updated to reflect the overall ICERs considered plausible as presented in Table 2	presented in the appendices (Section 8.1, Table 33). As described in the CS, not all parametric distributions for OS were deemed to be plausible for a variety of reasons, including: poor statistical fit, inability to capture the turning point in the trial hazard, and lack of clinical plausibility according to external clinical expert opinion. To account for uncertainty, sensitivity analyses were conducted using the log-logistic distribution for D+Gem/Cis and spline normal (2 knot) for Gem/Cis and results presented in the CS (Table 58). It is noted in section 6.2 of the EAR that the EAG considers the Gamma distribution to be as plausible as the spline 1 knot odds distribution for the D+Gem/Cis arm	ICER per QALY could lie between [redacted] and [redacted]. Clinical uncertainty around duration of survival for patients treated with D+Gem/Cis and who are still alive at the end of the trial period means that an assessment of clinical plausibility for each distribution considered is challenging. This was acknowledged by the company and was demonstrated by the differing opinions offered by the five clinical experts consulted by the company." Only a small number of parametric distributions were presented by the company to the clinical experts.

		However, the Company disagree with the use of this distribution, as outlined above. Section 6.2 of the EAR also states that the company's use of the spline 1 knot normal distribution for Gem/Cis was appropriate. While the Company accepts that there is to some extent uncertainty around OS beyond the TOPAZ-1 trial period, this has been appropriately explored both within the CS and in section 6.2 of the EAR. Therefore, the presentation of the ICER range of [redacted] and suggestion that any of the parametric distributions for OS could be plausible is considered misleading and will not aid decision-making.	

References

1. AstraZeneca. UK MC: KEE input on advanced biliary tract cancer (BTC) UK Questionnaire (durvalumab). Data on file 2023.
2. Quinn C, Garrison LP, Pownell AK, et al. Current challenges for assessing the long-term clinical benefit of cancer immunotherapy: a multi-stakeholder perspective. J Immunother Cancer 2020;8(2). DOI: 10.1136/jitc-2020-000648.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.5).

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Thursday 15 June**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted], [redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	AstraZeneca UK Ltd.
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	Not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	Not applicable

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Generalisability of TOPAZ-1 trial results to NHS clinical practice	No	**Subgroup data from the TOPAZ-1 trial should be considered in the context of the statistically significant and clinically meaningful outcomes of the ITT** • The pre-planned subgroup analyses, including analyses by race and region, were not powered or sized to detect statistically significant differences for any of the individual subgroup evaluations and no adjustments were made for multiplicity.[1] • The direction of the results is equivalent across all subgroups, i.e., the point estimate of the hazard ratio for D + Gem/Cis vs. Gem/Cis for OS and PFS is consistently <1. • In summary, these subgroup analyses are not appropriate for decision-making as race and region are not effect modifiers for D + Gem/Cis treatment. **An exploratory interaction test for region and treatment suggested a consistent OS effect across Asia and Row** • An exploratory, post hoc analysis using an unstratified Cox proportional hazards model to test the interaction between treatment and region suggested a consistent OS effect across Asia (HR, 0.72; 95% CI, 0.56–0.94) and RoW (HR, 0.89; 95% CI, 0.66–1.19); interaction test p=0.32.[2]

		The TOPAZ-1 ITT data was considered generalisable to UK clinical outcomes by UK clinical experts • As outlined in the CS (section B.2, summary box), UK clinicians reviewed the TOPAZ-1 data and confirmed the trial outcomes were generalisable to the outcomes expected for BTC patients in UK clinical practice.[3] • Clinicians also considered the OS subgroup analysis outcomes were generalisable to the FAS, highlighting that all subgroups experienced a favourable treatment effect of D + Gem/Cis compared to placebo + Gem/Cis.[3] • Thus, clinicians advocated for the broad use of D + Gem/Cis in all BTC patients who would otherwise be treated with Gem/Cis and have no contraindications to immunotherapy.[3] **The suggestion that outcomes for the Asian subgroups in the TOPAZ-1 trial are driven by patients with hepatitis B in the EAR should be disregarded** • The EAR describes clinical advice received by the EAG regarding potential clinical rationale for a more favourable treatment effect of D + Gem/Cis versus placebo + Gem/Cis for patients in the 'Asian race' and the 'Asian region' subgroups compared to patients in the 'non-Asian race' and 'rest of the world' subgroup. Clinical advisors to the EAG have suggested that the more favourable treatment effect may be driven by the relatively high incidence of hepatitis B in Asia and patients with BTC who have hepatitis B experiencing a more favourable response to immunotherapy. • No robust clinical evidence has been provided to support this suggested rationale. The single reference included in the EAR (Dong 2023) suggests that patients with hepatitis B have an overexpression of PD-L1, which is considered a biomarker for predicting the efficacy of immune checkpoint inhibitors, such as durvalumab. However, as demonstrated in the TOPAZ-1 trial, the favourable treatment benefit of D + Gem/Cis compared with placebo + Gem/Cis was demonstrated independent of the level of PD-L1 expression when used for the treatment of BTC.

		• An additional analysis of OS in patients with and without viral hepatitis was carried out and demonstrated a consistent OS benefit across these two groups. An unstratified Cox proportional hazards model was used to calculate the OS HRs:[1,2]
		  ○ Patients with previous or ongoing hepatitis B and/or previous hepatitis C infection: OS HR: 0.79 (95% CI: 0.53, 1.16).
		  ○ Patients without viral hepatitis: OS HR: 0.74 (95% CI: 0.56, 0.97).
		  ○ TOPAZ-1 ITT: OS HR: 0.76 (95% CI: 0.64, 0.91).
		• The consistent effect observed between patients with and without viral hepatitis was further supported by an interaction test; p=0.79.
		• As such, the clinical rationale outlined in the EAR is considered speculative and should be disregarded.
		Overall, the ITT population and associated clinical outcomes from the TOPAZ-1 clinical trial are considered generalisable to the UK population. Furthermore, the clear clinical support for broad use of D + Gem/Cis in all BTC patients,[3] in line with updated EMSO BTC guidelines,[4] consolidates the need to ensure patient access to this innovative treatment option, which represents the first advancement in therapy for underserved BTC patients in over a decade, without delay.

Issue 2: Modelling overall survival for treatment with durvalumab with gemcitabine and cisplatin	No	**The spline odds (1 knot) model provides a better fit to the observed data compared with the gamma model, as evidenced by the hazard plot, and provides a more clinically accurate long-term estimate of OS, reflecting the understood mechanism of action of immunotherapies** • The smoothed OS hazard for the TOPAZ-1 D + gem/cis arm and the hazards for the spline odds (1 knot) distribution and gamma distribution are presented in Figure 1, up to 36 months. The smoothed trial hazard shows changes in direction over time, [redacted]. As outlined in section B.3.4.2.2.1 of the CS, the smoothed trial hazards also shows that there is [redacted] but this is driven by the very low numbers of patients at risk at the end of the trial and therefore should not inform selection of parametric distribution models.

		• The spline odds (1 knot) hazard closely fits the trial hazard, mirroring the [redacted]. While the gamma hazard captures the [redacted] in the hazard observed in the TOPAZ-1 study; therefore, the gamma is a less optimal fit compared with the spline odd (1 knot) hazards. • As specified in NICE DSU TSD 21,[5] complex hazard functions, such as the hazard functions demonstrated by the D + Gem/Cis arm of the TOPAZ-1 trial, cannot be represented well by standard parametric models, and flexible models (such as spline-based models) that allow hazard functions with complex shapes are more appropriate.

		Figure 1: OS hazard plots (trial data [kernel method], spline odds [1 knot] and gamma) - D + Gem/Cis, (TOPAZ-1 trial, 6.5month update [DCO 25 Feb 2022])  **Immunotherapy modulates underlying disease dynamics and plausibly improves long-term overall survival expectations compared to standard chemotherapy treatment** • As stated in the CS, the OS base case for placebo + Gem/Cis was informed by the spline normal (1 knot). This distribution was considered appropriate by both the company and the EAG. The OS estimated by the spline normal (1 knot) at 10, 15 and 20 years is described in Table 1 and compared with OS

estimated by the spline odds (1 knot) and gamma distributions for the D + Gem/Cis arm.

Table 1: OS rates for D + Gem/Cis and placebo + Gem/Cis (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])

Trial arm	D + Gem/Cis		Placebo + Gem/Cis
Parametric distribution	**Spline odds (1 knot) (EAG preferred scenario and Company base case)**	**Gamma (EAG alternative scenario)**	**Spline normal (1 knot) (Company and EAG base case)**
OS rate at 10 years	1.4%	0.01%	0.01%
OS rate at 15 years	0.6%	0.00%	0.00%
OS rate at 20 years	0.4%	0.00%	0.00%

- The gamma distribution for the D + Gem/Cis arm infers that there is no long-term OS benefit for patients who receive this treatment option compared to the current SoC of cytotoxic chemotherapy. Given the known mechanism of action of IOs, this is therefore not considered plausible.
- As outlined in the CS, IOs exhibit non-conventional survival dynamics, such as delayed curve separation. Unlike chemotherapy or radiotherapy, where tumour cells are killed directly, immunotherapy requires time to mount an effective immune response, and for that response to be translated into an observable and durable clinical response. Immune checkpoint inhibitors have demonstrated the ability to induce long-term remission despite treatment discontinuation, which has been well documented in melanoma patients who

		achieve a complete response to treatment.[6] The TOPAZ-1 trial results support this: ○ As reported in the CS (section B.2.1.5, table 12), in the TOPAZ-1 trial (IA-2 [DCO: 11 Aug 21]), more than double the number of patients in the D + Gem/Cis arm achieved a complete response versus the placebo + Gem/Cis arm (2.1% [7/341 patients] in the D + Gem/Cis group versus 0.6% (2/343 patients) in the placebo + Gem/Cis group. ○ The ORR was also higher for the D + Gem/Cis group with a nominally significant p-value (ORR = 26.7% [91/341 patients] in the D + Gem/Cis group versus 18.7% [64/343 patients] in the placebo + Gem/Cis group, p=0.011). ○ The CS also reported the DoR from the TOPAZ-1 trial (section B.2.6.1.6, table 13), notably at ≥12 months, 26.1% of patients in the D + Gem/Cis group remained in response compared with 15.0% in the placebo + Gem/Cis group. • Based on the mechanism of action of IOs, their potential ability to modulate the underlying disease dynamics in some cancer patients, and lead to a durable, adaptive response compared with chemotherapy, it is not expected that the KM curves would re-join. Thus, a small number of patients are expected to experience a long-term sustained OS benefit compared to the placebo + Gem/Cis arm. • This is also aligned with the smoothed OS hazard for the TOPAZ-1 D + gem/cis arm, which, as discussed above, changes direction over time, [redacted] . The [redacted] in hazard of death plausibly reflects the emergence of patients who experience long-term sustained OS benefit. Ensuring a model is selected that captures this x[redacted] is imperative, as this determines the long-term extrapolated OS values. As outlined above, the spline odds (1 knot) captures this [redacted], whereas the gamma model does not, therefore the spline odds (1 knot) long-term OS estimates are more clinically plausible.

		Considering all the points above, the spline odds (1 knot) is the most plausible distribution to model D + Gem/Cis OS, with a small proportion of patients alive at 10, 15 and 20 years as determined by examination of the hazards plot and consideration of the mechanism of action of durvalumab. **External clinical experts considered spline odds (1 knot) to be the best fitting model** • As outlined in the CS (section B.3.4.2.2), external clinical expert opinion was sought in a validation meeting and the majority of clinicians stated the spline 1 knot odds was the most clinically plausible extrapolation.[3] • Gamma was considered by clinical experts to underestimate the proportion of patients expected to be alive at 3 years in the UK.[3] **Other established HTA agencies have agreed that the spline odds (1 knot) is the most appropriate distribution to inform OS for D + Gem/Cis** • Canada's Drug and Health Technology Agency (CADTH) have completed their assessment of the cost-effectiveness of D + Gem/Cis for the treatment of patients with locally advanced or metastatic BTC and published a positive reimbursement recommendation. • The CADTH base case adopted the spline odds (1 knot) function to estimate OS for the D + Gem/Cis arm, which is aligned with the company base case for this submission and the preferred EAG distribution.[7] • The CADTH decision is highly relevant for this appraisal due to generalisability of both the BTC population and treatment options to the UK. Overall, due to the optimal fit of the spline odd (1 knot) distribution to the trial data and generation of plausible long-term OS estimates, validated by clinical experts, this model should be considered the only appropriate selection for decision-making.

<table>
<tr>
<td>Issue 3: Modelling progression-free survival for treatment with durvalumab with gemcitabine and cisplatin</td>
<td>No</td>
<td>
The spline odds (1 knot) distribution is the most plausible choice for the D + Gem/Cis arm

The distribution which provided the best within-trial fit according to AIC and BIC statistics was the spline-based model on the hazard scale with 3 knots. The top five best fitting models according to these statistics are shown in Table 2 below.

Table 2 Top five PFS AIC/BIC for D + Gem/Cis (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])
<table>
<tr><th></th><th colspan="2">D + Gem/Cis</th></tr>
<tr><th>Model</th><th>AIC (Rank)</th><th>BIC (Rank)</th></tr>
<tr><td>Spline 3 knots, scale = hazard</td><td>1,679.09 (1)</td><td>1,698.25 (1)</td></tr>
<tr><td>Spline 3 knots, scale = odds</td><td>1,683.94 (2)</td><td>1,703.10 (2)</td></tr>
<tr><td>Spline 3 knots, scale = normal</td><td>1,688.78 (3)</td><td>1,707.94 (3)</td></tr>
<tr><td>Spline 2 knots, scale = odds</td><td>1,700.90 (4)</td><td>1,716.22 (6)</td></tr>
<tr><td>Spline 1 knot, scale = odds</td><td>1,704.05 (5)</td><td>1,715.55 (4)</td></tr>
</table>

However, the spline 3 knots on the hazard scale (the EAG preferred distribution) was considered to [redacted] in the trial hazard, as shown in Figure 2. This was a common issue across all spline models with 3 knots.

</td>
</tr>
</table>

		Figure 2 Progression-free survival extrapolated hazard plot, scale=hazard, 1-3 spline knots - D + Gem/Cis, (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])  Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500mg and cisplatin 25mg; • Therefore, spline-based models using 1- and 2-knots were considered instead. The best fitting models according to AIC and BIC were both on the odds scale. • Visual inspection of the raw hazard (Figure 3) and kernel smoothed hazard (Figure 4, solid black line) shows that the trial hazard changes over time,

[redacted] Since this observation is absent from the raw data it should be disregarded

- Visual inspection of the spline-based odds models hazards compared to the smooth hazard (Figure 4) suggests that the 1 knot model fits the data better than the 2-knot model and provides a similar extrapolated fit as the 3-knot model, and so this was selected in the Company base case.

Figure 3 Progression-free survival hazard plot (raw) - D + Gem/Cis (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])

[redacted]

Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500mg and cisplatin 25mg; PFS, progress-free survival

		Figure 4: Progression-free survival extrapolated hazard plot, scale=odds, 1-3 spline knots - D + Gem/Cis, (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])  Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500mg and cisplatin 25mg • The Company also favour 1 knot models over 3 knot models as it diminishes the risk of overfitting the data and ensures the extrapolation is not based upon trends observed towards the end of the follow-up period informed by fewer events. • The majority of the five clinical experts interviewed by the Company expected 5% of patients to be progression free at the 24-month landmark analysis, indicating that the spline odds (1 knot) distribution provided the most clinically plausible estimate at 24 months (4.96%).

		While AIC/BIC statistics are an important consideration when selecting parametric distributions, additional factors, such as hazard plots and external clinical input must also be considered. In this case, while the EAG preferred scenario has the lowest AIC/BIC score, it clearly overestimates the initial increase in trial hazards and risks overfitting the data. Hence, the spline odds (1 knot) is the most clinically plausible parametric distribution for extrapolating PFS outcomes for the D + Gem/Cis arm.
Issue 4: Modelling treatment costs based on time to treatment discontinuation	No	**Use of PFS data to model treatment costs is more reflective of real-world treatment costs** • Patients in the TOPAZ-1 trial received treatment until clinical or imaging (RECIST v1.1) disease progression or unacceptable toxicity, withdrawal of consent, or any other discontinuation criteria. Patients who were clinically stable at initial disease progression could continue to receive study treatment at the discretion of the investigator and patient.[1] • Should D + Gem/Cis for treatment of BTC receive a positive recommendation from NICE, it is expected that the reimbursement criteria will indicate D + Gem/Cis administration should continue until disease progression, in line with the TOPAZ-1 trial administration. • PFS is therefore considered a more accurate reflection of real-world treatment costs. **Utilities should be modelled consistently with modelling of costs** • If costs are modelled based on time to treatment discontinuation instead of PFS, utilities should be modelled consistently with this approach i.e., whether a patient is on or off treatment. • Using the spline 3 knot hazard distribution to model TTD for costs and utilities for patients treated with D + Gem/Cis increased the ICER for the comparison of D + Gem/Cis versus + Gem/Cis to [redacted] per QALY gained, an increase of [redacted] from the Company base case.

		• Using the spline 2 knot odds distribution to model TTD for costs and utilities for patients treated with placebo + Gem/Cis increased the ICER for the comparison of D + Gem/Cis versus placebo + Gem/Cis to [redacted] per QALY gained, an increase of [redacted] from the Company base case.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
There are no additional issues to raise from the EAR.			

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
There are no changes to the Company's base case ICER.			

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

References

1. Oh D-Y, He AR, Qin S, et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. NEJM Evidence 2022;1(8):EVIDoa2200015. DOI: doi:10.1056/EVIDoa2200015.
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3. AstraZeneca. UK MC: KEE input on advanced biliary tract cancer (BTC) UK Questionnaire (durvalumab). Data on file 2023.
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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]

Clinical expert statement and technical engagement response form

Thank you for agreeing to comment on the external assessment report (EAR) for this evaluation, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The EAR and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

The deadline for your response is **5pm** on **Thursday 15 June.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating unresectable or advanced biliary tract cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Mairéad McNamara
2. Name of organisation	University of Manchester/The Christie NHS Foundation Trust
3. Job title or position	Senior Lecturer/Honorary Consultant in Medical Oncology
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with unresectable or advanced biliary tract cancer? ☐ A specialist in the clinical evidence base for unresectable or advanced biliary tract cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.

8. What is the main aim of treatment for unresectable or advanced biliary tract cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim of treatment for patients with unresectable or advanced biliary tract cancer is to control disease, and not cure, and to try to improve quantity and quality of life.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Longer periods of control of disease without the need to change treatment and improved overall survival over current standard.
10. In your view, is there an unmet need for patients and healthcare professionals in unresectable or advanced biliary tract cancer?	Yes. Better and more treatment options so that patients can live longer and better.
11. How is unresectable or advanced biliary tract cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	Patients with advanced biliary tract cancer are currently treated with standard of care cisplatin/gemcitabine in the first-line advanced setting as per results of the ABC-02 clinical trial (Valle et al 2010, NEJM). This is included in the ESMO guidelines (Vogel et al 2023, Ann Oncol) and NCCN guidelines. The pathway is well defined and there is consensus among the treating physicians in the NHS regarding standard of care (cisplatin/gemcitabine) in this setting. I practice in the UK (England). If approved, the combination of cisplatin/gemcitabine/durvalumab would be adopted as standard of care in the first-line advanced setting for patients with biliary tract cancer in the UK.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	Durvalumab is not currently available as standard of care in combination with cisplatin and gemcitabine for patients with advanced biliary tract cancer in the first-line advanced setting in the UK. If approved, the combination of cisplatin/gemcitabine/durvalumab should be used in all available treatment locations for patients with advanced biliary tract cancer in the first-line setting.

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	Durvalumab and all other immunotherapy agents are currently given as per standard of care in all treatment locations in the UK for other cancer types such as lung cancer, melanoma and kidney cancer, so all treatment locations have experience in delivering immunotherapy and dealing with any adverse events.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, based on the reported results, it is expected that overall survival will be improved in patients receiving the durvalumab/cisplatin/gemcitabine combination versus standard of care cisplatin/gemcitabine. If patients have delayed progression, then one would expect improved quality of life for longer in patients receiving cisplatin/gemcitabine/durvalumab versus standard of care cisplatin/gemcitabine.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No. All included populations in the TOPAZ trial benefited from the durvalumab/cisplatin/gemcitabine combination (Oh et al 2022, NEJM Evidence).
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	No, as immunotherapy is currently given as a combination in many cancer types (e.g. lung cancer, melanoma, kidney cancer) and also in hepatocellular carcinoma (most clinicians treating patients with biliary tract cancer also treat patients with hepatocellular carcinoma), so all treatment locations have experience in delivering this treatment and in dealing with any potential side effects.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Standard protocols are always followed by systemic day ward therapy units, with clearly described guidelines for administration, delay, omitting, stopping treatment, and dealing with adverse events. These are developed by

	pharmacists in conjunction with clinicians through review of summary of product characteristics and published trial protocols and published manuscripts.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	Standard of care cisplatin/gemcitabine is delivered intravenously as will the combination of durvalumab with cisplatin and gemcitabine. Patients receiving the combination of cisplatin with gemcitabine and durvalumab may have longer time before progression of disease and so less symptoms associated with increased disease activity, and potentially more time to live a relatively normal life and experience life events.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This is the first reported trial in over 10 years that has shown a statistically significantly improved overall survival over standard of care cisplatin/gemcitabine, and so is a step change for these patients, improving overall survival to over 1 year, with patients thus potentially living long enough to receive more novel therapies in a clinical trial or agents in development.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The adverse events, including grade 3 or 4 adverse events, reported for the combination of durvalumab with cisplatin and gemcitabine do not deviate numerically from those reported for standard of care cisplatin/gemcitabine in the TOPAZ clinical trial.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials?	Yes, the results from the clinical trial reflect those of the patients treated in the UK on the trial, and would be adopted as standard of care if this combination was approved. The most important outcome for all patients is survival and this has been reported from the clinical trial. Surrogate outcome measures were not used as

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	primary objectives. No additional adverse events of using this immunotherapy have become available since the trial results were published.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
22. How do data on real-world experience compare with the trial data?	The results of this trial were published in 2022 and durvalumab in combination with standard of care cisplatin and gemcitabine is not approved in the UK and therefore there is currently no reported real-world experience available to date that I know of to answer this question.
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	I am not aware of any equality issues at this stage of the evaluation.

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the EAR, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the EAR. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Issue 1: Generalisability of TOPAZ-1 trial results to NHS clinical practice (see sections 1.3 and 3.2.3 of the EAR) • Looking at the patient characteristics of the TOPAZ-1 trial, do you consider the participants in the trial to be representative of people with unresectable or advanced biliary tract cancer in the NHS? • Would people with biliary tract cancer who also have viral hepatitis B have a more favourable response to durvalumab (with gemcitabine and cisplatin)?	Looking at the patient characteristics of the TOPAZ-1 trial, I do consider the participants in the trial to be representative of people with unresectable or advanced biliary tract cancer treated in the NHS. Patients from the UK were also recruited to this trial. I don't think that there is any data reported to say that people with biliary tract cancer who also have viral hepatitis B have a more favourable response to durvalumab (with gemcitabine and cisplatin). Please see subgroup analysis poster presented at ASCO 2022 for subgroup analysis of patients recruited from Asia versus rest of world – there were no significant differences in outcome (Regional subgroup analysis of the Phase 3 TOPAZ-1 study of durvalumab (D) plus gemcitabine and cisplatin (GC) in advanced biliary tract cancer (BTC), ASCO 2022).

Issue 2: Modelling overall survival for treatment with durvalumab with gemcitabine and cisplatin (see sections 1.5 and 6.2 of the EAR) • What would you estimate the overall survival rates to be with standard care for a person with unresectable or advanced biliary tract cancer at 2 years, 3 years and 5 years? • Following treatment with durvalumab (with gemcitabine and cisplatin) how much would you estimate these rates to change?	It is very difficult to predict this figure as it is not known. I would estimate the overall survival rates with standard care (cisplatin/gemcitabine) for a person with unresectable or advanced biliary tract cancer at 2 years, 3 years and 5 years to be approximately 10%, 4% and 1% respectively (McNamara et al 2020, Journal of Hepatology). Following treatment with durvalumab (with gemcitabine and cisplatin), I would estimate these rates to change to approximately 24% (this figure is available from Oh et al 2022), 10-15% and 5-10% respectively.
Issue 3: Modelling progression-free survival for treatment with durvalumab with gemcitabine and cisplatin (see sections 1.5 and 6.3 of the EAR) • What would you estimate the progression-free survival rates to be with standard care for a person with unresectable or advanced biliary tract cancer at 6 months, 1 year and 2 years? • Following treatment with durvalumab (with gemcitabine and cisplatin) how much would you estimate these rates to change?	It is very difficult to predict this figure as it is not known. I would estimate the progression-free survival rates with standard care (cisplatin/gemcitabine) for a person with unresectable or advanced biliary tract cancer at 6 months, 1 year and 2 years to be approximately 55%, 18% and 4% respectively (McNamara et al 2020, Journal of Hepatology). Following treatment with durvalumab (with gemcitabine and cisplatin) I would estimate these rates to change to approx. 55%, 25-30%%, 10% respectively.
Issue 4: Modelling treatment costs based on time to treatment discontinuation (see sections 1.5 and 6.4 of the EAR) • How long on average is the treatment duration with durvalumab (with gemcitabine and cisplatin)? • What proportion of people would likely remain on treatment with durvalumab (with gemcitabine and cisplatin) at 6 months, 1 year and 2 years?	On average, the treatment duration with durvalumab (with gemcitabine and cisplatin) is approximately 7 months. This value is extremely difficult to predict. The proportion of people who would likely remain on treatment with durvalumab (with gemcitabine and cisplatin) at 6 months, 1 year and 2 years would be approximately 55%, 25-30% and 10% respectively.

• Is progression-free survival an appropriate proxy measure for time to treatment discontinuation for durvalumab (with gemcitabine and cisplatin)?	Yes.
Are there any important issues that have been missed in EAR?	No.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Overall survival for patients with advanced biliary tract cancer has remained unchanged for over 1 decade.
The combination of cisplatin with gemcitabine and durvalumab is the fist combination to have reported an improved overall survival over 1 year in over a decade.
No additional unexpected adverse events were reported with the combination of cisplatin/gemcitabine and durvalumab.
Availability of additional treatment options for this patient population are urgently needed.
Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with unresectable or advanced biliary tract cancer or caring for a patient with unresectable or advanced biliary tract cancer. The text boxes will expand as you type.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 21 July 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with unresectable or advanced biliary tract cancer

Table 1 About you, unresectable or advanced biliary tract cancer, current treatments and equality

1. Your name	Andrea Sheardown
2. Are you (please tick all that apply)	☐ A patient with unresectable or advanced biliary tract cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with unresectable or advanced biliary tract cancer? ☐ A patient organisation employee or volunteer? ☒ Other (please specify): I am a Cholangiocarcinoma patient that had a successful Liver Resection in November 2015, followed by 6 months of Chemotherapy.
3. Name of your nominating organisation	AMMF – The Cholangiocarcinoma Charity
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

	☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with unresectable or advanced biliary tract cancer? **If you are a carer (for someone with unresectable or advanced biliary tract cancer) please share your experience of caring for them**	I am not currently living with an unresectable biliary tract cancer, but do have direct experience of living with this cancer in advanced stages, from when I was originally diagnosed with Intrahepatic Cholangiocarcinoma (CCA) in October 2015. It was a very traumatic experience to even get to the stage of diagnosis with the lack of expertise in this field at a local hospital. The symptoms I had been displaying were misread as indigestion or muscle strain, even my blood tests were all normal. I was only 44 when diagnosed with CCA, a mother to 3 young children then aged just 4, 13 & 15. I had been living a healthy lifestyle and always been physically active, so when I was initially given the devastating news that I had just weeks to live it was a huge shock to us all. Thankfully, I managed to push for a 2nd opinion from the team of Liver Specialists at The Queen Elizabeth Hospital in Birmingham and successfully managed to undergo a resection in November 2015 to remove the large tumour from my liver. With no clear treatment pathways available following my surgery, we were left with no other viable option than to seek a private consultation with a CCA specialist. Through this private referral I was then able to go on to have a 6-month course of Capecitabine chemotherapy. I was hospitalised 3 times over the 6 months due to some of the adverse side effects from this treatment.

	If at this stage, I had been able to have had the Molecular Profiling to determine the molecular mutations of my tumour, my treatment plan could have been quite different. This cancer has a very high reoccurrence rate, so there is a high probability of my cancer returning. So new treatments like durvalumab in a first line treatment setting could make a huge difference to CCA patients like me going forward and help to give extra precious time with loved ones!
7a. What do you think of the current treatments and care available for unresectable or advanced biliary tract cancer on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	7a. Currently CCA patients here in the UK are left with limited options if they are unable to have a resection. With the lack of current treatment pathways, patients find it exceedingly difficult to get referred to a CCA specialist soon enough for any effect treatment. Within the NHS many CCA patients like me are forced to seek private alternatives. If surgery is not an option, patients are instead offered a chemotherapy combination of Gemcitabine and Cisplatin, which has not changed in a number of years and has had extremely limited success. This treatment which may or may not extend life, often leaves patients with a diminished quality of life, and has a huge impact on both the patient and their families/carers. Without Molecular profiling and more targeted treatment therapies like those available in other countries, CCA patients here in the UK will always face an uncertain future. 7b. I am not alone with my frustrations on these limited treatment options available to CCA patients here in the UK. I participate regularly on the online

	forum 'Cholangiocarcinoma Support (UK & Europe)' and these same views and concerns are echoed across this forum too. CCA is still referred to as a cancer affecting the over 65's. However recent evidence has confirmed that CCA is increasing across all age groups and especially those classed in there 'prime of life'. This point is also echoed on the forums too.
8. If there are disadvantages for patients of current NHS treatments for unresectable or advanced biliary tract cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	There are very limited treatments options available for CCA patients, and for patients unable to have a resection, they must put themselves through a gruelling chemotherapy regime that hasn't changed for decades, with no guarantees of extending their life. The current chemotherapy can give many adverse side effects, leaving many patients very weak and needing extended stays in hospital. It can then adversely impact their chances of going on to a more targeted second line of treatments, which they can't access until they have been through this first line of treatment. This can have a huge impact on the quality of life to both the patient and their family. Another disadvantage to CCA patients here in the UK is the lack of Molecular Profiling at diagnosis. Currently it seems molecular profiling under the NHS is available to only very few CCA patients in the UK, with many seeking this privately.
9a. If there are advantages of durvalumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability	9a. The first line treatment for those with inoperable cholangiocarcinoma has not changed in over a decade. Gemcitabine and Cisplatin is effective for some but not all, in terms of length of survival. The addition of durvalumab offers a realistic improvement in survival, without additional toxicity and side

to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does durvalumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	effects, for a group of patients for whom there is so little in terms of effective treatment. 9b. For those with CCA, each of the advantages of this improved first line therapy is important. 9c. Having the addition of durvalumab adds to survival and, as the treatment is given during the same visit to the hospital as the Gem/Cis, there is no disadvantage for the patient in being away from their families for extra time. Also because durvalumab is an immunotherapy it doesn't require molecular profiling which seems to be so difficult for those with CCA to access.
10. If there are disadvantages of durvalumab over current treatments on the NHS please describe these. For example, are there any risks with durvalumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I understand this treatment is well tolerated. I am not aware of any disadvantages, only advantages, of this combination treatment over the standard treatment.
11. Are there any groups of patients who might benefit more from durvalumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I believe that Durvalumab with gemcitabine and cisplatin in a first line therapy, could give a potential lifeline to all those with an inoperable CCA.
12. Are there any potential equality issues that should be taken into account when considering unresectable or advanced biliary tract cancer and durvalumab? Please explain if you think any groups of people with this condition are particularly disadvantaged	I can't see any obvious reasons why this would be an issue. I am not aware of any potential equality issues.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	I would just like to express how frustrating it is to keep hearing that Cholangiocarcinoma is a 'rare' cancer. There is more and more data becoming available that conflicts with this statement, and unfortunately with the limited treatments available for this cancer, more people will lose their lives unnecessarily. It is critical that more first line treatments like Durvalumab become available to all CCA patients.

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Incidence of CCA in increasing, with mortality that parallels incidence.
- Currently there is very little effective treatment for CCA patients.
- Many CCA patients are not considered for surgery nor for clinical trials – 'centres of expertise' are needed for confirmation of diagnosis and treatment pathway, and for molecular profiling.
- All CCA patients should receive molecular profiling at diagnosis or during 1st line treatment.
- I believe that Durvalumab with gemcitabine and cisplatin in a first line therapy, could give a potential lifeline to all those with an inoperable CCA.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]

Patient expert statement and technical engagement response form

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The external assessment report (EAR) and stakeholder responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with unresectable or advanced biliary tract cancer or caring for a patient with unresectable or advanced biliary tract cancer. The text boxes will expand as you type.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

The deadline for your response is **5pm** on **Friday 21 July 2023.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Part 1: Living with this condition or caring for a patient with unresectable or advanced biliary tract cancer

Table 1 About you, unresectable or advanced biliary tract cancer, current treatments and equality

1. Your name	Helen Morement
2. Are you (please tick all that apply)	☐ A patient with unresectable or advanced biliary tract cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with unresectable or advanced biliary tract cancer? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	AMMF – The Cholangiocarcinoma Charity
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☒ I agree with it and **do not wish to** complete this statement ☐ I agree with it and **will be** completing I have completed the Patient Organisation Submission on behalf of AMMF – The Cholangiocarcinoma Charity. My comments for a Patient Expert submission would be the same. But in particular I would like to stress the following: The first line treatment for those with inoperable cholangiocarcinoma has not

	changed in over a decade. The addition of durvalumab - an immunotherapy which therefore does not require molecular profiling nor the presence of particular mutuations or fusions - to the standard first line therapy of gemcitabine and cisplatin, offers a realistic improvement in terms of survival for a group of patients for whom there is so little in terms of effective treatment.
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with unresectable or advanced biliary tract cancer? **If you are a carer (for someone with unresectable or advanced biliary tract cancer) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for unresectable or advanced biliary tract cancer on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for unresectable or advanced biliary tract cancer (for example, how they are given or	

taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of durvalumab over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does durvalumab help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	
10. If there are disadvantages of durvalumab over current treatments on the NHS please describe these. For example, are there any risks with durvalumab? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from durvalumab or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering unresectable or advanced biliary tract cancer and durvalumab? Please explain if you think any groups of people with this condition are particularly disadvantaged	

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13. Are there any other issues that you would like the committee to consider?	

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.

Thank you for your time.

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Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]

Technical engagement response form

As a stakeholder you have been invited to comment on the External Assessment Report (EAR) for this evaluation.

Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.5).

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See the NICE health technology evaluation guidance development manual (sections 5.4.1 to 5.4.10) for more information.

The deadline for comments is **5pm** on **Thursday 15 June**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Cholangiocarcinoma-UK (CCA-UK, Special Interest Group of the British Association of the Study of Livr Disease, BASL)
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	AstraZeneca contributed £5,000 in sponsorship for the CCA-UK Basic Science national meeting in February 2023
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	

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Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Issue 1: Generalisability of TOPAZ-1 trial results to NHS clinical practice	Yes	In the relevant clinical trial (TOPAZ-1) providing evidence for use of durvalumab, it was used in combination with gemcitabine and cisplatin for the treatment of unresectable, locally advanced or metastatic BTC. TOPAZ-1 included adults (aged ≥18 years) with BTC whose cancer had spread into nearby tissues or lymph nodes (locally advanced disease) or to other organs in the body (metastatic disease) and could not be surgically removed, or patients whose cancer had returned after previous surgery. To be included in the trial, participants had to be in good general health, and have good kidney function, which is similar criteria for other prior systemic therapy for patients with this disease.
Issue 2: Modelling overall survival for treatment with durvalumab with gemcitabine and cisplatin	Yes	In the TOPAZ-1 trial, overall survival was significantly greater in participants who received durvalumab + Gem/Cis compared to participants who received placebo + Gem/Cis: 23.6% vs 11.5% respectively.
Issue 3: Modelling progression-free survival for treatment with durvalumab with gemcitabine and cisplatin	Yes	TOPAZ-1 trial Participants who received durvalumab + Gem/Cis also lived longer on average without disease progression (7.2 months) compared to participants who received placebo + Gem/Cis (5.7 months).

Issue 4: Modelling treatment costs based on time to treatment discontinuation	Yes	Durvulamab + Gem/Cis is associated with an improvement in survival, a gain in QALYs and greater costs than Gem/Cis. The exact results, as I understand it, are considered to be commercially confidential and I do not have this data.

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the EAR that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the EAR	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the EAR	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the EAR	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case

PLEASE DESCRIBE HERE

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]

Technical engagement response form

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Your comments and feedback on the key issues below are really valued. The EAR and stakeholders' responses are used by the committee to help it make decisions at the committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the EAR that are likely to be discussed by the committee. The key issues in the EAR reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the EAR (section 1.5).

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the EAR that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this evaluation, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

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The deadline for comments is **5pm** on **Thursday 15 June**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	[redacted]
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	AstraZeneca UK Ltd.
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months [Relevant companies are listed in the appraisal stakeholder list.] Please state the name of the company, amount, and purpose of funding.	Not applicable
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry	Not applicable

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the EAR.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response	
Issue 1: Generalisability of TOPAZ-1 trial results to NHS clinical practice	No	**Subgroup data from the TOPAZ-1 trial should be considered in the context of the statistically significant and clinically meaningful outcomes of the ITT** • The pre-planned subgroup analyses, including analyses by race and region, were not powered or sized to detect statistically significant differences for any of the individual subgroup evaluations and no adjustments were made for multiplicity.[1] • The direction of the results is equivalent across all subgroups, i.e., the point estimate of the hazard ratio for D + Gem/Cis vs. Gem/Cis for OS and PFS is consistently <1. • In summary, these subgroup analyses are not appropriate for decision-making as race and region are not effect modifiers for D + Gem/Cis treatment.	Thank you for providing the additional analysis of OS in patients with and without viral hepatitis. This subgroup analysis is informative and suggests that it is unlikely that differences in treatment effect between subgroups defined by race and region are driven by the relatively high incidence of hepatitis B in Asia. However, the EAG's observation that the treatment effect was numerically greater for patients in Asia than patients in the rest of the world remains valid.

		An exploratory interaction test for region and treatment suggested a consistent OS effect across Asia and Row • An exploratory, post hoc analysis using an unstratified Cox proportional hazards model to test the interaction between treatment and region suggested a consistent OS effect across Asia (HR, 0.72; 95% CI, 0.56–0.94) and RoW (HR, 0.89; 95% CI, 0.66–1.19); interaction test p=0.32.[2] **The TOPAZ-1 ITT data was considered generalisable to UK clinical outcomes by UK clinical experts** • As outlined in the CS (section B.2, summary box), UK clinicians reviewed the TOPAZ-1 data and confirmed the trial outcomes were generalisable to the outcomes expected for BTC patients in UK clinical practice.[3] • Clinicians also considered the OS subgroup analysis outcomes were generalisable to the FAS, highlighting that all subgroups experienced a favourable treatment effect of D + Gem/Cis compared to placebo + Gem/Cis.[3] • Thus, clinicians advocated for the broad use of D + Gem/Cis in all BTC patients who would otherwise be treated with Gem/Cis and have no contraindications to immunotherapy.[3] **The suggestion that outcomes for the Asian subgroups in the TOPAZ-1 trial are driven by**	

		patients with hepatitis B in the EAR should be disregarded • The EAR describes clinical advice received by the EAG regarding potential clinical rationale for a more favourable treatment effect of D + Gem/Cis versus placebo + Gem/Cis for patients in the 'Asian race' and the 'Asian region' subgroups compared to patients in the 'non-Asian race' and 'rest of the world' subgroup. Clinical advisors to the EAG have suggested that the more favourable treatment effect may be driven by the relatively high incidence of hepatitis B in Asia and patients with BTC who have hepatitis B experiencing a more favourable response to immunotherapy. • No robust clinical evidence has been provided to support this suggested rationale. The single reference included in the EAR (Dong 2023) suggests that patients with hepatitis B have an overexpression of PD-L1, which is considered a biomarker for predicting the efficacy of immune checkpoint inhibitors, such as durvalumab. However, as demonstrated in the TOPAZ-1 trial, the favourable treatment benefit of D + Gem/Cis compared with placebo + Gem/Cis was demonstrated independent of the level of PD-L1 expression when used for the treatment of BTC. • An additional analysis of OS in patients with and without viral hepatitis was carried out and demonstrated a consistent OS benefit across these two groups. An unstratified Cox	

		proportional hazards model was used to calculate the OS HRs:[1,2] ○ Patients with previous or ongoing hepatitis B and/or previous hepatitis C infection: OS HR: 0.79 (95% CI: 0.53, 1.16). ○ Patients without viral hepatitis: OS HR: 0.74 (95% CI: 0.56, 0.97). ○ TOPAZ-1 ITT: OS HR: 0.76 (95% CI: 0.64, 0.91). • The consistent effect observed between patients with and without viral hepatitis was further supported by an interaction test; p=0.79. • As such, the clinical rationale outlined in the EAR is considered speculative and should be disregarded. Overall, the ITT population and associated clinical outcomes from the TOPAZ-1 clinical trial are considered generalisable to the UK population. Furthermore, the clear clinical support for broad use of D + Gem/Cis in all BTC patients,[3] in line with updated EMSO BTC guidelines,[4] consolidates the need to ensure patient access to this innovative treatment option, which represents the first advancement in therapy for underserved BTC patients in over a decade, without delay.	
Issue 2: Modelling overall survival for treatment with durvalumab with gemcitabine and cisplatin	No	**The spline odds (1 knot) model provides a better fit to the observed data compared with the gamma model, as evidenced by the hazard plot, and provides a more clinically accurate long-term**	The EAG considers that the spline odds 1 knot curve generates plausible OS estimates. However, OS beyond the TOPAZ-1 trial period remains uncertain and, as

		estimate of OS, reflecting the understood mechanism of action of immunotherapies • The smoothed OS hazard for the TOPAZ-1 D + gem/cis arm and the hazards for the spline odds (1 knot) distribution and gamma distribution are presented in Figure 1, up to 36 months. The smoothed trial hazard shows changes in direction over time, [redacted]. As outlined in section B.3.4.2.2.1 of the CS, the smoothed trial hazards also shows that there is [redacted], but this is driven by the very low numbers of patients at risk at the end of the trial and therefore should not inform selection of parametric distribution models. • The spline odds (1 knot) hazard closely fits the trial hazard, mirroring the [redacted]. While the gamma hazard captures the [redacted] in the hazard observed in the TOPAZ-1 study; therefore, the gamma is a less optimal fit compared with the spline odd (1 knot) hazards. • As specified in NICE DSU TSD 21,[5] complex hazard functions, such as the hazard functions demonstrated by the D + Gem/Cis arm of the TOPAZ-1 trial, cannot be represented well by standard parametric models, and flexible models (such as spline-based models) that allow hazard functions with complex shapes are more appropriate.	highlighted in the EAG report, the spline odds 1 knot curve generates notably different cost effectiveness results to the gamma curve, which the EAG considers generates OS results that are as clinically and statistically plausible as the spline odds 1 knot curve. The EAG considers that using hazard plots to inform choice of curve is of limited value when OS data are heavily censored.

		Figure 1: OS hazard plots (trial data [kernel method], spline odds [1 knot] and gamma) - D + Gem/Cis, (TOPAZ-1 trial, 6.5month update [DCO 25 Feb 2022])	

		 **Immunotherapy modulates underlying disease dynamics and plausibly improves long-term overall survival expectations compared to standard chemotherapy treatment** • As stated in the CS, the OS base case for placebo + Gem/Cis was informed by the spline normal (1 knot). This distribution was considered appropriate by both the company and the EAG. The OS estimated by the spline normal (1 knot) at 10, 15 and 20 years is described in Table 1 and compared with OS estimated by the spline odds (1 knot) and gamma distributions for the D + Gem/Cis arm.	

Table 1: OS rates for D + Gem/Cis and placebo + Gem/Cis (TOPAZ-1 trial, 6.5-month update [DCO 25 Feb 2022])

Trial arm	D + Gem/Cis	
Parametric distribution	**Spline odds (1 knot) (EAG preferred scenario and Company base case)**	**Gam (EAG alte scena**
OS rate at 10 years	1.4%	0.01
OS rate at 15 years	0.6%	0.00
OS rate at 20 years	0.4%	0.00

- The gamma distribution for the D + Gem/Cis arm infers that there is no long-term OS benefit for patients who receive this treatment option compared to the current SoC of cytotoxic chemotherapy. Given the known mechanism of action of IOs, this is therefore not considered plausible.
- As outlined in the CS, IOs exhibit non-conventional survival dynamics, such as delayed curve separation. Unlike chemotherapy or radiotherapy, where tumour cells are killed directly, immunotherapy requires time to mount an effective immune response, and for that response to be translated into an observable and durable clinical response. Immune

		checkpoint inhibitors have demonstrated the ability to induce long-term remission despite treatment discontinuation, which has been well documented in melanoma patients who achieve a complete response to treatment.[6] The TOPAZ-1 trial results support this: ○ As reported in the CS (section B.2.1.5, table 12), in the TOPAZ-1 trial (IA-2 [DCO: 11 Aug 21]), more than double the number of patients in the D + Gem/Cis arm achieved a complete response versus the placebo + Gem/Cis arm (2.1% [7/341 patients] in the D + Gem/Cis group versus 0.6% (2/343 patients) in the placebo + Gem/Cis group. ○ The ORR was also higher for the D + Gem/Cis group with a nominally significant p-value (ORR = 26.7% [91/341 patients] in the D + Gem/Cis group versus 18.7% [64/343 patients] in the placebo + Gem/Cis group, p=0.011). ○ The CS also reported the DoR from the TOPAZ-1 trial (section B.2.6.1.6, table 13), notably at ≥12 months, 26.1% of patients in the D + Gem/Cis group remained in response compared with 15.0% in the placebo + Gem/Cis group. • Based on the mechanism of action of IOs, their potential ability to modulate the underlying	

		disease dynamics in some cancer patients, and lead to a durable, adaptive response compared with chemotherapy, it is not expected that the KM curves would re-join. Thus, a small number of patients are expected to experience a long-term sustained OS benefit compared to the placebo + Gem/Cis arm. • This is also aligned with the smoothed OS hazard for the TOPAZ-1 D + gem/cis arm, which, as discussed above, changes direction over time, [redacted]. The [redacted] in hazard of death plausibly reflects the emergence of patients who experience long-term sustained OS benefit. Ensuring a model is selected that captures this [redacted] is imperative, as this determines the long-term extrapolated OS values. As outlined above, the spline odds (1 knot) captures this [redacted], whereas the gamma model does not, therefore the spline odds (1 knot) long-term OS estimates are more clinically plausible. Considering all the points above, the spline odds (1 knot) is the most plausible distribution to model D + Gem/Cis OS, with a small proportion of patients alive at 10, 15 and 20 years as determined by examination of the hazards plot and consideration of the mechanism of action of durvalumab. **External clinical experts considered spline odds (1 knot) to be the best fitting model** • As outlined in the CS (section B.3.4.2.2), external clinical expert opinion was sought in a validation meeting and the majority of clinicians	

		stated the spline 1 knot odds was the most clinically plausible extrapolation.[3] • Gamma was considered by clinical experts to underestimate the proportion of patients expected to be alive at 3 years in the UK.[3] **Other established HTA agencies have agreed that the spline odds (1 knot) is the most appropriate distribution to inform OS for D + Gem/Cis** • Canada's Drug and Health Technology Agency (CADTH) have completed their assessment of the cost-effectiveness of D + Gem/Cis for the treatment of patients with locally advanced or metastatic BTC and published a positive reimbursement recommendation. • The CADTH base case adopted the spline odds (1 knot) function to estimate OS for the D + Gem/Cis arm, which is aligned with the company base case for this submission and the preferred EAG distribution.[7] • The CADTH decision is highly relevant for this appraisal due to generalisability of both the BTC population and treatment options to the UK. Overall, due to the optimal fit of the spline odd (1 knot) distribution to the trial data and generation of plausible long-term OS estimates, validated by clinical experts, this model should be considered the only appropriate selection for decision-making.	

<table>
<tr>
<td>Issue 3: Modelling progression-free survival for treatment with durvalumab with gemcitabine and cisplatin</td>
<td>No</td>
<td>
The spline odds (1 knot) distribution is the most plausible choice for the D + Gem/Cis arm

The distribution which provided the best within-trial fit according to AIC and BIC statistics was the spline-based model on the hazard scale with 3 knots. The top five best fitting models according to these statistics are shown in Table 2 below.

Table 2 Top five PFS AIC/BIC for D + Gem/Cis (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])
<table>
<tr><th></th><th colspan="2">D + Gem/Cis</th></tr>
<tr><th>Model</th><th>AIC (Rank)</th><th>BIC (Rank)</th></tr>
<tr><td>Spline 3 knots, scale = hazard</td><td>1,679.09 (1)</td><td>1,698.25 (1)</td></tr>
<tr><td>Spline 3 knots, scale = odds</td><td>1,683.94 (2)</td><td>1,703.10 (2)</td></tr>
<tr><td>Spline 3 knots, scale = normal</td><td>1,688.78 (3)</td><td>1,707.94 (3)</td></tr>
<tr><td>Spline 2 knots, scale = odds</td><td>1,700.90 (4)</td><td>1,716.22 (6)</td></tr>
<tr><td>Spline 1 knot, scale = odds</td><td>1,704.05 (5)</td><td>1,715.55 (4)</td></tr>
</table>

However, the spline 3 knots on the hazard scale (the EAG preferred distribution) was considered to [redacted] in the trial hazard, as shown in Figure 2. This was a common issue across all spline models with 3 knots.

</td>
<td>Clinical advice to the company was that it was very difficult to predict PFS for patients treated with D+Gem/Cis.

The EAG considered that it was most appropriate to model PFS using the spline hazard 3 knots distribution as this has the highest ranking AIC and BIC statistics and generates estimates that most closely match the TOPAZ-1 trial data at 6 and 12 months.</td>
</tr>
</table>

		Figure 2 Progression-free survival extrapolated hazard plot, scale=hazard, 1-3 spline knots - D + Gem/Cis, (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])  Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500mg and cisplatin 25mg; • Therefore, spline-based models using 1- and 2-knots were considered instead. The best	

		fitting models according to AIC and BIC were both on the odds scale. • Visual inspection of the raw hazard (Figure 3) and kernel smoothed hazard (Figure 4, solid black line) shows that the trial hazard changes over time, [redacted] Since this observation is absent from the raw data it should be disregarded • Visual inspection of the spline-based odds models hazards compared to the smooth hazard (Figure 4) suggests that the 1 knot model fits the data better than the 2-knot model and provides a similar extrapolated fit as the 3-knot model, and so this was selected in the Company base case. **Figure 3 Progression-free survival hazard plot (raw) - D + Gem/Cis (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])**	

		 Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500mg and cisplatin 25mg; PFS, progress-free survival **Figure 4: Progression-free survival extrapolated hazard plot, scale=odds, 1-3 spline knots - D + Gem/Cis, (TOPAZ-1 trial, IA-2 [DCO 11 Aug 2021])**	

		 Abbreviations: D, durvalumab; DCO, data cut-off; Gem/Cis, gemcitabine 1,500mg and cisplatin 25mg • The Company also favour 1 knot models over 3 knot models as it diminishes the risk of overfitting the data and ensures the extrapolation is not based upon trends observed towards the end of the follow-up period informed by fewer events. • The majority of the five clinical experts interviewed by the Company expected 5% of patients to be progression free at the 24-month landmark analysis, indicating that the spline odds (1 knot) distribution provided the	

		most clinically plausible estimate at 24 months (4.96%). While AIC/BIC statistics are an important consideration when selecting parametric distributions, additional factors, such as hazard plots and external clinical input must also be considered. In this case, while the EAG preferred scenario has the lowest AIC/BIC score, it clearly overestimates the initial increase in trial hazards and risks overfitting the data. Hence, the spline odds (1 knot) is the most clinically plausible parametric distribution for extrapolating PFS outcomes for the D + Gem/Cis arm.	
Issue 4: Modelling treatment costs based on time to treatment discontinuation	No	**Use of PFS data to model treatment costs is more reflective of real-world treatment costs** • Patients in the TOPAZ-1 trial received treatment until clinical or imaging (RECIST v1.1) disease progression or unacceptable toxicity, withdrawal of consent, or any other discontinuation criteria. Patients who were clinically stable at initial disease progression could continue to receive study treatment at the discretion of the investigator and patient.[1] • Should D + Gem/Cis for treatment of BTC receive a positive recommendation from NICE, it is expected that the reimbursement criteria will indicate D + Gem/Cis administration should continue until disease progression, in line with the TOPAZ-1 trial administration.	The company efficacy estimates are based on TOPAZ-1 trial arm treatment durations. Therefore, the EAG considers that TOPAZ-1 trial TTD data, rather than PFS data, should be used to estimate time on treatment. The EAG does not consider that consistency is a robust argument for using on- and off-treatment utility values rather than PFS and PD health state utility values.

		• PFS is therefore considered a more accurate reflection of real-world treatment costs. **Utilities should be modelled consistently with modelling of costs** • If costs are modelled based on time to treatment discontinuation instead of PFS, utilities should be modelled consistently with this approach i.e., whether a patient is on or off treatment. • Using the spline 3 knot hazard distribution to model TTD for costs and utilities for patients treated with D + Gem/Cis increased the ICER for the comparison of D + Gem/Cis versus + Gem/Cis to [redacted] per QALY gained, an increase of [redacted] from the Company base case. • Using the spline 2 knot odds distribution to model TTD for costs and utilities for patients treated with placebo + Gem/Cis increased the ICER for the comparison of D + Gem/Cis versus placebo + Gem/Cis to [redacted] per QALY gained, an increase of [redacted] from the Company base case.	

Additional issues

All: Please use the table below to respond to additional issues in the EAR that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this evaluation (for example, at the clarification stage).

Table 3 Additional issues from the EAR

Issue from the EAR	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
There are no additional issues to raise from the EAR.			

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the EAR that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
There are no changes to the Company's base case ICER.			

Sensitivity analyses around revised base case
PLEASE DESCRIBE HERE

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