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.

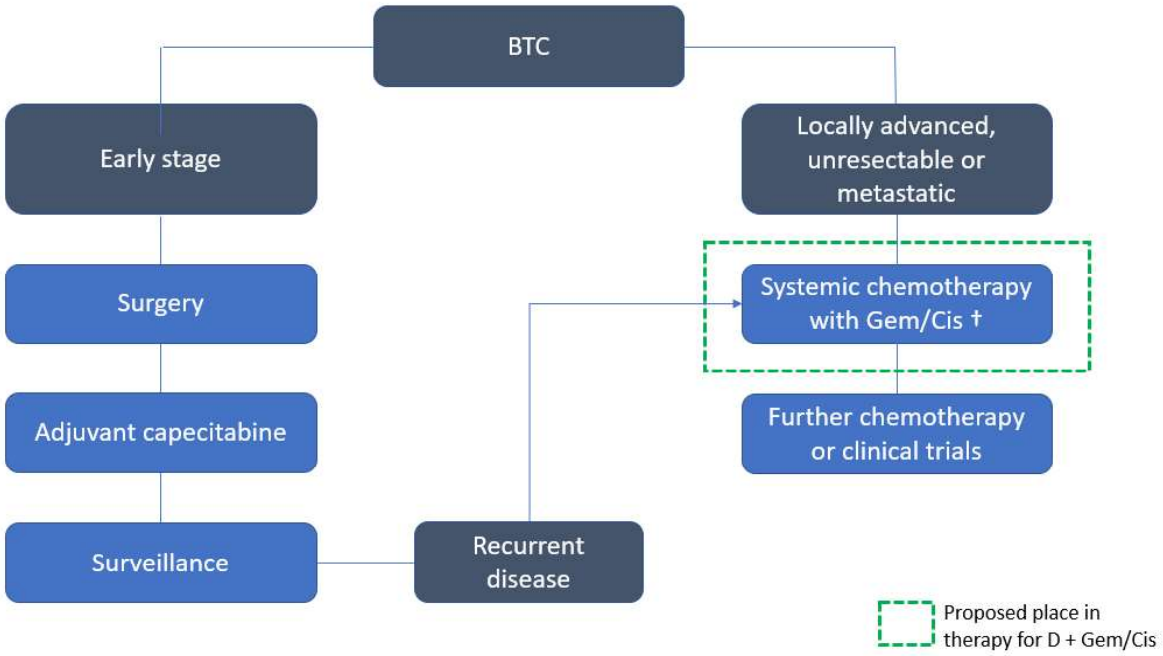

Figure 1 Company's overview of treatment pathway for NHS patients with unresectable or advanced biliary tract cancer

†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.

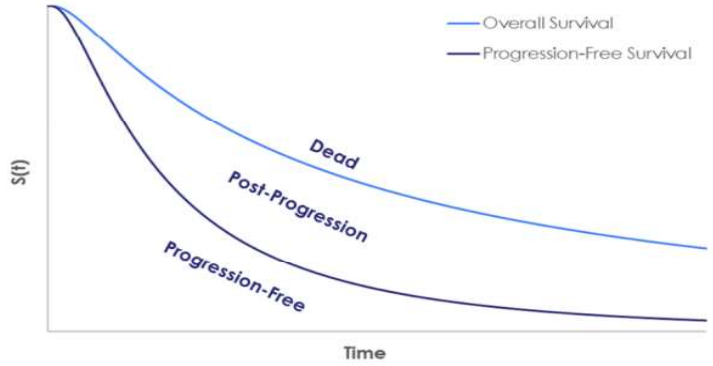

Figure 2 Company model schematic

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].

7 REFERENCES

1. 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. 2022.
2. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: Epidemiology and risk factors. Liver Int. 2019; 39:19-31.
3. Cancer Research UK. Types of bile duct cancer. 2020 [cited March 2023]; Available from: https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/types.
4. Cancer Research UK. What is bile duct cancer? 2020 [cited March 2023]; Available from: https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/about.
5. Cancer Research UK. Gallbladder cancer incidence statistics. 2021 [cited March 2023]; Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/gallbladder-cancer/incidence#heading-Two.
6. Cancer Research UK. Survival. 2020 [cited March 2023]; Available from: https://www.cancerresearchuk.org/about-cancer/gallbladder-cancer/survival.
7. Cancer Research UK. Survival for bile duct cancer. 2020 [cited March 2023]; Available from: https://www.cancerresearchuk.org/about-cancer/bile-duct-cancer/survival.
8. MHRA. Imfinzi Summary of Product characteristics. 2023 [cited April 2023]; Available from: https://mhraproducts4853.blob.core.windows.net/docs/c631685fa069c1e6b3c414043180b30082374d65.
9. AstraZeneca. IMFINZI 50 mg/mL concentrate for solution for infusion. Summary of Product Characteristics. 2023 [cited March 2023]; Available from: https://www.medicines.org.uk/emc/product/9495/smpc.
10. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A*, et al.* Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. NEJM 2010; 362:1273-81.
11. NHS England. National Cancer Drugs Fund List: NIV12CV. 2022 [cited April 2023]; Available from: https://www.england.nhs.uk/wp-content/uploads/2017/04/National-cancer-drugs-fund-list_ver1-234.pdf.
12. National Institute for Health and Care Excellence (NICE). Pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement: Technology appraisal guidance [TA722]. 2021 [cited March 2023]; Available from: https://www.nice.org.uk/guidance/ta722/documents/committee-papers.
13. National Institute for Health and Care Excellence (NICE). Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]: Final scope. 2022 [cited March 2023]; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10920/documents.
14. 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). Clinical Study Report 2022; Data on file.
15. 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. 2022; 1.
16. Valle JW, Wasan H, Lopes A, Backen AC, Palmer DH, Morris K*, et al.* Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): a randomised phase 2 trial. Lancet Oncol. 2015; 16:967-78.
17. Lee J, Park SH, Chang HM, Kim JS, Choi HJ, Lee MA*, et al.* Gemcitabine and oxaliplatin with or without erlotinib in advanced biliary-tract cancer: a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2012; 13:181-8.

18. Malka D, Cervera P, Foulon S, Trarbach T, de la Fouchardière C, Boucher E*, et al.* Gemcitabine and oxaliplatin with or without cetuximab in advanced biliary-tract cancer (BINGO): a randomised, open-label, non-comparative phase 2 trial. Lancet Oncol. 2014; 15:819-28.
19. Leone F, Marino D, Cereda S, Filippi R, Belli C, Spadi R*, et al.* Panitumumab in combination with gemcitabine and oxaliplatin does not prolong survival in wild-type KRAS advanced biliary tract cancer: A randomized phase 2 trial (Vecti-BIL study). Cancer. 2016; 122:574-81.
20. Valle JW, Vogel A, Denlinger CS, He AR, Bai LY, Orlova R*, et al.* Addition of ramucirumab or merestinib to standard first-line chemotherapy for locally advanced or metastatic biliary tract cancer: a randomised, double-blind, multicentre, phase 2 study. Lancet Oncol. 2021; 22:1468-82.
21. National Institute for Health and Care Excellence. Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]. 2022 [cited March 2023]; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10920.
22. National Institute for Health and Care Excellence. Pembrolizumab with gemcitabine and cisplatin for untreated advanced biliary tract cancer [ID4034]. 2022 [cited March 2023]; Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10925.
23. Centre for Reviews and Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. York: University of York; 2008 [cited March 2023]; Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf.
24. Oh DY, Lee KH, Lee DW, Yoon J, Kim TY, Bang JH*, 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; 7:522-32.
25. Vogel A, Boeck S, Waidmann O, Bitzer M, Wenzel P, Belle S*, et al.* 52MO A randomized phase II trial of durvalumab and tremelIMUmab with gemcitabine or gemcitabine and cisplatin compared to gemcitabine and cisplatin in treatment-naïve patients with CHolangio-and gallbladdEr Carcinoma (IMMUCHEC). AnnOncol. 2022; 33:S563.
26. Dong H, Xue C, Zheng Y, Zhang X, Hu Z, Lu X*, et al.* Efficacy and Safety of Immune Checkpoint Inhibitors in Patients with Cancer and Hepatitis B or C: A Systematic Review and Meta-Analysis. J Oncol. 2023; 2023:2525903.
27. 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.
28. 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). Clinical Study Protocol Version 8. 2022; Data on file.
29. Freeman SC, Cooper NJ, Sutton AJ, Crowther MJ, Carpenter JR, Hawkins N. Challenges of modelling approaches for network meta-analysis of time-to-event outcomes in the presence of non-proportional hazards to aid decision making: Application to a melanoma network. Stat Methods Med Res. 2022; 31:839-61.
30. European Organisation For Research And Treatment Of Cancer (EORTC). EORTC Quality of Life of cancer patients (QLQ-C30). 2021 [cited March 2023]; Available from: https://qol.eortc.org/questionnaire/eortc-qlq-c30/.
31. European Organisation For Research And Treatment Of Cancer (EORTC). EORTC Quality of Life Questionnaires (Cholangiocarcinoma and gallbladder cancer). 2023 [cited March 2023]; Available from: https://qol.eortc.org/questionnaire/qlq-bil21/.

32. EuroQol Research Foundation. EQ-5D. 2023 [cited March 2023]; Available from: https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/https://euroqol.org/eq-5d-instruments/.
33. National Institutes of Health National Cancer Institute. PRO-CTCAE Instrument & Form Builder. 2023 [cited March 2023]; Available from: https://healthcaredelivery.cancer.gov/pro-ctcae/instrument-pro.html.
34. MAPI research Trust. Patient Global Impressions Scale. 2023 [cited March 2023]; Available from: https://eprovide.mapi-trust.org/instruments/patient-global-impressions-scale-change-improvement-severity.
35. Sangchan A, Chaiyakunapruk N, Supakankunti S, Pugkhem A, Mairiang P. Cost utility analysis of endoscopic biliary stent in unresectable hilar cholangiocarcinoma: decision analytic modeling approach. Hepato-gastroenterology. 2014; 61:1175-81.
36. Suttichaimongkol T, Borntrakulpipat C, Sangchan A, Mairiang P, Mairiang E, Sukeepaisarnjaroen W, *et al.* Economic evaluation of palliative biliary drainage in unresectable hilar cholangiocarcinoma. J Med Assoc Thail. 2018; 101:S44-S52.
37. Roth JA, Carlson JJ. Cost-effectiveness of gemcitabine + cisplatin vs. gemcitabine monotherapy in advanced biliary tract cancer. J Gastrointest Oncol. 2012; 43:215-23.
38. Tsukiyama I, Ejiri M, Yamamoto Y, Nakao H, Yoneda M, Matsuura K, *et al.* A Cost-Effectiveness Analysis of Gemcitabine plus Cisplatin Versus Gemcitabine Alone for Treatment of Advanced Biliary Tract Cancer in Japan. J Gastrointest Cancer. 2017; 48:326-32.
39. Chen R, Zhang Y, Lin K, Huang D, You M, Lai Y, *et al.* Cost-Effectiveness Analysis of Capecitabine Plus Oxaliplatin Versus Gemcitabine Plus Oxaliplatin as First-Line Therapy for Advanced Biliary Tract Cancers. Front Pharmacol. 2022; 13:871262.
40. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ. 1996; 313:275-83.
41. Latimer N. NICE DSU Technical Support Document 14: Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2013 [cited April 2023]; Available from: https://www.ncbi.nlm.nih.gov/books/NBK395885/pdf/Bookshelf_NBK395885.pdf.
42. Rutherford MJ, Lambert PC, Sweeting MJ, Pennington B, Crowther MJ, Abrams KR, *et al.* NICE DSU Technical Support Document 21: Flexible methods for survival analysis 2020.
43. Hernandez-Alava M, Pudney S. Econometric modelling of multiple self-reports of health states: The switch from EQ-5D-3L to EQ-5D-5L in evaluating drug therapies for rheumatoid arthritis. J Health Econ. 2017; 55:139-52.
44. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value Health. 2010; 13:509-18.
45. Gov.uk. Drugs and pharmaceutical electronic market information tool (eMIT). 2022 [January 2023]; Available from: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit.
46. Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, Arora A, *et al.* Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2021; 22:690-701.
47. National Institute for H, Care E. British National Formulary. 2023 [January 2023]; Available from: https://bnf.nice.org.uk/.
48. European Society for Medical Oncology. Biliary tract cancer: An ESMO guide for patients. 2019 [cited March 2023]; Available from: https://www.esmo.org/content/download/266801/5310983/1/EN-Biliary-Tract-Cancer-Guide-for-Patients.pdf.
49. AstraZeneca. UK MC: KEE input on advanced biliary tract cancer (BTC) UK Questionnaire (durvalumab). Data on file. 2023.

50. NHS England. National Schedule of NHS Costs 2020/2021. Available from: https://www.england.nhs.uk/publication/2020-21-national-cost-collection-data-publication/.
51. Curtis L, Burns A. Unit costs of Health and Social Care PSSRU, University of Kent. 2019.
52. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. J Palliat Med. 2015; 29:899-907.
53. Office for National Statistics. National life tables: England and Wales. 2021; Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables/current.
54. McNamara MG, Lopes A, Wasan H, Malka D, Goldstein D, Shannon J, *et al.* Landmark survival analysis and impact of anatomic site of origin in prospective clinical trials of biliary tract cancer. J Hepatol. 2020; 73:1109-17.

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.

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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.