Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer (ID4031)

Slides for public – contains no confidential information

PART 1

Technology appraisal committee C [8 August 2023]

Chair: Stephen O'Brien

Lead team: Iftab Akram, Mark Corbett, Stella O'Brien

External assessment group (EAG): Liverpool Reviews & Implementation Group (LRiG)

Technical team: Madiha Adam, Anita Sangha, Sally Doss, Ross Dent

Company: AstraZeneca

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer (ID4031)

- ✓**Background**
- ❑Clinical evidence and key clinical issues to consider
- ❑Modelling and key cost effectiveness issues to consider
- ❑Other considerations and base case assumptions
- ❑Summary

NICE National Institute for Health and Care Excellence

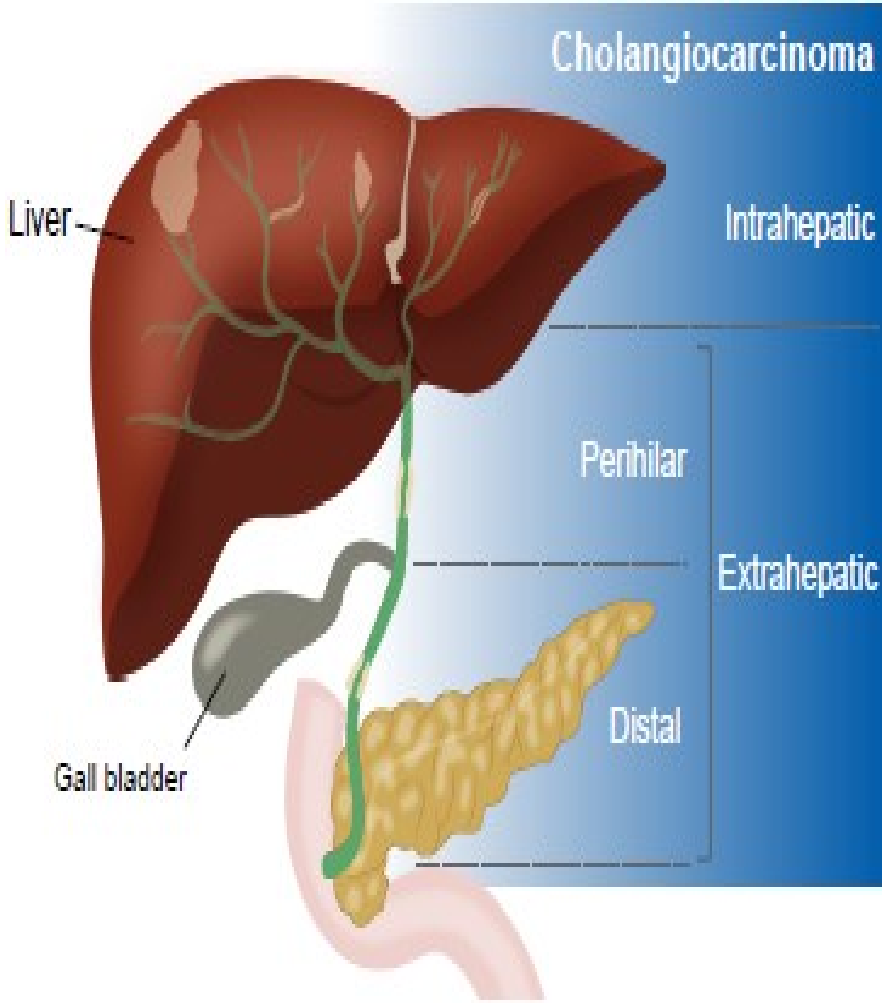
Biliary tract cancer (1)

Background

- The biliary tract includes the organs and ducts that make and store bile
- Biliary tract cancer (BTC) includes bile duct cancer (cholangiocarcinoma), gallbladder cancer and ampullary cancer

Epidemiology

- England per year: ~2,800 adults diagnosed with cholangiocarcinoma (including ampullary cancer) and ~1,100 with gallbladder cancer
- Bile duct cancer can develop at any age but most people who develop it are over 65 years
- Gallbladder cancer is more common in people aged between 85 to 89 years



Key sources: NICE final scope for ID4031 and Cancer Research UK
Abbreviations: BTC, biliary tract cancer

Biliary tract cancer (2)

Symptoms

- May include fatigue, abdominal pain, nausea, insomnia, depression, brain fog
- If bile ducts are blocked, this may cause jaundice, itchy skin, cholangitis (inflammation of bile duct system)

Disease prognosis

- Most affected adults are diagnosed and staged with unresectable, advanced or metastatic disease
    - median overall survival is usually <1 year with “mortality mirroring incidence”
- Approximately 20% of adults with BTC have early stage disease that is resectable and can be treated surgically with curative intent (up to 80% experience disease recurrence within 2 years)

Key sources: company submission, Annals of Oncology (DOI: https://doi.org/10.1093/annonc/mdz183.007)
Abbreviations: BTC, biliary tract cancer

Durvalumab (IMFINZI, AstraZeneca)

Marketing authorisation (MA)	• Durvalumab in combination with gemcitabine and cisplatin (Gem/Cis) is indicated for the first-line treatment of adults with locally advanced, unresectable, or metastatic biliary tract cancer • MHRA MA issued on 25 January 2023 (Project Orbis drug)
Mechanism of action	Monoclonal antibody that selectively blocks the interaction of programmed death-ligand 1 (PD-L1) with receptors PD-1 and CD80

Administration	• Durvalumab (1,500mg) is administered as an IV infusion
	  ○ every 3 weeks for up to 8 cycles in combination with Gem/Cis
	  ○ as maintenance monotherapy every 4 weeks until disease progression or unacceptable toxicity

Price	• List price is £2,466 for a 500 mg per 10 mL concentrate vial • The company has a confidential commercial arrangement [simple discount patient access scheme (PAS)] • Average cost of treatment: ~£[redacted] (includes durvalumab PAS, treatment duration → 5-year mean PFS extrapolated from TOPAZ-1)

Abbreviations: IV, intravenous; MHRA, Medicines and Healthcare Products Regulatory Agency; PAS, patient access scheme

Treatment pathway

Unresectable, advanced or metastatic BTC, including adults with recurrent disease after treatment with curative intent†

First line	**Gemcitabine + cisplatin (Gem/Cis)**	**Proposed: Durvalumab + Gem/Cis (ID4031)**
Second line	**Chemotherapy or clinical trials**	**Pemigatinib* for relapsed or refractory advanced CCA with FGFR2 fusion or rearrangement (TA722)**

Company's proposed positioning for durvalumab + Gem/Cis in the first line setting is to replace Gem/Cis as standard of care for unresectable or advanced BTC

† Includes surgery and adjuvant capecitabine: recurrence must be >6 months after surgery or completion of adjuvant therapy

* 5% receive pemigatinib in the company's model (based on clinical expert opinion)

Abbreviations: BTC, biliary tract cancer; CCA, cholangiocarcinoma; FGFR2, fibroblast growth factor receptor 2

Perspectives on living with BTC

Submissions from 2 patient experts, AMMF—The Cholangiocarcinoma Charity and British Liver Trust

People living with biliary tract cancer have unmet needs for:

- Earlier diagnosis before the cancer is inoperable, current diagnosis is at late stage with limited overall survival
- Effective and greater range of treatment options that improve what is currently a very poor quality of life
  - first line treatment for adults with inoperable cholangiocarcinoma has not changed in over a decade and offers "modest, if any, benefit"
  - patients, families and carers struggle to accept "there is so little in the treatment armoury"
  - multidisciplinary team support is needed for managing symptoms
- Centres of expertise and access to molecular profiling at the time of diagnosis

"[Gem/Cis] often leaves patients with a diminished quality of life…huge impact on both the patients…their families/carers."

"Patients and carers look to new technologies and therapies with the hope these will offer extended survival over the more standard chemotherapies and/or best supportive care that might be offered."

Abbreviations: AMMF, Alan Morement Memorial Fund; Gem/Cis, gemcitabine and cisplatin

Clinical perspectives

Submission and technical engagement response from Cholangiocarcinoma UK and 1 clinical expert

Current treatment and prognosis:

- Aim of treatment for adults with unresectable or advanced biliary tract cancer is
  - to control disease as no curative option is available
  - to improve length of survival and quality of life
- Additional treatment options are an urgent, unmet need

Durvalumab with gemcitabine and cisplatin (Gem/Cis):

- expected to improve overall survival versus standard of care
- no additional investment is needed to introduce the technology (for example, facilities, equipment, or training)

"This is the first reported trial in over 10 years that has shown a statistically significant improved overall survival over standard of care [Gem/Cis], and so is a step change for these patients…"

Abbreviations: Gem/Cis, gemcitabine and cisplatin

Other considerations

Innovation

- Company highlights that durvalumab (with Gem/Cis) is the first immunotherapy to be approved for first-line locally advanced, unresectable, or metastatic biliary tract cancer

- Company does not highlight any benefits not captured in the QALY calculations

Equality considerations

- A stakeholder commented that:
  - liver cancer disproportionally affects people from disadvantaged backgrounds
  - all patients need equal access to this treatment regardless of their location
  - NICE notes that access to treatments is an implementation issue that cannot be addressed by a NICE technology appraisal recommendation

Are there any equality issues that need to be considered?

Abbreviations: Gem/Cis, gemcitabine and cisplatin; QALY, quality-adjusted-life-year

Key issues

Key - Not resolved: Unresolvable:

Issue	Type of uncertainty	Resolved?	ICER impact
Generalisability of TOPAZ-1 trial results to NHS patients	Structural	No – for discussion	Not known
Modelling overall survival for patients treated with durvalumab with Gem/Cis	Methodological	No – for discussion	Large
Modelling progression-free survival for patients treated with durvalumab with Gem/Cis	Methodological	No – for discussion	Moderate
Modelling treatment costs based on time to treatment discontinuation	Methodological	No – for discussion	Large

Abbreviations: Gem/Cis, gemcitabine and cisplatin; ICER, incremental cost effectiveness ratio

Decision problem → population, intervention and outcomes

	Final scope	Company	EAG comments
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
Intervention	Durvalumab with gemcitabine and cisplatin	As per scope	As per scope
Outcomes	• Overall survival • Progression-free survival • Response rates (including overall response rates) • Time to treatment discontinuation • Adverse effects of treatment • Health-related quality of life	As per scope	Company presented clinical effectiveness evidence from the TOPAZ-1 trial for all outcomes listed in the NICE final scope

Decision problem → comparators

Final scope	Company considerations	EAG comments
Established clinical management without durvalumab including: • Gemcitabine with cisplatin For people with poor kidney function: • Gemcitabine with oxaliplatin For frailer people: • Gemcitabine alone • Fluorouracil (5-FU) alone • Capecitabine alone	• Gemcitabine with cisplatin is the only relevant comparator • People with poor kidney function or who are frail (ECOG PS>1) are unable to tolerate cisplatin and so treatment with durvalumab + Gem/Cis is not suitable for them	• Agree that people with poor kidney function are not offered treatment with cisplatin and so will not receive durvalumab + Gem/Cis or Gem/Cis • Some people with ECOG PS=2 who are at the fitter end of the scale can tolerate treatment with cisplatin and are currently treated with Gem/Cis

Is Gem/Cis the most appropriate comparator to durvalumab + Gem/Cis?

Abbreviations: ECOG, Eastern Cooperative Oncology Group; Gem/Cis, gemcitabine and cisplatin; PS, performance status

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer (ID4031)

- ❑ Background
- ✓ **Clinical evidence and key clinical issues to consider**
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Other considerations and base case assumptions
- ❑ Summary

NICE National Institute for Health and Care Excellence

Key clinical trial: TOPAZ -1

	TOPAZ – 1 [ongoing]
Design	Phase 3, international, double-blind, placebo-controlled randomised controlled trial
Population	Adults with previously untreated unresectable advanced or metastatic BTC, or who have developed recurrent disease >6 months after surgery or completion of adjuvant therapy
Intervention	Durvalumab with Gem/Cis every 3 weeks (up to 8 cycles) [n=341] Durvalumab monotherapy every 4 weeks until progression
Comparator	Matched placebo with Gem/Cis [n=344]
Primary outcome	Overall survival (OS)
Key secondary outcomes	Progression-free survival (PFS), objective response rate (ORR), time to treatment discontinuation* (TTD), adverse events (AEs) and health-related quality of life (HRQoL)
Locations	105 sites in 17 countries (8 sites in UK, n=47)

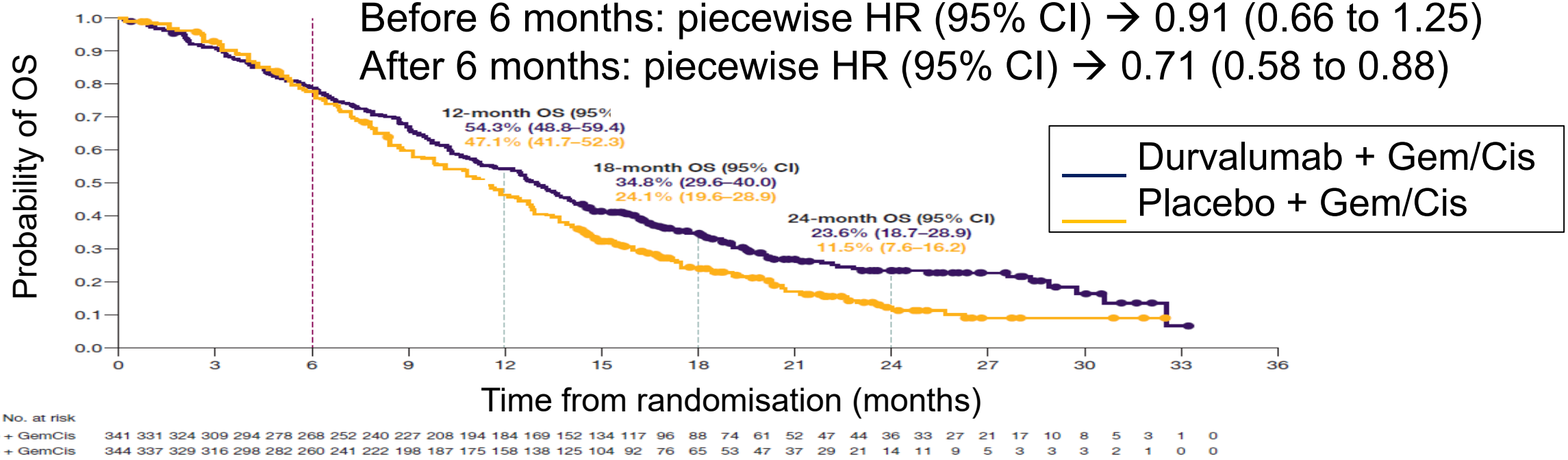
NICE

*TTD was not included in the pre-specified trial outcomes but calculated post-hoc by the company
Abbreviations: BTC, biliary tract cancer; Gem/Cis, gemcitabine and cisplatin

TOPAZ-1 results – Overall survival

Results from ITT/FAS population (6.5-month update – data cut-off February 2022)

Before 6 months: piecewise HR (95% CI) → 0.91 (0.66 to 1.25)
After 6 months: piecewise HR (95% CI) → 0.71 (0.58 to 0.88)



Median OS (95% CI), months		HR durvalumab + Gem/Cis vs placebo + Gem/Cis
Durvalumab + Gem/Cis	Placebo + Gem/Cis	
12.9 (11.6 to 14.1)	11.3 (10.1 to 12.5)	0.76 (95% CI 0.64 to 0.91)[a]

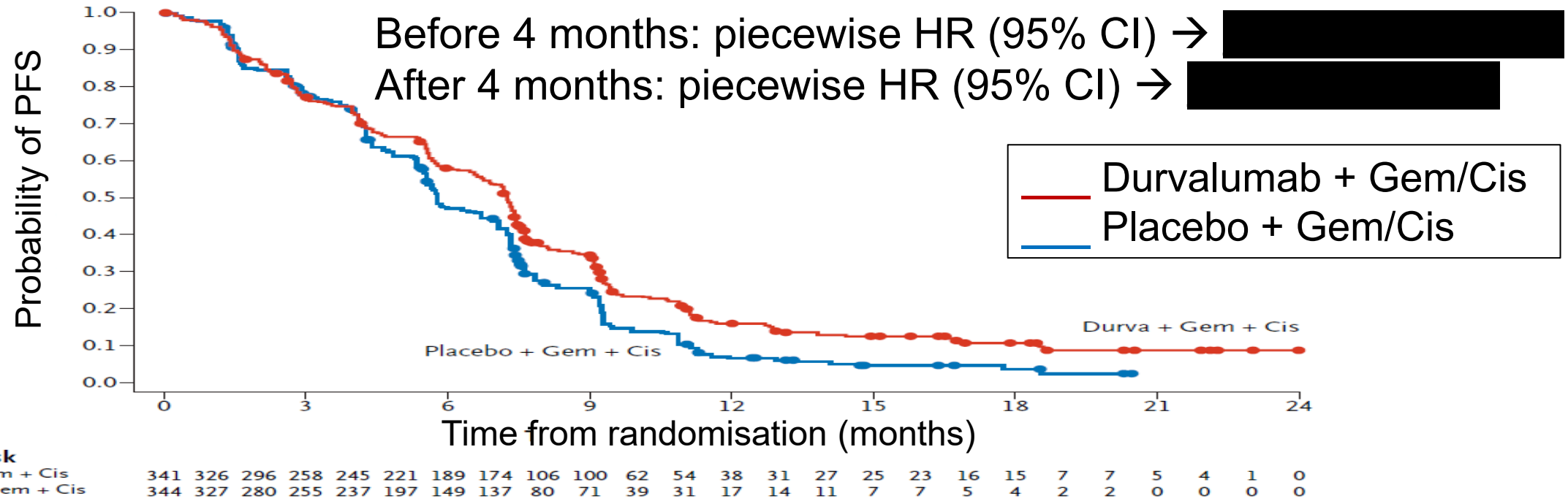
EAG → piecewise HRs are more informative than HR provided for the whole trial period

[a] No p-value reported as formal statistical testing was not performed at the 6.5 month updated analysis of OS

Abbreviations: CI, confidence interval; FAS, full analysis set; Gem/Cis, gemcitabine and cisplatin; HR, hazard ratio; ITT, intention to treat

TOPAZ-1 results – Progression-free survival

Results from ITT/FAS population (interim analysis 2 – data cut-off August 2021)



Median PFS (95% CI), months		HR durvalumab + Gem/Cis vs placebo + Gem/Cis
Durvalumab + Gem/Cis	Placebo + Gem/Cis	
7.2 (6.7 to 7.4)	5.7 (5.6 to 6.7)	0.75 (95% CI 0.63 to 0.89; p=0.001)

EAG → piecewise HRs are more informative than HR provided for the whole trial period

Abbreviations: CI, confidence interval; FAS, full analysis set; Gem/Cis, gemcitabine and cisplatin; HR, hazard ratio; ITT, intention to treat

Key issue: Generalisability of TOPAZ-1 trial results (1)

Background: trial population → age, ECOG PS and ampullary cancer

- EAG noted that people in trial are younger (median age 64 years) than those presenting with BTC in the NHS (average age around 70 years)
- Trial included people with ECOG PS of 0 or 1
  - Clinical advice to the EAG:
    - people with ECOG PS=2 who are fit enough may be offered Gem/Cis
    - clinicians would be cautious about using durvalumab + Gem/Cis in people with ECOG PS=2 due to patient frailty and lack of data from the TOPAZ-1 trial
- People with ampullary cancer were excluded from the TOPAZ-1 trial (because the genetic profile of ampullary cancer differs from the other BTC subtypes)
  - Clinical advice to the EAG:
    - appropriate to exclude patients with ampullary cancer from the trial
    - treatment for ampullary cancer is variable across treatment centres and includes either Gem/Cis or other chemotherapy regimens

Abbreviations: BTC, biliary tract cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status

Key issue: Generalisability of TOPAZ-1 trial results (2)

Background: trial population → outcomes for Asian subgroups

- Around half (54.6%) of people in TOPAZ-1 were recruited from centres in Asia
  - OS effect of durvalumab + Gem/Cis versus placebo + Gem/Cis was numerically greater for people in the 'Asian race' and 'Asian region' subgroups than for people in the 'non-Asian race' and 'rest of the world' subgroups
  - 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 responses to durvalumab + Gem/Cis (due to overexpression of PD-L1)

Company's response to technical engagement (1)

- Subgroup analyses were not powered to detect statistically significant differences and direction of results is equivalent across all subgroups (including by PD-L1 expression)
- Race and region are not effect modifiers for durvalumab + Gem/Cis treatment
- An exploratory interaction test for region and treatment suggested a consistent OS effect across Asia and rest of the world

Abbreviations: BTC, biliary tract cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status

Key issue: Generalisability of TOPAZ-1 trial results (3)

Company's response to technical engagement (2)

- Additional analysis of OS in people with and without viral hepatitis demonstrated a consistent OS benefit across these groups
- Clinical experts consider TOPAZ-1 ITT data generalisable to UK clinical outcomes

EAG comments

- Company's additional analysis of OS in people with and without viral hepatitis suggests it is unlikely that differences in treatment effect between subgroups defined by race and region are driven by the high incidence of hepatitis B in Asia
- EAG's observation that the treatment effect was numerically greater for people in Asia than the rest of the world remains valid

Comments from clinical expert and stakeholder

- Participants in the trial are representative of people with unresectable or advanced BTC treated in the NHS
- Cholangiocarcinoma is increasing across all age groups not just people over 65

Are the TOPAZ-1 trial results generalisable to NHS clinical practice?

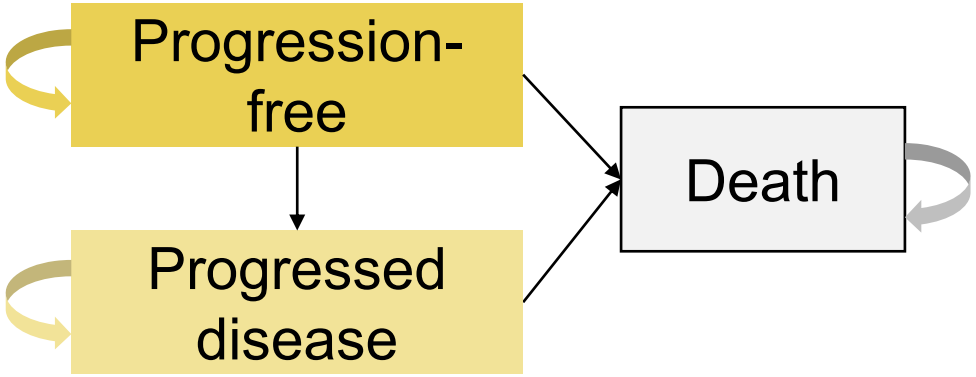
Abbreviations: BTC, biliary tract cancer; ITT, intention to treat; OS, overall survival

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer (ID4031)

- ❑ Background
- ❑ Clinical evidence and key clinical issues to consider
- ✓ **Modelling and key cost effectiveness issues to consider**
- ❑ Other considerations and base case assumptions
- ❑ Summary

NICE National Institute for Health and Care Excellence

Company's model overview



Health state	Utility value (mean)
Progression-free	[redacted]
Progressed disease	[redacted]
Utilities derived from post-hoc analyses of TOPAZ-1 trial data	

Partitioned survival model (area under the curve model)

- Same model structure used in NICE appraisal of pemigatinib (TA722)
- 3 mutually exclusive health states: progression-free, progressed disease and death
- Cycle length: 1 week. Half-cycle correction (applied to all costs and outcomes except first-line drug and administration costs during the first cycle)
- Time horizon: 20 years (lifetime)

EAG consider the model structure appropriate for addressing decision problem

How company incorporated evidence into model

Input	Assumption and evidence source
Baseline characteristics	TOPAZ-1 (ITT/full analysis set population)
Durvalumab + Gem/Cis and Gem/Cis efficacy	Direct extrapolation of TOPAZ-1 efficacy endpoints • DCO August 2021 → PFS, TTD • DCO February 2022 → OS Independent models fitted for OS, PFS and TTD
Utilities	TOPAZ-1 EQ-5D-5L data mapped to EQ-5D-3L
Costs	National Schedule of NHS costs, eMIT, BNF and PSSRU
Resource use	ESMO BTC guidelines, NICE TA722, and clinical opinion
Drug wastage	No vial wastage was assumed
Adverse events	• ≥Grade 3 AEs with an incidence of >5% from TOPAZ-1 trial • Grade 3 and 4 AE-related disutilities applied (first cycle only)
Subsequent treatments	• Eligible upon progression (using TOPAZ-1 PFS curves) • Proportions who progress on each arm based on TOPAZ-1

Abbreviations: AEs, adverse events; BNF, British National Formulary; DCO, data cut off; eMIT, electronic market information tool; ESMO, European Society for Medical Oncology; TTD, time to treatment discontinuation; PFS, progression free survival; PSSRU, Personal Social Services Research Unit

Key issue: Modelling OS for durvalumab + Gem/Cis (1)

Background

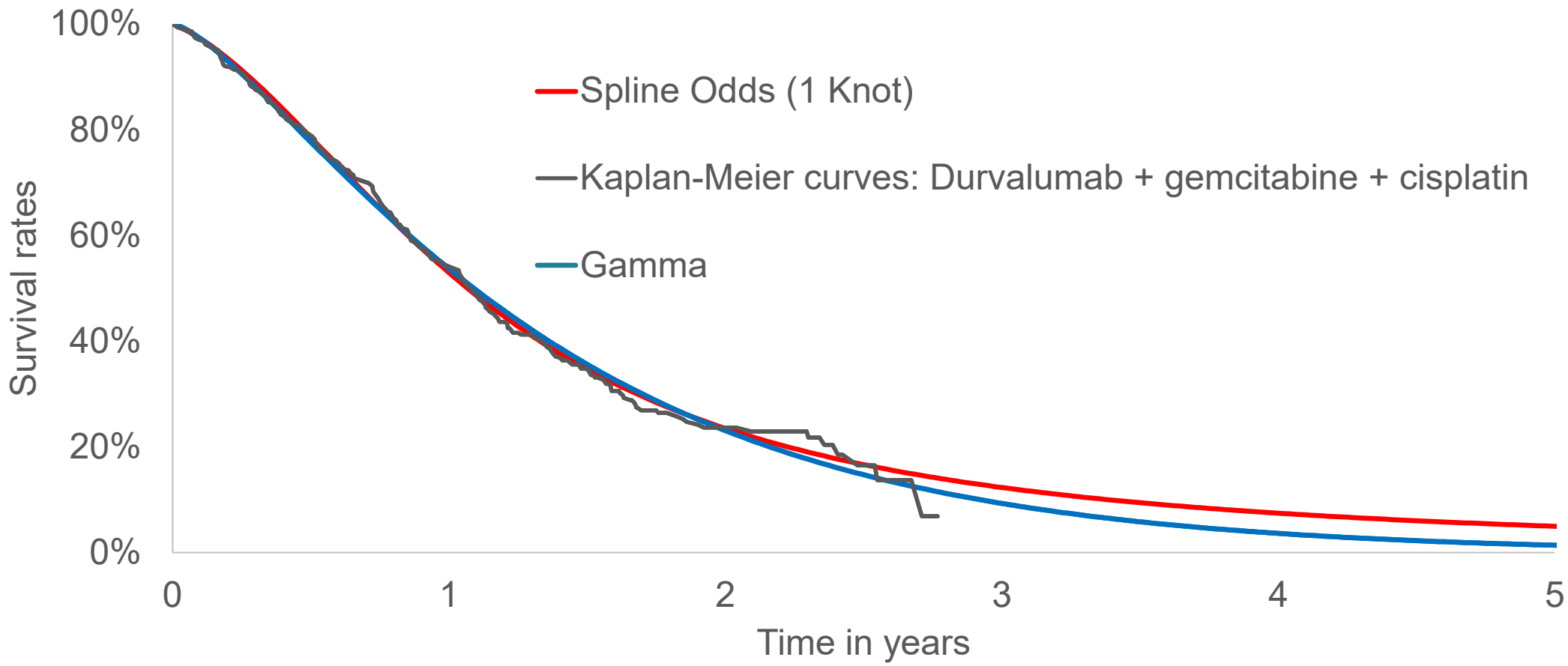
- Clinical experts found it challenging to comment on the clinical plausibility of OS extrapolations due to their limited experience with durvalumab + Gem/Cis
- Company and EAG agree that there are several distributions that statistically fit the TOPAZ-1 trial data equally well and are clinically plausible
  - Company base case & EAG preferred scenario → spline 1 knot odds distribution
  - EAG → Gamma distribution is a clinically and statistically plausible alternative

Distribution	AIC (rank)	BIC (rank)	Overall survival rates		
			2-year	3-year	5-year
Spline 1 knot odds	1914.00 (2)	1925.00 (4)	23.60%	12.37%	4.99%
Gamma	1913.54 (1)	1921.21 (1)	23.20%	9.37%	1.40%
TOPAZ-1			23.65%	-	-
Clinical expert TE response			24%	10-15%	5-10%

Abbreviations: Gem/Cis, gemcitabine and cisplatin; OS, overall survival; TE, technical engagement

Key issue: Modelling OS for durvalumab + Gem/Cis (2)

Fitted OS extrapolations: Durvalumab + Gem/Cis (TOPAZ-1, DCO February 2022)



Abbreviations: DCO, data cut off; Gem/Cis, gemcitabine and cisplatin; OS, overall survival

Key issue: Modelling OS for durvalumab + Gem/Cis (3)

Company response to technical engagement – long-term estimates of OS

- Gamma distribution for durvalumab + Gem/Cis arm infers that there is no long-term OS benefit compared to Gem/Cis → not plausible for an immunotherapy:
  - immunotherapies require time to produce an effective immune response and for that response to be translated into an observable and durable clinical response
  - small number of people are expected to experience a long-term sustained OS benefit compared to placebo + Gem/Cis arm
  - clinical experts considered spline 1 knot odds to be best fitting model and that the gamma model underestimates proportion of people alive at 3 years in the UK

Trial arm	Durvalumab + Gem/Cis		Placebo + Gem/Cis
Parametric distribution	Spline 1 knot odds	Gamma	Spline 1 knot normal (Company and EAG base case)
OS rate at 10 years	1.4%	0.01%	0.01%
OS rate at 15 years	0.6%	0.00%	0.00%
OS rate at 20 years	0.4%	0.00%	0.00%

Abbreviations: Gem/Cis, gemcitabine and cisplatin; OS, overall survival

Key issue: Modelling OS for durvalumab + Gem/Cis (4)

EAG comments

- OS beyond the TOPAZ-1 trial remains uncertain → both distributions generate plausible estimates, but selecting the gamma distribution has a large impact on the ICER
- EAG considers that using hazard plots to inform choice of survival curve is of limited value when OS data are heavily censored

Which distribution is more suitable – spline 1 knot odds or gamma?

Abbreviations: ICER, incremental cost effectiveness ratio; OS, overall survival

Key issue: Modelling PFS for durvalumab + Gem/Cis (1)

Background

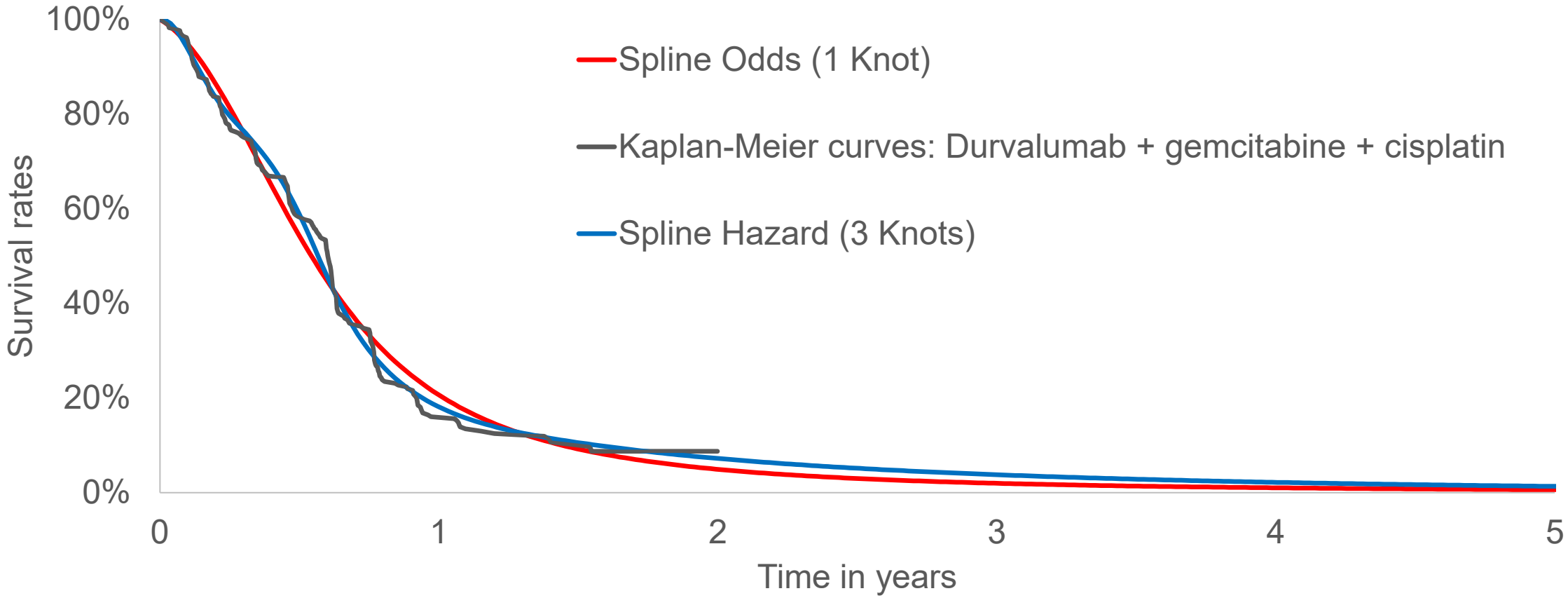
- Clinical experts found it challenging to comment on the clinical plausibility of PFS extrapolations due to their limited experience with durvalumab + Gem/Cis
- Company base case → spline 1 knot odds distribution selected
- EAG considers that the distribution selected by the company has a relatively poor statistical fit to TOPAZ-1 trial data compared to other distributions considered
  - prefer spline 3 knot hazard distribution → lowest AIC/BIC scores and matched TOPAZ-1 PFS data most closely at 6 and 12 months

Distribution	AIC (rank)	BIC (rank)	PFS rates		
			6-month	12-month	24-month
Spline 1 knot odds	1704.05 (5)	1715.55 (4)	54.43%	20.76%	4.96%
Spline 3 knot hazard	1679.09 (1)	1698.25 (1)	59.02%	18.22%	7.25%
TOPAZ-1			58.30%	16.00%	-
Clinical expert TE response			55%	25-30%	10%

Abbreviations: PFS, progression free survival; TE, technical engagement

Key issue: Modelling PFS for durvalumab + Gem/Cis (2)

Fitted PFS extrapolations: Durvalumab + Gem/Cis (TOPAZ-1, DCO August 2021)



Which distribution is more suitable – spline 1 knot odds or spline 3 knot hazard?

NICE

Abbreviations: DCO, data cut off; Gem/Cis, gemcitabine and cisplatin; PFS, progression free survival

Key issue: Modelling treatment costs based on TTD (1)

Background (1) – treatment duration: durvalumab + Gem/Cis

- The company modelled treatment costs using PFS as a proxy for TTD, despite TTD data being available from TOPAZ-1
- EAG considers that PFS is not a good proxy for TTD for durvalumab + Gem/Cis because TTD is always longer than PFS (based on Kaplan-Meier data) and so PFS will underestimate the true costs of treatment
- EAG considers that more accurate costs of treatment can be generated by fitting distributions to TOPAZ-1 TTD trial data:
  - company scenario using TTD to cost time on treatment selected spline 1 knot odds
  - EAG prefers spline 3 knot hazard (statistical fit and closely matches TOPAZ-1 values)

Distribution	AIC (rank)	BIC (rank)	Percentage continuing		
			6-month	12-month	24-month
Spline 1 knot odds	1748.93 (4)	1760.42 (4)	[redacted]	[redacted]	[redacted]
Spline 3 knot hazard	1727.49 (1)	1746.65 (1)	[redacted]	[redacted]	[redacted]
TOPAZ-1			[redacted]	[redacted]	-
Clinical expert TE response (same as PFS rates)			55%	25-30%	10%

Abbreviations: PFS, progression free survival; TTD, time to treatment discontinuation

Key issue: Modelling treatment costs based on TTD (2)

Background (2) – treatment duration: Gem/Cis

- Company clinical experts considered that people with BTC are typically prescribed Gem/Cis for a maximum duration of 6 months
- EAG considers that PFS is a reasonable proxy for TTD for people treated with Gem/Cis as TOPAZ-1 trial PFS and TTD Kaplan-Meier data closely match up to 6 months
- EAG prefer fitting distributions to TOPAZ-1 TTD trial data to generate costs of treatment:
  - company selected spline 3 knot hazard to model TTD for Gem/Cis
  - EAG prefers spline 2 knot odds (% continuing at 6-months most closely matches TOPAZ-1)

Distribution	AIC (rank)	BIC (rank)	Percentage continuing		
			6-month	12-month	24-month
Spline 3 knot hazard	1796.72 (3)	1815.93 (3)	[redacted]	[redacted]	[redacted]
Spline 2 knot odds	1795.97 (2)	1811.33 (1)	[redacted]	[redacted]	[redacted]
TOPAZ-1			[redacted]	[redacted]	-

Abbreviations: BTC, biliary tract cancer; PFS, progression free survival; TTD, time to treatment discontinuation

Key issue: Modelling treatment costs based on TTD (3)

Company response to technical engagement

- Using PFS data to model treatment costs is more reflective of real-world treatment costs
- People who were clinically stable at initial disease progression in TOPAZ-1 could continue to receive study treatment at the discretion of the investigator and patient
- Marketing authorisation specifies treatment until progression or unacceptable toxicity
- If costs are modelled based on TTD instead of PFS, utilities should be modelled consistently with this approach i.e., whether a person is on or off treatment

EAG comments

- Company efficacy estimates are based on TOPAZ-1 trial arm treatment durations, so TOPAZ-1 trial TTD data should be used to estimate time on treatment
- EAG does not consider that consistency is a robust argument for using on- and off-treatment utility values rather than PFS and progressed disease health state utility values

Clinical expert comments

- PFS is an appropriate proxy measure for treatment duration with durvalumab + Gem/Cis

Which is more appropriate – using PFS to model treatment costs or using TOPAZ-1 trial TTD data?

Abbreviations: PFS, progression free survival; TTD, time to treatment discontinuation

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer (ID4031)

- ❑ Background
- ❑ Clinical evidence and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ✓ **Other considerations and base case assumptions**
- ❑ Summary

NICE National Institute for Health and Care Excellence

Other issues for consideration

Modelling PFS for Gem/Cis

- Company used spline 1 knot normal distribution in base case
- EAG prefer spline 3 knot odds distribution → best statistical fit to TOPAZ-1 trial and generates PFS estimates that most closely matched TOPAZ-1 data at 12 months
  - selecting this distribution has a minimal impact on the ICER

Utility values

- EAG note PFS utility ([redacted]) is close to age-adjusted UK general population norm (0.818)
- People on durvalumab + Gem/Cis will spend more time in PFS state
- EAG consider that as the utility values were estimated using TOPAZ-1 trial data it is appropriate to use them, although their use may favour durvalumab + Gem/Cis

Minor amendments by EAG

- Correction of IV administration and neutropenia AE costs
- Removal of AE-related QALY decrement (impact of AEs captured in EQ-5D responses)

Abbreviations: AE, adverse event; ICER, incremental cost effectiveness ratio; PFS, progression free survival; QALY, quality-adjusted-life-year

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG preferred scenario
Minor amendments made by EAG	Not included	Included
Distribution used to model PFS for durvalumab + Gem/Cis	Spline 1 knot odds	Spline 3 knot hazard
Distribution used to model PFS for Gem/Cis	Spline 1 knot normal	Spline 3 knot odds
Distribution used to estimate treatment costs for durvalumab + Gem/Cis	Parametric distribution fitted to PFS data were used to cost treatment	Parametric distribution fitted to TTD data (Spline 3 knot hazard)
Distribution used to estimate treatment costs for Gem/Cis	Parametric distribution fitted to PFS data were used to cost treatment	Parametric distribution fitted to TTD data (Spline 2 knot odds)

EAG also present an additional scenario → includes same assumptions as in preferred scenario plus gamma distribution to model OS for durvalumab + Gem/Cis

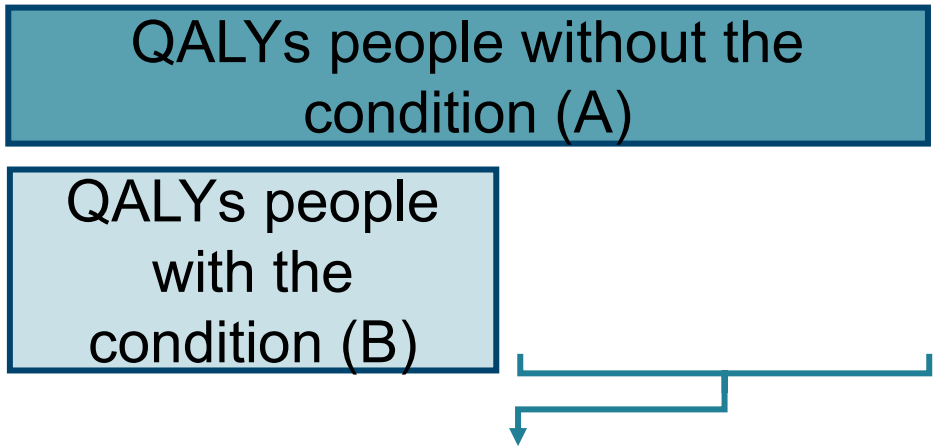
Abbreviations: OS, overall survival; PFS, progression free survival; TTD, time to treatment discontinuation

QALY weighting for severity (1)

NICE methods now include a QALY weighting system based on disease severity

Severity reflects future health lost by people living with a condition who have current standard care

Health: length and quality of life (QALYs)



Health lost by people with the condition: QALY shortfall

Absolute shortfall: total = A – B

Proportional shortfall: fraction = (A – B) / A

NICE QALY weighting for severity used to decide whether to apply additional weight, and how much

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
x1.2	12 to 18	0.85 to 0.95
x1.7	At least 18	At least 0.95

- QALY weightings for severity can be applied based on whichever of absolute or proportional shortfall implies the greatest severity
- If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

Abbreviations: QALY, quality-adjusted-life-year

QALY weighting for severity (2)

Data used in company QALY shortfall calculations

- Company used mean age ([redacted] years) and sex distribution (49.6% female) from TOPAZ-1
- QALYs accrued by people with BTC on standard care = total QALYs for Gem/Cis arm
- QALYs accrued by general population calculated using utility norms from Ara and Brazier (2010) and mortality estimates informed by the most recent ONS life tables
- Company consider that based on proportional shortfall → x1.2 weighting should apply

Outcome	Total QALYs	Absolute shortfall (has to be ≥12)	Proportional shortfall: • 0.85 to 0.95 for x1.2 • at least 0.95 for x1.7
General population	11.13	N/A	N/A
People with BTC on Gem/Cis	0.81	10.32	92.8%

EAG comments

- The methods used to estimate the company severity modifier were appropriate [using Schneider *et al* (2021) QALY shortfall calculator suggests x1.2 weighting would apply]
- EAG re-calculated severity based on its preferred scenario; modifier remained at x1.2

Abbreviations: BTC, biliary tract cancer; ONS, Office for National Statistics; QALY, quality-adjusted-life-year

QALY weighting for severity (3)

Age considerations

- TOPAZ-1 trial mean age was [redacted] years
- EAG clinical experts → average age for people with BTC is around 70 years

NICE technical team exploratory scenarios using higher starting ages

- QALY shortfalls were recalculated using higher starting ages [calculated using Schneider *et al.* (2021) QALY shortfall calculator]:
  - total QALYs for people with BTC on standard care were based on company probabilistic base case results (0.81), as values unknown for older populations
  - **suggest x1.2 weighting would apply based on proportional shortfall**

Age of population	Absolute shortfall	Proportional shortfall
70 years	8.33	91.1%
75 years	6.49	88.9%
80 years	4.73	85.4%

Does a severity weighting apply?

Abbreviations: BTC, biliary tract cancer; EAG, external assessment group; QALY, quality-adjusted-life-year

Cost-effectiveness results

As confidential discounts are available for subsequent treatments in the pathway, ICERs will be presented in Part 2 slides

ICER ranges have been presented below to aid transparency

Summary – durvalumab + Gem/Cis versus Gem/Cis

- Company base case probabilistic ICER:
  - no severity weighting: significantly above £30,000/QALY gained
  - x1.2 severity weighting: significantly above £30,000/QALY gained
- EAG preferred scenario (probabilistic results):
  - no severity weighting: significantly higher than company base case ICER
  - x1.2 severity weighting: significantly higher than company base case ICER

Abbreviations: ICER, incremental cost effectiveness ratio

Managed access

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Company consider durvalumab + Gem/Cis is not suitable for managed access:

- TOPAZ-1 trial is ongoing, with [redacted]
- Further analyses are not expected to reduce any potential uncertainties in cost effectiveness because OS data is already highly mature (76.9% at 6.5-month update, data cut off February 2022) and is a key driver of the model

Abbreviations: Gem/Cis, gemcitabine and cisplatin; OS, overall survival

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer (ID4031)

- ❑ Background
- ❑ Clinical evidence and key clinical issues to consider
- ❑ Modelling and key cost effectiveness issues to consider
- ❑ Other considerations and base case assumptions
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Key issues

Key - Not resolved: Unresolvable:

Issue	Type of uncertainty	Resolved?	ICER impact
Generalisability of TOPAZ-1 trial results to NHS patients	Structural	No – for discussion	Not known
Modelling overall survival for patients treated with durvalumab with Gem/Cis	Methodological	No – for discussion	Large
Modelling progression-free survival for patients treated with durvalumab with Gem/Cis	Methodological	No – for discussion	Moderate
Modelling treatment costs based on time to treatment discontinuation	Methodological	No – for discussion	Large

Abbreviations: Gem/Cis, gemcitabine and cisplatin

Thank you

NICE