National Institute for Health and Care Excellence

Health Technology Evaluation

Durvalumab with gemcitabine and cisplatin for treating unresectable or advanced biliary tract cancer [ID4031]
Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	AstraZeneca	Yes, a Single Technology Appraisal process is appropriate for this topic.	Thank you for your comment. No action required.
	Joint response from: National Cancer Research Institute, Association of Cancer Physicians, Royal College of Physicians, Royal College of Radiologists	It is appropriate to evaluate this therapy as a single technology appraisal.	Thank you for your comment. No action required.

Section	Stakeholder	Comments [sic]	Action
	(from now, referred to as NCRI-ACP-RCP-RCR)		
Wording	AstraZeneca	Yes.	Thank you for your comment. The wording of the remit has been updated to reflect the key clinical trial and population in the scope. Wording has been kept broad to maintain flexibility in the appraisal.
	NCRI-ACP-RCP-RCR	The wording of the remit is appropriate.	Thank you for your comment. The wording of the remit has been updated to reflect the key clinical trial and population in the scope. Wording has been kept broad to maintain flexibility in the appraisal.
Timing Issues	AstraZeneca	Advanced BTC patients have poor prognosis and first-line standard of care has been limited to gemcitabine plus cisplatin for over a decade. Durvalumab with gemcitabine and cisplatin represents the immunotherapy-based combination therapy to demonstrate an	Thank you for your comments. NICE has scheduled this topic into its work programme and

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		improvement in overall survival compared with current standard of care.[1] [redacted] Durvalumab combination therapy has also been granted a level 4 score on the ESMO Magnitude of Clinical Benefit Scale.[2] Therefore, AstraZeneca consider this appraisal to be urgent. References 1. Oh D-Y, He AR, Qin S et al. Durvalumab plus Gemcitabine and Cisplatin in Advanced Biliary Tract Cancer. The New England Journal of Medicine. 2022;1(8). 2. ESMO-MCBS scorecards. Durvalumab. For patients with locally advanced or metastatic biliary tract cancer. 2022 Available from: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards/scorecard-350-1 (Accessed October 2022)	aims to provide draft guidance to the NHS as soon as possible after marketing authorisation. No action required.
	NCRI-ACP-RCP-RCR	Advanced biliary tract cancer is a cancer of unmet need given the poor survival with currently-available therapies. This is the first breakthrough in the past 12 years of improving first-line treatment.	Thank you for your comments. NICE has scheduled this topic into its work programme and aims to provide draft guidance to the NHS as soon as possible after marketing authorisation. No action required.
Additional comments on the draft remit	AstraZeneca	There are no additional comments on the draft remit.	Thank you for your comment. No action required.

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	NCRI-ACP-RCP-RCR	No.	Thank you for your comment. No action required.
	AMMF – The Cholangiocarcinoma Charity	There is very little in the treatment armoury for CCA patients. The addition of durvalumab to the existing first line treatment of gemcitabine and cisplatin represents an opportunity for a more effective first line therapy.	Thank you for your comments. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	The first paragraph of the background section makes reference to hilar or perihilar and distal extrahepatic cholangiocarcinoma. In general, cholangiocarcinoma is categorised as 'intrahepatic' or 'extrahepatic'. Extrahepatic cholangiocarcinoma is further subdivided into perihilar and distal cholangiocarcinoma. It is suggested to simplify the description of subtypes to: intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma (which includes perihilar and distal cholangiocarcinoma) and gall bladder cancer.[3] Reference 3. Valle JW, Borbath I, Khan SA et al. Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2016. 27 (Supplement 5): v28-v37.	Thank you for your comments. The background section has been updated to simplify the description of cholangiocarcinoma subtypes as suggested.

Section	Consultee/ Commentator	Comments [sic]	Action
	NCRI-ACP-RCP-RCR	The background information provides the essential information.	Thank you for your comment. No action required.
	AMMF – The Cholangiocarcinoma Charity	The CCA incidence rate in England, is given as at 2013. The following is more current: CCA Incidence in England in 2019: 2635 Number of registered deaths due to CCA in 2019: 2754 CCA incidence, England, 2019 as a rate per 100,000: 4.68 Acknowledgement: NCRAS at NHS Digital	Thank you for your comments. The background section has been updated to include more recent data on the epidemiology of cholangiocarcinoma.
Population	AstraZeneca	Yes. The clinical effectiveness data used for the economic model will be from the TOPAZ-1 RCT and therefore the population for appraisal should align with the trial population. Patients included in the TOPAZ-1 trial had histologically confirmed unresectable, locally advanced or metastatic biliary tract cancer. Eligible patients had previously untreated disease that was unresectable or metastatic at initial diagnosis as well as patients who developed recurrent disease more than 6 months after surgery with curative intent and more than 6 months after adjuvant therapy.[1] The population for appraisal should be inclusive of these patients.	Thank you for your comments. The population has been updated to reflect the TOPAZ-1 trial and has been kept broad to maintain flexibility in the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
	NCRI-ACP-RCP-RCR	Yes, it would also include patients undergoing treatment with curative intent who have later relapsed (i.e., previously treated, but not for advanced disease).	Thank you for your comment. The population has been updated to reflect the TOPAZ-1 trial and has been kept broad to maintain flexibility in the appraisal.
Subgroups	AstraZeneca	The TOPAZ-1 study was not powered to demonstrate significant differences in treatment outcomes between subgroups. While a subgroup analysis from the TOPAZ-1 study is available, it should be interpreted with caution and in the context of the statistically significant results in the ITT population. While the TOPAZ-1 trial was not stratified according to PD-L1 expression status, published results demonstrate comparable effect sizes for the PD-L1 <1% and PD-L1 ≥1% subgroups. OS HR was 0.79 (95 CI: 0.58-1.09) and 0.75 (95% CI: 0.60-0.93) for the PD-L1 <1% and PD-L1 ≥1% subgroups, respectively.[4] Note, the overlapping confidence intervals. [redacted][5] As such, the findings from the TOPAZ-1 study indicate PD-L1 status has limited value in predicting clinical benefit of durvalumab plus gemcitabine and cisplatin in BTC. Furthermore, literature reporting on evidence for the predictive value of PD-L1 expression for response to IO therapy and for survival in BTC is also inconclusive.[6] Overall, this	Thank you for your comments. If evidence allows, results for relevant subgroups will be considered by the committee during the appraisal. No action required.

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		suggests PD-L1 status is neither prognostic for BTC nor predictive for BTC patients being treated with durvalumab. A PFS and OS benefit in favour of durvalumab plus gemcitabine and cisplatin was observed across tumour subtypes; however, the patient numbers in these subgroups in the TOPAZ-1 trial were small and, as stated above, not powered for statistical significance. Therefore, these results should be considered in the context of the significant results in the ITT population. References 4. Oh D-Y, He AR, Qin S et al. Updated overall survival from the Phase 3 TOPAZ-1 study of durvalumab or placebo plus gemcitabine and cisplatin in patients with advanced biliary tract cancer. ESMO Congress, September 2022, Paris. 5. AstraZeneca. Response Document, EMEA/H/C/004771/II/0046. 2022. Available upon request. 6. Vogel A, Bathon M & Saborowski A. Immunotherapies in clinical development for biliary tract cancer. Expert Opinion on Investigational Drugs. 2021. 30:4, 351-363.	
	NCRI-ACP-RCP-RCR	There is no obvious subgroup more (or less) likely to benefit in the exploratory subgroup analysis.	Thank you for your comment. If evidence allows, results for relevant subgroups will be considered by the committee during the appraisal. No action required.

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Comparators	AstraZeneca	Gemcitabine with cisplatin is the appropriate comparator for this appraisal. As per the 'technology' description in the draft scope, the [redacted] and in line with the TOPAZ-1 trial design, durvalumab for BTC will be administered in combination with gemcitabine and cisplatin. Therefore, it is not expected that the combination of durvalumab plus gemcitabine with cisplatin would be administered to patients who would not otherwise receive gemcitabine with cisplatin i.e. patients with poor kidney function or patients who are considered frail. For reference, 'frail' patients are considered patients with a performance status of >1	Thank you for your comments. The scope is intended to be broad, so as not to exclude potentially relevant comparators. The comparators in the scope reflect established clinical practice for treating unresectable advanced or metastatic biliary tract cancer. The committee can decide the most appropriate comparators based on evidence presented to it. No action required.
	NCRI-ACP-RCP-RCR	Cisplatin and gemcitabine are the main comparators. Oxaliplatin and gemcitabine for patients with renal impairment. Single-agent gemcitabine for PS2 patients (although these patients were excluded from the TOPAZ-1 study) Single agent 5-FU or capecitabine are not appropriate comparators.	Thank you for your comments. The scope is intended to be broad, so as not to exclude potentially relevant comparators. The comparators in the scope reflect established clinical practice for treating

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			unresectable advanced or metastatic biliary tract cancer. The committee can decide the most appropriate comparators based on evidence presented to it. No action required.
Outcomes	AstraZeneca	Yes, these outcomes are appropriate.	Thank you for your comment. No action required.
	NCRI-ACP-RCP-RCR	Yes.	Thank you for your comment. No action required.
Equality	AstraZeneca	There are no equality concerns.	Thank you for your comment. No action required.
	NCRI-ACP-RCP-RCR	No issues identified.	Thank you for your comment. No action required.
Other considerations	AstraZeneca	There are no further suggestions for the evaluation.	Thank you for your comment. No action required.

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	NCRI-ACP-RCP-RCR	No additional issues.	Thank you for your comment. No action required.
Questions for consultation	AstraZeneca	***What treatments are established clinical practice in the NHS for people with untreated advanced biliary tract cancer?*** ***Where do you consider durvalumab with gemcitabine and cisplatin will fit into the existing care pathway for untreated advanced biliary tract cancer?*** Response: It is anticipated that durvalumab with gemcitabine and cisplatin will become the new standard of care for the first-line treatment of patients with advanced or metastatic BTC (newly diagnosed or recurrent following >6 months since completion of treatment for earlier stage disease) who would otherwise receive gemcitabine with cisplatin and do not have a contraindication to immunotherapy. ***How relevant are the subgroups 'type of biliary tract cancer' and 'level of PD-L1 expression' in the scope? Are there any other subgroups of people in whom durvalumab with gemcitabine and cisplatin is expected to be more clinically effective and cost effective or other groups that should be examined separately?*** ***How will people eligible for durvalumab be identified?*** • ***Will implementation of additional testing be required to facilitate the use of this technology in NHS clinical practice?***	Thank you for your comments. If evidence allows, results for relevant subgroups will be considered by the committee during the appraisal. No action required.

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		Response: No additional testing is anticipated to facilitate the use of this technology in NHS practice. As previously outlined, PD-L1 expression level is not considered a prognostic factor for BTC patients or a predictive of the outcomes expected for patients treated with the combination of durvalumab with gemcitabine and cisplatin. Therefore, it is not anticipated there will be a requirement for PD-L1 testing. The overall survival benefit overserved with durvalumab in combination with gemcitabine and cisplatin was consistent across all subgroups analysed. As stated above, the TOPAZ-1 study was not powered to demonstrate significant differences in treatment outcomes between subgroups. As such, the subgroup analyses are not considered the most appropriate for decision making and the focus of this appraisal should be on the statistically significant results in the ITT population. ***Would durvalumab with gemcitabine and cisplatin be a candidate for managed access?*** Response: The TOPAZ-1 trial has achieved 76.9% overall OS event maturity. As such, any further OS data are not expected to resolve any uncertainties that may be identified in the appraisal; durvalumab with gemcitabine and cisplatin should not be a candidate for managed access. ***Do you consider that the use of durvalumab with gemcitabine and cisplatin can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?*** Response: All health-related benefits resulting from the use of durvalumab with gemcitabine and cisplatin are expected to be captured in the QALY calculation.	

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	NCRI-ACP-RCP-RCR	No additional questions.	Thank you for your comment. No action required.
Additional comments on the draft scope	AstraZeneca	There are no additional comments on the draft scope.	Thank you for your comment. No action required.
	NCRI-ACP-RCP-RCR	No.	Thank you for your comment. No action required.
	AMMF – The Cholangiocarcinoma Charity	The related interventional procedures listed against “Related NICE recommendations and NICE Pathways” are not available to the CCA patient, eg: SIRT was not approved after having been available for some time under the CtE process. It is currently listed as being available under clinical trial conditions, but the only trial, SIRCCA is closed to recruitment. Photodynamic therapy (PDT) is not used following the negative outcome of the PHOTOSTENT-02 trial some years ago. And the ”Endoscopic bipolar radiofrequency ablation” would seem to be in development.	Thank you for your comments. The ‘related NICE recommendations’ section of the scope intends to reflect published and in development NICE guidance that may be of relevance to the disease area for the appraisal. No action required.