National Institute for Health and Care Excellence

Health Technology Evaluation

Durvalumab in combination for neoadjuvant and adjuvant treatment of resectable gastric and gastro-oesophageal junction adenocarcinoma [ID6374]

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	AstraZeneca agrees with the proposed evaluation route of a single technology appraisal (STA).	Thank you for your comment.

Section	Stakeholder	Comments [sic]	Action
Wording	AstraZeneca	As noted under the 'Population' heading below, the wording of the remit should specify patients with resectable gastric and gastro-oesophageal junction adenocarcinoma. This aligns with the MATTERHORN trial [redacted].	Thank you for your comment. The title has been updated to replace 'cancer' with 'adenocarcinoma'.
Timing Issues	AstraZeneca	There are currently no targeted immune-oncology (IO) perioperative treatment options for patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (hereafter referred to as GOA), with perioperative chemotherapy representing standard of care [SoC]. Outcomes for patients with GOA are poor and there is a substantial unmet need for an effective treatment option in this patient population. As such, durvalumab in combination with fluorouracil, leucovorin, oxaliplatin and docetaxel (D-FLOT) should be evaluated with urgency to avoid any delays in access for patients. If recommended, D-FLOT would represent a step-change in the treatment paradigm for resectable GOA.	Thank you for your comment.

Section	Stakeholder	Comments [sic]	Action
Additional comments on the draft remit	AstraZeneca	No further comments.	Thank you for your comment.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action

Background information	AstraZeneca	The background section is largely accurate and reflects the majority of key points related to GOA. However, AstraZeneca wishes to highlight a few key points that should be included within the background section. It is important to highlight that the majority of gastric and gastro-oesophageal junction cancers are adenocarcinoma, with squamous cell carcinoma (SCC) being less common at the gastro-oesophageal junction. As the indication of interest in this appraisal is GOA specifically, it is critical to understand the epidemiology of adenocarcinomas and highlight that D-FLOT would provide an effective treatment for the majority of gastric and gastro-oesophageal junction cancers. The background section should provide stakeholders information on the epidemiology of GOA. In addition, details on the severity of GOA and the prognosis for patients based on current SoC should be highlighted, in order for stakeholders to understand the degree of unmet need for an effective treatment in this population. Suggested wording as follows: "Despite the curative intent of surgery and the addition of perioperative chemotherapy, recurrence rates with perioperative FLOT remain high, and fewer than half of patients are expected to have survived at 5 years (estimated 5-year OS of 45% in FLOT-4).[1]" The background section includes brief details on current treatment options and relevant guidelines (i.e., NICE Guideline 83 [NG83]). However, NG83 was published in 2018 (and has only undergone minor updates since publication), and has not been updated to include recommendations based on more recent clinical evidence from relevant trials (e.g., ESOPEC, FLOT4).[1-3] As discussed in more detail under the 'Comparators' header, ESMO guidelines represent more up-to-date and relevant treatment guidelines for GOA in UK clinical practice. When referring to the initial symptoms of GOA, AstraZeneca suggest that the terminology 'non-specific' should be used, rather than 'vague' ("initial symptoms of gastric or gastro-oesophageal junction cancer are **non-specific**	Thank you for your comment. The background section has been updated to include your suggested wording ("Despite the curative intent of surgery…") and "vague" has been replaced with "non-specific". The scope background section is intended to give a brief overview of the condition it is anticipated that recurrence rates on current treatment and unmet need will be considered during the evaluation. The scope gives details of the available NICE guidance on this disease. It is anticipated that the treatment pathway and what represents current

		[…]"). Referring to the symptoms experienced by patients with GOA as 'vague' is not an accurate portrayal of the experience of patients.	clinical practice in the NHS will be explored in the evaluation.

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Population	AstraZeneca	The population of interest in this appraisal is patients with resectable gastric and gastro-oesophageal junction adenocarcinoma. This aligns with the MATTERHORN trial [redacted]. The population in the scope should be updated to align with this.	Thank you for your comment. The population has been updated.
Subgroups	AstraZeneca	A number of pre-specified subgroup analyses were conducted on event-free survival (EFS) and overall survival (OS) in MATTERHORN, including programmed death-ligand 1 (PD-L1) expression level (TAP ≥ 1% vs TAP < 1%). Clinical subgroup analysis forest plots, including PD-L1 expression level, will be provided. If appropriate based on the available evidence, economic subgroup analyses based on PD-L1 expression level would be explored. However, PD-L1 expression is not anticipated to influence treatment decisions in resectable GOA, as confirmed by UK clinical experts, and the unmet need for an effective treatment exists across the GOA population. In addition, EFS benefit in favour of D-FLOT versus FLOT was observed across the ITT population. As such, the intention to treat (ITT) population from MATTERHORN remains the focus of this appraisal to ensure equity of access regardless of PD-L1 expression.	Thank you for your comment. No changes needed to the scope.
Comparators	AstraZeneca		

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		The technology being appraised is perioperative D-FLOT. Therefore, the population of interest represents patients that are suitable for a perioperative treatment regimen (at the time of treatment decision) and are able to tolerate FLOT chemotherapy. **Chemotherapy, before ***and*** after surgery (perioperative chemotherapy)** In this population, perioperative chemotherapy, specifically FLOT, represents the SoC. This is stated in ESMO Clinical Practice Guidelines for gastric cancer and supported by feedback from UK clinical experts received by AstraZeneca.[2, 4] As demonstrated in the FLOT4 trial, perioperative FLOT has superior efficacy over other perioperative chemotherapies (i.e., epirubicin, cisplatin and fluorouracil [ECF]/epirubicin, cisplatin and capecitabine [ECX]), and is therefore the preferred treatment option for FLOT-eligible patients.[1] As such, perioperative FLOT represents the only comparator to D-FLOT in this appraisal. The final scope should be updated to state 'FLOT chemotherapy before and after surgery' as the only comparator. **Treatments not considered comparators** Other treatments included within the draft scope are not considered comparators to D-FLOT. Treatments included as comparators appear to be based on NG83, which was published in 2018 (and has only undergone minor updates since publication).[2] Since development of NG83, new evidence has been published which has influenced clinical practice (e.g., ESOPEC, FLOT4). However, NG83 has not yet been updated to incorporate the additional clinical evidence. In the absence of recently updated NICE guidelines, this section focuses on ESMO guidelines (published 2022 [GC] and 2025 [oesophageal cancer and	Thank you for your comment. The comparators have been updated The list of comparators is intended to be inclusive at this stage. The appraisal committee will discuss the most appropriate comparator(s) during the development of this evaluation. This will depend on the final marketing authorisation, the current treatment pathway and current clinical practice.

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		GOJC]) and the recent clinical evidence supporting treatment recommendations to provide a more accurate representation of UK clinical practice for the treatment of GOA.[4, 5] Comments on the treatments included in the draft scope not considered as comparators are provided below: ***1. Other chemotherapies, before <u>and</u> after surgery (other perioperative chemotherapies)*** As noted above, perioperative FLOT is SoC for FLOT-eligible patients (i.e., the population eligible for D-FLOT), as stated in ESMO guidelines and supported by UK clinical experts.[2, 4, 5] In those patients who are unable to tolerate FLOT, other perioperative chemotherapy regimens are treatment options (e.g., ECF/ECX, leucovorin, fluorouracil and oxaliplatin [FOLFOX]).[4] However, these patients represent a distinct patient population who would not be suitable for D-FLOT. As such, other perioperative chemotherapy regimens (e.g., ECF/ECX, FOLFOX) are not considered comparators in this appraisal. *2.* ***Chemotherapy, before <u>or</u> after surgery*** ***Chemotherapy before surgery*** As noted above, the population in this appraisal is specifically patients who are treated with perioperative intent (i.e., at the start of neoadjuvant treatment are deemed suitable for perioperative treatment); in this population, perioperative FLOT is SoC. As such, chemotherapy before surgery (without perioperative intent) does not represent a comparator to perioperative D-FLOT. There is potential for patients receiving perioperative FLOT to discontinue treatment in the adjuvant phase, which is captured in the MATTERHORN	

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		trial. *Further details on the use of D-FLOT in the neoadjuvant setting only is provided under the 'Questions for consultation' heading.* ***Chemotherapy after surgery*** Per NG83, adjuvant chemotherapy only is an option for patients who did not receive neoadjuvant chemotherapy before surgery with curative intent. As outlined above, the population in this appraisal is patients who are treated with perioperative intent and therefore receive neoadjuvant treatment. As such, patients who do not receive neoadjuvant chemotherapy (i.e., receiving chemotherapy after surgery only) would not be candidates for perioperative D-FLOT, so chemotherapy after surgery is not a relevant comparator. ***3. Chemoradiotherapy, before and/or after surgery*** ESMO guidelines do not include neoadjuvant CRT as a treatment option for patients with GC.[4] As such, neoadjuvant CRT is not a relevant comparator for patients with GC. Neoadjuvant CRT is included in ESMO guidelines as a treatment option for patients with oesophageal cancer (not relevant to this appraisal) and GOJC.[4] However, neoadjuvant CRT is specifically positioned as an option for patients who are not able to tolerate perioperative FLOT, based on evidence from the ESOPEC trial demonstrating that perioperative FLOT shows superior efficacy to neoadjuvant CRT in patients with gastro-oesophageal adenocarcinoma.[3, 5] During an advisory board conducted by AstraZeneca, UK clinical experts confirmed that neoadjuvant CRT is only considered in patients who cannot tolerate FLOT, or used as palliative care in patients not planned for surgery.[6] The clinical experts noted that they would expect neoadjuvant CRT to be	

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		removed as a treatment option for patients with GOJC when the ESMO guidelines are next updated.[6] Patients ineligible for FLOT or not planned for surgery would not be eligible to receive D-FLOT. As such, neoadjuvant CRT is not a relevant comparator in this appraisal. ***4. Nivolumab, after surgery in adults who have residual disease after previous neoadjuvant chemoradiotherapy*** Nivolumab is licensed and recommended by NICE for use as an adjuvant treatment for GOJC (or oesophageal cancer) in patients who have previously received CRT in the neoadjuvant setting.[7] Adjuvant nivolumab is not an option for patients with GC. As outlined above, neoadjuvant CRT is only a treatment option for patients with GOJC who cannot tolerate FLOT (i.e., a separate population to the target population in this appraisal).[5, 6] Due to the requirement to receive neoadjuvant CRT, it follows that adjuvant nivolumab is only an option for patients with GOJC who cannot tolerate FLOT. As such, patients receiving neoadjuvant CRT followed by adjuvant nivolumab represent a separate population to those that will be candidates for D-FLOT. As such, adjuvant nivolumab is not a relevant comparator in this appraisal. Moreover, since publication of the ESMO guidelines recommending neoadjuvant CRT and adjuvant nivolumab as an option for GOJC (if a patient is not suitable for FLOT), data from the final OS analysis of CheckMate-577 show a lack of OS benefit for adjuvant nivolumab versus adjuvant placebo in the GOJC subgroup (HR: 1.14 [95% confidence intervals: 0.83, 1.56]).[8] In addition, there is a less pronounced OS benefit in the adenocarcinoma	

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		subgroup versus the squamous cell carcinoma (SCC) subgroup (HRs: 0.92 versus 0.72, respectively). No analysis is presented for the specific population of interest in this appraisal (i.e., gastro-oesophageal adenocarcinoma), however the data suggest limited/no benefit in both subgroups of interest. Based on these results, the use of perioperative FLOT as SoC for patients with GOJC who can tolerate FLOT is expected to be further consolidated, and use of adjuvant nivolumab will decline.	
Outcomes	AstraZeneca	The outcomes listed in the draft scope broadly reflect the most relevant outcomes to measure the health-related benefits and harms of perioperative treatment for resectable GOA. However, in the neoadjuvant and perioperative setting, EFS, rather than progression-free survival (PFS), is the most appropriate endpoint because it accounts for progression events both before and after surgery and captures a wider range of events.[9, 10] In MATTERHORN, EFS was defined as the time from randomisation until the date of one of the following events: 1) progression that precludes surgery or requires non-protocol therapy during the neoadjuvant period, 2) progression/recurrence during the adjuvant period, 3) progression/recurrence confirmed by biopsy post-surgery or 4) death due to any cause. EFS therefore captures all relevant events by including progression that precludes surgery, recurrence after surgery and death and is a more relevant endpoint due to the curative setting. As PFS is not a standard outcome in the perioperative setting and PFS data were not collected in MATTERHORN, PFS should be removed from the draft scope.	Thank you for your comment. ‘PFS’ has been removed as an outcome.

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Equality	AstraZeneca	A variety of factors increase the likelihood of developing gastric cancer, including both genetic and environmental factors. Considering environmental factors, smoking, a diet high in salt, being overweight and a high alcohol intake all increase the risk of developing GOA.[11-13] Many of these environmental factors are more prevalent in individuals from a lower socioeconomic background.[14] The availability of an effective treatment for GOA would help to benefit these individuals and narrow existing health inequalities related to the impact of GOA on populations from different socioeconomic backgrounds.	Thank you for your comment.
Other considerations	AstraZeneca	No further comments.	Thank you for your comment.

Questions for consultation	AstraZeneca	**Where do you consider durvalumab will fit into the existing care pathway for resectable gastric and gastro-oesophageal junction cancer?** In line with the MATTERHORN trial and expected licensed indication, D-FLOT is anticipated to be a treatment option for patients with resectable GOA. D-FLOT is anticipated to displace perioperative FLOT, in the population of patients who are eligible for treatment with FLOT chemotherapy with perioperative intent. **Will durvalumab be used in combination with chemotherapy both in the neoadjuvant and adjuvant setting, will durvalumab monotherapy be an option in the adjuvant setting?** Durvalumab will be administered in line with the expected marketing authorisation and in line with the dosing adopted in the MATTERHORN trial: in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant durvalumab monotherapy. Following 2 cycles of durvalumab with FLOT chemotherapy, durvalumab monotherapy will be administered for 10 further cycles. At the time of deciding the treatment approach for a patient, it would be intended for durvalumab to be administered in combination with FLOT in the adjuvant setting. However, a minority of patients may be unable to tolerate FLOT due to toxicity, so may receive durvalumab monotherapy in the adjuvant setting. Per the MATTERHORN trial protocol, adjuvant durvalumab monotherapy may continue if patients discontinued FLOT due to treatment-related toxicity before or after surgery. If neoadjuvant FLOT is discontinued due to treatment-related toxicity, the remaining neoadjuvant durvalumab should be discontinued and patients should proceed to surgery. As such, patients would not receive neoadjuvant durvalumab monotherapy. The impact of toxicities on discontinuation of FLOT and any impacts on efficacy are captured in the MATTERHORN trial, in line with expected treatment patterns in real-world clinical practice. The MATTERHORN trial is a robust source of data on the expected use and efficacy of D-FLOT in real-world clinical practice.	Thank you for your comment.

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Additional comments on the draft scope	AstraZeneca	NA – no further comments on the draft scope.	Thank you for your comments.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

None received