National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Tislelizumab for treating unresectable advanced oesophageal squamous cell cancer after platinum-based chemotherapy (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	BeiGene	Evaluating this topic via the Single Technology Appraisal (STA) route is appropriate and aligns well with the need to provide patients with additional effective treatments for second-line oesophageal squamous cell carcinoma in a timely manner. Please note that initial results from an indirect treatment comparison have shown that tislelizumab demonstrates an overall comparable efficacy and safety profile relative to nivolumab. In addition, recent UK clinical expert feedback from 1:1 interviews and an advisory board, has highlighted that comparable efficacy/safety profile is expected between tislelizumab and nivolumab due to the similarity in the mechanism of action.[1, 2] Therefore, a cost-comparison approach for tislelizumab compared to nivolumab may be considered appropriate.	Thank you for your comment. No action required.
Wording	BeiGene	BeiGene suggests the following alternative wording, which aligns with the marketing authorisation[3]: To appraise the clinical and cost effectiveness of tislelizumab within its marketing authorisation for treating unresectable, **locally** advanced **or**	Thank you for your comment. The scope has been updated to

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		metastatic oesophageal squamous cell cancer after platinum-based chemotherapy.	reflect the suggested changes.
Timing Issues	BeiGene	Patients with second-line oesophageal squamous cell carcinoma only have one targeted treatment available on the NHS in nivolumab,[4] therefore there is an unmet need for additional treatment options in this currently underserved space.	Thank you for your comment. Comments noted. NICE has scheduled this topic into its work programme. No action required.
Additional comments on the draft remit	BeiGene	No comments	Thank you for your comment. No action required.

Comment 2: the draft scope

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Background information	BeiGene	Yes, the information is complete. There is a minor typographical error - a duplicate of 'in' – within the second line of the second paragraph.	Thank you for your comment. The scope has been updated to reflect the suggested changes.

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Population	BeiGene	The population is aligned with the licensed population	Thank you for your comment. No action required.
Subgroups	BeiGene	No	Thank you for your comment. No action required.
Comparators	BeiGene	Nivolumab is the only appropriate comparator for the tislelizumab appraisal. Since its recommendation for use in the NHS in NICE TA707,4 nivolumab has displaced chemotherapy and become the standard of care treatment in second-line oesophageal squamous cell carcinoma in patients who can tolerate targeted immunotherapy, in line with European Society for Medical Oncology (ESMO) guidelines.5 Tislelizumab targets the same patient population as nivolumab and if recommended, would be used as an alternative to nivolumab. This positioning has recently been confirmed by leading UK clinical experts through engagement at an advisory board and also through 1:1 interviews.1, 2 **Chemotherapy including taxanes (docetaxel/paclitaxel) or irinotecan:** While chemotherapy was an appropriate comparator at the time of the nivolumab appraisal, NICE TA707,4 when no other targeted immunotherapy treatment options were available, it is no longer current standard of care at second-line and should not be considered a comparator. This is in line with current ESMO guidelines, where chemotherapy is considered for use as a third-line treatment following nivolumab, as shown in Figure 1.5 This has also recently been confirmed by leading UK clinical experts through engagement at an advisory board and 1:1 interviews.1, 2	Thank you for your comment. The scope has been updated to reflect the suggested changes.

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		Any patient for whom nivolumab is not an appropriate treatment option would similarly not be expected to be eligible for tislelizumab treatment. As such chemotherapy is not considered a comparator of interest, and hence should be removed from the final scope. **Best supportive care:** According to ESMO guidelines, best supportive care is only appropriate for patients who are unfit for targeted treatment and chemotherapy.5 As noted above, the target patient population for treatment with tislelizumab is the same population as that currently eligible for treatment with nivolumab. Within the NICE TA707 recommendation for nivolumab in second-line oesophageal squamous cell carcinoma, it was stated “Best supportive care was not considered to be a relevant comparator, because people who are not well enough to tolerate taxane therapy are unlikely to benefit from nivolumab”.4 This has been recently confirmed through two 1:1 interviews with UK clinical experts and a UK advisory board.1, 2 Therefore, best supportive care is not considered to be an appropriate comparator and hence should be removed from the final scope.	
Outcomes	BeiGene	Yes, the outcomes are appropriate. Note that the response rate in RATIONALE-302 is captured through objective response rate (ORR) and duration of response (DoR).[6]	Thank you for your comment. Commet noted. No action required.
Equality	BeiGene	There are potential equality issues which need to be considered when appraising a new treatment in oesophageal squamous cell carcinoma, these do not impact the remit and scope of the appraisal but have been included for awareness, please see below:	Thank you for your comments. The committee will consider all potential equalities issues during the

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		• Approximately 70% of oesophageal cancer diagnoses occur in men; there is a twofold to threefold difference in incidence and mortality rates between the sexes. [5] • The incidence of oesophageal cancer is strongly correlated to age, where around 41% of new cases in the UK between 2014 to 2015 were diagnosed in those over 75 years old.[7] • Mortality of oesophageal cancer is strongly correlated to age with around a fifth (19.0%) of people in England diagnosed with oesophageal cancer aged 15-54 surviving their disease for ten years or more, compared with around 5 in 100 (6.0%) people diagnosed aged 75-99 (2013-2017)[7] • There are important socio-economic influences in the incidence and mortality of oesophageal cancer which can lead to health inequalities. Incidence rates in England in females are 43% higher in the most deprived quintile compared with the least, and in males are 50% higher in the most deprived quintile compared with the least (2013-2017).[8] • In addition, oesophageal cancer deaths in England are more common in people living in the most deprived areas. Around a fifth (21.2%) of people in England diagnosed with oesophageal cancer in the least deprived group survive their disease for five years or more, compared with more than 1 in 10 (13.6%) people in the most deprived group (2016-2020).[7]	course of the evaluation.
Other considerations	BeiGene	**None**	Thank you for your comment. No action required.

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Questions for consultation	BeiGene	**Where do you consider tislelizumab will fit into the existing care pathway for treating advanced unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy?** Tislelizumab will be positioned as an alternative to nivolumab in the treatment of patients with oesophageal squamous cell carcinoma who have received chemotherapy as first-line treatment, as shown in ESMO guidelines in Figure 1 below. [5] This positioning has been confirmed with UK clinical experts through two recent 1:1 interviews and findings from an UK advisory board.[1, 2] **Figure 1. Treatment algorithm for advanced OSCC according to ESMO guidelines[5]**	Thank you for your comment. Comments noted. No action required.

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		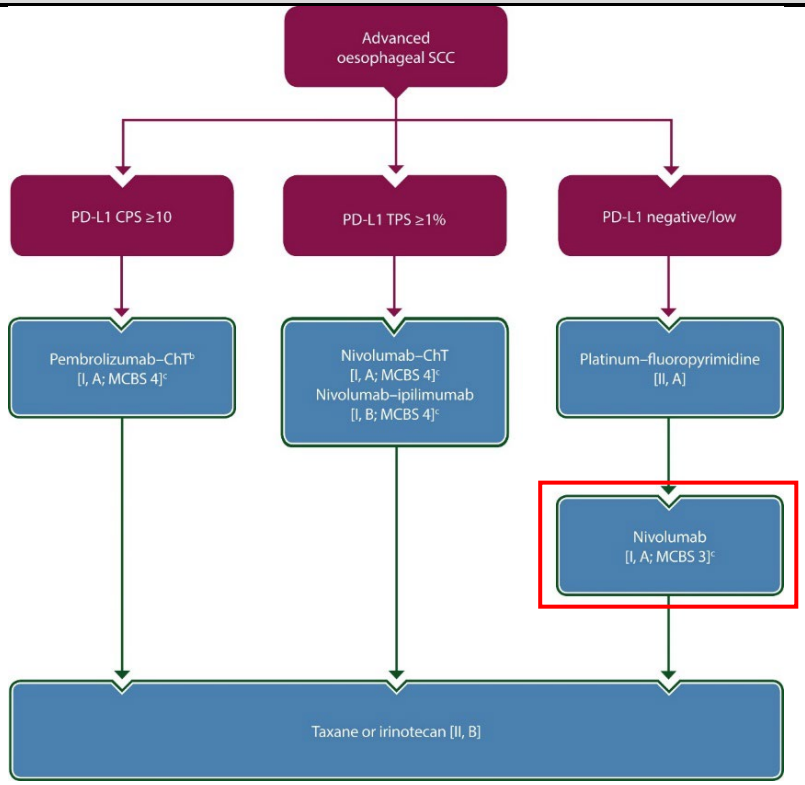 NOTE: Please note that the red box denotes where tislelizumab will be positioned within the treatment pathway Abbreviations: AC, adenocarcinoma; ChT, chemotherapy; CPG, Clinical Practice Guideline; CPS, combined positive score; EMA, European Medicines Agency; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Score; OGJ, esophagogastric junction; PDL1, programmed death-ligand 1; SCC, squamous-cell carcinoma; TPS, tumour proportion score. [a]For treatment of oesophageal AC and OGJ cancer, see the ESMO CPG for gastric cancer. [b]EMA approval is for tumours with PD-L1 CPS _10, FDA approval is irrespective of PD-L1 expression. [c]ESMO-MCBS v1.191 was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated by the ESMO-MCBS Working Group and validated by the ESMO Guidelines Committee (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).	

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		Please select from the following, will tislelizumab be: **A. Prescribed in primary care with routine follow-up in primary care** **B. Prescribed in secondary care with routine follow-up in primary care** **C. Prescribed in secondary care with routine follow-up in secondary care** **D. Other (please give details):** **For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention** Tislelizumab would be prescribed in secondary care with routine follow-up in secondary care, in line with current use of nivolumab.[9] **Would tislelizumab be a candidate for managed access?** It is not currently anticipated that tislelizumab will be a candidate for managed access. **Do you consider tislelizumab to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Patients with unresectable, locally advanced or metastatic oesophageal squamous cell cancer (after platinum-based chemotherapy) have fewer treatment options compared to patients treated in the first-line, where both nivolumab and pembrolizumab are available.[5, 10, 11] The approval of tislelizumab by NICE would provide increased patient and clinician choice in this underserved treatment space. Tislelizumab would also offer benefits to patients in terms of dosing convenience due to 3-weekly administration	Thank you for your comment. Comments noted. No action required.

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		compared to 2-weekly administration with nivolumab.[3, 9] This difference in dosing frequency will also allow clinicians to offer treatments with a schedule better personalised to their patients' preferences. Furthermore, 3-weekly administration schedules would reduce the resource burden to the NHS, compared with 2-weekly administration schedules. **Are there any subgroups of people in whom tislelizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately?** Data from RATIONALE-302 demonstrated consistent efficacy for tislelizumab across subgroups investigated within the study.[6] Therefore, it is anticipated that, as per the label,[3] adult patients with unresectable, locally advanced or metastatic oesophageal squamous cell carcinoma after prior platinum-based chemotherapy, will be able to receive and benefit from tislelizumab. **Do you consider that the use of tislelizumab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** It is anticipated that all health-related benefits will be included in the QALY calculation. However, as there is a paucity of targeted treatments in the second line setting for oesophageal squamous cell carcinoma, the introduction of tislelizumab, a new programmed death 1 (PD-1) agent, would provide increased patient and clinician choice in this underserved treatment space. **Is the technology likely to be similar in its clinical effectiveness and resource use to any of the comparators? Or in what way is it different to the comparators?** As noted above, nivolumab is considered to be the only appropriate comparator for the tislelizumab appraisal.	Thank you for your comment. Comments noted. No action required. Thank you for your comment. Comments noted. No action required. Thank you for your comment. Comments noted. No action required.

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		While there are no direct trials comparing the efficacy and safety of tislelizumab and nivolumab in patients with oesophageal squamous cell carcinoma who have received chemotherapy as first-line treatment, initial results from an indirect treatment comparison indicate that tislelizumab demonstrates an overall comparable efficacy and safety profile compared to nivolumab. Clinical opinion gathered through two 1:1 interviews with UK clinical experts and a UK advisory board,[1, 2] highlighted that they would anticipate a comparable efficacy/safety profile between tislelizumab and nivolumab due to the similarity in the mechanism of action.[1, 2] There is the potential for resource use benefits and additional patient choice benefits with the introduction of tislelizumab which is administered every 3 weeks, compared to nivolumab which is administered every 2 weeks.[3, 9] **Will the intervention be used in the same place in the treatment pathway as the comparator(s)? Have there been any major changes to the treatment pathway recently? If so, please describe.** As noted above, nivolumab is considered to be the only appropriate comparator for the tislelizumab appraisal. Since its recommendation for use in the NHS,[4] nivolumab has displaced chemotherapy and become the standard of care treatment in second-line oesophageal squamous cell carcinoma in patients who can tolerate targeted immunotherapy in line with ESMO guidelines.[5] Tislelizumab would be used as an alternative to nivolumab within the treatment pathway (see Figure 1). Since the publication of NICE TA707,[4] there have been no changes to the treatment options for the second line treatment of oesophageal squamous cell carcinoma.	Thank you for your comment. Comments noted. No action required.

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		Will the intervention be used to treat the same population as the comparator(s)? Leading UK clinicians have confirmed through an advisory board and 1:1 interviews that tislelizumab would be placed as an alternative to nivolumab within the treatment pathway.[1, 2] The licence wording for tislelizumab and nivolumab was tested within the 1:1 interviews and the UK clinic experts confirmed that the patient populations would be treated the same.[1, 3, 9]	Thank you for your comment. Comments noted. No action required.
		Overall is the technology likely to offer similar or improved health benefits compared with the comparators? Would it be appropriate to use the cost-comparison methodology for this topic? As noted above, nivolumab is considered to be the only appropriate comparator for the tislelizumab appraisal. As there is no head-to-head clinical study data to support this comparison, an indirect treatment comparison will be utilised within the submission and a cost-utility approach will be presented to provide a full assessment of the cost-effectiveness of benefit of tislelizumab. Initial results from an indirect treatment comparison have confirmed that tislelizumab demonstrates an overall comparable efficacy and safety profile compared with nivolumab. Clinical opinion obtained through a recent advisory board and 1:1 interviews,[1, 2] has highlighted that comparable efficacy/safety profile is expected between tislelizumab and nivolumab due to the similarity in the mechanism of action. Given these data and clinician insights, a cost-comparison approach may be considered appropriate. As such, it is anticipated that a cost-comparison analysis will be presented alongside the cost-utility analysis so that NICE can consider both approaches.	Thank you for your comment. Comments noted. No action required.
		Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.	Thank you for your comment. Comments

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		A full description of the pivotal trial data for tislelizumab of RATIONALE-302 will be presented within the submission.[6] RATIONALE-302 is a global randomised, controlled, open-label, multi-centre Phase III trial for tislelizumab compared with investigator's-choice chemotherapy in second line treatment of oesophageal squamous cell carcinoma. Given that nivolumab is the key comparator for the submission we will present relevant clinical information from the ATTRACTION-3 study.[12] The ATTRACTION-3 study is a multicentre, randomised, open-label, Phase III trial for nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy. [12] These studies will be used within an indirect treatment comparison to present comparative effectiveness evidence for tislelizumab compared to nivolumab	noted. No action required.
Additional comments on the draft scope	BeiGene	None	Thank you for your comment. No action required.

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

GIST Cancer UK