National Institute for Health and Care Excellence

Health Technology Evaluation

Retifanlimab with platinum-based chemotherapy for treating inoperable, locally recurrent or metastatic squamous cell anal canal cancer untreated with systemic chemotherapy ID6482

Response to stakeholder organisation comments on the draft remit and draft scope

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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Incyte	The draft scope states that "NICE intends to evaluate this technology through its Highly Specialised Technologies Evaluation Programme". Although squamous cell carcinoma of the anal canal (SCAC) is a rare disease, based on the routing criteria, Incyte believes that the Single Technical Appraisal process is appropriate for assessing retifanlimab for inoperable locally recurrent or metastatic SCAC.	Thank you for your comment and for clarifying that this topic is intended for STA. The routing for this topic is scheduled to follow the Single Technology Appraisal process. Any mention of "Highly Specialised Technologies Evaluation Programme"

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			has been removed from the scope.
Wording	Incyte	The anticipated licensed indication is [redacted]. To reflect the evaluation objective, Incyte believes the wording of the remit should be updated to: "*To appraise the clinical and cost effectiveness of retifanlimab **in combination with carboplatin and paclitaxel** within its marketing authorisation for treating inoperable locally recurrent or metastatic **squamous cell carcinoma of the anal canal (SCAC)** untreated with systemic chemotherapy.*" These proposed changes [redacted] and reflect the language commonly used in clinical practice in relation to disease terminology.	Thank you for your comment. The remit/ evaluation objective has been updated to reflect the proposed changes.
Timing Issues	Incyte	There is an urgent and high unmet need for innovative, targeted, and accessible treatments in advanced SCAC that improve clinical outcomes and are well tolerated by patients.	Thank you for your comment. No action required.

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		Individuals with inoperable locally recurrent or metastatic SCAC face considerable clinical challenges, as advanced disease is associated with poor prognosis and high mortality (1, 2). For example, the 5-year survival rate for patients with metastatic disease is approximately 20% (2). Current therapeutic options in patients with advanced disease are extremely limited, with management largely restricted to platinum-based chemotherapy (3), which provides a median overall survival (OS) of approximately 20 months (4). Advanced SCAC also imposes a substantial burden on quality of life (QoL). Patients with locally advanced disease report a significantly higher prevalence of symptoms such as constipation and abdominal pain ($p<0.02$), as well as perianal pain and weight loss ($p<0.01$), compared with those with less advanced tumours (5). These physical challenges are compounded by psychological distress, including anxiety and depression, as patients manage the side effects of treatment and face uncertainty and poor survival prospects (6). QoL deteriorates markedly in advanced disease, with functional limitations and emotional strain persisting throughout the treatment journey (7). No immunotherapies are currently licensed for use in SCAC at any line of therapy. A positive recommendation for retifanlimab in combination with carboplatin and paclitaxel (CP) would introduce the first immunotherapy-based regimen for patients with advanced SCAC which has not previously been treated with systemic chemotherapy. This would address a high unmet need and offer improved outcomes for patients, including longer progression-free and overall survival. Incyte believes that the NICE Single Technical Appraisal route is appropriate for delivering timely guidance.	

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	Anal Cancer Foundation	There is a clear unmet need for people with recurrent or advanced anal cancer, who often face a poor prognosis and have very limited treatment options once standard therapy has failed. No targeted or highly effective alternatives are available for this population. A new treatment option that can offer meaningful clinical benefit would therefore be of significant value to both patients and the NHS. As such, it is important that this technology is prioritised for timely evaluation, and we thank NICE for their consideration and the invitation to the Anal Cancer Foundation for the opportunity to contribute to this consultation.	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Incyte	1. Incyte proposes the following addition, as it is important to reflect the anticipated increase in the incidence of anal cancer: "*There were an estimated 1,600 new diagnoses of anal cancer each year in the UK (yearly average) from 2017 to 2019, of which two-thirds were in women.*[1] ***Furthermore, anal cancer incidence rates in the UK are projected to increase by 14% between 2023–2025 and 2038–2040, with around 2,400 new cases each year by 2038–2040 (8).***" 2. Incyte proposes the following addition: *"Treatment for anal cancer depends on the stage* ***and origin (e.g. anal margin or anal canal) (3)****."*	Thank you for your comment. The background section has been updated to reflect the proposed changes in line with NICE style.

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		3. Incyte proposes removing the following text, as it combines the treatment of carcinomas of the anal margin and the anal canal, which does not accurately reflect the 2021 European Society For Medical Oncology (ESMO) clinical practice guidelines for anal cancer, nor does it reflect the specific aetiology of relevance to this appraisal, namely carcinomas of the anal canal. Additionally, CP is the current standard of care (SoC) in the UK for inoperable locally recurrent or metastatic disease. Other regimens such as modified docetaxel, cisplatin, and 5-fluorouracil are more commonly used in other European countries: *"~~The cancer may be removed with a local resection for stage 1, or with abdominoperineal resection if the cancer is in the anal canal and comes back after chemoradiotherapy.[4] Chemoradiotherapy is standard treatment for stage 2 and 3 disease.[5] The common chemotherapy combinations are mitomycin C with either fluorouracil or capecitabine.[6] For inoperable anal canal cancer carboplatin plus paclitaxel or FOLFCIS (fluorouracil, folinic acid, and cisplatin) are used.[7] Docetaxel may be included.~~".* Instead, Incyte proposes aligning the treatment algorithm for SCAC with the following: ***"Radiotherapy with concomitant mitomycin C, in combination with either 5-fluorouracil or capecitabine, is recommended as SoC for patients with localised SCAC (Stage 1–3). Patients with residual or locally recurrent disease after chemoradiotherapy (CRT) are considered for salvage surgery (3). While most patients with localised SCAC do not require further treatment following CRT, approximately 20% develop local failures (3), for which salvage surgery is not always feasible. These patients (i.e. those with recurrent disease not amenable to surgery), as well as those with metastatic disease, are treated with CP (3). This regimen became SoC following the InterAACT trial, which demonstrated significantly***"	

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		longer median OS in patients receiving CP versus cisplatin plus 5-fluorouracil (20.0 months vs 12.3 months) (4).*"* 4. Incyte proposes the following amendments as immunotherapies are not currently recommended by NICE as second-line options, none have regulatory approval for use in SCAC, and the 2021 ESMO clinical practice guidelines only recommend their use in a clinical trial setting in patients who have progressed on first-line therapy. Nivolumab monotherapy may currently be given off-label to some patients in the second-line setting on compassionate grounds. "*Immunotherapy agents**, such as nivolumab and pembrolizumab,** do not have regulatory approval and are not currently recommended by NICE ~~such as nivolumab, pembrolizumab, or retifanlimab are recommended as second-line~~ **as** options for **inoperable locally recurrent or metastatic SCAC, but may be given off-label in clinical trial or compassionate use settings.***" Incyte proposes the following amendment to accurately reflect the inclusion criteria for the POD1UM-303 trial: *"Retifanlimab in combination with carboplatin and paclitaxel is being studied in a clinical trial compared with carboplatin and paclitaxel and placebo in adults with inoperable locally **recurrent** ~~advanced~~ or metastatic squamous cell anal carcinoma."*	

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	Anal Cancer Foundation	It is important to recognise some of the unique challenges an anal cancer diagnosis presents. An anal cancer diagnosis carries stigma related to the anatomical site, and due to its association with HPV. Combined with a low level of public and professional awareness this contributes to an under-recognition of symptoms and barriers to timely care. In addition, an anal cancer diagnosis is associated with a substantial and often under-reported quality-of-life burden. Even after treatment, patients may face severe challenges such as long term bowel dysfunction, faecal urgency or incontinence, pelvic pain, urinary changes and sexual difficulties, sometimes persisting for years after treatment. Combined with the challenges of stigma, these enduring effects can significantly impact daily living, emotional wellbeing, and social participation. For those with recurrent or metastatic diseases, these difficulties can be even more pronounced. The anal cancer disease community continues to face a limited rage of effective treatment options, and progress in developing new therapies has been slower than in many other cancer types. This appraisal is therefore critical to ensuring that patients have access to effective treatment options to improve progression free survival. It is worth noting that in the United States, the **preferred** first-line treatment for metastatic anal cancer in the latest NCCN guidelines is a combination of platinum-based chemotherapy and immunotherapy carboplatin + paclitaxel + retifanlimab p26 of the linked report. https://www.nccn.org/patients/guidelines/content/PDF/anal-patient.pdf	Thank you for your comment. No action required.

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Population	Incyte	Incyte proposes the following amendment: “Adult patients with inoperable locally recurrent or metastatic squamous cell carcinoma of the anal canal not previously treated with systemic chemotherapy in the recurrent or metastatic setting”. This is because most patients will receive chemotherapy as part of CRT for localised SCAC (Stage 1-3).	Thank you for your comment. The population in the table has been updated to include “in the recurrent or metastatic setting”.
Subgroups	Incyte	Not applicable.	Thank you for your comment. No action required.

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Comparators	Incyte	Incyte notes that not all treatments included in the draft scope are relevant comparators. In line with ESMO guidelines (3), and following the results from the InterAACT study (4), CP has become the SoC for patients with inoperable locally recurrent or metastatic SCAC in National Health Service (NHS) practice (9). CP is also recommended as the cytotoxic platform for future Phase 3 trials (3). In UK NHS clinical practice, regimens such as mitomycin C with either 5-fluorouracil or capecitabine, 5-fluorouracil and cisplatin with folinic acid or docetaxel, cisplatin with capecitabine, and capecitabine with carboplatin are not used as first-line treatments for patients with inoperable locally recurrent or metastatic SCAC (9). For example, NHS guidelines from Kent and Medway Cancer Collaborative note that CP is the only first-line systemic treatment option for metastatic disease, while cisplatin- or carboplatin-based combinations are listed as second-line options (9). Expert opinion from several UK-based clinicians also supports CP as the standard first-line treatment for this patient population. Therefore, Incyte proposes the following amendments to the comparators listed in the scope: *"~~Established clinical management without retifanlimab including, but not limited to:~~* • ~~*Mitomycin C with either fluorouracil or capecitabine*~~ • *Carboplatin and paclitaxel* • ~~*Fluorouracil and cisplatin with folinic acid, or docetaxel*~~ • ~~*Cisplatin and capecitabine*~~ ~~*Capecitabine and carboplatin*~~*"*	Thank you for your comment. No action required.

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Outcomes	Incyte	The outcomes listed in the scope are appropriate.	Thank you for your comment. No action required.
	Anal Cancer Foundation	It is essential that the health-related quality of life (HRQoL) outcome is measured in a way that reflects what truly matters to people living with anal cancer. Clinical endpoints such as overall survival and progression are vital, but in anal cancer the experience of living with the disease, and its treatments, carries a set of unique set of consequences (as previously described) that must be adequately captured. HRQoL measures should therefore be sensitive to mental health, emotional wellbeing, and the effects of this at times stigmatised and challenging diagnosis on confidence, relationships and day-to-day functioning. Enabling patients to preserve normality, continue meaningful activities and spend quality time with the people they love is significant and as such, an improvement in progression free survival can hold value beyond tumour control as it enables them to maintain social connection and dignity for longer. This should be reflected in how HRQoL outcomes are recorded and interpreted.	Thank you for your comment. NICE ensures that all relevant aspects of HRQoL are comprehensively captured in the analysis. No action required. We strongly encourage stakeholders to submit evidence on HRQoL to fully understanding the patient impact of the technology.
Equality	Incyte	No changes to the scope are needed to meet NICE's equality aims, and no equality issues are anticipated in relation to the proposed use of retifanlimab.	Thank you for your comment. No action required.

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Other considerations	Incyte	No further considerations.	Thank you for your comment. No action required.

Questions for consultation	Incyte	**Responses to questions for consultation** **1. What is established clinical management for people with inoperable locally recurrent or metastatic squamous cell carcinoma of the anal canal not previously treated with systemic chemotherapy?** Patients receive CP on a 28-day regimen, with carboplatin administered on Day 1 and paclitaxel administered on Days 1, 8, and 15, in line with ESMO guidance (based on the InterAACT study) and clinical protocols (3, 9), and clinical expert opinion. **2. Where do you consider retifanlimab will fit into the existing care pathway for inoperable locally recurrent or metastatic squamous cell anal canal cancer untreated with systemic chemotherapy?** In line with pivotal evidence from the POD1UM-303 trial (10) [redacted] retifanlimab will be added to CP as a first-line treatment for patients with inoperable locally recurrent or metastatic SCAC not previously treated with systemic chemotherapy. As for carboplatin, retifanlimab will be administered on Day 1 of the 28-day regimen (as described above). **3. Retifanlimab prescribing.** Option C: retifanlimab will be prescribed in secondary care with routine follow-up in secondary care. **4. For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention.** The prescribing and follow-up setting for comparators or subsequent treatments (when received) does not differ from retifanlimab.	Thank you for your comment. No action required.

		5. Would retifanlimab be a candidate for managed access? Incyte does not anticipate retifanlimab will be a candidate for managed access, [redacted] **6. Do you consider that the use of retifanlimab can result in any potential substantial health-related benefits that are unlikely to be included in the quality-adjusted life year calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** Inoperable locally recurrent or metastatic SCAC has a profound impact on patient survival and QoL (1, 6, 7). In addition, family caregivers of patients living with cancer often experience substantial physical, emotional, and social challenges, leading to a marked decline in their own QoL (11, 12). The clinically meaningful improvements in progression-free and overall survival demonstrated with retifanlimab in the POD1UM-303 trial (10) are likely to help patients maintain daily activities and spend more time with loved ones compared with the current SoC. These benefits may also alleviate caregiver burden and improve family wellbeing, effects that would not be captured in the quality-adjusted life year calculations within the cost-effectiveness analysis.	

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

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