National Institute for Health and Care Excellence

Health Technology Evaluation

Toripalimab with chemotherapy for untreated recurrent or metastatic nasopharyngeal cancer [ID6406] 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	LEO Pharma	Single technology appraisal is appropriate for toripalimab.	Thank you for your comment. No action required.
Wording	LEO Pharma	No further comments.	Thank you for your comment. No action required.
Timing Issues	LEO Pharma	As this is the first treatment for nasopharyngeal carcinoma, LEO Pharma believe there is a high unmet need. We agree with NICE's timelines for evaluation.	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	LEO Pharma	The draft scope highlights three types of NPC including keratinizing [sic], non-keratinizing [sic] and basaloid squamous cell carcinoma. However, there exist four histological subtypes of NPC, as classified by the World Health Organization (WHO): keratinizing (type I), non-keratinizing differentiated (type II), non-keratinizing undifferentiated (type III) and basaloid squamous cell carcinoma.1 NPC is classified as a rare cancer in the UK and EU, where a cancer type is considered rare if it affects fewer than 6 in 100,000 people annually.2 NPC incidence in the UK is significantly below this threshold, with an age-standardised rate of approximately 0.39 per 100,000 population.3 In the UK, there are an estimated 260 patients diagnosed with NPC each year4 (whereby 10-15% of cases are de novo metastatic disease, a further 10-15% are oligo-metastatic and the remaining 70-80% being localised/locally advanced at diagnosis amenable for curative intent).5 The epidemiology of NPC places the disease among the rarer subtypes of head and neck cancers. NICE should explicitly state this rarity, as it has implications for diagnosis, treatment pathways, and access to specialist care. Currently, patients with NPC that is recurrent, not amenable to surgery or radiotherapy, or metastatic are eligible to receive first-line systemic chemotherapy which is most often cisplatin-gemcitabine (providing the patient has adequate renal function and can therefore tolerate cisplatin). In patients whose disease progresses following first-line treatment, second- and subsequent-lines of therapy include single agent taxanes (docetaxel, paclitaxel), capecitabine, immunotherapies (pembrolizumab, nivolumab) or platinum rechallenge chemotherapy regimens.6-10	Thank you for your comments. The scope has been updated to reflect the 4 subtypes and current treatment practice.

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Population	LEO Pharma	The population should be updated in line with the marketing authorisation by the MHRA: "Toripalimab, in combination with cisplatin and gemcitabine, is indicated for the first-line treatment of adult patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma".	Thank you for your comment. The wording has been changed to reflect the MA.
Subgroups	LEO Pharma	No further comments.	Thank you for your comment. No action required.
Comparators	LEO Pharma	Clinical experts and guidelines confirm that cisplatin plus gemcitabine is the widely established, first-line standard of care for RM-NPC in UK clinical practice.5 While carboplatin may be substituted for cisplatin in patients who are unsuitable, and other chemotherapy combinations are occasionally used, these represent local variations rather than established national practice and are not consistently applied across centres.5 Broadly, clinical experts estimate that only 10-20% of patients receiving 1L therapy will be ineligible for cisplatin and therefore receive carboplatin.5 Where carboplatin is not routinely used as a first-line treatment for RM-NPC, its use is limited to exceptional circumstances where cisplatin is contraindicated. This is primarily in cases where patients have poor renal function or performance status. Insights from clinical experts have shown that patients with a glomerular filtration rate of <55 ml/min are often considered for carboplatin substitution; with cisplatin also generally reserved for patients with ECOG performance statuses of 0-1 (and occasionally PS2), whereas carboplatin may be used in those unable to tolerate cisplatin.5	Thank you for your comment. NICE aims to keep the comparators in the scope as broad as possible. However, NICE agrees that carboplatin should be removed as a comparator on the basis that the MHRA marketing authorisation indicates that there is no indication for use of toripalimab with carboplatin. The marketing authorisation specifically describes

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		These scenarios represent a small subset of the total RM-NPC population and do not therefore represent standard clinical practice for most patients with this disease. Furthermore, the JUPITER-02 trial protocol required renal function testing prior to trial enrolment: inclusion criteria were serum creatinine ≤1.5 x ULN, creatinine clearance ≥60 mL/min (according to Cockcroft-Gault formula) and an ECOG status of 0-1.12 Together, these reinforce the fact that cisplatin-gemcitabine is the standard therapy in patients with RM-NPC, and the trial population in which toripalimab has been investigated in was not that by which would typically receive carboplatin (due to each participant's adequate renal function as per the protocol). With regards to the MHRA marketing authorisation,11 it specifically describes the use of toripalimab only in combination with cisplatin-based chemotherapy. I.e., there is no indication for use with carboplatin, and thus substitution would fall outside of the licenced indication.11 Therefore, including carboplatin would not only be clinically inappropriate but also inconsistent with regulatory requirements. It is with these reasons in mind that LEO Pharma believe carboplatin should not be considered as a comparator for first-line treatment of RM-NPC within this appraisal.	the use of toripalimab only in combination with cisplatin-based chemotherapy. So, toripalimab with carboplatin would fall outside of the licenced indication.
Outcomes	LEO Pharma	No further comments	Thank you for your comment. No action required.
Equality	LEO Pharma	NPC has a notable geographical distribution and ethnic heterogeneity.3,13 Over 77% of the global incidence rate of NPC occurs in East Asia and Southeast Asia, particularly in southern China. NPC is frequent in populations of Southern Chinese, Northern African, and Alaskan origin.14	Thank you for your comment. Any equality issues raised will be considered in the equality impact

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		The Committee should assess whether recommendations could disproportionately affect people with protected characteristics, including ethnic minority groups and individuals with disabilities. This includes evaluating barriers such as language, cultural factors, and geographic access to specialist services.	assessment and by committee.
Other considerations	LEO Pharma	No further comments	Thank you for your comment. No action required.
Questions for consultation	LEO Pharma	Where do you consider toripalimab will fit into the existing care pathway for nasopharyngeal cancer? We consider toripalimab in combination with cisplatin and gemcitabine to be first line treatment for patients with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal cancer. What treatments are established clinical practice for adults with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma? Cisplatin plus gemcitabine is the recognised first-line standard of care for RM-NPC in UK clinical practice. While carboplatin may be substituted for cisplatin in patients who are unsuitable, and other chemotherapy combinations are occasionally used, these represent local variations rather than established national practice and are not consistently applied across centres.5 What would you consider appropriate comparators for toripalimab? • Chemotherapy without toripalimab including:	Thank you for your comments.

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		• Cisplatin • Gemcitabine • fluorouracil (5FU) • docetaxel • paclitaxel • capecitabine • Best supportive care In clinical practice, how would you determine if someone with nasopharyngeal carcinoma would not be able to have surgery or radiotherapy? Eligibility for surgery15 Surgical eligibility depends on: • Tumour location (e.g., if the tumour is localised to the cavity of the nasal pharynx or roof, surgery is more feasible), • Extensive local invasion (risk with carotid/cavernous sinus or nerve considerations often make patients not amenable to surgery) • Poor physical status (ECOG status >3) • Prior radiation to the head and neck (if less than 6-12 months, surgery is preferred to reirradiation) • Extent of disease Eligibility for radiotherapy6,16,17,18	

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		• Toxicity from previous radiotherapy • Bone necroses • Temporal lobe necroses • Cranial neuropathies and trismus, • Disease proximity to adjacent radiosensitive structures (optic chiasma, temporal lobe, brain stem) • Tumour infiltration into skull base Please select from the following, will toripalimab 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. C Would toripalimab be a candidate for managed access? No Do you consider that the use of toripalimab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?	

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		N/A Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. N/A Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics. No. How many people in England are likely to be eligible for this treatment? 69 patients per year.19 NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which toripalimab is licensed; • could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by	

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		making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts. As stated above in equality section.	
	Consultant Clinical Oncologist Norfolk and Norwich University Hospitals NHS Foundation Trust	1. Where do you consider toripalimab will fit into the existing care pathway for nasopharyngeal cancer? JUPITER-02 study suggested improvement in progression-free survival and overall survival combination with gemcitabine-cisplatin and suggested this as the new standard first-line treatment for patients with recurrent or metastatic nasopharyngeal carcinoma. DIAMOND suggested it can offer omission of concomitant cisplatin in locoregianal disease treated curatively. I certainly see it finding its place in the metastatic setting, as 1st line for patients that are considered for palliative systemic therapy (already recommended as preferred 1st line in the NCCN guidelines). 2. What treatments are established clinical practice for adults with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma?	Thank you for your comments.

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		Curative options for NPC do not include surgery. Radiotherapy +/- chemo is the treatment of choice. Standard of care at the moment for untreated recurrent or metastatic nasopharyngeal cancer is palliative chemotherapy. 3. What would you consider appropriate comparators for toripalimab? 4. In clinical practice, how would you determine if someone with nasopharyngeal carcinoma would not be able to have surgery or radiotherapy? Whether a patient is fit for curative dose RT +/- chemo depends on fitness, comorbidities, PS etc.	
	Consultant Clinical Oncologist & Clinical Lead in Head and Neck Oncology at Barts Cancer Centre	1. Where do you consider toripalimab will fit into the existing care pathway for nasopharyngeal cancer? There are two scenarios where Toripalimab will fit: - First line setting: For any patient with relapsed/metastatic nasopharyngeal cancer (not amenable to surgery/RT) who has not received prior PD--1/PD--L1 therapy and is fit for platinum, the standard first--line systemic option should be Gemcitabine + Platinum + toripalimab, and then toripalimab maintenance until progression or unacceptable toxicity (up to 24 months). This has now effectively replaced Gemcitabine + platinum alone as the default in first-line systemic regimen in the US (FDA approved) and EU (EMA approved) based on the results of the JUPITER-02 study (phase III study that compared toripalimab + GP vs GP alone, followed by toripalimab vs placebo	Thank you for your comments.

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		maintenance, and showed improved PFS 11.7 vs 8 m, and OS benefit: 3yOS 64% vs 49%, and manageable safety profile). - Second line setting: For relapsed/metastatic NPC progressing after prior platinum (GP or FP), where first line did not include a PD-1 inhibitor. This has been approved in different countries including US (FDA approved) based on the evidence provided by the POLARIS-02 study (objective responses of 21% and median duration of 15 months). 2. What treatments are established clinical practice for adults with recurrent, not amenable to surgery or radiotherapy, or metastatic nasopharyngeal carcinoma? The only treatment approved is palliative chemotherapy with a combination of platinum (cisplatin or carboplatin) + gemcitabine or 5FU (for a total of 6 cycles, or 18 weeks). There is no approved treatment for second line or beyond, although some centres in the UK may use taxanes (paclitaxel or docetaxel). 3. What would you consider appropriate comparators for toripalimab? The comparators to toripalimab in the first line would be Gemcitabine and Platinum. There are no real comparators for 2nd line of beyond, but the results could be compared with taxanes (although paucity of data in the use of taxane in this setting). 4. In clinical practice, how would you determine if someone with nasopharyngeal carcinoma would not be able to have surgery or radiotherapy? The decision is based on multiple factors which are always discussed in the MDT. These factors are: 1). Stage and extension of the recurrence (if distant metastases, patient would not benefit from RT or surgery). 2). Previous treatment received - if RT or CRT (as almost always), consideration of	

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		location of the recurrence with regards to previous RT field, previous RT dose, interval between previous treatment and recurrence. 3) Tolerance to previous CRT and residual toxicity following RT. 4). Amenable for complete resection (can negative margins be achieved?) 5) Performance status and other patient characteristics (ie, surgical risks, past medical history...). 6) Patient's preference.	
Additional comments on the draft scope	LEO Pharma	It is worth noting that the NICE guidelines included in Appendix B (Cancer of the upper aerodigestive tract [2016] and Head and Neck Cancer [2017]) are both nearly a decade old and clinical experts have expressed that they adhere more to BAHNO, ESMO, ASCO and NCCN guidelines.	Thank you for your comment. No action required.

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