National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations [ID3761]

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
Wording	British Thoracic Oncology Group	Yes. Clear an unambiguous. No changes needed.	Comment noted. No action required.
	Merck Serono Ltd	We consider the wording of the remit to be appropriate.	Comment noted. No action required.
Timing Issues	British Thoracic Oncology Group	MET altered lung cancer represents up to 4% of lung cancer patients. Tepotinib is an important addition to our treatment options. Clinical data is available demonstrating activity of these agents. As such, it is clinically urgent (but not an emergency) to have such agents appraised by NICE. There are no other MET targeting agents available / assessed by NICE at present.	Comment noted. In any appraisal NICE aims to publish guidance within 90 days of marketing authorisation.
	Merck Serono Ltd	Tepotinib has the potential to deliver substantial clinical benefits to patients with advanced stage non-small lung cancer (NSCLC) harbouring METex14 skipping mutations. Currently, there are no EMA or MHRA approved treatment options that specifically treat this population. Tepotinib will be the first precision medicine targeting MET for patients with NSCLC assessed by the MHRA and appraised by NICE. For now, patients with NSCLC with METex14 skipping mutations have no	Comment noted. In any appraisal NICE aims to publish guidance within 90 days of marketing authorisation.

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		targeted treatments available, and modest outcomes compared to those where targeted treatment options are available. As such, the appraisal should be treated as urgent. VISION data availability and timings The VISION trial (ClincialTrials.gov identifier: NCT02864992) is the pivotal study for tepotinib in patients with NSCLC harbouring MET alterations. The trial contains three cohorts: Cohort A (patients with METex14 skipping mutations; Cohort B (patients with MET amplification); and Cohort C (confirmatory part of study in patients with METex14 skipping mutations). The primary efficacy analysis for METex14 skipping mutations included 99 patients, covering both treatment naïve patients and treatment-experienced patients, with median follow-up of 17.4 months. Results are also available for 146 patients with up to 9 months of follow-up.[1] [redacted] estimated study completion date is February 2023. References Paik PK et al. N Engl J Med. 2020;383:931–943	
Additional comments on the draft remit	Merck Serono Ltd	None	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Thoracic Oncology Group	Accurate, with no errors noted.	Comment noted. No action required.
	Merck Serono Ltd	The background information is accurate. However, the following points should be included to provide relevant information on the patient population, making the prognosis and unmet medical need of this condition clear: • Unlike patients with other oncogene-driven forms of NSCLC (e.g., ALK, EGFR, and ROS1), patients with METex14 skipping mutations are typically 70 years of age or older. Around 60% of patients with METex14 skipping mutations are smokers, and they are also predominantly female, and with predominantly non-squamous histology.[1–3] • The section notes that patients with advanced NSCLC have low 1-year survival rates (one third to one fifth of patients). While this is true for NSCLC as a whole, it should be noted that patients with advanced NSCLC with METex14 skipping mutations have particularly poor outcomes. A large cohort study by Tong JH et al. demonstrated that the presence of METex14 skipping mutations in NSCLC was an independent prognostic factor that predicted poorer survival compared to patients without METex14 skipping mutations.[2] • Furthermore, it should be noted that current treatments for advanced NSCLC, including immunotherapies, are not always effective in patients with NSCLC with METex14 skipping mutations. In Sabari et al. 2018, patients with NSCLC and METex14 skipping mutations treated with immunotherapies had low ORR, and short duration of response and PFS.[3] • Therefore, although immunotherapies represent the current standard of care for advanced NSCLC, they may be unsuitable for patients with NSCLC harbouring METex14 skipping mutations, and as such there is a high unmet need for effective therapies specific to this mutation.	Comments noted. The background section is not meant to be exhaustive. The scope has been updated to that METex14 skipping mutations most occur in females and people with cancer of a non-squamous histology. Comment noted. The comparators listed in the scope represent current standard of care for advanced NSCLC. Scope unchanged.

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		References 1. Awad MM et al. J Clin Oncol. 2016;34:721–730. 2. Tong JH et al. Clin Cancer Res. 2016;22:3048–3056. 3. Sabari JK et al. Ann Oncol. 2018;29:2085–2091.	
The technology/ intervention	British Thoracic Oncology Group	Yes, no alterations needed.	Comment noted. No action required.
	Merck Serono Ltd	The description of the technology is accurate.	Comment noted. No action required.
Population	British Thoracic Oncology Group	Incidence of METex14 correctly stated. No subpopulations identified.	Comment noted. No action required.
	Merck Serono Ltd	The population is appropriately defined. Merck is submitting for a line-agnostic label in line with the VISION clinical trial, which will include both untreated disease (treatment naïve) and previously treated patients (treatment experienced).	Comment noted. No action required.
Comparators	British Thoracic Oncology Group	Yes – a wide range of these have been listed but this reflects the potential lines of use of Tepotinib (1L, previously treated), the different histology types MET may be found in (squamous, non-squamous), and the multiple treatment options supported by NICE for lung cancer.	Comment noted. No action required.
	Merck Serono Ltd	There are no treatment options for advanced NSCLC currently available in England that specifically target METex14 skipping mutations. In the absence of specific MET-targeted therapies, treatments currently used for patients without any identifiable biomarkers make up the current NHS standard of care. Merck acknowledges that the main comparators for tepotinib could be immunotherapies and/or chemotherapy i.e. established care without tepotinib.	Thank you for your comment. The comparators listed in the scope represent current standard of care for advanced NSCLC. The comparators listed

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		However, given that METex14 skipping mutations were not collected or reported in those clinical trials, it may not be feasible to compare them to the VISION trial. Particularly considering that METex14 skipping mutations is a negative prognostic factor. The results of such a comparison would be difficult to interpret given the underlying heterogeneity in the populations. Alternatively, a comparison to published data in patients with NSCLC with METex14 skipping mutations, treated with established management (e.g. immunotherapies/chemotherapy) may be a more appropriate comparison. Until a feasibility assessment is undertaken, it may be too early to specify the exact comparators in this appraisal. We therefore propose "established management without tepotinib" as a placeholder- an approach similar to that taken in TA630 for larotrectinib. Notwithstanding the point above, Merck has a number of specific comments on the comparators in the current draft scope: People with untreated non-squamous NSCLC: • Merck is aware that pembrolizumab with pemetrexed and platinum-based chemotherapy is currently undergoing Cancer Drugs Fund (CDF) review for TA557 (ID1584), with expected publication date 16th December 2020. Consistent with NICE's CDF position statement, the final scope should not include any CDF comparisons. People with previously treated non-squamous NSCLC: • For previously treated non-squamous NSCLC, atezolizumab plus bevacizumab, carboplatin and paclitaxel (TA584) is only recommended for patients who have had EGFR or ALK-targeted treatment as first-line therapy. This combination is not considered a relevant comparator for tepotinib, as patients with NSCLC with METex14 skipping mutations are mutually exclusive to those with EGFR or ALK mutations (or ROS-1) and are distinct populations.[1,2] People with untreated squamous NSCLC:	aims to be inclusive. The rationale for excluding any comparators from the evidence submission will be considered by the appraisal committee. Comment noted. The CDF review of TA557 (TA683) has now been published. These technologies are appropriate for inclusion in the scope. Comment noted. The comparators section of the scope has been updated to remove TA584 technologies.

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		• Merck is aware that pembrolizumab with carboplatin and paclitaxel (TA600) is currently undergoing CDF review. The NICE website communicates that 'this appraisal has not been defined as therapeutically critical' and has been paused with no updated timelines provided. In the event that NICE guidance is not issued ahead of the final scope, pembrolizumab with carboplatin and paclitaxel should not be considered a relevant comparator, for both PD-L1>50% and PD-L1 <50% groups. References 1. Awad MM et al. J Clin Oncol. 2016;34(7):721-30. Frampton GM et al. Cancer Discov. 2015;5:850–859.	Comment noted.
Outcomes	British Thoracic Oncology Group	Yes. Standard outcomes are quoted.	Comment noted. No action required.
	Merck Serono Ltd	The outcome measures listed are appropriate. However, Merck also requests that duration of response (DoR) is listed as an outcome, as this was an important secondary endpoint from the VISION trial.	Comment noted. The scope includes the standard outcomes for cancer appraisals. Information on outcomes not specified in the scope can be provided in the company submission. Scope unchanged.
Economic analysis	British Thoracic Oncology Group	The economic analysis is standard for this type of drug, and the timelines quotes are quite vague but this is reasonable. No alternations needed.	Comment noted. No action required.
	Merck Serono	The aspects of the economic analysis stated are appropriate. With regards to the cost of diagnostic tests, it is anticipated that national	Comment noted. No

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	Ltd	genomic testing for MET mutations will be included in the testing directory by the time of launch in England. Nonetheless, the economic model will include a scenario analysis where the costs associated with diagnostic testing for MET in people with advanced NSCLC are included.	action required.
Equality and Diversity	British Thoracic Oncology Group	No concerns.	Comment noted. No action required.
	Merck Serono Ltd	No comment on equality.	Comment noted. No action required.
Other considerations	British Thoracic Oncology Group	None.	Comment noted. No action required.
	Merck Serono Ltd	Genomic testing will play a key role in ensuring patients receive the right treatments at the right time with the best possible outcomes. Consistent with the commitments outlined in the NHS Long Term Plan, the NHS is systematically offering genome sequencing as part of routine care through a network of seven Genomic Laboratory Hubs. In order to take full advantage of this initiative, it is vital to ensure patients timely access to innovative treatments.	Comment noted. In any appraisal NICE aims to publish guidance within 90 days of marketing authorisation.
Innovation	British Thoracic Oncology Group	This is a first in-class drug targeting MET alterations in lung cancer, and as such is an important and innovative technology. At present we have no MET targeting drugs available. Tepotinib, if approved, will be an important addition to our armoury of drugs. 3-4% of lung cancer patients. Although a small proportion, is still a significant group of patients. The high response rate to Tepotinib (almost 50%) represents an active drug, and this figure is higher than that which we would expect with chemotherapy	Comment noted. The extent to which the technology may or may not be innovative will be considered in any future appraisal of tepotinib. Scope unchanged.

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		alone. Similarly, the duration of response (>11 months) is evidence of significant clinical activity, on a par with other targeted oncology drugs for lung cancer such as the first and second generation EGFR TKIs. As such, it is highly likely that having access to Tepotinib for patients with METex14 will result in improved survival and improved quality of life. Given that its use will be in patient with metastatic (advanced) lung cancer without other options for targeted treatments, this is all the more important. The QALY calculations are likely to capture the benefits of the drugs, within the recognised limitations of this approach. Most relevant publications related to the VISION clinical trials. The most substantial publication arising from this is:	
	Merck Serono Ltd	Tepotinib is an innovative therapy with the potential to make a substantial impact on health-related benefits to patients with advanced NSCLC with METex14 skipping mutations. Nonspecific treatment options currently available to this group of patients are associated with worse survival rates and poor outcomes compared to patients with the disease who do not present with a MET mutation. The US Food and Drug Administration (FDA) has accepted and granted Priority Review for tepotinib in patients with advanced NSCLC with METex14 skipping mutations in August 2020. Priority Review is intended to accelerate evaluation of applications for drugs that could offer improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications. Tepotinib was previously granted Breakthrough Therapy Designation by the FDA in September 2019 for the treatment of patients with metastatic NSCLC harbouring METex14 skipping mutations who progressed following platinum-based cancer therapy. [redacted] Furthermore, tepotinib was granted SAKIGAKE 'fast-track' designation and	Comment noted. The extent to which the technology may or may not be innovative will be considered in any future appraisal of tepotinib. Scope unchanged.

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		orphan drug designation by the MHLW in Japan and is now approved for use in Japan. [redacted] In the primary efficacy analysis of VISION, tepotinib showed an ORR of 46.5% (95% CI: 36-57) (as assessed by the independent review committee), a median duration of response of 11.1 months (95% CI: 7.2-NE), a median PFS of 8.5 months (95% CI: 6.7-11.0) and a median OS of 17.1 months (95% CI: 12.0-26.8). Furthermore, ORR for tepotinib was consistent across treatment lines. Tepotinib also demonstrated a manageable toxicity profile.[1] Together, these data support tepotinib as a step-change in the treatment of advanced NSCLC and if recommended, will be the first MET-targeting treatment available to patients in England, Wales and Northern Ireland. **Paik PK et al. N Engl J Med. 2020;383:931–943 and supplementary materials.**	
Questions for consultation	British Thoracic Oncology Group	N/A	Comment noted. No action required.
	Merck Serono Ltd	Our comments on comparators, outcomes, available data, and the appropriate population have been captured above. Other questions are answered below. How should best supportive care be defined? Best supportive care may be defined as described in NICE Guidelines 122 for Lung cancer: diagnosis and management (2019). It consists of palliative care and palliative radiotherapy, additional monitoring requiring additional health care resources, and a tailored regimen to control symptoms as endobronchial obstruction.	Comment noted. See response in 'Comparators' section. Comment noted. No action required.

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		Are the subgroups suggested in 'other considerations' appropriate? The sub-group analysis by previous therapy is considered appropriate. For tumour histology, it should be noted that only 7% of patients (n=7 in the primary efficacy analysis) were of squamous histology. PD-L1 expression was not collected or reported as part of the VISION trial, however Merck is investigating whether this can be retrospectively collected and evaluated in an ad hoc exploratory analysis. Where do you consider tepotinib will fit into the existing NICE pathway, Treating non-small-cell lung cancer? As a treatment option for patients with advanced NSCLC with METex14 skipping mutations. Under the existing NICE lung cancer pathways, the treatment of patients with METex14 skipping mutations with tepotinib could sit within a new pathway for advanced NSCLC. Barriers to adoption of this technology into practice As stated previously, it is anticipated that national genomic testing for MET mutations will be fully implemented by the time tepotinib is launched in England, so there should be no barriers with regards to identifying patients with NSCLC harbouring METex14 skipping mutations. Cost comparison methodology Cost comparison is not appropriate for this topic. Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? The primary outcomes measured in the trial/ used to drive the model are still relevant.	Comments noted. No action required.

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Additional comments on the draft scope	British Thoracic Oncology Group	None	Comment noted. No action required.
	Merck Serono Ltd	No additional comments	Comment noted. No action required.

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

MSD

Roche Products Ltd.