National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Atezolizumab in combination for treating advanced non-squamous non-small-cell lung cancer

Response to consultee and commentator 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

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	RCPath	OK	Comment noted. No changes to the scope are needed.
	AstraZeneca	Given that pivotal clinical trials for atezolizumab in untreated non-squamous non-small cell lung cancer (NSCLC) included stage IV patients only, we feel wording should be revised to "Atezolizumab for untreated **stage IV** non-squamous NSCLC." This avoids ambiguity with stage III patients, some of whom may also have "advanced" disease.	Comment noted. The remit states that atezolizumab in combination will be appraised within its marketing authorisation. No changes are needed.
	Roche Products Ltd	No. Reference should be made to the combination therapy and the combination specific to this appraisal. Please refer to comment 4 for the draft wording of the proposed marketing authorisation.	Comment noted. The remit states that atezolizumab in combination will be appraised within its

Section	Consultee/ Commentator	Comments [sic]	Action
			marketing authorisation. No changes are needed.
Timing Issues	RCPath	Urgent	Comment noted. No changes to the scope are needed.
	Roche Products Ltd	We expect the appraisal within normal timelines for cancer medicines to enable access for patients at the time of the expected marketing authorisation (see comment 4).	Comment noted.
Additional comments on the draft remit	British Thoracic Society	The British Thoracic Society supports this appraisal. There is an urgent need more treatment options for patients with advanced lung cancer given the very poor prognosis.	Comment noted.
	AstraZeneca	Given the breadth of scope (monotherapy + two combinations), lack of data on atezolizumab monotherapy in this setting (+timelines when these are likely to become available), and different populations investigated in IMpower 110 (PD-L1 TPS ≥1%) versus IMpower 132 and 150 trials, we question whether this appraisal should be restricted to atezolizumab as combination therapy only.	Comment noted. The remit has been updated in the scope.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Roche Products Ltd	In order to provide additional context, we suggest including the following information: • Approximately 70% of NSCLC tumours are of non-squamous histology (adenocarcinoma, large-cell and undifferentiated carcinoma) (1)	Comments noted. The background section is intended for a general overview only however the scope background section has been

Section	Consultee/ Commentator	Comments [sic]	Action
		• Lung cancer survival in the UK has changed little in the last 40 years (3% to 5%); five- and ten-year survival for lung cancer in the UK is 9.5% and 4.9% respectively (2) • The median survival in first-line advanced non-squamous NSCLC is approximately 11.3 to 13.9 months ((KEYNOTE-189, PARAMOUNT study) for patients treated with pemetrexed-based chemotherapy, which is the SoC chemotherapy regimen in first-line non-squamous NSCLC (3, 4) • Furthermore, a meta-analysis of pemetrexed plus platinum doublet chemotherapy as first-line treatment for advanced non-squamous NSCLC demonstrated a median overall survival of 16.05 months (5) • We suggest the paragraph stating "For non-squamous NSCLC that has not progressed immediately following initial therapy with a NICE-recommended platinum-based chemotherapy regimen, maintenance treatment with pemetrexed is recommended as an option (NICE technology appraisal guidance 190 and 402)" to be moved before the section on EGFR and ALK mutation-positive therapies, to ensure clarity.	amended accordingly where appropriate.
The technology/ intervention	AstraZeneca	The IMpower 150 study investigated carboplatin plus paclitaxel (cisplatin was not included). Therefore, we suggest the following revision for clarity: Atezolizumab as monotherapy, or with a platinum-based drug plus pemetrexed, or with carboplatin plus paclitaxel (with or without bevacizumab) [Applies to description of the technology as well]	Comment noted. The technology/ intervention section has been amended accordingly to reflect the IMpower 150 study.
	Roche Products Ltd	The text in the second paragraph should read "Atezolizumab is being studied" instead of "It has been studied", as the clinical trials that are being mentioned are ongoing and most of them have not reported results yet.	Comment noted. The technology section has been amended accordingly.

Section	Consultee/ Commentator	Comments [sic]	Action
		The intervention listed should be "Atezolizumab, in combination with bevacizumab, paclitaxel and carboplatin" to reflect the combination therapy in the draft wording of the proposed marketing authorisation (see comment 4).	The intervention listed has also been updated.
Population	AstraZeneca	Suggest wording is revised to "adults with untreated, advanced, **stage IV** non-squamous NSCLC" to reflect the patient population in pivotal Phase III RCTs for atezolizumab in this setting We feel it is important to highlight that atezolizumab as monotherapy should **only** be considered in PD-L1-selected patients (as per IMpower 110 study design)	Comment noted. The appraisal will focus on the population covered by the marketing authorisation. No changes to the scope are needed.
	Roche Products Ltd	No comment.	Noted.
Comparators	AstraZeneca	1. Suggest revising second bullet as follows, for clarity: • "Pemetrexed in combination with cisplatin (adenocarcinoma or large-cell carcinoma only) o With or without pemetrexed maintenance treatment" 2. EGFR TKIs and ALK inhibitors are not relevant comparators for this appraisal, given: - Both IMpower 110 and IMpower 132 clinical trials excluded patients with known *EGFR* and *ALK* mutations - IMpower 150 included *EGFR* or *ALK* mutation-positive patients who had experienced disease progression (during or after treatment) or intolerance to treatment with one or more EGFR TKIs/ALK inhibitors. This setting is not relevant to the scope of this appraisal. This is also consistent with the approach used in the "Pembrolizumab for untreated PD-L1 positive NSCLC with at least 1% tumour proportion	Comments noted. The second bullet point in the comparators section has been amended accordingly. For EGFR or ALK-positive non-squamous advanced NSCLC previously treated with targeted therapy, please note that the comparators have now been amended to

Section	Consultee/ Commentator	Comments [sic]	Action
		score" appraisal (ID1247) and NICE guidelines for first-line treatment of patients with advanced, metastatic (stage IV), *EGFR* or *ALK* mutation-positive NSCLC (CG121) 3. EGFR TKIs (afatinib, erlotinib, and gefitinib) and ALK inhibitors (ceritinib and crizotinib) have been transposed in the scope	include docetaxel and pembrolizumab.
	Roche Products Ltd	The comparators listed in the draft scope are representative of the standard treatments used in the NHS across patients with untreated NSCLC, regardless of histology or mutation status. However, not all these therapies are relevant comparators for the atezolizumab combination in study IMpower150 and we suggest the following amendments to the draft scope: • Since the patient population in our study (IMpower150) and the proposed marketing authorisation are for first-line metastatic non-squamous NSCLC, we consider that the only relevant chemotherapy comparator is "pemetrexed with a platinum drug with or without pemetrexed maintenance". Pemetrexed plus platinum is the SoC chemotherapy regimen for patients with first-line non-squamous NSCLC, based on both clinical expert opinion as well as market share data (Roche data on file). Whilst the other chemotherapy combinations being listed in the draft scope (docetaxel, gemcitabine, paclitaxel or vinorelbine) are treatment options for first-line NSCLC, they are not commonly used for the non-squamous histology (they collectively account for less than 12% in market share). As such, these chemotherapy options should not be considered relevant comparators for this appraisal. • Targeted therapies for EGFR and ALK-positive advanced NSCLC are also not relevant comparators for this appraisal. The inclusion criteria for our study (IMpower150) state that patients with a sensitising EGFR mutation or ALK translocation must have disease progression or	Comment noted. Comparators in the scope are any alternative treatment to the technology used in clinical practice. During the appraisal the committee will determine the relevant comparators for its decision making. Please note that the comparators for EGFR or ALK-positive non-squamous advanced NSCLC previously treated with targeted therapy have now been amended to include

Section	Consultee/ Commentator	Comments [sic]	Action
		intolerance of treatment with one or more approved targeted therapies. Therefore, combination of atezolizumab with bevacizumab, paclitaxel and carboplatin is positioned as a treatment option for EGFR and ALK-positive advanced NSCLC after targeted therapies and as such, these targeted therapies should not be included as comparators. The fact that EGFR and ALK-positive patients should have received targeted therapies first is also reflected in the draft wording of the proposed marketing authorisation (see comment 4)	docetaxel and pembrolizumab.
Outcomes	Roche Products Ltd	We suggest adding duration of response as an outcome, since this is an important clinical endpoint for cancer immunotherapies.	Comment noted. Duration of response will be captured under the outcome "response rate". No changes to the scope are needed.
Economic analysis	Roche Products Ltd	The economic analysis will follow the NICE reference case.	Comment noted. No changes to the scope are needed.
Equality and Diversity	Roche Products Ltd	No equality issues were identified	Comment noted. No changes to the scope are needed.
Innovation	AstraZeneca	The effectiveness of atezolizumab as monotherapy in PD-L1 selected patients (TPS ≥1%) is not known at present. However, it is unlikely to represent a step-change in the first-line treatment of stage IV non-squamous NSCLC patients, given pembrolizumab monotherapy has demonstrated a significant treatment benefit in this setting (KEYNOTE 042).	Comment noted. The committee will consider the innovative nature of the technology at the time of the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
		Pembrolizumab + chemotherapy also demonstrated a greater PFS benefit (versus chemotherapy alone) in untreated non-squamous NSCLC patients (KEYNOTE 189), relative to what was reported for atezolizumab plus bevacizumab and chemotherapy (versus bevacizumab and chemotherapy alone) in the IMpower 150 trial, based on naïve comparisons of trial data.	No changes to the scope are needed.
	Roche Products Ltd	Atezolizumab is an innovative treatment option, which in combination with bevacizumab, carboplatin and paclitaxel offers a step change in the management of first-line non-squamous NSCLC. Atezolizumab, a PD-L1 inhibitor, restores anti-cancer immunity by preventing T-cell deactivation. Bevacizumab, in addition to its established anti-angiogenic effects, further enhances atezolizumab's T-cell mediated killing, by inhibiting VEGF-related immunosuppression, promoting T-cell tumour infiltration and creating a favourable tumour microenvironment for T-cell reinvigoration. Furthermore, the addition of carboplatin/paclitaxel chemotherapy enhances the susceptibility of tumour cells to cytotoxic T-cells (6). Data available from phase III study IMpower150 has demonstrated significant clinical benefit of atezolizumab in combination with bevacizumab, carboplatin and paclitaxel compared to bevacizumab, carboplatin and paclitaxel, in patients across all levels of PD-L1 expression and including patients with sensitising EGFR or ALK genetic alterations. Based on the results of IMpower150, atezolizumab in combination with bevacizumab, carboplatin and paclitaxel is the first phase III immunotherapy-based combination to demonstrate a statistically significant and clinically meaningful improvement in OS and PFS across all patients in first-line non-squamous non-small-cell lung cancer, whilst also demonstrating a safety profile consistent with known safety risks. As such, this combination provides a potential new standard of care for patients with first-line non-squamous NSCLC.	Comment noted. The committee will consider the innovative nature of the technology at the time of the appraisal. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
Other considerations	RCPath	The main issue for pathologists in relation to treatment with this kind of drug is the probable need for an associated diagnostic test that may decide whether the patient is eligible for treatment. Data suggest that those with greater immunostaining of the tumour for PD-L1 have a better response. If this is the case, pathologists will have to be trained in interpretation and systems for validation will need to be put in place, as well as the cost of the test (and possible re-biopsy) taken into account. Impact on biomedical scientists' workloads/staff will also need to be taken into account.	Comments noted. Where NICE recommends that a treatment be funded by the NHS, it will also provide advice and tools to support the local implementation of its guidance. No changes to the scope are needed.
	Roche Products Ltd	None.	Comment noted.
Questions for consultation	NLCFN	Are the outcomes listed appropriate: Yes Are the subgroups suggested in 'other considerations appropriate: Yes Is testing for PD-L1 expression routine in the NHS for untreated, non-squamous NSCLC?: Yes all patients in this sub group are routinely tested for PD-L1 expression	Comments noted. No changes to the scope are needed.
	Roche Products Ltd	No additional remarks, apart from the ones listed below. • Where do you consider atezolizumab will fit into the existing NICE pathway, lung cancer?	Comments noted. No changes to the scope are needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		○ Consistent with our clinical study (IMpower150) and the wording of our proposed marketing authorisation, atezolizumab in combination with bevacizumab, carboplatin and paclitaxel is anticipated to be a first-line treatment option for patients with metastatic non-squamous non-small-cell lung cancer and a treatment option for patients with EGFR or ALK-positive tumour mutations after having received targeted therapy, if clinically indicated • Would it be appropriate to use the cost comparison methodology for this topic? ○ A cost comparison methodology could potentially be relevant for this appraisal, for the comparison of the atezolizumab combination with pembrolizumab in patients with tumours expressing PD-L1 (TPS >50%). This will depend on the results of an indirect treatment comparison with pembrolizumab, which are not yet available.	

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

MSD UK