National Institute for Health and Care Excellence

Single Technology Appraisal (STA/MTA)

Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after platinum-based chemotherapy

Response to consultee and commentator comments on the draft remit and draft scope (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	NCRI-ACP-RCP-RCR	Yes.	Comment noted. No action required.
	Roche	This is an appropriate topic for NICE to consider.	Comment noted. No action required.
	Royal College of Pathologists	Yes.	Comment noted. No action required.
	Pfizer	No comments.	No action required.
Wording	NCRI-ACP-RCP-RCR	Yes.	Comment noted. No action required.

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	Roche	Update to the remit based on the appropriate population: "To appraise the clinical and cost effectiveness of atezolizumab within its marketing authorisation for treating locally advanced or metastatic non-small-cell lung cancer after prior chemotherapy."	Comment noted. The remit has been updated accordingly.
	Royal College of Pathologists	Yes.	Comment noted. No action required.
	Pfizer	No comments.	No action required.
Timing Issues	NCRI-ACP-RCP-RCR	The current timing is appropriate as although atezolizumab is not licensed within the setting in NSCLC. The randomised phase II registration study has demonstrated similar results to other drugs in this class indicating good activity.	Comment noted. No action required.
	Roche	The phase III OAK study is anticipated to provide pivotal data to this appraisal. Based on the likely timings of data and CSR availability, there could be significant challenges in fully incorporating this information into the clinical and economic assessment, should NICE request a submission which is significantly in advance of Marketing Authorisation. Full data will be available for a submission in March 2017. Whilst there is a current unmet need in this population, recent appraisals within this space mean treatment options are available for patients within this space.	Comment noted. No action required.
	Royal College of Pathologists	Urgent.	Comment noted. No action required.
	Pfizer	No comments.	No action required.

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Additional comments on the draft remit	NCRI-ACP-RCP-RCR	None.	No action required.
	Roche	None.	No action required.
	Royal College of Pathologists	None.	No action required.
	Pfizer	No comments.	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Boehringer Ingelheim	Ref 1 (from 2014) was updated in a LUCADA publication in Dec 2015: http://www.hqip.org.uk/public/cms/253/625/19/354/2015-12-02%20National%20Lung%20Cancer%20Report.pdf?realName=9wvAlU.pdf More up-to-date data available there.	Comment noted. The scope has been updated accordingly.
	NCRI-ACP-RCP-RCR	Yes, The outcomes for advanced NSCLC are remains very poor which means there is still a huge unmet need. The evaluation of the technology is in the fitter NSCLC population, in whom we would expect slightly better outcomes cf 'all NSCLC patients'.	Comment noted. No action required.
	Roche	The median survival of people with lung cancer on their second line of treatment is approximately 6 months: Those on first line have a much higher median survival, and those currently untreated or on latter lines of treatment have a greatly reduced median survival.	Comment noted. No action required.

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	Royal College of Pathologists	OK.	Comment noted. No action required.
	Pfizer	No comments.	No action required.
The technology/ intervention	NCRI-ACP-RCP-RCR	Yes	Comment noted. No action required.
	Roche	Atezolizumab is a humanised monoclonal antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells. However, atezolizumab is an anti-programmed cell death ligand-1 (PD-L1), as opposed to an anti-programmed cell death 1 (PD-1). The description should be adjusted to reflect this.	Comment noted. This section of the scope has been updated accordingly.
	Royal College of Pathologists	Yes.	Comment noted. No action required.
	Pfizer	No comments.	No action required.
Population	NCRI-ACP-RCP-RCR	This is the appropriate population for the clinical data generated from the atezolizumab evidence.	Comment noted. No action required.
	Roche	The Marketing Authorisation Application seeks approval for the population: “adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.” Hence the population stated in the remit requires amendment to exclude mention of “platinum treatment”	Comment noted. The population of the scope has been updated to ‘People with locally advanced or metastatic non-small-cell lung cancer whose disease

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			has progressed after chemotherapy'.
	Royal College of Pathologists	For this drug and similar drugs, there is evidence of greater drug effect in patients with a high level of PD-L1 expression on tumour cells and also on tumour-infiltrating lymphocytes for atezolizumab. If immunohistochemistry is to be used as a marker to help guide the decision to give the drug, this will have significant implications for histopathology.	Comment noted. If the evidence allows, consideration will be given to subgroups based on biological markers (see 'Other considerations' section of the scope).
	Pfizer	People with locally advanced or metastatic non-small-cell lung cancer whose disease has progressed after platinum treatment. • This suggests that all patients, irrespective of histological and molecular subtype, should be considered for treatment with atezolizumab once they have received platinum chemotherapy. • We understand general consensus amongst treating clinicians in the UK is for patients with ALK or EGFR driver mutations, a respective ALK or EGFR targeted inhibitor is considered the preferred treatment option where available, in accordance with the current established evidence base and real world data. Once targeted therapy options have been exhausted (relating to the specific underlying driver mutation), only then would it be appropriate to consider other treatment options, including immunotherapy agents. • EGFR and ALK diagnostic testing is done routinely in the UK, with the purpose being to identify patients who can be offered an EGFR- or an ALK-inhibitor. Offering such patients atezolizumab instead would be counter to the purpose of this diagnostic testing, and to current clinician preference.	Comments noted. In view of comments from consultees, the population of the scope has been updated as follows: **'**People with locally advanced or metastatic non-small-cell lung cancer whose disease has progressed after chemotherapy'.

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		It is suggested the wording of the population is adjusted to reflect that patients with EGFR and ALK tumours should be first challenged with a targeted inhibitor, similar to what was included in the final scope for pembrolizumab (ID840): • "People with locally advanced or metastatic non-small-cell lung cancer, whose disease has progressed after platinum treatment and available targeted therapies for EGFR or ALK positive tumours."	
Comparators	Boehringer Ingelheim	Following TA403 publication on the 24 August 2016, ramucirumab should be taken out of this list	Comment noted. Ramucirumab has been removed as a comparator.
	NCRI-ACP-RCP-RCR	Yes, these summarise the relevant comparators accurately although it is unlikely that patients unfit for any chemotherapy, would be relevant for this therapy, so questionable whether BSC is an appropriate comparator.	Comments noted. Some consultees suggested that targeted treatments such as crizotinib (for people with ALK mutations), afatinib and erlotinib for EGFR mutation positive tumours) are likely to be used first for those with the respective mutation type. Therefore these have been removed as comparators from the scope.

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			Best supportive care is a relevant comparator if people refused docetaxel treatment and were not eligible for the other targeted treatments.
	Roche	The comparators listed in the draft scope are representative of the standard treatments used in the NHS across all patients with NSCLC. However, they are not all relevant comparators for atezolizumab and we suggest the following amendments to the draft scope: • Afatinib – Atezolizumab will be licensed for all patients with NSCLC after prior chemotherapy. However, where an EGFR-positive mutation has been identified, treatment in clinical practice tends to be with a targeted therapy. In the circumstance a targeted therapy has been initiated first line (afatinib is recommended as 1st line therapy), afatinib would not be used second line, after treatment failure. Where a targeted therapy was not used first line, a targeted therapy such as afatinib would be the treatment of choice thereafter. Therefore, this is not an appropriate comparator to atezolizumab. Furthermore, small patient populations (EGFR 1st line accounts for 10% of the population) will limit the evidence available to make any robust comparison. • Erlotinib –Similar to the situation described above, where an EGFR-TK mutation has been identified as positive, or is suspected as positive (as per the circumstances described in TA374), treatment in clinical practice tends to be with a targeted therapy. Therefore, this is not an appropriate comparator to atezolizumab. Furthermore, small patient populations (EGFR	Comments noted. We agree that targeted traetments such as crizotinib (for people with ALK mutations), afatinib and erlotinib for EGFR mutation positive tumours) are likely to be used first for those with the respective mutation type. Therefore these have been removed as comparators from the scope. Best supportive care is a relevant comparator if people refused docetaxel treatment and were not eligible for the other targeted treatments.

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		1st line accounts for 10% of the population) will limit the evidence available to make any robust comparison. • Crizotinib – where an ALK positive mutation has been identified, treatment in clinical practice tends to be with a targeted therapy. In addition, NICE guidance recommends crizotinib first line (ID865). Therefore crizotinib would not be used to treat patients' after treatment failure (2nd line). Therefore, this is not an appropriate comparator to atezolizumab. • Pembrolizumab has a Marketing Authorisation for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumours express PD-L1 as determined by an FDA-approved test with disease progression on or after platinum-containing chemotherapy. As such, pembrolizumab is not an appropriate comparator for the total population under consideration for atezolizumab. However, pembrolizumab could be considered an appropriate comparator in subgroup analyses. Nevertheless, as the diagnostic tool used to determine the PD-L1 status of patients being considered for pembrolizumab is different to that used for atezolizumab, only a crude comparison can be made due to differing patient populations. • Ramucirumab with docetaxel - The NICE final appraisal determination does not recommend ramucirumab in combination with docetaxel for treating locally advanced or metastatic non-small-cell lung cancer in adults whose disease has progressed after platinum-based chemotherapy, therefore (subject to appeal) it is not an appropriate comparator for atezolizumab as will not be used in clinical practice. • BSC – Given the availability of other treatments, it is assumed BSC alone is no longer an established treatment option for patients with metastatic NSCLC, who can tolerate, or are willing to have pharmacological intervention. Hence, BSC is not an appropriate comparator for atezolizumab.	The comparators in the scope have been updated as follows: • Docetaxel monotherapy • Nintedanib with docetaxel (for people with adenocarcinoma histology) • Nivolumab (subject to ongoing NICE appraisal) • Pembrolizumab (PD-L1-epxressing tumours; subject to ongoing NICE appraisal) • Best supportive care

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		Whilst all of the comparators are considered representative of the standard treatments used in the NHS, small patient populations and data availability may impact the extent to which atezolizumab can be compared to most of the comparators listed above.	
	Royal College of Pathologists	No comments.	No action required.
	Pfizer	In light of the above comments on population, if a patient had progressed following first-line platinum therapy, and this patient is an EGFR- or ALK-positive patient, treating clinicians would challenge the patients with a respective targeted inhibitor if one were available. If multiple are available, it is expected clinicians would challenge sequentially. We do not believe that in current UK clinical practice these patients would be offered a non-EGFR or non-ALK inhibitor. As such, we feel EGFR- and ALK-targeted inhibitors should be removed as comparators from this appraisal. Including these as comparators implies that atezolizumab would be used as an alternative to these.	Comments noted. We agree that targeted traetmentssuch as crizotinib (for people with ALK mutations), afatinib and erlotinib for EGFR mutation positive tumours) are likely to be used first for those with the respective mutation type. Therefore these have been removed as comparators from the scope. Best supportive care is a relevant comparator if people refused docetaxel treatment and were not eligible for the other targeted treatments.

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			The comparators in the scope have been updated as follows: • Docetaxel monotherapy • Nintedanib with docetaxel (for people with adenocarcinoma histology) • Nivolumab (subject to ongoing NICE appraisal) • Pembrolizumab (PD-L1-epxressing tumours; subject to ongoing NICE appraisal) • Best supportive care
Outcomes	NCRI-ACP-RCP-RCR	Yes, although overall survival data may be compromised by crossover.	Comment noted. This issue can be addressed in the company submission. No changes to the scope required.
	Roche	Median duration of response should be added to capture important health related benefits and harms.	No changes to the scope required.

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	Royal College of Pathologists	No comments.	No action required.
	Pfizer	No comments.	No action required.
Economic analysis	NCRI-ACP-RCP-RCR	Appropriate although it should be noted that NHS England have agreed to fund PD-L1 testing.	Comment noted. No changes to the scope required.
	Roche	No comments	No action required.
	Royal College of Pathologists	The level of expression testing will have significant implications for pathology costs as the tests are currently “companion diagnostics” and relatively expensive (and time consuming) if all advanced NSCC is to be assessed.	Comments noted. If appropriate, the appraisal should include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices.
	Pfizer	No comments.	No action required.
Equality and Diversity	NCRI-ACP-RCP-RCR	None.	No action required.
	Roche	No equality issues have been identified.	No action required.

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	Royal College of Pathologists	No comments.	No action required.
	Pfizer	No comments.	No action required.
Innovation	NCRI-ACP-RCP-RCR	Yes, this is unquestionably a highly innovative technology and the incorporation of this technology into our current pathways is clearly a step-change and may prove a paradigm shift in the management of NSCLC. We believe this class of drugs will replace first line platinum-combination chemotherapy for patients with high PD-L1 expressing tumours. For patients with lower expression (but some expression - >1%) I think it will become a treatment option post platinum-combination chemotherapy i.e. the setting of this appraisal	Comments noted. Consultees are encouraged to describe the innovative nature of the technology in their evidence submissions. The Committee will consider this information during the appraisal process
	Roche	Atezolizumab is the first medicinal product (humanised monoclonal antibody immunoglobulin IgG1 [IgG1]) that binds directly and selectively to PD-L1 immune checkpoint protein, thus preventing it from binding to receptors PD-1 and B7.1. This prevents down-regulation of T cell activity, allowing for the priming of new T cells to facilitate anticancer immune responses. In parallel, the PD-L2/PD-1 interaction is left intact, potentially preserving peripheral immune homeostasis. Data available from phase II studies (GO28754 [BIRCH] and GO28753 [POPLAR]) have demonstrated atezolizumab's clinically significant overall survival benefit, with a favourable toxicity profile.	Comments noted. Consultees are encouraged to describe the innovative nature of the technology in their evidence submissions. The Committee will consider this information during the appraisal process
	Royal College of Pathologists	No comments.	No action required.

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	Pfizer	No comments.	No action required.
Other considerations	NCRI-ACP-RCP-RCR	EGFR/ALK positive patient populations need to be considered separately although there inclusion is reasonable numbers of these subpopulations were small across the studies conducted with PD-L1 directed treatment.	Comments noted. The scope has been updated to include the following text: 'If the evidence allows, consideration will be given to subgroups based on biological markers.'
	Roche	No comments.	No action required.
	Royal College of Pathologists	The impact on laboratory staff do deal with the increased immunohistochemistry also needs to be considered as a cost implication	Comments noted. If appropriate, the appraisal should include consideration of the costs and implications of additional testing for biological markers, but will not make recommendations on specific diagnostic tests or devices.
	Pfizer	No comments.	No action required.

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Questions for consultation	NCRI-ACP-RCP-RCR	We would expect atezolizumab to fit into the NICE NSCLC pathway for patients with PD-L1 expressing tumours who have progressed on platinum based chemotherapy (+ EGFR or ALK targeted therapies for relevant patient populations). It will sit in parallel with nivolumab and pembrolizumab (if approved) and in preference to docetaxel / docetaxel + nindetanib / BSC for patients who are fit enough to receive it.	Comments noted. The remit, population and comparators have been updated accordingly.
	Roche	1. Is the population 'whose disease has progressed after platinum treatment' appropriate - Is atezolizumab likely to be used in people after any prior therapy or only after platinum therapy? If likely to be used after any prior therapy, should ceritinib be a comparator? The population in the remit is incorrect: Atezolizumab will be licensed for all patients with NSCLC after prior chemotherapy. However, ceritinib is only recommended in ALK-positive patients: as described above, where an ALK positive mutation has been identified, treatment in clinical practice tends to be with a targeted therapy. Therefore, ceritinib is not an appropriate comparator to atezolizumab. Furthermore, small patient populations (ALK mutation 1st line accounts for 3% of the population) will limit the evidence available to make any robust comparison. 2. Are there any subgroups of people in whom atezolizumab is expected to be more clinically effective and cost effective or other groups that should be examined separately? The Marketing Authorisation Application seeks approval for the population: "adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy". However, the clinical program allows for	Comments noted. The remit, population and comparators have been updated accordingly. Comment noted. In the other considerations section of the scope, it states that, 'If the evidence allows, consideration will be given to subgroups

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		subgroup analyses as defined by Tumour Cells/Immune Cells expression from an accompanying diagnostic test. 3. How should best supportive care be defined Best supportive care can be defined as the basket of symptomatic and supportive treatments designed to enhance comfort and quality of life but not delivered with the primary intention or expectation of prolonging life. For metastatic non-small cell lung cancer, this typically consists of pain relief and patient monitoring only, as active anti-tumour treatments are excluded by this definition. However other treatments could be included depending on the disease morbidity, for example steroids for brain metastases or palliative radiotherapy. 4. Where do you consider atezolizumab will fit into the existing NICE pathway, Lung cancer? Atezolizumab will be an option available (amongst other immunotherapies) for with NSCLC, who have had an inadequate response to chemotherapy.	based on biological markers.' Comments noted. No action required. Comments noted. The remit and population have been updated accordingly.
	Royal College of Pathologists	No comments.	No action required.
	Pfizer	No comments.	No action required.
Additional comments on the draft scope	NCRI-ACP-RCP-RCR	None.	No action required.
	Roche	None.	No action required.

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	Royal College of Pathologists	No comments.	No action required.
	Pfizer	No comments.	No action required.

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

Eli Lilly
Merck, Sharpe & Dohme