National Institute for Health and Care Excellence

Health Technology Evaluation

Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949] Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	BTOG	Yes – appropriate topic and suitable for a STA.	Thank you for your comment.
	Regeneron	No comments.	None
	Roche	None	None
Wording	BTOG	Yes. No comment.	None
	Regeneron	No comments.	None
	Roche	None	None
Timing Issues	BTOG	Medium.	None

Section	Stakeholder	Comments [sic]	Action
	Regeneron	Provision of an alternative immunochemotherapy combination treatment option that will improve clinician and patient choice and represent a cost-effective and potentially cost saving use of NHS resources.	Thank you for your comment.
	Roche	None	None
Additional comments on the draft remit	BTOG	Nil	None
	Regeneron	None.	None
	Roche	None	None

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	BTOG	Factually correct other than this sentence: If the squamous NSCLC expresses PD-L1 on less than 50% of its tumour cells people may be offered pembrolizumab (TA531) or atezolizumab (TA705) monotherapy. This should read *'more than 50%'*	Thank you for your comment. The scope has been amended to reflect this.
	Regeneron	The technology wording should be updated as follows to reflect the UK marketing authorisation status (approved by MHRA on 2nd February 2024) and MHRA approved label indication statement for cemiplimab in combination with platinum-based chemotherapy in previously untreated locally advanced/metastatic NSCLC:	Thank you for your comments. The scope has been amended in response.

Section	Consultee/ Commentator	Comments [sic]	Action
		"Cemiplimab in combination with platinum-based chemotherapy has UK marketing authorisation for first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells), with no EGFR, ALK or ROS1 aberrations, who have locally advanced NSCLC who are not candidates for definitive chemoradiation, or metastatic NSCLC" The following background text should be updated to reflect NICE guidance for pembrolizumab (TA531) and atezolizumab (TA705) monotherapies being recommended for patients with PD-L1 on 50% or more of tumour cells. *"If the squamous NSCLC expresses PD-L1 on ~~less than~~ 50% or more of its tumour cells people may be offered pembrolizumab (TA531) or atezolizumab (TA705) monotherapy."*	
	Roche	"If the squamous NSCLC expresses PD-L1 on *less* than 50% of its tumour cells people may be offered pembrolizumab (TA531) or atezolizumab (TA705) monotherapy." This is incorrect and should be 'more than'.	Thank you for your comment. The scope has been amended to reflect this
Population	BTOG	Yes	Thank you for your comment.
	Regeneron	The population wording should be updated as follows to reflect the MHRA approved label indication statement: *"first-line treatment of adult patients with NSCLC expressing PD-L1 (in ≥ 1% of tumour cells), with no EGFR, ALK or ROS1 aberrations, who have:* • *locally advanced NSCLC who are not candidates for definitive chemoradiation, or*	Thank you for your comment the scope has been amended to reflect this.

Section	Consultee/ Commentator	Comments [sic]	Action
		metastatic NSCLC"	
	Roche	None	None
Subgroups	BTOG	Suitable subgroups. Particular attention to disease stage should be made.	Thank you for your comment.
	Regeneron	<u>Prior surgery</u> It is unclear why prior surgery has been suggested as a relevant subgroup for this appraisal given: • Based on UK clinical expert feedback, history of prior surgery is not an important prognostic factor, is not relevant for clinical decision making in patients presenting with locally advanced (not eligible for definitive chemoradiation) or metastatic disease, and is not expected to be a treatment effect modifier for cemiplimab + platinum-based chemotherapy. • The efficacy and safety of cemiplimab in combination with platinum-based chemotherapy was evaluated in the part 2 of the registrational phase 3 EMPOWER-Lung 3 randomised, controlled trial (RCT) which included 466 patients with locally advanced NSCLC (stage IIIB/C) who were not candidates for definitive chemoradiation and patients with metastatic NSCLC, regardless of tumour PD-L1 expression status. Less than 5% of patients enrolled in the EMPOWER-Lung 3 RCT had prior surgery (4.7% in the ITT population), precluding robust subgroup analysis by prior surgery status. • Prior surgery was not considered a subgroup of interest in other recent NICE TAs for previously untreated advanced/metastatic NSCLC, including NICE TA705 (2021), TA683 (2021), NICE TA724 (2021), and TA770 (2022).	Thank you for your comments. History of prior surgery has been retained with updated wording. This subgroup was included due to its increasing relevance of in light of the NHS Targeted Lung Health Check program and its national roll out[1] and the possibility of this being a prognostic factor. There is emerging evidence to suggest this may be the case.[2] The subgroups have been retained in the final scope to allow committee to consider any evidence and clinical opinion in its entirety.

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		Regeneron therefore suggests this subgroup be removed from the appraisal scope. <u>Disease stage</u> • In NICE clinical guideline 122 and in routine NHS clinical practice, people with locally advanced disease not considered candidates for surgery or definitive chemoradiation are managed in the same way as people with metastatic disease. Subgroup analysis by disease stage therefore lacks relevance to UK clinical practice and treatment decisions. • Subgroup analysis of the EMPOWER-Lung 3 RCT show that cemiplimab + platinum-based chemotherapy improves PFS and OS vs chemotherapy alone both in patients with locally advanced disease who are not candidates for definitive chemoradiation and in patients with metastatic disease. Whilst the inclusion of patients with locally advanced disease who are not candidates for definitive chemoradiation (a historically under-represented patient group in clinical trials of other immunochemotherapy treatment options which have typically focussed on patients with metastatic disease) in EMPOWER-Lung 3 represents a strength of the evidence package, a relatively small number of patients with locally advanced disease included in the study (14.8% of the ITT population). Sample size considerations are compounded when also considering histology and/or PD-L1 expression levels. Further, the lack of inclusion of patients with locally advanced disease in pivotal studies of pembrolizumab + chemotherapy precludes indirect comparison (eg, via NMA) of cemiplimab + platinum-based chemotherapy compared with the most relevant comparator for this appraisal. • Regeneron therefore suggests this subgroup be removed from the appraisal scope.	

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	Roche	None	None.
Comparators	BTOG	1. SqNSCLC with PDL1 <50% - Comparison with 'Chemotherapy (gemcitabine or vinorelbine) should not be exclusive. Can include any platinum-based doublet (other than pemetrexed) ie could consider Paclitaxel also. 2. SqNSCLC with PDL1 >50% - Could be any platinum doublet (including paclitaxel) Should also include Carboplatin -Paclitaxel -Pemroblizumab All other comparators are included and consistent with current standard treatments in the NHS.	Thank you for your comments. The scope has been amended to reflect them.
	Regeneron	The wording for patient groups with PD-L1 expression level "less than 50%" should be updated to refer to "PD-L1 1-49%" to align with the MHRA approved indication for cemiplimab + platinum-based chemotherapy which does not cover use in patients with PD-L1 <1%. **For people with squamous NSCLC whose tumours express PD-L1 on less than 50% of cells** • Pembrolizumab with carboplatin and paclitaxel with olaparib maintenance (ID4006) is not a relevant comparator as the appraisal was suspended in January 2024 following an announcement from the manufacturer of olaparib that it is no longer pursuing a marketing authorisation.	Thank you for your comments. Pembrolizumab with olaparib maintenance has been removed as a comparator to reflect the suspension of ID4006 and ID4028 appraisals. Pembrolizumab with carboplatin and paclitaxel has been added to the section for

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		• Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) is not a relevant comparator as based on feedback from UK clinical experts, the current standard of care for NHS patients with previously untreated locally advanced (not eligible for definitive chemoradiation)/metastatic NSCLC with PD-L1 ≥ 1% and without targetable mutations is immunotherapy (± chemotherapy in line with licensed indications and NICE technology appraisal guidance recommendations). Chemotherapy alone is only used in patients who are contraindicated to immunotherapy. UK market share data on file suggest that approximately 5% of all patients with previously untreated locally advanced (not eligible for definitive chemoradiation)/metastatic NSCLC with PD-L1 ≥ 1% receive gemcitabine or vinorelbine with a platinum drug. **For people with squamous NSCLC whose tumours express PD-L1 on more than 50% of cells** • Chemotherapy (gemcitabine or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) is not a relevant comparator as based on feedback from UK clinical experts the current standard of care for NHS patients with previously untreated locally advanced (not eligible for definitive chemoradiation)/metastatic NSCLC with PD-L1 ≥ 1% and without targetable mutations is immunotherapy (± chemotherapy in line with licensed indications and NICE technology appraisal guidance recommendations). Chemotherapy is only used in patients who are contraindicated to immunotherapy. UK market share data on file suggest that approximately 5% of all patients with previously untreated locally advanced (not eligible for definitive chemoradiation)/metastatic NSCLC with PD-L1 ≥ 1% receive gemcitabine or vinorelbine with a platinum drug. • Pembrolizumab monotherapy and Atezolizumab monotherapy are not relevant comparators. Feedback from UK clinical experts suggests that	squamous disease (PD-L1 50% or more). The other comparators have been retained in the scope as at this stage of the evaluation, identifying comparators should be inclusive and they are all either recommended by NICE and/or used to some extent in the population covered by the marketing authorisation for this appraisal. This allows the committee to consider whether or not they are appropriate comparators.

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		decisions on whether to treat with immunotherapy monotherapy or an immunochemotherapy combination are based on individual patient characteristics. For example, use of immunochemotherapy combination regimens for patients with PD-L1 ≥ 50% is often limited to those with a high symptom burden, and NICE TA770 limits use of pembrolizumab + chemotherapy in patients with squamous disease and PD-L1 ≥ 50% to patients who require urgent clinical intervention. In contrast, immunotherapy monotherapy is often preferred (TA705) in many patients with PD-L1 ≥ 50% due to cumulative toxicity and tolerability considerations. It is therefore expected that cemiplimab + platinum-based chemotherapy would primarily be used as an alternative to pembrolizumab + chemotherapy (TA770) for patients with squamous disease and PD-L1 ≥ 50%, rather than displacing use of available immunotherapy monotherapy options (TA531, TA770) in this patient group. • Pembrolizumab with carboplatin and paclitaxel is recommended by NICE as an option for the subset of people with squamous NSCLC whose tumours express PD-L1 on 50% or more of cells and who need urgent clinical intervention (TA770). Given the anticipated place in therapy for cemiplimab + platinum-based chemotherapy as an alternative to existing immunochemotherapy combination options across histology/PD-L1 expression groups (see below), this should be added as a comparator to the scope. **For people with non-squamous NSCLC whose tumours express PD-L1 on less than 50% of cells** • Pemetrexed with platinum doublet chemotherapy is not a relevant comparator as based on feedback from UK clinical experts, current standard of care for NHS patients with. previously untreated locally advanced (not eligible for definitive chemoradiation)/metastatic NSCLC with	

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		PD-L1 ≥ 1% and without targetable mutations is immunotherapy (± chemotherapy in line with licensed indications and NICE technology appraisal guidance recommendations). Chemotherapy alone is only used in patients who are contraindicated to treatment with immunotherapy. • Atezolizumab in combination with bevacizumab, carboplatin, and paclitaxel is not a relevant comparator as based on feedback from UK clinical experts, uptake has been low since it was recommended by NICE as an option in 2019 due to its toxicity profile/tolerability considerations. UK market share data on file suggest that it used in a small proportion (< 10%) of patients with non-squamous disease and PD-L1 1-49%, and UK clinical experts highlighted that it is not used at all in some NHS trusts. **For people with non-squamous NSCLC whose tumours express PD-L1 on 50% or more of cells** • Pemetrexed with platinum doublet chemotherapy is not a relevant comparator as based on feedback from UK clinical experts, current standard of care for NHS patients with. previously untreated locally advanced (not eligible for definitive chemoradiation)/metastatic NSCLC with PD-L1 ≥ 1% and without targetable mutations is immunotherapy (± chemotherapy in line with licensed indications and NICE technology appraisal guidance recommendations). Chemotherapy alone is only used in patients who are contraindicated to treatment with immunotherapy. • Pembrolizumab monotherapy and Atezolizumab monotherapy are not relevant comparators. Feedback from UK clinical experts suggests that decisions on whether to treat with immunotherapy monotherapy or an immunochemotherapy combination are based on individual patient characteristics. For example, use of immunochemotherapy combination regimens for patients with PD-L1 ≥ 50% is often limited to those with a high symptom burden. In contrast, immunotherapy monotherapy is often "preferred" (TA705) in many patients with PD-L1 ≥ 50% due to cumulative toxicity and tolerability considerations. It is therefore expected that	

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		cemiplimab + platinum-based chemotherapy would primarily be used as an alternative to pembrolizumab + chemotherapy (TA683) for patients with non-squamous disease and PD-L1 ≥ 50%, rather than displacing use of available immunotherapy monotherapy options (TA531, TA770) in this patient group.	
	Roche	For squamous NSCLC whose tumours express PD-L1 on 50% or more of cells, the first bullet here is incorrect, it should be Pembrolizumab + carboplatin + paclitaxel	Thank you for your comment. This has been added with the wording to specify that it is only in people in need of urgent clinical intervention.
Outcomes	BTOG	Yes – appropriate	Thank you for your comment.
	Regeneron	No comments – the outcomes listed are appropriate.	Thank you for your comment.
	Roche	None	None
Equality	BTOG	No issues.	None
	Regeneron	No comments – Regeneron is not aware of any potential equality issues.	None
	Roche	None	None
	BTOG	Nil	None

Section	Consultee/ Commentator	Comments [sic]	Action
Other considerations	Regeneron	No comments.	None
	Roche	None	None
Questions for consultation	BTOG	Where do you consider cemiplimab will fit into the existing care pathway for non-small-cell lung cancer? *1st line NSCLC (locally advanced not curative) or metastatic* Have all relevant comparators been included in the scope? *Please see above* Have all relevant subgroups been included in the scope? *Yes – please see above* Would cemiplimab be a candidate for managed access? *Yes* Do you consider that the use of cemiplimab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? *No* Would PD-L1 tumour proportion score be a factor when considering whether to offer cemiplimab? *Yes* Are the subgroups included in the draft scope appropriate? *Please see above* Is having had surgery for NSCLC or not a relevant subgroup?	Thank you for your responses to the consultation comments.

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		I do not see this as particularly relevant.	
	Regeneron	<u>Where do you consider cemiplimab will fit into the existing care pathway for non-small-cell lung cancer?</u> It is anticipated that cemiplimab + platinum chemotherapy would primarily be used as an alternative to, and displace use of, existing immunochemotherapy combination treatment options recommended by NICE across histology (squamous and non-squamous) and PD-L1 expression levels (1-49% and ≥ 50%). Given the low uptake of atezolizumab in combination with bevacizumab, carboplatin, and paclitaxel in the non-squamous PD-L1 < 50% population in which it is recommended by NICE (TA584; < 10% UK market share in patients with non-squamous disease and PD-L1 1-49%, not used at all in some trusts), it is expected that cemiplimab + platinum-based chemotherapy would primarily be used as an alternative to pembrolizumab in combination with pemetrexed and platinum chemotherapy (TA683) in the non-squamous population and pembrolizumab in combination with carboplatin and paclitaxel (TA770) in the squamous population. <u>Have all relevant comparators been included in the scope?</u> For people with squamous NSCLC whose tumours express PD-L1 on 50% or more of cells, pembrolizumab with carboplatin and paclitaxel is recommended as an option for the subset of patients who need urgent clinical intervention (TA770). Given the anticipated place in therapy for cemiplimab with platinum-based chemotherapy as an alternative to existing immunochemotherapy combination options across histology/PD-L1 expression groups (see above), this should be added as a comparator to the scope.	Thank you for your responses to the consultation comments. Pembrolizumab with carboplatin and paclitaxel has been added to the comparators list.

Section	Consultee/ Commentator	Comments [sic]	Action
		Have all relevant subgroups been included in the scope? Regeneron does not propose any additional subgroups be considered for inclusion in the scope. Are the subgroups included in the draft scope appropriate? Is having had surgery for NSCLC or not a relevant subgroup? As described above, Regeneron does not consider disease stage and prior surgery to be appropriate subgroups that are relevant to clinical decision making and can be meaningfully addressed in this appraisal. Would cemiplimab be a candidate for managed access? The final OS analysis for EMPOWER-Lung 3 is already complete (2 years follow-up). Extended long-term survival data may become available during 2025 (specific timelines TBC). Do you consider that the use of cemiplimab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? The QALY is likely to capture any health-related benefits associated with cemiplimab + platinum-based chemotherapy. Would PD-L1 tumour proportion score be a factor when considering whether to offer cemiplimab? Yes, per the label indication approved by MHRA, cemiplimab + platinum-based chemotherapy would be considered only for patients expressing PD-L1 on ≥ 1% tumour cells.	

Section	Consultee/ Commentator	Comments [sic]	Action
	Roche	None	None
Additional comments on the draft scope	BTOG	Nil else.	None
	Regeneron	There is a reference to atezolizumab on page 6 of the draft scope that we believe should instead refer to cemiplimab. *"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 atezolizumab will be licensed"* The appraisal title should be updated to reflect the label approved by MHRA: *"Cemiplimab with platinum-based chemotherapy for untreated locally advanced (not candidates for definitive chemoradiation) or metastatic non-small-cell lung cancer"*	Thank you for your additional comments. The error on page six has been corrected. The appraisal title has been partially updated to specify platinum-based chemotherapy. Appraisal titles do not always fully match the marketing authorisation wording in order to be concise.
	Roche	None	None

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

None

References

1. Department of Health and Social Care. New lung cancer screening roll out to detect cancer sooner. June 2023. Accessed June 2024.

2. Su CC, Wu JT, Choi E, et al. Overall Survival Among Patients With De Novo Stage IV Metastatic and Distant Metastatic Recurrent Non–Small Cell Lung Cancer. *JAMA Netw Open.* 2023