Single Technology Appraisal

Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949]

Contents:

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NICE National Institute for Health and Care Excellence

Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Wednesday 26 March 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? 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 preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by 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 provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Regeneron UK

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NICE National Institute for Health and Care Excellence

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Regeneron's full draft guidance document consultation response has been provided in a separate Word document
2	
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4	
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Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949]

Regeneron response to NICE draft guidance document

26 March 2025

File name	Version	Contains confidential information	Date
ID3949 Cemiplimab DGD response [REDACTED]	1.0	Yes	26 March 2025

Contents

List of Tables

List of Figures

Executive summary

- **We have meaningfully addressed the committee's key uncertainties as far as it is possible within the consultation timeframe.**
- **All the analyses undertaken in response to the DGD further support and improve the overall evidence base (i.e., RCT evidence, network meta-analysis, consistent UK clinical expert opinion, evidence-based clinical guidelines) which indicates that there are no meaningful differences in clinical effectiveness between cemiplimab + chemotherapy and pembrolizumab + chemotherapy.**

[redacted]

- **Providing access to cemiplimab will allow clinicians the flexibility they need to better tailor treatment based on individual patient needs – at no additional cost to the NHS.**
- **We believe we have reduced the uncertainties significantly and explored viable net pricing options such that the committee can be satisfied that recommending cemiplimab + chemotherapy as a treatment option represents an overall low decision risk and will address a clear unmet medical need without any increase in NHS costs.**

Regeneron is grateful for the opportunity to respond to feedback from the NICE appraisal committee summarized within the Draft Guidance Consultation Document (DGD). While we are disappointed that cemiplimab with platinum-based chemotherapy did not receive an initial positive recommendation for treating advanced non-small-cell lung cancer, we are pleased that the appraisal committee:

- agreed with the proposed positioning of the technology in the treatment pathway and relevant comparator
- highlighted the feedback from the clinical experts in attendance that cemiplimab would be a welcome addition to the treatment pathway.

We also continue to proactively acknowledge the unavoidable limitations of the comparative effectiveness evidence, a consequence of:

- the absence of a head-to-head randomised, controlled trial (RCT) comparing cemiplimab + chemotherapy with the relevant decision problem comparator (i.e., pembrolizumab + chemotherapy)
- well-documented challenges with conducting indirect treatment comparisons (ITCs) in advanced/metastatic NSCLC (1, 2), as noted in previous NICE NSCLC TAs (e.g. TA705 (3))
- availability of only published cohort-level RCT evidence for the relevant comparator

We also understand the committee's concerns about the uncertainty in modelled outcomes derived from the NMA and applied in the original company cost-effectiveness model. To provide the Committee with a higher degree of certainty in the cost effectiveness estimates, we have (Topic 1):

- **conducted comprehensive population-adjusted ITCs (matching-adjusted indirect comparisons [MAICs]) to explore the uncertainty around the impact of differences in potential treatment effect modifiers between the EMPOWER-Lung 3 and the KEYNOTE-407/189 studies**, including factors identified by the committee in the DGD (eg, age, PD-L1 level, and smoking history)
- **accounted for the impact of crossover in the KEYNOTE-407 study by incorporating published crossover adjusted data** (4) into the MAIC. This was not possible for the KEYNOTE-189 MAIC as no crossover adjusted data have been published to the best of our knowledge, however as concluded by

the committee in NICE TA557, "*results of the crossover adjustments were comparable with the main analyses, with little change in the overall effect*" (5)

Results from these comprehensive additional analyses show that there are no clear differences in PFS and OS between cemiplimab + chemotherapy and pembrolizumab + chemotherapy

- Non-squamous (EMPOWER-Lung 3 vs KEYNOTE 189): Overall, **MAIC results were similar for PFS and OS regardless of the KEYNOTE-189 data** used, i.e., final analysis (median follow-up 31.0 months) versus extended follow-up (median follow-up 64.6 months). **The MAIC results improved the point estimate HR for PFS** of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy by **0.24 (1.13 unadjusted vs. 0.89 with anchored MAIC),** suggesting that less favourable baseline characteristics may have generated the slightly less favourable results for cemiplimab from the original unadjusted NMA. However, consistent with the unadjusted analysis, the MAIC nevertheless indicated comparable PFS with no statistically significant difference between cemiplimab + chemotherapy and pembrolizumab + chemotherapy. **OS results were statistically in favour of cemiplimab + chemotherapy**. However, it should be noted that OS results are unadjusted for crossover which was allowed per protocol in the KEYNOTE studies.
- Squamous (EMPOWER-Lung 3 vs KEYNOTE-407): Overall, **MAIC results were similar for PFS regardless of the KEYNOTE-407 data used**, i.e., final analysis (median follow-up 14.3 months) versus extended follow-up (median follow-up 56.9 months). **The point estimate HR for crossover-adjusted OS improved from 1.02 (unadjusted) to 0.93 with the MAIC**. Overall, the MAIC results indicated comparable PFS and OS with no statistically significant difference between cemiplimab + chemotherapy and pembrolizumab + chemotherapy, consistent with the original NMA.

Table 1: Summary of progression-free survival and overall survival MAIC results across key scenarios

Population	Outcome	Scenario	Adjustment	Base case (without brain mets or race)		Scenario (with brain mets and race)[a]	
				HR (95% CI)	P value	HR (95% CI)	P value
PD-L1 ≥1%, non-squamous	PFS	EMPOWER-Lung 3 vs. KN189 (final analysis)	Unweighted	1.13 (0.72, 1.78)	0.584	1.13 (0.72, 1.78)	0.584
			Anchored MAIC	0.89 (0.56, 1.41)	0.610	0.85 (0.52, 1.40)	0.532
		EMPOWER-Lung 3 vs. KN189 (extended follow-up)	Unweighted	1.11 (0.71, 1.73)	0.652	1.11 (0.71, 1.73)	0.652
			Anchored MAIC	0.87 (0.55, 1.37)	0.537	0.83 (0.51, 1.36)	0.468
	OS	EMPOWER-Lung 3 vs. KN189 (final analysis)	Unweighted	0.70 (0.43, 1.16)	0.166	0.70 (0.43, 1.16)	0.166
			Anchored MAIC	**0.52 (0.31, 0.90)**	**0.019**	**0.41 (0.24, 0.69)**	**0.001**
		EMPOWER-Lung 3 vs. KN189 (extended follow-up)	Unweighted	0.67 (0.41, 1.09)	0.109	0.67 (0.41, 1.09)	0.109
			Anchored MAIC	**0.50 (0.29, 0.85)**	**0.010**	**0.39 (0.24, 0.65)**	**<0.001**
PD-L1 ≥1%, squamous	PFS	EMPOWER-Lung 3 vs. KN407 (final analysis)	Unweighted	1.05 (0.64, 1.70)	0.858	1.05 (0.64, 1.70)	0.858
			Anchored MAIC	1.05 (0.57, 1.92)	0.881	0.86 (0.46, 1.62)	0.643
		EMPOWER-Lung 3 vs. KN407 (extended follow-up)	Unweighted	0.92 (0.57, 1.48)	0.722	0.92 (0.57, 1.48)	0.722
			Anchored MAIC	0.92 (0.50, 1.68)	0.783	0.76 (0.40, 1.42)	0.381
	OS	EMPOWER-Lung 3 vs. KN407 (final analysis, TSEsimp adjusted)	Unweighted	1.02 (0.54, 1.93)	0.940	1.02 (0.54, 1.93)	0.940
			Anchored MAIC	0.93 (0.47, 1.85)	0.832	0.84 (0.40, 1.76)	0.639

Bolded values indicate statistically significant results. **a)** Brain metastases were only included as a covariate in the non-squamous populations (KN189), because there were insufficient brain metastases in the squamous subgroup of EMPOWER-LUNG 3 (n=1 in PD-L1 ≥1%/squamous subgroup; n=2 in any PD-L1/squamous subgroup).
Green shading denotes values incorporated into the updated cost-effectiveness analysis.

Whilst **results from these comprehensive analyses should be interpreted in the context of well-documented methodological limitations associated with MAICs, PFS and OS results from these anchored MAIC exploratory analyses are consistent with:**

- the clinical expert consensus view expressed to Regeneron about the **anticipated similarity in effectiveness outcomes** with cemiplimab + chemotherapy relative to the pembrolizumab + chemotherapy based on the available evidence and their extensive clinical experience with immunotherapies in NSCLC

- results from the company NMA (including extensive NMA sensitivity analysis) and NMAs published by other researchers (6) which show **no clear differences in effectiveness between cemiplimab + chemotherapy and pembrolizumab + chemotherapy**

- evidence-based clinical guidelines, including from NCCN where cemiplimab + chemotherapy is the only IO + chemotherapy combination other than pembrolizumab + chemotherapy that has a 'preferred' guidelines recommendation across PD-L1 expression levels and histological subtypes for the treatment of patients with advanced/metastatic NSCLC (7). **NCCN has also assigned both options with a score of 4 out of 5 ('very effective') for efficacy across histology and PD-L1 expression level subgroups in its Evidence Blocks™ assessment, which is based on both published trial evidence and real-world clinical experience of the panel members in more diverse real-world settings**

- HTA precedent where the focus has been on comparing treatment costs given the absence of any evidence for a meaningful difference in effectiveness of different IOs:

    - NICE, including TA705 (atezolizumab monotherapy) in which the committee concluded despite the lack of head-to-head RCT evidence that ITC results "*suggest that atezolizumab is as effective as pembrolizumab in delaying disease progression and extending life*" (3).

    - International cost-effectiveness HTA organisations, including PBAC (Australia) and CADTH (Canada) who were "*unable to draw definitive conclusions on relative efficacy*" of cemiplimab + chemotherapy vs pembrolizumab + chemotherapy due to unavoidable limitations in the ITC, but subsequently recommended cemiplimab as an option subject to cemiplimab not increasing treatment costs (and assuming equivalent efficacy) compared with relevant IO + chemotherapy combinations (1, 2).

The committee's draft conclusion that the lack of observed/statistical differences for cemiplimab + chemotherapy vs pembrolizumab + chemotherapy in ITCs does not prove equal efficacy or non-inferiority is a valid point, but the **totality of the current available evidence base as summarized above consistently point towards it being reasonable to conclude that there are no meaningful differences in**

clinical effectiveness between cemiplimab + chemotherapy and pembrolizumab + chemotherapy.

We have updated the existing partitioned survival model (which has been universally accepted in previous NSCLC appraisals) with results from the MAIC as an alternative base-case analysis approach, including cross-over adjusted OS data from KEYNOTE-407. Developing a state-transition model approach per the committee's stated request for additional analyses was not feasible within the short time available for this response. However, we have further explored the uncertainty around modelled OS in our partitioned survival model by conducting a conservative scenario analysis in which the mortality HR for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy is assumed to be 1.

In our response, we have also addressed uncertainties around:

- Stopping rules (Section 2.2): We implemented the committee's preferred approach for IO stopping rules in the cost effectiveness model based on the maximum number of treatment cycles (cemiplimab maximum 36, pembrolizumab maximum 35) rather than a maximum fixed calendar duration. This better reflects treatment utilisation in the EMPOWER-Lung 3 and KEYNOTE 407/189 RCTs and is aligned with the current NHS England commissioning policy for pembrolizumab + chemotherapy (and the anticipated NHS England commissioning policy for cemiplimab + chemotherapy).

- Duration of treatment (Section 2.3): We addressed uncertainty around the reported duration of treatment in EMPOWER-Lung 3 and potential impact of treatment with cemiplimab beyond 108 weeks and/or beyond radiological disease progression in EMPOWER-Lung 3. Notably, no patients in EMPOWER-Lung 3 received more than the maximum protocol permitted 36 doses. Given the clarification provided in section 2.2 regarding maximum treatment duration/number of cemiplimab doses received by patients in EMPOWER-Lung 3, the similar observation in the KEYNOTE studies where some patients are reported to have remained on treatment beyond the 2 years specified in the protocols, and the lack of treatment beyond progression in UK clinical practice, we consider it more appropriate to adopt the same

approach to modelling time on treatment for both pembrolizumab and cemiplimab, as per our company base case (PFS = ToT), but with the minor amendment to the stopping rule based on maximum number of treatment cycles. Conversely, should an approach be adopted that models the observed use of IO post-progression, then this should include all IO use post-progression. We therefore include a scenario whereby the EAG's preferred ToT assumptions are applied (ToT vs. PFS HR 1.17 and 0.84, for cemiplimab and pembrolizumab, respectively) but the cemiplimab post-progression IO use is reweighted for the pembrolizumab + chemo arm of the model to sum to the total usage observed in the KEYNOTE studies While we acknowledge the committee's preference to use the actual Kaplan-Meier (KM) curve for ToT in the cemiplimab arm of the model, the extensive additional analyses conducted in this response, which incorporate adjusted cemiplimab + chemotherapy data, preclude using the ToT KM for these scenarios. Furthermore, given that the KEYNOTE ToT data are subject to the same issues as cemiplimab (treatment beyond 108 weeks; treatment beyond progression), we consider the use of HRs applied to trial PFS curves to be a fairer approach for modelling ToT in the absence of equivalent ToT KM data for pembrolizumab + chemotherapy. Given the implementation of adjusted survival data for cemiplimab, which would not be aligned with the observed time-on treatment in EMPOWER-Lung 3, we have not implemented the request to model time-on-treatment using the EMPOWER-Lung 3 Kaplan-Meier data

- Waning effect (Topic 3): We implemented the committee's preferred approach for gradual linear treatment waning. However, we have found no evidence that effect waning has been initiated from 2 years in any technology appraisal of an IO. A recent review of treatment effect waning in IO health technology assessments found that effect waning, whether gradual or immediate, typically started between 3 and 5 years (8). Whilst it is not feasible to provide additional evidence specifically for cemiplimab + chemotherapy given the ethical early stopping of the EMPOWER-Lung 3 study, 5-year follow-up data for cemiplimab monotherapy in NSCLC, from EMPOWER-Lung 1 further supports clinical expert feedback that longer-term data from the KEYNOTE

RCTs is appropriate for informing assumptions about long-term effects of cemiplimab + chemotherapy in the absence of direct evidence. We have therefore assumed a gradual linear treatment waning effect that starts at 3 years and finishes at 5 years for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy.

"…*advisors would be happy to assume that treatment benefit continues up to 5 years, and agreed that evidence on longer-term (e.g., 5-year) pembrolizumab + chemotherapy PFS/OS outcomes would be broadly generalizable to and appropriate for supporting assumptions about longer-term cemiplimab + chemotherapy PFS/OS outcomes*" [page 13-14, Data on file – NSCLC advisory board report].

- Proportion of people who would receive cemiplimab without pemetrexed in clinical practice (Topic 4): Approximately one-fifth (22%) of non-squamous patients in the cemiplimab + chemotherapy group of EMPOWER-Lung 3 received a pemetrexed-free regimen. Clinical expert feedback provided to Regeneron to date has been consistently that there is substantial heterogeneity across England and Wales at a patient population level (e.g., diverse population characteristics, needs, and preferences), a centre level (e.g., resource availability and considerations on Q3W vs Q6W dosing available with pembrolizumab, as highlighted by the committee in the DGD), and individual clinician level. It is not therefore possible to suggest a precise estimate of the proportion of patients who would receive cemiplimab without pemetrexed in clinical practice and what their characteristics would be. Furthermore, pemetrexed is associated with significant toxicity and as acknowledged in the DGD, may not be the preferred chemotherapy agent for all people with non-squamous disease, even where there are no clear contraindications. Clinical expert feedback to Regeneron has also been that the option to use a pemetrexed-free regimen (e.g. paclitaxel and carboplatin) alongside an IO in people with non-squamous disease would facilitate them to better tailor chemotherapy treatment to the complex and diverse needs of

individual patients they treat. As detailed in our evidence submission, post-hoc exploratory analyses were conducted to evaluate selected AEs reported for patients with non-squamous histology who received pemetrexed vs paclitaxel-containing regimens in EMPOWER-Lung 3 (Table 27). While acknowledging the limitations of such analyses, the data suggest the two treatments have a distinct AE profile that will allow clinicians to choose between them based on the comorbidity profile of their patients.

It should be noted that, even if use of cemiplimab without pemetrexed in the NHS is higher than that in the EMPOWER-Lung 3 RCT, the use of a pemetrexed-free regimen is less costly than the use of a pemetrexed-based regimen; the total costs of the pemetrexed-based regimens excluding maintenance is higher (by £61.56) than paclitaxel-based regimens. The total cost of treatment with cemiplimab + pemetrexed, assuming 25% of patients receiving pemetrexed go on to receive pemetrexed maintenance, is £394.44 higher per patient than with cemiplimab + paclitaxel.

- eMIT drug prices: We implemented minor updates to eMIT drug prices

The updates to the company base-case analysis (including alternative base-case approach using the MAIC instead of the NMA to inform comparative effectiveness) are summarised below using the current cemiplimab net price (previously agreed as part of NICE TA802) and pembrolizumab list price.

These results provide meaningful additional certainty about the cost effectiveness of cemiplimab + chemotherapy by showing that the standard NMA and population-adjusted approaches to indirect treatment comparison result in similar cost effectiveness estimates. We accept the standard cost-utility based value assessment framework, but in the context of the overall, current evidence base, re-iterate our willingness to also accept cost comparison as a pragmatic alternative basis for decision making. [redacted]

[redacted]

Table 2: Summary of updated company base-case analysis

Intervention	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER	NHB @£20,000 /QALY
Original company base-case approach (i.e., NMA for comparative effectiveness)								
Original company base case (no changes)								
Cemiplimab + CT	[redacted]	3.2571	[redacted]	[redacted]	0.33	[redacted]	Dominant	2.9714
Pembrolizumab + CT	126,144	2.9308	2.1494	-	-	-	-	-
Revision 1 - Updated eMIT prices								
Cemiplimab + CT	[redacted]	3.2571	[redacted]	[redacted]	0.33	[redacted]	Dominant	2.9717
Pembrolizumab + CT	126,199	2.9308	2.1494	-	-	-	-	-
Revision 2 – eMIT prices + updated stopping rule								
Cemiplimab + CT	[redacted]	3.2571	[redacted]	[redacted]	0.3263	[redacted]	Dominant	3.0072
Pembrolizumab + CT	127,522	2.9308	2.1494	-	-	-	-	-
Revision 3 –eMIT prices + updated stopping rule + gradual treatment waning from years 3 to 5								
Cemiplimab + CT	[redacted]	3.1905	[redacted]	[redacted]	0.30	[redacted]	Dominant	2.9972
Pembrolizumab + CT	127,346	2.8949	2.1232	-	-	-	-	-
Alternative company base-case approach (i.e., MAIC for comparative effectiveness)								
Cemiplimab + CT	[redacted]	4.3989	[redacted]	[redacted]	1.1895	[redacted]	Dominant	3.1181
Pembrolizumab + CT	125,899	3.2094	2.3524	-	-	-	-	-
Revision 1 - Updated eMIT prices								
Cemiplimab + CT	[redacted]	4.3989	[redacted]	[redacted]	1.19	[redacted]	Dominant	3.1178
Pembrolizumab + CT	125,973	3.2094	2.3524	-	-	-	-	-
Revision 2 – updated eMIT prices + updated stopping rule								
Cemiplimab + CT	[redacted]	4.3989	[redacted]	[redacted]	1.19	[redacted]	Dominant	3.1518
Pembrolizumab + CT	127,408	3.2094	2.3524	-	-	-	-	-
Revision 3 – updated eMIT prices + updated stopping rule + gradual treatment waning from years 3 to 5								
Cemiplimab + CT	[redacted]	4.1228	[redacted]	[redacted]	1.04	[redacted]	Dominant	3.1009
Pembrolizumab + CT	126,704	3.0807	2.2597	-	-	-	-	-

CT, chemotherapy; eMIT, electronic market information tool; ICER, incremental cost-effectiveness ratio; LY, life year; MAIC, matching adjusted indirect comparison; NMA, network meta-analysis; QALY, quality-adjusted life year

The table below summarises the Committee's preferences and requests for additional analyses and shows where each of these is addressed in this document.

Table 3 Summary of Committee preferences and additional requests

Committee request	Location in response document
Committee preference	
• Using a ratio between time on treatment and progression-free survival to calculate time on treatment for pembrolizumab	Section 2.1
• Using Kaplan–Meier data from EMPOWER-Lung 3, either directly or using the best fitting parametric survival curve fitted to that data, as per the NICE technical support document 14 to calculate time on treatment for cemiplimab. This should also include treatment costs for people who continued treatment beyond 108 weeks	Section 2.1
• The stopping rule for pembrolizumab to be implemented such that pembrolizumab is stopped after 35, 3-weekly cycles	Section 2.2
• Assuming a gradual waning of treatment effect for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy	SectionTopic 3
• Using the grade 3 and above adverse event rates from EMPOWER- Lung 3 and the KEYNOTE studies to model adverse event rates for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy, respectively	Section 5
Additional analysis requests	
• A Markov model based on progression-free survival data from the NMA, with the assumption of equal mortality risk post-progression for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy	Section 1.1
• Calculating time on treatment for cemiplimab using Kaplan–Meier time-on-treatment data from EMPOWER-Lung 3, either directly or using the best fitting parametric survival model fitted to that data, as per NICE technical support document 14. This should also include people who continued treatment beyond 108 week	Section 2.1
• Implementing the stopping rule for pembrolizumab such that pembrolizumab is stopped after 35, 3-weekly cycles	Section 2.2
• Implementing the stopping rule for cemiplimab such that it reflects EMPOWER-Lung 3	Section 2.2
• Further justification from the company to support a 5-year waning time point, including analysis of 5-year data from KEYNOTE-189 and KEYNOTE-407. For example, estimates	Section 3.2

of the hazards over time from the longer-term data from the KEYNOTE-189 and KEYNOTE-407 trials compared with the modelled hazards	
• Further evidence to support a 5-year waning time point based on data specifically for cemiplimab plus chemotherapy	Section 3.2
Acceptable ICER	
• The proportion of people with non-squamous NSCLC who would have cemiplimab without pemetrexed in clinical practice, and if EMPOWER-Lung 3 reflected	Section 4
• The comparative effectiveness of cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy	Section 1.2
• The use of a partitioned survival model	Section 1.1
• The impact on overall survival of treatment beyond progression for people in the cemiplimab plus chemotherapy arm	Section 2.3
• The impact on progression-free survival and overall survival of continued treatment beyond 108 weeks for people in the cemiplimab plus chemotherapy arm	Section 2.3
• The implementation of the stopping rules for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy	Section 2.2
• The long-term treatment effect of cemiplimab plus chemotherapy relative to pembrolizumab plus chemotherapy after stopping treatment	Section 2.2

Topic 1 Uncertainty in the indirect treatment comparison

Overall uncertainties in the ITC (DGD section 3.13)

"*The committee noted the high level of uncertainty in the comparative effectiveness of cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy*."

NMA transitivity assumption (DGD section 3.6)

"*NMAs are based on the assumption of sufficient clinical and methodological similarity (homogeneity) between the included studies, across all comparisons. This means they can be assumed to estimate the same (or similar) relative treatment effect, regardless of which treatments are actually included in each study. KEYNOTE-189 and KEYNOTE-407 included people irrespective of PD-L1 expression, and baseline characteristics were not reported according to PD-L1 expression status. So, the company assumed similarity in treatment effect modifiers between the KEYNOTE trials and EMPOWER-Lung…The committee noted that baseline characteristics specifically for people whose tumours express PD-L1 at 1% or more were not available for the KEYNOTE trials. But it noted that there were other potential treatment effect modifiers that differed between EMPOWER-Lung 3 and the KEYNOTE trials. These included:*

- *duration of treatment*
- *distribution of PD-L1 expression*
- *age*
- *performance status*
- *cancer stage at diagnosis*
- *smoking history*
- *study site locations (potential differences in resource use)*
- *treatments offered at second line and beyond"*

Impact of crossover (DGD section 3.6)

"The committee acknowledged that the lack of access to patient-level data from the KEYNOTE trials prevented the company from doing a crossover-adjusted analysis. The company stated that overall survival data from the chemotherapy arm from EMPOWER-Lung 3 was similar to that from the KEYNOTE studies. So, it said that crossover in the KEYNOTE studies did not appear to have a large effect

on overall survival. But the committee thought that without crossover-adjusted results, the impact of crossover in the KEYNOTE studies added uncertainty to the NMA results for overall survival."

Early stopping of EMPOWER-Lung 3 (DGD Section 3.6)

"The committee recognised that the KEYNOTE trials had longer post-progression follow up available than the EMPOWER-Lung 3 trial. So, the data on overall survival for pembrolizumab plus chemotherapy were more mature and less uncertain. It recalled that EMPOWER-Lung 3 was stopped early because of superior overall survival with cemiplimab (see section 3.5), which was potentially associated with a bias favouring cemiplimab plus chemotherapy. In contrast, the KEYNOTE trials did not end early, to the committee's knowledge. It concluded that the NMA results were highly uncertain, especially for overall survival."

Committee requests for additional analyses (DGD Section 3.15)

"The committee requested to see a Markov model structure based on progression-free survival data from the NMA, and with the assumption of equal mortality risk post-progression for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy"

1.1 Company response summary

<u>NMA transitivity assumption (DGD section 3.6)</u>

We continue to acknowledge the unavoidable limitations of the NMA approach that has typically been used in previous NICE NSCLC appraisals with decision problems that require indirect treatment comparisons as described in our evidence submission, the EAG assessment report and the committee discussion.

In order to address the committee's concerns regarding similarity between the cemiplimab + chemotherapy and pembrolizumab + chemotherapy studies, we have conducted additional adjusted ITCs as summarised below.

Exploratory PFS and OS matching-adjusted indirect comparisons (MAICs) adjusting as far as data allow for potential treatment effect modifiers, including age, ECOG PS, PD-L1 expression, and smoking status:

- **EMPOWER-Lung 3 (non-squamous histology subgroup) vs KEYNOTE-189**
- **EMPOWER-Lung 3** (**squamous histology subgroup) vs KEYNOTE-407** (Note that ECOG PS could not be matched for in this subgroup due to low ECOG 0 patient numbers in EMPOWER-Lung 3)

Impact of crossover (DGD section 3.6)

We have incorporated **published cross-over adjusted OS data from the final analysis of KEYNOTE-407 (4) (**Figure 5**) into our NMA and MAIC analysis.** This adjusts for subsequent IO received in the KEYNOTE-407 (squamous histology) chemotherapy + placebo arm):

To the best of our knowledge**, no crossover-adjusted data have been published to date for the relevant PD-L1 ≥1% subgroup of the KEYNOTE-189 study.**

Crossover-adjusted results were redacted in the NICE TA557 committee papers, but there is the suggestion that this made little difference: ***"The results of the crossover adjustments were comparable with the main analyses, with little change in the overall effect"*** (9) (note that this was only performed on the TPS <1% population which would not be eligible to receive pembrolizumab).

Early stopping of EMPOWER-Lung 3 (DGD Section 3.6)

Exploratory MAIC scenario analysis have been conducted for OS in the non-squamous subgroup using data from a 2-year follow-up period **common** to both the KEYNOTE-189 study **and** EMPOWER-Lung 3, in addition to using the extended follow-up data (see section 1.4). As crossover-adjusted OS data were only reported for the trial final analysis of KEYNOTE-407, only this timepoint is included in the MAIC analyses provided for the squamous subgroup, which aligns closely to follow-up time in EMPOWER-Lung 3.

Committee requests for additional analyses (DGD Section 3.15)

Partitioned survival model structures are a well-established approach to modelling NSCLC treatments in prior NICE TAs; all 9 NICE TAs identified in the SLR detailed in the company submission (section B.3.1) used a partitioned survival model structure. We understand the committee's concerns and whilst we are unable to develop a new Markov state transition model in the short timeframe available for development of this response, we hope that the MAICs will sufficiently reduce the committee's uncertainty about the comparative effectiveness of cemiplimab and pembrolizumab on PFS. Complementing the incorporation of this new evidence in the cost-effectiveness model (CEM) are further sensitivity analyses that assume that OS is equal between cemiplimab + chemotherapy and pembrolizumab + chemotherapy. We believe that these new analyses mitigate for the need to restructure the model as a Markov state transition model.

Results and conclusions from exploratory analyses conducted for Topic 1

Whilst **results from these comprehensive analyses should be interpreted in the context of methodological limitations associated with MAICs, PFS** and **OS results from these exploratory analyses are consistent with:**

- the clinical expert consensus view expressed to Regeneron about the **anticipated similarity in effectiveness outcomes** with cemiplimab + chemotherapy relative to the pembrolizumab + chemotherapy based on the available evidence and their extensive clinical experience with immunotherapies in NSCLC

- results from the company NMA (including extensive NMA sensitivity analysis) and NMAs published by other researchers (6) which show **no meaningful differences in effectiveness between cemiplimab + chemotherapy and pembrolizumab + chemotherapy**

- evidence-based clinical guidelines, including NCCN where cemiplimab + chemotherapy is the only IO + chemotherapy combination other than

pembrolizumab + chemotherapy that has a 'preferred' guidelines recommendation for the treatment of patients with advanced/metastatic NSCLC (7). **NCCN has also assigned both options with a score of 4 out of 5 ('very effective') for efficacy across histology and PD-L1 expression level subgroups in its Evidence Blocks™ assessment, which is based on both published trial evidence and real-world clinical experience of the panel members in more diverse real-world settings.**

- HTA precedent where the focus has been on comparing treatment costs given the absence of any evidence for a meaningful difference in effectiveness of different IOs:
    - NICE, including TA705 (atezolizumab monotherapy) in which the committee concluded despite the lack of head-to-head RCT evidence that ITC results "*suggest that atezolizumab is as effective as pembrolizumab in delaying disease progression and extending life*" (3).
    - International cost-effectiveness HTA organisations, including PBAC (Australia) as well as CADTH (Canada) who were "*unable to draw definitive conclusions on relative efficacy*" of cemiplimab + chemotherapy vs pembrolizumab + chemotherapy due to unavoidable limitations in the ITC, but subsequently recommended cemiplimab as an option subject to cemiplimab not increasing treatment costs (and assuming equivalent efficacy) compared with relevant IO + chemotherapy combinations (1, 2).

These **analyses further support consideration of cost comparison (assuming equivalent clinical outcomes) as a relevant approach to decision making.**

1.2 Matching adjusted indirect comparison

1.2.1 Matching-adjusted indirect comparison methods

To address the Committee's uncertainty around the NMA treatment effect estimates, we evaluated the feasibility of an alternative evidence synthesis approach using matching-adjusted indirect comparison (MAIC) methods described in NICE TSD18.

In networks consisting of only one or two trials per treatment, indirect treatment comparisons are highly vulnerable to systematic variation (bias) resulting from imbalances in effect modifier distributions. MAICs use individual patient data from one (or more) trial to reweight its population so that it matches the overall study population baseline characteristics of another study. A logistic regression model is then used to estimate weights for the individual patient data (IPD) for known prognostic or treatment effect-modifying variables (for example, ECOG performance status) that differ between trials. Using these weights, outcomes for the index treatment can then be predicted for the population in the external trial by reweighting the observed outcomes from the index trial. By balancing key covariates, MAICs 'relax' the standard NMA assumption that the distribution of treatment effect-modifiers is identical across studies. This can directly address heterogeneity caused by patient population differences and mitigate transitivity violations by creating a more similar target population for the indirect comparison. Notably, given the availability of a common comparator (i.e., chemotherapy) an 'anchored' MAIC was feasible, which only requires adjustment for treatment effect modifiers and requires less strong assumptions than an 'unanchored' MAIC.

Anchored MAICs were performed for PFS and OS in non-squamous and squamous populations. Given that baseline characteristics were not available in the published literature for the PD-L1 ≥1% subgroups of KEYNOTE-189 and 407, the EMPOWER-Lung 3 PD-L1 ≥1% population was matched to the ITT populations (i.e., any PD-L1) in the KEYNOTE trials, with an assumption that the distribution of characteristics at baseline in the PD-L1 ≥1% subgroups was similar to that of the ITT populations (see Appendix A for a comparison of baseline characteristics of the ITT vs. PD-L1≥1% populations from EMPOWER-Lung 3, which supports this assumption). This was considered the MAIC base case for both matching and analysis of outcomes. To assess the impact of this assumption on the MAIC results, scenario analyses were also performed using the ITT (any PD-L1) populations in the EMPOWER-Lung 3 and KEYNOTE trials (for matching and analysis of outcomes).

The following variables were included in the model (see detailed process for selection in section 1.2.1.1): **PD-L1 expression** (1-49% vs. ≥50% in the PD-L1 ≥1% scenarios; <1%

vs. 1-49% vs. ≥50% in the any PD-L1 scenarios), **age** (<65 vs. ≥65), **ECOG PS** (0 vs. 1) and **smoking history** (current and former smokers vs. never smokers). EMPOWER-Lung 3 patients with **stage IIIB/C disease at diagnosis** were removed prior to analysis to align with KEYNOTE-407 and KEYNOTE-189 inclusion criteria. Additionally, scenarios were also performed to explore the impact of including additional covariates in the model, namely **brain metastases (present vs absent) and race** (Asian vs. other, as a proxy for differences in geographic regions), which may also be considered potential effect modifiers. All MAICs for OS in the squamous population included crossover-adjusted OS results from KEYNOTE-407 (see section 1.3).

Detailed methodology for the MAIC, including details of the weighting model and assessment of weights, is available as a separate report submitted with this response (10).

1.2.1.1 Selection of covariates for inclusion in the MAIC

The NICE DGD included a list of "*potential treatment effect modifiers that differed between EMPOWER-Lung 3 and the KEYNOTE trials*" including **duration of treatment, PD-L1 expression levels, age, ECOG PS, cancer stage at diagnosis, smoking history, study site locations (potential differences in resource use)** and **treatments offered at second line and beyond**. We considered each of these as part of the following activities to identify potential treatment effect modifier covariates for inclusion in the MAICs:

1. A targeted literature review of published literature on prognostic factors and treatment effect modifiers in advanced/metastatic NSCLC
2. A review of PFS and OS subgroup analysis results from EMPOWER-Lung 3 and KEYNOTE 407/189
3. Consultation with clinical expert lung oncologists experienced in using pembrolizumab and other immunotherapies to treat people with NSCLC in the NHS

Targeted literature review

A TLR was conducted to identify published randomized controlled trials (RCTs), non-randomized prospective clinical trials, single-arm trials, and real-world evidence (RWE; prospective and retrospective observational studies) that provided data on prognostic factors and/or effect modifiers among adult patients with advanced or metastatic squamous or non-squamous NSCLC with no known driver mutations who were receiving immunotherapy in the first-line setting. As an ‘anchored’ MAIC was feasible, only effect modifiers are of interest, thus the information from precedent RCTs investigating the effects of immunotherapy vs. chemotherapy either alone or in combination were of interest.

Prognostic factors demonstrating evidence of effect modification are summarised in Table 4. Age, smoking status and PD-L1 expression were subsequently included within the MAIC as covariates. Sex was excluded as it correlated closely with smoking status (the majority of females were never-smokers and the majority of males were current or former smokers). As neither harmonised tumour mutational burden (TMB) nor SMARCA4 status (a prognostic gene) were reported across the EMPOWER-Lung 3 or KEYNOTE studies, these were not included within the MAIC.

Table 4: Treatment effect modifiers identified in the targeted literature review

Prognostic factor	Direction of effect	Associations with overall survival				Associations with progression-free survival	
		Elkrief 2023 (11)		R2810-ONC-1624		Elkrief 2023 (11)	
		Immunotherapy	Immunotherapy + chemotherapy	Cemiplimab	Chemotherapy	Immunotherapy	Immunotherapy + chemotherapy
Age (years)	**<65** vs. ≥65					✓	✓*
Sex	Female vs. male			✓	✓		
Smoking status	**Never smoker** vs. current/former smoker	✓	✓*			✓	✓*
Harmonized TMB	Continuous ↑					✓	✓*
SMARCA4	**Presence** vs. absence					✓*	✓
	Absence vs. presence					✓	✓*
PD-L1 expression	**1-49%** vs. ≥50%	✓	✓*				

Note: Dark blue shading indicates factor was significant in at least one multivariate model; **Bolding** indicates more favourable results in a given comparison; "*" indicates more favourable results for a given intervention in a comparison; "↑" indicates higher values were more favourable.
PD-L1, programmed death-ligand 1; TMB, tumour mutational burden.

Review of EMPOWER-Lung 3 and KEYNOTE 407/189 subgroup analysis

Pre-specified subgroup analyses can provide an indication of whether prognostic baseline characteristics are also effect modifiers, but this cannot be confirmed without formal interaction tests and sufficient sample sizes within individual subgroups. We therefore took an exploratory approach of examining whether the point estimate for any given subgroup fell outside or close to the boundary of the confidence interval of its counterpart across any of the EMPOWER-Lung 3 or KEYNOTE trials. Based on this rule**, age (>65 vs. ≤65), sex, smoking status, PD-L1 expression levels, ECOG performance status, presence of brain metastases and race** appeared to be potential effect modifiers for OS (see Table 25 in Appendix B). For PFS, **age (>65 vs. ≤65), sex, PD-L1 expression levels, ECOG performance status and cancer stage (locally advanced vs. metastatic)** appeared to be potential effect modifiers (see Table 26 in Appendix B).

Clinical expert validation

Four clinical expert lung oncologists were solicited for input during the consultation process to review the list of identified treatment effect modifiers for completeness and to rank them in order of importance for their potential to have a treatment modifying effect. As can be seen in Table 5, the rankings were varied, therefore the effect modifiers were included in the analysis where possible (either in the base case or scenario analyses) as described below.

Table 5: Clinical expert rankings of potential treatment effect modifiers

	TLR		RCT subgroup analysis		HCP feedback (1 most impactful)			
	PFS	OS	PFS	OS	Expert 1	Expert 2	Expert 3	Expert 4
Age (>65 vs ≤ 65)	☑			☑	1	6	0	7
Sex Male vs female	☑	☑	☑		8	-	6	8
ECOG PS (0 vs 1)			☑	☑	2	7	-	3
Smoking status (Never smoker vs other)	☑	☑		☑	9	4	4	1
PD-L1 level (1-49% vs >50%)†		☑			4	1	3	6
Stage at diagnosis (Locally advanced vs metastatic)			☑		5	-	2	5
Brain metastases at baseline (Yes vs no)				☑	3	5	1	4
Geographic location‡ (Asia vs Rest of World)				☑	10	-	-	9
Extended duration of initial IO treatment post-progression (Yes vs no)					6	2	5	-
Alternative IO treatment post-progression (Yes vs no					7	3	7	2

*For EMPOWER-Lung 3, a characteristic was identified as a potential treatment effect modifier if the HR for one subgroup was outside the confidence intervals for the other subgroup. †EMPOWER-Lung 3 ITT population also included patients with PD-L1 <1%. ‡Used as a proxy for race, which was identified as a potential treatment effect modifier in EMPOWER-Lung 3

ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; IO, immunotherapy; OS, overall survival; PD-L1 programmed death ligand 1; PFS, progression-free survival; TLR, targeted literature review

Final choice of covariates included in the MAIC

The covariates included in MAIC base case model were **age (>65 vs. ≤65), PD-L1 expression, ECOG PS** and **smoking status**. Sex was excluded on the basis of substantial overlap with smoking status; the majority of males were current/former smokers, and the majority of females were never smokers. Scenario analyses explored the inclusion of **brain metastases (present vs absent)** and **race** (Asian vs. non-Asian, as a proxy for study site location). **Cancer stage** was considered to have been adjusted for in the base case via removal of the locally advanced (stage IIIb) patients from the EMPOWER-Lung 3 dataset prior to matching to align with the KEYNOTE inclusion criteria. Note that sensitivity analyses were also conducted leaving locally advanced patients in before conducting the MAICs in order to increase sample size of rarer characteristics such as ECOG 0 PS and brain metastases. However, these analyses, which effectively assume no impact of cancer stage, led to unevenly distributed weights and unrealistic results that defied clinical expectations, such as the cemiplimab curves crossing the chemotherapy curves. This analysis is therefore not reported further within this response.

Of the initial list of effect modifiers proposed in the DGD, only **duration of treatment** and **treatments post-progression** remained unadjusted for in the MAIC. We address the issue of **duration of treatment** in more detail under section 1.5. In summary, the longer duration of treatment in EMPOWER-Lung 3 is primarily attributable to treatment beyond progression. We do not consider this to be an effect modifier as it is itself determined by patient response to treatment; patients in EMPOWER-Lung 3 could only receive treatment beyond progression if the investigator judged the patient to be experiencing clinical benefit and if the patient had not completed the 108-week treatment period. Regarding **treatments received post-progression,** we consider that use of the crossover-adjusted OS data from KEYNOTE-407 within the base-case MAIC has accounted for the majority of any bias from subsequent IO use in the chemotherapy arm. The absence of published crossover-adjusted estimates for KEYNOTE-189 and

commentary in the relevant NICE appraisal suggests that crossover did not have a significant impact in the non-squamous subgroup.

Due to the low proportion (1%) of patients receiving subsequent IO in the EMPOWER-Lung 3 trial, we have not been able to adjust for the use of IO post-progression **following initial IO** in the MAIC. As 20% (weighted average) of patients in the pembrolizumab + chemotherapy arms of the KEYNOTE studies received IO post-progression, use of IO post-progression following initial IO remains a significant source of bias against cemiplimab. While this bias impacts the MAIC and base case cost-effectiveness analyses, we attempt to adjust for it by capturing the imbalance in post-progression IO use in all modelling scenarios that reflect the longer time on treatment for cemiplimab vs. pembrolizumab from the clinical studies (see section 2.4).

1.2.1.2 Software and presentation of results

All analyses were performed using R version 4.4.1 (http://www.r-project.org/). Given the limited time available for this response, the *survival* package was used to estimate a constant HR for each data set. This is a limitation of these new analyses, though the proportional hazards assumption was only violated for three comparisons: weighted EMPOWER-Lung 3 vs. KEYNOTE-407 (**PFS**) and KEYNOTE-189 vs. chemotherapy for both follow-up periods (**OS**) (Table 6). Furthermore, the results of constant HR NMAs were generally found to be consistent with those of time-varying NMAs in conducted on these subgroups (not reported in the original company submission but reported in Appendix E of the NMA report submitted as data on file (12).

Results were summarized in terms of the relative treatment effects for cemiplimab + IC chemotherapy versus pembrolizumab + IC chemotherapy in terms of the unadjusted models (‘naïve’ comparison) as well as the MAICs. Time-to-event outcomes were summarized in terms of HRs and 95% CIs with KM curves. All results were presented alongside the effective sample size (ESS).

Table 6: Grambsch-Therneau tests of proportional hazards for comparisons in the MAIC

Trial	Intervention/ Comparator	Citation	Overall Survival Grambsch-Therneau test, p-value	Progression-Free Survival Grambsch-Therneau test, p-value
EMPOWER-Lung 3, June 2022 DCO (PD-L1 ≥1%, any histology)	Cemiplimab + IC chemotherapy vs. IC chemotherapy	Unweighted EMPOWER-Lung 3; KN189 comparison (n=160)	0.682	0.791
		Unweighted EMPOWER-Lung 3; KN407 comparison (n=120)	0.208	0.193
		Weighted EMPOWER-Lung 3; KN189 base case comparison (ESS=108.94)	0.239	0.672
		Weighted EMPOWER-Lung 3; KN407 base case comparison (ESS=98.46)	0.127	0.041
KEYNOTE-189 (PD-L1 ≥1%, non-squamous)	Pembrolizumab + IC chemotherapy vs. IC chemotherapy	Rodrigues-Abreu 2021 (13) (final analysis)	0.0426	0.7209
		Garassino 2023 (14) (extended follow-up)	0.0407	0.5081
KEYNOTE-407 (PD-L1 ≥1%, squamous)	Pembrolizumab + IC chemotherapy vs. IC chemotherapy	Paz-Ares 2020 (4) (final analysis; TSEsimp adjusted for OS)	0.1838	0.9292
		Novello 2023 (15) (extended follow-up)	0.8975	0.3939

ESS, effective sample size; PD-L1, programmed death ligand 1; IC, investigator's choice; OS, overall survival

1.2.2 MAIC results

1.2.2.1 MAIC baseline characteristics before and after matching

Baseline distributions of key patient characteristics considered to be potential treatment effect modifiers in EMPOWER-Lung 3, KEYNOTE-189, and KEYNOTE-407 before and

after matching in the base case analysis are shown in Table 7 and Table 8. After matching on the relevant covariates, key patient characteristics were balanced between EMPOWER-Lung 3 and each of the KEYNOTE trials**.**

The most inclusive model was used for the MAIC with all relevant covariates included (as the data allowed). In the PD-L1 ≥1%, non-squamous population, matching to KEYNOTE-189 resulted in an ESS of 108.94 for the EMPOWER-Lung 3 population, which corresponded to a 31.9% reduction from the original sample size (N = 160). In the PD-L1 ≥1%, squamous population, matching to KEYNOTE-407 resulted in an ESS of 98.46 for the EMPOWER-Lung 3 population, which corresponded to an 18.0% reduction from the original sample size (N = 120).

Table 7: Key patient characteristics before and after MAIC weighting (efficacy populations) – PD-L1 ≥1%, non-squamous

Patient characteristics		Observed EMPOWER-LUNG 3 N=160	Observed KEYNOTE-189 N=388	MAIC-adjusted EMPOWER-LUNG 3 ESS = 108.94
ESS reduction (% of original sample size)		N/A	N/A	31.9
PD-L1 expression	PD-L1 ≥50%	48.8	32.8	32.8
ECOG PS	1	73.6	56.2	56.2
Age	≥65 years	35.6	49.4	49.4
Smoking status	Current/former smoker	84.4	88.2	88.2

All values are reported in percentages; EMPOWER-Lung 3 cohort excludes stage IIIb locally advanced patients
ECOG PS, Eastern Cooperative Oncology Group performance score; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; N, number; PD-L1, programmed death-ligand 1.

Table 8: Key patient characteristics before and after MAIC weighting (efficacy populations) – PD-L1 ≥1%, squamous

Patient characteristics		Observed EMPOWER-LUNG 3 N=120	Observed KEYNOTE-407 N=353	MAIC-adjusted EMPOWER-LUNG 3 ESS = 98.46
ESS reduction (% of original sample size)		N/A	N/A	18.0
PD-L1 expression	PD-L1 ≥50%	43.3	26.1	26.1
Age	≥65 years	41.7	54.6	54.6
Smoking status	Current/former smoker	87.5	92.7	92.7

All values are reported in percentages. EMPOWER-Lung 3 cohort excludes stage IIIb locally advanced patients; ECOG PS could not be matched in this scenario, given that only 2/120 patients in the EMPOWER-LUNG 3 squamous/stage IV/PD-L1 ≥1% subgroup had ECOG 0.
ECOG PS, Eastern Cooperative Oncology Group performance score; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; N, number; PD-L1, programmed death-ligand 1.

1.2.2.2 Non-squamous histology, PD-L1 ≥1% (EMPOWER-Lung 3 vs KEYNOTE 189)

Table 9 presents the results of the unadjusted and anchored MAIC analyses of PFS and OS for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy in the PD-L1 ≥1%, non-squamous population, based on matching EMPOWER-Lung 3 to KEYNOTE-189, using the final analysis and extended follow-up from KEYNOTE-189. Corresponding figures of the KM curves from each trial (unweighted) and weighted curves from EMPOWER-LUNG 3 are presented in Figure 1 (PFS) and Figure 2 (OS).

Overall, MAIC results were similar for PFS and OS regardless of the KEYNOTE-189 data used, i.e., final analysis (median follow-up 31.0 months) versus extended follow-up (median follow-up 64.6 months). **The MAIC results, adjusting for imbalances in treatment effect modifiers, improved the point estimate HR for PFS** of cemiplimab + chemotherapy versus pembrolizumab + chemotherapy by **0.24 (1.13 unadjusted vs. 0.89 with anchored MAIC),** suggesting that less favourable baseline characteristics may have generated the numerically slightly less favourable results for cemiplimab + chemotherapy vs pembrolizumab + chemotherapy observed in the original (treatment effect modifier-unadjusted) NMA. However, consistent with the original NMA, the MAIC nevertheless indicated comparable PFS with no statistically significant difference between cemiplimab + chemotherapy and pembrolizumab + chemotherapy.

OS results were statistically in favour of cemiplimab + chemotherapy. However, it should be noted that OS results are unadjusted for crossover which was allowed per protocol in the KEYNOTE studies. Sections 1.3 and 1.2.2.3 present results from the NMA and MAIC, respectively, after incorporating published crossover adjusted data from KEYNOTE-407 (unavailable for KEYNOTE-189). Incorporation of crossover-adjusted data into the NMA in the squamous population increased the HR for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy by 0.11 (maximum increase to time-varying HRs) in the NMA (see Table 13 and Table 14).

The inclusion of additional covariates for **brain metastases and race** (as a proxy for geographic location) further **improved the point estimate HRs** in this subgroup (Table

12), but this analysis has conservatively not been included within the updated cost-effectiveness analyses.

Table 9: Progression-free survival and overall survival MAIC results for PD-L1 ≥1%, non-squamous population (EMPOWER-Lung 3 vs. KEYNOTE-189)

Outcome	Scenario	Adjustment	Comparison	N or ESS	HR (95% CI)	P value
PFS	EMPOWER-Lung 3 vs. KN189 (final analysis)	Unweighted	Cemi + chemo vs. chemo	160	0.48 (0.32, 0.70)	<0.001
		Weighted	Cemi + chemo vs. chemo	108.94	0.37 (0.25, 0.55)	<0.001
		Unweighted	Pembro + chemo vs. chemo	388	0.42 (0.33, 0.53)	NR
		Unweighted	Cemi + chemo vs. pembro + chemo	--	1.13 (0.72, 1.78)	0.584
		Anchored MAIC	**Cemi + chemo vs. pembro + chemo**	--	0.89 (0.56, 1.41)	0.610
	EMPOWER-Lung 3 vs. KN189 (extended follow-up)	Unweighted	Cemi + chemo vs. chemo	160	0.48 (0.32, 0.70)	<0.001
		Weighted	Cemi + chemo vs. chemo	108.94	0.37 (0.25, 0.55)	<0.001
		Unweighted	Pembro + chemo vs. chemo	388	0.43 (0.34, 0.54)	NR
		Unweighted	Cemi + chemo vs. pembro + chemo	--	1.11 (0.71, 1.73)	0.652
		Anchored MAIC	**Cemi + chemo vs. pembro + chemo**	--	0.87 (0.55, 1.37)	0.537
OS	EMPOWER-Lung 3 vs. KN189 (final analysis)	Unweighted	Cemi + chemo vs. chemo	160	0.44 (0.29, 0.68)	<0.001
		Weighted	Cemi + chemo vs. chemo	108.94	0.33 (0.20, 0.53)	<0.001
		Unweighted	Pembro + chemo vs. chemo	388	0.63 (0.48, 0.82)	NR
		Unweighted	Cemi + chemo vs. pembro + chemo	--	0.70 (0.43, 1.16)	0.166
		Anchored MAIC	**Cemi + chemo vs. pembro + chemo**	--	**0.52 (0.31, 0.90)**	**0.019**
	EMPOWER-Lung 3 vs. KN189 (extended follow-up)	Unweighted	Cemi + chemo vs. chemo	160	0.44 (0.29, 0.68)	<0.001
		Weighted	Cemi + chemo vs. chemo	108.94	0.33 (0.20, 0.53)	<0.001
		Unweighted	Pembro + chemo vs. chemo	388	0.66 (0.52, 0.84)	NR
		Unweighted	Cemi + chemo vs. pembro + chemo	--	0.67 (0.41, 1.09)	0.109
		Anchored MAIC	**Cemi + chemo vs. pembro + chemo**	--	**0.50 (0.29, 0.85)**	**0.010**

Covariates matched: PD-L1 expression, ECOG PS, age, smoking status. EMPOWER-Lung 3 cohort excludes stage IIIb locally advanced patients

Figure 1: Progression-free survival for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy in PD-L1 ≥1%, non-squamous population based on (A) KEYNOTE-189 final analysis and (B) KEYNOTE-189 extended follow-up

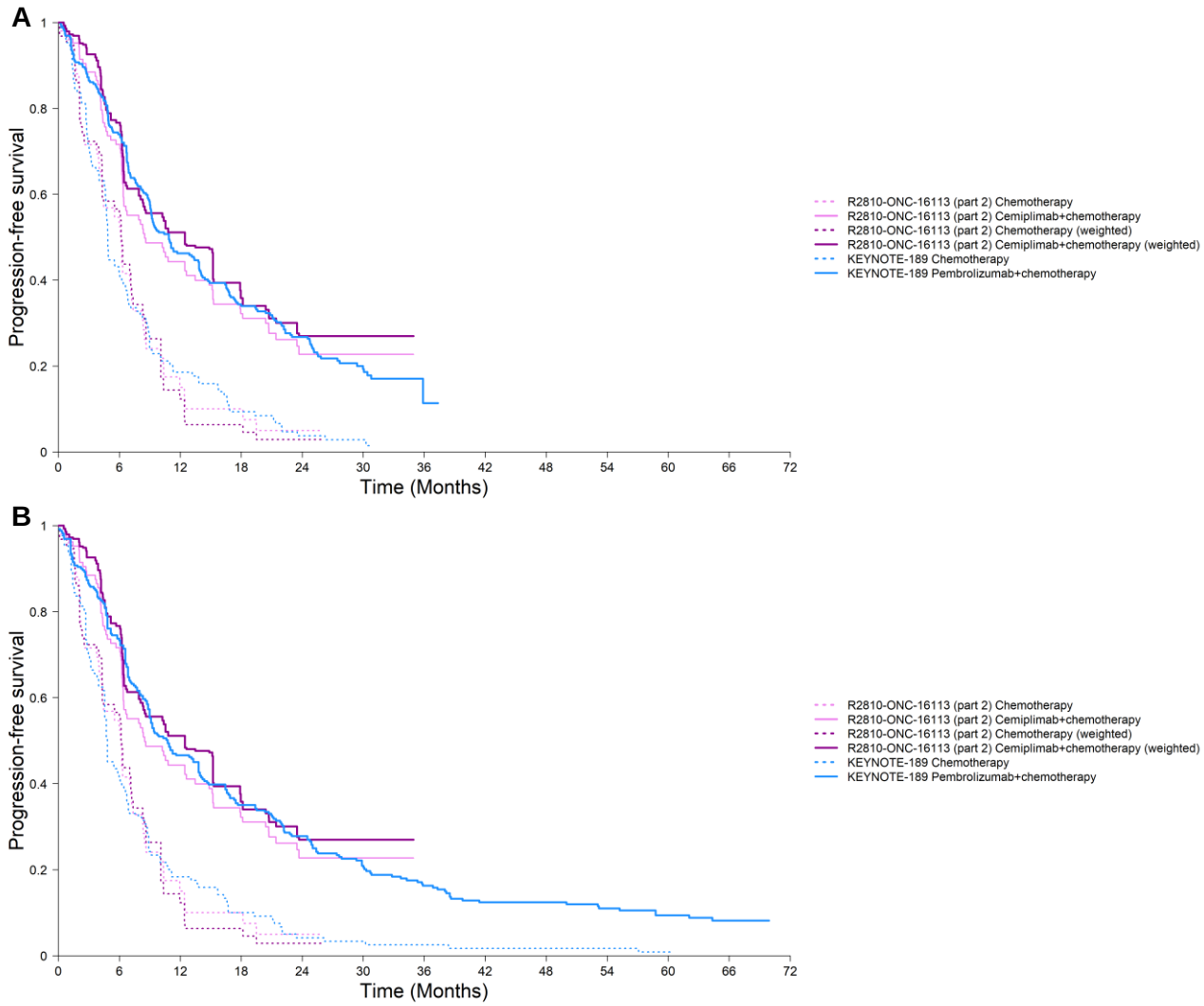
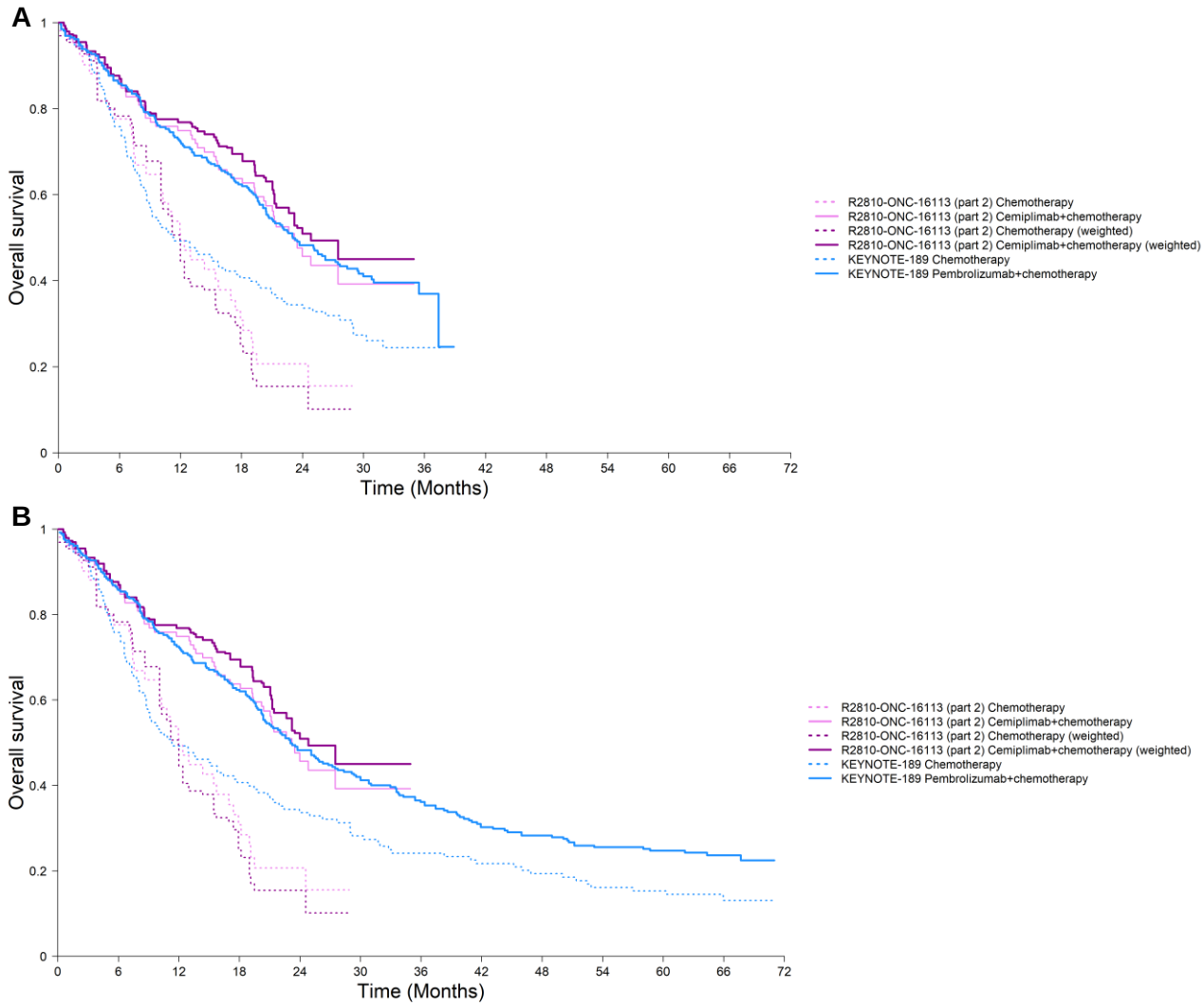


Figure 2: Overall survival for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy in PD-L1 ≥1%, non-squamous population based on (A) KEYNOTE-189 final analysis and (B) KEYNOTE-189 extended follow-up



1.2.2.3 Squamous histology, PD-L1 ≥1% (EMPOWER-Lung 3 vs KEYNOTE 407)

Table 10 presents the results of the unadjusted and anchored MAIC analyses of PFS and OS for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy in the PD-L1 ≥1%, squamous population, based on matching EMPOWER-LUNG 3 to KEYNOTE-407, using the final analysis and extended follow-up from KEYNOTE-407. Corresponding figures of the KM curves from each trial (unweighted) and weighted curves from EMPOWER-LUNG 3 are presented in Figure 3 (PFS) and Figure 4 (OS).

For OS, published KEYNOTE-407 crossover-adjusted data based on the simplified two-stage estimation method (no re-censoring) were used in the MAIC.

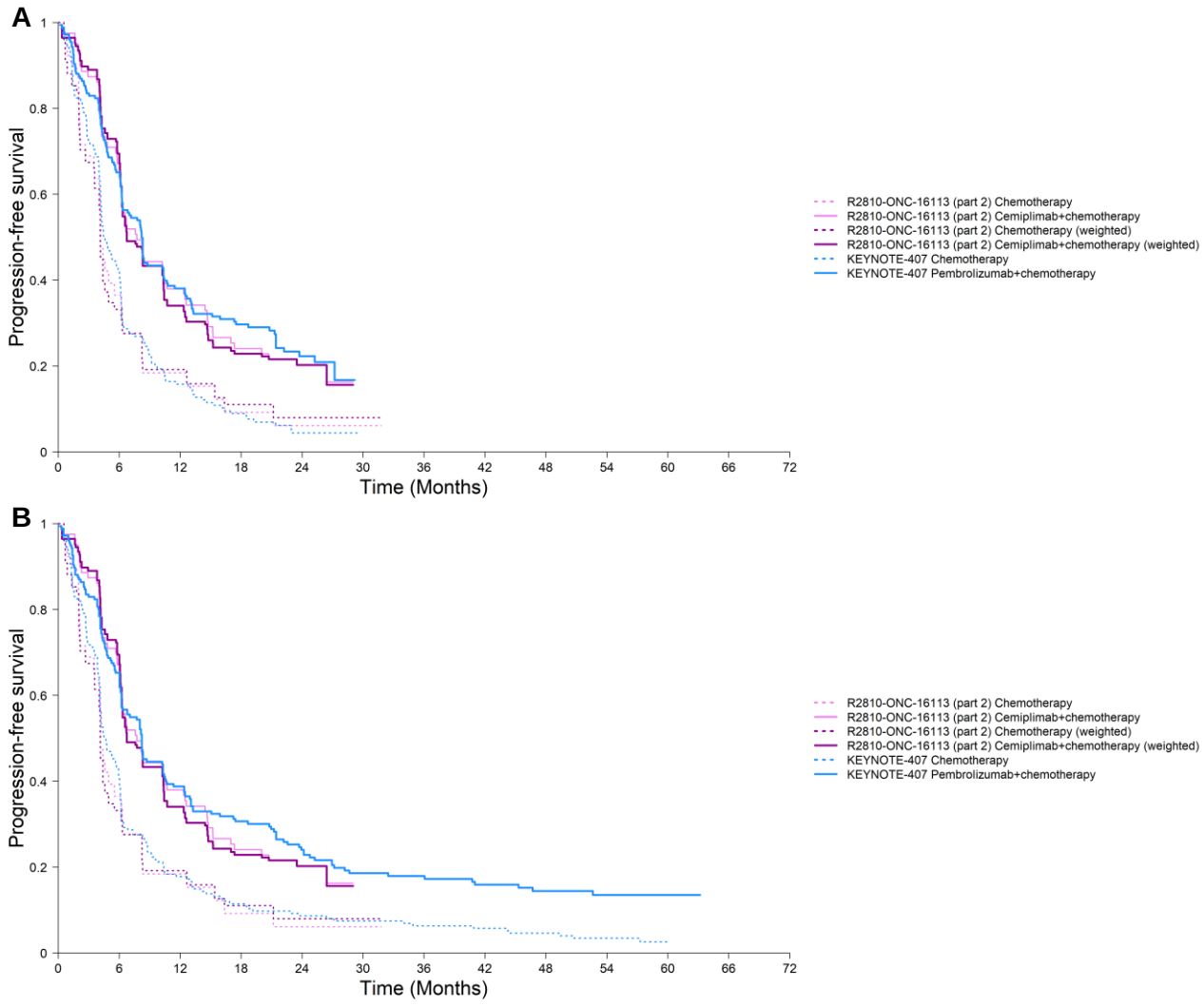
Overall, **MAIC results were similar for PFS regardless of the KEYNOTE-407 data used**, i.e., final analysis (median follow-up 14.3 months) versus extended follow-up (median follow-up 56.9 months). **The point estimate HR for (crossover-adjusted) OS improved from 1.02 unadjusted to 0.93 with the MAIC**. Overall, the MAIC results indicated comparable PFS and OS with no statistically significant difference between cemiplimab + chemotherapy and pembrolizumab + chemotherapy, consistent with the original NMA.

Table 10: Progression-free survival and overall survival MAIC results for PD-L1 ≥1%, squamous population (EMPOWER-Lung 3 vs. KEYNOTE-407)

Outcome	Scenario	Adjustment	Comparison	N or ESS	HR (95% CI)	P value
PFS	EMPOWER-Lung 3 vs. KN407 (final analysis)	Unweighted	Cemi + chemo vs. chemo	120	0.52 (0.34, 0.80)	0.003
		Weighted	Cemi + chemo vs. chemo	98.46	0.52 (0.31, 0.88)	0.015
		Unweighted	Pembro + chemo vs. chemo	353	0.50 (0.39, 0.64)	NR
		Unweighted	Cemi + chemo vs. pembro + chemo	--	1.05 (0.64, 1.70)	0.858
		Anchored MAIC	**Cemi + chemo vs. pembro + chemo**	--	1.05 (0.57, 1.92)	0.881
	EMPOWER-Lung 3 vs. KN407 (extended follow-up)	Unweighted	Cemi + chemo vs. chemo	120	0.52 (0.34, 0.80)	0.003
		Weighted	Cemi + chemo vs. chemo	98.46	0.52 (0.31, 0.88)	0.015
		Unweighted	Pembro + chemo vs. chemo	353	0.57 (0.45, 0.72)	NR
		Unweighted	Cemi + chemo vs. pembro + chemo	--	0.92 (0.57, 1.48)	0.722
		Anchored MAIC	**Cemi + chemo vs. pembro + chemo**	--	0.92 (0.50, 1.68)	0.783
OS	EMPOWER-Lung 3 vs. KN407 (final analysis, TSEsimp adjusted)	Unweighted	Cemi + chemo vs. chemo	120	0.53 (0.33, 0.85)	0.008
		Weighted	Cemi + chemo vs. chemo	98.46	0.48 (0.29, 0.81)	0.006
		Unweighted	Pembro + chemo vs. chemo	353	0.52 (0.34, 0.80)	NR
		Unweighted	Cemi + chemo vs. pembro + chemo	--	1.02 (0.54, 1.93)	0.940
		Anchored MAIC	**Cemi + chemo vs. pembro + chemo**	--	0.93 (0.47, 1.85)	0.832

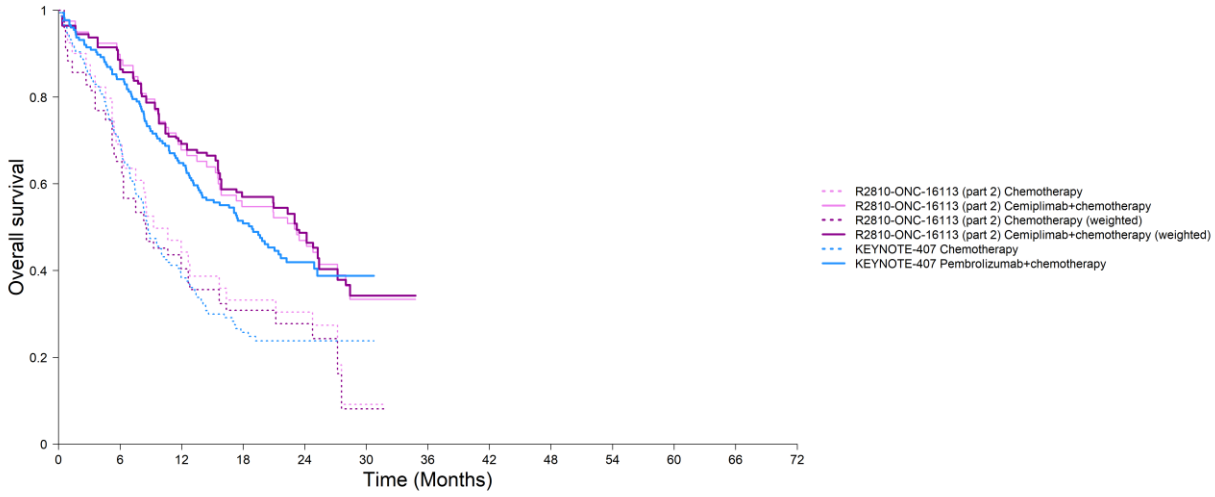
Covariates matched: PD-L1 expression, age, smoking status. ECOG PS could not be matched in this scenario, given that only 2/120 patients in the EMPOWER-Lung 3 squamous/stage IV/PD-L1 ≥1% subgroup had ECOG 0. EMPOWER-Lung 3 cohort excludes stage IIIb locally advanced patients
MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression-free survival

Figure 3: Progression-free survival for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy in PD-L1 ≥1%, squamous population based on (A) KEYNOTE-407 final analysis and (B) KEYNOTE-407 extended follow-up



R2810-ONC-16113 = EMPOWER-Lung 3

Figure 4: Overall survival for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy in PD-L1 ≥1%, squamous population based on KEYNOTE-407 final analysis with crossover adjustment



R2810-ONC-16113 = EMPOWER-Lung 3

1.2.2.4 Sensitivity analyses: Any PD-L1 (ITT)

The any PD-L1 (ITT) sensitivity analysis is not relevant to the NICE decision problem and was conducted purely to ensure the robustness of assuming that the baseline characteristics of the KEYNOTE studies were similar between the ITT and PD-L1≥1% populations.

Results in the any PD-L1 population, despite including the unlicensed PD-L1 negative subgroup from EMPOWER-Lung 3, were similar to those in the PD-L1≥1% MHRA-approved subgroup (Table 11). The MAIC point estimate HRs for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy improved vs. the unadjusted HRs in the non-squamous subgroup but increased in the squamous subgroup, as might be expected given that the squamous subgroup MAIC could not adjust for ECOG PS.

Table 11: Progression-free survival and overall survival MAIC results for any PD-L1, both histologies (EMPOWER-Lung 3 vs. KEYNOTE-407 or KEYNOTE-189)

Population	Outcome	Scenario	Adjustment	Base case (without brain mets)	
				HR (95% CI)	P value
Any PD-L1, non-squamous	PFS	EMPOWER-Lung 3 vs. KN189 (final analysis)	Unweighted	1.20 (0.83, 1.71)	0.329
			Anchored MAIC	0.98 (0.68, 1.42)	0.922
		EMPOWER-Lung 3 vs. KN189 (extended follow-up)	Unweighted	1.17 (0.82, 1.68)	0.384
			Anchored MAIC	0.96 (0.67, 1.39)	0.837
	OS	EMPOWER-Lung 3 vs. KN189 (final analysis)	Unweighted	1.23 (0.83, 1.83)	0.302
			Anchored MAIC	1.07 (0.72, 1.59)	0.736
		EMPOWER-Lung 3 vs. KN189 (extended follow-up)	Unweighted	1.15 (0.78, 1.69)	0.480
			Anchored MAIC	1.00 (0.68, 1.47)	0.997
Any PD-L1, squamous	PFS	EMPOWER-Lung 3 vs. KN407 (final analysis)	Unweighted	1.04 (0.69, 1.57)	0.838
			Anchored MAIC	1.14 (0.72, 1.79)	0.582
		EMPOWER-Lung 3 vs. KN407 (extended follow-up)	Unweighted	0.96 (0.64, 1.43)	0.839
			Anchored MAIC	1.05 (0.67, 1.64)	0.848
	OS	EMPOWER-Lung 3 vs. KN407 (final analysis, TSEsimp adjusted)	Unweighted	0.98 (0.58, 1.63)	0.924
			Anchored MAIC	1.05 (0.61, 1.79)	0.871

Note: Only comparisons in the non-squamous population were conducted for the scenario with brain metastases, as there were insufficient brain metastases in the squamous subgroup of EMPOWER-Lung 3 (n=2 in any PD-L1/squamous)
MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression-free survival

1.2.2.5 Conclusions of MAIC results across scenarios

A summary of MAIC results across all scenarios is provided in Table 12. Overall, MAIC results were **generally consistent between the base case and the scenarios**.

Impact of choice of effect modifiers

Results were **similar regardless of the covariates included in the model**; including brain metastases and race as covariates had little effect on the weights.

Impact of choice of populations

Results were generally similar between the PD-L1 ≥1% and any PD-L1 populations, although MAIC results were **slightly more favourable for cemiplimab + chemotherapy in the PD-L1 ≥1%, non-squamous population** than the any PD-L1, non-squamous population, with the biggest difference observed for OS. **MAIC results were similar between the PD-L1 ≥1%, squamous and any PD-L1, squamous populations**.

Impact of choice of analysis timepoint

Results were also similar regardless of whether the KEYNOTE final analysis or extended follow-up data were included for PFS.

Limitations

An important limitation of the MAICs is that the slightly less favourable MAIC results in the squamous subgroups may be due the inability to adjust for ECOG PS, given that only [redacted] patients in the EMPOWER-Lung 3 squamous/stage IV/PD-L1 ≥1% subgroup had ECOG 0 PS. Conversely, crossover-adjusted survival data were not available for the KEYNOTE-189 study (non-squamous subgroup) which may have led to slightly more favourable HRs for cemiplimab.

Due to time constraints, the MAICs were conducted on the basis of constant HRs. As noted in section 1.2.1.2, the proportional hazards assumption was only violated for three comparisons, and the results of constant HR NMAs were generally found to be consistent with those of the time-varying NMAs that do not rely on an assumption of constant proportional hazards. Furthermore, comparison of the constant HR NMA results (provided in Appendix E to the NMA report) with the constant HR MAIC results (provided in Table

9 and Table 10 above) suggests that the adjustment for potential treatment effect modifiers does not qualitatively change the conclusions that can be drawn on the relative treatment effects of cemiplimab + chemotherapy vs pembrolizumab + chemotherapy; indeed, the adjustment of potential treatment effect modifiers did not worsen but rather tended to improve the relative treatment effect estimates for cemiplimab + chemotherapy. We therefore do not anticipate that our implementation of a constant HR MAIC leads to results that are biased in favour of cemiplimab + chemotherapy, or would lead to qualitatively different conclusions on the relative treatment effects of cemiplimab + chemotherapy vs pembrolizumab + chemotherapy than would be reached with a time-varying HR MAIC.

Conclusion:

Whilst **results from these comprehensive analyses should be interpreted in the context of methodological limitations associated with MAICs, results from these exploratory analyses indicate there are no clinically meaningful differences in PFS and OS between cemiplimab + chemotherapy and pembrolizumab + chemotherapy. These results are consistent with:**

- the clinical expert consensus view expressed to Regeneron about the **anticipated similarity in effectiveness outcomes** with cemiplimab + chemotherapy relative to the pembrolizumab + chemotherapy based on the available evidence and their extensive clinical experience with immunotherapies in NSCLC

- results from the original company NMA (including extensive NMA sensitivity analysis) and NMAs published by other researchers (6) which show **no clear differences in effectiveness between cemiplimab + chemotherapy and pembrolizumab + chemotherapy**

- evidence-based clinical guidelines, including NCCN where cemiplimab + chemotherapy is the only IO + chemotherapy combination other than pembrolizumab + chemotherapy that has a ‘preferred’ guidelines

recommendation for the treatment of patients with advanced/metastatic NSCLC (7). **NCCN has also assigned both options with a score of 4 out of 5 ('very effective') for efficacy across histology and PD-L1 expression level subgroups in its Evidence Blocks™ assessment, which is based on both published trial evidence and real-world clinical experience of the panel members in more diverse real-world settings**

- HTA precedent where the focus has been on comparing treatment costs given the absence of any evidence for a meaningful difference in effectiveness of different IOs:
    - NICE, including TA705 (atezolizumab monotherapy) in which the committee concluded despite the lack of head-to-head RCT evidence that ITC results "*suggest that atezolizumab is as effective as pembrolizumab in delaying disease progression and extending life*" (3).
    - International cost-effectiveness HTA organisations, including PBAC (Australia) as well as CADTH (Canada) who were "*unable to draw definitive conclusions on relative efficacy*" of cemiplimab + chemotherapy vs pembrolizumab + chemotherapy due to unavoidable limitations in the ITC, but subsequently recommended cemiplimab as an option subject to cemiplimab not increasing treatment costs (and assuming equivalent efficacy) compared with relevant IO + chemotherapy combinations (1, 2).

These **analyses also further support consideration of cost comparison as a relevant approach for decision making.**

Table 12: Summary of progression-free survival and overall survival MAIC results across scenarios

Population	Outcome	Scenario	Adjustment	Base case (without brain mets or race)		Scenario (with brain mets and race)[a]	
				HR (95% CI)	P value	HR (95% CI)	P value
PD-L1 ≥1%, non-squamous	PFS	EMPOWER-Lung 3 vs. KN189 (final analysis)	Unweighted	1.13 (0.72, 1.78)	0.584	1.13 (0.72, 1.78)	0.584
			Anchored MAIC	0.89 (0.56, 1.41)	0.610	0.85 (0.52, 1.40)	0.532
		EMPOWER-Lung 3 vs. KN189 (extended follow-up)	Unweighted	1.11 (0.71, 1.73)	0.652	1.11 (0.71, 1.73)	0.652
			Anchored MAIC	0.87 (0.55, 1.37)	0.537	0.83 (0.51, 1.36)	0.468
	OS	EMPOWER-Lung 3 vs. KN189 (final analysis)	Unweighted	0.70 (0.43, 1.16)	0.166	0.70 (0.43, 1.16)	0.166
			Anchored MAIC	**0.52 (0.31, 0.90)**	**0.019**	**0.41 (0.24, 0.69)**	**0.001**
		EMPOWER-Lung 3 vs. KN189 (extended follow-up)	Unweighted	0.67 (0.41, 1.09)	0.109	0.67 (0.41, 1.09)	0.109
			Anchored MAIC	**0.50 (0.29, 0.85)**	**0.010**	**0.39 (0.24, 0.65)**	**<0.001**
PD-L1 ≥1%, squamous	PFS	EMPOWER-Lung 3 vs. KN407 (final analysis)	Unweighted	1.05 (0.64, 1.70)	0.858	1.05 (0.64, 1.70)	0.858
			Anchored MAIC	1.05 (0.57, 1.92)	0.881	0.86 (0.46, 1.62)	0.643
		EMPOWER-Lung 3 vs. KN407 (extended follow-up)	Unweighted	0.92 (0.57, 1.48)	0.722	0.92 (0.57, 1.48)	0.722
			Anchored MAIC	0.92 (0.50, 1.68)	0.783	0.76 (0.40, 1.42)	0.381
	OS	EMPOWER-Lung 3 vs. KN407 (final analysis, TSEsimp adjusted)	Unweighted	1.02 (0.54, 1.93)	0.940	1.02 (0.54, 1.93)	0.940
			Anchored MAIC	0.93 (0.47, 1.85)	0.832	0.84 (0.40, 1.76)	0.639
Any PD-L1, non-squamous	PFS	EMPOWER-Lung 3 vs. KN189 (final analysis)	Unweighted	1.20 (0.83, 1.71)	0.329	1.20 (0.83, 1.71)	0.329
			Anchored MAIC	0.98 (0.68, 1.42)	0.922	1.00 (0.68, 1.48)	0.999
		EMPOWER-Lung 3 vs. KN189 (extended follow-up)	Unweighted	1.17 (0.82, 1.68)	0.384	1.17 (0.82, 1.68)	0.384
			Anchored MAIC	0.96 (0.67, 1.39)	0.837	0.98 (0.66, 1.45)	0.920
	OS	EMPOWER-Lung 3 vs. KN189 (final analysis)	Unweighted	1.23 (0.83, 1.83)	0.302	1.23 (0.83, 1.83)	0.302
			Anchored MAIC	1.07 (0.72, 1.59)	0.736	1.00 (0.68, 1.46)	0.987
		EMPOWER-Lung 3 vs. KN189 (extended follow-up)	Unweighted	1.15 (0.78, 1.69)	0.480	1.15 (0.78, 1.69)	0.480
			Anchored MAIC	1.00 (0.68, 1.47)	0.997	0.93 (0.64, 1.35)	0.701
Any PD-L1, squamous	PFS	EMPOWER-Lung 3 vs. KN407 (final analysis)	Unweighted	1.04 (0.69, 1.57)	0.838	1.04 (0.69, 1.57)	0.838
			Anchored MAIC	1.14 (0.72, 1.79)	0.582	0.98 (0.61, 1.57)	0.938
		EMPOWER-Lung 3 vs. KN407 (extended follow-up)	Unweighted	0.96 (0.64, 1.43)	0.839	0.96 (0.64, 1.43)	0.839
			Anchored MAIC	1.05 (0.67, 1.64)	0.848	0.90 (0.57, 1.43)	0.663
	OS	EMPOWER-Lung 3 vs. KN407 (final analysis, TSEsimp adjusted)	Unweighted	0.98 (0.58, 1.63)	0.924	0.98 (0.58, 1.63)	0.924
			Anchored MAIC	1.05 (0.61, 1.79)	0.871	0.96 (0.55, 1.70)	0.898

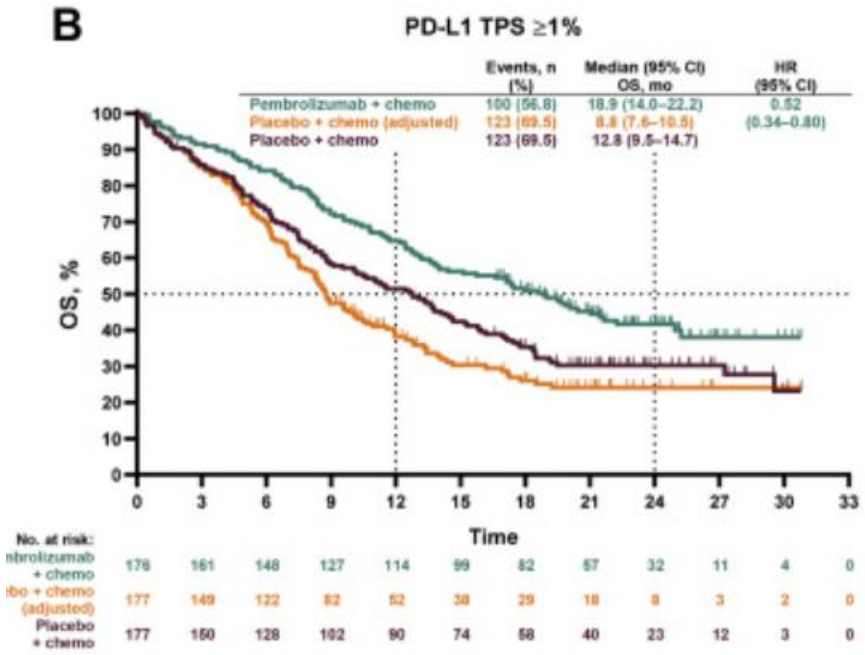
Bolded values indicate statistically significant results. **a)** Brain metastases were only included as a covariate in the non-squamous populations (KN189), because there were insufficient brain metastases in the squamous subgroup of EMPOWER-LUNG 3 (n=1 in PD-L1 ≥1%/squamous subgroup; n=2 in any PD-L1/squamous subgroup).
Green shading denotes values incorporated into the updated cost-effectiveness analysis.

1.3 Crossover in the KEYNOTE studies

1.3.1 Crossover-adjusted ITC scenario analysis methods

Although the DGD suggests no crossover-adjusted data for the KEYNOTE-407/189 RCTs have been reported to date, we have used crossover-adjusted results from the final analysis of the KEYNOTE-407 (squamous histology) study which have been published (4). To explore the impact of crossover on comparative effectiveness results, we incorporated the crossover-adjusted OS data from KEYNOTE-407 (Figure 5) in the MAIC as previously described in section 1.2 and NMA as discussed below.

Figure 5: Crossover-adjusted overall survival from KEYNOTE-407 (squamous histology)



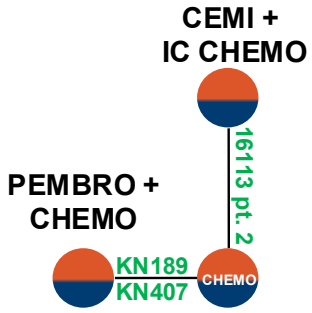
CI, confidence interval; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand 1; TPS, tumour proportion score

Source: Adapted from Paz-Ares et al, 2020 (4)

A fixed-effect, two-step multivariate NMA was performed with time-varying HRs for OS including crossover-adjusted results from the final analysis of KEYNOTE-407 in the PD-L1 ≥1%, any histology scenario, based on the evidence network shown in Figure 6. The same methods outlined previously (see Section B.2.9 and Appendix D in the original company submission) were followed, and the log-logistic model was

selected as the best fitting model for the two-step NMA (aligned with the best-fitting model for the non-crossover-adjusted analysis).

Figure 6: Evidence network for PD-L1 ≥1%, any histology scenario for overall survival



Time-varying OS HRs from the fixed-effect NMA for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy were consistent across the top three best fitting models. The results indicated comparable OS with no statistically significant differences between cemiplimab + chemotherapy and pembrolizumab + chemotherapy at all time points. Results using the best-fitting (log-logistic) model are presented in Table 13. Results of the original NMA unadjusted for crossover are presented in Table 14 for comparison. The estimated relative treatment effects were applied to a pooled reference modelled survival function (investigator's choice chemotherapy) to generate OS proportions over time for each intervention (Figure 7).

As expected, the point estimate HRs for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy increased when compared with the original NMA results that were unadjusted for crossover. Despite this, cemiplimab + chemotherapy demonstrated comparable OS results versus pembrolizumab + chemotherapy (3 months: HR 1.05, 95% CrI 0.58 to 1.77); 36 months: HR 0.95, 95% CrI 0.64 to 1.44) with 95% CrIs that included 1 at all timepoints (i.e., not statistically significant).

Table 13: Estimated overall survival time-varying hazard ratios for cemiplimab + chemotherapy versus competing interventions among patients with PD-L1 ≥1%, any histology from fixed-effect two-step network meta-analysis including KEYNOTE-407 crossover-adjusted data (log-logistic model)

Cemiplimab + chemotherapy vs.	Time-varying HR (95% CrI)							
	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Chemotherapy	**0.50 (0.31, 0.74)**	**0.51 (0.37, 0.69)**	**0.53 (0.40, 0.72)**	**0.56 (0.42, 0.77)**	**0.61 (0.45, 0.86)**	**0.65 (0.47, 0.93)**	**0.69 (0.49, 0.98)**	0.72 (0.51, 1.02)
Pembrolizumab + chemotherapy	1.05 (0.58, 1.77)	1.01 (0.67, 1.49)	0.99 (0.69, 1.43)	0.97 (0.68, 1.42)	0.96 (0.66, 1.43)	0.96 (0.65, 1.44)	0.95 (0.64, 1.44)	0.95 (0.64, 1.44)

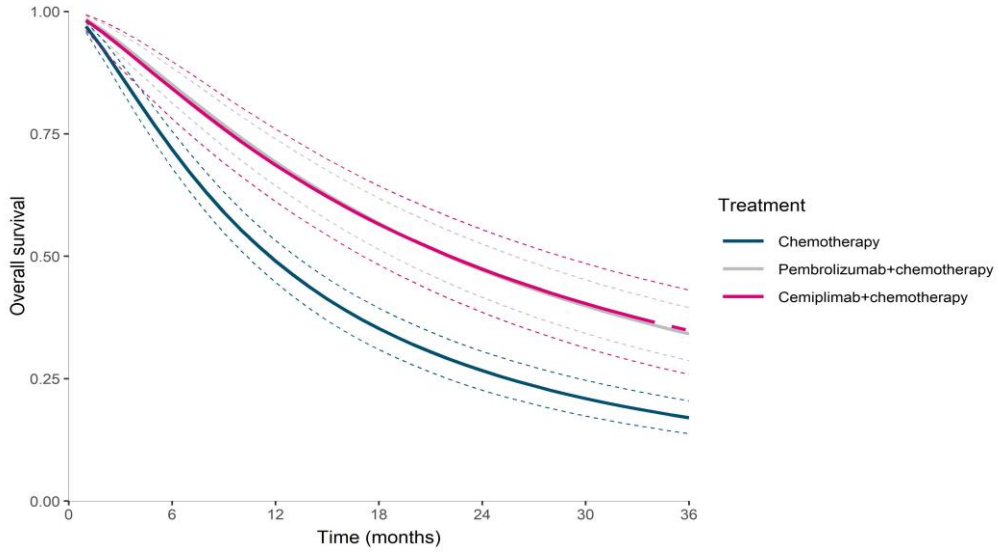
Cells shaded in light grey indicate timepoint past shortest median follow-up of treatments included in a given comparison; cells shaded in dark grey indicate estimates based on model extrapolations. The model presented is log-logistic, fixed-effect. All bolded values are statistically significant at the 0.05 significance level.
CrI, credible interval; HR, hazard ratio.

Table 14: Estimated overall survival time-varying hazard ratios for cemiplimab + chemotherapy versus competing interventions among patients with PD-L1 ≥1%, any histology from fixed-effect two-step network meta-analysis (log-logistic model) – original NMA, not cross-over adjusted

Cemiplimab + chemotherapy vs.	Time-varying HR (95% CrI)							
	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Chemotherapy	**0.52 (0.32, 0.76)**	**0.52 (0.37, 0.70)**	**0.53 (0.40, 0.72)**	**0.56 (0.42, 0.76)**	**0.60 (0.45, 0.85)**	**0.64 (0.47, 0.92)**	**0.68 (0.49, 0.97)**	0.70 (0.50, 1.00)
Pembrolizumab + chemotherapy	0.94 (0.52, 1.57)	0.90 (0.60, 1.32)	0.88 (0.62, 1.26)	0.87 (0.62, 1.26)	0.87 (0.61, 1.28)	0.87 (0.60, 1.30)	0.88 (0.60, 1.31)	0.88 (0.60, 1.32)

Cells shaded in light grey indicate timepoint past shortest median follow-up of treatments included in a given comparison; cells shaded in dark grey indicate estimates based on model extrapolations. The model presented is log-logistic, fixed-effect. All bolded values are statistically significant at the 0.05 significance level.
CrI, credible interval; HR, hazard ratio.

Figure 7: Estimated overall survival curves for cemiplimab + chemotherapy and competing interventions among patients with PD-L1 ≥1% and any histology from fixed-effect two-step network meta-analysis including KEYNOTE-407 crossover-adjusted data (log-logistic model)



Dashed lines represent model extrapolations. Dotted lines indicate 95% credible intervals.

1.3.2 Conclusions of crossover-adjusted ITC scenario analyses

Given the crossover design in KEYNOTE-407 and approximately 40% of patients in the chemotherapy arm crossing over to pembrolizumab monotherapy after disease progression (median follow-up 14.3 months) (4), the survival benefit of pembrolizumab + chemotherapy may have been underestimated in the original NMA. When adjusted using the simplified two-stage estimation method (no re-censoring), the OS HR became more favourable for pembrolizumab + chemotherapy versus chemotherapy (final analysis: unadjusted HR 0.67, 95% CI 0.51 to 0.87; crossover-adjusted HR 0.52, 95% CI 0.34 to 0.80). Upon incorporation of the KEYNOTE-407 crossover-adjusted results into the NMA, results continued to demonstrate comparability between cemiplimab + chemotherapy and pembrolizumab + chemotherapy in terms of overall survival, consistent with the base case NMA. This suggests that even after accounting for the bias introduced into KEYNOTE-407 by treatment switching, there are still no meaningful differences in OS between cemiplimab + chemotherapy and pembrolizumab + chemotherapy.

1.4 Impact of early stopping of EMPOWER-Lung 3 on OS outcomes

There is no evidence that the ethical early stopping of EMPOWER-Lung 3 has biased the ITC in favour of cemiplimab.

Note that due to the availability of crossover-adjusted data, the MAIC was conducted only on the crossover-adjusted final analysis data cut of KEYNOTE-407. However, for KEYNOTE-189, MAICs for OS were conducted for both the extended follow-up and final analysis timepoints. A comparison between these two follow-up times shows little change in results, with the point estimate HR for OS reducing by only 0.02 between the extended follow-up and final analysis (Table 15).

Table 15: Comparison of MAIC results for extended follow-up vs. final analysis; KEYNOTE-189 (non-squamous)

Population	Outcome	Scenario	Adjustment	Base case (without brain mets or race)	
				HR (95% CI)	P value
PD-L1 ≥1%, non-squamous	PFS	EMPOWER-Lung 3 vs. KN189 (final analysis)	Unweighted	1.13 (0.72, 1.78)	0.584
			Anchored MAIC	0.89 (0.56, 1.41)	0.610
		EMPOWER-Lung 3 vs. KN189 (extended follow-up)	Unweighted	1.11 (0.71, 1.73)	0.652
			Anchored MAIC	0.87 (0.55, 1.37)	0.537
	OS	EMPOWER-Lung 3 vs. KN189 (final analysis)	Unweighted	0.70 (0.43, 1.16)	0.166
			Anchored MAIC	**0.52 (0.31, 0.90)**	**0.019**
		EMPOWER-Lung 3 vs. KN189 (extended follow-up)	Unweighted	0.67 (0.41, 1.09)	0.109
			Anchored MAIC	**0.50 (0.29, 0.85)**	**0.010**

1.5 Topic 1 cost-effectiveness analysis results

Below we present cost effectiveness results comparing the outcomes between the company base case (time-varying NMA) and including the MAIC (relevant MAICs informing the updated CEM are highlighted in green in Table 12).

The MAIC results were incorporated into the model using a proportional hazards (rather than time-varying hazard ratio) modelling approach due to the short timeframe for this response. As explained in section 1.2.1.2, only a small number of comparisons violated the assumption of proportional hazards. Briefly:

- The extrapolated chemotherapy arms by histology (squamous vs. non-squamous) from EMPOWER-Lung 3 are used as the reference survival curves.
    - All extrapolations used the log-logistic function, which was a favoured functional form for the original time-varying NMA based on goodness of fit criteria across the four comparisons (see Appendix D of the original NMA report submitted as data on file (12))
    - Goodness of fit of different parametric functions to the EMPOWER-Lung 3 squamous and non-squamous subgroups was not provided as part of the original submission and are provided in this response in Appendix D.
- For each extrapolated EMPOWER-Lung 3 chemotherapy survival curve, the hazard rate over time is calculated.

- To estimate pembrolizumab + chemotherapy arm hazards, unweighted HRs from the updated analysis are applied to the chemotherapy hazards (see Table 9 and Table 10 for these unweighted pembrolizumab + chemotherapy vs. chemotherapy HRs).

- To estimate cemiplimab + chemotherapy arm hazards, weighted HRs from the MAIC are applied to the chemotherapy hazards (see Table 9 and Table 10 for these weighted cemiplimab + chemotherapy vs. chemotherapy HRs).

- A check is included to ensure alignment with MAIC adjusted HRs between pembrolizumab + chemotherapy and cemiplimab + chemotherapy.

- The hazards between the squamous and non-squamous subgroups are then weighted by the proportion of patients who were squamous and non-squamous in EMPOWER-Lung 3.

- Hazards for combined squamous and non-squamous subgroups are transformed back into survival for chemotherapy, pembrolizumab + chemotherapy, and cemiplimab + chemotherapy.

Note that results now incorporate updated eMIT chemotherapy prices, which has resulted in minor changes to the submitted company base case. Incorporation of the MAICs decreased incremental cost savings while increasing incremental QALYs, with cemiplimab + chemotherapy remaining dominant but with increasing net health benefit vs. the original company base case.

Table 16: Cost-effectiveness results incorporating the MAIC

Intervention	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER	NHB @£20,000 /QALY
Original company base case (time-varying NMA)								
Cemiplimab + CT	[redacted]	3.2571	[redacted]	[redacted]	0.33	[redacted]	Dominant	2.9714
Pembrolizumab + CT	126,144	2.9308	2.1494	-	-	-	-	-
Original company base case + updated eMIT prices								

Cemiplimab + CT	[redacted]	3.2571	[redacted]	[redacted]	0.33	[redacted]	Dominant	2.9717
Pembrolizumab + CT	126,199	2.9308	2.1494	-	-	-	-	-
MAIC + updated eMIT prices								
Cemiplimab + CT	[redacted]	4.3989	[redacted]	[redacted]	1.19	[redacted]	Dominant	3.1178
Pembrolizumab + CT	125,973	3.2094	2.3524	-	-	-	-	-

CT, chemotherapy; eMIT Drugs and pharmaceutical electronic market information tool; ICER, incremental cost-effectiveness ratio; LY, life years; MAIC, matching-adjusted indirect comparison; NHB, net health benefit, NMA, network-meta-analysis; QALYs, quality-adjusted life years

Topic 2 Stopping rule and time on treatment

Stopping rules for cemiplimab and pembrolizumab

The committee noted the high level of uncertainty about *"the implementation of the stopping rules for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy"* (DGD section 3.13). In particular, *"that the company included a 2-year stopping rule for cemiplimab in the model. This rule is not stated in the summary of product characteristics for cemiplimab. The company stated that it chose this stopping rule in line with guidance for pembrolizumab plus chemotherapy in TA683 and TA770. It added this was also in line with EMPOWER-Lung 3, in which the protocol allowed treatment for a maximum of 108 weeks. The CDF clinical lead stated that in clinical practice, pembrolizumab treatment given every 3 weeks is stopped after 35 cycles. The EAG stated that the company modelled the stopping rule for cemiplimab and pembrolizumab such that treatment stopped at 2 calendar years. The committee noted that this differed to how the stopping rule for pembrolizumab is implemented in NHS practice"* (DGD section 3.9)

The committee requested *"implementing the stopping rule for pembrolizumab such that pembrolizumab is stopped after 35, 3-weekly cycles"*, and *"implementing the stopping rule for cemiplimab such that it reflects EMPOWER-Lung 3"* (DGD section 3.15).

For the cost-effectiveness analysis, the committee preferred that *"the stopping rule for pembrolizumab to be implemented such that pembrolizumab is stopped after 35, 3-weekly cycles"* (DGD section 3.14)

Impact of treatment beyond 108 weeks in EMPOWER-Lung 3

The committee noted the high level of uncertainty about *"the impact on progression-free survival and overall survival of continued treatment beyond 108 weeks for people in the cemiplimab plus chemotherapy arm"* (DGD section 3.13).

In particular, the committee noted that *"based on Kaplan–Meier time-to-treatment-discontinuation data, some people in EMPOWER-Lung 3 appeared to have*

continued treatment beyond the protocol-defined maximum of 108 weeks. This was because at approximately 27 months, 42 people were still having cemiplimab." (DGD section 3.9)

Impact of treatment beyond progression in the cemiplimab arm in EMPOWER-Lung 3

The committee noted the high level of uncertainty about "*the impact on overall survival of treatment beyond progression for people in the cemiplimab plus chemotherapy arm*" (DGD section 3.13).

In particular, the committee noted that "*the EMPOWER-Lung 3 protocol allowed people to continue having cemiplimab after disease progression. The company stated that in EMPOWER-Lung 3, most people did not have access to post-progression second-line immunotherapy treatments, which likely led to staying on cemiplimab beyond progression longer than they would have otherwise. But the marketing authorisation for cemiplimab differs from the trial protocol and specifies that cemiplimab treatment 'may be continued until disease progression or unacceptable toxicity'. Based on this and clinical expert opinion, the company did not anticipate that treatment would continue after disease progression in clinical practice.*" (DGD section 3.8)

Modelling time on treatment

The committee noted that it was *"assumed that time on treatment was equal to progression-free survival for cemiplimab plus chemotherapy. The same assumption also applied for pembrolizumab plus chemotherapy. The company also provided a scenario analysis in which a ratio was applied to the progression-free survival curve to generate the time-on-treatment curve. This resulted in estimated ratios (for time on treatment compared with progression-free survival) of 1.17 for cemiplimab plus chemotherapy and 0.84 for pembrolizumab plus chemotherapy (a ratio above 1 indicated longer time on treatment than progression-free survival)…The EAG noted that assuming that time on treatment was equal to progression-free survival ignored that time on treatment affects progression-free survival and overall survival. It thought that this assumption*

underestimated the costs for cemiplimab plus chemotherapy and overestimated the costs for pembrolizumab plus chemotherapy" (DGD section 3.8)

For the cost effectiveness analysis, *"the committee preferred using a ratio between time on treatment and progression-free survival to calculate time on treatment for pembrolizumab" and "using Kaplan–Meier data from EMPOWER-Lung 3, either directly or using the best fitting parametric survival curve fitted to that data, as per the NICE technical support document 14 to calculate time on treatment for cemiplimab. This should also include treatment costs for people who continued treatment beyond 108 weeks"*

2.1 Summary of company response

Stopping rules for cemiplimab and pembrolizumab

We have updated the model stopping rules to more accurately reflect the rules in clinical practice for pembrolizumab (35 cycles) and to align with the EMPOWER-Lung 3 trial for cemiplimab (section 2.2).

Impact of treatment beyond 108 weeks in EMPOWER-Lung 3

We have explained the reasons for which treatment appeared to continue beyond 108 weeks in EMPOWER-Lung 3 (essentially dose pauses) and draw comparison with the KEYNOTE studies, where the same effect was seen (section 2.3.1).

Impact of treatment beyond progression in the cemiplimab arm in EMPOWER-Lung 3

We have explained the reasons for which patients continued treatment beyond progression in EMPOWER-Lung 3 and compare and contrast with the observed treatment beyond progression in the KEYNOTE studies, as well treatment with IO post-progression in general, whether that consists of sustained initial IO or alternative IO (section 2.3.2).

Modelling time on treatment

Given the implementation of adjusted survival data for cemiplimab, which would not be aligned with the observed time-on treatment in EMPOWER-Lung 3, we have not implemented the request to model time-on-treatment using the EMPOWER-Lung 3 Kaplan-Meier data. However, we hope that our explanation of the pattern on time-on-treatment observed in EMPOWER-Lung 3, as well as that in the KEYNOTE studies, provides sufficient reassurance for the approach taken (section 2.4).

2.2 Stopping rules for cemiplimab and pembrolizumab

In accordance with the Committee's preferences, we have updated the cost-effectiveness analysis base case**:**

- to reflect **a stopping rule for pembrolizumab based on the maximum number of pembrolizumab doses received (i.e., up to 35 doses, as specified in the KEYNOTE 189/407 study protocols) rather than the 2-year duration specified in the TA663/TA770 guidance.** This equates to stopping treatment at timepoint

- To reflect **a stopping rule for cemiplimab such that it reflects EMPOWER-Lung 3 (i.e., up to 36 doses – see additional clarifications in section 2.3 below), rather than the 2-year duration specified in the TA663/TA770 guidance.**

These stopping rules were implemented in the model by updating the maximum treatment duration (column Q of "Input_Drug_Costs" worksheet) from 24 months to:

- Pembrolizumab 3-weekly – 24.15 months = ((3x7x35)/365.25)x12
- Pembrolizumab 6-weekly – 24.84 months = ((6x7x18)/365.25)x12
- Cemiplimab 3-weekly – 24.84 months = ((3x7x36)/365.25)x12

The unit drug acquisition cost per cycle; pre-progression calculations in the model engines were then updated to ensure the fraction of the month beyond 24 months was appropriately accounted for within the model calculations (see the model *Change log* sheet for further details).

Note that although patients may have treatment beyond these timepoints if they experience dose pauses, the model does not explicitly capture dose pauses; thus stopping treatment after the specified number of treatment cycles in the model is expected to be a close approximation of the cost of extended treatment including dose pauses.

2.3 Impact of extended treatment on OS and PFS – cemiplimab

2.3.1 Impact of treatment beyond 108 weeks on OS and PFS – cemiplimab

As highlighted in the committee discussion, there was uncertainty around why a proportion of patients in the cemiplimab + chemotherapy arm of EMPOWER-Lung 3 were reported as having remained on treatment beyond the maximum 108 weeks specified in the study protocol (Company submission Doc B figure 30; ACM slide 20).

We can confirm that in the final OS analysis of EMPOWER-Lung 3, of the 52 patients reported to have remained on cemiplimab beyond 108 weeks, **no patients received more than the maximum number of doses specified in the protocol (36 doses, equivalent to 108 weeks dosed Q3W**).

A total of 312 patients in the EMPOWER-Lung 3 ITT population received at least one dose of cemiplimab,

- Of the 52 patients still on treatment beyond 108 weeks, 27 (51%) had a dose delay
- Further, treatment exposure per-protocol definition is a safety endpoint and includes an additional 21-day exposure window post-administration in the endpoint calculation. This would cause those patients who complete 108 weeks of therapy to have a reported treatment exposure >108 weeks.

Cemiplimab

Duration of treatment exposure to cemiplimab (in weeks) is calculated as the minimum of

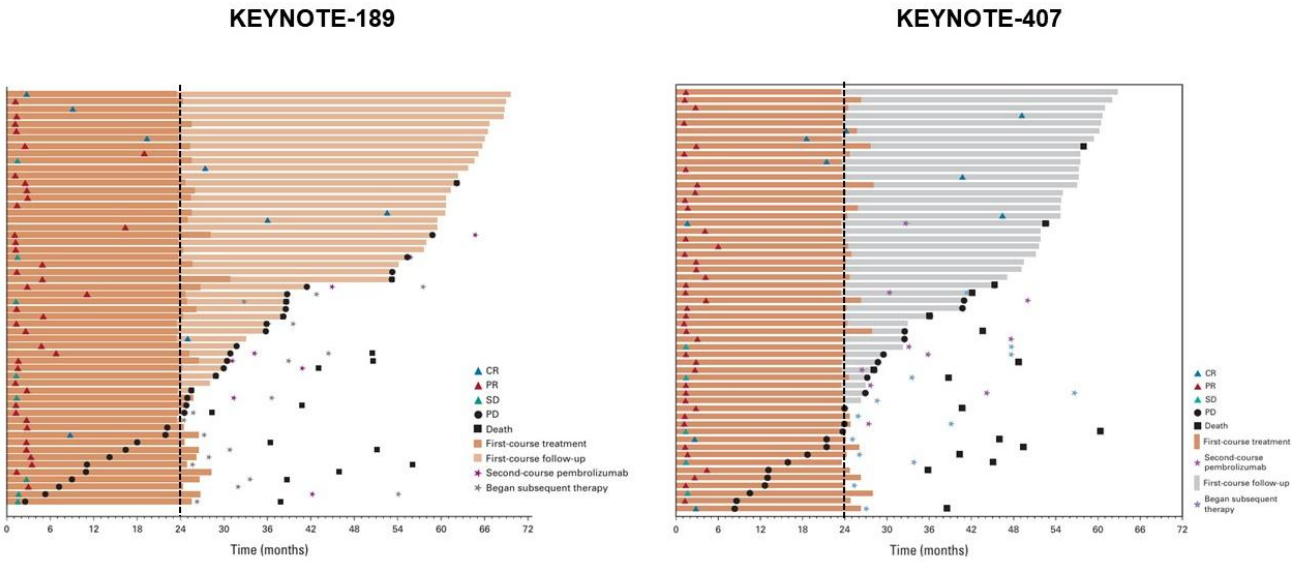
- [date of last dose – date of first dose + 21] / 7 or
- [date of clinical data cut-off or date of death – date of first dose + 1] / 7

The actual dose intensity = total dose received / duration of treatment exposure (week)

The relative dose intensity = actual dose intensity / planned dose intensity, where planned dose intensity (in week) = planned dose / 3.

It should be noted for comparison that published 5-year follow up of the KEYNOTE-189 and -407 trials also show that, of patients who received the maximum protocol permitted 35 doses, a meaningful proportion (approximately 45-60%) were similarly reported as having remained on treatment beyond the maximum 2-year treatment duration specified in the study protocols (Figure 8) and that the NICE pembrolizumab stopping rules specify 2 years of uninterrupted treatment**.**

Figure 8 Treatment beyond 2 years in KEYNOTE-189 and KEYNOTE-407



Graphs show data for patients who completed 35 cycles of pembrolizumab. Dotted line indicates maximum 2-year treatment duration.

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

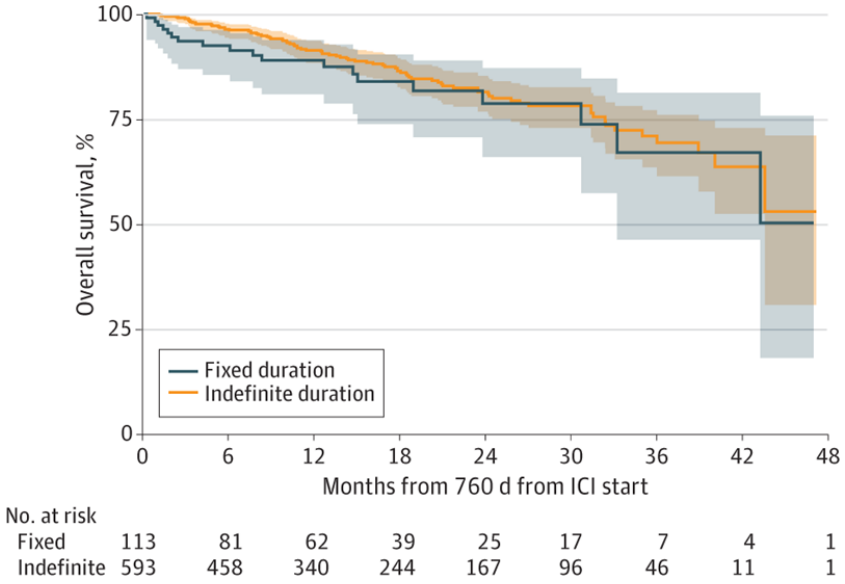
Source: Adapted from Garassino et al, 2023 (14); Adapted from Novello et al, 2023 (15)

Beside the similar observation across these RCTs, evidence that continued versus fixed-duration IO treatment leads to improved outcomes in this patient group is also lacking. A large, retrospective population cohort analysis of 706 patients from the Flatiron database (US) with advanced/metastatic NSCLC receiving first line IO-based therapy who were still on treatment at 2 years showed that (16):

- there were no statistically significant differences in OS between those who stopped treatment at 2-years (n = 113) and those who continued IO-based treatment indefinitely, including after adjustment for potential treatment effect modifiers such as age, sex, history of smoking, and PD-L1 status
- approximately 1 in 5 of those still on treatment at 2 years discontinued in the absence of disease progression or death in the following 2-month window, suggesting the potential that rather than outcomes being impacted by

treatment beyond the fixed calendar duration, patients who remain on treatment at later timepoints are predominantly those who have had the most durable responses to treatment.

Figure 9 Association between duration of IO treatment and OS in advanced/metastatic NSCLC



ICI, immune checkpoint inhibitor ; IO, immunotherapy; NSCLC, non-small cell lung cancer; OS, overall survival

Source: Taken from Sun et al, 2023 (16)

2.3.2 Impact of extended treatment beyond disease progression on OS – cemiplimab

A recent systematic review and meta-analysis (the OTHERS study) suggested that prolonged IO does not enhance outcomes in patients with advanced solid tumours (17). Notably, patients with NSCLC receiving IO plus standard of care for up to two years had better PFS (HR 0.85, 95% CI 0.76, 0.96) and OS (HR 0.84, 95% CI 0.68, 0.89) than those receiving IO plus standard of care until disease progression.

A total of [redacted] ([redacted]%) patients in the cemiplimab arm of EMPOWER-Lung 3 received extended on-study cemiplimab treatment beyond radiological disease progression, with a mean time between progression and treatment discontinuation of [redacted] months. This extended 1L treatment following progression is the major contributor to the greater time on treatment (ToT) vs. PFS observed for cemiplimab (hazard ratio [HR] = 1.17). Patients who did not receive extended 1L treatment post-progression (37.3% of the cohort), had a substantially shorter ToT vs. PFS (HR = 0.44 [95% CI

0.30, 0.63]). If the 62.7% of patients who received extended 1L cemiplimab treatment post-progression had instead discontinued upon progression (ToT vs. PFS HR = 1), the HR for the entire cohort would instead have been 0.79 (62.7% * 1 + 37.3% * 0.44). This HR is very similar to the 0.84 HR for ToT vs. PFS preferred by NICE committee for pembrolizumab.

Table 17: Protocol-specified treatment continuation in EMPOWER-Lung 3, KEYNOTE-407 and KEYNOTE-189

Trial	Protocol wording	Number (%) of patients who received treatment beyond progression
EMPOWER-3	Patients in treatment Arm B who experienced RECIST 1.1-defined progressive disease on anti-PD-1 antibody therapy could continue treatment if the investigator judged the patient to be experiencing clinical benefit and if the patient had not completed the 108-week treatment period.	[redacted] (18)
KEYNOTE 407	Subjects who received pembrolizumab, but were deemed to be benefiting clinically despite progression, were able to receive open-label pembrolizumab monotherapy to complete a total of 35 treatments	21/278† (8%) (19)
KEYNOTE 189	Subjects who received pembrolizumab in combination with chemotherapy, but were deemed to be benefiting clinically despite progression, were able to receive open-label pembrolizumab monotherapy to complete a total of 35 treatments	11/410†† (3%) (14)

†May include patients who received a second course of pembrolizumab.

††Total proportions receiving pembrolizumab post-progression were not reported. Based on counts receiving continuous pembrolizumab post-progression from Figure 2 in Garassino et al., 2023 (14), which only included patients who received at least 35 cycles of treatment.

Sources: EMPOWER-Lung 3 protocol, available in supplementary material to Gogishvili et al, 2022 (20); KEYNOTE-407 protocol, available in supplementary material to Paz-Ares et al 2018 (19); KEYNOTE-189 protocol, available in supplementary material to Gandhi et al 2018 (21)

Unlike with, for example, targeted EGFR NSCLC therapies where continuing extended 1L treatment beyond radiological disease progression is permitted by contemporary evidence-based guidelines including ESMO, continuation of extended 1L IO treatment in oncogene-negative patients following progression remains controversial. Notably, ESMO guidelines (22, 23):

- **continue to advocate use of RECIST v1.1** to evaluate response to PD-1/PD-L1 inhibitors

- highlight that pseudoprogression (the initial apparent worsening of the tumour prior to eventual improvement) is "***not often observed in NSCLC***" (reported in ≤5% of patients (24, 25))
- state that continued treatment with PD-1/PD-L1 inhibitors should "***not be considered for people with progressive disease"***

As suggested in the company submission, rather than due to evidence that continuing 1L IO treatment beyond radiological disease progression leads to improved outcomes in this patient group, the relatively high proportion of patients receiving cemiplimab in EMPOWER-Lung 3 after progression due to the previously described protocol criteria may because most people did not have access to subsequent, off-study 2L IO treatments in the locations the study was conducted.

As shown in Figure 8 (above) a proportion of patients in the KEYNOTE studies also received continued on-study pembrolizumab treatment following progressive disease, but in smaller numbers than in the EMPOWER-Lung 3 study. Conversely, 25.4% (14) and 11.9% (15) of patients in the pembrolizumab + chemotherapy arms of the KEYNOTE-189 and KEYNOTE-407 studies, respectively, received subsequent 2L post-progression IO, compared with only 1.0% of patients in EMPOWER-Lung 3.

Should NICE committee take the view that continued 1L IO treatment beyond disease progression may have impacted OS outcomes, then it follows that any IO use post-progression should be captured in the economic model, whether that is continued initial 1L treatment or alternative 2L subsequent treatment.

2.4 Topic 2 cost-effectiveness analysis results

Given the clarification provided in section 2.2 regarding maximum treatment duration/number of cemiplimab doses received by patients in EMPOWER-Lung 3, the similar observation in the KEYNOTE studies where some patients are reported to have remained on treatment beyond the 2 years specified in the protocols (Figure 8) and the lack of treatment beyond progression in UK clinical practice, we consider it more appropriate to adopt the same approach to modelling time on treatment for both pembrolizumab and cemiplimab, as per our company base case (PFS = ToT), but with the minor amendment to the maximum number of treatment cycles described in section 2.2.

Conversely, should an approach be adopted that models the observed use of IO post-progression, then this should include all IO use post-progression (both initial treatment and subsequent IOs). We therefore include a scenario whereby the EAG's preferred ToT assumptions are applied (ToT vs. PFS HR 1.17 and 0.84, for cemiplimab and pembrolizumab, respectively) but the cemiplimab post-progression IO use is reweighted for the pembrolizumab + chemo arm of the model to sum to the total usage observed in the KEYNOTE studies (Table 18).

While we acknowledge the committee's preference to use the actual Kaplan-Meier (KM) curve for ToT in the cemiplimab arm of the model, the extensive additional analyses conducted in this response, which incorporate adjusted cemiplimab + chemotherapy data, preclude using the ToT KM for these scenarios. Furthermore, given that the KEYNOTE ToT data are subject to the same issues as cemiplimab (treatment beyond 108 weeks; treatment beyond progression), we consider the use of HRs applied to trial PFS curves to be a less biased approach for modelling ToT given the absence of equivalent ToT KM data for pembrolizumab + chemotherapy.

Table 18: Proportions assigned subsequent IO in model scenario

	EMPOWER-Lung 3 **Applied to cemiplimab arm**	**KEYNOTE-189 (N = 410)**	**KEYNOTE-407 (N = 278)**	**KEYNOTES (weighted average)** **Applied to pembrolizumab arm**
Total proportions receiving IO post-progression	**1.0%**	**25.4%**	**11.9%**	**19.9%**
Pembrolizumab	0.6%	16.9%	7.9%	13.3%
Atezolizumab	0.3%	8.5%	4.0%	6.6%

The results of these additional scenarios are shown below.

Table 19: Cost-effectiveness results incorporating updated stopping rules and IO treatment assumptions

Intervention	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER	NHB @£20,000 /QALY
Original company base case approach (ie, NMA) + updated eMIT prices (see Table 16 **for comparison with original company base case)**								
Cemiplimab + CT	[redacted]	3.2571	[redacted]	[redacted]	0.33	[redacted]	Dominant	2.9717
Pembrolizumab + CT	126,199	2.9308	2.1494	-	-	-	-	-
Original company base case approach (ie, NMA) + updated stopping rule + updated eMIT prices								
Cemiplimab + CT	[redacted]	3.2571	[redacted]	[redacted]	0.33	[redacted]	Dominant	3.0072
Pembrolizumab + CT	127,522	2.9308	2.1494	-	-	-	-	-
Original company base case approach (ie, NMA) + updated stopping rule + updated eMIT prices + ToT vs. PFS HR = 1.17 for cemiplimab + CT and 0.84 for pembrolizumab + CT; Post-progression IO stratified by model arm								
Cemiplimab + CT	[redacted]	3.2571	[redacted]	[redacted]	0.33	[redacted]	Dominant	2.7746
Pembrolizumab + CT	126,855	2.9308	2.1494	-	-	-	-	-
Alternative company base-case approach (MAIC) + ToT = PFS + updated stopping rule + updated eMIT prices								
Cemiplimab + CT	[redacted]	4.3989	[redacted]	[redacted]	1.19	[redacted]	Dominant	3.1518
Pembrolizumab + CT	127,408	3.2094	2.3524	-	-	-	-	-
Alternative company base-case approach (MAIC) + ToT = PFS + updated stopping rule + updated eMIT prices + OS assumed equal								
Cemiplimab + CT	[redacted]	3.2094	[redacted]	[redacted]	0.00	[redacted]	Dominant	2.7439
Pembrolizumab + CT	127,408	3.2094	2.3524	-	-	-	-	-
Alternative company base-case approach (MAIC) + updated stopping rule + updated eMIT prices ToT vs. PFS HR = 1.17 for cemiplimab + CT and 0.84 for pembrolizumab + CT; Post-progression IO stratified by model arm								

Cemiplimab + CT	[redacted]	4.3989	[redacted]	[redacted]	1.19	[redacted]	Dominant	2.9027
Pembrolizumab + CT	126,441	3.2094	2.3524	-	-	-	-	-

CT, chemotherapy; eMIT Drugs and pharmaceutical electronic market information tool; ICER, incremental cost-effectiveness ratio; LY, life years; MAIC, matching-adjusted indirect comparison; NHB, net health benefit, NMA, network-meta-analysis; QALYs, quality-adjusted life years

Topic 3 Duration of treatment benefit

Gradual treatment waning

"For the cost-effectiveness analysis, the committee preferred assuming a gradual waning of treatment effect for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy treatment waning, rather than an immediate waning of treatment effect" (DGD section 3.14)

Onset and duration of waning effect

- "*The committee requested further justification from the company to support a 5-year waning time point, including analysis of 5-year data from KEYNOTE-189 and KEYNOTE-407. For example, estimates of the hazards over time from the longer-term data from the KEYNOTE-189 and KEYNOTE-407 trials compared with the modelled hazards*" (DGD section 3.15)
- *"further evidence to support a 5-year waning time point based on data specifically for cemiplimab plus chemotherapy*" (DGD section 3.15)

3.1 Gradual treatment waning

We agree with and have implemented a gradual/linear treatment waning effect in the revised company base-case analysis for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy as per the committee's preference.

3.2 Evidence to support onset and duration of waning effect

We have found no evidence that waning effect has been initiated from 2 years in any technology appraisal of an IO. A recent review of treatment effect waning assumptions in IO health technology assessments found that effect waning, whether gradual or immediate, typically started between 3 and 5 years (20).

We acknowledge the committee's request to show how the treatment effect changed over the follow-up period in the KEYNOTE studies, but note that both studies were subject to crossover to the pembrolizumab + chemotherapy arm (for which we have attempted to adjust for in our updated analyses in Topic 3). Crossover-adjusted KEYNOTE-407 data are not available for the extended follow-up. Thus, any analysis of treatment effect waning over time may not be applicable to cemiplimab.

However, Figure 10 and Figure 11 below present the discrete hazards over time from the model compared to hazards from KN-189 and KN-407. They suggest that waning of cemiplimab + chemotherapy and pembrolizumab + chemotherapy hazards to chemotherapy hazards from 24-60 months is a conservative assumption compared to KEYNOTE-189 and KEYNOTE-407 data, which show hazards decreasing up to end of follow-up for PFS and OS.

Figure 10: Comparison of OS hazard rates over time for modelled cemiplimab + chemotherapy, pembrolizumab + chemotherapy and chemotherapy alone vs. observed KEYNOTE studies

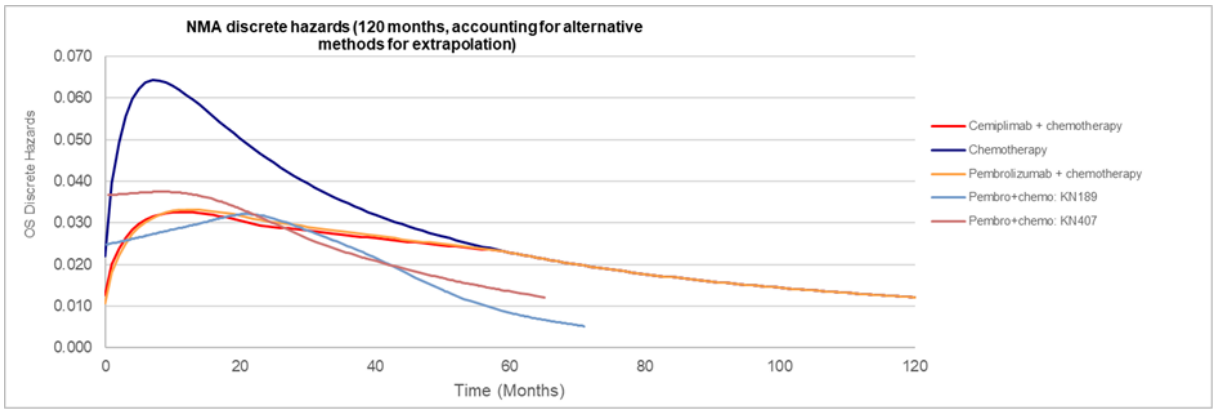
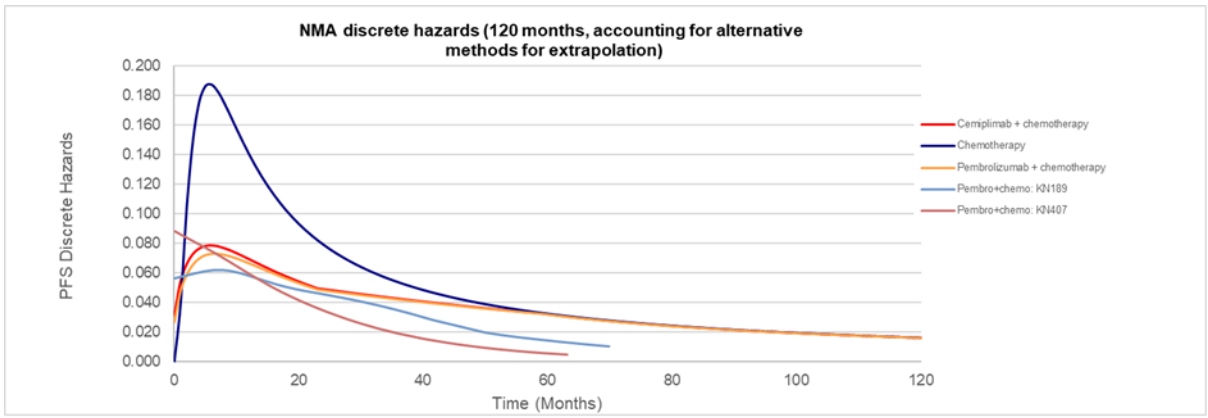


Figure 11: Comparison of PFS hazard rates over time for modelled cemiplimab + chemotherapy, pembrolizumab + chemotherapy and chemotherapy alone vs. observed KEYNOTE studies



Whilst it is not feasible to provide additional evidence specifically for cemiplimab + chemotherapy given the ethical early stopping of EMPOWER-Lung 3, long-term follow-up data from the EMPOWER-Lung 1 study (cemiplimab monotherapy versus

chemotherapy for people with advanced/metastatic NSCLC with PD-L1 ≥50%) are available. At the 5-year follow-up, cemiplimab monotherapy continued to show durable clinically meaningful OS and PFS benefits versus chemotherapy (26). Five-year OS rates were nearly twice with cemiplimab vs chemotherapy (26.1 months vs 13.3 months; HR 0.59, 95% CI 0.48-0.72, P<0.0001). This suggests the assumption of treatment benefit for cemiplimab + chemotherapy (including gradual linear waning) lasting for up to 5 years from the start of treatment is reasonable. This approach is supported by clinical expert feedback that longer-term data from the KEYNOTE RCTs is appropriate for informing assumptions about long-term effects of cemiplimab + chemotherapy in the absence of direct evidence. We have therefore assumed a gradual linear treatment waning effect that **starts at 3 years** and **finishes at 5 years** for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy.

"…*advisors would be happy to assume that treatment benefit continues up to 5 years, and agreed that evidence on longer-term (e.g., 5-year) pembrolizumab + chemotherapy PFS/OS outcomes would be broadly generalizable to and appropriate for supporting assumptions about longer-term cemiplimab + chemotherapy PFS/OS outcomes*"
[page 13-14, Data on file – NSCLC advisory board report].

3.3 Topic 3 cost-effectiveness analysis results

The impact of these updates to the company base-case cost-effectiveness analysis is shown below.

Table 20: Cost-effectiveness results incorporating gradual treatment effect wane

Intervention	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER	NHB @£20,000 /QALY
Original company base case approach (ie, NMA) + updated eMIT prices (see Table 16 **for comparison with original company base case)**								
Cemiplimab + CT	[redacted]	3.2571	[redacted]	[redacted]	0.33	[redacted]	Dominant	2.9717
Pembrolizumab + CT	126,199	2.9308	2.1494	-	-	-	-	-

Original company base case approach (ie, NMA) + Treatment effect waning between 3-5 years + updated eMIT prices								
Cemiplimab + CT	[redacted]	3.1905	[redacted]	[redacted]	0.30	[redacted]	Dominant	2.9617
Pembrolizumab + CT	126,023	2.8949	2.1232	-	-	-	-	-
Original company base case approach (ie, NMA) + Updated stopping rule + Treatment effect waning between 3-5 years + updated eMIT prices								
Cemiplimab + CT	[redacted]	3.1905	[redacted]	[redacted]	0.30	[redacted]	Dominant	2.9972
Pembrolizumab + CT	127,346	2.8949	2.1232	-	-	-	-	-
Alternative company base-case approach (MAIC) + Updated stopping rule + Treatment effect waning between 3-5 years + updated eMIT prices								
Cemiplimab + CT	[redacted]	4.1228	[redacted]	[redacted]	1.04	[redacted]	Dominant	3.1009
Pembrolizumab + CT	126,704	3.0807	2.2597	-	-	-	-	-
Original company base case approach (ie, NMA) + Updated stopping rule + updated eMIT prices + ToT vs. PFS HR = 1.17 for cemiplimab + CT and 0.84 for pembrolizumab + CT + Post-progression IO stratified by model arm + Treatment effect waning between 3-5 years								
Cemiplimab + CT	[redacted]	3.1905	[redacted]	[redacted]	0.2957	[redacted]	Dominant	2.7660
Pembrolizumab + CT	126,699	2.8949	2.1232	-	-	-	-	-
Alternative company base-case approach (MAIC) + updated stopping rule + updated eMIT prices + ToT vs. PFS HR = 1.17 for cemiplimab + CT and 0.84 for pembrolizumab + CT + Post-progression IO stratified by model arm + Treatment effect waning between 3-5 years								
Cemiplimab + CT	[redacted]	4.1228	[redacted]	[redacted]	1.0421	[redacted]	Dominant	2.8565
Pembrolizumab + CT	125,815	3.0807	2.2597	-	-	-	-	-

CT, chemotherapy; eMIT Drugs and pharmaceutical electronic market information tool; ICER, incremental cost-effectiveness ratio; LY, life years; MAIC, matching-adjusted indirect comparison; NHB, net health benefit, NMA, network-meta-analysis; QALYs, quality-adjusted life years

Topic 4 Chemotherapy distributions

Generalizability of investigator's choice EMPOWER-Lung 3 chemotherapy distributions to UK clinical practice

- *"The committee noted the high level of uncertainty about the proportion of people with non-squamous NSCLC who would have cemiplimab without pemetrexed in clinical practice, and if EMPOWER-Lung 3 reflected this." (DGD section 3.13)*
- "*The committee noted that in EMPOWER-Lung 3, most people with non-squamous NSCLC had a chemotherapy regimen with pemetrexed. It thought that this may suggest that most people in clinical practice with non-squamous NSCLC having cemiplimab would have a chemotherapy regimen with pemetrexed (DGD section 3.17)*
- *The committee also noted that for people with non-squamous NSCLC for whom pemetrexed is unsuitable, pembrolizumab plus chemotherapy would not be an appropriate comparator. But, it had not seen cost-effectiveness evidence in this population for any comparison other than cemiplimab plus chemotherapy compared with pembrolizumab plus chemotherapy.*

As described in the company submission, the EMPOWER-Lung 3 study also allowed use of a pemetrexed-free regimen (paclitaxel + carboplatin) in patients with non-squamous histology. Approximately one-fifth (22%) of non-squamous patients in the cemiplimab + chemotherapy group received a pemetrexed-free regimen (27).

Clinical expert feedback provided to Regeneron to date has been consistently that there is substantial heterogeneity across England and Wales at a patient population level (e.g., diverse population characteristics, needs, and preferences), a centre level (e.g., resource availability and considerations on Q3W vs Q6W dosing available with pembrolizumab, as highlighted by the committee in the DGD), and individual clinician level. It is not therefore possible to suggest a precise estimate of the proportion of patients who would receive cemiplimab without pemetrexed in clinical practice and what their characteristics would be. Similarly, it is not possible to define a subpopulation of patients who are currently given chemotherapy alone (rather than in combination with IO) purely because they cannot receive pemetrexed. It follows that

a cost-effectiveness analysis in this subpopulation (a subgroup of a subgroup of NSCLC patients) would also not be possible. However, we would anticipate that this group is likely to be modest.

Furthermore, pemetrexed is associated with significant toxicity and as acknowledged in the DGD, may not be the preferred chemotherapy agent for all people with non-squamous disease, even where there are no clear contraindications. Clinical expert feedback to Regeneron has also been that the option to use an alternative to a pemetrexed-based regimen (e.g. paclitaxel and carboplatin) alongside an IO in people with non-squamous disease would facilitate them to better tailor chemotherapy treatment to the complex and diverse needs of individual patients they treat. As detailed in our evidence submission, post-hoc exploratory analyses were conducted to evaluate selected AEs reported for patients with non-squamous histology who received pemetrexed vs paclitaxel-containing regimens in EMPOWER-Lung 3 (Table 27). While acknowledging the limitations of such analyses, **the data suggest the two treatments have a distinct AE profile that will allow clinicians to choose between them based on the comorbidity profile of their patients.**

Even if use of cemiplimab without pemetrexed in the NHS is higher than that in the EMPOWER-Lung 3 RCT, the total per patient costs of the pemetrexed-based regimens excluding maintenance is higher (by £61.56) than paclitaxel-based regimens (Table 21). In EMPOWER-Lung 3, [redacted] of patients who received pemetrexed-based regimens received pemetrexed maintenance treatment. The total cost of treatment with cemiplimab + pemetrexed, assuming 25% of patients receiving pemetrexed go on to receive pemetrexed maintenance, is £394.44 higher per patient compared with cemiplimab + paclitaxel. As a reminder, this cost saving for cemiplimab + chemotherapy is not currently reflected in the economic model, which assumes the KEYNOTE chemotherapy distributions in both comparator arms.

In short, unlike with NHS England commissioning policy for pembrolizumab + chemotherapy which permits only regimens including pemetrexed for people with non-squamous disease, it is anticipated that availability of cemiplimab would enable clinicians to use an alternative to pemetrexed in appropriate patients for whom it would be more suitable.

Table 21: Cost of paclitaxel vs. pemetrexed-based regimens

Regimen	Chemo A monthly acquisition cost	Chemo B monthly acquisition cost	Total monthly cost	Total cost per patient receiving regimen
Cemiplimab + paclitaxel regimen	Paclitaxel: £63.91	Carboplatin: £67.19	Acquisition: £131.11 Administration: £207.97 Total: £339.08	Acquisition: £393.11 Administration: £623.91 Total: £1,017.23
Cemiplimab + pemetrexed regimen (no maintenance pemetrexed)	Pemetrexed: £84.43	Carboplatin: £67.19	Acquisition: £151.63 Administration: £207.97 Total: £359.60	Acquisition: £454.88 Administration: £623.91 Total: £1,078.79 **(+ £61.56 vs cemiplimab + paclitaxel regimen)**
Cemiplimab + pemetrexed regimen (with 25% receiving maintenance pemetrexed)	Pemetrexed: £84.43	Carboplatin: £67.19	<u>In the first 3 months</u> Acquisition: £151.63 Administration: £207.97 Total: £359.60 <u>In subsequent months**</u> Acquisition: £21.11 Administration: £21.51 Total: £42.62	Acquisition: £619.73 Administration: £791.94 Total: £1,411.67 **(+ £394.44 vs cemiplimab + paclitaxel regimen**)

*Based on non-squamous EMPOWER-Lung 3 data from the cemiplimab + chemotherapy group
** Currently assuming a total of 47 weeks (10.81 months) of pemetrexed usage based on median duration of exposure from Baramidze et al. 2024 (28)

Topic 5 Adverse events

The committee preferred *"using the grade 3 and above adverse event rates from EMPOWER- Lung 3 and the KEYNOTE studies to model adverse event rates for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy, respectively" (DGD, section 3.14)*

As per the committee's preference, we have retained our base-case approach of using AE rates from EMPOWER-Lung 3 and the respective KEYNOTE studies. This assumption is included within all cost-effectiveness estimates in this response.

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Appendix A. Comparison of baseline characteristics and subgroup analysis in EMPOWER-Lung 3 and KEYNOTE 407/189

The following tables show the baseline distributions for the potential treatment effect modifiers identified in the TLR and by NICE in the DGD in the EMPOWER and KEYNOTE studies. As no baseline characteristics are available in the published literature for the PD-L1 ≥1% subgroups of the KEYNOTE-189 and 407 studies, an assumption had to made that the baseline distribution of those subgroups was similar to that of trial ITT populations. To investigate the likeliness of this assumption holding, Table 22 compares the baseline distribution of the PD-L1 ≥1% MHRA label population in EMPOWER-Lung 3 with that of the EMPOWER-Lung 3 ITT population. It is evident from this comparison that it is feasible and likely that baseline characteristics of the PD-L1 ≥1% subgroups from the KEYNOTE studies will also closely resemble those of their respective ITT population.

Table 22 Baseline distributions for potential treatment effect modifiers in EMPOWER-Lung 3

Characteristic	EMPOWER-Lung 3 – ITT population			EMPOWER-Lung 3 – MHRA label population (PD-L1 ≥1%)		
	Cemiplimab + chemo (n = 312)	Placebo + chemo (n = 154)	Total (n = 466)	Cemiplimab + chemo (n = 217)	Placebo + chemo (n = 110)	Total (n = 327)
Age (Years)						
≥65 years, n (%)	128 (41.0)	60 (39.0)	188 (40.3)	88 (40.6)	36 (32.7)	124 (37.9)
Sex, n (%)						
Female	44 (14.1)	31 (20.1)	75 (16.1)	32 (14.7)	22 (20.0)	54 (16.5%)
Male	268 (85.9)	123 (79.9)	391 (83.9)	185 (85.3)	88 (80.0)	273 (83.5)
Smoking status, n (%)						
Current or past smoker	269 (86.2)	130 (84.4)	399 (85.6)	186 (85.7)	93 (84.5)	279 (85.3)
Never smoker	43 (13.8)	24 (15.6)	67 (14.4)	31 (14.3)	17 (15.5)	48 (14.7)
PD-L1 expression, n (%						
<1%	95 (30.4)	44 (28.6)	139 (29.8)	N/A	N/A	N/A
1-49%	114 (36.5)	61 (39.6)	175 (37.6)	114 (52.5)	61 (55.5)	175 (53.5)
≥50%	103 (33.0)	103 (33.0)	152 (32.6)	103 (47.5)	49 (44.5)	152 (46.5)
ECOG PS, n (%)						
0	51 (16.3)	18 (11.7)	69 (14.8)	38 (17.5)	15 (13.6)	53 (16.2)
1	259 (83.0)	134 (87.0)	393 (84.3)	178 (82.0)	94 (85.5)	272 (83.2)
Missing	2 (0.6)	2 (1.3)	4 (0.9)	1 (0.5)	1 (0.9)	2 (0.6)
Cancer stage at diagnosis*, n (%)						
Metastatic	267 (85.6)	130 (84.4)	397 (85.2)	187 (86.2)	93 (84.5)	280 (85.6)
Locally advanced	45 (14.4)	24 (15.6)	69 (14.8)	30 (13.8)	17 (15.5)	47 (14.4)
Brain metastases, n (%)						
Yes	24 (7.7)	7 (4.5)	31 (6.7)	15 (6.9)	6 (5.5)	21 (6.4)
Location, n (%)						

Europe	270 (86.5)	138 (89.6)	408 (87.6)	187 (86.2)	101 (91.8)	288 (88.1)
Asia	42 (13.5)	16 (10.4)	58 (12.4)	30 (13.8)	9 (8.2)	39 (11.9)
Race, n (%)						
White	267 (85.6)	138 (89.6)	405 (86.9)	185 (85.3)	101 (91.8)	286 (87.5)
Asian	45 (14.4)	16 (10.4)	61 (13.1)	32 (14.7)	9 (8.2)	41 (12.5)
Harmonised TMB	NR	NR	NR	NR	NR	NR
SMARC A4	NR	NR	NR	NR	NR	NR

*Data are cancer stage at screening

PD-L1, programmed cell death ligand-1; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NR, not recorded; TMB, tumour mutational burden

Source: Gogishvili et al, 2022 (20); Libtayo EPAR, 2023 (29); Baramidze et al, 2024 (28)

Table 23 Baseline distributions for potential treatment effect modifiers among patients with squamous disease: EMPOWER-Lung 3 and KEYNOTE-407

Characteristic	EMPOWER-Lung 3 - Squamous			KEYNOTE 407		
	Cemiplimab + chemo (n = 95)	Placebo + chemo (n = 51)	Total (n = 146)	Pembrolizumab + chemo (n = 278)	Placebo + chemo (n = 281)	Total (n = 559)
Age (years)						
≥65 years, n (%)	39 (41.1)	17 (33.3)	56 (38.4)	151 (54.3)	154 (54.8)	305 (54.6)
Sex, n (%)						
Female	8 (8.4)	7 (13.7)	15 (10.3)	58 (20.9)	46 (16.4)	104 (18.6)
Male	87 (91.6)	44 (86.3)	131 (89.7)	220 (79.1)	235 (83.6)	455 (81.4)
Smoking status, n (%)						
Current or past smoker	85 (89.5)	44 (86.3)	129 (88.4)	256 (92.1)	262 (93.2)	518 (92.7)
Never smoker	10 (10.5)	7 (13.7)	17 (11.6)	22 (7.9)	19 (6.8)	41 (7.3)
PD-L1 expression, n (%)						
<1%	0	0	0	95 (34.2)	99 (35.2)	194 (34.7)
1-49	53 (55.8)	28 (54.9)	81 (55.5)	103 (37.1)	104 (37.0)	207 (37.0)

Characteristic	EMPOWER-Lung 3 - Squamous			KEYNOTE 407		
	Cemiplimab + chemo (n = 95)	Placebo + chemo (n = 51)	Total (n = 146)	Pembrolizumab + chemo (n = 278)	Placebo + chemo (n = 281)	Total (n = 559)
≥50%	42 (44.2)	23 (45.1)	65 (44.5)	73 (26.3)	73 (26.0)	146 (26.1)
ECOG PS, n (%)						
0	5 (5.3)	2 (3.9)	7 (4.8)	73 (26.3)	90 (32.0)	163 (21.2)
1	89 (93.7)	49 (96.1)	138 (94.5)	205 (73.7)	191 (68.0)	396 (70.8)
Missing	1 (1.0)	0	1 (0.7)	0	0	0
Cancer stage at diagnosis, n (%)						
Metastatic	79 (83.2)	41 (80.4)	120 (82.2)	278 (100)	281 (100)	559 (100)
Locally advanced	16 (16.8)	10 (19.6)	26 (17.8)	0	0	0
Brain metastases, n (%)						
Yes	1 (1.1)	0	1 (0.7)	20 (7.2)	24 (8.5)	44 (7.9)
Location, n (%)						
Europe	92 (96.8)	50 (98.0)	142 (97.2)	NR*	NR*	NR*
Asia	3 (3.2)	1 (2.0)	4 (2.7)	54 (19.4)	52 (18.5)	106 (19.0)
Rest of World	0	0	0	224 (80.6)	229 (81.5)	453 (81.0)
Race, n (%)						
White	90 (94.7)	50 (98.0)	140 (95.9)	NR	NR	NR
Asian	5 (5.3)	1 (2.0)	6 (4.1)			
Harmonised TMB	NR	NR	NR	NR	NR	NR
SMARC A4	NR	NR	NR	NR	NR	NR

*KEYNOTE-407 included sites in Europe, but the number of European patients is not reported separately; these patients are included under 'Rest of World'

PD-L1, programmed cell death ligand-1; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NR, not recorded; TMB, tumour mutational burden

Source: Regeneron data on file, 2024 (30); Paz-Ares et al, 2018 (19)

Table 24 Baseline values for potential treatment effect modifiers among patients with non-squamous disease: EMPOWER-Lung 3 and KEYNOTE-189

Characteristic	Non-squamous histology					
	EMPOWER-Lung 3			KEYNOTE-189		
	Cemiplimab + chemo (n = 122)	Placebo + chemo (n = 59)	Total (n = 181)	Pembrolizumab + chemo (n = 410)	Placebo + chemo (n = 206)	Total (n = 616)
Age (years)						
≥65 years, n (%)	49 (40.1)	19 (32.2)	68 (37.6)	213 (52.0)	91 (44.2)	304 (49.4)
Sex, n (%)						
Female	24 (19.7)	15 (25.4)	39 (21.5)	156 (38.0)	97 (47.1)	253 (41.1)
Male	98 (80.3)	44 (74.6)	142 (78.5)	254 (62.0)	109 (52.9)	363 ((58.9)
Smoking status, n (%)						
Current or past smoker	101 (82.8)	49 (83.1)	150 (82.9)	362 (88.3)	181 (87.9)	543 (88.1)
Never smoker	21 (17.2)	10 (16.9)	31 (17.1)	48 (11.7)	25 (12.1)	73 (11.9)
PD-L1 expression, n (%)						
<1%	0	0	0	127 (31.0)	63 (30.6)	190 (30.8)
1-49%	61 (50.0)	33 (55.9)	94 (51.9)	128 (31.2)	58 (28.2)	186 (30.2)
≥50%	61 (50.0)	26 (44.1)	87 (48.1)	132 (32.2)	70 (34.0)	202 (32.8)
ECOG PS, n (%)						
0	33 (27.0)	13 (22.0)	46 (25.4)	186 (45.4)	80 (38.8)	266 (43.2)
1	89 (73.0)	45 (76.3)	134 (74.0)	221 (53.9)	125 (60.7)	346 (56.2)
2	0	0	0	1 (0.2)	0	1 (0.2)
Missing	0	1 (1.7)	1 (0.6)	2 (0.5)	1 (0.5)	3 (0.5)
Cancer stage at diagnosis, n (%)						
Metastatic	108 (88.5)	52 (88.1)	160 (88.4)	410 (100)	206 (100)	616 (100)
Locally advanced	14 (11.5)	7 (11.9)	21 (11.6)	0	0	0

Characteristic	Non-squamous histology					
	EMPOWER-Lung 3			KEYNOTE-189		
	Cemiplimab + chemo (n = 122)	Placebo + chemo (n = 59)	Total (n = 181)	Pembrolizumab + chemo (n = 410)	Placebo + chemo (n = 206)	Total (n = 616)
Brain metastases, n (%)						
Yes	14 (11.5)	6 (10.2)	20 (11.0)	73 (17.8)	35 (17.0)	108 (17.5)
Location						
Europe	95 (77.9)	51 (86.4)	146 (80.7)	243 (59.3)	131 (63.6)	374 (60.7)
North America	0	0	0	111 (27.1)	46 (22.3)	157 (25.5)
Asia	27 (22.1)	8 (13.6)	35 (19.3)	4 (1.0)	6 (2.9)	10 (1.6)
Other region	0	0	0	52 (12.7)	23 (11.2)	75 (12.2)
Race, n (%)						
White	95 (77.9)	51 (86.4)	146 (80.7)	NR	NR	NR
Asian	27 (22.1)	8 (13.6)	35 (19.3)			
Harmonised TMB	NR	NR	NR	NR	NR	NR
SMARC A4	NR	NR	NR	NR	NR	NR

PD-L1, programmed cell death ligand-1; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NR, not recorded; TMB, tumour mutational burden

Source: Regeneron data on file, 2024 (30); Gandhi et al, 2018 (21)

Appendix B. Results of prespecified subgroup analyses from EMPOWER-Lung 3, KEYNOTE-189 and KEYNOTE-407

Table 25: Trial subgroup analyses: overall survival

Characteristic*	EMPOWER-Lung 3 – ITT population Events/patients HR (95% CI)	KEYNOTE-189 Events/patients HR (95% CI)	KEYNOTE-407 Events/patients HR (95% CI)
Overall survival			
Age			
<65 years	170/278 **0.53 (0.39-0.72)**	133/312 0.43 (0.31-0.61)	88/254 0.52 (0.34-0.80)
≥65 years	121/188 **0.81 (0.55-1.18)**	102/304 **0.64 (0.43-0.95)**	117/305 0.74 (0.51-1.07)
Sex†			
Female	44/75 **0.98 (0.54-1.78)**	92/253 0.29 (0.19-0.44)	38/104 **0.42 (0.22-0.81)**
Male	247/391 0.55 (0.42-0.71)	143/363 **0.70 (0.50-0.99)**	67/455 0.69 (0.51-0.94)
Smoking status			
Current or past smoker	251/399 0.58 (0.45-0.75)	211/543 0.54 (0.41-0.71)	NR NR
Never smoker	40/67 **0.85 (0.45-1.62)**	24/73 **0.23 (0.10-0.54)**	NR NR
PD-L1 expression			
<1%	100/139 **0.94 (0.62-1.42)‡**	84/190 0.59 (0.38-0.92)	73/194 0.61 (0.38-0.98)

Characteristic*	EMPOWER-Lung 3 – ITT population Events/patients HR (95% CI)	KEYNOTE-189 Events/patients HR (95% CI)	KEYNOTE-407 Events/patients HR (95% CI)
1-49%	105/205 0.50 (0.34-0.74)	65/186 0.55 (0.34-0.90)	76/207 0.57 (0.36-0.90)
≥50%	86/152 0.56 (0.36-0.86)	70/202 0.42 (0.26-0.68)	53/146 0.64 (0.37-1.10)
ECOG PS			
0	19/69 0.24 (0.12-0.51)	74/266 0.44 (0.28-0.71)	48/163 0.54 (0.29-0.98)
1	259/393 **0.70 (0.54-0.90)**	159/346 0.53 (0.39-0.73)	157/396 0.66 (0.48-0.90)
Cancer stage at diagnosis			
Metastatic	252/397 0.64 (0.49-0.83)	N/A	N/A
Locally advanced	39/69 0.50 (0.27-0.95)	N/A	N/A
Brain metastases at baseline			
Yes	19/31 **0.29 (0.11-0.75)**	51/108 **0.36 (0.20-0.62)**	NR
No	272/435 0.62 (0.51-0.83)	184/508 0.53 (0.39-0.71)	NR
Location			
Europe	259/408 0.61 (0.48-0.79)	NR	N/A
Asia	32/58 0.78 (0.36-1.69)	NR	34/106 0.44 (0.22-0.89)
Rest of World	N/A	NR	171/453

Characteristic*	EMPOWER-Lung 3 – ITT population Events/patients HR (95% CI)	KEYNOTE-189 Events/patients HR (95% CI)	KEYNOTE-407 Events/patients HR (95% CI)
	N/A		0.69 (0.51-0.93)
Race			
White	257/405 0.61 (0.47-0.78)	NR	NR
Non-white	34/61 **0.81 (0.38-1.74)**	NR	NR

EMPOWER-Lung 3 data are taken from the published 2-year follow-up. Subgroup analyses are not available in the 2-year follow-up publications for the KEYNOTE studies, so data are taken from the primary publications. **Bold** text indicates a subgroup where the point estimate is outside the CIs of its counterpart

*Identified in the TLR: age, sex, smoking, PD-L1; identified by NICE: age, smoking, performance status, PD-L1, disease stage, location. †Correlates with smoking status: rates of non-smoking associated lung cancer are higher among females than males (31). ‡versus PD-L1 1-49% and PD-L1 ≥50%.

PD-L1, programmed cell death ligand-1; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NR, not recorded; TLR, targeted literature review; TMB, tumour mutational burden

Source: Makharadze et al, 2023 (32); Gandhi et al, 2018 (21); Paz-Ares et al, 2018 (19)

Table 26: Trial subgroup analyses: progression-free survival

Characteristic	EMPOWER-Lung 3 – ITT population Events/patients HR (95% CI)	KEYNOTE-189 ITT population Events/patients HR (95% CI)	KEYNOTE-407 ITT population Events/patients HR (95% CI)
Progression-free survival			
Age			
<65 years	218/278 0.50 (0.38-0.66)	224/312 **0.43 (0.32-0.56)**	162/254 0.50 (0.37-0.69)
≥65 years	149/188 0.60 (0.42-0.85)	186/304 **0.75 (0.55-1.02)**	187/305 0.63 (0.47-0.84)
Sex†			

Characteristic	EMPOWER-Lung 3 – ITT population Events/patients HR (95% CI)	KEYNOTE-189 ITT population Events/patients HR (95% CI)	KEYNOTE-407 ITT population Events/patients HR (95% CI)
Female	57/75 **0.71 (0.42-1.20)**	174/253 **0.40 (0.29-0.54)**	65/104 0.49 (0.30-0.81)
Male	310/391 0.48 (0.38-0.62)	236/363 **0.66 (0.50-0.87)**	284/455 0.58 (0.46-0.73)
Smoking status			
Current or past smoker	318/399 0.52 (0.41-0.66)	365/543 0.49 (0.35-0.68)	NR
Never smoker	49/67 0.66 (0.37-1.17)	45/73 0.43 (0.23-0.81)	NR
PD-L1 expression			
<1%	116/139 **0.73 (0.50-1.08)‡**	146/190 0.75 (0.53-1.05)	122/194 0.68 (0.47-0.98)
1-49%	142/175 0.48 (0.34-0.68)	114/186 **0.55 (0.37-0.81)§**	127/207 0.56 (0.39-0.80)
≥50%	109/152 0.48 (0.32-0.72)	124/202 **0.36 (0.25-0.52)‖**	94/146 **0.37 (0.24-0.58)¶**
ECOG PS			
0	43/69 **0.20 (0.10-0.42)**	158/266 0.49 (0.35-0.68)	96/163 **0.45 (0.29-0.68)**
1	320/393 **0.60 (0.48-0.76)**	250/346 0.56 (0.43-0.72)	253/396 0.61 (0.48-0.78)
Cancer stage at diagnosis			
Metastatic	314/397 0.52 (0.41-0.66)	N/A	N/A

Characteristic	EMPOWER-Lung 3 – ITT population Events/patients HR (95% CI)	KEYNOTE-189 ITT population Events/patients HR (95% CI)	KEYNOTE-407 ITT population Events/patients HR (95% CI)
Locally advanced	53/69 **0.34 (0.19-0.61)**	N/A	N/A
Brain metastases at baseline			
Yes	25/31 0.61 (0.25-1.48)	81/108 0.42 (0.26-0.68)	NR
No	342/435 0.54 (0.43-0.70)	329/508 0.53 (0.43-0.67)	NR
Location			
Europe	330/408 0.55 (0.44-0.70)	NR	N/A
Asia	37/58 0.54 (0.43-0.70)	NR	61/106 0.49 (0.30-0.82)
Rest of World	N/A	NR	288/453 0.58 (0.46-0.73)
Race			
White	327/405 0.55 (0.44-0.69)	NR	NR
Non-white	40/61 0.53 (0.28-1.02)	NR	NR
Harmonised TMB	NR	NR	NR
SMARCA4	NR	NR	NR

EMPOWER-Lung 3 data are taken from the published 2-year follow-up. Subgroup analyses are not available in the 2-year follow-up publications for the KEYNOTE studies, so data are taken from the primary publications. **Bold** text indicates a subgroup where the point estimate is outside the CIs of its counterpart

*Identified in the TLR: age, sex, smoking, harmonised TMB, SMARCA4, PD-L1; identified by NICE: age, smoking, performance status, PD-L1, disease stage, location. †Correlates with smoking status: rates of non-smoking associated lung cancer are higher among females than males (31). ‡versus PD-L1 1-49% and PD-L1 ≥50%. §versus PD-L1 ≥50%. ‖versus PD-L1 1-49%. ¶versus PD-L1 ≤1% and PD-L1 1-49%

PD-L1, programmed cell death ligand-1; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NR, not recorded; TLR, targeted literature review; TMB, tumour mutational burden
Source: Makharadze et al, 2023 (32); Gandhi et al, 2018 (21); Paz-Ares et al, 2018 (19)

Appendix C. Adverse event profile of paclitaxel versus pemetrexed-based chemotherapy regimens

Table 27 TEAEs: pemetrexed and paclitaxel (non-squamous histology)

Event, n (%) of patients	Pemetrexed (n = 114)		Paclitaxel (n = 39)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TEAE	110 (96.5)	75 (65.8)	36 (92.3)	17 (43.6)
TEAEs in ≥10% of patients (either group)				
Blood and lymphatic system disorders	80 (70.2%)	33 (28.9%)	24 (61.5%)	5 (12.8%)
Anaemia	70 (61.4%)	26 (22.8%)	16 (41.0%)	1 (2.6%)
Neutropenia	21 (18.4%)	11 (9.6%)	5 (12.8%)	3 (7.7%)
Thrombocytopenia	17 (14.9%)	7 (6.1%)	6 (15.4%)	0
Investigations	69 (60.5%)	21 (18.4%)	20 (51.3%)	3 (7.7%)
ALT increased	20 (17.5%)	4 (3.5%)	11 (28.2%)	2 (5.1%)
Weight decreased	22 (19.3%)	3 (2.6%)	6 (15.4%)	0
AST increased	18 (15.8%)	1 (0.9%)	8 (20.5%)	0
WBC count decreased	21 (18.4%)	9 (7.9%)	0	0
Blood creatinine increased	14 (12.3%)	1 (0.9%)	2 (5.1%)	0
Blood alkaline phosphatase increased	4 (3.5%)	0	7 (17.9%)	0
Amylase increased	4 (3.5%)	1 (0.9%)	5 (12.8%)	1 (2.6%)

Event, n (%) of patients	Pemetrexed (n = 114)		Paclitaxel (n = 39)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Skin and subcutaneous tissue disorders	31(27.2%)	0	26 (66.7%)	0
Alopecia	6 (5.3%)	0	24 (61.5%)	0
Rash	13 (11.4%)	0	0	0
Musculoskeletal and connective tissue disorders	35 (30.7%)	2 (1.8%)	9 (23.1%)	1 (2.6%)
Arthralgia	16 (14.0%)	0	4 (10.3%)	0
Nervous system disorders	29 (25.4%)	3 (2.6%)	15 (38.5%)	0
Headache	5 (4.4%)	0	4 (10.3%)	0
Neuropathy peripheral	3 (2.6%)	0	4 (10.3%)	0
Infections and infestations	36 (31.6%)	11 (9.6%)	4 (10.3%)	1 (2.6%)
Pneumonia	14 (12.3%)	5 (4.4%)	2 (5.1%)	1 (2.6%)
Vascular disorders	16 (14.0%)	5 (4.4%)	5 (12.8%)	1 (2.6%)
Cardiac disorders	17 (14.9%)	5 (4.4%)	0	0
Psychiatric disorders	13 (11.4%)	0	4 (10.3%)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; WBC, white blood cell
Source: Rosen et al, 2025 (27)

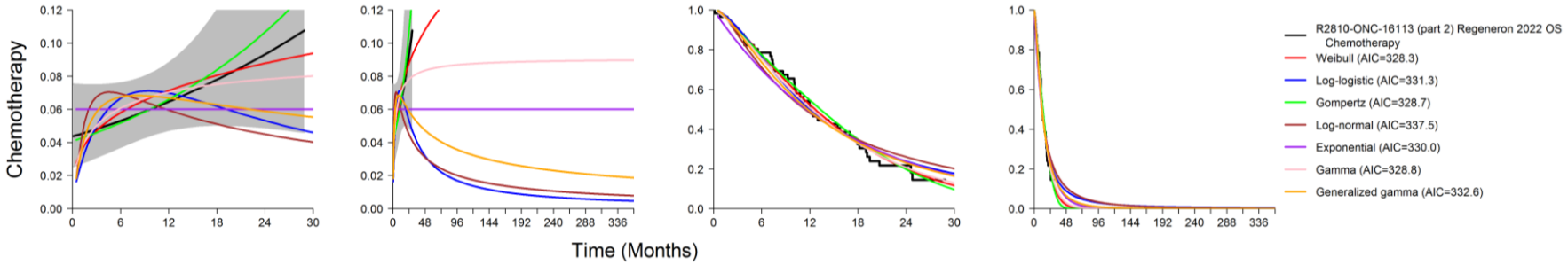
Appendix D. Goodness of fit of parametric survival functions to EMPOWER-Lung 3 PD-L1 ≥ histology subgroups, chemotherapy arm

Table 28: Statistical goodness of fit criteria

	OS				PFS			
	Non-squamous		Squamous		Non-squamous		Squamous	
	AIC	BIC	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	330.0182	332.0957	274.1927	276.1245	307.1147	309.1922	264.0397	265.9715
Weibull	328.2799	332.435	276.1211	279.9848	303.9598	308.1149	265.1123	268.976
Gompertz	328.6816	332.8367	276.1797	280.0433	308.1816	312.3367	265.3258	269.1894
Gamma	328.7859	332.941	276.0385	279.9021	302.5789	306.734	263.4579	267.3215
Log normal	337.5486	341.7036	276.0049	279.8686	306.3618	310.5169	256.6702	260.5339
Log logistic	331.3346	335.4897	275.5403	279.404	301.2881	305.4432	255.2548	259.1184
Generalized gamma	332.5589	336.714	275.4086	279.2723	304.641	308.7961	256.5144	260.378

AIC, Akaike Information Criterion; BIC, Akaike Information Criterion; PFS, progression-free survival; OS, overall survival

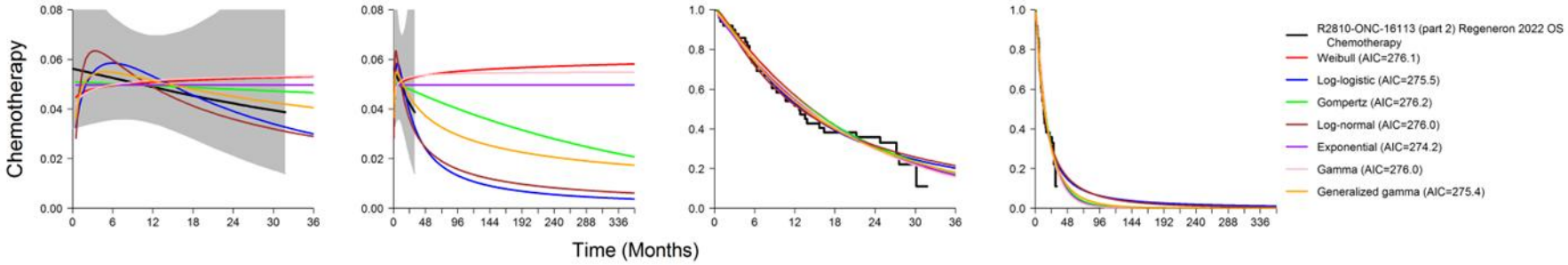
Figure 12: Hazard plots and visual fit - OS, non-squamous



Plots show from left to right, hazard rate (short term), hazard rate (long term), survival (short term), survival (long term).

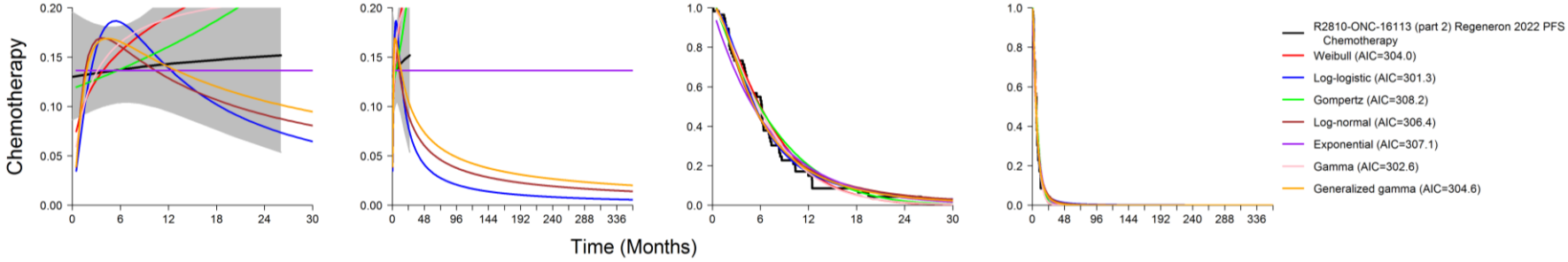
R2810-ONC-16113 = EMPOWER-Lung 3

Figure 13: Hazard plots and visual fit - OS, squamous



Plots show from left to right, hazard rate (short term), hazard rate (long term), survival (short term), survival (long term).
R2810-ONC-16113 = EMPOWER-Lung 3

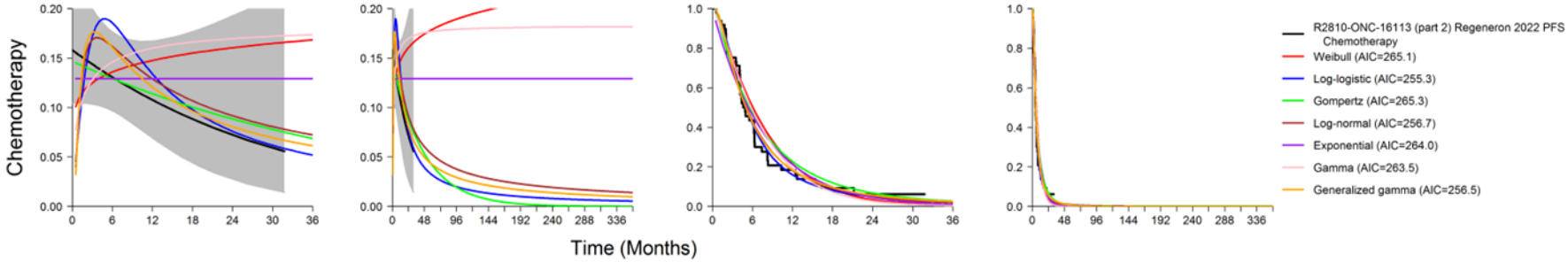
Figure 14: Hazard plots and visual fit - PFS, non-squamous



Plots show from left to right, hazard rate (short term), hazard rate (long term), survival (short term), survival (long term).

R2810-ONC-16113 = EMPOWER-Lung 3

Figure 15: Hazard plots and visual fit - PFS, squamous



Plots show from left to right, hazard rate (short term), hazard rate (long term), survival (short term), survival (long term).

R2810-ONC-16113 = EMPOWER-Lung 3

Cemiplimab with platinum-based chemotherapy for untreated advanced non-small-cell lung cancer [ID3949]

EAG review of company draft guidance consultation response

Produced by Newcastle University

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

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Any de-personalised data are highlighted in pink throughout the report.

EAG response to company draft guidance response

EAG critique of company DGC response

Issue 1 – Uncertainty in the indirect treatment comparisons

As noted in Draft Guidance Consultation Document (DGD) Section 3.13, "*The committee noted the high level of uncertainty in the comparative effectiveness of cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy*." In relation to this, the committee identified several issues which needed to be addressed by the company to reduce uncertainty in the results of the network meta-analysis (NMA). Each issue is described below, along with a summary of the company's response and a critique by the EAG. The EAG notes that the company performed separate MAIC effectiveness analyses for squamous and non-squamous histology sub-groups in their revised submission as the EMPOWER-Lung 3 clinical trial population was matched to each of the KEYNOTE trials, each of which had a different histology population: squamous and non-squamous.

In the cost-effectiveness analysis using MAIC evidence, the hazard rates for mortality and for mortality/disease progression were calculated as weighted averages of the hazard rates for squamous and non-squamous subgroups. These subgroup hazard rates were obtained using the hazard ratio estimates from the MAICs.

1) Uncertainty surrounding the transitivity assumption in the NMA:

In the EMPOWER-Lung 3 clinical trial for the MHRA label population, all participants expressed the PD-L1 protein on ≥1% of their tumour cells, whereas in two comparator trials (KEYNOTE-189 and KEYNOTE-407), participants were included regardless of their PD-L1 status and baseline characteristics were not reported according to PD-L1 status. It was therefore, not possible for the company to formally assess the transitivity assumption, which assumes that there is a similar distribution of clinical and methodological characteristics which could act as effect modifiers, between included studies and across all comparisons in an NMA network.[1] Furthermore, in section 3.6 of the DGD, the NICE committee identified characteristics that differed between the EMPOWER-Lung 3 and KEYNOTE-189 and KEYNOTE-407 clinical trials, which could act as effect modifiers, namely: duration of treatment, PD-L1 expression levels, age, ECOG PS, cancer stage at diagnosis, smoking history, study site locations (potential differences in resource use) and treatments offered at second line and beyond.

To address the DGD's concern regarding the validity of the transitivity assumption in the NMA, the company undertook matching-adjusted indirect comparisons (MAICs) to control for differences in participant characteristics between the EMPOWER-Lung 3, KEYNOTE-189 and KEYNOTE-407 clinical trials that could act as effect modifiers. To identify relevant effect modifiers, the company undertook a "targeted literature review" of published literature on prognostic factors and treatment effect modifiers in advanced/metastatic NSCLC. They also reviewed analyses from the EMPOWER-Lung 3 and KEYNOTE-189 and KEYNOTE-407 clinical trials, to identify sub-groups where the point estimate fell outside or close to the boundary of the confidence interval of its counterpart (e.g., sex: male v female). Finally, four clinical expert oncologists were asked to review the list of identified effect modifiers for completeness and to rank each variable in order of importance for their potential to have a treatment modifying effect. As the oncologists' rankings were varied, the company stated that

they included all the effect modifiers in their analyses. The final list of variables that were included in the MAIC analyses were: PD-L1 expression (1-49% vs. ≥50% in the PD-L1 ≥1% scenarios; <1% vs. 1-49% vs. ≥50% in the any PD-L1 scenarios), age (<65 vs. ≥65) and smoking history (current and former smokers vs. never smokers).

The EAG considers that the methods used by the company to identify prognostic factors appear logical, with triangulation of different methods to ensure robustness. The EAG notes that the company do not appear to have explained why study site locations (potential differences in resource use), which was identified as a potential effect modifier by the NICE committee in DGD section 3.6, was not addressed in their revised analyses. However, the EAG considers that the company were unable to adjust for country / location in the MAICs or perform sub-group analyses based on location, due to the lack of overlapping countries between the KEYNOTE and EMPOWER-Lung 3 trials.

2) Impact of cross-over

Cross-over of participants between treatment arms was permitted in the KEYNOTE clinical trials but not in the EMPOWER-Lung 3 clinical trial. Consequently, a proportion of participants in the control arms of the KEYNOTE trials received immunotherapy (IO), whereas they did not in the EMPOWER-Lung 3 study. This could dilute the relative effectiveness of pembrolizumab + chemotherapy compared to cemiplimab + chemotherapy. As noted by the NICE committee (section 3.6), without crossover-adjusted results, the impact of crossover in the KEYNOTE studies added uncertainty to the NMA results for overall survival (OS).

In response to the DGD's concern, the company obtained published cross-over adjusted overall survival (OS) data[2] from the final analysis (2-year follow up) of KEYNOTE-407 (patients with squamous histology). These data were incorporated into a MAIC analysis comparing cemiplimab + chemotherapy, using data from EMPOWER-Lung 3 (squamous sub-group), with pembrolizumab+ chemotherapy. The company reported that the point estimate (hazard ratio, HR) for OS in the squamous sub-group improved (in favour of cemiplimab) from 1.02 (0.54, 1.93) (unadjusted) to 0.93 (0.47, 1.85) (crossover-adjusted). The company stated that, to their knowledge, no crossover-adjusted data were publicly available for the relevant PD-L1 ≥1% subgroup of the KEYNOTE-189 study (patients with non-squamous histology). The company note, however, that it is stated in TA557 (for which KEYNOTE-189 was the pivotal trial) that "*results of the crossover adjustments were comparable with the main analyses, with little change in the overall effect*". The result the MAIC-adjusted final analysis (2-year follow-up) for EMPOWER-Lung 3 (non-squamous sub-group) versus KEYNOTE-189 (non-squamous histology) is reported in section 3 ("Early stopping of EMPOWER-Lung 3"), below.

The EAG considers that the company's approach to addressing the issue of crossover effects was appropriate, albeit that methods to address adjust for treatment cross-over are generally limited in their robustness.[3,4] The company reference 'TSE simp adjusted' in tables, TSE referring to two stage estimation. In some cases, two-stage estimation with inverse probability of censoring weights (TSEipcw) has been shown to be more robust than other methods.[4] It is not clear if this would apply in this case due to a lack of detail reported by the company. The results from the crossover adjusted analysis indicate that the point estimate for OS favoured cemiplimab for the squamous sub-group. However, the results remained non-significant indicating that uncertainty remains regarding the relative effectiveness of cemiplimab compared to pembrolizumab. The company reported that it was not possible to adjust for the

impacts of crossover effects in the non-squamous sub-group as the relevant data from the KEYNOTE-189 clinical trial were unavailable.

3) Early stopping of EMPOWER-Lung 3

The KEYNOTE clinical trials had a longer duration of follow up (5 years) compared to the EMPOWER-Lung 3 clinical trial (2 years), which stopped early owing to superior OS with cemiplimab compared to the control arm. It was noted by the NICE committee in the DGD (section 3.6) that the shorter follow-up period in the EMPOWER-Lung 3 clinical trial makes the data on OS for cemiplimab less mature and more uncertain than for pembrolizumab. The DGD considered that the early stopping of the EMPOWER-Lung 3 clinical trial was potentially associated with a bias favouring cemiplimab plus chemotherapy.

In response to the DGD's concern, the company undertook exploratory MAIC scenario analyses using data from a 2-year follow-up period common to the KEYNOTE and EMPOWER-Lung 3 clinical trials. For the non-squamous sub-group, using data from the KEYNOTE-189 clinical trial, the results for OS indicated that cemiplimab was significantly more effective than pembrolizumab (HR = 0.52, 95% CI 0.31, 0.90, p = 0.001). This analysis was not adjusted for crossover effects, as explained in section 2 ('Impacts of crossover'), above. For the squamous subgroup, using crossover-adjusted data from the KEYNOTE-407 clinical trial, cemiplimab was more effective than pembrolizumab based on the point estimate, however, this result was non-significant (HR = 0.93, 95% CI 0.47, 1.85, p = 0.639).

The EAG considers that the company's approach to addressing the different follow up times between the EMPOWER-Lung 3 and KEYNOTE-407 clinical trials would have removed any potential bias associated with differential follow-up times. Given the wide CIs, uncertainty remains in the effectiveness of cemiplimab and pembrolizumab for OS for the squamous sub-group. For the non-squamous sub-group, although the results indicate that cemiplimab may be more effective than pembrolizumab, this analysis was not adjusted for crossover effects which may impact the result in favour of cemiplimab.

Issue 2 – Stopping rule and time on treatment

Stopping rule

As noted in DGD section 3.13, the committee noted the high level of uncertainty about *"the implementation of the stopping rules for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy"* and that *"… in clinical practice, pembrolizumab treatment given every 3 weeks is stopped after 35 weeks".* In response, the company updated the model stopping rules to reflect the rules in clinical practice. The EAG are satisfied that this change is in line with the committee's preferences, and also note that these changes make very little difference to the cost-effectiveness results.

Time on treatment

As noted in DGD section 3.13, the committee were concerned about the high level of uncertainty regarding *"the impact on overall survival of treatment beyond progression for people in the cemiplimab plus chemotherapy arm"* and in particular that *"the EMPOWER-Lung*

3 protocol allowed people to continue having cemiplimab after disease progression", which differed from the marketing authorisation, and prefer *"using Kaplan–Meier data from EMPOWER-Lung 3, either directly or using the best fitting parametric survival curve fitted to that data, as per the NICE technical support document 14 to calculate time on treatment for cemiplimab".*

The company provided evidence from the wider literature that continued 1L IO treatment beyond treatment progression may not have an impact on OS. The EAG has not had the time to review this evidence.

Given their justification regarding the impact of treatment beyond progression on OS, in an updated analysis the company revert to modelling time on treatment as equal to PFS, as per the company base-case rather than using the committee's preference of using the actual Kaplan-Meier curve for ToT in the cemiplimab.

The company argue that if continued 1L IO treatment beyond disease progression is believed to impact OS outcomes, then any IO use post-progression should be captured in the economic model. The company include a scenario with the EAG preferred ToT ratio to PFS curve assumptions applied, but with the cemiplimab post-progression IO use reweighted for the pembrolizumab arm in line with the KEYNOTE studies; that is, in the cemiplimab arm of the model, 0.6% of patients receive pembrolizumab and 0.32% receive atezolizumab, whereas in the pembrolizumab arm of the model 13.3% receive pembrolizumab and 6.6% receive atezolizumab (average of KEYNOTE studies).

The EAG note that the company's approach to modelling ToT is not in line with the committee's preference, and reiterate that assuming that ToT is equal to PFS may underestimate the costs for cemiplimab + chemotherapy and overestimate the costs for pembrolizumab + chemotherapy. The EAG also note that the percentage of patients receiving IO post progression may be influenced by the duration of follow-up.

Issue 3 – Duration of treatment benefit

As noted in DGD Section 3.14, the committee's preference regarding the duration of treatment benefit to assume "*a gradual waning of treatment effect for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy treatment waning, rather than an immediate waning of treatment effect".* Furthermore, the committee requested "*further justification from the company to support a 5-year waning time point* [for pembrolizumab] *including analysis of 5-year data from KEYNOTE-189 and KEYNOTE-407"* and *"further evidence to support a 5-year waning time point based on data specifically for cemiplimab plus chemotherapy"*.

In response, the company have implemented a gradual/linear treatment waning effect in the revised company base-case analysis for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy, which starts at 3 years and finishes at 5 years for both cemiplimab + chemotherapy and pembrolizumab + chemotherapy. This is line with Scenario 5 from the original company submission. The company justify this assumption by stating that a recent review of treatment effect waning assumptions in IO health technology assessments found that effect waning typically started between 3 and 5 years. Although the company do not provide a reference for this statement, the EAG assumes they are referencing the recent review by Trigg *et al*.[5] The EAG note that the conclusions from Trigg *et al* state that there is

considerable heterogeneity *"…in both the methods used and justifications given for TE waning assumptions"*.

In relation to the committee's request for the analysis of 5-year data from KEYNOTE-189 and KEYNOTE-407, the company note that there are difficulties in analysing these data as both studies were subject to crossover, with crossover-adjusted analyses not available. The EAG acknowledge the difficulties in interpreting the long-term treatment effects given this crossover. The company provide two figures (Figure 10 and Figure 11) showing the discrete hazards over time from the model compared to the hazards from KEYNOTE-189 and KEYNOTE-407, and argue that this shows that treatment waning from 24-60 months (as preferred by the EAG) is a conservative assumption, as the hazards are still decreasing up to the end of follow up for both PFS and OS. The EAG note that these estimates are subject to considerable uncertainty. In addition, the hazards decrease over time for all the technologies, and it is not clear that hazard ratios for cemiplimab versus pembrolizumab or chemotherapy is maintained over time from these plots.

In relation to the committee's request for further evidence to support a 5-year waning time point for cemiplimab, the company state that they are unable to provide additional evidence from EMPOWER-Lung 3 due to its early stopping, and instead point to clinical expert feedback and long-term follow up data from EMPOWER-Lung 1 which showed that cemiplimab monotherapy continued to show durable clinically meaning OS and PFS benefit versus chemotherapy. The EAG note that given the differences between the EMPOWER-Lung 1 and EMPOWER-Lung 3 trials, this justification is subject to considerable uncertainty.

The company has implemented gradual treatment waning in line with the committee's preferences. However, the EAG note the ongoing uncertainty relating to the starting point of the treatment waning for IOs, with little evidence for a treatment waning beginning at 36 months, as in the company's updated base-case. As noted in the EAG report, in the EAG's preferred base-case the treatment waning begins at 24 months, in line with the stopping rule for both cemiplimab and pembrolizumab, and the fact that there was no Markov model in which an assumption of no difference in post-progression mortality rates could be tested.

Issue 4 – Chemotherapy distributions

As noted in DGD Section 3.13, the committee had concerns regarding the uncertainty surrounding the proportion of people with *"non-squamous NSCLC who have cemiplimab without pemetrexed in clinical practice, and if EMPOWER-Lung 3 reflected this".*

In response, the company acknowledge that there is significant heterogeneity in chemotherapy regimes across England and Wales at population, centre and individual clinician level, citing expert clinical feedback provided to Regeneron, and note that it is not possible to precisely estimate the proportion of cemiplimab without pemetrexed in clinical practice and what their characteristics would be. The company further argue that a cost-effectiveness analysis for this sub-population is not possible, and that any differences are likely to be modest. The EAG agree that given the data available, conducting a cost-effectiveness analysis for this specific sub-population is challenging.

The company outline some further issues with pemetrexed, specifically that it is associated

with significant toxicity and may not be the preferred chemotherapy agent for patients with non-squamous disease. The company note that exploratory analysis has indicated that pemetrexed and paclitaxel have distinct profiles that may *"allow clinicians to choose between them based on the comorbidity profile of their patients".* The EAG note that this exploratory analysis is uncertain by its nature and any conclusions should be treated with caution.

The company also note that assuming the KEYNOTE chemotherapy distributions in both comparator arms is in fact costing saving, with the total cost of treatment with cemiplimab + pemetrexed being £394.44 higher per patient compared with cemiplimab + paclitaxel (assuming 25% of patients receiving pemetrexed go on to receive pemetrexed maintenance) and state that this potential cost saving is not reflected in the economic model. The EAG note that such a cost saving is likely to have very little difference on the overall conclusions of the analysis.

Overall, the EAG note that although the uncertainty surrounding the proportion of people with non-squamous NSCLC who have cemiplimab without pemetrexed in clinical practice remains unresolved.

Issue 5 – Adverse events

As noted in DGD Section 3.14, the committee's preference regarding adverse events (AE) was to use *"the grade 3 and above adverse event rates from EMPOWER- Lung 3 and the KEYNOTE studies to model adverse event rates for cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy, respectively"*. Consequently, the company have retained their base-case approach of using AE rates from EMPOWER-Lung 3 and the respective KEYNOTE studies. The EAG are satisfied that this change is in line with the committee's preferences, and also note that these changes make very little difference to the cost-effectiveness results.

Model changes and analyses

The DGD stated that the committee preferred a Markov model with a scenario with the assumption of equal morality rates post-progression due to uncertainty in a survival benefit post-progression. The company stated they did not have the time to develop a Markov model. Instead, they tried to address concerns regarding effectiveness evidence using MAIC analyses as discussed in Issue 1, and they also included a scenario with no difference in OS between cemiplimab and pembrolizumab.

MAICs were conducted for each of the KEYNOTE trials as described in Issue 1, each of which has a different histology population: squamous and non-squamous. In the cost-effectiveness scenario analysis using MAIC evidence, the hazard rates for mortality and for mortality/disease progression were calculated as weighted averages of the hazard rates for squamous and non-squamous subgroups. These subgroup hazard rates were obtained using the hazard ratio estimates from the MAICs.

The equal OS assumption is potentially conservative with respect to cemiplimab when compared to a Markov model with equal mortality hazard rates post-progression as it assumes equal morality rates while progression-free and after disease progression.

The company

- updated the eMIT prices in the model,
- incorporated the committee's preferred stopping rule
- gradual treatment waning from 3 to 5 years

The scenario analyses included:

- equal OS
- ratios applied to PFS curves to derive time to treatment curves, with the addition of different IO use post-progression for cemiplimab and pembrolizumab (Issue 4).

Updated results

The original company base-case was updated to reflect the committee preferred stopping rule, gradual/linear treatment waning effect from 3 to 5 years and updated eMIT prices. In the updated model, the incremental cost and QALY were [redacted] and [redacted] respectively, resulting in the ICER to be [redacted] with respect to cemiplimab + chemotherapy vs pembrolizumab + chemotherapy. The EAG could not replicate the results for the scenario where PFS HRs were applied to time to treatment discontinuation (TTD). The PFS HR applied to the pembrolizumab + chemotherapy arm in the updated model was 1, while in the response document it was 0.84. So, EAG changed the PFS HR for the pembrolizumab + chemotherapy arm in the model to align with the response document. But it did not have a significant impact on the ICER because it remained [redacted] in both cases.

To address the uncertainty around indirect treatment comparison, the company incorporated the MAICs into the model to provide an alternative updated company base-case. The incremental cost and QALY were [redacted] and [redacted] respectively, with the ICER being [redacted]. The scenario with PFS HRs (1.17 for the treatment arm and 0.84 for the comparator arm) were applied to TTD and the ICER was [redacted]. For the scenario in which equal OS was assumed for cemiplimab + chemotherapy and pembrolizumab + chemotherapy, the EAG could not replicate the exact results provided by the company in the updated model. The incremental cost and QALY were different by an extremely small margin. But the ICER remained [redacted].

References

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