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

For committee and screen – contains no confidential information

Technology appraisal committee D [10 April 2025]

Chair: Raju Reddy

External assessment group: Newcastle University

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Company: Regeneron

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

- ✓ **Recap**
- ❑ Response to consultation
- ❑ Other considerations

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Cemiplimab (Libtayo ®, Regeneron)

Time to stopping treatment differs in license and trial

Marketing authorisation	In combination with platinum-based chemotherapy for 1st-line treatment of adults with NSCLC expressing programmed cell death-1 PD-L1 (in ≥1% of tumour cells), with **no** epidermal growth factor receptor, anaplastic lymphoma kinase or ROS proto-oncogene 1 aberrations, with NSCLC: • **locally advanced** and **not suitable for definitive chemoradiation**, or • **metastatic**
Treatment duration	'Until disease progression or unacceptable toxicity' *differs from trial*
Mechanism	Inhibits PD-1 activity; enhances anti-cancer immune response
Administration	• 350 mg IV every 3 weeks • Stopping rule in trial: up to 36 doses
Testing	• PD-L1 test part of NHS routine practice
Price	• List price: £4,650 per 350mg vial • Average cost of cemiplimab with chemotherapy at list price in 1st year: £61,351 • Commercial arrangement in place for cemiplimab

Company narrowed target population for a subset of total NICE scope population:

- People 'who would **otherwise be offered treatment with an immunotherapy + chemotherapy combination**'

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IV, Intravenous; NSCLC, Non-small-cell lung cancer; PD-L1, Programmed cell death ligand 1

Key clinical trial – EMPOWER-Lung 3 Part 2

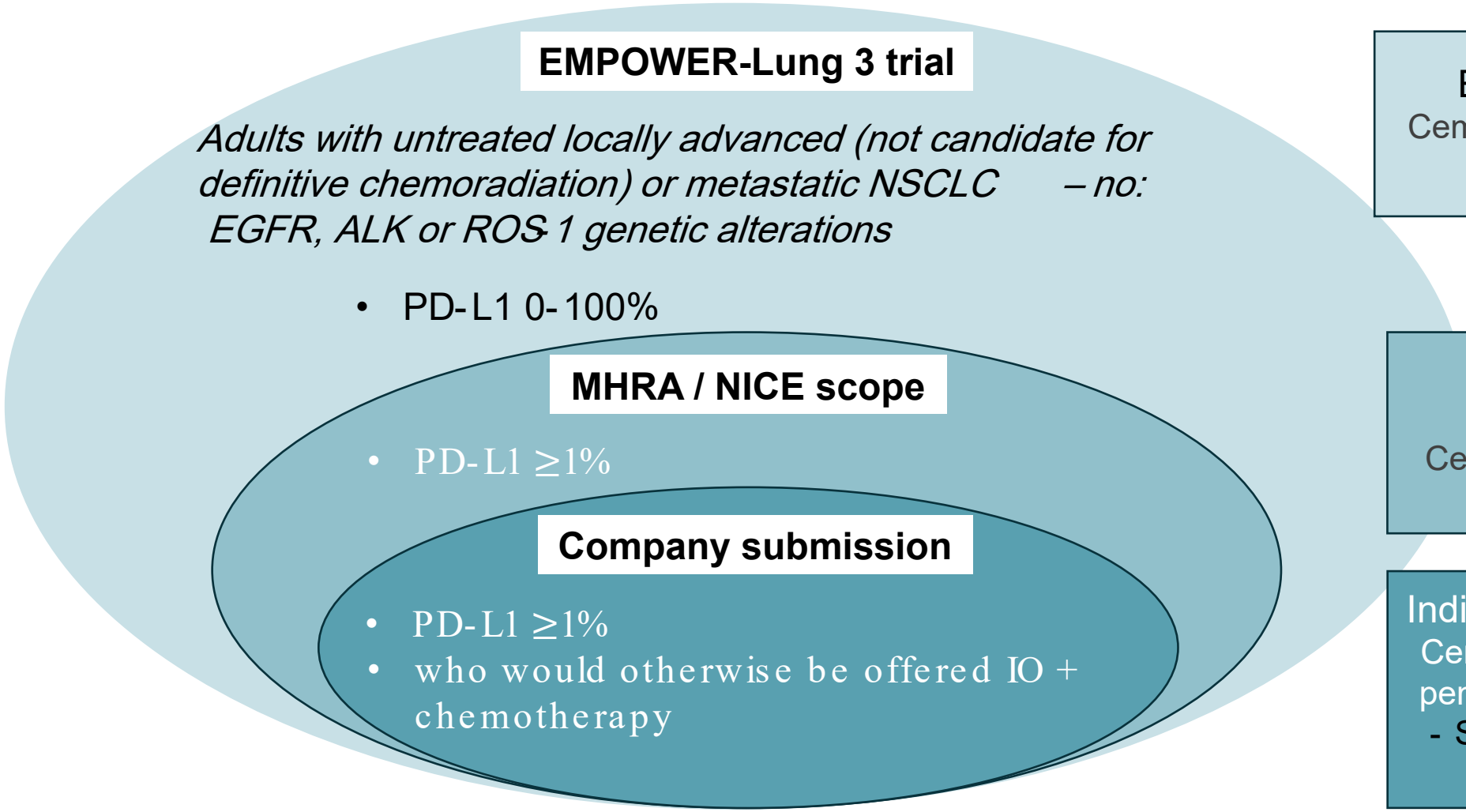
RECAP

Comparator in trial (placebo +) chemotherapy only not comparator in company's base case

Design	Phase 3 randomised, double-blind, 2:1, placebo-controlled superiority trial
Population	Adults with untreated advanced (14% locally advanced; 86% metastatic) squamous (43%) or non-squamous (57%) NSCLC with no EGFR, anaplastic lymphoma kinase or ROS proto-oncogene 1 aberrations, **irrespective** of PD-L1 expression
Intervention	Cemiplimab 350 mg IV every 3 weeks, **maximum** 36 doses **treatment beyond progression 'allowed by protocol'** + 4 cycles chemotherapy + pemetrexed until progression for non-squamous
Comparator	Placebo IV every 3 weeks, maximum 36 doses + 4 cycles chemotherapy + pemetrexed as above Protocol did not permit treatment switching
1° outcome	Overall survival
2° outcomes	Progression-free survival, objective response rates, duration of response, health-related quality of life (EORTC QLQ-C30/QLQ-LC13)
Locations	74 sites: China, Georgia, Greece, Malaysia, Poland, Romania, Russia, Thailand, Turkey, Ukraine
Duration	**Trial stopped early** on recommendation of independent data monitoring committee. 14 June 2022. Potential additional follow-up over next 18 months
In model?	Yes: overall survival, progression-free survival, EORTC-QLQ C30

EORTC, European Organization for the Research and Treatment of Cancer; IV, Intravenous; NSCLC; Non-small-cell lung cancer; PD-L1, Programmed cell death ligand 1; QLQ-C30, Quality of Life Questionnaire- 30 item; QLQ-LC13, Quality of Life Questionnaire-Lung Cancer 13

Populations included in EMPOWER -Lung 3 trial, marketing authorisation and company submission



Clinical evidence by population:

EMPOWER-Lung 3: ITT
Cemiplimab + chemotherapy vs. placebo + chemotherapy

EMPOWER-Lung 3: MHRA label population
Cemiplimab + chemotherapy vs. placebo + chemotherapy

Indirect treatment comparison
Cemiplimab + chemotherapy vs. pembrolizumab + chemotherapy
- See appendix for methods and results

Abbreviations: ITT; intention to treat, PD-L1; programmed death ligand 1, NSCLC; non small cell lung cancer, EGFR; epidermal growth factor receptor, ALK; Anaplastic lymphoma kinase, ROS-1; ROS oncogene 1, IO; immunotherapy, MHRA; medicines and healthcare products

Committee's key conclusions from ACM1

Cemiplimab should not be used; further information needed to decide all preferred assumptions

Issue	Committee's preferred assumption
Target population & comparators	• Company's target population is appropriate • Pembrolizumab plus chemotherapy is appropriate comparator • 'Only if urgent clinical intervention is needed' criterion would apply if recommended for people with squamous PD-L1 ≥50% disease (as in TA770)
Chemotherapy	• Uncertain what % of people with non-squamous NSCLC would have cemiplimab without pemetrexed in clinical practice
NMA	• Highly uncertain; OS potentially biased in favour of cemiplimab plus chemotherapy
Model structure	• Partitioned survival model may be biased in favour of cemiplimab plus chemotherapy
Time to treatment discontinuation	• Cemiplimab: use Kaplan–Meier data from EMPOWER-Lung 3, either directly or using best fitting parametric survival curve • Pembrolizumab: use ratio between time on treatment and progression-free survival
Stopping rule	• Stopping rule for cemiplimab should reflect trial (up to 36 doses) • Stop pembrolizumab after 35, 3-weekly cycles (reflecting clinical practice)
Treatment waning	• Apply gradual waning of treatment effect
Adverse events	• Use grade 3+ AE rates from EMPOWER Lung 3 and KEYNOTE trials
Acceptable ICER	• Around £20,000 per QALY

Abbreviations: ACM, appraisal committee meeting; PD -L1; programmed death ligand 1, NSCLC; non small cell lung cancer, OS; overal l survival, AE, adverse event; ICER, incremental cost -effectiveness ratio; QALY, quality -adjusted life year; AE, adverse event

Committee's requests for additional analyses

Committee wanted an alternative model structure and more evidence on time on treatment, stopping rules and treatment waning

Request	Company response	ICER impact
Markov model based on PFS from NMA and equal mortality risk post-progression	• Not provided	Unknown
Cemiplimab KM data for time on treatment	• Not provided	Unknown
Implement stopping rule for cemiplimab to reflect EMPOWER-Lung 3	• Updated to maximum of 36 doses	Low
Stop pembrolizumab after 35, 3-weekly cycles	• Updated to maximum of 35, 3 weekly cycles	Low
Further justification for 5-year waning time point	• Updated to gradual linear treatment waning to align with committee preference • Waning implemented from 3-5 years based on KEYNOTE trial follow up data	Low

Abbreviations: PFS; progression free survival, NMA; network meta analysis, KM; Kaplan Meier, ICER; incremental cost effective ness ratio

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

- ❑ Recap
- ✓ **Response to consultation**
- ❑ Other considerations

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★Committee preferred assumption

Overview of company's response

1 consultation response received from company. No responses received from experts, patient or clinical organisations, or web comments

Company included some of committee's preferred assumptions in updated base case:

Changes in company's updated base case
★ • Stopping rules for cemiplimab and pembrolizumab based on maximum number of treatment cycles ★ • Gradual waning of treatment effect • Updated eMIT prices for chemotherapy
Changes in company's alternative base case
• MAIC for comparative effectiveness
Company's further scenario analyses
• ToT:PFS ratio (EAG preference) for time on treatment but reweighted post-progression IO use for pembro-chemo to sum to the total usage observed in the KEYNOTE studies • Alternative company base case scenario (with MAIC) assuming equivalent OS for cemiplimab plus chemo and pembrolizumab plus chemo

Abbreviations: eMIT; electronic market information tool, MAIC; matching adjusted indirect comparison, TOT; time on treatment, PFS; progression free survival, OS; overall survival, IO; immunotherapy

Key issues

Issue	ICER impact
Indirect treatment comparison • Is the indirect evidence comparing cemiplimab + chemo with pembrolizumab + chemo sufficient for decision-making? • If so, which approach is preferred?	Large
Model structure • Have the committee's concerns with the partitioned survival model been addressed	Unknown
Stopping rule and time on treatment • What is the committee's preferred method for modelling time on treatment?	Moderate
Duration of treatment benefit • What start and end points should be used for gradual waning of treatment effect?	Low

Key issues: Uncertainty in the indirect treatment comparison

Background

- Company compared cemiplimab plus chemo with pembrolizumab plus chemo using NMAs
- Lack of crossover-adjusted results in KEYNOTE-407/189 trials and differences in baseline characteristics between trials adds uncertainty to NMAs, especially for overall survival

Company

- Conducted MAICs adjusting for age, ECOG status*, smoking status and PD-L1 expression – see appendix
- Incorporated published crossover adjusted OS data from KEYNOTE-407 into MAICs and NMAs - see appendix. No crossover adjusted data available for KEYNOTE-189 trial
  - Crossover-unadjusted NMA remains company base case in model
- Results further support no meaningful differences in efficacy between cemiplimab plus chemo and pembrolizumab plus chemo

EAG comments

- Methods of identifying prognostic factors appear logical but no explanation for study site location not being adjusted for
- Methods to adjust for treatment cross-over are generally limited in their robustness; uncertainty remains for relative effectiveness

*ECOG status could not be matched for in squamous subgroup (KEYNOTE-407) due to low ECOG 0 patient numbers in EMPOWER-Lung 3

Is the indirect evidence comparing cemiplimab + chemo with pembrolizumab + chemo sufficient for decision-making? If so, which approach is preferred?

Abbreviations: MAIC, matching adjusted indirect comparison; NMA, network meta-analyses, OS; overall survival, PD-L1; programmed death ligand 1, EGOC; European cooperative oncology group

MAIC results

See appendix for MAIC results across other scenarios

Company: results indicate comparable PFS and OS between cemiplimab (EMPOWER-Lung 3) and pembrolizumab (KN189/KN407)

Population	Outcome	Scenario	Adjustment	Base case results	
				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
	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**
PD-L1 ≥1%, squamous	PFS	EMPOWER-Lung 3 vs. KN407 (final analysis)	Unweighted	1.05 (0.64, 1.70)	0.858
			Anchored MAIC	1.05 (0.57, 1.92)	0.881
	OS	EMPOWER-Lung 3 vs. KN407 (final analysis, crossover adjusted)	Unweighted	1.02 (0.54, 1.93)	0.940
			Anchored MAIC	0.93 (0.47, 1.85)	0.832

Bolded values = statistically significant

Included in alternative company base case

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Abbreviations: MAIC, matching adjusted indirect comparison, PFS; progression free survival, OS; overall survival, HR; hazard ratio, CI; confidence interval

Key issues: Model structure

Background

- Committee requested a Markov model structure based on PFS data from NMA, and with assumption of equal mortality risk post-progression for cemiplimab plus chemo and pembrolizumab plus chemo

Company

- Developing a state-transition model per committee's request was not feasible in the short time available
- Partitioned survival model structures are well-established for modelling NSCLC in prior NICE TAs
- Updated existing partitioned survival model with results from MAIC as alternative base-case, to reduce committee's uncertainty about comparative effectiveness of cemiplimab and pembrolizumab on PFS
- Explored uncertainty around modelled OS by scenario analysis: mortality HR for cemiplimab plus chemo versus pembrolizumab plus chemo is assumed to be 1
- Accept cost-utility based value assessment framework but in context of overall evidence base re-iterate willingness to use cost comparison as alternative basis for decision making

EAG comments

- Equal OS scenario potentially conservative- may underestimate cemiplimab OS when compared to a Markov model with equal mortality hazard rates post-progression as it assumes equal morality rates for progression-free and post progression states

Have the committee's concerns with the partitioned survival model been addressed?

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Abbreviations: MAIC, matching adjusted indirect comparison; NMA, network meta-analyses, NSCLC; non small cell lung cancer, TA; technology appraisal, OS; overall survival, HR; hazard ratio

Key issues: Stopping rule and time on treatment

☑ Included in updated company base case

Background

- Committee noted uncertainty from treatment continued beyond company's 108 week stopping rule and treatment beyond disease progression for cemiplimab
- Committee preferred ratio between ToT and PFS to calculate ToT for pembrolizumab (as Kaplan–Meier data unavailable)
- Committee requested:
  - Further analyses using the cemiplimab ToT Kaplan–Meier data from EMPOWER-Lung 3, either directly or using best fitting parametric survival model
  - Stopping rule for cemiplimab reflects EMPOWER-Lung 3 trial ☑
  - Stopping rule for pembrolizumab reflects NHS practice of 35, 3-weekly cycles ☑

Company

- Not provided cemiplimab ToT using Kaplan-Meier data as adjusted survival data would not be aligned with observed ToT in EMPOWER-Lung 3
  - Base case kept ToT = PFS assumption for cemiplimab + chemo and pembrolizumab + chemo
- Of 52 patients having cemiplimab beyond 108 weeks in trial, none had more than the maximum 36 doses
  - 27 (51%) had a dose delay
  - Treatment exposure definition includes additional 21-day exposure window post-administration
- If modelling IO use post-progression, should include both initial treatment and subsequent IOs
  - Included scenario with ToT:PFS ratio approach and reweighting of pembro post progression IO

Abbreviations: PFS; progression free survival, IO; immunotherapy, ToT, time on treatment, HR; hazard ratio

Key issues: Stopping rule and time on treatment

Treatment	Ratio time on treatment:PFS	Source
Cemiplimab + chemotherapy	1.17	EMPOWER-Lung 3
Pembrolizumab + chemotherapy	0.84	KEYNOTE-407 and -189, weighted by histology

EAG comments

- Satisfied that stopping rule update meets committee's preferences
  - Updated stopping rules have low impact on cost-effectiveness results
- Company's approach to modelling ToT is not in line with committee's preference
- Assuming ToT is equal to PFS may underestimate costs for cemiplimab + chemotherapy and overestimate costs for pembrolizumab + chemotherapy
- Percentage of patients receiving IO post progression may be influenced by duration of follow-up
- EAG changed PFS HR for pembrolizumab + chemotherapy arm in model to align with company's response document - low impact on ICER

What is the committee's preferred method for modelling time on treatment?

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Abbreviations: PFS; progression free survival, IO; immunotherapy, ToT, time on treatment, HR; hazard ratio, ICER; incremental cost effectiveness ratio

Key issues: Duration of treatment benefit

Background

- Committee preferred a gradual treatment effect waning approach and requested:
  - Further justification from company to support a 5-year waning time point, including analysis of 5-year data from KEYNOTE-189 and KEYNOTE-407
    - E.g. hazards from longer-term data of KEYNOTE-189/407 trials compared with modelled hazards
  - Further evidence to support 5-year waning time point based on data for cemiplimab plus chemo

Company

- Updated base case to align with committee preference for gradual treatment waning
- Assumed treatment effect waning from years 3 to 5 for cemiplimab + chemo and pembrolizumab + chemo
- Provided comparison of KEYNOTE data and modelled hazards; supported by clinical expert feedback to be applicable to cemiplimab plus chemo in the absence of direct evidence
- 5-year follow-up from EMPOWER-Lung 1 (cemiplimab monotherapy versus chemo for people with advanced/metastatic NSCLC with PD-L1 ≥50%) suggests assumption of treatment benefit for cemiplimab + chemo lasting for up to 5 years is reasonable: OS HR 0.59, 95% CI 0.48-0.72, P<0.0001

EAG comments

- Company's hazard estimates and justification from EMPOWER-Lung 1 subject to considerable uncertainty
- Uncertainty remains around starting point of treatment waning for IOs
- EAG's preferred base-case includes treatment waning from 2 years, in line with stopping rule for both cemiplimab and pembrolizumab

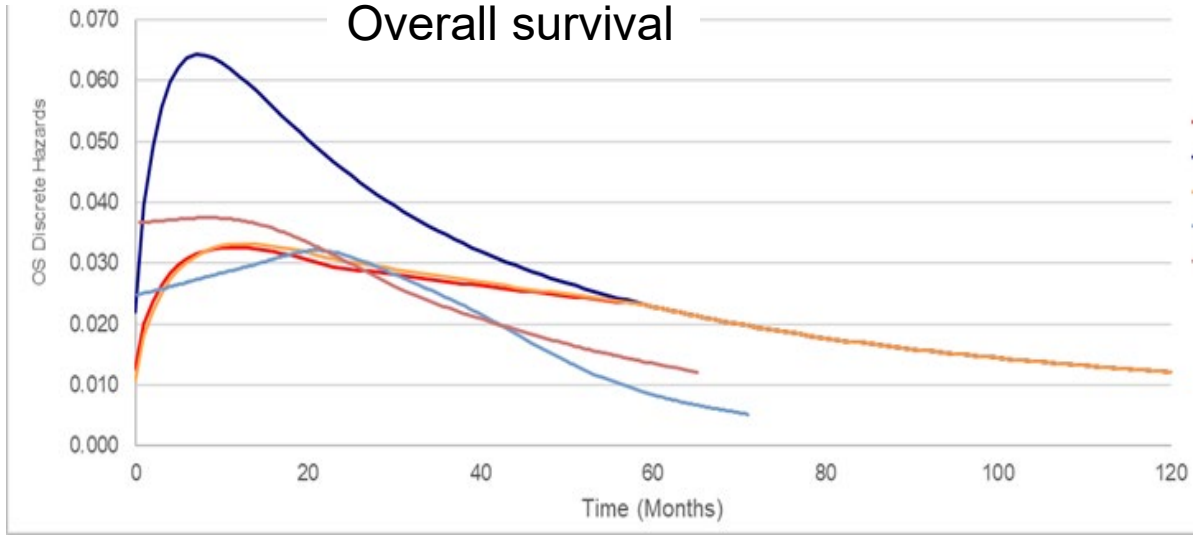
NICE What start and end points should be used for gradual waning of treatment effect?

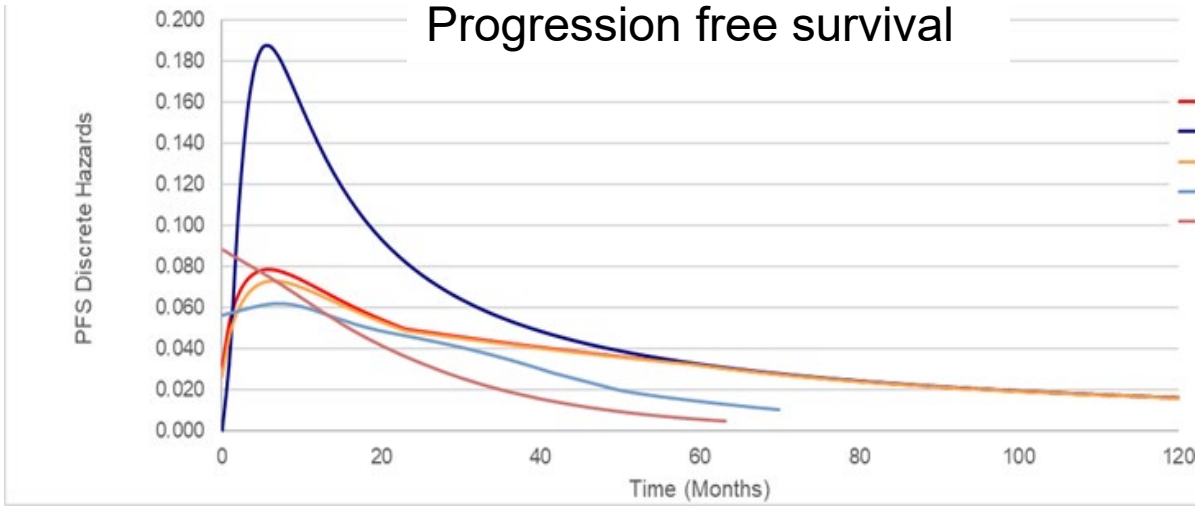
Abbreviations: PFS; progression free survival, OS; overall survival, PD-L1; programmed death ligand 1 HR; hazard ratio, CI; confidence intervals, IO; immunotherapy

Key issues: Duration of treatment benefit

Cemiplimab + chemo
Chemo alone
Pembro + chemo
Pembro + chemo: KN189
Pembro + chemo: KN407

Discrete hazard rates over time for modelled cemiplimab + chemotherapy, and pembrolizumab + chemotherapy and chemotherapy alone compared to observed hazards from KEYNOTE studies





Company: hazards suggest waning of hazards to chemotherapy hazards from 24-60 months is a conservative assumption compared to KEYNOTE-189 and -407 data, which show hazards decreasing up to end of follow-up for PFS and OS

EAG: hazards rates decrease over time for all treatments. But not clear that hazard ratios for cemiplimab versus pembrolizumab or chemotherapy are maintained over time from these plots

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Abbreviations: PFS; progression free survival, OS; overall survival

Other issues addressed in company's response

DG	Issue	Company response
3.5	Impact of early stopping of EMPOWER-Lung 3 on OS outcomes	• No evidence ethical early stopping of EMPOWER-Lung 3 biased indirect comparison in favour of cemiplimab • MAICs for OS conducted for both extended follow-up and final analysis timepoints showed little change in results • **EAG:** Company's approach removes any potential bias associated with differential follow-up times
3.17	For people with non-squamous NSCLC for whom pemetrexed is unsuitable, pembrolizumab plus chemo would not be an appropriate comparator	• Not possible to define a subpopulation who are given chemotherapy alone purely because they cannot receive pemetrexed • A cost-effectiveness analysis in this subpopulation would not be possible • **EAG:** agree cost-effectiveness analysis challenging to do • Anticipate that this group is likely to be modest

Abbreviations: DG; Draft guidance, OS; overall survival, NSCLC; non small cell lung cancer, MAIC; matching adjusted indirect comparison,

Summary of company and EAG base case assumptions

Cemiplimab + chemotherapy vs. pembrolizumab + chemotherapy

Assumption	Updated company base case	Alternative company base case	EAG base case	Committee preferred assumptions ACM1
ITC	NMA (without crossover-adjustment)	MAIC (with crossover-adjustment)	NMA (without crossover-adjustment)	NMA results (without crossover adjustment) highly uncertain
Time on treatment – cemiplimab	Assumed ToT = PFS		ToT:PFS ratio	Use KM data or parametric extrapolations
Time on treatment – pembrolizumab	Assumed ToT = PFS		ToT:PFS ratio	ToT:PFS ratio
Treatment effect waning	Gradual linear waning		Gradual linear waning	Gradual linear waning
	Waning from 3 years to 5 years		Waning from 2 years to 5 years	Further justification needed
Adverse event rates (Grade 3+) - See appendix	As per respective trials for each treatment arm		Adverse events for pembrolizumab + chemotherapy applied to both treatment arms	As per respective trials for each treatment arm

Committee preferred assumption

Abbreviations: NMA; network meta-analysis, MAIC; matching adjusted indirect comparison, ITC; indirect treatment comparison, ToT; time on treatment, PFS; progression free survival, QALY; quality adjusted life year, ICER; incremental cost effectiveness ratio, OS; overall survival, PFS; progression free survival, HR; hazard ratio, IO; immunotherapy

Cost-effectiveness results

- All ICERs reported in PART 2 slides because they include confidential discounts
- When confidential discounts included, updated company base case above range normally considered cost-effective use of NHS resources
- EAG base case substantially above range normally considered cost-effective use of NHS resources

EAG, External assessment group; ICER: Incremental cost effectiveness ratio; NMA, Network meta-analysis; PD-L1, Programmed cell death ligand 1; PFS, Progression-free survival; OS, Overall survival

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

- ❑ Recap
- ❑ Response to consultation
- ✓ **Other considerations**

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Equality considerations

Equality considerations

- For people with non-squamous NSCLC, pembrolizumab is given with pemetrexed plus platinum chemo. Cemiplimab can be used without pemetrexed (given with paclitaxel plus platinum chemo)
  - A clinical expert considered this a potential equality issue because pemetrexed is associated with toxicity and may not be suitable for all people

Committee welcomed further comment during consultation on any particular groups with a protected characteristic for whom pemetrexed would not be suitable

– *no further comments provided during consultation*

Abbreviations: NSCLC; Non-small cell lung cancer

Uncaptured benefits and disadvantages

- **Company**: Cemiplimab + chemotherapy allows greater flexibility to tailor chemotherapy treatment to individuals compared with pembrolizumab + chemotherapy. In EMPOWER Lung-3, option to use:
  - a pemetrexed-free option (with paclitaxel + carboplatin), in non-squamous NSCLC

  → pemetrexed associated with toxicity and may not be suitable for all people
  - carboplatin area under curve 5 (AUC5) dose as alternative to higher carboplatin AUC6 dose, in squamous NSCLC

  → higher dose associated with incremental toxicity

  ↳ **EAG**: AUC5 carboplatin dose not routinely possible for squamous NSCLC in UK as NHS commissioning policy mandates that patients are 'fit' to initiate treatment with AUC6 carboplatin
- **Draft guidance document:**
  - Section 3.4: Committee uncertain what % of people with non-squamous NSCLC would have cemiplimab without pemetrexed in clinical practice, or if EMPOWER-Lung 3 reflected this
  - Section 3.17: committee noted potentially uncaptured disadvantage of cemiplimab plus chemo was more frequent 3-weekly administration compared with 6-weekly option of pembrolizumab plus chemo
- **Company's DGD response:**
  - In EMPOWER-Lung 3, 22% of patients with non-squamous histology in cemiplimab + chemo group received a pemetrexed-free regimen
  - Substantial heterogeneity across England and Wales. Not possible to suggest % of patients who would receive cemiplimab without pemetrexed in clinical practice and what their characteristics would be

Abbreviations: NSCLC; non small cell lung cancer, AUC; area under curve, DGD; draft guidance document

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

Supplementary appendix

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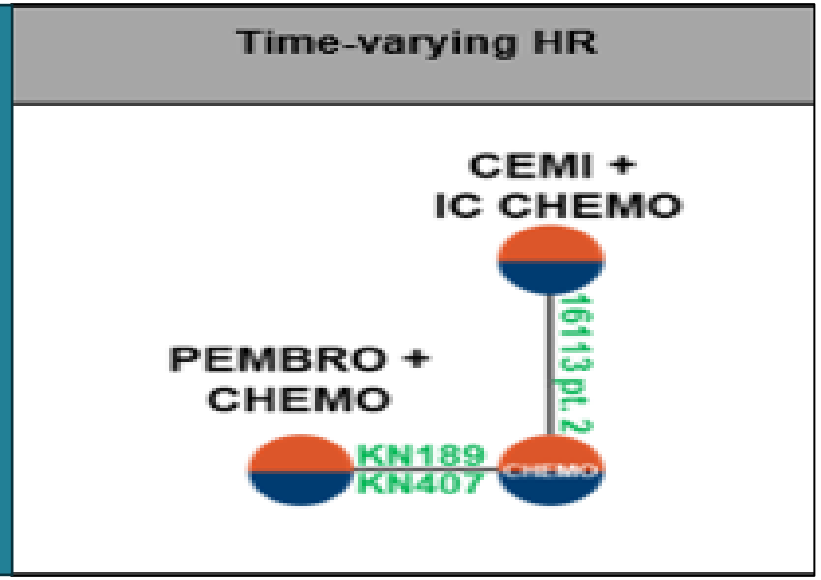
Network meta -analysis overview for PFS and OS

No direct data comparing cemiplimab + chemotherapy with pembrolizumab + chemotherapy; company conducted indirect treatment comparison

PD-L1≥1%, any histology base case



Lead team comments

- Potential treatment effect modifiers that differ between trials: follow-up duration, PD-L1 levels, age, performance status, study site locations, subsequent treatments
- Potential for difference in overall impact on progression-free survival versus overall survival

16113 pt.2 – EMPOWER Lung 3 part 2; KN189 – KEYNOTE 189; KN407 – KEYNOTE 407

Company

- Limited publicly available evidence for pembrolizumab + chemotherapy
- Indirect comparison shows no clinically meaningful differences, consistent with UK expert opinion

EAG

- Plausible that cemiplimab + chemotherapy is at least as effective as pembrolizumab + chemotherapy
- 95% credible intervals too wide to rule out important differences in favour of either treatment

AE, Adverse event; CrI, Credible interval; HR, Hazard ratio; NMA, Network meta-analysis; PD-L1, Programmed cell death ligand 1

Indirect comparison to comparator – any histology PD-L1 ≥1%

Base case point estimates uncertain - trend towards improved overall survival (without crossover) but point estimates increase when adjusted for crossover. Worse progression-free survival for cemiplimab + chemotherapy compared with pembrolizumab + chemotherapy

OS log-logistic, fixed effect model

Cemiplimab + chemotherapy vs.	Time-varying hazard ratio (95% CrI)							
	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
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)

NEW: Crossover-adjusted OS log-logistic, fixed effect model

Cemiplimab + chemotherapy vs.	Time-varying hazard ratio (95% CrI)							
	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
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)

PFS log-logistic, fixed effect model

Cemiplimab + chemotherapy vs.	Time-varying hazard ratio (95% CrI)							
	3 months	6 months	9 months	12 months	18 months	24 months	30 months	36 months
Pembrolizumab + chemotherapy	1.09 (0.77, 1.53)	1.06 (0.79, 1.45)	1.04 (0.76, 1.45)	1.03 (0.74, 1.45)	1.02 (0.72, 1.43)	1.01 (0.72, 1.42)	1.00 (0.72, 1.40)	1.00 (0.72, 1.38)

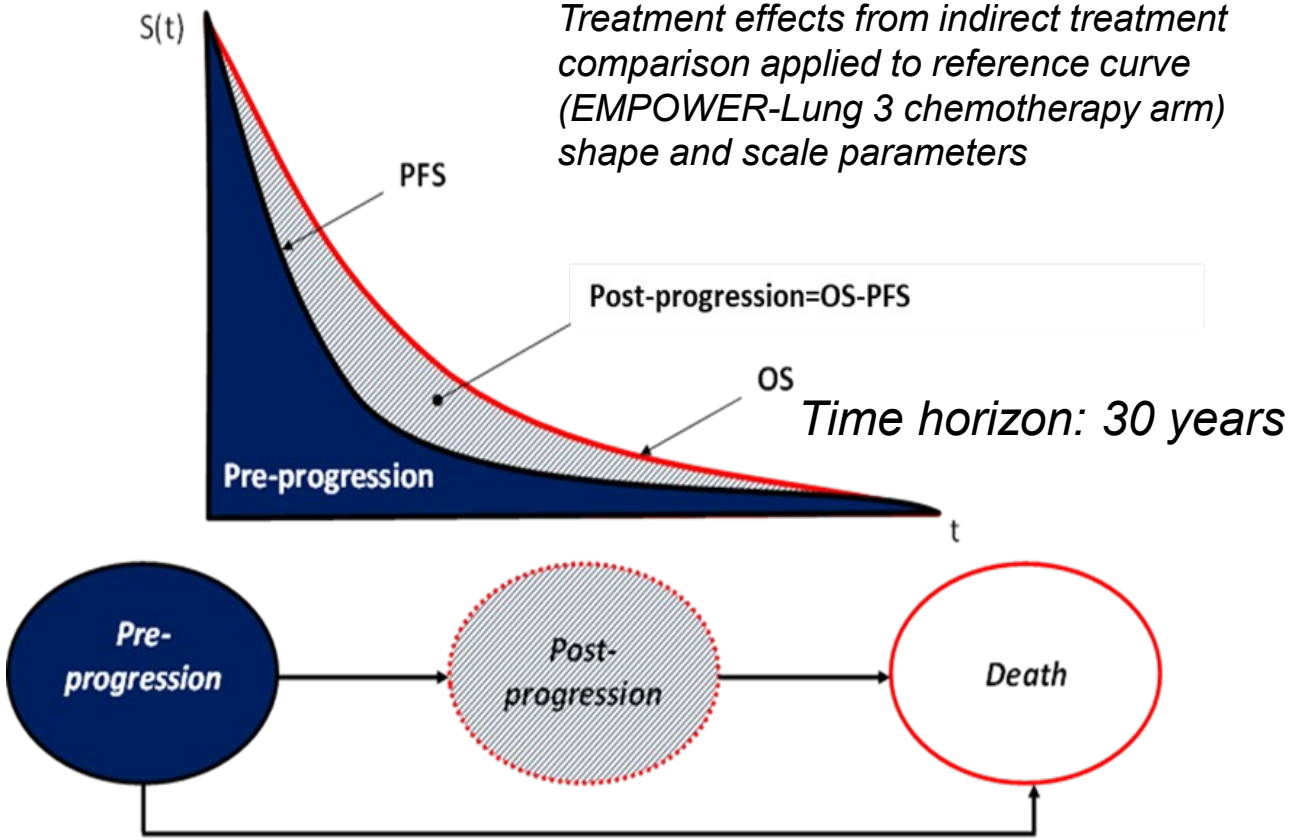
Hazard ratio below 1 indicates favourable result for cemiplimab + chemotherapy

NICE CrI, Credible interval; NMA, Network meta-analysis; OS, Overall survival; PD-L1, Programmed cell death ligand 1; PFS, Progression-free survival

Company's partitioned survival model

Cemiplimab + chemotherapy vs pembrolizumab + chemotherapy

Company also did cost comparison analysis = effectiveness 2-years



Treatment effects from indirect treatment comparison applied to reference curve (EMPOWER-Lung 3 chemotherapy arm) shape and scale parameters

Time horizon: 30 years

EAG: model structure appropriate

Impact on **cost effectiveness**:

- Choice of parametric model for overall survival
- Treatment discontinuation modelling
- Treatment waning modelling
- Utilities for progression-free and progressed-disease health states

Draft guidance:

- Incremental QALY gain mainly from NMA HR point estimates favouring cemiplimab plus chemotherapy for OS (highly uncertain)

EAG, External assessment group; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year

Recap – Key areas of uncertainty

Cemiplimab should not be used

Issue	Uncertainty
Population	• Proportion of people with non-squamous NSCLC who would have cemiplimab without pemetrexed and if EMPOWER-Lung 3 reflected this
Comparator	• Comparative effectiveness of cemiplimab plus chemotherapy and pembrolizumab plus chemotherapy
Economic model	• Use of partitioned survival model
Time to treatment discontinuation	• Impact on OS of treatment beyond progression for people in the cemiplimab plus chemotherapy arm • Impact on PFS and OS of treatment beyond 108 weeks with cemiplimab plus chemotherapy
Treatment waning	• Long term treatment effect of cemiplimab plus chemotherapy compared with pembrolizumab after stopping treatment

Abbreviations: NSCLC; non small cell lung cancer, PFS; progression free survival, OS; overall survival

Company's MAIC methods (1/2)

- Anchored MAICs performed for PFS and OS in non-squamous and squamous populations following TSD18
- Constant HR estimated for each data set
- Crossover in KEYNOTE trials:
  - Incorporated published crossover adjusted OS data from final analysis of KEYNOTE-407 (squamous histology)
  - No crossover adjusted data published to date for relevant PD-L1 ≥1% subgroup of KEYNOTE-189 but TA557 committee papers note "The results of the crossover adjustments were comparable with the main analyses, with little change in the overall effect"
- Baseline characteristics
  - Base case: EMPOWER-Lung 3 PD-L1 ≥1% population matched to ITT populations (any PD-L1) in KEYNOTE trials
- Co-variates included in the MAIC:
  - Base case: PD-L1 expression (1-49% vs. ≥50%), age (<65 vs. ≥65), ECOG PS (0 vs. 1), smoking status (current and former smokers vs. never smokers). Also, cancer stage via removal of the locally advanced (stage IIIb) patients from EMPOWER-Lung 3 dataset prior to matching
  - Scenarios: Brain metastases (present or absent) and race (Asian vs. other) as proxy for study site
  - Of modifiers proposed in DG, only duration of treatment and treatments post-progression remained unadjusted for
- Early stopping of EMPOWER-Lung 3
  - Exploratory MAIC scenarios conducted for OS in non-squamous subgroup using 2-year follow-up common to both KEYNOTE-189 and EMPOWER-Lung 3, in addition to using extended follow-up data
  - Crossover-adjusted OS data only reported for final analysis of KEYNOTE-407. Only this timepoint is included in MAIC analyses for squamous subgroup, which aligns to follow-up time in EMPOWER-Lung 3

Abbreviations: MAIC; matching adjusted indirect comparison, PFS; progression free survival, OS; overall survival, PD-L1; programmed death ligand 1, ITT; intention to treat, ECOG; eastern cooperative oncology group

Company's MAIC methods (2/2)

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.

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.

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Abbreviations: MAIC; matching adjusted indirect comparison, PD-L1; programmed death ligand 1, ECOG; eastern cooperative oncology group

Summary of PFS and OS MAIC results across key scenarios

Full summary table including final analysis results

Bolded values = statistically significant

Included in alternative company base case

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

a, Brain metastases were only included as a covariate in the non-squamous populations; 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).

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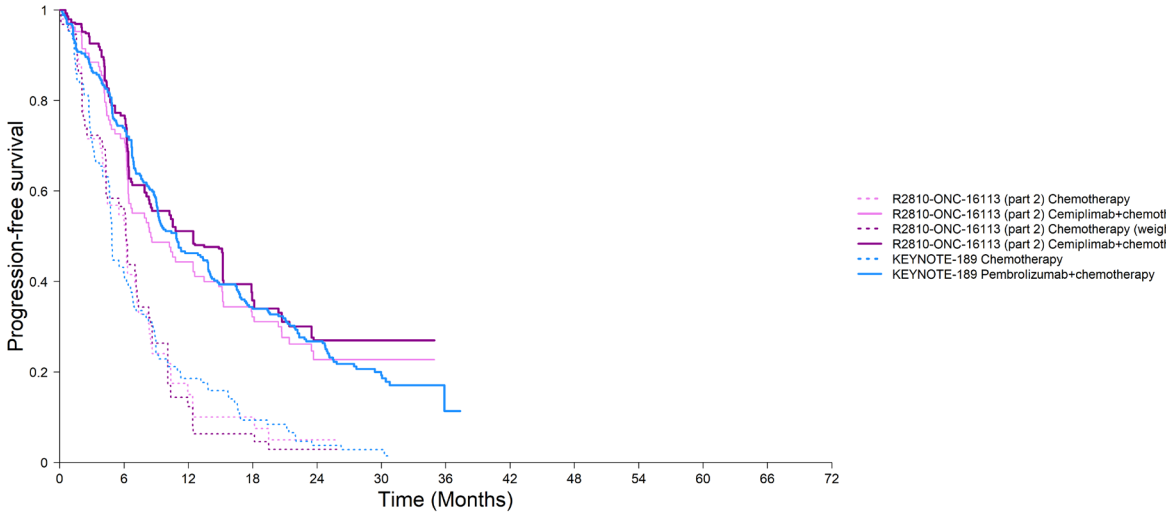
Abbreviations: PFS; progression free survival, OS; overall survival, MAIC; matching adjusted indirect comparison, PD-L1; program med death ligand 1

MAIC adjustment – progression free survival

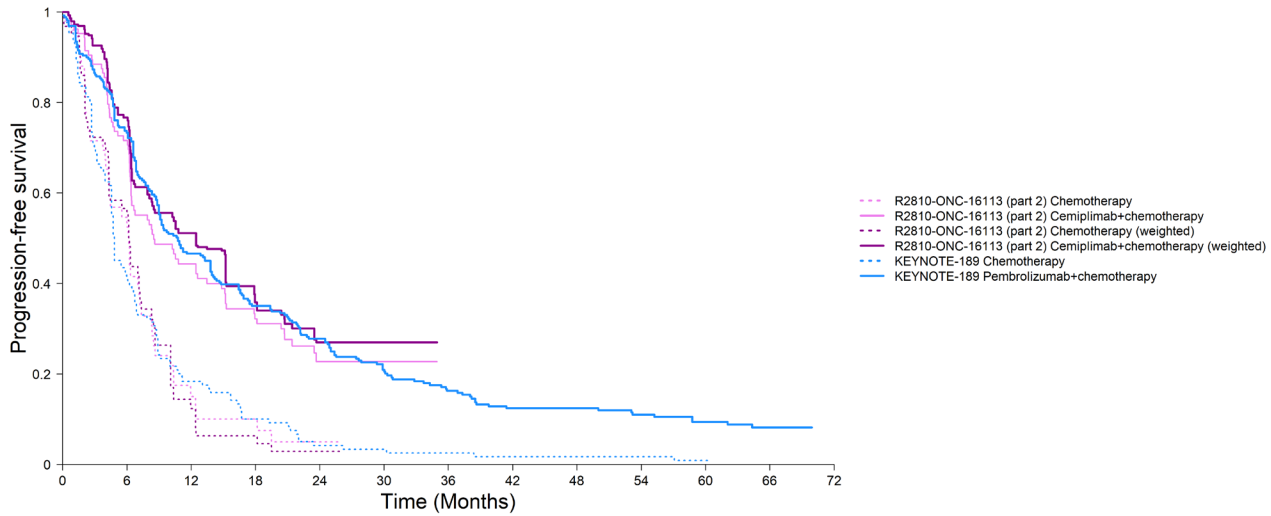
Adjusting for treatment effect modifiers numerically improved improved PFS point estimate but no significant difference

Progression-free survival for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy in PD-L1 ≥1%, non-squamous population based on KEYNOTE-189

KEYNOTE-189 final analysis



KEYNOTE-189 extended follow up



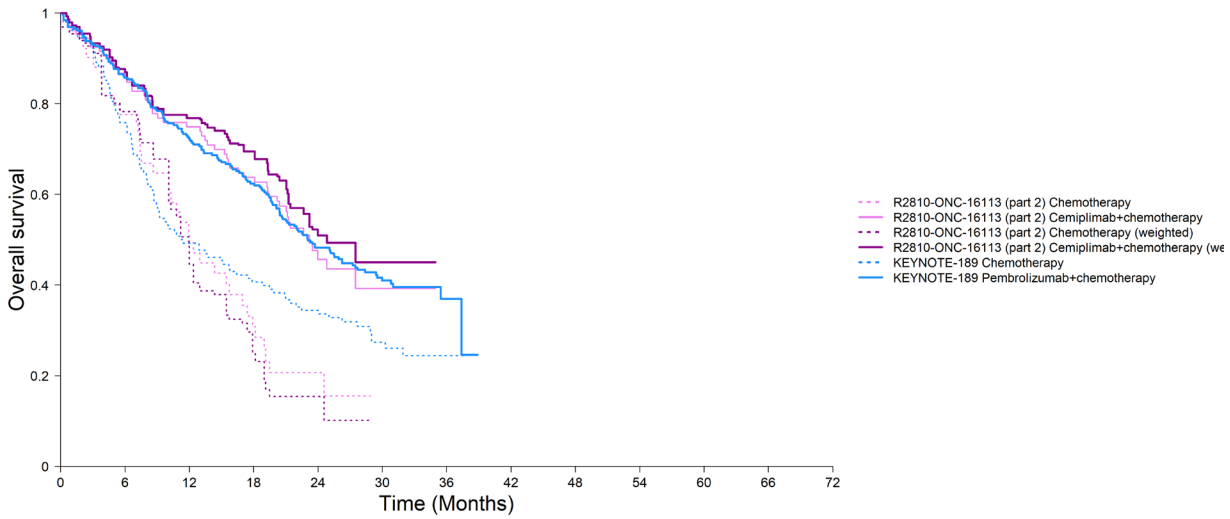
Abbreviations: PFS; progression free survival, PD-L1; programmed death ligand 1

MAIC adjustment - overall survival

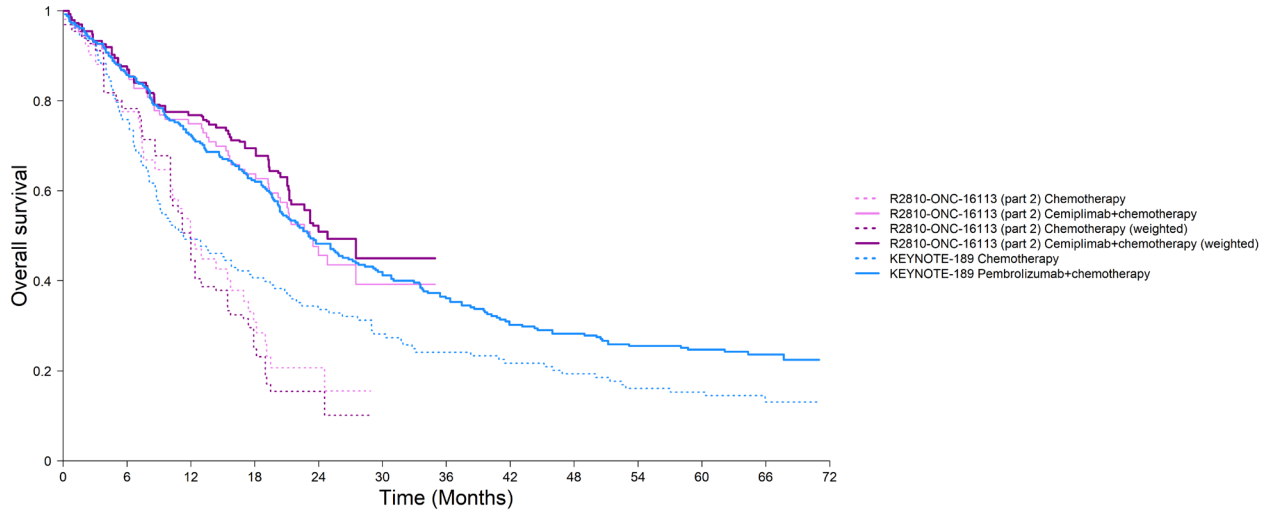
Similar MAIC results for PFS and OS regardless of the KEYNOTE-189 data used

Overall survival for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy in PD-L1 ≥1%, non-squamous population based on KEYNOTE-189

KEYNOTE- 189 final analysis



KEYNOTE-189 extended follow up



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Abbreviations: MAIC; matching adjusted indirect comparison, PFS; progression free survival, OS; overall survival, PD-L1; programmed death ligand 1, ECOG PS; eastern cooperative oncology group performance status

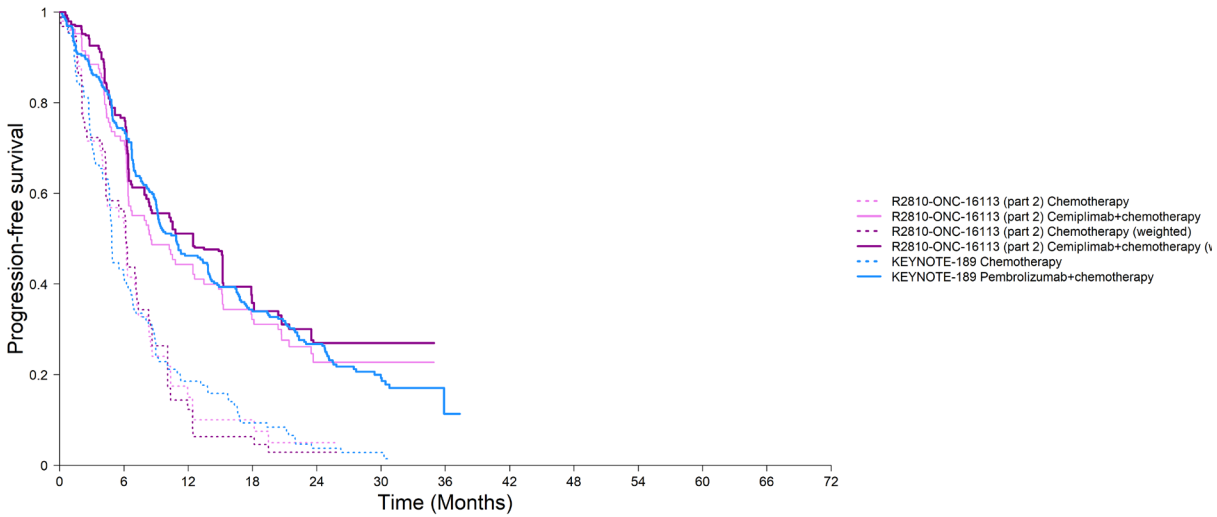
MAIC adjustment – progression free survival

MAIC results were similar between the PD-L1 ≥1%, squamous and any PD-L1, squamous populations

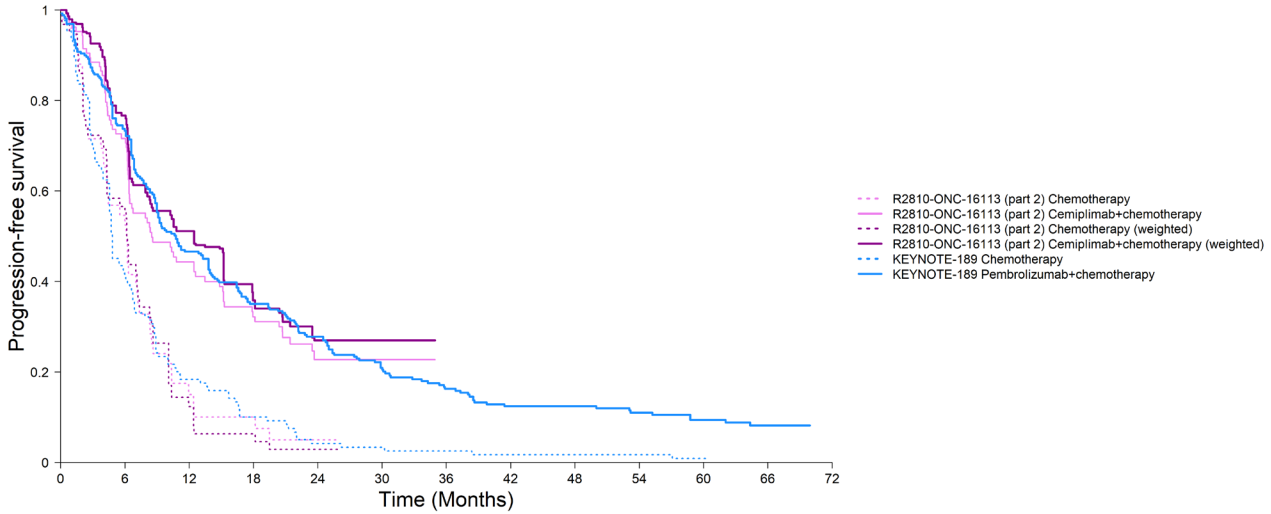
Slightly less favourable for squamous subgroup

Progression-free survival for cemiplimab + chemotherapy versus pembrolizumab + chemotherapy in PD-L1 ≥1%, squamous population* based on KEYNOTE-407

KEYNOTE-407 final analysis



KEYNOTE-407 extended follow up



*No adjustment for ECOG PS in squamous subgroups due to low numbers with ECOG 0 in EMPOWER-Lung 3 trial subgroup

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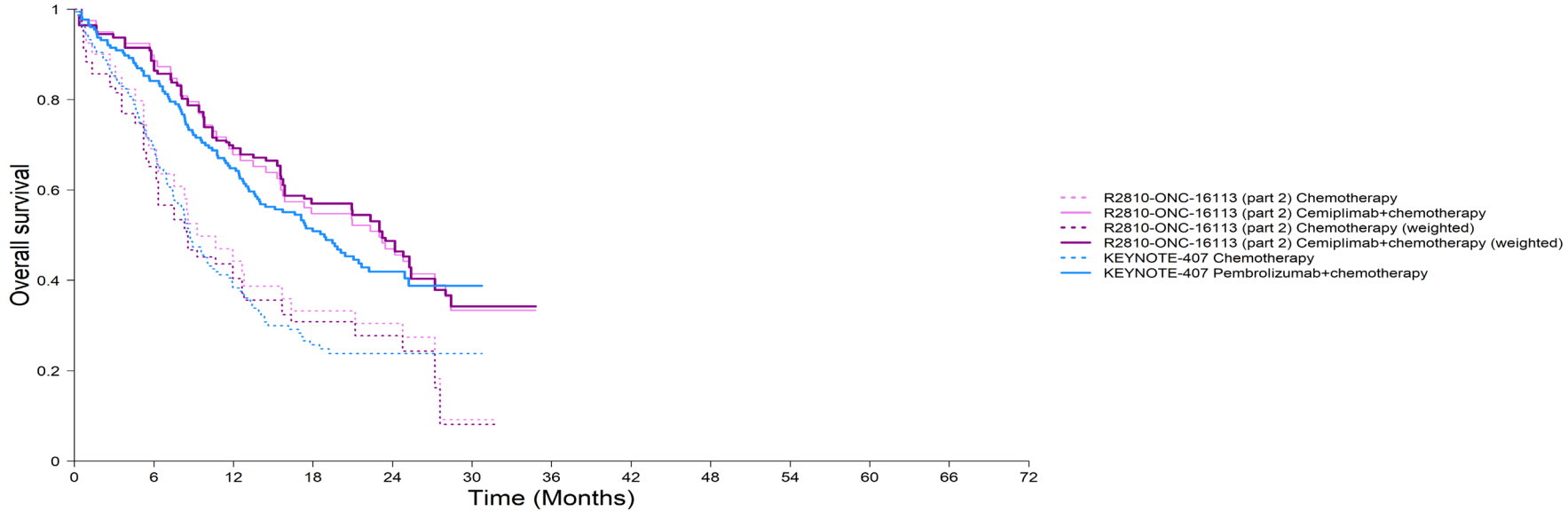
Abbreviations: MAIC; matching adjusted indirect comparison, PD-L1; programmed death ligand 1, ECOG PS; eastern cooperative oncology group performance status

MAIC adjustment - overall survival

MAIC results were similar between the PD-L1 ≥1%, squamous and any PD-L1, squamous populations

Slighlty less favourable for squamous subgroup

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



*No adjustment for ECOG PS in squamous subgroups due to low numbers with ECOG 0 in EMPOWER-Lung 3 trial subgroup

Abbreviations: MAIC; matching adjusted indirect comparison, PD-L1; programmed death ligand 1, ECOG PS; eastern cooperative oncology group performance status

Reweighted IO usage as observed in KEYNOTE studies

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%

Abbreviations: IO; immunotherapy