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

For public – contains redacted information

Technology appraisal committee D [12 February 2025]

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Company: Regeneron

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

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary
- ❑ Supplementary appendix

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Key issues

Issue	ICER impact
Choice of target population and comparators	Unknown 
Indirect treatment comparison	Unknown 
Assumptions regarding time on treatment	Large 
Assumptions regarding extrapolating treatment effect	Moderate 

Background on non-small-cell lung cancer

Lung cancer is leading cause of cancer-related deaths in UK

Epidemiology

- Estimated 37,259 cases of lung cancer in England and Wales in 2023
- Lung cancer is leading cause of cancer-related deaths in UK
- 85% to 90% of lung cancer cases estimated to be non-small-cell lung cancer (NSCLC)

Diagnosis and classification

- Classified by histology - squamous cell or non-squamous cell (adeno- and large cell)
- 'Targetable' mutations or % cells with Programmed Cell Death Ligand 1 [PD-L1] determine treatment
- Staged from 0 to 4 based on Tumour, Nodes, Metastasis criteria
- Often diagnosed at advanced (stage 3) or metastatic stage (stage 4)

Symptoms and prognosis

- Early stages may be asymptomatic, later symptoms include fatigue, cough, chest pain
- 'Curative-intent' surgery often used for stage 1 to 3 NSCLC, but recurrence common
- 5-year survival: 68% (stage 1), 49% (stage 2), 25% (stage 3) and 9% (stage 4)

Evidence base:

- No trials of cemiplimab with platinum-based chemotherapy compared with company's choice of comparator

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

Patient perspectives

New treatment options needed for advanced non-small cell lung cancer

Submissions from Roy Castle Lung Cancer Foundation

- 1-year survival rate for lung cancer at all stages (diagnosed in 2022) in England is 48% → lower for advanced lung cancer
- Despite current therapy, outcomes remain poor
  Immunotherapy has provided a new treatment option
- Symptoms (e.g. breathlessness, cough and weight loss) difficult to treat without active anti-cancer therapy, and distressing for loved ones to observe
- Results of EMPOWER Lung-3 study of cemiplimab + chemotherapy broadly in line with pembrolizumab in KEYNOTE trials
- Side effects a disadvantage of cemiplimab + chemotherapy

"Cemiplimab brings a needed treatment alternative to standard of care in the advanced non-small cell lung cancer treatment setting"

"Lung cancer patients with advanced disease have a particularly poor outlook, with an obvious impact on family and carers"

Cemiplimab (Libtayo®, Regeneron)

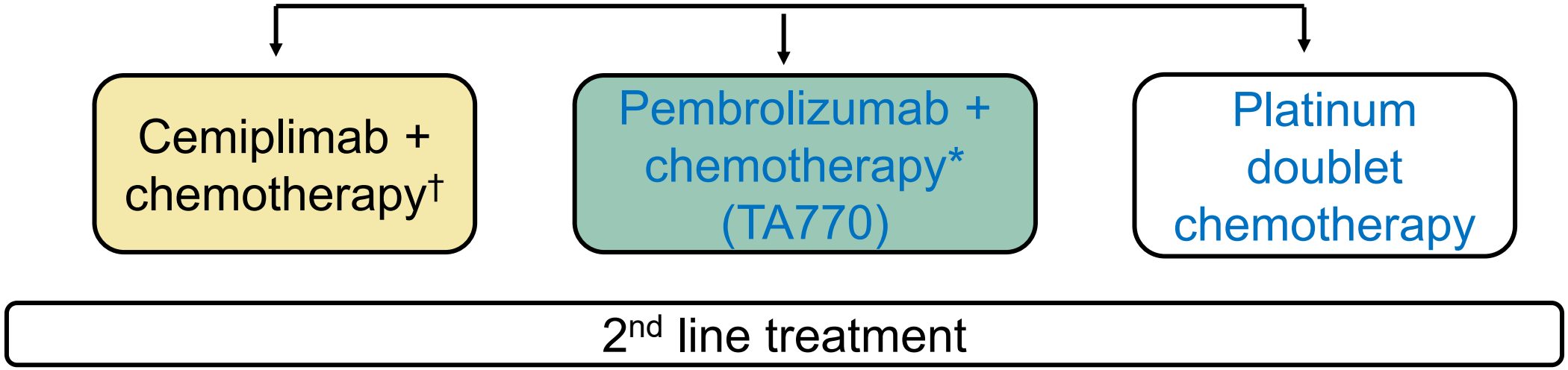
'Immunotherapy' not 'targeted' therapy so population has no targetable mutations, Time to stopping treatment differs in license and trial

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 • 2-year stopping rule anticipated by company
Testing	• PD-L1 test part of NHS routine practice
Price	• List price: £4650 per 350mg vial • Average cost of cemiplimab with chemotherapy at list price in 1st year: £61,351 • Commercial arrangement in place for cemiplimab

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

Treatment pathway: squamous, PD-L1 <50%

Company: pembrolizumab + chemotherapy most relevant comparator
License – PD-L1 ≥1% locally advanced - not a candidate for definitive chemoradiation - or metastatic



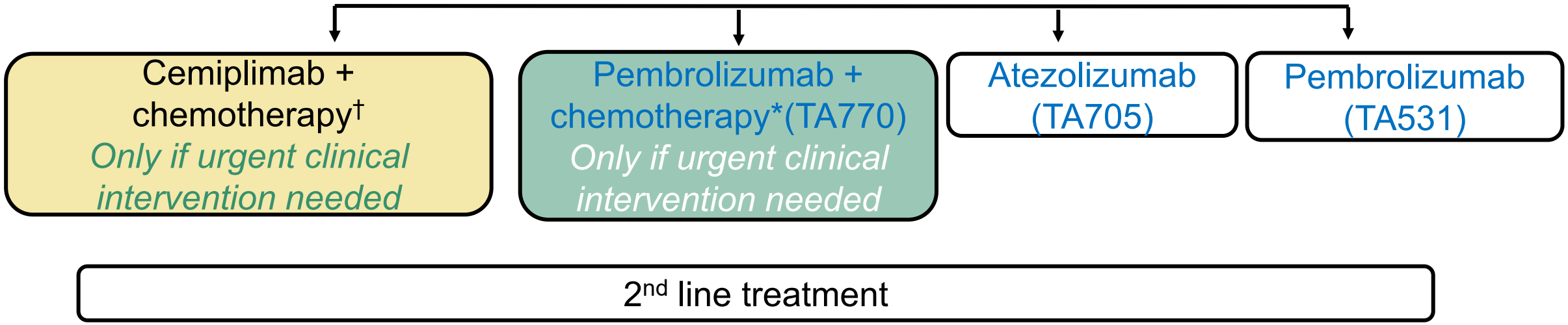
* Paclitaxel with carboplatin
† Paclitaxel with carboplatin or cisplatin

Proposed positioning
Comparator in company's submission
Blue text Comparator in scope

Treatment pathway: squamous, PD-L1 ≥50%

Different comparators than for PD-L1 <50%

Company: pembrolizumab + chemotherapy most relevant comparator



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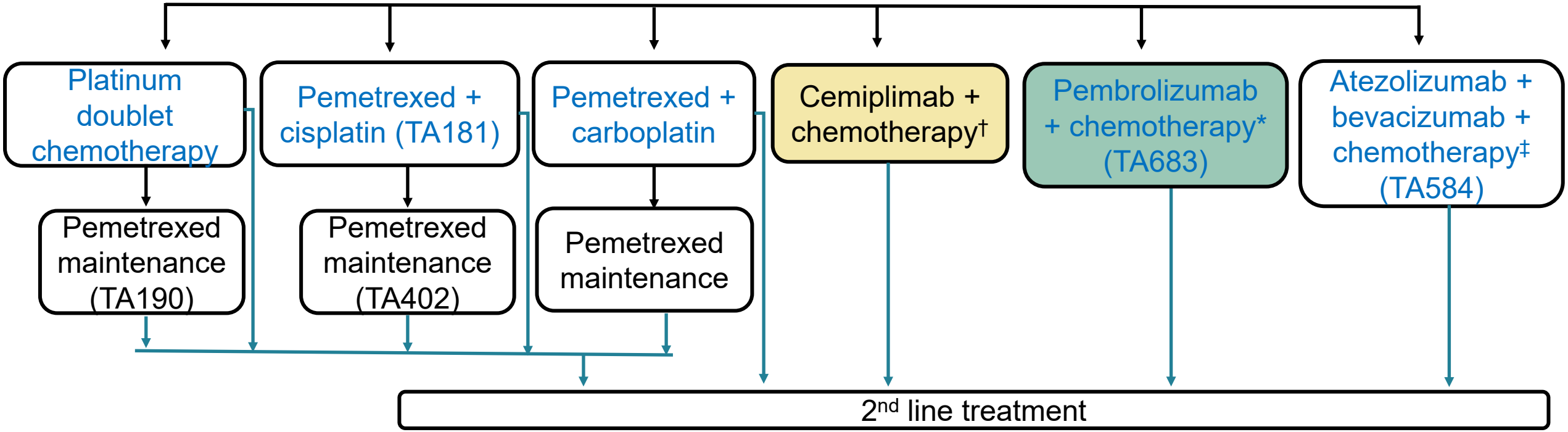
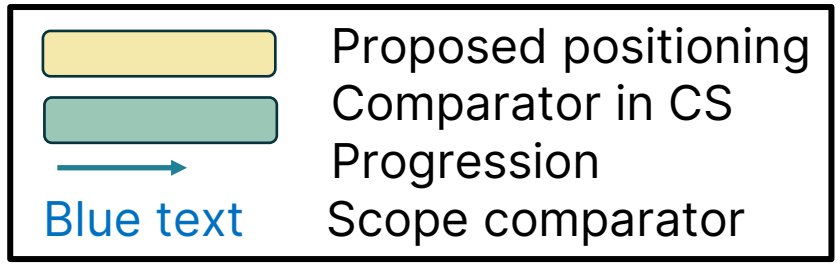


* Carboplatin or cisplatin with pemetrexed

† Paclitaxel or pemetrexed with carboplatin or cisplatin

‡ carboplatin and paclitaxel

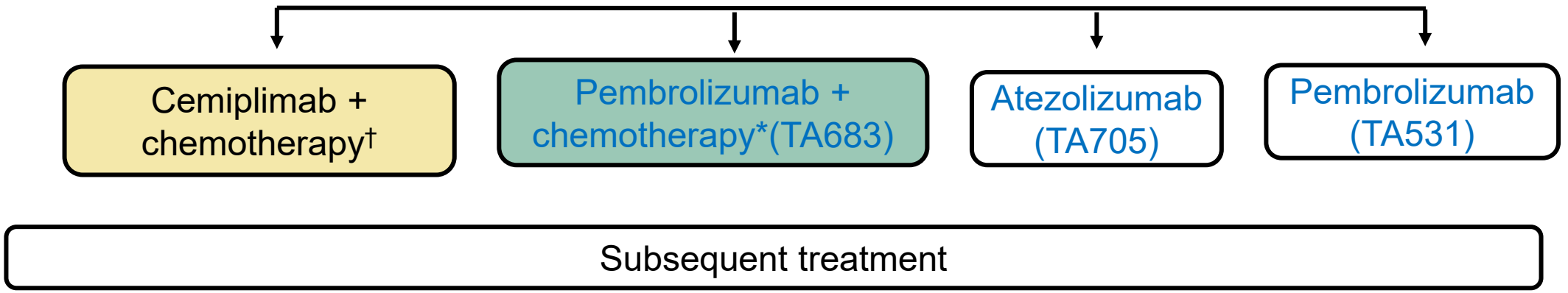


NSCLC, Non-small-cell lung cancer; PD-L1, Programmed cell death ligand 1; TA, Technology appraisal

Treatment pathway: non-squamous, PD-L1 ≥50%

Different comparators than for PD-L1 <50%

Company: pembrolizumab + chemotherapy most relevant comparator



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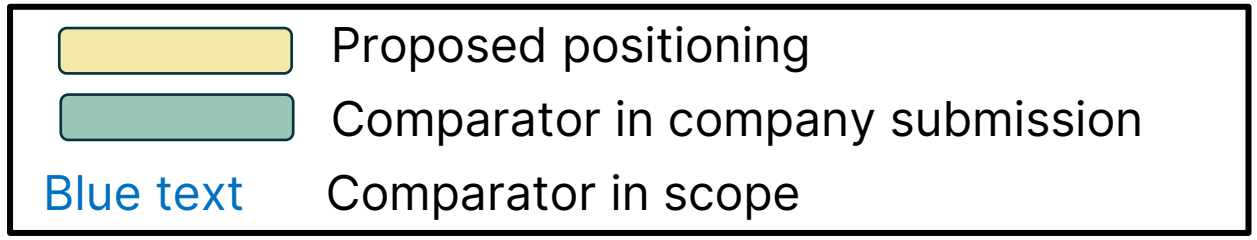

NSCLC, Non-small-cell lung cancer; PD-L1, Programmed cell death ligand 1; TA, Technology appraisal

Clinical perspectives - British Thoracic Oncology Group

Aim of treatment: improve survival and delay progression while maintaining quality of life

- Improvement in median overall survival of 3 months with cemiplimab + platinum-based chemotherapy over control a clinically significant treatment response
- Key trial overrepresents squamous cell (more difficult to treat) and stage III patients
- Cemiplimab more effective in PD-L1≥1% (PD-L1 positive) than PD-L1<1% (PD-L1 negative)
- Current standard care pembrolizumab option to give every 6 weeks; cemiplimab given every 3 weeks.

"Comparatively to other cancer types, NSCLC have relatively poor outcomes and as such treatments in this area are required"

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

Key issues: Target population and relevant comparators (1)

Company provides evidence for only a subset of population in marketing authorisation - pembrolizumab + chemotherapy most relevant comparator

Background

- NICE scope population: 'Adults with untreated locally advanced (not a candidate for definitive chemoradiation) or metastatic NSCLC, which expresses PD-L1 on 1% or more of tumour cells and has no EGFR, ALK or ROS-1 genetic alterations'

Company

- Provided evidence for a subset of total NICE scope population
- People '**who would otherwise be offered treatment with an immunotherapy + chemotherapy combination**'
- Pembrolizumab + chemotherapy most relevant comparator

ALK, Anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, Non-small-cell lung cancer; PD-L1, Programmed cell death ligand 1

Target population and comparators by histology + % PDL-1 (2)

Company: Chemotherapy alone, immunotherapy monotherapy and atezolizumab + chemotherapy are not relevant comparators

PD-L1	1 to 49%	≥50%	Company comments
Squamous	Pembrolizumab + carboplatin + paclitaxel		**Yes**
		Only if urgent	
	Platinum doublet chemotherapy		**No** Immunotherapy routinely offered irrespective of histology or PD-L1 unless contraindicated
	-	Pembrolizumab	**No** Chemotherapy helps achieve a rapid response → do not anticipate cemiplimab + chemotherapy to be used instead of immunotherapy monotherapy
	-	Atezolizumab	
Non squamous	**PD-L1 1 to 49%**	**PD-L1 ≥50%**	
	Pembrolizumab + pemetrexed + platinum chemotherapy		**Yes**
	Pemetrexed + platinum doublet chemotherapy		As above for squamous
	Atezolizumab + bevacizumab +carboplatin+ paclitaxel (ABCP)	-	**No** Not common in UK practice (≈ 8%)
	-	Pembrolizumab	**No** As for squamous
	-	Atezolizumab	

EAG, External assessment group; PD-L1, Programmed cell death ligand 1

Key issues: Target population and comparators (3)

EAG comments

- In squamous PD-L1 ≥50% group, pembrolizumab + chemotherapy recommended only if need urgent intervention; based on company's proposed population, people who do **not** require intervention urgently, would not be eligible to receive cemiplimab + chemotherapy
- EAG's clinical adviser: pembrolizumab + chemotherapy is only suitable comparator based on company's target population
- Either cemiplimab + chemotherapy or pembrolizumab + chemotherapy would only be offered to
  - people who are not contraindicated to immunotherapy + chemotherapy and
  - people with PD-L1 ≥50%, squamous histology who require urgent clinical intervention

What is committee's view on company's choice of target population?
Could the target population be identified by clinicians?
Is pembrolizumab + chemotherapy the only relevant comparator?

EAG, External assessment group; NSCLC, Non-small-cell lung cancer; PD-L1, Programmed cell death ligand 1

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

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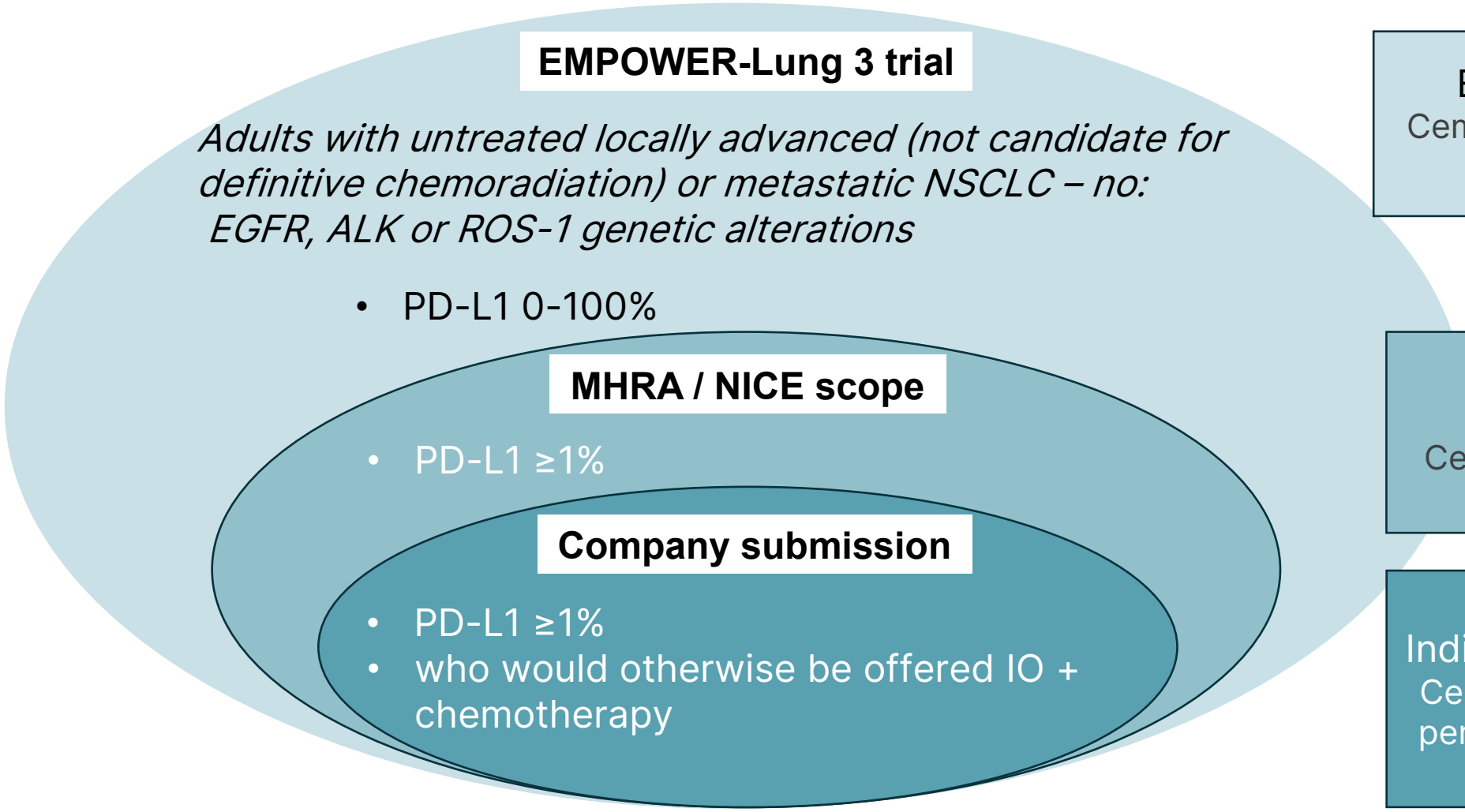
Key clinical trial – EMPOWER-Lung 3 Part 2

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** 108 weeks = **2 years** **treatment beyond progression 'allowed by protocol'** + 4 cycles chemotherapy + pemetrexed until progression for non-squamous
Comparator	Placebo IV every 3 weeks maximum 108 weeks = 2 years + 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

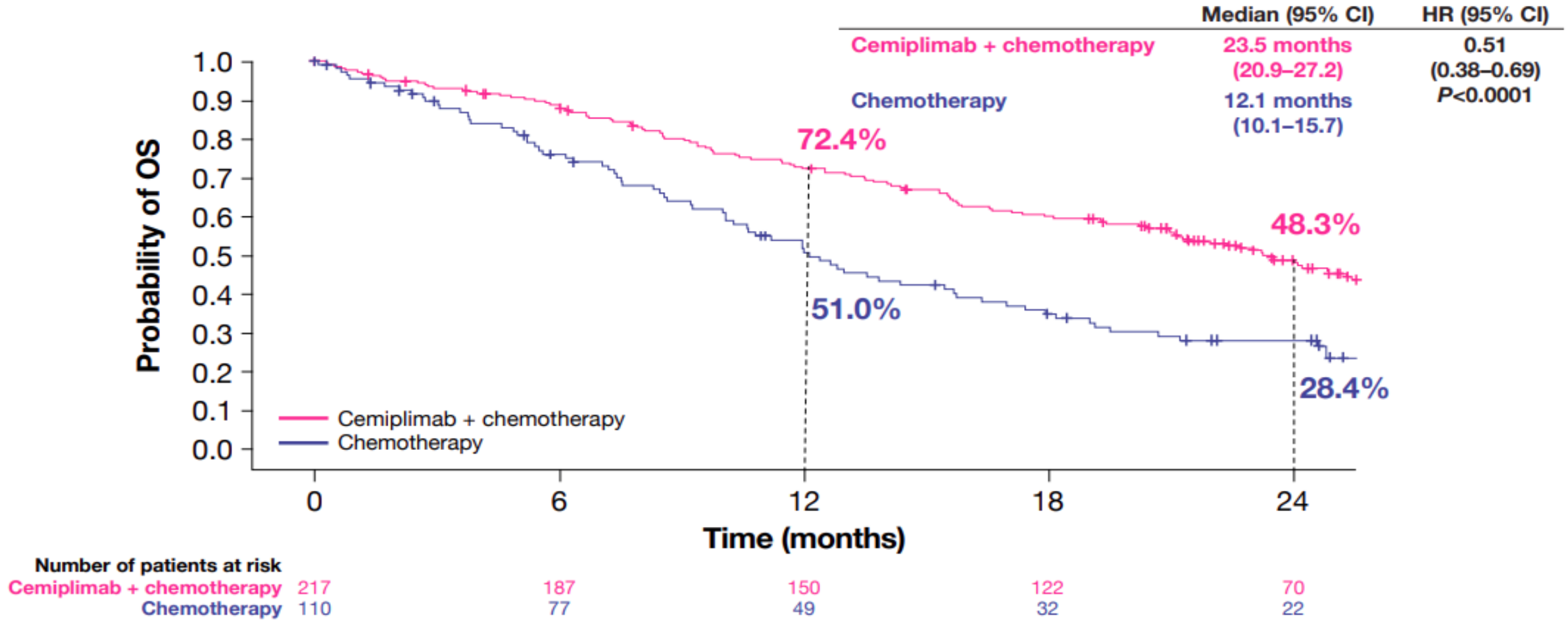
Indirect treatment comparison
Cemiplimab + chemotherapy vs. pembrolizumab + chemotherapy

ALK, Anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ITT, Intention to treat; MHRA, Medicines and Healthcare products Regulatory Agency; NSCLC, Non-small-cell lung cancer; PD-L1, Programmed cell death ligand 1

Key clinical trial results – overall survival PD-L1 ≥1%

1 year ↑ in median OS for cemiplimab + chemotherapy compared with placebo + chemotherapy

Chemotherapy comparator not in company's model; trial ended early for benefit



What is the potential impact of the trial having stopped early for benefit?

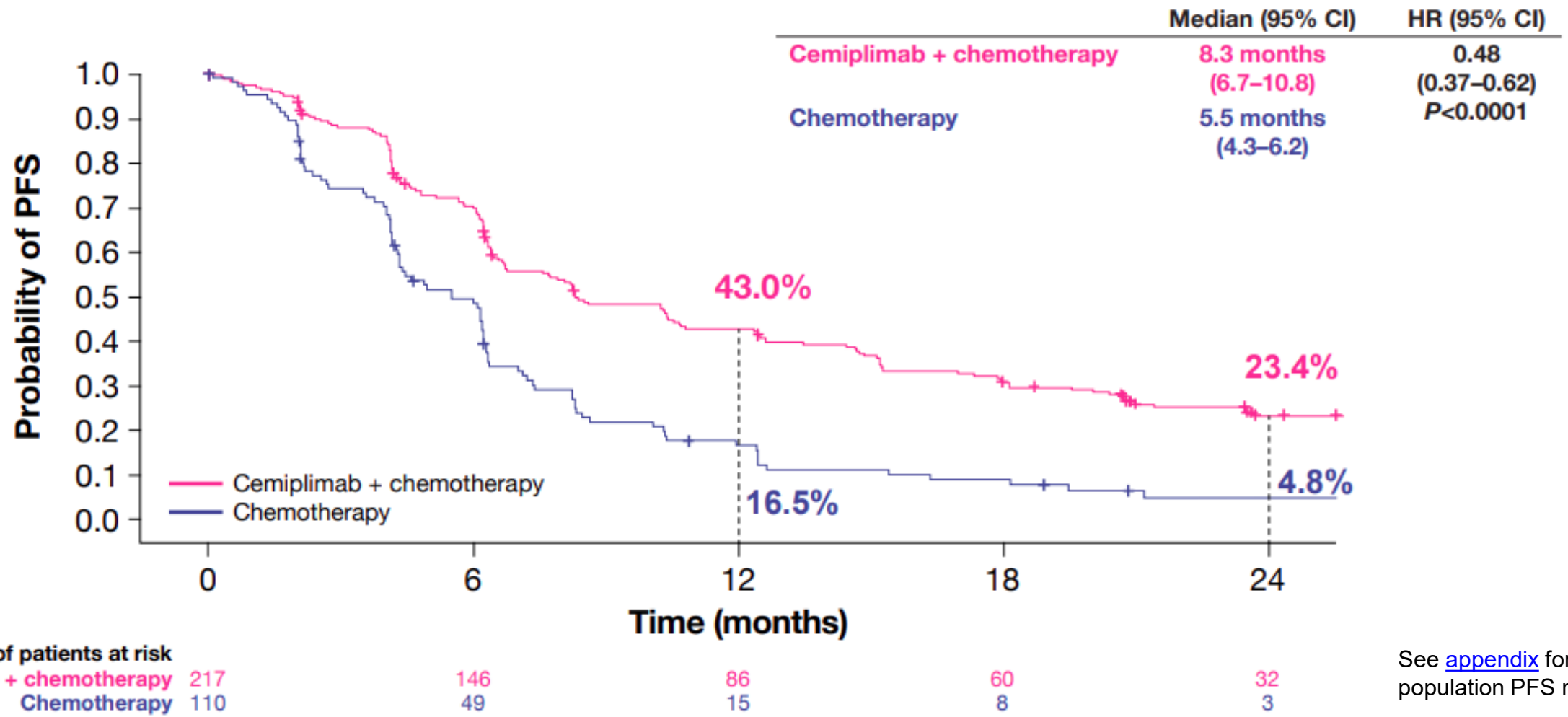
See appendix for ITT population OS results

CI, Confidence interval; HR, Hazard ratio; MHRA, ITT, Intention to treat; Medicines and Healthcare products Regulatory Agency; NSCLC, Non-small-cell lung cancer; OS, Overall survival; PD-L1, Programmed cell death ligand 1

Key clinical trial results – progression-free survival PD-L1 ≥1%

2.8 months improvement in median PFS compared with placebo + chemotherapy

Control treatment not in company base case



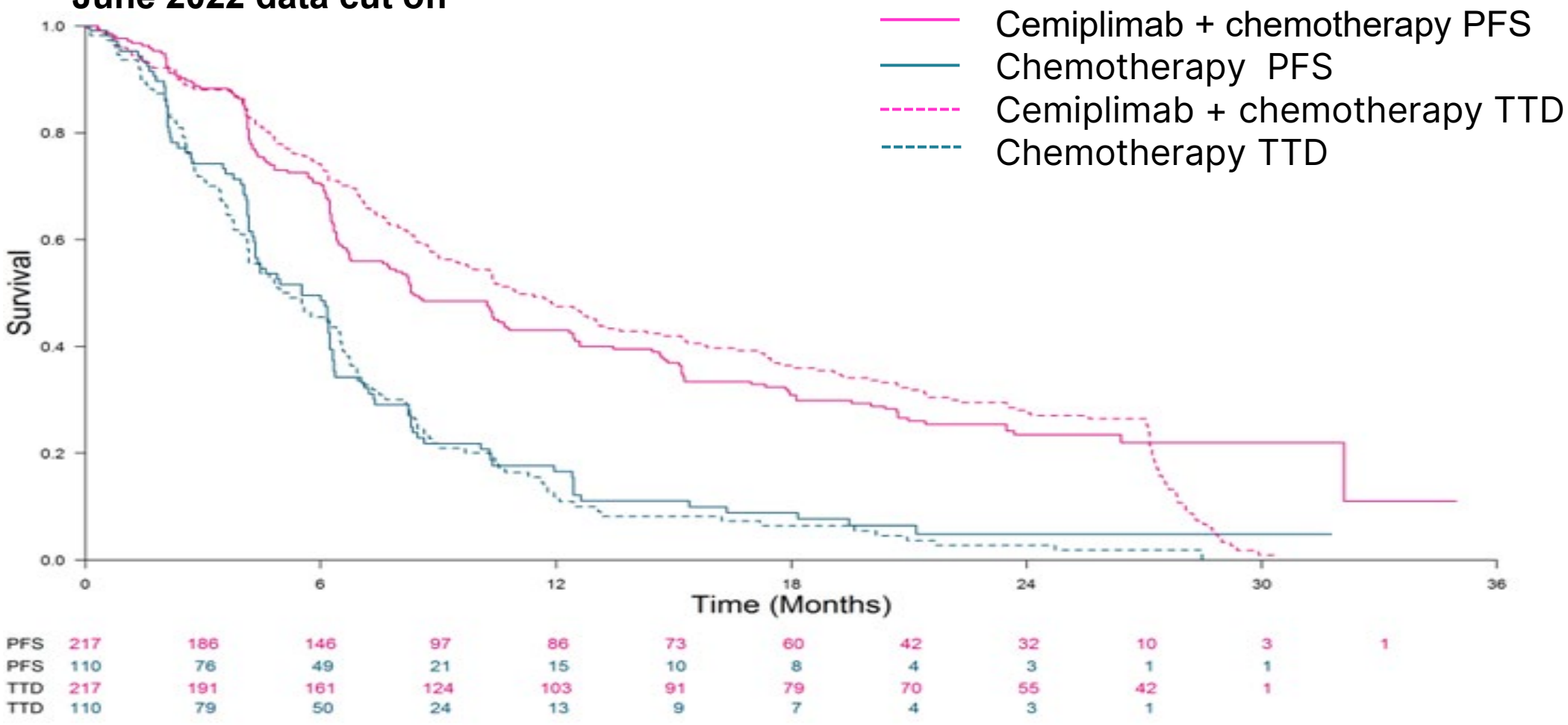
See appendix for ITT population PFS results

CI, Confidence interval; HR, Hazard ratio; MHRA, Medicines and Healthcare products Regulatory Agency; NSCLC, Non-small-cell lung cancer; PD-L1, Programmed cell death ligand 1; PFS, Progression-free survival

Progression-free survival and time to treatment discontinuation in EMPOWER-Lung 3 trial - any histology PD-L1 ≥1%

Some people in EMPOWER-LUNG 3 continued cemiplimab treatment beyond progression

June 2022 data cut off



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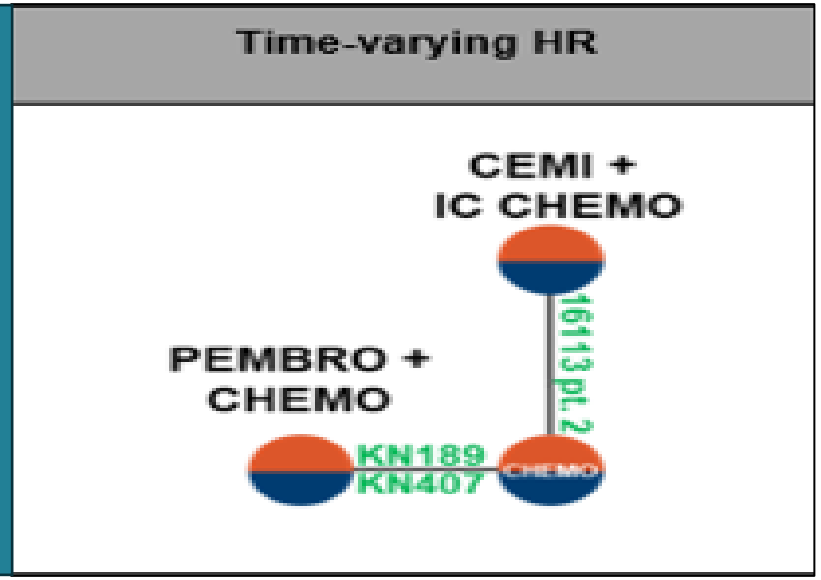
PD-L1, Programmed cell death ligand 1; PFS, Progression-free survival; TTD, Time to treatment discontinuation

Network meta-analysis overview for PFS and overall survival

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 but worse progression-free survival for cemiplimab + chemotherapy compared with pembrolizumab + chemotherapy

Overall survival (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)

Progression-free survival (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

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

Key issues: Validity of indirect treatment comparison (1)

Little data by PD-L1 status for comparator trials; not possible to assess 'transitivity'

Background

- Company base case network meta-analyses population PD-L1 level ≥1%

Company

- Trials included people with PD-L1 <1% and PD-L1 ≥1%
- Comparator trials did not report baseline characteristics according to PD-L1 status → so assumed similar treatment effect

EAG

- Little data according to PD-L1 status and few 'closed loops'
  so not possible to assess transitivity
- Possible to identity differences between trials for some prognostic factors:
  - chemotherapy regimens differed across trials → variation may impact NMA results
  - trials of pembrolizumab + chemotherapy allowed crossover following progression; but did not report adjusted results. EMPOWER Lung-3 trial did not allow crossover → may favour cemiplimab because crossover could dilute OS treatment effect for pembrolizumab + chemotherapy

EAG, External assessment group; NMA, Network meta-analysis; PD-L1, Programmed cell death ligand 1

Key issues: Validity of indirect treatment comparison (2)

Lead team comments

- KEYNOTE studies, including pivotal trial KEYNOTE-189 for pembrolizumab plus chemotherapy, conducted in different countries than EMPOWER-Lung 3
- EMPOWER-Lung 3: China, Georgia, Greece, Malaysia, Poland, Romania, Russia, Thailand, Turkey and Ukraine –appendix
- KEYNOTE-189: Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Israel, Italy, Japan, Netherlands, Spain, UK and USA –appendix
- May differ in health care resource use and standard of care with implications for
  - validity of transitivity assumption and
  - generalisability to UK practice

Is the indirect evidence comparing cemiplimab + chemotherapy with pembrolizumab + chemotherapy sufficient for decision-making?

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

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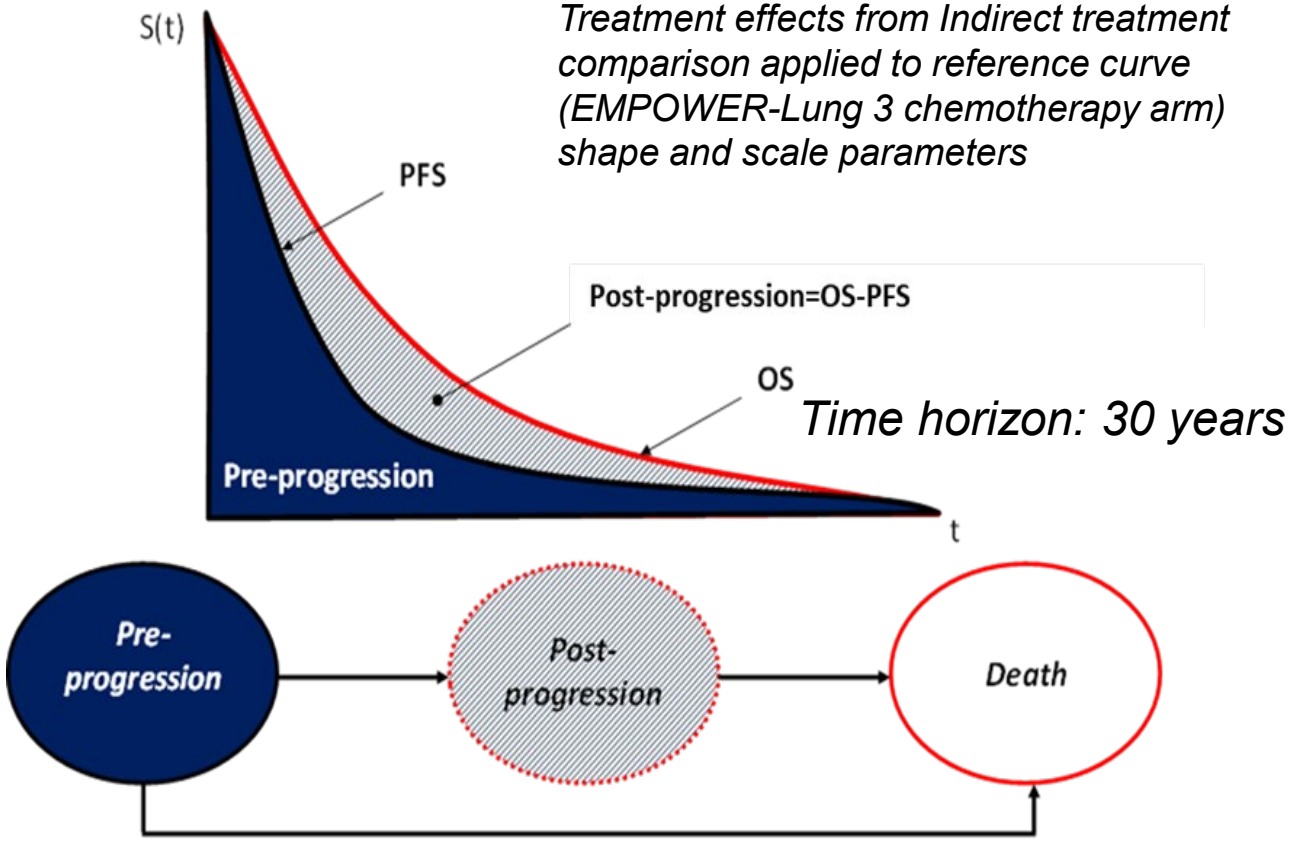
Company's partitioned survival model

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

- Monthly cycle length

Treatment affects **quality-adjusted life years**:

- ↑ overall survival
- ↓ pre-progression survival time
- ↑ post-progression survival time
- ↓ grade 3+ adverse events
- *Most gain in overall survival after treatment*

Treatment affects **costs**:

- ↑ treatment acquisition costs if time on treatment for cemiplimab>pembrolizumab - EAG base case and company scenario
- ↑ total disease management costs
- ↓ adverse events

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

EAG, External assessment group; OS, Overall survival; PFS, Progression-free survival

Key Issue: Duration of treatment – affect costs

Company assume time on treatment = PFS; EAG uses ratio of time on treatment:PFS

Background

- EMPOWER-Lung 3 protocol allows treatment to continue beyond disease progression

Company

- Assume time on treatment = progression free survival
- Interpret ratios with caution as violates assumption of independence of groups

EAG

- Assuming time on treatment = PFS ignores that time on treatment impacts outcomes
- Underestimates costs for cemiplimab + chemotherapy and overestimates costs for pembrolizumab + chemotherapy

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

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

EAG, External assessment group; PFS, Progression-free survival; ToT, Time on treatment

Key issue: Waning of treatment effect beyond stopping treatment (1)

Company continues to extrapolate treatment effect from year 2 to year 5 for both treatments; EAG assume gradual convergence of hazards from year 2 to year 5

Background

- Model includes 2-year stopping rule for both cemiplimab and pembrolizumab – reflects trial

Company

- Continues extrapolating of treatment effect from year 2 to year 5 for both treatments, then hazard of progression and death **immediately** set equal to chemotherapy alone
- 5-year time-point supported by KEYNOTE-189 and 407 - continued benefit beyond treatment stopping
- UK experts: continued benefit after 2 years; reasonable to generalise long-term follow up data for pembrolizumab and assume same waning for cemiplimab
- Many NICE technology appraisals use this

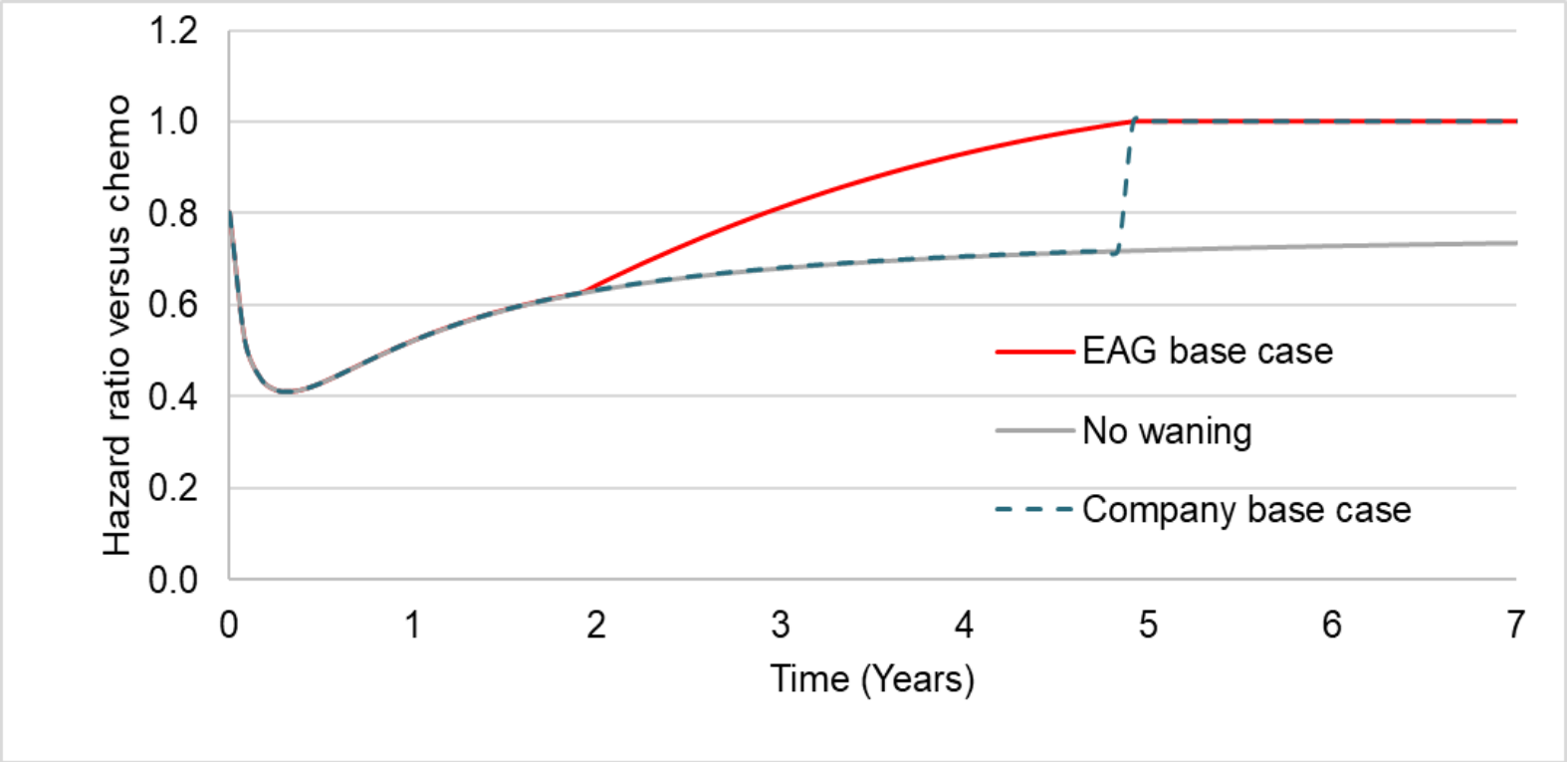
EAG

- 'Immediate' waning at 5 years:
  - overestimates benefit both cemiplimab and pembrolizumab
  - doesn't reflect immunotherapy mechanism → 'gradual' waning more realistic
- EAG base case 'gradual' waning of effect for both treatments beginning at 2 years and ending at 5 years

EAG, External assessment group; OS, Overall survival; PFS, Progression-free survival

Key issue: Waning of treatment effect beyond stopping treatment (2)

Company and EAG base case treatment effect waning assumption



Other considerations

- In TA683 pembrolizumab + chemotherapy for untreated, metastatic non-squamous NSCLC, committee accepted linear waning from 3 to 5 years
- In TA770 pembrolizumab + chemotherapy for untreated, metastatic squamous NSCLC, committee accepted treatment effect lasting to 5 years based on 5-year follow up from KEYNOTE-407

Is a 2 year stopping rule appropriate for cemiplimab?

What is the committee's preferred modelling of treatment effect following stopping treatment?

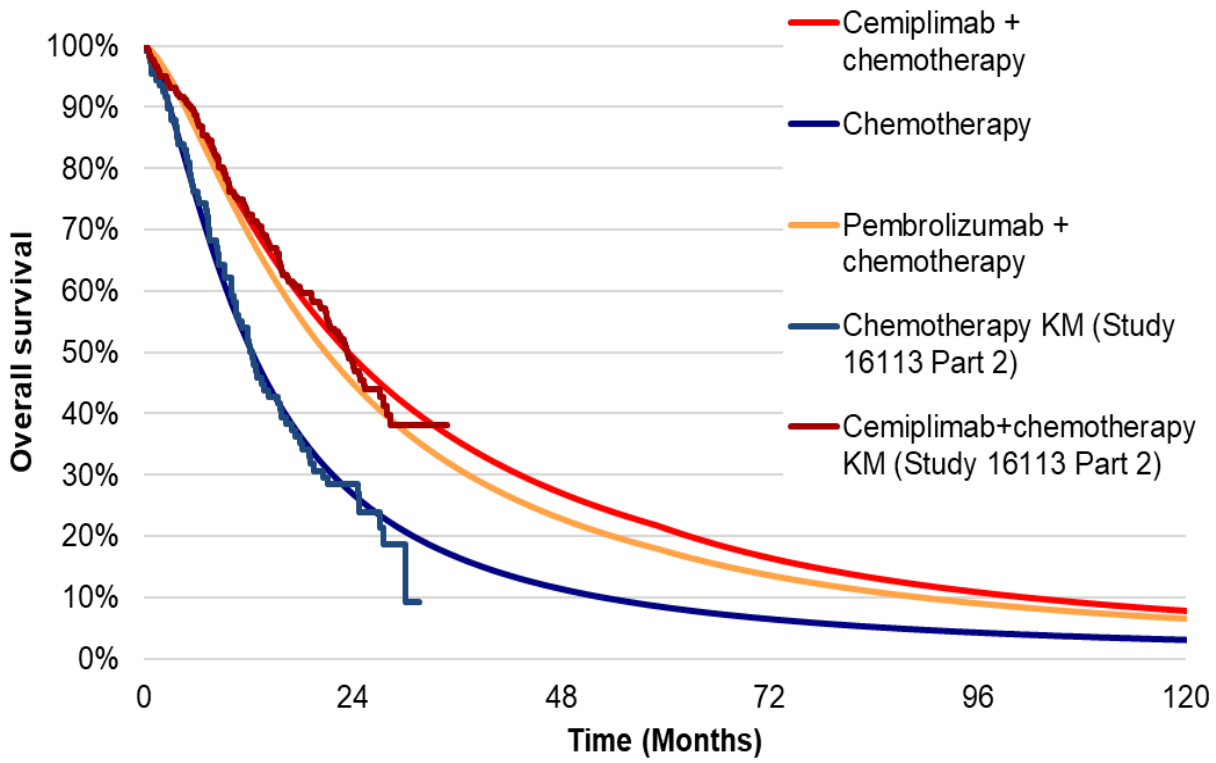
Note: figure for illustrative purposes

EAG, External assessment group; NSCLC, Non-small-cell lung cancer; TA, Technology appraisal

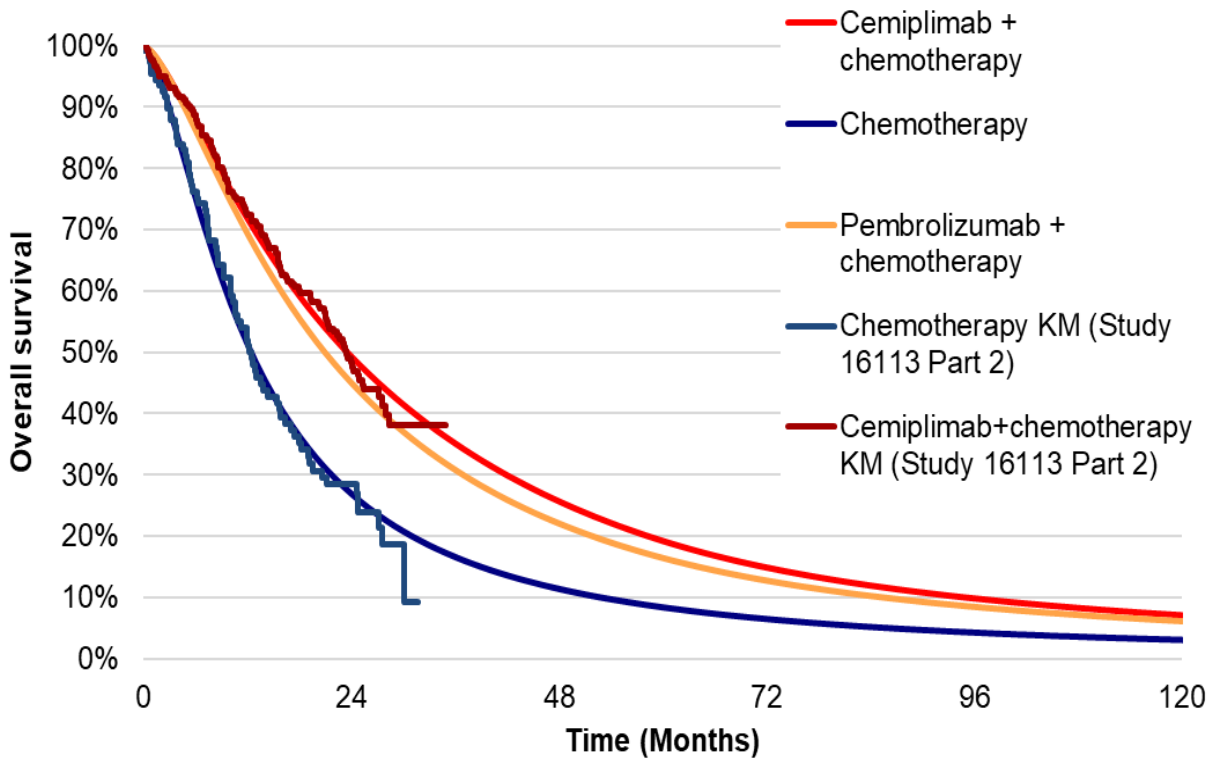
Extrapolating overall survival - company and EAG base cases

Visually similar company and EAG base case extrapolations

Company
treatment effect maintained from 2 years to 5 years



EAG
treatment waning from 2 years to 5 years



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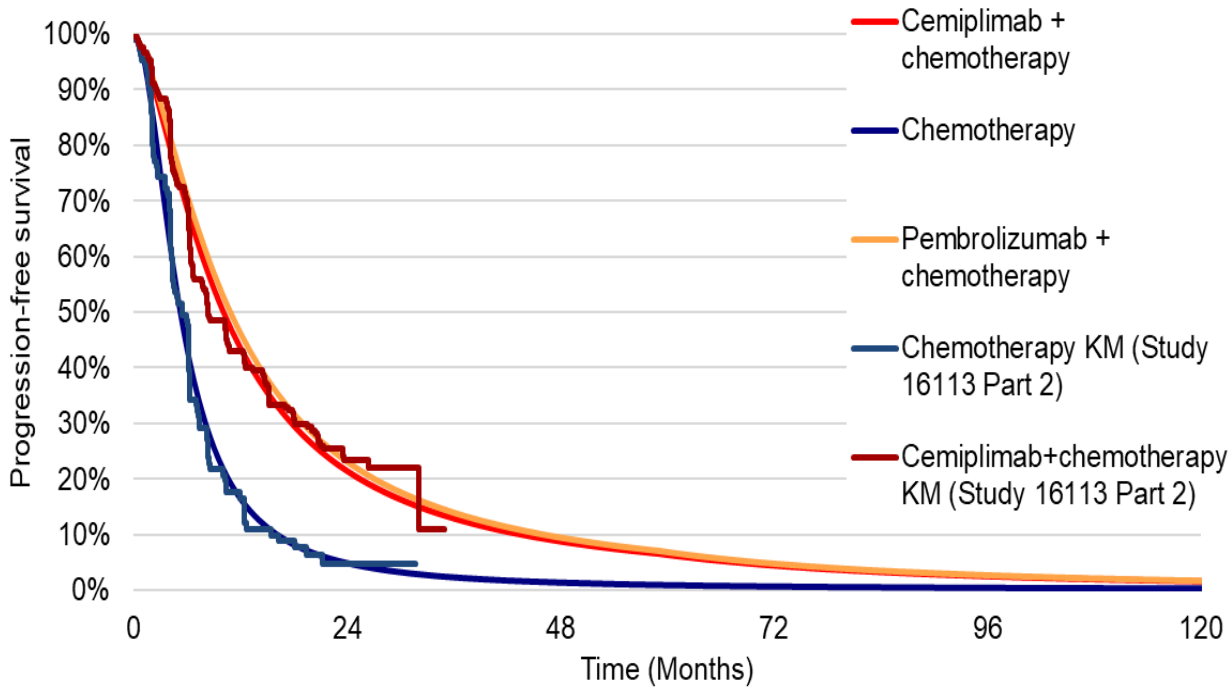
EAG, External assessment group; KM, Kaplan Meier

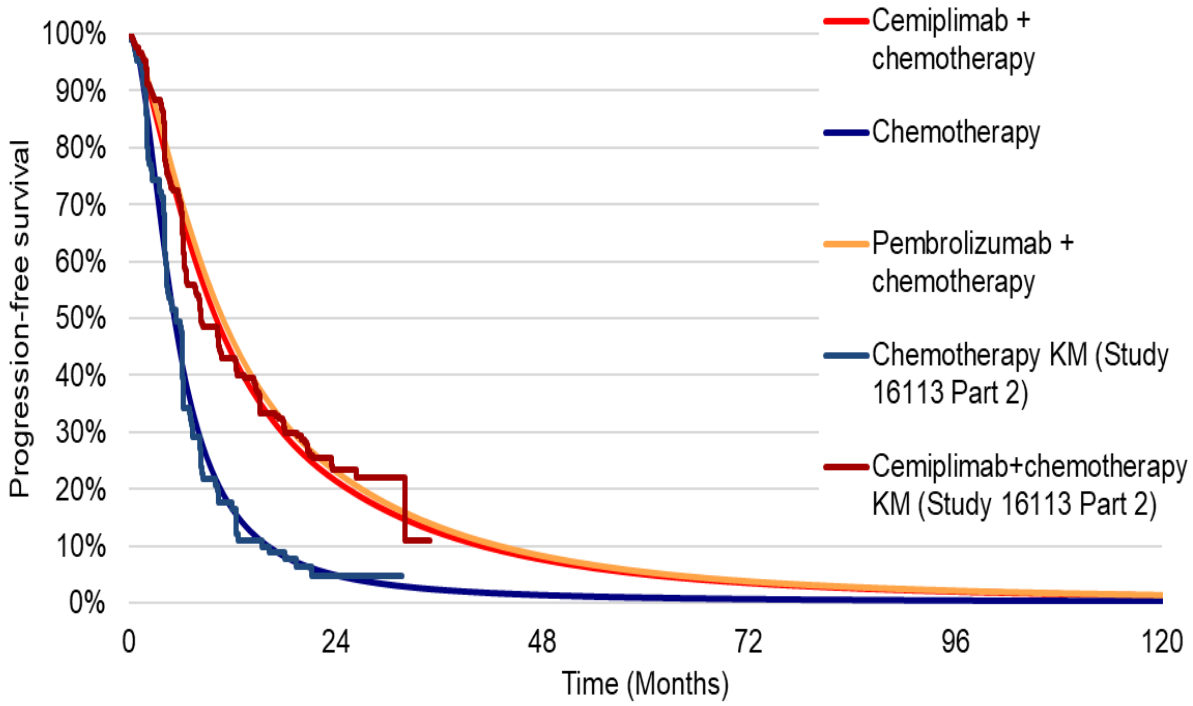
Extrapolating PFS - company and EAG base cases

Visually similar company and EAG base case extrapolations

Company
treatment effect maintained from 2 years to 5 years



EAG
treatment waning from 2 years to 5 years



NICE

EAG, External assessment group; KM, Kaplan Meier

Summary of company and EAG base case assumptions

Cemiplimab + chemotherapy vs. pembrolizumab + chemotherapy

Assumption	Company	EAG
Time on treatment	Assumed time on treatment = PFS	Ratio to time on treatment:PFS
Treatment effect waning	Continued extrapolation of treatment effect for PFS and OS from 2 years to 5 years	Gradual linear waning of treatment effect for PFS and OS from 2 years to 5 years
Adverse event rates (Grade 3+) - See appendix	**Cemiplimab + chemotherapy**: EMPOWER LUNG 3 **Pembrolizumab + chemotherapy**: KEYNOTE-189 + KEYNOTE-407 trials (weighted by histology of EMPOWER-Lung 3 trial)	Adverse events for pembrolizumab + chemotherapy applied to both treatment arms

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EAG, External assessment group; OS, Overall survival, PFS, Progression-free survival;

Cost-effectiveness results

- All ICERs reported in PART 2 slides because they include confidential discounts
- When confidential discounts included, company base case above range normally considered cost-effective use of NHS resources
- EAG base case significantly above range normally considered cost-effective use of NHS resources
- Results include company and EAG base cases (cost-utility and cost comparison analyses), sub-group analysis based on histology and PD-L1 expression, scenarios about PFS & OS curves, NMA assumptions and utility values

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

Impact of changes from company base case to EAG base case

EAG's base case results in higher incremental costs and lower incremental QALYs

No.	Scenario (applied to company base case)	Incremental costs (£) vs. pembrolizumab + chemotherapy	Incremental QALYs vs. pembrolizumab +chemotherapy	Incremental cost-effectiveness ratio
0	**Company base case**	See part 2	See part 2	See part 2
1	Gradual treatment effect waning from 2 years to 5 years	↓	↓	↑
2	Time on treatment calculated using hazard ratios relative to PFS	↑	↔	↑
3	Equal rates for adverse events	↑	↔	↑
1 to 3 combined	EAG base case	↑	↓	↑

AE, Adverse event; EAG, External assessment group; PFS, Progression-free survival; ToT, Time on treatment; QALY, Quality-adjusted life year

Equality considerations and uncaptured benefits

Equality considerations

No equalities issues were raised during course of this appraisal

Uncaptured benefits

- **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 (Blueteq protocol) mandates that patients are 'fit' to initiate treatment with AUC6 carboplatin

AUC, Area under curve; EAG, External Assessment Group; NSCLC, Non-small cell lung cancer

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ✓ **Summary**
- ❑ Supplementary appendix

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Key committee questions

Parameter	Key Committee Questions
Proposed positioning and comparators	• What is the committee's view on the company's choice of target population? • Could the target population be identified by clinicians? • Does the committee agree that pembrolizumab + chemotherapy is the only relevant comparator?
Clinical evidence	• What is the potential impact of the trial having stopped early for benefit?
Indirect treatment comparison	Is the indirect evidence comparing cemiplimab + chemotherapy with pembrolizumab + chemotherapy sufficient for decision-making?
Treatment discontinuation	What is the committee's preferred method for modelling time on treatment for cemiplimab + chemotherapy and pembrolizumab + chemotherapy
Extrapolating treatment effect beyond stopping treatment	• Is a 2 year stopping rule appropriate for cemiplimab? • What is the committee's preferred method for modelling treatment effect following stopping treatment for cemiplimab + chemotherapy and pembrolizumab + chemotherapy?
Adverse events rates	Does the committee prefer rates sourced from the relevant clinical trials, or the same across treatments?

AE, Adverse event; ToT, Time on treatment

Key issues

Issue	ICER impact	Slide(s)
Choice of target population and appropriate comparators	Unknown 	13, 14, 15
Validity of indirect treatment comparison	Unknown 	24, 25
Uncertainty in assumptions regarding time on treatment	Large 	28
Uncertainty in assumptions regarding extrapolating treatment effect	Moderate 	29, 30

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

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Summary
- ✓ **Supplementary appendix**

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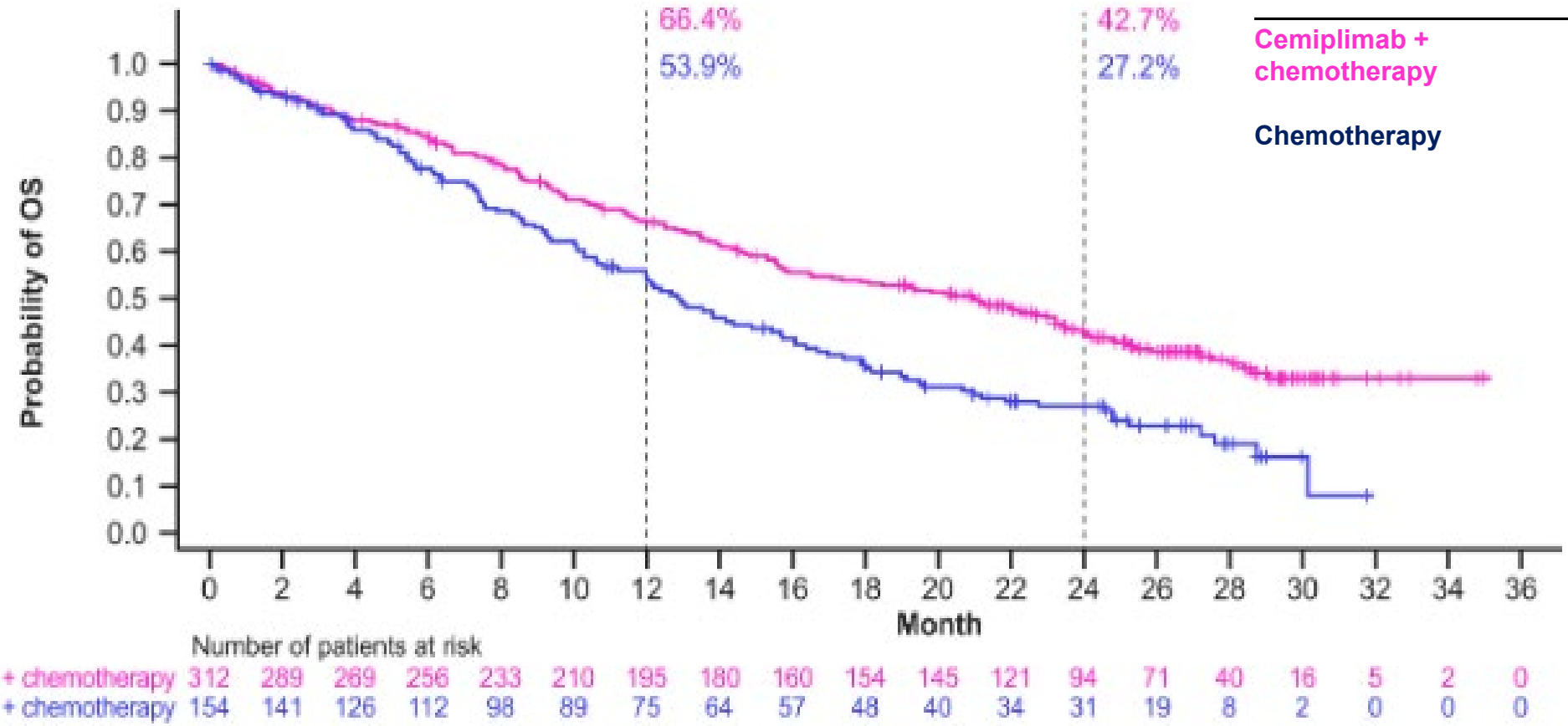
Comparators in scope differ if squamous or not, PD-L1 < or ≥ 50%

Company choses only pembrolizumab + chemotherapy

	PD-L1 <50%	PD-L1 ≥ 50%
Squamous	• Pembrolizumab + chemotherapy • Platinum doublet chemotherapy	• Pembrolizumab + chemotherapy • Atezolizumab • Pembrolizumab • Platinum doublet chemotherapy
Non-squamous	• Pemetrexed + platinum doublet chemotherapy • Pembrolizumab + chemotherapy • Atezolizumab + bevacizumab + chemotherapy	• Pemetrexed + platinum doublet chemotherapy • Pembrolizumab + chemotherapy • Atezolizumab • Pembrolizumab

Key clinical trial results – overall survival any PD-L1

8.2 months improvement in median OS for cemiplimab + chemotherapy compared with placebo + chemotherapy in ITT population

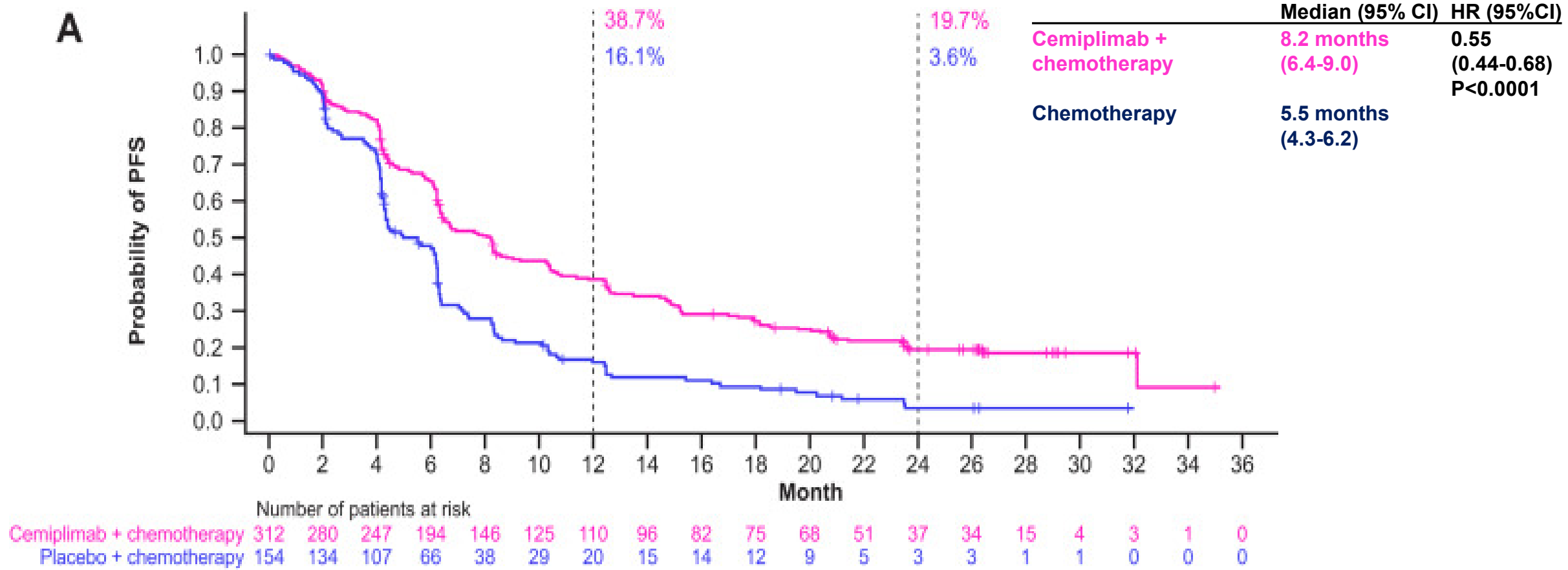


	Median (95% CI)	HR (95%CI)
Cemiplimab + chemotherapy	21.1 months (15.9-23.5)	0.65 (0.51-0.82) P=0.0003
Chemotherapy	12.9 months (10.6-15.7)	

CI, Confidence interval; HR, Hazard ratio; MHRA, Medicines and Healthcare products Regulatory Agency; NSCLC, Non-small-cell lung cancer; OS, Overall survival; PD-L1, Programmed cell death ligand 1

Key clinical trial results – progression-free survival any PD-L1

2.7 months improvement in median PFS for cemiplimab + chemotherapy compared with placebo + chemotherapy in ITT population



	Median (95% CI)	HR (95%CI)
Cemiplimab + chemotherapy	8.2 months (6.4-9.0)	0.55 (0.44-0.68) P<0.0001
Chemotherapy	5.5 months (4.3-6.2)	

CI, Confidence interval; HR, Hazard ratio; MHRA, Medicines and Healthcare products Regulatory Agency; NSCLC, Non-small-cell lung cancer; PD-L1, Programmed cell death ligand 1; PFS, Progression-free survival

Key clinical trial: KEYNOTE-189

	KEYNOTE-189
Design	Phase 3 randomised, double-blind, placebo-controlled trial
Population	Adults (≥18 years old) with metastatic non-squamous NSCLC who had not previously received systemic therapy for advanced disease and in whom epidermal growth factor receptor or anaplastic lymphoma kinase directed therapy was not indicated
Intervention	Pembrolizumab 200 mg IV every 3 weeks plus pemetrexed and platinum for 4 cycles, followed by pembrolizumab plus pemetrexed. Treatment with pembrolizumab for up to 35 study treatments
Comparator	Saline placebo plus pemetrexed and platinum for 4 cycles, followed by saline plus pemetrexed. Treatment with saline for up to 35 study treatments
Duration	5-year follow up available
Primary outcome	Overall survival, progression-free survival
Secondary outcomes	Objective response rates, duration of response
Locations	143 centres in 16 countries in North America, Europe, the Middle East, Asia and Australia
Used in model?	Yes (overall survival, progression-free survival)

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IV, Intravenous; NSCLC, Non-small-cell lung cancer

Key clinical trial: KEYNOTE-407

	KEYNOTE-407
Design	Phase 3 randomised, double-blind, placebo-controlled trial
Population	Adults (≥18 years old) with metastatic squamous NSCLC who had not previously received systemic therapy for advanced disease
Intervention	Pembrolizumab 200 mg IV every 3 weeks plus investigator's choice of paclitaxel or nab-paclitaxel plus carboplatin for 4 cycles followed by pembrolizumab for up to 31 cycles
Comparator	Placebo IV every 3 weeks plus investigator's choice of paclitaxel or nab-paclitaxel plus carboplatin for 4 cycles followed by placebo for up to 31 cycles
Duration	5-year follow up available
Primary outcome	Overall survival, progression-free survival
Secondary outcomes	Objective response rates, duration of response
Locations	137 centres in 17 countries in North America, Europe, the Middle East, Asia and Australia
Used in model?	Yes (overall survival, progression-free survival)

IV, Intravenous; NSCLC, Non-small-cell lung cancer

Network meta-analysis methodology overview

- Company conducted Network Meta-analyses (NMA) to evaluate efficacy and safety of cemiplimab + chemotherapy vs scoped comparators. Base case NMA was comparison of cemiplimab + chemotherapy vs pembrolizumab + chemotherapy
- Relevant studies identified through systematic literature review. Following feasibility assessment, company identified 10 studies, with 4 studies relevant to the base case analyses (cemiplimab + chemotherapy vs pembrolizumab + chemotherapy)
- Due to violation of proportional hazards assumption, company performed 2-step multivariable NMA outlined by Cope. et al, 2020→ involved fitting the seven standard parametric distributions for each arm of each trial and then synthesizing the parameters of these distributions
- Fixed effect models used for base case analyses; sensitivity analyses performed using random effects models
- Base case efficacy analyses comprised PD-L1 ≥1% any histology population in line with MHRA label (base case safety analyses comprised any PD-L1 expression any histology population). Scenarios also presented based on PD-L1 expression and histology:
  - PD-L1 1-49%, squamous histology
  - PD-L1 ≥50%, squamous histology
  - PD-L1 1-49%, non-squamous histology
  - PD-L1 ≥50%, non-squamous histology

EAG comments

- NMA statistical methods, included studies and sensitivity analyses are appropriate

MHRA, Medicines and Healthcare products Regulatory Agency; NMA, Network meta-analysis; PD-L1, Programmed cell death ligand 1

Comparison of trials included in company base case efficacy network meta-analyses

	Histology		PD-L1 level*		Stage	
	Squamous	Non squamous	PD-L1<1%	PD-L1≥1%	Locally advanced	Metastatic
EMPOWER LUNG-3 ITT population	42.9%	57.1%	29.8%	70.2%	14.8%	85.2%
EMPOWER LUNG-3, PD-L1≥1% sub-population	44.6%	55.4%	0%	100%	14.4%	85.6%
KEYNOTE-189 ITT population	0%	100%	30.8%	63%	0%	100%
KEYNOTE-407 ITT population	100%	0%	34.7%	63.1%	0%	100%

*PD-L1 level may not add to 100% as PD-L1 not evaluable for some people in KEYNOTE trials

PD-L1, Programmed cell death ligand 1

Overview of baseline characteristics and crossover in studies used in base case network meta-analyses base case

Trial	Treatment	Pop.	N	Median follow up (months)	Age, median	Geographic region, n (%)		ECOG performance status, n (%)		Crossover, n (%)
						East Asian	Non-East Asian	0	1	
EMPOWER-Lung 3 (part 2)	Cemi + IC chemo	ITT, any PD-L1, any histology	312	28.4	63.0	45 (14.4)	267 (85.6)	51 (16.3)	259 (83.0)	-
	IC chemo		154		63.0	16 (10.4)	138 (89.6)	18 (11.7)	134 (87.0)	0 (0)
KEYNOTE-189	Pembro + IC chemo	ITT, any PD-L1. non-squamous	410	64.6	65.0	4 (1.0)	406 (99.0)	186 (45.4)	221 (53.9)	-
	IC chemo		206		63.5	6 (2.9)	200 (97.1)	80 (38.8)	125 (60.7)	84 (40.8)
KEYNOTE-407	Pembro + IC chemo	ITT, any PD-L1, squamous	278	56.9	65.0	54 (19.4)	224 (80.6)	73 (26.3)	205 (73.7)	-
	IC chemo		281		65.0	52 (18.5)	229 (81.5)	90 (32.0)	191 (68.0)	117 (41.6)
KEYNOTE pooled weighted averages by treatment arm	Pembro + chemo	Any PD-L1, any histology	-	-	64.8	(8.4)	(91.6)	(38.1)	(61.9)	-
	Chemo		-		64.2	(11.5)	(88.5)	(36.2)	(63.8)	-

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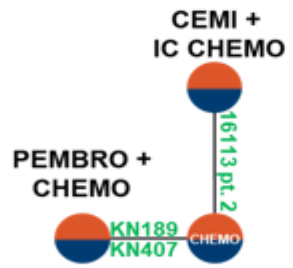
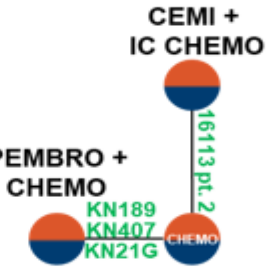
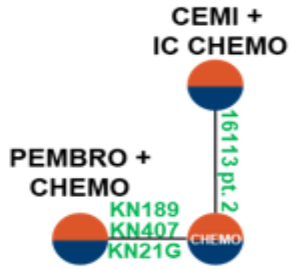
ECOG, Eastern Oncology Cooperative Group, IC, investigator's choice; ITT, Intention to treat; PD-L1, Programmed cell death ligand 1

Compared to relevant comparator whole trial population - safety

No significant differences between cemiplimab + chemotherapy vs. pembrolizumab + chemotherapy

Evidence network diagrams for safety

Scenario	Safety		
	Grade 3 to 5 all-cause AEs	Grade 3 to 5 IMAEs	DAEs
Any PD-L1, any histology (safety base case)			

16113 pt.2 – EMPOWER Lung 3 part 2; KN189 – KEYNOTE 189; KN407 – KEYNOTE 407; KN21G – KEYNOTE 021G

Network meta-analyses fixed effect model

Cemiplimab + chemotherapy vs.	Odds ratio (95% CrI)		
	Grade 3 to 5 all-cause adverse events (AEs)	Grade 3 to 5 immune-mediated AE	Discontinuation due to all-cause AEs
Pembrolizumab + chemotherapy	1.53 (0.95, 2.49)	1.58 (0.27, 9.78)	0.55 (0.22, 1.50)

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

How company incorporated evidence into base case model (1)

Inputs, assumptions and evidence source for company base case model

Input	Assumption and evidence source
Baseline characteristics	Based on EMPOWER-Lung 3 PD-L1 ≥1% any histology population: • Median age – 62 years; female (%) – 54%; mean weight – 72.79kg; mean body surface area – 1.834m^2
Efficacy	**Progression-free survival:** • Chemotherapy: Log-logistic distribution fit to progression-free survival data from EMPOWER-Lung 3. • Cemiplimab + chemotherapy, pembrolizumab + chemotherapy: application of treatment effects from the two-step NMA to shape and scale parameters for the reference curve **Overall survival:** • Chemotherapy: Log-logistic distribution fit to overall survival data from EMPOWER-Lung 3 • Cemiplimab + chemotherapy, pembrolizumab + chemotherapy: application of treatment effects from two-step NMA to shape and scale parameters for the reference curve
Chemotherapy backbone	Assumed same chemotherapy backbone for cemiplimab + chemotherapy and pembrolizumab + chemotherapy (based on observed distribution of chemotherapies from the pooled arms of the EMPOWER-Lung 3 study)

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NMA, Network meta-analysis; PD-L1, Programmed cell death ligand 1

How company incorporated evidence into base case model (2)

Inputs, assumptions and evidence source for company base case model

Input	Assumption and evidence source
Treatment duration	Assumed time on treatment equal to progression-free survival for all interventions
Treatment waning	Treatment effect was extrapolated until 5 years (3 years beyond the 2-year stopping rule)
Treatment stopping rules	• Chemotherapy: max of 4 cycles, people with non-squamous NSCLC can receive pemetrexed maintenance therapy until progression • Cemiplimab + chemotherapy: 24 months for cemiplimab, max of 4 cycles of chemotherapy and people with non-squamous NSCLC can receive pemetrexed maintenance therapy until progression. • Pembrolizumab + chemotherapy: 24 months for pembrolizumab, max of 4 cycles of chemotherapy and pemetrexed maintenance therapy until progression.
Utilities	• Health state utilities: utility values from EORTC-QLQ-C30 from EMPOWER-Lung 3 mapped to the EQ-5D-3L, using Longworth et al (2014) mapping algorithm and UK tariff (Dolan et al. 1997) • Adverse event disutilities: disutilities associated with experiencing Grade 3+ adverse events identified from targeted reviews of previously published economic evaluations and health technology assessment submissions

EORTC, European Organization for the Research and Treatment of Cancer; EQ-5D-3L, EuroQol- 5 dimensions-3 levels; NSCLC, Non-small-cell lung cancer; QLQ-C30, Quality of Life Questionnaire- 30 item

How company incorporated evidence into base case model (3)

Inputs, assumptions and evidence source for company base case model

Input	Assumption and evidence source
Costs	• Costs included for drug acquisition, administration, subsequent treatment, routine care, end-of-life care and adverse events • Healthcare resource utilisation based on NICE TA531
Severity	• Severity modifier not applied

EMPOWER-Lung 3 study recruitment

EMPOWER-Lung 3 study part 2 enrolment per site and country

Country	Study sites by country	Patients enrolled per country
China	17	26
Georgia	6	171
Greece	6	13
Malaysia	9	21
Poland	9	43
Romania	5	9
Russia	22	141
Thailand	7	11
Turkey	4	22
Ukraine	5	9
Total	90	466

KEYNOTE-189 study recruitment

KEYNOTE-189 enrolment per site

Country	Number of Sites
Australia	8
Austria	8
Belgium	2
Canada	6
Denmark	3
Finland	2
France	6
Germany	11
Ireland	5
Israel	6
Italy	12
Japan	4
Netherlands	3
Spain	12
UK	7
USA	48

Time to treatment discontinuation extrapolations – EAG base case

Cemiplimab + chemotherapy TTD Kaplan Meier curve digitised from company submission, document B figure 30 to assess fit to cemiplimab + chemotherapy TTD curve generated using ratio method

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EAG, External assessment group; KM, Kaplan Meier TTD, Time to treatment discontinuation

Other issue: Adverse event rates

Company source AE rates from clinical trials; EAG assume AE rates are equal across treatments to align with chemotherapy backbone

Background

- Model included Grade 3+ adverse events (AEs) which occurred in ≥5% of people in any treatment arm within relevant trials
- Model assumes same chemotherapy used in combination with cemiplimab and pembrolizumab

Company

- Grade 3+ treatment-emergent AEs sourced from EMPOWER-Lung 3 for cemiplimab + chemotherapy
- Grade 3+ treatment-emergent AEs sourced from KEYNOTE-189 and KEYNOTE-407 trials for pembrolizumab + chemotherapy, weighted by histology reported in EMPOWER-Lung 3
- Frequency of AEs included in the model validated by UK clinical expert

EAG comments

- EAG clinical expert: Grade 3+ AEs included in model would almost exclusively be caused by chemotherapy regime rather than immunotherapies
- As chemotherapy backbone regime assumed to be same across treatments, this results in misalignment between AE rates and chemotherapy regime
- EAG base: AE profile for pembrolizumab + chemotherapy applied to both treatment arms

Does the committee prefer rates sourced from the relevant clinical trials, or the same across treatments?

AE, Adverse event; EAG, External assessment group

Adverse event rates used in company model

Adverse event	Cemiplimab + chemotherapy	Pembrolizumab + chemotherapy
Anaemia	10.90%	17.65%
Fatigue	2.88%	6.38%
Neutropenia	6.41%	19.46%
Thrombocytopenia	3.21%	8.48%