NICE National Institute for Health and Care Excellence

Slides for public observers – redacted

Pembrolizumab with carboplatin and paclitaxel for untreated metastatic squamous non-small-cell lung cancer (CDF review of TA600)

Chair's presentation

2nd Appraisal Committee meeting

Lead team:

Chair Lindsay Smith

ERG: ScHARR (University of Sheffield)

Technical team: Vicky Gillis-Elliott, Victoria Kelly, Jasdeep Hayre

Company: MSD

14th October 2021

Key clinical and cost-effectiveness issues

Can the 'PD-L1 ≥ 50% with urgent clinical need' subgroup be defined?	
Is there evidence to support the use of pembrolizumab combination in the PD-L1 TPS ≥50% with an urgent clinical subgroup?	
Should cost-effectiveness decisions on the PD-L1 subgroups be treated as a single (<50% weighted) group and if so should this be weighted by real word use or clinical trial use?	
Should a waning of treatment effect for OS and PFS be applied at 5 years?	
Should the costs of subsequent treatment reflect those in KEYNOTE-407?	
Is the updated KEYNOTE survival data robust enough to reduce uncertainty?	
Has the end-of life criteria been met in any of the PD-L1 TPS subgroups?	
Are there any equality issues that the appraisal committee can take into account in its decision making?	

NICE  Unknown impact  Small impact  Model driver

ACD preliminary recommendation

Pembrolizumab plus carboplatin and paclitaxel is not recommended, within its marketing authorisation, for untreated metastatic squamous non small-cell lung cancer in adults

Summary of Company ACD response

Population	Seek ongoing access in population that had access in CDF • All PD-L1 TPS <50% - including <1% and 1% to 49% subgroup • Focus now on subgroup TPS≥50% who need an urgent clinical response who cannot receive pembrolizumab monotherapy
Weighted subgroups	Supports weighted stratification of PD-L1 TPS <50% subgroup but suggests this should be weighted using real-world evidence not KEYNOTE-407 distribution
Uncertainty in the evidence base	Suggest uncertainty in evidence base is low: • Long term treatment effect for 4 years • Committee preferred costs of subsequent therapies did not reflect KEYNOTE-407 • Indirect treatment comparison for pembrolizumab monotherapy in TPS≥50% subgroup is not relevant
End-of-Life	• Suggest end-of-life life met in the subgroup TPS≥50% who need an urgent clinical response

ACD considerations - Areas of uncertainty (1)

Issue	Committee's considerations

Stratification by PD-L1 subgroups (ACD sections 3.1, 3.2, 3.3, 3.4, 3.5, 3.6, 3.11, and 3.12)	• KEYNOTE-407, stratified by PD-L1 status (TPS ≥1% vs.<1%) to pembro combination/ placebo and subgroup analyses by PD-L1 status (TPS <1%, 1-49%, ≥50%)
	• Treatments differ in practice
	  • PD-L1 <50% = platinum-based combination chemotherapy
	  • PD-L1 ≥ 50%) = pembrolizumab monotherapy (small number needing rapid response = combination pembrolizumab and chemotherapy)
	• Committee agreed clinical effectiveness decisions should reflect clinical practice - PD-L1 status (< 50% and ≥ 50%)
	• KEYNOTE-407 not generalisable to clinical practice (did not reflect options for PD-L1 ≥ 50% subgroup)
	• **Committee concluded it would prefer CE estimates to be based on clinical practice; that is, stratified by TPS of <50% and ≥ 50%**

Extrapolating overall and progression free survival for PD-L1 subgroup ≥ 50% (ACD section 3.6)	• Company did an ITC of pembrolizumab combination therapy and pembrolizumab monotherapy • ERG suggested ITC favours pembrolizumab monotherapy, although results highly uncertain. • **Concluded: the modelled overall survival estimates for PD-L1 subgroup ≥ 50% were highly uncertain**

ACD considerations –Areas of uncertainty (2)

Issue	Committee's considerations
Waning of treatment effect (ACD section 3.9)	• Company base case included 5-year waning applied to OS and ERG applied 5- yr waning to both OS and PFS • Committee considered no evidence to support this. Precedent from other immunotherapies was 3-5 yr waning. • **Concluded: treatment effect lasting between 3 and 5 years after starting treatment is appropriate for decision making**
End of life criteria (ACD sections 3.11 and 3.12)	• **Concluded pembrolizumab combination meets extension to life criterion and short life criterion in PD-L1 subgroup <50% but not clear in PD-L1 subgroup ≥ 50%**
Costs of subsequent immunotherapies (ACD section 3.8)	• Company – costs apply for all standard care and subsequent treatment (committee preference from TA600) • ERG: Costs only apply to those who had subsequent treatment • In KEYNOTE-407 a small number had chemotherapy after standard care. Company assumptions may overestimate costs (underestimate ICER) • **Concluded: costs of subsequent treatments should reflect those in KEYNOTE-407**

Summary of company's ACD response

Committee preferred assumptions at ACM 1	Implemented by company?	Company comments
Weighted subgroups for PD-L1 TPS <50%	✓/X	Subgroups with PD-L1 TPS <50% and ≥50% but weighted by real world data not KEYNOTE-407 trial data
TPS ≥50%	X	Only want committee to focus on those with an urgent clinical need who cannot receive pembrolizumab monotherapy.
Waning of treatment effect between 3 and 5 years	X	KEYNOTE-407 OS data beyond 3 years does not show effect wanes at that time PFS assumes lifelong benefit
Log-logistic model to OS and hybrid-model to PFS	✓	Updated models for TPS >1%, 1-49% and ITT using sept 2020 data cut
Subsequent treatments in line with KEYNOTE-407	✓	Will accept "within trial" approach using KEYNOTE-407 data
Stopping rule at 35 cycles	✓	No comments
Pre/ post progression utilities	✓	No comments
TTD based on KM estimates	✓	No comments

Recap from 1st meeting

History of appraisal: pembrolizumab with carboplatin and paclitaxel

TA600 published Sept 2019:
Pembrolizumab, with carboplatin and paclitaxel is **recommended for use within the Cancer Drugs Fund as an option for untreated metastatic squamous NSCLC in adults** only if

- pembrolizumab is stopped at 2 years of uninterrupted treatment, or earlier if disease progresses, and
- the company provides pembrolizumab according to the managed access agreement.

ID1683 CDF review of TA600

- **Oct 2020:** Company submission
- **July 2021:** Technical engagement

Further data collection from CDF:

1) Managed access agreement
2) Additional data from KEYNOTE-407

CDF review ACM1 August 2021

ID1683 Appraisal consultation document draft recommendations:
Pembrolizumab plus carboplatin and paclitaxel is not recommended, within its marketing authorisation, for untreated metastatic squamous NSCLC in adults

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Abbreviations: ACM: appraisal committee meeting, CDF: cancer drugs fund, NSCLC: non small-cell lung cancer

Pembrolizumab with carboplatin and paclitaxel

Marketing authorisation (September 2019)	Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults
Dosage and administration	Pembrolizumab given as part of combination therapy: • 200 mg administered every 3 weeks, alternatively 400 mg every 6 weeks, as an intravenous infusion
Patient access scheme	A commercial access agreement has been approved which provides a simple discount to the list price

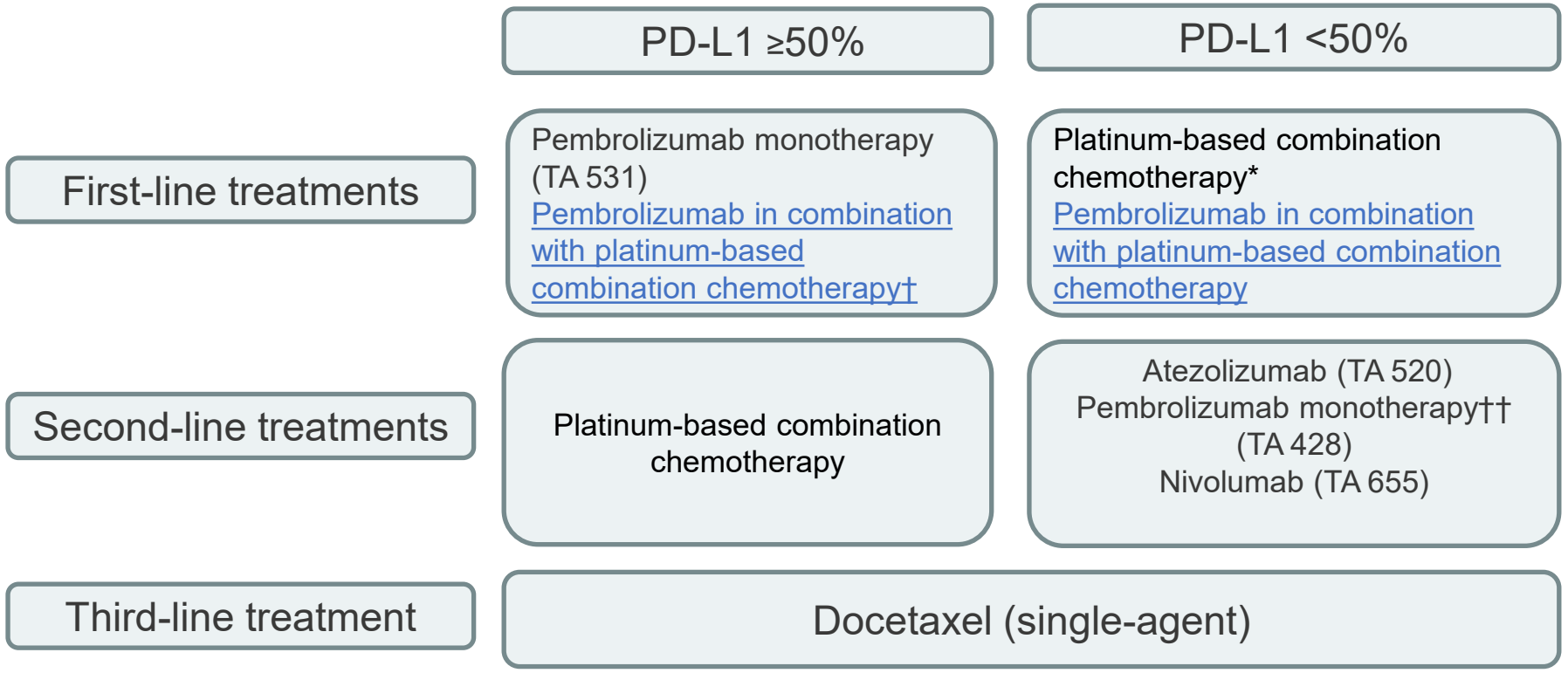
Committee conclusion in TA600:
Considerable uncertainty in OS standard care groups:

- Further overall survival data in ITT population and PD- L1 TPS subgroups* would inform decisions on effectiveness of pembrolizumab combination therapy vs standard care
- Further overall survival data in standard care group (subsequent immunotherapy benefits) would inform decisions on end of life criteria

Abbreviations: NSCLC: non small cell lung cancer, ITT: intention-to-treat, OS: overall survival, PD-L1: programmed death ligand 1, TPS: tumour proportion score
*subgroups defined as TPS <1%, 1-49% and ≥50%

Treatment pathway

Position of pembrolizumab combination therapy in treatment pathway for untreated squamous NSCLC setting



Platinum-based combination chemotherapy - gemcitabine, paclitaxel, vinorelbine plus carboplatin or cisplatin
** unless unable to tolerate platinum therapy*
† for TPS ≥50% only and requires an urgent clinical response (e.g. impending major airway obstruction) and issue has been fully discussed with the patient
†† for TPS>1% only CDF = Cancer Drugs Fund
Note - treatment may involve re-challenging with platinum-based chemotherapy in second-line for some patients

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Primary clinical evidence: KEYNOTE 407

Design	Phase III, multicentre, double-blind randomised controlled trial
Population	Adults with untreated, metastatic, squamous NSCLC
Subgroups	Subgroups by PD-L1 expression (<1%, 1-49%, ≥50%) NB: PD-L1 <50% (weighted) was not part of KEYNOTE-407 protocol
Intervention	Pembrolizumab with carboplatin and paclitaxel/nab-paclitaxel
Comparator	In KEYNOTE-407 • Saline placebo plus chemotherapy In clinical practice • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab monotherapy (in PD-L1-positive NSCLC if the tumour expresses a tumour proportion score of at least 50%)
Outcomes	• Overall Survival • Progression-Free Survival
Follow up for CDF review	• TA600: Interim analysis (data cut April 2018) • CDF review: Final analysis (data cut May 2019) • CDF review TE: Company provided overall survival data from additional follow-up (data cut September 2020)

Abbreviations: NSCLC; non small-cell lung cancer, PD-L1 programmed death ligand 1

New evidence

KEYNOTE-407: Clinical evidence

- September 2020 data cut in the ITT only previously presented but was not included in company's model for ACM1 – median time from randomisation to cut-off of 40.1 months
- Company now using this data cut to inform the economic modelling

	Overall survival	Progression-free survival
	Hazard ratio (95% CI)	Hazard ratio (95% CI)
ITT,	0.71 (0.59–0.86)	0.59 (0.49–0.71)
PD-L1 TPS <1% subgroup	[redacted]	[redacted]
PD-L1 TPS 1-49% subgroup	[redacted]	[redacted]
PD-L1 TPS ≥50% subgroup	[redacted]	[redacted]

No hazard ratios provided for weighted PD-L1 TPS <50% subgroup

Abbreviations: CI: confidence interval, ITT: intention to treat,

ACD consultation responses:

Consultation comments

- MSD (company)
- British Thoracic Oncology Group (BTOG)

- **Web comments**

- No web- based comments were received

PD-L1 ≥50% Subgroup

RECAP:
Pembrolizumab monotherapy is mostly used for PD-L1 tumour proportion scores ≥50% but a few people needing a rapid response may benefit from initial pembrolizumab combination therapy

Company comments:

- Not seeking access in the full subgroup with PD-L1 TPS ≥50% but is seeking continued access for those that need an urgent clinical response
- Confirmation from NHS CDF clinical lead- 11% of PD-L1 ≥50% subgroup have urgent clinical response
- ITC between pembrolizumab combination and pembrolizumab monotherapy is now redundant – relevant comparator is chemotherapy
- Updated KEYNOTE-407 trial data for pembrolizumab combination therapy compared with chemotherapy in the TPS≥50%: median OS of XXXXX months and XXXXX months; incremental median OS gain of XXXX months

ERG comments:

- ITC used to inform model reflects people recruited into KEYNOTE-407 and KEYNOTE-042 with TPS ≥50%, without any additional criteria related to urgent need of clinical response
- No evidence presented of clinical benefit for this specific subgroup of people – median OS presented reflects broader TPS ≥50% group and not those with an urgent clinical need

- **Can the 'PD-L1 ≥50% with urgent clinical need' subgroup be defined?**
- **Is there evidence to support the use of pembrolizumab combination in the PD-L1 TPS ≥50% with an urgent clinical subgroup?**

New evidence

PD-L1 <50% Subgroups (1)

RECAP:
The intention-to-treat population did not reflect clinical practice. Decisions about clinical effectiveness should be based on the weighted values for PD-L1 status (that is, PD-L1 tumour proportion scores of less than 50% and 50% or more).

Company comments

- Favours the consideration of 3 subgroups (TPS <1%, 1-49%, and >50%) and accepts the weighted approach for the <50% subgroup proposed by the committee at ACM1 such that within this subgroup, costs and outcomes are weighted by the subgroup analyses for the <1% and 1-49% subgroups but weighted by real world utilisation of the Pembro combo to these subgroups instead of KEYNOTE-407 distribution
- The baseline characteristics from the trial for each subgroup do not indicate any difference between the populations

PD-L1 TPS subgroup	Pembrolizumab combination therapy usage – June 2020*^	KEYNOTE-407 distribution	CDF distribution usage
<1%	22%	35.5%	48%
1-49%	68%	37.8%	41%
≥50%	10%	26.7%	11%
*Source: IQVIA Market Research Data, July 2021 ^Company preferred source to weight group			

New evidence

PD-L1 <50% Subgroups (2)

Consultee comments:

- "correct that current therapeutic options for squamous cell NSCLC available on the NHS only differ between PD-L1 >50% (single-agent Pembrolizumab) and PD-L1 <50% (Pembrolizumab, Paclitaxel and Carboplatin)
- "in practice most thoracic oncologists would still categorise patients into low (<1%), weak (1-49%) and high (>50%) when assessing a patient's tumour type and making treatment decisions. Indeed, after histology sub-type (squamous vs. non-squamous) this is the most important pathological characteristic".
- "Whether a squamous cell carcinoma is negative or weak positive would influence how an oncologist would view the relative benefits of 1st and 2nd line treatment options"

ERG response:

- It may not be appropriate to combine PD-L1 subgroups <1%, 1 to 49%
  - Company note PD-L1 TPS <50% subgroup is not homogenous
  - Cost-effectiveness is likely to differ between TPS <1% and 1 to 49% subgroups
  - Weighting across groups may mask if a technology is not cost-effective in one subgroup

Note: Combined <1% and 1-49% PD-L1 TPS subgroups, weighting based on number in each subgroup in KEYNOTE-407 (48.38% with PD-L1<1% and 51.62% with PD-L1 1-49%)

Should cost-effectiveness decisions on the PD-L1 subgroups be treated as a single (<50% weighted) group and if so should this be weighted by real word use or clinical trial use?

New evidence

Waning of treatment effect (1)

RECAP:

- For consistency with previous appraisals of immunotherapies for NSCLC, a treatment effect lasting between 3 and 5 years after starting treatment was appropriate for decision making.

Company comments:

- Long-term OS KM data for ITT (Sept 2020 data cut) provides no evidence that treatment effect on OS begins to wane with follow-up beyond 36 months (shown in next slide)
- No evidence to support waning of treatment effect at 5 years, particularly not in PFS
- Prepared to accept ERG's waning of treatment effect at 5 years, in absence of any supportive evidence to conclude on appraisal

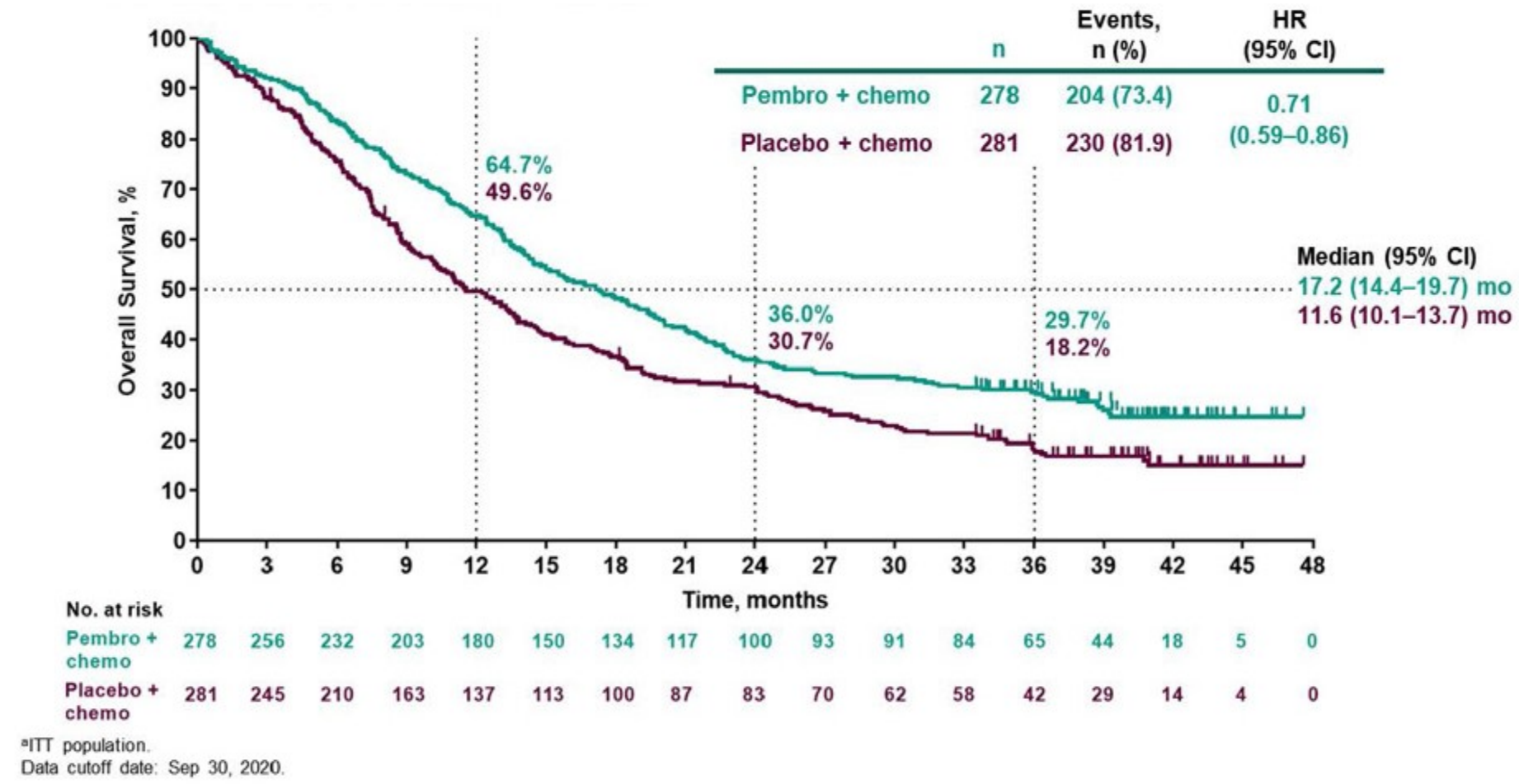
ERG response:

- No data beyond 4 years and unclear if effects on PFS and/or OS persist beyond this time
- ERG does not believe evidence is conclusive in supporting indefinite treatment effects –
- OS plot (see next slide) indicates high levels of censoring and few OS events in both groups at later timepoints.
- ERG suggest KM curves are not very intuitive. Using hazard functions and log cumulative hazards for PFS and OS would assess if treatment effect persists over longer period
- Company's updated model assumes waning of OS at 5 years (instant loss) but does not include waning of PFS
- Company's ACD response does not include any consideration of the plausibility of the selected models within each PD-L1 TPS subgroup.

Waning of treatment effect (2)

New evidence

Overall survival Kaplan Meier data: KEYNOTE-407 ITT population (September 2020 data)



[a]ITT population.
Data cutoff date: Sep 30, 2020.

Should a waning of treatment effect for OS and PFS be applied at 5 years?

Costs of subsequent treatment

RECAP: Company assumed costs of subsequent immunotherapies apply to all having standard care and subsequent treatment but in KEYNOTE-407 xxx who had subsequent therapy after standard care had chemotherapy as subsequent treatment. Committee conclude costs of subsequent treatment should have reflected treatments in KEYNOTE 407.

Company comments:

- Recognise subsequent treatment use in KEYNOTE-407 deviates from NHS clinical practice
- Can accept ERG approach but suggest data is insufficient to estimate a statistically robust adjustment so suggest committee could choose midpoint within the range of uncertainty between ERG and company assumptions

Consultee comments:

- Always some who do not have subsequent immunotherapy after 1st line chemotherapy
- When KEYNOTE-407 was running, 2nd line immunotherapy not as widely available in all countries
- Do not agree with ERG approach (only for those having subsequent treatment). Does not reflect clinical practice

ERG response:

- ERG view remains unchanged: Company ICER likely to underestimate,
- ERG's preferred analysis consistent with trial but limited because it does not reflect clinical practice
- More appropriate to align health outcomes with costs required to generate those outcomes
- Taking midpoint ICER between analyses, may not be meaningful

Should the costs of subsequent treatment reflect those in KEYNOTE-407?

New evidence

Uncertainty in the evidence base

Uncertainty over long-term treatment effect on overall and progression-free survival from KEYNOTE-407

Company comments:

- Evidence base is mature, extrapolation is robust and has “the most clinically plausible 5-year and 10-year survival estimates” (ACD section 3.7)
- Disagree with suggestion of high degree of uncertainty in the evidence base
- Provided updated overall and progression-free survival data for the PD-L1 subgroups for KEYNOTE-407 (Sept 2020 cut off)
- Do not believe there are high levels of uncertainty in the 3 subgroup estimates

OS and PFS events that have occurred in KEYNOTE-407 since original appraisal (TA600)

	TA 600		September 2020 Data cut	
ITT population	OS	PFS	OS	PFS
Pembrolizumab	30.6%	54.7%	73.4%	83.1%
Standard chemo	42.7%	70.1%	81.9%	91.5%

ERG response:

- Uncertainty may have arisen because company had not provided longer term (Sept 2020) data for PD-L1 TPS subgroups at time of ACD
- Still some uncertainty of long-term outcomes in specific PD-L1 TPS subgroups
- Parametric survival models were selected on goodness-of fit but company do not consider plausibility of chosen models within each PD-L1 TPS subgroup

Is the updated KEYNOTE survival data robust enough to reduce uncertainty?

New evidence

End of Life (1)

RECAP: Both EOL criterion likely met for the subgroup with PD-L1 less than 50%, but not for the subgroup with scores of 50% or more

Company comments:

- End of life criteria is met for PD-L1 TPS <1% and TPS 1-49%
- Suggest modified subgroup with PD-L1 TPS ≥50% and need for urgent clinical response is also highly likely to meet the end of life criteria
  - Urgent clinical need implies short survival - clinical consensus shows survival is less than 24 months - If patients were not in such a severe health state they would be suitable for pembrolizumab monotherapy
  - In KEYNOTE-407 median OS met in PD- L1 TPS ≥50% and relevant population (with urgent clinical need) would be a sicker group so all would meet short life criterion

PD- L1 TPS ≥50% subgroup	Median OS from KEYNOTE-407	Modelled mean (life year gains)
Pembrolizumab combination	[redacted] months	[redacted]
Chemotherapy	[redacted] months	[redacted]

New evidence

End of Life (2)

ERG response:

- Company has not presented evidence to show extension to life is at least 3 months for the PD-L1 TPS ≥50% urgent clinical need subgroup
- ERG presented updated analysis using latest data cut – consider it is unclear is whether EOL is met and in which subgroups

Model	Treatment group	Modelled Life year gains	Additional OS gain (years)
PD-L1 TPS <1%	Pembrolizumab	[redacted]	XXXX
	Chemotherapy	[redacted]	
PD-L1 TPS 1-49%	Pembrolizumab	[redacted]	XXXX
	Chemotherapy	[redacted]	
PD-L1 TPS <50%, KEYNOTE407 weighted	Pembrolizumab	[redacted]	XXXX
	Chemotherapy	[redacted]	
PD-L1 TPS <50%, IQVIA weighted	Pembrolizumab	[redacted]	XXXX
	Chemotherapy	[redacted]	
PD-L1 TPS <50%, CDF weighted	Pembrolizumab	[redacted]	XXXX
	Chemotherapy	[redacted]	

Has the end-of life criteria been met in any of the PD-L1 TPS subgroups?

Equality and innovation

Recap: No relevant equalities issues were identified and all relevant benefits of the technology were captured in the QALY

Company comments:

- ACD highlighted poor outcomes in people with squamous NSCLC
- Company suggest smoking-related comorbidities in this group impact lower socio-economic groups
- Company believe significant equity issues especially in <1% or 1-49% PD-L1 subgroups
- Need to consider socio-economic determinants of health inequality that lead to increased smoking rates in decision-making
- Company also note pembrolizumab combination therapy is an innovative technology in treatment of squamous NSCLC, a disproportionally under-served patient population

Consultee comments:

- ACD section 3.1: states role of biomarkers such as PD-L1 to predict cancers most likely to respond to immunotherapy is less well established in squamous than non squamous NSCLC. Most thoracic oncologists would view a PD-L1 negative, low (1-49%) or high (>50%) result in squamous and non-squamous equally useful to direct anti-cancer therapy. In clinical practice, there is not a significant difference between the role of PD-L1 in squamous and non-squamous lung cancer.

Are there any equality issues that the appraisal committee can take into account in its decision making?

Company & ERG updated model assumptions

Analysis	Company	ERG
Company updated base case	• Log-logistic model fit for OS (both arms) • Hybrid model fit for PFS (both arms) • KM estimates for TTD • Utilities based on pre or post progression status • Stopping rule – costs applied for 35 cycles • Duration & costs of subsequent treatments based on KEYNOTE-407, KEYNOTE-010, KEYNOTE-024, OAK • Waning of treatment effect for OS at 5 years (instant stop) • Stratification into 3 PD-L1 TPS subgroups (<1%, 1 -49% and ≥50% - that have urgent clinical need)	• ✓ • ✓ • ✓ • ✓ • ✓ • ✓ • ✓/X includes scenario with waning of PFS at 5 years • ✓ ERG preference to examine these separately
Weighted analysis	• Weighted PD-L1 subgroups (0-49% based on real-world data)	• ✓ presents results of weighting with real world data, KEYNOTE-407 & CDF distribution

Cost-effectiveness estimates

Because of confidential discounts, the results are confidential and will be presented in Part 2

Key clinical and cost-effectiveness issues

Can the 'PD-L1 ≥ 50% with urgent clinical need' subgroup be defined?	
Is there evidence to support the use of pembrolizumab combination in the PD-L1 TPS ≥50% with an urgent clinical subgroup?	
Should cost-effectiveness decisions on the PD-L1 subgroups be treated as a single (<50% weighted) group and if so should this be weighted by real word use or clinical trial use?	
Should a waning of treatment effect for OS and PFS be applied at 5 years?	
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Is the updated KEYNOTE survival data robust enough to reduce uncertainty?	
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