Public observer – contains redacted data

NICE National Institute for Health and Care Excellence

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

Lead team presentation

Lead team: Robert Hodgson, Malcolm Oswald, Chris Parker

ERG: ScHARR (University of Sheffield)

Chair: Gary McVeigh

Technical team: Vicky Gillis-Elliott, Christian Griffiths, Jasdeep Hayre

Company: MSD

CDF review committee meeting 12th August 2021

Key Issues

Issues discussed at Technical engagement	
Issue 4: The indirect comparison for the PD-L1 ≥50% subgroup is not robust	**To discuss**
Issue 1:Uncertainty surrounding the long-term treatment effect of pembrolizumab combination therapy on PFS and OS **Should the log-logistic extrapolation model be used to model the treatment effect of overall survival and progression free survival?**	**To discuss**
Issue 3: Committee's preferred assumptions regarding subsequent immunotherapy use do not reflect experience of KEYNOTE-407 **Should the model include subsequent treatment costs for both immunotherapy and chemotherapy treatments?**	**To discuss**
Issue 5: Uncertainty whether pembrolizumab combination therapy meets NICE's End-of-Life criteria **Does pembrolizumab combination therapy meet NICE's end of life criteria?** **Should end of life criteria be considered in terms of PD-L1 subgroups?**	**To discuss**
Other areas of uncertainty	
Issue 2: No additional safety data are presented in the CDF-company submission	**To discuss**
Other: Waning of treatment effect for progression-free survival	**To discuss**

Appraisal background

TA600 recommendation:
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

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

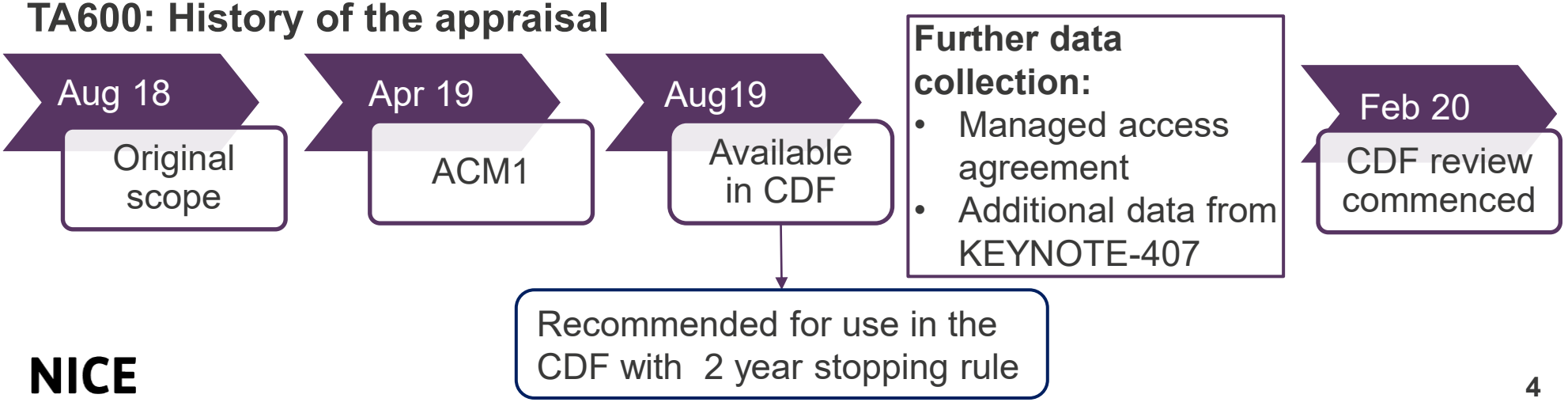
- Further overall survival data in ITT population and PD- L1 TPS subgroups* would inform decisions on effectiveness of pembrolizumab combination therapy vs standard care
- Further overall survival data in standard care group (subsequent immunotherapy benefits) would inform decisions on end of life criteria
- Committee preferred assumptions were in line with the ERGs pessimistic scenario analysis

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%
Based on ERG report for CDF review

Appraisal background

Marketing authorisation	Pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous NSCLC in adults
Based on scope:	
Population	Adults with untreated, metastatic, squamous NSCLC
Comparators	• Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab monotherapy (for PD-L1 ≥50% subgroup with no EGFR- or ALK positive tumour mutations only)
Outcomes	Includes overall survival and progression-free survival

TA600: History of the appraisal



Background - Treatment pathway from TA600

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

	PD-L1 ≥50%	PD-L1 <50%
First-line treatments	Pembrolizumab monotherapy (TA 531) Pembrolizumab in combination with platinum-based combination chemotherapy†	Platinum-based combination chemotherapy* Pembrolizumab in combination with platinum-based combination chemotherapy
Second-line treatments	Platinum-based combination chemotherapy	Atezolizumab (TA 520) Pembrolizumab monotherapy†† (TA 428) Nivolumab (TA 655)
Third-line treatment	Docetaxel (single-agent)	

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

Patient and carer perspectives

No patient submissions were received for CDF review

Original submission from TA600

- Roy Castle Lung Cancer Foundation
  - Significant unmet need in squamous NSCLC population
  - Poor prognosis following diagnosis
  - Significant impact on family and carers
  - Currently no potentially curative therapy options
  - Pembrolizumab monotherapy for PD-L1 ≥50% a welcome recent advance
  - Outcomes for the PD-L1 <50% remain particularly poor
  - Potential extensions in life is of great importance to people with squamous NSCLC and their families

Clinician perspectives

Clinical responses for CDF review were upon technical engagement issues only

Original submissions from TA600:

- NCRI/BTOG
  - Clinical improvement and survival are important outcomes
  - Lack of progression is also meaningful, as this usually corresponds with quality of life
  - There may be people with PD-L1 ≥50% who benefit more with pembrolizumab monotherapy – less toxic than in combination
- Submission from clinical expert
  - Unmet need, role of biomarkers (i.e PD-L1) to predict response to immunotherapy less established in squamous NSCLC
  - 1st time data presented for chemotherapy and immunotherapy in combination for squamous NSCLC
  - Restriction of performance status of 0-1 in key clinical trial will represent only a proportion of patients
  - Lack of real-world data in this setting

KEYNOTE- 407 results – overall population

Overall survival

Additional XX months of data collection through the CDF (cut-off May 2019)

	KEYNOTE-407 final data cut (cut-off May 2019, database lock XXXX XXXX)				KEYNOTE-407 (cut-off April 2018) data at CDF entry TA600			
Treatment	Number of events	Median OS (months) (95% CI)	Treatment vs. Control		Number of events	Median OS (months) (95% CI)	Treatment vs. Control	
			Hazard ratio (95% CI)	p-value			Hazard ratio (95% CI)	p-value
Control (n=281)	197	11.6 (10.1, 13.7)	----	-----	120	11.3 (9.5, 14.8)	---	---
Pembrolizumab combination (n=278)	168	17.1 (14.4, 19.9)	0.71 (0.58, 0.88)	XX XXXX X	85	15.9 (13.2, ..)	0.64 (0.49, 0.85)	p= 0.0008

:CI= confidence interval *Source: ERG report for CDF review table 6 & Original CS for TA600 table 15*

Control: Saline placebo with carboplatin & paclitaxel (or nab-paclitaxel)

Pembrolizumab combination: Pembrolizumab with carboplatin and paclitaxel (or nab-paclitaxel)

KEYNOTE- 407 results – overall population

Progression free survival

Additional XX months of data collection through the CDF (cut-off May 2019)

	KEYNOTE-407 final data cut (cut-off May 2019, database lock XXXX XXXX)				KEYNOTE-407 (cut-off April 2018) data at CDF entry TA600			
Treatment		Median OS (months) (95% CI)	Treatment vs. Control		Number of events	Median OS (months) (95% CI)	Treatment vs. Control	
			Hazard ratio (95% CI)	p-value			Hazard ratio (95% CI)	p-value
Control (n=281)	252	5.1 (4.3, 6.0)	---	-----	197	4.8 (4.3, 5.7)	---	---
Pembrolizumab combination (n=278)	217	8.0 (6.3, 8.4)	0.57 (0.47, 0.69)	XXXX XX	152	6.4 (6.2, 8.3)	0.56 (0.45, 0.70)	p <0.0001

CI: confidence interval *Source: ERG report for CDF review table 6 & Original CS forTA600 table 18*

Control: Saline placebo with carboplatin & paclitaxel (or nab-paclitaxel)

Pembrolizumab combination: Pembrolizumab with carboplatin and paclitaxel (or nab-paclitaxel)

KEYNOTE- 407 results: PD-L1 subgroups

Overall survival

Data cut-off May 2019

Population	N	Number of events	Median, months (95% CI)	HR, intervention vs. control (95% CI)
PD-L1 TPS <1% subgroup				
Pembrolizumab combination	95	[redacted]	[redacted]	0.79 (0.56, 1.11) [redacted]
Control	99	[redacted]	[redacted]	
PD-L1 TPS 1-49% subgroup				
Pembrolizumab combination	103	[redacted]	[redacted]	0.59 (0.42, 0.84) [redacted]
Control	104	[redacted]	[redacted]	
PD-L1 TPS ≥50% subgroup				
Pembrolizumab combination	73	[redacted]	[redacted]	0.79 [redacted]
Control	73	[redacted]	[redacted]	[redacted]

Source: ERG report for CDF review table 5 Data cut off May 2019
CI: confidence interval; HR: hazard ratio; NE: not evaluable; OS; overall survival; ITT: intention-to-treat, PD-L1: programmed death ligand 1, TPS: tumour proportion score

KEYNOTE-407 results : PD-L1 subgroups

Progression-free survival

Data cut-off May 2019

Population	N	Number of events	Median, months (95% CI)	HR, intervention vs. control (95% CI)
PD-L1 TPS <1% subgroup				
Pembrolizumab combination	95	[redacted]	[redacted]	0.67 (0.49, 0.91)
Control	99	[redacted]	[redacted]	[redacted]
PD-L1 TPS 1-49% subgroup				
Pembrolizumab combination	103	[redacted]	[redacted]	0.52 (0.38, 0.71)
Control	104	[redacted]	[redacted]	[redacted]
PD-L1 TPS ≥50% subgroup				
Pembrolizumab combination	73	[redacted]	[redacted]	0.43 (0.29, 0.63)
Control	73	[redacted]	[redacted]	[redacted]

Source: ERG report for CDF review table 6 Data cut off May 2019
CI: confidence interval; HR: hazard ratio; OS: overall survival; ITT: intention-to-treat, PD-L1: programmed death ligand 1, TPS: tumour proportion score

CDF review TA600 – Model amendments (1)

Model feature	Company original model (TA600)	Company updated model (CDF review)	ERG comments
Model type	Survival model	Partitioned survival model	Updates are in line with ERG pessimistic analysis
KEYNOTE 407 (data cut)	IA2 (April 2018)	Final (May 2019)**	_____
Progression free survival pembrolizumab combination & standard care	Hybrid model - KM to week 26 then log-normal fit PFS data from KEYNOTE-407	As original	Updates are in line with ERG pessimistic analysis (model fit to final data cut)**
Overall survival pembrolizumab combination & standard care	Hybrid model - KM used up to week 52 of KEYNOTE-407, mortality data from SEER*	Log-logistic fit to KEYNOTE-407 OS data (no cut-point)	Updates are in line with ERG pessimistic analysis (model fit to final data cut**

Abbreviations: IA2: 2nd interim analysis; KM: Kaplan Meier;
*RR for death in pembrolizumab combination taken from months 7-12 of KEYNOTE-407. Constant mortality rate assumed beyond 13 years.
** Note final cut off date is not the latest data-cut used in the TE analyses
Adapted from table 7 ERG report

CDF review TA600 – Model amendments (2)

Model feature	Company original model (TA600)	Company updated model (CDF review)	ERG comments
TTD – pembrolizumab combination therapy	Generalised gamma fit to KEYNOTE-407 TTD data (truncated at 35 cycles) Exponential to PD-L1 ≥50% subgroup	Generalised gamma fit to KEYNOTE-407 TTD data (truncated at 35 cycles) Weibull to PD-LI ≥50% subgroup	Generally in line with ERG pessimistic analysis (model fit to final data cut*
TTD – standard care	KM estimates from KEYNOTE-407	KM estimates from KEYNOTE-407	Update in line with ERG pessimistic analysis (fit to final data cut)*
Stopping rule	Pembrolizumab costs applied up to 35 cycles	Pembrolizumab costs applied up to 35 cycles	In line with ERG pessimistic analysis
Duration of treatment	No treatment effect waning assumed	Treatment effect waning assumed at 5 years	Not in ERG pessimistic analysis but little impact on ICER Waning not applied to PFS in whole population

Abbreviations: PFS: Progression free survival, TTD: Time to treatment discontinuation
Adapted from table 7 ERG report

* Company provided KM estimates to final data cut (May-2019) but not latest data-cut used in the TE analyses

CDF review TA600 – Model amendments (3)

Model feature	Company original model (TA600)	Company updated model (CDF review)	ERG comments
Subsequent treatments	KEYNOTE-407	KEYNOTE-407,OAK, KEYNOTE-010 & KEYNOTE-024	In line with ERG pessimistic analysis. New sources account for administrative censoring
Utilities	Time to death utilities estimated according to 4 categories based on KEYNOTE-407 data	Based on progression status: Progression-free (KEYNOTE-407) Post-progression (Khan et al)	In line with ERG pessimistic analysis. Post-progression utilities adjusted on 2nd line immunotherapy use
Indirect comparison in TPS ≥50% subgroup	Constant HR	Time-varying HRs OS adjusted for treatment switching	Time-varying HRs in original CS but not base case analysis in TA600 Analysis updated in current submission

Abbreviations: HR: Hazard ratio; TPS; Tumour proportion score
Adapted from table 7 ERG report

Issues to discuss after technical engagement

Outstanding issues after technical engagement	Impact on ICERs	Slide
Issue 4: The indirect comparison for the PD-L1 ≥50% subgroup is not robust		16 to 17
Issue 1: Uncertainty surrounding long-term treatment effect of pembrolizumab combination therapy on PFS and OS		18 to 20
Issue 3: Committee's preferred assumptions on subsequent immunotherapy use do not reflect experience of KEYNOTE-407		21 to 22
Issue 5: Uncertainty whether pembrolizumab combination therapy meets NICE's End-of-Life criteria		23 to 27
Issue 2: No additional safety data are presented in the CDF-company submission		28
Other: Waning of treatment effect for progression-free survival		29

 Unknown impact

 Small impact

 Model driver

Key Issue 4: indirect comparison of PD-L1 ≥ 50% subgroup

ERG & company agree issue resolved - Company provided suggested re-analysis
But lead team suggest this issue may need further discussion

Re-analysis	Company updates	ERG comments
1	OS fitted to log-logistic distribution Adjusted for treatment switching & re-censoring for KEYNOTE-042 & KEYNOTE-407	Time-varying HRs reported to month 24 & Kaplan-Meier plots included for each treatment arm
2	OS fit to log-logistic distribution Re-analysis using failure odds transformation	Time-varying ORs reported to month 24 no Kaplan-Meier plots
3	Population-adjustment but does not include treatment switching adjustment Modifiers = ECOG performance status, smoking status, age, gender & tumour size	Time-varying HRs reported to month 24 & Kaplan-Meier plots
4	Same as additional analysis 3, but treatment switching adjustment is included (re-censoring not included)	Time-varying HRs to month 24 & Kaplan-Meier plots (treatment switching adjustment)

Key Issue 4: indirect comparison of PD-L1 ≥ 50% subgroup

Chair notes this issue might be resolved but standard care for untreated NSCLC and PD-L1 ≥ 50% is pembrolizumab monotherapy

Previous technology appraisal has suggested that overall survival is similar for pembrolizumab combination and pembrolizumab monotherapy in PD-L1 ≥ 50% subgroup

TA683: Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, NSCLC

"*Although the point estimate suggested better overall survival for pembrolizumab combination compared with pembrolizumab monotherapy, the 95% credible interval showed that this was not statistically significant.*" (section 3.3)

"*The committee recalled that results from the indirect treatment comparison showed no statistically significant difference in the overall survival estimates for pembrolizumab combination compared with monotherapy. It concluded that the overall survival estimates for the high PD-L1 subgroup were uncertain*." (section 3.6)

Issue 1: Long-term effect on PFS & OS

TA600 conclusion

- SEER database not appropriate (does not include 2nd-line immunotherapies)
- Log logistic model (no cut point for each treatment arm) more appropriate for overall population
- Unclear which extrapolation is most appropriate for subgroup analyses, (evidence not robust)

Company update (CDF review ID1683)

KEYNOTE-407 final analysis (median follow up 14.3 months)

- OS: fitted log-logistic model to May 2019 data-cut of KEYNOTE-407 (no cut-point, models fitted independently to data for each treatment group)
  - Log-logistic had lowest AIC and second lowest BIC and most clinically plausible OS 5-year and 10-year estimates
- PFS: Used hybrid Kaplan-Meier estimates up to week-26 then fit parametric models independently to data for each treatment group).
  - Log normal - lowest AIC & BIC chosen as base case distribution

ERG (CDF review ID1683)

OS: Log-logistic model for both treatment groups is reasonable
PFS: Company do not state if clinical plausibility of alternative parametric models was considered
ERG sensitivity analyses: Based on alternative parametric models for both OS & PFS
Increase ICER in both but less sensitive to choice of PFS model

Issue 1: Long-term effect on PFS & OS

CDF review Technical engagement

Clinical expert:

- Advantage of combination chemotherapy-immunotherapy up front is everyone can access treatment - less than 50% will access subsequent therapy if sequential approach is taken

Company:

- Provided additional survival follow up data (Sept 2020- see slide 20)
- Log-logistic model - reinforces PFS & OS benefit

ERG:

- Agrees additional data reduce uncertainty
- Company did not incorporate updated KM plots for TTD, PFS & OS into their economic model
- ERG has included updated OS models in the economic model but was not able to update PFS (hybrid model) because company did not re-fit the log-normal model parameters

Should the log-logistic extrapolation model be used to model the treatment effect of overall survival and log normal be used for progression free survival?

Issue 1: long-term effect on PFS & OS

Company's new evidence

Survival outcomes for KEYNOTE-407 additional follow up data Sept 2020 in ITT population Note: no additional evidence for PD-L1 subgroups

	Pembrolizumab combination (n = 278)	Control (n = 281)
Median overall survival months (95% CI)	17.2 (14.4–19.7)	11.6 (10.1–13.7)
Overall survival HR (95% CI)	0.71 (0.59–0.86)	-
3-y overall survival rate, % (95% CI)	29.7 (24.5–35.2)	18.2 (13.8–23.0)
Median PFS, months (95% CI)	8.0 (6.3–8.5)	5.1 (4.3–6.0)
PFS HR (95% CI)	0.59 (0.49–0.71)	-
3-y PFS rate, % (95% CI)	16.1 (12.0–20.8)	6.5 (3.9–10.0)
Median PFS2* months (95% CI)	13.8 (12.2–15.9)	9.1 (8.0–10.3)
PFS2* HR (95% CI)	0.59 (0.49–0.71)	-
Overall response rate % (95% CI)	62.6 (56.6–68.3)	38.8 (33.1–44.8)
Median duration of response Months (range)	9.0 (1.3+ to 45.0+)	4.9 (1.3+ to 44.8+)

Data cut off Sept 2020 *indicates time from randomization to second/subsequent PD on next-line treatment/death
Abbreviations: CI: confidence interval; HR: hazard ratio; OS: overall survival; PFS: progression free survival

Issue 3: Subsequent immunotherapies

TA600 Committee conclusion

- In clinical practice a higher proportion will expect to have subsequent treatment than in KEYNOTE-407
- Committee preference: In standard care 50% will be offered subsequent treatments (75% atezolizumab, 25% pembrolizumab) – no one expected to have subsequent chemotherapy

Company update (CDF review ID1683)

Updated costs of subsequent therapy using May 2019 data-cut of KEYNOTE-407 in-line with committee preference from TA600

ERG (CDF review ID1683)

- Committee preferred assumptions overestimate costs of subsequent immunotherapy use in standard care (underestimate ICER) because company applied costs to all people in standard care who had subsequent treatment
  - ERG: In May 2019 analysis of KEYNOTE-407 XXX who had subsequent therapy after standard care had chemotherapy as subsequent treatment
  - ERG amended model to include costs of all subsequent-line therapies in KEYNOTE-407 including costs of subsequent IOs and costs of chemotherapy

Issue 3: Subsequent immunotherapies

CDF Review Technical engagement responses

Clinical expert:
Chemotherapy was the only option for subsequent therapy in some centres during KEYNOTE-407

- People eligible in KEYNOTE 407 would now have access to 2nd line immunotherapies
- Further chemotherapy is highly unlikely to be next treatment

Company:
Sought qualitative feedback from 10 clinicians on 2nd line treatment options

- All Clinicians confirm 2nd line treatment would be a single agent immunotherapy
- Company suggest their base case is sufficient for decision making with no changes needed

ERG

- Agrees KEYNOTE-407 differs from usual clinical practice
- Model applies 100% costs for immunotherapy
- Company model shows higher costs of immunotherapy, but not additional benefits so underestimates ICER
- ERG's analysis consistent with KEYNOTE-407 but does not fully reflect current clinical practice

Should the model include subsequent treatment costs for both immunotherapy and chemotherapy treatments?

Issue 5: End of life

TA600 Committee conclusion

- Preferred ERG model estimated people live an average (mean) 2.17 years on chemotherapy (overall population)
- PD-L1 ≥50% may live longer than estimated by model but subgroups unsuitable for decision-making
- Concluded pembrolizumab with carboplatin and paclitaxel might meet end of life criteria

Company update (CDF review ID1683)

Short life criterion:

- KEYNOTE-407 Median OS = 11.6 months, modelled mean = 2.26 years (undiscounted)
- Clinical experts view in TA600 - life expectancy is under 24 months
- Squamous have poorer prognosis

3 month OS gain:

- KEYNOTE-407 median OS gain = 5.5 months, modelled OS gain = 5.7 months (0.69 undiscounted life years gained)

ERG (CDF review ID1683)

- Company's base case model suggests mean OS in comparator group is greater than 24 months and parametric models suggest mean OS gain of 3 months or more

ERG:

- Uncertain whether the first criterion is met
- Likely second criterion met, but uncertainty of long-term OS benefit

Issue 5: End of life

CDF review technical engagement responses:

- **Company:**

1. **Short life criterion:** Has been met
   - Median OS from KEYNOTE-407= 11.6 months in SoC arm (Sept 2020 data cut)
   - Mean OS from model predicts 27.1 months in SoC arm (ITT population)
   - In KEYNOTE-407 28% treated with standard chemotherapy alive at 24 months
2. **Three month OS gain:** Latest data cut provide certainty OS gain can be maintained
   - Median OS gain = 5.6 months for pembrolizumab combination vs SoC (Sept 2020 data cut)
   - OS benefit (0.71 HR) maintained from May 2019 to Sept 2020 data cut)

- **ERG:**
- ERG view unchanged

ERG preferred model (Sept 2020 cut) shows mean life year gains in overall population (see slide 25 for impact on mean life year gains in PD-L1 subgroups)

	Model results			Data from Kaplan-Meier	
Treatment group	Mean Life year gains	% alive at 12 months	% alive at 24 months	% alive at 12 months	% alive at 24 months
Pembrolizumab combination	XXXX	62.9%	40.3%	64.7%	36.0%
Standard chemotherapy	XXXX	50.6%	28.5%	49.8%	30.8%

Issue 5: End of life

impact on Life year gains (Based on OS data May 2019) Note: model based on mean life year gains. Updated OS data from later cut-off not provided for PD-L1 subgroups

Model	Treatment group	Life years	
		Company	ERG
PD-L1 TPS <1%	Pembrolizumab combination	XXXX	XXXX
	Standard chemotherapy	XXXX	XXXX
PD-L1 TPS 1-49%	Pembrolizumab combination	XXXX	XXXX
	Standard chemotherapy	XXXX	XXXX
PD-L1 TPS <50% (weighted) *	Pembrolizumab combination	XXXX	XXXX
	Standard chemotherapy	XXXX	XXXX
PD-L1 TPS ≥50%	Pembrolizumab combination	XXXX	XXXX
	Pembrolizumab monotherapy	XXXX	XXXX

- Incorporates different weights for PD-L1 TPS <1% and P-L1 TPS 1-49% subgroups Weighted values calculated by ERG

Source table 17 and table 20 ERG report
(please note these values currently do not reflect those in table 13 in ERG appendix)

Does pembrolizumab combination therapy meet NICE's end of life criteria?

Issue 5: End of life

CDF review technical engagement responses:

End of life in PD-L1 subgroups

- **Company:**
  - End of life should not be stratified in PD-L1 subgroups because KEYNOTE-407 trial protocol did not stratify for PD-L1 subgroups greater or less than 50%
  - CDF restricts pembrolizumab combination therapy use in PD-L1 ≥ 50% to those with an urgent critical need
  - Company suggest for an ongoing technology appraisal (ID1566, Nivolumab with ipilimumab and chemotherapy for untreated metastatic NSCLC) survival with current therapies is less than 24 months in PD-L1% < 50%

  "For the subgroup with squamous NSCLC and a PD-L1 TPS of below 50%....The clinical experts stated that the life expectancy for this subgroup was likely to be less than 2 years, even with immunotherapy." (ID1566 ACD)
- **ERG:**
- Company's CE estimates may not be meaningful because proposed use only in clinically vulnerable for PDL1 ≥ 50% is not reflected in company's economic comparison for this subgroup

Should end of life criteria be considered in terms of PD-L1 subgroups?

Issue 5: End of life

End of life in PD-L1 subgroups

KEYNOTE 407 considers PD-L1 status on 3 subgroups (PD-L1 <1%, 1-49, ≥ 50%)

Other TA guidance has considered PD-L1 status on 2 subgroups (PD-L1 <50% and ≥ 50%)

PD-L1 status considerations in ID1566 - ongoing technology appraisal (Nivolumab with ipilimumab and chemotherapy for untreated metastatic NSCLC)

- Current treatment is based on histology (non-squamous or squamous NSCLC) and PD-L1 tumour proportion score (PD-L1 < 50% and PD-L1 ≥ 50%), in line with NICE guidance
- Committee was satisfied that nivolumab combination was likely to meet the criteria for end of life treatments in the subgroup with squamous NSCLC and PD-L1 TPS <50 but the criteria were not met for all other populations

PD-L1 status considerations in TA683

(Pembrolizumab with pemetrexed and platinum chemotherapy for untreated, metastatic, NSCLC)

- Standard care for people with PD-L1 ≥ 50% is pembrolizumab monotherapy
- Indirect treatment comparison showed no statistically significant difference in OS between pembrolizumab combination and monotherapy in PD-L1 ≥ 50%
- Committee concluded pembrolizumab combination did not meet end of life criteria for PD-L1 ≥ 50%

Should end of life criteria be considered in terms of PD-L1 subgroups?

Additional area of uncertainty
Issue 2: No additional safety data

Company update (CDF review TA1683)

Company's updated economic model includes costs associated with AEs (April 2018 cut-off) but does not include additional safety data

ERG (CDF review ID1683)

CDF review terms of reference does not require additional AE data but longer-term AE data would provide a more complete understanding of toxicity profile

- Data from KEYNOTE- 407 limited to 30 days after last dose of study treatment
- AEs not included in company's systematic literature review or network meta analyses

CDF review technical engagement responses:

Clinical expert:

- Longer follow up from immunotherapy studies including KEYNOTE 407 has not raised any safety concerns

Company:

- No new safety issues identified and long-term data unlikely to impact on current CE estimates

ERG:

- Agrees unlikely to have material impact on ICER

Additional area of uncertainty
Waning of treatment effect

TA600 Committee conclusion

- Original company base case assumed no waning of benefit but committee concluded a lifetime benefit was implausible & 3 to 5 year duration of treatment effect was more appropriate

Company update (CDF review ID1683)

- Applied 5 year duration of treatment benefit to overall survival in base case & included scenarios for 3 and 4 years
- Company state although no evidence to support treatment benefit will wane after 5 years, this was chosen for consistency with previous immunotherapies

ERG (CDF review ID1683)

- Assumption that treatment effect on overall survival is lost after 5 years does not apply to treatment effects on progression free survival except in the PD-L1 ≥50% subgroup
- ERG included treatment effect waning on progression free survival in its base case
- This does not have a large impact on ICER

Cost-effectiveness estimates

These are based on list prices

Comparator PAS prices are confidential and will be included in Part 2 slides

Modelling assumptions

Analysis	Key features
Company base case	• Log-logistic model fit for OS (both arms) • Hybrid model fit for PFS (both arms) • Generalised gamma fit to TTD data in pembrolizumab combination & KM estimates to standard care • 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 at 5 years
ERG base case	As company base case including • Correction to KM estimates for TTD using cumulative probabilities (pembrolizumab combination) • Updated distribution of subsequent-line therapies • Inclusion of waning of treatment effect for PFS
ERG scenario analysis	• Alternative choice of OS parametric models • Alternative choice of PFS parametric models
ERG exploratory analysis	• Weighted PD-L1 subgroups (0-49% and ≥50%)

Decision-making with south west quadrant ICERs

- South-west quadrant ICERs are presented as costs saved per QALY lost
- The higher the ICER, the more cost is saved per QALY lost, so high ICERs are better here and the commonly assumed decision rule of accepting ICERs below a given threshold is reversed
- This is reflected in decision making in previous appraisals with south-west quadrant ICERs (e.g. TA433, TA561)
- Positive recommendations are made when the costs saved are sufficient to cover the QALY loss
- Usually, south-west quadrant ICERs have led to positive recommendations when ICERs are substantially above £20,000 to 30,000 per QALY lost
- As with other decision-making, more certainty is needed the closer to the margins of cost-effectiveness the ICERs are

Company base case results

Overall population (deterministic) using longer-term OS models (data cut-off September 2020 and latest PAS discount)

Option	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company updated base case	XXXX	XXXXXXX	£25,431

Compares pembrolizumab combination vs standard care
Includes pembrolizumab combination PAS price vs comparator list price

For comparator & subsequent treatment discounts the ICER will increase

ERG base case results

Overall population (deterministic) using longer-term OS models (data cut-off September 2020 and latest PAS discount)

Option	Inc. QALYs	Inc. costs	ICER (per QALY gained)
Company updated base case	XXXX	XXXXXX	£25,431
1- KM estimates for TTD	XXXX	XXXXXX	£26,761
2- Updated distribution of subsequent therapies	XXXX	XXXXXX	£31,518
3- Waning of treatment effect for PFS	XXXX	XXXXXX	£26,372
ERG preferred analysis (ERG analysis 1 to 3 combined)	XXXX	XXXXXX	£33,961

Compares pembrolizumab combination vs standard care
Includes pembrolizumab combination PAS price vs comparator list price

For comparator & subsequent treatment discounts the ICER will increase

Company base case results

Based on May 2019 data cut-off and latest PAS discount

PD-L1 subgroups (deterministic)

Option	Inc. QALYs	Inc. costs	ICER (per QALY gained)
PD-L1 TPS <1%	XXXX	XXXXXXX	£34,018
PD-L1 TPS 1-49%	XXXX	XXXXXXX	£21,527
PD-L1 TPS ≥50%*	XXXXX	XXXXXXX	£17,563 (SWQ)

Weighted PD-L1 subgroups (deterministic) ERG exploratory analysis

Option*	Inc. QALYs	Inc. costs	ICER (per QALY gained)
PD-L1 TPS <49% (weighted)	XXXX	XXXXXXX	£24,880
PD-L1 TPS ≥50%*	XXXXX	XXXXXXX	£17,563 (SWQ)

Compares pembrolizumab combination vs standard care
Includes pembrolizumab combination PAS price vs comparator list price
For comparator & subsequent treatment discounts the ICER will increase
No additional data provided for the latest September 2020 data-cut for PD-L1 subgroups

* No comparator treatment discounts. ICER is a decision making ICER
ICERs in SW quadrant: the higher the ICER, the more cost is saved per QALY lost

ERG base case results

Based on May 2019 data cut-off and latest PAS discount

PD-L1 subgroups (deterministic)

Option	Inc. QALYs	Inc. costs	ICER (per QALY gained)
PD-L1 TPS <1%	XXXX	XXXXXXX	£47,252
PD-L1 TPS 1-49%	XXXX	XXXXXXX	£30,201
PD-L1 TPS ≥50%*	XXXXX	XXXXXXX	£15,623 (SWQ)

Weighted PD-L1 subgroups (deterministic) ERG exploratory analysis

Option	Inc. QALYs	Inc. costs	ICER (per QALY gained)
PD-L1 TPS <49% (weighted)	XXXX	XXXXXXX	£34,843
PD-L1 TPS ≥50% *	XXXXX	XXXXXXX	£15,623 (SWQ)

Compares pembrolizumab combination vs standard care
Includes pembrolizumab combination PAS price vs comparator list price
*No comparator treatment discounts. ICER is a decision making ICER

For comparator & subsequent treatment discounts the ICER will increase
No additional data provided for the latest September 2020 data-cut for PD-L1 subgroups
ICERs in SW quadrant: the higher the ICER, the more cost is saved per QALY lost

ERG sensitivity analysis

Based on May 2019 data cut-off and latest PAS discount

Impact of alternative parametric models – Overall survival: Overall population (deterministic)

OS model	Inc. QALYs	Inc. Costs	ICER (per QALY gained)
Exponential	XXXXX	XXXXXXX	£47,439
Weibull	XXXXX	XXXXXXX	£56,254
Gompertz	XXXXX	XXXXXXX	£75,534
Log-normal	XXXXX	XXXXXXX	£36,817
Log-logistic (base case)	XXXXX	XXXXXXX	£36,973
Generalised gamma	XXXXX	XXXXXXX	£57,490

Progression free survival: Overall population (deterministic)

PFS model	Inc. QALYs	Inc. Costs	ICER (per QALY gained)
Exponential	XXXXX	XXXXXXX	£47,151
Weibull	XXXXX	XXXXXXX	£43,382
Gompertz	XXXXX	XXXXXXX	£38,688
Log-normal (base case)	XXXXX	XXXXXXX	£36,973
Log-logistic	XXXXX	XXXXXXX	£37,676
Generalised gamma	XXXXX	XXXXXXX	£37,815

Compares pembrolizumab combination vs standard care
Includes pembrolizumab combination PAS price vs comparator list price
For comparator & subsequent treatment discounts the ICER will increase

NICE

ERG sensitivity analysis

Alternative parametric models- Overall survival : PD-L1 (deterministic)

Based on May 2019 data cut-off and latest PAS discount

OS model	Inc. QALYs	Inc. Costs	ICER (per QALY gained)
PD-L1 TPS <1%			
Exponential	XXXX	XXXXXXX	£67,889
Weibull	XXXX	XXXXXXX	£84,396
Gompertz	XXXX	XXXXXXX	£130,197
Log-normal	XXXX	XXXXXXX	£50,809
Log-logistic (base case)	XXXX	XXXXXXX	£47,252
Generalised gamma	XXXX	XXXXXXX	£181,015
PD-L1 TPS 1-49%			
Exponential	XXXX	XXXXXXX	£39,176
Weibull	XXXX	XXXXXXX	£41,613
Gompertz	XXXX	XXXXXXX	£39,647
Log-normal	XXXX	XXXXXXX	£29,607
Log-logistic (base case)	XXXX	XXXXXXX	£30,201
Generalised gamma	XXXX	XXXXXXX	£36,993
PD-L1 TPS ≥50%*			
Exponential	XXXX	XXXX	£120,923 (SWQ)
Weibull	XXXXX	XXXXXXX	£10,490 (SWQ)
Gompertz	XXXXX	XXXXXXX	£10,996 (SWQ)
Log-normal	XXXXX	XXXXXXX	£16,292 (SWQ)
Log-logistic (base case)	XXXXX	XXXXXXX	£15,623 (SWQ)
Generalised gamma	XXXXX	XXXXXXX	£12,832 (SWQ)

Includes pembrolizumab combination PAS price vs comparator list price For comparator & subsequent treatment discounts the ICER will increase. *No comparator treatment discounts. ICER is a decision making ICER

ERG sensitivity analysis

Alternative parametric models- Progression free survival : PD-L1 (deterministic)

Based on May 2019 data cut-off and latest PAS discount

PFS model	Inc. QALYs	Inc. Costs	ICER (per QALY gained)
PD-L1 TPS <1%			
Exponential	XXXX	XXXXXXX	£54,935
Weibull	XXXX	XXXXXXX	£51,884
Gompertz	XXXX	XXXXXXX	£46,926
Log-normal (base case)	XXXX	XXXXXXX	£47,252
Log-logistic	XXXX	XXXXXXX	£46,611
Generalised gamma	XXXX	XXXXXXX	£46,007
PD-L1 TPS 1-49%			
Exponential	XXXX	XXXXXXX	£36,513
Weibull	XXXX	XXXXXXX	£34,558
Gompertz	XXXX	XXXXXXX	£29,193
Log-normal (base case)	XXXX	XXXXXXX	£30,201
Log-logistic	XXXX	XXXXXXX	£30,510
Generalised gamma	XXXX	XXXXXXX	£33,241
PD-L1 TPS ≥50%*			
Exponential	XXXXX	XXXXXXX	£7,884 (SWQ)
Weibull	XXXXX	XXXXXXX	£10,313 (SWQ)
Gompertz	XXXXX	XXXXXXX	£14,350 (SWQ)
Log-normal (base case)	XXXXX	XXXXXXX	£15,623 (SWQ)
Log-logistic	XXXXX	XXXXXXX	£15,228 (SWQ)
Generalised gamma	XXXXX	XXXXXXX	£15,261 (SWQ)

Compares pembrolizumab combination PAS price with comparator list price

*No comparator treatment discounts. ICER is a decision making ICER

ERG preferred analysis

Including company's additional analyses for PD-L1 ≥50% subgroup

Option	Inc. QALYs	Inc. costs	ICER (per QALY gained)
ERG original preferred CDF-CS analysis	XXXXX	XXXXXX	£15,623 (SWQ)
Company's additional analysis 1 (with re-censoring)	XXXXX	XXXXXXX	£13,196 (SWQ)
Company's additional analysis 2 (failure odds transformation)	XXXXX	XXXXXX	£14,001 (SWQ)
Company's additional analysis 4 (with population-adjustment and switching adjustment)	XXXXX	XXXXXX	£25,661 (SWQ)

Compares pembrolizumab combination vs standard care
Includes pembrolizumab combination PAS price vs comparator list price

For comparator & subsequent treatment discounts the ICER will increase
ICERs in SW quadrant: the higher the ICER, the more cost is saved per QALY lost