Slides for public – redacted

NICE National Institute for Health and Care Excellence

Pembrolizumab with pemetrexed and platinum-based chemotherapy for untreated, metastatic, non-squamous non-small-cell lung cancer [ID1584]

(CDF review of TA557)

Lead team presentation

Lead team:	Matt Bradley, Soo Fon Lim, Malcolm Oswald
Evidence review group (ERG):	Peninsula Technology Assessment Group (PenTAG)
Company:	Merck Sharp & Dohme
Technical team:	Gary McVeigh, Verena Wolfram, Victoria Kelly, Linda Landells
First appraisal committee meeting:	6th October 2020

Key issues

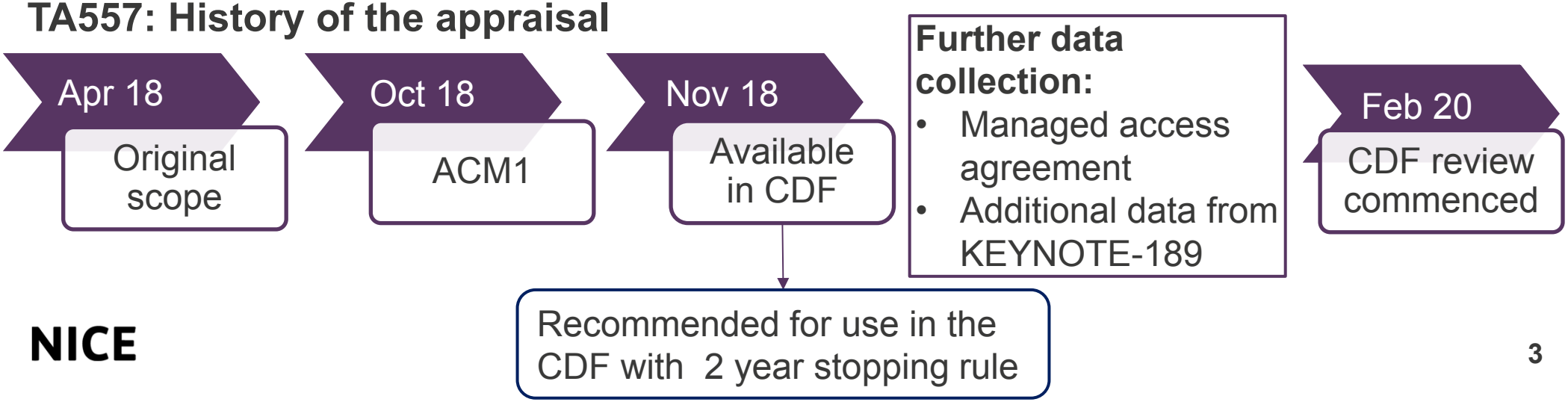
Issue 3: Extrapolation of overall survival	Is the log-logistic distribution or the generalised gamma distribution the most clinically plausible extrapolation of OS, for both the pembrolizumab combination and standard of care arms?
Issue 4: Extrapolation of time-on-treatment	Is the exponential or the generalised gamma distribution the most appropriate extrapolation of time-on-treatment, for both the pembrolizumab combination and standard of care arms?
Issue 6: Treatment effect duration	Is a 2-year, 3-year or 5-year sustained treatment effect without waning for pembrolizumab plausible? Is there any additional evidence which could be used to inform the duration of treatment effect for pembrolizumab in this indication?
Issue 7: Health-related quality of life	What is the most appropriate approach to incorporate both progression status and time-to-death within the estimation of utilities?
Retreatment costs	Should the costs of second-line treatments in the intervention arm be taken into account in the cost-effectiveness model?
Dose intensity	Should the updated dose intensity data for drug costs be used in the model?
End of life	Are end-of-life criteria met for the PD-L1 subgroups?

Appraisal background

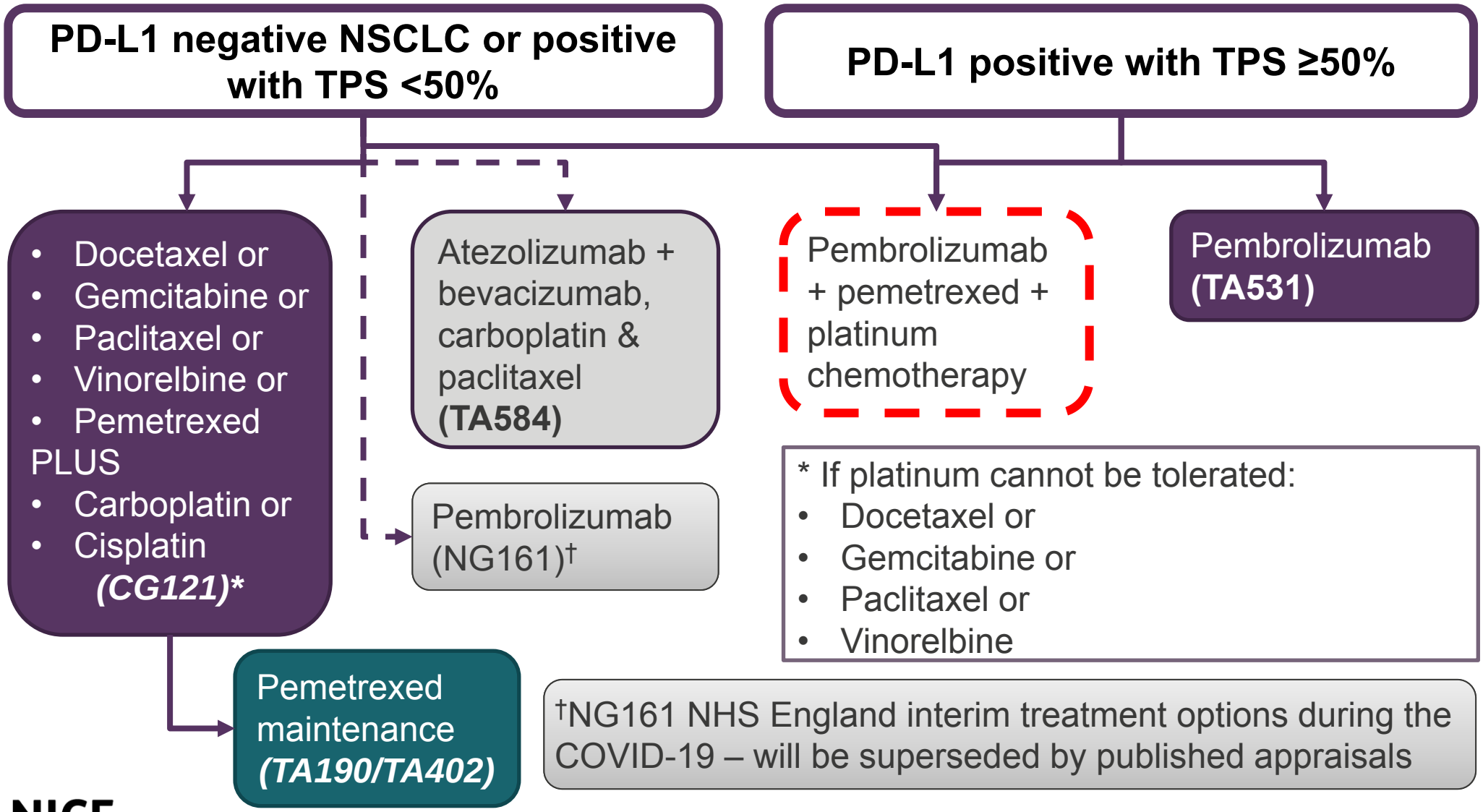
Marketing authorisation	'[Pembrolizumab combination] is indicated for the first line treatment of metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations'

Based on scope:	
Population	Untreated metastatic non-squamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations
Comparators	• Pemetrexed in combination with a platinum drug (carboplatin or cisplatin) • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) • Pembrolizumab monotherapy (for PD-L1 ≥50% subgroup)
Outcomes	Includes overall survival and progression-free survival

TA557: History of the appraisal



Treatment pathway for NSCLC without EGFR or ALK mutation



TPS = Tumour proportion score

Patient organisation comments

Roy Castle Lung Cancer Foundation

- People with advanced/metastatic lung cancer have poor survival rates
- Poor outcomes even with therapy
- Impact on family and carers
- Symptoms (breathlessness, cough, weight loss) difficult to treat without anti-cancer therapy
- These symptoms can be distressing for family/carers to observe
- Immunotherapy has brought a new therapy option
- There is an unmet treatment need for this condition

Advantages of pembrolizumab:

- Potential for extension to life (very important to patients and families)
- Patient access through CDF

Disadvantages of pembrolizumab:

- Side effects

Expert comments

- Treatment substantially improves overall survival compared with chemotherapy
- Treatment substantially increases 2-year survival which is also seen in clinical practice
- Treatment improves QoL compared to chemotherapy, particularly after the platinum component stops
- No additional toxicity compared to chemotherapy alone
- Will lose less patients between 1st and 2nd line treatment
- Treatment is already recommended for the 1st line treatment of PS0-1 patients in ESMO, ASCO and NCCN guidelines
- Treatment was easily implemented when it entered the CDF and has been treatment of choice since
- Increase 1st line time on chemotherapy chairs

KEYNOTE-189 results – overall population (1)

Overall survival

Pembrolizumab combination compared with pemetrexed plus platinum

Additional [redacted] months of data collection through the CDF (cut-off [redacted])

	KEYNOTE-189 final data cut (cut-off [redacted], database lock [redacted])			KEYNOTE-189 data at CDF entry (TA557)		
Treatment	**Median OS (months) (95% CI)**	**Treatment vs. Control**		**Median OS (months) (95% CI)**	**Treatment vs. Control**	
		Hazard ratio (95% CI)	**p-value**		**Hazard ratio (95% CI)**	**p-value**
Control (n=206)	[redacted]	---	---	11.3 (8.7, 15.1)	---	---
Pembrolizumab combination (n=410)	[redacted]	[redacted]	[redacted]	Not reached	0.49 (0.38, 0.64)	0.00001

CI: confidence interval

Control: Saline placebo + pemetrexed + platinum combination therapy

Pembrolizumab combination: Pembrolizumab + pemetrexed + platinum combination therapy

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KEYNOTE-189 results – overall population (2)

Progression-free survival

Pembrolizumab combination compared with pemetrexed plus platinum

Additional [redacted] months of data collection through the CDF (cut-off [redacted])

Treatment	KEYNOTE-189 final data cut (cut-off [redacted], database lock [redacted])			KEYNOTE-189 data at CDF entry (TA557)		
	Median PFS (months) (95% CI)	Treatment vs. Control		Median PFS (months) (95% CI)	Treatment vs. Control	
		Hazard ratio (95% CI)	p-value		Hazard ratio (95% CI)	p-value
Control (n=206)	[redacted]	---	---	4.9 (4.7, 5.5)	---	---
Pembrolizumab combination (n=410)	[redacted]	[redacted]	[redacted]	8.8 (7.6, 9.2)	0.52 (0.43, 0.64)	0.0001

CI: confidence interval

Control: Saline placebo + pemetrexed + platinum combination therapy

Pembrolizumab combination: Pembrolizumab + pemetrexed + platinum combination therapy

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Effectiveness – PD-L1 ≥50% subgroup (1)

TA557

Company	FAD
• Indirect treatment comparison (ITC) pembrolizumab combination versus pembrolizumab monotherapy • Data from KEYNOTE-24 • Non-statistically significant increase in overall survival; large effect BUT wide confidence intervals	• Individual patient data from KEYNOTE-021G should be included • No difference in overall survival for pembrolizumab combination versus pembrolizumab mono

CDF Review

Company

- Updated analysis from original submission includes data from KEYNOTE-021G,
- KEYNOTE-024, KEYNOTE-042, KEYNOTE-189 (additional follow-up data)

KEYNOTE	Population	Intervention	Comparator
189	Untreated, metastatic NSCLC	Pembro combo	Pemetrexed
021G	Untreated, Stage IIIB or IV	Pembro combo	Chemo
024	Advanced NSCLC PD-L1 TPS ≥50%	Pembro	Platinum-based chemo
042	Untreated advanced NSCLC	Pembro	Platinum-based chemo

ERG

- Tests of proportional hazards assumptions not presented
- Not possible to assess appropriateness of the hazard ratios as summary estimates
- But, methods for the company's ITC are broadly appropriate

Effectiveness – PD-L1 ≥50% subgroup (2)

Overall survival from updated company analysis

	Pembrolizumab combination			Pembrolizumab monotherapy			Chemotherapy			ITC hazard ratio (95% CI) P-value
	N	Event n (%)	Median survival time months (95% CI)	N	Event n (%)	Median survival time months (95% CI)	N	Event n (%)	Median survival time months (95% CI)	
Study 189 + 021G										
Study 042 + 024										

Effectiveness – PD-L1 ≥50% subgroup (3)

Progression-free survival from updated company

	Pembrolizumab combination			Pembrolizumab monotherapy			Chemotherapy			ITC hazard ratio (95% CI) P-value
	N	Event n (%)	Median survival time months (95% CI)	N	Event n (%)	Median survival time months (95% CI)	N	Event n (%)	Median survival time months (95% CI)	
Study 189 + 021G										
Study 042 + 024										

Key considerations from TA557

Committee's preferences from TA557	Company's approach at CDF review		Issue raised in TR
Adults with untreated, metastatic, non-squamous NSCLC lacking EGFR- and/or ALK-positive mutation	✓		Resolved – not raised in TR
Pembrolizumab combination vs 'other chemotherapy' treatments – network meta-analysis	✓	Results for the comparison not presented in this submission but company provided rationale	Issue 1 resolved
Pembrolizumab combination vs pembrolizumab mono in PD-L1 ≥50% subgroup – indirect treatment comparison	✓	Provided at clarification	Issue 2 resolved
Overall survival – log-logistic or generalised gamma	✗	Log-logistic only – based on new data	Issue 3
Background mortality – include adjustment	✗	• not applied = no double counting • OS cap by survival rate for general population	Resolved – not raised in TR
Utilities – use progression-based approach	✗	Based on clinical expert opinion	Issue 7
Treatment benefit of pembrolizumab – cap at 3 years and 5 years	✓	Scenarios provided	Issue 6
End of life criteria	✓	PD-L1 <50%	Not raised in TR
	✗	PD-L1 ≥50%	

Issues resolved after technical engagement

	Summary	Company response
1	TA557 – included 'other' chemotherapy treatments as a comparator CDF review – company did not update original NMA **Committee and ERG agree this issue is resolved**	Update of NMA not needed because: • Original NMA showed no statistically significant difference between the treatments • Clinical experts agree that KEYNOTE-189 used relevant comparator • Clinical practice remains unchanged • SLR updated to Oct 2019 and no significant publications found to change comparator
2	TA557 – included comparison of pembrolizumab combination with pembrolizumab monotherapy for TPS ≥50% **Committee and ERG agree this issue is resolved**	Updated ITC including available evidence • KEYNOTE-189 additional [redacted] months data • OS ([redacted]) • PFS ([redacted])
5	Time horizon **Committee and ERG agree this issue is resolved**	• Company increased time horizon to 25 years • 25 years would be sufficient with either OS curve (log-logistic or generalised gamma)

Outstanding issues after technical engagement

Issue 3: Extrapolation of overall survival	• Slides 15 and 16
Issue 4: Extrapolation of time-on-treatment	• Slide 17
Issue 6: Treatment effect duration	• Slides 18 and 19
Issue 7: Health-related quality of life	• Slide 20
Retreatment costs	• Slide 21
Dose intensity	• Slide 22
End of life	• Slides 23 and 24

Issue 3: Extrapolation of overall survival (1)

TA557

Company	FAD
2-phase piecewise model with an exponential distribution at a 28-week cut-off	✗ log-logistic and generalised gamma curves provide most plausible estimate

CDF Review

Company:

- Explored log-logistic extrapolation only because
  - It gave clinically plausible 5-year OS estimates for both arms
  - Was best statistical fit for SoC arm

ERG:

- Considered both log-logistic and generalised gamma plausible
- Preferred generalised gamma because it better fit pembrolizumab combination arm (with gradual treatment waning effect from 2 to 5 years)
- With both extrapolations 5-year overall survival of standard care arm is within the 5 to 11% considered in TA557 FAD

Updated technical team judgement

- Generalised gamma distribution is appropriate; provides clinically plausible 5-year overall survival estimates for both arms of the clinical trial.

Issue 3: Extrapolation of overall survival (2)

Comparison of the company extrapolation (log logistic) no treatment waning until 5-years versus ERG approach applying generalised gamma with a gradual 2-5 year treatment-waning effect

- For standard of care extrapolations are similar
- For pembrolizumab combination predicted 5-year survival estimates are [redacted]% for log logistic and [redacted]% for generalised gamma distribution

Is the log-logistic distribution or the generalised gamma distribution the most clinically plausible extrapolation of OS, for both the pembrolizumab combination and standard of care arms?

Issue 4: Extrapolation of time-on-treatment (1)

TA557

Company	FAD
• Exponential for pembrolizumab combination • Weibull for standard care	✓company's approach was suitable

CDF Review

Company:

- Exponential and generalised gamma had best statistical fit for both treatment arms (using AIC/BIC statistics and visual inspection)
  - Proportional hazards may hold with exponential curve
  - Used exponential for extrapolation of ToT for both arms in their updated model
- Choice of curve has minimal impact on ICER

ERG:

- Preferred generalised gamma for both treatment arms
  - Inappropriate to assume constant hazards for ToT & no evidence to support the proportional hazards assumption for ToT
  - Generalised gamma does not require assumptions around proportional hazards
  - Generalised gamma best fitting model based on AIC, and exponential based on BIC

Updated technical team judgement

Use a generalised gamma curve for both treatment arms

Is the exponential or the generalised gamma distribution the most appropriate extrapolation of time-on-treatment, for both the pembrolizumab combination and standard of care arms?

Issue 6: Treatment effect duration

TA557	Company	FAD
	• 2-year stopping rule • Life-time treatment effect	✓2-year stopping rule ✗ treatment effect waning between 3 and 5 years

CDF Review

Company:

- Applied treatment-waning effect to the pembrolizumab combination arm
  - Base case – treatment benefit persists to 5 years before waning
  - 2 Scenario analyses – treatment benefit persists to 3 or 10 years before waning
- Evidence suggests sustained treatment effect of pembrolizumab: KEYNOTE-001, KEYNOTE-010, KEYNOTE-021G, KEYNOTE-024

ERG:

- Uncertain at what timepoint treatment-waning effect should be applied
  - Base case – continuous treatment-waning effect between 3 and 5 years
- Other KEYNOTE trials are of limited relevance because of differences in population, interventions and dose

Updated technical team judgement

- Duration of relative treatment effect of pembrolizumab remains uncertain
- In TA557 committee concluded that duration of between 3 and 5 years is plausible. No new clinical evidence to justify any change to conclusion

Is a 2-, 3- or 5-year sustained treatment effect without waning for pembrolizumab plausible?
Is there any additional evidence which could be used to inform the duration of treatment effect for pembrolizumab in this indication?

Issue 7: Health-related quality of life

TA557

Company	FAD
Utility values based on time-to-death	✗ progression status & time-to-death were both important to a patient's HRQoL; suggest combined approach

Options for combined approaches	FAD preference
1) Progression based utilities with a decrement applied in the last year of life	✓
2) Time-to-death utilities with decrement applied to account for progression	✗

CDF Review

Company:

- Used combined approach 2 (time-to-death utilities with decrement applied to account for progression)
  - Time-to-death has more health states, offers good fit to data, accepted in other appraisal

ERG:

- Applied committee's preferred assumption from TA557
- ERG commented that both approaches have limitations
  - Combined approach may double count effects of progression or being close to death
  - Neither approach has been updated using the KEYNOTE-189 final analysis data

Updated technical team judgement:

No change on FAD preference (approach 1)

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What is the most appropriate approach to incorporate both progression status and time-to-death within the estimation of utilities?

Retreatment costs

CDF Review

Company:

- KEYNOTE-189 allowed for subsequent treatments
- Provided scenario analysis including costs of subsequent treatment
  - Adjusted to reweight nivolumab to the other therapies as second-line immunotherapies in the intervention arm not considered clinical practice
- Included one-off weighted subsequent therapy costs specific to each treatment arm
  - Pembrolizumab combination subsequent treatment costs included for ITT and PD-L1 ≥50% population
  - Chemotherapy subsequent treatment costs included for ITT population only
  - Pembrolizumab subsequent treatment costs included for PD-L1 ≥50% population only

ERG:

- Benefits of retreatment captured in the OS
- Uncertain how costs of retreatment captured in company model

Should the costs of second-line treatments in the intervention arm be taken into account in the cost-effectiveness model?

Dose intensity

TA557

- To inform drug costs, company used dosing intensity taken from KEYNOTE-189
- Percentage of actual vs expected number of treatment cycles:
  - Pembrolizumab combination = [redacted]
  - Chemotherapy = [redacted]
- The costs for the associated drugs were adjusted in the company model

CDF Review

Company:

- Applied the same costs based on the data from the interim (original) analysis in their model
- Provided the ERG with updated dose intensities data from the final analysis

ERG:

- Noted that the dose intensities changed from interim to final analysis
- Updated data shows [redacted] proportion of actual vs expected treatment cycles:
  - Pembrolizumab combination = [redacted]
  - Chemotherapy = [redacted]
- ERG base case includes the updated values and costs

Technical team judgement:

- Prefer ERG's approach to use updated dose intensity data for drug costs in the model

Should the updated dose intensity data for drug costs be used in the model?

End of life – ITT population KEYNOTE-189

Pembrolizumab combination compared with pemetrexed plus platinum

KEYNOTE-189

End of life criterion	Criterion met	Reason
Life expectancy	✓	Comparator arm; median OS = 11 months
Life gain	✓	Likely to exceed 3 months

Updated technical team judgement

- About 1/3 of people in KEYNOTE-189 had PD-L1≥50% and would get a different comparator

✓ On balance the End of life criteria are met for ITT population in KEYNOTE-189

Is the end-of-life criteria met for the ITT (overall) population in KEYNOTE-189?
Are the results from KEYNOTE-189 generalisable to people seen in the NHS?

End of life – people with PD-L1 <50%

Pembrolizumab combination compared with pemetrexed with carboplatin or cisplatin (standard care) or chemotherapy with carboplatin or cisplatin

TA557

End of life criterion	Criterion met	Reason
Life expectancy	✓	Standard care arm; mean OS = 15 months
Life gain	✓	Likely to exceed 3 months

CDF Review

Company:

End of life criterion	Criterion met	Company results
Life expectancy	✓	Standard care arm – model = 2.00 undiscounted life years Base case – survival is 24 months Alternative OS extrapolations <24 months
Life gain	✓	> 3months for all OS extrapolations

Updated technical team judgement

✓ End of life criteria met for people with PD-L1 <50%

Is the end-of-life criteria met for people with PD-L1 <50%?

End of life – people with PD-L1 ≥50%

Pembrolizumab combination compared with pembrolizumab monotherapy

TA557

End of life criterion	Criterion met	Reason
Life expectancy	✗	Standard care arm; mean OS = 28 months ITC results are uncertain
Life gain	✗	Mean life extension >3 months ITC showed no statistically significant difference

CDF Review

Company:

- ✓Subgroup meets end-of-life criteria based on
  - Clinical expert suggesting life expectancy unlikely to exceed 12-18 months
  - Median survival time when receiving single agent immunotherapy likely <24 months
  - US retrospective study median OS = 18.9 to 19.1 months with pembrolizumab monotherapy

ERG:

- Some uncertainty in estimates of life expectancy
- Likely that mean OS >24 months
- Company model results in [redacted] life years in pembrolizumab monotherapy arm

Updated technical team judgement

- KEYNOTE-024 median OS = 26 months

✗ End of life criteria not met for people with PD-L1 ≥50%

Is the end-of-life criteria met for people with PD-L1 ≥50%?

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Immature evidence base	• Still a high level of uncertainty in long-term survival outcomes • The analyses are based on extrapolated mean values	Lack of long-term data increases uncertainty in the decision

Cost effectiveness results (1)

Assumptions used in base case models

Assumption	Company	ERG
Stopping rule	2 year	
Time horizon Issue 5 technical report	25 year	
OS extrapolation Issue 1 technical report	**Log logistic for both arms**	**Generalised gamma for both arms**
PFS extrapolation	KM with 21-week cut-off then Weibull distribution	
Background mortality	No adjustments	
Time on treatment extrapolation Issue 4 technical report	**Exponential for both arms**	**Generalised gamma for both arms**
Treatment effect Issue 6 technical report	**Treatment effect lasts to year 5, no waning**	**Gradual waning between years 3 to 5**
Utilities Issue 7 technical report	**Based on time to death only**	**Based on progression status with a decrement applied for people likely to live <360 days**
Dose intensity	**From original data cut**	**Updated from Final Analysis**

Cost effectiveness results – pembro PAS (1)

ERG preferred assumptions and impact on the cost-effectiveness estimate – Overall population

Deterministic ICERs for pembrolizumab with pemetrexed and platinum chemotherapy compared to pemetrexed and carboplatin or cisplatin

- 25-year time horizon as accepted during technical engagement
- Same assumptions like for overall population

Alteration	Technical team rationale	ICER	Change from base case
Company base case	Deterministic ICER	[redacted] **>£30,000**	
1. OS – generalised gamma for both arms	Issue 3	[redacted]	+£21,671
2. TWE – between years 3 to 5	Issue 6	[redacted]	+£7,232
3. ToT – generalised gamma for both arms	Issue 4	[redacted]	+£851
4. Dose intensity from the final analysis of KEYNOTE-189	See dose intensity slide	[redacted]	-£104
5. Utilities - progression based utilities with a decrement in the last year of life	Issue 7		
Cumulative impact of ERG's preferred assumptions on the cost-effectiveness estimate	–	[redacted] **>£50,000**	**+£22,890**

✓Technical team agree with all the ERG's assumptions

Cost effectiveness results – pembro PAS (2)

ERG preferred assumptions and impact on the cost-effectiveness estimate – PD-L1 ≥50% subgroup

Deterministic base case for pembrolizumab with pemetrexed and platinum chemotherapy compared to pemetrexed and carboplatin or cisplatin

- 25-year time horizon as accepted during technical engagement

Alteration	Technical team rationale	ICER	Change from base case
Company base case	Deterministic	[redacted] **>£30,000**	
1. OS – generalised gamma for pembro combination, Kaplan-Meier for monotherapy	Issue 3	[redacted]	-£7,763
2. TWE – between years 3 to 5	Issue 6	**N/A**	
3. ToT – generalised gamma for both arms	Issue 4	[redacted]	£2,460
4. Dose intensity from the final analysis of KEYNOTE-189	See dose intensity slide	[redacted]	-£169
5. Utilities - progression based utilities with a decrement in the last year of life	Issue 7		
Cumulative impact of ERG's preferred assumptions on the cost-effectiveness estimate	–	[redacted] **>£30,000**	**-£5,780**

✓Technical team agree with all the ERG's assumptions

Cost effectiveness results – pembro PAS (3)

Base case ICERs for overall population and PD-L1 ≥50%

Overall population – pembrolizumab with pemetrexed and platinum chemotherapy compared to standard care with pemetrexed and carboplatin or cisplatin

Probabilistic	Pembrolizumab combination		Chemotherapy		ICER £/QALY	+/-£
	QALYs	Costs	QALYs	Costs		
Company	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] **>£30,000**	
ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] **>£50,000**	+£23,646

PD-L1 ≥50% subgroup – pembrolizumab with pemetrexed and platinum chemotherapy compared to pembrolizumab monotherapy; same assumptions like for overall population

Deterministic	Pembrolizumab combination		Pembrolizumab monotherapy		ICER £/QALY	+/-£
	QALYs	Costs	QALYs	Costs		
Company	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] **>£30,000**	
ERG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] **>30,000**	-£5,780

Other issues for information

Issue	Comments
Implementation of company model	• No changes to the model structure, population, intervention, perspective, time horizon or discounting in the model • Minor errors in the model corrected • ERG report and technical report based on corrected model
PFS	• Company provided a piecewise approach (Kaplan-Meier curve followed up until Week 21, followed by a Weibull model) • In the updated model, progression status informs utility values • ERG prefer to explore option of using fully parametric approach • But, the base-case projections (KM + Weibull) provided by the company are a reasonable fit to the Kaplan-Meier curves • So are considered a suitable basis for informing decision making • Other models that consider alternative cut points also considered
Innovation	The technical team considers that all relevant benefits associated with the drug are adequately captured in the model.
Equality considerations	No equality issues were identified in the original appraisal. No new issues have been raised in this CDF review process.

Key issues

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End of life	Are end-of-life criteria met for the PD-L1 subgroups?