REDACTED SLIDES

NICE National Institute for Health and Care Excellence

Pembrolizumab with carboplatin and paclitaxel or nab-paclitaxel for untreated metastatic squamous non-small-cell lung cancer [ID1306]

Lead team presentation

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Company: MSD

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Key Issues

- **Survival estimates from different modelling approaches:** What is the most appropriate survival model? [Issue 1]
- **Subsequent treatments:** Are second-line immunotherapy benefits captured adequately in the various models? [Issue 3]
- **Treatment effect:** What is the most appropriate method to model the treatment effect of pembrolizumab combination therapy? [Issue 4]
- **Utility values:** What method is most appropriate to capture changes in health-related quality of life? [Issue 6]
- **End of life:** Does pembrolizumab combination therapy meet NICE's end of life criteria? [Issue 7]
- **Cancer Drugs Fund:** Does pembrolizumab combination therapy meet the criteria for inclusion in the CDF? [Issue 8]
- **Subgroup analyses:** How do subgroup considerations affect decision-making? [Issue 9 – New Issue]

Pembrolizumab (Keytruda, Merck Sharp & Dohme)

Description of technology	Humanised, anti-programmed cell death 1 (PD-1) antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells
Marketing authorisation	KEYTRUDA, 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 200 mg by intravenous (IV) infusion prior to chemotherapy on Day 1 of each 21-day cycle and paclitaxel (200 mg/m^2 by IV infusion on Day 1 of each 21-day cycle for 4 cycles) OR nab-paclitaxel (100 mg/m^2 by IV infusion on Days 1, 8, 15 of each 21-day cycle for 4 cycles) PLUS carboplatin AUC 6 by IV infusion on Day 1 of each 21-day cycle for 4 cycles
Stopping rule	35 cycles (2 years) or until disease progression

Background (1)

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 (CDF) (TA 483)
Third-line treatment	Docetaxel (single-agent)	

Platinum-based combination chemotherapy - gemcitabine, paclitaxel, vinorelbine plus carboplatin or cisplatin

** unless unable to tolerate platinum therapy*

† PD-L1 TPS>1% only CDF = Cancer Drugs Fund

Note - treatment may involve re-challenging with platinum-based chemotherapy in second-line for some patients

[redacted]

Background (2)

Comparators	Standard care chemotherapy (PD-L1 TPS <50%), pembrolizumab monotherapy (PD-L1 TPS ≥50%)
Subgroups	PD-L1 TPS <1%,1-49%, ≥50%
Key clinical trial	KEYNOTE 407, randomised controlled trial comparing pembrolizumab with carboplatin and paclitaxel/nab-paclitaxel with carboplatin and paclitaxel/nab-paclitaxel
Key results	OS HR 0.64 (95% CI 0.49, 0.85); p=0.0008 PFS HR 0.56 (95% CI 0.45, 0.70);p=<0.0001
Comparison with pembrolizumab monotherapy	Indirect comparison
Key result	Median OS not reached in PD-L1 TPS ≥50%
Model	Partitioned survival model - based on three health states: first-line treatment, not receiving first-line treatment (including second-line treatment), and death
Company base-case ICER	£25,828 to £35,839 per QALY gained
Technical team preferred ICER	£33,631* to £45,680* per QALY gained *May be higher due to [Issue 3]

[redacted]

Patient and carer perspectives

- Submission from: 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

[redacted]

Clinician perspective

- Submission from 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 respond 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

[redacted]

CDF clinical lead perspective

- The most commonly used regimen in England is carboplatin plus gemcitabine
- Carboplatin in combination with a taxane (paclitaxel, docetaxel) is very rarely used as first line therapy
- Nab-paclitaxel is not commissioned by NHS England, therefore is not relevant in this appraisal
- Significant interest in pembrolizumab in combination with carboplatin and paclitaxel in the untreated PD-L1 TPS 0-49% population as it allows use of immunotherapy first line in a population of people who currently only access immunotherapy second line
- Since the approval of atezolizumab monotherapy in patients previously treated with chemotherapy, atezolizumab has largely displaced use of pembrolizumab in the second line setting
- The ratio of patients treated with second line atezolizumab to second line pembrolizumab is currently approaching about 3 to 1

[redacted]

CDF clinical lead perspective

- People fit enough for immunotherapy would not choose to wait to have immunotherapy second line as approximately 50% of first-line patients do not proceed to further systemic therapy (PD-L1 0-49%)
- In the PD-L1 TPS≥50% population, there is uncertainty around the proportion of people who will receive pembrolizumab combination therapy rather than pembrolizumab monotherapy
- NHS England considers that many of the PD-L1 TPS≥50% group will elect to receive pembrolizumab monotherapy in order to avoid the additional toxicity of combination chemotherapy
- KEYNOTE-407 interim analysis represent a very immature dataset
- Uncertainty as to the longer term immune-related toxicities of this combination

[redacted]

CDF clinical lead perspective

- Indirect treatment comparison between pembrolizumab in combination with chemotherapy versus pembrolizumab monotherapy in the PD-L1 TPS ≥50% group showed similar outcomes for efficacy
- However - increased toxicity would be seen in those treated with the combination of pembrolizumab and chemotherapy
- NHS England considers the modelling of survival in the comparator arm in the PD-L1 0-49% group to be underestimated
- Using historical data from the pre-immunotherapy era for the comparator chemotherapy group in the PD-L1 0-49% analysis is flawed
- Lifetime treatment effect is over optimistic as previous NICE appraisals considered 3 to 5 year effect durations

[redacted]

CDF clinical lead perspective

- If NICE recommends a treatment cap at 2 years, NHS England confirms its willingness to commission a maximum 2 year treatment duration of pembrolizumab in this indication, as it has already done so for other immunotherapy options in NSCLC
- NHS England would wish to commission use of pembrolizumab in combination in people with an ECOG performance status of 0 or 1, as in the KEYNOTE-407 trial

[redacted]

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
2	Uncertainty around where pembrolizumab combination therapy in the treatment pathway • reserved for second-line use in subgroups with PD-L1 TPS <50%? • used instead of pembrolizumab monotherapy for PD-L1 ≥50%?	Clinical expert opinion agreed that the technology would be used as indicated	If approved by NICE, pembrolizumab combination therapy would be used as a treatment option as per its indication	Not applicable
5	Within the Company's submission, they present indirect treatment comparisons for all relevant comparators for the population	All standard chemotherapy regimens used for treating PD-L1 TPS <50% can be considered equal in efficacy	ITC only required for comparison in the subgroup PD-L1 TPS ≥50%	Company – Yes ERG – Yes

[redacted]

Outstanding issues after technical engagement

- **Issue 1: Extrapolating overall survival**
- **Issue 3: Subsequent treatments**
- **Issue 4: Treatment effect**
- **Issue 6: Health-related quality of life measurement**
- **Issue 7: End of life criteria**
- **Issue 8: Cancer Drugs Fund**
- **Issue 9: Subgroup analysis** [New Issue]

[redacted]

Issue 1: Extrapolation of overall survival

- Company's base case model used the SEER database in both treatment arms to inform survival outcomes, along with Kaplan-Meier data from KEYNOTE-407
- In modelling survival for intervention arm, the company applied a relative risk (from months 7 to 12 in KEYNOTE-407) indefinitely
- SEER data has not been used to directly model survival in previous NICE appraisals

Response from engagement

Company:

- The SEER database, while not ideal, is appropriate in absence of recent UK data
- Standard parametric methods not suitable – leads to implausible survival estimates in SoC arm
- 2 clinical advisors to the ERG agree that estimates for SoC arm are reasonable
- KM/Log-logistic model provides a clinically plausible 5 year survival in SoC arm – but the KM/SEER is the most appropriate method of extrapolation
- This is because clinical plausibility (of log-logistic model) is based on estimates on SEER database – therefore more relevant to use actual SEER database

[redacted]

Issue 1: Extrapolation of overall survival **(2)**

- Company's base case model used the SEER database in both treatment arms to inform survival outcomes, along with Kaplan-Meier data from KEYNOTE-407
- In modelling survival for intervention arm, the company applied a relative risk (from months 7 to 12 in KEYNOTE-407) indefinitely
- SEER data has not been used to directly model survival in previous NICE appraisals

ERG comment:

- SEER unlikely relevant due to the lack of second-line immunotherapies in this database
- Outcomes highly uncertain – clinical advisors to ERG agreed that company's model likely overestimated survival outcomes for intervention arm
- All clinical advisors to ERG stated difficulty of estimating long-term outcomes
- ERG adopted two survival modelling approaches: based on different estimates from clinical advisors: optimistic (advisors 1&2) and pessimistic (advisor 3)
- Optimistic model uses company's KM/SEER model for SoC arm, as two clinical advisors stated these estimates are reasonable (noted caution of using SEER). KM/log-logistic used for intervention arm (with a 19-week cut-point)
- Pessimistic model uses log-logistic extrapolations in both arms, based on third clinical advisor (with no cut points)

[redacted]

Issue 1: Extrapolation of overall survival (3)

- Company's base case model used the SEER database in both treatment arms to inform survival outcomes, along with Kaplan-Meier data from KEYNOTE-407
- In modelling survival for intervention arm, the company applied a relative risk (from months 7 to 12 in KEYNOTE-407) indefinitely
- SEER data has not been used to directly model survival in previous NICE appraisals

Description of ERG models

Model	Optimistic analysis – Exploratory analysis 5a	Pessimistic analysis - Exploratory analysis 5b
OS model - pembrolizumab combination therapy	Company's KM/log logistic model (19-week cut-point)	ERG's log logistic model (no cut-point)
OS model - SoC chemotherapy	Company's KM/SEER model (19-week cut-point)	ERG's log logistic model (no cut-point)
PFS model - pembrolizumab combination therapy	Company's piecewise log normal model (26-week cut-point)	Company's piecewise log normal model (26-week cut-point)
PFS model – SoC chemotherapy	Company's piecewise log normal model (26-week cut-point)	Company's piecewise log normal model (26-week cut-point)

[redacted]

Issue 1: Extrapolation of overall survival (4)

- Company's base case model used the SEER database in both treatment arms to inform survival outcomes, along with Kaplan-Meier data from KEYNOTE-407
- In modelling survival for intervention arm, the company applied a relative risk (from months 7 to 12 in KEYNOTE-407) indefinitely
- SEER data has not been used to directly model survival in previous NICE appraisals

Technical report:

- The ERG's approach best captures the high uncertainty around long-term outcomes, with its optimistic and pessimistic modelling
- The ERG models also limit the use of SEER data

❑ Optimistic model - SEER is used only in SoC arm

❑ Pessimistic model – SEER is not used in either treatment arm

- All clinical advisors stated that using the SEER database (with a relative risk ratio - months 7 to 12 in KEYNOTE-407 trial) produced too optimistic overall survival results for the pembrolizumab combination arm of the trial
- Technical team consider both the ERG's models to be preferable to the company's model

[redacted]

Issue 1: Extrapolation of overall survival (5)

Clinical expert estimates

	Clinical Advisor 1		Clinical Advisor 2		Clinical Advisor 3		Clinical Advisor 4		
Overall Survival	**5 years**	**10 years**	**5 years**	**10 years**	**5 years**	**10 years**	**5 years**	**10 years**	**20 years**
Pembrolizumab combination	20%	11%	20%	11%	15-20%	5-10%	18%*	11%	4%
Standard care	8%	3%	8%	3%	8-10%	5%	9%*	3%	0%
Progression-free survival	**5 years**	**10 years**	**5 years**	**10 years**	**5 years**	**10 years**	**5 years**	**10 years**	**20 years**
Pembrolizumab combination	10%	-	10%	-	10%	-	10%	5%	4%
Standard care	3%	-	3%	-	3%	-	3%	0%	0%

Clinical advisors 1 to 3 = ERG advisors, Clinical advisor 4 = NICE advisor

*updated following technical engagement TC

[redacted]

Issue 1: Extrapolation of overall survival **(6)**

- Figure redacted - academic in confidence

[redacted]

KEY QUESTION: What is the most appropriate survival model?

Issue 3: Subsequent treatments

- Second-line immunotherapies for PD-L1 <50% - relatively recent addition to treatment pathway
- SEER database does not capture benefits from these treatments
- Models account for second-line costs, but do not explicitly capture the benefits

Response from engagement

Clinical expert opinion:

- It is likely that ~50% of people in the SoC arm would receive second-line immunotherapy following disease progression
- Of these people, 65% would likely receive pembrolizumab monotherapy and 35% would receive atezolizumab

Company:

- Updated assumed proportion of people in SoC arm who receive second-line immunotherapy, as per clinical opinion received during tech engagement
- Updated types and proportions of second-line immunotherapy (as per clinical opinion)
- Also updated the assumed duration spent on these treatments based on median time from TA 428 (Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy)

Issue 3: Subsequent treatments (2)

- Second-line immunotherapies for PD-L1 <50% - relatively recent addition to treatment pathway
- SEER database does not capture benefits from these treatments
- Models account for second-line costs, but do not explicitly capture the benefits

Response from engagement

ERG:

- Updated proportions receiving second-line immunotherapy and types of immunotherapy, and assumed a longer duration than the company
- The ERG believes that the company's use of median exposure time is likely to underestimate treatment duration
- Within TA 428 (Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy) PFS was used as a proxy for treatment duration; the (discounted) mean PFS time was approximately 7.3 months. This is considerably higher than the company's median estimate of 106 days (3.5 months)
- Notes that increasing the proportions favours pembrolizumab combination arm as only costs increase and not benefits, due to no causal link between these treatments and benefits

[redacted]

Issue 3: Subsequent treatments (3)

- Second-line immunotherapies for PD-L1 <50% - relatively recent addition to treatment pathway
- SEER database does not capture benefits from these treatments
- Models account for second-line costs, but do not explicitly capture the benefits

Response from engagement

Technical report:

- As none of the models include an explicit link between receiving second-line line treatment and benefits - survival is likely underestimated in SoC arm (particularly in models using SEER)
- ICERs therefore likely to be underestimated, but it is unknown by how much
- May impact on End of Life criteria considerations, as expected survival in the SoC arm forms part of the criteria **[Issue 7 and Issue 9]**

[redacted]

KEY QUESTION: Are second-line immunotherapy benefits captured adequately in the various models?

Issue 4: Treatment effect

- Company's base case model assumes a lifetime treatment effect
- Company's updated base case assumes a 3 year treatment effect post treatment discontinuation (with scenario analysis with a 5 year effect from initiation)
- Previous NSCLC appraisals assumed 3 to 5 year treatment effect duration

Response from engagement

Company:

- Unclear what is the true treatment effect of pembrolizumab combination – but no data to suggest a waning of treatment effect

ERG:

- ERG clinical advisors agreed that a lifetime treatment effect to be overly optimistic
- ERG clinical advisors noted considerable uncertainty relating to the duration of treatment response and its impact on OS outcomes.
- Removing the treatment effect at earlier timepoints substantially increases the ICER for pembrolizumab combination therapy
- Company has not presented any new evidence relating to the duration over which the treatment effect may apply; this remains a key area of uncertainty
- Using a relative risk for model treatment effects for time-to-event outcomes is statistically inappropriate

[redacted]

Issue 4: Treatment effect (2)

- Company's base case model assumes a lifetime treatment effect
- Company's updated base case assumes a 3 year treatment effect post treatment discontinuation (with scenario analysis with a 5 year effect from initiation)
- Previous NSCLC appraisals assumed 3 to 5 year treatment effect duration

Technical report:

- Lifetime treatment effect likely to be too optimistic – 3 to 5 years more appropriate
- Technical team prefer the ERG models for estimating survival (as described in issue 1)
- ERG models do not use an implicit treatment effect – HR varies over time

[redacted]

KEY QUESTION: What is the most appropriate method to model the treatment effect of pembrolizumab combination therapy?

Issue 6: Health-Related Quality of Life

- Company uses time-to-death (TTD) from KEYNOTE-407 in updated base case (1)
- Company uses progression-based utilities from KEYNOTE-407 in updated base case (2)
- EQ-5D Utilities collected shortly after disease-progression (at most 30 days)
- TTD utilities similar to those of general population (age adjusted) for states (<360 days) and (180-360 days)

Response from engagement

Company:

- Time to death (TTD) utility approach allows a better reflection of the HRQoL experienced by patients
- Utility values from KEYNOTE-407 should be used
- Utility values for states of (<360 days) and (180-360 days) are not implausible as cancer patients have been reported to value health states higher than general population
- Do not agree with ERG's use of a post-progression utility value from Khan et al (which was based on the TOPICAL trial)

[redacted]

Issue 6: Health-Related Quality of Life (2)

- Company uses time-to-death (TTD) from KEYNOTE-407 in updated base case (1)
- Company uses progression-based utilities from KEYNOTE-407 in updated base case (2)
- EQ-5D utilities collected shortly after disease-progression (at most 30 days)

ERG:

- EQ-5D data was collected shortly after disease progression in KEYNOTE-407 – estimates likely to be biased (irrespective of TTD or progression-based approach)
- Company does not provide any evidence to justify high utility values in TTD
- External data is therefore needed – TOPICAL trial (Khan et al) is a reasonable source of post-progression utility as:

  (1) EQ-5D data was collected in progressed patients and (2) few patients in placebo group received active therapy after disease progression (estimates unlikely to be contaminated by post-progression treatments)
- Khan et al is also in line with NICE reference case and has been used in previous NICE appraisals (e.g. TA411 – necitumumab for NSCLC)

[redacted]

KEY QUESTION: What method is most appropriate to capture changes in Health-related quality of life?

Issue 7: End of Life Criteria

Extension to life of pembrolizumab combination therapy

- Company's model (base case) predicts a mean life extension of 3.09 years
- ERG optimistic model predicts a mean life extension of 1.98 years
- ERG pessimistic model predicts a mean life extension of 1.06 years

Response from engagement:

Company:

- The extension to life is over 3 months.

Technical Report:

- The company's model and both ERG optimistic and pessimistic models estimate that the extension to life is over 3 months when comparing pembrolizumab combination therapy to current standard NHS treatment
- The technical team believe that there is sufficient evidence to indicate that the treatment offers an extension to life of at least an additional 3 months, compared to current NHS treatments

[redacted]

Issue 7: End of Life Criteria (2)

Life expectancy of the standard care group (All PD-L1 expression types)

- Company models predict SoC group mean survival of 1.97 years
- ERG optimistic model predicts SoC group mean survival of 1.97 years
- ERG pessimistic model predicts SoC group mean survival of 2.17 years

Response from engagement:

Company:

- Life expectancy of adults with metastatic squamous NSCLC is less than 24 months (2 years) due to the clinical characteristics of the population and the limited treatment options for this group

ERG:

- There is uncertainty surrounding whether the EoL criteria are met
  - Mainly due to uncertainty regarding expected survival duration of patients receiving first-line SoC chemotherapy with a proportion receiving second-line line immunotherapy
- ERG believes that OS may be underestimated in the SoC group

[redacted]

Issue 7: End of Life Criteria (3)

Life expectancy of the standard care group (All PD-L1 expression types)

- Company models predict SoC group mean survival of 1.97 years
- ERG optimistic model predicts SoC group mean survival of 1.97 years
- ERG pessimistic model predicts SoC group mean survival of 2.17 years

Technical report:

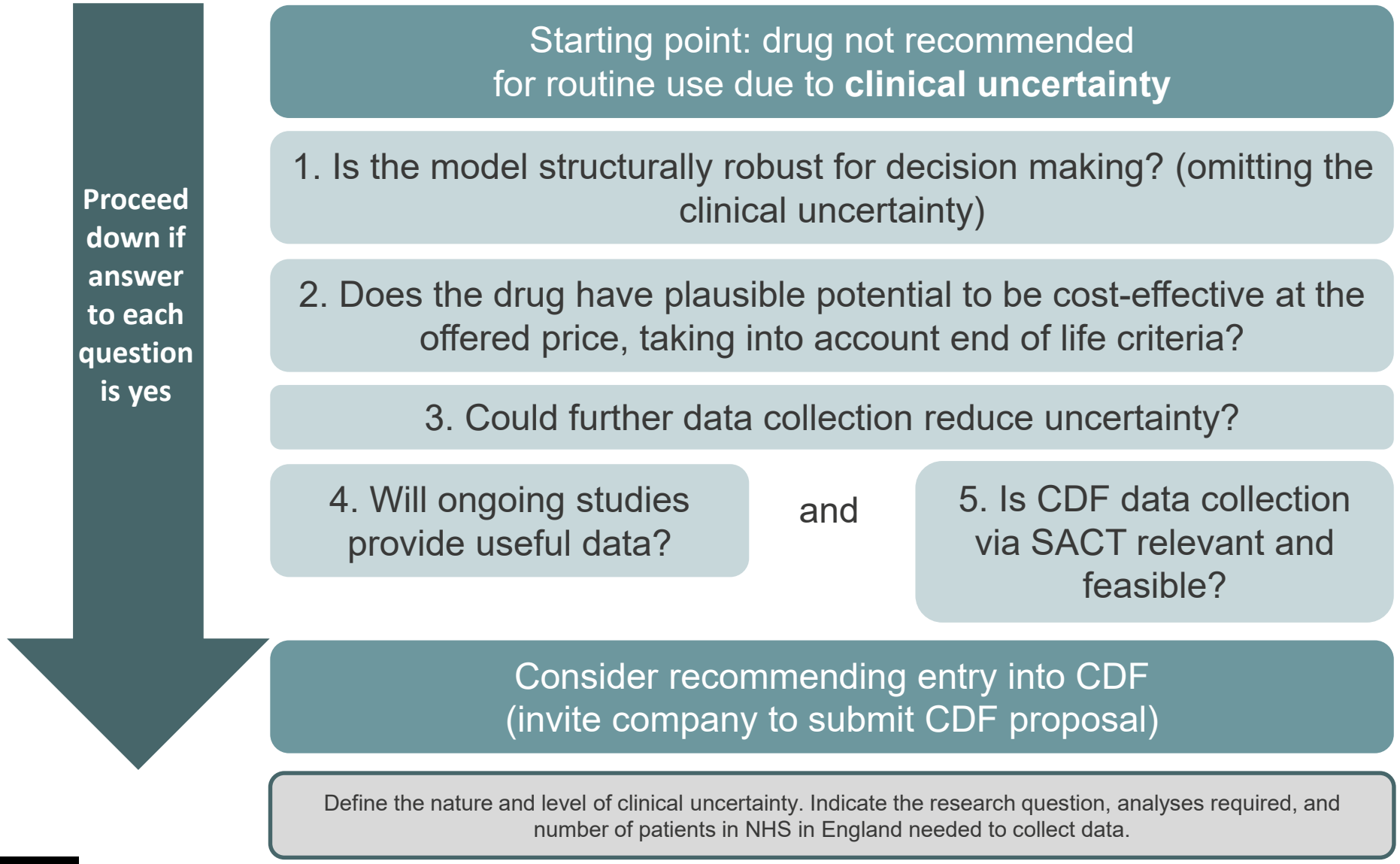
- As the modelling (both company and ERG) does not explicitly account for second-line immunotherapy survival gains in the SoC arm, the technical team and the ERG believe that life expectancy for the SoC arm is underestimated, but it is not known by how much
- High uncertainty around the life expectancy of the patient group receiving SoC chemotherapy, but it is likely to be over 24 months for the full untreated squamous NSCLC population
- End of life criteria should also be considered for PD-L1 TPS subgroups [Issue 9]

[redacted]

KEY QUESTION: Does Pembrolizumab combination therapy meet NICE's end of life criteria?

Issue 8: Cancer Drugs Fund (1)

Committee decision making criteria:



[redacted]

Issue 8: Cancer Drugs Fund (2)

- The duration of clinical trial data presented within the company's submission is short, leading to considerable uncertainty regarding longer term benefits in both arms of KEYNOTE-[redacted]
- Further data may help resolve uncertainty in long term outcomes

Response from engagement:

Company:

- Considers pembrolizumab combination suitable for the Cancer Drugs Fund
- Additional data collection is planned
- Data from the final analysis of KEYNOTE-407 expected to be available i[redacted]

Technical report:

- At the current value proposition, pembrolizumab combination therapy does not appear to have plausible potential for cost-effectiveness with technical team preferred ICERs all above the £20,000–£30,000 per QALY gained range when commercial arrangements are considered
- It is therefore unlikely to meet the criteria for inclusion in the Cancer Drugs Fund

[redacted]

KEY QUESTION: Does pembrolizumab combination therapy meet the criteria for inclusion in the Cancer Drugs Fund?

Issue 9 [New]: Subgroup analysis

- Within the NHS, people whose tumours express PD-L1 TPS <1% or 1-49%, receive standard chemotherapy as first-line treatment
- People whose tumours express PD-L1 TPS ≥50% receive pembrolizumab monotherapy
- Pembrolizumab monotherapy was not included within the comparator arm of KEYNOTE-407 trial
- An indirect treatment comparison (ITC) (using network meta-analysis [NMA]) between pembrolizumab combination therapy and pembrolizumab monotherapy was included in the company's submission to account for this

Technical report:

- KEYNOTE-407 comparators are relevant for people whose tumours express PD-L1 TPS <1% and 1-49% - therefore a ITC is not needed for these subgroups
- For people with a PD-L1 TPS ≥50%, the ITC is needed
  - There are concerns with the robustness of this ITC, as it is unclear how the company sourced the time to treatment discontinuation
- Life expectancy of SoC varies by PD-L1 TPS subgroup and by model. This may impact whether pembrolizumab is considered cost-effective for these subgroups

[redacted]

Issue 9 [New]: Subgroup analysis (2)

End of Life considerations by PD-L1 TPS subgroups

PD-L1 TPS Subgroup	Analysis	Life Years Gained SoC arm (mean)	Incremental Life Years Gained Intervention arm (mean)
<1%	Company base case	1.66	2.30
	ERG optimistic	1.97	1.98
	ERG pessimistic	1.40	1.88
1-49%	Company base case	1.80	2.26
	ERG optimistic	2.02	1.59
	ERG pessimistic	2.09	1.03
≥ 50%	Company base case	4.55	-0.65
	ERG optimistic	2.00	2.02
	ERG pessimistic	4.01	- (Dominated)

[redacted]

KEY QUESTION: How do subgroup considerations affect decision-making?

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Immature evidence base	The interim analysis from KEYNOTE-407 is of short duration. Median overall survival in the trial has not yet been reached in all subgroups	Unknown
Long term adverse events of pembrolizumab combination therapy.	If pembrolizumab combination therapy has more adverse events than standard care treatments for this indication, then this results in a reduction in health benefits	Unknown – but if it was shown that the intervention caused more/more severe adverse events – ICER increases
Trial does not reflect current SoC within the NHS for people with strong PD-L1 expression ≥50%	People with a PD-L1 expression of ≥50% would routinely be given pembrolizumab monotherapy. A direct comparison between the intervention and pembrolizumab monotherapy cannot be made	Unknown - Uncertainty around cost-effectiveness estimates as an indirect comparison is used

Cost effectiveness results: Updated company base case

Total costs (£)	Incremental costs (£)	Total QALYs	Incremental QALYs	ICER (£/QALY)
Company base case (1) • **Updated with:** ➢ Corrected errors, removing nivolumab (CDF) in modelling ➢ Updated proportions - second-line immunotherapy + types of immunotherapy ➢ Inclusion of disease management costs based on progression status				
£71,778	£43,290	2.94	1.68	**£25,828**
Company base case (2) • **Updated with:** ➢ KEYNOTE-407 progression-based utilities ➢ 3 year treatment effect post treatment discontinuation (* Also includes all of amendments in base case (1))				
£66,550	£38,061	2.26	1.06	**£35,839**

[redacted]

Cost effectiveness results: Technical team preferred ICERS

Total Costs (£)	Incremental costs (£)	Total QALYs	Incremental QALYs	ICER (£/QALY)
ERG preferred optimistic analyses • **Includes:** ➢ Company's KM/SEER extrapolation for SoC group survival estimates ➢ Log-Logistic extrapolation for intervention group survival estimates (19-week cut-point)				
£66,008	£34,128	2.17	1.01	**£33,631**
ERG preferred pessimistic analyses • **Includes:** ➢ Log-logistic extrapolation for SoC and intervention group survival estimates ➢ No cut-points				
£62,832	£29,782	1.91	0.65	**£45,680**
Both ERG models include: (1) progression-based disease management costs (2) updated second-line SoC treatment proportions + durations and (3) progression-based HRQoL: post-progression utility value from Khan et al				

Cost effectiveness results by PD-L1 TPS subgroup

Analysis	Total Costs (£)	Incremental costs (£)	Total QALYs	Incremental QALYs	ICER (£/QALY)
PD-L1 TPS <1% - pembrolizumab combination therapy versus carboplatin plus paclitaxel					
Company base case	£70,453	£42,583	2.89	1.70	**£24,976**
ERG optimistic	£64,296	£30,316	2.03	0.94	**£32,343**
ERG pessimistic	£61,898	£30,125	1.85	0.93	**£32,245**
PD-L1 TPS 1-49% - pembrolizumab combination therapy versus carboplatin plus paclitaxel					
Company base case	£76,126	£46,977	2.97	1.67	**£28,122**
ERG optimistic	£69,348	£36,879	2.13	0.96	**£38,244**
ERG pessimistic	£67,684	£34,753	1.91	0.71	**£49,149**

[redacted]

Cost effectiveness results by PD-L1 TPS subgroup (2)

Analysis	Total Costs (£)	Incremental costs (£)	Total QALYs	Incremental QALYs	ICER (£/QALY)
PD-L1 TPS ≥50% pembrolizumab combination therapy versus carboplatin plus paclitaxel					
Company base case	£65,042	£37,069	2.85	1.56	**£23,691**
ERG optimistic	£64,708	£33,269	2.11	0.91	**£36,592**
ERG pessimistic	£63,425	-	2.01	-	**Dominated**
PD-L1 TPS ≥50% pembrolizumab combination therapy versus pembrolizumab monotherapy					
Company base case	£65,042	£9,930	2.85	-0.12	**Dominated**
ERG optimistic	£64,708	-	2.11	-	**Dominated**
ERG pessimistic	£63,425	-	2.01	-	**Dominated**

**Company base case results come from updated company base case (1)*

[redacted]

Key Issues

- **Survival estimates from different modelling approaches:** What is the most appropriate survival model? [Issue 1]
- **Subsequent treatments:** Are second-line immunotherapy benefits captured adequately in the various models? [Issue 3]
- **Treatment effect:** What is the most appropriate method to model the treatment effect of pembrolizumab combination therapy? [Issue 4]
- **Utility values:** What method is most appropriate to capture changes in health-related quality of life? [Issue 6]
- **End of life:** Does pembrolizumab combination therapy meet NICE's end of life criteria? [Issue 7]
- **Cancer Drugs Fund:** Does pembrolizumab combination therapy meet the criteria for inclusion in the CDF? [Issue 8]
- **Subgroup analyses:** How do subgroup considerations affect decision-making? [Issue 9 – New Issue]