Slides for public – redacted

NICE National Institute for Health and Care Excellence

Pembrolizumab for previously treated advanced or metastatic urothelial cancer [ID1536] *(review of TA519)*

Lead team presentation

Lead team:	David Bowen, Gillian Ells, Malcolm Oswald
Evidence review group (ERG):	Warwick Evidence
Company:	Merck Sharp & Dohme
Technical team:	Lindsay Smith, Amy Crossley, Nicola Hay, Linda Landells
First appraisal committee meeting:	22nd October 2019

TA519 recommendation

Pembrolizumab is currently available for use within the Cancer Drugs Fund as an option for treating locally advanced or metastatic urothelial carcinoma in adults who have had platinum-containing chemotherapy, only if:

- Pembrolizumab is stopped at 2 years of uninterrupted treatment or earlier in the event of disease progression

  and

- The conditions in the managed access agreement for pembrolizumab are followed

In the original appraisal, the committee considered that pembrolizumab had plausible potential to be cost effective, and further data collection would reduce the uncertainty around overall survival and continued treatment effect. Therefore, it could be recommended for use in the Cancer Drugs Fund (CDF).

Key issues to resolve

Issue 1: Is log-normal or Weibull the most appropriate extrapolation of PFS, for both pembrolizumab and UK SoC arms?

Issue 2: How should treatment switching be factored into the decision making?

Issue 3: **A)** What proportion of patients in pembrolizumab arm and UK SoC arm would be expected to be alive at 10 years?

B) Which OS extrapolation is most appropriate – Weibull, log-normal, log-logistic or generalised gamma?

Issue 4: Is a 2-year, 3-year or 5-year duration of treatment effect from start of pembrolizumab treatment appropriate?

Issue 5: Are cost-effectiveness results for PD-L1 sub-groups appropriate for decision making?

Pembrolizumab (KEYTRUDA, Merck Sharp & Dohme)

Marketing authorisation (MA):

'[Pembrolizumab] as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy'

Administration & dose	Intravenous infusion, 200 mg every 3 weeks* for up to two years of uninterrupted treatment or earlier in the event of disease progression
Mechanism of action	Humanised monoclonal antibody acts on the programmed cell death-1 (PD-1) receptor, part of the immune checkpoint pathway
Cost	List price: 100mg vial = £2,630 Average length of treatment: 6.84 months (10.46 cycles) Average cost per course (at list price): £55,019.60 Presented analyses incorporate a simple discount patient access scheme (PAS)

*Since TA519, European Medicines Agency (EMA) has also approved a 400 mg every 6 weeks dosing schedule (minimal effect on cost effectiveness), but 200 mg every 3 weeks used in base case in line with terms of engagement for the review

Scope

Population

As in marketing authorisation, but limited to people for whom cisplatin is suitable in first line
(there is a separate indication for those who are not eligible for cisplatin)

Comparators

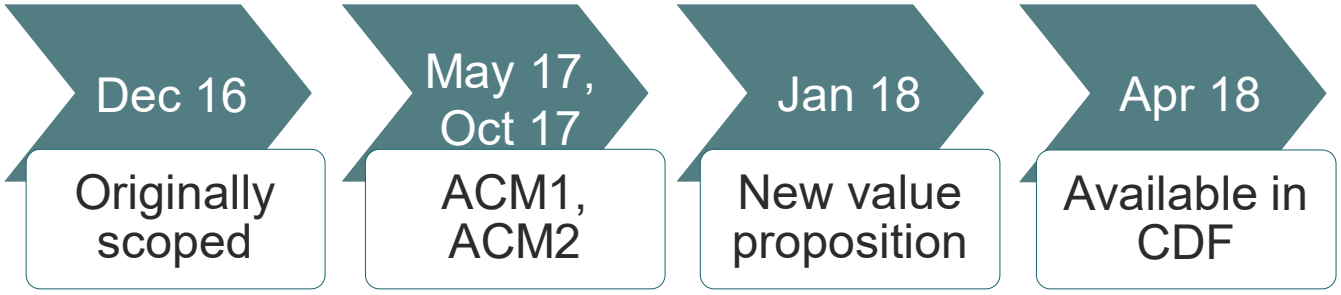
Docetaxel, paclitaxel, best supportive care

Outcomes

Includes overall survival and progression-free survival

Original appraisal and CDF

TA519: History of the appraisal



Further data collection:

- Managed access agreement
- Additional data from KEYNOTE-045

Locally advanced or metastatic urothelial carcinoma pathway

First line

Platinum-based therapy, such as:

- Cisplatin + gemcitabine
- Accelerated MVAC + G-CSF

When cisplatin is unsuitable:

- Carboplatin + gemcitabine

(Indication subject to a separate appraisal)

*Disease progression on/ after **platinum**-based therapy*

Second line

Taxanes (paclitaxel, docetaxel)

Best supportive care

Pembrolizumab

Access through CDF (TA519), subject of this review

Since original appraisal, atezolizumab recommended for routine commissioning (TA525), nivolumab not recommended (TA530)

This follows the original scope in TA519 (section 6.25 of process guide, no changes to scope allowed), and shows positioning of interventions which have been appraised since. Re-treatment with first line chemotherapy removed (as per TA519 FAD section 3.4).

FAD: final appraisal determination; G-CSF: granulocyte-colony stimulating factor; MVAC: methotrexate, vinblastine, doxorubicin and cisplatin

Additional 22 months of data collection in trial (cut-off Nov 2018) compared to last data seen by committee

KEYNOTE-045	Phase III RCT, n = 542
Population	People with metastatic or locally advanced/ unresectable urothelial cancer that has recurred or progressed following platinum-based chemotherapy. ECOG performance status of 0, 1 or 2
Intervention	Pembrolizumab 200 mg IV every 3 weeks
Comparator	One of the following, IV every 3 weeks: • Paclitaxel 175 mg/m^2 • Docetaxel 75 mg/m^2 • Vinflunine 320 mg/m^2 (not in UK SoC)
Primary outcome	OS and PFS (per RECIST 1.1)
Key subgroups	PD-L1 positive tumours (CPS≥1%), strongly PD-L1 positive tumours (CPS≥10%)

Key abbreviations in appraisal	
SoC	Comparator arm of KEYNOTE-045 = paclitaxel, docetaxel or vinflunine
UK SoC	Committee preferred comparator in original appraisal = paclitaxel or docetaxel
ITT	Trial results that have not been adjusted for treatment switching (relevant to analyses with and without vinflunine included in comparator arm)

CPS: Combined Proportion Score; ECOG: Eastern Cooperative Oncology Group; RECIST: Response Evaluation Criteria in Solid Tumours

Updated clinical evidence – overall survival (OS)

Pembrolizumab versus UK SoC – adjusted for treatment switch to anti-PD-L1 treatment in UK SoC arm using 2-stage analysis

	Updated results from KEYNOTE-045 (cut-off Nov 2018, database lock Mar 2019)				Results from KEYNOTE-045 presented in first appraisal committee meeting of TA519		
Treatment	**N**	**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 (UK SoC)	182	7.0 (5.5, 8.7)	---	---	7.4 (6.1, 8.3)	---	---
Control (UK SoC), adjusted ¶	182	6.2 (5.2, 7.4)	---	---	6.9 (5.3, 8.1)	---	---
Pembrolizumab (200 mg Q3W)	188	10.1 (7.6, 12.9)	**0.64 (0.49, 0.81)**	0.0139	10.3 (8.0, 11.8)	[redacted]	Unknown

¶ Survival times shrunk for the patients eligible to receive subsequent therapy and who actually received subsequent anti-PD-L1/PD1 therapy.

CI: confidence interval; Q3W: every 3 weeks

Updated clinical evidence – progression-free survival (PFS)

Pembrolizumab versus UK SoC – no adjustment for treatment switching

		Updated results from KEYNOTE-045 (cut-off Nov 2018, database lock Mar 2019)			Results from KEYNOTE-045 presented in first appraisal committee meeting of TA519		
Treatment	**N**	**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 (UK SoC)	182	3.3 (2.3, 3.5)	---	---	3.3 (2.3, 3.4)	---	---
Pembrolizumab (200 mg Q3W)	188	2.1 (2.0, 2.2)	**0.95 (0.76, 1.19)**	0.6183	2.1 (2.0, 2.2)	[redacted]	0.956

Patient perspectives

- Submissions from Action Bladder Cancer UK and Fight Bladder Cancer
- Urothelial cancer “very difficult for both patient and carer, being characterised by: chronic fatigue, pain, nausea…leading to a low and deteriorating QoL”
- “has the highest recurrence rate of any cancer”
- “Postcode lottery... different levels and quality of treatment from different hospitals”
- “Advanced/metastatic urothelial cancer prognosis is very poor with very limited treatments”
- Pembrolizumab:
  - ranked by some patients as “extremely effective at controlling their bladder cancer” with much milder side-effects
  - “offers hope to many, extra time to many and possibly be curative for some”

Committee preference from original appraisal:	Did company follow/ address this in CDF review?
End of life criteria apply	N/A (criteria still met)
UK standard of care (SoC) includes paclitaxel and docetaxel (vinflunine excluded), but best supportive care should be comparator also	✗ (presented paclitaxel and docetaxel)
2-year stopping rule	✓ (stopping rule still applies)
Lifetime treatment effect implausible, treatment effect duration capped at 3 or 5 years	**✓ (5 years base case, 3 and 10 years as scenarios)**
Weibull curve for progression-free survival (PFS) extrapolation	✗
2-phase piecewise approach for OS	✓
Best time to switch to parametric curve uncertain (24 weeks or 40 weeks)	✓(24 weeks in base case, 40 weeks scenario analysis)
Several plausible OS curves, considered log-logistic (ERG preferred) and log-normal (company preferred)	**✓ (but 4 curves considered plausible by ERG with newer data cut)**
Simplified 2-stage method to adjust for treatment switching	**✓(but ERG had concerns so presented alternative)**
Utility estimates should be based on progression state (not on time-to-death), pooled across treatment arms, and exclude vinflunine	✓

Issue resolved after technical engagement:

Issue	Summary	Engagement response	Technical team consideration	Included in updated base case?
3 (partially)	In TA519, time to begin OS extrapolation was uncertain – committee considered 24 weeks and 40 weeks. Both company and ERG presented 24 week cut off in their base cases for CDF review	Overall, support 24 weeks as appropriate cut off point	24 week cut off for OS extrapolation should be used	Company ✓ ERG ✓

Outstanding issues after technical engagement:

Issue 1: Choice of extrapolation for progression-free survival (slides 12-14)

Issue 2: Treatment switching (slides 15-16)

Issue 3: Extrapolation of OS (slides 22-25) *

Issue 4: Duration of treatment effect (slides 17-21) *

Issue 5: PD-L1 sub-groups (slides 26-28)

* *Issue 4 being addressed before Issue 3 in meeting, as may inform Issue 3 decision*

Issue 1: Choice of extrapolation for progression-free survival (PFS) (1)

TA519:

Committee preferred piecewise approach of extrapolating trial data at 21 weeks, using a Weibull curve.

Review:

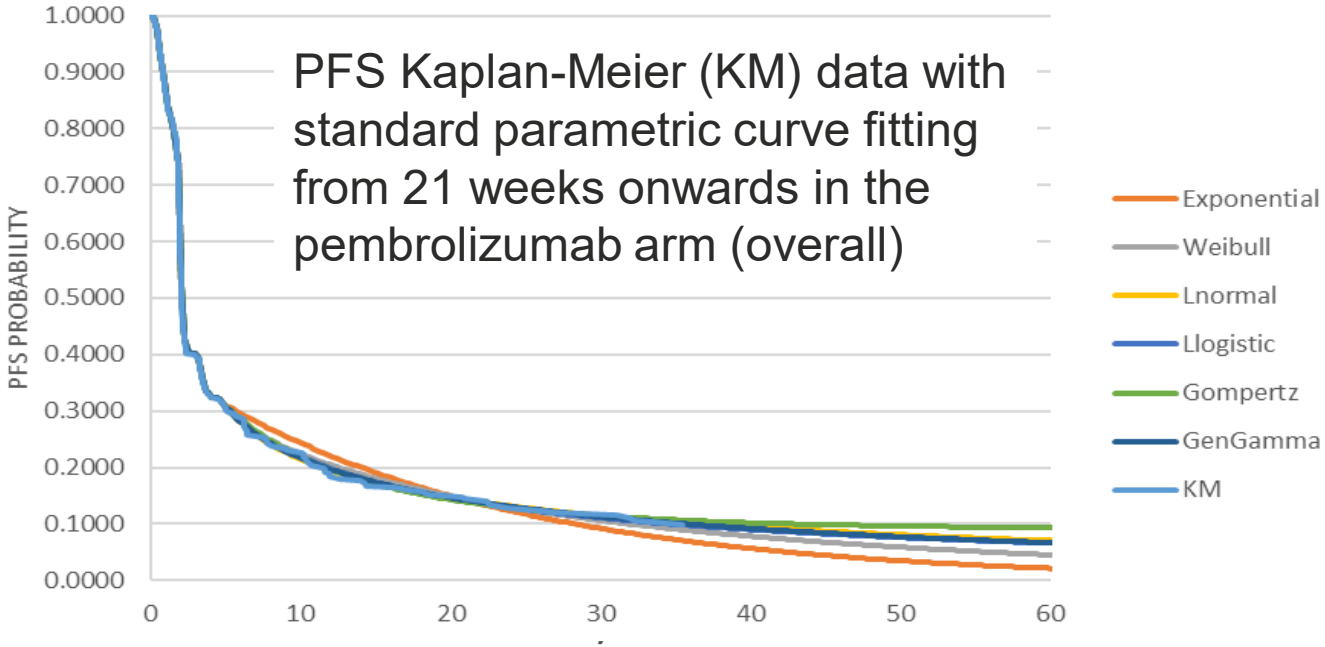
- Updated data indicated pembrolizumab does not significantly reduce risk of a PFS event compared to UK SoC (hazard ratio [95% CI] = 0.95 [0.76, 1.19])
- Both company and ERG used piecewise approach, extrapolation from 21 weeks
- **Company** chose **log-normal for pembrolizumab** arm, based on statistical and visual fit to the updated KEYNOTE-045 data. Did not find clear choice for **UK SoC arm, used log-normal** to be consistent with pembrolizumab arm.
- **ERG** chose **Weibull for both arms**:
  - better statistical fit to UK SoC arm, among best fitting curves of pembrolizumab arm
  - most consistent with KEYNOTE-045 trial and was a reasonable visual fit to cumulative hazard plots provided by company

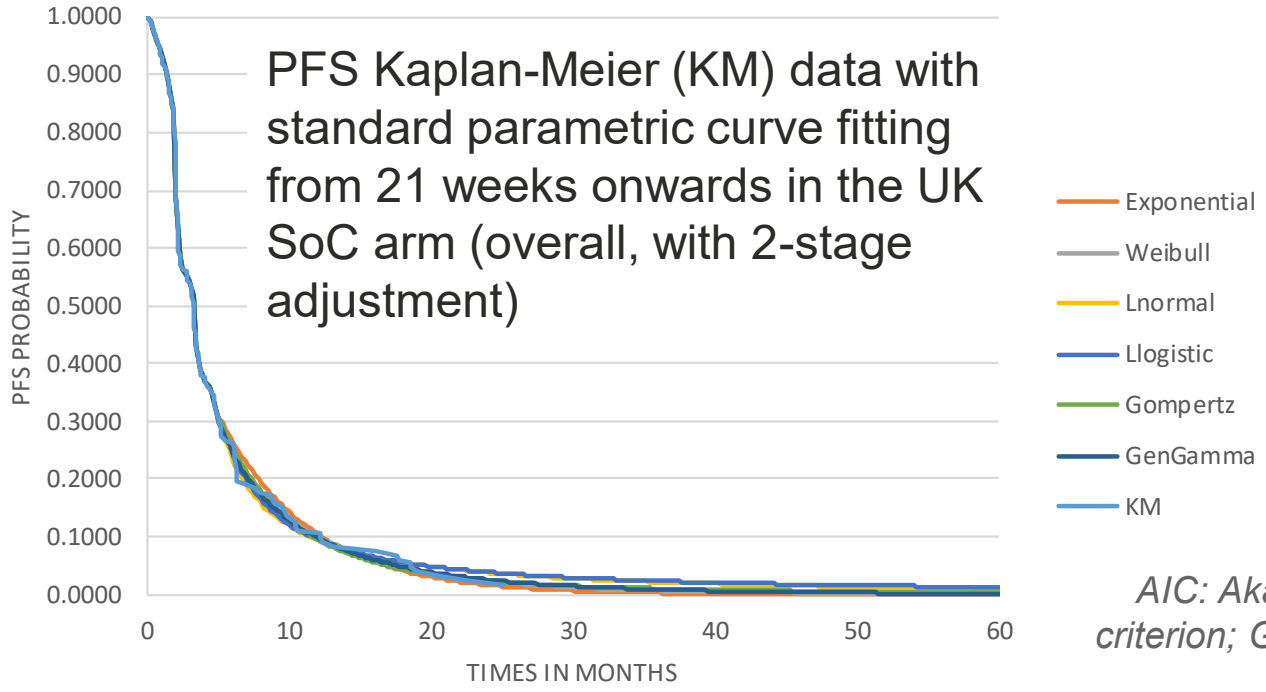
Preliminary judgement:

It is acceptable to extrapolate the Kaplan-Meier PFS data after 21 weeks. For both the pembrolizumab and UK SoC arms from the clinical trial, it is appropriate to use a Weibull extrapolation.

Issue 1: Choice of extrapolation for progression-free survival (PFS) (2)

Company:





ERG:

Best fit (lowest) values are underlined. Values with a difference ≥2 from the lowest value are greyed out (routine, supported in literature)

	Model for pembrolizumab for week 21+ in overall population	
	AIC	BIC
Exponential	529.4	531.8
Weibull	**525.4**	**530.2**
Gompertz	**524.2**	**529.0**
Llogistic	**523.9**	**528.7**
Lnormal	**<u>523.5</u>**	**<u>528.3</u>**
GenGamma	**525.5**	532.7
	Model for control for week 21+ in overall population	
	AIC	**BIC**
Exponential	**383.5**	**<u>385.4</u>**
Weibull	**<u>382.8</u>**	**386.6**
Gompertz	**383.9**	387.7
Llogistic	385.5	389.3
Lnormal	385.8	389.6
GenGamma	**384.7**	390.3

AIC: Akaike information criterion; BIC: Bayesian information criterion; GenGamma: generalised gamma; Lnormal: log-normal; Llogistic: log-logistic

Issue 1: Choice of extrapolation for progression-free survival (PFS) (3)

Engagement comments:

- Weibull was committee's preferred distribution when topic first appraised. Remains ERG's preferred distribution for re-appraisal, case persuasive. No robust change in evidence to necessitate change to different methodology for modelling PFS.

Company:

- Weibull 4th best fitting to pembrolizumab arm based on AIC/BIC statistics, differences between Weibull and log-normal for UK SoC modest. Log-normal better visual fit to pembrolizumab KM data (Weibull penalizes projected PFS in pembrolizumab arm, 3% lower than log-normal).
- Company's clinical expert thought fitting to pembrolizumab arm first and applying same to UK SoC reasonable. Tail for log-normal more aligned to clinical longer-term expectations for pembrolizumab.

ERG:

- Clear that only Weibull consistently among best fitting to both arms according to both AIC and BIC. Considerable inconsistency in company's modelling of PFS compared to TA519.
- Company comment that log-normal "clearly a better fit" to pembrolizumab subjective, particularly as curves almost indistinguishable for first 30 months of follow-up. Beyond 36 months, unclear how many still at risk, single event can be very influential to visual fit at late stage of follow-up, may be misleading to consider fits to tail data when selecting a parametric fit.

Final technical report judgement:

Acceptable to extrapolate Kaplan-Meier PFS data after 21 weeks. For both the pembrolizumab and UK SoC arms from the clinical trial, it is appropriate to use a Weibull extrapolation.

Is log-normal or Weibull the most appropriate extrapolation of PFS, for both pembrolizumab and UK SoC arms?

Issue 2: Treatment switching (1)

TA519:

Several techniques to adjust overall survival for chemotherapy arm to account for subsequent immunotherapy were investigated. Company and ERG used 2-stage method (acknowledged it had disadvantages). Committee concluded 2-stage method appropriate.

Review:

- Acceleration factor for 2-stage method was 5.37 (95% CI [3.231, 10.094]) (based on 25 patients) in review, compared to factor in TA519, which was 3.86 (95% CI [1.79, 11.68]) (based on 14 patients). **Larger acceleration factor (and more patients it applied to) → adjustment had much greater influence on OS, costs, benefits and ICER.**
- **Company** maintained 2-stage technique to remove any additional OS benefit patients may have received from change in treatment.
- **ERG** used 2-stage method in base case with ITT analysis as scenario analysis. ITT approach may overestimate survival time in the UK SoC arm, but 2-stage approach might underestimate survival times too much. Advised that **ITT analysis should also be carefully considered - believed true OS benefit lay somewhere between OS result of the two methods.**

Preliminary judgement:

Additional KEYNOTE-045 data likely to affect impact of 2-stage method on ICER, so it is relevant to reconsider adjustment for treatment switching in CDF review. Both 2-stage and ITT analyses should be considered during decision-making.

Issue 2: Treatment switching (2)

Engagement comments:

- Treatment switching should be adjusted for. Reasonable to allow for crossover whilst recognising uncertainty this brings. With maximum 2-year treatment duration, survival benefit of further immunotherapy must be considered (difficult as this may be) and excluded from pembrolizumab arm.

Company:

- Not appropriate to use unadjusted ITT analysis. 2-stage without re-censoring standard approach aligned with previous pembrolizumab submissions.
- Acknowledge increased acceleration factor magnitude, unsurprising - analysis still involves limited number of patients, calculations sensitive to small numbers. Sensitivity reflected in wide confidence intervals.
- Adjusted analysis based on longest follow-up data from KEYNOTE-045 (~4 years based on 1st patient randomised), consider this more reliable than data based on shorter follow-up.

ERG's response:

- Issues with 2-stage: survival times for UK SoC too severely penalised; assumes switchers to anti-PD-1/PD-L1 received same OS benefit in terms of a time ratio/acceleration factor (immuno-oncology therapies not effective in all patients, likely some received no benefit from switching); no pre-specified rule on treatment switching, no clear rationale why some switched and others didn't→possible selection bias, influential acceleration factor maybe capturing benefits of prognostic factor not just treatment.

Final technical report judgement:

ICERs from both the 2-stage adjusted approach and the ITT approach for switching from UK SoC should be carefully considered.

How should treatment switching be factored into the decision making?

Issue 4: Treatment effect duration (1)

TA519:

Committee aware that duration of treatment effect after implementation of a stopping rule is area of uncertainty for new immunotherapies, but concluded lifetime continued treatment effect implausible. Terms of engagement for review indicated committee's preference from TA519 to cap benefit of pembrolizumab at 3 years or 5 years (from start of treatment).

Review:

- **Company** used **5-year in base case**, **supported with KEYNOTE-001 data (non-small-cell lung cancer (NSCLC) and melanoma)**, scenarios with 3-year and 10-year.
- **ERG** used 3 years in base case, explored 2, 5 and 10-year. Concerns with KEYNOTE-001 as evidence (different indications, no stopping rule, no comparator). Suggested data on duration of treatment response and number of responders from KEYNOTE-045 could have informed decision on duration of treatment effect. **Investigated 2-year due to uncertainty around duration of treatment effect, and no meaningful data available from 2-stage adjustment beyond 2 years**.

Preliminary judgement:

Some publicly available evidence from previous data cut suggests treatment effect duration could be <3 years, so it may be appropriate to consider the possibility of a treatment effect between 2 and 3 years. Technical team recognises there is some evidence to suggest 5-year treatment effect for pembrolizumab in other cancer types. Technical team considers 3-year duration to be most plausible scenario it has seen, cannot conclude whether 5-year treatment effect is plausible based on the evidence.

Issue 4: Treatment effect duration (2)

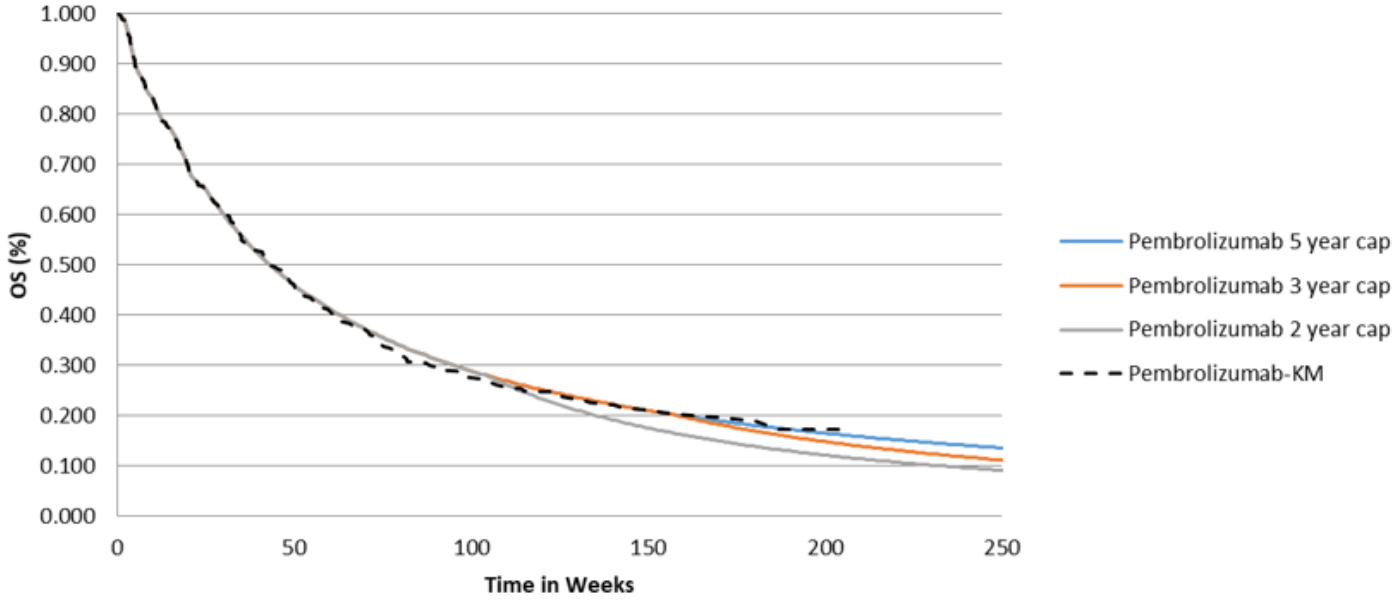
Engagement comments:

Company:

- With additional follow-up data (median 40.9 months, range 36.6-48.9 months*), HR decreases, sustained treatment effect of pembrolizumab. Trend observed regardless of whether comparator is UK SoC comparator arm or full KEYNOTE-045 comparator arm, or comparison made with adjusted or unadjusted data (i.e. ITT approach) in control arm.

- With 2-year or 3-year duration of treatment effect for pembrolizumab, extrapolation in pembrolizumab arm does not fit well to observed KM data from latest cut; underestimate OS KM curve and treatment effect of pembrolizumab. Assumption of 2-year or 3-year treatment effect cap inappropriate – any longer-term benefit with pembrolizumab not taken into consideration.

[redacted]



* 48.9 months is correct value – [redacted] confirmed as typographical error by company

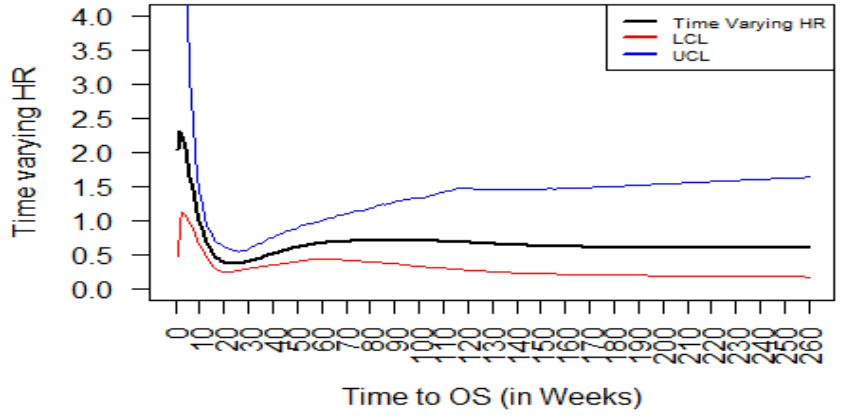
Issue 4: Treatment effect duration (3)

Engagement comments:

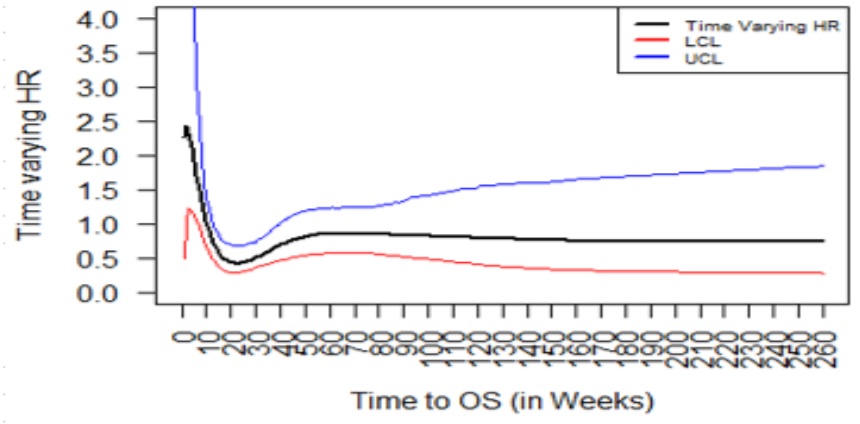
Company:

- 5-year for pembrolizumab supported by time varying HR analyses of pembrolizumab vs. 2-stage adjusted UK SoC. Clinical expert confirmed plateau in HR after week 170 (~3 years) consistent with their clinical experience in population - those relapse-free after 2-3 years can expect long-term survival, more favourable outcomes. HR analysis without adjusting for treatment switching shows consistency with adjusted.

Time varying HR for pembrolizumab vs. 2-stage adjusted UK SoC with 95% CI



Time varying HR for pembrolizumab vs. unadjusted UK SoC with 95% CI



- DOR, ORR and maximum follow-up duration based on Nov 2018 data-cut further supportive evidence of a long-term, durable response.
- Data supporting long-term survival benefit available from studies across pembrolizumab clinical study program, particularly KEYNOTE-001 (NSCLC, melanoma), KEYNOTE-006 (melanoma) and KEYNOTE-024 (NSCLC).

Issue 4: Treatment effect duration (4)

ERG's response:

Summary:

- Majority of information provided by company unrelated to estimation of a relative benefit of pembrolizumab to UK SoC beyond 3 years.
- Maximum follow-up from KEYNOTE-045 is 4 years, but only 1 death occurs in UK SoC beyond 3 years in the unadjusted (ITT) arm, with no events occurring after this in 2-stage adjusted analysis. Estimation of relative treatment effect of pembrolizumab compared to UK SoC not possible beyond this point. Maintain preference for a 3-year effect duration over a 5-year duration.

Other points:

- Improved hazard ratio with extended follow-up likely explained by greater data completeness.
- By comparing pembrolizumab OS extrapolation to observed data, company disregards impact that curve choice may have on such an assessment. Affects initial pembrolizumab fit and estimate of UK SoC hazard rate, which is reverted to after 2/3/5 years. Despite this, ERG acknowledges that 2-year effect duration applied to log-logistic appears to not fit well to observed data. However, 3-year duration better fit, only deviates from observed data in tail.
- Data available does not allow for meaningful hazard ratio to be calculated beyond 2 years of trial follow-up for 2-stage adjusted UK SoC population. Unclear how company interprets this analysis as support for 5-year treatment effect.
- Relevance of TA584 unclear-different treatment, different disease. TA525 for same indication so more relevant, but assumption that 3-year post-stopping-treatment duration effect equivalent to 5-year stopping rule likely incorrect.

Issue 4: Treatment effect duration (5)

ERG's response (continued):

- Trials in other indications brought up as supporting evidence lack relevance/transferability/do not provide support of sustained effect relative to comparator.
- KN-045 – Agree evidence of sustained response of pembrolizumab, but same is true for those who respond on UK SoC. No evidence suggesting hazard rate beyond 3 years for long-term responders is different across treatment arms. Data suggests long-term responders in both arms experience similar outcomes.

Other engagement comments:

- 3-year treatment effect = effect following 2 years of treatment then 1 year of follow-up (2+1). Data reasonably robust to 3 years, reasonable to be cautious and assume duration of treatment effect more in line with 3 years than 5 years.
- Be careful drawing parallels to other diseases – melanoma and NSCLC completely different compared to urothelial cancer. Always been an immunological avenue for treating melanoma; lung cancer is a very mutation-rich cancer. Pembrolizumab does not work in every disease, failed in trials in triple negative breast cancer, hepatocellular carcinoma, gastric/gastro-oesophageal junction cancer and myeloma.
- Impact of stopping immunotherapy at 2 years unknown in any disease. KEYNOTE-045 follow-up too immature to estimate effect drop-off. Will be some patients who continue to benefit at 5 years, not all. Pembrolizumab effects not permanent for most responders (median DOR 29.7 months). 3 years seems reasonable treatment effect duration.

Is a 2-year, 3-year or 5-year duration of treatment effect from start of pembrolizumab treatment appropriate?

Final technical report judgement:

3-year treatment effect (2+1, which represents 2 years of treatment and 1 year of follow-up) appears most plausible, but committee may wish to consider 5-year effect also, as well as the conservative 2-year scenario analysis.

Issue 3: Choice of extrapolation for overall survival (OS) (1)

TA519:

Committee decided long-term survival was uncertain, would consider both company (log-normal both arms) and ERG's (log-logistic both arms) preferred OS extrapolation in decision-making.

Review:

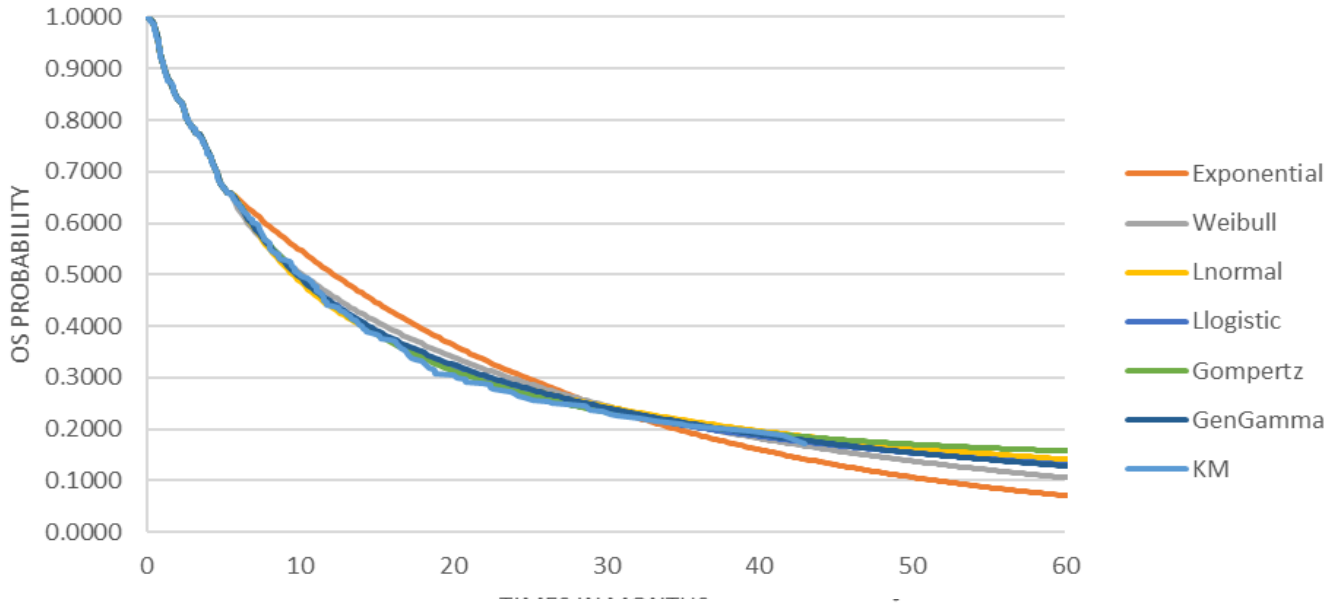
- **Company** chose log-logistic, based on statistical and visual fit to updated data. **Gives 3.2% 5-year survival rate for UK SoC arm, consistent with 2-3% figure suggested by clinical expert in TA519**.
- **ERG** concluded Weibull, log-normal, log-logistic and generalised gamma all plausible (based on cumulative hazard plot for different OS extrapolations). **Reliance on goodness-of-fit statistics alone should be avoided for immature data.**
  - **Proportion of patients alive at 10 years unknown.** If long-term survival plausible, generalized gamma most suitable, log curve may have been appropriate. If long-term survival not plausible, Weibull most suitable.
  - Clinician advised some sustained long-term benefit could be plausible for patients receiving pembrolizumab. This supported selection of one of the log curves → **ERG used log-logistic in base case**.

Preliminary judgement:

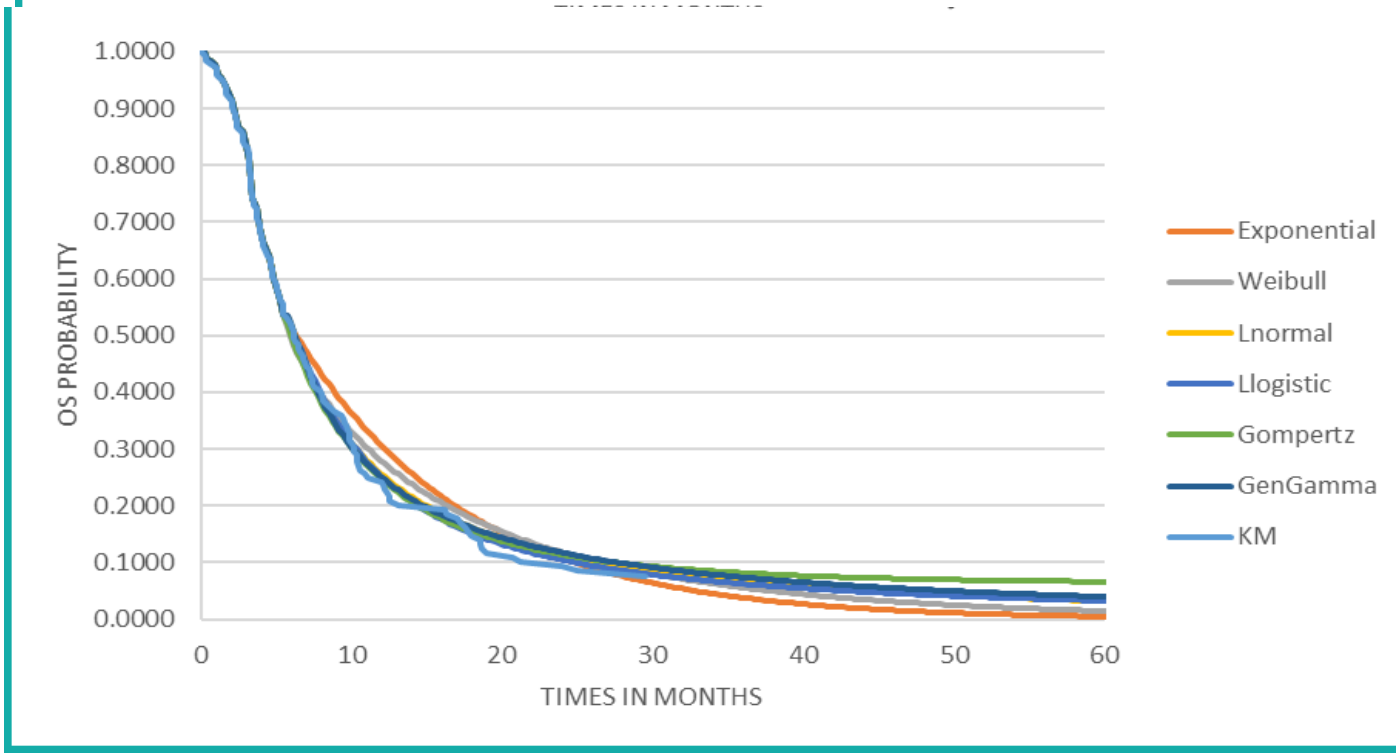
In light of updated OS data, log-logistic used in company and ERG's base cases could be plausible. OS data still immature, may be relevant to consider ICERs of 4 plausible extrapolation distributions. Further information may be needed on plausibility of long-term survival after pembrolizumab in indication to inform choice of OS extrapolation.

Issue 3: Choice of extrapolation for overall survival (OS) (2)

OS parametric function fitting in the pembrolizumab arm



OS parametric function fitting in the UK SoC (paclitaxel or docetaxel) arm with 2-stage adjustment



Issue 3: Choice of extrapolation for overall survival (OS) (3)

Engagement comments:

Company:

- Inappropriate to include OS extrapolations which do not reflect that some patients experience long-term survival with pembrolizumab. Only log-normal should be included in scenario analyses.
- Log-logistic has 2nd best goodness-of-fit data for both arms, 5-year survival predictions in line with 5-11% accepted in TA519.

ERG's response:

- Agree with majority of company's comments on issue, but company's upper estimate of 2% survival at 10 years in UK SoC arm may be too optimistic based on comments from ERG's clinical advisor.
- Company's preferred OS curve and anticipated long-term survival profile plausible but unsupported by evidence.

OS - Goodness of fit data for pembrolizumab and UK SOC, at 24 weeks point of extrapolation:

	Model for pembrolizumab in overall population		Model for control in overall population	
	AIC	BIC	AIC	BIC
Exponential	1384	1387.1	680	682.5
Weibull	1373.3	1379.6	676	680.9
Gompertz	1365.3	1371.7	663.4	668.3
Log-logistic	1366.4	1372.7	664.1	669
Log-normal	1369	1375.3	664.3	669.2
Generalised gamma	1369.8	1379.3	665.7	673.1

ICERs for 4 OS extrapolations ERG think plausible:

Scenario for OS extrapolation	Incremental QALYs	ICER
Log-logistic (company base case)	0.74	£47,123
Weibull	0.52	£62,503
Log-normal	0.70	£49,549
Generalised gamma	0.69	£49,894

(figures shown with no other assumptions changed from company's base case)

Issue 3: Choice of extrapolation for overall survival (OS) (4)

ERG's response (continued):

- Company appear to exclude generalised gamma despite it providing similar extrapolations to the log curves. Considerable uncertainty remains for long-term OS. Log-normal, log-logistic and generalised gamma could all be considered plausible, with Weibull as plausible scenario if no patients experience the long-term survival benefit described by company.

Other engagement comments:

- Significant comorbidities in population, median age in CDF 70. Number of 10-year survivors with pembrolizumab will be small though significantly greater than with chemotherapy.
- Small number of patients treated with chemotherapy do very well. Biologically plausible that patients treated with pembrolizumab will do better, small/modest number of long-term survivors following treatment with pembrolizumab.
- No direct evidence to support 10-year survival. KEYNOTE-045 update shows 20.7% alive at 36 months on pembrolizumab,10-year estimate should be lower. Implausible that >5% will be alive at 10 years. Very rare long-term survivors after 2nd line therapy, 1-2%.
- Log-logistic fits in with biological plausibility.

Final technical report judgement:

Very low proportion (<5%) of survivors at 10 years biologically plausible.
Log curves (log-logistic or log-normal), generalised gamma and Weibull curves for extrapolation of OS should be considered.

A) What proportion of patients in pembrolizumab arm and UK SoC arm would be expected to be alive at 10 years?

B) Which OS extrapolation is most appropriate – Weibull, log-normal, log-logistic or generalised gamma?

Issue 5: PD-L1 expression sub-groups (1)

TA519:

Pembrolizumab appeared to be more effective for people with urothelial carcinoma expressing the PD-L1 protein than for people who do not, but cost-effectiveness (CE) results for sub-groups were not reliable, as ICERs behaved counterintuitively compared to clinical outcomes. Committee did not consider company's CE results plausible or reliable for decision-making, could only make a recommendation for whole population.

Review:

- MA for pembrolizumab in indication does not have PD-L1 expression requirement. Updated data showed that pembrolizumab, when compared to UK SoC, reduced risk of death by 26% in the entire population, by 42% in patients with PD-L1 Combined Positive Score (CPS)≥1%, and by 49% in patients strongly positive for PD-L1, CPS≥10%.
- Company submitted PD-L1 sub-group analyses on technical team request, but unlike in TA519, did not provide data for CPS<1% sub-group.

Preliminary judgement:

Relevant to reconsider PD-L1 sub-groups in light of the updated evidence. EMA revised the marketing authorisation for pembrolizumab for untreated locally advanced or metastatic urothelial cancer when cisplatin is unsuitable, to restrict patient eligibility to people with high levels of PD-L1. Technical team considers that the role of PD-L1 expression remains unclear.

Issue 5: PD-L1 expression sub-groups (2)

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Results for PD-L1 subgroup (**CPS<1%**) based on unadjusted (ITT) population							
UK SoC	[redacted]	1.45	0.96	-	-	-	-
Pembrolizumab, CPS<1%	[redacted]	1.96	1.31	£27,740	0.50	0.35	£78,974
Results for PD-L1 subgroup (**CPS≥1%**) based on unadjusted (ITT) population							
UK SoC	[redacted]	1.30	0.88	-	-	-	-
Pembrolizumab, CPS≥1%	[redacted]	2.41	1.67	£35,523	1.11	0.78	£45,370
Results for PD-L1 subgroup (**CPS≥10%**) based on unadjusted (ITT) population							
UK SoC	[redacted]	1.42	0.94	-	-	-	-
Pembrolizumab, CPS≥10%	[redacted]	2.40	1.64	£32,617	0.99	0.70	£46,485

Results shown based on company's base case settings, with population changed from all comers.
PD-L1 testing costs added when population changed from all comers.

Company provided analyses for CPS≥1% and CPS≥10%, NICE technical team ran analysis for CPS<1% in company's model.

Engagement comments:

Company:

- No additional evidence to justify decision making based on PD-L1 subgroups. Same conclusions on these hold as in TA519.
- PD-L1 prognostic factor not predictive biomarker in indication.
- Inappropriate to run 2-stage adjusted analyses based on PD-L1 subgroups (numbers who received subsequent anti-PD1/PD-L1 therapy too small), results likely biased/unreliable, same cut-off to run analyses used for previous cuts/other indications.

Issue 5: PD-L1 expression sub-groups (3)

ERG's response:

- Unable to draw clear conclusion based on existing evidence from KEYNOTE-045. Hazard ratios CPS≥1% HR= 0.58 [95% CI: 0.40, 0.84] and CPS ≥10% HR= 0.51 [95% CI: 0.32, 0.81]), both lower than for ITT population (HR= 0.74 [95% CI: 0.59, 0.94]).
- Not aware that company have presented any formal statistical test of interactive effect of pembrolizumab with PD-L1 subgroups using most recent data cut.
- Meta-analysis by Shen et al. suggests PD-1/L1 inhibitors may be more effective in patients with PD-L1 expression across different cancer types. Meta-analysis by Ghate et al. of urothelial cancer studies suggests PD-L1 expression may be prognostic factor.

Other engagement comments:

- Plausible for greater benefit in people with higher PD-L1 expression. EMA limited use of atezolizumab and pembrolizumab in 1st line to high PD-L1 expression. Trial data: numbers in subgroups modest, comparator group significantly reduced (vinflunine excluded). Opportunity for robust decision making limited.
- Different effects in PD-L1 sub-groups based on KEYNOTE-045 data.
- Different effect in PD-L1 sub-groups but not in this indication/disease stage, regardless of choice of drug or test in post-platinum setting. However, PD-L1 status weakly prognostic, may impact ICER.

Are cost-effectiveness results for PD-L1 sub-groups appropriate for decision making?

Final technical report judgement:

Committee may wish to consider if PD-L1 sub-group results are plausible and reliable for decision-making in light of updated data.

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Dosing of pembrolizumab	Pembrolizumab recommended for use in CDF with dosing schedule 200 mg Q3W. EMA adopted positive opinion for new extended dosing schedule for pembrolizumab for all monotherapy indications in EU, including indication in this CDF review.	If 100% of patients on pembrolizumab are on 400 mg Q6W, ICER changes by +£529 from company's base case.
Resource use and costs	In line with terms of engagement (ToE), resource use and cost inputs used in cost-effectiveness model were unchanged from original appraisal, except for inclusion of a new patient access scheme (PAS) discount for the technology.	True input values may have changed, impact on ICER unknown.
Best supportive care not included as a comparator	Best supportive care was included as a comparator in both the scope and the ToE. However, the ToE also indicated the ERG base case model from the original appraisal should be used. This was based on the company's submitted model for TA519, which did not include best supportive care as a comparator.	Outcomes and costs of best supportive care not illustrated, therefore not reflected in the ICER.

Cost effectiveness results (1)

Alteration	Technical team rationale	Incremental QALYS	ICER	Change from company base case ICER
Scenario 1: 2-stage adjustment for treatment switching				
1. Company base case (2-stage adjustment for treatment switching)	–	0.74	£47,123	–
a) Weibull distribution to extrapolate PFS after 21 weeks	Technical team agreed with ERG's amendments.	0.72	£48,518	+£1,395
b) 3-year treatment effect duration	Technical team agreed with ERG's 3-year duration of treatment effect.	0.65	£51,970	+£4,847
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	–	0.63	**£53,678**	+£6,555

Cost effectiveness results (2)

Alteration	Technical team rationale	Incremental QALYS	ICER	Change from company base case ICER
Scenario 2: no adjustment for treatment switching (ITT approach)				
2. Company base case, but without adjustment for treatment switching	Technical team considered that true OS benefit lay somewhere between OS result of the 2-stage and ITT methods.	0.55	£56,422	+£9,299
a) Weibull distribution to extrapolate PFS after 21 weeks	Technical team agreed with ERG's amendments.	0.52	£58,850	+£11,727
b) 3-year treatment effect duration	Technical team agreed with ERG's 3-year duration of treatment effect.	0.49	£62,400	+£15,277
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	–	0.46	**£65,469**	+£18,346

Key issues to resolve

Issue 1: Is log-normal or Weibull the most appropriate extrapolation of PFS, for both pembrolizumab and UK SoC arms?

Issue 2: How should treatment switching be factored into the decision making?

Issue 3: **A)** What proportion of patients in pembrolizumab arm and UK SoC arm would be expected to be alive at 10 years?

B) Which OS extrapolation is most appropriate – Weibull, log-normal, log-logistic or generalised gamma?

Issue 4: Is a 2-year, 3-year or 5-year duration of treatment effect from start of pembrolizumab treatment appropriate?

Issue 5: Are cost-effectiveness results for PD-L1 sub-groups appropriate for decision making?