Public slides - Redacted

Lead team presentation – Clinical

Pembrolizumab for previously treated advanced or metastatic urothelial cancer

1st Appraisal Committee meeting

Committee D, 31 May 2017

Lead team: Malcolm Oswald, Rachel Elliott , William Turner

Companies: Merck Sharp & Dohme

Chair: Gary McVeigh

Evidence review group: Warwick Evidence

NICE team: Thomas Strong, Christian Griffiths, Helen Knight

Metastatic urothelial carcinoma
Disease background

- Around 10,100 new cases of bladder cancer in the UK each year, resulting in 5,400 deaths
- 90% of bladder cancers are urothelial carcinomas
- Remainder are squamous cell bladder cancers (5%) and adenocarcinomas of bladder (1–2%)
- 90–95% of urothelial carcinomas develop in bladder
- Tumours can also originate in renal pelvis, urethra or ureter as these are also lined by urothelial cells
- 55% of new cases occur in people 75+, ~75% in men
- 5-year survival rate for metastatic disease is low*

* The most plausible 5-year survival rate is a key issue which will be discussed in the economic section

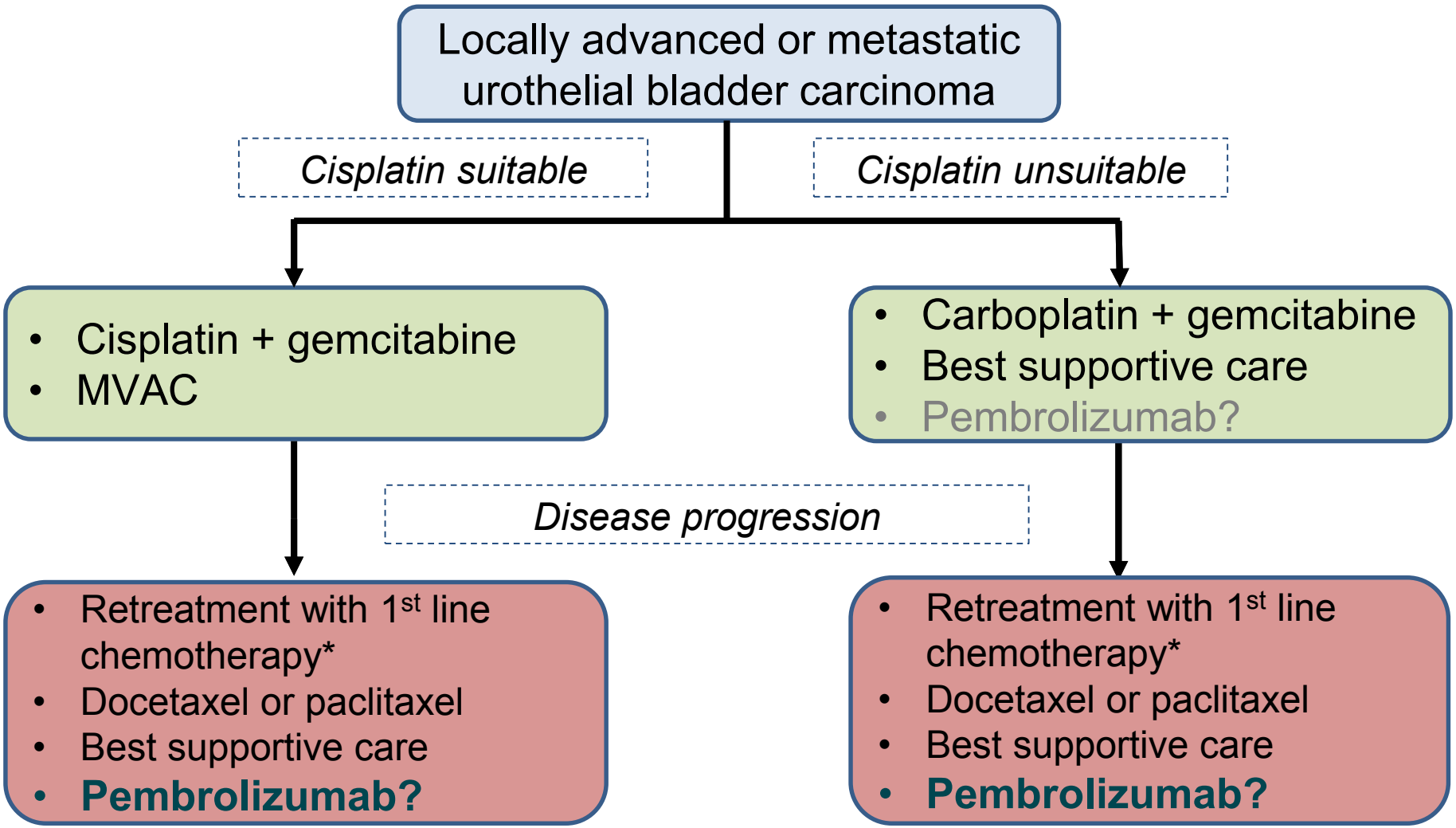
Pembrolizumab (KEYTRUDA)

Merck Sharp & Dohme

Anticipated marketing authorisation	Locally advanced or metastatic urothelial carcinoma in adults: • **who have received prior chemotherapy** • who are not eligible for cisplatin chemotherapy*
Administration & dose	Intravenous infusion, 200mg every 3 weeks until disease progression or unacceptable toxicity
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: 5.60 months (8.81 cycles) Average cost per course (at list price): £46,341 Presented analyses incorporate a simple discount PAS

*Due to a late change in expected marketing authorisation, final scope released by NICE and company decision problem only includes people who have progressed on or after **platinum-containing** chemotherapy, and **does not** include people who are ineligible for cisplatin-containing chemotherapy. Population ineligible for cisplatin-containing chemotherapy is proceeding through scoping separately.

Clinical pathway of care



⊙ ***Is pembrolizumab placed appropriately in the treatment pathway?***

Patient perspectives

Comments from Bladder Cancer UK, Fight Bladder Cancer

- “Living with this condition is very difficult due to the constant treatments, check-ups and appointments that are needed due to its high recurrence rate”
- “Currently no effective second line treatment and prognosis is currently extremely poor”
- “People are opting for bladder removal due to experiencing or worrying about intolerable side effects”
- “No new treatments for urothelial cancer for over 35 years”
- “The new immunotherapy treatments could see a step change in treating this much ignored cancer, and…offer hope to many”
- “Further research/trials to optimise the treatment and develop biomarkers would be highly desirable”

Clinician perspective

Comments from Royal College of Physicians

- “In Keynote-045 trial, outline and control arm reflected current clinical practice in the UK”
- Pembrolizumab is “generally well tolerated” compared to chemotherapy
- “Testing for biomarkers like PD-L1 is not recommended for routine use in urothelial cancer”
- Tumour evaluation by CT (scan) needed every 8-10 weeks. Consideration should be made of the rare occurrence of pseudo-progression
- “Pembrolizumab will be similar to the use of standard chemotherapy with IV infusion every 3 weeks”
- Training straightforward and “no new equipment or facilities are needed”
- “In responding and stable patients treatment with pembrolizumab will be until unequivocal progression”

NHS England comments

- Taxanes and best supportive care are the relevant comparators
- If NICE recommends pembrolizumab, NHS England treatment criteria likely to include:
  - For urothelial patients with:
    - disease progression during/following previous platinum-based combination chemotherapy for inoperable locally advanced or metastatic cancer
    - ECOG performance status score of 0 or 1 or (with caution) 2
  - Treatment until disease progression or excessive toxicity or for a maximum of 2 years, whichever is the sooner
  - No treatment breaks of more than 4 weeks (unless solely to allow immune toxicities to settle)

Decision problem

Deviations from final scope

	Final Scope	Company submission and rationale
Comparator	• Retreatment with 1st line • Docetaxel • Paclitaxel • BSC	• Docetaxel • Paclitaxel No evidence for retreatment with 1st line chemotherapy BSC not considered a relevant comparator, as alternative active treatments are available

Subgroups	• Cancer histology
	• Biological markers (PD-L1)
		• PD-L1 positive subgroups
		  • Combined proportion score (CPS) ≥1%
		  • CPS ≥10%
		• Specific histology subgroups
		  • Predominant transitional cell carcinoma (TCC)
		  • Pure TCC
		90% of bladder cancer and 87% of ureter and renal pelvis cancer is TCC histology. 71% of KEYNOTE-045 is pure TCC

Source: table 1 (18-19), company submission

⊙ ***Is the company decision problem appropriate for decision-making?***

Clinical evidence
KEYNOTE-045

Design	Multi-site (4 UK patients), Open-label randomised controlled trial
Recruitment	Planned n=470; recruited n=528; UK standard of care subgroup n=370
Population	• urothelial cancer of the renal pelvis, ureter, bladder, or urethra • progression or recurrence of urothelial cancer following first-line platinum-containing regimen (cisplatin or carboplatin) • no more than 2 prior lines of systemic chemotherapy • ECOG Performance status of 0, 1 or 2
Intervention	Pembrolizumab, 200 mg IV every 3 weeks (Q3W)
Comparator	Investigators choice of: Paclitaxel 175 mg/m2 Q3W; Docetaxel 75 mg/m^2 Q3W; Vinflunine 320 mg/m^2 Q3W*
Key pre-defined subgroups	• Geographic region of enrolling site (EU vs. non-EU) • Prior platinum therapy (carboplatin vs. cisplatin) • PD-L1 positive (CPS ≥1%) and strongly positive (CPS ≥10%) • Cancer histology (pure transitional cell vs mixed histology)
Post-hoc subgroups	• UK Standard of care (UK SOC) – Comparator of paclitaxel and docetaxel only (removal of vinflunine data)

Source: table 7 (page 48); table 10 (page 66-69); of the company submission

KEYNOTE-045
Clinical outcomes

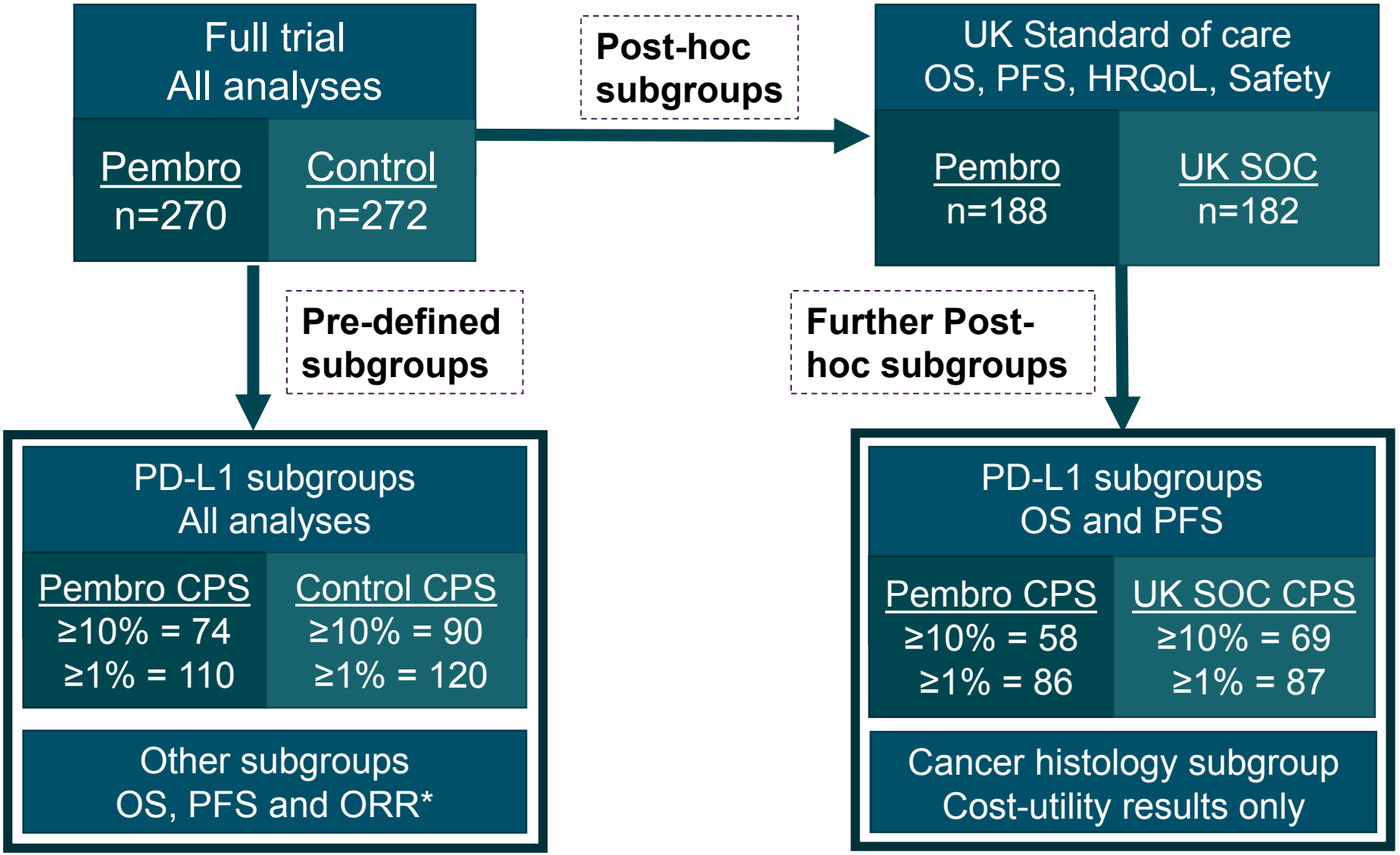
Primary	• **Progression-free survival (PFS) per RECIST 1.1 by Blinded Independent Central Review (BICR)** • **Overall Survival (OS)**
Secondary/ exploratory outcomes	• Safety and tolerability profile • PFS per Modified RECIST (mRECIST) 1.1 by BICR • Objective response rate (ORR), either complete or partial, per RECIST or mRECIST* 1.1 by BICR • Time to response (TTR) defined by time from randomisation to the first assessment of a complete or partial response • Response duration per RECIST 1.1 by BICR • PFS per RECIST 1.1 from randomisation to specific time-points by BICR; • Health related quality of life (HRQoL) using EORTC and EQ-5D-3L
Data-cut	All results from planned second interim analysis – September 2016 median pembrolizumab follow-up: 10.3 months (range: 0.2 to 20.8)

*mRECIST requires a confirmation of PD (≥4 weeks after the initial PD assessment) for people who remain on treatment following a documented PD per RECIST 1.1
Source: section 4.3.1 (pages 57 – 60), company submission

⊙ ***Is RECIST or mRECIST more appropriate for decision-making?***

KEYNOTE-045

Subgroups and reported outcomes



KEYNOTE-045

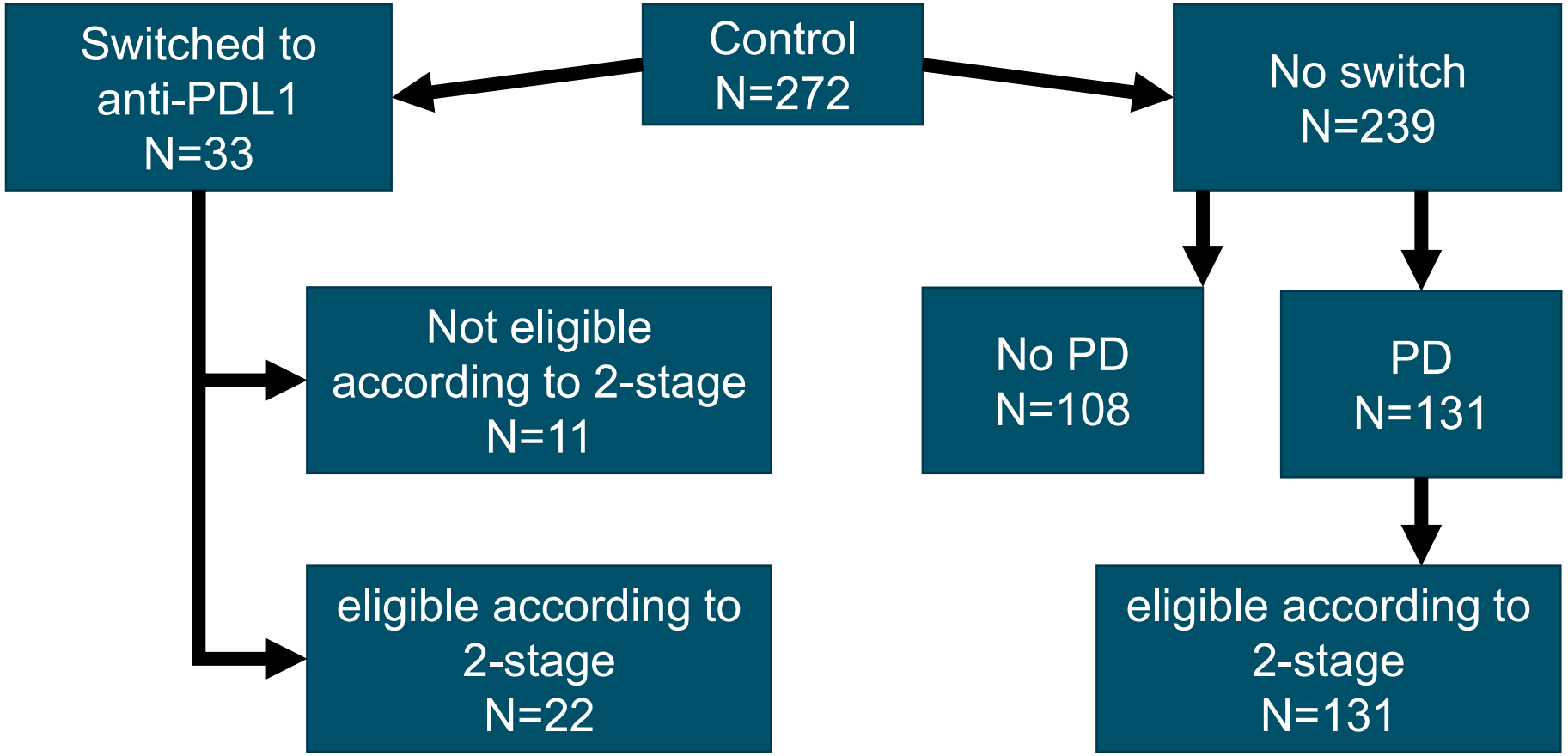
Key baseline characteristics

	UK SOC (n=182)	Pembrolizumab (n=188)
Mean age (sd)	65.1 (8.9)	66.0 (10.0)
% ECOG 0/1/2*	39.6 / 58.8 / 1.1	46.3 / 51.1 / 1.1
% prior platinum therapy cisplatin/carboplatin/other	79.1 / 19.8 / 1.1	73.9 / 25.0 / 0.5
% EU / Non-EU	26.9 / 73.6	29.3 / 70.7
% smoking: never / ex / current	30.2 / 59.3 / 9.3	41.0 / 49.5 / 9.0
% TCC histology pure / predominant	69.8 / 29.7	67.6 / 31.9
% PD-L1 <1% / ≥1% / missing	50.0 / 47.8 / 2.2	51.6 / 45.7 / 2.7
% PD-L1 <10% / ≥10% / missing	59.3 / 37.9 / 2.7	66.0 / 30.9 / 3.2
% at baseline lymph node / visceral	14.8 / 85.2	11.7 / 87.8

*Subjects with ECOG 2 could only be enrolled if liver metastases were absent, haemoglobin ≥10 g/dL, and time from completion (last dose) of most recent chemotherapy ≥ 3 months (90 days).
Source: adapted from table 9 (page 150), company appendix 9

KEYNOTE-045
Treatment switching

- People allowed to receive anti PD-L1/PD-1 treatment after disease progression
- Company preferred methodology was to adjust using the 2-stage method



Source: Adapted from figure 22 (page 118), company submission

ERG Comments
Treatment switching

RPSFT least suitable because:

- censors patients prior to the time point at which they switched treatments and generates artificial survival times for those who switch
- assumes a common treatment effect for switchers to the experimental arm, and those who receive intervention in the full trial – but people in KEYNOTE-045 were able to switch to a range of anti PD-L1/PD-1 treatments

IPCW:

- assumes there are no unobserved confounders, and weights patients according to their similarities to the censored switched patients – but the risk factors of bladder cancer and survival are uncertain

2-Stage:

- suitable as switching is linked to disease progression – but some subjects switched without progression which confounds analysis.

⊙ ***What is the most appropriate method to account for crossover?***

KEYNOTE-045

Primary outcomes

		Median months (95% CI)	HR (95% CI); p-value
PFS	**Pembro#**	2.1 (2.0, 2.2)	-
	Trial control	3.3 (2.3, 3.5)	0.98 (0.81, 1.19); p=0.41648*
	UK SOC	[redacted]	[redacted]
OS	**Pembro#**	10.3 (8.0, 11.8)	-
	Trial control	7.4 (6.1, 8.3)	0.73 (0.59, 0.91); p=0.00224*
	UK SOC	[redacted]	[redacted]
	UK SOC + RPSFT	[redacted]	[redacted]
	UK SOC + 2-stage	[redacted]	[redacted]
	UK SOC + IPCW	[redacted]	[redacted]

*One-sided p-value; ^Two-sided p-value; #Pembrolizumab median months from the full trial population
RPSFT - Rank Preserving Structural Failure Time; IPCW - Inverse Probability of Censoring Weights
Sources: table 24 (page 98) + table 47 (page 135) + table 68 (page 179), company submission; table 1 (page 5), company response to additional clarification request

KEYNOTE-045

Progression-free survival – UK SOC

Source: Figure 1 (page 5), company response to additional clarification request

KEYNOTE-045

Overall survival – UK SOC + 2-stage adjustment

Source: Figure 34 (page 181), company submission

KEYNOTE-045

PD-L1 subgroups (UK SOC)

		Overall	*CPS ≥1%*	*CPS ≥10%*
PFS HR (95% CI)	**UK SOC**	[redacted]	[redacted]	[redacted]
OS HR (95% CI)	**UK SOC Unadjusted**	[redacted]	[redacted]	[redacted]
	+ RPSFT	[redacted]	[redacted]	[redacted]
	+ 2-stage	[redacted]	[redacted]	[redacted]
	+ IPCW	[redacted]	[redacted]	[redacted]
ORR* (95% CI)	**Trial control**	9.6 (3.5,15.9); p=0.00106	16.9 (7.7,27.0); p=0.00022	19.3 (8.6,31.7); 0.00020

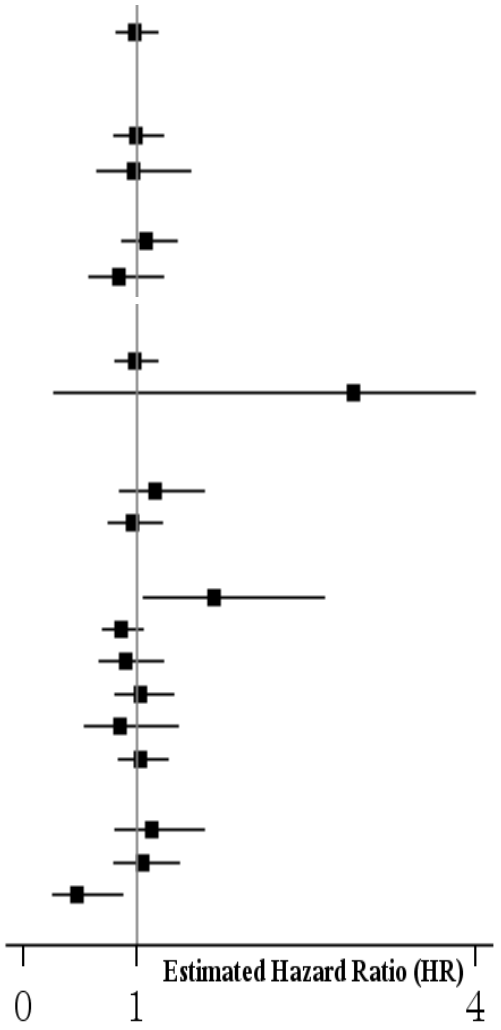
*Objective response rate (ORR) difference ^Two-sided p-value; HR, Hazard ratio, CI, Confidence interval; RPSFT, Rank Preserving Structural Failure Time; IPCW, Inverse Probability of Censoring Weights
Source: adapted from table 4-8 (page 52-56), ERG report; table 24-26, 47-48 (page 98-101, 135-137), Company submission; table 1-3 (page 5-7) company response to additional clarification request

⊙ ***Is pembrolizumab more clinically effective in PD-L1 positive subgroups?***

KEYNOTE-045

Other subgroups (PFS)

Overall		437/542	0.98	(0.81, 1.19)
Prior Platinum Therapy				
	Cisplatin	324/411	0.99	(0.79, 1.24)
	Carboplatin	109/126	0.97	(0.64, 1.48)
Histology				
	Transitional Cell	315/383	1.08	(0.86, 1.36)
	Mixed Transitional/non-transitional histology	119/155	0.84	(0.57, 1.24)
ECOG Status (0/1 vs 2)				
	0 or 1	423/526	0.98	(0.80, 1.19)
	2	5/6	2.92	(0.26, 32.93)
ECOG Status (0 vs 1/2)				
	0	170/225	1.16	(0.84, 1.60)
	1 or 2	258/307	0.96	(0.74, 1.23)
Geographic Region				
	East-Asia	85/106	1.68	(1.05, 2.67)
	Non-East Asia	352/436	0.86	(0.69, 1.06)
	EU	178/223	0.90	(0.66, 1.24)
	Non-EU	259/319	1.03	(0.80, 1.33)
	US	80/106	0.85	(0.53, 1.37)
	Non-US	357/436	1.03	(0.83, 1.28)
Smoking Status				
	Never Smoker	149/187	1.13	(0.80, 1.60)
	Former Smoker	229/284	1.05	(0.79, 1.38)
	Current Smoker	56/67	0.47	(0.25, 0.88)

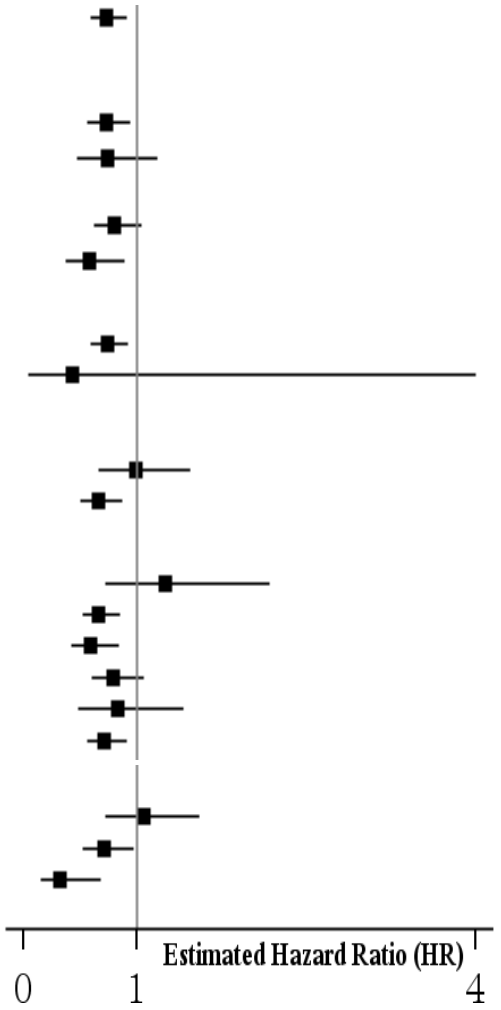


Source: adapted from Figure 29 (page 131-132), company submission

KEYNOTE-045

Other subgroups (OS)

Overall		334/542	0.73	(0.59, 0.91)
Prior Platinum Therapy				
	Cisplatin	248/411	0.73	(0.56, 0.94)
	Carboplatin	82/126	0.74	(0.47, 1.18)
Histology				
	Transitional Cell	240/383	0.80	(0.62, 1.04)
	Mixed Transitional/non-transitional histology	93/155	0.58	(0.37, 0.89)
ECOG Status (0/1 vs 2)				
	0 or 1	323/526	0.74	(0.59, 0.92)
	2	5/6	0.43	(0.04, 4.20)
ECOG Status (0 vs 1/2)				
	0	106/225	0.99	(0.66, 1.47)
	1 or 2	222/307	0.66	(0.50, 0.87)
Geographic Region				
	East-Asia	62/106	1.25	(0.72, 2.18)
	Non-East Asia	272/436	0.66	(0.52, 0.85)
	EU	137/223	0.59	(0.42, 0.84)
	Non-EU	197/319	0.79	(0.60, 1.06)
	US	61/106	0.83	(0.48, 1.41)
	Non-US	273/436	0.71	(0.56, 0.91)
Smoking Status				
	Never Smoker	118/187	1.06	(0.72, 1.55)
	Former Smoker	170/284	0.71	(0.52, 0.97)
	Current Smoker	43/67	0.32	(0.15, 0.68)



Source: adapted from Figure 28 (page 128-129), company submission

⊙ ***Should any subgroups be considered in decision-making?***

Adverse events

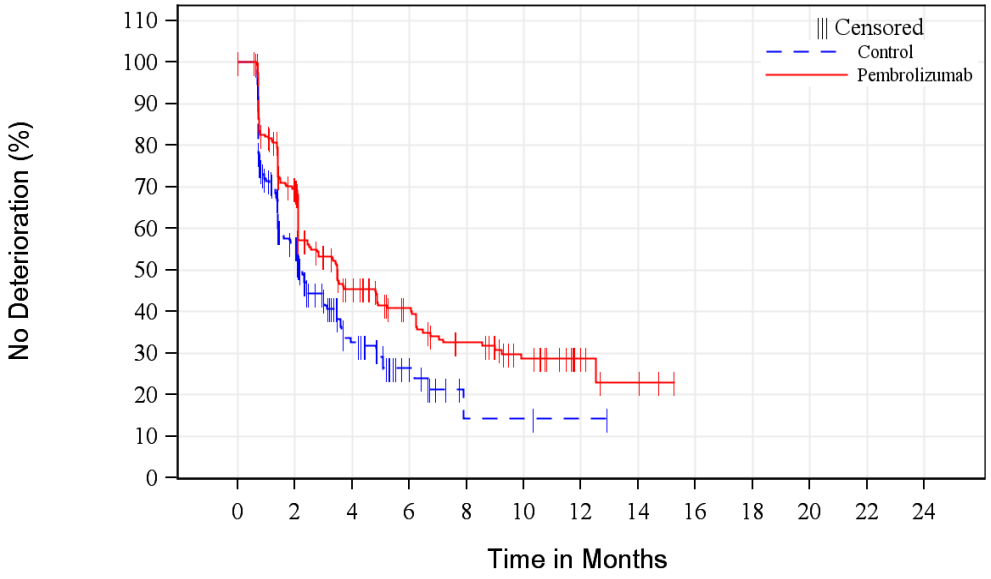
- All-Patients-as-Treated (APaT) used for analysis of safety. APaT population consisted of all people who received at least 1 dose of study treatment
- Adverse events considered by the investigator to have a reasonable possibility of being related to the technology were classified as drug-related adverse events
- Model includes disutility of all Grade 3+ adverse events with incidence over 5% (any grade) from the KEYNOTE-045 the UK standard of care population

	Pembrolizumab	UK SOC
Grade 3+ adverse event included in model		
Anaemia	8.3%	11.9%
Febrile neutropenia	0.0%	4.76%
Neutropenia	0.0%	11.9%
Diarrhoea (including grade 2)	5.3%	5.36%
Fatigue	3.8%	5.95%
Neutrophil count decreased	0.4%	14.29%
White blood cell count decreased	0.4%	5.95%
Pneumonia	2.6%	4.17%
Hypophosphatemia	0.80%	3.57%

Sources: Table 72 (page 188), company submission; appendix 19, company appendices

Health-related quality of life (HRQoL)

- APaT population used for analysis of quality of life data
- HRQoL in model was estimated using the EQ-5D-3L, collected every 3 weeks for the first 9 weeks, then every 6 weeks up to drug discontinuation or at 30-day-post-study safety follow-up, but no further
- Pembrolizumab prolonged the time to deterioration measured by EORTC



Number of subject at risk

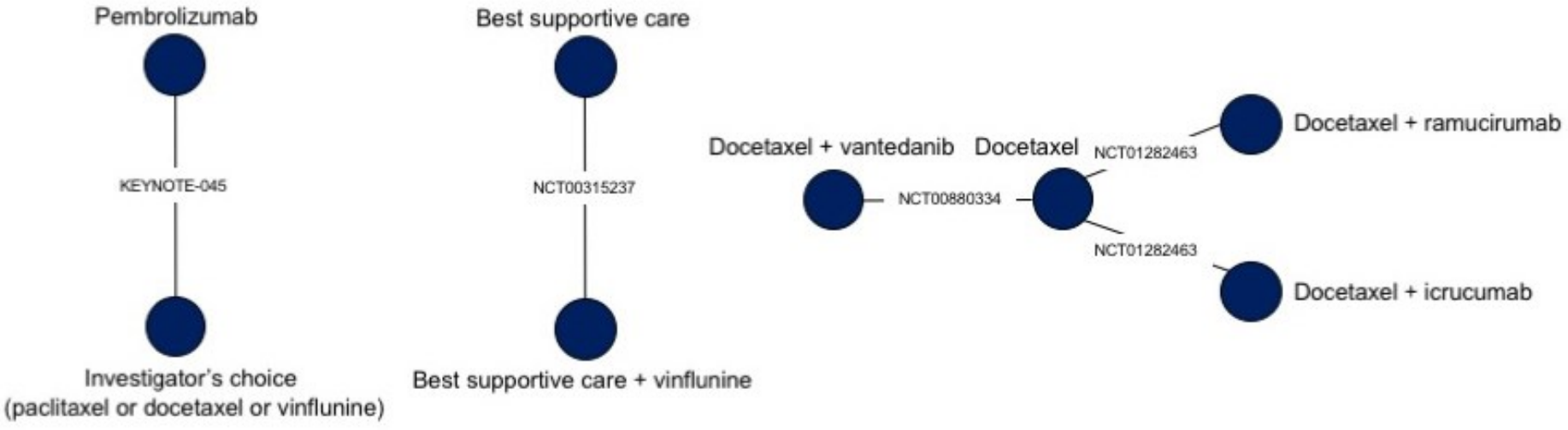
Control	243	101	34	12	2	2	1	0	0	0	0	0	0
Pembrolizumab	260	144	77	55	39	27	6	3	0	0	0	0	0

Source: Figure 27 (page 152), company submission

Indirect treatment comparison

Company raised issues with performing this analysis:

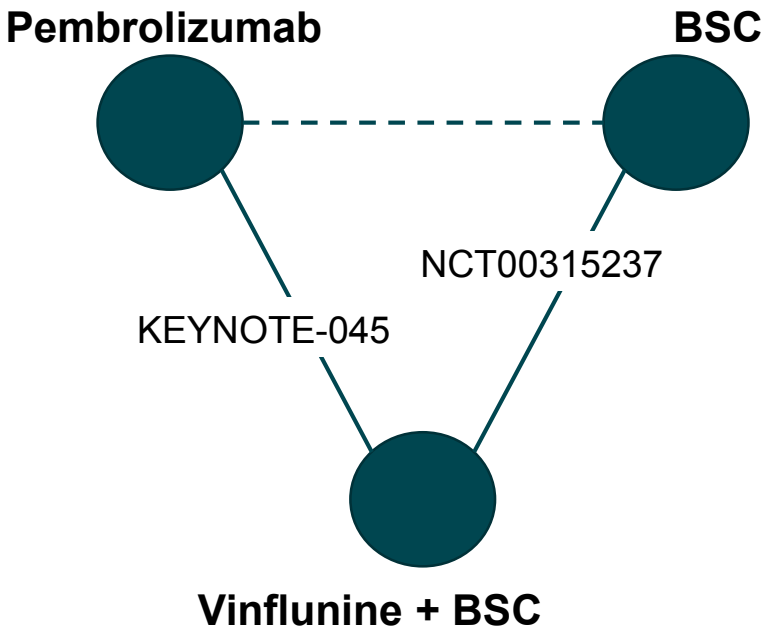
- Differences at baseline across the trials
  - NCT00315237 only included Asian patients without EGFR mutation, and had highest proportion of ECOG 1 scores
- Adverse events and HRQoL inconsistently reported across trials
- Can't connect networks for comparison of interest



Source: Figure 30 (page 144), company submission

ERG Comments
Indirect treatment comparisons

- Disagree that NCT00315237 only included Asian patients, as not reported in publications and had 21 sites in North America or Europe
- ERG believe that the vinflunine arm in KEYNOTE-045 could be assumed to have also received BSC, and the network could be connected
- However BSC relevant for people with poor performance status (ECOG 3-4), who would not tolerate active treatment. Neither trial recruited this group, and the relevance would therefore be questionable
- The ERG did not conduct an indirect treatment comparison



⊙ ***Would an indirect comparison be useful for decision-making?***

ERG comments
Conclusions

- KEYNOTE-045 was of low risk of bias in most domains with the exception of blinding owing to open-label design
- Compared to UK standard of care both PD-L1 subgroups and full population, pembrolizumab reduces the risk of death but has a similar PFS - although the proportion of people progression-free is numerically higher in the pembrolizumab groups
- The subgroups show consistency with the overall findings
- Owing to open-label design it is difficult to draw reliable conclusions from the quality of life results
- Safety profile of pembrolizumab was more favourable than that of the trial control

Key issues for consideration
Clinical evidence

- Where will the technology be used in the treatment pathway?
- Is the KEYNOTE-045 clinical evidence generalisable to UK clinical practice?
- What is the most appropriate method of adjusting for treatment switching?
- Are PFS results using RECIST or mRECIST criteria more appropriate for decision making?
- Is the technology clinically effective:
  - In the whole population?
  - In the PD-L1 subgroups?
  - In the cancer histology subgroups?
  - Is the treatment effect maintained in the long-run?
- Is best supportive care an appropriate comparator?
- Is there value in an indirect treatment comparison between pembrolizumab and best supportive care

Public slides - Redacted

Lead team presentation – Cost

Pembrolizumab for previously treated advanced or metastatic urothelial cancer

1st Appraisal Committee meeting

Committee D, 31 May 2017

Lead team: Malcolm Oswald, Rachel Elliott , William Turner

Companies: Merck Sharp & Dohme

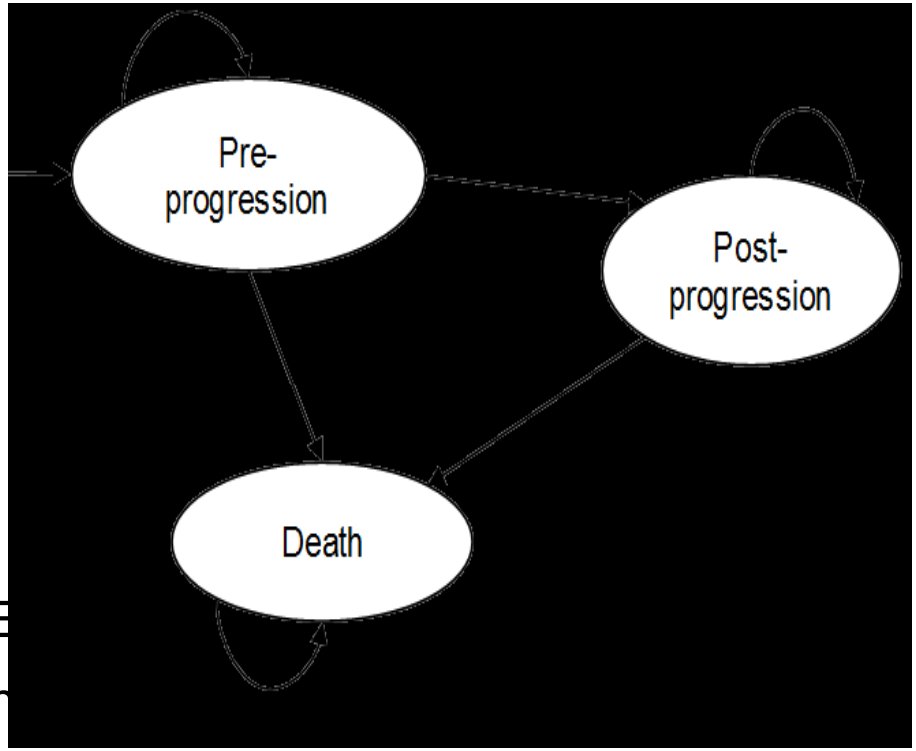
Chair: Gary McVeigh

Evidence review group: Warwick Evidence

NICE team: Thomas Strong, Christian Griffiths, Helen Knight

Model structure

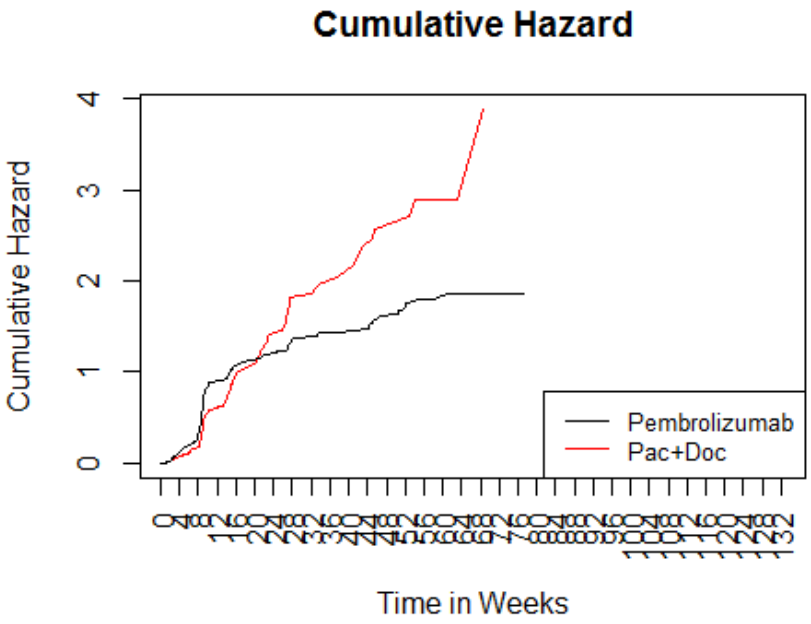
- 3 state partitioned-survival model
- Time horizon: 35 years
- Starting age 65.5 years
- Cycle length: 1 week with half-cycle correction
- 1 line of subsequent therapy modelled
- 2-phase piecewise method (KEYNOTE 045 KM data plus parametric approach to estimate PFS and OS
- Fully parametric curves fitted for time on treatment



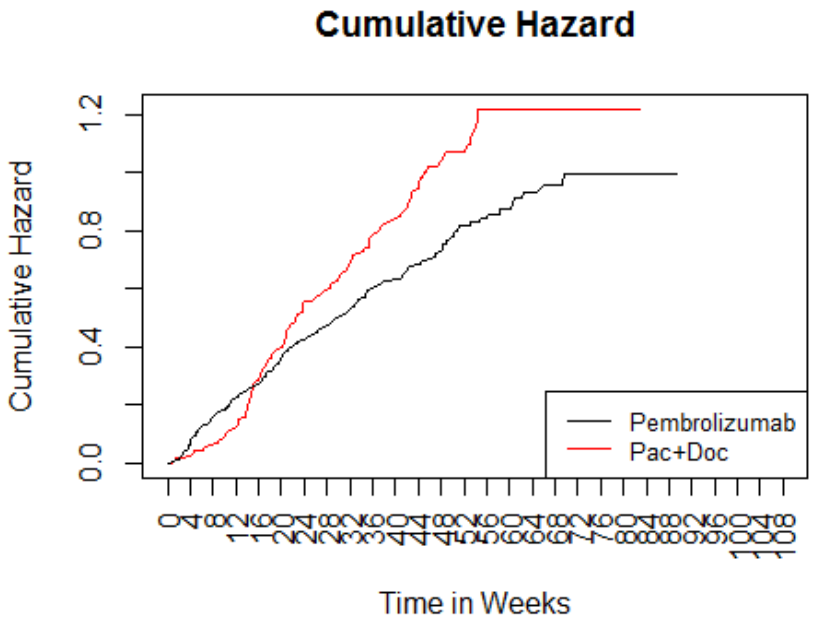
Source: figure 33 (page 175), company submission

Company survival curves
Proportional hazards assumption

Progression-free survival



Overall Survival



- The proportional hazards assumption does not hold
- Separate models were fitted based on the individual patient data from KEYNOTE-045

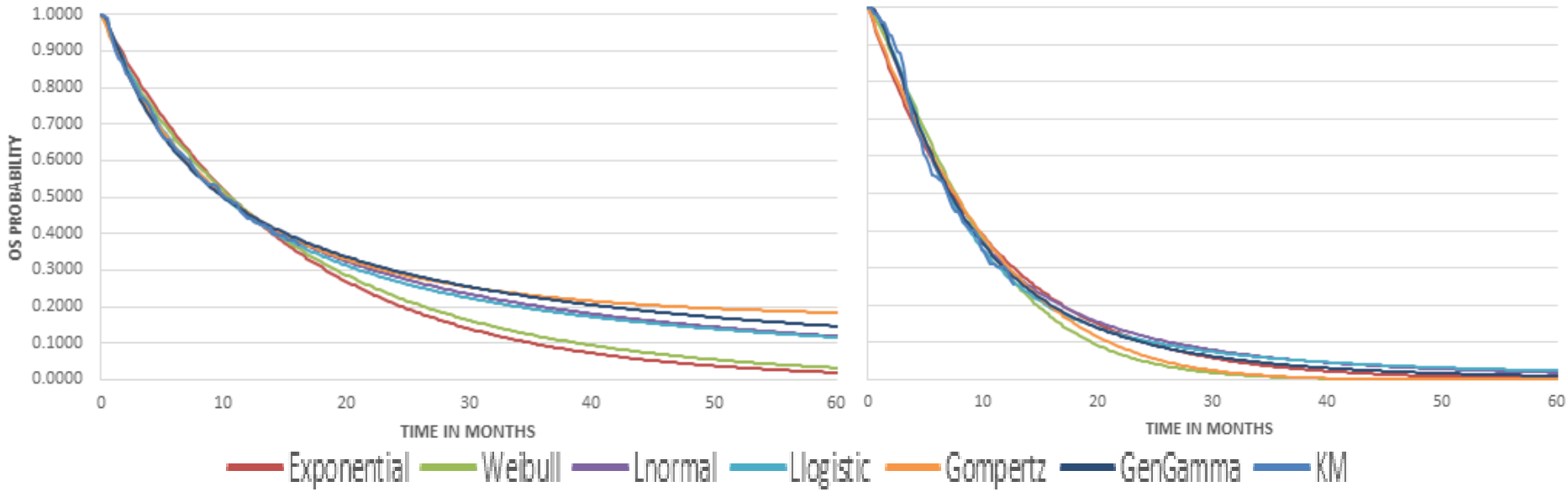
Source: figure 36 and Figure 38 (page 183 and 185), company submission

Company survival curves
fully-fitted parametric model

- Company explored fully-fitted parametric curves

Pembrolizumab

UK SOC – 2 stage adjusted



Source: figure 35 (page 182), company submission

- As the cumulative hazard plot is not constant over time, the company preferred using 2-phase piecewise models

⊙ ***Is a 2-phase piecewise model more appropriate for decision-making?***

Company survival curves
Overall survival (I)

- KM data until week 40, then fitted parametric curves
  - Justification: “OS curves start separating from week 24… clear change in the slope after around 40 weeks”

Fitted Function	Pembrolizumab		UK SOC, 2-stage adjusted	
	AIC	BIC	AIC	BIC
Exponential	339.1	342.1	165.1	167.1
Weibull	340.5	346.4	165	169.1
Gompertz	338.1	344	160.4	164.5
Log-logistic	339.4	345.3	163.7	167.7
Log-normal	337.5	343.4	161.8	165.9
G.Gamma	338.5	347.3	160.2	166.3

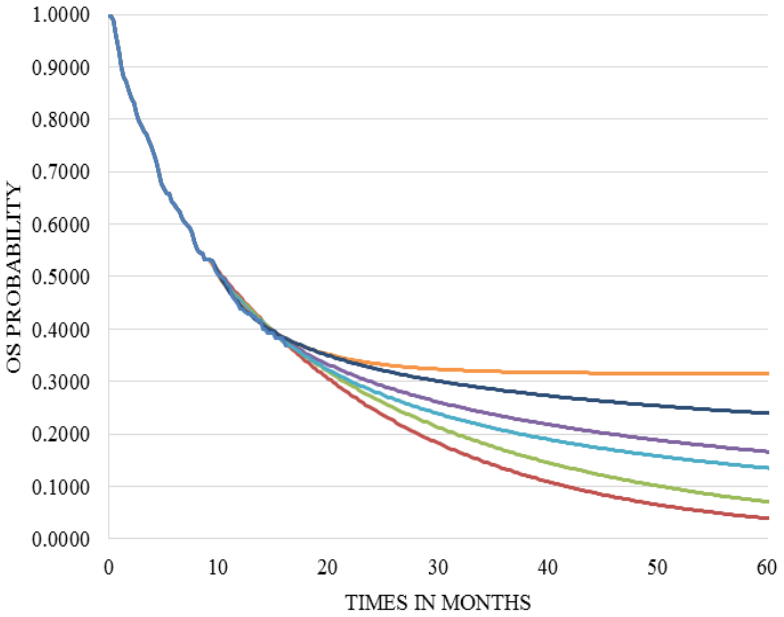
AIC, Akaike information criterion; BIC, Bayesian information criterion
Source: table 69*, page 184 of the company submission

- Curves with closest statistical fit regarded as clinically implausible - approximately 17% and up to 24% 5 year OS rate
- Company prefer Log-normal distribution, as projected 7.8% OS rate at 5 years is closest to available data (9-11%; CRUK)

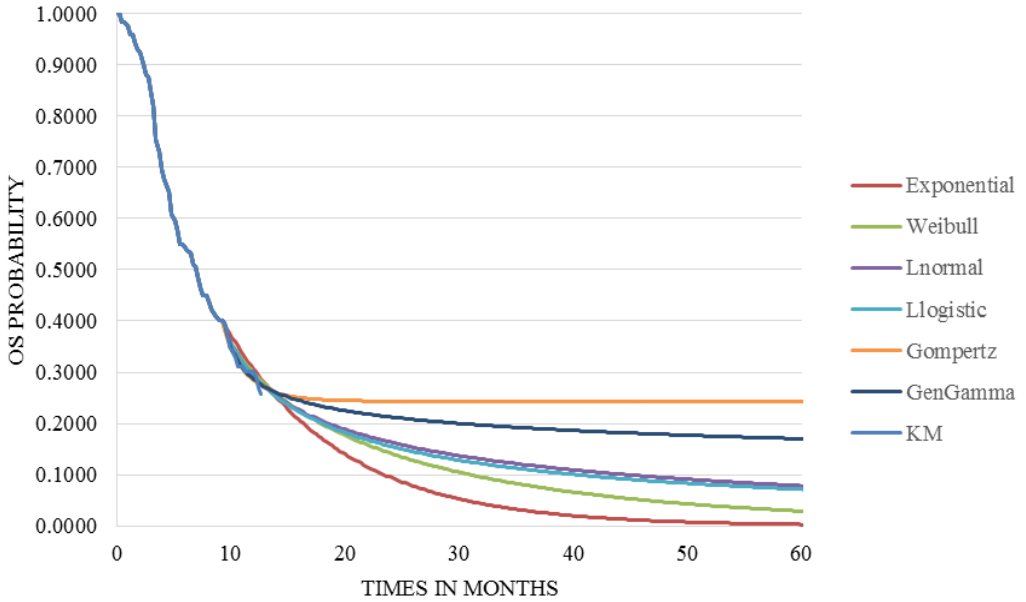
Company survival curves
Overall survival (II)

- Company base case used Log-normal curve (purple)

Pembrolizumab



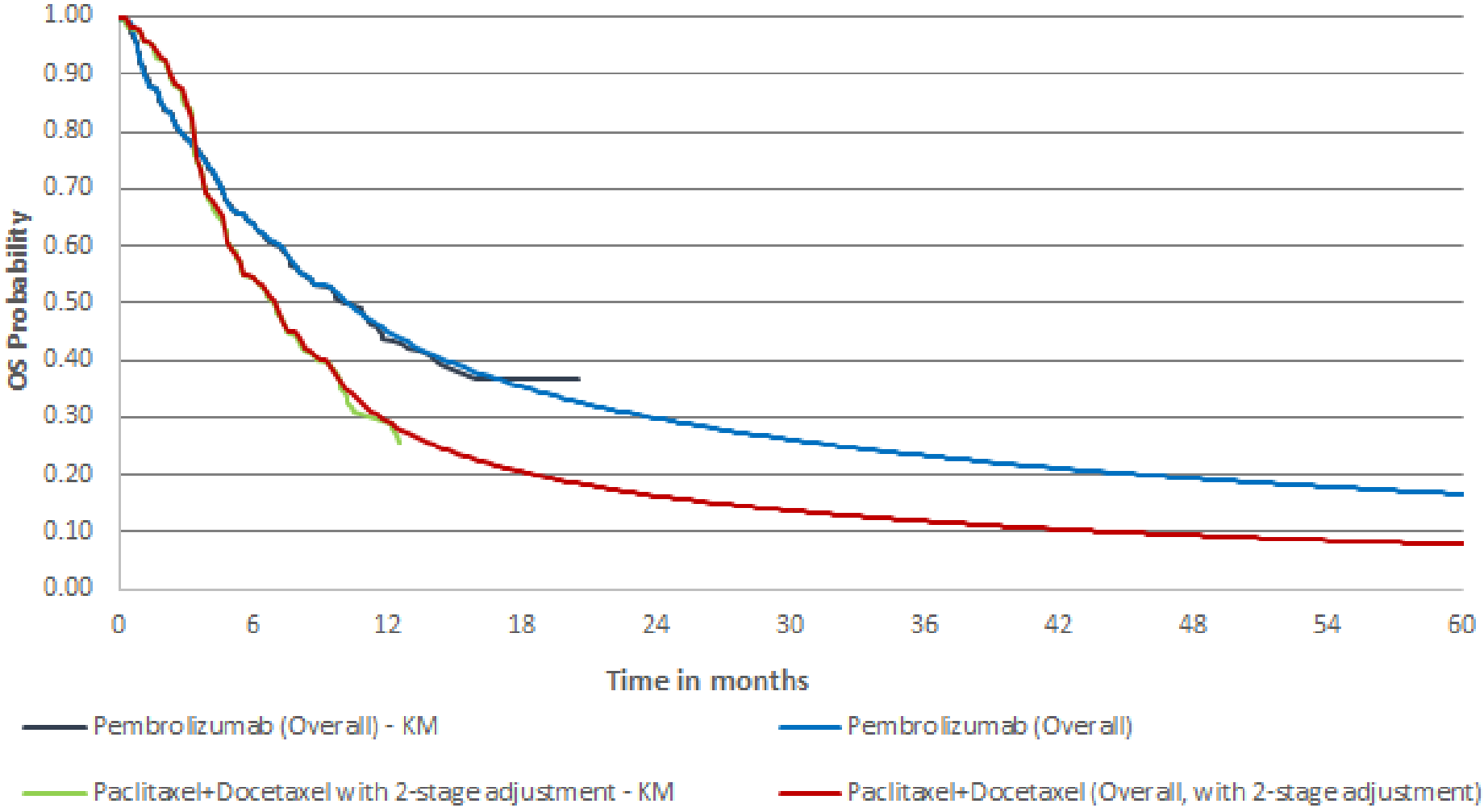
UK SOC – 2 stage adjusted



Source: adapted from figures 7 and 8 (page 85), ERG report

Company survival curves

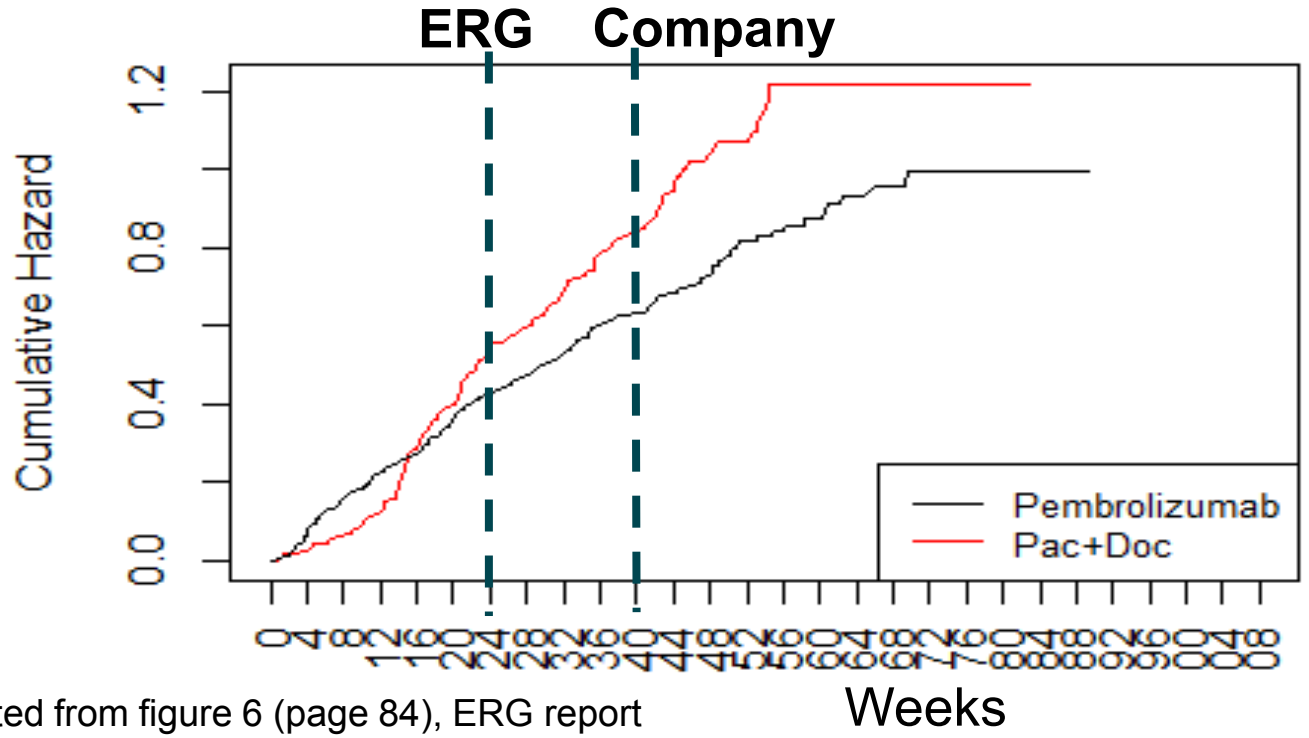
Overall survival (III)



Source: figure 37 (page 184), company submission

ERG Comments
Overall survival (IV)

- ERG agree that proportional hazard assumption does not hold
- Cumulative hazard plot looks consistent after week 16, and using this time-point would maximise the data available for extrapolation – but the closest time-point the model allows is week 24



Source: adapted from figure 6 (page 84), ERG report

⊙ ***What cut-off for extrapolation is most appropriate?***

ERG Comments
Overall survival (V)

- ERG consider 9-11% 5-year OS estimate from CRUK to be an overestimate
- Clinical expert and results from systematic review indicate that 2-3% 5-year overall survival more consistent with current clinical practice
- Based on AIC/BIC Log-logistic is best fit, and clinically plausible

Overall survival	Exponential	Weibull	Log-normal	Log-logistic	Gompertz	Generalised gamma
24-week cut-off – ERG base case						
1-year	30.2%	30.1%	29.3%	**28.9%**	30.1%	29.4%
3-year	3.5%	2%	6.9%	**6.5%**	9.1%	12.7%
5-year	0.4%	0.1%	2.9%	**3.2%**	5.9%	8.9%
10-year	0%	0%	0.7%	**1.2%**	4.6%	5.6%
40-week cut-off – Company base case						
1-year	30%	29.4%	**28.8%**	28.8%	28.1%	28.3%
3-year	2.9%	7.9%	**11.9%**	11%	24.3%	19.1%
5-year	0.3%	2.9%	**7.8%**	7.1%	24.3%	17%
10-year	0%	0.4%	**4.2%**	4%	24.3%	14.8%

Source: adapted from table 22 (page 93), ERG report; bolded red figures represent the base cases

⊙ ***What is the most plausible long-term overall survival for UK SOC?***
⊙ ***Which extrapolation curve should be used in the basecase?***

Company survival curves
Progression-free survival (I)

- KM data until week 21 (3rd assessment), then parametric curves
  - Company justification: “clear separation of the curves observed”

Fitted Function	Pembrolizumab		UK SOC	
	AIC	BIC	AIC	BIC
Exponential	339	341.4	154.1	155.4
Weibull	340.7	345.5	150.6	153.1
Gompertz	340.2	345	155.9	158.4
Log-logistic	340.2	344.9	153.6	156.1
Log-normal	339.9	344.6	153.4	155.9
G.Gamma	341.8	348.9	149.8	153.6

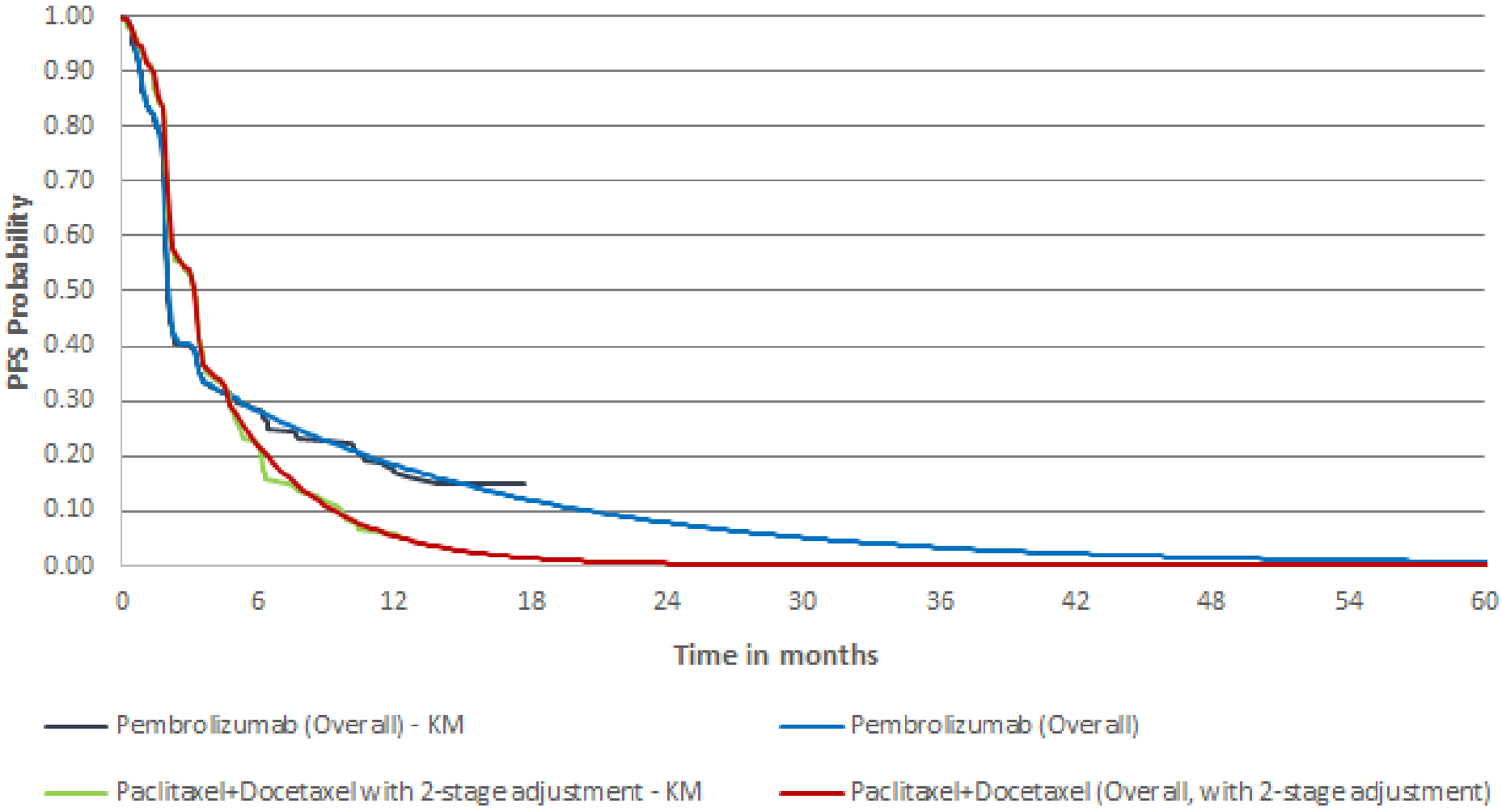
AIC, Akaike information criterion; BIC, Bayesian information criterion

Source: table 71, page 184 of the company submission

- Exponential best statistical and visual fit for pembrolizumab
- No clear best statistical fit for UK SOC, and distributions very close visually
- Exponential curve selected for UK SOC to maintain consistency with pembrolizumab arm

Company survival curves

Progression-free survival (II)



Source: figure 41 (page 187), company submission

Company survival curves
Time-on-treatment (ToT) (I)

- Fully fitted parametric curves

Fitted Function	Pembrolizumab		UK SOC	
	AIC	BIC	AIC	BIC
Exponential	1923.8	1927.4	1133.1	1136.3
Weibull	1870.5	1877.7	1126.8	1133.1
Gompertz	1890.9	1898.1	1134.1	1140.4
Log-logistic	1885	1892.2	1167.2	1173.5
Log-normal	1899.8	1906.9	1177.1	1183.3
G. Gamma	1872.1	1882.8	1122.2	1131.6

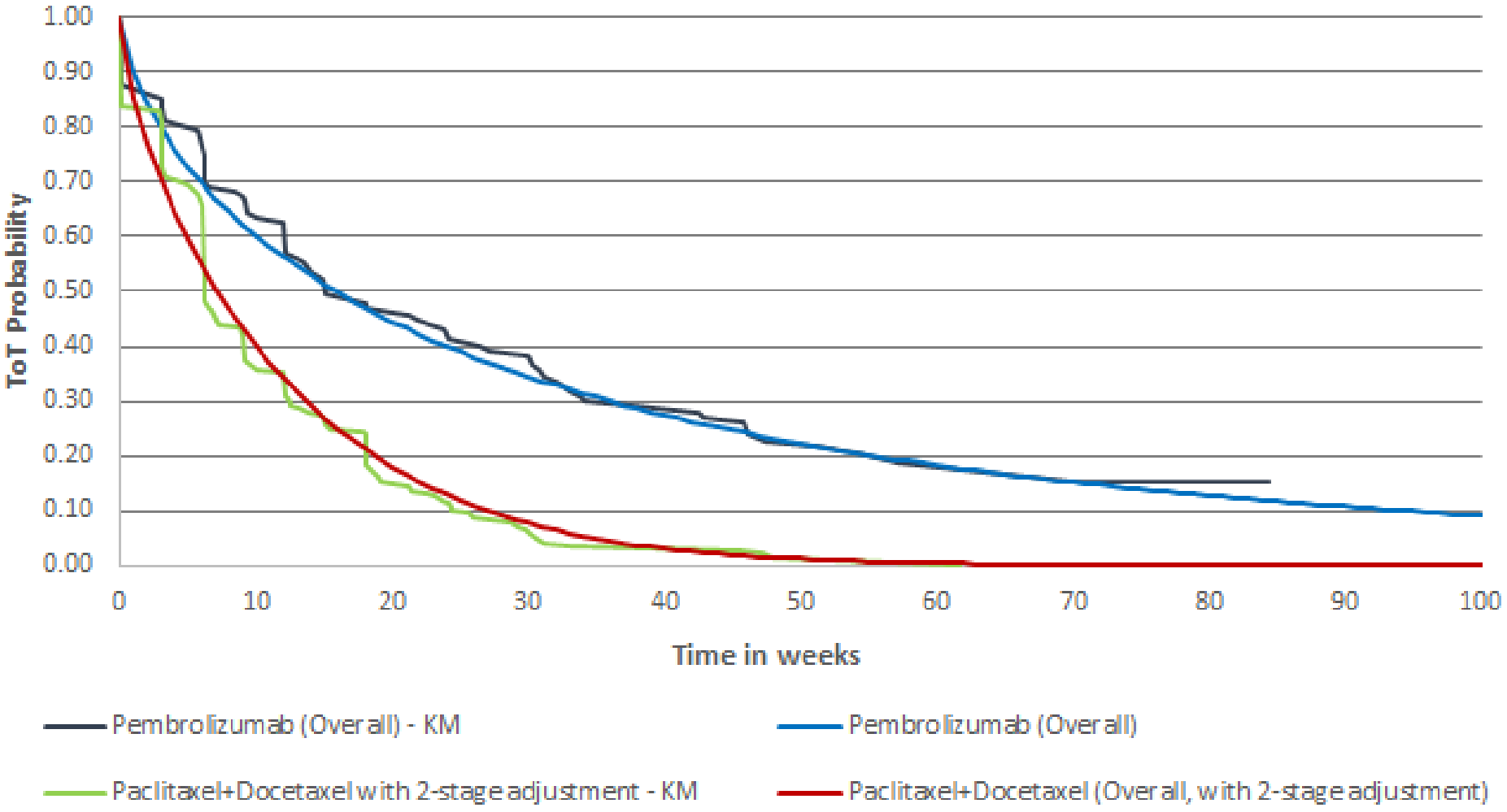
AIC, Akaike information criterion; BIC, Bayesian information criterion

Source: table 71 (page 184), company submission

- Stopping rules: 24 months pembrolizumab; 18 weeks UK SOC
  - 24 months for pembrolizumab reflects KEYNOTE-045 protocol
  - 18 weeks for UK SOC reflects UK clinical practice
- Curves selected were Weibull for pembrolizumab and GenGamma for UK SOC due to lowest AIC/BIC

Survival curves

Time-on-treatment (ToT) (II)



Source: figure 46 (page 207), company submission

Utility values

- Company base case:
  - utilities based on time-to-death, as data for post-progression is very limited as it is usually collected directly after progression and more health states offers a better HRQoL data fit
  - vinflunine data included to maximise the data for analysis
  - mean utility scores by health status were estimated per treatment arm (pembrolizumab and UK SOC arms) and pooled for both arms, as no statistical or clinically meaningful difference between arms
  - age-related utility decrement of 0.0045 is applied per year from the age of 65 until 75 as per *Kind et al*. No decrease after 75yrs of age
- Company explored several scenarios for incorporating the utility values in their analyses
- For scenarios using utilities based on progression state, progression date was determined by RECIST 1.1 BICR progression date

ERG Comments
Utility values *(I)*

- Company use pooled utility by time to death (days), using trial control data (i.e. inclusion of people using vinflunine). The ERG note:
  - not common in practice – previously used in melanoma and NSCLC
  - groupings of time periods was not strongly justified
  - average scores were not weighted per person and were averaged across from all eligible questionnaires
- ERG prefer a pooled utility by progression status, excl. vinflunine data
- ERG use newer algorithm to estimate age-related utility decrements
- Utility values are lower for pembrolizumab compared with UK SOC when measured based on time to death, but higher based on progression status. ERG unsure of cause for inconsistency, but suggest:
  - lack of accounting for treatment switching
  - survival of people with lower performance score in the pembrolizumab arm

⊙ ***Should age-related utility decrements for people >75 be incorporated?***

ERG Comments

Utility values *(II)*

	Pembro	Trial control	Pembro + trial control pooled	UK SOC	Pembro + UK SOC pooled	TA272
Time to death based (days) – Company base case						
≥360	0.765	0.804	**0.778**	0.823	0.780	-
180-360	0.686	0.699	**0.693**	0.673	0.680	-
90-180	0.566	0.612	**0.590**	0.595	0.578	-
30-90	0.457	0.446	**0.451**	0.414	0.435	-
<30	0.336	0.311	**0.325**	0.337	0.337	-
Progression based – ERG base case						
Pre-progress	0.757	0.698	0.731	0.709	**0.741**	0.65
Post-progress	0.680	0.565	0.641	0.554	**0.647**	0.25

Source: adapted from table 31 (page 108), ERG report; bolded red figures represent the base cases

- ***Is it clinically plausible that people on pembrolizumab have higher, lower, or similar utilities compared with people on taxanes?***
- ***Should utilities in the model be pooled, or treatment-specific?***
- ***Should vinflunine utility data be incorporated to maximise data?***

Base case results

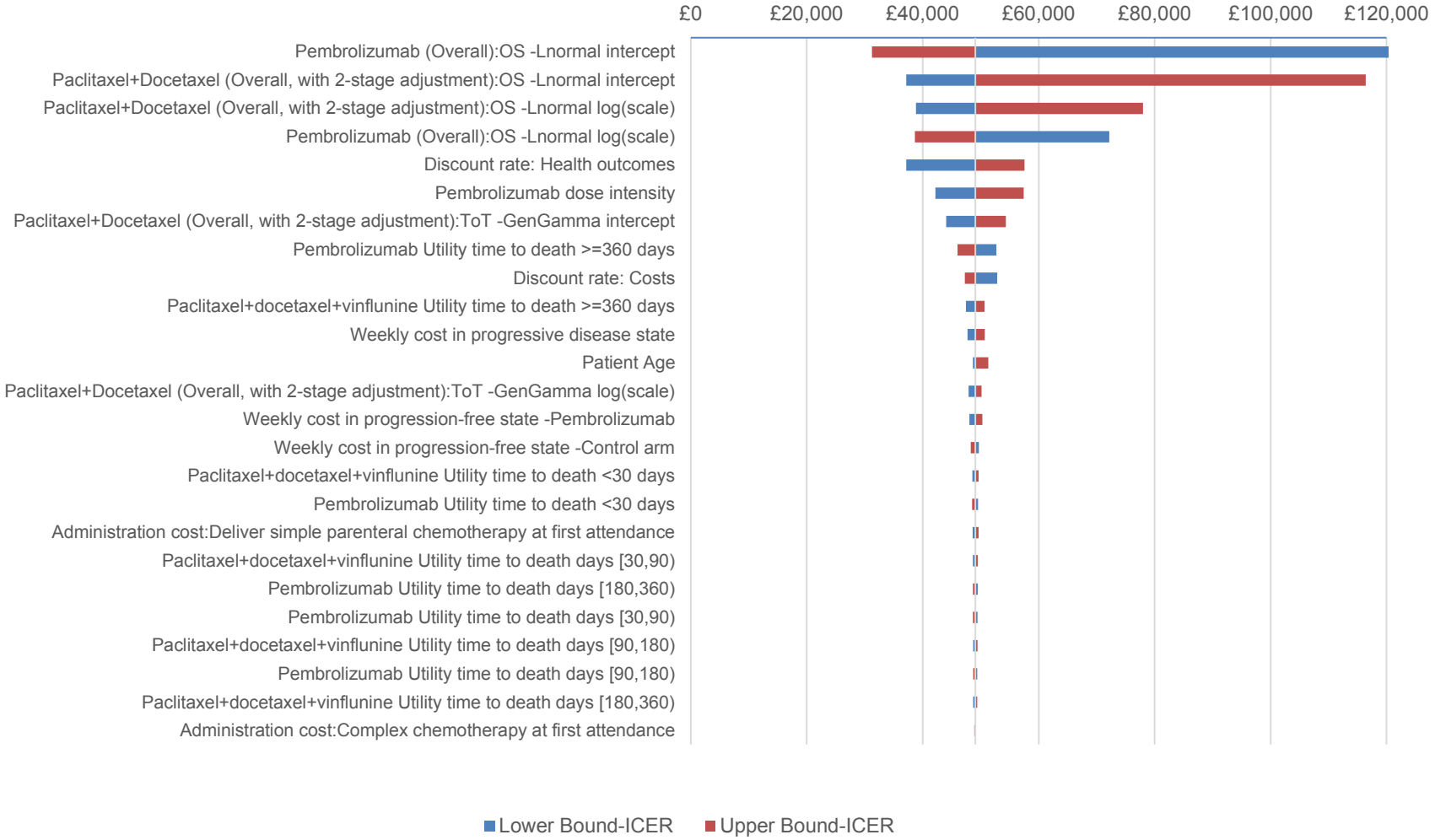
	Total costs (£)	Total QALYs	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Company – Deterministic					
UK SOC	£20,938	1.10	-	-	**-**
Pembro	£60,053	1.95	£39,115	0.85	**£45,833**
Company – Probabilistic					
UK SOC	£21,367	1.13	-	-	**-**
Pembro	£60,634	1.98	£39,267	0.85	**£46,194**
ERG – Deterministic					
UK SOC	£17,439	0.73	**-**	**-**	**-**
Pembro	£57,457	1.51	£40,017	0.78	**£51,235**
ERG – Probabilistic					
UK SOC	£17,689	0.75	-	-	-
Pembro	£57,986	1.54	£40,298	0.79	**£50,902**

Incr., incremental; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

ERG results source: table 1 (page 4), ERG appendix probabilistic basecase and subgroup analyses

Company sensitivity analyses
Tornado diagram

- ICER sensitive to varying the overall survival extrapolation



Source: Company model

Company scenario analyses (I)

Scenario		Pembrolizumab vs UK SOC			
		Inc. costs	Inc. QALY	ICER	Δ ICER
	Base case	£39,115	0.85	£45,833	-
1.a	No switching adjustment	£34,296	0.54	£64,101	+£18,268
1.b	Switchover – RPSFT	£44,022	1.40	£31,509	-£14,324
1.c	Switchover – IPCW	£38,350	0.77	£49,874	+£4,041
2.a	OS cut-off – 24 weeks	£42,693	1.25	£34,168	-£11,665
2.b	OS cut-off – 32 week	£42,999	1.28	£33,613	-£12,220
4	UK SOC PFS extrapolation based on gen. gamma	£39,392	0.85	£46,158	+£325
5	No half cycle correction	£38,732	0.85	£45,374	-£459
6	UK SOC - UK market shares	£39,239	0.85	£45,978	+£145
7	Utilities - Progression (pooled)	£39,115	0.72	£54,665	+£8,832
8.a	Utilities – Time to death (per treatment arm)	£39,115	0.79	£49,555	+£3,722
8.b	Utilities – Progression (per treatment arm)	£39,115	0.92	£42,738	-£3,095
9	No age-related disutilities	£39,115	0.88	£44,418	-£1,415

Source: adapted from table 92 (page 34), addendum 1, company revised appendices

Company scenario analyses (II)

- Economic model assumes people stop treatment at 2 years – which is not included in the expected marketing authorisation
- Extrapolated curves assume pembrolizumab remains effective irrespective of time or implementation of a stopping rule

Probabilistic results	Lifetime treatment effect	10 year treatment effect	5 year treatment effect	3 year treatment effect
100% continue	£53,484	£55,801	£60,592	£65,656
25% continue	£48,238	£50,280	£54,502	£58,967
0% continue	£46,194	£48,129	£52,130	£56,360

Source: adapted from table 2 (page 38), company response to clarification (section B)

⊙ ***Should a 2-year stopping rule be included in the recommendation?***
⊙ ***Is a lifetime treatment effect plausible?***

ERG Comments

Individual impact of ERG's changes

	Incr. Costs	Incr. QALY	ICER	Change
Company base-case model	**£39,115**	**0.85**	**£45,833**	**-**
ERG models				
Exclusion of vinflunine data from utilities	£39,115	0.86	£45,712	**-£121**
Progression status utilities (pooled)	£39,115	0.72	£54,665	**+£8,832**
Ara and Brazier utility decrements	£39,115	0.84	£46,673	**+£840**
UK market share of docetaxel and paclitaxel	£39,239	0.85	£45,978	**+£145**
Log-logistic OS modelling	£37,029	0.62	£59,246	**+£13,413**
Cut-off point of 24 weeks for OS modelling	£42,693	1.25	£34,168	**-£11,665**

Source: table 59 (page 139), ERG report

ERG Comments

Scenario analyses of CS base-case model (I)

- The ERG explored other scenarios which were not included in their base-case

	Incr. Costs	Incr. QALY	ICER	Change
Company base-case model	**£39,115**	**0.85**	**£45,833**	**-**
ERG scenarios				
Treatment specific utilities, time-to death, exclusion of vinflunine data	**£39,115**	**0.78**	**£50,074**	**+£4,241**
Treatment specific utilities, progression based, excl. vinflunine	**£39,115**	**0.92**	**£42,301**	**-£3,532**
Pooled utilities, progression-based, utility values from TA272	**£39,115**	**0.34**	**£114,082**	**+£68,249**
Treatment specific adverse event disutility, time-to-death	**£39,115**	**0.64**	**£60,714**	**+£14,881**
Treatment specific adverse event disutility, progression-based	**£39,115**	**0.79**	**£49,652**	**+£3,819**
AE costs from alternative sources	**£38,376**	**0.85**	**£44,967**	**-£866**

Source: tables 45-51 (page 127-130), ERG report

⊙ ***Should any of these scenarios be incorporated into the basecase?***

ERG Comments
Sensitivity analyses (I)

- Overall Survival 2 piecewise model is sensitive to choice of cut-off for extrapolation

Scenario	Pembrolizumab vs UK SOC					
	5-year OS	Incr. costs	Incr. LYG	Incr. QALYs	ICER	Δ ICER
ERG base case	3.2%	£40,017	1.25	0.78	£51,235	-
Overall survival; ERG preferred assumptions; 40 week time-point						
Exponential	0.3%	£35,028	0.51	0.35	£100,765	+£49,530
Weibull	2.9%	£35,006	0.51	0.34	£101,593	+£50,358
Gompertz	24.3%	£39,432	1.15	0.72	£55,118	+£3,883
Log-logistic	7.1%	£37,153	0.82	0.53	£70,304	+£19,069
Log-normal	7.8%	£39,239	1.12	0.71	£55,407	+4,172
G. Gamma	17%	£38,116	0.96	0.61	£62,809	+11,574
Overall survival; ERG preferred assumptions; 24 week time-point						
Exponential	0.4%	£34,648	0.46	0.31	£110,621	+£59,386
Weibull	0.1%	£35,928	0.64	0.43	£83,381	+£32,146
Gompertz	5.9%	£47,846	2.38	1.45	£33,092	-£18,143
Log-logistic	3.2%	£40,017	1.25	0.78	£51,235	£0
Log-normal	2.9%	£42,816	1.65	1.02	£41,807	-£9,428
G. Gamma	8.9%	£32,242	0.10	0.11	£295,841	£244,606
Source: ERG addendum, cut-off extrapolation scenarios						

ERG Comments
Sensitivity analyses (II)

- The ERG explored a fully-fitted parametric model for overall survival extrapolation

Scenario	Pembrolizumab vs UK SOC					
	5-year OS	Incr. costs	Incr. LYG	Incr. QALY	ICER	Δ ICER
ERG base case	3.2%	£40,017	1.25	0.78	£51,235	-
Overall survival; ERG preferred assumptions; fully-fitted (0 week time-point)						
Exponential	0.34%	£34,142	0.37	0.26	£131,018	+£79,783
Weibull	0.01%	£35,213	0.54	0.37	£96,353	+£45,118
Gompertz	0.00%	£49,213	2.58	1.57	£31,360	-£19,875
Log-logistic	2.38%	£39,142	1.11	0.71	£55,486	+£4,251
Log-normal	1.87%	£38,956	1.08	0.69	£56,366	+£5,131
G. Gamma	0.98%	£41,903	1.52	0.95	£44,147	-£7,088
Source: ERG addendum, cut-off extrapolation scenarios						

⊙ ***What is the committee's judgement on the uncertainty of the ICERS in the company's and ERG's basecase?***

Subgroup analyses (Company and ERG)
Crossover adjustment

- Crossover adjustment not always possible due to low sample size

Population	Comparators	OS for comparator arm			
		ITT unadjusted	Two-stage	RPSFT	IPCW
Basecase	UK SOC	✓	✓	✓	✓
ITT – histology subgroup	UK SOC ▪ Predominant transitional cell carcinoma ▪ Pure transitional cell carcinoma	✓	✗	✗	✗
CPS<1%	UK SOC	✓	✗	✓	✗
CPS≥1%	UK SOC	✓	✗	✓	✓
CPS≥10%	UK SOC	✓	✗	✓	✗

Source: adapted from table 66, page 178 of the company submission

⊙ ***What crossover adjustment is most appropriate for the subgroups?***

Subgroup overview (I)

- Difference in estimates driven by the sensitivity to overall survival extrapolation

	Company			ERG		
	Incr. LYG	ICER	Δ ICER	Incr. LYG	ICER	Δ ICER
Base case	**1.120**	**£45,833**	**-**	**1.250**	**£51,235**	**-**
Cancer histology subgroup						
Predomin-antly TCC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pure TCC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG, Life year gains; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years
Incr. LYGs are not reported in the company submission or ERG report, and have been calculated by the NICE technical team from LYGs reported per treatment arm

⊙ ***Are the cost-effectiveness results for the cancer histology subgroup clinically plausible?***

Subgroup overview (II)

	Company			ERG		
	Incr. LYG	ICER	Δ ICER	Incr. LYG	ICER	Δ ICER
Base case	**1.120**	**£45,833**	**-**	**1.250**	**£51,235**	**-**
PD-L1 CPS<1% subgroup (50.81% of KEYNOTE-045 trial)						
ITT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPSFT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS≥1% subgroup (46.8% of KEYNOTE-045 trial)						
ITT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPSFT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IPCW	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD-L1 CPS≥10% subgroup (34.3% of KEYNOTE-045 trial)						
ITT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RPSFT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

⊙ ***Are lower LYGs in the PD-L1 subgroups clinically plausible?***
⊙ ***Are the subgroup results informative for decision-making?***

ERG Conclusions

- Company model appears to be logical, methodologically sound and to have captured key features of people with advanced or metastatic urothelial cancer
- Model most sensitive to changes made to the overall survival extrapolation
  - ERG would liked to have seen greater consideration of other survival curves for both OS and PFS in the scenario analysis
- Other key area of uncertainty relates to method of estimating utility values
- The majority of the incremental life-year benefit derives from the extrapolated data rather than observed data
- For subgroup analyses the company varied the survival modelling but used the same model parameters as in the base-case analysis (such as age and gender)
- Adverse event costs may have been underestimated in the company model:
  - Common AEs from cancer treatment, such as dyspnoea, hypertension, and abdominal pain were not considered
  - AEs considered in 1st cycle of the model

Innovation

- Company considered pembrolizumab to be innovative:
  - Pembrolizumab was granted a Promising Innovative Medicines (PIM) and positive EAMS Scientific Opinion for the treatment of melanoma and NSCLC
  - Platinum-based chemotherapy and taxane regimens remain the foundation of second-line treatment for the majority of patients with urothelial cancer, and have not significantly improved the 1-year and 5-year survival rates
  - Because of its distinct mechanism of action, pembrolizumab has demonstrated significant survival benefit and improved tolerability profile compared to chemotherapy regimens and is expected to provide a durable response for patients with advanced or metastatic urothelial cancer, following treatment with platinum-containing chemotherapy

⊙ ***Should any innovation considerations to be taken into account?***

End-of-life criteria

Criterion	Data available
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Median OS is lower than 24 months: Following treatment with platinum-based chemotherapy, people have a short life expectancy with median survival measured in only a few months
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months	Pembrolizumab offers an extension to life of at least 3 months compared with UK SOC: • Median OS for pembrolizumab in trial was 10.3 (95% CI, 8.0, 11.8) months compared with 6.9 (95% CI, 5.3, 8.1) months for UK SOC (using 2-stage model for adjustment) • Economic model (company base case) estimates mean number of months of life gained is 32.5 months compared with 19 months with UK SOC
ERG critique	Overall, the ERG agree that pembrolizumab fulfils end-of-life treatment

⊙ ***Does pembrolizumab meet end-of-life criteria?***

Key issues for consideration
Cost-effectiveness evidence (I)

- Appropriateness and plausibility of the cost-effectiveness evidence for:
  - The overall population (pembrolizumab versus UK standard of care)?
  - The PD-L1 negative, positive, and strongly positive subgroups?
  - The cancer histology subgroups?
- For the survival modelling:
  - most plausible 10-year overall survival estimate?
  - most appropriate week to switch from K-M data to parametric curves?
  - most appropriate parametric curves?
- Is it plausible that pembrolizumab has a lifetime treatment effect, irrespective of time or implementation of a stopping rule?

Key issues for consideration
Cost-effectiveness evidence (II)

- For incorporation of utility estimates:
  - use of time-to-death method versus the progression-based method?
  - use of pooled utilities versus individual utilities per treatment arm?
  - choice of algorithm to apply age-related disutility?
- For incorporation of adverse events:
  - use of pooled adverse event disutility versus disutility per treatment arm?
- Any significant health benefits not captured or equality issues to be taken into account?
- What are the most plausible ICERs?