Chair's presentation

Pembrolizumab for previously treated advanced or metastatic urothelial cancer

2nd Appraisal Committee meeting

Committee D, 26 October 2017

Lead team: Malcolm Oswald, Rachel Elliott, William Turner

Chair: Gary McVeigh

ERG: Warwick Evidence

NICE technical team: Thomas Strong, Christian Griffiths

Company: Merck Sharp & Dohme

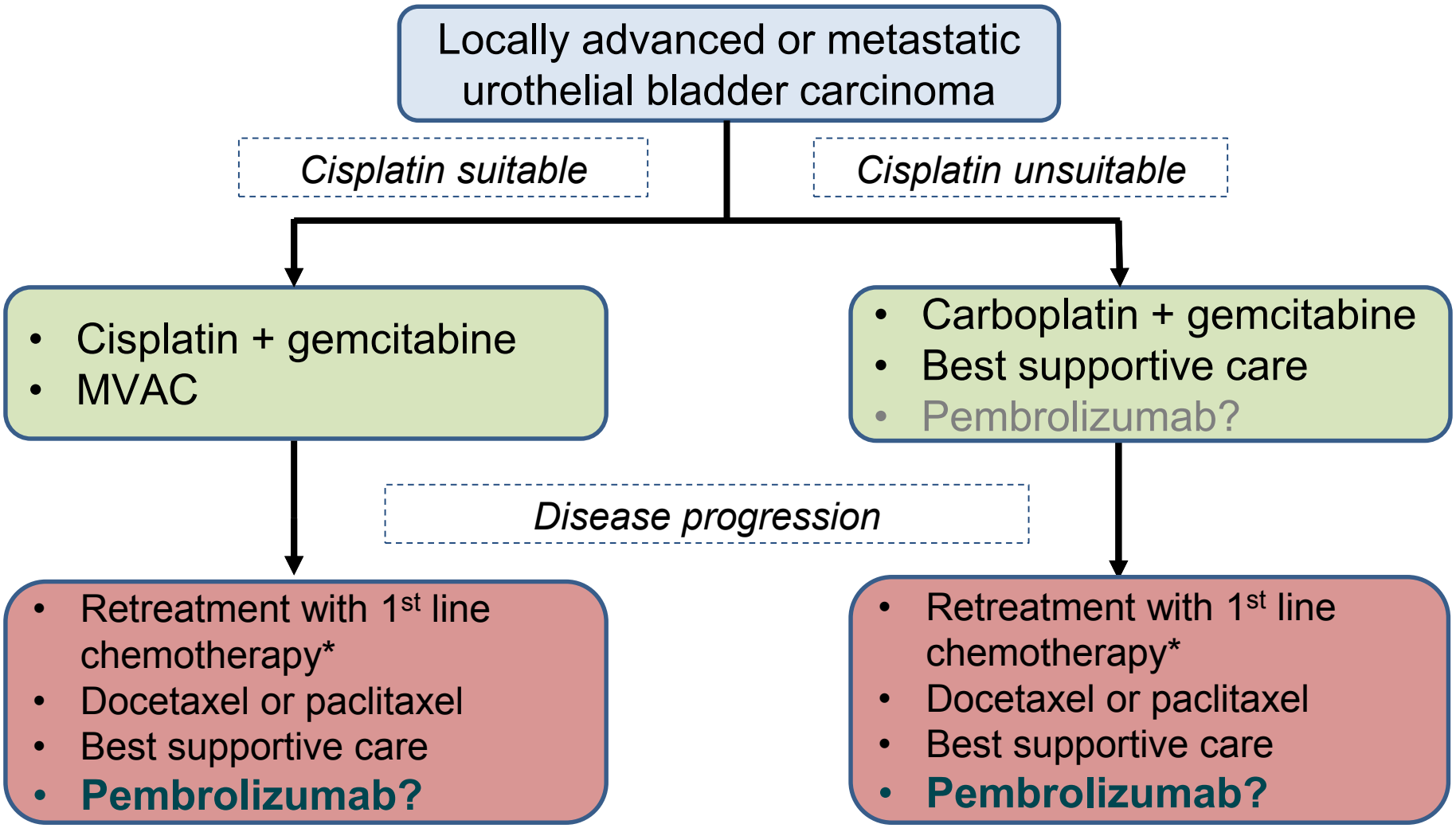
Pembrolizumab (KEYTRUDA)

Merck Sharp & Dohme

Marketing authorisation	Locally advanced or metastatic urothelial carcinoma in adults: • **who have received prior platinum-containing 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 **does not** include people who are ineligible for cisplatin-containing chemotherapy. Population ineligible for cisplatin-containing chemotherapy is proceeding through a separate appraisal

Clinical pathway of care



ACD preliminary recommendation

Committee did not recommend

- All plausible estimates are higher than what NICE normally considers acceptable for end-of-life treatments
- There are several plausible overall survival extrapolation curves and the ICER is highly sensitive to this parameter
- Other plausible scenarios and assumptions not fully accounted for which would increase the estimate further. These include:
  - Non-lifetime duration of continued treatment effect
  - Inclusion of rare adverse events associated with immunotherapy

Recap – Remaining uncertainty

Time point at which to extrapolate	• Company prefers cut-off point of 40 weeks, as at this point the cumulative hazards are consistently moving apart • ERG preferred cut-off point of 24 weeks (wanted to explore 16 week time-point, the point at which the cumulative hazards cross, but unable to in model provided) • Committee agreed on piece-wise approach, but unable to make a judgement on time-point
Extrapolation curve to use	• Company preferred a log-normal parametric as closest 5-year overall survival to CRUK data, at 7.8% • ERG preferred log-logistic curve as 5-year UK standard of care survival is 3.2% - which clinical expert suggests appropriate • Committee concluded there are several plausible curves
Adverse events	• Only adverse events with incidence >5% included • Including rare adverse events associated with immunotherapy would increase ICER
Continued treatment effect	Committee concluded this an area of uncertainty for new immunotherapies, but a lifetime continued treatment effect is implausible

ACD consultation responses

- Consultee comments from:
  - MSD (Pembrolizumab)
  - Fight Bladder Cancer
  - BUG-NCRI-ACP-RCP-RCR
- Clinical and patient experts:
  - 1x Clinical expert
- Commentator comments from:
  - None
- Web comments from:
  - None

ACD consultation comments

Comments from consultees, clinical expert, and patient and professional organisations

- Disappointed with the negative recommendation
- Clinical evidence shows pembrolizumab is clinically effective
- Slowing clinical deterioration means reduced cost for primary care input, palliative interventions, such as radiotherapy, ureteric stents with attendant hospital admissions, blood transfusions for haematuria etc.
- No improvement in survival from metastatic bladder cancer for 20 years, so high unmet need for new treatment options
- Hope early reconsideration can be made if/when further data can be provided by the company

Company's new evidence

- 4 months additional data from KEYNOTE-045 for the overall population
- New confidential discount on the list price of pembrolizumab
- Gompertz extrapolation curve for progression-free survival extrapolation
- Updated company base case (no other changes from company ACM1 assumptions)
- Scenario analysis incorporating committee's preferred assumptions and updated clinical evidence for the overall population
- Rationale for not using committee's preferred utility values

	Incr. Costs	Incr. QALY	ICER	Change
Company ACM1 base case	**£39,115**	**0.85**	**£45,833**	-
Company ACM2 base case	£43,620	0.90	£48,601	+£2,768
Company ACM2 base case + committee preferred assumptions	£43,674	0.88	£49,644	+£3,811

Source: Adapted from table 1 and 3, page 2 and 4, MSD additional analyses

Utility values
Company comments

- Time-to-death approach is appropriate:
  - Precedent set in the appraisal of pembrolizumab in NICE TA447 (Pembrolizumab for untreated PD-L1+ metastatic non-small cell lung cancer)
  - Utility value at 360 days or more before death was 0.778, which is below estimate for UK population norm of 0.79 as reported in TA447
  - Survey of people and caregivers indicates pembrolizumab often has no or mild adverse events and high quality of life compared to chemotherapy is plausible
  - Sample sizes consistently higher than accepted by committee in TA447
  - Approach to missing data is consistent with previous appraisals
- If utilities are progression-based, values should not be pooled
  - When using time-to death approach no statistically significant difference, but progression-based values are significantly different ($p<0.05$)
  - Differences greater than minimally important difference (MID) in EQ-5D scores for cancers, considered to be 0.08 for UK-based scores

Utility values

Recap of values submitted at ACM1

- ERG still prefer pooled progression-based values, they highlight that major differences in patient experience are captured by adverse event disutility

	Pembrolizumab	UK SOC	Pembrolizumab + UK SOC pooled	ID995 pooled (nivolumab)
Time to death based (days) – Company preferred assumption				
≥360	0.765	0.823	0.780	-
180-360	0.686	0.673	0.680	-
90-180	0.566	0.595	0.578	-
30-90	0.457	0.414	0.435	-
<30	0.336	0.337	0.337	-
Progression based – ACM1 committee preferred assumption				
Pre-progression	0.757	0.709	0.741	0.736
Post-progression	0.680	0.554	0.647	0.623
Source: adapted from table 31, page 108, ERG report; ID995 economic model				

⊙ ***Any change in committee's preferred assumption from ACM1?***

Adverse events
Company's new evidence

- Company consider only include Grade 3+ adverse events with an incidence of at least 5% is in line with previous NICE appraisals
- Company explored including the costs of all Grade 3+ adverse events
- ERG highlights that:
  - Changes to adverse event disutility and duration have not been included
  - Any adverse events included, such as those not attributed to treatment
  - Impact may increase if scenario extended to lower grade adverse events

	Incr. Costs	Incr. QALY	ICER	Change
Company base-case	**£43,620**	**0.90**	**£48,601**	**-**
Grade 3+ AEOSIs in both treatment arms	£43,675	0.90	£48,661	+£60

Source: table 13, page 11, MSD additional analyses

ERG preferred analysis

- For their preferred analysis the ERG use:
  - Committee preferred assumptions from ACM1
  - Additional KEYNOTE-045 data submitted by the company
  - Alternative progression-free survival extrapolation
  - ERG's ACM1 preferred overall survival extrapolation

	Incr. Costs	Incr. QALY	ICER	Change
Company ACM2 base case	**£43,620**	**0.90**	**£48,601**	**-**
Company ACM2 base case + committee preferred assumptions	£43,674	0.88	£49,644	+£1,043
ERG ACM2 preferred analysis	£42,994	0.81	£52,892	+£4,291

Source: Adapted from table 13, page 35, ERG addendum

Progression-free survival extrapolation
ERG comments (I)

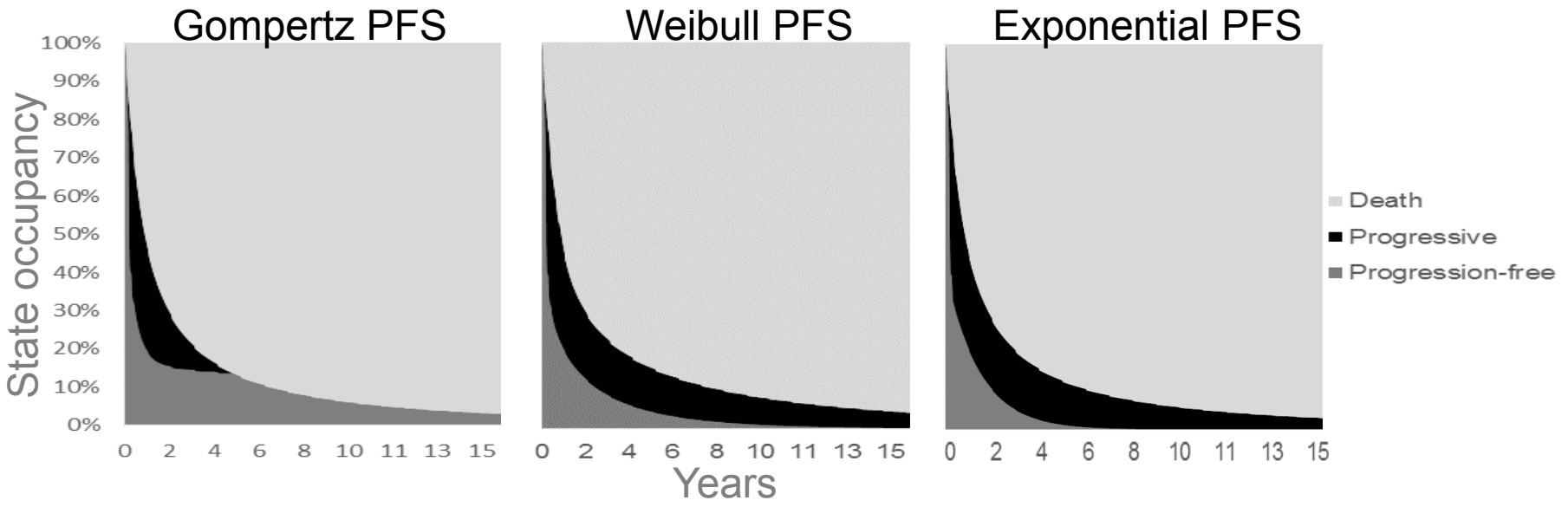
- Original company submission used an exponential extrapolation
- New company base case uses Gompertz curve (no justification)
- The Gompertz curve would assume that all people who progress after pembrolizumab would die by year 6
- ERG prefer the Weibull distribution, which produced the most plausible balance of pre- and post-progression survival benefit

	Incr. Costs	Incr. QALY	ICER	Change
ERG ACM2 preferred assumptions	**£42,994**	**0.81**	**£52,892**	**-**
ERG ACM2 preferred assumptions + Gompertz PFS curve	£43,862	0.90	£48,886	-£4,006
ERG ACM2 preferred assumptions + Exponential PFS curve	£42,793	0.79	£53,941	+£1,049

Source: Company model; Table 16, page 35, ERG addendum post ACD

Progression-free survival extrapolation
ERG comments (II)

Pembrolizumab markov trace, ERG preferred assumptions



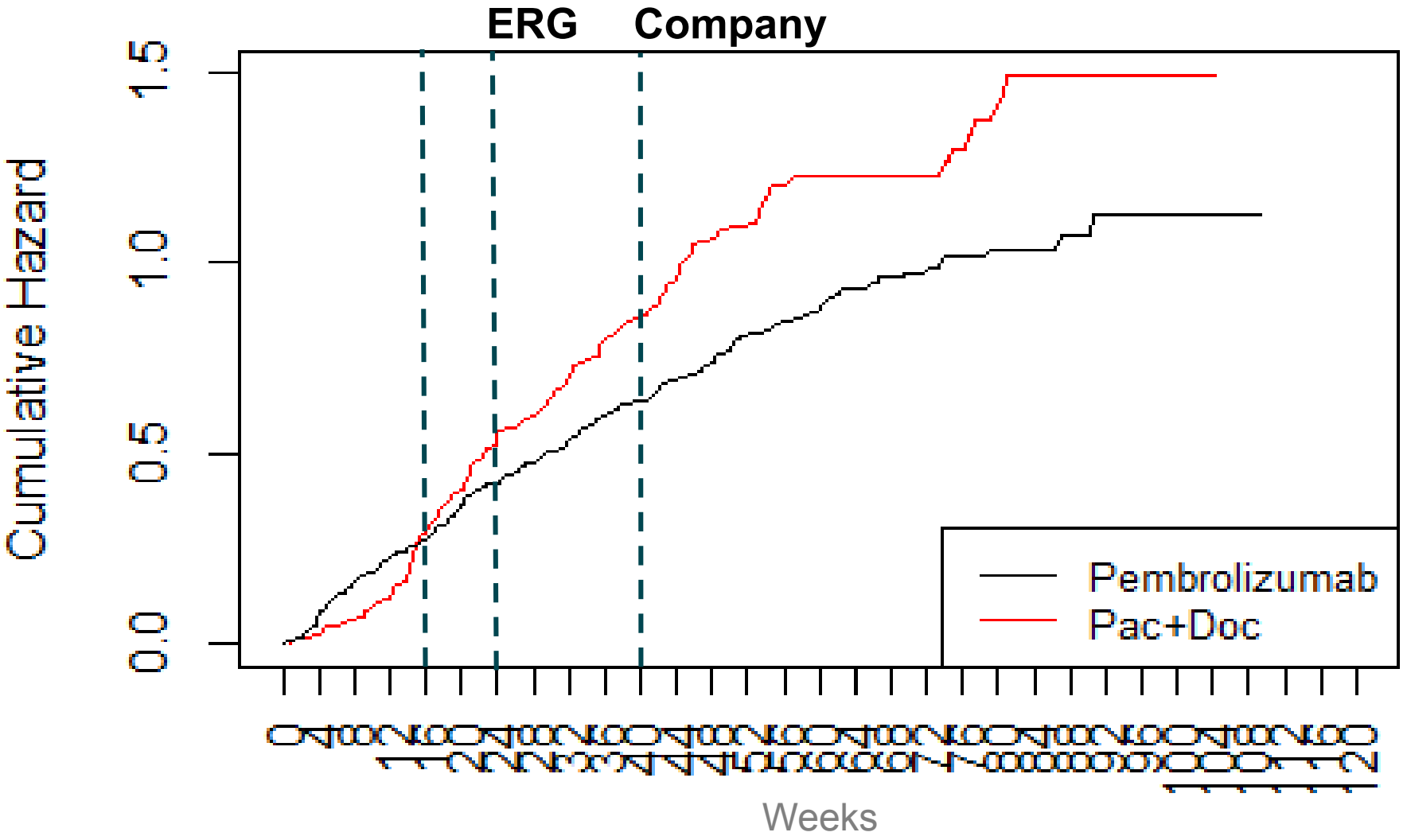
	Pembrolizumab		UK SOC	
	AIC	BIC	AIC	BIC
Exponential	376.6	379.0	308.4	310.3
Weibull	373.1	377.9	308.9	312.5
Gompertz	367.6	372.3	309.7	313.3

Sources: Pembrolizumab markov trace, company model; table 2, page 7, company post ACD clari response

⊙ ***What is the most plausible progression-free survival extrapolation?***

Overall survival extrapolation

Updated OS cumulative hazard plot



Source: Adapted from figure 1, page 1, MSD post ACD clari response

Overall survival extrapolation
Company and ERG extrapolation rationales

Assumption	Rationale
Company's preferred assumption	
Week 40 cut-off	• Clear change in the slope of the cumulative hazards • Sufficient remaining patients to fit parametric curves (~53% and 40% alive in pembrolizumab and UK SOC arms)
Log-normal curve	• Best statistical fit of the curves with plausible survival estimates • Prefer a log-logistic curve if a 16-week cut-off were chosen based on better statistical fit
ERG's preferred assumptions	
Week 24 cut-off	• Closer to the point at which the hazards cross • Gives more data for the extrapolation • Noticeable change in the gradient prior to this point
Log-logistic curve	• 5 year UK standard of care OS rate was considered most plausible by ERG • Of the distributions with plausible survival estimates, log-logistic had lowest AIC for pembrolizumab arm

Overall survival extrapolation
Goodness of fit

- Many curves within the estimated 2–11% 5-year OS accepted by committee

Scenario	UK standard of care					Pembrolizumab	
	2-year OS	5-year OS	10-year OS	AIC	BIC	AIC	BIC
16 week cut-off time-point							
Log-logistic	15.8%	6.2%	3.0%	729.4	735.0	725.2	731.0
Log-normal	17.0%	6.6%	2.8%	731.0	736.5	725.8	731.6
Gamma	14.8%	3.8%	0.9%	731.7	740.0	727.2	736.0
24 week cut-off time-point							
Gompertz	15.9%	9.2%	8.1%	475.8	480.8	863.9	870.2
Log-logistic	13.4%	4.2%	1.7%	473.3	478.2	864.7	871.0
Log-normal	13.9%	3.7%	1.1%	470.1	475.1	866.0	872.4
Gamma	17.1%	9.3%	6.1%	468.4	475.8	867.0	876.5
40 week cut-off time-point							
Weibull	15.4%	3.9%	0.7%	241.8	245.8	515.6	521.4
Log-logistic	16.2%	7.8%	4.5%	240.9	245.0	514.1	519.9
Log-normal	16.6%	8.2%	4.5%	239.1	243.2	512.0	517.8

Source: Company model; Table 1, page 6, company post ACD clari response

Overall survival extrapolation

Impact on the ICERs

Scenario	Pembrolizumab vs UK SOC			
	Incr. costs	Incr. LYG	Incr. QALYs	ICER
16 week cut-off time-point; ERG preferred assumptions				
Log-logistic	£43,322	1.30	0.84	£51,490
Log-normal	£44,847	1.52	0.97	£46,150
Gamma	£43,478	1.32	0.86	£50,583
24 week cut-off time-point; ERG preferred assumptions				
Gompertz	£48,464	2.05	1.28	£37,989
Log-logistic	£42,994	1.25	0.81	£52,892
Log-normal	£45,104	1.56	1.00	£45,303
Gamma	£36,662	0.33	0.27	£136,233
40 week cut-off time-point; ERG preferred assumptions				
Weibull	£38,866	0.65	0.46	£85,031
Log-logistic	£40,926	0.95	0.63	£64,872
Log-normal	£42,533	1.18	0.77	£55,314

Source: Company model

⊙ ***What is the most plausible overall survival extrapolation?***

Sensitivity analyses

	Incr. Costs	Incr. QALY	ICER	Change
ERG ACM2 base case	**£42,994**	**0.81**	**£52,892**	**-**
Utilities; ERG ACM2 preferred assumptions				
Unpooled, progression-based	£42,994	0.96	£44,710	-£8,182
Pooled, time-to-death based	£42,994	0.94	£45,871	-£7,021
Utilities from ID995 – nivolumab	£42,994	0.79	£54,248	+£1,356
Continued treatment effect; ERG ACM2 preferred assumptions				
3 year treatment effect	£40,419	0.59	£68,225	+ £15,333
5 year treatment effect	£41,607	0.70	£59,729	+ £6,837
10 year treatment effect	£42,620	0.78	£54,455	+ £1,563
Continued treatment effect; Company preferred OS curve; Weibull PFS curve				
3 year treatment effect	£41,227	0.66	£62,675	+£9,783
5 year treatment effect	£41,830	0.71	£58,905	+£6,013
10 year treatment effect	£42,348	0.75	£56,170	+£3,278

Source: Company model; Table 16, page 35, ERG addendum post ACD

Cancer Drugs Fund

- When the uncertainty in clinical and cost effectiveness data is too great to recommend for routine use, the committee can recommend in CDF if:
  - ICERs have plausible potential to be cost-effective
  - Clinical uncertainty can be addressed through collection of outcome data from patients treated in the NHS
  - Data collected (including research underway) will be able to inform subsequent update (normally within 24 months)
- MSD would consider the option of a recommendation into the CDF
- MSD expects the availability of a final data cut from the KEYNOTE-045 study in [redacted]

Key issues for consideration

- Are there any changes in committee's preferred assumptions from ACM1?
  - Utility values?
  - Progression-free survival extrapolation?
  - Time-point and curve for extrapolation of overall survival?
- Most plausible ICER for pembrolizumab
- Could pembrolizumab be recommended for routine commissioning or through the CDF?