All confidential data redacted ***

NICE National Institute for Health and Care Excellence

SLIDES FOR PUBLIC

Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy [ID1536]

Post-appeal slides

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Company: Merck Sharp & Dohme (MSD)

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Summary of scope and history

Population (marketing authorisation)

Treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy

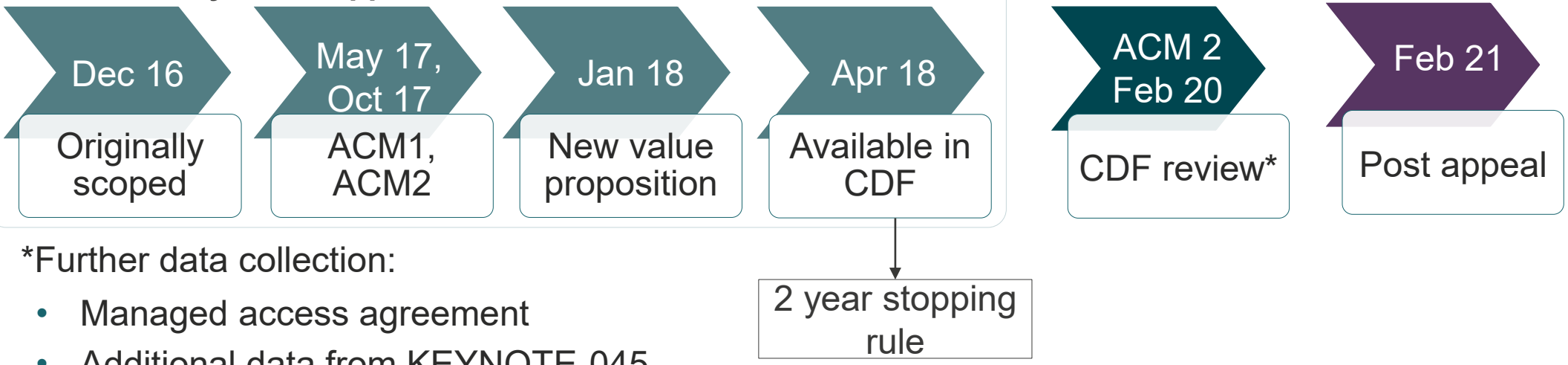
Comparators

Docetaxel, paclitaxel, best supportive care

Outcomes

Includes overall survival and progression-free survival

TA519: History of the appraisal



*Further data collection:

- Managed access agreement
- Additional data from KEYNOTE-045

Summary of trial

KEYNOTE-045	Phase III RCT, n = 542
Population	People with metastatic or locally advanced or 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 standard of care [SoC])
Primary outcome	OS and PFS (per RECIST 1.1)

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)

ECOG: Eastern Cooperative Oncology Group; RECIST: Response Evaluation Criteria in Solid Tumours

Summary of appeal panel decision

Appeal was upheld on 3 grounds

Appeal point		Conclusion
1a.1 Treatment effect duration	Inconsistent with TA525 → in breach of the Methods Guide & principle of procedural fairness	Insufficient justification of why approach to duration of treatment effect differed to TA525
1a.2 Re-treatment costs	Procedurally unfair to introduce paragraph 3.19 ("The costs of pembro are likely underestimated in the model") at a late stage	Company did not have a satisfactory opportunity to address this point before the FAD was published.
2.5 Treatment switching adjustment	The conclusion that new data from KEYNOTE-045 "shows the 2-stage method may not be appropriate, and the unadjusted method should also be taken into account" results from a flawed and unreasonable interpretation of the evidence	• General acceptance that unadjusted data were biased. • Cttee did not consider a range of acceleration factors. • Not reasonable to give equal weight to a method that was previously agreed to be the least appropriate.

Previous FAD conclusions

Issue (FAD section)	Conclusion	Cost-effectiveness results presented
A 3 to 5-year treatment effect duration from start of pembro is plausible (3.18)	Accepted by appeal panel	ICERs with both 3 and 5-year treatment effect
There are 3 plausible OS extrapolations (3.20)	Accepted by appeal panel	ICERs with all 3 plausible OS extrapolations. Company did not appeal this point but prefers log-logistic function for OS.

Key issues

- Justify the appropriateness of the conclusion about treatment effect duration differing with the conclusion in TA525 (FAD 3.18).

- Is the committee satisfied that the company has had an opportunity to respond to retreatment issue? If so, what implications does this have for decision making?

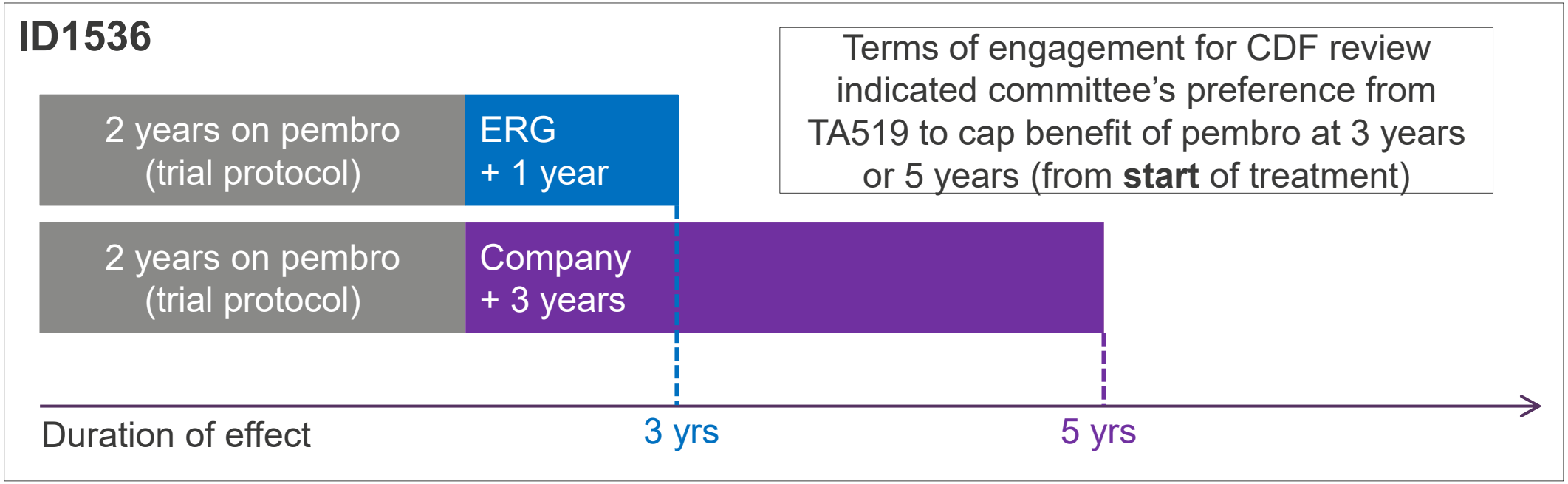
- Which 2-stage treatment switching adjustment is the most appropriate for decision making?

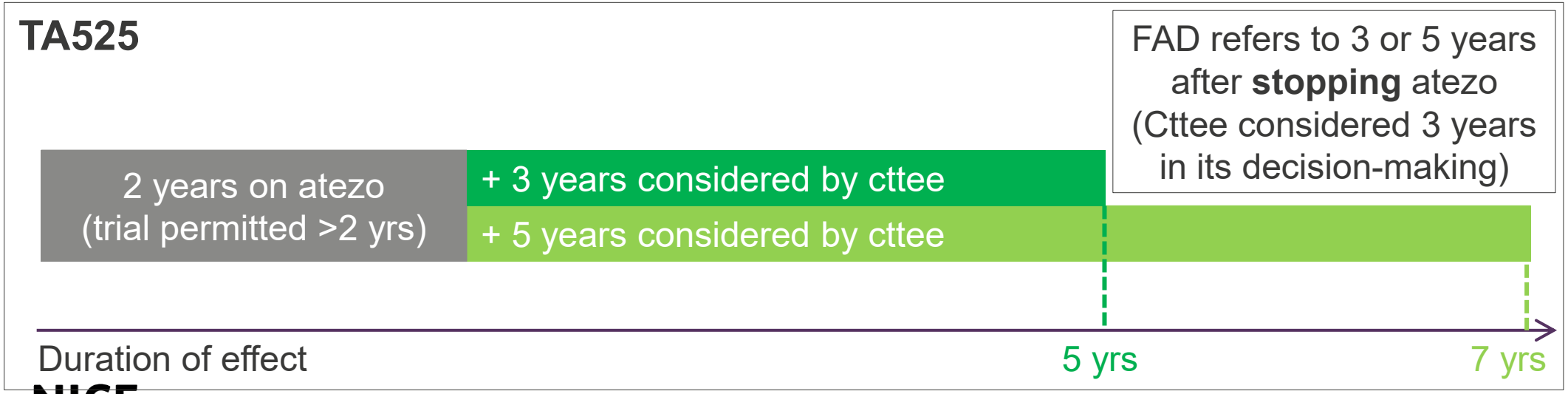
Appeal 1a.1 – Panel conclusions

- Ground 1a.1 – Fundamental differences with the approach taken in TA525 evidence an inconsistent methodology, in breach of the Methods Guide and the principle of procedural fairness
  - … Notwithstanding that the Committee's approach can be regarded as reasonable looked at in isolation, the fact that different approaches have been taken in past relevantly similar appraisals means that, if a different approach is now to be taken, that departure from past approach or practice must be explained, and not only the reasons for the decision in isolation. …

Appeal 1a.1 Consistency of treatment effect conclusion

Insufficient justification of why approach to duration of treatment effect differed to TA525





Appeal 1a.1 Consistency of treatment effect conclusion

Company: prefers 5-yr treatment effect cap after start of pembro (consistent with atezo '2+3')

Modelling of treatment duration should be equivalent across the 2 appraisals:

- Pembro & atezo are both immune checkpoint monoclonal antibodies with same indication & mechanism
- 2-year stopping rule for pembro in KEYNOTE-045, NICE recommends atezo for 2 years and max 25 month follow up in IMvigor211
- No material difference between 2 appraisals→ same approach should be used

Slide amended post ACM3

Appeal 1a.1 Consistency of treatment effect conclusion

ERG: prefers 3-yr effect cap after start of pembro ('2+1') when Weibull used for ToT	
In atezo TA525: – treatment effect duration appears unsupported by strong evidence – no 2-year treatment cap in IMvigor211 but limited follow up – atezo was allowed to continue after progression, so benefit may have lasted longer	In pembro ID1536: – extended follow up from KEYNOTE-045 suggests treatment benefit unlikely to be sustained for 5 yrs – some patients were retreated with pembro after progression (no retreatment with atezo) – very few events after 3 years (1 death in unadjusted UK SoC arm, none after adjustment) – In model: [redacted]% of pts alive at 2 yrs are predicted to still be on treatment, vs. 52% in TA525

NICE technical team	
In atezo TA525: – Company provided following scenarios: 5-yr ('2+3'), 7-yr ('2+5') and lifetime treatment effect – Cttee's preferred ICERs within acceptable range so no further analyses needed for decision-making	In pembro ID1536 : – Company provided following scenarios: 3-yr ('2+1') and 5-yr ('2+3') treatment effect

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What differences between the appraisals caused the committee to reach a different conclusion about treatment effect duration?

Appeal 1a.2 – Panel conclusions

- Ground 1a.2 – It is procedurally unfair to have introduced paragraph 3.19 (“The costs of pembrolizumab are likely underestimated in the model”) in the FAD at a very late stage, without explanation or any opportunity to respond
  - …The company should be given a chance to respond to the committee’s concern that the costs of pembrolizumab may have been under-estimated in the model. The company’s response should be considered in reaching a final decision…

Appeal 1a.2 Cost of retreatment

Company did not have satisfactory opportunity to address this before FAD was published

Background

FAD 3.19: pembro costs likely to be underestimated because a small proportion were retreated and these costs not included in the model

Company

- In KEYNOTE-045 (2018 data cut), 10 patients (4%) in pembro arm were retreated:
  - 8 completed initial treatment; 1 didn't but had complete response; 1 stopped initial course for unknown reasons
  - **Median** retreatment cycles: 10 (min 3; max 18) → 30 weeks
- Provided "conservative" scenario analysis: one-off retreatment cost at **24 weeks**

ERG

- Retreated n=10 estimated to be [redacted]% of pts alive at 2 yrs or [redacted]% alive at 3 yrs
- 24 weeks appears to be based on earliest retreatment → not representative of group
  - 8/10 completed full initial 2-years, so assume average retreatment starts after 2-yrs + allow 1 year for progression detection. Others may have been retreated with further follow up
  - Pessimistic assumption of **mean** cycles = 12 cycles has little effect on ICER
  - Prefers to apply cost of 10 cycles at **3 years**, but timing has little effect on ICER

Is the committee satisfied that the company has had an opportunity to respond to the retreatment cost issue?

Appeal 2.5 – Panel conclusions

- Ground 2.5 – The conclusion that new data from KEYNOTE-045 “shows the 2-stage method may not be appropriate, and the unadjusted method should also be taken into account” results from a flawed and unreasonable interpretation of the evidence
  - …The committee should re-consider how potential biases in the 2-stage method could be addressed and re-consider the relative weight given to the 2-stage method versus other models in their decision-making.

Appeal 2.5 The acceleration factor

Committee did not consider a range of acceleration factors. Not reasonable to give equal weight to unadjusted approach (previously agreed to be the least appropriate)

Background

- In KEYNOTE-045, 40 (22%) patients from UK SoC population switched to anti PD-1/PD-L1
- In TA519, 2-stage method (2SM) to adjust for switching was accepted using AF=3.86 (applied to n=14)
- In ID1536, 2SM had larger impact on OS so existing uncertainties (e.g. selection bias, assuming average adjustment for all switchers) were more important:
  - AF=5.37, applied to n=25
  - FAD 3.6: true OS benefit probably between adjusted and unadjusted analyses
  - Unadjusted analyses were least appropriate in TA519

Company scenarios	ERG
Base case AF=5.37 (no re-censoring)	Likely over-adjusts (see next slide)
AF=3.23 (lower 95% CI; more conservative for pembro)	Most appropriate AF (see next slide)
AF=5.37 (from ID1536) & apply re-censoring	Considerably reduces follow up, may not be useful
AF=5.32 (include patients having vinflunine)	Vinflunine not licensed in England
AF=5.37 (based on n=25 switched at progression) applied to all 40 switching (including n=15 switched at different times)	Does not address previous ERG concern that n=15 not included in calculation of AF

ERG	Company has not provided information for ERG to verify AF calculation and output

Appeal 2.5 The acceleration factor

ERG

- AF calculated based on 25 switchers after progression, but was not applied to further 15 who switched at different times. Company did not provide an established rule for switching.
- ERG recreated patient level data → OS in 25 patients affected by 2SM, [redacted] died and [redacted] censored. Expected some switchers not to benefit (in line with KEYNOTE-045 trial).
- Company reports [redacted]% of switchers had post-progression survival >4.5 months, which is higher than 65% in original pembro arm who were alive at 4.5 months when pembro started showing OS benefit – may be due to different comparators.
- Additional benefit is unlikely to be due to switching alone. Company tried to adjust for other factors by including covariates (e.g. age, gender, ECOG).
- AF=5.37 implies switchers would have had shorter post-prog survival than the average patient → attributes too much benefit to switching → likely over-adjusts control arm
- Unable to validate the company's adjustment for confounding factors (no data or output)
- **Prefers more conservative AF=3.23**

Mean post-progression survival, months		AF 5.37	AF 3.23
Switchers (after 2SM)	…due to switching	[redacted]	[redacted]
	…not due to switching	[redacted]	[redacted]
Whole SoC arm		7.2	7.3

What AF should be used in the 2-stage adjustment for treatment switching?

Slide amended post ACM3

Company vs. ERG assumptions

Model input	TA519	Cttee preferred ID1536	Post appeal	
			Company base case	ERG analyses
Treatment effect duration from **starting** pembro	Lifetime effect is implausible (3 years after **stopping** pembro plausible)	3 or 5 years	5 years	3 years if Weibull model used for ToT
Treatment switching adjustment	2SM (AF 3.86, n=14)	True OS benefit between 2SM (AF 5.37, n=25) & unadjusted ITT	AF 5.37	AF 3.23
Retreatment costs	Not included	Yes, should be added	Scenario analysis	One-off cost at 3 years
OS	Both lognormal and log-logistic plausible	Log-logistic, lognormal & generalised gamma plausible	Log-logistic	ICERs with all 3 plausible OS functions

Abbreviations: AF, acceleration factor; OS, overall survival; 2SM, 2-stage method; ToT, time on treatment

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Company cost-effectiveness results (new PAS)

	Total			Incremental		Deterministic ICER
Technology	Costs	LYG	QALYs	Costs	QALYs	
Company base case (AF 5.37, 5 yr treatment effect)						
UK SoC	[redacted]	[redacted]	[redacted]			
Pembro	[redacted]	[redacted]	[redacted]	£30,933	0.72	£43,181*
Company scenario analyses						
1. AF 5.37, 3-yr treatment effect				£29,934	0.63	£47,599
2. AF 3.23, 5-yr treatment effect				£30,608	0.69	£44,532
3. AF 5.37 and apply re-censoring, 5-yr effect				£31,466	0.77	£41,038
4. AF 3.23 and 3-yr treatment effect				£29,457	0.59	£50,247
5. AF 5.37 and apply re-censoring, 3-yr effect				£30,202	0.66	£46,063
6. One-off cost for retreatment at 24 weeks				£32,278	0.72	£45,060
ERG alternative 6: retreatment cost at 3 years				£32,166	0.72	£44,903

*PSA ICER £43,834

ERG & NICE scenarios (new PAS)

Deterministic ICERs reported – ERG consider these to be consistent with probabilistic results

Acceleration factor	Effect duration	OS model	Retreatment costs		
			At 24 weeks	At 3 years	Not included
5.37	5 years	Log-logistic	£45,060	£44,903	£43,181 [C]
		Lognormal	£47,110 [N]	£46,943 [N]	£45,114 [N]
		Gen. gamma	£47,731 [N]	£47,562 [N]	£45,703 [N]
	3 years	Log-logistic	£49,739	£49,561	£47,599
		Lognormal	£54,295	£54,095	£51,899
		Gen. gamma	£51,121	£50,936	£48,904
3.23	5 years	Log-logistic	£46,490	£46,327	£44,532
		Lognormal	£49,268 [N]	£49,091 [N]	£47,152 [N]
		Gen. gamma	£48,330 [N]	£48,158 [N]	£46,273 [N]
	3 years	Log-logistic	£52,543	£52,351	£50,247
		Lognormal	£58,542	£58,323	£55,910
		Gen. gamma	£49,029	£48,855	£46,933

[C] Company base case

[N] Obtained by NICE (checked by ERG); ERG does not believe a 5-yr effect is plausible if a Weibull ToT model is used

Key issues

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