

# Chair's presentation

Carfilzomib for previously treated multiple myeloma

3<sup>rd</sup> Appraisal Committee meeting

Committee C

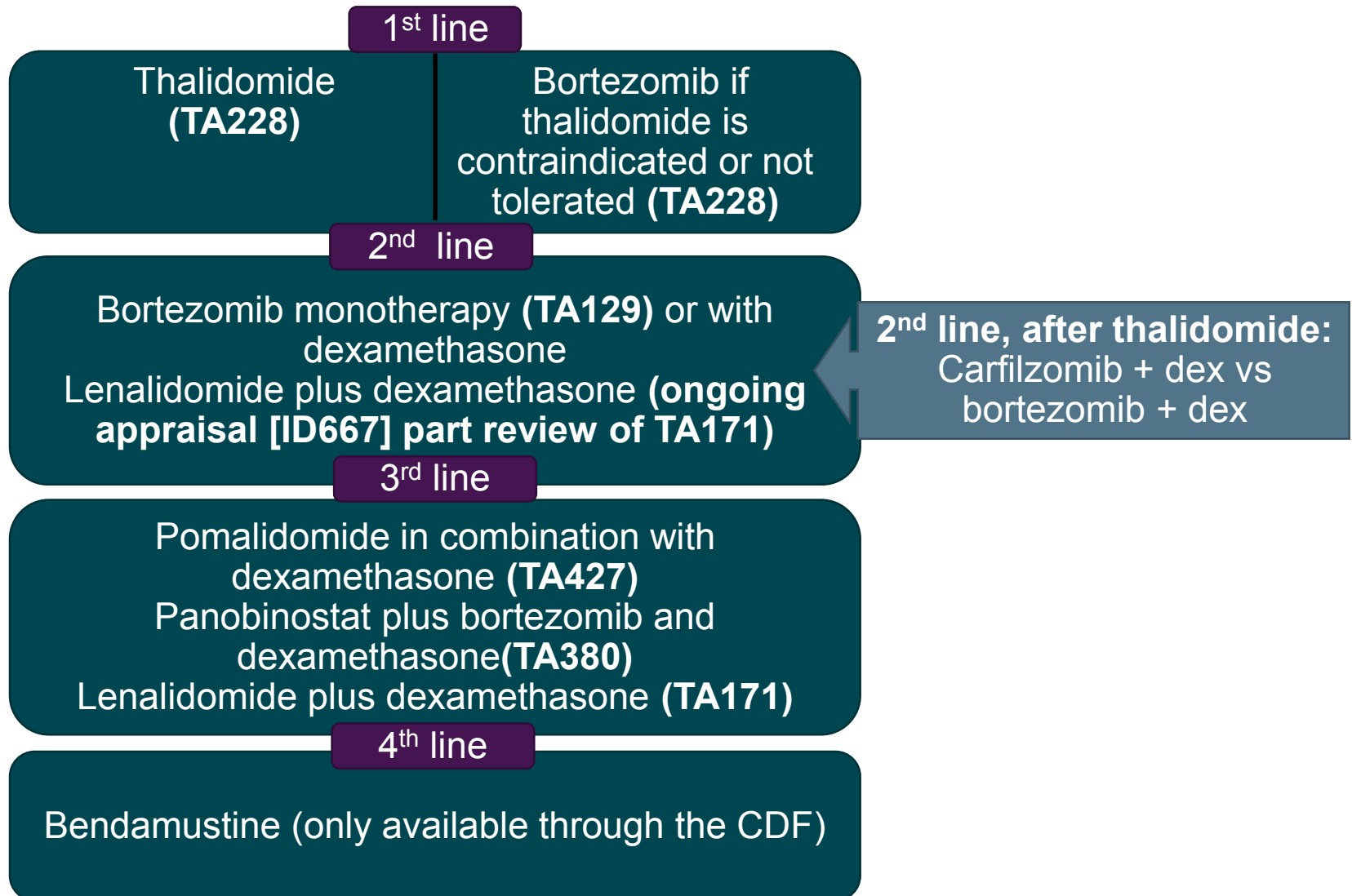
Lead team: Peter Selby and Andrea Manca

ERG: BMJ-TAG

Company: Amgen

# Carfilzomib's placement and comparison for consideration - 3<sup>rd</sup> meeting

## 1 prior therapy no prior bortezomib subgroup



# Background and appraisal history

- 1<sup>st</sup> committee discussion: 15<sup>th</sup> October 2016
  - ACD: carfilzomib not recommended
- 2<sup>nd</sup> committee discussion: 12<sup>th</sup> February 2017
  - FAD: carfilzomib not recommended at 3<sup>rd</sup> line but recommended in CDF at 2<sup>nd</sup> line – ongoing ENDEAVOR trial could resolve uncertainty over the survival projections and inform on the choice of parametric distribution
  - FAD suspended: NICE made aware the ENDEAVOR trial had informed on final OS endpoint and no more data will be collected – CDF no longer appropriate
- 3<sup>rd</sup> committee discussion: 12<sup>th</sup> April 2017
  - NICE and Chair agree to allow the company to submit new evidence

# Background and appraisal history: Committee considerations

- Need for new treatment at 2<sup>nd</sup> and 3<sup>rd</sup> relapse of disease
- Effectiveness estimates were uncertain – based on post-hoc subgroup analysis
  - Satisfied that choice of covariates was sufficiently explored
- Economic model: preferred assumptions
  - Cost and effectiveness of bortezomib should reflect its licensed dosing schedule – maximum 8 cycles, including PAS
  - Utilities mapped from trials
- Overall survival extrapolations were uncertain
- Most plausible ICER
  - 2<sup>nd</sup> line: in the range of £26,300 to £44,800 per QALY gained
    - Between company and ERG estimates (Weibull vs Gompertz extrapolations)
  - 3<sup>rd</sup> line: uncertain, and above £41,400 per QALY gained
- End of life criteria were not met

# Background and appraisal history: Conclusions

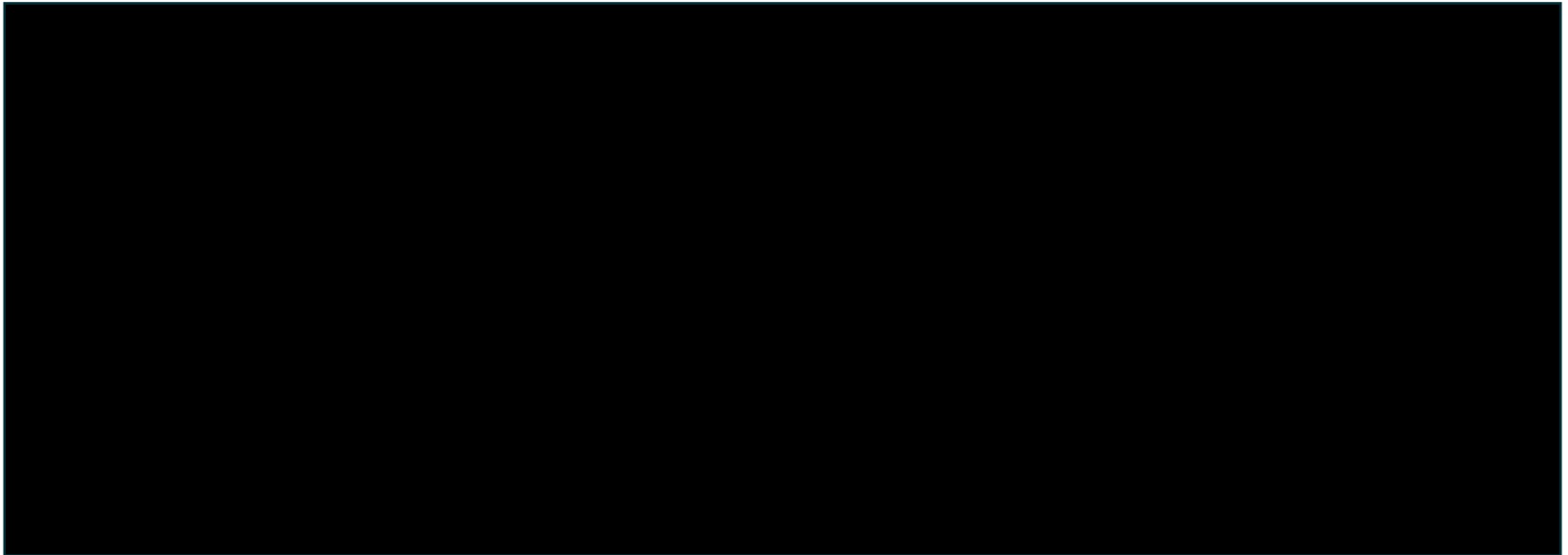
Carfilzomib in combination with lenalidomide and dexamethasone was not a cost effective use of NHS resources for people who have had 2 prior therapies and not had prior carfilzomib or lenalidomide (i.e. 3<sup>rd</sup> line)

**Carfilzomib in combination with dexamethasone is recommended for use within the Cancer Drugs Fund as an option for treating multiple myeloma in adults, only if they have had 1 prior therapy and have not had prior bortezomib (i.e. 2<sup>nd</sup> line), and the conditions in the managed access agreement for carfilzomib are followed**

- CDF recommendation no longer appropriate
- Company presents new evidence at this meeting

# Clinical effectiveness: new overall survival evidence

**2<sup>nd</sup> line, 1 prior therapy/no prior bortezomib post-hoc subgroup**



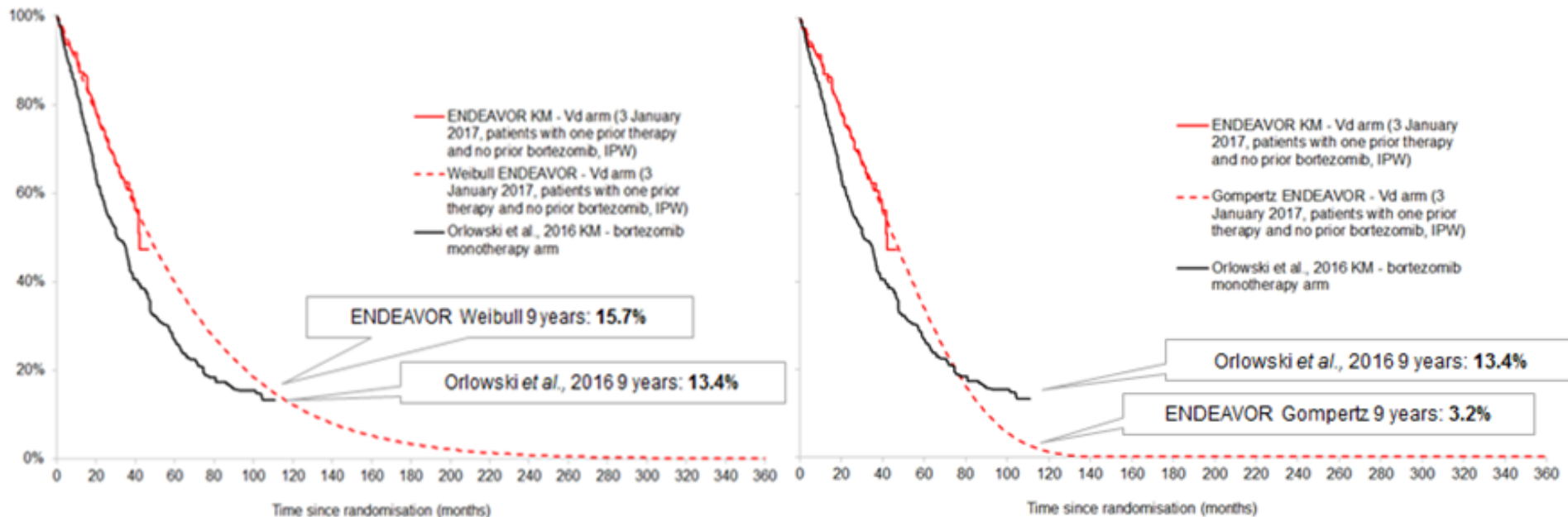
- ERG commented that the new OS data are based on stepwise selection of covariates – uncertain
  - Previously discussed alternatives (including LASSO): ERG present scenario analysis based on unadjusted HRs
  - *Committee was satisfied that the choice of covariates was sufficiently explored and the efficacy estimates were reasonable for decision making*

# New Kaplan-Meier curves and extrapolations

## 1 prior therapy and no prior bortezomib subgroup



# Validation of Bort/dex extrapolation – Orłowski trial



- Study of Bort monotherapy vs Bort plus pegylated doxorubicin, patients with  $\geq 1$  prior therapy
  - Bort mono arm presents a conservative comparison with Bort/dex in ENDEAVOR
- Company concluded:
  - Gompertz is clinically implausible for Bort/dex – survival at 9 years 3.2% vs 13.4% in Orłowski trial
  - Weibull more comparable to Orłowski at 9 years: 15.7% vs 13.4%
- 11/12 clinical experts supported plausibility of Weibull over Gompertz



# ERG comments on new company evidence

Agree that the Weibull appears to give a more plausible projection than the Gompertz but highlight:

- No analysis was provided with other standard distributions so the most appropriate curve could lie between the Weibull and Gompertz
- Orłowski trial is not directly comparable to ENDEAVOR but agree patients are likely to have a worse prognosis in Orłowski
  - Bort monotherapy rather than with dexamethasone
  - Median duration of treatment was shorter (105 days compared to 188 days in ENDEAVOR)
- 9 year estimate is from the tail end of the curve where numbers at risk are considerably small
  - Survival at 7.8 years is more reliable – shows 15% survival in Orłowski compared to 24% with the Weibull extrapolation

# Company's new base case results

Included committee preferred assumptions

- Utilities mapped from ENDEAVOR trial
- Bortezomib complex PAS estimated at 15%
- Capping treatment of bortezomib to 8 cycles and adjusting efficacy (estimated at 46.5% with new OS data – 34.9% with old data)

	<b>Total costs</b>	<b>Total QALYs</b>	<b>Inc. costs</b>	<b>Inc. QALYs</b>	<b>Inc. ICER</b>
<b>Bort/dex</b>	£69,626	2.20			
<b>Car/dex</b>	£118,077	3.96	£48,451	1.75	<b>£27,629</b>
<b>Company's old equivalent ICER with the same assumptions - £28,797</b>					

# ERG comments on new company evidence and exploratory analysis

- Agree with the company's Weibull extrapolation
- Have concerns with the analysis used to adjust for bortezomib's efficacy – matched-adjusted indirect comparison is unreliable
  - ERG removed adjustment of bortezomib efficacy from the company's new base case but still capped costs to 8 cycles

	<b>Total costs</b>	<b>Total QALYs</b>	<b>Inc. costs</b>	<b>Inc. QALYs</b>	<b>Inc. ICER</b>
<b>Bort/dex</b>	£75,417	2.91			
<b>Car/dex</b>	£118,077	3.96	£42,660	1.05	<b>£40,744</b>

# ERG scenario analyses

		Company model (Bort efficacy adjusted)	ERG model (Bort efficacy not adjusted)	
<b>Covariate selection</b>	Base case: step-wise	£27,629	£40,744	Effect of covariate selection: + £2k – £8k
	Scenario: unadjusted HR	£29,995	£48,598	
<b>Extrapolation</b>	Base case: Weibull	£27,629	£40,744	Effect of extrapolation function: + £11k – £19k
	Scenario: Gompertz	£39,052	£59,764	
		Effect of Bort efficacy adjustment: + £13k – £21k		

# ERG scenario analysis

## Adjusting bortezomib efficacy

- ERG reiterated that the company MAIC is uncertain
- Explored effect of reducing treatment effect for bortezomib efficacy after 8 cycles in 10% increments

Increase in HR	ICER: Car/dex vs Bort/dex
0%	£40,744
10%	£35,324
20%	£31,922
30%	£29,612
40%*	£27,958

*\*Note: Estimated by NICE using the company's new model*

- Company MAIC suggests a reduced benefit of 46.5% for OS
  - *Note: at previous discussion, reduction in OS benefit from MAIC was 34.9%; MAIC has been updated based on latest OS data*

# Key considerations

- Clinical plausibility of the extrapolations
  - Most appropriate parametric extrapolation curve: Weibull or Gompertz
- Modelling assumptions
  - Is it still appropriate to adjust for Bort efficacy if costs are capped to 8 cycles?
    - Committee previously concluded this was appropriate
- Most plausible ICER for carfilzomib in combination with dexamethasone compared to bortezomib in combination with dexamethasone
- Previous committee conclusion remains unchanged
  - Carfilzomib in combination with lenalidomide and dexamethasone is not recommended as an option for previously treated multiple myeloma in adults who have had 2 prior therapies