Chair's presentation

Carfilzomib for previously treated multiple myeloma

3rd Appraisal Committee meeting
Committee C
Lead team: Peter Selby and Andrea Manca
ERG: BMJ-TAG
Company: Amgen

Carfilzomib's placement and comparison for consideration - 3rd meeting

1 prior therapy no prior bortezomib subgroup

1st line

Thalidomide **(TA228)**

Bortezomib if thalidomide is contraindicated or not tolerated **(TA228)**

2nd line

Bortezomib monotherapy **(TA129)** or with dexamethasone
Lenalidomide plus dexamethasone **(ongoing appraisal [ID667] part review of TA171)**

2nd line, after thalidomide: Carfilzomib + dex vs bortezomib + dex

3rd line

Pomalidomide in combination with dexamethasone **(TA427)**
Panobinostat plus bortezomib and dexamethasone**(TA380)**
Lenalidomide plus dexamethasone **(TA171)**

4th line

Bendamustine (only available through the CDF)

Background and appraisal history

- 1st committee discussion: 15th October 2016
  - ACD: carfilzomib not recommended
- 2nd committee discussion: 12th February 2017
  - FAD: carfilzomib not recommended at 3rd line but recommended in CDF at 2nd 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
- 3rd committee discussion: 12th 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 2nd and 3rd 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
  - 2nd line: in the range of £26,300 to £44,800 per QALY gained
    - Between company and ERG estimates (Weibull vs Gompertz extrapolations)
  - 3rd 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. 3rd 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. 2nd 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

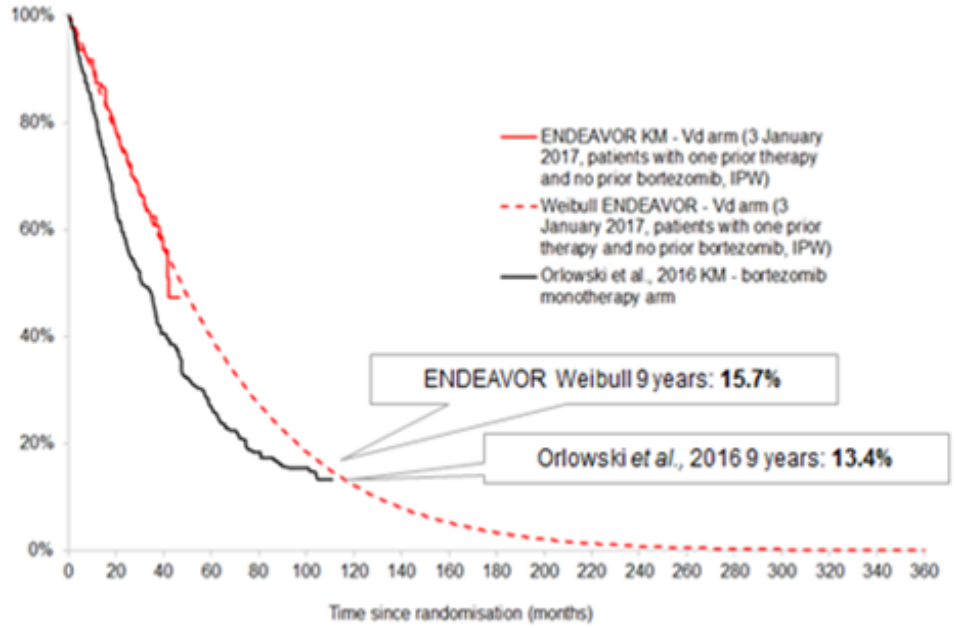
Clinical effectiveness: new overall survival evidence

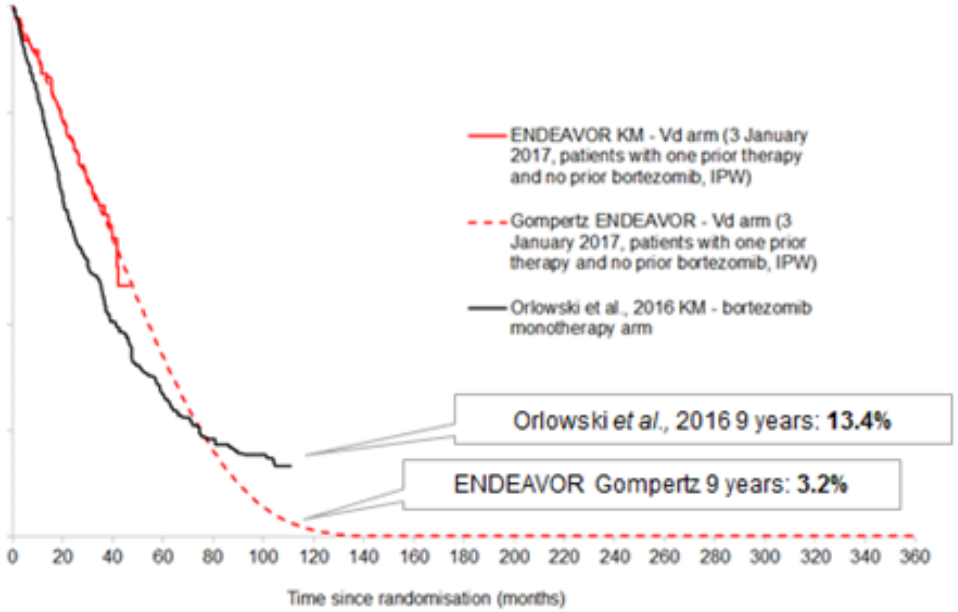
2nd line, 1 prior therapy/no prior bortezomib post-hoc subgroup

- 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 – Orlowski trial





- Study of Bort monotherapy vs Bort plus pegylated doxorubicin, patients with ≥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 Orlowski trial
  - Weibull more comparable to Orlowski 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
- Orlowski trial is not directly comparable to ENDEAVOR but agree patients are likely to have a worse prognosis in Orlowski
  - 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 Orlowski 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)

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

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

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

ERG scenario analyses

		Company model (Bort efficacy adjusted)	ERG model (Bort efficacy not adjusted)
Covariate selection	Base case: step-wise	£27,629	£40,744
	Scenario: unadjusted HR	£29,995	£48,598
Extrapolation	Base case: Weibull	£27,629	£40,744
	Scenario: Gompertz	£39,052	£59,764

Effect of covariate selection:
+ £2k – £8k

Effect of extrapolation function:
+ £11k – £19k

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