NICE National Institute for Health and Care Excellence

PART 1

Slides for public- contains no ACIC

Carfilzomib with dexamethasone and lenalidomide for treating multiple myeloma after at least 1 previous therapy

Chair's presentation

Chair: Stephen O'Brien
ERG: BMJ Technology Assessment Group
Technical team: Anita Sangha, Alexandra Filby, Ross Dent
Company: Amgen
ACM2: 12 January 2021

Key issues for consideration

Key issues	
1. Extrapolation of overall survival	Has the committee seen any evidence to change its conclusion on the preferred overall survival extrapolation?
2. Utility values	Is the use of treatment specific utility values appropriate for carfilzomib?
3. Treatment benefit after stopping treatment	Is the assumption of a consistent treatment benefit after stopping treatment with CRd clinically plausible, or would there be a waning of treatment effect over time?
4. Cost-effectiveness results	Is carfilzomib with lenalidomide and dexamethasone cost effective? What is an acceptable ICER range, taking into account uncertainty, the modelling of health-related quality of life and innovation?

Carfilzomib (Kyprolis, Amgen)

Marketing authorisation	Carfilzomib in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for the treatment of adult patients with multiple myeloma, who have received at least one prior therapy.
Appraisal population	• This is a part review of NICE technology appraisal (TA) 657 which recommends ***carfilzomib with dexamethasone as an option for treating multiple myeloma in adults, only if they have had only 1 previous therapy*** • This appraisal considers carfilzomib in a triplet regimen with lenalidomide and dexamethasone
Administration	Intravenous infusion

Note: TA657 guidance has recently been updated (previously known as TA457) to expand the recommendation to include people who have had bortezomib as a first-line therapy. This is because treatments for multiple myeloma in the NHS have changed since the guidance was first published.

Carfilzomib (Kyprolis, Amgen)

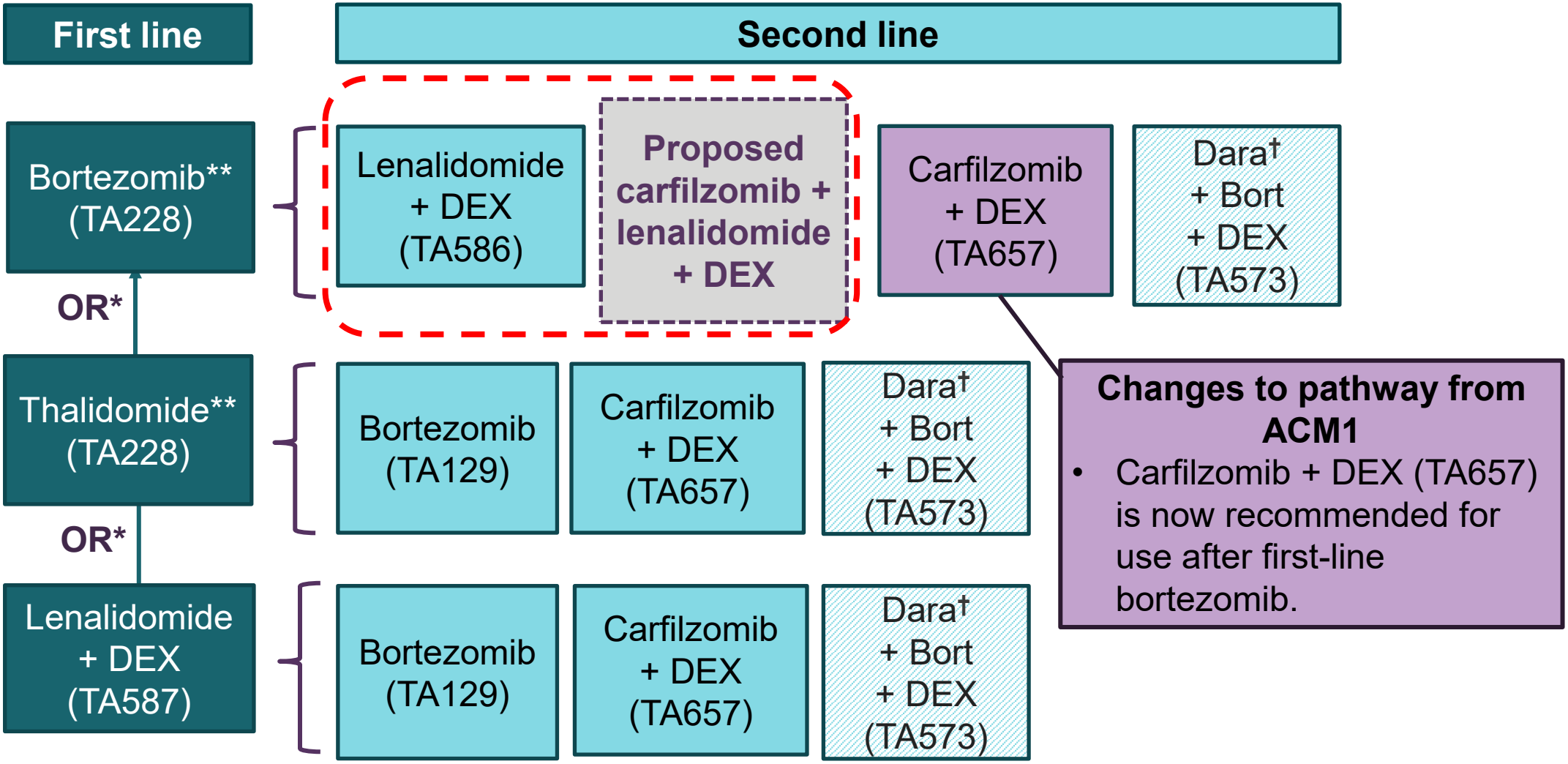
Mechanism of action	Selective irreversible proteasome inhibitor.
Price	The list price of carfilzomib is £1,056 for a 60-mg vial (excluding VAT). The company has a confidential commercial arrangement (simple discount patient access scheme). 1 cycle of carfilzomib with lenalidomide and dexamethasone (CRd) consists of 28-days treatment. The cost of 18 cycles of treatment with carfilzomib is £81,219 (based on the list price).* In the ASPIRE trial, carfilzomib was administered for a median of 18 cycles and a median duration of 72 weeks.

*Based on the average cost of a course of treatment included in Table 2 of the company submission calculated by technical team

ACD: preliminary recommendation

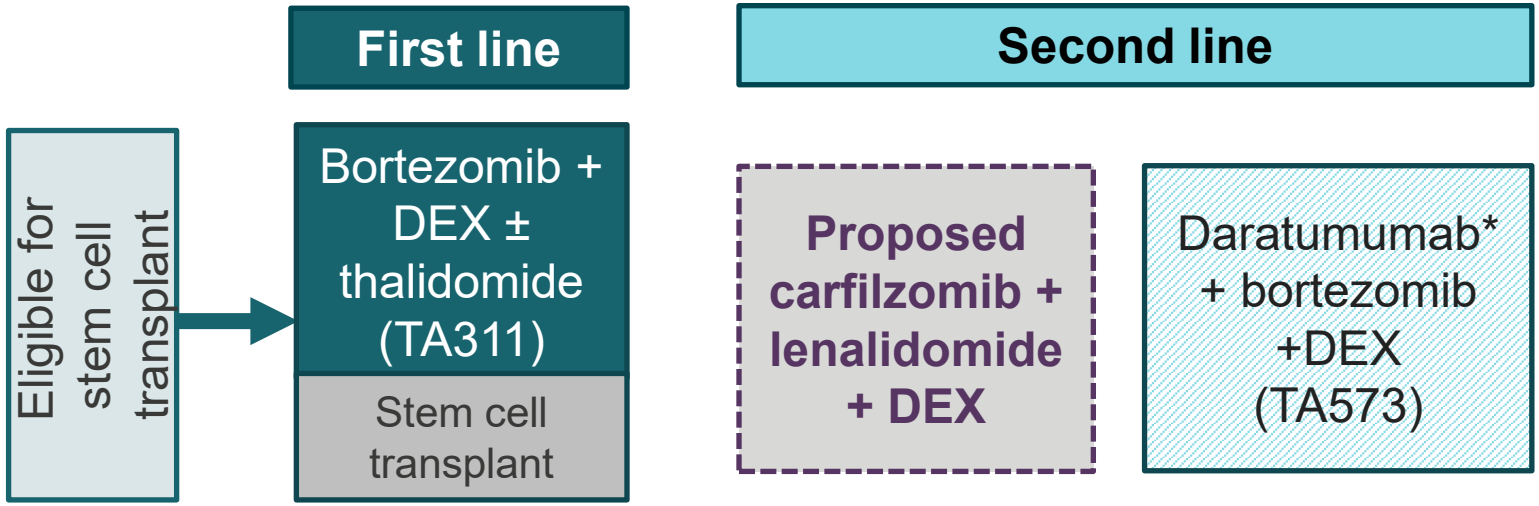
Carfilzomib with lenalidomide and dexamethasone is not recommended, within its marketing authorisation, for previously treated multiple myeloma in adults

Treatment pathway – Ineligible for stem cell transplant



NICE guidance recommendations are dependent on a person's previous treatment.
Red dashed line includes intervention and comparator included in the company's economic model
*If thalidomide is contraindicated or cannot be tolerated;
**Taken in combination with alkylating agent + corticosteroid.
DEX = dexamethasone
† Daratumumab + bortezomib + DEX is currently recommended for use within the Cancer Drugs Fund.

Treatment pathway – Eligible for stem cell transplant



NICE guidance recommendations are dependent on a person's previous treatment.
DEX = dexamethasone
***Currently recommended for use within the Cancer Drugs Fund**

Committee's conclusions in appraisal consultation document (ACD):

- The population relevant to this appraisal is people who have had 1 previous treatment with bortezomib, whether or not a stem cell transplant is suitable.
- Daratumumab with bortezomib and dexamethasone (DVd) was recommended for use within the Cancer Drugs Fund → based on NICE's position statement on the use of Cancer Drugs Fund comparators in appraisals, lenalidomide and dexamethasone is the only relevant comparator.

Background

Clinical trial	ASPIRE (n=792). Open-label, randomised, multicentre trial
Population	Adults with R/R MM who have received 1 to 3 prior therapies
Intervention	Carfilzomib with lenalidomide and dexamethasone (CRd)
Comparator	Lenalidomide plus dexamethasone (Rd). Direct comparison.
Key results	**ITT population** PFS: HR CRd vs Rd = 0.659, OS: HR CRd vs Rd = 0.794 **Second-line prior bortezomib, no prior lenalidomide subgroup** See slides 10 to 11
Model	Partitioned survival model. 3 health states including progression-free, progressed and death.
Company ICER	£43,952 per QALY gained (includes carfilzomib PAS only)
ERG ICER	£50,960 per QALY gained (includes carfilzomib PAS only, ICER is lower when lenalidomide PAS is included)

Abbreviations: HR = hazard ratio; OS = overall survival; PFS = progression-free survival; R/R MM = relapsed or refractory multiple myeloma

Committee's considerations in ACD

Committee's considerations on the clinical evidence presented

Issue	Brief recap	Committee's conclusion
Post hoc subgroups	<u>Company post hoc subgroup</u>. • Includes all patients from ASPIRE who had 1 previous bortezomib treatment. • Not all patients received prior bortezomib as part of their last treatment regimen ([redacted]) and some patients ([redacted]) had lenalidomide treatment either at the same time or afterwards in the same treatment phase. <u>ERG post hoc subgroup</u> • Includes all patients from ASPIRE who had received only 1 previous bortezomib treatment and no previous lenalidomide. • This is because it is not current standard practice to have bortezomib and lenalidomide as a first-line treatment in the NHS (during COVID-19 first-line regimens in multiple myeloma may have temporarily changed).	The ERG subgroup should be used because it reflects current practice in the NHS and is the most likely previous treatment for patients who would have CRd at second-line.

ASPIRE PFS- ERG's post hoc subgroup (second-line prior bortezomib and no prior lenalidomide)

[redacted]

Median (95% CI), months		HR CRd vs Rd
CRd	Rd	
[redacted]	[redacted]	[redacted]

ASPIRE OS - ERG's post hoc subgroup (second-line prior bortezomib and no prior lenalidomide)

[redacted]

Median (95% CI), months		HR CRd vs Rd
CRd	Rd	
[redacted]	[redacted]	[redacted]

Committee's considerations in ACD

Committee's considerations on modelling assumptions

Issue	Brief recap	Committee's conclusion
Extrapolation of overall survival (OS)	• The company consider that extrapolation from ASPIRE data may underestimate long-term survival. • To estimate OS for CRd and Rd, the company used a combination of extrapolated ASPIRE OS data and real-world evidence from a French Registry (MyelomaToul) of patients who had lenalidomide as a second-line treatment. • The ERG considered that a clinically plausible extrapolation could be estimated entirely from the mature ASPIRE data (72 months follow-up).	Exponential model for estimating OS for both treatment arms was preferred because it uses data entirely from ASPIRE.

Committee's considerations in ACD

Committee's considerations on modelling assumptions

Issue	Brief recap	Committee's conclusion
Utility values	• Disease-specific questionnaire (EORTC QLQ-C30 GHS) used in ASPIRE showed a statistically significant difference between treatment arms. • From cycle 3 onwards, the pre-progression utility values capture a mean increase in utility from baseline for both treatments, as well as a treatment-specific increase in utility if a patient is on CRd. • ERG base case removed treatment-specific utility gain and mean increase in utility from cycle 3 onwards. • Disutility values for adverse events were applied separately.	Treatment-specific utility values may be reasonable, but the committee preferred pre-progression utility values to be the same for both treatment arms.

Health state	Company base case values for ERG subgroup		ERG base case	
	CRd	Rd	CRd	Rd
Pre-progression (cycles 1 and 2)	[redacted]	[redacted]	[redacted]	[redacted]
Pre-progression (later cycles)	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression	[redacted]	[redacted]	[redacted]	[redacted]

Committee's considerations in ACD

Committee's considerations on modelling assumptions

Issue	Brief recap	Committee's conclusion
Duration of treatment benefit after stopping treatment	• A relative treatment benefit was applied to every cycle in the company's model for CRd, beyond the observed ASPIRE data (72-months). • ERG's exponential model also included a treatment benefit for CRd after stopping treatment. The use of mature data from ASPIRE may have captured some waning of treatment effect. • The application of a prolonged treatment benefit may potentially overestimate survival and be favourable to CRd.	There is uncertainty about how long any treatment benefit lasts after stopping treatment with CRd.

New evidence submitted

ACD consultation responses

- Consultee comments from:
  - Amgen (company) – **new evidence**
  - UK Myeloma Forum/British Society for Haematology/Royal College of Pathologists
  - Myeloma UK

Patient and professional group comments

Comparators

- Stakeholders commented that most patients have DVd at second-line in clinical practice.

Post-hoc subgroup

- Stakeholders consider that patients who have had prior lenalidomide at first-line and are not refractory should not be excluded because:
  - This contradicts clinical practice where patients who have had prior lenalidomide and are not refractory to it are eligible for ixazomib with lenalidomide and dexamethasone (NICE TA505, combination recommended for use within the CDF)
  - Patients exposed to prior lenalidomide in a clinical trial setting may be disadvantaged if CRd is restricted to people who are lenalidomide naive.

Utility values

- Treatment specific utility values should be used as the disease-specific questionnaire administered in the ASPIRE trial showed a significant improvement in health-related quality of life of patients treated with CRd compared to Rd. This is because of improved and faster disease control.
- Approach should be consistent with the application of utility values across all relapsed multiple myeloma technology appraisals.

Patient and professional group comments

Overall survival and duration of treatment benefit

- “ASPIRE study is the only phase III relapsed multiple myeloma trial with long follow up ever considered by NICE committee with over 6 years actual follow up. The trial demonstrates a clear improvement in overall survival which often remains immature when other combinations have been considered by NICE”

- Carfilzomib frequency is reduced after 12 months and stopped after 18 months in ASPIRE. The overall survival curves do not show a reduction in survival for CRd at these time points, which suggests that a significant proportion of patients benefit from treatment after carfilzomib is stopped.

Cost-effectiveness threshold

- One stakeholder highlighted concerns about the committee's conclusion in the ACD, that because of the uncertainty in relative treatment benefit, an acceptable ICER would be no higher than the middle of the range normally considered as cost-effective. They had not seen this before in previous myeloma technology appraisals.

Extrapolation of overall survival

Comments received, no new evidence

RECAP:
- Company combined trial data (ASPIRE) and registry data to estimate OS
- Committee concluded data from ASPIRE should be used with an exponential extrapolation

Company comments

- "As feedback from clinical experts suggests long-term survival with CRd is expected to be at least comparable with DVd, both the Amgen and ERG ICER estimates may reasonably be considered conservative when taking in to account clinically plausible long-term survival extrapolations in other MM appraisals."
- "In the TA573 FAD, it states that the committee preferred the ERG's more conservative survival estimate for the daratumumab combination at 20 years of 11%"
- Company conducted a scenario analysis using the committee's preferred assumptions where the proportion of CRd patients alive at 20 years was set to 11% (OS estimates for Rd remain unchanged), which reduced the ICER from £50,960 to £35,513 (carfilzomib PAS only)

Overall survival extrapolation	10 years		20 years	
	CRd	Rd	CRd	Rd
ASPIRE Weibull distribution	16%	5%	2%	0%
Adjusted MyelomaToul model + HR (company base case)	21%	9%	6%	1%
ASPIRE exponential distribution (cmte preferred)	19%	8%	4%	1%

Comments received, no new evidence

Extrapolation of overall survival

ERG comments

- No change from preference for the exponential model to estimate OS entirely from ASPIRE for both treatment arms.
- ERG highlights that in the FAD for TA573 the committee "was aware of the substantial uncertainty in the extrapolation, which predicted survival up to 30 years based on a trial with a median follow-up of under 3 years, and in the relative treatment effect of daratumumab in the long term".
- The ERG consider that it is inappropriate to improve OS for CRd based on immature data for another combination treatment, when mature ASPIRE data are available.
- Data from ASPIRE should be used for the base-case analysis because:
  - trial data are now mature
  - data is from the subgroup of interest
  - patient characteristics have been adjusted to limit bias
  - it maintains the observed treatment effect between the trial arms.

NICE technical team comments

- DVd (NICE TA573) is recommended for use in the CDF, therefore the guidance will be reviewed after more data is collected on overall survival.

⊙ *Has the committee seen any evidence to change its conclusion on the preferred overall survival extrapolation?*

Comments received, no new evidence

Treatment-specific utility values

- Committee concluded treatment-specific utility values may be reasonable, but it preferred pre-progression utility values to be the same for both treatment arms

- Background: Disutility values for adverse events were applied separately

Company comments

- Overall response rate was significantly higher in the CRd arm compared with the Rd arm (87.1% versus 66.7%).
- The proportion of patients who achieved a complete response or better was higher in the CRd arm than in the Rd arm (31.8% versus 9.3%).
- Patients who received CRd experienced a faster response compared with Rd (mean time to response 1.6 versus 2.3 months).
- Clinical experts suggested that the difference in response profiles observed for CRd and Rd would likely result in treatment specific differences in quality of life.
- **During the original appraisal of carfilzomib with dexamethasone in NICE TA657, treatment specific utility values were accepted and formed part of the NICE committee's preferred assumptions for carfilzomib.**
- **Application of treatment-specific utility values reduced the committee preferred ICER from £50,960 to £45,919 per QALY gained (carfilzomib PAS only).**

Comments received, no new evidence

Treatment-specific utility values

ERG comments (remain unchanged from ACM1)

- The ERG notes that the mean change in utility over time was [redacted] for CRd versus Rd, even though all patients have progression-free disease.
- The ERG's clinical expert suggested that there may be a quicker response to treatment for patients receiving CRd compared with Rd, but there was no clinical reason for there to be a treatment-specific utility benefit in addition to the benefit provided by any gains in progression-free survival.
- Therefore, the ERG considers the company's approach may be unreliable and may overestimate the overall quality-adjusted life-years (QALYs) in favour of carfilzomib.
- The ERG prefers for utility values to be based on progression status alone without a treatment effect applied or an increase in utility from baseline.
- ERG notes that the company have not provided evidence to quantify how improvements in overall response rate translate to an improvement in HRQoL utility values.

⊙ *Is the use of treatment-specific utility values appropriate for carfilzomib?*

New evidence submitted

Treatment benefit after stopping treatment

RECAP:
- Committee concluded there is uncertainty about how long any treatment benefit lasts after stopping treatment with CRd

Company's new evidence

- Company submitted additional evidence aiming to resolve the committee's concerns that the carfilzomib treatment effect may wane after treatment stops.
- "Across all populations explored, no trend suggesting a reduction in the hazard ratio over time was observed within the >6-years of follow up in these analyses. This is supported with conclusions drawn from KM plots, Schoenfeld residuals and cumulative hazard plots which all suggest that a consistent treatment effect beyond the observed timeframe in the clinical trial remains appropriate".
- Company consider that based on this evidence, "it is highly unlikely that a strong and sustained treatment effect observed over such a long duration would diminish after the trial follow-up period."
- "Considering a reduced upper threshold on the basis of uncertainty fails to reflect the maturity of the data available, and places an additional, unjust burden on patient access to an effective combination therapy"

New evidence submitted

Treatment benefit after stopping treatment

Company's new evidence

ERG base case (second-line prior bortezomib and no prior lenalidomide) - Estimated hazard ratio based on empirical death rates

[redacted]

Technical team notes that this point may be misleading. Deaths were 0 in Rd arm at this timepoint so should be plotted as infinity rather than 0

New evidence submitted

Treatment benefit after stopping treatment

ERG response to company's new evidence

- ERG agrees that the assumption of proportional hazards cannot be rejected and that the KM curves do not demonstrate a substantial convergence.
- ASPIRE data is quite mature and so it is likely that treatment waning associated with CRd is captured in the data:
  - treatment duration for CRd was a maximum of 18 cycles
  - median PFS and OS follow-up was 48.8 and 67.1 months, respectively.
- The empirical death rate and estimated hazard ratio (based on empirical death rates) plots do not strongly support the assumption of a consistent treatment benefit with CRd, but there is not enough evidence to reject the assumption.
- Including a treatment waning effect may not be appropriate.

⊙ *Is the assumption of a consistent treatment benefit after stopping treatment with CRd plausible, or would there be a waning of treatment effect over time?*

Cost effectiveness results

- **Because of confidential discounts for lenalidomide and some of the subsequent therapies, the cost-effectiveness results are confidential and will be discussed in part 2 of the committee meeting.**
- Lenalidomide is a cost-driver in combination therapy with CRd.
- Lenalidomide's (Revlimid, Celgene) license exclusivity is expected to expire in 2022. This means that generic formulations of lenalidomide are likely to become available and its price will reduce, reducing the cost of CRd combination therapy.
- The analyses in part 2 include a commercial arrangement agreed between the company and NHS England consisting of a simple discount patient access scheme [redacted]

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