NICE National Institute for Health and Care Excellence

PART 1

Slides for public observers

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

Lead team presentation

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Company: Amgen
ACM1: 7 July 2020

Disease background

- Multiple myeloma (MM) is a form of cancer that arises from plasma cells (a type of white blood cell) in the bone marrow.
- Myeloma cells produce large quantities of an abnormal antibody known as paraprotein, which lacks the capacity to fight infection, and suppress the development of normal blood cells (white, red and platelets).
- MM refers to the presence of these cells in more than one affected bone.
- MM is highly relapsing and remitting where periods with symptoms need treating.
- Common symptoms:
  - Bone pain, bone fractures, anaemia, infections, hypercalcaemia
- Incidence and survival*
  - In 2017, 5,034 people were diagnosed in England. Average age over 75.
  - More common in men than women and a higher incidence in people of African family origin.
  - 5-year survival rate approx. 52%

*Sources: Cancer Research UK and Office for National Statistics

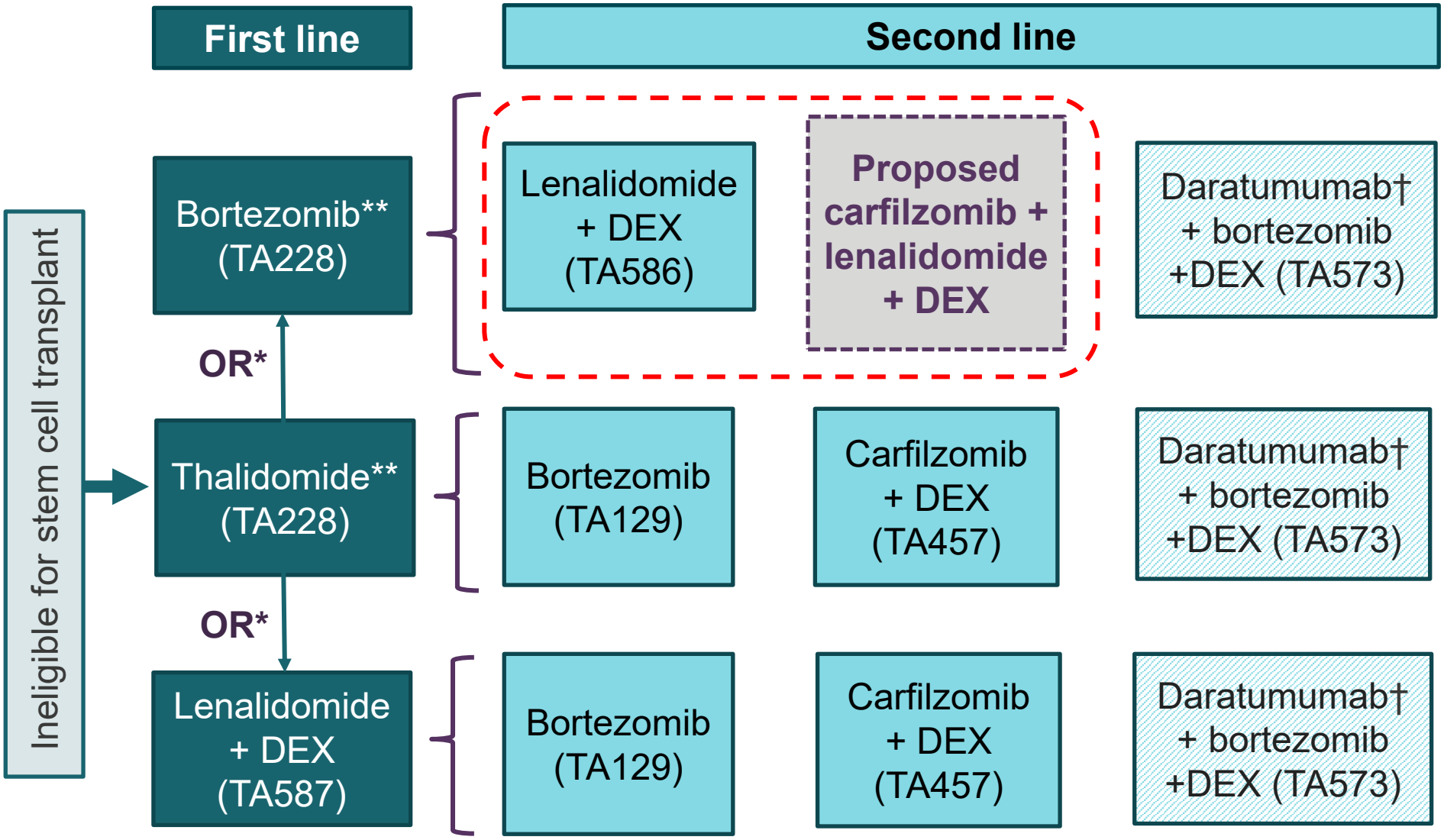
Carfilzomib (Kyprolis, Amgen)

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 457 which recommends ***carfilzomib with dexamethasone as an option for treating multiple myeloma in adults, only if they have had only 1 previous therapy, which did not include bortezomib.*** • This appraisal considers carfilzomib in a triplet regimen with lenalidomide and dexamethasone
Administration	Intravenous infusion

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 average cost of a course of treatment with CRd is: • Cycle 1 = £4,663 (at list price). • Cycles 2 to 12 = £5,104 per cycle (at list price) • Cycles 13 onwards = £3,402 per cycle (at list price).

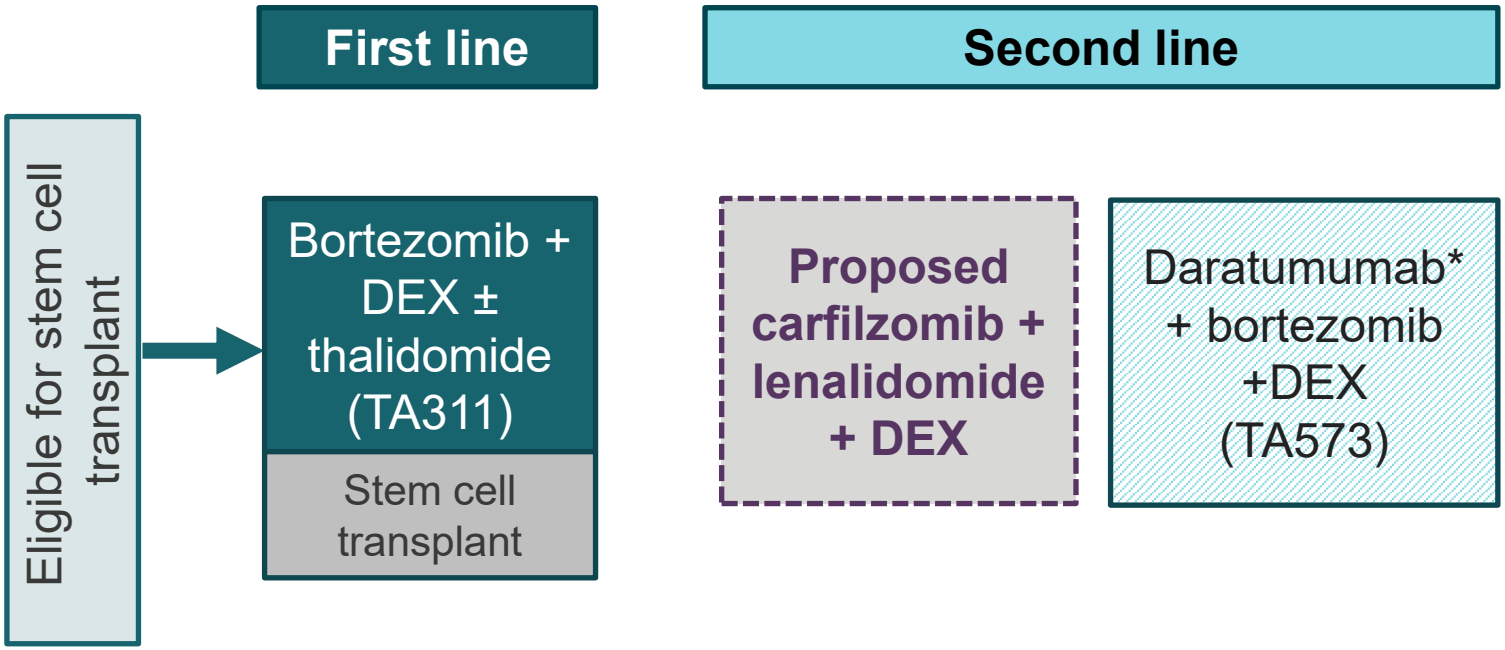
Treatment pathway – Ineligible for stem cell transplant (SCT)



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

† Currently recommended for use within the Cancer Drugs Fund (as a treatment option in people who have had 1 previous treatment) and therefore is not considered a comparator in this appraisal.

Treatment pathway – Eligible for stem cell transplant (SCT)



NICE guidance recommendations are dependent on a person's previous treatment.
DEX = dexamethasone
***Currently recommended for use within the Cancer Drugs Fund (as a treatment option in people who have had 1 previous treatment) and therefore is not considered as a comparator in this appraisal.**

Patient and carer perspectives

- Patients and carers value treatment options which achieve a high response rate and promote a sustained remission and good quality of life.

> *"Anything that could extend the remission period and ultimately the length and quality of life would be very welcome."*

- Multiple myeloma is a relapsing-remitting cancer which can often become resistant to treatment. Relapsed patients often experience a poorer prognosis and greater disease burden. Treatment options with different mechanisms of action are important for patients.

> *"Myeloma creeps up on you, engulfs you and, if you win the battle, leaves you wondering when it will come back."*
>
> *"The treatment pathway should not unfairly restrict treatment options."*

- Patients need the flexibility of treatments that adapt to the reality of their lives. Overall, patients and carers value treatments that are in line with their personal goals.

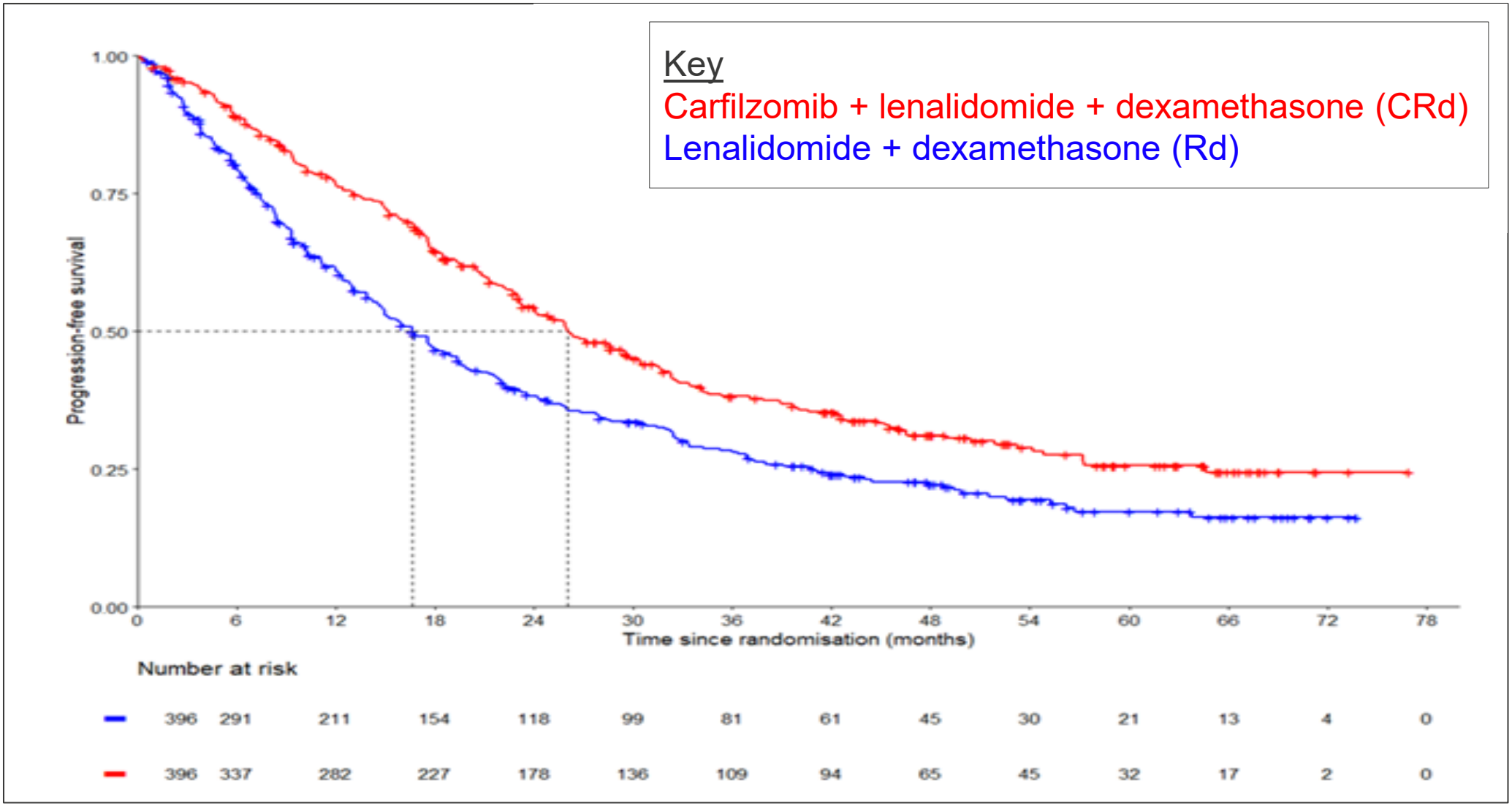
> *"I have a business to run and that's very disruptive. That said, when you need to be treated and the only treatment available is delivered in the hospital you just get on with it; getting your treatment becomes your job, your purpose."*
>
> *"I feel angry that I'm not going to get the future I wanted, but the hardest thing to feel is how my life at the moment is in limbo."*

ASPIRE - Open-label, randomised, multicentre trial

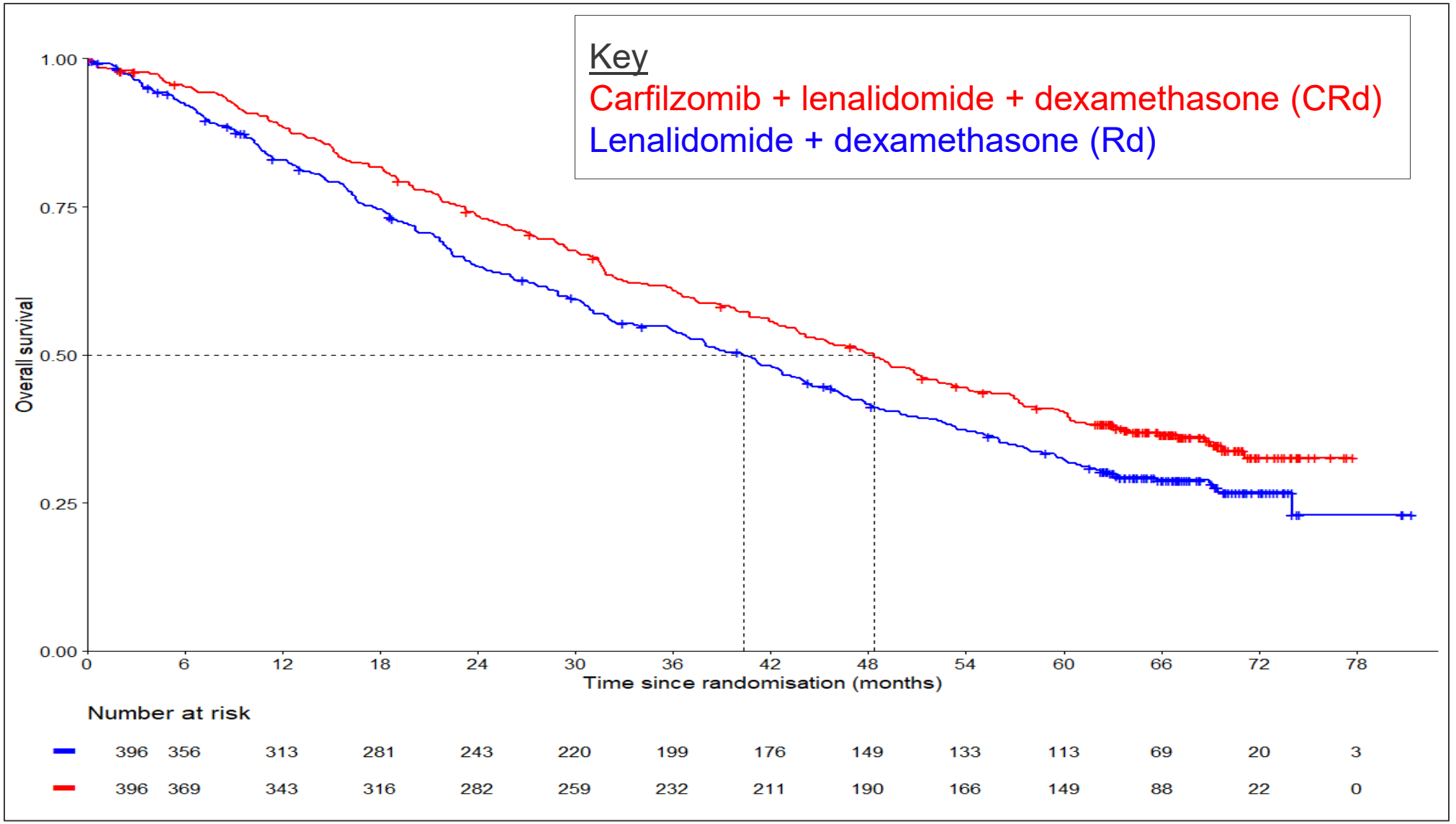
Population and setting	• **Adults with R/RMM who have received 1 to 3 prior therapies (n=792)** • **129 centres across 20 countries in Europe, North America and Israel 6 sites with 16 patients were enrolled in the UK**
Intervention	• Carfilzomib with lenalidomide and dexamethasone (CRd) • 28-day treatment cycles
Comparator	• Lenalidomide plus dexamethasone (Rd) • 28-day treatment cycles • Direct comparison
Primary outcomes	Progression-free survival
Secondary outcomes	Overall survival, response rates, time to next treatment, adverse effects of treatment, Health-related quality of life
Abbreviations: R/RMM = relapsed or refractory multiple myeloma	

- Data from the ASPIRE trial informed the appraisal of carfilzomib with dexamethasone in NICE technology appraisal 457 (TA457), which included comparative treatment effectiveness results from the planned interim analysis (data cut-off June 2014).
- In TA457, the clinical and cost effectiveness of carfilzomib in a triplet therapy with lenalidomide and dexamethasone was only considered at third-line and was not recommended due to immature overall survival data.

ASPIRE unadjusted progression-free survival (ITT population)



ASPIRE unadjusted overall survival (ITT population)



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ASPIRE effectiveness results (ITT population)

ASPIRE	Median (95% CI), months		HR CRd vs Rd	p value
	CRd N = 396	Rd N = 396		
Progression-free survival	**26.1 (23.2 to 30.3)**	**16.6 (14.5 to 19.4)**	**0.659 (95% CI 0.553 to 0.784)**	**p=<0.0001**
Overall survival	48.3 (42.4 to 52.8)	40.4 (33.6 to 44.4)	0.794 (95% CI 0.667 to 0.945)	p=0.0045

Abbreviations: CRd = carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone; ITT = intention to treat

April 2017 data cut-off

NICE

Subgroups (1)

Discussed further in issue 2

- Focus of this appraisal is on a post hoc subgroup of the ASPIRE trial who have received only 1 prior therapy with a bortezomib-based regimen.
- Company conducted an inverse probability weighted (IPW) analysis of post hoc subgroup data to produce effect estimates for progression-free survival and overall survival.

Company subgroup

- Company post hoc subgroup (**second-line prior bortezomib**) includes a broader definition of first-line therapy.
- Company state that in their subgroup population [redacted] of patients had both 1 prior line of treatment and were previously treated with bortezomib.
- ERG notes that in the company's subgroup not all patients had received prior bortezomib [redacted] as part of their **last treatment regimen** and that some patients had undergone treatment with lenalidomide [redacted] in their last regimen.
- Company consider that it is plausible that a minority of patients could be exposed to prior lenalidomide and still be considered eligible for treatment with CRd.

Subgroups (2)

Discussed further in issue 2

ERG subgroup

- ERG post hoc subgroup includes a stricter definition of first-line therapy based on the current treatment pathway for multiple myeloma. ERG clinical experts stated that patients would not receive bortezomib with lenalidomide as a first-line treatment in the NHS in England (prior to COVID-19).
- The ERG preferred subgroup includes patients from the ASPIRE trial who had received only 1 prior therapy with bortezomib and no lenalidomide (**second-line prior bortezomib/no prior lenalidomide**).

ASPIRE IPW adjusted progression-free survival - Company's post hoc subgroup (second-line prior bortezomib)

ASPIRE IPW adjusted overall survival - Company's post hoc subgroup (second-line prior bortezomib)

ASPIRE IPW adjusted effectiveness results – Company's post hoc subgroup (second-line prior bortezomib)

ASPIRE	Median (95% CI), months		HR CRd vs Rd
	CRd	Rd	
Progression- free survival	[redacted]	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]	[redacted]

Adjusted for covariates selected using stepwise logistic regression
Variables adjusted for: [redacted]
Abbreviations: IPW = inverse probability weighted (analysis);
CRd = carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone

December 2017 data cut-off

ASPIRE IPW adjusted progression-free survival - ERG's post hoc subgroup (second-line prior bortezomib and no prior lenalidomide)

ASPIRE IPW adjusted overall survival - ERG's post hoc subgroup (second-line prior bortezomib and no prior lenalidomide)

* Note slide has been updated since committee meeting as incorrect figure had been included.

ASPIRE IPW adjusted effectiveness results - ERG's post hoc subgroup (second-line prior bortezomib and no prior lenalidomide)

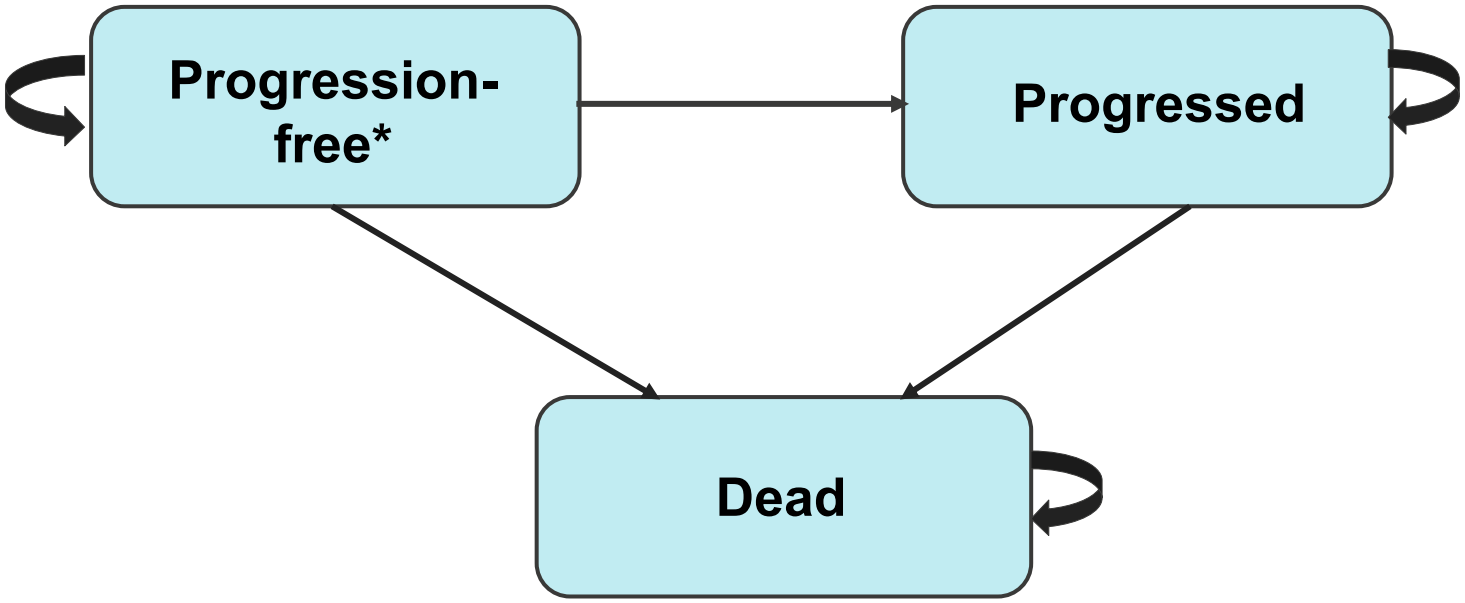
ASPIRE	Median (95% CI), months		HR CRd vs Rd
	CRd	Rd	
Progression- free survival	[redacted]	[redacted]	[redacted]
Overall survival	[redacted]	[redacted]	[redacted]

Adjusted for covariates selected using stepwise logistic regression
Variables adjusted for: [redacted]

Abbreviations: IPW = inverse probability weighted (analysis); CRd = carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone; NA = not applicable.

December 2017 data cut-off

Company's model structure



Partitioned survival model:

- Three health states including progression-free, progressed and death
- Cycle length of 28 days with half-cycle correction
- Lifetime time horizon (40 years)
- All patients enter the model at the progression-free health state and are assumed to start treatment (CRd or Rd)

* Patients in the progression-free health state can either be on-treatment and off-treatment (if experience unacceptable toxicity)

Key issues considered at technical engagement	Status
1 –Treatment pathway a) Is the positioning of carfilzomib clear in both treatment pathways? b) Have all the relevant comparators been considered?	Resolved
2 – Post hoc subgroups a) In clinical practice, is it possible for patients to receive lenalidomide and bortezomib as a first-line treatment even though this is not recommended in NICE guidance? b) Which post hoc subgroup of the ASPIRE trial reflects NHS clinical practice?	For discussion
3 – Utility values used in model a) Are there additional treatment-specific benefits with carfilzomib with lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone, other than gains in progression-free survival and overall survival? b) Are the utility values used in the company's economic model appropriate and reliable for decision-making?	For discussion
4 – Extrapolation of overall survival a) Should data be used entirely from the ASPIRE trial or in combination with real world data to extrapolate overall survival? b) Is the exponential or the company's preferred model more appropriate for extrapolation of overall survival?	For discussion

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
1a	The company positioning of carfilzomib with lenalidomide and dexamethasone is narrower than the marketing authorisation, which does not stipulate prior bortezomib treatment. The ERG's clinical experts consider that the technology is likely to offer the most benefit at the proposed position.	Stakeholders agree with the company positioning for carfilzomib triplet therapy in both those eligible and ineligible for SCT.	The positioning of carfilzomib in the treatment pathways is appropriate and clear.	Not applicable

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
1b	Based on the positioning of carfilzomib in the treatment pathway, the company consider lenalidomide plus dexamethasone as the primary relevant comparator. Company and clinical experts consider that people receiving a bortezomib-based regimen at first line would be unlikely to have subsequent bortezomib monotherapy.	Stakeholders consider that daratumumab with bortezomib and dexamethasone should be considered as an additional comparator (NICE technology appraisal 573, recommended for use within the Cancer Drugs Fund), given that many patients are receiving this as second-line therapy in clinical practice.	Lenalidomide plus dexamethasone is the only relevant comparator. As per NICE's position statement, technologies that have been recommended by NICE for use within the Cancer Drugs Fund cannot be considered established practice and are therefore not considered as comparators in new appraisals.	Not applicable

Outstanding issues after technical engagement

- **Issue 2:** Post hoc subgroups
  - Slide 25-26, 2 options
- **Issue 3:** Utility values
  - Slides 27-29, 2 options
- **Issue 4:** Extrapolation of overall survival
  - Slides 30-33, 2 options

Small impact

For discussion

Issue 2: Post hoc subgroups (1)

Background

- The company has included in their base case assumptions a subgroup of patients from the ASPIRE trial who had received 1 prior therapy with bortezomib (**second-line prior bortezomib**).
- The company consider that a small number of patients may receive lenalidomide and bortezomib as a first-line treatment, and still be considered eligible for treatment with CRd.

Stakeholder comments

- Bortezomib with lenalidomide (and dexamethasone) is not current standard of care in England for first-line treatment.
- Patients who have received bortezomib and lenalidomide are likely to have been treated in a private setting or as part of a clinical trial. NICE is currently appraising lenalidomide for the maintenance treatment of multiple myeloma after autologous stem cell transplantation (ID475).
- Due to COVID-19, patients who are eligible for SCT may have been switched from a bortezomib-based to lenalidomide-based induction treatment or may have received lenalidomide after bortezomib-based induction (population size affected unknown).

For discussion

Issue 2: Post hoc subgroups (2)

ERG comments

- Company's base case consists of a subgroup of patients who had not all received prior bortezomib as part of their last treatment regimen [redacted] and that some patients had undergone treatment with lenalidomide [redacted].
- Company's base case does not reflect NICE-approved first-line treatment and consider the ERG base case: **second-line prior bortezomib/no prior lenalidomide** to be more reflective of clinical practice**.**
- The ERG considers that the impact of the change in induction treatment is difficult to quantify, with lack of data on the proportion of people affected and uncertainty around the length of time that COVID-19 will continue to affect clinical services.

Impact on ICER - small

- The use of the ERG's preferred subgroup reduces the ICER

Which post hoc subgroup of the ASPIRE trial reflects NHS clinical practice and should be included in the model?

For discussion

Issue 3: Utility values (1)

Background

- For cycles 1-2 in the progression-free health state, the company used the same baseline utility value as patients in ASPIRE with 1 prior therapy with bortezomib, for both treatment groups.
- From cycle 3 onwards, the utility values in the economic model 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 carfilzomib (in combination with lenalidomide and dexamethasone).

Stakeholder comments

- Overall response rate and HRQoL scores (measured by the EORTC QLQ-C30 GHS) in the ASPIRE trial were significantly higher for carfilzomib with lenalidomide and dexamethasone (CRd) compared with lenalidomide plus dexamethasone (Rd) over 18 cycles of treatment.
- Based on the above, it is reasonable to use different treatment-specific utilities for CRd and Rd in the economic model.
- The company's approach to include treatment-specific utility values was accepted in NICE technology appraisal 457.
- As the ASPIRE trial was open-label, there may be a level of information bias in the patient responses to the HRQoL questionnaires, depending on whether a patient was receiving CRd or Rd.

Issue 3: Utility values (2)

For discussion

ERG comments

- 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.
- 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.
- ERG considers its approach to remove the treatment specific utility gain, as well as mean increase in utility from cycle three onwards provides a conservative estimate of the ICER.
- 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.

Health state	Company base case (second-line prior bortezomib)		Company base case for ERG subgroup (second-line prior bortezomib/no prior lenalidomide)	
	CRd	Rd	CRd	Rd
Pre-progression (cycles 1 and 2)	0.714	0.714	[redacted]	[redacted]
Pre-progression (later cycles)	0.761	0.745	[redacted]	[redacted]
Post-progression	0.698	0.698	[redacted]	[redacted]

Abbreviations: CRd = carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone.

For discussion

Issue 3: Utility values (3)

Impact on ICER - Small 

- Removal of treatment effect and average increase in baseline utility for cycle 3 onwards for pre-progression health state utility value, increases the ICER.

Are there additional treatment-specific benefits with CRd compared with Rd, other than gains in progression-free survival and overall survival?

Are the utility values used in the company's economic model appropriate and reliable for decision-making?

Issue 4: Extrapolation of overall survival (1)

For discussion

Background

- The company selected the Weibull distribution as the best fit to the inverse probability weighted (IPW) KM overall survival data. They consider that extrapolation from ASPIRE trial data may underestimate long-term survival, producing pessimistic results for the Rd arm (when compared with estimates presented in related technology appraisals). For both treatment arms, the company used a hybrid of extrapolated ASPIRE IPW overall survival data and real-world evidence from a French registry (MyelomaToul) of multiple myeloma patients who received lenalidomide as a second-line treatment.
- MyelomaToul data was adjusted to account for the mortality difference between the registry data and the IPW second-line prior bortezomib Rd data from ASPIRE.
- For the CRd arm, the Weibull distribution was used for the first 72 months, and then hazards from the hybrid Rd curve, using the IPW overall survival hazard ratio, were applied for the remainder of the model.

Stakeholder comments

- Real world evidence is relevant to confirm trial extrapolations, if populations are comparable.
- Weibull distribution appears to be more conservative, exponential distribution is more clinically plausible.
- Company highlighted results from a multistate model which were used to inform the most appropriate extrapolation of overall survival in the ITT ASPIRE population. The multistate model suggested longer estimates of overall survival than those predicted by the Weibull model and were consistent with the external MyelomaToul data.

Issue 4: Extrapolation of overall survival (2)

For discussion

ERG comments

- ERG's clinical experts agreed that the longer-term survival estimates for patients treated with lenalidomide plus dexamethasone (Rd) based on ASPIRE were conservative.
- The company's adjustment of survival for the Rd arm, results in an inflation of survival for the CRd arm, compared with extrapolated estimates based on IPW ASPIRE data.
- Company confirmed that when using MyelomaToul data to validate the ASPIRE extrapolations, the exponential distribution provides the most clinically plausible predictions of longer-term survival. ERG also notes that subgroup data in the MyelomaToul model does not entirely match the company's base case population.
- For the ERG's preferred subgroup, the exponential distribution was the best statistical fit. ERG considers that a clinically plausible extrapolation of overall survival for CRd can be estimated entirely from mature ASPIRE trial data.
- ERG notes that as the company's multistate model is based on the ITT population, it is not directly applicable to the subgroup of interest for this appraisal.

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 (ERG base case)	**19%**	**8%**	**4%**	**1%**

Abbreviations: CRd = carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone.

For discussion

Issue 4: Extrapolation of overall survival (3)

ERG additional comments

- ERG clinical experts agree with the company that the extrapolation of Rd using the Weibull distribution lacks clinical validity.
- The ERG agree with the company that the exponential distribution produces clinical plausible extrapolations for Rd (and also had a good visual and statistical fit to the observed data).

Comparison of overall survival curves for CRd

For discussion

Issue 4: Extrapolation of overall survival (4)

Impact on ICER - Small 

- Using the exponential distribution for overall survival (from ASPIRE only), increases the ICER

Should data be used entirely from the ASPIRE trial or in combination with real world data to extrapolate overall survival?

Is the exponential or the company's preferred model more appropriate for extrapolation of overall survival?

Additional areas of uncertainty

Issue	Why issue is important	Impact on ICER
Subsequent treatment costs	Subsequent treatment costs included in the model may not reflect those received in the ASPIRE trial and may include treatments not recommended by NICE. The ERG noted that investigational drugs were omitted from subsequent treatment costs, which may underestimate the total costs included in the economic model.	Minimal impact
Monitoring costs	The ERG's clinical experts noted that monitoring costs may be underestimated in the model.	Minimal impact
Adverse events	The ERG's clinical experts raised concerns for the resource use assumed for the treatment of adverse events.	Minimal impact

Other issues for information

Issue	Why issue is important	Impact on ICER
Drug wastage	Company have not included drug wastage in the model as they expect carfilzomib drug wastage to be minimal.	Minimal impact
Adverse events	Cardiac disorders were omitted in the economic model as a serious adverse reaction. The ERG's clinical experts highlighted that the Summary of Product Characteristics for carfilzomib reports cardiac disorders as a special warning and a precaution for use. Certain cardiac events occurred [redacted] in those receiving CRd compared with Rd.	Minimal impact

Other issues for information

Issue	Why issue is important	Impact on ICER
Stopping treatment after 18 cycles	In ASPIRE, carfilzomib was stopped after 18 cycles whereas the marketing authorisation allows for treatment until progression or unacceptable toxicity. The KM shows more than half of patients predicted to remain on treatment at 18 cycles. • Treatment costs for carfilzomib were not included in the company's economic model after 18 cycles. • But neither was potential increased patient survival associated with elongated treatment. >4 years follow up after 18 cycles, so observed OS not restricted to carfilzomib treatment period.	Unknown If treated until progression/ toxicity, costs increase in the ERG base case by: ~£11,000 using the exponential distribution to extrapolate carfilzomib TTD ~£7,000 using the Weibull distribution to extrapolate carfilzomib TTD. QALY gains unknown

Does the committee consider that stopping treatment with carfilzomib at 18 cycles is enforceable and clinically plausible?

Cost effectiveness results - company base case

ICERs include carfilzomib PAS only

Deterministic results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Rd	[redacted]	4.08	2.58	60,467	2.54	1.38	**43,952**
CRd	[redacted]	6.62	3.96				

CRd= carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone ICER = incremental cost effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

Probabilistic results (2,000 iterations)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Rd	[redacted]	4.08	2.58	63,873	2.70	1.42	**44,902**
CRd	[redacted]	6.78	4.00				

Cost effectiveness results – ERG preferred assumptions

Deterministic ICERs include carfilzomib PAS only

Scenario	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Company base case	60,467	1.38	**43,952**
Issue 2: Post hoc subgroup			
ERG preferred subgroup: second-line prior bortezomib/no prior lenalidomide	54,626	1.35	40,335
Issue 2+3: Post hoc subgroup + Utility values			
Removal of treatment effect and increase in utility from baseline for cycle 3 onwards for pre-progression health state utility value	54,626	1.23	44,438
Issue 2+4: Post hoc subgroup + Extrapolation of overall survival *			
Exponential distribution using ASPIRE trial data, not Myeloma Toul	53,017	1.15	45,919
ERG base case (Issues 2 + 3 + 4)	53,017	1.04	**50,960**

* Note this is the ICER for the ERG base case using company utility values.

Combination therapies

Company comments

- Company consider the increased efficacy of adding carfilzomib to lenalidomide and dexamethasone to be penalised by the increased costs of background therapy (additional Rd) which are required to be given until disease progression.
- This may result in combination therapies being unable to demonstrate cost-effectiveness even at zero price, if the prolonged use of the background therapy is not considered to be cost-effective.
- In the company base case analysis, [redacted] of the total CRd acquisition cost was associated with Rd and [redacted] comprised of carfilzomib (analysis conducted at lenalidomide list price).

Does the committee consider that the costs of background therapy should be included in the model?

Scenario analyses (CRd vs Rd)	ICER (£/QALY) Analysis conducted at lenalidomide list price
Exclude additional cost of Rd in the CRd treatment arm	16,751
Price of carfilzomib £0	[redacted]

Source company submission. CRd = carfilzomib/lenalidomide/dexamethasone; Rd = lenalidomide/dexamethasone.

Other issues for consideration

End-of-life criteria

- End-of-life criteria as per NICE methods guide:
  - The treatment is indicated for patients with a short life expectancy, **normally less than 24 months** and
  - there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.
  - Committees will need to be satisfied that estimates of the extension to life are sufficiently robust and the assumptions used in the modelling are plausible, objective and robust
- Carfilzomib with lenalidomide and dexamethasone (CRd) meets the extension to life criterion, but does not meet the short life expectancy criterion. **Survival for Rd is estimated in the model to be 4.08 years and the survival extension with CRd is estimated to be 2.54 years**.
- Company notes that Committees can show discretion and highlights the appraisal of pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer (NICE TA509).
- The technical team note that flexibility in the application of the end-of-life criteria in NICE TA509 was accepted by the committee as an exceptional circumstance, as pertuzumab had been available on the Cancer Drugs Fund for several years.

Does the technology meet end-of-life criteria?

Other issues for consideration

Cancer Drugs Fund

- Company has not expressed an interest in carfilzomib being considered through the Cancer Drugs Fund, due to mature head-to-head data available from the ASPIRE trial.
- Technical team considers that carfilzomib is unlikely to be a candidate for the Cancer Drugs Fund.

Innovation

- Company considers carfilzomib with lenalidomide and dexamethasone to be innovative
- Technical team considers that all relevant benefits associated with the drug are adequately captured in the model.

Equality considerations

- None identified.
- Are there any equality issues?

Key issues considered at technical engagement	Status
1 –Treatment pathway a) Is the positioning of carfilzomib clear in both treatment pathways? b) Have all the relevant comparators been considered?	Resolved
2 – Post hoc subgroups a) In clinical practice, is it possible for patients to receive lenalidomide and bortezomib as a first-line treatment even though this is not recommended in NICE guidance? b) Which post hoc subgroup of the ASPIRE trial reflects NHS clinical practice?	For discussion
3 – Utility values used in model a) Are there additional treatment-specific benefits with carfilzomib with lenalidomide and dexamethasone compared with lenalidomide plus dexamethasone, other than gains in progression-free survival and overall survival? b) Are the utility values used in the company's economic model appropriate and reliable for decision-making?	For discussion
4 – Extrapolation of overall survival a) Should data be used entirely from the ASPIRE trial or in combination with real world data to extrapolate overall survival? b) Is the exponential or the company's preferred model more appropriate for extrapolation of overall survival?	For discussion