For Projector – no confidential information

NICE National Institute for Health and Care Excellence

Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma

Chair's presentation

2nd appraisal committee B meeting

Chair: Amanda Adler

Lead team: Nick Latimer, Sanjeev Patel, Tony Wootton

Technical team: Alan Moore, Emily Eaton Turner, Linda Landells

Company: Sanofi

ERG: School of Health and Related Research (ScHARR), University of Sheffield

16th July 2020

Recap: Decision problem

Summary of appraisal

Marketing authorisation	Combined with pomalidomide (POM) + dexamethasone (DEX), to treat relapsed and refractory multiple myeloma in adults who have received 2 or more prior therapies including lenalidomide (LEN) + proteasome inhibitor* whose disease progressed on last therapy
Population	Company position 4th line; exploratory analysis at 3rd line License allows 3rd line use and later NICE scope 3rd line use and later
Intervention	**Isatuximab (ISA)**: humanised monoclonal antibody CD38 Pomalidomide: immunomodulating agent Dexamethasone: corticosteroid
Comparators	**NICE scope 4th line:** 1. POM/DEX 2. Panobinostat (PANO) + bortezomib (BORT) + DEX **Company 4th line:** POM/DEX
Clinical trial	ICARIA-MM: open-label, RCT, ISA/POM/DEX vs. POM/DEX Company use post-hoc subgroup of people at 4th line Median follow-up: 11.6 months

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* Proteasome inhibitors include bortozomib, carfilzomib, ixazomib

Draft recommendations in appraisal consultation document (ACD)

- ‘Company proposes that isatuximab plus pomalidomide and dexamethasone is for …people who have had at least 3 treatments before. Current treatment at this point is usually pomalidomide plus dexamethasone, or daratumumab alone (in the Cancer Drugs Fund)
- ‘.. trial evidence in this group suggests that isatuximab plus pomalidomide and dexamethasone delays the disease progressing and increases how long people live compared with pomalidomide plus dexamethasone. But the trial is not yet finished, so it is not certain how much more clinical benefit isatuximab plus pomalidomide and dexamethasone ...’
- ‘The most likely cost-effectiveness estimates …are much higher than what NICE normally considers a cost-effective use of NHS resources. Therefore, it is **not recommended**.’

Key Issues

1) Trial short, data 'immature'. To extrapolate deaths beyond end of trial, committee preferred using Weibull distribution for both ISA/POM/DEX and POM/DEX to model overall survival (key driver of cost effectiveness).
   Company still chooses exponential distribution for ISA/POM/DEX but has changed to Weibull for POM/DEX. What are the most appropriate distributions to model overall survival in each arm?
2) Should company adjust for daratumumab and lenalidomide use beyond 4th line used in its trial but not in NHS practice? If not, should costs be removed?
3) Does the company model treatment waning reasonably?
4) Is evidence for treatment at 3rd line sufficient for decision making?
5) If not for routine commissioning does ISA/POM/DEX meet criteria to include in Cancer Drug Fund – 'part 2'

Recap: Pharmacological treatment options

Isatuximab license specifies must have prior lenalidomide and a proteasome inhibitor

Monoclonal antibodies:
Daratumumab (DARA), **Isatuximab (ISA)**

Proteasome inhibitors:
Bortezomib (BORT), Carfilzomib (CARF), Ixazomib (IXA)

Immunomodulatory agents:
Thalidomide (THAL), Pomalidomide (POM), Lenalidomide (LEN)

Alkylating agents:
Cyclophosphamide, Bendamustine, Melphalan

Histone deacetylase inhibitor:
Panobinostat (PANO)

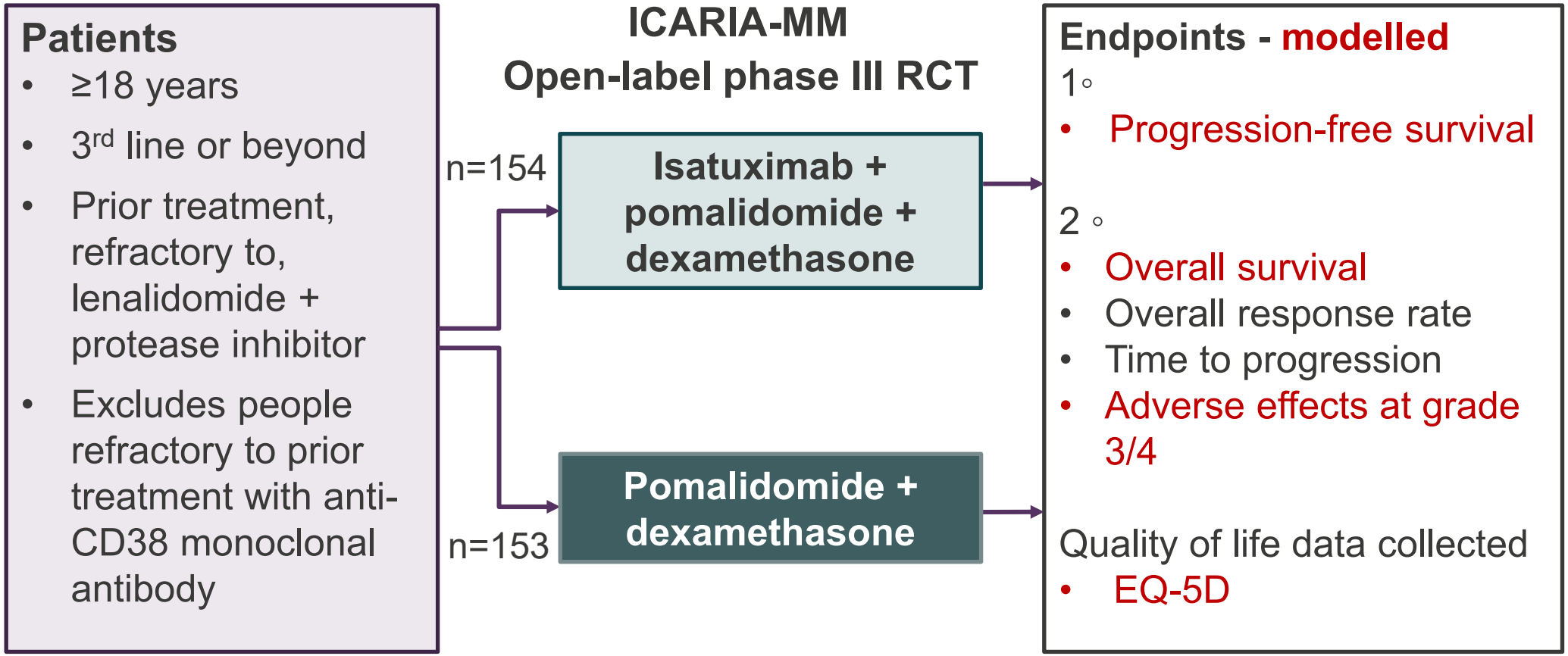
Multiple Myeloma Treatment Pathway

License allows 3rd line or later and requires lenalidomide and proteasome inhibitor before; company proposes 4th line; Cancer Drug Fund (CDF) treatments not comparators

	Eligible for stem cell transplant	**Not eligible** for stem cell transplant		
1st line	**Bortezomib** + dexamethasone ± thalidomide (TA311) followed by chemotherapy + autologous stem cell transplant (ASCT)	Thalidomide + alkylating agent + corticosteroid (TA228)	**Lenalidomide** + dexamethasone [if thalidomide not an option] (TA587)	**Bortezomib** + alkylating agent + corticosteroid [if thalidomide not an option] (TA228)
2nd line	**Bortezomib** + second ASCT	**Carfilzomib** + dexamethasone [if not previously received bortezomib] (TA457)	Daratumumab + **bortezomib** + dexamethasone (TA573) [CDF]	**Lenalidomide** + dexamethasone [if previously received bortezomib] (TA586)
3rd line	Panobinostat + **bortezomib** + dexamethasone (TA380)	**Ixazomib + lenalidomide** + dexamethasone (TA505) [CDF]	**Lenalidomide** + dexamethasone (TA171)	**Isatuximab + pomalidomide + dexamethasone (ID1477)?**
4th line	Daratumumab (TA510) [CDF]	Panobinostat + bortezomib + dexamethasone (TA380)	**Isatuximab + pomalidomide + dexamethasone (ID1477)?**	Pomalidomide + dexamethasone (TA427)	Ixazomib + lenalidomide + dexamethasone (TA505) [CDF]

Evidence from ICARIA-MM trial

Company focuses on a post-hoc subgroup who received 3 treatments n=110 (ISA/POM/DEX: n=52, POM/DEX: n=58)



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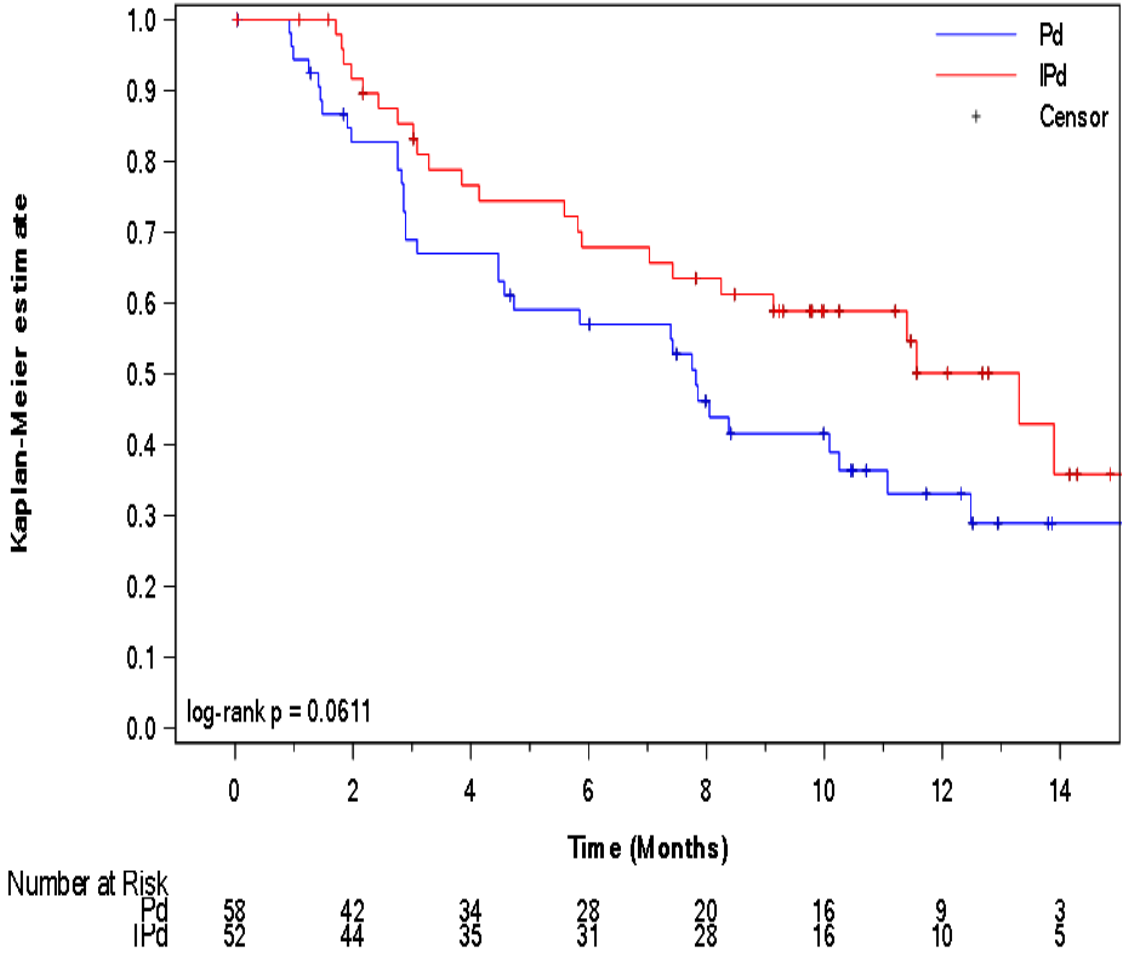
Results recap ICARIA-MM: progression-free survival 4th line subgroup

Data immature, low numbers at risk at 14 months



	ISA/POM/ DEX (n=52)	POM/ DEX (n=58)
Events, n	**23** (44%)	**33** (57%)
Median, months (95% CI)	**13.3** (7.4 to not calculable)	**7.8** (4.5 to 11.1)
Hazard ratio stratified by age, rounded (95% CI) Log-Rank test p-value		0.60 (0.35 to 1.03) p=0.061

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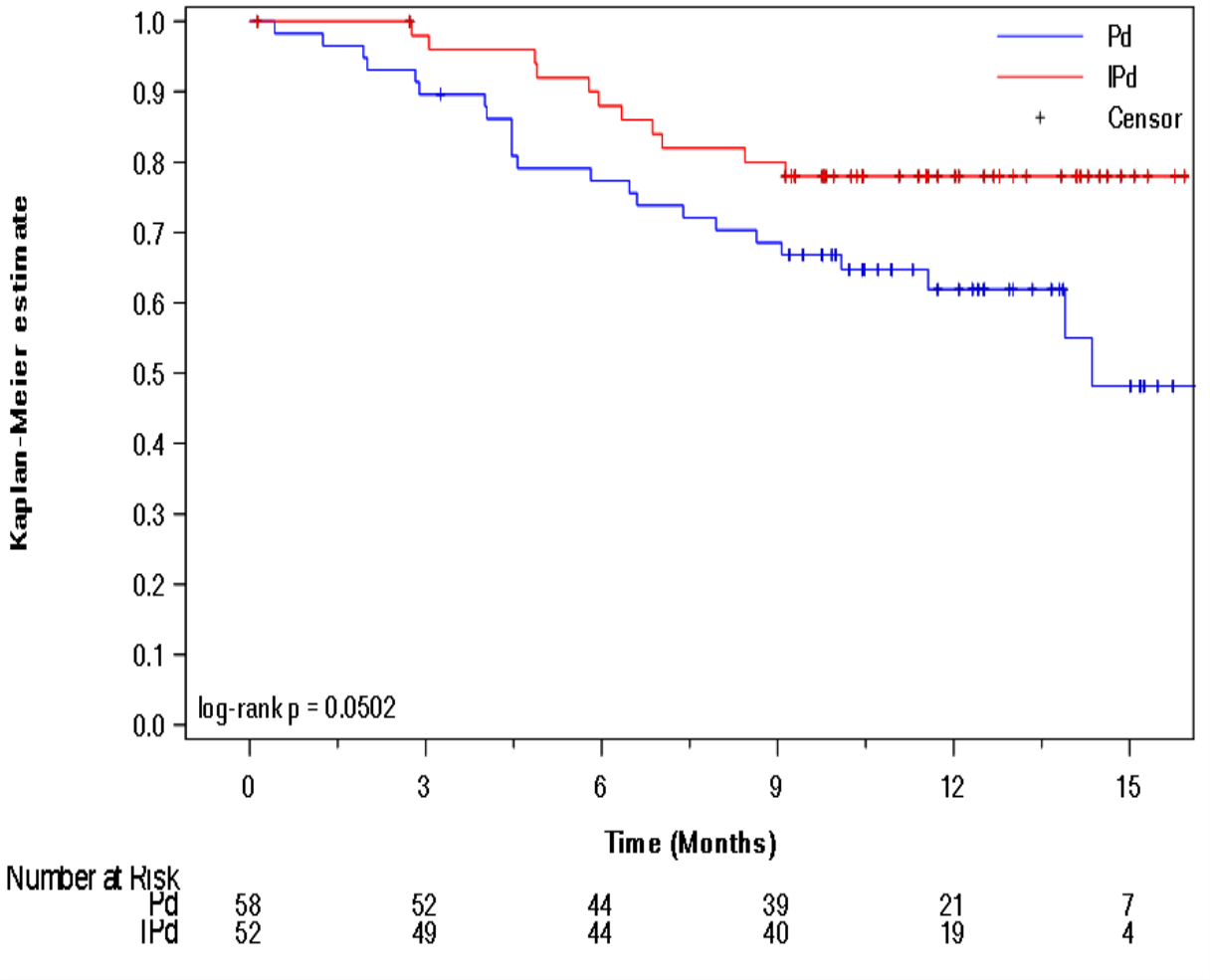
Results recap ICARIA-MM: overall survival in 4th line subgroup

Intention to treat unadjusted for later therapies, data immature, few at risk at 15 months



	ISA/POM/DEX (n=52)	POM/DEX (n=58)
Events, n	**11** (21%)	**23** (40%)
Median, months (95% CI)	Not reached	**14.4** (11.6 to not calculable
Hazard ratio stratified by age (95% CI) Log-Rank test p-value	0.49 (0.24 to 1.02) p=0.0502	

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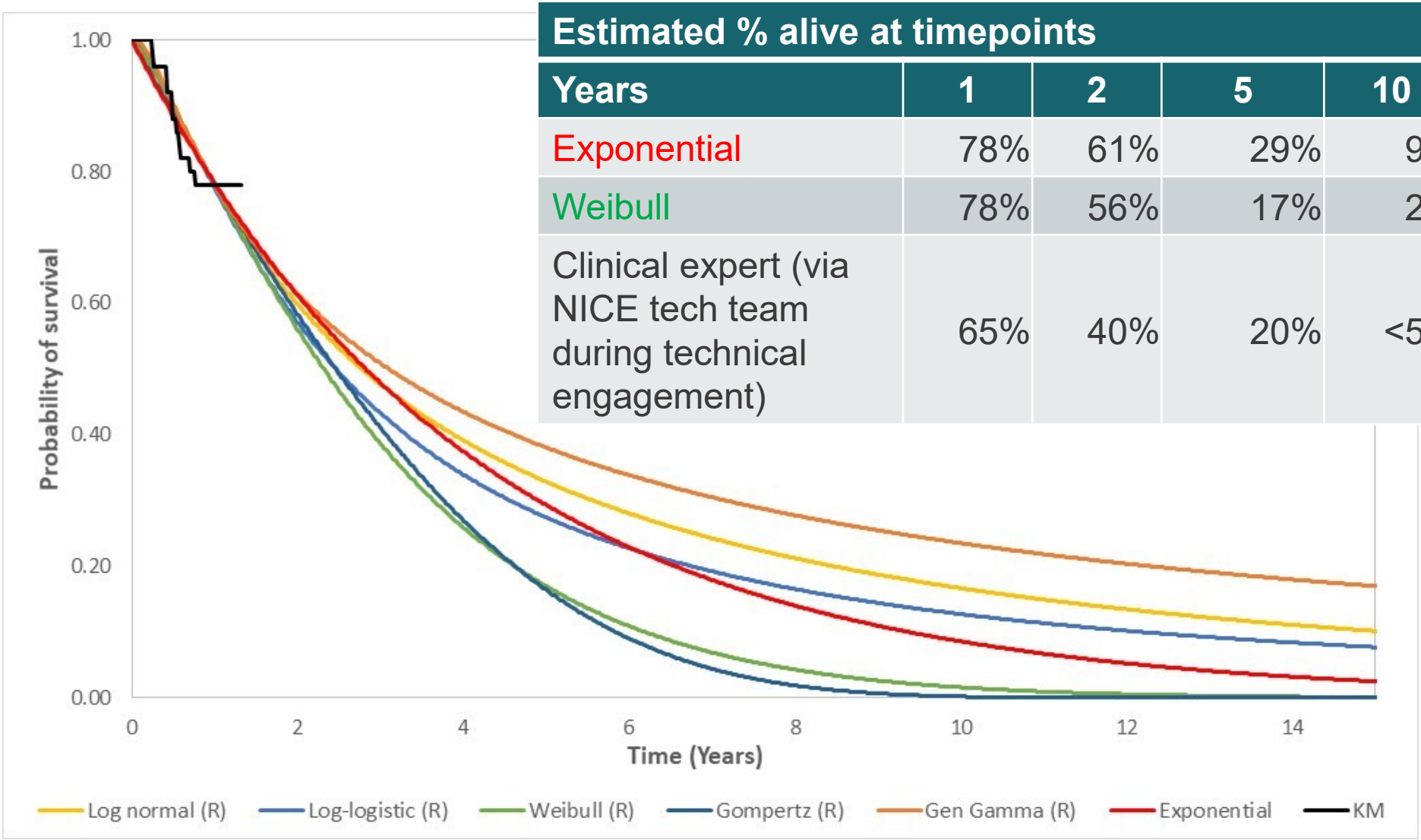
Recap ISA/POM/DEX:

Company chose exponential distribution to extrapolate overall survival

Committee preferred Weibull based on clinical input at 1st meeting

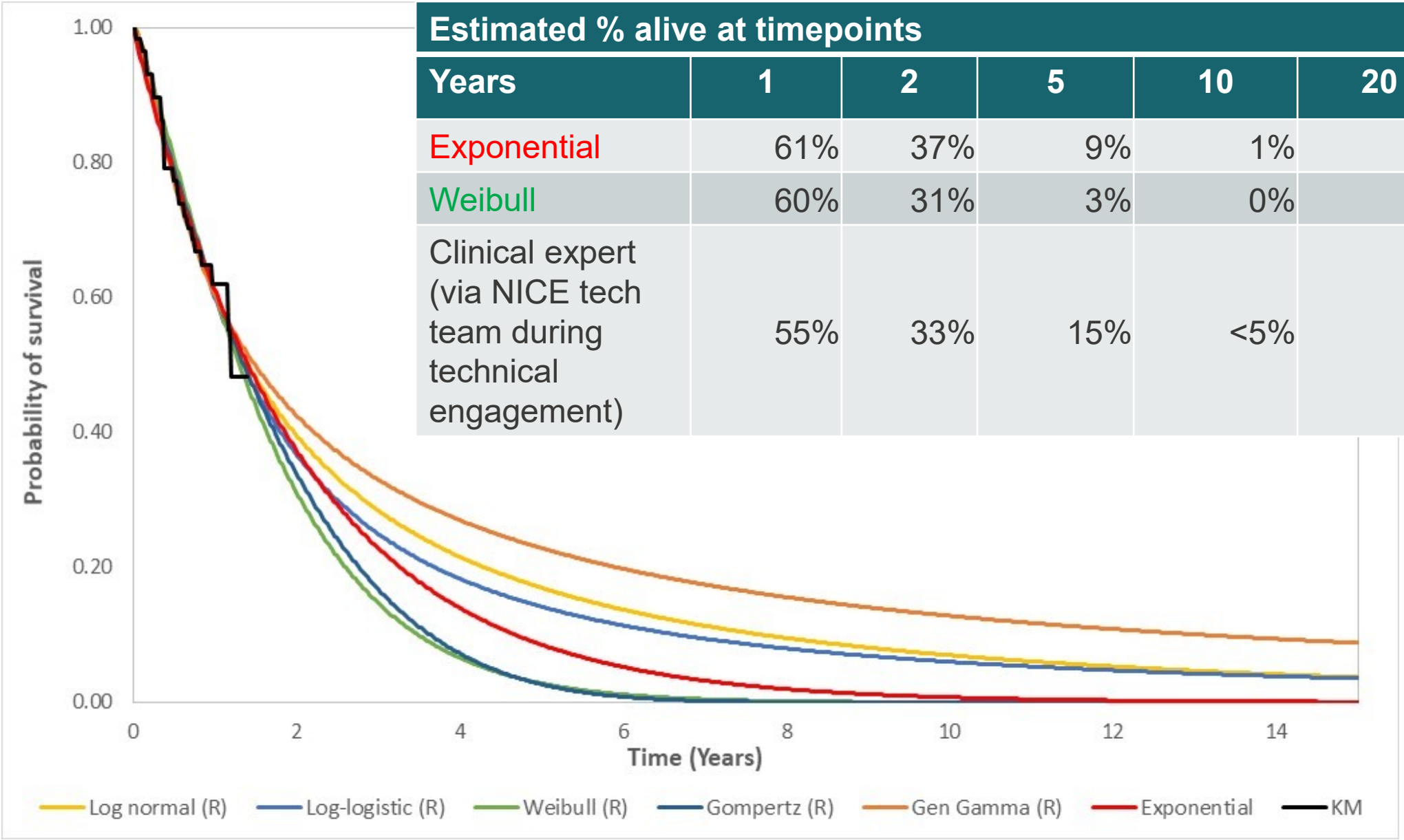


Estimated % alive at timepoints					
Years	**1**	**2**	**5**	**10**	**20**
Exponential	78%	61%	29%	9%	0%
Weibull	78%	56%	17%	2%	0%
Clinical expert (via NICE tech team during technical engagement)	65%	40%	20%	<5%	0%

Recap POM/DEX:

Company originally chose exponential curve to extrapolate overall survival
Committee preferred Weibull based on clinical input at 1st meeting

Estimated % alive at timepoints					
Years	**1**	**2**	**5**	**10**	**20**
Exponential	61%	37%	9%	1%	0%
Weibull	60%	31%	3%	0%	0%
Clinical expert (via NICE tech team during technical engagement)	55%	33%	15%	<5%	0%



Appraisal Consultation ACD committee key conclusions (1)

Issue	Committee conclusions	Addressed in responses?
Position in treatment pathway	• Company positioning at 4th line appropriate given clinical practice, but heard unmet need at 3rd line • Committee welcomes evidence from company for 3rd line ISA/POM/DEX versus relevant comparator	✓
Comparator at 4th line	POM/DEX is relevant comparator PANO/BORT/DEX rarely used	Not required
Subgroup analysis	Analysis for people with 3 prior treatments in ICARIA-MM acceptable for decision making	Not required

Anti-CD38 monoclonal antibody treatments	• For people already treated with anti-CD38 antibody ISA/POM/DEX:
	  • **Would not** use if disease progressed on treatment
	  • **Would** use if treatment stopped for reasons other than disease progression
	• No evidence presented for people who have previously had an anti-CD38 antibody
		Not required

ACD key committee conclusions (2)

Issue	Committee heard/conclusions	Addressed in responses?
Extrapolating key clinical outcomes beyond trial	**Overall survival:** • Company chose **exponential** for both treatments • **Weibull** most plausible for both treatments **Progression free survival:** • Company jointly fitted **lognormal** distribution, i.e, same curve to data for both treatment arms with treatment group as covariate, implying constant treatment effect over time • Choice did not impact cost effectiveness much **Time on treatment:** • Company choice of exponential reasonable • Other distributions worsen cost effectiveness	✓
Treatment waning	• Heard clinical experts state that relative benefit of ISA/POM/DEX would unlikely last for a lifetime • Company should include waning of relative treatment effect in its model	✓

ACD key committee conclusions (3)

Issue	Committee heard/conclusions	Addressed in responses?
Treatments after 4th line	• Appropriate to adjust for treatments not given in NHS • Company's method to adjust may be appropriate, but need more information	✓ (partially)
Drug wastage	Wastage occurs; company accounts for it	Not required
Health related quality of life (utility) and adverse events	• Company did not include adverse events effects on utility values in model • More adverse events, but fewer people stopping treatment in ISA/POM/DEX arm of trial • On balance, utility values appropriate	Not required

ACD key committee conclusions (4)

Issue	Committee heard/conclusions	Addressed in responses?
NICE End-of- life criteria	Model using committee's preferred distribution estimates: • Standard care overall survival mean <2 years • ISA/POM/DEX likely extends life mean >3 months Criteria met at 4th line	Not required
Cancer Drugs Fund (CDF)	ICARIA-MM trial will finish March 2021 Further data could reduce uncertainties surrounding key drivers of cost-effectiveness, notably: ✓ overall survival ✓ time on treatment At current price, ISA/POM/DEX does not have 'plausible potential' to be cost-effective	✓
No analyses with committees preferences	• Weibull distribution to extrapolate overall survival for both treatments • Adjust for 5th line and beyond: daratumumab + lenalidomide • Waning of relative treatment effect	✓

ACD consultation responses

Consultee:

- Sanofi, manufacturer of isatuximab

Patient experts:

- Myeloma UK
- 1 patient expert

Clinical experts:

- 1 expert

Other:

- UK Myeloma Forum

Patient perspective

Summary of responses received from Myeloma UK and 1 patient expert

- ‘Outcome will have considerable physical and psychological impact upon the lives of relapsed and refractory patients’
- Acknowledge key issues of short follow-up data
- ‘In the absence of data from the ICARIA or other trials, patients refractory to daratumumab should not receive isatuximab at fourth line’
- ISA/POM/DEX should be available to people who ‘missed the opportunity’ for daratumumab at 2nd line.. and to those whose disease has not been refractory to prior anti-CD38 antibody
- Patients value PFS over other factors: ISA/POM/DEX has clear PFS advantage
- ‘Clear evidence that this treatment is significantly better’ than comparator
- ISA/POM/DEX:
  - highly likely to be more effective than daratumumab monotherapy
  - combines an anti-CD38 antibody, an immunomodulatory drug and a corticosteroid - different mechanisms of action at 4th line
  - MHRA considered it a “Promising Innovative Medicine”

Clinical perspective

Summary of responses received from clinical expert and UK Myeloma Forum

- Disappointed
- Clear unmet need at 4th line for people with multiple myeloma and 4th line is the most appropriate position in current pathway for ISA/POM/DEX
- Current practice: daratumumab monotherapy (via CDF) given at 4th line and POM/DEX at 5th line. Better to combine an anti-CD38 antibody with an immunomodulatory drug rather than using across 2 lines of treatment
- A sizeable number of people will not have had daratumumab by 4th line
- ISA/POM/DEX is a step change in treatment - combines well-tolerated anti-CD38 antibody (ISA) with most potent available immunomodulatory drug (POM)
- Poor clinical outcomes and treatment response at 5th line and beyond irrespective of treatment

Company's response

	Company	What's new or not

Long term survival	• Exponential remains best for ISA/POM/DEX, not committee's choice of Weibull
	• Weibull OK for comparator
		• No new data for ISA/POM/DEX
		• Supportive evidence for exponential curve for ISA/POM/DEX provided:
		  • Long term survival data for daratumumab
		  • Surrogate endpoints and 'synthetic' data
		  • Different mechanism between treatments justifies different curves
		• Published KM POM/DEX data which company considers to support Weibull for POM/DEX

Treatment waning	No data to inform this. May already be included in analysis	• Waning scenario provided (when 90% stop ISA/POM/DEX)
Adjusting for treatments beyond 4th line	Appropriate to not adjust benefits or costs of these treatments	Company provided details of its adjustment analysis presented in 1st meeting
3rd line population	Evidence limited by data and indirect comparison	Analyses provided
Price of isatuximab	Patient access scheme (PAS) exists 'Complicated' by POM which has own confidential PAS	Unchanged If CDF, then additional commercial arrangements required

Survival beyond end of trial for people treated with ISA/POM/DEX

Case for company's preferred extrapolation and against committee preferred extrapolation

Overall survival: company response

- The ‘key area of uncertainty’
- Data immature ~30% events ‘limited OS data’…clinicians have ’limited experience’
- ‘A range of clinically plausible curves’
- Company disagree with Weibull for ISA/POM/DEX (prefer exponential); agree with committee preference of Weibull distribution for POM/DEX

Company provides:

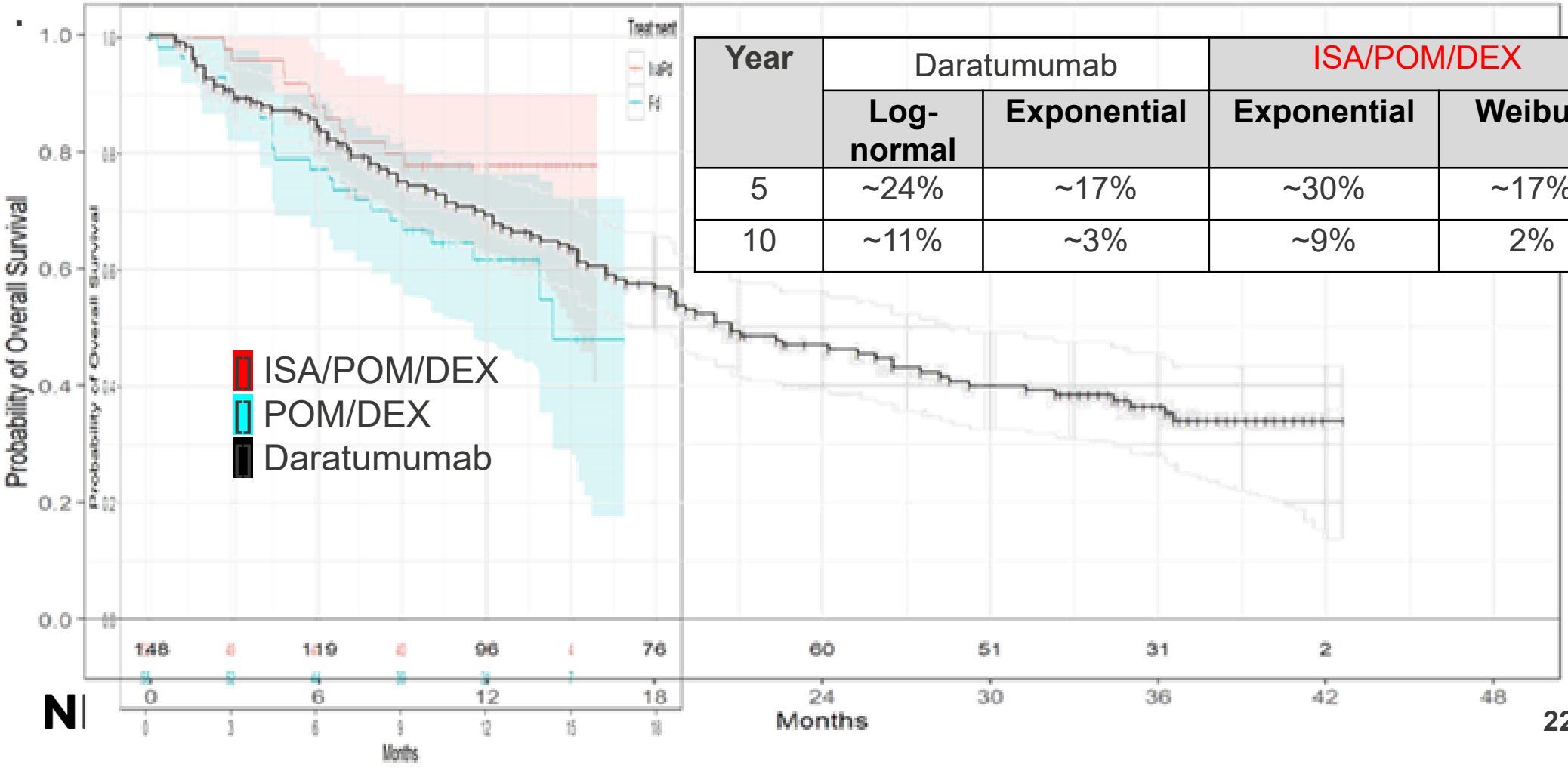
- ISA/POM/DEX - exponential distribution – unchanged from original base case
    1. Comparing to daratumumab monotherapy data at 4th line
    2. Using surrogates to support company’s choice
        - Residual disease
        - Progression free survival
    3. ‘Synthetic’ overall survival using imputed data
    4. Different mechanisms, different curves
- POM/DEX - Weibull distribution – changed from original base case
    - Compared to published literature

Overall survival: daratumumab data

Daratumumab monotherapy new data - not a comparator

- Company naïvely indirectly compares ISA/POM/DEX to daratumumab monotherapy at 4th line
- ISA/POM/DEX better than daratumumab – aligns with company's survey of 21 clinicians
- Exponential and log-normal distribution fit daratumumab monotherapy data best

4th line OS KM data from ICARIA-MM and combined data for daratumumab from pooled GEN501 + SIRIUS trials (n= 148, median follow-up 36.6 months, median survival 20.5 months [16.6 to 28.1])



Year	Daratumumab		ISA/POM/DEX	
	Log-normal	Exponential	Exponential	Weibull
5	~24%	~17%	~30%	~17%
10	~11%	~3%	~9%	2%

ERG comments: using daratumumab data

- Reasonable to expect that treatments of same class follow the same underlying statistical model, but cautions against making inferences based on pooling data from different studies
- Pooled SIRUS and GEN501 data on visual inspection of empirical hazard function suggests a **decreasing** rather than **constant** hazard
  - ERG prefers log-logistic distribution for daratumumab data (shape parameter β greater than one)
  - ERG applies log-normal distribution to ISA/POM/DEX arm in scenario analysis (based on available data)
- Similar empirical hazard function for ISA/POM/DEX and daratumumab data: no evidence of constant hazard function over time
  - ERG prefers exponential over Weibull as ERG does not believe hazards are increasing
- Independently fitted Weibull appropriate for POM/DEX if a different distribution chosen for ISA/POM/DEX – ERG provides this in its analysis

◉ *What is committee's view that this analyses confirms that ISA/POM/DEX improves survival compared with DARA alone? Should DARA alone curve apply to ISA/POM/DEX?*

Overall survival – surrogates depth and duration of response

Company: minimal residual disease negative and 'partial response' prognostic for PFS and OS

ICARIA-MM trial: MRD status only recorded in small number of patients

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- Steeper downward slope in PFS and OS in earlier months driven by people with less than partial response. Those with partial response or better drive tails of OS curves (i.e slope less steep over time)

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MRD: minimal residual disease; PFS: progression-free survival; OS: overall survival

ERG: surrogates depth and duration of response

- Could not find data which company reference for association between complete response/presence of minimal residual disease (MRD) and shorter PFS
- Accepts that PFS and OS may differ but ICARIA-MM evidence uncertain
- If PFS and OS events early in ICARIA-MM trial are mainly in people with less than partial response, and people with better response have events later as company asserts, then this would be consistent with a higher hazard rate at the beginning of the study
- No statistically significant difference in HRs when interaction between response level, treatment effect and treatment effect by response level interaction but there appeared to be a trend

NICE

MRD: minimal residual disease; PFS: progression-free survival; OS: overall survival; HR: hazard ratio

Overall survival using PFS as a surrogate

Company argues PFS supports it choice of exponential curve for OS for ISA/POM/DEX and uses PFS:OS results from literature in alternative analysis

Study	Mean of median PFS (months)	Mean of median OS (months)	Ratio PFS:OS deceleration factor	Comment from company
Felix et al. 2013	22.5	39.1	1.7	Not appropriate. Based on studies at earlier lines of treatment used in sensitivity analysis
Dimopoulos et al. 2017	8.3	24.3	2.9	Most plausible. Although not estimated from data from the same drug class
SIRIUS trial daratumumab monotherapy phase 2 of 2 doses	Not reported	Not reported	5.0	Same drug class

ERG comments: Dimopoulos meta-analysis a workshop abstract; not peer-reviewed

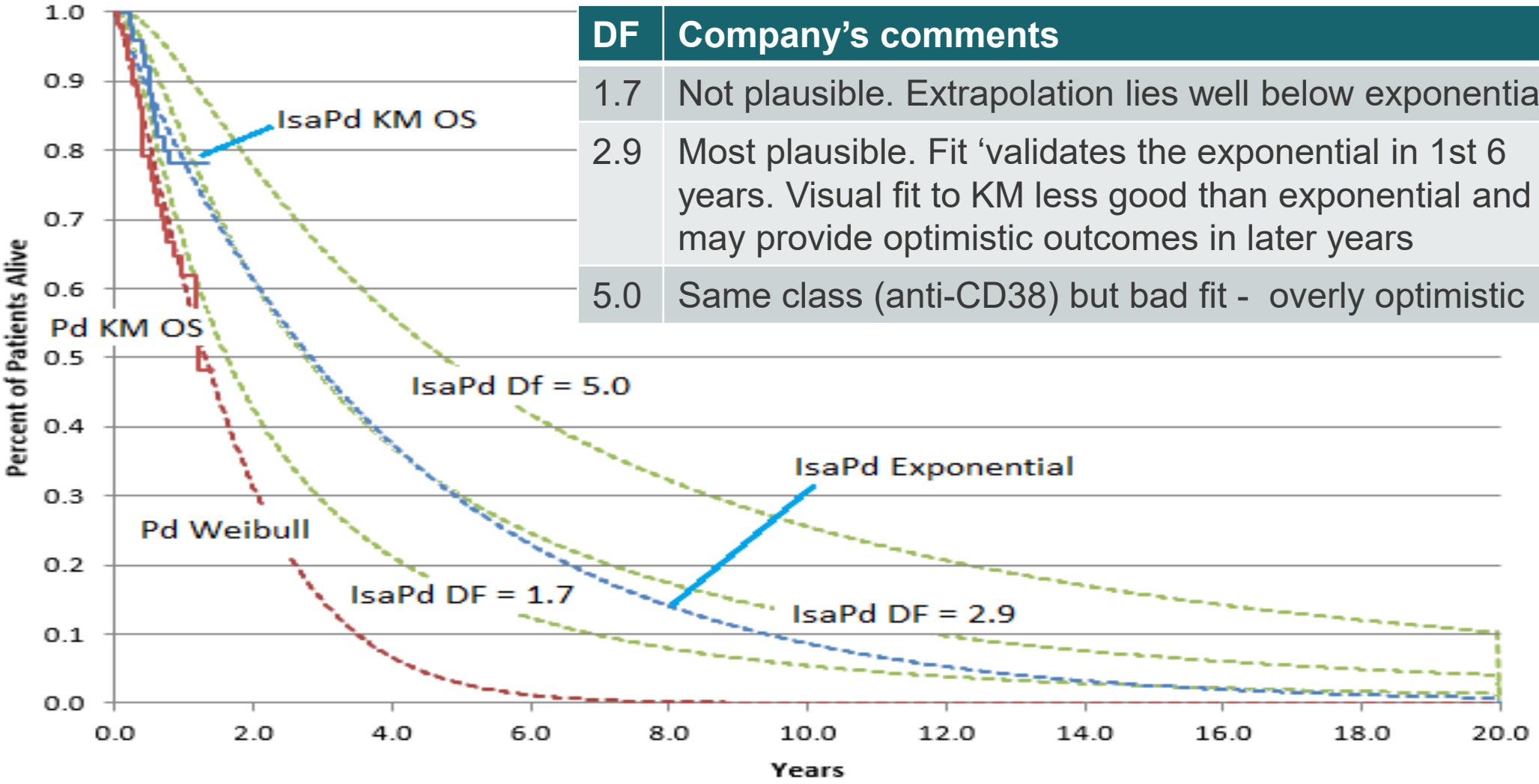
Ratio of PFS to OS is an uncertain parameter; uncertainty has not been discussed by company

PFS: progression-free survival; OS: overall survival

Overall survival using surrogates PFS

Company applied deceleration factors of 1.7, 2.9 and 5.0 to extrapolated PFS data using lognormal distribution (committee preference) for PFS for ISA/POM/DEX from ICARIA-MM to predict OS

DF	Company's comments
1.7	Not plausible. Extrapolation lies well below exponential
2.9	Most plausible. Fit 'validates the exponential in 1st 6 years. Visual fit to KM less good than exponential and may provide optimistic outcomes in later years
5.0	Same class (anti-CD38) but bad fit - overly optimistic



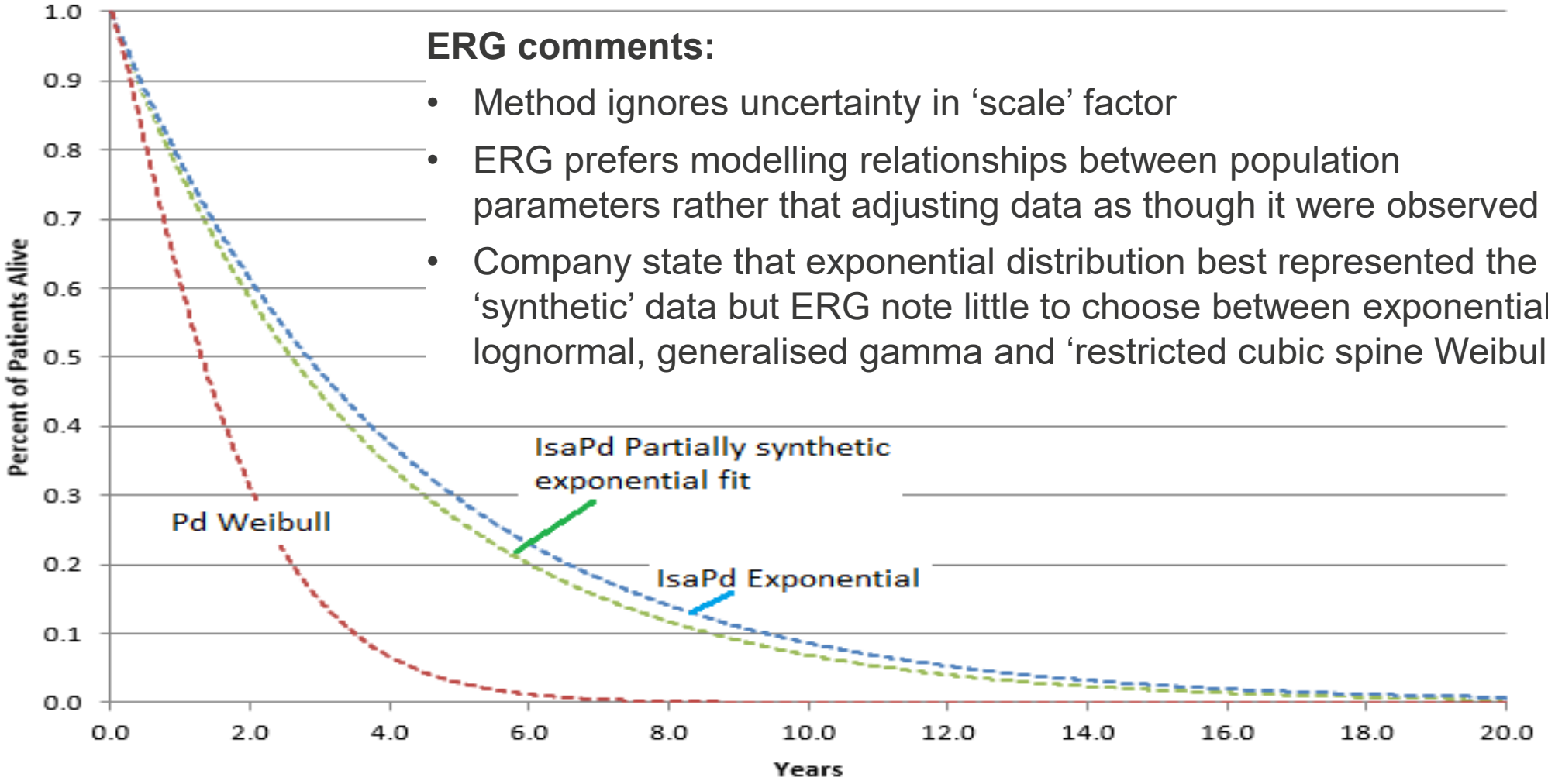
◉ *What are committee views on use of surrogates to justify choosing exponential over Weibull to extrapolate overall survival beyond end of trial?*

‘Partially synthetic’ data for overall survival

Company generated ‘partially synthetic’ OS data using observed PFS and OS data from ICARIA-MM and imputed data calculated using deceleration factor of 2.9

States analysis supports exponential distribution – best fit to the synthetic data

Partially synthetic curve compared with exponential ISA/POM/DEX



ERG comments:

- Method ignores uncertainty in ‘scale’ factor
- ERG prefers modelling relationships between population parameters rather that adjusting data as though it were observed
- Company state that exponential distribution best represented the ‘synthetic’ data but ERG note little to choose between exponential, lognormal, generalised gamma and ‘restricted cubic spine Weibull’

Isatuximab's mechanisms of action

Different mechanisms justifies different curves for ISA/POM/DEX + POM/DEX

- Isatuximab's multiple mechanisms of action targets both myeloma cells and immune system
  - Complement-dependent cytotoxicity, antibody—dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis
- Isatuximab gives improved anti-tumour immune response as it targets not only MM cells but also immunosuppressive cells
- Company claim that the synergistic effect of immunomodulatory agents and anti-CD38 therapies is significant and that the immunomodulatory effect is likely to extend beyond treatment duration

ERG comments

- Reasonable for distributions used to model OS to be different by treatment because of different mechanism of action

◉ *What is committee's view on whether different mechanisms of ISA/POM/DEX and POM/DEX warrant different extrapolation functions for data on survival?*

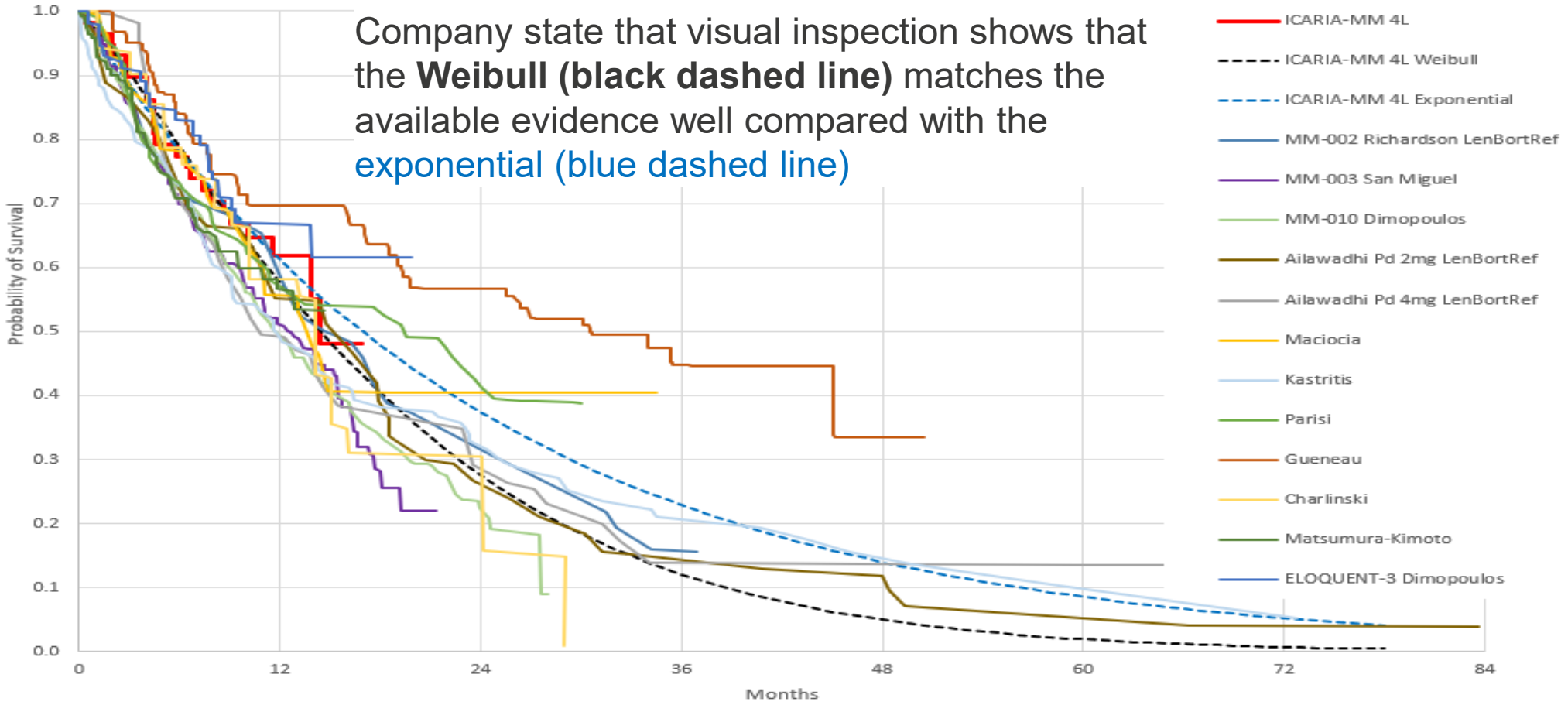
ERG comments on extrapolating overall survival using exponential curve for ISA/POM/DEX

- **Exponential distribution:**
  - assumes average hazard of death is constant across patients' lifetime
  - arises as a mixture of Weibull distributions with fixed shape parameter, $\nu > 1$
- **Company** is asserting that either:
  - marginal risk of death is constant over lifetime of patients and shape parameter of Weibull distribution is 1.0 with probability 1.0, or
  - there are groups of patients with common shape parameter but different scale parameters in whom hazard of death increases over time
- **ERG** does not consider either:
  - it reasonable to assert with probability one that parameters take particular values and that a model is the true model
  - that company has presented any evidence to show that there are groups of patients with common shape parameter but different scale parameters in whom marginal risk of death increases over time
- Not appropriate to jointly-fit Weibull for ISA/POM/DEX if a different distribution is used for POM/DEX. Independent Weibull should be used

◉ *What is committee's view on the appropriate way to extrapolate immature data?*

Overall survival – POM/DEX

Company use published overall survival trial literature of POM/DEX to support use of Weibull to estimate OS in POM/DEX arm of ICARIA-MM (committee preference – clinical expert input at 1st meeting)



ERG comments:

- Greater proportion of people were less fit in POM studies compared with ICARIA-MM
- Company did not fit any parametric models to published POM/DEX KM data
- Company did not provide any supporting evidence that the data generating process is a Weibull distribution for each POM/DEX study

Treatments 5th line and beyond

How to adjust trial results and costs for treatments used in trial but not NHS, and used more in control arm than ISA/POM/DEX

Adjustment for subsequent treatments

Committee concluded some treatments given following 4th line disease progression in ICARIA-MM did not reflect NHS clinical practice and analysis should adjust for this. Company prefers not to adjust costs or benefits of these treatments

Company

- Recognises some treatments taken post progression in ICARIA-MMM do not reflect NHS clinical practice
- Clinical experts stated 5th line treatments unlikely to make people live longer
- Company provided information on co-variates used and range of weights estimated in inverse probability of censored weights (IPCW) from 1st meeting
- Reconstructing individual patient data from the data set and fitting parametric curve to both trial arms produced counterintuitive results: survival outcomes slightly improved when daratumumab and lenalidomide treatments removed

ERG

- Company position contradictory; believe 5th line treatments ineffective but include costs, which are high and these treatments not recommended in England at this line
- Suggest that committee intended the costs of daratumumab and lenalidomide to be removed from company's analysis and explored this scenario

◉ *Has committee heard evidence to change its view about adjusting for treatments? If not, is IPCW appropriate/done appropriately? If not, should costs be included?*

Treatment ‘waning’

Committee: Company should include waning of relative treatment effect in its model

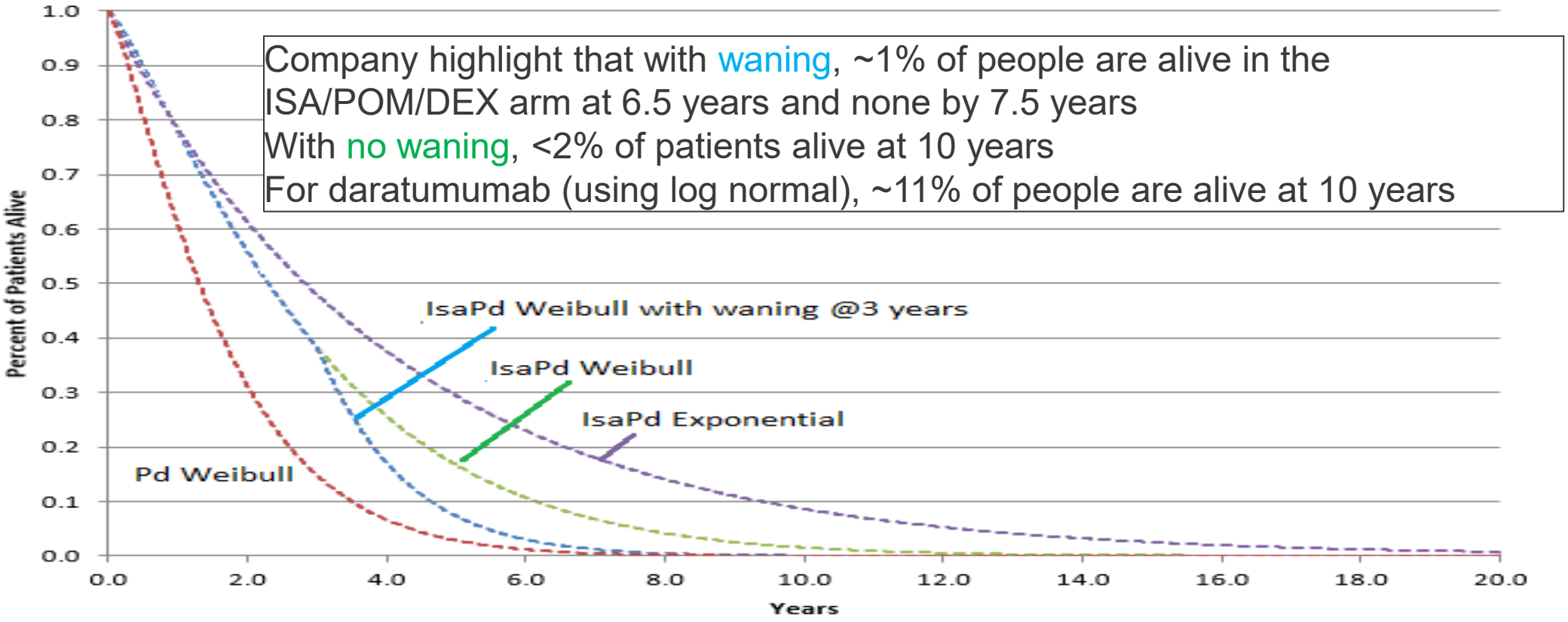
Treatment waning

Committee stated a preference to include waning of relative treatment effect of ISA/POM/DEX – company disagree but provide exploratory analysis

Company

- No obvious point when treatment waning should occur. Company chose applying a HR=1 when 90% of patients discontinue on ISA/POM/DEX (~3 years in model)
- Modelling already incorporates waning, considering numbers receiving at least a partial response with ISA/POM/DEX

Comparison of Weibull curve with treatment waning scenario



ERG comments: treatment waning

- Company's revised base case has potential to include waning treatment effect as different extrapolation functions fitted to each arm
- Company should have reported the appropriate measure of relative treatment effect over the lifetime to allow ERG to assess whether and when models predict a waning treatment effect

◉ *How should treatment waning be modelled?*

3rd line treatment with ISA/POM/DEX

3rd line positioning of ISA/POM/DEX

Company provide analysis on 3rd line population but notes lack of data, non-robust methods and inappropriate comparator

Company

- 4th line positioning appropriate for current pathway and based on unmet need
- 3rd line cohort is smaller (n=90) and than 4th line
- Cost effectiveness results reported using a matched-adjusted indirect comparison (MAIC) versus PANO/BORT/DEX, comparator in NICE scope, which company views as not a relevant comparator
- End of life criteria may be met at 3rd line
- Given immaturity of 3rd line data, and non-robust MAIC method, results exploratory

ERG comments

- Agree that comparing ISA/POM/DEX with PANO/BORT/DEX 3rd line not appropriate as committee decided PANO/BORT/DEX not used until 4th line
- POM/DEX dominates ISA/POM/DEX at 3rd line – not credible
- Disputes company claim that end of life criteria may be met at 3rd line based on 3rd line survival data from the POM/DEX arm of ICARIA-MM and modelled estimates

◉ *Are company's 3rd line analysis robust enough for decision-making?*
◉ *N.b. results in part 2*

Challenges in pricing isatuximab

Challenges of branded combination treatment

Company states to demonstrate that ISA/POM/DEX is cost-effectiveness provide alternative analysis removing POM costs from ISA/POM/DEX

Company

- ICER driven by POM (high list price) and increased PFS time (5.5 months) with ISA/POM/DEX when both ISA and POM costs occur in ISA/POM/DEX combination
- Company propose removing "background/backbone" POM costs using two approaches
  - POM costs of ISA/POM/DEX arm removed when POM costs common to both arms (i.e POM costs only occur in ISA/POM/DEX arm for extended ISA/POM/DEX treatment duration [v POM/DEX arm])
  - POM costs of ISA/POM/DEX removed for extended treatment duration v POM/DEX (i.e POM costs occur in ISA/POM/DEX arm only when occurred in POM/DEX arm)

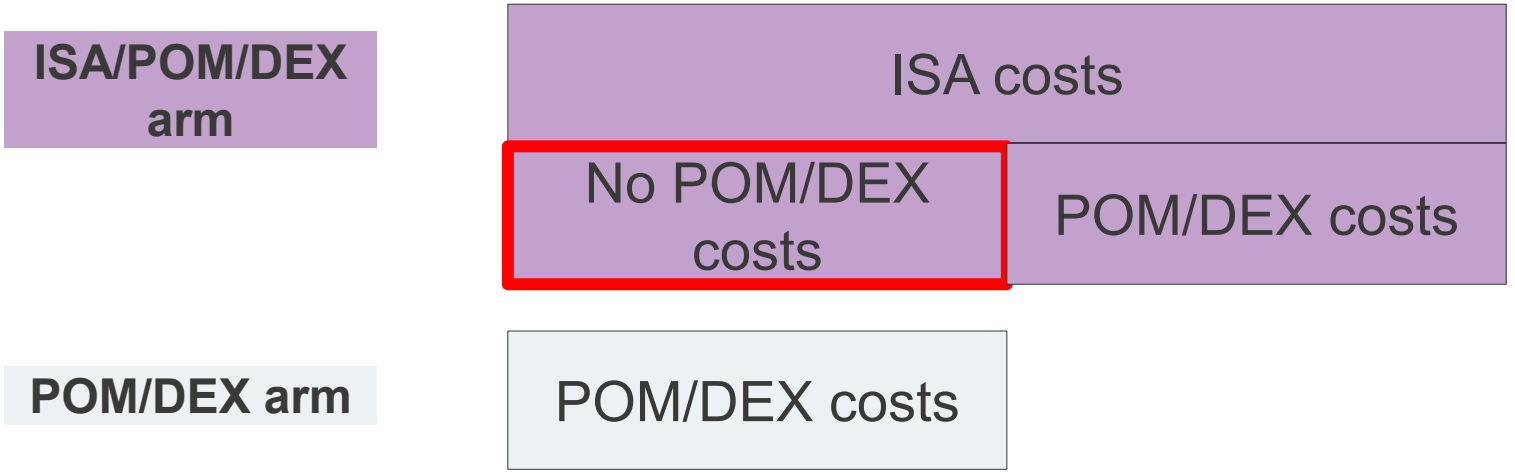
Diagram given on next slide

ERG comments

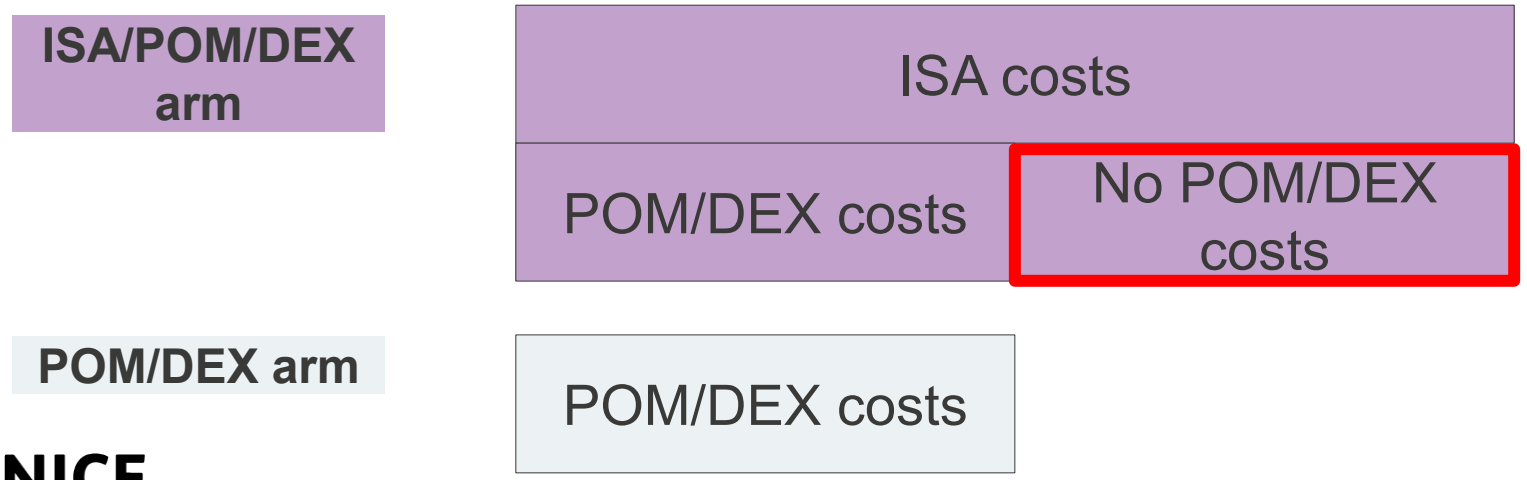
- No exemption in NICE methods guide to provide additional QALY weights where these are generated by more than 1 branded intervention

Company's two approaches for removing "backbone/background" POM/DEX costs from ISA/POM/DEX arm

Approach 1: no POM/DEX costs in ISA/POM/DEX arm when people **having POM/DEX** in POM/DEX arm



Approach 2: no POM/DEX costs in ISA/POM/DEX arm when people **stop having POM/DEX** in POM/DEX arm



NICE

Innovation

- Committee concluded that the model adequately captures all benefits
- Company disagrees

Company

- High psychological impact of disease when treatment options become limited
- Committee should include “element of hope” in decision-making process: people with cancer highly value hope in later lines of treatment (Lakdawalla et al 2012)
- Impact on caregiver quality of life many of whom are elderly should be considered

ERG comments

- Company does not discuss the likely loss of hope or increased carer burden associated with treatments that would be displaced by ISA/POM/DEX: net impact on societal health, which could be negative, is unknown
- Not known to what extent increased hope may be captured within the anxiety and depression dimension of the EQ-5D

◉ Has the committee heard evidence to change its conclusion that the model adequately captures all benefits?

Committee preferences + company updated base-case

Committee preference	Company comments/changes	ISA/POM/DEX	POM/DEX
Weibull to extrapolate overall survival both treatments	Agree with Weibull for POM/DEX but not for ISA/POM/DEX	1. Exponential (base case) 2. Deceleration factor 3. Partially synthetic data	Weibull
Adjust for 5th line treatments	Details of IPCW method provided	No adjustment for benefits or costs	
Waning	Company do not agree with this request; waning likely already included in base case	Waning implemented as scenario: immediate switch to HR=1 when ~90% of people had discontinue treatment	
Wastage – modelling appropriate		No change	

Additional analyses conducted by ERG on company base case

- Removed cost of daratumumab (DARA) and lenalidomide (LEN) 5th line treatments
- Log normal for ISA/POM/DEX OS extrapolation and independent Weibull for POM/DEX and DARA & LEN costs removed
- Independent Weibull for extrapolating POM/DEX OS and DARA & LEN costs removed

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential PAS discounts for comparators

Cancer Drug Fund - CDF - recommendation criteria

Committee previously concluded more data would reduce uncertainties

Proceed down if answer to each question is yes

Starting point: drug not recommended for routine use due to **clinical uncertainty**

TBD in Part 2

1. Is the model structurally robust for decision making? (omitting the clinical uncertainty)

⊙ *Agree?*

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

TBD in Part 2

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection via SACT relevant and feasible?

⊙ *ICARIA-MM? Other sources?*

Consider recommending entry into CDF (invite company to submit CDF proposal)

TBD in Part 2

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required, and number of patients in NHS in England needed to collect data.

NICE

Cancer Drugs Fund – company case

Company re-iterates support for ISA/POM/DEX in Cancer Drugs Fund (CDF) to supply treatment to NHS while it continues to collect data from its on-going trial

Company

- More data from ICARIA-MM can inform
  - Extrapolating overall survival
  - Adjusting for post progression trial treatments
- Uncertainty with current ICARIA-MM data: 99 completed PFS and OS events (32%)
- 'Interim' data cut planned when ~90% of 220 deaths occur – anticipated early **********
- Final OS analysis with ~220 deaths anticipated between ********** providing ********** of data
- CDF recommendation can also provide information through systemic anti-cancer therapy data collection which can inform time on treatment + patient characteristics

Key Issues

1) Trial short, data 'immature'. To extrapolate deaths beyond end of trial, committee preferred using Weibull distribution for both ISA/POM/DEX and POM/DEX to model overall survival (key driver of cost effectiveness).
   Company still chooses exponential distribution for ISA/POM/DEX but has changed to Weibull for POM/DEX. What are the most appropriate distributions to model overall survival in each arm?
2) Should company adjust for daratumumab and lenalidomide use beyond 4th line used in its trial but not in NHS practice? If not, should costs be removed?
3) Does company model treatment waning reasonably?
4) Is evidence for treatment at 3rd line sufficient for decision making?
5) If not for routine commissioning does ISA/POM/DEX meet criteria to include in Cancer Drug Fund – 'part 2'