NICE National Institute for Health and Care Excellence

For projector: Slides contain no confidential information

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

Lead team presentation

1st 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

13th May 2020

Abbreviations and definitions

4th line treatments [not in CDF] and scoped comparators:
ISA/POM/DEX: Isatuximab with pomalidomide and dexamethasone
POM/DEX: Pomalidomide with dexamethasone
PANO/BORT/DEX: Panobinostat with bortezomib and dexamethasone

LEN: Lenalidomide
CARF: Carfilzomib
DARA: Daratumumab
IXA: Ixazomib
DEX: Dexamethasone
ASCT: Autologous stem cell transplant
CDF: Cancer Drug Fund
Proteasome inhibitor: bortezomib, carfilzomib, ixazomib
CD38: a cell surface glycoprotein
Monoclonal antibody against CD38: **isatuximab**, daratumumab
TTD, Time to treatment discontinuation: duration of treatment

Key Issues

1) Is company's positioning of ISA/POM/DEX as a 4th line treatment option appropriate?
2) Are the 4th line subgroup data from the ICARIA-MM trial robust?
3) Is PANO/BORT/DEX a relevant comparator for ISA/POM/DEX at 4th line?
4) Does the indirect treatment comparison include all relevant evidence? Are the results from the matched adjusted indirect comparison valid?
5) Should the population in the NHS eligible for ISA/POM/DEX be those not already treated with a prior anti-CD38 monoclonal antibody?
6) What are the most appropriate models for extrapolating overall survival (OS), progression-free survival (PFS) and time to treatment discontinuation (TTD)?
7) Are the results of the clinical trial biased by treatments given at 5th line? How valid are the company's adjustment analyses?
8) Does ISA/POM/DEX meet NICE's end of life criteria?
9) Is ISA/POM/DEX a suitable candidate for the Cancer Drugs Fund?

Multiple Myeloma (MM)

- Malignant, progressive and incurable form of cancer that arises from plasma cells (type of white blood cell) in the bone marrow
- Myeloma cells suppress development of normal blood cells that are responsible for:
  - fighting infection - white blood cells
  - carrying oxygen around the body - red blood cells
  - blood clotting - platelets
- Symptoms include bone pain, fractures, anaemia, infections and hypercalcaemia
- Described by cycles of remission and relapse. People diagnosed with MM will generally receive several different regimens but when refractory to those agents, survival is limited
- Treatment aims to prolong survival and maintain a good quality of life by controlling the disease and relieving symptoms
- Choice of subsequent therapy is influenced by previous treatment and response to it, duration of remission, comorbidities and patient preference

Multiple Myeloma Treatment Pathway

License allows 3rd line or later; company proposes 4th line; 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)	Lenalidomide + dexamethasone [if thalidomide not an option] (TA587)	Thalidomide + alkylating agent + corticosteroid (TA228)	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)	
4th line	Daratumumab (TA510) [CDF]	Panobinostat + bortezomib + dexamethasone (TA380)	Isatuximab + pomalidomide + dexamethasone (ID1477)	Pomalidomide + dexamethasone (TA427)	Ixazomib + lenalidomide + dexamethasone (TA505) [CDF]

NICE appraisals in Multiple Myeloma (by most recent publication date)

TA number & Treatment	Recommendation/pathway position
TA587: Lenalidomide + DEX	Previously untreated people not eligible for stem cell transplant and only if thalidomide is contraindicated or the person cannot tolerate thalidomide
TA586: Lenalidomide + DEX	After only 1 previous treatment, which included bortezomib
TA171: Lenalidomide + DEX	After 2 or more previous treatments
TA573: Daratumumab, bortezomib + DEX [CDF]	After 1 previous treatment
TA510: Daratumumab monotherapy [CDF]	After 3 previous treatments including both a proteasome inhibitor and an immunomodulator, and progressed on last therapy
TA505: Ixazomib, LEN + DEX [CDF]	After 2 or 3 previous treatments
TA457: Carfilzomib + DEX	After only 1 previous treatment, which did not include bortezomib
TA427: Pomalidomide + DEX	After 3 previous treatments including both lenalidomide and bortezomib
TA380: Panobinostat, bortezomib + DEX	After at least 2 previous treatments including bortezomib and an immunomodulatory agent
TA311: Bortezomib induction +ASCT	Previously untreated people eligible for stem cell transplant
TA228: Bortezomib & thalidomide	Previously untreated people not eligible for stem cell transplant

Isatuximab (Sarclisa, Sanofi)

Mechanism of action	• Isatuximab: humanised monoclonal antibody against CD38 • Pomalidomide: immunomodulating agent • Dexamethasone: corticosteroid
Marketing authorisation	"in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor* and have demonstrated disease progression on the last therapy"
Dosage and administration	• ISA: Intravenous, weight-based dosing 10 mg/kg, weekly for 4 weeks (days 1,8,15 and 22), then every 2 weeks • POM: Oral, flat dosing 4 mg on days 1 to 21 of each 28-day cycle • DEX: Intravenous or oral, flat dosing 40 mg (or 20 mg if patient ≥75 years old) on days 1,8,15 and 22 of each 28-day cycle
List price	• ISA: [redacted] (100 mg vial); [redacted] (500 mg vial) • POM: £2,221 per week • DEX: £15.41 per week • Average cost of course of treatment (ISA/POM/DEX): [redacted] • Approved simple patient access scheme discount for isatuximab

NICE **Proteasome inhibitor –bortezomib, carfilzomib, ixazomib*

Patient and carer perspectives

Submission from **Myeloma UK**

- Currently no cure but treatments can halt disease progression and improve quality of life
- Complications can be significant including severe bone pain, bone destruction, kidney damage, fatigue and depleted immune system
- Disease burden often even more significant for people who experience multiple relapses
- Impact on carers significant and challenging
- A range of treatment options with different mechanisms of action at each stage of the pathway is vital
- Current unmet need. Treatment options limited by further relapses
- Patients prefer oral treatments over intravenous infusions but some welcome treatment delivered in safety of a hospital

Professional perspectives

Submission from **UK Myeloma Forum**

- Multiple myeloma is an incurable disease, with eventual development of drug resistance
- Treatments needed to increase progression-free survival or control disease with manageable side effects
- Professionals vary practice 3rd line therapy and beyond
- Expect clinicians to offer ISA/POM/DEX in current NHS practice at 3rd or 4th line
- No significant difference in adverse events expected compared with current treatments in NHS practice
- Recognised in myeloma that significant proportion not able to be offered therapy with each subsequent line. Combinations ensure more people are able to access effective therapy at earlier time point

Cancer Drugs Fund clinical lead statement (1)

Current pathway

- Recent considerable pathway change - LEN/DEX available at 1st, 2nd and 3rd line
- POM/DEX recommended at 4th line or later so potential pathway 'gap' at 3rd line when previously received LEN and proteasome inhibitor-based treatments
- PANO/BORT/DEX recommended from 3rd line but clinicians normally use after POM/DEX due to toxicity and NHS England allowing re-use of bortezomib without needing to use PANO/BORT/DEX

Positioning of ISA/POM/DEX & comparators

- Company positioning at 4th line over 3rd line is disappointing given that majority of patients in ICARIA-MM trial were at 3rd line
- NHS practice POM/DEX use is at least 90% at 4th line (comparator in ICARIA-MM trial)
- PANO/BORT/DEX use is around 10% or less at 4th line

Prior anti-CD38 monoclonal antibody treatment

- Very strong biological plausibility for a high degree of cross resistance between daratumumab and isatuximab
- EAMS restricted eligibility to those naïve to, or who had not progressed on, prior anti-CD38 antibody treatment. 96% of people on isatuximab EAMS scheme treatment naïve to an anti-CD38 antibody, due to high tolerability of daratumumab
- ICARIA-MM trial provides no evidence for those who progressed on prior anti-CD38 antibody treatment. NICE should exclude this population from recommendations

EAMS: Early Access to Medicines Scheme

Cancer Drugs Fund clinical lead statement (2)

Immaturity of overall survival and progression-free survival data

- Median duration of follow up 11.6 months. OS data 32% mature and PFS data had only ~50% of events. Data analysis cut-off data October 2018
- Intention-to-treat PFS KM curve for ISA/POM/DEX flattens just above the median value with considerable number of censored patients on this plateau
- Expectation that further OS data shows statistical difference in OS between arms in intention-to-treat population (if subsequent daratumumab use is allowed for), but uncertain if timing of these analyses will address OS modelling uncertainties

Post-hoc analysis

- PFS in post hoc subgroup (3 prior treatments) shows no statistical difference between trial arms (HR 0.60, 95% CI 0.35 to 1.03), same for OS (HR 0.49, 95% CI 0.24 to1.02)

Cost-effectiveness

- Company choose exponential model for OS despite 2/3 clinical experts preferring the Weibull model. No experts choose the company's log-normal model for PFS
- 43% GCSF prophylaxis modelled in both arms is unlikely in NHS practice
- Subsequent treatments included in the company base case do not reflect NHS practice

Cancer drugs fund (CDF)

- Potential CDF data collection likely to be modest as ISA/POM/DEX eligible population reducing due to 2nd line DARA use and the limited time that treatment options are in the CDF
- CDF is not the appropriate mechanism to provide data on ISA/POM/DEX use in a population who have progressed on daratumumab

KM: Kaplan Meier, OS: overall survival, PFS: progression-free survival, HR: hazard ratio, GCSF: Granulocyte-colony stimulating factor

Decision problem

Scope includes 2 comparators; company focuses on 1 in submission

	Final scope issued by NICE	Company submission
Population	Adults with relapsed or refractory multiple myeloma who have received at least 2 or more previous treatments, including lenalidomide and a proteasome inhibitor	Company positioned at 4th line
Intervention	Isatuximab in combination with pomalidomide and dexamethasone	
Comparator	After 3 prior therapies; 1. Pomalidomide + dexamethasone (POM/DEX) 2. Panobinostat + with bortezomib and dexamethasone (PANO/BORT/DEX)	Focus on POM/DEX. Do not consider PANO/BORT/DEX a relevant comparator. State rarely used at 4th line in the NHS due to toxicity and perceived lack of effectiveness
Outcomes	• Progression-free survival • Overall survival • Response rates • Duration of response • Time to progression • Time to next treatment • Adverse effects of treatment • Health-related quality of life	Also include duration on treatment time-to-discontinuation (TTD) to estimate treatment duration in the model

Clinical effectiveness

Pharmacological treatment options

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

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

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

Alkylating agents:
Cyclophosphamide, Bendamustine, Melphalan

Histone deacetylase inhibitor:
Panobinostat (PANO)

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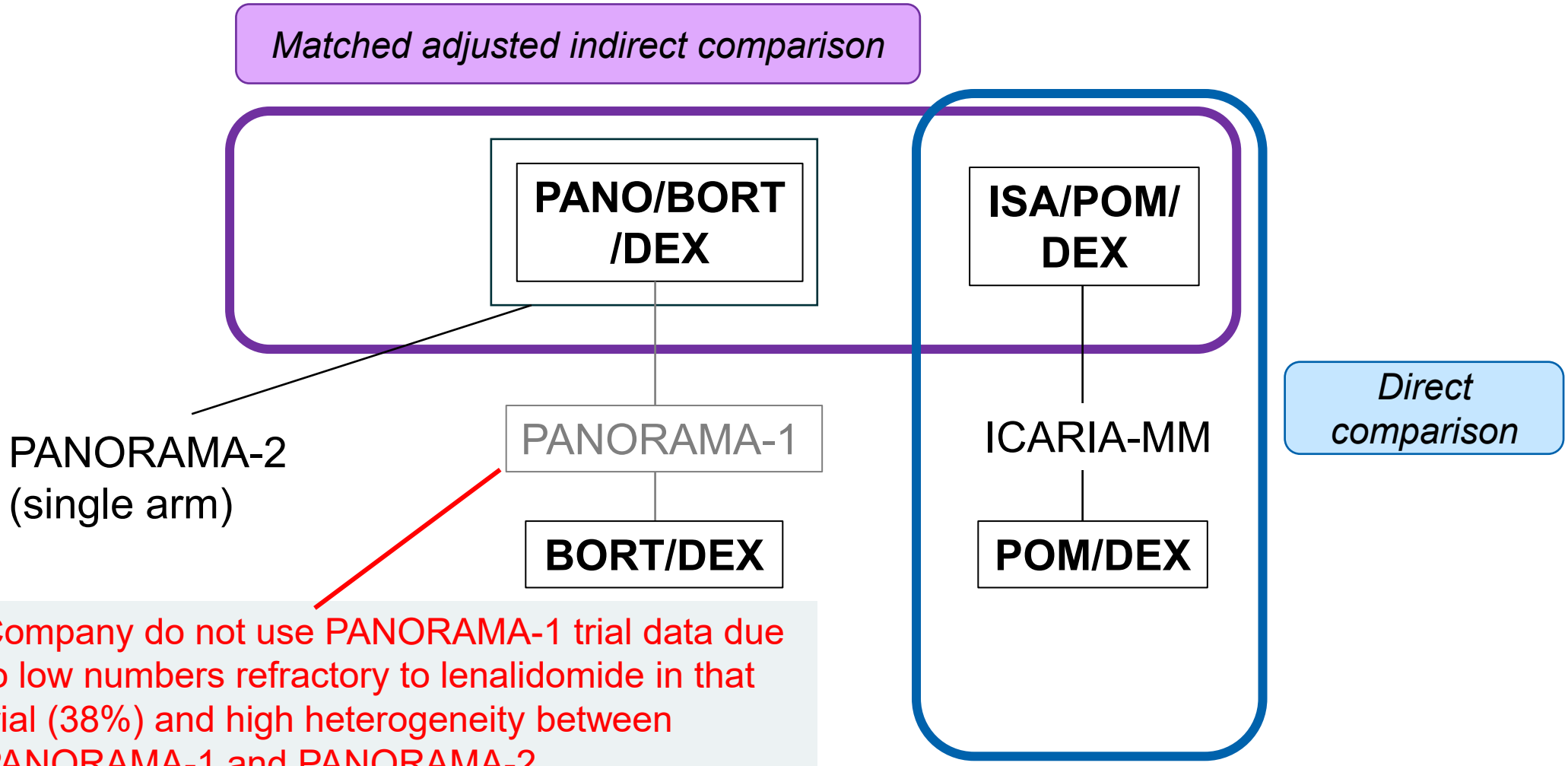
Evidence overview: Indirect and direct treatment comparison

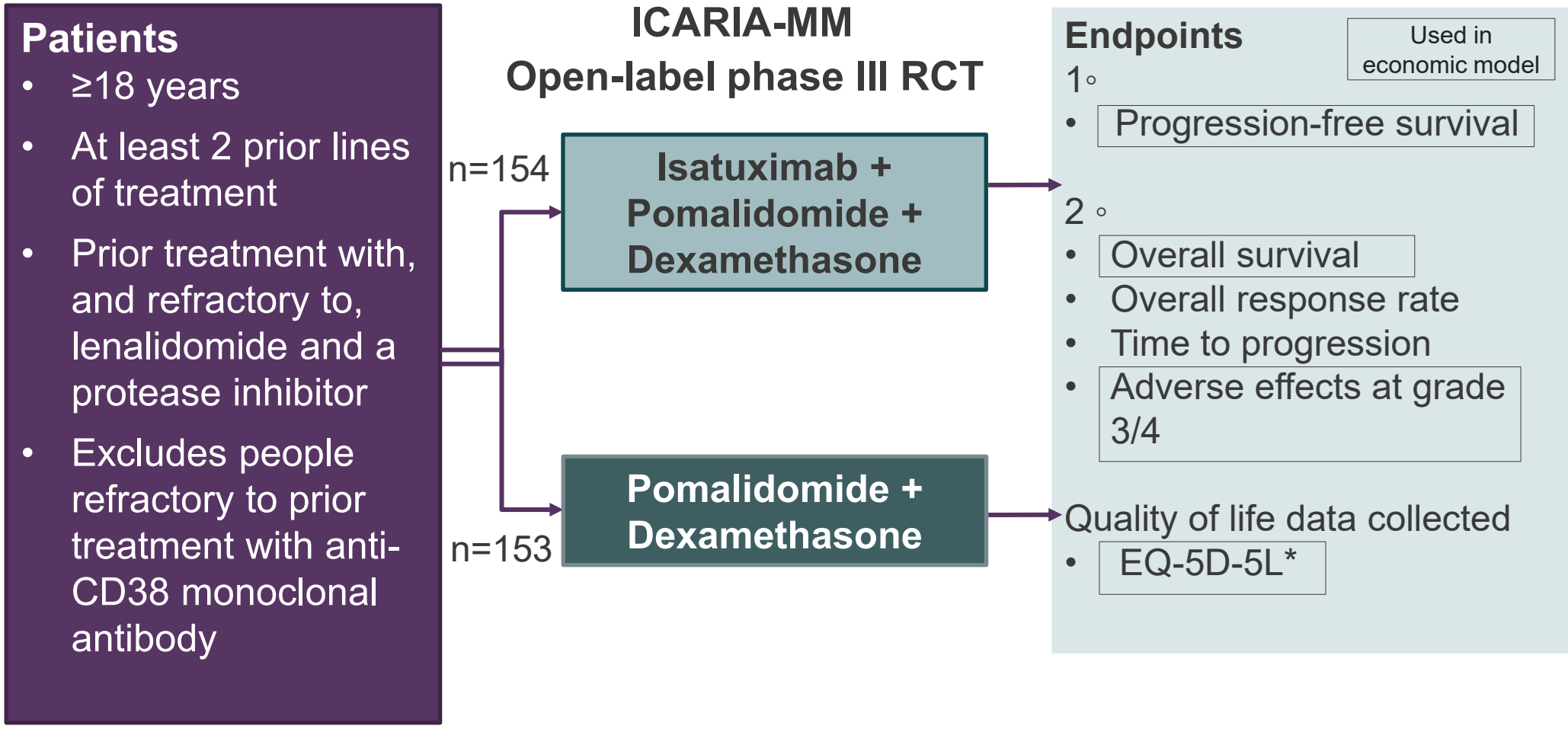


- Company do not use PANORAMA-1 trial data due to low numbers refractory to lenalidomide in that trial (38%) and high heterogeneity between PANORAMA-1 and PANORAMA-2

Ref: Manufacturer submission appendix K.4.1.1.2 (diagram reproduced)
PANORAMA-1: multicentre, randomised, placebo-controlled, double blind phase III trial

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)



**Company mapped EQ-5D-5L to EQ-ED-3L*

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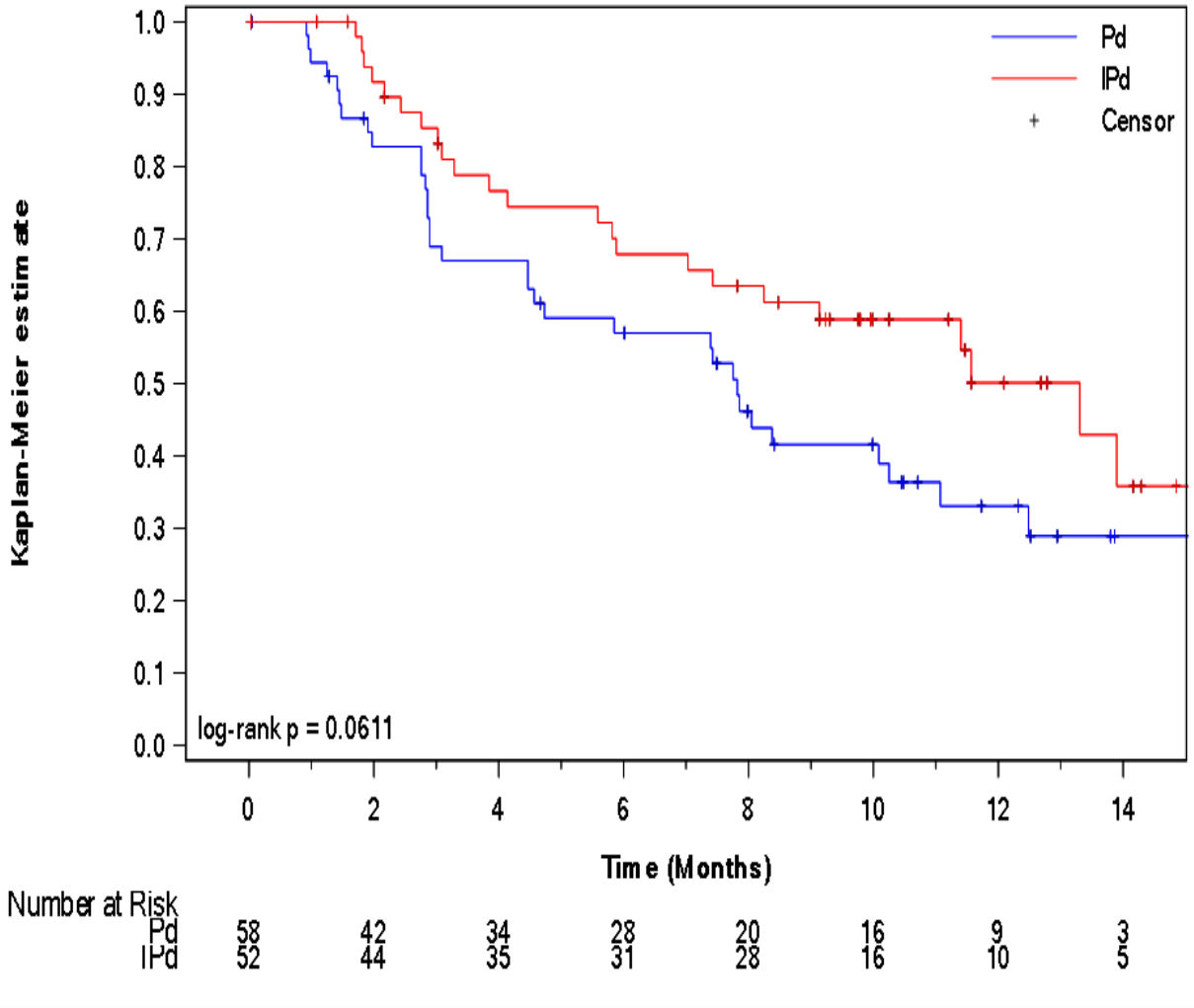
Abbreviations: EQ-5D-5L=EuroQol 5-Dimension 3-Level

Results ICARIA-MM trial progression-free *survival in 4th line subgroup*

Data immature, with low numbers at risk at 14 months



	ISA/POM/ DEX (n=52)	POM/ DEX (n=58)
Number of events, n (%)	**23** (44.2)	**33** (56.9)
Median PFS, months (95% CI)	**13.3** (7.4 to not calculable)	**7.82** (4.5 to 11.1)
Stratified* hazard ratio (95% CI) Log-Rank test p-value	**0.598** (0.348 to 1.030) p=0.0611	

*by age

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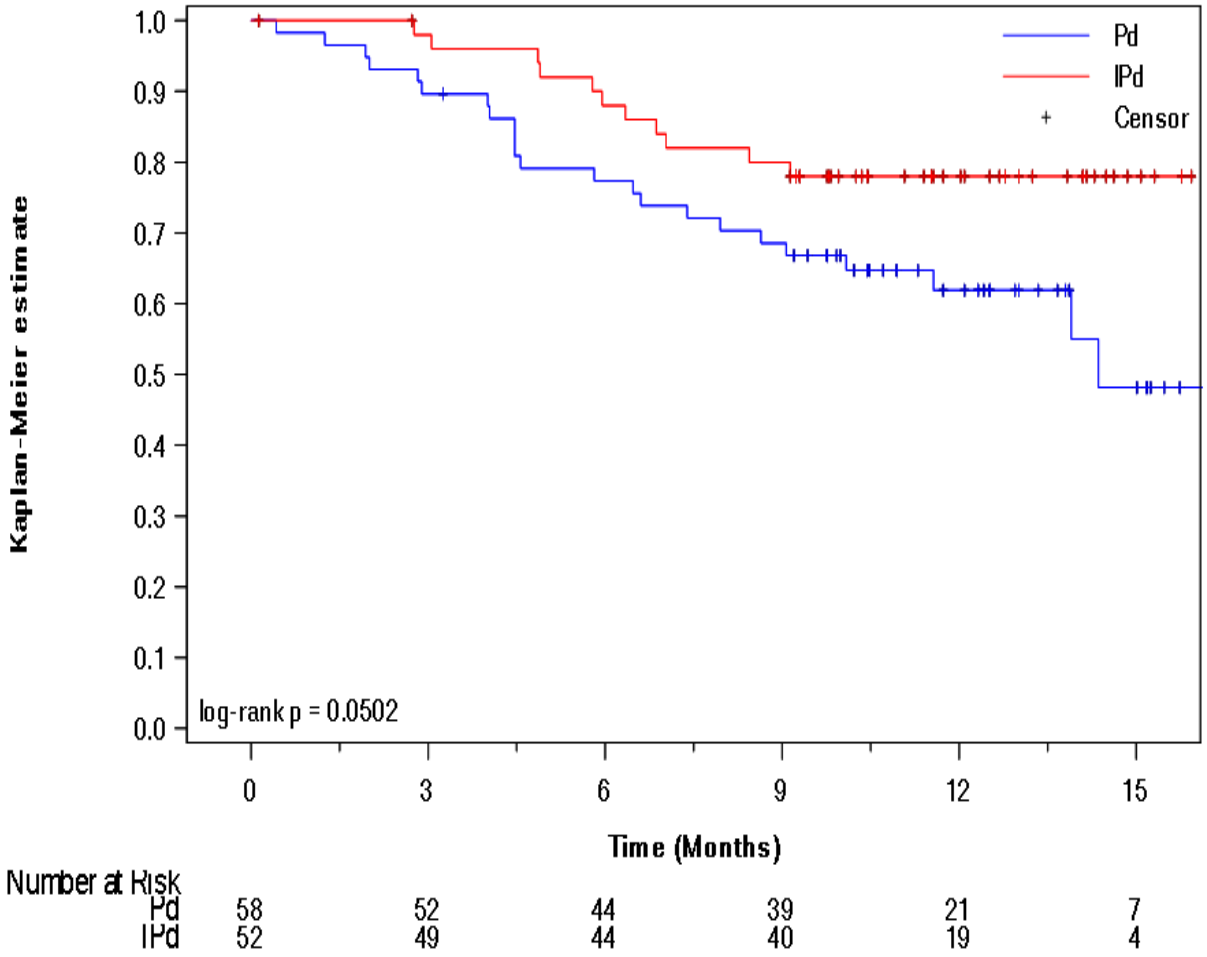
Results ICARIA-MM trial overall survival in 4th line subgroup

Low numbers at risk at 15 months. Company note OS data are immature and substantial numbers of people censored



	ISA/POM/DEX (n=52)	POM/DEX (n=58)
Number of events, n (%)	**11** (21.2%)	**23** (39.7%)
Median OS, months (95% CI)	Not reached	**14.4** (11.6 to not calculable
Stratified* hazard ratio (95% CI) Log-Rank test p-value		**0.49** (0.24 to 1.02) p=0.0502

*by age

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Ref: Manufacturer submission, appendices

Company positions ISA/POM/DEX 4th line

License requires prior lenalidomide and a proteasome inhibitor and allows use at 3rd line or later

4th line positioning	
Company	• Clinical expert opinion - high unmet need for people with disease double refractory after LEN and a proteasome Inhibitor • POM/DEX, recommended 4th line by NICE, is comparator in ICARIA-MM trial • License requires prior treatment with lenalidomide and a proteasome inhibitor – market research (Oct/Nov 2019, n=95 patients) suggests lenalidomide is generally used at 3rd line, 32% via routine commissioning and 51% via CDF • ISA/POM/DEX is available through the Early Access to Medicines Scheme (EAMS) at 4th line based on high unmet need
Clinical expert	• 4th line positioning appropriate for majority • ISA/POM/DEX would replace POM/DEX at 4th line • Would also likely replace DARA monotherapy (currently available via CDF), due to superior clinical outcomes
ERG	4th line positioning broadly supported by clinical advisors
Myeloma UK	4th line positioning supported

Could use ISA/POM/DEX at other points in pathway

License requires prior lenalidomide and a proteasome inhibitor

3rd line positioning	
Jansen (commentator)	Unmet need at 3rd line. Current treatment options of LEN/DEX or IXA/LEN/DEX (CDF) are not available for people who are previously exposed and refractory to LEN so PANO/BORT/DEX is the only available treatment option 3rd line and is not well tolerated
Clinical expert	Minority of people may receive ISA/POM/DEX at 3rd line (prior LEN and BORT use by 3rd line). High LEN uptake at 1st line in newly diagnosed who are not eligible for stem cell transplant

Beyond 4th line positioning	
Myeloma UK	Unmet need at 5th line and beyond where treatment options limited

ICARIA-MM trial 4th line subgroup not pre-specified

4th line subgroup not subject to randomisation

Company

- Company considers 4th line subgroup to be robust
- Conducted statistical tests to understand consistency of effect in the ITT and 4th line population for PFS, assessing confounding factors and evaluation of interaction effects of subgroups. Baseline characteristics similar to ITT population.

ERG

- Baseline balance is irrelevant, and analysis should include all measured prognostic factors irrespective of baseline balance or statistical significance
- Note considerable uncertainty in estimate of treatment effect in 4th line patients

Technical team judgement

- Treatment effect is more uncertain in the 4th line subgroup than in the ITT population

◉ *Technical team concluded the company's positioning of ISA/POM/DEX at 4th line is acceptable - what is the committee's view?*
◉ *Is the 4th line subgroup data appropriate for decision-making?*

Comparators at 4th line

Company consider scope comparator PANO/BORT/DEX not relevant

Relevance of PANO/BORT/DEX as a comparator at 4th line	
Company	• PANO/BORT/DEX at 4th line and later = 6% of market share. Reserved for later lines due to toxicity and results from PANORAMA 2 not seen in practice • Similar views in previous NICE TAs (510 & 427). Use not changed much pre or post DARA monotherapy recommendation at 4L [via CDF] • Data suggests PANO/BORT/DEX less benefit if previously refractory to BORT • Experts consulted state PANO/BORT/DEX is not a comparator
Clinical expert	• POM/DEX is the appropriate comparator at 4th line. If DARA (via CDF) was not available, POM/DEX would be standard of care • No other relevant comparators at 4th line - PANO/BORT/DEX currently used 5th line and later when all current therapies exhausted. Could be used at 4th line, but not best therapy due to lack of response and toxicity
ERG	• Clinical advice to ERG mixed on PANO/BORT/DEX use at 4th line - 2 experts said it is used and 1 said it is not • Company new data, if correct, shows POM/DEX used considerably more than PANO/BORT/DEX
Myeloma UK	• POM/DEX only appropriate comparator. PANO/BORT/DEX, while approved at 4th line, is reserved for later treatment lines given toxicity and is not a comparator • POM/DEX, PANO/BORT/DEX, bendamustine are 5th line options in NHS

◉ *Is PANO/BORT/DEX a relevant comparator?*

Indirect comparison required to compare ISA/POM/DEX with PANO/BORT/DEX

Company did a matched adjusted indirect comparison (MAIC) to compare ISA/POM/DEX with PANO/BORT/DEX

ICARIA-MM trial: ISA/POM/DEX

PANORAMA 2 trial: PANO/BORT/DEX

PANOROMA 2 trial: Phase II, single arm trial of PANO/BORT/DEX

Characteristics matched:

- Age
- ECOG status
- Gender
- Presence of one of Del17p, t(4;14) or t(14;16)
- ISS stage at study entry
- Number of prior therapies
- Time since diagnosis
- Previous stem cell transplant
- Prior treatment with LEN
  - Effective Sample size = 91

Hazard Ratio for PFS: 0.369 (0.259 to 0.526)
Hazard Ratio for OS: 0.642 (0.380 to 1.082)

Company applied the hazard rations from the Cox regression in the MAIC to the survival distribution for ISA/POM/DEX from ICARIA-MM trial

Matched-adjusted indirect comparison

Validity of matched-adjusted indirect comparison	
Company	Company noted ERG issues with MAIC: • Stated input from clinical experts on relevant prognostic factors • Acknowledged issue of using hazard ratios from Cox regression when proportionality assumption violated in trials informing comparison (unclear how this biases the comparison) • Approach taken requires the assumption that the hazards for PANO/BORT/DEX are proportional to those of ISA/POM/DEX • Acknowledge issues with quality of evidence from PANORAMA-2 and face validity issues with MAIC predicted outcomes • PANORMA-2 best source of comparable evidence available
ERG	• ERG accepts process company used to assess variables included in propensity score model • However, it is not possible to state that the final propensity score model is the final model in any MAIC, and residual bias may exist

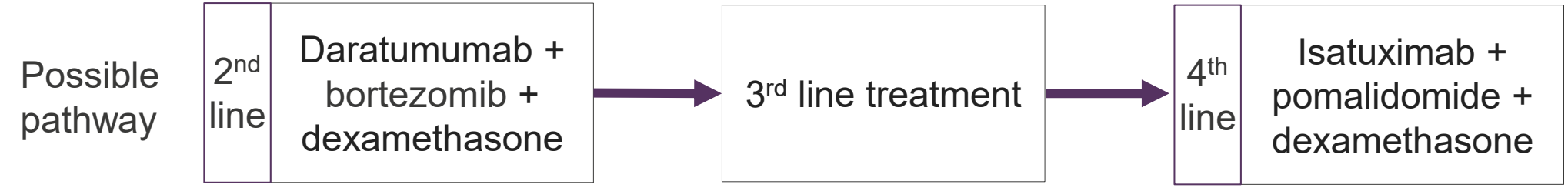
Technical team opinion

- Results from MAIC are uncertain and appear to lack face validity – PANO/BORT/DEX estimated to have a shorter time to progression but longer overall survival than POM/DEX

◉ What are the committee's views on the indirect comparison? Are the results of the MAIC valid?

ICARIA-MM trial excluded people refractory to previous treatment with anti-CD38 monoclonal antibody

Previous treatment with another anti-CD38 drug may affect isatuximab's effectiveness
Daratumumab is available at 2nd line via the Cancer Drugs Fund*



People not refractory to prior anti-CD38 monoclonal antibody	
Company	• ICARIA-MM trial excluded people refractory to anti-CD38 antibody but included people with prior exposure but not refractory • 1 person with prior anti-CD38 antibody exposure included in trial
Clinical expert	• ISA/POM/DEX use appropriate if not refractory to prior anti-CD38 treatment (there are other reasons for discontinuing) • Treatment break between anti-CD38 antibody treatments not needed
ERG	• Clinical advice said would consider ISA/POM/DEX in DARA-exposed patients if they were not refractory to daratumumab and had a non-anti-CD38-based treatment in-between
Myeloma UK	• Patients who have been exposed, but not refractory, to DARA should access ISA/POM/DEX - in line with ICARIA-MM trial inclusion criteria

**Daratumumab is an anti-CD38 monoclonal antibody*

People refractory to prior anti-CD38 monoclonal antibody	
Company	• ISA and DARA are different anti-CD38 monoclonal antibodies - binding to different epitopes on human cell surface antigen CD38 • Combination of anti-CD38 and immunomodulatory agent (ISA with POM) more effective than with a proteasome inhibitor (i.e DARA with BORT at 2nd line). POM could be a superior immunomodulatory agent to LEN
Clinical expert	• Appropriate to exclude people previously refractory to an anti-CD38 monoclonal antibody
Myeloma UK	• Evidence that synergistic effects between immunomodulatory agents and DARA potentially overcome refractoriness to both anti-myeloma agents (Van de Donk and Usmani 2018)

Other comments from the company

- Market research shows retreatment with anti-CD38 monoclonal antibody, particularly if patient not refractory to prior anti-CD38 monoclonal antibody or has a line of treatment in-between
- Clinical support for re-treatment in appropriate population, despite lack of formal evidence. Suggest CDF can be used to address this issue

◉ *Has the committee seen evidence of the treatment in people with disease refractory to an anti-CD38 drug?*
◉ *What is the relevant population the treatment is recommended?*

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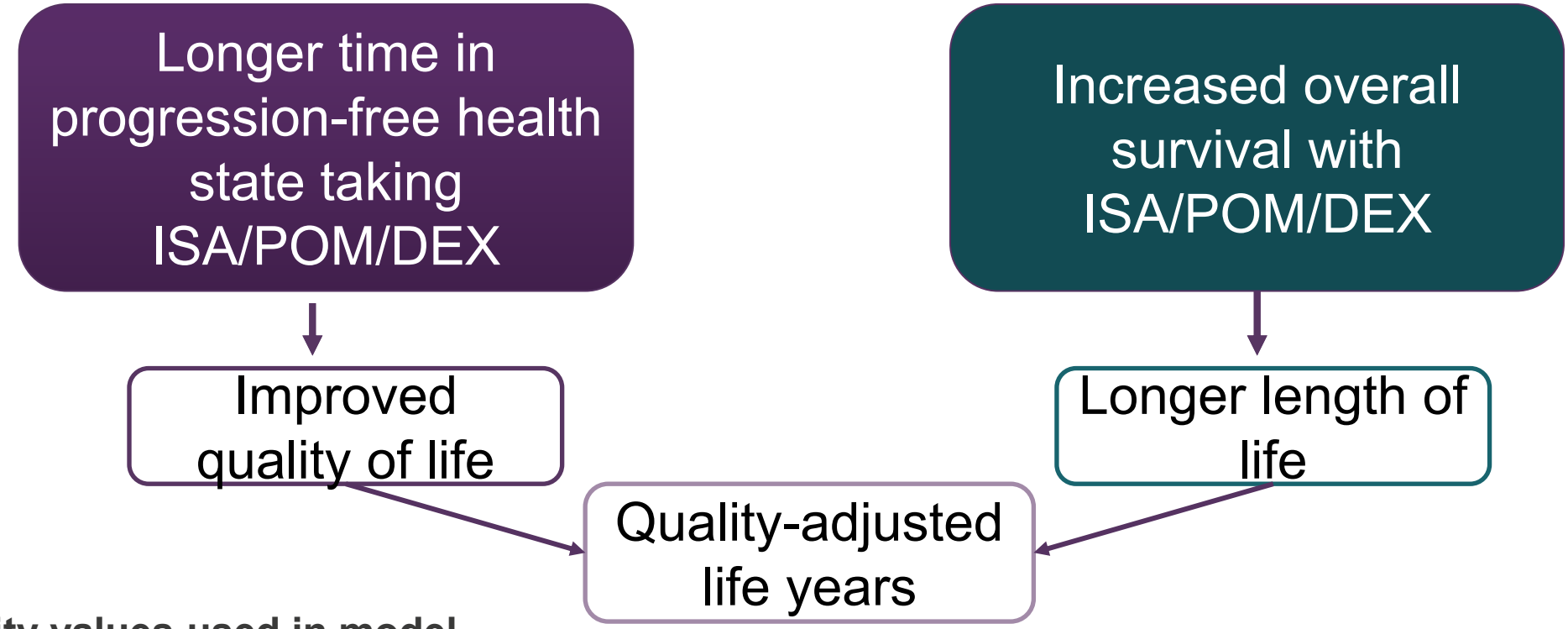
Note prior anti-CD38 treatment an exclusion criteria for the managed access agreement for DARA monotherapy (TA510: CDF)

Cost effectiveness

Overview: how quality-adjusted life years accrue



Utility values used in model

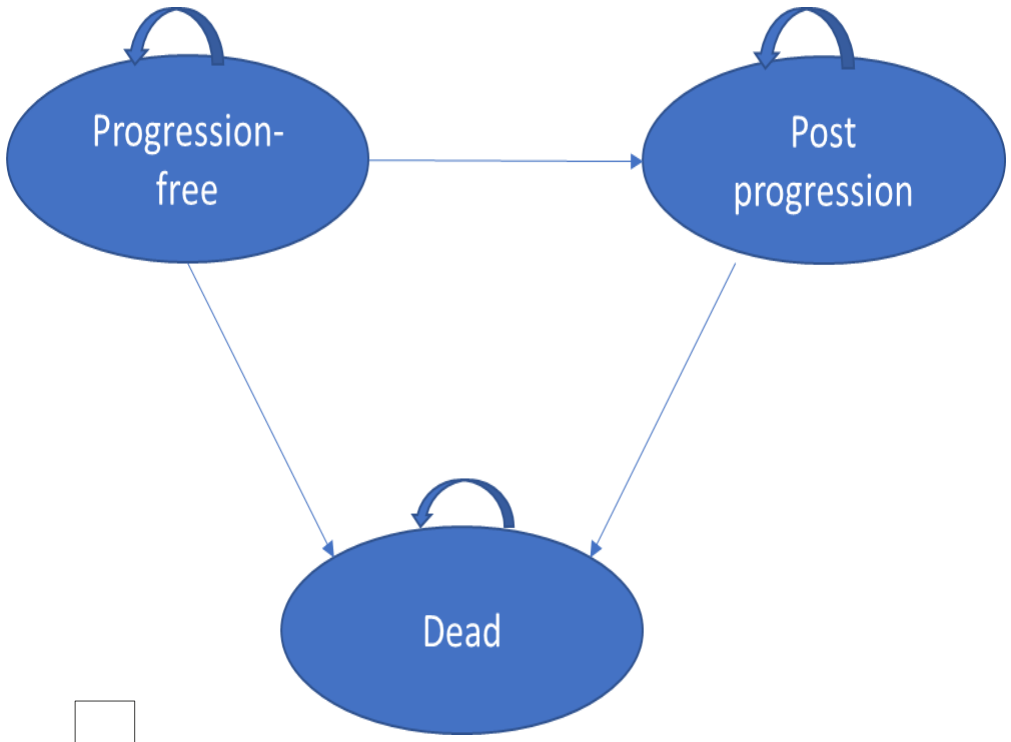
Health state	Mean utility		
	ISA/POM/DEX	POM/DEX	PANO/BORT/DEX†
Progression-free	0.719	0.717	0.719
Post-progression	0.611	0.611	0.611
End-of life (terminal) decrement	0.225	0.225	0.225

† Utility values for PANO/BORT/DEX assumed equal to ISA/POM/DEX. However, 0.035 QALYs deducted in 1st cycle for differing AE profiles.

EQ-5D-5L health state utility index (mapped to EQ-5D-3L values). Data collected in ICARIA-MM trial on day 1 of treatment cycle (2 weeks) and 60 days (±5 days) after last study treatment administration assumes disutility of adverse events already captured in the mean utility values from ICARIA-MM data

Company's partitioned survival model

Model Structure



Model assumptions

Comparison with **POM/DEX**:

- Drug costs estimated using TTD survival functions
- Proportion receiving 5th line treatment following each arm based on data from ICARIA-MM trial.
- Duration of subsequent therapy – external data*
- Frequency of follow-up and monitoring independent of treatment and progression status
- 10 most frequent 5th line medications in the ICARIA-MM trial used
- Terminal care costs same for both arms
- Adverse events only included if occurred in ≥5% of patients in ICARIA-MM and ≥Grade 3

Comparison with **PANO/BORT/DEX**:

- HRs from MAIC applied to OS and PFS for ISA/POM/DEX
- HR obtained for PFS used for TTD
- Health state utilities, adverse events + 5th line proportion/treatments assumed same in both arms

- Estimated proportions in each health state based on parametric survival curves fitted to clinical trial data for PFS and OS for ISA/POM/DEX vs POM/DEX
- Time horizon: 20 years. Cycle length: 1 week

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*Kantar Health for Western Europe

Extrapolating overall survival, progression free survival, and time to treatment discontinuation beyond end of trial

Data immature – increases uncertainty of extrapolations

Key driver of cost effectiveness

	Base case		ERG sensitivity analysis
	Company	ERG	
Overall survival	Exponential	Exponential	• Jointly fitted log normal • Jointly fitted Weibull ★
Progression free survival	Jointly fitted lognormal	Jointly fitted lognormal	• Exponential • Jointly fitted Weibull
Time to treatment discontinuation	Exponential	Exponential	• Jointly fitted log logistic ★ • Jointly fitted Weibull ★

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★ Alternative choices which significantly impacts ICER estimate

Extrapolating overall survival

ICARIA-MM data is immature: long term extrapolation of key outcomes required

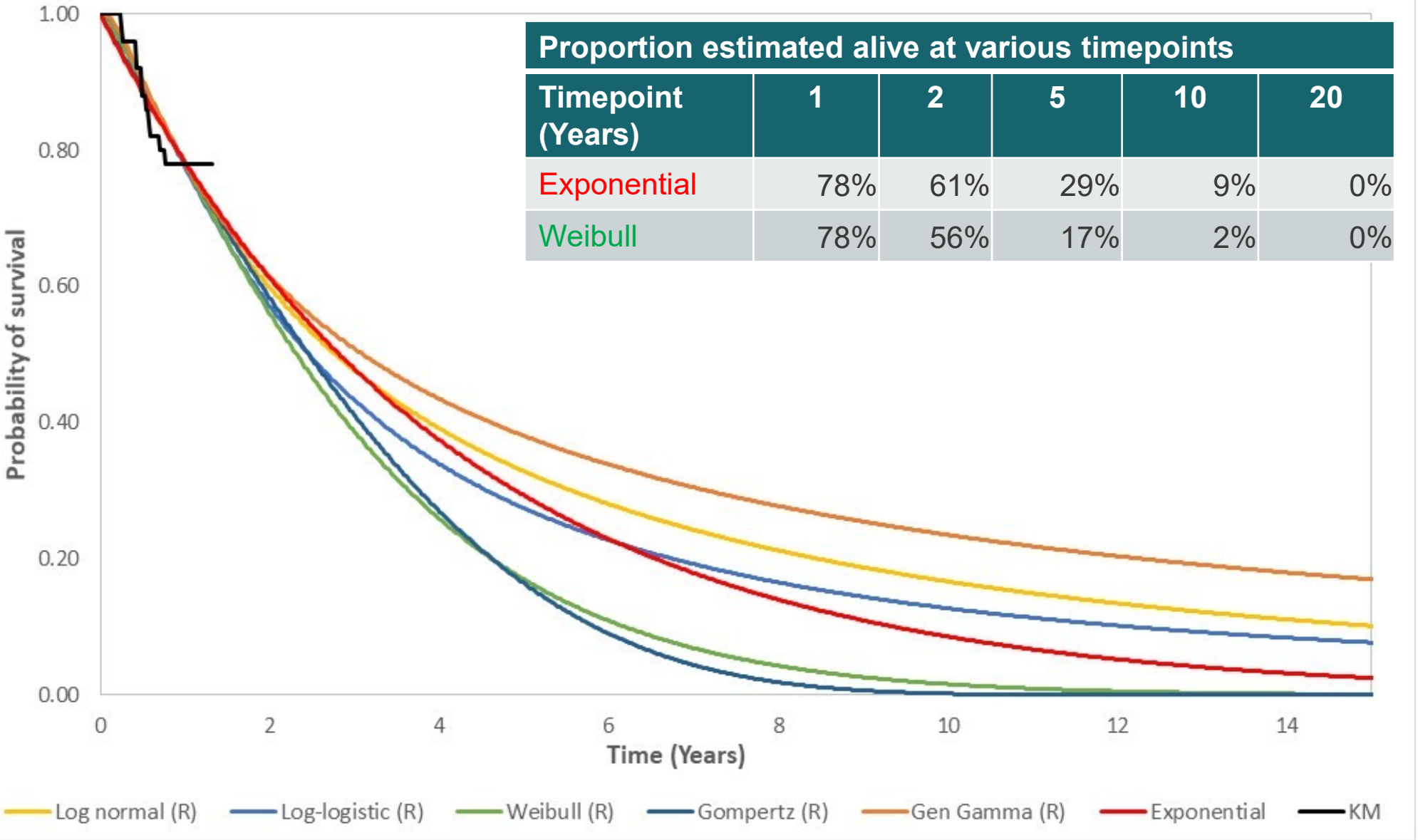
Extrapolating Overall Survival	
Company	• Exponential distribution showed best statistical fit (lowest Bayesian Information Criteria 'BIC'), acceptable visual fit and clinically plausible OS estimates consistent with long term OS data from MM-003* (POM/DEX arm) • May underestimate OS for ISA/POM/DEX at distribution tail over trial period • 15% of patients alive at 28 months in MM-003 trial (POM/DEX arm) – exponential distribution predicts 30% alive (POM/DEX arm) • POM/DEX PFS Kaplan-Meier in MM-003 trial below that of 4th line subgroup of ICARIA-MM, suggesting poorer prognosis. Similar conclusions from OS data
ERG	• Exponential function showed lower BIC values, but only 4 points lower than Weibull function – only positive, and not strong evidence for exponential • Company states Weibull distribution may not have clinical plausibility for certain timepoints: all patients predicted to die by 5 years on POM/DEX and by 10 years on ISA/POM/DEX – at 10 years, exponential distribution estimates 10% alive on ISA/POM/DEX and 0% alive on POM/DEX • OS trial data for ISA/POM/DEX are immature so models estimates of proportion alive at 10 years are uncertain

NICE MM-003 trial: POM/DEX v high dose DEX in those with ≥ 2 prior treatment lines

Company extrapolated overall survival using exponential distribution

ISA/POM/DEX: alternative distributions for extrapolation

Proportion estimated alive at various timepoints					
Timepoint (Years)	1	2	5	10	20
Exponential	78%	61%	29%	9%	0%
Weibull	78%	56%	17%	2%	0%



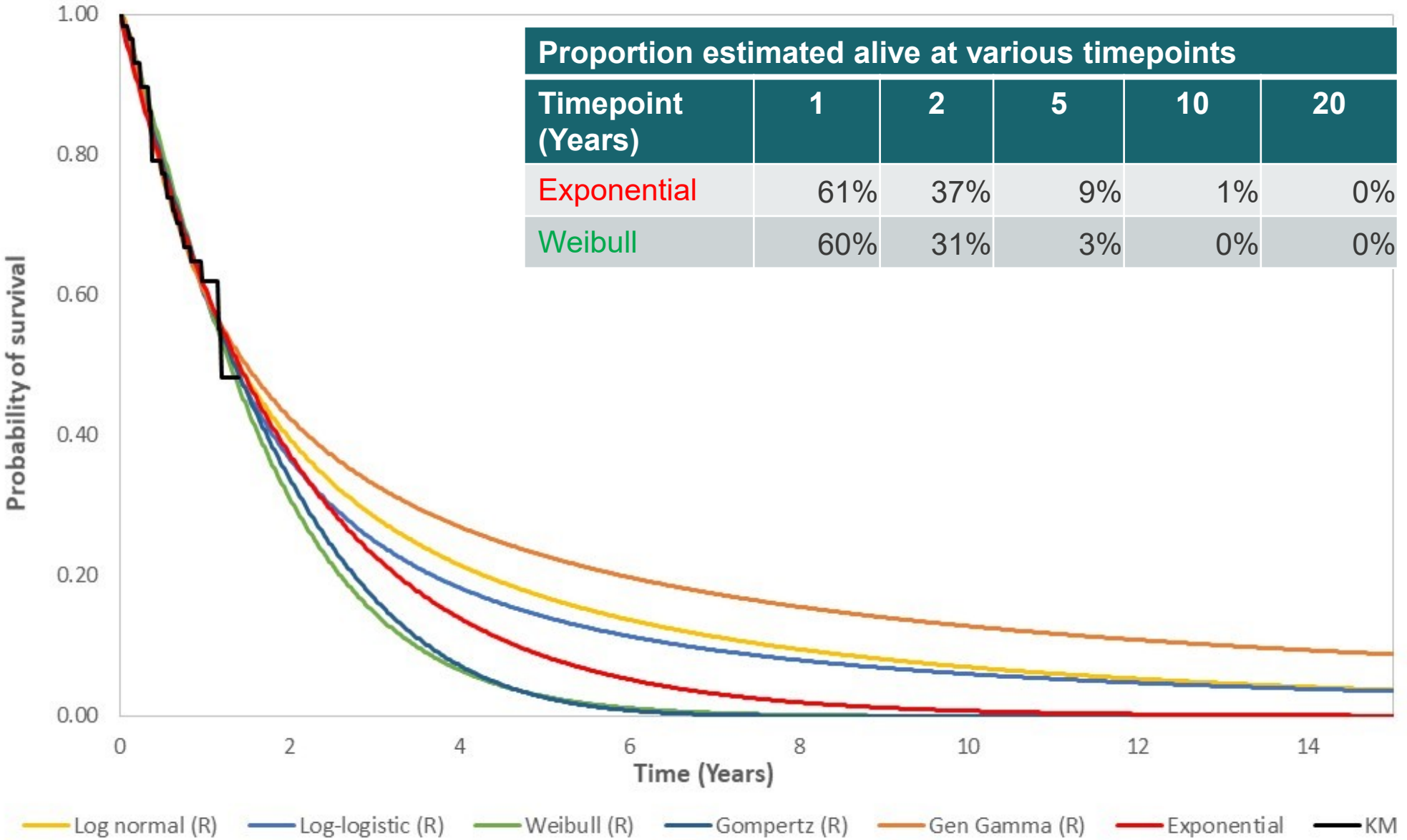
Clinical expert estimated the following proportion alive at x years:
65%: 1 year | 40%: 2 years | 20%: 5 years | <5%:10 years | 0%: 20 years

NICE

Company extrapolated overall survival using exponential distribution

POM/DEX: alternative distributions for extrapolation

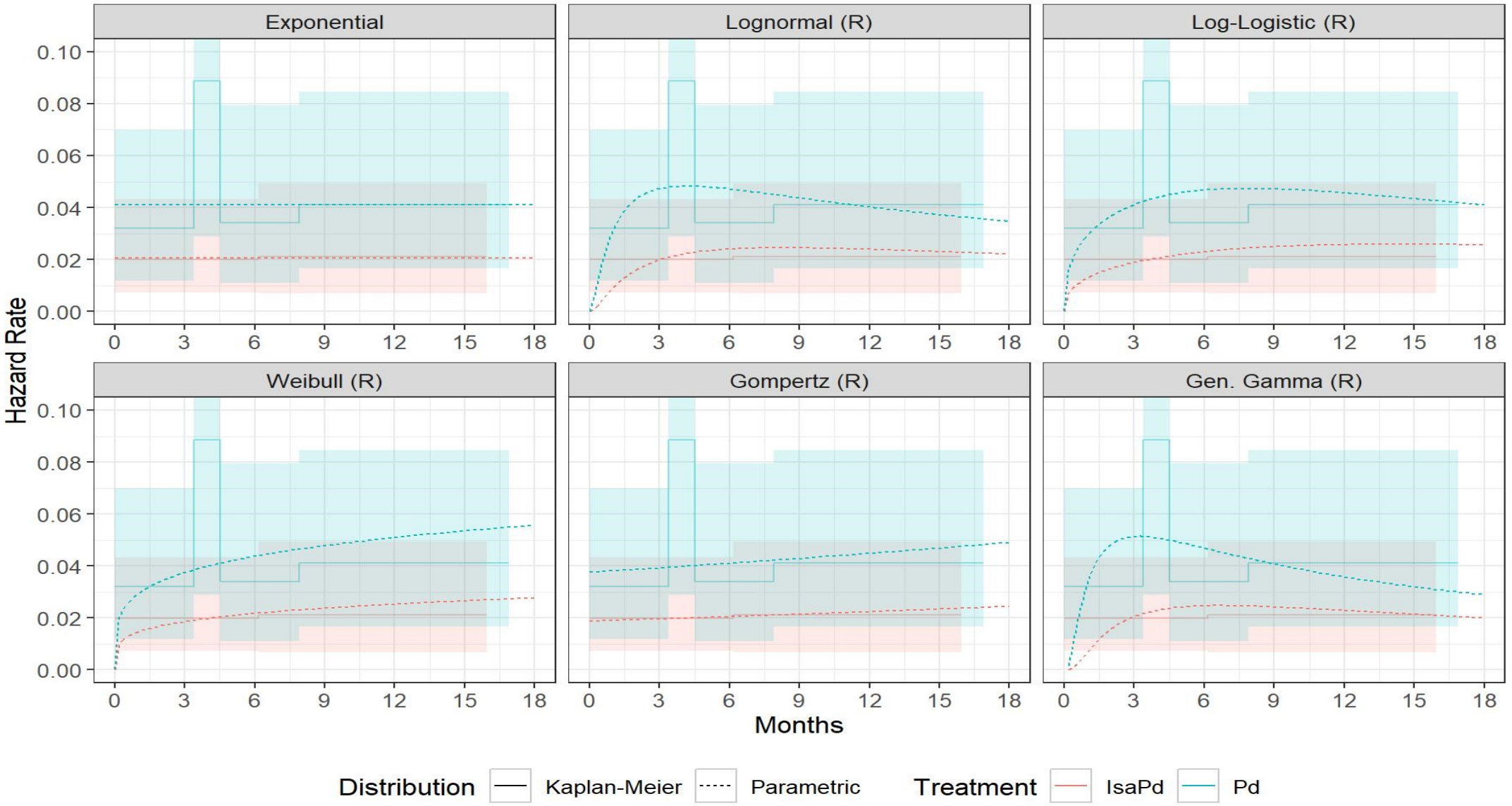
Proportion estimated alive at various timepoints					
Timepoint (Years)	1	2	5	10	20
Exponential	61%	37%	9%	1%	0%
Weibull	60%	31%	3%	0%	0%



Clinical expert estimated the following proportion alive at x years:
55%: 1 year | 33%: 2 years | 15%: 5 years | <5%:10 years | 0%: 20 years

Underlying hazard rates by distribution – Overall Survival

Hazard rates for alternative overall survival distributions. 4th line subgroup ICARIA-MM, by treatment from 0 to 18 months

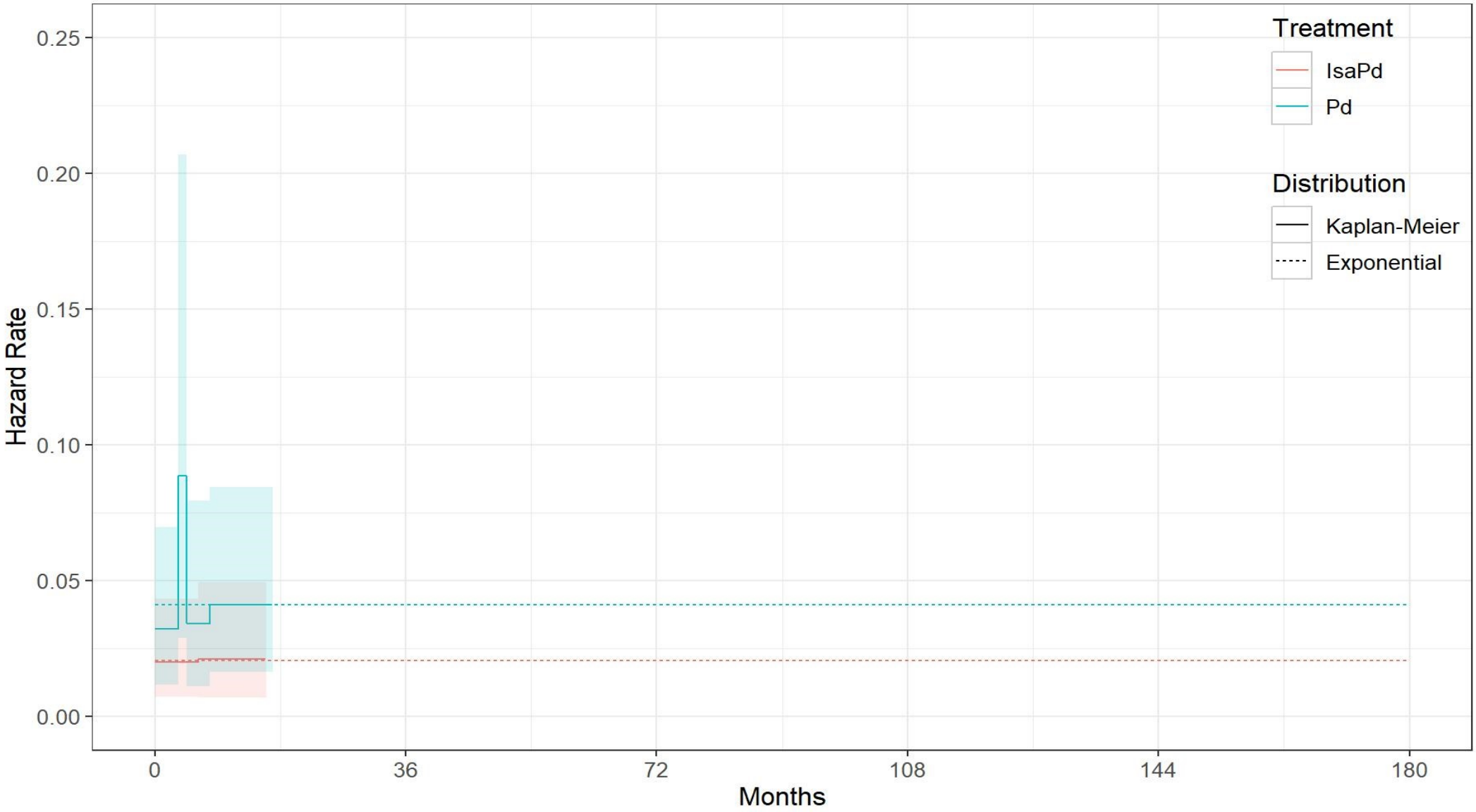


Company use the exponential distribution in base case for estimating overall survival - the exponential has constant hazards. The Weibull and Gompertz have increasing hazards, other distributions have decreasing hazards.

Underlying hazard rates by distribution – Overall Survival

Hazard rates for exponential distribution, 4th line subgroup ICARIA-MM, by treatment over 15 years

Exponential Distribution



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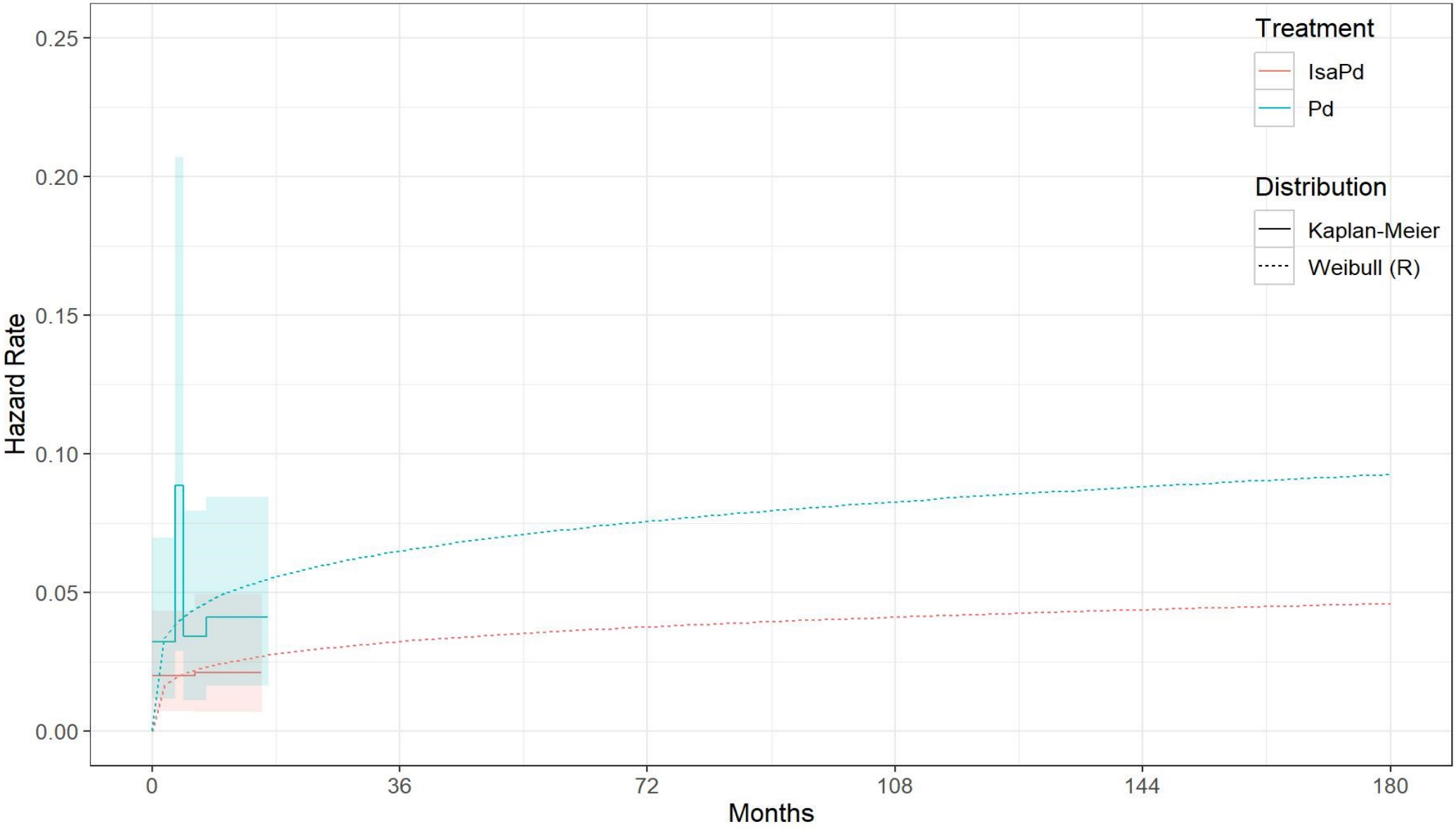
Underlying hazard rates by distribution – Overall Survival

Hazard rates for Weibull distribution, 4th line subgroup ICARIA-MM, by treatment over 15 years

Weibull Distribution



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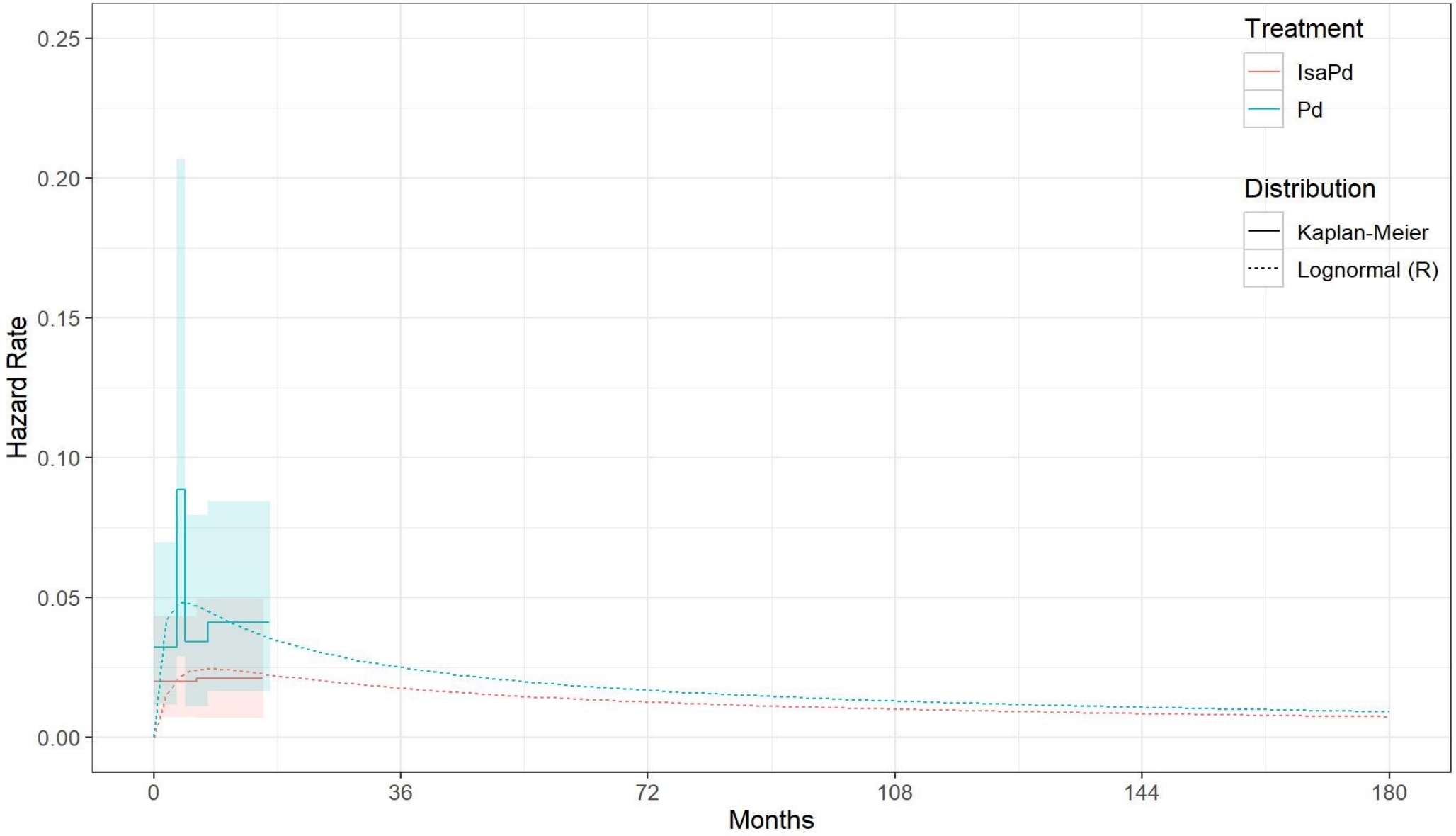
Underlying hazard rates by distribution – Overall Survival

Hazard rates for Log-logistic distribution, 4th line subgroup ICARIA-MM, by treatment over 15 years

Log-logistic Distribution



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Extrapolating progression-free survival and time to treatment discontinuation

Extrapolating progression-free survival	
Company	• Jointly-fitted lognormal chosen on statistical and visual fit • PFS from MM-003 trial* (POM/DEX) was 3.7 months (lower than the 7.5 months in ICARIA-MM). Sensitivity analysis showing results for preferred curves chosen by clinical experts (RSC jointly fitted Weibull and jointly fitted Weibull)
ERG	• Use of alterative PFS extrapolations has limited ICER impact
Extrapolating time-to-treatment discontinuation	
Company	• Exponential distribution showed lowest BIC, good visual fit and test of linearity of Schoenfeld residuals suggest that the proportional hazard assumption is not violated • Sensitivity analysis conducted for alternative distributions
ERG	• All alternative TTD extrapolations increase ICER • Exponential distribution had a BIC value less than five lower than the log-logistic distribution - only positive, not strong, evidence for exponential distribution

NICE MM-003 trial: POM/DEX v high dose DEX in those with ≥ 2 prior treatment lines

Company extrapolated time to treatment discontinuation using exponential distribution

ISA/POM/DEX: alternative distributions to extrapolate time to treatment discontinuation

Figure redacted due to commercial in confidence data

Company extrapolated time to treatment discontinuation using exponential distribution

POM/DEX: alternative distributions to extrapolate time to treatment discontinuation

Figure redacted due to commercial in confidence data

Other comments

Clinical expert opinion:

- Beyond 5th line there is poor survival - small subgroup may be alive at 10 years (<10%)

Technical team opinion:

- Company's base case extrapolations for key outcomes supported by the ERG – but ERG notes other potentially viable distributions for key outcomes and that extrapolations highly uncertain due to immature data
- Technical team note some support from clinical experts for the Weibull extrapolation for OS – this choice significantly increases the ICER estimate
- OS estimates from exponential extrapolation appear to overestimate survival in the POM/DEX arm, but may also overestimate survival in the ISA/POM/DEX arm
- OS estimates using the Weibull method may be conservative, underestimating survival, particularly at the tail

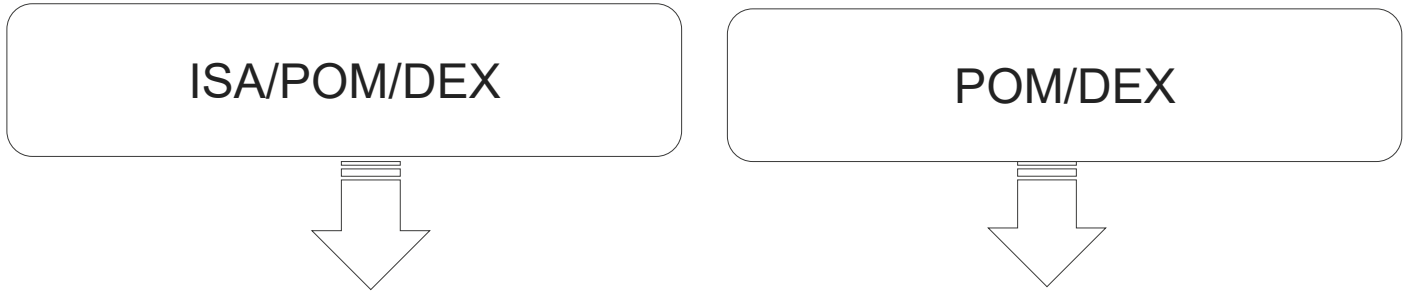
- Which distributions are most appropriate to model OS, PFS and TTD?
- How much uncertainty is associated with long term estimates?

Subsequent treatments

Most treatments 5th line and beyond given to those in the 4th line subgroup in the ICARIA-MM trial not used NHS clinical practice and types of 5th line treatment varied by trial arm

ICARIA-MM 4th line subgroup

4th line



5th line

ICARIA-MM 4th line subgroup treatments following progression

Treatment	ISA/POM/DEX arm	POM/DEX arm
Bendamustine	11%	12%
Bortezomib	25%	17%
Carfilzomib	18%	21%
Daratumumab	**7%**	**38%**
Etoposide	11%	0%
Thalidomide	4%	0%
Lenalidomide	**14%**	**2%**
Melphalan	11%	0%
Panobinostat	4%	0%
Pomalidomide	7%	7%

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Treatments adjusted for by the company in exploratory analyses

5th line treatments

Company:

- Acknowledge 5th line treatments in ICARIA-MM trial may not reflect UK practice
- Clinical experts stated 5th line treatments unlikely to impact survival
- Company present scenario with 5th line treatment and duration based on input from clinical expert
- Company adjusted 5th line daratumumab and lenalidomide use on overall survival
  - Deemed analyses 'exploratory'
  - Analysis using inverse probability of censoring weighting (IPCW),
    - without daratumumab 5th line HR **********
    - without daratumumab or lenalidomide HR **********
    - both consistent with HR 0.49 (95% CI: 0.24 to 1.02) for 4th line population
  - Deemed other adjustment approaches such as rank preserving structural failure time model (RPSFT), two-stage estimation (TSE) or a Markov cohort model (MCM) 'infeasible' or 'inappropriate'
  - IPCW analysis may not capture all contributing factors to treatment switching and has low numbers informing analysis: caution required

ERG:

- ERG did not fully assess analyses, but company's arguments for excluding the RPSFT, the TSE and the MCM methods appear reasonable
- Expect increased ICERs as daratumumab is relatively expensive and removing its cost unfavourable to ISA/POM/DEX (higher use in POM/DEX arm)
- Underlying life years gained and QALYs in POM/DEX arm remained constant in this analysis as these were the data HRs applied to
- Anticipated that life years and QALYs gained would be lower due to lack of daratumumab or lenalidomide at 5th line. This limitation unlikely to impact ICER

Clinical expert opinion:

- No standard treatment at 5th line or beyond - poor clinical outcomes at this stage
- Results reported in the ICARIA-MM trial are likely to be generalisable
- Response rate to any 5th line therapy in the trial likely >30% (more likely ~20%)

Technical team opinion:

- Higher DARA use at 5th line not used in NHS practice may impact OS more in POM/DEX arm
- Company's adjustments uncertain and exploratory, but show ICER may be underestimated – higher 5th line treatment costs in POM/DEX arm

◉ *Are the cost-effectiveness estimates biased due to subsequent trial treatments?*
◉ *Has the company adequately controlled for treatments in trial not in the NHS?*

 RPSFT: rank preserving structural failure time; TSE: two-stage estimation method; MCM: Markov cohort model approach; HR: hazard ratio; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio

End of life criteria

Life expectancy mean < 2 years; life extension mean > 3 months vs. standard care

Company:

- Company's clinical experts state life expectancy is <2 years
- Median OS in POM/DEX arm of ICARIA-MM trial 14.4 months
  - 13.1 months in MM-003 trial
- PFS is 'correlated' with OS – median PFS is 13.3 months in ISA/POM/DEX arm and 7.8 months in POM/DEX arm
- Company base case predicts median OS of 33.3 months in ISA/POM/DEX arm and 14.1 months in POM/DEX arm
- Observational evidence of people treated with POM/DEX also supports criteria:
  - median OS after a median of 3 prior treatments reported as 10.9 months (Miles and Wells 2015)
  - after a median of 4/5 prior treatments between 8.6 and 13.7 months (TA427 and Maciocia et al)
- Clear that ISA/POM/DEX provides considerably more life extension than POM/DEX - despite immature OS data in ICARIA-MM trial

ERG:

- Mean discounted overall survival duration is ***** years for POM/DEX in company base case (exponential extrapolation)
- Median overall survival <14 months in company's observational evidence, but mean values not calculable – would be longer
- Survival estimates reduced when 5th line DARA and LEN removed
- ISA/POM/DEX likely to give survival benefit compared to POM/DEX based on trial data
- Company base case comparison shows mean OS for PANO/BORT/DEX was ***** years, with ISA/POM/DEX survival gain of > **** years

Clinical expert opinion:

- Published data supports overall survival of less than 2 years
- Data for those refractory to both lenalidomide or pomalidomide and either bortezomib or carfilzomib, and exposure to an alkylating agent - overall survival was 13 months (Kumar et al). Another published study states similar overall survival at 4th line for people who have received POM/DEX (Maciocia et al)

Myeloma UK:

- Meets end of life criteria. Published data shows survival is <2 years (Gooding et al 2015)

Janssen – commentator

- End of life previously accepted in both TA427 (POM/DEX) and TA510 (DARA)
- Modelled mean survival of >2 years in POM/DEX arm may be overestimated as POM/DEX patients in trial allowed DARA at 5th line – increasing survival

Technical team opinion:

- End of life previously accepted in most recent 4th line myeloma appraisal – DARA monotherapy, TA510 in 2018 (based on short life expectancy being met). Clinical expert support for <2 year survival with standard care
- Mean survival values likely to be higher than reported median values
- Choice of either exponential or Weibull extrapolation impacts modelled survival
- Likely that ISA/POM/DEX extends life by >3 months

◉ Is life expectancy after 3 prior therapies on average less than 2 years with standard care?
◉ Does ISA/POM/DEX extend life by more than on average 3 months compared to standard care?

Drug wastage and relative dose intensities

Company state vial sharing possible and explore zero drug wastage in scenario analysis. Relative dose intensity (RDI) of POM higher in POM/DEX arm than ISA/POM/DEX arm.

Drug wastage

Company base case includes wastage in line with previous NICE submissions. In submission company stated possibility of vial sharing (scenario analysis)

ERG considers company base case wastage assumption appropriate and considers a zero wastage assumption to be extreme

Relative dose intensities (RDI)

Company: RDI of POM lower on ISA/POM/DEX than POM/DEX as ISA dose reductions were not permitted but dose omissions were (i.e due to Grade 4 neutropenia). POM dose reductions permitted (as per summary of product characteristics). In ICARIA trial more neutropenia observed in ISA/POM/DEX arm

ERG: Difficult to interpret impact of different dosing intensities. Scenario analysis which assumes 100% relative dose intensities are extreme

Technical team believe base case assumptions are appropriate (that is assuming RDI from ICARIA trial and drug wastage in line with previous myeloma appraisals)

◉ *Are base case assumptions for drug wastage and relative dose intensities appropriate?*

*Relative dose intensity: ratio of "delivered" to the "planned" dose intensity

Equality considerations and innovation

Innovation

- Company considers ISA/POM/DEX innovative
- Technical team considers that all relevant benefits are adequately modelled

Equalities issues

No issues identified

◉ Is ISA/POM/DEX a 'step change' in treatment? Are there benefits not included in the model?
◉ Are there any equality issues?

Issues resolved after technical engagement

Summary	Stakeholder responses	Technical team consideration
Model time horizon: Company base case was 15-years	Company amended base case to 20 years as recommended by ERG	20 years is more appropriate as it captures all differences between arms
Health utilities: Probabilistic sampling allowed utility values for progression free health state to be lower than for progressed disease	Company amended so utility value for progression free health state always greater than for progressed disease. ERG content	Results more believable
Costs: cycle length of model (1 week) shorter than frequency of treatments provided in clinical practice	Company amended to cost drugs at start of cycle - as recommended by ERG	Amendments more accurately reflect costs

Cost-effectiveness results

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

Consideration for the Cancer Drugs Fund (CDF)

ICARIA-MM final data cut expected Q2 2021 (after 220 deaths in intention-to-treat population [n=307], approximately 70%). At Oct 2018 data-cut approximately 32% of ITT population had died: n=43 in ISA/POM/DEX arm, n=56 in POM/DEX arm

Company

- CDF entry would allow further data collection to address key uncertainties such as:
- Immature overall survival data
    - High levels of censoring in current data (overall survival: 78.8% in ISA/POM/DEX arm and 60.3% in POM/DEX censored, 4th line) - trial ongoing
- Real world evidence
    - Limited evidence of UK 4th line outcomes. EAMS scheme currently collecting data in this population
- Understanding retreatment with anti-CD38 outcomes
    - Non refractory to prior anti-CD38 treatment or had intervening treatment

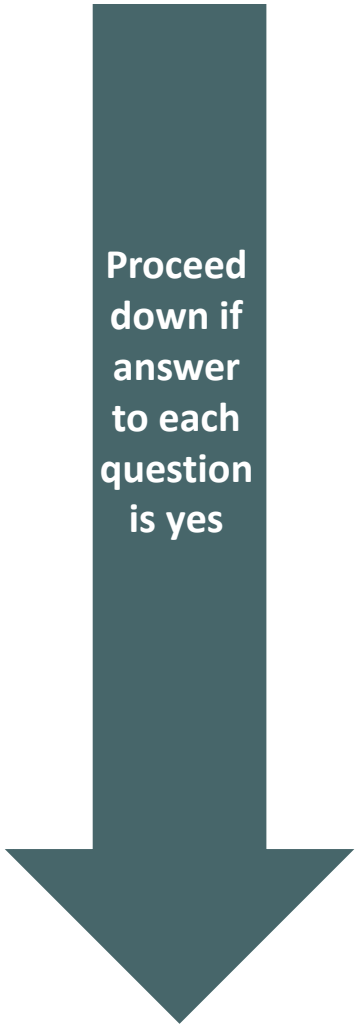
Myeloma UK

- CDF can confirm overall survival improvement
- Clear clinical benefit delivered in ICARIA-MM for PFS and ORR. Difficult to reach median OS in trials - Further data enables more information on treatment's value

Technical team opinion

- Further data collection from ICARIA-MM trial may reduce clinical outcome uncertainties, however impact of subsequent trial treatments may remain
- There are low numbers at risk in the trial at the data cut-off point, but a later data cut may provide more data at these timepoints
- ISA/POM/DEX needs to show plausible cost-effectiveness to enter CDF

Committee decision making: CDF recommendation criteria



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

◉ *Will data from the Cancer Drugs Fund reduce uncertainty?*

Key Issues

1) Is company's positioning of ISA/POM/DEX as a 4th line treatment option appropriate?
2) Are the 4th line subgroup data from the ICARIA-MM trial robust?
3) Is PANO/BORT/DEX a relevant comparator for ISA/POM/DEX at 4th line?
4) Does the indirect treatment comparison include all relevant evidence? Are the results from the matched adjusted indirect comparison valid?
5) Should the population in the NHS eligible for ISA/POM/DEX be those not already treated with a prior anti-CD38 monoclonal antibody?
6) What are the most appropriate models for extrapolating overall survival (OS), progression-free survival (PFS) and time to treatment discontinuation (TTD)?
7) Are the results of the clinical trial biased by treatments given at 5th line? How valid are the company's adjustment analyses?
8) Does ISA/POM/DEX meet NICE's end of life criteria?
9) Is ISA/POM/DEX a suitable candidate for the Cancer Drugs Fund?