Isatuximab in combination with bortezomib, lenalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant [ID3981]

For projector – all CON information is redacted

Technology appraisal committee B [07 May 2025]

Chair: Charles Crawley

Lead team: David McAllister, Anna Pracz, Tony Wooton

External assessment group: Liverpool Reviews and Implementation Group (LRiG)

Technical team: Luke Cowie, Nigel Gumbleton, Richard Diaz

Company: Sanofi

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- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on multiple myeloma

Multiple myeloma is a rare, incurable haematological cancer

Causes

- Multiple myeloma (MM) is a rare cancer that develops from bone marrow plasma cells. Its exact cause is unknown but it is associated with genetic risk factors and older age, and is more common in men

Epidemiology

- MM is the 19th most common cancer, accounting for 2% of all cancer cases in the UK. There are approximately 6,000 new cases of myeloma in the UK annually, with 5,316 reported in England in 2022

Diagnosis

- The median age at diagnosis is 72 years. At diagnosis, the option of autologous stem cell transplant (ASCT) following high dose induction chemotherapy is offered to people who meet suitability criteria. Approximately two thirds of people are not considered suitable for ASCT

Symptoms and prognosis

- Symptoms include hypercalcaemia, renal failure, anaemia, bone loss and susceptibility to infections. In England, the 5-year and 10-year survival rates for people with myeloma are 55% and 30%, respectively

Equalities considerations

- No equality issues

Are there any potential equality issues to consider?

Patient perspectives

New treatments are needed for people who cannot have ASCT

Submission from Myeloma UK

- Complications of MM can be debilitating, and painful; including severe pain, bone destruction, kidney damage, fatigue and depleted immune system
- Many people are diagnosed with severe complications such as spinal fracture, or reduced kidney function, leading to a higher burden for carers
- MM is an incurable, relapsing and remitting cancer. The constant possibility of relapse has a huge psychological impact on people
- Treatment is often continuous and ongoing appointments and treatments have a big impact on quality of life
- People who cannot have ASCT tend to be older or frailer. These people can also experience a higher rate of side effects whilst on treatment and may also have more complications
- There is a clear need for treatment that delivers comparable outcomes to ASCT for people who can't have or tolerate it

"I can handle physical pain, but I can't handle the impact on my mental health. For pain, you can take a painkiller and feel a bit better, but it isn't the same for mood. There are good days and bad days; it is so unpredictable."

"Myeloma has had a major impact on my quality of life… Some of the simplest tasks become impossible… such as going to the bathroom or making a cup of tea… things we take for granted."

MM, multiple myeloma; ASCT, autologous stem cell transplant

Clinical perspectives

IsaVRd offers advantages over current standard of care

Submission from Oxford University Hospitals NHS Foundation Trust

- Current standard of care for 2 thirds of people is DRd. If approved, IsaVRd would likely be standard of care for up to 80% of people with newly diagnosed MM who are ineligible for ASCT (less suitable for older, frailer patients with comorbidities)
- IsaVRd is a step change 4 drug combination offering longer remissions and less risk of relapse
- Longer time to relapse means that fewer people would require earlier retreatment with other drug combinations in the treatment pathway
- Side-effects of IsaVRd are well defined and usually manageable with appropriate monitoring and dose reductions
- Drugs in the combination are all already widely used within the NHS, so no new additional resources are required to deliver it

The unmet needs that are addressed are common ones in myeloma – the requirement for better therapies that control the disease for longer, as patients inevitably relapse

IsaVRd offers potential significant advantages for patients with certain profiles of myeloma, such as those presenting with renal failure, or genetically high-risk disease

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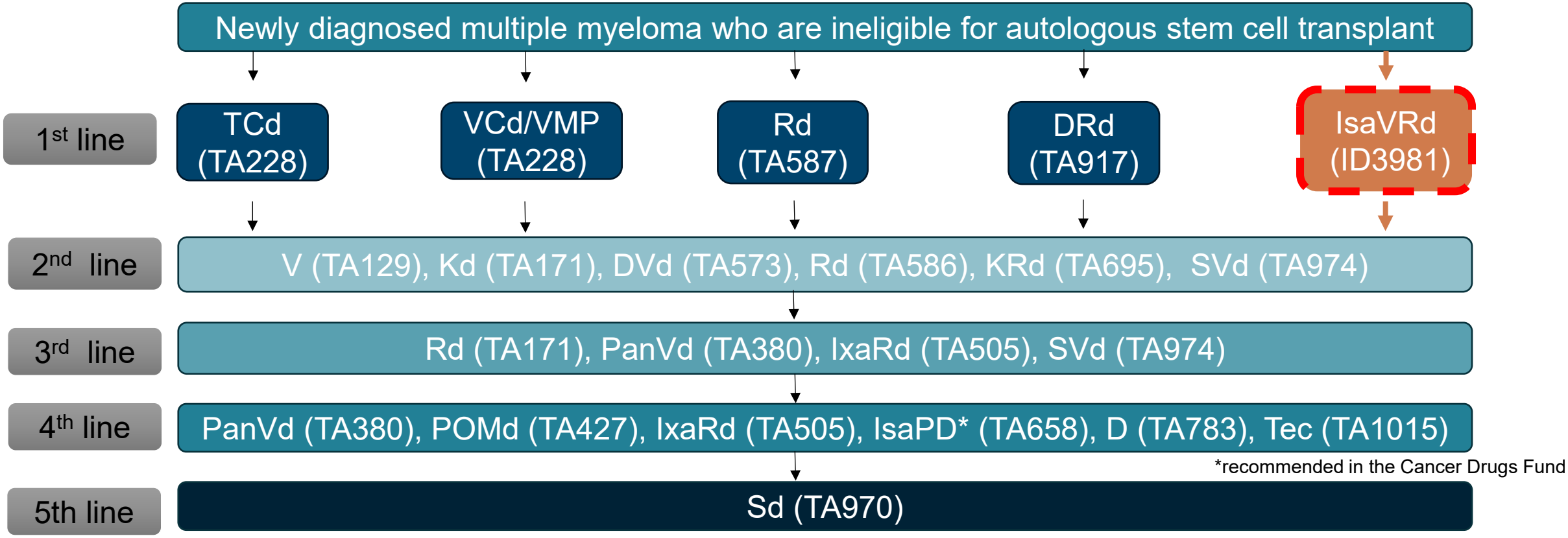
DRd, daratumumab, lenalidomide & dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide & dexamethasone; ASCT, autologous stem cell transplant; MM, multiple myeloma

Treatment pathway



- Would people whose cancer is not suitable for DRd be offered IsaVRd?
- Does committee agree that DRd is the most relevant comparator?

D, daratumumab; DRd, daratumumab, lenalidomide & dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide & dexamethasone; IsaPd, isatuximab, pomalidomide & dexamethasone; IxaRd, ixazomib, lenalidomide & dexamethasone; Kd, carfilzomib & dexamethasone; KRd, carfilzomib, lenalidomide & dexamethasone; PanVd, Panobinostat, bortezomib & dexamethasone; POMd, pomalidomide & dexamethasone; Rd, lenalidomide & dexamethasone; Sd, Selinexor & dexamethasone; SVd, selinexor, bortezomib & dexamethasone; TCd, thalidomide, cyclophosphamide & dexamethasone; TA, technology appraisal; VCd, Bortezomib, cyclophosphamide & dexamethasone; VMP, bortezomib, melphalan & prednisone; V, bortezomib; Tec, teclistamab

Isatuximab (SARCLISA, Sanofi)

Marketing authorisation (January 2025)	• Isatuximab is indicated in combination with bortezomib, lenalidomide, and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant
Mechanism of action	Isatuximab has multiple modes of action, including Fc-dependent immune mechanisms (ADCC, CDC, ADCP), Fc-independent direct apoptosis, inhibition of CD38 ectoenzyme activity, and immunomodulation, e.g. NK cell activation
Administration	• Isatuximab is given at 10 mg/kg by intravenous (IV) infusion • Given for 4 induction cycles (6 weeks each) followed by a continuous treatment period where isatuximab is eventually given 4-weekly until disease progression or unacceptable toxicity • Combination includes VRd

Price	• List price for isatuximab is £506.94 per 100mg/5ml vial and £2,534.69 per 500mg/25ml vial
	• Average weekly acquisition cost for IsaVRd:
	  ○ Induction - £2,175.28
	  ○ Continuous (first year) - £1,864.64
	  ○ Continuous (after first year) - £932.71
	• There is a simple discount PAS for isatuximab

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; CD38, cluster of differentiation 38; CDC, complement-dependent cytotoxicity; IsaRd, isatuximab, lenalidomide, and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; NK, natural killer; PAS, patient access scheme

Key issues

Issue	ICER impact
IMROZ trial data are immature	Unknown
IMROZ trial comparator and Company ITCs	Unknown
Modelling OS and PFS	Large
Overall survival benefit	Large
TTD & Subsequent treatment costs	Small
Utility values	Large

ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival

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Key clinical trial: IMROZ

Clinical trial design and outcomes

IMROZ trial design
IMROZ baseline characteristics

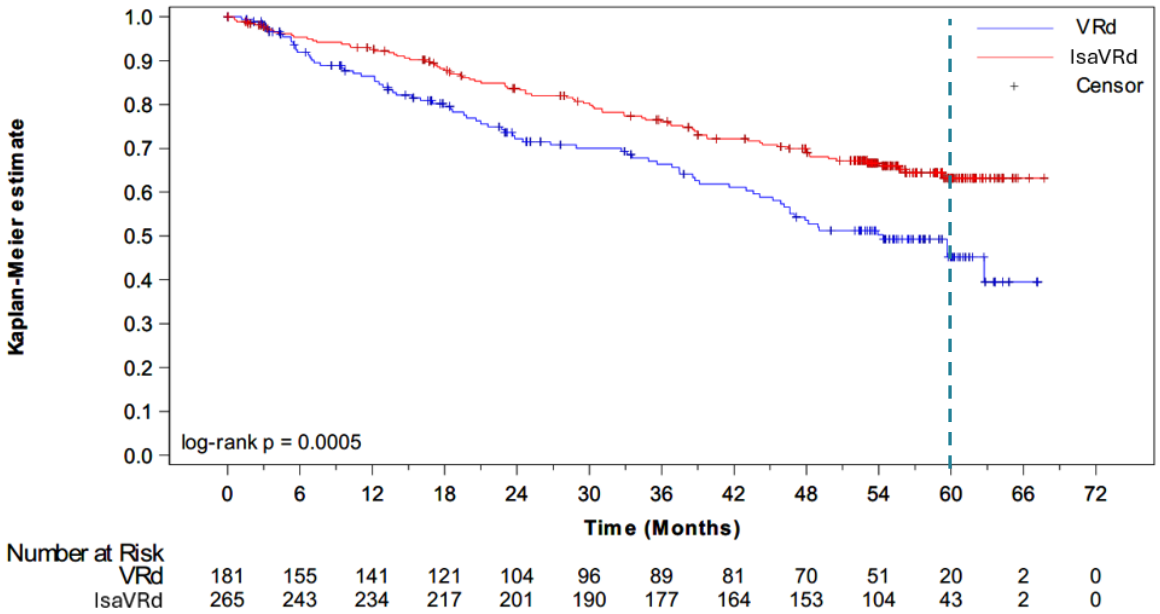
	IMROZ (NCT03319667)
Design	Prospective, multicentre, international, randomised, open-label, 2-arm parallel group study
Population	Adults with newly diagnosed MM not eligible for transplant due to: • being 65 years or older (people older than 80 excluded from IMROZ), or • being less than 65 years with comorbidities impacting possibility of transplant
Intervention	IsaVRd (n=265)
Comparator	VRd (n=181)
Primary outcomes	PFS (defined as time from date of randomisation to progression or death)
Key secondary outcomes	OS (defined as time from date of randomisation to death), TTD
Locations	93 sites across 21 countries
Data cut	26 September 2023 (additional data cut expected Q1/Q2 2025)

MM, multiple myeloma; PFS, progression-free survival; OS, overall survival; TTD, time to treatment discontinuation; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone

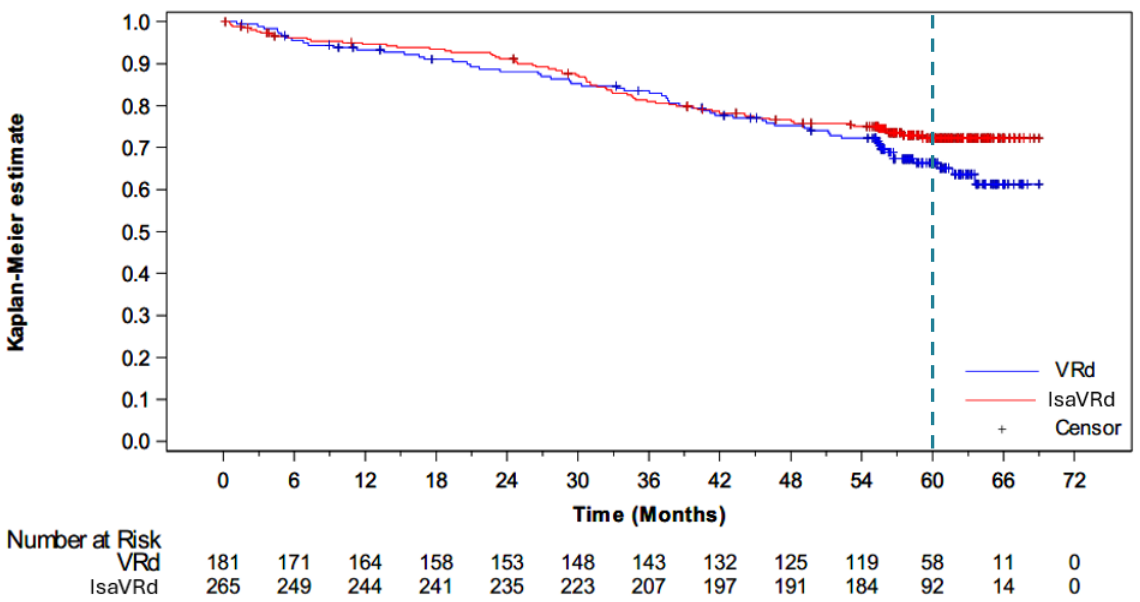
Key Issue: IMROZ trial data

IsaVRd (n=265) improves PFS and OS compared to VRd (n=181)

VRd vs IsaVRd – PFS



VRd vs IsaVRd – OS



	IsaVRd	VRd
Events (%)	84 (31.7%)	78 (43.1%)
Median, months	NR	54.34 (45.207 to NR)
HR (95% CI)	0.596 (0.406 to 0.876) p=0.0005	

	IsaVRd	VRd
Deaths (%)	69 (26%)	59 (32.6%)
Median, months	NR	NR
Estimated HR (99.9725% CI)	0.776 (0.407 to 1.48) p=0.0760	

Are IMROZ trial data sufficient for decision making?

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VRd, bortezomib, lenalidomide and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; PFS, progression-free survival; OS, overall survival; CI, confidence interval; NR, not reached

Key issue: IMROZ trial comparator and company ITCs

MAIC and IPW data sources

Background

- IMROZ trial comparator (VRd) is not used in the NHS and is not listed as a comparator in final NICE scope
- Company did NMAs and unanchored ITCs (MAICs [constant HR and time-varying HR] and IPW) to generate clinical effectiveness evidence for the comparison of IsaVRd versus DVd, VMP, Rd and VCd

Company

- A network meta-analysis was considered for comparison with DRd, Rd, and VMP. But limited by inclusion of a non-randomised subgroup from the SWOG S0777 trial (as a proxy for transplant ineligible population) in order to form a connected network
- Considered NMA results not robust
- So, did unanchored MAICs to estimate comparative efficacy between IsaVRd and DRd, Rd and VMP
- An IPW analysis was preferred for the comparison with VCd (using Flatiron database IPD)

ITC results

- PFS HRs (95% CI) for IsaVRd versus:
  - DRd [redacted] ([redacted] to [redacted]); VMP 0.20 (0.15 to 0.27); Rd [redacted] ([redacted] to [redacted]); VCd 0.34 (0.25 to 0.47)
- OS HRs (95% CI) for IsaVRd versus:
  - DRd [redacted] ([redacted] to [redacted]); VMP 0.50 (0.37 to 0.67); Rd [redacted] ([redacted] to [redacted]); VCd 0.48 (0.33 to 0.69)

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NMA, network meta-analysis; ITC, indirect treatment comparison; MAIC, matched-adjusting indirect comparison; HR, hazard ratio; IPW, inverse probability weighting; OS, overall survival; PFS, progression-free survival; IPD, individual patient data

Key issue: IMROZ trial comparator and company ITCs

EAG comments

- Agrees with company that NMA results unlikely to be robust because of SWOG S0777 trial
- Considers that company MAIC (constant HR) was implemented appropriately, but notes unanchored comparisons rely on potential prognostic factors and treatment effect modifiers being accounted for
- Not possible to adjust for 3 out of 9 of identified prognostic factors/treatment effect modifiers, so could potentially introduce bias from unmeasured confounding
- Disagrees with company's rationale for using time-varying HR MAIC in its base case analysis (reasonable to assume that PH assumption holds for all comparisons)
- Agrees with company choice to use IPW methods to generate comparative clinical effectiveness results for comparison of IsaVRd versus VCd, but notes risk of bias due to unmeasured confounding; clinical advice to EAG is that extent of any bias is unknown

Prognostic variable	Adjusted for?
Chromosomal abnormality 1q21+	**No**
ECOG PS	Yes
LDH levels	**No**
Creatinine clearance	Yes
MM type IgG	Yes
Frailty	**No**
Age	Yes
ISS stage	Yes
Cytogenic risk	Yes

Are the company's preferred ITC approaches (unanchored MAIC and IPW) the most appropriate for decision making?

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NMA, network meta-analysis; ITC, indirect treatment comparison; MAIC, matched-adjusting indirect comparison; HR, hazard ratio; IPW, inverse probability weighting; PH, proportional hazards; ISS, International Staging System; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, Lactate Dehydrogenase; IgG, immunoglobulin G; MM, multiple myeloma

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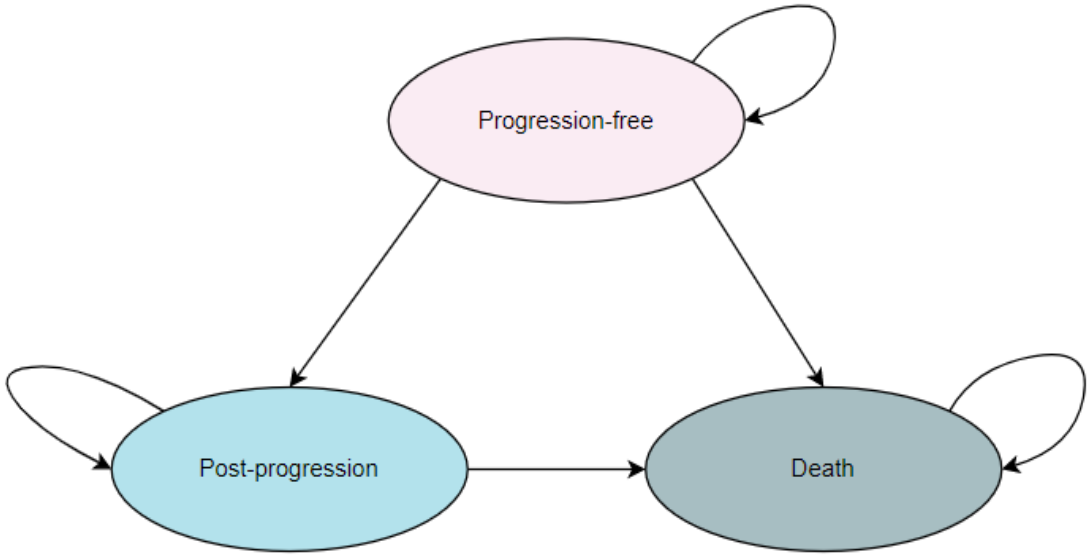
Company's model overview: Partitioned Survival model

- 3 health states (progression-free survival, post-progression survival, and death)



- Technology affects **QALYs** and **costs** by:
  - OS and PFS gain
  - Utility benefit in PFS health state
  - Treatment and administration costs

Area	Company assumptions/sources
Time horizon	Lifetime (29 years)
Mean age	71.6 years (IMROZ)
Source of clinical effectiveness data	IMROZ
Source of AEs	IMROZ
Source of utilities	IMROZ for PFS. PPS utility value sourced from the literature
Source of resource use	NHS Reference Costs 2022-23
Source of drug costs	BNF 2023; eMIT 2023; NHS Reference Costs 2022-23
Severity modifier	No
Treatment effect waning	No
Stopping rule	No

Is the model structure sufficient for decision making?

BNF = British National Formulary; PFS = progression-free survival; PPS, post-progression survival; eMIT, Drugs and pharmaceutical electronic market information tool; AE, adverse event

Key Issue: Modelling OS and PFS

ICER impact: Large

Background

- Company modelling approach:

Jointly fitted Gompertz (OS) and gamma (PFS) parametric distributions to MAIC adjusted IMROZ trial 68 months follow up data (IsaVRd) and comparator OS and PFS K-M data → Estimated time varying hazard ratios by comparing IsaVRd and comparator survival estimates at different time points → Time varying hazard ratios applied to IMROZ trial ITT OS (Gompertz) and PFS (gamma) to generate survival estimates for comparators

- At clarification, EAG considered applying time-varying hazard ratios overly complicated and requested analyses with 60 months follow up data and separate parametric distributions for IsaVRd and comparators
- Company maintained approach of applying time varying hazard ratios but provided scenario A = 60 months follow up. And scenario B (updated company base case) = 68 months IMROZ follow up and final OS analysis for DRd at 100 months

EAG comments

- Between 60 and 68 months, no OS or PFS events happened in IsaVRd arm. Survival estimates using distributions fitted to 60 months of IMROZ trial more in line with clinician estimates than 68 months. EAG prefer 60 months follow up

- Is the company approach of applying time-varying hazards appropriate? Or should separate parametric distributions for IsaVRd and comparator trial data be applied directly in the model?
- Should 60 months or 68 months IMROZ trial follow up be used for decision making? Should 60 months or 100 months DRd follow up be used for decision making?

MAIC, matched-adjusting indirect comparison; ITT, intention to treat; OS, overall survival; PFS, progression free survival

Key Issue: Modelling OS and PFS distributions

ICER impact: Large

Background

- For IsaVRd at 60 months, company prefer generalised gamma for OS & Weibull for PFS

EAG comments

- NICE DSU TSD 14 - fit of alternative models should be assessed systematically including AIC/BIC tests and clinical plausibility based upon expert judgement
- Gompertz distribution a better fit than generalised gamma for OS based on AIC/BIC, and generates estimates closer to clinician landmark estimates
- Gompertz distribution for PFS is comparatively ranked to Weibull and also generates estimates more closely aligned to clinical expert opinion

Fit statistics of OS extrapolation – IsaVRd

Distribution	AIC	AIC rank	AIC delta	BIC	BIC rank	BIC delta
Generalised gamma	865	6	4	876	11	6
Gompertz	863	2	2	870	5	2

Fit statistics of PFS extrapolation – IsaVRd

Distribution	AIC	AIC rank	AIC delta	BIC	BIC rank	BIC delta
Weibull	992	2	2	999	2	6
Gompertz	992	4	2	999	4	6

Full AIC and BIC statistics

OS and PFS extrapolations with clinician estimates

- Should generalised gamma or Gompertz be used for OS?
- Should Weibull or Gompertz be used for PFS?

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OS, overall survival; PFS, progression free survival; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Key Issue: Overall survival benefit

ICER impact: Large

Company

- MAIC results (time-varying HR) suggest OS benefit for IsaVRd compared with DRd - HR less than 1

EAG comments

- MAIC adjusted analysis HR v DRd = [redacted] ([redacted] to [redacted])
- MAIC adjusted analysis does not provide statistically significant evidence of a difference in survival between treatments at 1 to 5 year time-points
- Whilst the survival differences appear small, the company life year gain estimates account for approximately 30% of the total QALY gain for IsaVRd
- EAG prefers to set OS for DRd to be equal to IsaVRd

Is there evidence of a survival benefit for IsaVRd compared with DRd?

IsaVRd (IMROZ trial MAIC adjusted) versus DRd (MAIA trial) data: OS

People treated with IsaVRd and DRd - mortality rate equal for first 12 months, may be higher for DRd between months 12 and 24, may be higher for IsaVRd between months 24 and 36, becoming equal again from month 36 onwards

MAIC, matched-adjusting indirect comparison, HR, hazard ratio; OS, overall survival

Key Issue: TTD & Subsequent treatment costs

ICER impact: Small

Background

- IMROZ and MAIA trial data used to estimate the proportion of people who have subsequent treatments

Company

- Modelled PFS substantially longer for patients treated with IsaVRd (median=[redacted] weeks) compared to DRd (median=[redacted] weeks), and TTD for IsaVRd (median=[redacted] weeks) lower than for DRd (median=[redacted] weeks)

EAG comments

- IsaVRd and DRd treatment to progression regimens. DRd AE profile less favourable, EAG expects TTD for IsaVRd longer than DRd. Prefer TTD equal for IsaVRd and DRd due to no statistically significant difference
- In model some people stop IsaVRd and have no other treatment until progression. Total cost associated with IsaVRd (and ICERs per QALY gained) could be underestimated in the company model if:
  - difference between PFS and TTD modelled for IsaVRd is not reflected in NHS practice, or
  - people who stop treatment with IsaVRd receive subsequent treatments before progression
- Likely to be confounding in naïve analysis of IMROZ and MAIA
- To reflect this uncertainty, EAG scenario sets subsequent treatment costs equal for IsaVRd and DRd
- True ICERs likely somewhere between this scenario and company base case

How should TTD be modelled? Is it plausible to use PFS as a proxy for time to next treatment? Is the company's approach to modelling subsequent treatment costs appropriate?

Subsequent treatment costs

PFS, progression-free survival; OS, overall survival; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; TTD, time to treatment discontinuation

Key Issue: Utility values

Company and EAG utility values

ICER impact: Large

Background

- IMROZ trial post-progression health state utility value was not used to inform the company's model

Company

- IMROZ post-progression health state utility value overly optimistic because records clustered after the progression event, and not sufficiently robust because derived from a small number of people
- Prefers post-progression value from TA587 (lenalidomide plus dexamethasone for untreated MM) = 0.557

EAG comments

- Does not agree that HRQoL data from 97 people with progressed disease in IMROZ is too small a sample
- IMROZ trial post-progression utility value is similar to that in TA974 (selinexor plus bortezomib and dexamethasone for previously treated MM), where progressed-disease value was 0.660
- TA587 PFS utility values also low compared to IMROZ so post-progression utility value also low (0.557)
- Prefers IMROZ trial pooled Independent Central Review PPS value ([redacted]) to represent utility for people treated with IsaVRd and DRd
- As this value is higher than PFS utility values for other comparators, EAG applies utility decrement experienced by people treated with IsaVRd and DRd on moving to the post-progression health state ([redacted]) to the PFS value for the other comparator treatments

Is IMROZ or TA587 preferred for estimating post-progression health state utility value?

MM, multiple myeloma; HRQoL, health-related quality of life; PFS, progression-free survival; PPS, post-progression survival

Summary of company and EAG base case assumptions

	Company	EAG
OS	Generalised gamma (68 month IMROZ analysis + 100 month MAIA analysis for DRd)	OS for DRd equal to OS for IsaVRd + Gompertz (60 month IMROZ analysis)
PFS	Weibull (68 month IMROZ analysis)	Gompertz (60 month IMROZ analysis)
TTD	MAIC results	DRd TTD equal to IsaVRd TTD
Subsequent treatments	IMROZ and MAIA trial data	IMROZ and MAIA trial data (+ scenario exploring equal subsequent treatments costs for IsaDRd and DRd)
Utility values	Progressed disease utility value from TA587	Progressed disease utility value from IMROZ
Drug costs	NHS Reference Costs 2022/23	Updated drug administration costs from NHS Cost Collection 2023/24

OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation; MAIC, matched-adjusting indirect comparison

Cost-effectiveness results:

- Cost effectiveness results cannot be reported here because of confidential discounts for included technologies
- Company base case ICER is substantially above £30,000 per QALY gained
- EAG base case ICER is substantially above £30,000 per QALY gained

- All results are presented in Part 2 slides for committee

ICER; incremental cost effectiveness ratio, QALY; quality adjusted life year

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Managed access

Criteria for a managed access recommendation

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.
- Company did not submit a managed access proposal, no managed access feasibility assessment

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Key issues

Issue	Questions for committee
IMROZ trial data are immature	Is IMROZ trial data sufficient for decision making?
IMROZ trial comparator and Company ITCs	Are the company's preferred ITC approaches (unanchored MAIC and IPW) the most appropriate for decision making?
Modelling OS and PFS	Should 60 months or 68 months IMROZ trial follow up be used for decision making? Should 60 months or 100 months DRd follow up be used for decision making? Should generalised gamma or Gompertz be used for OS? Should Weibull or Gompertz be used for PFS?
Overall survival benefit	Is there evidence of a survival benefit for IsaVRd compared with DRd?
TTD & Subsequent treatment costs	How should TTD be modelled? Is it plausible to use PFS as a proxy for time to next treatment? Is the company's approach to modelling subsequent treatment costs appropriate?
Utility values	Is IMROZ or TA587 preferred for estimating post-progression health state utility value?

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ITC, indirect treatment comparison; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation; MAIC, matched-adjusting indirect comparison; IPW, inverse probability weighting

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Supplementary appendix

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Equality considerations

Highlighted issues do not relate to protected characteristics and are therefore not classed as potential equalities issues

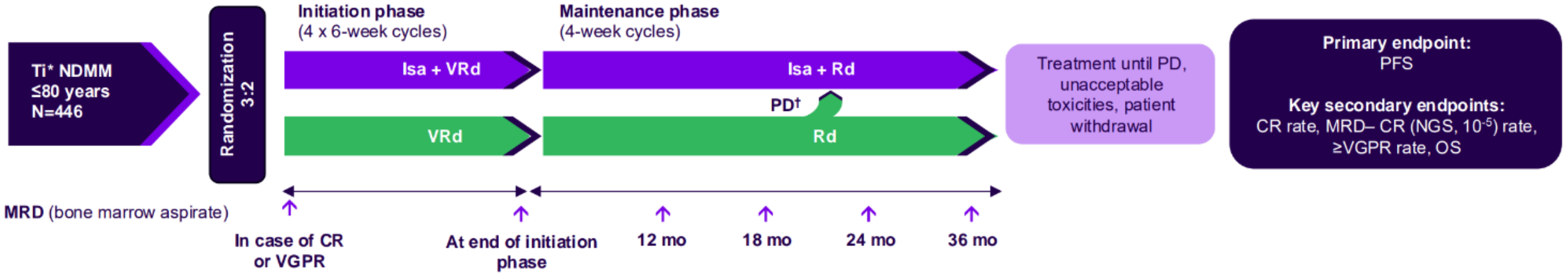
- Transplant-eligible people currently benefit from quadruplet induction therapy with DVTd, but transplant-ineligible people do not. Access to IsaVRd therapy would help mitigate this inequality
- At scoping consultation, stakeholders identified that costs incurred by hospital visits and time off work to receive treatment will have a more significant impact on people with lower incomes
- Current variability of access to treatments at present due to ineligibility for autologous stem cell transplant and renal impairment, as well as worse outcomes for people with High Cytogenetic Risk Abnormalities (HCRA) and 1q21 amplification

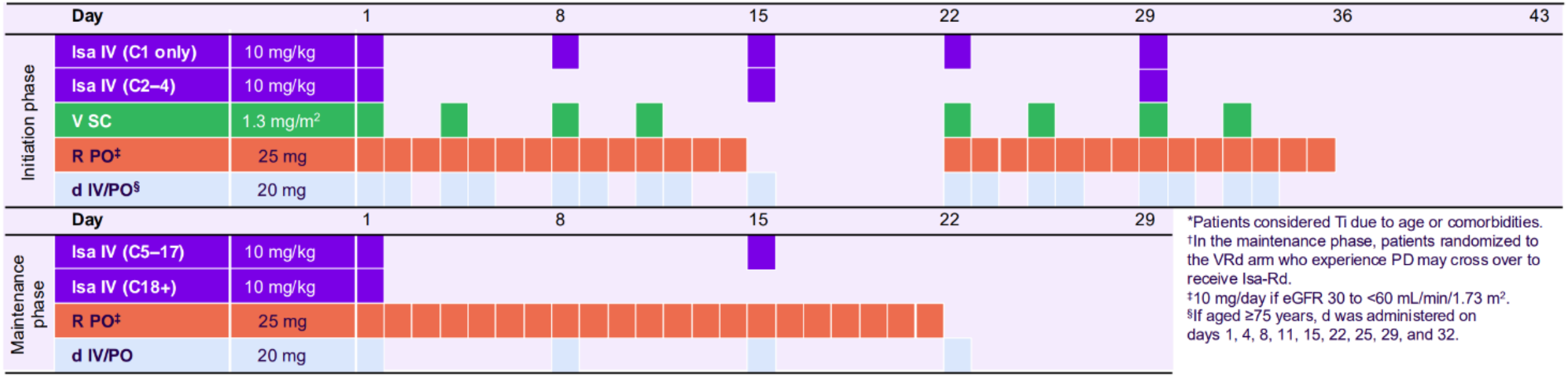
These highlighted issues do not relate to protected characteristics and are therefore not classed as potential equalities issues

IsaVRd: isatuximab, bortezomib, lenalidomide & dexamethasone; DVTd, daratumumab plus bortezomib, thalidomide, and dexamethasone

IMROZ trial design

Back to key issue slide





*Patients considered Ti due to age or comorbidities.
†In the maintenance phase, patients randomized to the VRd arm who experience PD may cross over to receive Isa-Rd.
‡10 mg/day if eGFR 30 to <60 mL/min/1.73 m².
§If aged ≥75 years, d was administered on days 1, 4, 8, 11, 15, 22, 25, 29, and 32.

C, cycle; CR, complete response; d, dexamethasone; eGFR, estimated glomerular filtration rate; Isa, isatuximab; IV, intravenous; mo, month; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGS, next generation sequencing; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, per os; R, lenalidomide; Rd, lenalidomide and dexamethasone; SC, subcutaneous; Ti, transplant ineligible; B, bortezomib; VGPR, very good partial response; VRd, bortezomib, lenalidomide, and dexamethasone.

IMROZ baseline characteristics

Back to key issue slide

	IsaVRd (N=265)	VRd (N=181)	All (N=446)
Age (years)			
Mean (SD)	71.7 (4.0)	71.5 (4.8)	71.6 (4.4)
Median	72.0	72.0	72.0
Sex [n (%)]			
Female	122 (46.0)	87 (48.1)	209 (46.9)
Male	143 (54.0)	94 (51.9)	237 (53.1)
Race [n (%)]			
American Indian or Alaska Native	4 (1.5)	1 (0.6)	5 (1.1)
Asian	31 (11.7)	17 (9.4)	48 (10.8)
Black or African American	2 (0.8)	2 (1.1)	4 (0.9)
Native Hawaiian or other Pacific Island	1 (0.4)	1 (0.6)	2 (0.4)
White	192 (72.5)	131 (72.4)	323 (72.4)
Not reported/Missing	35 (13.2)	29 (16.0)	64 (14.3)
Geographical region [n (%)]			
Europe	169 (63.8)	106 (58.6)	275 (61.7)
North America	3 (1.1)	5 (2.8)	8 (1.8)
Asia	31 (11.7)	15 (8.3)	46 (10.3)
Other Countries	62 (23.4)	55 (30.4)	117 (26.2)

Key Issue: IMROZ trial data are immature

Background

- Most recent trial results are from the September 2023 data cut (median follow-up was 59.73 months)
- Median PFS not reached in the IsaVRd arm
- Median OS not reached in either the IsaVRd or the VRd arms

Company

- Company expects the final data cut to become available Q1/Q2 2025

EAG comments

- The third and final data cut is not expected to be available within the timeframe of this appraisal
- There are no alternative approaches that could be considered

Is IMROZ trial data sufficient for decision making?

VRd, bortezomib, lenalidomide and dexamethasone; IsaVRd, isatuximab, bortezomib, lenalidomide, and dexamethasone; PFS, progression-free survival; OS, overall survival

Key Issue: Modelling OS and PFS AIC and BIC statistics

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Fit statistics of OS extrapolation – IsaVRd

Distribution	AIC	AIC rank	AIC delta	BIC	BIC rank	BIC delta
Exponential	862	1	0	865	0	1
Gamma	864	4	2	871	6	4
Generalised gamma	865	6	4	876	11	6
Gompertz	863	2	2	870	5	2
Log-logistic	864	5	3	871	6	5
Log-normal	870	7	8	877	12	7
Weibull	864	3	2	871	6	3

Fit statistics of PFS extrapolation – IsaVRd

Distribution	AIC	AIC rank	AIC delta	BIC	BIC rank	BIC delta
Exponential	990	1	0	994	1	0
Gamma	992	3	2	999	3	6
Generalised gamma	994	6	4	1005	7	11
Gompertz	992	4	2	999	4	6
Log-logistic	992	5	2	1000	5	6
Log-normal	996	7	6	1003	6	10
Weibull	992	2	2	999	2	6

NICE

OS, overall survival; PFS, progression-free survival; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

Key Issue: Modelling OS and PFS with clinician estimates

OS: proportion of people alive at key time points

Distribution	IsaVRd OS generated using IMROZ trial data					
	68 months	60 months	68 months	60 months	68 months	60 months
	10 years		15 years		20 years	
Generalised gamma	51.70%	48.33%	34.50%	29.26%	17.30%	14.56%
Gompertz	52.36%	47.56%	35.40%	27.71%	17.74%	13.48%
Clinician estimates %, (95% CI)	45% (35% to 55%) Max: 60%		24% (15% to 33%) Max: 35%		11% (5% to 17%) Max: 20%	

Company base case (Scenario B)

Company scenario A

EAG base case

PFS: proportion of people progression-free at key time points

Distribution	IsaVRd PFS Generated using IMROZ trial data					
	68 months	60 months	68 months	60 months	68 months	60 months
	10 years		15 years		20 years	
Gamma	40.20%	39.60%	25.19%	23.92%	12.61%	11.90%
Gompertz	40.62%	38.59%	25.69%	22.58%	12.86%	11.23%
Weibull	40.15%	39.44%	25.10%	23.78%	12.57%	11.83%
Clinician estimates %, (95% CI)	28% (23% to 33%) Max: 40%		11% (2% to 16%) Max: 20%		2% (0% to 6%) Max: 10%	

NICE

OS, overall survival; PFS, progression-free survival; CI, confidence interval

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Key Issue: Landmark OS HR

Time (years)	Landmark OS HR (95% CI) for IsaVRd versus comparators			
	DRd	Rd	VMP	VCd
1	[redacted]	[redacted]	0.66 (0.43, 1.01)	0.51 (0.32, 0.82)
2	[redacted]	[redacted]	0.56 (0.40, 0.78)	0.47 (0.32, 0.68)
5	[redacted]	[redacted]	0.34 (0.17, 0.66)	0.36 (0.20, 0.62)
5.67*	[redacted]	[redacted]	0.30 (0.13, 0.67)	0.33 (0.17, 0.65)
10	[redacted]	[redacted]	0.15 (0.03, 0.79)	0.22 (0.06, 0.94)
28	[redacted]	[redacted]	0.01 (0.00, 1.94)	0.04 (0.00, 5.32)

* 68 months IMROZ trial follow up

NICE

OS, overall survival; HR. hazard ratio; CI, confidence interval

Key Issue: Landmark PFS HR

Time (years)	Landmark PFS HR (95% CI) for IsaVRd versus comparators			
	DRd	Rd	VMP	VCd
1	[redacted]	[redacted]	0.21 (0.15, 0.29)	0.35 (0.25, 0.47)
2	[redacted]	[redacted]	0.18 (0.13, 0.26)	0.33 (0.24, 0.45)
5	[redacted]	[redacted]	0.16 (0.11, 0.26)	0.32 (0.21, 0.48)
5.67*	[redacted]	[redacted]	0.16 (0.11, 0.26)	0.32 (0.21, 0.48)
10	[redacted]	[redacted]	0.15 (0.10, 0.26)	0.31 (0.20, 0.50)
28	[redacted]	[redacted]	0.14 (0.08, 0.27)	0.31 (0.18, 0.52)

* 68 months IMROZ trial follow up

PFS, progression-free survival; HR. hazard ratio; CI, confidence interval

MAIC and IPW data sources

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Treatment	Studies providing data for the company MAICs	Study design	OS data	PFS data
IsaVRd	IMROZ trial	Phase III, multicentre, international, open-label RCT	Individual patient-data	Individual patient-data
Unanchored MAIC				
DRd	MAIA trial	Phase III, multicentre, international, open-label RCT	TA917	Kumar et al. 2022
Rd	MAIA trial	Phase III, multicentre, international, open-label RCT	TA917	Kumar et al. 2022
	FIRST trial	Phase III, multicentre, international, open-label RCT	Facon et al. 2018	Facon et al. 2018
VMP	ALCYONE trial	Phase III, multicentre, international, open-label RCT	Mateos et al. 2022	Mateos et al. 2022
IPW				
VCd	Flatiron database	US retrospective cohort study	Individual patient-data	Individual patient-data

OS, overall survival; PFS, progression-free survival; MAIC, matched-adjusting indirect comparison; RCT, randomised controlled trial; IPW, inverse probability weighting

Subsequent treatment costs

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Treatment line	IsaVRd	DRd	Rd	VCd	VMP
Acquisition costs					
Second-line subsequent treatment cost	[redacted]	[redacted]	£97,819	£72,670	£81,311
Third-line subsequent treatment cost	[redacted]	[redacted]	£12,334	£40,144	£53,028
Fourth-line subsequent treatment cost	[redacted]	[redacted]	£7,295	£7,345	£7,384
Total acquisition costs	[redacted]	[redacted]	£117,448	£120,158	£141,722
Administration costs					
Second-line subsequent treatment cost	£11,995	£15,442	£19,818	£15,960	£17,063
Third-line subsequent treatment cost	£1,546	£2,794	£3,213	£853	£532
Fourth-line subsequent treatment cost	£340	£451	£592	£396	£233
Total administration costs	£13,881	£18,687	£23,623	£17,210	£17,828
Overall costs					
Total	[redacted]	[redacted]	£141,071	£137,369	£159,549

Company and EAG utility values

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	IsaVRd	DRd	VMP	Rd	VCd	Source
Company						
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IMROZ trial data
PPS	0.557	0.557	0.557	0.557	0.557	TA587*
EAG						
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IMROZ trial data
PPS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	IMROZ trial data

* TA587: lenalidomide plus dexamethasone for previously untreated multiple myeloma

PFS, progression-free survival; PPS, post-progression survival