Isatuximab in combination with bortezomib, lenalidomide, and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable [ID3981]

For Projector-confidential information redacted

Technology appraisal committee B [02 July 2025]

Chair: Charles Crawley

Lead team: David McAllister, Anna Pracz, Tony Wooton

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

Technical team: Alice Pritchard, Christian Griffiths, Richard Diaz

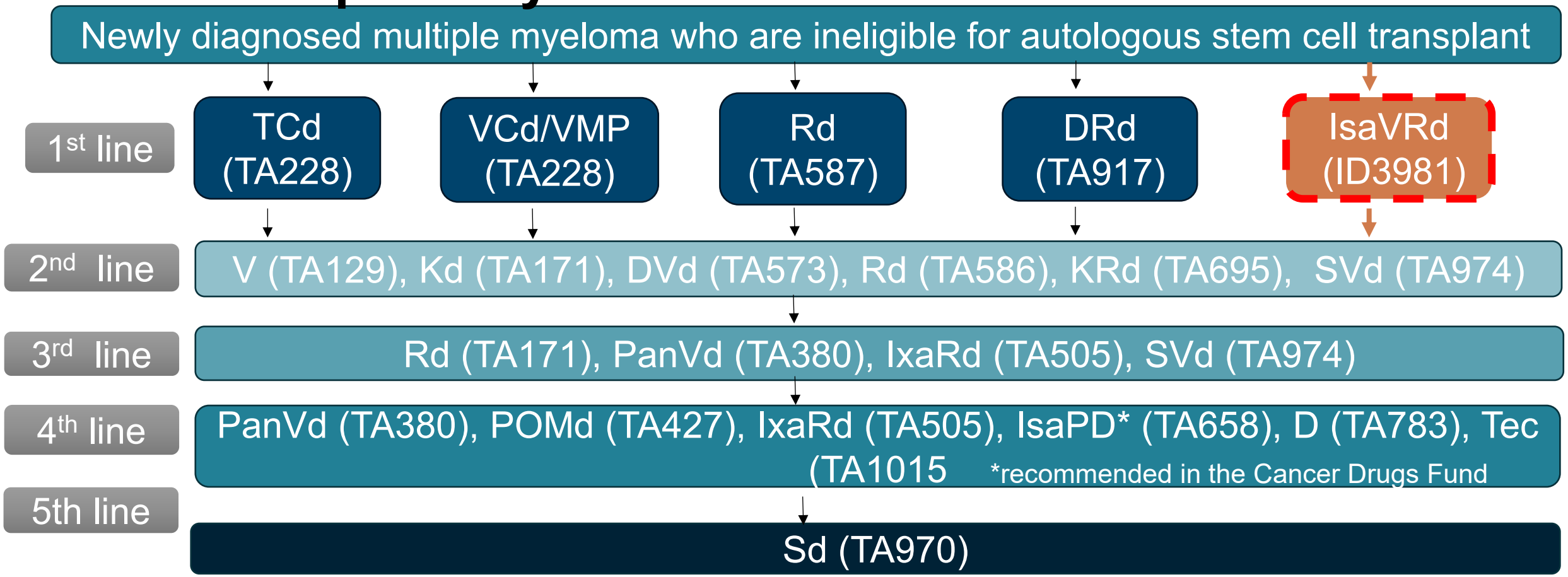
Company: Sanofi

ACM 1 – draft guidance recommendation

Isatuximab plus bortezomib, lenalidomide and dexamethasone should not be used for untreated multiple myeloma in adults when an autologous stem cell transplant is unsuitable.

- Committee concluded that the cost-effectiveness estimates were uncertain and further justifications for assumptions were needed

Treatment pathway



C, cyclophosphamide; d, dexamethasone; D, daratumumab; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; M, melphalan; P, prednisone; Pan, Panobinostat; POM, pomalidomide; R lenalidomide; Sv, Selinexor; T, thalidomide; TA, technology appraisal; Tec, teclistamab; V bortezomib

Key issues from 1st Committee Meeting and Company's Response 1/2

Key issues and company response

Key issue ACM1	Committee preference	Company response
IMROZ trial data is immature	• Trial data immature, uncertainty • Trial results suitable for decision making	• IMROZ trial data informs model
IMROZ trial comparator and Company ITCs	• Dar-Len-Dex is most relevant comparator • Requested updated NMA analysis	• Updated NMA and MAIC analysis, maintained use of updated MAIC
Modelling OS and PFS	• Model OS and PFS for IsaVRd and comparators: apply HR from NMA to appropriate reference curve (DRd OS and PFS curve from MAIA trial or DRd SACT data)	• Applied HRs from updated MAIC • Used OS and PFS DRd reference curves from MAIA trial

Abbreviations : d, dexamethasone; D, daratumumab; HR, hazard ratio; Isa, isatuximab; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; R lenalidomide; SACT, systemic anti-cancer therapy; V bortezomib

Key issues from 1st Committee Meeting and Company's Response 2/2

Key issues and company response

Key issue ACM1	Committee preference	Company response
Overall survival benefit	• Further evidence to support OS benefit for IsaVRd	• Further evidence provided
TTD and Subsequent treatment costs	• Correct model to include selinexor and teclistamab as subsequent lines treatment • Further justification for differences between TTD and PFS	• Updated model to include subsequent treatments • Maintain PFS and TTD modelling assumptions
Utility values	• Prefer post-progression utility values from IMROZ, or treatment-independent progressed-disease utility values derived by applying decrement based on Hatswell et al. to IMROZ PFS utility	• Applied decrement based on Hatswell et al. to IMROZ PFS utility values

Abbreviations: D, daratumumab; HR, hazard ratio; Isa, isatuximab; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; R, lenalidomide; TTD, time to treatment discontinuation; V bortezomib

Key issues for committee discussion at 2nd committee meeting

Key issues outstanding at second committee meeting

	Issue	ICER impact
Clinical-effectiveness	Company ITCs	Unknown
	Overall survival benefit	Large
Cost-effectiveness	Modelling PFS and OS	Large
	TTD and subsequent treatment costs	Small
	Utility values	Small

Abbreviations: ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison, OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation

Response to DG consultation (1/4)

Summary of responses from stakeholders

Abbreviations:

d, dexamethasone; D, daratumumab; DG, draft guidance; Isa, isatuximab; IV, intravenous; MM, multiple myeloma; R lenalidomide; SC, subcutaneous; TA, technology appraisal; TTD, time to treatment discontinuation; V bortezomib

Stakeholder comments (Johnson & Johnson, Myeloma UK, UK Myeloma Society)

Modelling TTD:

- Modelling TTD: IsaVRd shorter than DRd not consistent with trial
- Median treatment duration of IMROZ longer (53.2 months) than median treatment duration in MAIA trial (47.5 months). J&J provided further data that is confidential

Inappropriate drug administration costs in company model

- IsaVRd compared to DRd has similar administration costs, not plausible when isatuximab is IV injection and daratumumab is SC injection. Other MM appraisals (TA917, TA763, TA897, TA1015) used N10AF for SC administration costs

Modelling adverse events:

- Counterintuitive: 4th agent added, 11 extra IV administrations for administering isatuximab compared to SC daratumumab in 2 years after initiation of treatment

Response to DG consultation (2/4)

Summary of responses from stakeholders (Johnson & Johnson, Myeloma UK, UK Myeloma Society)

Differences between TTD and PFS plausible and consistent with evidence:

- PFS benefit driven by bortezomib, shown in SWOG S0777 trial.
- IsaVRD (IMROZ trial) higher MRD negativity, and for longer duration, (58.1%) compared to DRD (32.1%) (MAIA). MRD negativity linked with increased PFS and OS.
- MRD negativity associated with mental wellbeing person as cancer undetectable compared to knowing cancer is still there but controlled. Carer QoL not accounted for
- Small number discontinued treatment due to progression, supports PFS benefit
- PFS longer than TTD fits with clinical experience. People stop treatment due to side effects or preference at a time when they are in remission and will continue to remain in this state for a while. Depth of response (complete response or MRD negativity) is greater for quadruplet therapy compared to triplet. IsaVRd expected to have more side effects than DRd

Abbreviations: d, dexamethasone; D, daratumumab; DG, draft guidance; Isa, isatuximab; IV, intravenous; MM, multiple myeloma; MRD, minimal residual disease; R lenalidomide; OS, overall survival; PFS, progression-free survival; SOC, standard of care; TA, technology appraisal; TTD, time to treatment discontinuation; QoL, quality of life; V bortezomib

Response to DG consultation (3/4)

Summary of responses from stakeholders (Johnson & Johnson, Myeloma UK, UK Myeloma Society)

OS benefit

- Plausible that addition of proteosome inhibitor to an anti-CD38/IMID backbone (quadruplet versus induction therapy) does provide survival benefit
- Likely to be excess mortality in IMROZ trial, positive COVID results reported for number of people that died during IMROZ. People with myeloma had high mortality from COVID during this period (around 50%), whilst MAIA study was not conducted during COVID, so this issue did not affect DRd

Longer remission times compared to current SOC improve QoL:

- IMROZ trial 63% still in remission after 5 years, 5 year survival rate of myeloma 55%
- Relapse affects QoL, disrupts lives, adds anxiety for people with MM and carers

NICE

Abbreviations: D, daratumumab; DG, draft guidance; HDT-SCT, high-dose chemotherapy and autologous stem cell transplant; Isa, isatuximab; R lenalidomide; V bortezomib; QoL, quality of life

Response to DG consultation (4/4)

Summary of responses from stakeholders (Johnson & Johnson, Myeloma UK, UK Myeloma Society)

IsaVRD provides longer first remission:

- First remission: person has highest QoL, often longest remission time period.
- Subsequent treatment lines: worse outcomes and side effects, less effective, reduced remission time from other lines treatment. Need to account reduced number will receive subsequent treatment on IsaVRD

Unmet need:

- IsaVRD gives similar depth of responses compared to those reached following HDT-SCT for people ineligible for HDT-SCT

Benefit receiving quadruplet therapy:

- Quadruplet therapy most effective, has flexibility to mitigate side effects, more likely to remain on treatment

Abbreviations: D, daratumumab; DG, draft guidance; HDT-SCT, high-dose chemotherapy and autologous stem cell transplant; Isa, isatuximab; R lenalidomide; V bortezomib; QoL, quality of life

Clinical Effectiveness

NICE National Institute for Health and Care Excellence

Key Issue: Company ITCs

ICER impact: Unknown

Company did NMA using SWOG S0777 study to inform cost-effectiveness

Recap

- NMA: used non-randomised subgroup from SWOG 0777 trial (as proxy for transplant ineligible population). Did unanchored MAIC.
- Committee: NMA: ITT population, no intent-to-transplant subgroup proxy transplant ineligible

Company: updated ITC results, base case uses updated MAIC, scenarios provided

ITC method	PFS (HR, 95% CI)	OS (HR, 95% CI)	Company Comment
MAIC (base case)	[redacted]	[redacted]	Constant HR MAIC anchored to DRd curves in MAIA trial, key effect modifiers adjusted, Cox PH ratio limited to IMROZ follow-up for IsaVRD and DRd
NMA no intent to transplant	[redacted]	[redacted]	Includes those who chose not to have transplant and those ineligible. less risk confounding in treatment effect.
NMA ITT	[redacted]	[redacted]	Differences baseline characteristics of ITT creates bias, transitivity not met

Abbreviations: CI, confidence interval; d, dexamethasone; D, daratumumab; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; ITT, intention to treat; Isa, isatuximab; NMA, network meta-analysis; MAIC, matching-adjusted indirect comparison; PH, proportional hazards; PFS, progression-free survival; OS, overall survival; R lenalidomide; V bortezomib

Key Issue: Company ITCs

EAG recommend using non-time varying MAIC

Abbreviations: : d, dexamethasone; D, daratumumab; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; ITT, intention to treat; Isa, isatuximab; NMA, network meta-analysis; MAIC, matching-adjusted indirect comparison; OS, overall survival; R lenalidomide; V, bortezomib

ICER impact: Unknown

EAG comments

- Not suitable to use final MAIA data cut in ITC, data suggests changing OS HR over time, worsening for DRd. OS HR may worsen for IMROZ trial as data collected

EAG comment on ITC methods

ITC method	EAG comment
MAIC	• Company's original non-time varying MAIC more robust.
NMA no intent to transplant	• No baseline trial characteristics for transplant ineligible. Cannot compare severity of disease of the transplant ineligible between SWOG S0777 and IMROZ trial population. Could have confounding, which cannot be quantified, and direction of resultant bias unknown. EAG do not recommend this analysis
NMA ITT	• SWOG S0777 and IMROZ ITT populations different - using data from 2 trials will not produce meaningful estimate of treatment effectiveness of IsaVRd relative to comparators. EAG do not recommend this analysis.

NICE

What is the most appropriate ITC for decision making?

Key Issue: Overall survival benefit

ICER impact: Large

Company provided further justification for OS benefit of IsaVRd

Recap

- MAIC results suggest OS benefit for IsaVRd compared with DRd as HR less than 1 but did not provide statistically significant different in OS between 1 and 5 years
- Committee: requested further evidence of OS benefit for IsaVRd compared with DRd

Company

- NMA using no intent to transplant subgroup from SWOG S0777 estimated HR for OS [redacted] for IsaDRd compared to DRd.
- Evidence from SWOG S0777, adding in bortezomib to Rd significantly improved OS in:
  - ❖ No intent to transplant subgroup: HR of 0.583 (95% CI 0.371 to 0.917, p=0.0134)
  - ❖ ITT population: HR of 0.709 (95% CI: 0.536 to 0.938, p=0.0114)
- So, would expect survival benefit adding in bortezomib
- Survival benefit driven by responses induced by bortezomib, such as:
  - ❖ improved MRD rates in IsaVRd (58.1% in IMROZ) compared with DRd. 46.7% had MRD negativity for at least 12 months, MRD established surrogate for PFS and OS in MM- sustained MRD rate predictor of long-term survival

Abbreviations: CI, confidence interval; d, dexamethasone; D, daratumumab; HR, hazard ratio; ITT, intent to treat; ; Isa, isatuximab; MAIC, MAIC, matching-adjusted indirect comparison; MM, multiple myeloma; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; R lenalidomide; V, bortezomib

Key Issue: Overall survival benefit

ICER impact: Large

Uncertainty remains whether IsaVRd provides OS benefit

EAG comments

- NMA for no intent to transplant is not robust to evidence survival gain, potential confounding in analysis
- Adding bortezomib to Rd improving OS, does not mean that adding bortezomib to IsaRd improves OS
- Not known whether MRD negativity test is used in NHS practice. In IMROZ trial, impact on MRD negativity unknown for people continuing IsaVRd

Has the further evidence provided by company supported an OS benefit of IsaVRd compared to DRd?

Abbreviations: ; d, dexamethasone; D, daratumumab; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; ; Isa, isatuximab; OS, overall survival; R lenalidomide; V, bortezomib

Cost Effectiveness

NICE National Institute for Health and Care Excellence

Key Issue: Modelling OS and PFS

ICER impact: Large

Background

- Company: Time-varying HRs applied to IMROZ ITT OS and PFS
- Committee: Apply HR from NMA to Dar-Len-Dex OS and PFS curve from MAIA trial or DRd SACT data)

Company

- DRd reference curves from MAIA trial used for anchoring HRs. Aligned DRd extrapolation to TA917. Generalised gamma for OS extrapolation

IsaVRd OS rates in model

	10 years	15 years	20 years
Original	52.40%	35.40%	17.70%
New base case	[redacted]	[redacted]	[redacted]
Clinician estimates %	35% to 55%	15% to 33%	5% to 17%

IsaVRd PFS rates in model

	10 years	15 years	20 years
Original	40.2%	25.2%	12.6%
New base case	[redacted]	[redacted]	[redacted]
Clinician estimates %	23% to 33%	2% to 16%	0% to 6%

Abbreviations: d, dexamethasone; D, daratumumab; HR, hazard ratio; Isa, isatuximab; ITT, intention to treat; NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; TA, technology appraisal; SACT, systemic anti-cancer therapy; TTD, time to treatment discontinuation; R lenalidomide; V, bortezomib

confidential

Key Issue: Modelling OS and PFS

ICER impact: Large

Type here summary of EAG comments

EAG comments

- Updated company base case long term OS estimates more aligned to clinician estimate
- Decision to anchor MAIA trial DRd or IMROZ trial IsaVRd PFS and OS data, should be based on assessment which trial population is most similar to NHS population

Are the long-term estimates for OS and PFS plausible?

Abbreviations: d, dexamethasone; D, daratumumab; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Isa, isatuximab; OS, overall survival; PFS, progression free survival; R lenalidomide; V, bortezomib;

ICER impact: Small

Key Issue: TTD and Subsequent treatment costs

Background

- Modelled longer PFS for people treated with IsaVRd compared to DRd. TTD for IsaVRd lower than for DRd .
- Committee: Further justification in modelling TTD and PFS

Company

- Updated subsequent treatment distributions

Evidence for longer PFS:

- ❖ Longer PFS due to higher rate of MRD negativity
- ❖ MAIC explored MRD negativity, IsaVRd increased odds of achieving MRD negativity

Equivalent TTD for IsaVRd and DRd:

- MAIC TTD HR of [redacted]
- Both target CD38, similar tolerability
- IMROZ trial population fitter than MAIA which explains difference in side effect profile
- 72.5% discontinued for other reasons than progression and higher MRD rates support TTD

MRD negativity MAIC results

Method	Odds Ratio (95% CI)
Unadjusted OR	[redacted]
MAIC adjusted OR	[redacted]
MAIC adjusted bootstrap median OR	[redacted]

CI, confidence interval; d, dexamethasone; D, daratumumab; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ; Isa, isatuximab; MAIC, matching-adjusted indirect comparison; ; MRD, minimal residual disease; OR, odds ratio; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation; R lenalidomide; V, bortezomib;

ICER impact: Small

Key Issue: TTD & Subsequent treatment costs

EAG comments

Subsequent treatment:

- Not clear why greater proportion of people receive second-line treatment with SVd for people treated with DRd

Longer PFS compared to TTD:

- Company provided some potentially plausible reasons to support prolonged PFS
- Concerns remain that prolonged PFS after stopping treatment is not reasonable
- Time to next treatment in IMROZ trial could have been more informative, may have been evidence that prolonged PFS was not due to receiving subsequent therapy prior to progression

Are the assumptions regarding PFS and TTD suitable for decision making?

Abbreviations: d, dexamethasone; D, daratumumab; EAG, external assessment group; ICER, incremental cost-effectiveness ratio; Isa, isatuximab; PFS, progression free survival; R lenalidomide; Sv, Selinexor; TTD, time to treatment discontinuation; V, bortezomib;

ICER impact: Small

Key Issue: Utility values

Background

- IMROZ trial post-progression utility values not used to inform company model
- Committee: prefer post-progression utility values from IMROZ, or treatment-independent progressed-disease utility values derived by applying decrement based on Hatswell et al. to IMROZ PFS utility

Company

- Utility decrement, taken from Hatswell et al., 0.030 applied to IMROZ PFS utility
- Applied decrement between 1st and 2nd line treatment from Hatswell because: model included 1 PPS health state that aggregated all subsequent treatment lines

Applied decrement of 0.030 to IMROZ PFS utility values

	IsaVRd	DRd	Rd	VMP	VCd
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PPS (Hatswell decrement between 1L and 2L	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

EAG comments: Company approach reasonable

Is the company approach suitable for decision making?

Abbreviations: 1L, first-line, 2L, second-line; C, cyclophosphamide; d, dexamethasone; D, daratumumab; Isa, isatuximab; PFS, progression-free survival; R, lenalidomide;; M; melphalan; P, prednisone; PPS, post-progression survival; V, bortezomib;

Summary of company and EAG base case assumptions

	Company	EAG
OS	MAIC constant HR anchored to DRd curves of MAIA trial, generalised gamma for OS. Scenarios: 68 months IMROZ/100 months DRd, 60 months IMROZ/100 months DRd	Prefers not to use final MAIA data cut Company's original, non-time varying, MAIC more robust
PFS	Constant HR from MAIC anchored to DRd curves of MAIA trial, gamma for PFS	non-time varying MAIC more robust
TTD	MAIC results	Align with company, concerns remain with extended PFS compared to TTD
Subsequent treatments	Includes Sv and Tec, % estimated from clinical expert input	Unclear why difference in proportion people receiving Sv in arms of model
Utility values	Based on Hatswell et al, applied utility decrement to IMROZ PFS utilities	Align with company
Drug costs	Cost code SB12Z SC administration costs	Other MM appraisals use N10AF
Starting age in model	75 years, from Djebbari et al. SACT data unavailable	inappropriate to have starting age in model that differs from the trial age

Abbreviations: d, dexamethasone; D, daratumumab; EAG, external assessment group; HR, hazard ratio; Isa, isatuximab; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; ; R lenalidomide; SACT, systemic anti-cancer therapy; Sv, Selinexor; Tec, teclistamab; TTD, time to treatment discontinuation; V, bortezomib;

Key issues

Issue	Questions for committee
Company ITCs	What is the preferred ITC method?
Modelling OS and PFS	Is the company's updated modelling of PFS and OS appropriate for decision making?
Overall survival benefit	Is there sufficient evidence of a survival benefit for IsaVRd compared with DRd?
TTD & Subsequent treatment costs	Has the company provided plausible evidence for PFS and TTD assumptions in the model?
Utility values	Is the company's approach to modelling utility values appropriate?

Other modelling issues

Issue	Questions for committee
Treatment administration costs	Which is the preferred cost code for SC administration?
Starting age in the model	What is the preferred starting age in the model?

Abbreviations: d, dexamethasone; D, daratumumab; ITC, indirect treatment comparison ; Isa, isatuximab MAIC, matched-adjusting indirect comparison; OS, overall survival; PFS, progression-free survival; R lenalidomide; TTD, time to treatment discontinuation; V, bortezomib;

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

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]

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

NICE National Institute for Health and Care Excellence

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

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]

Supplementary appendix

NICE National Institute for Health and Care Excellence

Back to key issue slide

IMROZ and SWOG S0777 ITT baseline characteristics

Characteristic	SWOG 0777 trial (n=74)	IMROZ trial (n=465)	Difference
Median Age	63 years	72 years	+9 years
Frailty	Not reported	Not reported	NA
ISS Stage III	34% (155/460)***	26.9% (120/465)	–6.1%
High-risk cytogenetics	33% (out of 316 patients)**	16.6% (74/446)	–16.4%
ECOG PS >1	12% (53/441)***	11.0% (49/446)	–1%
LDH ≥ 190 U/L	36% (163/454)***	12.7% (56/446)	-23.3%
Renal impairment eGFR<60 ml min 1.73 m^2	Not reported	28.7% (128/446)	NA
Chromosomal abnormality 1q21+	Not reported	37.0% (165/446)	NA
MM type (IgG)	Not reported	64.6% (286/446)	NA
Transplant Rate*	35% (161/460)***	0%	–35%

*Not pre-identified as a treatment effect modifier creates confounding with treatment effect in trial. ** SWOG S0777 first data-cut ***SWOG S0777 second data-cut

Key Issue: Company ITC scenarios

Main slides, Company ITC

Provided scenarios using different follow-up data cuts for IMROZ trial

Background

- Produced scenarios using parametric MAIC, using either:
  - ❖ 68 months IMROZ follow-up data and 100 months MAIA follow-up data
  - ❖ 60 months IMROZ follow-up data and 100 months MAIA follow-up data
- These scenarios have large impact on ICER

Abbreviations: CI, confidence interval; d, dexamethasone; D, daratumumab; HR, hazard ratio; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; ITT, intention to treat; Isa, isatuximab; NMA, network meta-analysis; MAIC, matching-adjusted indirect comparison; PH, proportional hazards; PFS, progression-free survival; OS, overall survival; R lenalidomide; V bortezomib

Subsequent treatment distributions

TTD and Subsequent treatment costs

Background

- Updated treatment distributions based on input of 2 clinical experts

	Regimen	IsaVRd	DRd
2nd line	Kd	27.5%	27.5%
	Vd	17.5%	17.5%
	VCd	30.0%	25.0%
	SVd	25.0%	30.0%
3rd line	PanVd	20.0%	20.0%
	CTd	65.0%	65.0%
	SVd	15.0%	15.0%
4th line	Pd	27.5%	27.5%
	PanVd	2.5%	2.5%
	Teclistamab	70.0%	70.0%

Abbreviations: C, cyclophosphamide; d, dexamethasone; D, daratumumab; Isa, isatuximab; Ixa, ixazomib; K, carfilzomib; M, melphalan; P, prednisone; Pan, Panobinostat; POM, pomalidomide; R lenalidomide; Sv, Selinexor; T, thalidomide; TA, technology appraisal; Tec, teclistamab; V bortezomib