Medicinrådet

Bilag til Medicinrådets vurdering af isatuximab i kombination med bortezomib, lenalidomid og dexamethason til behandling af nydiagnosticeret knogle-marvskræft - ikke kandidater til HDT

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. isatuximab i kombination med bortezomib, lenalidomid og dexamethason
2. Forhandlingsnotat fra Amgros vedr. isatuximab i kombination med bortezomib, lenalidomid og dexamethason
3. Ansøgers endelige ansøgning vedr. isatuximab i kombination med bortezomib, lenalidomid og dexamethason

Notat til Medicinrådets vurderingsrapport for isatuximab i kombination med bortezomib, lenalidomid og dexamethason

Sanofi takker for muligheden for at afgive et notat til Medicinrådets til vurderingsrapport. Vi anerkender kompleksiteten i vurderingen af førstelinje-behandling ved nydiagnosticeret myelomatose hos ikke-HDT-egnede patienter, men finder det nødvendigt at påpege en række væsentlige metodiske og kliniske forhold, som efter vores opfattelse systematisk forvrider både den sundhedsøkonomiske analyse og den samlede konklusion.

1. Antagelser om efterfølgende behandling med cilta-cel er inkonsistente og klinisk ubegrundede

Medicinrådet har i den sundhedsøkonomiske analyse indført antagelsen om, at 15 % af patienterne behandlet med IsaBorLenDex modtager cilta-cel i 2. linje, mens tilsvarende 15 % af patienterne behandlet med DarLenDex modtager cilta-cel i 3. linje. Omvendt antages det, at patienter behandlet med DarBorMelPred ikke modtager cilta-cel i 3. linje.

Denne asymmetriske tilgang savner klinisk begrundelse. To kliniske eksperter har overfor Sanofi tilkendegivet, at kriterierne for behandling med cilta-cel i praksis i overvejende grad er knyttet til lenalidomid-refraktæritet og performance status (ECOG 0-1) – ikke til hvilken anti-CD38 kombination patienten har modtaget i første linje. Hvis denne asymmetri skyldes en implicit antagelse om, at eksempelvis mere skrøbelige patienter i højere grad modtager DarBorMelPred, bemærkes det, at en omkostningseffektivitetsanalyse kun er meningsfuld og retvisende, såfremt det er den samme patientpopulation på tværs af behandlingsarmene.

Medicinrådets antagelse indebærer derfor en systematisk forskelsbehandling mellem behandlingsarmene, hvor IsaBorLenDex-armen belastes med meget betydelige efterfølgende omkostninger, som ikke konsekvent tilskrives øvrige relevante komparatorer. Dette har afgørende betydning for ICER'en og kan ikke betragtes som metodisk neutralt.

2. Behandlingsvarighed lig PFS tilsidesætter modne TTD-data

Medicinrådet har anvendt ekstrapolerede PFS-kurver som proxy for behandlingsvarighed (TTD) for alle behandlinger med henvisning til ønsket om "ensartet tilgang på tværs af behandlingsarmene".
Denne antagelse står i direkte modstrid med de observerede data fra de relevante studier, idet der både foreligger:

- observerede modne TTD-data fra IMROZ-studiet, hvor median behandlingslængde er 53,2 måneder, mens median PFS ikke er nået, og
- observerede modne TTD-data fra daratumumab-studierne (MAIA, ALCYONE), hvor median TTD er nået og systematisk kortere end PFS.

At se bort fra modne TTD-data for at erstatte dem med en antagelse, der entydigt forlænger behandlingsvarigheden mest i IsaBorLenDex-armen (ca. +39 %), mens tilsvarende forskelle for DarLenDex (+23,3 %) og DarBorMelPred (+14,8 %) er væsentligt mindre, indebærer ikke ensartethed, men derimod forskelsbehandling.

Som beskrevet i ansøgningen er den observerede forskel mellem TTD og PFS i IMROZ-studiet klinisk forventelig og veldokumenteret. Kun 27,5 % af

behandlingsophør i IsaBorLenDex-armen skyldes sygdomsprogression, mens hovedparten af ophør sker af andre årsager, herunder bivirkninger og patientrelaterede forhold. Det indebærer, at størstedelen af patienterne ophører behandling, mens de fortsat er progressionsfri.

Endvidere har IMROZ-studiet en lang median opfølgningstid på knap 5 år, hvilket muliggør observation af sene behandlingsophør relateret til kumulativ toksicitet, behandlingsbyrde og patientpræferencer. I studier med kortere opfølgningstid ville disse ophør i vidt omfang ikke være observeret, og forskellen mellem TTD og PFS ville derfor fremstå mindre.

Den markante forskel mellem TTD og PFS i IMROZ afspejler således modne, direkte observerede data og realistisk klinisk praksis snarere end metodiske forhold. At se bort fra disse data til fordel for en generel antagelse om, at behandlingsvarighed svarer til PFS, kan derfor ikke anses som hverken klinisk eller metodisk velbegrundet.

3. Manglende præsentation af budgetkonsekvenser er uforståelig
Medicinrådet vælger ikke at fremlægge en budgetkonsekvensanalyse med henvisning til en kommende opdatering af behandlingsvejledningen. Dette er bemærkelsesværdigt, idet:

- Sanofi har dokumenteret betydelige besparelser (-10,9 mio. DKK i år 5) ved blot 20 % markedsandel i første linje,
- isatuximab repræsenterer den billigste anti-CD38 versus det mest omsatte lægemiddel, og bidrager dermed til konkurrenceudsættelse af et betydeligt marked på ca. 750 mio. kr.
- budgetpåvirkning traditionelt indgår som et centralt beslutningsgrundlag og er medtaget i beslutninger for andre behandlinger for myelomatose.

Det er uklart, hvorfor en dokumenteret potentiel besparelse for sundheds-væsenet ikke gøres tilgængelig for hverken offentligheden eller Rådet.

4. Samlet vurdering
På tværs af analysen ses et mønster, hvor:

- efterfølgende behandling antages tidligere og dyrere for IsaBorLenDex,
- behandlingsvarigheden systematisk forlænges i IsaBorLenDex-armen
- budgetmæssige besparelser udelades fra beslutningsgrundlaget.

Disse forhold kan samlet set ikke betragtes som metodisk neutrale og fører til en konklusion om, at IsaBorLenDex ikke er omkostningseffektivt, på trods af at IsaBorLenDex konsistent har vist bedre kliniske effektmål end komparatorer, og at isatuximab er billigere end daratumumab vial-for-vial. Sanofi opfordrer derfor Medicinrådet til at genoverveje disse antagelser og sikre et mere konsistent og transparent beslutningsgrundlag.

Afslutningsvis ønsker Sanofi at pointere, at isatuximab fra juni 2026 vil være tilgængelig i en subkutan formulering med medfølgende device, hvilket vil optimere administrationen af isatuximab inden for alle godkendte indikationer.

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18.12.2025

KLE/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.01.2026
Leverandør	Sanofi
Lægemiddel	Sarclisa (isatuximab)
Ansøgt indikation	Sarclisa i kombination med bortezomib, lenalidomid og dexamethason (BorLenDex) er indiceret, til behandling af voksne patienter med nydiagnosticeret myelomatose, som er uegnede til autolog stamcelletransplantat.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende pris på Sarclisa (isatuximab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Sarclisa	20 mg/ml, 5 ml	3.744,32	[redacted]	[redacted]	[redacted]	[redacted]
Sarclisa	20 mg/ml, 25 ml	18.718,28	[redacted]	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.

Det betyder, at hvis Medicinrådet ikke anbefaler Sarclisa, indkøbes lægemidlet til nuværende SAIP.

Aftaleforhold

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

[redacted]

Tabel 2. viser lægemiddeludgifter til Sarclisa og Darzalex (daratumumab) over 3 års behandling. Udgifterne til kombinationsbehandlinger er ikke medregnet, da udgifterne er minimale. Udgifterne er medtaget for en 3-årig periode da dette er behandlingslængde for en stor andel af patienterne.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient over 3 års behandling

Lægemiddel	Styrke (paknings-størrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling over 3 år (156 uger) (SAIP, DKK)
Sarclisa 3 års behandling, 156 uger	20 mg/ml, (25 ml)	Dosis 10 mg/kg (i.v.). Cyklus 1 (42 dages cyklus): dag 1, 8, 15, 22 og 29. Cyklus 2 til 4 (42 dages cyklus): dag 1, 15 og 29 i hver cyklus Cyklus 5 til 17 (28 dages cyklus): dag 1 og 15 i hver cyklus Cyklus 18 og derefter: hver 4 uge	[redacted]	[redacted]
Darzalex 3 års behandling, 156 uger	1800 mg, 1 stk	Uge 1 til 6: ugentlig (i alt 6 doser), s.c. Uge 7 til 24: hver 3. uge (i alt 6 doser), s.c. Uge 25 og frem: hver 4 uge, s.c.	[redacted]	[redacted]

*Patientvægt 73,4 kg jfr. Medicinrådets vurderingsrapport.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Anbefalet	Link til anbefaling
Sverige	Under vurdering	Link til status

Opsummering

[redacted]

Application for the assessment of isatuximab (Sarclisa) in combination with bortezomib, lenalidomide and dexamethasone for patients with newly diagnosed Multiple Myeloma (NDMM) ineligible for Autologous Stem Cell Transplantation

sanofi

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Table of contents

Contact information **1**

Tables and Figures **9**

Abbreviations **17**

1. Regulatory information on the medicine **19**

2. Summary table **20**

3. The patient population, intervention, choice of comparator(s) and relevant outcomes **23**

3.1 The medical condition 23

3.1.1 The pathophysiology of myeloma patients 23

3.1.2 Patient prognosis, preferably for a Danish patient population. Provide the prognosis with the current treatment options. 24

3.1.3 The influence of the condition on the patients' functioning and health-related quality of life. 24

3.2 Patient population 25

3.3 Current treatment options 26

3.4 The intervention 27

3.4.1 The intervention in relation to Danish clinical practice 28

3.5 Choice of comparator(s) 28

3.6 Cost-effectiveness of the comparator(s) 33

3.7 Relevant efficacy outcomes 33

3.7.1 Definition of efficacy outcomes included in the application 33

4. Health economic analysis **35**

4.1 Model structure 35

4.2 Model features 37

5. Overview of literature **38**

5.1 Literature used for the clinical assessment 38

5.2 Literature used for the assessment of health-related quality of life 41

5.3 Literature used for inputs for the health economic model 41

6. Efficacy **42**

6.1 Efficacy of IsaVRd compared to VRd for TIE NDMM patients 42

6.1.1 Relevant studies 42

6.1.2 Comparability of studies 47

6.1.2.1 Comparability of patients across studies 47
6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment 47
6.1.4 Efficacy – results per IMROZ 47
6.1.4.1 PFS 48
6.1.4.2 OS 50
6.2 Efficacy of IsaVRd compared to DVMP for TIE NDMM patients 51
6.2.1 Relevant studies 51
6.2.2 Comparability of studies 53
6.2.2.1 Comparability of patients across studies 53
6.2.3 Comparability of the study population(s) with Danish patients eligible for treatment 54
6.2.4 Efficacy – results per IMROZ 54
6.2.5 Efficacy – results per ALCYONE 55
6.2.5.1 PFS 55
6.2.5.2 OS 55
6.3 Efficacy of IsaVRd compared to DRd for TIE NDMM patients 56
6.3.1 Relevant studies 56
6.3.2 Comparability of the study population(s) with Danish patients eligible for treatment 58
6.3.3 Efficacy – results per IMROZ 58
6.3.4 Efficacy – results per MAIA 58
6.3.4.1 PFS 58
6.3.4.2 OS 59

7. Comparative analyses of efficacy 59
7.1.1 Differences in definitions of outcomes between studies 59
7.1.2 Method of synthesis 60
7.1.2.1 Weighting 60
7.1.2.2 Proportional hazard assessment 61
7.1.3 Results from the comparative analysis 61
7.1.4 Efficacy – results per PFS 62
7.1.5 Efficacy – results per OS 64

8. Modelling of efficacy in the health economic analysis 66
8.1 Presentation of efficacy data from the clinical documentation used in the model 66
8.1.1 Extrapolation of efficacy data for IsaVRd compared to VRd 67
8.1.1.1 Extrapolation of PFS for IsaVRd compared to VRd 67
8.1.1.2 Extrapolation of OS for IsaVRd compared to VRd 71
8.1.1.3 Extrapolation of TTD for IsaVRd compared to VRd 75
8.1.2 Extrapolation of efficacy data for IsaVRd compared to DVMP and DRd 79
8.1.2.1 Extrapolation of PFS for IsaVRd compared to DVMP 79
8.1.2.2 Extrapolation of PFS for IsaVRd compared to DRd 81
8.1.2.3 Extrapolation of OS for IsaVRd compared to DVMP 83

8.1.2.4 Extrapolation of OS for IsaVRd compared to DRd 85
8.1.3 Calculation of transition probabilities 87
8.2 Presentation of efficacy data from additional documentation 87
8.3 Modelling effects of subsequent treatments 87
8.4 Other assumptions regarding efficacy in the model 87
8.5 Overview of modelled average treatment length and time in model health state 87

9. Safety 88
9.1 Safety data from the clinical documentation 88
9.2 Safety data from external literature applied in the health economic model 94

10. Documentation of health-related quality of life (HRQoL) 94
10.1 Presentation of the health-related quality of life (EQ-5D-5L) 95
10.1.1 Study design and measuring instrument 95
10.1.2 Data collection 95
10.1.3 HRQoL results 98
10.2 Health state utility values (HSUVs) used in the health economic model 101
10.2.1 HSUV calculation 101
10.2.2 Mapping 102
10.2.3 Disutility calculation 102
10.2.4 HSUV results 103
10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy 104
10.3.1 Study design 104
10.3.2 Data collection 104
10.3.3 HRQoL Results 105
10.3.4 HSUV and disutility results 105

11. Resource use and associated costs 105
11.1 Medicines - intervention and comparator 105
11.2 Medicines– co-administration 107
11.3 Administration costs 108
11.4 Disease management costs 109
11.5 Costs associated with management of adverse events 110
11.6 Subsequent treatment costs 111
11.6.1 Costing of subsequent treatment 111
11.6.2 Distribution of patients into subsequent treatments 113
11.6.3 Application of subsequent treatment costs 114
11.7 Patient costs 115
11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost) 116

12. Results 116
12.1 Base case overview 116

12.1.1 Base case results for IsaVRd compared to VRd 117
12.1.2 Base case results for IsaVRd compared to DVMP 118
12.1.3 Base case results for IsaVRd compared to DRd 119
12.2 Sensitivity analyses 120
12.2.1 Deterministic sensitivity analyses 120
12.2.1.1 Deterministic sensitivity analyses for IsaVRd compared to VRd 120
12.2.1.2 Deterministic sensitivity analyses for IsaVRd compared to DVMP 122
12.2.1.3 Deterministic sensitivity analyses for IsaVRd compared to DRd 124
12.2.2 Probabilistic sensitivity analyses 126

13. Budget impact analysis 128

14. List of experts 130

15. References 130

Appendix A. Main characteristics of studies included 137

Appendix B. Efficacy results per study 152

Appendix C. Comparative analysis of efficacy 156
C.1 Estimation of weights for DVMP 157
C.2 Estimation of weights for DRd 160
C.3 PFS 162
C.3.1 Data input DVMP 162
C.3.2 Proportional hazards assessment 163
C.3.3 Constant relative effects 165
C.3.4 Time-varying relative effects 166
C.3.4.1 Time-varying HR 166
C.3.4.2 Weighted parametric survival models 168
C.3.5 Conclusion of the PFS MAIC for IsaVRd versus DVMP 171
C.3.6 Data input DRd 172
C.3.7 Proportional hazards assessment 173
C.3.8 Constant relative effects 174
C.3.9 Time-varying relative effects 175
C.3.9.1 Time-varying HR 175
C.3.9.2 Weighted parametric survival models 177
C.3.10 Conclusion of the PFS MAIC for IsaVRd versus DRd 180
C.4 OS 181
C.4.1 Data input DVMP 181
C.4.2 Proportional hazards assessment 182
C.4.3 Constant relative effects 183
C.4.4 Time-varying relative effects 184
C.4.4.1 Time-varying HR 184
C.4.4.2 Weighted parametric survival models 186

C.4.5 Conclusion of the OS MAIC for IsaVRd versus DVMP 189
C.4.6 Data input DRd 190
C.4.7 Proportional hazards assessment 190
C.4.8 Constant relative effects 192
C.4.9 Time-varying relative effects 192
C.4.9.1 Time-varying HR 193
C.4.9.2 Weighted parametric survival models 195
C.4.10 Conclusion of the OS MAIC for IsaVRd versus DRd 198

Appendix D. Extrapolation 200
D.1 Extrapolation of PFS for IsaVRd compared to VRd 200
D.1.1 Methodology 200
D.1.2 Flatiron real world evidence study 200
D.1.3 Data input for extrapolations 210
D.1.4 Evaluation of Proportional Hazards 211
D.1.5 Model 213
D.1.6 Evaluation of statistical fit (AIC and BIC) 213
D.1.7 Evaluation of visual fit 214
D.1.8 Evaluation of hazard functions 216
D.1.9 Validation and discussion of extrapolated curves 217
D.1.10 Adjustment of background mortality 223
D.1.11 Adjustment for treatment switching/cross-over 223
D.1.12 Waning effect 223
D.1.13 Cure-point 223
D.2 Extrapolation of OS for IsaVRd compared to VRd 224
D.2.1 Data input 224
D.2.2 Evaluation of Proportional Hazards 224
D.2.3 Model 227
D.2.4 Evaluation of statistical fit (AIC and BIC) 227
D.2.5 Evaluation of visual fit 228
D.2.6 Evaluation of hazard functions 230
D.2.7 Validation and discussion of extrapolated curves 231
D.2.8 Adjustment of background mortality 235
D.2.9 Adjustment for treatment switching/cross-over 235
D.2.10 Waning effect 235
D.2.11 Cure-point 235
D.3 Extrapolation of TTD for IsaVRd compared to VRd 235
D.3.1 Data input 235
D.3.2 Evaluation of Proportional Hazards 236
D.3.3 Model 238
D.3.4 Evaluation of statistical fit (AIC and BIC) 238
D.3.5 Evaluation of visual fit 239
D.3.6 Evaluation of hazard functions 241
D.3.7 Validation and discussion of extrapolated curves 242
D.3.8 Adjustment of background mortality 245
D.3.9 Adjustment for treatment switching/cross-over 246

D.3.10 Waning effect 246
D.3.11 Cure-point 246
D.4 Extrapolation of PFS for IsaVRd compared to DVMP 246
D.4.1 Data input 246
D.4.2 Evaluation of Proportional Hazards 247
D.4.3 Model 248
D.4.4 Evaluation of statistical fit (AIC and BIC) 249
D.4.5 Evaluation of visual fit 250
D.4.6 Validation and discussion of extrapolated curves 251
D.4.6.1 Proportional Hazards Model 251
D.4.6.2 Time-Varying HR Model 252
D.4.7 Adjustment of background mortality 254
D.4.8 Adjustment for treatment switching/cross-over 254
D.4.9 Waning effect 254
D.4.10 Cure-point 255
D.5 Extrapolation of PFS for IsaVRd compared to DRd 255
D.5.1 Data input 255
D.5.2 Evaluation of Proportional Hazards 255
D.5.3 Model 257
D.5.4 Evaluation of statistical fit (AIC and BIC) 257
D.5.5 Evaluation of visual fit 258
D.5.6 Validation and discussion of extrapolated curves 259
D.5.6.1 Proportional Hazards Model 259
D.5.6.2 Time-Varying HR Model 260
D.5.7 Adjustment of background mortality 262
D.5.8 Adjustment for treatment switching/cross-over 262
D.5.9 Waning effect 262
D.5.10 Cure-point 262
D.6 Extrapolation of OS for IsaVRd compared to DVMP 264
D.6.1 Data input 264
D.6.2 Evaluation of Proportional Hazards 264
D.6.3 Model 265
D.6.4 Evaluation of statistical fit (AIC and BIC) 266
D.6.4.1 Time-Varying HR Model 266
D.6.5 Evaluation of visual fit 267
D.6.5.1 Time-Varying HR Model 267
D.6.6 Validation and discussion of extrapolated curves 268
D.6.6.1 Proportional Hazards Model 268
D.6.6.2 Time-Varying HR Model 269
D.6.7 Adjustment of background mortality 271
D.6.8 Adjustment for treatment switching/cross-over 271
D.6.9 Waning effect 271
D.6.10 Cure-point 271
D.7 Extrapolation of OS for IsaVRd compared to DRd 271
D.7.1 Data input 271
D.7.2 Evaluation of Proportional Hazards 272

D.7.3 Model 273
D.7.4 Evaluation of statistical fit (AIC and BIC) 274
D.7.4.1 Time-Varying HR Model 274
D.7.5 Evaluation of visual fit 275
D.7.5.1 Time-Varying HR Model 275
D.7.6 Validation and discussion of extrapolated curves 276
D.7.6.1 Proportional Hazards Model 276
D.7.6.2 Time-Varying HR Model 277
D.7.7 Adjustment of background mortality 279
D.7.8 Adjustment for treatment switching/cross-over 279
D.7.9 Waning effect 279
D.7.10 Cure-point 279
D.8 Extrapolation of TTD for DVMP and DRd 280

Appendix E. Serious adverse events 282

Appendix F. Health-related quality of life 284
F.1 Presentation of the health-related quality of life (EORTC QLQ-C30) 284
F.1.1 Study design and measuring instrument 284
F.1.2 Data collection 284
F.1.3 HRQoL results EORTC QLQ-C30 286
F.1.4 HRQoL results EORTC QLQ-C30 - GHS/QoL and functioning scores 286
F.1.5 HRQoL results EORTC QLQ-C30 - Symptom Domains 287
F.2 Presentation of the health-related quality of life (EORTC QLQ-MY20) 288
F.2.1 Study design and measuring instrument 288
F.2.2 Data collection 288
F.2.3 HRQoL results - EORTC QLQ-MY20 289

Appendix G. Probabilistic sensitivity analyses 291
G.1 PSA in the case of “non-proportional hazards” MAIC 295

Appendix H. Literature searches for the clinical assessment 297

H.1 Efficacy and safety of the intervention and comparator(s) 297
H.1.1 Search strategies 299
H.2 Systematic selection of studies 319
H.3 PRISMA flow diagram 322
H.4 Included studies 324
H.5 Excluded fulltext references 325
16.6 Quality assessment 328
H.6 Unpublished data 328

Appendix I. Literature searches for health-related quality of life 330
I. Health-related quality-of-life search 330
I.1 Search strategies 330

I.2 Unpublished data 330

Appendix J. Literature searches for input to the health economic model 331
J. External literature for input to the health economic model 331
Example: Targeted literature search for [estimates] 331

Tables and Figures

List of Tables:

Table 1 Incidence and prevalence in the past 5 years 25
Table 2 Estimated number of patients eligible for treatment (NDMM TIE patients) 26
Table 3 Overview of comparator VRd 28
Table 4 Overview of comparator DVMP 30
Table 5 Overview of comparator DRd 32
Table 6 Efficacy outcome measures relevant for the application 33
Table 7 Features of the economic model 37
Table 8 Relevant literature included in the assessment of efficacy and safety 39
Table 9 Relevant literature included for (documentation of) health-related quality of life 41
Table 10 Relevant literature used for input to the health economic model 41
Table 11 Overview of study design for studies included in the comparison 44
Table 12 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety 47
Table 13 Characteristics in the relevant Danish population and in the health economic model 47
Table 14 Results from the IMROZ trial of IsaVRd vs. VRd for TIE NDMM patients 48
Table 15 PFS – Primary analysis based on disease assessment by the IRC by treatment group in the IMROZ trial (ITT population) 49
Table 16 Probability of overall survival in the IMROZ trial (ITT population) 50
Table 17 Overview of study design for studies included in the comparison 52
Table 18 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety, DVMP 53
Table 19 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety, DRd 56
Table 20 Results from the comparative analysis (MAIC) of IsaVRd vs. DVMP for TIE NDMM patients 61
Table 21 Results from the comparative analysis (MAIC) of IsaVRd vs. DRd for TIE NDMM patients 61
Table 22 Landmark PFS estimates from the comparative analysis (MAIC) of IsaVRd vs. DVMP for TIE DNMM patients 63
Table 23 Landmark PFS estimates from the comparative analysis (MAIC) of IsaVRd vs. DRd for TIE NDMM patients 64
Table 24 Landmark OS estimates from the comparative analysis (MAIC) of IsaVRd vs. DVMP for TIE NDMM patients 65

Table 25 Landmark OS estimates from the comparative analysis (MAIC) of IsaVRd vs. DRd for TIE NDMM patients 66
Table 26Summary of assumptions associated with extrapolation of PFS for IsaVRd compared to VRd 68
Table 27 Summary of assumptions associated with extrapolation of OS for IsaVRd compared to VRd 71
Table 28 Summary of assumptions associated with extrapolation of TTD for IsaVRd compared to VRd 75
Table 29 Reason for treatment discontinuation 76
Table 30 Summary of assumptions associated with extrapolation of PFS for IsaVRd compared to DVMP 79
Table 31 Summary of assumptions associated with extrapolation of PFS for IsaVRd compared to DVMP 81
Table 32 Summary of assumptions associated with extrapolation of OS for IsaVRd compared to DVMP 83
Table 33 Summary of assumptions associated with extrapolation of OS for IsaVRd compared to DRd 85
Table 34 Estimates in the model 88
Table 35 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction 88
Table 36 Overview of safety events 89
Table 37 Serious adverse events 90
Table 38 Adverse events used in the health economic model 91
Table 39 Adverse events that appear in more than X % of patients 94
Table 40 Overview of included HRQoL instruments 94
Table 41 Pattern of missing data and completion EQ-5D-5L 95
Table 42 Demographic characteristics and endpoints of patients with missing EQ-5D-5L values vs. the rest of the population 97
Table 43 HRQoL summary statistics, change from baseline in EQ VAS scores from MMRM 100
Table 44 Parameters included in the HSUV estimates 101
Table 45 Disutility's of adverse events 102
Table 46 Overview of health state utility values [and disutilities] 104
Table 47 Overview of health state utility values [and disutilities] 105
Table 48 Overview of literature-based health state utility values N/A 105
Table 49 Medicines used in the model 106
Table 50 Package information on medicines included in the model. 107
Table 51 Concomitant treatments used in the model 108
Table 52 Package information on medicines included in the model. Source: Medicinpriser.dk (1 December 30, 2024) 108
Table 53 Administration costs used in the model 109
Table 54 Disease management costs used in the model 109
Table 55 Cost associated with management of adverse events 110
Table 56 Medicines of subsequent treatments 111
Table 57 Second line treatment distribution based on first line treatment received 114
Table 58 Third line treatment distribution based on first line treatment received 114

Table 59. Median PFS for subsequent lines of treatment. 115
Table 60 Patient costs used in the model 115
Table 61 Base case overview 116
Table 62 Base case results for IsaVRd compared to VRd, discounted estimates 117
Table 63 Base case results for IsaVRd compared to DVMP, discounted estimates 118
Table 64 Base case results for IsaVRd compared to DRd, discounted estimates 119
Table 65 One-way sensitivity analyses results for IsaVRd compared to VRd 120
Table 66 Scenario analysis results for IsaVRd compared to VRd 122
Table 67 One-way sensitivity analysis results for IsaVRd compared to DVMP 122
Table 68 Scenario analysis results for IsaVRd compared to DVMP 124
Table 69 One-way sensitivity analysis results for IsaVRd compared to DRd 124
Table 70 Scenario analysis results for IsaVRd compared to DRd 126
Table 71 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share) 129
Table 72 Expected budget impact of recommending the medicine for the indication 129
Table 73 Main characteristic of IMROZ 137
Table 74 Main characteristic of ALCYONE 142
Table 75 Main characteristic of MAIA 147
Table 76 Results from the IMROZ study, total population (ITT) 152
Table 77 Results per study from the Alcyone trial, total population (ITT) 153
Table 78 Results per study from the MAIA trial, total population (ITT) 154
Table 79 Baseline characteristics before and after matching – IsaVRd (IMROZ) vs DVMP (ALCYONE) 159
Table 80 Baseline characteristics before and after matching – IsaVRd (IMROZ) vs DRd (MAIA) 161
Table 81 Kaplan–Meier summary of progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 163
Table 82 Hazard ratios for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 165
Table 83 Landmark HRs for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 166
Table 84 Landmark survival estimates for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 170
Table 85 Kaplan–Meier summary of progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA) 172
Table 86: Hazard ratios for progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA) 174
Table 87 Landmark HRs for progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA) 176
Table 88 Landmark survival estimates for progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA) 179
Table 89 Kaplan–Meier summary of overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 182
Table 90 Hazard ratios for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 183
Table 91 Landmark HRs for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 185

Table 92: Landmark survival estimates for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 188
Table 93 Kaplan–Meier summary of overall survival – IsaVRd (IMROZ) vs DRd (MAIA) 190
Table 94 Hazard ratios for overall survival – IsaVRd (IMROZ) vs DRd (MAIA) 192
Table 95 Landmark HRs for overall survival – IsaVRd (IMROZ) vs DRd (MAIA) 194
Table 96: Landmark survival estimates for overall survival – IsaVRd (IMROZ) vs DRd (MAIA) 197
Table 97 Attrition for patients who did not receive HSCT (non-HSCT cohort) 200
Table 98 Summary of overlapping patient baseline characteristics across IMROZ and Flatiron 202
Table 99 Missing data in Flatiron and IMROZ 204
Table 100 Table of unweighted and weighted characteristics – IMROZ, VRd 207
Table 101 Summary statistics of OS by treatment arm 209
Table 102 Summary statistics of PFS by treatment arm 210
Table 103 Model comparison statistics – jointly fitted parametric survival models for PFS 213
Table 104 Percentage of patients' overall survival at landmark timepoints for alternative parametric models for VRd and estimates from TA917 218
Table 105 Percentage of patient overall survival at landmark timepoints for alternativ parametric models for IsaVRd – IMROZ ITT population 222
Table 106 Model comparison statistics – jointly fitted parametric survival models for OS 227
Table 107 Percentage of patients' overall survival at landmark timepoints for alternative parametric models for VRd and estimates from TA917 – IMROZ ITT population 232
Table 108 Percentage of patients overall survival at landmark timepoints for alternative parametric models for IsaVRd – IMROZ ITT population 233
Table 109 Model comparison statistics – jointly fitted parametric survival models for TTD 238
Table 110 Percentage of patients who have not discontinued treatment at landmark timepoints for alternative parametric models for VRd 242
Table 111 Percentage of patients who have not discontinued treatment at landmark timepoints for alternative parametric models for IsaVRd 245
Table 112 Model comparison statistics – IsaVRd (IMROZ) vs DVMP (ALCYONE) – PFS 249
Table 113 Landmark survival estimates for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 253
Table 114 Model comparison statistics – IsaVRd (IMROZ) vs. DRd (MAIA) - PFS 258
Table 115 Landmark survival estimates for progresson free survival – IsaVRd (IMROZ) vs. DRd (MAIA) 261
Table 116 Model comparison statistics – IsaVRd (IMROZ) vs DVMP (ALCYONE) – OS 266
Table 117 Landmark survival estimates for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 270
Table 118 Model comparison statistics – IsaVRd (IMROZ) vs DRd (MAIA) – OS 274

Table 119 Landmark survival estimates for overall survival – IsaVRd (IMROZ) vs DRd (MAIA) 278
Table 120 Median PFS and median DoT used for calculation of TTD 280
Table 121 Overview of included HRQoL instruments 284
Table 122 Pattern of missing data and completion - EORTC QLQ-C30 285
Table 123 Pattern of missing data and completion - EORTC QLQ-MY20 288
Table 124 Overview of parameters in the PSA 291
Table 125 Bibliographic databases included in the literature search 298
Table 126 Other sources included in the literature search 298
Table 127 Conference material included in the literature search 298
Table 128 Search strategy table for Embase (OVID). Date searched: April 29, 2024 300
Table 129 Search strategy table for MEDLINE (OVID). Date searched: April 29, 2024 303
Table 130 Search strategy table for CENTRAL (Cochrane Central register of Controlled Trials. EBM Reviewers) (OVID). Date searched: April 29, 2024 307
Table 131 Search strategy table for CDSR (Cochrane Database of Systematic Reviews. EBM Reviewers) (OVID). Date searched: April 29, 2024 310
Table 132 Search strategy for EconLit. Date searched: April 29, 2024 313
Table 133 Search strategy table for APA PsycInfo (Ovid). Date searched: April 29, 2024 316
Table 134 Inclusion and exclusion criteria used for assessment of studies 320
Table 135 Overview of study design for studies included in the analysis 324
Table 136 Bibliographic databases included in the literature search 330
Table 137 Other sources included in the literature search 330
Table 138 Conference material included in the literature search 330
Table 139 Sources included in the search 331
Table 140 Sources included in the targeted literature search 331

List of Figures:

Figure 1 Overview of treatment guideline in Denmark 27
Figure 2 Health state occupancy at time T 36
Figure 3 IMROZ study design and treatment schedule 42
Figure 4 Progression-free survival in the IMROZ trial (Kaplan-Meier analysis, ITT population, IRC-assessed) 49
Figure 5 Interim OS analysis in ITT population of the IMROZ trial 50
Figure 6 Progression free survival 72 month follow up with DVMP versus VMP. Source: [51] 55
Figure 7 Overall survival (A) and subgroup analysis of overall survival (B) with DVMP and VMP in the intent-to-treat population. Source: [51] 56
Figure 8 Progression free survival 64.5 months follow up with DRd versus Rd 58
Figure 9 Overall survival with DRd and Rd in the intent-to-treat population 59
Figure 10 Progression-free survival parametric survival model jointly fitted to IsaVRd and VRd up to 28 years displayed against external data from Flatiron 70
Figure 11 Overall survival – parametric survival model jointly fitted to IsaVRd and VRd up to 28 years displayed against external data from Flatiron 74

Figure 12 Time to discontinuation – parametric survival model jointly fitted to IsaVRd and VRd up to 28 years 78
Figure 13 Survival model estimates for IsaVRd (IMROZ) and DVMP (ALCYONE) based on proportional hazards – [redacted] - PFS 80
Figure 14 Survival model estimates for IsaVRd (IMROZ) and DRd (MAIA) based on proportional hazards – [redacted] - PFS 82
Figure 15 Survival model estimates for IsaVRd (IMROZ) and DVMP (ALCYONE) based on proportional hazards – [redacted] - OS 85
Figure 16 Survival model estimates for IsaVRd (IMROZ) and DRd (MAIA) based on proportional hazards – [redacted] - OS 87
Figure 17 Change from baseline in EQ-5D-5L index scores, IsaVRd vs. VRd (ITT population) 99
Figure 18 Change from baseline in EQ VAS scores, IsaVRd vs. VRd (ITT population) 99
Figure 19 One-way sensitivity analysis results for IsaVRd compared to VRd 121
Figure 20 One-way sensitivity analysis results for IsaVRd compared to DVMP, ICER 124
Figure 21 One-way sensitivity analysis results for IsaVRd compared to DRd, ICER 125
Figure 22 Cost-effectiveness acceptability curves 126
Figure 23 Scatter plot from PSA 127
Figure 24 Convergence plot for the estimated incremental costs of IVRd vs. VRd 128
Figure 25 Network diagram 157
Figure 26 Histogram of weights – IsaVRd (IMROZ) vs DVMP (ALCYONE) 158
Figure 27 Histogram of weights – IsaVRd (IMROZ) vs DRd (MAIA) 160
Figure 28 Kaplan–Meier plot of progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 163
Figure 29 Log-cumulative hazard plot for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 164
Figure 30 Schoenfeld residual plot for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 164
Figure 31 Time-varying HRs for IsaVRd (IMROZ) versus DVMP (ALCYONE) – progression-free survival 167
Figure 32 Progression-free survival estimates for IsaVRd (IMROZ) and DVMP (ALCYONE) 169
Figure 33 Kaplan–Meier plot of progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA) 172
Figure 34 Log-cumulative hazard plot for progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA) 173
Figure 35 Schoenfeld residual plot for progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA) 174
Figure 36 Time-varying HRs for IsaVRd (IMROZ) versus DRd (MAIA) – progression-free survival 176
Figure 37 Progression-free survival estimates for IsaVRd (IMROZ) and DRd (MAIA) 178
Figure 38: Kaplan–Meier plot of overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 181
Figure 39 Log-cumulative hazard plot for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 182

Figure 40 Schoenfeld residual plot for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 183
Figure 41 Time-varying HRs for IsaVRd (IMROZ) versus DVMP (ALCYONE) – overall survival 185
Figure 42 Overall survival estimates for IsaVRd (IMROZ) and DVMP (ALCYONE) 187
Figure 43: Kaplan–Meier plot of overall survival – IsaVRd (IMROZ) vs DRd (MAIA) 190
Figure 44 Log-cumulative hazard plot for overall survival – IsaVRd (IMROZ) vs DRd (MAIA) 191
Figure 45 Schoenfeld residual plot for overall survival – IsaVRd (IMROZ) vs DRd (MAIA) 192
Figure 46 Time-varying HRs for IsaVRd (IMROZ) versus DRd (MAIA) – overall survival 194
Figure 47 Overall survival estimates for IsaVRd (IMROZ) and DRd (MAIA) 196
Figure 48 Flow diagram for the derivation of the Flatiron first-line VRd data set 203
Figure 49 OS Kaplan–Meier curve – weighted Flatiron VRd results 209
Figure 50 PFS Kaplan–Meier curve – weighted Flatiron VRd results 210
Figure 51 Kaplan–Meier plots - PFS 211
Figure 52 Log-cumulative hazards plot – PFS 211
Figure 53 Log-cumulative hazard over time for alternative parametric distributions - PFS 212
Figure 54 Schoenfeld residuals - FPS 212
Figure 55 Parametric survival model jointly fitted to IsaVRd up to 6 years - PFS 215
Figure 56 Parametric survival model jointly fitted to VRd up to 6 years - PFS 215
Figure 57 Observed and smoothed hazards - PFS 216
Figure 58 Smoothed hazards with parametric survival models jointly fitted to VRd - PFS 216
Figure 59 Smoothed hazards with parametric survival models jointly fitted to IsaVRd - PFS 217
Figure 60 Parametric survival model fitted separately to IsaVRd and VRd up to 28 years with Flatiron VRd > R - PFS 220
Figure 61 Parametric survival model jointly fitted to VRd up to 28 years – PFS and OS 221
Figure 62 Kaplan–Meier plots - OS 224
Figure 63 Log-cumulative hazards plot – OS 224
Figure 64 Log-cumulative hazard over time for alternative parametric distributions - OS 225
Figure 65 Schoenfeld residuals - OS 226
Figure 66 Parametric survival model jointly fitted to IsaVRd up to 6 years - OS 229
Figure 67 Parametric survival model jointly fitted to VRd up to 6 years - OS 229
Figure 68 Observed and smoothed hazards – OS 230
Figure 69 Smoothed hazards with parametric survival models jointly fitted to VRd – OS 231
Figure 70 Smoothed hazards with parametric survival models jointly fitted to IsaVRd - OS 231
Figure 71 Parametric survival model fitted separately to IsaVRd and VRd up to 28 years with Flatiron VRd > R - OS 234

Figure 72 Kaplan–Meier plots - TTD 236
Figure 73 Log-cumulative hazards plot – TTD 236
Figure 74 Log-cumulative hazard over time for alternative parametric distributions - TTD 237
Figure 75 Schoenfeld residuals - TTD 237
Figure 76 Parametric survival model jointly fitted to IsaVRd up to 6 years - TTD 240
Figure 77 Parametric survival model jointly fitted to VRd up to 6 years - TTD 240
Figure 78 Observed and smoothed hazards – TTD 241
Figure 79 Smoothed hazards with parametric survival models jointly fitted to VRd - TTD 241
Figure 80 Smoothed hazards with parametric survival models jointly fitted to IsaVRd - TTD 242
Figure 81 Parametric survival model fitted separately to IsaVRd and VRd up to 28 years – TTD 244
Figure 82 Kaplan–Meier plots of PFS - IsaVRd (IMROZ) vs. DVMP (ALCYONE) 246
Figure 83 Log-cumulative hazard plot for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 247
Figure 84 Schoenfeld residual plot for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 248
Figure 85 Weighted parametric survival models estimates for IsaVRd (IMROZ) and DVMP (ALCYONE) - PFS 250
Figure 86 Survival models estimates for IsaVRd (IMROZ) and DVMP (ALCYONE) based on proportional hazards – [redacted] - PFS 252
Figure 87 Kaplan–Meier plots of PFS - IsaVRd (IMROZ) vs. DRd (MAIA) 255
Figure 88 Log-cumulative hazard plot for progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA) 256
Figure 89 Schoenfeld residual plot for progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA) 256
Figure 90 Weighted parametric survival models estimates for IsaVRd (IMROZ) and DRd (MAIA) - PFS 258
Figure 91 Survival model estimates for IsaVRd (IMROZ) and DRd (MAIA) based on proportional hazards – [redacted] - PFS 260
Figure 92 Kaplan–Meier plots of OS - IsaVRd (IMROZ) vs. DVMP (ALCYONE) 264
Figure 93 Log-cumulative hazard plot for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 264
Figure 94 Schoenfeld residual plot for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE) 265
Figure 95 Overall survival estimates for IsaVRd (IMROZ) and DVMP (ALCYONE) 267
Figure 96 Survival model estimates for IsaVRd (IMROZ) and DVMP (ALCYONE) based on proportional hazards – [redacted] - OS 269
Figure 97 Kaplan–Meier plots of OS - IsaVRd (IMROZ) vs. DRd (MAIA) 272
Figure 98 Log-cumulative hazard plot for overall survival – IsaVRd (IMROZ) vs DRd (MAIA) 272
Figure 99 Schoenfeld residual plot for overall survival – IsaVRd (IMROZ) vs DRd (MAIA) 273
Figure 100 Overall survival estimates for IsaVRd (IMROZ) and DRd (MAIA) 275

Figure 101 Survival model estimates for IsaVRd (IMROZ) and DRd (MAIA) based on proportional hazards – [redacted] - OS 277
Figure 102 Estimation of TTD curve for DVMP 281
Figure 103 Estimation of TTD curve for DRd 281
Figure 103 List of serious adverse events in≥2% of patients in any group by primary system organ class and preferred terms. 282
Figure 104 Forest plot of MMRM overall estimate of change from baseline in the EORTC QLQ-C30 GHS/QoL and functioning scores - ITT 286
Figure 105 Forest plot of MMRM overall estimate of change from baseline in EORTC QLQ-C30 symptom scores - ITT 288
Figure 106 Forest plot of MMRM overall estimate of change from baseline in EORTC QLQ-MY20 symptom scores - ITT 290

Abbreviations

AE	adverse event
ASCT	autologous stem cell therapy/ autologous stem cell transplant
CI	Confidence interval
CrCl	creatinine clearance
d	Dexamethasone
D	Daratumumab (Darzalex®)
DMC	Danish Medicines Council
DRd	Daratumumab (Darzalex®), lenalidomide (Revlimid®) and dexamethasone
DVd	Daratumumab (Darzalex®), bortezomib (Velcade®) and dexamethasone
DVMP	Daratumumab (Darzalex®), bortezomib (Velcade®), melphalan and prednisone
DVRp	Daratumumab (Darzalex®), bortezomib (Velcade®), lenalidomide (Revlimid®) and prednisone
E	elotuzumab (Empliciti®)
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
EQ-5D-3L	European Quality of Life - 5 Dimensions – 3 level
EQ-5D-5L	European Quality of Life - 5 Dimensions – 5 level
ESS	Effective sample size
HDT	high-dose therapy
HRQoL	health-related quality of life
IRC	Independent Response Committee
IRT	Interactive Response Technology
IPTW	Inverse Propensity for Therapy Weighting
Isa	Isatuximab (Sarclisa®)
IsaVRd	Isatuximab (Sarclisa®), bortezomib (Velcade®), lenalidomide (Revlimid®) and dexamethasone
ISS	International Staging System
ITC	indirect treatment comparison
ITT	intention-to-treat
IV	intravenous infusion
LOT	line of therapy
LY	life years
mAb	monoclonal antibodies
MAIC	Matching-adjusted indirect comparison
MICE	Multiple Imputation by Chained Equations

MM	multiple myeloma
mOS	median overall survival
mPFS	median progression free survival
MRD	minimal residual disease
NA	not available
NDMM	newly diagnosed multiple myeloma
NE	not estimated
NGS	next-generation sequencing
NR	not reached
NS	not significant
OS	overall survival
P	Prednisone
PPP	pharmacy purchase price
PMM	Pattern Mixture Models
PD	progressive disease
PFS	progression free survival
PH	proportional hazards
PK	pharmacokinetics
PO	peroral/per os/oral administration
PR	partial response
PRO	patient-reported outcome
QALYs	Quality-adjusted life years
QD	once daily
QoL	quality of life
QW	weekly (administration)
R	Lenalidomide (Revlimid®)
RMST	restricted mean survival time
RRMM	relapsed refractory multiple myeloma
SAE	serious adverse events
SC	subcutaneous
SCT	stem cell transplant
SmPC	summary of product characteristics
TEAE	treatment emergent adverse events
TIE	transplant ineligible
TTE	Time-to-event
TTP	time to progression
V	Bortezomib (Velcade®)
VGPR	very good partial response
VMp	Bortezomib (Velcade®), melphalan and prednisone
VRd	Bortezomib (Velcade®), lenalidomide (Revlimid®) and dexamethasone

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Sarclisa
Generic name	Isatuximab
Therapeutic indication as defined by EMA	The EMA indication extension submitted: SARCLISA is indicated in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who are ineligible for autologous stem cell transplant (ASCT)
Marketing authorization holder in Denmark	Sanofi A/S
ATC code	L01FC02
Combination therapy and/or co-medication	Isatuximab should be administered in combination with dexamethasone (d), bortezomib (V) and lenalidomide (R).
(Expected) Date of EC approval	January 22nd, 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Sarclisa is indicated: 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 (PI) and have demonstrated disease progression on the last therapy [1]. In combination with carfilzomib and dexamethasone, for the treatment of adult patients with MM who have received at least one prior therapy [1].
Other indications that have been evaluated by the DMC (yes/no)	**The DMC has evaluated isatuximab [2, 3] for the following indications:**

Overview of the medicine	
	Patients with MM who previously have received at least two relevant treatments Lenalidomide-sensitive patients with MM who have previously undergone at least one course of treatment for the disease.
Joint Nordic assessment (JNHB)	**Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)?** No – the reimbursement and clinical landscape is different in each of the four countries, DK (VRd/DVMP), NO (DRd), SE (DRd), FI (DRd). **Is the product suitable for a joint Nordic assessment?** No - This is not possible due to different reimbursement situations in the four countries. Thus, the clinical guidelines differ.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Isatuximab is a concentrate for solution for infusion. Isatuximab is available in a package with 1.5 ml or 25 ml glass vial in the concentration 20 mg/ml, containing 100 mg or 500 mg isatuximab. Sanofi expects to get EMA approval of a subcutaneous formulation with a flat dose in the second quarter of 2026.

2. Summary table

Summary	
Indication relevant for the assessment	Isatuximab in combination with bortezomib, lenalidomide and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma (NDMM) who are not eligible for autologous stem cell transplant (ASCT)
Dosage regiment and administration	The dosage administration is divided into two phases: Induction phase (4 cycles of 6 weeks) and continuous phase (4-week cycles). Dosage regime from Facon et al. 2024 (study 1, IMROZ) [4]: In the induction phase, the combination of isatuximab, bortezomib, lenalidomide, and dexamethasone is administered four times in six-week cycles (42 days). Bortezomib: Administered on days 1, 4, 8, 11, 22, 25, 29, and 32 at a dosage of 1.3 mg/m^2. (SC) Lenalidomide: Administered continuously on days 1- 14 and days 22-35 at a dosage of 25 mg. (PO)

Summary	
	Dexamethasone: Administered on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 at a dosage of 20 mg. (IV/PO) Isatuximab (Cycle 1): Administered on days 1, 8, 15, 22, and 29 at a dosage of 10 mg/kg. (IV) Isatuximab (Cycle 2-4): Administered on days 1, 15, and 29 at a dosage of 10 mg/kg. (IV). Meaning that the dose frequency is changed from once a week to once every other week. In the continuous phase, isatuximab, lenalidomide and dexamethasone is administered in cycles of four weeks (28 days). Lenalidomide: Administered continuously on days 1-21 at a dosage of 25 mg. (PO) Dexamethasone: Administered on days 1, 18, 15, and 22 at a dosage of 20 mg. (IV/PO) Isatuximab: Administered on days 1 and 15 in cycle 5-17 and thereafter Q4W at a dosage of 10 mg/kg. Meaning that the frequency is changed from once every two weeks to once every 4th week.
Choice of comparator	**Comparator 1:** Active Comparator: Bortezomib/lenalidomide/dexamethasone = VRd arm Induction treatment with 4 times 6-week cycles with SC bortezomib + oral lenalidomide + IV or oral dexamethasone Continuous treatment with 4-week cycles with oral lenalidomide + IV or oral dexamethasone **Current treatment comparator 2:** Daratumumab (SC) in combination with bortezomib (SC), melphalan (PO) and prednisone (PO) (DVMP) [5]. **Current treatment comparator 3:** Daratumumab (SC) in combination with lenadomide (PO), IV or oral dexamethasone (DRd) [5].
Prognosis with current treatment (comparator)	VRd has a median OS of 81 months and a median PFS of 43,9 months [6-9]. DVMP has a median OS of 81 months and a median PFS of 58,4 months [6-9]. DRd has an estimated 60-month OS rate of 66.6% and a median PFS of 61.9 months [6-9].
Type of evidence for the clinical evaluation	IMROZ investigates the efficacy of adding the anti-CD38 monoclonal antibody isatuximab to the first-line treatment consisting of bortezomib (V), lenalidomide (R), and

Summary	
	dexamethasone (d) (VRd). This study includes patients from 18 to 80 years of age [4].
Most important efficacy endpoints (Difference/gain compared to comparator)	IMROZ: estimated PFS at 60 months of 63.2% (98.5% CI:0.562-0.694) for isatuximab-VRd compared to 45.2% (98.5% CI:0.356-0.542) in the VRd group (at a median follow up of 59.7 months)
Most important serious adverse events for the intervention and comparator	In the IMROZ study IsaVRd was well-tolerated with no new safety signals. The incidence of AEs leading to definitive discontinuation was 22.8% with IsaVRd and 26.0% with VRd [10]. Serious AEs were reported in 70.7% of patients in the IsaVRd group and 67.4% of patients in the VRd group [10]. The incidence of infection of Grade ≥3 was 44.9% for IsaVRd and 38.1% for VRd. The incidence of infection of Grade ≥3 was lower among patients who received antibiotic prophylaxis than among those who did not (43.5% vs. 51.0% in the IsaVRd group, and 35.2% vs. 48.7% in the VRd group). [10].
Impact on health-related quality of life	Clinical documentation: For EQ VAS, a trend towards improvement was observed for IsaVRd in comparison to a trend towards worsening for VRd. The difference between treatment arms over 63 cycles was not notable (overall mean adjusted difference IsaVRd vs VRd 2.14; 95% CI: -0.28, 4.56). Health economic model: Assumed equal to both comparators.
Type of economic analysis that is submitted	Cost-utility using a partitioned survival model.
Data sources used to model the clinical effects	IMROZ (NCT03319667) [10], ALCYONE (NCT02195479) [11, 12] and MAIA (NCT02252172) [13]
Data sources used to model the health-related quality of life	EQ-5D-5L from IMROZ
Life years gained	IsaVRd vs. VRd: 2.0 years IsaVRd vs. DVMP: 1.0 years IsaVRd vs. DRd: 0.5 years
QALYs gained	IsaVRd vs. VRd: 1.0 years IsaVRd vs. DVMP: 0.6 years IsaVRd vs. DRd: 0.3 years
Incremental costs	IsaVRd vs. VRd: DKK 2,459,908 IsaVRd vs. DVMP: DKK 830,859

Summary	
	IsaVRd vs. DRd: DKK -140,876
ICER (DKK/QALY)	IsaVRd vs. VRd: 2,487,633 DKK/QALY IsaVRd vs. DVMP: 1,450,856 DKK/QALY IsaVRd vs. DRd: (DKK -448,703/QALY) Dominant
Uncertainty associated with the ICER estimate	The results were most sensitive to changes to the choice of parametric function when extrapolating OS and PFS and the estimate of HR between treatment and comparator for OS and PFS.
Number of eligible patients in Denmark	Incidence: 250 TIE NDMM Prevalence: 0 (treatment only considered for newly diagnosed patients)
Budget impact (in year 5)	Budget savings 10.9 million DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Multiple myeloma (MM) is an incurable, progressive and fatal hematologic malignancy characterized by clonal proliferation of bone marrow plasma cells, which secrete excessive amounts of monoclonal immunoglobulin (M-protein). MM is characterized by an underlying immune dysfunction and patchy accumulation of blood cells leading to increased serum calcium (hypercalcemia), renal insufficiency, anemia, and bone lesions (collectively known as CRAB symptoms) and infections. Advanced age, underlying comorbidities, poor performance status, and MM-related burden, especially in patients with high-risk cytogenetic disease, further contribute to a complex profile of MM patients and may influence treatment choice [14].

3.1.1 The pathophysiology of myeloma patients

MM arises from a malignant transformation of a type of white blood cell, the plasma cell, within the bone marrow. This transformation disrupts normal bone marrow function,

leading to immunosuppression, which increases the risk of infections and can cause anemia. Consequently, patients may experience fatigue, shortness of breath, and other anemia-related symptoms.

Within the bone marrow, the disease also promotes increased activity of osteoclasts, cells responsible for bone recreation, while reducing the activity of osteoblasts, which are essential for bone formation. This imbalance leads to progressive bone destruction, placing patients at higher risk of fractures, causing bone pain, and resulting in elevated calcium levels in the blood.

In most cases of MM, a non-functional antibody, known as the M protein, or fragments of this antibody (free light chains), are detectable in the blood and urine. These are produced by malignant plasma cells, and in some patients, the free light chains may accumulate in the kidneys, potentially leading to kidney damage or even kidney failure. Measuring levels of M protein and free light chains is crucial for both diagnosing MM and monitoring disease progression [6, 9].

3.1.2 Patient prognosis, preferably for a Danish patient population. Provide the prognosis with the current treatment options.

The latest survival data on Danish patients are: 3-year survival ≤ 70 years: 81.3%; 3-year survival > 70 years: 58.8%; 3-year survival of the whole group: 68.6%. 5-year survival ≤ 70 years: 72.1%; 5-year survival > 70 years: 39.6%; 5-year survival of the whole group: 53% [15].

3.1.3 The influence of the condition on the patients' functioning and health-related quality of life.

MM is associated with symptoms that can significantly impact a patient's health-related quality of life. MM is characterized by an underlying immune dysfunction, patchy accumulation of blood cells leading to infections, and one or more myeloma defining symptoms (i.e. CRAB symptoms) such as hypercalcemia, renal failure, anemia, and bone impairment [16].

Due to profound immunodeficiency and presence of at least one CRAB symptom at diagnosis, MM patients are highly susceptible to developing sequelae which, if the disease is not appropriately managed, can lead to multiple organ damage with fatal outcomes.

Imbalance of osteoclast and osteoblast activity leads to bone lesions in 80%-90% of NDMM patients which can result in bone pain and fractures [17]. Bone-related symptoms are the most frequent. Bone pain affects over 80% of patients and is one of the most common symptoms. Myeloma bone pain usually involves the spine and ribs and worsens with activity [18].

As the bones contain a high calcium level, this tumor-induced bone destruction can lead to high extracellular calcium [19]. The kidney's limited ability to clear excess calcium load from the circulation results in hypercalcemia, which is the second most common cause of renal failure in MM [20]. Real-world studies and IMWG clinical guidelines suggest that

renal impairment at diagnosis (defined as an estimated GFR<60 mL/min/1.73m2) affect 34% to 50% of NDMM patients [21].

In MM patients, the over-proliferation of myeloma cells “crowds out” the healthy cells and reduces the production of red blood cells leading to anemia; this in turn may facilitate further tumor growth, lead to compromised cardiovascular function, and result in reduced performance and daily activities, tiredness and fatigue, ultimately resulting in poor HRQoL[22]. More recent real-world studies have shown that 47%–55% of NDMM patients present with anemia [23, 24].

As MM eventually progresses to relapsed and refractory disease where response to therapy declines, progressive bone marrow failure, bone lesions, compression fractures of the spine, and hypercalcemia can be factors that may lead to death [18, 24].

3.2 Patient population

The present application targets NDMM patients who are ineligible for high dose chemotherapy and stem cell transplant. In a recent RWE study, the prevalence of MM is estimated to 3,470 patients, including patients who are eligible for high dose chemotherapy. MM patients often present with advanced age at diagnosis and have underlying comorbidities. The median age at diagnosis is 72 years old [15, 25].

The incidence and prevalence for NDMM patients is provided in Table 1.

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Incidence in Denmark	405	355	364	390	392
Prevalence in Denmark	2,746	2,877	2,999	3,109	3,230

Source: Sanofi RWE – data on file [25]

The present application concerns NDMM TIE patients. Following its recent recommendation for DRd, DMC estimates that 250 NDMM patients meet the criteria for starting treatment with CD38 per year and it is assumed that the population remains the same from year 1 to year 5.

Table 2 Estimated number of patients eligible for treatment (NDMM TIE patients)

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	250	250	250	250	250

3.3 Current treatment options

As this application concerns TIE NDMM patients, only their treatment options will be discussed.

According to the Danish Medicines Council (DMC), the first-line treatment for NDMM typically involves either a combination of bortezomib, lenalidomide, and dexamethasone (VRd) or daratumumab combined with bortezomib, melphalan, and prednisolone (DVMP) and recently daratumumab combined with lenalidomide, and dexamethasone (DRd) has been recommended. In cases where patients prefer oral treatment, lenalidomide and dexamethasone (Rd) may be prescribed [26].

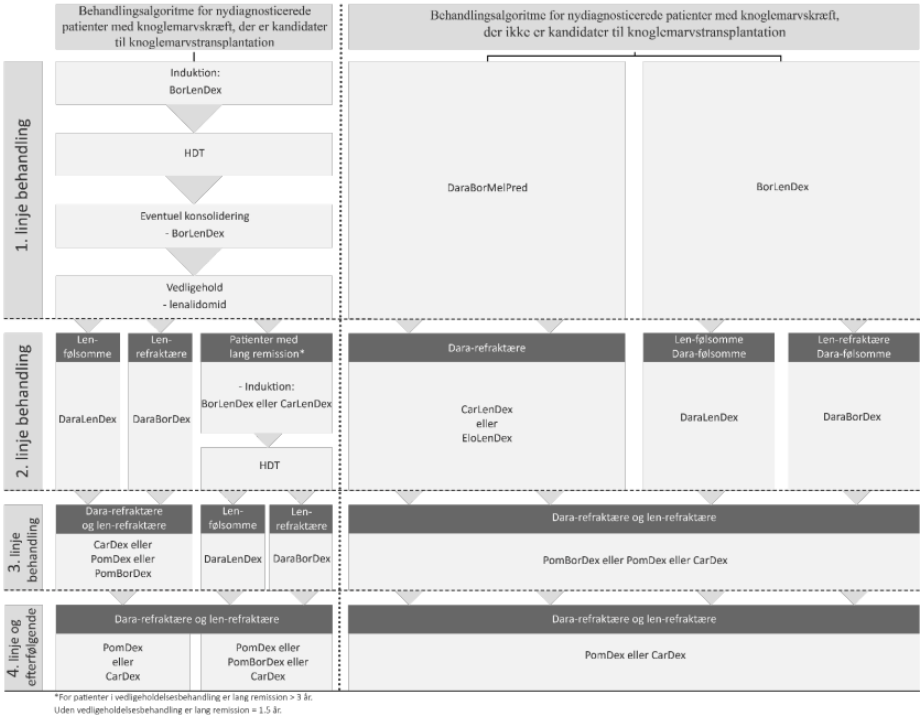
The second-line treatment is determined based on the first-line therapy. For patients who received daratumumab in the first line and become refractory to it, carfilzomib, lenalidomide and dexamethasone (KRd) or elotuzumab, lenalidomide and dexamethasone (ERd) would be offered[26].

Patients initially treated with VRd are divided into two groups: those who are sensitive to lenalidomide and daratumumab and those who are refractory to lenalidomide but sensitive to daratumumab. The first group would receive DRd, while the second group would receive DVd[26].

In the third line of treatment, patients are typically refractory to both daratumumab and lenalidomide. This group is offered one of three combinations: pomalidomide, bortezomib, and dexamethasone (PVd); pomalidomide and dexamethasone (Pd); or carfilzomib and dexamethasone (Cd)[26].

In fourth line of treatment, patients are both daratumumab refractory and lenalidomide refractory these patients would receive pomalidomide in combination with dexamethasone (Pd) or carfilzomib in combination with dexamethasone (Cd).

Figure 1 Overview of treatment guideline in Denmark



Source: [26]

3.4 The intervention

An overview of the information regarding Isatuximab can be found in the table below.

Overview of intervention	
Indication relevant for the assessment	Isatuximab in combination with bortezomib, lenalidomide, and dexamethasone, for the treatment of adult patients with newly diagnosed active MM who are not eligible for autologous stem cell transplant (ASCT).
ATMP	N/A
Method of administration	Intravenous
Dosing	10.0 mg/kg
Dosing in the health economic model (including relative dose intensity)	10.0 mg/kg (93.58%)
Should the medicine be administered with other medicines?	Yes

Overview of intervention	
Treatment duration / criteria for end of treatment	The dosage administration is divided into two phases: Induction phase (4 cycles of 6 weeks) and continuous phase (4-week cycles). In the continuous phase, isatuximab, bortezomib, lenalidomide and dexamethasone is administered in cycles of four weeks (28 days).
Necessary monitoring, both during administration and during the treatment period	Patients should be closely monitored both during each infusion and throughout the treatment period. Infusion-related reactions may occur, especially early in treatment, so premedication is advised, and patients should be observed during administration. Over the full course of treatment, regular blood tests are needed to monitor for neutropenia, and signs of infection should be watched continuously. Blood type should be confirmed before treatment, as Sarclisa can interfere with compatibility testing for several months. Monitoring for secondary cancers, particularly skin malignancies, is also recommended during and after therapy.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	There are no additional diagnostic tests or methods required for patient selection that are not already part of standard clinical practice in Denmark.
Package size(s)	Isatuximab is available as a concentrate for solution for infusion in a package with a 5 ml or 25 ml glass vial in the concentration 20 mg/ml, containing 100 mg or 500 mg isatuximab.

3.4.1 The intervention in relation to Danish clinical practice

Currently, four treatment lines are available for myeloma patients who are ineligible for autologous stem cell transplant. The introduction of Isatuximab (IsaVRd) is expected to provide an alternative to the current first-line treatments, which include DVMP and VRd. The introduction of the potent 1st line treatment IsaVRd will enhance the initial treatment options outlined in the current guideline.

There are no additional diagnostic tests or methods required for patient selection that are not already part of standard clinical practice in Denmark.

3.5 Choice of comparator(s)

The three comparators 1) VRd (bortezomib, lenalidomide and dexamethasone), 2) DVMP (daratumumab, bortezomib, melphalan, prednisone) and 3) DRd (daratumumab, lenalidomide and dexamethasone) are described in three separate tables below.

Table 3 Overview of comparator VRd

Overview of comparator: VRd	
Generic name	Bortezomib, lenalidomide, dexamethasone (VRd)
ATC code	L01XG01, L04AX04, H02AB02
Mechanism of action	**V:** Bortezomib specifically inhibits the activity of the S26 proteasome, thereby hindering the proteolysis of intracellular ubiquitinated proteins. This leads to reduced adhesion and increased apoptosis in myeloma cells. **R:** Lenalidomide binds to the protein cereblon and inhibits its function. The protein is found in the cells of the bone marrow and is involved in, among other things, the cell's metabolism, signaling and in the formation of new blood vessels. **d:** Dexamethasone is a hormone of the type glucocorticoids, also known as corticoids or corticosteroids, and has several effects on the white blood cells, which are part of the body's natural defenses, the immune system. Dexamethasone is like the glucocorticoids that the body produces naturally.
Method of administration	**V:** Injections – subcutaneous **R:** Peroral **d:** Peroral
Dosing	**V:** Given as a single treatment in a 3-week cycle. Initially 1.3 mg/m² body surface area on days 1, 4, 8, and 11 in a 21-day cycle. Additional cycles depend on dose response. There must be at least 72 hours between two doses. **R:** Cycles 1-21: 25 mg daily on days 1-14 in a 21-day cycle[27] **d:** 40 mg weekly
Dosing in the health economic model (including relative dose intensity)	**V**: 1.3 mg/m2 (RDI 86.65%) **R**: 25 mg (RDI 83.45%) **d**: 20 mg (RDI 79.34%)
Should the medicine be administered with other medicines?	**V:** Yes - should be administered together with lenalidomide and dexamethasone. **R:** Yes - should be administered together with bortezomib and dexamethasone. **d:** Yes, with bortezomib and lenalidomide, or daratumumab, bortezomib, melphalane and prednisolone.
Treatment duration/ criteria for end of treatment	Until progression or worsening.
Need for diagnostics or other tests (i.e. companion diagnostics)	No.

Overview of comparator: VRd	
Package size(s)	**V:** Bortezomib is a concentrate for solution for infusion. Bortezomib is available in a package containing 3.5 mg. Each vial must be reconstituted with 3.5 ml of isotonic sodium chloride injection solution to achieve a final concentration of 1 mg/ml. **R**: Lenalidomide comes in hard capsules in packages of 21 with strengths of 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, and 25 mg. **d:** Available in different package sizes with strengths of 1 mg, 4 mg and 40 mg of dexamethasone per tablet.

Table 4 Overview of comparator DVMP

Overview of comparator: DVMP	
Generic name	Daratumumab, bortezomib, melphalan, and prednisone (DVMP)
ATC code	L01FC01, L01XG01, L01AA03, H02AB06
Mechanism of action	**D:** Daratumumab is a humanized monoclonal antibody targeting the membrane protein CD38, which is expressed on many immune cells and especially on malignant plasma cells. Cells are killed by antibody-dependent cytotoxicity. **V:** Bortezomib specifically inhibits the activity of the S26 proteasome, thereby hindering the proteolysis of intracellular ubiquitinated proteins. This leads to reduced adhesion and increased apoptosis in myeloma cells. **M:** Melphalan belongs to a group of medicines called cytotoxic (also called chemotherapy) and works by reducing the number of abnormal cells that the body creates. **P:** Synthetic glucocorticoid with relatively low mineralocorticoid activity. Decreases inflammation via suppression of the migration of polymorphonuclear leukocytes and reversing increased capillary permeability. It also suppresses the immune system by reducing the activity and the volume of the immune system.
Method of administration	**D:** Subcutaneous or IV infusion **V:** Injections – subcutaneous **M:** Peroral **P:** Peroral

Overview of comparator: DVMP	
Dosing	**D:** 1,800 mg SC or 16 mg/kg body weight IV Week 1 to 8: weekly (total of 8 doses). Week 9 to 24: every two weeks (total of 8 doses). Week 25 until disease progression: every four weeks. **V:** Given as a single treatment in a 3-week cycle. Initially 1.3 mg/m² body surface area on days 1, 4, 8, and 11 in a 21-day cycle. Additional cycles depend on dose response. There must be at least 72 hours between two doses. **M:** Several dosing regimens are used, e.g. Daily administration of initially 0.10 mg/kg body weight, after 10 days 0.03 mg/kg body weight*, or* Intermittent treatment series with a higher dose, e.g. 4-8 mg/m2 body surface area daily, for 5 days every 5-6 weeks. Treatment must also be controlled by leukocyte counts and platelet counts and the extent of general adverse reactions. **P:** 60 mg/m2 body surface area daily for days 1-4 during cycles 1-9 [14].
Dosing in the health economic model (including relative dose intensity)	**D:** 1,800 mg sc (RDI 100.0%) **V:** 1.3 mg/m2 (RDI 96.4%) **M:** 9.0 mg/m2 (RDI 95.0%) **P:** 60 mg/m2 (RDI 96.4%)
Should the medicine be administered with other medicines?	Yes, the treatment is a combination treatment, consisting of DVMP
Treatment duration/ criteria for end of treatment	Until disease progression, following the 25 weeks.
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	**D: Solution for injection:** 1 vial (15 ml) containing 1,800 mg of daratumumab. **Concentrate for solution for IV infusion:** 5 or 20 ml containing 20 mg daratumumab/ml. **V:** Bortezomib is a concentrate for solution for infusion. Bortezomib is available in a package containing 3.5 mg. Each vial must be reconstituted with 3.5 ml of isotonic sodium chloride injection solution to achieve a final concentration of 1 mg/ml. **M:** Comes in packages of 25 tablets containing 2 mg of melphalane **P:** Comes in packages of 100 tablets containing 5 or 25 mg of prednisolone, or packages of 10 tablets containing 25 mg of prednisolone.

Table 5 Overview of comparator DRd

Overview of comparator: DRd	
Generic name	Daratumumab, lenalidomide, and dexamethasone (DRd)
ATC code	L01FC01, L04AX04, H02AB02
Mechanism of action	**D:** Daratumumab is a humanized monoclonal antibody targeting the membrane protein CD38, which is expressed on many immune cells and especially on malignant plasma cells. Cells are killed by antibody-dependent cytotoxicity. **R**: Lenalidomide binds to the protein cereblon and inhibits its function. The protein is found in the cells of the bone marrow and is involved in, among other things, the cell's metabolism, signaling and in the formation of new blood vessels. **d**: Dexamethasone is a hormone of the type glucocorticoids, also known as corticoids or corticosteroids, and has several effects on the white blood cells, which are part of the body's natural defenses, the immune system. Dexamethasone is like the glucocorticoids that the body produces naturally.
Method of administration	**D**: Subcutaneous or IV infusion **R**: Peroral **d**: Peroral
Dosing	**D:** 1,800 mg SC or 16 mg/kg body weight IV Week 1 to 8: weekly (total of 8 doses). Week 9 to 24: every two weeks (total of 8 doses). Week 25 until disease progression: every four weeks. **R:** 25mg on day 1-21 in 28 day cycles **d:** 40 mg every week
Dosing in the health economic model (including relative dose intensity)	**D:** 1,800 mg sc (RDI 100.0%) **R**: 25 mg (RDI 76.2%) **d**: 40 mg (RDI 84.2%)
Should the medicine be administered with other medicines?	Yes, the treatment is a combination treatment, consisting of DRd
Treatment duration/ criteria for end of treatment	Until disease progression, following the 25 weeks.
Need for diagnostics or other tests (i.e. companion diagnostics)	No

Overview of comparator: DRd	
Package size(s)	**D: Solution for injection:** 1 vial (15 ml) containing 1,800 mg of daratumumab. **Concentrate for solution for IV infusion:** 5 or 20 ml containing 20 mg daratumumab/ml. **R**: Lenalidomide comes in hard capsules in packages of 21 with strengths of 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg, 20 mg, and 25 mg. **d:** Available in different package sizes with strengths of 1 mg, 4 mg and 40 mg of dexamethasone per tablet.

3.6 Cost-effectiveness of the comparator(s)

The comparators VRd, DVMP and DRd are recommended as the cost-effective standard treatments for TIE NDMM patients by the DMC [6, 28].

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

In this section, we define the efficacy outcomes considered relevant and necessary to evaluate the effect of IsaVRd vs. comparators and describe the rationale for the chosen efficacy outcomes.

Table 6 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Progression Free Survival (PFS)	Median follow-up time: 59.7 months	PFS is defined as the time from randomization to the first documented disease progression (based on assessment by the independent review committee) or death, which-ever occurred first (assessed in a time-to-event analysis) [10].	An IRC, whose members were unaware of the treatment assignments, determined disease response and progression according to efficacy data (assessed at a central laboratory), bone marrow assessment for plasma-cell infiltration (assessed at the local laboratory), and centrally reviewed imaging according to the IMWG criteria. Between-group comparisons were

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
			conducted with the use of a stratified log-rank test procedure with the randomization stratification factors. The significance level at the interim analysis (P = 0.0074) used an O'Brien–Fleming alpha-spending function to control the one-sided type I error at 2.5%, which resulted in a 98.5% confidence interval [10].
Overall survival (OS)	Median follow-up time: 59.7 months	OS was defined as the time from randomization to death from any cause [10].	OS was assessed in a time-to-event analysis [10].
Quality of Life (QoL)	On Day 1 of each treatment cycle, at the end of treatment (EOT) visit, and 90 days (±5 days) after the last study treatment administration.	QoL was assessed using three different instruments: EQ-5D-5L, EORTC QLQ-C30 and EORTC QLQ-MY20 [10].	QoL was investigated in several different ways including change from baseline using Mixed-effect repeated measure regression models (MMRMs) [10].

* Time point for data collection used in analysis (follow up time for time-to-event measures)
IRC, Independent Review Committee.

Validity of outcomes

Progression free survival (PFS)

PFS is a well-established endpoint for survival in cancer and MM studies, frequently utilized by the Danish Medicines Council (DMC) in health economic models [7, 29]. PFS is widely recognized as a reliable primary endpoint and serves as a surrogate for overall survival (OS) in NDMM studies [21].

Overall survival (OS)

OS is considered the gold-standard endpoint for oncology trials and serves as the most compelling endpoint to demonstrate the benefits of novel therapeutics. Regulatory approval and patient reimbursement globally depend on OS results combined with patient-reported outcomes. These tendencies also apply to NDMM studies, and several

studies have investigated OS among NDMM patients [10, 30, 31]. Additionally, recent DMC recommendations have included OS as a relevant endpoint [29].

Quality of life (QoL)

EORTC QLQ-C30: The EORTC QLQ-C30 is a patient-reported outcome measure (PROM) designed to assess the functional health, symptom burden and HRQoL of patients with localized-to-advanced cancer. The EORTC QLQ-C30 demonstrates good evidence of content validity for the assessment of functional health, symptom burden and health-related quality of life in patients with localized to advanced cancer [32].

EORTC QLQ-MY20: The EORTC QLQ-MY20 is an extension of EORTC QLQ-C30, and a specialized tool designed to assess the quality of life in myeloma patients. The EORTC QLQ-MY20 is considered a reliable and valid instrument for patient-reported quality of life of myeloma patients [32-34].

4. Health economic analysis

The health economic analysis is a cost-utility analysis assessing the incremental cost per quality-adjusted life year (QALY) of treating patients with TIE NDMM with IsaVRd compared to treatment with VRd and DVMP, respectively.

4.1 Model structure

A partitioned survival model (PSM) with states defined based on PFS and OS was used to evaluate the cost-effectiveness. The PSM approach has been used in other submissions to the DMC for treatments for NDMM [29].

The PSM model uses three mutually exclusive health states to assess patient outcomes[1]: Progression-free (PF) state; Post-progression (PP) state and Death.

The proportion of patients occupying each health state are calculated using PFS and OS curves. These curves are estimated by efficacy data. Costs and utilities are applied per health state. All patients enter the model in the PF health state, where they are assumed to receive IsaVRd, VRd, DVMP or DRd. Patients remain in the PF health state until they experience disease progression or die.

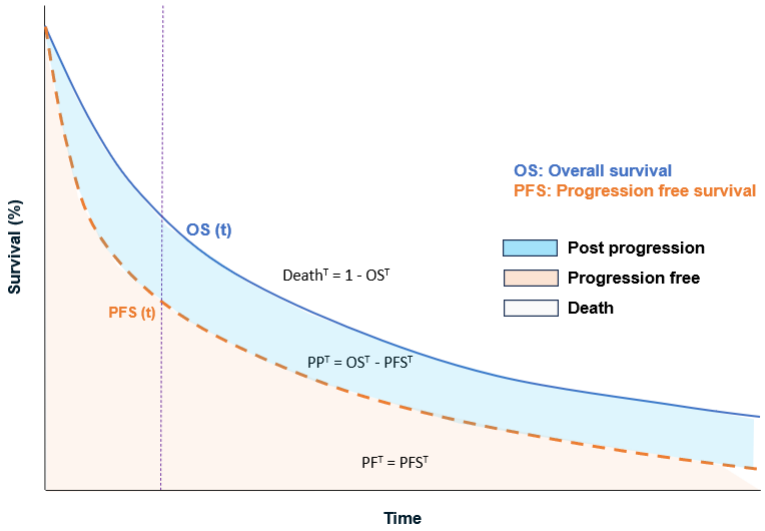
Within the PF health state patients may or may not be receiving treatment. 'On treatment' status depends on TTD, conditional that TTD is not greater than PFS. Within the PF health state, patients incur the cost of the intervention or comparator (drug acquisition costs, drug administration costs, transport and patient-time costs) according to their TTD; disease monitoring costs and drug-related AE costs are also applied within this health state, along with a PF utility and AE utility decrements. Patients in the PP

[1] Note that Time to Treatment Discontinuation (TTD) is modelled to calculate the proportion of patients receiving 1L treatments and then calculate the first-line drug cost. However, the health state utility pre-progression does not depend on whether the patient is on first line treatment or not.

health state incur PP monitoring costs and subsequent therapy costs, along with a PP utility. Patients who transition to death incur end-of-life costs. This partitioned survival analysis uses independently fitted PFS and OS curves to calculate a health state's occupancy at a given time using the area under the curve approach. The proportion of patients in the PF state is calculated directly using the extrapolated PF curve at time T (PF^T) (meaning that, at a given time T, the PF curve is used to directly determine the proportion of patients who have not experienced disease progression). The proportion of patients in the death health state is calculated as $1 – OS^T$, where OS^T is the survivor function (the probability that a patient is alive) at time T. The proportion of patients in the PP state is equal to OS^T minus PF^T. Health state occupancy is shown graphically in Figure 2.

The OS hazard is capped by the age and gender-matched general population mortality hazard and that all patients are assumed to be dead at 100 years old. The PFS hazard is capped by the OS hazard for the same time period to ensure that OS is always greater than or equal to PFS.

Figure 2 Health state occupancy at time T



Key: OS, overall survival; PD, progressed disease; PF, progression-free; PFS, progression-free survival.

The biggest strength of the PSM model structure is its ease of construction and the direct incorporation of the PFS and OS data collected from the clinical trial when estimating state classification. In IMROZ, the pivotal trial informing model efficacy, the primary and key secondary trial endpoints were the time-to-event outcomes PFS and OS. These two outcomes directly correspond with the required survival functions used in a three-state PSM. As MM is a chronic and incurable disease, patients do not need to move backwards between the health states, further aligning with the PSM structure.

4.2 Model features

The features of the economic model are based on the standard model in the DMC method guideline. Table 7 presents a summary of the model features.

Table 7 Features of the economic model

Model features	Description	Justification
Patient population	Patients with TIE NDMM	Based on EMA indication and trial population
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (28 years) Based on mean age at diagnosis in the Danish population (71 years) and the assumption that all patients die before age 100.	To capture all health benefits and costs in line with DMC guidelines.
Cycle length	14 days	This cycle length is considered sufficiently short to accurately capture key clinical outcomes and dosing schedules of IsaVRd, VRd and DVMP
Half-cycle correction	Yes	To improve accuracy
Discount rate	3.5 %	According to DMC guidelines
Intervention	1L treatment with IsaVRd	EMA indication
Comparator(s)	VRd and DVMP	According to DMC treatment guideline [26]
Outcomes	OS, PFS, QALY (EQ-5D-5L)	To estimate the number of patients in each health state and to calculate QALY

The health economic model is Excel-based. The deterministic results are updated automatically if any input values or parameters are changed. To obtain updated deterministic one-way sensitivity analysis (OWSA) results and probabilistic sensitivity analysis (PSA) results, the user must click on the "Run OWSA" button and the "Run PSA" button, respectively.

5. Overview of literature

5.1 Literature used for the clinical assessment

This section will present the literature used for the clinical assessment.

The literature consists of a Phase III head-to-head study comparing the addition of isatuximab (Isa) to the current treatment in Denmark (VRd) [10], a Phase III indirect comparison which evaluated the added value of weekly bortezomib (V) to Isatuximab plus lenalidomide and dexamethasone (IsaRd versus IsaVRd) [35, 36], as well as a Phase II study evaluating isatuximab (Isa) in combination with bortezomib (V) and lenalidomide (R) with minimal dexamethasone (d) as a first-line treatment [37].

For the indirect comparison a systematic literature search was conducted to identify literature for the HE-model. A list of relevant inclusion and exclusion criteria was selected to reflect the clinical practice in Denmark and the relevant comparators. In short, only the relevant treatment options DVMP and DRd was selected (Table 8). The criteria are described more in depth in appendix J.

Table 8 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
T. Facon *et al.*, "Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma," *New England Journal of Medicine*, Jun. 2024, doi: 10.1056/nejmoa2400712. [10]	IMROZ	NCT03319667	Study Start (Actual): 2017-12-07 Primary Completion (Est.): 2026-04-05 Study Completion (Est.): 2027-06-30 [38]	IsaVRd to VRd for non-frail transplant-ineligible NDMM patients. Age-range: 55-80 years.
X. Leleu *et al.*, "Isatuximab, lenalidomide, dexamethasone and bortezomib in transplant-ineligible multiple myeloma: the randomized phase 3 BENEFIT trial," *Nat Med*, vol. 30, no. 8, pp. 2235–2241, Aug. 2024, doi: 10.1038/s41591-024-03050-2. [35]	BENEFIT	NCT04751877	Study Start (Actual): 2021-07-17 Primary Completion (Est.): 2024-04-02 Study Completion (Est.): 2027-08-17 [39]	IsaVRd to IsaRd for non-frail transplant-ineligible NDMM patients. Age-range: 65-79 years.
F. B. B. Askeland *et al.*, "Replacing Steroids in Transplant-Ineligible Multiple Myeloma: The Phase 2 Isatuximab-Bortezomib-Lenalidomide-Dexamethasone Rest Study," *Blood*, vol. 140, no. Supplement 1, pp. 12623–12625, Nov. 2022, doi: 10.1182/blood-2022-15662 5. [37] F. B. B. Askeland *et al.*, "Isatuximab, bortezomib, lenalidomide, and limited dexamethasone in patients with transplant-ineligible multiple myeloma (REST): a multicentre, single-arm, phase 2	REST	NCT04939844	Primary completion: 2024-06 Study completion: 2026-10	Not a comparative study, evaluates the effect of minimal dexamethasone for isatuximab in combination with bortezomib and lenalidomide in Frail, Transplant-ineligible NDMM patients. The study provides data on IsaVRd in frail TIE NDMM patients. Age-range: 70-88 years.

Reference (Full citation incl. reference number)	Trial name	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
trial," *Lancet Haematology*, vol. 12, Issue 2, E120-127, Feb. 2025. [40]				
Mateos M-V, Cavo M, Blade J, Dimopoulos MA, Suzuki K, Jakubowiak A, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial. Lancet (London, England). 2020;395(10218):132–41. [41]	ALCYONE	NCT02195479	Study Start (Actual): 2014-12-09 Primary Completion (Actual): 2017-11-21 Study Completion (Actual.): 2024-08-07	Treatment Arm A (VMP Alone) Participants will receive velcade (bortezomib) 1.3 milligram per square meter (mg/m^2) as subcutaneous injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by once weekly at Weeks 1, 2, 4 and 5 in Cycles 2 to 9, melphalan 9 mg/m^2 , orally, once daily (on Days 1-4) and prednisone 60 mg/m^2, orally, once daily, on Days 1 to 4 of each cycle up to Cycle 9. [42]
Kumar SK, Moreau P, Bahlis NJ, et al. Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) Alone in Transplant-Ineligible Patients with Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of the Phase 3 Maia Study. *Blood*. 2022; 140(Supplement 1):10150-3. [13]	MAIA	NCT02252172	Study Start (Actual): 2015-02-16 Primary Completion (Actual.): 2018-09-24 Study Completion (Actual.): 2024-10-02	Active Comparator: Daratumumab + Lenalidomide + Dexamethasone (DRd) [43]

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

Table 9 Relevant literature included for (documentation of) health-related quality of life

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
N/A	N/A	N/A

5.3 Literature used for inputs for the health economic model

Table 10 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A	N/A	N/A	N/A

6. Efficacy

This section presents the evidence for the efficacy of IsaVRd for TIE NDMM patients compared to VRd and DVMP, respectively. The comparison of IsaVRd and VRd is presented in section 6.1 and the comparison of IsaVRd and DVMP is presented in section 6.2.

6.1 Efficacy of IsaVRd compared to VRd for TIE NDMM patients

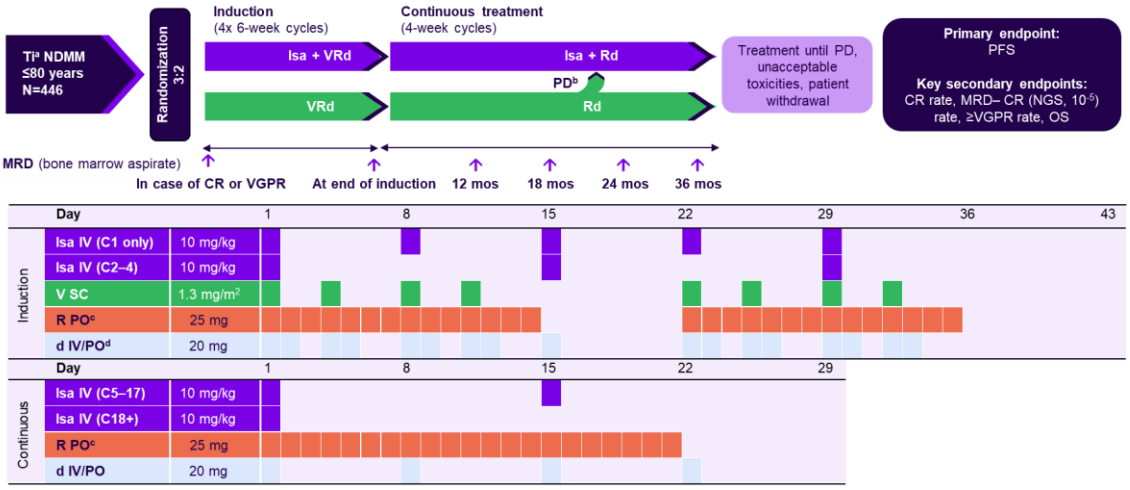
6.1.1 Relevant studies

The efficacy and safety of IsaVRd compared to VRd for TIE NDMM patients has been assessed in the IMROZ trial, a prospective, multicenter, multinational, randomized, open-label, parallel-group, 2-arm study. The current application uses the latest available predefined data cutoff of September 26, 2023 (Interim efficacy analysis when 162 PFS events occurred).

can be found in **Error! Reference source not found.**.

Figure 3 presents the study design and an overview of the study can be found in **Error! Reference source not found.**.

Figure 3 IMROZ study design and treatment schedule



a. Patients considered transplant ineligible (non-transplant) due to age or comorbidities.

b. In the continuous phase, patients randomized to the VRd arm who experience PD maycross overr to receive IsaRd

c. 10 mg/day if eGFR 30–<60 mL/min/1.73m2.

d. If aged ≥75 years, d was administered on days 1, 4, 8, 11, 15, 22, 25, 29, and 32.

CR, complete response; C, cycle; d, dexamethasone; eGFR, estimated glomerular filtration rate; Isa, isatuximab-irfc; IV, intravenous; MRD, minimal residual disease; NDMM, newly diagnosed multiple myeloma; NGS, next-generation sequencing; OS, overall survival; PD, progression disease; PFS, progression-free survival; PO, per os (oral); SC, subcutaneous; V, bortezomib; VGPR, very good partial response [4]

Table 11 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patienpopulation	Intervention	Comparator	Outcomes and follow-up time
IMROZ NCT03319667 T. Facon *et al.*, "Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma," New England Journal of Medicine, Jun. 2024, doi: 10.1056/nejmoa2400712. [10]	Phase III, randomized, multicenter, open label study of IsaVRd vs VRd in non-transplant NDMM	Study dates: December 27, 2017 – September 26, 2023 (Interim efficacy analysis when 167 PFS events occurred)	N= 446 (IsaVRd arm, n=265; VRd arm, n=181) Non-transplant NDMM due to age (≥65 years) or patients <65 years with comorbidities impacting possibility of transplant, no prior treatment for multiple myeloma, ECOG < 2.	Isa: 10 mg/kg Cycle 1 QW on D1, 8, 15, 22, 29; Cycle 2-4 D1, 15, and 29 (6-week cycles); Cycle 5-17 D1, 15 (4-week cycles); Cycle 18 D1 and thereafter Q4W V: 1.3 mg/m2 D1, 4, 8, 11, 22, 25, 29, and 32 42-day cycles only R: 25 mg[a] QD D1-14 and 22-35 in a 42-day cycle 25 mg QD D1-21 of a 28-day cycle in continuous treatment period and crossover d: 20 mg QD Cycles 1-4 Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 if <75 years old. Otherwise, D1, 4, 8, 11, 15, 22, 25, 29, and 32. D1, 18, 15, and 22 during continuous treatment periods.. On the day of isatuximab infusion, 20 mg of dexamethasone is administered as premedication and as part of the backbone treatment before isatuximab. On the day of isatuximab administration, the following order is recommended: Acetaminophen 650 mg to 1000 mg PO. Ranitidine 50 mg IV (or equivalent). Diphenhydramine 25 mg to 50 mg IV (or equivalent). Dexamethasone 20 mg IV.	V, R, and d were administered following the same dosing and treatment schedule as in the IsaVRd group.	PFS*, CR rate*, rate of MRD-negativity (≥10^{-5}) in patients with CR*, ≥VGPR rate*, OS*, Safety*, ORR*, TTP*, PFS by MRD status*, DOR*, Time to first response*, Time to best response*, PFS2*, Sustained MRD-negativity*, PK, Immunogenicity, Quality of life**

Notes: [a] Lenalidomide was administered at 10 mg/day for participants with CrCl ≥30 to <60 mL/min.

* Time-to-event endpoints measured at the interim analysis cut-off date of September 26th, 2023. Median follow-up (as of September 26, 2023): 59.73 months. The interim analysis was performed after 162 events of disease progression or death had occurred (which was 73% of the 222 events specified for the planned final analysis).

Trial name, NCT-number (reference)	Study design	Study duration	Patienpopulation	Intervention	Comparator	Outcomes and follow-up time

** PRO measures were administered on Day 1 of each treatment cycle, at the end of treatment (EOT) visit, and 90 days (±5 days) after the last study treatment administration.

Key: AE, adverse event; CrCl, creatinine clearance; CR, complete response; d, dexamethasone; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; Isa, isatuximab-irfc; IsaVRd, isatuximab-irfc + bortezomib, lenalidomide, dexamethasone; MM, multiple myeloma; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q4W, every 4 weeks; QD, once a day; QW, weekly; R, lenalidomide; TTP, time to progression; V, bortezomib; VGPR, Very Good Partial Response; PFS2, Median second progression-free survival

Source: [10, 44-49]

6.1.2 Comparability of studies

N/A for head-to-head studies according to DMC guidelines.

6.1.2.1 Comparability of patients across studies

N/A as the efficacy of IsaVRd compared to VRd is based solely on IMROZ.

Table 12 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	[Study name]		[Study name]		[Study name]	
	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]	[int./ comp.]
N/A						

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Table 13 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population [15]	Value used in health economic model (reference if relevant)
Mean age	75	75 [25]
Male %	55 %	55 % [25, 49]
Mean patient weight (kg)	73,4	73,4
Mean body surface area	1,84	1,84
Proportion of patients with regular renal function (>60L/min)	N/A	70,9

6.1.4 Efficacy – results per IMROZ

Efficacy results from the ITT populations in the IMROZ study are presented in this section.

[redacted]

[redacted]

Table 14 Results from the IMROZ trial of IsaVRd vs. VRd for TIE NDMM patients

Outcome measure	IsaVRd (N=265)	VRd (N=181)	Results
PFS	Median: NR (NR to NR)	Median: 54.34 months (95% CI: 45.207–NR)	Stratified HR[1]: 0.60 (98.5% CI 0.41–0.88)
OS	Median: NR (NR to NR)	Median: NR (NR to NR)	HR: 0.78 (99.97% CI: 0.41–1.48)

Key: CI, confidence interval; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; NR, not reached; PFS, progression-free survival; RMST, restricted mean survival time.

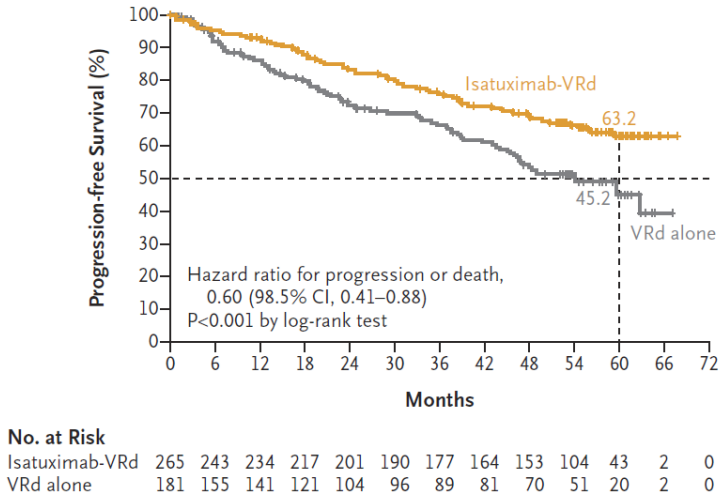
Notes: [1] Stratified by age (<70 years vs ≥70 years) and Revised International Staging System (R-ISS) stage (I or II vs. III or not classified) according to IRT.

Source: [45, 46, 48, 49]

6.1.4.1 PFS

At the cutoff date (September 26, 2023), 84 (31.7%) and 78 (43.1%) PFS events had occurred in the IsaVRd and VRd groups, respectively [10]. During median follow-up of 59.7 months, median PFS was not reached in the IsaVRd group, and it was 54.34 months (95% CI: 45.207-NR, log-rank P<0.001) in the VRd group [10]. The stratified hazard ratio was 0.596 (98.5% CI: 0.41–0.88) characterizing a reduction of 40.4% in risk for disease progression or death with IsaVRd compared to VRd [10, 46]. Kaplan-Meier analyses (Figure 4) showed early separation of PFS curves between the IsaVRd and VRd arms (Figure 4)[45]. The current trend suggests that the projected median PFS in the IsaVRd arm will reach ~90 months [10, 46]. Table 15 provides a summary of PFS probabilities at 24, 36, 48, and 60 months. At 60 months (5-year rate), PFS probability was 63.2% in the IsaVRd group and 45.2% in the VRd group.

Figure 4 Progression-free survival in the IMROZ trial (Kaplan-Meier analysis, ITT population, IRC-assessed)



Median follow-up time: 59.7 months; The interim analysis of PFS was performed after 162 events of disease progression or death had occurred (which was 73% of the 222 events specified for the planned final analysis). Tick marks indicate censored data.
Log-rank p value stratified on age (<70 years old vs. ≥70 years old) and R-ISS stage (I or II vs. III or not classified) according to IRT.
d, dexamethasone; CI, confidence interval; IRC, Independent Response Committee; IRT, interactive response technology; ITT, intention-to-treat; R, lenalidomide; V, bortezomib. Source: [10]

Table 15 PFS – Primary analysis based on disease assessment by the IRC by treatment group in the IMROZ trial (ITT population)

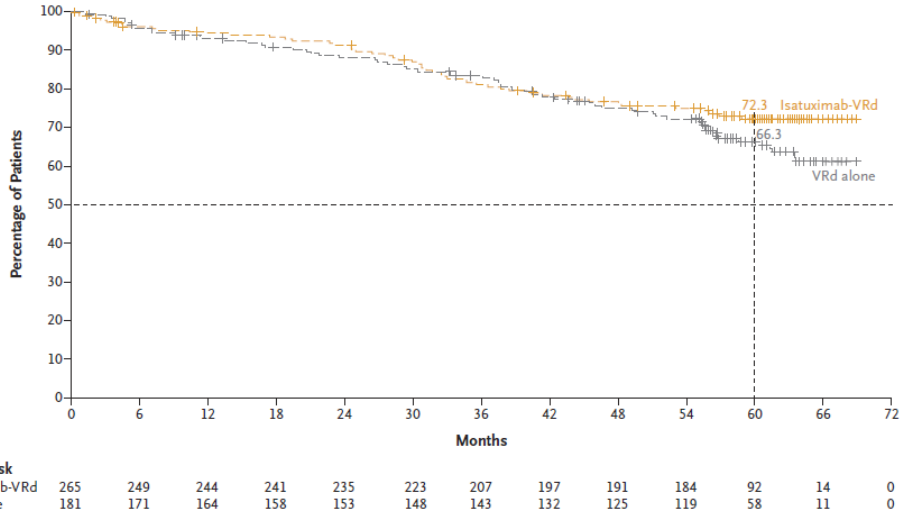
	IsaVRd (N=265)	VRd (N=181)
Number (%) of events	84 (31.7%)	78 (43.1%)
Number (%) of patients censored	181 (68.3%)	103 (56.9%)
PFS probability (95% CI)[a]		
6 months	0.953 (0.920–0.973)	0.919 (0.867–0.951)
12 months	0.926 (0.886–0.952)	0.864 (0.803–0.908)
18 months	0.882 (0.835–0.916)	0.796 (0.726–0.850)
24 months	0.837 (0.785–0.877)	0.722 (0.646–0.785)
30 months	0.803 (0.748–0.847)	0.701 (0.622–0.766)
36 months	0.761 (0.702–0.809)	0.664 (0.583–0.732)
42 months	0.722 (0.661–0.774)	0.611 (0.528–0.684)
48 months	0.699 (0.637–0.753)	0.535 (0.451–0.613)
54 months	0.666 (0.602–0.723)	0.503 (0.417–0.582)
60 months	0.632 (0.562–0.694)	0.452 (0.356–0.542)
66 months	0.632 (0.562–0.694)	0.395 (0.264–0.523)

Data cutoff: September 26, 2023 with a median follow-up time: 59.73 months
[a] Estimated using Kaplan-Meier method.
Key: CI, confidence interval; *d, dexamethasone;* IRC, Independent Response Committee; IRT, Interactive Response Technology; *Isa, isatuximab-irfc;* ITT, intention-to-treat; NR, not reached; PFS, progression-free survival; *R, lenalidomide; V, bortezomib.*
Source: [10]

6.1.4.2 OS

OS was assessed as a key secondary outcome. At data cutoff (September 26, 2023), at a median follow-up of 59.7 months, 69 (26%) and 59 (32.6%) death events occurred in the IsaVRd and VRd groups, respectively (Figure 5). The interim results showed a favorable OS trend for IsaVRd versus VRd with an HR passing the pre-specified futility threshold (set to HR>1.1), and follow-up is on-going [10]. The HR of 0.78 (99.97% CI: 0.41–1.48) conferred a 22.4% reduction in the risk of death for IsaVRd vs VRd [10, 46]. Table 16 provides a summary of OS probabilities at 24, 36, 48, and 60 months.

Figure 5 Interim OS analysis in ITT population of the IMROZ trial



[a] Data cutoff: September 26, 2023.
[b] HR passed the prespecified futility threshold (>1.1); follow-up is ongoing.
CI, confidence interval; d, dexamethasone; HR, hazard ratio; Isa, isatuximab-irfc; ITT, intention to treat; OS, overall survival; R, lenalidomide; V, bortezomib
Source: [46]

Table 16 Probability of overall survival in the IMROZ trial (ITT population)

	IsaVRd (N=265)	VRd (N=181)
n (%) death events	69 (26.0)	59 (32.6)
Survival probability		
at 24 months	91.1%	88.1%
at 36 months	81.0%	83.5%
at 48 months	76.6%	75.3%
at 60 months	72.3%	66.3%

Data cutoff: September 26, 2023
Median follow-up: 59.7 months
d, dexamethasone; Isa, isatuximab-irfc; ITT, intention-to-treat; R, lenalidomide; V, bortezomib
Source: [10]

6.2 Efficacy of IsaVRd compared to DVMP for TIE NDMM patients

6.2.1 Relevant studies

The efficacy and safety of IsaVRd compared to DVMP for TIE NDMM patients has been assessed in an ITC based on the IMROZ study (IsaVRd arm) and the ALCYONE study (DVMP arm). presents an overview of the studies.

Table 17 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
IMROZ NCT03319667 [10]	See Table 11					
ALCYONE NCT02195479 [41]	Phase III, Randomized, Controlled, Open-label Study of Bortezomib-Melphalan-Prednisone (VMP) Compared to Daratumumab in Combination With VMP (DVMP) in TIE NDMM patients.	Study dates: 2014-12-09 – 2017-11-21 (Final data collection date for primary outcome measure) – 2024-08-07 (actual study completion date)	N= 706 (DVMP arm, n=350; VMP arm, n=356 Non-transplant NDMM due to age (≥65 years) or patients <65 years with comorbidities impacting possibility of transplant, no prior treatment for multiple myeloma, ECOG ≤ 2	**D** IV[a]: 16 mg/kg, intravenous infusion, QW for 6 weeks in Cycle 1, Q3W in Cycle 2 to 9 and thereafter, Q4W until documented progression, unacceptable toxicity, or end of study. **D** SC[a]: Fixed dose of 1800 mg, subcutaneous injection, Q4W until documented progression, unacceptable toxicity, or end of study. **V:** 1.3 mg/m^2, subcutaneous injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by QW at Weeks 1, 2, 4, 5 in Cycles 2 to 9. **M:** 9 mg/m^2, orally, Cycle 1-9 QD on D1-4. **P:** 60 mg/m^2, orally, Cycle 1-9 QD on D1-4. **Dexamethasone:** 20 mg IV or PO, 1 hour or less prior to D administration as premedication and prednisone substitute.	V: 1.3 mg/m^2, subcutaneous injection, twice weekly at Weeks 1, 2, 4 and 5 in Cycle 1 followed by QW at Weeks 1, 2, 4, 5 in Cycles 2 to 9. M: 9 mg/m^2, orally, Cycle 1-9 QD on D1-4. P: 60 mg/m^2, orally, Cycle 1-9 QD on D1-4.	PFS*, ORR**, VGPR or better**, CR or better**, Negative MRD**, OS***, PFS2*, sCR**, TTP*, Time to Response****, DOR*, TNT*, M-protein response*, QoL (Baseline months 3, 6, 9, 12 and 18)

Notes: [a] Following amendment 7, participants could switch from daratumumab IV to daratumumab SC.

* From randomization to either disease progression or death whichever occurs first (up to 2.4 years) (for TTP: From randomization to either disease progression or death due to PD whichever occurs first (up to 2.4 years)). ** From randomization to disease progression (up to 2.4 years). *** From randomization to death (up to approximately 2.4 years). **** From randomization to first documented PR or better (up to 2.4 years)

Key: Q4W, every 4 weeks; QD, once a day; QW, weekly; D, Daratumumab; V, Bortezomib; M, Melphalan; p, Prednisone. Source: [50, 51]

6.2.2 Comparability of studies

The comparability between the IMROZ and ALCYONE trials are considered very high, as there is little variation in study design, inclusion/exclusion criteria, baseline characteristics and outcome data across trials.

6.2.2.1 Comparability of patients across studies

The baseline characteristics of patients included in the IMROZ and ALCYONE trials are shown in Table 18. There are some differences age, ISS stage, ECOG PS, cytogenetic risk, MM type, and creatinine clearance. These characteristics were identified as potential prognostic factors or effect modifier; hence the comparative analysis uses population-adjustment methods to account for the observed differences in patient characteristics as discussed in section 7.1.2. The patient characteristics of the IMROZ study after matching is also included in Table 18.

Table 18 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety, DVMP

	IMROZ		IMROZ (with matching)		ALCYONE	
	IsaVRd (N=265)	[comp.]	IsaVRd [redacted]	[comp.]	DVMP (N=350)	[comp.]
Age (mean)	71,7		[redacted]		71,0	
Male (%)	54%		[redacted]		46%	
Race (%)						
White	73%		[redacted]		85%	
Other	14%		[redacted]		15%	
Missing/ not reported	13%		[redacted]		0%	
ISS stage (%)						
I	34%		[redacted]		20%	
II	41%*		[redacted]		40%	
III	25%		[redacted]		40%	
ECOG PS (%)						
0–1	89%		[redacted]		74%	
≥ 2	11%		[redacted]		26%	

	IMROZ		IMROZ (with matching)		ALCYONE	
	IsaVRd (N=265)	[comp.]	IsaVRd [redacted]	[comp.]	DVMP (N=350)	[comp.]
Cytogenetic risk (%)						
High	15%		[redacted]		17%	
Standard	78%		[redacted]		83%	
Missing	7%		[redacted]		0%	
Time since diagnosis, months (mean)	2.03		[redacted]		0.82	
MM type (%)						
IgG	65%		[redacted]		41%	
non-IgG	35%		[redacted]		59%	
Creatinine clearance (%)						
< 60 mL/min	25%		[redacted]		43%	
≥ 60 mL/min	75%*		[redacted]		57%	
LDH levels, IU/L (mean)	199.1		[redacted]		NR	

Key: ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size, IgG, immunoglobulin G; ISS, International Staging System; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; LDH, lactate dehydrogenase; NR, not reported.

Notes: Matching characteristics included age, ISS stage, ECOG PS, cytogenetic risk and multiple myeloma type.

* Missing ISS stage is grouped into ISS stage II as this is the largest group.

6.2.3 Comparability of the study population(s) with Danish patients eligible for treatment

This information is presented in section 6.1.3.

6.2.4 Efficacy – results per IMROZ

The results of the IMROZ trial are described in section 6.1.4.

6.2.5 Efficacy – results per ALCYONE

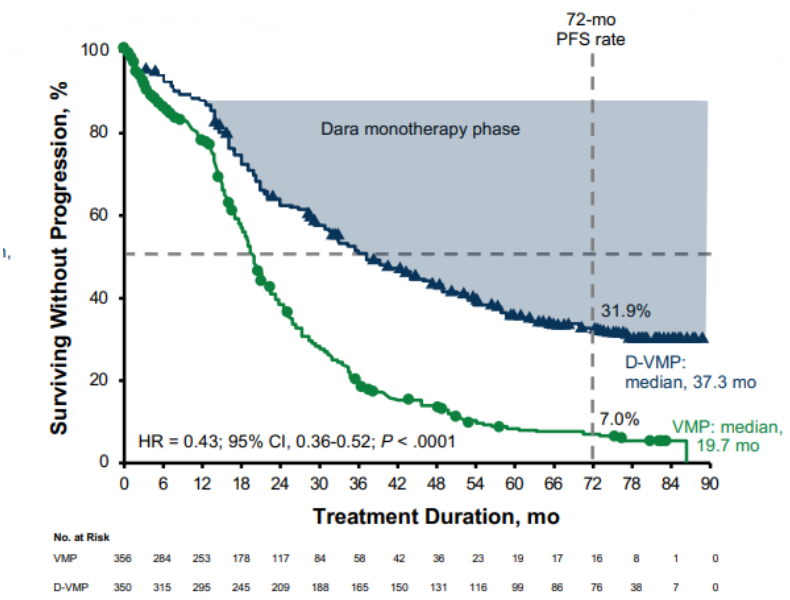
Efficacy results from the ITT populations in the ALCYONE study are presented in this section. The ALCYONE trial compared a group of patients with DVMP and VMP. The primary efficacy outcome was PFS, and the key secondary efficacy outcome was OS.

6.2.5.1 PFS

The primary efficacy outcome was PFS. The Kaplan–Meier estimate of the 12-month rate of progression free survival was 86.7% (95% CI, 82.6 to 89.9) in the daratumumab group and 76.0% (95% CI,71.0 to 80.2) in the control group; the 18-month rate of progression-free survival was 71.6% (95% CI, 65.5 to 76.8) in the daratumumab group and 50.2% (95% CI, 43.2 to 56.7) in the control group.

The median PFS for DVMP was reached at 37.3 months and for VMP the median PFS was 19.7 months at 72 month follow up. The HR was 0.43 (85% CI 0.36-0.52); P<0.0001. At the 72 month follow up progression free survival was 31.9% in the DVMP arm versus 7% in the VMP arm.

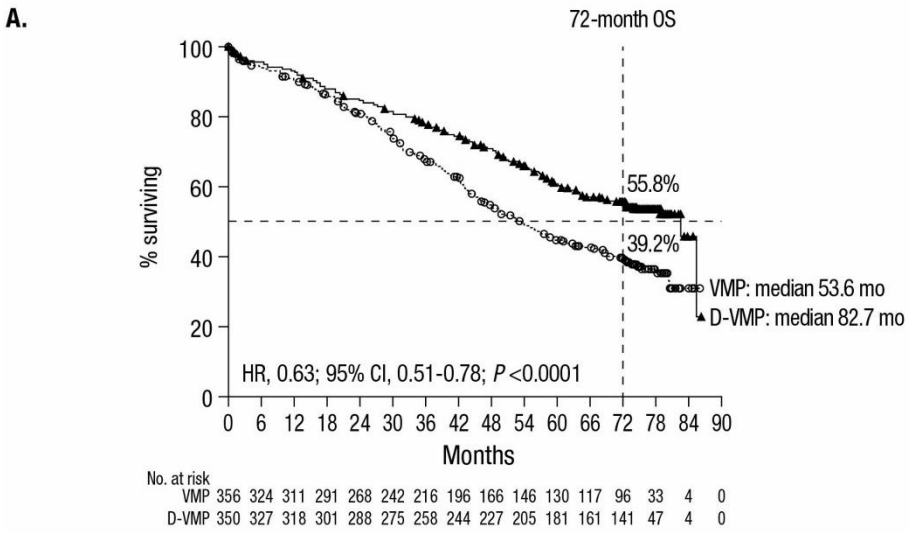
Figure 6 Progression free survival 72 month follow up with DVMP versus VMP. Source: [51]



6.2.5.2 OS

OS was assessed as a key secondary outcome. At follow up at 72 months the overall survival rate was estimated to 55.8% for DVMP and 39.2% for VMP. The median OS for DVMP was reached at 82.7 months and for VMP the median OS was 53.6 months. The HR was 0.63 (95% CI, 0.51-0.78).

Figure 7 Overall survival (A) and subgroup analysis of overall survival (B) with DVMP and VMP in the intent-to-treat population. Source: [51]



6.3 Efficacy of IsaVRd compared to DRd for TIE NDMM patients

6.3.1 Relevant studies

The efficacy and safety of IsaVRd compared to DRd for TIE NDMM patients has been assessed in an ITC based on the IMROZ study (IsaVRd arm) and the MAIA study (DRd arm). Table 19 presents an overview of the studies.

Table 19 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety, DRd

	IMROZ		IMROZ (with matching)		MAIA	
	IsaVRd (N=265)	[comp.]	IsaVRd [redacted]	[comp.]	DRd (N=350)	[comp.]
Age (mean)	71,7		[redacted]		73.0**	
Male (%)	54%		[redacted]		51%	
Race (%)						
White	73%		[redacted]		NR	
Other	14%		[redacted]		NR	
Missing/ not reported	13%		[redacted]		NR	

	IMROZ		IMROZ (with matching)		MAIA	
	IsaVRd (N=265)	[comp.]	IsaVRd [redacted]	[comp.]	DRd (N=350)	[comp.]
ISS stage (%)						
I	34%		[redacted]		27%	
II	41%*		[redacted]		44%	
III	25%		[redacted]		29%	
ECOG PS (%)						
0–1	89%		[redacted]		83%	
≥ 2	11%		[redacted]		17%	
Cytogenetic risk (%)						
High	15%		[redacted]		15%	
Standard	78%		[redacted]		85%	
Missing	7%		[redacted]		0%	
Time since diagnosis, months (mean)	2.03		[redacted]		1.4	
MM type (%)						
IgG	65%		[redacted]		61%	
non-IgG	35%		[redacted]		39%	
Creatinine clearance (%)						
< 60 mL/min	25%		[redacted]		44%	
≥ 60 mL/min	75%*		[redacted]		56%	
LDH levels, IU/L (mean)	199.1		[redacted]		NR	

Key: ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size, IgG, immunoglobulin G; ISS, International Staging System; LDH, lactate dehydrogenase; NR, not reported.

Notes: Matching characteristics included age, ISS stage, ECOG PS, cytogenetic risk and multiple myeloma type.

	IMROZ		IMROZ (with matching)		MAIA	
	IsaVRd (N=265)	[comp.]	IsaVRd [redacted]	[comp.]	DRd (N=350)	[comp.]

* Missing ISS stage was grouped with ISS stage II as this was the largest group.

** Mean assumed based on the median.

6.3.2 Comparability of the study population(s) with Danish patients eligible for treatment

This information is presented in section 6.1.3.

6.3.3 Efficacy – results per IMROZ

The results of the IMROZ trial are described in section 6.1.4.

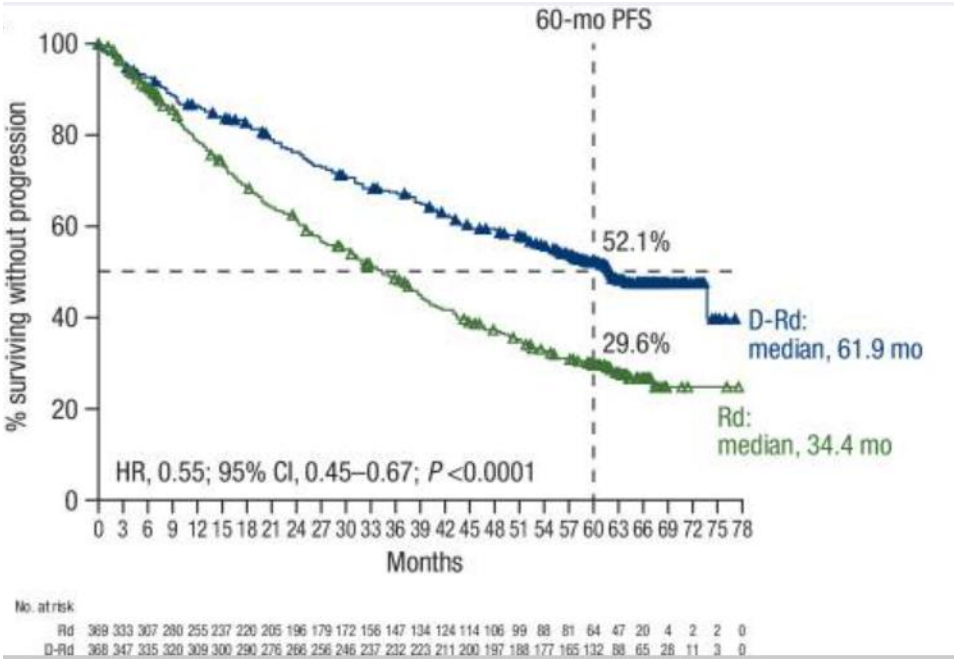
6.3.4 Efficacy – results per MAIA

Efficacy results from the ITT populations in the MAIA study are presented in this section. The MAIA trial compared a group of patients with DRd and Rd. The primary efficacy outcome was PFS, and the key secondary efficacy outcome was OS.

6.3.4.1 PFS

The primary efficacy outcome was PFS, was improved with DRd versus Rd (median, 61.9 vs 34.4 months. The estimated 60-month PFS rates were 52.1% and 29.6% for DRd and Rd respectively.

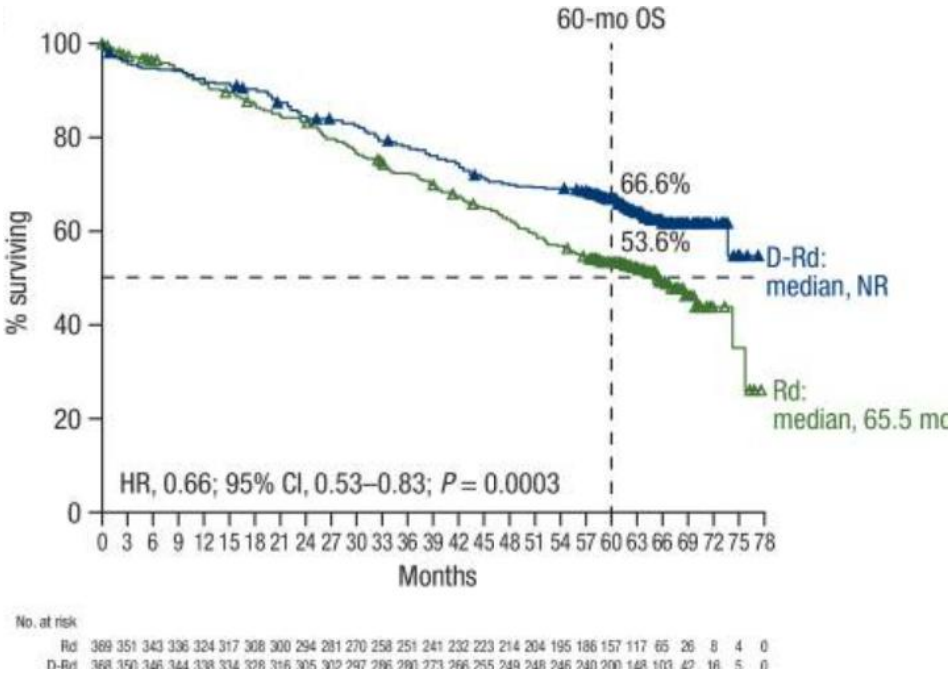
Figure 8 Progression free survival 64.5 months follow up with DRd versus Rd



6.3.4.2 OS

OS was assessed as a key secondary outcome. At median follow up at 64.5 months the median OS was not reached in the DRd group versus 65.5 months in the Rd group. Estimated 60-month OS rates were 66.6% and 53.6% for DRd and Rd respectively.

Figure 9 Overall survival with DRd and Rd in the intent-to-treat population



7. Comparative analyses of efficacy

This section describes the comparative analysis of efficacy of IsaVRd compared to DVMP and DRd. As the efficacy of IsaVRd compared to VRd is assessed directly in a head-to-head study this section is not applicable for that comparison.

7.1.1 Differences in definitions of outcomes between studies

A comparative analysis is carried out for the efficacy outcomes PFS and OS, which are the key drivers of the health economic analysis. The efficacy outcomes are described in section 3.7.

In all three studies, disease progression was defined in accordance with the International Myeloma Working Group criteria. In the IMROZ study disease progression is assessed by the independent review committee, however, the ALCYONE study did not report whether disease progression was independent, or investigator assessed. In the MAIA study disease progression was assessed by investigators.

OS is defined in the same way in both studies.

7.1.2 Method of synthesis

Network meta-analysis (NMA) was considered but was ultimately deemed inappropriate due to several limitations with the only clinical trial (SWOG S0777) to connect IsaVRd to the wider evidence base including DVMP and DRd. The main reservation was that the SWOG S0777 did not have a pre-specified transplant ineligible subpopulation and therefore the NMA would rely solely on a link based on a proxy for transplant ineligibility (>65 years) that would not preserve randomization. Please see Appendix C for further details. As NMA was consequently deemed infeasible due to the absence of a connected evidence network, unanchored matched-adjusted indirect comparison (MAIC) was employed. A detailed description of the MAIC is provided in Appendix C, including a description of the variables used for the adjustment, histograms of the raw MAIC and rescaled weights, Kaplan–Meier curves (for both the unweighted and the weighted population) and a graphical check of the proportional hazards assumption.

7.1.2.1 Weighting

In the MAICs, patient baseline characteristics were matched between IsaVRd and DVMP and DRd respectively by re-weighting individual patients in the IMROZ data. Patient characteristics initially included in the calculation of MAIC weights were age, International Staging System (ISS) stage, Eastern Cooperative Oncology Group (ECOG) PS, cytogenetic risk, MM type, and creatinine clearance. These characteristics were identified as potential prognostic factors and/or effect modifiers through consultations with clinical experts and analyses of the IMROZ data.

For DVMP in the ALCYONE study, the ESS of the weighted population was low (36 patients; 7.3% of the original sample size). To preserve the ESS, creatinine clearance was excluded from the matching as it was the lowest ranked prognostic variable (of those reported) by clinicians. The ESS of the weighted IsaVRd population following the exclusion of creatinine clearance was 129 patients, which is 49% of the original sample size. For DRd in the MAIA study, the ESS of the weighted population was high at 177 patients, which is 67% of the original sample.

Table 18 in section 6.2.2.1 shows the patient baseline characteristics for DVMP before and after matching. Patient populations with respect to the matching variables were well balanced following adjustment. The matched IsaVRd population has a greater proportion of male patients (difference 7%), a lower proportion of white patients (difference 9%), and a marginally longer time since diagnosis compared with the DVMP population (difference 0.98 months). Since these variables were not identified as potential prognostic factors or effect modifiers, these imbalances are not anticipated to bias results.

In Table 19 in 6.3.1 shows the patient baseline characteristics for DRd before and after matching. Patient populations with respect to the matching variables were well balanced following adjustment. Although not included in the matching, the matched IVRd and DRd populations had similar proportions of male patients (difference of 5%) and mean time since diagnosis (difference of 0.6 months).

For further details please see Appendix C.

7.1.2.2 Proportional hazard assessment

For both DVMP and DRd the PH assumption was assessed through inspection of the log-cumulative hazard plot (LCH) and Schoenfeld residuals, and tested statistically using the Schoenfeld Individual Test.

[redacted]

7.1.3 Results from the comparative analysis

Table 20 and Table 21 shows the results of the MAIC of IsaVRd versus DVMP and DRd, respectively assuming proportional hazard ratios.

Table 20 Results from the comparative analysis (MAIC) of IsaVRd vs. DVMP for TIE NDMM patients

Outcome measure	IsaVRd weighted (ESS=[redacted])	DVMP (N=350)	Result from MAIC using Cox PH methods
PFS	Median: NE (NE to NE)	Median: 36.06 months (95% CI: 31.55 to 47.32)	[redacted]
OS	Median: NE (NE to NE)	Median: 82.76 months (95% CI: 72.66 to NE)	[redacted]

Key: CI, confidence interval; DVMP, daratumumab + bortezomib + melphalan + prednisone; ESS, effective sample size; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; NE, not evaluable; PH, proportional hazards; PFS, progression-free survival; RMST, restricted mean survival time.

Notes: [1] Up to the maximum PFS time in the IsaVRd arm (67.7 months). [2] MAIC (weighted Cox PH model) using bootstrapping (median HR) with percentile CI. [3] Up to the maximum OS time in the IsaVRd arm (69.0 months).

Source: Sanofi data on file.

Table 21 Results from the comparative analysis (MAIC) of IsaVRd vs. DRd for TIE NDMM patients

Outcome measure	IsaVRd weighted ( )	DRd (N=368)	Result from MAIC using Cox PH methods
PFS	Median: NE (NE to NE)	Median: 61.66 months (95% CI: 54.75 to NE)	[redacted]
OS	Median: NE (NE to NE)	Median: NE (95% CI: 74.10 to NE))	[redacted]

Key: CI, confidence interval; DRd, daratumumab + lenalidomide + dexamethasone; ESS, effective sample size; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; NE, not evaluable; PH, proportional hazards; PFS, progression-free survival; RMST, restricted mean survival time.

Notes: [1] Up to the maximum PFS time in the IsaVRd arm (67.7 months). [2] MAIC (weighted Cox PH model) using bootstrapping (median HR) with percentile CI. [3] Up to the maximum OS time in the IsaVRd arm (69.0 months).

Source: Sanofi data on file.

7.1.4 Efficacy – results per PFS

The median PFS was not reached for IsaVRd and was 36.06 months (95% CI: 31.55 to 47.32) for DVMP.

[redacted]

The median PFS was not reached for IsaVRd and was 61.66 months (95% CI: 54.75 to NE) for DRd.

[redacted]

[redacted]

Results for the other six parametric distributions are presented as sensitivity analyses in Appendix C.

[redacted]

Table 22 Landmark PFS estimates from the comparative analysis (MAIC) of IsaVRd vs. DVMP for TIE DNMM patients

Time (years)	Gamma		
	IsaVRd: % of patients progression-free (95% CI)	DVMP: % of patients progression-free (95% CI)	HR
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
5.67*	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]

* maximum follow up in IMROZ trial

[redacted]

Results for the other six parametric distributions are presented as sensitivity analyses in Appendix C.

[redacted]

[redacted]

Table 23 Landmark PFS estimates from the comparative analysis (MAIC) of IsaVRd vs. DRd for TIE NDMM patients

Time (years)	Gamma		
	IsaVRd: % of patients progression-free (95% CI)	DRd: % of patients progression-free (95% CI)	HR
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
5.67*	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]

* maximum follow up in IMROZ trial

[redacted]

7.1.5 Efficacy – results per OS

The median OS was not reached for IsaVRd and was 82.76 months (95% CI: 72.66 to NE) for DVMP (Table 20).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 24 Landmark OS estimates from the comparative analysis (MAIC) of IsaVRd vs. DVMP for TIE NDMM patients

Time (years)	Gompertz		
	IsaVRd: % of patients alive (95% CI)	DVMP: % of patients alive (95% CI)	HR
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
5.67*	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]

* maximum follow up in IMROZ trial

Results for the other six parametric distributions are presented as sensitivity analyses in Appendix C.

[redacted]

[redacted]

Table 25 Landmark OS estimates from the comparative analysis (MAIC) of IsaVRd vs. DRd for TIE NDMM patients

Time (years)	Gompertz		
	IsaVRd: % of patients alive (95% CI)	DVMP: % of patients alive (95% CI)	HR
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]
5.67*	[redacted]	[redacted]	[redacted]
10	[redacted]	[redacted]	[redacted]
28	[redacted]	[redacted]	[redacted]

Results for the other six parametric distributions are presented as sensitivity analyses in Appendix C.

[redacted]

[redacted]

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

This section describes how efficacy is modelled in the health economic analysis. The methodology differs between the two comparators; hence the presentation is divided

into two. The comparison of IsaVRd and VRd is presented in section 8.1.1 and the comparison of IsaVRd to DVMP and DRd is presented in section 8.1.2.

8.1.1 Extrapolation of efficacy data for IsaVRd compared to VRd

The extrapolation of efficacy data for IsaVRd compared to VRd utilizes data for the IMROZ trial (ITT population) only. The data cut is September 26, 2023, at a median follow-up of 59.7 months.

In accordance with DMC recommendations, the proportional hazards (PH) assumption was assessed by inspecting the log-cumulative hazard plot (LCH) and Schoenfeld residuals, and was further tested statistically using the Schoenfeld Individual Test.

[redacted]

In line with DMC recommendations and NICE DSU TSD 14, internal and external validation methods were used to assess model fit and facilitate survival curve selection. [52, 53]

The internal validation methods include model fit statistics (AIC/BIC), examination of log-cumulative hazard plots, and visual inspection, where the survival and hazard functions from parametric models are overlaid with the observed data from IMROZ. External validation incorporated clinical opinion and external data to assess plausibility of extrapolations from alternative parametric models. The external data assessed is the real-world Flatiron Health MM Enhanced DataMart data source where patients not receiving HSCT and receiving 1st line therapy with VRd were inverse propensity for therapy weighted (IPTW) to patients in the VRd arm of IMROZ. Please see further details in Appendix D.

8.1.1.1 Extrapolation of PFS for IsaVRd compared to VRd

For PFS, model selection was informed by a combination of statistical fit, graphical assessment, and external validation. Given that the proportional hazards (PH) assumption was not violated, a proportional hazards framework was applied to parametric survival models.

Across all standard parametric distributions assessed, the gamma, Weibull, and Gompertz models provided the most clinically and statistically appropriate fit for VRd. These distributions aligned well with observed hazard trends from IMROZ, provided reasonable long-term extrapolations relative to real-world data from Flatiron, and maintained consistency with OS projections.

[redacted] Further details on model fit, hazard function assessments, and external validation are provided in Appendix B

Figure 10 shows the different fitted curves for PFS together with the KM-data for IMROZ [redacted] Furthermore, the figure presents KM data from Flatiron which is used for external validation.

Table 26 Summary of assumptions associated with extrapolation of PFS for IsaVRd compared to VRd

Method/approach	Description/assumption
Data input	[redacted]
Model	[redacted]
Assumption of proportional hazards between intervention and comparator	[redacted]
Function with best AIC fit	[redacted]
Function with best BIC fit	[redacted]
Function with best visual fit	[redacted]
Function with best fit according to evaluation of smoothed hazard assumptions	[redacted]

Method/approach	Description/assumption
Validation of selected extrapolated curves (external evidence)	[redacted]
Function with the best fit according to external evidence	[redacted]
Selected parametric function in base case analysis	[redacted]
Adjustment of background mortality with data from Statistics Denmark	[redacted]
Adjustment for treatment switching/cross-over	[redacted]
Assumptions of waning effect	[redacted]
Assumptions of cure point	[redacted]

Figure 10 Progression-free survival parametric survival model jointly fitted to IsaVRd and VRd up to 28 years displayed against external data from Flatiron

Key: Exp, exponential; Gamma, gamma; GG, generalized gamma; Gomp, Gompertz; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; KM, Kaplan–Meier; ITT, intention-to-treat; Llog, log-logistic; Lnor, log-normal; R, lenalidomide; VRd, bortezomib + lenalidomide + dexamethasone; Weib, Weibull.

8.1.1.2 Extrapolation of OS for IsaVRd compared to VRd

For OS, model selection was guided by statistical fit, clinical plausibility, and external validation against real-world data.

[redacted]

[redacted]

[redacted] The assumptions associated with extrapolation of OS for IsaVRd compared to VRd and full details on model selection criteria, hazard function assessments, and external validation are provided in Appendix C.

Figure 11 shows the different fitted curves for OS together with the KM-data for IMROZ ([redacted]). Furthermore, the figure presents KM data from Flatiron which is used for external validation.

Table 27 Summary of assumptions associated with extrapolation of OS for IsaVRd compared to VRd

Method/approach	Description/assumption
Data input	[redacted]
Model	[redacted]
Assumption of proportional hazards between intervention and comparator	[redacted]

Method/approach	Description/assumption
Function with best AIC fit	[redacted]
Function with best BIC fit	[redacted]
Function with best visual fit	[redacted]
Function with best fit according to evaluation of smoothed hazard assumptions	[redacted]
Validation of selected extrapolated curves (external evidence)	[redacted]
Function with the best fit according to external evidence	[redacted]
Selected parametric function in base case analysis	[redacted]
Adjustment of background mortality with data from Statistics Denmark	[redacted]
Adjustment for treatment switching/cross-over	[redacted]
Assumptions of waning effect	[redacted]

Method/approach	Description/assumption
Assumptions of cure point	[redacted]

Figure 11 Overall survival – parametric survival model jointly fitted to IsaVRd and VRd up to 28 years displayed against external data from Flatiron

Key: Exp, exponential; Gamma, gamma; GG, generalized gamma; Gomp, Gompertz; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; KM, Kaplan–Meier; Llog, log-logistic; Lnor, log-normal; R, lenalidomide; VRd, bortezomib + lenalidomide + dexamethasone; Weib, Weibull.

8.1.1.3 Extrapolation of TTD for IsaVRd compared to VRd

[redacted]

[redacted]

[redacted]

Table 28 Summary of assumptions associated with extrapolation of TTD for IsaVRd compared to VRd

Method/approach	Description/assumption
Data input	[redacted]
Model	[redacted]
Assumption of proportional hazards between intervention and comparator	[redacted]
Function with best AIC fit	[redacted]
Function with best BIC fit	[redacted]
Function with best visual fit	[redacted]
Function with best fit according to evaluation of smoothed hazard assumptions	[redacted]
Validation of selected extrapolated	[redacted]

Method/approach	Description/assumption
curves (external evidence)	
Function with the best fit according to external evidence	[redacted]
Selected parametric function in base case analysis	[redacted]
Adjustment of background mortality with data from Statistics Denmark	[redacted]
Adjustment for treatment switching/cross-over	[redacted]
Assumptions of waning effect	[redacted]
Assumptions of cure point	[redacted]

[redacted]

Table 29 Reason for treatment discontinuation

	Number of patients (%)
[redacted]	[redacted]
[redacted]	
[redacted]	[redacted]

	Number of patients (%)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Figure 12 Time to discontinuation – parametric survival model jointly fitted to IsaVRd and VRd up to 28 years

Key: Exp, exponential; Gamma, gamma; GG, generalized gamma; Gomp, Gompertz; ITT, intention-to-treat; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; KM, Kaplan–Meier; Llog, log-logistic; Lnor, log-normal; VRd, bortezomib + lenalidomide + dexamethasone; Weib, Weibull.

8.1.2 Extrapolation of efficacy data for IsaVRd compared to DVMP and DRd

The extrapolation of efficacy data for IsaVRd compared to DVMP and DRd is based on the comparative analyses of efficacy presented in section 7 and is thus based on MAIC using data from the IMROZ, ALCYONE and MAIA trials.

[redacted]

8.1.2.1 Extrapolation of PFS for IsaVRd compared to DVMP

The assumptions associated with extrapolation of PFS for IsaVRd compared to DVMP are presented in Table 30.

Table 30 Summary of assumptions associated with extrapolation of PFS for IsaVRd compared to DVMP

Method/approach	Description/assumption
Data input	[redacted]
Model	[redacted]
Assumption of proportional hazards between intervention and comparator	[redacted]
Function with best AIC fit	[redacted]
Function with best BIC fit	[redacted]
Function with best visual fit	[redacted]
Function with best fit according to evaluation of smoothed hazard assumptions	[redacted]
Validation of selected	[redacted]

Method/approach	Description/assumption
extrapolated curves (external evidence)	
Function with the best fit according to external evidence	[redacted]
Selected parametric function in base case analysis	[redacted]
Adjustment of background mortality with data from Statistics Denmark	[redacted]
Adjustment for treatment switching/cross-over	[redacted]
Assumptions of waning effect	[redacted]
Assumptions of cure point	[redacted]

[redacted]

Figure 13 Survival model estimates for IsaVRd (IMROZ) and DVMP (ALCYONE) based on proportional hazards [redacted] - PFS

8.1.2.2 Extrapolation of PFS for IsaVRd compared to DRd

The assumptions associated with extrapolation of PFS for IsaVRd compared to DRd are presented in Table 31.

Table 31 Summary of assumptions associated with extrapolation of PFS for IsaVRd compared to DVMP

Method/approach	Description/assumption
Data input	
Model	
Assumption of proportional hazards between intervention and comparator	
Function with best AIC fit	
Function with best BIC fit	
Function with best visual fit	
Function with best fit according to evaluation of	

Method/approach	Description/assumption
smoothed hazard assumptions	
Validation of selected extrapolated curves (external evidence)	[redacted]
Function with the best fit according to external evidence	[redacted]
Selected parametric function in base case analysis	[redacted]
Adjustment of background mortality with data from Statistics Denmark	[redacted]
Adjustment for treatment switching/cross-over	[redacted]
Assumptions of waning effect	[redacted]
Assumptions of cure point	[redacted]

[redacted]

Figure 14 Survival model estimates for IsaVRd (IMROZ) and DRd (MAIA) based on proportional hazards – [redacted] - PFS

8.1.2.3 Extrapolation of OS for IsaVRd compared to DVMP

The assumptions associated with extrapolation of OS for IsaVRd compared to DVMP are presented in Table 32.

Table 32 Summary of assumptions associated with extrapolation of OS for IsaVRd compared to DVMP

Method/approach	Description/assumption
Data input	
Model	
Assumption of proportional hazards between intervention and comparator	
Function with best AIC fit	
Function with best BIC fit	
Function with best visual fit	
Function with best fit	

Method/approach	Description/assumption
according to evaluation of smoothed hazard assumptions	
Validation of selected extrapolated curves (external evidence)	[redacted]
Function with the best fit according to external evidence	[redacted]
Selected parametric function in base case analysis	[redacted]
Adjustment of background mortality with data from Statistics Denmark	[redacted]
Adjustment for treatment switching/cross-over	[redacted]
Assumptions of waning effect	[redacted]
Assumptions of cure point	[redacted]

[redacted]

Figure 15 Survival model estimates for IsaVRd (IMROZ) and DVMP (ALCYONE) based on proportional hazards – [redacted] - OS

8.1.2.4 Extrapolation of OS for IsaVRd compared to DRd

The assumptions associated with extrapolation of OS for IsaVRd compared to DRd are presented in Table 33.

Table 33 Summary of assumptions associated with extrapolation of OS for IsaVRd compared to DRd

Method/approach	Description/assumption
Data input	[redacted]
Model	[redacted]
Assumption of proportional hazards between intervention and comparator	[redacted]
Function with best AIC fit	[redacted]
Function with best BIC fit	[redacted]
Function with best visual fit	[redacted]

Method/approach	Description/assumption
Function with best fit according to evaluation of smoothed hazard assumptions	[redacted]
Validation of selected extrapolated curves (external evidence)	[redacted]
Function with the best fit according to external evidence	[redacted]
Selected parametric function in base case analysis	[redacted]
Adjustment of background mortality with data from Statistics Denmark	[redacted]
Adjustment for treatment switching/cross-over	[redacted]
Assumptions of waning effect	[redacted]
Assumptions of cure point	[redacted]

[redacted]

Figure 16 Survival model estimates for IsaVRd (IMROZ) and DRd (MAIA) based on proportional hazards – [redacted] - OS

8.1.3 Calculation of transition probabilities

N/A.

8.2 Presentation of efficacy data from additional documentation

N/A

8.3 Modelling effects of subsequent treatments

The overall survival (OS) and progression-free survival (PFS) outcomes are modeled without explicitly attributing survival benefits to subsequent treatments. This is because the survival curves reflect trial data for first-line treatment, which already implicitly includes the effects of subsequent therapies observed during the trial.

8.4 Other assumptions regarding efficacy in the model

N/A

8.5 Overview of modelled average treatment length and time in model health state

Table 34 presents estimates for the modelled average and modelled median of the PFS and OS measures predicted by the extrapolation model.

Table 34 Estimates in the model

	Modelled average	Modelled median	Observed median
Progression Free Survival (PFS)			
IsaVRd	8.57 years	7.51 years	Not reached
VRd	5.76 years	4.52 years	4.53 years
DRd	7.15 years	5.63 years	5.16 years
DVMP	5.41 years	3.99 years	3.1 years
Overall Survival (OS)			
IsaVRd	9.71 years	9.28 years	Not reached
VRd	7.71 years	7.36 years	Not reached
DRd	9.17 years	8.66 years	Not reached
DVMP	8.68 years	8.09 years	6.9 years

Table 35 presents an overview of the modelled average treatment length and time in spend in the two modelled health states, “progression free” and “progressed” (calculated as OS subtracted by PFS).

Table 35 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length (years)	Progression free state (years)	Progressed state (years)
IsaVRd	[redacted]	[redacted]	[redacted]
VRd	[redacted]	[redacted]	[redacted]
DVMP	[redacted]	[redacted]	[redacted]

9. Safety

In this section, we present safety data on NDMM TIE patients from the IMROZ.

9.1 Safety data from the clinical documentation

An overview of the safety events in the IMROZ study is presented in Table 36. In IMROZ, the safety population comprised 263 patients in the IsaVRd group and 181 patients in the

VRd (total: 446 patients). Treatment-related adverse events (TEAEs) are related to at least 1 drug of the combination.

Table 36 Overview of safety events

	IsaVRd (N=263)	VRd (N=181)	Difference, % (95 % CI)
Number of adverse events, n	Not recorded	Not recorded	
Number and proportion of patients with ≥1 adverse events, n (%)	262 (99.6%)	178 (98.%3)	1.3% (-0.7%, 3.3%)
Number of serious adverse events*, n	Not reported	Not reported	
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	186 (70.7%)	122 (67.4%)	3.3% (-5.4%, 12.1%)
Number of CTCAE grade ≥ 3 events, n	Not reported	Not reported	
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	Not reported	Not reported	
Number of adverse reactions, n	Not reported	Not reported	
Number and proportion of patients with ≥ 1 adverse reactions, n (%) Defined as the number of patients with any TEAE related to study drug. For the VRd arm the number of patients with TEA for bortezomib, lenalidomide and	6 (2.3%)	51 (28.2%)	25.9% (19.1%, 32.7%)

	IsaVRd (N=263)	VRd (N=181)	Difference, % (95 % CI)
dexamethasone was summed.			
Number and proportion of patients who had a dose reduction, n (%)	Not reported	Not reported	
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	138 (52.1%)	137 (75.5%)	23.4% (not reported)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	60 (22.8%)	47 (26.0%)	3.2% (-5.0%, 11.3%)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Safety was assessed throughout the study period, with the final assessment occurring 30 days following the last administration of study treatment. The cutoff date for safety analyses was September 26, IMROZ study

§ CTCAE v. 5.0 must be used if available.

Source: [10, 49]

Table 37 presents the frequency of all treatment-emergent adverse events (those of grade 3 or higher). A list of all serious adverse events observed in IMROZ is presented in Appendix E.

Table 37 Serious adverse events

Adverse events	IsaVRd (N=263)		VRd (N=181)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	262 (99.6%)	Not reported	178 (98.3%)	Not reported
Neutropenia	79 (30%)	Not reported	37 (20%)	Not reported
Thrombocytopenia	31 (12%)	Not reported	19 (10%)	Not reported

Adverse events	IsaVRd (N=263)		VRd (N=181)	
Pneumonia	53 (20%)	Not reported	23 (13%)	Not reported
Cataract	41 (16%)	Not reported	20 (11%)	Not reported
Diarrhea	20 (8%)	Not reported	15 (8%)	Not reported
Fatigue	21 (8%)	Not reported	12 (7%)	Not reported
Pulmonary embolism	13 (5%)	Not reported	11 (6%)	Not reported
Asthenia	7 (3%)	Not reported	4 (2%)	Not reported
Peripheral sensory neuropathy	19 (7%)	Not reported	11 (6%)	Not reported
Syncope	15 (6%)	Not reported	10 (6%)	Not reported
Covid-19 pneumonia	21 (8%)	Not reported	7 (4%)	Not reported

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

AEs occurring within the 30-day follow-up and new TAES were followed up until resolution or stabilization. The cutoff date for safety analyses was September 26,2023 (time point). IMROZ study.

In the health economic model, AEs are used to estimate hospital-related costs associated with the events and the disutility's experienced in the progression-free health state. These costs are calculated as a lump sum incurred at the start of the model. The adverse events included in the model are those of grade 3 or higher with an incidence of 5% or more

Table 38 Adverse events used in the health economic model

Adverse events	IsaVRd	VRd	DRd	DVMP		
	Frequency used in economic model for comparator	Frequency used in economic model for comparator	Frequency used in economic model for comparator	Frequency used in economic model for comparator	Source	Justification

Adverse events	IsaVRd	VRd	DRd	DVMP		
Adverse event, n (%)	262 (99.6)	178 (98,3)	368 (100%)	346(98,85%)	A	
Neutropenia	79 (30,04%)	37 (20%)	197 (54%)	138 (39,8%)	A	Input based on clinical trials and existing recommendations from DMC
Anaemia	0	0	61 (17%)	55 (15,9%)	A	Input based on clinical trials and existing recommendations from DMC
Lymphopenia	0	0	60 (16%)	0	A	Input based on clinical trials and existing recommendations from DMC
Leukopenia	0	0	42 (12%)	0	A	Input based on clinical trials and existing recommendations from DMC
Thrombocytopenia	31 (12%)	19 (10%)	32 (9%)	119 (34,39%)	A	Input based on clinical trials and existing recommendations from DMC
Pneumonia	53 (20%)	23 (13%)	70 (19%)	39 (11,27%)	A	Input based on clinical trials and existing recommendations from DMC
Hypokalaemia	0	0	46 (13%)	0	A	Input based on clinical trials and existing recommendations from DMC
Cataract	41 (16%)	20 (11%)	40 (11%)	0	A	Input based on clinical trials and existing recommendations from DMC
Diarrhea	20 (8%)	15 (8%)	32 (9%)	9 (2,60%)	A	Input based on clinical trials and existing

Adverse events	IsaVRd	VRd	DRd	DVMP		
						recommendations from DMC
Fattigue	21 (8%)	12 (7%)	32 (9%)	0	A	Input based on clinical trials and existing recommendations from DMC
Hypertension	0	0	31 (9%)	0	A	Input based on clinical trials and existing recommendations from DMC
Hyperglycaemia	0	0	28 (8%)	0	A	Input based on clinical trials and existing recommendations from DMC
Pulmonary embolism	13 (5%)	11 (6%)	26 (7%)	0	A	Input based on clinical trials and existing recommendations from DMC
Asthenia	7 (3%)	4 (2%)	19 (5%)	0	A	Input based on clinical trials and existing recommendations from DMC
Acute Kidney injury	0	0	19 (5%)	0	A	Input based on clinical trials and existing recommendations from DMC
Chronic kidney disease	0	0	19 (5%)	0	A	Input based on clinical trials and existing recommendations from DMC
Peripheral sensory neuropathy	19 (7%)	11 (6%)	0 (0%)	5 (1,45%)	A	Input based on clinical trials and existing recommendations from DMC
Syncope	15 (6%)	10 (6%)	0 (0%)	0	A	Input based on clinical trials and existing recommendations from DMC

Adverse events	IsaVRd	VRd	DRd	DVMP		
Covid-19 penumonia	21 (8%)	7 (4%)	0 (0%)	0	A	Input based on clinical trials and existing recommendations from DMC

Notes: A: IsaVRd and VRd: IMROZ data on file. DVMP: [31]. DRd: [30]

9.2 Safety data from external literature applied in the health economic model

N/A

Table 39 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A							

10. Documentation of health-related quality of life (HRQoL)

In the health economic model, utilities were derived based on EQ-5D-5L data from the IMROZ trial.

Table 40 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	IMROZ	Assess clinical effectiveness in terms of HRQoL improvements and deriving utilities

10.1 Presentation of the health-related quality of life (EQ-5D-5L)

10.1.1 Study design and measuring instrument

In the IMROZ trial, the EQ-5D-5L questionnaire was administered to patients to measure HRQoL. The results from the EQ-5D-5L are used in the health economic analysis as recommended by the DMC, including both the ED-5D descriptive system and the EQ VAS.

10.1.2 Data collection

In the IMROZ clinical trial, all HRQoL questionnaires were administered to patients on day 1 of every cycle (70 cycles in total), at the end of treatment visit, and 90 days (±5 days) after last study treatment administration. The questionnaires were completed by the patient at the site prior to discussing their health/disease status, and prior to study treatment administration, or other study-related procedures.

Table 41 presents information on missing data and completion for a selected number of time point (every 10th cycle, EOT and follow up).

Table 41 Pattern of missing data and completion EQ-5D-5L

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
C10D1	[redacted]	[redacted]	[redacted]	[redacted]
C20D1	[redacted]	[redacted]	[redacted]	[redacted]
C30D1	[redacted]	[redacted]	[redacted]	[redacted]
C40D1	[redacted]	[redacted]	[redacted]	[redacted]
C50D1	[redacted]	[redacted]	[redacted]	[redacted]

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
C60D1	[redacted]	[redacted]	[redacted]	[redacted]
C70D1	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]
90 day follow up	[redacted]	[redacted]	[redacted]	[redacted]

Source: Sanofi data on file.

[redacted]

[redacted]

Table 42 Demographic characteristics and endpoints of patients with missing EQ-5D-5L values vs. the rest of the population

	Without EQ-5D-5L values: Patients with no baseline value and/or no post-baseline values (N=40)	With EQ-5D-5L values: Patients with a baseline value and at least one post-baseline value (N=406)
Mean age, years (SE)	[redacted]	[redacted]
Male %	[redacted]	[redacted]
Race - n (%)		
White	[redacted]	[redacted]
Other	[redacted]	[redacted]
Missing/ not reported	[redacted]	[redacted]
Geographical region		
Europe	[redacted]	[redacted]
North America	[redacted]	[redacted]
Asia	[redacted]	[redacted]
Other countries	[redacted]	[redacted]
Endpoints		
Kaplan-Meier estimates of PFS in months		
25% quantile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75% quantile (95% CI)	[redacted]	[redacted]
Kaplan-Meier estimates of OS in months		
25% quantile (95% CI)	[redacted]	[redacted]
Median (95% CI)	[redacted]	[redacted]
75% quantile (95% CI)	[redacted]	[redacted]
Best Overall Response [n(%)] as per IRC		

Stringent complete response	[redacted]	[redacted]
Complete response	[redacted]	[redacted]
Very good partial response	[redacted]	[redacted]
Biochemical CR but with missing bone marrowa	[redacted]	[redacted]
Near-CRb	[redacted]	[redacted]
Partial response	[redacted]	[redacted]
Minimal response	[redacted]	[redacted]
Stable disease	[redacted]	[redacted]
Non Progressive disease	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Unconfirmed progressive disease	[redacted]	[redacted]
Not evaluable/Not assessed	[redacted]	[redacted]

Source: Sanofi data on file.

10.1.3 HRQoL results

Longitudinal analysis for change from baseline in scores was performed using an MMRM. Analysis was limited to Cycle 63, as only timepoints with at least 10 patients having non-missing data in both treatment groups were included in the models. Figure 17 illustrates the change from baseline in the EQ-5D-5L index score through Cycle 63 in the ITT population.

[redacted]

Figure 17 Change from baseline in EQ-5D-5L index scores, IsaVRd vs. VRd (ITT population)

Source: Sanofi data on file.
CI = Confidence interval; ITT = Intent-To-Treat; IsaVRd = Isatuximab in combination with bortezomib, lenalidomide and dexamethasone; LS = Least square; VRd = Bortezomib, lenalidomide and dexamethasone; SE = Standard Error.

Figure 18 Change from baseline in EQ VAS scores, IsaVRd vs. VRd (ITT population)

Source: Sanofi data on file
CI = Confidence interval; EQ VAS = EQ visual analogue scale; ITT = Intent-To-Treat; IsaVRd = Isatuximab in combination with bortezomib, lenalidomide and dexamethasone; VRd = Bortezomib, lenalidomide and dexamethasone; SE = Standard Error.

Figure 18 provides the results in terms of change from baseline in EQ VAS score up to Cycle 63 in the ITT population.

Table 43 HRQoL summary statistics, change from baseline in EQ VAS scores from MMRM

	IsaVRd		VRd		IsaVRd vs.VRd
	N	Mean (SE)	n	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C5D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C10D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C15D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C20D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C25D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C30D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C35D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C40D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C45D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C50D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C55D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C60D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
C63D1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: Estimates are based on a mixed model repeated measures treating time continuous: Change=Treatment arm + spline(Time) + Baseline PRO score + Age + Revised International Staging System (R-ISS) stage + spline(Time)*Baseline PRO score + Time*Treatment arm (spline is a natural cubic spline term). The model includes intercept and spline(time) terms as random coefficients. An unstructured variance-covariance matrix has been used to model within-subject error.
Source: Sanofi data on file

10.2 Health state utility values (HSUVs) used in the health economic model

To demonstrate the potential impact of treatment on patient's quality of life, the health economic model accounts for HRQoL measurements tied to the pre-progression and progressed, and disutilities associated with adverse events.

10.2.1 HSUV calculation

Statistical utility analyses were conducted to determine the utility regressions informing health state utility values (HSUV) by treatment. Mixed-effect repeated measure regression models (MMRMs) were used to estimate the average utility value in each health state (before and after progression) after adjusting for prognostic factors and multiple observations from a given patient. Univariate models were fit to determine the variables included in the saturated model. Stepwise selection was applied to fit the chosen model.

Table 44 presents the parameters included in the calculation of HSUV based on the Danish preference-weights from the general Danish population. In the health economic analysis, the HSUVs have been age-adjusted according to the methods guide.

Table 44 Parameters included in the HSUV estimates

	Parameter value	Standard error
Intercept	[redacted]	[redacted]
Baseline utility	[redacted]	[redacted]
Age	[redacted]	[redacted]
Sex (ref: Male)	[redacted]	[redacted]
Progression status (ref: Not progressed)	[redacted]	[redacted]
ECOG PS (ref: ≤ 1)	[redacted]	[redacted]
SEMMGR1Non-I	[redacted]	[redacted]

Source: Sanofi data on file

The formula for calculating the utility weights for the pre-progressed and progressed state is:
Utility=Intercept+Baseline utility+Age+Sex+Progression status+ECOG+SEMMGR1Non-I, where SEMMGR1Non-I is Multiple myeloma non-IgG.

The equation is evaluated in the means of the variables. Varying the progressed state from 0 to 1 respectively provides the estimate for the non-progressed state and the progressed state. Estimates can be found in Table 46 below.

10.2.2 Mapping

N/A. No mapping has been applied.

10.2.3 Disutility calculation

Treating myeloma patients with medication often led to various adverse events and these adverse events are associated with deteriorating health and HRQoL during and after treatment. The 19 most common adverse events are presented with disutility in Table 45. As disutility has not been discovered for Isatuximab in any studies the utility values were derived from the literature [54]. Moreover, some conservative estimates based on earlier recommendations from NICE were conducted. As standard error and confidence intervals were not available for the adverse events the models assumed that the standard error for the disutility is 10%. As estimating disutility from different sources are subjected to uncertainty, we further assessed the uncertainty in the sensitivity analysis by altering the standard error to 15%.

Table 45 Disutility's of adverse events

Adverse event	Disutility	Event duration (days)	Total event utility	Source / comment
Neutropenia	-0.145	7	-0.003	TA917 (DRd NICE) [55] , [56], [56]
Anemia	-0.310	180	-0.153	TA917 (DRd NICE) [55]
Lymphopenia	-0.070	15.5	-0.003	TA917 (DRd NICE) [55]
Leukopenia	-0.070	14.7	-0.003	TA917 (DRd NICE) [55]
Thrombocytopenia	-0.310	7	-0.006	TA917 (DRd NICE) [55]
Pneumonia	-0.190	7	-0.004	TA917 (DRd NICE) [55]

Adverse event	Disutility	Event duration (days)	Total event utility	Source / comment
Hypokalemia	-0.070	11.4	-0.002	Conservative assumption based on TA917 (DRd NICE) [55]
Cataract	-0.010	28	-0.001	TA917 (DRd NICE) [55]
Diarrhea	-0.100	12	-0.003	Based on [54]
Fatigue	-0.120	14.6	-0.005	TA917 (DRd NICE) [55]
Hypertension	-0.150	11.4	-0.005	conservative assumption based on TA917 (DRd NICE) [55]
Hyperglycemia	-0.150	14.7	-0.006	TA917 (DRd NICE) [55]
Pulmonary embolism	-0.310	7	-0.006	TA917 (DRd NICE) [55]
Asthenia	-0.120	14.6	-0.005	TA917 (DRd NICE) [55]
Acute Kidney injury	-0.180	7	-0.003	TA917 (DRd NICE) [55]
Chronic Kidney disease	-0.050	365.25	-0.050	TA917 (DRd NICE) [55]
Peripheral sensory neuropathy	-0.020	49.98	-0.002	TA870 (Ixazomib citrate NICE) [57]
Syncope	0.000	14.00125	0.000	TA970 (Sd NICE) - assumed same as vision blurred [58]
Covid-19 pneumonia	-0.100	7	-0.004	TA917 (DRd NICE) [55] - assumed same as pneumonia

10.2.4 HSUV results

The utilities values resulting from the MMRM regression analysis are presented in Table 45 for the two relevant HSUV states.

Table 46 Overview of health state utility values [and disutilities]

	Results [95% CI]	Number of patients and observations	Instrument	Tariff (value set) used	Comments
HSUV Progression free	0.796 [0.7804 to 0.8109]	14.280 observations on 402 patients	EQ-5D-5L	DK	Estimate is based on mean of both trial arms.
HSUV Progressed	0.777 [0.7545 to 0.7991]	272 observations on 97 patients	EQ-5D-5L	DK	Estimate is based on mean of both trial arms.
Total AE disutilities					
IsaVRd	-0.004	N/A	N/A	N/A	The estimate is based on several sources
VRd	-0.003	N/A	N/A	N/A	The estimate is based on several sources
DRd	-0.035	N/A	N/A	N/A	The estimate is based on several sources
DVMP	-0.028	N/A	N/A	N/A	The estimate is based on several sources

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

N/A

10.3.1 Study design

N/A

10.3.2 Data collection

N/A

10.3.3 HRQoL Results

N/A

10.3.4 HSUV and disutility results

N/A

Table 47 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

Table 48 Overview of literature-based health state utility values N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
N/A				

11. Resource use and associated costs

The model's costs were estimated based on a limited societal perspective following the DMC guidelines. This encompasses expenses related to drug acquisition and administration, disease management costs pre- and post-disease progression, adverse event-related costs, as well as patient time and transportation costs. All expenses in the model are subject to a 3.5% annual discount rate as per the Danish Ministry of Finance guidelines [59]. In the following, descriptions of each cost element and how the element was valued in the health economic analysis are presented.

11.1 Medicines - intervention and comparator

In Table 49 below information about dosing and relative dose intensity for the medicines used in the application is presented. The dosing regiments of the medicines are described in section 3.4 (IsaVRd) 3.5 (VRd and DVMP) and not replicated here.

For weight- or BSA-based drugs, the mean dose with drug wastage is estimated using the 'method of moments' method. The method of moments is a technique that allows estimation of the mean number of vials required per treatment administration when dosing is based on weight or BSA. This method accounts for the distribution of a patient population's weight or BSA, as opposed to a point estimate, by fitting a normal distribution to weight and BSA data. It also assumes that patients only receive whole

vials (no vial sharing), therefore accounting for drug wastage. Using information on pricing associated with different vial sizes, the cheapest cost combination of vials is then solved for over a range of doses based on the distribution of patient weights. The variations in weight and BSA were obtained from the IMROZ trial ITT population.

Table 49 Medicines used in the model

Treat-ment	Medicine	Dose	Relative dose intensity	Source	Frequency	Vial sharing
IsaVRD	**Isatuximab (I)**	10,0 mg/kg IV	93.58%	Facon et al. 2024, p 6, reported as median RDI [10]	[b]	No
	Bortezomib (V)	1,3 mg/m2 SC	90.28%		[b]	No
	Lenalidomide (R)	25 mg[a] PO	77.74%		[b]	No
	Dexamethasone (d)	20 mg PO	83.45%		[b]	No
VRd	**Bortezomib (V)**	1,3 mg/m2 SC	86.65%	Facon et al. 2024, p 6, reported as median RDI [10]	[b]	No
	Lenalidomide (R)	25 mg[a] PO	83.45%		[b]	No
	Dexamethasone (d)	20 mg PO	79.34%		[b]	No
DVMP	**Daratumumab (D)**	1800 mg SC	100.0%	Chari et al. 2021 [60] Mateos et al. 2018, table S4 [31] Reported as median RDI	[b]	No
	Bortezomib (V)	1,3 mg/m2	96.4%		[b]	No
	Melphalane (M)	9,0 mg/m2	95.0%		[b]	No
	Prednisone (P)	60,0 mg/m2	96.4%		[b]	No
DRd	**Daratumumab (D)**	1800 mg SC	100.0%	Chari et al. 2021, reported as median [60] Facon et al. 2019, table S4, reported as means	[b]	No
	Lenalidomide (R)	25 mg[a] PO	76.2% (7.9–240.9)		[b]	No
	Dexamethasone (d)	40 mg PO	84.2% (11.0–110.7)		[b]	No

Treat-ment	Medicine	Dose	Relative dose intensity	Source	Frequency	Vial sharing
				and ranges [30]		

a) 10 mg for patients with CrCl ≥ 30 to < 60 mL/min).

b) The dosing regimens are described in detail in section 3.4 (IsaVRd) 3.5 (VRd and DVMP).

The dosing schedules and costs of the induction phase were modelled by week. For the dosing schedules of the continuous phase and single regimens, an average frequency of administrations per model cycle was calculated and applied to the drug costs to obtain the average cost per model cycle. For lenalidomide where the prescribed dose is determined by patient's renal function, the model weighed the cost per administration for the 25 mg and 10 mg doses by the proportion of patients in IMROZ with regular renal function (70.9%) and with moderately impaired renal function (29.1%), respectively.

In Table 50 the package information and pharmacy purchase price (PPP) on the medicine included in the model are presented.

Table 50 Package information on medicines included in the model.

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Isatuximab (I) IV	100 mg	1	3.776,33
Bortezomib (V)	2,5 mg	1	1.850
Lenalidomide (R)	5 mg	21	26.200
Dexamethasone (d) Oral	40 mg	20	1.490
Melphalan (M)	25 mg	25	304,84
Prednisone (p)	100 mg	25	207,67
Daratumumab (D)	1800 mg	1	36.418,71

Source: Medicinpriser.dk (December 30th, 2024)

11.2 Medicines– co-administration

In Table 51 information about concomitant medications used in the application is presented.

Table 51 Concomitant treatments used in the model

Treatment requiring concomitant medication	Medicine	Dose	Dosing schedule	Source
Isatuximab	Paracetamol	1,000 mg	Prior to isatuximab infusion	IMROZ trial protocol [61]
	Diphenhydramine	50 mg		
	H2 blocker	50 mg		
Daratumumab	Paracetamol	1,000 mg	Prior to daratumumab infusion	Darzalex SmPC [62]
	Diphenhydramine	50 mg		
	Methylprednisolone	20 mg	Post daratumumab infusion	
Bortezomib	Aciclovir	200 mg	Daily	Velcade SmPC [63]

In Table 52 the package information and PPP on the concomitant medications are presented.

Table 52 Package information on medicines included in the model. Source: Medicinpriser.dk (1 December 30, 2024)

Medicine	Strength	Package size	Pharmacy purchase price [DKK]
Paracetamol	500 mg	100 tablets	15.18
Diphenhydramine	1.4	125 ml oral solution	53.64
H2 blocker	50 mg	14 tablets	53.60
Methylprednisolone	20 mg	1 vial	277.83
Aciclovir	800 mg	25 tablets	118.95

11.3 Administration costs

Administration costs are calculated based on the unit cost per administration and the number of administrations patients receive across the different treatment regimens. These costs have been determined using the DRG tariff 17MA98 MDC17 2025 for both subcutaneous and intravenous administration. No administration costs have been

assumed for oral medications, as they are administered concurrently with the IV/SC treatments.

Table 53 Administration costs used in the model

Drug name	Administration type	Frequency	Unit cost DKK	DRG code	Reference
Isatuximab	IV	All administrations*	2,136.00	17MA98	DRG 2025
Bortezomib	SC	All administrations*	2,136.00	17MA98	DRG 2025
Daratumumab	SC	All administrations*	2,136.00	17MA98	DRG 2025

* The frequencies in the dosing regimens are described in detail in section 3.4 (IsaVRd) 3.5 (VRd and DVMP).

11.4 Disease management costs

Disease management costs were accrued in each health state (i.e., pre- and post-progression) separately in the model. The types and frequencies of healthcare resource were based on those used in the NICE assessment for daratumumab with lenalidomide and dexamethasone for untreated multiple myeloma when a stem cell transplant is unsuitable (TA917) [64]. It was assumed that different kinds of tests (such as full blood count, biochemistry, protein electrophoresis, immunoglobin and urinary light chain excretion) were the same across treatments and included in the DRG-tariff and thus excluded from the analysis. The frequency of routine follow-up care (hematologist visit) is assumed to be the same for all comparators. However, the treatments containing a regimen that is administrated at the hospital to progression (i.e. IsaVRd and DVMP), the cost of the regular follow-up visits are assumed to be captured in the administration costs when the patient is under treatment.

Table 54 Disease management costs used in the model

Activity	Frequency	Unit cost DKK	DRG code	Reference
Pre-progression – on treatment: Haematologist visit	Every 30th day*	2,136	17MA98	DRG 2025
Pre-progression – off treatment: Haematologist visit	Every 12th week	2,136	17MA98	DRG 2025
Post-progression: Haematologist visit	Every 30th day	2,136	17MA98	DRG 2025

* For IsaVRd and DVMP the cost is assumed to be captured in the administration costs.

11.5 Costs associated with management of adverse events

The analysis accounts for the AE costs attributed to those of grade ≥3 occurring in greater than 5% of patients. The frequencies of the adverse events were presented in section 9.

Unit costs concerning AEs were derived from the DRG-tariffs are presented in Table 55. AE costs are proportionally allocated based on the incidence rate of the respective AEs within each treatment group and furthermore, the costs are treated as a lump-sum, upfront expenditure for each treatment arm in the model.

Table 55 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
Neutropenia	16MA98	2208
Anaemia	16MA98	2208
Lymphopenia	16MA98	2208
Leukopenia	16MA98	2208
Thrombocytopenia	16MA98	2208
Pneumonia	02MA01	1330
Hypokalaemia	0646	1992
Cataract	23MA03	1085
Diarrhoea	05MA98	4977
Fatigue	23MA03	5271
Hypertension	05MA98	1268
Hyperglycaemia	23MA03	5271
Pulmonary embolism	04MA95	1330
Asthenia	23MA03	5271
Acute Kidney injury	11MA98	1543
Chronic kidney disease	11MA98	1543
Peripheral sensory neuropathy	01MA98	2012
Syncope	05MA98	1268

11.6 Subsequent treatment costs

The costs associated with subsequent treatments in the second, third, and fourth lines of multiple myeloma (MM) treatment are included in the model. These costs are calculated in two steps: First, the costs of each subsequent treatment line are estimated. Following this, these costs are multiplied by the distribution of patients receiving each treatment regimen to calculate the overall costs across all treatment lines.

11.6.1 Costing of subsequent treatment

The costs of subsequent treatments were calculated separately for each line of therapy, accounting for both drug acquisition and administration costs. These costs were based on the unit prices of the medicines and the reported treatment durations, estimated using the median TTP/PFS.

Table 56 provides an overview of the medicines included in the subsequent treatments, their doses, RDI, dosing frequency, and assumptions regarding vial sharing. The dosing frequency is expressed as the total number of doses over the treatment duration, with treatment duration estimated using the median TTP/PFS. Wastage was included using the 'method of moments' method

Table 56 Medicines of subsequent treatments

Treatment regiment	Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
2nd line of treatment					
Kd	Carfilzomib (IV)	56 mg/m2	82.7%	122 doses over 18.7 months	No, MoM
	Dexamethasone (Oral)	20 mg	82.7%	163 doses over 18.7 months	N/A
Rd	Lenalidomide (oral)	25 mg	86%	390 doses over 17.1 months	N/A
	Dexamethasone (Oral)	40 mg	86%	163 doses over 17.1 months	N/A
KRd	Carfilzomib (IV)	56 mg/m2	90%	122 doses over 29.6 months	No, MoM
	Lenalidomide (oral)	25 mg	90%	390 doses over 29.6 months	N/A
	Dexamethasone (Oral)	40 mg	90%	163 doses over 29.6 months	N/A

Treatment regiment	Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
PVd	Pomalidomide (Oral)	4 mg	85%	179 doses over 8.8 months	No
	Bortezomib (Sc)	1,3 mg/m2 SC	80%	42 doses over 8.8 months	No, MoM
	Dexamethasone (Oral)	40 mg	80%	83 doses over over 8.8 months	No
PCd	Pomalidomide (Oral)	4 mg	80%	201 doses over 8.8 months	N/A
	Cyclophosphamide (Oral)	50 mg	80%	201 doses over 8.8 months	N/A
	Dexamethasone (Oral)	20 mg	80%	77 doses over 8.8 months	N/A
DRd	Daratumumab (D) SC	1800mg	100%	47 doses over 34 months	N/A
	lenalidomide (R) 25	25mg	66%	776 doses over 34 months	N/A
	dexamethasone (d) oral	40mg	78%	148 doses over 34 months	N/A
DVd	Daratumumab (D) SC	1800mg	100%	38 doses over 27.6 months	N/A
	bortezomib (V)	1,3 mg/m2 SC	85.4%	32 doses over 27.6 months	No, MoM
	dexamethasone (d) oral	20mg	98.4	64 doses over 27.6 months	N/A
3rd line of treatment					
Kd	Carfilzomib (IV)	56 mg/m2	87.2%	122 doses over 18.7 months	No, MoM
	Dexamethasone (Oral)	20 mg	87.2%	163 doses over 18.7 months	N/A
Pd	Pomalidomide (Oral)	4 mg	90.1%	107 doses over 4.7 months	N/A

Treatment regiment	Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
	Dexamethasone (Oral)	40 mg	90.1%	20 doses over 4.7 months	N/A
PVd	Pomalidomide (Oral)	4 mg	85%	179 doses over 8.8 months	N/A
	Bortezomib (SC)	1,3 mg/m2	80%	42 doses over 8.8 months	No, MoM
	Dexamethasone (Oral)	40 mg	80%	83 doses over 8.8 months	N/A
PCd	Pomalidomide (Oral)	4 mg	80%	201 doses over 8.8 months	N/A
	Cyclophosphamide (Oral)	50 mg	80%	201 doses over 8.8 months	N/A
	Dexamethasone (Oral)	20 mg	80%	77 doses over 8.8 months	N/A

Note: MoM: Wastage is calculated using Methods of Moments.

11.6.2 Distribution of patients into subsequent treatments

The distribution of patients into subsequent treatments was informed by input from a clinical expert. A summary of the subsequent treatments used in the model, categorized by comparator regimen and treatment line is inserted in Table 57 and Table 58.

Table 57 Second line treatment distribution based on first line treatment received

Second-line treatment	IsaVRd	VRd	DVMP	DRd
KRd	5%	-	35%	35%
Rd	5%	-	10%	10%
DVd	-	45%	-	-
DRd	-	15%	-	-
Kd	25%	-	22%	22%
PVd	5%	7%	-	-
PCd	15%	-	-	-
No subsequent treatment	45%	33%	33%	33%
Total	100%	100%	100%	100%

Table 58 Third line treatment distribution based on first line treatment received

Third line treatment	IsaVRd	VRd	DVMP	DRd
Kd	25%	20%	10%	10%
Pd	5%	30%	40%	40%
PVd	-	5%	5%	5%
PCd	25%		-	-
No subsequent treatment	45%	45%	45%	45%
Total	100%	100%	100%	100%

11.6.3 Application of subsequent treatment costs

Subsequent treatment costs are applied as a one-off cost when patients discontinue first-line treatment, as determined by the PFS curve. For subsequent treatment lines, these costs are applied at each model cycle to the proportion of patients discontinuing treatment at that time.

The median PFS used in the model for second line treatment are found in Table 59. The estimates are based on the median PFS shown in the studies.

Table 59. Median PFS for subsequent lines of treatment.

Treatment	Median PFS Months	Source
2nd line of treatment		
KRd	29.6	[65] ASPIRE
Rd	17.1	[66] Pooled MM-009/MM-010
DVd	27.6	[67] CASTOR
DRd	34.0	[68] POLLUX
Kd	18.7	[69] ENDEAVOR
PVd	8.8	[70] OPTIMISMM
PCd	8.8	Assumed to be equal to PVd - Clinical expert
3rd line of treatment		
Kd	9.2	[69] ENDEAVOR
Pd	4.7	[71] MM-003
PVd	8.8	[70] OPTIMISMM
PCd	8.8	Assumed to be equal to PVd - Clinical expert

11.7 Patient costs

In accordance with DMC guidelines, patient-related time and costs were included in the model. No caregiver time or costs were included in the model. The patient time associated with isatuximab and background therapy treatment was based on the time spent on treatment-related activities at the hospital. Based on the DMC guideline, a cost of DKK 188 per patient hour was applied.

Table 60 Patient costs used in the model

Activity	Time spent per administration	Cost per administration (DKK)
Isatuximab first IV dose at hospital	360 minutes	1,128
Isatuximab subsequent IV dose	180 minutes	564

Activity	Time spent per administration	Cost per administration (DKK)
Injection First/subsequent dose	15 minutes	47

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

N/A

12. Results

12.1 Base case overview

Table 61 provides an overview of the settings applied in the base case of the health economic analysis.

Table 61 Base case overview

Feature	Description
Comparators	VRd, DVMP and DRd
Type of model	Partitioned survival model (PSM)
Time horizon	28 years (lifetime)
Treatment line	1st line. Costs for subsequent treatment (2L-3L) lines are included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in IMROZ trial [47]. Danish population weights were used to estimate health-state utility values.
Costs included	Medicine costs, Hospital costs, Costs of adverse events, Patient- and transportation costs
Dosage of medicine	Based on weight and BSA
[redacted]	[redacted]
Parametric function / model for PFS	[redacted]

Feature	Description
	[redacted]
Parametric function / model for OS	[redacted]
Inclusion of waste	Yes (methods of moments)
Mean duration (estimated) in the model's stages (undiscounted) Progression-free survival Overall survival	[redacted]

12.1.1 Base case results for IsaVRd compared to VRd

Table 62 presents an overview of the base case results.

Table 62 Base case results for IsaVRd compared to VRd, discounted estimates

	IsaVRd	VRd	Difference
[redacted]			
[redacted]			
[redacted]			

	IsaVRd	VRd	Difference
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Total costs	4,235,918	1,776,011	2,459,908
Life years gained (Progression-free)	8.6	5.8	2.8
Life years gained (Progressed)	1.1	1.9	-0.8
Total life years	**9.7**	**7.7**	**2.0**
QALYs (Progression-free)	5.3	3.8	1.5
QALYs (Progressed)	0.6	1.1	-0.5
QALYs (adverse reactions)	0.0	0.0	0.0
Total QALYs	**6.0**	**5.0**	**1.0**
Incremental costs per life year gained			**1,228,561**
Incremental cost per QALY gained (ICER)			**2,487,633**

12.1.2 Base case results for IsaVRd compared to DVMP

Table 63 presents an overview of the base case results for IsaVRd compared to DVMP.

Table 63 Base case results for IsaVRd compared to DVMP, discounted estimates

	IsaVRd	DVMP	Difference
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

	IsaVRd	DVMP	Difference
[redacted]	[redacted]	[redacted]	[redacted]
Total costs	**4,235,918**	**3,405,059**	**830,859**
Life years gained (Progression-free)	8.6	5.4	3.2
Life years gained (Progressed)	1.1	3.3	-2.1
Total life years	**9.7**	**8.7**	**1.0**
QALYs (Progression-free)	5.3	3.6	1.7
QALYs (Progressed)	0.6	1.8	-1.2
QALYs (adverse reactions)	0.0	0.0	0.0
Total QALYs	**6.0**	**5.4**	**0.6**
Incremental costs per life year gained			**804,867**
Incremental cost per QALY gained (ICER)			**1,450,856**

12.1.3 Base case results for IsaVRd compared to DRd

Table 64 presents an overview of the base case results for IsaVRd compared to DRd.

Table 64 Base case results for IsaVRd compared to DRd, discounted estimates

	IsaVRd	DRd	Difference
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Total costs	**4,235,918**	**4,376,794**	**-140,876**

	IsaVRd	DRd	Difference
Life years gained (Progression-free)	8.6	7.1	1.4
Life years gained (Progressed)	1.1	2.0	-0.9
Total life years	**9.7**	**9.2**	**0.5**
QALYs (Progression-free)	5.3	4.6	0.8
QALYs (Progressed)	0.6	1.1	-0.5
QALYs (adverse reactions)	0.0	0.0	0.0
Total QALYs	**6.0**	**5.7**	**0.3**
Incremental costs per life year gained			**-259,131**
Incremental cost per QALY gained (ICER)			**-448,703**

12.2 Sensitivity analyses

Uncertainty in the input parameters in the model has been explored through DSA, a PSA and scenario analyses which are presented in this section.

12.2.1 Deterministic sensitivity analyses

Sensitivity was assessed by varying the input parameters of the model by selecting the 2.5th percentile to represent the lower bound and the 97.5th percentile to represent the upper bound. When standard errors are not available, a 10% standard error is assumed to inform the 95% CI.

12.2.1.1 Deterministic sensitivity analyses for IsaVRd compared to VRd

Table 65 One-way sensitivity analyses results for IsaVRd compared to VRd

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	2 459 908	0,99	2 487 633
RDI induction isatuximab (I) IV (0.68 - 1.00)	2.5th pctl.	a)	1 832 385	0,99	1 853 038
	97.5th pctl.	a)	2 620 492	0,99	2 650 027
	2.5th pctl.	a)	2 650 840	0,99	2 680 717

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Subsequent treatment acquisition cost VRd (DKK941,580.89 - DKK1,394,815.48)	97.5th pctl.	a)	2 249 581	0,99	2 274 936
Utility at baseline: Pooled (0.579 - 0.859)	2.5th pctl.	a)	2 459 908	0,93	2 650 209
	97.5th pctl.	a)	2 459 908	1,04	2 365 204
Subsequent treatment acquisition cost IVRd (DKK516,591.43 - DKK765,255.25)	2.5th pctl.	a)	2 363 387	0,99	2 390 024
	97.5th pctl.	a)	2 566 233	0,99	2 595 156
RDI continuous IVRd (IRd) lenalidomide (R) 25 (0.61 - 0.91)	2.5th pctl.	a)	2 369 713	0,99	2 396 422
	97.5th pctl.	a)	2 530 257	0,99	2 558 774
RDI continuous VRd (Rd) lenalidomide (R) 25 (0.65 - 0.96)	2.5th pctl.	a)	2 519 787	0,99	2 548 187
	97.5th pctl.	a)	2 420 176	0,99	2 447 453
Weight (71.96 - 74.84)	2.5th pctl.	a)	2 414 768	0,99	2 441 984
	97.5th pctl.	a)	2 505 047	0,99	2 533 281
RDI continuous IVRd (IRd) isatuximab (I) IV (0.68 - 1.00)	2.5th pctl.	a)	2 404 345	0,99	2 431 444
	97.5th pctl.	a)	2 474 024	0,99	2 501 909
Proportion of patients with regular renal function (56.3% - 83.6%)	2.5th pctl.	a)	2 428 305	0,99	2 455 674
	97.5th pctl.	a)	2 487 336	0,99	2 515 370
RDI continuous IVRd (IRd) lenalidomide (R) 10 (0.61 - 0.91)	2.5th pctl.	a)	2 429 249	0,99	2 456 628
	97.5th pctl.	a)	2 483 821	0,99	2 511 815

Key: Pctl.: percentile. a) To assess the impact of this parameter

Figure 19 One-way sensitivity analysis results for IsaVRd compared to VRd

Table 66 presents the incremental cost, incremental QALYs and the associated Incremental cost-effectiveness ratio (ICER) for different scenario analyses.

Table 66 Scenario analysis results for IsaVRd compared to VRd

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	[redacted]	[redacted]	[redacted]
Time horizon of 10 year	Time horizon of 10 year	In accordance with DMC guidelines	[redacted]	[redacted]	[redacted]
Time horizon of 15 years	Time horizon of 15 years	In accordance with DMC guidelines	[redacted]	[redacted]	[redacted]
0% discounting	0% discounting	In accordance with DMC guidelines	[redacted]	[redacted]	[redacted]

12.2.1.2 Deterministic sensitivity analyses for IsaVRd compared to DVMP

Table 67 One-way sensitivity analysis results for IsaVRd compared to DVMP

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	[redacted]	[redacted]	[redacted]
Hazard ratio vs. IVRd OS DVMP (0.93 - 1.60)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Hazard ratio vs. IVRd PFS, DVMP (1.51 - 2.58)	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
RDI induction isatuximab (I) IV (0.68 - 1.00)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
Subsequent treatment acquisition cost DVMP (DKK595,404.75 - DKK882,005.75)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
Subsequent treatment acquisition cost IVRd (DKK516,591.43 - DKK765,255.25)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
Proportion of patients with regular renal function (56.3% - 83.6%)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
RDI continuous IVRd (IRd) lenalidomide (R) 25 (0.61 - 0.91)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
Weight (71.96 - 74.84)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
Utility at baseline: Pooled (0.579 - 0.859)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
RDI continuous IVRd (IRd) isatuximab (I) IV (0.68 - 1.00)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]

Key: Pctl.: percentile. a) To assess the impact of this parameter

Figure 20 One-way sensitivity analysis results for IsaVRd compared to DVMP, ICER

Note: With a HR of 0.93 IsaVRd is dominated by DVMP, hence the lower bound in not shown in the figure.

Table 68 Scenario analysis results for IsaVRd compared to DVMP

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-			
Time horizon of 10 year	Time horizon of 10 year	In accordance with DMC guidelines			
Time horizon of 15 years	Time horizon of 15 years	In accordance with DMC guidelines			
0% discounting	0% discounting	In accordance with DMC guidelines			

12.2.1.3 Deterministic sensitivity analyses for IsaVRd compared to DRd

Table 69 One-way sensitivity analysis results for IsaVRd compared to DRd

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-			
Hazard ratio vs. IVRd PFS, DRd (1.04 - 1.79)	2.5th pctl.	a)			
	97.5th pctl.	a)			

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
RDI induction isatuximab (I) IV (0.68 - 1.00)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
Subsequent treatment acquisition cost DRd (DKK595,404.75 - DKK882,005.75)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
Subsequent treatment acquisition cost IVRd (DKK516,591.43 - DKK765,255.25)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
Hazard ratio vs. IVRd OS DRd (0.85 - 1.48)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
RDI continuous IVRd (IRd) lenalidomide (R) 25 (0.61 - 0.91)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
RDI continuous DRd lenalidomide (R) 25 (0.53 - 0.78)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
Weight (71.96 - 74.84)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
RDI continuous IVRd (IRd) isatuximab (I) IV (0.68 - 1.00)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]
RDI continuous IVRd (IRd) lenalidomide (R) 10 (0.61 - 0.91)	2.5th pctl.	a)	[redacted]	[redacted]	[redacted]
	97.5th pctl.	a)	[redacted]	[redacted]	[redacted]

Key: Pctl.: percentile. a) To assess the impact of this parameter

Figure 21 One-way sensitivity analysis results for IsaVRd compared to DRd, ICER

[redacted]

Table 70 Scenario analysis results for IsaVRd compared to DRd

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	[redacted]	[redacted]	[redacted]
Time horizon of 10 year	Time horizon of 10 year	In accordance with DMC guidelines	[redacted]	[redacted]	[redacted]
Time horizon of 15 years	Time horizon of 15 years	In accordance with DMC guidelines	[redacted]	[redacted]	[redacted]
0% discounting	0% discounting	In accordance with DMC guidelines	[redacted]	[redacted]	[redacted]

12.2.2 Probabilistic sensitivity analyses

To assess the uncertainty surrounding the variables included in the model, a PSA was performed using 500 iterations. The PSA evaluated the result of the health economics analysis when several parameters of the models were varied simultaneously. Figure 22 presents the cost-effectiveness acceptability curves (CEAC) that illustrates the cost-effectiveness probability at different willingness-to-pay thresholds. Figure 23 presents the scatter plot from the PSA. Figure 24 presents a convergence plot of the estimated incremental costs for IVRd vs. VRd as a function of the number of PSA simulations.

Figure 22 Cost-effectiveness acceptability curves

Figure 23 Scatter plot from PSA

Figure 24 Convergence plot for the estimated incremental costs of IVRd vs. VRd

13. Budget impact analysis

The purpose of the budget impact analysis was to estimate the budgetary impact of recommending IsaVRd as first line treatment for TIE NDMM patients. The budget impact was estimated per year in the first 5 years after the recommendation of IsaVRd. The budget impact analysis compares the expenditures in the scenario where IsaVRd is recommended as a possible first-line standard treatment and the scenario where IsaVRd is not recommended as a possible standard treatment. The total budget impact per year is the difference between the two scenarios. The budget impact analysis is based on the same health economic model as the cost-utility analysis; however, patient and transportation costs are excluded, and the costs are not discounted.

Number of patients (including assumptions of market share)

The number of patients in the budget impact model was informed by the estimate of the patient population in section 3.2. It is expected that 250 NDMM patients meet the criteria for starting treatment with IsaVRd per year. Following its recent recommendation for DRd, DMC recommends that 40% of patients are treated with CD38 therapies (DVMP and DRd) and that DRd has a 27% market share and DVMP has 13% market share. For the budget impact analysis, the remaining 60% are assumed to be treated with VRd.

If IsaVRd is recommended as standard treatment it is assumed that it will have a market share of 50% of the 1st line CD38 market for the TIE patients (20% total market share) throughout the 5-year time horizon. This assumption is done as IsaVRd is placed in the 1st line of therapy and therefore no patients are expected to switch therapy upon positive recommendation for IsaVRd.

For all therapies first year patients starting therapy are assumed to have an average therapy length of 6 months assuming that they will start therapy equally in all months of the first year.

If IsaVRd is not recommended as standard treatment it is assumed that the current market share of 27% DRd, 13% DVMP and 60% VRd will continue.

The model is constructed as an open-cohort model with new patients entering the model each year. The analysis assumes that patients commence treatment at the start of each year. Patients are leaving the cohort due to mortality and advances to further lines of treatment based on the same assumptions as in the cost utility model.

Table 71 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
	Recommendation, Patients (% market share)				
IsaVRd	50 (20 %)	50 (20 %)	50 (20 %)	50 (20 %)	50 (20 %)
VRd	150 (60 %)	150 (60 %)	150 (60 %)	150 (60 %)	150 (60 %)
DRd	33 (13 %)	33 (13 %)	33 (13 %)	33 (13 %)	33 (13 %)
DVMP	17 (7 %)	17 (7 %)	17 (7 %)	17 (7 %)	17 (7 %)
Total	250 (100 %)	250 (100 %)	250 (100 %)	250 (100 %)	250 (100 %)
	Non-recommendation, Patients (% market share)				
IsaVRd	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
VRd	150 (60 %)	150 (60 %)	150 (60 %)	150 (60 %)	150 (60 %)
DRd	67 (27 %)	67 (27 %)	67 (27 %)	67 (27 %)	67 (27 %)
DVMP	33 (13 %)	33 (13 %)	33 (13 %)	33 (13 %)	33 (13 %)
Total	250 (100 %)	250 (100 %)	250 (100 %)	250 (100 %)	250 (100 %)

Budget impact

An overview of the results of the budget impact analysis is presented in Table 72.

Table 72 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	96.4	209.6	296.7	359.9	414.7
The medicine under consideration is NOT recommended	96.1	205.2	294.3	366.7	425.5
Budget impact of the recommendation	0.4	4.4	2.4	-6.8	-10.9

14. List of experts

Dr. Agoston Szabo, myeloma treating doctor at Rigshospitalet,

15. References

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[3] DMC, "Medicinrådets anbefaling vedrørende isatuximab i kombination med carfilzomib og dexamethason til behandling af patienter med knoglemarvskræft, der tidligere har modtaget mindst én behandling," 2022.

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Appendix A. Main characteristics of studies included

Table 73 Main characteristic of IMROZ

Trial name: IMROZ	NCT number: NCT03319667
Objective	Demonstrate the benefit of IsaVRd in prolonging PFS as compared to VRd in TIE NDMM patients.
Publications – title, author, journal, year	Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone for Multiple Myeloma, T. Facon et al., New England Journal of Medicine, 2024 [47]
Study type and design	Open label randomized controlled phase 3 study. Currently active, not recruiting. Patients were randomly assigned in a 3:2 ratio to receive either IsaVRd or VRd. Randomization was stratified according to country (not China vs. China), age (<70 vs. ≥70 years), and Revised International Staging System disease stage (stage I or II vs. III vs. not classified). [47] Patients randomized in the VRd arm were allowed to crossover to receive isatuximab in combination with lenalidomide and dexamethasone only in case of progression during the continuous treatment period. Patients who permanently discontinued lenalidomide and dexamethasone due to a related AE occurring less than 6 months before the crossover, consent withdrawal, or for any reason other than progressive disease (PD), were not eligible for crossover. 25 patients crossed over to receive IsaVRd. [49]
Sample size (n)	N= 446 (IsaVRd arm, n=265; VRd arm, n=181)
Main inclusion criteria	a) Multiple myeloma, as defined by the IMWG criteria b) Evidence of measurable disease: • Serum M-protein ≥1.0 g/dL measured using serum protein immunoelectrophoresis and/or • Urine M-protein ≥200 mg/24 h measured using urine protein immunoelectrophoresis and/or • Serum free light chain multiple myeloma without measurable disease in serum or urine as per previous criteria (serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio <0.26 or >1.65). c) Patients who are newly diagnosed and not considered for high-dose chemotherapy due to age ≥65 years or <65 years with important comorbidities likely to have a negative impact on tolerability of high-dose chemotherapy with stem cell transplant.

Trial name: IMROZ	NCT number: NCT03319667
Main exclusion criteria	a) Less than 18 years (or country's legal age of majority if the legal age is >18 years) and more than 80 years of age. b) Diagnosis of peripheral neuropathy Grade >1 or Grade 1 with pain. c) Diagnosis of amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma (multiple myeloma with absence of related organ or tissue impairment end organ damage). d) Diagnosis of Waldenström's disease, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions. e) Prior or current systemic therapy or SCT for multiple myeloma, apart from an emergency use of a short course (equivalent of dexamethasone 40 mg/day for 4 days) of corticosteroids, if completed within 14 days prior to randomization. f) Concomitant plasma cell leukemia. g) Any major procedure within 14 days before the initiation of the study treatment: plasmapheresis, major surgery (kyphoplasty is not considered a major procedure), radiotherapy (except if palliative intent). h) ECOG PS >2. i) Hemoglobin <8 g/dL. j) Platelets <70 × 109/L if <50% of BM nucleated cells are plasma cells, and ≤30 × 109/L if ≥50% of BM nucleated cells are plasma cells. Platelet transfusion is not allowed within 3 days before the screening hematological test. k) Absolute neutrophil count (ANC) <1000/µL (1 × 109/L). The use of granulocyte colony-stimulating factor (G-CSF) is not allowed to reach this level. l) Creatinine Clearance <30 mL/min/1.73 m^2 m) Total bilirubin >1.5 × upper limit of normal (ULN), except for known Gilbert syndrome. n) Corrected serum calcium >14 mg/dL (>3.5 mmol/L). o) Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 × ULN. p) Hypersensitivity (or contraindication) to dexamethasone, sucrose histidine (as base and hydrochloride salt), boron, mannitol, and polysorbate 80 or any of the components of study therapy that are not amenable to premedication with steroids, or H2 blockers that would prohibit further treatment with these agents. q) Any of the following within 6 months prior to randomization: a. Second/third degree heart block,

Trial name: IMROZ	NCT number: NCT03319667

b. Poorly controlled hypertension,

c. Myocardial infarction,

d. Severe/unstable angina pectoris,

e. Coronary/peripheral artery bypass graft,

f. New York Heart Association class III or IV congestive heart failure,

g. Grade ≥3 arrhythmias,

h. Stroke or transient ischemic attack.

r) Left-ventricular ejection fraction <40%.

s) Prior malignancy. Adequately treated basal cell or squamous cell skin, or superficial (pTis, pTa, and pT1) bladder cancer, or low risk prostate cancer, or any in situ malignancy after curative therapy are allowed, as well as any other cancer for which cytotoxic chemotherapy has been completed ≥3 years prior to enrollment and from which the patient has been disease-free for ≥3 years.

t) Known acquired immunodeficiency syndrome (AIDS)-related illness or known HIV disease requiring antiviral treatment, or active hepatitis A (defined as positive HA antigen or positive IgM), B (defined as either positive HBs antigen or positive hepatitis B viral DNA test above the lower limit of detection of the assay), or C infection (defined as a known positive hepatitis C antibody result or known quantitative hepatitis C (HCV) ribonucleic acid (RNA) results greater than the lower limits of detection of the assay). HIV serology at screening will be tested for German patients.

u) Malabsorption syndrome or any condition that can significantly impact the absorption of lenalidomide (eg, hereditary problems of galactose intolerance, Lapp lactose deficiency).

v) Unable or unwilling to undergo thromboprophylaxis as per local clinical practice.

w) Any of the following within 3 months prior to randomization: treatment resistant peptic ulcer disease, erosive esophagitis or gastritis, infectious or inflammatory bowel disease, diverticulitis, pulmonary embolism, or other uncontrolled thromboembolic events.

x) Any severe acute or chronic medical condition which could impair the ability of the patient to participate in the study or interfere with interpretation of study results (e.g., systemic infection unless anti-infective therapy is employed), or inability of the patient to comply with the study procedures.

y) Pregnant or breastfeeding woman or woman who intends to become pregnant during the participation in the study. Woman of childbearing potential unwilling to prevent pregnancy by the use of 2 reliable methods of contraception for ≥4 weeks before the start of study treatment, during treatment (including dose interruptions), and for at

Trial name: IMROZ	NCT number: NCT03319667
	least 28 days following discontinuation of study lenalidomide, or for 3 months after discontinuation of bortezomib treatment, or 5 months after discontinuation of isatuximab, whichever occurs last, and/or who are unwilling or unable to be tested for pregnancy before study treatment initiation (2 negative tests), weekly during the first 6 weeks of treatment, every 21 days for induction Cycles 2 to 4, and then every 28 days while on therapy (or every 14 days in case of irregular menstrual cycles), and for at least 28 days following discontinuation of study lenalidomide (14 and 28 days for in case of irregular menstrual cycles), or monthly for 3 months after discontinuation of bortezomib treatment, or 5 months after discontinuation of isatuximab, whichever occurs last. z) Male participants who disagree to practice true abstinence or disagree to use a condom during sexual contact with a pregnant woman or a WOCBP while participating in the study, during dose interruptions, and for at least 28 days following discontinuation of study lenalidomide, or for 3 months after discontinuation of bortezomib treatment, or 5 months after discontinuation of isatuximab, whichever occurs last, even if he has undergone a successful vasectomy.
Intervention	The dosage administration was divided into two phases: An induction phase (4 cycles of 6 weeks) and a continuous phase (4-week cycles). **In the induction phase, the combination of Isatuximab, Bortezomib, Lenalidomide, and Dexamethasone was administered four times in six-week cycles (42 days).** Bortezomib (SC): Administered on days 1, 4, 8, 11, 22, 25, 29, and 32 at a dosage of 1.3 mg/m². Lenalidomide (PO): Administered continuously on days 1- 14 and days 22-35 at a dosage of 25 mg. Dexamethasone (IV/PO): Administered on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 at a dosage of 20 mg. Isatuximab (IV) (Cycle 1): Administered on days 1, 8, 15, 22, and 29 at a dosage of 10 mg/kg. Isatuximab (IV) (Cycle 2-4): Administered on days 1, 15, and 29 at a dosage of 10 mg/kg. **In the continuous phase, isatuximab, bortezomib, lenalidomide and dexamethasone was administered in cycles of four weeks (28 days).** Isatuximab (IV) (Cycle 1-17): Administered on days 1 and 15 at a dosage of 10 mg/kg. Isatuximab (IV) (Cycle 18+): Administered on day 1 at a dosage of 10 mg/kg. Lenalidomide (PO): Administered continuously on days 1-21 at a dosage of 25 mg.

Trial name: IMROZ	NCT number: NCT03319667
	Dexamethasone (IV/PO): Administered on days 1, 8, 15, and 22 at a dosage of 20 mg. [47, 49]
Comparator(s)	V, R, and d were administered following the same dosing and treatment schedule as in the IsaVRd group.
Follow-up time	Median follow-up (as of September 26, 2023): 59.73 months.
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was progression-free survival as assessed by an independent review committee. Secondary endpoints include OS, assessed in a time-to-event analysis and Quality of Life, assessed using the EQ-5D-5L questionnaire, administered to patients on day 1 of every cycle (70 cycles in total), at the end of treatment visit, and 90 days (±5 days) after last study treatment administration. The questionnaires were completed by the patient at the site prior to discussing their health/disease status, and prior to study treatment administration, or other study-related procedures. [47, 49] **Other endpoints:** Secondary endpoints were CR rate*, rate of MRD-negativity (≥10^{-5}) in patients with CR*, ≥VGPR rate*, Safety*, ORR*, TTP*, PFS by MRD status*, DOR*, Time to first response*, Time to best response*, PFS2*, Sustained MRD-negativity*, PK, Immunogenicity, Quality of life
Method of analysis	All the efficacy analyses were conducted in the intention-to-treat population, which included all the patients who underwent randomization. The safety population included all the patients who had received at least one dose of trial drug. For the primary end point, between-group comparisons were conducted with the use of a stratified log-rank test procedure with the randomization stratification factors. The significance level at the interim analysis (P = 0.0074) used an O'Brien–Fleming alpha-spending function to control the one-sided type I error at 2.5%, which resulted in the reported 98.5% confidence interval for the primary analysis. The significance level for the interim analysis of overall survival was 0.0001, which resulted in the reported 99.97% confidence interval. The median progression-free survival, the probability of being free from disease progression, and corresponding confidence intervals were calculated by means of the Kaplan–Meier method. Hazard ratio estimates were obtained with the use of a stratified Cox proportional-hazards model. [47]
Subgroup analyses	**Frail vs. non-frail subgroup analysis:** A retrospective, post hoc subgroup analysis of the IMROZ study, which

Trial name: IMROZ	NCT number: NCT03319667
	evaluated the use of IsaVRd followed by IsaRd compared with VRd followed by Rd across frail and non-frail subgroups. Using simplified frailty score*** and regardless of age cutoff, 29% of patients were frail (28% IsaVRd; 32% VRd), and 70% were non-frail (72% IsaVRd; 67% VRd); 1% were missing data. The median age of the frail group was 75, and 71 for non-frail participants, regardless of treatment arm. Source: Sanofi data on file.
Other relevant information	N/A

Notes:

* Time-to-event endpoints measured at the interim analysis cut-off date of September 26th, 2023. Median follow-up (as of September 26, 2023): 59.73 months. The interim analysis was performed after 162 events of disease progression or death had occurred (which was 73% of the 222 events specified for the planned final analysis).

** PRO measures were administered on Day 1 of each treatment cycle, at the end of treatment (EOT) visit, and 90 days (±5 days) after the last study treatment administration.

*** Developed from the International Myeloma Working Group (IMWG) frailty score, the simplified frailty score determines outcomes based on frailty using scores for age, Charlson Comorbidity Index (CCI), and Eastern Cooperative Oncology Group Performance Status (ECOG PS). Frailty scores at baseline were calculated based on age, modified CCI (calculated using medical history at baseline), and ECOG PS. Patients with a frailty score of 0/1 were considered non-frail, and those with scores ≥2 were classified as frail

Key: AE, adverse event; CrCl, creatinine clearance; CR, complete response; d, dexamethasone; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; Isa, isatuximab-irfc; IsaVRd, isatuximab-irfc + bortezomib, lenalidomide, dexamethasone; MM, multiple myeloma; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; R, lenalidomide; TTP, time to progression; V, bortezomib; VGPR, Very Good Partial Response; PFS2, Median second progression-free survival

Table 74 Main characteristic of ALCYONE

Trial name: ALCYONE	NCT number: NCT02195479
Objective	Determine whether DVMP will prolong PFS compared to VMP in TIE NDMM patients.
Publications – title, author, journal, year	Daratumumab Plus Bortezomib, Melphalan, and Prednisone Versus Bortezomib, Melphalan, and Prednisone in Transplant-Ineligible Newly Diagnosed Multiple Myeloma: Frailty Subgroup Analysis of ALCYONE, M. V. Mateos, M. A. Dimopoulos, M. Cavo, et al., Clinical Lymphoma Myeloma Leukemia, 2021. Prognostic value of minimal residual disease negativity in myeloma: combined analysis of POLLUX, CASTOR, ALCYONE, and MAIA, M. Cavo, J. San-Miguel, S. Z. Usmani, et al., Blood, 2022.

Trial name: ALCYONE	NCT number: NCT02195479
	Sustained minimal residual disease negativity in newly diagnosed multiple myeloma and the impact of daratumumab in MAIA and ALCYONE, J. San-Miguel, H. Avet-Loiseau, B. Paiva, et al., Blood, 2022. Health-related quality of life in patients with newly diagnosed multiple myeloma ineligible for stem cell transplantation: results from the randomized phase III ALCYONE trial, S. Knop, M. V. Mateos, M. A. Dimopoulos, et al., BMC Cancer, 2021. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): a randomised, open-label, phase 3 trial, M. V. Mateos, M. Cavo, J. Blade, et al., Lancet, 2020. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma, M. V. Mateos, M. A. Dimopoulos, M. Cavo, et al., New England Journal of Medicine, 2018.
Study type and design	Open label randomized controlled phase 3 study. Completed. Randomization was stratified according to International Staging System (ISS) disease stage (I, II, or III, with higher stages indicating a poorer prognosis; stages are determined based on albumin and β2-microglobulin levels), geographic region (Europe vs. other), and age (<75 years vs. ≥75 years). Treatment assignments were not blinded.[31]
Sample size (n)	N= 706, DVMP (n=350), VMP (356)
Main inclusion criteria	a) Documented multiple myeloma satisfying the calcium elevation, renal insufficiency, anemia, and bone abnormalities (CRAB) diagnostic criteria, monoclonal plasma cells in the bone marrow greater than or equal to 10 percent (%) or presence of a biopsy proven plasmacytoma, and measurable secretory disease, as assessed by the central laboratory, and defined in protocol. b) Participants who are newly diagnosed and not considered candidates for high-dose chemotherapy with stem cell transplantation (SCT) due to: being age >=65 years, or in participants <65 years: presence of important comorbid conditions likely to have a negative impact on tolerability of high dose chemotherapy with stem cell transplantation. c) Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2. d) Meet the clinical laboratory criteria as specified in the protocol. e) A woman of childbearing potential must have a negative serum pregnancy test at screening within 14 days prior to randomization.

Trial name: ALCYONE		NCT number: NCT02195479
	f)	Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously.
Main exclusion criteria	a)	A diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma
	b)	A diagnosis of Waldenstrom's disease, or other conditions in which IgM M-protein is present in the absence of clonal plasma cell infiltration with lytic bone lesions
	c)	Prior or current systemic therapy or SCT for multiple myeloma, except for an emergency use of a short course (equivalent of dexamethasone 40 mg/day for 4 days) of corticosteroids before treatment
	d)	Peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute common terminology criteria for adverse events (NCI CTCAE) Version 4
	e)	A history of malignancy (other than multiple myeloma) within 3 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years)
	f)	Radiation therapy within 14 days of randomization
	g)	Plasmapheresis within 28 days of randomization
	h)	Known chronic obstructive pulmonary disease (COPD) (defined as a forced expiratory volume in 1 second [FEV1] <50% of predicted normal), known moderate or severe persistent asthma within the last 2 years or currently has uncontrolled asthma of any classification (controlled intermittent asthma or controlled mild persistent asthma is allowed)
	i)	Known or suspected COPD must have a FEV1 test during screening
	j)	Known to be seropositive for human immunodeficiency virus (HIV), known to have hepatitis B surface antigen positivity, or history of hepatitis C
	k)	Any concurrent medical or psychiatric condition or disease (example active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study
Intervention	Velcade (SC) (Cycle 1): Twice weekly in Weeks 1, 2, 4 and 5, at a dosage of 1.3 mg/m^2	

Trial name: ALCYONE	NCT number: NCT02195479
	Velcade (SC) (Cycle 2-9): Once weekly in Weeks 1, 2, 4 and 5, at a dosage of 1.3 mg/m^2 Melphalan (PO) (Cycle 1-9): Once daily on Days 1-4, at a dosage of 9 mg/m^2 Prednisone (PO) (Cycle 1-9): Once daily on Days 1-4, at a dosage of 60 mg/m^2 Daratumumab (IV) [a] (Cycle 1): Once weekly, at a dosage of 16 mg/kg Daratumumab (IV) (Cycle 2-9): Once every three weeks, at a dosage of 16 mg/kg Daratumumab (IV) (Cycle 10+): Once every 4 weeks until documented progression, unacceptable toxicity or end of study, at a dosage of 16 mg/kg Daratumumab (SC) [a]: Once every 4 weeks until documented progression, unacceptable toxicity or end of study, at a dosage of 1800 mg Dexamethasone (IV/PO): Given 1 hour or less prior to daratumumab administration as premedication and prednisone substitute, at a dosage of 20 mg 350 participants were randomly assigned to the D-VMP group.
Comparator(s)	V, M, and p were administered following the same dosing and treatment schedule as in the DVMP group. 356 participants were randomly assigned to the VMP group.
Follow-up time	Median follow-up of 74.7 months.
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was progression-free survival, assessed in a time-to-event analysis. Disease progression was defined in accordance with IMWG criteria and assessed in a central laboratory. Secondary endpoints include OS, assessed in a time-to-event analysis. **Other endpoints:** The following were included as secondary endpoints in the study, but are not included in this application: ORR**, VGPR or better**, CR or better**, Negative MRD**, PFS2*, sCR**, TTP*, Time to Response***, DOR*, TNT*, M-protein response*, QoL (Baseline months 3, 6, 9, 12 and 18) [50, 51]

Trial name: ALCYONE	NCT number: NCT02195479
Method of analysis	The primary analysis population was the intention-to-treat population of all the patients who underwent randomization. The safety population comprised patients who received any dose of trial treatment. Continuous variables were summarized with descriptive statistics, and categorical variables were summarized in frequency tables. Time-to-event variables were evaluated with the Kaplan–Meier method. Response to trial treatment was determined with the use of a validated computer algorithm. Binary end points, such as response rate, were assessed with a stratified Cochran–Mantel–Haenszel test, and an odds ratio and two-sided 95% confidence interval were calculated. If the between-group difference in the primary end point was significant at the time of the second interim analysis, the efficacy secondary end points of overall response rate and rates of very good partial response or better, complete response or better, and negative status for minimal residual disease, as ordered here, were sequentially tested, each with an overall two-sided alpha level of 0.05.[31] Of two planned interim analyses, the first evaluated only safety after 100 patients had received at least two treatment cycles or had discontinued treatment. The second assessed safety and efficacy when 231 events of disease progression or death had occurred (i.e., 64% of the planned 360 events for the final analysis; an alpha of 0.0103 was spent). The final overall survival analysis was planned to occur after 330 deaths.[31]
Subgroup analyses	Post-hoc frailty analysis: Frailty scores were calculated retrospectively for all patients using age, CCI (based on a retrospective review of each patient's medical history), and baseline ECOG PS score [72]. Patients were classified as fit (0), intermediate (1), or frail (≥2); a nonfrail category combined fit and intermediate patients. For OS and PFS evaluation, patients within the nonfrail and frail subgroups were further divided by ISS stage (I/II vs. III). Patients with missing data were excluded from frailty evaluation.
Other relevant information	N/A

Notes: [a] Following amendment 7, participants could switch from daratumumab IV to daratumumab SC.

* From randomization to either disease progression or death whichever occurs first (up to 2.4 years) (for TTP: From randomization to either disease progression or death due to PD whichever occurs first (up to 2.4 years)).

** From randomization to disease progression (up to 2.4 years).

*** From randomization to first documented PR or better (up to 2.4 years)

Table 75 Main characteristic of MAIA

Trial name: MAIA	**NCT number: , NCT02252172**
Objective	To compare how well daratumumab combined with lenalidomide and dexamethasone works versus lenalidomide and dexamethasone alone in prolonging progression-free survival in newly diagnosed multiple myeloma patients who are not eligible for high-dose chemotherapy or stem cell transplant.
Publications – title, author, journal, year	Facon T, Kumar SK, Plesner T, Orlowski RZ, Moreau P, Bahlis N, Basu S, Nahi H, Hulin C, Quach H, Goldschmidt H, O'Dwyer M, Perrot A, Venner CP, Weisel K, Mace JR, Raje N, Tiab M, Macro M, Frenzel L, Leleu X, Ahmadi T, Wang J, Van Rampelbergh R, Uhlar CM, Tromp B, Delioukina M, Vermeulen J, Usmani SZ. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol, 2021. Cavo M, San-Miguel JFF, Usmani SZ, Weisel KC, Dimopoulos MAA, Avet-Loiseau H, Paiva B, Bahlis NJ, Plesner T, Hungria VTM, Moreau P, Mateos MV, Perrot A, Iida S, Facon T, Kumar SK, van de Donk NWCJ, Sonneveld P, Spencer A, Krevvata M, Heuck C, Wang J, Ukropec J, Kobos R, Sun S, Qi M, Munshi NC. Prognostic value of minimal residual disease negativity in myeloma: combined analysis of POLLUX, CASTOR, ALCYONE, MAIA. Blood, 2021. San-Miguel J, Avet-Loiseau H, Paiva B, Kumar S, Dimopoulos MA, Facon T, Mateos MV, Touzeau C, Jakubowiak A, Usmani SZ, Cook G, Cavo M, Quach H, Ukropec J, Ramaswami P, Pei H, Qi M, Sun S, Wang J, Krevvata M, DeAngelis N, Heuck C, Van Rampelbergh R, Kudva A, Kobos R, Qi M, Bahlis NJ. Sustained minimal residual disease negativity in newly diagnosed multiple myeloma and the impact of daratumumab in MAIA and ALCYONE. Blood, 2022. Perrot A, Facon T, Plesner T, Usmani SZ, Kumar S, Bahlis NJ, Hulin C, Orlowski RZ, Nahi H, Mollee P, Ramasamy K, Roussel M, Jaccard A, Delforge M, Karlin L, Arnulf B, Chari A, He J, Ho KF, Van Rampelbergh R, Uhlar CM, Wang J, Kobos R, Gries KS, Fastenau J, Weisel K. Health-Related Quality of Life in Transplant-Ineligible Patients With Newly Diagnosed Multiple Myeloma: Findings From the Phase III MAIA Trial. J Clin Oncol, 2021. Facon T, Kumar S, Plesner T, Orlowski RZ, Moreau P, Bahlis N, Basu S, Nahi H, Hulin C, Quach H, Goldschmidt H, O'Dwyer M, Perrot A, Venner CP, Weisel K, Mace JR, Raje N, Attal M, Tiab M, Macro M, Frenzel L, Leleu X, Ahmadi T, Chiu C, Wang J, Van Rampelbergh R, Uhlar CM, Kobos R, Qi M, Usmani SZ; MAIA Trial Investigators. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. N Engl J Med, 2019.
Study type and design	A Phase 3, randomized (study drug assigned by chance), open-label (participants and researchers are aware about the treatment, participants are receiving), activecontrolled (study in which the

Trial name: MAIA	NCT number: , NCT02252172
	experimental treatment or procedure is compared to a standard treatment or procedure), parallel-group (each group of participants will be treated at the same time), and multicenter (when more than one hospital or medical school team work on a medical research study) study in participants with newly diagnosed multiple myeloma and who are not candidates for high dose chemotherapy and ASCT.
Sample size (n)	N= 737
Main inclusion criteria	• Documented multiple myeloma satisfying the CRAB (calcium elevation, renal insufficiency, anemia and bone abnormalities) criteria, monoclonal plasma cells in the bone marrow greater than or equal to (>=) 10 percent (%) or presence of a biopsy proven plasmacytoma and measurable disease as defined by any of the following: (a) immunoglobulin (Ig) G myeloma (serum monoclonal paraprotein [M-protein] level >=1.0 gram/deciliter [g/dL] or urine M-protein level >=200 milligram[mg]/24 hours[hrs]; or (b) IgA, IgM, IgD, or IgE multiple myeloma (serum Mprotein level >=0.5 g/dL or urine M-protein level >=200 mg/24 hrs); or (c) light chain multiple myeloma without measurable disease in serum or urine (serum immunoglobulin free light chain >=10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio). • Participants must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2. • Participants who are newly diagnosed and not considered for high-dose chemotherapy due to: being age >=65 years; or participants less than (<) 65 years with presence of important comorbid condition(s) likely to have a negative impact on tolerability of high dose chemotherapy with stem cell transplantation. Sponsor review and approval of participants below 65 years of age was required before randomization. • Women of childbearing potential must commit to either abstain continuously from sexual intercourse or to use 2 methods of reliable birth control simultaneously as deemed appropriate by the Investigator. Contraception must begin 4 weeks prior to dosing and must continue for 3 months after the last dose of daratumumab. • Men, who is sexually active with a woman of child-bearing potential must agree to use a latex or synthetic condom, even if he had a successful vasectomy, must agree to use an adequate contraception method as deemed appropriate by the Investigator, and must also agree to not donate sperm during the study and for 4 weeks after last dose of lenalidomide and 4 months after last dose of daratumumab.

Trial name: MAIA	NCT number: , NCT02252172
Main exclusion criteria	Participant with a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance (presence of serum M-protein <3g/dl; absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the M-protein), or smoldering multiple myeloma (asymptomatic multiple myeloma with absence of related organ or tissue impairment end organ damage Participant with a diagnosis of Waldenström's disease, or other conditions in which IgM M protein present in the absence of a clonal plasma cell infiltration with lytic bone lesions Participant with a history of malignancy (other than multiple myeloma) within 5 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the Investigator, with concurrence with the Sponsor's medical monitor, is considered cured with minimal risk of recurrence within 5 years). Participant with prior or current systemic therapy or SCT for multiple myeloma, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for 4 days) of corticosteroids before treatment. Participant who had a radiation therapy within 14 days of randomization. Participant with known chronic obstructive pulmonary disease (COPD) (defined as a forced expiratory volume in 1 second [FEV1] < 50% of predicted normal), persistent asthma, or a history of asthma within the last 2 years (controlled intermittent asthma or controlled mild persistent asthma is allowed). Participants with known or suspected COPD must have a FEV1 test during Screening. Participant is known to be seropositive for human immunodeficiency virus (HIV) or hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg] or antibodies to hepatitis B surface and core antigens [anti-HBs and anti-HBc, respectively]) or hepatitis C (anti-HCV antibody positive or HCV-ribonucleic acid [RNA] quantitation positive).
Intervention	Daratumumab 16 mg/kg once a week for 8 weeks followed by once every other week for 16 weeks and lastly one every 4 weeks. Lenalidomide 25 mg orally on day 1 until 21 of each 28-day cycle Dexamethasone (Dara+Rd) 40mg orally or intravenously once a week
Comparator(s)	Lenalidomide and Dexamethasone (Rd) Participants will take lenalidomide daily on Days 1–21 of each 28-day cycle and dexamethasone weekly. Treatment continues until disease progression, unacceptable side effects, or study end (up to 7 years).

Trial name: MAIA	NCT number: , NCT02252172
Follow-up time	Study is ongoing: current data cut reports a median follow-up of 56.2 months.
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint **progression-Free Survival (PFS):** Time from randomization to disease progression or death, up to 3.5 years. Secondary endpoints measures overall survival Other endpoints: No other secondary end points in the study are included in this application.
Method of analysis	All efficacy analyses were intention-to-treat analyses. Progression-free Survival: For the primary endpoint of PFS, the primary analysis consisted of a stratified log-rank test for the comparison of the PFS distribution between the 2 treatment arms. The Kaplan-Meier method was to be used to estimate the distribution of overall PFS for each treatment. The treatment effect (HR) and its two-sided 95% CIs were estimated using a stratified Cox regression model with treatment as the sole explanatory variable. The PFS2 was analysed similarly. Overall Survival: OS was measured from the date of randomization to the date of death. Data for subjects who were alive at the date of the last contact or had an unknown vital status were censored at the date when last known alive at the updated CCO of 19 February 2021. The distribution of OS for the 2 treatment groups were compared based on a log-rank test stratified. with International Staging System (ISS) staging (I, II, III), region (North America vs. Other), and age (<75 years vs. >75 years) as randomized. Hazard ratio and its 95% CI were estimated based on a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. >75 years) as randomized. A HR<1 indicates an advantage for Dara+Rd. A modified linear alpha spending function was used to determine the alpha level at this interim analysis; the pre-specified stopping boundary was p=0.0414. Deaths: The number of subjects who died during the study and within 30 days of last study treatment dose, and the primary cause of death were summarized as of the CCO of 19 February 2021. The primary cause of death was collected on the case report form page.

Trial name: MAIA	NCT number: , NCT02252172
Subgroup analyses	• Sex (male, female) • Age (<75 yeaars, >75 years) • Race (white, other) • Region (North America, other) • Baseline renal function (creatine clearance (>60mL/min, <60mL/min) • Baseline hepatic function (normal, impaired) • ISS staging (I, II, III) • Type of MM (IgG, non-IgG) • Cytogenetic risk (high risk, standard risk) • ECOG performance score (0,1 >2)
Other relevant information	COVID-19 Related Changes in Conduct Protocol Amendment 8 was issued on 3 April 2020. The primary reason for Amendment 8 was to provide flexibility for study investigators during the global coronavirus (COVID19) pandemic. The Amendment allowed subjects who were receiving daratumumab IV (16 mg/kg), the option to switch to daratumumab SC (1800 mg). The overall impact of the COVID-19 pandemic on this study was minor and did not affect the integrity, safety, data quality, or interpretation of results. Study recruitment and the analysis performed for the primary CSR were completed before the start of the COVID19 pandemic and not impacted. Further, there was no impact on the study power for the primary and the major secondary analysis or for this interim OS analyses. Overall, there was no specific impact of COVID-19 to the study population that would require cessation of study treatment.

Appendix B. Efficacy results per study

Table 76 Results from the IMROZ study, total population (ITT)

Results of IMROZ (NCT03319667)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median Progression-free Survival	IsaVRd	265	NR (NR–NR)	HR*: 0.596 (0.406–0.876)	N/A	N/A	0.6	0.41-0.88	0.001	Estimated using Kaplan-Meier method. Hazard ratio estimates were obtained with the use of a stratified Cox proportional hazards model*.	[10]
	VRd	181	54.3 (45.20–NR)								
Median OS	IsaVRd	265	NR (NR–NR)	HR: 0.78 (99.97% CI: 0.41–1.48)	N/A	N/A	N/A	N/A	N/A	Estimated using Kaplan-Meier method.	[45, 46, 48, 49]
	VRd	181	NR (NR–NR)								

*Stratified hazard ratio (98,5% CI). Stratified by age (<70 years vs ≥70 years) and Revised International Staging System (R-ISS) stage (I or II vs. III or not classified) according to Interactive Response Technology.

NR, not reached.

Table 77 Results per study from the ALCYONE trial, total population (ITT)

Results of ALCYONE Trial (NCT02195479)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median Overall survival (median follow-up: 74,7 months)	DVMP	350	82,7 months (73.2-82.0)	29,1 months	(NR)	NR	HR: 0.63	0.51–0.78	0.0001	The median survival is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm.	
	VMP	356	53.6 months (62.6-72.6)								
Progression-free survival (median follow-up:	DVMP	350	37.3 months (NS)	17,6 months	(NR)	NR	HR: 0.43	0.36-0.52	0,0001	The median survival is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm.	
	VMP	356	19.7 months (NS)								

Table 78 Results per study from the MAIA trial, total population (ITT)

Results of MAIA Trial (NCT02195479)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median Overall survival (median follow-up: 64.5 months)	DRd	368	Not reached (5-yr OS: 66.3%)	NR	NR	NR	HR: 0.66	0.53–0.83	<0.001	The median survival is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm.	
	Rd	369	Not reached (5-yr OS: 53.1%)								
Progression-free survival (median follow-up: 64.5 months)	DRd	368	61.9 mo	+30.9 mo vs Rd	NR	NR	HR: 0.55	0.45–0.67	<0.0001	The median survival is based on the Kaplan-Meier estimator. The HR is based on a Cox proportional hazards model with adjustment for the variables used for stratification for randomization, and study arm.	
	Rd	369	31.0 mo								

Appendix C. Comparative analysis of efficacy

This section describes the details of the Matching Adjusted Indirect Comparison (MAIC) of IsaVRd (IMROZ) versus DVMP (ALCYONE) and DRd (MAIA) as well as the conciderations around producing an NMA.

Originally the plan was to do an NMA and connected network of evidence could be formed using the 16 studies deemed suitably similar for ITCs (see Figure 25). However, the network relied critically on the use of results from a non-randomized subgroup patients aged ≥ 65 years from the SWOG S0777 trial as a proxy for the transplant-ineligible population (under the assumption that most patients over the age of 65 years would not be eligible for transplant). As the data from the age ≥ 65 years subgroup of SWOG S0777 was used to connect IMROZ (and therefore IVRd) to the wider evidence base the robustness of this connection was vital to the validity of all comparisons in the network. However, several limitations were identified for SWOG S0777 that might lead to substantial bias in network meta-analysis (NMA), including the following:

- SWOG S0777 enrolled patients who were eligible for transplants and those who were ineligible for transplant. Outcome data were not reported separately for the transplant-ineligible subgroup. Although results for a subgroup of patients aged ≥ 65 years were reported, and aged ≥ 65 years was initially considered as a potential proxy for transplant ineligibility based on clinical feedback, age criteria alone are insufficient to define transplant eligibility according to the German guidelines. In addition, the number of patients who reported no intent to transplant at baseline in SWOG S0777 was lower than the total number of patients in the subgroup of patients aged ≥ 65 years: 106 Rd patients were aged ≥ 65 years whereas 72 patients had no intent to transplant, and 91 VRd patients aged >65 years but 73 had no intent to transplant. This suggests that at least 34 (32%) and 18 (20%) of Rd and VRd patients in the age ≥ 65 years subgroup were transplant eligible.

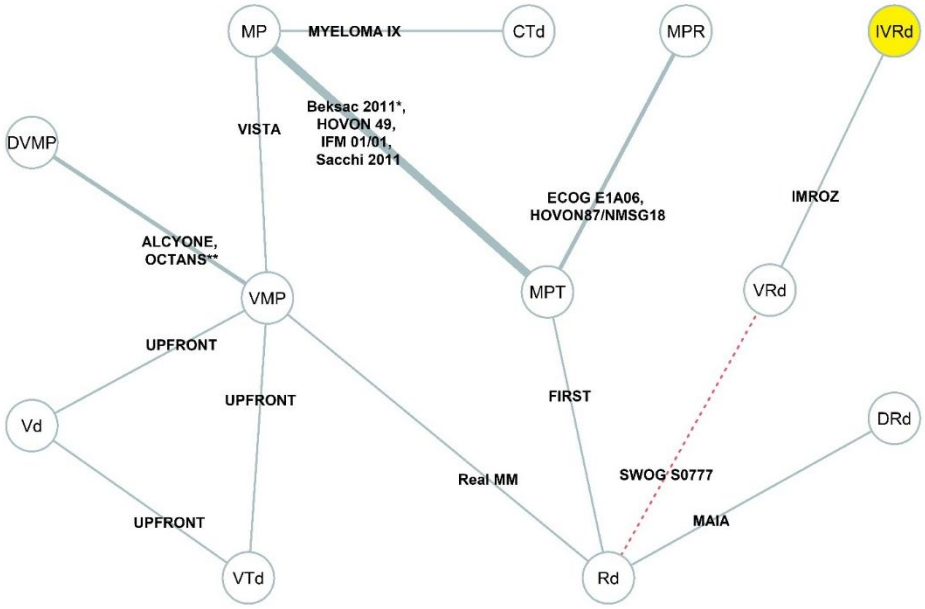
- Randomization in SWOG S0777 was not stratified by age; thus, randomization was not fully preserved between treatment arms within the age ≥ 65 years subgroup. As a result, imbalances might exist in the patient characteristics between treatment arms, which could bias the Kaplan–Meier estimates and relative treatment effects. The inclusion of evidence that is not fully randomized in NMA may lead to results that do not provide a valid and reliable estimate of the relative efficacy.

- Bortezomib (V) was administered intravenously in SWOG S0777, causing resultant neuropathy; this resulted in a large proportion (23%) of patients prematurely discontinuing VRd induction treatment. As such, OS and PFS outcomes for the VRd arm may be confounded by early treatment discontinuation and may not be reliable. Conversely, bortezomib was administered subcutaneously in IMROZ, which is associated with a lower rate of Grade 2+ peripheral neuropathy as compared with intravenous administration.17 Due to differences in administration, the observed VRd

outcomes in SWOG S077 may be worse and bias the comparison against IVRd if VRd in SWOG S077 is assumed the same as VRd in IMROZ (as in NMA)

Given the limitations described above, an NMA based on the connected network of 16 studies would likely produce unreliable relative efficacy estimates for IVRd versus the comparators (except VRd, as IMROZ is the only evidence informing the relative effect between IVRd and VRd). Excluding SWOG S0777 from the network results in disconnecting between IMROZ and the wider evidence base, as IMROZ does not contain a common comparator with any other trials except SWOG S0777. As such, unanchored matching-adjusted indirect comparisons (MAIC) were conducted, consistent with the recommendations in the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) Technical Support Document (TSD) 18 when there are no common comparators between trials.

Figure 25 Network diagram

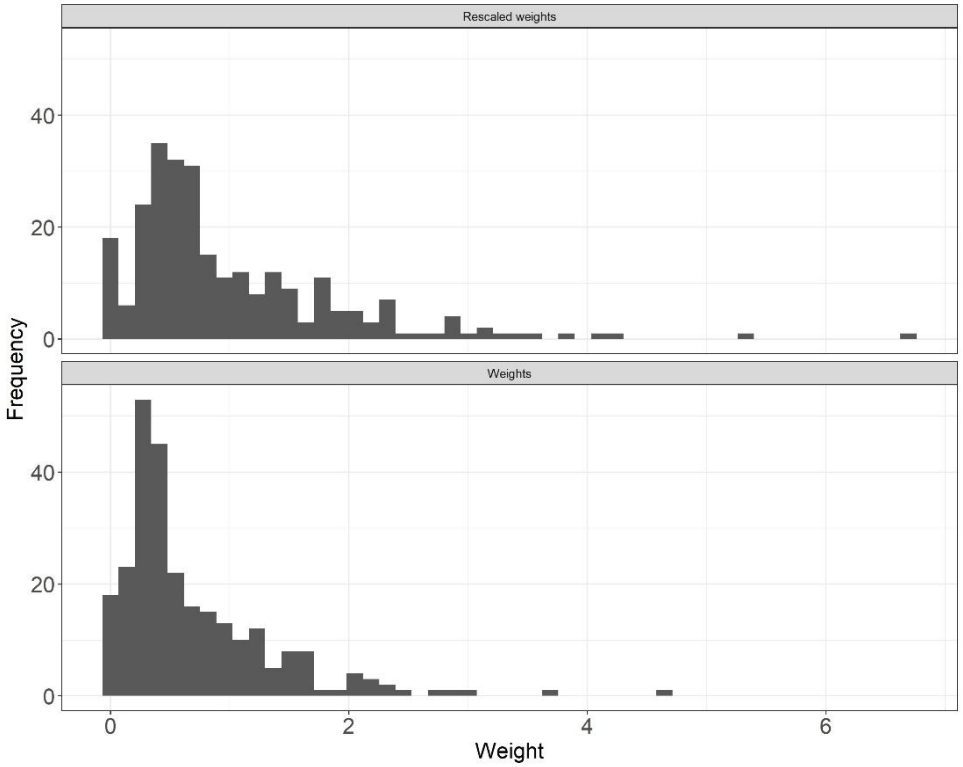


C.1 Estimation of weights for DVMP

The MAIC of IsaVRd versus DVMP was initially conducted using the following matching characteristics: age, ISS stage, ECOG PS, cytogenetic risk, MM type, and creatinine clearance. These characteristics were identified as potential prognostic factors or effect modifiers. However, the ESS of the weighted population was low (36 patients; 7.3% of the original sample size). Additionally, extreme weights were estimated for some patients (e.g. one patient had a weight of 30.1). To preserve the ESS, creatinine clearance was excluded from the matching as it was the lowest ranked prognostic variable (of those reported) by clinicians. The ESS of the weighted IsaVRd population following the exclusion of creatinine clearance was 141 patients, which is 53% of the original sample size.

Figure 26 presents histograms of the raw MAIC and rescaled weights. The rescaled weights show a high concentration of weights between 0 and 2, with very few patients having weights greater than 2 (meaning there were no patients with extreme weights that might distort the MAIC results). Higher weight shows that a patient has more similar characteristics to the summary characteristics for DVMP-treated patients in ALCYONE and therefore has a greater influence on adjusted comparative efficacy estimates. Conversely, patients with smaller weights hold little weight in the subsequent analysis; 18 patients had weights < 0.1, meaning they had little overlap with ALCYONE in terms of adjusted patient characteristics.

Figure 26 Histogram of weights – IsaVRd (IMROZ) vs DVMP (ALCYONE)



Key: DVMP, daratumumab + bortezomib + melphalan + prednisone; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Notes: The lower histogram shows the MAIC weights estimated directly from the model. The rescaled weights are the MAIC weights adjusted such that the sum of the weights is equivalent to the original sample size to aid interpretation. A rescaled weight of 1 means the patient holds the same weight as a patient in the original population.

Table 79 shows the patient baseline characteristics before and after matching. Patient populations with respect to the matching variables were well balanced following adjustment. The matched IsaVRd population has a greater proportion of male patients (difference 7%), a lower proportion of white patients (difference 9%), and a marginally longer time since diagnosis compared with the DVMP population (difference 0.98 months). Since these variables were not identified as potential prognostic factors or effect modifiers, these imbalances are not anticipated to bias results. Creatinine clearance was removed from the analyses to preserve ESS, so there is an imbalance

between treatments for this characteristic – the matched IsaVRd population has a greater proportion of patients with creatinine clearance > 60 mL/min compared with the DVMP population (difference 15%). Exploratory analyses of the IMROZ data indicated that patients with creatinine clearance > 60 mL/min would have better OS and PFS; therefore, this imbalance is anticipated to favor IsaVRd. However, since this was the lowest ranked available characteristic by clinicians, the impact of the bias is expected to be low.

Table 79 Baseline characteristics before and after matching – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Characteristic	IMROZ (IsaVRd) Before matching (N = 265) After matching (ESS = 141 [53%])		ALCYONE (DVMP) N = 350	Absolute difference in matched populations
Age, years (mean)	71.7	71.0	71.0	0
Male (%)	54%	53%	46%	7%
Race (%)				
White	73%	66%	85%	9%
Other	14%	20%	15%	5%
Missing/ not reported	13%	14%	0%	4%
ISS stage (%)				
I	34%	20%	20%	0%
II	41%*	40%	40%	0%
III	25%	40%	40%	0%
ECOG PS (%)				
0–1	89%	74%	74%	0%
≥ 2	11%	26%	26%	0%
Cytogenetic risk (%)				
High	15%	17%	17%	0%
Standard	78%	83%	83%	0%
Missing	7%	0%	0%	0%
Time since diagnosis, months (mean)	2.03	1.83	0.82	0.98
Multiple myeloma type (%)				
IgG	65%	41%	41%	0%
non-IgG	35%	59%	59%	0%
Creatinine clearance (%)				
< 60 mL/min	25%	28%	43%	15%

≥ 60 mL/min	75%*	72%	57%	15%
LDH levels, IU/L (mean)	199.1	193.8	NR	NA

Key: DVCd, daratumumab + bortezomib + cyclophosphamide + dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size, IgG, immunoglobulin G; ISS, International Staging System; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; LDH, lactate dehydrogenase; NR, not reported.

Notes: Matching characteristics included age, ISS stage, ECOG PS, cytogenetic risk and multiple myeloma type. For the calculation of the absolute difference in matched populations, raw mean differences were used for the continuous variables and % difference was used for the categorical variables.

* Missing ISS stage is grouped into ISS stage II as this is the largest group.

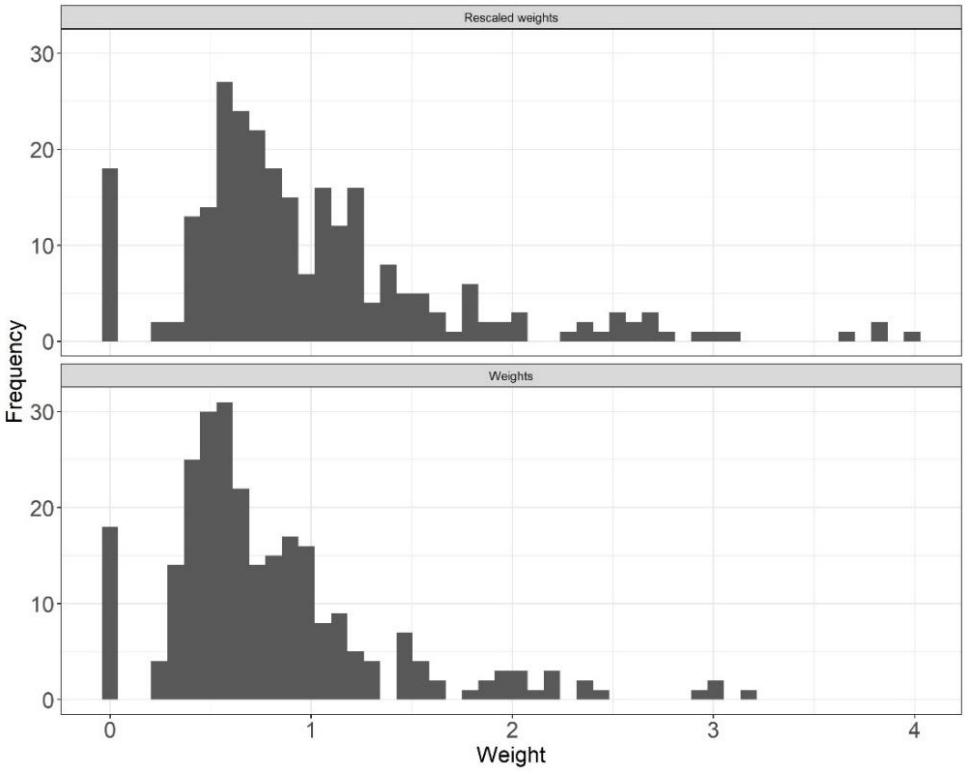
** Assumed based on the median.

C.2 Estimation of weights for DRd

The following patient characteristics were used to match the IVRd population from IMROZ to the DRd population from MAIA: age, ISS stage, ECOG PS, cytogenetic risk, creatinine clearance, and MM type. These characteristics were identified as potential prognostic factors or effect modifiers. Characteristics reported for MAIA that were not included in the matching included sex and time since diagnosis.

The ESS of the weighted IVRd population was 177 patients after matching, which was 67% of the original sample size (N = 265), suggesting reasonable population overlap. Figure 27 presents histograms of the raw MAIC and rescaled weights. The rescaled weights show a high concentration of weights between 0 and 2, with a small number of observations greater than 2 (meaning no patients had extreme weights that could distort the MAIC results). A higher weight indicates that a patient has more similar characteristics to the summary characteristics for DRd-treated patients in MAIA and therefore has a greater influence on adjusted comparative efficacy estimates. Conversely, patients with smaller weights hold little weight in the subsequent analysis; 18 patients had weights < 0.1, meaning they had little overlap with MAIA in terms of adjusted patient characteristics.

Figure 27 Histogram of weights – IsaVRd (IMROZ) vs DRd (MAIA)



Key: DRd, daratumumab + lenalidomide + dexamethasone; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Notes: The lower histogram shows the MAIC weights estimated directly from the model. The rescaled weights are the MAIC weights adjusted such that the sum of the weights is equivalent to the original sample size to aid interpretation. A rescaled weight of 1 means the patient holds the same weight as a patient in the original population.

Table 80 shows the patient baseline characteristics for IVRd and DRd before and after matching. Patient populations with respect to the matching variables were well balanced following adjustment. Although not included in the matching, the matched IVRd and DRd populations had similar proportions of male patients (difference of 5%) and mean time since diagnosis (difference of 0.6 months).

Table 80 Baseline characteristics before and after matching – IsaVRd (IMROZ) vs DRd (MAIA)

Characteristic	IMROZ (IsaVRd) Before matching (N = 265) After matching (ESS = 177 [67%])		MAIA (DRd) N = 368	Absolute difference in matched populations
Age, years (mean)	71.7	73.0	73.0**	0
Male (%)	54%	56%	51%	5%
Race (%)				
White	73%	74%	NR	NA
Other	14%	13%	NR	NA
Missing/ not reported	13%	13%	NR	NA

ISS stage (%)				
I	34%	27%	27%	0%
II	41%*	44%	44%	0%
III	25%	30%	29%	1%
ECOG PS (%)				
0–1	89%	83%	83%	0%
≥ 2	11%	16%	17%	1%
Cytogenetic risk (%)				
High	15%	15%	15%	0%
Standard	78%	85%	85%	0%
Missing	7%	0%	0%	0%
Time since diagnosis, months (mean)	2.0	2.0	1.4	0.6
Multiple myeloma type (%)				
IgG	65%	61%	61%	0%
non-IgG	35%	39%	39%	0%
Creatinine clearance (%)				
< 60 mL/min	25%	44%	44%	0%
≥ 60 mL/min	75%*	56%	56%	0%
LDH levels, IU/L (mean)	199.1	198.1	NR	NA

Key: DRd, daratumumab + lenalidomide + dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size, IgG, Immunoglobulin G; ISS, International Staging System; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; LDH, lactate dehydrogenase; NA, not applicable; NR, not reported.

Notes: Matching characteristics included age, ISS stage, ECOG PS, cytogenetic risk, multiple myeloma type and creatinine clearance. For the calculation of the absolute difference in matched populations, raw mean differences were used for the continuous variables and % difference was used for the categorical variables.

* Missing ISS stage was grouped with ISS stage II as this was the largest group.

** Mean assumed based on the median.

C.3 PFS

C.3.1 Data input DVMP

[redacted]

[redacted]

Figure 28 Kaplan–Meier plot of progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Key: DVMP, daratumumab + bortezomib + melphalan + prednisone; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Table 81 Kaplan–Meier summary of progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Treatment (study)	N/ ESS (% of original sample size)	Events	Median survival (95% CI; months)	Difference in RMST (95% CI; months)*
[redacted]				
[redacted]				
[redacted]				

Key: CI, confidence interval; DVMP, daratumumab + bortezomib + melphalan + prednisone; ESS, effective sample size; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; NE, not evaluable; PH, proportional hazards; PFS, progression-free survival; RMST, restricted mean survival time.

Notes: * Up to the maximum PFS time in the IsaVRd arm (67.7 months).

C.3.2 Proportional hazards assessment

The PH assumption was assessed through inspection of LCH curves (Figure 29) and Schoenfeld residuals (Figure 30), and tested statistically using the Schoenfeld Individual Test.

[redacted]

Figure 29 Log-cumulative hazard plot for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Key: DVMP, daratumumab + bortezomib + melphalan + prednisone; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Figure 30 Schoenfeld residual plot for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Key: DVMP, daratumumab + bortezomib + melphalan + prednisone; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

C.3.3 Constant relative effects

Table 82 Hazard ratios for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Method	Hazard ratio (95% CI)

Key: BCa, bias-corrected and accelerated; CI, confidence interval; HR, hazard ratio; SE, standard error.

Notes:

C.3.4 Time-varying relative effects

C.3.4.1 Time-varying HR

Time-varying HRs were estimated based on weighted parametric survival models. This section presents the time-varying HRs; the weighed parametric survival models are presented in the following section.

Table 83 presents landmark HRs for IsaVRd versus DVMP for each of the seven parametric distributions considered; time-varying HRs are also presented graphically in Figure 31.

[redacted]

Results for the other six parametric distributions are presented as sensitivity analyses.

[redacted]

Table 83 Landmark HRs for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

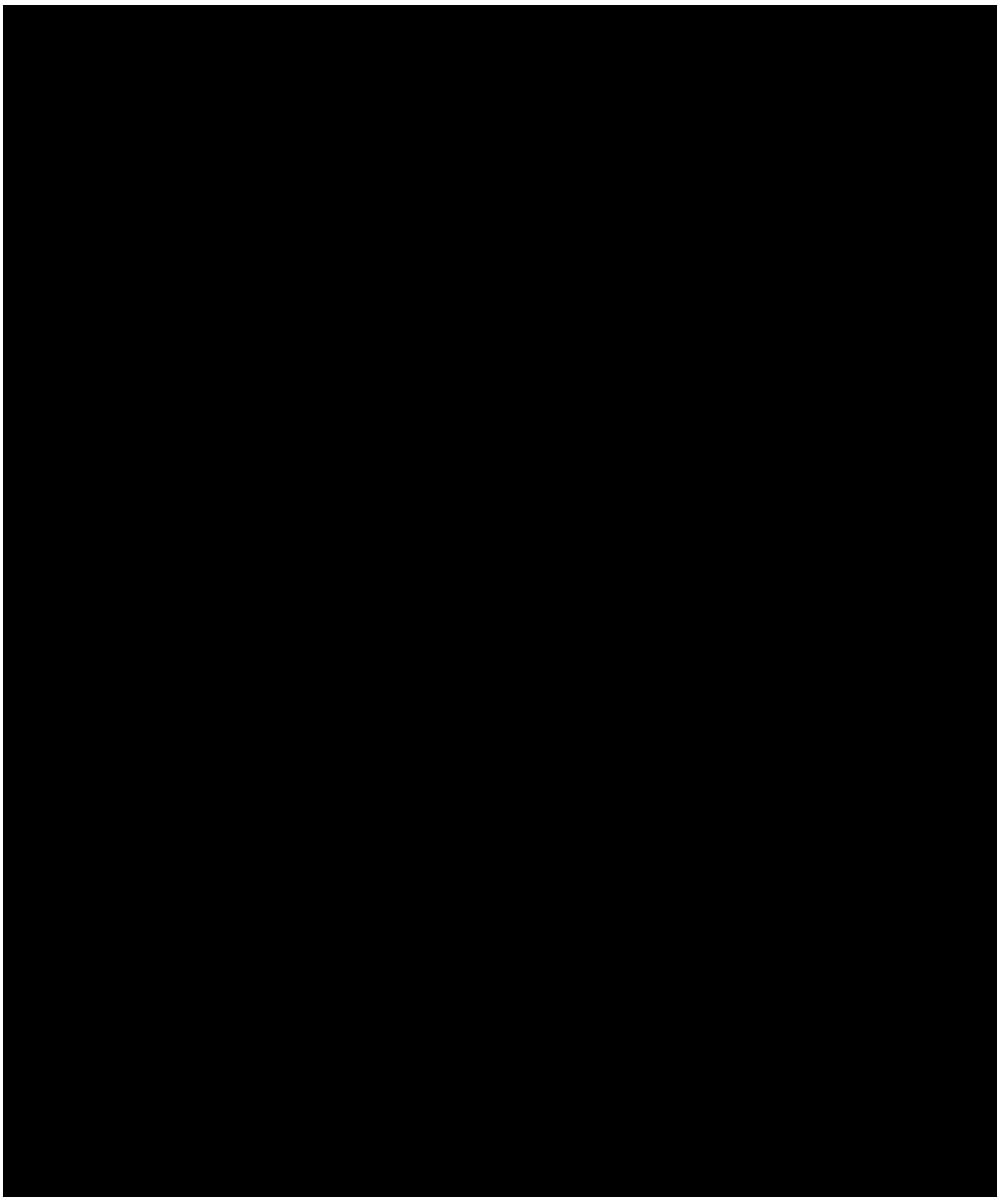
Time (years)	HR (95% CI) for IsaVRd versus DVMP						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
1	[redacted]						
2	[redacted]						
5	[redacted]						
5.67*	[redacted]						
10	[redacted]						
28	[redacted]						

Key: CI, confidence interval; DVMP, daratumumab, bortezomib + melphalan + prednisone; HR, hazard ratio; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

[redacted]

* Maximum IMROZ follow-up.

Figure 31 Time-varying HRs for IsaVRd (IMROZ) versus DVMP (ALCYONE) – progression-free survival



Key: CI, confidence interval; DVMP, daratumumab + bortezomib + melphalan + prednisone; HR, hazard ratio; IsaVRd. isatuximab + lenalidomide + dexamethasone.

C.3.4.2 Weighted parametric survival models

Figure 32 presents the fitted gamma and six supporting parametric survival models overlaid with the Kaplan–Meier curves for weighted IsaVRd and DVMP; corresponding landmark PFS estimates are shown in Table 83.

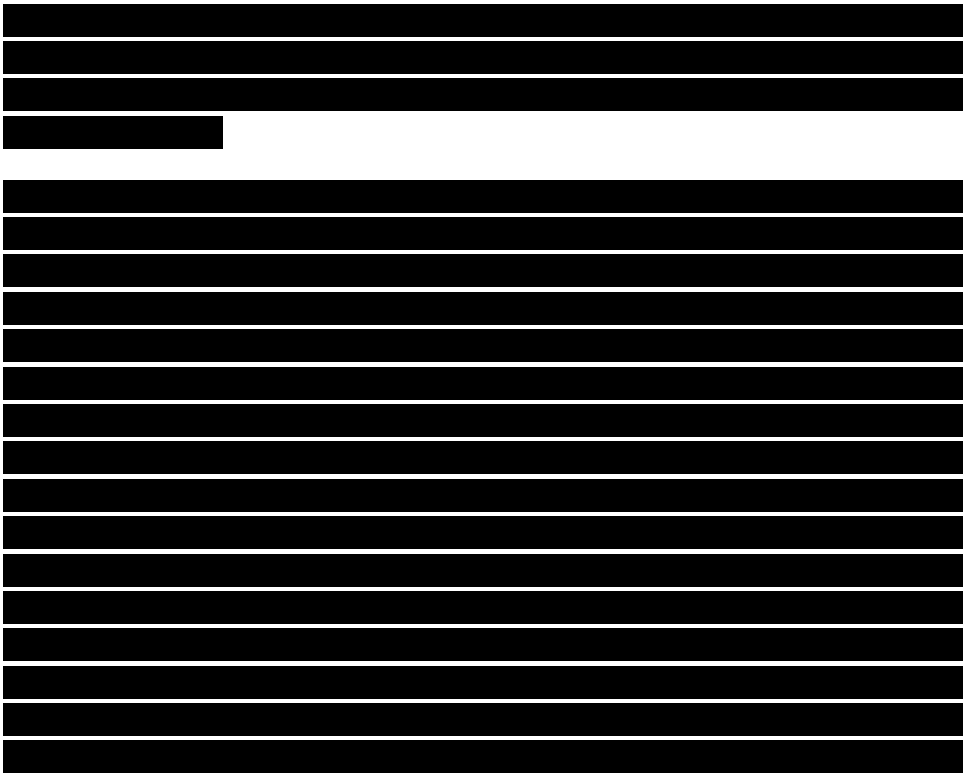


Figure 32 Progression-free survival estimates for IsaVRd (IMROZ) and DVMP (ALCYONE)

Key: DVMP, daratumumab + bortezomib + melphalan + prednisone; IsaVRd. isatuximab + lenalidomide + dexamethasone.

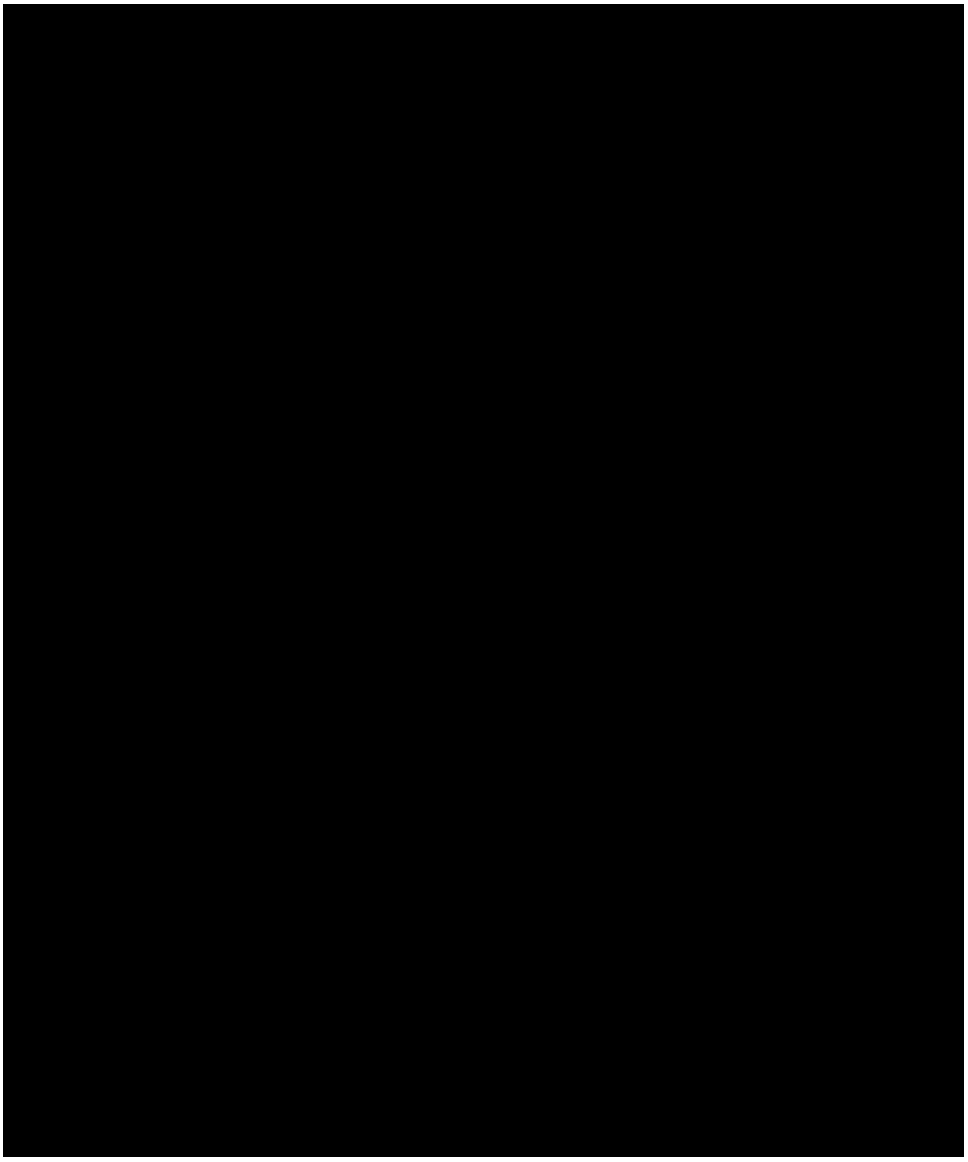


Table 84 Landmark survival estimates for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Time (years)	% of patients progression-free (95% CI)						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
IsaVRd							
1	[redacted]						

2	[redacted]						
5	[redacted]						
5.67*	[redacted]						
10	[redacted]						
28	[redacted]						
DVMP							
1	[redacted]						
2	[redacted]						
5	[redacted]						
5.67*	[redacted]						
10	[redacted]						
28	[redacted]						

Key: CI, confidence interval; DVMP: daratumumab, bortezomib + melphalan + prednisone; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

* Maximum IMROZ follow-up.

C.3.5 Conclusion of the PFS MAIC for IsaVRd versus DVMP

[redacted]

[redacted]

C.3.6 Data input DRd

[redacted]

Figure 33 Kaplan–Meier plot of progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA)

[redacted]

Key: DRd, daratumumab + lenalidomide + dexamethasone; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Table 85 Kaplan–Meier summary of progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA)

Treatment (study)	N/ ESS (% of original sample size)	Events	Median survival (95% CI; months)	Difference in RMST (95% CI; months)*
IVRd unadjusted (IMROZ)	[redacted]	[redacted]	[redacted]	[redacted]
IVRd weighted (IMROZ)	[redacted]	[redacted]	[redacted]	[redacted]
DRd (MAIA)	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; DRd, daratumumab + lenalidomide + dexamethasone; ESS, effective sample size; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; NE, not evaluable; PH, proportional hazards; RMST, restricted mean survival time.

C.3.7 Proportional hazards assessment

The PH assumption was assessed through inspection of LCH curves (Figure 34) and Schoenfeld residuals (Figure 35) and tested statistically using the Schoenfeld Individual Test.

[redacted]

Figure 34 Log-cumulative hazard plot for progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA)

Key: DRd, daratumumab + lenalidomide + dexamethasone; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Figure 35 Schoenfeld residual plot for progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA)

Key: DRd, daratumumab + lenalidomide + dexamethasone; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

C.3.8 Constant relative effects

Table 86 shows the constant HRs estimated using Cox PH methods before and after matching

Table 86: Hazard ratios for progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA)

Method	Hazard ratio (95% CI)
HR (95% CI) from unadjusted Cox model	
HR (95% CI) from weighted Cox model	
HR (95% CI) from weighted Cox model (robust SE)	
Bootstrap median HR (95% CI)	
Bootstrap median HR (95% BCa CI)	

Key: BCa, bias-corrected and accelerated; CI, confidence interval; HR, hazard ratio; SE, standard error.

Notes:

[redacted]

C.3.9 Time-varying relative effects

C.3.9.1 Time-varying HR

Time-varying HRs were estimated based on weighted parametric survival models. This section presents the time-varying HRs; the weighed parametric survival models are presented in the following section.

In Table 87 landmark estimates of PFS HRs for IVRd versus DRd for each of the seven parametric distributions considered, with time-varying HRs displayed graphically in Figure 36.

[redacted]

Results for the other six parametric distributions are presented as sensitivity analyses in Table 87.

[redacted]

[redacted]

Table 87 Landmark HRs for progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA)

Time (years)	HR (95% CI) for IsaVRd versus DRd						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
1	[redacted]						
2	[redacted]						
5	[redacted]						
5.67*	[redacted]						
10	[redacted]						
28	[redacted]						

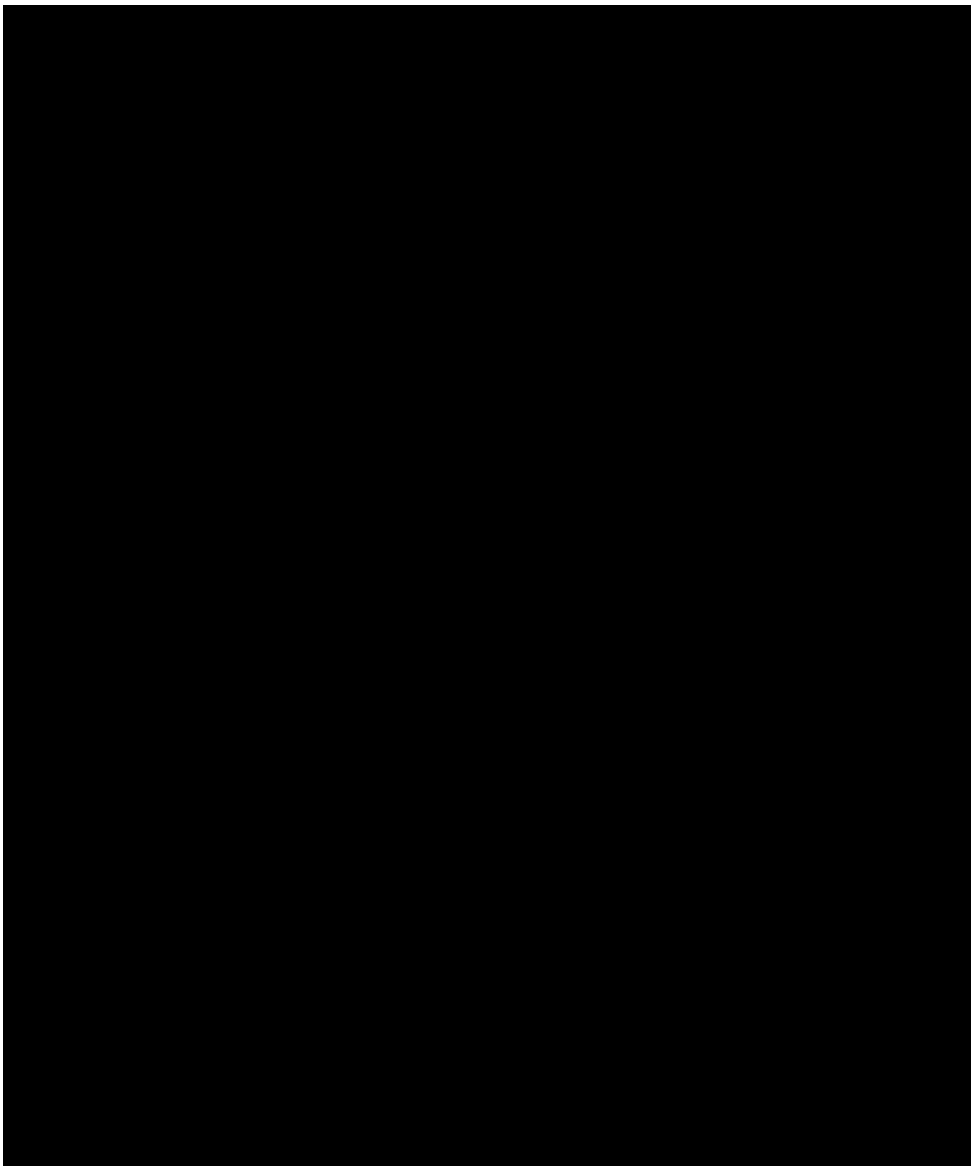
Key: CI, confidence interval; DRd, daratumumab + lenalidomide + dexamethasone; HR, hazard ratio; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; PFS, progression-free survival; PH, proportional hazards.

Notes:

[redacted]

* Maximum IMROZ follow-up.

Figure 36 Time-varying HRs for IsaVRd (IMROZ) versus DRd (MAIA) – progression-free survival



Key: CI, confidence interval; DRd, daratumumab + lenalidomide + dexamethasone; HR, hazard ratio; IsaVRd. isatuximab + lenalidomide + dexamethasone.

C.3.9.2 Weighted parametric survival models

Figure 37 presents the fitted gamma and six supporting parametric survival models overlaid with the Kaplan–Meier curves for weighted IVRd and DRd; corresponding landmark PFS estimates are available in Table 88.

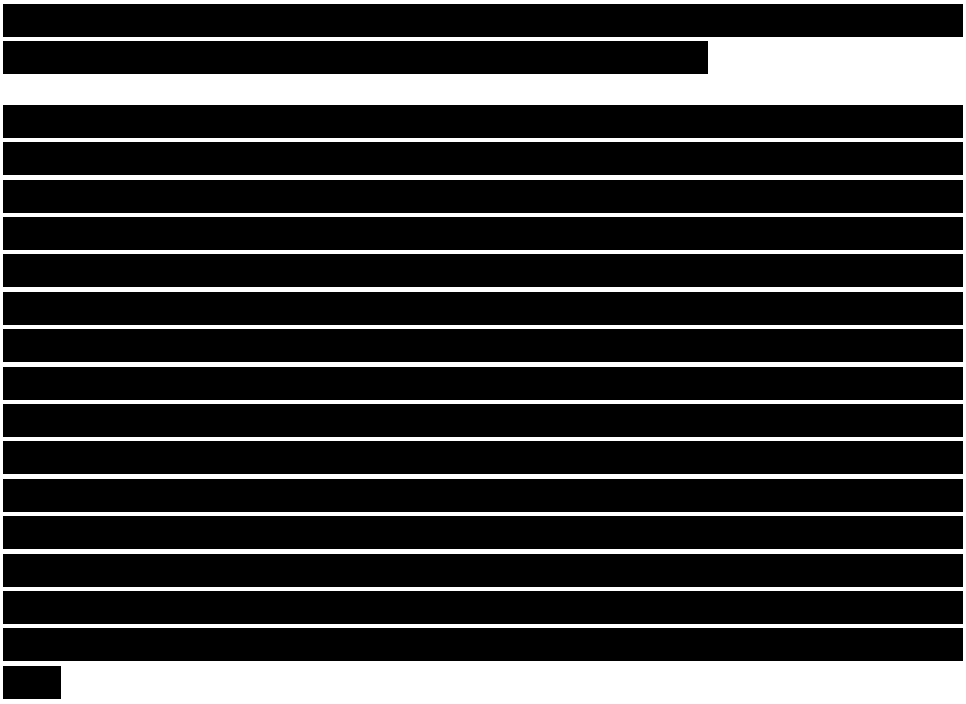
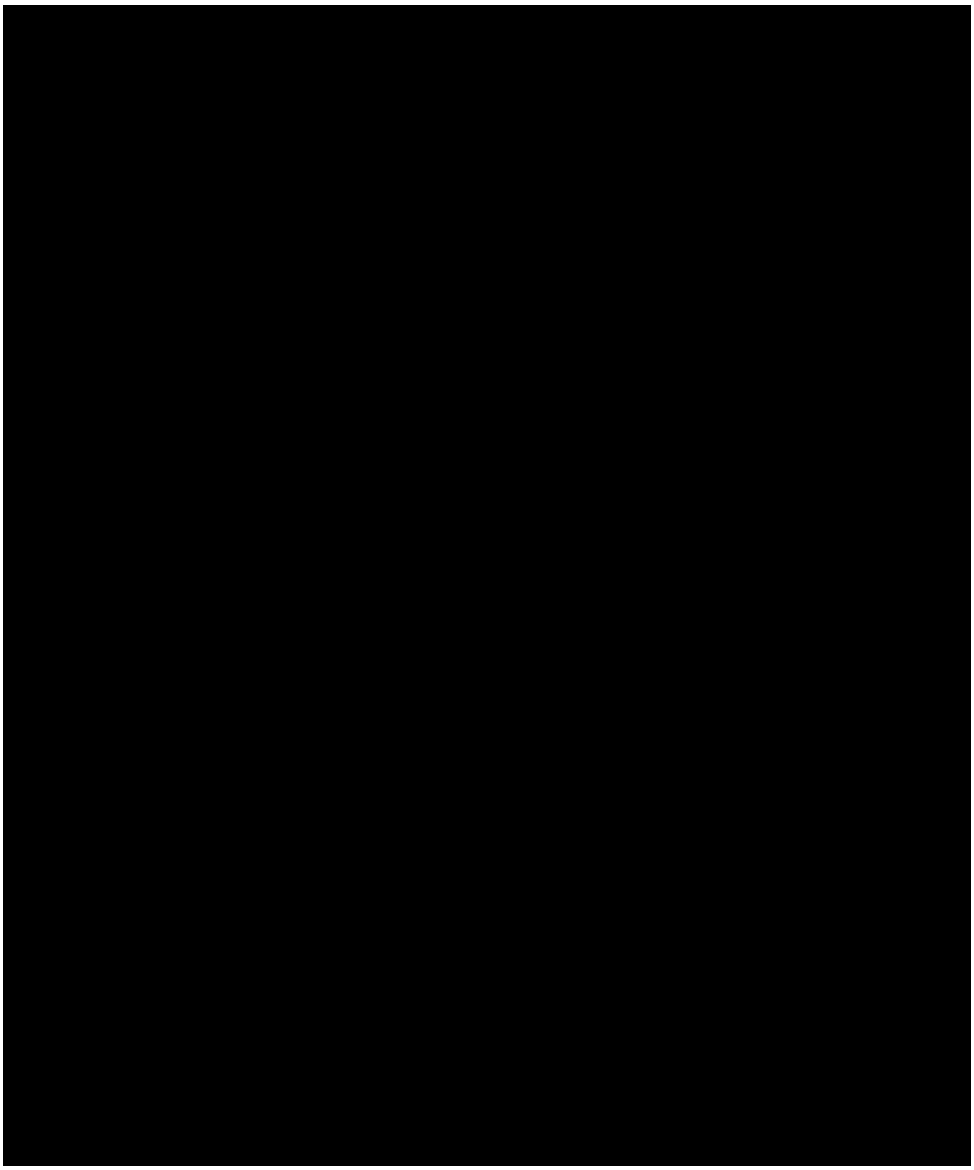


Figure 37 Progression-free survival estimates for IsaVRd (IMROZ) and DRd (MAIA)



Key: DRd, daratumumab + lenalidomide + dexamethasone; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Table 88 Landmark survival estimates for progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA)

Time (years)	% of patients progression-free (95% CI)						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
IsaVRd							
1	[redacted]						

2	[redacted]						
5	[redacted]						
5.67*	[redacted]						
10	[redacted]						
28	[redacted]						
DRd							
1	[redacted]						
2	[redacted]						
5	[redacted]						
5.67*	[redacted]						
10	[redacted]						
28	[redacted]						

Key: CI, confidence interval; DRd, daratumumab + lenalidomide + dexamethasone; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; PFS, progression-free survival.

* Maximum IMROZ follow-up.

C.3.10 Conclusion of the PFS MAIC for IsaVRd versus DRd

[redacted]

[redacted]

C.4 OS

C.4.1 Data input DVMP

[redacted]

Figure 38: Kaplan–Meier plot of overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Key: DVMP, daratumumab + bortezomib + melphalan + prednisone; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Table 89 Kaplan–Meier summary of overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Treatment (study)	N/ ESS (% of original sample size)	Events	Median survival (95% CI; months)	Difference in RMST (95% CI; months)*
IsaVRd unadjusted (IMROZ)	[redacted]	[redacted]	[redacted]	[redacted]
IsaVRd weighted (IMROZ)	[redacted]	[redacted]	[redacted]	[redacted]
DVMP (ALCYONE)	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; DVMP, daratumumab + bortezomib + melphalan + prednisone; ESS, effective sample size; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; NE, not evaluable; PH, proportional hazards; RMST, restricted mean survival time.

Notes: * Up to the maximum OS time in the IsaVRd arm (69.0 months).

C.4.2 Proportional hazards assessment

The PH assumption was assessed through inspection of LCH curves (Figure 39) and Schoenfeld residuals (Figure 40), and tested statistically using the Schoenfeld Individual Test.

[redacted]

Figure 39 Log-cumulative hazard plot for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

[redacted]

Key: DVMP, daratumumab + bortezomib + melphalan + prednisone; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Figure 40 Schoenfeld residual plot for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Key: DVMP, daratumumab + bortezomib + melphalan + prednisone; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

C.4.3 Constant relative effects

Table 90 Hazard ratios for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Method	HR (95% CI)

Key: BCa, bias-corrected and accelerated; CI, confidence interval; HR, hazard ratio; SE, standard error.

Notes:

.

C.4.4 Time-varying relative effects

C.4.4.1 Time-varying HR

Time-varying HRs were estimated based on weighted parametric survival models. This section presents the time-varying HRs; the weighed parametric survival models are presented in the following section.

Table 91 presents the OS landmark time-varying HRs for IsaVRd versus DVMP based on the weighted parametric survival models; time-varying HRs are also displayed in Figure 41.

[redacted]

Results for the other six parametric distributions are presented as sensitivity analyses in Table 91.

[redacted]

[redacted]

Table 91 Landmark HRs for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Time (years)	HR (95% CI) for IsaVRd versus DVMP						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
1	[redacted]						
2	[redacted]						
5	[redacted]						
5.67	[redacted]						
10	[redacted]						
28	[redacted]						

Key: CI, confidence interval; DVMP, daratumumab + bortezomib + melphalan + prednisone; HR, hazard ratio; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Notes:

[redacted]

* Maximum IMROZ follow-up.

Figure 41 Time-varying HRs for IsaVRd (IMROZ) versus DVMP (ALCYONE) – overall survival

[redacted]

Key: CI, confidence interval; DVMP, daratumumab + bortezomib + melphalan + prednisone; HR, hazard ratio; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

C.4.4.2 Weighted parametric survival models

[redacted]

[redacted]

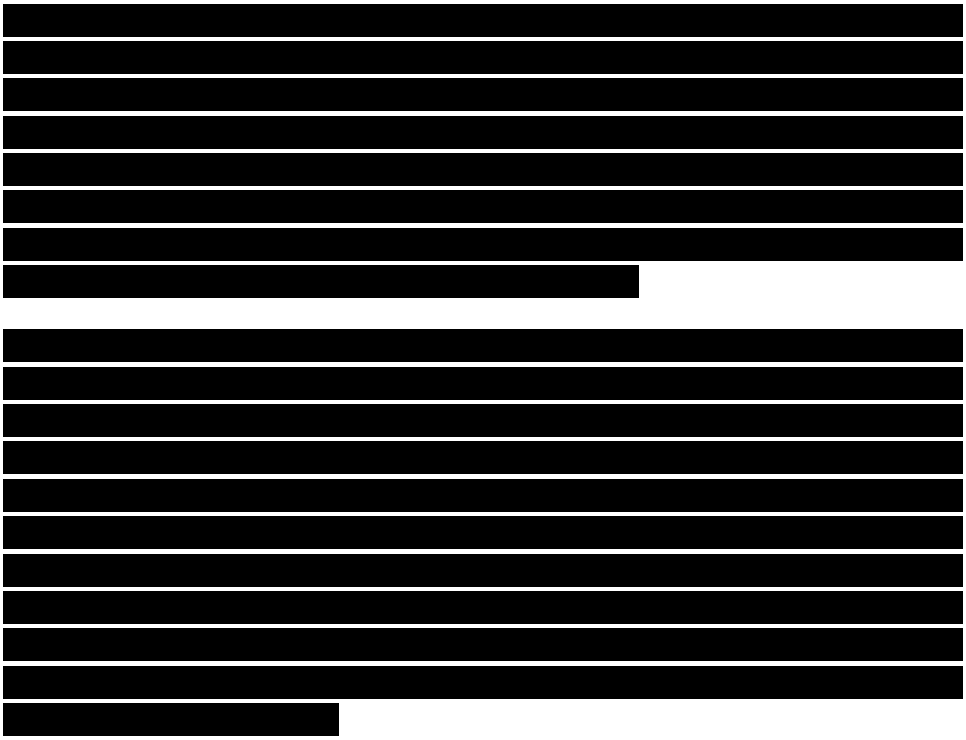
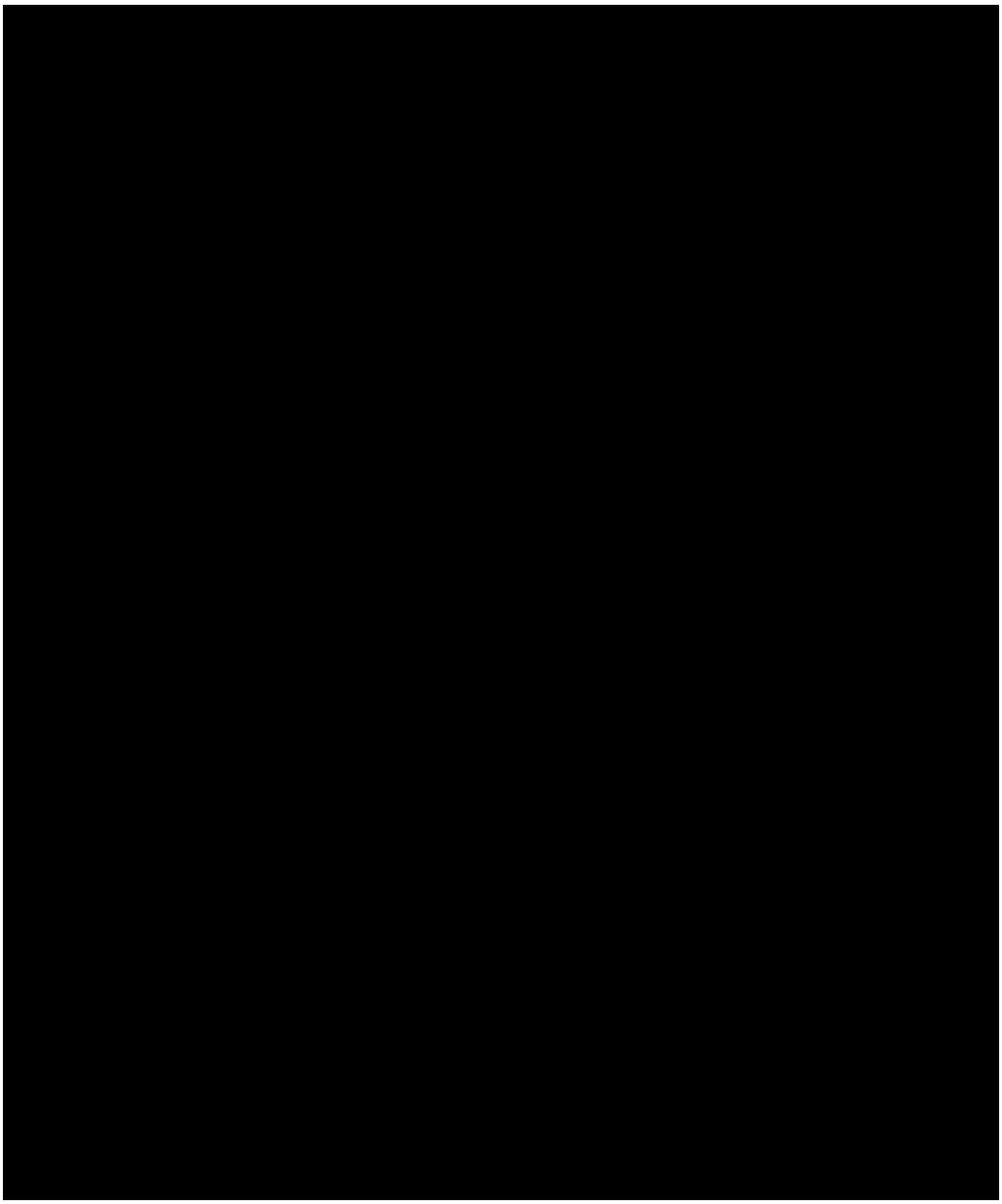


Figure 42 Overall survival estimates for IsaVRd (IMROZ) and DVMP (ALCYONE)



Key: DVMP, daratumumab + bortezomib + melphalan + prednisone; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Table 92: Landmark survival estimates for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Time (years)	% of patients alive (95% CI)						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
IsaVRd							
1	[redacted]						

2	[redacted]						
5	[redacted]						
5.67*	[redacted]						
10	[redacted]						
28	[redacted]						
DVMP							
1	[redacted]						
2	[redacted]						
5	[redacted]						
5.67*	[redacted]						
10	[redacted]						
28	[redacted]						

Key: CI, confidence interval; DVMP, daratumumab + bortezomib + melphalan + prednisone; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Notes: * Maximum IMROZ follow-up.

C.4.5 Conclusion of the OS MAIC for IsaVRd versus DVMP

[redacted]

C.4.6 Data input DRd

[redacted]

Figure 43: Kaplan–Meier plot of overall survival – IsaVRd (IMROZ) vs DRd (MAIA)

[redacted]

Key: DRd, daratumumab + lenalidomide + dexamethasone; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Table 93 Kaplan–Meier summary of overall survival – IsaVRd (IMROZ) vs DRd (MAIA)

Treatment (study)	N/ ESS (% of original sample size)	Events	Median survival (95% CI; months)	Difference in RMST (95% CI; months)*
[redacted]				
[redacted]				
[redacted]				

Key: CI, confidence interval; DRd, daratumumab + lenalidomide + dexamethasone; ESS, effective sample size; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; NE, not evaluable; PH, proportional hazards; RMST, restricted mean survival time.

C.4.7 Proportional hazards assessment

[redacted]

Figure 44 Log-cumulative hazard plot for overall survival – IsaVRd (IMROZ) vs DRd (MAIA)

[redacted]

Key: DRd, daratumumab + lenalidomide + dexamethasone; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Figure 45 Schoenfeld residual plot for overall survival – IsaVRd (IMROZ) vs DRd (MAIA)

Key: DRd, daratumumab + lenalidomide + dexamethasone; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

C.4.8 Constant relative effects

Table 94 shows the constant HRs estimated using Cox PH methods before and after matching.

Table 94 Hazard ratios for overall survival – IsaVRd (IMROZ) vs DRd (MAIA)

Method	HR (95% CI)
HR (95% CI) from unadjusted Cox model	
HR (95% CI) from weighted Cox model	
HR (95% CI) from weighted Cox model (robust SE)	
Bootstrap median HR (95% CI)	
Bootstrap median HR (95% BCa CI)	

Key: BCa, bias-corrected and accelerated; CI, confidence interval; HR, hazard ratio; SE, standard error.

C.4.9 Time-varying relative effects

C.4.9.1 Time-varying HR

Time-varying HRs were estimated based on weighted parametric survival models. This section presents the time-varying HRs; the weighed parametric survival models are presented in the following section.

Landmark estimates of OS HRs for IVRd versus DRd are presented in Table 95 for each of the seven parametric distributions considered, with time-varying HRs displayed graphically in Figure 46.

[redacted]

[redacted]

[redacted]

Table 95 Landmark HRs for overall survival – IsaVRd (IMROZ) vs DRd (MAIA)

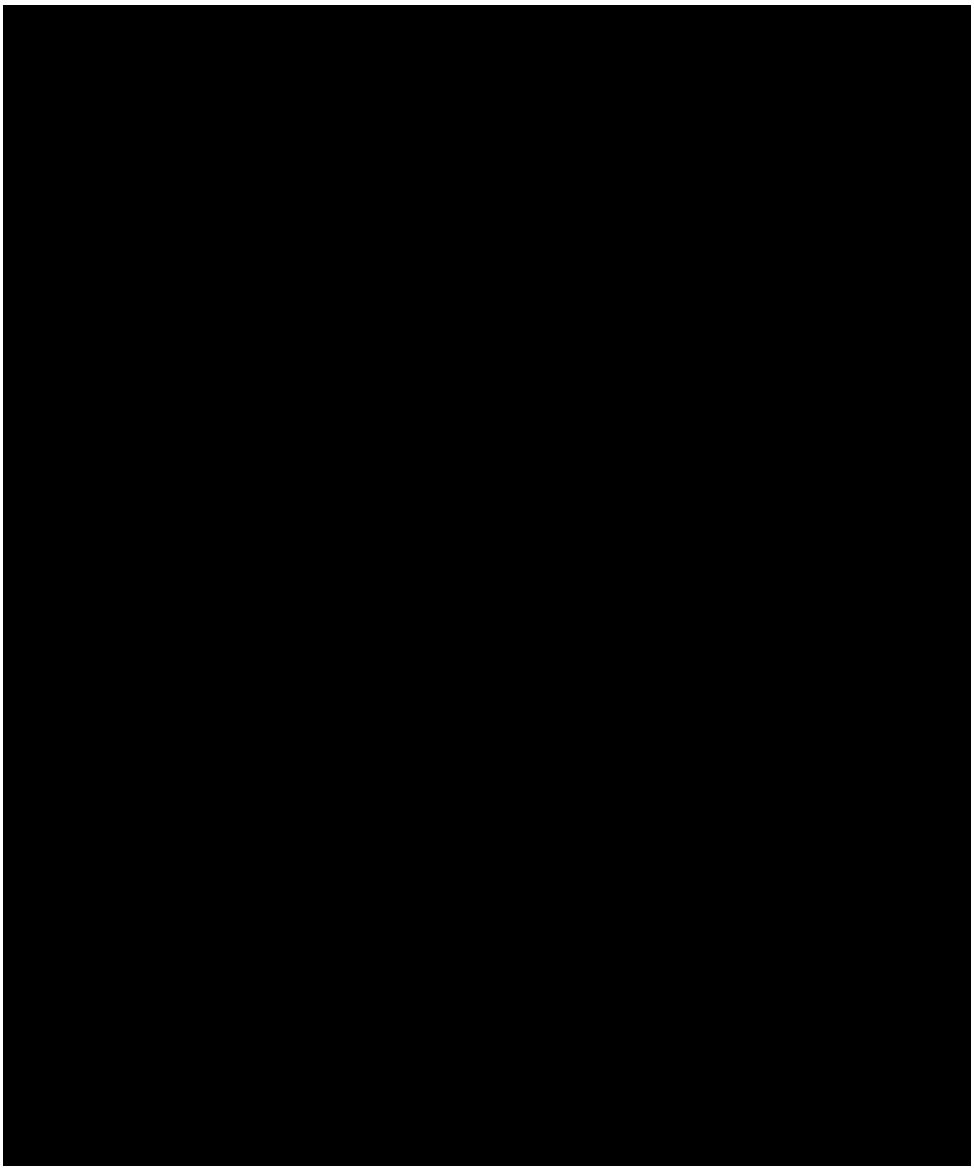
Time (years)	HR (95% CI) for IsaVRd versus DRd						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
1	[redacted]						
2	[redacted]						
5	[redacted]						
5.67*	[redacted]						
10	[redacted]						
28	[redacted]						

Key: CI, confidence interval; DRd, daratumumab + lenalidomide + dexamethasone; HR, hazard ratio; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Notes: HR < 1 indicates reduced hazard of death for IVRd. Blue highlight indicates the preferred distribution for estimating time-varying HRs. For comparison, the constant HR based on the preferred Cox PH method is 0.91 (95% CI: 0.68 to 1.17).

* Maximum IMROZ follow-up.

Figure 46 Time-varying HRs for IsaVRd (IMROZ) versus DRd (MAIA) – overall survival



Key: CI, confidence interval; DRd, daratumumab + lenalidomide + dexamethasone; HR, hazard ratio; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Notes: HR < 1 indicates reduced hazard of death for IVRd.

C.4.9.2 Weighted parametric survival models

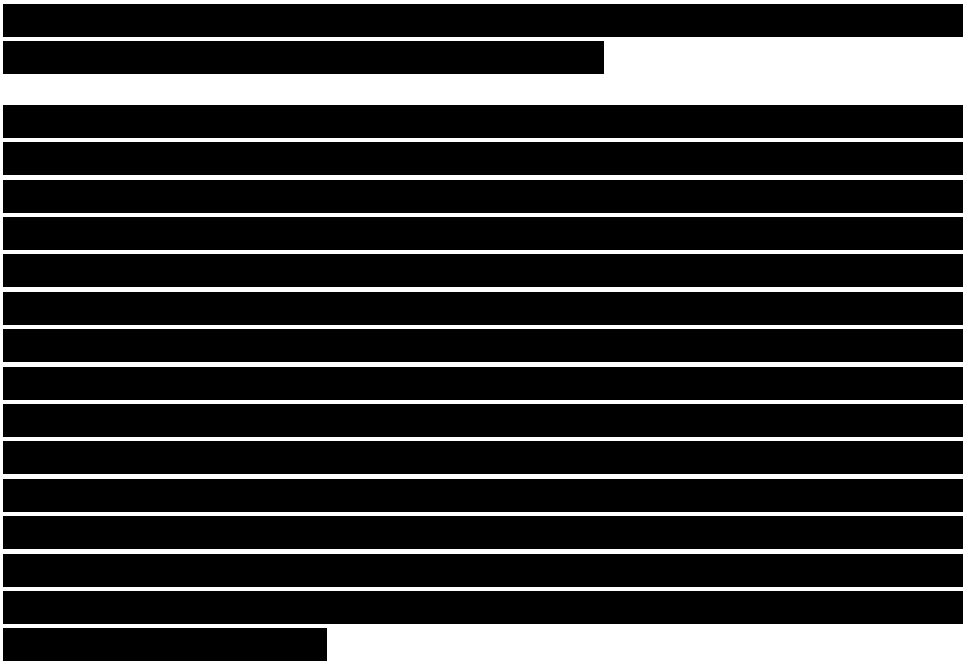
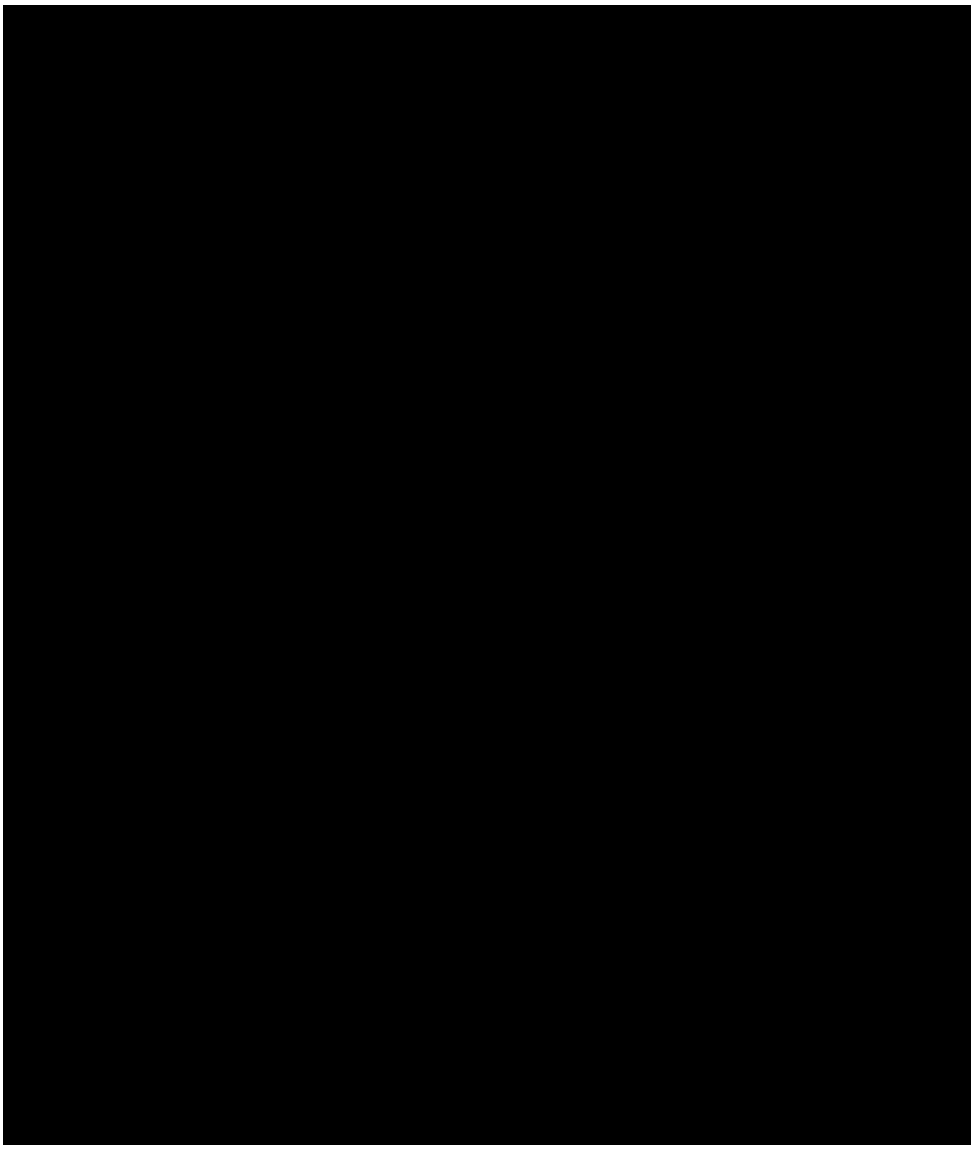


Figure 47 Overall survival estimates for IsaVRd (IMROZ) and DRd (MAIA)



Key: DRd, daratumumab + lenalidomide + dexamethasone; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

Table 96: Landmark survival estimates for overall survival – IsaVRd (IMROZ) vs DRd (MAIA)

Time (years)	% of patients alive (95% CI)						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
IsaVRd							
1	[redacted]						
2	[redacted]						

5	[redacted]						
5.67*	[redacted]						
10	[redacted]						
28	[redacted]						
DRd							
1	[redacted]						
2	[redacted]						
5	[redacted]						
5.67*	[redacted]						
10	[redacted]						
28	[redacted]						

Key: CI, confidence interval; DRd, daratumumab + lenalidomide + dexamethasone; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone.

C.4.10 Conclusion of the OS MAIC for IsaVRd versus DRd

[redacted].

Appendix D. Extrapolation

D.1 Extrapolation of PFS for IsaVRd compared to VRd

D.1.1 Methodology

In line with DMC recommendations and NICE DSU TSD 14, internal and external validation methods were used to assess model fit and facilitate survival curve selection.

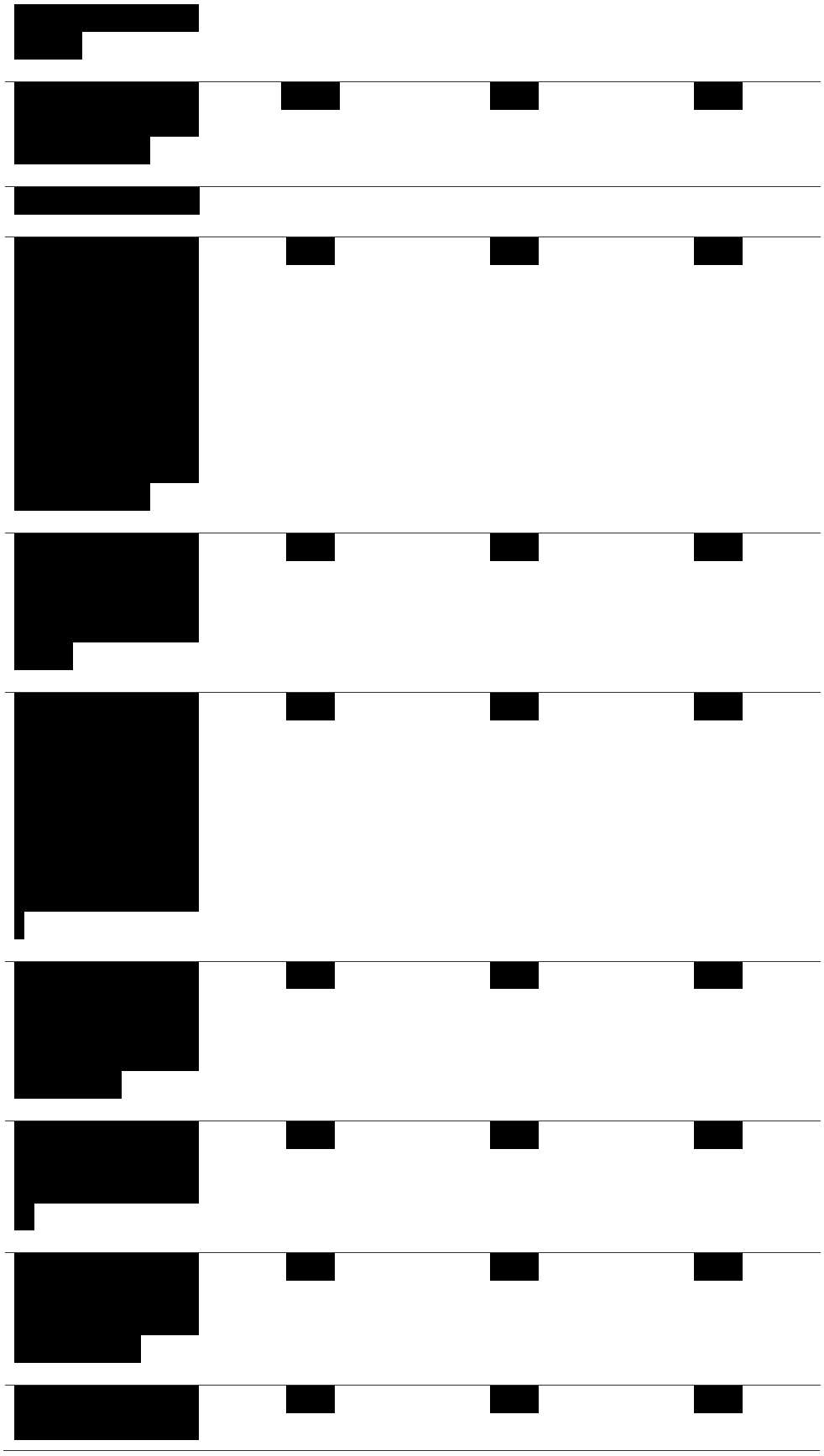
The internal validation methods include model fit statistics (AIC/BIC), examination of log-cumulative hazard plots, and visual inspection, where the survival and hazard functions from parametric models are overlaid with the observed data from IMROZ. External validation incorporated clinical opinion and external data to assess plausibility of extrapolations from alternative parametric models. The external data assessed is the real-world Flatiron Health MM Enhanced DataMart data source where patients not receiving HSCT and receiving 1st line therapy with VRd were inverse propensity for therapy weighted (IPTW) to patients in the VRd arm of IMROZ.

D.1.2 Flatiron real world evidence study

[redacted]

Table 97 Attrition for patients who did not receive HSCT (non-HSCT cohort)

Criteria	N	% of patients	% of previous steps
[redacted]			
[redacted]			
[redacted]			



[redacted]

[redacted]

[redacted]

Table 98 Summary of overlapping patient baseline characteristics across IMROZ and Flatiron

Characteristic	IMROZ – data availability	Flatiron – data availability
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Figure 48 Flow diagram for the derivation of the Flatiron first-line VRd data set

[redacted]

[redacted]

[redacted]

Table 99 Missing data in Flatiron and IMROZ

Characteristic	IMROZ	Flatiron (VRd)
	[redacted]	[redacted]
Age	[redacted]	[redacted]
ECOG	[redacted]	[redacted]
ISS stage	[redacted]	[redacted]
Time from MM diagnosis to treatment	[redacted]	[redacted]
Cytogenetic risk	[redacted]	[redacted]
Chromosomal abnormality 1q21+	[redacted]	[redacted]

Key: 1L, first-line; ECOG; Eastern Cooperative Oncology Group; MM, multiple myeloma; R-ISS, Revised International Staging System; VRd, bortezomib + lenalidomide + dexamethasone.

[redacted]

[redacted]

[redacted]

Table 100 Table of unweighted and weighted characteristics – IMROZ, VRd

Characteristic	IMROZ (VRd)	IMROZ (I + VRd)	IMROZ (pooled)	Flatiron VRd (unfiltered)	Flatiron VRd (filtered)	Flatiron VRd imputed ^ (filtered)	Flatiron VRd weighted * (filtered)
[redacted]							

Figure 49 OS Kaplan–Meier curve – weighted Flatiron VRd results

Key: IVRd, Isatuximab + bortezomib + lenalidomide + dexamethasone; OS, overall survival; VRd, Bortezomib + lenalidomide + dexamethasone.

Table 101 Summary statistics of OS by treatment arm

[redacted]

Figure 50 PFS Kaplan–Meier curve – weighted Flatiron VRd results

Key: IVRd, Isatuximab + bortezomib + lenalidomide + dexamethasone; PFS, progression-free survival; VRd, Bortezomib + lenalidomide + dexamethasone.

Table 102 Summary statistics of PFS by treatment arm

Treatment	Patients	Events	Censors	Median survival, Months (95% CI)	Restricted mean survival, months (SE)
[redacted]					

[redacted]

D.1.3 Data input for extrapolations

[redacted]

Figure 51 Kaplan–Meier plots - PFS

D.1.4 Evaluation of Proportional Hazards

[redacted]

Figure 52 Log-cumulative hazards plot – PFS

[redacted]

Figure 53 Log-cumulative hazard over time for alternative parametric distributions - PFS

[redacted]

Figure 54 Schoenfeld residuals - PFS

D.1.5 Model

Given the lack of statistical evidence against the PH assumption, a proportional hazards approach was used, fitting models that incorporate a term for the relative treatment effect (hazard ratio) based on standard parametric distributions, including exponential, Weibull, Gompertz, gamma, log-normal, log-logistic, and generalized gamma.

D.1.6 Evaluation of statistical fit (AIC and BIC)

Table 103 presents model comparison statistics for the jointly fitted parametric survival models.

Table 103 Model comparison statistics – jointly fitted parametric survival models for PFS

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential				
Gamma				
Generalized gamma				
Gompertz				

Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

D.1.7 Evaluation of visual fit

Figure 55 and Figure 56 show the fitted PFS curves for IsaVRd and VRd based on standard parametric distributions, overlaid with the Kaplan-Meier (KM) data for the follow-up period.

[redacted]

Figure 55 Parametric survival model jointly fitted to IsaVRd up to 6 years - PFS

Figure 56 Parametric survival model jointly fitted to VRd up to 6 years - PFS

D.1.8 Evaluation of hazard functions

[redacted]

[redacted]

[redacted]

Figure 57 Observed and smoothed hazards - PFS

[redacted]

Figure 58 Smoothed hazards with parametric survival models jointly fitted to VRd - PFS

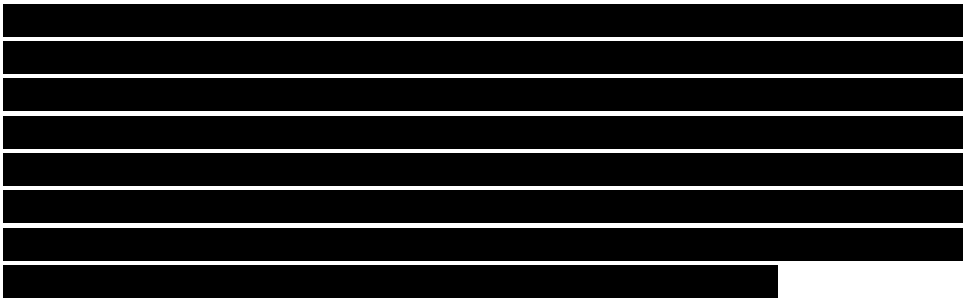


Figure 59 Smoothed hazards with parametric survival models jointly fitted to IsaVRd - PFS

D.1.9 Validation and discussion of extrapolated curves

[redacted]

[redacted]

[redacted]

[redacted]

Table 104 Percentage of patients' overall survival at landmark timepoints for alternative parametric models for VRd and estimates from TA917

Treatment	Estimation	5 years	10 years	15 years
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Key: CI, confidence interval; DRd, daratumumab + lenalidomide + dexamethasone; ITT, intention-to treat; NR, not reported; OS, overall survival; Rd, lenalidomide + dexamethasone; VRd, bortezomib + lenalidomide + dexamethasone.

Figure 60 Parametric survival model fitted separately to IsaVRd and VRd up to 28 years with Flatiron VRd > R - PFS

Figure 61 Parametric survival model jointly fitted to VRd up to 28 years – PFS and OS

IsaVRd

[redacted]

Table 105 Percentage of patient overall survival at landmark timepoints for alternativ parametric models for IsaVRd – IMROZ ITT population

Treat-ment	Estimation	5 years	10 years	15 years
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

Key: IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; NR, not reported; OS, overall survival; Rd, lenalidomide + dexamethasone.

[redacted]

[redacted]

D.1.10 Adjustment of background mortality

The model incorporates background mortality in the Danish population using life tables provided by the DMC.

D.1.11 Adjustment for treatment switching/cross-over

The OS extrapolations are not adjusted for switching/cross-over even though a significant number of patients in the VRd arm switches to the IsaVRd treatment.

D.1.12 Waning effect

The model allows to apply a treatment waning with the possibility of considering a convergence point for a given proportion of patients. In the base case no treatment waning was applied.

D.1.13 Cure-point

No cure-point is considered in the health economic model due to MM being MM is a chronic, progressive condition where continuous treatment is required.

D.2 Extrapolation of OS for IsaVRd compared to VRd

D.2.1 Data input

Extrapolation of the OS was based on the ITT population from IMROZ. Figure 62 presents the Kaplan-Meier (KM) plots for IsaVRd and VRd.

Figure 62 Kaplan–Meier plots - OS

D.2.2 Evaluation of Proportional Hazards

Figure 63 Log-cumulative hazards plot – OS

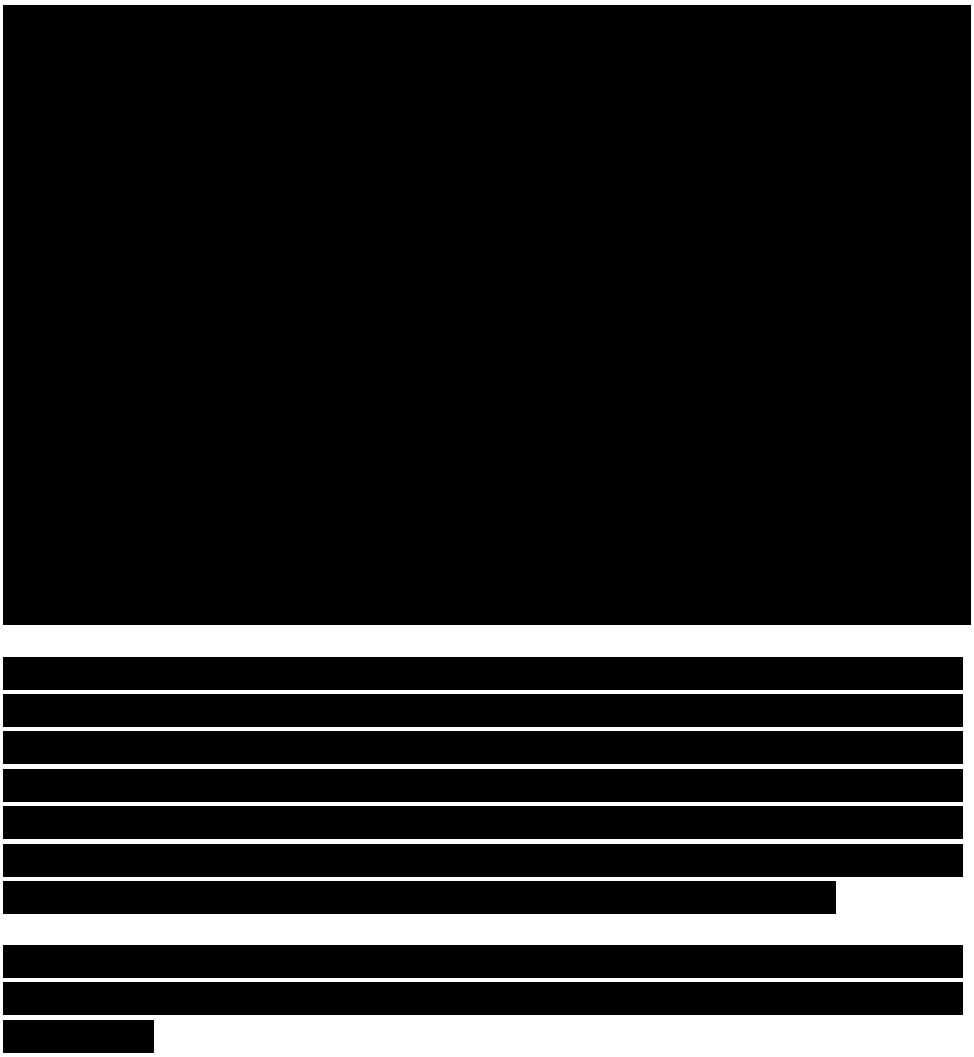


Figure 64 Log-cumulative hazard over time for alternative parametric distributions - OS

Figure 65 Schoenfeld residuals - OS

D.2.3 Model

D.2.4 Evaluation of statistical fit (AIC and BIC)

Table 106 Model comparison statistics – jointly fitted parametric survival models for OS

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential				
Gamma				
Generalized gamma				
Gompertz				
Log-logistic				

Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]

D.2.5 Evaluation of visual fit

[redacted]

Figure 66 Parametric survival model jointly fitted to IsaVRd up to 6 years - OS

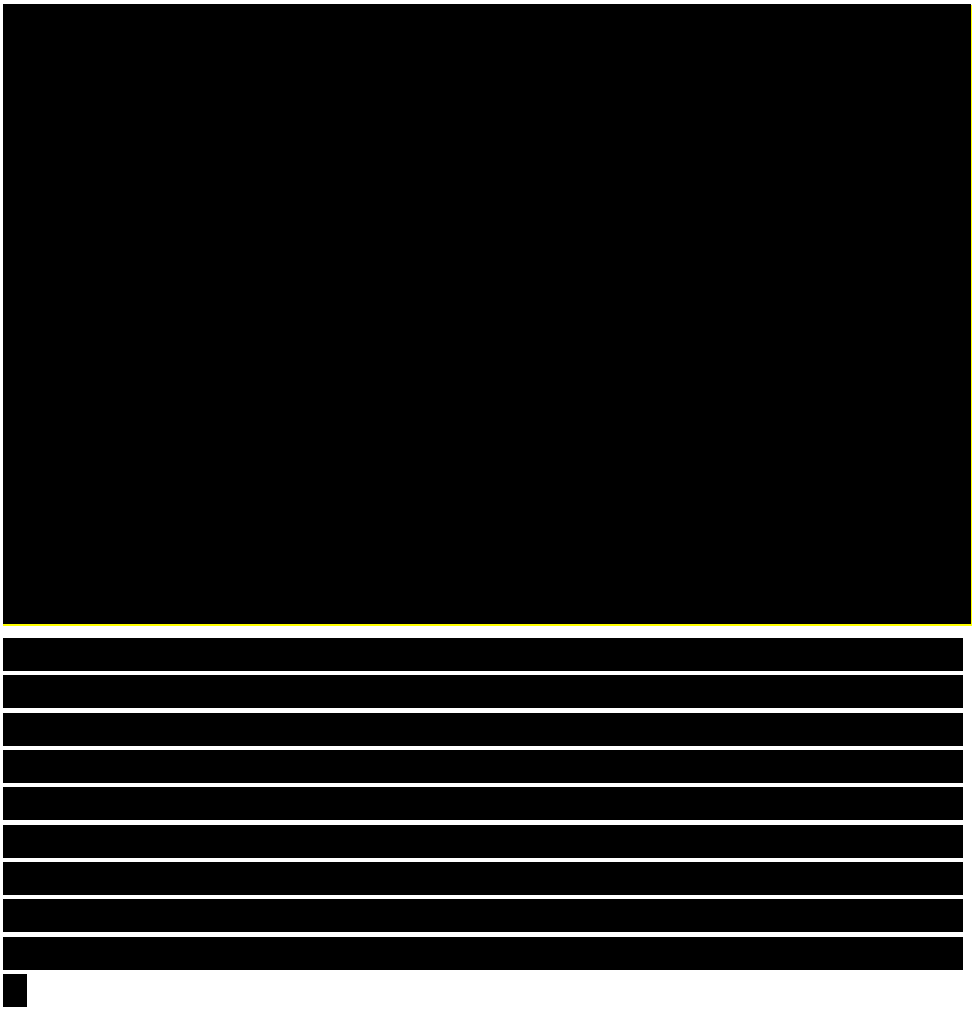
Figure 67 Parametric survival model jointly fitted to VRd up to 6 years - OS

D.2.6 Evaluation of hazard functions

Figure 68 presents the smoothed hazard function for the VRd arm in IMROZ, showing a constant hazard up to 2 years, followed by a gradual increase. While smoothed hazard plots should be interpreted cautiously due to their sensitivity to smoothing parameters, this pattern suggests a monotonically increasing hazard over time. This rules out models assuming a decreasing hazard, such as the log-normal and log-logistic distributions. The exponential model, which assumes a constant hazard, is also unlikely to fit well. The remaining models—including generalized gamma, Gompertz, Weibull, and gamma—can accommodate a monotonically increasing hazard.

Overlaying the parametric model hazards with the smoothed hazard suggests that generalized gamma and Gompertz fit the VRd data particularly well towards the end of follow-up (Figure 68), aligning with the external validation in next section.

Figure 68 Observed and smoothed hazards – OS



[redacted]

Figure 69 Smoothed hazards with parametric survival models jointly fitted to VRd – OS

Figure 70 Smoothed hazards with parametric survival models jointly fitted to IsaVRd - OS

D.2.7 Validation and discussion of extrapolated curves

VRd

[redacted]

[redacted]

[redacted]

Table 107 Percentage of patients' overall survival at landmark timepoints for alternative parametric models for VRd and estimates from TA917 – IMROZ ITT population

Treatment	Estimation	5 years	10 years	15 years
Rd	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
VRd	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

[redacted]

IsaVRd

[redacted]

Table 108 Percentage of patients overall survival at landmark timepoints for alternative parametric models for IsaVRd – IMROZ ITT population

Treat-ment	Estimation	5 years	10 years	15 years
IsaVRd	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

Key: IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; NR, not reported; OS, overall survival; Rd, lenalidomide + dexamethasone.

Figure 71 Parametric survival model fitted separately to IsaVRd and VRd up to 28 years with Flatiron VRd > R - OS

[redacted]

D.2.8 Adjustment of background mortality

The model incorporates background mortality in the Danish population using life tables provided by the DMC.

D.2.9 Adjustment for treatment switching/cross-over

The OS extrapolations are not adjusted for switching/cross-over even though a significant number of patients in the VRd arm switch to the IsaVRd treatment.

D.2.10 Waning effect

The model allows to apply a treatment waning with the possibility of considering a convergence point for a given proportion of patients. In the base case no treatment was applied.

D.2.11 Cure-point

No cure-point is considered in the health economic model due to MM being MM is a chronic, progressive condition where continuous treatment is required.

D.3 Extrapolation of TTD for IsaVRd compared to VRd

D.3.1 Data input

Extrapolation of the TTD was based on the ITT population from IMROZ. Figure 72 presents the Kaplan-Meier (KM) plots for IsaVRd and VRd.

Figure 72 Kaplan–Meier plots - TTD

D.3.2 Evaluation of Proportional Hazards

[redacted]

Figure 73 Log-cumulative hazards plot – TTD

[redacted]

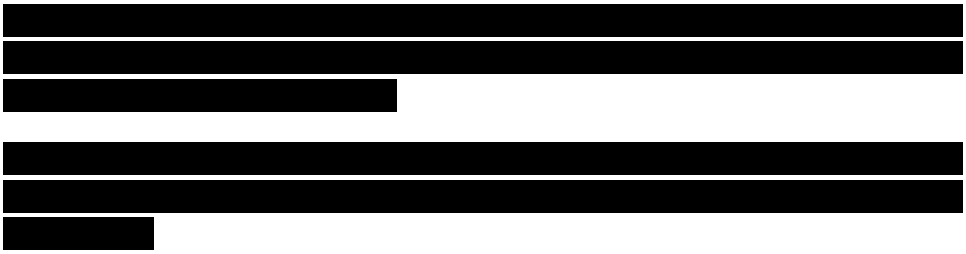


Figure 74 Log-cumulative hazard over time for alternative parametric distributions - TTD

Figure 75 Schoenfeld residuals - TTD

D.3.3 Model

[redacted]

D.3.4 Evaluation of statistical fit (AIC and BIC)

[redacted]

Table 109 Model comparison statistics – jointly fitted parametric survival models for TTD

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]

Weibull	[redacted]	[redacted]	[redacted]	[redacted]

D.3.5 Evaluation of visual fit

[redacted]

Figure 76 Parametric survival model jointly fitted to IsaVRd up to 6 years - TTD

Figure 77 Parametric survival model jointly fitted to VRd up to 6 years - TTD

D.3.6 Evaluation of hazard functions

[redacted]

[redacted]

Figure 78 Observed and smoothed hazards – TTD

Figure 79 Smoothed hazards with parametric survival models jointly fitted to VRd - TTD

[redacted]

Figure 80 Smoothed hazards with parametric survival models jointly fitted to IsaVRd - TTD

D.3.7 Validation and discussion of extrapolated curves

[redacted]

Table 110 Percentage of patients who have not discontinued treatment at landmark timepoints for alternative parametric models for VRd

Time (years)	% Patients who have not discontinued treatment (95% CI)						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CI, confidence interval; ITT, intention-to-treat; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; VRd, bortezomib + lenalidomide + dexamethasone.

Notes: * IMROZ median follow-up was 59.73 months at the data cut-off of 26SEP2023; ** 28 years corresponds to the time horizon of the global cost-effectiveness model.

Figure 81 Parametric survival model fitted separately to IsaVRd and VRd up to 28 years – TTD

[redacted]

Table 111 Percentage of patients who have not discontinued treatment at landmark timepoints for alternative parametric models for IsaVRd

Time (years)	% Patients who have not discontinued treatment (95% CI)						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
[redacted]							

Key: CI, confidence interval; ITT, intention-to-treat; IsaVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; VRd, bortezomib + lenalidomide + dexamethasone.

Notes: * IMROZ median follow-up was 59.73 months at the data cut-off of 26SEP2023; ** 28 years corresponds to the time horizon of the global cost-effectiveness model.

[redacted]

D.3.8 Adjustment of background mortality

The model incorporates background mortality in the Danish population using life tables provided by the DMC.

D.3.9 Adjustment for treatment switching/cross-over

The OS extrapolations are not adjusted for switching/cross-over even though a significant number of patients in the VRd arm switch to the IsaVRd treatment.

D.3.10 Waning effect

The model allows to apply a treatment waning with the possibility of considering a convergence point for a given proportion of patients. In the base case no treatment was applied.

D.3.11 Cure-point

No cure-point is considered in the health economic model due to MM being MM is a chronic, progressive condition where continuous treatment is required.

D.4 Extrapolation of PFS for IsaVRd compared to DVMP

D.4.1 Data input

The extrapolation of progression-free survival (PFS) for IsaVRd versus DVMP was based on a Matching-Adjusted Indirect Comparison (MAIC) using data from the IMROZ and ALCYONE trials. The Kaplan-Meier (KM) survival estimates were derived from the adjusted IsaVRd population (IMROZ) and the DVMP population (ALCYONE).

Figure 82 Kaplan–Meier plots of PFS - IsaVRd (IMROZ) vs. DVMP (ALCYONE)

D.4.2 Evaluation of Proportional Hazards

[redacted]

Figure 83 Log-cumulative hazard plot for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Figure 84 Schoenfeld residual plot for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

D.4.3 Model

[redacted]

1. [redacted]

2. [redacted]

3. [redacted]

[redacted]

D.4.5 Evaluation of statistical fit (AIC and BIC)

Time-Varying HR Model

[redacted]

Table 112 Model comparison statistics – IsaVRd (IMROZ) vs DVMP (ALCYONE) – PFS

Distribution	AIC	AIC rank	BIC	BIC rank
[redacted]				
[redacted]				
[redacted]				

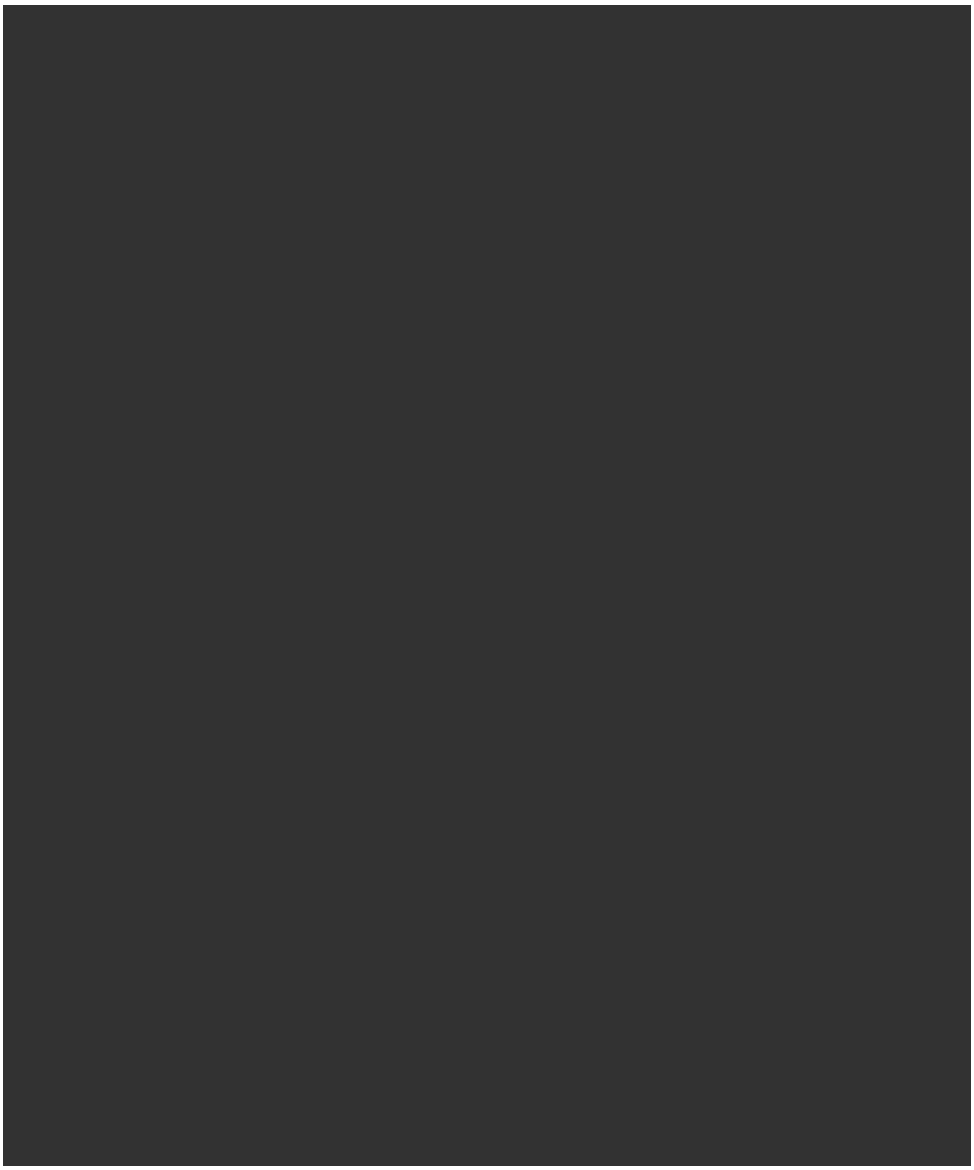
[redacted]

D.4.6 Evaluation of visual fit

Time-Varying HR Model

[redacted]

Figure 85 Weighted parametric survival models estimates for IsaVRd (IMROZ) and DVMP (ALCYONE) - PFS



[redacted]

D.4.7 Validation and discussion of extrapolated curves

D.4.6.1 Proportional Hazards Model

[redacted]

[redacted]

[redacted]

[redacted]

Figure 86 Survival models estimates for IsaVRd (IMROZ) and DVMP (ALCYONE) based on [redacted] - PFS

[redacted]

D.4.6.2 Time-Varying HR Model

To determine which of the seven parametric survival distributions used to estimate time-varying HRs was the most appropriate, consideration was given to the survival extrapolation of the IMROZ intention-to-treat (ITT) population (see Appendix D.1.).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 113 Landmark survival estimates for progression-free survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Time (years)	% of patients progression-free (95% CI)						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
IsaVRd							
1	[redacted]						
2	[redacted]						

5	[redacted]						
5.67*	[redacted]						
10	[redacted]						
28	[redacted]						
DVMP							
1	[redacted]						
2	[redacted]						
5	[redacted]						
5.67*	[redacted]						
10	[redacted]						
28	[redacted]						

* Maximum IMROZ follow-up.

D.4.8 Adjustment of background mortality

The model incorporates background mortality in the Danish population using life tables provided by the DMC.

D.4.9 Adjustment for treatment switching/cross-over

The OS extrapolations are not adjusted for switching/cross-over even though a significant number of patients in the VRd arm switch to the IsaVRd treatment.

D.4.10 Waning effect

The model allows to apply a treatment waning with the possibility of considering a convergence point for a given proportion of patients. In the base case no treatment was applied.

D.4.11 Cure-point

No cure-point is considered in the health economic model due to MM being MM is a chronic, progressive condition where continuous treatment is required.

D.5 Extrapolation of PFS for IsaVRd compared to DRd

D.5.1 Data input

The extrapolation of progression-free survival (PFS) for IsaVRd versus DRd was based on a Matching-Adjusted Indirect Comparison (MAIC) using data from the IMROZ and MAIA trials. The Kaplan-Meier (KM) survival estimates were derived from the adjusted IsaVRd population (IMROZ) and the DRd population (MAIA).

[redacted]

Figure 87 Kaplan–Meier plots of PFS - IsaVRd (IMROZ) vs. DRd (MAIA)

D.5.2 Evaluation of Proportional Hazards

[redacted]

[redacted]

Figure 88 Log-cumulative hazard plot for progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA)

Figure 89 Schoenfeld residual plot for progression-free survival – IsaVRd (IMROZ) vs DRd (MAIA)

D.5.3 Model

[redacted]

4. [redacted]

5. [redacted]

6. [redacted]

[redacted]

D.5.5 Evaluation of statistical fit (AIC and BIC)

Time-Varying HR Model

[redacted]

Table 114 Model comparison statistics – IsaVRd (IMROZ) vs. DRd (MAIA) - PFS

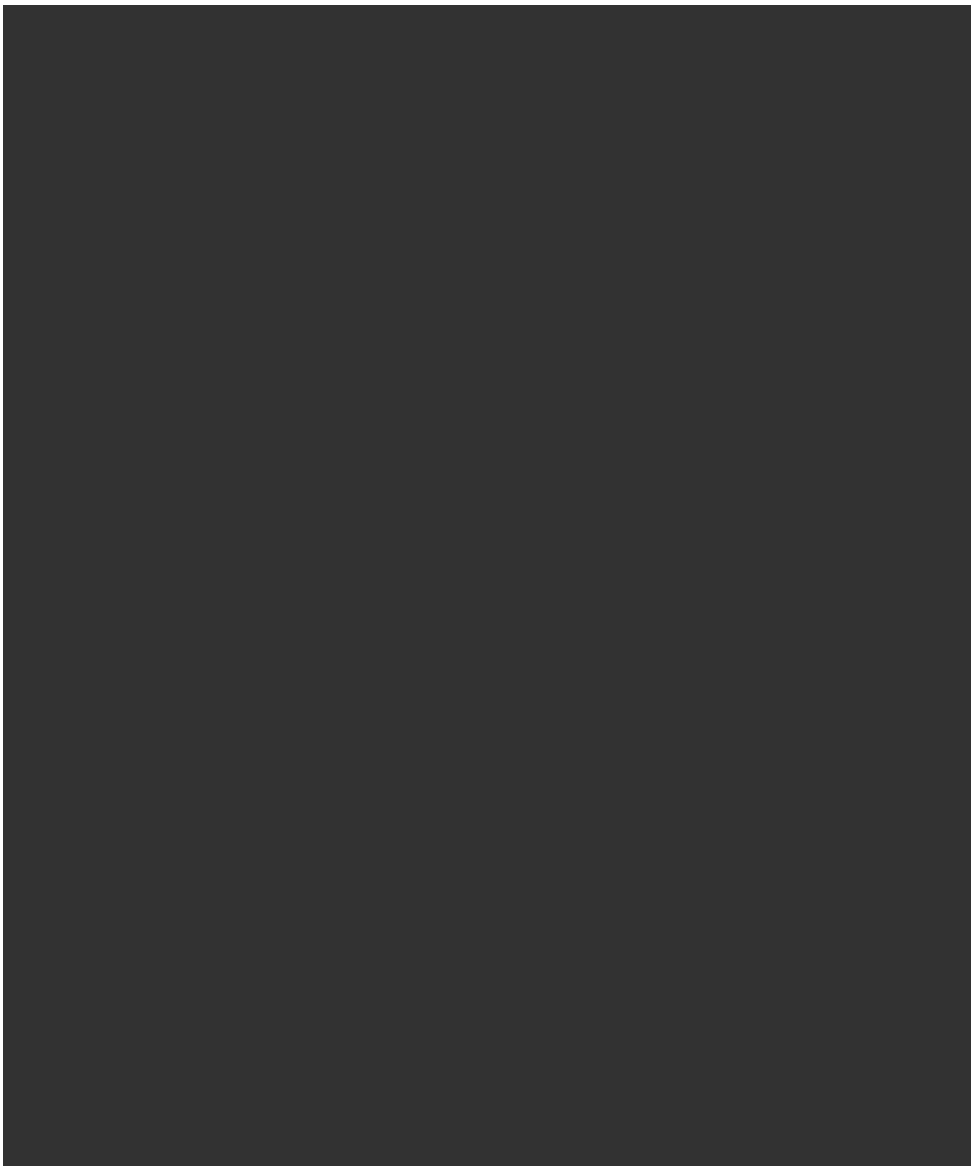
Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]

D.5.6 Evaluation of visual fit

Time-Varying HR Model

[redacted]

Figure 90 Weighted parametric survival models estimates for IsaVRd (IMROZ) and DRd (MAIA) - PFS



[redacted]

D.5.7 Validation and discussion of extrapolated curves

D.5.6.1 Proportional Hazards Model

A proportional hazards (PH) approach was selected as the base case to ensure consistency in the extrapolation of PFS.

[redacted]

[redacted]

[redacted]

[redacted]

Figure 91 Survival model estimates for IsaVRd (IMROZ) and DRd (MAIA) based [redacted] - PFS

[redacted]

D.5.6.2 Time-Varying HR Model

To determine which of the seven parametric survival distributions used to estimate time-varying HRs was the most appropriate, consideration was given to the survival extrapolation of the IMROZ intention-to-treat (ITT) population (see Appendix D.1.).

To ensure methodological consistency and comparability, the same parametric survival model should be applied across all treatment arms. Since IsaVRd and VRd were evaluated within the same clinical trial (IMROZ), it would be inappropriate to fit different types of survival models to each arm without strong justification.

[redacted]

[redacted]

Table 115 Landmark survival estimates for progresson free survival – IsaVRd (IMROZ) vs. DRd (MAIA)

Time (years)	% of patients progression-free (95% CI)						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
IsaVRd							
1	[redacted]						
2	[redacted]						
5	[redacted]						
5.67*	[redacted]						

10	[redacted]						
28	[redacted]						
DRd							
1	[redacted]						
2	[redacted]						
5	[redacted]						
5.67*	[redacted]						
10	[redacted]						
28	[redacted]						

Key: CI, confidence interval; DRd, daratumumab + lenalidomide + dexamethasone; IVRd, isatuximab + bortezomib + lenalidomide + dexamethasone; PFS, progression-free survival.

*Maximum IMROZ follow-up

D.5.8 Adjustment of background mortality

The model incorporates background mortality in the Danish population using life tables provided by the DMC.

D.5.9 Adjustment for treatment switching/cross-over

The OS extrapolations are not adjusted for switching/cross-over even though a significant number of patients in the VRd arm switch to the IsaVRd treatment.

D.5.10 Waning effect

The model allows to apply a treatment waning with the possibility of considering a convergence point for a given proportion of patients. In the base case no treatment waning was applied.

D.5.11 Cure-point

No cure-point is considered in the health economic model due to MM being MM is a chronic, progressive condition where continuous treatment is required.

D.6 Extrapolation of OS for IsaVRd compared to DVMP

D.6.1 Data input

The extrapolation overall survival (OS) for IsaVRd versus DVMP was based on a Matching-Adjusted Indirect Comparison (MAIC) using data from the IMROZ and ALCYONE trials. The Kaplan-Meier (KM) survival estimates were derived from the adjusted IsaVRd population (IMROZ) and the DVMP population (ALCYONE).

[redacted]

Figure 92 Kaplan–Meier plots of OS - IsaVRd (IMROZ) vs. DVMP (ALCYONE)

D.6.2 Evaluation of Proportional Hazards

[redacted]

Figure 93 Log-cumulative hazard plot for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Figure 94 Schoenfeld residual plot for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

D.6.3 Model

[redacted]

[redacted]

1. [redacted]

2. [redacted]

3. [redacted]

[redacted]

D.6.5 Evaluation of statistical fit (AIC and BIC)

D.6.4.1 Time-Varying HR Model

[redacted]

Table 116 Model comparison statistics – IsaVRd (IMROZ) vs DVMP (ALCYONE) – OS

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]

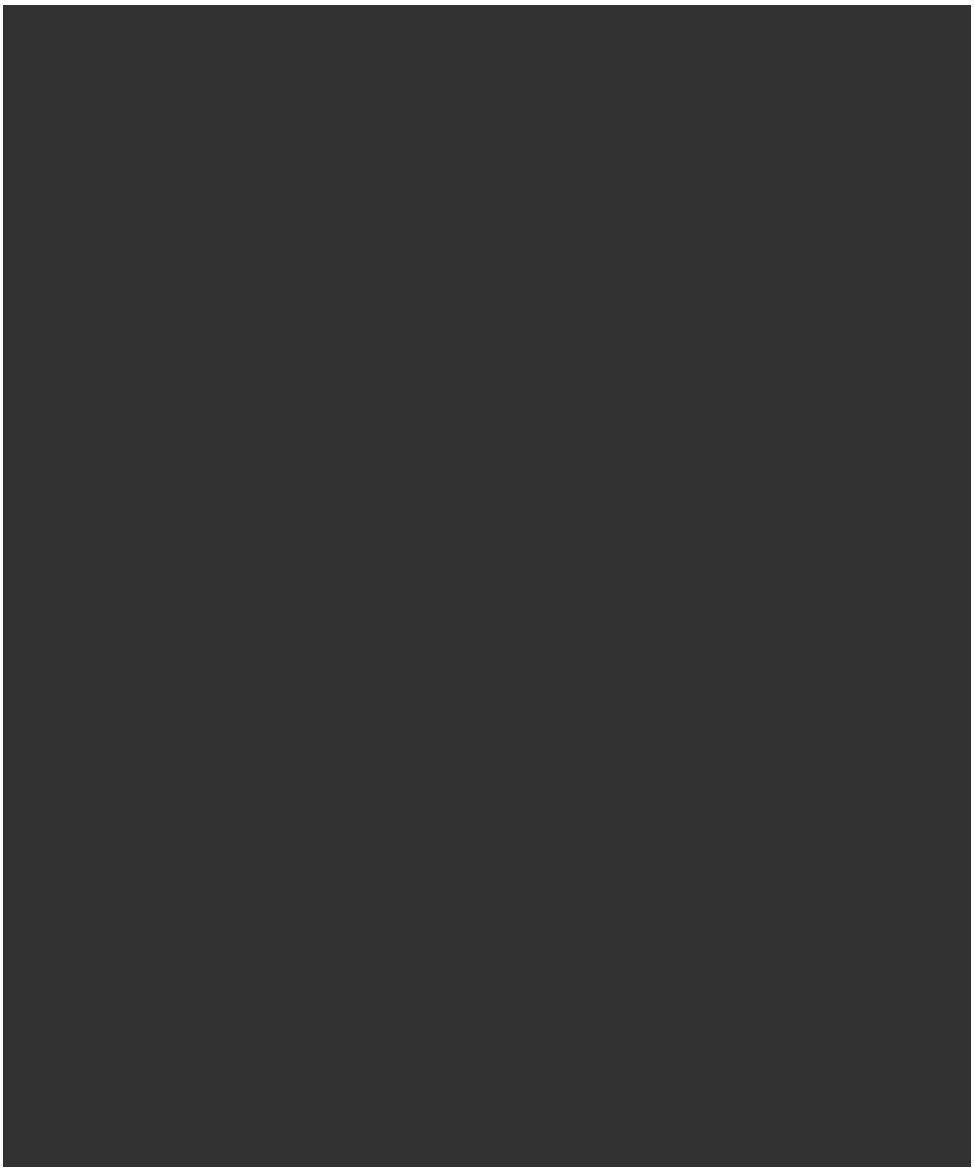
Gompertz	[redacted]		[redacted]	
Log-logistic	[redacted]		[redacted]	
Log-normal	[redacted]		[redacted]	
Weibull	[redacted]		[redacted]	
Gamma	[redacted]		[redacted]	

D.6.6 Evaluation of visual fit

D.6.5.1 Time-Varying HR Model

Figure 95 The fitted parametric survival models overlaid with the Kaplan–Meier curves for weighted IsaVRd and DVMP. The models provide a good visual fit to both the IsaVRd and DVMP Kaplan–Meier curves.

Figure 95 Overall survival estimates for IsaVRd (IMROZ) and DVMP (ALCYONE)



[redacted]

D.6.7 Validation and discussion of extrapolated curves

D.6.6.1 Proportional Hazards Model

[redacted]

[redacted]

[redacted]

[redacted]

Figure 96 Survival model estimates for IsaVRd (IMROZ) and DVMP (ALCYONE) based [redacted] - OS

D.6.6.2 Time-Varying HR Model

To determine which of the seven parametric survival distributions used to estimate time-varying HRs was the most appropriate, consideration was given to the survival extrapolation of the IMROZ intention-to-treat (ITT) population (see Appendix D.1.).

To ensure methodological consistency and comparability, the same parametric survival model should be applied across all treatment arms. Since IsaVRd and VRd were evaluated within the same clinical trial (IMROZ), it would be inappropriate to fit different types of survival models to each arm without strong justification.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 117 Landmark survival estimates for overall survival – IsaVRd (IMROZ) vs DVMP (ALCYONE)

Time (years)	% of patients alive (95% CI)						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
IsaVRd							
1	[redacted]						
2	[redacted]						
5	[redacted]						
5.67*	[redacted]						
10	[redacted]						

28	[redacted]
DVMP	
1	[redacted]
2	[redacted]
5	[redacted]
5.67*	[redacted]
10	[redacted]
28	[redacted]

D.6.8 Adjustment of background mortality

The model incorporates background mortality in the Danish population using life tables provided by the DMC.

D.6.9 Adjustment for treatment switching/cross-over

The OS extrapolations are not adjusted for switching/cross-over even though a significant number of patients in the VRd arm switch to the IsaVRd treatment.

D.6.10 Waning effect

The model allows to apply a treatment waning with the possibility of considering a convergence point for a given proportion of patients. In the base case no treatment waning was applied.

D.6.11 Cure-point

No cure-point is considered in the health economic model due to MM being MM is a chronic, progressive condition where continuous treatment is required.

D.7 Extrapolation of OS for IsaVRd compared to DRd

D.7.1 Data input

The extrapolation overall survival (OS) for IsaVRd versus DRd was based on a Matching-Adjusted Indirect Comparison (MAIC) using data from the IMROZ and MAIA trials. The Kaplan-Meier (KM) survival estimates were derived from the adjusted IsaVRd population (IMROZ) and the DRd population (MAIA).

[redacted]

Figure 97 Kaplan–Meier plots of OS - IsaVRd (IMROZ) vs. DRd (MAIA)

D.7.2 Evaluation of Proportional Hazards

[redacted]

Figure 98 Log-cumulative hazard plot for overall survival – IsaVRd (IMROZ) vs DRd (MAIA)

Figure 99 Schoenfeld residual plot for overall survival – IsaVRd (IMROZ) vs DRd (MAIA)

D.7.3 Model

[redacted]

4. [redacted]

5. [redacted]

6. [redacted]

[redacted]

D.7.5 Evaluation of statistical fit (AIC and BIC)

D.7.4.1 Time-Varying HR Model

[redacted]

Table 118 Model comparison statistics – IsaVRd (IMROZ) vs DRd (MAIA) – OS

Distribution	AIC	AIC rank	BIC	BIC rank
Exponential	[redacted]	[redacted]	[redacted]	[redacted]
Generalized gamma	[redacted]	[redacted]	[redacted]	[redacted]

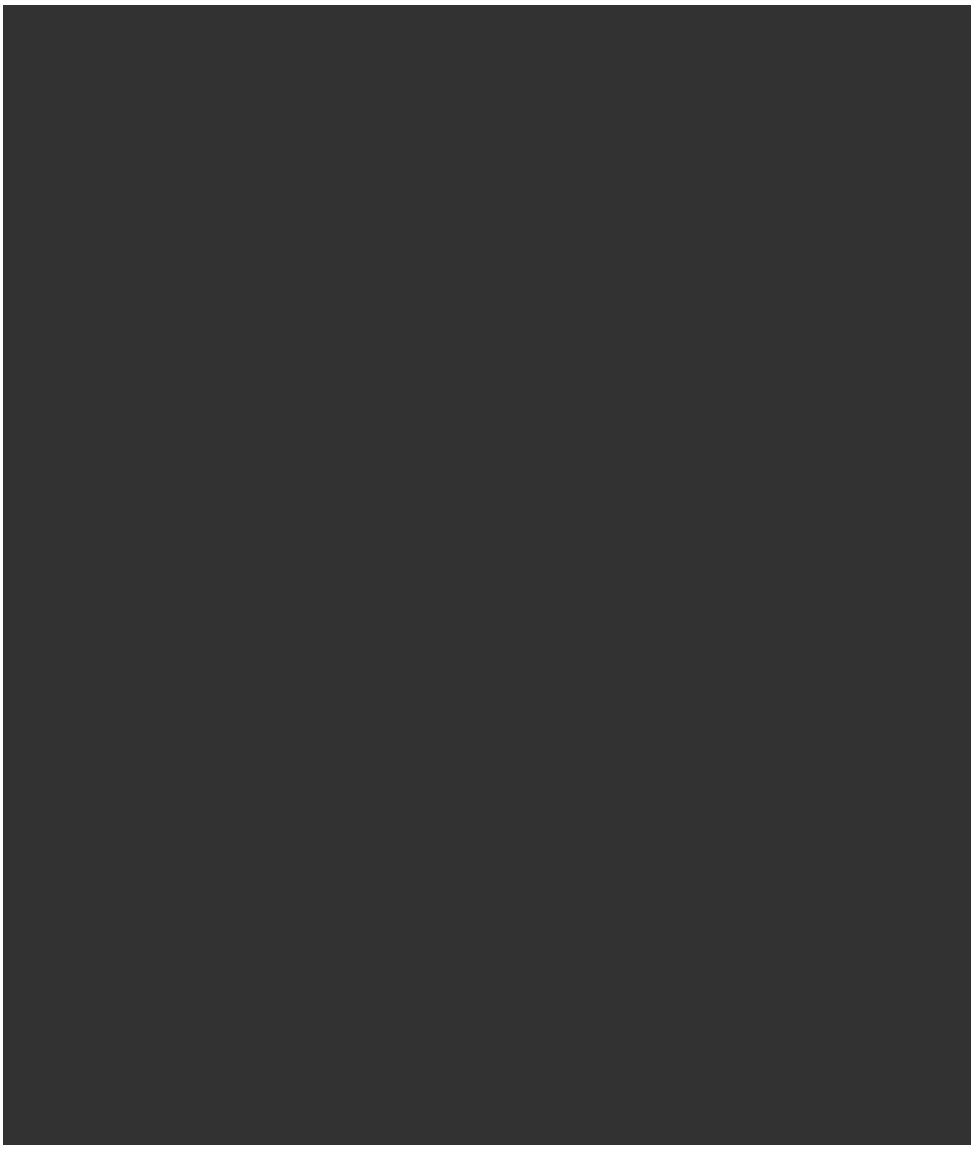
Gompertz	[redacted]		[redacted]	
Log-logistic	[redacted]		[redacted]	
Log-normal	[redacted]		[redacted]	
Weibull	[redacted]		[redacted]	
Gamma	[redacted]		[redacted]	

D.7.6 Evaluation of visual fit

D.7.5.1 Time-Varying HR Model

[redacted]

Figure 100 Overall survival estimates for IsaVRd (IMROZ) and DRd (MAIA)



[redacted]

D.7.7 Validation and discussion of extrapolated curves

D.7.6.1 Proportional Hazards Model

[redacted]

[redacted]

[redacted]

[redacted]

Figure 101 Survival model estimates for IsaVRd (IMROZ) and DRd (MAIA) based [redacted] - OS

D.7.6.2 Time-Varying HR Model

To determine which of the seven parametric survival distributions used to estimate time-varying HRs was the most appropriate, consideration was given to the survival extrapolation of the IMROZ intention-to-treat (ITT) population (see Appendix D.1.).

To ensure methodological consistency and comparability, the same parametric survival model should be applied across all treatment arms. Since IsaVRd and VRd were evaluated within the same clinical trial (IMROZ), it would be inappropriate to fit different types of survival models to each arm without strong justification.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 119 Landmark survival estimates for overall survival – IsaVRd (IMROZ) vs DRd (MAIA)

Time (years)	% of patients alive (95% CI)						
	Exponential	Gamma	Generalized gamma	Gompertz	Log-logistic	Log-normal	Weibull
IsaVRd							
1	[redacted]						
2	[redacted]						
5	[redacted]						

5.67*	[redacted]
10	[redacted]
28	[redacted]
DRd	
1	[redacted]
2	[redacted]
5	[redacted]
5.67*	[redacted]
10	[redacted]
28	[redacted]

D.7.8 Adjustment of background mortality

The model incorporates background mortality in the Danish population using life tables provided by the DMC.

D.7.9 Adjustment for treatment switching/cross-over

The OS extrapolations are not adjusted for switching/cross-over even though a significant number of patients in the VRd arm switch to the IsaVRd treatment.

D.7.10 Waning effect

The model allows to apply a treatment waning with the possibility of considering a convergence point for a given proportion of patients. In the base case no treatment waning was applied.

D.7.11 Cure-point

No cure-point is considered in the health economic model due to MM being MM is a chronic, progressive condition where continuous treatment is required.

D.8 Extrapolation of TTD for DVMP and DRd

For DVMP and DRd, which are not included in the IMROZ trial, the time to discontinuation (TTD) cannot be extrapolated using MAIC as TTD is not reported as an outcome in clinical trials and is redacted heavily in HTA submissions (due to its use in regimen pricing analyses). Therefore, alternative sources to calculate TTD are needed for comparators included in the model that were not evaluated in IMROZ.

This is done by leveraging the evidence on median duration of treatment (DoT), which is more often reported in pivotal trial publications than TTD. Of note, both DoT and TTD are comparable metrics used in healthcare to evaluate how long patients continue a specific treatment before discontinuing it. Both metrics are valuable for understanding patient adherence and treatment persistence. However, the key difference between the two measures is that TTD is a time to event outcome while median DoT is not, and therefore DoT does not consider censoring. In the absence of TTD the median DoT could be considered a suitable proxy for median TTD so long as the trial follow-up is longer than the median TTD and there is little censoring.

The ratio between the reported median PFS and the median DoT is used to calculate a TTD curve based on the PFS curve for that comparator. For an exponential distribution defined by a single parameter, the ratio of the median TTD in proportion to the median PFS equals the TTD vs PFS hazard ratio (if an exponential distribution is fitted to the mPFS and mDoT the parameter will, apart from a constant, be the inverse of the median. Hence if we take the ratio of these, the constant cancels, and we get the hazard ratio which is also the ratio of medians). This logic allows for use of the median DoT and median PFS as a HR applied to PFS to calculate TTD.

This approach can be applied to all treatments regardless of whether they treat to progression or not. This approach requires the following assumptions:

- The mDoT is a good proxy of mTTD
- The use of median DoT and median PFS as an HR applied to PFS to calculate TTD, despite not corresponding to an exponential distribution, still provides a good approximation to TTD (note that the base case distribution for PFS is gamma distribution)

The values for median PFS and median DoT are presented in Table 120 together with the resulting HR which are used to calculate TTD.

Table 120 Median PFS and median DoT used for calculation of TTD

Treatment	mPFS	mDoT	HR: mDoT vs. mPFS
IVRd	[redacted]	[redacted]	[redacted]
VRd	[redacted]	[redacted]	[redacted]
DVMP	[redacted]	[redacted]	[redacted]

Treatment	mPFS	mDoT	HR: mDoT vs. mPFS
DRd	[redacted]	[redacted]	[redacted]

The TTD-curves for DVMP and DRd used in the model is presented in Figure 102 and Figure 103.

Figure 102 Estimation of TTD curve for DVMP

Figure 103 Estimation of TTD curve for DRd

Appendix E. Serious adverse events

Figure 104 List of serious adverse events in≥2% of patients in any group by primary system organ class and preferred terms.

	Isa-VRd (n=263)	VRd (n=181)
Any Class	186 (70.7)	122 (67.4)
Infections and infestations	**116 (44.1)**	**66 (36.5)**
Pneumonia	50 (19.0)	23 (12.7)
COVID-19 pneumonia	21 (8.0)	7 (3.9)
Bronchitis	7 (2.7)	3 (1.7)
Sepsis	6 (2.3)	6 (3.3)
Urinary tract infection	5 (1.9)	5 (2.8)
Nervous system disorders	24 (9.1)	23 (12.7)
Syncope	6 (2.3)	6 (3.3)
Transient ischemic attack	3 (1.1)	5 (2.8)
Eye disorders	7 (2.7)	3 (1.7)
Cataract	6 (2.3)	2 (1.1)
Cardiac disorders	20 (7.6)	18 (9.9)
Atrial fibrillation	8 (3.0)	8 (4.4)
Cardiac failure	1 (0.4)	6 (3.3)
Respiratory, thoracic, and mediastinal disorders	20 (7.6)	15 (8.3)
Pulmonary embolism	11 (4.2)	6 (3.3)
Gastrointestinal disorders	25 (9.5)	17 (9.4)
Diarrhea	5 (1.9)	9 (5.0)

Musculoskeletal and connective tissue disorders	16 (6.1)	12 (6.6)
Pathological fracture	3 (1.1)	7 (3.9)
Renal and urinary disorders	6 (2.3)	7 (3.9)
Acute kidney injury	4 (1.5)	4 (2.2)
General disorders and administration site conditions	21 (8.0)	14
Pyrexia	6 (2.3)	3 (1.7)
General physical health deterioration	1 (0.4)	4 (2.2)
Injury, poisoning and procedural complications	23 (8.7)	13 (7.2)
Femur fracture	6 (2.3)	1 (0.6)

Appendix F. Health-related quality of life

In IMROZ trial two additional HRQoL instruments other EQ-5D-5L than were administered. This Appendix presents the results.

Table 121 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	IMROZ	Assess clinical effectiveness in terms of HRQoL improvements and deriving utilities
EORTC QLQ-C30	IMROZ	Assess the clinical effectiveness in terms of HRQoL improvements
EORTC QLQ-MY20	IMROZ	Assess the clinical effectiveness in terms of HRQoL improvements

F.1 Presentation of the health-related quality of life (EORTC QLQ-C30)

F.1.1 Study design and measuring instrument

In the IMROZ trial, the EORTC QLQ-C30 questionnaire was administered to patients to measure HRQoL.

The EORTC QLQ-C30 instrument [73] is a generic questionnaire consisting of 30 items developed to assess symptoms and functioning of cancer patients. The instrument yields a global health status/QoL scale, five functional scales (Physical functioning [PF], Role functioning [RF], Cognitive functioning [CF], Emotional functioning [EF], and Social functioning [SF]), three symptom scales (Fatigue [FA], Pain [PA], and Nausea/Vomiting [NV]) and six additional single items (Dyspnea [DY], Insomnia [SL], Appetite Loss [AP], Constipation [CO], Diarrhea [DI], and Financial Difficulties [FI]) as symptoms commonly reported by cancer patients and the perceived financial impact of the disease.

The first 5 items of the C30 assesses cancer patients' activities in general while items 6-30 assess cancer patients' activities during the past week.

F.1.2 Data collection

Please see section 10.1.2.

Table 122 presents information on missing data and completion for a selected number of time points (every 10th cycle, EOfollow-up). For missing data imputation, missing data were imputed latently by MMRM based on missing at random assumption (the MMRM model is described in section 10.2.1).

Table 122 Pattern of missing data and completion - EORTC QLQ-C30

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
C10D1	[redacted]	[redacted]	[redacted]	[redacted]
C20D1	[redacted]	[redacted]	[redacted]	[redacted]
C30D1	[redacted]	[redacted]	[redacted]	[redacted]
C40D1	[redacted]	[redacted]	[redacted]	[redacted]
C50D1	[redacted]	[redacted]	[redacted]	[redacted]
C60D1	[redacted]	[redacted]	[redacted]	[redacted]
C70D1	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]
90 day follow up	[redacted]	[redacted]	[redacted]	[redacted]

Source: Sanofi data on file

F.1.3 HRQoL results EORTC QLQ-C30

[redacted]

F.1.4 HRQoL results EORTC QLQ-C30 - GHS/QoL and functioning scores

[redacted]

Figure 105 Forest plot of MMRM overall estimate of change from baseline in the EORTC QLQ-C30 GHS/QoL and functioning scores - ITT

Source: Sanofi, Data on file

F.1.5 HRQoL results EORTC QLQ-C30 - Symptom Domains

[redacted]

Figure 106 Forest plot of MMRM overall estimate of change from baseline in EORTC QLQ-C30 symptom scores - ITT

[redacted]

F.2 Presentation of the health-related quality of life (EORTC QLQ-MY20)

F.2.1 Study design and measuring instrument

In the IMROZ trial, the EORTC QLQ-MY20 questionnaire was administered to patients to measure HRQoL.

The EORTC QLQ-MY20 is to be used in conjunction with the EORTC QLQ-C30 to assess symptoms and side effects due to the treatment or the disease which impact HRQoL in patients with MM [33]. This instrument contains 20 items in 4 independent subscales covering 2 functional domains (future perspective and body image) and 2 symptom scales (Disease symptoms and side effects of treatment). As with the QLQ-C30, QLQ-MY20 domain scores are averaged and transformed linearly to a score ranging from 0-100. Higher scores for Disease symptoms and side effects of treatment indicate more symptoms and side effects and lower HRQoL, whereas a high score for future perspective and body image represents better outcomes.

F.2.2 Data collection

Please see section 10.1.2

Table 123 presents information on missing data and completion for a selected number of time points (every 10th cycle, EOT and follow-up). For missing data imputation, missing data were imputed latently by MMRM based on missing at random assumption (the MMRM model is described in section 10.2.1).

Table 123 Pattern of missing data and completion - EORTC QLQ-MY20

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
C10D1	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
C20D1	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
C30D1	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
C40D1	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
C50D1	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
C60D1	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
C70D1	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
End of treatment	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
90 day follow up	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

F.2.3 HRQoL results - EORTC QLQ-MY20

[redacted]

[redacted]

[redacted]

[redacted]

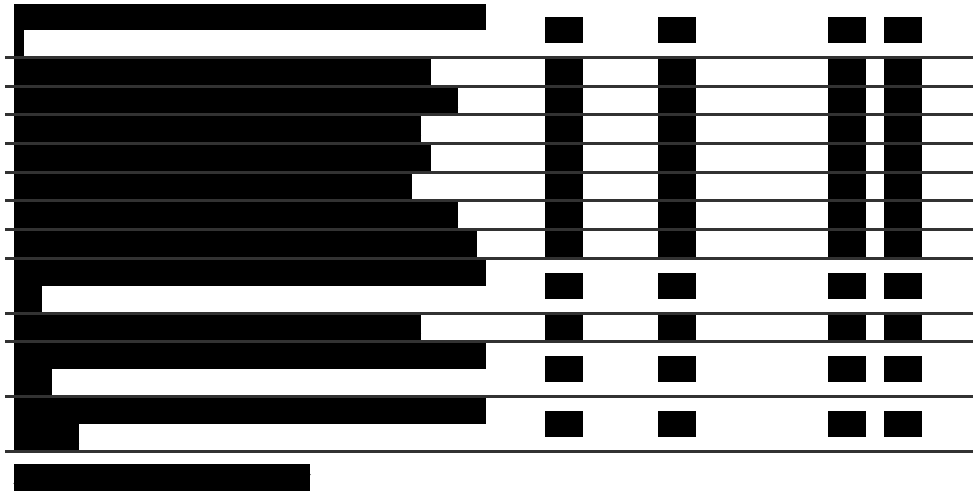
Figure 107 Forest plot of MMRM overall estimate of change from baseline in EORTC QLQ-MY20 symptom scores - ITT

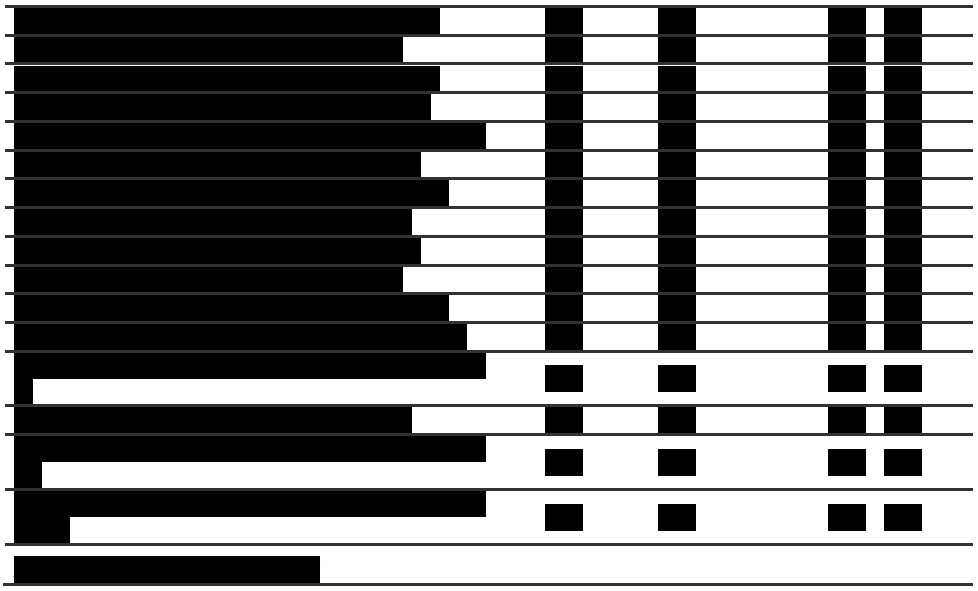
Appendix G. Probabilistic sensitivity analyses

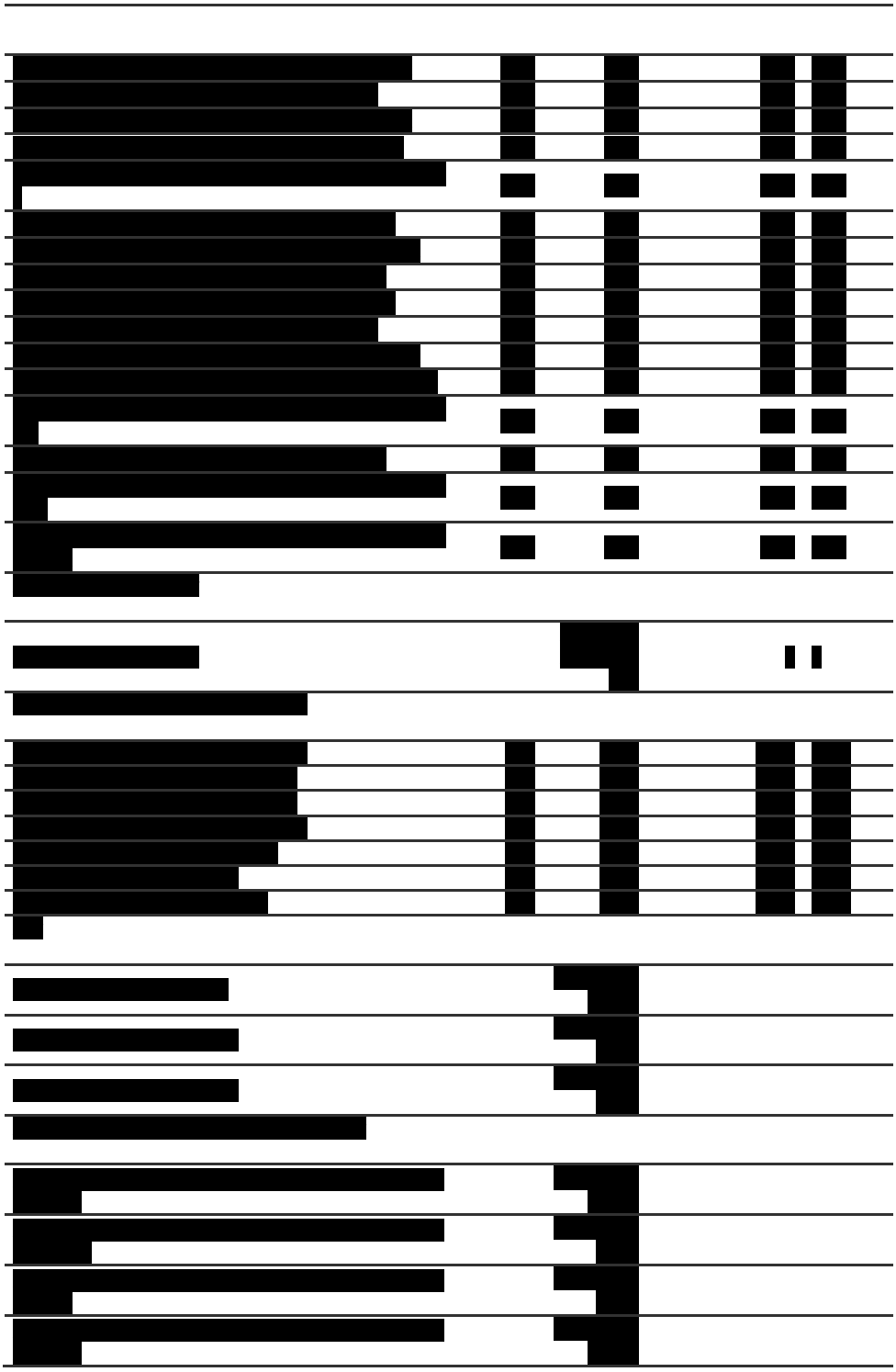
Table 124 shows all parameters included in the PSA including the point estimate, and lower and upper bound and selected probability distributions used in the PSA.

Table 124 Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
[redacted]				







G.1 PSA in the case of "non-proportional hazards" MAIC

In the base case, the PFS and OS for DVMP and DRd is modelled through an MAIC under the assumption of proportional hazards. In this case, the HR for IsaVRd vs. DVMP and the the HR for IsaVRd vs. DRd are included directly in the PSA based on its 95% CI.

In the case of selecting non-proportional hazards (i.e. outside the base case) the HR are time-varying and cannot be directly included in the PSA. Instead the parameters used in the Parametric Survival Modeling (PSM) is included in the PSA, i.e. the shape and scale parameters and an associated variance/covariance matrix.

To assess the uncertainty associated with the PSM, the variance-covariance matrix is used. In each PSA run, we apply a random number that samples the variance-covariance parameters. The same random number is used for both shape and scale, ensuring that they maintain symmetry in their extrapolation.

Taking this one step further. The PSM parameters are based on adjusted Isatuximab data compared to comparator data. The isatuximab data is adjusted to match the baseline characteristics of the comparator population. In the CE model, we extrapolate the PSM parameters for both the adjusted isatuximab data and the comparator data. We apply the same random number to both arms to maintain a certain level of symmetry in the extrapolation; we also seek to maintain symmetry between the treatment arms.

When we use the PSM parameters we calculate a time-varying HR, which is subject to the uncertainty testing above. So it moves and behaves with symmetry, hence the time-varying HR doesn’t create implausible extrapolations.

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

A systematic literature review (SLR) was conducted in April 2024 to identify comparator evidence on the efficacy, safety, and tolerability of treatments for patients with NDMM with the aim to conduct an NMA. The literature searches included 76 randomized controlled trials (RCTs), with 33 in the transplant-ineligible population, 30 in the transplant-eligible population, six with a mixture of both eligible and ineligible patients, and seven with unclear transplant status.

As the aim change to performing a MAIC and as only DVMP and DRd are relevant external comparators, an extra exclusion was performed to ensure that only relevant studies were included.

The initial SLR in March 2021 identified 14,130 references from database searches, with 1,800 full-text reports considered for inclusion. Out of which, a total of 1,800 full text reports were considered for inclusion. Of these, 1,302 were excluded, including reports of deprioritized interventions. A total of 520 reports were included, covering 49 RCTs across 520 publications.

The 2022 SLR update identified 3,551 records, with 253 duplicates removed. Of 3,298 references screened, 3,064 were excluded, and 234 full texts were reviewed, with 187 excluded.

In the 2023 update, 1,160 records were identified, 183 duplicates removed, and 977 references screened. After excluding 894, 83 full texts were reviewed, with 64 excluded. Additionally, 17 conference abstracts from grey literature were included, resulting in 36 references from 16 trials.

In the 2024 April, 1,981 records were identified, with 337 duplicates removed. After screening 1,644 references, 1,595 were excluded, and 49 full texts were reviewed, excluding 35. The evidence in the SLR updates comprised a total 76 RCTs, out of which 28 RCTs have been identified from the SLR updates from 235 publications.

Table 125 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	All time	29.04.2024
Medline	Medline.com	All time	29.04.2024
Cochrane Central Register of Controlled Trials **CENTRAL**	Cochrane	All time	29.04.2024
Cochrane Database of Systematic Reviews (CDSR)	Cochrane	All time	29.04.2024

Abbreviations:

Table 126 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A

Abbreviations:

Table 127 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Hematology (ASH)	ASH Annual Meeting & Exposition - Hematology.org	Search was conducted on the relevant website for conferences	Newly diagnosed multiple myeloma, Daratumumab, transplant ineligible	29.04.2024
American Society of Clinical Oncology (ASCO), including the ASCO Gastrointestinal (GI) Symposium	Attend | ASCO Gastrointestinal Cancers Symposium	Search was conducted on the relevant website for conferences	Newly diagnosed multiple myeloma, Daratumumab, transplant ineligible	29.04.2024

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
European Society for Medical Oncology (ESMO)	European Society for Medical Oncology	Search was conducted on the relevant website for conferences	Newly diagnosed multiple myeloma, Daratumumab, transplant ineligible	29.04.2024
European Haematology Association (EHA)	The European Hematology Association (EHA)	Search was conducted on the relevant website for conferences	Newly diagnosed multiple myeloma, Daratumumab, transplant ineligible	29.04.2024
British Society of Haematology (BSH)	BSH Annual Scientific Meeting (ASM)	Search was conducted on the relevant website for conferences	Newly diagnosed multiple myeloma, Daratumumab, transplant ineligible	29.04.2024

H.1.1 Search strategies

The search was performed across the four databases listed in Table 125 and the conferences referenced in Table 127. Relevant MeSH terms were selected and applied for each database, with the search terms provided in Table 128-Table 133 or each respective database. A PICO table was used to structure the search, which was limited to patients aged 18 and above. Various treatment combinations for multiple myeloma (MM) were chosen to gather comprehensive data on efficacy, with any comparator included. The selected outcomes for the search were overall survival (OS), progression-free survival (PFS), and minimal residual disease (MRD) negativity.

Table 128 Search strategy table for Embase (OVID). Date searched: April 29, 2024

Search Number	Search Terms	Results
1	exp randomization/ or exp controlled clinical trial/ or exp "controlled clinical trial (topic)"/ or exp placebo effect/ or exp placebo/ or exp clinical trial/ or exp "clinical trial (topic)"/ or exp control group/ or exp randomized controlled trial/ or exp "randomized controlled trial (topic)"/ or (controlled clinical trial$ or randomised controlled trial$ or randomized controlled trial$ or rct or (random$ adj2 (alloca$ or assign$ or distribut$ or group$)) or ((single or double or triple or treble) adj2 (blind$ or mask$)) or placebo$).ti,ab,kw. or exp single blind procedure/ or exp crossover procedure/ or exp double blind procedure/ or exp triple blind procedure/	2.919.019
2	(case study or case report or abstract report or comment).mp. or (editorial or letter or note). pt. or exp case report/ or exp case study/ or exp editorial/	6.118.100
3	exp animal/ not (exp animal/ and exp human/)	5.247.578
4	(review or 'literature review'). pt. not ('meta-analysis'.pt. or *meta-analysis as topic/ or systematic review.ti. or systematic literature review.ti. or meta-analysis.ti,ab. or metaanalysis.ti,ab.)	3.029.804
5	or/2-4	14.022.667
6	1 not 5	2.259.553
7	exp multiple myeloma/	102.391
8	exp plasmacytoma/ or exp paraproteinemias/	191.408
9	(myeloma$ or (multiple adj2 myeloma$) or plasmacytom$ or plasmocytom$ or mgus or (monoclonal adj2 gammopath$) or plasma cell myeloma).ti,ab.	118.157
10	or/7-9	215.962
11	exp melphalan/ or (melphalan or alanine nitrogen mustard or l-phenylalanine mustard or l-sarcolysin or l-sarcolysin phenylalanine mustard or l-sarcolysine or phenylalanine mustard or phenylalanine nitrogen mustard or alkeran or alkerana or melfalan or melphalanum or sarkolysin or cb-3025 or wr-19813 or l-pam or lpam).ti,ab.	45.076
12	exp bortezomib/ or (bortezomib or velcade or ldp 341 or mln341 or ps-341).ti,ab.	43.022
13	exp carfilzomib/ or (carfilzomib or kyprolis or pr-171).ti,ab.	7.968

14	exp cyclophosphamide/ or (cyclophosphamide or ciclofosfamida or ciclofosfamide or claphene or cp monohydrate or cyclophospham or cyclophosphamid monohydrate or cyclophosphamidum or cyclophosphan or cyclophosphanum or cytophosphane or mitoxan or syklofosfamid or zytoxan or clafen or cytoxan or neosar or revimmune or carloxan or cicloxal or cycloblastin or cycloblastine or cyclo-cell or cyclostin or cyclostine or cytophosphan or endoxan or endoxana or enduxan or fosfaseron or genoxal or ledoxina or procytox or sendoxan or asta b 518 or b-518 or b518 or wr-138719).ti,ab.	266.169
15	exp daratumumab/ or (daratumumab or jnj-54767414 or darzalex or humax cd38 or monoclonal antibody humax cd38).ti,ab.	7.728
16	exp doxorubicin/ or (doxorubicin or adriamycin or doxil or dox-sl or evacet or lipodox or chloridrato de doxorrubicina or adriacin or adriblastina or adriblastine or adrimedac or doxo-cell or doxolem or doxorubin or farmiblastina or fi-106).ti,ab.	236.674
17	exp elotuzumab/ or (elotuzumab or empliciti or huluc63).ti,ab.	2.038
18	exp panobinostat/ or (panobinostat or farydak or faridak or lbh 589 or lbh 589a or lbh 589b or lbh589 or lbh589a or lbh589b or nvp lbh 589 or nvp lbh589).ti,ab.	5.564
19	exp ixazomib/ or (ixazomib or ninlaro or mln9708).ti,ab.	3.321
20	exp lenalidomide/ or (lenalidomide or imid-1 or revlimid or cc-5013 or cdc 501).ti,ab.	29.637
21	exp bendamustine/ or (bendamustine or bendeka or cimet 3393 or cytostasan or cytostasane or imet 3393 or levact or ribomustin or ribovact or treanda or zimet 3393 or zimet3393).ti,ab.	10.924
22	exp pomalidomide/ or (pomalidomide or pomalyst or imnovid or cc-4047 or cc4047).ti,ab.	6.445
23	exp thalidomide/ or (thalidomide or synovir or thalomid or contergan or distaval or kevadon or neurosedyn or pantosediv or sedoval k-17 or softenon or talimol).ti,ab.	33.782
24	exp dexamethasone/ or (dexamethasone or desamethasone or dexamethasonum or hexadecadrol or maxidex or methylfluorprednisolone or aacidexam or adexone or aknichthol dexa or alin depot or alin oftalmico or amplidermis or anemul mono or auricularum or auxiloson or baycuten or cortidexason or cortisumman or decacort or decalix or decameth or dectancyl or dekacort or deltafluorene or desameton or dexacortal or dexacortin or dexafarma or dexafluorene or dexalocal or dexa-mamallet or dexamecortin or dexamonozon or dexapos or dexa-rhinosan or dexa-scheroson or dexa-sine or dexinoral or dexone or dinormon or	209.255

	dluorodelta or dortecortin or lokalison-f or loverine or millicorten or mymethasone or orgadrone or spersadex or visumetazone).ti,ab.	
25	exp prednisone/ or exp prednisolone/ or (ancortone or apo-prednisone or biocortone or colisone or cortan or cortidelt or cortiprex or cutason or dacorten or de cortisyl or decortancyl or decortin or decortine or decortisyl or dehydrocortisone or dekortin or delitisone or dellacort a or delta cortelan or delta cortisone or delta dome or delta e or delta prenovis or delta-dome or deltacorten or deltacortene or deltacortisone or deltacortone or deltasone or deltison or deltisona or deltra or di adreson or di-adreson or diadreson or drazone or encorton or encortone or enkorton or fernisone or hostacortin or insone or liquid pred or lodotra or me-korti or meprison or metacortandracin or meticorten or meticortine or nisona or nsc 10023 or nsc10023 or orasone or orisane or panafcort or paracort or pehacort or precort or precortal or prednicen-m or prednicorm or prednicot or prednidib or prednison or prednisone alcohol or prednisone intensol or prednisone$ or prednitone or pronison or pronisone or pronizone or pulmison or rayos or rectodelt or servisone or steerometz or sterapred or ultracorten or urtilone or winpred).ti,ab.	355.078
26	exp etoposide/ or (etopophos or celltop or citodox or eposin or epsidox or etomedac or etomedec or etophos or etopol or etopos or etoposid or etoposide toniribate or etoposido or etopoxan or etosid or lastet or lastet-s or nexvep or nk 171 or nk171 or nsc 141540 or nsc141540 or posid or toposar or topresid or vepesid or vepeside or vespid or vp 16 or vp 16 213 or vp 16-213 or vp 16213 or vp-tec or vp16 or vp16 213 or vp16-213 or vp16213).ti,ab.	107.158
27	exp vincristine/ or (vincristine or l 37231 or l37231 or leurocristine or Vincasar).ti,ab.	118.065
28	exp vorinostat/ or (vorinostat or "mk 0683" or mk0683 or vorinostat msd or Zolinza).ti,ab.	12.660
29	exp nivolumab/ or (nivolumab or bms 936558 or bms936558 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or opdivo).ti,ab.	42.983
30	exp pembrolizumab/ or (keytruda or lambrolizumab or mk 3475 or mk3475 or sch 900475 or sch900475).ti,ab.	41.450
31	exp atezolizumab/ or (mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or tecentriq or tecntriq).ti,ab.	17.453
32	exp durvalumab/ or (imfinzi or medi 4736 or medi4736).ti,ab.	11.849
33	((pd 1 or pd l1 or pd-1 or pd-l1) adj2 (inhibition or inhibitors or inhibitor or inhibit$)).ti,ab. or checkpoint inhibitors.mp. or exp programmed death 1 ligand 1/ or exp programmed death 1 receptor/ or exp Programmed Cell Death 1 Receptor/	118.885

34	exp isatuximab/ or (isatuximab or sar 650984 or sar650984 or Sarclisa).ti,ab.	1.268
35	3412470a0v.mp. or (melflufen hydrochloride or melflufen or ygalo).ti,ab. or exp melphalan flufenamide/	278
36	(cereblon modulator$ or imids or (immunomodulatory adj3 imide)).ti,ab. or exp imid/ or exp Immunomodulating Agents/ or exp cd38 antibody/ or exp cd138 antibody/ or (cd38 antigen or cd138 antigen or cd 38 antigen or cd 138 antigen or ((cd38 or cd138 or 'cd 138' or 'cd 38' or 'cd 138') adj2 (antigen or antiboby))).ti,ab. or exp "adp ribosyl cyclase/cyclic adp ribose hydrolase 1"/ or exp syndecan 1/ or exp Syndecan-1/ or exp proteasome inhibitor/ or exp Proteasome Inhibitors/	2.368.633
37	exp chimeric antigen receptor/ or (chimeric antigen receptors or chimeric immunoreceptor or chimeric immunoreceptors or chimeric antigen).mp. or ucar t.ti,ab.	32.992
38	exp histone deacetylase inhibitor/ or (hdac inhibitor or histone deacetylase inhibitor$ or hdaci or hdis).ti,ab.	68.837
39	or/11-38	2.653.334
40	6 and 10 and 39	15.327
41	40 not conference abstract.pt.	6.310
42	limit 40 to (conference abstract and yr="2021-current")	2.349
43	41 or 42	8.659
44	limit 43 to english	8.394
45	limit 44 to dc="20230701-20240426"	1.222

Table 129 Search strategy table for MEDLINE (OVID). Date searched: April 29, 2024

Search Number	Search Terms	Results
1	exp Random Allocation/ or (controlled clinical trial or clinical trial or randomized controlled trial).pt. or exp Controlled Clinical Trials as Topic/ or exp Placebo Effect/ or exp Placebos/ or exp Clinical Trials as Topic/ or exp Control Groups/ or exp Randomized Controlled Trials as Topic/ or (controlled clinical trial$ or randomised controlled trial$ or randomized controlled trial$ or rct or (random$ adj2 (alloca$ or assign$ or distribut$ or group$)) or ((single or double or triple or treble) adj2	1.652.195

	(blind$ or mask$)) or placebo$).ti,ab,kw. or exp Single-Blind Method/ or exp Cross-Over Studies/ or exp Double-Blind Method/	
2	(case study or abstract report or note).mp. or (comment or case reports or editorial or letter).pt.	4.583.079
3	exp animal/ not (exp animal/ and exp human/)	5.215.958
4	(review or 'literature review').pt. not ('meta-analysis'.pt. or *meta-analysis as topic/ or systematic review.ti. or systematic literature review.ti. or meta-analysis.ti,ab. or metaanalysis.ti,ab.)	3.133.485
5	or/2-4	12.452.083
6	1 not 5	1.319.477
7	exp Multiple Myeloma/	49.016
8	exp Plasmacytoma/ or exp Paraproteinemias/	70.630
9	(myeloma$ or (multiple adj2 myeloma$) or plasmacytom$ or plasmocytom$ or mgus or (monoclonal adj2 gammopath$) or plasma cell myeloma).ti,ab.	73.750
10	or/7-9	96.002
11	exp Melphalan/ or (melphalan or alanine nitrogen mustard or l-phenylalanine mustard or l-sarcolysin or l-sarcolysin phenylalanine mustard or l-sarcolysine or phenylalanine mustard or phenylalanine nitrogen mustard or alkeran or alkerana or melfalan or melphalanum or sarkolysin or cb-3025 or wr-19813 or l-pam or lpam).ti,ab.	12.121
12	exp Bortezomib/ or (bortezomib or velcade or ldp 341 or mln341 or ps-341).ti,ab.	11.362
13	(carfilzomib or kyprolis or pr-171).ti,ab.	1.509
14	exp Cyclophosphamide/ or (cyclophosphamide or ciclofosfamida or ciclofosfamide or claphene or cp monohydrate or cyclophospham or cyclophosphamid monohydrate or cyclophosphamidum or cyclophosphan or cyclophosphanum or cytophosphane or mitoxan or syklofosfamid or zytoxan or clafen or cytoxan or neosar or revimmune or carloxan or cicloxal or cycloblastin or cycloblastine or cyclo-cell or cyclostin or cyclostine or cytophosphan or endoxan or endoxana or enduxan or fosfaseron or genoxal or ledoxina or procytox or sendoxan or asta b 518 or b-518 or b518 or wr-138719).ti,ab.	82.054
15	(daratumumab or jnj-54767414 or darzalex or humax cd38 or monoclonal antibody humax cd38).ti,ab.	1.556

16	exp Doxorubicin/ or (doxorubicin or adriamycin or doxil or dox-sl or evacet or lipodox or chloridrato de doxorrubicina or adriacin or adriblastina or adriblastine or adrimedac or doxo-cell or doxolem or doxorubin or farmiblastina or fi-106).ti,ab.	91.963
17	(elotuzumab or empliciti or huluc63).ti,ab.	375
18	exp Panobinostat/ or (panobinostat or farydak or faridak or lbh 589 or lbh 589a or lbh 589b or lbh589 or lbh589a or lbh589b or nvp lbh 589 or nvp lbh589).ti,ab.	1.160
19	(ixazomib or ninlaro or mln9708).ti,ab.	590
20	exp Lenalidomide/ or (lenalidomide or imid-1 or revlimid or cc-5013 or cdc 501).ti,ab.	6.292
21	exp Bendamustine Hydrochloride/ or (bendamustine or bendeka or cimet 3393 or cytostasan or cytostasane or imet 3393 or levact or ribomustin or ribovact or treanda or zimet 3393 or zimet3393).ti,ab.	1.924
22	(pomalidomide or pomalyst or imnovid or cc-4047 or cc4047).ti,ab.	1.148
23	exp Thalidomide/ or (thalidomide or synovir or thalomid or contergan or distaval or kevadon or neurosedyn or pantosediv or sedoval k-17 or softenon or talimol).ti,ab.	12.920
24	exp Dexamethasone/ or (dexamethasone or desamethasone or dexamethasonum or hexadecadrol or maxidex or methylfluorprednisolone or aacidexam or adexone or aknichthol dexa or alin depot or alin oftalmico or amplidermis or anemul mono or auricularum or auxiloson or baycuten or cortidexason or cortisumman or decacort or decalix or decameth or dectancyl or dekacort or deltafluorene or desameton or dexacortal or dexacortin or dexafarma or dexafluorene or dexalocal or dexa-mamallet or dexamecortin or dexamonozon or dexapos or dexa-rhinosan or dexa-scheroson or dexa-sine or dexinoral or dexone or dinormon or dluorodelta or dortecortin or lokalison-f or loverine or millicorten or mymethasone or orgadrone or spersadex or visumetazone).ti,ab.	82.276
25	exp Prednisone/ or exp Prednisolone/ or (ancortone or apo-prednisone or biocortone or colisone or cortan or cortidelt or cortiprex or cutason or dacorten or de cortisyl or decortancyl or decortin or decortine or decortisyl or dehydrocortisone or dekortin or delitisone or dellacort a or delta cortelan or delta cortisone or delta dome or delta e or delta prenovis or delta-dome or deltacorten or deltacortene or deltacortisone or deltacortone or deltasone or deltison or deltisona or deltra or di adreson or di-adreson or diadreson or drazone or encorton or encortone or enkorton or fernisone or hostacortin or insone or liquid pred or lodotra or me-korti or meprison or metacortandracin or meticorten or meticortine or nisona or nsc 10023 or nsc10023 or orasone or orisane or panafcort or paracort or pehacort or precort or	109.307

	precortal or prednicen-m or prednicorm or prednicot or prednidib or prednison or prednisone alcohol or prednisone intensol or prednisone$ or prednitone or pronison or pronisone or pronizone or pulmison or rayos or rectodelt or servisone or steerometz or sterapred or ultracorten or urtilone or winpred).ti,ab.	
26	exp Etoposide/ or (etopophos or celltop or citodox or eposin or epsidox or etomedac or etomedec or etophos or etopol or etopos or etoposid or etoposide toniribate or etoposido or etopoxan or etosid or lastet or lastet-s or nexvep or nk 171 or nk171 or nsc 141540 or nsc141540 or posid or toposar or topresid or vepesid or vepeside or vespid or vp 16 or vp 16 213 or vp 16-213 or vp 16213 or vp-tec or vp16 or vp16 213 or vp16-213 or vp16213).ti,ab.	21.420
27	exp Vincristine/ or (vincristine or l 37231 or l37231 or leurocristine or Vincasar).ti,ab.	34.091
28	exp Vorinostat/ or (vorinostat or "mk 0683" or mk0683 or vorinostat msd or Zolinza).ti,ab.	2.860
29	exp Nivolumab/ or (nivolumab or bms 936558 or bms936558 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or opdivo).ti,ab.	10.083
30	(pembrolizumab or keytruda or lambrolizumab or mk 3475 or mk3475 or sch 900475 or sch900475).ti,ab.	8707
31	(mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or tecentriq or tecntriq).ti,ab.	74
32	(imfinzi or medi 4736 or medi4736).ti,ab.	60
33	((pd 1 or pd l1 or pd-1 or pd-l1) adj2 (inhibition or inhibitors or inhibitor or inhibit$)).ti,ab. or checkpoint inhibitors.mp.	35.243
34	(isatuximab or sar 650984 or sar650984 or Sarclisa).ti,ab.	243
35	3412470a0v.mp. or (melflufen hydrochloride or melflufen or ygalo).ti,ab.	60
36	(cereblon modulator$ or imids or (immunomodulatory adj3 imide)).ti,ab. or exp imid/ or exp Immunomodulating Agents/ or exp cd38 antibody/ or exp cd138 antibody/ or (cd38 antigen or cd138 antigen or cd 38 antigen or cd 138 antigen or ((cd38 or cd138 or 'cd 138' or 'cd 38' or 'cd 138') adj2 (antigen or antiboby))).ti,ab. or exp Syndecan-1/ or exp Proteasome Inhibitors/	12.004
37	exp Receptors, Chimeric Antigen/ or (chimeric antigen receptors or chimeric immunoreceptor or chimeric immunoreceptors or chimeric antigen).mp. or ucar t.ti,ab.	12.452

38	exp Histone Deacetylase Inhibitors/ or (hdac inhibitor or histone deacetylase inhibitor$ or hdaci or hdis).ti,ab.	18.034
39	or/11-38	446.882
40	6 and 10 and 39	2.093
41	limit 40 to english	2.004
42	limit 41 to dt="20230701-20240426"	40

Table 130 Search strategy table for CENTRAL (Cochrane Central register of Controlled Trials. EBM Reviewers) (OVID). Date searched: April 29, 2024

Search Number	Search Terms	Results
1	exp Random Allocation/ or (controlled clinical trial or clinical trial or randomized controlled trial).pt. or exp Controlled Clinical Trials as Topic/ or exp Placebo Effect/ or exp Placebos/ or exp Clinical Trials as Topic/ or exp Control Groups/ or exp Randomized Controlled Trials as Topic/ or (controlled clinical trial$ or randomised controlled trial$ or randomized controlled trial$ or rct or (random$ adj2 (alloca$ or assign$ or distribut$ or group$)) or ((single or double or triple or treble) adj2 (blind$ or mask$)) or placebo$).ti,ab,kw. or exp Single-Blind Method/ or exp Cross-Over Studies/ or exp Double-Blind Method/	1.191.330
2	(case study or abstract report or note).mp. or (comment or case reports or editorial or letter).pt.	37.005
3	exp animal/ not (exp animal/ and exp human/)	3.665
4	(review or 'literature review').pt. not ('meta-analysis'.pt. or *meta-analysis as topic/ or systematic review.ti. or systematic literature review.ti. or meta-analysis.ti,ab. or metaanalysis.ti,ab.)	0
5	or/2-4	40.633
6	1 not 5	1.161.470
7	exp Multiple Myeloma/	2.439
8	exp Plasmacytoma/ or exp Paraproteinemias/	2.607
9	(myeloma$ or (multiple adj2 myeloma$) or plasmacytom$ or plasmocytom$ or mgus or (monoclonal adj2 gammopath$) or plasma cell myeloma).ti,ab.	6.511

10	or/7-9	6.859
11	exp Melphalan/ or (melphalan or alanine nitrogen mustard or l-phenylalanine mustard or l-sarcolysin or l-sarcolysin phenylalanine mustard or l-sarcolysine or phenylalanine mustard or phenylalanine nitrogen mustard or alkeran or alkerana or melfalan or melphalanum or sarkolysin or cb-3025 or wr-19813 or l-pam or lpam).ti,ab.	2.276
12	exp Bortezomib/ or (bortezomib or velcade or ldp 341 or mln341 or ps-341).ti,ab.	2.476
13	(carfilzomib or kyprolis or pr-171).ti,ab.	565
14	exp Cyclophosphamide/ or (cyclophosphamide or ciclofosfamida or ciclofosfamide or claphene or cp monohydrate or cyclophospham or cyclophosphamid monohydrate or cyclophosphamidum or cyclophosphan or cyclophosphanum or cytophosphane or mitoxan or syklofosfamid or zytoxan or clafen or cytoxan or neosar or revimmune or carloxan or cicloxal or cycloblastin or cycloblastine or cyclo-cell or cyclostin or cyclostine or cytophosphan or endoxan or endoxana or enduxan or fosfaseron or genoxal or ledoxina or procytox or sendoxan or asta b 518 or b-518 or b518 or wr-138719).ti,ab.	13.585
15	(daratumumab or jnj-54767414 or darzalex or humax cd38 or monoclonal antibody humax cd38).ti,ab.	660
16	exp Doxorubicin/ or (doxorubicin or adriamycin or doxil or dox-sl or evacet or lipodox or chloridrato de doxorrubicina or adriacin or adriblastina or adriblastine or adrimedac or doxo-cell or doxolem or doxorubin or farmiblastina or fi-106).ti,ab.	10.434
17	(elotuzumab or empliciti or huluc63).ti,ab.	159
18	exp Panobinostat/ or (panobinostat or farydak or faridak or lbh 589 or lbh 589a or lbh 589b or lbh589 or lbh589a or lbh589b or nvp lbh 589 or nvp lbh589).ti,ab.	119
19	(ixazomib or ninlaro or mln9708).ti,ab.	278
20	exp Lenalidomide/ or (lenalidomide or imid-1 or revlimid or cc-5013 or cdc 501).ti,ab.	2.726
21	exp Bendamustine Hydrochloride/ or (bendamustine or bendeka or cimet 3393 or cytostasan or cytostasane or imet 3393 or levact or ribomustin or ribovact or treanda or zimet 3393 or zimet3393).ti,ab.	904
22	(pomalidomide or pomalyst or imnovid or cc-4047 or cc4047).ti,ab.	522

23	exp Thalidomide/ or (thalidomide or synovir or thalomid or contergan or distaval or kevadon or neurosedyn or pantosediv or sedoval k-17 or softenon or talimol).ti,ab.	2.056
24	exp Dexamethasone/ or (dexamethasone or desamethasone or dexamethasonum or hexadecadrol or maxidex or methylfluorprednisolone or aacidexam or adexone or aknichthol dexa or alin depot or alin oftalmico or amplidermis or anemul mono or auricularum or auxiloson or baycuten or cortidexason or cortisumman or decacort or decalix or decameth or dectancyl or dekacort or deltafluorene or desameton or dexacortal or dexacortin or dexafarma or dexafluorene or dexalocal or dexa-mamallet or dexamecortin or dexamonozon or dexapos or dexa-rhinosan or dexa-scheroson or dexa-sine or dexinoral or dexone or dinormon or dluorodelta or dortecortin or lokalison-f or loverine or millicorten or mymethasone or orgadrone or spersadex or visumetazone).ti,ab.	15.177
25	exp Prednisone/ or exp Prednisolone/ or (ancortone or apo-prednisone or biocortone or colisone or cortan or cortidelt or cortiprex or cutason or dacorten or de cortisyl or decortancyl or decortin or decortine or decortisyl or dehydrocortisone or dekortin or delitisone or dellacort a or delta cortelan or delta cortisone or delta dome or delta e or delta prenovis or delta-dome or deltacorten or deltacortene or deltacortisone or deltacortone or deltasone or deltison or deltisona or deltra or di adreson or di-adreson or diadreson or drazone or encorton or encortone or enkorton or fernisone or hostacortin or insone or liquid pred or lodotra or me-korti or meprison or metacortandracin or meticorten or meticortine or nisona or nsc 10023 or nsc10023 or orasone or orisane or panafcort or paracort or pehacort or precort or precortal or prednicen-m or prednicorm or prednicot or prednidib or prednison or prednisone alcohol or prednisone intensol or prednisone$ or prednitone or pronison or pronisone or pronizone or pulmison or rayos or rectodelt or servisone or steerometz or sterapred or ultracorten or urtilone or winpred).ti,ab.	15.750
26	exp Etoposide/ or (etopophos or celltop or citodox or eposin or epsidox or etomedac or etomedec or etophos or etopol or etopos or etoposid or etoposide toniribate or etoposido or etopoxan or etosid or lastet or lastet-s or nexvep or nk 171 or nk171 or nsc 141540 or nsc141540 or posid or toposar or topresid or vepesid or vepeside or vespid or vp 16 or vp 16 213 or vp 16-213 or vp 16213 or vp-tec or vp16 or vp16 213 or vp16-213 or vp16213).ti,ab.	2.487
27	exp Vincristine/ or (vincristine or l 37231 or l37231 or leurocristine or Vincasar).ti,ab.	4.539
28	exp Vorinostat/ or (vorinostat or "mk 0683" or mk0683 or vorinostat msd or Zolinza).ti,ab.	292

29	exp Nivolumab/ or (nivolumab or bms 936558 or bms936558 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or opdivo).ti,ab.	3.055
30	(pembrolizumab or keytruda or lambrolizumab or mk 3475 or mk3475 or sch 900475 or sch900475).ti,ab.	3.145
31	(mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or tecentriq or tecntriq).ti,ab.	156
32	(imfinzi or medi 4736 or medi4736).ti,ab.	253
33	((pd 1 or pd l1 or pd-1 or pd-l1) adj2 (inhibition or inhibitors or inhibitor or inhibit$)).ti,ab. or checkpoint inhibitors.mp.	2.441
34	(isatuximab or sar 650984 or sar650984 or Sarclisa).ti,ab.	195
35	3412470a0v.mp. or (melflufen hydrochloride or melflufen or ygalo).ti,ab.	35
36	(cereblon modulator$ or imids or (immunomodulatory adj3 imide)).ti,ab. or exp imid/ or exp Immunomodulating Agents/ or exp cd38 antibody/ or exp cd138 antibody/ or (cd38 antigen or cd138 antigen or cd 38 antigen or cd 138 antigen or ((cd38 or cd138 or 'cd 138' or 'cd 38' or 'cd 138') adj2 (antigen or antiboby))).ti,ab. or exp Syndecan-1/ or exp Proteasome Inhibitors/	295
37	exp Receptors, Chimeric Antigen/ or (chimeric antigen receptors or chimeric immunoreceptor or chimeric immunoreceptors or chimeric antigen).mp. or ucar t.ti,ab.	367
38	exp Histone Deacetylase Inhibitors/ or (hdac inhibitor or histone deacetylase inhibitor$ or hdaci or hdis).ti,ab.	492
39	or/11-38	57.794
40	6 and 10 and 39	2.275
41	limit 40 to english	2.235
42	limit 41 to up="202307-202403"	718

Table 131 Search strategy table for CDSR (Cochrane Database of Systematic Reviews. EBM Reviewers) (OVID). Date searched: April 29, 2024

Search Number	Search Terms	Results
1	(controlled clinical trial or clinical trial or randomized controlled trial).pt. or (controlled clinical trial$ or randomised controlled trial$ or randomized controlled trial$ or rct or (random$ adj2 (alloca$ or	7.935

	assign$ or distribut$ or group$)) or ((single or double or triple or treble) adj2 (blind$ or mask$)) or placebo$).ti,ab.	
2	(case study or abstract report or note or comment or case reports or editorial or letter).mp.	9.960
3	1 not 2	1.655
4	(myeloma$ or (multiple adj2 myeloma$) or plasmacytom$ or plasmocytom$ or mgus or (monoclonal adj2 gammopath$) or plasma cell myeloma).ti,ab.	24
5	(melphalan or alanine nitrogen mustard or l-phenylalanine mustard or l-sarcolysin or l-sarcolysin phenylalanine mustard or l-sarcolysine or phenylalanine mustard or phenylalanine nitrogen mustard or alkeran or alkerana or melfalan or melphalanum or sarkolysin or cb-3025 or wr-19813 or l-pam or lpam).ti,ab.	6
6	(bortezomib or velcade or ldp 341 or mln341 or ps-341).ti,ab.	2
7	(carfilzomib or kyprolis or pr-171).ti,ab.	0
8	(cyclophosphamide or ciclofosfamida or ciclofosfamide or claphene or cp monohydrate or cyclophospham or cyclophosphamid monohydrate or cyclophosphamidum or cyclophosphan or cyclophosphanum or cytophosphane or mitoxan or syklofosfamid or zytoxan or clafen or cytoxan or neosar or revimmune or carloxan or cicloxal or cycloblastin or cycloblastine or cyclo-cell or cyclostin or cyclostine or cytophosphan or endoxan or endoxana or enduxan or fosfaseron or genoxal or ledoxina or procytox or sendoxan or asta b 518 or b-518 or b518 or wr-138719).ti,ab.	42
9	(daratumumab or jnj-54767414 or darzalex or humax cd38 or monoclonal antibody humax cd38).ti,ab.	1
10	(doxorubicin or adriamycin or doxil or dox-sl or evacet or lipodox or chloridrato de doxorrubicina or adriacin or adriblastina or adriblastine or adrimedac or doxo-cell or doxolem or doxorubin or farmiblastina or fi-106).ti,ab.	25
11	(elotuzumab or empliciti or huluc63).ti,ab.	0
12	(panobinostat or farydak or faridak or lbh 589 or lbh 589a or lbh 589b or lbh589 or lbh589a or lbh589b or nvp lbh 589 or nvp lbh589).ti,ab.	0
13	(ixazomib or ninlaro or mln9708).ti,ab.	0
14	(lenalidomide or imid-1 or revlimid or cc-5013 or cdc 501).ti,ab.	9

15	(bendamustine or bendeka or cimet 3393 or cytostasan or cytostasane or imet 3393 or levact or ribomustin or ribovact or treanda or zimet 3393 or zimet3393).ti,ab.	1
16	(pomalidomide or pomalyst or imnovid or cc-4047 or cc4047).ti,ab.	1
17	(thalidomide or synovir or thalomid or contergan or distaval or kevadon or neurosedyn or pantosediv or sedoval k-17 or softenon or talimol).ti,ab.	14
18	(dexamethasone or desamethasone or dexamethasonum or hexadecadrol or maxidex or methylfluorprednisolone or aacidexam or adexone or aknichthol dexa or alin depot or alin oftalmico or amplidermis or anemul mono or auricularum or auxiloson or baycuten or cortidexason or cortisumman or decacort or decalix or decameth or dectancyl or dekacort or deltafluorene or desameton or dexacortal or dexacortin or dexafarma or dexafluorene or dexalocal or dexa-mamallet or dexamecortin or dexamonozon or dexapos or dexa-rhinosan or dexa-scheroson or dexa-sine or dexinoral or dexone or dinormon or dluorodelta or dortecortin or lokalison-f or loverine or millicorten or mymethasone or orgadrone or spersadex or visumetazone).ti,ab.	69
19	(ancortone or apo-prednisone or biocortone or colisone or cortan or cortidelt or cortiprex or cutason or dacorten or de cortisyl or decortancyl or decortin or decortine or decortisyl or dehydrocortisone or dekortin or delitisone or dellacort a or delta cortelan or delta cortisone or delta dome or delta e or delta prenovis or delta-dome or deltacorten or deltacortene or deltacortisone or deltacortone or deltasone or deltison or deltisona or deltra or di adreson or di-adreson or diadreson or drazone or encorton or encortone or enkorton or fernisone or hostacortin or insone or liquid pred or lodotra or me-korti or meprison or metacortandracin or meticorten or meticortine or nisona or nsc 10023 or nsc10023 or orasone or orisane or panafcort or paracort or pehacort or precort or precortal or prednicen-m or prednicorm or prednicot or prednidib or prednison or prednisone alcohol or prednisone intensol or prednisone$ or prednitone or pronison or pronisone or pronizone or pulmison or rayos or rectodelt or servisone or steerometz or sterapred or ultracorten or urtilone or winpred).ti,ab.	47
20	(etopophos or celltop or citodox or eposin or epsidox or etomedac or etomedec or etophos or etopol or etopos or etoposid or etoposide toniribate or etoposido or etopoxan or etosid or lastet or lastet-s or nexvep or nk 171 or nk171 or nsc 141540 or nsc141540 or posid or toposar or topresid or vepesid or vepeside or vespid or vp 16 or vp 16 213 or vp 16-213 or vp 16213 or vp-tec or vp16 or vp16 213 or vp16-213 or vp16213).ti,ab.	0
21	(vincristine or l 37231 or l37231 or leurocristine or Vincasar).ti,ab.	9

22	(vorinostat or "mk 0683" or mk0683 or vorinostat msd or Zolinza).ti,ab.	1
23	(nivolumab or bms 936558 or bms936558 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or opdivo).ti,ab.	6
24	(pembrolizumab or keytruda or lambrolizumab or mk 3475 or mk3475 or sch 900475 or sch900475).ti,ab.	4
25	(mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or tecentriq or tecntriq).ti,ab.	0
26	(imfinzi or medi 4736 or medi4736).ti,ab.	0
27	((pd 1 or pd l1 or pd-1 or pd-l1) adj2 (inhibition or inhibitors or inhibitor or inhibit$)).ti,ab. or checkpoint inhibitors.mp.	37
28	(isatuximab or sar 650984 or sar650984 or Sarclisa).ti,ab.	0
29	3412470a0v.mp. or (melflufen hydrochloride or melflufen or ygalo).ti,ab.	0
30	(cereblon modulator$ or imids or (immunomodulatory adj3 imide) or (cd38 antigen or cd138 antigen or cd 38 antigen or cd 138 antigen or ((cd38 or cd138 or 'cd 138' or 'cd 38' or 'cd 138') adj2 (antigen or antiboby)))).ti,ab.	0
31	(chimeric antigen receptors or chimeric immunoreceptor or chimeric immunoreceptors or chimeric antigen).mp. or ucar t.ti,ab.	8
32	(hdac inhibitor or histone deacetylase inhibitor$ or hdaci or hdis).ti,ab.	0
33	or/5-32	215
34	3 and 4 and 33	1
35	(202307$ or 202308$ or 202309$ or 202310$ or 202311$ or 202312$ or 2024$).up.	2.714
36	34 and 35	1

Table 132 Search strategy for EconLit. Date searched: April 29, 2024

Search Number	Search Terms	Results
1	(controlled clinical trial or clinical trial or randomized controlled trial).pt. or (controlled clinical trial$ or randomised controlled trial$ or randomized controlled trial$ or rct or (random$ adj2 (alloca$ or assign$	5.493

	or distribut$ or group$)) or ((single or double or triple or treble) adj2 (blind$ or mask$)) or placebo$).ti,ab.	
2	(case study or abstract report or note or comment or case reports or editorial or letter).mp.	85.957
3	1 not 2	5.364
4	(myeloma$ or (multiple adj2 myeloma$) or plasmacytom$ or plasmocytom$ or mgus or (monoclonal adj2 gammopath$) or plasma cell myeloma).ti,ab.	21
5	(melphalan or alanine nitrogen mustard or l-phenylalanine mustard or l-sarcolysin or l-sarcolysin phenylalanine mustard or l-sarcolysine or phenylalanine mustard or phenylalanine nitrogen mustard or alkeran or alkerana or melfalan or melphalanum or sarkolysin or cb-3025 or wr-19813 or l-pam or lpam).ti,ab.	1
6	(bortezomib or velcade or ldp 341 or mln341 or ps-341).ti,ab.	2
7	(carfilzomib or kyprolis or pr-171).ti,ab.	2
8	(cyclophosphamide or ciclofosfamida or ciclofosfamide or claphene or cp monohydrate or cyclophospham or cyclophosphamid monohydrate or cyclophosphamidum or cyclophosphan or cyclophosphanum or cytophosphane or mitoxan or syklofosfamid or zytoxan or clafen or cytoxan or neosar or revimmune or carloxan or cicloxal or cycloblastin or cycloblastine or cyclo-cell or cyclostin or cyclostine or cytophosphan or endoxan or endoxana or enduxan or fosfaseron or genoxal or ledoxina or procytox or sendoxan or asta b 518 or b-518 or b518 or wr-138719).ti,ab.	3
9	(daratumumab or jnj-54767414 or darzalex or humax cd38 or monoclonal antibody humax cd38).ti,ab.	1
10	(doxorubicin or adriamycin or doxil or dox-sl or evacet or lipodox or chloridrato de doxorrubicina or adriacin or adriblastina or adriblastine or adrimedac or doxo-cell or doxolem or doxorubin or farmiblastina or fi-106).ti,ab.	2
11	(elotuzumab or empliciti or huluc63).ti,ab.	1
12	(panobinostat or farydak or faridak or lbh 589 or lbh 589a or lbh 589b or lbh589 or lbh589a or lbh589b or nvp lbh 589 or nvp lbh589).ti,ab.	1
13	(ixazomib or ninlaro or mln9708).ti,ab.	1
14	(lenalidomide or imid-1 or revlimid or cc-5013 or cdc 501).ti,ab.	4

15	(bendamustine or bendeka or cimet 3393 or cytostasan or cytostasane or imet 3393 or levact or ribomustin or ribovact or treanda or zimet 3393 or zimet3393).ti,ab.	3
16	(pomalidomide or pomalyst or imnovid or cc-4047 or cc4047).ti,ab.	1
17	(thalidomide or synovir or thalomid or contergan or distaval or kevadon or neurosedyn or pantosediv or sedoval k-17 or softenon or talimol).ti,ab.	5
18	(dexamethasone or desamethasone or dexamethasonum or hexadecadrol or maxidex or methylfluorprednisolone or aacidexam or adexone or aknichthol dexa or alin depot or alin oftalmico or amplidermis or anemul mono or auricularum or auxiloson or baycuten or cortidexason or cortisumman or decacort or decalix or decameth or dectancyl or dekacort or deltafluorene or desameton or dexacortal or dexacortin or dexafarma or dexafluorene or dexalocal or dexa-mamallet or dexamecortin or dexamonozon or dexapos or dexa-rhinosan or dexa-scheroson or dexa-sine or dexinoral or dexone or dinormon or dluorodelta or dortecortin or lokalison-f or loverine or millicorten or mymethasone or orgadrone or spersadex or visumetazone).ti,ab.	4
19	(ancortone or apo-prednisone or biocortone or colisone or cortan or cortidelt or cortiprex or cutason or dacorten or de cortisyl or decortancyl or decortin or decortine or decortisyl or dehydrocortisone or dekortin or delitisone or dellacort a or delta cortelan or delta cortisone or delta dome or delta e or delta prenovis or delta-dome or deltacorten or deltacortene or deltacortisone or deltacortone or deltasone or deltison or deltisona or deltra or di adreson or di-adreson or diadreson or drazone or encorton or encortone or enkorton or fernisone or hostacortin or insone or liquid pred or lodotra or me-korti or meprison or metacortandracin or meticorten or meticortine or nisona or nsc 10023 or nsc10023 or orasone or orisane or panafcort or paracort or pehacort or precort or precortal or prednicen-m or prednicorm or prednicot or prednidib or prednison or prednisone alcohol or prednisone intensol or prednisone$ or prednitone or pronison or pronisone or pronizone or pulmison or rayos or rectodelt or servisone or steerometz or sterapred or ultracorten or urtilone or winpred).ti,ab.	5
20	(etopophos or celltop or citodox or eposin or epsidox or etomedac or etomedec or etophos or etopol or etopos or etoposid or etoposide toniribate or etoposido or etopoxan or etosid or lastet or lastet-s or nexvep or nk 171 or nk171 or nsc 141540 or nsc141540 or posid or toposar or topresid or vepesid or vepeside or vespid or vp 16 or vp 16 213 or vp 16-213 or vp 16213 or vp-tec or vp16 or vp16 213 or vp16-213 or vp16213).ti,ab.	0
21	(vincristine or l 37231 or l37231 or leurocristine or Vincasar).ti,ab.	1
22	(vorinostat or "mk 0683" or mk0683 or vorinostat msd or Zolinza).ti,ab.	0

23	(nivolumab or bms 936558 or bms936558 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or opdivo).ti,ab.	5
24	(pembrolizumab or keytruda or lambrolizumab or mk 3475 or mk3475 or sch 900475 or sch900475).ti,ab.	4
25	(mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or tecentriq or tecntriq).ti,ab.	0
26	(imfinzi or medi 4736 or medi4736).ti,ab.	0
27	((pd 1 or pd l1 or pd-1 or pd-l1) adj2 (inhibition or inhibitors or inhibitor or inhibit$)).ti,ab. or checkpoint inhibitors.mp.	2
28	(isatuximab or sar 650984 or sar650984 or Sarclisa).ti,ab.	0
29	3412470a0v.mp. or (melflufen hydrochloride or melflufen or ygalo).ti,ab.	0
30	(cereblon modulator$ or imids or (immunomodulatory adj3 imide) or (cd38 antigen or cd138 antigen or cd 38 antigen or cd 138 antigen or ((cd38 or cd138 or 'cd 138' or 'cd 38' or 'cd 138') adj2 (antigen or antiboby)))).ti,ab.	0
31	(chimeric antigen receptors or chimeric immunoreceptor or chimeric immunoreceptors or chimeric antigen).mp. or ucar t.ti,ab.	2
32	(hdac inhibitor or histone deacetylase inhibitor$ or hdaci or hdis).ti,ab.	15
33	or/5-32	45
34	3 and 4 and 33	2
35	(202307$ or 202308$ or 202309$ or 202310$ or 202311$ or 202312$ or 2024$).up.	44.799
36	34 and 35	0

Table 133 Search strategy table for APA PsycInfo (Ovid). Date searched: April 29, 2024

Search Number	Search Terms	Results
1	(controlled clinical trial or clinical trial or randomized controlled trial).pt. or (controlled clinical trial$ or randomised controlled trial$ or randomized controlled trial$ or rct or (random$ adj2 (alloca$ or assign$ or distribut$ or group$)) or ((single or double or triple or treble) adj2 (blind$ or mask$)) or placebo$).ti,ab.	143.766

2	(case study or abstract report or note or comment or case reports or editorial or letter).mp.	234.572
3	1 not 2	139.590
4	(myeloma$ or (multiple adj2 myeloma$) or plasmacytom$ or plasmocytom$ or mgus or (monoclonal adj2 gammopath$) or plasma cell myeloma).ti,ab.	471
5	(melphalan or alanine nitrogen mustard or l-phenylalanine mustard or l-sarcolysin or l-sarcolysin phenylalanine mustard or l-sarcolysine or phenylalanine mustard or phenylalanine nitrogen mustard or alkeran or alkerana or melfalan or melphalanum or sarkolysin or cb-3025 or wr-19813 or l-pam or lpam).ti,ab.	18
6	(bortezomib or velcade or ldp 341 or mln341 or ps-341).ti,ab.	76
7	(carfilzomib or kyprolis or pr-171).ti,ab.	19
8	(cyclophosphamide or ciclofosfamida or ciclofosfamide or claphene or cp monohydrate or cyclophospham or cyclophosphamid monohydrate or cyclophosphamidum or cyclophosphan or cyclophosphanum or cytophosphane or mitoxan or syklofosfamid or zytoxan or clafen or cytoxan or neosar or revimmune or carloxan or cicloxal or cycloblastin or cycloblastine or cyclo-cell or cyclostin or cyclostine or cytophosphan or endoxan or endoxana or enduxan or fosfaseron or genoxal or ledoxina or procytox or sendoxan or asta b 518 or b-518 or b518 or wr-138719).ti,ab.	577
9	(daratumumab or jnj-54767414 or darzalex or humax cd38 or monoclonal antibody humax cd38).ti,ab.	2
10	(doxorubicin or adriamycin or doxil or dox-sl or evacet or lipodox or chloridrato de doxorrubicina or adriacin or adriblastina or adriblastine or adrimedac or doxo-cell or doxolem or doxorubin or farmiblastina or fi-106).ti,ab.	207
11	(elotuzumab or empliciti or huluc63).ti,ab.	1
12	(panobinostat or farydak or faridak or lbh 589 or lbh 589a or lbh 589b or lbh589 or lbh589a or lbh589b or nvp lbh 589 or nvp lbh589).ti,ab.	7
13	(ixazomib or ninlaro or mln9708).ti,ab.	1
14	(lenalidomide or imid-1 or revlimid or cc-5013 or cdc 501).ti,ab.	17
15	(bendamustine or bendeka or cimet 3393 or cytostasan or cytostasane or imet 3393 or levact or ribomustin or ribovact or treanda or zimet 3393 or zimet3393).ti,ab.	6

16	(pomalidomide or pomalyst or imnovid or cc-4047 or cc4047).ti,ab.	5
17	(thalidomide or synovir or thalomid or contergan or distaval or kevadon or neurosedyn or pantosediv or sedoval k-17 or softenon or talimol).ti,ab.	157
18	(dexamethasone or desamethasone or dexamethasonum or hexadecadrol or maxidex or methylfluorprednisolone or aacidexam or adexone or aknichthol dexa or alin depot or alin oftalmico or amplidermis or anemul mono or auricularum or auxiloson or baycuten or cortidexason or cortisumman or decacort or decalix or decameth or dectancyl or dekacort or deltafluorene or desameton or dexacortal or dexacortin or dexafarma or dexafluorene or dexalocal or dexa-mamallet or dexamecortin or dexamonozon or dexapos or dexa-rhinosan or dexa-scheroson or dexa-sine or dexinoral or dexone or dinormon or dluorodelta or dortecortin or lokalison-f or loverine or millicorten or mymethasone or orgadrone or spersadex or visumetazone).ti,ab.	3.787
19	(ancortone or apo-prednisone or biocortone or colisone or cortan or cortidelt or cortiprex or cutason or dacorten or de cortisyl or decortancyl or decortin or decortine or decortisyl or dehydrocortisone or dekortin or delitisone or dellacort a or delta cortelan or delta cortisone or delta dome or delta e or delta prenovis or delta-dome or deltacorten or deltacortene or deltacortisone or deltacortone or deltasone or deltison or deltisona or deltra or di adreson or di-adreson or diadreson or drazone or encorton or encortone or enkorton or fernisone or hostacortin or insone or liquid pred or lodotra or me-korti or meprison or metacortandracin or meticorten or meticortine or nisona or nsc 10023 or nsc10023 or orasone or orisane or panafcort or paracort or pehacort or precort or precortal or prednicen-m or prednicorm or prednicot or prednidib or prednison or prednisone alcohol or prednisone intensol or prednisone$ or prednitone or pronison or pronisone or pronizone or pulmison or rayos or rectodelt or servisone or steerometz or sterapred or ultracorten or urtilone or winpred).ti,ab.	528
20	(etopophos or celltop or citodox or eposin or epsidox or etomedac or etomedec or etophos or etopol or etopos or etoposid or etoposide toniribate or etoposido or etopoxan or etosid or lastet or lastet-s or nexvep or nk 171 or nk171 or nsc 141540 or nsc141540 or posid or toposar or topresid or vepesid or vepeside or vespid or vp 16 or vp 16 213 or vp 16-213 or vp 16213 or vp-tec or vp16 or vp16 213 or vp16-213 or vp16213).ti,ab.	45
21	(vincristine or l 37231 or l37231 or leurocristine or Vincasar).ti,ab.	129
22	(vorinostat or "mk 0683" or mk0683 or vorinostat msd or Zolinza).ti,ab.	26
23	(nivolumab or bms 936558 or bms936558 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or opdivo).ti,ab.	26

24	(pembrolizumab or keytruda or lambrolizumab or mk 3475 or mk3475 or sch 900475 or sch900475).ti,ab.	16
25	(mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or tecentriq or tecntriq).ti,ab.	0
26	(imfinzi or medi 4736 or medi4736).ti,ab.	0
27	((pd 1 or pd l1 or pd-1 or pd-l1) adj2 (inhibition or inhibitors or inhibitor or inhibit$)).ti,ab. or checkpoint inhibitors.mp.	79
28	(isatuximab or sar 650984 or sar650984 or Sarclisa).ti,ab.	0
29	3412470a0v.mp. or (melflufen hydrochloride or melflufen or ygalo).ti,ab.	0
30	(cereblon modulator$ or imids or (immunomodulatory adj3 imide) or (cd38 antigen or cd138 antigen or cd 38 antigen or cd 138 antigen or ((cd38 or cd138 or 'cd 138' or 'cd 38' or 'cd 138') adj2 (antigen or antiboby)))).ti,ab.	7
31	(chimeric antigen receptors or chimeric immunoreceptor or chimeric immunoreceptors or chimeric antigen).mp. or ucar t.ti,ab.	21
32	(hdac inhibitor or histone deacetylase inhibitor$ or hdaci or hdis).ti,ab.	510
33	or/5-32	5.963
34	3 and 4 and 33	5
35	(202307$ or 202308$ or 202309$ or 202310$ or 202311$ or 202312$ or 2024$).up.	164.873
36	34 and 35	0

H.2 Systematic selection of studies

All retrieved studies were assessed against the eligibility criteria (see Table 134). Primary (Level 1, title and abstract) screening was performed by two independent reviewers who reviewed each reference identified in the literature search. Any uncertainty or conflict regarding the inclusion/exclusion decision of studies was checked by a third reviewer.

For secondary (Level 2) screening, the full articles were obtained. These were reviewed by two independent reviewers against the eligibility criteria. Any uncertainty regarding the inclusion of a study was checked by a third reviewer.

All included and excluded decisions were recorded in Microsoft Excel, together with the reasons for these decisions, in alignment with the PICOS framework. A single reason for exclusion was recorded, even when the studies were excluded on multiple criteria. The

decision recorded was according to the order of the PICOS criteria as per the previous SLR (i.e. review/editorial, followed by age, animal/in-vitro, disease, line of therapy, study design, interventions, and language).

To avoid the double reporting of results, multiple reports of single studies were identified based on patient population, location and setting, intervention details, baseline data and study data, including trial name and registry number.

The inclusion and exclusion criteria are shown in Table 134 below.

Table 134 Inclusion and exclusion criteria used for assessment of studies

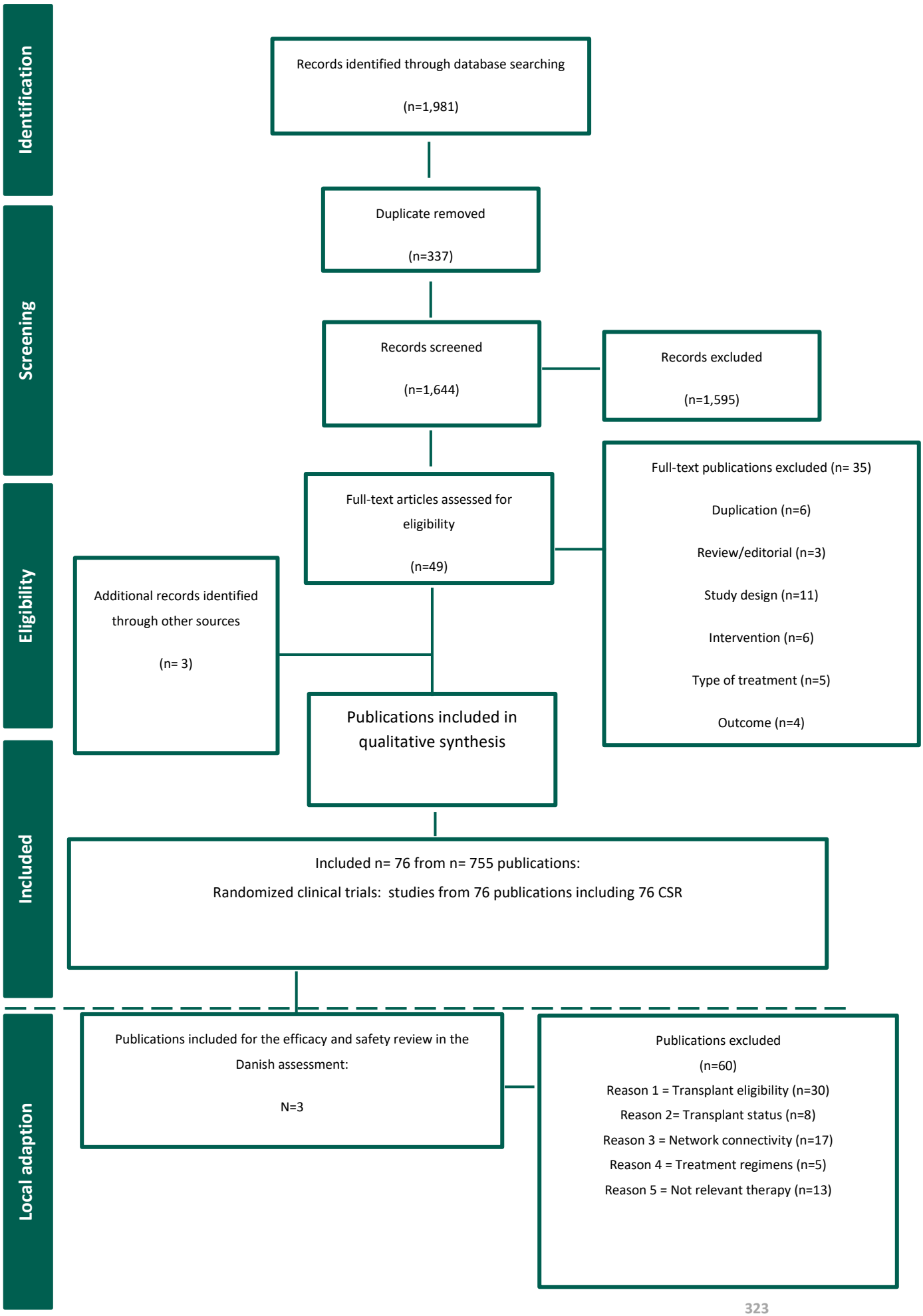
Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Adult (age ≥ 18 years) patients with newly diagnosed or previously untreated MM (both transplant-eligible and transplant-ineligible patient populations) [a]	Paediatric population Healthy volunteers Patients with RRMM	N/A
Intervention	IsaVRd (Sarclisa® [isatuximab], Velcade [bortezomib], Revlimid® [lenalidomide], dexamethasone) VCd (Velcade [bortezomib], cyclophosphamide, dexamethasone) VTd (Velcade [bortezomib], thalidomide, dexamethasone) RVd or VRd (Velcade [bortezomib], Revlimid [lenalidomide], dexamethasone) Rd (Revlimid [lenalidomide], dexamethasone) Vd (Velcade [bortezomib], dexamethasone) CTd (cyclophosphamide, thalidomide, dexamethasone) DVMP or D-Vmp (daratumumab with Velcade [bortezomib], melphalan, prednisone) DRd (daratumumab, Revlimid [lenalidomide], dexamethasone) VMP (Velcade [bortezomib], melphalan, prednisone)	Any non-pharmacological Interventions Interventions not mentioned in inclusion criteria Studies where interventions were used as maintenance therapy unless studies also included an evaluation of induction and/or consolidation therapies	N/A

	DVRd (Darzalex [daratumumab], Velcade [bortezomib], Revlimid [lenalidomide], dexamethasone) ERd (elotuzumab, Revlimid [lenalidomide], dexamethasone) EKRd (Elotuzumab, Kyprolis [carfilzomib], Revlimid [lenalidomide], dexamethasone) MPR (melphalan, prednisone with Revlimid [lenalidomide])b MPT (melphalan, prednisone with thalidomide)b DVCd (Darzalex [daratumumab], Velcade [bortezomib], cyclophosphamide and dexamethasone)		
Comparators	Any, including but not limited to: Placebo Best supportive care (author defined) Any other pharmacological/non-pharmacological intervention (such as HSCT)[c]	No limit on comparators	N/A
Outcomes	Overall survival, progression-free survival, event-free survival Time to Progression, Time to Next Treatment, Overall Response Rate, Complete response (CR), Stringent CR, Partial Response (PR), Very Good PR, Stable Disease Minimal Residual Disease (MRD) negativity Duration of treatment, disease control rate, duration of response, time to response, time to treatment failure Health-related quality of life (EORTC-QLQ-C30 and QLQ-MY20, EQ-5D, etc.) Safety, tolerability (Serious Adverse Events [SAEs], Grade 3 or 4, discontinuation due to AE)	Trials which primary or secondary outcomes are not included in the list of inclusion criteria	N/A

	Subgroups (for extractions): MRD		
Study design/publication type	Phase IIb/III/IV/unclear RCTs Systematic reviews (for identifying unique studies not captured otherwise)	Reviews, letters, comments and editorials Case studies or case reports RCTs Phase I–IIa Non-RCTs, single arm trials, RWE/observational studies Pharmacokinetic studies Economic studies	N/A
Language restrictions	English	Non-english	N/A

H.3 PRISMA flow diagram

The PRISMA diagram is illustrated to provide an overview of the identified literature.


Identification
Screening
Eligibility
Included
Local adaption
Records identified through database searching
(n=1,981)
Duplicate removed
(n=337)
Records screened
(n=1,644)
Records excluded
(n=1,595)
Full-text articles assessed for eligibility
(n=49)
Full-text publications excluded (n= 35)
Duplication (n=6)
Review/editorial (n=3)
Study design (n=11)
Intervention (n=6)
Type of treatment (n=5)
Outcome (n=4)
Additional records identified through other sources
(n= 3)
Publications included in qualitative synthesis
Included n= 76 from n= 755 publications:
Randomized clinical trials: studies from 76 publications including 76 CSR
Publications included for the efficacy and safety review in the Danish assessment:
N=3
Publications excluded
(n=60)
Reason 1 = Transplant eligibility (n=30)
Reason 2= Transplant status (n=8)
Reason 3 = Network connectivity (n=17)
Reason 4 = Treatment regimens (n=5)
Reason 5 = Not relevant therapy (n=13)

H.4 Included studies

Table 135 shows the 3 relevant RCT studies which was identified through the literature search. The table contains information regarding the aim, study design, population, intervention and outcome from each study.

Table 135 Overview of study design for studies included in the analysis

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
IMROZ	Demonstrate the benefit of IsaVRd in prolonging PFS as compared to VRd in TIE NDMM patients.	RCT, open-label, Phase III	446	IsaVRd (n=265) vs VRd (n=181)	PFS*	CR rate*
MAIA	Compare the efficacy of DRd to that of Rd in terms of PFS for TIE NDMM patients.	RCT, open-label, Phase III	737	DRd (n=368) vs Rd (n=369)	PFS**	CR rate**
ALCYONE	Determine whether DVMP will prolong PFS compared to VMP in TIE NDMM patients.	RCT, open-label, Phase III	706	DVMP (n=350) vs VMP (n=356)	PFS***	ORR**

Note: FPI, First Participant In; TIE, Transplant Ineligible; NDMM, Newly Diagnosed Multiple Myeloma; RR, Response Rate, TTR, Time To Relapse

* Time-to-event endpoints measured at the interim analysis cut-off date of September 26th, 2023. Median follow-up (as of September 26, 2023): 59.73 months. The interim analysis was performed after 162 events of disease progression or death had occurred (which was 73% of the 222 events specified for the planned final analysis).

** From randomization to disease progression, death, subsequent anti-myeloma therapy, withdrawal of consent to study participation or clinical cut-off (CCO) whichever occurs first (up to 3.5 years).

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period

*** From randomization to disease progression (or death for PFS) whichever occurs first (up to 2.4 years).

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H.5 Excluded fulltext references

Thirty-one studies were not deemed suitable for inclusion in ITCs and were excluded from the evidence base: eight studies were excluded based on transplant status being unknown or including mixed transplant-eligible and -ineligible populations; 17 based on network connectivity and investigating non-relevant comparators; four based on study design; one based on differences in patient characteristics; and one due to the non-reporting of relevant outcome data.

Standardized reason for exclusion	Study name	Detailed reason for exclusion
Transplant status (N = 8)*	CEPHEUS	Unclear transplant-eligibility and lack of relevant outcome data
	ECOG-ACRIN E4A03	Mixed transplant-eligible and -ineligible population. Data not reported for transplant-eligible patients only and no suitable proxy available
	ENDURANCE	Mixed transplant status
	Li 2019	Mixed transplant-eligible and -ineligible population. Data not reported for transplant-eligible patients only and no suitable proxy available
	Mookerjee 2017	Representative of transplant-eligible population
	Sahai 2013	Transplant status of patients is unclear
	SWOG-1211	Transplant status of patients is unclear

	Zheng 2021	Representative of transplant-eligible population
Network Connectivity (N = 17)	AMaRC 03-16	Does not connect to a network
	Beroycob 2020	Reduced to single-arm trial when non-relevant comparators were excluded which cannot be used in NMA
	CLARION	Reduced to single-arm trial when non-relevant comparators were excluded which cannot be used in NMA
	ELOQUENT-1	Reduced to single-arm trial when non-relevant comparators were excluded which cannot be used in NMA
	EMN20	Reduced to single-arm trial when non-relevant comparators were excluded which cannot be used in NMA
	GEM2005MAS65/GEM05	Reduced to single-arm trial when non-relevant comparators were excluded which cannot be used in NMA
	GEM-CLARIDEX	Reduced to single-arm trial when non-relevant comparators were excluded which cannot be used in NMA
	IFM 2017-03	Reduced to single-arm trial when non-relevant comparators were excluded which cannot be used in NMA
	JCOG1105	Compared two alternative dosing regimens of VMP
	KEYNOTE-185	Reduced to single-arm trial when non-relevant comparators were excluded which cannot be used in NMA

	Kubo 2020	Reduced to single-arm trial when non-relevant comparators were excluded which cannot be used in NMA
	MYELOMA IX	Reduced to single-arm trial when non-relevant comparators were excluded which cannot be used in NMA
	PETHEMA/GEM2010MAS65	Reduced to single-arm trial when non-relevant comparators were excluded which cannot be used in NMA
	RV-MM-PI-0752	Compared the same induction treatment (Rd) with and without lenalidomide (R) maintenance
	San-Miguel 2014	Reduced to single-arm trial when non-relevant comparators were excluded which cannot be used in NMA
	SWOG-S0232	Reduced to single-arm trial when non-relevant comparators were excluded which cannot be used in NMA
Treatment regimens (N = 5)	EMN01	A lower dose of R was given in the Rd arm during weeks 36 to progression due to the induction-maintenance design (10 mg versus 25 mg)
	Hungria 2016	Variations were observed in the CTd regimens used in Hungria 2016 and the CTd arm of MYELOMA IX
	MM-015	Placebo maintenance was given in the MP arm following MP induction whereas R maintenance was given in the MPR arm. Other trials in the network had either fixed-length MP or consistent maintenance therapy across both arms

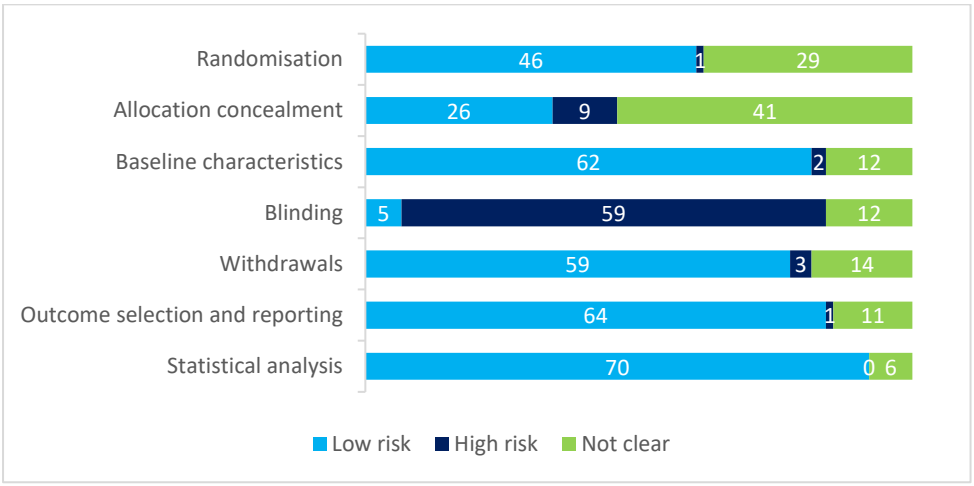
	Palumbo 2008	Different treatment designs compared with other trials investigating MP versus MPT
	Waage 2010	Different treatment designs compared with other trials investigating MP versus MPT
Outcome data (N = 1)	Suzuki 2019	Does not report relevant outcome data

Key: EMA, European Medicine Agency; ITC, Indirect treatment comparison; NMA, network meta-analysis, Rd; Lenalidomide + dexamethasone, VMP, Bortezomib + melphalan + prednisone.

Note: *30 transplant-eligible studies were also excluded that are not listed here.

16.6 Quality assessment

All included studies were subject to a quality appraisal using the standard NICE checklist. Quality assessment was done by a single independent reviewer and was quality checked by a second, senior reviewer.



Most of the trials were of good quality as the method of randomization was reported in more than 50% of the studies, indicating a low risk of bias. In addition to this, the risk of bias was low in about 85% of the trials since the groups had comparable baseline characteristics. Risk of bias was also low in 95% of the trials in terms of unexpected imbalances in the dropouts and in 90% of the trials regarding statistical analysis. However, there was a high risk of selection bias in about 50% of the trials as the allocation concealment was not reported in them. There was also a high risk of bias regarding blinding in approximately 80% of the trials, as the majority were open label. Only 7% were double-blinded and the risk of bias was unclear in about 10% of the trials.

H.6 Unpublished data

N/A

Appendix I. Literature searches for health-related quality of life

I. Health-related quality-of-life search

Table 136 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
N/A	N/A	N/A	N/A

Abbreviations:

Table 137 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A

Table 138 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	N/A	N/A	N/A	N/A

I.1 Search strategies

I.2 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

J. External literature for input to the health economic model

N/A

Table 139 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
N/A	**N/A**	**N/A**	**N/A**

Abbreviations:

Example: Targeted literature search for [estimates]

Table 140 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
N/A	N/A	N/A	N/A

Abbreviations:

[Describe the selection process and criteria for inclusion or exclusion.]

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk