Key considerations for treatment selection and sequencing in patients with RRMM: Lessons from real-life clinical practice

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Expert panel

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Agenda

Navigating treatment decisions in patients with RRMM who have relapsed following 1–3 prior lines of therapy

Addressing the complexities of treatment choice in heavily pretreated patients with RRMM following >3 prior lines of therapy

Unravelling sequencing strategies for patients with RRMM in the early- and later-line settings

RRMM, relapsed or refractory multiple myeloma.

Navigating treatment decisions in patients with RRMM who have relapsed following 1–3 prior lines of therapy

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Selected phase III trials in RRMM: ≤3 lines of therapy

Trial	Regimen (ratio)	mFU, mo	ORR, %	mPFS, mo	OS, mo
ELOQUENT-2 (N=635)[1,2]	Elo-Rd vs Rd (1:1)	48	79 vs 66	19 vs 15	48 vs 40*
APOLLO (N=304)[3]	Dara-Pd vs Pd (1:1)	17	69 vs 46	12 vs 7	—
CASTOR (N=498)[4,5]	Dara-Vd vs Vd (1:1)	19	85 vs 63	17 vs 7	50 vs 39†
CANDOR (N=466)[6,7]	Dara-Kd vs Kd (2:1)	≈27	84 vs 75	29 vs 15	NR vs NR
ICARIA-MM (N=307)[8,9]	Isa-Pd vs Pd (1:1)	12	60 vs 35	12 vs 7	25 vs 18‡
IKEMA (N=302)[10,11]	Isa-Kd vs Kd (3:2)	44	87 vs 84	36 vs 19	—
OPTIMISSM (N=559)[12]	PVd vs Vd (1:1)	16	82 vs 50	11 vs 7	—
BOSTON (N=402)[13]	SVd vs Vd (1:1)	13 vs 17	76 vs 62	14 vs 9	NR vs 25§

Treatment for patients with RRMM varies, as some patients have received prior stem cell transplants which dictates up-front drug regimen selection, in particular the timing and dosing of R.
Specific data from clinical trials on patients refractory to R are lacking to guide critical clinical decisions for these patients[14]

Direct comparisons between trials should not be made due to differences in trial design.
*Minimum follow-up = 70.6 mo; †median follow-up = 72.6 mo; ‡median follow-up = 35.3 mo; §median follow-up = 17.3 mo (SVd) vs 17.5 mo (Vd).
d, dexamethasone; dara, daratumumab; elo, elotuzumab; FU, follow-up; isa, isatuximab; K, carfilzomib; m, median; mo, months; NR, not reached; ORR, overall response rate; OS, overall survival; P, pomalidomide; PFS, progression-free survival; R, lenalidomide; RRMM, relapsed or refractory multiple myeloma; S, selinexor; V, bortezomib.

1. Dimopoulos MA, et al. *Cancer*. 2018;124:4032–43; 2. Dimopoulos MA, et al. *Blood Cancer J*. 2020;10:91; 3. Dimopoulos MA, et al. *Lancet Oncol*. 2021;22:801–12; 4. Sonneveld P, et al. *J Clin Oncol*. 2023;41:1600–9; 5. Mateos M-V, et al. *Clin Lymphoma Myeloma Leuk*. 2020;20:509–18; 6. Usmani SZ, et al. *Lancet Oncol*. 2022;23:65–76; 7. Dimopoulos MA, et al. *Lancet*. 2020;396:186–97; 8. Richardson PG, et al. *Lancet Oncol*. 2022;23:416–27; 9. Attal M, et al. *Lancet*. 2019;394:2096–107; 10. Moreau P, et al. *Lancet*. 2021;397:2361–71; 11. Moreau P, et al. *Ann Oncol*. 2022;33:664–5; 12. Richardson PG, et al. *Lancet Oncol*. 2019;20:781–94; 13. Grosicki S, et al. *Lancet*. 2020;396:1563–73; 14. Raje N, et al. *Blood Cancer J*. 2023;13:41.

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Factors influencing treatment sequencing in patients with RRMM[1,2]

Disease characteristics

- Genetic alterations
  - Cytogenic risk
- Duration of prior remission
- Extramedullary disease
- Tumour burden
- Rate of increase of M-protein
- End-organ function

Patient characteristics

- Age and frailty
- Performance status
- Comorbidities*
- Bone marrow reserve
- Patient preference
- Clinical trial eligibility
- Treatment compliance/access

Prior therapy

- Prior therapy and refractoriness
  - IMiD
  - PI
  - anti-CD38 mAb
- Response observed
- Toxicities experienced
- SCT
  - Eligibility
  - Prior SCT

Treatment goals vary among patients with RRMM. Disease control, extension of survival and maintenance of QoL are important considerations when setting treatment goals[1]

*For example, CVD, COPD, renal impairment and polyneuropathy.

CD, cluster of differentiation; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; IMiD, immunomodulatory drug; mAb, monoclonal antibody; PI, proteasome inhibitor; QoL, quality of life; RRMM, relapsed or refractory multiple myeloma; SCT, stem cell transplant.

1. Podar K, Leleu X. *Cancers (Basel)*. 2021;13:5154; 2. van de Donk, NWCJ. *Hematology Am Soc Hematol Educ Program*. 2020;2020:248–58.

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Patient with RRMM, case 1: Younger, R-refractory

Male, 54 years

Patient and disease characteristics

- No comorbidities
- Performance status: 0
- Bone marrow: 50% with t(11;14)

Prior therapy

- Treated initially with RVd and auto-SCT
  - R-maintenance

Current situation

- Disease has progressed after 3 years

What should the patient be offered next?

Auto-SCT, autologous stem cell transplant; d, dexamethasone; R, lenalidomide; RRMM, relapsed or refractory multiple myeloma; V, bortezomib.

Patient with RRMM, case 2: Older, non-R-refractory

Female, 78 years

Patient and disease characteristics

- Hypertension and evidence of renal insufficiency
- Performance status: 1
- Bone marrow: 60% with t(4;14)

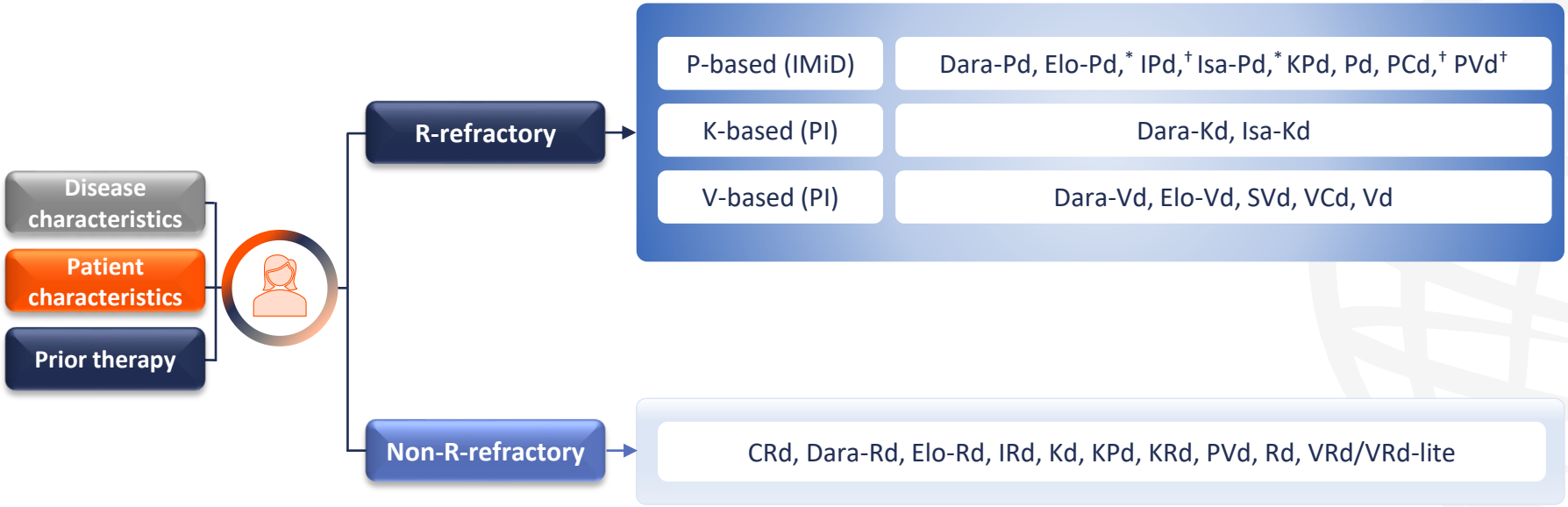
Prior therapy

- Auto-SCT ineligible; treated initially with VCd
  - Progression: 8 months
- Second line: Dara-Rd
  - Progression: 10 months

What should the patient be offered next?

Auto-SCT, autologous stem cell transplant; C, cyclophosphamide; d, dexamethasone; dara, daratumumab; R, lenalidomide; RRMM, relapsed or refractory multiple myeloma; V, bortezomib.

Selected treatment options following early relapse[1–3]



*After two prior therapies including R and a PI; †after two prior therapies including an IMiD and a PI and disease progression on/within 60 days of completion of last therapy.
C, cyclophosphamide; d, dexamethasone; dara, daratumumab; elo, elotuzumab; I, ixazomib; IMiD, immunomodulatory drug; isa, isatuximab; K, carfilzomib; P, pomalidomide; PI, proteasome inhibitor; R, lenalidomide; S, selinexor; V, bortezomib.

1. NCCN. Clinical Practice Guidelines in Oncology: Multiple myeloma. Version 3. 2023. Available at: www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf (accessed 10 May 2023);
2. Podar K, Leleu X. *Cancers (Basel)*. 2021;13:5154; 3. van de Donk NWCJ. *Hematology Am Soc Hematol Educ Program*. 2020;2020:248–58.

Addressing the complexities of treatment choice in heavily pretreated patients with RRMM following >3 prior lines of therapy

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RRMM, relapsed or refractory multiple myeloma.

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Selected recommendations for patients treated with >3 prior lines of therapy[1]*

>3 lines of therapy	>4 lines of therapy including, an anti-CD38 mAb, a PI and an IMiD
• Earlier line combinations that have not been used previously, including P, K, Isa and S • High dose/fractionated C • Bendamustine +/- Vd **or** Kd **or** Rd	• Idecabtagene vicleucel • Ciltacabtagene autoleucel • Teclistamab ○ Belantamab mafodotin-blmf†

Patients with RRMM in later lines may be triple or quadruple refractory; in still later relapses they may also be penta-exposed, or even penta-refractory[2]

*Selected regimens. Regimens are ordered according to NCCN category of evidence and consensus alphabetically; †useful in certain circumstances if available through the compassionate use programme.
C, cyclophosphamide; CAR, chimeric antigen receptor; CD, cluster of differentiation; d, dexamethasone; IMiD, immunomodulatory drug; Isa, isatuximab; K, carfilzomib; mAb, monoclonal antibody; P, pomalidomide; PI, proteasome inhibitor; R, lenalidomide; RRMM, relapsed or refractory multiple myeloma; S, selinexor; V, bortezomib.

1. NCCN. Clinical Practice Guidelines in Oncology: Multiple myeloma. Version 3.2023. Available at: www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf (accessed 10 May 2023);
2. Nathwani N, et al. *Am Soc Clin Oncol Educ Book*. 2021;41:358–75.

Patient with RRMM, case 1: Younger, R-refractory

Male, 54 years

Patient and disease characteristics
- No comorbidities
- Performance status: 0
- Bone marrow: 50% with t(11;14)

Prior therapy
- Treated initially with RVd and auto-SCT
- R-maintenance

59 years

Patient and disease characteristics
- Renal insufficiency (creatinine 1.9 mg/dL)
- Evidence of extramedullary disease
- Performance status: 1

Prior therapy
- Second line: Dara-Pd
- Third line: Venetoclax-Vd
- Fourth line: KCd

What should the patient be offered next?

Auto-SCT, autologous stem cell transplant; C, cyclophosphamide; d, dexamethasone; Dara, daratumumab; K, carfilzomib; P, pomalidomide; R, lenalidomide; RRMM, relapsed or refractory multiple myeloma; V, bortezomib.

Patient with RRMM, case 2: Older, non-R-refractory

Female, 78 years → **81 years**

Patient and disease characteristics

- Hypertension and evidence of renal insufficiency
- Performance status: 1
- Bone marrow: 60% with t(4;14)

Prior therapy

- Auto-SCT ineligible; treated initially with VCd
  - Progression: 8 months
- Second line: Dara-Rd
  - Progression: 10 months

Patient and disease characteristics

- History of coronary heart disease (EF: 50%)
- Performance status: 2

Prior therapy

- Third line: KPd
- Fourth line: KCd
  - Progression: 2 months

What should the patient be offered next?

Auto-SCT, Autologous stem cell transplant; C, cyclophosphamide; d, dexamethasone; dara, daratumumab; EF, ejection fraction; K, carfilzomib; P, pomalidomide; R, lenalidomide; RRMM, relapsed or refractory multiple myeloma; V, bortezomib.

Unravelling sequencing strategies for patients with RRMM in the early- and later-line settings

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Emerging therapeutic strategies for RRMM

ADC[1]

- Anti-BCMA + amanitin derivative
- Modakafusp alpha*

BsAb

Targets

- BCMA-CD3[1]
- BCMA-CD38[1]
- GPRC5D-CD3[2]
- FcRH5-CD3[2]

CAR T-cell therapies[1,2]

Targets

- Anti-BCMA allo-CAR T
- GPRC5D CAR T

IMiD – CELMoDs[3]

- Iberdomide
- Mezigdomide

Novel small molecules

- **Anti-BCL-2**: BGB-11417[4]
- **Anti-GLS1**: Telaglenastat[5]
- **Anti-HDAC class I and IIb**: Purinostat mesylate[6]

New therapeutic options for patients with RRMM in the later line include ADCs, BsAbs and CAR T cells; trials are currently underway to translate approved CAR T cells into the earlier line setting[3]

*Immunocytokine.

ADC, antibody-drug conjugate; allo, allogenic; BCL-2, B-cell leukaemia/lymphoma-2; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; CAR, chimeric antigen receptor; CD, cluster of differentiation; CELMoD, cereblon E3 ligase modulating drug; FcRH5, Fc receptor-homolog 5; GLS, glutaminase; GPRC5D, G protein–coupled receptor, class C, group 5; HDAC, histone deacetylase; IL, interleukin; IMiD, immunomodulatory drug; RRMM, relapsed or refractory multiple myeloma.

1. Shah N, et al. *Leukemia.* 2020;34:985–1005; 2. Podar K, Leleu X. *Cancers (Basel)*. 2021;13:5154; 3. Raje N, et al. *Blood Cancer J*. 2023;13:41; 4. Quach H, et al. *Blood.* 2022;140(Suppl. 1):7269–71; 5. Gonsalves WI, et al. *Blood*. 2022;140(Suppl. 1):7315–6; 6. Wang J, et al. *Blood*. 2022;140(Suppl. 1):6612–3.

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Male, 54 years

Patient and disease characteristics
- No comorbidities
- Performance status: 0
- Bone marrow: 50% with t(11;14)

Prior therapy
- Treated initially with RVd and auto-SCT
- R-maintenance

59 years

Patient and disease characteristics
- Renal insufficiency (creatinine 1.9 mg/dL)
- Evidence of extramedullary disease
- Performance status: 1

Prior therapy
- Third line: Dara-Pd
- Fourth line: Venetoclax-Vd
- Fifth line: KCd

60 years

Prior therapy
- Idecabtagene vicleucel
  - Relapse: 18 months

What should the patient be offered next?

Auto-SCT, autologous stem cell transplant; C, cyclophosphamide; d, dexamethasone; dara, daratumumab; K, carfilzomib; P, pomalidomide; R, lenalidomide; RRMM, relapsed or refractory multiple myeloma; V, bortezomib.

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