Multiple Myeloma (MM) Refractory to Lenalidomide: A Systematic Literature Review (SLR) of Randomised Controlled Trials (RCTs)

McNamara S[1], Kazeem G[1], Carter JA[2], Bitetti J[3], Wang F[4]

[1]GSK, Stevenage, Hertfordshire, UK; [2]OPEN Health, Bethesda, MD, USA; [3]GSK, Zug, Switzerland; [4]GSK, Collegeville, PA, USA.

Introduction

- In an expanding and growing landscape for treatment of patients with multiple myeloma (MM), lenalidomide is increasingly used in early lines of therapy.[1–3]
- Patients treated with lenalidomide, particularly in maintenance settings, frequently experience relapse and become refractory.[1, 4]
- Randomised controlled trials (RCTs) in second line and beyond (2L+) include patients with varying prior lenalidomide exposure resulting in variable outcomes.[5]
- Understanding the evidence in support of therapies and their associated outcomes is critical.

Objective

To review the outcomes of patients with relapsed/refractory MM who are refractory to lenalidomide in 2L+ RCTs.

Methods

- A systemic literature review (SLR) identifying RCTs reporting data on patients with lenalidomide-refractory MM was conducted following the PRISMA-P checklist **(Figure 1)**.[6]
- Reports published up to December 2021 were identified through EMBASE, MEDLINE and additional electronic databases.
- Two independent reviewers screened the records and any discordance was resolved via discussion.
- The PICO framework was used to develop literature search strategies in broad populations of patients with relapsed/refractory MM to ensure comprehensive and bias-free searches.
- Results were subsequently refined to solely those studies reporting data on lenalidomide-refractory patients.

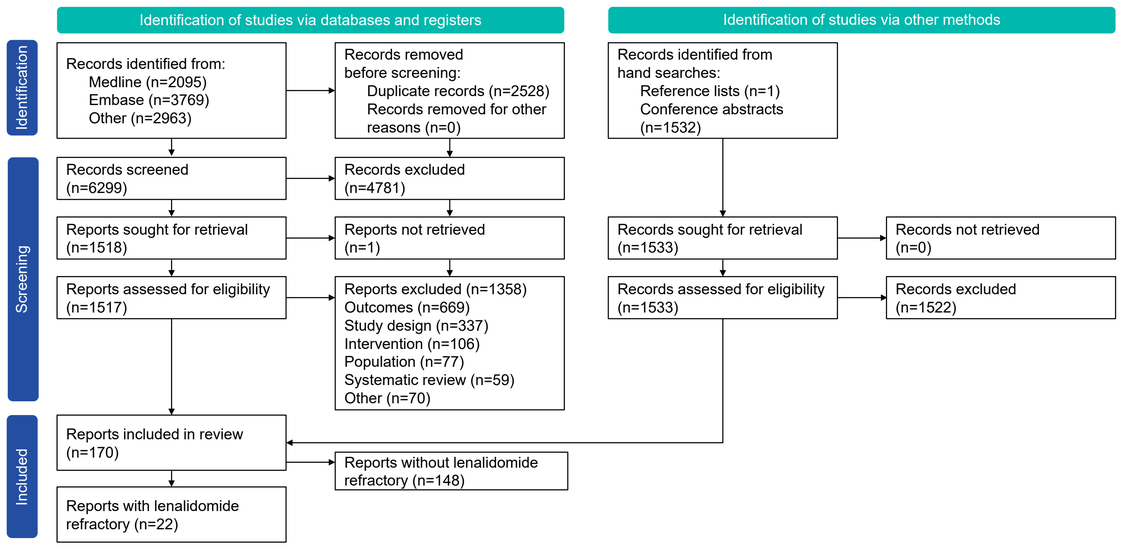
Conclusions

- While highly variable, the outcomes for patients with MM who are lenalidomide-refractory remain suboptimal.
- Patients who are refractory to lenalidomide experienced worse outcomes than populations containing a mix of non-refractory and refractory patients.
- High unmet need remains for novel, more efficacious therapies with new mechanisms of action in this hard-to-treat patient population.

Results

- A total of 8827 studies were identified, of which patients with relapsed/refractory MM were reported in 47 studies (**Figure 1**).

Figure 1: **PRISMA diagram for identified studies**



- Patients with lenalidomide-refractory MM were included in 22 reports comprising 13 studies: APOLLO; ARROW; ASPIRE; BOSTON; CANDOR; CASTOR; ELOQUENT-3; ENDEAVOR; ICARIA-MM; IKEMA; MM-002; NIMBUS/MM-003; and OPTIMISMM (**Table 1**).

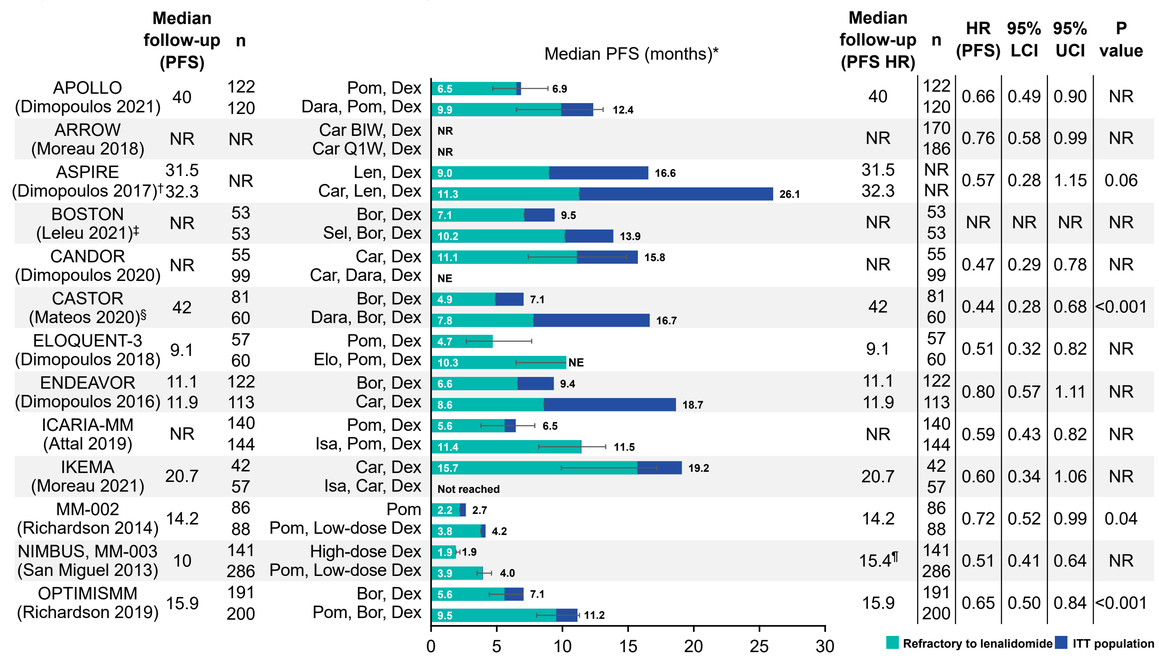
Table 1: **Reports with patients refractory to lenalidomide**

Study	Publication	RCT phase	Number of prior treatment lines	Treatment group	Median follow-up (months)	Cohort assessed (n)
APOLLO	Dimopoulos 2021[7]	III	≥1	Pom, Dex	40	122
				Dara, Pom, Dex	40	120
	Sonneveld 2021[8]	III	≥1	Pom, Dex	16.9	120
				Dara, Pom, Dex	16.9	116
ARROW	Moreau 2018[9]	III	≥2	Car BIW, Dex	NR	170
				Car Q1W, Dex	NR	186
ASPIRE	Dimopoulos 2017[10]	III	1–3	Len, Dex	31.5	NR
				Car, Len, Dex	32.3	NR
BOSTON	Leleu 2021[11]	III	≥1	Bor, Dex	NR	53
				Sel, Bor, Dex	NR	53
CANDOR	Dimopoulos 2020[12]	III	1–3	Car, Dex	NR	55
				Car, Dara, Dex	NR	99
CASTOR	Chanan-Khan 2016[13]	III	≥1	Bor, Dex	7.4	60
				Dara, Bor, Dex	7.4	45
	Lentzsch 2017[14]	III	≥1	Bor, Dex	19.4	81
				Dara, Bor, Dex	19.4	60
	Spencer 2018[15]	III	≥1	Bor, Dex	19.4	60
				Dara, Bor, Dex	19.4	45
	Mateos 2020[16]	III	≥1	Bor, Dex	42	81
				Dara, Bor, Dex	42	60
ELOQUENT-3	Dimopoulos 2018[17]	II	≥2	Pom, Dex	9.1	57
				Elo, Pom, Dex	9.1	60
	Dimopoulos 2019[18]	II	≥2	Pom, Dex	18.3	57
				Elo, Pom, Dex	18.3	60
	Dimopoulos 2021[19]	II	≥2	Pom, Dex	≥45	57
				Elo, Pom, Dex	≥45	60
ENDEAVOR	Dimopoulos 2016[20]	III	1–3	Bor, Dex	11.1	122
				Car, Dex	11.9	113
	Orlowski 2019[21]	III	1–3	Bor, Dex	43.7	123
				Car, Dex	44.3	113
ICARIA-MM	Attal 2019[22]	III	≥2	Pom, Dex	NR	140
				Isa, Pom, Dex	NR	144
IKEMA	Moreau 2021[23]	III	1–3	Car, Dex	20.7	42
				Isa, Car, Dex	20.7	57
MM-002	Richardson 2011[24]	I/II	≥2	Pom	NR	NR
				Pom, Low-dose Dex	NR	NR
	Richardson 2014[25]	II	≥2	Pom	14.2	86
				Pom, Low-dose Dex	14.2	88
NIMBUS, MM-003	San Miguel 2013[26]	III	≥2	Pom	10	141
				Pom, Low-dose Dex	10	286
	San Miguel 2015[27]	III	≥2	High-dose Dex	15.4	141
				Pom, Low-dose Dex	15.4	286
OPTIMISMM	Richardson 2019[28]	III	1–3	Bor, Dex	15.9	191
				Pom, Bor, Dex	15.9	200

BIW, bi-weekly/twice weekly; Bor, bortezomib; Car, carfilzomib; Dara, daratumumab; Dex, dexamethasone; Elo, elotuzumab; Isa, isatuximab; Len, lenalidomide; NR, not reported; Pom, pomalidomide; Q1W, every week; RCT, randomized controlled trial; Sel, selinexor

- Median progression-free survival (PFS) was reported in 12 studies (**Figure 2**), and ranged from 1.9 months in the NIMBUS study of high-dose dexamethasone to 15.7 months in the IKEMA study of carfilzomib and dexamethasone. Median PFS was not reported for patients who were refractory to lenalidomide in ARROW.
  - Median PFS was not yet reached in the IKEMA study (isatuximab, carfilzomib, and dexamethasone, median follow-up 20.7 months) or the CANDOR study (carfilzomib, daratumumab, and dexamethasone, median follow-up not reached).
  - Hazard ratios (HR) for PFS ranged from 0.44 (95% CI, 0.28–0.68) in the CASTOR study, assessing the addition of daratumumab to treatment of bortezomib and dexamethasone, to 0.80 (95% CI, 0.57–1.11) in the ENDEAVOR study comparing weekly carfilzomib treatment plus dexamethasone versus twice weekly carfilzomib plus dexamethasone (**Figure 2**).

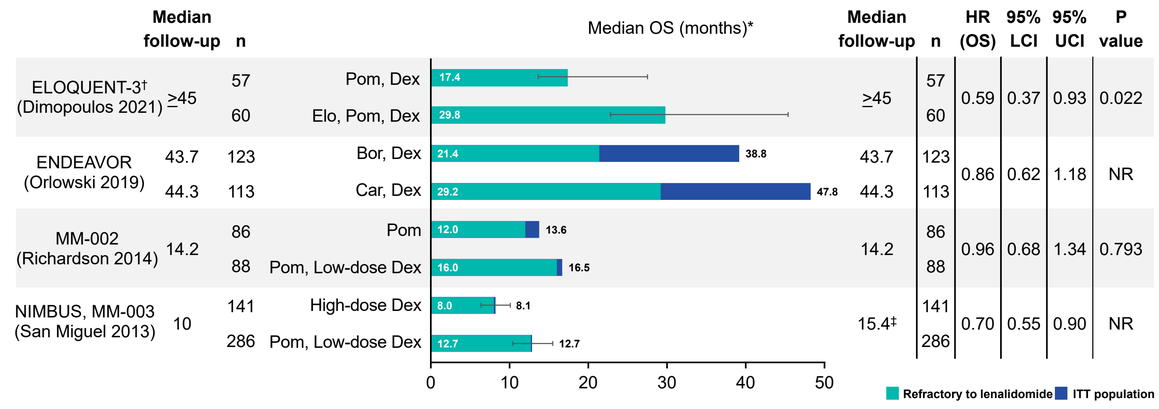
Figure 2: **PFS in patients refractory to lenalidomide & ITT population**



**Error bars are shown for the len-refractory population where available; no error bars are shown for the ITT population. †ITT PFS from Siegel 2018 (median follow-up 48.0-48.8 months).[29] ‡ITT PFS from Grosicki 2020 (median follow-up 13.2–16.5 months).[30] §ITT PFS from Wiesel 2019 (median follow-up 47 months).[31] ¶NIMBUS, MM-003 PFS HR from San Miguel 2015.[27] BIW, bi-weekly/twice weekly; Bor, bortezomib; Car, carfilzomib; Dara, daratumumab; Dex, dexamethasone; Elo, elotuzumab; Isa, isatuximab; ITT, intention to treat; Len, lenalidomide; LCI, lower confidence interval; NE, not evaluable; NR, not reported; Pom, pomalidomide; Q1W, every week; Sel, selinexor; UCI, upper confidence interval*

- Median overall survival (OS) varied from 8 months (high-dose dexamethasone [NIMBUS]) to 29.8 months (pomalidomide and dexamethasone plus elotuzumab [ELOQUENT-3] (**Figure 3**).
- HRs for OS ranged from 0.59 (95% CI, 0.37–0.93) in the ELOQUENT-3 study comparing pomalidomide and dexamethasone alone to pomalidomide and dexamethasone plus elotuzumab, to 0.96 (95% CI, 0.68–1.34) in the MM-002 study comparing treatment with pomalidomide and low-dose dexamethasone to treatment with pomalidomide alone (**Figure 3**).

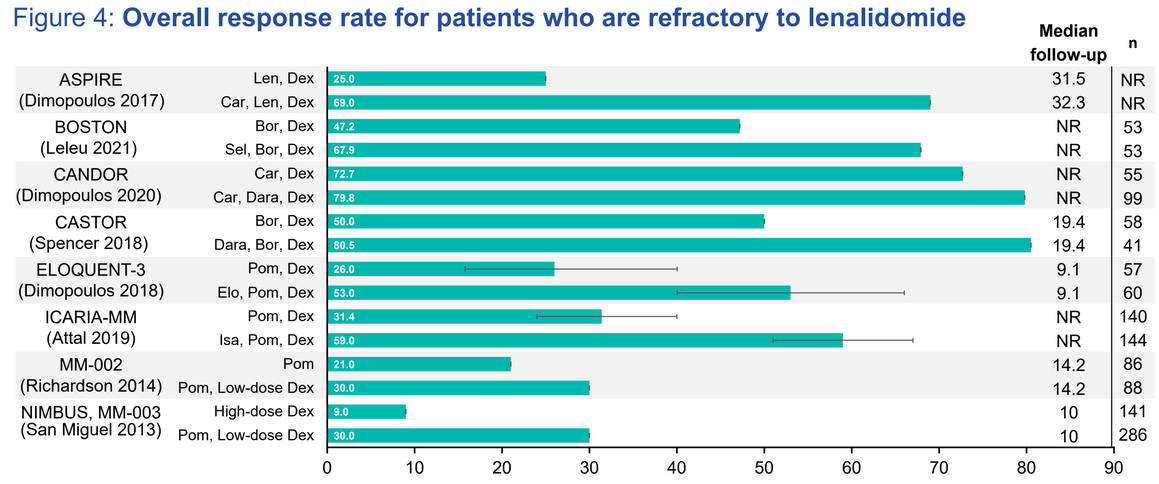
Figure 3: **Overall survival (OS) in patients refractory to lenalidomide & ITT population**



**Error bars are shown for the len-refractory population where available; no error bars are shown for the ITT population. †Len-refractory population is the ITT population. ‡NIMBUS, MM-003 OS HR from San Miguel 2015.[27] Bor, bortezomib; Car, carfilzomib; Dex, dexamethasone; Elo, elotuzumab; ITT, intention to treat; LCI, lower confidence interval; NR, not reached; Pom, pomalidomide; UCI, upper confidence interval*

- Data from the intention to treat (ITT) population are shown in **Figures 2 & 3** where available, to contextualise the lenalidomide-refractory data. Survival outcomes in lenalidomide-refractory patients were generally worse than the ITT population.
- Overall response rates (ORR) ranged from 9% (high-dose dexamethasone [NIMBUS]) to 81% (daratumumab, bortezomib, and dexamethasone [CASTOR]) (**Figure 4**).

Figure 4: **Overall response rate for patients who are refractory to lenalidomide**



Bor, bortezomib; Car, carfilzomib; Dara, daratumumab; Dex, dexamethasone; Elo, elotuzumab; Isa, isatuximab; Len, lenalidomide; NR, not reported; Pom, pomalidomide; Sel, selinexor

References

1. de Arriba de la Fuente F, et al. *Cancers*. 2022;15(1):155.
2. Moreau P, et al. *Blood Cancer J*. 2019;9(4):38.
3. Moreau P, et al. *Lancet Oncol*. 2021;22(3):e105–18.
4. Mohyuddin GR, et al. *Blood*. 2020;136:10–12.
5. Kumar S, et al. *Blood Cancer J*. 2022;12(6):98.
6. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). http://prisma-statement.org/prismastatement/checklist. Accessed October 19, 2023.
7. Dimopoulos, MA. *Lancet Oncology.* 2021;22(6):801–12.
8. Sonneveld, P. *Blood.* 2021;138(S1):2747.
9. Moreau, P. *Lancet Oncol.* 2018;19(7):953–64.
10. Dimopoulos, MA. *Blood Cancer J*. 2017;7(4):e554.
11. Leleu, X. *J Clin Oncol.* 2021;39(S15):8024.
12. Dimopoulos, M. *Lancet.* 2020;396(10245):186–97.
13. Chanan-Khan, AA. *Blood.* 2016;128(22):3313.
14. Lentzsch, S. *Blood*. 2017;130(S1):1852.
15. Spencer, A. *Haematologica*. 2018;103(12):2079–87.
16. Mateos, MV. *Clin Lymphoma Myeloma Leuk*. 2020;20(8):509-18.
17. Dimopoulos, MA. *N Engl J Med*. 2018;379:1811-22.
18. Dimopoulos, MA. *Clin Lymphoma Myeloma Leuk*. 2019;19(10):e15–16.
19. Dimopoulos, MA. *Clin Lymphoma Myeloma Leuk*. 2021;21(2):S143–44.
20. Dimopoulos, MA. *Lancet Oncol*. 2016;17(1):27–38.
21. Orlowski, RZ. *Clin Lymphoma Myeloma Leuk.* 2019;19(8):522–30.e1.
22. Attal, M. *Lancet*. 2019;394(10214):2096–107.
23. Moreau, P. Lancet. 2021;397(10292):2361–71.
24. Richardson, PG. *Blood*. 2011;118(21):634.
25. Richardson, PG. *Blood*. 2014;123(12):1826–32.
26. San Miguel, J. *Lancet Oncol.* 2013;14(11):1055–66.
27. San Miguel, J. *Haematologica*. 2015;100(10):1334–9.
28. Richardson, PG. *Lancet Oncol.* 2019;20(6):781–94.
29. Siegel, DS. *J Clin Oncol.* 2018;36(8):728–34.
30. Grosicki, S. *Lancet.* 2020;396(10262):1563–73.
31. Wiesel, K. *J Hematol Oncol.* 2020;13(1):115.

Disclosures

Funding: Study was funded by GSK (214940). Writing, editorial support, and formatting assistance for this poster were provided by Nakeirah Christie, PhD, of Fishawack Communications Ltd, part of Avalere Health, funded by GSK.

Conflicts of interest: **SM**, **GK**, **JB** and **FW** are employees of and holds stocks/shares in GSK. **JAC** is an employee of OPEN Health, which received research consulting fees related to the conduct of this review.

ISPOR Europe | 12–15 November 2023 | Copenhagen, Denmark

Presenting author: Simon McNamara, simon.j.mcnamara@gsk.com