Real-world Effectiveness of Monoclonal Antibodies for Patients with Multiple Myeloma: A Systematic Literature Review

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Background

- Monoclonal antibodies (MAbs) have become the mainstay of multiple myeloma (MM) treatment.
- Four FDA-approved MAbs are daratumumab, isatuximab, elotuzumab, and teclistamab-cqyv. (Belantamab mafodotin-blmf was withdrawn in 2022.)
- While randomized clinical trials (RCTs) have shown that MAbs are efficacious in treating MM, most RCTs had restrictive participation criteria, which may limit their generalizability.
- Real-world evidence (RWE) can assess the effectiveness of MAbs in a diverse population with different characteristics, comorbid conditions, and treatment scenarios.
- Objective: To investigate and summarize the RWE of the effectiveness of MABs in treating MM.

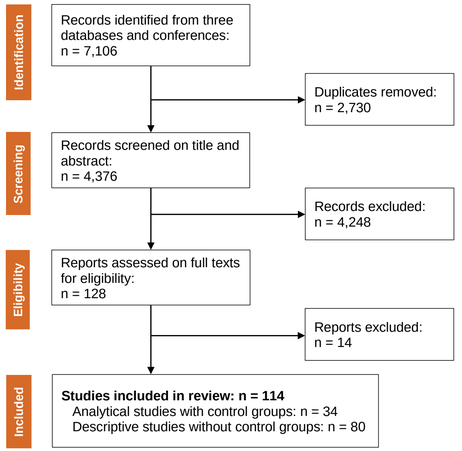
Methods

Protocol and Registration	• Followed 2020 PRISMA guidelines • PROSPERO #CRD42022375979
Search Strategy	• Study period: 2012-2022 • Database: PubMed, Web of Science, CINAHL, and grey literature • Search terms: MAbs, MM, and five MAbs names
Inclusion	MAbs (interventions or main components), MM, and final endpoints
Exclusion	RCTs, case reports, animal studies, correspondence, reviews, etc.
Effectiveness	PFS, OS, ORR, CR, VGPR, PR, etc.
RWE design	Cohort study, case-control study, cross-sectional study, descriptive study, etc.
Risk of bias	ROBINS-I tools and Newcastle-Ottawa Scale (NOS)
Data collection	Endnote, Excel, and Google form

Abbreviations: CI, confidence interval; CR, complete response; CBR, clinical benefit rate; D-Pd, Daratumumab, pomalidomide, and dexamethasone; D-Rd, daratumumab, lenalidomide, and dexamethasone; D-Vd, daratumumab, bortezomib, and dexamethasone; DCT, daratumumab-based combination therapy; DOR, duration of response; FH, Flatiron Health; HR, hazard ratio; IMWG, Control-International Myeloma Working Group; K-Rd, Carfilzomib, lenalidomide, dexamethasone; MAbs, monoclonal antibodies; NR, not reached; NDMM, newly diagnosed multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PS, propensity score; PR, partial response; RMG, Registry of Monoclonal Gammopathies; RWE, real-world evidence; RRMM, relapsed or refractory multiple myeloma; TTNT, time-to-next treatment; VGPR, very good partial response; V-Rd, bortezomib-lenalidomide-dexamethasone.

* van de Donk 2022 is abstract only

Flow Chart



Bias and Quality Assessment

Newcastle-Ottawa Scale for Evaluating the Quality of Selected Cohort Studies with Control Groups

Study	Represen-tativeness of the exposed cohort	Selection of the Non-exposed cohort	Ascer-tainment of exposure	Incident outcome	Compara-bility of cohorts	Assess-ment of outcome	Enough length of follow-up	Adequacy of follow-up of cohorts	**Total score**	**Level of evidence**
van de Donk 2022	1	0	1	1	2	1	1	0	7	Medium
Morabito 2021	1	1	1	1	2	1	1	0	8	Medium
Durie 2020	1	0	1	1	2	1	1	1	8	High
Lovas 2019	1	1	1	1	0	1	0	0	5	Low
Kumar 2018	1	0	1	1	2	1	1	1	8	High
Jelinek 2018	1	0	1	1	2	1	1	1	8	High
Lakshman 2017	1	1	1	1	0	1	1	1	7	Medium
Usmani 2017	0	0	1	1	2	1	1	1	7	Medium

Study Characteristics of Selected Cohort Studies

Study	Data sources	Setting	Sample size	Study design	Population	MAb-based therapy	Exposure	Controls	Effectiveness outcomes
van de Donk 2022*	MajesTEC-1 trial; LocoMMotion study	EU & US	398	Cohort study (PS weighting)	RRMM	Teclistamab-cqyv	Teclistamab-cqyv	Real-world control arm from the prospective LocoMMotion study	PFS, OS, ORR, VGPR, CR, DOR
Morabito 2021	Multi-center retrospective study, EHR	Italy	883	Cohort study (Adjusted comparisons)	RRMM	Elotuzumab	K-Rd	E-Rd	PFS, OS, VGPR + CR
Durie 2020	MAIA trial; US Flatiron EHR	Global & US	2,075	Cohort study (PS weighting)	Transplant-ineligible NDMM	Daratumumab	D-Rd	Rd in the MAIA trial V-Rd, Rd, and Vd in the FH EHR cohort	PFS, OS
Kumar 2018	GEN501 and SIRIUS trials; IMWG chart review	Global	691	Cohort study (PS matching)	RRMM	Daratumumab	Daratumumab monotherapy	Real-world standard of care from the IMWG retrospective chart review	PFS, OS
Lakshman 2017	EHR	Mayo clinic, US	126	Cohort study	RRMM	Daratumumab	D-Pd, D-Rd, D-Vd, other DCTs	Comparative effectiveness of four daratumumab-based combinations	PFS, OS, TTNT, ORR. CBR, CR, VGPR

Main Effectiveness Results of Selected Cohort Studies

Study	Effectiveness	Exposure	Controls	Comparisons	Relative measures	*p*-value
van de Donk 2022*	PFS	Not shown	Not shown	Teclistamab-cqyv vs. real-world control group	HR 0.47 (0.34-0.67)	<0.0001
	ORR	Not shown	Not shown	Teclistamab-cqyv vs. real-world control group	RR 2.31 (1.75-2.87)	<0.0001
Morabito 2021	2-year PFS	K-Rd: 49.3%	E-Rd: 41.2%	K-Rd vs. E-Rd	Adjusted HR: 0.54 (0.42-0.69)	<0.0001
	VGPR + CR	K-Rd: 53.9%	E-Rd: 37%	K-Rd vs. E-Rd	Adjusted HR: 1.28 (1.00-1.64)	0.05
Durie 2020	PFS	Not reached for D-Rd in MAIA trial	36.8 months for Rd in the MAIA trial 30.8 months for Rd in the FH database cohort 39 months for V-Rd in the FH database cohort 23.6 months for Vd in the FH database cohort	D-Rd vs V-Rd in the FH database cohort	HR 0.68 (0.48-0.98)	0.04
				D-Rd vs Vd in the FH database cohort	HR 0.48 (0.33-0.69)	0.001
Kumar 2018	PFS	Dara-monotherapy: 3.9 months in the RCTs	1.6 months in the real-world standard of care	Dara-monotherapy versus standard of care	HR: 0.56 (0.42-0.74)	Not shown
	OS	Dara-monotherapy: 19.9 months in the RCTs	9.2 months in the real-world standard of care	Dara-monotherapy versus standard of care	HR: 0.44 (0.31-0.63)	Not shown
Lakshman 2017	PFS	D-Pd: 5.2 (2.7-NR) months	D-Rd: 7.8 (5.0-NR) months D-Vd: 3.8 (2.0-NR) months Other DCTs: 3.9 (2.8-8.2) months	Four combinations of daratumumab	Not shown	0.34

Discussion

- Most studies showed higher effectiveness of MAbs than standard therapies, but one study reported lower effectiveness of E-Rd compared to K-Rd.
- RWE studies comparing MAbs treatment arms from RCTs against external real-world controls are the application of pragmatic trials.
- Daratumumab-based therapies were effective when compared to different comparators and in various populations and settings.
- Multiple RWE studies (n>6) evaluated the comparative effectiveness of different daratumumab-based combinations, and daratumumab triplet therapies appear to have similar PFS and OS.
- The quality of RWE studies was uneven and inconsistent. Several studies did not control for important confounders and used short (<24 months) follow-up periods to inadequately measure changes in patient survival.
- Other MAbs may be effective in real-world settings, but most RWE studies solely evaluated daratumumab-based treatments (n=85).

Conclusion

- This review summarizes the current RWE evaluating the effectiveness of MAbs for MM.
- Daratumumab demonstrated consistent effectiveness, regardless of different comparators or study populations.
- The effectiveness of other MAbs cannot be fully determined due to the lack of well-designed and controlled RWE.
- Additional real-world studies using large sample size and proper designs are needed to assess the effectiveness of MAbs for treating MM.

References

1. van de Donk NWCJ et al. *J Clin Oncol.* 2022 40:16_suppl, 8016-8016.
2. Morabito F et al. *Eur J Haematol*. 2022;108(3):178-189.
3. Durie BGM et al. *Am J Hematol*. 2020;95(12):1486-94.
4. Kumar S et al. *Leuk Lymphoma*. 2019;60(1):163-71.
5. Lakshman A et al. *Am J Hematol*. 2017;92(11):1146-55.