A systematic review of clinical efficacy and safety data in penta-refractory multiple myeloma: findings indicate the challenges for HTA submission

HTA236

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Background/Introduction

- Penta-refractory multiple myeloma (PR-MM) describes disease that is refractory to two proteosome inhibitors (PIs), two immunomodulatory drugs (IMiDs), and an anti-CD38 monoclonal antibody (mAb).
- Patients with PR-MM have poor prognosis and represent a high unmet need due to the limited treatment options.[1,2]
- To permit reimbursement of novel treatments for PR-MM via European HTA, clinical evidence is required to assess the relative clinical effectiveness *versus* current standard of care (SoC).
- Relative clinical effectiveness is usually estimated through indirect treatment comparisons (ITCs) that require baseline characteristics and time to event data, i.e., progression-free survival (PFS) and overall survival (OS), in the form of medians and Kaplan-Meier (KM) curves, for both the novel treatment and current SoC.

Objective

- To assess how the currently available clinical evidence in PR-MM meets evidence requirements for HTA of novel treatments.

Methods

- A systematic review was conducted to identify interventional and observational clinical evidence for 29 treatments used in Europe to treat relapsed and/ or refractory multiple myeloma (RRMM) (PROSPERO: CRD42023397589).
- Database and grey literature searching were performed in February 2023, according to Cochrane Guidance, and reported according to PRISMA/ PRISMA-S.
- Records were screened by two researchers independently, against a predefined PICOS (**Table 1**).
- Following screening, a data hierarchy assessment was performed to:
  - Identify the highest form of evidence available for each RRMM intervention (e.g., non-RCTs were only included in the evidence synthesis if RCT data were not available, and observational data only included in evidence synthesis if RCT and non-RCT data were not available);
  - Ensure studies reporting inclusion of PR-MM participants (≥10) were represented.

Table 1 PICOS criteria

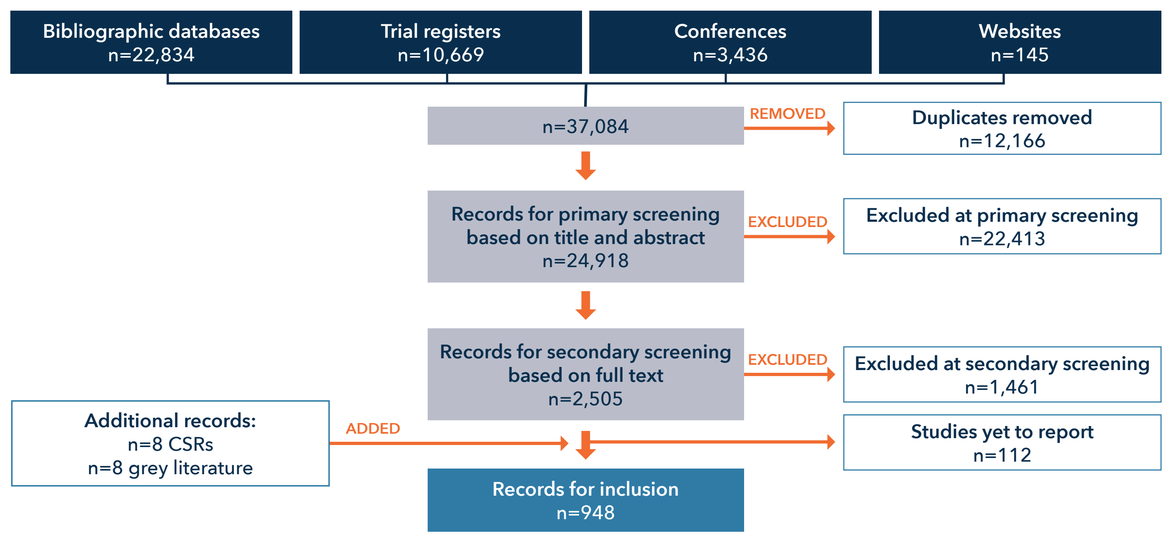
Eligibility criteria	Inclusion criteria
Population	Adults (≥18 years) with RRMM with ≥1 prior line of therapy
Interventions	Belamaf; BORT mono; BSC[a]; CCT[a]; Cilta-cel; DARA mono; DKd; DPd; DRd; DVd; ElotPd; ElotRd; Ide-cel; IsaKd; IsaPd; IxaRd; Kd; KRd; Melfd; PanoVd; PCycd; Pd; PVd; Rd; Sd; SVd; TEC; Vd; VenVd
Comparators	Trials that include a comparator of any type (including but not limited to the interventions listed above), including placebo, or trials with no comparator
Outcomes	• Survival and response: BOR, CBR, DoR, EFS, ORR, OS, PFS, ToT, TTNT, TTP, TTR • Safety and tolerability: TEAEs, TEAES leading to discontinuation/ dose reduction, TRAEs, serious/ severe TEAEs or TRAEs, deaths • HRQoL: EQ-5D, EORTC QLQ-C30, EORTC QLQ-MY20, EORTC QLQ-CIPN20, FACT-G, FACT-MM
Study design and publication types	• RCTs • Single-arm non-RCTs • Open-label extension trials • Retrospective and prospective observational studies • Peer review publications • Abstracts and conference presentations • Guidelines • Trial protocols • Systematic reviews • HTA/ regulatory guidance documents • Horizon scanning documents
Limits	• No date limits applied, except for conference abstracts (2021 – 2023) • No language restrictions[b]

a Trials of BSC and CCT were only eligible in a PR-MM population
b Records were translated to judge eligibility. Where this was not possible, records are detailed in the report

Results

- In total, 948 records were eligible for inclusion, including 81 prospective, phase 2 or 3 interventional clinical trials (37 RCTs, 2 randomised non-inferiority trials, and 42 non-RCTs), and >100 observational studies reported across 223 records (**Figure 1**).
- Following the data hierarchy assessment, 35 of the eligible studies (23 RCTs, 8 non-RCTs and 4 observational studies) were taken forward to evidence synthesis, providing clinical evidence for 27 of the eligible interventions listed in the PICOS, with the addition of real-world (RW) SoC (a PICOS refinement actioned due to the paucity of clinical evidence in PR-MM).
- While early RRMM therapies were tested in RCTs, later line therapies (4L+) were evidenced by single-arm or single-assignment multi-cohort studies.
- A total of six interventional non-RCTs and four RW observational studies reporting inclusion of patients with PR-MM were identified by the systematic review (**Table 2**).
- The ITT populations of these ten studies were triple-class refractory (TCR) or triple-class exposed (TCE) MM patients; the STORM trial of Sd had the largest proportion of PR-MM patients.
- Data reporting for PR-MM was heterogenous across the ten studies (**Table 2**):
  - Baseline characteristic data for PR-MM patients were reported in one non-RCT and two observational studies, only;
  - ORR data for PR-MM patients were available for the majority of the identified studies;
  - PFS and OS data for PR-MM patients were reported only in observational studies of RW SoC;
  - Safety data were not reported separately for PR-MM patients in any of the identified studies.

Figure 1: PRISMA diagram



Databases searched: MEDLINE (MEDALL); Embase; Cochrane: CDSR; Cochrane CENTRAL; CRD database DARE; CRD database HTA; CRD database NHS EED.
Trial registers searched: clinicaltrials.gov; ICTRP; EUCTR.
Websites searched: NICE; SMC; NIHRIO tech briefings; EMA; MHRA; TLV; NIPH; DTC; FIMEA; NCPE; RIZIV-INAMI; ZIN.
Conferences searched: Embase; CPCI-S; ASCO; ASH; BSH; EHA; EMN; ESMO.

Table 2: Overview of the ten studies reporting PR-MM clinical evidence (February 2023)

Study information								Data reported for PR-MM						
Trial name/ ID	Study design	Primary endpoint	Intervention	N of participants		Median prior lines, n (range)		Baseline	ORR	PFS		OS		Safety
				ITT (definition)	PR-MM (%)	ITT	PR-MM			Median	KM	Median	KM	
STORM (Part 2) [3,4]	Ph2b single-arm	ORR by IRC	Sd	122 (TCR, penta-exposed)	83 (68)	7 (3-18)	8 (4-18)	✓	✓	✗	✗	✗	✗	✗
DREAMM-2 (licensed dose) [5,6]	Ph2 single-arm	ORR	Belamaf	97 (≥3 prior lines, refractory to a PI and IMiD, and refractory and/ or intolerant to anti-CD38 mAb)	41 (42.3)	7 (3-21)	NR	✗	✓	✗	✗	✗	✗	✗
MajesTEC-1 (Cohort A) [7,8]	Ph2a single-arm cohorts	ORR by IRC	TEC mono	165 (≥3 prior lines and TCE)	50 (30.3)	5 (2-14)	NR	✗	✓	✗	✗	✗	✗	✗
CARTITUDE-1 [9,10]	Ph1b/2 single-arm	ORR by IRC	Cilta-cel	97 (≥3 prior lines, refractory to a PI and IMiD, and TCE)	4 (42)	6 (3-18)	NR	✗	✓	✗	✗	✗	✗	✗
CARTITUDE-2 (Cohort C) [11]	Ph2 single-arm cohorts	MRD-negativity	Cilta-cel	20 (Quad exposed to PI, IMiD, anti-CD38 mAb, and BsAb)	11 (55)	8 (4-13)	NR	✗	✗	✗	✗	✗	✗	✗
KarMMa (all enrolled) [12]	Ph2 single-arm	ORR by IRC	Ide-cel	140 (3 prior lines and TCE)	37 (26.4)	6 (3-16)	NR	✗	✓	✗	✗	✗	✗	✗
LocoMMotion [13,14]	Prospective observational	ORR by RRC	RW SoC	248 (≥3 prior lines, refractory to a PI and IMiD, and TCE)	44 (17.7)	4 (2-13)	NR	✗	✓	✓	✗	✓	✗	✗
Kim *et al*. 2021 [15]	Retrospective observational	Not specified	RW SoC	120 (TCE)	25 (20.83)	NR	NR	✗	✓	✓	✓	✓	✗	✗
MAMMOTH [16,17]	Retrospective observational	Not specified	RW SoC	275 (Refractory to daratumumab or isatuximab)	70 (25)	4 (1-16)	5 (2-16)	✓	✓	✗ [a]	✗ [a]	✓	✓	✗
Gill *et al*. 2021 [18]	Retrospective observational	Not specified	RW SoC	162 (Quad/ penta exposed or refractory)	112 (69)	6 (4-8)	7 (5-9)	✓	✗	✓	✓	✓	✓	✗

a PFS data are reported from MAMMOTH but only for the subgroup of PR-MM reported in Costa *et al*. 2021 (n=53, who had subsequent treatment with a non-investigational agent)

Conclusions/ Discussion

- There is currently limited efficacy and safety data specific to PR-MM patients, mostly evidenced in single-arm or single-assignment multi-cohort studies on a broader ITT population (i.e. TCE or TCR MM patients).
- This is likely due to limited numbers of PR-MM patients and the lack of approved treatments for this population to permit conduct of RCTs.
- Although ORR is available in most of the identified studies for PR-MM patients, the lack of PFS, OS, and safety data in the same population makes it difficult to draw any conclusion on the relative efficacy of these treatment options for PR-MM patients.
- Moreover, the paucity of PFS and OS medians and KM curves, the heterogenous reporting of baseline demographics, and the limited sample size of PR-MM subgroups, bring challenges in conducting robust ITCs.

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Abbreviations
Belamaf, belantamab mafodotin; **BORT** mono, bortezomib monotherapy; **BsAb**, bispecific antibody; **BOR**, best overall response; **BSC**, best supportive care; **CBR**, clinical benefit rate; **CCT**, conventional chemotherapy; **Cilta-cel**, ciltacabtagene autoleucel; **CSRs**, clinical study reports; **DARA**, daratumumab mono; **DKd**, daratumumab + carfilzomib + dexamethasone; **DoR**, duration of response; **DPd**, daratumumab + pomalidomide + dexamethasone; **DRd**, daratumumab + lenalidomide + dexamethasone; **DVd**, daratumumab + bortezomib + dexamethasone; **EFS**, event free survival; **ElotPd**, elotuzumab + pomalidomide + dexamethasone; **ElotRd**, elotuzumab + lenalidomide + dexamethasone; **HRQoL**, health-related quality of life; **HTA**, Health Technology Assessment; **Ide-cel**, idecabtagene autoleucel; **IMiD**, immunomodulatory drug; **IRC**, independent review committee; **IsaKd**, isatuximab + carfilzomib + dexamethasone; **IsaPd**, isatuximab + pomalidomide + dexamethasone; **ITC**, indirect treatment comparison; **ITT**, intention-to-treat; **IxaRd**, ixazomib + lenalidomide + dexamethasone; **Kd**, carfilzomib + dexamethasone; **KM**, Kaplan-Meier; **KRd**, carfilzomib + lenalidomide + dexamethasone; **mAb**, monoclonal antibody; **Melfd**, melflufen + dexamethasone; **MM**, multiple myeloma; **NR**, not reported; **ORR**, overall response rate; **OS**, overall survival; **PanoVd**, panobinostat + bortezomib + dexamethasone; **PCycd**, pomalidomide + cyclophosphamide + dexamethasone; **Pd**, pomalidomide + dexamethasone; **PFS**, progression free survival; **PI**, proteosome inhibitor; **PICOS**, Population, Interventions, Comparators, Outcomes, Study design; **PRISMA**, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **PRISMA-S**, Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement; **PR-MM**, penta-refractory multiple myeloma; **PVd**, pomalidomide + bortezomib + dexamethasone; **RCT**, randomised controlled trial; **Rd**, lenalidomide + dexamethasone; **RRMM**, relapsed and/ or refractory multiple myeloma; **RRC**, response review committee; **RW**, real world; **Sd**, selinexor + dexamethasone; **SoC**, standard of care; **STEAE**, serious/ severe treatment emergent adverse event; **SVd**, selinexor + bortezomib + dexamethasone; **TCE**, triple-class exposed; **TCR**, triple-class refractory; **TEAE**, treatment emergent adverse event; **TEC**, teclistamab; **ToT**, time on treatment; **TRAE**, treatment-related adverse event; **TTNT**, time to next treatment; **TTP**, time to progression; **TTR**, time to response; **Vd**, bortezomib + dexamethasone; **VenVd**, venetoclax + bortezomib + dexamethasone.

Disclosures
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