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Mihaela Musat, Jessicca Rege, Anna Forsythe
Oncoscope, Miami, FL, USA

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How should PICOs evolve when treatment sequencing changes?

A living evidence case study in triple-class exposed multiple myeloma (TCE-RRMM)

BACKGROUND

EU Joint Clinical Assessment (JCA) requires early development of evidence-based PICO scenarios that reflect rapidly evolving treatment landscape. In triple-class exposed multiple myeloma expanding treatment options, emerging biomarkers, and shifting treatment sequencing create substantial challenges for defining relevant populations and comparators.

OBJECTIVES

To evaluate the use of **Oncoscope** Real-Time AI-Assisted Systematic Literature Review **(REAL-SLR)** database to support transparent, continuously updated PICO mapping for JCA planning.

METHODS

Oncoscope REAL-SLR is a **PRISMA-aligned,** continuously updated evidence base organized by tumor type, including multiple myeloma (MM). Interventional trials in MM are identified through publications and conference abstracts and mapped according to prior drug-class exposure, refractoriness, risk, line of therapy, interventions, comparators, and outcomes. Regulatory documents, European and US clinical guidelines, and health technology assessments (HTAs) supplement the evidence mapping. Oncoscope structured evidence maps were used to identify potential JCA-relevant PICO scenarios in triple-class-exposed relapsed/refractory MM (TCE-RRMM).

RESULTS

- Evidence mapping of 440 RRMM studies included in Oncoscope REAL-SLR identified seven base-case PICO scenarios comprising 29 potential comparators across seven clinically relevant subpopulations defined by prior lines of therapy (1–2, 3, or ≥4), prior BCMA-targeted therapy/CAR-T eligibility, and refractoriness.
- Seven initial PICO scenarios were further divided into 10, 8, 5, and 5 scenarios for the UK, Germany, France, and Sweden, respectively.
- The main driver is differing comparator frameworks: NICE appraises individually named comparators, whereas G-BA groups multiple regimens. This further fragments PICOs by line of therapy and refractoriness to prior treatments.
- The landscape remains dynamic: teclistamab + daratumumab received EMA approval after abstract submission; NICE appraisal of cilta-cel and G-BA evaluation of linvoseltamab are expected early next year.
- Although reimbursed and used in Germany, currently approved T-cell engagers are not included as established comparators.
- Continuous evidence monitoring identified pivotal bispecific antibody trials supporting earlier use of BCMA-directed therapies, suggesting prior BCMA exposure may become a key population-defining characteristic in future JCAs.

KEY TAKEAWAYS

Treatment sequencing changes and geographic variation in comparator use can substantially alter JCA-relevant PICOs in TCE-RRMM.

Living evidence approaches may identify comparator shifts before formal HTA assessment, reduce evidence-generation risk, and improve JCA preparedness in rapidly evolving oncology indications.

Figure 1. **REAL-SLR evidence capture summary (as of June 12, 2026)**



Figure 2. **Roadmap from Oncoscope Database to PICO mapping in TCE RRMM**

7 base-case PICO scenarios

29 potential comparators

27 EMA-label-eligible for TCE, ≥1 prior line

24 reimbursed in UK / DE / FR / SE

TCE data in pivotal trial

Direct or anchored/unanchored ITC feasible

1. **Teclistamab** (MajesTEC-1, 100% TCE)
2. **Elranatamab** (MagnetisMM-3, 100% TCE)
3. **Talquetamab** (MonumenTAL-1, 100% TCE; post-BCMA)
4. **Ciltacabtagene autoleucel** (CARTITUDE-4, 26% TCE subgroup)
5. **Idecabtagene vicleucel** (KarMMa-3, 100% TCE)
6. **Belantamab mafodotin + pomalidomide + dexamethasone** (DREAMM-8, ~25% TCE subgroup)
7. **Selinexor + dexamethasone** (STORM, 100% TCR; ≥4 prior, penta-refractory)
8. **Linvoseltamab** (LINKER-MM1, 100% TCE)

No TCE trial data. Expected real-world use

Possibility for ITC versus external control (RWE cohort); low certainty accepted

9. **Pomalidomide + dexamethasone** (Pd)
10. **Pomalidomide + bortezomib + dexamethasone** (PVd)
11. **Carfilzomib + dexamethasone** (Kd)
12. **Elotuzumab + pomalidomide + dexamethasone** (EPd)
13. **Selinexor + bortezomib + dexamethasone** (SVd)
14. **Daratumumab + pomalidomide + dexamethasone** (DPd)*
15. **Daratumumab + carfilzomib + dexamethasone** (DKd)*
16. **Daratumumab + bortezomib + dexamethasone** (DVd)*
17. **Isatuximab + pomalidomide + dexamethasone** (Isa-Pd)*
18. **Isatuximab + carfilzomib + dexamethasone** (Isa-Kd)*

*anti-CD38 regimens apply to the exposed-non-refractory subpopulations

No TCE trial data. Lower expected real-world use

Lower chance to provide comparative analysis

19. **Carfilzomib + lenalidomide + dexamethasone** (KRd)*
20. **Elotuzumab + lenalidomide + dexamethasone** (ERd)*
21. **Daratumumab + lenalidomide + dexamethasone** (DRd)*
22. **Ixazomib + lenalidomide + dexamethasone** (IRd)*
23. **Panobinostat + bortezomib + dexamethasone** (pre-anti-CD38; NICE alternative comparator)
24. **Belantamab mafodotin + bortezomib + dexamethasone** (DREAMM-7 excluded anti-CD38-refractory; recent approval, reassess potential as comparator as RWE emerges)
25. **Daratumumab monotherapy**
26. **Melflufen+dexamethasone** (label includes TCR, but not marketed in UK/FR)
27. **Teclistamab+daratumumab** (MajesTEC-3; ~5%TCE; pending reimbursement; reassess potential as comparator)

*Lenalidomide-sensitive regimens, rarely used in TCE

Table 1. **Evidence-based PICO mapping for hypothetical drug X in 2L+, TCE RRMM**

PICO	Population (TCE)	Potential comparators	Particularities
PICO 1	2L	Kd; SVd; BVd; KRd, ERd; BPd; PVd; KPd*; PCd*; IRd; DKd; DVd; DRd; DPd; Isa-Kd; cilta-cel; teclistamab + daratumumab	**BPd, PVd:** prior len; **DPd:** len-refractory only at 2L; **Cilta-cel:** len-refractory; **KRd/ERd/DRd:** len-sensitive; **Tec+Dara:** SmPC pending; anti-CD38-refractory excluded from pivotal trial
PICO 2	3L, not anti-CD38 refractory	PICO 1 comparators + Pd; EPd; Isa-Pd; DPd; dara monotherapy; ide-cel; Pano-Vd	**Pd:** prior len + bortezomib; **EPd/Isa-Pd:** prior len + PI, PD on last; **Dara mono**: prior PI + IMiD, PD on last
PICO 3	3L, anti-CD38 refractory	Kd; SVd; KRd; PVd; BPd; BVd; Pd; ERd; EPd; IRd; KPd*; PCd*; Pano-Vd; cilta-cel; ide-cel	**Pano-Vd:** ≥2 prior incl. bortezomib + IMiD; **IRd/KRd/ERd:** len-sensitive
PICO 4	4L, not BCMA-refractory	PICO 2-3 comparators + teclistamab; talquetamab; elranatamab; linvoseltamab; melflufen+dex.	**Melflufen+dex:** TCR, ≥3 y post-ASCT; BCMA-directed agents conditional if prior BCMA-exposure
PICO 5	4L, BCMA-refractory¶	Talquetamab; melflufen+dex; Kd; KRd; ERd; PVd; Pd; EPd; SVd; IRd; Pano-Vd	**IRd/KRd/ERd:** len-sensitive
PICO 6	5L+, not BCMA-refractory	PICO 4 comparators + Sd	**Sd** label includes ≥4 prior lines of therapy and penta-drug refractory
PICO 7	5L+, BCMA-refractory¶	PICO 5 comparators + Sd	**Sd** label includes ≥4 prior lines of therapy and penta-drug refractory

*No EMA label specific for the combination; ¶ Assumption that majority of patients in this population are also anti-CD38 refractory

Table 2. **How UK, Germany, France and Sweden reimbursement landscapes influence PICO scenarios**

Base-case PICO (TCE)	UK — NICE / NHS England		Germany — G-BA		France — HAS		Sweden — TLV / NT-rådet	
1 **2L**	1a-UK	**Anti-CD38 sensitive** • Kd; DVd	1a-DE	**2L–4L bucket** ***- len sensitive*** • DVd; DKd; Isa-Kd; Kd	1a-FR	**2L lenalidomide sensitive** • DVd; DKd; Kd; Isa-Kd	1a-SE	**2L lenalidomide sensitive** • BPd • DVd; Isa-Kd; Kd
	1b-UK	**Anti-CD38 refractory** • BPd • Kd; SVd	1b-DE	***- len refractory*** • DPd; PVd (anti-CD38 refractory)	1b-FR	**2L, lenalidomide refractory** • cilta-cel • DPd; PVd	1b-SE	**2L lenalidomide-refractory** • cilta-cel • DPd; PVd
2 **3L** anti-CD38-sensitive	2-UK	**Anti-CD38 sensitive/refractory & len sensitive** • IRd, Rd, Pano-Vd (comparators likely do not have RWE data in TCE population)	2a-DE	***- 3L, len sensitive*** • Same as 1a-DE	2a-FR	**3L lenalidomide sensitive** • ide-cel • Isa-Pd; EPd; DPd	2a-SE	**3L lenalidomide sensitive** • Isa-Pd; DPd; PVd
			2b-DE	***- 3L, len refractory*** • Same as 1b-DE • Isa-Pd; EPd; DPd	2b-FR	**3L lenalidomide refractory** • cilta-cel; ide-cel • Isa-Pd; EPd; DPd	2b-SE	**3L lenalidomide refractory** • cilta-cel • Isa-Pd; DPd; PVd
3 **3L**, anti-CD38-refractory	3-UK	**Anti-CD38 sensitive/refractory & len refractory** • SVd	3a-DE	***- 3L–4L anti-CD38 refractory & len sensitive*** • Kd; EPd	not carved out → same as 2-FR without anti-CD38-based combos (Isa-Pd and DPd)		not carved out → same as 2-SE without anti-CD38-based combos (Isa-Pd and DPd)	
			3b-DE	***- 3L–4L anti-CD38 refractory & len refractory*** • PVd				
4 **4L** not BCMA-refractory	4a-UK	**4L+, BCMA-naive** • teclistamab; elranatamab talquetamab • Pd; Isa-Pd	not carved out → within 3a/3b-DE		4-FR	**4L+ population** • teclistamab; elranatamab; talquetamab • Sd (5L+) • Pd-based combos	4-SE	**4L+ population** • teclistamab / elranatamab; • Sd (5L+) • Pd-based combos
	4b-UK	**4L+, BCMA-exposed** • Same as 4a-UK, but teclistamab and elranatamab excluded after prior BCMAxCD3 bispecific						
5 **4L** BCMA-refractory	5-UK	**4L+** • talquetamab • Pd	not carved out → no BCMA agent in zVT; same as PICO 4-DE		not carved out → within 4-FR: talquetamab; Pd-based combos		not carved out → within 4-SE: Pd-based combos only (talquetamab not reimbursed)	
6 **5L+** not BCMA-refractory	6a-UK	**5L+, BCMA-naive** • teclistamab; elranatamab; talquetamab; Sd (penta-refractory) • Pd; Isa-Pd	6a-DE	**5L+, anti-CD38 sensitive** • Kd; EPd; PVd • DPd; Isa-Pd • DVd; DKd; Isa-Kd	within 4-FR + Sd (5L+ penta-refr.)		within 4-SE + Sd (5L+penta-refr.)	
	6b-UK	**5L+, BCMA-exposed** • Same as 6a-UK, but teclistamab and elranatamab excluded after prior BCMAxCD3 bispecific	6b-DE	**5L+, anti-CD38 refractory** • Kd; EPd; PVd; Pd				
7 **5L+** BCMA-refractory	7-UK	**5L+ population** • talquetamab; Sd (penta-refractory) • Pd	not carved out → same as 6a/6b-DE		not carved out → within 4-FR: talquetamab; Sd; Pd-based		not carved out → within 4-SE: Sd; Pd-based	

Colored cell = assessed as its own national population; no color cell = not carved out nationally (falls into the population named). Comparator color: **purple** = TCE trial data; **plum** = TCE comparison requires RWE. Germany: 2L–4L = G-BA '1–3 prior lines' vs. '≥4 prior lines' population.

TREATMENT REGIMENS

BPd/BVd, belantamab mafodotin + pomalidomide/bortezomib + dexamethasone; **Cilta-cel**, ciltacabtagene autoleucel; **Dara**, daratumumab; **Dex**, dexamethasone; **DKd/DPd/DRd/DVd**, daratumumab + carfilzomib/pomalidomide/lenalidomide/bortezomib + dexamethasone; **Ide-cel**, idecabtagene vicleucel; **Elra**, elranatamab; **EPd/ERd**, elotuzumab + pomalidomide/lenalidomide + dexamethasone; **Isa-Kd/Isa-Pd**, isatuximab + carfilzomib/pomalidomide + dexamethasone; **IRd**, ixazomib + lenalidomide + dexamethasone; **Kd/KPd/KRd**, carfilzomib + dexamethasone / pomalidomide + dexamethasone / lenalidomide + dexamethasone, respectively; **Len**, lenalidomide; **Pano-Vd**, panobinostat + bortezomib + dexamethasone; **PCd**, pomalidomide + cyclophosphamide + dexamethasone; **Pd/PVd**, pomalidomide + dexamethasone / bortezomib + dexamethasone, respectively; **Sd/SVd**, selinexor + dexamethasone / bortezomib + dexamethasone; **Tec**, teclistamab; **zVT**, zweckmäßige Vergleichstherapie.

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ABBREVIATIONS

2L/3L/4L/5L+, second/third/fourth/fifth-or-later line of therapy; **anti-CD38**, anti-CD38 monoclonal antibody; **ASCT**, autologous stem-cell transplantation; **BCMA**, B-cell maturation antigen; **DE/FR/SE/UK**, Germany/France/Sweden/United Kingdom; **EMA**, European Medicines Agency; **G-BA**, Gemeinsamer Bundesausschuss (German Federal Joint Committee); **HAS**, Haute Autorité de Santé; **HTA CG**, Health Technology Assessment Coordination Group; **IMiD**, immunomodulatory drug; **ITC**, indirect treatment comparison; **JCA**, Joint Clinical Assessment; **NT-rådet**, Swedish New Therapies Council; **PD**, progressive disease; **PI**, proteasome inhibitor; **PICO**, population, intervention, comparator, outcome; **REAL-SLR**, Real-Time AI-Assisted Systematic Literature Review; **refr.**, refractory; **RRMM**, relapsed/refractory multiple myeloma; **RWE**, real-world evidence; **SmPC,** summary of product characteristics; **TCE**, triple-class exposed (prior IMiD, PI, and anti-CD38 therapy); **TCR**, triple-class refractory; **TLV**, Tandvårds- och läkemedelsförmånsverket (Swedish Dental and Pharmaceutical Benefits Agency).