European Joint Clinical Assessment: How Many PICOs are Too Many?

HTA109

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Summary

- The JCA will be a new step that **unifies assessments** across Europe, and most critically will be the **synthesis of expectations from a range of countries through the scoping process**[2]
- In complex spaces with multiple options, assessment is expected to be substantially complicated
- For example, despite EMA approval and guideline recommendations[1,5], **there exists a divergence of access to RRMM therapies** across the EU[4], reflecting the ways in which **different HTA bodies perceive clinical viability** and therefore the array of PICOs that can be evaluated
- This access divergence and surplus of PICOs can be ameliorated by **simplifying the scoping process, such as by categorizing and grouping 'equivalent' comparators based on patient and clinical feedback**

Introduction & Objectives

Beginning in 2025, oncology medicines submitted for European regulatory approval will also be subject to European Joint Clinical Assessment (JCA) process[2]. The scope for the JCA will be developed based on Member State requests for inclusion of data relating to specific patient poulations (P), interventions (I), comparators (C), and outcomes (O)[2]. This regulatory change seeks to make the HTA process more efficient and facilitate patient access among EU Member States.

However, there is growing concern among industry experts that differences in treatment landscape across countries may lead to a large number of distinct assessments[3], complicating the design and execution of clinical trials, especially in complex disease landscapes. This sentiment is further echoed by the patient representatives, highlighting the risk or losing the benefits anticipated from the HTA regulation due to fragmentation of assessments in the scoping process[3]

In this study, we aimed to simulate a hypothetical JCA scoping process in the crowded relapsed / refractory multiple myeloma (RRMM) space to understand the potential number of PICOs that might be requested and identify avenues for limiting the overall number within the final scope.

Methods

Available RRMM treatment and reimbursement guidelines were assessed in a representative group of Member States to identify key patient population and comparator dynamics for a hypothetical intervention for patients with 2 or more lines of prior therapy. Potential PICOs that can be requested by each Member State were assessed. PICOs were then consolidated based on previously provided examples to identify minimum number of PICOs in the final scope.

Results

IMiD *Imnovid (P)* *Revlimid (R)* *Thalidomide (T)*	**Alkylating Agents** *Cyclophosphamide (Cy)* *Melphalan (M)*	**CD38** Darzalex (D) Isatuximab (Isa)	**CAR-T Therapy** Carvykti Abecma
Glucocorticoids *Prednisone (p)* *Dexamethasone (d)*	**PI** *Kyprolis (K)* *Velcade (V)* Ninlaro (N)	**Other** Empliciti (E) Selinexor (S) Venetoclax (Ven)	**BiTEs** Tecvayli

Figure 1 | RRMM Product Therapy Classes[1] [*Italics: Genericized*]

2L+

- KRd
- Kd
- PVd
- DKd
- DRd
- ERd
- NRd
- IsaKd
- SVd
- VRd
- DVd
- VenVd

3L+

- KDd
- DPd
- SVd
- IsaPd
- D-mono
- VenVd
- IsaKd
- PCy-d
- Sd
- DVd
- EPd

DPd (2L), Abecma, Carvykti and Tecvayli (4L+) are EMA-approved but not yet included in the ESMO guidelines[5]

Figure 2 | ESMO-Recommended 2L+ RRMM Therapies by LoT[1]

EU RRMM Treatment Access

Product (LoT)	DVd (2L+)	IsaKd (2L+)	DKd (2L+)	Kd (2L+)	PVd (2L+)	SVd (2L+)	DPd (2L/3L+)	IsaPd (3L+)	EloPd (3L+)	Carvykti (4L+)	Abecma (4L+)	Tecvayli (4L+)
FRA												
DEU												
ITA												
ESP												
SWE												
BEL												
POL												
NOR												
CZE												
LTU												

REIMBURSED, NO RESTRICTIONS | REIMBURSED WITH RESTRICTIONS / PRICING IMPLICATIONS | NOT REIMBURSED | ONGOING / NO REVIEW

Figure 3 | RRMM Therapy EU HTA Reimbursement Outcomes[4]

The Issue from a RRMM Viewpoint

The options for 2L-4L treatments for refractory/relapsed multiple myeloma (RRMM) are numerous, leading to an overall complex comparator space. Based upon the most recent clinical guidelines established by ESMO[1,] there are 18 individual therapies across 8 drug classes (Figure 1)[1,] used in combination or isolation (Figure 2)[1].

Making a single clinical evaluation of a new therapy in such a crowded space is challenging, evidenced in Figure 3 by the inconsistent reimbursement outcomes of the same regimen across Member States[4]. This lack of consensus reflects the variation in each country agency's evaluation criteria, demonstrating potential for the variety of requested comparators across countries, and the impracticality of developing evidence and performing an assessment for each potential request. This is especially apparent in complex disease landscapes like MM and can have ramifications for future clinical trial design if manufacturers must cater to the inclusion of all PICOs.

PICO Breakdown and Example

	EXPLANATION	EXAMPLE PICOS FOR A NEW RRMM THERAPY	
		RRMM Population	# Variables
P	As observed in Figure 2, one regimen can be indicated for multiple populations/lines of treatment[1], and the proposed reimbursed population for a new therapy may differ across countries due to the variation in therapies reimbursed for each population currently[4].	2L 3L 4L+ → 2/3L 4L+ *Combine 2L and 3L*	3 → 2
I	Regarding intervention selection, it is imperative to be clear how a therapy may be utilized through the clinical trial design (e.g., combination partners)		
C	Looking at Figure 3, comparator selections/baskets for a new 2L RRMM therapy would vary among Member States[4], reflecting different local access landscapes; i.e., certain nations such as Poland only consider doublets as viable comparators[4], as they have yet to reimburse others. Further, all nations except Germany that evaluated CAR-Ts and BiTEs had differing levels of reimbursement across these classes[4].	**2L RRMM Comparators** KRd, DKd, NRd, VRd, Kd, DRd, DPd, IsaKd, DVd, PVd, Erd, SVd, VenVd → Triplet w/ IMiDs, triplet w/ PIs, triplet w/ CD38s, triplet others, doublet PIs → Triplets Doublets	*Consider comparators of the same class as 'equivalent'* 13+ → 5 *Consider with the same number of components as 'equivalent'* 5 → 2
O	Each Member State values different endpoints to be clinically relevant, which leads to further permutations of PICO combinations. For instance, PFS is not patient-relevant in Germany[4], and MRD analyses are accepted to varying extents depending on payer familiarity and philosophy[4]. Thus, a single holistic conclusion of clinical trial outcomes accepted by all countries will be unlikely.		

Conclusions:

As exemplified by a landscape assessment of 2L-4L RRMM in the EU, the JCA committee are likely to encounter challenges with the large number of potential and requested PICOs from the Member States. Not only are these impractical from an evidence generation perspective, but there exist clear inefficiencies in this process that aims to unify the clinical assessment of an intervention across the EU. The population and comparator aspects are likely to present the greatest heterogeneity in PICOs, and each country will also have their own position regarding the appropriate intervention and outcomes evaluated. The HTA coordination group will need to agree upon methods of consolidating PICOs in a way that does not compromise local situations and still allows for an appropriate clinical judgement of the medicine. To achieve this, it will be important to work with the medical professional community and patient advocates to identify 'equivalent' PICOs and streamline the assessment scope in order to lower the process burden for both assessors and technology developers.

Individual countries are at different stages of readiness for the transition, based on a survey of N=3 payers (Germany, Italy, Spain), and it will be important for each to gain familiarity with the process and current drug approvals in the year leading up to the JCA implementation. The pharmaceutical industry must also rise to adapt to this change, as clinical trials will need to be designed in anticipation of acceptance by the EU JCA overall, rather than targeting specific countries. This is a call to action for further evidence generation and evaluation of the transition from individual to joint clinical assessments.

References

1 Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2021) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7861652/pdf/hs9-5-e528.pdf

2 Joint Clinical Assessment of Medicinal Products: Submission of early information by Health Technology Developers. Public Health (2024) https://health.ec.europa.eu/latest-updates/joint-clinical-assessment-medicinal-products-submission-early-information-health-technology-2024-06-21_en

3 APM Health Europe: Patients combine to handle proliferating PICOs in EU health technology assessment (2024)

4 HTA Reports/Outcomes: HAS, G-BA, AIFA, AEMPS, TLV, KCE, AOTMiT, DMP, SÚKL, and VVKT

5 EMA Market Authorization: DPd, Abecma, Carvytki, and Tecvayli

Abbreviations

HTA: Health Technology Assessment; **PICO:** Population, Intervention, Comparator, Outcome; **RRMM:** Refractory/Relapsed Multiple Myeloma; **LoT:** Line of Therapy; **JCA:** European Joint Clinical Assessment; **EMA:** European Medicines Agency; **ESMO:** European Society for Medical Oncology; **mAb:** Monoclonal Antibodies; **CAR-T:** Chimeric Antigen Receptor T-cell; **BiTE:** Bispecific T-cell Engager; **EU:** European Union; **MRD:** Measurable Residual Disease; **QoL:** Quality of Life; **PFS:** Progression-Free Survival; **OS:** Overall Survival; **ORR:** Overall Response Rate; **CR:** Complete Response; **VGPR:** Very Good Partial Response; **PR:** Partial Response; **DoR:** Duration of Response; **G3+:** Grade 3 and Higher Adverse Event Rate; **SAE:** Serious Adverse Event Rate; **TEAE:** Treatment-Emergent Adverse Event Rate; **EORTC**: European Organisation for Research and Treatment of Cancer; **EQ-5D:** EuroQol-5; **PGIC:** Patient Global Impression of Change

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