HTA102

Are EU JCA Evidence Requirements Achievable?: Insights from a Retrospective Evidence Analysis for Rare and Non-Rare EU Treatment Landscapes

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Online version and linked PICO simulation

Objective

To retrospectively assess to what extent evidence presented at the time of European Medicines Agency (EMA) regulatory process would have aligned to Joint Clinical Assessment (JCA) evidence requirements, for an oncology product in an:

- Orphan, first-to-market landscape (metastatic Merkel cell carcinoma [MCC]) and
- A densely-populated competitive landscape (advanced renal cell carcinoma [RCC])

Background

- **Mandatory EU JCA** for first-indication oncology and orphan medicines will be introduced in 2025 and 2028, respectively. Ahead of this, guidance on **evidence requirements for the JCA dossier** has been published by EUnetHTA 21.[1]
- As timelines for EMA regulatory approval and JCA dossier submission will be closely integrated, it is anticipated that manufacturers will be expected to generate and present a broader body of evidence, including comparative data, earlier in the product lifecycle.
- To explore challenges for manufacturers, we retrospectively assessed to what extent evidence presented at the time of EMA regulatory process would have aligned to JCA evidence requirements. Avelumab was used as an example product, in an orphan, first-to-market landscape (MCC) and in a densely-populated landscape (RCC) (**Table 1**).

Methods

- Following a population, intervention, comparator and outcome (PICO) **PICO scoping exercise** (see **ISPOR Europe 2024 Poster #HTA216**), evidence available in EMA European Public Assessment Reports (EPAR) for avelumab in MCC and RCC was assessed against the EUnetHTA 21 practical guidelines for JCA reporting (**Figure 1**).[2–5] Evidence published after marketing authorisation was not considered.
- For relevant **comparators** identified through PICO scoping, comparator information included in the EPAR was assessed against EUnetHTA guidance on comparative data (D4.3).[2]
- For relevant **subpopulations** identified through PICO scoping, subpopulation information included in the EPAR was assessed against EUnetHTA guidance on subgroup analyses (D4.5).[4]
- The **overall EPAR evidence package** was assessed against guidance on the validity of studies (D4.6).[5]
- Relevant outcomes from trials presented in the EPAR were not assessed against guidance on endpoints (D4.4),[3] as outcomes presented in the EPAR were tailored to EMA requirements, and are therefore expected to be narrower in scope than the JCA requirements.

Results

PICO Scoping

- Results of the simulated PICO scoping exercise are presented in **ISPOR EU 2024 Poster #143800**; please scan the QR code above to see the associated poster.

Evidence Requirements Assessment

- Results of the evidence assessment are summarised in **Figure 1**.

Limitations

- The EMA EPAR used to assess evidence may represent a limited picture of the evidence available to a company at regulatory approval.
- Comparative data are not required at EMA regulatory approval, therefore, there may have been additional comparative data available that were not included in the EMA EPAR. Any assessment of the number of comparators may therefore not be a reflection of the full evidence base.

TABLE 1

Overview of assessed indications for avelumab

Indication	Regulatory landscape	Data package[a]	EMA approval date
Monotherapy for the treatment of adult patients with MCC[6]	Orphan, first-to-market landscape	♦ Phase II, open-label single-arm study ♦ Retrospective observational study ♦ Two phase I, open-label, 2-phase (dose escalation and treatment expansions) studies	14 December 2015
Combination treatment with axitinib in adult patients with RCC[7]	Densely-populated competitive landscape	♦ Phase III head to head (H2H) randomised, open-label study ♦ Phase Ib open-label dose-finding study	19 September 2019

[a]Presented at the time of EMA regulatory submission and summarised in the EMA EPAR.

FIGURE 1

Assessment of EPAR data package against JCA requirements

JCA Evidence Requirements	Question	MCC Rating	MCC Summary	RCC Rating	RCC Summary
Comparators and methods of comparison (D4.3)	**How many PICO comparators did the company submit evidence for?**	●	Evidence presented for n=4/4 PICO comparators identified	●	Evidence presented for n=1/7 PICO comparators identified
	Were relevant studies included in the EPAR representative of EU members states?	●	All comparative studies conducted in the US	●	Comparative study conducted in 10+ European sites
	Was the method of comparison appropriate (direct, indirect or naïve)?	●	Only naïve comparisons of single arm and retrospective observational studies were performed	●	Direct H2H evidence was presented; statistical methods to compare primary endpoint may not have been appropriate
Applicability of the evidence (D4.5)	**Were PICO subpopulations considered in trial stratification criteria?**	●	Pivotal trial did not stratify patients based on PICO subpopulations	●	Pivotal trial did not stratify patients based on PICO subpopulations
	Were pre-planned subgroup analyses conducted for all PICO subpopulations of interest?	●	Subgroup analyses were available for n=0/2 PICO subpopulations identified	●	Subgroup analyses were available for n=4/8 PICO subpopulations identified
Validity of studies (D4.6)	**What was the risk of bias associated with the studies the presented?**	●	High risk of bias; short duration single-arm trial design and naïve comparisons	●	Moderate risk of bias; open-label trial design and method for handling of missing data
	Would there have been challenges related to study design?	●	Challenges with single-arm study design and naïve comparison expected	●	Choice of combination therapy, comparator and some analyses could be criticised
	Was real-world evidence (RWE) presented in the regulatory submission? What form?	✓	A retrospective observational study was included in the package	✗	RWE did not form part of the evidence package; all studies were interventional

Legend: Met requirements: ● Strongly ● Mostly ● Somewhat — **Did not** meet requirements: ● Strongly ● Mostly ● Somewhat

Key recommendations for meeting JCA evidence requirements for manufacturers

Conduct **early PICO scoping** and comparator landscaping to plan pivotal trial analyses and evidence generation activities to align to JCA requirements.

Include **careful consideration of subpopulations** that may be relevant, guided by PICO scoping activities and key comparator subgroups.

Engage in **early clinician/payer discussions** to validate the results of PICO scoping and landscaping.

At the pivotal trial design stage, consider the need to **generate comparative evidence to fulfil PICO requirements** at the same time as evidence for regulatory submission. Manufacturers should consider:

- **Populations:** Stratified randomisation by key expected (sub)populations.
- **Comparators:** Selection of comparators that facilitate connected networks in future evidence synthesis.
- **Outcomes:** Alignment of outcome definitions with those in key comparator trials.

Specific recommendations for manufacturers of rare disease medicines:

- Given clinical trials for rare diseases are likely to be small, with only a few patients identified in some countries, it may be difficult to make sure the population is representative of all EU member states. Clinical validation of the **generalisability of the trial population** will be important.
- As it is unclear whether there will be any **flexibility in the JCA process for rare disease medicines**, engage in Joint Scientific Consultation (JSC) as early as possible to obtain feedback on trial design and evidence generation strategies, to ensure outputs are aligned to evidence requirements.
- Use the JSC process to explore how RWE can be used to supplement the clinical package as there is currently a **lack of clarity on how RWE will be assessed**.

Abbreviations: EMA: European Medicines Agency; **EPAR:** European public assessment report; **EU:** European Union; **H2H:** head to head; **JCA:** Joint Clinical Assessment; **JSC:** Joint Scientific Consultation; **MCC:** Merkel cell carcinoma; **PICO:** population, intervention, comparator, outcome; **RCC:** renal cell carcinoma; **RWE:** real-world evidence; **US:** United States.

References: [1]EUNetHTA 21. Joint HTA work. Available at: https://www.eunethta.eu/jointhtawork/ [Last accessed 01 Oct 24]; [2]EUnetHTA 21. D4.3 Direct And Indirect Comparisons. Available at: https://www.eunethta.eu/d4-3/ [Last accessed 04 Sep 24]; [3]EUnetHTA 21. D4.4 Endpoints. Available at: https://www.eunethta.eu/d4-4/ [Last accessed 04 Sep 24]; [4]EUnetHTA 21. D4.5 Applicability of Evidence. Available at: https://www.eunethta.eu/d4-5/ [Last accessed 04 Sep 2024]; [5]EUnetHTA 21. D4.6 Validity of Clinical Studies. Available at: https://www.eunethta.eu/d4-6/ [Last accessed 04 Sep 2024]; [6]European Medicines Agency. Assessment Report. Bavencio. Procedure No.: EMEA/H/C/004338/0000. 2017; [7]European Medicines Agency. Assessment Report. Bavencio. Procedure No.: EMEA/H/C/004338/II/0009/G. 2019.

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