HTA350

HTA Bodies Request Fewer Than 50% of Guideline-Defined PICOs: Evidence from Eight EU Markets and Lessons for EU JCA

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Introduction and objectives

- The scope of Joint Clinical Assessment (JCA) is defined by the population, intervention, comparator, and outcomes (PICO) framework, with input from all EU MS (PICO survey). Given limited time to prepare the dossier once the JCA scope is announced, Health Technology Developers (HTDs) must predict the likely PICO scope before it is announced, and prioritise evidence generation accordingly. This analysis quantifies divergence between guideline-defined PICOs and PICOs requested in HTA across eight EU markets, and identifies factors driving PICO inclusion, modification, and exclusion.

Methods

- The analysis covered countries with explicit definition of the PICO scope in national HTAs – the Czech Republic (SUKL), Germany (G-BA), Denmark (DMC), Finland (FIMEA), France (HAS), the Netherlands (ZIN), Poland (AOTMiT) and Sweden (TLV). Five recently approved oncology therapies with HTAs available in ≥6/8 countries were purposively selected to cover diverse tumour types, treatment lines, and orphan status: zolbetuximab, amivantamab, zanubrutinib, glofitamab, trastuzumab deruxtecan. Additionally, all three products with JCA report available as of 31 Aug 2026 were included (Table 1).
- HTA reports were identified through IQVIA's Market Access Insights platform. PICOs defined by HTA bodies / JCA were extracted together with rationales for PICO inclusion or exclusion (if provided). One PICO was defined as one population - one comparator pair if 'AND' approach was used, or one population – several comparators if 'OR' approach was used. Patient-individualised therapy was considered one comparator.
- We extracted all potential PICOs from national and/or ESMO guidelines (versions mentioned in HTAs), falling under HTA-reviewed indications. One PICO was defined as one population – one comparator pair. We did not apply OR approach to guideline-defined PICOs because OR/AND grouping reflects HTA evidence requirements, which clinical guidelines do not specify.

Table 1: Scope of the analysis

Product	Indication	Tx line	ODD	CZ	DE	DK	FI	FR	NL	PL	SE
Amivantamab	NSCLC, EGFR Ex20ins	1L	No								
Glofitamab	DLBCL, R/R	3L+	Yes*								
Trastuzumab deruxtecan	Breast cancer, HER2-low	2L+	No								
Zanubrutinib	CLL	1L+	No								
Zolbetuximab	Gastric cancer, HER2-, CLDN18.2+	1L	Yes								
Tarlatamab	ES-SCLC	2L	Yes	JCA report							
Lurbinectedin	ES-SCLC	1L maint.	Yes	JCA report							
Tovorafenib	pLGG, BRAF+	2L+	Yes	JCA report							

Table 1. **Glofitamab initially held orphan designation for DLBCL granted in 2021 but officially withdrawn in March 2025 after HTA reports were published*

HTA report available and included

JCA report available and included

Results

- On average, HTA bodies requested 2.7 PICOs per assessment (median: 2; range: 1–14) versus 19.4 identified in the guidelines (median: 10; range: 1–81). The mean number of PICOs requested in HTA ranged from 1.4 (median: 1.0; range: 1–4) for amivantamab to 4.8 (median: 3.5; range: 1–14) for zanubrutinib, while the mean per HTA agency ranged from 1.0 (median: 1.0) for ZIN to 6.2 (median: 5.0) for AOTMiT (Table 2).
- The ratio of HTA PICOs to guideline-defined PICOs decreased as the number of guideline-defined PICOs increased (Spearman ρ = −0.67, p<0.001, n=38) (Figure 1).
- Overall, 57% of guideline-defined PICOs across all products and countries were not requested in HTA, 40% were modified, and 3% were included unchanged. Exclusion rates varied by country (23% for HAS to 73% for ZIN and TLV) (Figure 2).
- The most common exclusion reasons were prioritisation of more relevant comparators, different mechanism of action (for zanubrutinib), and lack of reimbursement. For 105 (27%) excluded PICOs, rationale for exclusion was not provided in the HTA report (Figure 3).
- Average number of PICOs in HTA vs guidelines falls further than exclusion rates because modifications consolidated multiple guideline PICOs into single HTA PICOs by requesting broader populations than in the guidelines and grouping comparators with 'OR' approach or under individualised treatment.
- Inclusion of PICOs was mainly driven by alignment with clinical guidelines, clinical expert opinion, reimbursement status, use in clinical practice. Among 109 PICOs requested in HTA / JCA for all analysed products, 8 (7%) were not included in the clinical guidelines but were requested based on clinical expert input, reimbursement or currently ongoing HTA.
- In JCA, the mean number of requested PICOs was 5.3 (median: 7; range: 1–8), versus 28.7 identified in the ESMO and national guidelines (median: 39; range: 4–43) (Table 2). Among PICOs identified in the guidelines, 9% were requested in JCA unchanged, 30% were requested with modifications and 61% were not requested at all (Figure 2).

Table 2: Average number of PICOs across HTA agencies

	N of PICOs in HTA: mean / median (range)	N of PICOs in guidelines: mean / median (range)	Δ
FIMEA	2.0 / 1.0 (1–4)	8.0 / 8.0 (7–9)	−6.0
DMC	1.5 / 1.0 (1–3)	11.8 / 9.5 (1–27)	−10.3
G-BA	1.8 / 1.0 (1–5)	16.6 / 9.0 (3–39)	−14.8
TLV	2.8 / 3.0 (1–4)	18.2 / 12.0 (6–44)	−15.4
AOTMiT	6.2 / 5.0 (1–14)	23.6 / 9.0 (4–54)	−17.4
HAS	1.8 / 1.0 (1–4)	20.2 / 9.0 (4–66)	−18.4
ZIN	1.0 / 1.0 (1–1)	21.7 / 16 (10–39)	−20.7
JCA	5.3 / 7.0 (1–8)	28.7 / 39.0 (4–43)	−23.4
SUKL	3.0 / 2.0 (2–5)	30.2 / 16.0 (3–81)	−27.2

Figure 2: Inclusion of guideline PICOs in the HTA scope by HTA agency

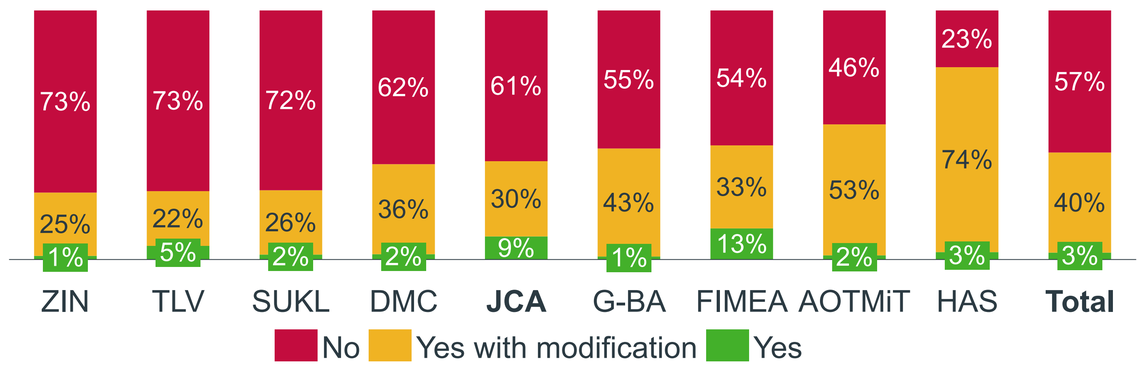


Figure 1: HTA-to-guideline PICO ratio by number of guideline-defined PICOs

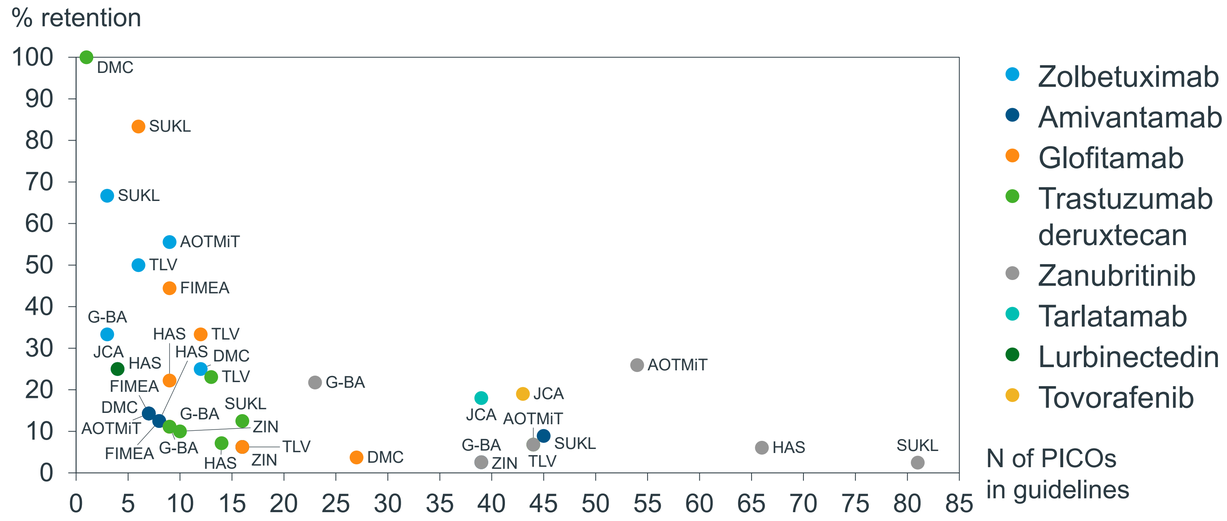


Figure 1. *% retention was calculated as N of PICOs requested in HTA / JCA divided by the N of PICOs identified in the guidelines. One observation with retention exceeding 100% (more PICOs in HTA than in the guidelines) was excluded from the visualisation to improve readability.*

Figure 3: Reasons for not requesting comparators from guidelines in HTA

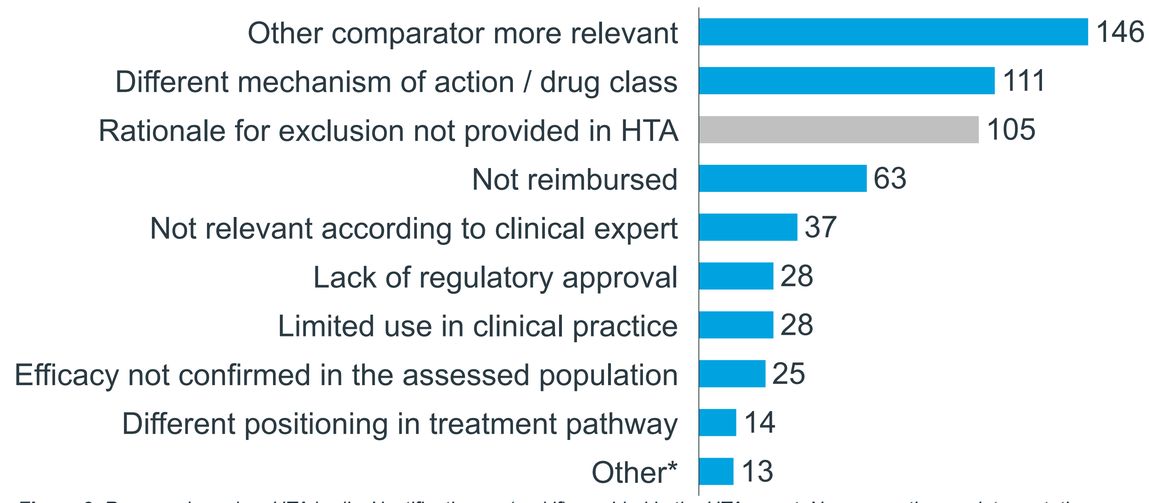


Figure 3. *Reasons based on HTA bodies' justification as (and if) provided in the HTA report. No assumptions or interpretations made. Reasons are not mutually exclusive – more than one reason could apply to one comparator. *Other reasons include: uncertain cost-effectiveness (n=4), not being requested by other HTA bodies (n=4), no added benefit (n=3), not yet SoC (n=2)*

Conclusions and implications

- HTA bodies systematically narrow the PICO scope relative to clinical guidelines across countries and products, suggesting that guideline alignment is necessary but insufficient to predict JCA PICOs. As the number of guideline-defined PICOs increases, HTA bodies tend to retain a progressively smaller proportion of them, indicating increasing consolidation of guideline-derived PICOs.
- HTA reports do not always provide sufficient transparency regarding PICO selection, with rationale for exclusion unavailable for 27% of excluded PICOs. This may limit predictability of future HTA and JCA evidence requirements.
- Health technology developers should verify the guideline recommendations against reimbursement status, published HTA reports, real-world use and clinical expert opinion to prioritise the most relevant PICOs.

Limitations

- Purposive sampling of 5 products
- Only 3 JCA reports included
- Only 8 / 27 EU MS included
- Guidelines differ in terms of level of details and complexity

Abbreviations: 1L/2L+/3L+ – line of therapy (first-, second-, third-line or later); AOTMiT – Polish Agency for Health Technology Assessment and Tariff System; CLDN18.2 – Claudin 18.2; CLL – Chronic Lymphocytic Leukaemia; CZ – Czech Republic; DE – Germany; DK – Denmark; DLBCL – Diffuse Large B-Cell Lymphoma; DMC – Danish Medicines Council; EGFR – Epidermal Growth Factor Receptor; ESMO – European Society for Medical Oncology; ES-SCLC – Extensive-Stage Small Cell Lung Cancer; EU – European Union; Ex20ins – Exon 20 insertion; FI – Finland; FIMEA – Finnish Medicines Agency; FR – France; G-BA – German Federal Joint Committee; HAS – French National Authority for Health; HER2 – Human Epidermal Growth Factor Receptor 2; HTA – Health Technology Assessment; HTD – Health Technology Developer; JCA – Joint Clinical Assessment; maint. – maintenance; MS – Member State; N – Number; NL – Netherlands; NSCLC – Non-Small Cell Lung Cancer; ODD – Orphan Drug Designation; PICO – Population, Intervention, Comparator, Outcomes; PL – Poland; pLGG – Paediatric Low-Grade Glioma; R/R – Relapsed/Refractory; SE – Sweden; SoC – Standard of Care; SUKL – Czech State Institute for Drug Control; TLV – Swedish Dental and Pharmaceutical Benefits Agency; Tx – Treatment; ZIN – Dutch National Health Care Institute; Δ – Difference; ρ – Spearman's rank correlation coefficient; **Disclaimer:** The authors declare no conflicts of interest. This research received no external funding.