HTA103

Preparing for Joint Clinical Assessment: HTA Comparators, Clinical Practice, and Real-World First-line NSCLC Treatment in the EU4 + UK

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Background

- The EU Health Technology Assessment (HTA) Regulation introduces Joint Clinical Assessments (JCAs) to support harmonized relative effectiveness assessments across Member States[1]
- **Comparator selection** is a critical component of PICO scoping, influencing the evidence base used for JCA evaluations and subsequent national HTA considerations[2]
- Alignment between HTA-defined comparators, clinical practice recommendations,[3,4] and real-world (RW) standards of care[5] is important to ensure assessments reflect contemporary treatment practice
- Advanced non-small cell lung cancer (NSCLC) represents a relevant case study due to its rapidly evolving treatment landscape, expanding biomarker-driven therapies, and increasing complexity of treatment selection across Europe

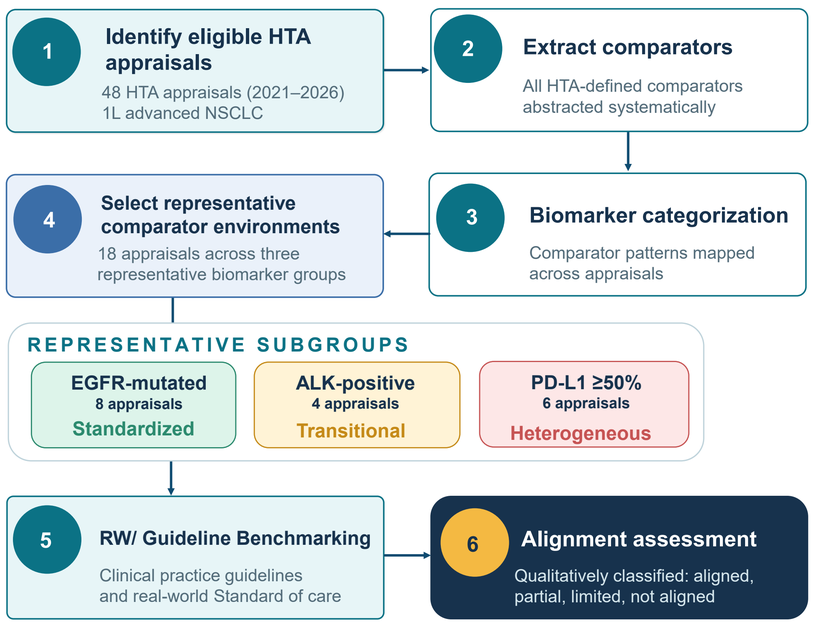
Objective

- To evaluate whether comparators used in national HTA appraisals of first-line advanced NSCLC are consistent with clinical practice guideline recommendations and RW treatment patterns across the EU4+UK and
- To identify areas of convergence and divergence relevant to future EU JCA implementation

Methods

- A targeted review included HTA appraisals (2021-2026) from NICE, G-BA, HAS, AIFA, and AEMPS for first-line (1L) advanced NSCLC and comparators extracted[6-11]
- Biomarker subgroups represented within the appraisals were mapped and the comparator landscape was assessed across molecularly defined populations
- To evaluate alignment across distinct comparators, biomarker subgroups were categorized by comparator landscape characteristics. Comparators were classified as **standardized** (single dominant comparator used consistently across appraisals), **transitional** (multiple competing comparators reflecting an evolving treatment landscape), or **heterogeneous** (substantial variation in comparator selection across appraisals)
- **Three subgroups were selected for detailed alignment assessment: EGFR-mutated (standardized), ALK-positive (transitional), and PD-L1 ≥50% (heterogeneous)**
- Clinical practice recommendations were obtained from ESMO and country-specific NSCLC guidelines (NICE, Germany S3 guideline, HAS/INCa, AIOM, and SEOM) contemporaneous with the HTA appraisal where available[12-16]
- RW-treatment patterns were derived from published observational studies reflecting RW SoC, defined as most frequently used treatment regimen[17-20]
- HTA-defined comparators were benchmarked against guideline-recommended and RW treatments, qualitative alignment assessed: aligned (dominant RW/guideline treatment included as primary comparator), partially aligned (included, but not primary comparator), limited alignment (only indirectly represented) or not aligned (not represented)

Figure 1: Framework for HTA Comparator Identification and Alignment Assessment



Results

1. HTA Comparator Landscape

Review of 48 HTA appraisals identified distinct comparator environments across biomarker-defined 1L advanced NSCLC populations (**Table 1**)

Table 1: HTA Comparator Landscape Across 48 NSCLC Appraisals (2021–2026)

Biomarker subgroup	HTA appraisals (n)	Dominant HTA comparator pattern	Comparator environment*
EGFR-mutated	8	Osimertinib	Standardized
ALK-positive	4	Alectinib or brigatinib or crizotinib	Transitional
PD-L1 ≥50%	6	Pembrolizumab monotherapy, chemotherapy ± immunotherapy, chemotherapy alone	Heterogeneous
PD-L1+	7	Chemotherapy, pembrolizumab	Heterogenous
RET fusion+	2	Platinum chemotherapy ± pembrolizumab, chemotherapy alone	Heterogeneous
BRAF V600E+	2	Chemotherapy comparators	Transitional
EGFR exon20ins	2	Platinum chemotherapy or doublet	Transitional
ROS1+	1	Entrectinib	Standardized
EGFR/ALK WT	16	Pembrolizumab + chemotherapy, chemotherapy alone,	Heterogeneous

***Comparator environment definitions:** *Standardized* = single dominant comparator used consistently across appraisals; *Transitional* = evolving comparator landscape with multiple competing standards; *Heterogeneous* = substantial variation in comparator selection across appraisals.
Abbreviations: ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; EGFR exon20ins = epidermal growth factor receptor exon 20 insertion mutation; HTA = health technology assessment; PD-L1 = programmed death-ligand 1; RET = rearranged during transfection; ROS1 = ROS proto-oncogene 1 receptor tyrosine kinase; TKI = tyrosine kinase inhibitor; WT = wild type.

Results (contd.)

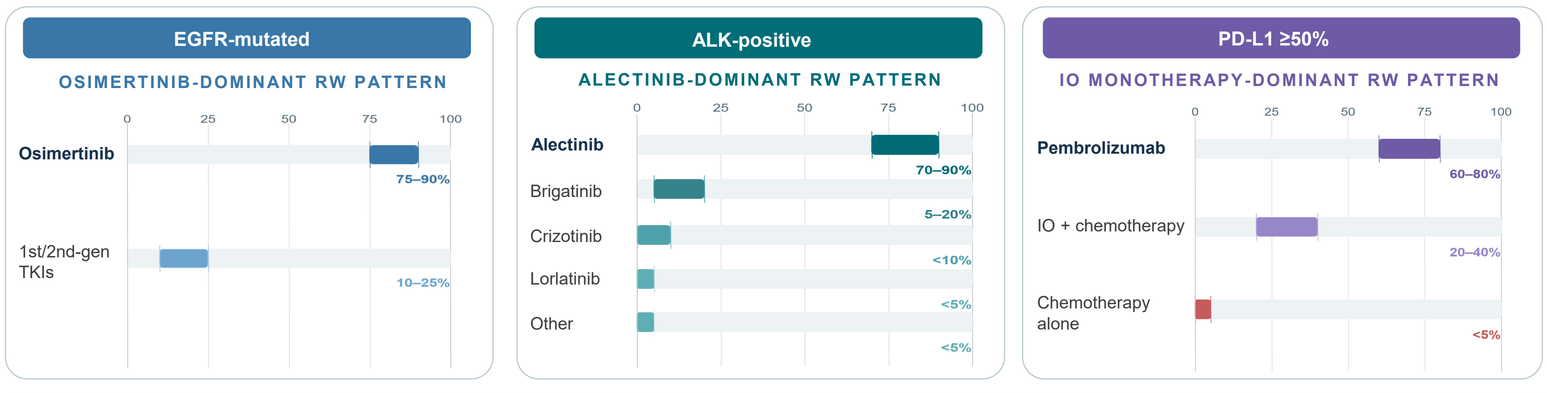
1. HTA Comparator Landscape

- **EGFR-mutated NSCLC** exhibited a **standardized comparator environment**, with osimertinib consistently used as the dominant comparator across appraisals
- **ALK-positive NSCLC** represented a **transitional comparator environment**, characterized by comparisons among multiple next-generation ALK inhibitors (alectinib, brigatinib, and lorlatinib)
- **PD-L1 ≥50% NSCLC** demonstrated a **heterogeneous comparator environment**, with substantial variation in comparator selection across jurisdictions and appraisals
- **Other biomarker-defined populations**, (RET fusion+, BRAF V600E+, and EGFR exon20ins) were characterized by limited appraisal numbers and emerging comparator pathways. Additional PD-L1+ subgroup were not defined for tumor proportion score, while EGFR/ALK WT encompass mixed subgroup population
- **EGFR-mutated, ALK-positive, and PD-L1 ≥50% populations were selected for further alignment assessment** since they represented most common and distinct comparator environments identified across the reviewed HTA appraisals. Guideline recommendations and RW treatment patterns were subsequently evaluated for these representative populations

2. Real-World Treatment Context by Biomarker Subgroup

- RW evidence demonstrated differing levels of treatment concentration across the three representative biomarker subgroups (**Figure 2**)
- Treatment use was highly concentrated around a single therapy in EGFR-mutated and ALK-positive NSCLC, where osimertinib and alectinib accounted for the majority of reported first-line use, respectively
- In contrast, PD-L1 ≥50% NSCLC exhibited a more distributed treatment landscape, with substantial use of both Pembrolizumab and chemo-immunotherapy
- These treatment patterns, together with corresponding guideline-recommended therapies, served as benchmarks for subsequent alignment assessment

Figure 2: Real-World Treatment Context Supporting Identification of the Dominant Treatment



3. Alignment of Comparators across HTA, Guidelines and RW Treatment

- Alignment between HTA comparators, guideline recommendations, and RW treatment patterns differed substantially across biomarker-defined populations (**Figure 3**)
- **EGFR-mutated NSCLC** demonstrated the highest level of concordance, with osimertinib consistently identified as the HTA comparator, guideline-recommended therapy, and dominant RW treatment across all assessed countries, resulting in complete alignment
- **ALK-positive NSCLC** also showed comparatively high alignment, with alectinib represented in most assessed HTA appraisals and consistently identified as the guideline and RW benchmark
- In contrast, **PD-L1 ≥50% NSCLC** exhibited the greatest variability in alignment, reflecting a more heterogeneous treatment landscape
- For PD-L1 ≥50% disease, RW practice and guideline recommendations consistently favored IO monotherapy, whereas several HTA appraisals continued to use chemotherapy-based comparators

Figure 3: Alignment heat map across representative biomarker-defined populations

EGFR-mutated

Country	HTA	Guideline	RW	Alignment
UK	Osimertinib	Osimertinib	Osimertinib	●
DE	Osimertinib	Osimertinib	Osimertinib	●
FR	Osimertinib	Osimertinib	Osimertinib	●
ES	Osimertinib	Osimertinib	Osimertinib	●
IT	Osimertinib	Osimertinib	Osimertinib	●

ALK-positive

Country	HTA	Guideline	RW	Alignment
UK	Alectinib	Alectinib, Brigatinib	Alectinib	●
DE	Alectinib	Lorlatinib, Alectinib, Brigatinib	Alectinib	●
FR	Crizotinib		Alectinib	●
IT	Alectinib	Alectinib, Brigatinib	Alectinib	●

PD-L1 ≥50%

Country	HTA	Guideline	RW	Alignment
UK	Pembrolizumab mono	IO mono	IO mono	●
DE (2021)	Chemotherapy	IO mono	IO mono	●
DE (2023)	Pembrolizumab mono	IO mono	IO mono	●
FR	Chemotherapy	IO mono/ chemo-IO	IO mono	●
ES	Chemo-IO	IO mono	IO mono	●

DE = Germany; ES = Spain; FR = France; HTA = Health Technology Assessment; IO = Immunotherapy; IT = Italy; mono = monotherapy; RW = Real-world; UK = United Kingdom

Alignment legend: ● **Aligned:** dominant RW/guideline treatment included as primary comparator; ● **Partially aligned:** included, but not primary comparator; ● **Limited alignment:** only indirectly represented; ● **Not aligned:** not represented

4. Patterns Across Biomarker Subgroups and by Country

- Alignment was highest in EGFR-mutated (100%; 8/8) and ALK-positive (75%; 3/4) populations, and lowest in PD-L1 ≥50% NSCLC (33.3% aligned; 16.7% partially aligned); **Figure 4**
- At the country level, alignment was greatest in the UK (100%; 4/4) and Italy (100%; 3/3), followed by Germany (80%; 4/5), Spain (50%; 1/2), and France (25%; 1/4); **Figure 5**
- The observed variation across populations and jurisdictions illustrates a key challenge for EU JCA PICO scoping: defining comparators that accommodate differences in national clinical practice while supporting a common European assessment

Figure 4: Alignment by Biomarker Subgroup Across 18 HTA appraisals

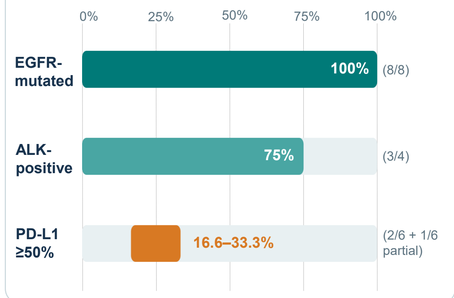
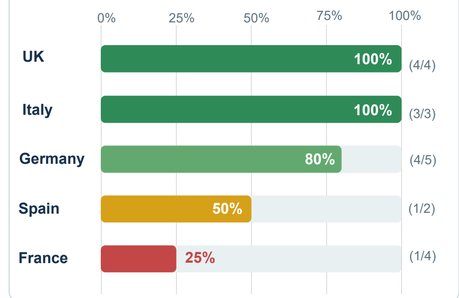


Figure 5: Alignment by Country across 18 selected HTA appraisals



Note: Biomarker and country-level denominators reflect the number of eligible HTA appraisals, not the number of biomarker subgroups or unique treatment recommendations..

Conclusions

- Comparator alignment was greatest in EGFR-mutated NSCLC, comparatively high in ALK-positive NSCLC, and more variable in PD-L1 ≥50% population
- Greater divergence was observed in populations with multiple treatment approaches, underscoring the importance of considering the treatment context when interpreting HTA comparator selection
- Guideline recommendations and contemporary RW treatment patterns may provide complementary context for comparator evaluation during PICO scoping for future EU JCAs

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Disclosure

This study was conducted by Evidinno Outcomes Research Inc. Ramandeep Kaur, Divya Pushkarna, Mir Sohail Fazeli, Jean-Paul Collet and Mir-Masoud Pourrahmat report employment with Evidinno Outcomes Research Inc. Masoud Toussi reports employment with United BioSource LLC. Authors report no other conflict of interest.

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