Optimizing PICO Scoping in EU HTA: Lessons from an HTA Coordination Group PICO exercise in advanced NSCLC to inform future best practice

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Objectives

- The stepwise implementation of Joint Clinical Assessment (JCA) under the EU Health Technology Assessment (HTA) Regulation (Regulation (EU) 2021/22821)[1] began from 12 January 2025 with new oncology drugs and advanced therapy medicinal products (ATMP)s
- The JCA assessment scope will be presented in the form of the PICO framework, outlining Population(s), Intervention, Comparator(s) and Outcomes for comparative assessment and specifying data requirements for Health Technology Developers (HTD)s
- In preparation for the implementation of the EU JCA, the HTA Coordination Group (HTACG) conducted a series of PICO exercises in spring 2024 to test and improve the content of the 'Guidance on the scoping process'[2]
- These exercises were carried out in three sequential rounds, each pairing one Medicinal Product (MP) and one Medical Device (MD), selected based on prior regulatory evaluation; MPs with a positive Committee for Medicinal Products for Human Use (CHMP) opinion and MDs with a scientific opinion from expert panels
- Adagrasib (Krazati®), indicated for advanced non-small cell lung cancer (NSCLC) with Kirsten rat sarcoma viral oncogene (KRAS) G12C mutation, was selected as one of the test cases. The HTACG published the results of the PICO exercise in early 2025, providing a consolidated set of PICOs[3]
- We undertook an analysis of the published PICOs for adagrasib, based upon clinical expertise on treatment pathways and the trial population, to demonstrate the potential value of an HTD perspective during the scoping process based. This analysis also drew on the broader clinical evidence base and insights from subsequent adagrasib HTA submissions. Our goal was to identify areas of methodological strength and demonstrate the potential for early consolidation of the JCA scope to reduce complexity and streamline the process
- It should be noted that the final (i.e., endorsed) version of the guidance was drawn up after these exercises have been conducted. Therefore, the PICOs discussed here, have no impact or consequences on national assessments or evaluations

Methods

We conducted a systematic review of the published adagrasib PICOs, focusing on two key dimensions

Population Relevance

We assessed the alignment between the populations defined in each PICO and:

- The approved EMA indication for adagrasib (Krazati®) in advanced NSCLC with KRAS G12C mutation[4]
- The target patient populations enrolled in adagrasib pivotal clinical trials, KRYSTAL-1[5] and KRYSTAL-12[6] (confirmatory head-to-head trial)

Comparator Relevance

We evaluated the clinical appropriateness of each proposed comparator by considering:

- The precise target population defined in the PICOs
- Current treatment guidelines at both European Union (EU)[7,8] and national Member State (MS) level
- National assessment scopes and clinical feedback per publicly available adagrasib HTA assessments in the EU (France[9], Germany[10], Italy[11]) and in England[12]
- Design and scope of adagrasib pivotal clinical trials, KRYSTAL-1[5] and KRYSTAL-12[6], as well as the previous treatments of the enrolled patient population
- Utilization rate of proposed comparators[15]

Results

- HTACG PICO exercise for adagrasib identified a notably broad scope comprising 13 PICOs, with 8 distinct populations and 15 comparators, and an extensive outcomes list, with instruments not included in adagrasib pivotal trials (**Figure 1, Figure 2**)
- Our retrospective analysis identified several limitations in both populations and comparators proposed in the HTACG PICO exercise for adagrasib. These limitations primarily stem from a misalignment between the proposed PICOs and the real-world treatment pathways and agents used in clinical practice, as well as the actual clinical evidence generated in the KRYSTAL-1[5] and KRYSTAL-12[6] trials

1. Population Relevance

Clinical relevance of three PICO populations was unclear, including for

- **PICO 6** (patients progressed after 1L Immune Checkpoint Inhibitor (ICI) and have *NOT* received platinum-based doublet chemotherapy (PDC))
- **PICO 11** (patients progressed after 1st line treatment with cytotoxic chemotherapy)
- **PICO 12** (patients progressed after 1st line PD-(L)1 mono

Although the EMA indication for adagrasib[4] allows use after at least one prior systemic therapy, the relevance of these narrowly defined subpopulations is questionable for several reasons:

- **Limited real-world representations:** These subgroups do not reflect the predominant treatment pathways observed in clinical practice. Real-world data show that the majority of patients receive combination regimens in the 1L, particularly immuno-oncology (IO) + chemotherapy[13]. Patients receiving only IO or only chemotherapy in 1L, often do so due to clinical characteristics, specific contraindications, comorbidities or access limitations, and thus represent a minority of the broader NSCLC population
- **Exclusion from pivotal trials:** Both KRYSTAL studies excluded patients who had received only prior IO or only cytotoxic chemotherapy, further limiting the applicability of these populations to the clinical evidence base

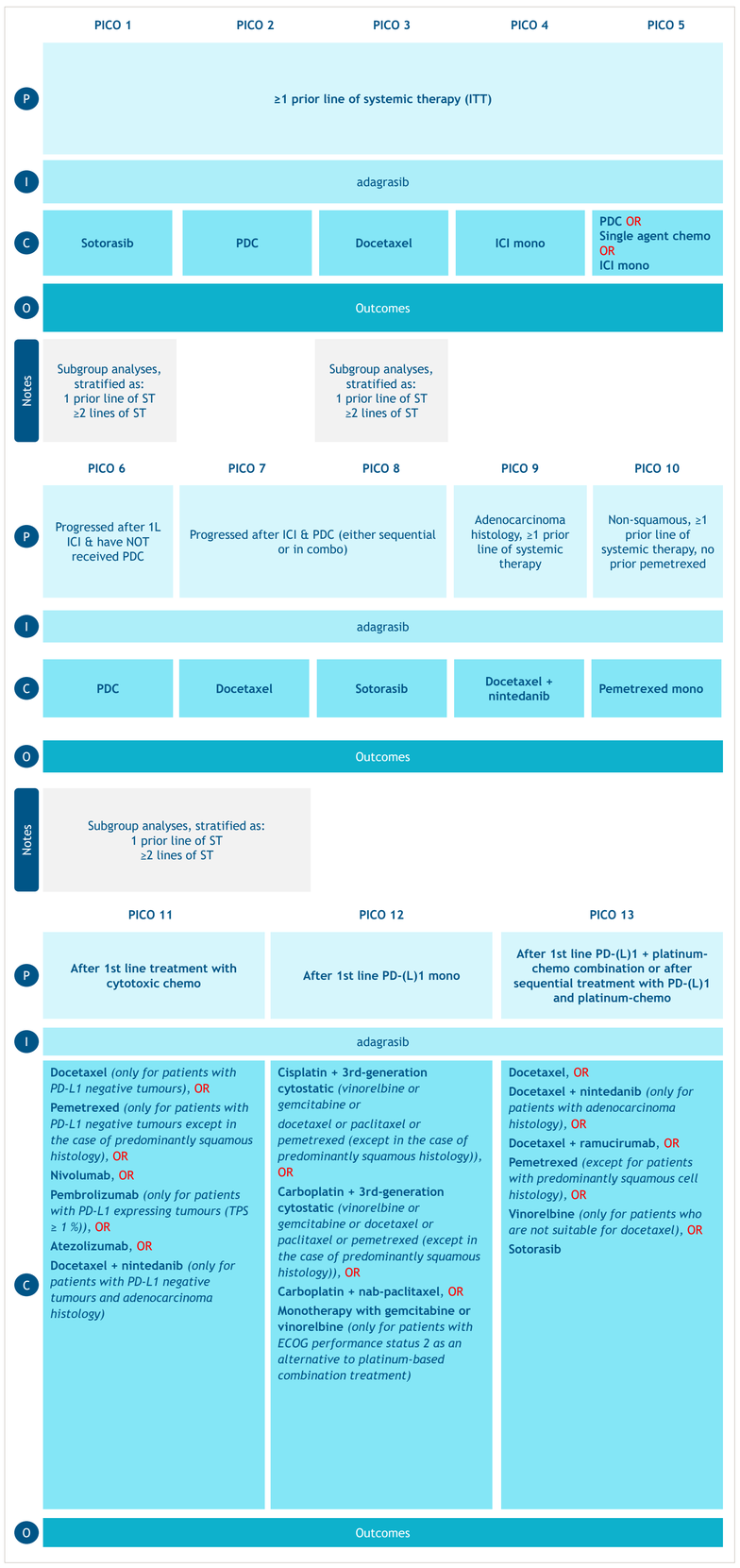
This misalignment underscores the need for the JCA scope to align with real-world treatment patterns and ensure that assessed populations are representative of those patients most likely to receive therapy in practice

2. Comparator Relevance

Relevance of three PICO comparators, **PDC (PICO 2), ICI monotherapy (PICO 4), and PDC OR single agent chemotherapy OR ICI monotherapy (PICO 5)** was unclear based on prevailing treatment patters and the target population:

- **Limited real-world use**: In routine clinical practice, rechallenging patients with the same class of agents, i.e., PDC or ICI monotherapy, is uncommon after progression on those therapies[14,15]. Rechallenge with prior therapies is typically reserved for select cases with long treatment-free intervals or specific contraindications, and does not represent standard practice
  - Furthermore, relevance of different ICIs (pembrolizumab, atezolizumab and nivolumab) depends on prior exposure and PD-L1 status, which was not specified
- **Misalignment with clinical trials**: 98.3% of patients in **KRYSTAL-1[5] and 100% of patients in KRYSTAL-12[6]** had received prior IO and PDC. Consequently, rechallenging these patients with ICIs or PDC, as proposed in these PICOs, does not reflect clinical practice and has limited value to inform HTA or pricing and reimbursement (P&R) decisions at the national level

Figure 1. Results of the HTA CG PICO exercise for adagrasib. Populations: PICOs 1-5 are based on the intention-to-treat (ITT) population; PICOs 6-8 are defined based on prior therapy; PICO 9 is defined by histology; PICO 10 is defined by histology and prior therapy; PICO 11-13 is defined based on prior therapy



3. Redundancy in PICOs

Several PICOs were identified as potentially redundant and would have likely been consolidated during the final consolidation phase of the JCA scoping, had the exercise been conducted under the finalized guidance:

- **PICO 5** could have been consolidated with **PICOs 2, 3, 4**
- **PICO 6** could have been consolidated with **PICO 12**
- **PICO 7 and 8** could have been consolidated with **PICO13**

In addition, given that 98.3% and 100% of patients had received prior IO and PDC in KRYSTAL-1 and KRYSTAL-12 studies respectively, some of the PICOs represent nearly identically patient populations and would be addressed with the same data based on KRYSTAL-1[5] and KRYSTAL-12[6] trials

- **PICO 6** is redundant to **PICO 2**
- **PICO 7** is redundant to **PICO 3**
- **PICO 8** is redundant to **PICO 1**

Figure 2. Outcomes listed in the HTA CG PICO exercise for adagrasib, included instruments not included in adagrasib pivotal trials

OUTCOMES LIST

Effectiveness	Safety

• Overall survival (OS)
• Progression-free survival (PFS)
• QoL assessed by disease specific questionnaire, preferer ably EORTC QLQ-C30/LC-13 and preferably measured as:
  ○ Change from BL to w12 for QLQ-LC13 and QLQ C30 scales
  ○ Time to deterioration for the subscales of QLQ-LC13 and QLQ-C30
  ○ Responder analyses of changes in symptom scores (response as 15% reduction)
• QoL assessed by generic questionnaires, preferably EQ-5D and SF36
• Overall response rate (ORR)
• Time to response
• Time to progression on subsequent treatment (PFS2)
• Time to progression of brain metastases
	• Adverse events (AE) in total (i.e., all AEs combined irrespective of seriousness)
	• Serios AEs and severe AEs with severity graded to pre-defined criteria, reported in total and by system organ class and preferred term
	  ○ Total
	  ○ System Organ Class
	  ○ Preferred Term
	• Death related to AEs
	• Treatment discontinuation due to AEs
	• Treatment interruption due to AEs
	• Dose reductions due to AEs

Comparison with national assessments

- For comparison, we also analyzed publicly available national HTA assessments of adagrasib. In all analyzed assessments (France, Germany, Italy, England), evidence was requested only for the intention-to-treat (ITT) population
- In France[9], the French National Authority for Health (HAS) assessment* used only docetaxel as the primary comparator for the ITT population. PDC, ICI and sotorasib were also considered as relevant comparators, but without any formal evaluation
- In Germany[10], the Federal Joint Committee (G-BA) consultation suggested that the G-BA would request evidence for the following 3 subpopulations, based on prior therapy:
  - After IO mono – corresponding to PICO 12
  - After chemotherapy – corresponding to PICO 11
  - After IO + chemotherapy – corresponding to PICO 13
- The comparators defined for PICOs 11-13 correspond to those suggested in the G-BA consultation.
- In Italy[11], the Italian Medicines Agency (AIFA) assessment selected sotorasib as the comparator, as it was considered the standard of care at the time of evaluation
- Notably, in England[12], the National Institute for Health and Care Excellence (NICE) draft scope for adagrasib initially proposed seven comparators. However, following consultation with the HTD and expert clinicians, this was reduced to three in the final scope, reflecting a more pragmatic and evidence-based approach that aligns with clinical practice and available data (**Figure 3**)
- These national examples demonstrate the value of early and structured engagement of HTDs and clinical experts with local HTA bodies in refining the assessment scope. Such collaboration not only ensures that the selected populations and comparators are clinically meaningful and feasible, but also helps to streamline the evidence requirements and reduce unnecessary complexity

*Outcomes used in the HAS assessment: Efficacy (PFS, ORR, OS), QoL (LCSS, EQ5D-5L), Safety (AE, Grade >=3 AE, Serious AE, AE leading to death, AE leading to treatment stop, AE leading to dose reduction, AE leading to treatment interruption)

Figure 3. Comparators in the draft and final scope of adagrasib NICE assessment

NICE assessment

Draft scope	Final scope *following consultation with HTD and clinical experts*
• Docetaxel • Docetaxel with nintedanib • Sotorasib • Nivolumab (for NSCLC previously treated with platinum-based chemotherapy only) • Atezolizumab (for NSCLC previously treated with platinum-based chemotherapy only) • Pembrolizumab (for NSCLC previously treated with platinum-based chemotherapy only) • Platinum-based chemotherapy (for NSCLC previously treated with immunotherapy monotherapy)	• Docetaxel • Docetaxel with nintedanib • Sotorasib

Conclusion

- Our findings highlight the need for early and structured engagement with HTDs and clinical experts, particularly in cases involving a high number of consolidated PICOs and complex evidence requirements
- Our retrospective analysis revealed that several of adagrasib PICOs lacked clinical applicability due to misalignment with the trial population. This divergence underscores the need for the scoping process to consider trial design, not just the indication statement, to avoid requesting PICOs that cannot feasibly be addressed in a comparative effectiveness
- Moreover, the population and comparator limitations identified in the JCA scope, were not observed in the publicly available national HTAs of adagrasib. The difference in the assessment scope between JCA and national HTAs therefore further underscores a key role that the HTDs have in refining and ensuring the scope remains both manageable and relevant
- Importantly, the current approach also places significant burden on assessors and co-assessors, who must review an increasing number of complex and potentially redundant data and analyses. A more focused and pragmatic scope would help alleviate the workload for assessors, while also providing greater clarity for individual MS, ensuring their evidence needs are effectively addressed.
- Streamlining the scoping process through collaborative input from the HTD can:
  - Improve the precision and usability of PICOs at the national level
  - Reduce redundancy and avoid clinically irrelevant comparisons
  - Facilitate more efficient evidence generation and submission planning
- As the EU HTA framework continues to mature, embedding HTDs perspectives into scoping exercises will be critical to ensure that JCAs are both methodologically robust and practically implementable. We look forward to ongoing dialogue and joint efforts to ensure that the JCA process evolves towards a more efficient, relevant, and sustainable model, one that benefits assessors, HTDs, and ultimately, patient across Europe

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Abbreviations

PICO: Population, Intervention, Comparator, Outcomes; **NSCLC**: Non-Small Cell Lung Cancer; **HTA**: Health Technology Assessment; **HTACG**: HTA Coordination Group; **HTD**: Health Technology Developer; **JCA**: Joint Clinical Assessment; **MP**: Medicinal Product; **MD**: Medical Device; **CHMP**: Committee for Medicinal Products for Human Use; **KRAS**: Kirsten Rat Sarcoma Viral Oncogene; **EMA**: European Medicines Agency; **HAS**: Haute Autorité de Santé (French National Authority for Health); **G-BA**: Gemeinsamer Bundesausschuss (Federal Joint Committee); **NICE**: National Institute for Health and Care Excellence; **PDC**: Platinum-Based Doublet Chemotherapy; **ICI**: Immune Checkpoint Inhibitor; **IO**: Immuno-Oncology; **ITT**: Intention-To-Treat; **AIFA**: Agenzia Italiana del Farmaco (Italian Medicines Agency); **WCLC**: World Conference on Lung Cancer

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