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MSR89

Zero at Submission: PICO Feasibility for Adagrasib in KRAS G12C-Mutated NSCLC

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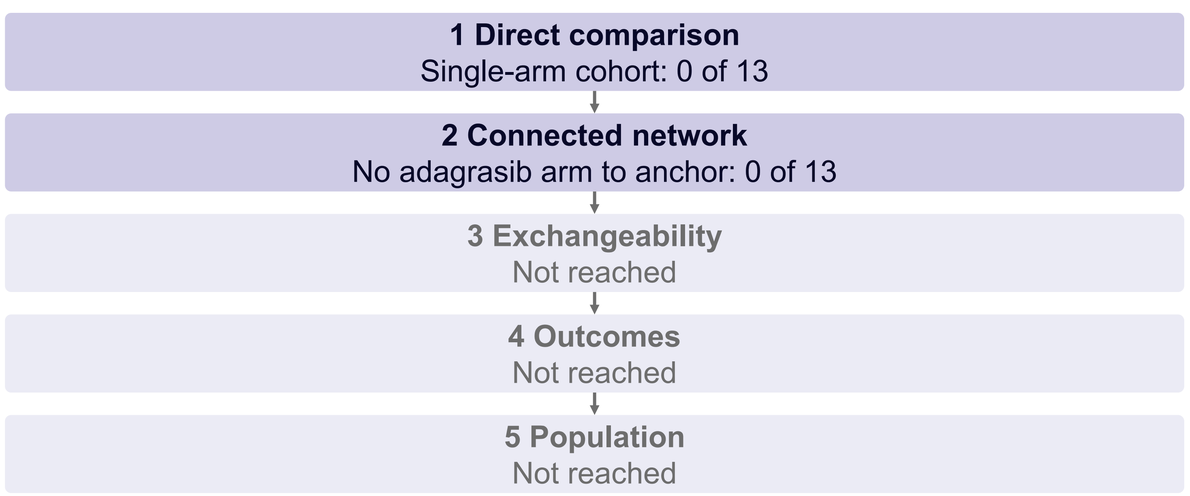
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BACKGROUND

In a joint clinical assessment (JCA), the developer "is required to address all PICOs" and should justify any missing indirect comparison [1]. Six pilot PICO exercises (spring 2024) were published by the European Commission on 3 February 2025 [2].

Exercise MP03 covered adagrasib, conditionally authorised on 5 January 2024 on a single-arm cohort [3,4]: how many of its PICOs could the evidence at submission answer?

Figure 1. Five-step feasibility algorithm: all 13 PICOs stopped at steps 1–2

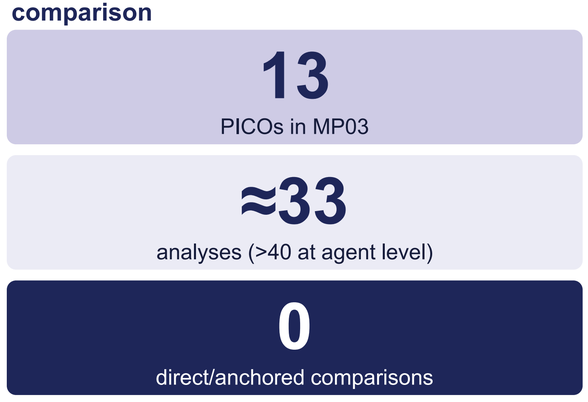


Source: [5].
Abbreviation: PICO, population, intervention, comparator, outcome.

OBJECTIVE

To quantify how many of the 13 consolidated PICOs of the MP03 adagrasib exercise could be answered with the evidence available at submission, and how many later data resolved.

Figure 3. MP03 scope at submission: 13 PICOs, about 33 analyses and no direct or anchored comparison



Source: [5]. Abbreviation: PICO, population, intervention, comparator, outcome.

METHODS

Structured expert feasibility assessment of the published MP03 scope, anchored to the evidence supporting the conditional authorisation: the single-arm KRYSTAL-1 cohort [2,4,5].

Scope
13 consolidated PICOs and requested subgroups extracted verbatim from the published MP03 scope

Counting
Each intervention-versus-comparator pairing and requested stratum counted as one analysis

Search
ClinicalTrials.gov and PubMed searched for comparator trials; KRYSTAL-1 mapped to each PICO

Classification
Pre-specified 5-step sequential algorithm (Figure 1); feasible = direct or anchored

Review
Two reviewers (second checked the first); consensus on divergences; no inter-rater statistic

RESULTS

Scope: 13 PICOs, one intervention (adagrasib monotherapy); PICOs 1–5 covered the full eligible population, PICOs 6–13 subpopulations defined by prior therapy, several restricted by histology or PD-L1 status.

Comparators: the most fragmented of the three medicinal-product exercises: sotorasib, docetaxel, platinum doublets, immune-checkpoint inhibitors and PD-L1- or histology-gated regimens (Figure 2).

Analytical burden: counting comparator pairings and requested strata (PICOs 1 and 3: two each; PICO 7: three), the scope expanded to about 33 analyses; more than 40 with PICO 11–13 regimens counted at agent level (Figure 3).

Feasibility at submission: KRYSTAL-1 was single-arm, so no PICO passed step 1 (direct comparison); with no adagrasib comparator arm, none passed step 2 (connected network) (Figure 1). Result: 0 of 13 PICOs had a direct or anchored comparison (Figure 2).

Unanchored option: every comparison required unanchored methods. Member State Coordination Group on HTA (HTACG) guidance prefers anchored comparisons and, without a connected network, directs unanchored ones to methods for non-randomised evidence (Box 1) [1]. Under the authors' pre-specified feasibility criteria (feasible = direct or anchored), these were not counted as feasible.

After submission: the randomised KRYSTAL-12 trial (adagrasib vs docetaxel) improved progression-free survival (hazard ratio 0.58) [6], with immature overall survival; it addresses PICO 3 only (authors' judgement).

Figure 2. Comparator evidence by PICO: no direct or anchored comparison at submission; the later KRYSTAL-12 RCT addressed PICO 3

		At submission		After submission
PICO	**Comparator(s)**	**Direct**	**Anchored**	**Later RCT**
1, 8	Sotorasib	○	○	○
3	Docetaxel	○	○	● **Yes: KRYSTAL-12**
7	Docetaxel	○	○	○
2, 6	Platinum doublet	○	○	○
4	ICI monotherapy	○	○	○
5	Chemo or ICI	○	○	○
9, 10	Doc+nint; Pem	○	○	○
11–13	Multiple*	○	○	○
PICOs with this evidence		**0 of 13**	**0 of 13**	**1 of 13 (PICO 3)**

○ No ● Yes

Source: [5], Table 2; [6]. *Multiple regimens incl. docetaxel (PICOs 11, 13) and sotorasib (PICO 13); some PD-L1/histology-gated.
Abbreviations: Chemo, chemotherapy; Doc, docetaxel; ICI, immune-checkpoint inhibitor; nint, nintedanib; PD-L1, programmed death-ligand 1; Pem, pemetrexed; PICO, population, intervention, comparator, outcome; RCT, randomised controlled trial.

BOX 1. WHAT HTACG GUIDANCE SAYS

- Anchored ITCs "should always be used in preference to unanchored methods"
- No connected network: unanchored ITCs use non-randomised-evidence methods
- Q&A §1.7; Methodological Guideline §5 (p.24); Practical §5.5

Abbreviations: HTACG, Member State Coordination Group on HTA; ITC, indirect treatment comparison; Q&A, questions and answers.

IMPLICATIONS

Single-arm evidence left the whole scope without a direct or anchored comparison, knowable from the evidence at submission.

Developers	HTA bodies and policymakers
Test each PICO against the evidence held at submission before dossier work; 0 of 13 PICOs had a direct or anchored comparison, so plan unanchored analyses using non-randomised-evidence methods, or justify their absence (Q&A §1.7).	Screen feasibility before the scope is final; 13 PICOs generated about 33 analyses and none had a direct or anchored comparison at submission.

Limitation: one pilot exercise; expert classification without an inter-rater statistic.

Abbreviations: HTA, health technology assessment; PICO, population, intervention, comparator, outcome; Q&A, questions and answers.

CONCLUSIONS

- **For a single-arm-supported oncology product, a 13-PICO scope yielded no direct or anchored comparison at submission; a later randomised trial addressed one PICO and does not retroactively close the gap at assessment.**
- **The result was foreseeable from the evidence at submission, supporting feasibility screening before a full dossier and a modified pathway that characterises uncertainty rather than documenting evidence absence.**

REFERENCES

1. HTACG. Q&A on general methodological and procedural issues for JCAs, 14 May 2026; Methodological and Practical Guidelines for Quantitative Evidence Synthesis: Direct and Indirect Comparisons, 8 March 2024.
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