# WHAT THE FIRST COMPLETED EU JOINT CLINICAL ASSESSMENT DOES NOT TELL US: A STRUCTURED ANALYSIS OF THE TOVORAFENIB JCA AND REMAINING METHODOLOGICAL UNCERTAINTIES

HTA235

## CONCLUSIONS

The tovorafenib JCA established the first precedent for how assessors apply JCA methodology in a rare paediatric oncology indication with a single-arm trial; however, key areas of uncertainty remain unanswered. Most critically, this single, highly specific precedent may generalize poorly: given vague guidance, future assessors may take substantially different approaches. Future appraisals will provide additional precedence for both assessors and HTDs navigating JCA submissions.


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## AFFILIATIONS

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## REFERENCES


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## ABBREVIATIONS

BRAF: B-Raf Proto-Oncogene; CG: coordination group; EMA: European Medicine Agency; EU: European Union; HTA: health technology assessment; HTD: Health Technology Developer; JCA: Joint Clinical Assessment; LGG: Low-Grade Glioma; MAIC: Matching-Adjusted Indirect Comparison; PICO: population, intervention, comparator, outcomes; SLR: Systematic Literature Review; TPCV: thioguanine, procarbazine, lomustine, and vincristine; TSC: Tuberous Sclerosis Complex; US: United States; USA: United States of America; V600: Valine at amino acid position 600; V600E: BRAF V600E Mutation

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## INTRODUCTION

- From January 2025, the mandatory Joint Clinical Assessment (JCA) for comparative clinical review across EU Member States came into force. In June 2026, tovorafenib, developed for relapsed/refractory paediatric low-grade glioma harbouring a BRAF fusion, rearrangement, or V600 mutation, became the first completed JCA.[1]

## STUDY OBJECTIVE & METHODOLOGY

- The objective was to analyse the first completed JCA report to understand remaining unaddressed areas for future submissions with different evidence bases.
- We conducted a structured review of the JCA for tovorafenib, examining the population, intervention, comparator, outcomes (PICO) framework, primary evidence base, systematic literature review (SLR), and statistical methods against JCA guidance requirements, with a focus on highlighting remaining areas of uncertainty.

## RESULTS

- Eight PICOs were defined across three populations. The included evidence came from FIREFLY-1[1], a single-arm, open-label, multicentre trial (**Figure 1**).
- Limited comparator evidence was identified; the health technology developer (HTD) submitted indirect evidence of relative treatment effect for only 2/8 PICOs (numbers 5 and 7) via an unanchored matching-adjusted indirect comparison (MAIC) versus dabrafenib + trametinib (PICO 5) and trametinib (PICO 7) (**Figure 1)**.
- The unanchored MAIC for PICO 5 re-weighted individual patient-level data from FIREFLY-1[1] to create a pseudo-population that matched the cohort described in Bouffet et al., 2023 for comparison (**Figure 1**).[1,2]
- MAIC analyses relied heavily on several assumptions. The HTD acknowledged that the following assumptions may not hold, thereby introducing bias: 1) all prognostic factors and effect modifiers are included in the model; 2) there is sufficient overlap between the two trial populations for included variables; 3) outcomes are reported in sufficiently similar way between the trials to allow for valid comparison (e.g., definitions, assessment, summary measure).
- The HTA-CG noted that the inability to confirm whether the covariance structures of the included variables were the same, or mutually independent, across both studies also introduced a potential risk of bias.
- PICO 7 was excluded from the report entirely given insufficiently-reported comparator data (**Figure 1**).

### FIGURE 1. OVERVIEW OF THE FIRST JCA REPORT

| TREATMENT | PICO 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| **Population** | **1** (EMA) | | | | **2** (>1yr, V600E) | | **3** (>6mo, other) | |
| **Comparator** | | | | | | | | |
| Individualised treatment? | YES | YES | NO | NO | NO | YES | NO | YES |
| Vinblastine | ✓ | ✓ | | ✓ | | ✓ | | ✓ |
| Carboplatin + vincristine | ✓ | ✓ | ✓ | | | ✓ | | ✓ |
| TPCV combination therapy | ✓ | ✓ | | | | | | |
| Dabrafenib + trametinib | ✓ | ✓ | | | ✓ | | | |
| Everolimus | ✓ | | | | | | | |
| Bevacizumab + chemo | ✓ | | | | | | | |
| Trametinib | | | | | | | ✓ | |

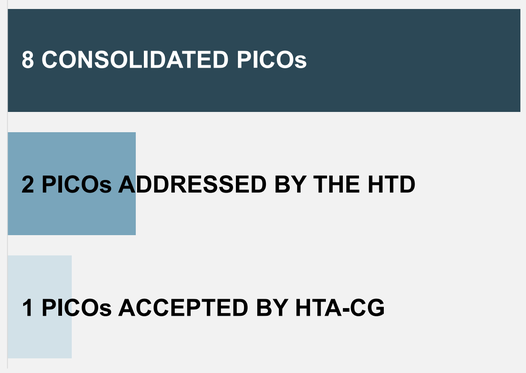
**CO-ASSESSORS**

IQWiG NCPE

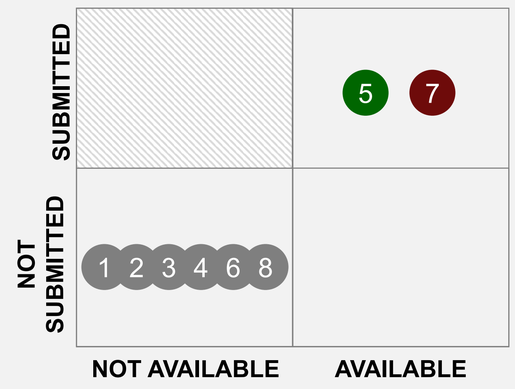
**EXPERT ENGAGEMENT**

1 carer and 1 clinical expert (NOPHO/SIOP/PanCare) provided formal input at scope and draft report stages.

**PICOs OVERVIEW**




**COMPARABLE EVIDENCE**




**KEY**

- Comparative evidence not submitted
- Comparative evidence submitted and accepted
- Comparative evidence submitted but not accepted

**SUBMITTED CLINICAL TRIAL EVIDENCE: FIREFLY-1[1]**

- Open-label, multi-centre, multi-arm, **non-comparative**, non-randomised **pivotal** Phase 2 study.
- N=137 children.
- 2-year data submitted (3-year data released while the assessment was ongoing).

**SUBMITTED INDIRECT EVIDENCE**

- Unanchored MAIC versus dabrafenib + trametinib for PICO 5 (accepted).[2]
- Unanchored MAIC versus trametinib for PICO 7 (**not accepted**).[3,4]

- The first JCA involved a highly specific evidence scenario that prevents broader generalisation of the process itself and how the JCA will develop PICOs, consider evidence, and / or respond to unanswered PICOs – ultimately leaving more questions than answers.

### FIGURE 2. WHAT WE KNOW FOLLOWING THE FIRST JCA

**FIRST JCA EVIDENCE SCENARIO**

*Tested precedent*

- ☑ Rare condition
- ☑ Paediatric oncology
- ☑ Single-arm trial
- ☑ Limited comparator evidence
- ☑ Unanchored MAIC

*Untested by this precedent*

- All PICOs with available evidence were addressed. Therefore, the first JCA did not provide precedence for situations in which the HTD declines to submit evidence for a PICO(s) when evidence exists / is available (e.g., inappropriate comparator, infeasible analysis).
- Requested outcomes were consistent across all populations / comparators. However, the report indicates that not all outcomes will require comparative estimates, and that descriptive comparisons *are* acceptable in some cases; these cases are not currently defined. Understanding when quantitative versus descriptive reporting can be utilised is not clear.
- This first report was for a rare paediatric indication providing very little insight regarding how PICOs will be developed / consolidated for non-rare indications with large bodies of evidence.