COMPARISON OF THE PICOS FROM THE FIRST JCA REPORT ON TOVORAFENIB AND GUIDELINE RECOMMENDATIONS IN PEDIATRIC LOW-GRADE GLIOMA

HTA274

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Objectives

The EU-HTA framework represents the central gateway to European pricing and reimbursement. Exhaustive PICO (Population, Intervention, Comparator, Outcome) prediction remains a major challenge for pharmaceutical companies in the preparation of the Joint Clinical Assessment (JCA). This analysis compares the Population (P) - and Comparator (C) - components from the PICO scope in the first JCA procedure for tovorafenib in 2L/+ pediatric low-grade glioma (LGG) [1] with European guideline recommendations. The findings aim to inform clinical development strategies and facilitate optimal preparation for future EU-HTA assessment.

Methods

Guidelines were identified using a dual search approach. First, relevant guidelines referenced in the JCA dossier and report were extracted. Second, a structured free-text search was conducted to identify additional guidelines across EU-HTA member countries, using the search terms “Glioma” AND “Guideline” AND <country>. Each identified guideline was screened to determine whether it was specific to the pediatric population or contained information on the treatment of pediatric patients. Duplicates were removed, and only the most recent version of each guideline was retained. Across a total of 30 countries screened (all 27 EU member states plus Liechtenstein, Norway, and Iceland), 5 guidelines containing relevant information on the treatment of 2L/+ pediatric LGG were identified. Two of the guidelines were European [2, 3] while the remaining guidelines were from France [4], the Netherlands [5] and Romania [6]. Guideline recommendations were subsequently compared against the P - and C - components specified in the JCA of tovorafenib, in order to assess whether and to what extent these components are supported by current guideline recommendations.

Results

The subpopulations defined in the PICO scope were consistent with the patient population enrolled in the pivotal trial of tovorafenib (FIREFLY-1) and with the approved indication of dabrafenib + trametinib [7, 8]. Collectively, the five guidelines showed considerable overlap in their recommended comparator therapies, however, between individual guidelines, recommendations for the comparator diverged. The PICO scope also included comparator therapies not supported by guideline recommendations, while some guideline-recommended comparators were not captured within the PICO scope.

Table 1: Overview of Guideline Recommendations for Comparators specified in the PICO Scope of Tovorafenib

PICO	Comparator	EU 2019	RO 2021	FRA 2022	EU 2024	NL 2024
1, 2, 4, 6, 8	Vinblastine	✓ a	✓ b	✓	✗	✓
1, 2, 3, 6, 8	Carboplatin + Vincristine	✓ c	✓	✓ d	✗	✗
1, 2	TPCV	✓ e	✗	✓ b	✗	✗
1, 2, 5	Dabrafenib + Trametinib	✗	✗	✗	✓ f	✗
1	Everolimus	✗	✗	✗	✗	✗
1	Bevacizumab + Chemotherapy	✓ g	✓ g	✗	✗	✗
7	Trametinib	✗	✗	✓ b	✗	✓ h

EU: Europe; FRA: France; NL: Netherlands; RO: Romania; TPCV: thioguanine, procarbazine, CCNU (Lomustine), and vincristine.

a: for patients with prior carboplatin hypersensitivity
b: for KIAA1549-BRAF-mutation
c: for patients without hearing impairment and initial favorable response
d: “LGG2004” referenced (trial arms Carboplatin + Vincristine (+Etoposid)
e: can be offered as further alternative
f: for patients ≥1 year of age
g Irinotecan as chemotherapy
h: for patients ≤ 1 year
Sources: [2-6, 9]

✓ recommended in guideline
✗ not recommended in guideline
✓ not clearly defined

Results (continued)

Everolimus was the only agent that was not recommended in any of the guidelines. In both PICO 1, PICO 2 and PICO 5, dabrafenib + trametinib was recommended in only one of the five guidelines, and restricted to patients aged ≥1 year, aligning with the approved label population of both dabrafenib + trametinib [3, 7, 8]. The limited inclusion of dabrafenib + trametinib in clinical guidelines may reflect the timing of its marketing authorization for pediatric LGG by the end of 2023/beginning of 2024 [7, 8], after most reviewed guidelines had already been published.
Conversely, radiotherapy was recommended across all five identified guidelines [2–6] but fell outside the PICO comparator scope. The guidelines also described several further systemic treatment alternatives not captured as PICO comparators: Alternating cycles of cisplatin/vincristine (regimen A) and cyclophosphamide/vincristine (regimen B), recommended as an alternative consolidation regimen in cases of carboplatin hypersensitivity [2]. Cisplatin/etoposide is listed as a further rescue option in progressive LGG. Treatment elements of the BB-SFOP regimens B and C (etoposide + cisplatin and vincristine + cyclophosphamide), which have been incorporated into other treatment approaches, remain additional treatment alternatives for LGG [2]. Additional alternatives mentioned include metronomic therapy, described as a patient-friendly option for heavily pretreated patients [2], oral vinorelbine or FLUVAbrex [4], as well as temozolomide [5, 6].

Across the identified guidelines, treatment decisions were mostly described as individualized and multidisciplinary, shaped by factors such as resectability, preservation of neurological and visual function, prior treatment lines, and other patient-specific considerations that may justify deviating from standard algorithms [2, 3, 5, 6].

Conclusions

This analysis reveals that the definition of the P component can be derived from the pivotal trial and the approved indication of relevant medicinal products. Guideline recommendations for the C component specified in the PICO scope appeared to show some degree of variability, with agents such as dabrafenib + trametinib and everolimus only sparsely recommended. This heterogeneity should be interpreted in the context of differing guideline update cycles, which may lead to variable incorporation of novel therapeutic agents into clinical recommendations. Furthermore, treatment options such as radiotherapy and other systemic alternatives referenced in guidelines were not captured within the PICO scope.

Overall, guideline recommendations alone appear insufficient to fully anticipate the PICO scope of a JCA procedure. A comprehensive understanding therefore requires further consideration of additional factors not captured by this analysis, such as local insights, knowledge of individualized treatment practice, and in-depth knowledge of HTA agency requirements. Since this analysis is limited to the first JCA procedure of tovorafenib, additional insights into PICO development may emerge as more JCA reports become available.

Recent Developments since the Abstract Submission

Since the time of abstract submission, three further JCA procedures have been published, in addition to the first JCA procedure (tovorafenib) discussed in this poster:

- lurbinectedin (Zepzelca)
- tarlatamab (Imdylltra)
- onasemnogene abeparvovec (Itvisma)

A preliminary review points to a broadly comparable picture emerging across these further procedures with regard to the P and C components, in relation to European guideline recommendations. Further in-depth assessments of these procedures are needed before concrete conclusions can be drawn.

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