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MSR284

Uncertainty Without Certainty: The Verdict the First Orphan JCA Never Gave

Imen SOUSSI[1], Wael FOURATI[1], Aleksandra CABAN[2], Laurent BOYER[3], Mondher TOUMI[3]

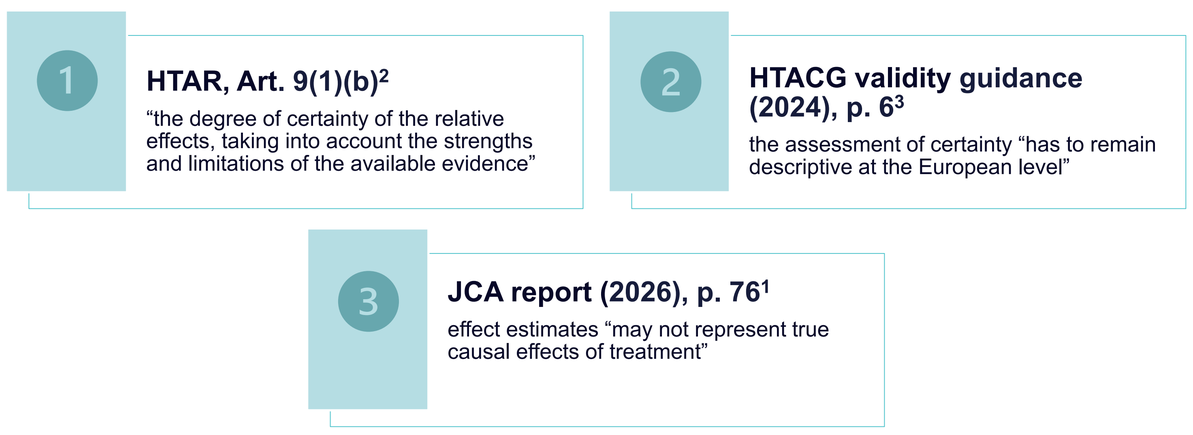
1 Clever-Access, Tunis, Tunisia; 2 Clever-Access, Krakow, Poland; 3 Aix-Marseille University, Marseille, France

BACKGROUND

Tovorafenib, an orphan medicine with conditional EU marketing authorisation for BRAF-altered paediatric low-grade glioma (pLGG) after ≥1 prior systemic therapy, was the subject of the first published JCA (JCA-MP-2024-06; endorsed 30 April 2026)[1]. Its pivotal evidence was a single-arm study (FIREFLY-1).

Article 9(1)(b) HTAR[2] requires a description of the degree of certainty of relative effects, whereas HTACG guidance[3] requires certainty assessment to remain descriptive at the European level (Figure 1).

Figure 1. Three texts, three positions on certainty



Abbreviations: Art., Article; **HTACG,** Health Technology Assessment Coordination Group; **HTAR,** Health Technology Assessment Regulation; **JCA,** joint clinical assessment.

OBJECTIVE

To examine whether the first orphan oncology JCA delivered an explicit statement of the degree of certainty of relative effects or stopped at documenting uncertainty.

15 uncertainty factors listed for PICO 5

4 qualitative characterisations

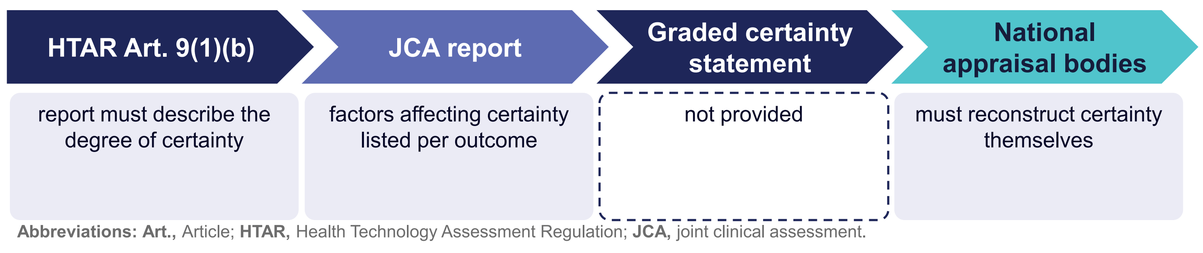
0 graded certainty statements

METHODS

Methodological case analysis of the published JCA report (v1.0)[1] for tovorafenib, the first orphan oncology JCA.

1. **Extract** — All passages on certainty or uncertainty in the report
2. **Classify** — Each as a listed limitation, a qualitative characterisation or a graded certainty conclusion
3. **Compare** — With Article 9(1)(b) HTAR[2] and HTACG guidance (validity[3]; evidence synthesis[4])
4. **Consider** — What the report leaves national bodies to reconstruct

Figure 2. From documented uncertainty to the missing certainty statement[1,2]



Abbreviations: Art., Article; **HTAR,** Health Technology Assessment Regulation; **JCA,** joint clinical assessment.

RESULTS

The report[1] states that factors affecting certainty "are identified". It lists six general uncertainties for PICO 5, the only answered PICO (unanchored non-randomised evidence; unadjustable population differences; residual confounding; small ESS; flawed sensitivity analyses; nominal p-values), plus outcome-specific factors for ORR, PFS and safety (**Table 1**).

Qualitative characterisations exist. Estimates "may not represent true causal effects", bias is "of unknown magnitude and direction", ORR interpretation is "highly uncertain" and safety "may negatively affect certainty"[1] (**Table 1**).

No outcome received a graded certainty conclusion (e.g., high, moderate, low or very low), no recognised grading framework was applied, and no summary statement links the listed factors to a degree of certainty, leaving national bodies to reconstruct it (**Figure 2**).

This is consistent with HTACG guidance[3] (**Figure 1**), which argues that grading systems entail appraisal, "since appraisal includes value judgement". The evidence-synthesis guideline[4] states that its use of "uncertainty" should not be read as GRADE (Grading of Recommendations Assessment, Development and Evaluation) "certainty of evidence". The dossier template[5], however, asks developers to state "the degree of certainty of the relative effectiveness and relative safety with regard to the PICO(s)", and the report template[6] itself states that "an assessment of the degree of certainty … shall be performed" (**Figure 3**).

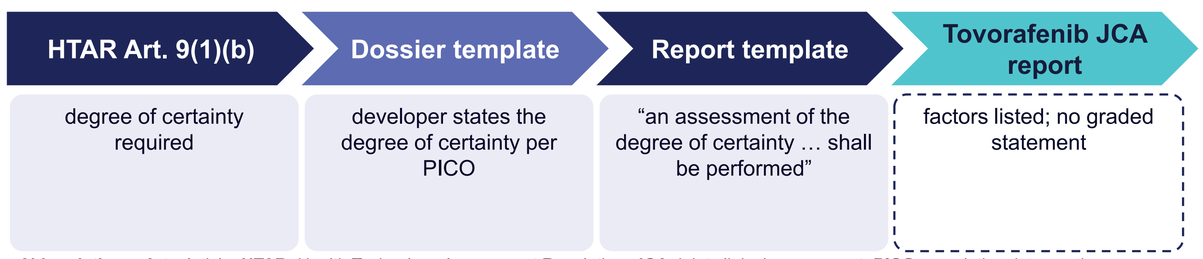
The requirement therefore runs from HTAR[2] through the dossier template[5] to the report template[6], yet the report converts none of its 15 listed factors into a stated degree of certainty for PICO 5; that judgement passes to each national appraisal.

Table 1. Certainty-related content for PICO 5 in the report[1]

Level	Factors listed	Qualitative wording	Graded certainty
All outcomes	6 (e.g., unanchored ITC; residual confounding; small ESS)	"may not represent true causal effects"; bias "of unknown magnitude and direction"	None ⊗
ORR	5 (e.g., HGG criteria; INV vs IRC discrepancy)	"highly uncertain"	None ⊗
PFS	3 (PH assumption; censoring; selective reporting)	—	None ⊗
Safety	1 (exposure duration not adjustable)	"may negatively affect certainty"	None ⊗

Abbreviations: ESS, effective sample size; **HGG,** high-grade glioma; **INV,** investigator; **IRC,** independent review committee; **ITC,** indirect treatment comparison; **ORR,** objective response rate; **PFS,** progression-free survival; **PH,** proportional hazards; **PICO,** population, intervention, comparator, outcome.

Figure 3. Certainty requested vs delivered[1,2,5,6]



Abbreviations: Art., Article; **HTAR,** Health Technology Assessment Regulation; **JCA,** joint clinical assessment; **PICO,** population, intervention, comparator, outcome.

IMPLICATIONS

Until JCA reports state a graded degree of certainty, developers and HTA bodies can each act to close the gap.

Developers	HTA bodies and policymakers
state a structured certainty assessment per PICO in the dossier, as the template requests[5], so that the reasoning is on record.	set a transparent, structured route from listed limitations to a graded certainty conclusion, without value judgement; the report listed 15 factors for PICO 5 and gave 0 graded certainty statements.

***Limitation**: based on a single report assessment*

CONCLUSIONS

- **Documenting uncertainty is not the same as stating certainty. The framework needs a transparent, structured route from listed limitations to a graded certainty conclusion.**
- **Otherwise, the central deliverable of the JCA is left for each national body to reconstruct.**

REFERENCES

1. Member State Coordination Group on HTA. Joint Clinical Assessment Report of Tovorafenib, Version 1.0 (JCA-MP-2024-06). Brussels: European Union; 2026.
2. Regulation (EU) 2021/2282. OJ L 458, 22.12.2021.
3. HTACG. Guidance on Validity of Clinical Studies. 4 July 2024.
4. HTACG. Methodological Guideline for Quantitative Evidence Synthesis: Direct and Indirect Comparisons. 8 March 2024.
5. HTACG. Guidance on filling in the JCA dossier template – Medicinal products. 8 October 2024.
6. Commission Implementing Regulation (EU) 2024/1381 of 23 May 2024, Annex II §4.3. OJ L, 24.5.2024.

Scan the QR code or email us to arrange a meeting.

Contact information: contact@clever-access.com