Tuesday, June 16th, 2026

Tovorafenib's Joint Clinical Assessment Report
Comments by Cancer Patients Europe & the European Access Academy

The long-awaited first Joint Clinical Assessment (JCA) – for Ipsen's Orphan Drug Tovorafenib (Ojemda®), indicated as monotherapy for the treatment of patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies[1] – has just been finalized. The procedure was initiated on March 23rd, 2025, the JCA report was endorsed by the Member State Coordination Group on HTA on April 30th, 2026, and the procedural review by the European Commission was concluded on May 19th, 2026, followed by the publication of the report and related documentation on June 9th, 2026.[2] The assessor was Ireland's National Centre for Pharmacoeconomics (NCPE) and the co-assessor was Germany's Institute for Quality and Efficiency in Health Care (IQWiG).

It remains to be seen to what extent the EU Member States will utilize and consider the JCA report in their procedures. In Germany, the national HTA process has already been initiated, in other countries e.g., in Ireland and the Netherlands, the national procedures will start once and if the health technology developer (HTD) submits an application for reimbursement.

From the CPE & EAA Perspective, a number of points should be noted:
There is a limited evidence base in BRAF-altered relapsed/refractory paediatric LGG, and no treatments are available which are specifically authorized in this indication. Consequently, this is a medical condition with a high unmet medical need, and patients are treated with individualized therapy. The best available evidence at the current state is based on Firefly-1, a single-arm trial, while an RCT of Tovorafenib vs. current standard of care chemotherapy in first-line LGG patients (Firefly-2) is ongoing. Due to the limited available evidence, the risk of bias both for type 1 error (falsely assuming an additional benefit) and for type 2 error (falsely not offering a potentially beneficial medicine to those severely affected children and adolescents) is particularly high in this case. In the JCA procedure, only one carer (parent of a child with pLGG) and one clinical expert were involved, and the documentation does not include any records on how or even if their input was considered. Thus, expert involvement, which is one of the most critical factors for a successful implementation of the EU HTA regulation, was extremely limited.

Cancer Patients Europe (CPE) & the European Access Academy (EAA) Faculty

[1] https://www.ema.europa.eu/en/documents/product-information/ojemda-epar-product-information_en.pdf
[2] https://health.ec.europa.eu/publications/joint-clinical-assessment-report-tovorafenib-ojemda_en

Tovorafenib: A Glance on One Slide

Indication:

- Monotherapy for the treatment of patients 6 months of age and older with paediatric low-grade glioma (LGG) harbouring a BRAF fusion or rearrangement, or BRAF V600 mutation, who have progressed after one or more prior systemic therapies

Guidelines:

- EJC 2024*:
  - Only first line recommendations
  - Mentioning Tovorafenib US approval and EU OD and Firefly 2 planning in 1st line
  - Mentioning targeted treatments for BRAF
- SIOPE 2022**:
  - Only first line recommendations
  - Mentioning targeted treatments for BRAF

Clinical Data:

Firefly 1[†]:

- P: BRAF altered rr pLGG; fusion: n=101 (74%), rearrangement or fusion: n=14 (10%), V600E mutation: n=22 (16%)
- I: Type II RAF Inhibitor
- C: n/a
- O: efficacy results based on arm 1 (IRC):
  - RANO-HGG: ORR 67%; DOR 16.6m; TTR 3.0m;
  - RAPNO: ORR 51%; DOR 13.8m; TTR 5.3m;
- S: Phase 2; arm 1 (n = 77); arm 2 extension after arm 1 closure (n = 60); data cut-off @ 15 months

EPAR Conclusions:

- Unmet medical need as no authorised treatments in indication
- Positive Benefit Risk Ratio
- Orphan Designation
- Conditional Marketing Authorization: Firefly II RCT data in 1st line expected to provide required additional information

Scoping & HTD Dossier:

- Scoping: 3 Populations/ 8 PICOs; 2 addressed by HTD @ 2yr cut-off
- PICO 5: BRAF V600E; pts > 1yr; comparator dabrafenib & trametinib; PAIC: ORR (Odds Ratio 8.23 [1.11; 61.27]; p = 0.040; RANO-LGG; IRC); sensitivity analyses not significant
- PICO 7: BRAF fusion, rearrangement or V600 (non-E) mutation; comparator trametinib; ORR (Odds Ratio 16.01 [6.03; 42.49]; p<0.001; RANO HGG; IRC)
- Claiming ORR statistical superiority and commenting on high unmet need

JCA-report; focus PICO 5; in addition, significantly more severe AEs (CTCAE >=3)

PICO 5 unanchored MAIC vs Bouffet[§]; dichotomous outcomes

- 6m PFS (RANO LGG; IRC): RR 1.09 [0.92; 1.30]
- 12m PFS (RANO LGG; IRC): RR 0.92 [0.61; 1.38]
- CR+PR (RANO HGG; INV): OR 0.56 [0.08; 3.84]; p = 0.551
- CR+PR (RANO HGG; IRC): OR 7.26 [0.98; 53.68]; p = 0.052

Cave: Population in Bouffet includes pts with HGG rather than LGG and without prior systemic treatment

PICO 5 unanchored MAIC vs Bouffet[§]; time to event

- 13.67m vs 36.9m; HR 4.8 [2.14; 11.14]; p = 0.011; RMST difference: -6.64 [-13.16;-0.12]; p = 0.046

PICO 7 not considered due to insufficient evidence

* https://www.ejcped.com/action/showPdf?pii=S2772-610X%2824%29000078-X; ** https://siope.eu/media/documents/esop-low-grade-gliomas-lgg.pdf; † https://doi.org/10.1038/s41591-023-02668-y; § https://www.nejm.org/doi/full/10.1056/NEJMoa2308815; AE: Adverse Event, BRAF: V-Raf Murine Sarcoma Viral Oncogene Homolog B encoding rapidly accelerated fibrosarcoma protein, CR: complete response, CTCAE: Common Terminology Criteria for Adverse Events, DOR: Duration of Response, EPAR: European Product Assessment Report, EJC: European Journal of Cancer, HGG: High Grade Glioma, HR: Hazard Ratio, HTD: Health Technology Developer, INV: investigator assessed, IRC: independent review committee, (p)LGG: (paediatric) Low Grade Glioma, m: months, MAIC: Matching-adjusted indirect comparison, OD: Orphan Designation, ORR: Objective Response Rate, PAIC: Predictive-adjusted indirect comparison, PFS: progression-free survival, PICO: Population/ Intervention/ Comparator/ Outcomes, PR: partial response, pts: patients, RAF: rapidly accelerated fibrosarcoma kinases, RANO: Response Assessment in Neuro-Oncology, RAPNO: Response Assessment in Neuro-Oncology, RCT: Randomised Controlled Trial, rr: relapsed or refractory, RMST: Restricted Mean Survival Time, RR: Relative Risk, SIOPE: European Society for Paediatric Oncology, TTR: Time to Response, yr: year

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Tovorafenib: Topline Comments

- Medical Condition with a high unmet medical need
- Limited evidence base in BRAF-altered relapsed/refractory (R/R) pLGG
- No specifically licensed comparator treatments available, therefore patients are currently treated with individualised treatment
- Firefly 1, best available evidence for Tovorafenib is based on a single-arm trial
- Firefly 2, an RCT versus current standard of care chemotherapy in first line LGG patients is currently ongoing
- Due to the limited evidence-base determination of relative effectiveness harbours a particularly high risk of bias in both directions:
  - *Type 1 error: falsely assuming an additional benefit*
  - *Type 2 error: falsely not offering a potentially beneficial medicine to those severely affected children and adolescents*
- Only one parent carer and one clinical expert were included – without any records on how or even if input was considered, i.e. limited expert involvement, which is one of the most critical factors for a successful implementation of the regulation