Updated 3-year analysis

Clinical stability following tovorafenib treatment in relapsed/refractory pediatric low-grade glioma: updated results from the phase 2 FIREFLY-1 trial

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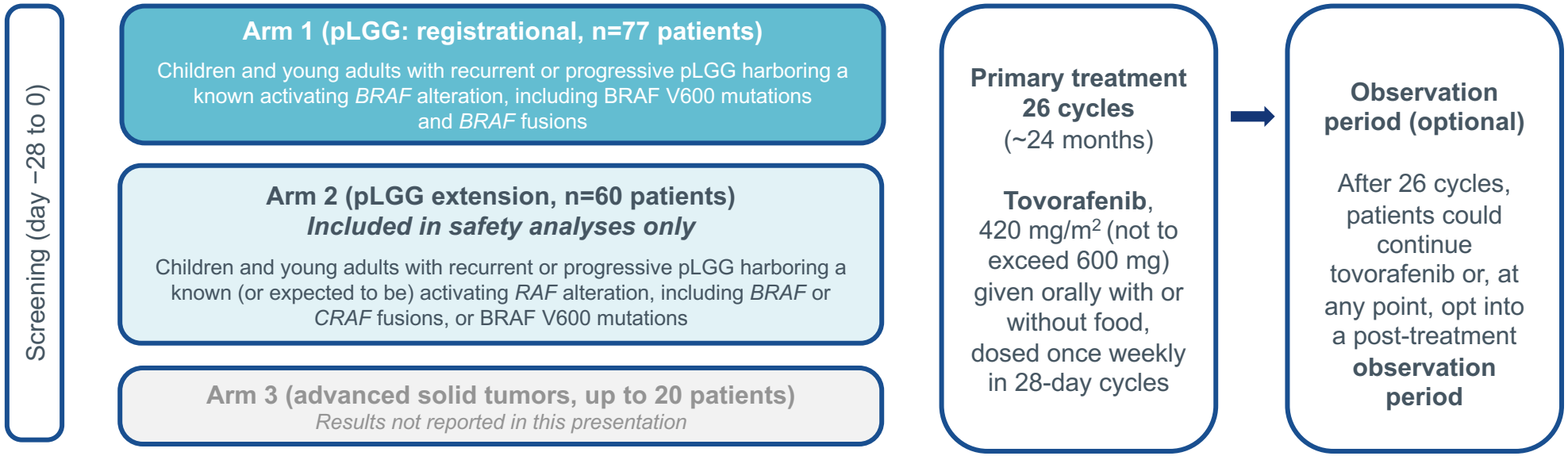
Tovorafenib in relapsed or refractory *BRAF*-altered pLGG: 3-year FIREFLY-1 update

Updated 3-year analysis

- **Tovorafenib:** a selective, CNS-penetrant, type II RAF inhibitor, administered orally once weekly, with or without food[1,2]
- **FDA approved** for use in relapsed or refractory *BRAF*-altered pLGG[1]
- **3-year FIREFLY-1 (NCT04775485) update** includes a post-treatment observation period[3]
- Updated median study duration: **40.6 months** in Arm 1 (data cutoff June 6, 2025)*



*Duration on study is defined as (end of study date – first dose date +1)/30.4375; for ongoing patients, data cutoff date is used for end of study date.
CNS, central nervous system; FDA, Food and Drug Administration; ORR, overall response rate; pLGG, pediatric low-grade glioma; RAPNO-LGG, Response Assessment in Pediatric Neuro-Oncology low-grade glioma.
1. OJEMDA [package insert]. Brisbane CA: Day One Biopharmaceuticals, Inc. 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/218033s002s003lbl.pdf. [Accessed October 2025]. FDA label for OJEMDA based efficacy on ORR by RAPNO-LGG. Recommended starting dose: 380 mg/m² orally once weekly in patients aged 6 months and older with relapsed or refractory pLGG harboring a *BRAF* fusion or rearrangement, or BRAF V600 mutation; 2. Kilburn LB, et al. *Nat Med*. 2024;30(1):207–217; 3. A Study to Evaluate DAY101 in Pediatric and Young Adult Patients With Relapsed or Progressive Low-Grade Glioma and Advance Solid Tumors (FIREFLY-1). Clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04775485 [Accessed July 2025].

After 26 tovorafenib cycles, patients could enter an observation period*

Exploratory endpoints, time to next treatment and treatment-free interval, were assessed

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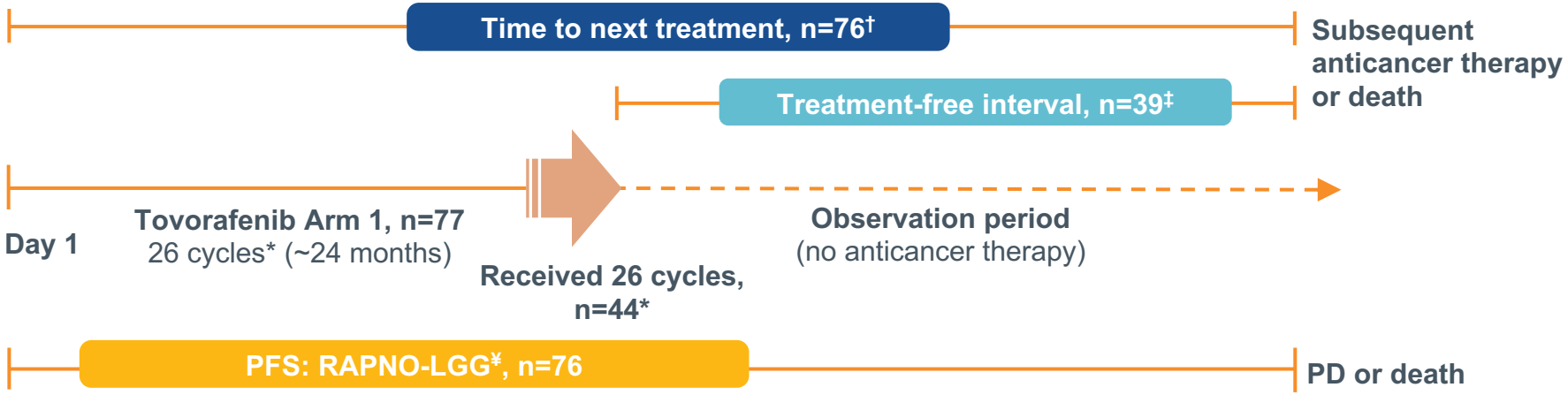

Endpoints (Arm 1): Primary and secondary

Primary

- ORR per RANO-HGG

Secondary

- Safety
- ORR per RAPNO-LGG¥
- CBR
- TTR
- DOR
- PFS based on RAPNO-LGG¥

Endpoints (Arm 1): Exploratory and post hoc

Exploratory

- ORR and CBR per RANO-LGG
- **Time to next treatment:** composite endpoint of the time from the date of the first tovorafenib dose to the start date of the first subsequent anticancer therapy (including retreatment with tovorafenib), or date of death, whichever was earlier
- **Treatment-free interval:** composite endpoint of time from the last dose of tovorafenib to the start of subsequent treatment or date of death, whichever was earlier

Post hoc

- **Clinical progression:** composite endpoint of first visual PD, deteriorating clinical status, or death, whichever was earliest
- **Radiographic progression:** composite endpoint of first PD (>25% increase compared to nadir¶) in target lesion and/or non-target lesion, any new lesions, or death, whichever was earliest

June 6, 2025 data cutoff. *A cycle was counted if a patient had at least 1 dose in a cycle; patients were treated for a planned period of 26 cycles, after which they could continue tovorafenib or opt to enter an observation period. †1 patient of 77 patients in Arm 1 had a target lesion not meeting the minimum size at baseline per IRC; the remaining 76 were included in the time to next treatment analysis. ‡Among the 44 patients with ≥26 cycles, 5 did not enter post-treatment observation: 4 remain on primary treatment, 1 died, 2 discontinued due to PD, and 2 discontinued due to other reasons but opted out of post-treatment observation; among the 39 post-treatment observation patients, 4 received <26 cycles of treatment because of prolonged dose hold due to growth suppression. ¥Hereafter referred to as RAPNO. ¶Defined as the as the lowest tumor size (measured by SPPD per RAPNO) at any timepoint.

CBR, clinical benefit rate; DOR, duration of response; HGG, high-grade glioma; IRC, independent radiology review committee; LGG, low-grade glioma; ORR, overall response rate; PFS, progression-free survival; RANO, Response Assessment in Neuro-Oncology; RAPNO, Response Assessment in Pediatric Neuro-Oncology; PD, progressive disease; SPPD, sum of product of perpendicular diameters; TTR, time to response.

No new safety signals were observed in the 3-year update

Safety analysis set (Arms 1 and 2, n=137)[1]

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No new safety signals observed

	Safety analysis set (n=137), n (%)
All TEAEs	137 (100)
All TRAEs	136 (99)
Grade ≥3 TEAEs	113 (82)
Grade ≥3 TRAEs	91 (66)
TEAEs leading to discontinuation	19 (14)
TRAEs leading to discontinuation	18 (13)

Preferred term*	Safety analysis set (n=137) Grade ≥3 TRAEs, n (%)
Any	91 (66)
Decreased growth velocity	46 (34)
Anemia	19 (14)
CPK increased	15 (11)
Maculopapular rash	11 (8)
ALT increased	7 (5)

June 6, 2025 data cutoff. Adverse events were cumulative events from day 1 to the earliest of (last dose + 30 days, start date of subsequent anticancer treatment, data cut, end of study). *TRAEs reported at grade ≥3 in ≥5% of patients.
AESI, adverse event of special interest; ALT, alanine aminotransferase; CPK, creatine phosphokinase; TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events.

1. Kilburn LB, et al. *Nat Med.* 2024;30(1):207–217.

Deep, durable responses with tovorafenib evaluated by IRC-assessed RAPNO

Efficacy-evaluable patients (Arm 1, n=76)*

Updated 3-year analysis

Response by RAPNO IRC

Exposure	3-year Arm 1 (n=76)*
Completed ≥26 cycles of treatment, n (%)	44/76 (58)
Response (IRC)	
ORR,† n (%)	40 (53)
Best Overall Response, n (%)	
CR	0
PR	30 (39)
MR	10 (13)
SD‡	22 (29)
PD	13 (17)
NE	1 (1)
Median change in tumor size,¥ % (range)	-47.3 (-97.3–162.0)
Median DOR, months (95% CI)¶	19.4 (13.8–27.2)
Median TTR, months (range)	5.4 (1.6–17.5)

June 6, 2025 data cutoff. *1 patient of 77 had a target lesion not meeting the minimum size at baseline per IRC. †ORR for RAPNO included MRs (i.e., ORR=CR+PR+MR). For CR, PR, and MR, confirmation of response by a subsequent scan approximately 3 months after the initial response was required. ‡Of any duration. ¥As measured by SPPD per RAPNO at last scan prior to last dose. ¶Medians and 95% CIs were calculated using the Kaplan-Meier method; responders who had not progressed at the time of data cutoff were censored at the date of their last adequate imaging examination.

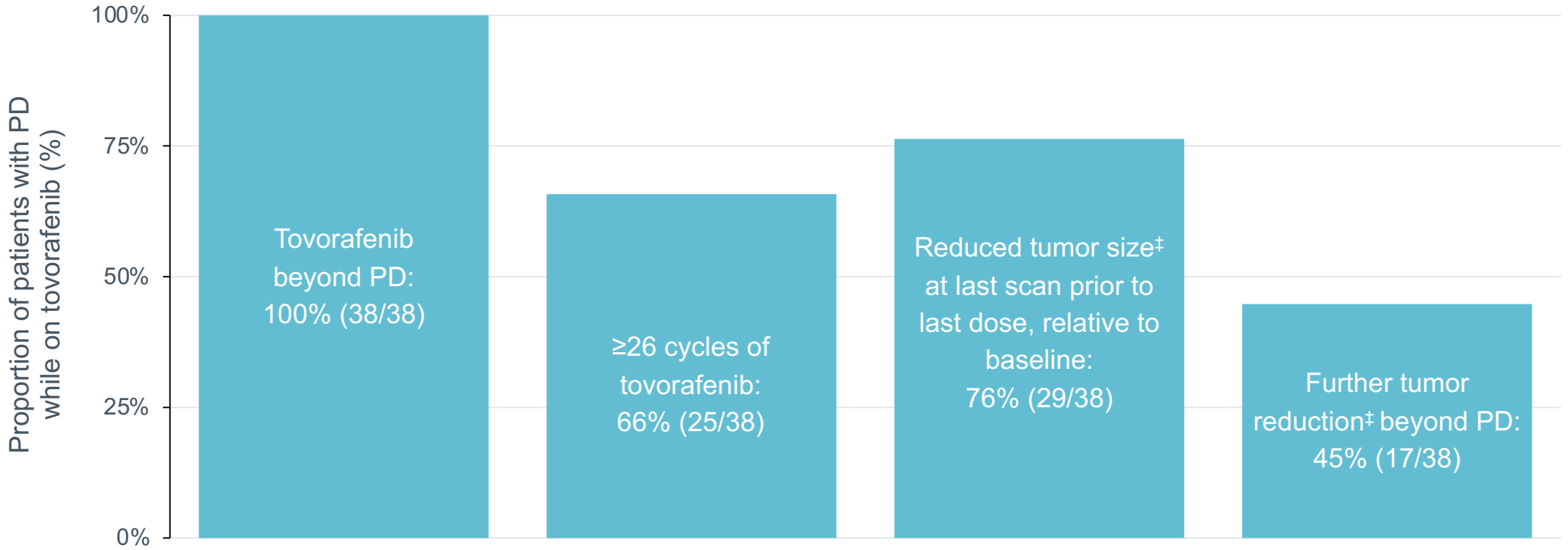
CI, confidence interval; CR, complete response; DOR, duration of response; IRC, independent radiology review committee; MR, minor response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; RAPNO, Response Assessment in Pediatric Neuro-Oncology; SD, stable disease; SPPD, sum of the products of the perpendicular diameters; TTR, time to response.

Many patients continued tovorafenib beyond RAPNO-defined radiographic progression (PD) by IRC

Efficacy-evaluable patients (Arm 1, n=76)*

Updated 3-year analysis

In the 3-year follow-up analysis, 38† patients had RAPNO-defined PD while on tovorafenib



June 6, 2025 data cutoff. *1 patient of 77 had a target lesion not meeting the minimum size at baseline per IRC. †58 patients had RAPNO-defined PD events reported by the data cutoff. Of patients who had RAPNO-defined PD on tovorafenib, there are 37/38 patients with a scan at PD. One patient was assessed as having PD per RAPNO by IRC because of visual acuity. ‡As measured by SPPD per RAPNO at EOT.

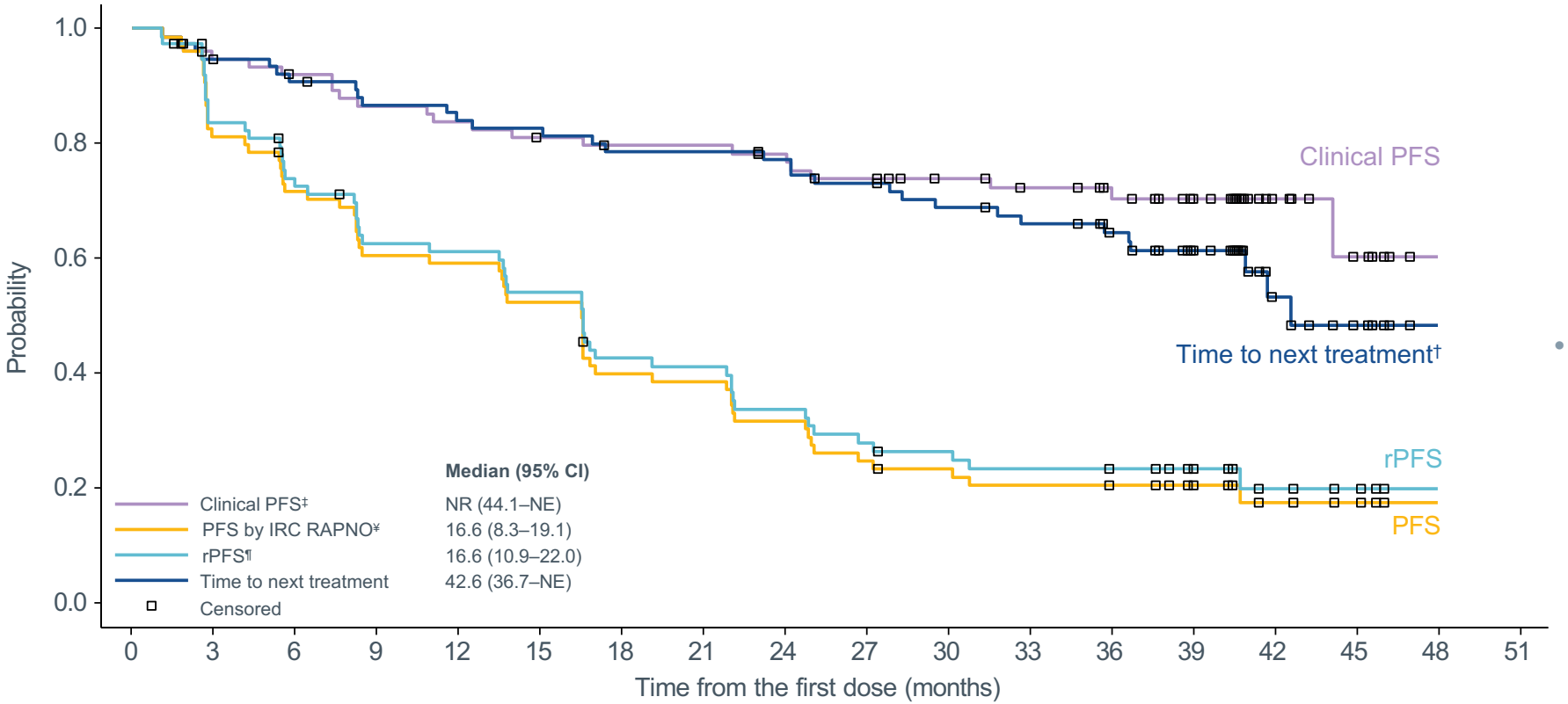
EOT, end of treatment; IRC, independent radiology review committee; PD, progressive disease; RAPNO, Response Assessment in Pediatric Neuro-Oncology; SPPD, sum of product of perpendicular diameters.

RAPNO PFS demonstrates efficacy with tovorafenib; time to next treatment more accurately reflects the full clinical benefit

Efficacy-evaluable patients (Arm 1, n=76)*

Updated 3-year analysis

Median time to next treatment§ was 42.6 months (95% CI 36.7–NE)



- RAPNO defines radiographic PD as a ≥25% increase in tumor size *from nadir*[Ŧ]*—not baseline*
  - Deep responses induced by tovorafenib lower the PD threshold—modest measurement variability on scans can score as PD
- Time to next treatment is a better assessment of clinical benefit than RAPNO PFS
  - More closely aligned with clinician-driven intervention than RAPNO PFS

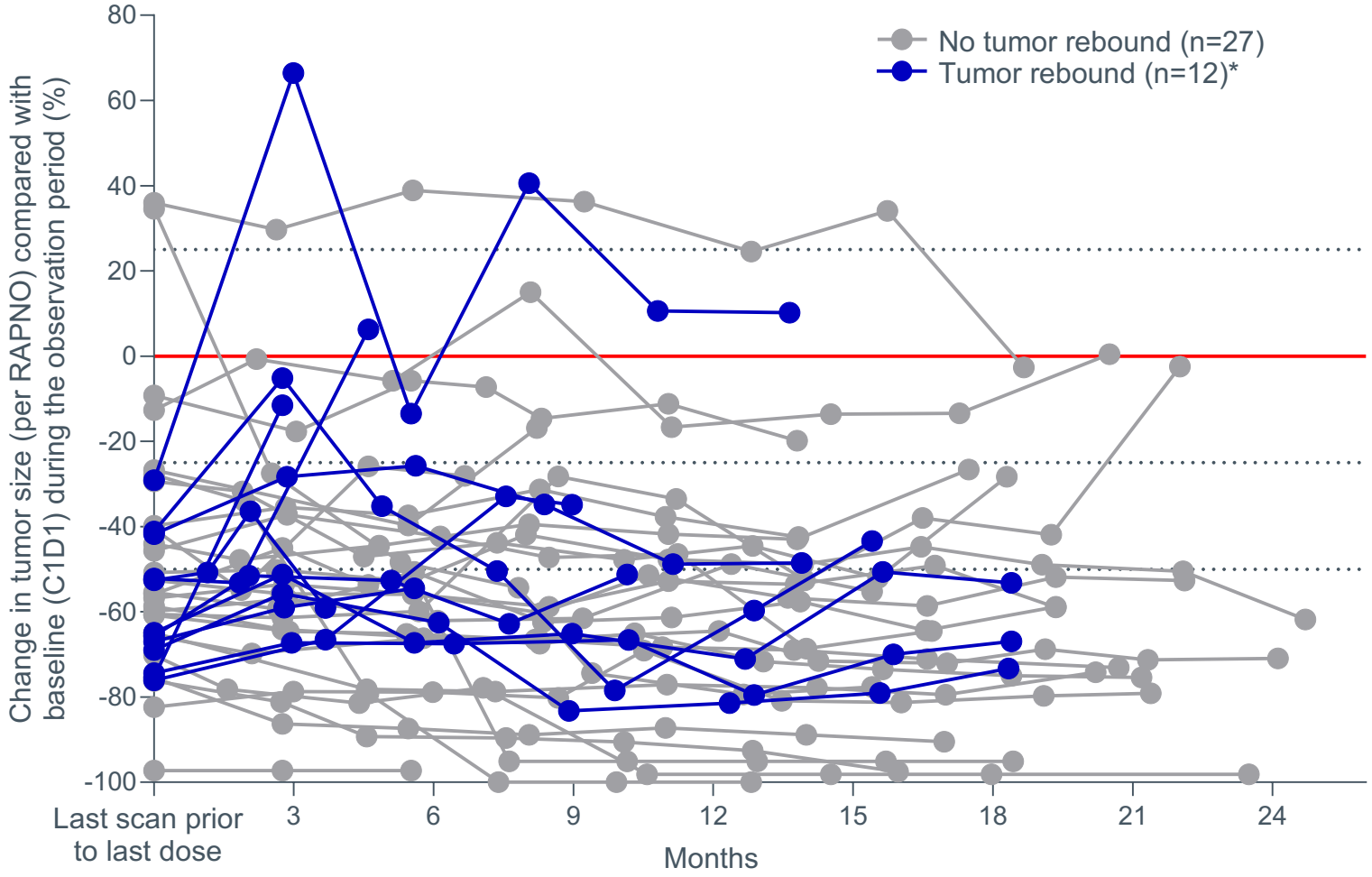
June 6, 2025 data cutoff. *1 patient of 77 had a target lesion not meeting the minimum size at baseline per IRC. †Time to next treatment: an exploratory composite endpoint of time from the date of the first tovorafenib dose to the start date of the first subsequent anticancer therapy (including retreatment with tovorafenib), or date of death, whichever was earlier. ‡Clinical PFS = clinical deterioration per RAPNO, defined as neurologic or functional decline that is unequivocally attributable to tumor progression and not explained by treatment-related effects. ¥RAPNO PFS event can occur due to either radiographic PD or clinical deterioration (clinical PD). ¶rPFS=radiographic progression per RAPNO, defined as a ≥25% increase in the tumor size (as measured by SPPD per RAPNO) of measurable lesions relative to the nadir, or the appearance of new lesions. §Based on Kaplan-Meier estimate. ŦDefined as the as the lowest tumor size (as measured by SPPD per RAPNO) at any timepoint.

CI, confidence interval; IRC, independent radiology review committee; NE, not evaluable; NR, not reached; PD, progressive disease; PFS, progression-free survival; RAPNO, Response Assessment in Pediatric Neuro-Oncology; rPFS, radiographic progression-free survival; SPPD, sum of product of perpendicular diameters.

Tumor rebound was minimal in the first 6 months off therapy

Post-treatment observation period: Tumor kinetics after last scan prior to last dose (n=39)

Updated
3-year analysis



	Post-treatment observation patients, n=39	
	3 months post-EOT†	6 months post-EOT†
Median time between prior scan and last dose, months (range)	1.8 (0–4.2)	
Median tumor size‡ change from baseline (C1D1) after the last dose, % (Q1, Q3)	-51 (-64, -33)	-55 (-67, -35)
≥25% increase in tumor size‡ from last scan prior to last dose, n (%)	12 (31%)	

V600 mutation (n=6):
4 of 12 total patients with rebound
2 of 27 total patients without rebound

June 6, 2025 data cutoff. Time 0 is the date of the last tumor assessment before the final dose of primary tovorafenib treatment; plot lines extend to the last follow-up assessment (prior to tovorafenib retreatment if applicable).
*Tumor rebound was defined as a ≥25% increase in tumor size within 6 months of the last dose of tovorafenib as determined by the change in tumor size (as measured by SPPD per RAPNO) from the last scan before the final dose of tovorafenib.[1] †"3 months" is the first scan after the last dose, and "6 months" is any scan after EOT within 6 months. ‡As measured by SPPD per RAPNO.
C1D1, cycle 1, day 1; EOT, end of treatment (last dose); Q, quartile; RAPNO, Response Assessment in Pediatric Neuro-Oncology; SPPD, sum of product of perpendicular diameters.

1. O'Hare P, et al. *Neuro Oncol*. 2024;26(8):1357–1366.

Early evidence of retreatment activity observed in the tovorafenib-retreated cohort

Post-treatment observation patients: Tovorafenib retreatment (n=8)

Updated
3-year analysis

Patients retreated with tovorafenib	n=8
Median change, % (range)*	-38.3 (-80.9–0)
Median duration of retreatment, months (range)	9.0 (2.6–18.0)
Median number of tovorafenib cycles administered during retreatment	10.5

At time of data cutoff:

- All 8 patients receiving tovorafenib retreatment were still on therapy
- Median tumor size† was smaller than the median tumor size recorded prior to retreatment initiation

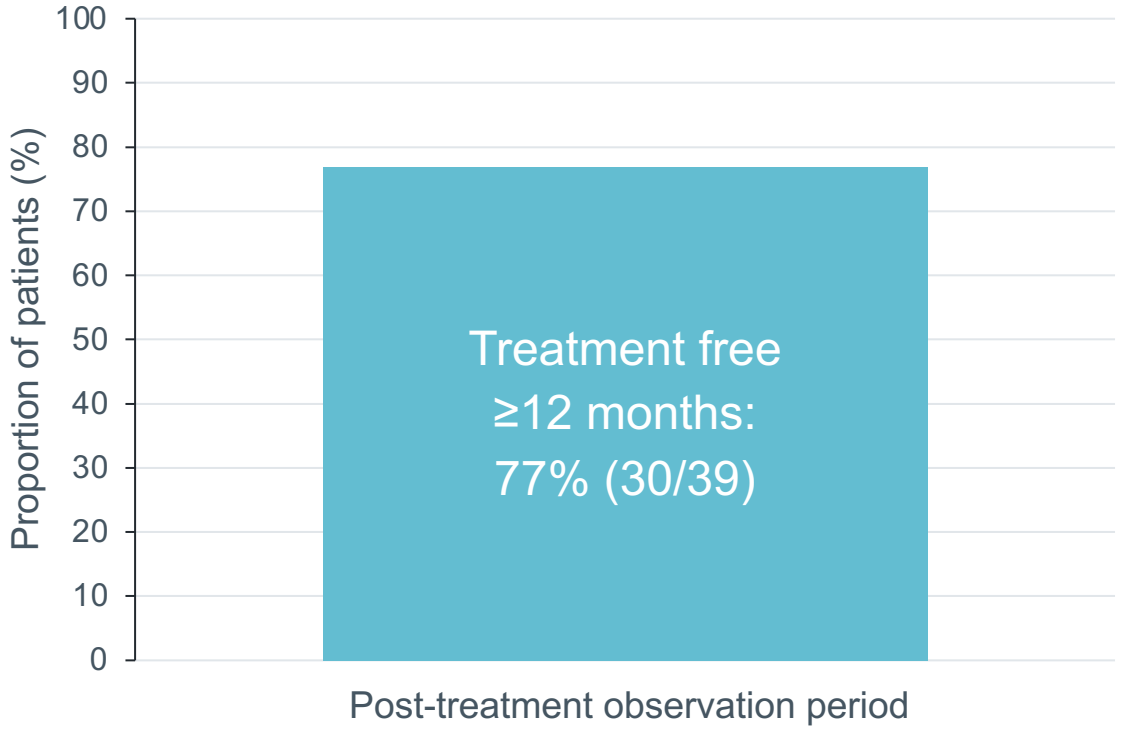
June 6, 2025 data cutoff. *Based on maximum % change from last scan before retreatment. † As measured by SPPD per RAPNO.
RAPNO, Response Assessment in Pediatric Neuro-Oncology; SPPD, sum of product of perpendicular diameters.

77% of 39 patients were treatment free for at least 12 months; median treatment-free interval not yet reached

Post-treatment observation period: Treatment-free interval (n=39)*

Updated 3-year analysis

	Post-treatment observation patients n=39†
Median duration of treatment, months (range)	24.6 (16.0–38.7)
Median follow-up from last dose to subsequent anticancer therapy, months (range)	16.0 (1.4–24.5)
Treatment-free interval, months Median (95% CI)	NR (NE–NE)



June 6, 2025 data cutoff. *Treatment-free interval: an exploratory endpoint of time from the last dose of tovorafenib to the start of subsequent treatment or date of death, whichever was earlier. †Among the 44 patients with ≥26 cycles, 5 did not enter post-treatment observation: 4 remain in primary treatment, 1 died, 2 discontinued due to PD and 2 discontinued due to other reasons but opted out of post-treatment observation; among the 39 post-treatment observation patients, 4 received <26 cycles of treatment because of prolonged dose hold due to growth suppression.
CI, confidence interval; NE, not evaluable; NR, not reached; PD, progressive disease.

Conclusions

Updated
3-year analysis

- Tovorafenib is a selective, CNS-penetrant, type II RAF inhibitor administered orally once weekly, with or without food
- This 3-year follow-up analysis of FIREFLY-1 showed:
  - **77% of patients who went into observation had a treatment-free interval* of ≥12 months**
    - Median treatment-free interval not yet reached
  - **Prolonged median time to next treatment†** (42.6 months [95% CI 36.7–NE])
  - Minimal tumor rebound (in the first 6 months) off therapy
  - Early evidence of tovorafenib retreatment activity
  - No new safety signals
- **These results suggest prolonged clinical stability and durability beyond planned tovorafenib treatment and further establish tovorafenib as a standard of care in relapsed/refractory pLGG**

June 6, 2025 data cutoff. *Treatment-free interval: an exploratory endpoint of time from the last dose of tovorafenib to the start of subsequent treatment or date of death, whichever was earlier. †Time to next treatment: an exploratory endpoint of time from the date of the first tovorafenib dose to the start date of the first subsequent anticancer therapy (including retreatment with tovorafenib), or date of death, whichever was earlier.
CI, confidence interval; CNS, central nervous system; NE, not evaluable; pLGG, pediatric low-grade glioma.

Acknowledgments

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Thank you to all patients, families, caregivers, and clinical investigators for their participation in this study

We are deeply grateful for the site coordinators and study staff who are instrumental in making this work possible

More information on the FIREFLY-1 clinical trial (NCT04775485) can be found at www.clinicaltrials.gov

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