NCOG-05. Health-related Quality of Life (HRQOL) in the phase 2 FIREFLY-1 (PNOC026) trial of the type II RAF inhibitor tovorafenib in relapsed/refractory (r/r) pediatric low-grade glioma (pLGG)

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Background

- pLGG is the most common type of brain tumor in children, with patients experiencing significant disease- and treatment-related morbidities and late effects that may persist throughout life with physical, visual, endocrine, and educational impacts[1–6]
  - Disease-related impacts include seizures, behavioral changes, visual disturbances, cognitive dysfunction, and endocrine dysfunction[3,6,7]
  - Treatment-related effects include cerebrovascular disease, and secondary neoplasms[4,8–12]
- Tovorafenib is an oral, selective, central nervous system (CNS)-penetrant, type II RAF inhibitor that received United States (US) Food and Drug Administration (FDA) accelerated approval for patients ≥6 months of age with r/r *BRAF*-altered pLGG[13]
- Results from the ongoing FIREFLY-1 (NCT04775485) phase 2 study in this population showed clinically meaningful tumor responses and a manageable safety profile[14]

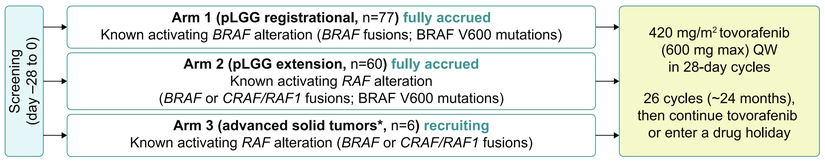
Objective

- An exploratory objective of FIREFLY-1 was to evaluate changes in quality of life and health utilities measures

Methods

- HRQOL outcomes, gathered from the PedsQL™ 3.0 Cancer Module (parent and/or self reports), were analyzed for patients enrolled in arm 1 of the FIREFLY-1 study with r/r *BRAF*-altered pLGG who were treated with tovorafenib
  - The study design for FIREFLY-1 (**Figure 1**) has been described previously[14]
- Tovorafenib was administered once weekly (420 mg/m^2) for a period of 2 years or until disease progression

Figure 1. FIREFLY-1 study design



*That relapsed, progressed, or were nonresponsive to available therapies.

- PedsQL™ 3.0 Cancer Module scores were measured on BLD1 (baseline, day 1) and D1 of every third cycle thereafter (**Table 1**)

Table 1. PedsQL™ 3.0 Cancer Module: Domains[15]

	Domain	# items*
8 subscales	Pain and hurt	2
	Nausea	5
	Procedural anxiety	3
	Treatment anxiety	3
	Worry	3
	Cognitive problems	5
	Perceived physical appearance	3
	Communications	3
	Total score	**27**

All range: 0–100;
higher scores=better HRQOL/lower symptoms

Proxy-, self-administered, and hybrid versions of the PedsQL™ 3.0 Cancer Module questionnaire were offered in FIREFLY-1 depending on the age of the patient or need for parent reporter

*Child, Young Adult, Adult, and Parent Reports for the PedsQL™ 3.0 Cancer Module for Children (8–12 years of age), Teens (13–17 years of age), Young Adults (18–25 years of age), and Adults (≥26 years of age).[15]

- Due to a small number of parent reports received, only patient self-reports of PedsQL™ 3.0 Cancer Module were analyzed (**Table 2**)† [December 22, 2022 data cutoff]
- Data were aggregated‡ across 4 age groups (5–7 years old (y/o), 8–12 y/o, 13–17 y/o, and 18–25 y/o)
- As completion of self-reports by patients remaining on the study diminished from baseline (BL) [51 participants] to C13 (cycle 13) [32 participants], the analysis was limited up to C13 to limit attrition bias (**Table 2**)

†The US FDA discourages use of proxy reports.[16] ‡As the individual age groups had low patient numbers.

Table 2. PedsQL™ 3.0 Cancer Module: Number of questionnaires completed at each time point across age groups

	Toddler (2–4 y/o)		Young Child (5–7 y/o)		Child (8–12 y/o)		Teen (13–17 y/o)		Young Adult (18–25 y/o)		Total	
	Parent	Self	Parent	Self	Parent	Self	Parent	Self	Parent	Self	Parent	**Self**
BL	8	-	3	15	7	22	0	14	0	0	18	**51**
C4	8	-	3	11	5	24	0	13	0	1	16	**49**
C7	3	-	3	8	6	25	0	10	0	1	12	**44**
C10	2	-	4	8	5	27	1	7	0	2	12	**44**
C13	2	-	3	6	4	19	1	7	0	0	10	**32**

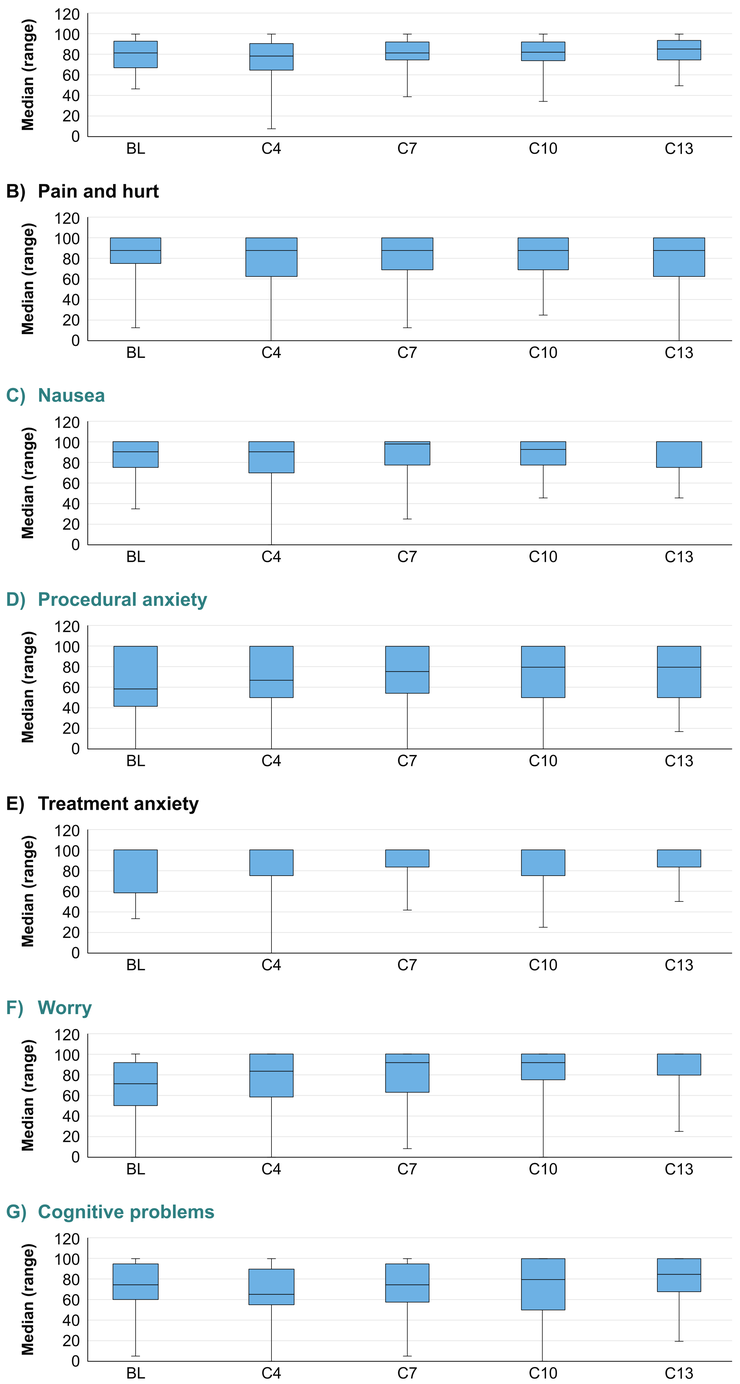
- Median PedsQL™ 3.0 Cancer Module scores for the aggregated self-report group were calculated for each domain
- The percentages of patients with meaningful changes in improvement and worsening were calculated for BL to C4 and BL to C13
  - Meaningful changes in improvement or worsening self-report measures, which were descriptive in nature, were defined using the likely change index (LCI)[17]
  - Specific LCI thresholds for improvement or worsening of the select domains reported in this analysis§ are provided in the legends of **Figure 2II**

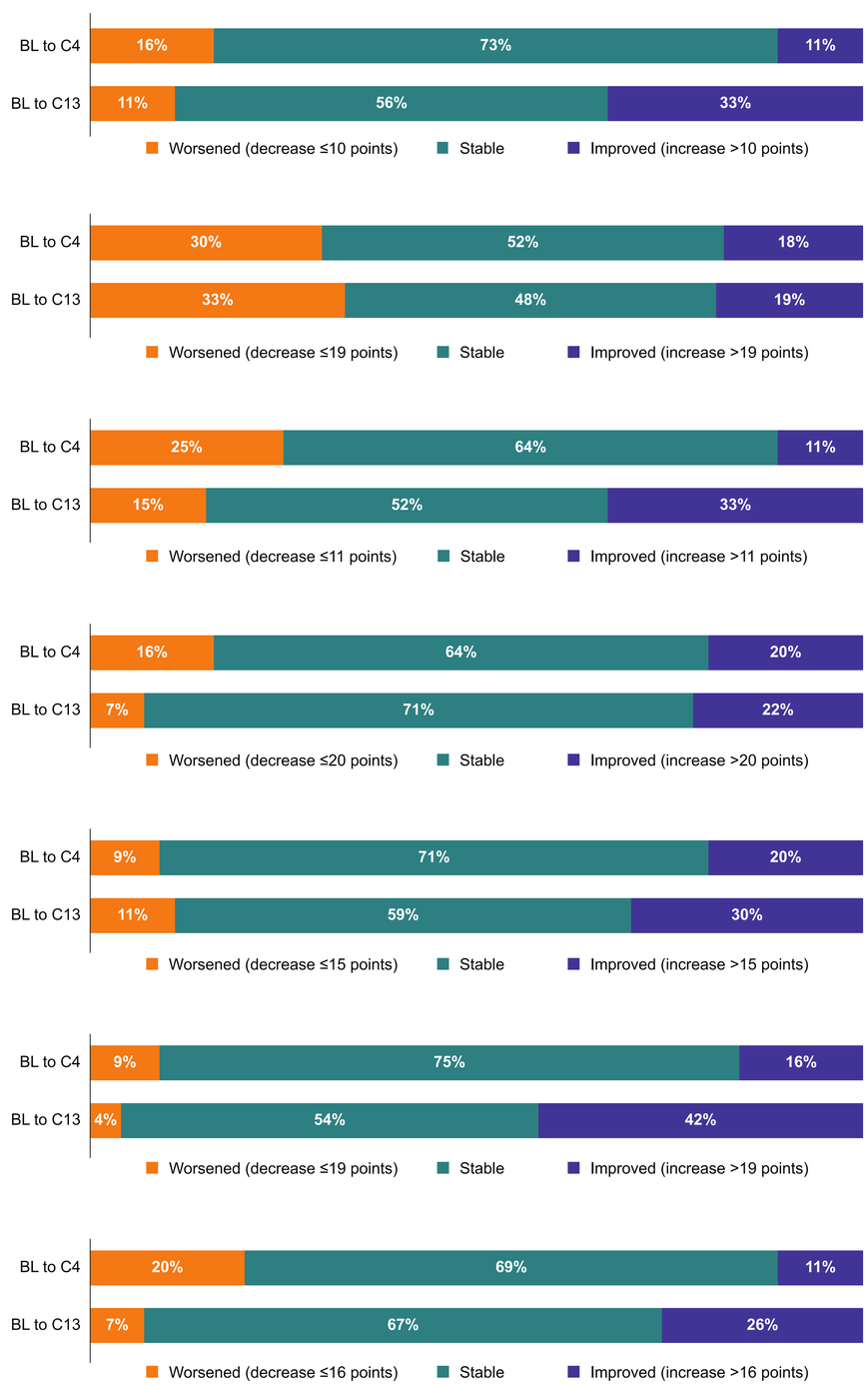
Results

- Median changes from BL to C13 improved in the aggregated self-report population in the following 5 of 7 select domains analyzed (**Figure 2**)§ : Total score (A), nausea (C), procedural anxiety (D), worry (F), and cognitive problems (G)

Figure 2. Select domains in FIREFLY-1 per the PedsQL™ 3.0 Cancer Module:

Figure 2I. Median values (aggregated self-report population) | **Figure 2II. Changes in improvement or worsening per LCI**





Domains that showed improvement in the median value from BL to C13 are colored green.
The number of questionnaires completed at each time point can be seen in the Total column of **Table 2**.
§The results for perceived physical appearance and communication are not presented because the LCIs were not calculated as reliabilities were too low for these scales to recommend individual interpretation (0.49 and 0.66, respectively).[15]

Conclusions

- HRQOL generally remained stable, or improved, as measured by the PedsQL™ 3.0 Cancer Module, in the majority of patients with r/r pLGG during the first year of treatment with tovorafenib
- The ability to complete longer-term HRQOL analyses was limited mainly by reduced completion of parent and self-reports by the majority of patients remaining in the study at later time points
  - The extent of attrition bias is unknown but may have contributed to more favorable results, as patients who progressed stopped treatment

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