Post hoc analysis of rashes reported in patients (pts) with *BRAF*-altered relapsed/refractory (r/r) pediatric low-grade glioma (pLGG) treated with the type II RAF inhibitor tovorafenib in FIREFLY-1

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Background

- pLGGs are the most prevalent brain tumor in children and comprise 30–40% of all pediatric central nervous system (CNS) tumors[1]
  - Nearly 70% have alterations in the mitogen-activated protein kinase (MAPK) pathway, therefore, targeted therapy with BRAF and MEK inhibitors (BRAFi and MEKi) are effective[2]
- As clinical use of MAPK inhibitors (MAPKis) has expanded and the duration of exposure increased, the importance of characterizing adverse events (AEs) has increased in order to inform proactive management[3]
  - Dermatologic AEs are some of the most common AEs[3,4]
  - Further characterization and guidance on managing MAPKi AEs has recently been provided[5]
- A retrospective analysis of 99 children who received a type I BRAFi and/or MEKi for any indication over the 6-year analysis period showed there was a mean per patient of ~3.5 cutaneous reactions (cRxns) during treatment[6]
  - Acneiform rash occurred 3 to 4 times more frequently with a MEKi vs a type I BRAFi or combination treatment (type I BRAFi + MEKi)
    - Acneiform rash was 1 of the most common treatment-altering cRxns
    - A third of patients required alterations in oncologic therapy despite most cRxns being Grade (G) 1 or G2
- Tovorafenib, a selective, oral, CNS-penetrant, type II RAF inhibitor, is approved in the US for the treatment of *BRAF*-altered r/r pLGG in patients ≥6 months (mos) of age, based on the FIREFLY-1 trial (NCT04775485)[7,8]

Objectives

- Characterize treatment-emergent (TE) rashes in patients with r/r pLGG treated with tovorafenib in FIREFLY-1

Methods

- The protocol rash management algorithm recommended gentle skin care and sun protective measures for all patients; dermatology visits were recommended at baseline and every 3 mos if rash symptoms impaired function or were psychosocially bothersome, and/or if treatment per the algorithm failed[8]
  - Guidance on management of follicular and eczematous reactions, paronychia, and hand-foot syndrome was also provided
- This post hoc analysis included 137 patients with pLGGs (arm 1: 77; arm 2: 60) treated with ≥1 dose of tovorafenib (420 mg/m^2 once weekly [600 mg max]) in FIREFLY-1 as of May 10, 2024
- TE rashes, graded by investigators, were grouped as maculopapular/erythematous/eczematous (M/E/E) or acneiform/pustular (A/P)
- Key definitions:
  - **Rash episode**: all rash events occurring over continuous days
  - **Second rash episode**: any subsequent episode occurring ≥2 days after the prior episode end date
  - **Rash episode grade assignment**: maximum grade out of all continuous events included in the episode
  - **Complete rash resolution**: when the rash is reported as resolved

Results

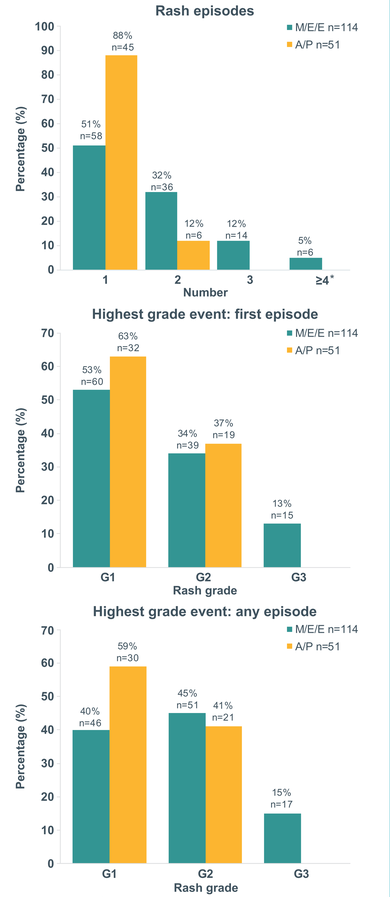
Table 1. Patient and baseline characteristics[a,b]

Characteristic	M/E/E (n=114)	A/P (n=51)
Age, years		
Median (range)	8 (1–24)	11 (1–24)
<12 years of age	84 (74)	26 (51)
≥12 years of age	30 (26)	25 (49)
Gender, n (%)		
Male	60 (53)	23 (45)
Female	54 (47)	28 (55)
Race, n (%)[c]		
White	75 (66)	36 (71)
Asian	5 (4)	7 (13)
Black	2 (2)	0
Multiple	3 (3)	0
Other	6 (5)	2 (4)
Not specified	23 (20)	6 (12)
Ethnicity, n (%)		
Hispanic or Latino	4 (4)	1 (2)
Not Hispanic or Latino	87 (76)	43 (84)
Not stated/unknown	23 (20)	7 (14)
***BRAF* alteration status, n (%)**		
BRAF fusion	97 (85)	43 (84)
KIAA1549::BRAF fusion	83 (73)	39 (76)
Other	14 (12)	4 (8)
BRAF V600E mutation	17 (15)	8 (16)
Prior lines of systemic therapy		
Median (range)	3 (1–10)	2 (1–10)
Number of prior lines, n (%)		
1	27 (24)	14 (27)
2	27 (24)	12 (24)
≥3	60 (53)	25 (49)
Prior MAPKi, n (%)		
Prior MEKi	69 (61)	23 (45)
Prior type I BRAFi	11 (10)	6 (12)
Prior MEKi and type I BRAFi	8 (7)	3 (6)
Any MAPKi	72 (63)	26 (51)
History of atopy, n (%)		
Asthma	1 (1)	1 (2)
Seasonal allergies	8 (7)	4 (8)
Food allergies	0	0
Atopic dermatitis/eczema	2 (2)	1 (2)
Acne	10 (9)	6 (12)
Family history of atopy	0	0

Percentages may not add to 100% due to rounding. Of the 137 patients in arms 1 and 2 from FIREFLY-1, 9 (7%) did not experience M/E/E or A/P rash episodes. [a]38/127 (30%) had both types of rashes. [b]Results for A/P G3 not included as only 1 patient had this type of rash; time to onset (TTO) of rash was 3 mos and the duration of rash was 8 days. [c]There were no Native Hawaiian or other Pacific Islander, American Indian, or Alaska Native participants.

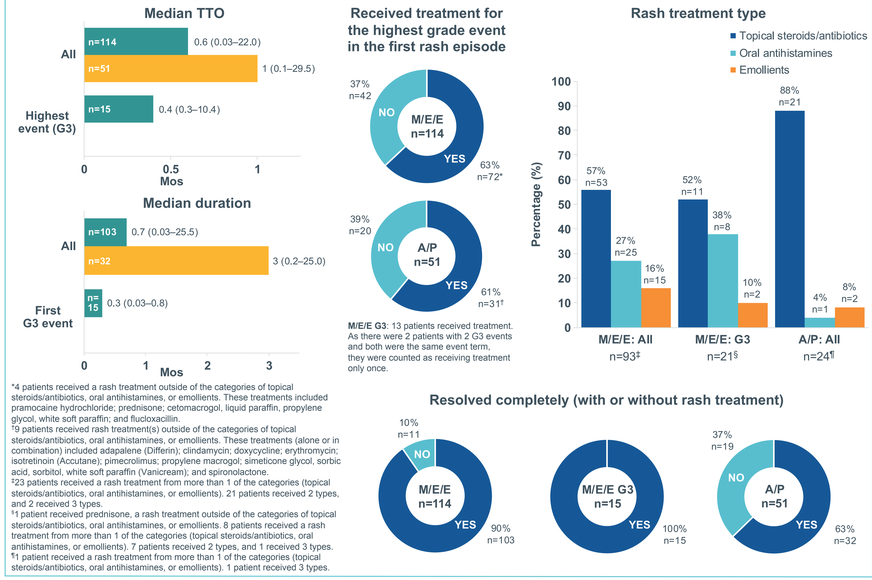
- In FIREFLY-1, 89% (114/128) had a M/E/E rash episode, 41% (52/128) had an A/P rash episode, and 30% (38/128) had both types (**Table 1**)
- As of the data cutoff, the median duration of primary tovorafenib treatment in FIREFLY-1 was 22 mos (range: 2–32) in the M/E/E group, and 20 mos (range: 1–29) in the A/P group
- Prophylactic treatment of rashes was used in 26/114 (23%) patients with M/E/E (moisturizer, 15 [13%]; topical antibiotics, 11 [10%]) and 8/51 (16%) with A/P (moisturizer, 5 [10%]; topical antibiotics 3 [6%])
- Median TTO of the highest grade event in the first rash episode was 0.6 mo in M/E/E (**Figure 2**)
- The highest grade event in first rash episode resolved in 0.7 mo in M/E/E (0.3 mo if G3) and 3 mos in A/P (**Figure 2**)
- 49% (56/114) of patients with a M/E/E episode and 12% (6/51) of patients with an A/P episode had recurrence of the same rash type
  - There was only 1 (of 56, 2%) patient with a G3 event (M/E/E) in a second episode; all others were G1 (M/E/E: 33/56 [59%]; A/P: 3/6 [50%]) or G2 (M/E/E: 22/56 [39%]; A/P: 3/6 [50%])

Figure 1. Rash episode incidence and severity



*The maximum incidence of M/E/E episodes was 7.

Figure 2. Characterization of the highest grade event in the first rash episode



*4 patients received a rash treatment outside of the categories of topical steroids/antibiotics, oral antihistamines, or emollients. These treatments included pramocaine hydrochloride; prednisone; cetomacrogol, liquid paraffin, propylene glycol, white soft paraffin; and flucloxacillin.
†9 patients received rash treatment(s) outside of the categories of topical steroids/antibiotics, oral antihistamines, or emollients. These treatments (alone or in combination) included adapalene (Differin); clindamycin; doxycycline; erythromycin; isotretinoin (Accutane); pimecrolimus; propylene macrogol; simeticone glycol, sorbic acid, sorbitol, white soft paraffin (Vanicream); and spironolactone.
‡23 patients received a rash treatment from more than 1 of the categories (topical steroids/antibiotics, oral antihistamines, or emollients). 21 patients received 2 types, and 2 received 3 types.
§1 patient received prednisone, a rash treatment outside of the categories of topical steroids/antibiotics, oral antihistamines, or emollients. 8 patients received a rash treatment from more than 1 of the categories (topical steroids/antibiotics, oral antihistamines, or emollients). 7 patients received 2 types, and 1 received 3 types.
¶1 patient received a rash treatment from more than 1 of the categories (topical steroids/antibiotics, oral antihistamines, or emollients). 1 patient received 3 types.

M/E/E G3: 13 patients received treatment. As there were 2 patients with 2 G3 events and both were the same event term, they were counted as receiving treatment only once.

Table 2. Median time to complete resolution of the highest grade rash event in the first rash episode

	M/E/E (n=103)		A/P (n=32)	
	n (%)	Mos (range)	n (%)	Mos (range)
No rash treatment	37 (36)	0.7 (0.03–24.9)	11 (34)	5.0 (0.2–13.1)
Rash treatment	66 (64)	0.6 (0.03–25.5)	21 (66)	2.6 (0.2–25.0)
No tovorafenib dose reduction	96 (93)	0.5 (0.3–1.4)	31 (97)	2.8 (0.2–25.0)
Tovorafenib dose reduction[a]	7 (7)	0.7 (0.03–25.5)	1[a] (3)	5.2
No tovorafenib dose interruption	86 (83)	0.9 (0.03–25.5)	32 (100)	3.0 (0.2–25.0)
Tovorafenib dose interruption	17 (17)	0.3 (0.03–1.4)	-	-

[a]Tovorafenib dose reductions to manage rash were 1 level (5 patients) or 2 levels (2 patients) in the M/E/E group and 1 level in the A/P group.
n represents patients with complete resolution of the highest grade rash event in the first rash episode. There were 11 (of 114, 10%) in the M/E/E group and 19 (of 51, 37%) in the A/P group whose highest grade rash events in the first rash episode were not completely resolved at time of data cutoff. Rash treatment included all treatments and was not limited to topical steroids/antibiotics, oral antihistamines, or emollients.

Conclusions

- TE rash is common with tovorafenib but is generally low grade and resolves quickly (within 3 mos). First rash episodes occur early in the treatment course (typically within the first cycle)
  - 85% of M/E/E and 100% of A/P rash episodes were G1 and G2
  - Median TTO of the first rash episode was 0.6 mos for M/E/E and 1 mo for A/P
  - On average, the first M/E/E rash episode resolved within 0.7 mos and the first A/P rash episode resolved within 3 mos
- First rash episodes were manageable with at home treatment without discontinuation of tovorafenib
  - A/P rashes appeared to resolve more quickly than M/E/E rashes with rash treatment
  - Few patients required dose modifications or interruptions
  - Only 1 patient permanently discontinued tovorafenib, due to an unresolved M/E/E rash
- A/P rash episodes typically resolved without recurrence
- Recurrence of M/E/E rash episodes occurred in ~50% of patients and recurrent events were predominantly low grade

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