Preliminary clinical activity of the type II RAF inhibitor tovorafenib in *RAF* fusion-driven recurrent/progressive sarcomas

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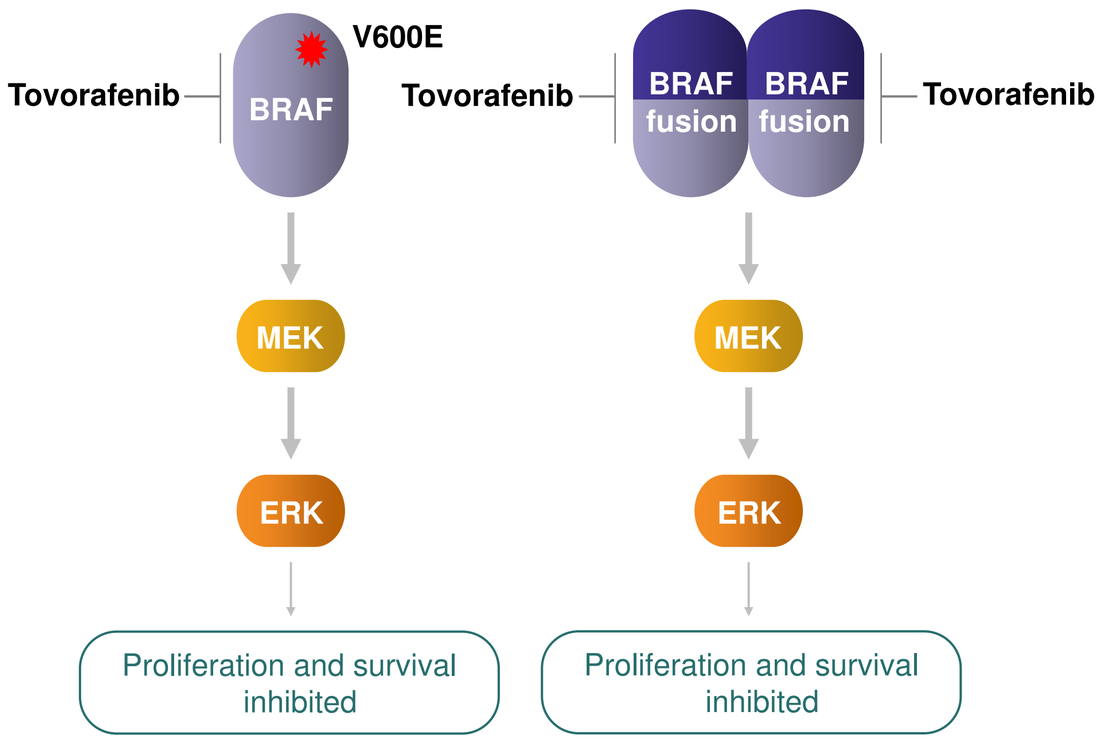
Background

- RAF proteins are key signaling components in the mitogen-activated protein kinase/extracellular signal regulated kinase (MAPK) pathway, which regulates cell proliferation and survival
- Activating *BRAF* and *CRAF/RAF1 (RAF1)* fusions (collectively, *RAF* fusions) are rare oncogenic alterations in sarcoma[1,2]
- Tovorafenib is an investigational, selective, CNS-penetrant, type II RAF inhibitor dosed once weekly that is in development for patients with tumors harboring an activating *RAF* alteration. Preclinical studies in murine models have shown that:[3]
  - Tovorafenib has activity against monomeric (class I alterations [e.g., BRAF V600E mutations) and dimeric (class II alterations, including fusions) forms of RAF signaling (Figure 1)
  - In contrast to type I BRAF inhibitors, tovorafenib does not induce RAS-dependent paradoxical activation of the MAPK pathway
- Single-agent tovorafenib activity has been seen in pediatric patients with low-grade gliomas harboring *BRAF* fusions or V600E mutations, adults with melanomas harboring *BRAF* fusions or mutations, and a child with a spindle cell sarcoma harboring a novel *SNX8-BRAF* fusion[4-8]
- Here, we report early clinical activity of tovorafenib monotherapy in two adolescent and young adult (AYA) patients, one with an inoperable, locally advanced *BRAF*-fusion inflammatory myofibroblastic tumor (IMT) and another with a *RAF1*-fusion spindle cell sarcoma, as of September 30, 2023

Figure 1. Tovorafenib mechanism of action

Tovorafenib inhibits RAS-independent MAPK signaling in *RAF*-altered tumors including BRAF V600E mutants and *RAF* fusions (*BRAF* and *CRAF*)



Methods

- Two ongoing open-label, multicenter, phase 2 clinical studies are evaluating the efficacy and safety of tovorafenib monotherapy:
  - FIREFLY-1 (PNOC026; NCT04775485): in pediatric and AYA patients (6 months to 25 years of age) with relapsed/refractory *RAF*-fusion advanced solid tumors (arm 3)
  - Substudy DAY101-102a of FIRELIGHT-1 (NCT04985604): in AYA and adult patients ≥12 years of age with *RAF*-fusion, or C*RAF/RAF1*-amplified solid tumors
- In both trials, tovorafenib is administered orally, once weekly (QW) in 28-day cycles until disease progression with the following dosing guidance:
  - FIREFLY-1: 420 mg/m^2 (not to exceed 600 mg)
  - Substudy DAY101-102a of FIRELIGHT-1:
    - AYA patients (12 to <18 years of age): 420 mg/m^2 (not to exceed 600 mg)
    - Adult patients (≥18 years of age): 600 mg
- Primary endpoint for both trials: Overall response rate per RECIST version 1.1

Results

- Early clinical results are reported for (Table 1):
  - Patient 1 from FIREFLY-1 arm 3, is a 15-year-old female with a locally advanced pelvic IMT harboring an *ETV6-BRAF* fusion
  - Patient 2 from substudy DAY101-102a of FIRELIGHT-1, is a 30-year-old female with metastatic undifferentiated spindle cell sarcoma harboring an *APPL2-RAF1* fusion

Disclosures: NvE and JvdL: Nothing to disclose. DDC, SH, and LMK: Employees of Day One Biopharmaceuticals and have received Day One Bio stock options. PM: Employee of Day One Biopharmaceuticals and has received Day One Bio stock and stock options. JL: Advisory board to AZ, Daichi Sankyo, Trutino Biosciences, Oncxerna, Guardant Health AMEA, Mirati.

Table 1. Patient characteristics

Characteristic	Patient 1	Patient 2
Study	FIREFLY-1, arm 3	Substudy DAY101-102a of FIRELIGHT-1
Age, years	15	30
Sex	Female	Female
ECOG status	0	1
Primary cancer	IMT	Spindle cell sarcoma
***RAF* fusion type**	*ETV6-BRAF*	*APPL2-RAF1*
Date of diagnosis	November 26, 2022	March 13, 2015
Prior therapy:		
Surgery	No	Yes
Radiotherapy	No	Yes
Chemotherapy	No	Yes
Prior lines of systemic treatment	0	2
Date first tovorafenib dose received	December 5, 2022	July 27, 2022
Tovorafenib dose initiated	600 mg QW	600 mg QW
Treatment status/cycles completed*	Completed/2.75	Ongoing/15 (C16 in progress)
AE-related dose reduction*	Reduction to 500 mg QW for the remainder of treatment	Reduction to 500 mg QW; treatment at that dose continues
AE-related dose interruption*	No	Yes
AE grade ≥3*	No	Yes
Best RECIST v1.1 response to tovorafenib*	SD	PR

*Data cutoff September 30, 2023.

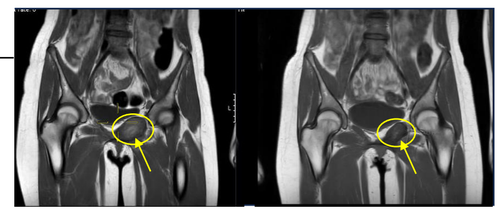
AE, adverse event; C, cycle; ECOG, Eastern Cooperative Oncology Group; IMT, inflammatory myofibroblastic tumor; PR, partial response; QW, once weekly; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SD, stable disease.

Patient 1 (FIREFLY-1 arm 3) with *ETV6-BRAF* locally advanced pelvic IMT

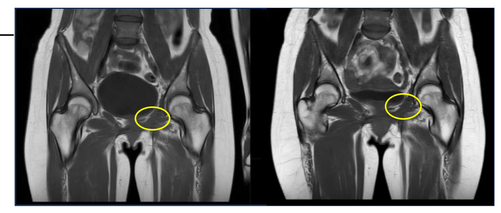
Parameter	Description/outcome
Prior therapy	• Surgical resection of the large tumor contraindicated due to high morbidity risk
Tovorafenib treatment to date	• Initiated at 600 mg QW; dose reduced to 500 mg (C2D22 [week 4]) for the remainder of treatment due to G1/G2 TRAEs (acneiform rash, myalgia, fatigue) • 2.75 cycles administered
Response to tovorafenib	After 2 cycles, 16% reduction (investigator-assessed) in the target lesion (confirmed SD per RECIST v1.1), allowing for complete tumor resection • Treatment continued for 3 additional weeks; the tumor was resected with R0 margins – No significant surgery-related morbidities reported • Tovorafenib discontinued post-surgery due to low risk of relapse* • No tumor recurrence or subsequent anti-cancer therapies
Safety outcomes (TRAEs)	• G2 myalgia, fatigue, headache (resolved post-dose reduction) • Transient G1/2 maculopapular rash, G2 acneiform rash; resolved with supportive care meds and dose reduction • G1 anorexia, anemia, periorbital and localized edema, elevated CPK, elevated LDH, skin discoloration, chest erythema, pyrexia, nausea, vomiting

MRI scans of the pubic bone

A) Baseline (Dec 2022) B) Post-C2 (Jan 2023)



C) FU1 MRI (June 2023) D) FU2 MRI (Sept 2023)



*Tovorafenib discontinued March 2023, remains off anti-cancer therapy as of September 2023.

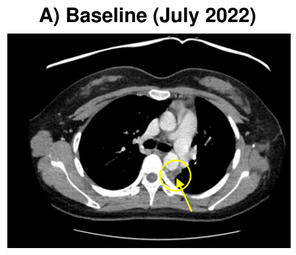
C, cycle; CPK, creatine phosphokinase; D, day; FU, follow-up; G, grade; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; QW, once weekly; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SD, stable disease; TRAEs, treatment-related adverse events.

Patient 2 (DAY101-102a substudy of FIRELIGHT-1) with *APPL2-RAF1* metastatic undifferentiated spindle cell sarcoma

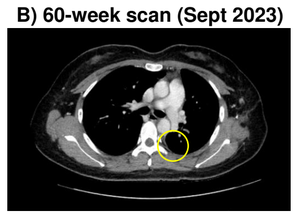
Parameter	Description/outcome
Prior therapies	• Radiotherapy (oral cavity and spine) • Multiple surgical resections – Mandibular mass removal, right partial mandibulectomy, lung lobectomy, wedge resection of lung • Cisplatin/etoposide, 3 cycles (best response: SD) • Docetaxel/gemcitabine, 6 cycles (best response: PR)
Tovorafenib treatment to date	• Initiated at 600 mg QW; dose interrupted following C2 for 7 weeks due to G3 TRAEs; when restarted, reduced to 500 mg; treatment at that dose continues • 15 cycles administered; C16 ongoing at data cutoff
Response to tovorafenib	• Confirmed PR per RECIST v1.1 – 8-week scan: 47% decrease from BL – 60-week scan: 72% decrease from BL
Safety outcomes (TRAEs)	• G1 acne, pruritus, hypothyroidism • G2 rash • G3 elevated CPK • G3 left retinal hemorrhage with a concomitant eye trauma (C2D27): resolved after 5 weeks post-dose interruption and subsequent dose reduction; no recurrence

CT scans of stump site metastatic lesion: Lung, LLL

A) Baseline (July 2022)



B) 60-week scan (Sept 2023)



BL, baseline; C, cycle; CPK, creatine phosphokinase; CT, computed tomography; D, day; G, grade; LLL, left lower lobe; PR, partial response; QW, once weekly; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SD, stable disease; TRAEs, treatment-related adverse events.

Conclusions

- Tovorafenib demonstrated clinical activity and a manageable safety profile in these two AYA patients with *RAF*-fusion sarcomas:
  - Early tumor shrinkage minimizing potential morbidities in Patient 1 where surgical intervention was not previously possible
  - Continued rapid, durable tumor response in Patient 2 who had refractory disease and received multiple lines of therapy including surgery, radiation and chemotherapy
- These reports provide additional evidence of the antitumor activity of tovorafenib in *RAF* fusion-driven solid tumors beyond pediatric low-grade glioma
- Genomic profiling of all sarcomas is warranted to identify rare oncogenic gene fusions as it may help identify a potential targeted therapy
- Both FIREFLY-1 arm 3 and FIRELIGHT-1 are enrolling patients

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