



Clinical activity of the type II pan-RAF inhibitor tovorafenib in *BRAF*-fusion melanoma

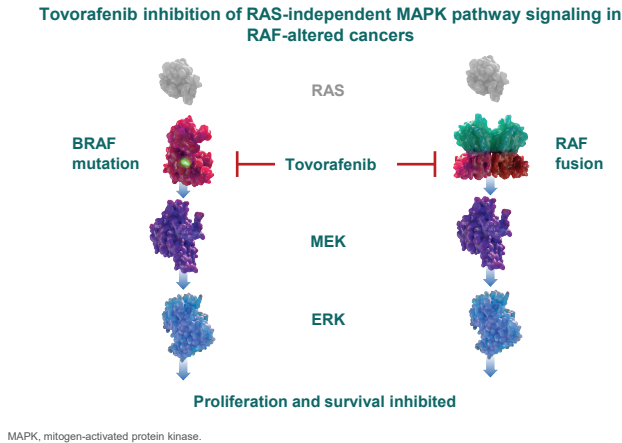
Jeeyun Lee, MD,¹ Natraj R. Ammakkanavar, MD,² Aprajita Saini, MS,³ Mark W. Kieran MD, PhD,³ Lisa M. Kopp, DO, MPH,³ Bert H. O'Neil, MD²

¹Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; ²Community North Cancer Center, Indianapolis, IN, United States of America; ³Day One Biopharmaceuticals, Brisbane, CA, United States of America

Background

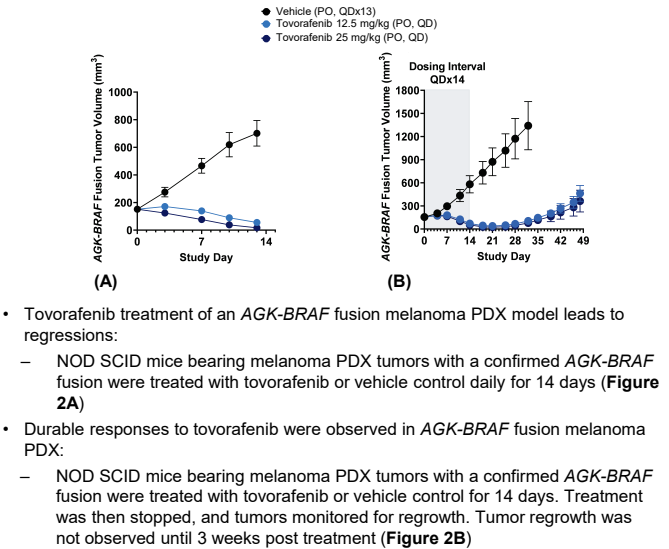
- A distinct molecular subset of melanoma with no other known driver mutations harbors *BRAF* fusions:¹
 - BRAF* fusions occur in 2.6-6.7% of all melanomas²
- Tovorafenib is an investigational, oral, selective, CNS-penetrant, type II pan-RAF inhibitor targeting both monomeric and dimeric forms of RAF³ (**Figure 1**)
- Preclinical and clinical data have indicated that tovorafenib is not associated with paradoxical activation of the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway as has been reported for type I *BRAF* inhibitors³⁻⁵
- Single-agent tovorafenib activity has been observed in *BRAF*- and *NRAS*-mutated melanoma, low-grade gliomas harboring *RAF*-fusions, and a patient with a novel *SNX8-BRAF* fusion spindle cell sarcoma⁴⁻⁷

Figure 1. Tovorafenib mechanism of action



In vivo proof of concept: antitumor efficacy

Figure 2. Antitumor activity of tovorafenib in *BRAF*-fusion melanoma PDX models

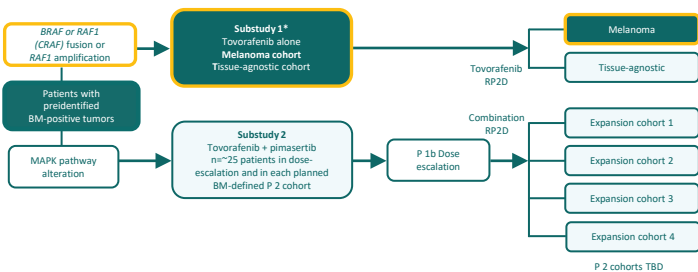


NOD SCID, nonobese diabetic severe combined immunodeficiency; PDX, patient-derived xenograft; PO, oral administration; QD, once daily.

FIRELIGHT-1

- FIRELIGHT-1 (NCT04985604) is an open-label, multicenter, phase (P) 1b/2 umbrella study of tovorafenib monotherapy or combination therapy in patients ≥ 12 years of age with recurrent, progressive or refractory solid tumors harboring molecularly defined alterations of components of the MAPK pathway (**Figure 3**)
- Substudy 1 (DAY101-102a) is investigating tovorafenib monotherapy in patients with a recurrent, progressive or refractory melanoma (cohort 1) or other solid tumor (cohort 2) harboring activating *BRAF* or *RAF1* (*CRAF*) fusions or *RAF1* amplifications:
 - Primary endpoint: overall response rate per RECIST v1.1
 - Tovorafenib administered to adult patients (≥ 18 years of age) at 600 mg once weekly (QW) and for patients 12 to <18 years of age at 420 mg/m² QW (not to exceed 600 mg)

Figure 3. FIRELIGHT-1 trial design



*Projected enrollment: tovorafenib alone (n=43); melanoma cohort (n=18); tissue-agnostic cohort (n=25). BM, biomarker; MAPK, mitogen-activated protein kinase; P, phase; RECIST, response evaluation criteria in solid tumors; RP2D, recommended P 2 dose; TBD, to be determined.

Results

- Preliminary clinical activity of tovorafenib monotherapy in the first 3 patients with *BRAF* fusion melanoma is reported (data cutoff Feb 8, 2023; **Table 1**)

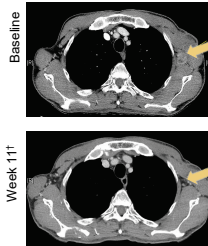
Table 1. Patient and disease characteristics

	Patient 1	Patient 2	Patient 3
Age (years)	53	35	71
Sex	M	M	M
ECOG status	0	1	0
Primary cancer	Cutaneous melanoma, non-Spitzoid	Malignant melanoma	Cutaneous melanoma, non-Spitzoid
<i>BRAF</i> fusion	AGK-BRAF	TRIM33-BRAF	MKRN1-BRAF
Stage at diagnosis	III	Unknown	II
Prior therapy:			
Surgery	Yes	No	No
Radiotherapy	No	Yes	Yes
Immune checkpoint inhibitor	Yes	Yes	Yes
Prior lines of targeted treatment	1	2	1
Tovorafenib dose	600 mg QW	600 mg QW	600 mg QW
TRAE $\geq$ G3 ^a	No	No	No
Dose modification/discontinuation due to AE ^a	No	No	No
Dose interruptions ^a	No	No	No
Treatment ongoing ^a	Yes	Yes	Yes
Current cycle ^a	5	5	3
Best RECIST response to tovorafenib ^a	CR	PR	PR [†]

^aData cutoff Feb 8, 2023. [†]Patient 3 is awaiting a confirmatory scan. AE, adverse event; CR, complete response; ECOG, Eastern Cooperative Oncology Group; G, grade; M, male; PR, partial response; QW, once weekly; RECIST, response evaluation criteria in solid tumors; TRAE, treatment-related adverse event.

Patient 1 with AGK-BRAF fusion cutaneous melanoma

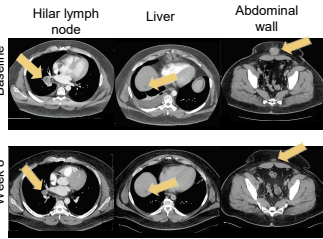
Parameter	Description/outcome
Prior therapies	- Multiple lymphadenectomies and skin lesion excision surgery - Pembrolizumab (11 weeks): - Best response: SD
Tovorafenib treatment to date in FL-1 102a (melanoma cohort)*	600 mg QW 5 cycles with no dose interruption or modifications due to AEs
Antitumor activity results to date*	CR (11-week scan) [†] ; confirmed at 16 weeks [‡]
Safety results to date*	TRAEs: - transient rash (G1 and G2) - anemia (G2) TEAE: - neck pain (G1)



^aData cutoff Feb 8, 2023. [†]Out of window per protocol. [‡]per RECIST v1.1. AE, adverse event; CR, complete response; G, grade; FL-1, FIRELIGHT-1; QW, once weekly; RECIST, response evaluation criteria in solid tumors; SD, stable disease; TEAE, treatment-emergent adverse event; TRAEs, treatment-related adverse events.

Patient 2 with TRIM33-BRAF fusion malignant melanoma

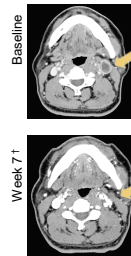
Parameter	Description/outcome
Prior therapies	- Radiation - Nivolumab (12 mo, adjuvant setting): - No best response, disease resected - Nivolumab + ipilimumab (3 cycles): - Best response: PD after 2 mo
Tovorafenib treatment to date in FL-1 102a (melanoma cohort)*	600 mg QW 5 cycles with no dose interruption or modifications due to AEs
Antitumor activity results to date*	PR (8-week scan); confirmed at 16 weeks [†]
Safety results to date*	TRAEs: - rash - maculopapular (G1) - headache (G1) - fatigue (G1)



^aData cutoff Feb 8, 2023. [†]per RECIST v1.1. AE, adverse event; G, grade; FL-1, FIRELIGHT-1; mo, months; QW, once weekly; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors; TRAEs, treatment-related adverse events.

Patient 3 with MKRN1-BRAF fusion cutaneous melanoma

Parameter	Description/outcome
Prior therapies	- Radiation - Pembrolizumab (2 mo): - Best response: SD
Tovorafenib treatment to date in FL-1 102a (melanoma cohort)*	600 mg QW 3 cycles with no dose interruption or modifications due to AEs
Antitumor activity results to date*	PR (7-week scan) [†] ; is awaiting a confirmatory scan
Safety results to date*	TRAEs: - urticaria (G1) - hand-foot syndrome (G1)



^aData cutoff Feb 8, 2023. [†]In window per protocol. [‡]per RECIST v1.1. AE, adverse event; G, grade; FL-1, FIRELIGHT-1; mo, months; QW, once weekly; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease; TRAEs, treatment-related adverse events.

Conclusions

- Early results from the first 3 patients of this ongoing trial showed that tovorafenib:
 - Displayed encouraging antitumor activity in *BRAF*-fusion melanoma
 - 2 PRs* and 1 CR per RECIST v1.1
 - Was generally well tolerated:
 - All TAEs and TRAEs were G1 or G2
 - As of Feb 8, 2023, all 3 patients remained on tovorafenib with no dose reduction or treatment interruption

^aPatient 3 is awaiting a confirmatory scan. CR, complete response; G, grade; PR, partial response; TEAE, treatment-emergent adverse event; TRAEs, treatment-related adverse events.

References

- Hutchinson KE, et al. *Clin Cancer Res*. 2013;19(24):6696-6702.
- Bottom, T. et al. *Cell Rep*. 2019;29(3):573-588.
- Sun Y, et al. *Neuro Oncol*. 2017;19(6):774-785.
- Olczanski, et al. *Ann Oncol*. 2017;28(suppl. 5): abstr. 4583.
- Kilbuck, et al. *Neuro Oncol*. 2022;24(suppl. 7):vi89 and presented poster.
- Wright K, et al. *Neuro Oncol*. 2020;22(suppl 2):i46, and associated presentation.
- Offer K, et al. Poster P250 presented at: 2021 Connective Tissue Oncology Society Annual Meeting; November 10-13, 2021; Virtual Meeting.

Presenting author contact

Jeeyun Lee, MD: jyunlee@skku.edu

19th EADO Congress 2023: Paper #174