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

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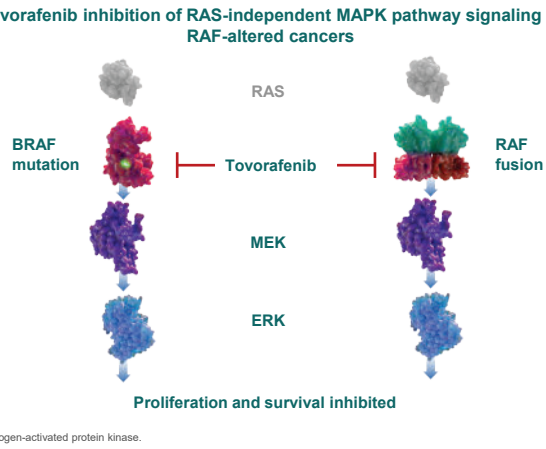
Background

- 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 melanomas[2]
- Tovorafenib is an investigational, oral, selective, CNS-penetrant, type II pan-RAF inhibitor targeting both monomeric and dimeric forms of RAF[3] (**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 inhibitors[3-5]
- 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 sarcoma[4-7]

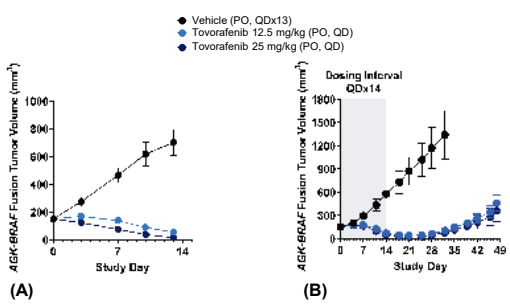
Figure 1. Tovorafenib mechanism of action



MAPK, mitogen-activated protein kinase.

In vivo proof of concept: antitumor efficacy

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



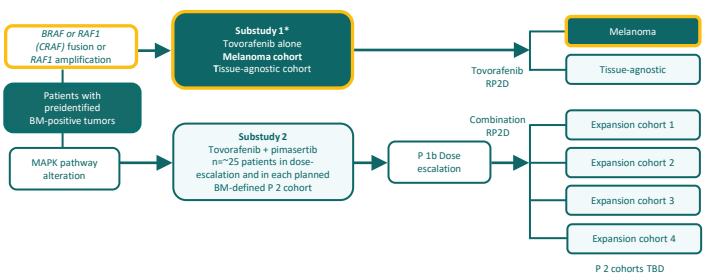
- Tovorafenib treatment of an *AGK-BRAF* fusion melanoma PDX model leads to regressions:
  - NOD SCID mice bearing melanoma PDX tumors with a confirmed *AGK-BRAF* fusion were treated with tovorafenib or vehicle control daily for 14 days (**Figure 2A**)
- Durable responses to tovorafenib were observed in *AGK-BRAF* fusion melanoma PDX:
  - NOD SCID mice bearing melanoma PDX tumors with a confirmed *AGK-BRAF* fusion were treated with tovorafenib or vehicle control for 14 days. Treatment was then stopped, and tumors monitored for regrowth. Tumor regrowth was not observed until 3 weeks post treatment (**Figure 2B**)

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/m^2 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**)

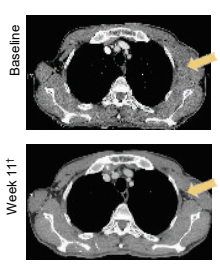
Table 1. Patient and disease characteristics

	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
***BRAF* 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 ≥G3*	No	No	No
Dose modification/discontinuation due to AE*	No	No	No
Dose interruptions*	No	No	No
Treatment ongoing*	Yes	Yes	Yes
Current cycle*	5	5	3
Best RECIST response to tovorafenib*	CR	PR	PR†

*Data cutoff Feb 8, 2023. †Patient 3 is awaiting a confirmatory scan.
AE, adverse events; 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

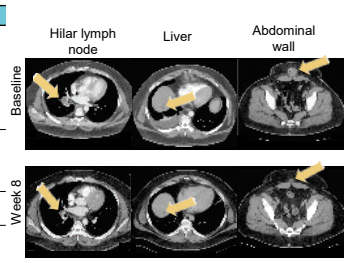
Parameter	Description/outcome
Prior therapies	• Multiple lymphadenectomies and skin lesion excision surgery • Pembrolizumab (11 weeks): – Best response: SD
Tovorafenib treatment to date in FL-1 102a (melanoma cohort)*	• 600 mg QW • 5 cycles with no dose interruption or modifications due to AEs
Antitumor 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)



*Data 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

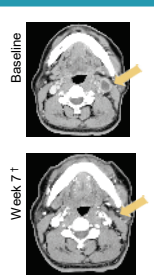
Parameter	Description/outcome
Prior therapies	• Radiation • Nivolumab (12 mo, adjuvant setting): – No best response, disease resected • Nivolumab + ipilimumab (3 cycles): – Best response: PD after 2 mo
Tovorafenib treatment to date in FL-1 102a (melanoma cohort)*	• 600 mg QW • 5 cycles with no dose interruption 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)



*Data 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)



*Data 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 TEAEs and TRAEs were G1 or G2
    - As of Feb 8, 2023, all 3 patients remained on tovorafenib with no dose reduction or treatment interruption

*Patient 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

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