Preclinical efficacy of BDTX-4933, a brain-penetrant, orthosteric RAF inhibitor, targeting oncogenic RAF conformation shared by groups of BRAF and upstream driver mutations

Yoon-Chi Han, Pui Yee Ng, Luisa Shin Ogawa, Shao Ning, Miao Chen, Darlene Romashko, Elizabeth Buck
Black Diamond Therapeutics

EORTC 2023
Abstract: 33930

Abstract

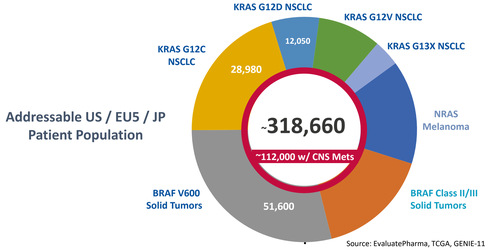
Introduction
RAF is a key direct downstream effector of RAS which activates the MAPK (RAF-MEK-ERK) signaling cascade for cell proliferation and growth. Alterations in the MAPK pathway, such as RAS, NF1, and BRAF, lead to increased RAF dimerization and activation that result in tumor growth. Currently approved BRAF inhibitors are selective against monomeric BRAF mutations and largely inactive against dimeric RAF mutants. Additionally, these agents may also promote deleterious paradoxical activation of RAF in select contexts. Moreover, FDA-approved KRAS G12C mutant-selective inhibitors are ineffective for cancer patients who harbor other (non-G12C) KRAS, NRAS, and NF1 mutations which all lead to increased active RAF dimers. There remains a high unmet medical need for a CNS penetrant RAF inhibitor that targets a broad spectrum of oncogenic RAF conformations in the context of RAS, RAF, and other upstream driver mutations.

Results
BDTX-4933 is a next generation MasterKey RAF inhibitor designed to address the shortcomings of earlier generation RAF inhibitors. BDTX-4933 is a brain-penetrant orthosteric inhibitor that potently targets the oncogenic RAF dimer conformation promoted by RAF mutations and its upstream oncogenic alterations such as KRAS, NRAS, and NF1 mutations. In a wide spectrum of BRAF and RAS mutant tumor cells, BDTX-4933 potently and selectively inhibits cell proliferation by blocking RAF hetero- and homo-dimers with high binding affinity and long resident time. In vivo, once daily oral dosing of BDTX-4933 resulted in robust and sustained target engagement, inhibiting ERK phosphorylation without inducing paradoxical activation. BDTX-4933 exhibits high CNS exposure leading to dose-dependent tumor growth inhibition, and survival benefit in mice implanted intracranially with xenograft BRAF mutant tumors. In a mouse breadth of efficacy study with patient derived xenografts (PDX), BDTX-4933 demonstrated tumor growth inhibition and regression as a single agent across models expressing a variety of BRAF, KRAS, NRAS, and NF1 oncogenic mutations. In a PDX model of BRAF V600E positive tumor that progressed following BRAF and MEK combination therapy, BDTX-4933 achieved robust tumor growth regression. Furthermore, BDTX-4933 achieves tumor growth regression across PDX models derived from NSCLC expressing KRAS-G12V/D mutations as a single agent.

Conclusions
BDTX-4933 has a potential best-in-class RAF inhibitor profile to treat cancer patients harboring BRAF mutations or RAF dimer-promoting upstream genetic alterations. BDTX-4933 is currently in a Phase I clinical study in patients with solid tumors harboring sensitive BRAF and RAS alterations (NCT05786924). For more information on this active Phase 1 clinical study, please contact: ClinicalTrials@bdtx.com.

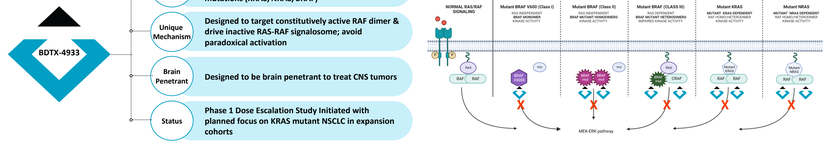
MAPK Pathway Mutations Affecting KRAS/NRAS/BRAF are Among the Most Common Oncogenic Mutations in Human Cancer

Learn more about the on-going BDTX-4933 Phase 1 Clinical Study



BLACK DIAMOND THERAPEUTICS

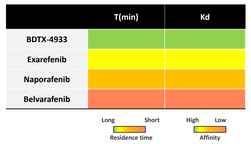
BDTX-4933 Targets the Constitutively Active RAF Conformation in the Context of a Spectrum of MAPK Mutations (KRAS/NRAS/BRAF)



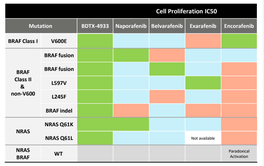
BDTX-4933 Potently and Selectively Inhibits the Proliferation of Tumor Cells Expressing a Spectrum of BRAF/RAS Mutations; Potential Best-in-Class Potency vs other RAF Inhibitors

Potent inhibition of BRAF & CRAF homodimers and heterodimers in KRAS mutant cell line models

Superior binding & residence time vs other RAF inhibitors in preclinical models

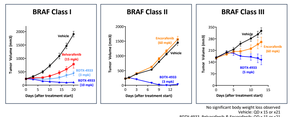


Potent and selective inhibition of proliferation across tumor cell lines with MAPK pathway mutations



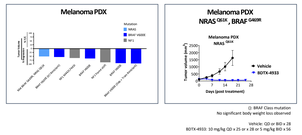
BDTX-4933 Achieves Dose Regression Across Tumor Models Expressing a Spectrum of MAPK Pathway Mutations

BDTX-4933 achieves strong anti-tumor activity across all BRAF mutation classes in In Vivo cell line-derived xenograft models



No significant body weight loss observed
Vehicle: QD x 21 or x21
BDTX-4933, Belvarafenib & Encorafenib: QD x 14 or x21

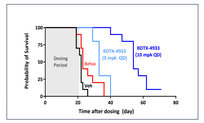
BDTX-4933 achieves tumor regression across patient derived xenograft tumors expressing a spectrum of MAPK mutations



◊: BRAF Class mutation
No significant body weight loss observed

Vehicle: QD or BID x 28
BDTX-4933: 10 mg/kg QD x 21 or x 28 or 5 mg/kg BID x 56

BDTX-4933 promotes survival advantage in intracranial tumor model with BRAF-V600E



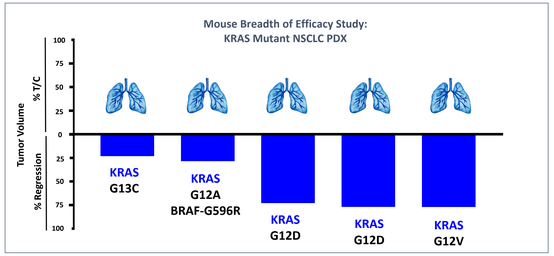
BDTX-4933 Effectively Inhibits Signaling Downstream of KRAS Mutations

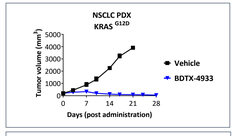
BDTX-4933 Inhibits MAPK signaling in the context of KRAS mutations in NSCLC cell line models, with potential best-in-class profile

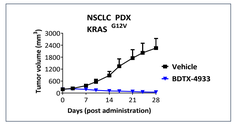
KRAS mutant Cell lines	BDTX-4933	Encorafenib	Naporafenib	Belvarafenib
G12V NSCLC				

pERK IC_{50} color code: < 50nM | 50-500nM | >500nM

BDTX-4933 Achieves Tumor Regression in NSCLC PDX Models Expressing a Spectrum of KRAS Mutations







◊: BRAF Class mutation
No significant body weight loss observed

Vehicle: QD x 28 or BID x 56
BDTX-4933: 10 mg/kg QD x 28 or 5 mg/kg BID x 56

Summary

- Potential best-in-class potency and selectivity against a spectrum of MAPK mutations that drive a constitutively active RAF conformation
- Unique mechanism of action to potently target a constitutively activated RAF conformation in the context of oncogenic MAPK mutations including KRAS mutations
- Tumor growth regression achieved across tumor models including PDX expressing a spectrum of oncogenic MAPK driver mutations, including NSCLC PDX with KRAS-G12/13X mutations
- Preclinical data supports drug development across MAPK alterations, and initial focus will be on KRAS-G12/13X NSCLC
- BDTX-4933 is currently in a Phase I clinical study in patients with solid tumors including KRAS non-G12C NSCLC (NCT05786924). For more information on this active Phase 1 study, please contact: ClinicalTrials@bdtx.com.