Preclinical characterization of a brain penetrant RAF inhibitor, BDTX-4933, targeting oncogenic BRAF Class I/II/III and RAS mutations

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Abstract: #3415

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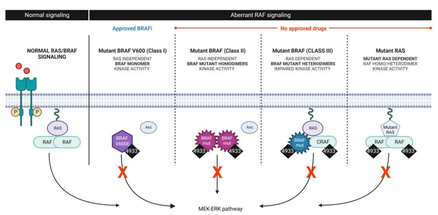
Background

Mutations in BRAF and RAS are often oncogenic and lead to a constitutively active MAPK pathway that promotes aberrant cell proliferation and tumor growth. Currently approved BRAF inhibitors are selective against monomeric BRAF V600 mutants. These drugs are largely inactive against non-V600 dimeric BRAF mutants and have poor brain penetration. Although there is an FDA-approved KRAS G12C mutant-selective inhibitor, there are no approved inhibitors for cancer patients who harbor other (non-G12C) KRAS and NRAS mutations which promote tumor growth likely through constitutively active RAF dimers. Furthermore, brain metastasis is frequently reported, with around 70% of melanoma patients at later stages of disease, and with frequent relapse occurring primarily at the brain metastatic site. There remains a high unmet clinical need for a CNS penetrant oral RAF inhibitor that targets a broad spectrum of BRAF mutations and constitutively active RAF dimers without paradoxical activation of the MAPK signaling pathway.

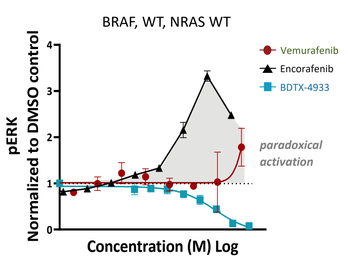
Results

BDTX-4933 is a potent, reversible, CNS penetrant RAF MasterKey inhibitor designed to target the oncogenic conformation of RAF in response to any of the 3 classes of BRAF mutations or to RAS mutations. The compound inhibits not only all classes (I, II, and III) of BRAF mutations but also targets constitutively active RAF dimers promoted by upstream oncogenic MAPK pathway alterations, such as RAS mutations. In a panel of cancer cell lines that endogenously express BRAF or RAS mutations, BDTX-4933 demonstrates inhibition of the MAPK pathway signaling without paradoxical activation, resulting in potent inhibition of cellular proliferation. BDTX-4933 shows target engagement, inhibiting ERK phosphorylation, in tumor models in vivo, achieving strong anti-tumor efficacy and tumor regression across many tumor models driven by either BRAF or RAS mutations. Furthermore, BDTX-4933 exhibits high CNS exposure leading to dose-dependent tumor growth inhibition, and a survival benefit in mice implanted intracranially with xenograft BRAF mutant tumors.

BDTX-4933 addresses unmet need remaining for all classes of BRAF and RAS driven cancers

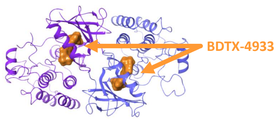


BDTX-4933 is highly potent in cell lines with a wide spectrum of oncogenic BRAF and NRAS mutations without inducing paradoxical activation



BDTX-4933 is an active-site inhibitor that binds to both protomers of a mutant BRAF dimer

Crystal structure of dimeric BRAF G469A in complex with BDTX-4933



Potent inhibition of BRAF & CRAF homodimers and heterodimers in KRAS mutant cells*

Compounds	BDTX-4933	Encorafenib	Belvarafenib	Naporafenib	Fore8394
BRAF homodimer					
CRAF homodimer					
BRAF:CRAF heterodimer					

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

* ARAF, ARAF+BRAF, or ARAF+CRAF were KO by CRISPR in KRAS mutant cells

Mutation		BDTX-4933	Naporafenib	FORE8394	Belvarafenib	Exarafenib	Encorafenib
BRAF Class I	V600E						
BRAF Class II	BRAF-CUL1 fusion						
	BRAF indel						
NRAS	NRAS Q61K			N/A			
NRAS BRAF	WT						Paradoxical Activation

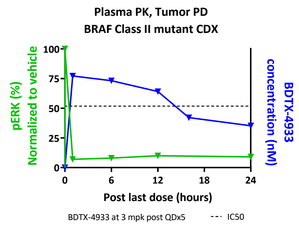
Proliferation IC_{50} color code: < 50nM | 50-200nM | >200nM | >1000nM

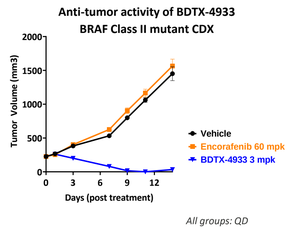
BDTX-4933 demonstrates high on-target inhibition

Target Engagement, pERK IC_{50}						
Cancer cell lines with BRAF mutation		BDTX-4933	Naporafenib	FORE8394	Encorafenib	Belvarafenib
Class I	V600E					
Class II & III (Non-V600)	K601E					
	Fusion					
NRAS	Q61R					

pERK IC_{50} color code: < 50nM | 50-150nM | >150nM

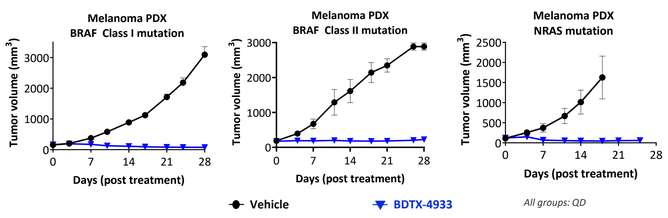
BDTX-4933 achieves excellent PK and sustained PD response which leads to robust anti-tumor efficacy



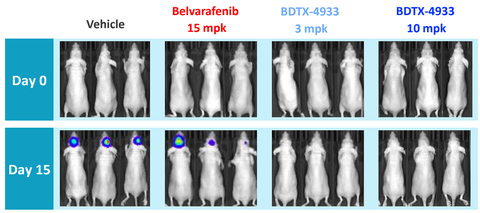


All groups: QD

BDTX-4933 shows strong anti-tumor efficacy in BRAF and NRAS mutant PDX models

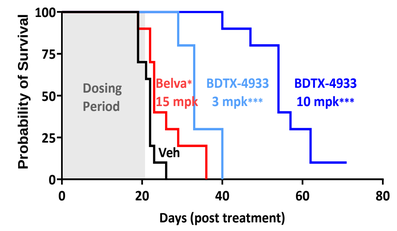


BDTX-4933 is brain-penetrant and exhibits robust anti-tumor activity in a mouse intracranial tumor model



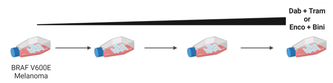
All groups: QD

BRAF V600E intracranial model



*P<0.05, ***P<0.0001

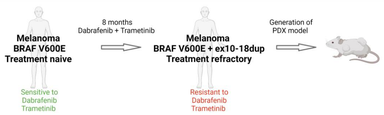
BDTX-4933 overcomes BRAFi + MEKi combo resistance (in vitro)



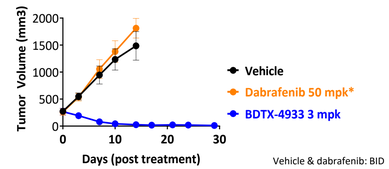
Compounds	BDTX-4933	Dabrafenib	Trametinib	Encorafenib	Binimetinib	Naporafenib	Belvarafenib	Exarafenib
Parental								
Dab + Tram Resistant				N/A	N/A			
Enco + Bini Resistant		N/A	N/A					

Proliferation IC_{50} color code: < 150nM | 150-500nM | >500nM

BDTX-4933 overcomes BRAFi + MEKi combo resistance (in vivo)



Dabrafenib + Trametinib resistant melanoma PDX
BRAF V600E + ex10-18 dup (PDX)



Vehicle & dabrafenib: BID
BDTX-4933: QD

Conclusions

BDTX-4933 has a best-in-class profile to treat cancer patients harboring BRAF mutations or RAF dimer-promoting upstream genetic alterations. Preclinical data warrant clinical trials in patients with oncogenic alterations in the RAS-RAF pathway.

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