AACR-NCI-EORTC Virtual International Conference on
MOLECULAR TARGETS AND CANCER THERAPEUTICS
October 7-10, 2021

Pre-clinical evaluation of next-generation inhibitor targeting a wide spectrum of oncogenic BRAF dimers

Yoon-Chi Han[1], Pui Yee Ng[2], Ryan Schulz[1], Shao Ning Yang[1], Alana Lelo[1] , Luisa Shin Ogawa[2], Matthew O'Connor[2], Noboru Ishiyama[3], Ivan Jewett[2], Darlene Romashko[1], Andrei Salomatov[1], Shalabh Thakur[3], Sherri Smith[2], Elizabeth Buck[1], Christopher Roberts[2], Matthew Lucas[2], and Tai-An Lin[1]

[1] Black Diamond Therapeutics, New York, US
[2] Black Diamond Therapeutics, Cambridge, US
[3] Black Diamond Therapeutics, Toronto, CA.

Expanding the reach of precision medicine through the development of novel MasterKey therapies

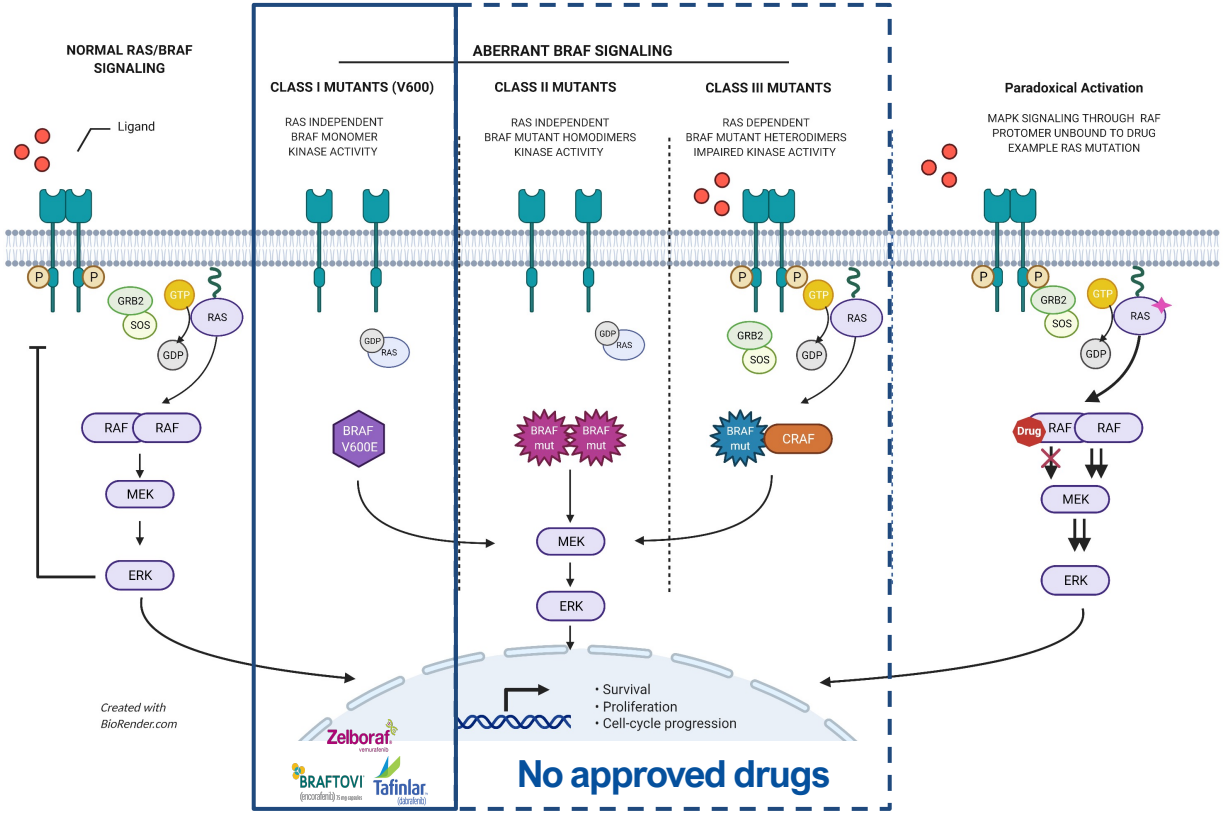
Addressing significant unmet need for novel precision oncology therapies for patients

Uniquely de-orphan oncogenic mutations to develop single therapies designed to inhibit specific mutation families

Our proprietary computational Mutation Allostery Pharmacology (MAP) drug discovery engine is designed to develop a spectrum-selective (MasterKey) small molecule therapy

Robust pipeline of oral, potent and selective small molecule kinase inhibitors across a range of indications and target groups including EGFR, HER2, BRAF and FGFR

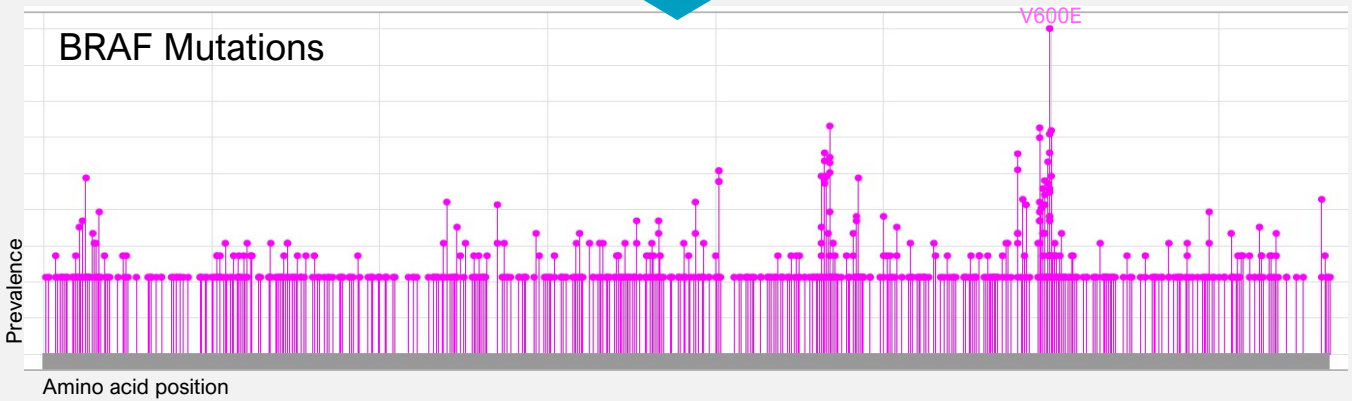
Addressing multiple gaps in approved agents

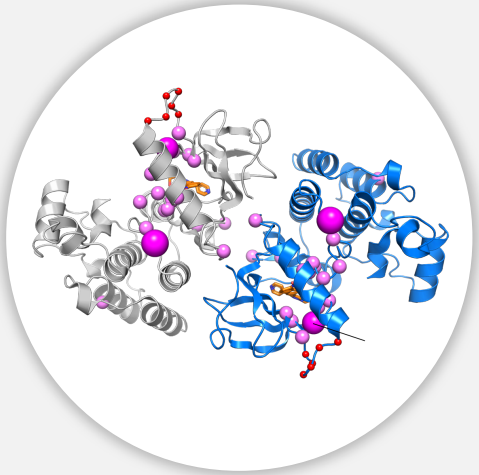


Adapted from Clin Cancer Res; 25(23) December 1, 2019

Development of MasterKey inhibitor against oncogenic BRAF dimers

MasterKey Inhibitor





BDTX-A demonstrates MasterKey inhibitor profile

AACR American Association for Cancer Research FINDING CURES TOGETHER | NIH NATIONAL CANCER INSTITUTE | EORTC European Organisation for Research and Treatment of Cancer — The future of cancer therapy

IC_{50} Color Code: < 50 nM | 50 – 150 nM | >150 nM

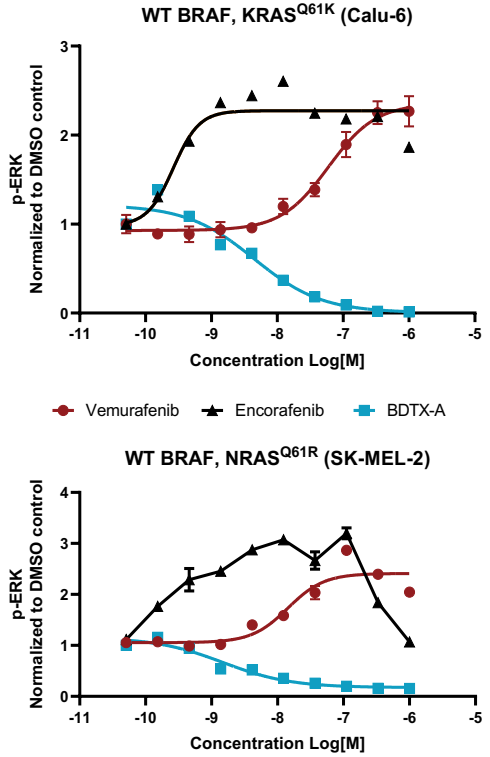
Cell Proliferation

Cell Line	BRAF Mutation (Class)	BDTX-A	LXH-254	PLX8394	Encorafenib
BaF3	G464V (II)				
	G464R (II)				
	G469R (II)				
	G469A (II)				
	G466A (III)				
	L597R (II)				
	L597Q (II)				
	K601N (II)				
	K601E (II)				
	F247L (III)				
	KIAA1549 fusion (II)				

BDTX-A demonstrates MasterKey inhibitor profile without inducing paradoxical activation

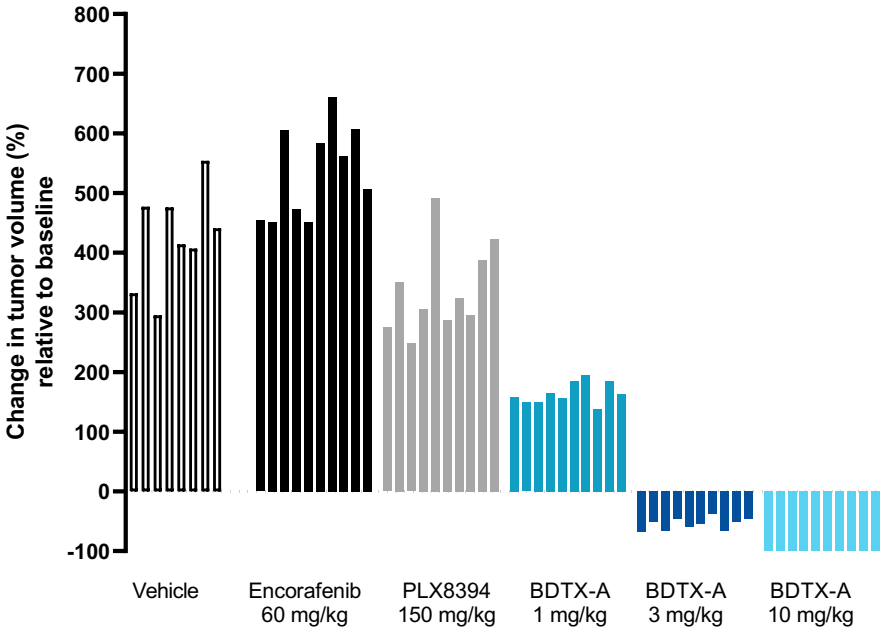
IC_{50} Color Code	< 50 nM	50 – 150 nM	>150 nM	↑ Paradoxical activation

	Cell Line	Mutation (Class)	BDTX-A	LXH-254	PLX8394	Encorafenib
Cell Proliferation	WM1789	BRAF K601E, S363F (II)				
	H2405	BRAF Indel (II)				
	WM3928	SKAP2-BRAF fusion (II)				
	SK-MEL-23	CUL1-BRAF fusion (II)				
	WM3629	BRAF D594G, NRAS G12D (III)				
	CHL-1	WT BRAF, WT NRAS	>500	>500	>500 ↑	>500 ↑
pERK	WM1789	BRAF K601E, S363F (II)				
	H2405	BRAF Indel (II)				
	WM3928	SKAP2-BRAF fusion (II)				
	SK-MEL-23	CUL1-BRAF fusion (II)				
	WM3629	BRAF D594G, NRAS G12D (III)				
	CHL-1	WT BRAF, WT NRAS	>500			

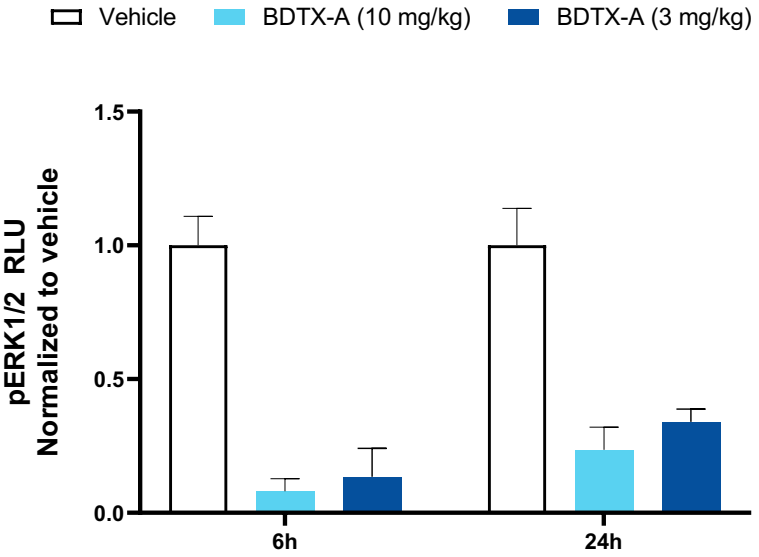


BDTX-A exhibits dose-dependent anti-tumor efficacy and pERK inhibition *in vivo*

BRAF-KIAA1549 fusion (BaF3)



Inhibition of pERK



Conclusion

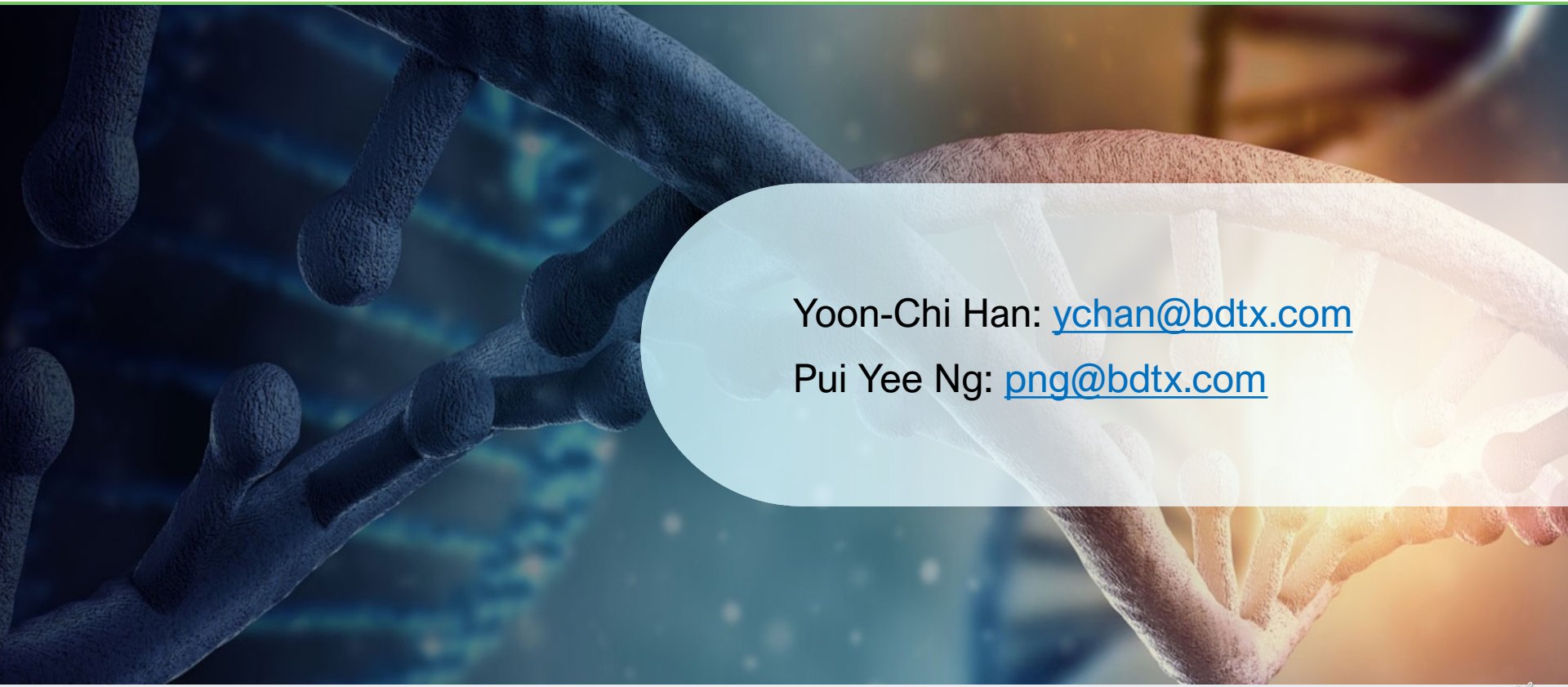
We discovered a small molecule inhibitor, BDTX-A, that is potent against tumor cells expressing a wide spectrum of oncogenic BRAF dimers

Broad activity (“MasterKey” profile) of BDTX-A is further demonstrated in cell lines that harbor endogenous oncogenic dimer-inducing BRAF mutations without inducing paradoxical activation

BDTX-A demonstrates robust anti-tumor efficacy and target engagement of dimeric BRAF oncogene in mouse models.

These data support the continued development of BDTX-A to extend the prospect of precision medicine in patients.

Contact Information



Yoon-Chi Han: ychan@bdtx.com

Pui Yee Ng: png@bdtx.com