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DISCOVERY AND CHARACTERIZATION OF SELECTIVE, FGFR1 SPARING, INHIBITORS OF FGFR2/3 ONCOGENIC MUTATIONS FOR THE TREATMENT OF CANCERS

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On Behalf of Black Diamond Therapeutics Project Team

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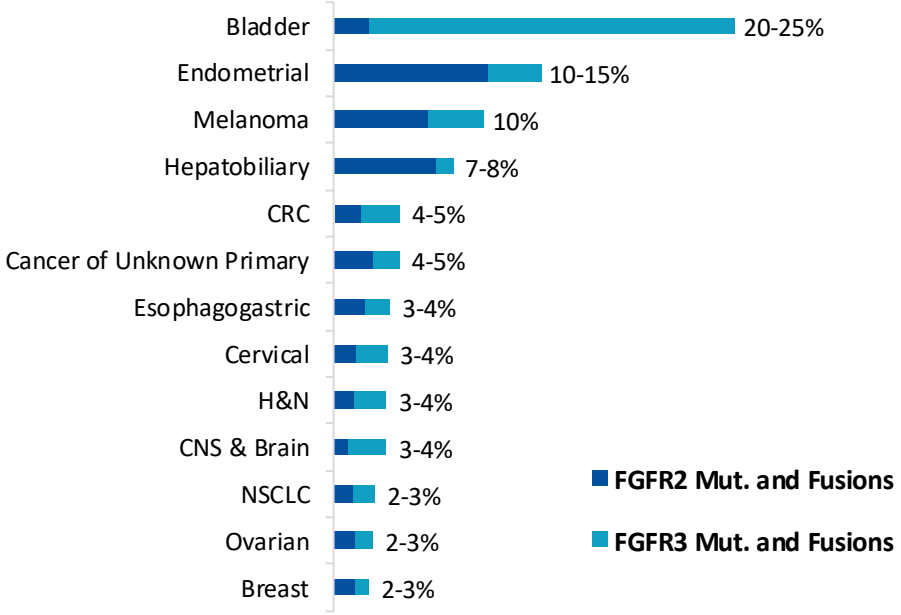
FGFR2 and FGFR3: Important Oncogenic Drivers in Solid Tumors, Poorly Served by Available Therapies

FGFR2/3: potent oncogenic drivers across human tumors

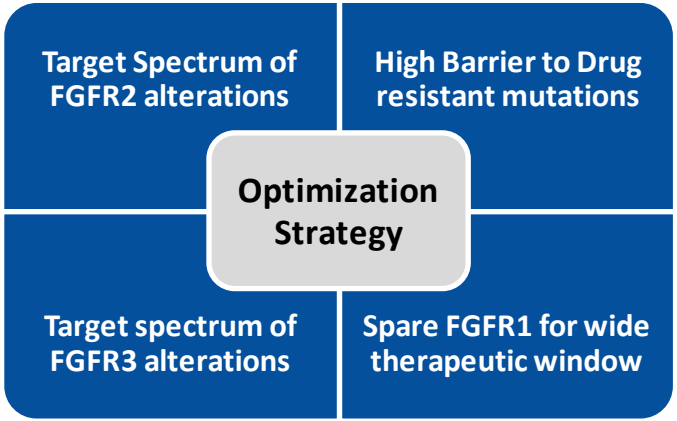
Prevalence of FGFR2/3 mutations and fusions in Solid Tumors



Current drugs limited by lack of selectivity & poor resistance profile

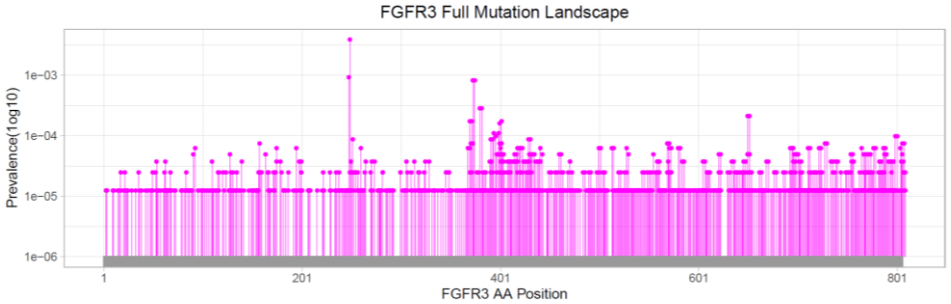
1. **Approved pan-FGFR inhibitors suffer from FGFR1-mediated hyperphosphatemia leading to frequent dose interruptions or reductions and limited efficacy.**
2. **Treatment emergent secondary resistance mutations at key residues ("gatekeeper") within the kinase domain.**

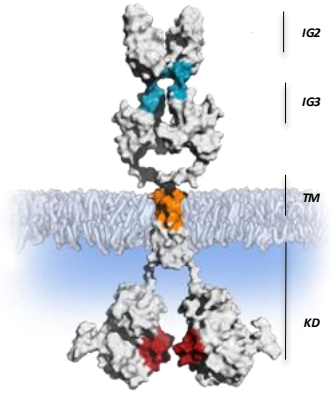
Black Diamond Approach



Black Diamond's Proprietary MAP Platform Enabled the Identification and Validation of Previously Uncharacterized FGFR2 and FGR3 Oncogenic Driver Mutations

MAP platform identifies novel, clinically relevant and actionable FGFR3 allosteric mutations



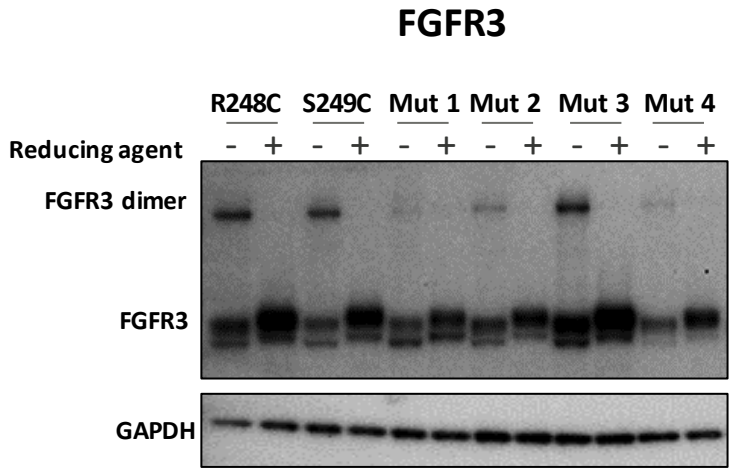


Mutation-Allostery-Pharmacology (MAP) platform is a genomic and proteomic ruled-based algorithm that reveals allosteric oncogenes:

- **Revealing the topography of oncogenic mutation hotpots**
- **Increasing oncogenicity prediction**
- **Aggregating spectrum of mutations to be drugged by a single compound**

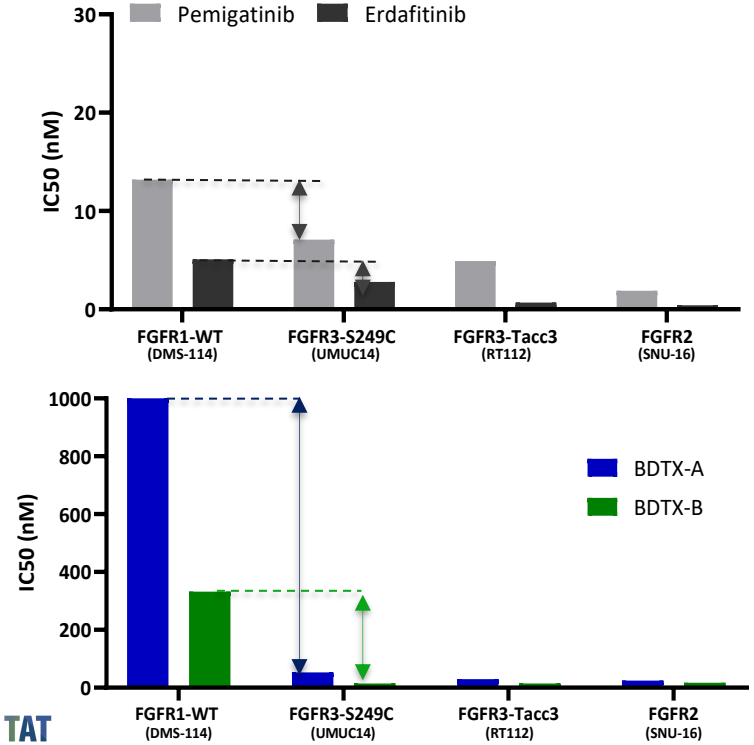
Validation of previously-uncharacterized spectrum of Allosteric FGFR3 dimer-inducing mutations

FGFR3 mutants are activated by covalent dimerization

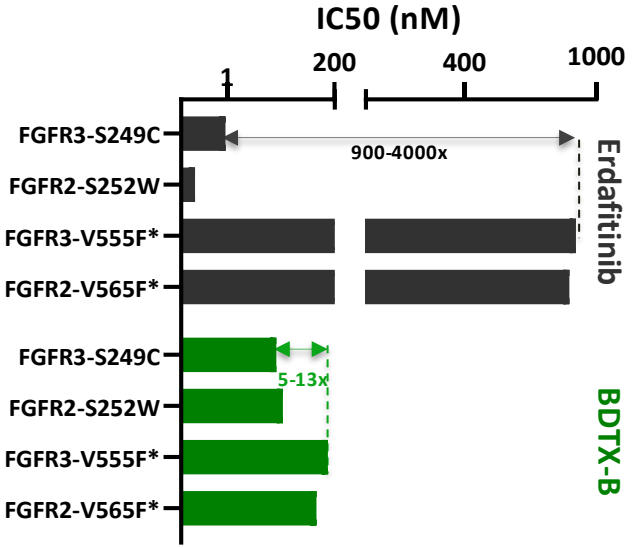


BDTX FGFR2/3 Leads Differentiated By Broad Selectivity Profile While Sparing Wild Type FGFR1

BDTX FGFR2/3 leads demonstrate 19-40 fold selectivity vs WT-FGFR1

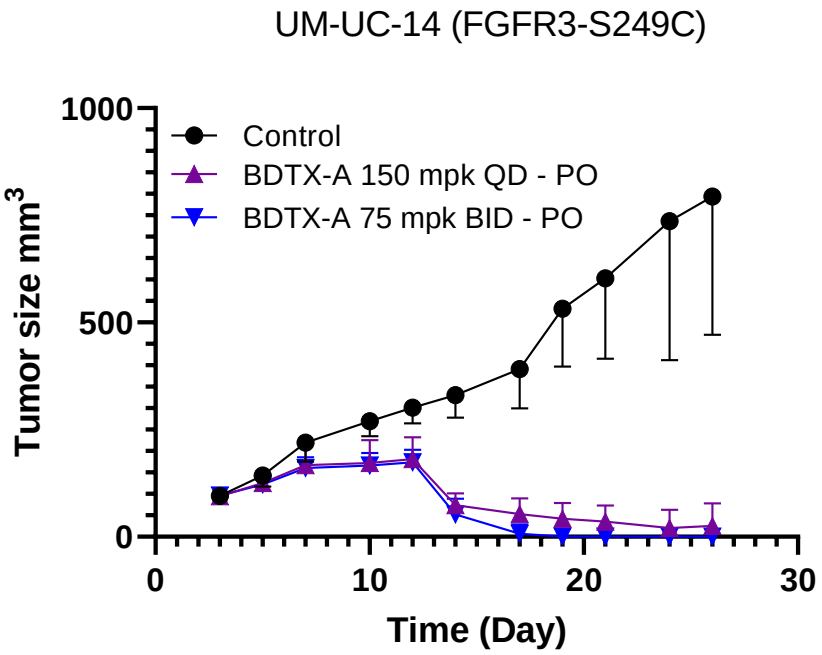


BDTX FGFR2/3 leads demonstrate improved potency against ATP-site gatekeeper mutations



*Gatekeeper mutants constructs in MCF10A cells:
FGFR3-V555X, X=M, L, F
FGFR2-V565X, X=I, F

BDTX-A Promotes Tumor Growth Regression of FGFR3 Mutant PDX Tumors



Efficacy in Nu/Nu mice using the UM-UC-14 FGFR3-S249C-driven bladder PDX model

BDTX-A achieves in-vivo POC:

- **BDTX-A 150 mpk PO-QD, TGI=106%**
- **BDTX-A 75 mpk PO-BID, TGI=113%**

Black Diamond to Deliver the Next Generation of Oncogenic FGFR Inhibitors

Approved Drugs

Target FGFR2	Drug resistant mutations
Target FGFR3	Target FGFR1

Black Diamond Approach

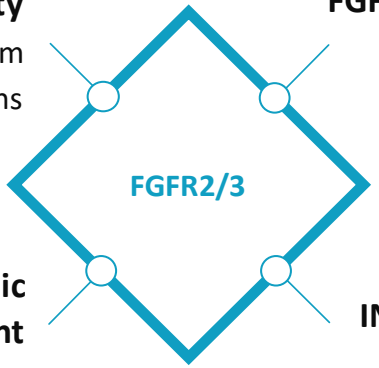
Target Spectrum of FGFR2 alterations	High Barrier to Drug resistant mutations
Optimization Strategy	
Target spectrum of FGFR3 alterations	Spare FGFR1 for wide therapeutic window

Strong Pre-Clinical Activity

- Potent activity vs broad FGFR2/3 mutant spectrum
  - Demonstrated potency vs resistance mutations

FGFR1 Sparing

- Capture efficacy "left on the table"
- Improved safety profile



Enables Tumor Agnostic Clinical Development

IND Anticipated in 2022

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