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

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

Prevalence of FGFR2/3 mutations and fusions in Solid Tumors

- **Bladder**: 20-25%
- **Endometrial**: 10-15%
- **Melanoma**: 10%
- **Hepatobiliary**: 7-8%
- **CRC**: 4-5%
- **Cancer of Unknown Primary**: 4-5%
- **Esophagogastric**: 3-4%
- **Cervical**: 3-4%
- **H&N**: 3-4%
- **CNS & Brain**: 3-4%
- **NSCLC**: 2-3%
- **Ovarian**: 2-3%
- **Breast**: 2-3%

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

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

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

MAP platform reveals allosteric oncogenes:
- Revealing the topography of oncogenic mutation hotpots
- Increasing oncogenicity prediction
- Aggregating spectrum of mutations to be drugged by a single compound

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-V565F*

Erdafitinib

Pemigatinib

FGFR1-WT FGFR3-S249C FGFR3-Tacc3 FGFR2

0 10 20 30

IC50 (nM)

FGFR1-WT (DMS-114) FGFR3-S249C (UMUC14) FGFR3-Tacc3 (RT112) FGFR2 (SNU-16)

BDTX-A BDTX-B

0 200 400 1000

IC50 (nM)

FGFR3-S249C
FGFR2-S252W
FGFR3-V555F*
FGFR2-V565F*

0 200 400 1000

IC50 (nM)

Erdafitinib

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

UM-UC-14 (FGFR3-S249C)

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

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