Poster #3097

Clinical Pharmacokinetics of BDTX-189, an Inhibitor of Allosteric ErbB Mutations, in Patients With Advanced Solid Malignancies in MasterKey-01 Study

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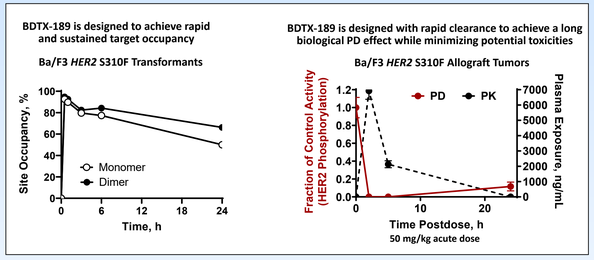
Introduction

- Allosteric oncogenic mutations occur outside the canonical ATP-binding site of EGFR and HER2, and there are no approved therapies that target such mutations
- BDTX-189 is a potent, selective, irreversible inhibitor of 48 allosteric EGFR and HER2 mutant variants under clinical evaluation in the ongoing MasterKey-01 trial (NCT04209465)

BDTX-189 was designed to achieve rapid and sustained active site occupancy with rapid plasma clearance (**Figure 1**)[1]

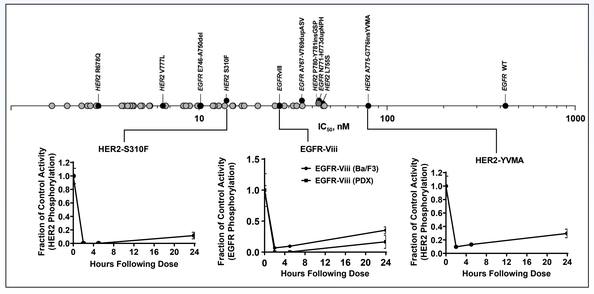
Figure 1. In Vitro Cell-Based Study Using Active Site Probe Demonstrating Rapid and Sustained Active Site Occupancy of HER2 S310F by BDTX-189 (Left Panel) and Acute PK/PD Experiment Demonstrating Sustained PD Modulation Achieved With Short Duration of Exposure to BDTX-189 In Vivo (Right Panel)



h, hours; HER2, human epidermal growth factor receptor 2; PD, pharmacodynamics; PK, pharmacokinetics.

BDTX-189 differentiated by potent, sustained inactivation of multiple allosteric ErbB mutants in vivo; PK/PD properties afford target coverage across a range of half maximal inhibitory concentration (IC_{50}) values (**Figure 2**)[1]

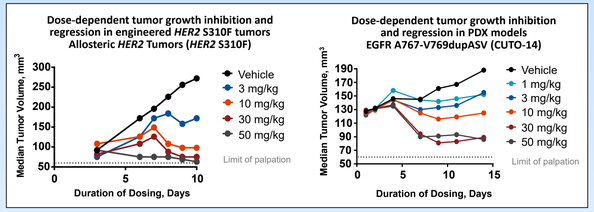
Figure 2. In Vitro IC_{50} and In Vivo Acute PK/PD Activity (50 mg/kg PO) Across a Range of EGFR and HER2 Mutants



EGFR, epidermal growth factor receptor; PDX, patient-derived xenograft; PO, orally; WT, wild type.

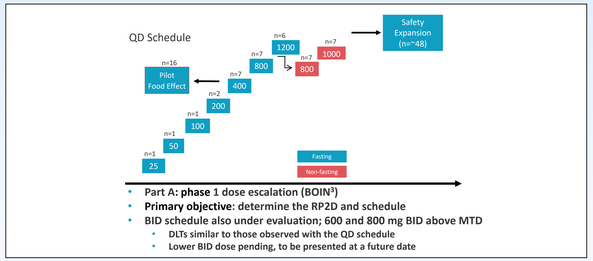
BDTX-189 achieves dose-dependent regression of tumors harboring allosteric *HER2* and *EGFR* mutations at well-tolerated doses (**Figure 3**)[1]

Figure 3. Tumor Growth Inhibition and Regression in *HER2* S310F Tumor Allografts in Mice Dosed With BDTX-189 QD (Left Panel), and in *EGFR* Exon 20 Insertion PDX in Mice Dosed With BDTX-189 QD (Right Panel)



QD, once daily.

Figure 4. MasterKey-01 Study Schema[2]



- **Part A: phase 1** dose escalation (BOIN[3])
- **Primary objective**: determine the RP2D and schedule
- BID schedule also under evaluation; 600 and 800 mg BID above MTD
  - DLTs similar to those observed with the QD schedule
  - Lower BID dose pending, to be presented at a future date

BID, twice daily; BOIN, Bayesian Optimal Interval Design; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose.

Methods

PK Methodology and Evaluations Within the MasterKey-01 Study

Single-Dose and Multiple-Dose PK Assessed in Dose Escalation

- Detailed blood sampling for PK on C1D1 and C1D15 with multiple time points collected over 24 h

Effect of Food on the PK of BDTX-189 Assessed in a Four-Day Lead-in Phase

- A 400-mg single dose fed/fasted randomized crossover design, study Day –4 and Day –1 before initiating QD dose schedule on C1D1
- Administration of BDTX-189 after fasting for at least 10 h or immediately after consuming a standardized high-fat or low-fat breakfast (meal content consistent with FDA guidance)

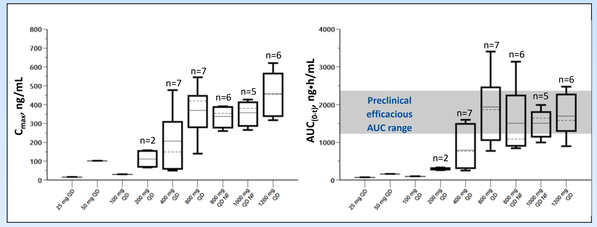
Analysis Methods

- Blood plasma samples analyzed by liquid chromatography/mass spectrometry (LC-MS/MS) methods to quantify BDTX-189 concentrations
- Non-compartmental methods used to calculate PK parameters, including area under the curve (AUC), maximum concentration (C_{max}), time to maximum concentration (t_{max}), and half-life ($t_{1/2}$)

Results

Dose-dependent increases in exposure up to 800 mg QD (**Figure 5**)

Figure 5. Box and Whisker Plots Showing the Relationship Between BDTX-189 Dose and Exposure (C1D1 C_{max} and $AUC_{(0-t)}$) for 25 mg QD to 1200 mg QD

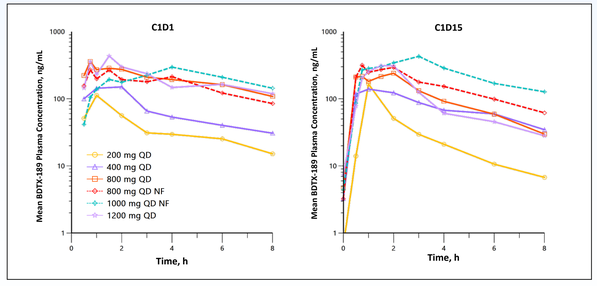


Box represents interquartile range, arithmetic mean (solid line), median (dotted line), tails (min/max). $AUC_{(0-t)}$, area under the plasma concentration-time curve; NF, non-fasted, administered with a meal of patient's preference.

- Dose-dependent increases in exposure up to 800 mg, plateau in exposure observed at >800 mg
- IC_{50} mutational spectrum corrected for plasma protein binding represented by 25-400 ng/mL range
- C_{max} coverage at 800 mg QD consistent with that observed at efficacious doses in mouse models
- **Within target efficacious range defined by AUC in mouse models harboring allosteric ErbB–mutated tumors at ≥800 mg QD**

BDTX-189 PK profile characterized by rapid oral absorption with a short elimination $t_{1/2}$ consistent with preclinical projections (**Figure 6**)

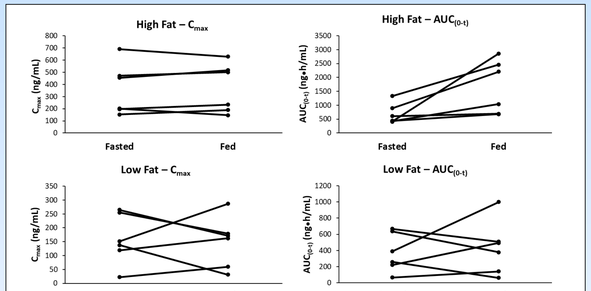
Figure 6. Mean Concentration-Time Profiles for C1D1 and C1D15 After QD Oral Administration of BDTX-189 at 200 mg (n=2), 400 mg (n=7), 800 mg (n=7 C1D1; n=14 C1D15), 800 mg Non-Fasted (n=6), 1000 mg Non-Fasted (n=5 C1D1; n=2 C1D15), and 1200 mg (n=6 C1D1; n=3 C1D15)



- Rapidly absorbed, with a short median elimination $t_{1/2}$ of 1.3-4.4 h, consistent with preclinical projections
- No apparent accumulation or change in exposure at steady state

Single-dose crossover pilot food effect study suggests similar BDTX-189 exposures under fed and fasted conditions (**Figure 7**)

Figure 7. Stick Plots of Individual BDTX-189 C_{max} and $AUC_{(0-t)}$ Values After Administration in the Fasted and Fed States (High-Fat Meal, n=6; Low-Fat Meal, n=6). Tabulated Summary of Key PK Parameters



Parameter	Fasted	High Fat	Low Fat
Geometric mean ratio, C_{max}	N/A	1.03	0.94
Geometric mean ratio, $AUC_{(0-t)}$	N/A	2.28	1.05
Median $t_{1/2}$, h	1.4	1.6	1.4
Median t_{max}, h	1.5	4.0	3.5

N/A, not applicable.

- Pilot food-effect data suggests similar exposures under fed and fasted conditions, with C_{max} ratio and AUC ratio of 1.0 and 2.3, respectively, with a high-fat meal, and 0.9 and 1.0, respectively, with a low-fat meal
- Administration of BDTX-189 with food resulted in an approximately 2.5-fold increase in median t_{max} relative to administration in the fasted state, and no change in median $t_{1/2}$

Summary and Conclusions

- **BDTX-189 is a potent, selective, irreversible inhibitor of the family of 48 allosteric EGFR and HER2 mutant variants**
- **Prospective preclinical modeling predicted active dose levels in humans in the 400-800 mg QD range, based on the exposure–tumor growth inhibition relationship in multiple mouse tumor models harboring allosteric *ErbB* mutations[1]**
- **In MasterKey-01, BDTX-189 demonstrated rapid oral absorption and a short PK $t_{1/2}$ consistent with the desired PK/PD profile, with exposures at 800 mg QD in the efficacious target range based on preclinical data**
- **Pilot food-effect data suggests similar exposures under fed and fasted conditions. In addition, the non-fasting QD dosing regimen showed similar systemic exposure relative to dosing in the fasted state**
- **The MasterKey-01 trial is ongoing, including refinement of the dosing regimen and identification of the recommended Phase 2 dose and schedule**

References

1. Ottaviani G, et al. Poster #LB127, AACR 2021.
2. Schram AM, et al. Poster #3086, ASCO 2021.
3. Yuan Y, et al. *Clin Cancer Res.* 2016;22(17):4291-4301.

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