Poster #3086

Safety and Preliminary Efficacy From the Phase 1 Portion of MasterKey-01: A First-in-Human Dose-Escalation Study to Determine the Recommended Phase 2 Dose, Pharmacokinetics and Preliminary Antitumor Activity of BDTX-189, an Inhibitor of Allosteric *EGFR/HER2* Mutations, in Patients With Advanced Solid Malignancies

MasterKey-01
NCT04209465

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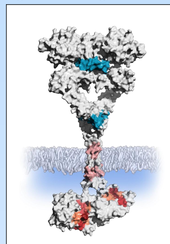
Background

Allosteric oncogenic mutations occur outside the ATP binding site of *EGFR* and *HER2* and are grouped into MTCs on the basis of receptor structure and mechanism of oncogenicity (**Figure 1A**)[1]

Figure 1A. Oncogenic MTCs for EGFR and HER2

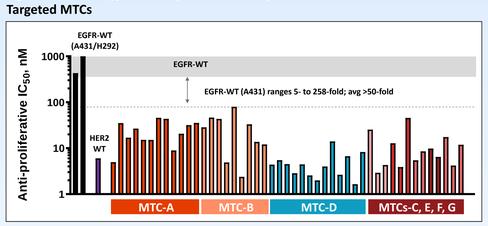


MTC	Description
MTC-A	EGFR Exon 20 insertion
MTC-B	HER2 Exon 20 insertion
MTC-C	HER2 Exon 20 missense
MTC-E	HER2 KD β-sheet missense
MTC-F	HER2 KD α-loop missense
MTC-G	HER2 JMD missense
MTC-D	HER2 ECD missense

- There are currently no therapies approved to target allosteric *EGFR/HER2* mutations
  - EGFR-WT toxicities (eg, rash and diarrhea) limit exposure needed to target this family of mutations

BDTX-189 was designed as a small molecule, ATP-competitive, and irreversible inhibitor of the spectrum of oncogenic allosteric *EGFR/HER2* MTCs and *HER2*-WT and customized to spare *EGFR*-WT to minimize toxicity (**Figure 1B**)[1]

Figure 1B. Phenotypic Activity, and Selectivity vs WT-EGFR, for BDTX-189 Across Targeted MTCs

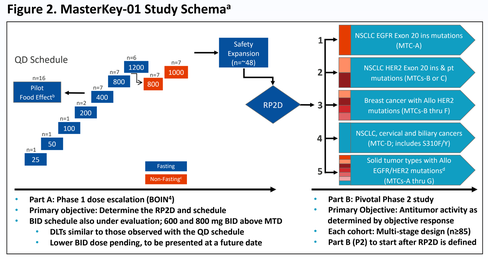


- BDTX-189 achieves dose-dependent regression and tumor growth inhibition across tumor models, including patient-derived xenografts[1,2]
- Active dose levels in humans were projected to be in the 400–800-mg QD range, based on the exposure–tumor growth inhibition relationship in multiple mouse tumor models harboring *EGFR/HER2* allosteric mutations[2]
- MasterKey-01 Part A is the Phase 1 dose escalation study of BDTX-189 to evaluate the RP2D, schedule, safety profile, PK, and preliminary evidence of efficacy in patients with solid tumors harboring diverse *EGFR* and *HER2* alterations[3]

Methods/Study Design

BDTX-189 is being evaluated in the MasterKey-01 trial to determine RP2D for Part B pivotal Phase 2 study (**Figure 2**)

Figure 2. MasterKey-01 Study Schema[a]



- **Part A: Phase 1 dose escalation (BOIN[4])**
- **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**
- **Part B: Pivotal Phase 2 study**
- **Primary Objective: Antitumor activity as determined by objective response**
- **Each cohort: Multi-stage design (n≥85)**
- **Part B (P2) to start after RP2D is defined**

[a]Figure summarizes number of patients in Full Analysis Set (ie, those who received at least 1 dose of study drug).
[b]Single dose crossover study at 400 mg. On day 5, patients begin dosing with 800 mg QD.
[c]Administered with meal of patient's preference.
[d]Patients not otherwise eligible for first 4 cohorts.

Key Study Eligibility Criteria

Parts A & B

- Histological- or cytological-confirmed locally advanced or metastatic solid tumor with no standard of care therapy or for whom standard therapy is considered unsuitable or intolerable, as determined by the Investigator
- ECOG PS 0–1
- Adequate organ function, including LVEF ≥50% and QTc ≤480 msec
- Treated, asymptomatic CNS malignancy allowed
- Concomitant proton-pump inhibitors excluded

Part A (Phase 1) Only

- Solid tumor harboring:
  - Allosteric *HER2 or 3* mutation
  - *EGFR/HER2* exon 20 insertion mutation
  - HER2+
  - *EGFR* exon 19 or *L858R* mutation
- Tumor tissue and measurable disease not mandatory
- Fresh biopsy for pharmacodynamics assessment at relevant doses

Part B (Phase 2) Only

- Solid tumor harboring
  - Allosteric *HER2* mutation
  - *EGFR/HER2* exon 20 insertion mutation
- Mutation by Institution CLIA-certified next-generation sequencing test
- Tumor tissue for retrospective confirmation
- Measurable disease by RECIST 1.1
- Response to prior EGFR/HER2-directed TKI excluded

Baseline Characteristics

The demographics for MasterKey-01 includes heavily pretreated patients expressing multiple *EGFR/HER2* alterations across multiple solid tumor types (**Table 1**)

Table 1. Demography

Characteristics	25–400 mg QD Fasting n = 12	800 mg QD (+ FE) Fasting n = 21	800 mg QD (+ FE) *Non-Fasting* n = 9	1000 mg QD *Non-Fasting* n = 7	1200 mg QD Fasting n = 6
Age, median (range)	64 (45-75)	65 (39-83)	59 (45-70)	63 (40-80)	57 (47-64)
ECOG PS, 0/1	4/8	3/18	7/2	4/3	1/5
Race (White/Asian/Black/Other[a])	9/0/1/2	13/2/1/5	7/1/0/1	4/2/0/1	4/2/0/0
# of prior lines of therapy[b]					
1 line	3	4	0	1	0
2 lines	2	3	6	2	2
≥3 lines	7	14	3	4	4
Tumor types					
Lung	4	9	5	0	2
Breast	1	2	0	1	2
CRC (colon, rectal)	3	0	1	1	0
Biliary tract (cholangio, gall bladder)	1	2	0	0	0
Esophageal	1	1	0	0	0
Other[c]	2	7	3	5	2
Mutations					
EGFR Exon 20 mutations (MTC-A)	2	3	3	0	0
HER2 Exon 20 alterations (MTCs-B & C)	4	4	1	1	1
Allo-HER2 mutations (MTCs-D thru G)	5	4	2	2	0
Canonical EGFR/HER2 mutations (Exon 19 del, L858R) or HER3	0	3	0	0	1
HER2 amplified	1	5	3	2	4
Other allo-HER2 mutations	0	2	0	0	0
Missing	0	0	0	2	0

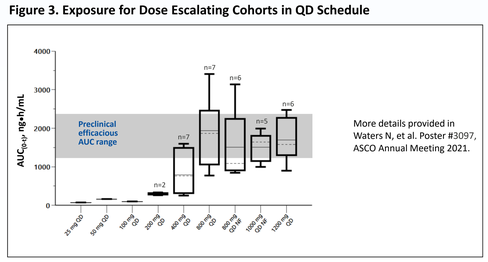
[a]Denotes American Indian/Alaskan, multiple, not reported, other or unknown. [b]Line of therapy data not yet available in clinical database for all patients. [c]Includes cervical, CUP, endometrial, kidney, liver, ovarian, prostate, pancreas, salivary, signet ring cell, urothelial, and uterine.

Pharmacokinetics

Predicted efficacious exposure achieved at ≥800 mg QD (**Figure 3**)

- Dose-dependent increases in exposure up to 800 mg QD, plateau of exposures observed at >800 mg QD

Figure 3. Exposure for Dose Escalating Cohorts in QD Schedule



More details provided in Waters N, et al. Poster #3097, ASCO Annual Meeting 2021.

Safety

800 mg is the preliminary RP2D for the QD schedule (**Tables 2** and **3**)

- No DLTs observed at doses of ≤800 mg QD fasting and non-fasting in the dose escalation cohorts
- 1200 mg QD fasting exceeded the MTD
- 1000 mg QD non-fasting did not exceed the MTD by BOIN, but will not be explored further because of overall toxicity profile

Table 2. DLTs and Adverse Events Requiring Dose Reductions in QD Schedule

	25-400 mg QD Fasting	800 mg QD (Fasting and *Non-Fasting*)	1000 mg QD *Non-Fasting*	1200 mg QD Fasting
Patients with DLTs/DLT-evaluable[a] patients (during dose escalation)	0/12	0/12	2/6[c]	2/5
DLT adverse events	NA	NA	•Diarrhea (2 G3) •Nausea (G1) •Increased creatinine (G3) •Bilirubin increased (G2)	•Diarrhea (1 G2; 1 G3) •Vomiting (G2)
Patients with AEs requiring dose reduction/total patients[b]	0/12	6/30	1/7	2/6
Dose reduction adverse events	NA	•Diarrhea (1 G2; 1 G3) •Nausea (1 G2; 1 G3) •Fatigue (G2) •ALT increased (G2)	•Diarrhea (G2) •Back pain (G3)	•Diarrhea (1 G2; 1 G3) •Vomiting (G2)

[a]DLT evaluable: patients in dose escalation Phase (excluding food effect) who receive at least 75% of the planned doses during Cycle 1 and complete all required safety evaluations or who have a DLT in Cycle 1.
[b]Includes full analysis group, including patients enrolled to food-effect lead-in cohort.
[c]As of April 23, 2021.

- Most common (≥20%) treatment-emergent adverse events regardless of causality at 800 mg QD (fasting or non-fasting) were nausea, diarrhea, vomiting, fatigue, ALT increased, and AST increased
  - Majority were grade 1-2 with no need for dose modification
  - Intolerable grade 2 and grade 3 events were mostly reversible with dose hold and/or reduction
  - Dose reduction was observed in 6 of 30 patients (20%)
  - Skin disorders, including rash, were infrequent
- 800 mg non-fasting is the preliminary RP2D for the QD schedule
  - 1000 mg QD non-fasting did not exceed the MTD but will not be explored further because of overall toxicity profile
  - Administration with food may favorably modulate GI tolerability

Table 3. Most Common Treatment-Related Adverse Events

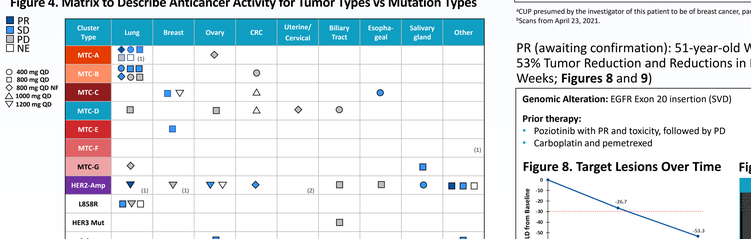
Related Adverse Event (reported in ≥3 patients in any cohort)	25-400 mg QD Fasting n=12		800 mg QD + food-effect Fasting n=21		800 mg QD + food-effect *Non-Fasting* n=9		800 mg QD + food-effect *Fasting & Non-Fasting* n=30		1000 mg QD *Non-Fasting* n=7[a]		1200 mg QD Fasting n=6	
	Any Grade %	Grade 3 %	Any Grade %	Grade 3 %	Any Grade %	Grade 3 %	Any Grade %	Grade 3 %	Any Grade %	Grade 3 %	Any Grade %	Grade 3 %
Any Related AE	50	0	95	24	89	22	93	23	100	43	83	50
Diarrhea	25	0	52	10	44	0	50	7	86	29	50	33
Nausea	17	0	48	5	56	11	50	7	43	0	33	0
Vomiting	8	0	29	5	33	0	30	3	29	0	67	0
ALT increased	8	0	24	10	11	11	20	10	29	0	17	0
AST increased	8	0	14	5	11	0	13	3	14	0	17	0
Blood bilirubin increased	0	0	0	0	0	0	0	0	43	0	0	0
Fatigue	8	0	19	0	22	0	20	0	57	14	17	0
Skin disorders[a]	8	0	14	0	11	0	13	0	0	0	17	0
Decreased appetite	8	0	14	0	0	0	10	0	14	0	0	0

[a]Include following adverse event terms: rash, dermatitis acneiform, rash morbilliform, dry skin, urticaria. [b]Data incomplete as of cutoff date. Note: No Grade 4 or 5 events reported.

Efficacy

Evidence of anticancer activity, including PRs, across tumor types and mutations (**Figure 4**)

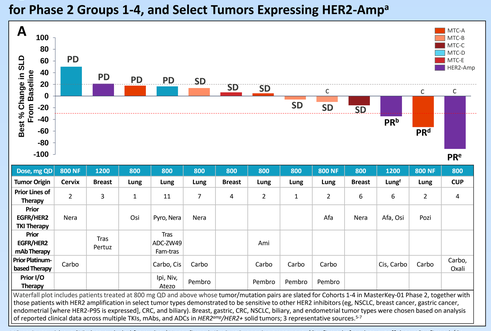
Figure 4. Matrix to Describe Anticancer Activity for Tumor Types vs Mutation Types



Responses are not necessarily confirmed. SD observed at least 30 days after first dose of study drug and includes 2 patients with non-measurable disease at baseline with non-CR/non-PD assessment.
Number in parentheses represent number of patients on-treatment, but yet to have a post-baseline assessment.
NE = patients who discontinued treatment prior to first post-baseline assessment or who are otherwise not evaluable per RECIST criteria.
Two patients excluded due to missing mutation information.
Tumor category of "Other" includes kidney (n=1), pancreas (n=1), prostate (n=1), CUP (n=1), and urinary bladder (n=1).

Evidence of anticancer activity in patient groups treated with ≥800 mg QD (**Figure 5**)

Figure 5A. Best Response for Subset of Patients in Tumor/Mutation Pairs Slated for Phase 2 Groups 1-4, and Select Tumors Expressing HER2-Amp[a]

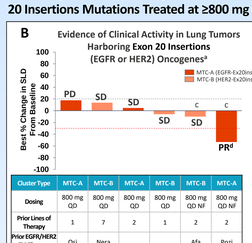


Dose, mg QD	800 NF	1200	800	800	800	800	800	800	800 NF	800	1200	800 NF	800
Tumor Origin	Cervix	Breast	Lung	Lung	Lung	Breast	Lung	Lung	Lung	Breast	Lung[f]	Lung	CUP
Prior Lines of Therapy	2	3	1	11	7	4	2	1	2	6	6	2	4
Prior EGFR/HER2 TKI Therapy	Nera		Osi	Pyro, Nera	Nera				Afa	Nera	Afa, Osi	Pozi	
Prior EGFR/HER2 mAb Therapy		Tras Pertuz		Tras ADC-ZW49 Fam-tras			Ami						
Prior Platinum-based Therapy	Carbo			Carbo, Cis	Carbo		Carbo	Carbo	Carbo		Cis, Carbo	Carbo	Carbo, Oxali
Prior I/O Therapy				Ipi, Niv, Atezo	Pembro		Pembro	Pembro	Pembro				

Waterfall plot includes patients treated at 800 mg QD and above whose tumor/mutation pairs are slated for Cohorts 1-4 in MasterKey-01 Phase 2, together with those patients with HER2 amplification in select tumor types demonstrated to be sensitive to other HER2 inhibitors (eg, NSCLC, breast cancer, gastric cancer, endometrial [where HER2-PS5 is expressed], CRC, and biliary). Breast, gastric, CRC, NSCLC, biliary, and endometrial tumor types were chosen based on analysis of reported clinical data across multiple TKIs, mAbs, and ADCs in HER2[mut]/HER2+ solid tumors; 3 representative sources.[1,2]

[a]12 patients without SLD data excluded from plot. [b]Unconfirmed. [d]Patient is ongoing treatment. [e]Confirmed after data cutoff date. [f]Confirmed. [c]Co-occurring EGFR Exon 19 del mutation.

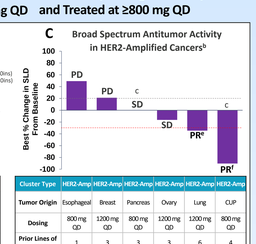
Figure 5B. Best Response for Subset of Patients With Lung Cancer expressing *EGFR/HER2* Exon 20 Insertions Mutations Treated at ≥800 mg QD



Cluster Type	MTC-A	MTC-B	MTC-A	MTC-B	MTC-B	MTC-A
Dosing	800 mg QD	800 mg QD	800 mg QD	800 mg QD	800 mg QD NF	800 mg QD NF
Prior Lines of Therapy	1	7	2	1	2	2
Prior EGFR/HER2 TKI Therapy	Osi	Nera			Afa	Pozi
Prior EGFR/HER2 mAb Therapy			Ami			
Platinum-based Therapy		Carbo	Carbo	Carbo	Carbo	Carbo
I/O Therapy		Pembro	Pembro	Pembro	Pembro	

Waterfall plot reflects data for a subset of patients from the Figure 5A, representing NSCLC patients expressing EGFR or HER2 Exon 20 ins mutations and treated at doses of ≥800 mg QD.

Figure 5C. Best Response for Subset of Patients Expressing *HER2* Amplification and Treated at ≥800 mg QD



Cluster Type	HER2-Amp	HER2-Amp	HER2-Amp	HER2-Amp	HER2-Amp	HER2-Amp
Tumor Origin	Esophageal	Breast	Pancreas	Ovary	Lung	CUP
Dosing	800 mg QD	1200 mg QD	800 mg QD	1200 mg QD	1200 mg QD	800 mg QD
Prior Lines of Therapy	1	3	3	3	6	4
Prior EGFR/HER2 TKI Therapy					Afa, Osi	
Prior EGFR/HER2 mAb Therapy	Tras	Tras Pertuz		Marget		
Platinum-based Therapy	Oxali		Oxali	Carbo	Cis Carbo	Carbo, Oxali

Waterfall plot represents patients with HER2 amplification and treated at ≥800 mg QD. This includes patients from all tumor types expressing HER2 amplification, including and beyond those included in Figure 5A.

[a]Three patients without SLD data excluded from plot. [b]Eight patients without SLD data excluded from plot. [e]Patient is ongoing treatment. [d] Confirmed after data cutoff date. [e]Unconfirmed. [f]Confirmed.

Patient Case Studies

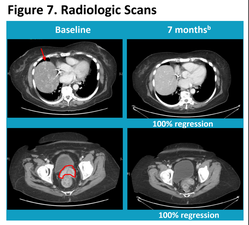
Confirmed PR: 73-year-old Woman With Cancer of Unknown Primary[a]; PR With 90% Reduction (On Study 24+ Weeks; **Figures 6** and **7**)

Genomic Alteration: HER2-amplification
Prior therapy:
- Carbo/taxol
- FOLFIRINOX
- Everolimus

Treatment regimen: on study
- BDTX-189 800 mg daily (fasting)
- No ongoing related toxicity, had brief episodes of G1 diarrhea

Figure 6. Target Lesions Over Time

Figure 7. Radiologic Scans



[a]CUP presumed by the investigator of this patient to be of breast cancer, pancreato-biliary or upper gastrointestinal origin.
[b]Scans from April 23, 2021.

PR (awaiting confirmation): 51-year-old Woman With NSCLC (EGFR Exon 20) With 53% Tumor Reduction and Reductions in Diffuse Lung Disease (On Study 13+ Weeks; **Figures 8** and **9**)

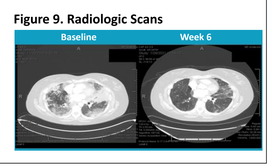
Genomic Alteration: EGFR Exon 20 insertion (SVD)

Prior therapy:
- Poziotinib with PR and toxicity, followed by PD
- Carboplatin and pemetrexed

Treatment regimen: on study
- BDTX-189, 800 mg QD NF
- Controlled, low-grade diarrhea
- Off oxygen starting at ~9 weeks

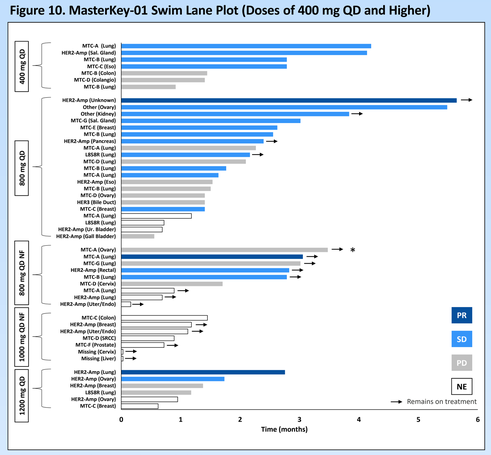
Figure 8. Target Lesions Over Time

Figure 9. Radiologic Scans



Swim Lane Plot

Figure 10. MasterKey-01 Swim Lane Plot (Doses of 400 mg QD and Higher)



*PD per RECIST because a lesion was not documented at baseline.

Conclusions and Discussion

- **BDTX-189 is an orally available inhibitor of *EGFR/HER2* alterations currently being evaluated in the MasterKey-01 P1/2 study**
  - **QD escalation is complete; BID escalation still underway**
  - **Predicted efficacious exposures achieved at ≥800 mg QD**
- **BDTX-189 was well tolerated at 800 mg QD**
  - **Medically manageable gastrointestinal AEs predominated, the majority grade 1 or 2**
  - **Skin disorders were low grade and infrequent**
- **Preliminary evidence of anticancer activity was observed in heavily pretreated patients across tumor types and MTCs**
  - **Anticancer activity was observed in patients who received prior EGFR/HER2 targeted therapies, a clinical setting where other TKIs perform poorly[8,9]**
- **These data support further evaluation of BDTX-189 in multiple cancer types with multiple *EGFR/HER2* genetic alterations**

References

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Abbreviations

afa, afatinib; ALT, alanine aminotransferase; ami, amivantamab; AMP, amplified; AST, aspartate transaminase; atezo, atezolizumab; AUC, area under the curve; $AUC_{0\text{-}tf}$, area under the plasma concentration-time curve; BID, twice daily; BOIN, Bayesian Optimal Interval Design; carbo, carboplatin; colangio, cholangiocarcinoma; cis, cisplatin; CLIA, Clinical Laboratory Improvement Amendments; cPR, confirmed partial response; CRC, colorectal cancer; CUP, cancer of unknown primary; DLT, dose-limiting toxicity; ECD, extracellular domain; EGFR, epidermal growth factor receptor; ECOG, Eastern Cooperative Oncology Group; fam-tras, fam-trastuzumab; FE, food effect; HER2, human epidermal growth factor receptor 2; Eso, esophageal; I/O, immuni-oncology; ipi, ipilimumab; JMD, juxtamembrane domain; KD, kinase domain; LVEF, left ventricular ejection fraction; mAb, monoclonal antibody; marget, margetuximab; MTC, mutational cluster; MTD, maximum tolerated dose; NE, nonevaluable; nera, neratinib; NF, non-fasting; niv, nivolumab; NSCLC, non–small cell lung cancer; osi, osimertinib; oxali, oxaliplatin; PD, progressive disease; pertuz, pertuzumab; pembro, pembrolizumab; PK, pharmacokinetics; pozi, poziotinib; PR, partial response; PS, performance status; pyro, pyrotinib; QD, once daily; QTc, QT interval; RECIST, response evaluation criteria in solid tumors; RP2D, recommended Phase 2 dose; Sal. Gland, salivary gland; SD, stable disease; SLD, sum of longest diameters; SRCC, signet ring cell cancer; TKI, tyrosine kinase inhibitor; tras, trastuzumab; uPR, unconfirmed PR; Ur. Bladder, urinary bladder; Uter/Endo, uterus/endometrial; WT, wild-type.

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Data presented is as of April 2, 2021, unless otherwise noted. This is an ongoing study and is undergoing active data entry and cleaning