BLACK DIAMOND THERAPEUTICS, INC.

Abbreviated Clinical Study Report

Masterkey-01: A Phase 1/2, Open-Label, Two-Part, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of BDTX-189, an Inhibitor of [redacted] Mutations, in Patients with Advanced Solid Malignancies

Protocol Identifier:	BDTX-189-01
Indication studied:	Solid tumors (advanced solid malignancies)
Developmental phase of study:	Phase 1/2
Investigational product:	BDTX-189
Sponsor:	Black Diamond Therapeutics, Inc. [redacted]
Study initiation date:	16 Jan 2020 (First patient, first dose)
Study completion date:	02 Sep 2022 (Study discontinuation)
Sponsor medical monitor:	[redacted] Telephone: [redacted]
Date report issued:	12 July 2023

This study was conducted in accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

Confidentiality Statement

1. SYNOPSIS

Name of Sponsor/Company:
Black Diamond Therapeutics, Inc.

Name of Finished Product:
BDTX-189 Tablet

Name of Active Ingredient:
BDTX-189

Title of Study: Masterkey-01: A Phase 1/2, Open-Label, Two-Part, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of BDTX-189, an Inhibitor of [redacted] Mutations, in Patients with Advanced Solid Malignancies

Study center(s):
20 sites enrolled patients in the study (3 additional sites had screen failures only).

Publications (reference):

Schram AM, Rodon J, Patel MR, Jauhari S, Sachdev J, et al. 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 [redacted] mutations, in patients with advanced solid malignancies. J Clin Oncol. 39 (2021): 3086.

Waters N, Patel MR, Schram AM, Rodon J, Jauhari S, et al. Clinical pharmacokinetics of BDTX-189, an inhibitor of [redacted] in patients with advanced solid malignancies in MasterKey-01 study. J Clin Oncol. 39 (2021): 3097.

Study period: Approximately 2.5 years Date first patient enrolled: 16 Jan 2020 (First patient first dose) Date last patient completed: 02 Sep 2022 (Study discontinuation)	**Phase of development:** Phase 1/2

Objectives:

Study BDTX-189-01 was planned as a 2-phase study; however, only phase 1 (part A) was completed because the study and the associated development program were terminated early by the sponsor. Phase 2 (part B) was not initiated. Although preliminary data demonstrated a favorable safety profile and early signs of clinical activity using BDTX-189, the sponsor terminated the study and the program due to the rapid evolution of the treatment landscape in non-small cell lung cancer (NSCLC) harboring either [redacted] or [redacted] mutations, allowing for near-term prioritization of the sponsor's other pipeline products.

Primary:

- Phase 1: Determine the recommended phase 2 dose (RP2D) and schedule of BDTX-189 administered orally in patients with advanced solid malignancies.
- Phase 2 (not completed): Assess the antitumor activity of BDTX-189 as a single agent in patients with [redacted] mutations, including [redacted] mutations.

Secondary:

- Phases 1 and 2 (phase 2 not completed): Assess the safety and tolerability of BDTX 189
- Phases 1 and 2 (phase 2 not completed): Investigate the pharmacokinetics (PK) of BDTX-189 using population PK methods and explore correlations between PK, response, and/or safety findings
- Phase 1: Establish the PK of BDTX-189 and circulating metabolite profile after a single dose and at steady state
- Phase 1: Evaluate the preliminary efficacy and antitumor activity of BDTX-189 as a single oral agent
- Phase 1: Assess the effect of food on the PK of BDTX-189
- Phase 2 (not completed): Assess additional measures of efficacy and antitumor activity of BDTX 189 as a single agent
- Phase 2 (not completed): Assess patient outcome by evaluation of patient-reported outcomes

Methodology:

Dose Escalation Phase 1 (Part A):

BDTX-189 was given orally in 21-day cycles at escalating doses. A Bayesian optimal interval (BOIN) design was used to determine the maximum tolerated dose (MTD). The selected MTD was to be based on safety, tolerability, PK, food effect, and preliminary antitumor activity of BDTX-189. Prior to enrollment into a subsequent dose cohort, the Safety Review Committee (SRC) reviewed the data regarding the cohort and made recommendations to the sponsor as to the action for the next dose cohort; they also participated in the determination of the MTD/RP2D. One patient each was enrolled in the 25, 50, and 100 mg cohorts; 2 patients were enrolled in the 200 mg cohort once daily. If no grade 2 or higher drug-related adverse event (AEs) were observed, cohorts of 3 or more patients were planned at up to 400, 800, 1200, and 1600 mg once daily; patients were dosed at 400, 800, 1000, and 1200 mg once daily. The target toxicity rate for the MTD was $\phi = 0.3$. During dose escalation, patients were treated initially under fasted conditions, but patients in later cohorts (800 mg and 1000 mg once daily) received treatment under not fasted conditions.

A parallel, twice-daily, dose-escalation of BDTX-189 on a 21-day schedule was also evaluated. Depending on the PK, tolerability, or pharmacodynamic analysis of the once daily dosing, the initial plan was to enroll patients in twice daily cohorts using a separate BOIN design. The design parameters were dependent on the cumulative observations from the once daily dose cohorts, but cohorts were tentatively planned at total daily doses of 400 mg, 800 mg, 1600 mg, and 2000 mg; twice daily dosing occurred at 800 mg twice daily fasted, but the dose was subsequently reduced to a 600 mg twice daily not fasted and then to 400 mg twice daily not fasted.

A separate pilot food effect assessment was completed to evaluate the effect of food on the PK of BDTX-189 at 400 mg once daily. Once the SRC deemed that the 400 mg daily dose regimen was tolerable, a fed (high- or low-fat meal)/fasted randomized crossover (fed-fasted or fasted-fed), single-dose, lead-in part was initiated (cycle 1 day -4 and -1 only). The outcome of the 400 mg food effect analyses supported the subsequent assessment of 800 mg and 1000 mg once daily in the not fasted state. Patients enrolled in the separate food effect lead-in assessment were rolled over to dose escalation cohorts. A safety expansion cohort was planned to receive treatment at the MTD or lower dose to further evaluate the safety, PK, and preliminary efficacy of BDTX-189; 17 patients were treated in the safety expansion cohort at the MTD/RP2D (determined to be 800 mg once daily not fasted). A reformulated 200 mg tablet with 40% drug load (small tablet) was introduced during the safety expansion.

Phase 2 was not initiated during the study and no patients were enrolled.

Number of patients (planned and analyzed):

Approximately 128 patients were planned to be enrolled in phase 1; 91 patients were enrolled in phase 1. Approximately 491 patients were planned to be enrolled in phase 2; however, phase 2 was not initiated.

Diagnosis and main criteria for inclusion:

Participants were patients at least 18 years of age with histologically or cytologically confirmed metastatic or locally advanced solid tumors with documented recurrence or disease progression from standard anticancer therapy carrying genetic alterations that were possibly associated with antitumor activity based on preclinical data for BDTX-189 as defined in the protocol. All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and a life expectancy of ≥ 3 months. For the phase 1 portion of the study, no standard therapy could be available according to the investigator. For the safety expansion cohort, measurable disease was required according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1.

Patients were excluded who had concurrent [redacted] mutations or a known [redacted] mutation, had received other recent antitumor therapy (defined in the protocol), or had a treatment response to approved or investigational [redacted] or [redacted] therapies. Patients with concurrent malignancies that could require active treatment that might interfere with the interpretation of the current study, had significant liver or hematologic laboratory abnormalities, significant cardiovascular disease, leptomeningeal or untreated central nervous system malignancies, or presence of poorly controlled gastrointestinal disorders were also excluded.

Test product, dose and mode of administration, batch number:

BDTX-189 tablets for oral administration; doses included 25, 50, 100, 200, 400, 800, 1000, and 1200 mg once daily and 400, 600, and 800 mg twice daily. Batch lot numbers include the following: 25 mg tablet - 3848978, 384808, 3848081, 3973887, 4128933, 4142224, and 4168838; 200 mg tablet (20% drug load) – 4211952, 4246715, 68923.10, 68923.12, 68923.13, 68923.14, 68923.15, 73137.01, 73137.02, 73137.03, 73940.1; 200 mg tablet (40% drug load) - FP285101-C21002, FP285101-C21003, FP285101-C21004, FP285101-CA21001

Duration of treatment: The longest duration of treatment was 596 days (approximately 1.5 years) until the sponsor terminated the study. Two patients continued treatment in a single-patient Investigational New Drug (IND).

Reference therapy, dose and mode of administration, batch number:

None

Criteria for evaluation:

Efficacy: Radiographic evaluations of tumor burden were collected. Categorization of objective tumor response to treatment was based on RECIST v1.1 criteria including complete response (CR), partial response (PR), stable disease (PR and stable disease only for patients with measurable disease at baseline), non-CR/non-progressive disease (only for patients with no measurable disease at baseline), progressive disease, or not evaluable.

PK: Blood samples were collected for PK evaluation at the predefined timepoints described in the protocol. The individual concentration-time data for BDTX-189 were evaluated with noncompartmental analysis.

Safety: Safety assessments consisted of monitoring and recording AEs and serious AEs (SAEs), and measurement of protocol-specified hematology, clinical chemistry, and other protocol-specified tests that were deemed critical to the safety evaluation of the study drug. AEs and SAEs were coded by preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA, Version 25.0). The severity of an AE was assessed by the investigator using the National Cancer Institute (NCI) common terminology Criteria for Adverse Events (CTCAE), Version 5.0.

Statistical methods: Not applicable for an abbreviated CSR. Planned analyses were defined in the Statistical Analysis Plan (11 Aug 2022).

SUMMARY – CONCLUSIONS

EFFICACY RESULTS: Early evidence of clinical activity was observed, despite the heavily pretreated population across evaluated tumor types and alterations. Of the 91 patients treated with BDTX-189, 1 (1.1%) patient had a best single RECIST response of CR (unconfirmed) and 4 (4.4%) patients had a best single response of PR (confirmed and unconfirmed). The patients with responses were all treated with BDTX-189 at ≥ 800 mg once daily; no responses were observed for any once daily dose groups ≤ 400 mg or for any of the twice daily dose groups. Patients with [redacted] amplified or overexpressing tumor alterations at baseline had the highest number of confirmed responses.

PK RESULTS: Oral absorption of BDTX-189 was generally rapid with a median time to maximum plasma concentration (t_{max}) ranging from 0.5 to 4 hours across dose groups and exposure days (Days 1 and 15). Median elimination halflife ($t_{½}$) was short and ranged from 2.26 to 4.45 hours for the 400 mg, 800 mg and 1200 mg once daily fasted dose groups, and 1.69 to 2.20 hours for the 800 and 1000 mg once daily not fasted groups. Exposures (maximum plasma concentration [C_{max}] and area under the plasma concentration-time curve from time 0 to 24 hours postdose [AUC_{0-24}]) increased with increasing dose, but in a less than dose proportional manner before an exposure plateau was reached at doses ≥800 mg. Following multiple dosing (day 15), exposures in the 800 mg once daily not fasted cohort were similar to that in the 800 mg once daily fasted cohort.

The pilot food effect assessment showed that when BDTX-189 was taken with a high-fat breakfast, higher C_{max} and area under the plasma concentration-time curve from time 0 to 8 hours postdose (AUC_{0-8}) exposures, and a slightly delayed t_{max}, were seen compared with fasted exposures.

SAFETY RESULTS: Overall, no dose-limiting toxicities (DLTs) were grade >3 and none were considered serious across dose groups. The majority of DLTs were gastrointestinal in nature including diarrhea, vomiting, and nausea. The first DLT was reported at the dose of 1200 mg once daily fasted. Two patients experienced DLTs of diarrhea (one patient also experienced DLTs of grade 2 vomiting and grade 1 nausea) at 1200 mg once daily fasted; therefore, this dose was considered above the MTD. Dosing was then reduced to 800 mg once daily not fasted, in which one patient experienced grade 3 ALT increased. The dose was increased to 1000 mg once daily not fasted for the next cohort; however, 2 patients reported DLTs in this dose group of grade 3 diarrhea (one patient also experienced a DLT of grade 1 nausea) and the dose was also considered above the MTD.

Across all dose groups, BDTX-189 was generally well tolerated with medically manageable toxicities. Overall, the safety profile compared favorably in the context of other agents in the drug class including the gastrointestinal effects and fatigue, but without the typical dermatologic reactions. Approximately 60% to 80% of all patients had at least one dose modification during the study. Of note, the percentage of days with a dose reduction or drug interruption were substantially higher for the 800 mg once daily fasted group compared with the 800 mg not fasted group (95% versus 13%).

All patients (100%) in the study experienced at least one treatment-emergent AE (TEAE) across all dose groups. Two patients experienced AEs leading to death: one patient in the 400 mg twice daily not fasted group and one patient in the 600 mg twice daily not fasted group each died from treatment-related pneumonitis. For patients receiving once daily dosing during dose escalation, the most common treatment-related AEs reported by preferred terms were diarrhea, nausea, vomiting, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, and fatigue. Treatment-related SAEs experienced by ≥ 2 patients treated once daily were pneumonia and vomiting. No SAEs were experienced by more than 1 patient treated in the total 800 mg once daily dose group. Twice daily dose groups had a similar AE profile as the once daily dose groups. Patients in the 800 mg once daily not fasted group experienced fewer gastrointestinal events, fewer TEAEs leading to dose interruption or dose reduction, and fewer TEAEs leading to discontinuation of study drug as compared with the 800 mg once daily fasted group.

With little evidence of clinical activity at the lower once daily and twice daily doses, a greater number of DLTs reported in the higher doses, slightly higher exposure, and fewer gastrointestinal AEs, the sponsor in collaboration with the SRC concluded that 800 mg once daily not fasted was the appropriate MTD and RP2D for BDTX-189.

CONCLUSIONS:

- The BDTX-189 MTD and RP2D were identified as 800 mg once daily not fasted.
- Early evidence of clinical activity was observed, despite the heavily pretreated patient population.
- Of the 5 patients with a best single RECIST response (unconfirmed or confirmed) of CR or PR, 4 patients received 800 mg once daily (2 fasted and 2 not fasted); 3 patients had [redacted] amplified or overexpressing tumor alterations at baseline.
- BDTX-189 was generally well tolerated with medically manageable toxicities under the conditions of this study.

Date of the report: 12 July 2023