A Phase 1 Study to Assess BDTX-1535, an Oral EGFR Inhibitor, in Patients with Glioblastoma or Non-Small Cell Lung Cancer

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Abstract: CT127

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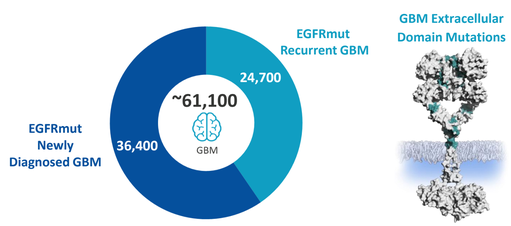
Background

Epidermal growth factor receptor (EGFR) is a potent oncogene commonly altered in many cancers, including non-small cell lung cancer (NSCLC) and glioblastoma multiforme (GBM). While currently approved EGFR-targeted agents have shown robust clinical benefits in NSCLC patients with common EGFR mutations, acquired and intrinsic resistance to treatment are frequently observed. No targeted therapy has been approved for GBM. EGFR can be expressed as complex heterogenous alterations and often co-occur as splice variants, mutations and amplification in GBM. Targeting oncogenic EGFR alterations remains a critical unmet medical need in both NSCLC and GBM.

BDTX-1535 is a brain penetrant, mutant selective, irreversible EGFR MasterKey inhibitor targeting osimertinib acquired resistance mutations in 2nd line NSCLC patients as well as 1st line NSCLC intrinsic EGFR mutations. In GBM, BDTX-1535 targets EGFR alterations. BDTX-1535 is an orally available, 4th generation EGFR inhibitor and is designed to treat CNS tumors and metastases. Preclinical studies suggest that BDTX-1535 has the potential to be clinically active in suppressing tumor growth in patients with GBM and NSCLC with or without CNS metastases.

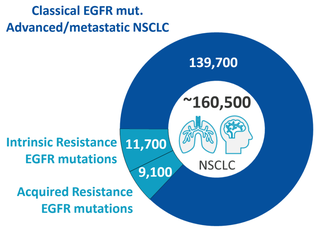
Addressable Patient Population (US/EU/Japan/China) With EGFR Mutations

GBM Patient Population

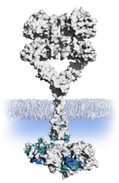


GBM Extracellular Domain Mutations

NSCLC Patient Population



NSCLC Kinase Domain Mutations



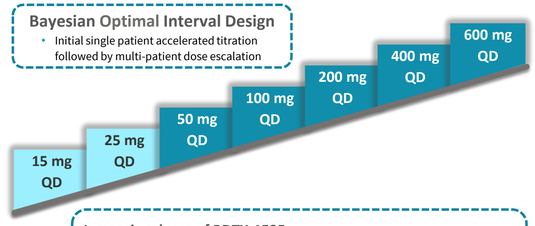
Study Design (NCT05256290)

- A Phase 1, first-in-human, open-label, multicenter study to assess the safety, tolerability, PK, CNS activity, and preliminary antitumor activity of BDTX-1535 in patients with either advanced/metastatic NSCLC harboring sensitive EGFR mutations, with or without CNS disease, or GBM expressing EGFR alterations
  - Enrollment was initiated in 2022 and dose escalation is ongoing. Dose Expansion cohorts are expected to open in 2H 2023. For additional information, please contact BDTX_1535_101_Study@bdtx.com
- Two-part study: monotherapy dose escalation and disease-specific dose expansion including 3 monotherapy cohorts and one cohort in combination with temozolomide in newly diagnosed GBM
- Estimated enrollment: 120 participants

Monotherapy Dose Escalation Cohort

- Advanced/metastatic NSCLC with acquired resistance EGFR mutation (eg, C797S), following a 3rd generation EGFR inhibitor in the 1st-line setting
- Advanced/metastatic NSCLC with uncommon EGFR mutations (eg, G719X), following standard of care therapy with an EGFR inhibitor
- Recurrent GBM with confirmed EGFR alterations (including amplification, mutation, and/or variant)

Bayesian Optimal Interval Design
- Initial single patient accelerated titration followed by multi-patient dose escalation



Increasing doses of BDTX-1535
- Participants will receive a daily oral dose of BDTX-1535 as part of a 21-day cycle
- Intra-patient dose escalation is allowed after completion of ≥ 2 cycles without experiencing ≥Grade 2 toxicity deemed to be related to BDTX-1535

Objectives and Endpoints

Primary
- Incidence of study treatment-related dose-limiting toxicities during Cycle 1
- Determination of maximum tolerated dose and/or recommended Phase 2 dose

Secondary
- Safety, tolerability and PK
- Preliminary anti-tumor activity: ORR, DoR and DCR
- RECIST, version 1.1 for NSCLC or RANO for GBM
- PFS (including PFS6 and PFS12) and brain metastasis-free survival in NSCLC patients

Exploratory
- Biomarker parameter estimates

Preliminary Recommended Phase 2 Dose (RP2D) or Maximum Tolerated Dose (MTD)
Provisionally determined based on safety, tolerability PK, PD and preliminary anti-tumor activity

Disease Specific Dose Expansion Cohorts

Monotherapy (BDTX-1535) Expansion

- Advanced/metastatic NSCLC with acquired resistance EGFR mutation (eg, C797S), following a 3rd generation EGFR inhibitor in the 1st -line setting
- Advanced/metastatic NSCLC with uncommon EGFR mutations (eg, G719X), following standard of care therapy with an EGFR inhibitor
- Recurrent GBM with confirmed EGFR alterations with or without amplifications

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- Participants will receive a daily oral dose of BDTX-1535 as part of a 21-day cycle treatment
- Dose optimization for RP2D doses and evaluation of safety, PK, preliminary efficacy, biomarker parameter estimates, and select patient-reported outcome questions

Combination (BDTX-1535 + TMZ) Expansion

- Newly diagnosed GBM (postsurgical resection and radiation therapy with TMZ) harboring EGFR mutations or variants

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- Participants will receive BDTX-1535 with standard doses of TMZ as part of a 28-day cycle treatment
- Evaluation of safety, tolerability and combination RP2D

Eligibility Criteria

Key Inclusion Criteria Required for ALL Patients

- Minimum age: 18 years
- Dose escalation: Disease may be evaluable or measurable. Dose expansion: Disease must be measurable by RECIST v1.1 criteria (NSCLC) or RANO criteria (GBM)
- Adequate bone marrow or organ function
- Life expectancy of ≥ 3 months

Major Disease Specific Inclusion Criteria

Inclusion Criteria Required for NSCLC Patients Only
- Histologically or cytologically confirmed NSCLC, without small cell lung cancer transformation
- Locally advanced or metastatic disease, with or without CNS metastases
- Disease progression after standard of care or who refuse or are intolerant to treatment:
  - NSCLC with uncommon EGFR mutations (eg, G719X), following standard of care therapy with an EGFR inhibitor.
  - NSCLC with acquired resistance EGFR mutation (eg, C797S), following a 3rd generation EGFR inhibitor in the 1st line setting (in the absence of concurrent T790M)
- EGFR mutations identified by NGS in the absence of other known resistance mutations (eg, T790M, MET)

Inclusion Criteria Required for GBM Patients Only
- Histologically confirmed diagnosis of GBM according to 2021 WHO criteria wild-type IDH GBM and astrocytoma with molecular features of GBM
- Tumor evidence of EGFR alterations including amplification, variants, or mutations as determined in a local laboratory by NGS
- Karnofsky performance status ≥ 60%

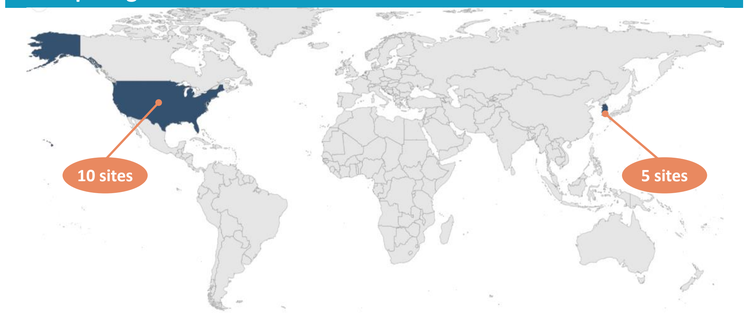
Recurrent GBM Patients Only
- Disease progression after treatment with available therapies that are known to confer clinical benefit, or who refuse or are intolerant to treatment.
- Radiological diagnosis of recurrent disease following available standard of care therapy of surgery, radiation, and/or TMZ

Newly Diagnosed GBM Patients Only
- Recovered from maximal debulking surgery (gross total resection or partial resection are also acceptable)
- Received radiation therapy and TMZ at least 6 weeks, but no more than 8 weeks, prior to Cycle 1 Day 1

Key Exclusion Criteria Required for ALL Patients

- Known resistant mutations in tumor tissue or ctDNA, including EGFR T790M, EGFR exon 20 insertion mutations, MET (including MET amplification), KRAS, or HER2 (C805S, T798I, or T862A)
- GBM patient treated with a prior EGFR inhibitor
- Symptomatic or radiographic leptomeningeal disease
- Symptomatic brain metastases or spinal cord compression requiring increasing corticosteroids or urgent clinical intervention

Participating Clinical Sites



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