A Phase 1 Study to Assess BDTX-1535, an Oral 4th Generation EGFR Inhibitor, in Patients with Non-Small Cell Lung Cancer and Glioblastoma

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Background
Epidermal growth factor receptor (EGFR) is a potent oncogene commonly altered in non-small cell lung cancer (NSCLC) and glioblastoma multiforme (GBM). Upon progression on 1st line osimertinib, NSCLC patients may present with a broad spectrum of classical, acquired and intrinsic resistance EGFR mutations. No targeted therapy has been approved for GBM. Targeting a broad spectrum of oncogenic EGFR alterations in NSCLC and GBM remains a critical unmet medical need.

BDTX-1535 is a 4th generation orally available brain penetrant irreversible EGFR Masterkey inhibitor targeting classical and intrinsic EGFR mutations and acquired after osimertinib C797S EGFR mutations in NSCLC. In GBM, BDTX-1535 has been previously shown to target multiple EGFR alterations found in NSCLC and GBM.

Study Design (NCT05256290)
- **Objectives and Endpoints**
  - Primary
    - Safety, tolerability and PK, ORR, DCR and PFS for BDTX-1535 for patients with EGFR T790M or T790M+ in GBM
    - Safety and PK, ORR and DCR of BDTX-1535 for patients with EGFR L858R in NSCLC
  - Secondary
    - PK, safety, tolerability, ORR and DCR of BDTX-1535 for patients with EGFR C797S
    - Safety and tolerability of BDTX-1535 in patients with classical EGFR mutations
    - Safety and tolerability of BDTX-1535 in GBM patients with CNS metastases

Eligibility Criteria

Key Inclusion Criteria Required for ALL Patients
- Metastatic or relapsed EGFR+ NSCLC
- Disease must be measurable by RECIST v1.1 criteria (NSCLC) and RANO-BM for patients with CNS metastases
- Adequate bone marrow or organ function
- Life expectancy of at least 3 months

NSCLC Inclusion Criteria for Expansion Cohorts
- Histologically or cytologically confirmed NSCLC, without small cell lung cancer transformation
- Locally advanced or metastatic disease, with or without CNS disease
- Ongoing or recent anticancer therapy
- Select patient based on classical or acquired EGFR mutations

EGFR Mutations Targeted by BDTX-1535
- L858R
- Del19
- EGFR C797S
- G719X
- L861X
- T790M
- Amplification, insertion, deletion, translocation, single point mutation, frameshift mutation

Key Exclusion Criteria Required for All Patients
- Known resistance to EGFR inhibitors including EGFR L858R insertions
- Presence of brain metastases or multiple brain metastases
- Symptomatic or radiographic leptomeningeal disease
- Ongoing or recent anticancer therapy
- Ongoing or recent radiation therapy

Study Sites
- For study sites visit: https://clinicaltrials.gov/ct2/NCT05256290

**NSCLC EGFR Mutation Landscape After 1st Line Osimertinib**

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<tr>
<th>Intrinsically Driven</th>
<th>Classical Drivers</th>
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<tbody>
<tr>
<td>Exon 19 deletion (eg, Del19)</td>
<td>L858R</td>
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<tr>
<td>G719X</td>
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<tr>
<td>L861X</td>
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**Study Expansion Cohorts (Open To Enrolment)**

Cohort 1: NSCLC with intrinsic driver EGFR mutations: advanced/metastatic NSCLC with intrinsic driver EGFR mutations (eg, G719X) following up to 2 lines of therapy with only 1 prior EGFR TKI regimen (third-generation preferred; other approved EGFR TKI acceptable)

Cohort 2: NSCLC with acquired resistance C797S EGFR mutation: advanced/metastatic NSCLC with acquired resistance C797S EGFR mutation following up to 2 lines of therapy, including only one EGFR TKI, which must be a third generation EGFR TKI (eg, osimertinib)

Cohort 3: Treatment naïve NSCLC with intrinsic driver EGFR mutations (eg, G719X) pending RP2D assessment in Cohort 1 and Cohort 2 (pending FDA discussion)

**Dose Escalation Is Complete** (see Poster Abstract# 35817)

**BTDX-1535 Monotherapy Dose Escalation (Study Completed)**

**Objectives and Endpoints**
- Primary
  - Incidence of study treatment-related adverse events occurring during Cycle 1
  - Determination of maximum tolerated dose and/or recommended Phase 2 dose

**BTDX-1535 NSCLC Expansion Cohorts**

Cohort 1: NSCLC with intrinsic driver EGFR mutations:advanced/metastatic NSCLC with intrinsic driver EGFR mutations (eg, G719X) following up to 2 lines of therapy with only 1 prior EGFR TKI regimen (third-generation preferred; other approved EGFR TKI acceptable)

Cohort 2: NSCLC with acquired resistance C797S EGFR mutation:advanced/metastatic NSCLC with acquired resistance C797S EGFR mutation following up to 2 lines of therapy, including only one EGFR TKI, which must be a third generation EGFR TKI (eg, osimertinib)

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