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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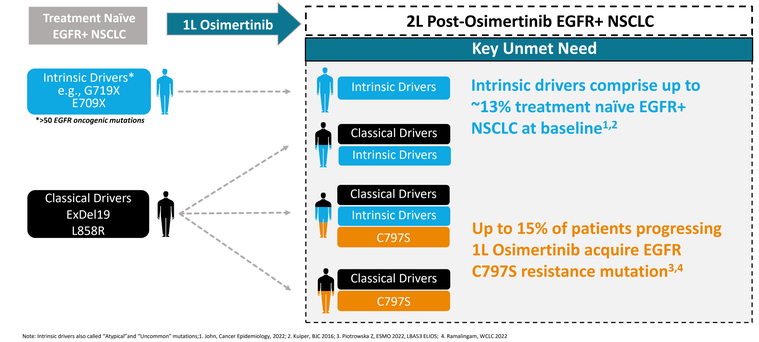
Abstract: 35836

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.

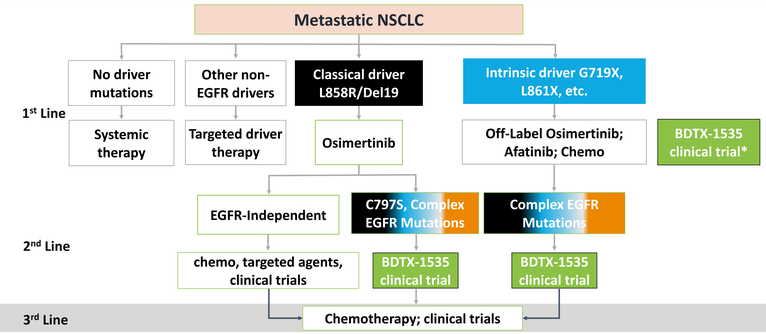
BDTX-1535 is a 4th generation orally available brain penetrant irreversible EGFR MasterKey inhibitor targeting classical and intrinsic EGFR mutations and acquired after osimertinib C797S EGFR mutations in NSCLC. In GBM, BDTX-1535 has been preclinically shown to target multiple EGFR alterations found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

NSCLC EGFR Mutation Landscape After 1st Line Osimertinib



Note: Intrinsic drivers also called "Atypical"and "Uncommon" mutations;1. John, Cancer Epidemiology, 2022; 2. Kuiper, BJC 2016; 3. Piotrowska Z, ESMO 2022, LBA53 ELIOS; 4. Ramalingam, WCLC 2022

NSCLC Treatment Landscape After 1st Line Osimertinib



* pending FDA discussion

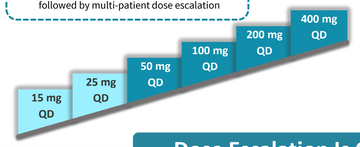
Study Design (NCT05256290)

- 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**
- Two-part study: monotherapy dose escalation and disease-specific dose expansions including 3 monotherapy cohorts in NSCLC. Expansion cohort in GBM is pending for further data assessment
- Dose escalation is complete and NSCLC **dose expansion cohort enrollment was initiated in 2023**
- GBM patients enrolled in dose escalation are being followed for progression free survival
- For additional information, please contact ClinicalTrials@bdtx.com
- Estimated enrollment: 120 participants

BDTX-1535 Monotherapy Dose Escalation (Study Completed)

- 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 intrinsic driver 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



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 RECIST1.1 for NSCLC or RANO for GBM
- PFS

Exploratory
- Biomarker parameter estimates

Dose Escalation Is Complete (see Poster Abstract# 35817)

NSCLC Expansion Cohorts (Open To Enrollment)

BDTX-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 the 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 (e.g., 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)

Objectives and Endpoints

Primary
- Overall response rate (ORR) as assessed per RECIST v1.1 or RANO-BM for patients with brain metastases

Secondary
- Durability of response (DoR)
- Safety, tolerability and PK
- Progression-free survival (PFS)
- Select patient-reported outcome questions

Exploratory
- Biomarker parameter estimates

Eligibility Criteria

Key Inclusion Criteria Required for ALL Patients

- Minimum age: 18 years
- 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 ≥ 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 metastases
- Disease progression after standard of care or who refuse or are intolerant to treatment:
  - **Cohort 1: NSCLC with intrinsic resistance EGFR mutations (eg, G719X), following ≤2 standard-of-care therapy including only one prior EGFR inhibitor (3rd generation preferred)**
  - **Cohort 2: NSCLC with acquired resistance C797S EGFR mutation, following ≤2 standard-of-care therapy with the only prior EGFR inhibitor being the 1st line 3rd generation (eg, osimertinib)**

  Note: therapies targeted for 3rd generation EGFR tyrosine kinase resistance are excluded for this patient population.
- EGFR mutations identified by NGS in the absence of other known resistance mutations (eg, T790M, MET)

EGFR Mutations Targeted by BDTX-1535

Classical Drivers [1]	Acquired Resistance [2]	Intrinsic Drivers [3]		
L858R exon 19 deletions (eg, *E746_A750del*)	*C797S*	*A859S*	*L718Q*	*S720F*
		D761Y	*L718Q/V*	*S768I*
		E709A/G/Q/V	*L718V*	*S811F*
		E709_T710delinsD	*L747S*	*V689M*
		G719A/C/D/R/S	*L792H*	*V769L/M*
		G724S	*L861R/Q*	*V774M*
		G779C	*P772L*	
		I744_K745insKIPVAI	*Q812Q*	
		L62R	*R776H*	

[1] Also referred to as common or canonical mutations
[2] Also referred to as secondary mutations
[3] Also referred to as non-classical, uncommon, atypical, inherent, or primary resistance mutations

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)
- Symptomatic or radiographic leptomeningeal disease
- Symptomatic brain metastases or spinal cord compression requiring increasing corticosteroids or urgent clinical intervention
- Ongoing or recent anticancer therapy.
- Ongoing or recent radiation therapy.

Study Sites

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

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