A Phase 1 Study to Assess BDTX-1535, an Oral 4th Generation EGFR Inhibitor, in Patients with Non-Small Cell Lung cancer and Glioblastoma: Preliminary Dose Escalation Results

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Background

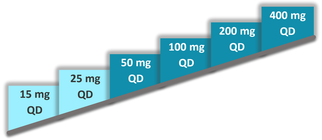
Epidermal growth factor receptor (*EGFR*) is a potent oncogene commonly altered in non-small cell lung cancer (NSCLC) and glioblastoma (GBM). For NSCLC, *EGFR* tyrosine kinase activity can be driven by classical driver (L858R and Ex19del), intrinsic (atypical or uncommon) driver (eg, L718Q, L861Q, S768I) mutations, and acquired after 3rd generation *EGFR* tyrosine kinase inhibitor (TKI) resistance C797S mutation. GBM is characterized by presence of extracellular domain *EGFR* alterations including mutations and fusions.

BDTX-1535 is an oral, highly potent, brain penetrant, selective, irreversible 4th generation that targets all these 3 classes of *EGFR* mutations in NSCLC and multiple EGFR alterations in GBM. BDTX-1535-101 is a first-in-human study enrolling patients with NSCLC harboring *EGFR* mutations following standard of care *EGFR* TKI therapy, or patients with recurrent GBM expressing *EGFR* alterations to determine the BDTX-1535 recommended Phase 2 dose (RP2D) (**NCT05256290**).

Initial dose escalation data demonstrating anti-tumor activity of BDTX-1535 in 12 efficacy evaluable NSCLC patients was announced on 27 June 2023.

Monotherapy Dose Escalation Study Design

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



Dose escalation of BDTX-1535
- Participants received 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 related to BDTX-1535
- 54 patients enrolled in dose escalation as of July 24, 2023

Objectives and Endpoints

Primary
- Determination of maximum tolerated dose (MTD) and RP2D

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

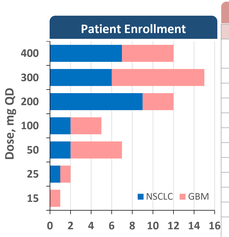
Exploratory
- Correlative biomarkers (ctDNA for NSCLC)

Patient Eligibility

NSCLC patients:
- Advanced/metastatic NSCLC with acquired resistance C797S EGFR mutation after prior EGFR TKI (3rd generation)
- Advanced/metastatic NSCLC with intrinsic driver EGFR mutations (eg, G719X) after prior EGFR TKI
- Other known resistance mechanisms are not eligible (exon20 insertion, T790M, met amplification, etc)

GBM patients:
- Recurrent GBM with EGFR alterations (including amplification, mutation, and/or variant)

Patient Characteristics (All Patients, N = 54)



GBM (n =27)	
Patient Characteristics	**All Treated**
Age, mean (range)	58.7 (41, 85)
Female	10 (37%)
Karnofsky PS	
90	4 (17%)
80	12 (50%)
70	5 (21%)
60	3 (13%)
Prior lines of therapies	
median (min, max)	2 (1, 4)
Prior anti-cancer agents	
TMZ	27 (100%)
Anti-angiogenic or CPIs	11 (41%)
Chemo	7 (26%)

NSCLC (n=27)	
Patient Characteristics	**All Treated**
Age, mean (range)	64 (46, 81)
Female	18 (67%)
ECOG PS	
0	7 (26%)
1	20 (74%)
Prior lines of therapies	
median (min, max)	2 (1, 9)
Prior anti-cancer agents	
EGFR TKI	27 (100%)
Chemo	19 (70%)
Anti-angiogenic or CPIs	11 (41%)
HER3-ADC	2 (7%)
Prior EGFR TKIs	
Osimertinib	23 (85%)
1st line treatment	17 (74%)
Erlotinib or gefitinib	9 (33%)
Afatinib	3 (11%)
Dacomitinib	1 (4%)
BLU-701	1 (4%)

BDTX-1535-101 Data Extract 24July2023

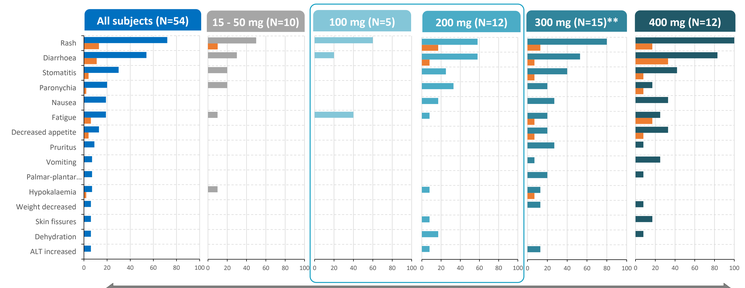
BLACK DIAMOND THERAPEUTICS

Dose Escalation Safety and PK Profile (All Patients, N=54)

- Most common treatment related adverse events (AEs) were rash, diarrhea, stomatitis, paronychia, nausea and fatigue
- Majority of treatment related AEs were mild or moderate
- No treatment related Grade 3 events were reported at 100 mg QD
- Most common treatment related Grade 3 events were rash, diarrhea, fatigue, decreased appetite, stomatitis

- No Grade 4 AEs were reported
- No dose limiting toxicity (DLTs) were observed at ≤200 mg
  - 1 DLT at 300 mg QD (with rash prophylaxis): diarrhea
  - 5 DLTs at 400mg QD: diarrhea, rash, anorexia, fatigue, stomatitis
- Maximum tolerated dose is 300mg QD
- Dose reductions: 1 (8%) pt at 200 mg QD; 5 (33%) pts at 300 mg QD

BDTX-1535 Treatment-Related Adverse Events*



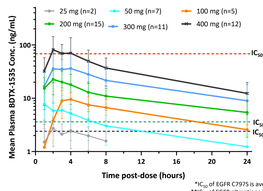
* Treatment emergent adverse events (TEAEs) occurring in ≥6% patients; **all patients in 300 mg cohort received rash prophylaxis
Rash group terms: rash, rash maculo-papular, dermatitis acneiform

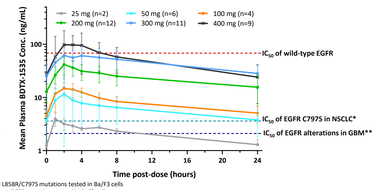
BDTX-1535 Plasma PK Profile on Day 1 By Dose Level (GBM and NSCLC Patients)

- Plasma exposure of BDTX-1535 increased dose proportionally
- Half-life of ~15h supports once daily dosing

BDTX-1535 Plasma PK Profile at Steady State By Dose Level (GBM and NSCLC Patients)

- Expected target coverage was achieved at dose levels ≥100mg QD
- Exposure-Safety assessment correlated with dose modifications during dose escalation





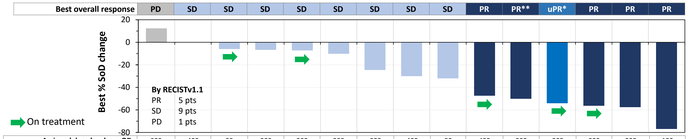
*IC90 of EGFR C797S is average of IC90 of Exon19del/C797S and L858R/C797S mutations tested in Ba/F3 cells
**IC90 of EGFR alterations in GBM is average IC90 of most prevalent EGFR mutations tested in Ba/F3 cells

Conclusions

- BDTX-1535 was well-tolerated up to 300mg QD with dose modifications proportionate to drug exposure
- Safety and tolerability profile was consistent with EGFR TKI class of drugs with no new safety signal
- Expected EGFR target coverage was achieved at dose levels ≥100mg QD
- NSCLC patients demonstrated profound decrease in mutant EGFR variant allele frequency and plasma ctDNA clearance at ≥100mg QD doses which was accompanied by radiographic response
- Confirmed radiographic responses by RECISTv1.1 were observed in heavily pretreated NSCLC patients with intrinsic driver mutations and acquired resistance C797S mutation
- Enrollment expansion cohorts to assess ORR in NSCLC patients with acquired resistance C797S or intrinsic driver EGFR mutations after prior EGFR TKI therapy is ongoing
- Evaluation of 100 mg QD and 200 mg QD doses for dose optimization for a pivotal study is ongoing in the expansion cohorts
- Additional dose escalation GBM patient data will be presented at a future scientific meeting

BDTX-1535 Efficacy and Biomarker Assessment in NSCLC Patients (N=27)

Radiographic Responses by RECISTv1.1 Were Observed in NSCLC Patients With EGFR Intrinsic Drivers and Acquired Resistance C797S Mutations



Assigned dose level, mg QD		300	400	25	200	200	200	400	50	400	300	200	200	300	100
EGFR mutation (Retrospective Central Testing)	Classical	L858R		Ex19Del#	Ex19del	L858R#	Ex19del	Ex19del		Ex19del	Ex19del	Ex19del	L858R		L858R	L858R
	Acquired	C797S		C797S#	C797S		C797S	C797S		C797S	C797S	C797S			C797S	C797S
	Intrinsic	L833V	G719A			E709V*		G724S	S768I				E709V	L747P		L718Q
Prior lines of therapy	1st line	Osi	Osi	Osi	Osi	Gefi	Osi	Osi	Erlo	Osi	CPI	Osi	Osi	Osi	C	Osi
	2nd line	Daco, Osi	C			C	CPI, C		C		Osi	Osi+Gefi	C	CPI/C	Osi	
	>2 line	CPI, C	Afa								C	BLU-701	C	C	C	

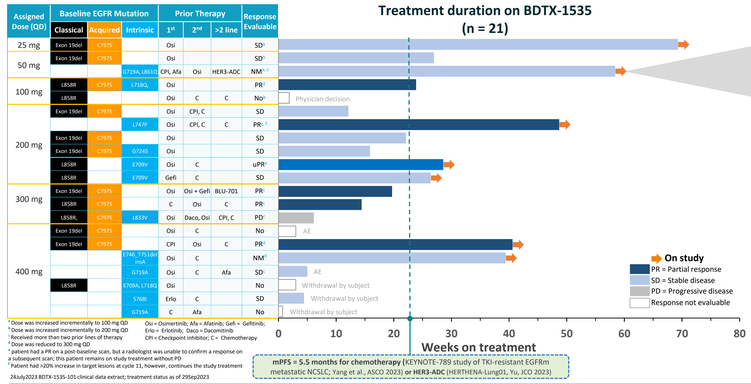
Osi = Osimertinib; Afa = Afatinib; Gefi = Gefitinib; Daco = Dacomitinib; Erlo = Erlotinib; CPI = Checkpoint inhibitor, C = Chemotherapy; # - mutations were absent on confirmatory test; * patient had a PR on a post-baseline scan, but a radiologist was unable to confirm a response on a subsequent scan; this patient remains on study treatment without evidence of PD. **%SoD was updated to -50% from prior data release
24July2023 BDTX-1535-101 clinical data extract

Efficacy Evaluable Subgroup of NSCLC Patients

Efficacy Evaluable Group	Number of Patients
Total NSCLC patients enrolled	27
Ineligible EGFR mutation based on retrospective NGS testing *	3
No tumor assessment at the time of data cut	3
Total NSCLC patients with eligible EGFR mutations (swimmers plot)	21
Non measurable disease	2
Discontinuation prior to post-baseline tumor assessment	4
Response evaluable patients ** (waterfall plot)	15

* retrospective central testing identified 3 patients from South Korea who received 1st generation EGFR TKI and had ineligible mutations at the time of study start
** includes 2 patients treated at starting doses below 100mg QD

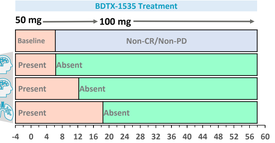
Emerging Evidence of Durable Anti-tumor Response of BDTX-1535 in NSCLC



* Dose was increased incrementally to 100 mg QD
* Dose was increased incrementally to 200 mg QD
* Received more than two prior lines of therapy
* Dose was reduced to 300 mg QD
* patient had a PR on a post-baseline scan, but a radiologist was unable to confirm a response on a subsequent scan; this patient remains on study treatment without PD
* Patient had >20% increase in target lesions at cycle 11, however, continues the study treatment
Osi = Osimertinib; Afa = Afatinib; Gefi = Gefitinib; Erlo = Erlotinib; Daco = Dacomitinib
CPI = Checkpoint inhibitor; C = Chemotherapy
24July2023 BDTX-1535-101 clinical data extract; treatment status as of 29Sep2023

mPFS = 5.5 months for chemotherapy (KEYNOTE-789 study of TKI-resistant EGFRm metastatic NCSLC; Yang et al., ASCO 2023) **or HER3-ADC** (HERTHENA-Lung01, Yu, JCO 2023)

Radiographic Response In A Patient With Complex G719A + L861Q EGFR Mutations (Non-Measurable Disease Only) *



* Patient received prior chemotherapy, CPI, afatinib, osimertinib, HER3-ADC, RT

Enrollment is ongoing into NSCLC disease-specific expansion cohorts

Cohort 1: NSCLC patients with acquired resistance C797S after ≤2 prior lines of therapy with osimertinib as the only prior EGFR TKI

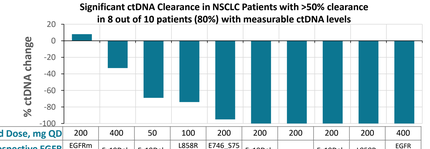
Cohort 2: NSCLC patients with intrinsic driver mutations after ≤2 prior lines of therapy with osimertinib as the preferred prior EGFR TKI

NSCLC Patients Reflect Real World Complex EGFR Mutation Landscape That Emerge After Frontline Osimertinib

Classical mutation	Acquired resistance mutation	Intrinsic driver mutation
Exon 19del L858R	C797S	E709A/V L718Q G724S L833V G719A L861Q L747P S768I T751K K754E L747_E759del E746_T751delinsA L747_T751delinsP

Classical Driver C797S — 12 patients
Classical Driver Intrinsic Drivers — 5 patients
Classical Driver C797S Intrinsic Drivers — 3 patients
Intrinsic Drivers — 7 patients

Plasma ctDNA Biomarker Assessment Shows Complete Clearance of Mutant EGFR VAF and ctDNA in NSCLC Patients



Assigned Dose, mg QD		200	400	50	100	200	200	200	200	200	400
Retrospective EGFR mutation testing at baseline		EGFRm not detected	Ex19Del, C797S	Ex19Del, C797S	L858R L748Q C797S	E746_S75 2delinsV, C797S	Ex19Del, C797S	L747P	Ex19Del, C797S	L858R, E709V	EGFR E746_T751 delinsA
Status of EGFR mutant VAF at C3D1	Classical	EGFRm not detected	Absent	Absent @CSD1	-58%	-96%	Absent		Absent	Absent	
	Acquired		Absent	Absent @CSD1	Absent	Absent	Absent		Absent		
	Intrinsic				Absent			Absent		Absent	Absent

ctDNA – circulating tumor DNA; VAF – variant allele frequency