BDTX-1535 – A MasterKey EGFR Inhibitor Targeting Classical, Non-Classical and the C797S Resistance Mutation to Address the Evolved Landscape of EGFR Mutant NSCLC

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THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Making Cancer History®

Etienne Dardenne

I have the following financial relationships to disclose:

Stockholder in: Black Diamond Therapeutics

Employee of: Black Diamond Therapeutics

I will not discuss off-label use and/or investigational use in my presentation.

- Small molecules directed against oncogenic EGFR mutations expressed in NSCLC is a 20-year success story.

- The EGFR mutational landscape in NSCLC continues to evolve – today we present real world data that reveals new mutations and treatment opportunities.

- BDTX-1535: potentially first- and best-in-class fourth-generation EGFR inhibitor designed to address the evolved mutational landscape; previously disclosed pre-clinical and clinical data for BDTX-1535 is put into context.

- BDTX-1535: Phase 1 clinical proof-of-concept achieved, Phase 2 trial in progress across 1L, 2L, and 3L NSCLC patients.

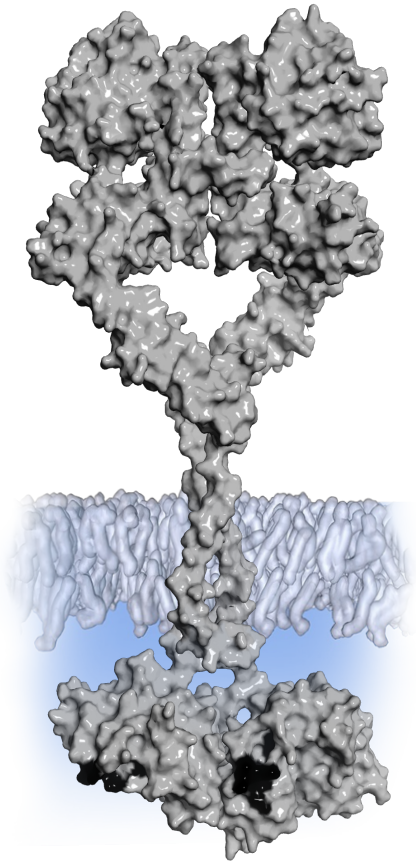
BDTX-1535 clinical data from 2023 EORTC

BDTX-1535 clinical trial information

Real World Data Describe a Broad EGFR Mutational Landscape in NSCLC & Reveal New Opportunities for EGFR Targeting

2004

Two classical EGFR oncogenic mutations first described[1]



L858R & Ex19del *(classical)*

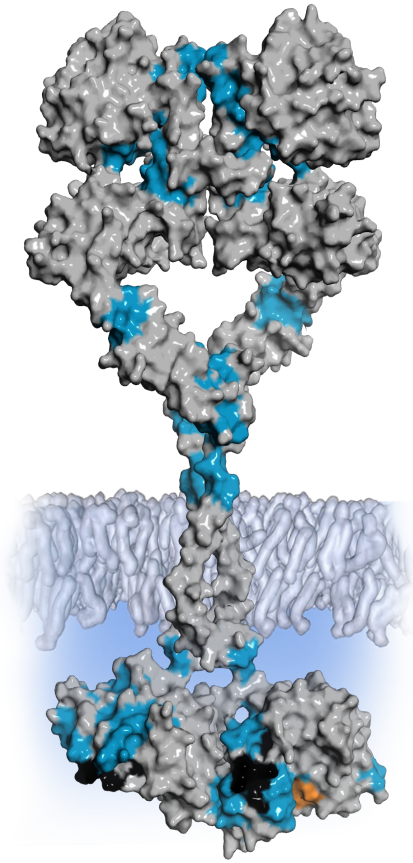
Today

Real World Data reveals a broad landscape of classical & non-classical EGFR oncogenic mutations in NSCLC

GUARDANTINFORM™ FOUNDATION MEDICINE®

Black Diamond examined 235,761 sequenced NSCLC cases

- **>100 EGFR mutations (classical & non-classical*)**
- **Distinct co-mutational profiles for L858R vs Ex19del**
- **Resistance mutations evolve with TKI therapies**



**non-classical EGFR mutations also referred to as: atypical, second-site, uncommon, intrinsic, or PACC mutations*

1. Paez et a. Science 2004

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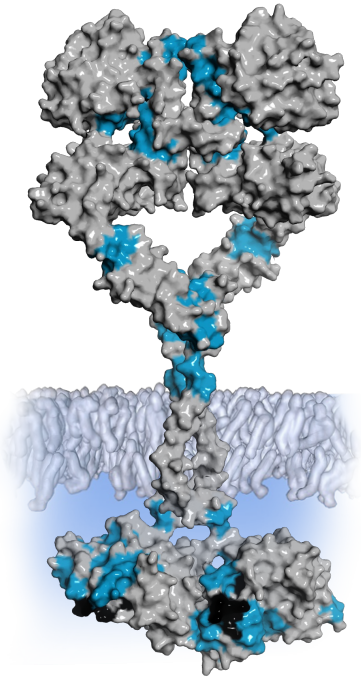
20-30% of Newly Diagnosed EGFRm NSCLC Patients Carry Non-Classical Mutations; Are Not Adequately Addressed by Current Therapies[1]

Classical and non-classical driver mutations are distributed across EGFR structure



Ectodomain-Juxtamembrane *(non-classical)*

50+ mutations

R108X
R222X
A289X
C598X
S645X
…

PACC[1] & others *(non-classical)*

60+ mutations

E709X
G719X
T725M
L754E
L747X
S768I
V769X
L861X
L833X
…

Non-Classical
Classical

22-30% of newly diagnosed EGFRm NSCLC express non-classical mutations

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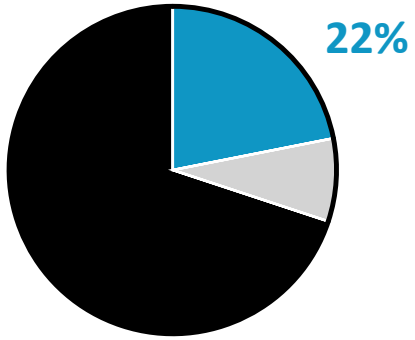
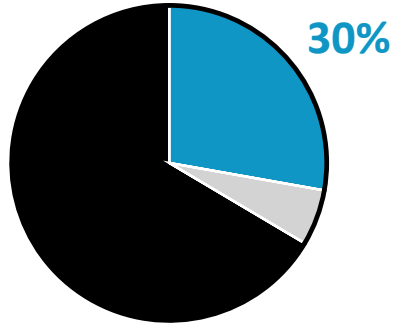


Black Diamond Therapeutics analyses of 94,939 sequencing reports from <u>treatment naïve NSCLC</u>

PROJECTGENIE
Genomics Evidence Neoplasia Information Exchange



Adapted from Du et al. 2023. Analysis of the AACR GENIE database of 22,050 cases of NSCLC

Non-Classical
Exon20ins
Classical

Current therapies do not adequately address non-classical EGFR mutations[1]

1. Borgeaud M. JTO 2024

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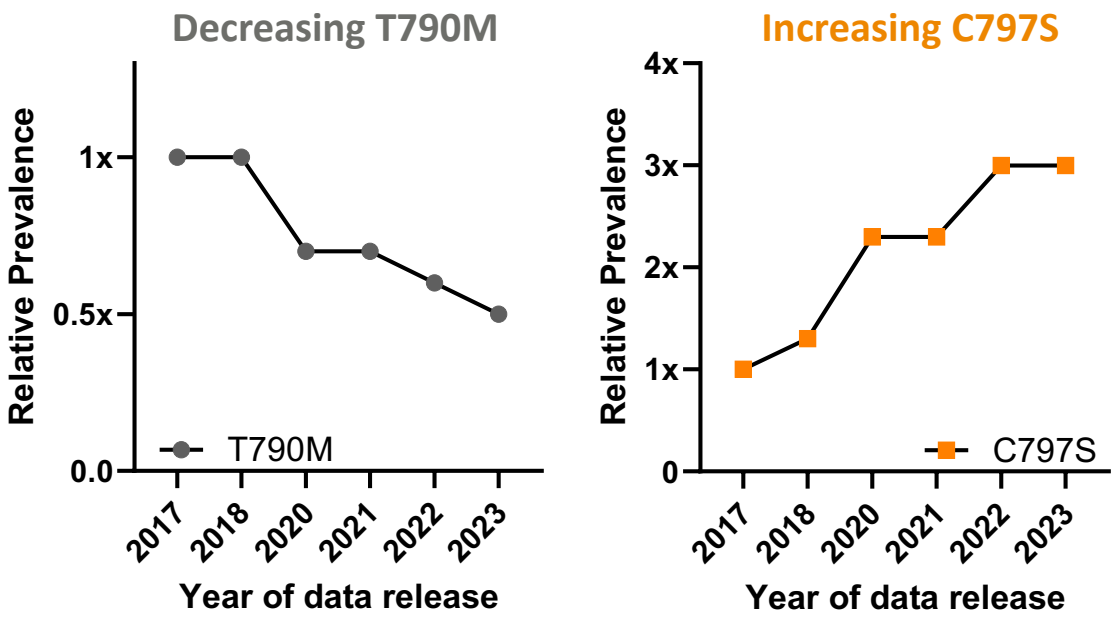
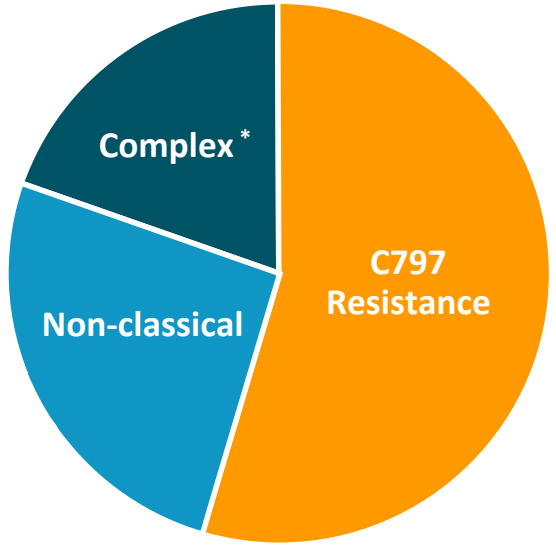
C797S and Non-Classical Mutations are Major Mechanisms of Acquired On-Target EGFR Resistance

On-target EGFR resistance mechanisms have shifted since approval of 3G TKI osimertinib in 1L setting

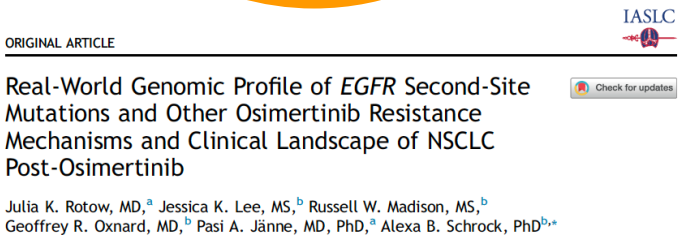


Black Diamond Therapeutics analyses of Foundation Medicine's FoundationInsights™ platform

C797S & non-classical mutations are major mechanisms of on-target EGFR resistance in patients post-osimertinib[1]



*either more than 1 non-classical mutation, or non-classical + C797


ORIGINAL ARTICLE

IASLC

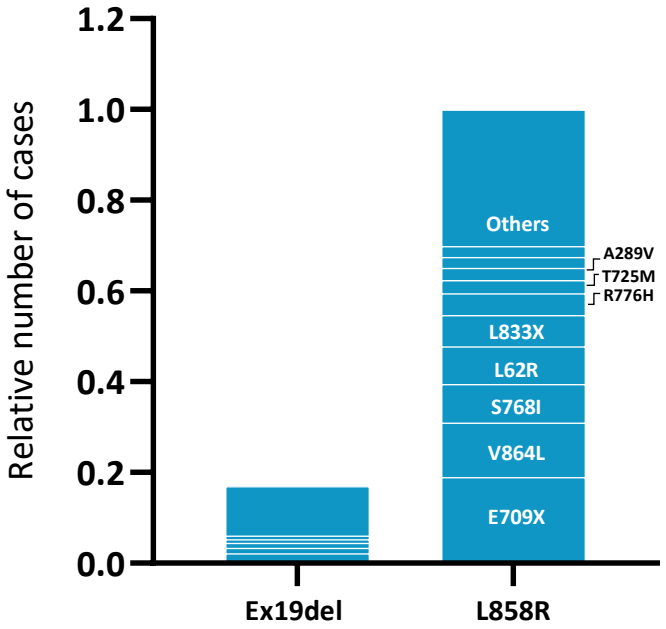
Real-World Genomic Profile of *EGFR* Second-Site Mutations and Other Osimertinib Resistance Mechanisms and Clinical Landscape of NSCLC Post-Osimertinib

Julia K. Rotow, MD,[a] Jessica K. Lee, MS,[b] Russell W. Madison, MS,[b] Geoffrey R. Oxnard, MD,[b] Pasi A. Jänne, MD, PhD,[a] Alexa B. Schrock, PhD[b,*]

1. Adapted from Rotow, JK., et al., Journal of Thoracic Oncology, 2023. (non-classicals represented as L792, G796, G724, L718).

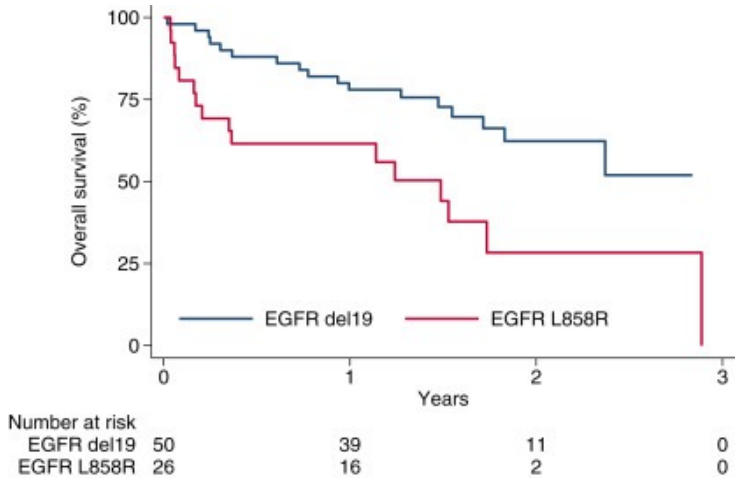
BDTX-1535 Potently Targets Non-Classical EGFR Mutations Commonly Co-Expressed with L858R Which are Insensitive to Osimertinib

EGFR-L858R tumors more frequently co-express non-classical EGFR mutations before exposure to EGFR TKI



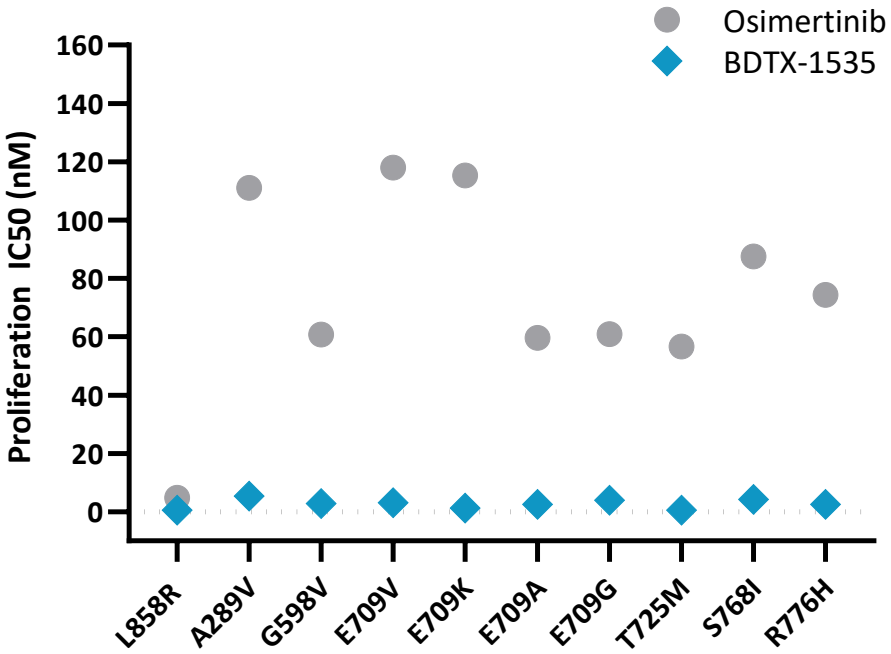
Black Diamond Therapeutics analyses of 94,939 sequencing reports from treatment naïve NSCLC (Guardant Health)

Patients with L858R do less well on osimertinib therapy vs Ex19del



Gijtenbeek et al 2023. Overall survival by type of mutation in patients with stage IV EGFR mutated NSCLC and brain metastasis who received first-line treatment with osimertinib

Non-classical mutations co-expressed with L858R are insensitive to osimertinib but sensitive to BDTX-1535



EGFR mutation frequently associated with L858R

Pre-clinical data; EGFR mutations are engineered in Ba/F3 cells

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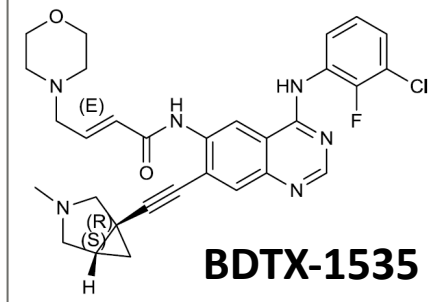
BDTX-1535: A MasterKey EGFR Inhibitor Achieving Potent Inhibition of *EGFR* ***Classical*** (Ex19del and L858R) & ***Non-Classical*** Mutations while Sparing EGFR-WT

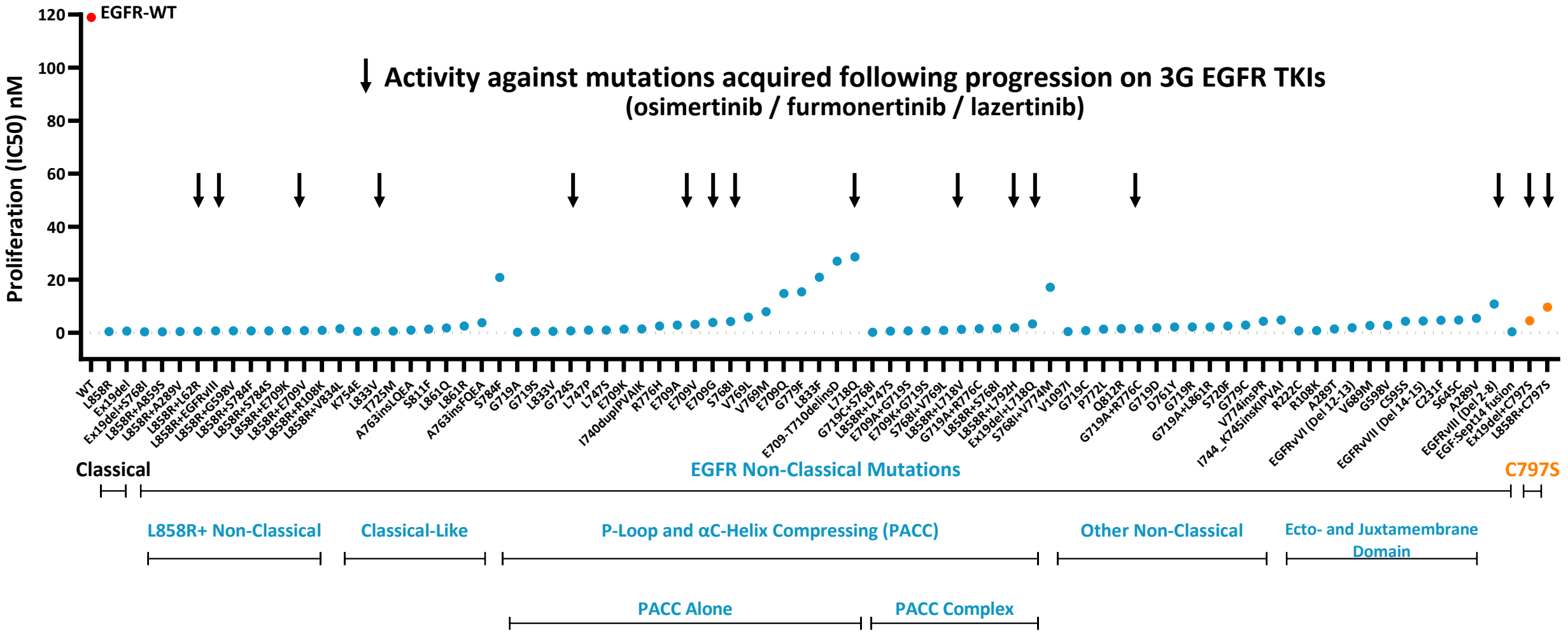


- Potent cellular IC_{50} across all non-classical subtypes, complex mutations, and C797S resistance
- ≤10nM potency across >90% of validated oncogenic mutations and complex mutations
- Selective over wild type EGFR

Pre-clinical data IC50 potency data generated in collaboration with Heymach Lab, MD Anderson Cancer Center
EGFR-WT: H292 Cell line. All other EGFR mutations are engineered in Ba/F3 cells

BLACK DIAMOND THERAPEUTICS

BDTX-1535: A MasterKey EGFR Inhibitor Achieving Potent Inhibition of *EGFR* ***Classical*** (Ex19del and L858R) & ***Non-Classical*** Mutations while Sparing EGFR-WT



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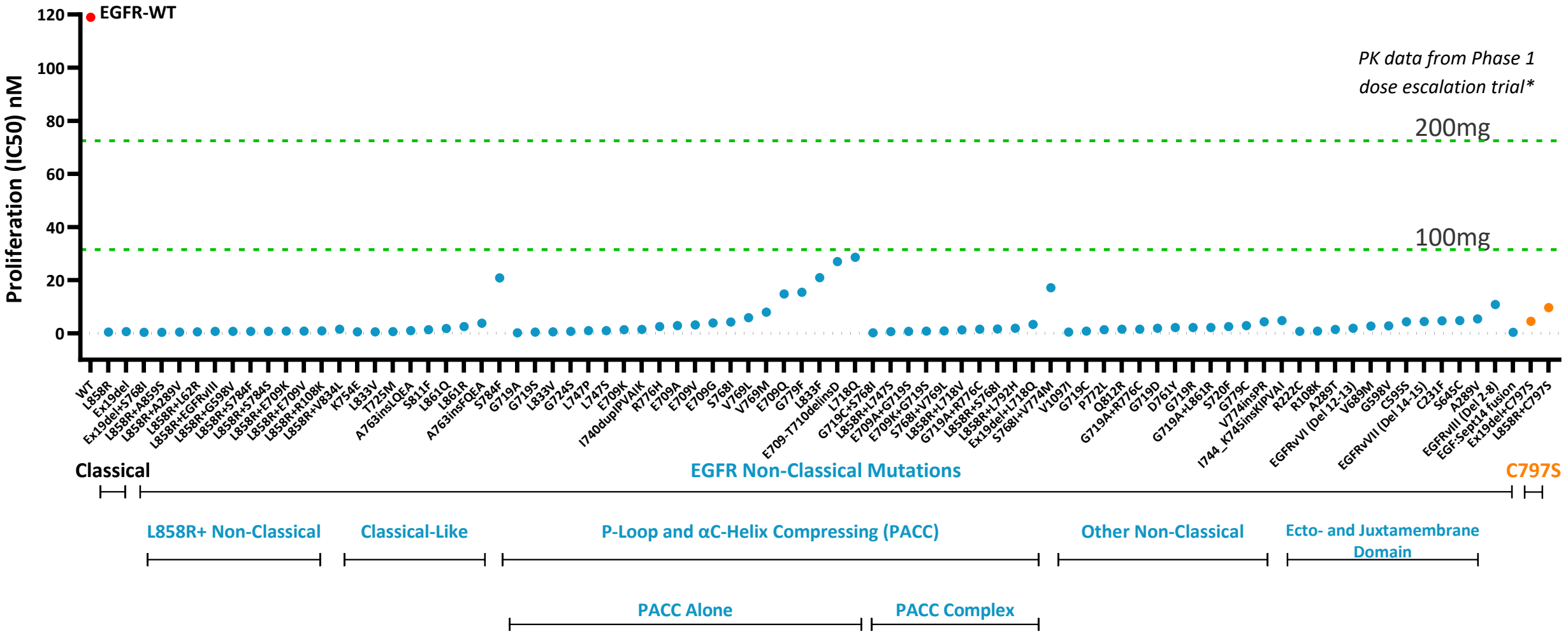
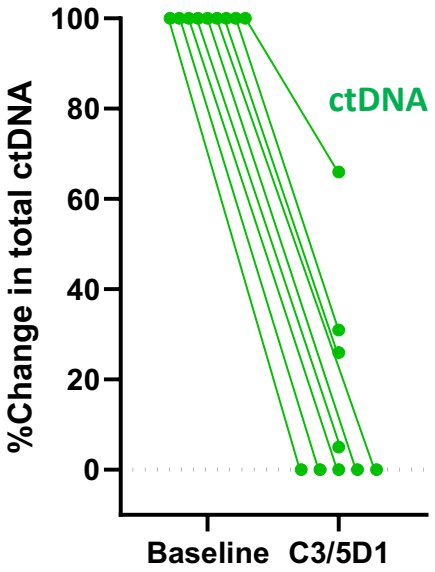
BDTX-1535 Achieves Coverage of the EGFR Mutation Spectrum at the Well-Tolerated Oral Doses of 100-200mg QD



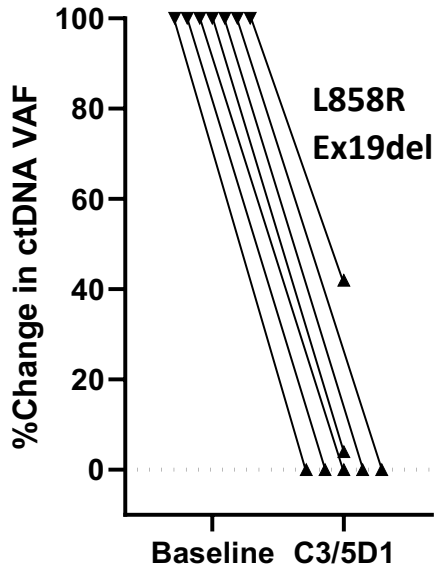
*Cmax at 100mg and 200mg QD doses plotted for human PK. PK data adapted from poster at EORTC/AACR/NCI International Conference on Molecular Targets and Cancer Therapeutics October 2023

BDTX-1535 Drives Clearance of Mutant EGFR VAF and ctDNA in Phase 1 Trial

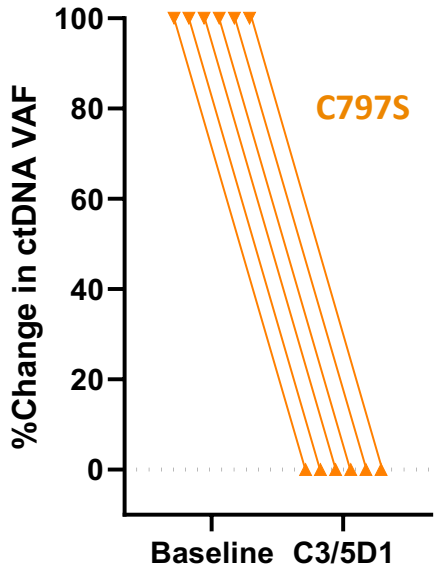
Clearance of plasma ctDNA (9/9 patients)



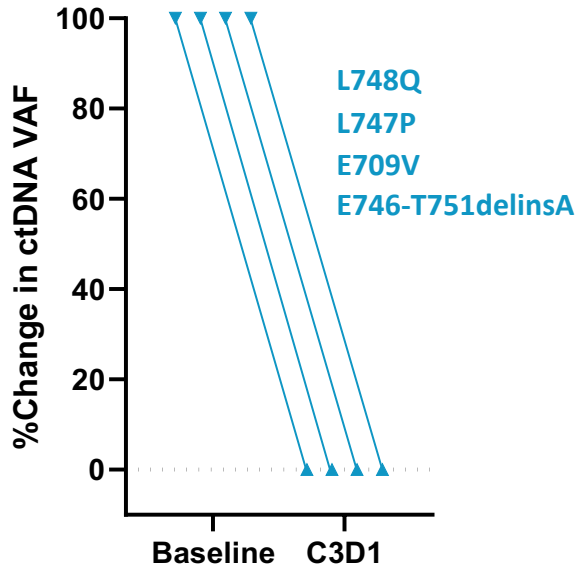
Clearance classical mutations (7/7 patients)



Clearance of C797S (6/6 patients)



Clearance of non-classical mutations (4/4 patients)



Clearance of plasma ctDNA as well as clearance of EGFR Classical, Non-Classical, and C797S observed with BDTX-1535

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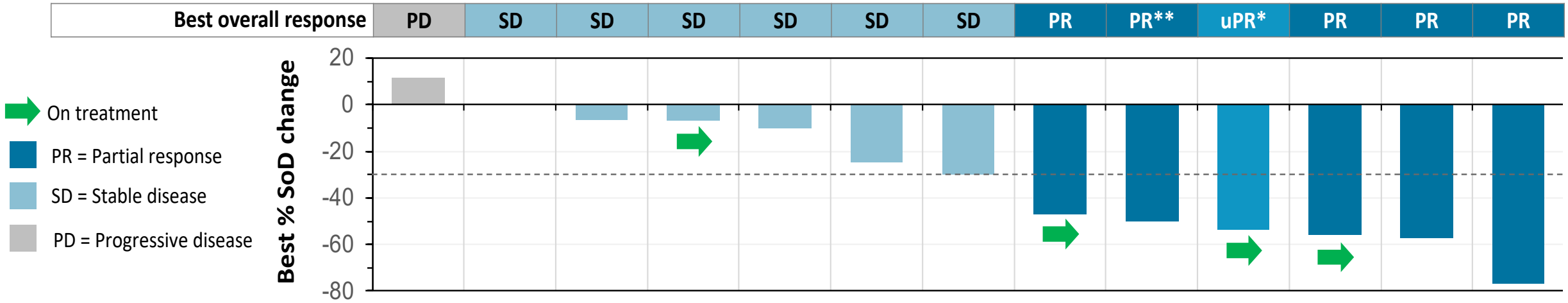
Data adapted from poster at EORTC/AACR/NCI International Conference on Molecular Targets and Cancer Therapeutics October 2023. Select patients expressed more than one mutation and are represented on multiple plots

BDTX-1535 Achieves Radiographical Responses in Efficacy-Evaluable NSCLC Patients Across Relevant Mutations in Phase 1 Trial



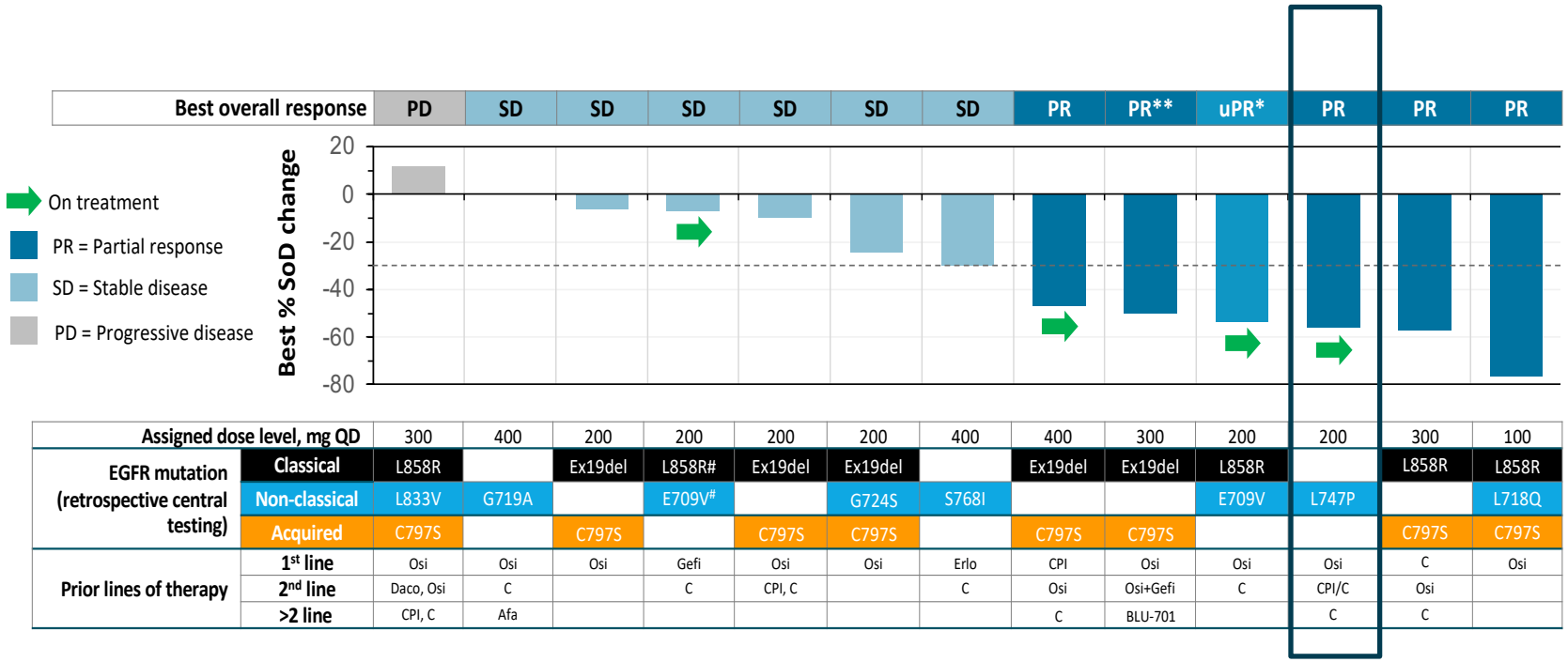
Assigned dose level, mg QD		300	400	200	200	200	200	400	400	300	200	200	300	100
EGFR mutation (retrospective central testing)	Classical	L858R		Ex19del	L858R#	Ex19del	Ex19del		Ex19del	Ex19del	L858R		L858R	L858R
	Non-classical	L833V	G719A		E709V[#]		G724S	S768I			E709V	L747P		L718Q
	Acquired	C797S		C797S		C797S	C797S		C797S	C797S			C797S	C797S
Prior lines of therapy	1st line	Osi	Osi	Osi	Gefi	Osi	Osi	Erlo	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	

Efficacy-Evaluable Patients
5 cPR, 1 uPR of 13 by RECIST
5 cPR, 1 uPR of 11 by RECIST post osimertinib

Osi = Osimertinib; Afa = Afatinib; Gefi = Gefitinib; Daco = Dacomitinib; Erlo = Erlotinib; CPI = Checkpoint inhibitor, C = Chemotherapy; # - mutations were absent on confirmatory test; * uPR=unconfirmed partial response-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
Data adapted from Poster at EORTC/AACR/NCI International Conference on Molecular Targets and Cancer Therapeutics October 2023

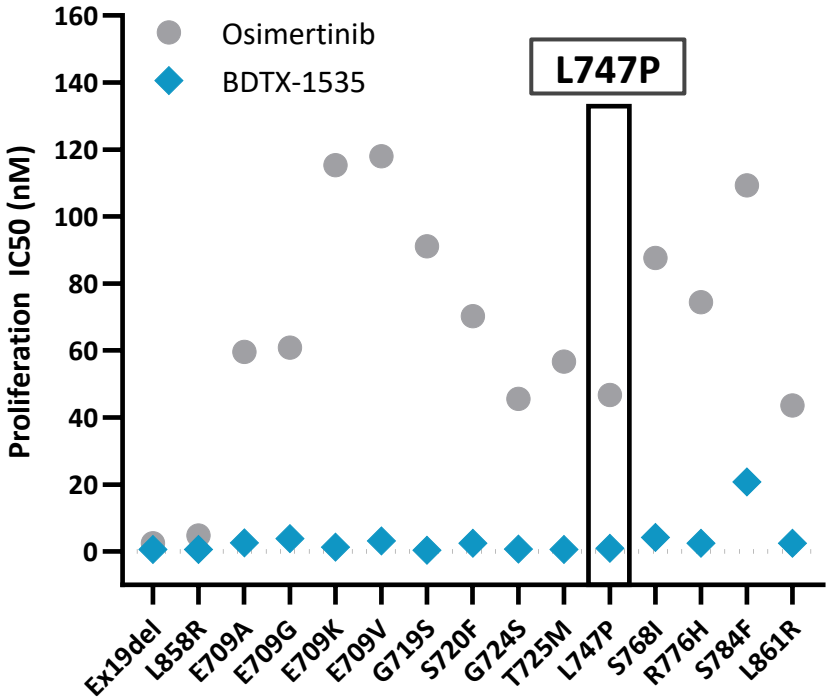
BLACK DIAMOND THERAPEUTICS

BDTX-1535 Achieves Radiographical Responses in Efficacy-Evaluable NSCLC Patients Across Relevant Mutations in Phase 1 Trial



Best overall response		PD	SD	SD	SD	SD	SD	SD	PR	PR**	uPR*	PR	PR	PR
Assigned dose level, mg QD		300	400	200	200	200	200	400	400	300	200	200	300	100
EGFR mutation (retrospective central testing)	Classical	L858R		Ex19del	L858R#	Ex19del	Ex19del		Ex19del	Ex19del	L858R		L858R	L858R
	Non-classical	L833V	G719A		E709V#		G724S	S768I			E709V	L747P		L718Q
	Acquired	C797S		C797S		C797S	C797S		C797S	C797S			C797S	C797S
Prior lines of therapy	1st line	Osi	Osi	Osi	Gefi	Osi	Osi	Erlo	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	

BDTX-1535: potent inhibition of non-classical mutations that are insensitive to osimertinib



Pre-clinical data; EGFR mutations are engineered in Ba/F3 cells

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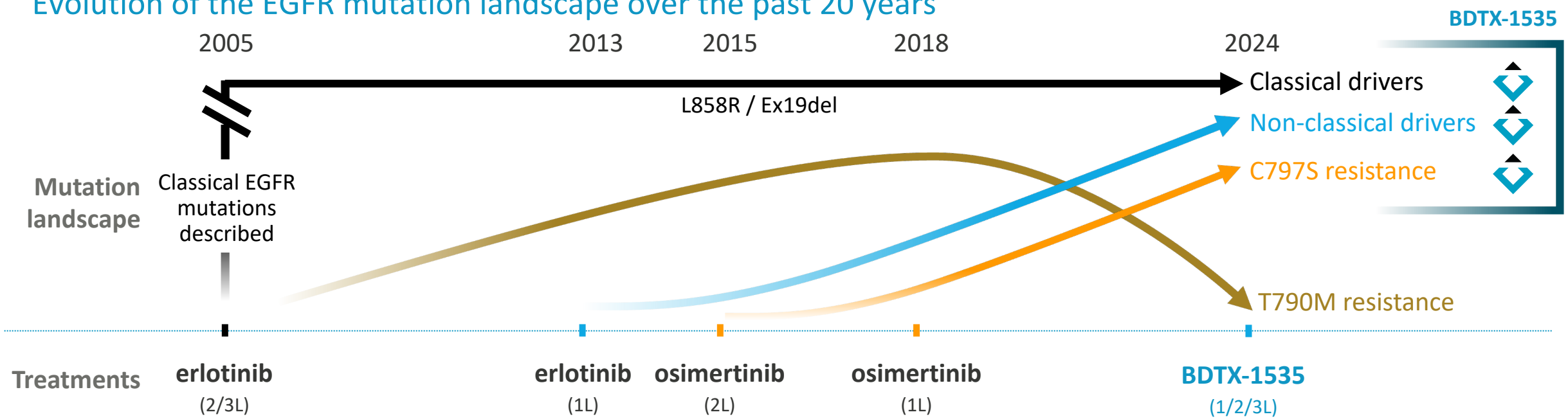
BDTX-1535: Potential First- and Best-in-Class Therapy to Address Major Unmet Medical Needs in EGFRm NSCLC (Classical, Non-Classical, and C797S Resistance Mutation)

Evolution of the EGFR mutation landscape over the past 20 years



BDTX-1535: opportunity to address all relevant mutations—critical for a 4th generation EFGR TKI

BDTX-1535: Currently in Phase 2 Trial for 1L/2L/3L EGFRm NSCLC; Multiple Additional Opportunities

	Non-Classical	Classical (L858R)	Classical (Ex19del)
2/3L	✓ Ongoing P2	✓ Ongoing P2 C797S Non-classical	✓ Ongoing P2 C797S Non-classical
1L	✓ Ongoing P2	Potential opportunity (patients co-expressing non-classical or following adjuvant osimertinib)	Potential opportunity (following adjuvant osimertinib)
Adjuvant	Potential opportunity	Potential opportunity (patients co-expressing non-classical)	

BDTX-1535 clinical data from 2023 EORTC

BDTX-1535 clinical trial information

We thank the patients and investigators who are participating in our clinical trials