Black Diamond Therapeutics, Inc.

Developing MasterKey Therapies to Defeat Cancer Resistance

BLACK DIAMOND THERAPEUTICS

April 10, 2024
Needham Healthcare Conference

Forward-Looking Statements

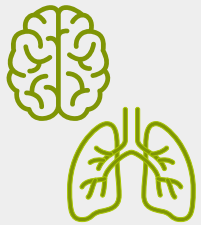
Statements contained in this presentation regarding matters that are not historical facts are “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Such statements include, but are not limited to, statements regarding: the continued development and advancement of BDTX-1535 and BDTX-4933, including the ongoing clinical trials and the timing of clinical updates for BDTX-1535 in patients with NSCLC and in patients with recurrent GBM, and for Phase 1 clinical trial results for BDTX-4933, the potential of BDTX-1535 to benefit patients with NSCLC in earlier lines of therapy, potential future development plans for BDTX-1535 in NSCLC and GBM, including in first-line settings, and the Company’s expected cash runway. Any forward-looking statements in this statement are based on management’s current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. Risks that contribute to the uncertain nature of the forward-looking statements include those risks and uncertainties set forth in its Annual Report on Form 10-K for the year ended December 31, 2023, filed with the United States Securities and Exchange Commission and in its subsequent filings filed with the United States Securities and Exchange Commission. All forward-looking statements contained in this presentation speak only as of the date on which they were made. The Company undertakes no obligation to update such statements to reflect events that occur or circumstances that exist after the date on which they were made.

Black Diamond Therapeutics At-a-Glance

Clinical-stage company **advancing MasterKey therapies** designed to expand the addressable patient population

Experienced team with deep understanding of cancer biology and oncology drug development

Pipeline of oral, brain penetrant drug candidates selectively **targeting families of oncogenic mutations**



Lead asset BDTX-1535 shows **durable clinical responses in NSCLC**, with additional opportunity in GBM

Multiple clinical catalysts across the pipeline in 2024

Strong balance sheet, with runway into Q2 2025; ended Q4 2023 with $131.4M in cash

Advancing Wholly Owned Pipeline Across Multiple Oncology Indications

Target	Drug Candidate	Indication	Pre-clinical / Phase 1 / Phase 2 / Phase 3
EGFR	**BDTX-1535**	NSCLC	**Phase 2 data in 2L/3L patients expected Q3 2024** **Phase 2 data in 1L patients expected 2025**
		GBM	**Phase 1 and "window of opportunity" data expected Q2 2024**
RAF	**BDTX-4933**	KRAS mutant NSCLC RAF/RAS mutant solid tumors	**Phase 1 enrolling** **data expected Q4 2024**
FGFR2/3	**BDTX-4876**	Achondroplasia or solid tumors	Partnering candidate
Undisclosed	Undisclosed	Multiple Solid tumors	Partnering candidate

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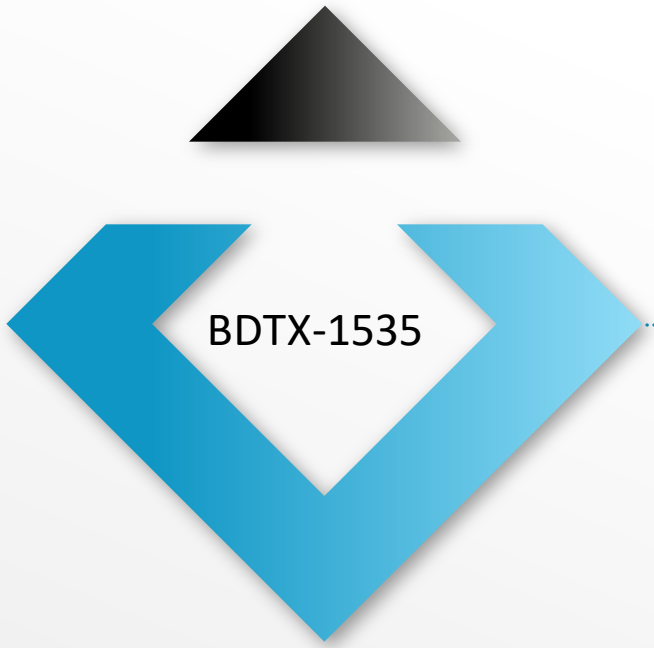
BDTX-1535: Most Advanced 4th Gen EGFR Inhibitor with Potential Best-In-Class Profile



MasterKey	**Targets EGFR classical drivers, non-classical drivers, and resistance mutations**
Spares WT-EGFR	**Selective for mutations versus WT-EGFR to deliver favorable safety profile**
Covalent	**Oral small molecule with covalent MOA for potency and durability**
Brain-Penetrant	**Designed to treat CNS tumors and brain metastases**
Phase 2 NSCLC	**2L/3L post-osimertinib Ph 2 data expected Q3 2024** **1L non-classical Ph 2 data expected in 2025**

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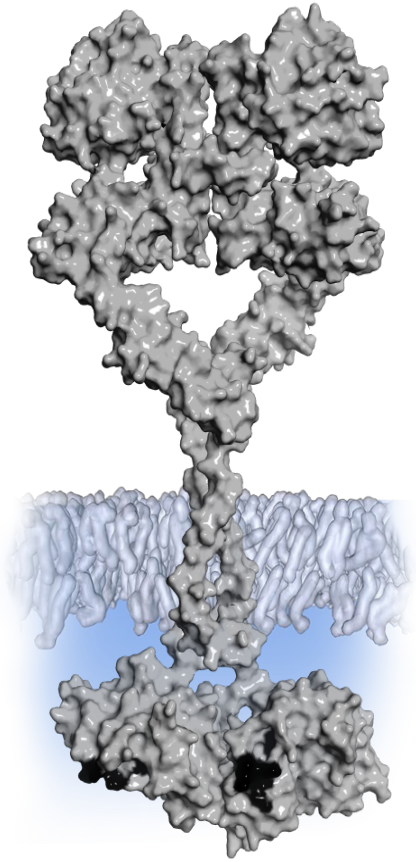
WT=Wild-Type; MOA=mechanism of action; CNS=Central Nervous System; NSCLC=Non-Small Cell Lung Cancer

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)*

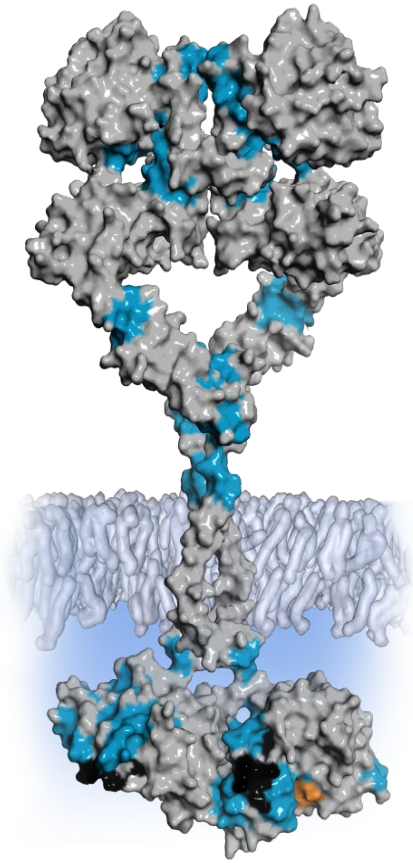
Today

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*

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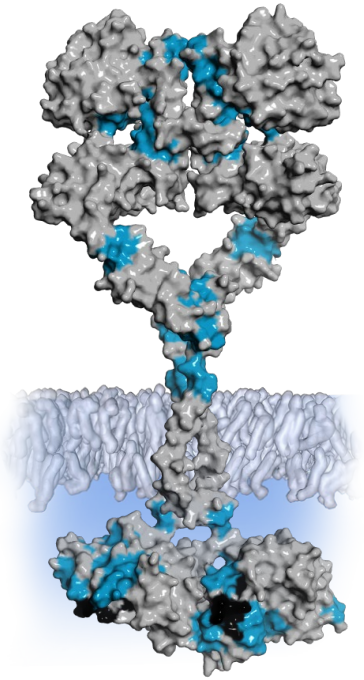
1. Paez et a. Science 2004
BDTX AACR 2024 oral presentation

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)*

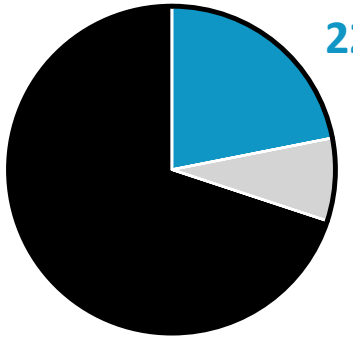
60+ mutations

E709X
G719X
T725M
L754E
L747X
S768I
V769X
L861X
L833X
…

Non-Classical
Classical

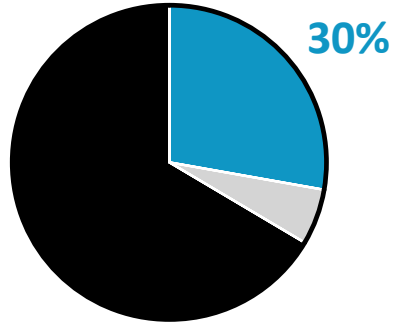
22-30% of newly diagnosed EGFRm NSCLC express non-classical mutations

GUARDANTINFORM™



Non-Classical
Exon20ins
Classical

PROJECTGENIE
Genomics Evidence Neoplasia Information Exchange



Black Diamond Therapeutics analyses of 94,939 sequencing reports from treatment naïve NSCLC

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

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

1. Borgeaud M. JTO 2024
BDTX AACR 2024 oral presentation

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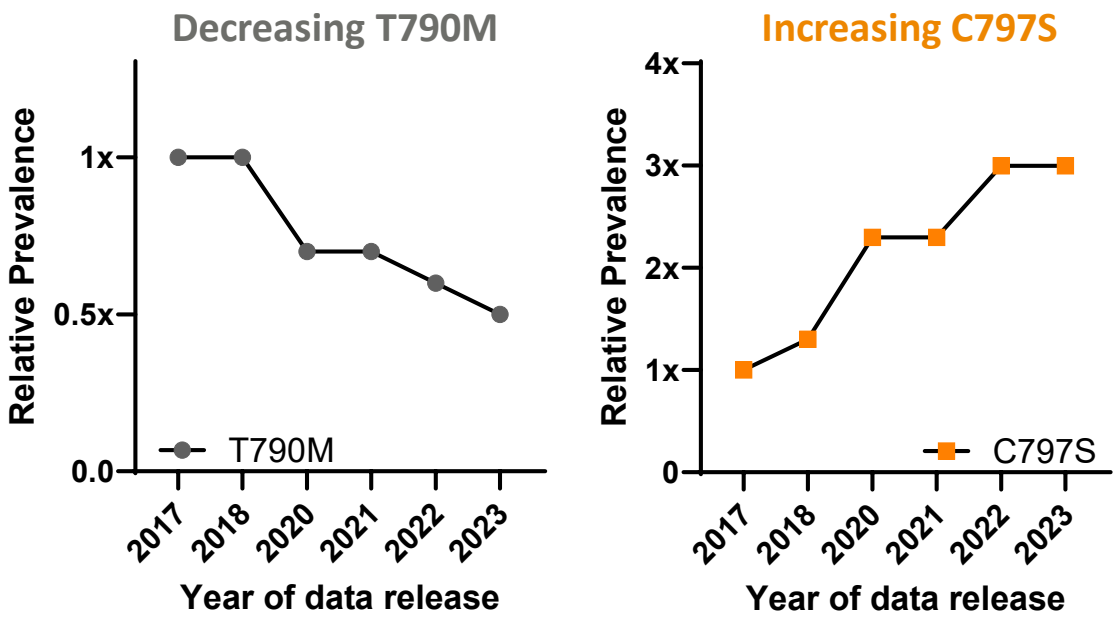
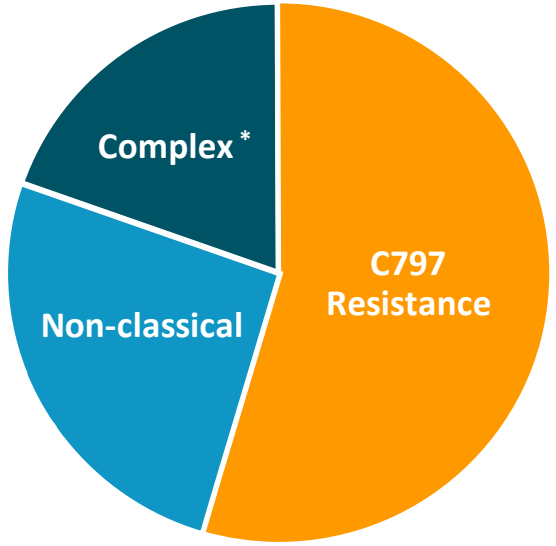
C797S and Non-Classical Mutations are Major Mechanisms of Acquired On-Target EGFR Resistance

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

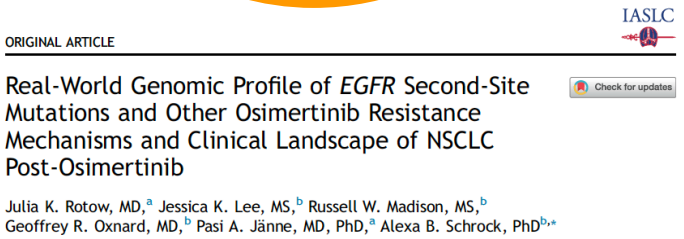


Black Diamond Therapeutics analyses of Foundation Medicine's FoundationInsights™ platform

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

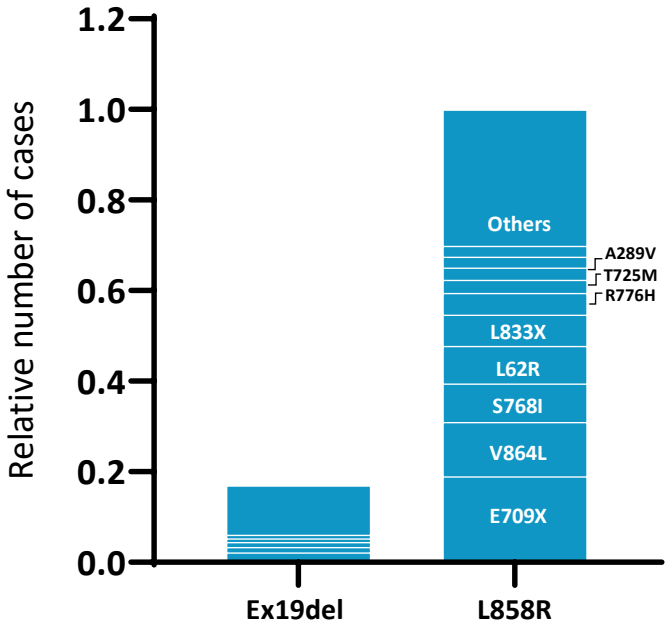
Check for updates

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).

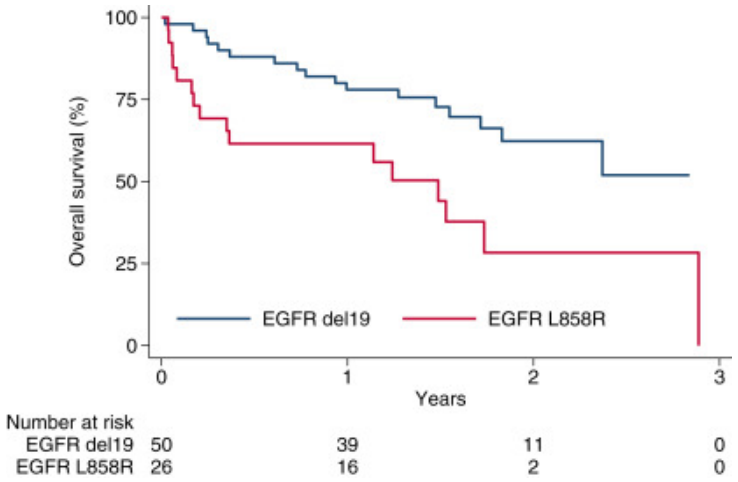
BDTX-1535 Potently Targets Non-Classical EGFR Mutations Commonly Co-Expressed with L858R Which are Insensitive to Osimertinib

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



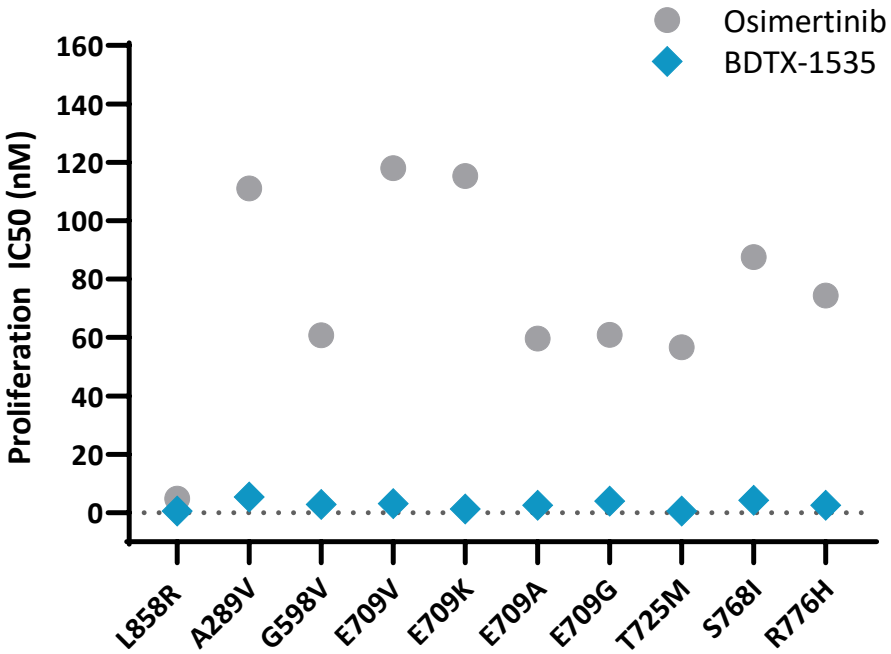
Black Diamond Therapeutics analyses of 94,939 sequencing reports from treatment naïve NSCLC (Guardant Health)

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

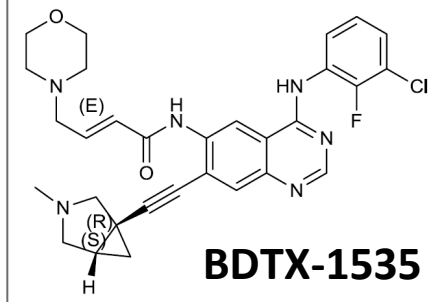
Non-classical mutations co-expressed with L858R are insensitive to osimertinib but sensitive to BDTX-1535



EGFR mutation frequently associated with L858R

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

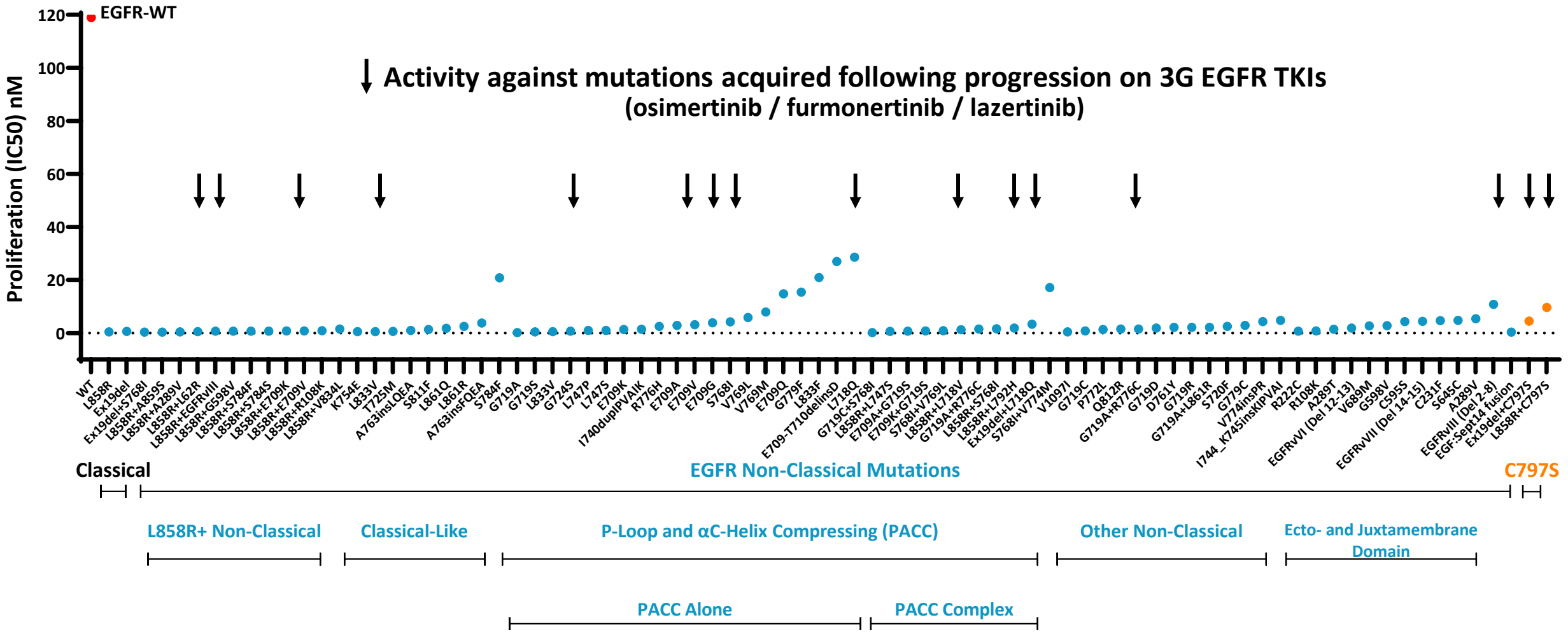
BDTX-1535: A MasterKey EGFR Inhibitor Achieving Potent Inhibition of *EGFR* ***Classical*** (Ex19del and L858R) & ***Non-Classical*** Mutations while Sparing EGFR-WT



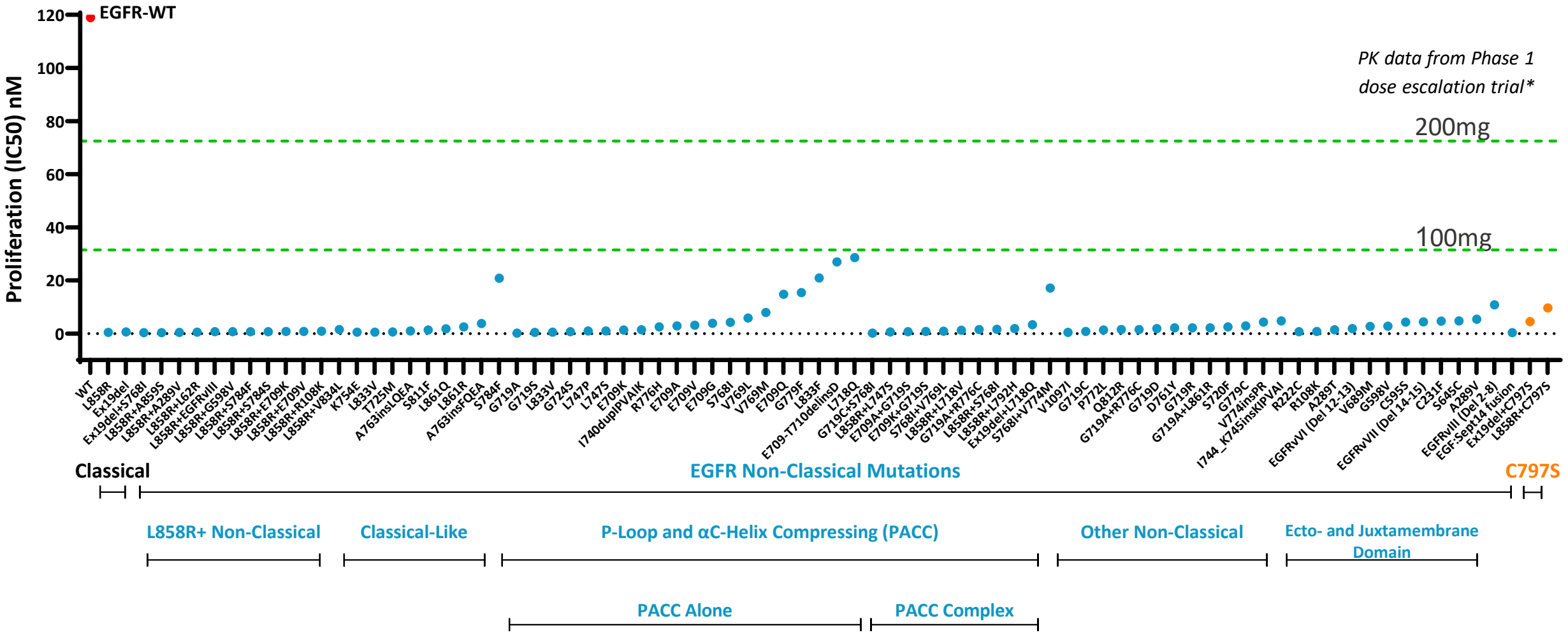
- Potent cellular IC_{50} across all non-classical subtypes, complex mutations, and C797S resistance
- ≤10nM potency across >90% of validated oncogenic mutations and complex mutations
- Selective over wild type EGFR

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
BDTX AACR 2024 oral presentation

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



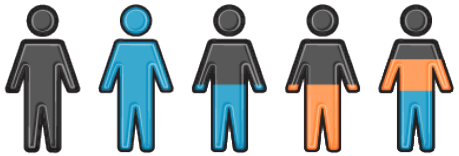
BDTX-1535 Achieves Coverage of the EGFR Mutation Spectrum at the Well-Tolerated Oral Doses of 100-200mg QD



*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 AACR 2024 oral presentation

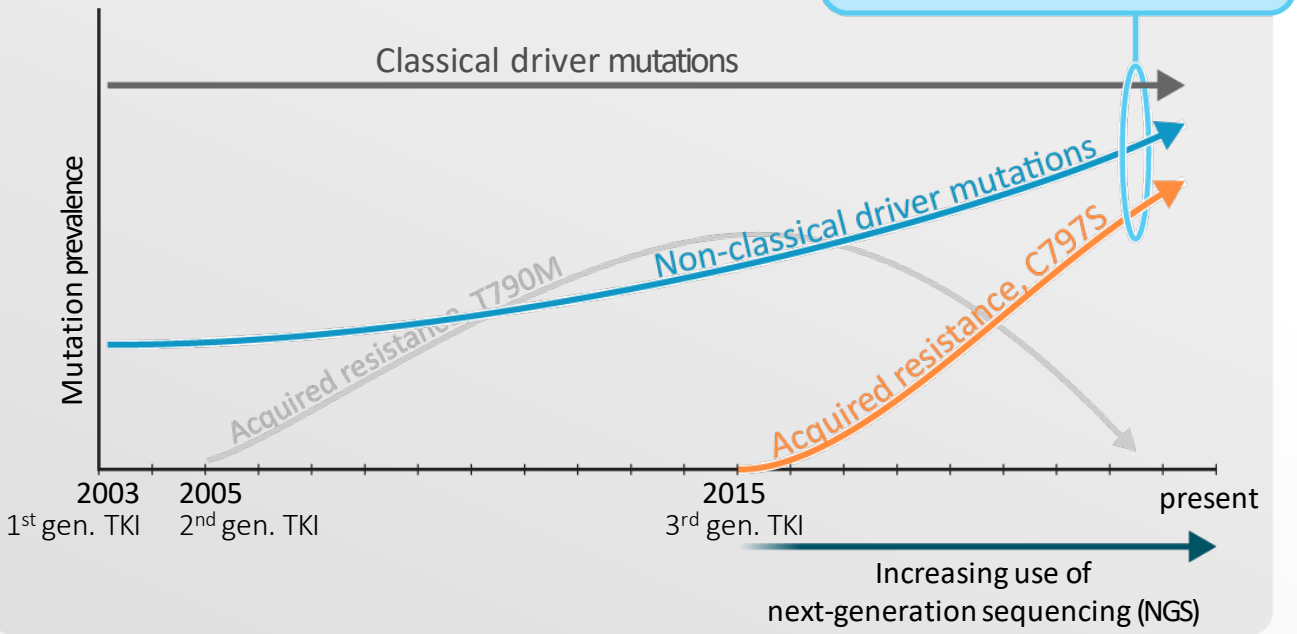
BDTX-1535 Addresses the Most Clinically Relevant EGFR Mutations in NSCLC: Classical / Non-Classical Drivers and C797S Resistance

BDTX-1535, the **most advanced 4th generation TKI,** covers the current mutation landscape



Classical drivers
Non-classical drivers
Acquired resistance, C797S

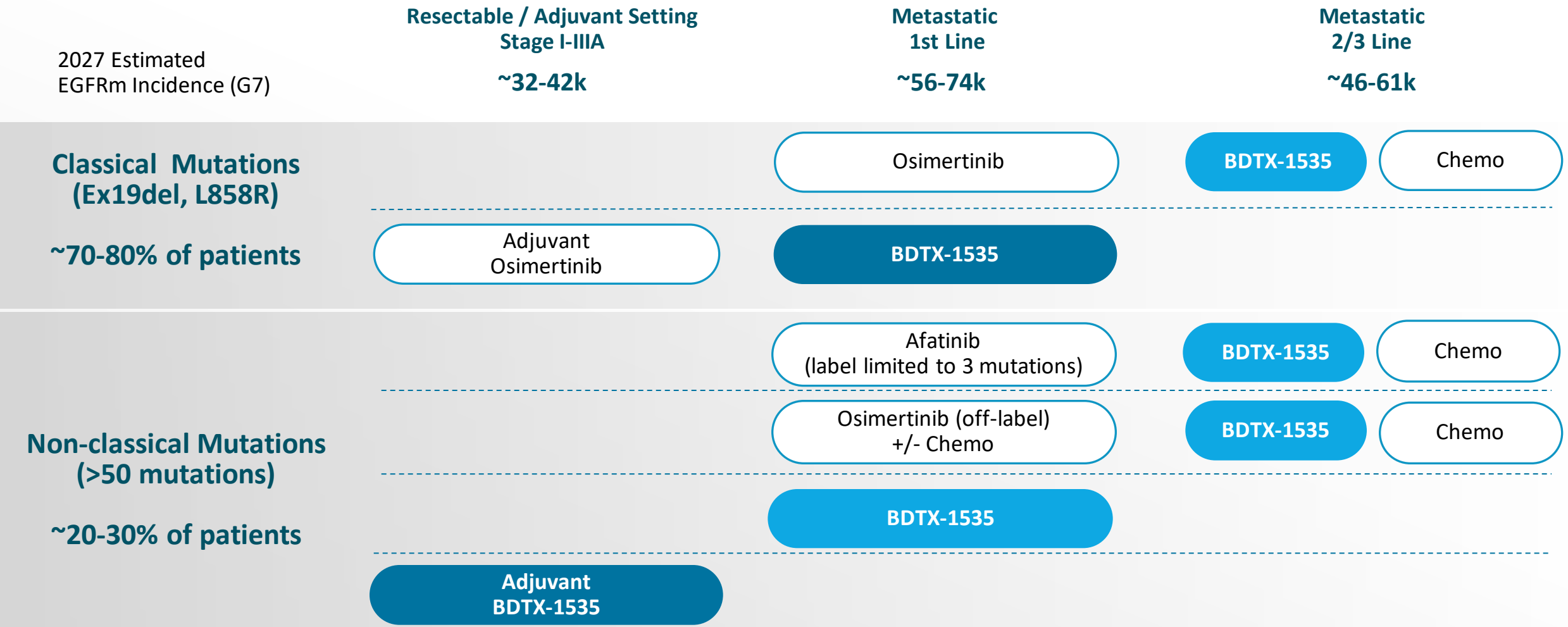
EGFR mutation prevalence, 2003 - present



BDTX-1535: potential to benefit patients across multiple lines of therapy

- **oral administration**
- **well tolerated**
- **brain penetrant**

BDTX-1535 Potential Position: A Well-Tolerated Oral Therapy In Early-Line EGFRm NSCLC



Reference: Kantar Treatment Architecture; Global Data; Data Monitor Pharma Intelligence; SEER/NCI data; Zhang et al., Oncotarget 2016; Du et al., Biomolecules 2023

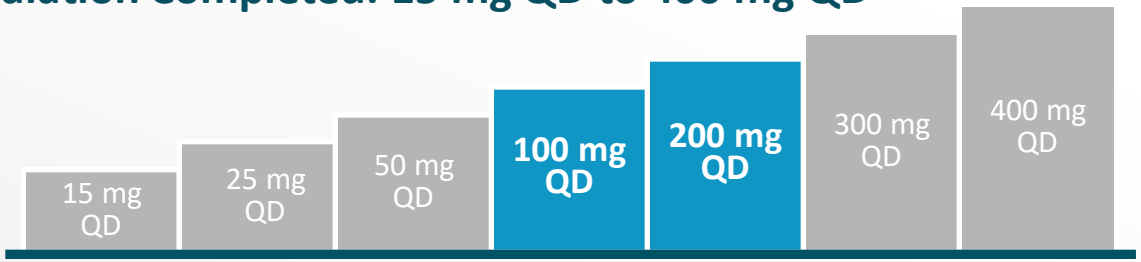
BDTX-1535 Phase 1 Dose Escalation: Summary

Mutation Matched Phase 1 Study Inclusion Criteria

Recurrent NSCLC Cohort			Recurrent GBM Cohort	
EGFR mutations at the time of progression: – Non-classical driver, OR – Acquired resistance C797S	Progression after EGFR TKI	Exclusion of EGFR T790M, Ex20ins, KRAS mutations, cMET amplification	EGFR alterations at resection/diagnosis	Wild-type isocitrate dehydrogenase (IDH)

Dose Escalation Completed: 15 mg QD to 400 mg QD

- **Primary objective:** PK and safety
- **Secondary objective:** Anti-tumor activity



- Target coverage and clinical activity at ≥ 100 mg, MTD at 300 mg
- Phase 2 in 2L/3L NSCLC enrolling at 100 mg QD and 200 mg QD

NSCLC Key Data Takeaways

- **Once-daily dosing delivers sufficient exposure to inhibit EGFR mutations**
- **Manageable EGFR TKI safety profile at 200 mg (similar to osimertinib)**
- **Radiographic responses and durable anti-tumor activity across multiple mutation families**
- **ctDNA reduction confirms loss of mutant alleles, which is predictive of clinical benefit[1]**
- **Phase 2 data expected Q3 2024**

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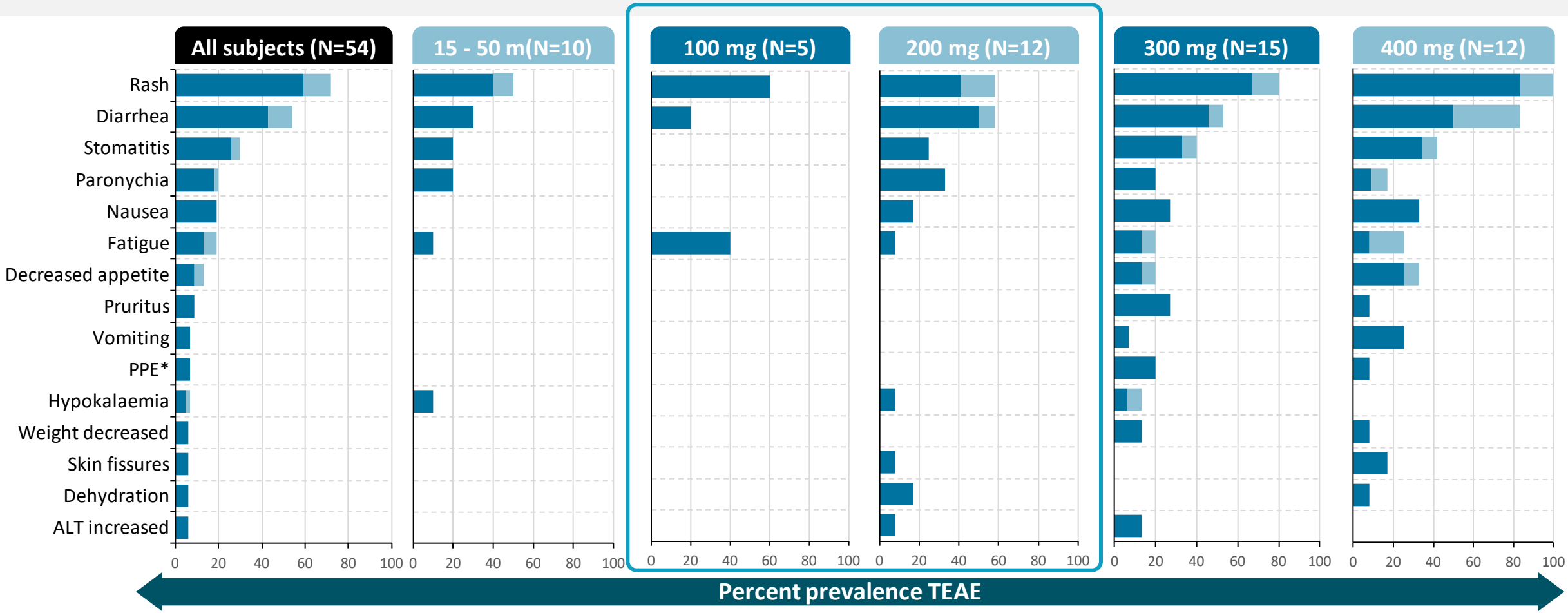
1. Thompson, JC., et al., British Journal of Cancer, 2023

Dose Escalation Treatment Emergent Adverse Events Related to BDTX-1535: Well-Tolerated Profile



Grade 1 and 2 events
Grade 3 events

No Grade 4 AEs were reported	• No dose limiting toxicity (DLTs) were observed at ≤200 mg • Maximum tolerated dose is 300mg QD	Dose reductions: 1 (8%) pt at 200 mg QD; 5 (33%) pts at 300 mg QD

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

*PPE = Palmar-plantar erythrodysaesthesia syndrome

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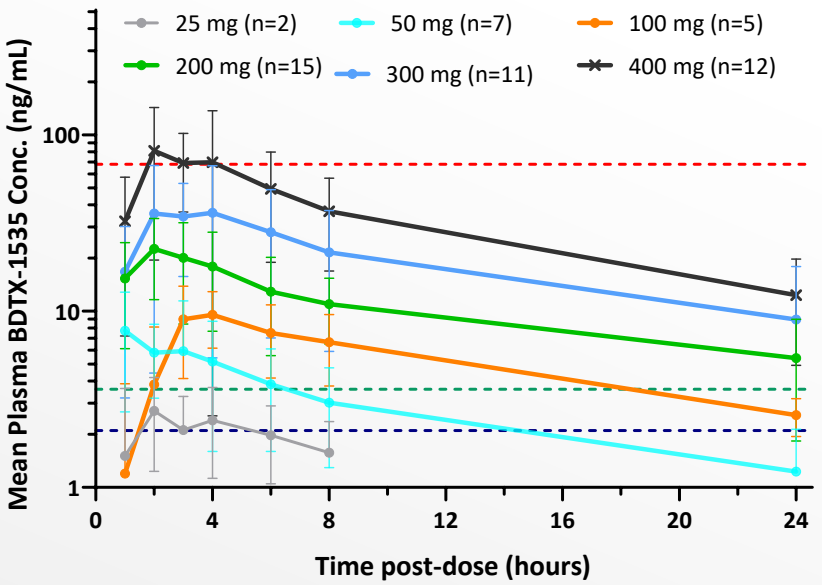
Data from Poster at EORTC/AACR/NCI International Conference on Molecular Targets and Cancer Therapeutics October 2023

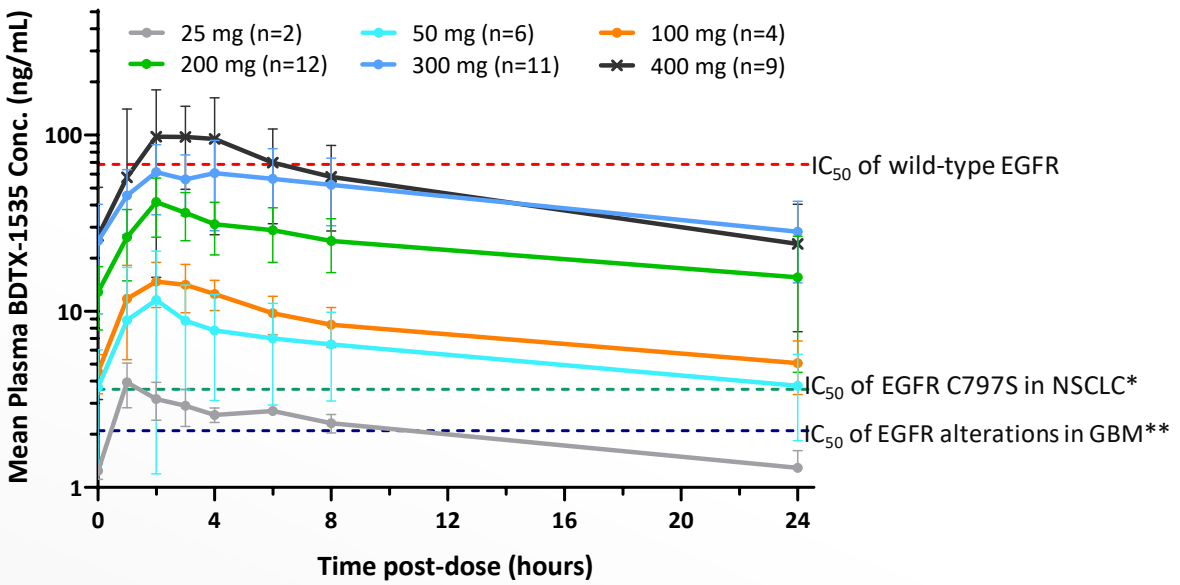
BDTX-1535 Linear Plasma PK Profile Supports Daily Dosing To Achieve 24-Hour Target Coverage

Mean plasma concentration-time profile of BDTX-1535

Day 1
C1D1 mean (±SD)



Steady State
C1D15 mean (±SD)



- Target blockade based on preclinical IC50 was achieved at BDTX-1535 ≥ 100 mg QD
- Exposure was dose proportional with half-life ~15 hours to support daily dosing
- Clinical anti-tumor activity observed at ≥ 100 mg QD

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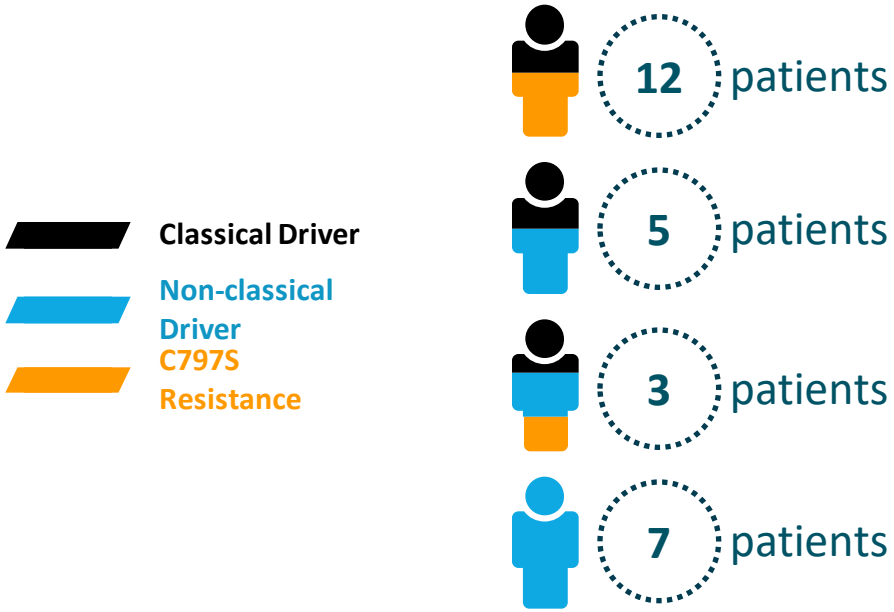
Data from Poster at EORTC/AACR/NCI International Conference on Molecular Targets and Cancer Therapeutics October 2023
**IC_{50} of EGFR alterations in GBM is average IC_{50} of most prevalent EGFR mutations tested in BaF3 cells
*IC_{50} of EGFR C797S is average of IC_{50} of Exon19del/C797S and L858R/C797S mutations tested in Ba/F3 cells

NSCLC Dose Escalation Patients Reflect Real-World EGFR Mutation Landscape Post Osimertinib

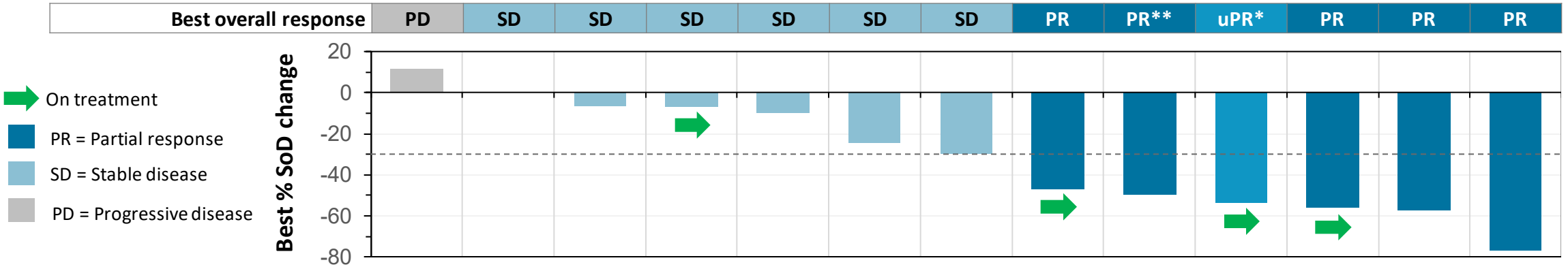
20 of 27 patients with 2 or more mutations



Classical driver mutations	Non-classical driver mutations	Acquired resistance mutation
Exon 19del L858R	E709A/V L718Q G724S L833V G719A L861Q L747P S768I T751K K754E L747_E759del E746_T751delinsA L747_T751delInsP	C797S

Data from Poster at EORTC/AACR/NCI International Conference on Molecular Targets and Cancer Therapeutics October 2023

Radiographical Responses in Efficacy-Evaluable NSCLC Patients Across All Relevant Mutations



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	

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 from Poster at EORTC/AACR/NCI International Conference on Molecular Targets and Cancer Therapeutics October 2023

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

Post-Osimertinib Patients
5 cPR, 1 uPR of 11 by RECIST

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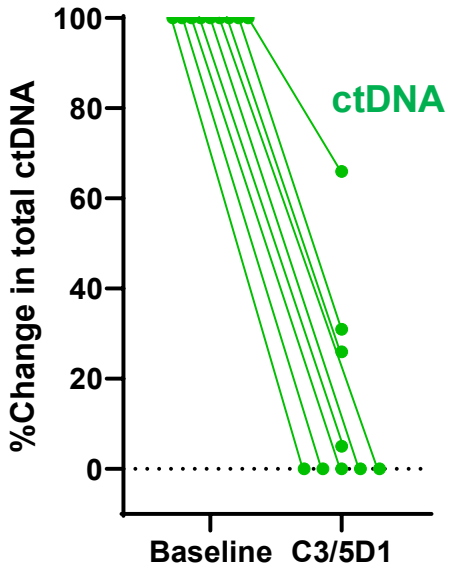
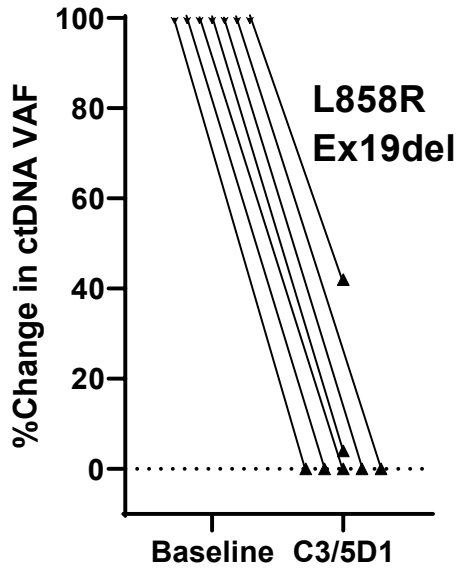
BDTX-1535 Drives Clearance of Mutant EGFR VAF and ctDNA in Phase 1 Trial

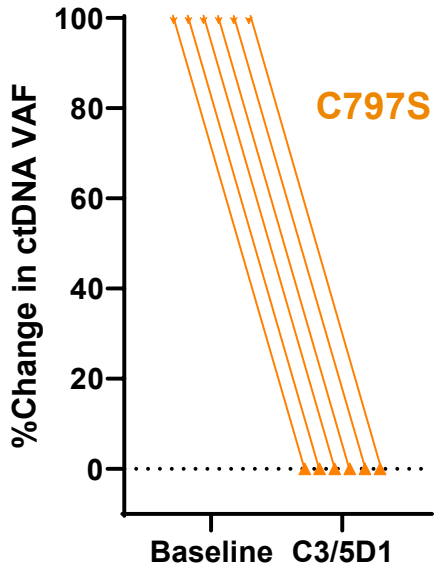
Clearance of plasma ctDNA (9/9 patients)



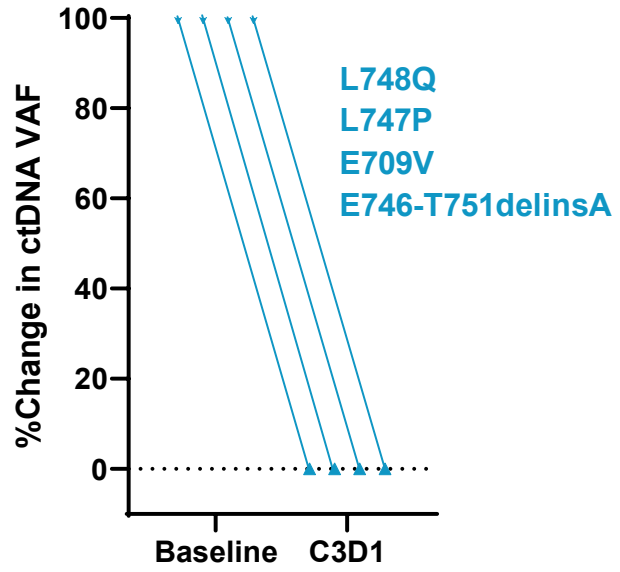
Clearance classical mutations (7/7 patients)



Clearance of C797S (6/6 patients)



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



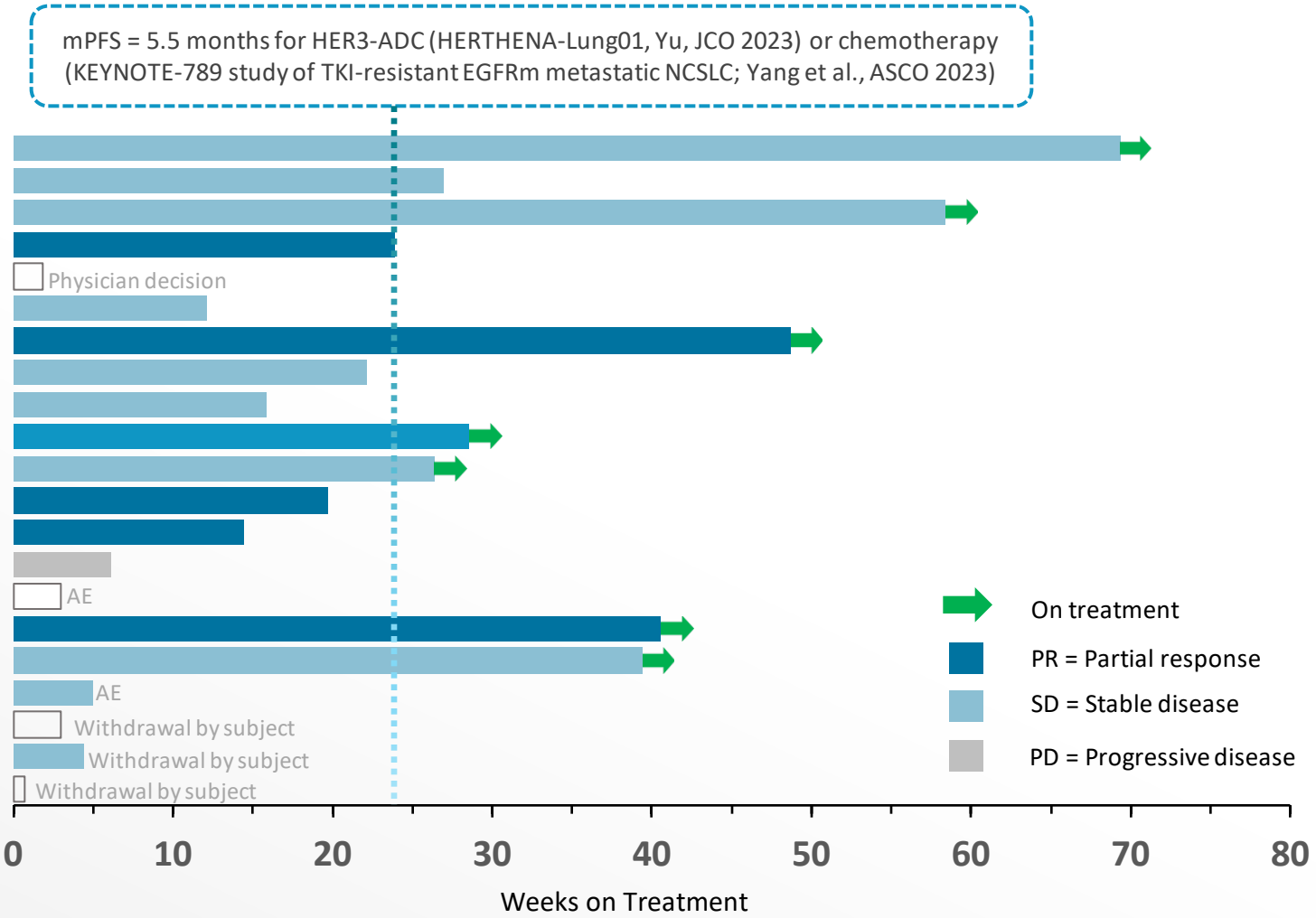
Clearance of plasma ctDNA as well as clearance of EGFR Classical, Non-Classical, and C797S observed with BDTX-1535

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: Emerging Evidence of Durable Tumor Response in NSCLC

Assigned Dose (QD)	Baseline EGFR Mutation			Prior Therapy			Response Evaluable
	Classical	Non-classical	Acquired	1st	2nd	>2 line	
25 mg	Exon 19del		C797S	Osi			SD[a]
50 mg	Exon 19del		C797S	Osi			SD[b]
		G719A, L861Q		CPI, Afa	Osi	HER3-ADC	NM[a, c]
100 mg	L858R	L718Q,	C797S	Osi			PR[d]
	L858R			Osi	C	C	No[b]
200 mg	Exon 19del		C797S	Osi	CPI, C		SD
		L747P		Osi	CPI, C	C	PR[c, f]
	Exon 19del		C797S	Osi			SD
	Exon 19del	G724S	C797S	Osi			SD
	L858R	E709V		Osi	C		uPR[e]
	L858R	E709V		Gefi	C		SD
300 mg	Exon 19del		C797S	Osi	Osi + Gefi	BLU-701	PR[c]
	L858R		C797S	C	Osi	C	PR[c]
	L858R,	L833V	C797S	Osi	Daco, Osi	CPI, C	PD[c]
400 mg	Exon 19del		C797S	Osi	C		No
	Exon 19del		C797S	CPI	Osi	C	PR[d]
		E746_T751del insA		Osi	C		NM[d]
		G719A		Osi	C	Afa	SD[c]
	L858R	E709A, L718Q		Osi			No
		S768I		Erlo	C		SD
		G719A		C	Afa		No

[a] Dose was increased incrementally to 100 mg QD
[b] Dose was increased incrementally to 200 mg QD
[c] Received more than two prior lines of therapy
[d] Dose was reduced to 300 mg QD
[e] 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
[f] Patient had >20% increase in target lesions at cycle 11, however, continues the study treatment



BDTX-1535: Phase 2 Trial Enrolling in 1L and 2L/3L NSCLC

2L/3L

Cohort 1

Patients with non-classical driver mutations after ≤2 prior lines of therapy with osimertinib as the preferred prior EGFR TKI

Cohort 2

Patients with acquired resistance C797S after ≤2 prior lines of therapy with osimertinib as the only prior EGFR TKI

1L

Cohort 3

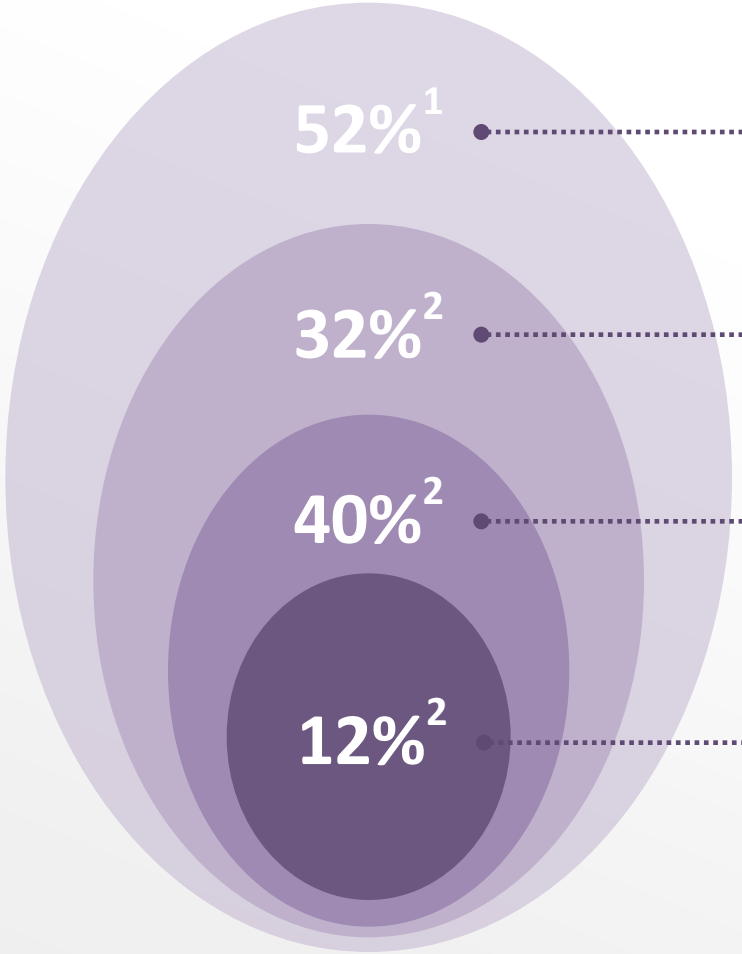
Patients with non-classical driver mutations and no prior treatment

- Enrolling up to 40 patients each cohort
- 2L/3L patients enrolling at 100 mg QD and 200 mg QD
- ORR primary endpoint
- Phase 2 data in 2L/3L patients expected Q3 2024
- FDA Fast Track Designation granted for 2L EGFRm/C797S
- End of Phase 1 FDA feedback received, 1L cohort initiated

BDTX-1535: Opportunity in Glioblastoma

Black Diamond Therapeutics

Treatment of EGFR-Driven GBM Requires Inhibition of Complex EGFR Mutations: Potent Preclinical Inhibition by BDTX-1535



Of all GBM samples carry oncogenic EGFR alterations

Of all GBM samples had EGFR extracellular-domain (ECD) mutations, according to real-world evidence

Of all ECD-driven tumors were complex, containing 2 or more ECD mutations

Of complex ECD-driven tumors were highly heterogeneous, with 3 or more ECD mutations

~7,000

GBM patients in the US are diagnosed each year with EGFR mutations that have been shown in preclinical studies to be inhibited by BDTX-1535

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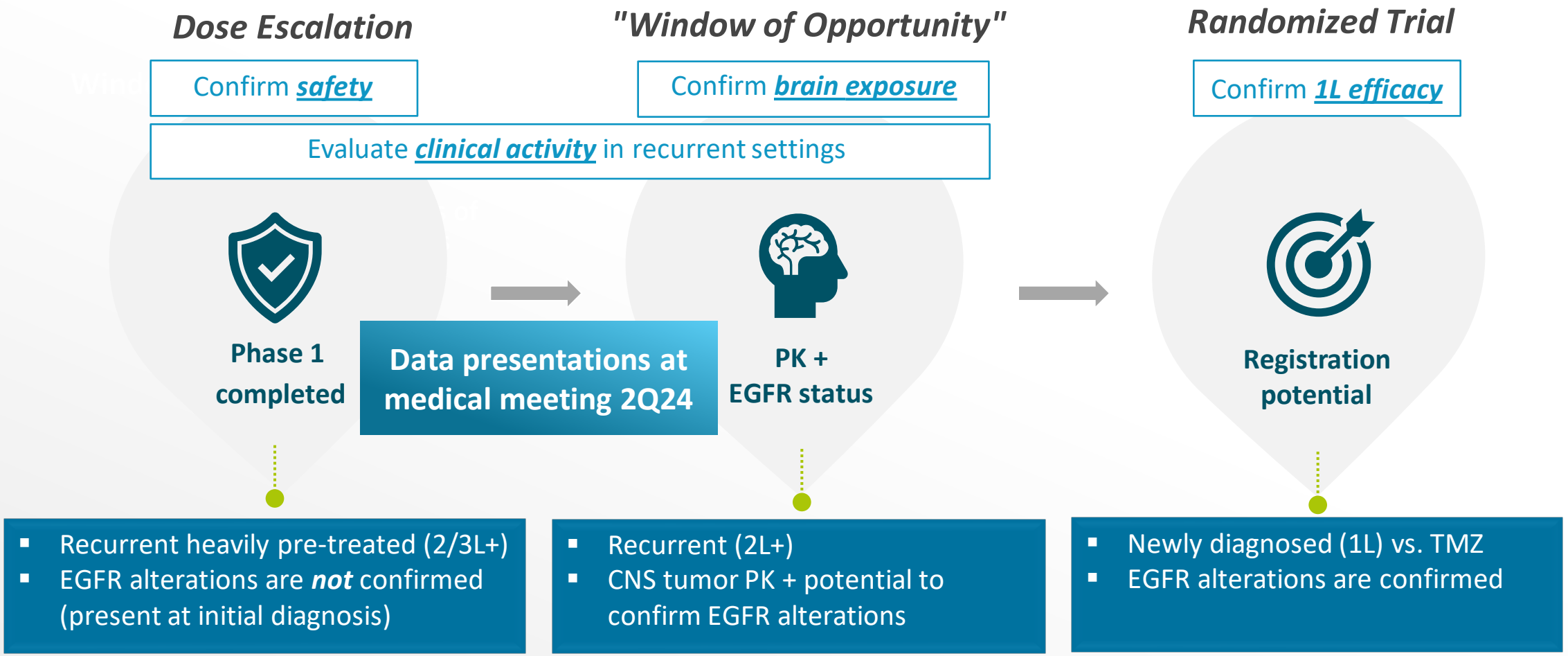
1. Saadeh, F., et al., The International Journal of Biological Markers, 2018 2. Real world evidence data from Tempus Labs analysis of 2,540 GBM patient samples

BDTX-1535: Potential to Overcome Limitations of Prior Attempts to Drug EGFR in GBM

Lessons From Past Failures	BDTX-1535
Heterogenic expression of EGFR oncogenic alterations within tumors	**Potent MasterKey inhibition of co-occurring EGFR alterations and amplification**
Paradoxical activation of EGFR GBM oncogenes induced by reversible inhibitors	**Covalent MOA and no paradoxical activation**
Poor tolerability driven by on target WT-EGFR activity	**Spares WT-EGFR in normal cells while retaining potent activity against EGFR alterations**
Low brain exposure due to a lack of CNS penetrance	**Designed to be brain-penetrant to treat CNS tumors**

MOA=mechanism of action; CNS=Central Nervous System; WT=Wild-Type; GBM=Glioblastoma Multiforme; NSCLC=Non-Small Cell Lung Cancer

BDTX-1535 GBM Development Path Designed for Sequential De-Risking



BDTX-4933:
Potential Best-in-Class Brain-Penetrant RAF MasterKey Inhibitor

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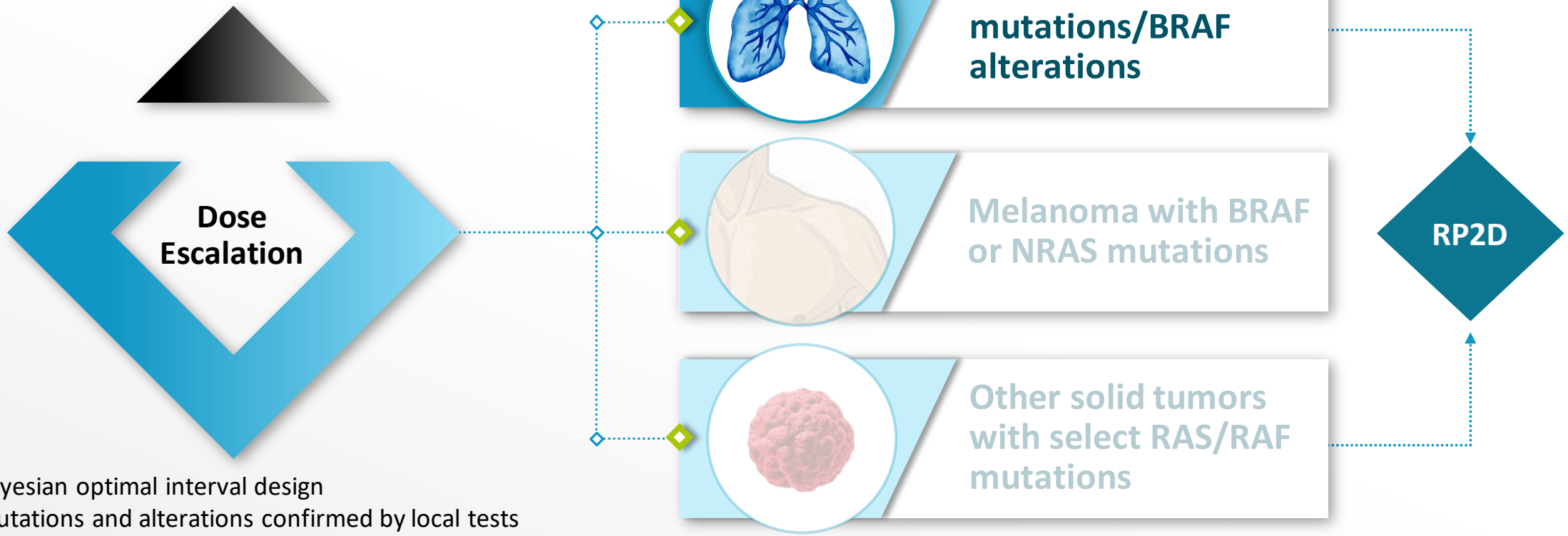
BDTX-4933: Oral, Brain-Penetrant, RAF MasterKey Inhibitor

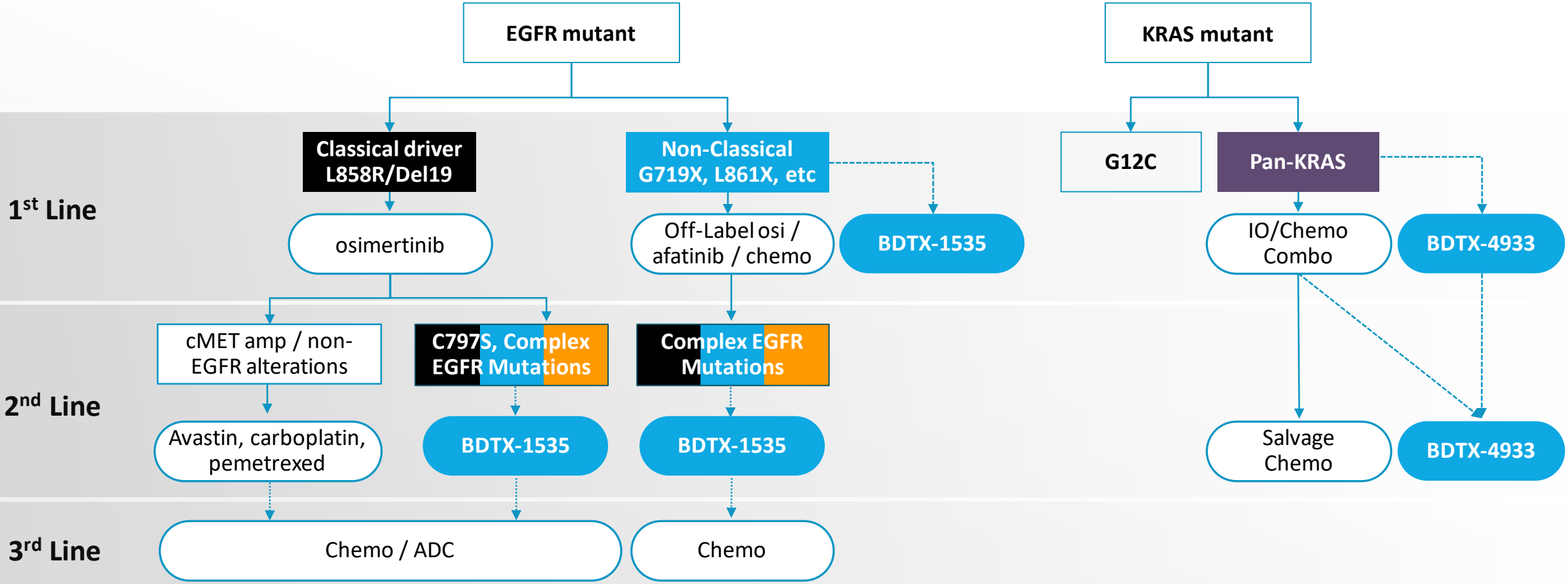
MasterKey	Potent preclinical inhibition of BRAF, KRAS, and NRAS alterations (“RAF-RAS clamp”)
Unique Pharmacology	Designed to target oncogenic conformation of RAF and avoid paradoxical activation
Brain Penetrant	Designed to be brain-penetrant to treat CNS disease
Status	Phase 1 data expected Q4 2024

BDTX-4933: Focused, Biomarker-Driven Phase 1 Trial Initiated Data Anticipated in Q4 2024

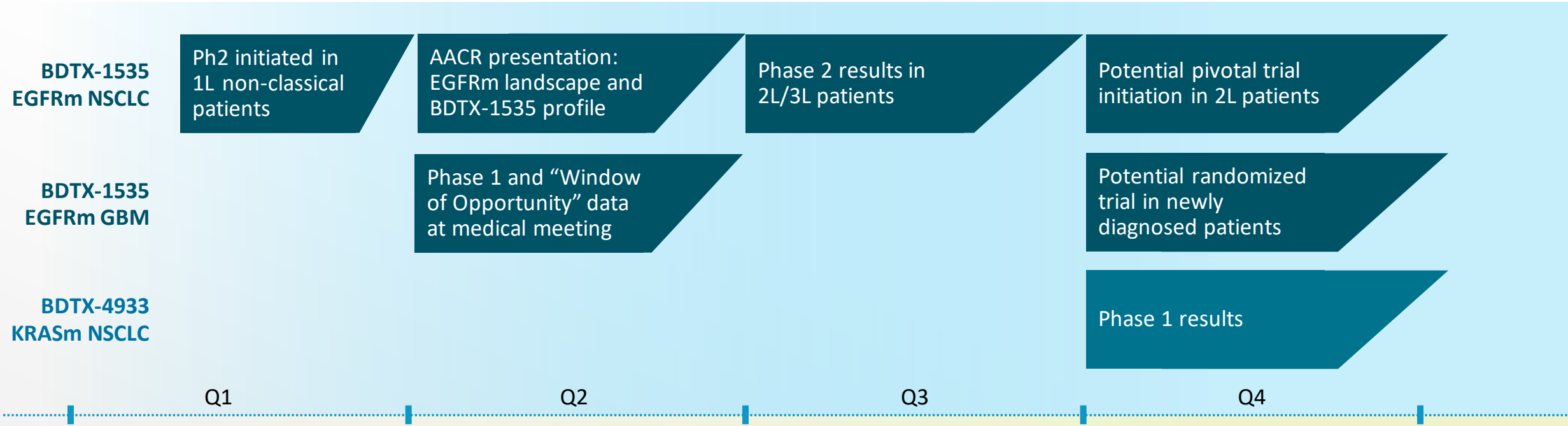


- Bayesian optimal interval design
- Mutations and alterations confirmed by local tests

BDTX-1535 and BDTX-4933: Potential for NSCLC Franchise



Anticipated 2024 Key Milestones



Financial Summary

$131.4m
as of December 31, 2023

Cash runway into Q2 2025

Thank You

Partnership: partnership@bdtx.com

Investors: investors@bdtx.com

Media: media@bdtx.com

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