Theseus Pharmaceuticals

A new generation of medicines to address cancer resistance

November 2021

Nasdaq | THRX

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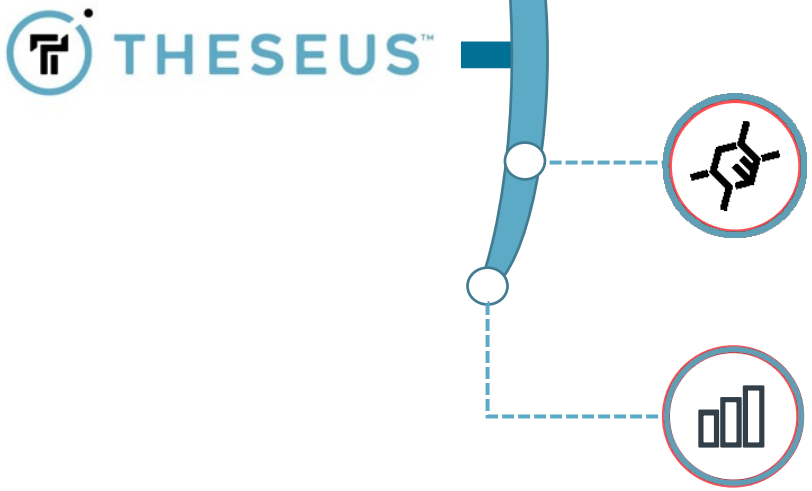
Theseus – working to outsmart cancer resistance

***Pan-variant** inhibitors:*

Therapeutics that inhibit all major genetic variants arising in an oncogenic target that cause resistance to cancer treatments



Led by scientific team from ARIAD

Differentiated, predictive R&D approach

- We believe we can accurately predict clinical outcomes for TKIs based on our PRA model

Multiple therapies in pipeline with several near-term catalysts

- **Lead program**, THE-630: next-generation pan-KIT inhibitor for refractory GIST
  - IND cleared, with Phase 1/2 clinical trial initiation expected late 4Q 2021 - mid 1Q 2022
- **Second program:** fourth-generation EGFR inhibitor for NSCLC; DC nomination expected 1H 2022

Strong financial position

- Completed $178.8 million IPO in October 2021

World class management team

Extensive experience and track record in TKI discovery, development, and commercialization

Tim Clackson, PhD
CEO
Former President, Xilio
Former President of R&D, CSO, ARIAD

Bill Shakespeare, PhD
Co-founder, President of R&D
Former VP Drug Discovery, ARIAD

Brad Dahms
CFO
Former CFO, Selecta Biosciences

David Dalgarno, D. Phil
Co-founder, CTO
Former VP Research Technologies, ARIAD

Vic Rivera, PhD
Co-founder, CSO
Former VP Preclinical & Translational Research, ARIAD

David Kerstein, MD
CMO
Former CMO, Anchiano
Former Sr. Med Dir, ARIAD & Takeda

Many members of leadership team worked together for over 20 years at ARIAD

Prior success at ARIAD validates pan-variant approach

Members of Theseus team discovered and developed five clinical-stage product candidates at ARIAD, including three approved TKIs: ICLUSIG® and ALUNBRIG®, pan-variant inhibitors, and EXKIVITY™

ARIAD PRODUCTS

TKI	Target	IND Filing	Approval
ICLUSIG® (ponatinib) tablets 45mg / 30mg / 15mg / 10mg	**Pan-BCR-ABL**	2007	2012
ALUNBRIG® BRIGATINIB 180mg | 90mg | 30mg TABLETS	**Pan-ALK**	2011	2017
EXKIVITY™ mobocertinib 40 mg capsules	**EGFR-ex20**	2015	2021

Theseus is leveraging the experience cultivated at ARIAD to build next-generation pan-variant kinase inhibitors

Our research and discovery approach

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The Problem

- Cancers can have any number of many known genetic variants that lead to treatment resistance
- Variants may already exist at diagnosis or emerge after any line of therapy
- Individual patients often have more than one resistance-causing genetic variant

Identify clinically validated targets with clear unmet need

Structure-guided drug design with predictive screening methodologies

Translationally-driven, biomarker-guided clinical development

The Power of ‘Pan-ness’ and the Predictive Resistance Assay (PRA)

Seeking to develop truly “pan-variant” targeted therapies that address all known drug resistance mutations with a single agent

The Power of ‘Pan’

- Therapeutics with **pan-variant coverage** have a broad range of activity against all genetic variants that have been shown to contribute to treatment resistance
- Pan-variant inhibitors may potentially provide substantially improved efficacy outcomes in **late lines** of therapy, by **inhibiting** all resistance mutants potentially present in tumors
- Pan-variant inhibitors can provide substantial improvements in **early lines** of therapy compared to current standard of care by anticipating mutations and **preventing** their emergence in the first place

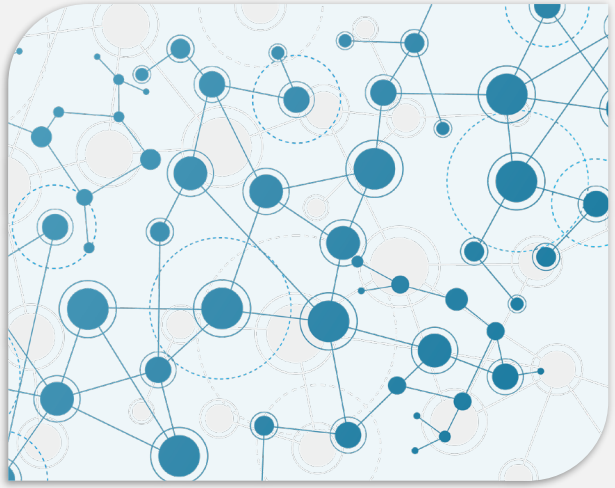
The Theseus Strategy

The **Predictive Resistance Assay (PRA)**, honed over many years, guides development of pan-variant inhibitors that are uniquely designed to target all known clinically relevant mutations in a given cancer, thereby outsmarting cancer resistance

Our discovery engine iterates structure-guided design, PRAs

Structure-guided design

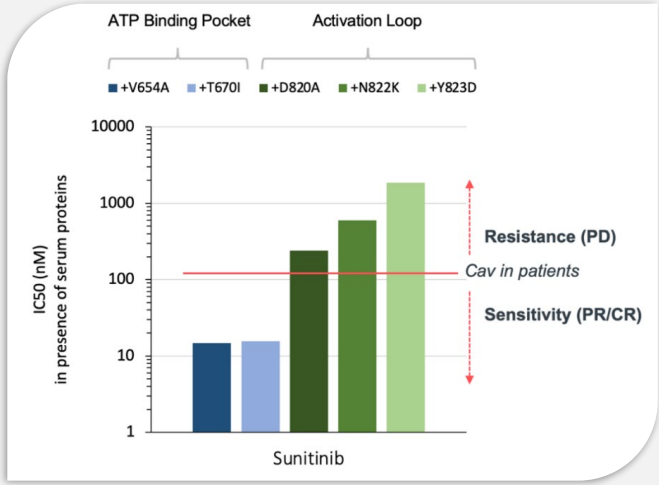
- Begin with small molecule with several, spatially **distributed molecular touchpoints** at target binding site on TKI
  - Molecule maintains physical contact—and likely, activity—against any number of multiple variants



Optimize 'pan-ness' by iterating between experimental, computational analysis of molecule

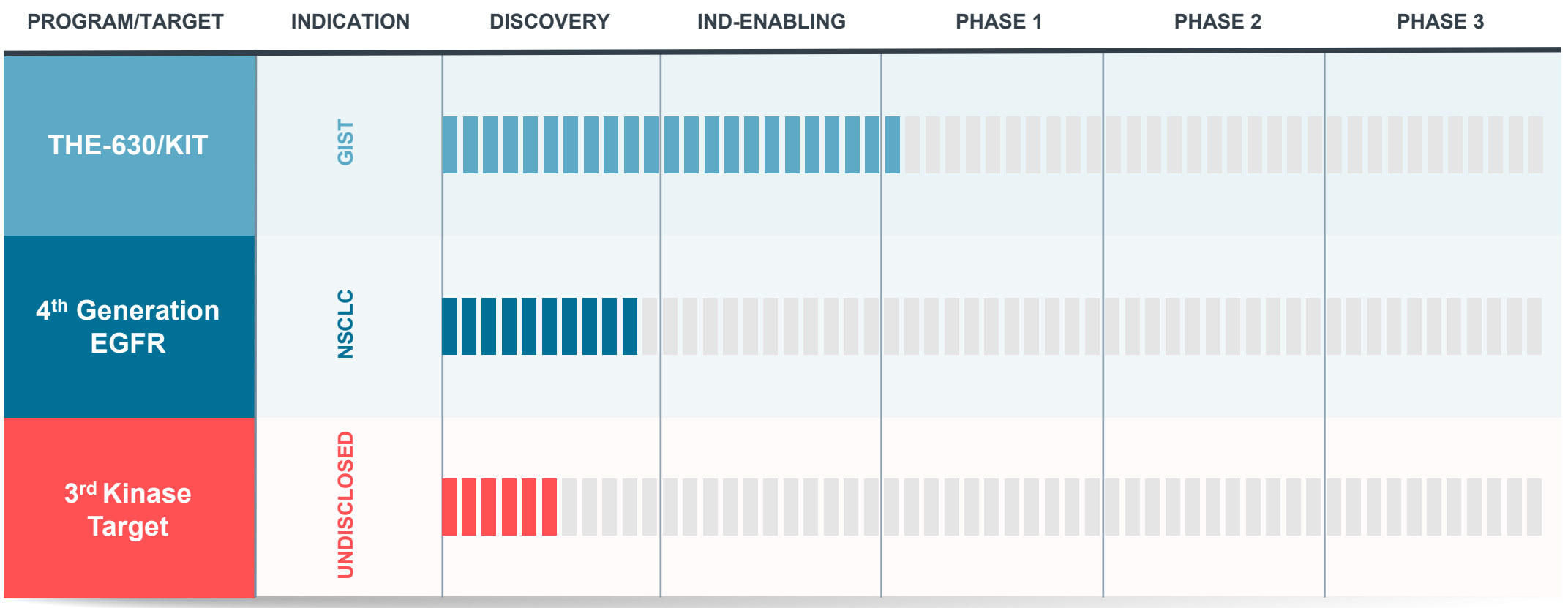
Predictive Resistance Assay (PRA)

- Cell-based assay with human serum proteins; mimics the physiological environment
- **Helps predict clinical outcomes** for tyrosine kinase inhibitors (TKIs) in the context of **anticipated mutations**



Our pipeline

Developing pan-variant tyrosine kinase inhibitors for cancers with great unmet need



Several potential targets in research and discovery

*We hold a worldwide exclusive license to THE-630 in our therapeutic area of focus through the ARIAD License Agreement, as defined and described in the section titled "Business—ARIAD License Agreement." in the prospectus filed with the Securities Exchange Commission

THE-630: Pan-KIT Inhibitor

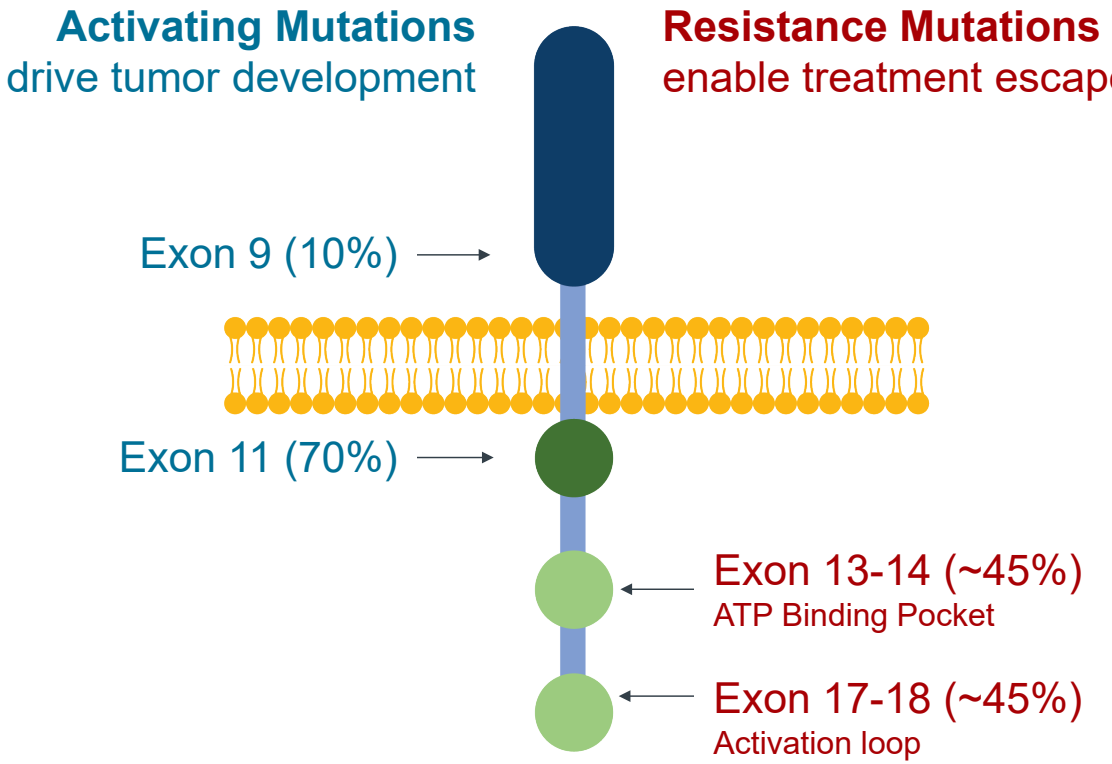
Gastrointestinal stromal tumors (GIST) overview

GIST is the **most common sarcoma of the GI tract** with **~4,000-6,000** new cases in the U.S. each year

Key features of GIST

- **Genetics** of primary sensitivity and secondary resistance are **well understood**
- Remains KIT-driven **through multiple lines of therapy**
- Tumor heterogeneity: patients' tumors frequently **have multiple subclones**, each with a different mutation, which creates **need for pan-variant inhibitor**

Gastrointestinal stromal tumors (GIST): Activating and resistance mutations in KIT



KIT-driven activating mutations

- **~80%** of cases are driven by mutations that activate kinase activity of KIT

KIT-driven resistance mutations

- **Up to 90%** of relapse cases are driven by secondary resistance mutations in KIT

Current limitations of GIST treatment options create significant unmet medical need

Line	Therapy	ORR	Median PFS (*Months*)
1st	**Imatinib**	51.4%	18.9
2nd	**Sunitinib**	6.8%	5.5
3rd	**Regorafenib**	4.5%	4.8
4th	**Ripretinib**	9.4%	6.3

Treatment limitations

- Most patients who receive first-line imatinib relapse due to the emergence of secondary mutations
- Subsequent lines of therapy are **significantly less effective**
  - response rates 4.5% - 9.4%
  - median PFS: 4.8 months - 6.3 months
- Patients exposed to side effects of multiple therapies

A truly pan-KIT inhibitor could address limitations of current GIST treatments

Note: ORR means Objective Response Rate; PFS means Progression Free Survival

We believe our PRA model allows us to predict the deficiencies of current GIST therapies

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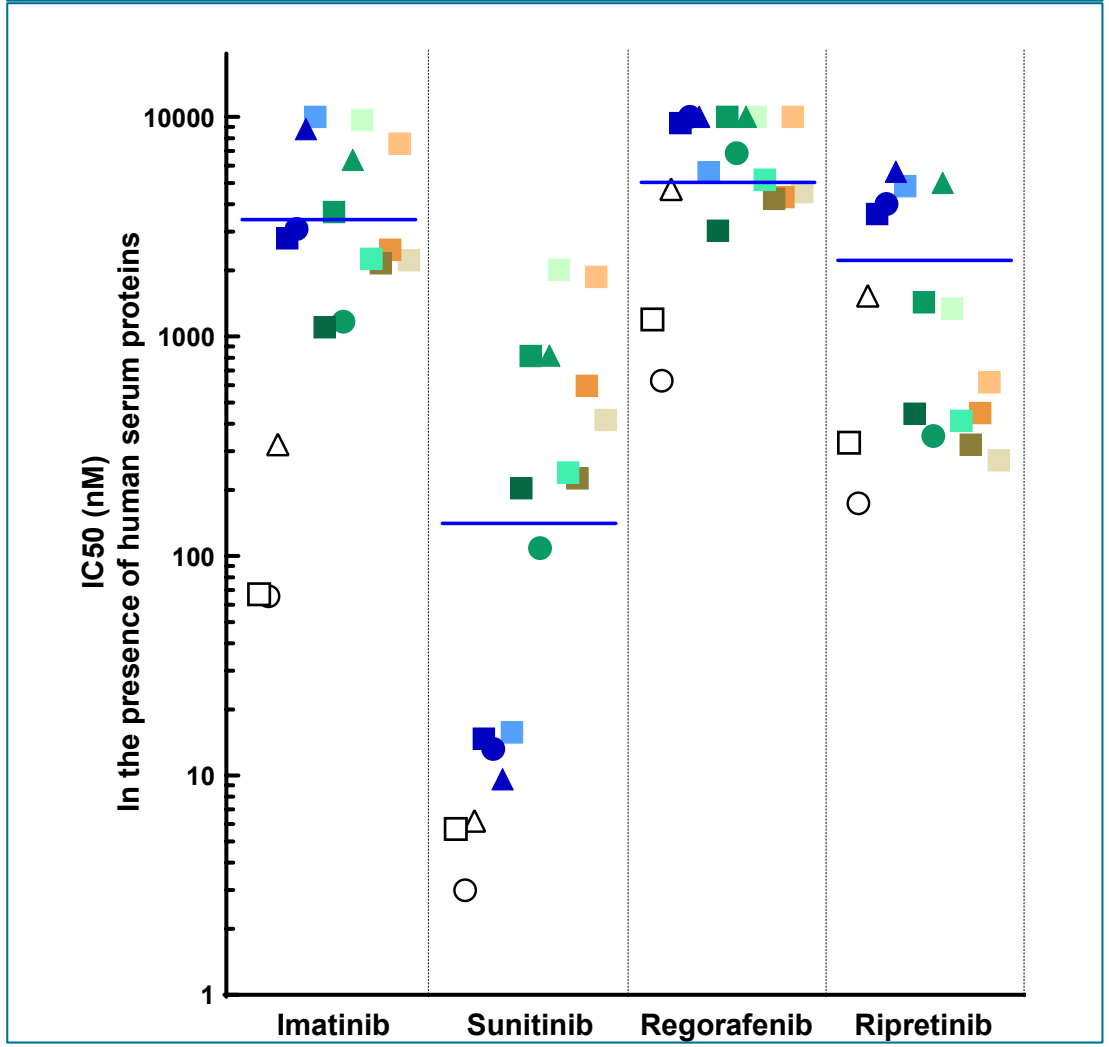
Activity of approved TKIs in the PRA against KIT activation and resistance mutations

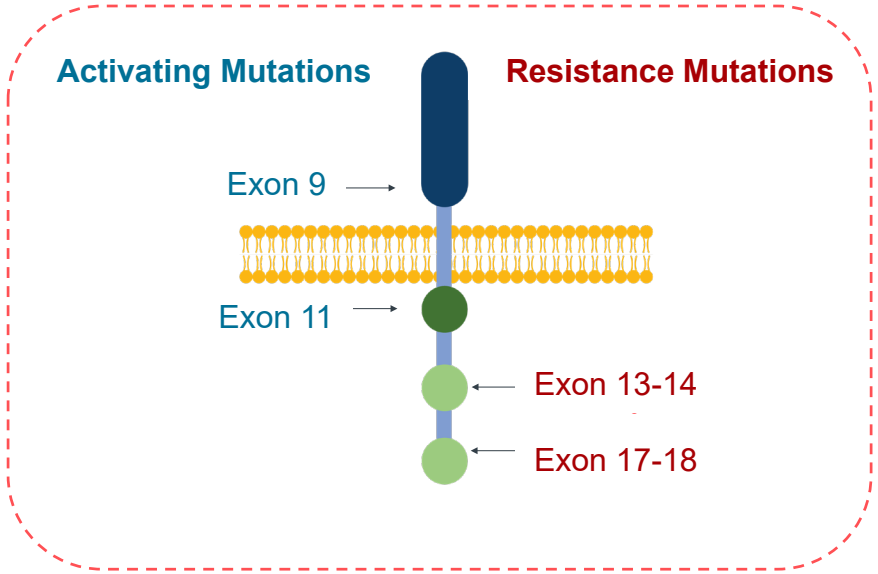


PRA predicts resistance of multiple mutations to currently approved GIST therapies

Note: PR/CR means partial/complete response; SD means stable disease; PD means progressive disease. Cav is calculated as the Area Under the Curve, or AUC, over a 24-hour period and divided by 24

None of the available GIST therapies are pan-KIT inhibitors

Therapy	PRA Predicted Response			
	Activating Mutations		Resistance Mutations	
	Exon 9	Exon 11	Exon 13-14 ATP Binding Pocket	Exon 17-18 Activation Loop
Imatinib	●	●	●	●
Sunitinib	●	●	●	●
Regorafenib	●	●	●	●
Ripretinib	●	●	●	●



PRA-Predicted Best Response

PR/CR ● SD ● PD

PRA predicts that in GIST, known KIT mutations may yield resistance to any approved TKI therapies

Note: PR/CR means partial/complete response; SD means stable disease; PD means progressive disease

PRA predicts that THE-630 has pan-KIT activity

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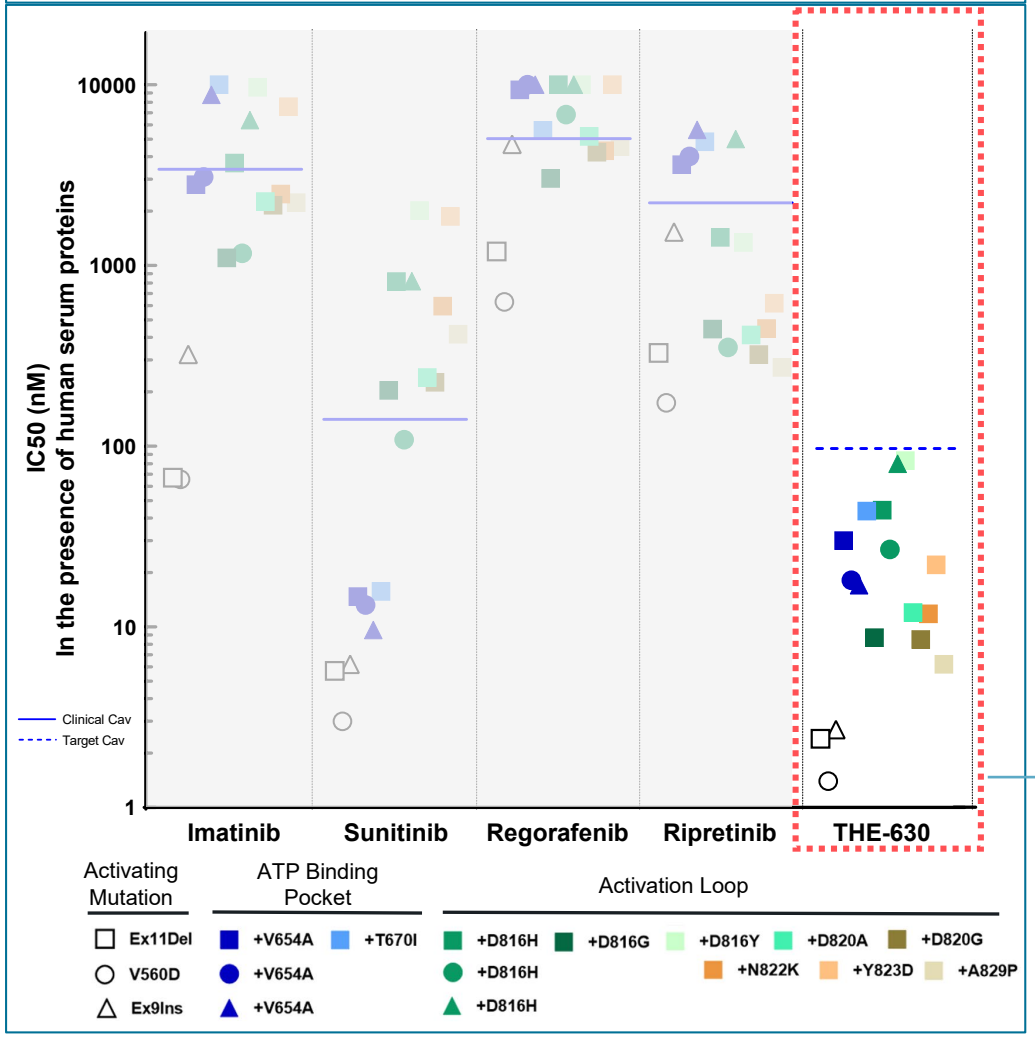
Activity of THE-630 and approved TKIs in the PRA against KIT activation and resistance mutations



Therapy	PRA Predicted Response			
	Activating Mutations		Resistance Mutations	
	Exon 9	Exon 11	Exon 13-14 ATP Binding Pocket	Exon 17-18 Activation Loop
Imatinib	●	●	●	●
Sunitinib	●	●	●	●
Regorafenib	●	●	●	●
Ripretinib	●	●	●	●
THE-630*	●	●	●	●

PRA-Predicted Best Response

PR/CR ● SD ● PD

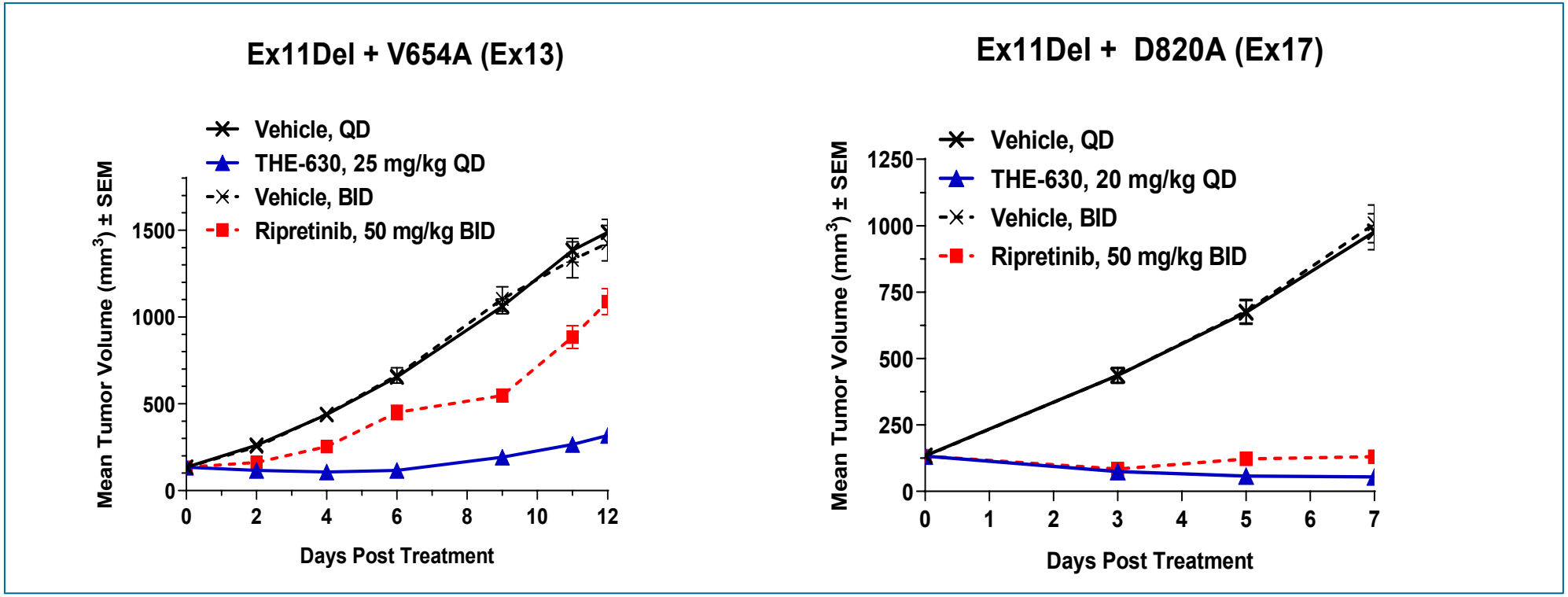
THE-630 has the potential to be a next-generation, pan-KIT inhibitor for GIST patients

*Based on 100 nM target Cav

Note: PR/CR means partial/complete response; SD means stable disease; PD means progressive disease. Cav is calculated as the Area Under the Curve, or AUC, over a 24-hour period and divided by 24

THE-630 has the profile of a pan-KIT inhibitor for GIST *in vivo*

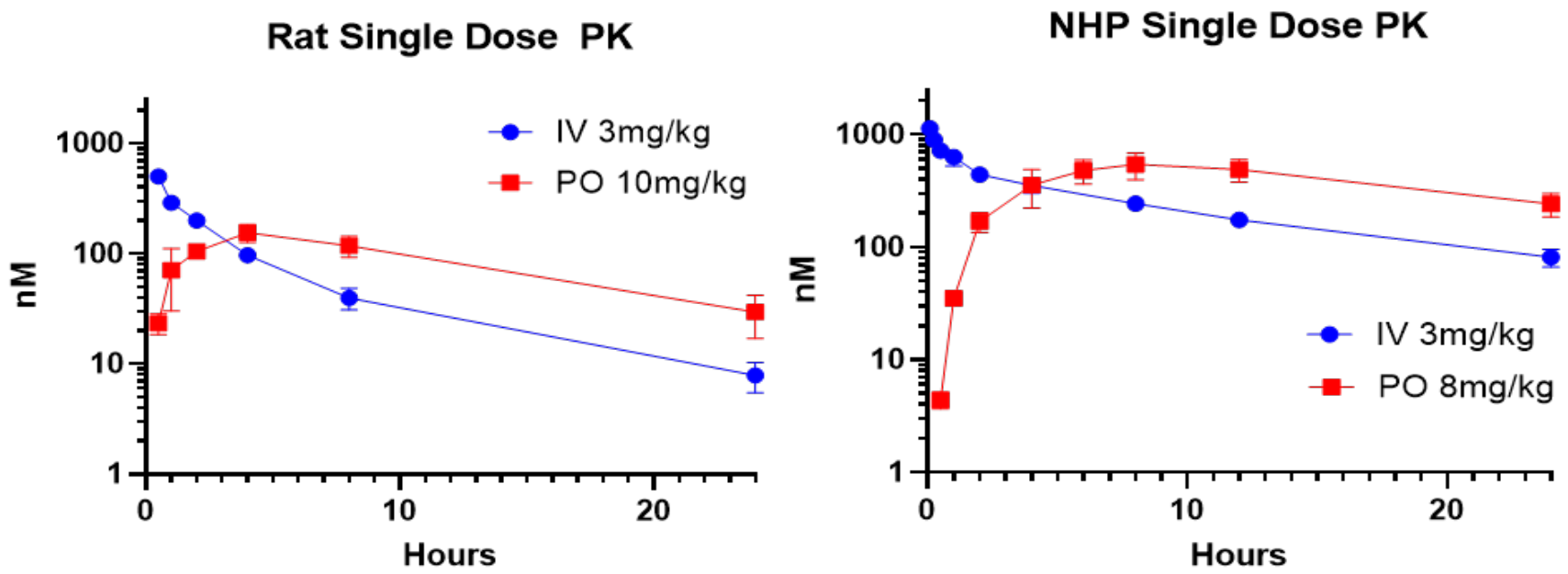
Model: Ex11Del activating mutation + indicated resistance mutation



- **Ripretinib:** Strong anti-tumor activity against activation loop (D820A/Ex17) but **not ATP binding pocket** (V654A/Ex13) mutations
- **THE-630:** Strong anti-tumor activity against **both classes of resistance mutations**

Note: QD is once daily dosing. BID is twice daily

THE-630 PK supports once-daily oral dosing



Orally bioavailable across multiple species – mice, rats and NHPs

In primate PK studies,target plasma levels of THE-630 sustained above 100nM

Results of toxicology studies support clinical evaluation of THE-630

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Kinome Selectivity

- Designed to avoid key counter-targets
- Kinome selectivity *in vitro* comparable to the approved KIT inhibitor ripretinib
  - **50/330 inhibited by THE-630; 43/330 for ripretinib**

In Vitro and *In Vivo* Pharmacology

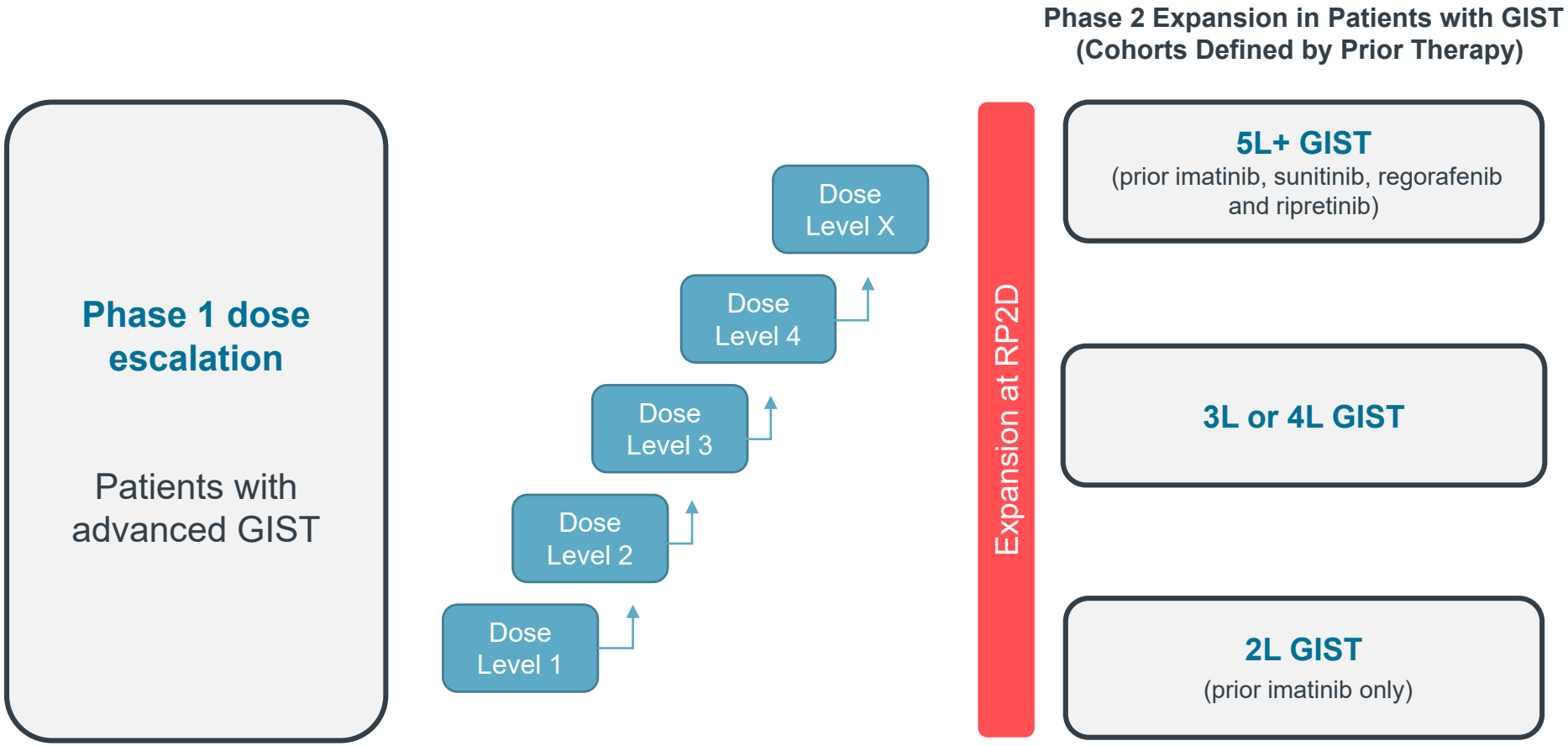
- No drug-drug interactions or cardiac toxicity liabilities identified in standard pharmacology assays
- No adverse effects seen in standard Good Laboratory Practice *in vivo* safety pharmacology studies

GLP Toxicology in Non-Human Primates

- No observed adverse effect level identified in non-human primates provides PK coverage at or above IC50s for all KIT mutants evaluated in PRA
- Good Laboratory Practice studies used to derive planned first in human doses

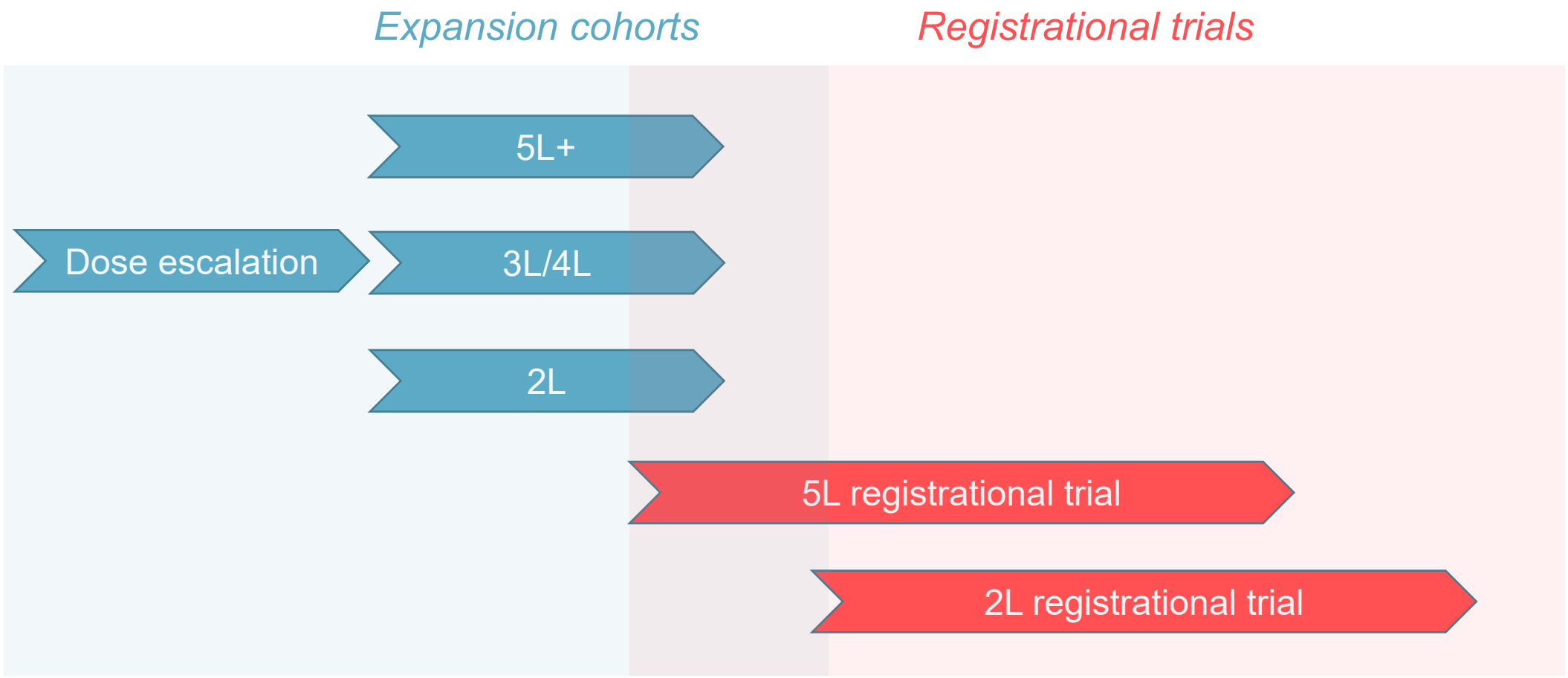
Phase 1/2 dose escalation and dose expansion trial design

First-in-human trial for THE-630 is expected to be a phase 1/2 trial with dose escalation and dose expansion cohorts; the phase 1 portion is expected to be initiated between late 4Q 2021 and mid 1Q 2022



Registration strategy for THE-630

Based on data from the planned phase 1/2 trial in patients with advanced GIST and regulatory feedback, we intend to commence a registration trial in fifth-line GIST followed by the initiation of a registration trial in second-line GIST



Fourth-Generation EGFR Inhibitor

Lung cancer overview

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Second-most commonly diagnosed cancer worldwide

~2.2 million

New cases diagnosed globally in 2020

NSCLC is the most common form of lung cancer

~85%

Percentage of lung cancers diagnosed as NSCLC

EGFR mutations are a leading driver of NSCLC

up to 50%

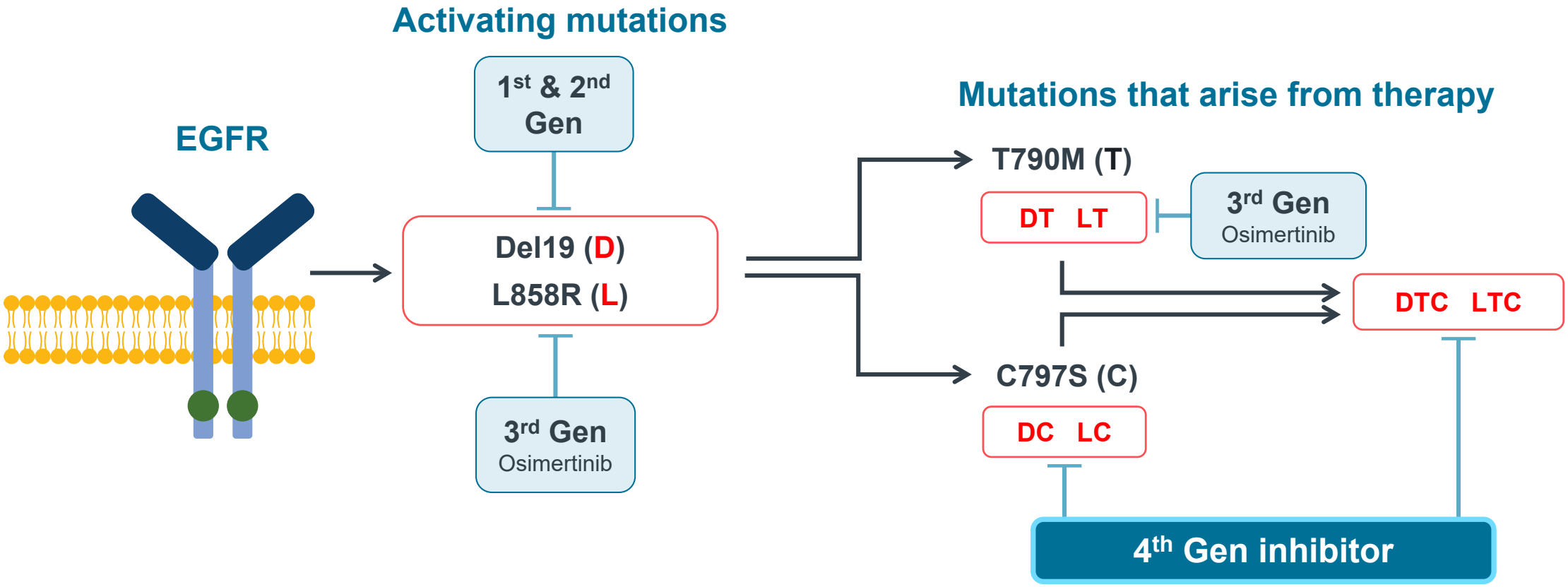
NSCLC tumors driven by activating mutations in EGFR

Majority of EGFR mutations in exons 19 or 21

~90%

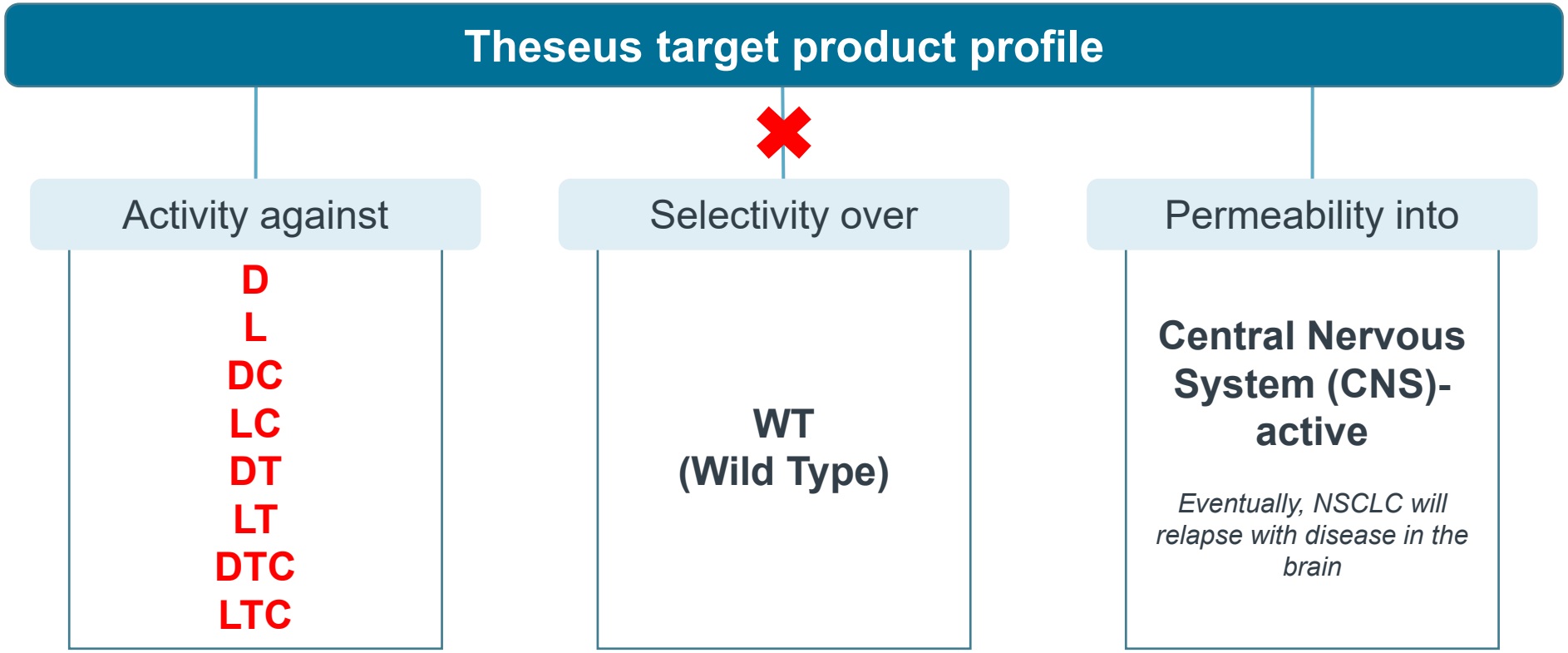
EGFR mutations which are in exon 19 or 21 of the gene that encodes EGFR

Resistance to osimertinib represents a significant unmet need in EGFR-mutant NSCLC



In patients whose tumors progress on osimertinib, C797S and other resistance mutations in EGFR have been observed at a frequency of up to ~12% after first-line osimertinib and ~20% after second-line osimertinib

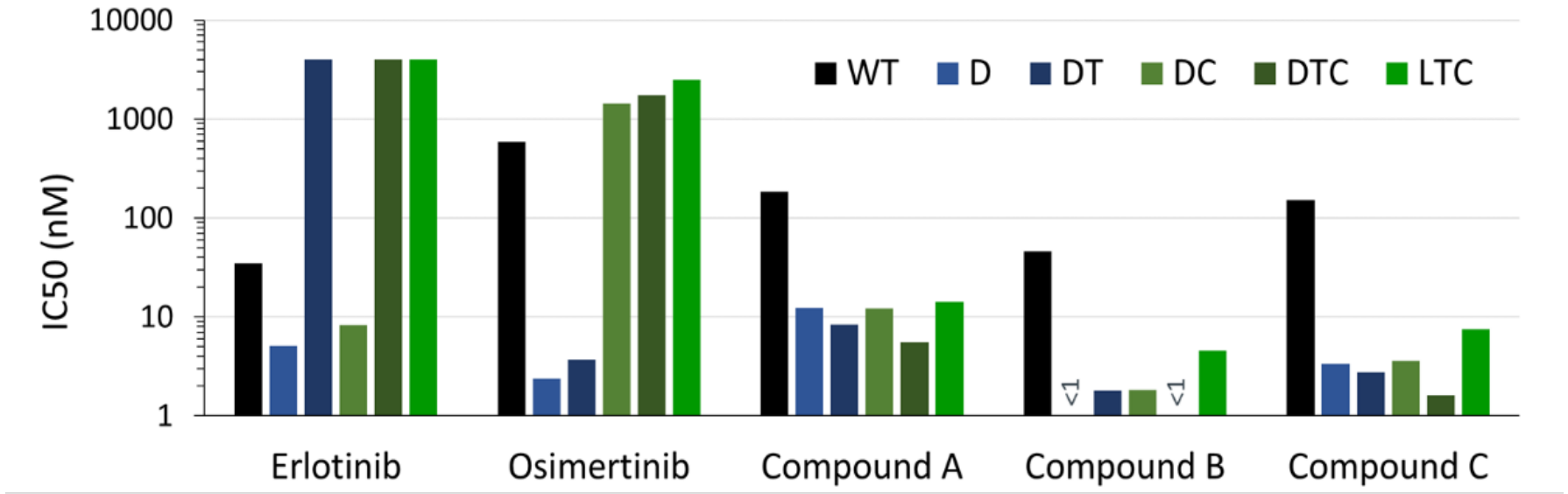
Theseus target product profile—coverage over all known mutants, selectivity over wild type EGFR, CNS activity



Identifying compounds that cross the blood brain barrier and have activity in the CNS is essential

Novel series exhibit potent EGFR mutant activity in cells with selectivity over wild-type

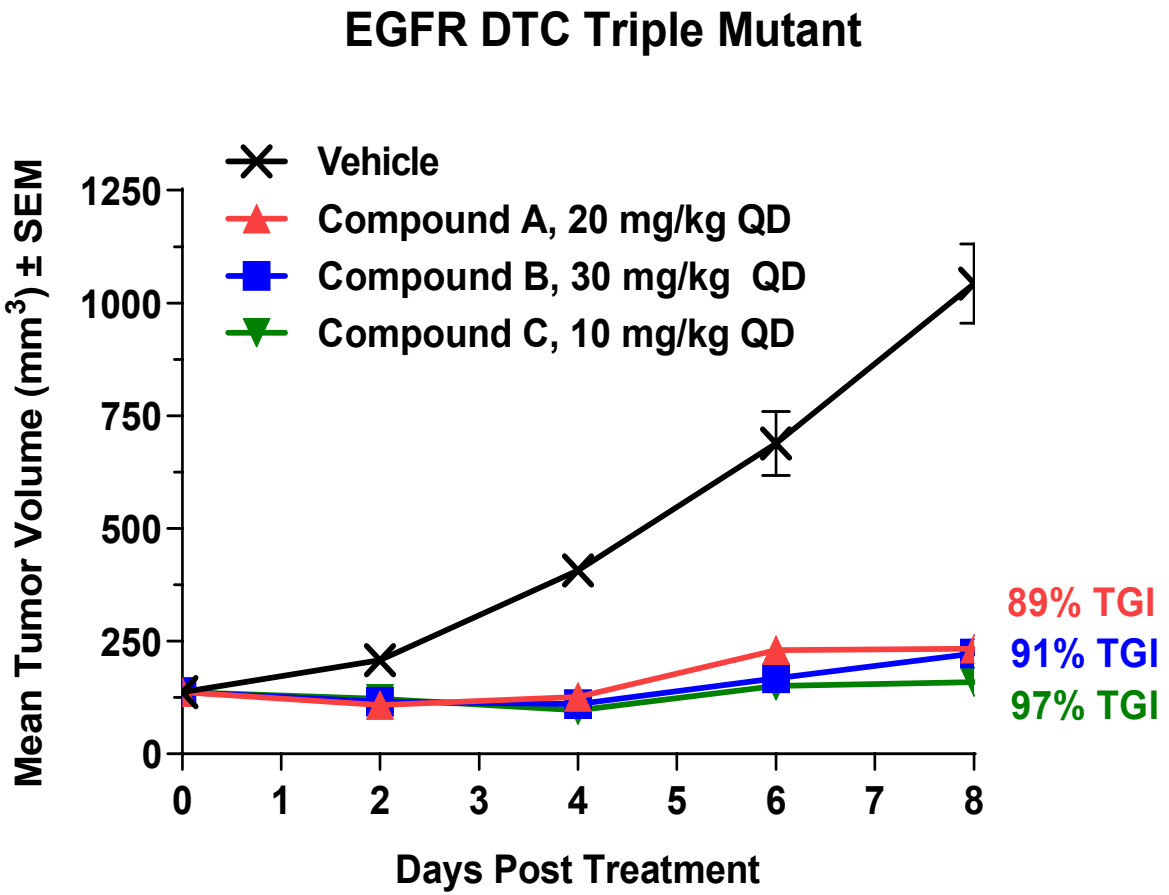
Development candidate nomination expected in 1H 2022



Potency against WT EGFR vs EGFR mutants in cellular assays

Theseus compounds demonstrated low nanomolar IC50 values against single-, double- and triple-mutant EGFR variants, with selectivity over WT EGFR

Novel series shows *in vivo* anti-tumor activity in triple-mutant DTC model



Theseus compounds exhibited strong anti-tumor activity in DTC model at doses well-tolerated in mice

Note: QD is once daily dosing

Theseus Compound B demonstrates strong anti-tumor activity against single(L)-, double(LT)-, and triple(LTC)-mutant EGFR variants *in vivo*

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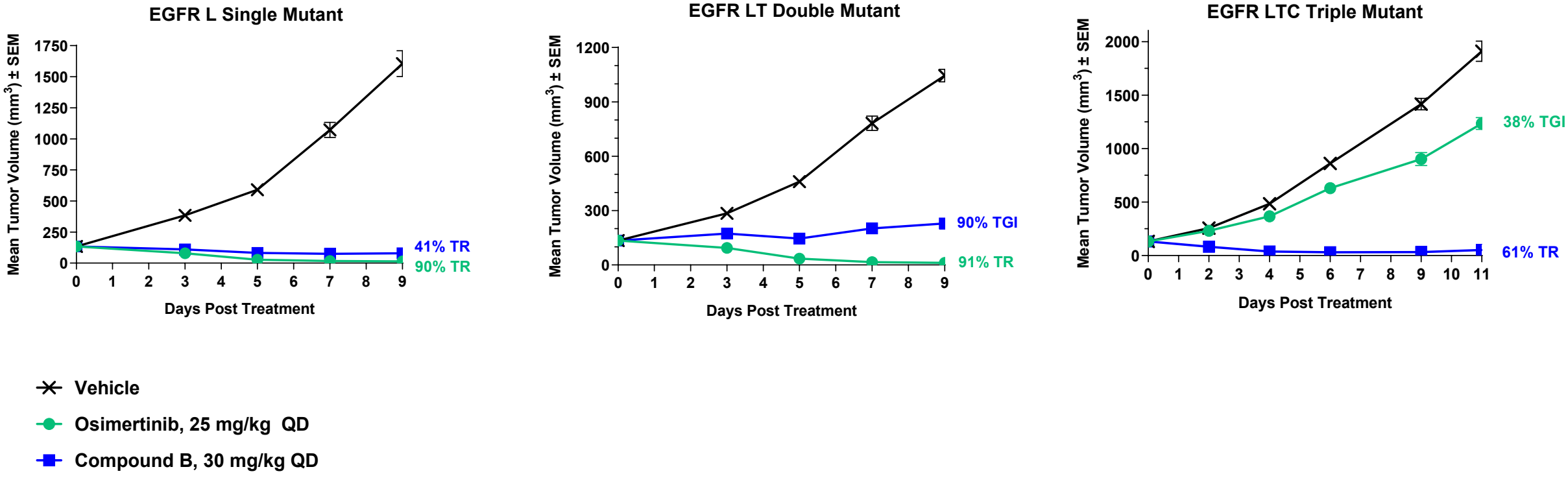
Intracranial mouse models to assess CNS activity are currently under development



Note: QD is once daily dosing. TR is Tumor Regression. TGI is Tumor Growth Inhibition

Roadmap to success

Multiple near-term inflection points	• IND clearance for THE-630; expect initiation of phase 1/2 clinical trial between late 4Q 2021 and mid 1Q 2022 • DC nomination 1H 2022 for fourth-gen EGFR program
Team to succeed	Leveraging prior and proven achievements in the discovery, development and commercialization of cancer therapeutics
Importance of 'Pan'	True pan-variant approach tackling cancer resistance and addressing a wider range of drug resistance mutations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