

precision that moves™

STAYING ONE STEP AHEAD OF DISEASE



welcome

**JEFF ALBERS**

Chief Executive Officer



# Forward-looking statements

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. The words “may,” “will,” “could,” “would,” “should,” “expect,” “plan,” “anticipate,” “intend,” “believe,” “estimate,” “predict,” “project,” “potential,” “continue,” “target” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. In this presentation, forward-looking statements include, without limitation, statements regarding plans and timelines for the development of avapritinib, pralsetinib, fisogatinib, and BLU-263, including the timing, design, implementation, enrollment, plans and announcement of results regarding the ongoing and planned clinical trials for the drug candidates of Blueprint Medicines Corporation (the “Company”); plans and timelines for current and future marketing applications for avapritinib and pralsetinib; plans, timelines and expectations for the review and administrative split by the Food and Drug Administration (the “FDA”) of the new drug application (“NDA”) for avapritinib for the treatment of adult patients with PDGFRA Exon 18 mutant GIST, regardless of prior therapy, and fourth-line GIST, including any extension of the regulatory action date for the fourth-line GIST population; plans, timelines and expectations for top-line data from the VOYAGER trial; plans and timelines for nominating additional development candidates and expectations for those development candidates to be first-in-class; the potential benefits of the Company’s current and future drug candidates in treating patients; expectations regarding the Company’s existing cash, cash equivalents and investments; and the Company’s strategy, goals and anticipated milestones, business plans and focus. The Company has based these forward-looking statements on management’s current expectations, assumptions, estimates and projections. While the Company believes these expectations, assumptions, estimates and projections are reasonable, such forward-looking statements are only predictions and involve known and unknown risks, uncertainties and other important factors, many of which are beyond the Company’s control and may cause actual results, performance or achievements to differ materially from those expressed or implied by any forward-looking statements. These risks and uncertainties include, without limitation, risks and uncertainties related to the delay of any current or planned clinical trials or the development of the Company’s drug candidates, including avapritinib, pralsetinib, fisogatinib and BLU-263, or the licensed products, including BLU-782; the Company’s advancement of multiple early-stage efforts; the Company’s ability to successfully demonstrate the efficacy and safety of its drug candidates and gain approval of its drug candidates on a timely basis, if at all; the preclinical and clinical results for the Company’s drug candidates, which may not support further development of such drug candidates; actions or decisions of regulatory agencies or authorities, which may affect the initiation, timing and progress of clinical trials; the FDA’s intent to administratively split the proposed indications for avapritinib into two separate NDAs, which may not mean that either indication is approved; a delay in the review of the proposed indications as a result of the administrative split of the current NDA; FDA concerns regarding whether the response rate in the fourth-line GIST population was reasonably likely to predict clinical benefit in that population; there can be no assurance that the VOYAGER top-line data will be sufficient for the FDA’s review of the proposed fourth-line indication or that there will not be a delay in the availability of VOYAGER top-line data; the Company’s ability to obtain, maintain and enforce patent and other intellectual property protection for any drug candidates it is developing; the Company’s ability to develop and commercialize companion diagnostic tests for its current and future drug candidates; and the success of the Company’s current and future collaborations, partnerships, and license, including its cancer immunotherapy collaboration with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. (collectively, “Roche”), its collaboration with CStone Pharmaceuticals (“CStone”), and its license agreement with Clementia Pharmaceuticals Inc. (“Clementia”).

These and other risks and uncertainties are described in greater detail under “Risk Factors” in the Company’s filings with the Securities and Exchange Commission (“SEC”), including the Company’s most recent Quarterly Report on Form 10-Q and any other filings the Company has made or may make with the SEC in the future. The Company cannot guarantee future results, outcomes, levels of activity, performance, developments, or achievements, and there can be no assurance that the Company’s expectations, intentions, anticipations, beliefs, or projections will result or be achieved or accomplished. The forward-looking statements in this presentation are made only as of November 5, 2019, and except as required by law, the Company undertakes no obligation to update any forward-looking statements contained in this presentation as a result of new information, future events or otherwise.

This presentation also contains estimates, projections and other statistical data made by independent parties and by the Company relating to market size and growth and other data about the Company’s industry. These data involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of the Company’s future performance and the future performance of the markets in which the Company operates are necessarily subject to a high degree of uncertainty and risk.

# Our core mission and foundational principles

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Blueprint Medicines aims to deliver on the promise of precision medicine to improve and extend the lives of patients with cancer and rare diseases.

**HIGHLY SELECTIVE  
INHIBITORS**



**PATIENT  
SELECTION**



**ADAPTIVE  
ABILITY**



# Our core mission and foundational principles

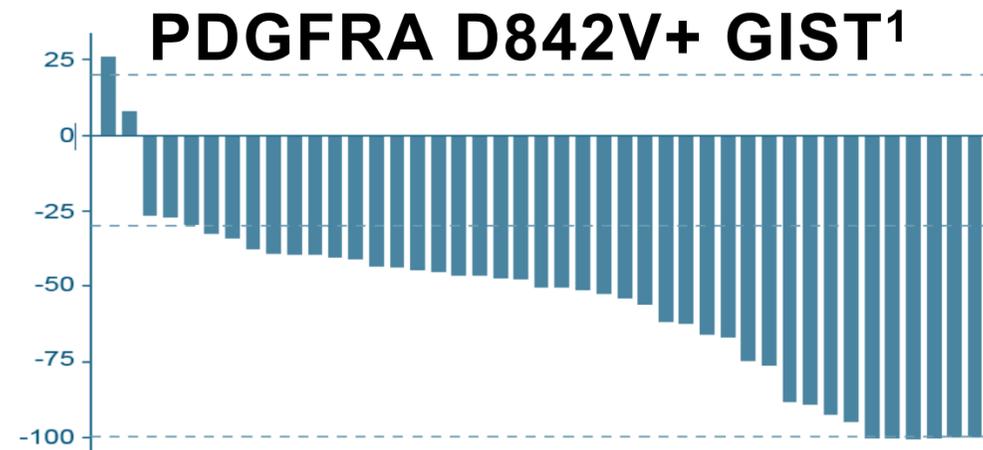
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Blueprint Medicines aims to deliver on the promise of precision medicine to improve and extend the lives of patients with cancer and rare diseases.



# Principles in action: expedited development of avapritinib and pralsetinib

**AVAPRITINIB**

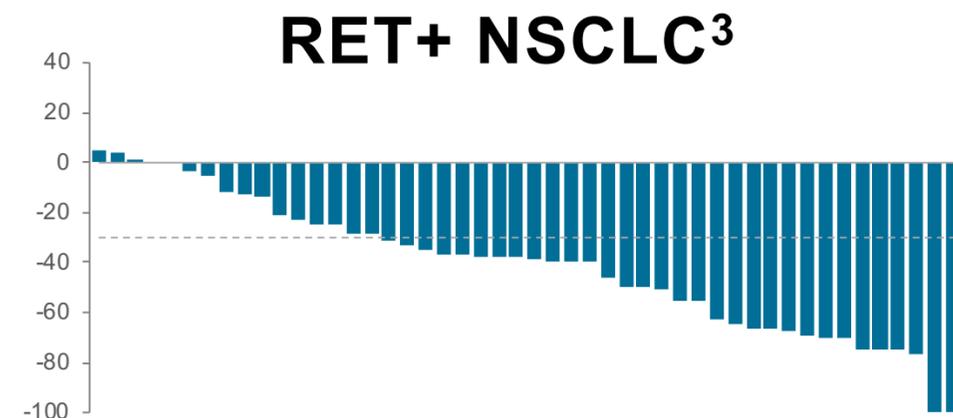


**Breakthrough  
therapy  
designation<sup>2</sup>**

**~4 years**

from IND to initial  
NDA submission

**PRALSETINIB**



**Breakthrough  
therapy  
designation<sup>4</sup>**

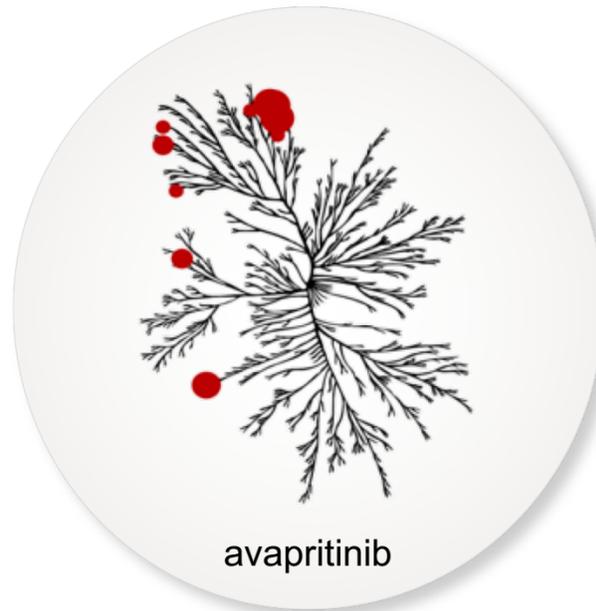
**~3 years**

from IND to planned  
initial NDA submission

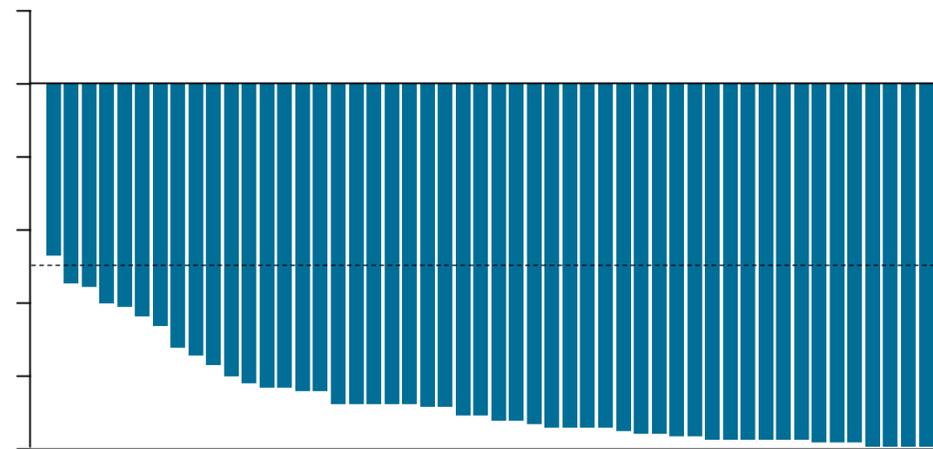
# The rapid evolution of Blueprint Medicines



## HIGHLY SELECTIVE KINASE MEDICINE DISCOVERY PLATFORM



## RAPID CLINICAL PROOF-OF-CONCEPT ACROSS MULTIPLE PROGRAMS



Avapritinib in advanced systemic mastocytosis: change in serum tryptase<sup>1</sup>

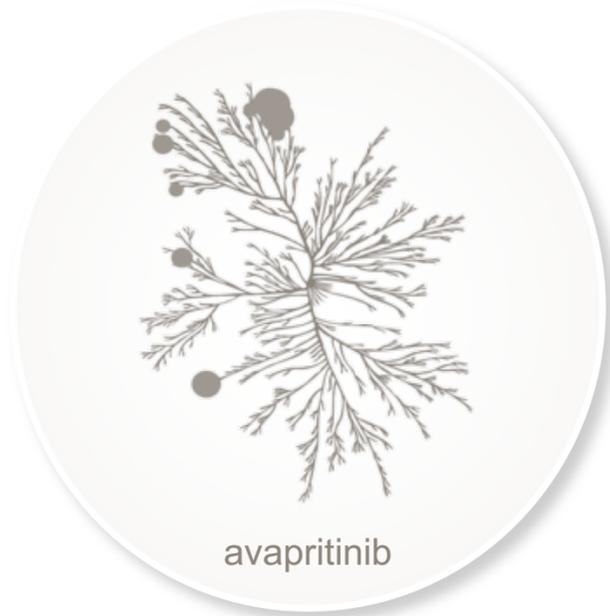
- Integrated commercialization
- Indication expansion
- Therapeutic area leadership
- Innovative kinase biology



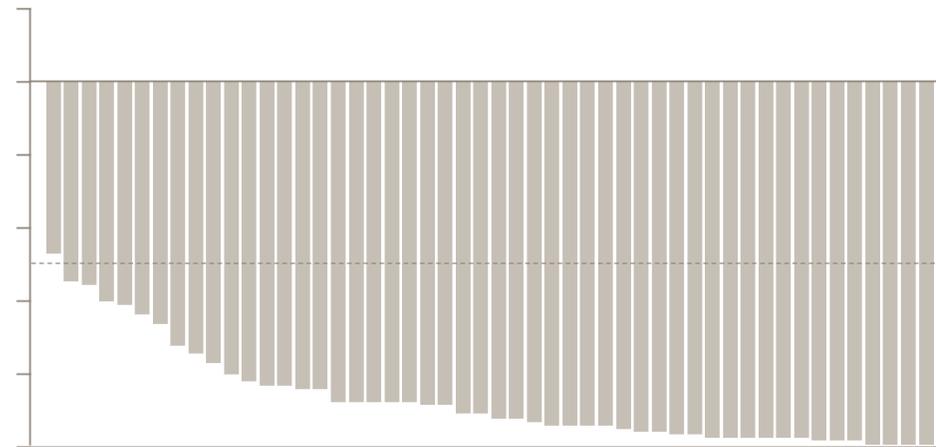
# Our focus today: three key themes



HIGHLY SELECTIVE KINASE MEDICINE  
DISCOVERY PLATFORM



RAPID CLINICAL  
PROOF-OF-CONCEPT ACROSS  
MULTIPLE PROGRAMS



Avapritinib in advanced systemic mastocytosis:  
change in serum tryptase<sup>1</sup>

Integrated commercialization

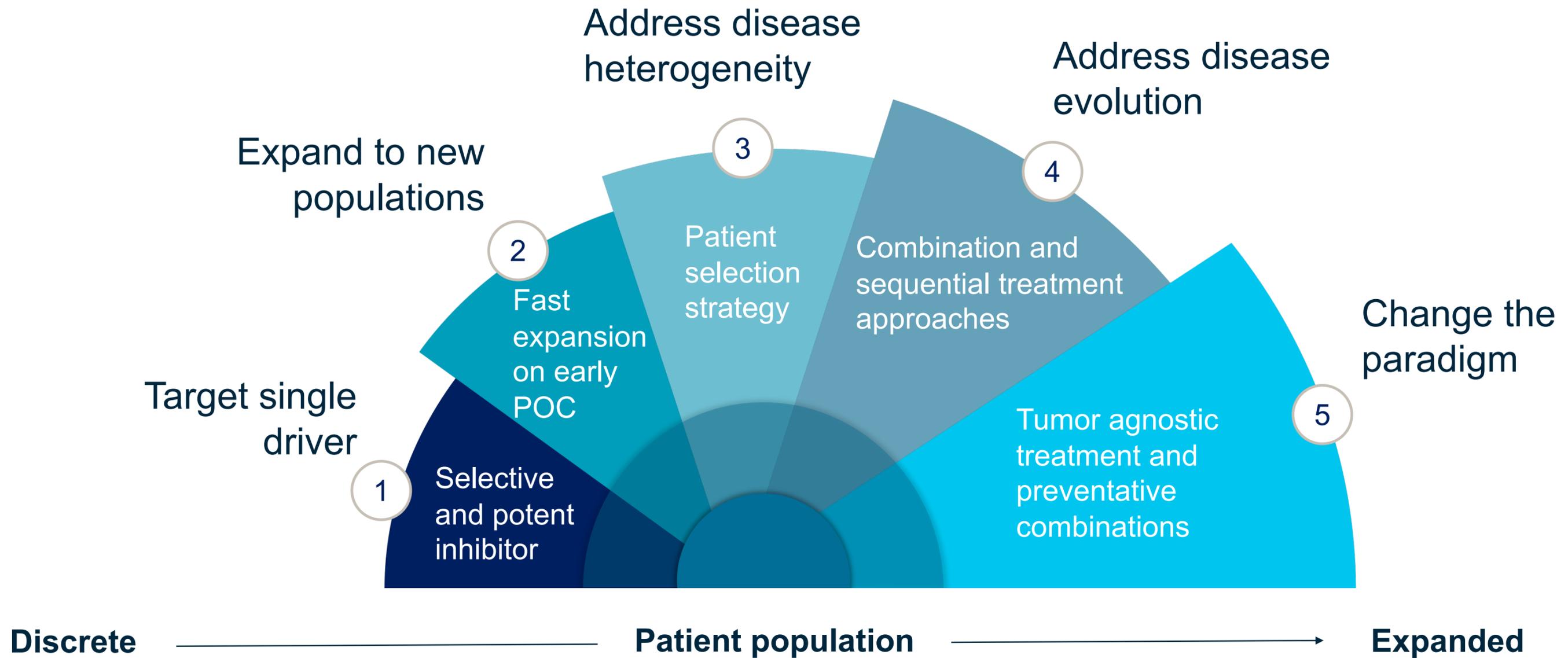
Indication expansion

Therapeutic area leadership

Innovative kinase biology

# INDICATION EXPANSION

We aim to make transformative precision therapies and expand their application to additional patient populations over time



We aim to make transformative precision therapies and expand their application to additional patient populations over time

## **BLU-263**

**A next-generation KIT inhibitor  
for mast cell disorders**

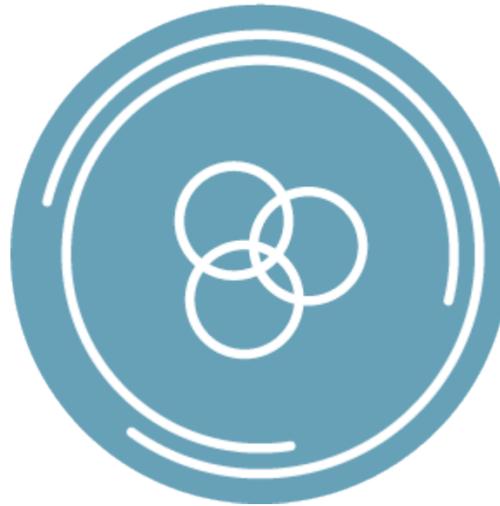
# THERAPEUTIC AREA LEADERSHIP

With a cornerstone precision therapy, we can rapidly reinvest insights and realize efficiencies

Next-generation  
inhibitors



Combination  
strategies



Enhanced  
patient selection



CLINICAL  
AND  
COMMERCIAL  
SCALE

TRANSLATIONAL INSIGHTS

With a cornerstone precision therapy, we can rapidly reinvest insights and realize efficiencies

# **First-in-class EGFR inhibitors** for treatment-resistant non-small cell lung cancer

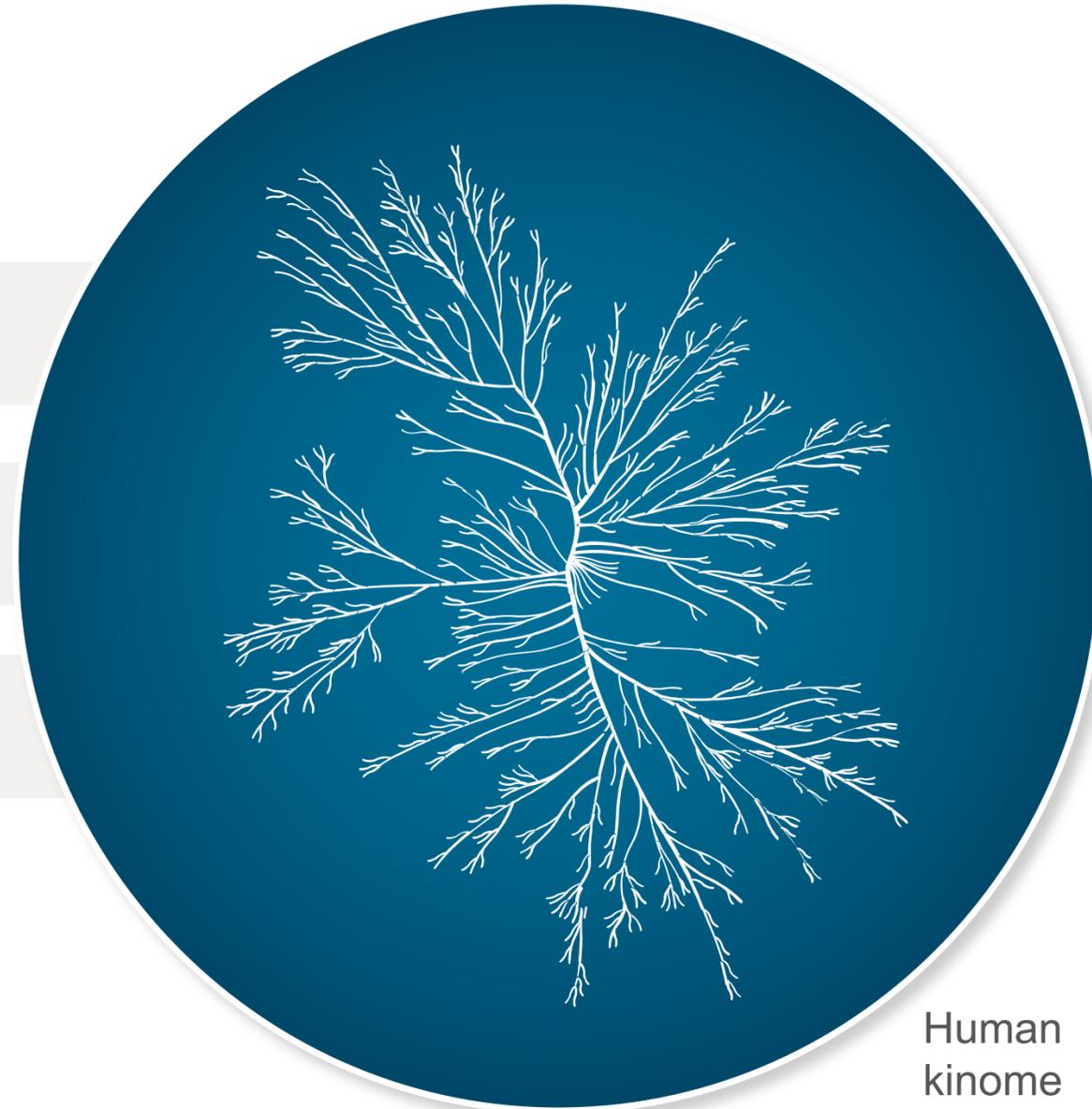
# INNOVATION

Our scientific platform enables us to explore new kinase biology, representing even larger opportunities to impact patient care

**GENETIC DRIVERS**

**IMMUNOKINASES**

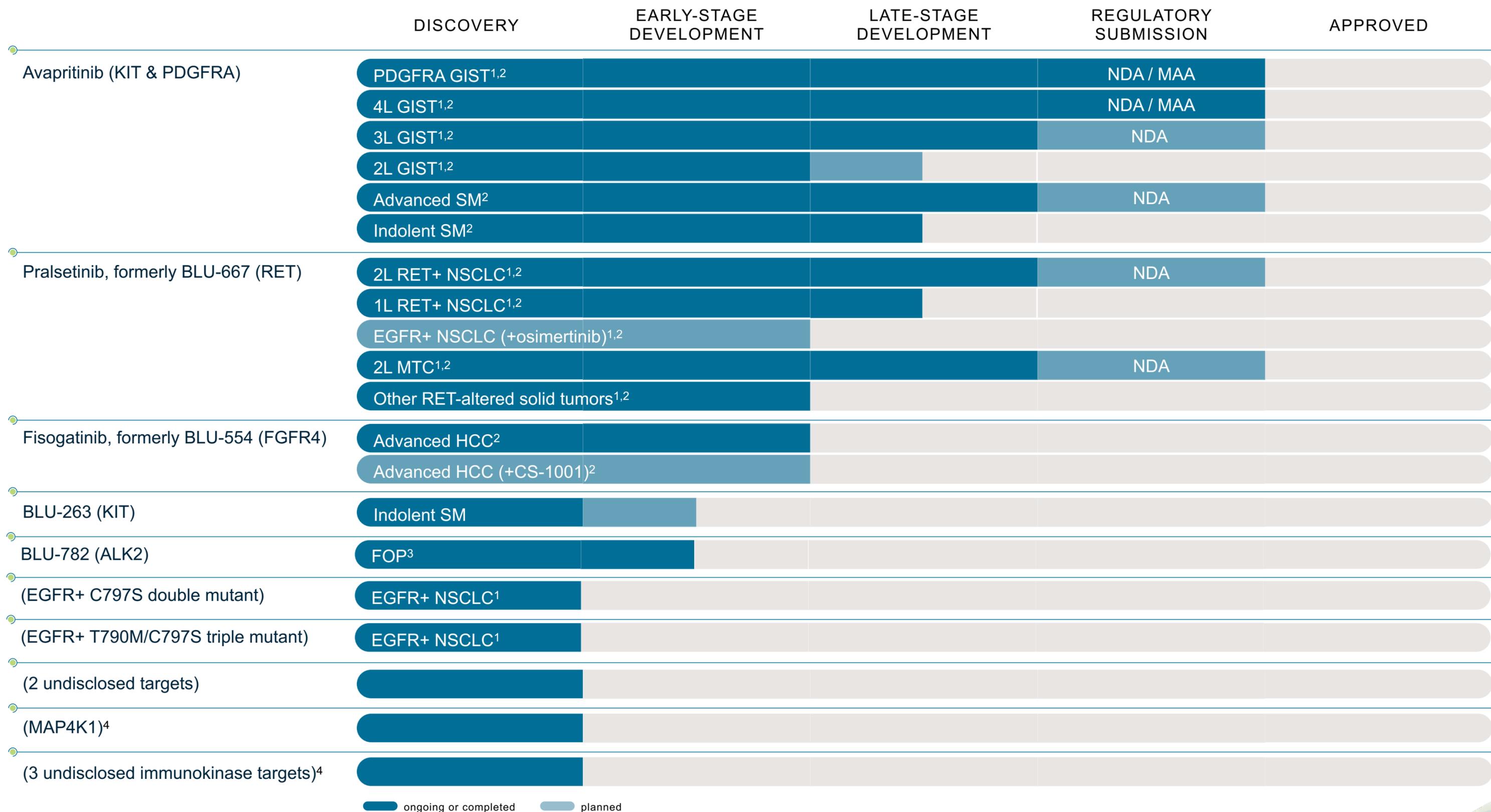
**NOVEL BIOLOGY**



Human kinome

Our scientific platform enables us to explore new kinase biology, representing even larger opportunities to impact patient care

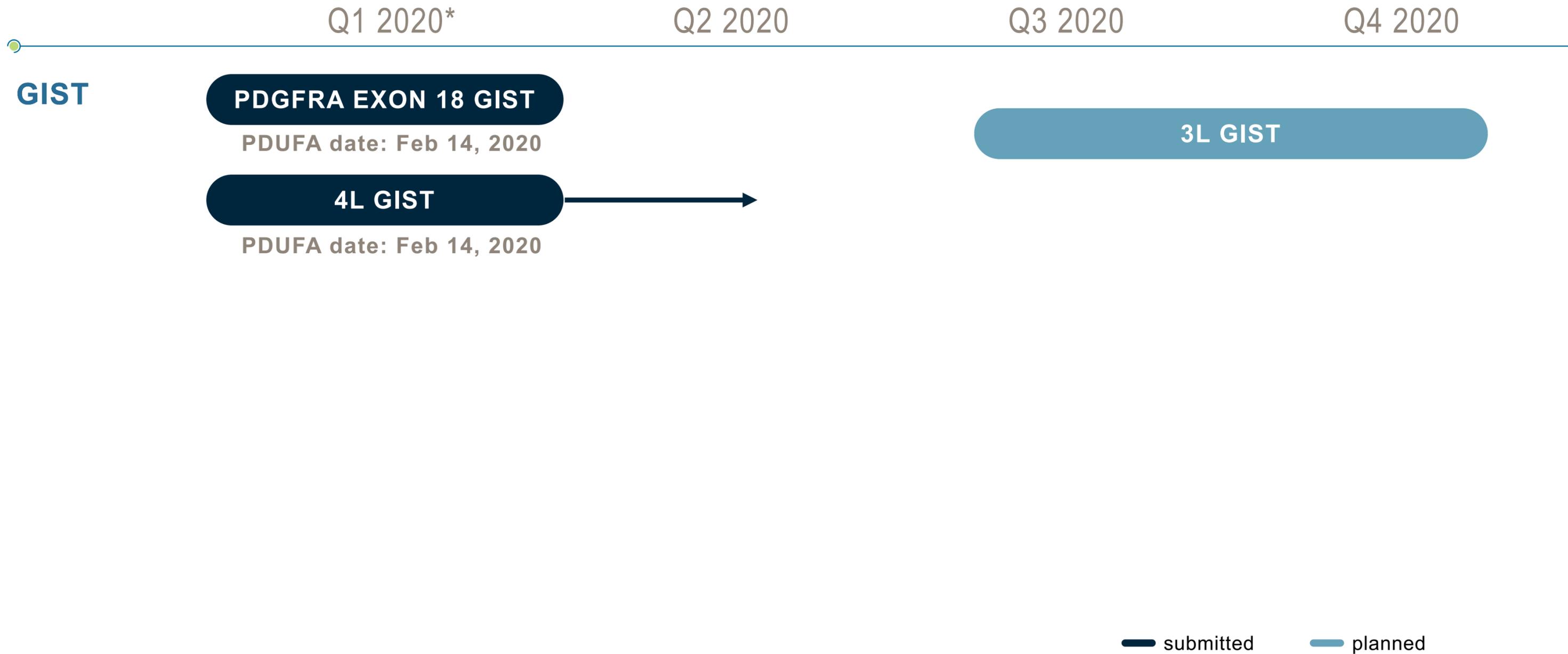
# First-in-class MAP4K1 immunokinase inhibitor



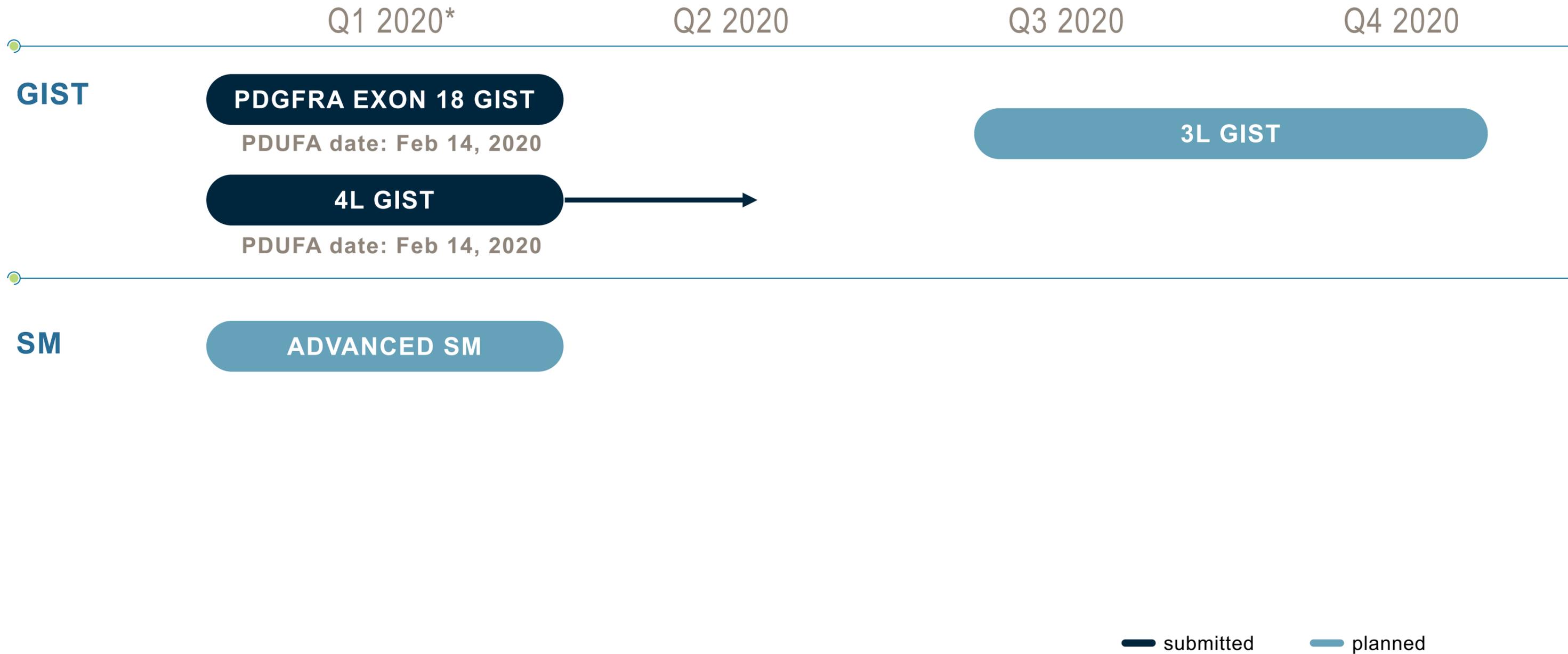
1. Unresectable or metastatic disease. 2. CStone Pharmaceuticals has exclusive rights to develop and commercialize avapritinib, pralsetinib and fisogatinib in Mainland China, Hong Kong, Macau and Taiwan. Blueprint Medicines retains all rights in the rest of the world. 3. Clementia Pharmaceuticals has exclusive, worldwide rights to develop and commercialize BLU-782. 4. In collaboration with Roche. Blueprint Medicines has U.S. commercial rights for up to two programs. Roche has worldwide commercialization rights for up to two programs and ex-U.S. commercialization rights for up to two programs. 1L, first-line; 2L, second-line; 3L, third-line; 4L, fourth-line; FOP, fibrodysplasia ossificans progressiva; GIST, gastrointestinal stromal tumors; HCC, hepatocellular carcinoma; MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer.



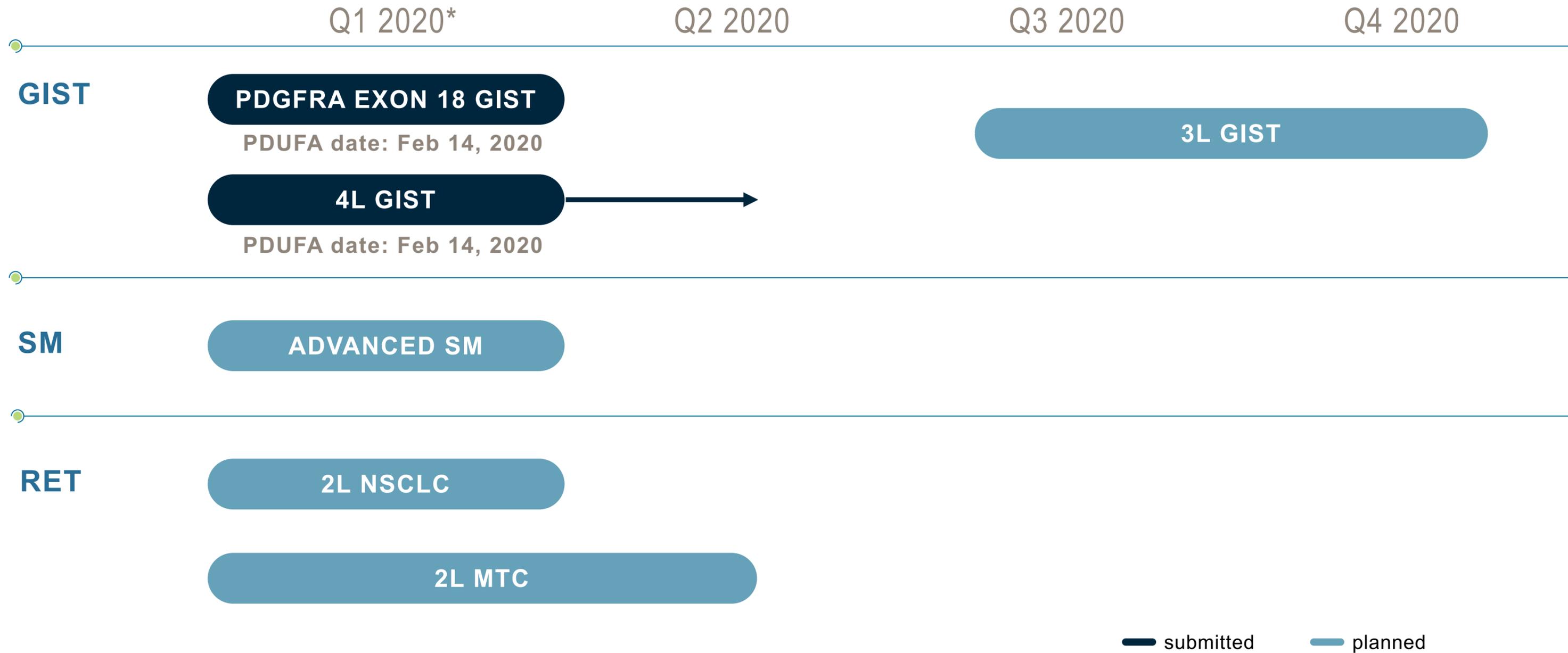
# Submitted and planned New Drug Applications in 2020



# Submitted and planned New Drug Applications in 2020



# Submitted and planned New Drug Applications in 2020



# R&D Day agenda

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Welcome and company vision

**Jeff Albers**, Chief Executive Officer

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Solving patient needs in systemic mastocytosis

**Cem Akin, MD, PhD**, Professor of Medicine, University of Michigan  
**Andy Boral, MD, PhD**, Chief Medical Officer  
**Christina Rossi**, Chief Commercial Officer

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Q&A – Part 1

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BREAK

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A prolific platform for precision medicine

**Marion Dorsch, PhD**, Chief Scientific Officer

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Addressing tumor evolution in lung cancer

**Tim Guzi, PhD**, Senior Vice President, Chemistry

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Cancer immunotherapy: a new frontier

**Klaus Hoeflich, PhD**, Vice President, Biology

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Q&A – Part 2

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Closing remarks

**Jeff Albers**, Chief Executive Officer

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# Addressing patient needs in systemic mastocytosis

**Cem Akin, M.D., Ph.D.**

Professor of Medicine, University of Michigan

**Andy Boral, M.D., Ph.D.**

Chief Medical Officer

**Christy Rossi**

Chief Commercial Officer



*K.G., living  
with SM*

# Systemic mastocytosis is one disease with a common genetic driver

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**ADVANCED SYSTEMIC MASTOCYTOSIS**

**INDOLENT SYSTEMIC MASTOCYTOSIS**

**KIT D816V**  
mutation  
frequency

~95% of  
patients

# Overview of indolent systemic mastocytosis

**CEM AKIN, MD, PhD**

Professor of Medicine,  
University of Michigan



# Disclosures

- Cem Akin, MD, PhD
- Investigator: Blueprint Medicines' ongoing Phase 2 PIONEER trial in indolent systemic mastocytosis
- Consultant: Blueprint Medicines, Novartis
- Avapritinib is an investigational agent being developed by Blueprint Medicines and has not been approved by the Food and Drug Administration or any other health authority for use in the United States or any other jurisdiction for any indication

# Patient 1 – Indolent SM

- 45-year-old female
- Had onset of skin lesions at age 7
- Diagnosed at age 14 by a skin biopsy
- Initially only symptoms were skin lesions and exercise induced wheezing
- 29 years: Nausea, diarrhea, increased itching, flushing, bone pain
- Passed out twice, blood pressure was undetectable
- 30 years: Bone marrow biopsy: 20% infiltration with mast cells. Tryptase 76 ng/ml
- Symptoms progressed over the next 10 years, reacting to scents, perfumes, increasing bone pain, flushing, lightheadedness, fatigue
- Ultraviolet therapy unable to control skin symptoms
- Started saline infusions (one liter) every other week, had a port placed.
- Progressive loss of quality of life

# Patient 1 – Indolent SM

- Medications:
  - Cetirizine 10 mg daily
  - Fexofenadine 180 mg daily
  - Montelukast 10 mg daily
  - Benadryl every 4-6 hours
  - Hydroxyzine as needed
  - Diclofenac as needed
  - EpiPen as needed
  - Omalizumab once monthly injection
  - Omeprazole daily
  - Zofran daily
  - Ranitidine 300 mg daily
  - Entecort 6 mg daily
  - Topamax
  - Saline infusions

## Patient 2 – Indolent SM

- 51-year-old male
- Skin lesions as a teenager
- Diagnosed at age 31 by skin biopsy
- Tryptase was 15, and no bone marrow biopsy was performed initially
- Age 47: Developed life-threatening symptoms
  - Episodes of abdominal cramping, flushing, shortness of breath, chest pain and decrease in consciousness
  - Cardiac catheterization 20% occlusion
- Age 49: Daily episodes, bone marrow biopsy: 3 minor criteria for SM; prescribed EpiPen, fexofenadine, levocetirizine, montelukast, ranitidine, cromolyn
- Initiated prednisone 10 mg daily and initiated omalizumab preapproval but denied
- 3 days later, had a hypotensive event and had a myocardial infarction, cardiac arrest, requiring resuscitation. Tryptase was 178 during event.
- Started omalizumab and midostaurin with control of life threatening attacks but continuation of fatigue, skin symptoms and diarrhea
- Discontinued midostaurin due to nausea and vomiting

# Urticaria pigmentosa in a patient with indolent SM



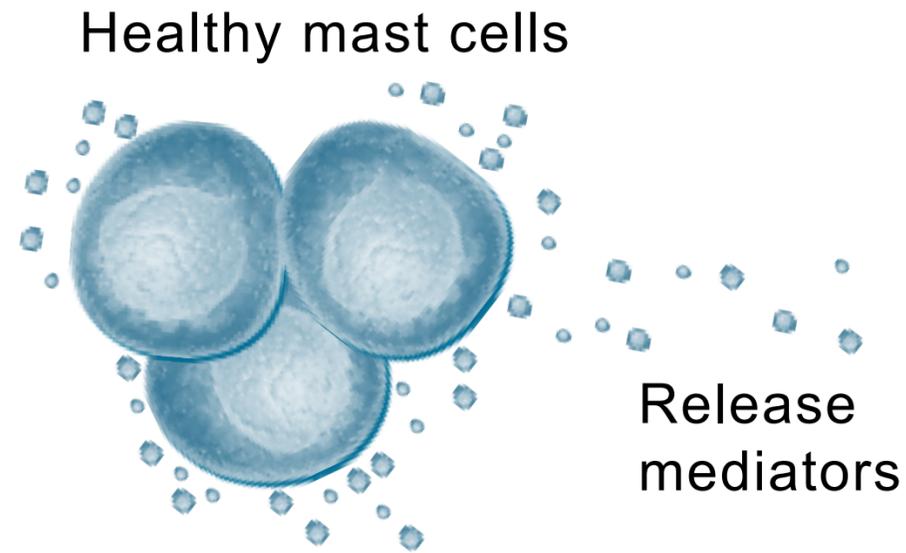
# Healthy mast cells play a key role in the immune-inflammatory response

STIMULUS

MAST CELL MORPHOLOGY

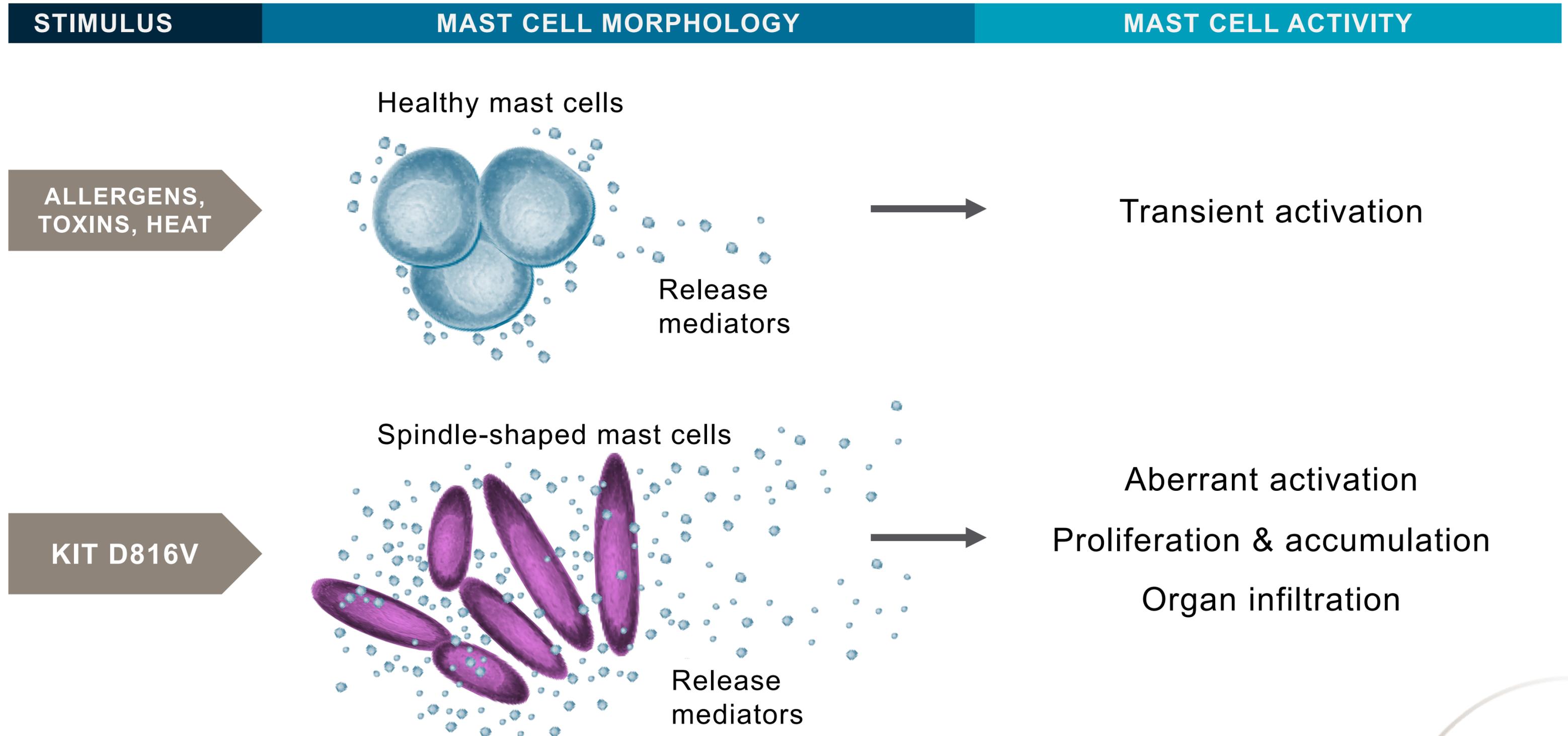
MAST CELL ACTIVITY

ALLERGENS,  
TOXINS, HEAT

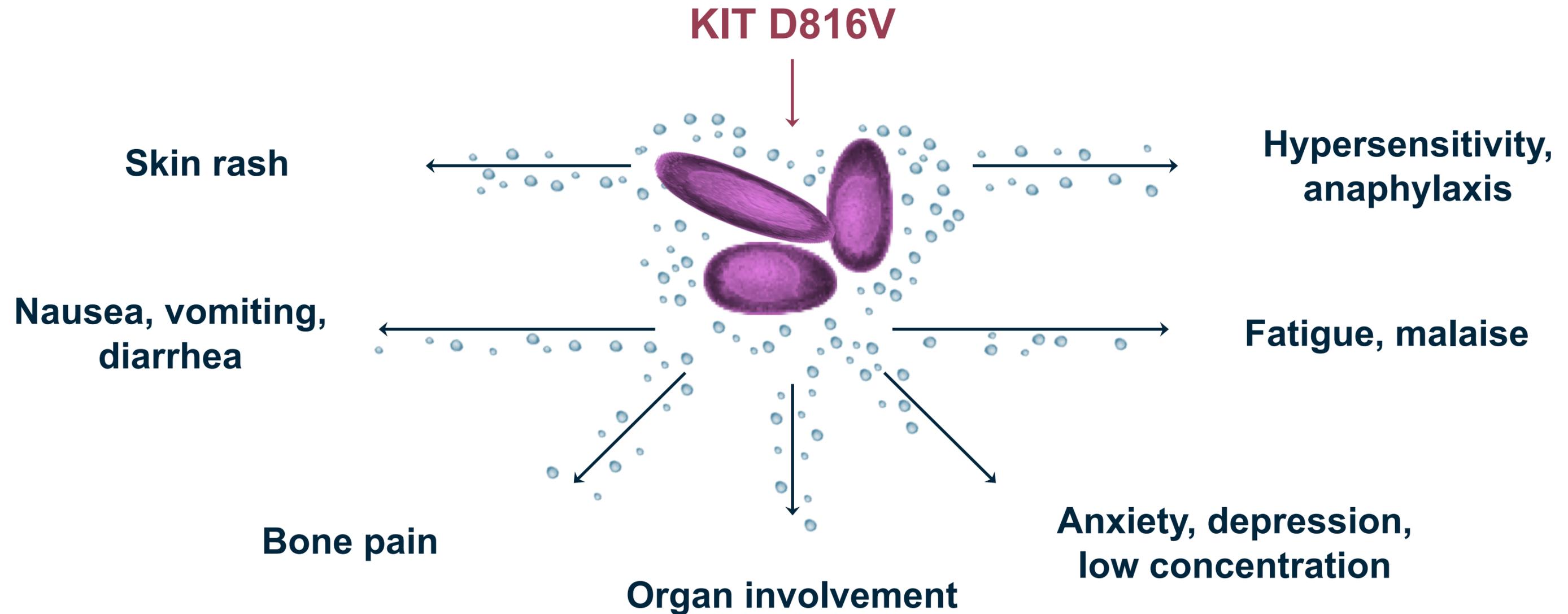


Transient activation

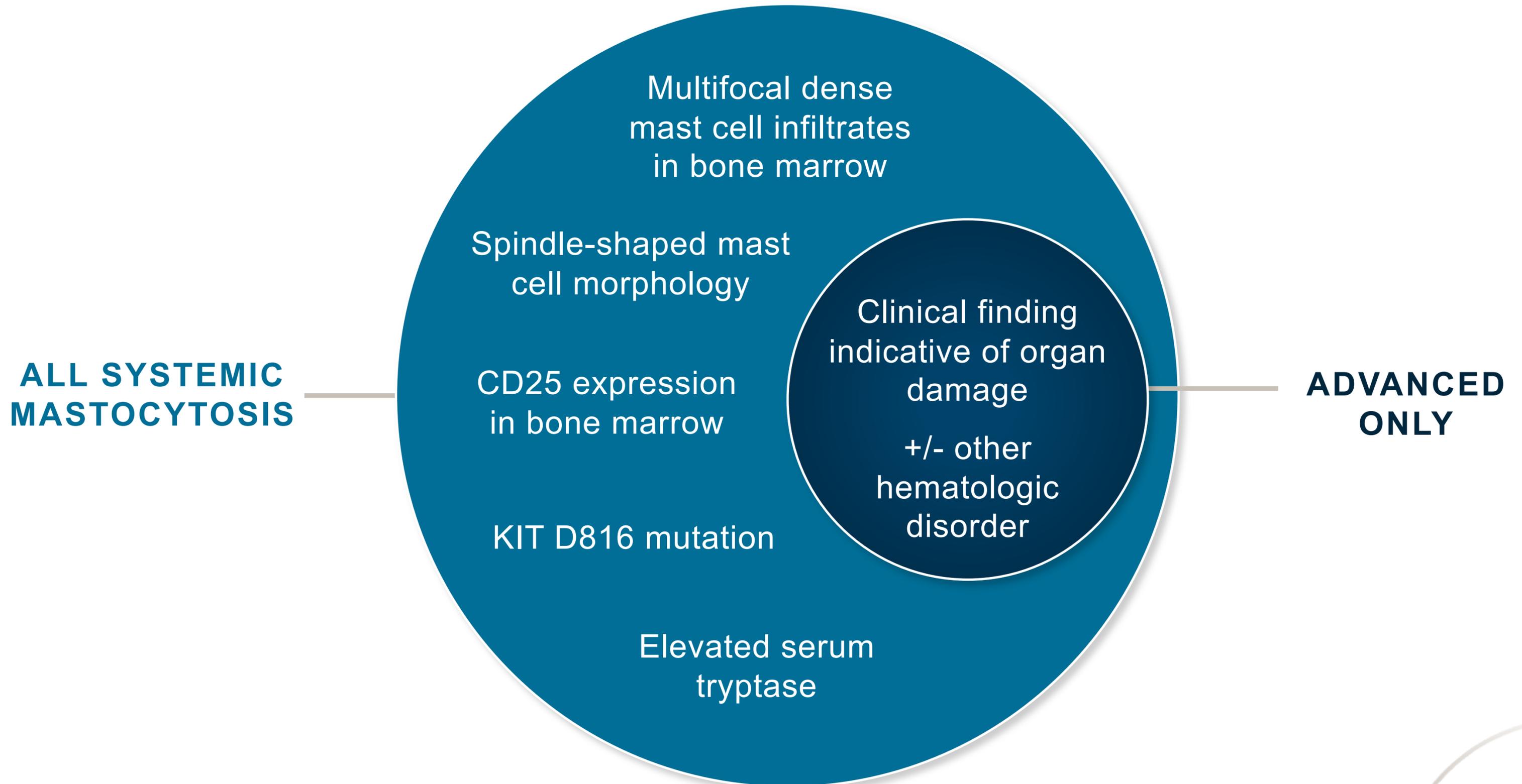
# In nearly all SM patients, KIT D816V aberrantly activates mast cells



Aberrant mast cell activation and proliferation results in chronic, severe and often unpredictable symptoms

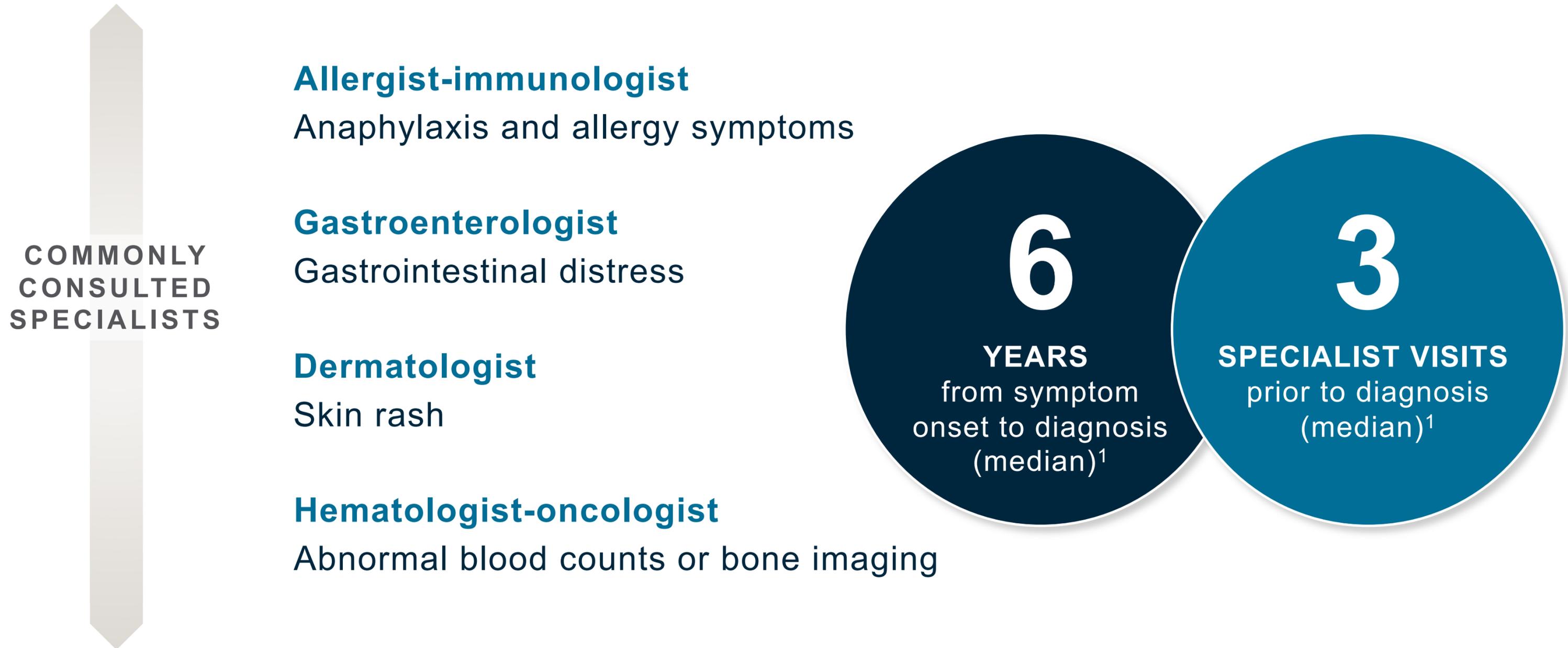


# Systemic mastocytosis diagnostic criteria<sup>1</sup>



<sup>1</sup> Valent, et al. Blood, 2016.

# Nearly all patients with SM experience diagnostic delay



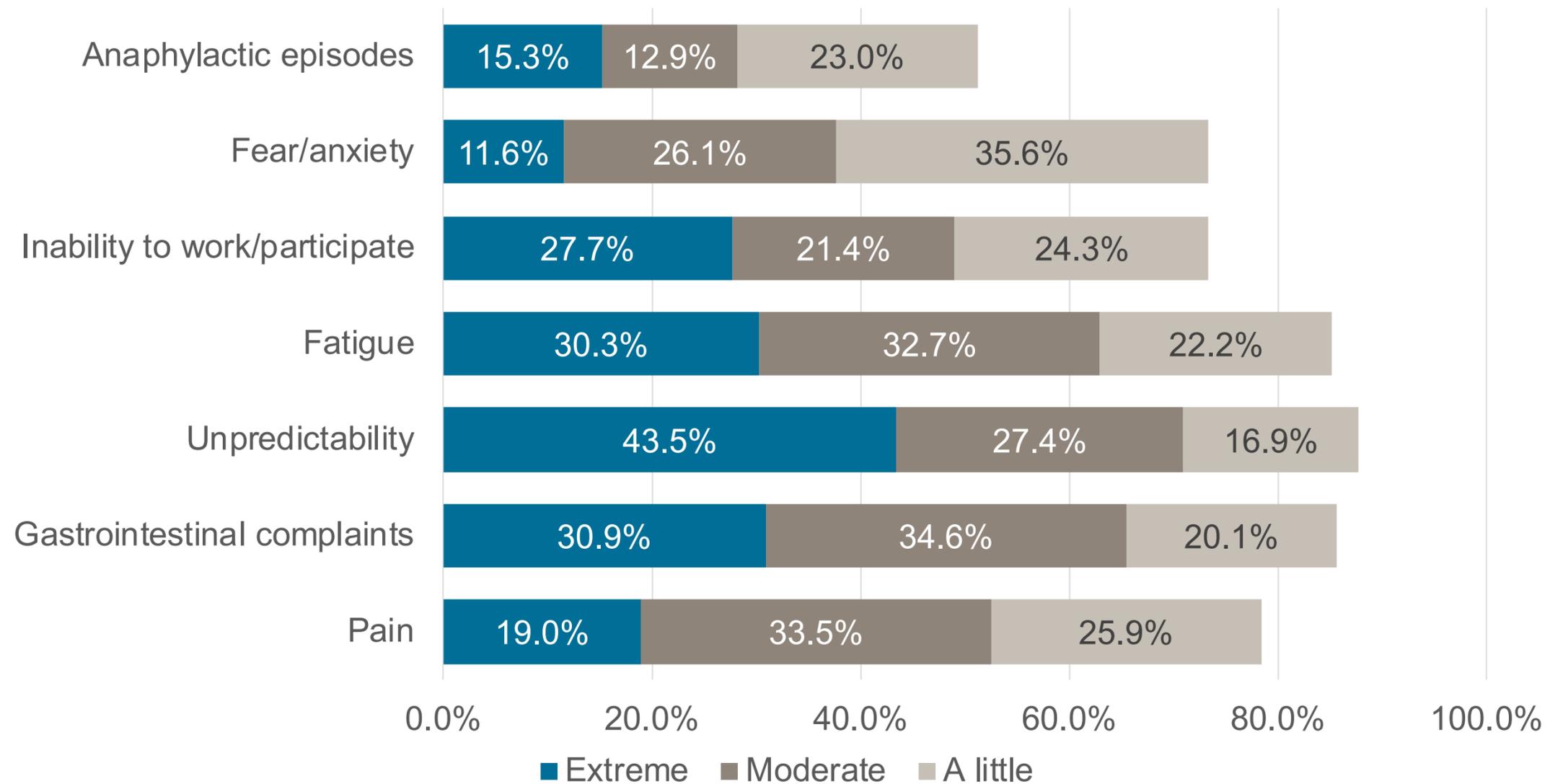
# Indolent SM patients report high symptom burden

Frequency of moderate to severe symptoms within last year, despite best available therapy

	ISM (n=109)	AdvSM (n=15)		ISM (n=109)	AdvSM (n=15)
<b>Systemic symptoms</b>			<b>Gastrointestinal symptoms</b>		
Fatigue/tiredness *	75%	87%	Abdominal pain	50%	60%
Pain (not abdominal)	55%	60%	Bloating	51%	60%
Headache	45%	40%	Diarrhea	39%	53%
Sweating	34%	47%	Nausea	39%	73%
Swelling	32%	40%	Flatulence	29%	40%
Anaphylaxis	35%	40%	Vomiting	15%	60%
Difficulty breathing	29%	47%	<b>Skin symptoms</b>		
			Itching	52%	47%
			Flushing	49%	40%
			Skin changes	49%	40%

# Psychosocial impact of disease symptoms is often severe

**>60% of patients with systemic mastocytosis and other mast cell disorders (n=420) reported their ability to cope was moderately to extremely affected, despite best available therapy**

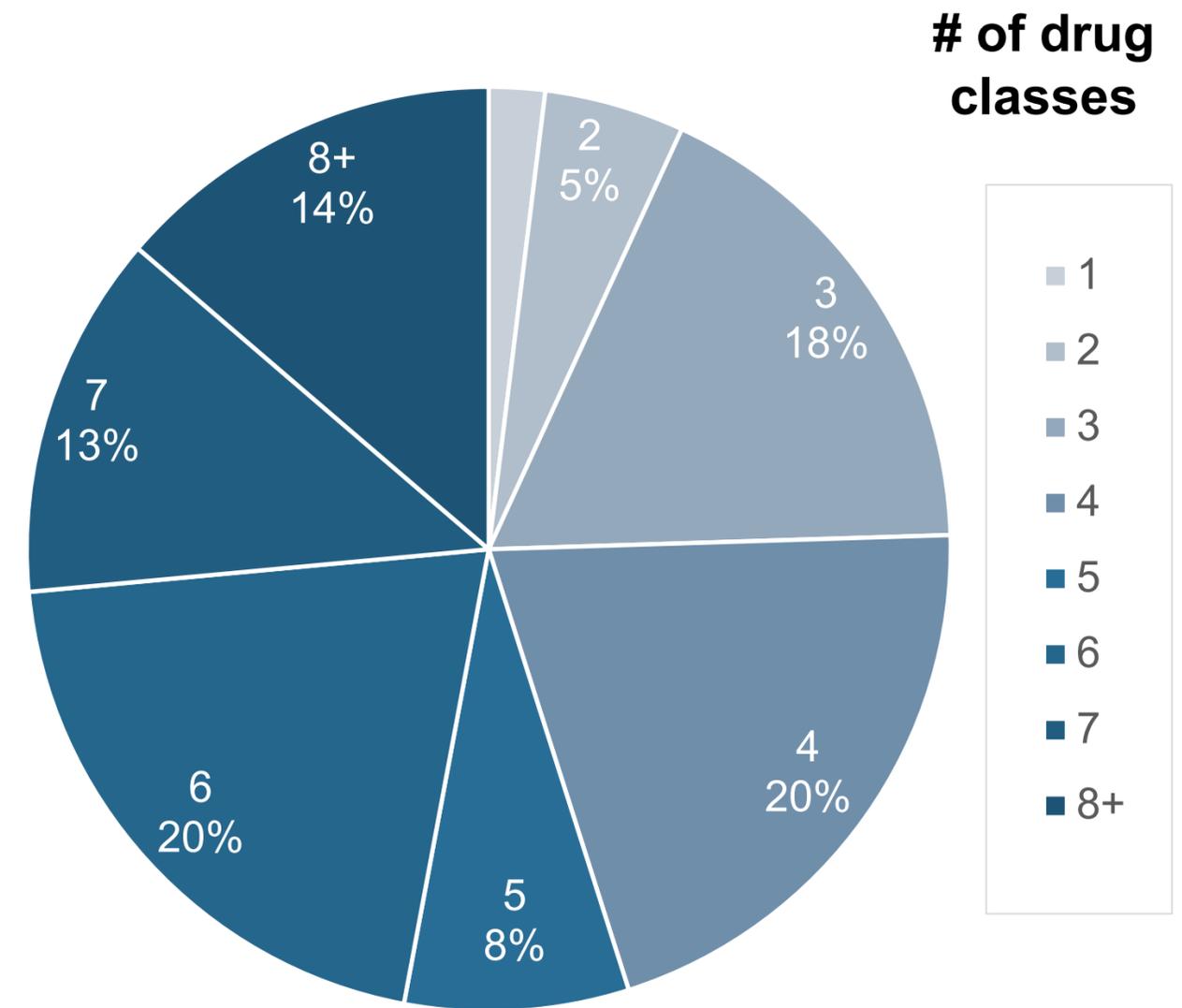


# Patients with indolent SM have significant polypharmacy burden

Drug Class	% of patients that have received this type of treatment
H1 Antihistamines	98%
H2 Antihistamines	93%
Cromolyn Sodium	66%
Leukotriene Inhibitors	62%
Corticosteroids	55%
Epinephrine	48%
Proton Pump Inhibitors	46%
Anti-IgE	18%
Cytoreductive Agents	15%

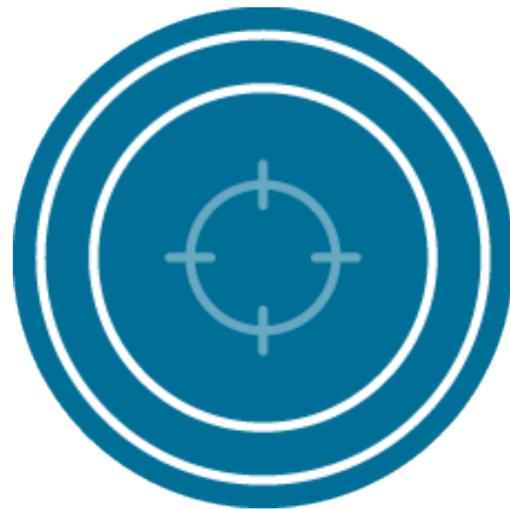
N=103

~75% of ISM patients have taken  $\geq 4$  classes of drugs to manage their disease



# Target profile for a disease-modifying therapy for systemic mastocytosis

Targets the  
KIT D816V  
driver mutation



Reduces mast cell  
burden and systemic  
symptoms



Reduces  
polypharmacy  
burden



# Avapritinib for indolent systemic mastocytosis

**ANDY BORAL, MD, PhD**

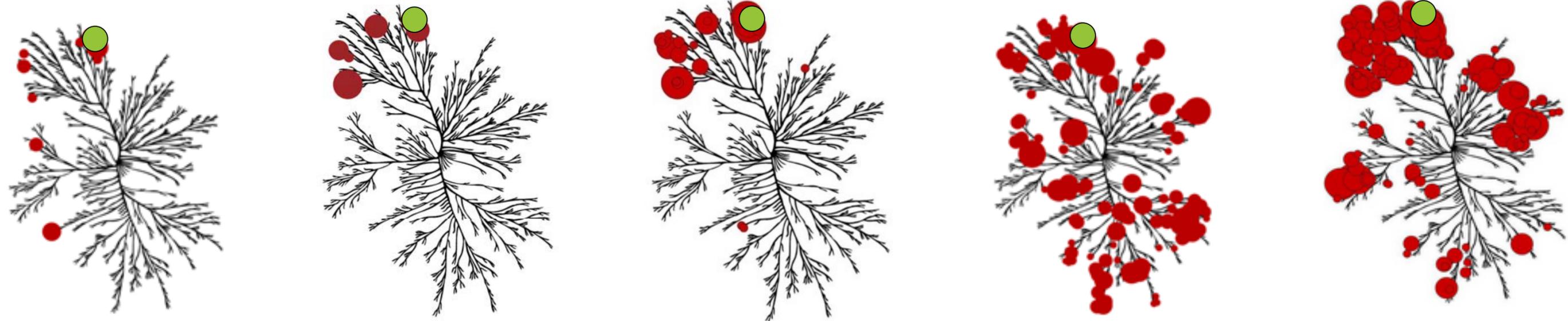
Chief Medical Officer



# Systemic mastocytosis represents the largest opportunity for avapritinib



# Avapritinib was specifically designed to inhibit KIT D816V



avapritinib

Gleevec<sup>®</sup> (imatinib)

masitinib

Rydapt<sup>®</sup> (midostaurin)

ripretinib

● Binding to KIT

● Binding to other kinases (size is proportional to binding)

## KIT D816V biochemical IC<sub>50</sub>

avapritinib*	imatinib*	masitinib <sup>#</sup>	midostaurin*	ripretinib <sup>#</sup>
0.27 nM	8150 nM	>1000 nM	2.9 nM	2.6 nM

Biochemical binding by DiscoverRX at 3uM

# EXPLORER data showed profound clinical activity in patients with advanced SM

BEST RESPONSE  
PER IWG-MRT-ECNM CRITERIA<sup>1</sup>  
ALL DOSES (N=39)

## BREAKTHROUGH THERAPY DESIGNATION<sup>2</sup>

Plan to submit NDA for avapritinib for advanced SM in Q1 2020, based on combined data from EXPLORER and PATHFINDER trials

77%  
Confirmed  
ORR

74%  
12-month  
DOR rate

## SAFETY (n=69)

- Avapritinib was generally well-tolerated
- Most adverse events reported by investigators were Grade 1 or 2
- 66% of patients had Grade 3 and 4 treatment-related AEs
- Cytopenias were the most common Grade 3 and 4 treatment-related AE
- Across all doses, 4% of patients discontinued treatment due to treatment-related AEs

<sup>1</sup> Data presented at the European Hematology Association Annual Meeting in June 2019. Data cutoff date: January 2, 2019.

<sup>2</sup> Avapritinib granted Breakthrough Therapy Designation for the treatment of advanced SM, including the subtypes of aggressive SM, SM with an associated hematologic neoplasm and mast cell leukemia. ORR, overall response rate; DOR, duration of response; AE, adverse event.

# Disease spectrum across systemic mastocytosis and other mast cell disorders

## Advanced SM

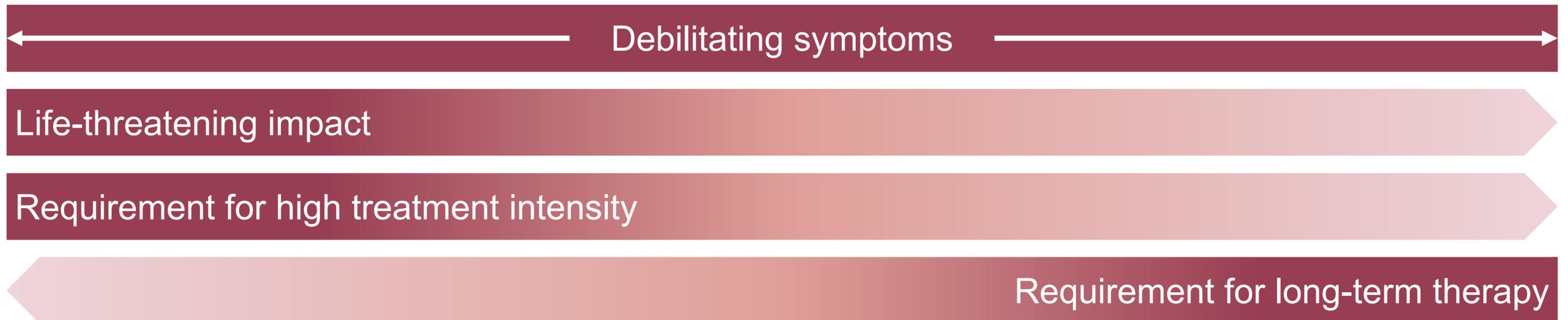
Aggressive SM  
SM with an associated  
hematologic neoplasm  
Mast cell leukemia

## Indolent SM

Indolent SM  
Smoldering SM

## Mast cell disorders

Mast cell activation syndrome  
Hereditary alpha tryptasemia  
Severe mast cell mediated asthma  
Severe anaphylaxis



# Comprehensive systemic mastocytosis clinical trial program

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## EXPLORER

Advanced SM

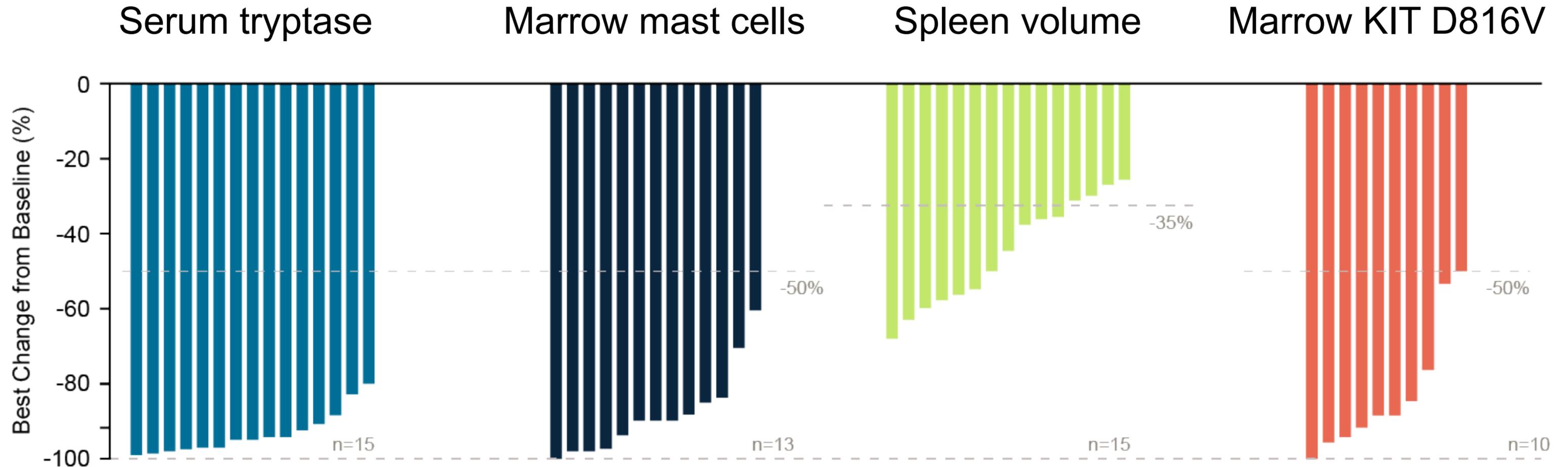
Phase 1 dose-escalation trial  
with open-label expansion

## PATHFINDER

Advanced SM

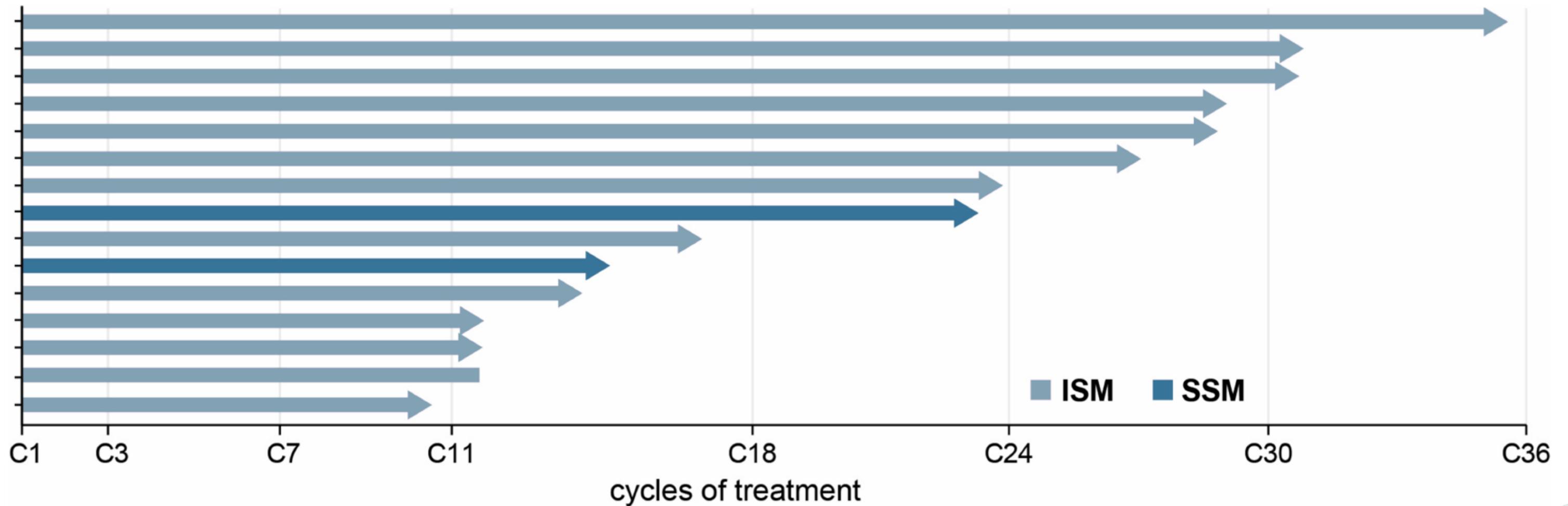
Phase 2 single-arm trial

# Indolent SM patients enrolled in EXPLORER trial had deep reductions on objective measures of mast cell burden



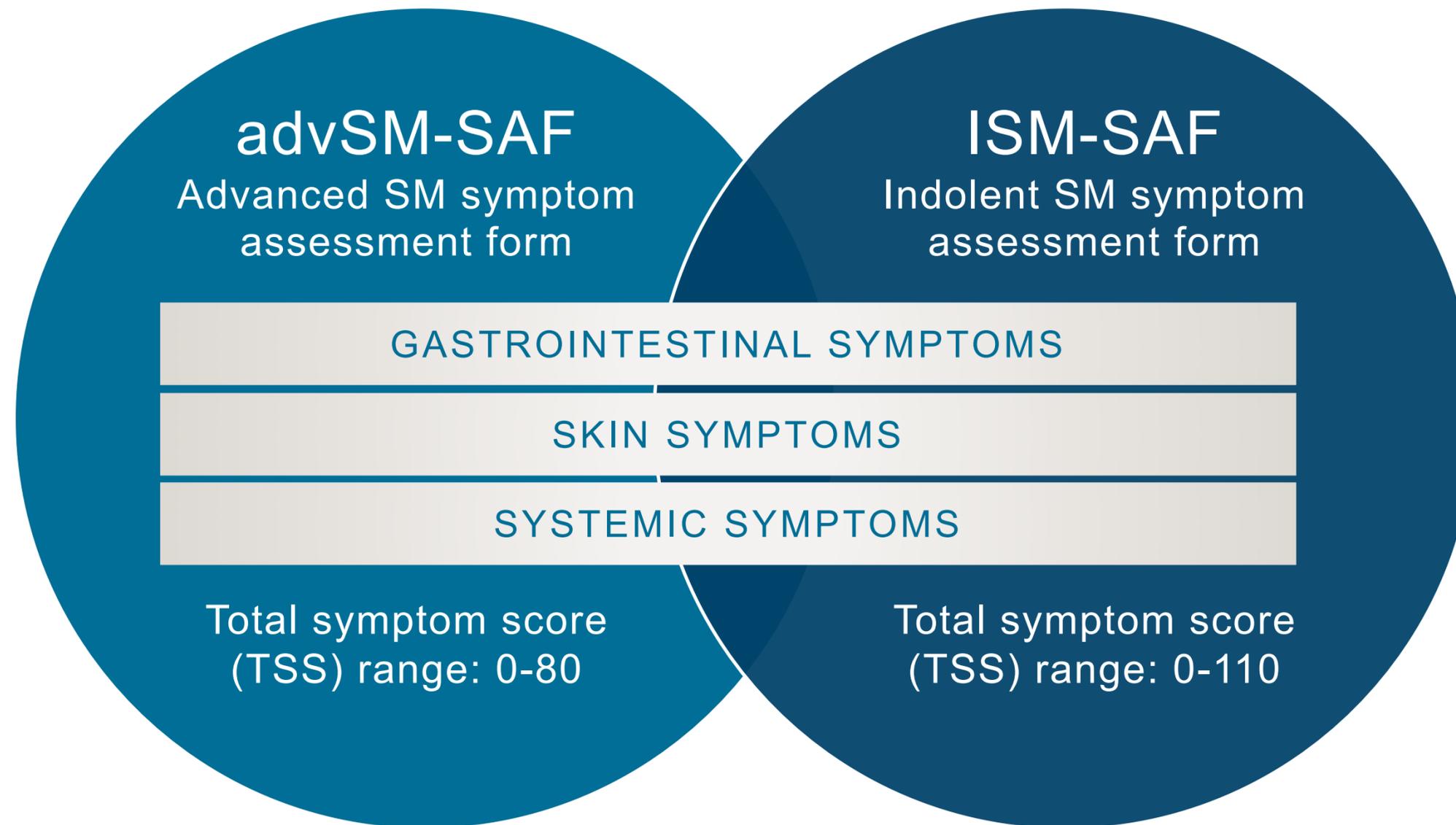
# EXPLORER data show ISM and SSM patients with long durations of therapy at low doses

- 14 of 15 (93%) remain on treatment up to nearly 3 years (cycle 36)
- Current average dose is 126 mg with 73% now treated at 100 mg QD

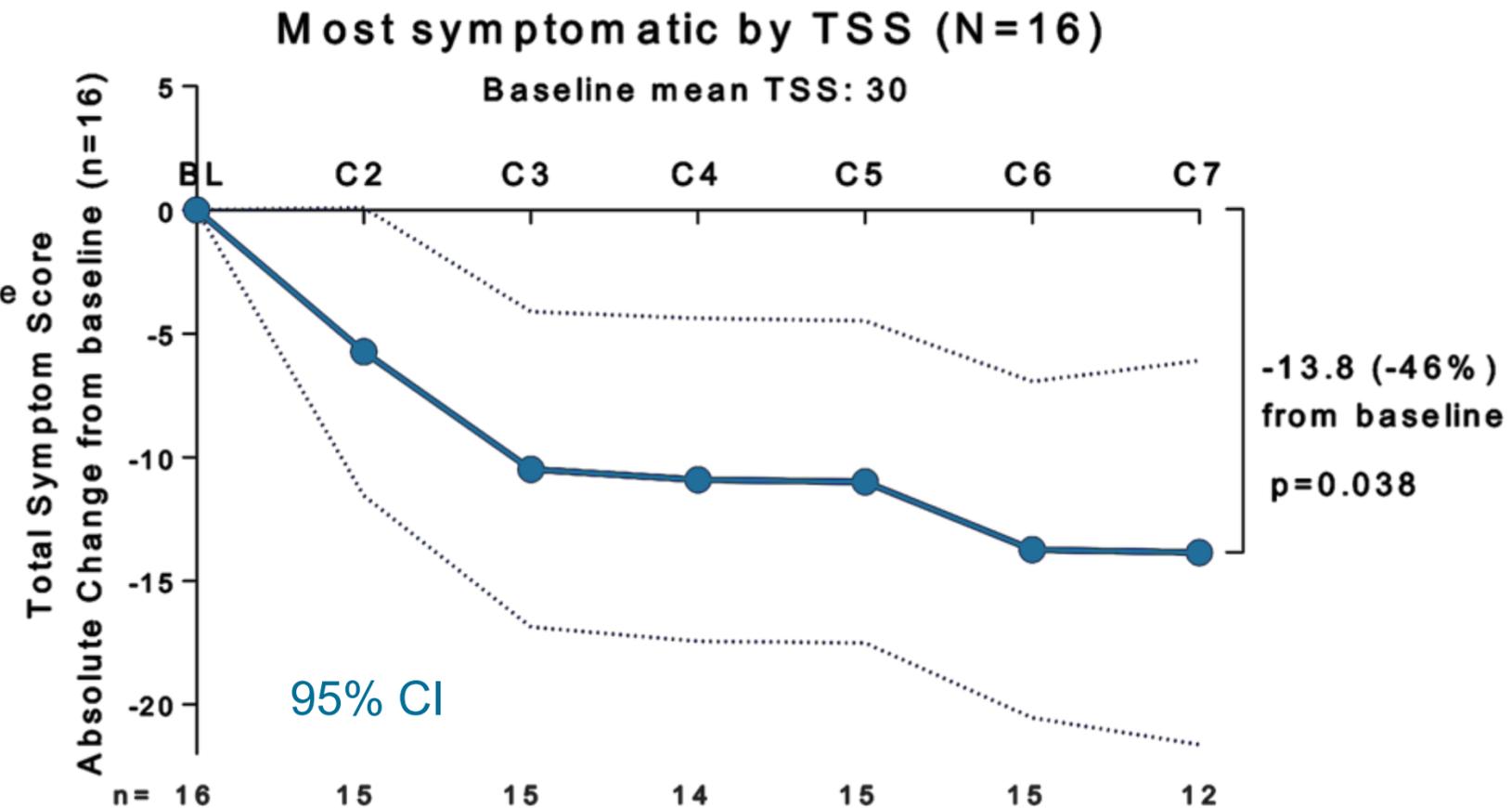
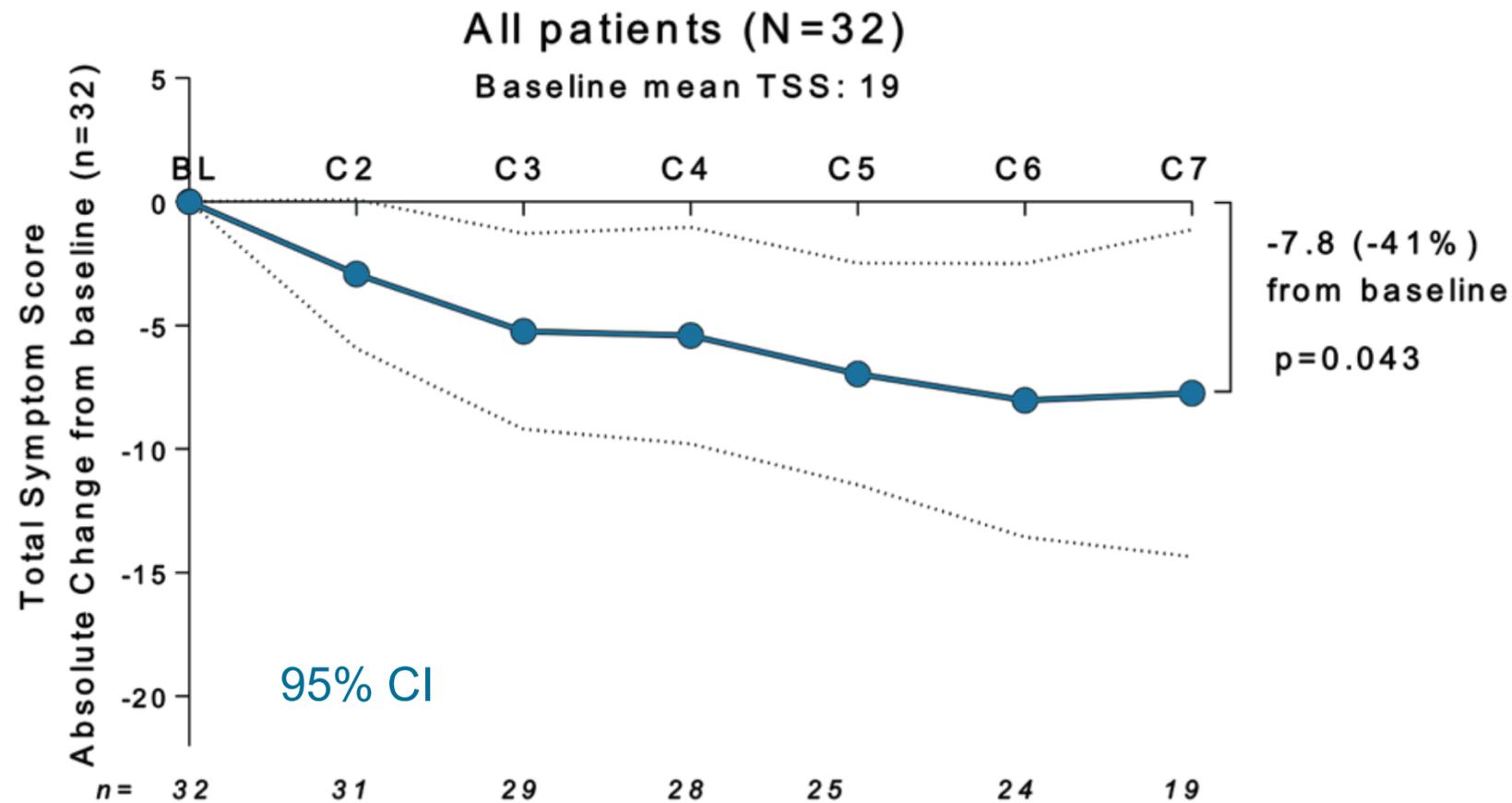


# Highly similar, but tailored PRO surveys for advanced and indolent SM

**~70% OVERLAP**  
between advSM-SAF and ISM-SAF



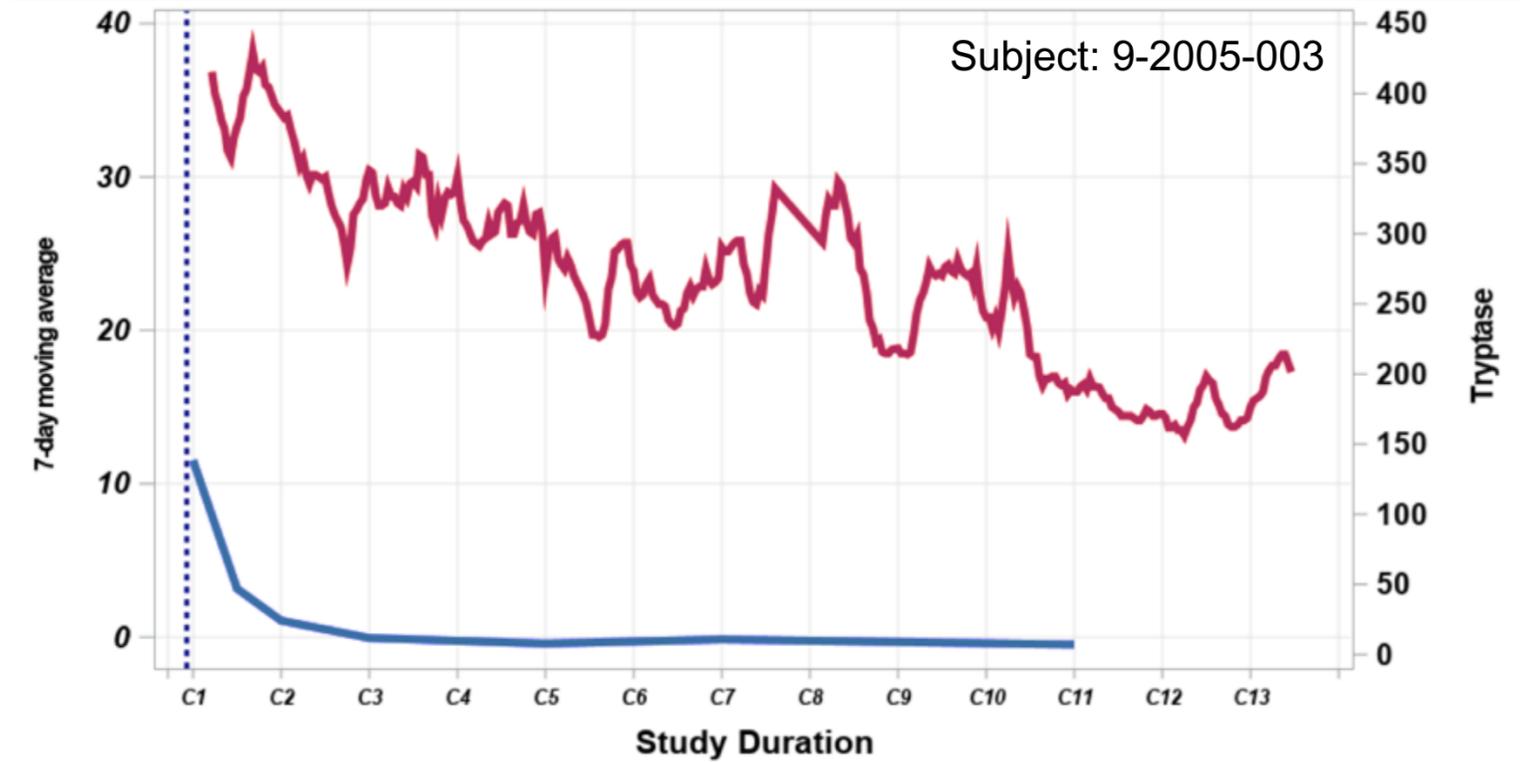
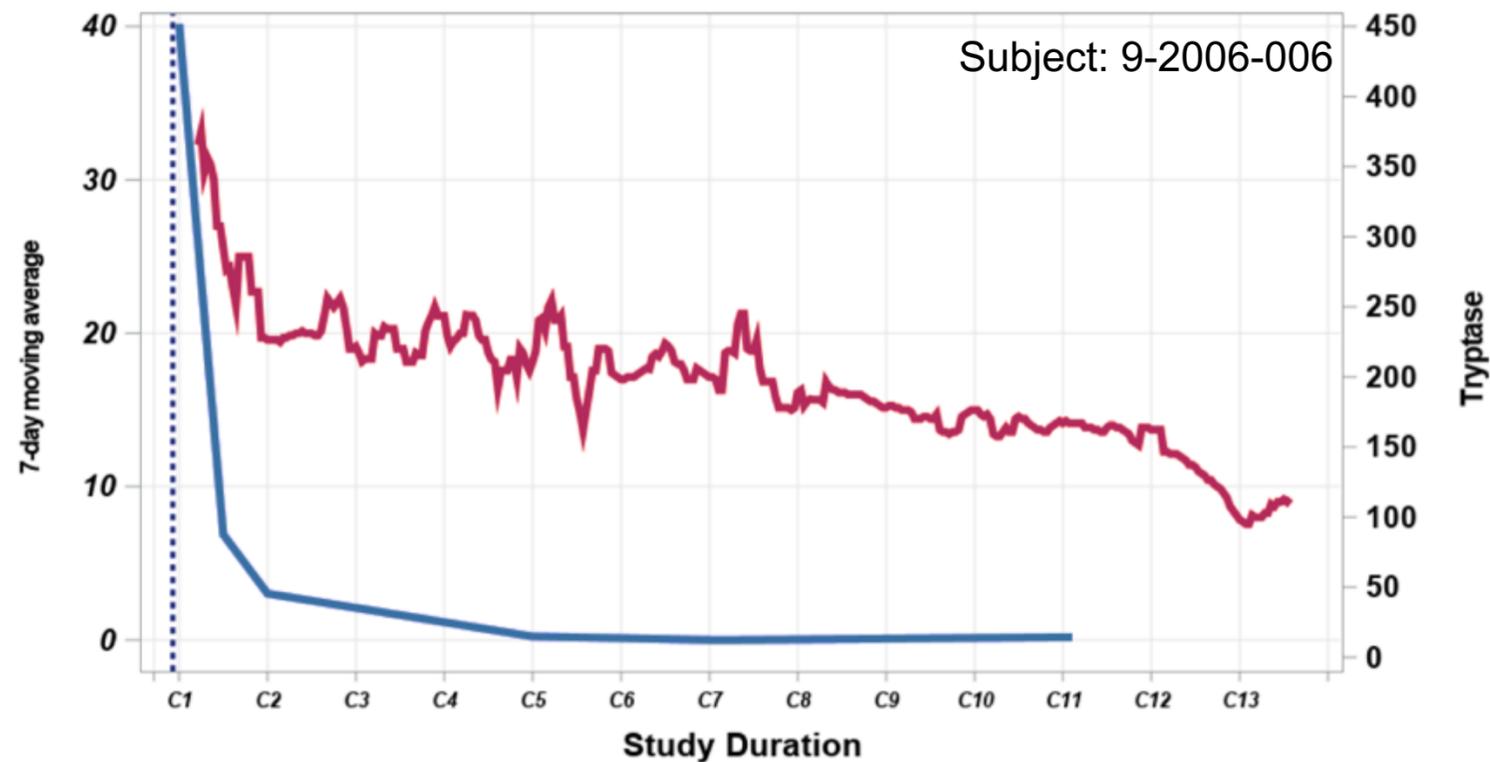
# EXPLORER data showed significant symptom improvements on advSM-SAF



**~40% MEAN REDUCTION OF SYMPTOMS FROM BASELINE TSS**

# EXPLORER data show quantitative measures of mast cell burden are predictive of symptom reductions

## SERUM TRYPTASE VERSUS ADVSM-SAF TOTAL SYMPTOM SCORE



— Serum tryptase      — advSM-SAF total symptom score



# EXPLORER data showed reduction in polypharmacy burden



## Advanced SM

Phase 1 dose-escalation trial  
with open-label expansion

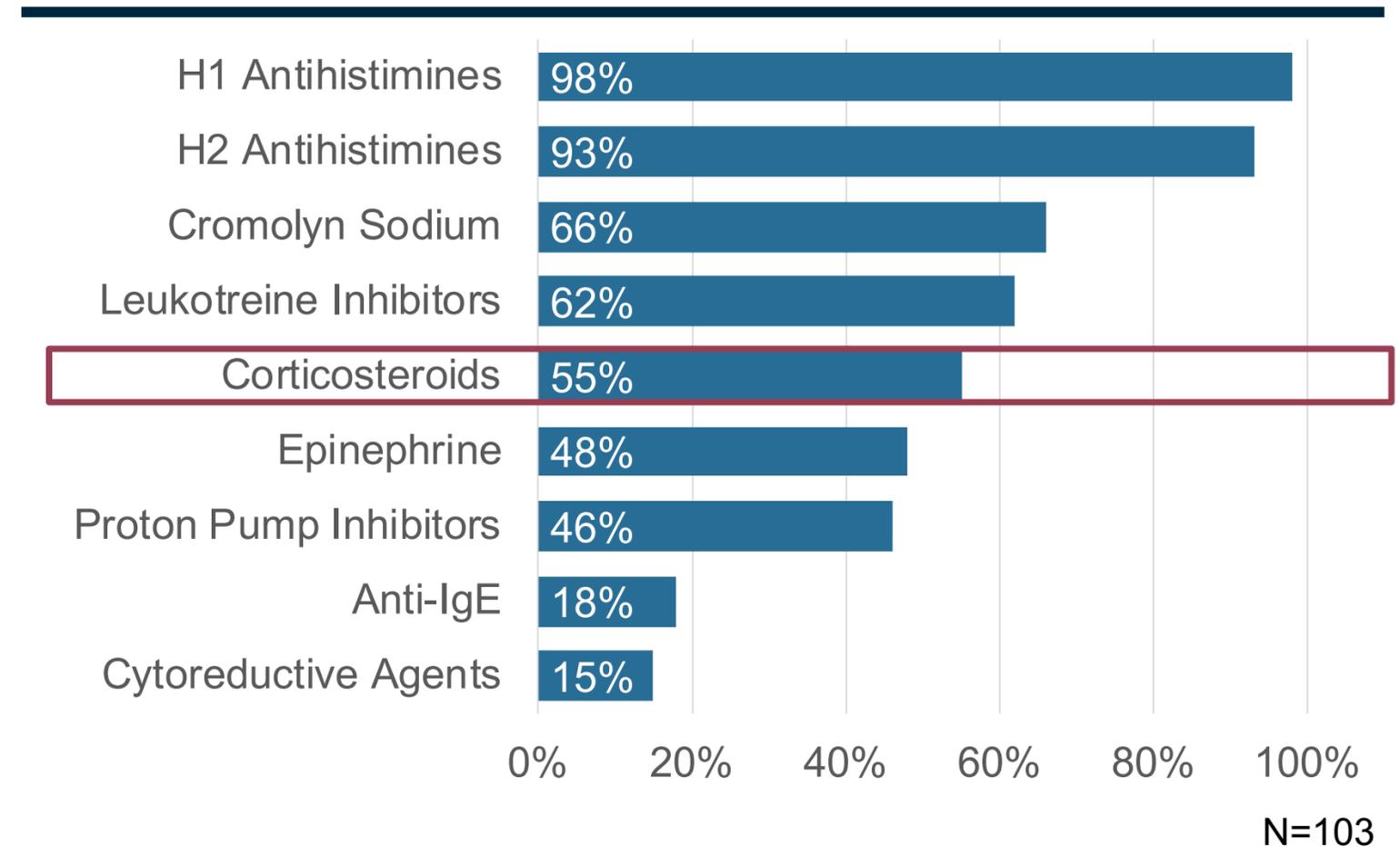
## Concomitant Medication Analysis<sup>1</sup>

Of 22 patients with baseline corticosteroids:

- 18/22 (80%) decreased their steroid dose
- 9/22 (41%) discontinued their steroids entirely

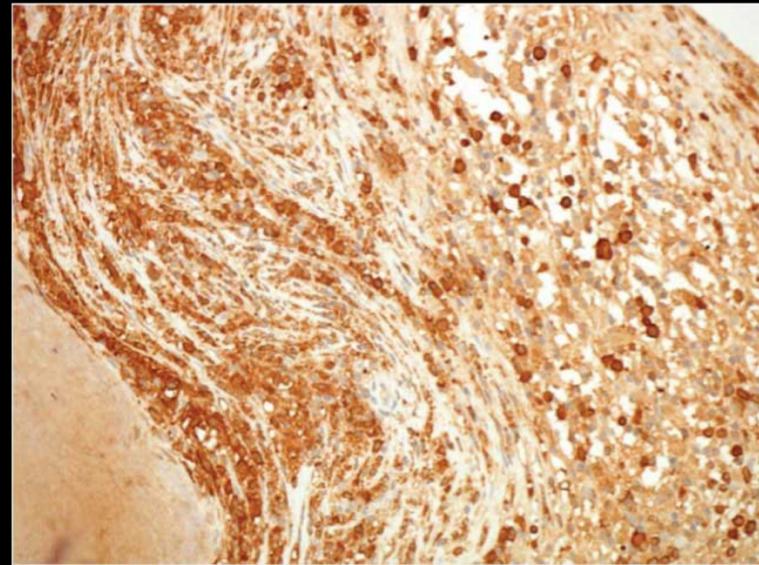
## Polypharmacy Burden in Indolent SM<sup>2</sup>

Drug class    % of patients that have received this type of treatment

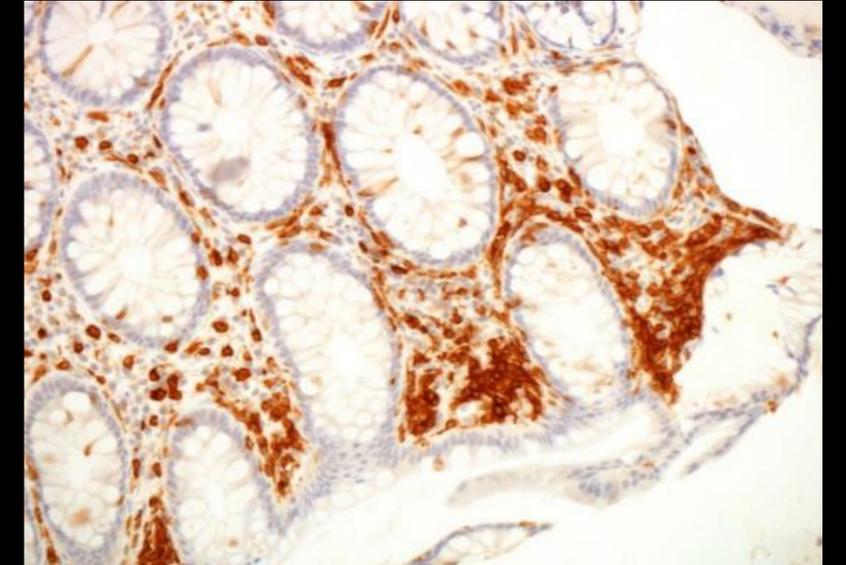


# 45-year-old woman with evolving systemic mastocytosis

MARROW CD117 (50% MC)



COLON CD25 (>100 MCS/HPF)

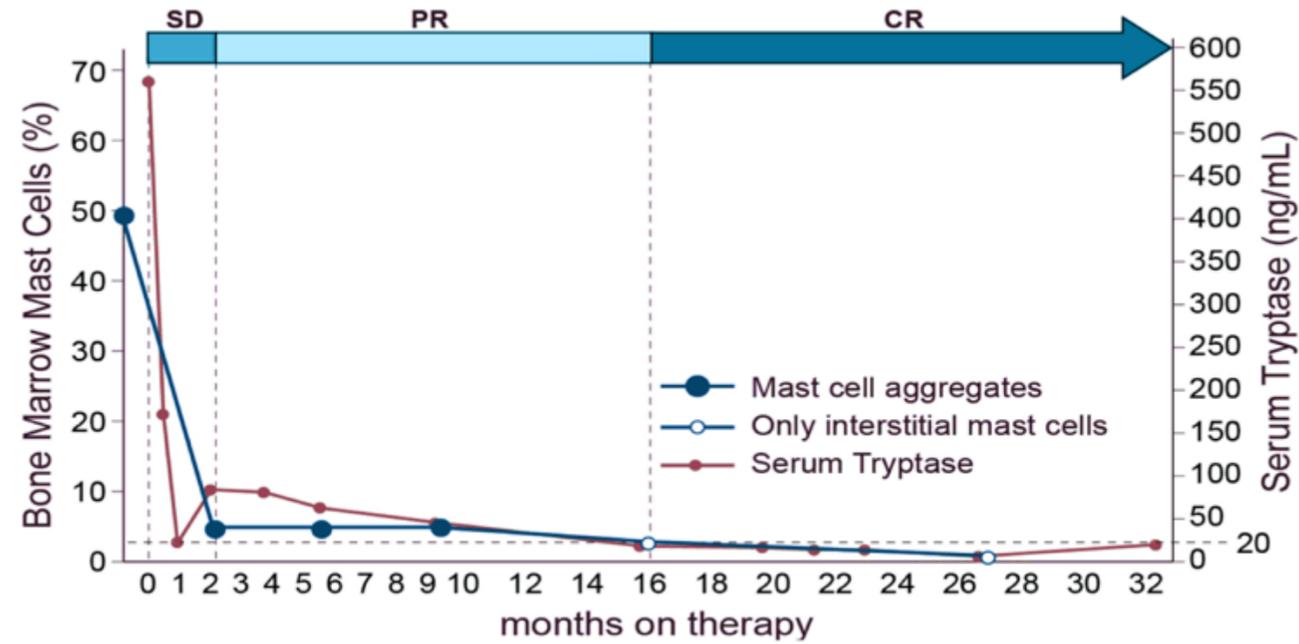


2015: Indolent systemic mastocytosis

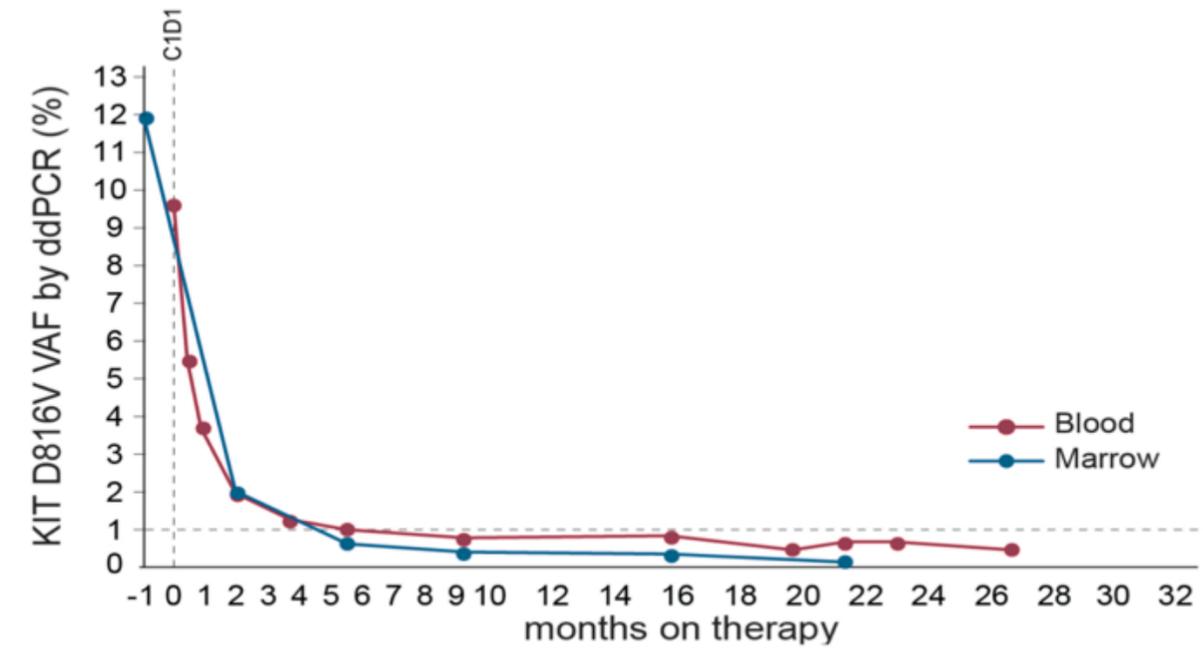
2016: Aggressive systemic mastocytosis

- ~30 pound weight loss in prior 6 months
- Stomach, duodenum, colon MC infiltration
- 5cm palpable splenomegaly
- Anemic (hemoglobin 9.9g/dL)
- Marrow MCs 50%, tryptase 562ng/mL
- Enrolled on EXPLORER study
- **SM-AHN** on central pathology review

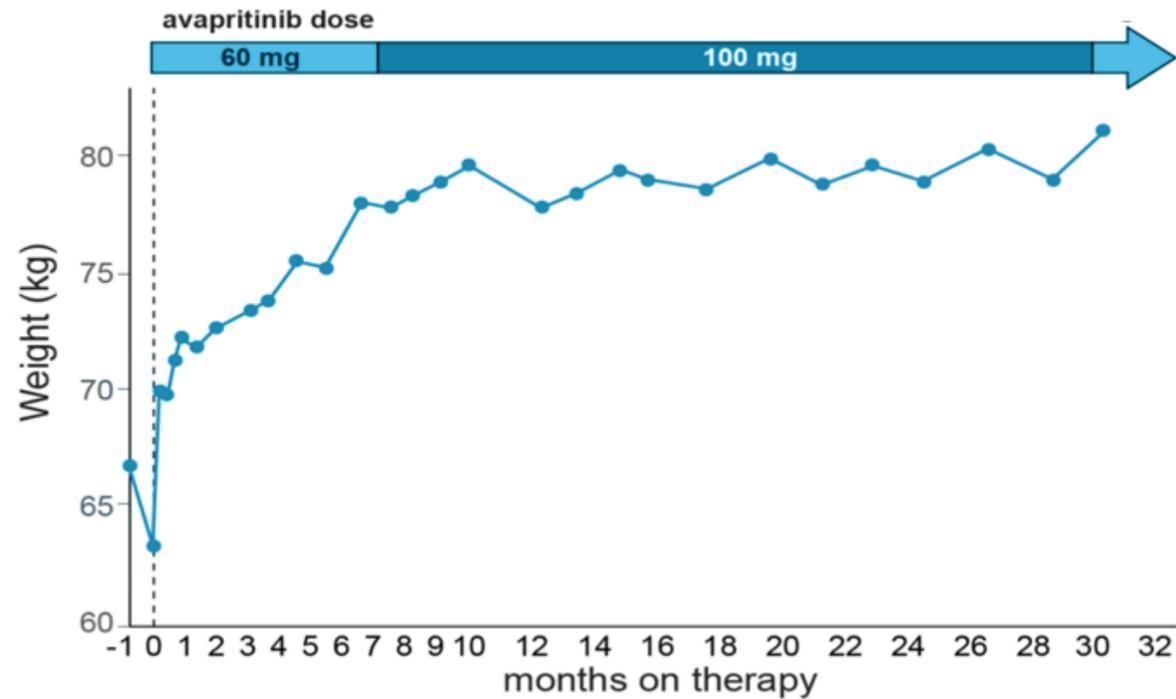
## BONE MARROW MAST CELLS & SERUM TRYPTASE



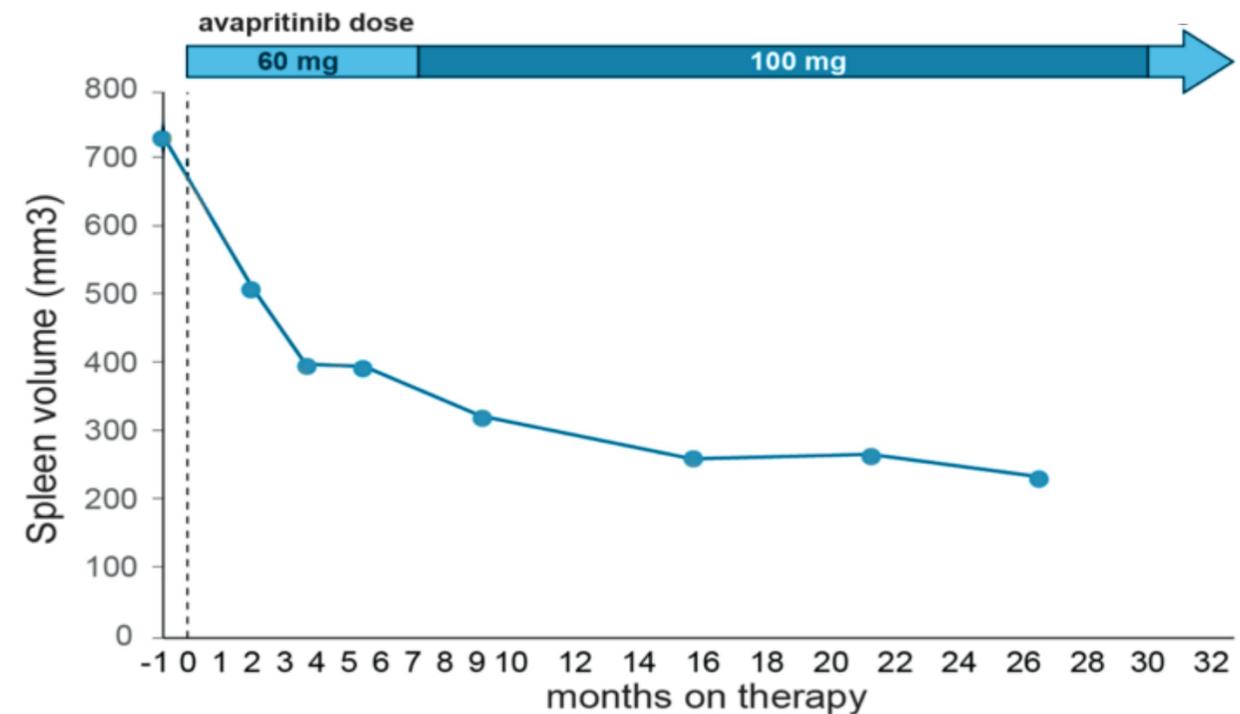
## KIT D816V MUTANT ALLELE FRACTION



## WEIGHT



## SPLEEN VOLUME

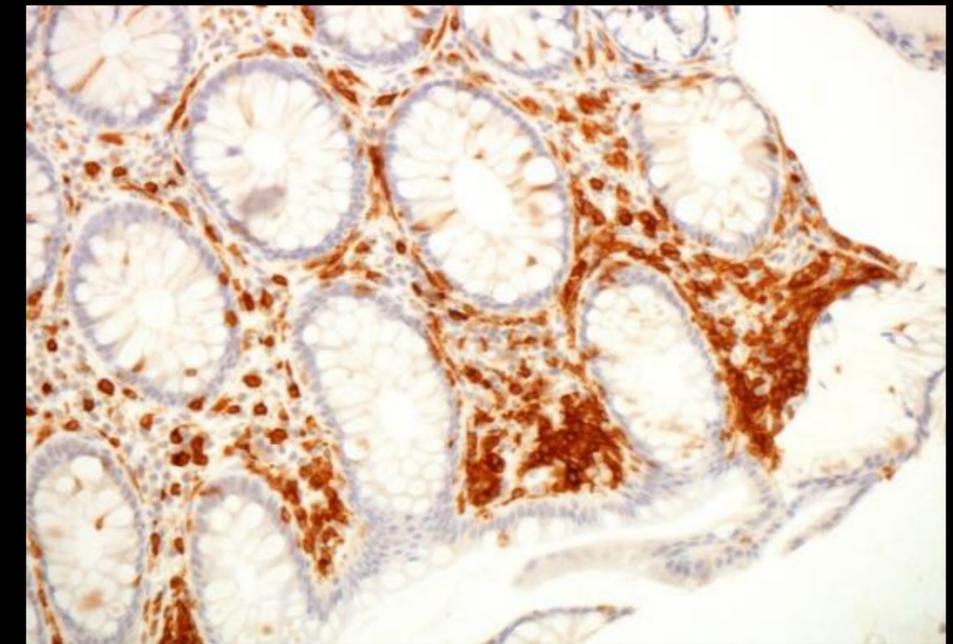
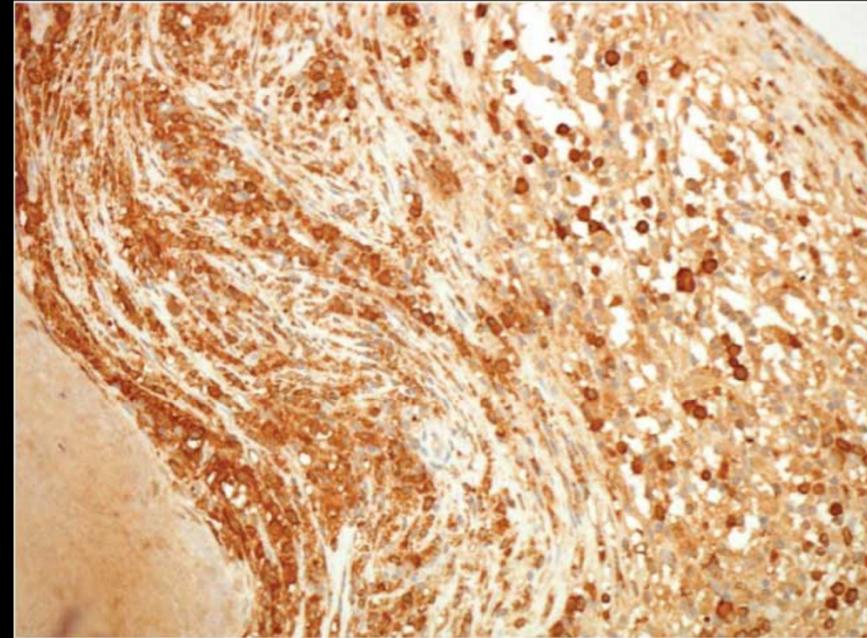


**MARROW CD117**

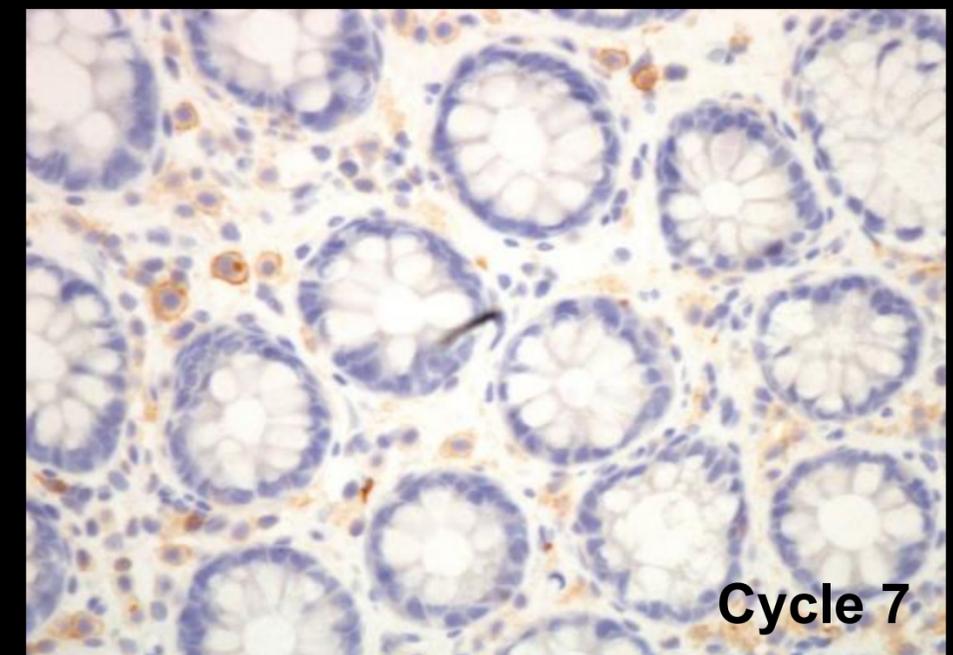
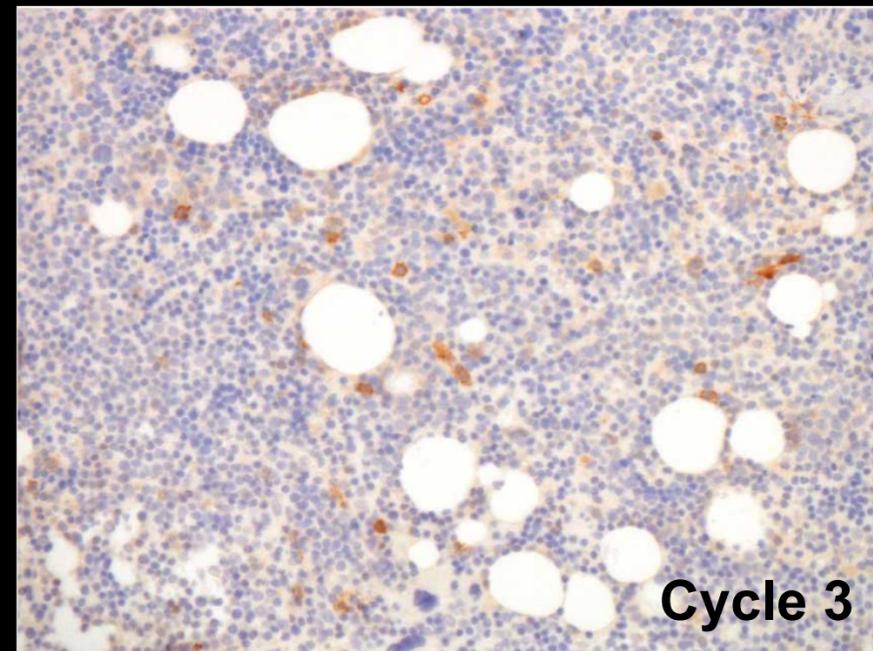
**MRI ABDOMEN**

**COLON CD25**

**BASELINE**



**ON STUDY**





**BASELINE**



**6 MONTHS**



**29 MONTHS**





**BASELINE**



**6 MONTHS**



**29 MONTHS**



# Comprehensive systemic mastocytosis clinical trial program

---

## EXPLORER

Advanced SM

Phase 1 dose-escalation trial  
with open-label expansion

## PATHFINDER

Advanced SM

Phase 2 single-arm trial

## PIONEER

Indolent SM

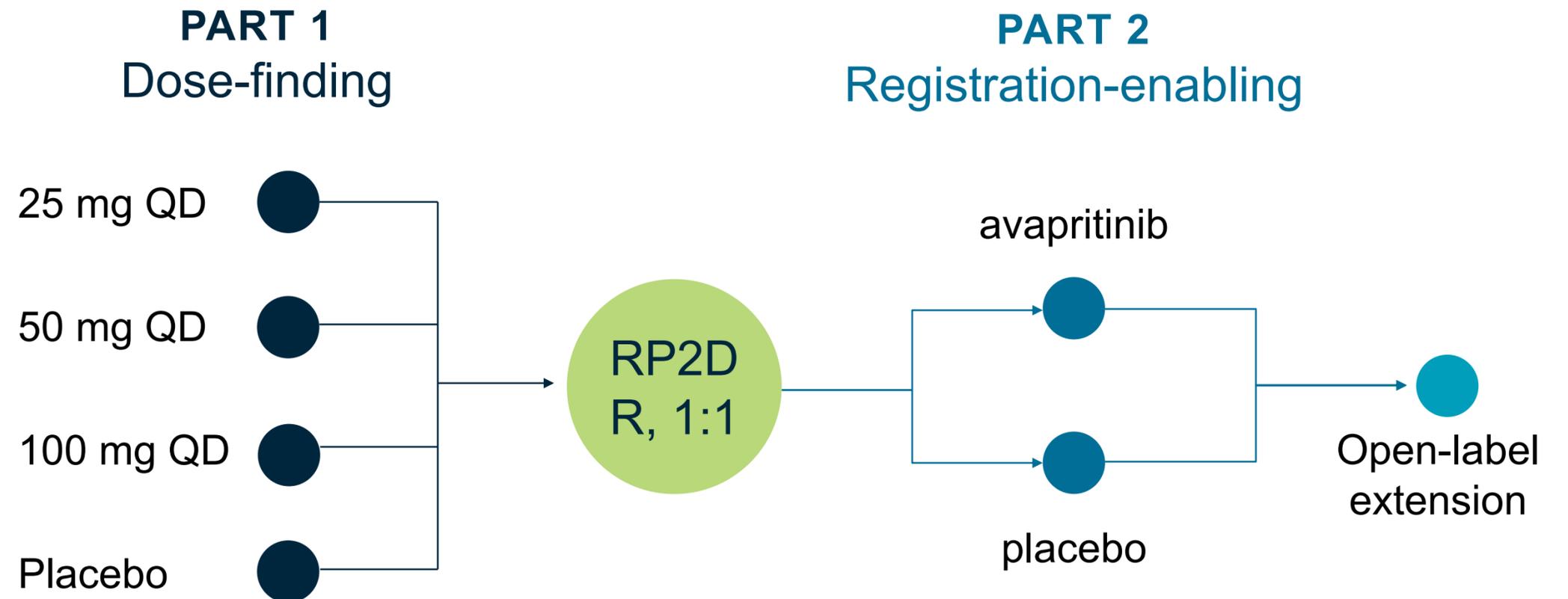
Phase 2 randomized, double-blind,  
placebo-controlled trial

# PIONEER trial designed to evaluate avapritinib in indolent SM

## PIONEER

### Indolent SM

Phase 2 registration-enabling randomized, placebo-controlled trial in patients with indolent SM



- **Eligibility:** Moderate-to-severe indolent or smoldering SM
- **Key endpoints:** ISM-SAF total symptom score (primary), quantitative measures of mast cell burden, safety
- Enrollment of Part 1 is complete with 39 patients on study; no patients have discontinued due to an adverse event to date<sup>1</sup>
- Plan to disclose initial data from Part 1 at ASH meeting in December 2019
  - Investor event and webcast planned for Sunday, December 8

# A comprehensive program for mast cell disorders

**CHRISTINA ROSSI**

Chief Commercial Officer

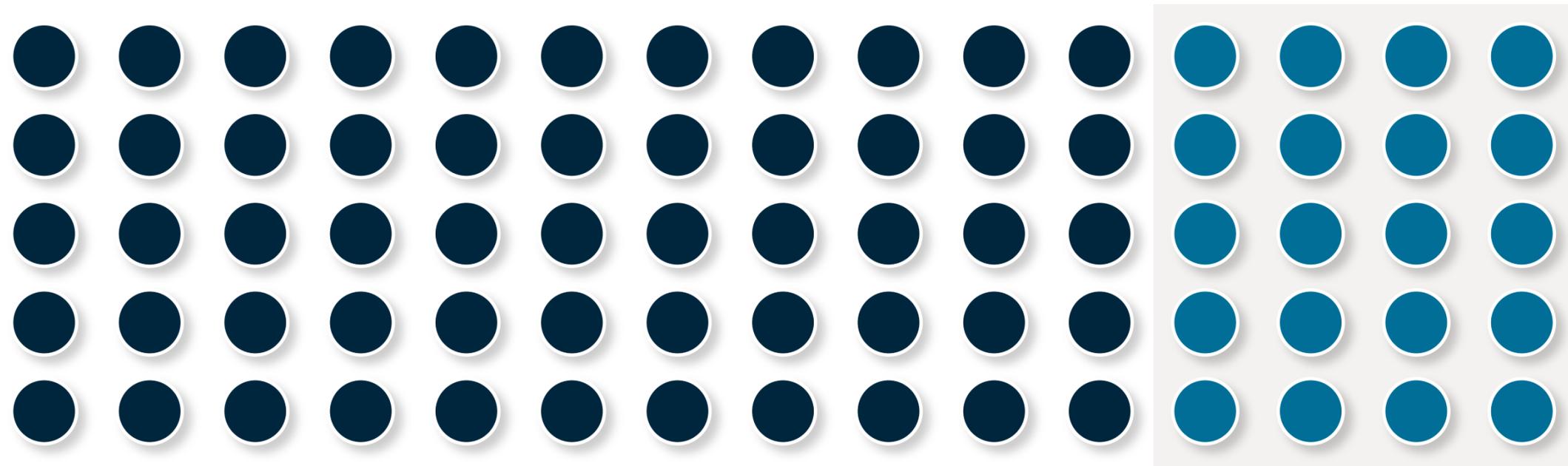


# Expanded SM opportunity based on increased understanding of the disease

## SYSTEMIC MASTOCYTOSIS EPIDEMIOLOGY

**~75,000**

prevalent patients in major markets<sup>1</sup>



**~20,000**  
**patients**  
are identifiable  
within claims  
data in the  
United States<sup>2</sup>

MOST ADULTS WITH CUTANEOUS SYMPTOMS WILL SHOW SYSTEMIC DISEASE WHEN FULLY INVESTIGATED

# Focused efforts designed to identify patients and reduce diagnostic delay

## Tailored healthcare provider awareness



**Educate** on relevant signs and symptoms by specialty

Invest in **data and insights** to efficiently target

## Pathology and reference lab partnerships



Initiate strategic lab partnerships to **enable solutions**

**Share best practices** on how to optimally suspect & diagnose

## Activate patient and caregivers



**Empower and educate** potential undiagnosed patients with clear call to action

AIM TO ACCELERATE SYSTEMIC MASTOCYTOSIS DIAGNOSIS TIMELINES

We aim to make transformative precision therapies and expand their application to additional patient populations over time

## **BLU-263**

**A next-generation KIT inhibitor  
for mast cell disorders**

# Disease spectrum across systemic mastocytosis and other mast cell disorders

## Advanced SM

Aggressive SM  
SM with an associated  
hematologic neoplasm  
Mast cell leukemia

## Indolent SM

Indolent SM  
Smoldering SM

## Mast cell disorders

Mast cell activation syndrome  
Hereditary alpha tryptasemia  
Severe mast cell mediated asthma  
Severe anaphylaxis



# BLU-263 designed to enable deep reach into the mast cell disorder spectrum

## Advanced SM

Aggressive SM

SM with an associated hematologic neoplasm

Mast cell leukemia

## Indolent SM

Indolent SM

Smoldering SM

## Mast cell disorders

Mast cell activation syndrome

Hereditary alpha tryptasemia

Severe mast cell mediated asthma

Severe anaphylaxis

AVAPRITINIB

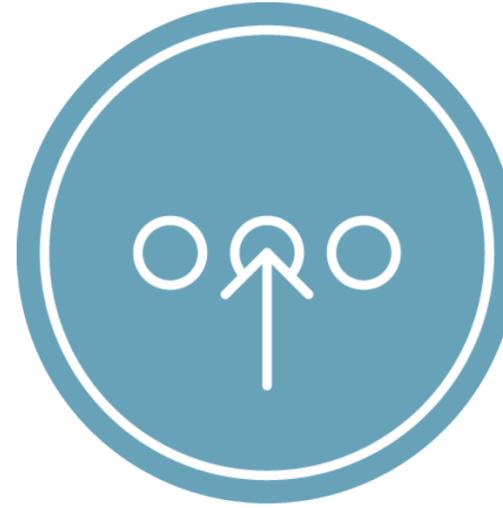
BLU-263

# BLU-263 was rapidly progressed based on insights from avapritinib



## POTENT

Sub-nanomolar potency  
against KIT D816V



## SELECTIVE

Highly selective for KIT,  
with low off-target activity



## CNS PROFILE

Designed to not cross  
blood-brain barrier

PLAN TO SUBMIT IND APPLICATION FOR INDOLENT SM TO FDA IN 1H 2020

# BLU-263: a compelling preclinical profile

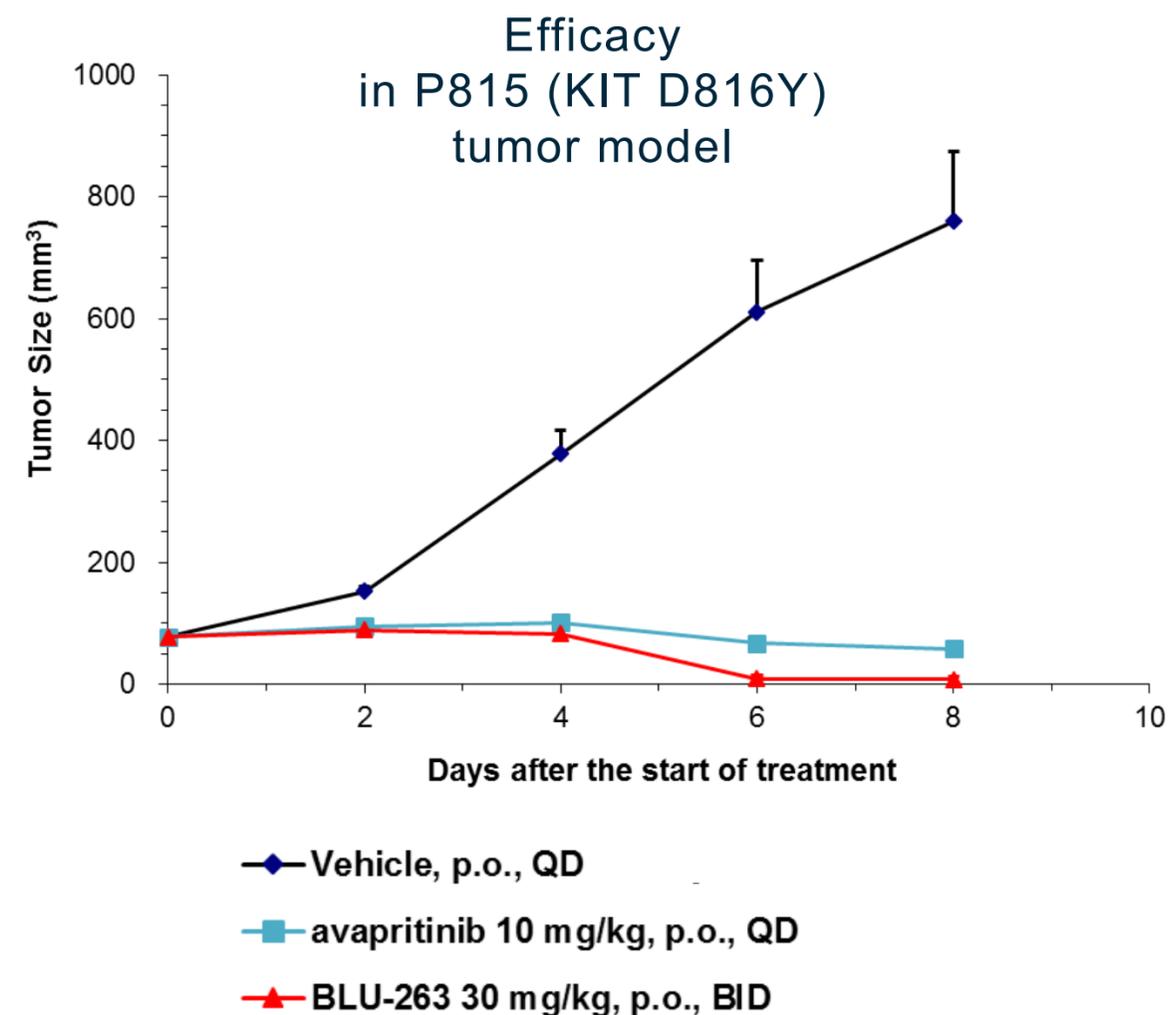
## EQUIVALENT POTENCY

Compound	KIT D816V IC <sub>50</sub> (nM)	PDGFRA D842V IC <sub>50</sub> (nM)	KIT V560G/D816V IC <sub>50</sub> (nM)
BLU-263	0.2	0.3	0.1
Avapritinib	0.22	0.24	0.1
Imatinib	>10000	>10000	>10000

## DIFFERENTIATED SELECTIVITY AND CNS PROFILES

Measure	avapritinib	BLU-263
Nav1.2 sodium channel IC <sub>50</sub>	280 nM	>10 μM
Rat K <sub>p,uu</sub> homogenate	0.40	0.024

## EQUIVALENT IN VIVO EFFICACY



# Ongoing avapritinib clinical trials

## Advanced SM

Aggressive SM  
SM with an associated  
hematologic neoplasm  
Mast cell leukemia

## Indolent SM

Indolent SM  
Smoldering SM

## Mast cell disorders

Mast cell activation syndrome  
Hereditary alpha tryptasemia  
Severe mast cell mediated asthma  
Severe anaphylaxis

AVAPRITINIB EXPLORER 

AVAPRITINIB PIONEER 

AVAPRITINIB PATHFINDER 

# Planned BLU-263 clinical trial and future potential exploration

## Advanced SM

Aggressive SM  
SM with an associated hematologic neoplasm  
Mast cell leukemia

## Indolent SM

Indolent SM  
Smoldering SM

## Mast cell disorders

Mast cell activation syndrome  
Hereditary alpha tryptasemia  
Severe mast cell mediated asthma  
Severe anaphylaxis

AVAPRITINIB EXPLORER 

AVAPRITINIB PIONEER 

BLU-263 (under evaluation)

AVAPRITINIB PATHFINDER 

BLU-263 (trial planned)\*



# Q & A



break



# A prolific platform for precision medicine

**MARION DORSCH, PhD**

Chief Scientific Officer

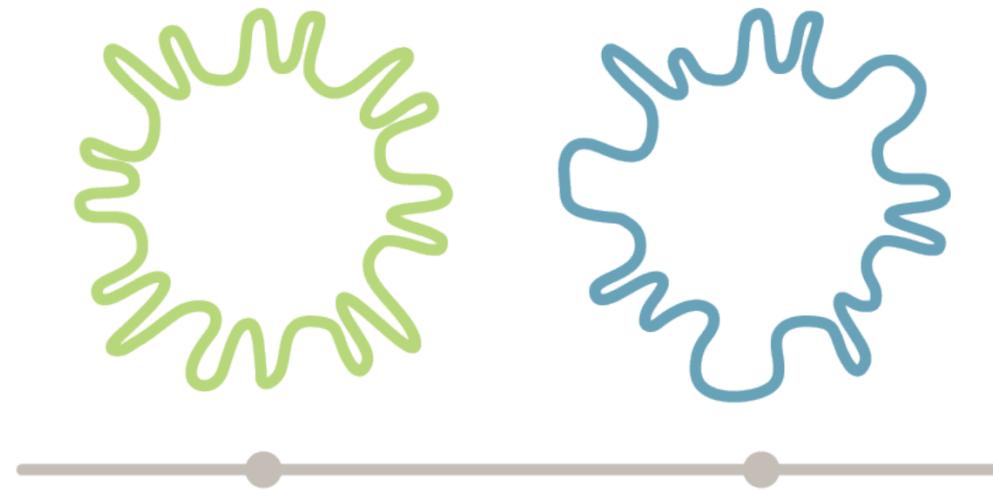


# Cancer is a genetic disease that evolves and becomes more elusive

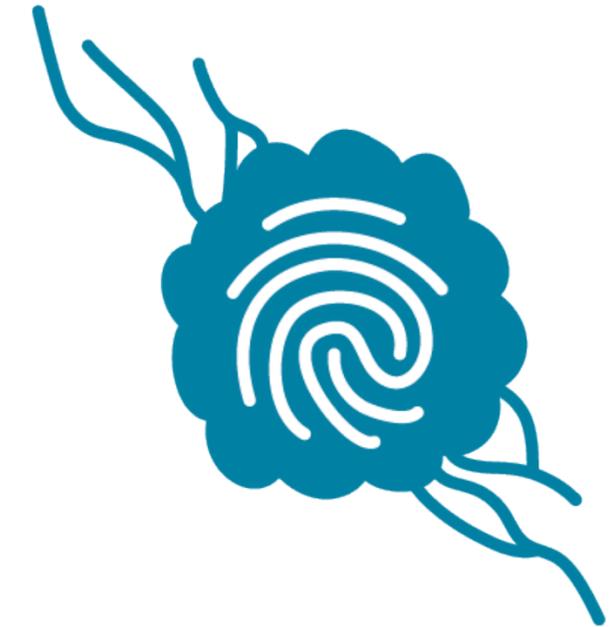
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***Cancer is a disease driven by genomic aberrations***



***Cancer evolves over time with new molecular changes***



***Tumors and their microenvironments are inherently complex***

# Blueprint Medicines is built to tackle the challenges of treating cancer

## TRANSFORMATIVE BENEFIT

- **Deep biological knowledge** to identify areas of transformative potential
- Ability to design **highly selective medicines** against challenging profiles

## URGENCY

- Streamlined discovery approach enabled by a **proprietary library**
- **Integrated research capability** to rapidly adapt to evolving insights

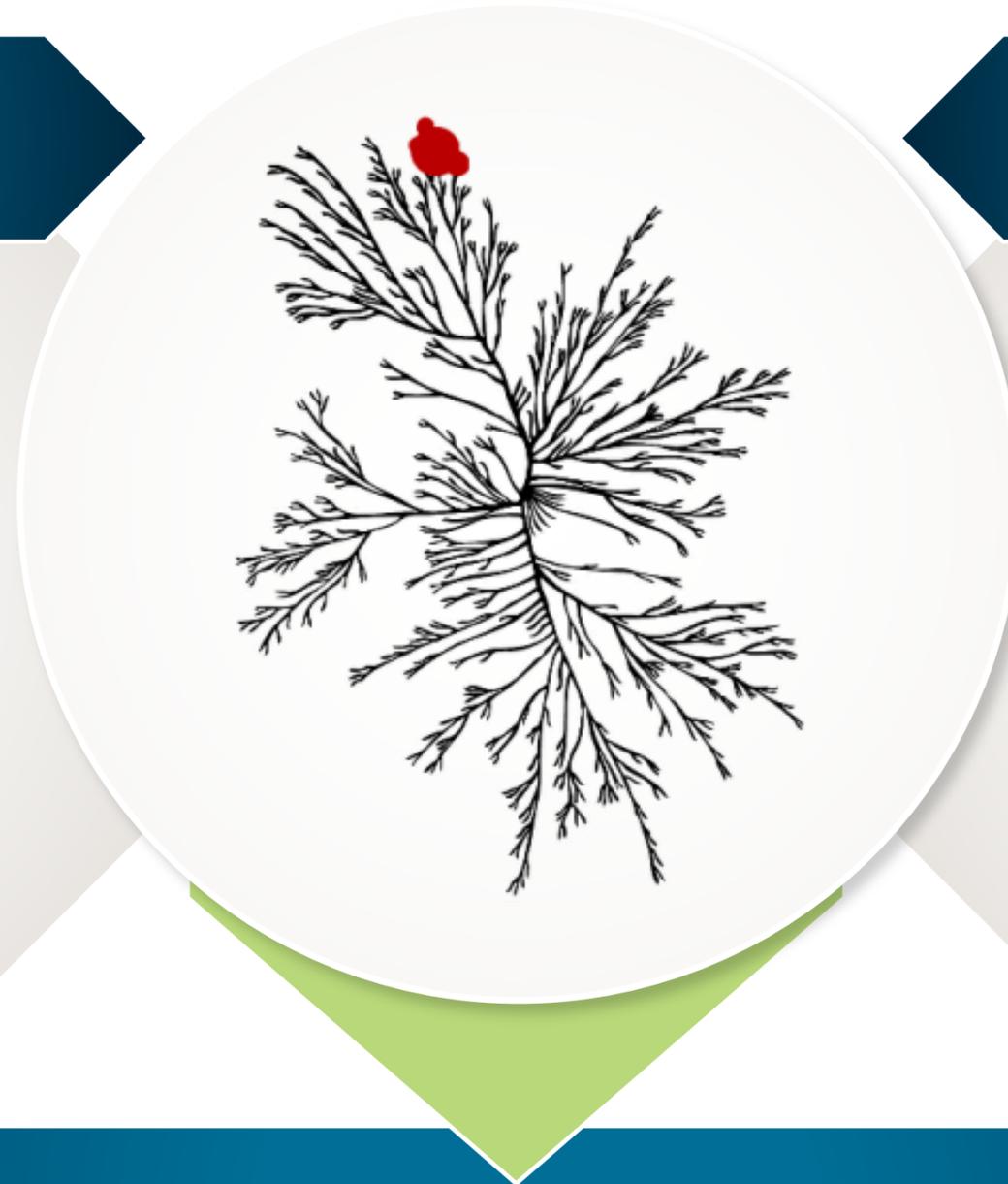
## EFFICIENCY

- Research portfolio driven by programs with **high probability of success**
- **Early go/no-go decisions** with a gated, data-driven operating model

# A simple, reliable and reproducible approach to designing targeted therapies

## PROPRIETARY COMPOUND LIBRARY

- Unique collection of small molecule kinase inhibitors
- High-quality chemistry starting points
- Tools to uncover novel targets and biology



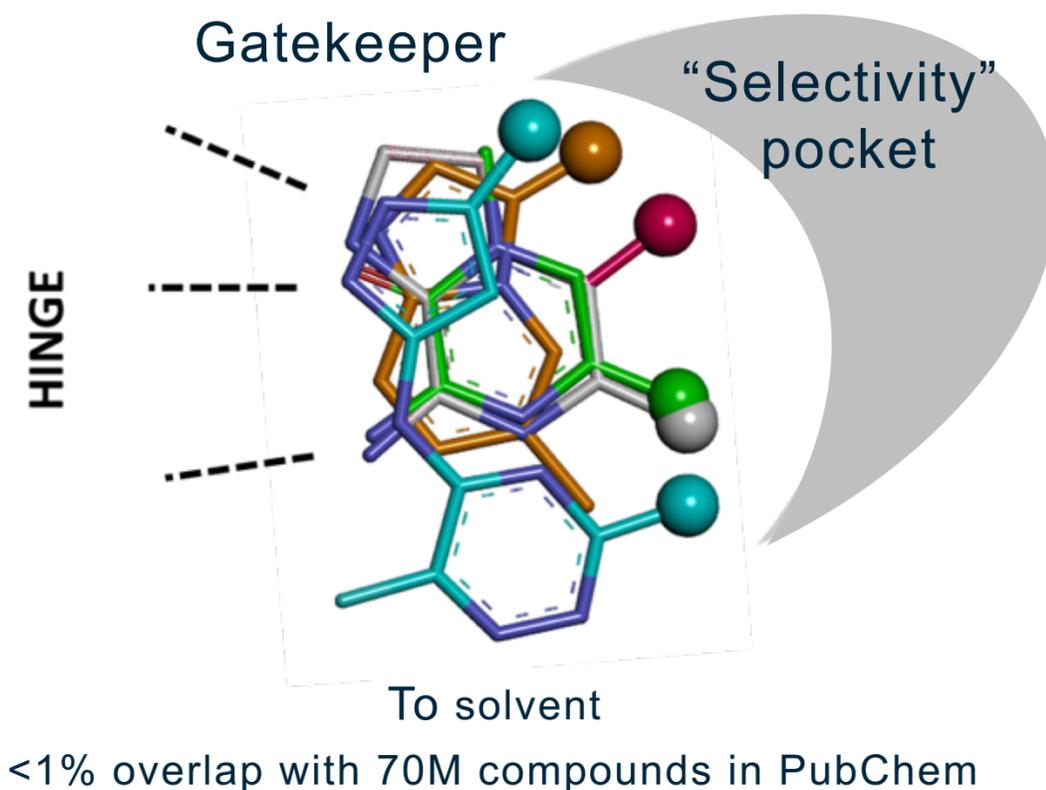
## DEEP BIOLOGICAL INSIGHTS

- New insights into the biology of kinases as disease drivers
- Identification of new drug targets from Kinases of Unknown Biology (KUBs)

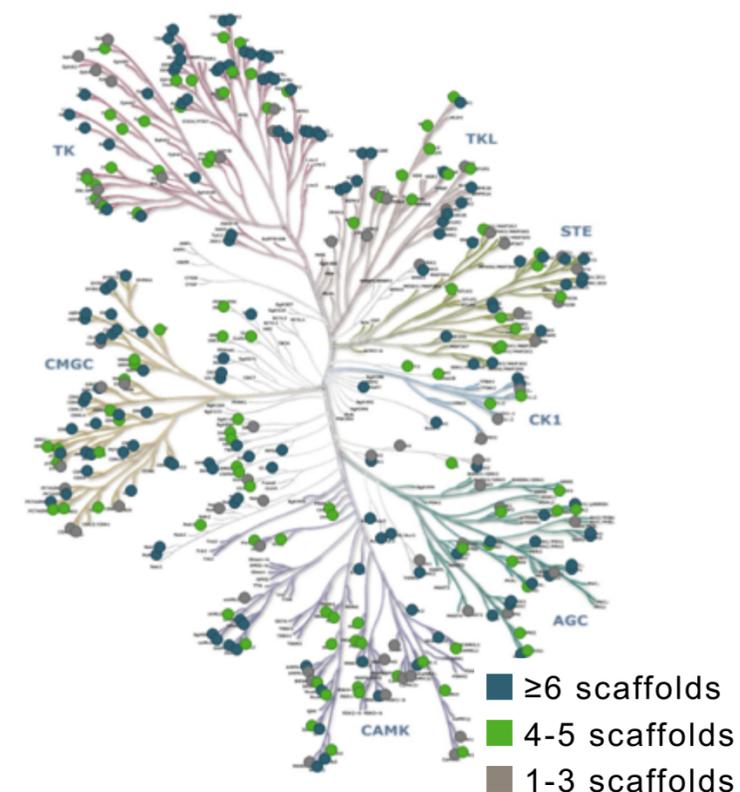
HIGHLY SELECTIVE AND POTENT KINASE INHIBITOR DRUG CANDIDATES

# Isolate selective starting points within our proprietary compound library

## Rationally designed



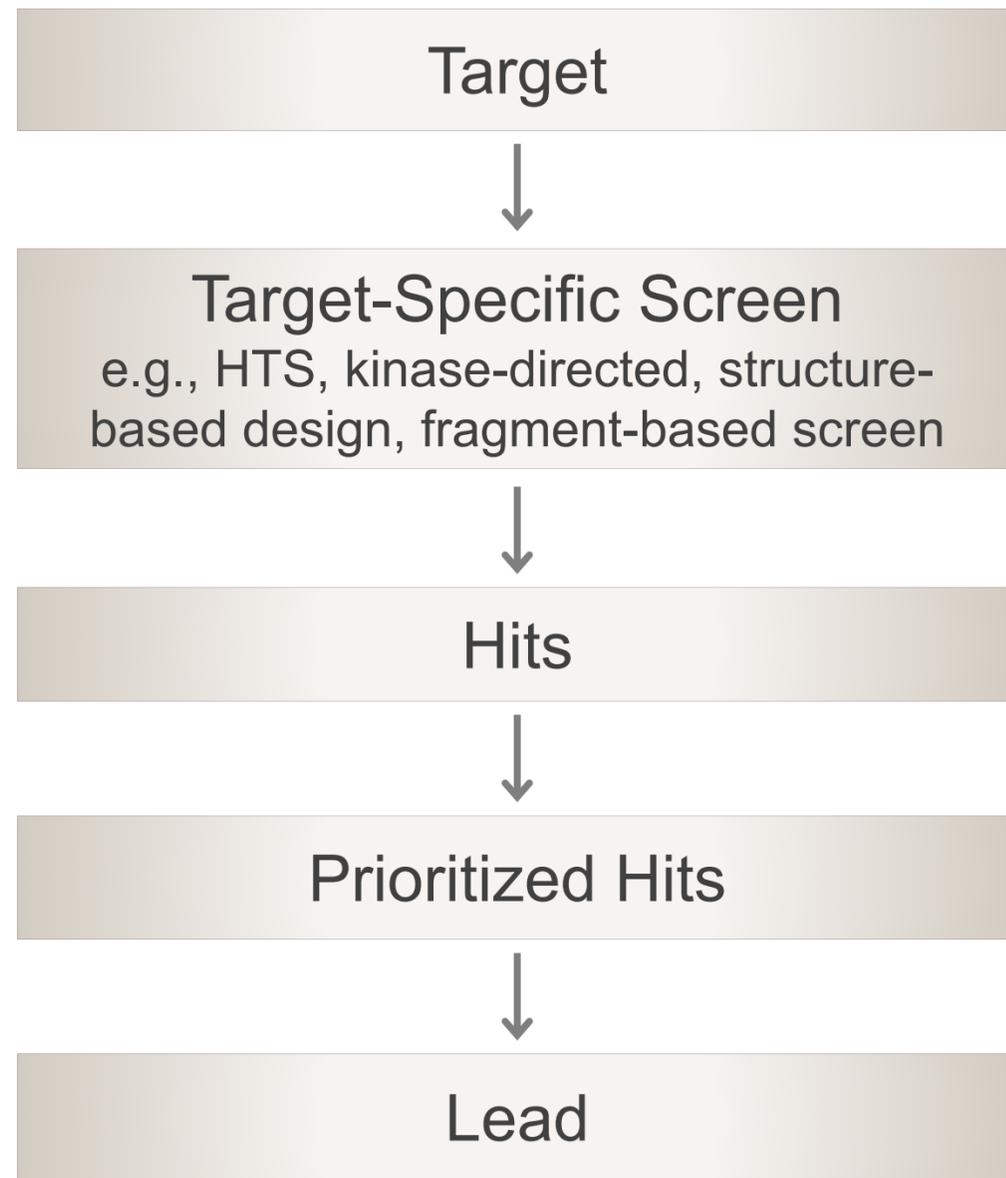
## Broad and deep kinome coverage



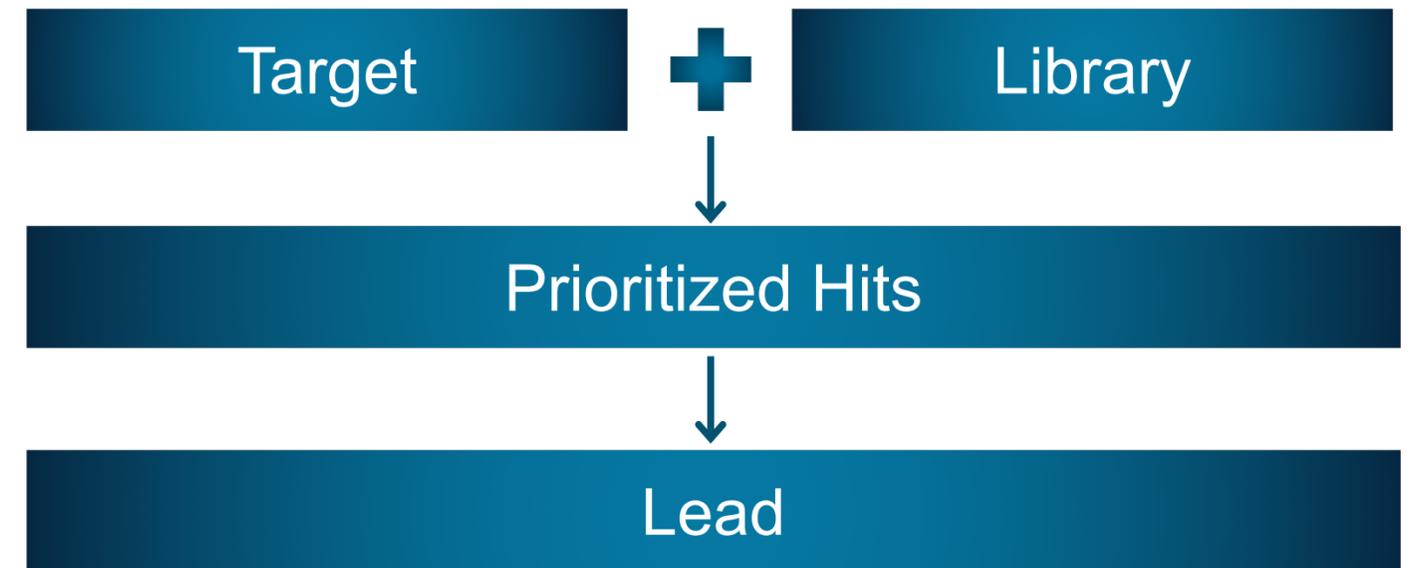
DESIGNED TO BALANCE NOVELTY, POTENCY, AND SELECTIVITY  
SCREENED AGAINST A LARGE PANEL OF KINASES  
ITERATIVE PROCESS

# Accelerate the discovery process by shortening the time to lead identification

## TRADITIONAL APPROACH



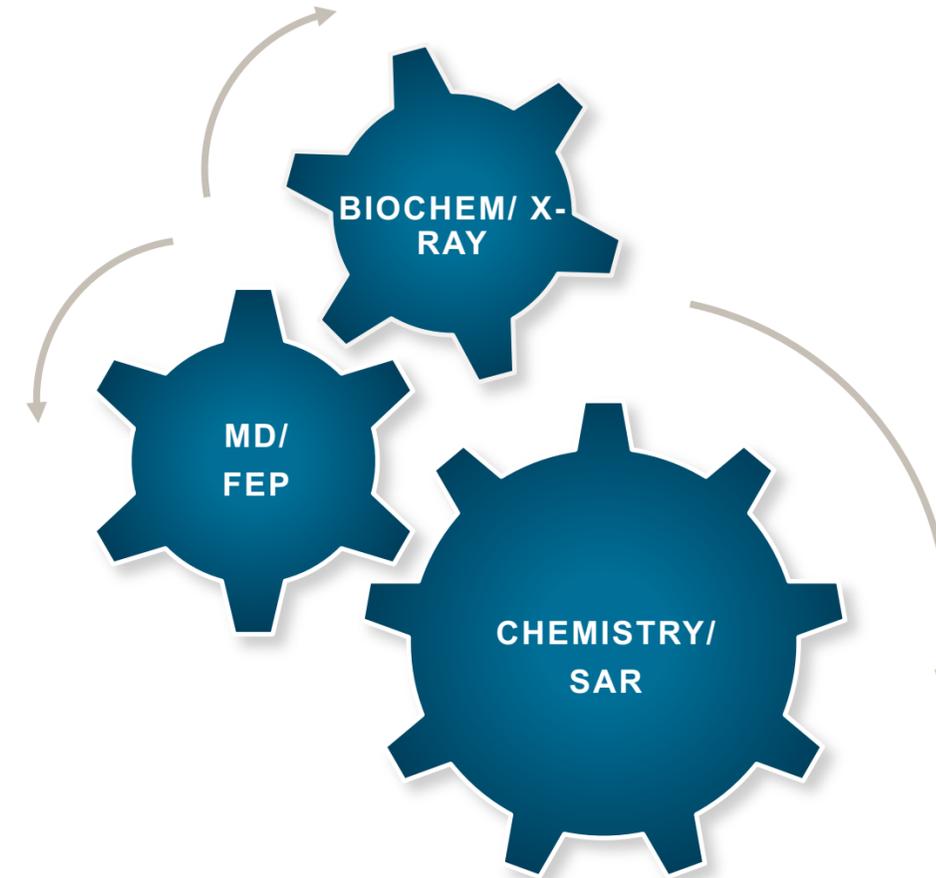
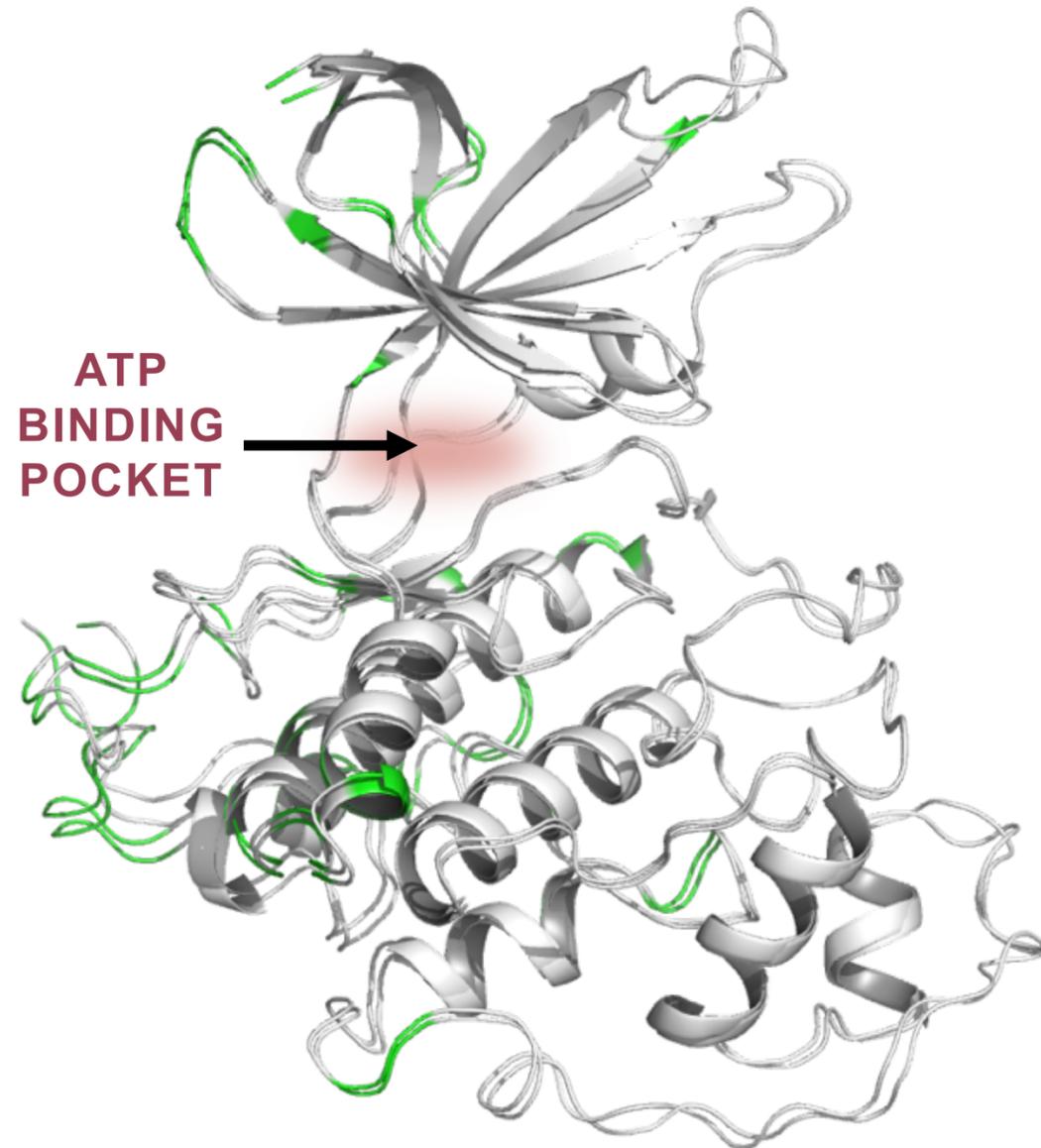
## BLUEPRINT MEDICINES' ACCELERATED APPROACH



- ✓ No target-specific screen needed
- ✓ Annotation yields prioritized hits
- ✓ Full understanding of selectivity
- ✓ Informed optimization

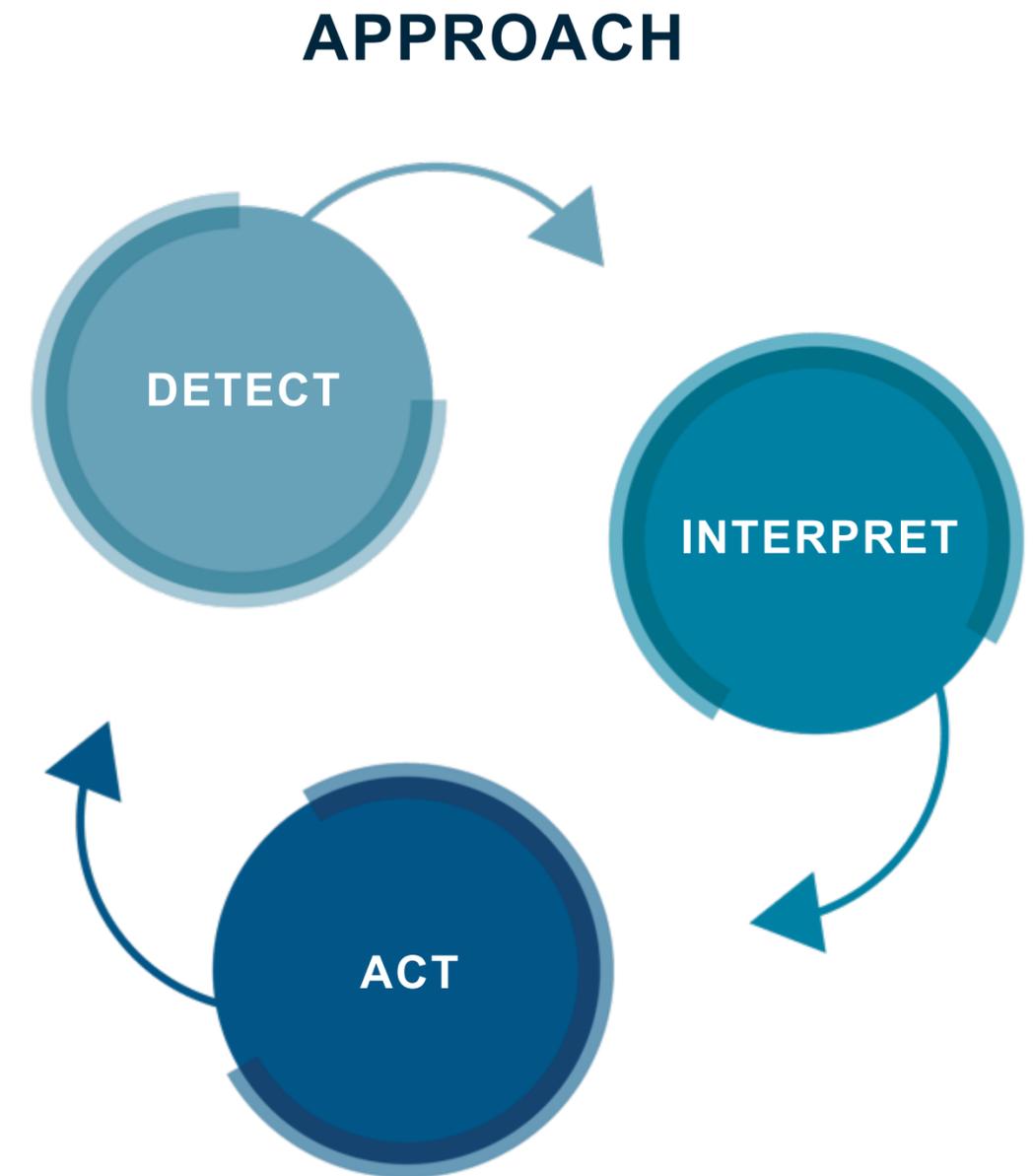
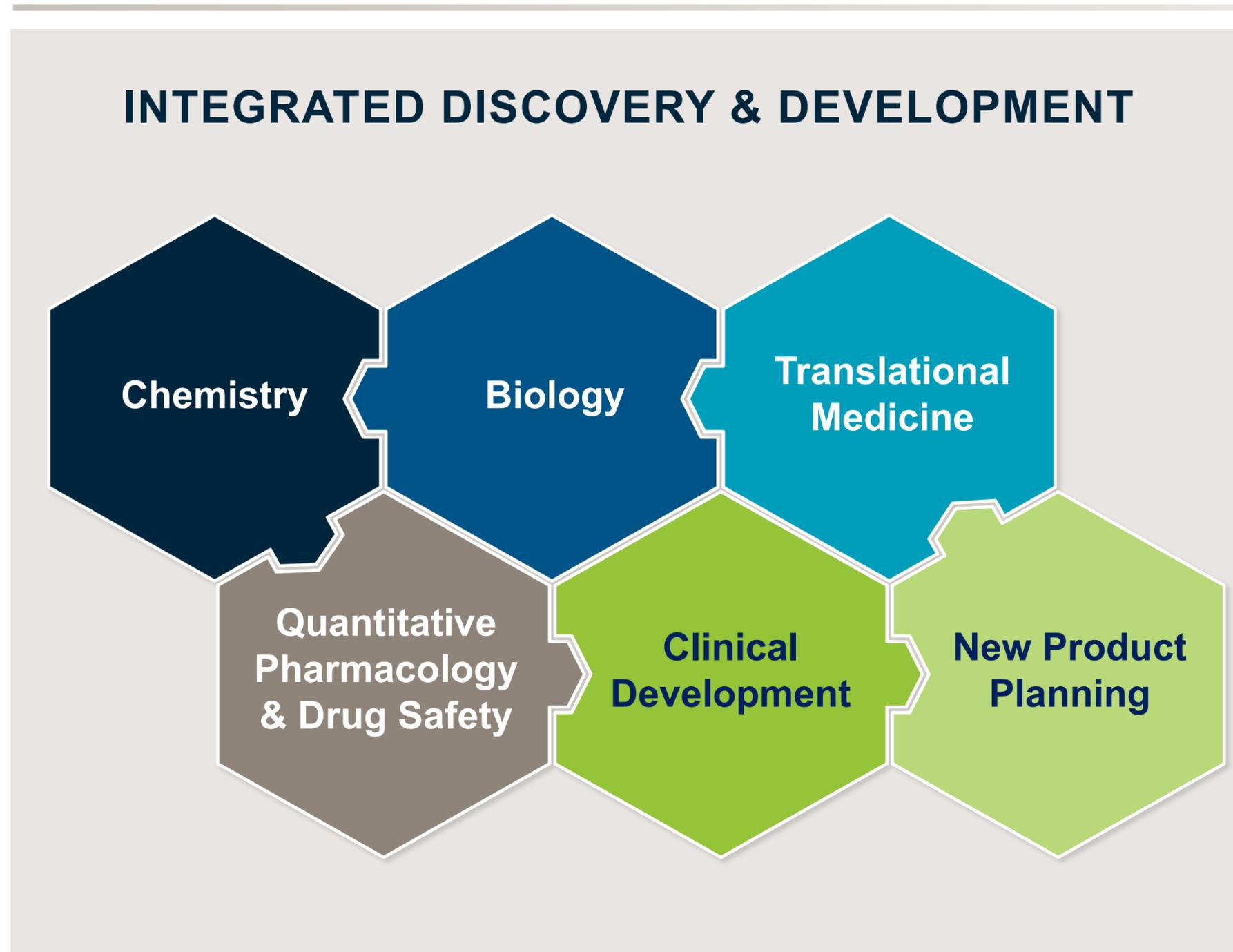
# Refine selectivity against challenging targets by integrating data

PARALOGS WITH  
HIGH DEGREE OF SIMILARITY  
(DIFFERENCES SHOWN IN GREEN)



- Structural bioinformatics
- Molecular Dynamics (MD)
- Free Energy Perturbations (FEP)
- Cheminformatics

# A closely integrated discovery model enables sustainable innovation

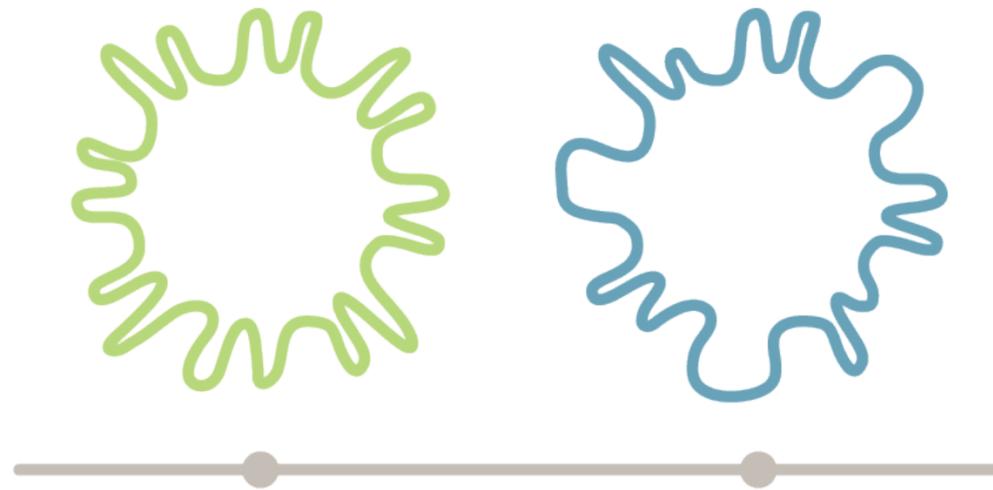


# Cancer is a genetic disease that evolves and becomes more elusive

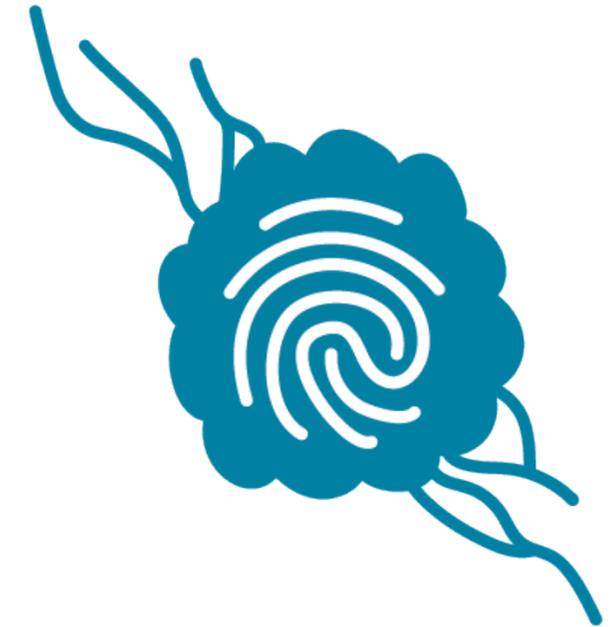
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***Cancer is a disease driven by genomic aberrations***



***Cancer evolves over time with new molecular changes***



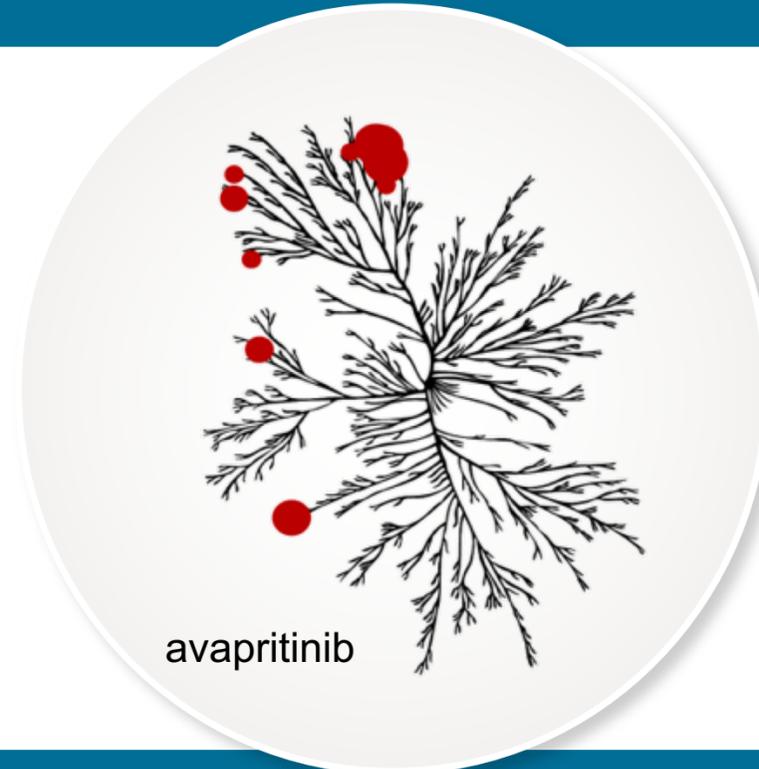
***Tumors and their microenvironments are inherently complex***

# Rapidly drive to transformative outcomes in early clinical testing



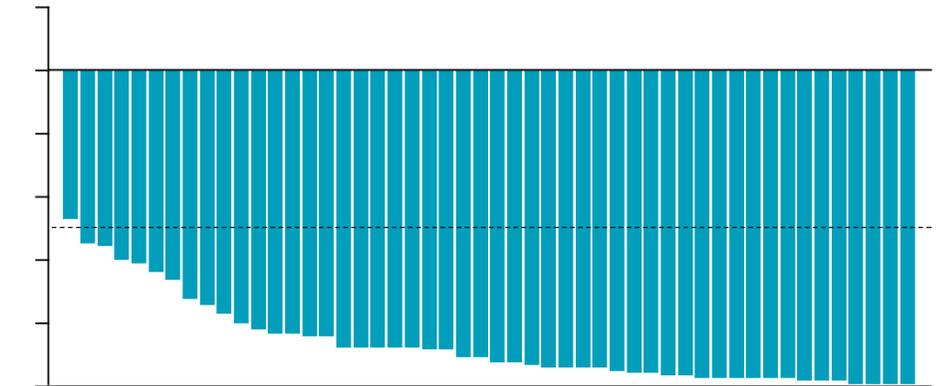
**Cancer is a disease driven by genomic aberrations**

**KIT D816V**  
biochemical potency **IC<sub>50</sub> 0.22 nM**



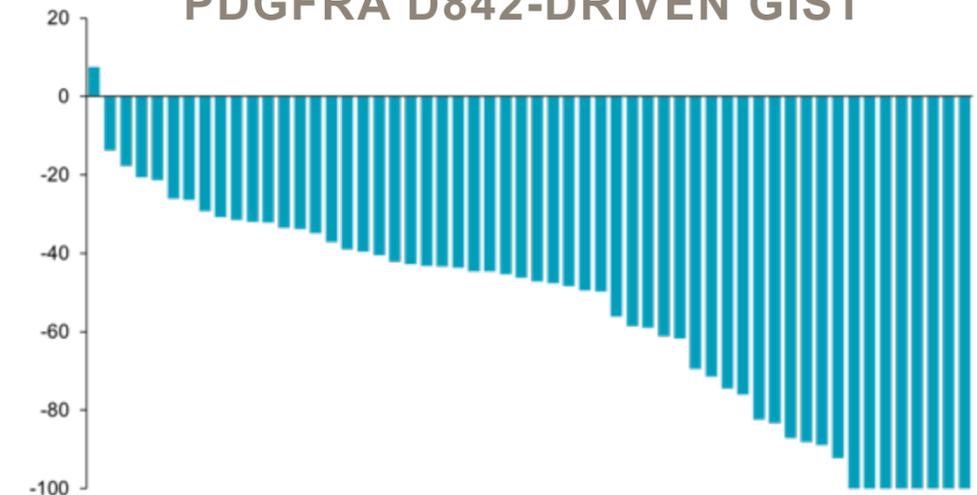
**PDGFRA D842V**  
biochemical potency **IC<sub>50</sub> 0.24 nM**

## ADVANCED SYSTEMIC MASTOCYTOSIS



Maximum reduction in serum tryptase<sup>1</sup>

## PDGFRA D842-DRIVEN GIST

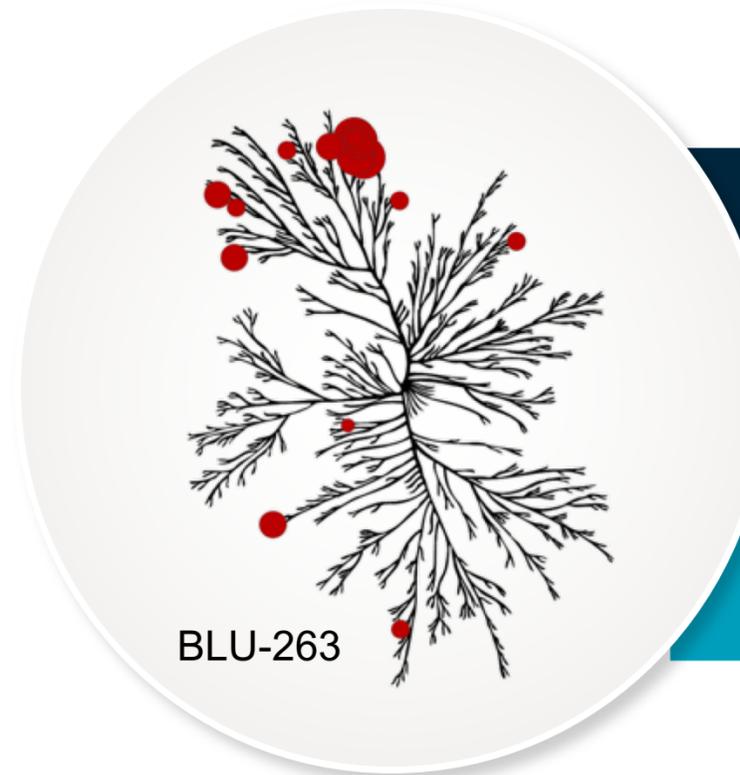


Maximum reduction in target tumors<sup>2</sup>

# Leverage clinical insights to enable next generation inhibitors



***Cancer is a disease driven by genomic aberrations***



**EQUIVALENT POTENCY**

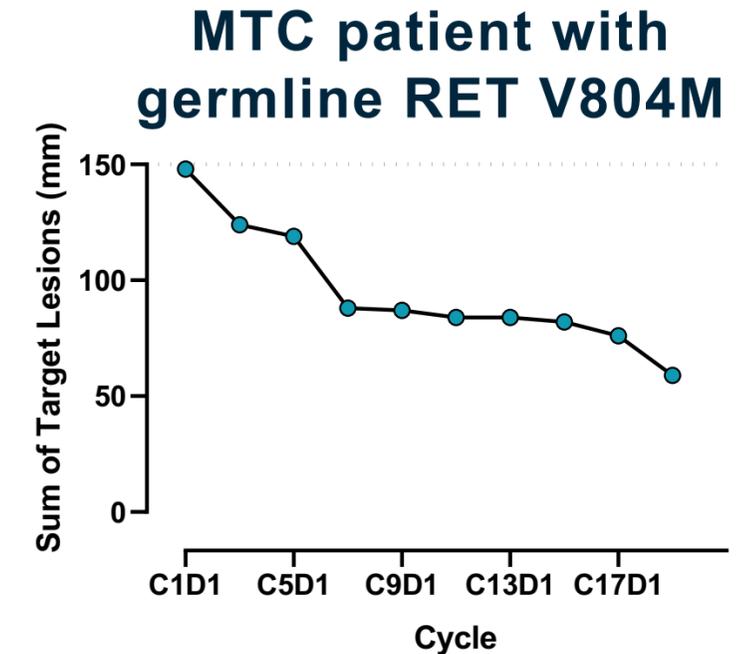
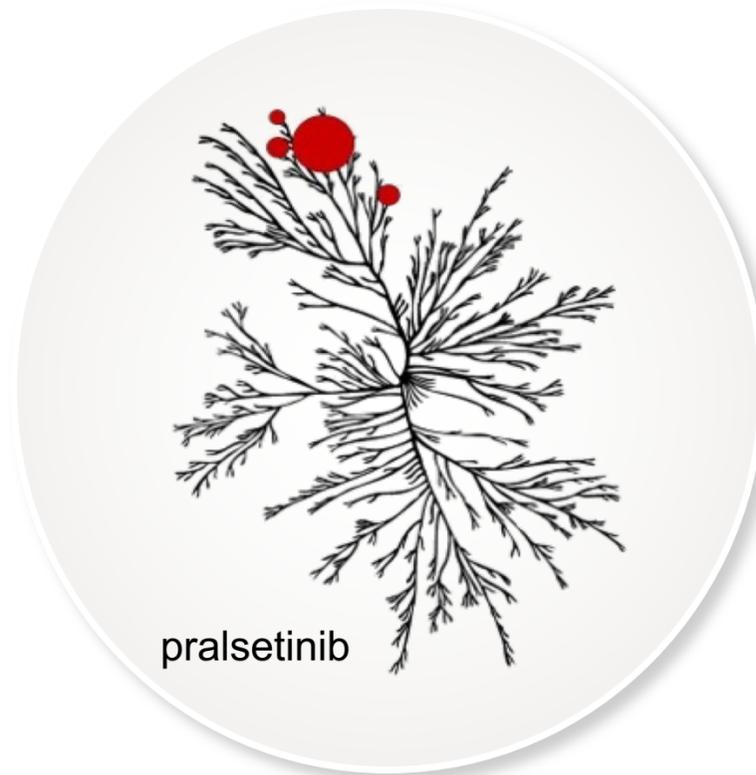
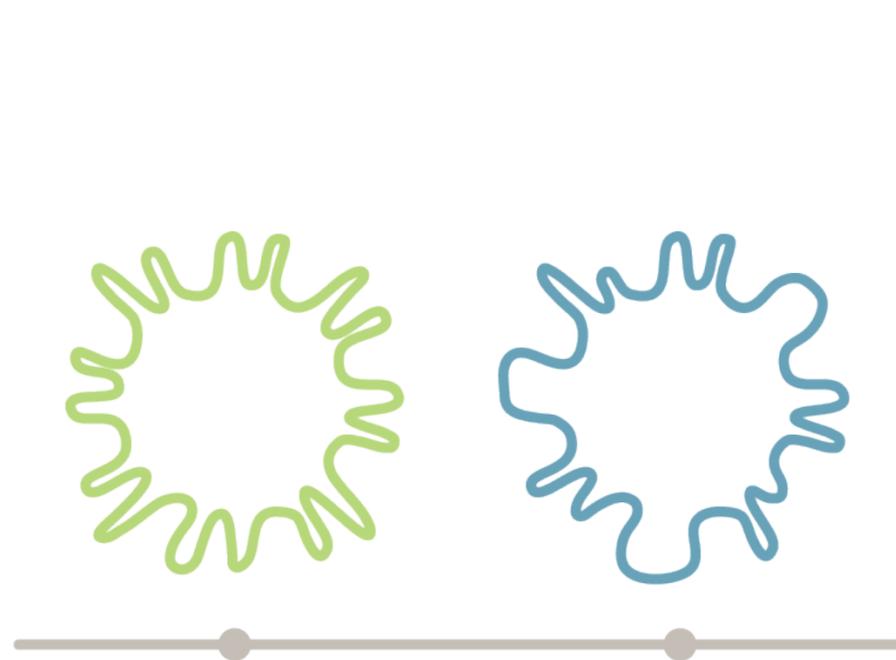
**IMPROVED SELECTIVITY**

**LOWER CNS PENETRATION**

## Biochemical potency (IC<sub>50</sub>, nM)

Compound	KIT D816V	PDGFRA D842V	KIT V560G/D816V
BLU-263	0.2	0.3	0.1
Avapritinib	0.22	0.24	0.1

# Predict and prevent resistance prospectively



Ongoing PR >19 months

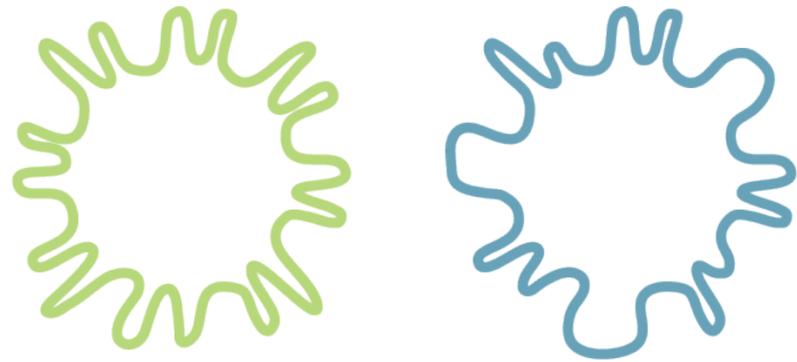
**Cancer evolves over time with new molecular changes**

## Biochemical potency (IC<sub>50</sub>, nM)

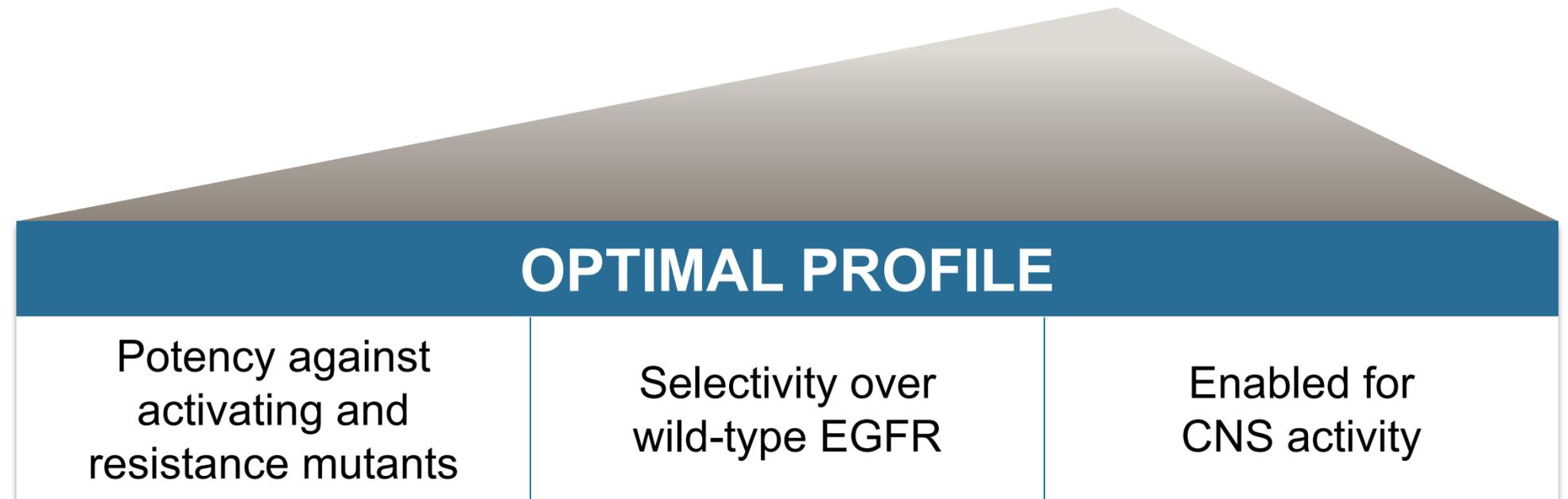
WT RET	CCDC6-RET	M918T	RET V804L	RET V804M
0.4 nM	0.4 nM	0.4 nM	0.3 nM	0.4 nM

# Navigate challenging target profiles to tackle tumor evolution

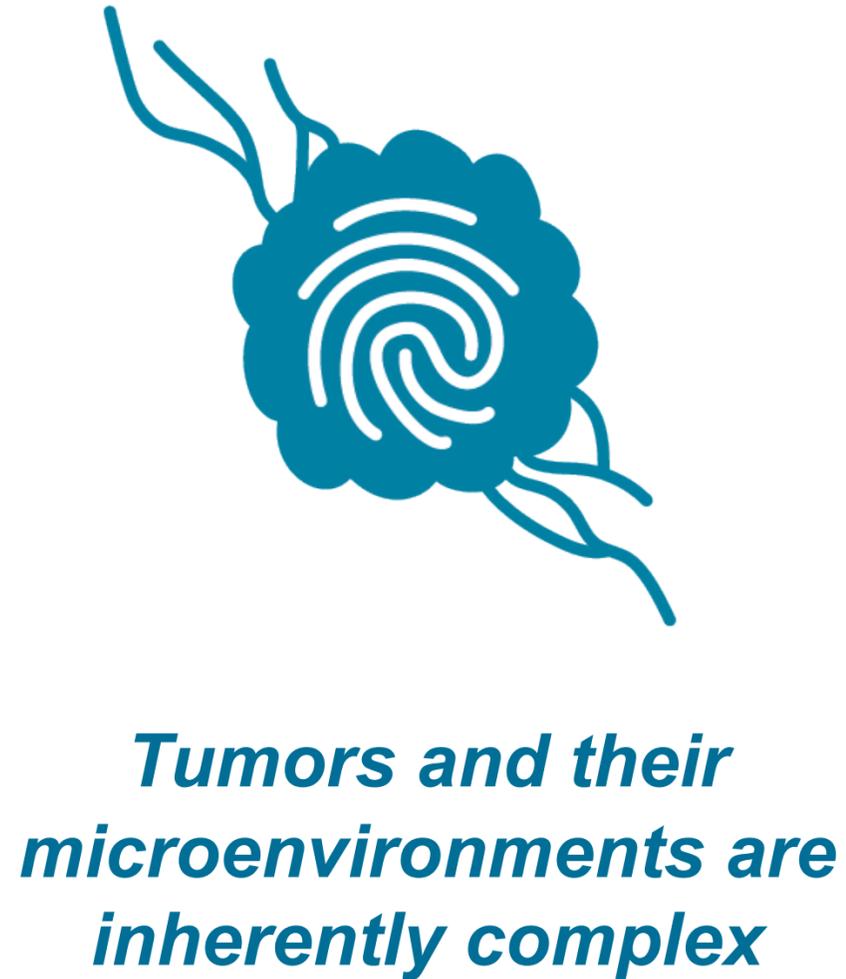
## EGFR+ NSCLC treatment paradigm



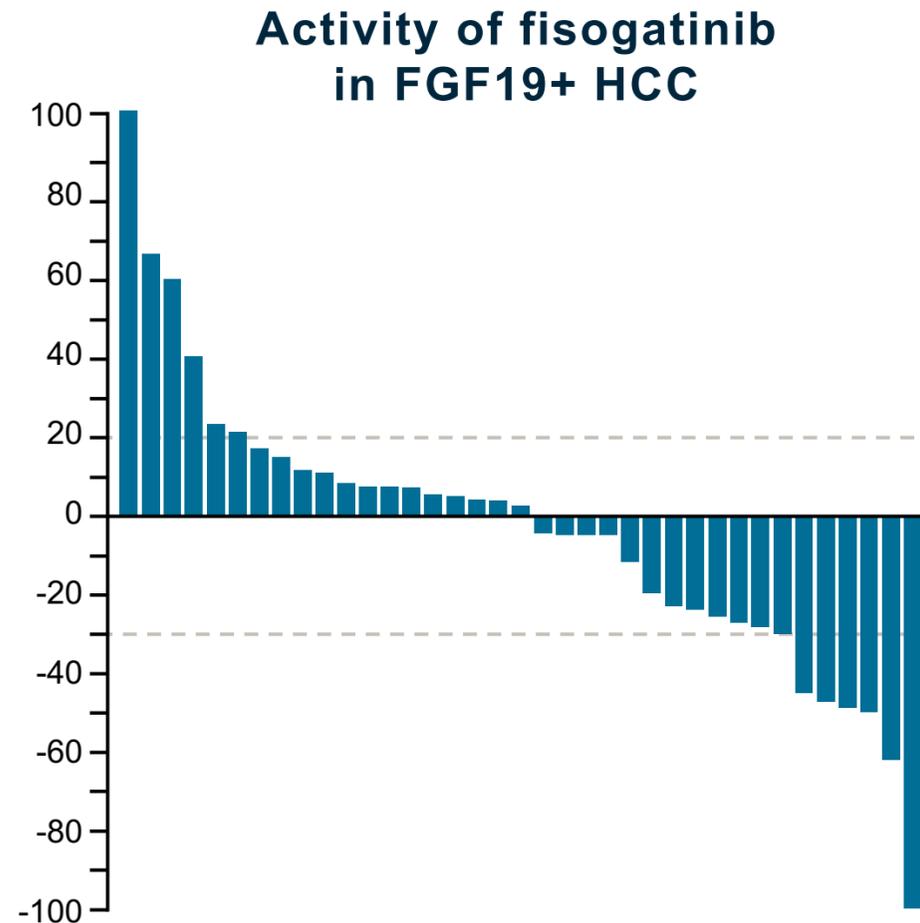
***Cancer evolves over time  
with new molecular  
changes***



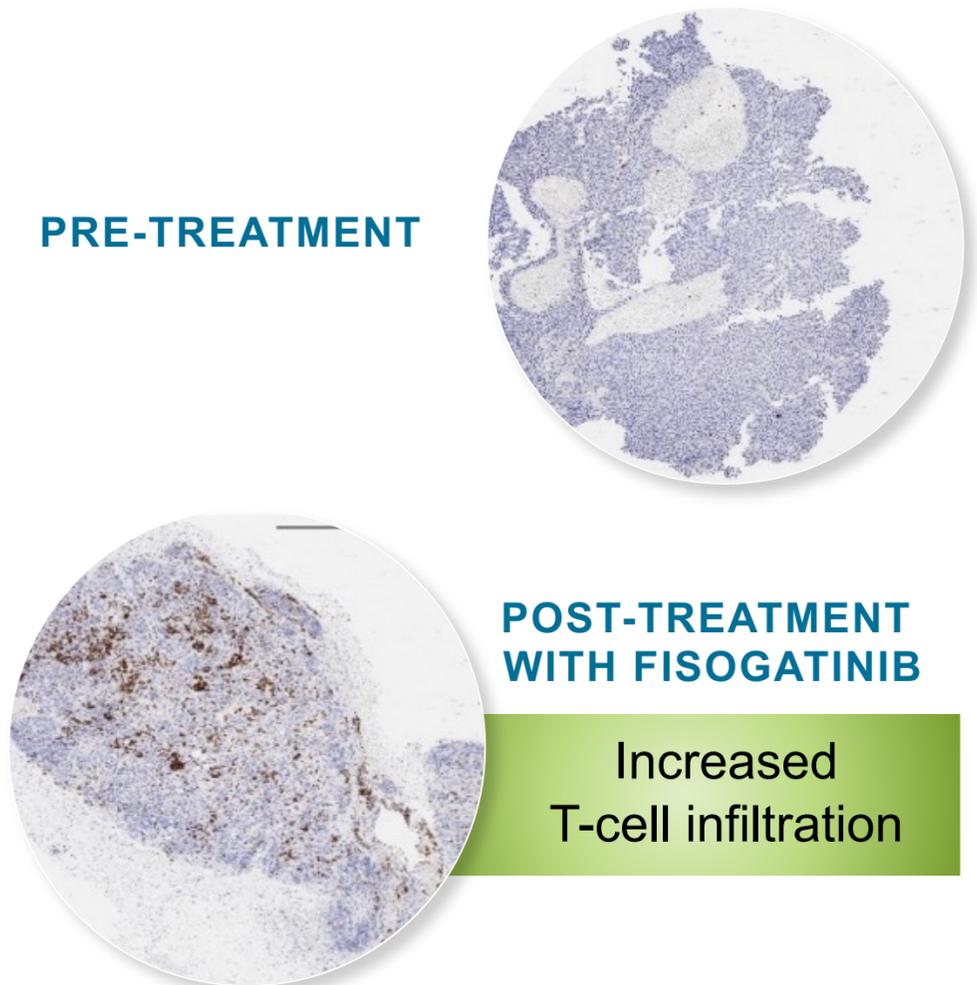
# Interrogate mechanisms to identify transformative combination opportunities



## CLINICAL PROOF-OF-CONCEPT DATA<sup>1</sup>

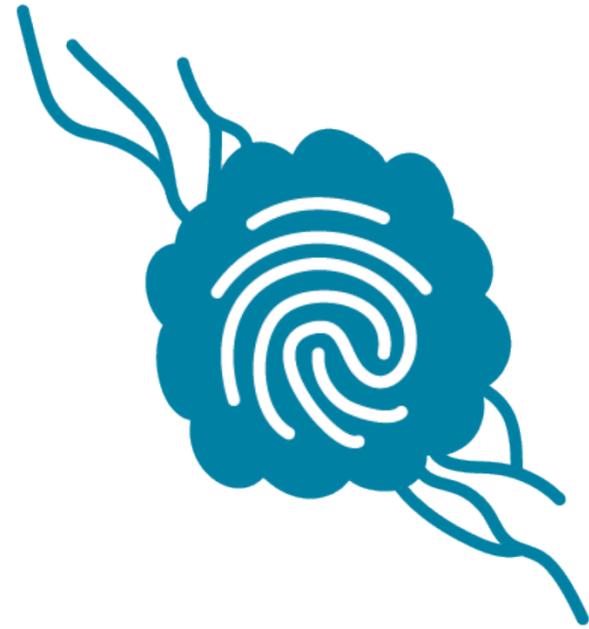


## HUMANIZED PRECLINICAL MODEL



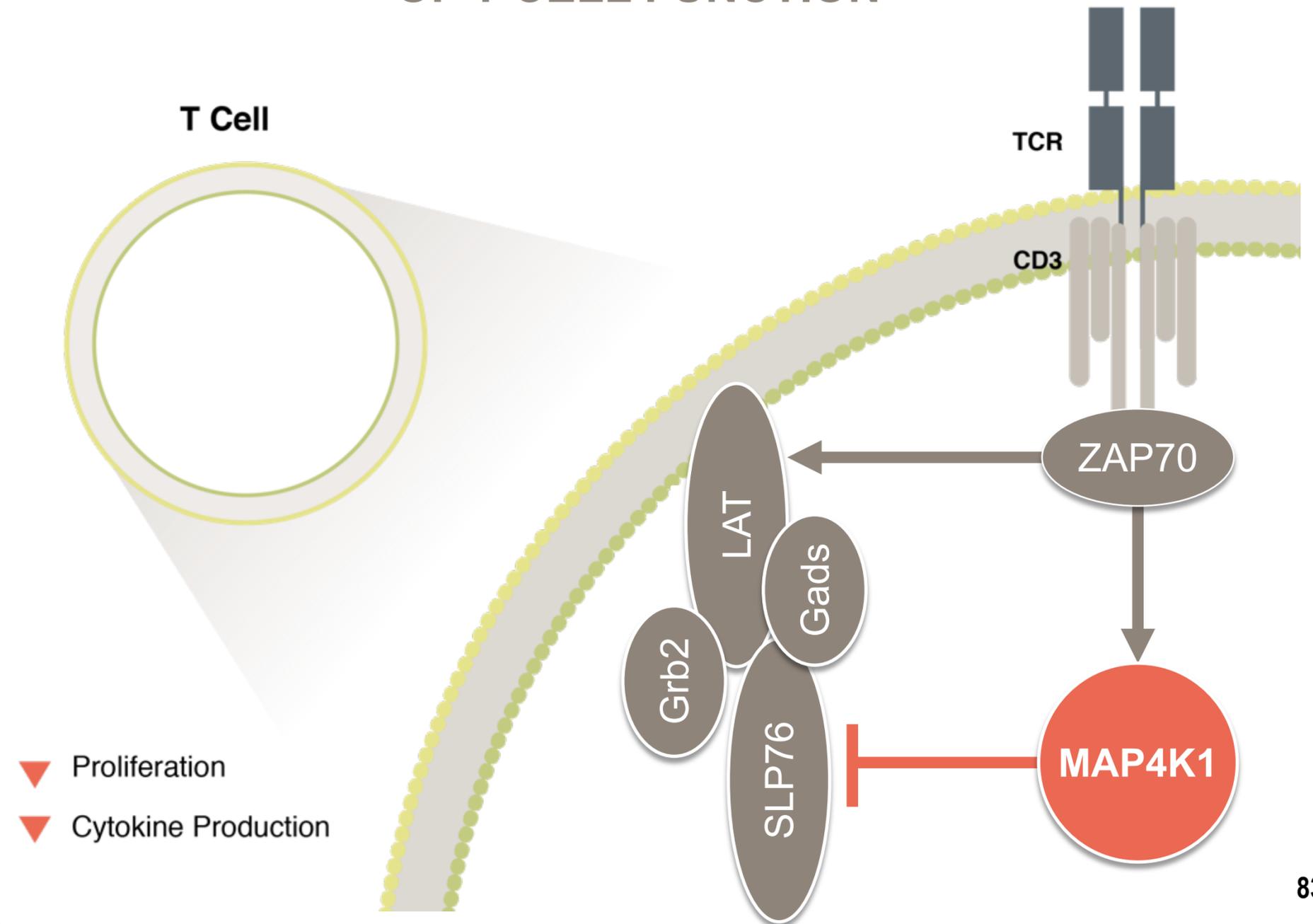
Plan to initiate combination trial of fisogatinib and CStone's anti-PDL1 CS-1001 in Q4 2019

# Harness the immune system to attack complex tumors



*Tumors and their microenvironments are inherently complex*

## MAP4K1 IS A NEGATIVE REGULATOR OF T-CELL FUNCTION



# Blueprint Medicines is built to tackle the challenges of treating cancer

## TRANSFORMATIVE BENEFIT

- **Deep biological knowledge** to identify areas of transformative potential
- Ability to design **highly selective medicines** against challenging profiles

## URGENCY

- Streamlined discovery approach enabled by a **proprietary library**
- **Integrated research capability** to rapidly adapt to evolving insights

## EFFICIENCY

- Research portfolio driven by programs with **high probability of success**
- **Early go/no-go decisions** with a gated, data-driven operating model

Continued productivity: planned research milestones in 1H 2020

---

**Submit IND application for BLU-263**

**Name 2 new development candidates**

A video player interface with a dark blue background featuring concentric circles and a grid pattern. The text "NON-SMALL CELL LUNG CANCER" is centered in white. The bottom control bar includes a play button, a progress bar showing 00:07, a total duration of 05:54, and icons for full screen, volume, and settings.

NON-SMALL CELL LUNG CANCER

00:07 05:54

# Addressing tumor evolution in lung cancer

**TIM GUZI, PhD**

Senior Vice President, Chemistry

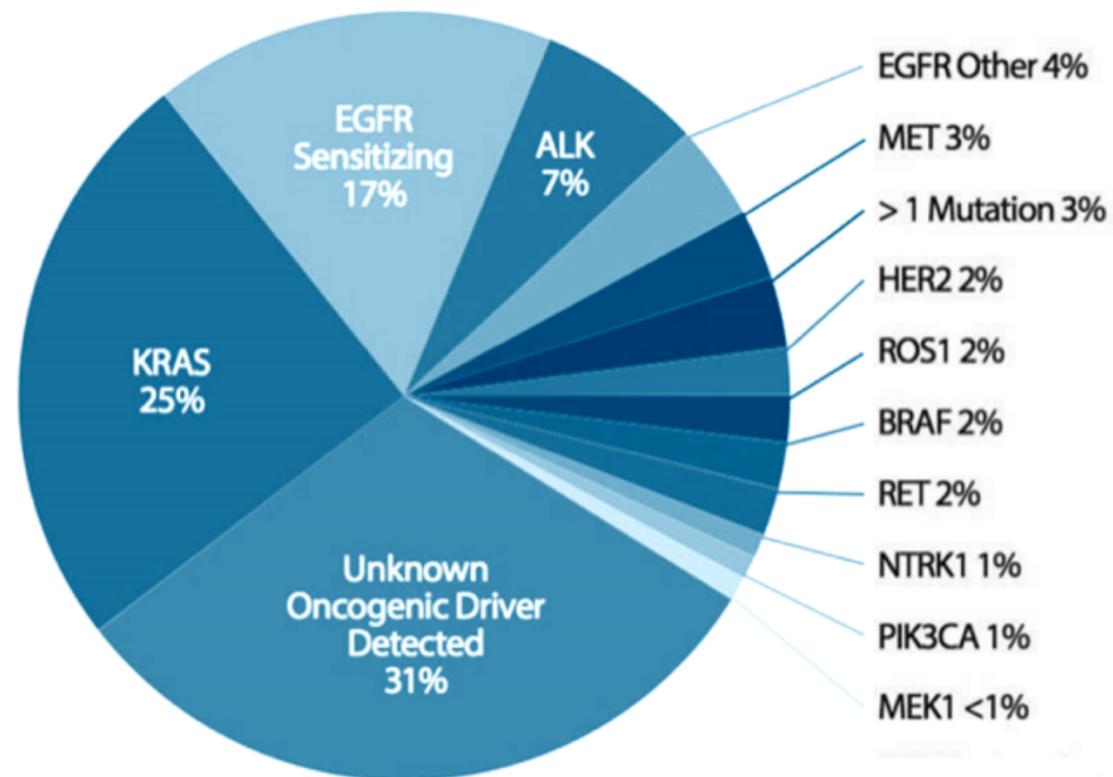


*L.O., living with NSCLC*



# Lung cancer is a kinase-driven disease primed for targeted therapy

## IDENTIFIABLE ONCOGENIC DRIVERS<sup>1</sup>



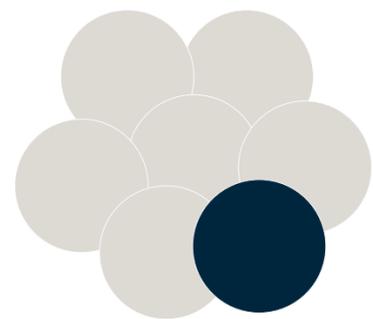
## EVOLVING NSCLC TESTING PARADIGM

- ~70-80% of NSCLC patients are tested for EGFR and ALK alterations
- Reimbursement of NGS testing is improving (e.g., Medicare National Coverage Determination)
- Precedent exists for testing post-progression with osimertinib plasma-based companion diagnostic
- Plasma-based testing technology is increasingly comparable to tissue-based testing

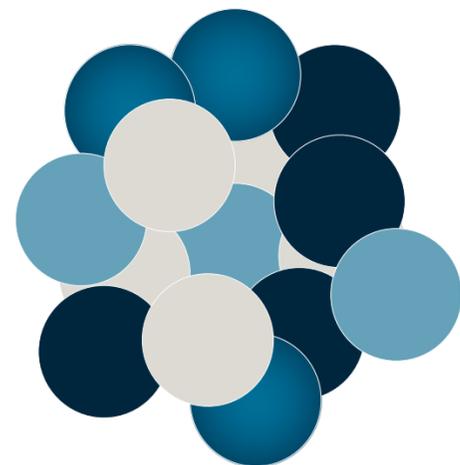
LUNG CANCER REMAINS THE LEADING CAUSE OF CANCER DEATH GLOBALLY<sup>2</sup>

# Tumor evolution and three approaches for achieving durable patient benefit

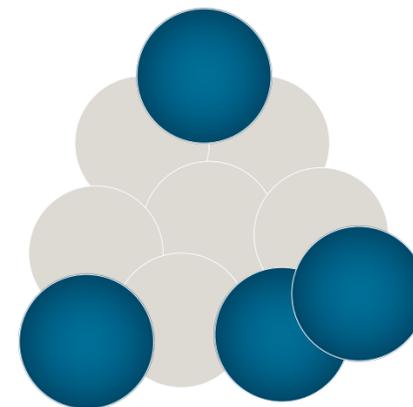
1L TARGETED THERAPY



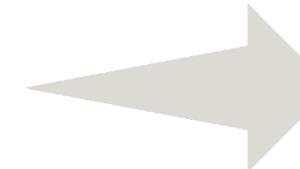
INITIAL  
ACTIVATING  
ONCOGENIC  
DRIVER



INCREASING  
TUMOR  
MOLECULAR  
HETEROGENEITY



SURVIVAL  
OF RESISTANT  
CLONES



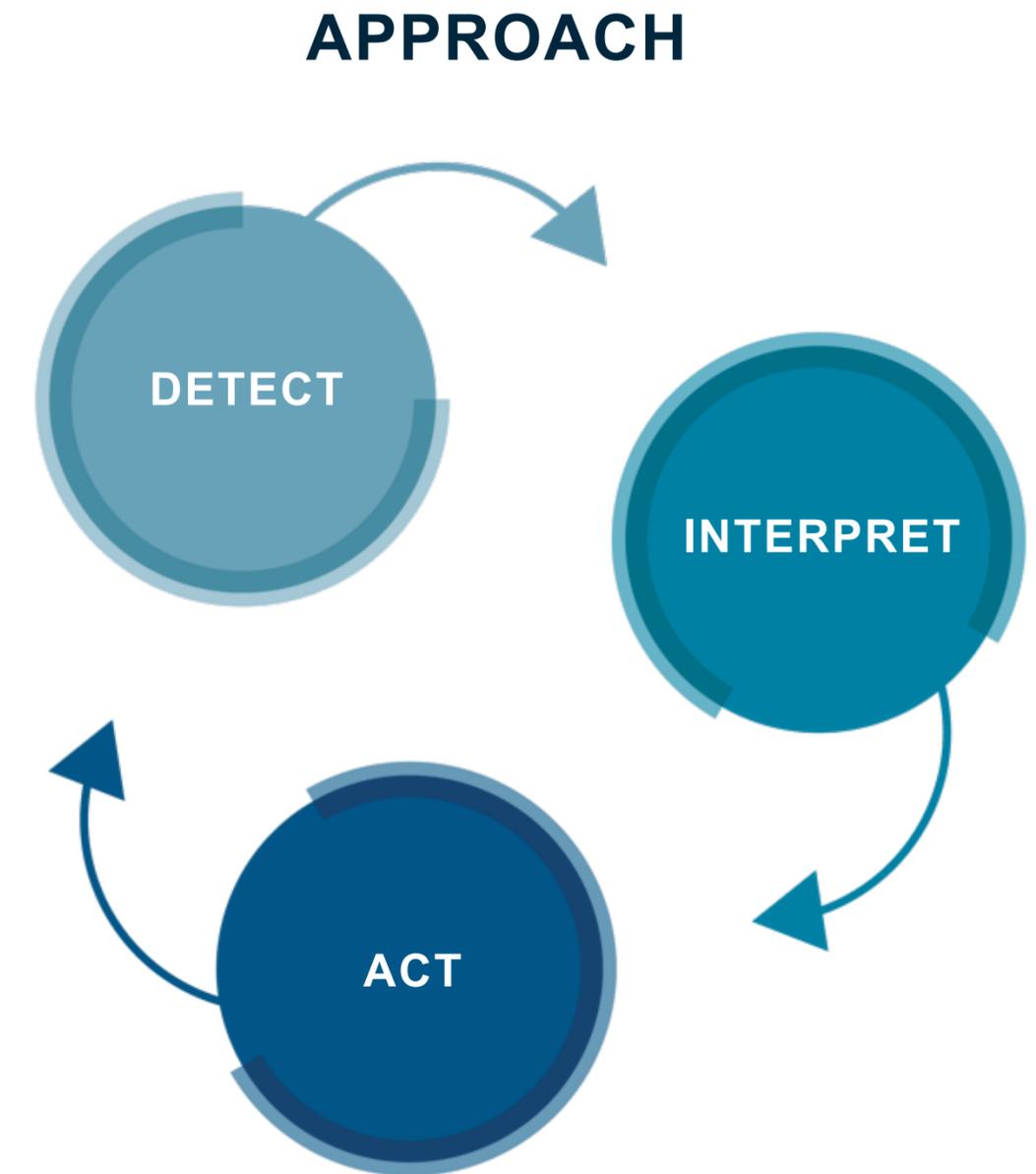
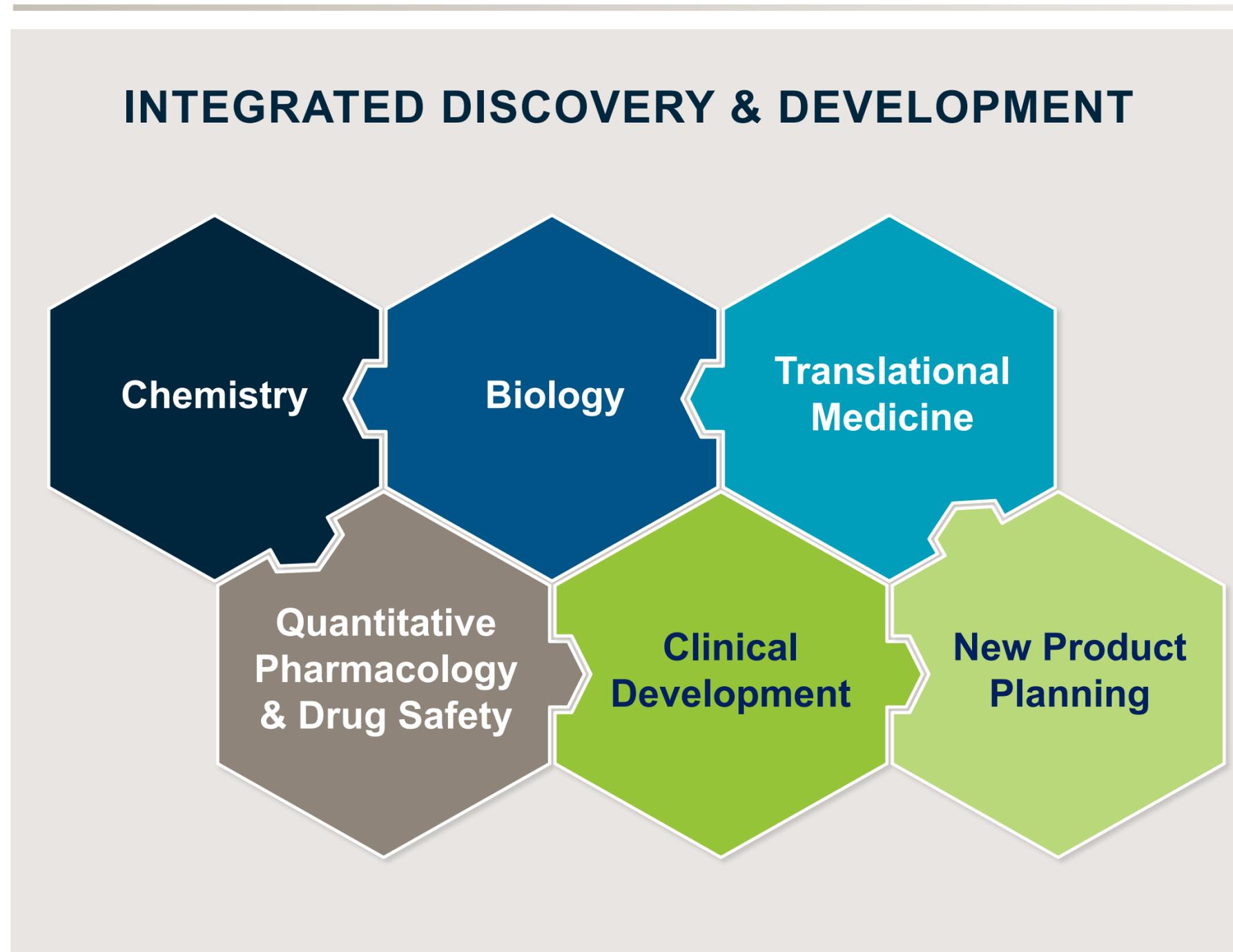
**OPTIMIZED 1L**

**SEQUENTIAL**

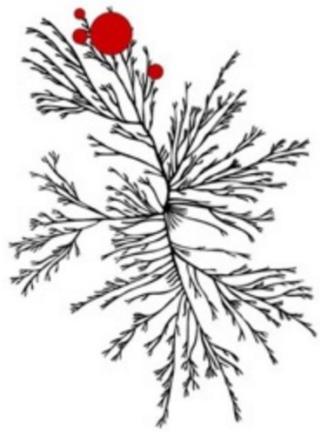
**COMBINATION**

**Potency & selectivity essential for success**

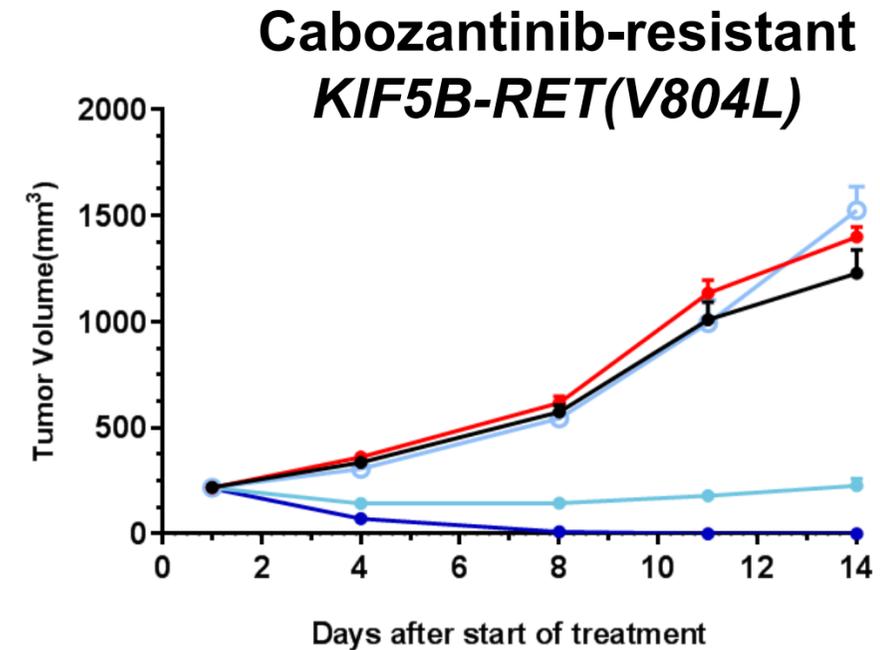
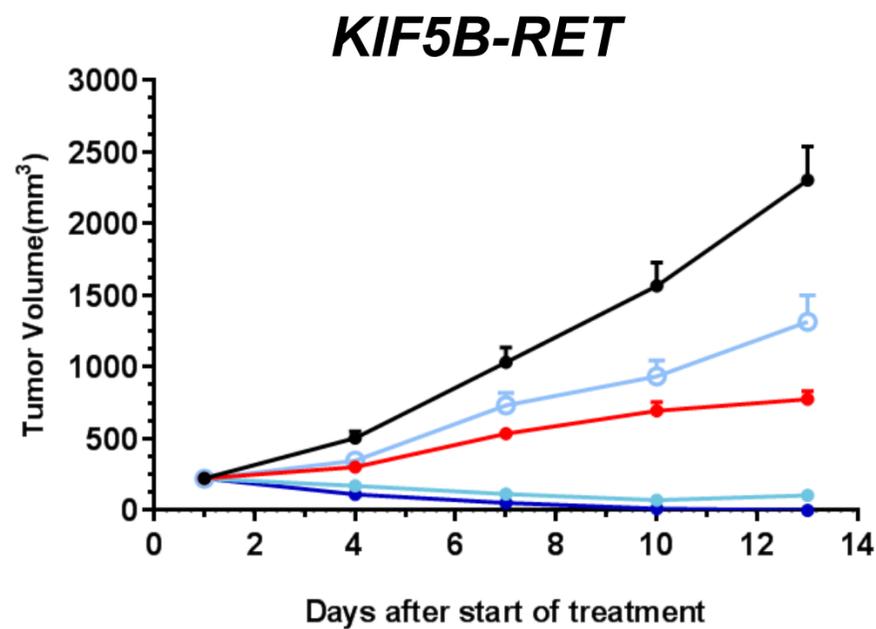
# A closely integrated discovery model enables sustainable innovation



# NSCLC patients with RET fusions have no highly effective treatment options



**Pralsetinib:** high kinome selectivity for RET



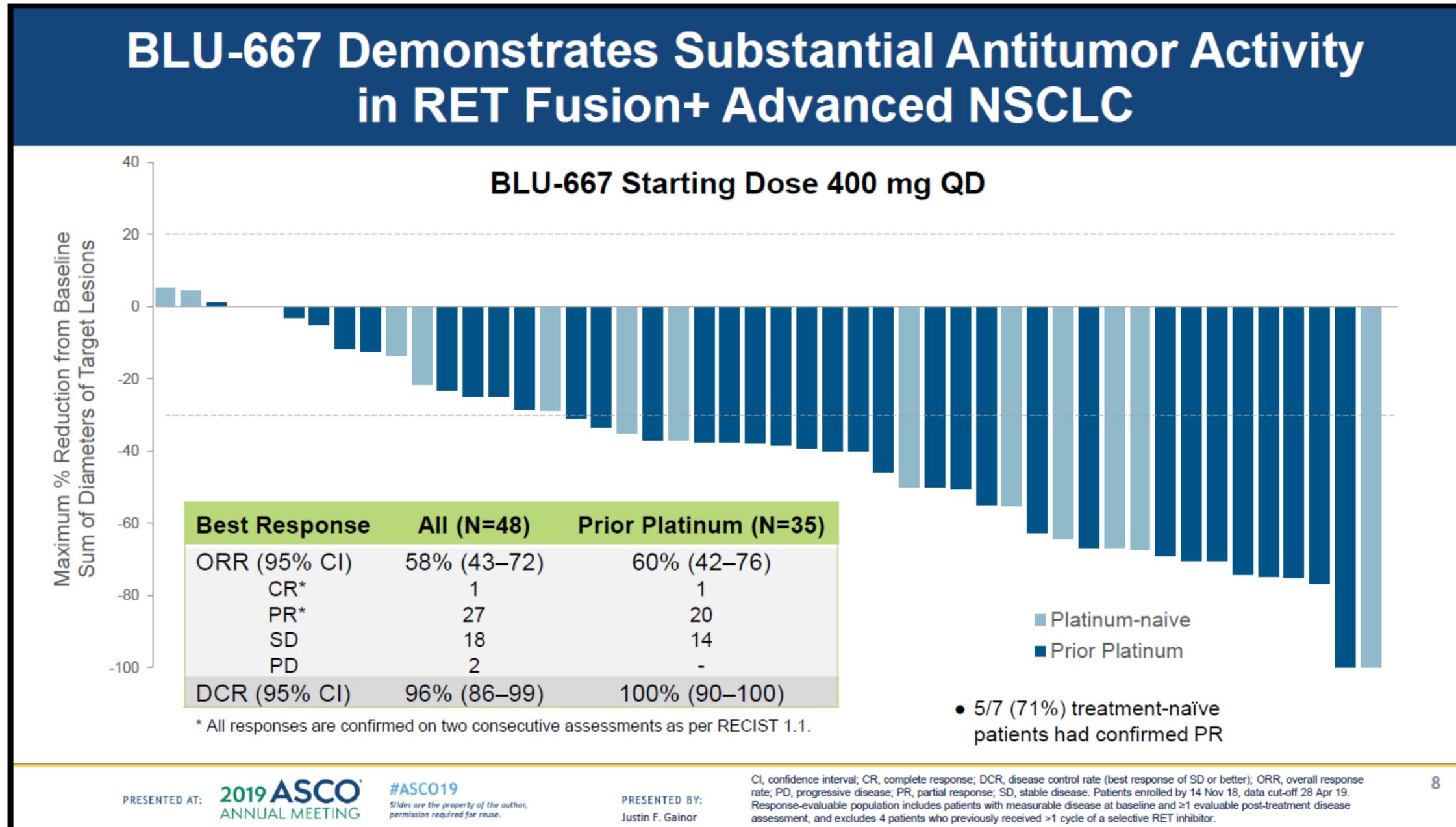
- Vehicle QD
- cabozantinib 60 mg/kg QD
- pralsetinib 3 mg/kg BID
- pralsetinib 10 mg/kg BID
- pralsetinib 30 mg/kg BID



**RET+ NSCLC**

- **Chemotherapy:** nonspecific, low response rates, significant toxicity
- **Checkpoint inhibition:** Preliminary evidence for lack of benefit in RET-altered NSCLC<sup>1</sup>
- **Multi-kinase inhibitors:** ↓ activity, ↑ off-target toxicity<sup>2,3</sup>
- Growing understanding of RET-driven resistance
- No selective RET inhibitors are approved

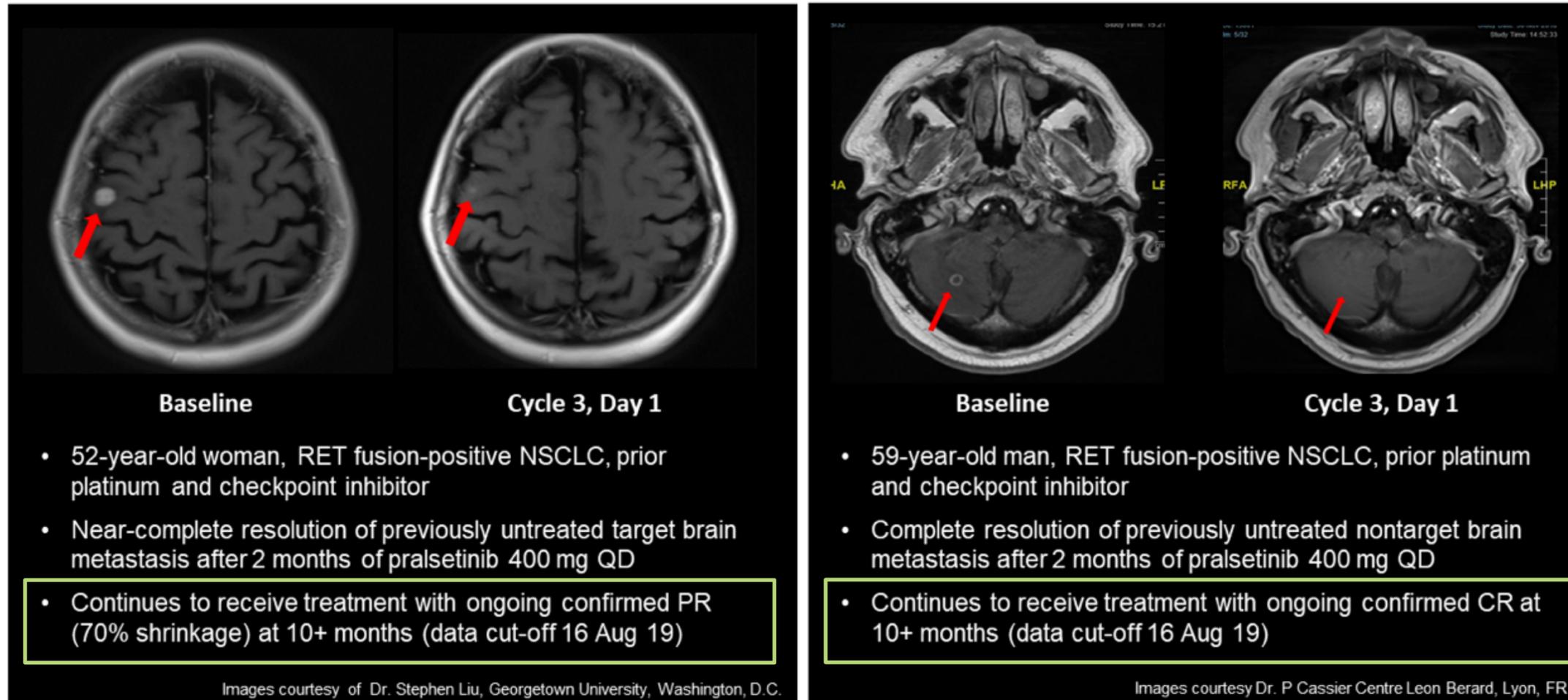
# Promising data supporting pralsetinib in RET+ NSCLC



**Gainor, et al. ASCO, 2019.**

# Evidence of durable CNS activity with pralsetinib

## Pralsetinib was active against intracranial metastases in the clinical setting



Evans, et al. IASLC, 2019.

# Case reports highlight the potential for combination therapy with pralsetinib

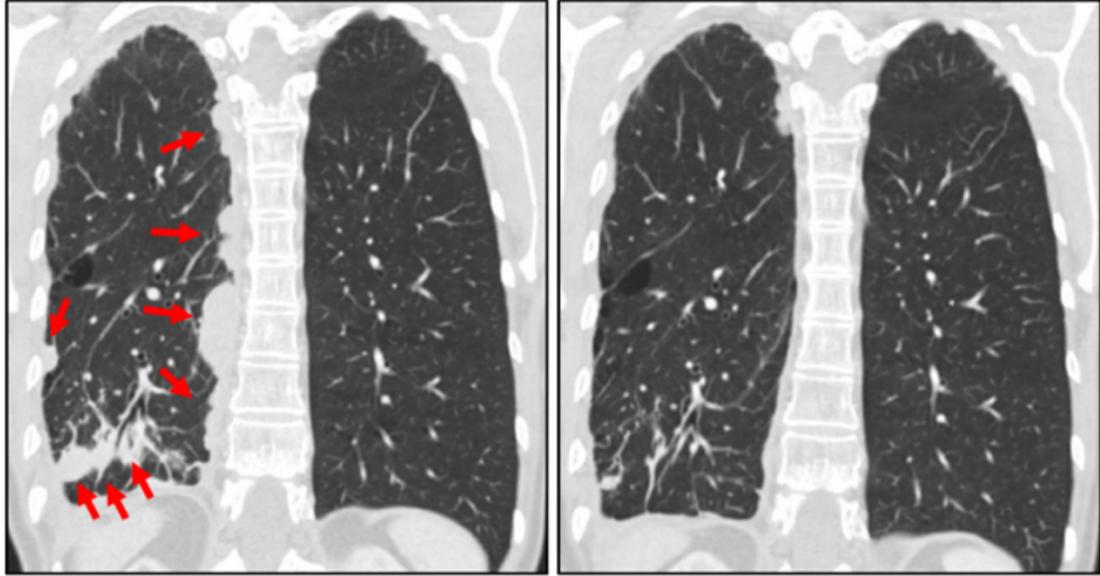
**IASLC**  **IASLC 19th World Conference on Lung Cancer**  
September 23–26, 2018 Toronto, Canada

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER [WCLC2018.IASLC.ORG](http://WCLC2018.IASLC.ORG) #WCLC2018

## Response to Osimertinib (osi) + BLU-667 in the Clinic

- 60yo F with EGFR del19 NSCLC received afatinib x 1 year, then osi for T790M x 18 mos.
- Post-osi biopsy (MGH NGS/Rearrangement Panel)- *CCDC6-RET* fusion, T790M “lost”
- Treated with Osimertinib + BLU-667 on single-patient IND protocol.
  - Osimertinib 80mg QD
  - BLU-667 200mg QD x 2 weeks, then 300 mg QD
- To date, the safety profile of Osi/BLU-667 includes only grade 1 AE’s, including:
  - Fatigue, leukopenia, high BP, dry mouth, AST/ALT elevation
- Treatment with Osi/BLU-667 is ongoing.

**RECIST 1.1 Partial Response (-78%)\***



Baseline 8 weeks

*\*PR Pending confirmation* **WCLC 2018**

MA26.03 - Osimertinib and BLU-667 in RET-positive EGFR-mutant NSCLC. Presented by Zofia Piotrowska, MGH, Boston USA. 09.26.2018.

Piotrowska, et al. IASLC, 2018.

# Pralsetinib is a potential best-in-class selective RET inhibitor and the cornerstone of our lung cancer portfolio



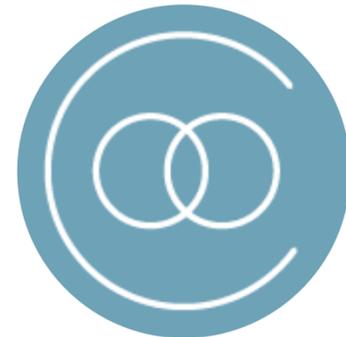
**EQUIPOTENT INHIBITION**  
of RET fusions and mutations,  
including predicted gatekeeper  
resistance mutations



**CLINICAL RESPONSES**  
in 2 of 4 patients previously  
treated with selpercatinib<sup>1</sup>



**HIGH RESPONSE RATES  
AND DURABLE ACTIVITY**  
in NSCLC and MTC patients<sup>1</sup>



**FDA BREAKTHROUGH  
THERAPY DESIGNATIONS**  
for NSCLC and MTC



**STRONG ACTIVITY AGAINST  
BRAIN METASTASES**  
in patients with NSCLC<sup>1</sup>

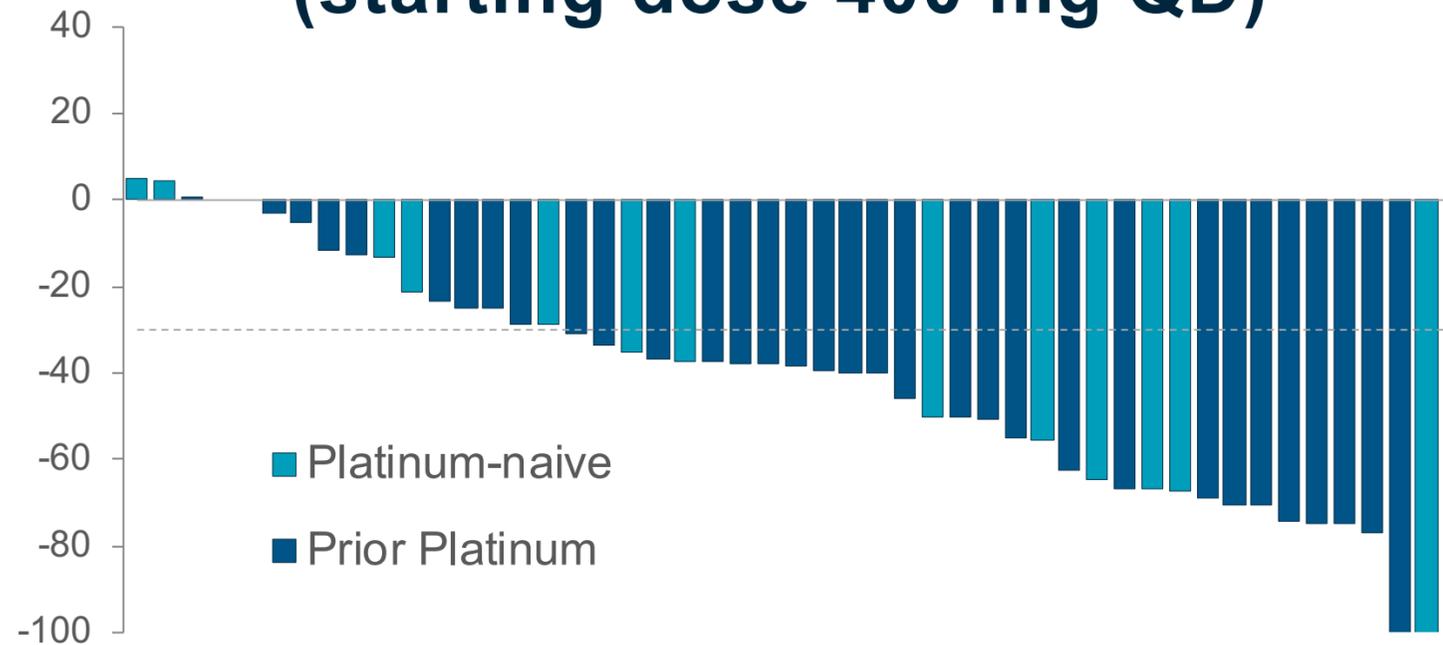


**WELL-TOLERATED WITH  
LOW DISCONTINUATION RATES**  
in advanced cancer populations<sup>1</sup>

# A roadmap to transformative benefit by targeting the primary driver and predicted resistance mutations

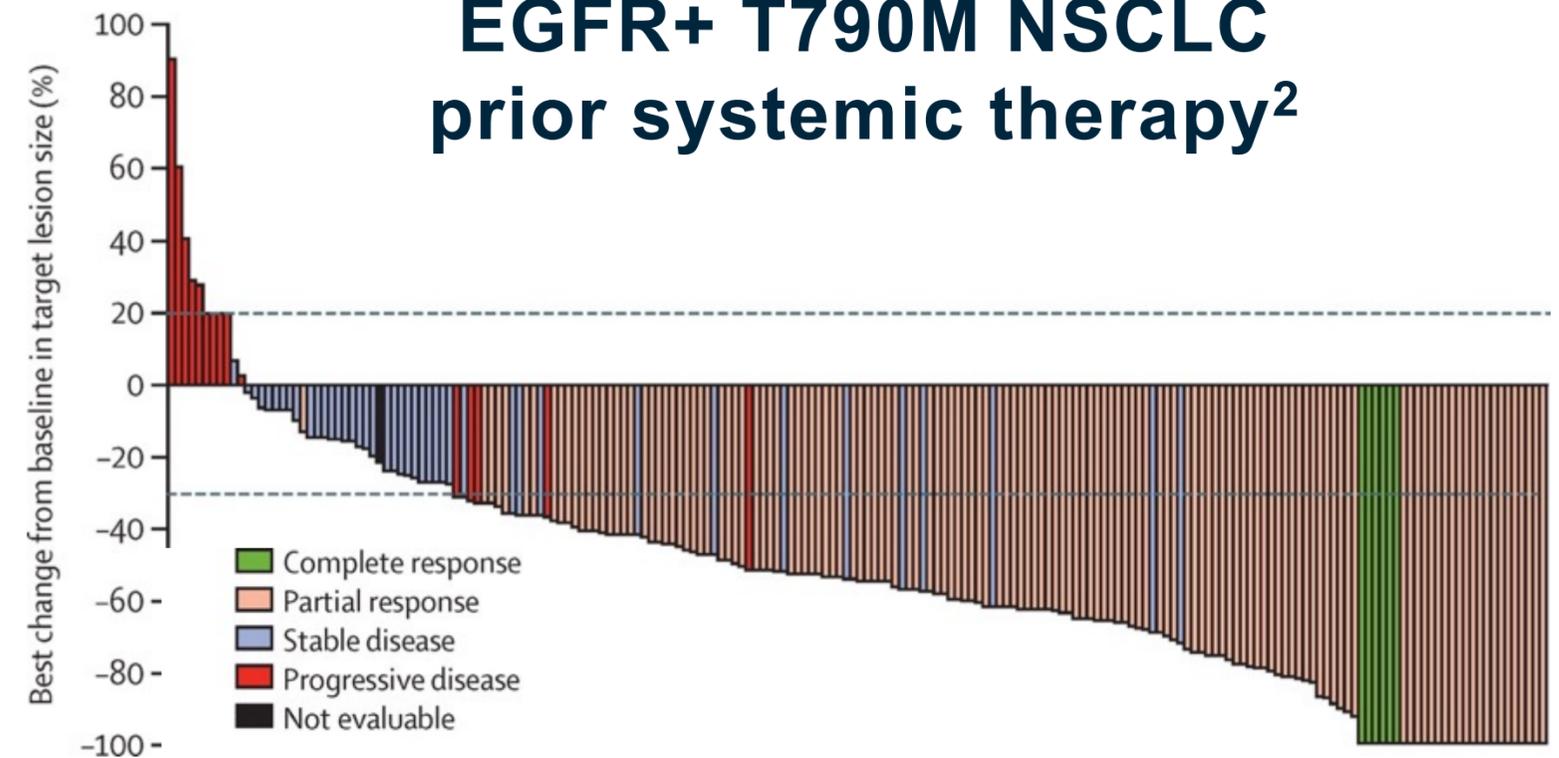
## PRALSETINIB

### RET fusion+ NSCLC (starting dose 400 mg QD)<sup>1</sup>



## OSIMERTINIB

### EGFR+ T790M NSCLC prior systemic therapy<sup>2</sup>

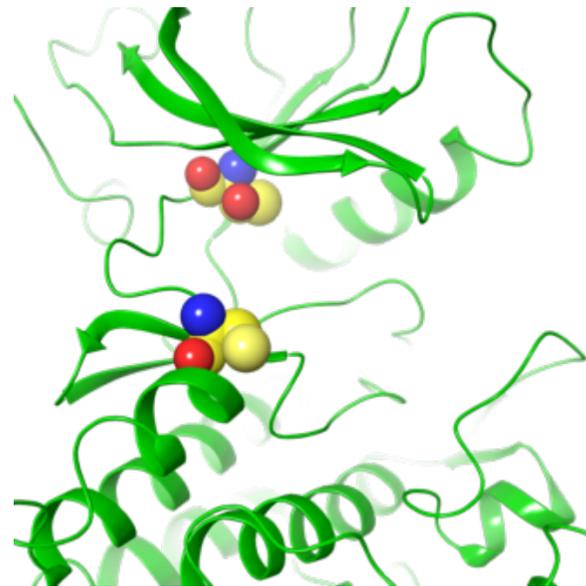


With a cornerstone precision therapy, we can rapidly reinvest insights and realize efficiencies

# **First-in-class EGFR inhibitors** for treatment-resistant non-small cell lung cancer

# Emerging data show potential resistance profiles following first-line and second-line osimertinib treatment in EGFR+ NSCLC

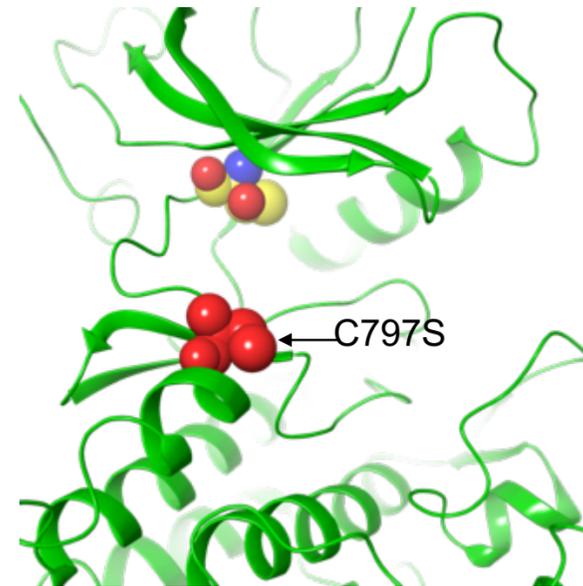
Exon 19/L858R



EGFR+

ONCOGENIC  
DRIVER

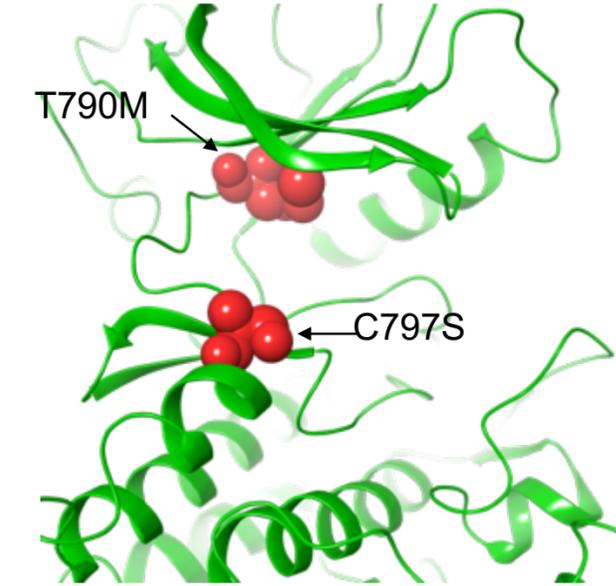
+ C797S



CS

FOLLOWING 1L  
OSIMERTINIB

+ T790M and C797S



TMCS

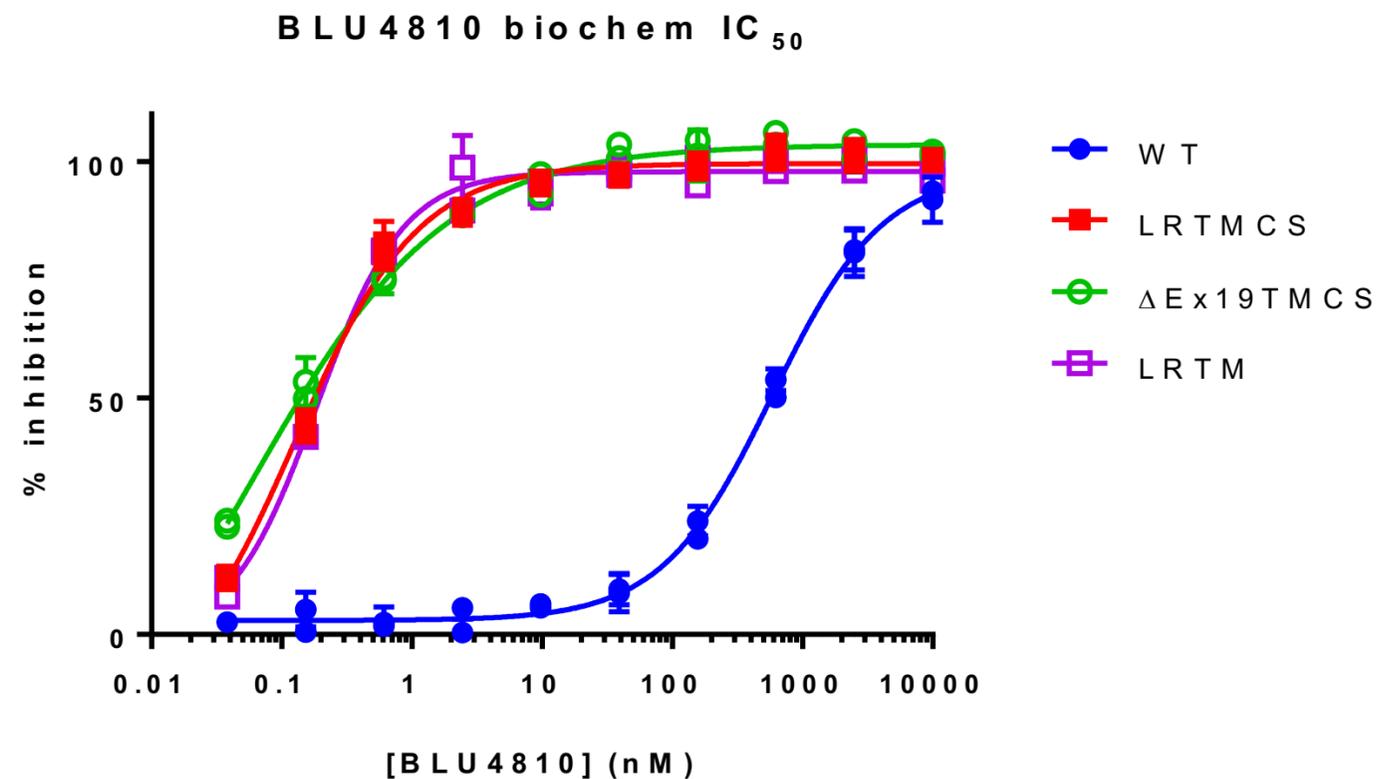
FOLLOWING 2L  
OSIMERTINIB

# Our vision: optimized EGFR+ treatment regardless of prior therapy



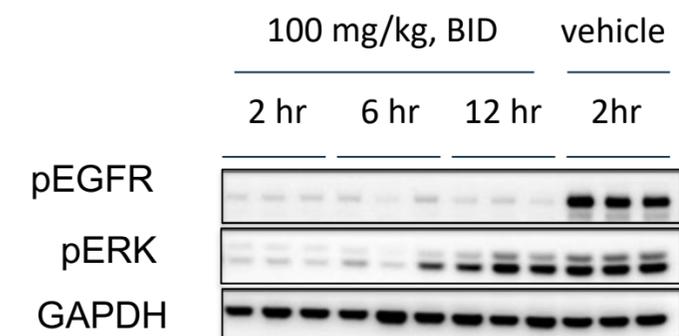
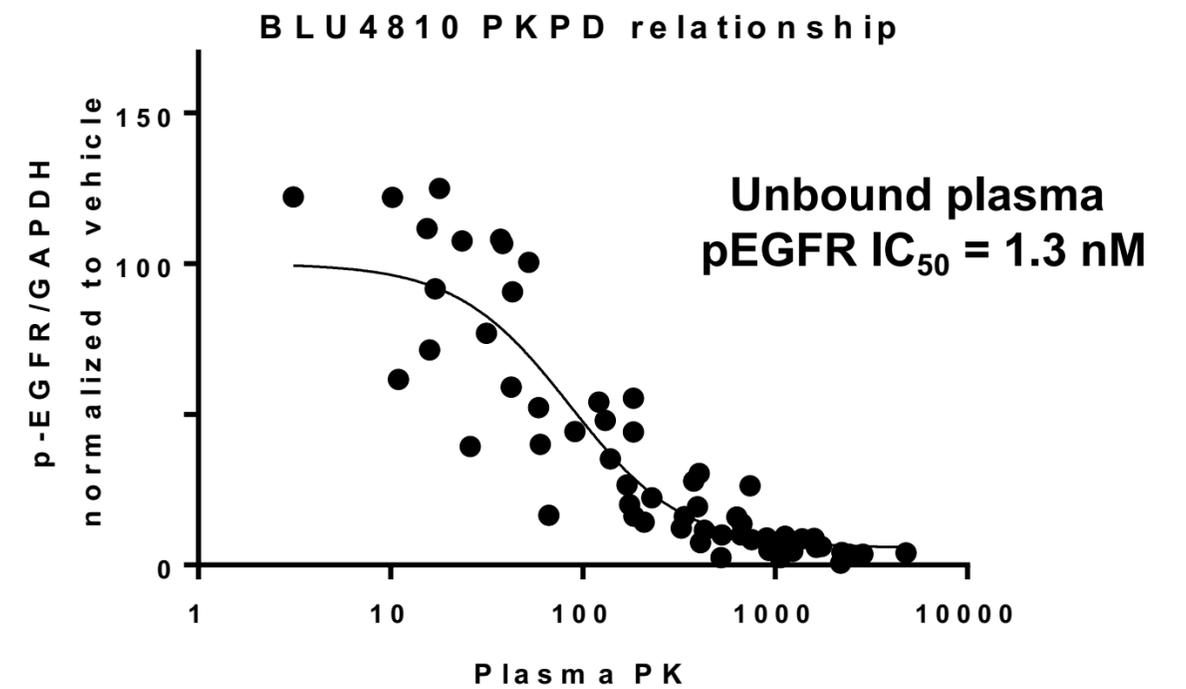
# BLU4810 is a potent and selective EGFR+ TMCS inhibitor

POTENT AGAINST RESISTANT EGFR MUTANTS AND SELECTIVE OVER WILD-TYPE (WT) EGFR



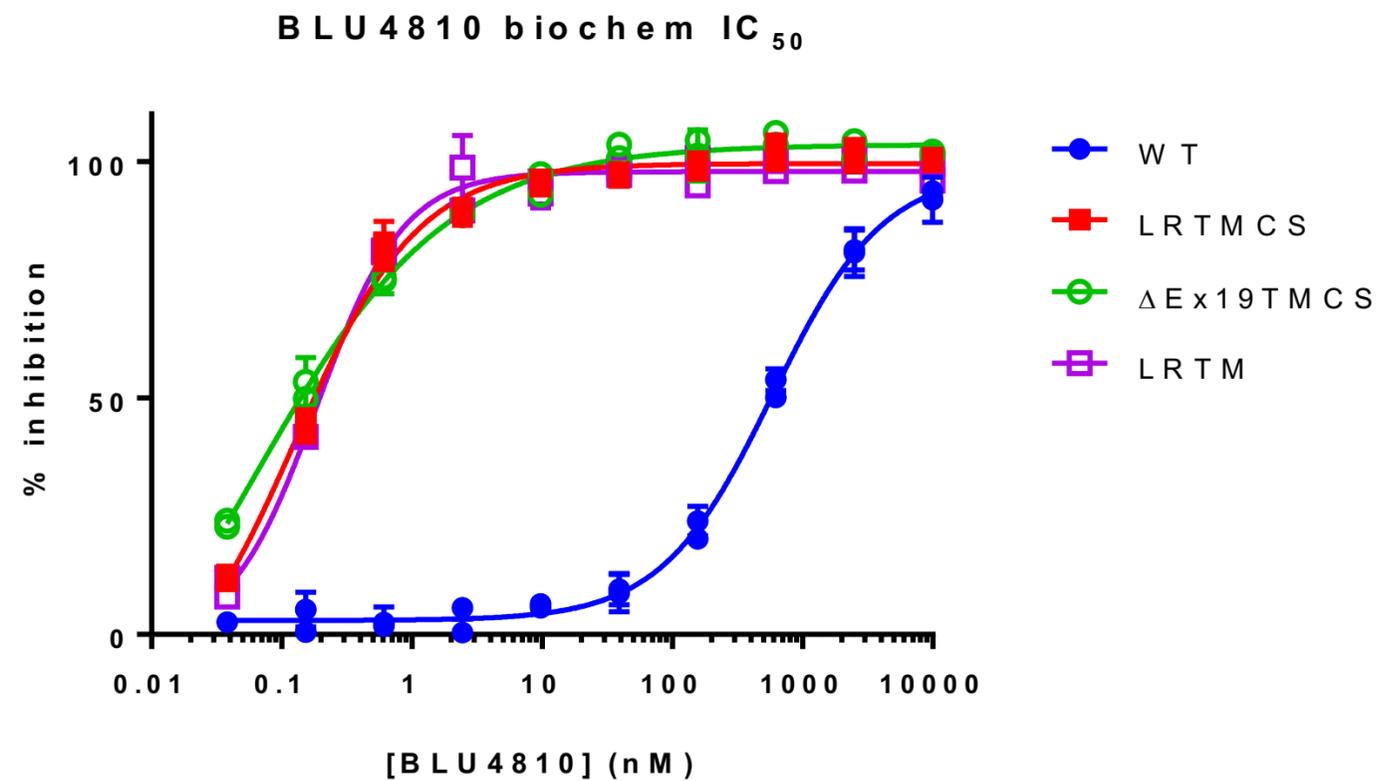
- Potent against double and triple EGFR resistant mutants
- Highly selective over wild-type EGFR
- Robust in vivo growth inhibition comparable to osimertinib

>IC<sub>90</sub> COVERAGE FOR 12 HOURS



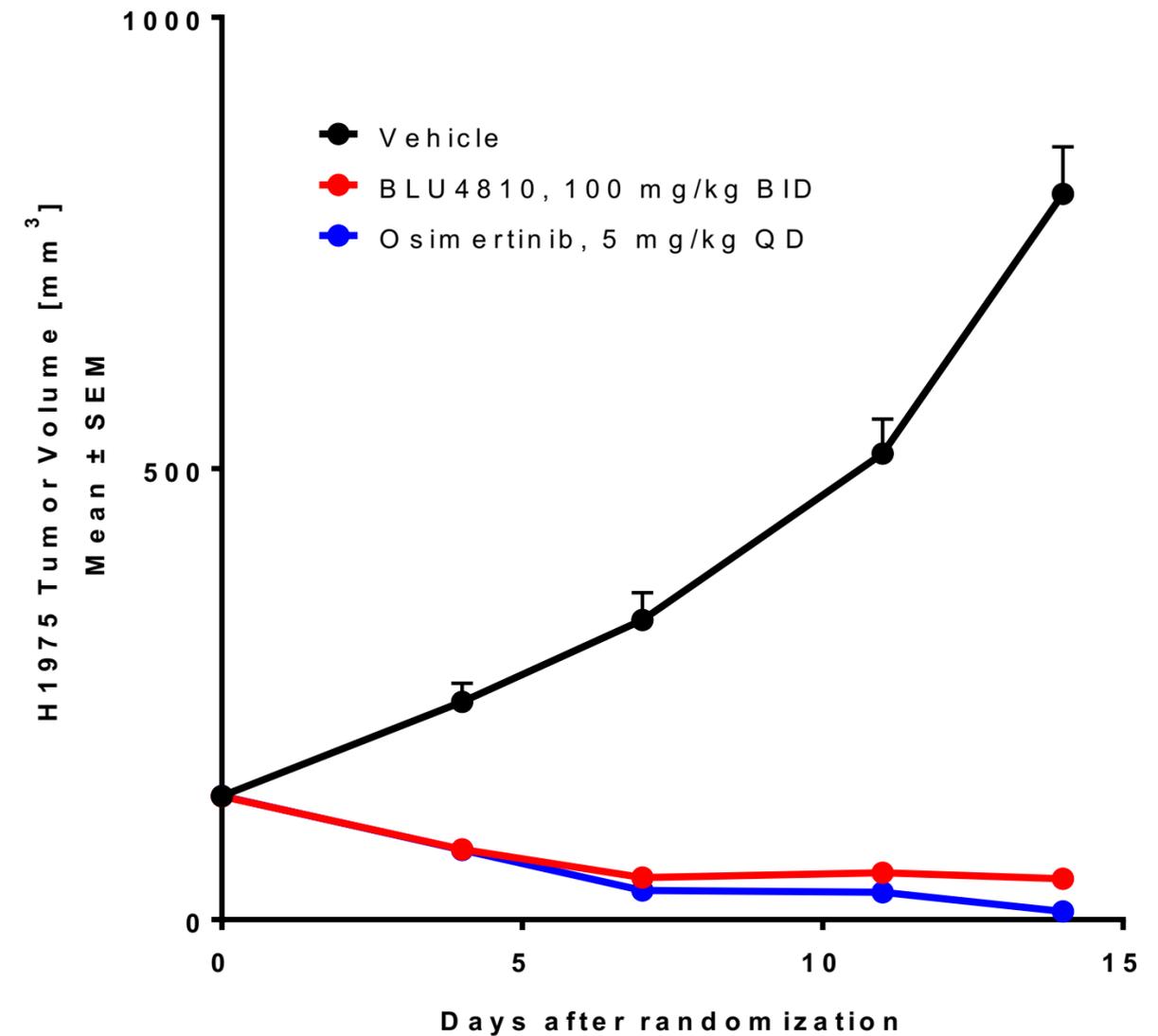
# BLU4810 is a potent and selective EGFR+ TMCS inhibitor

## POTENT AGAINST RESISTANT EGFR MUTANTS AND SELECTIVE OVER WILD-TYPE (WT) EGFR



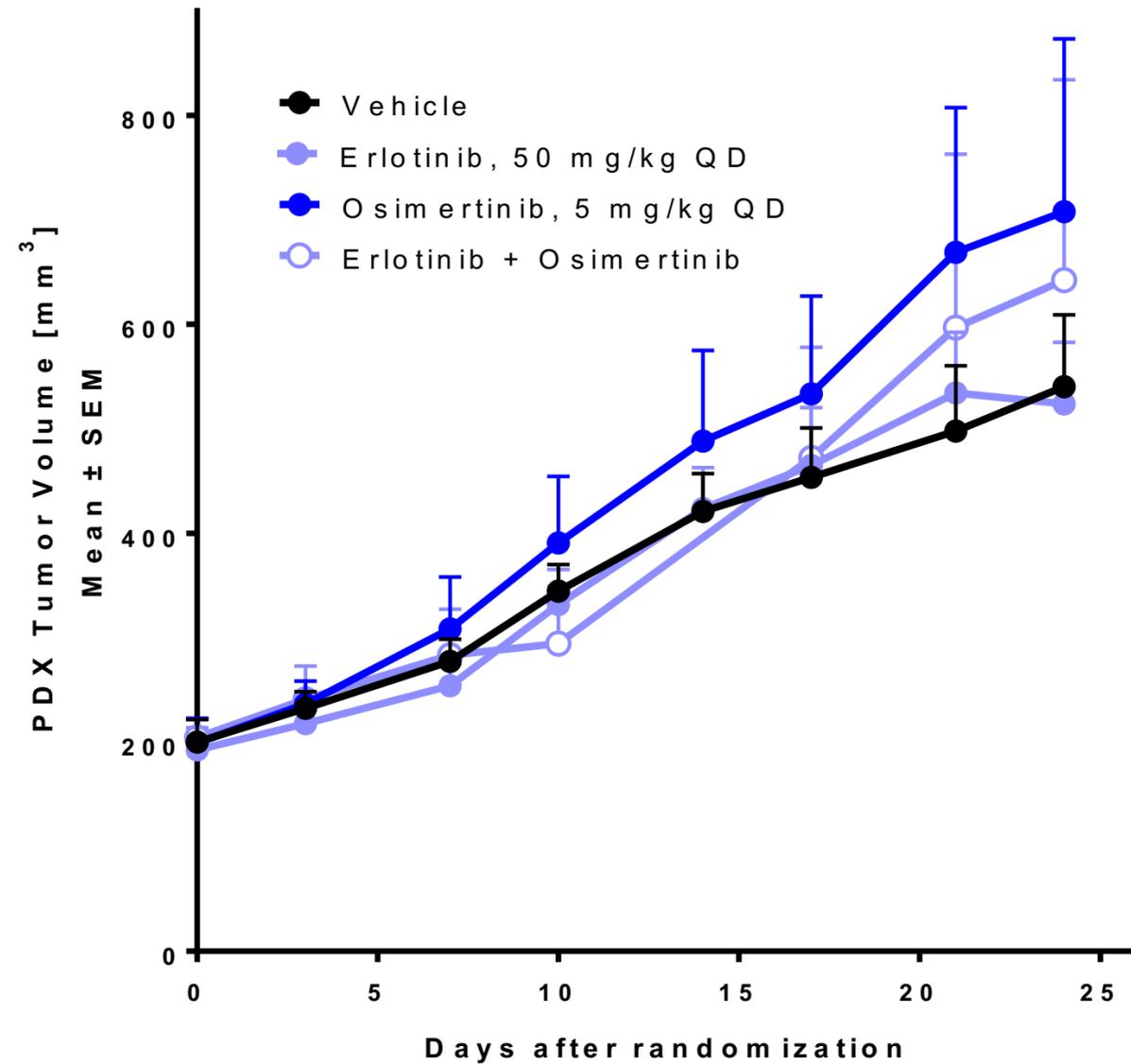
- Potent against double and triple EGFR resistant mutants
- Highly selective over wild-type EGFR
- Robust in vivo growth inhibition comparable to osimertinib

## TUMOR GROWTH INHIBITION IN EGFR+TM CDX MODEL

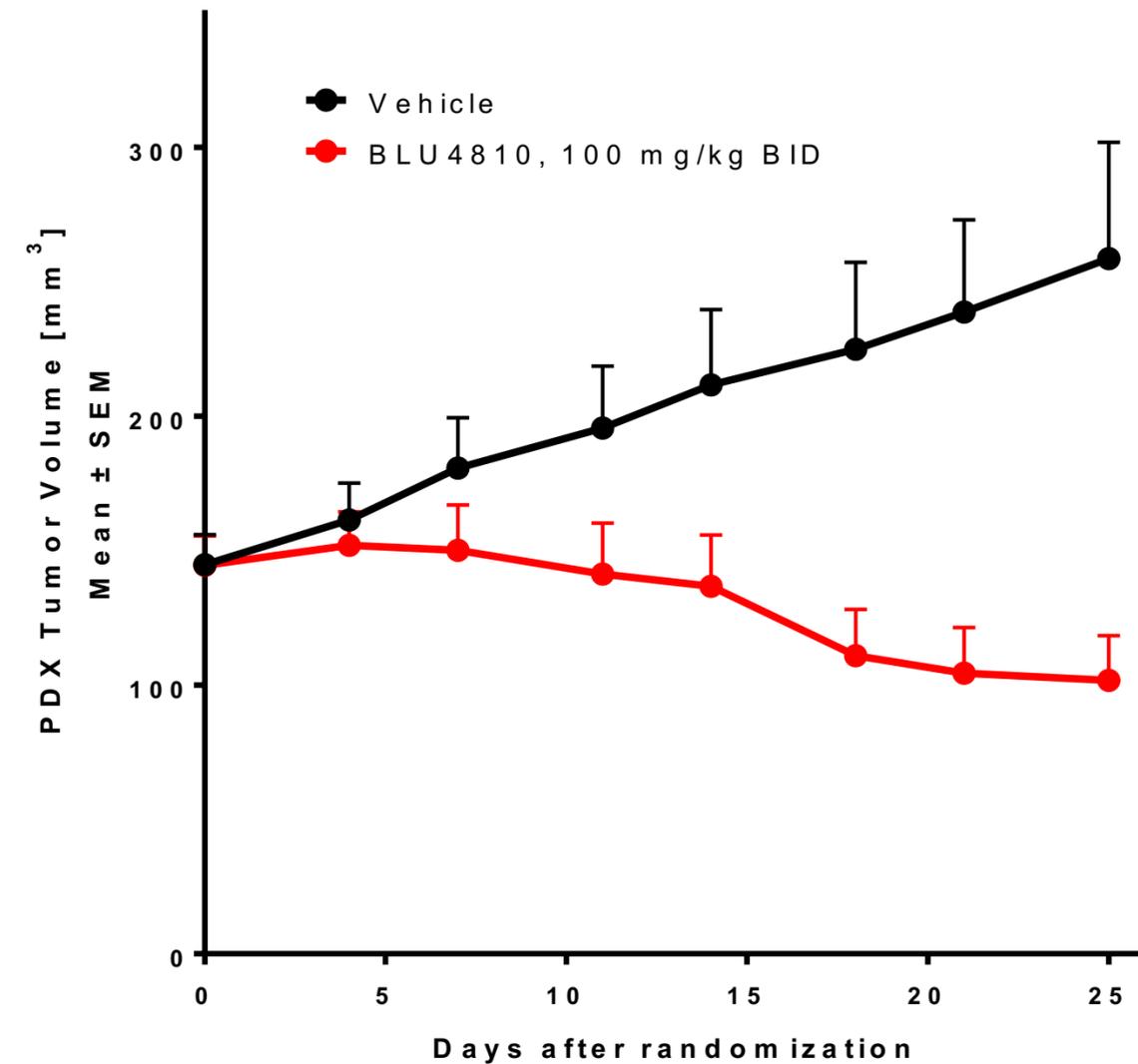


# Anti-tumor activity in a EGFR+ TMCS patient-derived tumor model

## PDX MODEL RESISTANT TO ERLOTINIB AND OSIMERTINIB

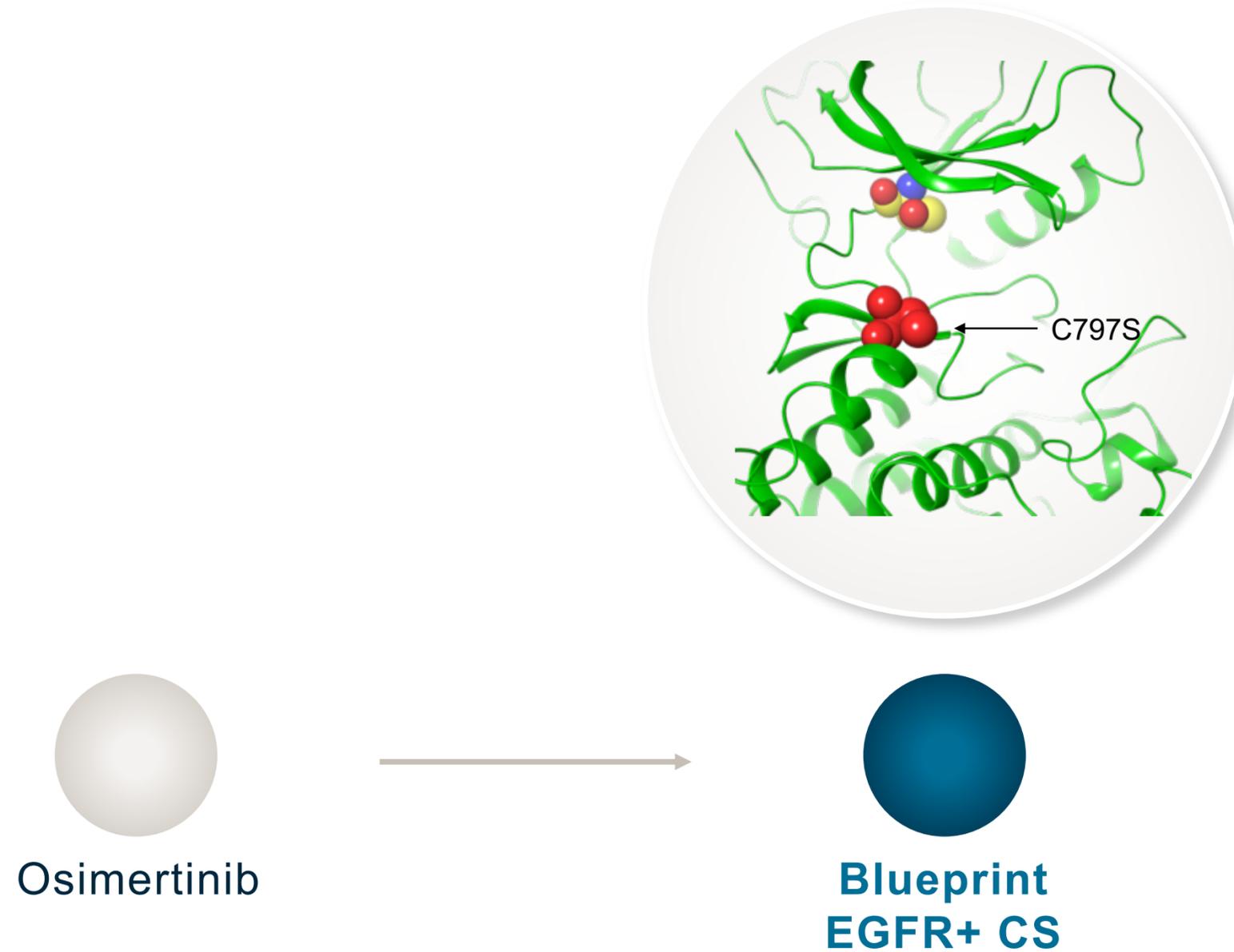


## TUMOR REGRESSION WITH 100 MG/KG BID DOSING OF BLU4810



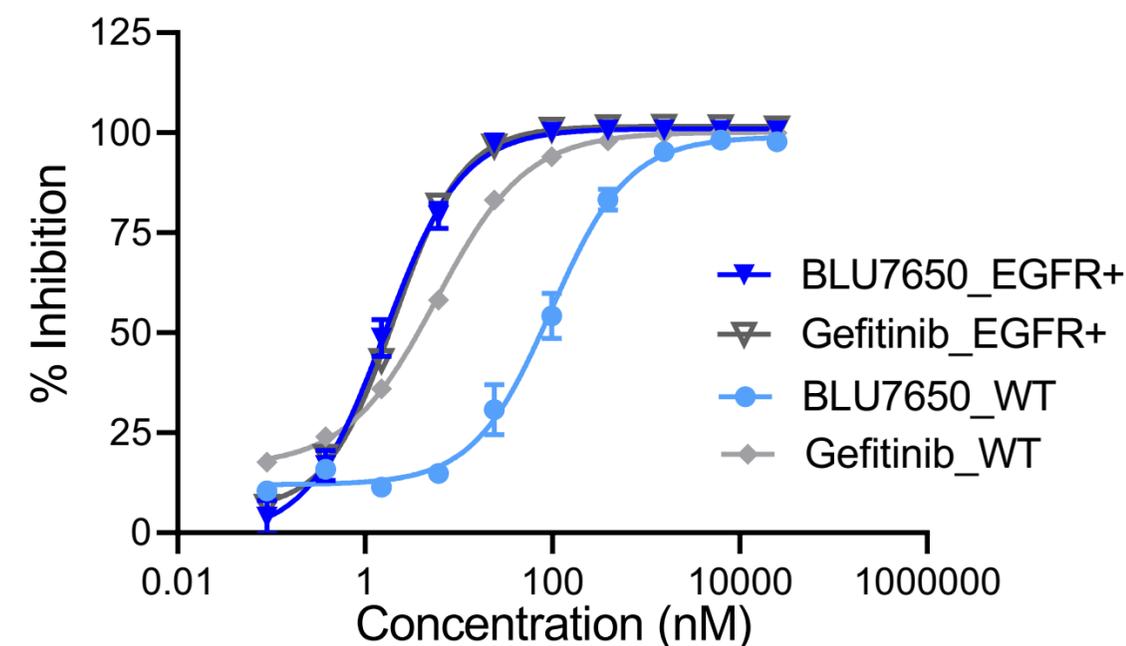
EGFR+ TMCS model from a patient who went through seven lines of therapy, including chemotherapy, erlotinib and osimertinib

# Our vision: optimized EGFR+ treatment regardless of prior therapy



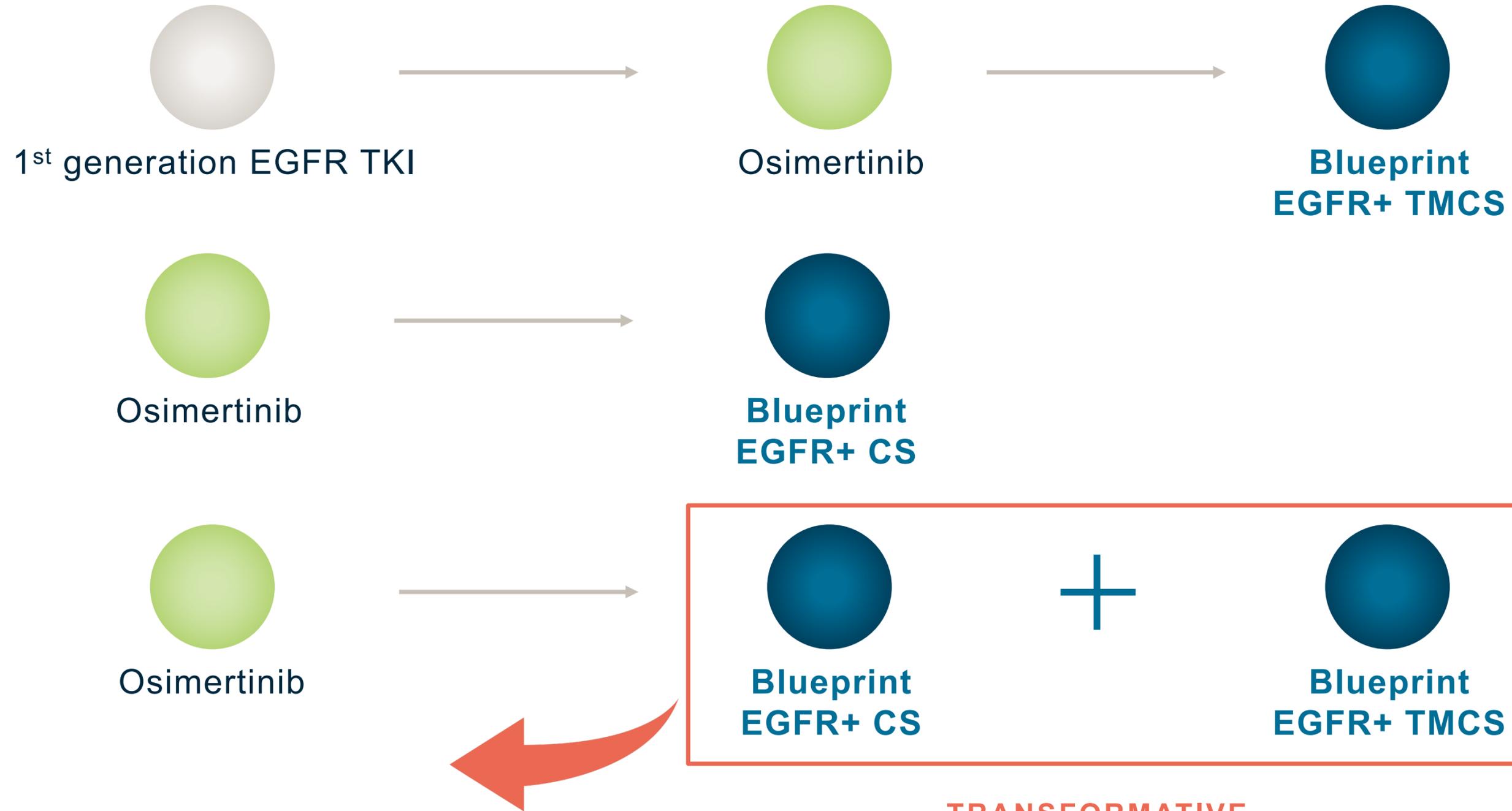
# EGFR+ CS series are potent, selective and brain penetrant

	Biochemical assay		Cellular assay		
	EGFR+ (IC50, nM)	Selectivity over WT	EGFR+ (IC50, nM)	WT (IC50, nM)	Selectivity over WT
Gefitinib	0.8	6x	1	10	10x
Erlotinib	0.6	9x	4	85	23x
Osimertinib	4	13x	3	139	52x
BLU7650 (Series 1)	0.7	50x	1	87	73x
BLU5649 (Series 2)	2	20x	6	426	71x



- Lead series show favorable properties required for a best-in-class target product profile
- Preliminary examples show good brain penetration

# Our vision: optimized EGFR+ treatment regardless of prior therapy



TRANSFORMATIVE  
PREVENTIVE  
COMBINATION

# We aim to bring our approach to delivering durable benefit to additional patient populations

---

## Durability



### **HIGHLY SELECTIVE INHIBITORS**

Potent inhibition of genetic drivers leads to rapid and deep responses

## Patient selection



### **BIOMARKER DRIVEN**

Understanding of disease heterogeneity enables responder hypotheses

## Tumor evolution



### **ADAPTIVE ABILITY**

Research engine rapidly empowers solutions for acquired resistance

# Cancer immunotherapy: a new frontier for kinase medicines

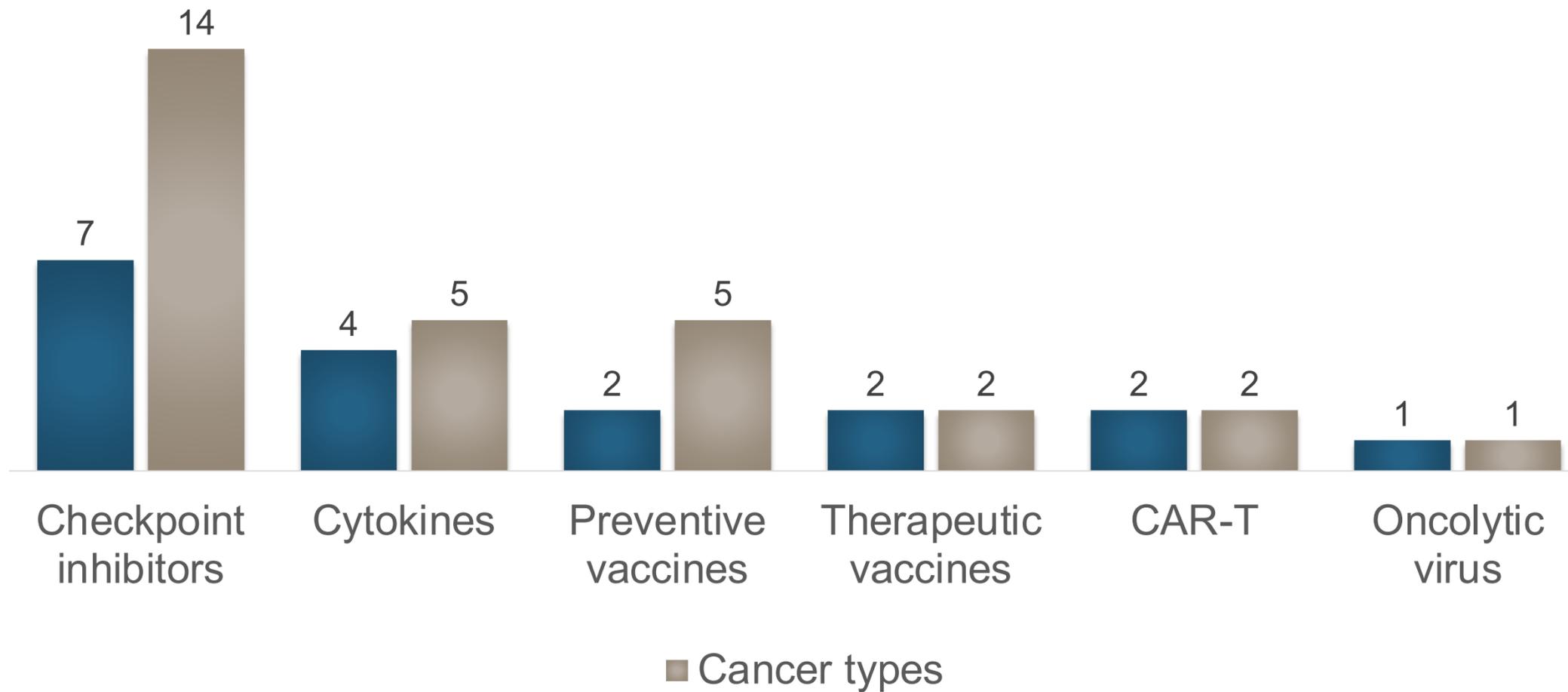
**KLAUS HOEFLICH, PhD**

Vice President, Biology



# The impact of cancer immunotherapy spans several different treatment modalities and a breadth of indications

APPROVED CANCER IMMUNOTHERAPIES BY MECHANISM AND CANCER TYPE

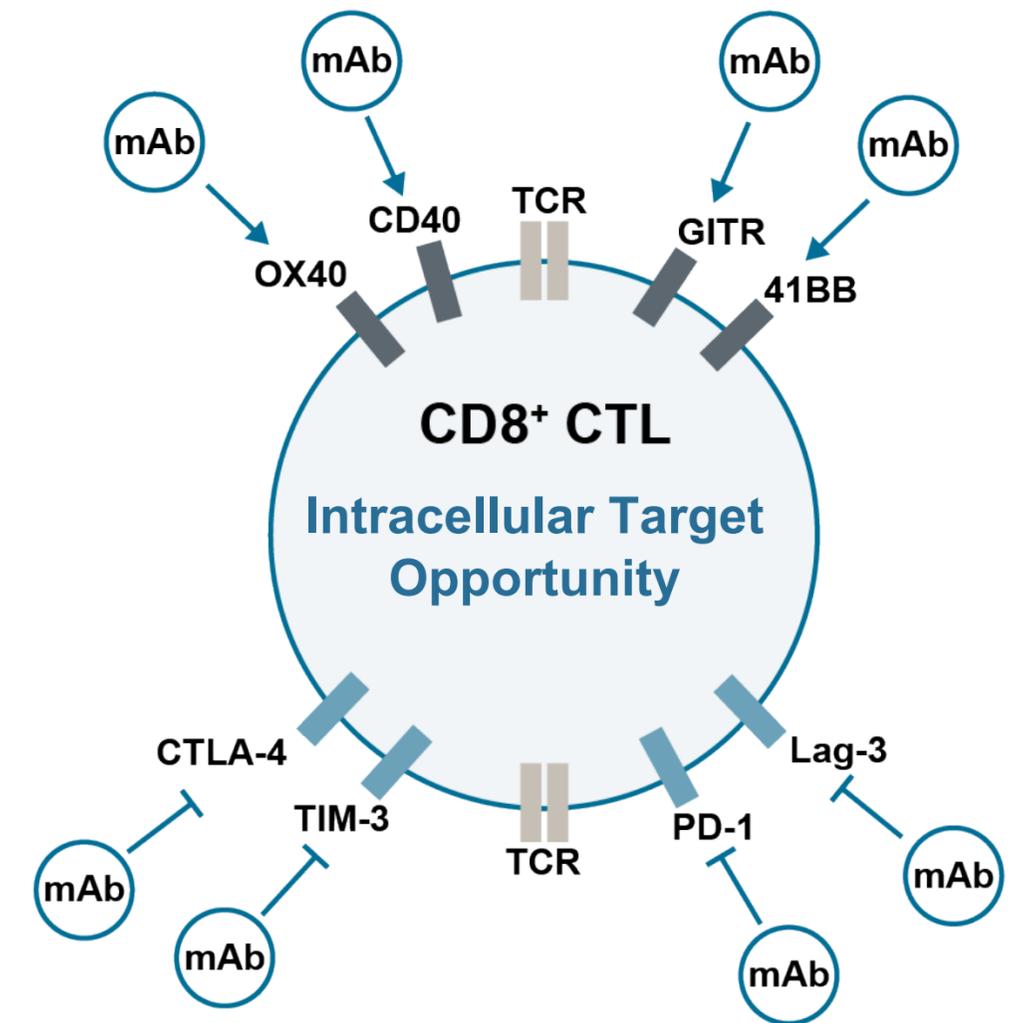


Modality	1 <sup>st</sup> approval / Latest Approval
Checkpoint inhibitors	2011 (Melanoma) / 2019 (Breast)
Cytokines	1992 (Kidney) / 2011 (Melanoma)
Preventive vaccines	2009 (Cervical cancer) / 2014 (various)
Therapeutic vaccines	2010 (Prostate)
CAR-T	2017 (ALL) / 2018 (Lymphoma)
Oncolytic Virus	2015 (Melanoma)

TO DATE, NO SMALL MOLECULE CANCER IMMUNOTHERAPIES ARE APPROVED

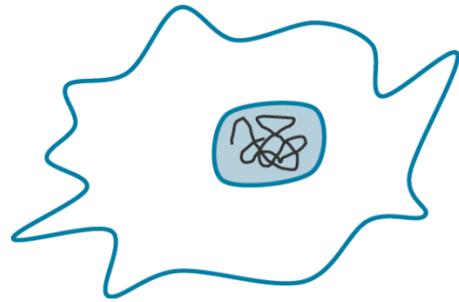
# Kinase inhibition: A new approach to affecting anti-tumor immune response

- **Most immunotherapies today are biologics targeting surface targets**
- **Targeting intracellular targets with selective small molecule inhibitors:**
  - Promotes exploration of novel modes of action
  - Enhances opportunities for combinations with tumor-targeted agents and biologic immunotherapies
- **Targeting kinases to enhance immune response against cancer is an emerging field**



# Cancer immunotherapy complements our precision medicine strategy

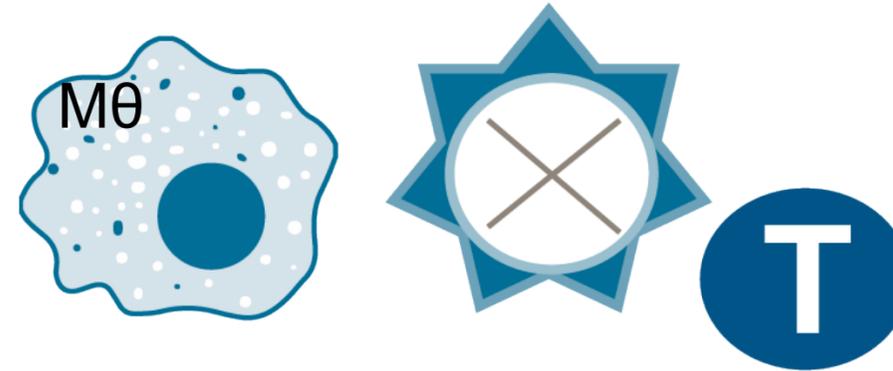
## Kill tumor cells



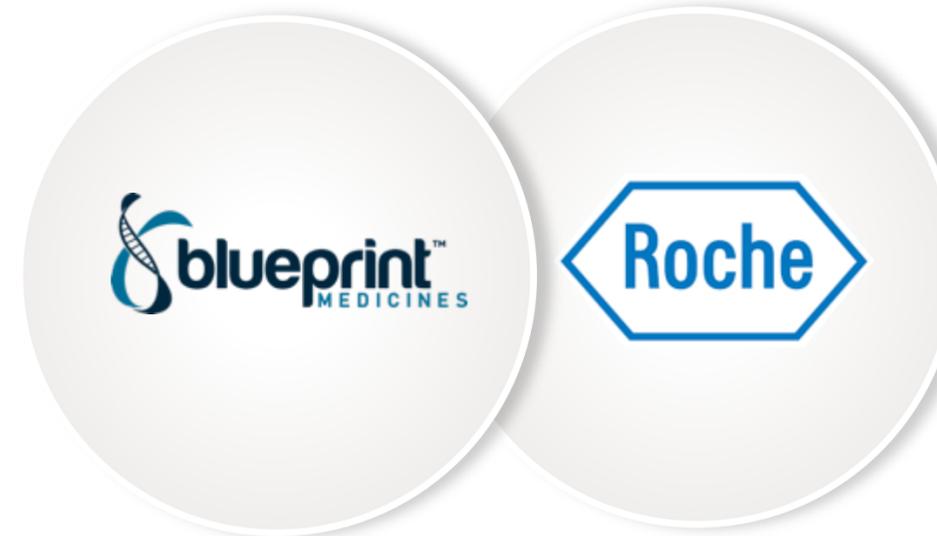
Turn off drivers  
Sensitize to immune attack



## Activate the immune system



Tumor detection  
Tumor killing



# A strategic collaboration to transform the field of cancer immunotherapy

Robust kinase research platform and development capabilities



Cancer immunotherapy expertise, assets and infrastructure

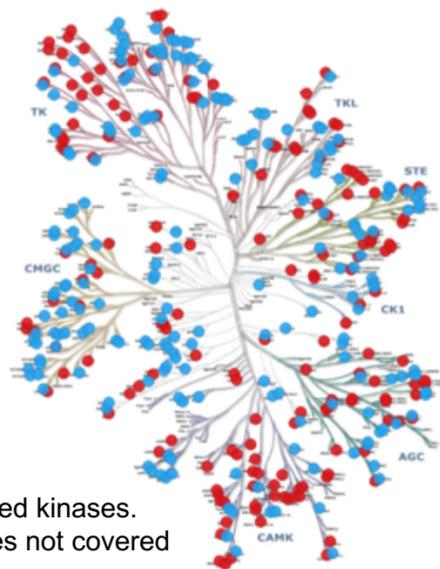
## 2016: EXPLORE COMPELLING TARGETS

- **Goal:** Explore a range of immunokinase targets to advance cancer immunotherapy
  - Immediately actionable
  - Novel via cell-based phenotypic screens
- Interrogate and validate with genetic and tool compound approaches

## 2019: PROGRESS TOWARDS THE CLINIC

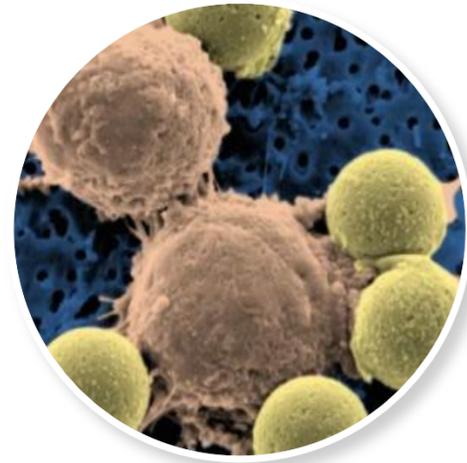
- **Achieved:** 4 targets selected focusing on distinct and complementary immune mechanisms
  - Activate effector cells
  - Prime immune response
  - Tumor cell killing
  - Prevent evasion from immune detection

# Novel screens identify actionable kinase targets for cancer immunotherapy

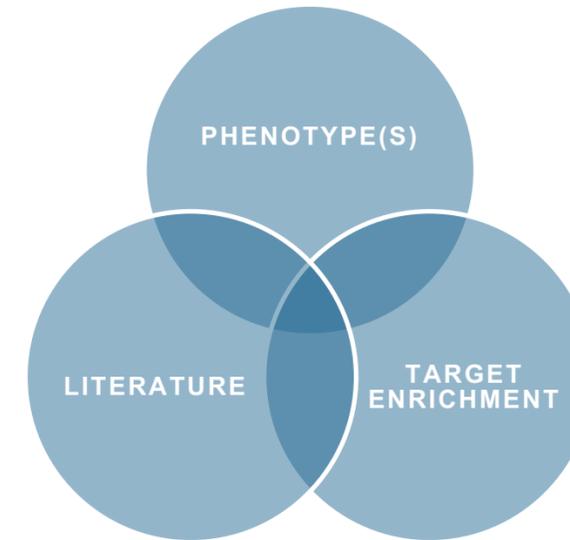


Blue: Covered kinases.  
Red: Kinases not covered

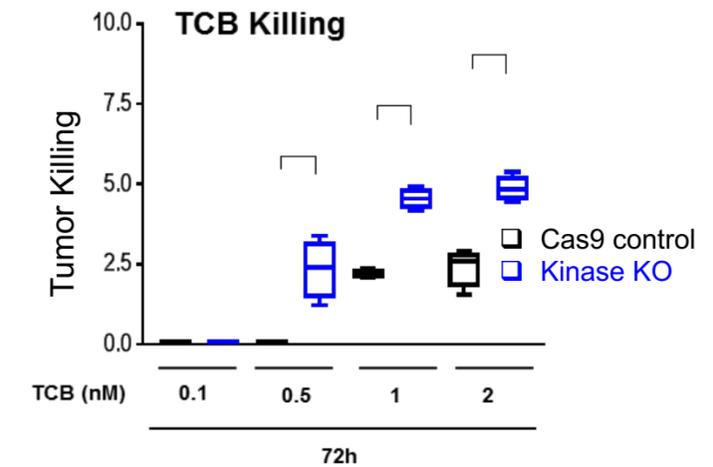
Blueprint tool  
compound set



IO functional screens  
Tumor-T cell co-culture screens  
T cell exhaustion screen  
Antigen presentation  
enhancement screen



Target  
deconvolution



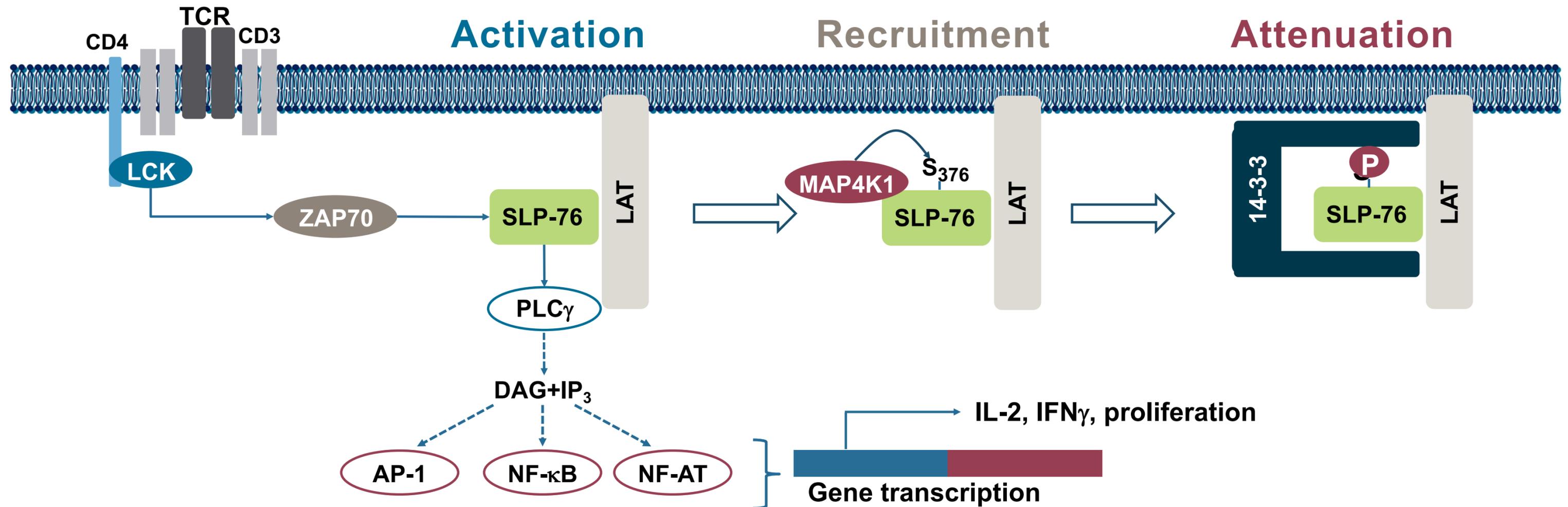
Target  
validation

TWO KINASE DISCOVERY PROGRAMS HAVE ORIGINATED  
FROM CELL-BASED PHENOTYPIC SCREENS WITHIN THE ROCHE COLLABORATION

Our scientific platform enables us to explore new kinase biology, representing even larger opportunities to impact patient care

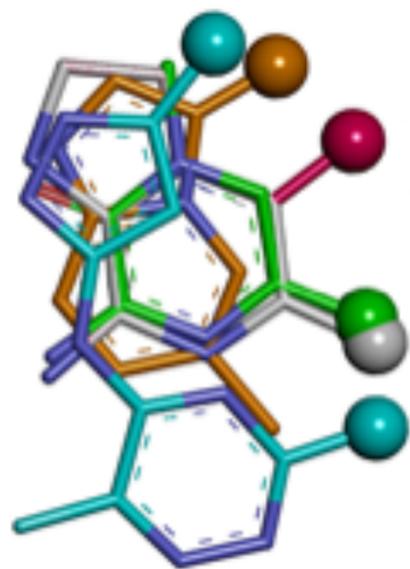
# First-in-class MAP4K1 immunokinase inhibitor

# MAP4K1 is a negative regulator of T cell function

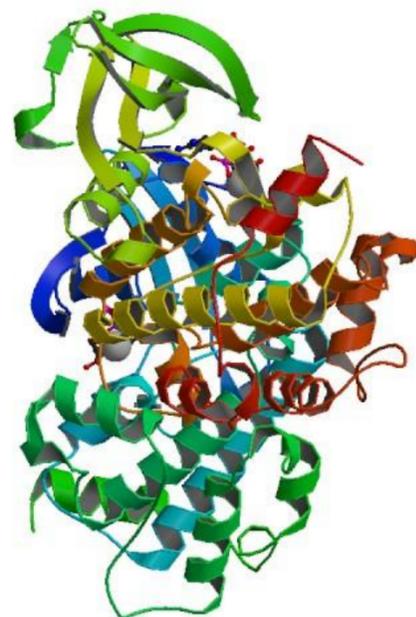


- MAP4K1 is a SER/THR kinase selectively expressed in DCs, T- and B-cells
- Negatively regulates TCR and BCR signaling, DC maturation
- MAP4K1<sup>-/-</sup> or MAP4K1<sup>KD/KD</sup> mice exhibit enhanced tumor immunity

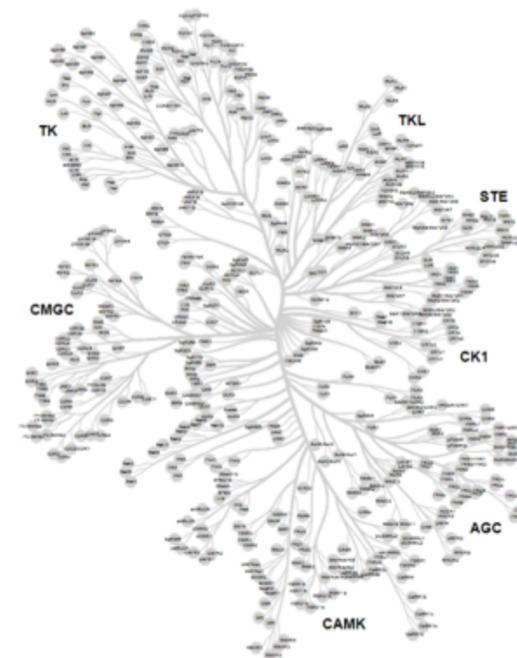
# Our platform has enabled design of potent and selective MAP4K1 inhibitors



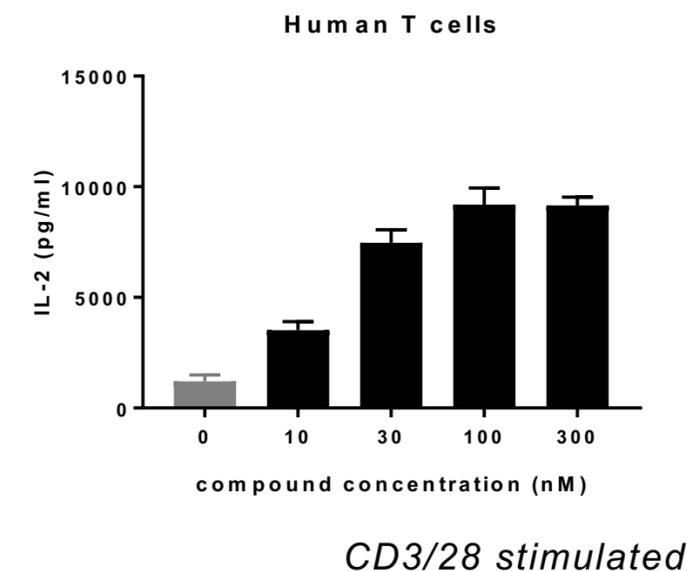
Multiple lead series identified directly from our library



Structural insights and kinase expertise to optimize for potency and selectivity



Deep and systematic biology interrogation uncovered key off-target insights (undisclosed)

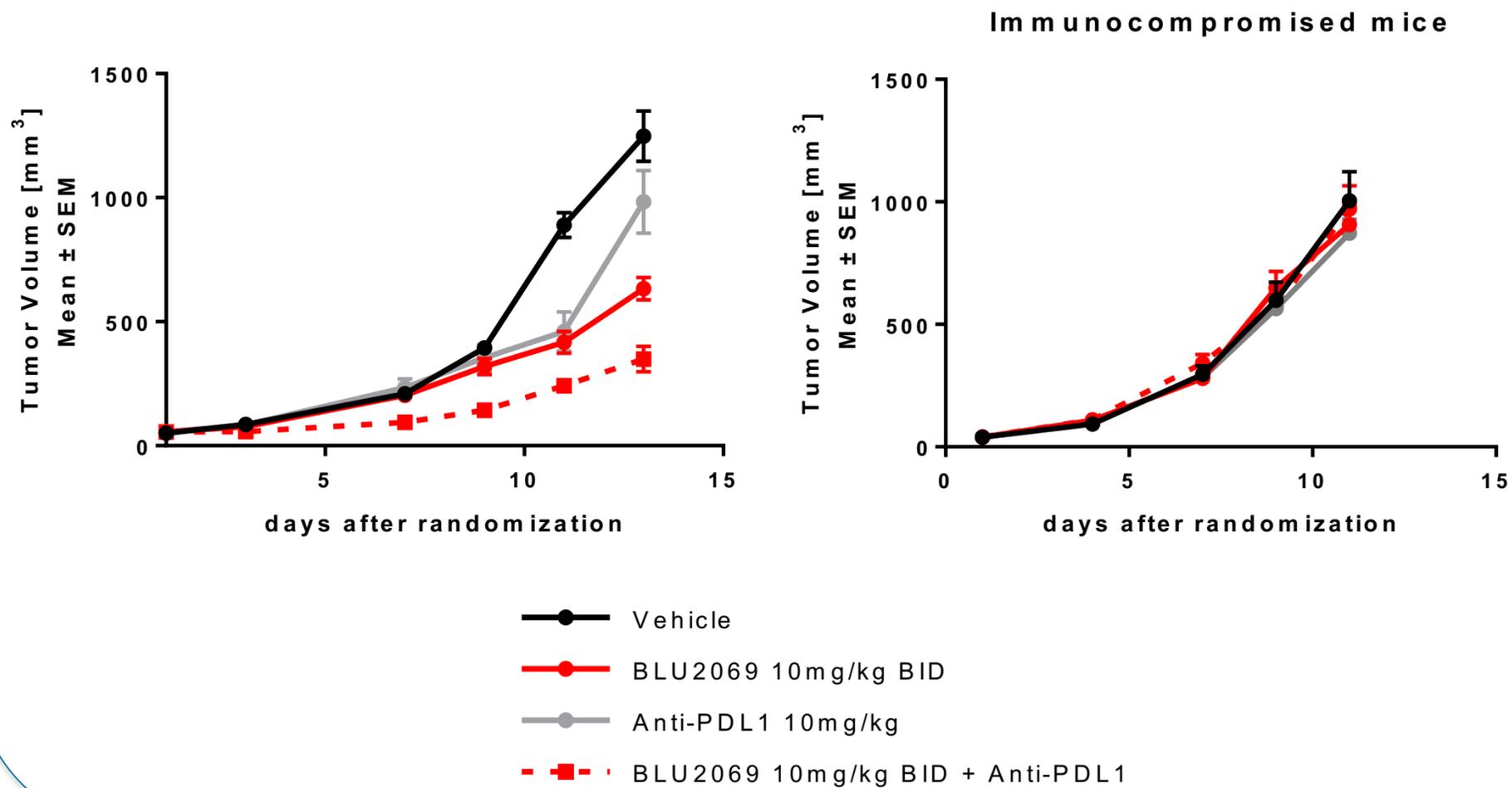


Minimal off-target activity  
Robust T cell activation

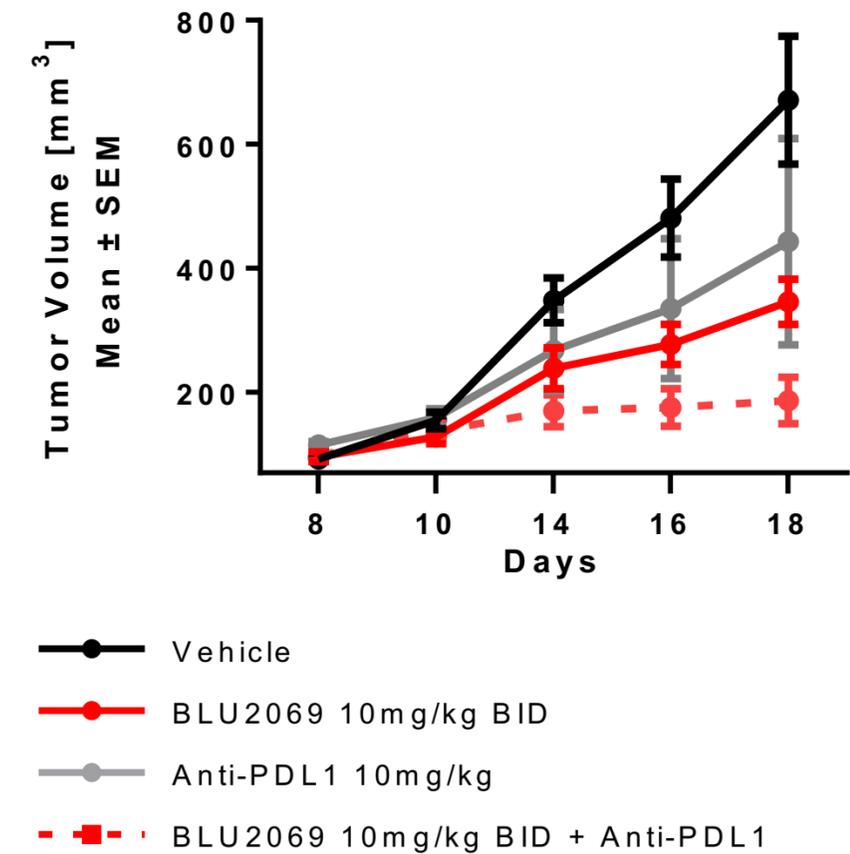
- Sub-nanomolar potency for MAP4K1
- 100-1000x selectivity for MAP4K1 vs. anti-targets
- Favorable pharmacokinetic and physicochemical properties

# MAP4K1 exhibits immune-dependent anti-tumor activity in multiple syngeneic models via an immune-dependent mechanism

## MOUSE SARCOMA



## MOUSE COLON

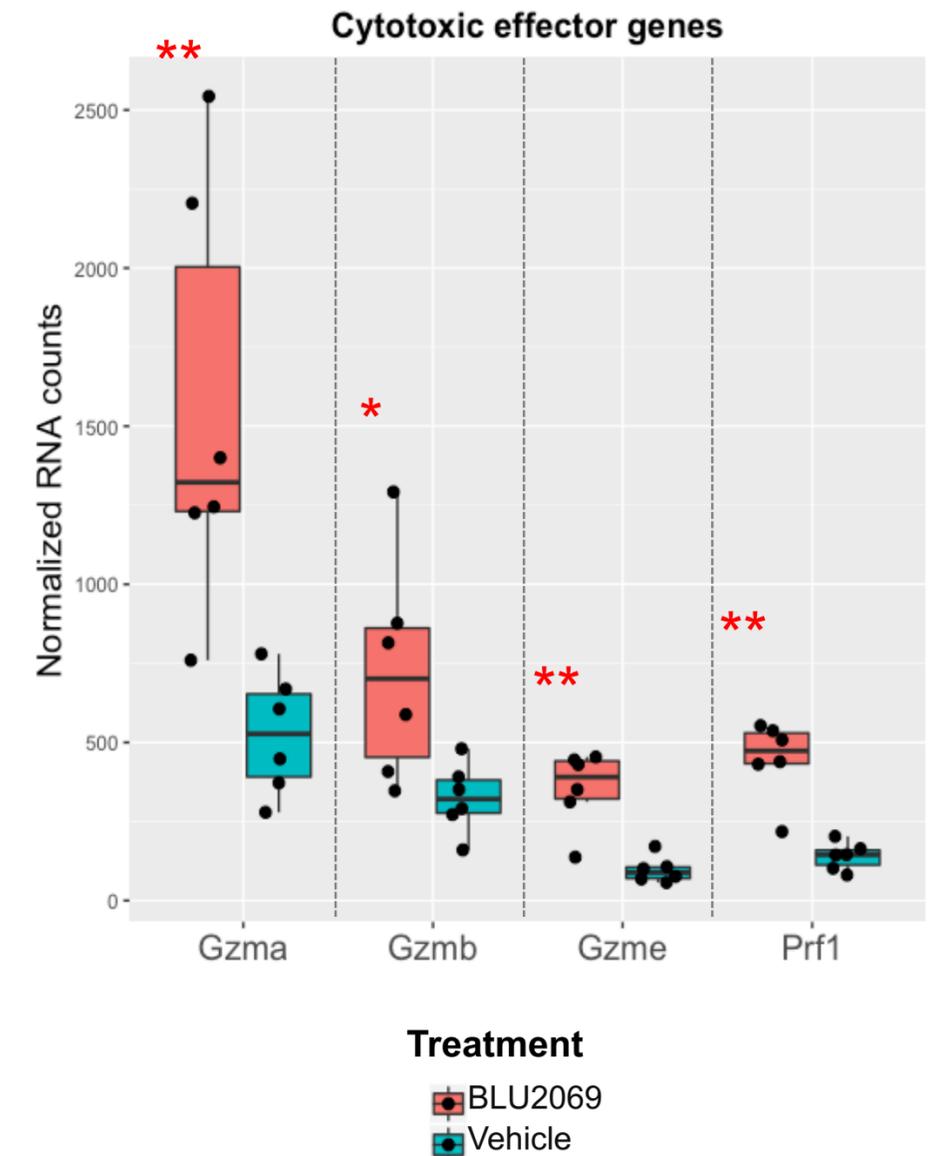
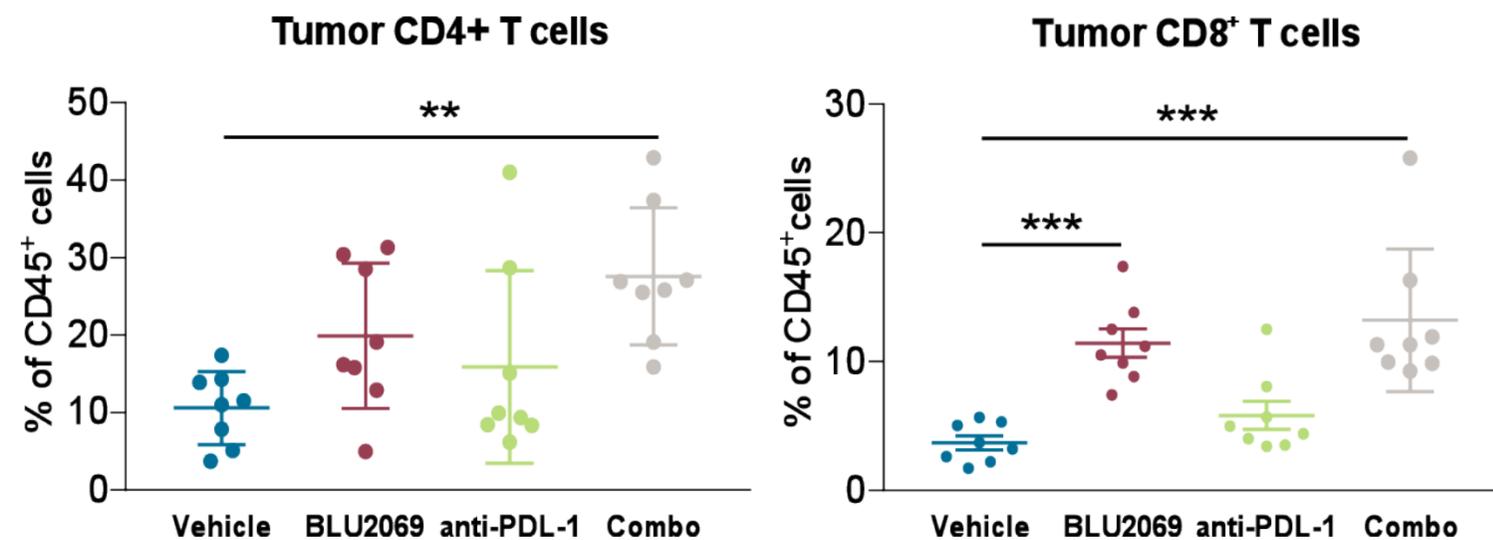


# MAP4K1 inhibition enhances T cells responses and cytokines

## Key findings

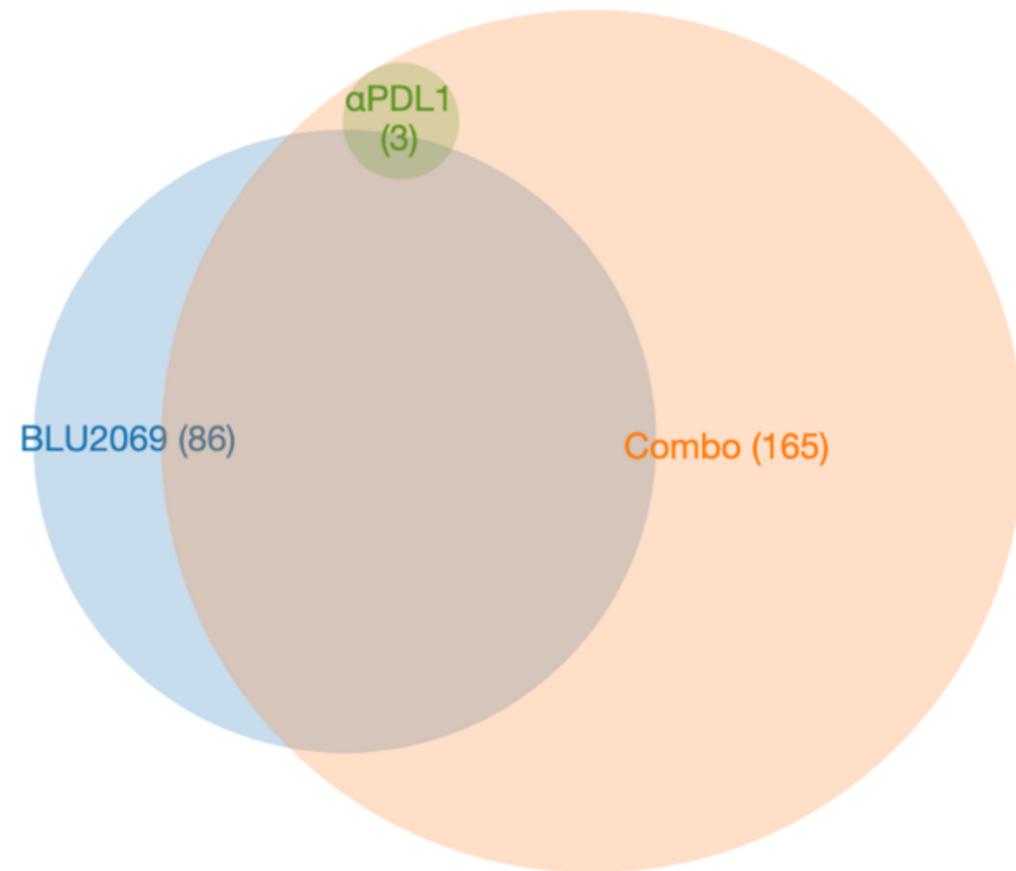
- Increased frequency of CD8<sup>+</sup> TILS with single agent treatment
- Enhanced cytokines in plasma of combo treated mice
- Immune-phenotype is in line with MAP4K1 KI mouse

### Flow cytometry analysis of tumor infiltrating lymphocytes

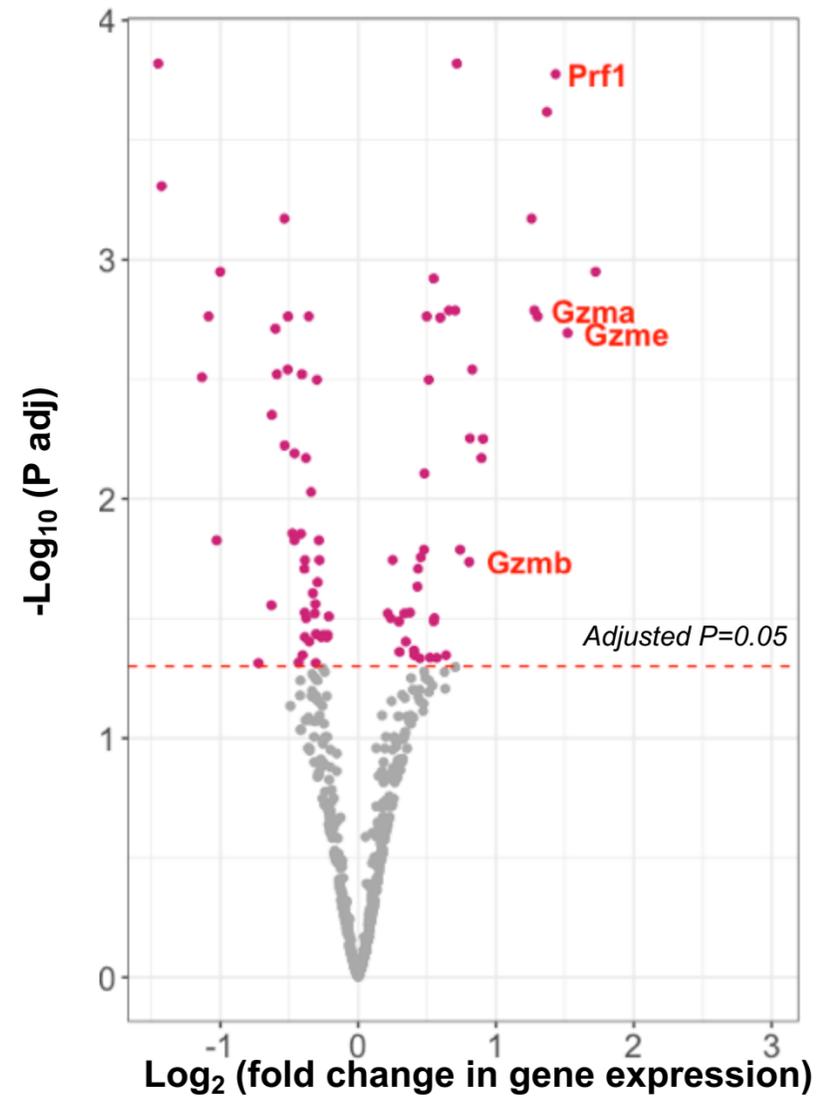


# MAP4K1 inhibition induces stronger tumor T cell responses than anti-PD-L1

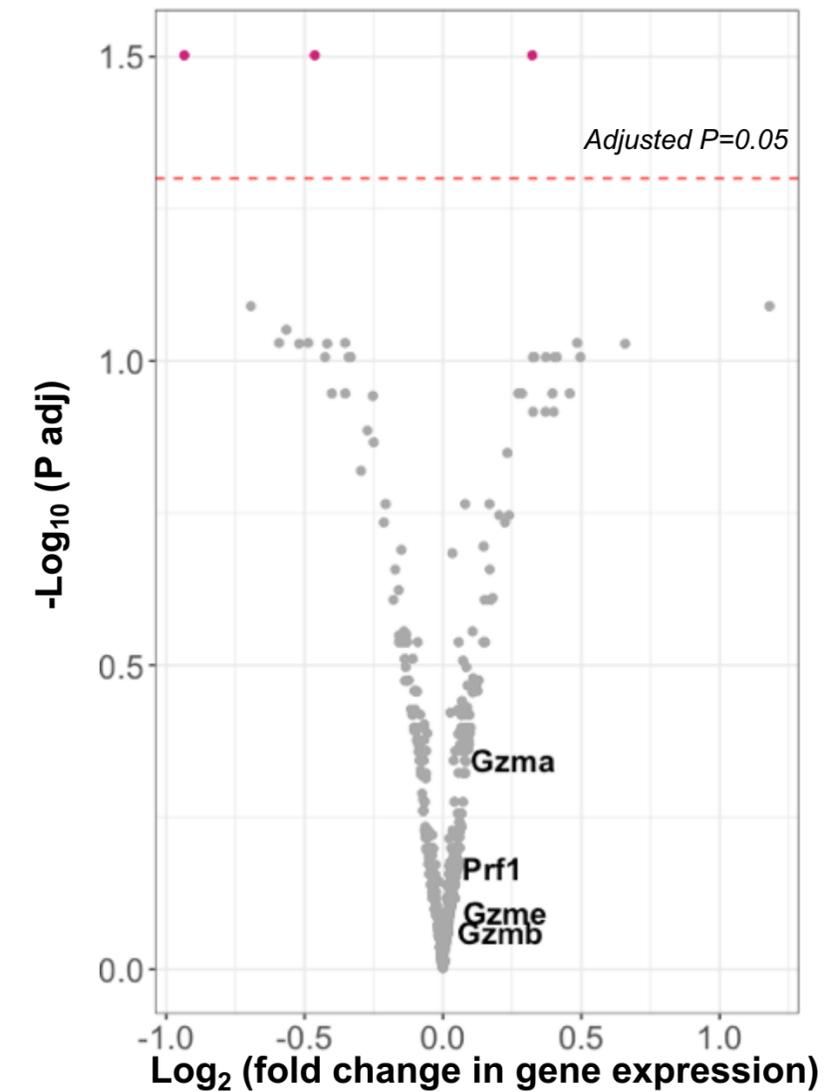
## Differentially expressed gene overlap



## Differential expression (BLU2069/vehicle)

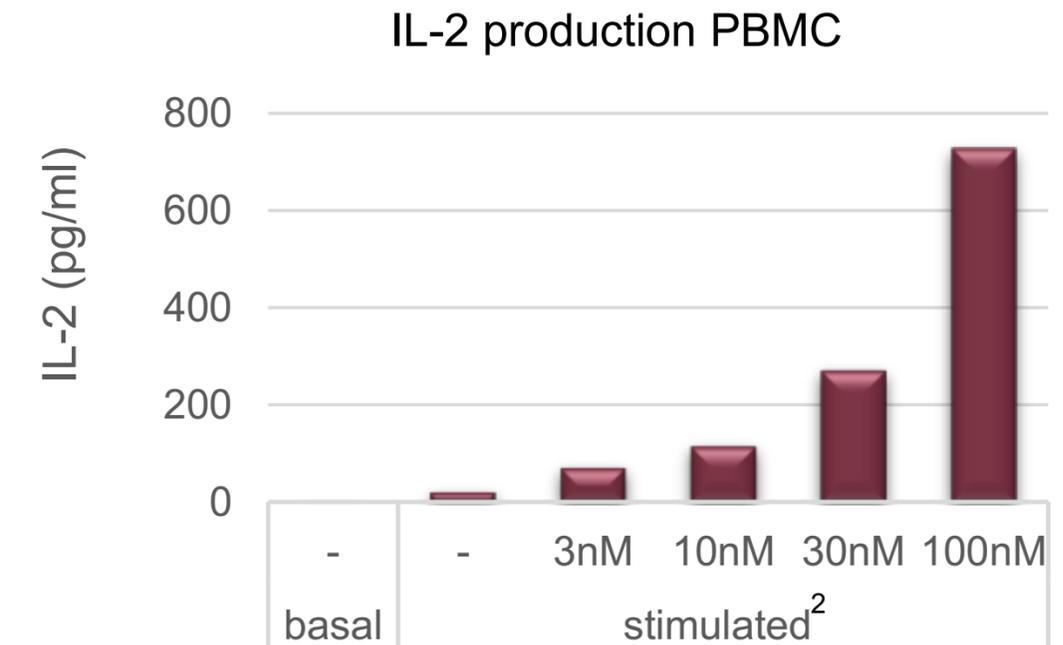
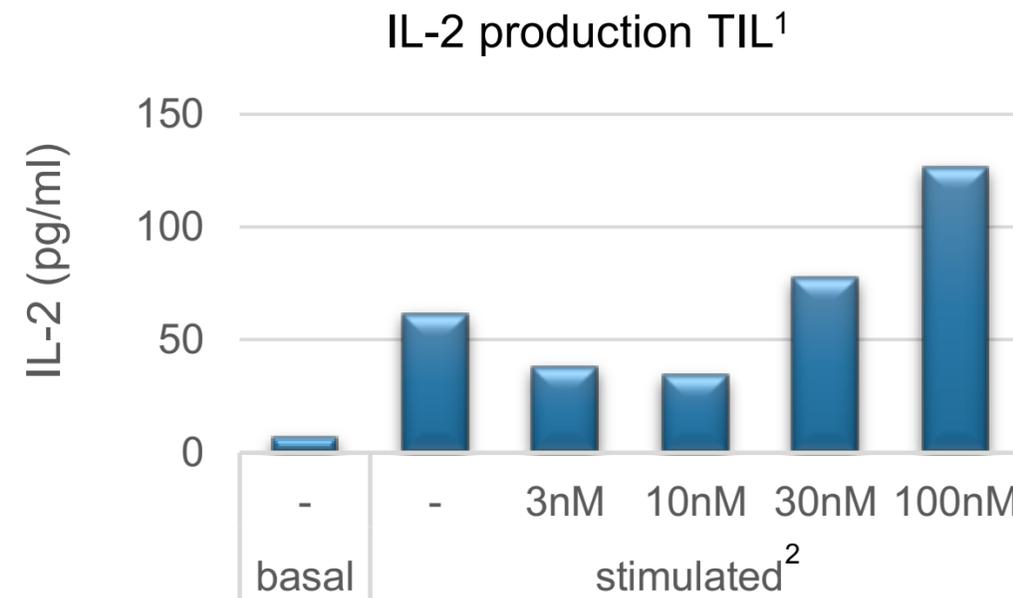
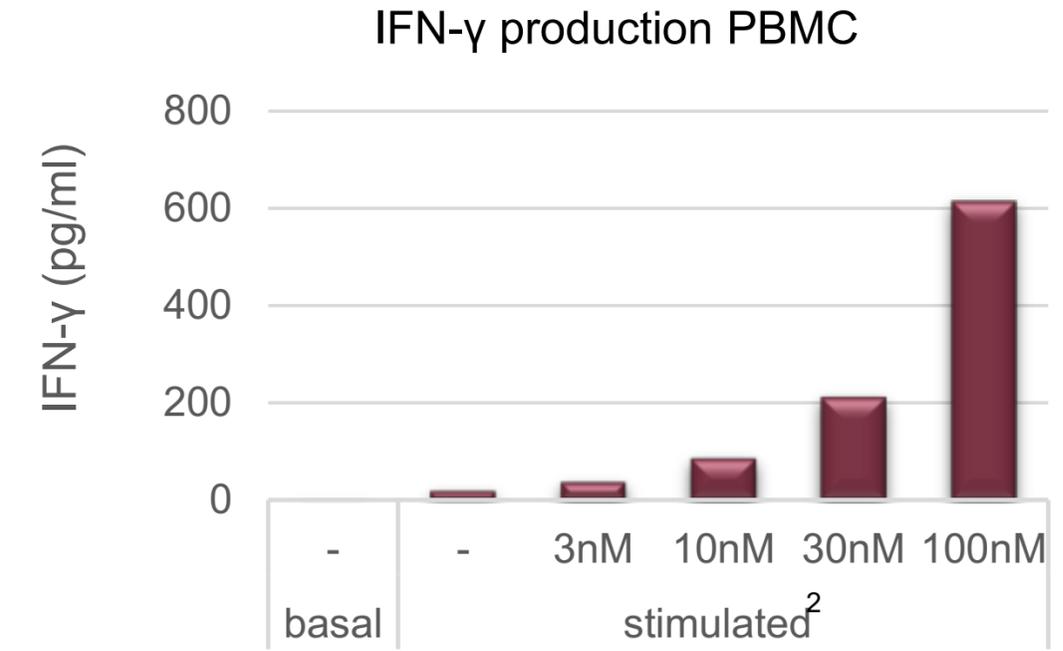
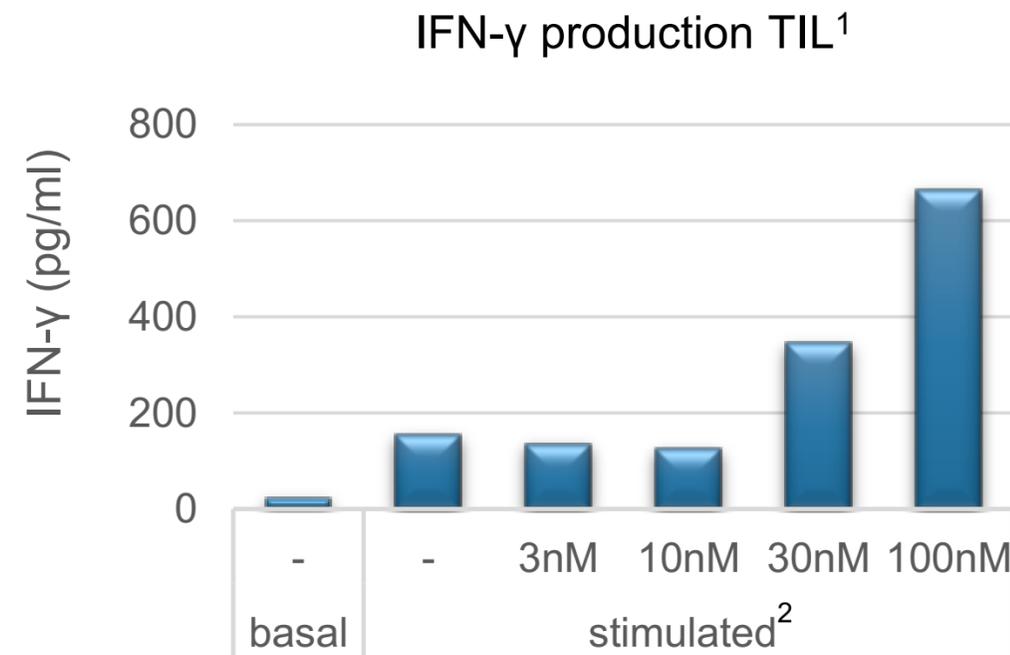
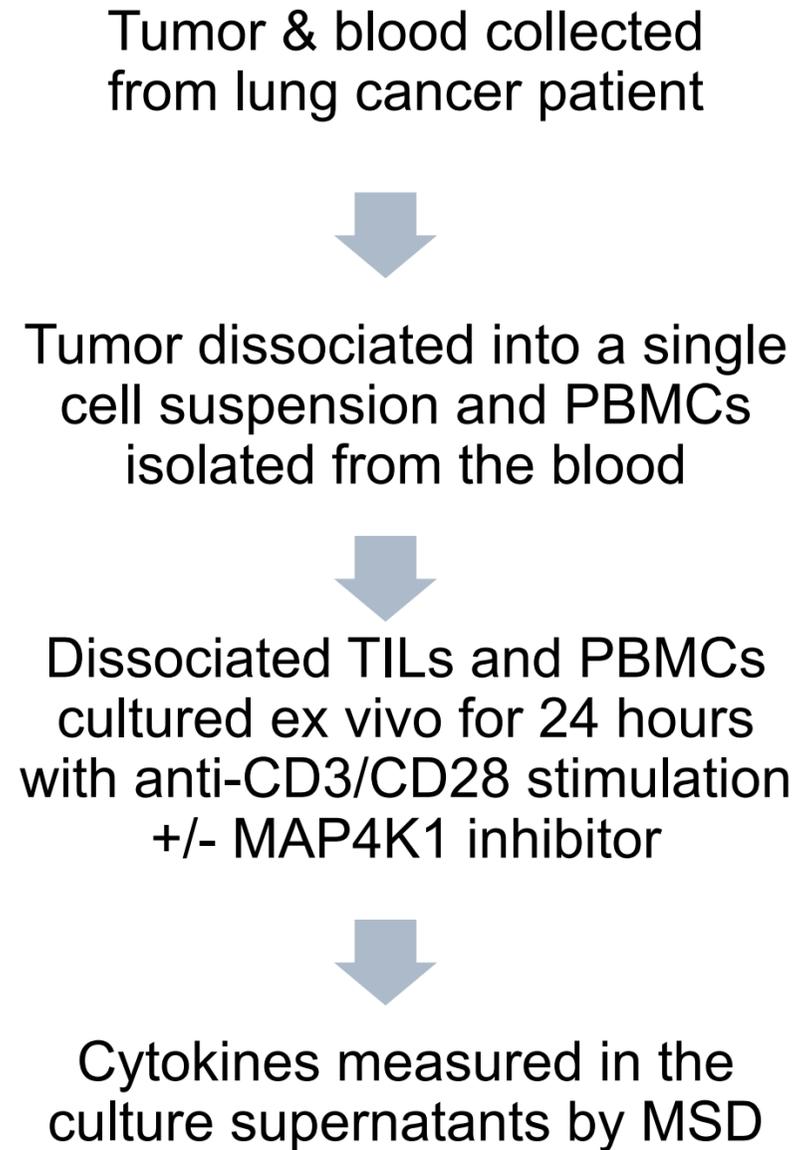


## Differential expression (Anti-PD-L1/vehicle)



Significantly differentially expressed genes in red

# MAP4K1 increases cytokine production from both blood and tumor infiltrating lymphocytes derived from lung adenocarcinoma patient



## Unique and diverse portfolio of novel cancer immunotherapy targets

---

- MAP4K1 path to development candidate is representative of the broader undisclosed cancer immunotherapy portfolio under the Roche collaboration
  - ▶ Plan to nominate potential first-in-class MAP4K1 development candidate in 1H 2020
- Collaboration has contributed to the diversification and expansion of Blueprint Medicines' portfolio derived from our platform

# Outlook for the future



HIGH SUCCESS RATE | EFFICIENCY | PLATFORM EXPANSION



# Q & A



**Jeff Albers**

Chief Executive Officer



# closing remarks

# Third quarter 2019 financial results

## Balance Sheet

Cash, Cash Equivalents and Investments

September 30, 2019\*

\$594.5M

December 31, 2018

\$494.0M

## Statement of Operations

Collaboration Revenue

\$9.1M

\$1.1M

Research & Development Expenses

\$81.5M

\$64.6M

General & Administrative Expenses

\$25.6M

\$12.0M

Net Loss

\$(94.3)M

\$(72.7)M

## Three Months Ended September 30,

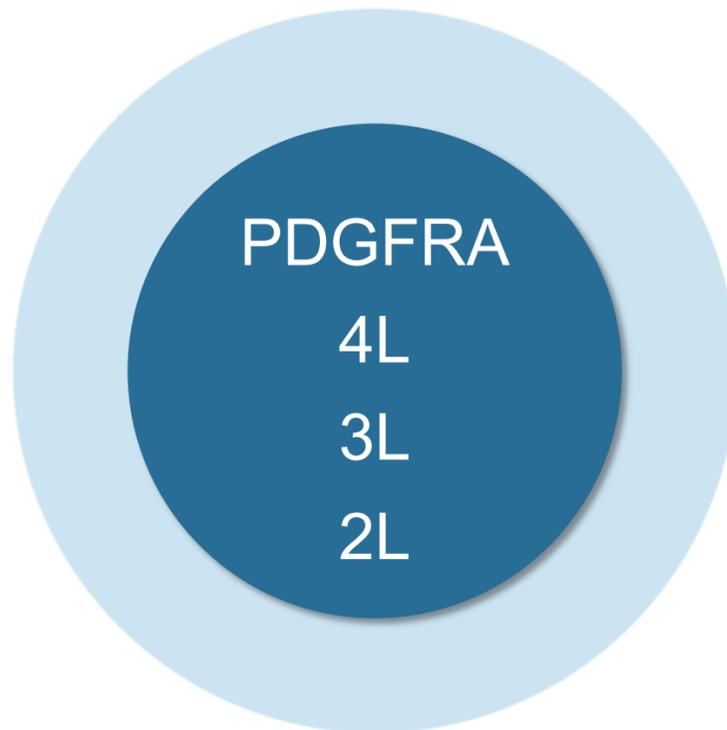
2019\*

2018\*

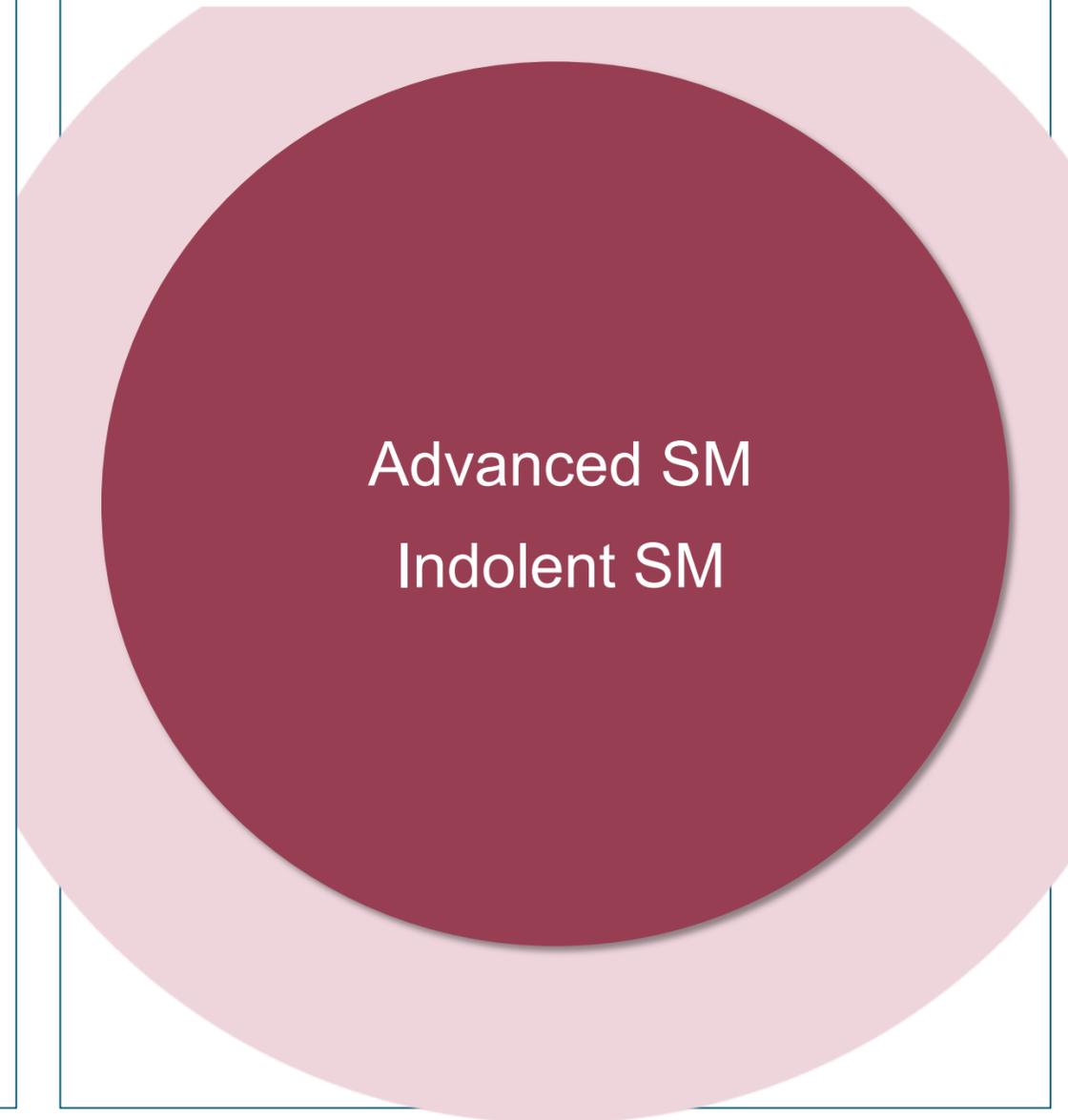
BASED ON CURRENT OPERATING PLANS,  
EXPECT EXISTING CASH BALANCE WILL FUND OPERATIONS INTO THE SECOND HALF OF 2021\*\*

# We are pursuing a highly attractive set of opportunities across our portfolio

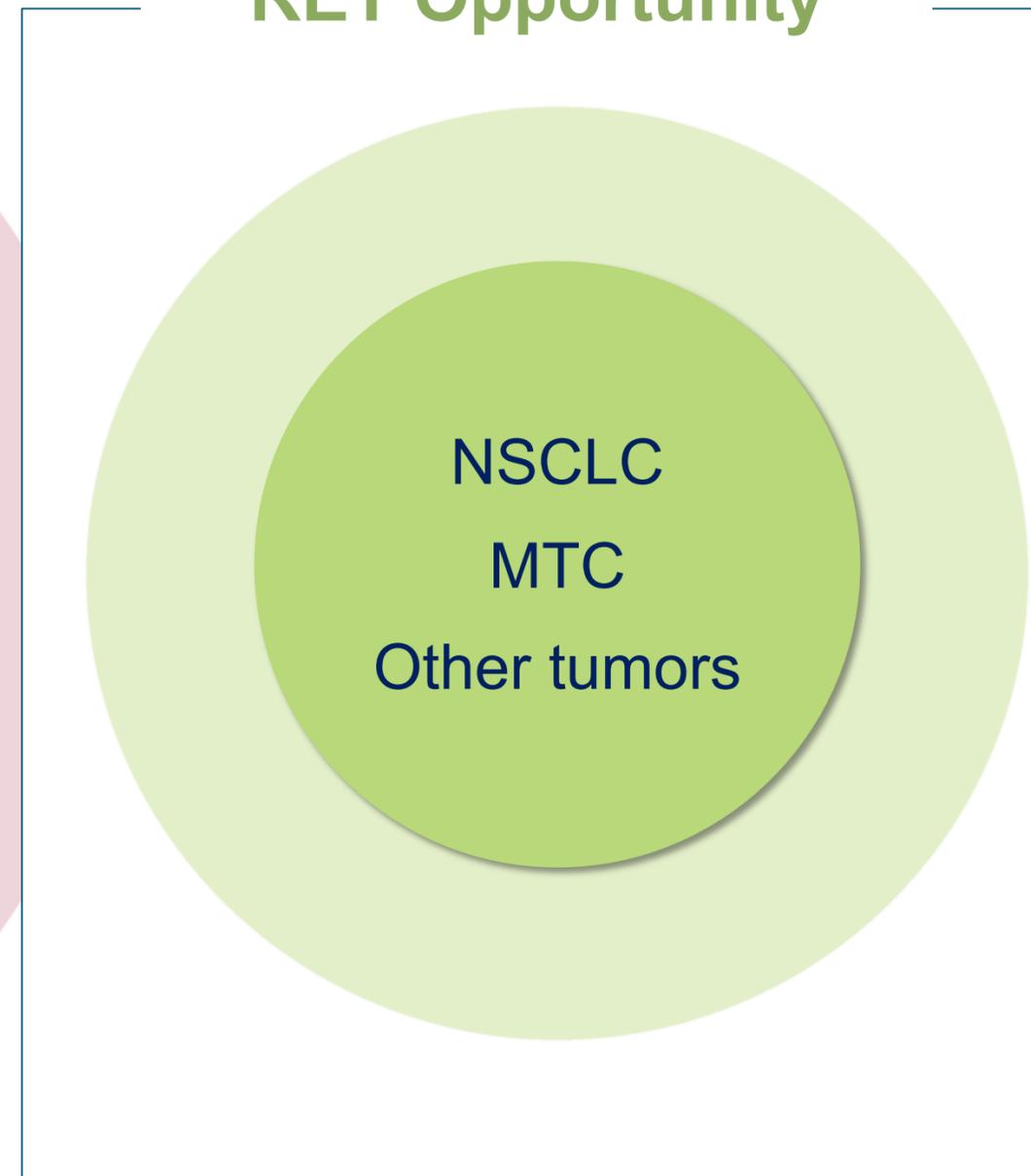
## GIST Opportunity

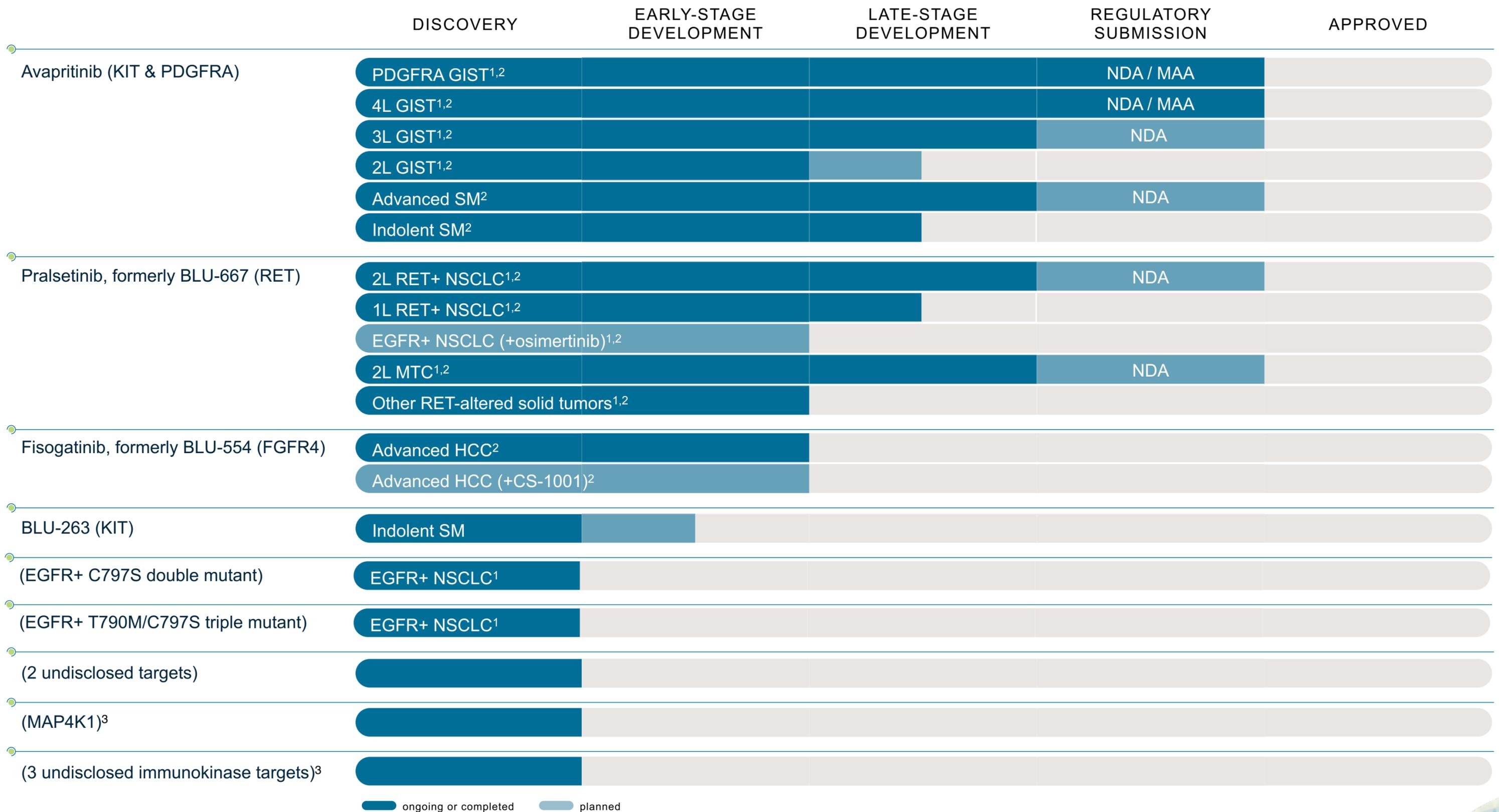


## SM Opportunity



## RET Opportunity





1. Unresectable or metastatic disease. 2. CStone Pharmaceuticals has exclusive rights to develop and commercialize avapritinib, pralsetinib and fisogatinib in Mainland China, Hong Kong, Macau and Taiwan. Blueprint Medicines retains all rights in the rest of the world. 3. In collaboration with Roche. Blueprint Medicines has U.S. commercial rights for up to two programs. Roche has worldwide commercialization rights for up to two programs and ex-U.S. commercialization rights for up to two programs. 1L, first-line; 2L, second-line; 3L, third-line; 4L, fourth-line; FOP, fibrodysplasia ossificans progressiva; GIST, gastrointestinal stromal tumors; HCC, hepatocellular carcinoma; MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer.



thank  
you

