UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of Earliest Event Reported): **November 5, 2019**

Blueprint Medicines Corporation

(Exact name of registrant as specified in its charter)

Delaware	**001-37359**	**26-3632015**
(State or other jurisdiction of incorporation)	(Commission File Number)	(I.R.S. Employer Identification No.)

45 Sidney Street **Cambridge, Massachusetts**	**02139**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: **(617) 374-7580**

(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Securities registered pursuant to Section 12(b) of the Exchange Act:

Title of each class	Trading symbol(s)	Name of each exchange on which registered
Common stock, par value $0.001 per share	BPMC	Nasdaq Global Select Market

Item 2.02 Results of Operations and Financial Condition.

On November 5, 2019, Blueprint Medicines Corporation (the "Company") announced its financial results for the quarter ended September 30, 2019 and other business highlights. The full text of the press release issued in connection with the announcement is furnished as Exhibit 99.1 to this Current Report on Form 8-K (the "Form 8-K") and is incorporated by reference herein.

The information responsive to Item 2.02 of this Form 8-K, including Exhibit 99.1 attached hereto, is intended to be furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended (the "Securities Act"), or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 7.01 Regulation FD Disclosure.

On November 5, 2019, the Company intends to make a slide presentation at its Research and Development Day. The slide presentation is furnished as Exhibit 99.2 to this Form 8-K and is incorporated by reference herein.

The information responsive to Item 7.01 of the Form 8-K, including Exhibit 99.2 attached hereto, is intended to be furnished and shall not be deemed "filed" for purposes of Section 18 of the Exchange Act, or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

The following exhibits relating to Item 2.02 and Item 7.01 of this Form 8-K shall be deemed to be furnished and not filed:

Exhibit No.	Description
99.1	Press release issued by Blueprint Medicines Corporation on November 5, 2019
99.2	Presentation dated November 5, 2019
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

BLUEPRINT MEDICINES CORPORATION

Date: November 5, 2019

By: /s/ Jeffrey W. Albers
Jeffrey W. Albers
Chief Executive Officer

Exhibit 99.1

Blueprint Medicines Outlines Precision Therapy Research Vision, Provides Update on Discovery and Clinical-Stage Portfolio at R&D Day and Reports Third Quarter 2019 Financial Results

-- R&D Day presentation discloses four research programs demonstrating the transformative science, urgency and efficiency underpinning the company's integrated precision medicine platform --

-- Enrollment target reached in Phase 3 VOYAGER trial of avapritinib in third-line GIST --

-- Initial data from PIONEER trial of avapritinib in indolent systemic mastocytosis to be presented at ASH --

-- Planned new drug applications for avapritinib for advanced systemic mastocytosis and pralsetinib for previously treated RET fusion non-small cell lung cancer on track for submission to FDA in Q1 2020 --

CAMBRIDGE, Mass., November 5, 2019 – Blueprint Medicines Corporation (NASDAQ:BPMC), a precision therapy company focused on genomically defined cancers, rare diseases and cancer immunotherapy, is hosting its first R&D Day in New York City today.

During the event, Blueprint Medicines will outline its vision to become a leading platform-enabled, fully-integrated, global precision therapy company. The R&D Day presentation will highlight opportunities to expand the reach of the company's therapeutic candidates to broader patient populations, integrate and scale scientific, clinical and commercial capabilities to build therapeutic area leadership, and fully utilize the company's scientific platform to design innovative medicines targeting novel kinase biology. In addition, today the company reported financial results and provided a business update for the quarter ended September 30, 2019.

"As we prepare to launch our first medicine and submit multiple additional marketing applications next year, today we are unveiling our next wave of internally discovered research and clinical-stage precision therapies with the potential to deliver durable clinical benefits to additional patient populations," said Jeff Albers, Chief Executive Officer of Blueprint Medicines. "By fully leveraging our integrated research capabilities and reinvesting insights from our ongoing clinical programs, we continue to build a powerful research engine with the potential to deliver transformative treatment advances to patients as well as rapid and sustainable growth to Blueprint Medicines."

R&D Day Presentation Areas of Focus

- Highlight the significant medical need in indolent systemic mastocytosis (SM), a rare disease characterized by debilitating and unpredictable symptoms despite best available therapy. Based on an improved understanding of the disease, Blueprint Medicines now estimates there are approximately 75,000 patients with SM in the major markets, which consist of the United States, France, Germany, Italy, Spain, United Kingdom and Japan.
- Announce a comprehensive strategy to address a broad population of patients with SM and other mast cell disorders with the company's drug candidates avapritinib and BLU-263, a next-generation KIT inhibitor. Blueprint Medicines plans to submit an investigational new drug (IND) application to the U.S. Food and Drug Administration (FDA) for BLU-263 for indolent SM in the first half of 2020.

- Introduce two research programs targeting well-characterized resistance mutations in patients with EGFR-driven non-small cell lung cancer (NSCLC), highlighting Blueprint Medicines' differentiated capability for designing highly selective investigational medicines that address tumor evolution and resistance to targeted therapy.
- Highlight a research program under Blueprint Medicines' cancer immunotherapy collaboration with Roche targeting MAP4K1, which is believed to play a role in T cell regulation.

Third Quarter 2019 Highlights and Recent Progress

Avapritinib: Gastrointestinal stromal tumors (GIST)

- Completed target enrollment in the Phase 3 VOYAGER trial of avapritinib versus regorafenib in patients with third- and fourth-line GIST.
- Announced the FDA intends to administratively split the new drug application (NDA) for avapritinib into two separate NDAs (one for PDGFRA Exon 18 mutant GIST, regardless of prior therapy, and one for fourth-line GIST) and requested top-line data from the ongoing Phase 3 VOYAGER trial to inform its review of the proposed fourth-line GIST indication. The PDUFA action date for both indications is currently February 14, 2020. For the fourth-line indication, an extension of up to three months for the PDUFA action date will likely be required to enable Blueprint Medicines to provide the top-line VOYAGER data to the FDA.

Avapritinib: Systemic mastocytosis (SM)

- Completed enrollment of Part 1 of the Phase 2 PIONEER trial of avapritinib in patients with indolent SM.

BLU-782: Fibrodysplasia ossificans progressiva (FOP)

- Entered into an exclusive, worldwide license agreement with Clementia Pharmaceuticals, a subsidiary of Ipsen, for the development and commercialization of BLU-782 as a potential treatment for patients with FOP and other indications.

Key Upcoming Milestones

The company expects to achieve the following milestones in the fourth quarter of 2019:

- Present initial data from Part 1 of the Phase 2 PIONEER trial of avapritinib in indolent SM at the 61st American Society of Hematology (ASH) Annual Meeting and Exposition.
- Initiate a Phase 3 trial evaluating pralsetinib in first-line RET-fusion NSCLC.
- Initiate a Phase 1b/2 trial in China evaluating fisogatinib in combination with CS1001, CStone Pharmaceuticals' anti-PD-L1 inhibitor, in patients with HCC.

The company expects to achieve the following milestones related to planned marketing applications in 2020:

- Submit an NDA to the FDA for avapritinib for the treatment of advanced SM based on data from the Phase 1 EXPLORER trial and Phase 2 PATHFINDER trial in the first quarter of 2020.
- Submit an NDA to the FDA for pralsetinib for the treatment of patients with RET-fusion NSCLC previously treated with platinum-based chemotherapy in the first quarter of 2020.

- Submit an NDA to the FDA for pralsetinib for the treatment of patients with MTC previously treated with an approved multi-kinase inhibitor in the first half of 2020.
- Submit a supplemental NDA to the FDA for avapritinib for the treatment of third-line GIST in the second half of 2020.

Third Quarter 2019 Financial Results

- **Cash Position**: As of September 30, 2019, cash, cash equivalents and investments were $594.5 million, as compared to $494.0 million as of December 31, 2018. This increase reflects net proceeds of approximately $327.4 million from the company's follow-on underwritten public offering of common stock, which closed in April 2019, partially offset by cash used in operations. Cash, cash equivalents and investments as of September 30, 2019 do not include the $25.0 million upfront payment received in connection with entering into the worldwide license agreement with Clementia Pharmaceuticals or an $8.0 million research milestone achieved under the Roche collaboration, both of which were earned in October 2019.
- **Collaboration Revenues:** Collaboration revenues were $9.1 million for the third quarter of 2019, as compared to $1.1 million for the third quarter of 2018. This increase was primarily due to revenue recognized under the CStone and Roche collaborations. During the third quarter of 2019, the company recognized $6.0 million in milestone revenue under the CStone collaboration compared to no revenue recognized for the same period in 2018. During the third quarter of 2019, the company recognized $3.1 million in revenue under the Roche collaboration compared to $1.1 million for the same period in 2018.
- **R&D Expenses:** Research and development expenses were $81.5 million for the third quarter of 2019, as compared to $64.6 million for the third quarter of 2018. This increase was primarily due to increased clinical and manufacturing expenses driven by the company’s lead programs and increased personnel expenses. Research and development expenses included $7.7 million in stock-based compensation expenses for the third quarter of 2019.
- **G&A Expenses**: General and administrative expenses were $25.6 million for the third quarter of 2019, as compared to $12.0 million for the third quarter of 2018. This increase was primarily due to increased personnel expenses and increased professional fees for commercial-readiness and other activities. General and administrative expenses included $7.3 million in stock-based compensation expenses for the third quarter of 2019.
- **Net Loss:** Net loss was $94.3 million for the third quarter of 2019, or a net loss per share of $1.93, as compared to a net loss of $72.7 million for the third quarter of 2018, or a net loss per share of $1.66.

Financial Guidance

Based on its current plans, Blueprint Medicines expects that its existing cash, cash equivalents and investments, together with the $25.0 million upfront cash payment received under its license agreement with Clementia and an $8.0 million research milestone achieved in the fourth quarter of 2019 under the Roche collaboration, but excluding any additional potential option fees, milestone payments or other payments from Roche, CStone Pharmaceuticals or Clementia Pharmaceuticals, will be sufficient to enable it to fund its operating expenses and capital expenditure requirements into the second half of 2021.

Conference Call Information

Blueprint Medicines will host a live webcast of its R&D Day event at 8:30 a.m. ET today. The webcast may be accessed under “Events and Presentations” in the Investors & Media section of Blueprint Medicines' website at http://ir.blueprintmedicines.com. The archived webcast will be available on Blueprint Medicines’ website approximately two hours after the conference call and will be available for 90 days following the call.

About Blueprint Medicines

Blueprint Medicines is a precision therapy company striving to improve human health. With a focus on genomically defined cancers, rare diseases and cancer immunotherapy, we are developing transformational medicines rooted in our leading expertise in protein kinases, which are proven drivers of disease. Our uniquely targeted, scalable approach empowers the rapid design and development of new treatments and increases the likelihood of clinical success. We are currently advancing three investigational medicines in clinical development, along with multiple research programs. For more information, visit www.BlueprintMedicines.com and follow us on Twitter (@BlueprintMeds) and LinkedIn.

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements regarding plans and timelines for the development of avapritinib, pralsetinib, fisogatinib, and BLU-263, including the timing, designs, implementation, enrollment, plans and announcement of results regarding Blueprint Medicines’ ongoing and planned clinical trials for its drug candidates, including avapritinib, pralsetinib, fisogatinib and BLU-263; plans and timelines for nominating additional development candidates; plans and timelines for submitting an IND application to the FDA for BLU-263; plans and timelines for submitting marketing applications for avapritinib and pralsetinib; the potential benefits of Blueprint Medicines' current and future drug candidates in treating patients; plans, timelines and expectations for the FDA's review and administrative split of the NDA for avapritinib for the treatment of adult patients with PDGFRA Exon 18 mutant GIST, regardless of prior therapy, and fourth-line GIST; plans, timelines and expectations for top-line data from the VOYAGER trial; plans, timelines and expectations for the commercialization of avapritinib for the treatment of GIST, if approved by the FDA; potential benefits of the license agreement between Blueprint Medicines and Ipsen; expectations regarding Blueprint Medicines' existing cash, cash equivalents and investments; and Blueprint Medicines' strategy, goals and anticipated milestones, business plans and focus. 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. Any forward-looking statements in this press release are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, risks and uncertainties related to the delay of any current or planned clinical trials or the development of Blueprint Medicines' drug candidates, including avapritinib, pralsetinib, fisogatinib and BLU-263, or licensed products, including BLU-782; 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 FDA will not ask for additional clinical trials for avapritinib; 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; Blueprint Medicines' advancement of multiple early-stage efforts; Blueprint Medicines' ability to successfully demonstrate the safety and efficacy of its drug candidates and gain approval of its drug candidates on a timely basis, if at all; the preclinical and clinical results for Blueprint Medicines' drug candidates, which may not support further development of such drug candidates; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials; Blueprint Medicines' ability to develop and commercialize companion diagnostic tests for its current and future drug candidates; and the success of Blueprint Medicines' current and future collaborations and licensing arrangement, including its cancer immunotherapy collaboration with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc., its collaboration with CStone Pharmaceuticals, and its license to Clementia Pharmaceuticals. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in Blueprint Medicines' filings with the Securities and Exchange Commission (SEC), including Blueprint Medicines’ most recent Quarterly Report on Form 10-Q and any other filings that Blueprint Medicines has made or may make with the SEC in the future. Any forward-looking statements contained in this press release represent Blueprint Medicines' views only as of the date hereof and should not be relied upon as representing its views as of any subsequent date. Except as required by law, Blueprint Medicines explicitly disclaims any obligation to update any forward-looking statements.

Blueprint Medicines Corporation
Selected Condensed Consolidated Balance Sheet Data
(in thousands)
(unaudited)

	September 30, 2019	December 31, 2018
Cash, cash equivalents and investments	$ 594,459	$ 494,012
Working capital [1]	419,584	439,464
Total assets	737,925	540,124
Deferred revenue	41,331	46,167
Total liabilities	221,581	121,115
Total stockholders' equity	516,344	419,009

[1] Blueprint Medicines defines working capital as current assets less current liabilities.

Blueprint Medicines Corporation
Condensed Consolidated Statements of Operations Data
(in thousands, except per share data)
(unaudited)

	Three Months Ended September 30,	
	2019	2018
Collaboration revenue	$ 9,139	$ 1,095
Operating expenses:		
Research and development	81,453	64,562
General and administrative	25,647	12,041
Total operating expenses	107,100	76,603
Other income (expense):		
Other income (expense), net	3,692	2,799
Interest expense	(6)	(14)
Total other income	3,686	2,785
Net loss	$ (94,275)	$ (72,723)
Net loss per share — basic and diluted	$ (1.93)	$ (1.66)
Weighted-average number of common shares used in net loss per share — basic and diluted	48,921	43,915

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Exhibit 99.2


precision that moves™
STAYING ONE STEP AHEAD OF DISEASE
blueprint™ MEDICINES
© 2019 Blueprint Medicines Corporation

JEFF ALBERS

Chief Executive Officer

blueprint MEDICINES

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

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

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

TRANSFORMATIVE BENEFIT

Life-changing
outcomes for patients

URGENCY

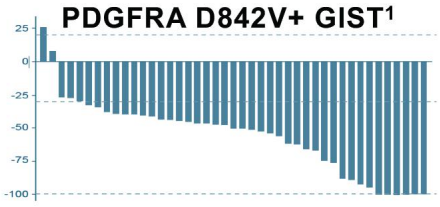
Expedited development
and regulatory pathways

EFFICIENCY

Increased probability
of success

Principles in action: expedited development of avapritinib and pralsetinib

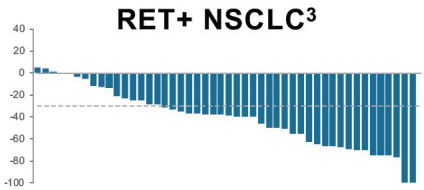
AVAPRITINIB



Breakthrough therapy designation[2]

~4 years
from IND to initial NDA submission

PRALSETINIB



Breakthrough therapy designation[4]

~3 years
from IND to planned initial NDA submission

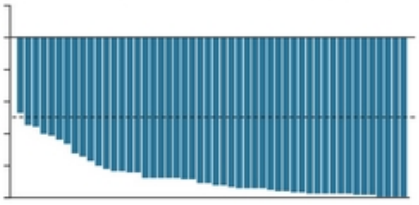
1. Data presented at ASCO 2019 Annual Meeting on June 1, 2019. Data cutoff date: November 16, 2018. 2. Avapritinib granted Breakthrough Therapy Designation for the treatment of patients with unresectable or metastatic GIST harboring the PDGFRA D842V mutation. 3. Data presented at ASCO Annual Meeting in June 2019. Includes NSCLC patients treated at the recommended Phase 2 dose of 400 mg QD and enrolled as of November 14, 2018 with follow-up through a data cutoff date of April 28, 2019. 4. Pralsetinib granted Breakthrough Therapy Designation for the treatment of patients with RET-fusion positive NSCLC that has progressed following platinum-based chemotherapy and for the treatment of patients with RET mutation-positive MTC that requires systemic treatment and for which there are no acceptable alternative treatments.

The rapid evolution of Blueprint Medicines

IMAGINING A NEW PLATFORM	BUILDING THE PIPELINE	REALIZING THE VISION
2011 – 2014	2015 – 2019	2020 – FUTURE

HIGHLY SELECTIVE KINASE MEDICINE DISCOVERY PLATFORM

RAPID CLINICAL PROOF-OF-CONCEPT ACROSS MULTIPLE PROGRAMS



Avapritinib in advanced systemic mastocytosis: change in serum tryptase[1]

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

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content. 1 Data presented at the European Hematology Association Annual Meeting in June 2019. Data cutoff date: January 2, 2019.

Our focus today: three key themes

IMAGINING A NEW PLATFORM	BUILDING THE PIPELINE	REALIZING THE VISION
2011 – 2014	2015 – 2019	2020 – FUTURE

HIGHLY SELECTIVE KINASE MEDICINE DISCOVERY PLATFORM

RAPID CLINICAL PROOF-OF-CONCEPT ACROSS MULTIPLE PROGRAMS

Avapritinib in advanced systemic mastocytosis: change in serum tryptase[1]

- Integrated commercialization
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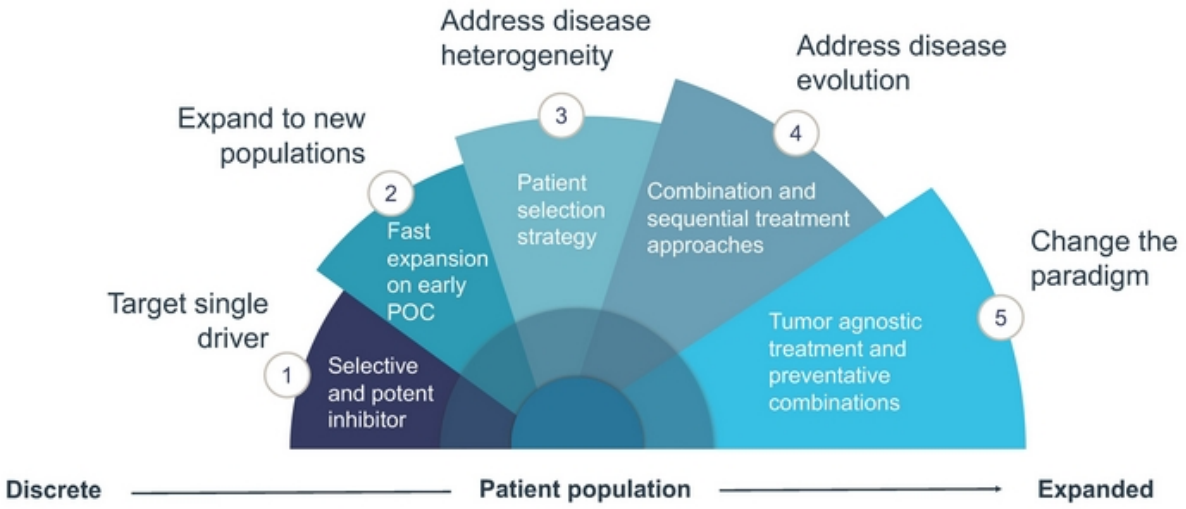
INDICATION EXPANSION

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



INDICATION EXPANSION

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

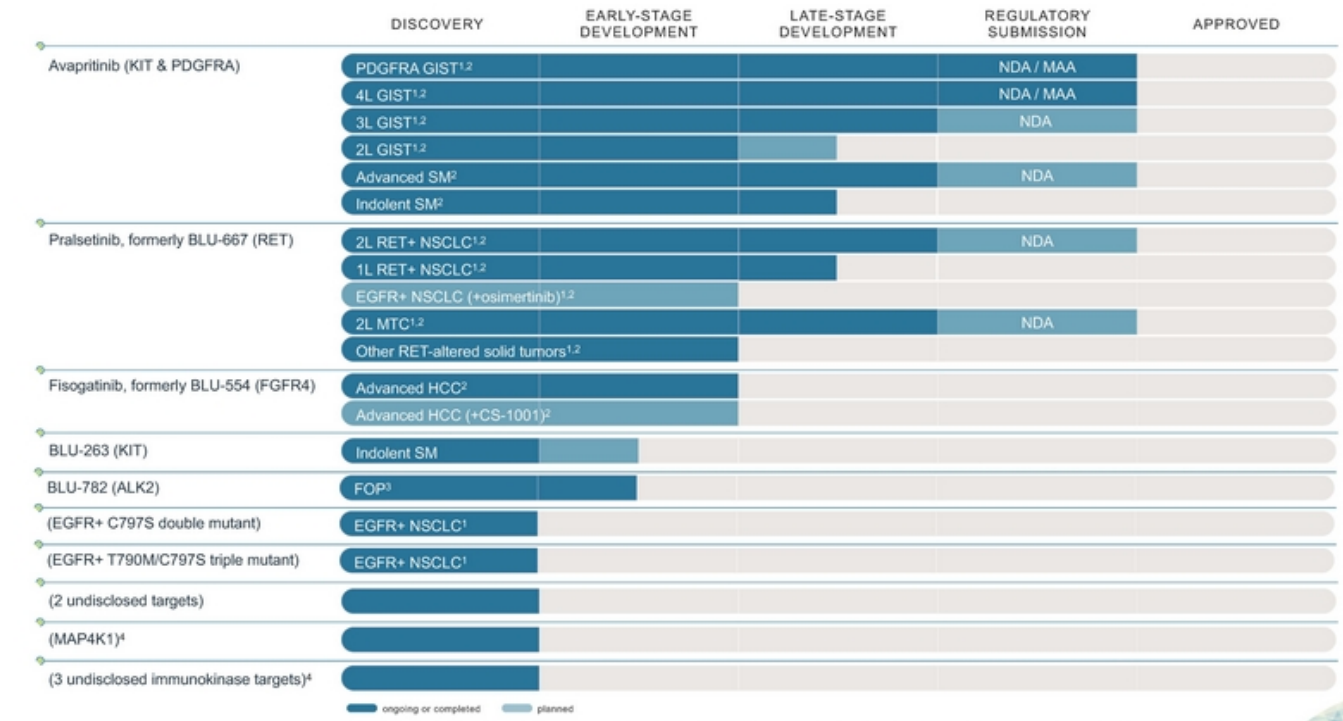
Human kinome

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content.

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 collaboration target under the cancer immunotherapy collaboration with Roche.



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 planned

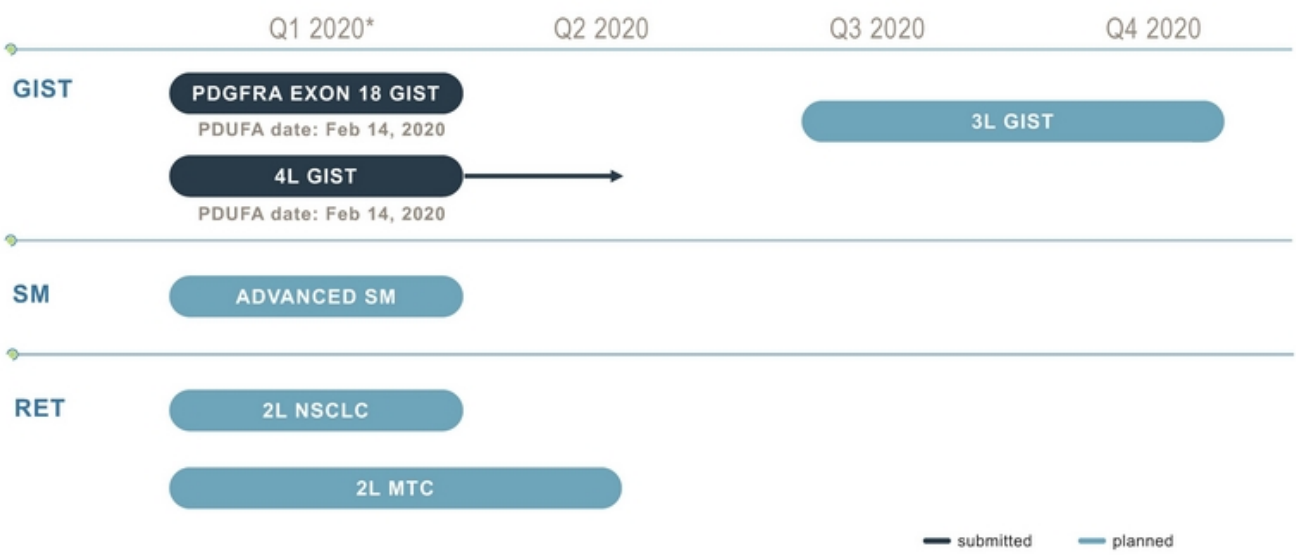
* Assumes administrative split by FDA into two separate NDAs for proposed indications under initial NDA submitted for avapritinib in GIST and extension of up to 3 months for the PDUFA date for the 4L indication. PDUFA, Prescription Drug User Fee Act

Submitted and planned New Drug Applications in 2020

submitted planned

* Assumes administrative split by FDA into two separate NDAs for proposed indications under initial NDA submitted for avapritinib in GIST and extension of up to 3 months for the PDUFA date for the 4L indication. PDUFA, Prescription Drug User Fee Act

Submitted and planned New Drug Applications in 2020



* Assumes administrative split by FDA into two separate NDAs for proposed indications under initial NDA submitted for avapritinib in GIST and extension of up to 3 months for the PDUFA date for the 4L indication. PDUFA, Prescription Drug User Fee Act

R&D Day agenda

Welcome and company vision	**Jeff Albers,** Chief Executive Officer
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
Q&A – Part 1	
BREAK	
A prolific platform for precision medicine	**Marion Dorsch, PhD,** Chief Scientific Officer
Addressing tumor evolution in lung cancer	**Tim Guzi, PhD,** Senior Vice President, Chemistry
Cancer immunotherapy: a new frontier	**Klaus Hoeflich, PhD,** Vice President, Biology
Q&A – Part 2	
Closing remarks	**Jeff Albers,** Chief Executive Officer


blueprint MEDICINES
SYSTEMIC MASTOCYTOSIS
00:08
05:26
20

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

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Systemic mastocytosis is one disease with a common genetic driver

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

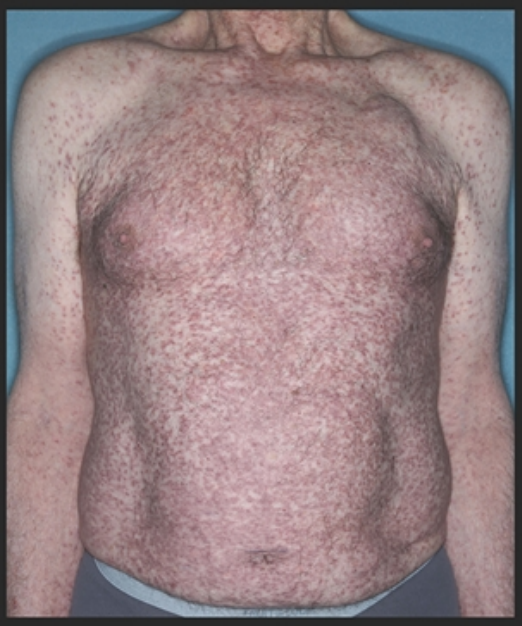
Patient 1 – Indolent SM

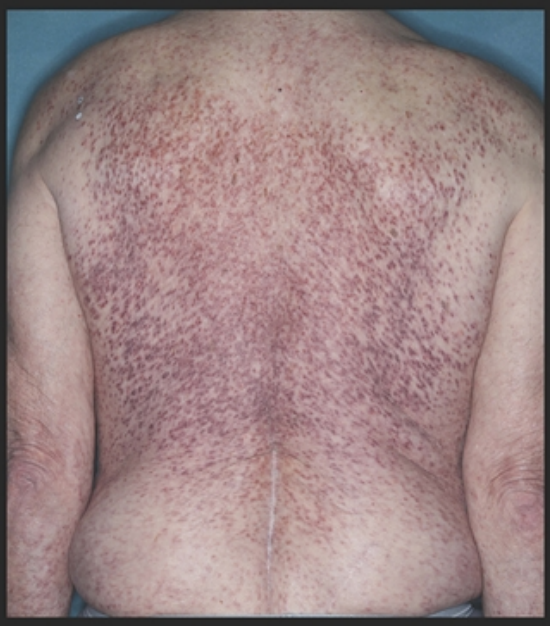
- Medications:
  - Cetirizine 10 mg daily
  - Fexofenadine 180 mg daily
  - Montelukast 10 mg daily
  - Benadryl every 4-6 hours
  - Hydroxyzine as needed
  - Diclofenac as needed
  - EpiPen as needed
  - Omalizumab once monthly injection
  - Omeprazole daily
  - Zofran daily
  - Ranitidine 300 mg daily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

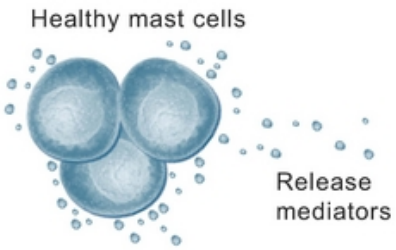
Urticaria pigmentosa in a patient with indolent SM



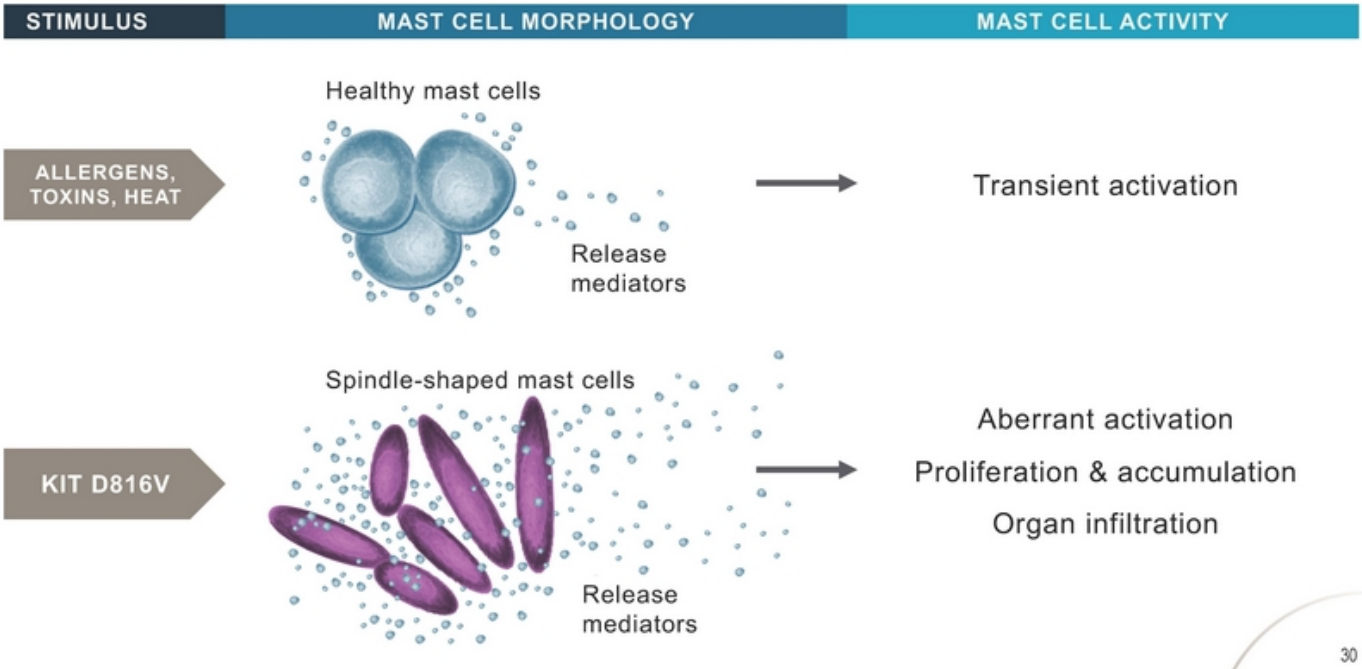


Patient permission granted for use of photos.

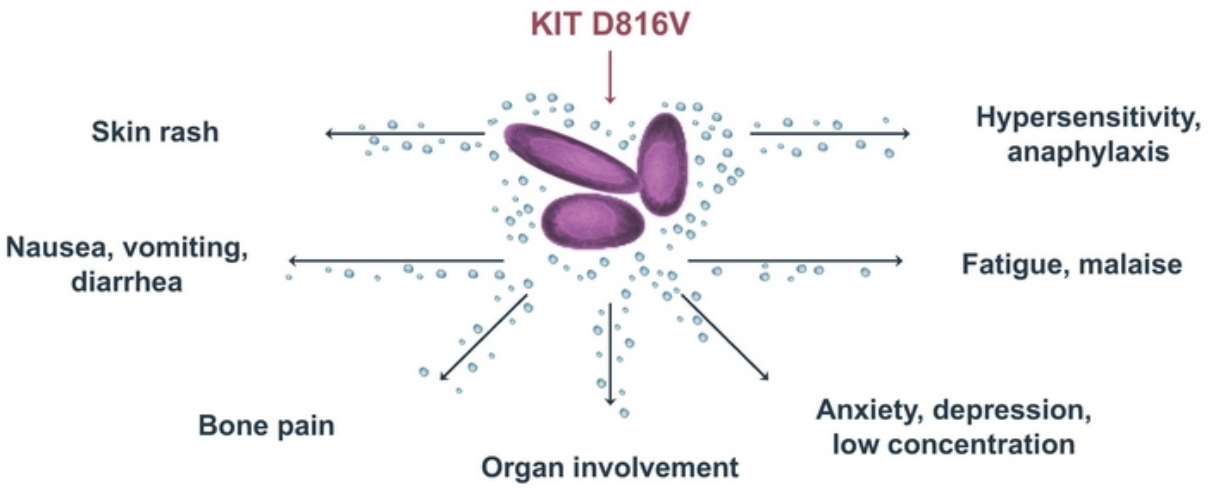
Healthy mast cells play a key role in the immune-inflammatory response

STIMULUS	MAST CELL MORPHOLOGY	MAST CELL ACTIVITY
ALLERGENS, TOXINS, HEAT		Transient activation

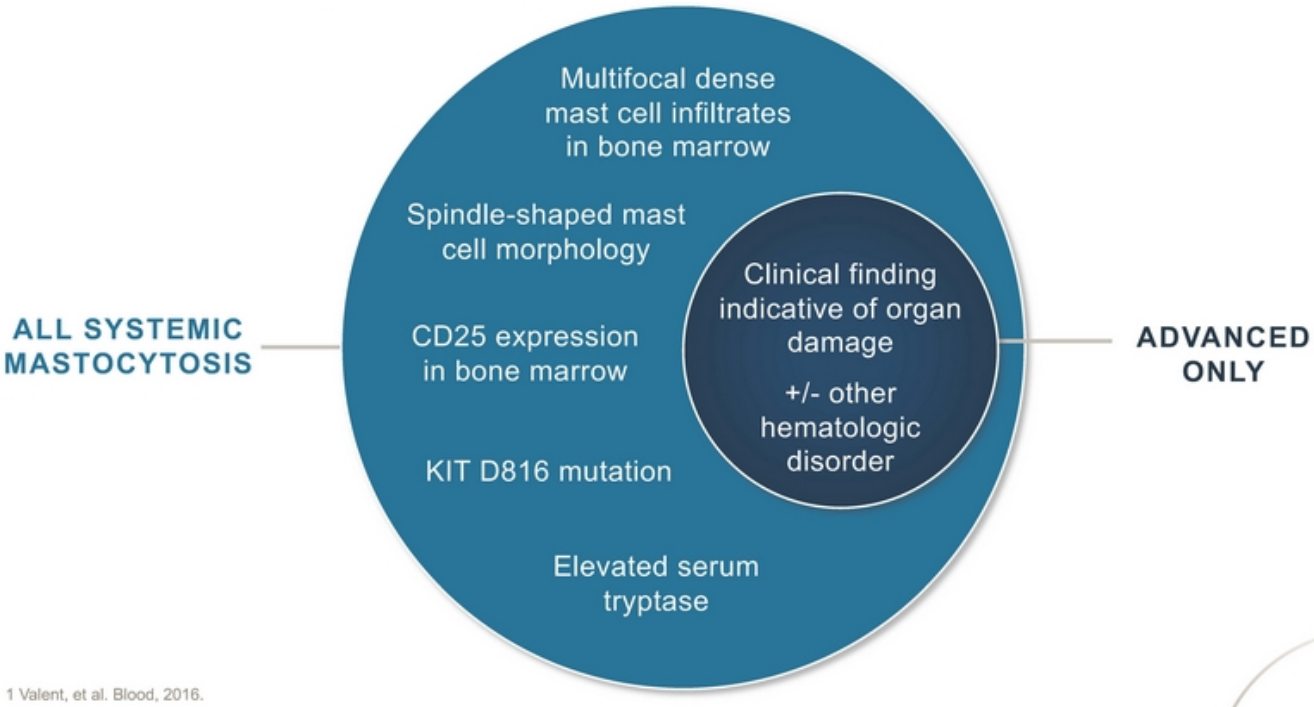
In nearly all SM patients, KIT D816V aberrantly activates mast cells



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



Systemic mastocytosis diagnostic criteria[1]



1 Valent, et al. Blood, 2016.

Nearly all patients with SM experience diagnostic delay

COMMONLY CONSULTED SPECIALISTS

Allergist-immunologist
Anaphylaxis and allergy symptoms

Gastroenterologist
Gastrointestinal distress

Dermatologist
Skin rash

Hematologist-oncologist
Abnormal blood counts or bone imaging

1 Mast Cell Connect registry data on file. Enrollment initiated December 1, 2015. Data cutoff date: August 20, 2019.

Indolent SM patients report high symptom burden

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

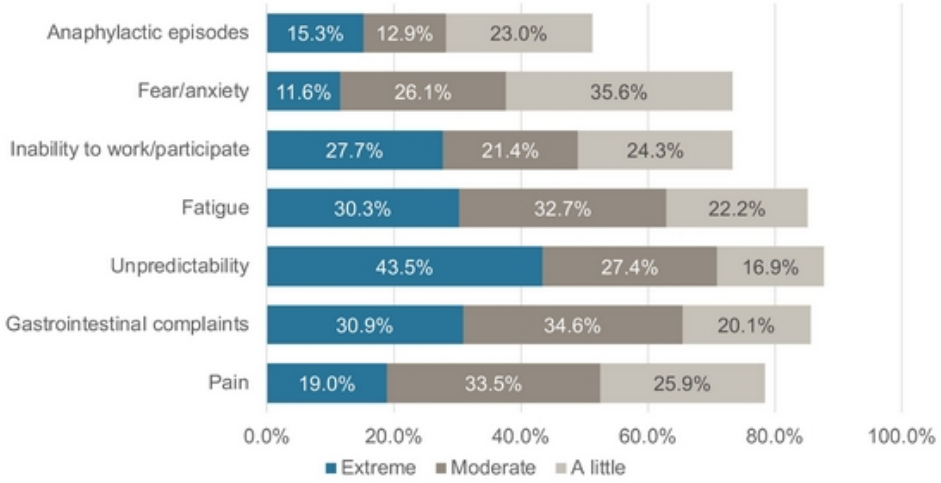
	ISM (n=109)	AdvSM (n=15)
Systemic symptoms		
Fatigue/tiredness *	75%	87%
Pain (not abdominal)	55%	60%
Headache	45%	40%
Sweating	34%	47%
Swelling	32%	40%
Anaphylaxis	35%	40%
Difficulty breathing	29%	47%

	ISM (n=109)	AdvSM (n=15)
Gastrointestinal symptoms		
Abdominal pain	50%	60%
Bloating	51%	60%
Diarrhea	39%	53%
Nausea	39%	73%
Flatulence	29%	40%
Vomiting	15%	60%
Skin symptoms		
Itching	52%	47%
Flushing	49%	40%
Skin changes	49%	40%

Mast Cell Connect registry data on file. Enrollment initiated December 1, 2015. Data cutoff date: August 20, 2019.

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



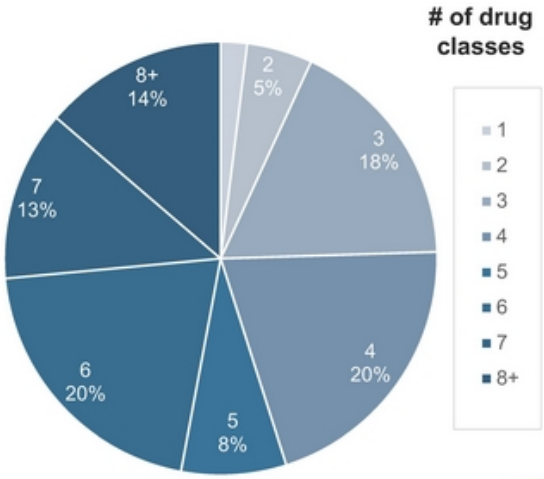
S. Jennings, N. Russell, B. Jennings, V. Slee, L. Sterling, M. Castells, *et al.*The Mastocytosis Society survey on mast cell disorders: patient experiences and perceptions; J Allergy Clin Immunol Pract, 2 (2014), pp. 70-76.

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%
Leukotreine Inhibitors	62%
Corticosteroids	55%
Epinephrine	48%
Proton Pump Inhibitors	46%
Anti-IgE	18%
Cytoreductive Agents	15%

N=103

~75% of ISM patients have taken ≥4 classes of drugs to manage their disease



Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF) Observational Study July 2018. Data cutoff: March 2018.

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

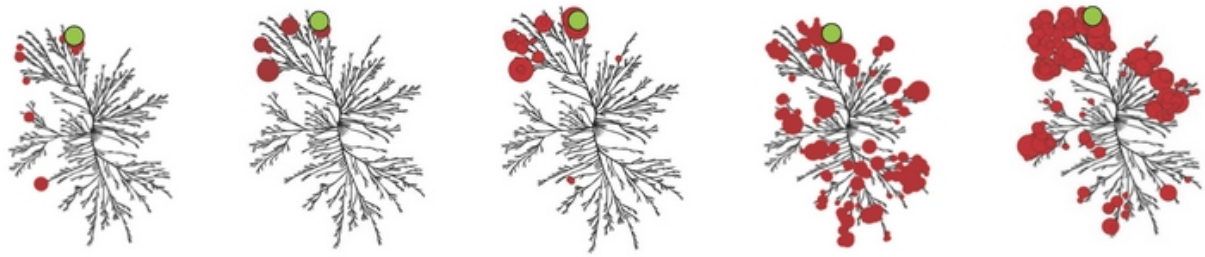
Chief Medical Officer

blueprint MEDICINES

Systemic mastocytosis represents the largest opportunity for avapritinib

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content.

Avapritinib was specifically designed to inhibit KIT D816V



avapritinib | Gleevec® (imatinib) | masitinib | Rydapt® (midostaurin) | ripretinib

Binding to KIT | Binding to other kinases (size is proportional to binding)

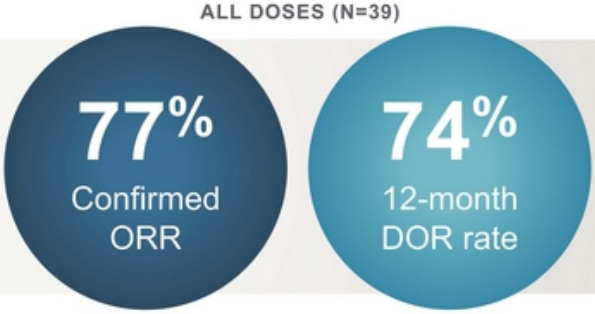
KIT D816V biochemical IC_{50}				
avapritinib*	imatinib*	masitinib#	midostaurin*	ripretinib#
0.27 nM	8150 nM	>1000 nM	2.9 nM	2.6 nM

Biochemical binding by DiscoverRX at 3uM

*Evans EK et al. Sci Transl Med. 2017;9(414). #Blueprint Medicines internal data on file. Kinome illustrations reproduced courtesy of Cell Signaling Technology, Inc. (CSTI) (www.cellsignal.com). Blueprint Medicines is not responsible for the content of the CSTI site. The trademarks appearing in this presentation are the property of their respective owners.

EXPLORER data showed profound clinical activity in patients with advanced SM

BEST RESPONSE PER IWG-MRT-ECNM CRITERIA[1] ALL DOSES (N=39)



BREAKTHROUGH THERAPY DESIGNATION[2]

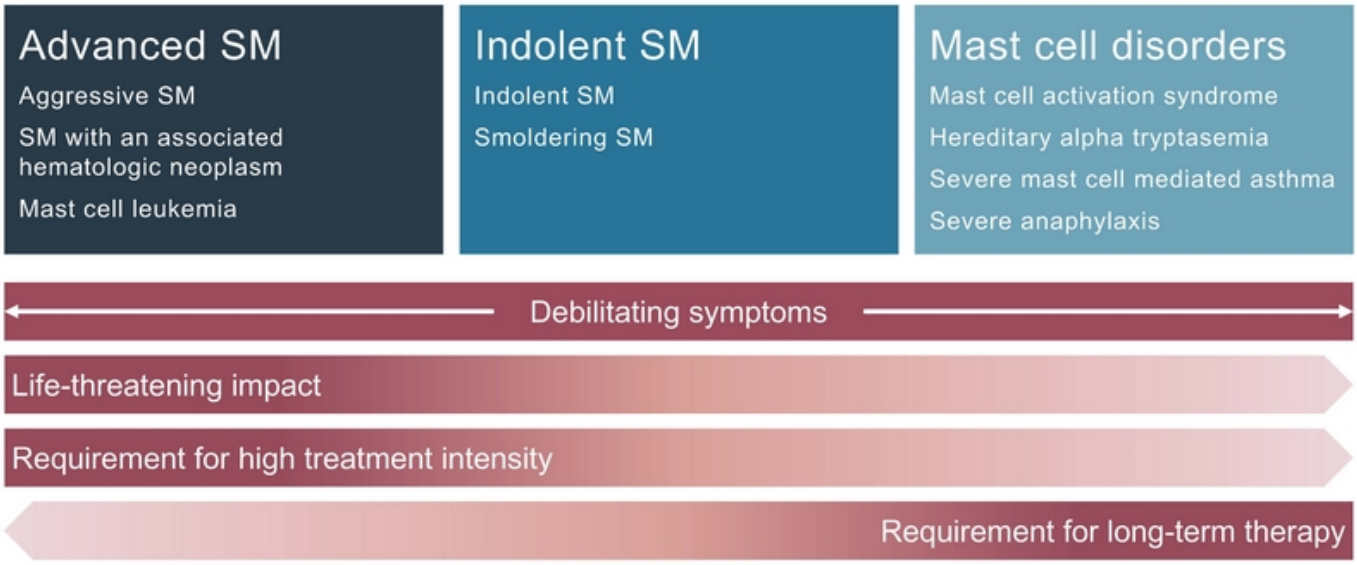
Plan to submit NDA for avapritinib for advanced SM in Q1 2020, based on combined data from EXPLORER and PATHFINDER trials

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

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



Comprehensive systemic mastocytosis clinical trial program

EXPLORER

Advanced SM

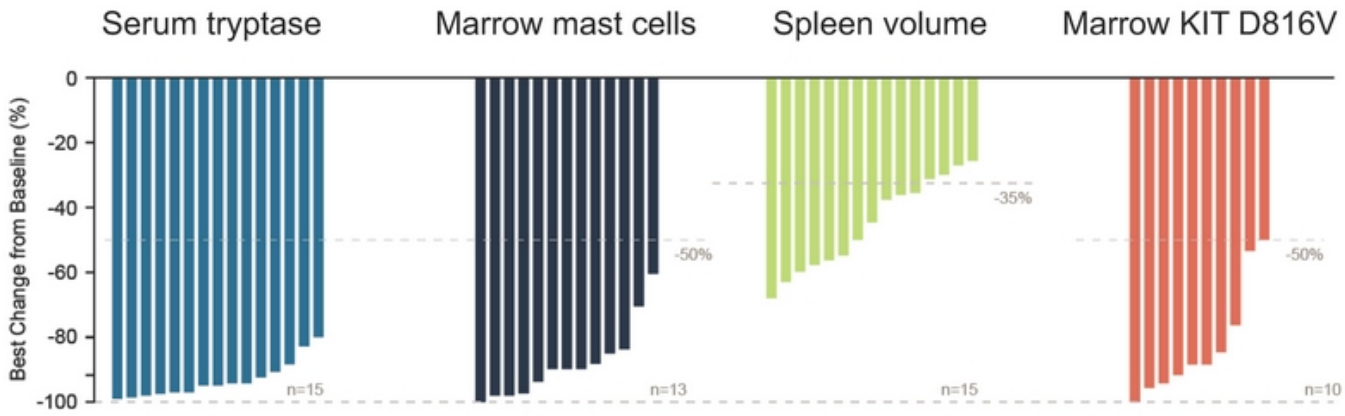
Phase 1 dose-escalation trial
with open-label expansion

PATHFINDER

Advanced SM

Phase 2 single-arm trial

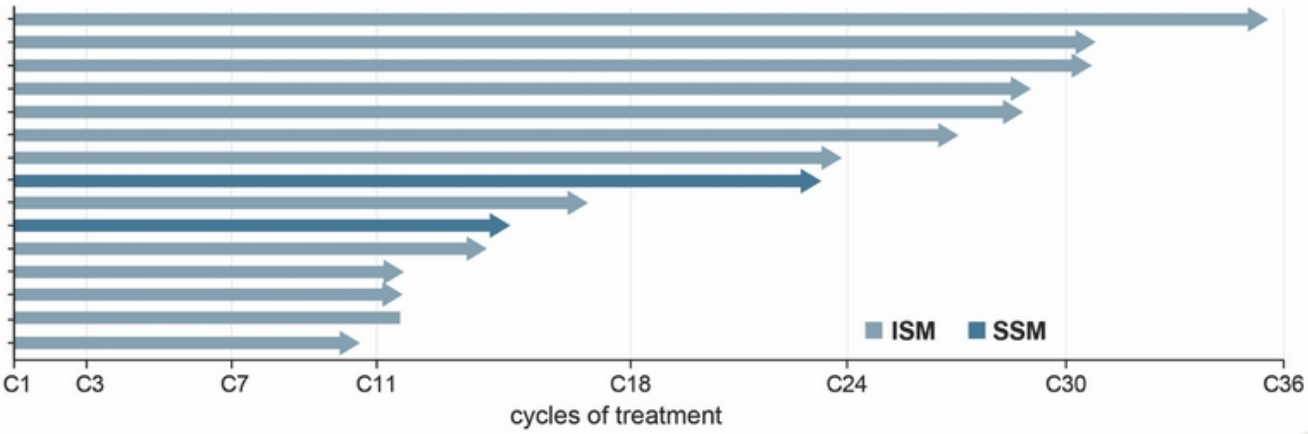
Indolent SM patients enrolled in EXPLORER trial had deep reductions on objective measures of mast cell burden



Data presented at the European Hematology Association Annual Meeting in June 2019. Data cutoff date: January 2, 2019.

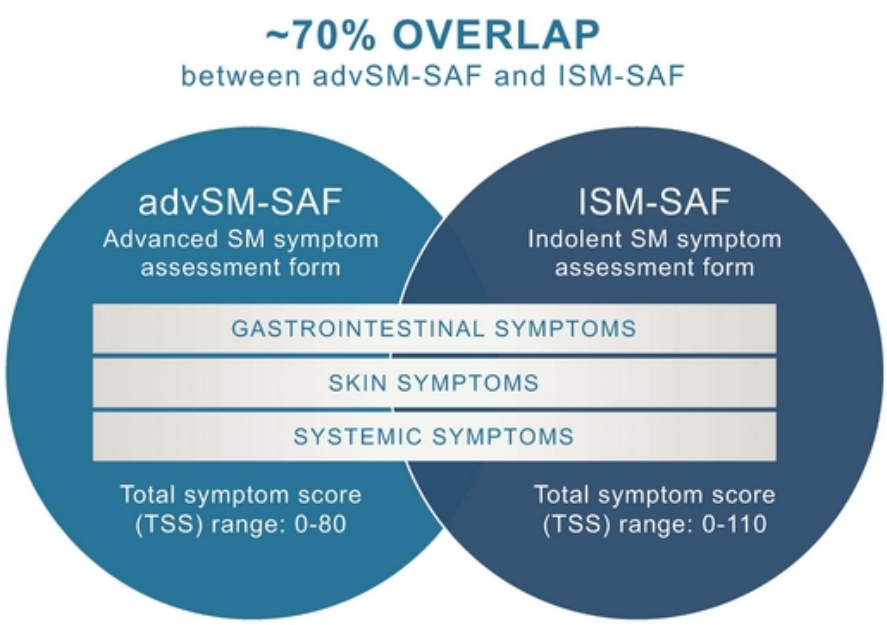
EXPLORER data show ISM and SSM patients with long durations of therapy at low doses

- 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

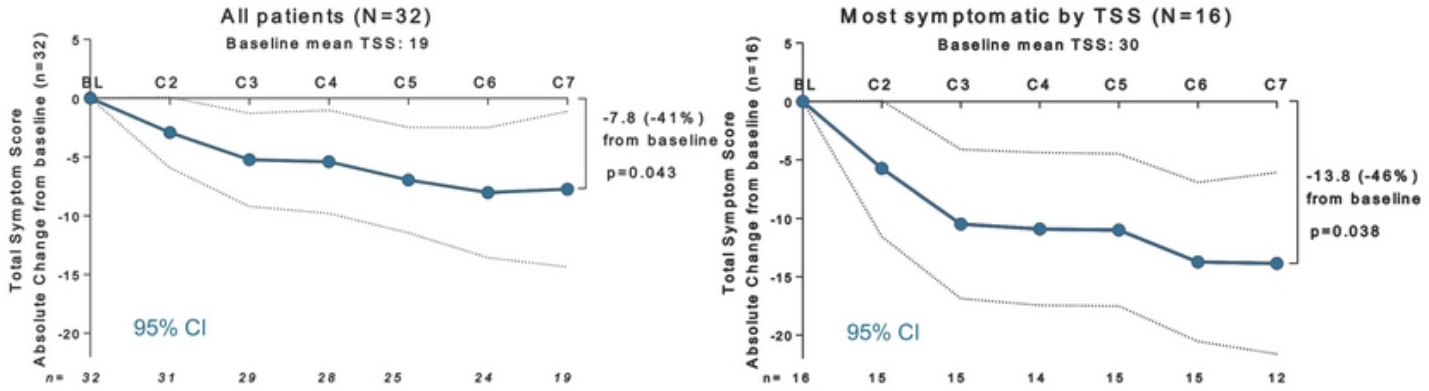


New analysis from EXPLORER trial. Data cutoff date: January 2, 2019.
ISM, indolent SM; QD, once daily; SSM, smoldering SM.

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



EXPLORER data showed significant symptom improvements on advSM-SAF

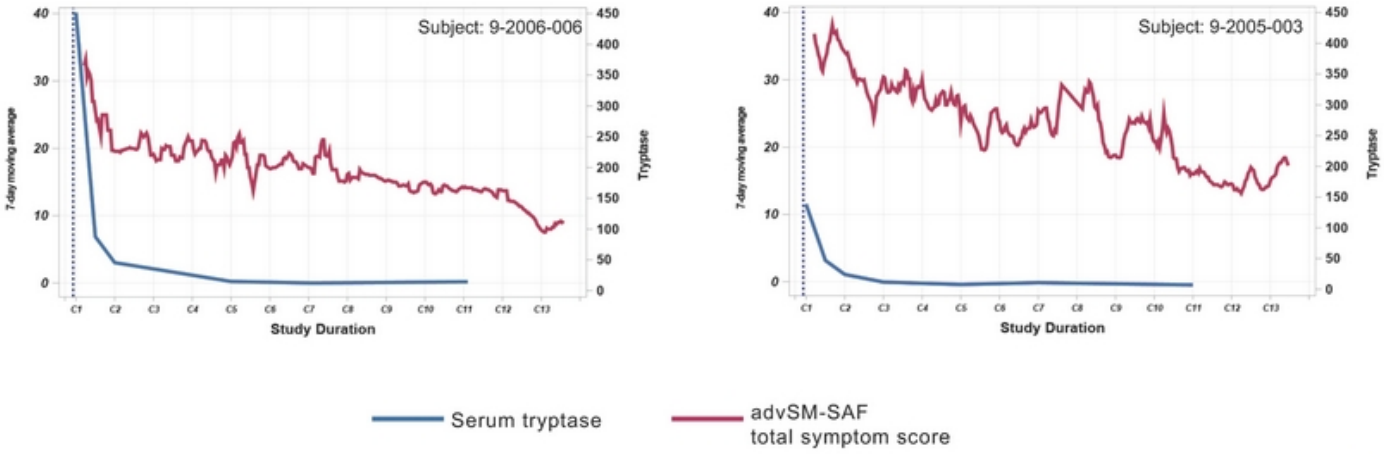


~40% MEAN REDUCTION OF SYMPTOMS FROM BASELINE TSS

Data previously presented at ASH Annual Meeting in December 2018. Data cutoff date: September 30, 2018.
TSS, total symptom score. CI, confidence interval.

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

SERUM TRYPTASE VERSUS ADVSM-SAF TOTAL SYMPTOM SCORE



New analysis from EXPLORER trial. Data cutoff date: January 2, 2019.

EXPLORER data showed reduction in polypharmacy burden

EXPLORER

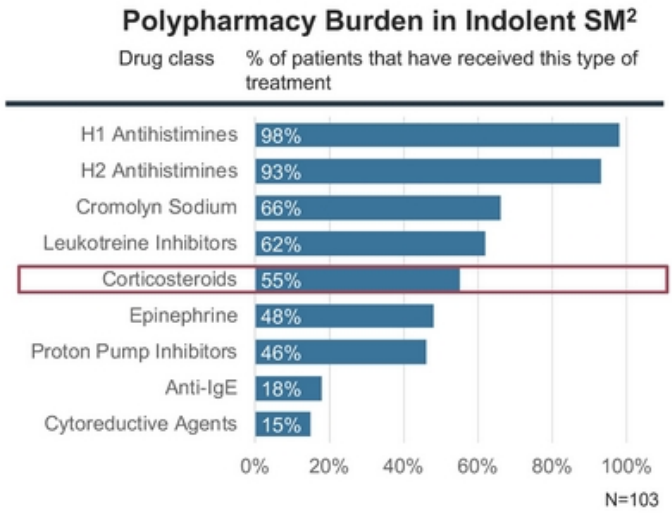
Advanced SM

Phase 1 dose-escalation trial
with open-label expansion

Concomitant Medication Analysis[1]

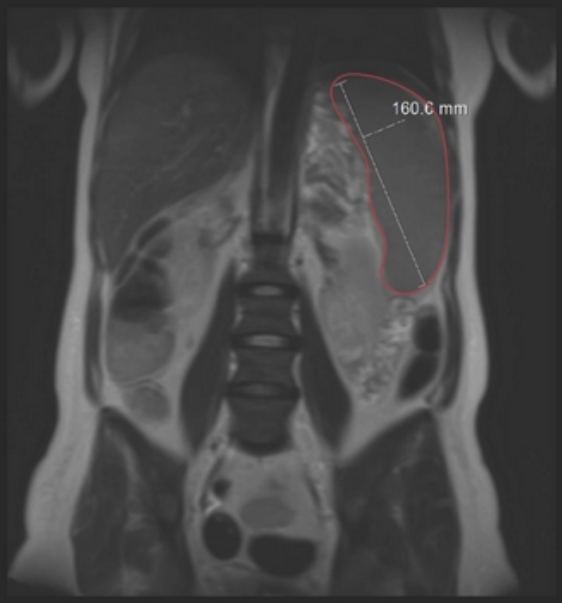
Of 22 patients with baseline corticosteroids:

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

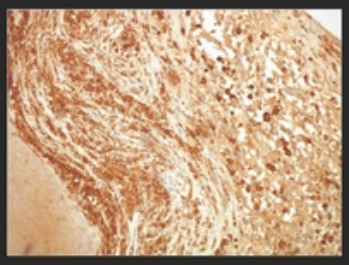


1 Data previously presented at ASH Annual Meeting in December 2018. Data cutoff date: September 30, 2018. 2 Indolent Systemic Mastocytosis Symptom Assessment Form (ISM-SAF) Observational Study July 2018. Data cutoff date March 2018.

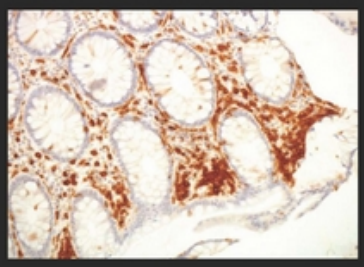
45-year-old woman with evolving systemic mastocytosis



MARROW CD117 (50% MC)



COLON CD25 (>100 MCS/HPF)



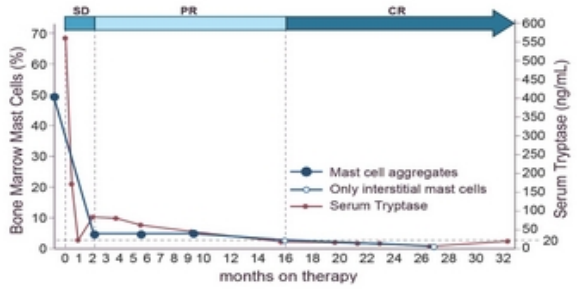
2015: Indolent systemic mastocytosis

2016: Aggressive systemic mastocytosis

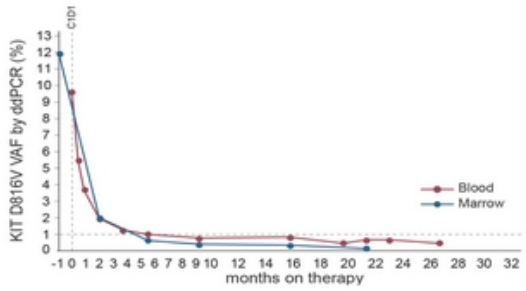
- ~30 pound weight loss in prior 6 months
- Stomach, duodenum, colon MC infiltration
- 5cm palpable splenomegaly
- Anemic (hemoglobin 9.9g/dL)
- Marrow MCs 50%, tryptase 562ng/mL
- Enrolled on EXPLORER study
- **SM-AHN** on central pathology review

Case courtesy of Dr. Deepti Radia, Guys and St. Thomas Trust. Data cutoff date: January 2, 2019.

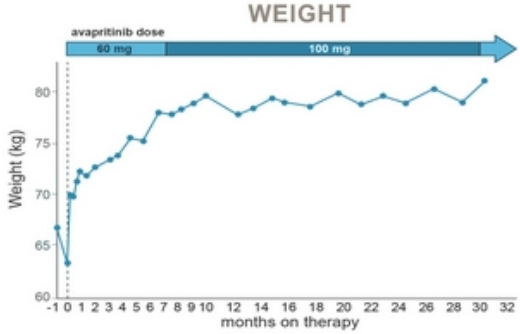
BONE MARROW MAST CELLS & SERUM TRYPTASE



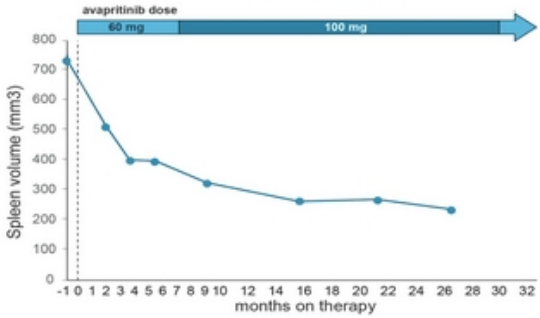
KIT D816V MUTANT ALLELE FRACTION



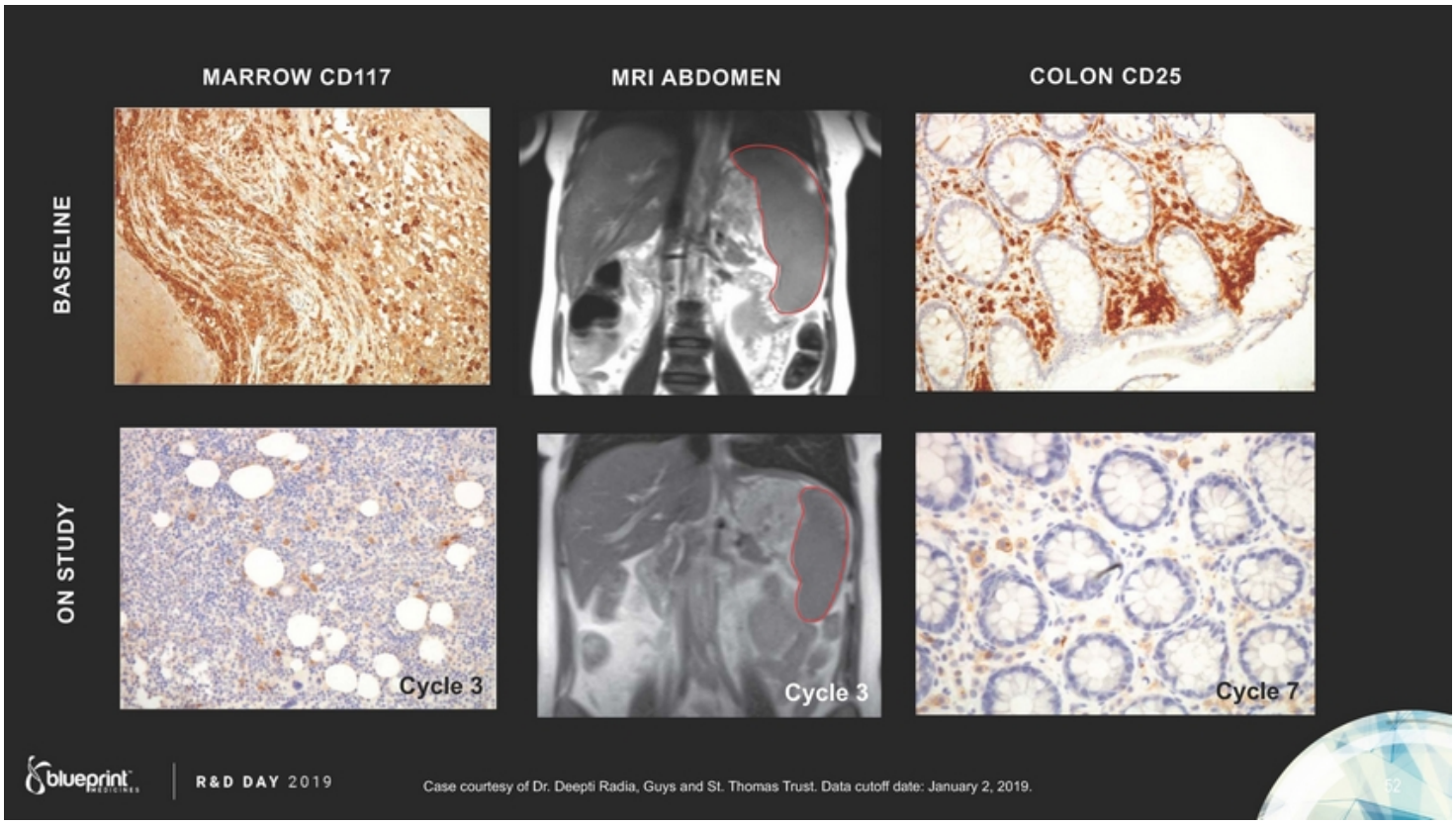
WEIGHT

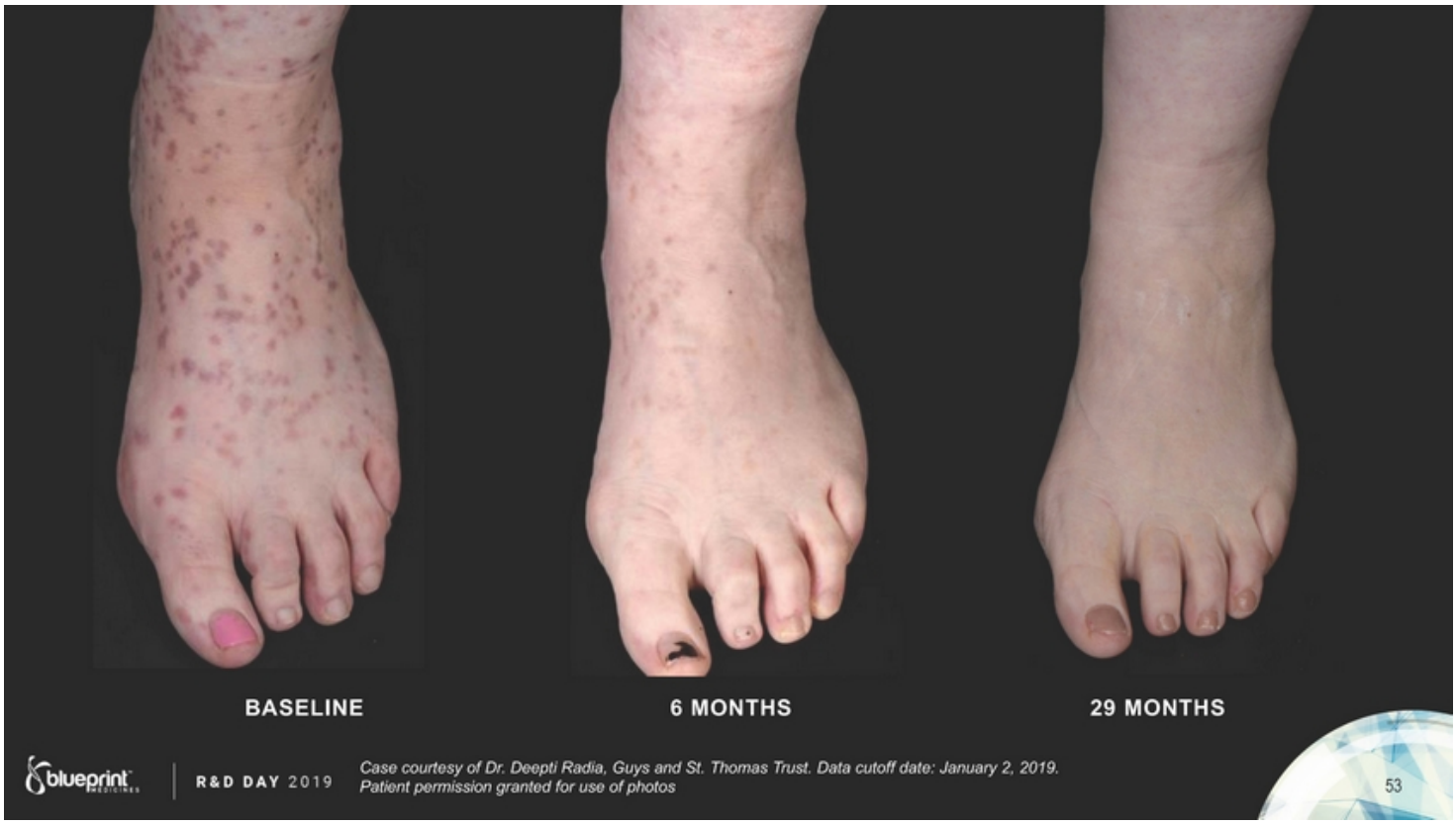


SPLEEN VOLUME



Case courtesy of Dr. Deepti Radia, Guys and St. Thomas Trust. Data cutoff date: January 2, 2019.


MARROW CD117
MRI ABDOMEN
COLON CD25
BASELINE
ON STUDY
Cycle 3
Cycle 3
Cycle 7
blueprint MEDICINES
R&D DAY 2019
Case courtesy of Dr. Deepti Radia, Guys and St. Thomas Trust. Data cutoff date: January 2, 2019.


BASELINE
6 MONTHS
29 MONTHS
blueprint MEDICINES
R&D DAY 2019
Case courtesy of Dr. Deepti Radia, Guys and St. Thomas Trust. Data cutoff date: January 2, 2019.
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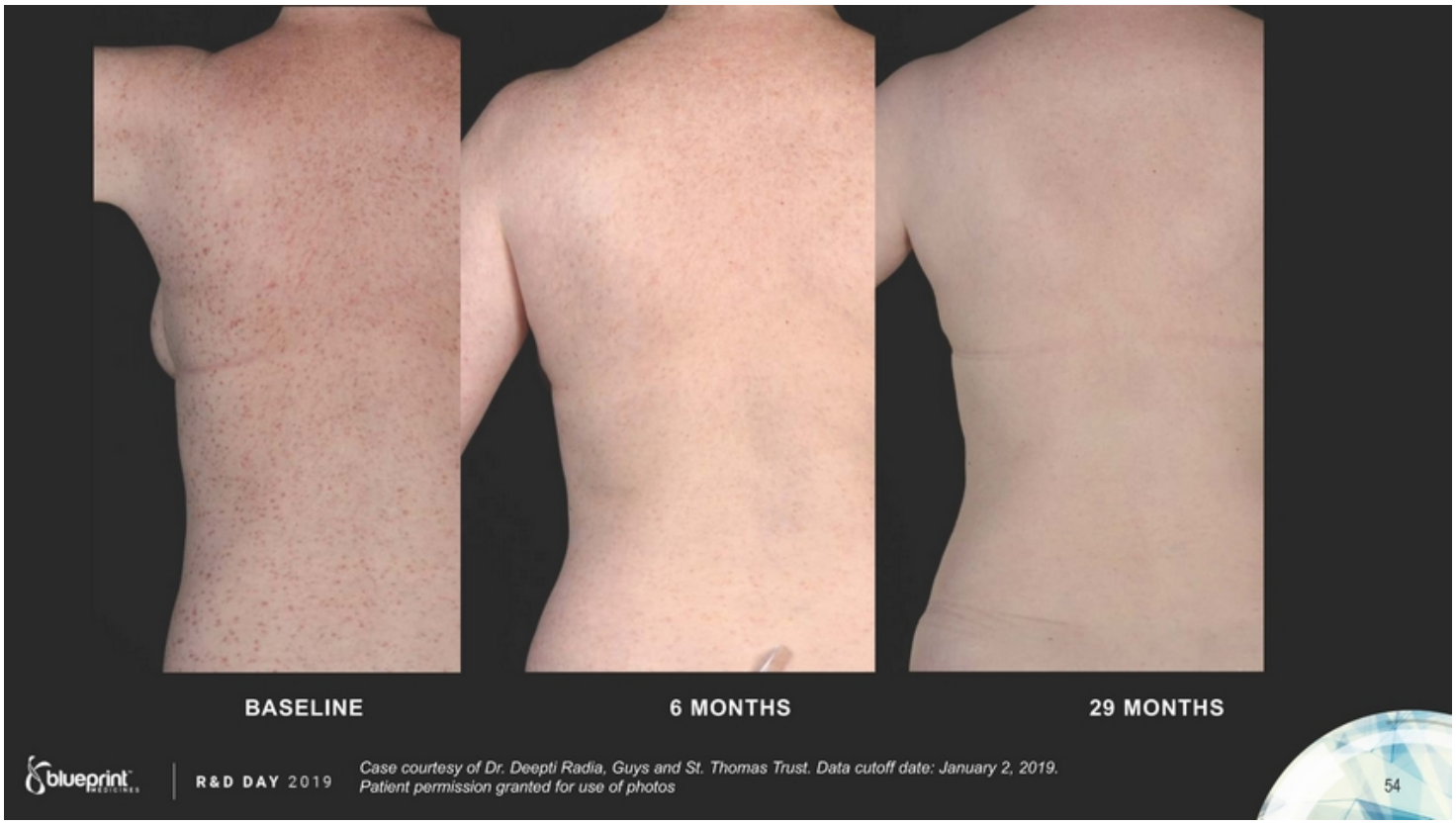

blueprint MEDICINES | R&D DAY 2019

Case courtesy of Dr. Deepti Radia, Guys and St. Thomas Trust. Data cutoff date: January 2, 2019.
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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

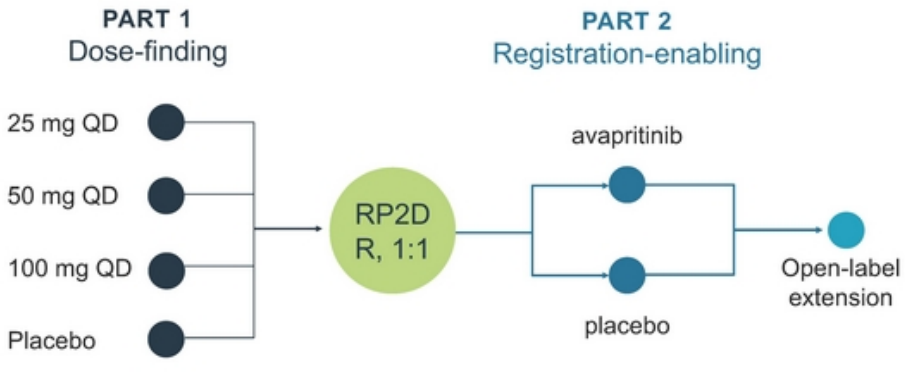
Phase 2 randomized, double-blind,
placebo-controlled trial

PIONEER trial designed to evaluate avapritinib in indolent SM

PIONEER

Indolent SM

Phase 2 registration-enabling randomized, placebo-controlled trial inpatients 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[1]
- Plan to disclose initial data from Part 1 at ASH meeting in December 2019
  - Investor event and webcast planned for Sunday, December 8

[1] As of November 1, 2019. R, randomized; RP2D, recommended part 2 dose; ASH meeting, American Society of Hematology Annual Meeting & Exposition

A comprehensive program for mast cell disorders

CHRISTINA ROSSI

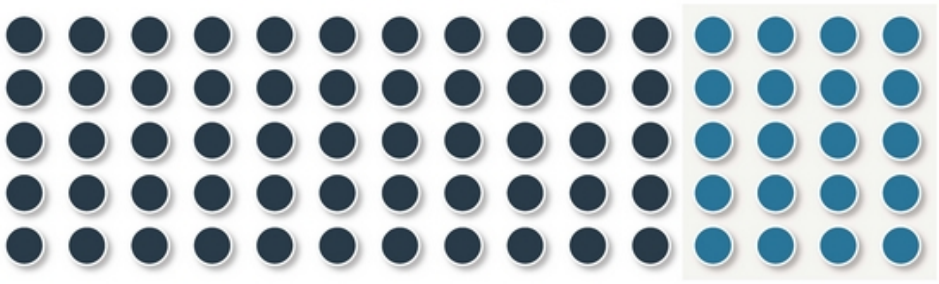
Chief Commercial Officer

blueprint MEDICINES

Expanded SM opportunity based on increased understanding of the disease

SYSTEMIC MASTOCYTOSIS EPIDEMIOLOGY

~75,000
prevalent patients in major markets[1]



~20,000 patients are identifiable within claims data in the United States[2]

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

Major markets include US, EU5 and Japan. 1. Cohen S et al Br J Haematol (2014) 166(4):521-8 and World Bank Population estimates. 2. Blueprint Medicines analysis of claims data for mastocytosis.

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

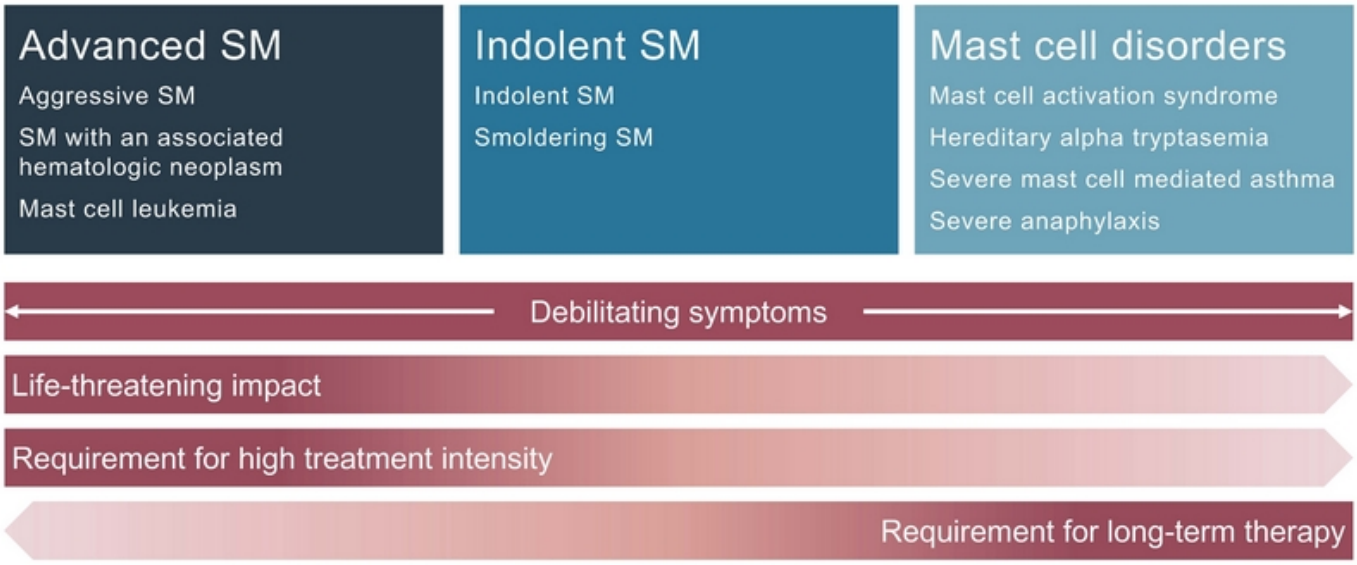
INDICATION EXPANSION

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



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

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

CNS, central nervous system; IND application, investigational new drug application..

BLU-263: a compelling preclinical profile

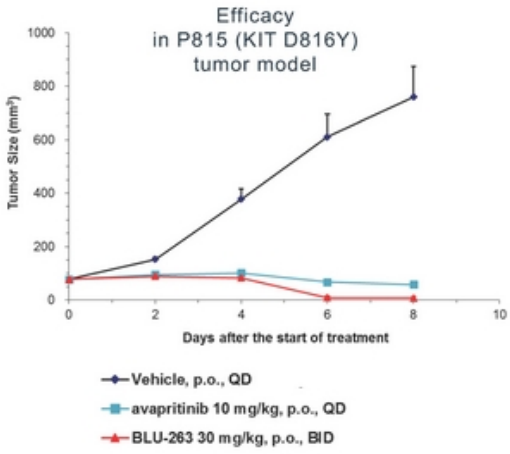
EQUIVALENT POTENCY

Compound	KIT D816V IC_{50} (nM)	PDGFRA D842V IC_{50} (nM)	KIT V560G/D816V IC_{50} (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_{50}	280 nM	>10 µM
Rat $K_{p,uu}$ homogenate	0.40	0.024

EQUIVALENT IN VIVO EFFICACY



BID, twice daily.

Ongoing avapritinib clinical trials

Advanced SM

Aggressive SM

SM with an associated hematologic neoplasm

Mast cell leukemia

AVAPRITINIB EXPLORER

AVAPRITINIB PATHFINDER

Indolent SM

Indolent SM

Smoldering SM

AVAPRITINIB PIONEER

Mast cell disorders

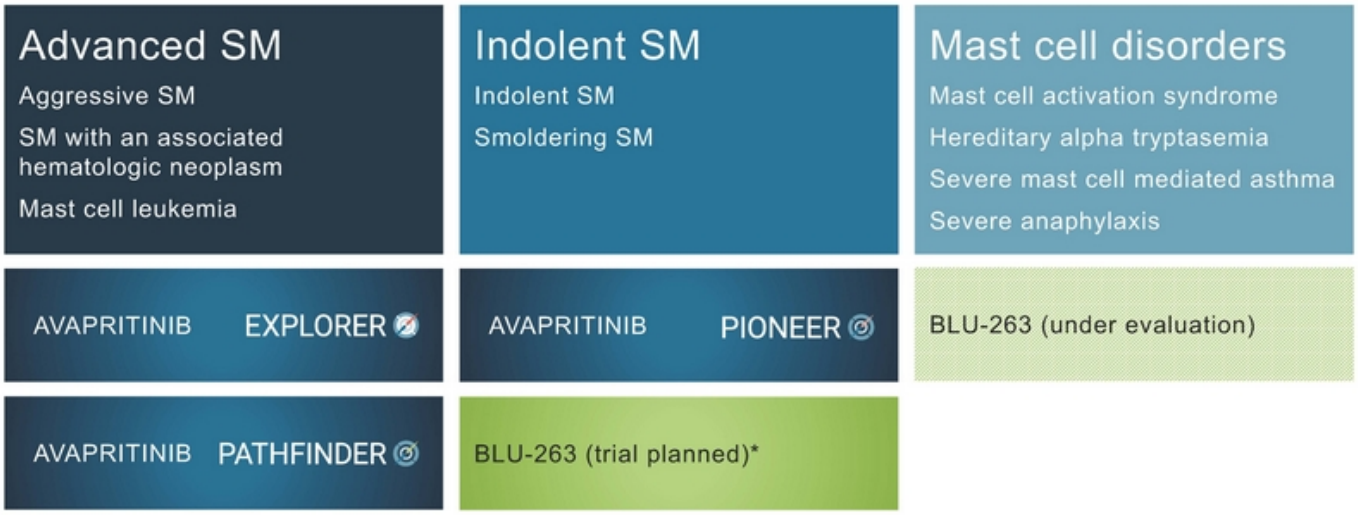
Mast cell activation syndrome

Hereditary alpha tryptasemia

Severe mast cell mediated asthma

Severe anaphylaxis

Planned BLU-263 clinical trial and future potential exploration



* Plan to submit IND application in 1H 2020.

blueprint MEDICINES

Q&A


break
blueprint
MEDICINES

A prolific platform for precision medicine

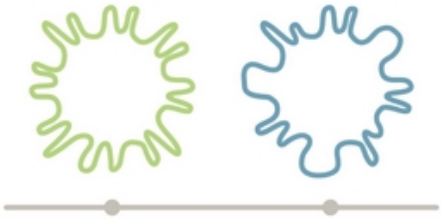
MARION DORSCH, PhD

Chief Scientific Officer

blueprint MEDICINES

Cancer is a genetic disease that evolves and becomes more elusive

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

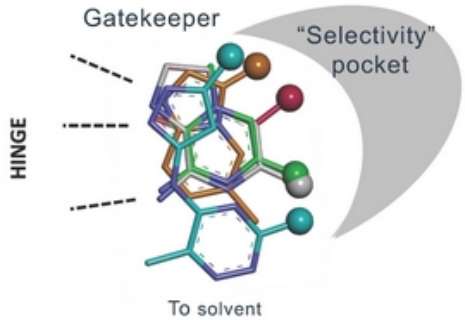
- New insights into the biology of kinases as disease drivers
- Identification of new drug targets from Kinases of Unknown Biology (KUBs)

HIGHLY SELECTIVE AND POTENT KINASE INHIBITOR DRUG CANDIDATES

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content.

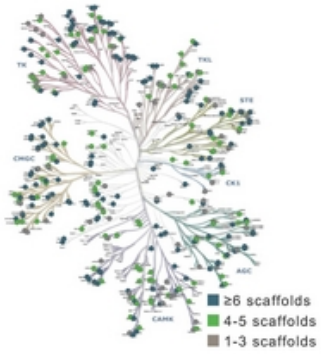
Isolate selective starting points within our proprietary compound library

Rationally designed



<1% overlap with 70M compounds in PubChem

Broad and deep kinome coverage



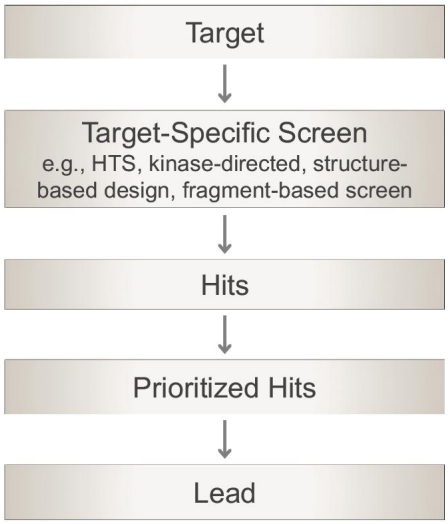
DESIGNED TO BALANCE NOVELTY, POTENCY, AND SELECTIVITY

SCREENED AGAINST A LARGE PANEL OF KINASES

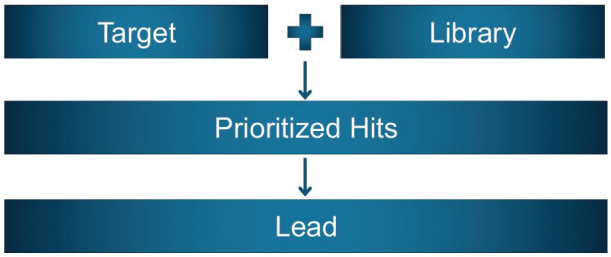
ITERATIVE PROCESS

Accelerate the discovery process by shortening the time to lead identification

TRADITIONAL APPROACH



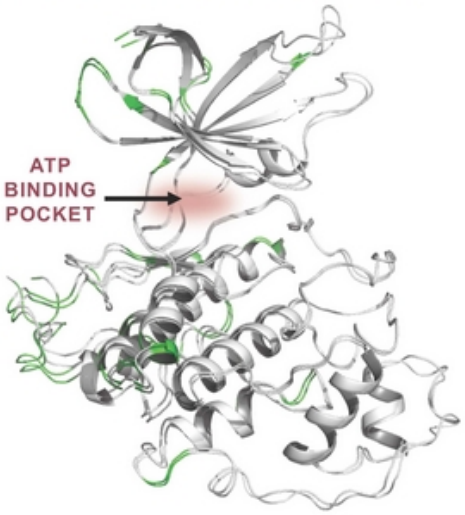
BLUEPRINT MEDICINES' ACCELERATED APPROACH

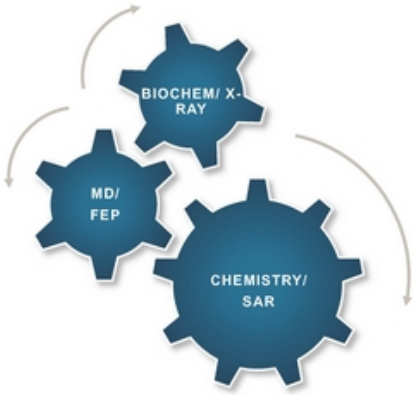


- ✓ No target-specific screen needed
- ✓ Annotation yields prioritized hits
- ✓ Full understanding of selectivity
- ✓ Informed optimization

Refine selectivity against challenging targets by integrating data

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

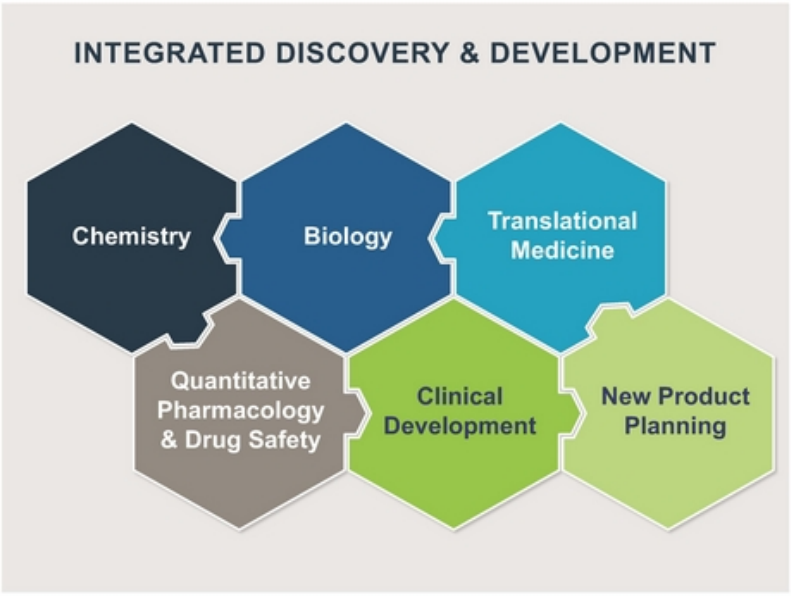


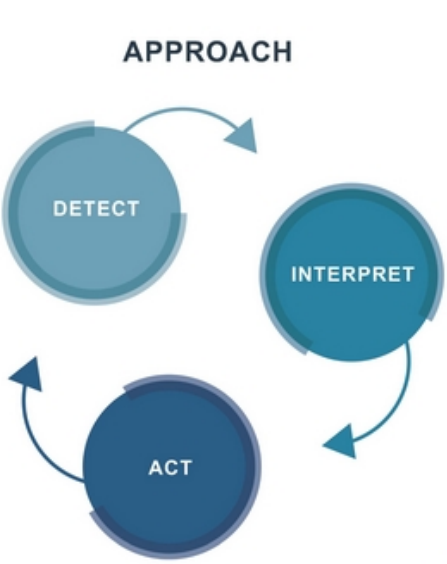


- Structural bioinformatics
- Molecular Dynamics (MD)
- Free Energy Perturbations (FEP)
- Cheminformatics

ATP, adenosine triphosphate.

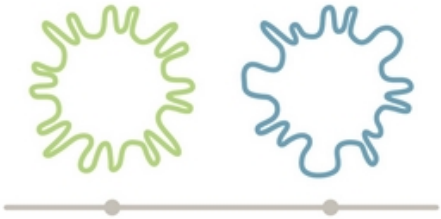
A closely integrated discovery model enables sustainable innovation





Cancer is a genetic disease that evolves and becomes more elusive

Cancer is a disease driven by genomic aberrations

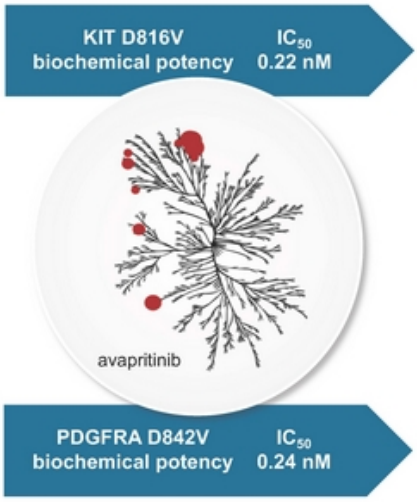


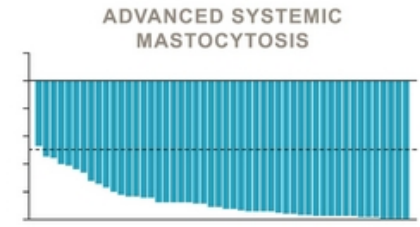
Cancer evolves over time with new molecular changes

Tumors and their microenvironments are inherently complex

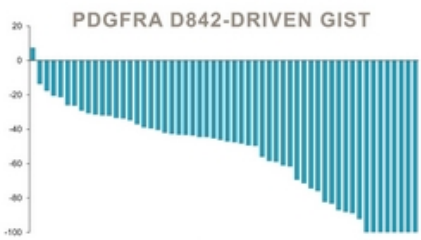
Rapidly drive to transformative outcomes in early clinical testing

Cancer is a disease driven by genomic aberrations





Maximum reduction in serum tryptase[1]



Maximum reduction in target tumors[2]

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content. 1. Data presented at the European Hematology Association Annual Meeting in June 2019. Data cutoff date: January 2, 2019. 2. Data presented at ASCO 2019 Annual Meeting on June 1, 2019. Data cutoff date: November 16, 2018.

Leverage clinical insights to enable next generation inhibitors

Cancer is a disease driven by genomic aberrations

EQUIVALENT POTENCY

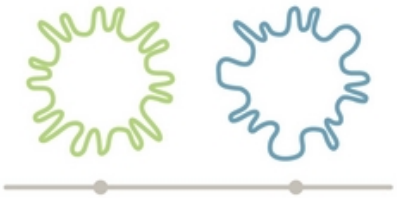
IMPROVED SELECTIVITY

LOWER CNS PENETRATION

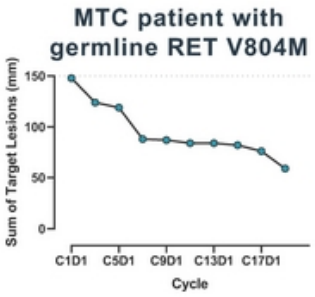
Biochemical potency (IC_{50}, nM)

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



Cancer evolves over time with new molecular changes



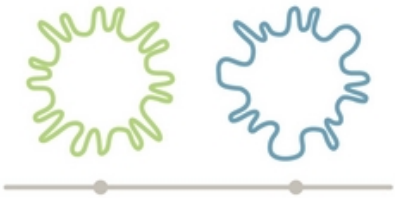
Ongoing PR >19 months

Biochemical potency (IC_{50}, 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

Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content. PR, partial response.

Navigate challenging target profiles to tackle tumor evolution



Cancer evolves over time with new molecular changes

EGFR+ NSCLC treatment paradigm

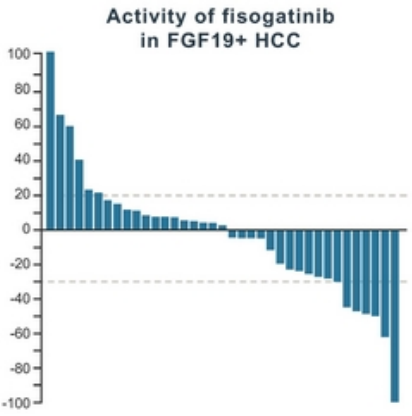
Osimertinib → **2L EGFR inhibitor**

OPTIMAL PROFILE		
Potency against activating and resistance mutants	Selectivity over wild-type EGFR	Enabled for CNS activity

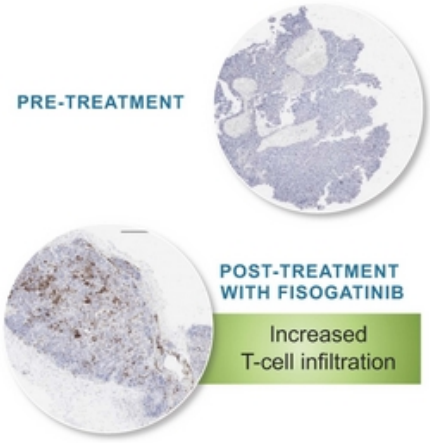
Interrogate mechanisms to identify transformative combination opportunities

Tumors and their microenvironments are inherently complex

CLINICAL PROOF-OF-CONCEPT DATA[1]



HUMANIZED PRECLINICAL MODEL

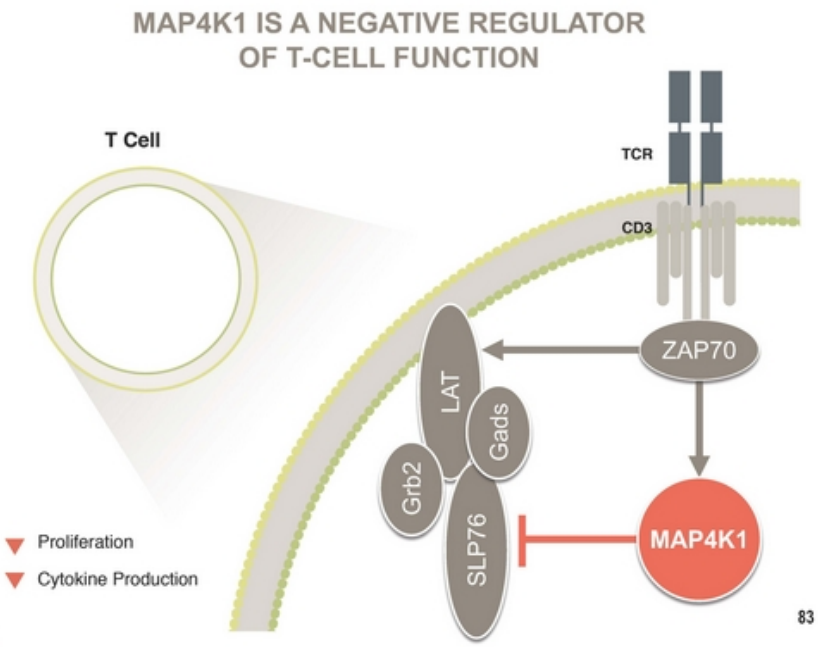


Plan to initiate combination trial of fisogatinib and CStone's anti-PDL1 CS-1001 in Q4 2019

[1] Data presented at ILCA annual meeting in September 2017. Data cutoff date: August 18, 2017.

Harness the immune system to attack complex tumors

Tumors and their microenvironments are inherently complex



Hernadez, et al. Cell Reports, 2018.

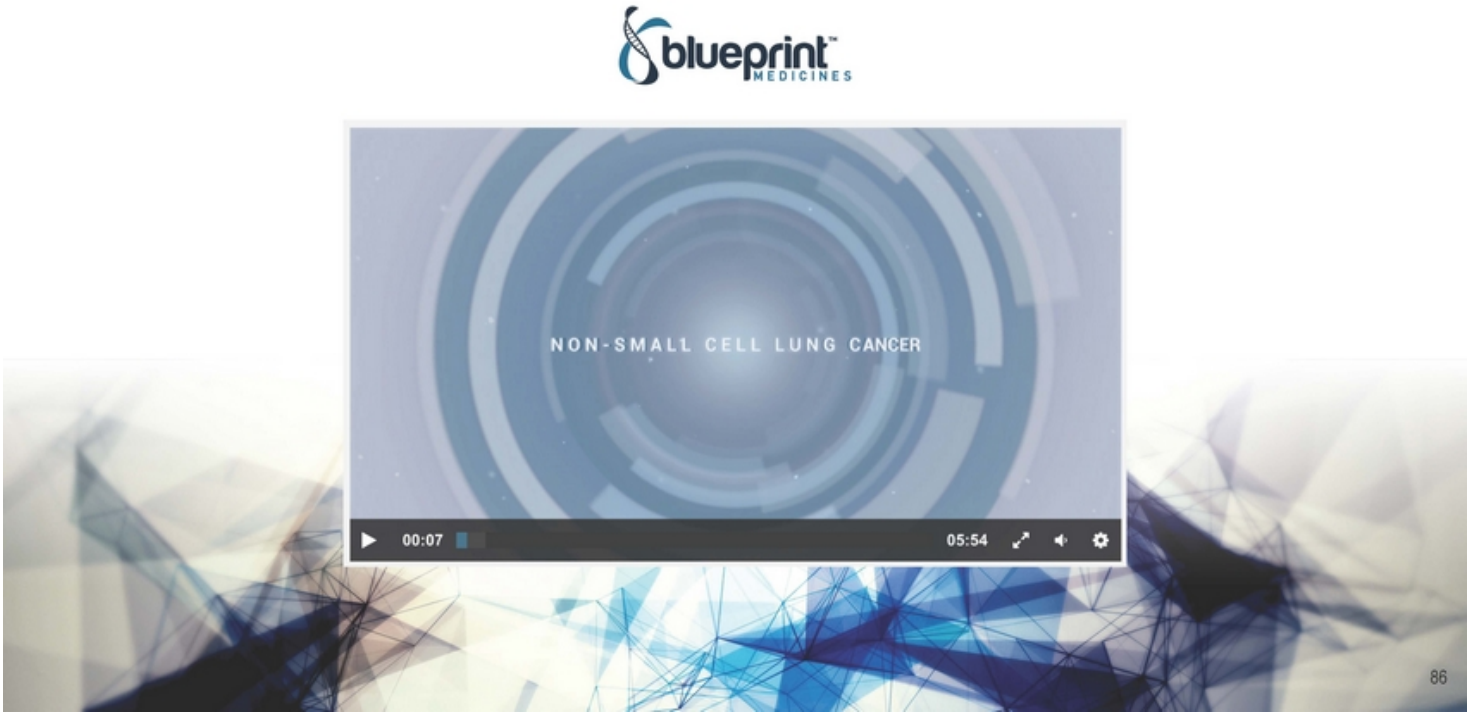
Blueprint Medicines is built to tackle the challenges of treating cancer

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


blueprint MEDICINES
NON-SMALL CELL LUNG CANCER
00:07
05:54
86

Addressing tumor evolution in lung cancer

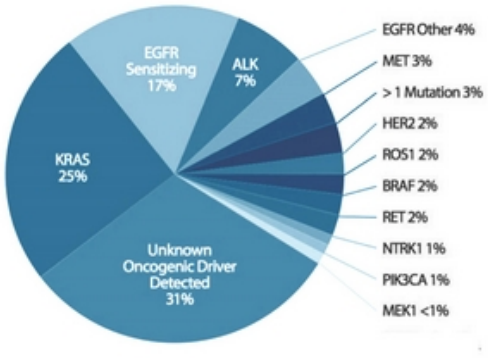
TIM GUZI, PhD

Senior Vice President, Chemistry

blueprint MEDICINES

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

IDENTIFIABLE ONCOGENIC DRIVERS[1]



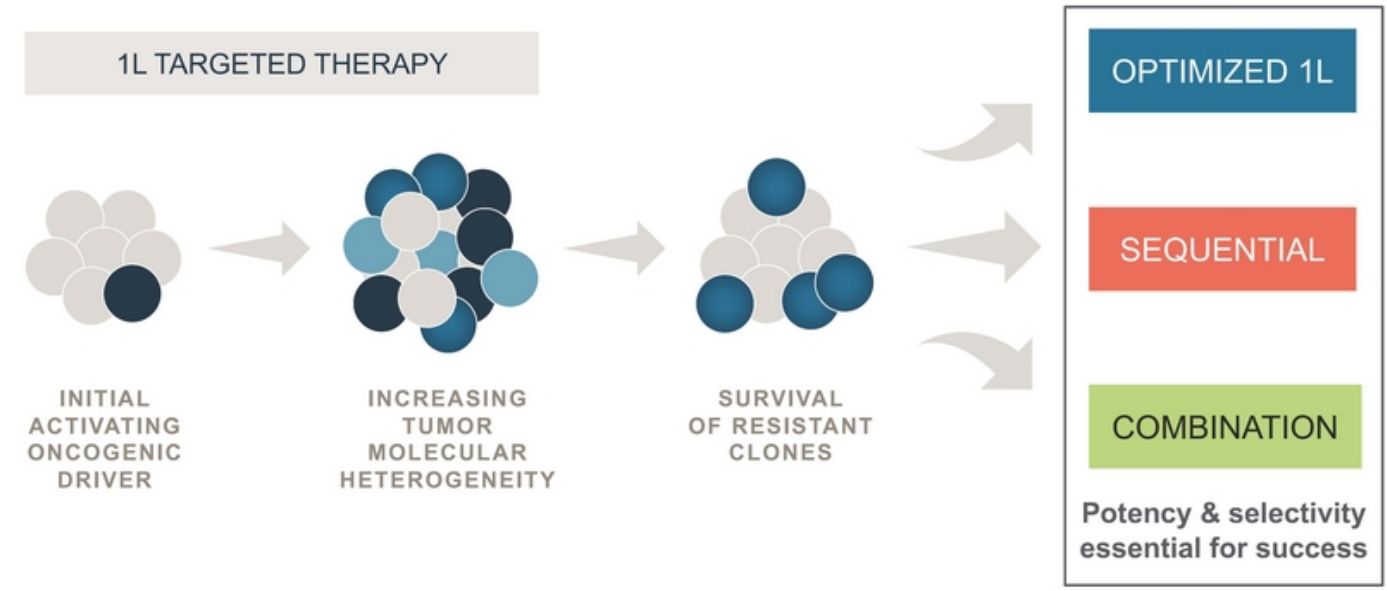
EVOLVING NSCLC TESTING PARADIGM

- ~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[2]

[1] Oncogenic drivers in lung adenocarcinoma. Lung Cancer Foundation of America website (www.lcfamerica.org). Accessed October 27, 2019.
[2] Key Statistics for Lung Cancer. American Cancer Society website (www.cancer.org). Accessed October 27, 2019.

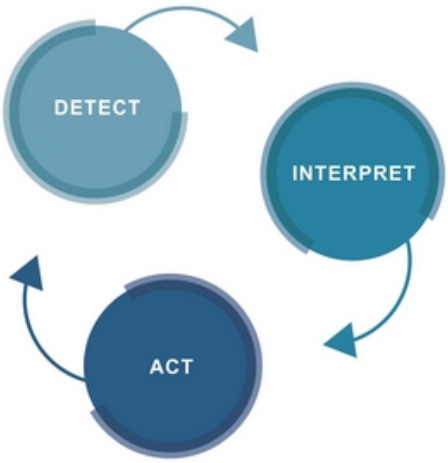
Tumor evolution and three approaches for achieving durable patient benefit



A closely integrated discovery model enables sustainable innovation

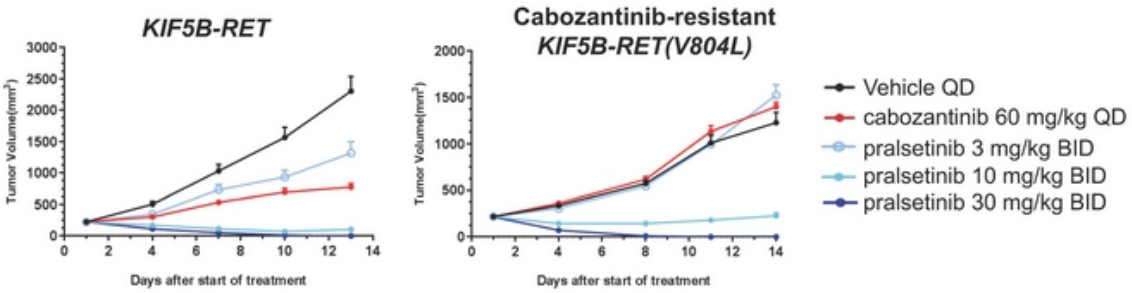
INTEGRATED DISCOVERY & DEVELOPMENT

APPROACH



NSCLC patients with RET fusions have no highly effective treatment options

Pralsetinib: high kinome selectivity for RET

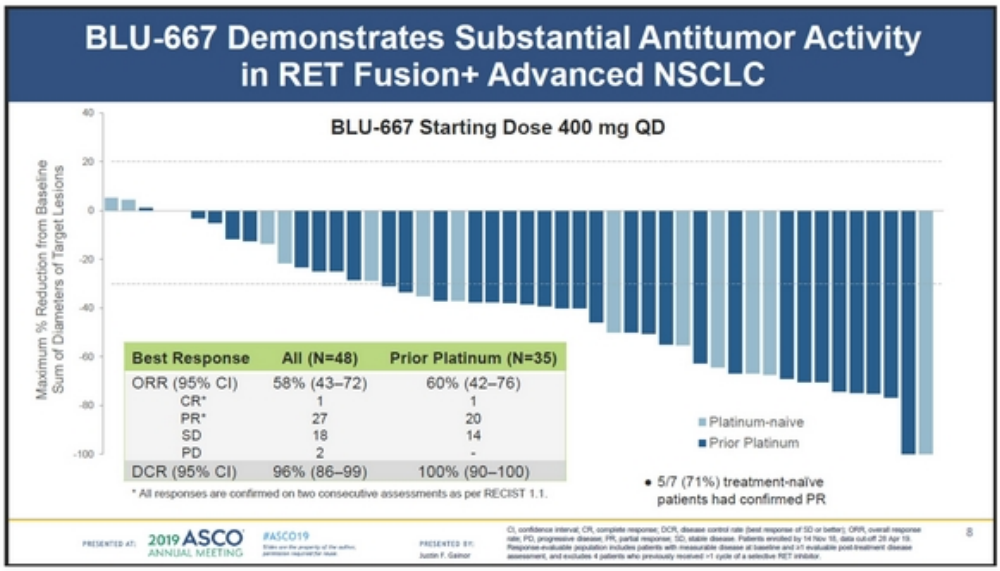


RET+ NSCLC

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

Kinome illustration reproduced courtesy of Cell Signaling Technology Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content. [1] Mazieres, et al. JCO 2018. [2] Drillon, et al. Lancet 2017. [3] Yoh, et al. Lancet Respir Med 2017.

Promising data supporting pralsetinib in RET+ NSCLC

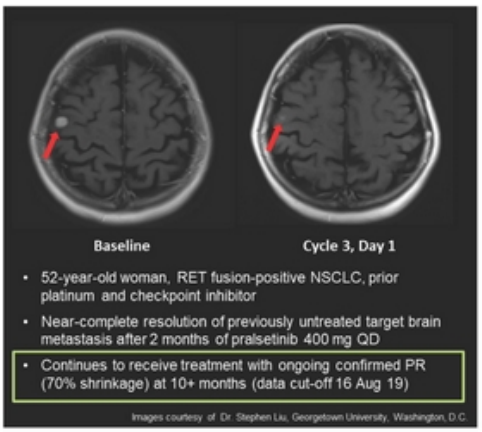


Gainor, et al. ASCO, 2019.

Data presented at ASCO Annual Meeting in June 2019. Data cutoff date: April 28, 2019.

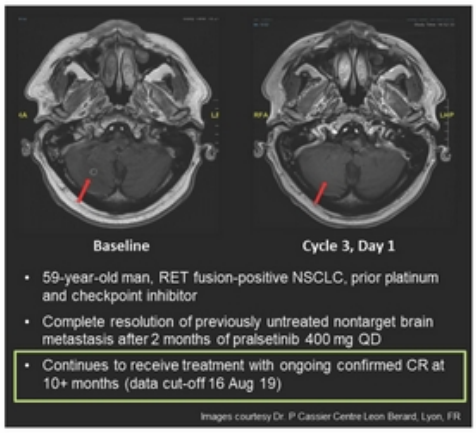
Evidence of durable CNS activity with pralsetinib

Pralsetinib was active against intracranial metastases in the clinical setting



- 52-year-old woman, RET fusion-positive NSCLC, prior platinum and checkpoint inhibitor
- Near-complete resolution of previously untreated target brain metastasis after 2 months of pralsetinib 400 mg QD
- Continues to receive treatment with ongoing confirmed PR (70% shrinkage) at 10+ months (data cut-off 16 Aug 19)

Images courtesy of Dr. Stephen Liu, Georgetown University, Washington, D.C.



- 59-year-old man, RET fusion-positive NSCLC, prior platinum and checkpoint inhibitor
- Complete resolution of previously untreated nontarget brain metastasis after 2 months of pralsetinib 400 mg QD
- Continues to receive treatment with ongoing confirmed CR at 10+ months (data cut-off 16 Aug 19)

Images courtesy Dr. P Cassier Centre Leon Berard, Lyon, FR

Evans, et al. IASLC, 2019.

Data presented at IASLC World Conference on Lung Cancer in September 2019. Data cutoff date: August 16, 2019.

Case reports highlight the potential for combination therapy with pralsetinib

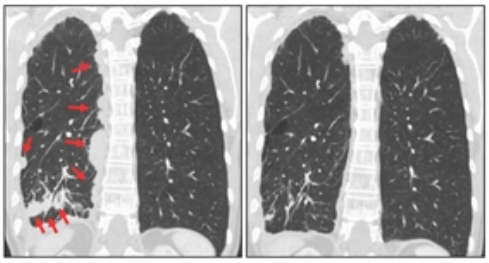
IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

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

Data presented at IASLC World Conference on Lung Cancer in September 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[1]

HIGH RESPONSE RATES AND DURABLE ACTIVITY
in NSCLC and MTC patients[1]

FDA BREAKTHROUGH THERAPY DESIGNATIONS
for NSCLC and MTC

STRONG ACTIVITY AGAINST BRAIN METASTASES
in patients with NSCLC[1]

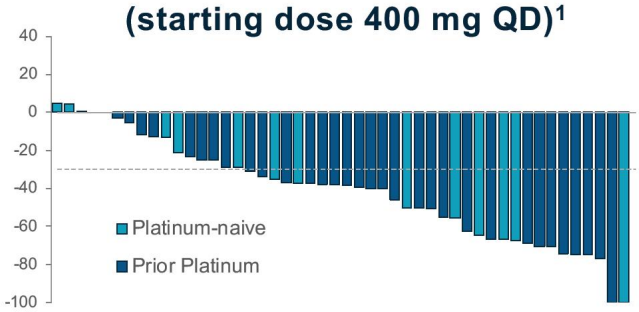
WELL-TOLERATED WITH LOW DISCONTINUATION RATES
in advanced cancer populations[1]

1. Data presented at ASCO Annual Meeting in June 2019. Data cutoff date: April 28, 2019.

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

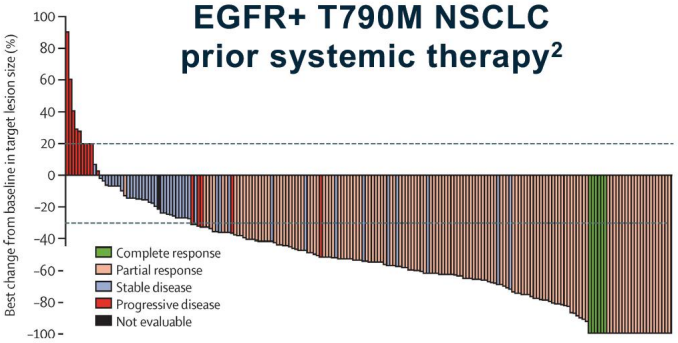
PRALSETINIB

RET fusion+ NSCLC (starting dose 400 mg QD)[1]



OSIMERTINIB

EGFR+ T790M NSCLC prior systemic therapy[2]



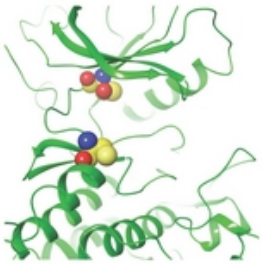
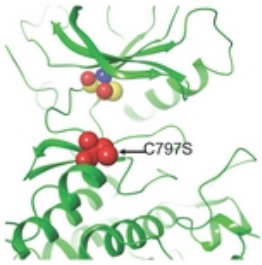
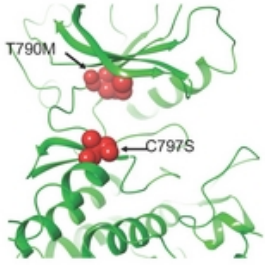
1 Data presented at ASCO Annual Meeting in June 2019. Includes NSCLC patients treated at the recommended Phase 2 dose of 400 mg QD and enrolled as of November 14, 2018 with follow-up through a data cutoff date of April 28, 2019. m, months. 2 The Lancet Oncology 2016 17, 1643-1652DOI: (10.1016/S1470-2045(16)30508-3).

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

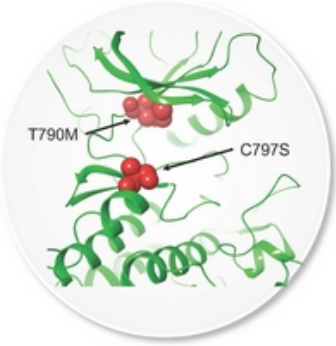
First-in-class EGFR inhibitors

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	+ C797S	+ T790M and C797S
		
EGFR+	CS	TMCS
ONCOGENIC DRIVER	FOLLOWING 1L OSIMERTINIB	FOLLOWING 2L OSIMERTINIB

Our vision: optimized EGFR+ treatment regardless of prior therapy

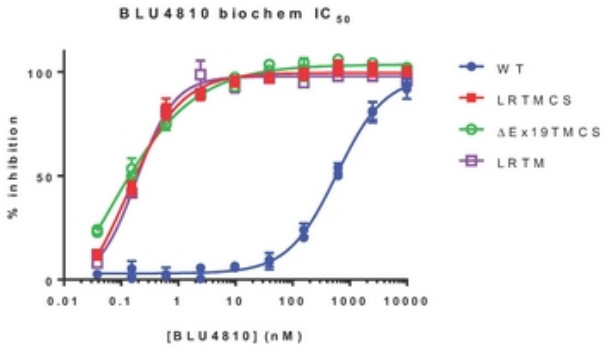


1st generation EGFR TKI → Osimertinib → **Blueprint EGFR+ LRTMCS**

TKI, tyrosine kinase inhibitor.

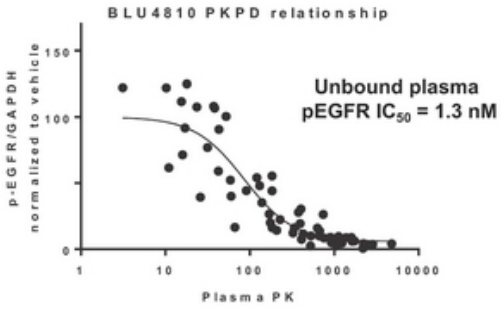
BLU4810 is a potent and selective EGFR+ TMCS inhibitor

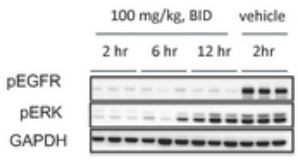
POTENT AGAINST RESISTANT EGFR MUTANTS AND SELECTIVE OVER WILD-TYPE (WT) EGFR



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

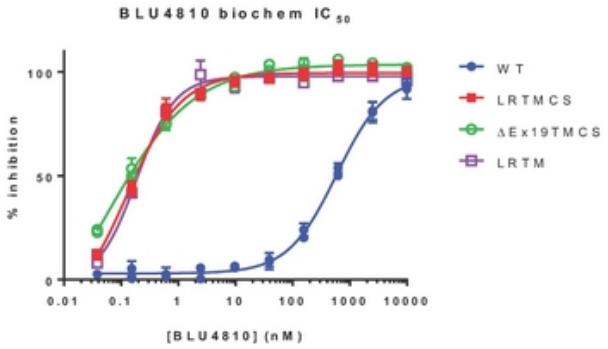
>IC90 COVERAGE FOR 12 HOURS





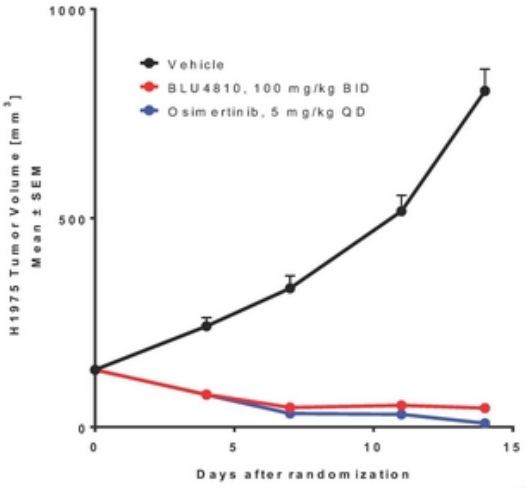
BLU4810 is a potent and selective EGFR+ TMCS inhibitor

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



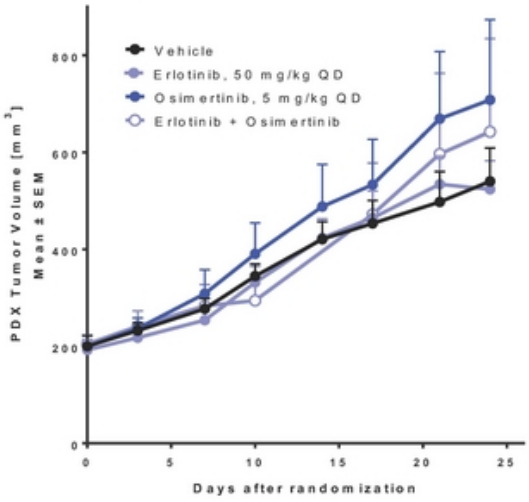
- Potent against double and triple EGFR resistant mutants
- Highly selective over wild-type EGFR
- Robust in vivo growth inhibition comparable to osimertinib

TUMOR GROWTH INHIBITION IN EGFR+TM CDX MODEL

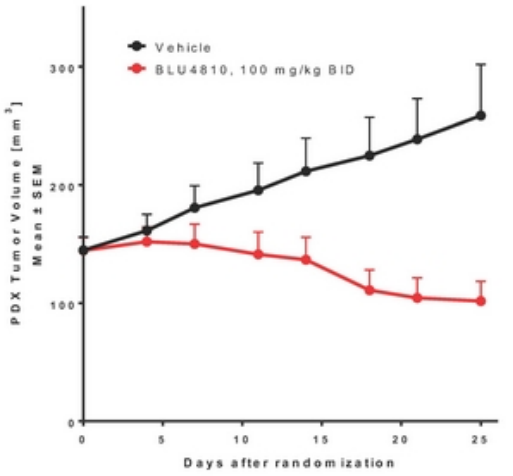


Anti-tumor activity in a EGFR+ TMCS patient-derived tumor model

PDX MODEL RESISTANT
TO ERLOTINIB AND OSIMERTINIB

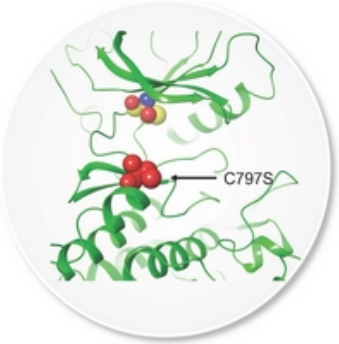


TUMOR REGRESSION WITH
100 MG/KG BID DOSING OF BLU4810



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

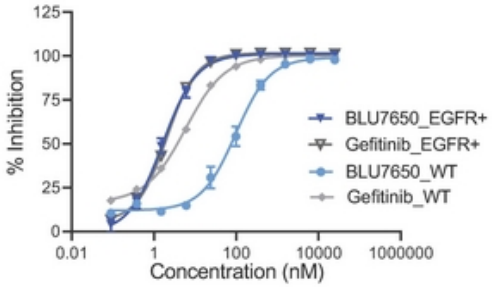


Osimertinib

Blueprint EGFR+ CS

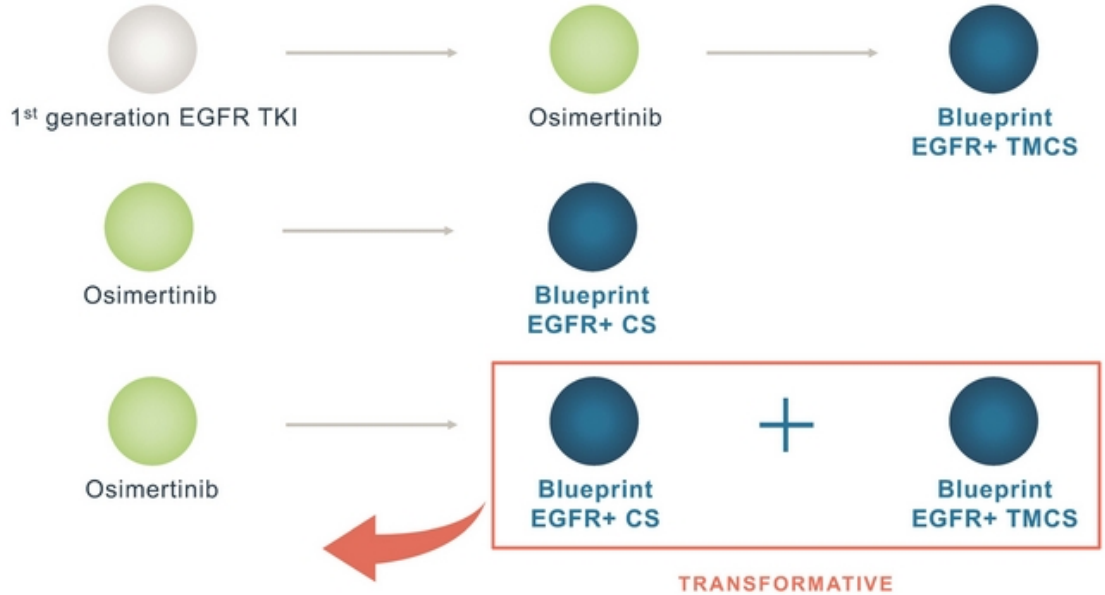
EGFR+ CS series are potent, selective and brain penetrant

	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

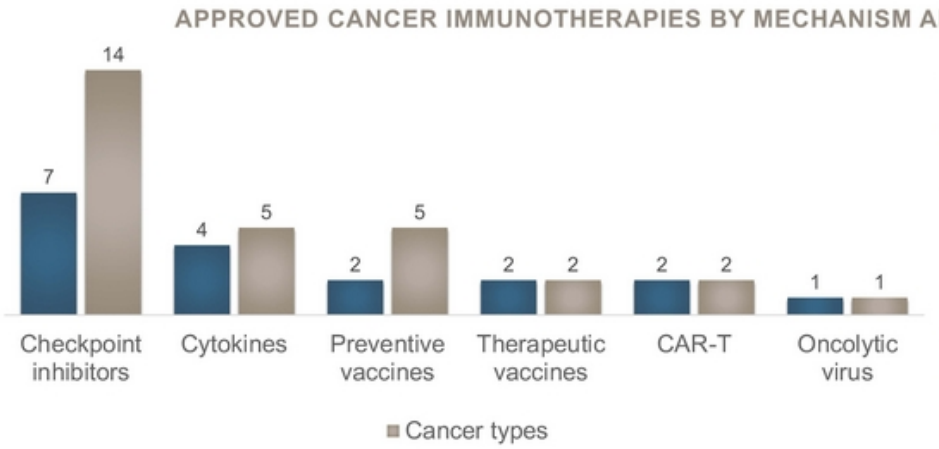
Cancer immunotherapy: a new frontier for kinase medicines

KLAUS HOEFLICH, PhD

Vice President, Biology

blueprint MEDICINES

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

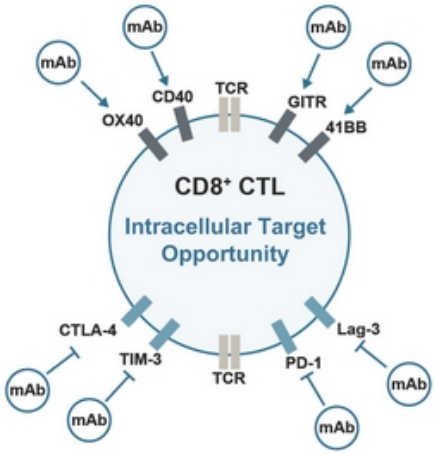


Modality	1st approval / Latest Approval
Checkpoint inhibitors	2011 (Melanoma) / 2019 (Breast)
Cytokines	1992 (Kidney) / 2011 (Melanoma)
Preventive vaccines	2009 (Cervical cancer) / 2014 (various)
Therapeutic vaccines	2010 (Prostate)
CAR-T	2017 (ALL) / 2018 (Lymphoma)
Oncolytic Virus	2015 (Melanoma)

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**

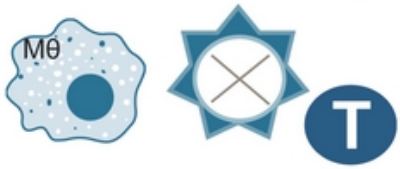


Cancer immunotherapy complements our precision medicine strategy

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

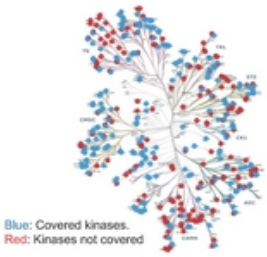
- **Goal:** Explore a range of immunokinase targets to advance cancer immunotherapy
  - Immediately actionable
  - Novel via cell-based phenotypic screens
- Interrogate and validate with genetic and tool compound approaches

2019: PROGRESS TOWARDS THE CLINIC

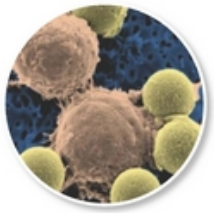
- **Achieved:** 4 targets selected focusing on distinct and complementary immune mechanisms
  - Activate effector cells
  - Prime immune response
  - Tumor cell killing
  - Prevent evasion from immune detection

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.

Novel screens identify actionable kinase targets for cancer immunotherapy



Blueprint tool compound set

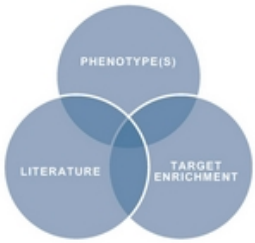


IO functional screens

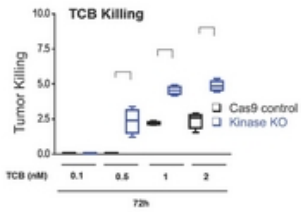
Tumor-T cell co-culture screens

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

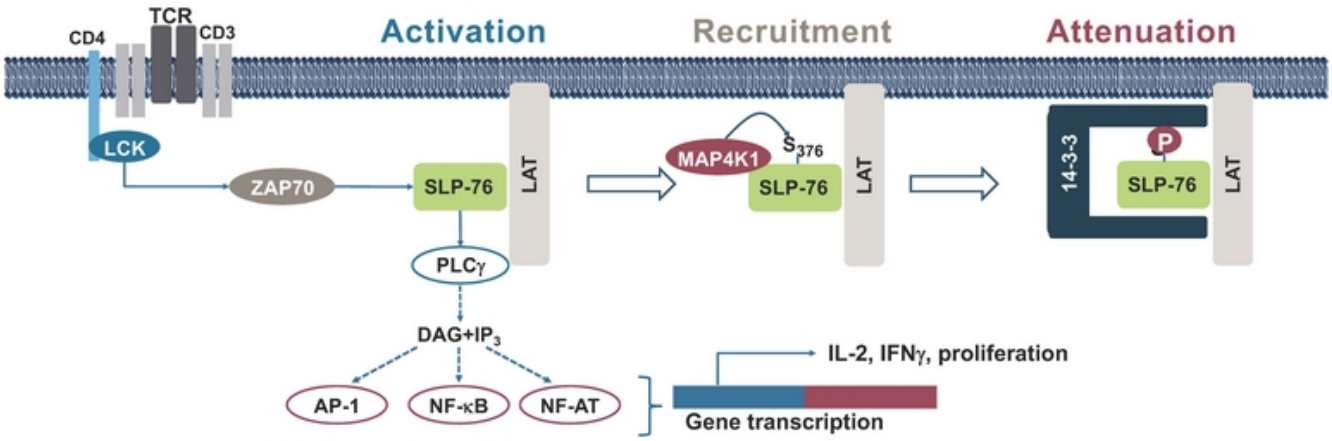
Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)(CSTI). The foregoing website is maintained by CSTI and Blueprint Medicines is not responsible for its content. Cpd; compound; DMSO, dimethyl sulfoxide; IO, immunotherapy; TCB, T-cell bispecific antibody

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 collaboration target under the cancer immunotherapy collaboration with Roche.

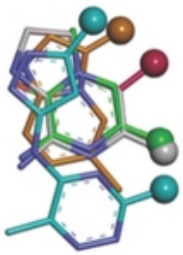
MAP4K1 is a negative regulator of T cell function



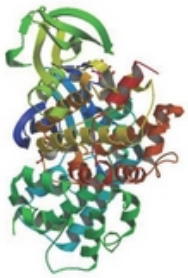
- MAP4K1 is a SER/THR kinase selectively expressed in DCs, T- and B-cells
- Negatively regulates TCR and BCR signaling, DC maturation
- MAP4K1$^{-/-}$ or MAP4K1$^{KD/KD}$ mice exhibit enhanced tumor immunity

J. Exp. Med. (2007) 2004: 681-91. Cancer Immunol Immunother (2010) 59: 419-29. Cell Reports 2018; 25(1):80-94.
BCR, B cell receptor; DC, dendritic cell; IO, immunotherapy; Ser, serine; TCR, T cell receptor; Thr, threonine.

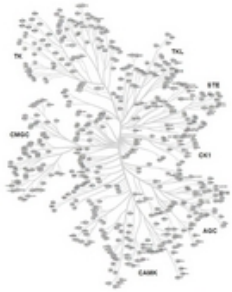
Our platform has enabled design of potent and selective MAP4K1 inhibitors



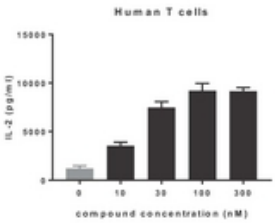
Multiple lead series identified directly from our library



Structural insights and kinase expertise to optimize for potency and selectivity



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

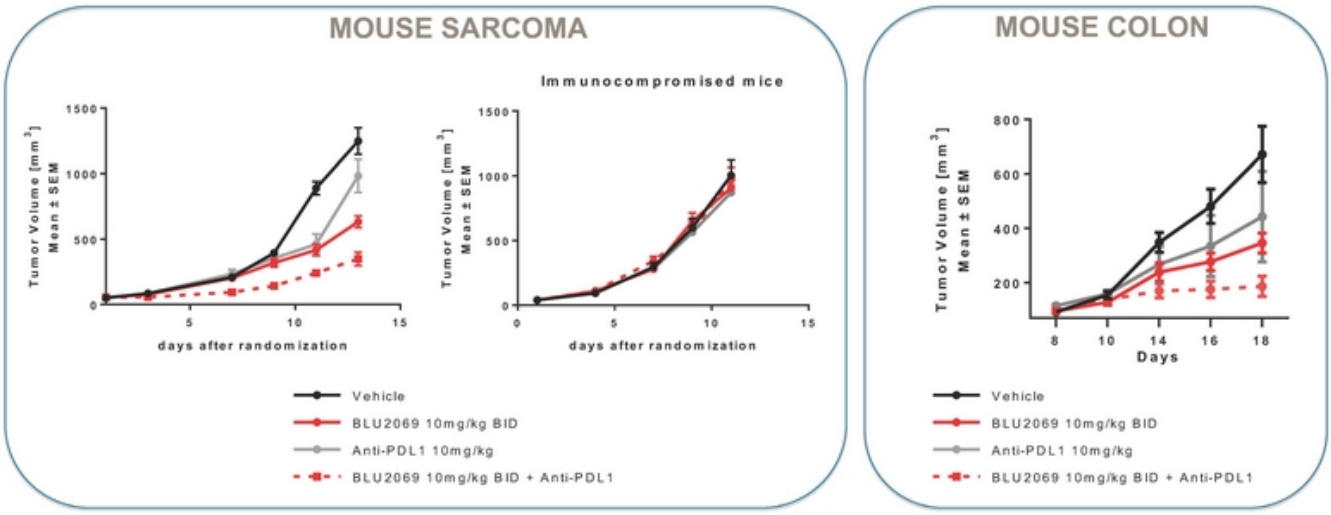


CD3/28 stimulated

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

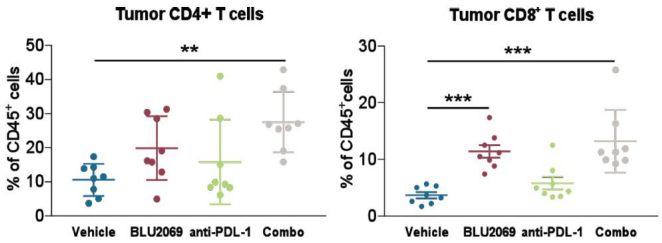


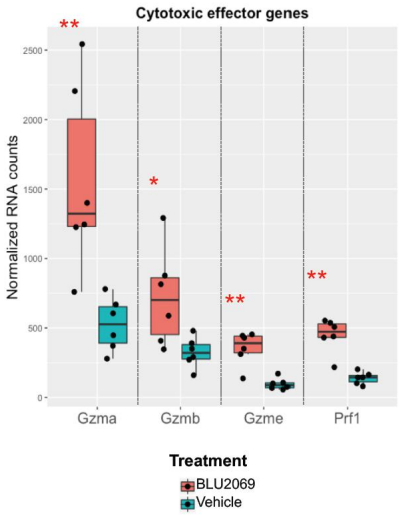
MAP4K1 inhibition enhances T cells responses and cytokines

Key findings

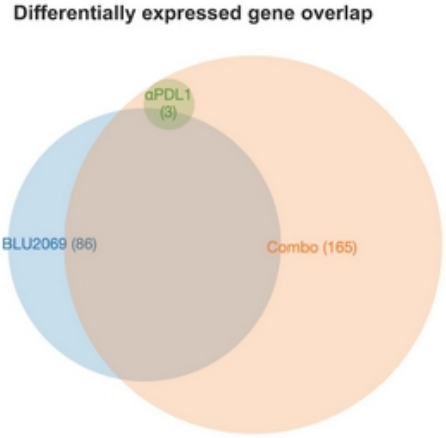
- Increased frequency of CD8⁺ TILS with single agent treatment
- Enhanced cytokines in plasma of combo treated mice
- Immune-phenotype is in line with MAP4K1 KI mouse

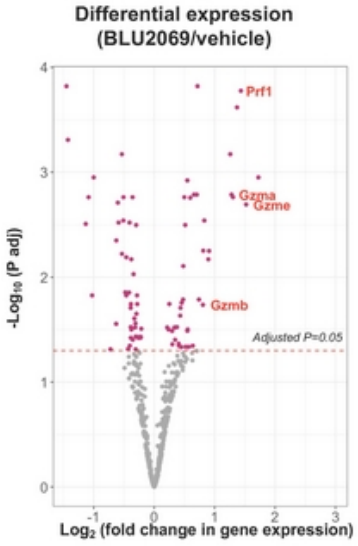
Flow cytometry analysis of tumor infiltrating lymphocytes

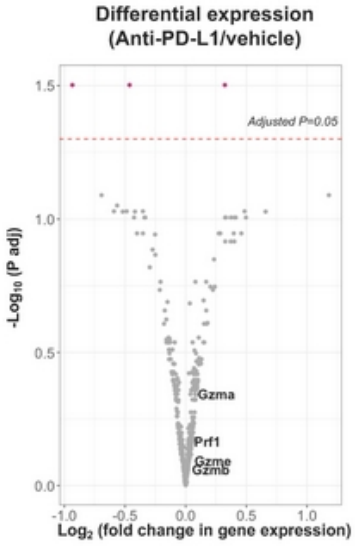




MAP4K1 inhibition induces stronger tumor T cell responses than anti-PD-L1







Significantly differentially expressed genes in red

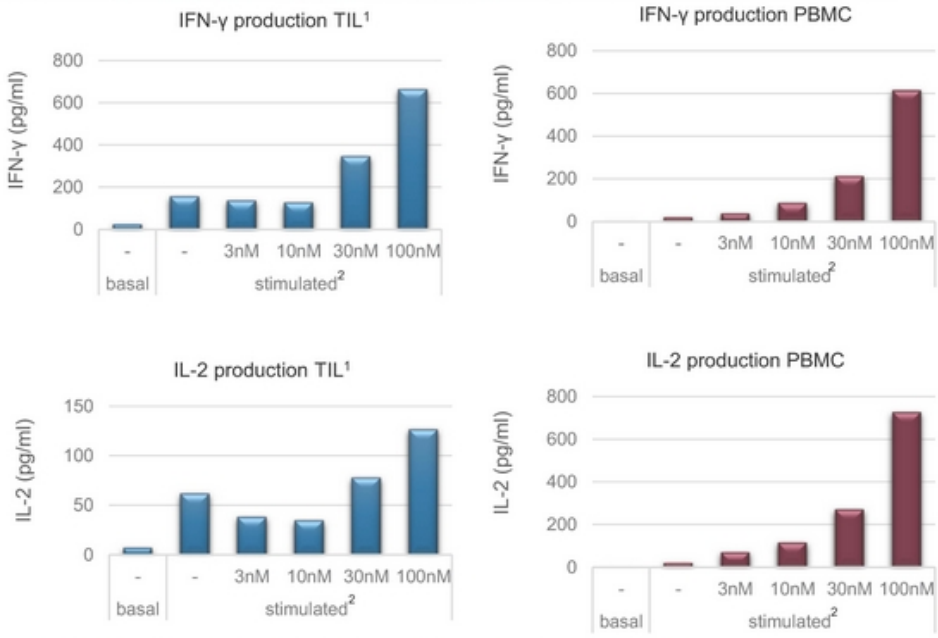
MAP4K1 increases cytokine production from both blood and tumor infiltrating lymphocytes derived from lung adenocarcinoma patient

Tumor & blood collected from lung cancer patient

Tumor dissociated into a single cell suspension and PBMCs isolated from the blood

Dissociated TILs and PBMCs cultured ex vivo for 24 hours with anti-CD3/CD28 stimulation +/- MAP4K1 inhibitor

Cytokines measured in the culture supernatants by MSD



¹ TIL, tumor infiltrating lymphocytes. ² CD3/28 stimulated. PBMC, peripheral blood mononuclear cells.

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

GIST patient visit @ Blueprint Medicines, 2019.

blueprint MEDICINES

Q&A

Jeff Albers

Chief Executive Officer

Third quarter 2019 financial results

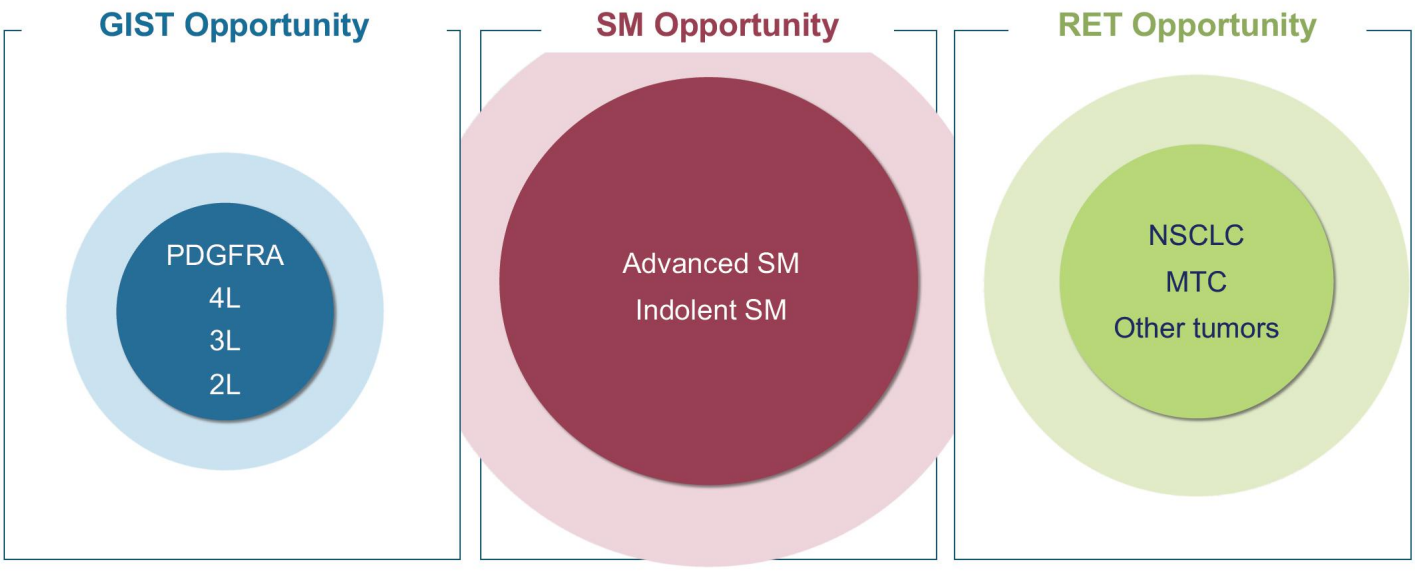
Balance Sheet	September 30, 2019*	December 31, 2018
Cash, Cash Equivalents and Investments	$594.5M	$494.0M

Statement of Operations	Three Months Ended September 30,	
	2019*	2018*
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

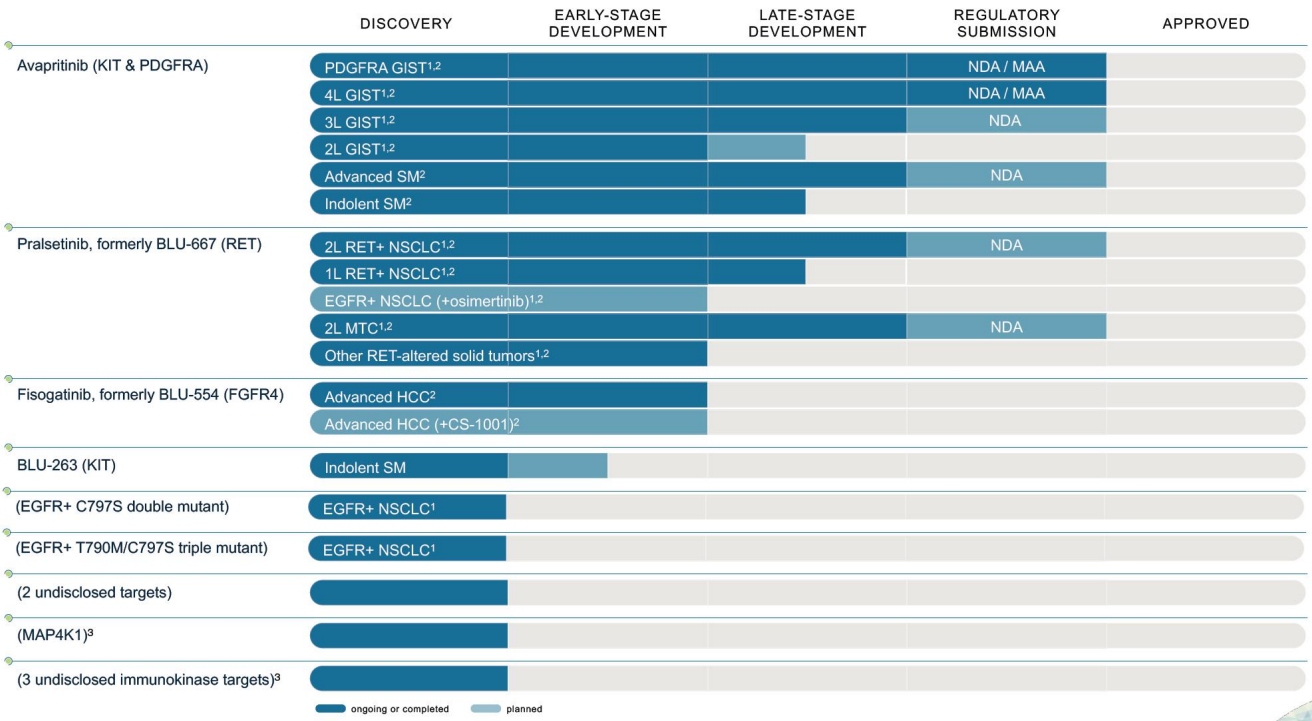
BASED ON CURRENT OPERATING PLANS,
EXPECT EXISTING CASH BALANCE WILL FUND OPERATIONS INTO THE SECOND HALF OF 2021**

* Unaudited
** Includes $25.0 million upfront cash payment from Clementia and $8.0 million research milestone achieved in the fourth quarter of 2019 under the Roche collaboration but excludes any additional potential option fees, milestone payments or other payments from Roche, CStone or Clementia.

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



Figures are illustrative.



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.

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