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 1, 2022**

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 1, 2022, Blueprint Medicines Corporation (the "Company") announced its financial results for the quarter ended September 30, 2022 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 and is incorporated by reference herein.

The information in this Current Report on 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, or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 7.01 Regulation FD.

On November 1, 2022, the Company is hosting an investor conference call and webcast to review its financial results and other business highlights. A copy of the presentation for the investor conference call and for the webcast is furnished as Exhibit 99.2 to this Current Report on Form 8-K.

The information in Item 7.01 of this Current Report on 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 of 1933, as amended, 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 Items 2.02 and 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 1, 2022
99.2	Corporate slide presentation of Blueprint Medicines Corporation dated November 1, 2022
104	Cover Page Interactive Data File (embedded within the Inline XBRL document and incorporated as Exhibit 101)

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 1, 2022

By: /s/ Kathryn Haviland
Kathryn Haviland
Chief Executive Officer

Exhibit 99.1

Blueprint Medicines Outlines 2027 Blueprint to Achieve Precision Medicine at Scale and Reports Third Quarter 2022 Financial Results at Investor Day 2022

-- On track to submit supplemental new drug application for AYVAKIT® (avapritinib) in non-advanced SM in Q4 2022, with an anticipated U.S. launch in mid-2023 --

-- Reports updated data from the SYMPHONY trial of BLU-945 demonstrating clinical activity and a differentiated safety profile, supporting combination development in first-line EGFR-mutant non-small cell lung cancer --

-- Expects to achieve the high-end of total revenue guidance of $180 million to $200 million for full-year 2022 --

-- Blueprint Medicines to webcast Investor Day 2022 event today at 8:30 a.m. ET --

CAMBRIDGE, Mass., November 1, 2022 – Blueprint Medicines (NASDAQ: BPMC) today announced its 2027 Blueprint to achieve precision medicine at scale, a five-year business strategy to expand the company's reach to broader patient populations by leveraging its scientific leadership, proven development capability and integrated business. The company plans to highlight this business strategy, including commercial plans to bring AYVAKIT to patients with non-advanced systemic mastocytosis (SM), at its Investor Day event today. In addition, Blueprint Medicines today reported financial results and provided a business update for the third quarter ended September 30, 2022.

"The opportunity to bring AYVAKIT to patients with non-advanced SM, based on the positive results of the PIONEER study, will enable us to scale our impact and address the needs of a significantly larger patient population in the near term." said Kate Haviland, Chief Executive Officer of Blueprint Medicines. "This morning at our Investor Day, we will highlight our 2027 Blueprint strategy to double our impact in five years across multiple metrics of portfolio strength. We plan to achieve this scale with the potential launch of AYVAKIT in non-advanced SM, multiple advancing clinical development programs for EGFR-mutant lung cancer and CDK2-vulnerable breast cancer, and an expansive precision therapy research pipeline, all of which build on our R&D achievements to date and leverage our fully integrated global infrastructure."

"In addition, today we are reaffirming total revenue guidance for full-year 2022, while we lower product revenue guidance based on performance in the third quarter and our near-term expectations for growth. Over the last year, we have established AYVAKIT as the standard of care in patients who are being actively treated for their advanced SM, and we are now focusing on increasing treatment rates in patients with SM and an associated hematologic neoplasm, where there has been lower adoption. In parallel, we are prioritizing efforts to bring AYVAKIT to patients with non-advanced SM, which, if approved, would represent a 15-fold or larger opportunity based on the number of patients with moderate-to-severe non-advanced SM who are diagnosed, being treated for their SM, and observable in U.S. claims data today."

2027 Blueprint Global Business Strategy

Building on Blueprint Medicines' significant achievements over the last decade, including the regulatory approval of two internally discovered precision therapies within the company's first decade, the five-year 2027 Blueprint strategy aims to double the company's impact across multiple measures of portfolio strength in about half the time.

Blueprint Medicines aims to achieve the following by the end of 2027:

- Products: 4+ marketed products for oncology, hematology, or mast cell disorders (versus 2 today)
- Portfolio: 3+ disease leadership areas (versus 1, mast cell disease, today)
- Clinical: 4+ late-stage clinical programs (versus 2 today)
- Research: 25+ cumulative development candidates nominated (versus 14 today) derived from 2 research platforms (versus 1, kinase inhibitor platform, today)

45 Sidney Street
Cambridge, MA 01741

Investor Day Presentation Highlights

At the Investor Day event, Blueprint Medicines plans to:

- Review the go-to-market plan for AYVAKIT in non-advanced SM and facilitate a panel discussion with disease experts on perceptions of the registration-enabling PIONEER trial data, the current state of SM care, and the potential role of a new disease-modifying therapy. Participants will include:
    - Frank Siebenhaar, MD, Assistant Professor, Charité University, and PIONEER trial investigator
    - Pankit Vachhani, MD, Assistant Professor, University of Alabama, and PIONEER trial investigator
    - James Wedner, MD, Professor, Washington University in St. Louis
- Highlight clinical progress informing development strategies for the company's EGFR portfolio therapies, including updated Phase 1/2 SYMPHONY trial dose escalation data supporting plans to prioritize development of BLU-945 in combination with osimertinib in first-line EGFR L858R-positive non-small cell lung cancer (NSCLC).
- Introduce a new research program targeting wild-type KIT, which aims to build on the company's KIT target leadership to advance a best-in-class oral precision therapy for common mast cell diseases adjacent to systemic mastocytosis, including chronic urticaria.

Third Quarter 2022 Highlights and Recent Progress

AYVAKIT®/AYVAKYT® (avapritinib): SM and PDGFRA gastrointestinal stromal tumor

- Reported global net product revenues of $28.6 million for the third quarter of 2022.
- Announced positive top-line results from the registration-enabling Part 2 of the PIONEER trial of AYVAKIT in patients with non-advanced SM, demonstrating clinically meaningful and highly significant improvements across the primary and all key secondary endpoints, including patient-reported symptoms and objective measures of mast cell burden. AYVAKIT had a favorable safety profile compared to the control arm, supporting the potential for long-term treatment. Read the press release here.
- Published results from the TouchStone study of patient and healthcare provider perceptions of SM disease burden, which highlighted that SM is associated with severe and burdensome symptoms including anaphylactic events, frequent emergency department visits, use of multiple symptom-directed medications, reduced ability to work, impaired physical functioning and poor quality of life. Read the press release here.

GAVRETO® (pralsetinib): RET-altered cancers

- As previously recorded and reported by Roche, GAVRETO global product sales were 20 million CHF year to date which excludes sales in the Greater China territory driven by CStone Pharmaceuticals.

BLU-945, BLU-701, BLU-525, and BLU-451: EGFR-mutant NSCLC

- Based on emerging clinical and preclinical data, Blueprint Medicines plans to prioritize development of BLU-525, a back-up EGFR inhibitor candidate, and deprioritize further development of BLU-701. Compared to BLU-701, BLU-525 has a distinct chemical structure with improved kinome selectivity and differentiated metabolism, and equivalent EGFR mutation coverage, wild-type EGFR selectivity, and central nervous system penetration. The company plans to submit an investigational new drug application to the U.S. Food and Drug Administration (FDA) for BLU-525 in the first quarter of 2023.
- Blueprint Medicines, with Guardant Health, presented real-world data from patients with EGFR-mutant NSCLC identifying the EGFR C797X mutation as the most common resistance mechanism to osimertinib at the International Association for the Study of Lung Cancer 2022 World Conference on Lung Cancer. Read the press release here.

Key Upcoming Milestones

Blueprint Medicines expects to achieve the following near-term milestones:

- Submit a supplemental New Drug Application to the FDA for AYVAKIT for non-advanced SM in the fourth quarter of 2022.
- Present detailed data from the registration-enabling Part 2 of the PIONEER trial of AYVAKIT in non-advanced SM at a medical congress in late 2022 or early 2023.
- Report top-line 12-week data from Part 1 of the HARBOR trial of BLU-263 in non-advanced SM in the fourth quarter of 2022.
- Submit an IND to the FDA for BLU-525 for the treatment of EGFR-mutant NSCLC in the first quarter of 2023.

- Present initial data from the Phase 1/2 CONCERTO study of BLU-451 in patients with EGFR-mutant NSCLC in the first half of 2023.
- Present initial data from the Phase 1/2 VELA trial of BLU-222 in CDK2-vulnerable cancers in the first half of 2023.

Third Quarter 2022 Results

- **Revenues**: Revenues were $66.0 million for the third quarter of 2022, including $28.6 million of net product revenues from sales of AYVAKIT/AYVAKYT, $9.8 million in collaboration and license revenues, and $27.5 million in license revenues- related party. Blueprint Medicines recorded revenues of $24.2 million in the third quarter of 2021, including $17.3 million of net product revenues from sales of AYVAKIT/AYVAKIT and $6.9 million in collaboration and license revenues.
- **Cost of Sales:** Cost of sales was $3.0 million for the third quarter of 2022, as compared to $3.8 million for the third quarter of 2021.
- **R&D Expenses:** Research and development expenses were $128.0 million for the third quarter of 2022, as compared to $84.4 million for the third quarter of 2021. This increase was primarily due to increased clinical supply manufacturing and clinical development activities due to the progression and expansion of our clinical trials and increased costs related to early discovery effort. Research and development expenses included $10.0 million in stock-based compensation expenses for the third quarter of 2022.
- **SG&A Expenses:** Selling, general and administrative expenses were $57.6 million for the third quarter of 2022, as compared to $49.8 million for the third quarter of 2021. This increase was primarily due to increased costs associated with expanding our commercial infrastructure for commercialization of AYVAKIT/AYVAKYT. General and administrative expenses included $14.1 million in stock-based compensation expenses for the third quarter of 2022.
- **Net Loss**: Net loss was $133.2 million for the third quarter of 2022, or a net loss per share of $2.23, as compared to a net loss of $117.2 million for the third quarter of 2021, or a net loss per share of $2.00.
- **Cash Position**: As of September 30, 2022, cash, cash equivalents and investments were $1,192.6 million, as compared to $1,034.6 million as of December 31, 2021.

Financial Guidance

Blueprint Medicines anticipates it will achieve the high end of previously provided revenue guidance for full-year 2022 of approximately $180 million to $200 million, including approximately $108 million to $111 million in AYVAKIT net product revenues. The company continues to expect that its existing cash, cash equivalents and investments, together with anticipated future product revenues, will provide sufficient capital to enable the company to achieve a self-sustainable financial profile.

Conference Call Information

Blueprint Medicines will host a live conference call and webcast at 8:30 a.m. ET today for Investor Day and to discuss third quarter 2022 financial results. The live webcast of the event will be available under "Events and Presentations" in the Investors & Media section of Blueprint Medicines' website at http://ir.blueprintmedicines.com/. A replay of the webcast will be archived on Blueprint Medicines' website for 90 days following the event.

About Blueprint Medicines

Blueprint Medicines is a global precision therapy company that invents life-changing therapies for people with cancer and blood disorders. Applying an approach that is both precise and agile, we create medicines that selectively target genetic drivers, with the goal of staying one step ahead across stages of disease. Since 2011, we have leveraged our research platform, including expertise in molecular targeting and world-class drug design capabilities, to rapidly and reproducibly translate science into a broad pipeline of precision therapies. Today, we are delivering approved medicines directly to patients in the United States and Europe, and we are globally advancing multiple programs for systemic mastocytosis, lung cancer and other genomically defined cancers, and cancer immunotherapy. 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, strategies, timelines and expectations for interactions with the FDA and other regulatory authorities; to submit a supplemental New Drug Application to the FDA for AYVAKIT in non-advanced SM, with a subsequent submission of a type II variation marketing authorization application to the European Medicines Agency; plans and timing for presenting detailed data from the PIONEER trial of AYVAKIT in patients with non-advanced SM, and, expectations regarding the potential benefits of AYVAKIT in treating patients with non-advanced SM; statements regarding plans and expectations for Blueprint Medicines' current or future approved drugs and drug candidates; the potential benefits of any of Blueprint Medicines' current or future approved drugs or drug candidates in treating patients; and Blueprint Medicines' financial performance, strategy, goals and anticipated milestones, business plans and focus. The words “aim,” “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 impact of the COVID-19 pandemic to Blueprint Medicines’ business, operations, strategy, goals and anticipated milestones, including Blueprint Medicines’ ongoing and planned research and discovery activities, ability to conduct ongoing and planned clinical trials, clinical supply of current or future drug candidates, commercial supply of current or future approved products, and launching, marketing and selling current or future approved products; Blueprint Medicines’ ability and plans in continuing to establish and expand a commercial infrastructure, and successfully launching, marketing and selling current or future approved products; Blueprint Medicines’ ability to successfully expand the approved indications for AYVAKIT/AYVAKYT and GAVRETO or obtain marketing approval for AYVAKIT/AYVAKYT in additional geographies in the future; the delay of any current or planned clinical trials or the development of Blueprint Medicines’ current or future drug candidates; 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 either as monotherapies or in combination with other agents or may impact the anticipated timing of data or regulatory submissions; the timing of the initiation of clinical trials and trial cohorts at clinical trial sites and patient enrollment rates; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials; Blueprint Medicines’ ability to obtain, maintain and enforce patent and other intellectual property protection for AYVAKIT/AYVAKYT, GAVRETO or any drug candidates it is developing; Blueprint Medicines’ ability to develop and commercialize companion diagnostic tests for AYVAKIT/AYVAKYT, GAVRETO or any of its current and future drug candidates; Blueprint Medicines' ability to successfully expand its operations, research platform and portfolio of therapeutic candidates, and the timing and costs thereof; Blueprint Medicines' ability to realize the anticipated benefits of its executive leadership transition plan; and the success of Blueprint Medicines’ current and future collaborations, financing arrangements, partnerships or licensing arrangements. 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 Annual Report on Form 10-K, as supplemented by its 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.

Trademarks

Blueprint Medicines, AYVAKIT, AYVAKYT, GAVRETO and associated logos are trademarks of Blueprint Medicines Corporation.

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Blueprint Medicines Corporation
Selected Condensed Consolidated Balance Sheet Data

(in thousands)
(unaudited)

	September 30, 2022	December 31, 2021
Cash, cash equivalents and investments	$ 1,192,640	$ 1,034,643
Working capital (1)	1,052,155	404,260
Total assets	1,458,392	1,252,225
Deferred revenue (2)	16,624	36,576
Liability related to the sale of future royalties and revenues (2)	423,653	-
Term loan (2)	138,350	-
Total liabilities	818,085	281,490
Total stockholders' equity	640,307	970,735

(1) Blueprint defines working capital as current assets less current liabilities.
(2) Includes both current and long-term portions of the balance

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

	Three Months Ended, September 30		Nine Months Ended, September 30	
	2022	**2021**	**2022**	**2021**
Revenues:				
Product revenue, net	$ 28,634	$ 17,270	$ 80,929	$ 37,658
Collaboration and license revenue	9,843	6,918	56,826	35,401
License revenue - Related Party	27,500	-	27,500	-
Total revenues	65,977	24,188	165,255	73,059
Cost and operating expenses:				
Cost of sales	3,000	3,790	12,965	10,385
Collaboration loss sharing	1,665	3,269	7,076	3,269
Research and development	127,981	84,419	359,579	244,157
Selling, general and administrative	57,608	49,806	173,354	141,093
Total cost and operating expenses	$ 190,254	141,284	552,974	398,904
Other income (expense):				
Interest income (expense), net	(8,396)	552	(7,527)	1,923
Other income (expense), net	396	(522)	575	(1,109)
Total other income (expense)	$ (8,000)	30	(6,952)	814
Loss before income taxes	$ (132,277)	(117,066)	(394,671)	(325,031)
Income tax expense	(886)	(175)	(4,200)	(368)
Net loss	$ (133,163)	$ (117,241)	$ (398,871)	$ (325,399)
Net loss per share — basic and diluted	$ (2.23)	$ (2.00)	$ (6.70)	$ (5.58)
Weighted-average number of common shares used in net loss per share — basic and diluted	59,758	58,647	59,564	58,361


precision at scale™
INVESTOR DAY 2022
blueprint MEDICINES
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JIM BAKER

SVP, Corporate Affairs

blueprint MEDICINES

Our speakers today

KATE HAVILAND
Chief Executive Officer

PHILINA LEE, PHD
Chief Commercial Officer

BECKER HEWES, MD
Chief Medical Officer

FOUAD NAMOUNI, MD
President, R&D

PERCY CARTER, PHD
Chief Scientific Officer

CHRISTY ROSSI
Chief Operating Officer

Agenda

Our blueprint to achieve precision at scale	**Kate Haviland,** Chief Executive Officer
Delivering the first precision therapy for SM	**Philina Lee, PhD,** Chief Commercial Officer
Clinical perspectives on Non-Advanced SM	**Becker Hewes, MD,** Chief Medical Officer **Frank Siebenhaar, MD,** Assistant Professor, Charité University **Pankit Vachhani, MD,** Assistant Professor, University of Alabama **James Wedner, MD,** Professor, Washington University in St. Louis
BREAK	
Expanding patient impact with precision medicine leadership Transforming treatment of EGFR-mutant lung cancer	**Fouad Namouni, MD,** President, R&D
Research innovation at scale	**Percy Carter, PhD,** Chief Scientific Officer
Portfolio growth strategy	**Christy Rossi,** Chief Operating Officer
Q&A	
Closing remarks	**Kate Haviland,** Chief Executive Officer

SM, systemic mastocytosis.

Forward-looking statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements regarding plans, strategies, timelines and expectations for interactions with the U.S. Food and Drug Administration (FDA) and other regulatory authorities; plans to submit a sNDA to the FDA for AYVAKIT in non-advanced SM, with a subsequent submission of a type II variation marketing authorization application to the European Medicines Agency (EMA); plans and timing for presenting detailed data from the PIONEER trial of AYVAKIT in patients with non-advanced systemic mastocytosis (SM), and; expectations regarding the potential benefits of AYVAKIT in treating patients with non-advanced SM; statements regarding plans and expectations for the company's current or future approved drugs and drug candidates; the potential benefits of any of the company's current or future approved drugs or drug candidates in treating patients; and the company's financial performance, strategy, goals and anticipated milestones, business plans and focus.

The words "aim," "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 impact of the COVID-19 pandemic to the company's business, operations, strategy, goals and anticipated milestones, including the company's ongoing and planned research and discovery activities, ability to conduct ongoing and planned clinical trials, clinical supply of current or future drug candidates, commercial supply of current or future approved products, and launching, marketing and selling current or future approved products; the company's ability and plans in continuing to establish and expand a commercial infrastructure, and successfully launching, marketing and selling current or future approved products; the company's ability to successfully expand the approved indications for AYVAKIT/AYVAKYT and GAVRETO or obtain marketing approval for AYVAKIT/AYVAKYT in additional geographies in the future; the delay of any current or planned clinical trials or the development of the company's current or future drug candidates; the company's advancement of multiple early-stage efforts; the company's 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 the company's drug candidates, which may not support further development of such drug candidates either as monotherapies or in combination with other agents or may impact the anticipated timing of data or regulatory submissions; the timing of the initiation of clinical trials and trial cohorts at clinical trial sites and patient enrollment rates; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials; the company's ability to obtain, maintain and enforce patent and other intellectual property protection for AYVAKIT/AYVAKYT, GAVRETO or any drug candidates it is developing; the company's ability to develop and commercialize companion diagnostic tests for AYVAKIT/AYVAKYT, GAVRETO or any of its current and future drug candidates; the company's ability to successfully expand its operations, research platform and portfolio of therapeutic candidates, and the timing and costs thereof; the company's ability to realize the anticipated benefits of its executive leadership transition plan; and the success of the company's current and future collaborations, financing arrangements, partnerships or licensing arrangements. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in the company's filings with the Securities and Exchange Commission (SEC), including the company's most recent Annual Report on Form 10-K, as supplemented by its most recent Quarterly Report on Form 10-Q and any other filings that the company has made or may make with the SEC in the future. The forward-looking statements in this presentation are made only as of the date hereof, 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. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements.

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 blueprint to achieve precision at scale

KATE HAVILAND

Chief Executive Officer

OUR MISSION

Make real the promise of precision therapy to extend and improve life for as many people as possible

Suki, patient with non-advanced systemic mastocytosis

blueprint™ MEDICINES

Not for promotional use

Blueprint's proven track record of success

FDA, U.S. Food and Drug Administration; IND, investigational new drug application; POC, proof-of-concept.

Our evolution to a commercial stage company

Compelling **peak revenue and high margin** opportunities leveraging operational efficiencies

People, tools and capabilities to capture the compelling growth opportunities

Sustainable **disease leadership in Systemic Mastocytosis** through a decade of research, relationships and market building

Our commercial portfolio creates value certainty and opportunity for near-term growth

AREA	PDGFRA GIST	RET-altered cancers	Advanced SM	Non-Advanced SM
GLOBAL TAMs	~12,000 patients			
PRODUCTS	2 marketed products			Anticipated Approval Mid-2023

Q3 financial results

Total revenue and operating expenses favorable to consensus

Expect to achieve high-end of $180M - $200M top-line revenue guidance for 2022

Revising AYVAKIT revenue guidance to $108M to $111M for 2022

GIST, gastrointestinal stromal tumor; TAM, total addressable market (US, EU4 and UK markets).

Patient impact and growth driven by Precision at Scale

AYVAKIT avapritinib | tablets · GAVRETO pralsetinib · AYVAKIT avapritinib | tablets · AYVAKIT avapritinib | tablets · LUNG CANCER PORTFOLIO · BLU-222

AREA	PDGFRA GIST	RET-altered cancers	Advanced SM	Non-Advanced SM*	EGFRm NSCLC*	CDK2 vulnerable breast & other cancers*
GLOBAL TAMs	~250,000+ patients					
PRODUCTS	4+ marketed products by the end of 2027					

CDK2, cyclin dependent kinase 2; EGFRm, EGFR-mutant; NSCLC, non-small cell lung cancer. * Includes TAMs for AYVAKIT based on potential approval in Non-Advanced SM and other investigational therapies based on potential future approvals in other target indications.

“2027 Blueprint” strategy - double our impact, in half the time

blueprint™ 2027

	2011-2022	Planned 2022-2027
Approved medicines	2	4+
Disease leadership areas	1	3+
Late-stage clinical programs	2	4+
Research platforms	1	2
Cumulative development candidates	14	25+

Key questions to be answered today

What is the opportunity in Non-Advanced SM and how does our Advanced SM experience inform our view?

Do we have a winning approach to improve outcomes for patients with EGFR-mutant NSCLC?

How will we leverage our expertise and infrastructure to drive continued innovation and long-term growth?

Precision at Scale:
Bringing AYVAKIT to patients across the spectrum of systemic mastocytosis

What is the opportunity in Non-Advanced SM and how does our Advanced SM experience inform our view?

1. Growing the number of Advanced SM patients treated with AYVAKIT each quarter and addressing challenges in underpenetrated patient populations
2. Expanding AYVAKIT to treat patients with Non-Advanced SM is a significant opportunity for near-term growth
3. PIONEER data establish the basis for AYVAKIT to become the standard of care for patients with moderate- to-severe Non-Advanced SM upon FDA approval

Precision at Scale:
Delivering improved outcomes for people with EGFR-mutant NSCLC

Do we have a winning approach to improve outcomes for patients with EGFR-mutant NSCLC?

1. BLU-945 monotherapy was clinically active and showed a differentiated safety profile. However, durability of response was limited due to frequent off-target drivers in 2L+ patients
2. Prioritizing development of BLU-945 in combination with osimertinib in 1L L858R, based on exciting preclinical data and early clinical safety data
3. Pulling forward BLU-525, the backup compound for BLU-701, to bring the best candidate into development with minimal disruption to the overall timeline
4. Encouraging early activity data from the BLU-451 dose escalation trial

1L, first-line; 2L+, second-line or later.

Precision at Scale:
Driving innovation for long-term growth

How will we leverage our expertise and infrastructure to drive continued innovation and long-term growth?

1. Creating synergies between our robust discovery, clinical and commercial capabilities to build an optimized portfolio
2. Announcing a new program targeting wild-type KIT, which builds on our knowledge of KIT and leadership position in mast cell disorders
3. Leveraging our kinase discovery platform as a unique advantage to pursue targeted protein degradation

Delivering the first precision therapy for systemic mastocytosis

PHILINA LEE, PHD

Chief Commercial Officer

blueprint MEDICINES

OUR MISSION

Make real the promise of precision therapy to extend and improve life for as many people as possible

Melanie, patient with non-advanced systemic mastocytosis

blueprint™ MEDICINES

Not for promotional use

AYVAKIT is the first precision therapy to target the underlying cause of SM

AYVAKIT® avapritinib | tablets

COMPELLING PROFILE DEMONSTRATED ACROSS CLINICAL TRIALS

- Reduced mast cell burden
- Improved disease symptoms
- Improved quality of life
- Deep and durable clinical responses
- Positive benefit-risk profile
- One pill, once daily dosing

We are well positioned to deliver on the promise of AYVAKIT in SM

- AYVAKIT has the potential to **benefit patients across the spectrum of SM**
  - This represents a >$1B opportunity
- We have established AYVAKIT as the **standard of care for patients treated for AdvSM**
  - Focused on **increasing the treated patient population** to drive near-term growth
- Our Non-AdvSM U.S. launch strategy focuses on **~7,500 patients with moderate to severe disease who are seeking treatment today**
- We are **well-positioned to launch AYVAKIT for Non-AdvSM**
  - First to market, a strong product profile, a leadership position built over nearly a decade, and an experienced team in the market today for AdvSM

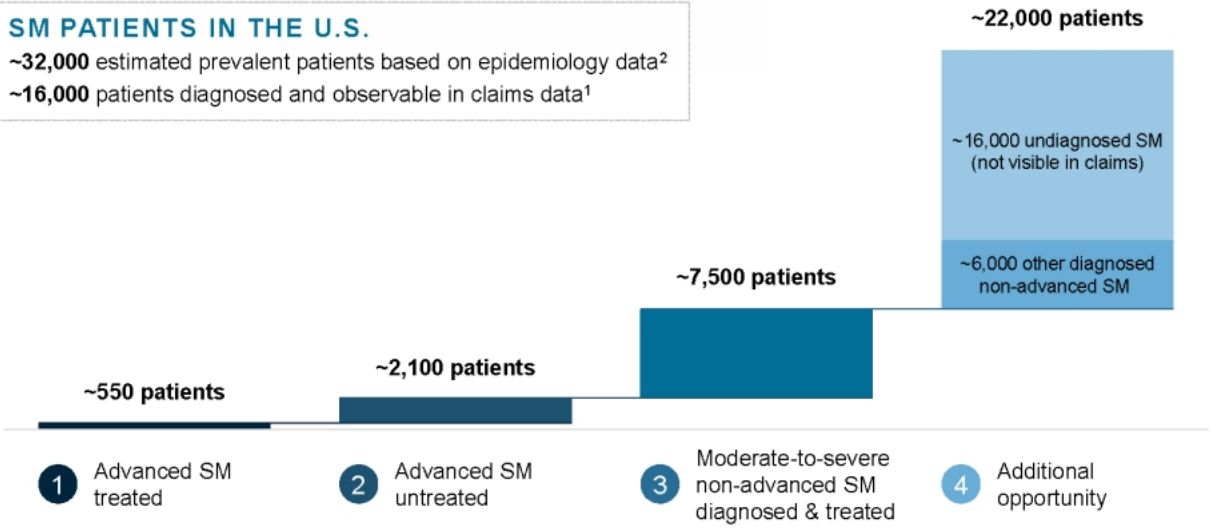
AdvSM, Advanced SM; Non-AdvSM, Non-Advanced SM.

Systemic mastocytosis represents a blockbuster opportunity

SM PATIENTS IN THE U.S.

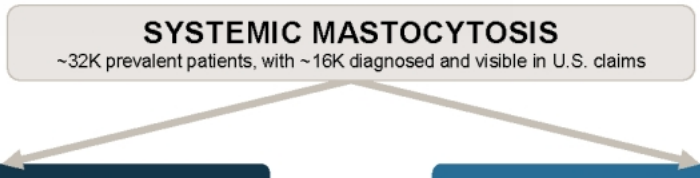
~32,000 estimated prevalent patients based on epidemiology data[2]

~16,000 patients diagnosed and observable in claims data[1]



1. U.S. claims data analyses on file. 2. Cohen, Br J Haematol, 2014.

Systemic mastocytosis is a spectrum of disease



ADVSM (5-10%)

- Mast cell proliferation leads to organ damage and shortened overall survival
- Managed primarily by hematologist oncologists whose treatment goals are focused on overall survival
- Three sub-types of disease create significant heterogeneity; majority of patients have SM-AHN, a medically complex disease

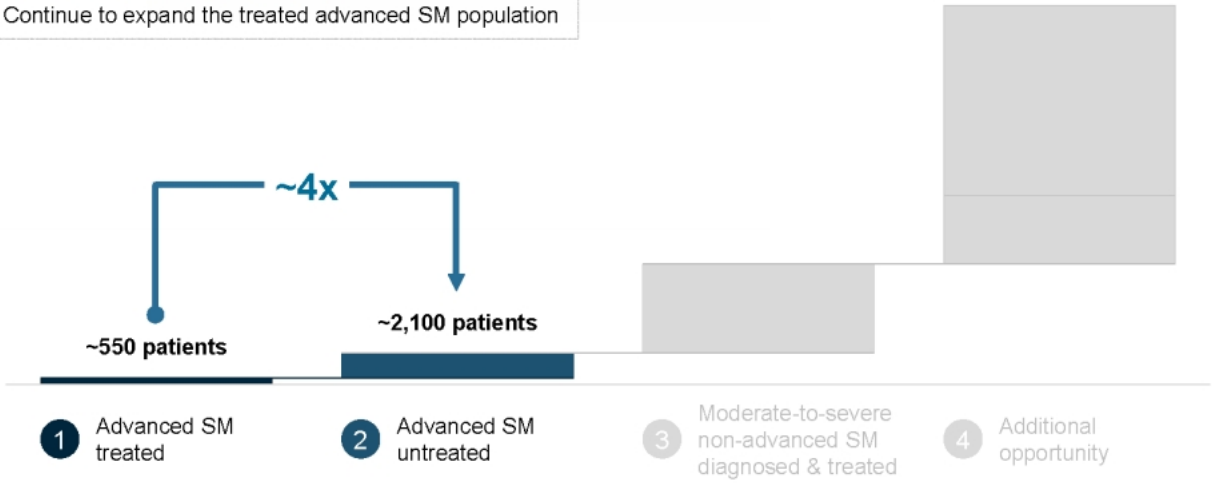
NON-ADVSM (90-95%)

- Mast cell over-activation leads to debilitating symptoms and poor quality of life
- Managed primarily by hematologist oncologists, as well as allergist immunologists who are focused on symptom burden and quality of life
- More homogenous disease biology, with a range of clinical presentations leading to a spectrum of severity

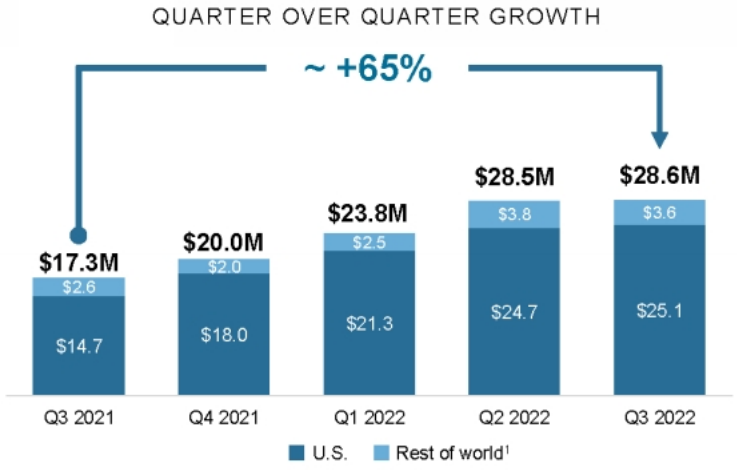
AHN, associated hematologic neoplasm.

AYVAKIT has become the standard of care in treated AdvSM in the U.S.

GROWTH OPPORTUNITY
Continue to expand the treated advanced SM population



Growth in AYVAKIT revenue one year into the Advanced SM launch



KEY DRIVERS

- AVYAKIT is the standard of care in the U.S.
  - ~60% share of treated patients in Q3
  - ~75% of new patient starts / switches
  - Number of patients on therapy continues to grow
- Increasing HCP experience with AYVAKIT
  - ~350 new accounts since launch
  - >50 new accounts in Q3

KEY CHALLENGES

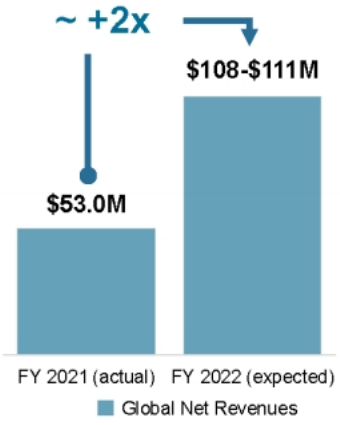
- Initial penetration in SM-AHN is lower than other subtypes
- Omicron COVID-19 impacted patient visits and new patient diagnoses
- FX headwinds in international business

FX, foreign exchange.

1. Rest of world sales exclude Greater China.

Trending to double AYVAKIT net product revenues compared to last year

YEAR OVER YEAR GROWTH



- Updating AYVAKIT net product revenue guidance for full-year 2022 to $108M - $111M, based on:
  - Continued expected growth of treated patients at a slower pace, driven by expansion of SM-AHN treatment rates
  - Financial impacts driven by FX and German price reform
- Reasons to believe in continued growth
  - Total number of patients on therapy continues to grow
  - Majority of SM-AHN anticipated to be addressable over time
  - Duration of treatment continues to trend favorably (~18 months), trending towards longer duration in recently prescribed patients, who are primarily TKI-naïve

TKI, tyrosine kinase inhibitor.

We are taking action to drive change in AdvSM clinical practice

HCP education, including peer-to-peer, on SM-AHN and urgency to treat

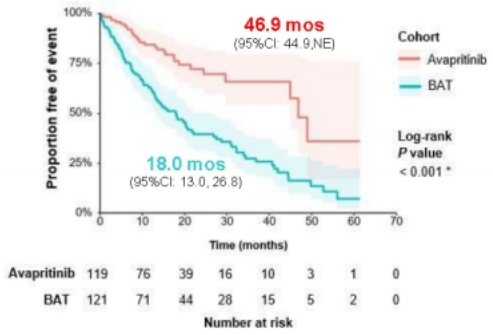
Real-time data alerts to field, enhanced by machine learning, to flag patients most likely to start therapy

Additional data generation, including impact of long-term treatment and data on combination approaches

Incremental field team expansion, ahead of anticipated NonAdvSM launch, will broaden our reach to call on additional providers treating AdvSM patients

Key initiatives to grow the treated AdvSM patient population

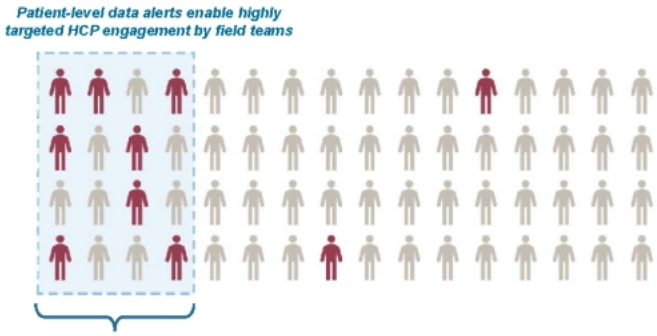
INITIATIVE 1: EDUCATING HCPs ON URGENCY TO TREAT



*P < 0.05

AYVAKIT improved OS in SM-AHN patients compared to best available therapy in a retrospective analysis.[1] In October, NCCN guidelines for SM were updated to cite these study results.

INITIATIVE 2: INCREASING FIELD EFFICIENCY WITH AI/MACHINE LEARNING



A 20% subset of SM patients identified though AI / machine learning approaches generates ~80% of new SM-directed TKI starts

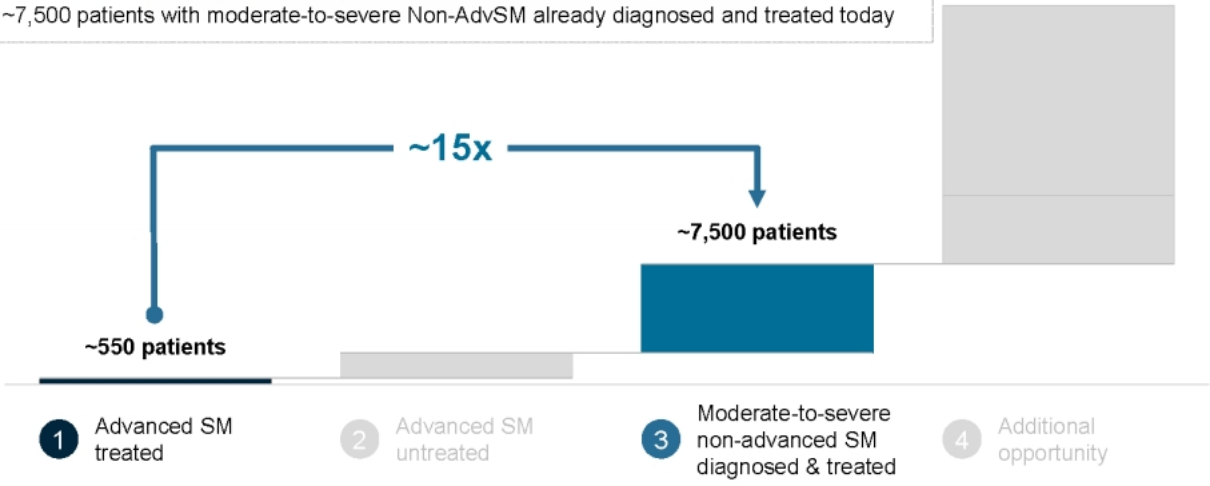
= SM patient initiating a TKI or cytoreductive therapy

1. A multi-center, global, observational, retrospective chart review study was conducted at 6 study sites (4 European, 2 US) to identify and collect data from AdvSM patients who received BAT. SM-AHN patients were identified using inclusion/exclusion criteria similar to the EXPLORER and PATHFINDER trials. The follow-up times for the midostaurin, cladribine, and BAT cohorts were truncated to match the maximum follow-up time of the avapritinib cohort. Reiter et al. Overall Survival in Patients with Systemic Mastocytosis with Associated Hematologic Neoplasm Treated with Avapritinib Versus Best Available Therapy. Presented at EHA 2022. BAT, best available therapy. AI, artificial intelligence.

Non-advanced SM is a significant opportunity with high growth potential

GROWTH OPPORTUNITY

~7,500 patients with moderate-to-severe Non-AdvSM already diagnosed and treated today



1 Advanced SM treated

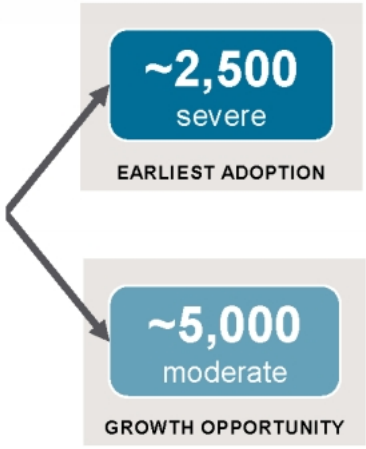
2 Advanced SM untreated

3 Moderate-to-severe non-advanced SM diagnosed & treated

4 Additional opportunity

Our U.S. launch strategy focuses on addressing the needs of ~7,500 patients

~7,500 patients
diagnosed with moderate-to-severe Non-AdvSM, treated with symptom-directed polypharmacy

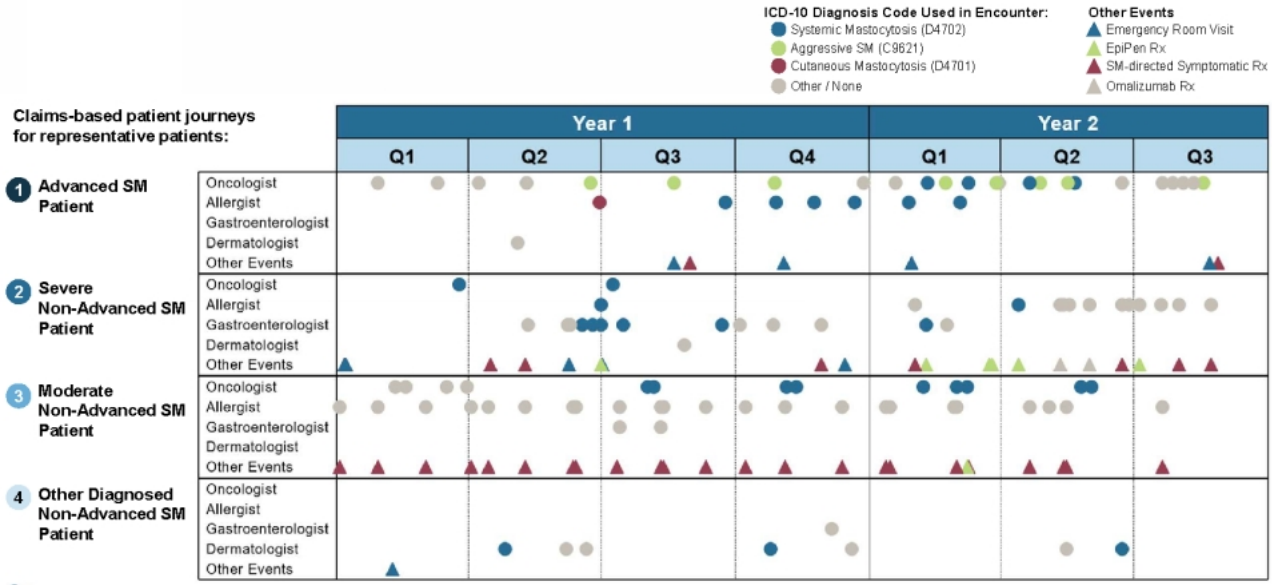


- Higher burden of disease (e.g., higher frequency of anaphylaxis, organomegaly, compromised bone)
- Polypharmacy burden includes higher utilization of TKIs, cytoreductive therapies, and omalizumab

- Moderate burden of disease
- Polypharmacy burden includes long-term use of steroids, cromolyn sodium or Rx antihistamines

U.S. claims data analyses on file. Rx, prescription.

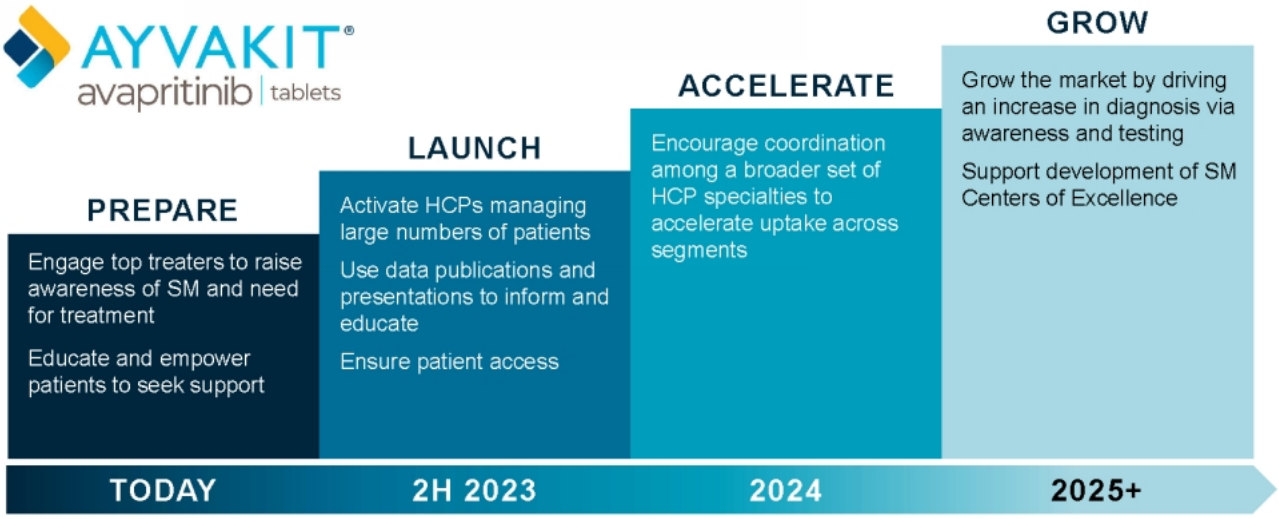
Claims data illustrate disease burden and informs field targeting



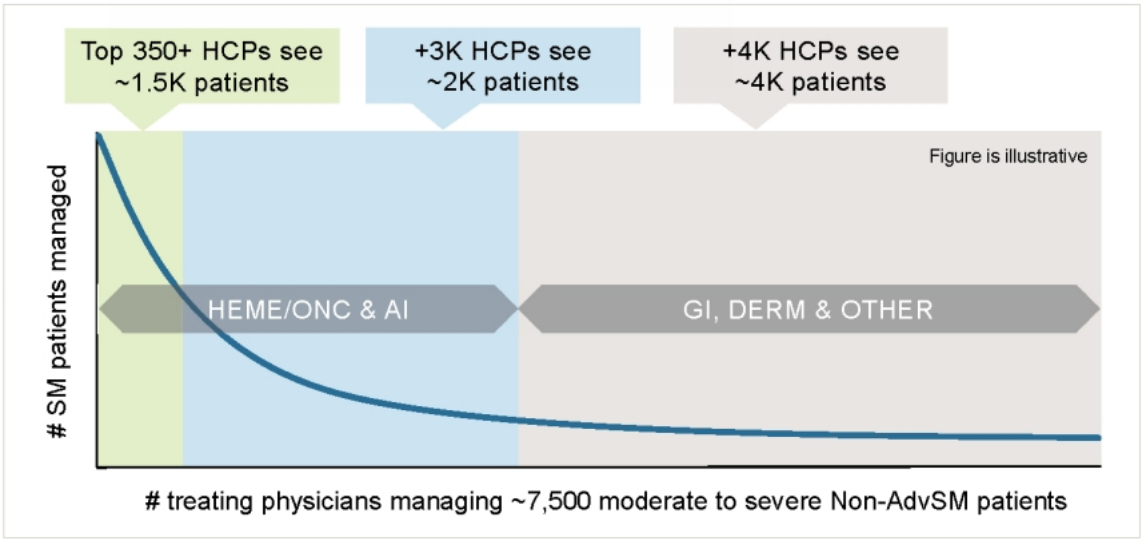
1. Claims algorithm considers number & type of SM diagnosis codes, comorbidities including associated hematologic neoplasms (AHNs) and evidence of organ damage (e.g., splenomegaly, hepatomegaly, compromised bone, etc.), in addition to prescription therapies (e.g., trial of TKIs / cytoreductive therapies, cromolyn sodium, long-term steroid use, omalizumab, epi-pen, etc.). CM, cutaneous mastocytosis; ISM, indolent systemic mastocytosis. Both medical and pharmacy claims are captured.

Launch strategy to drive continued growth in Non-Advanced SM

AYVAKIT® avapritinib | tablets



Analytics based on provider segmentation enables efficient, targeted outreach



U.S. claims data on file. AI, allergist immunologist; derm, dermatologist; heme/onc, hematologist oncologist; GI, gastroenterologist.

Favorable access to AYVAKIT today provides a strong foundation

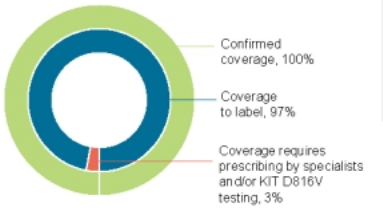
DOSES AVAILABLE TODAY

All doses approved for AdvSM and GIST, including the 25mg dose, are available and covered by payers

100% PAYER COVERAGE

100% payer coverage for all AYVAKIT NDCs, including 25mg[1]

AVYAKIT AdvSM Coverage, by Percentage of Lives



RAPID TIME TO FILL

AYVAKIT sees rapid time to fill and payer prior authorization approvals

Average Days to Fill*	**4.9**
Average Days to PA Approval*	**2.6**

Expect strong access for Non-Advanced SM at launch based on rare disease profile, significant medical need, and lack of approved treatments

*September 2022, prior 90-day lookback period.
1. Market research data on file, Complete Market Payer Research Conducted in September, 2022. NDC, national drug code. PA, prior authorization.

Patient support streamlines the access process for patients

your blueprint®

PATIENT SUPPORT MODEL

1. Minimizes out-of-pocket cost burden for patients
2. Streamlines the access process for patients
3. Provides ongoing information and support to enable adherence

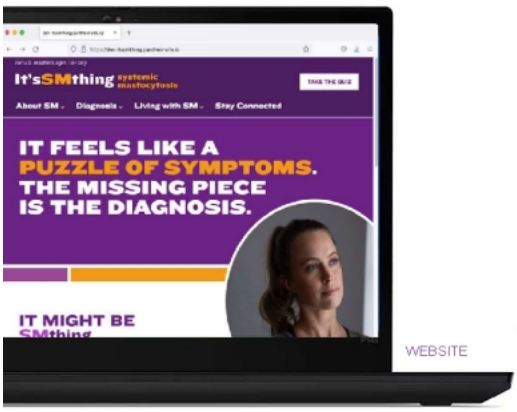
Nearly half of patients receiving AYVAKIT have enrolled in YourBlueprint, exceeding industry benchmarks

SUPPORT OFFERED

- Patient Assistance Program
- Copay Assistance*
- QuickStart
- Coverage Interruption
- Reimbursement Support Resources
- Dose Exchange

* For eligible patients.

An educated patient can be a catalyst for disease treatment



WEBSITE

SOCIAL

It'sSMthing patient and caregiver education campaign

First launched in Q1 2022

~7K patients and caregivers have opted in for routine engagement

~1.3K downloads of a doctor discussion guide

High interest in HCP and patient ambassador webinar series (started in Q3)

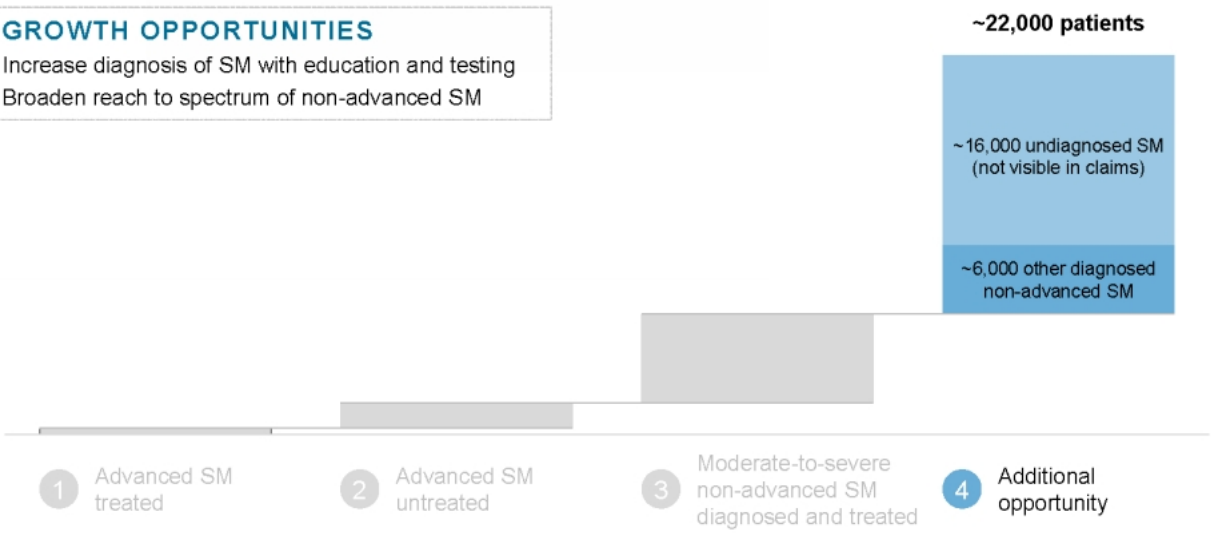
Patient education efforts amplified by long-standing, committed partnerships with patient advocacy groups

Breadth of opportunity to drive long-term AYVAKIT growth

GROWTH OPPORTUNITIES

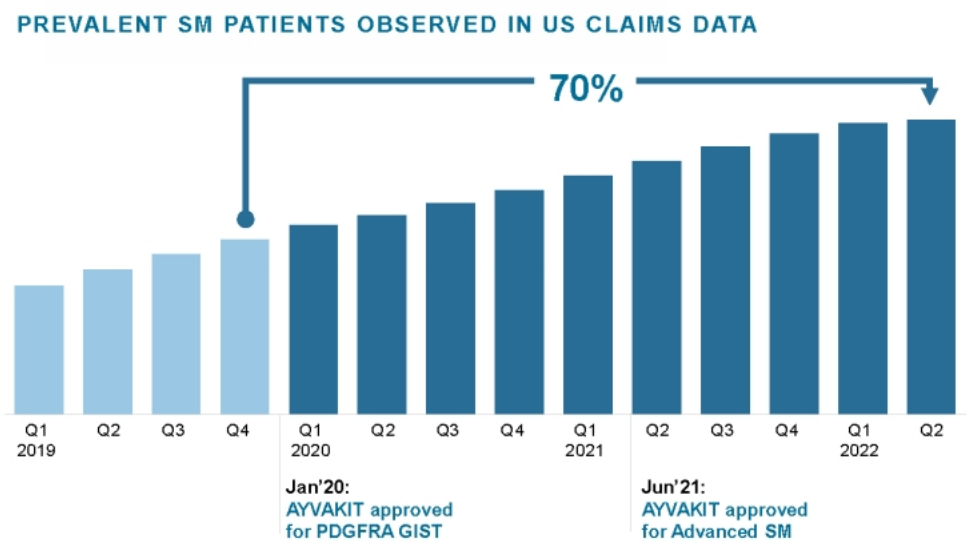
Increase diagnosis of SM with education and testing

Broaden reach to spectrum of non-advanced SM



1. U.S. claims data analyses on file. 2. Cohen, Br J Haematol, 2014.

Our efforts with the SM community have grown the number of diagnosed patients



U.S. claims data analyses on file.

We are well positioned to deliver on the promise of AYVAKIT in SM

- AYVAKIT has the potential to **benefit patients across the spectrum of SM**
  - This represents a >$1B opportunity
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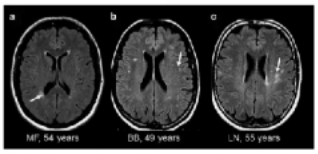
- We are **well-positioned to launch AYVAKIT for Non-AdvSM**
  - First to market, a strong product profile, a leadership position built over nearly a decade, and an experienced team in the market today for AdvSM.

Clinical perspectives on non-advanced SM

BECKER HEWES, MD

Chief Medical Officer

Uncontrolled mast cell proliferation and activation in Non-Advanced SM causes severe and unpredictable symptoms across multiple organ systems[1-3]

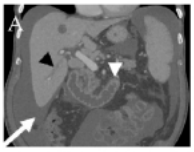


Brain fog, depression, migraines, anxiety

NEUROPSYCHIATRIC

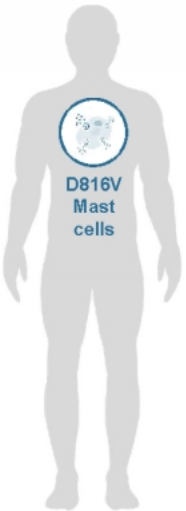
Syncope, dizziness, palpitations, **Hypotensive anaphylaxis**

CARDIOVASCULAR



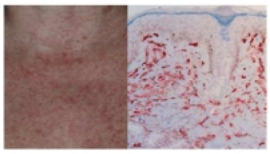
Diarrhea, nausea/vomiting, pain

GASTROINTESTINAL



SYSTEMIC
fatigue, malaise, weight loss

SKIN

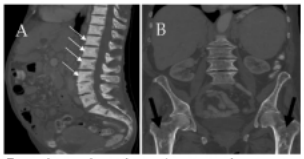


Darier's sign, dermatographism, extreme flushing, pruritus

RESPIRATORY

Dyspnea, congestion, throat swelling, wheezing

MUSCULOSKELETAL



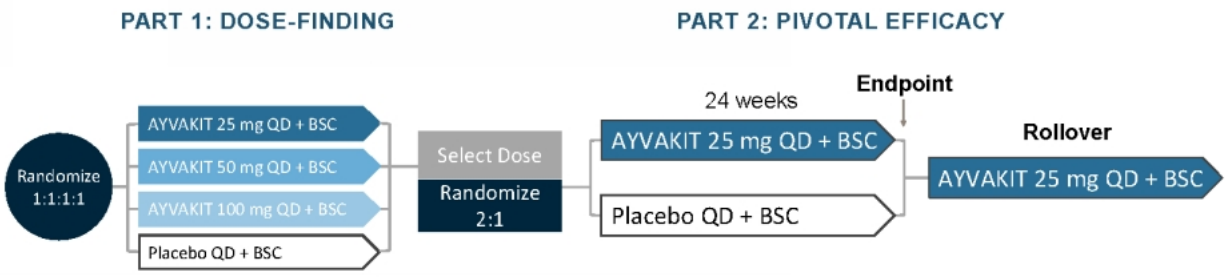
Bone/muscle pain, osteoporosis

Elsaiey, A. et al. Mastocytosis- A Review of Disease Spectrum with Imaging Correlation. *Cancers.* 2021; 13(20):5102.
Boddaert, N et al. Neuroimaging: evidence of brain abnormalities in mastocytosis. *Translational Psychiatry* 2017; 7, e1197.
Berezowska, S., et al. Adult-onset mastocytosis in the skin is highly suggestive of systemic mastocytosis. *Mod Pathol* 2014; 27,19–29.

PIONEER

THE FIRST STUDY TO SHOW DISEASE MODIFICATION AND BENEFIT IN INDOLENT SYSTEMIC MASTOCYTOSIS

PIONEER: Largest clinical trial in Non-Advanced SM



Today's Topics

1 INTERPRETATION OF THE STUDY RESULTS

- Dose selection
- Patient selection
- Placebo performance

2 PHYSICIAN INTERPRETATION OF THE DATA

- Clinical meaningfulness
- Decision to prescribe if approved

3 WHEN WILL WE GET MORE DATA?

Data cutoff as of June 23, 2022. QD, once daily; BSC, best supportive care; QD, once daily; SD, standard deviation.

AYVAKIT demonstrated highly significant and clinically meaningful impact

CLINICAL OUTCOME MEASURES		P VALUE[1]
Primary Endpoint	Mean Change in TSS	0.003
Secondary Endpoints[2]	≥30% Reduction in TSS	0.009
	≥50% Reduction in TSS	0.005
	Mean Change in Most Severe Symptom Score	0.015
	≥50% Reduction in Serum Tryptase	<0.0001
	≥50% Reduction in KIT D816V VAF	<0.0001
	≥50% Reduction in Bone Marrow MC Aggregates	<0.0001

Data cutoff as of June 23, 2022. 1. One-sided p-value < 0.025 indicates statistical significance. 2. For secondary endpoints, reductions in TSS and objective measures of mast cell burden represent proportion of patients with ≥30% and ≥50% reductions. All endpoints are key secondary endpoints, except for "Mean Change in Most Severe Symptom Score", which is an additional secondary endpoint. TSS, total symptom score; VAF, variant allele fraction; MC, mast cell.

AYVAKIT decreased patient-reported symptoms and objective measures of disease burden

PART 2: PRIMARY ENDPOINT

Mean change in Total Symptom Score (TSS)
[95% CI]

	AYVAKIT	Control
week 24	**-15.6** [-18.6 – -12.6]	**-9.2** [-13.1 – -5.2]

rollover

	AYVAKIT
week 48	**-20.2** [-24.7 – -15.7]

PART 2: SECONDARY ENDPOINT

Proportion of patients with ≥50% reduction in serum tryptase
[95% CI]

	AYVAKIT	Control
week 24	**53.9%** [45.3 – 62.3]	**0.0%** [0.0 – 5.1]

Data cutoff as of June 23, 2022. CI, confidence interval; SD, standard deviation

AYVAKIT was well-tolerated with a safety profile favorable to control

	AYVAKIT	Control
AEs, n (%)	128 (90.8)	66 (93.0)
SAEs, n (%)	7 (5.0)	8 (11.3)
Discontinuation due to TRAEs, n (%)	1 (0.7)	0 (0.0)
TRAEs in ≥5% of AYVAKIT patients, by preferred term		
Headache, n (%)	11 (7.8)	7 (9.9)
Nausea, n (%)	9 (6.4)	6 (8.5)
Peripheral edema, n (%)	9 (6.4)	1 (1.4)
Periorbital edema, n (%)	9 (6.4)	2 (2.8)

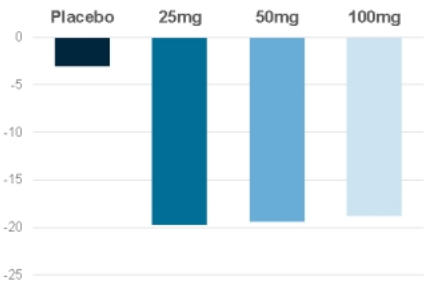
- No ICB events
- Lower rate of cognitive effect AEs[1] reported for AYVAKIT (2.8%) vs. control (4.2%)
- No Grade 3 cognitive effect AEs[1] for AYVAKIT (0%) vs. control (1.4%)
- In the AYVAKIT arm, 93% of edema AEs were Grade 1, with remainder Grade 2
- Higher Part 2 completion rate for AYVAKIT (96.5%) vs. control (93.0%)

Data cutoff as of June 23, 2022. 1. Cognitive effect AEs refer to 17 pooled terms identified across AYVAKIT clinical studies. AE, adverse event; ICB, intracranial bleed; SAE, serious adverse event; TRAE, treatment-related adverse event.

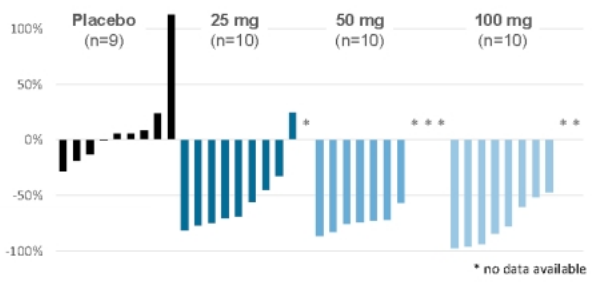
Maximum symptom improvement seen with 25 mg irrespective of tryptase reduction

Part 1

TSS REDUCTION FROM BASELINE
week 24



% CHANGE IN SERUM TRYPTASE FROM BASELINE
week 24



Part 2

- **DEEP SYMPTOM REDUCTION**
- **SYMPTOM REDUCTION WAS NOT CORRELATED WITH TRYPTASE REDUCTION**

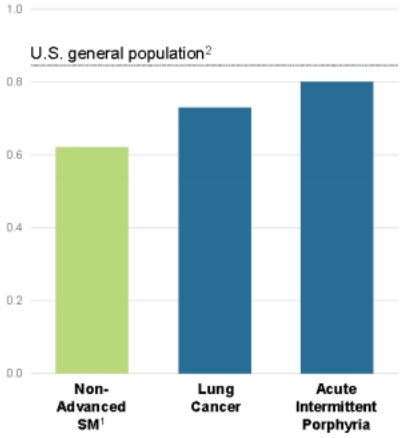
Patients with High Baseline Tryptase*	
Comparison of % change in TSS & % change in tryptase	Low Correlation Coefficient 0.38

* >50 ng/ml at baseline. TSS, total symptom score.

Non-Advanced SM patients had poor QoL and improved on AYVAKIT

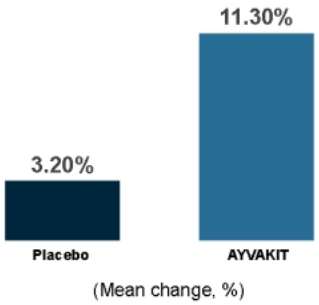
EQ-5D IS A WIDELY-USED QOL TOOL

NON-ADVANCED SM PATIENT QOL IS LOWER THAN SOME TERMINAL DISEASES



PIONEER Trial

AYVAKIT LED TO CLINICALLY MEANINGFUL INCREASES IN QOL AT 24 WEEKS



QOL, Quality of Life
1. Average EQ-5D score of all PIONEER patients at baseline; 2. Jiang R, et al., Qual Life Research. 2021;30; 3. Pickard AS, et al., Qual Life Outcomes. 2007.

AYVAKIT showed reduction in polypharmacy: illustrative example oral cromolyn

	MEDICATION CLASSES
MULTIPLE SYMPTOMS	H1 inhibitors H2 inhibitors Leukotriene inhibitors Systemic steroids Anti-IgE antibodies
GASTROINTESTINAL	Proton Pump Inhibitors **Oral Cromolyn** Anti-diarrheals
ANAPHYLAXIS	EpiPens
OSTEOPOROSIS	Bisphosphonates
PAIN	NSAIDS Opiates

ORAL CROMOLYN SODIUM

- High concentration oral formulation of cromolyn sodium
- Recommended dose 2 vials diluted in water 4x day, before meals and at bedtime

PIONEER

- 58 patients used at baseline

Patients who reduced their dose or frequency of taking oral cromolyn sodium by month 6

AYVAKIT 25 mg QD + BSC	13/58 (22%)
Placebo QD + BSC (Control)	0/31 (0%)

Anti-IgE, anti-immunoglobulin E; NSAIDS, non-steroidal anti-inflammatory drugs.

CASE PRESENTATIONS & PANEL DISCUSSION

PANKIT VACHHANI, MD

Assistant Professor of Medicine
Hematology Oncology
University of Alabama School of Medicine
Birmingham, Alabama
Pioneer Investigator

H. JAMES WEDNER, MD

Professor of Medicine
Division of Allergy and Immunology
Washington University
St. Louis, Missouri

FRANK SIEBENHAAR, MD

Assistant Professor
Head IFA Outpatient Clinic for Allergology
Charité University
Berlin, Germany
Pioneer Investigator

Drs. Vachhani, Wedner and Siebenhaar have consulting relationships with Blueprint Medicines

Case 1 – Prof. Siebenhaar

PATIENT JOURNEY

34-year-old man

- Allergic rhinitis, asthma in 1990
- **Diagnosed @ 20yrs old**
  - non-advanced SM in 2008
- KIT D816V positive
- Baseline tryptase < 20ng/ml

BASELINE SYMPTOMOLOGY

GI: recurrent, unpredictable diarrhea

Neuro: Brain fog, dizziness, headache

Skin: lesions < 60%; triggered by exercise, shower, hot bath

Skeletal: Bone pain

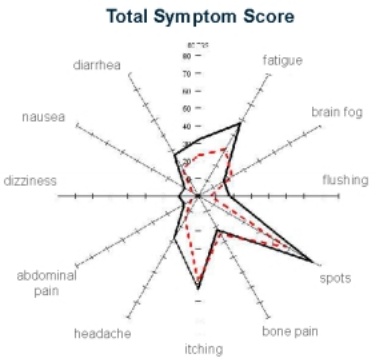
POLYPHARMACY

- Ebastine (H1-blocker)
- Famotidine
- Cromoglycate
- Epipen

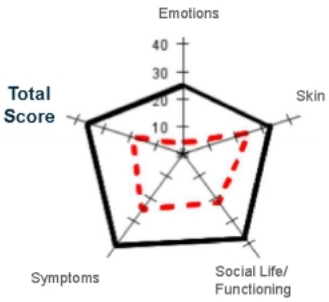
PATIENT ADOPTED LIFESTYLE TO SYMPTOMS	Working from home, fatigue	Forgot what "normal" felt like

Case 1 – Symptom & QoL improvement after 6 months AYVAKIT treatment

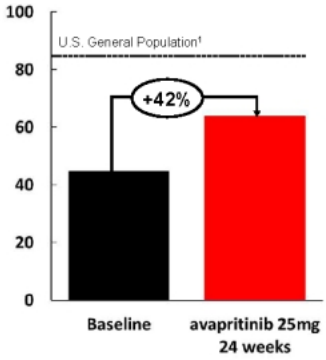
ISM – SYMPTOM ASSESSMENT FORM
(lower = health improvement)



MC-QOL
(lower = health improvement)



EQ-5D
(higher = health improvement)



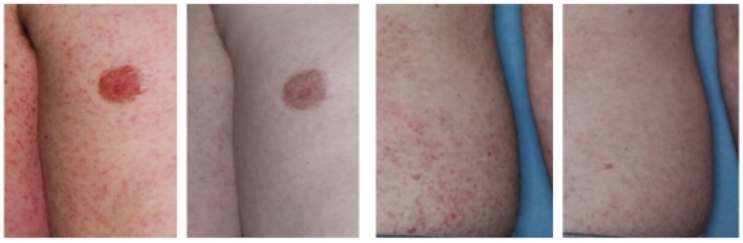
Baseline — avapritinib 25 mg @ 24 weeks

1. Jiang R, et al., Qual Life Research. 2021;30. ISM, indolent SM; MC-QOL, mastocytosis quality of life questionnaire.

Case 1 – Symptoms and overall improvements

SKIN IMPROVEMENTS

Before | After | Before | After



AYVAKIT OUTCOMES

- **Patient reports "life-changing" improvement**, including continued improvement in QoL
  - Ability to be more productive at work
- No new symptoms, and reduction in skin and GI symptoms
- No diarrhea after 6 months

THIS PATIENT REMAINS ON AYVAKIT TODAY

Patients' permission granted for use of photos. GI, gastrointestinal.

Case 2 – Dr. Vachhani

PATIENT JOURNEY

39-year-old mother of four

- First symptoms in 2017
- **Diagnosed @ 36 yrs old**
  - non-advanced SM in 2019
- KIT D816V positive
- Prior midostaurin, interferon, IV famotidine
- Baseline tryptase < 20ng/ml

BASELINE SYMPTOMOLOGY

GI: Chronic diarrhea, pain with food

Neuro: Brain fog

Skin: Typical SM lesions on trunk and limbs

Skeletal: Bone Pain

Systemic: Recurrent anaphylaxis, flushing

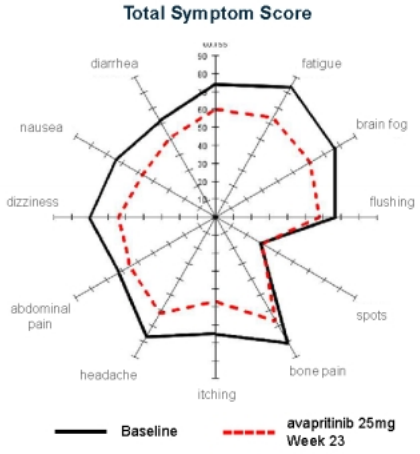
POLYPHARMACY

- Oral cromolyn
- famotidine
- levocertrizine
- fexofenadine
- omalizumab
- doxepin
- montelukast (others)
- **Epipen (99 in one year)**

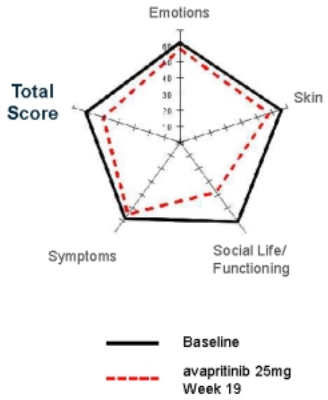
PATIENT ADOPTED LIFESTYLE TO SYMPTOMS	Stopped working and traveling	Had to isolate, wear N95 mask in pubic before COVID pandemic	Unable to attend kids' events	Multiple episodes of life-threatening anaphylaxis

Case 2 – Quality of life improvements

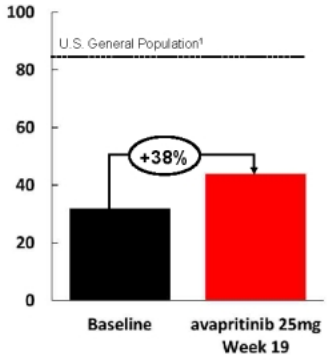
ISM – SYMPTOM ASSESSMENT FORM
(lower = health improvement)



MC-QOL
(lower = health improvement)



EQ-5D
(higher = health improvement)



1. Jiang R, et al., Qual Life Research. 2021;30

Dr. Wedner's Practice – Washington University Division of Allergy & Immunology

Systemic Mastocytosis Practice

- Treats multiple disorders including HAE, resistant atopic diseases, & routine allergy disorders
- Currently ~50 patients with SM
  - ~5-10 advanced SM
  - ~20 very bad/debilitating
  - ~20 significant disease

Referral basis

- ER anaphylaxis patients
- Allergists
- Dermatologists – hives and skin lesions, dermatographism
- Gastroenterologists – diarrhea and GI pain
- Neuro – unexplained brain fog

ER, emergency room; HAE, hereditary angioedema.

Case Study #3 – Dr. Wedner

Presentation

41-year-old woman

- Referred by local ER for anaphylaxis
- **GI**: Frequent stomach upset
- **Skin**: Years of itching and skin flushing
- **Systemic:** Occasional shortness of breath

Additional History & Testing

- **Skin:** spots, severe flushing episodes
- **GI:** Nausea, vomiting & frequent diarrhea "Food allergy?"
- Darier's Sign on Physical Exam
- Osteopenia
- Tryptase = 42
- ddPCR – D816V pos
- Marrow mast cells

Polypharmacy

- Certrizine
- Famotidine
- Montelukast
- Zyflo CR
- Ketotifen
- Gastrocrom
- EpiPen

CURRENT SYMPTOMS	Persistent GI symptoms	Episodic flushing and itching	Anxiety about anaphylaxis	Spots

ddPCR, digital droplet polymerase chain reaction.

A new era for patients with Systemic Mastocytosis

AYVAKIT® avapritinib | tablets

Non-Advanced SM is a devastating disease without any disease modifying treatment options

PIONEER data support AYVAKIT's efficacy as the first disease modifying agent, with safety data at 25 mg highlighting potential for long-term treatment

Patient impact was reflected on multiple measures of symptom and QoL improvement

On track to submit sNDA to FDA for Non-Advanced SM by the end of 2022

sNDA, supplemental new drug application.

CLINICAL PANEL Q&A

PANKIT VACHHANI, MD

Assistant Professor of Medicine
Hematology Oncology
University of Alabama School of Medicine
Birmingham, Alabama
Pioneer Investigator

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Assistant Professor
Head IFA Outpatient Clinic for Allergology
Charité University
Berlin, Germany
Pioneer Investigator


break
blueprint
MEDICINES

Expanding patient impact with precision medicine leadership

FOUAD NAMOUNI, MD

President, R&D

blueprint MEDICINES

Our proven research and development engine

development candidates nominated

success rate from IND to clinical POC

breakthrough therapy designations

years from IND to first approval

approved medicines

FDA approved indications

Targeting areas of high medical need and scaled patient impact

MAST CELL DISEASES

AYVAKIT: KIT D816V

BLU-263: KIT D816V

Research: wt-KIT

LUNG CANCER

GAVRETO: RET

BLU-945: EGFR

BLU-701: EGFR

BLU-525: EGFR

BLU-451: EGFR ex20

BREAST CANCER

BLU-222: CDK2

Research: undisclosed

CANCER IMMUNOTHERAPY

Research: MAP4K1

Research: undisclosed

Multiple additional undisclosed research programs in areas of medical need

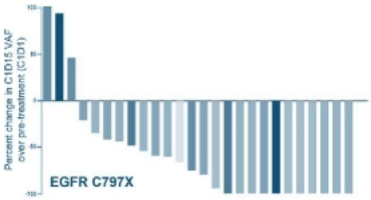
wt-KIT, wild-type KIT.

We will achieve R&D scale by leveraging our strengths

LEADING PRECISION MEDICINE RESEARCH PLATFORM

Pairing of kinase and targeted protein degradation platforms builds on our **knowledge and experience**

ADVANCED TRANSLATIONAL MEDICINE APPROACHES



Robust scientific capabilities enable effective and efficient clinical strategy in complex disease areas

CULTURE OF INNOVATION

- Scientific rigor and depth
- Urgency to help patients
- Efficient resource allocation

Our talented and committed team forms the foundation of our **strong R&D infrastructure**

Transforming treatment of EGFRm lung cancer

FOUAD NAMOUNI, MD

President, R&D

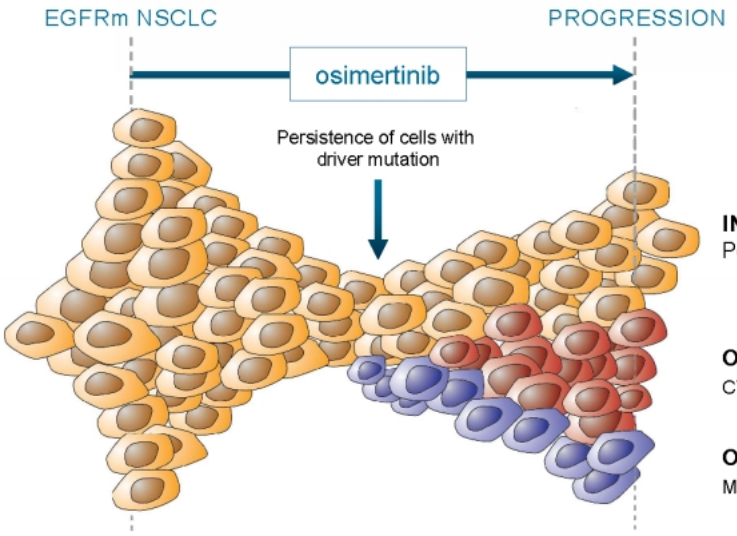
Our progress in addressing the medical need in EGFRm NSCLC

- Lung cancer is the leading cause of cancer death globally[1]
- EGFR is one of the most common oncogenic drivers in lung cancer[1]
- There are ~60,000 first-line EGFRm NSCLC patients in major markets[2]
- Patients with the EGFR L858R driver mutation have poorer outcomes

- Working to address medical needs in EGFR-driven NSCLC through rational combinations
- Advancing multiple clinical candidates with best-in-class potential derived from our strong discovery capability
- Leveraging our knowledge and experience in NSCLC to generate decision-making data that is informing our development strategy

1. American Cancer Society. Key Statistics About Lung Cancer. https://www.cancer.org/cancer/lung-cancer/about/key-statistics. 2. Approximate patient numbers covering major markets – US, EU4, UK, and Japan. 1. Excludes rare mutations including exon 20 insertions. Internal estimates adapted from Ramalingam, et al. NEJM, 2020; Decision Resources Group: NSCLC Forecast and Epidemiology; and Harrison Seminars in Cancer Biology, 2020.

Patients with EGFRm NSCLC have significant medical needs despite standard of care



INCOMPLETE DRIVER INHIBITION
Poorer outcomes for L858R versus ex19del

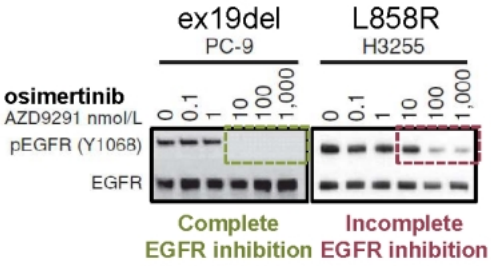
ON TARGET EGFR RESISTANCE
C797X, L718X, L792X, G796X, etc.

OFF TARGET RESISTANCE
MET, ALK, RET, KRAS, BRAF, CCNE1, etc.

Poorer outcomes in EGFR L858R are associated with incomplete EGFR inhibition

OSIMERTINIB OUTCOMES IN FLAURA 1L NSCLC[1]

OSIMERTINIB INHIBITION OF EGFR CELL LINES[2]



1. Soria NEJM 2014; Ramalingam NEJM 2020. 2. Cross et al., Cancer Dis, 2014. ex19del, exon 19 deletion mutation; mo, months; PFS, progression free survival; OS, overall survival.

Our EGFR portfolio strategy is comprehensive and modular

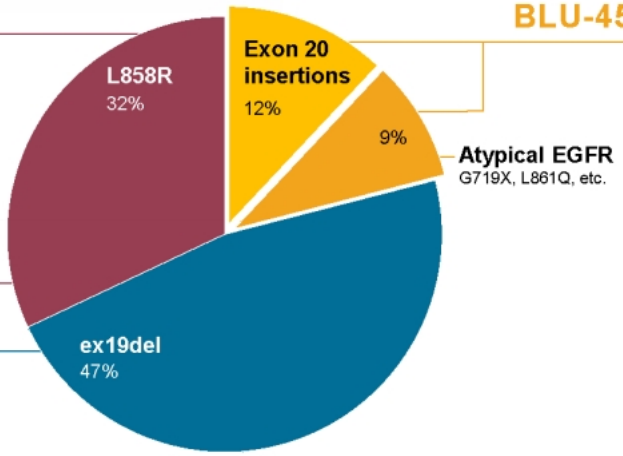
BLU-945

- More potent on L858R than ex19del
- Covers EGFR T790M and C797S

BLU-451

BLU-701/525

- Potent coverage of L858R and ex19del
- Covers EGFR C797S



Target coverage based on preclinical data; Ref: Riess 2018 J Thorac Oncol.

BLU-945 dose escalation data in late-line patients

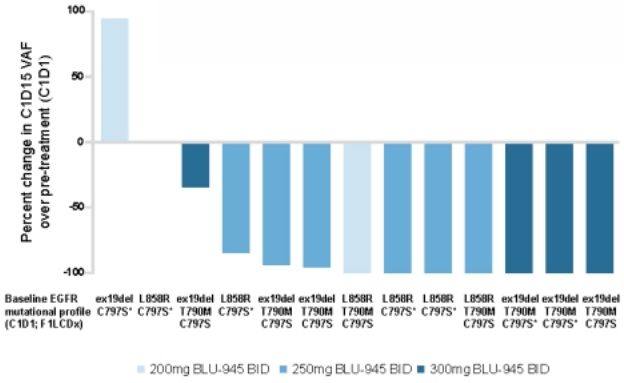
- Updated BLU-945 monotherapy dose escalation data show:
  - **Differentiated safety** with limited wild-type-EGFR-related adverse events that were not dose limiting
  - **Robust target ctDNA responses** leading to tumor shrinkage
  - No durability of benefit, likely due to late-line disease heterogeneity and off-target resistance
- There is a **significant medical need** in 1L EGFR L858R
  - In treatment-naïve patients, EGFRm NSCLC is mainly driven by activating EGFR mutations
  - Patients with **EGFR L858R have poorer outcomes** versus ex19del with standard of care osimertinib
  - Preclinical data in 1L EGFR L858R model showed **BLU-945 + osimertinib was better than monotherapy**
  - Minimal evidence of wild-type-EGFR-related toxicity for **BLU-945 + osimertinib combination** in early dose escalation data

Prioritizing development of BLU-945 + osimertinib in 1L EGFR L858R

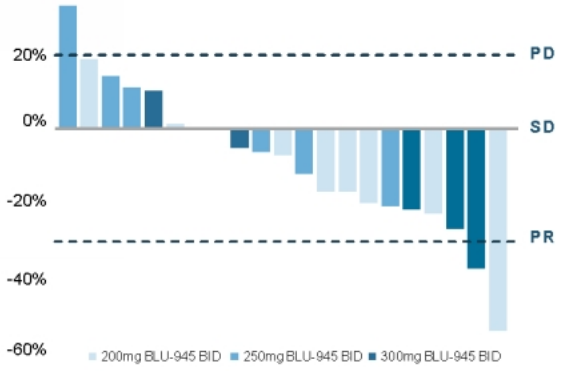
ctDNA, circulating tumor DNA.

BLU-945 monotherapy dose escalation data support combination development

EGFR C797S ctDNA CLEARANCE



TUMOR SHRINKAGE

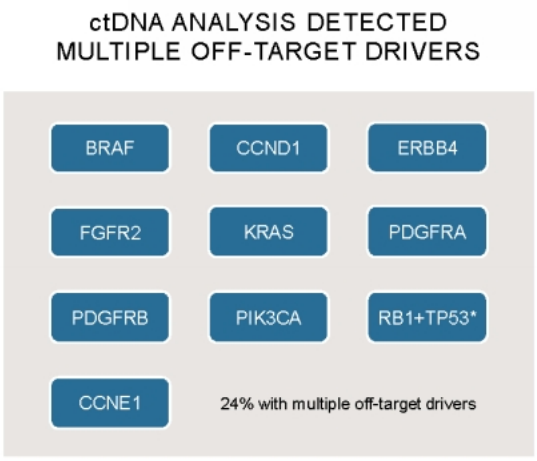


BLU-945 WAS GENERALLY WELL-TOLERATED

- Minimal evidence of wild-type-EGFR-related toxicity
- Reported DLTs were non-EGFR-related
  - LFT elevations, fatigue, nausea and vomiting

Data cutoff date: September 13, 2022. BID, twice daily; C1D1, cycle 1 day 1; C1D15, cycle 1 day 15; DLT, dose-limited toxicity; LFT, liver function tests. PD, progressive disease; PR, partial response; RP2D, recommended phase 2 dose; SD, stable disease; VAF, variant allele fraction.

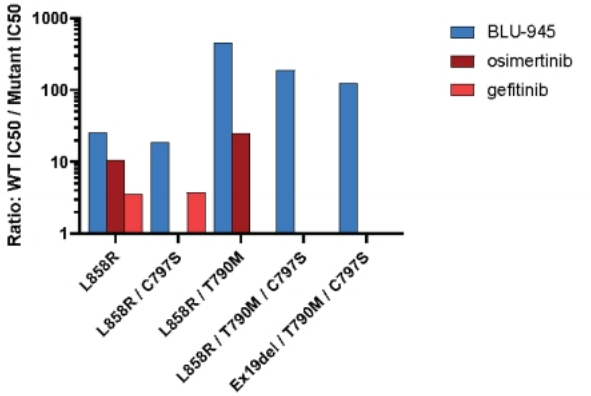
Significant off-target resistance limits opportunity for EGFR targeted therapy in 2L+

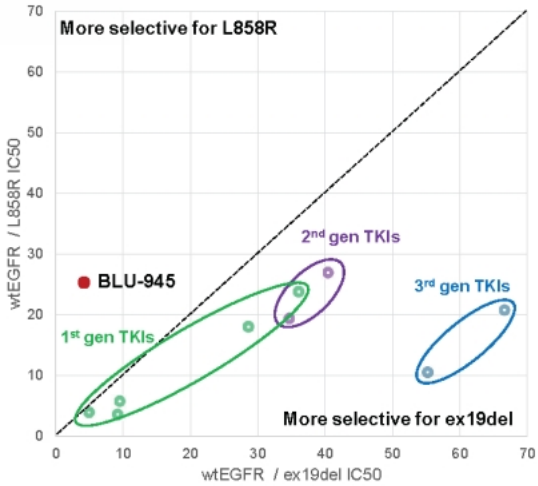


- Significant tumor heterogeneity detected at baseline in late-line patients with multiple off-target drivers of resistance
- Increase in off-target drivers also detected at end-of-treatment in a subset of patients
- Off-target resistance likely driving limited responses and poor durability despite robust EGFR inhibition seen by ctDNA
- Optimization of EGFR pathway inhibition is likely to be more successful in front-line, in the absence of multiple resistance mechanisms

Data cutoff date: September 13, 2022. **RB1 and TP53 loss is evidence for likely histological transformation; Offin M. J Thorac Oncol, 2019.

BLU-945's unique selectivity profile enables a wide therapeutic index and more potent inhibition of L858R with or without on-target resistance

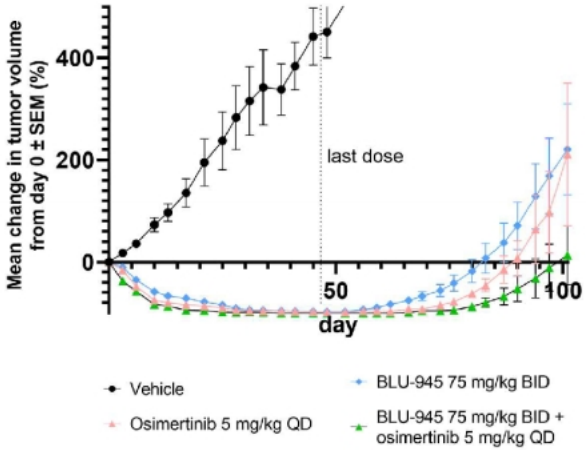


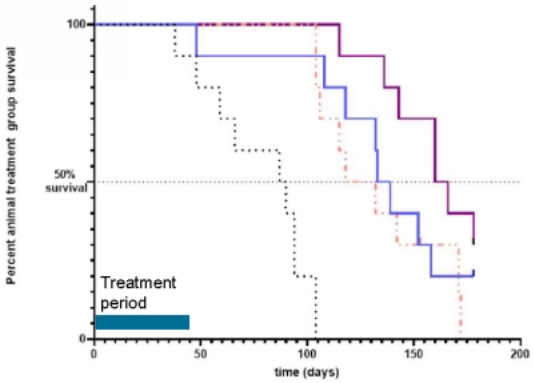


Data on file. IC50, half-maximal inhibitory concentration; WT, wild-type; wtEGFR, wild-type EGFR.

BLU-945 and osimertinib combine to more completely inhibit EGFR and extend survival in treatment-naïve L858R preclinical models

LUN439 PDX (treatment naïve L858R)





Treatment	mOS (days)	p-value (vs osi)
Vehicle	89	<0.0001
BLU-945 75mg/kg	136	ns
Osimertinib 5mg/kg	125	-
BLU-945 75mg/kg + Osimertinib 5mg/kg	163	0.04

Tavera-Mendoza. EORTC-NCI-AACR, 2022. mOS, median overall survival; PDX, patient-derived xenograft model; SEM, standard error of the mean.

Early SYMPHONY trial dose escalation data show BLU-945 + osimertinib combination has been generally well-tolerated to date

Symphony

BLU-945 + OSIMERTINIB 80 MG DOSE ESCALATION

Patients with EGFRm NSCLC and >1 prior TKI

BLU-945 QD + 80 MG OSIMERTINIB	BLU-945 BID + 80 MG OSIMERTINIB
200 mg QD	100 mg BID
300 mg QD	150 mg BID
400 mg QD (recently opened)	

QD and BID dose escalation is ongoing

Minimal evidence of wild-type-EGFR-related toxicity

No DLTs reported to date

Upon RP2D selection, plan to initiate expansion cohort in patients with 1L L858R

Data cutoff date: September 13, 2022.

Plan to prioritize BLU-525, with minimal disruption to overall EGFR portfolio timeline

- Phase 1 HARMONY trial dose escalation update
  - BLU-701 showed early evidence of activity at low doses
  - Drug metabolism pathway has limited dose escalation
- Plan to prioritize BLU-525 and deprioritize BLU-701
  - Different chemical structure with different metabolism pathway
  - Similar EGFR mutational coverage
  - Improved kinome selectivity
  - Improved CNS penetration
- Next steps:
  - Plan to submit IND to FDA for BLU-525 in Q1 2023
  - Patients currently enrolled in the HARMONY trial will be able to continue treatment

CNS, central nervous system.

BLU-451 escalation ongoing with early response in EGFR ex20ins patient

Phase 1 CONCERTO trial dose escalation update
- Currently enrolling 400mg QD
- No DLTs reported to date
- No treatment-related grade 3+ AEs reported to date

63 yo F with ex20ins NSCLC

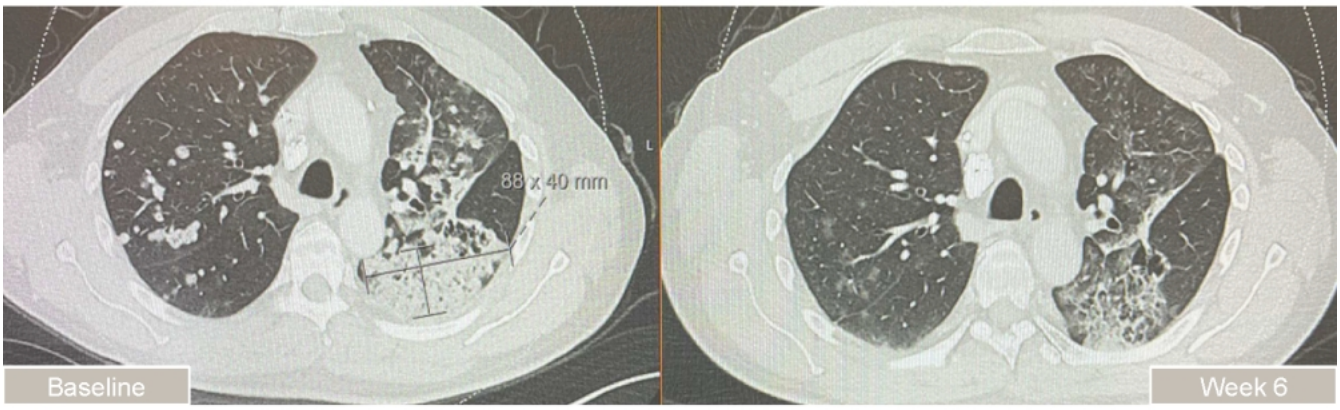
Prior therapies:
- carbo/pemetrexed/pembro
- CLN-081 (dc'd for toxicity)
- BDTX-189 (dc'd for PD)

BLU-451 200 mg QD

Only related AE is grade 1 rash

Confirmed PR (-58%)

Treatment ongoing in cycle 5



A cycle is 21 days. Data cutoff date: October 11, 2022. AE, adverse event. Ex20ins, exon 20 insertion mutation.

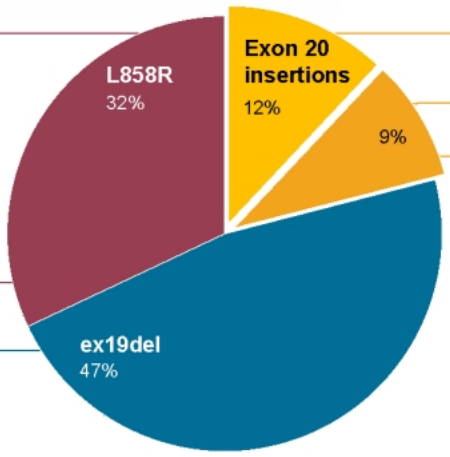
Our EGFR portfolio strategy is comprehensive and modular

BLU-945

+ osimertinib
1L NSCLC with EGFR L858R

BLU-525

+ BLU-945
1L NSCLC with EGFRmut



BLU-451

- 2L+ exon20 NSCLC
- 1L exon20 NSCLC

Atypical EGFR
G719X, L861Q, etc.

Precision at Scale:
Delivering improved outcomes for people with EGFR-mutant NSCLC

Do we have a winning approach to improve outcomes for patients with EGFR-mutant NSCLC?

1. BLU-945 monotherapy was clinically active and showed a differentiated safety profile. However, durability of response was limited due to frequent off-target drivers in 2L+ patients
2. Prioritizing development of BLU-945 in combination with osimertinib in 1L L858R, based on exciting preclinical data and early clinical safety data
3. Pulling forward BLU-525, the backup compound for BLU-701, to bring the best candidate into development with minimal disruption to the overall timeline
4. Encouraging early activity data from the BLU-451 dose escalation trial

Research innovation at scale

PERCY CARTER, PHD

Chief Scientific Officer

blueprint MEDICINES

Blueprint's Science Leadership Team

ROB MEISSNER, PHD
SVP, Chemical Sciences

STEVE MILLER, PHD
VP, Precision Open Innovation

RONDA RIPPLEY, PHD
VP, Quantitative Pharmacology & Drug Safety

SCOTT RIBICH, PHD
VP, Biology Drug Discovery

RACHEL ERLICH, PHD
VP, Translational Medicine & Integrated Research

TIM LABRANCHE, DVM, PHD
VP, Preclinical Safety & Comparative Medicine

JASON BRUBAKER, PHD
VP, Medicinal Chemistry

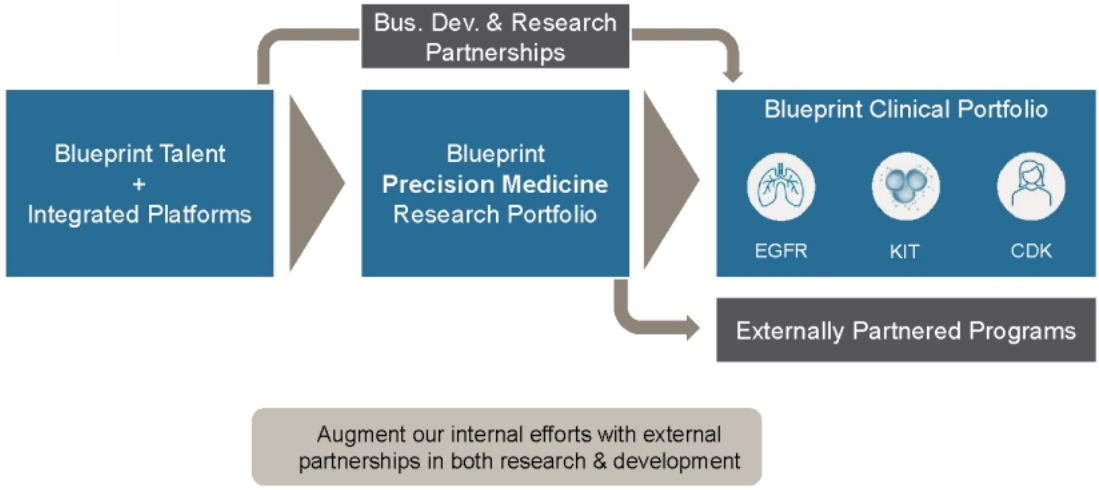
LAKSHMI MUTHUSWAMY, PHD
Director, Computational Biology & Bioinformatics

Research at Blueprint Medicines

Develop both our talent and platforms

- Support development and enhancement of three therapeutic areas
- Lead the creation of new therapeutic opportunities

Research at Blueprint Medicines



Augment our internal efforts with external partnerships in both research & development

We have a focused approach to portfolio construction

At all stages, early to late, we progress programs that have:

Transformative Potential

Provides meaningful benefit to patients with high medical need

Precision Approach

Well-defined patient identification strategy, compatible with real world

Defined Value Inflections

Delineated data-driven decision points at all R&D stages

Blueprint Edge

Benefits from our focused approach to small molecule drug discovery

Today's update

Blueprint Clinical Portfolio  EGFR KIT CDK	▪ EGFR Backup Candidate ▪ CDK2 program
Blueprint **Precision Medicine** Research Portfolio	▪ Wild-type KIT program ▪ Immuno-oncology collaboration with Roche
Blueprint Talent + Integrated Platforms	Targeted Protein Degradation Efforts

Our EGFR portfolio has potential to address all known driver mutations and associated resistance mechanisms

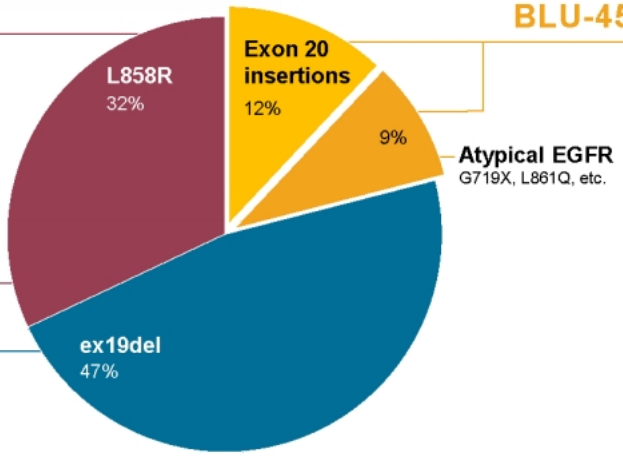
BLU-945

- More potent on L858R than ex19del
- Covers EGFR T790M and C797S

BLU-451

BLU-525

- Potent coverage of L858R and ex19del
- Covers EGFR C797S



Target coverage based on preclinical data; Ref: Riess 2018 J Thorac Oncol.

BLU-525 is an improved brain penetrant, reversible EGFR inhibitor

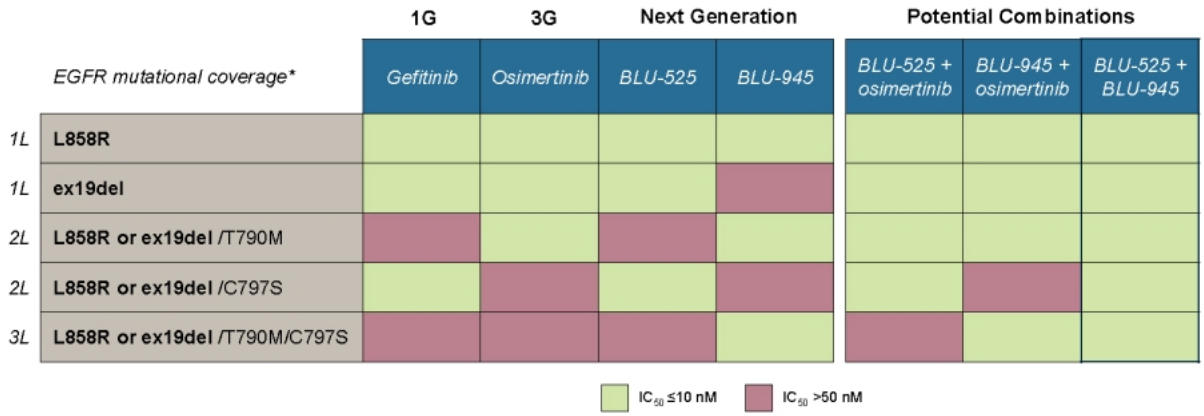
		BLU-701	BLU-525
Potency (IC_{50}, nM) [WT-selectivity]	**Exon19Deletion** (enzyme / cell pEGFR PC9)	0.5 [109x] / 1.3 [83x]	0.9 [19x] / 1.2 [96x]
	Exon19Deletion C797S (cell pEGFR Ba/F3 Ex19Del/CS)	1.8 [107x]	9.5 [12x]
	L858R (enzyme / cell pEGFR Ba/F3 LR)	2.6 [21] / 3.3 [33x]	1.6 [10x] / 4.2 [27x]
	L858R C797S (cell pEGFR Ba/F3 LR/CS)	3.3 [33x]	8.5 [14x]
Kinome Selectivity	S(10) @ 3 μM	0.060	0.015
Brain Penetration	Rat IV infusion (Kpuu)	0.98	1.3

- Key advantages of BLU-525 over BLU-701:
  - Differentiated chemical structure → altered metabolic profile
  - Improved kinome selectivity, but retains high potency and wild-type EGFR selectivity
  - Improved safety profile in non-GLP and GLP toxicology studies (rodent, non-rodent)

GLP, good laboratory practice. nM, nanomolar; IV, intravenous; uM, micromolar. See also: L. Tavera-Mendoza et al. AACR-NCI-EORTC 2022, Barcelona, Spain, October 26–28.

BLU-525 is an improved brain penetrant, reversible EGFR inhibitor

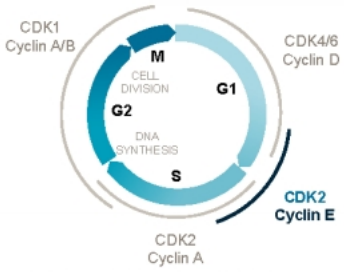
Together, BLU-525 and BLU-945 will cover both common EGFR mutations and associated primary resistance mutations



* Based on biochemical IC_{50}. 3L, third line; 1G, first generation; 3G, third generation.

Targeting cancer pathways vulnerable to CDK2 inhibition

CDK-CYCLIN COMPLEXES REGULATE THE CELL CYCLE



ABERRANT CYCLIN E (CCNE1) DRIVES CELL PROLIFERATION

Critical Role in Progression

1L combo & CDK4/6i Resistance

HR+ / HER2- Breast Cancer

Precision Medicine

*CCNE1+ Solid Tumors**

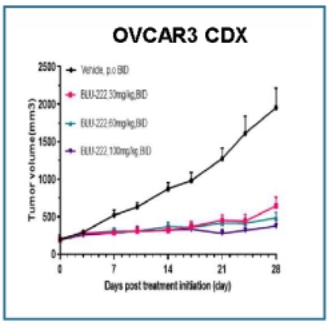
- **Ovarian Cancer (20%)**
- **Endometrial Carcinoma (11%)**
- Gastric Cancer (11%)
- Esophageal Cancer (8%)
- Triple Negative Breast Cancer (11%)
- Lung Adenocarcinoma (5%)
- Others

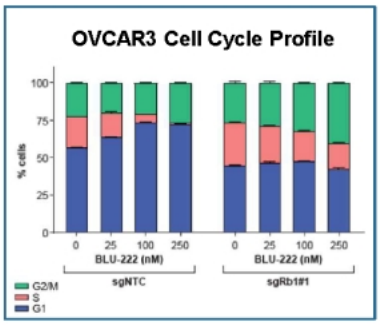
- **No targeted therapies** approved to address these mechanisms of disease or resistance
- **Strong biological rationale** with preclinical and/or clinical validation
- However, molecular **selectivity has been challenging** to achieve historically by others

*CCNE1 amplification frequency represented as percentage of total patient samples. Data from the National Cancer Institute's The Cancer Genome Atlas Program (www.cancer.gov/tcga). HR+/HER2-, hormone receptor-positive, HER2-negative.

BLU-222 is a highly potent and selective CDK2 inhibitor

		BLU-222
CELL	pRb IC_{50} (nM)	4.2
	pLamin / pRb (CDK1/2)	84x
ENZYME (1mM ATP)	CDK2 IC_{50} (nM)	2.6
	CDK4/2	150x
	CDK6/2	105x
	CDK7/2	2,700x
	CDK9/2	2,300x
	S(10)	0.045





- BLU-222 has excellent **potency, CDK-family selectivity, and overall kinome selectivity**
- ADME and toxicology profiles are projected to **enable clinical combination strategies**
- Pre-clinical studies in CCNE1-amplified setting has been discussed, and **work in pre-clinical breast cancer modeling will be disclosed at SABCS 2022**

ADME, absorption, distribution, metabolism, and excretion; CDX, cell-derived xenograft; sgNTC, single-guide RNA against nontargeting control; sgRb, single-guide RNA against Rb. SABCS, San Antonio Breast Cancer Symposium. For initial BLU-222 poster, see: Victoria Brown et al. AACR Annual Meeting, 2022.

Broad R&D effort to support ongoing development of BLU-222

Vela

PHASE 1 DOSE ESCALATION
(ENROLLING; UPDATE ON RESULTS IN 1H23)

Multiple dose cohorts* → **RP2D**

- Safety
- Preliminary clinical activity
- Patient selection strategy

**Includes monotherapy and combination regimens*

PHASE 2 EXPANSION (PLANNED)

- BLU-222 + ER antagonist **(ER+/HER2- breast)**
- BLU-222 + CDK4/6i + ER antagonist **(ER+/HER2- breast)**
- BLU-222 Monotherapy **(CCNE1+ tumors)**
- BLU-222 + Chemotherapy **(CCNE1+ tumors)**
- BLU-222 Monotherapy **(Other CCNE1+ tumors / Basket)**

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

TRANSLATIONAL MEDICINE COLLABORATION WITH MD ANDERSON
(ONGOING; PLANNED FOR 3 YEARS)

- New biomarker hypotheses
- Rational Combinations
- Indication expansion

CDK4/6i, CDK4/6 inhibitor.

Scientific leadership in KIT biology

GIST, gastrointestinal stromal tumor; mMCAS, monoclonal mast cell activation syndrome.

Expanding our leadership in mast cell-mediated diseases

Wild-type **KIT plays a central role in mast cell** survival, proliferation, and activation. Mast cells are primary effector cells in several allergic-inflammatory diseases, including **both inducible and spontaneous chronic urticaria.**

Chronic Urticaria is a debilitating inflammatory skin disorder characterized by wheals (hives)

- Complications include swelling/hives in inopportune sites (mouth, airway, genitals) and anaphylaxis
- Sleep disruption, stress, & anxiety due to severe itching are major contributors to disease burden

Chronic Urticaria statistics

~2M *Total estimated point prevalence in the U.S.+EU**	**1.4%** *Lifetime incidence**
37% *Patients with both wheals (hives) and angioedema***	**1/3** *Patients with poor disease control***

*See: J. Fricke, J. et al. *Allergy* **2020**, *75*, 423; note that point prevalence was estimated based on regional data (Fricke) and current populations
See: P. Kolkhir, et al. *Nature Reviews: Disease Primers* **2022, *8* 61;

Aim to discover best-in-class wild-type KIT inhibitors

Attribute	Ideal Candidate	BLU8758
pKIT / proliferation IC_{50}	< 10 nM pKIT IC_{50}	4 nM / 17 nM
PDGFR / FLT3 selectivity	> 50x / > 50x	700x/ >580x
Kinase Selectivity; S(10)	< 0.1	0.06
Drug/Drug Interactions	Low potential	Low/Moderate
Peripherally Restricted	Kpuu < 0.1	Kpuu = 0.04

- We have identified multiple examples of compounds meeting our target product profile
- Advanced candidates have safety and ADME profiles consistent with either single agent or combination therapy

ADME, absorption, distribution, metabolism, and excretion.

A strategic collaboration with the potential to transform the field of cancer immunotherapy

Robust kinase research platform & development capabilities

blueprint MEDICINES

Roche

Cancer immunotherapy expertise, assets and infrastructure

2016 EXPLORE COMPELLING TARGETS

- **Goal:** Explore a range of immunokinase targets to advance cancer immunotherapy
- Interrogate and validate with genetic and tool compound approaches

2019 ADVANCE THROUGH LEAD OPTIMIZATION

- 4 targets investigated focusing on distinct and complementary immune mechanisms

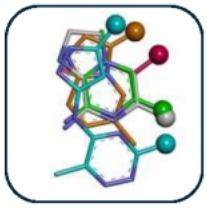
2022 DELIVERY OF TOP PROGRAMS

- **Achieved:** 2 targets advanced through lead optimization to stage of Development Candidate (DC)
- MAP4K1: DC achieved; first-in-patient anticipated 2023
- 2nd target: DC anticipated 2023

In collaboration with Roche, Blueprint Medicines and Roche are conducting activities for up to two programs, including the program targeting MAP4K1. For one of the programs, Blueprint Medicines has U.S. commercial rights and Roche has ex-U.S. commercialization rights. For one of the programs, Roche has worldwide commercialization rights.

Platform diversification expands our vision and impact

KINASE MEDICINE DISCOVERY PLATFORM



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AGILE DEGRADER DISCOVERY PLATFORM

EXPECTED BENEFITS OF INTRODUCING DEGRADERS

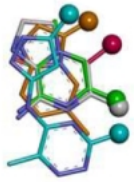
- Success with challenging kinases
- Enhanced selectivity
- Differentiated pharmacology
- Portfolio optionality

- Internal investment provides flexibility across our portfolio
- Collaboration with Proteovant & VantAI introduces expertise and expands reach

Degrader figure from Nalawansha & Crews, *Cell Chemical Biology* **2020**, *27*, 998 – 1014.

Strategy: Leverage the Blueprint library

Our initial approach prioritizes heterobifunctional degraders, which can capitalize both on existing proprietary chemical matter and known E3 ligases.



BLUEPRINT KINASE INHIBITOR LIBRARY

POTENT, SELECTIVE HETEROBIFUNCTIONAL DEGRADER

- Select potent, selective, and drug-like ligands from the kinase inhibitor library
- Optimize target degradation using well-studied E3 ligases
- Optimize degrader properties, selectivity, and potency via linker

LIBRARY STRATEGY APPLIES TO BOTH INTERNAL PROGRAMS AND PROTEOVANT COLLABORATION

Portfolio impact

Early Example: Internal kinase program with family selectivity challenges (oncology)

- Exploratory work revealed a selectivity divergence in inhibitor vs degrader SAR, and ability to tune selectivity

	Blueprint Degrader 1	Blueprint Degrader 2	Blueprint Degrader 3
Paralog A DC_{50} (Dmax) @ 6h	60 nM (63%)	110 nM (67%)	>10 µM
Paralog B DC_{50} (Dmax) @ 6h	>10 µM	30 nM (82%)	37 nM (86%)
Profile	A-Selective	A/B-Dual	B-Selective

Impact: opportunistic program initiation

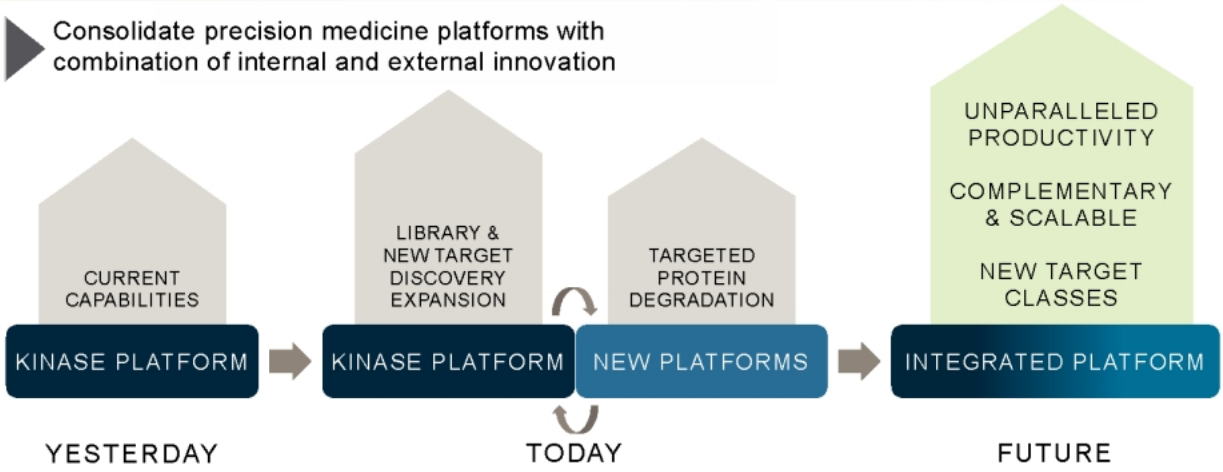
- Heterobifunctional degrader effort now initiating for high-value Paralog B
- High selectivity observed vs. two key family off-targets; broader selectivity studies to come

This year, we have started **five early degrader programs**: three internal and two with Proteovant

SAR, structure activity relationship.

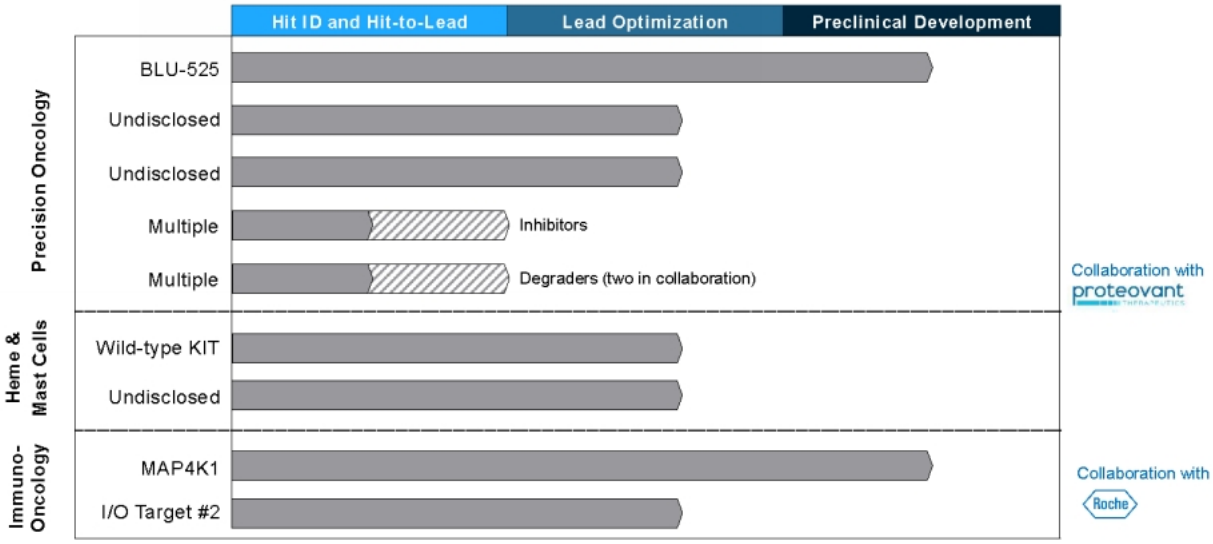
Expanding the research platform to increase innovation & productivity

Consolidate precision medicine platforms with combination of internal and external innovation



EXPANSION AIMS TO DOUBLE THE HISTORIC OUTPUT OF OUR DISCOVERY ENGINE BY 2025

Pre-clinical portfolio



Precision at Scale:
Driving innovation for long-term growth

How will we leverage our expertise and infrastructure to drive continued innovation and long-term growth?

1. Creating synergies between our robust discovery, clinical and commercial capabilities to build an optimized portfolio
2. Announcing a new program targeting wild-type KIT, which builds on our knowledge of KIT and leadership position in mast cell disorders
3. Leveraging our kinase discovery platform as a unique advantage to pursue targeted protein degradation

Scaling our leadership in precision medicine

CHRISTY ROSSI

Chief Operating Officer

A clear portfolio strategy to achieve our 2027 vision

LEAD WITH THE SCIENCE

Patient needs

Important targets

Blueprint edge

DIVERSIFY RISK

Next-gen strategies

Balance risk & return

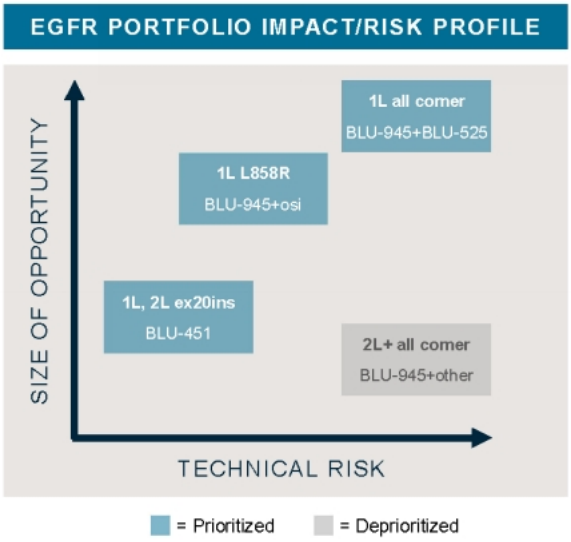
BUILD SCALE

Target & disease leadership areas

LEVERAGE PARTNERSHIPS

Scientific, clinical & commercial partnerships

Diversified EGFRm NSCLC portfolio with a compelling risk-return profile

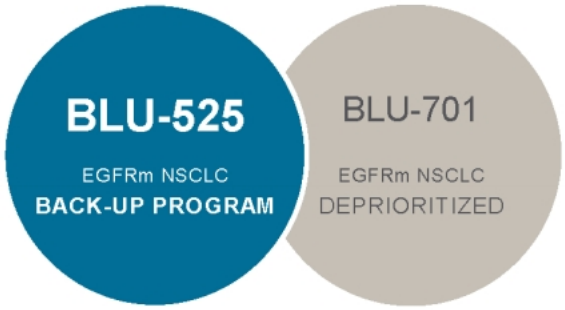


ASSET AND OPPORTUNITY DIVERSITY ENABLES:

- Balanced risk profile
- Attractive commercial opportunity
- Scientific, clinical, and commercial economies of scale

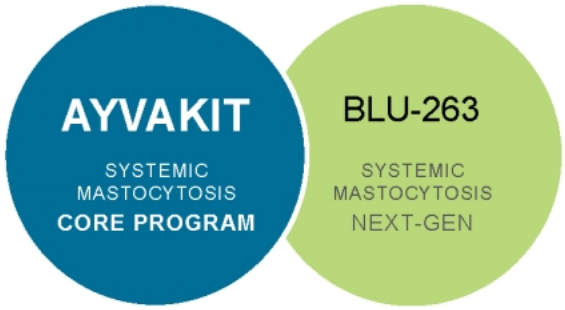
Strategic use of back-up and next-gen programs in high value opportunities

ROUTINE BACK-UP STRATEGIES ACROSS PORTFOLIO



Goal: manage development risk at the program and portfolio levels

DEEP BIOLOGICAL INSIGHTS ENABLE NEXT-GENERATION PROGRAMS



Goal: expand patient impact, disease area leadership and program lifecycle

We are leaders in systemic mastocytosis

AYVAKIT®
avapritinib | tablets

~540 patient years of SM clinical data

3 FDA breakthrough therapy designations

2 FDA and EMA approved indications*

On track to submit sNDA to FDA
for non-advanced SM by the end of 2022

EMA, European Medicines Authority. * AYVAKIT is FDA approved for the treatment of adults with unresectable or metastatic PDGFRA exon 18 mutant gastrointestinal stromal tumor (GIST) and adults with Advanced SM. AYVAKYT is EMA approved for adults with unresectable or metastatic PDGFRA D842V mutant GIST and adults with Advanced SM after at least one systemic therapy.

Deep disease insights drive perspectives on medical needs

SYSTEMIC MASTOCYTOSIS

~32K prevalent patients, with ~16K diagnosed and visible in claims in U.S.

ADVSM (5-10%)

- AVYAKIT is the standard of care
- Areas for continued innovation:
  - Long term follow up and OS
  - Combination data

NON-ADVSM (90-95%)

- PIONEER trial data demonstrate compelling benefit/risk profile
- First mover advantage is significant
- High bar for differentiation

Business development is a key lever in our portfolio strategy

>$1.1B of capital brought in to-date inclusive of upfront, milestones and royalties

FOP, fibrodysplasia ossificans progressiva; I/O, immunotherapy; WW, worldwide.

Our portfolio to deliver Precision at Scale

AYVAKIT avapritinib | tablets | GAVRETO pralsetinib | AYVAKIT avapritinib | tablets | AYVAKIT avapritinib | tablets | LUNG CANCER PORTFOLIO | BLU-222

AREA	PDGFRA GIST	RET-altered cancers	Advanced SM	Non-Advanced SM	EGFRm NSCLC	CDK2 vulnerable breast & other cancers
GLOBAL TAMs	~250,000+ patients					
PRODUCTS	4+ marketed products by the end of 2027					

Includes TAMs for AYVAKIT based on potential approval in Non-Advanced SM and other investigational therapies based on potential future approvals in other target indications.

Anticipated near-term milestones

PROGRAM	AREA OF FOCUS	MILESTONE	TIMING
AYVAKIT	Non-Advanced SM	Submit sNDA to FDA	Q4 2022
		Present full registrational data from PIONEER trial	Q4 2022 / Q1 2023
BLU-263		Report top-line 12-week Part 1 data from HARBOR trial	Q4 2022
BLU-525	EGFRm NSCLC	Submit IND to FDA	Q1 2023
BLU-451		Report BLU-451 dose escalation data	1H 2023
BLU-222	CDK2-vulnerable cancers	Report BLU-222 dose escalation data	1H 2023

Precision at Scale: key themes from today's presentation

Expanding AYVAKIT to treat patients with non-advanced SM to realize a compelling near-term growth opportunity

Tackling important medical problems representing significant opportunities in lung, breast and other cancers

Building on proven research track record to broaden the opportunities we can pursue to drive long-term growth

KATE HAVILAND

Chief Executive Officer

“2027 Blueprint” strategy - double our impact, in half the time

blueprint™ 2027

	2011-2022	Planned 2022-2027
Approved medicines	2	4+
Disease leadership areas	1	3+
Late-stage clinical programs	2	4+
Research platforms	1	2
Cumulative development candidates	14	25+

blueprint™ MEDICINES