Pioneering the Science of Time

JEFFERIES HEALTHCARE CONFERENCE
JUNE 9, 2022

Kristine G.
Systemic mastocytosis patient
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, timelines and expectations for interactions with the FDA and other regulatory authorities; 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’ 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 report 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 report, 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, 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 report 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.

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Blueprint Medicines is a global leader in precision therapy

AYVAKIT®
avapritinib | tablets

GAVRETO®
pralsetinib | 100mg capsules

Ongoing global collaboration with Roche and Genentech for the development and commercialization of GAVRETO

AYVAKIT is approved for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations, and adult patients with advanced SM, including aggressive SM, SM with an associated hematologic neoplasm and mast cell leukemia. GAVRETO is approved for the treatment of adult patients with RET-fusion positive NSCLC, adult and pediatric patients with advanced or metastatic RET-mutant medullary thyroid cancer who require systemic therapy and adult, and pediatric patients with advanced or metastatic RET fusion-positive thyroid cancer who require systemic therapy and who are radioactive iodine-refractory. FDA, U.S. Food and Drug Administration; GIST, gastrointestinal stromal tumor; NSCLC, non-small cell lung cancer; SM, systemic mastocytosis. Not for promotional use.
Blueprint is uniquely positioned with a diversity of significant growth drivers

**GLOBAL COMMERCIAL EXECUTION**

- Global commercial expansion
- $115 - $130M in AYVAKIT product revenue in '22

**CLINICAL STAGE GROWTH**

- **PIONEER**
  - Topline results expected late summer '22
  - sNDA and launch in non-advanced SM, if approved

- **Symphony**
  - BLU-945+osi early clinical data 2H '22
  - BLU-701 first clinical data expected 2H '22
  - BLU-451 first clinical data expected 1H '23

- **Harmony**
  - BLU-222 in breast cancer and other CDK2-vulnerable tumors
  - First clinical data expected 1H '23

- **Concerto**
  - BLU-945+osi early clinical data 2H '22
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**LEADING PRECISION MEDICINE DISCOVERY PLATFORM**

- R&D day 2H 2022
- Two new development candidates by end of 2022

Ongoing global collaboration with Roche and Genentech for the development and commercialization of GAVRETO. FDA, U.S. Food and Drug Administration; EC, European Commission; PDGFRA, platelet-derived growth factor receptor alpha; GIST, gastrointestinal stromal tumor; SM, systemic mastocytosis; sNDA, supplemental new drug application; R&D, research and development; POC, proof-of-concept; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; CDK2, cyclin-dependent kinase 2

Not for promotional use.
Global Commercial Execution
We are establishing the standard of care for advanced SM

AYVAKIT COMMERCIAL GROWTH

NEW PATIENT STARTS

~40% growth in AdvSM market treated with TKIs / cytoreductive agents since launch

~70% share of new AdvSM patient starts

~65 new accounts activated in Q1 2022

DURATION OF THERAPY

~18 month trending average duration of therapy, showing increasing trend

1. Reported data represent estimations. Analysis based on US claims data

Not for promotional use.
Retrospective analysis showed a longer OS among AYVAKIT patients

OS AMONG PATIENTS WITH SM-AHN TREATED WITH AYVAKIT VS. BAT

18.0 mos (95%CI: 13.0, 26.8)

46.9 mos (95%CI: 44.9, NE)

Log-rank P value < 0.001 *

Avapritinib 119 76 39 16 10 3 1 0

BAT 121 71 44 28 15 5 2 0

Number at risk

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. 1. 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. Abstract #P1013. 2. Reiter et al. Overall Survival in Patients with Advanced Systemic Receiving Avapritinib Versus Midostaurin or Cladribine. Presented at EHA 2022. Abstract #P1014 BAT, best available therapy; KM, Kaplan-Meier; OS, overall survival; AdvSM, advanced systemic mastocytosis; AVA, AYVAKIT; MIDO, midostaurin; CLAD, cladribine; SM-AHN, systemic mastocytosis with associated hematologic neoplasm

OS OF PATIENTS WITH ADVSM TREATED WITH AYVAKIT VS. MIDOSTAURIN OR CLADRIBINE

28.6 mos (95%CI: 18.2, 44.6)

23.4 mos (95%CI: 14.8, 40.6)

NR (95%CI: 46.9, NE)

Log-rank P value

AVA vs. MIDO < 0.001 *

AVA vs. CLAD < 0.001 *

AVA 176 110 56 28 19 5 1 0

MIDO 99 66 45 34 24 15 10 0

CLAD 49 35 22 17 9 4 3 0

Number at risk

*P < 0.05
Clinical Stage Growth

Rob T.
Advanced cancer patient

Not for promotional use.
Non-advanced SM patients have high medical need despite available therapies\(^1\)

**SYSTEMIC MASTOCYTOSIS SYMPTOMS\(^2\)**

- Brain fog
- Pruritis, flushing and pigmented skin lesions
- Life-threatening organ infiltration and damage
- Unpredictable, life-threatening anaphylaxis
- Debilitating fatigue
- GI upset with vomiting, diarrhea and nausea

75\% of patients have taken **4+ classes of therapies** to address significant symptom burden\(^3\)

\(\geq\)80\% of patients report **limitations in their work and/or daily activities**\(^3\)

83\% of patients are **frustrated at lack of treatment options** that do not address the underlying driver of disease\(^4\)

95\% of SM cases driven by the **KIT D816V mutation**


Not for promotional use.
PIONEER Part 2 primary endpoint to be updated to mean change in TSS

What is the same?
- The PIONEER study is powered for key primary and secondary analyses of clinical benefit based on the ISM-SAF TSS
  - Mean change in TSS
  - Proportion of patients with a ≥30% reduction in TSS

What is changing?
- In recent discussions with FDA to finalize the SAP in advance of database lock we have aligned on:
  - Mean change in TSS to be the primary endpoint - previously a key secondary endpoint
  - Proportion of patients with a ≥30% reduction in TSS will be a key secondary endpoint – previously the primary endpoint

Why?
- Characterizes benefit of avapritinib across a wider range of patients
- Harmonizes with the EMA
PIONEER Part 1 showed statistically significant difference in mean change in TSS between avapritinib and placebo.


2. PIONEER Part 1. Based upon a data cutoff of March 31, 2020. TSS, total symptom score; SE, standard error

Not for promotional use.
Key secondary endpoints are important to fully characterize the impact of avapritinib on patients with non-advanced SM

**PIONEER PART 1**

≥ 30% REDUCTION IN TSS AT 24 WEEKS¹
AVAPRITINIB 25 MG VS. PLACEBO

**PIONEER PART 1**

≥ 50% REDUCTION IN TRYPTASE AT 24 WEEKS¹*
AVAPRITINIB 25 MG VS. PLACEBO

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*24 weeks or last assessment before, if 24 weeks not available. TSS, total symptom score.
PIioneer Part 2 topline on track for late summer 2022

Randomize 2:1
Avapritinib 25 mg QD + BSC
Placebo QD + BSC

Primary endpoint
Mean change in TSS at 24 weeks

Rollover
Avapritinib 25 mg QD + BSC

Eligibility
- Age ≥18 years
- ISM confirmed by central pathology review
- No restriction on prior therapy
- Moderate-to-severe symptoms

Key secondary endpoints
- Proportion of patients with reduction in TSS
- Reduction in measures of mast cell burden
- Change in measures of QoL

PLANS TO SUBMIT sNDA BY END OF 2022

TSS, total symptom score; QD, once daily; BSC, best supportive care; ISM, indolent systemic mastocytosis; QoL, quality of life; MC-QoL, Mastocytosis Quality of Life Questionnaire; PGIS, Patient's Global Impression of Symptom Severity; PGIS, Patient’s Global Impression of Change; SF-12, Short Form Health Survey

Not for promotional use.
Our portfolio of EGFR therapies is purpose-built to address medical needs

<table>
<thead>
<tr>
<th>TREATMENT GOALS</th>
<th>BLUEPRINT MEDICINES EGFR PORTFOLIO</th>
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<tbody>
<tr>
<td>Effectively block the EGFR pathway</td>
<td><strong>BLU-945</strong></td>
</tr>
<tr>
<td>• Potent EGFR mutation coverage:</td>
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</tr>
<tr>
<td>o LR and LR/CS</td>
<td>o Ex19del and LR</td>
</tr>
<tr>
<td>o TM and TM/CS regardless of activating mutation</td>
<td>o CS regardless of activating mutation</td>
</tr>
<tr>
<td>o Potential for broader coverage at higher exposures</td>
<td>• Highly CNS penetrant</td>
</tr>
<tr>
<td>• Highly selective over wild-type EGFR</td>
<td>• Potent inhibitor of all common Ex20ins and other uncommon activation mutations</td>
</tr>
<tr>
<td>Establish 2L+ SOC with combinations that treat on- and off-target resistance</td>
<td><strong>BLU-701</strong></td>
</tr>
<tr>
<td>• Potent EGFR mutation coverage:</td>
<td>• Highly selective over wild-type EGFR</td>
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<td>• CNS penetrant</td>
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</table>

CS, C797S resistance mutation; Ex20in, activating exon 20 insertion mutations; LR, L858R activating mutation; TM, T790M resistance mutation.

Not for promotional use.
BLU-945 potency and selectivity enable wide therapeutic index and broad EGFR coverage, with promising early clinical monotherapy data

**DOSE-DEPENDENT REDUCTIONS IN ctDNA...**

*One patient had two different DNA mutations in C797S. Note: reductions in individual variant allele fractions as shown; therefore, patients with multiple mutations may be represented on both plots. All T790M and C797S allele fractions with available baseline and C1D15 data are shown. Increases of greater than 100% were truncated at 100%.*

**...AND ANTI-TUMOR ACTIVITY, WITH TUMOR SHRINKAGE REPORTED AT DOSES ≥200 MG QD**

In the 400 mg cohort, all detectable T790M and C797S alleles showed reduction, including three that fell below the limit of detection (clearance)

**GENERALLY WELL-TOLERATED‡, WITH NO SIGNIFICANT ADVERSE EVENTS ASSOCIATED WITH WILD-TYPE EGFR INHIBITION**

*As of the data cut-off (March 9, 2022), 33 patients have been treated with BLU-945 at 25–400 mg once daily (QD) in the first 5 cohorts.*

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‡Most common AEs by preferred term in ≥10% of patients included nausea, headache, fatigue, cough, dyspnea, vomiting, hyponatremia, dry mouth, and anemia.

ctDNA, circulating tumor DNA; C, cycle; D, day; F1LCdx, FoundationOne Liquid CDx assay; QD, once daily CR, complete remission; PD, progressive disease; PR, partial remission; SD, stable disease; EOT, end of treatment. As of the data cut-off (March 9, 2022), 33 patients have been treated with BLU-945 as at 25–400 mg once daily (QD) in the first 5 cohorts.
Phase 1/2 trials to rapidly generate data in broad populations, informing development and registration strategies

<table>
<thead>
<tr>
<th>1L</th>
<th>2L+</th>
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<tbody>
<tr>
<td>945 + osi</td>
<td>LR</td>
</tr>
<tr>
<td>701 + osi</td>
<td>All comer</td>
</tr>
<tr>
<td>701 + chemo</td>
<td>All comer</td>
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<tr>
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<td>945 + chemo</td>
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<tr>
<td>945 + 701</td>
<td>Ex19del/LR + CS</td>
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<tr>
<td>701 + osi</td>
<td>Ex19del/LR + CS</td>
</tr>
<tr>
<td>701</td>
<td>Ex19del/LR + CS</td>
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**PLANNED INITIATION OF PHASE 1/2 SYMPHONY / HARMONY TRIAL COHORTS**

- **Q2 2022**: 945 + osi LR + CS +/- TM
- **Q2 2022**: 945 LR + CS +/- TM
- **2H 2022**: 945 + 701 Ex19del/LR + CS
- **2H 2022**: 701 + osi Ex19del/LR + CS
- **2023**: 701 Ex19del/LR + CS
Opportunity to influence the treatment paradigm for more than 100K patients across multiple CDK2-vulnerable cancers

CDK-CYCLIN COMPLEXES
REGULATE THE CELL CYCLE

CDK1 Cyclin A/B
CDK4/6 Cyclin D
CDK2 Cyclin A
CDK2 Cyclin E

M
G1
G2
S

CELL DIVISION
DNA SYNTHESIS

ABERRANT CYCLIN E (CCNE1)
DRIVES CELL PROLIFERATION

ER+/HER2-
BREAST CANCER

CDK4/6 INHIBITOR GLOBAL SALES ($, BILLIONS)


$0.7 $2.1 $3.2 $4.6 $6.0 $7.0 $7.7

CCNE1-AMPLIFIED TUMORS

Uterine
Ovarian
Stomach
Esophageal
Uterine
Lung
Breast

FREQUENCY OF CCNE1 AMPLIFICATION

0% 10% 20% 30% 40%

BLU-222 WILL ADDRESS THE SPECTRUM OF OPPORTUNITY IN CDK2-VULNERABLE CANCERS

1. Approximate patient numbers covering major markets – US, EU4, UK, and Japan. 2. Data from company reports. 3. 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). CDK, cyclin dependent kinases; ER+/HER2-, estrogen receptor-positive, HER2-negative
Not for promotional use.
BLU-222 is advancing toward clinical proof-of-concept

PHASE 1/2 TRIAL OF BLU-222 IN CDK2 VULNERABLE CANCERS

PHASE 1 DOSE ESCALATION
(NOW ENROLLING)

Multiple dose cohorts*
*Includes monotherapy and combination regimens
  - Safety
  - Preliminary clinical activity
  - Patient selection strategy

PHASE 2 EXPANSION
(PLANNED)

RP2D

Combo with ER antagonist – ER+/HER2- breast
Combo with CDK4/6i + ER antagonist – ER+/HER2- breast
Monotherapy – CCNE1 tumors
Combo with chemotherapy – CCNE1 tumors
Monotherapy – multiple other CCNE1 tumors (basket cohort)

PHASE 1/2 VELA TRIAL OF BLU-222 INITIATED IN Q1 2022 AND FIRST PATIENT DOSED

CCNE1, cyclin E; CDK4/6i, CDK4/6 inhibitor; ER, estrogen receptor.

Not for promotional use.
Anticipated clinical data milestones over the next year

<table>
<thead>
<tr>
<th>Clinical Data</th>
<th>Timeline</th>
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<tbody>
<tr>
<td>Symphony</td>
<td>1H 2023</td>
</tr>
<tr>
<td>Harmony</td>
<td>2H 2022</td>
</tr>
<tr>
<td>Vela</td>
<td>1H 2023</td>
</tr>
<tr>
<td>Concerto</td>
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</tbody>
</table>

- **POC**, proof-of-concept
- Late summer 2022
- 2H 2022
- 1H 2023

**Early clinical data for**
- BLU-945+osimertinib, BLU-701 monotherapy
- Part 1 data for BLU-263
- Clinical data for BLU-222
- Clinical data for BLU-451

*Topline results, with additional detail presented at a medical conference at a later date*
Leading Precision Medicines Drug Discovery Platform
Research platform expansion to drive innovation & expanded 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
Business development plays a key role in our company's value creation and long-term portfolio growth.

Global Strategic Partnerships
Access complementary expertise to maximize program value and global impact on patients

Geographic Expansion
Pioneering early development partnerships in China; expanding to additional key markets through regional distributors

Buy-Side Transactions
Tap into external innovations to complement organic portfolio build

Program Partnerships
Tap into external resources & expertise to enhance internal programs

Over $1.1B earned to-date inclusive of upfront, milestones and royalties

Not for promotional use.

* Fibrodysplasia ossificans progressiva
Strong financial position with total revenues currently estimated for 2022 between $180 and $200 million

<table>
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<td>Total revenue</td>
<td>$62.7M</td>
<td>$21.6M</td>
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<tr>
<td>Net product sales</td>
<td></td>
<td></td>
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<tr>
<td>Collaboration revenue</td>
<td>$23.8M</td>
<td>$9.0M</td>
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<tr>
<td>Cost of sales</td>
<td>$5.1M</td>
<td>$0.1M</td>
</tr>
<tr>
<td>Collaboration loss sharing</td>
<td>$3.3M</td>
<td>--</td>
</tr>
<tr>
<td>Research &amp; development expense¹</td>
<td>$103.1M</td>
<td>$79.7M</td>
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<tr>
<td>Selling, general &amp; admin expense²</td>
<td>$57.1M</td>
<td>$42.0M</td>
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<tr>
<td>Net loss</td>
<td>$(106.0)M</td>
<td>$(99.7)M</td>
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</table>

<table>
<thead>
<tr>
<th>Balance Sheet (unaudited)</th>
<th>3/31/2022</th>
<th>12/31/2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cash, cash equivalents and investments</td>
<td>$893.4M</td>
<td>$1,034.6M</td>
</tr>
</tbody>
</table>

ON TRACK TO ACHIEVE $115 TO $130 MILLION IN AYVAKIT NET PRODUCT REVENUES IN 2022

1. Includes stock-based compensation expense of $10.0M and $8.9M in the three months ended 3/31/22 and 3/31/21, respectively. 2. Includes stock-based compensation expense of $13.4M and $11.7M in the three months ended 3/31/22 and 3/31/21, respectively.

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  - Global commercial expansion
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- **GAVRETO** pralsetinib tablets

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