Pioneering the Science of Time

JEFFERIES HEALTHCARE CONFERENCE

JUNE 9, 2022

blueprint MEDICINES

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.

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

OUR FIRST DECADE OF ACHIEVEMENT

2 internally discovered medicines

FDA & EMA approved across **5** indications

within **10** years, and with

5 breakthrough therapy designations

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

AYVAKIT® avapritinib | tablets

GAVRETO® pralsetinib | 100mg capsules

- 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

Harmony

- BLU-701 first clinical data expected 2H '22

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- BLU-451 first clinical data expected 1H '23

Vela

- BLU-222 in breast cancer and other CDK2-vulnerable tumors
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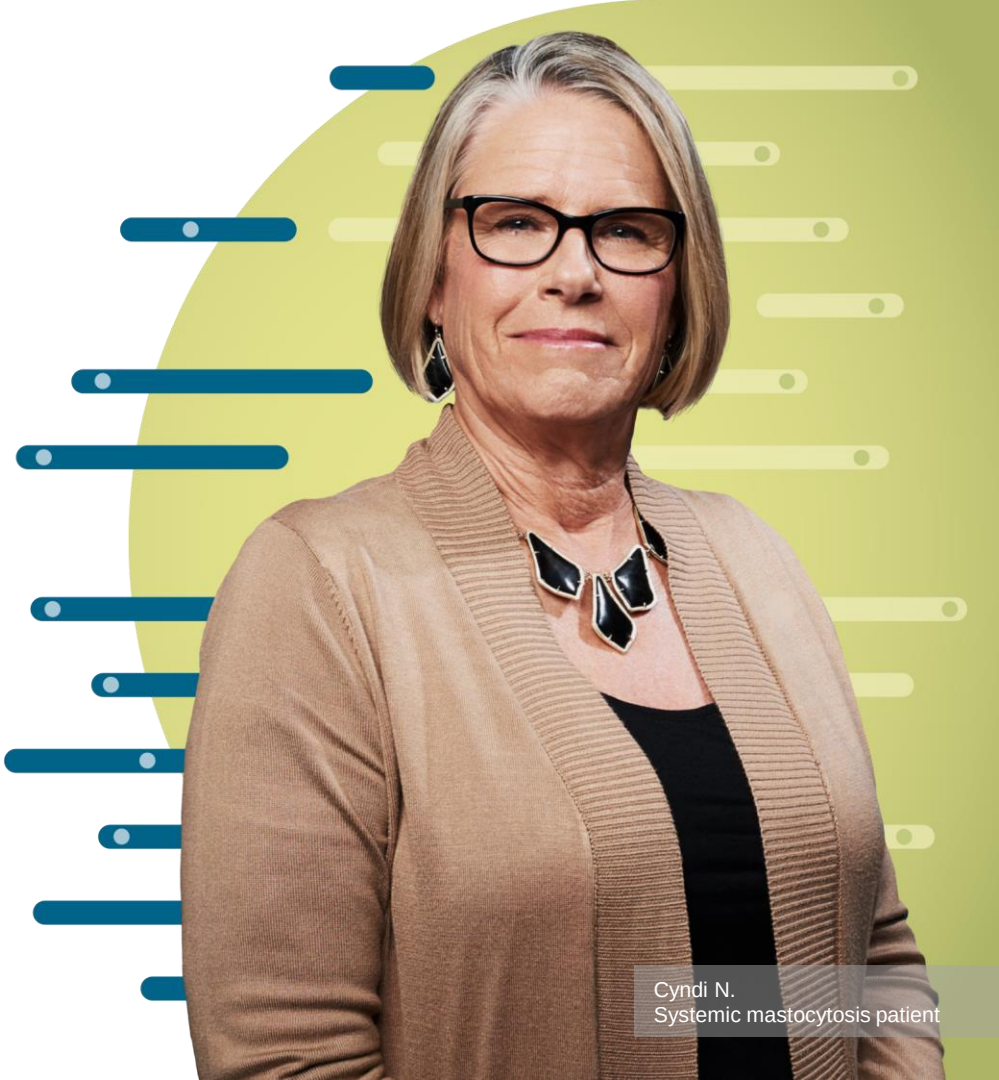
LEADING PRECISION MEDICINE DISCOVERY PLATFORM

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

blueprint™ MEDICINES

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

Global Commercial Execution



blueprint™ MEDICINES

We are establishing the standard of care for advanced SM

AYVAKIT®
avapritinib | tablets

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

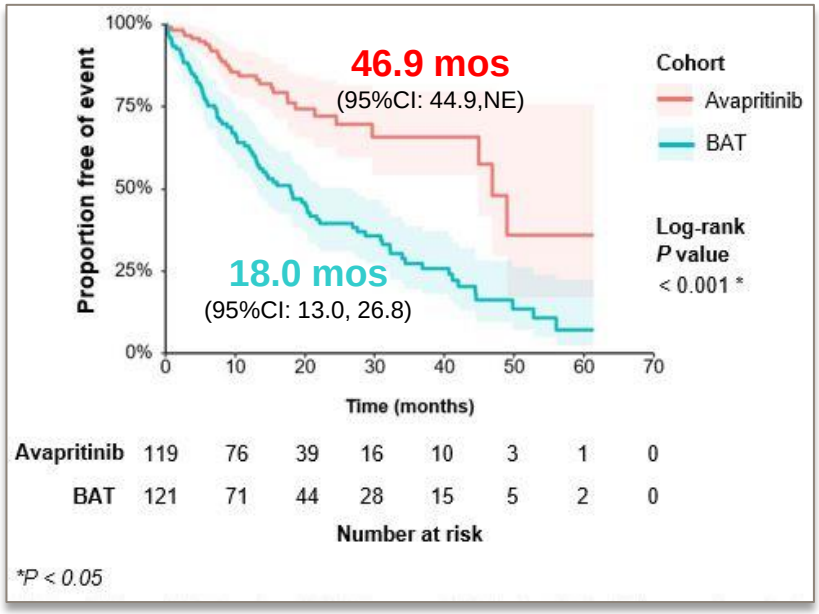
DURATION OF THERAPY

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

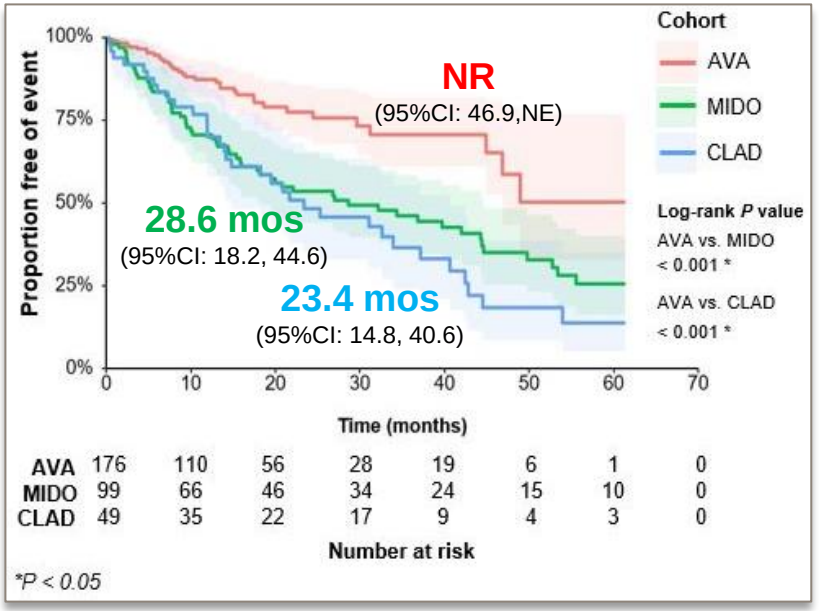
1. Reported data represent estimations. Analysis based on US claims data

Retrospective analysis showed a longer OS among AYVAKIT patients

OS AMONG PATIENTS WITH SM-AHN TREATED WITH AYVAKIT VS. BAT[1]



OS OF PATIENTS WITH ADVSM TREATED WITH AYVAKIT VS. MIDOSTAURIN OR CLADRIBINE[2]



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 avaprtinib 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

Clinical Stage Growth

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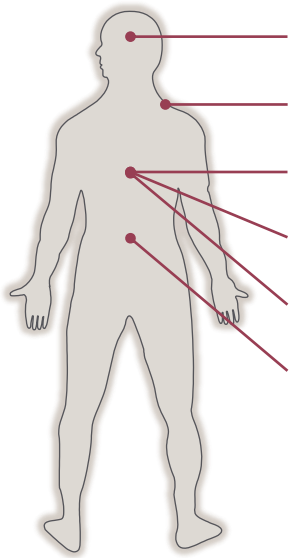
Non-advanced SM patients have high medical need despite available therapies[1]

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

95% of SM cases driven by the KIT D816V mutation

of patients have taken **4+ classes of therapies** to address significant symptom burden[3]

of patients report **limitations in their work and/or daily activities**[3]

of patients are **frustrated at lack of treatment options** that do not address the underlying driver of disease[4]

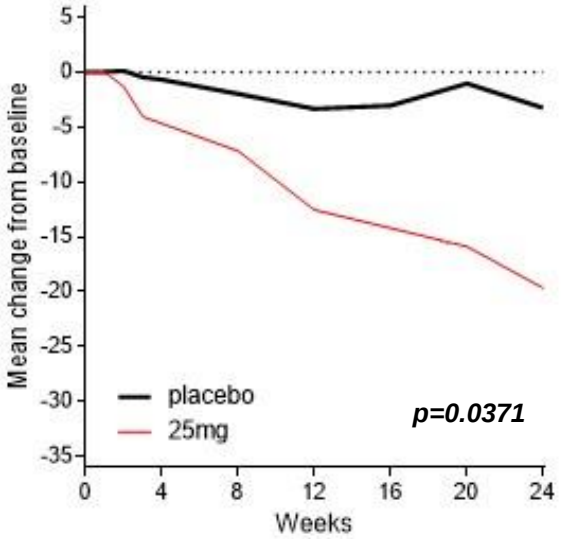
1. Jennings SV et al. Immunol Allergy Clin North Am. 2018;38(3):505-525. 2. Sperr WR, et al. Lancet Haematol, 2019. 3. Data on file. Adelphi Observational Study. July 2018. Data cutoff March 2018. 4. van Anrooij B et al. Allergy. 2016 Nov;71(11):1585-1593.

PIONEER Part 2 primary endpoint to be updated to mean change in TSS

PIONEER PART 1

MEAN CHANGE IN TSS AT 24 WEEKS[1]

AVAPRITINIB 25 MG VS. PLACEBO



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?

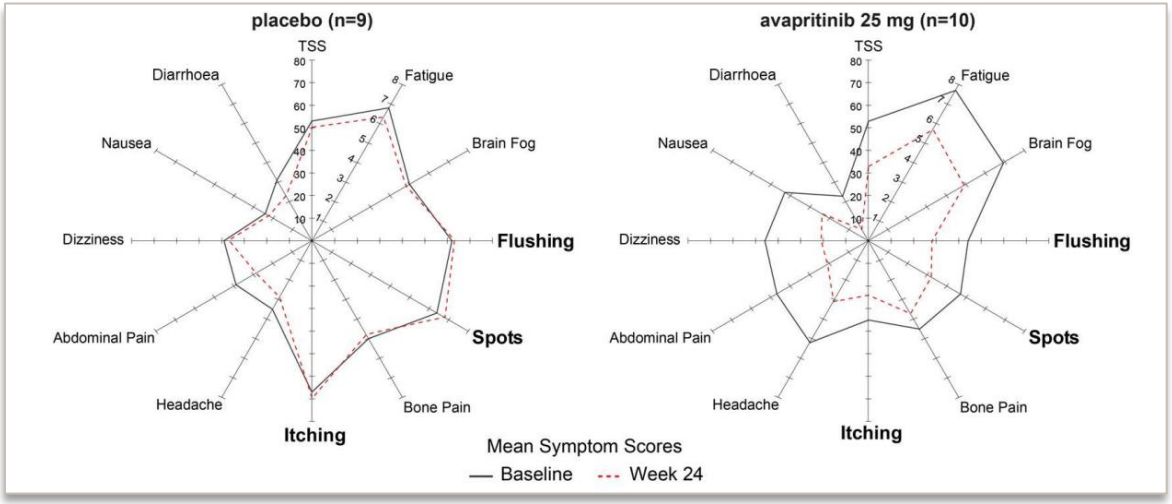
- Characterizes benefit of avapritinib across a wider range of patients
- Harmonizes with the EMA

ALIGNMENT WITH FDA ON PRIMARY EFFICACY ANALYSIS FOR PIONEER PART 2

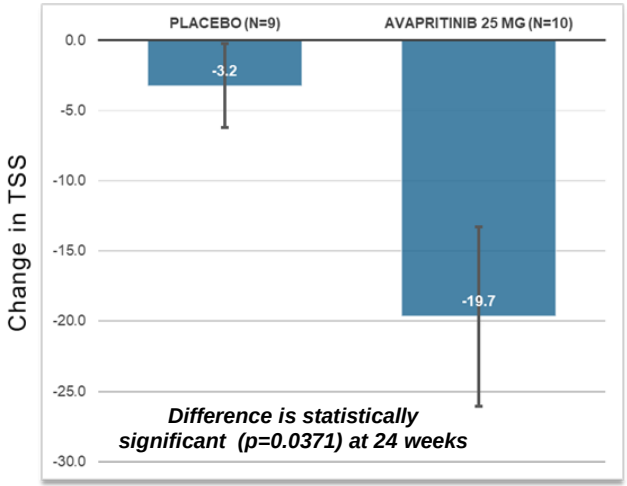
1. PIONEER Part 1. Based upon a data cutoff of March 12, 2020. TSS, total symptom score; FDA, Food and Drug Administration; ISM-SAF, Indolent Systemic Mastocytosis Symptom Assessment Form; SAP, statistical analysis plan; EMA, European Medicines Agency

PIONEER Part 1 showed statistically significant difference in mean change in TSS between avapritinib and placebo

MEAN CHANGE IN TSS BY SYMPTOM AT 24 WEEKS[1]
AVAPRITINIB 25 MG VS. PLACEBO
PRESENTED AT EAACI 2020



MEAN CHANGE IN TSS AT 24 WEEKS[2]
AVAPRITINIB 25 MG VS. PLACEBO (+/- SE)



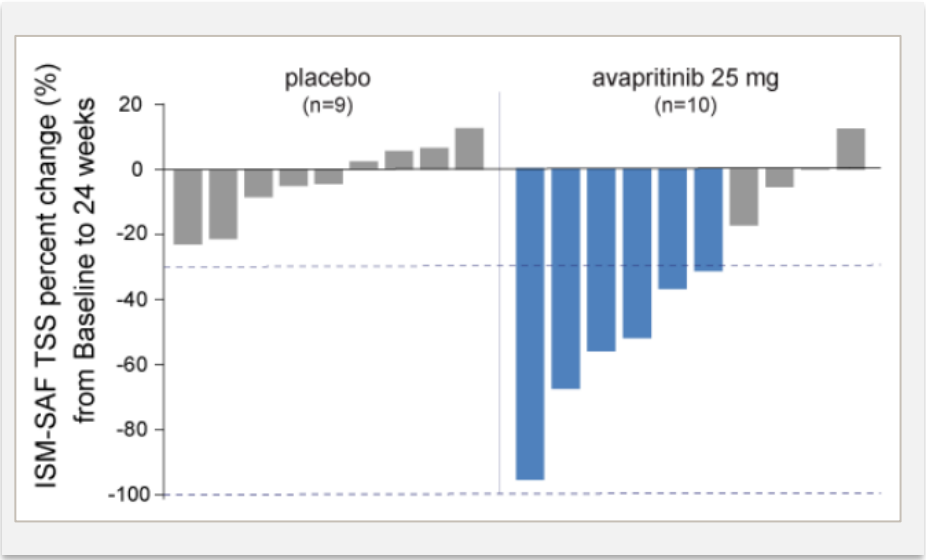
1. Hartmann K. et al. Avapritinib reduces cutaneous symptoms and mast cell burden in patients with indolent systemic mastocytosis in the PIONEER study. Presented at the European Academy of Allergy Clinical Immunology Annual Meeting. June 2020. Based upon a data cutoff of March 31, 2020. 2. PIONEER Part 1. Based upon a data cutoff of March 31, 2020. TSS, total symptom score; SE, standard error

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 WEEKS[1]

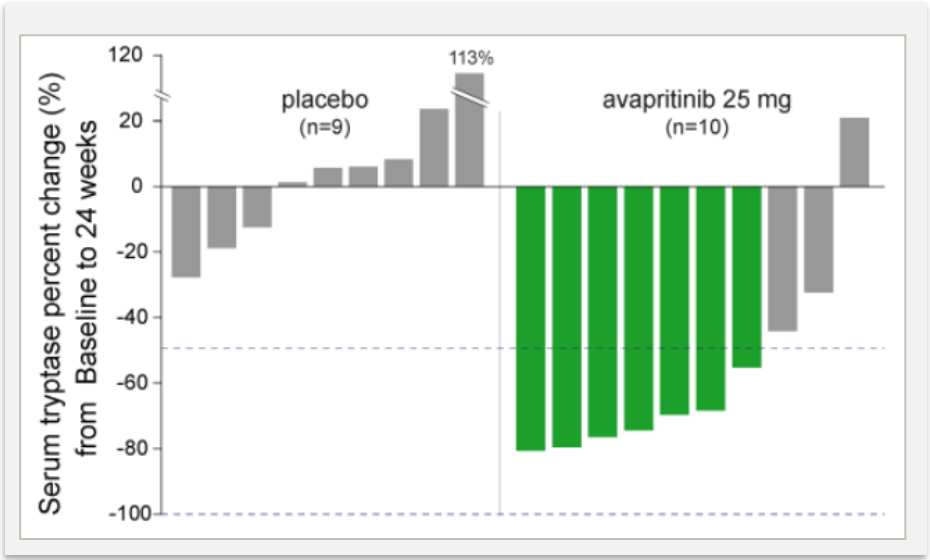
AVAPRITINIB 25 MG VS. PLACEBO



PIONEER PART 1

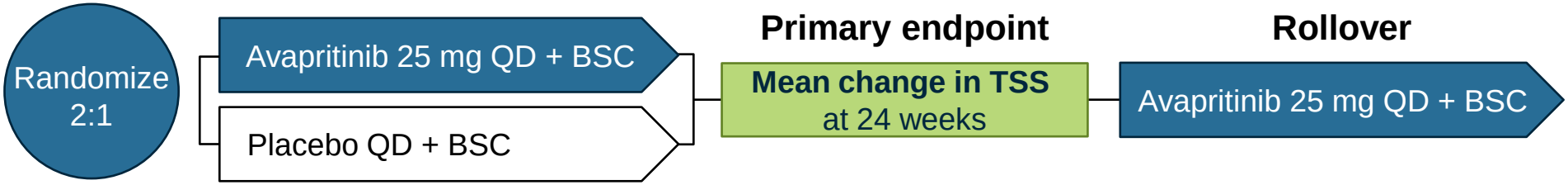
≥ 50% REDUCTION IN TRYPTASE AT 24 WEEKS[1*]

AVAPRITINIB 25 MG VS. PLACEBO



1. Hartmann K. et al. Avapritinib reduces cutaneous symptoms and mast cell burden in patients with indolent systemic mastocytosis in the PIONEER study. Presented at the European Academy of Allergy Clinical Immunology Annual Meeting. June 2020. Based upon a data cutoff of March 31, 2020.
*24 weeks or last assessment before, if 24 weeks not available. TSS, total symptom score

PIONEER Part 2 topline on track for late summer 2022



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

Our portfolio of EGFR therapies is purpose-built to address medical needs

TREATMENT GOALS

Effectively block the EGFR pathway

Establish 2L+ SOC with combinations that treat on- and off-target resistance

BLUEPRINT MEDICINES EGFR PORTFOLIO

BLU-945

- Potent EGFR mutation coverage:
  - LR and LR/CS
  - TM and TM/CS regardless of activating mutation
  - Potential for broader coverage at higher exposures
- Highly selective over wild-type EGFR

BLU-701

- Potent EGFR mutation coverage:
  - Ex19del and LR
  - CS regardless of activating mutation
- Highly CNS penetrant

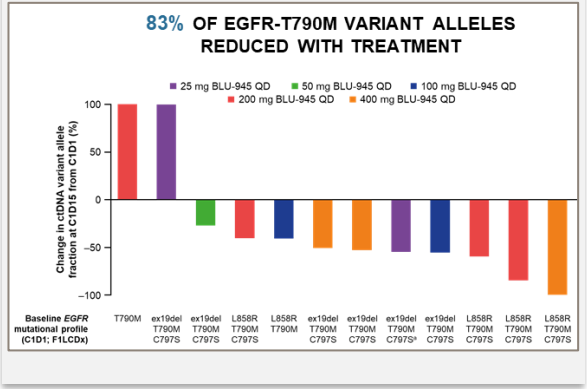
BLU-451

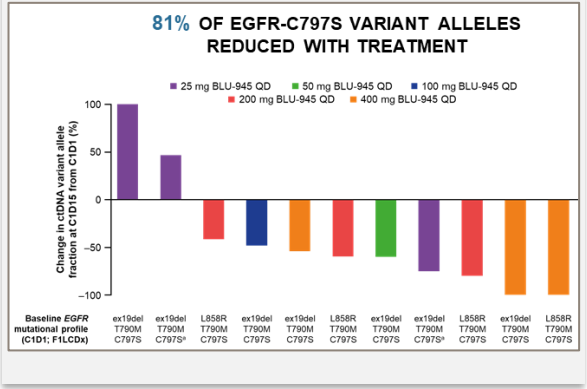
- Potent inhibitor of all common Ex20ins and other uncommon activation mutations
- Highly selective over wild-type EGFR
- CNS penetrant

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

BLU-945 potency and selectivity enable wide therapeutic index and broad EGFR coverage, with promising early clinical monotherapy data

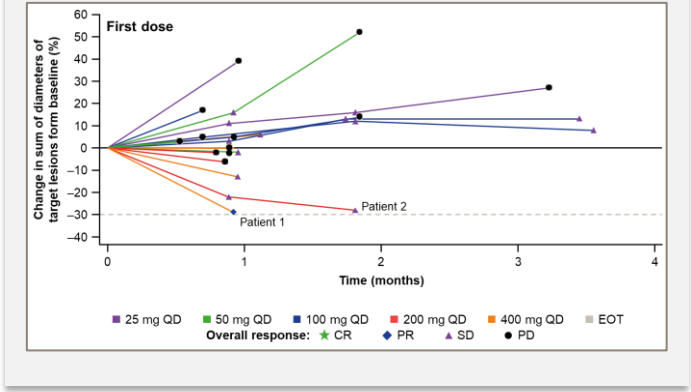
DOSE-DEPENDENT REDUCTIONS IN ctDNA…





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

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

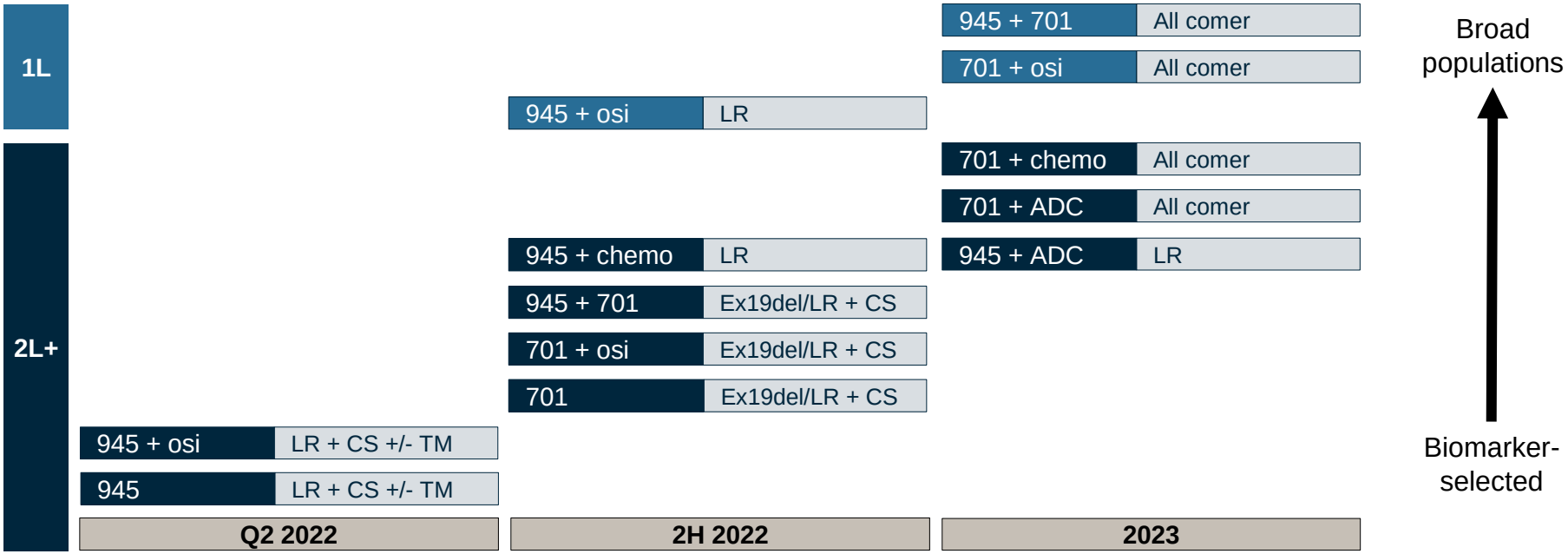


Unconfirmed PR reported in patient with ex19del/T790M/C797S treated at 400 mg QD

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

[a]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 [b]Patients with measurable target lesions at baseline with post-baseline scans (investigator assessed). An unconfirmed PR is a PR in which tumor reduction ≥30% has occurred but has not yet been confirmed via a subsequent scan. † 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 at 25–400 mg once daily (QD) in the first 5 cohorts.

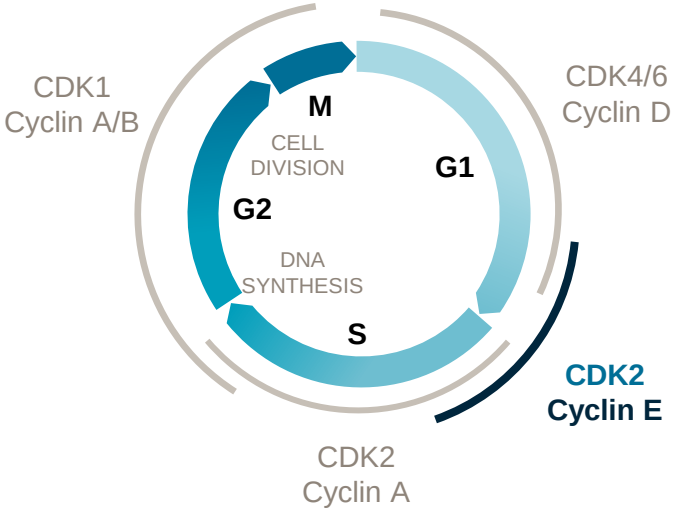
Phase 1/2 trials to rapidly generate data in broad populations, informing development and registration strategies



PLANNED INITIATION OF PHASE 1/2 SYMPHONY / HARMONY TRIAL COHORTS

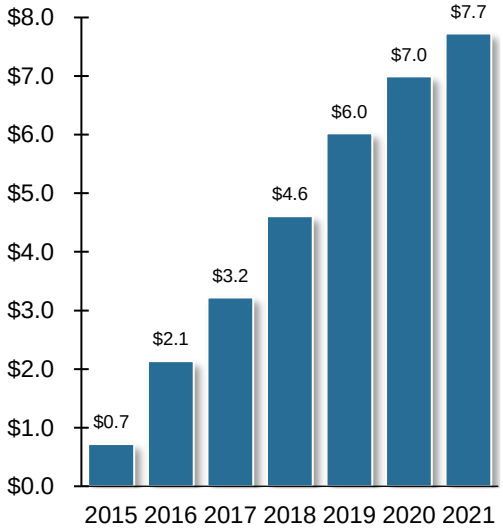
Opportunity to influence the treatment paradigm for more than 100K patients across multiple CDK2-vulnerable cancers[1]

CDK-CYCLIN COMPLEXES REGULATE THE CELL CYCLE



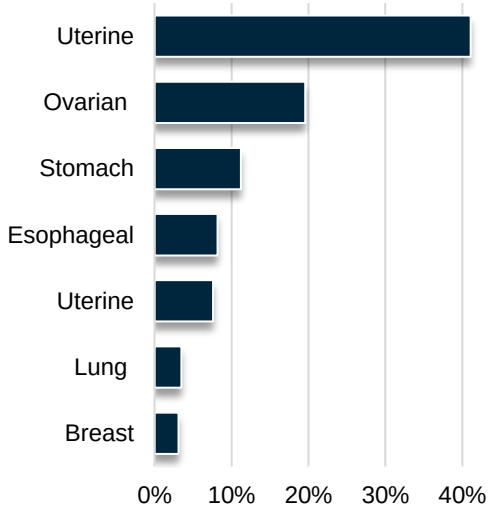
ABERRANT CYCLIN E (CCNE1) DRIVES CELL PROLIFERATION

ER+/HER2- BREAST CANCER



CDK4/6 INHIBITOR GLOBAL SALES ($, BILLIONS)[2]

CCNE1-AMPLIFIED TUMORS



FREQUENCY OF CCNE1 AMPLIFICATION[3]

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 kinas; ER+/HER2-, estrogen receptor-positive, HER2-negativ

BLU-222 is advancing toward clinical proof-of-concept

Vela

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

PHASE 1 DOSE ESCALATION (NOW ENROLLING)

Multiple dose cohorts* → RP2D

**Includes monotherapy and combination regimens*

- Safety
- Preliminary clinical activity
- Patient selection strategy

PHASE 2 EXPANSION (PLANNED)

- 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

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

Anticipated clinical data milestones over the next year

PIONEER

Topline results, with additional detail presented at a medical conference at a later date

Late summer 2022

Symphony **Harmony**

Early clinical data for BLU-945+osimertinib, BLU-701 monotherapy

HARBOR

Part 1 data for BLU-263

2H 2022

Vela

Clinical data for BLU-222

Concerto

Clinical data for BLU-451

1H 2023

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POC, proof-of-concept

Not for promotional use.

Leading Precision Medicines Drug Discovery Platform

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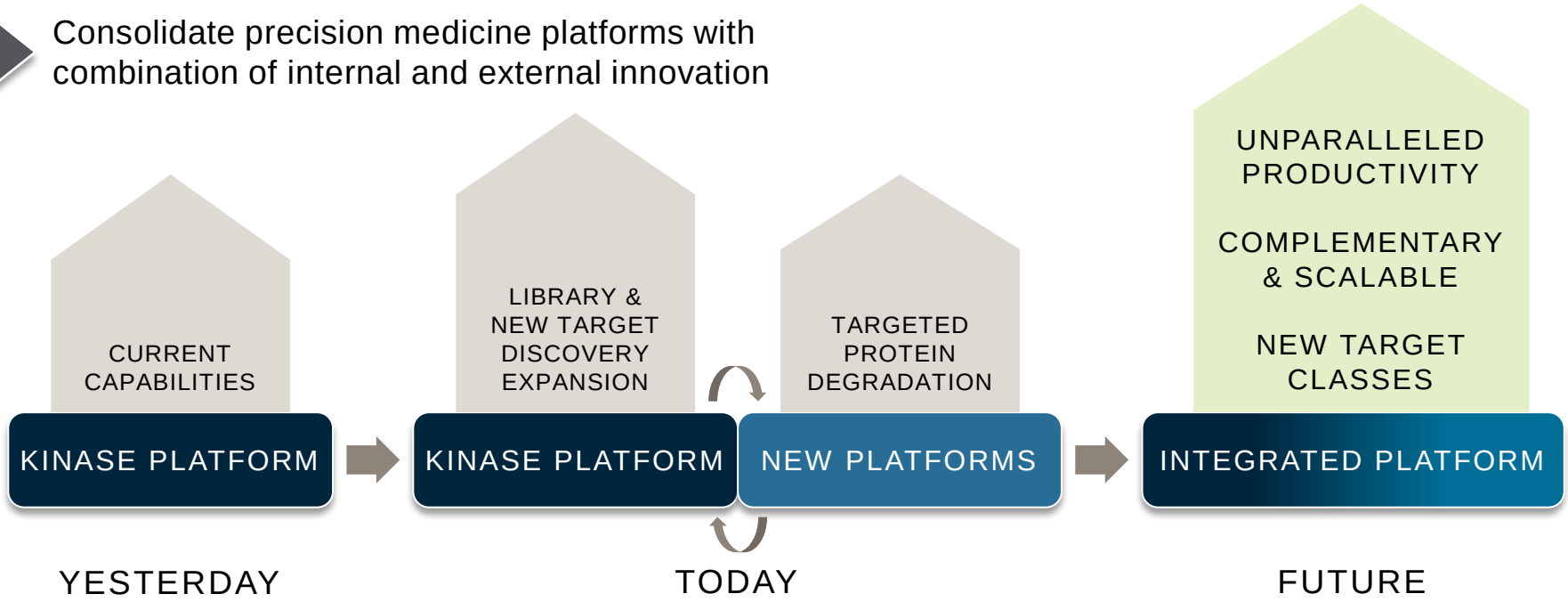
Not for promotional use.

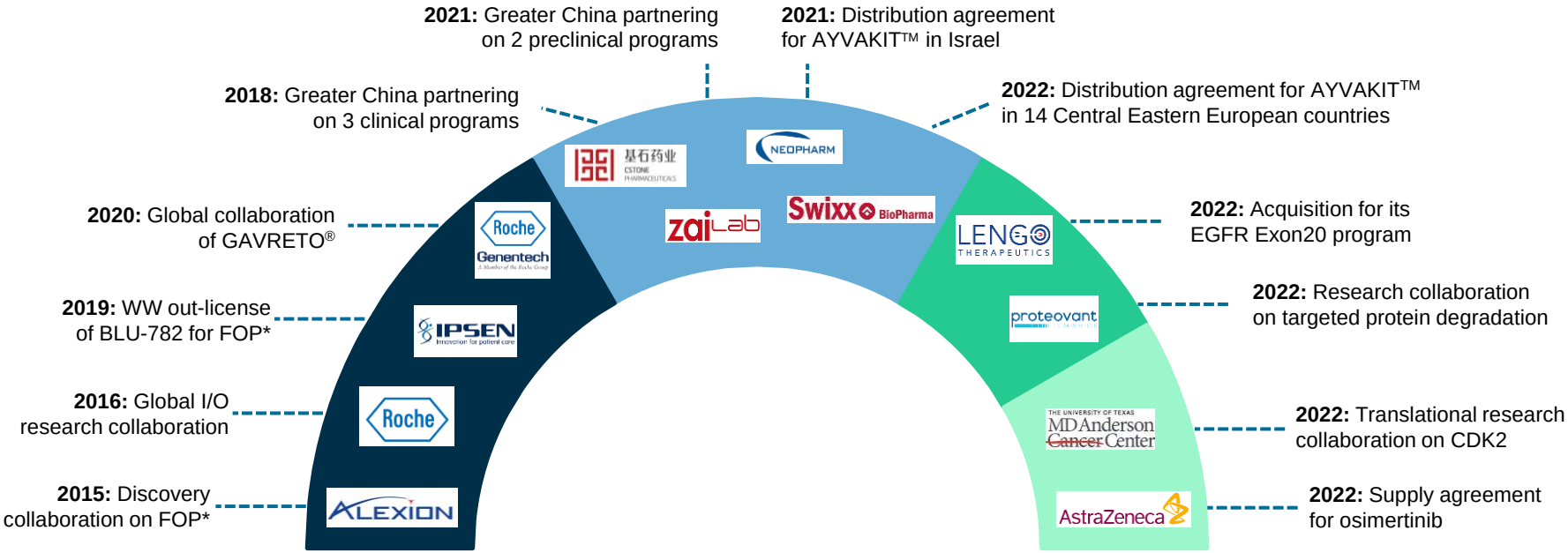
Research platform expansion to drive innovation & expanded productivity

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

* Fibrodysplasia ossificans progressiva

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

Statement of Operations (unaudited)	Three Months Ended 3/31/2022	Three Months Ended 3/31/2021
Total revenue	$62.7M	$21.6M
Net product sales	$23.8M	$9.0M
Collaboration revenue	$38.9M	$12.6M
Cost of sales	$5.1M	$0.1M
Collaboration loss sharing	$3.3M	--
Research & development expense[1]	$103.1M	$79.7M
Selling, general & admin expense[2]	$57.1M	$42.0M
Net loss	$(106.0)M	$(99.7)M

Balance Sheet (unaudited)	3/31/2022	12/31/2021
Cash, cash equivalents and investments	$893.4M	$1,034.6M

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.

Blueprint is uniquely positioned with a diversity of significant growth drivers

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AYVAKIT® avapritinib | tablets

GAVRETO® pralsetinib | 100mg capsules

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