Precision that Moves

AACR 2022 ANNUAL MEETING
INVESTOR PRESENTATION
APRIL 8, 2022

Blueprint Medicines call participants

PREPARED REMARKS

Introduction and portfolio overview	**Kate Haviland** Chief Executive Officer
Initial data from the SYMPHONY trial of BLU-945 presented at the AACR Annual Meeting 2022	**David Spigel, M.D.** Chief Scientific Officer Sarah Cannon Research Institute
Portfolio strategy and next steps	**Fouad Namouni, M.D.** President, Research and Development
Q&A	**All**

Forward-looking statements

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. 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. In this presentation, forward-looking statements include, without limitation, express or implied statements regarding plans, strategies, timelines and expectations for the current or future approved drugs and drug candidates of Blueprint Medicines Corporation (the "Company"), including timelines for the initiation of clinical trials and trial cohorts, the results of ongoing and planned clinical trials, data publications, marketing applications and approvals; the anticipated benefits of the preclinical profiles of the Company's drug candidates; the Company's plans, strategies and timelines for the development of the Company's drug candidates as monotherapies and combination with other agents; anticipated indications for the Company's drug candidates; plans and timelines for additional marketing applications for avapritinib and pralsetinib and, if approved, commercialization of avapritinib and pralsetinib in additional indications or in additional geographies; the potential benefits of any of the Company's current or future approved drugs or drug candidates in treating patients; the Company's scientific platform expansion plans and plans to announce new research programs; and the Company's financial performance, strategy, goals and anticipated milestones, business plans and focus.

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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.

Blueprint Medicines is poised for growth in 2022 and beyond

KEY GOALS

Transform the lives of patients with systemic mastocytosis by improving treatment options across the spectrum disease

Advance our clinical-stage pipeline targeting difficult-to-treat and prevalent cancer drivers

Harness our research engine to bring forward new precision oncology and hematology programs

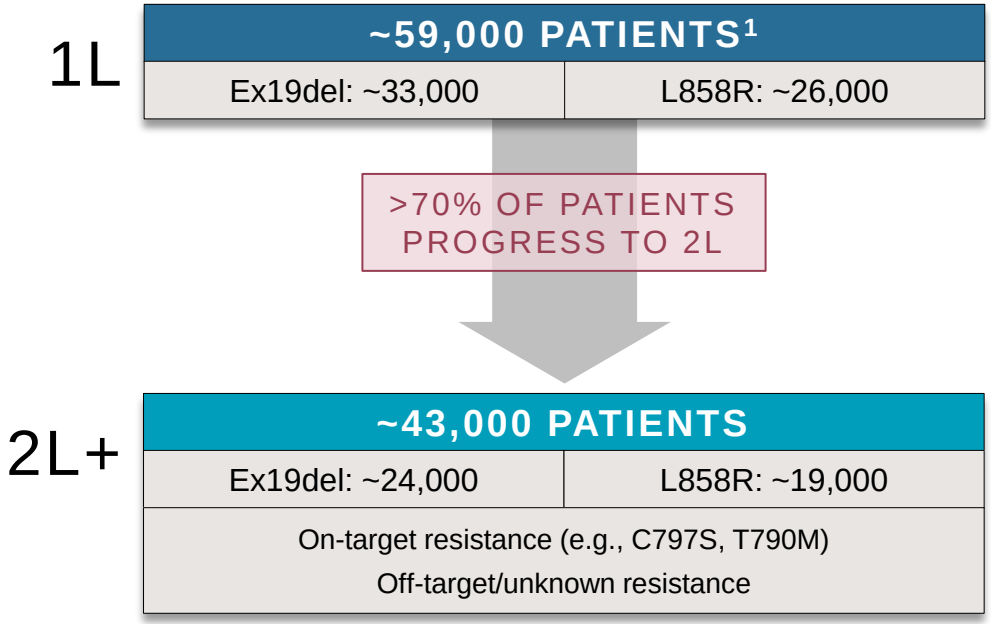
STRONG FINANCIAL POSITION WITH ~$1B CASH AT YEAR-END 2021*

* Cash, cash equivalents and investments as of December 31, 2021.

Increasing tumor resistance and complexity drives disease progression, with no approved therapies after 1L standard of care osimertinib

EGFR-MUTANT NSCLC

ESTIMATED INCIDENT PATIENTS PER YEAR



CHALLENGES

- Lower OS and PFS in patients with L858R activating mutation
- On- and off-target resistance increasingly emerges
- CNS is a common site of disease progression

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. Ex19del, exon 19 deletion mutations; CNS, central nervous system; OS, overall survival; PFS, progression free survival.

Opportunities for our next-generation EGFR precision therapies

EGFR-MUTANT NSCLC
ESTIMATED INCIDENT PATIENTS PER YEAR

1L

~59,000 PATIENTS[1]

Ex19del: ~33,000	L858R: ~26,000

>70% OF PATIENTS PROGRESS TO 2L

2L+

~43,000 PATIENTS

Ex19del: ~24,000	L858R: ~19,000
On-target resistance (e.g., C797S, T790M) Off-target/unknown resistance	

OPPORTUNITIES

- Enhance activity on L858R activating mutation
- Prevent or treat on-target resistance
- Treat off-target resistance with well-tolerated combos
- Prevent or treat brain mets with enhanced CNS penetration

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. CNS, central nervous system.

Our portfolio of EGFR therapies are 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
- 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.

Emerging evidence of activity of BLU-945 in patients with advanced EGFR-mutant NSCLC utilizing circulating tumor DNA in the Phase 1/2 SYMPHONY study

Elaine Shum, Yasir Elamin, Karen L Reckamp, Zofia Piotrowska, Julie Rotow, Daniel SW Tan, Koichi Goto, Jagan Parepally, Faris Albayya, Melinda Louie-Gao, Renata Sawtell, Alena Zalutskaya, **David Spigel**

American Association for Cancer Research
Annual Meeting 2022
April 8, 2022

Disclosures

Dr. David Spigel, MD, Chief Scientific Officer, Sarah Cannon Research Institute

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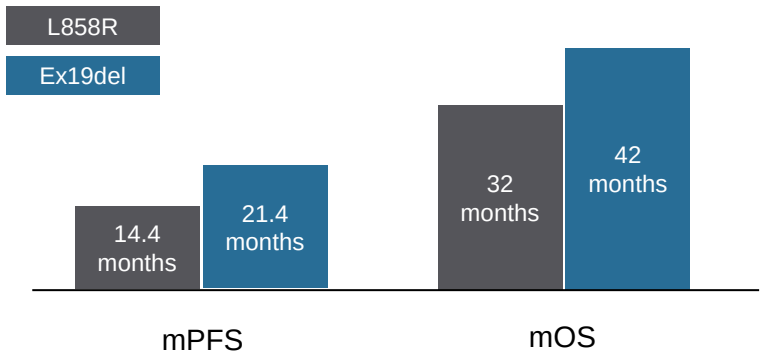
*All payments made to Sarah Cannon Research Institute

blueprint™ MEDICINES

Combinations are needed to prevent and treat mutational heterogeneity, and prolong patient benefit in EGFR mutant NSCLC

Osimertinib prolongs PFS and OS…

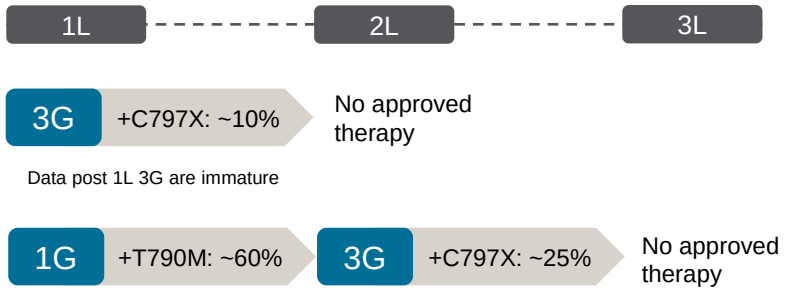
FLAURA study in 1L EGFRm NSCLC
osimertinib median PFS and OS[1]



…but patients with L858R have worse outcomes versus exon 19 deletion

In addition, resistance inevitably emerges…

Estimated frequency of EGFR resistance



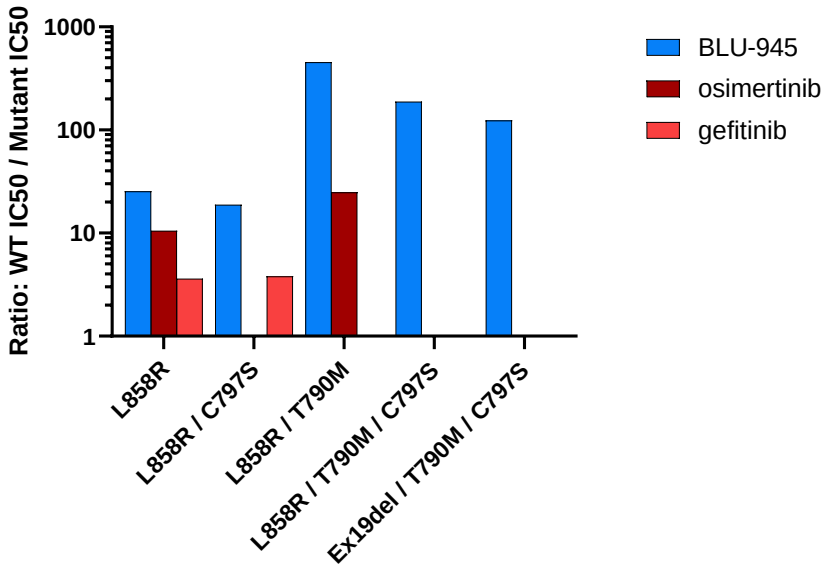
Off-target resistance may occur independently or co-occur with EGFR resistance

…with C797X and T790M the most common EGFR resistance mutations[2]

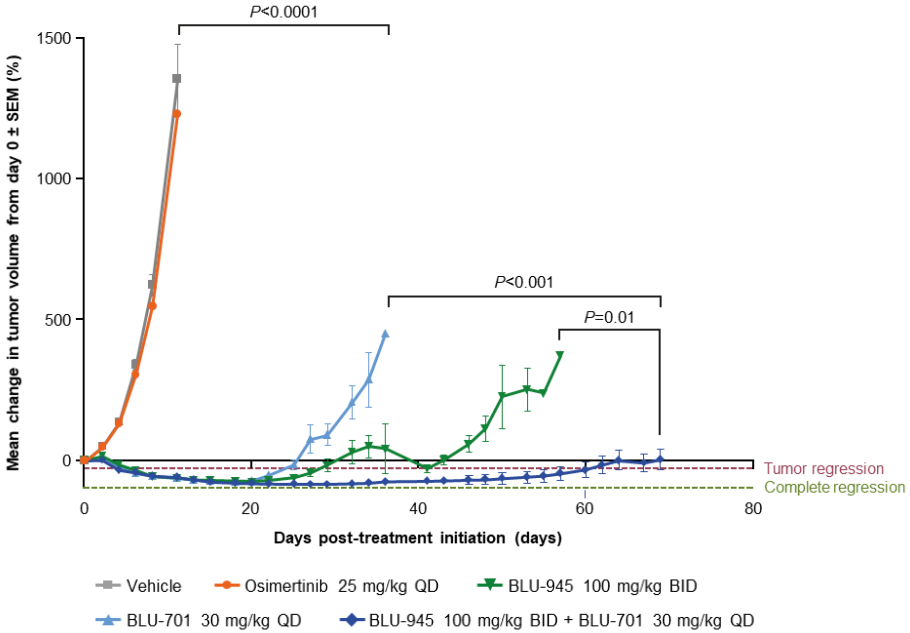
1. Supplemental data in Soria et al NEJM 2018. Ramalingam et al NEJM 2020. 2. Leonetti, et al. British Journal of Cancer, 2019. 1L, first-line; 2L, second-line; 3L, third-line; 1G, first-generation; 2G, second-generation; 3G, third-generation; mPFS, median progression free survival; mOS, median overall survival.

BLU-945 potency and selectivity enable wide therapeutic index and broad EGFR coverage, including activating L858R mutation

BLU-945's therapeutic index enables potent inhibition of EGFR mutants compared to SOC therapies[1]

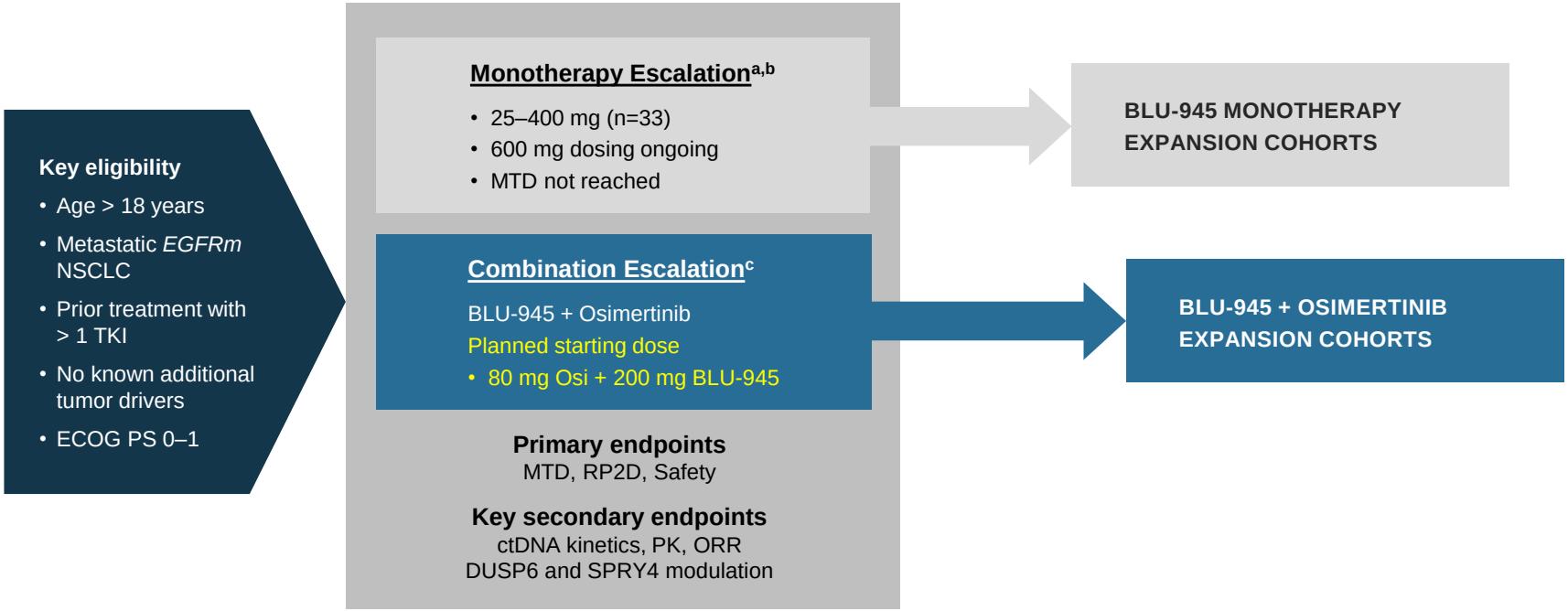


BLU-945 is active alone in combination with BLU-701 in an osimertinib-resistant L858R/C797S CDX model[2]



1. Company data on file. IC_{50} measured by pEGFR in cells. 2. Data presented at AACR annual meeting 2022. Abstract #3328.

SYMPHONY first-in-human clinical trial of BLU-945



[a]Based on Bayesian Optimal Interval escalation design (BOIN); [b]BID dosing will also be evaluated; [c]Part 1B and Phase 2 have not been initiated and are dependent on Part 1A results. ctDNA, circulating tumor DNA; DUSP6, dual specificity phosphatase 6; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFRm, mutant epidermal growth factor receptor gene; PK, pharmacokinetics; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, overall response rate; Osi; osimertinib; RP2D, recommended phase 2 dose; SPRY4, sprouty RTK signaling antagonist 4; TKI, tyrosine kinase inhibitor.

Demography and baseline characteristics

Characteristic		All patients (N=33)
Median age (range), years		61 (39–78)
Female, n (%)		23 (70)
Race, n (%)	White	14 (42)
	Asian	18 (55)
	Other/unknown	1 (3)
Smoking history, n (%)	Current/former	10 (30)
	Never	22 (67)
	Unknown	1 (3)
ECOG PS, n (%)[a]	0	8 (24)
	1	23 (70)
	2	2 (6)
History of CNS disease, n (%)		21 (64)
Prior therapy, median (range)		4 (1–9)
	Prior osimertinib	32 (97)
	1-2	7 (21)
	≥3	26 (79)

Characteristic		All patients (N=33)
EGFR mutation status at C1D1 by central ctDNA NGS assessment[b], n (%)		
	EGFRm/T790M/C797S	11 (33)
	EGFRm/T790M	1 (3)
	EGFRm/C797S	1 (3)
	EGFRm primary only	6 (18)
	T790M only	1 (3)
	No EGFR mutations detected	9 (27)
	Not available[c]	4 (12)

- As of the data cut-off, ~33 patients treated with BLU-945 at 25–400 mg once daily (QD) and dose escalation is ongoing
- Most patients were non-smokers and the majority (n=26 [79%]) had received ≥3 lines of prior systemic therapy

[a]Original study protocol permitted ECOG PS of 0–2, but was later amended to ECOG PS of 0–1; [b]Patients with EGFR-mutant NSCLC are enrolled based on local mutation assessment of tumor biopsy or blood ctDNA with central ctDNA assessment at C1D1; [c]Results for all patients were not available at the time of the data cut. C, cycle; ctDNA NGS, circulating tumor DNA next generation sequencing; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFRm, primary EGFR activating mutation, exon 19 deletion or L858R. 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.

BLU-945 was generally well-tolerated in the ongoing Phase 1 trial

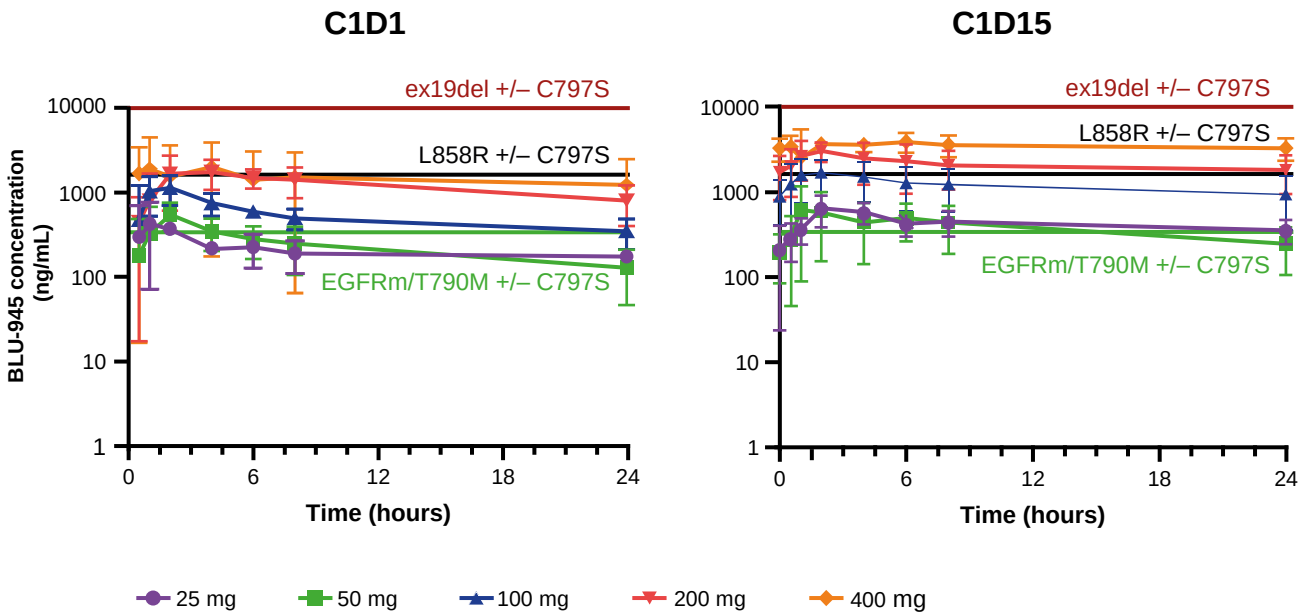
Most common AEs by preferred term in ≥10% of patients

AEs, regardless of causality, n (%)	All AEs N=33		Treatment-related AEs N=33	
	Any grade	Grade 3	Any grade	Grade 3
Nausea	10 (30)	2 (6)	7 (21)	1 (3)
Headache	6 (18)	2 (6)	1 (3)	0
Fatigue	6 (18)	0	5 (15)	0
Cough	5 (15)	0	1 (3)	0
Dyspnea	5 (15)	1 (3)	0	0
Vomiting	5 (15)	1 (3)	3 (9)	1 (3)
Hyponatremia	4 (12)	0	0	0
Dry Mouth	4 (12)	0	3 (9)	0
Anemia	4 (12)	1 (3)	0	0

- No Grade 4 or 5 AEs
- One DLT, grade 3 transaminitis, in 400 mg QD cohort
  - Improved with dose interruption; patient remains on therapy
- AEs associated with EGFR wild-type inhibition were minimal
- No interstitial lung disease or QTc prolongation
- 8 (24%) serious AEs, with 2 (6%) deemed to be related:
  - Grade 3 vomiting
  - Grade 3 transaminitis
- No treatment discontinuations due to AEs
- Dose escalation continues and the MTD has not yet been determined

AE, adverse event; DLT, dose-limiting toxicity; MTD, maximum tolerated dose. 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.

BLU-945 exposure showed increasing IC_{90} coverage of activating and resistance mutations at higher doses

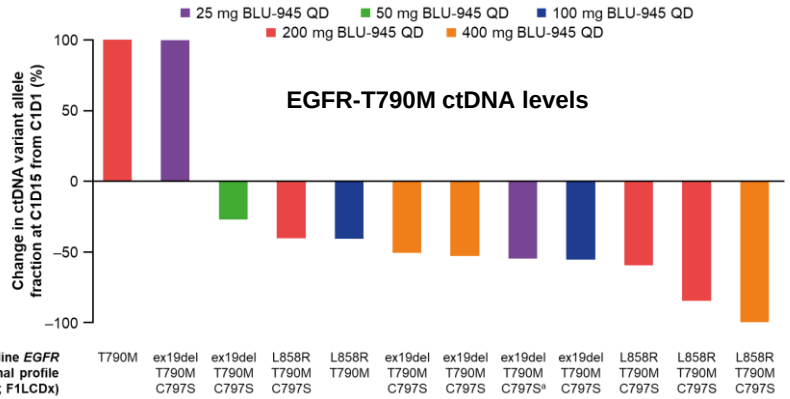


- The average effective half-life was 24.1 hours (calculated from the extent of accumulation)
- Exposure at 400 mg exceeds:
  - EGFRm/T790M +/− C797S IC_{90} in all patients
  - L858R +/− C797S IC_{90} in most patients

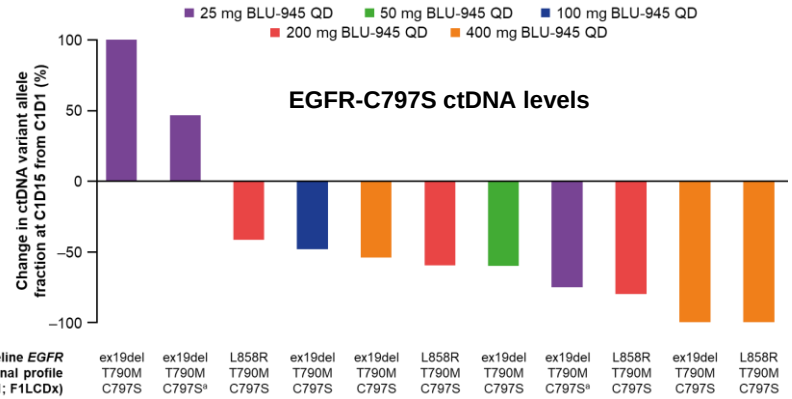
Dashed lines represent IC_{90} for indicated EGFR mutants. C, Cycle; D, day; QD, once daily. As of the data cut-off (March 9, 2022), 33 patients have been treated with BLU-945 at 25–400 mg once daily (QD) in the first 5 cohorts.

BLU-945 treatment led to dose-dependent reductions in ctDNA

83% OF EGFR-T790M VARIANT ALLELES REDUCED WITH TREATMENT



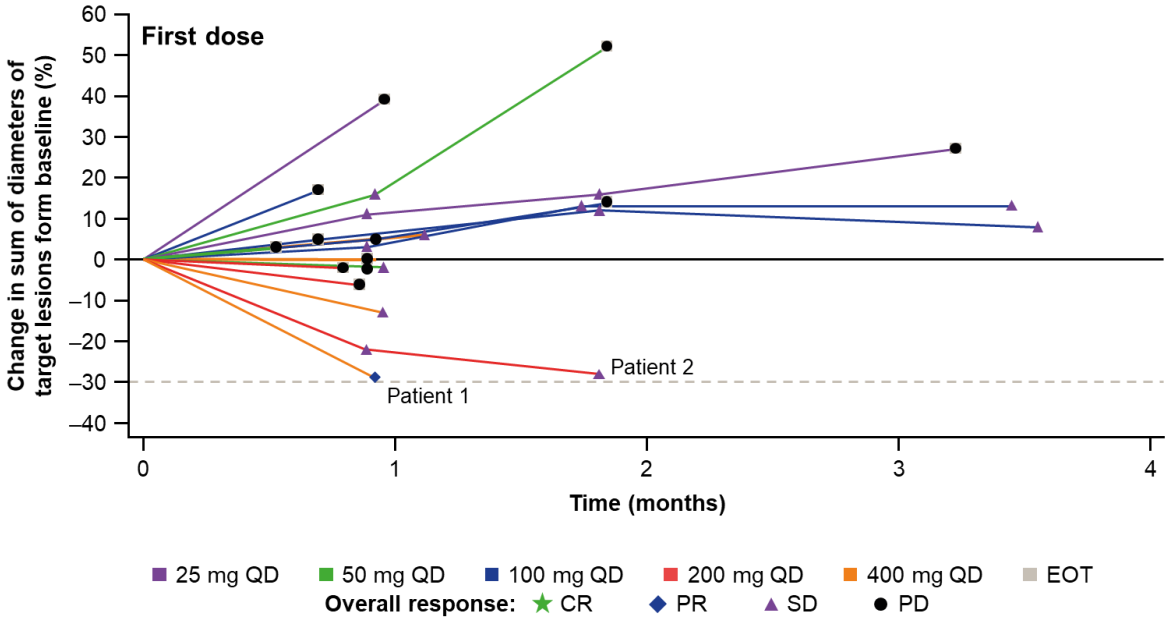
81% OF EGFR-C797S VARIANT ALLELES REDUCED WITH TREATMENT



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

[a]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%. C, Cycle; ctDNA, circulating tumor DNA; D, day; F1LCDx, FoundationOne Liquid CDx assay; QD, once daily.1. Ku BM et al. Oncology. 2022; Epub ahead of print. PMID: 35196661; 2 Ma L et al. Front Oncol. 2021;11:643199; 3. Fernandes MGO et al. Cells. 2021;10:1912. 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.

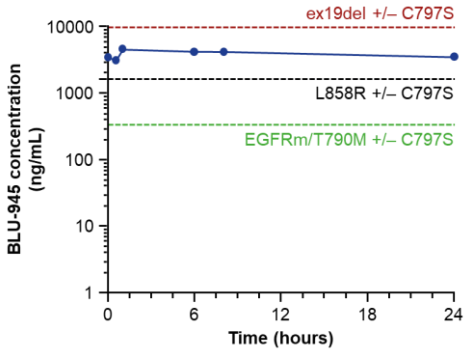
BLU-945 showed dose-dependent anti-tumor activity, with tumor shrinkage reported at doses ≥200 mg QD

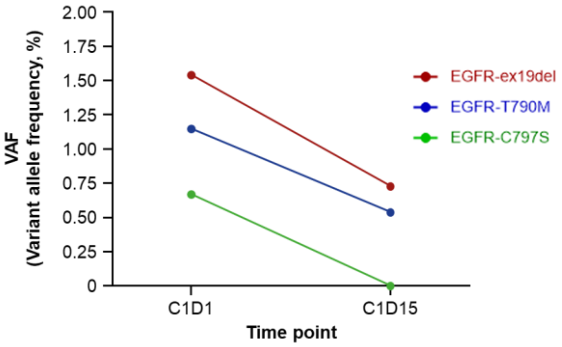


- Unconfirmed PR reported in patient with ex19del/T790M/C797S treated at 400 mg QD
- Dose escalation from 100 to 200 mg QD led to stabilization of tumor growth in two patients

[a]Patients with measurable target lesions at baseline with post-baseline scans (investigator assessed); [b]Data cut off, March 9, 2022; CR, complete remission; EOT, end of treatment; PD, progressive disease; PR, partial remission; QD, once daily; SD, stable disease. An unconfirmed PR is a PR in which tumor reduction ≥30% has occurred but has not yet been confirmed via a subsequent scan. 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.

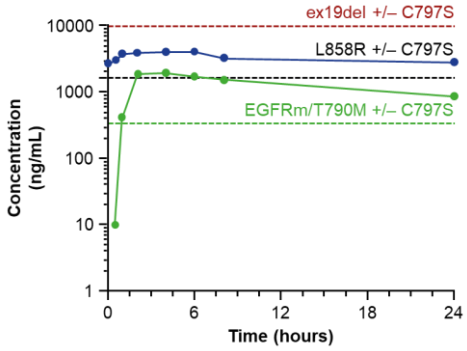
Patient cases: BLU-945 demonstrated encouraging signs of clinical activity in patients treated at higher doses

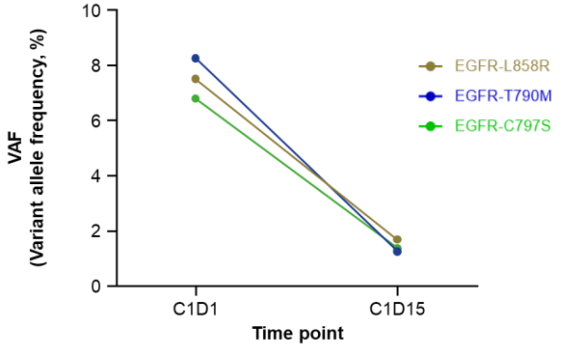




Patient 1

- 69-year-old Caucasian female, no smoking history
- Diagnosed stage IV NSCLC
- Three prior therapies with best response of SD
- Multiple target and non-target lesions, including non-target in brain
- 400 mg QD
- All detectable mutations decreased at C1D15, with C797S clearance
- **Unconfirmed PR; 30% tumor reduction at C2D1**



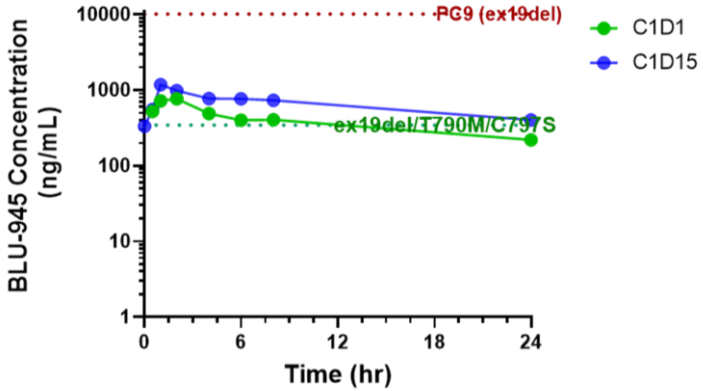


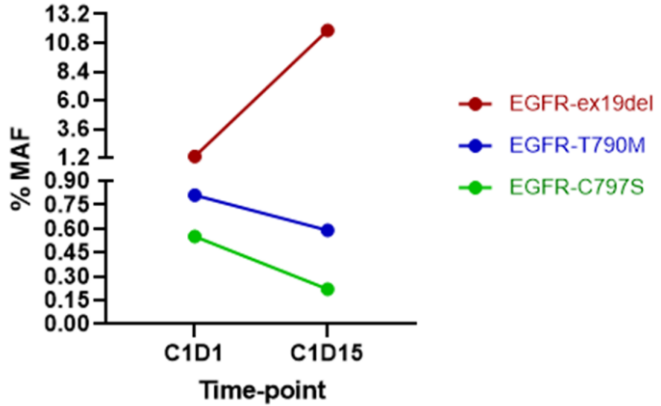
Patient 2

- 70-year-old Asian female, no smoking history
- Diagnosed stage IVB
- Three prior therapies, achieved PRs and PD
- Multiple target and non-target lesions
- 200 mg QD
- All detectable mutations decreased at C1D15
- **21% and 28% tumor reduction at C2D1 and C3D1, respectively**

QD, once daily. SD, stable disease. PR, partial response. PD, progressive disease. An unconfirmed PR is a PR in which tumor reduction ≥30% has occurred but has not yet been confirmed via a subsequent scan. 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.

Patient case: ctDNA and exposure analyses in patient treated at 50 mg highlight polyclonal disease and potential of combination treatment





- 57-year-old Asian female
- Several prior therapies (multiple TKIs, chemo, I/O)
- No brain metastases at screening
- Treated with BLU-945 at 50 mg QD
- EOT at C2D1 due worsening pleural effusion

- Divergence in mutation allele fractions suggest polyclonal disease with some tumors harboring ex19del alone
- Combination therapy and/or increasing BLU-945 exposure at higher doses may hold promise for treating late-line polyclonal disease

QD, once daily. EOT, end of treatment. I/O, immunotherapy. 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.

Conclusions

- In the ongoing Phase 1 trial, BLU-945, a highly potent and selective oral EGFR inhibitor, was generally well tolerated at clinically active doses in heavily pre-treated patients with EGFRm NSCLC
    - Few AEs characteristic of wild-type EGFR toxicity observed at doses up to 400 mg QD
- Despite presence of EGFR mutations conferring resistance to osimertinib, treatment with BLU-945 resulted in rapid dose-dependent reductions in ctDNA, consistent with preclinical data
- Increasing BLU-945 doses were associated with increasing antitumor activity, with tumor shrinkage noted at doses of 200 mg QD and above, including an unconfirmed partial response at 400 mg QD
- The clonal evolution and resulting mutational complexity of EGFR-driven NSCLC tumor cells demonstrates the need for precision medicine combinations to improve clinical outcomes
- Initial safety and clinical activity results support expanded clinical development of BLU-945 in combination with osimertinib and other complementary agents

AE, adverse event. QD, once daily. ctDNA, circulating tumor DNA. An unconfirmed PR is a PR in which tumor reduction ≥30% has occurred but has not yet been confirmed via a subsequent scan. 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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- SYMPHONY trial investigators and research coordinators
- Clinical trial sites:

Cedars-Sinai Medical Center, Los Angeles, CA

Dana-Farber Cancer Institute, Boston, MA

Kanagawa Cancer Center, Yokohama-shi, Kanagawa, Japan

Massachusetts General Hospital, Boston, MA

National Cancer Centre Singapore, Singapore

National Cancer Center Hospital, Chuo Ku, Tokyo, Japan

National Cancer Center Hospital East, Kashiwa, Chiba, Japan

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NYU Langone Health, Laura and Isaac Perlmutter Cancer Center, New York, NY

Samsung Medical Center, Seoul, Korea

Sarah Cannon Research Institute, Nashville, TN

Seoul National University, Department of Internal Medicine, Seoul, Korea

The Royal Marsden NHS Foundation Trust, Sutton, Surrey, UK

The University of Texas MD Anderson Cancer Center, Houston, TX

UC Irvine Health, Chao Family Comprehensive Cancer Center, Orange, CA

University of Colorado Hospital - Anschutz Cancer Pavilion (ACP), Aurora, CA

Vall d'Hebron University Hospital, Oncology Department, Barcelona, Spain

Yonsei Cancer Center, Severance Hospital, Yonsei University, Seoul, Korea

- Colleagues at Blueprint Medicines Corporation

Portfolio strategy and next steps

Fouad Namouni, MD, President, R&D

Early BLU-945 dose escalation data achieve clinical proof-of-concept

Dose-dependent reductions in ctDNA allele fractions for EGFR resistance mutations targeted by BLU-945

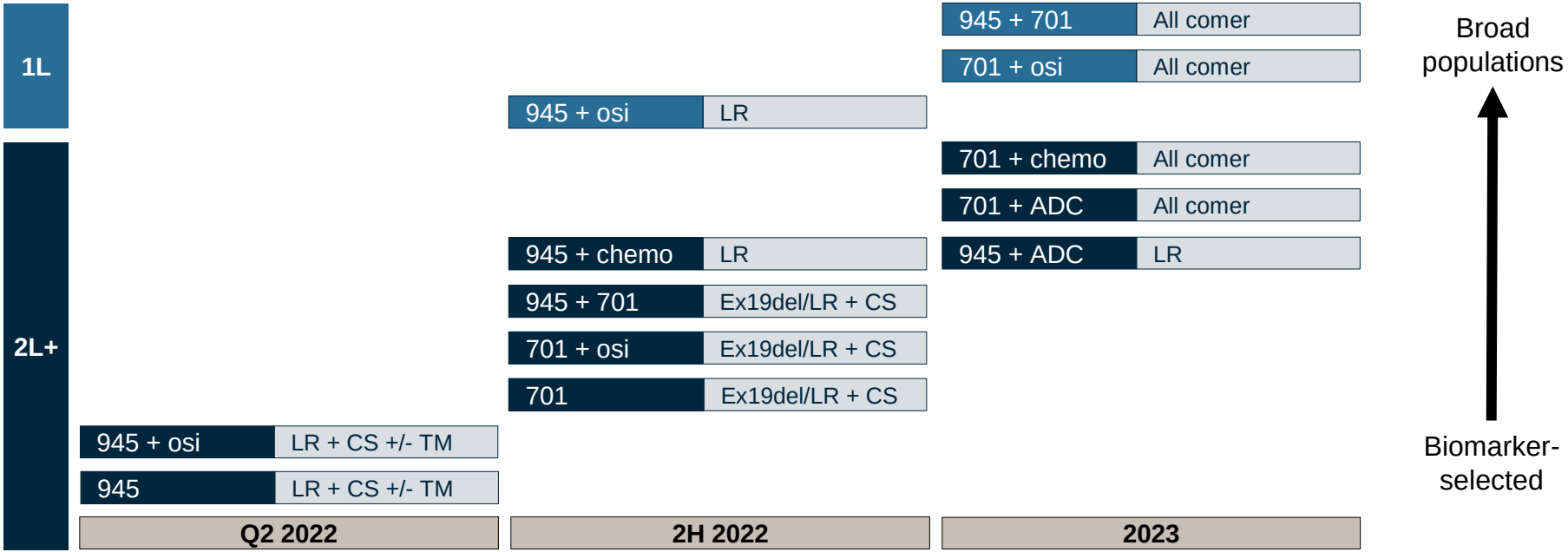
Increasing coverage of EGFR activating and resistance mutations at higher doses, based on pharmacokinetic data

Dose-dependent antitumor activity, with reductions in target lesions observed at 200 mg QD and higher

Generally well-tolerated, with no significant adverse events associated with wild-type EGFR inhibition

DATA SUPPORT INITIATION OF BROAD COMBINATION DEVELOPMENT STRATEGY

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

Phase 1/2 VELA trial of BLU-222 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)

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

blueprint MEDICINES

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

Significant progress across our portfolio will drive near-term news flow

Top-line PIONEER trial data in non-advanced SM with potential to significantly expand AYVAKIT label

MID-2022

Multiple anticipated datasets for EGFR and CDK2 programs with potential to unlock broad patient opportunities

2H 2022 THRU 2023

Plan to unveil new research programs and vision for scientific platform expansion at R&D Day

2H 2022

Thank You