Blueprint Medicines’ Highly Selective RET Inhibitor BLU-667 Shows Durable Anti-Tumor Activity in Patients with RET-Altered Cancers in Updated ARROW Trial Data Presented at ASCO 2019

-- 60% ORR in post-platinum RET-fusion NSCLC and 63% ORR in RET-mutant MTC patients previously treated with multi-kinase inhibitors; median durations of response not reached --

-- Responses observed across treatment-naïve and previously treated patients, and regardless of RET alteration or tumor type --

-- Strong activity against brain metastases in NSCLC patients --

-- Plan to submit initial NDA to FDA for BLU-667 in RET-fusion NSCLC in first quarter of 2020 --

-- Blueprint Medicines to host investor event and webcast on Monday, June 3, 2019 at 6:30 p.m. CT --

CAMBRIDGE, Mass., June 3, 2019 – Blueprint Medicines Corporation (NASDAQ: BPMC), a precision therapy company focused on genomically defined cancers, rare diseases and cancer immunotherapy, today announced updated data from the ongoing registration-enabling ARROW trial of BLU-667 in patients with RET-altered cancers. The data presented at the American Society of Clinical Oncology (ASCO) 2019 Annual Meeting show durable clinical activity in patients with RET-altered non-small cell lung cancer (NSCLC), medullary thyroid cancer (MTC) and other cancers. Designed by Blueprint Medicines, BLU-667 is a potent and highly selective oral inhibitor of RET fusions and mutations, including predicted resistance mutations.

The new results support Blueprint Medicines’ plans to submit an initial New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for BLU-667 for the treatment of patients with RET-fusion NSCLC previously treated with platinum-based chemotherapy in the first quarter of 2020, and an NDA to the FDA for the treatment of patients with RET-mutant MTC previously treated with an approved multi-kinase inhibitor (MKI) in the first half of 2020.

“Targeted therapies have transformed the management of multiple oncogenic subsets of lung cancer, but RET-fusion positive lung cancers have not derived similar benefit from current therapeutic approaches. To date, no selective RET inhibitors are approved,” said Justin Gainor, M.D., director of Targeted Immunotherapy at Massachusetts General Hospital Cancer Center and an investigator on the ARROW trial. “In the data presented at ASCO, BLU-667 demonstrated high response rates across multiple populations of RET-altered cancer patients, including patients with untreated brain metastases.”

“This growing body of evidence supports our plans to rapidly advance BLU-667, a highly selective RET inhibitor, for the treatment of patients with RET-altered cancers,” said Andy Boral, M.D., Ph.D., Chief Medical Officer at Blueprint Medicines. “We remain on track to submit our first New Drug Application to the FDA for BLU-667 for previously treated RET-fusion non-small cell lung cancer patients in the first quarter of 2020. Based on the encouraging data to date and FDA feedback, we are now working to expand ARROW trial enrollment for treatment-naïve patients with RET-fusion positive non-small cell lung cancer, with the goal of supporting an accelerated path to registration in first-line patients. In addition, based on the strong data for BLU-667 across RET alteration and tumor types, we plan to continue to work with investigators and global regulatory authorities to bring BLU-667 to the broader population of patients with RET-altered cancers who could potentially benefit from this treatment.”
Highlights from ASCO Presentations of ARROW Trial Data

The presented data include 120 patients with RET-fusion NSCLC, 64 patients with RET-mutant MTC and 12 patients with other RET-altered cancers (nine papillary thyroid cancer (PTC), two pancreatic cancer and one intrahepatic bile duct carcinoma) enrolled in the ARROW trial as of a data cutoff date of April 28, 2019. The patients with RET-fusion NSCLC and RET-mutant MTC received a starting dose of 400 mg once daily (QD), which is the recommended Phase 2 dose (RP2D). Patients with other RET-altered cancers were included regardless of starting dose.

At baseline, 40 percent of the RET-fusion NSCLC patients had brain metastases. Brain metastases commonly occur in NSCLC patients, and the prognosis in these patients is typically poor. Regardless of starting dose and including the dose-escalation portion of the ARROW trial, the RET-fusion NSCLC patients have been on treatment up to 24 months.

For clinical activity data, NSCLC and MTC patients were evaluable if they were enrolled as of November 14, 2018 with follow-up through the data cutoff date, which enabled them to have at least two radiographic scans. Tumor response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Clinical Activity Data — RET-Fusion NSCLC

As of the data cutoff date, 48 patients with RET-fusion NSCLC were evaluable for response assessment, including 35 patients previously treated with platinum-based chemotherapy.

- Nearly all patients (90 percent) had radiographic tumor reductions.
- The objective response rate (ORR) was 60 percent (one complete response and 20 partial responses (PR); all responses were confirmed), and the disease control rate\(^1\) (DCR) was 100 percent in the patients previously treated with platinum-based chemotherapy.
- The ORR was 71 percent (five confirmed PRs) in seven patients naïve to prior systemic treatment.
- Across all patients, the median duration of response (DOR) was not reached, and 82 percent of responders remained on treatment as of the data cutoff date.
- In nine patients with measurable brain metastases, 78 percent had shrinkage of brain metastases.
- No patients starting at the 400 mg QD dose had disease progression due to new brain involvement.
- BLU-667 was highly active regardless of RET fusion partner, including RET-KIF5B and RET-CCDC6.

Clinical Activity Data — RET-Mutant MTC and Other RET-Altered Cancers

As of the data cutoff date, 32 patients with RET-mutant MTC were evaluable for response assessment, including 16 patients previously treated with the MKIs cabozantinib or vandetanib.

- The ORR was 63 percent (nine confirmed PRs, one PR pending confirmation) and the DCR was 94 percent in RET-mutant MTC patients previously treated with cabozantinib or vandetanib.
- Across all RET-mutant MTC patients, the median DOR was not reached and all responders remained on treatment as of the data cutoff date, with treatment durations up to 15.6 months for patients receiving a starting dose of 400 mg QD.

As of the data cutoff date, clinical activity data were reported in patients with other RET-altered cancers:

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\(^1\) Defined as the rate of complete responses, PRs and stable disease in patients evaluable for response assessment.
Six patients with PTC were evaluable for response assessment by RECIST version 1.1. In these patients, the ORR was 83 percent (three confirmed PRs, two PRs pending confirmation).

Five patients with PTC have remained on treatment for one year or longer, and eight patients with PTC remained on treatment as of the data cutoff date.

Additional responses were observed in patients with other RET-fusion cancers, including pancreatic cancer (one confirmed PR, one PR pending confirmation) and intrahepatic bile duct carcinoma (one confirmed PR).

Four patients (two with RET-fusion NSCLC, two with RET-mutant MTC) enrolled in the ARROW trial were previously treated with LOXO-292. Among them:

Two patients had a PR, one of which was confirmed as of the data cutoff date, and one of which was pending as of the data cutoff date and subsequently confirmed prior to the presentation.

One patient had stable disease with radiographic tumor reductions and remained on treatment as of the data cutoff date.

Safety Data

As of the data cutoff date, 226 patients received a starting dose of 400 mg QD and were evaluable for safety. Across all patients, BLU-667 was well-tolerated and most adverse events (AEs) reported by investigators were Grade 1 or 2. Across all grades, the most common treatment-emergent AEs (regardless of relationship to BLU-667) reported by investigators (≥15 percent) were constipation, hypertension, increased aspartate aminotransferase, neutropenia, diarrhea, fatigue, anemia, increased alanine aminotransferase and increased blood creatinine. Investigator-reported Grade 3 or 4 treatment-related AEs (≥2 percent) included neutropenia, hypertension, anemia, increased blood creatine phosphokinase and leukopenia.

Across all patients, only 4 percent of patients discontinued treatment with BLU-667 due to treatment-related AEs. Seven percent of patients with RET-fusion NSCLC discontinued treatment with BLU-667 due to treatment-related AEs, and no patients with RET-mutant MTC discontinued treatment with BLU-667 due to treatment-related AEs.

These updated data for BLU-667 were reported in two presentations at the ASCO 2019 Annual Meeting, including a poster presentation on trial results in thyroid cancer on Saturday, June 1 (Abstract Number: 6018) and an oral presentation on trial results in NSCLC on Monday, June 3 (Abstract Number: 9008). Copies of the data presentations are available in the “Science—Publications and Presentations” section of Blueprint Medicines’ website at www.BlueprintMedicines.com.

BLU-667 Clinical Development Update

Based on encouraging clinical activity in patients with NSCLC naïve to prior systemic therapy and feedback from the FDA, Blueprint Medicines today announced plans to expand the enrollment target of the ongoing ARROW trial cohort for treatment-naïve patients with RET-fusion NSCLC, with the goal of supporting expedited development in first-line RET-fusion NSCLC.

Investor Event and Webcast Information

Blueprint Medicines will host an investor event on Monday, June 3, 2019 beginning at 6:00 p.m. CT (7:00 p.m. ET) in Chicago to provide a portfolio update, including a review of updated clinical data from the ongoing ARROW trial of
BLU-667 in patients with RET-altered cancers and the ongoing registration-enabling NAVIGATOR trial in patients with PDGFRA Exon 18 mutant and fourth-line gastrointestinal stromal tumors (GIST). Formal presentations and the live webcast will begin at 6:30 p.m. CT (7:30 p.m. ET). The event will be webcast live and can be accessed under the “Investors & Media—Events & Presentations” section of Blueprint Medicines’ website at www.BlueprintMedicines.com. A replay of the webcast will be available approximately two hours after the event and will be available for 30 days following the event.

About the ARROW Trial

ARROW is a Phase 1 clinical trial designed to evaluate the safety, tolerability and efficacy of BLU-667 in multiple ascending doses in adults with RET-altered NSCLC, MTC and other advanced solid tumors. The trial consists of two parts: a dose escalation portion, which is now complete, and an expansion portion, in which enrollment is ongoing. The expansion portion consists of seven defined cohorts of patients treated with BLU-667 at the RP2D of 400 mg QD: (1) RET-fusion NSCLC patients previously treated with a platinum-based chemotherapy, (2) RET-fusion NSCLC patients who have not previously received a platinum-based chemotherapy, (3) RET-mutant MTC patients previously treated with cabozantinib or vandetanib, (4) RET-mutant MTC patients who have not previously received cabozantinib or vandetanib, (5) patients with other RET-fusion tumors, (6) patients with other RET-mutant tumors and (7) RET-altered solid tumor patients previously treated with a selective RET inhibitor. Trial objectives include assessing response, pharmacokinetics, pharmacodynamics and safety. The trial is enrolling patients at multiple sites in the United States, European Union and Asia.

Patients and physicians interested in the ARROW clinical trial can contact the Blueprint Medicines study director at arrow@blueprintmedicines.com or 1-617-714-6707. Additional details are available at www.BlueprintClinicalTrials.com/ARROW or www.clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT03037385).

About RET-Altered Solid Tumors

RET activating fusions and mutations are key disease drivers in many cancer types, including NSCLC and MTC. RET fusions are implicated in approximately 1 to 2 percent of patients with NSCLC and approximately 10 to 20 percent of patients with PTC, while RET mutations are implicated in approximately 90 percent of patients with advanced MTC. In addition, oncogenic RET alterations are observed at low frequencies in colorectal, breast, pancreatic and other cancers, and RET fusions have been observed in patients with treatment-resistant, EGFR-mutant NSCLC.

Currently, there are no approved therapies that selectively target RET-driven cancers, although there are several approved MKIs with RET activity being evaluated in clinical trials. To date, clinical activity attributable to RET inhibition has been uncertain for these approved MKIs, likely due to insufficient inhibition of RET and off-target toxicities. There is a need for precision therapies that provide durable clinical benefit by selectively targeting RET alterations and anticipated resistance mutations.

About BLU-667

BLU-667 is an investigational, once-daily oral precision therapy specifically designed for highly potent and selective targeting of oncogenic RET alterations. Blueprint Medicines is developing BLU-667 for the treatment of patients with RET-altered NSCLC, MTC and other solid tumors. The FDA has granted Breakthrough Therapy Designation to BLU-667 for the treatment of RET-fusion positive NSCLC that has progressed following platinum-based chemotherapy,
BLU-667 was designed by Blueprint Medicines’ research team, leveraging the company’s proprietary compound library. In preclinical studies, BLU-667 consistently demonstrated sub-nanomolar potency against the most common RET fusions, activating mutations and predicted resistance mutations. In addition, BLU-667 demonstrated markedly improved selectivity for RET compared to pharmacologically relevant kinases, including approximately 90-fold improved potency for RET versus VEGFR2. By suppressing primary and secondary mutants, BLU-667 has the potential to overcome and prevent the emergence of clinical resistance. Blueprint Medicines believes this approach will enable durable clinical responses across a diverse range of RET alterations, with a favorable safety profile.

Blueprint Medicines has an exclusive collaboration and license agreement with CStone Pharmaceuticals for the development and commercialization of BLU-667 and certain other drug candidates in Mainland China, Hong Kong, Macau and Taiwan. Blueprint Medicines retains development and commercial rights for BLU-667 in the rest of the world.

About Blueprint Medicines

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

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements regarding plans and timelines for the clinical development of BLU-667; expectations regarding the potential benefits of BLU-667 in treating patients with RET-fusion NSCLC, RET-mutant MTC and other RET-altered cancers; plans and timelines for submitting an NDA to the FDA for BLU-667 for the treatment of RET-fusion NSCLC and RET-mutant MTC; plans, timelines and expectations for interactions with global regulatory authorities; plans to expand the enrollment target of the ongoing ARROW trial cohort for treatment-naïve RET-fusion NSCLC patients; expectations regarding the expedited development of BLU-667 in first-line RET-fusion NSCLC; plans to initiate a Phase 3 trial of BLU-667 in first-line RET-fusion NSCLC; and Blueprint Medicines’ strategy, goals and anticipated milestones, business plans and focus. The words “may,” “will,” “could,” “would,” “should,” “expect,” “plan,” “anticipate,” “intend,” “believe,” “estimate,” “predict,” “project,” “potential,” “continue,” “target” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements in this press release are based on management’s current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this press release, including, without limitation, risks and uncertainties related to the delay of any current or planned clinical trials or the development of Blueprint Medicines’ drug candidates, including avapritinib, BLU-667, BLU-554 and BLU-782; Blueprint Medicines’ advancement of multiple early-stage efforts; Blueprint Medicines’ ability to successfully demonstrate the safety and efficacy of its drug candidates and gain approval of its drug candidates on a timely basis, if at all; the preclinical and clinical results
for Blueprint Medicines’ drug candidates, which may not support further development of such drug candidates; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials; Blueprint Medicines’ ability to develop and commercialize companion diagnostic tests for its current and future drug candidates; and the success of Blueprint Medicines’ current and future collaborations, including its cancer immunotherapy collaboration with F. Hoffmann-La Roche Ltd and Hoffmann-La Roche Inc. and its collaboration with CStone Pharmaceuticals. These and other risks and uncertainties are described in greater detail in the section entitled “Risk Factors” in Blueprint Medicines’ Quarterly Report on Form 10-Q for the period ended March 31, 2019, as filed with the Securities and Exchange Commission (SEC) on May 9, 2019, 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.

Investor Relations Contact

Kristin Hodous
617-714-6674
ir@blueprintmedicines.com

Media Relations Contact

Andrew Law
617-844-8205
media@blueprintmedicines.com