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): **June 1, 2019**

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:

- o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- o 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 7.01 Regulation FD Disclosure.

On June 1, 2019, Blueprint Medicines Corporation (the "Company") issued a press release announcing updated data from its Phase 1 NAVIGATOR clinical trial evaluating avapritinib for the treatment of patients with advanced gastrointestinal stromal tumors ("GIST"). The data were presented on Saturday, June 1, 2019 in a poster presentation at the American Society of Clinical Oncology 2019 Annual Meeting ("ASCO Annual Meeting") in Chicago, Illinois. A copy of the press release is furnished as Exhibit 99.1 to this Current Report on Form 8-K, and a copy of the presentation is furnished as Exhibit 99.2 to this Current Report on Form 8-K.

On June 3, 2019, the Company issued a press release announcing updated data from its Phase 1 ARROW clinical trial evaluating BLU-667 for the treatment of patients with RET-altered non-small cell cancer ("NSCLC"), medullary thyroid cancer ("MTC") and other advanced solid tumors. The data for patients with RET-mutant MTC and other RET-altered cancers were presented on Saturday, June 1, 2019 in a poster presentation at the ASCO Annual Meeting. The data for patients with RET-fusion NSCLC will be presented on Monday, June 3, 2019 in an oral presentation at the ASCO Annual Meeting. A copy of the press release is furnished as Exhibit 99.3 to this Current Report on Form 8-K, a copy of the presentation for patients with RET-mutant MTC and other RET-altered cancers is furnished as Exhibit 99.4 to this Current Report on Form 8-K and a copy of the presentation for patients with RET-fusion NSCLC is furnished as Exhibit 99.5 to this Current Report on Form 8-K.

The information in Item 7.01 of this Current Report on Form 8-K, including Exhibits 99.1, 99.2, 99.3, 99.4 and 99.5, 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 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	Description
99.1	Press release issued by Blueprint Medicines Corporation on June 1, 2019
99.2	Presentation by Blueprint Medicines Corporation for avapritinib in advanced GIST at the ASCO Annual Meeting on June 1, 2019
99.3	Press release issued by Blueprint Medicines Corporation on June 3, 2019
99.4	Presentation by Blueprint Medicines Corporation for BLU-667 in RET-mutant MTC and other RET-altered cancers at the ASCO Annual Meeting on June 1, 2019
99.5	Presentation by Blueprint Medicines Corporation for BLU-667 in RET-fusion NSCLC at the ASCO Annual Meeting on June 3, 2019

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: June 3, 2019

By: /s/ Tracey L. McCain

Tracey L. McCain
Chief Legal Officer

Blueprint Medicines Presents NAVIGATOR Trial Data in PDGFRA Exon 18 Mutant GIST and Fourth-Line GIST at ASCO 2019 Supporting Planned Marketing Applications for Avapritinib

-- 86% ORR and median DOR not reached in PDGFRA Exon 18 mutant GIST --

-- 22% ORR and 10.2 month median DOR in fourth-line GIST --

-- On track to submit NDA to FDA in June 2019 and MAA to EMA in third quarter of 2019 --

CAMBRIDGE, Mass., June 1, 2019 – Blueprint Medicines Corporation (NASDAQ: BPMC), a precision therapy company focused on genomically defined cancers, rare diseases and cancer immunotherapy, today announced data from the registration-enabling NAVIGATOR trial of avapritinib in patients with PDGFRA Exon 18 mutant gastrointestinal stromal tumors (GIST) and fourth-line GIST. These results were presented at the American Society of Clinical Oncology (ASCO) 2019 Annual Meeting and will form the basis for planned worldwide marketing applications for avapritinib, an investigational, highly selective KIT and PDGFRA inhibitor for patients with advanced GIST. The data demonstrate clinical activity and favorable tolerability in patients with PDGFRA Exon 18 mutant and fourth-line GIST, two populations with no effective therapies.

Data from the ongoing NAVIGATOR trial in patients with PDGFRA Exon 18 mutant GIST, which primarily includes the D842V mutation, and fourth-line GIST support Blueprint Medicines' plans to submit a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) in June 2019 and a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) in the third quarter of 2019. Avapritinib has received FDA Breakthrough Therapy Designation for the treatment of patients with unresectable or metastatic GIST harboring the PDGFRα D842V mutation.

In patients with PDGFRA Exon 18 mutant GIST, the objective response rate (ORR) was 86 percent and the median duration of response (DOR) was not reached. In patients with fourth-line GIST, the ORR was 22 percent and the median DOR was 10.2 months. ORR and DOR per central radiographic review will be the primary registrational endpoints. Avapritinib was well-tolerated with most adverse events (AEs) reported by investigators as Grade 1 or 2. These results were as of a data cutoff date of November 16, 2018.

"These data highlight the potential of avapritinib to shift the treatment paradigm for GIST toward a precision medicine approach based on the genomic driver of disease," said Michael Heinrich, M.D., Professor of Medicine at Oregon Health & Science University and an investigator on the NAVIGATOR trial. "In the PDGFRα D842V population where we currently have no effective agents, avapritinib demonstrated remarkable activity regardless of line of therapy. I believe these results will further catalyze the use of mutational testing in GIST patients prior to starting therapy, which is currently recommended by treatment guidelines. Importantly, avapritinib has also demonstrated the potential to suppress complex and heterogenous mutational profiles associated with treatment-resistant fourth-line GIST. Combined with the well-tolerated safety profile of avapritinib, I believe these data show the broad potential of avapritinib to advance care across the GIST treatment landscape."

“These results further demonstrate the activity and favorable tolerability of avapritinib, a potent and highly selective PDGFRA and KIT inhibitor, in two patient populations with tumor mutations resistant to currently available therapies,” said Andy Boral, M.D., Ph.D., Chief Medical Officer at Blueprint Medicines. “Based on the strength of these data and the clear medical needs in PDGFRA Exon 18 mutant and fourth-line GIST, we look forward to working closely with global regulatory authorities to bring this important advance in treatment to patients as expeditiously as possible. In addition, the previously reported preliminary data in third-line and second-line GIST support our broad clinical development program and highlight the potential of avapritinib to become a foundational GIST treatment.”

Highlights from ASCO Presentation of NAVIGATOR Trial Data

As of the data cutoff date of November 16, 2018, 204 patients were treated with avapritinib at a starting dose of 300 or 400 mg once daily (QD). Patients with PDGFRA Exon 18 mutant GIST were treated across all lines of therapy. Patients with fourth-line or later GIST had a median of four prior lines of therapy (ranging from three to 11) prior to receiving avapritinib.

Clinical Activity Data

As of the data cutoff date, 43 patients with PDGFRA Exon 18 mutant GIST (including 38 patients with PDGFRα D842V-driven GIST) and 111 patients with fourth-line GIST were treated at a starting dose of 300 or 400 mg QD and evaluable for response assessments. Patients were evaluable if they had at least one centrally reviewed radiographic scan, and data are based on modified Response Evaluation Criteria in Solid Tumors version 1.1 (mRECIST 1.1 criteria) for GIST.

In evaluable patients with PDGFRA Exon 18 mutant GIST:

- The ORR was 86 percent, with three confirmed complete responses (CR) and 34 partial responses (PR; one pending confirmation).
- The ORR was 100 percent (two CRs and three PRs; all responses were confirmed) in the first-line treatment setting.
- The median DOR was not reached.
- 28 patients (78 percent) remained in response as of the data cutoff date.
- Median follow-up was 10.9 months.

In evaluable patients with fourth-line GIST:

- The ORR was 22 percent, with one confirmed CR and 23 PRs (one pending confirmation[1]).
- The median DOR was 10.2 months.
- Median follow-up was 10.8 months.

Safety Data

Avapritinib had a favorable safety profile in patients treated at a starting dose of 300 or 400 mg QD, with most AEs determined by investigators to be Grade 1 or 2 as of the data cutoff date. Across all patients, 8 percent of patients discontinued treatment with avapritinib due to treatment-related AEs. A lower incidence of commonly reported AEs was reported at 300 mg QD dosing compared to 400 mg QD dosing.

Across all grades, the most common treatment-emergent AEs (regardless of relationship to avapritinib) reported by investigators (≥25 percent) were nausea, fatigue, anemia, cognitive effects, periorbital edema, vomiting, decreased appetite, diarrhea, increased lacrimation and peripheral edema. Investigator-reported Grade 3 or 4 treatment-related AEs (≥2 percent) included anemia, fatigue, cognitive effects, increased blood bilirubin, diarrhea, hypophosphatemia, decreased neutrophil count, neutropenia and lymphopenia.

These data on avapritinib were presented at the ASCO 2019 Annual Meeting in a poster presentation on Saturday, June 1 (Abstract Number: 11022). A copy of the poster is available in the "Science—Publications and Presentations" section of Blueprint Medicines' website at www.BlueprintMedicines.com.

About the Avapritinib Clinical Development Program in GIST

Blueprint Medicines is pursuing a broad clinical development program for avapritinib across all lines of GIST. Avapritinib is currently being evaluated in two global registration-enabling clinical trials for GIST: the Phase 1 NAVIGATOR trial and the Phase 3 VOYAGER trial.

The NAVIGATOR trial is designed to evaluate the safety, tolerability and clinical activity of avapritinib in patients with unresectable or metastatic GIST. The trial consists of two parts, a dose escalation portion and an expansion portion. Trial objectives include assessing response using blinded central radiology review, as well as pharmacokinetics and pharmacodynamic measures. The expansion cohorts of the trial enrolled patients at multiple sites in the United States, European Union and Asia.

The VOYAGER trial is a global, open-label, randomized, Phase 3 trial designed to evaluate the safety and efficacy of avapritinib versus regorafenib in patients with third- or fourth-line GIST. The trial is designed to enroll approximately 460 patients randomized 1:1 to receive either avapritinib or regorafenib at multiple sites in the United States, Canada, European Union, Australia and Asia.

In the second half of 2019, Blueprint Medicines plans to initiate COMPASS-2L, a global, randomized, Phase 3 precision medicine trial. The trial will evaluate the safety and efficacy of avapritinib versus sunitinib in second-line GIST patients with pre-specified disease genotypes.

Patients and physicians interested in the Phase 3 VOYAGER trial can contact the Blueprint Medicines study director at VOYAGER@blueprintmedicines.com or 1-617-714-6707. For more information about the VOYAGER trial, please visit www.BlueprintClinicalTrials.com/VOYAGER. Additional details are available on www.clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT03465722).

About GIST

GIST is a sarcoma, or tumor of bone or connective tissue, of the gastrointestinal (GI) tract. Tumors arise from cells in the wall of the GI tract and occur most often in the stomach or small intestine. Most patients are diagnosed between the ages of 50 to 80, and diagnosis is typically triggered by GI bleeding, incidental findings during surgery or imaging and, in rare cases, tumor rupture or GI obstruction.

Most GIST cases are caused by a spectrum of clinically relevant mutations that force the KIT or PDGFRA protein kinases into an increasingly active state. Because currently available therapies primarily bind to

the inactive protein conformations, certain primary and secondary mutations typically lead to treatment resistance and disease progression.

Treatment options for KIT-driven GIST patients who progress beyond imatinib are currently limited. There are no effective treatment options for patients with metastatic PDGFRα D842V-driven GIST, and progression occurs in a median of approximately three to four months with available therapy. In unresectable or metastatic GIST, clinical benefits from existing treatments can vary by mutation type. Mutational testing is critical to tailor therapy to the underlying disease driver and is recommended in expert guidelines.

About Avapritinib

Avapritinib is an investigational, oral precision therapy that selectively and potently inhibits KIT and PDGFRA mutant kinases. It is a type 1 inhibitor designed to target the active kinase conformation; all oncogenic kinases signal via this conformation. Avapritinib has demonstrated broad inhibition of KIT and PDGFRA mutations associated with GIST, including potent activity against activation loop mutations that are associated with resistance to currently approved therapies. In contrast to approved multi-kinase inhibitors, avapritinib has shown marked selectivity for KIT and PDGFRA over other kinases. In addition, avapritinib is uniquely designed to selectively bind and inhibit D816V mutant KIT, the common driver of disease in approximately 95 percent of all systemic mastocytosis (SM) patients. Preclinical studies have shown avapritinib potently inhibited KIT D816V at sub-nanomolar potencies with minimal off-target activity.

Blueprint Medicines is initially developing avapritinib for the treatment of advanced GIST, advanced SM, and indolent and smoldering SM. The FDA has granted avapritinib two Breakthrough Therapy Designations, one for the treatment of unresectable or metastatic GIST harboring the PDGFRα D842V mutation and one for the treatment of advanced SM, including the subtypes of aggressive SM, SM with an associated hematologic neoplasm and mast cell leukemia.

Blueprint Medicines has an exclusive collaboration and license agreement with CStone Pharmaceuticals for the development and commercialization of avapritinib and certain other drug candidates in Mainland China, Hong Kong, Macau and Taiwan. Blueprint Medicines retains development and commercial rights for avapritinib 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 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 avapritinib; expectations regarding the potential benefits of avapritinib in treating patients with GIST; plans and timelines for submitting an NDA to the FDA for avapritinib for the treatment of PDGFRA Exon 18 mutant GIST and fourth-line GIST; plans and timelines for submitting an MAA to the EMA for avapritinib for the treatment of PDGFRα D842V mutant GIST and fourth-line GIST; expectations regarding clinical data for avapritinib in third-line and second-line GIST; plans, timelines and expectations for interactions with global regulatory authorities; 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.

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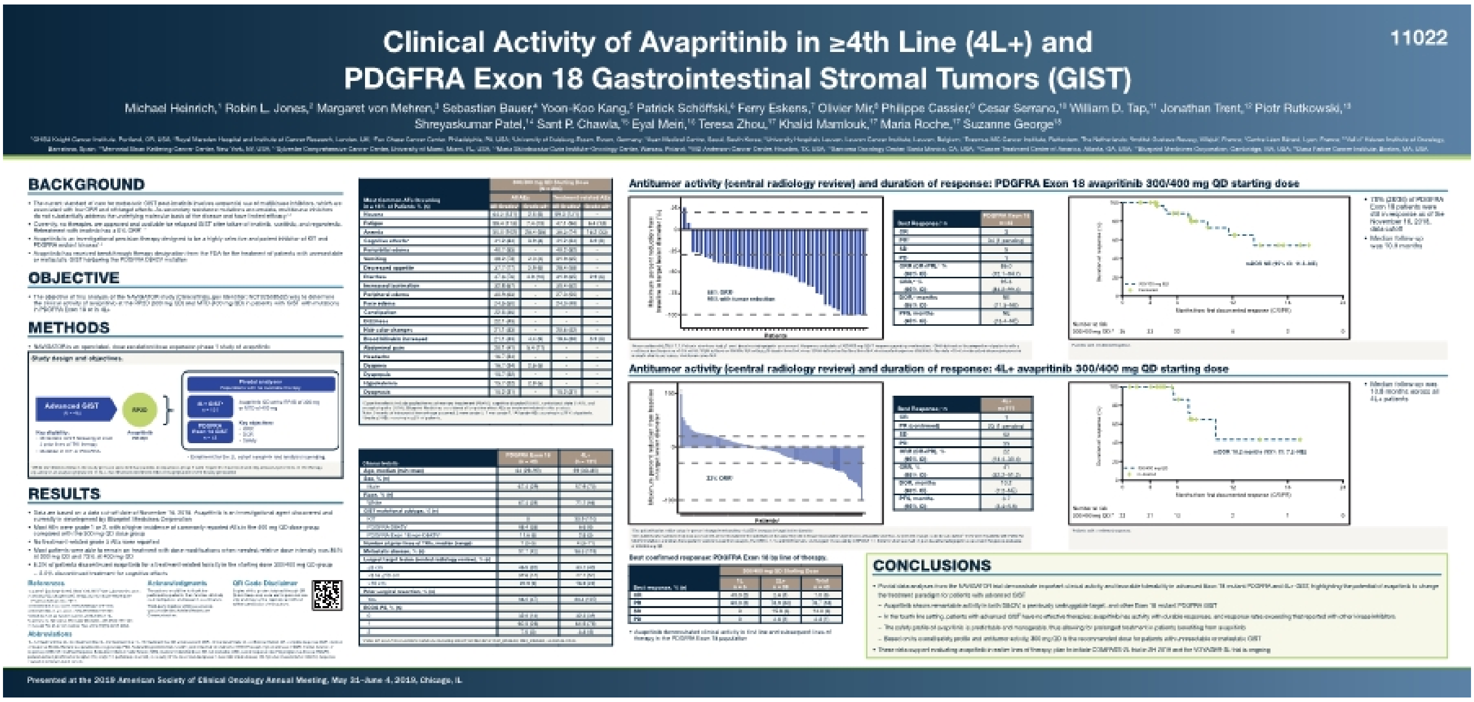
Exhibit 99.2


Clinical Activity of Avapritinib in ≥4th Line (4L+) and
PDGFRA Exon 18 Gastrointestinal Stromal Tumors (GIST)
11022
Michael Heinrich, Robin L. Jones, Margaret von Mehren, Sebastian Bauer, Yoon-Koo Kang, Patrick Schöffski, Ferry Eskens, Olivier Mir, Philippe Cassier, Cesar Serrano, William D. Tap, Jonathan Trent, Piotr Rutkowski, Shreyaskumar Patel, Sant P. Chawla, Eyal Meiri, Teresa Zhou, Khalid Mamlouk, Maria Roche, Suzanne George
BACKGROUND
OBJECTIVE
METHODS
Study design and objectives
Advanced GIST
RESULTS
References
Acknowledgements
QR Code Disclaimer
Abbreviations
Antitumor activity (central radiology review) and duration of response: PDGFRA Exon 18 avapritinib 300/400 mg QD starting dose
Antitumor activity (central radiology review) and duration of response: 4L+ avapritinib 300/400 mg QD starting dose
Best confirmed response: PDGFRA Exon 18 by line of therapy
CONCLUSIONS
Presented at the 2019 American Society of Clinical Oncology Annual Meeting, May 31–June 4, 2019, Chicago, IL

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-naive 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 (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:

- 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, and RET-mutation positive MTC that requires systemic treatment and for which there are no acceptable alternative treatments.

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 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.

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Activity and Tolerability of BLU-667, a Highly Potent and Selective RET Inhibitor, in Patients with Advanced RET-altered Thyroid Cancers

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[1]Oregon Health & Science University, Portland, OR; [2]Massachusetts General Hospital, Boston, MA; [3]The University of Texas MD Anderson Cancer Center, Houston, TX; ... [17]Blueprint Medicines Inc, Cambridge, MA

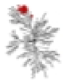
BACKGROUND

- RET alterations are targetable oncogenic drivers in multiple tumor types, including ~90% of advanced medullary thyroid cancer (MTC)[1] and ~20% of papillary thyroid cancer (PTC)[2,3]
- No selective RET inhibitors are approved

BLU-667: Designed to Treat RET-Altered Cancers

BLU-667 potently and selectively inhibits RET alterations, including those that confer resistance to MKI, while sparing VEGFR.[4]

BLU-667: High kinome selectivity for RET[a]



	BLU-667 IC_{50}	Cabozantinib IC_{50}	Vandetanib IC_{50}
Wild-type RET	0.4	11	4
RET V804L Gatekeeper resistance	0.3	45	3597
RET V804M Gatekeeper resistance	0.4	162	726
RET M918T Mutation	0.4	8	7
CCDC6-RET Fusion	0.4	34	20
VEGFR2 Anti-target	35	2	4

BLU-667 vs. pharmacologically relevant kinases:
- BLU-667 is ~90-fold more selective for RET than VEGFR2
- BLU-667 is 20-fold more selective for RET than JAK1

IC_{50}, half maximal inhibitory concentration; MKI, multikinase inhibitor. [a]Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CST). The foregoing website is maintained by CST, and Blueprint Medicines is not responsible for its content.

METHODS

ARROW: BLU-667 Dose-Escalation/Expansion Study

Part 1: Dose Escalation (Complete; N=62)

RET-altered advanced solid tumors

BLU-667 30-600 mg PO daily (QD or BID)

Phase 2 dose determined (400 mg QD)

Part 2: Expansion Cohorts (Ongoing)

BLU-667 400 mg QD
- Unresectable, advanced solid tumor
- RET alteration status by local tumor testing
- No additional driver mutation
- ECOG PS 0-1
- Progressive disease or intolerant to SOC therapy, or not a candidate

Primary objectives:
- Overall response rate (RECIST 1.1)
- Safety

Expansion cohorts:
- MTC, prior cabozantinib or vandetanib (n=60)
- MTC, no prior cabozantinib or vandetanib (n=40)
- RET fusion+ tumors, including PTC (n=40)
- RET fusion+ NSCLC, prior platinum (n=80)
- RET fusion+ NSCLC, platinum naïve (n=40)
- Other RET-mutated tumors (n=20)
- RET-altered, prior selective RET inhibitor (n=20)

ARROW is registered with clinicaltrials.gov (NCT03037385)

BID, twice daily dosing; ECOG PS, Eastern Cooperative Oncology Group performance status; PO, orally; QD, once daily dosing; RECIST, response evaluation criteria in solid tumors; SOC, standard of care.

Data are preliminary and based on a data cut-off date of April [illegible], 2019. BLU-667 is an investigational agent discovered and currently in development by Blueprint Medicines Corporation (Blueprint Medicines).

QR Code Disclaimer

References

1. [illegible]
2. [illegible]
3. [illegible]
4. Subbiah, et al. Cancer Discov. [illegible]

Presented at the Annual Congress of the American Society of Clinical Oncology Annual Meeting, June 1, 2019, Chicago, IL

RESULTS: ADVANCED RET-MUTATED MTC

Patient Baseline Characteristics

Characteristic	RET-mutated MTC (400 mg QD Starting Dose) All (N=64)	Prior Cabo or Vand (N=43)
Age (years), median (range)	59 (25–81)	57 (26–81)
Male, n (%)	42 (66)	27 (63)
ECOG PS, n (%)		
0	21 (33)	9 (21)
1-2	43 (66)	33 (79)
Metastatic disease, n (%)	64 (100)	43 (100)
Prior systemic regimens, median (range)	1 (0–10)	2 (1–10)
Any prior anticancer treatment	50 (78)	43 (100)
Cabozantinib or vandetanib, n (%)	43 (67)	43 (100)
Cabozantinib and vandetanib, n (%)	13 (20)	13 (30)
RET mutation, n (%)		
M918T	36 (56)	26 (61)
C634R/S/W	10 (16)	7 (16)
V804M	3 (5)	2 (5)
Other	15 (23)	8 (19)

Cabo, cabozantinib; vand, vandetanib.

Tolerability

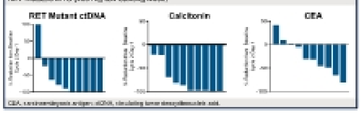
Among 64 patients with RET-mutated MTC receiving BLU-667 starting dose of 400 mg QD:
- Treatment-related toxicity is generally low-grade and reversible
- No patients discontinued BLU-667 due to treatment-related toxicity (4% across the entire study)

Adverse Event Term	RET-mutated MTC (400 mg QD Starting Dose; N=64) Treatment-Emergent (≥15% overall) n (%) All	Grade ≥3	Treatment-Related n (%) All	Grade ≥3
Hypertension	26 (41)	16 (25)	19 (30)	10 (16)
Constipation	21 (33)	1 (2)	12 (19)	1 (2)
Neutropenia[a]	17 (27)	7 (11)	16 (25)	7 (11)
Anemia	14 (22)	3 (5)	4 (6)	1 (2)
Aspartate aminotransferase increased	14 (22)	-	9 (14)	-
Leukopenia[b]	14 (22)	1 (2)	11 (17)	-
Alanine aminotransferase increased	13 (20)	-	8 (13)	-
Diarrhea	13 (20)	3 (5)	4 (6)	1 (2)
Headache	12 (19)	-	5 (8)	-
Blood creatinine increased	11 (17)	-	7 (11)	-
Fatigue	11 (17)	-	4 (6)	-
Hypocalcemia	11 (17)	4 (6)	4 (6)	1 (2)

Additional grade ≥3 treatment-related AEs (≥2%): blood creatine phosphokinase increased (3%).
[a]Combined term including decreased neutrophil count. [b]Combined term including decreased white blood cell count.

Reduction of RET Mutant ctDNA, Calcitonin, and CEA

RET-mutated MTC (400 mg QD Starting Dose)

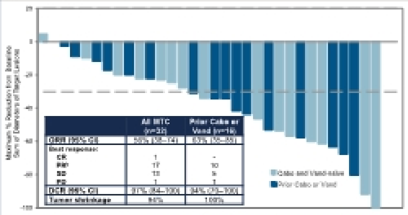


CEA, carcinoembryonic antigen; ctDNA, circulating tumor deoxyribonucleic acid.

Antitumor Activity

Tumor Response

RET-mutated MTC (400 mg QD starting dose)[a]

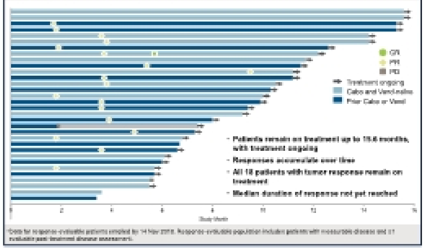


	All MTC (n=32)	Prior Cabo or Vand (n=16)
ORR (95% CI)	56% (38–74)	63% (35–85)
Best response:		
CR	1	-
PR[b]	17	10
SD	13	5
PD	1	1
DCR (95% CI)	97% (84–100)	94% (70–100)
Tumor shrinkage	94%	100%

ORR, overall response rate; DCR, disease control rate (best response of SD or better). [a]Data for response-evaluable patients enrolled by 14 Nov 2018. Response-evaluable population includes patients with measurable disease and ≥1 evaluable post-treatment disease assessment. [b]Two patients (one previously received vand, one cabo/vand-naïve) are pending confirmation of response.

Treatment and Response Duration

RET-mutated MTC (400 mg QD starting dose)[a]



- Patients remain on treatment up to 15.6 months, with treatment ongoing
- Responses accumulate over time
- All 18 patients with tumor response remain on treatment
- Median duration of response not yet reached

[a]Data for response-evaluable patients enrolled by 14 Nov 2018. Response-evaluable population includes patients with measurable disease and ≥1 evaluable post-treatment disease assessment.

RESULTS: ADVANCED RET FUSION+ PTC

Patient Baseline Characteristics

Characteristic	RET fusion+ PTC (All Starting Doses, N=9[a])
Age (years), median (range)	56 (33–70)
Male, n (%)	3 (33)
ECOG PS, n (%)	
0	4 (44)
1-2	5 (56)
Metastatic disease, n (%)	9 (100)
Prior systemic regimens, median (range)	2 (0–5)
Any prior anticancer treatment	8 (89)
Sorafenib or lenvatinib, n (%)	3 (33)
Radioactive iodine, n (%)	8 (89)
RET fusion partner	
CCDC6	4 (44)
NCOA4	4 (44)
Other (SNRNP70)	1 (11)

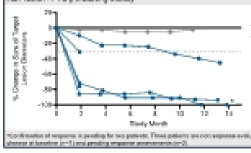
[a]Includes 2 patients with starting doses of 200 mg and 300 mg QD in dose escalation.

Tolerability

Among 9 patients with RET fusion+ PTC (regardless of starting dose):
- Safety profile similar to MTC
- No patients discontinued BLU-667 due to treatment-related toxicity

Antitumor Activity

RET fusion+ PTC (All starting doses)



- ORR: 83% (5/6)[a]
- 5 pts have received treatment for ≥1 year
- 8 of 9 pts continue treatment

[a]Confirmation of response is pending for two patients. Three patients are not response-evaluable due to absence of measurable disease at baseline (n=1) and pending response assessments (n=2).

CONCLUSIONS

- BLU-667 demonstrates broad and durable antitumor activity in patients with advanced, RET-altered MTC and PTC
  - 63% ORR and 94% DCR in RET-mutated MTC previously treated with cabozantinib or vandetanib; 83% ORR in PTC
  - Responses observed regardless of treatment history or RET mutation genotype (including gatekeeper mutation V804M)
  - Well-tolerated at 400 mg QD; all responding patients with MTC remain on treatment
- Breakthrough therapy designation granted for RET-mutated MTC requiring systemic treatment and for which there are no acceptable alternative treatments
- Additional cohorts continue to assess benefit of BLU-667 in multiple other RET-mutated and RET fusion+ solid tumors

Acknowledgments

We thank the participating patients, their families, all study co-investigators, research coordinators and site managers who contributed to this study. [illegible]

Clinical Activity and Tolerability of BLU-667, a Highly Potent and Selective RET Inhibitor, in Patients with Advanced RET-Fusion+ Non-small Cell Lung Cancer

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PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Justin F. Gainor
PRESENTATION DATE: June 3, 2019

Disclosures

Justin F. Gainor, MD

- Honoraria: Pfizer, Novartis, Theravance, Merck, Incyte, Roche
- Consulting or advisory role: Bristol-Myers Squibb, Ariad/Takeda, Genentech/Roche, Loxo, Blueprint Medicines, Amgen, Agios, Regeneron, Oncorus
- Research funding: Novartis, Genentech, Takeda
- Institutional Research funding: Tesaro, Moderna, Blueprint Medicines, Bristol-Myers Squibb, Jounce, Array Biopharma, Adaptimmune, Novartis, Alexo, Merck
- Travel: Novartis, Pfizer, Takeda, Genentech/Roche
- Employment: Ironwood Pharmaceuticals (Spouse)

BLU-667 is an investigational agent discovered by and currently in development by Blueprint Medicines Corporation (Blueprint Medicines)

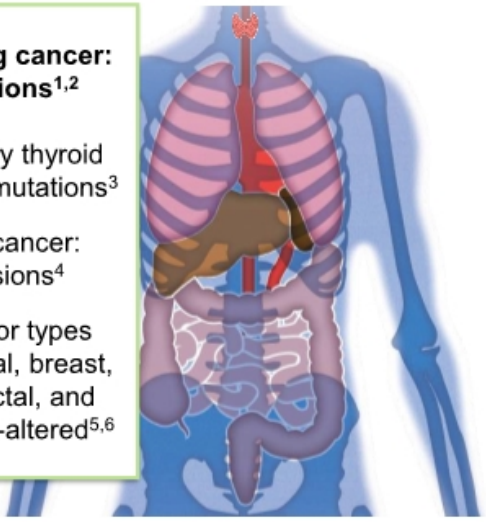
RET Alterations: Diverse Oncogenic Drivers Lacking Targeted Therapeutic Approach

Non-small cell lung cancer: ~1-2% RET fusions[1,2]

Advanced medullary thyroid cancer: ~90% RET mutations[3]

Papillary thyroid cancer: ~20% RET fusions[4]

Multiple other tumor types including esophageal, breast, melanoma, colorectal, and leukemia: <1% RET-altered[5,6]



NSCLC patients with RET fusions have not significantly benefited from existing therapy

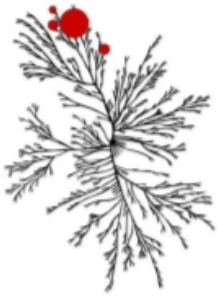
- Chemotherapy: nonspecific, low response rates, significant toxicity
- Checkpoint inhibition: Preliminary evidence for lack of benefit in RET-altered NSCLC[7]
- Multikinase inhibitors: ↓ activity, ↑ off-target toxicity[8,9]

No selective RET inhibitors are approved

NSCLC, non-small cell lung cancer; ORR, overall response rate; PFS, progression-free survival. 1. Lipson, et al. *Nat Med* 2012; 2. Takeuchi, et al. *Nat Med* 2012; 3. Romei, et al. *Oncotarget* 2016; 4. Santoro, et al. *J Clin Invest* 1992; 5. Kato, et al. *Clin Cancer Res* 2017; 6. Ballerini, et al. *Leukemia* 2012; 7. Mazieres, et al. *JCO* 2018; 8. Drilon, et al. *Lancet* 2017; 9. Yoh, et al. *Lancet Respir Med* 2017

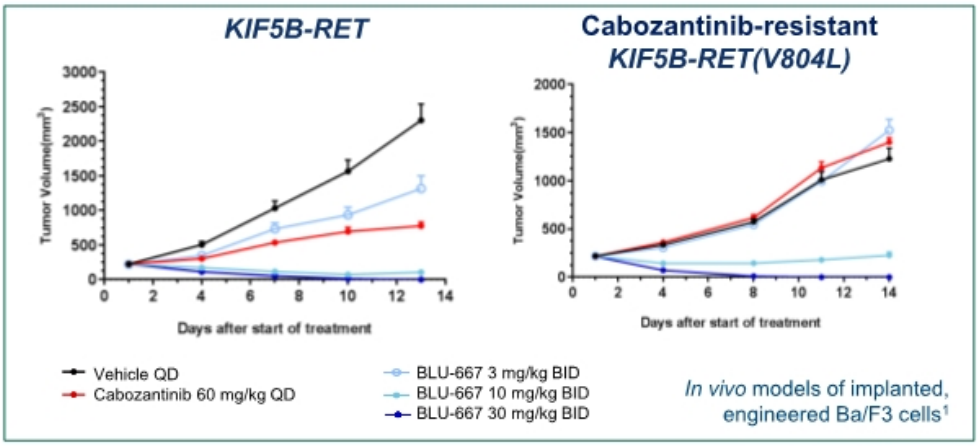
BLU-667 Potently and Selectively Inhibits RET Alterations and Resistance Mutants

BLU-667: High kinome selectivity for RET[a]



BLU-667 vs. pharmacologically relevant kinases:

- ~90-fold more selective for RET than VEGFR2
- 20-fold more selective for RET than JAK1



In vivo models of implanted, engineered Ba/F3 cells[1]

BLU-667 Cellular activity in KIF5B-RET[2]

	KIF5B-RET	KIF5B-RET V804L	KIF5B-RET V804M	KIF5B-RET V804E
BLU-667	10.1 nM (1x)	8.1 nM (0.8x)	14.1 nM (1.4x)	8.1 nM (0.8x)

[a]Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content. BLU-667 is an investigational agent discovered and currently in development by Blueprint Medicines Corporation (Blueprint Medicines). 1. Subbiah, et al. *Cancer Discovery* 2018; 2. Blueprint internal data

ARROW: BLU-667 Dose-Escalation and Expansion Study

Part 1: Dose-Escalation (N=62; Complete)[1]

RET-altered advanced solid tumors

BLU-667: 30-600 mg by daily oral administration (QD or BID)

Phase 2 dose determined (400 mg QD) →

ARROW is registered with clinicaltrials.gov (NCT03037385)

Part 2: Expansion Cohorts (Ongoing)

BLU-667 400 mg QD

- Unresectable, advanced solid tumor
- RET alteration status by local tumor testing
- No additional driver mutation
- ECOG PS 0-1
- Asymptomatic brain metastases allowed
- Progressive disease or intolerant to SOC therapy, or not a candidate

Primary objectives:

Overall response rate (RECIST 1.1)

Safety

- RET fusion+ NSCLC, prior platinum (n=80)
- RET fusion+ NSCLC, platinum naïve (n=40)
- MTC, prior cabozantinib or vandetanib (n=60)
- MTC, no prior cabozantinib or vandetanib (n=40)
- Other RET fusion+ tumors (n=40)
- Other RET-mutated tumors (n=20)
- RET-altered, prior selective RET inhibitor (n=20)

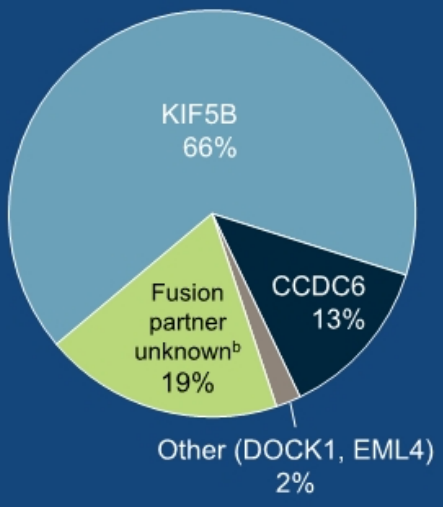
BID, twice daily dosing; ECOG PS, Eastern Cooperative Oncology Group performance status; MTC, medullary thyroid cancer; QD, once daily dosing; RECIST, response evaluation criteria in solid tumors; SOC, standard of care.

1. Subbiah, et al. *Cancer Res* 2018.

Baseline Characteristics
RET Fusion+ Advanced NSCLC Patients

Characteristic	RET-Fusion+ Advanced NSCLC 400 mg QD Starting Dose	
	All (N=120)	Prior Platinum (N=91)
Age (years), median (range)	60 (28-87)	60 (28-85)
Male, n (%)	59 (49)	45 (49)
ECOG PS, n (%)		
0	46 (38)	33 (36)
1-2	74 (62)	58 (64)
Brain metastases, n (%)	48 (40)	36 (40)
Prior systemic regimens, median (range)	2 (0-11)	2 (1-11)
Any prior anticancer treatment	101 (84)	91 (100)
Chemotherapy, n (%)	92 (77)	91(100)
PD-1 or PD-L1 inhibitor, n (%)	47 (39)	41 (45)
Chemotherapy + PD-(L)1 combination, n (%)	41 (34)	41 (45)
Multikinase inhibitor, n (%)	21 (18)	20 (22)
Smoking history[a]		
Current/Prior	41 (34)	33 (36)
Never	78 (65)	57 (63)
Histology		
Adenocarcinoma	114 (95)	87 (96)
Other	6 (5)	4 (4)

RET Fusion Partner



ECOG PS, Eastern Cooperative Oncology Group Performance Status. [a]Smoking history is unknown for one patient. [b]Includes RET fusion+ by fluorescence *in situ* hybridization (FISH); RET fusion partner to be determined via central analysis. Data cut-off date: 28 Apr 2019.

BLU-667 is Well Tolerated by Patients with RET Fusion+ Advanced NSCLC

	RET Fusion+ Advanced NSCLC 400 mg QD Starting Dose (N=120)			
	Treatment-Emergent (≥15% overall)		Treatment-Related	
Adverse Events	All	Grade ≥3	All	Grade ≥3
Constipation	30%	2%	17%	2%
Neutropenia[a]	26%	13%	26%	13%
AST increased	24%	5%	20%	2%
Fatigue	21%	3%	13%	3%
Hypertension	20%	13%	13%	10%
Anemia	18%	7%	11%	4%
Diarrhea	18%	2%	9%	-
Pyrexia	18%	-	2%	-
ALT increased	17%	3%	13%	2%
Cough	17%	-	3%	-
Dry mouth	17%	-	12%	-

Additional grade ≥3 treatment related AEs (≥2%): increased CPK (3%), leukopenia[b] (3%).

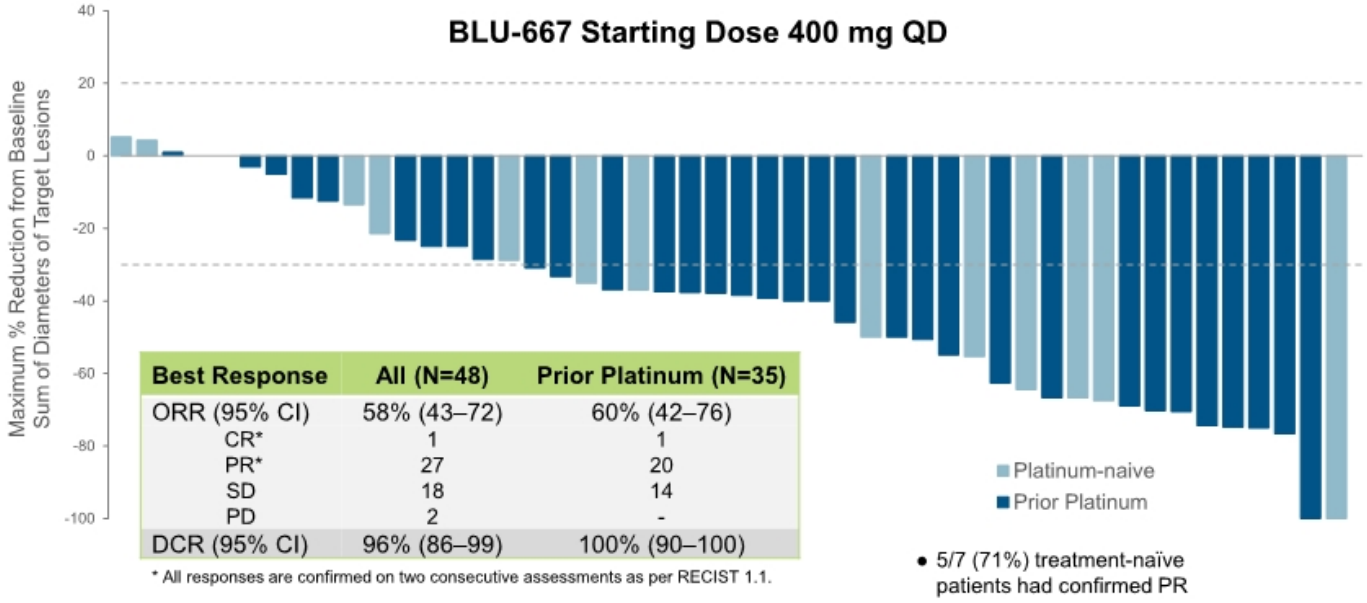
Among 120 pts with advanced NSCLC receiving BLU-667 starting dose of 400 mg QD:

- Treatment-related toxicity is generally low-grade and reversible
- 7% discontinued BLU-667 due to treatment-related toxicity*
  - Pneumonitis, respiratory distress/ hypoxemia, mucositis/colitis, myelosuppression, gait disturbance, anemia

* *Across the entire study (n=276), rate of discontinuation due to treatment-related toxicity is 4%.*

[a]Combined term including decreased neutrophils and neutropenia. [b]Combined term including leukopenia and white blood cell count decreased. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase. Data cut-off date: 28 Apr 2019.

BLU-667 Demonstrates Substantial Antitumor Activity in RET Fusion+ Advanced NSCLC



Best Response	All (N=48)	Prior Platinum (N=35)
ORR (95% CI)	58% (43–72)	60% (42–76)
CR*	1	1
PR*	27	20
SD	18	14
PD	2	-
DCR (95% CI)	96% (86–99)	100% (90–100)

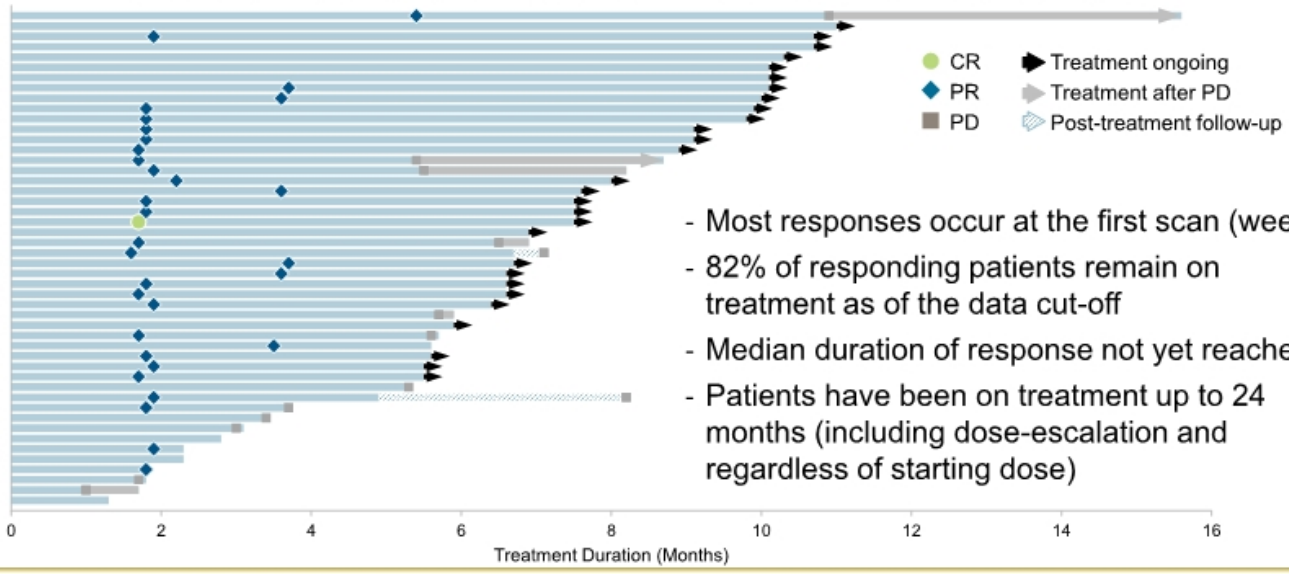
* All responses are confirmed on two consecutive assessments as per RECIST 1.1.

- 5/7 (71%) treatment-naïve patients had confirmed PR

CI, confidence interval; CR, complete response; DCR, disease control rate (best response of SD or better); ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease. Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19. Response-evaluable population includes patients with measurable disease at baseline and ≥1 evaluable post-treatment disease assessment, and excludes 4 patients who previously received >1 cycle of a selective RET inhibitor.

BLU-667 Induces Rapid and Durable Responses in RET Fusion+ Advanced NSCLC

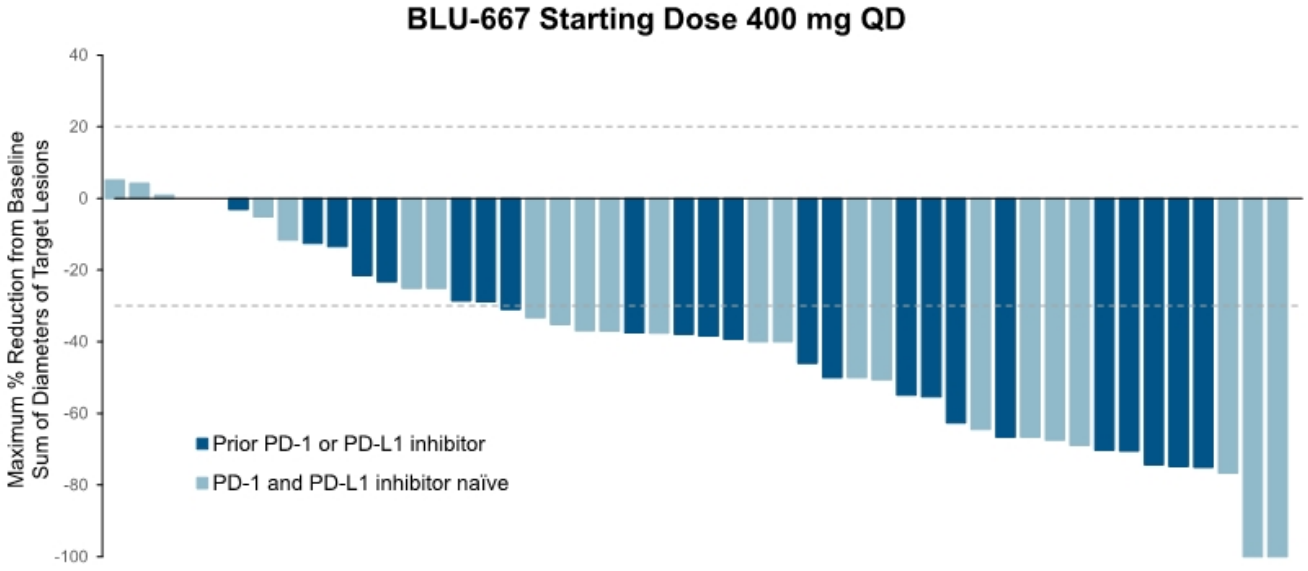
Duration of Treatment and Response: BLU-667 Starting Dose 400 mg QD



- Most responses occur at the first scan (week 8)
- 82% of responding patients remain on treatment as of the data cut-off
- Median duration of response not yet reached
- Patients have been on treatment up to 24 months (including dose-escalation and regardless of starting dose)

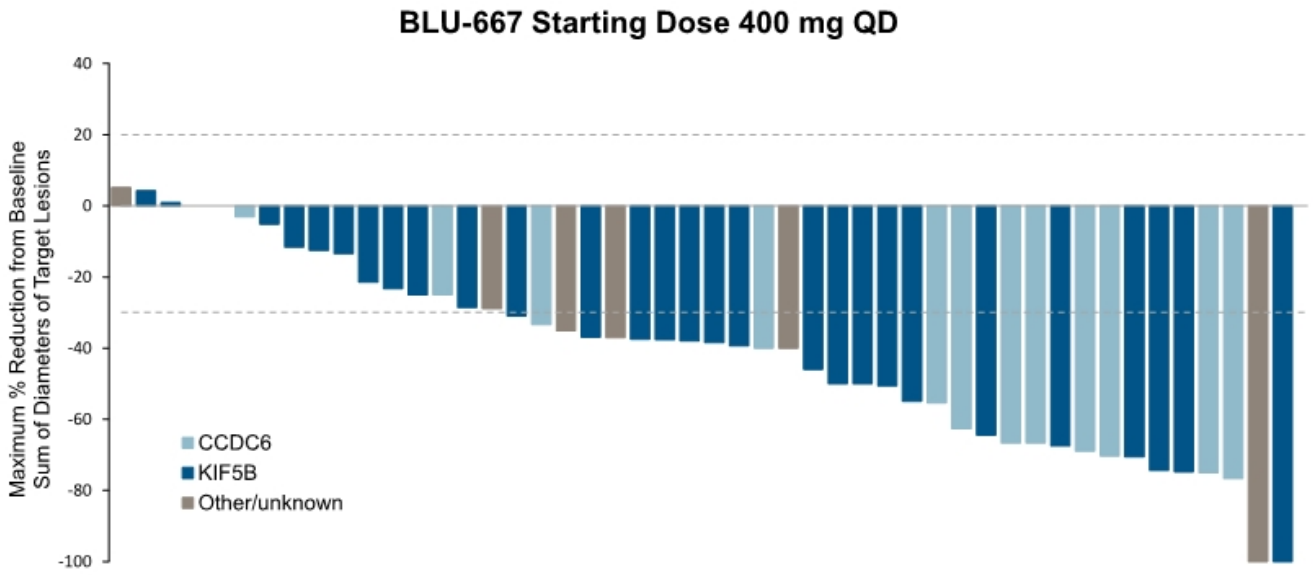
Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19.

BLU-667 is Active Regardless of Prior Checkpoint Treatment



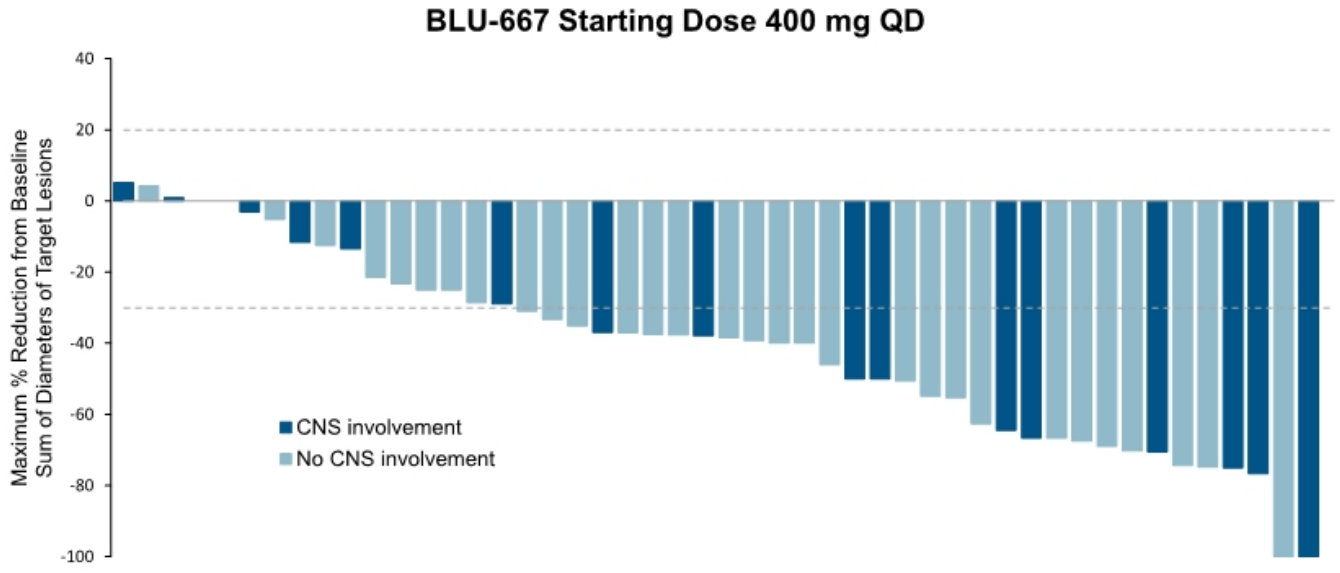
Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19.

BLU-667 is Active Across RET Fusion Genotypes



Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19.

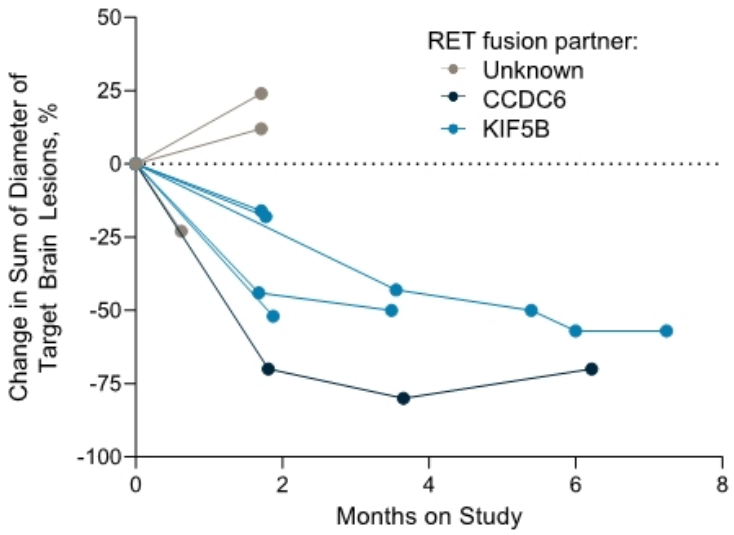
BLU-667 is Active Regardless of CNS Involvement



CNS, central nervous system
Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19.

BLU-667 is Active Against Intracranial Metastases

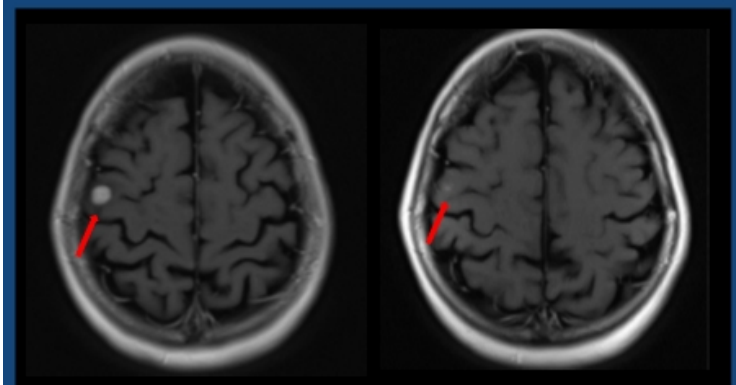
Shrinkage of Brain Metastases[a]



- 7 of 9 (78%) patients had shrinkage of measurable brain metastases
- No patients at 400 mg QD starting dose had progression due to new CNS involvement

[a]Data shown for 9 patients with brain lesion(s) identified as RECIST 1.1 target lesions at baseline. Data cut-off date: 28 Apr 2019.

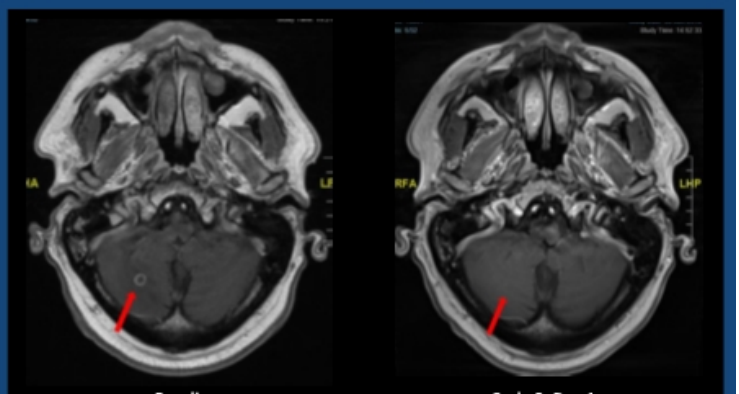
BLU-667 is Active Against Intracranial Metastases



Baseline | Cycle 3, Day 1

- 52-year-old woman, RET fusion+ NSCLC, prior platinum and checkpoint inhibitor
- Near-complete resolution of previously untreated target brain metastasis after two months of BLU-667 400 mg QD
- Continues to receive treatment with ongoing confirmed PR (70% shrinkage) at ~6 months

Images courtesy of Dr. Stephen Liu, Georgetown University, Washington, D.C.

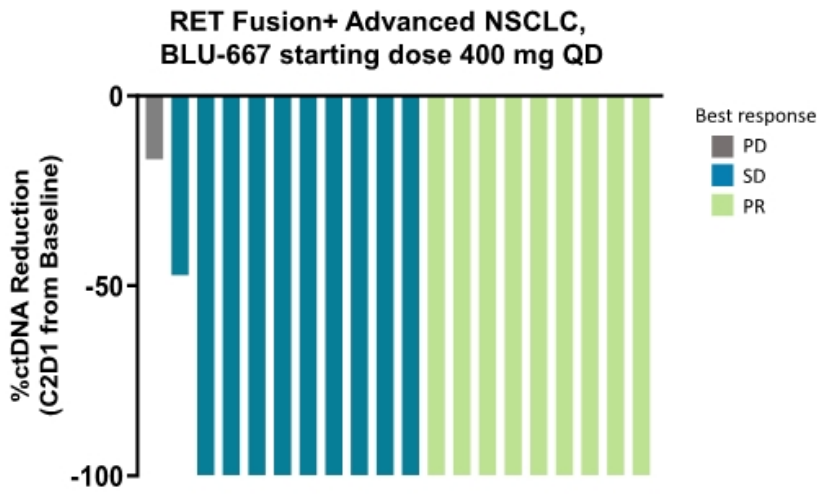


Baseline | Cycle 3, Day 1

- 59-year-old man, RET fusion+ NSCLC, prior platinum and checkpoint inhibitor
- Complete resolution of previously untreated nontarget brain metastasis after two months of BLU-667 400 mg QD
- Continues to receive treatment with ongoing confirmed PR (67% shrinkage) at ~6 months

Images courtesy Dr. P Cassier Centre Leon Berard, Lyon, FR

Rapid and Robust Clearance of RET Variant ctDNA with BLU-667



Among patients receiving a BLU-667 starting dose of 400 mg QD:

- 18/20 (90%) with detectable RET fusion ctDNA at baseline had complete clearance within the first cycle
- Clearance of genomic driver variants ctDNA has been associated with improved cancer outcomes[1–3]

ctDNA: circulating tumor DNA. Data cut-off date: 28 Apr 2019. 1. Cabel, et al. *Ann Oncol* 2017; 2. Mok, et al. *Clin Cancer Res* 2015; 3. Drilon, et al. *Nat Rev Clin Oncol* 2018; Awad, et al. *J Thorac Oncol* 2018.

BLU-667 has Activity in Other RET Fusion+ Malignancies

- PR in 2/2 patients with metastatic pancreatic cancer
  - 67 yo male, CCDC6-RET fusion, continues with confirmed PR (53% shrinkage) at ~6 months
  - 31 yo male, TRIM33-RET and JMJD1C-RET fusions, continues treatment after PR (41% shrinkage) at first response assessment
- PR in a patient with intrahepatic bile duct carcinoma
  - 51 yo female, NCOA4-RET fusion, continues with confirmed PR (67% shrinkage) at ~15 months
- ORR 83% (5/6)* in RET-fusion PTC (Abstract 6018 presented June 1, 2019)
- Safety profile similar to what was seen in RET fusion+ NSCLC

* Confirmation of response is pending for two patients. Data cut-off date: 28 Apr 2019.

Conclusions

- BLU-667 demonstrates broad and durable antitumor activity in patients with RET fusion+ advanced NSCLC
  - 60% ORR and 100% DCR in patients previously treated with platinum chemotherapy, and 58% ORR in all RET fusion+ patients
  - Responses observed regardless of treatment history, RET fusion partner or CNS involvement
  - Active against intracranial metastases
  - Well tolerated at 400 mg QD with most AEs grade 1/2
- BLU-667 has FDA breakthrough therapy designation in RET fusion+ NSCLC that progressed following platinum based chemotherapy
- Data support expansion of ARROW trial in treatment-naïve NSCLC patients and continued enrollment of other RET-altered solid tumor groups

RP2D, recommended phase 2 dose.
Data are preliminary and based on a data cut-off date of April 28, 2019.

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  - University of Pennsylvania, Philadelphia, PA, United States
  - University of California Irvine Medical Center, Irvine, CA, United States
  - University of Miami, Miami, FL, United States
  - Georgetown University Medical Center, Washington, District of Columbia, United States
  - University of Washington, Seattle, WA, United States
  - University of Michigan, Ann Arbor, MI, United States
  - Cornell University, New York, NY, United States
  - University of Colorado, Aurora, CO, United States
  - Washington University School of Medicine, St. Louis, MO, United States
  - Mayo Clinic, Rochester, MN, United States
  - Mayo Clinic, Jacksonville, FL, United States
  - Mayo Clinic, Phoenix, AZ, United States
  - Texas Oncology, Dallas, TX, United States
  - Thoraxklinik Heidelberg, Heidelberg, Germany
  - Universitatsklinikum Essen, Essen, Germany
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