

# 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

Justin F. Gainor<sup>1</sup>, Dae Ho Lee<sup>2</sup>, Giuseppe Curigliano<sup>3</sup>, Robert C. Doebele<sup>4</sup>, Dong-Wan Kim<sup>5</sup>, Christina S. Baik<sup>6</sup>, Daniel Shao-Weng Tan<sup>7</sup>, Gilberto Lopes<sup>8</sup>, Shirish M. Gadgeel<sup>9</sup>, Philippe Alexandre Cassier<sup>10</sup>, Matthew H. Taylor<sup>11</sup>, Stephen V. Liu<sup>12</sup>, Benjamin Besse<sup>13</sup>, Michael Thomas<sup>14</sup>, Viola Weijia Zhu<sup>15</sup>, Hui Zhang<sup>16</sup>, Corinne Clifford<sup>16</sup>, Michael R. Palmer<sup>16</sup>, Christopher D. Turner<sup>16</sup>, Vivek Subbiah<sup>17</sup>

<sup>1</sup>Massachusetts General Hospital, Boston, MA; <sup>2</sup>University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea, Republic of (South); <sup>3</sup>University of Milano, European Institute of Oncology, Division of Early Drug Development, Milan, Italy; <sup>4</sup>University of Colorado Cancer Center, Aurora, CO; <sup>5</sup>Seoul National University Hospital, Seoul, Korea, Republic of (South); <sup>6</sup>Fred Hutchinson Cancer Research Center, Seattle, WA; <sup>7</sup>National Cancer Center, Singapore, Singapore; <sup>8</sup>Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL; <sup>9</sup>University of Michigan/Rogel Cancer Center, Ann Arbor, MI; <sup>10</sup>Centre Léon-Bérard, Lyon, France; <sup>11</sup>Oregon Health & Science University, Portland, OR; <sup>12</sup>Georgetown University Medical Center, Washington, DC; <sup>13</sup>Paris-Sud University, Orsay and Gustave Roussy, Villejuif, France; <sup>14</sup>Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany; <sup>15</sup>Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA; <sup>16</sup>Blueprint Medicines Inc, Cambridge, MA; <sup>17</sup>The University of Texas MD Anderson Cancer Center, Houston, TX

# 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)

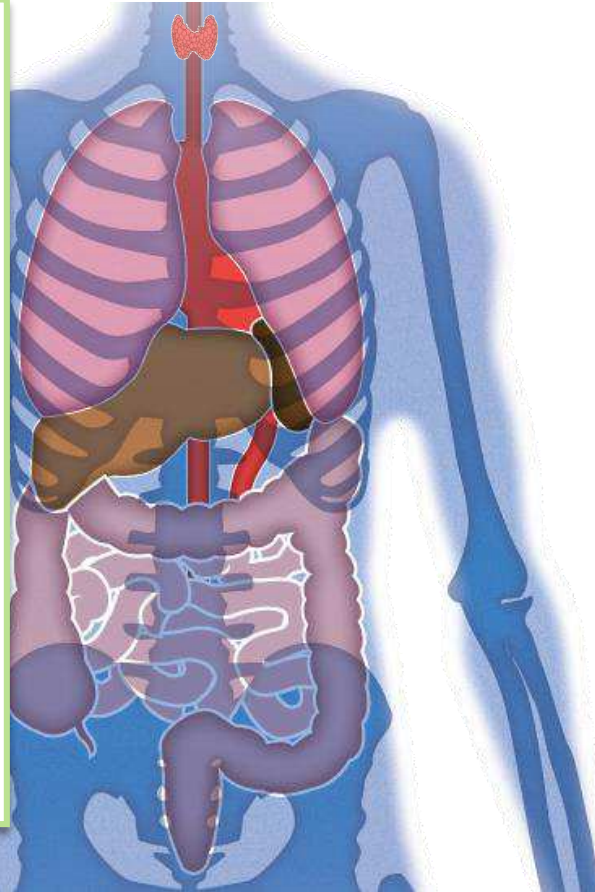
# RET Alterations: Diverse Oncogenic Drivers Lacking Targeted Therapeutic Approach

**Non-small cell lung cancer:  
~1-2% RET fusions<sup>1,2</sup>**

Advanced medullary thyroid cancer: ~90% RET mutations<sup>3</sup>

Papillary thyroid cancer:  
~20% RET fusions<sup>4</sup>

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



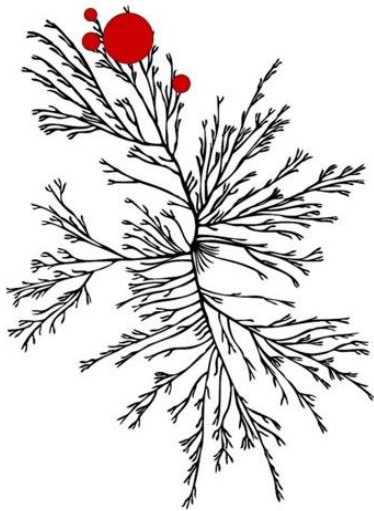
**NSCLC patients with RET fusions have not significantly benefited from existing therapy**

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

No selective RET inhibitors are approved

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

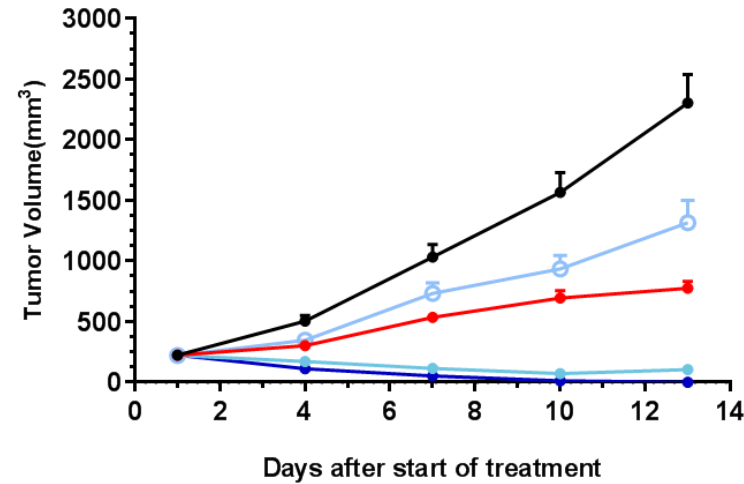
## BLU-667: High kinome selectivity for RET<sup>a</sup>



BLU-667 vs. pharmacologically relevant kinases:

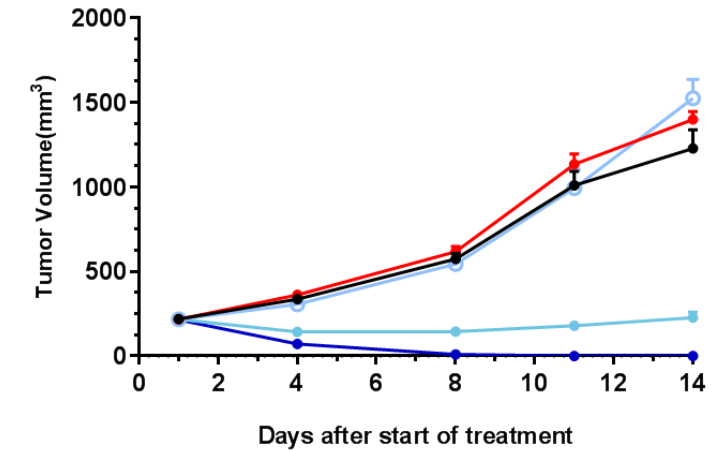
- ~90-fold more selective for RET than VEGFR2
- 20-fold more selective for RET than JAK1

### KIF5B-RET



● Vehicle QD  
 ● Cabozantinib 60 mg/kg QD  
 ● BLU-667 3 mg/kg BID  
 ● BLU-667 10 mg/kg BID  
 ● BLU-667 30 mg/kg BID

### Cabozantinib-resistant KIF5B-RET(V804L)



*In vivo* models of implanted, engineered Ba/F3 cells<sup>1</sup>

### BLU-667 Cellular activity in KIF5B-RET<sup>2</sup>

	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)

# ARROW: BLU-667 Dose-Escalation and Expansion Study

## Part 1: Dose-Escalation (N=62; Complete)<sup>1</sup>

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 \(NCT03037385\)](https://clinicaltrials.gov/ct2/show/study/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)

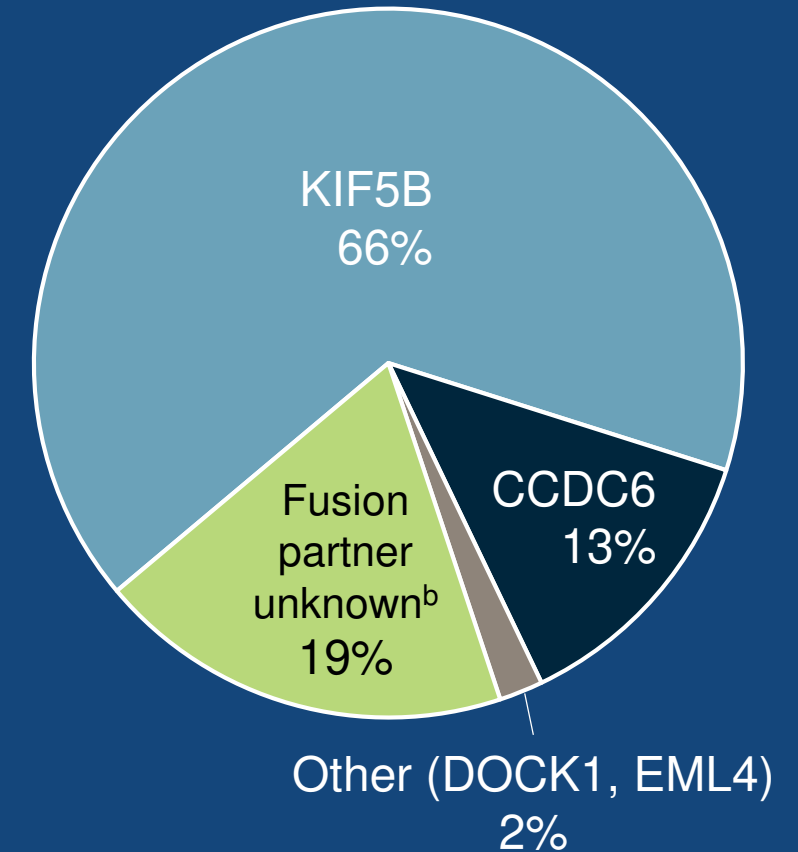
RET-altered, prior selective RET inhibitor (n=20)

# 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 <sup>a</sup>		
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



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

## RET Fusion+ Advanced NSCLC 400 mg QD Starting Dose (N=120)

Adverse Events	Treatment-Emergent (≥15% overall)		Treatment-Related	
	All	Grade ≥3	All	Grade ≥3
Constipation	30%	2%	17%	2%
Neutropenia <sup>a</sup>	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%	-

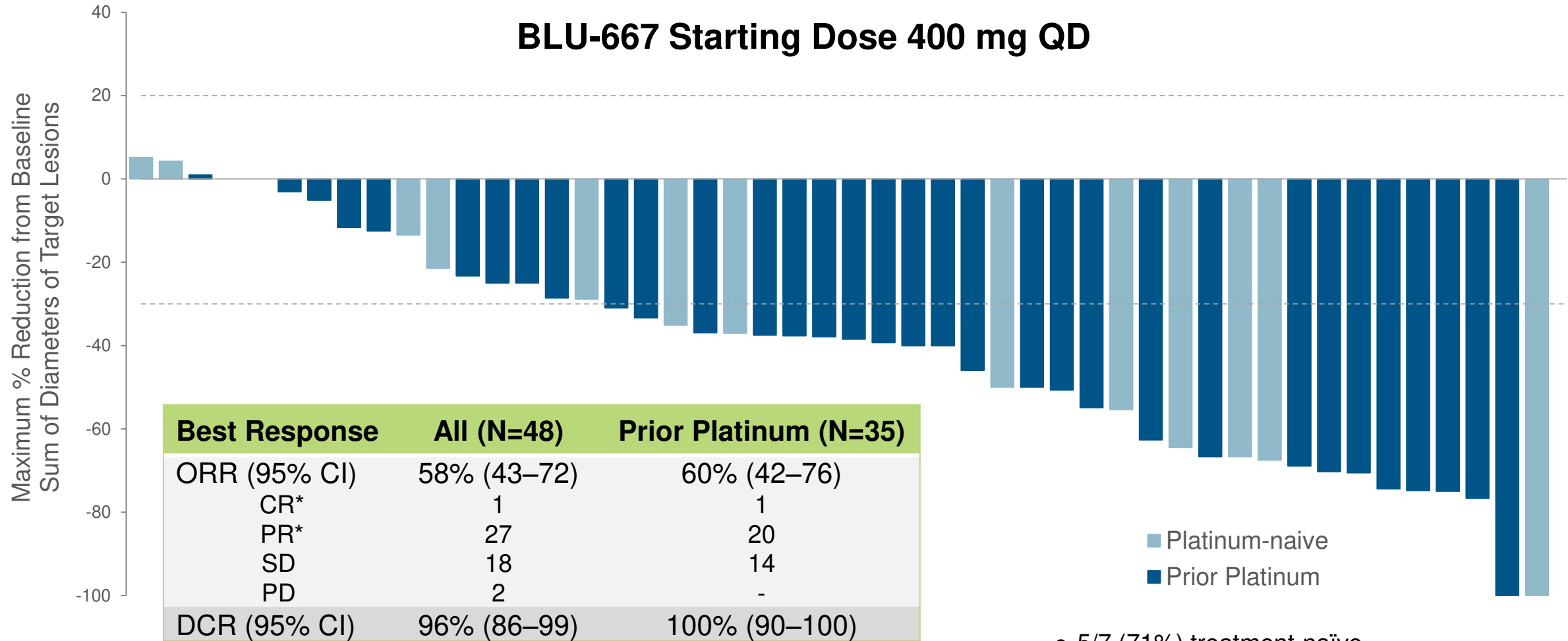
Additional grade ≥3 treatment related AEs (≥2%): increased CPK (3%), leukopenia<sup>b</sup> (3%).

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%.

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



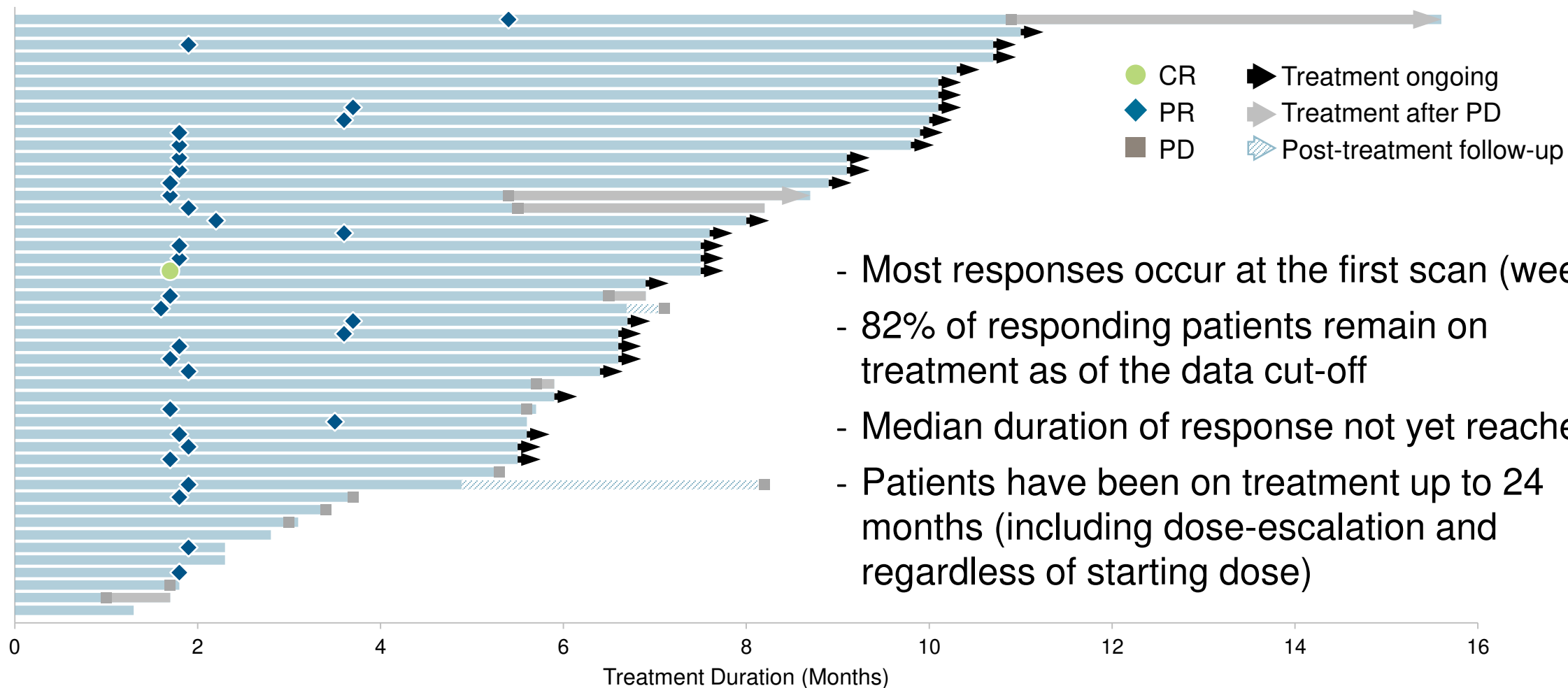
\* All responses are confirmed on two consecutive assessments as per RECIST 1.1.

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



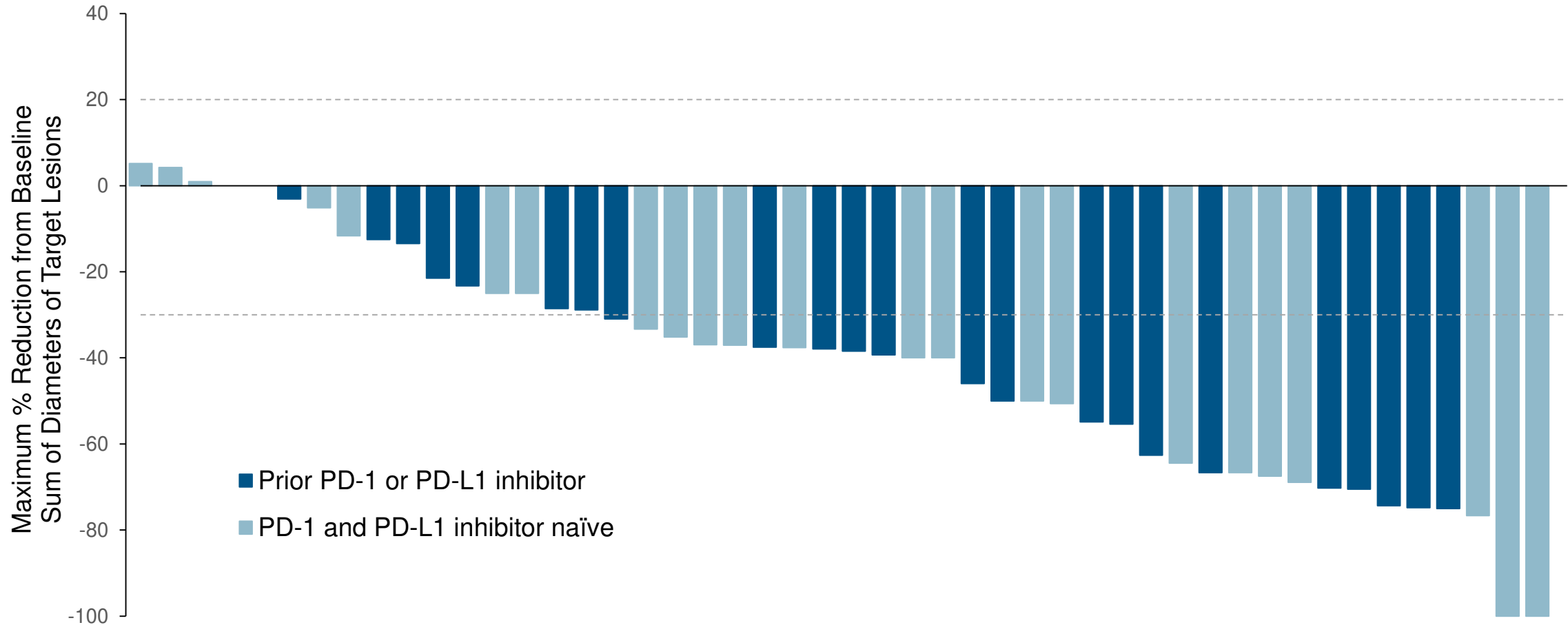
# BLU-667 Induces Rapid and Durable Responses in RET Fusion+ Advanced NSCLC

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



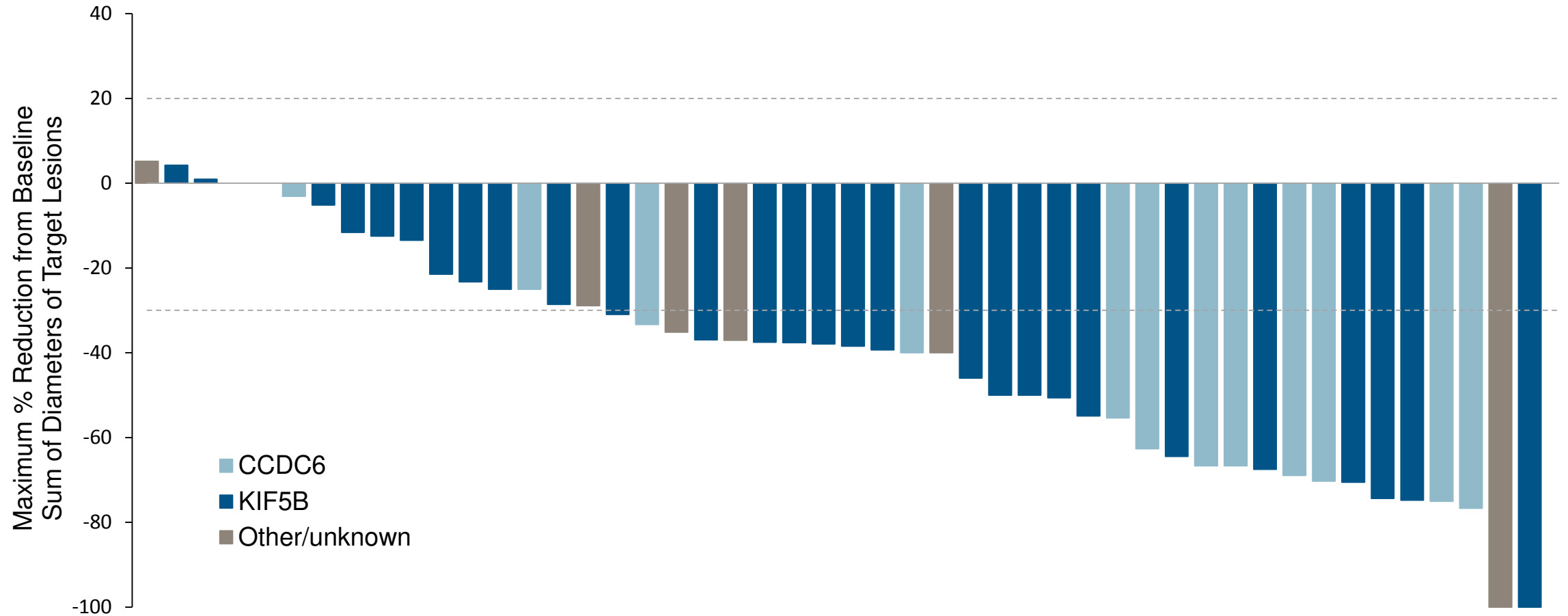
# BLU-667 is Active Regardless of Prior Checkpoint Treatment

## BLU-667 Starting Dose 400 mg QD



# BLU-667 is Active Across RET Fusion Genotypes

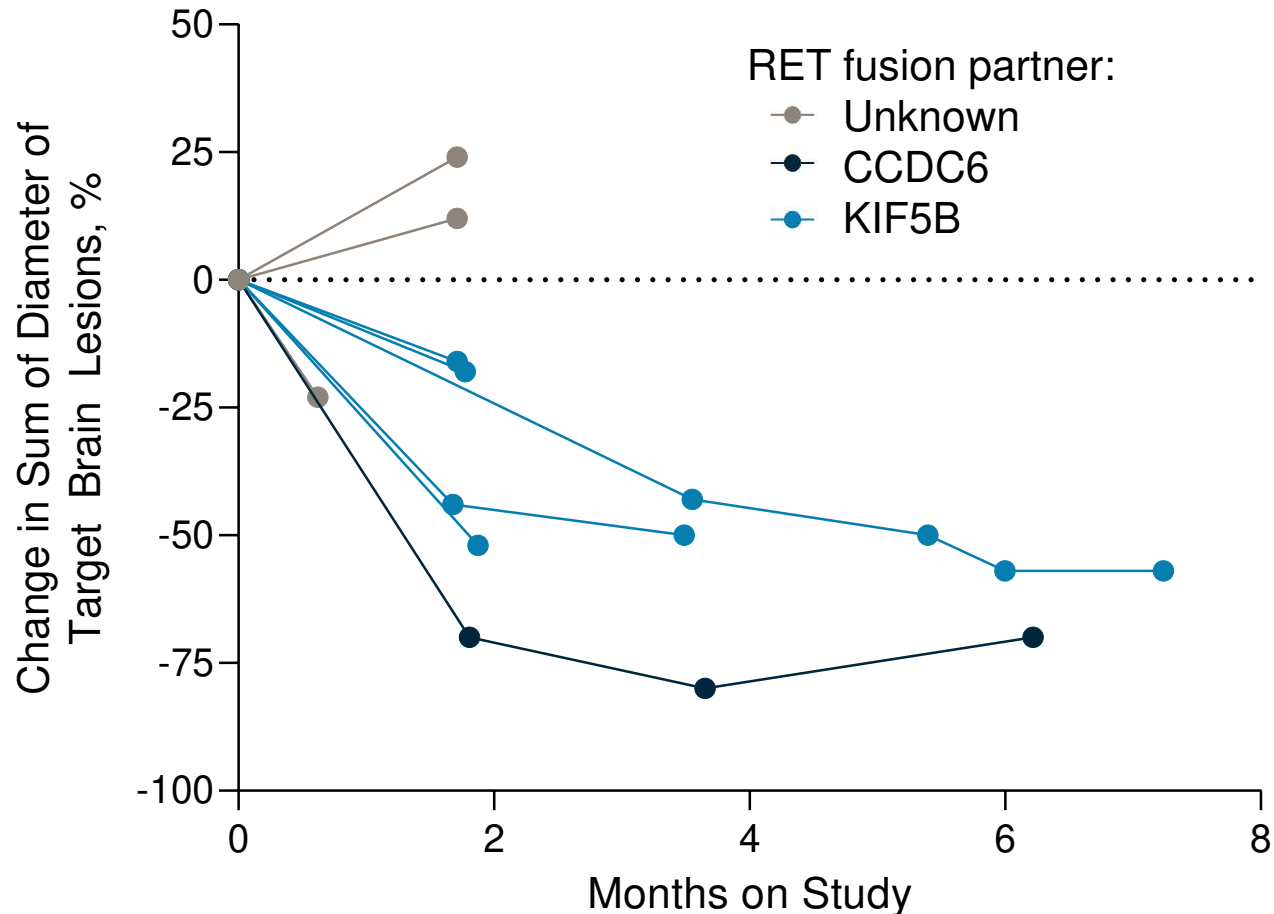
## BLU-667 Starting Dose 400 mg QD





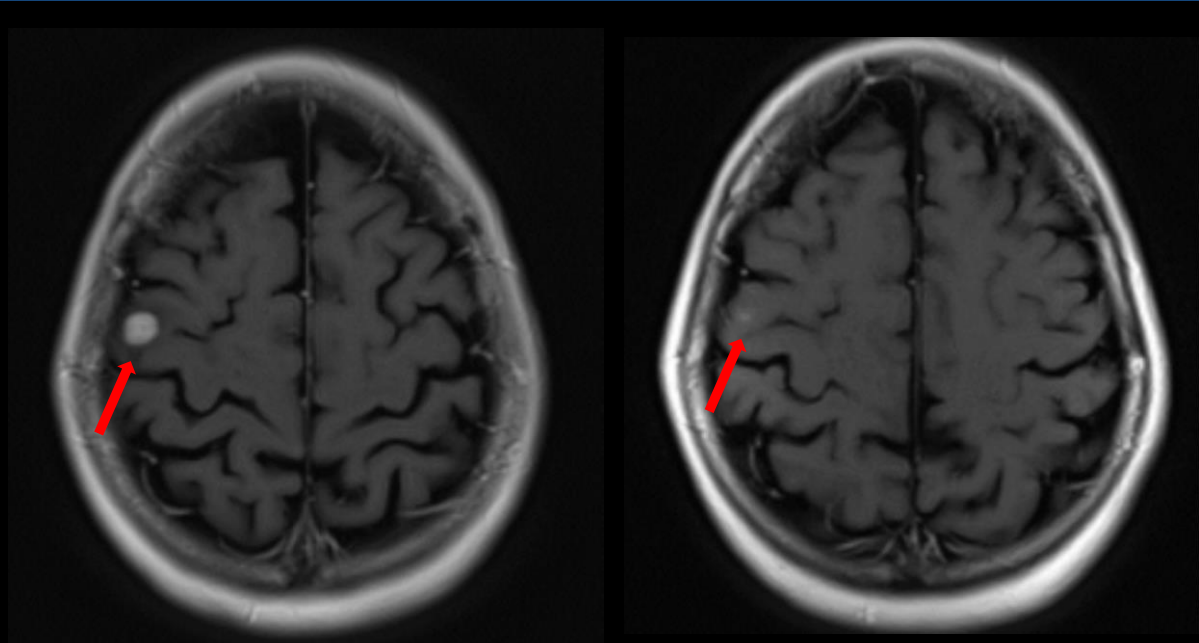
# BLU-667 is Active Against Intracranial Metastases

## Shrinkage of Brain Metastases<sup>a</sup>



- 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

# BLU-667 is Active Against Intracranial Metastases

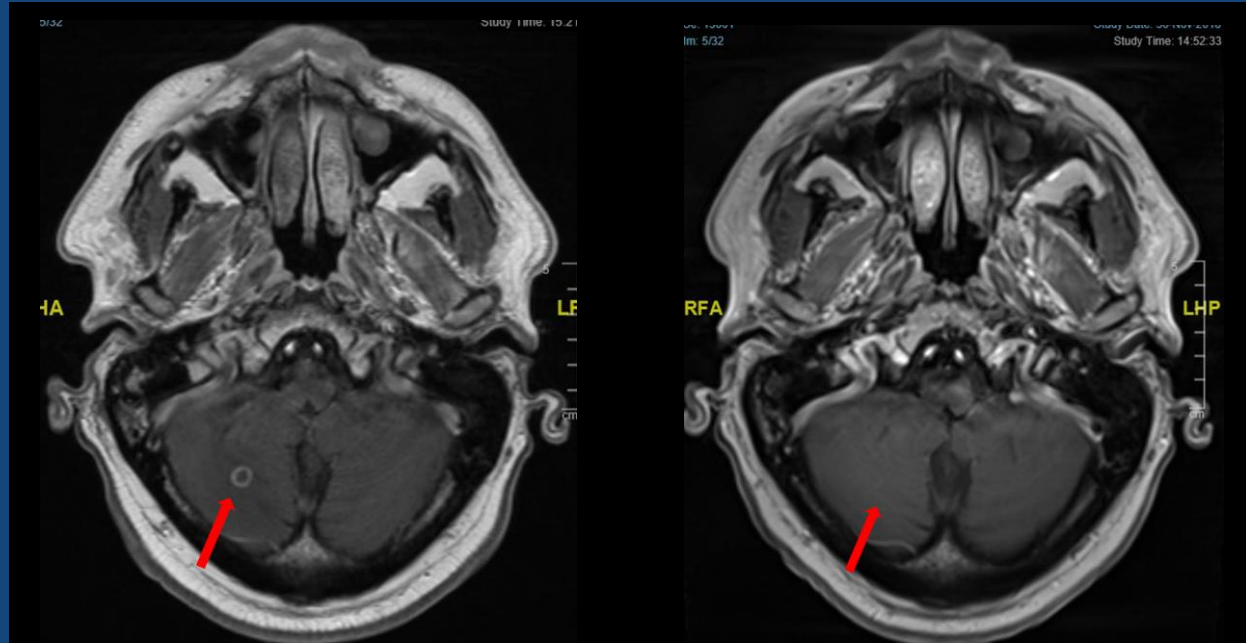


Baseline

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

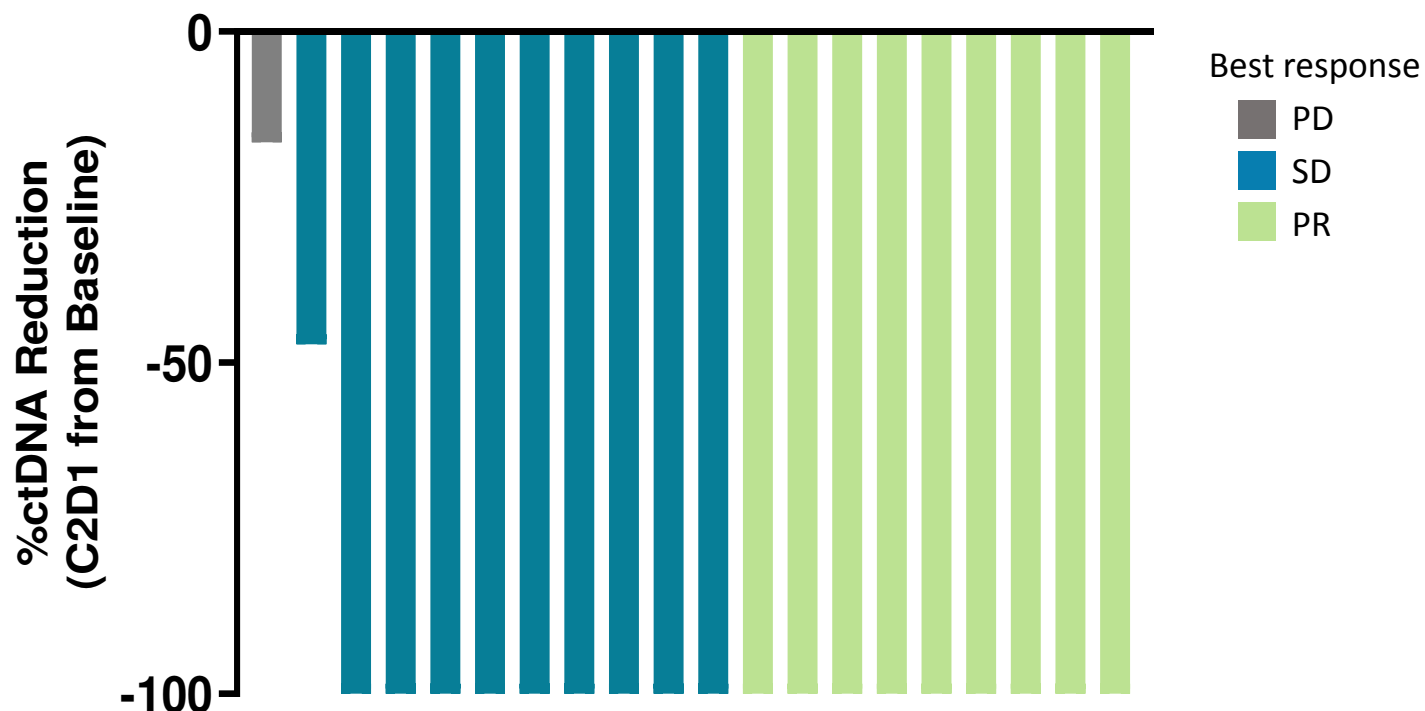
Cycle 3, Day 1

- 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

RET Fusion+ Advanced NSCLC,  
BLU-667 starting dose 400 mg QD



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<sup>1-3</sup>

# 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



# 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

# Acknowledgments

- Participating patients and families
- BLU-667-1101 Investigators and research coordinators
  - The University of Texas MD Anderson Cancer Center, Houston, TX, United States
  - Oregon Health & Science University, Portland, OR, United States
  - Massachusetts General Hospital Cancer Center, Boston, MA, United States
  - 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
  - Universitätsklinikum Essen, Essen, Germany
  - Pius-Hospital Oldenberg, Oldenberg, Germany
  - Vall d'Hebron University Hospital, Barcelona, Spain
  - Hospital Universitario 12 de Octubre, Madrid, Spain
  - Hospital Universitario Ramon y Cajal, Madrid, Spain
  - Hospital Clinic Barcelona, Barcelona, Spain
  - Hospital Duran I Reynals, Barcelona, Spain
  - Centre Leon Berard, Lyon, France
  - Gustave Roussy, Villejuif, France
  - Institut Claudius Regaud, Toulouse, France
  - CHU de Rennes, Rennes, France
  - CHRU de Lille, Lille, France
  - Institut Bergonie, Bordeaux, France
  - University College of London NHS Foundation Trust, London, UK
  - Guy's Hospital St. Thomas NHS Foundation Trust, London, UK
  - The Christie NHS Foundation Trust, Manchester, UK
  - University of Milano, Istituto Europeo di Oncologia, Milan, Italy
  - Grande Ospedale Metropolitano Niguarda, Milan, Italy
  - University Medical Center Gronigen, Gronigen, Netherlands
  - National Cancer Centre Singapore, Singapore, Singapore
  - Seoul National University Hospital, Seoul, Republic of Korea
  - Asan Medical Center, Seoul, Republic of Korea
  - Severance Hospital, Seoul, Republic of Korea
  - National Taiwan University Hospital, Taipei, Taiwan
- Colleagues at Blueprint Medicines Corporation