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 BY: Justin F. Gainor

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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
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- Employment: Ironwood Pharmaceuticals (Spouse)

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

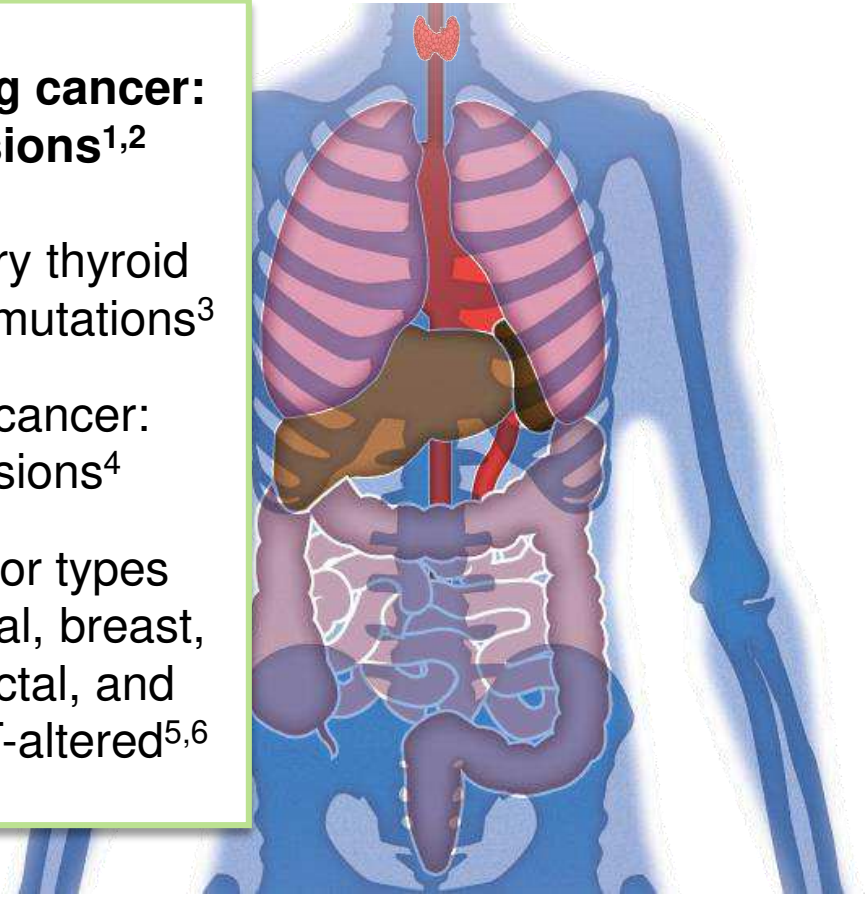
RET Alterations: Diverse Oncogenic Drivers Lacking Targeted Therapeutic Approach

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

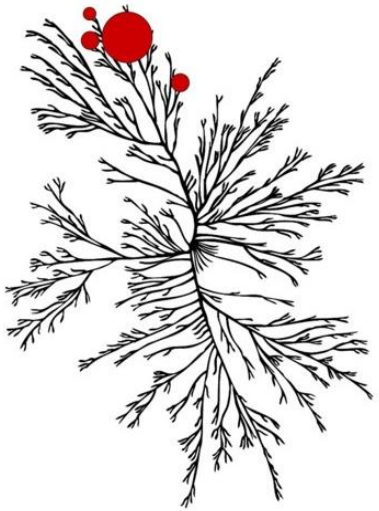
- Chemotherapy: nonspecific, low response rates, significant toxicity
- Checkpoint inhibition: Preliminary evidence for lack of benefit in RET-altered NSCLC[7]
- Multikinase inhibitors: ↓ activity, ↑ off-target toxicity[8,9]

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* 2018; 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. Drillon, et al. *Lancet* 2017; 9. Yoh, et al. *Lancet Respir Med* 2017

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

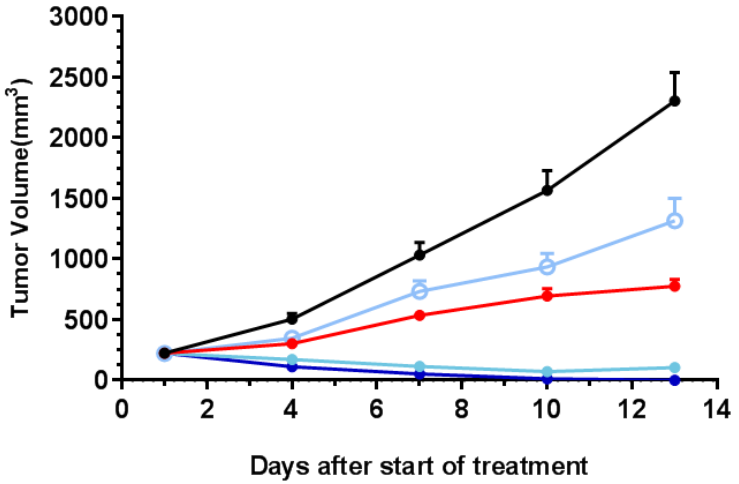
BLU-667: High kinome selectivity for RET[a]



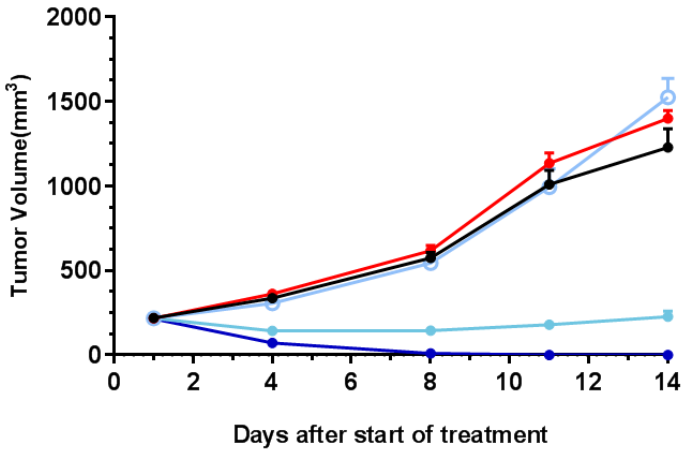
BLU-667 vs. pharmacologically relevant kinases:

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

KIF5B-RET



Cabozantinib-resistant *KIF5B-RET(V804L)*



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

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)**

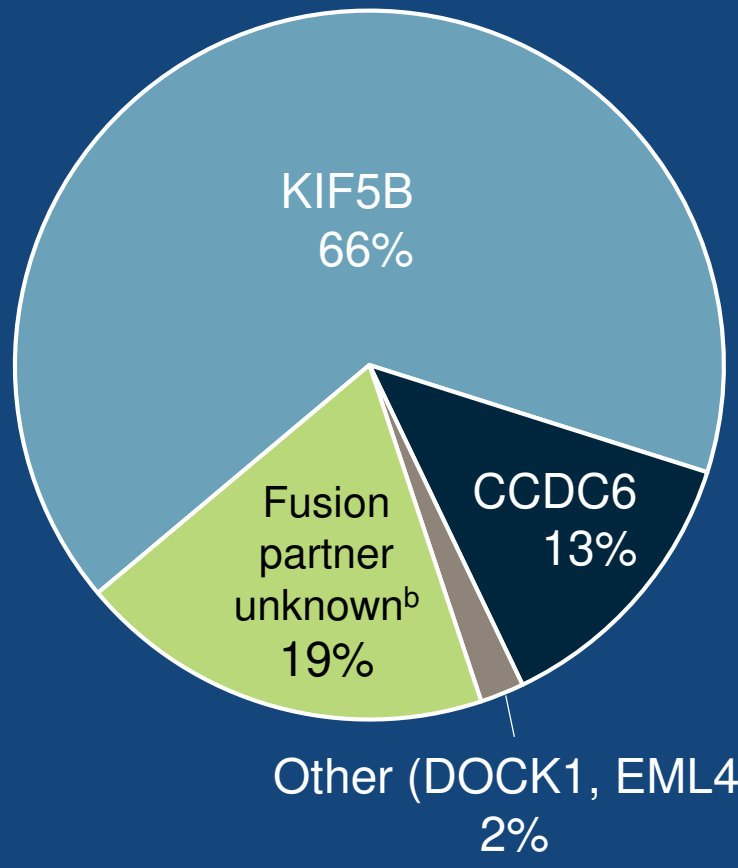
BID, twice daily dosing; ECOG PS, Eastern Cooperative Oncology Group performance status; MTC, medullary thyroid cancer; QD, once daily dosing; RECIST, response evaluation criteria in solid tumors; SOC, standard of care.

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%).

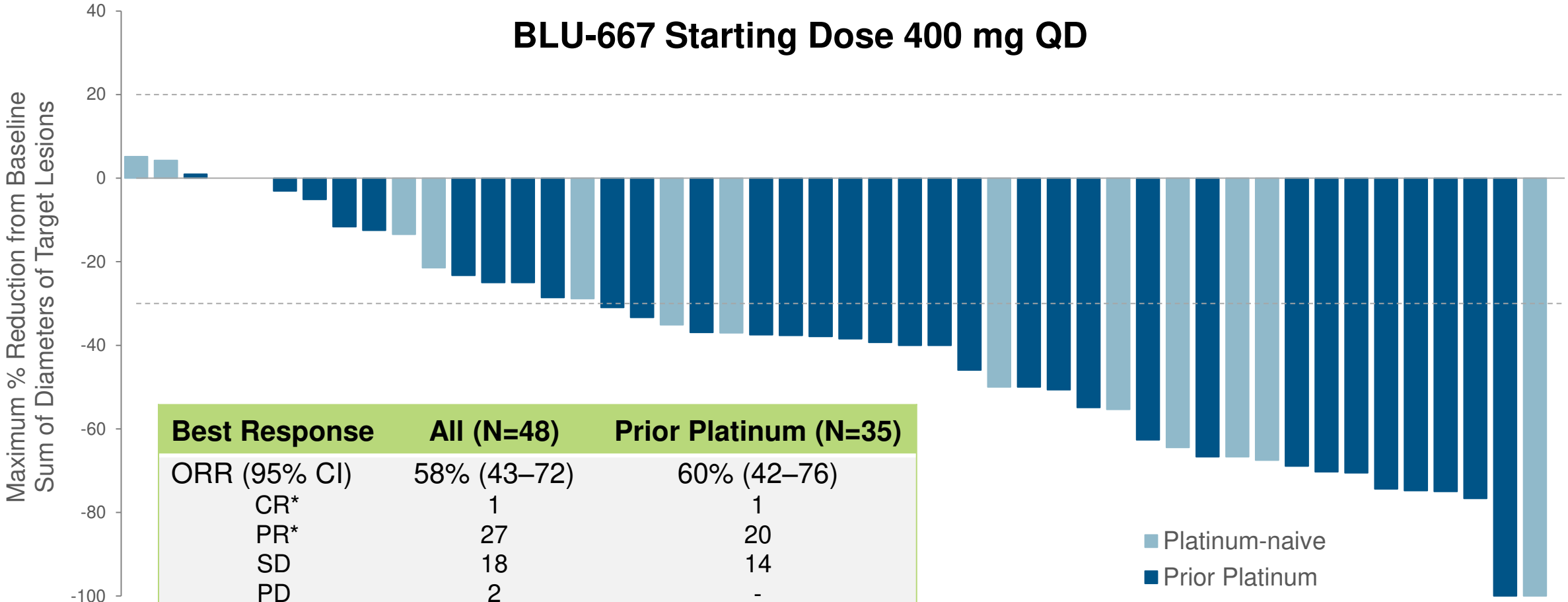
Among 120 pts with advanced NSCLC receiving BLU-667 starting dose of 400 mg QD:

- 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)

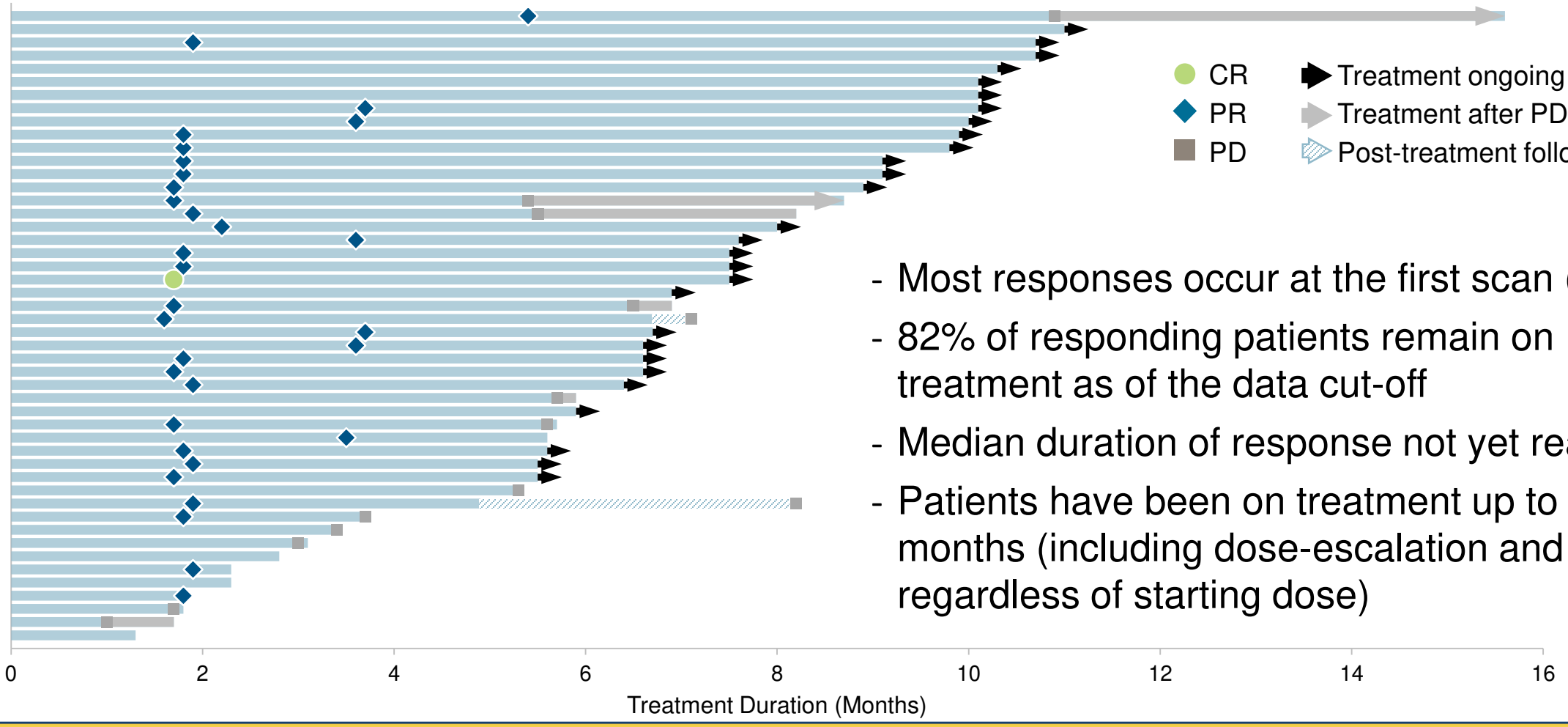
* All responses are confirmed on two consecutive assessments as per RECIST 1.1.

- 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

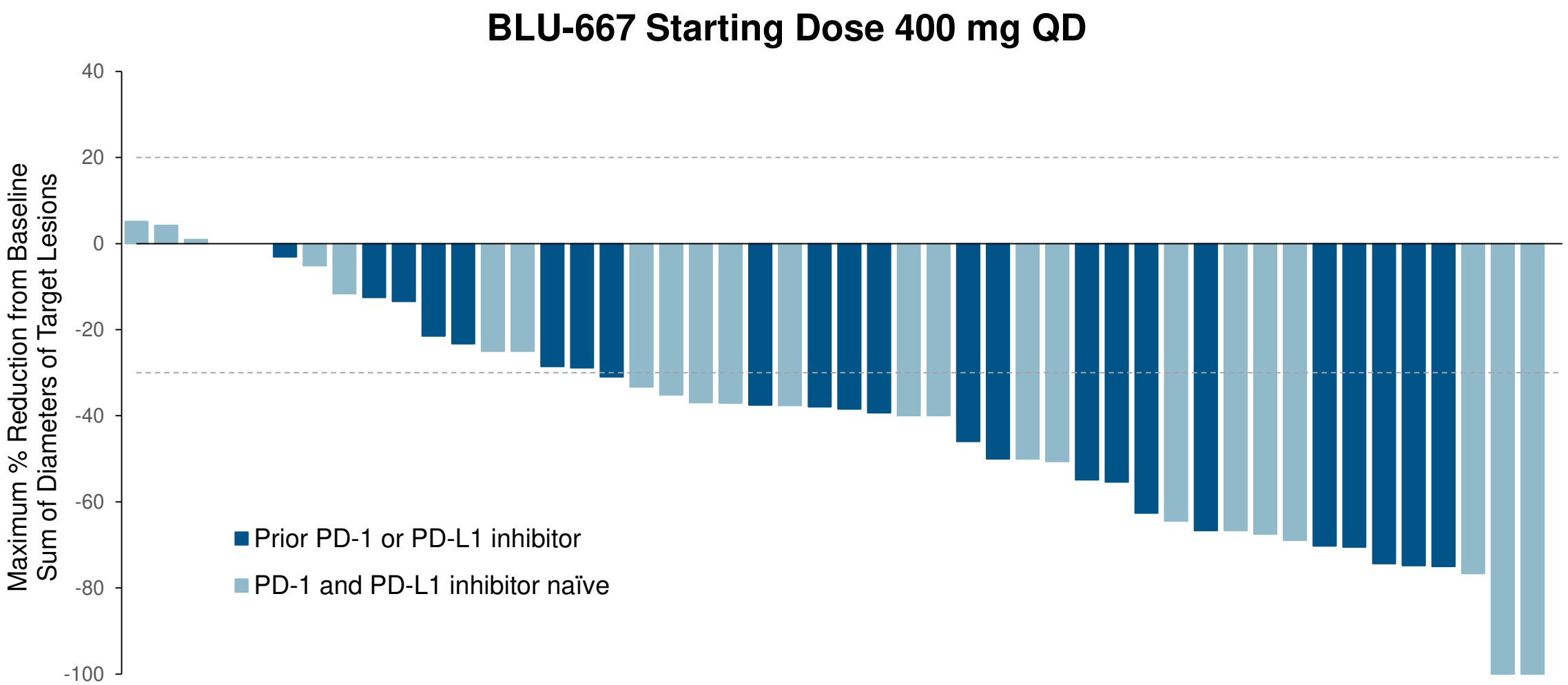
Duration of Treatment and Response: BLU-667 Starting Dose 400 mg QD



- 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)

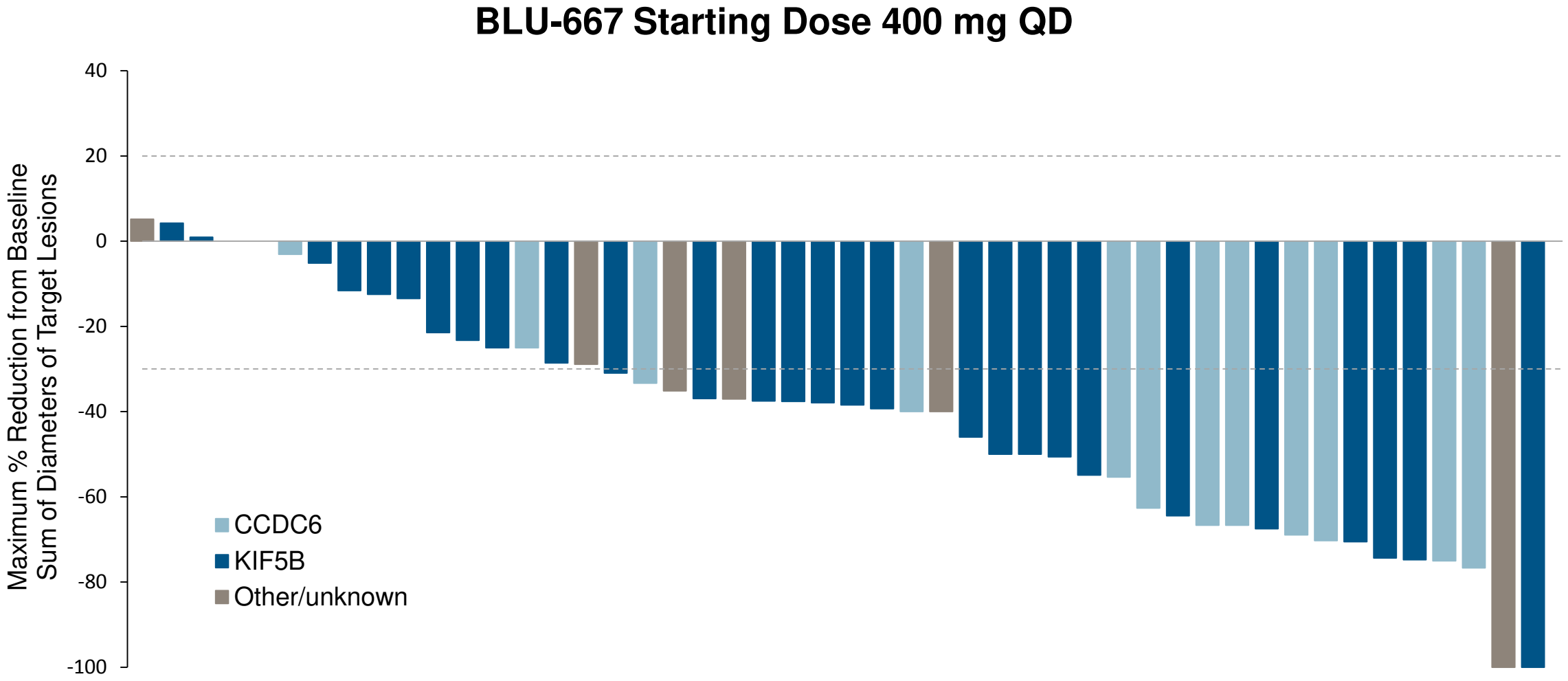
Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19.

BLU-667 is Active Regardless of Prior Checkpoint Treatment



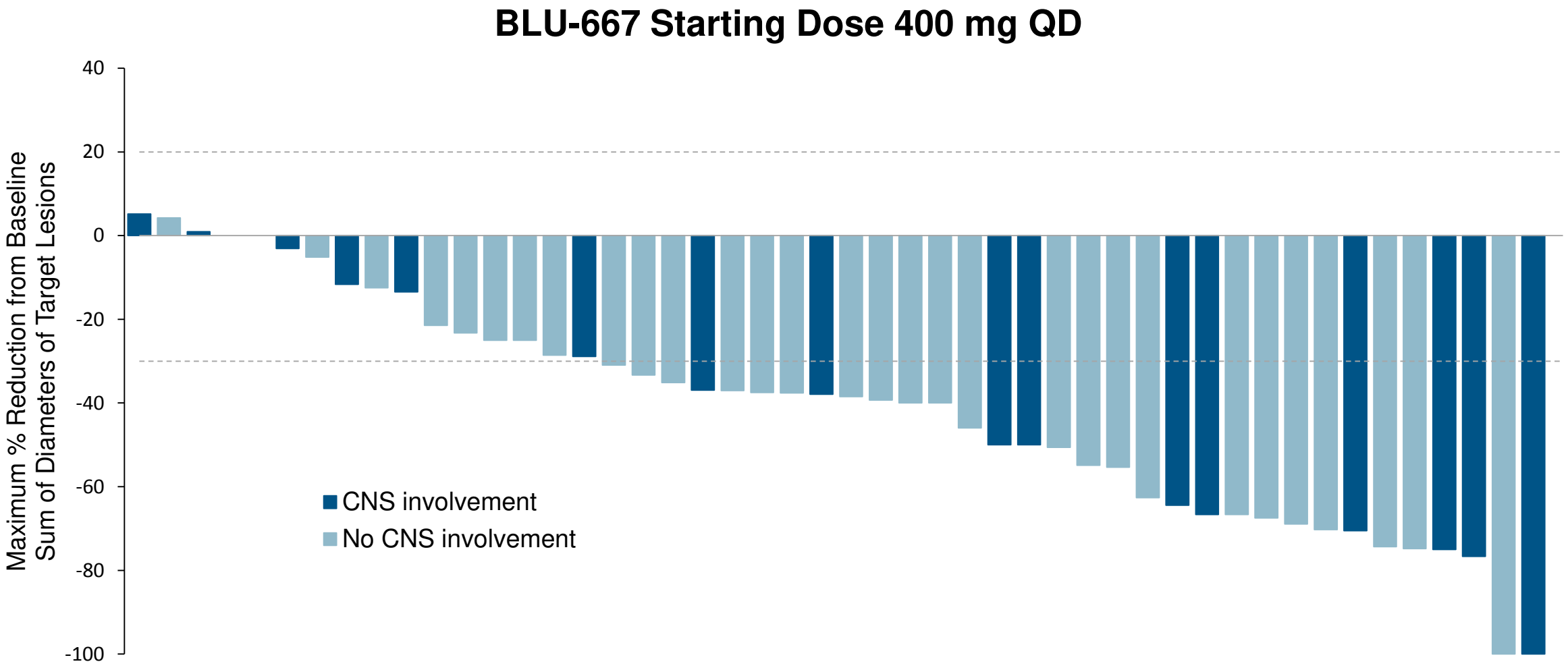
Patients enrolled by 14 Nov 18, data cut-off 28 Apr 19.

BLU-667 is Active Across RET Fusion Genotypes



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

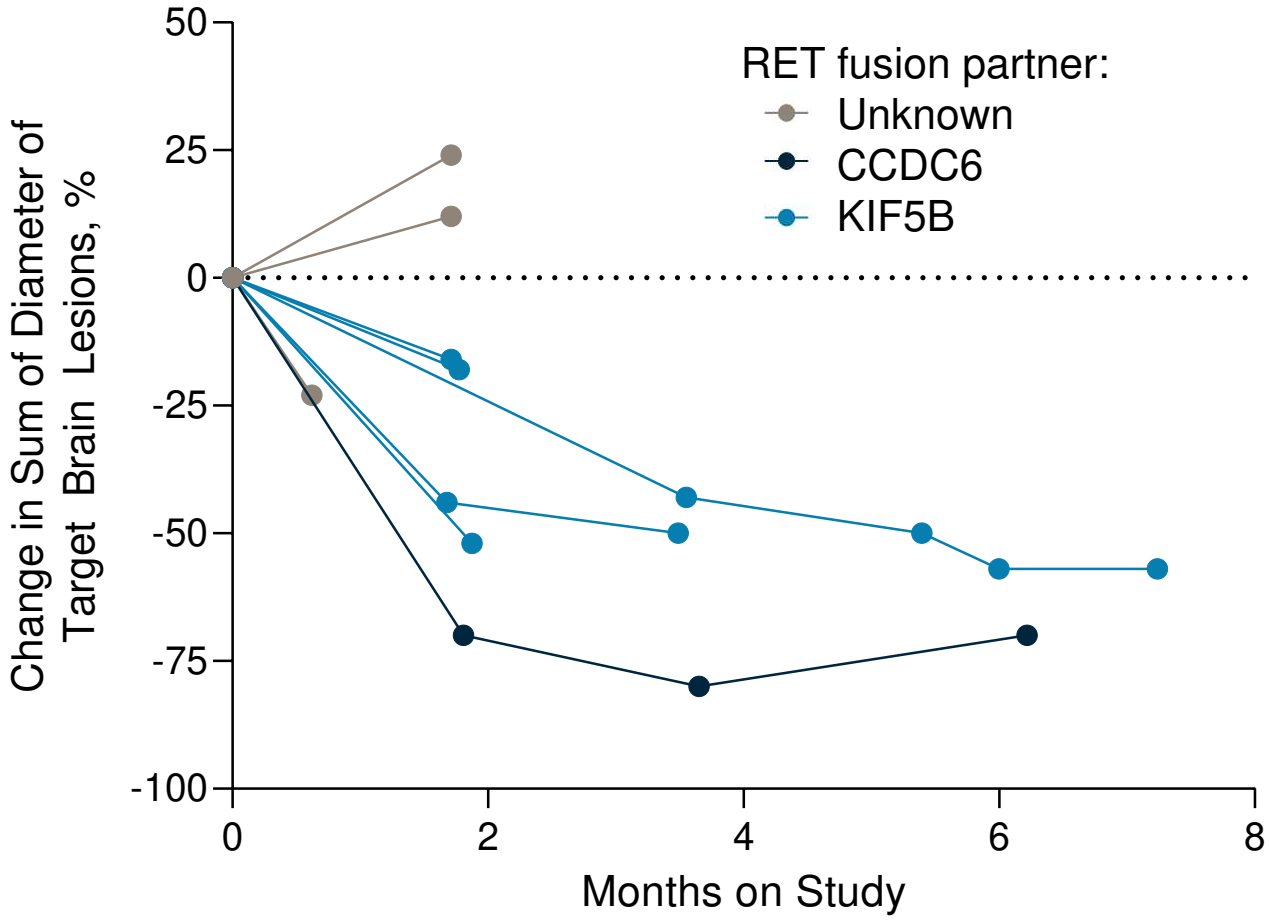
BLU-667 is Active Regardless of CNS Involvement



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

BLU-667 is Active Against Intracranial Metastases

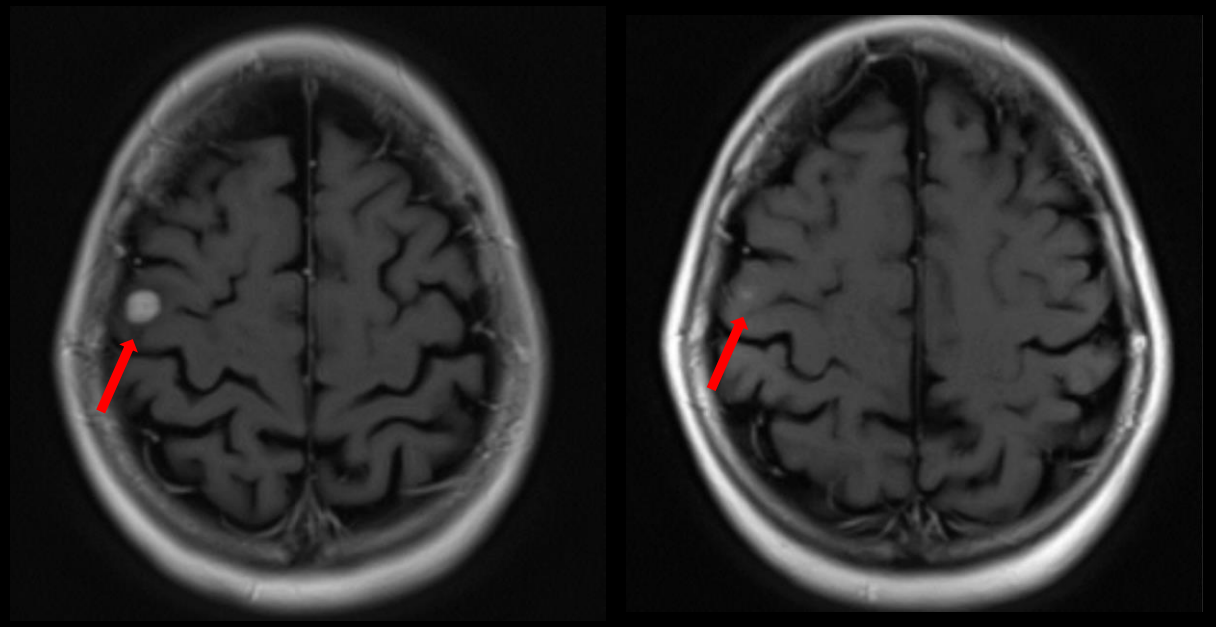
Shrinkage of Brain Metastases[a]



- 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.

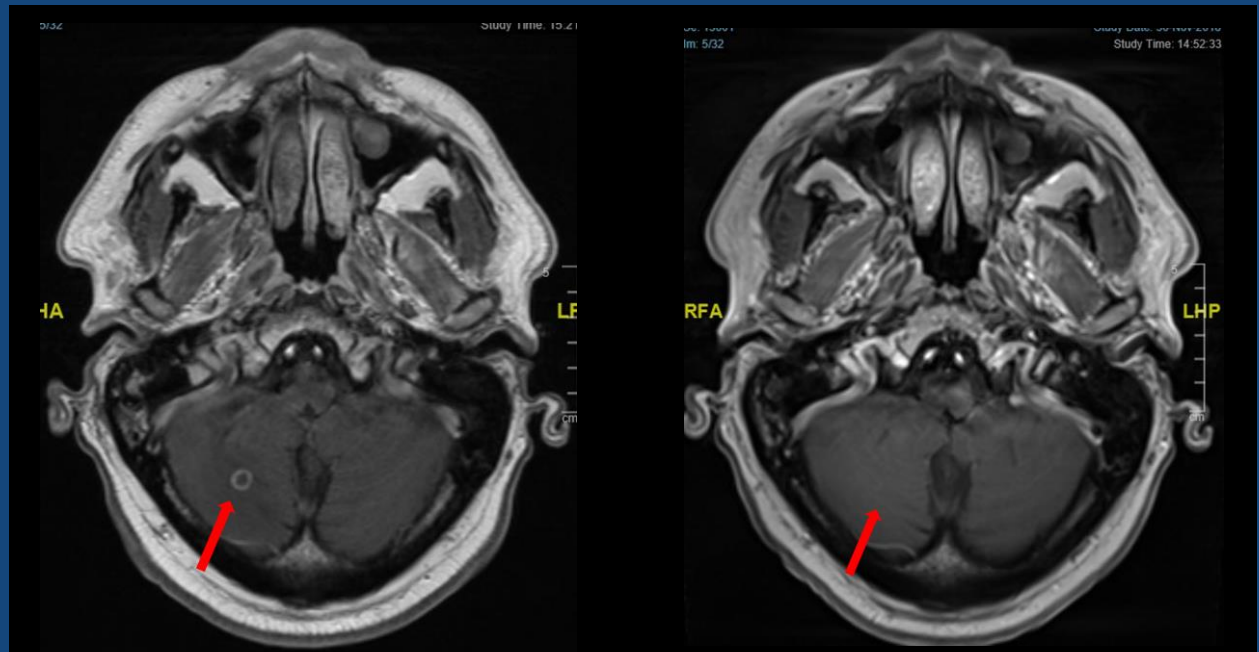
BLU-667 is Active Against Intracranial Metastases



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.

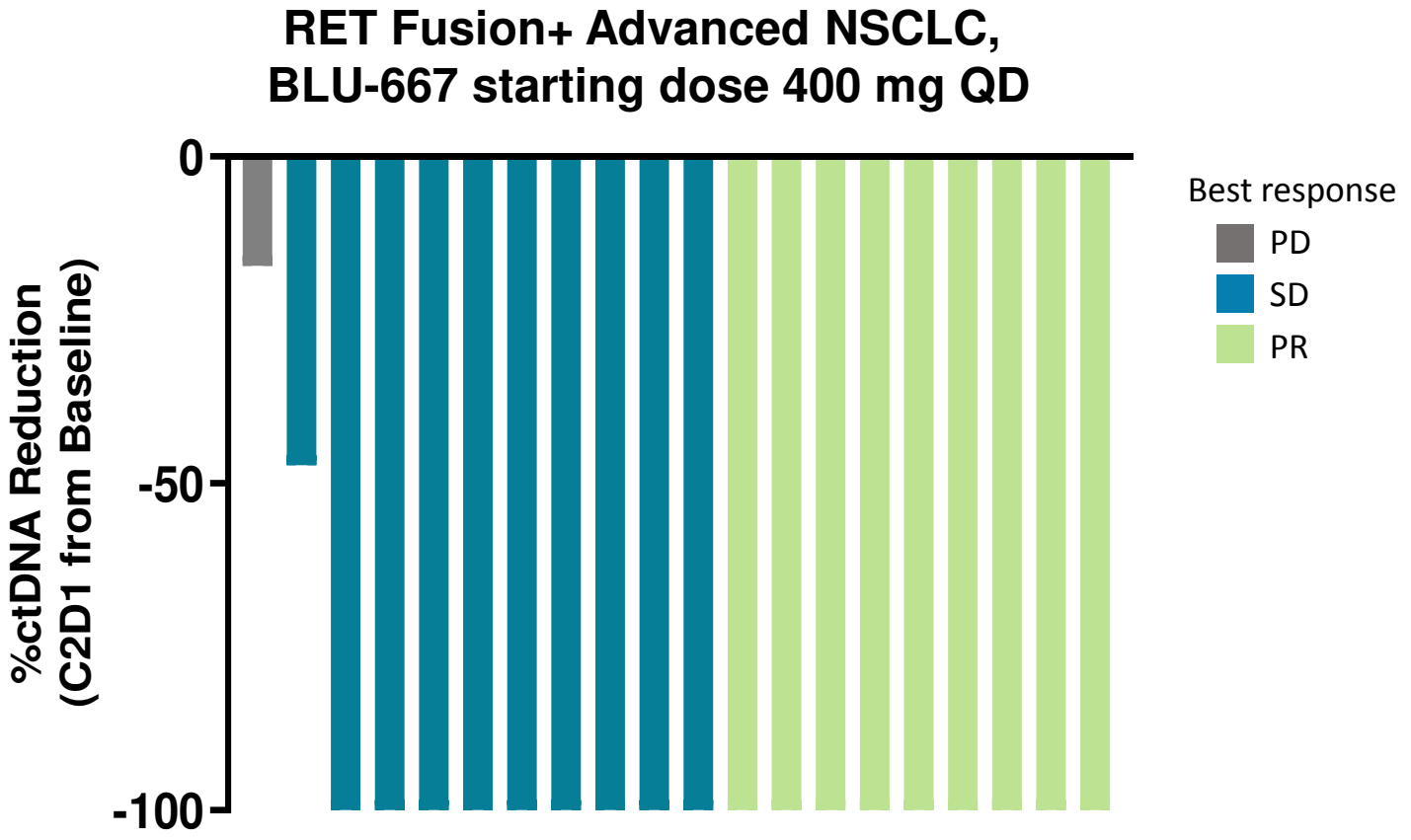


Baseline | Cycle 3, Day 1

- 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
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  - 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
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  - Mayo Clinic, Rochester, MN, United States
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  - Hospital Universitario 12 de Octubre, Madrid, Spain
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