Clinical activity of BLU-667, a highly selective RET inhibitor, in advanced *RET*-altered thyroid cancers: updated results from the phase 1 ARROW study

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Disclosures

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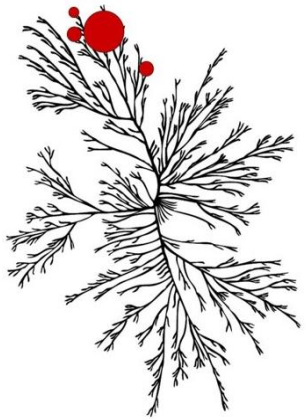
- **Research support:** Sanofi-Genzyme
- **Consultant:** Blueprint Medicines Corporation
- **Advisory board:** Loxo Oncology

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

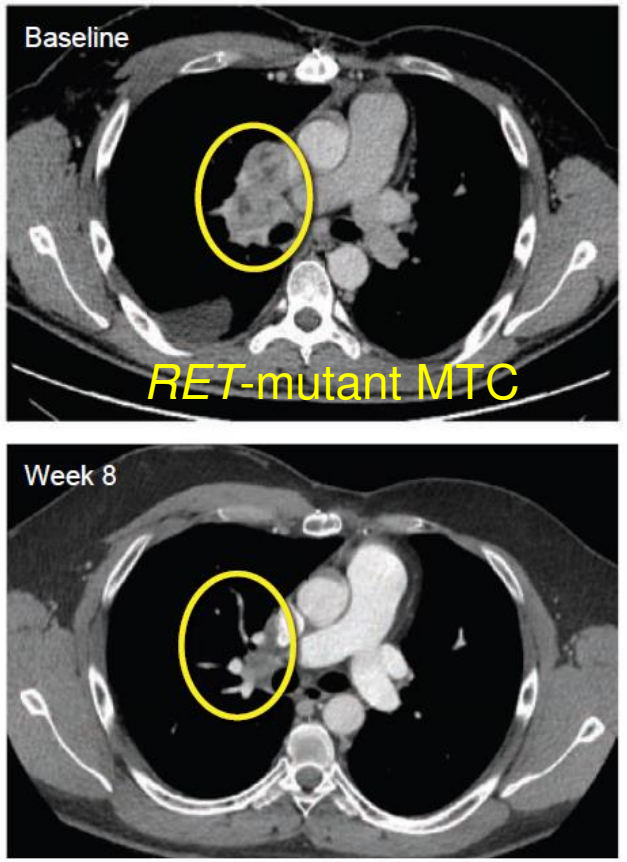
BLU-667 is designed to treat *RET*-altered cancers



BLU-667 potently inhibits RET alterations and resistance mutants while sparing VEGFR2

	Biochemical IC50 (nM)			
	RET M918T Most common in MTC	RET V804M Gatekeeper resistance in MTC	CCDC6-RET Occurs in PTC	VEGFR2
BLU-667	0.4	0.4	0.4	35
Cabozantinib	8	45	34	2
Vandetinib	7	3597	20	4
Sorafenib	23	32	ND	21
Lenvatinib	3	360	4	0.7

PHASE 1, PART 1:
PROOF OF CONCEPT



VEGFR, vascular endothelial growth factor receptor; IC50, half maximal inhibitory concentration; MTC, medullary thyroid cancer; CCDC6, coiled-coil domain containing 6; PTC, papillary thyroid cancer; ND, not determined. Kinome illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com) (CSTI). The foregoing website is maintained by CSTI, and the authors and Blueprint Medicines are not responsible for its content

Hu et al. International Thyroid Oncology Group (ITOG) 2018
Subbiah et al. American Association for Cancer Research (AACR) 2018 (clinical trials plenary presentation)
Subbiah et al. Precision Targeted Therapy with BLU-667 for *RET*-Driven Cancers. Cancer Discovery, July 2018

ARROW trial: first-in-human study with BLU-667

PART 1: Dose escalation – *complete*

Objective: *Determine MTD/RP2D* ✓

Proof of concept ✓

BOIN design
Advanced MTC, NSCLC*, or other solid tumor*

MTD/RP2D 400 mg PO daily

*All NSCLC and other solid tumors were RET-altered in cohorts higher than 30 mg QD

Part 1: *62 patients treated*
53 treated at 30 – 600 mg QD
9 treated at 200 – 300 mg divided BID dosing

PART 2: Dose expansion – ongoing

Objective: *Determine Overall Response Rate*

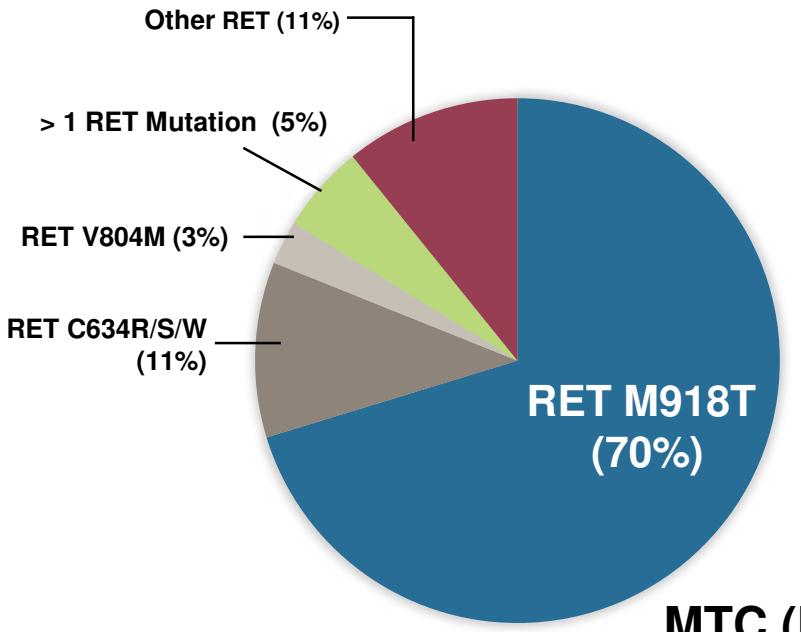
- ***RET*-altered NSCLC with prior MKI**
- ***RET*-altered NSCLC with no prior MKI**
- **MTC with prior MKI**
- **MTC with no prior MKI**
- **Other *RET*-altered solid tumors (including PTC)**
- ***RET*-altered solid tumors with prior selective RET TKI**

MTD, maximum tolerated dose; RP2D, recommended Part 2 dose; BOIN, Bayesian optimal interval; MTC, medullary thyroid cancer; NSCLC, non–small cell lung cancer; QD, once daily; BID, twice daily; PO, orally; ORR, overall response rate; MKI, multikinase inhibitor; PTC, papillary thyroid cancer; TKI, tyrosine kinase inhibitor. NCT03037385

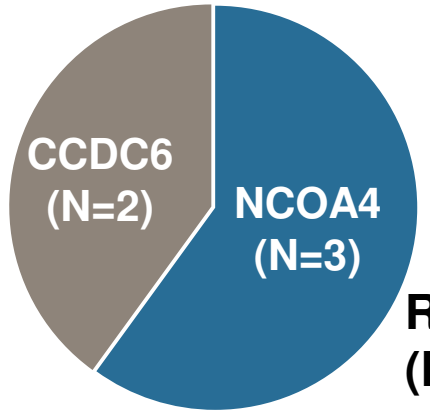
Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

Patient demographics and baseline characteristics

Parameter	Total (N=69)
Age (years), median (range)	57 (19-85)
Sex, male, n (%)	42 (61)
ECOG, PS, n (%) 0	26 (38)
1-2	43 (62)
Metastatic disease, n (%)	65 (94)
Prior systemic therapy, n (%)	51 (74)
Multikinase inhibitor	21 (30)
Number of prior regimen, median (range)	1 (0-8)
Tumor type, n (%)	
Medullary thyroid cancer	**37 (54)**
RET fusion papillary thyroid cancer	**5 (7)**
RET fusion non–small cell lung cancer	23 (33)
RET fusion intrahepatic bile duct carcinoma	1 (1)
RET mutation retroperitoneal paraganglioma	1 (1)
Non-RET altered solid tumors	2 (3)



MTC (N=37)



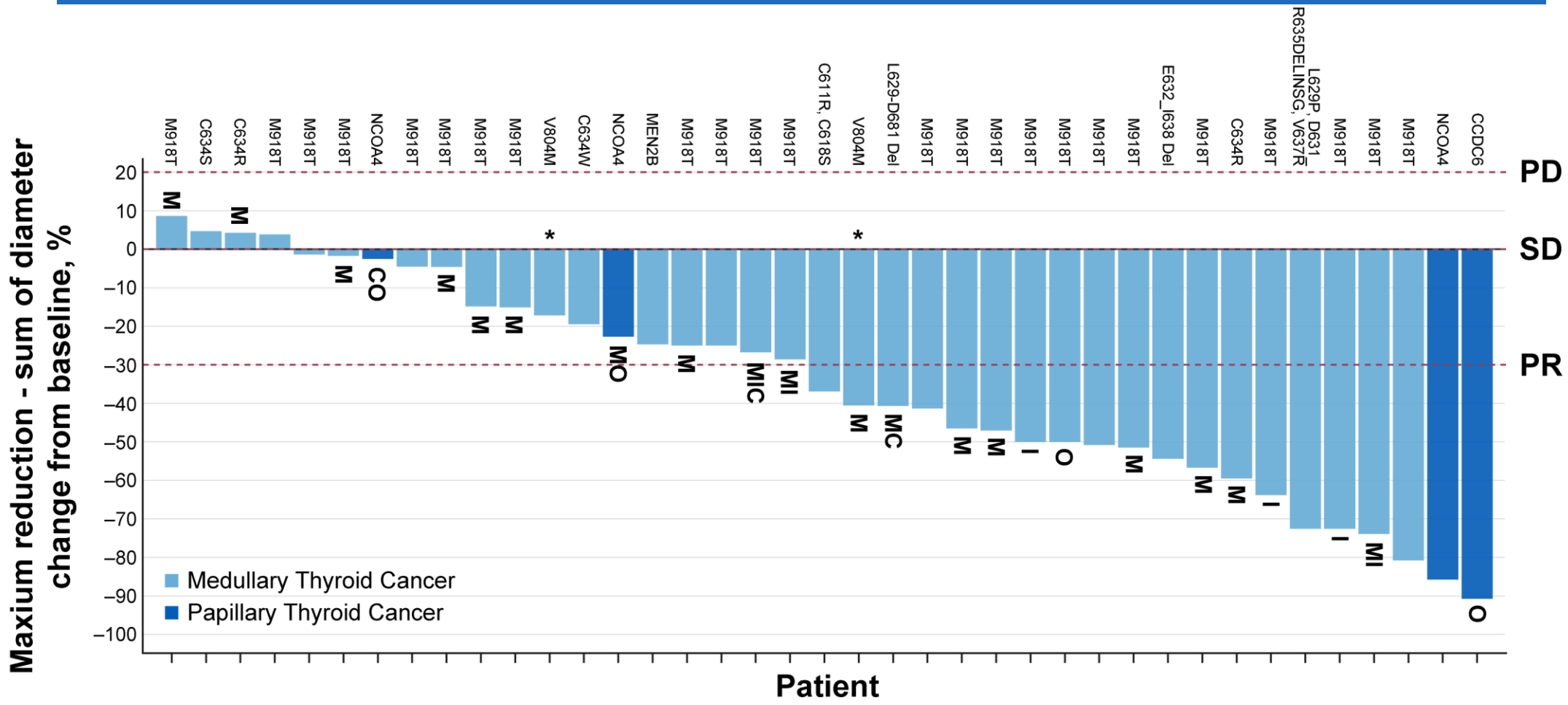
RET Fusion PTC (N=5)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; MKI, multikinase inhibitor; MTC, medullary thyroid cancer; PTC, papillary thyroid cancer; NSCLC, non–small cell lung cancer; CCDC6, coiled-coil domain containing 6; NCOA4, nuclear receptor coactivator 4.

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

BLU-667 has profound activity in *RET*-altered thyroid cancer

90% of evaluable *RET*-altered thyroid cancer patients had tumor shrinkage

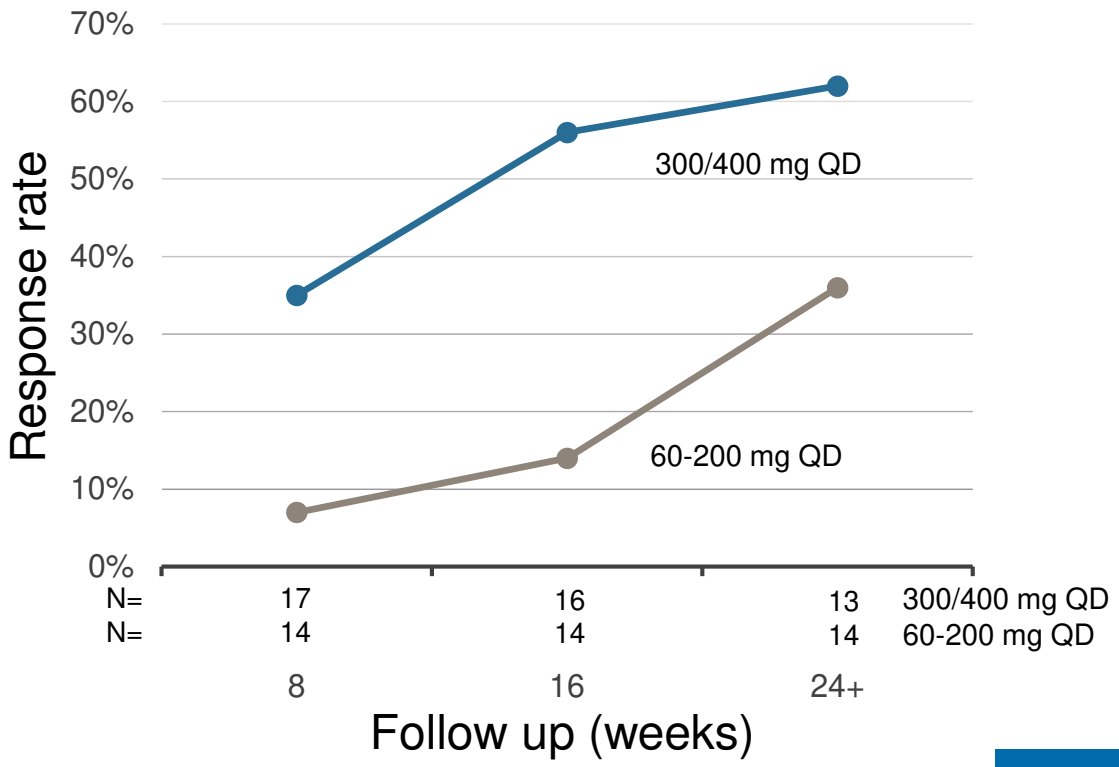


Responses seen regardless of RET alteration, including RET V804M,* or prior treatment

NCO4A, nuclear receptor coactivator 4; CCDC6, coiled-coil domain containing 6; M, prior MKI therapy; C, prior chemotherapy; O, other therapy; I, prior immunotherapy; PD, progressive disease; SD, stable disease; PR, partial response.

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

Response rate in MTC patients increases with dose and duration of therapy



MTC Response Evaluable# Patients

Best response n, (%)	Total All doses All cycles (N=35)	300/400 mg QD		
		At 8 weeks (N=17)	At 16 weeks (N=16)	At 24+ weeks (N=13)
ORR	**17 (49)**	6 (35)	9 (56)	**8 (62)**
CR	1 (3)	1 (6)	1 (6)	1 (8)
PR	16 (46)	5 (29)	8 (50)	7 (54)
SD	18 (51)	10 (59)	7 (44)	5 (39)
PD	0 (0)	0 (0)	0 (0)	0 (0)
Pending confirmation:	2 PR	1 CR, 5 PR	3 PR	

62% Response Rate at 24+ weeks in MTC at 300/400 mg QD

#Evaluable patients at a specific week considers only post baseline assessments up to at that week of therapy (based on cycle start), or those that discontinued therapy or progressed prior to that.

MTC, medullary thyroid cancer; QD, once daily; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors. Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018.

High ORR in MTC patients treated with BLU-667 regardless of prior MKI Treatment

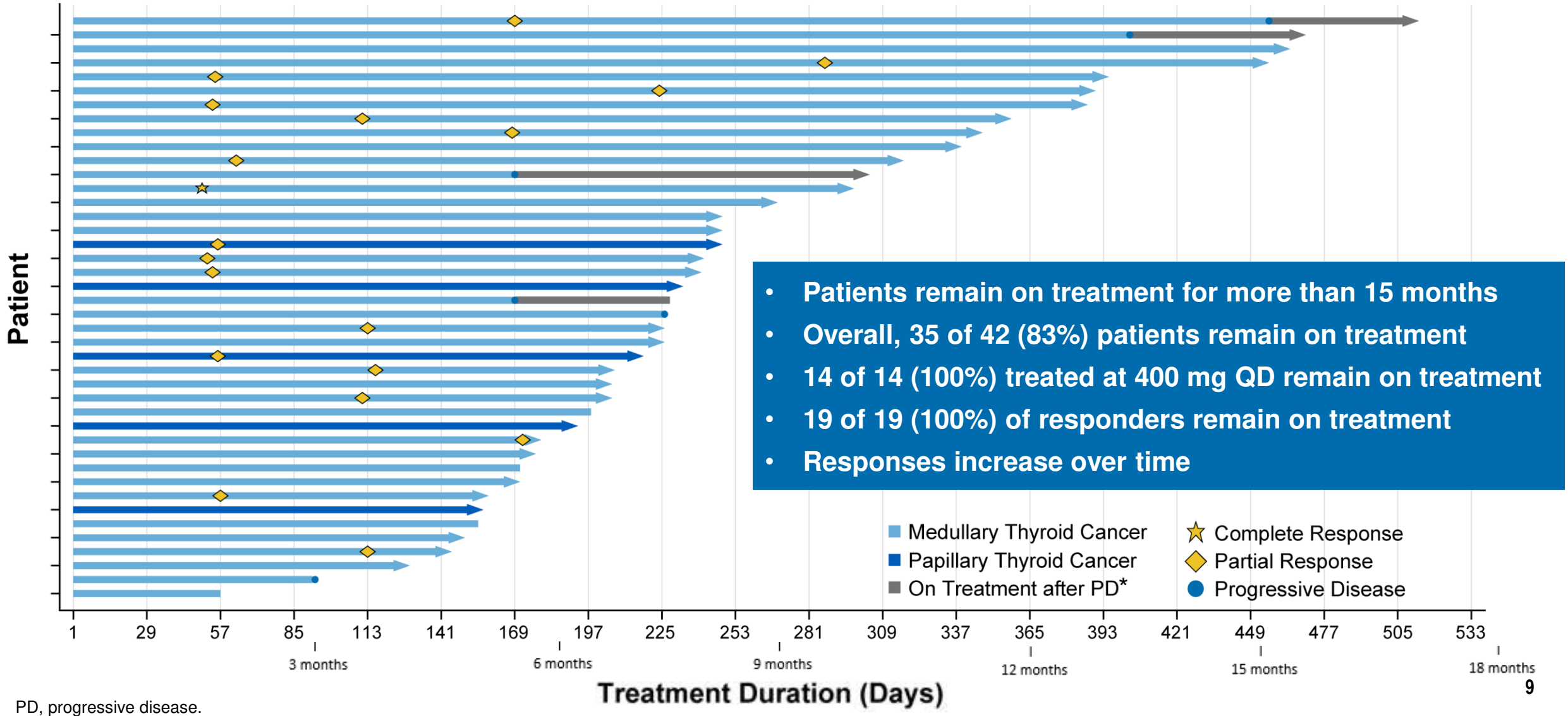
MTC Response Evaluable# Patients

Best Response	Total (n=35) n (%)	No prior MKI (n=18) n (%)	Prior MKI (n=17) n (%)
ORR (CR+PR)	**17 (49)**	**9 (50)**	**8 (47)**
CR	1 (3)	1 (6)	-
PR*	16 (46)	8 (44)	8 (47)
SD	18 (51)	9 (50)	9 (53)

MKI, multikinase inhibitor; ORR, overall response rate; CR, complete response; PR, partial response; SD, stable disease; RECIST, Response Evaluation Criteria in Solid Tumors.
*2 PRs pending confirmation
#Evaluable patients at all cycles include all dosed patients with RECIST target lesions with 1 or more post-baseline assessments or progressed or ended therapy for any reason.

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

BLU-667 shows durable responses in thyroid cancer patients



- Patients remain on treatment for more than 15 months
- Overall, 35 of 42 (83%) patients remain on treatment
- 14 of 14 (100%) treated at 400 mg QD remain on treatment
- 19 of 19 (100%) of responders remain on treatment
- Responses increase over time

PD, progressive disease.

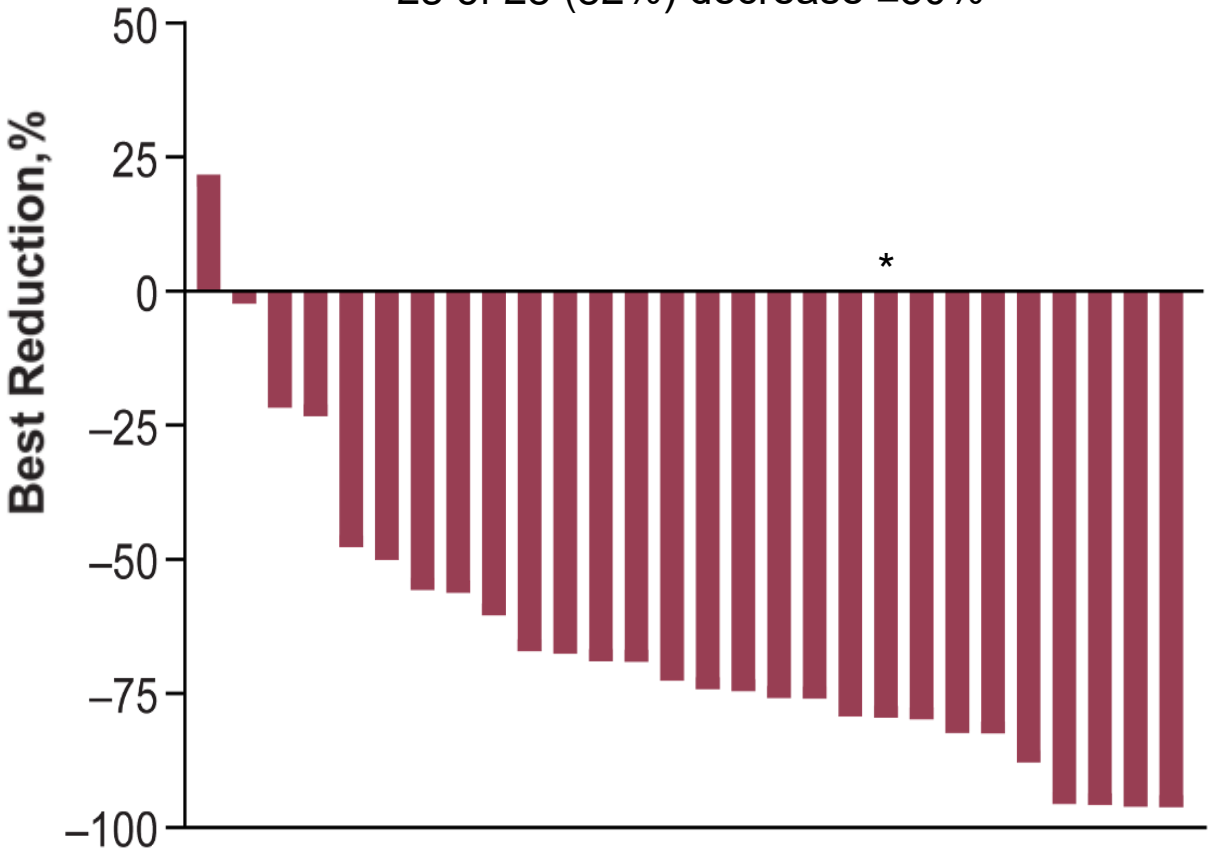
* Patients were allowed to continue on treatment following progressive disease if there was continued clinical benefit.

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

Significant declines in MTC tumor markers

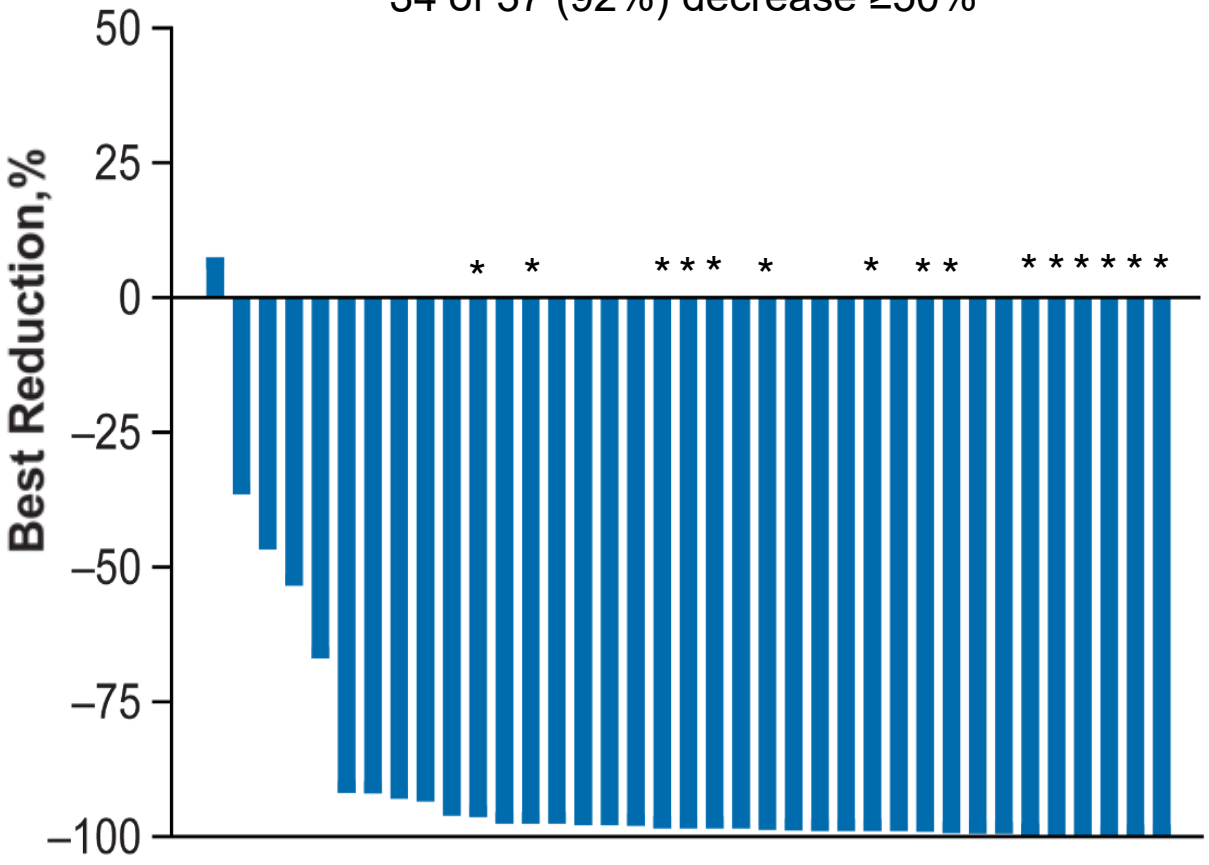
Carcinoembryonic Antigen (CEA)

23 of 28 (82%) decrease ≥50%



Calcitonin

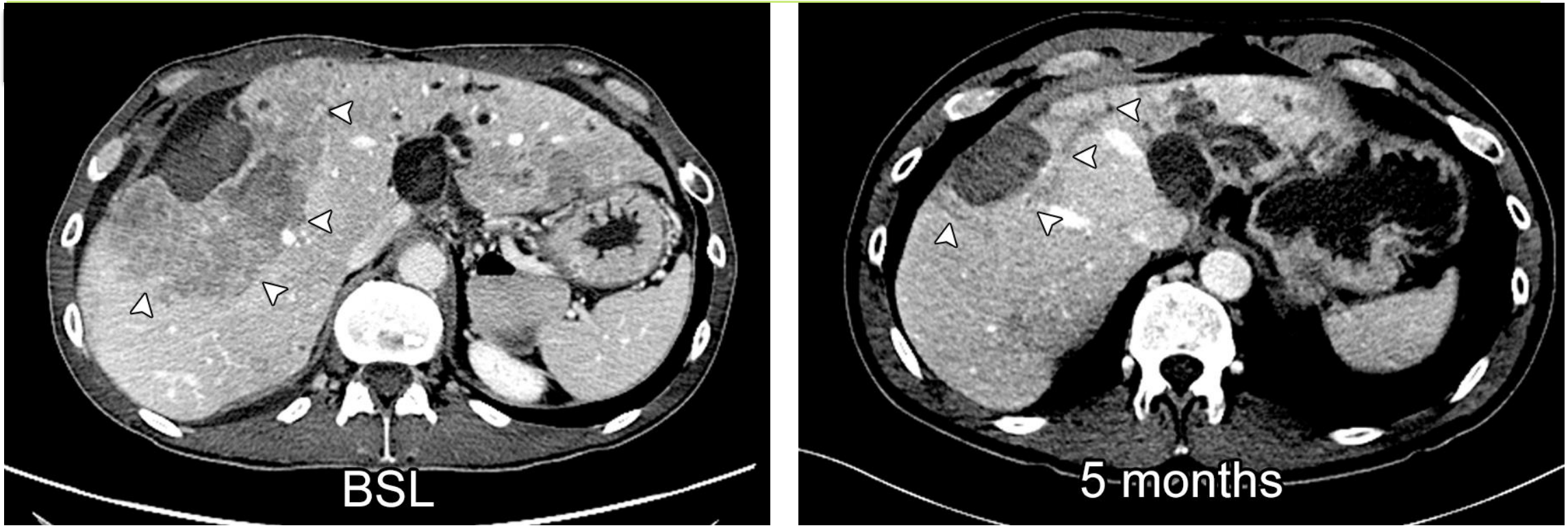
34 of 37 (92%) decrease ≥50%



MTC, medullary thyroid cancer; CEA, carcinoembryonic antigen.
*Tumor marker normalized.

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

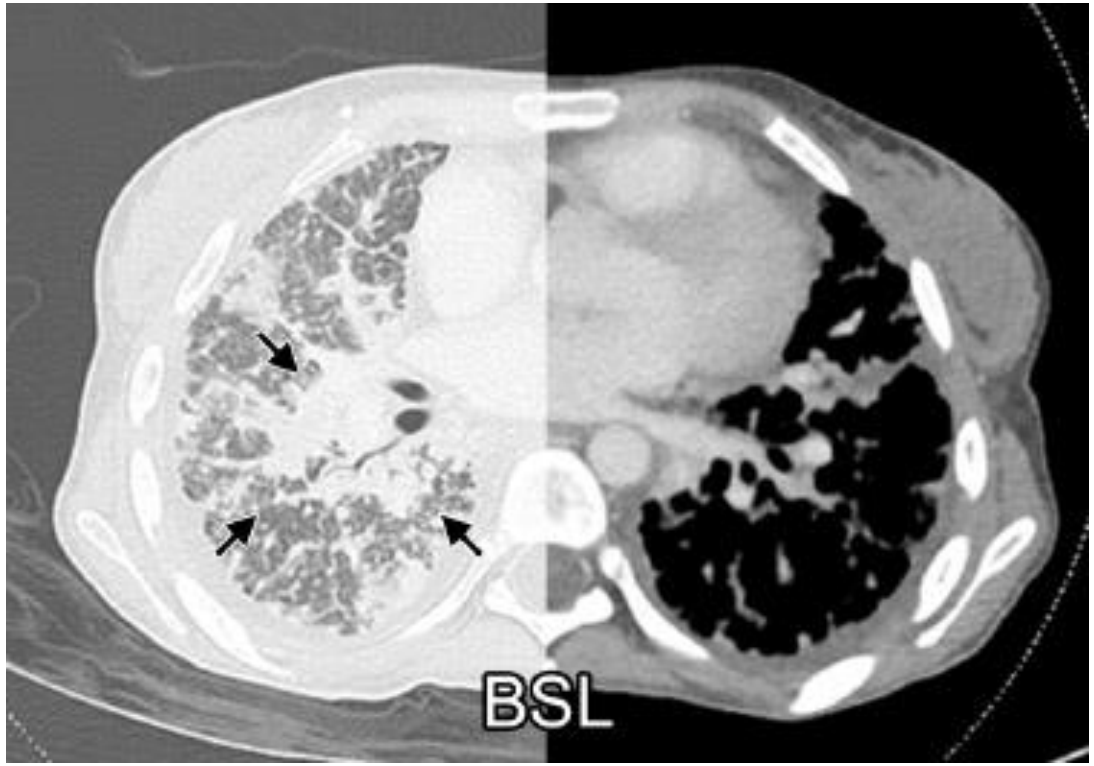
BLU-667 demonstrates potent activity in germline *RET* V804M mutant MTC

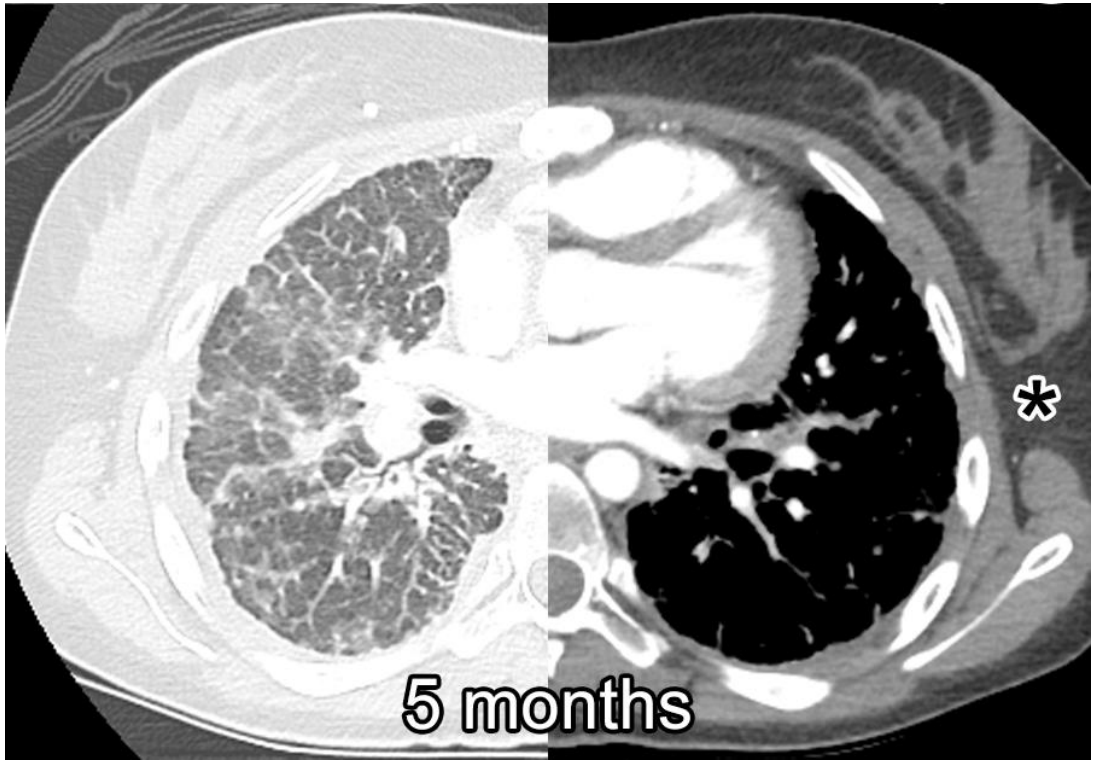


- 52-year-old male gastroenterologist with MTC (germline *RET* V804M gatekeeper mutation) with metastases to neck and mediastinal lymph nodes, lungs, liver and bone
- Progressive disease in liver on sunitinib (AE's: anorexia, weight loss, diarrhea, hand/foot syndrome, fatigue)
- Initiated BLU-667 at 100 mg BID and escalated to 400 mg QD at C3D1
- By C5D1, showed -41% (PR) reduction in liver metastases; gaining weight (BMI increased from 18.9 to 23.5), no diarrhea
- Remains on treatment in Cycle 7 with continued PR

MTC, medullary thyroid cancer; BSL, baseline; PD, progressive disease; AE, adverse event; BID, twice daily; QD, once daily; PR, partial response; BMI, body mass index. Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

BLU-667 induced dramatic improvement in young PTC patient





- 23-year-old woman with PTC, sclerosing variant (*CCDC6-RET* fusion) who presented 6 years ago with symptomatic diffuse lung metastases requiring supplemental oxygen (O_2) since diagnosis; treated with I-131 (total activity 351 mCi) with subsequent fibrosis
- Progressed on sorafenib and early this year on lenvatinib (increasing O_2 needs, pleural effusions and intubated 3 times over 6 wks)
- Initiated BLU-667 at 400 mg once daily → RECIST SD (no target lesion/non-target lymphangitic lung metastases)
- Symptomatic response: O_2 weaned monthly to room air within 5 months, baseline BMI 14.8 steadily increased to 22.3 after 6 mos
- Remains on treatment at Cycle 8 and plans to start college and get her driver's license this Fall

PTC, papillary thyroid cancer; BSL, baseline; CCDC6, coiled-coil domain containing 6; O2, oxygen; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; BMI, body mass index. Patient had non-measurable disease at baseline and is not represented on current waterfall plot. Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

Safety - BLU-667 is well tolerated

All doses and patients, N=69							
	Treatment-emergent AEs (≥15% overall)					Treatment-related AEs	
Adverse Event	Any event n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3	Grade 4
Constipation	24 (35)	22 (32)	2 (3)	-	-	-	-
Aspartate aminotransferase increased	23 (33)	20 (29)	3 (4)	-	-	-	-
Anemia	21 (30)	8 (12)	7 (10)	6 (9)	-	4 (6)	-
Hypertension	21 (30)	5 (7)	5 (7)	11 (16)	-	6 (9)	-
White blood cell count decreased	20 (29)	7 (10)	10 (15)	3 (4)	-	3 (4)	-
Diarrhea	19 (28)	11 (16)	3 (4)	5 (7)	-	4 (6)	-
Neutropenia	19 (28)	5 (7)	5 (7)	6 (9)	3 (4)	5 (7)	2 (3)
Alanine aminotransferase increased	17 (25)	16 (23)	-	1 (1)	-	1 (1)	-
Blood creatinine increased	16 (23)	15 (28)	1 (1)	0	-	0	-
Fatigue	13 (19)	9 (13)	3 (4)	1 (1)	-	1 (1)	-
Headache	12 (17)	9 (13)	2 (3)	1 (1)	-	1 (1)	-

Most AEs were Grade 1

Only 2 discontinuations for related AEs*

AE, adverse event; ALT, alanine aminotransferase.
*Discontinuations for related AEs: ↑ALT (gr3) and pneumonitis (gr2)

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

Conclusions

- **BLU-667** has demonstrated:
  - Responses across *RET* genotypes, which increase with dose and time on treatment
    - **Durable and high ORR of 62%** at 300/400 mg QD in patients with MTC at 24+ weeks
    - **100%** of MTC patients treated at 400 mg daily remain on treatment
    - **ORR of ~50%** in MTC patient regardless of prior MKI treatment
    - Patients remain on treatment for more than 15 months
    - **100%** of responders remain on treatment
- BLU-667 is well tolerated at efficacious doses in MTC and PTC patients
- Results warrant further clinical development in MTC and PTC
- **ARROW** trial Part 2 dose expansion is open and enrolling globally in the United States, Europe, and Asia

ORR, overall response rate; QD, once daily; MTC, medullary thyroid cancer; MKI, multikinase inhibitor; PTC, papillary thyroid cancer. Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

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  - The Knight Cancer Institute, Oregon Health & Science University, Portland, OR, United States
  - Massachusetts General Hospital Cancer Center, Boston, MA, United States
  - Chao Family Comprehensive Cancer Center University of California Irvine Medical Center, Irvine, CA, United States
  - University of Colorado, Aurora, CO, United States
  - University of Miami, Miami, FL, United States
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  - Vall d'Hebron University Hospital, Barcelona, Spain
  - University of Milano, Istituto Europeo di Oncologia, Milan, Italy
  - Seoul National University Hospital, Seoul, Republic of Korea
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