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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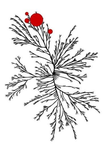
BACKGROUND

- 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) (CSTI). The foregoing website is maintained by CSTI, and Blueprint Medicines is not responsible for its content.

METHODS

ARROW: BLU-667 Dose-Escalation/Expansion Study

Part 1: Dose-Escalation (Complete; N=62) → **Part 2: Expansion Cohorts (Ongoing)**

RET-altered advanced solid tumors

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

Phase 2 dose determined (400 mg QD)

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

- 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 28, 2019. BLU-667 is an investigational agent discovered and currently in development by Blueprint Medicines Corporation (Blueprint Medicines).

References

1. Romei, et al. *Oncotarget*. 2018;9:9875-9884.
2. Santoro, et al. *J Clin Invest*. 1992;89(5):1517-1522.
3. Song, et al. *Endocrinol Metab*. 2015;30:252-262.
4. Subbiah, et al. *Cancer Discov*. 2018;8(7):836-849.

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 (19–81)	57 (25–81)
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

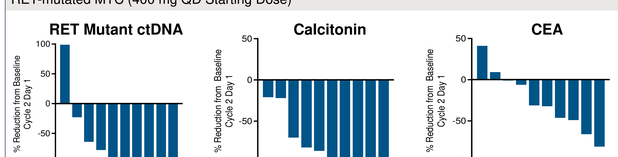
Among 64 patients with RET-mutated MTC receiving BLU-667 starting dose of 400 mg QD:
- Treatment-related toxicity is generally low-grade and reversible
- No patients discontinued BLU-667 due to treatment-related toxicity (4% across the entire study)

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)	15 (23)	19 (30)	10 (16)
Constipation	21 (33)	1 (2)	12 (19)	1 (2)
Neutropenia[a]	17 (27)	7 (11)	15 (23)	7 (11)
Anemia	14 (22)	3 (5)	6 (9)	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)	6 (9)	1 (2)
Headache	12 (19)	-	5 (8)	-
Blood creatinine increased	11 (17)	-	7 (11)	-
Fatigue	11 (17)	-	6 (9)	-
Hypocalcemia	11 (17)	4 (6)	4 (6)	1 (2)

Additional grade ≥3 treatment related AEs (≥2%): blood creatine phosphokinase increased (5%).
[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)

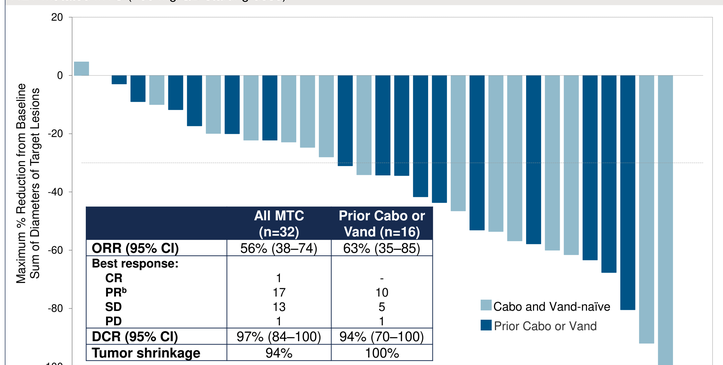


CEA, carcinoembryonic antigen; ctDNA, circulating tumor deoxyribonucleic acid.

Antitumor Activity

Tumor Response

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

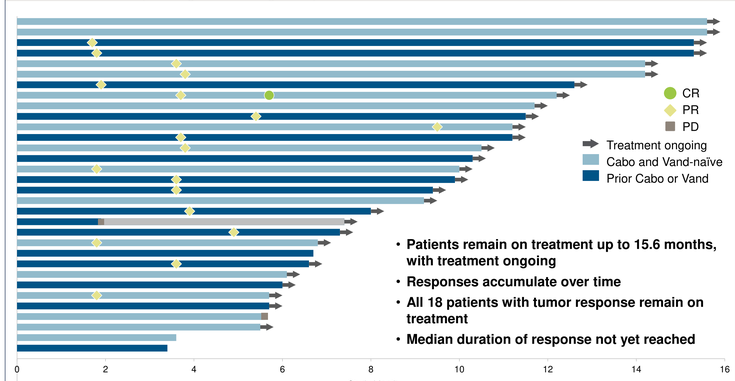


	All MTC (n=32)	Prior Cabo or Vand (n=16)
ORR (95% CI)	56% (38–74)	63% (35–85)
Best response:		
CR	1	-
PR[b]	17	10
SD	13	5
PD	1	1
DCR (95% CI)	97% (84–100)	94% (70–100)
Tumor shrinkage	94%	100%

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)	66 (23–70)
Male, n (%)	5 (56)
ECOG PS, n (%)	
0	4 (44)
1-2	5 (56)
Metastatic disease, n (%)	9 (100)
Prior systemic regimens, median (range)	2 (0–8)
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)

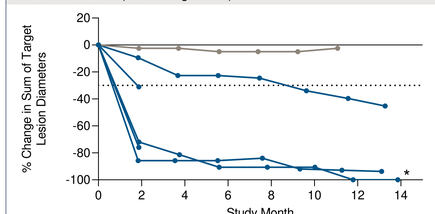
[a]Includes 2 patients with starting doses of 200 mg and 300 mg QD in dose-escalation.

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
  - Reponses 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 data managers who contributed to this study. Third-party writing assistance was provided by Ashfield Healthcare and funded by Blueprint Medicines.