LIBRETTO-321, A Phase 2 Study of the Efficacy and Safety of Selpercatinib in Chinese Patients with Advanced *RET*-altered Thyroid Cancer

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BACKGROUND

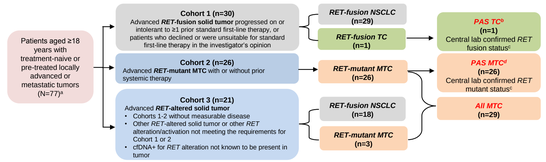
- Selpercatinib is a first-in-class, highly selective, potent inhibitor of the rearranged during transfection (RET) kinase with central nervous system (CNS) activity.
- In the phase 1/2 LIBRETTO-001 study, selpercatinib induced robust and durable responses in patients with *RET*-altered thyroid cancer [a] and other cancers.[1-5]
- Based on these results, selpercatinib was approved in multiple countries for the treatment of *RET*-altered thyroid cancer and *RET* fusion-positive non-small cell lung cancer (NSCLC).

OBJECTIVE

- The LIBRETTO-321 (NCT04280081) trial evaluated the efficacy and safety of selpercatinib in Chinese patients with solid tumors harboring an activating *RET* alteration.
- Here, we report findings in patients with *RET*-mutant medullary thyroid cancer (MTC) and *RET* fusion-positive thyroid cancer (data cut-off: 25 March 2021).

[a]Objective response rates by independent review: 69% and 71% in previously treated and untreated *RET*-mutant medullary thyroid cancer[6], respectively; 77% and 92% in previously treated and untreated *RET* fusion-positive thyroid cancer, respectively[6].

STUDY DESIGN



- An ongoing, open-label, multi-center, phase 2 study conducted in China.
- **Treatment**: Oral selpercatinib 160 mg BID was administered in 28-day cycles until progressive disease, unacceptable toxicity, withdrawal of consent or death; treatment beyond progression was permitted with continued benefit.
- **Primary endpoint:** ORR per RECIST v1.1 by IRC.
- **Secondary endpoints:** ORR per RECIST v1.1 by investigator, DOR, CNS ORR, CNS DOR, CBR, TTR, TTBR, PFS, OS, PK, safety.
- **Exploratory endpoint**: Biochemical response (defined as normalization or a ≥50% decrease in calcitonin or CEA levels from baseline sustained for ≥4 weeks).

[a]Number of patients enrolled and treated as of 25 March 2021; [b]Patients with *RET* fusion-positive TC in cohort 1 whose *RET* status was confirmed by central laboratory (as only 1 patient had *RET* fusion-positive TC, PAS TC = All TC); [c]*RET* alterations in the tumor were detected using the KingMed NGS 529 plus kit; [d]Patients with *RET*-mutant MTC in cohort 2 whose *RET* status was confirmed by central laboratory.

BID, twice daily; CEA, carcinoembryonic antigen; cfDNA, cell-free deoxyribonucleic acid; CBR, clinical benefit rate; CNS, central nervous system; DOR, duration of response; MTC, medullary thyroid cancer; NGS; next generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PAS, primary analysis set; PK, pharmacokinetics; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; *RET*, rearranged during transfection; TC, thyroid cancer; TTBR, time to best response; TTR, time to response

KEY RESULTS

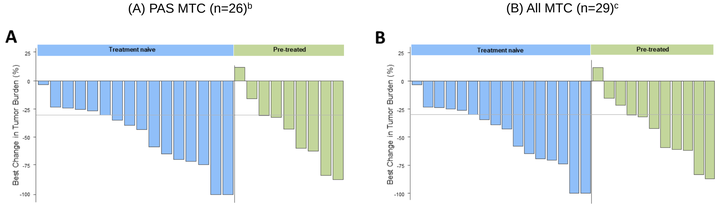
Tumor Responses to Selpercatinib in Patients with *RET*-mutant MTC, as Assessed by IRC[a]

	PAS MTC[b] (n=26)			All MTC[c] (n=29)		
	All (n=26)	Pre-treated (n=9)	Treatment naive (n=17)	All (n=29)	Pre-treated (n=12)	Treatment naive (n=17)
BOR, n (%)						
CR	2 (7.7)	1 (11.1)	1 (5.9)	3 (10.3)	2 (16.7)	1 (5.9)
PR	13 (50.0)[d]	4 (44.4)	9 (52.9)	14 (48.3)[d]	5 (41.7)	9 (52.9)
SD	10 (38.5)	4 (44.4)	6 (35.3)	11 (37.9)	5 (41.7)	6 (35.3)
SD ≥16 wks	1 (3.8)	0	1 (5.9)	0	0	0
PD	0	0	0	0	0	0
Not evaluable	1 (3.8)	0	1 (5.9)	1 (3.4)	0	1 (5.9)
ORR, n (%),	15 (57.7)	5 (55.6)	10 (58.8)	17 (58.6)	7 (58.3)	10 (58.8)
95% CI[e]	36.9-76.6	21.2-86.3	32.9-81.6	38.9-76.5	27.7-84.8	32.9-81.6

Total % may be different than the sum of the individual due to rounding. [a]Median follow up: PAS MTC, 8.7 months; All MTC, 9.0 months; [b]Patients with *RET*-mutant MTC in cohort 2 whose *RET* status was confirmed by central laboratory (1 patient did not receive a post-baseline tumor assessment); [c]All enrolled patients with *RET*-mutant MTC (1 patient did not receive a post-baseline tumor assessment); [d]Excluding 3 patients with a PR pending confirmation; [e]Confidence intervals are based on the Clopper-Pearson method

BOR, best overall response; CI, confidence interval; CR, complete response; IRC, independent review committee; MTC, medullary thyroid cancer; ORR, objective response rate; PAS, primary analysis set; PD, progressive disease PR, partial response; RET, rearranged during transfection; SD, stable disease

Waterfall Plots Showing the Best Change in Tumor Size in Patients with *RET*-mutant MTC as Assessed by IRC in the PAS MTC (A) and All MTC (B)[a]



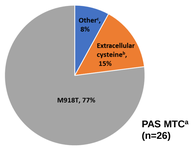
[a]Median follow up: PAS MTC, 8.7 months; All MTC, 9.0 months; [b]Patients with *RET*-mutant MTC in cohort 2 whose *RET* status was confirmed by central laboratory (1 patient did not receive a post-baseline tumor assessment); [c]1 patient not included because of no post-baseline tumor assessment. 1 patient not included because of non-target lesion only.

IRC, Independent Review Committee; MTC, medullary thyroid cancer; PAS, primary analysis set; *RET*, rearranged during transfection; SD, stable disease

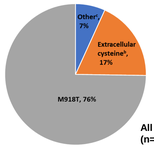
Patient Characteristics

Characteristic	PAS MTC[a] (n=26)	All MTC (n=29)
Female, n (%)	6 (23.1)	6 (20.7)
Median age (range), years	50 (23-70)	46 (23-70)
ECOG PS, n (%)		
0	15 (57.7)	17 (58.6)
1	11 (42.3)	12 (41.4)
Median prior systemic regimens, n (range)	0 (0-3)	0 (0-3)
Prior multikinase inhibitor, n (%)	4 (15.4)	7 (24.1)
Treatment naive, n (%)	17 (65.4)	17 (58.6)
Measurable disease (by investigator), n (%)	26 (100.0)	27 (93.1)

RET mutations



PAS MTC[a] (n=26)

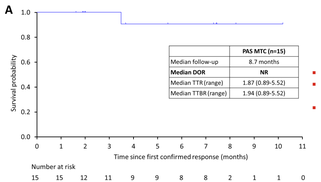


All MTC (n=29)

[a]Patients with *RET*-mutant MTC in cohort 2 whose *RET* status was confirmed by central laboratory; [b]Mutations included C634R, C634W, and C630Y; [c]V899-E902DEL and E632-L633DEL mutations in 1 patient each

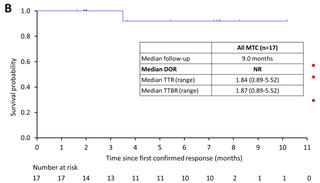
ECOG PS, Eastern Cooperative Oncology Group performance status; MTC, medullary thyroid cancer; PAS, primary analysis set; TC, thyroid cancer

Duration of Response Assessed by IRC in Patients Who Had Confirmed CR or PR: PAS MTC (A) and All MTC (B)



	PAS MTC (n=15)
Median follow-up	8.7 months
Median DOR	NR
Median TTR (range)	1.87 (0.89-5.52)
Median TTBR (range)	1.94 (0.89-5.52)

- Median DOR was not reached.
- 9-month DOR rate: 90.9% (95% CI, 50.8-98.7).
- 93.3% of responses on-going after a median follow-up of 8.7 months.



	All MTC (n=17)
Median follow-up	9.0 months
Median DOR	NR
Median TTR (range)	1.84 (0.89-5.52)
Median TTBR (range)	1.87 (0.89-5.52)

- Median DOR was not reached.
- 9-month DOR rate: 92.3% (95% CI, 56.6-98.9).
- 94.1% of responses on-going after a median follow-up of 9.0 months.

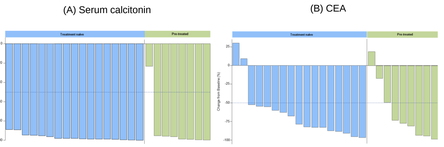
CI, confidence interval; CR, complete response; DoR, duration of response; IRC, Independent Review Committee; MTC, medullary thyroid cancer; PAS, primary analysis set; PR, partial response; TTBR, time to best response; TTR, time to response

Biochemical Response in the PAS MTC

Response[a]	Calcitonin (n=25)[b]	CEA (n=23)[b]
ORR, % (95% CI)	92.0 (74.0-99.0)	87.0 (66.4-97.2)
BOR, n (%)		
CR	4 (16.0)	2 (8.7)
PR	19 (76.0)	18 (78.3)
SD	1 (4.0)	2 (8.7)
PD	0	0
Not evaluable	1 (4.0)	1 (4.3)

[a]Normalization or ≥50% decrease in calcitonin or CEA levels from baseline sustained for ≥4 weeks; PR, ≥50% decrease from baseline serum levels; SD: between +50% and –50% change from baseline serum levels; PD, ≥50% increase from baseline serum levels; [b]Biochemical response evaluable population included patients with abnormal baseline levels of calcitonin or CEA, respectively, and at least one post-baseline measurement.

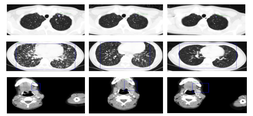
Waterfall Plots of the Best Changes in Serum Calcitonin (A) and Serum CEA (B) in the PAS MTC



BOR, best overall response; CEA, carcinoembryonic antigen; CI, confidence interval; CR, complete response; ORR, objective response rate; PAS, primary analysis set; PD, progressive disease; PR, partial response; SD, stable disease

Antitumor Activity in *RET* Fusion-positive Thyroid Cancer, as Assessed by IRC

- 19-year-old female with *CCDC6 RET* fusion-positive papillary thyroid cancer.
- Metastatic disease in lungs and lymph nodes.
- Previous surgeries and ^{131}I treatment but naive to systemic treatment.
- ECOG PS 0
- Received selpercatinib 160 mg BID.
- Confirmed PR at 8 weeks.
- Maximum tumor burden reduction of 43%.
- Remains on treatment at 23.4 weeks.



BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; PR, partial response; RET, rearranged during transfection

Adverse Events in All Selpercatinib-treated Patients (N=77)[a]

	Treatment-emergent Adverse Event					Treatment-related Adverse Event				
Adverse Event, %	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 4	Any Grade
Alanine aminotransferase increased[b]	30 (39.0)	8 (10.4)	11 (14.3)	1 (1.3)	50 (64.9)	11 (14.3)	1 (1.3)		48 (62.3)
Aspartate aminotransferase increased[b]	31 (40.3)	4 (5.2)	12 (15.6)	0	47 (61.0)	12 (15.6)	0		47 (61.0)
Blood bilirubin increased	21 (27.3)	9 (11.7)	0	0	30 (39.0)	0	0		30 (39.0)
Thrombocytopenia[b]	18 (23.4)	4 (5.2)	6 (7.8)	2 (2.6)	30 (39.0)	6 (7.8)	2 (2.6)		29 (37.7)
Hypertension[b]	2 (2.6)	11 (14.3)	15 (19.5)	0	28 (36.4)	12 (15.6)	0		26 (33.8)
Hypoalbuminaemia	18 (23.4)	6 (7.8)	2 (2.6)	0	26 (33.8)	1 (1.3)	0		20 (26.0)
Diarrhea[b]	21 (27.3)	3 (3.9)	1 (1.3)	0	25 (32.5)	1 (1.3)	0		22 (28.6)
White blood cell count decreased	11 (14.3)	11 (14.3)	3 (3.9)	0	25 (32.5)	3 (3.9)	0		24 (31.2)
Dry mouth[b]	22 (28.6)	0	0	0	22 (28.6)	0	0		21 (27.3)
Blood alkaline phosphatase increased	14 (18.2)	6 (7.8)	1 (1.3)	0	21 (27.3)	1 (1.3)	0		19 (24.7)
Bilirubin conjugated increased	13 (16.9)	5 (6.5)	2 (2.6)	0	20 (26.0)	2 (2.6)	0		20 (26.0)
Neutrophil count decreased	7 (9.1)	10 (13.0)	3 (3.9)	0	20 (26.0)	3 (3.9)	0		19 (24.7)
Electrocardiogram QT prolonged[b]	12 (15.6)	1 (1.3)	6 (7.8)	0	19 (24.7)	5 (6.5)	0		15 (19.5)
Hypernatraemia	19 (24.7)	0	0	0	19 (24.7)	0	0		16 (20.8)
Blood creatinine increased[b]	11 (14.3)	7 (9.1)	0	0	18 (23.4)	0	0		18 (23.4)
Blood lactate dehydrogenase increased	16 (20.8)	2 (2.6)	0	0	18 (23.4)	0	0		16 (20.8)
Weight increased	7 (9.1)	11 (14.3)	0	0	18 (23.4)	0	0		9 (11.7)
Gamma-glutamyltransferase increased	10 (13.0)	5 (6.5)	2 (2.6)	0	17 (22.1)	2 (2.6)	0		16 (20.8)
Oedema[b]	13 (16.9)	4 (5.2)	0	0	17 (22.1)	0	0		14 (18.2)
Pyrexia[b]	15 (19.5)	2 (2.6)	0	0	17 (22.1)	0	0		12 (15.6)

- TEAEs led to discontinuation of selpercatinib in 5.2% (n=4; 3 [3.9%] considered related to selpercatinib), and dose reduction in 32.5% (n=25), of patients.
- One patient died due to a TEAE considered unrelated to selpercatinib.

[a]AEs listed here are TEAEs that occurred at any grade in ≥20% of patients. The relatedness of AEs to treatment was determined by the investigators; [b]Consolidated AE term

AE, adverse event; TEAE, treatment-emergent adverse event

CONCLUSIONS

- **Selpercatinib showed robust and durable anti-tumor activity in Chinese patients with advanced *RET*-altered thyroid cancer in the LIBRETTO-321 phase 2 study**
  - PAS MTC
    - IRC-assessed ORR was 57.7% (95% CI, 36.9-76.6). 9-month DOR rate was 90.9% (95% CI, 50.8-98.7). 90.9% of the responses were ongoing at a median follow-up of 8.7 months.
  - All MTC
    - IRC-assessed ORR was 58.6 (95% CI, 38.9–76.5). 9-month DOR rate was 92.3% (95% CI, 56.6-98.9). 94.1% of the responses were ongoing at a median follow-up of 9.0 months.
    - Biochemical ORRs were 92% (95% CI, 74.0-99.0) for calcitonin and 87% (95% CI, 66.4-97.2) for CEA.
  - Single patient with TC
    - IRC-assessed PR.
    - Rapid response (by 8 weeks).
    - Treatment and response are ongoing at 23.4 weeks.
- **Favorable safety profile**
  - Selpercatinib was well tolerated, and most AEs were manageable and reversible.
  - Only 3.9% of patients discontinued selpercatinib due to treatment-related AEs.
- These findings were consistent with previous data in the global population from LIBRETTO-001,[2] suggesting that selpercatinib is a promising treatment option for Chinese patients with *RET*-altered thyroid cancer.
- The first global phase 3 trial of selpercatinib versus physician choice of cabozantinib or vandetanib in kinase inhibitor-naive progressive advanced or metastatic *RET*-mutant MTC is currently underway (LIBRETTO-531; NCT04211337).

AE, adverse event; CEA, carcinoembryonic antigen; CI, confidence interval; DOR, duration of response; IRC, Independent Review Committee; MTC, medullary thyroid cancer; ORR, objective response rate; PAS, primary analysis set; PR, partial response; *RET*, rearranged during transfection; TC, thyroid cancer

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