Journal Club

Tumor-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumors other than lung or thyroid tumors

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Tumour-agnostic efficacy and safety of selpercatinib in patients with *RET* fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial

Vivek Subbiah, Jürgen Wolf, Bhavana Konda, Hyunseok Kang, Alexander Spira, Jared Weiss, Masayuki Takeda, Yuichiro Ohe, Saad Khan, Kadoaki Ohashi, Victoria Soldatenkova, Sylwia Szymczak, Loretta Sullivan, Jennifer Wright, Alexander Drilon

Summary

Background Selpercatinib is a first-in-class, highly selective RET kinase inhibitor with CNS activity that has shown efficacy in *RET* fusion-positive lung and thyroid cancers. *RET* fusions occur rarely in other tumour types. We aimed to investigate the efficacy and safety of selpercatinib in a diverse group of patients with *RET* fusion-positive non-lung or thyroid advanced solid tumours (ie, a tumour-agnostic population).

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TABLE OF CONTENTS

01
Background

Tumor-agnostic therapy

- Cancer treatment based on the cancer's genetic and molecular features without regard to the cancer type or where the cancer started in the body.
- Also called Tissue-agnostic therapy
- Basket trial

Approved tumor-agnostic drugs-1

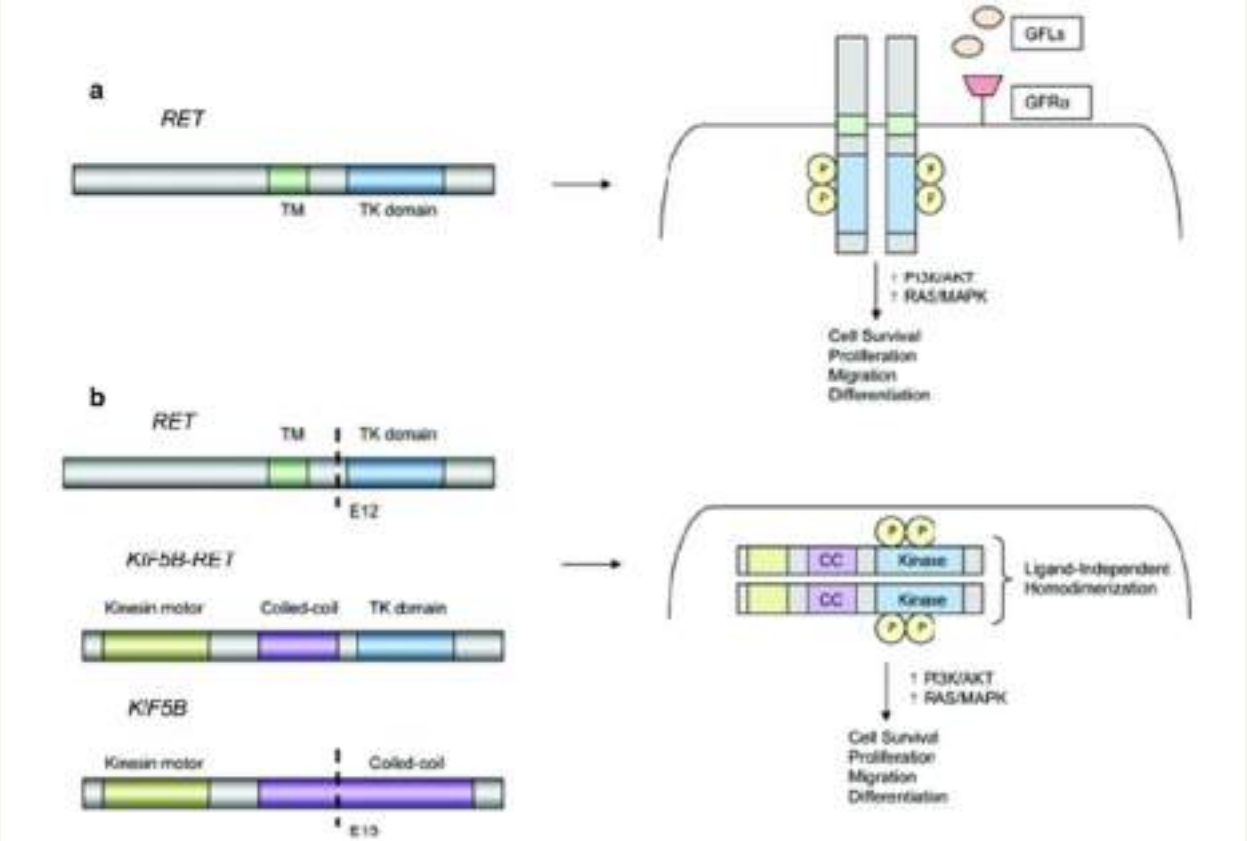
Drug	Mechanism	Indication
Larotrectinib	TRK inhibitor	Solid tumors with NTRK fusion
Entrectinib	TRK inhibitor	Solid tumors with NTRK fusion ROS1-postive NSCLC
Pembrolizumab	PD-1 inhibitor	MSI-H or dMMR cancer , TMB-H cancer Other specific types of cancer
Dostarlimab	PD-1 inhibitor	Solid tumors, recurrent or advanced, dMMR Endometrial cancer, recurrent or advanced, dMMR

MSI-H-Microsatellite instability-high
dMMR-Defective mismatch repair
TMB-H-Tumor mutation burden-high

Approved tumor-agnostic drugs-2

Drug	Mechanism	Indication
Dabrafenib	BRAF inhibitor	Melanoma, NSCLC, Solid tumors or Thyroid cancer with BRAF mutation
Trametinib	MEK inhibitor	Melanoma, NSCLC, Solid tumors or Thyroid cancer with BRAF mutation

RET fusion

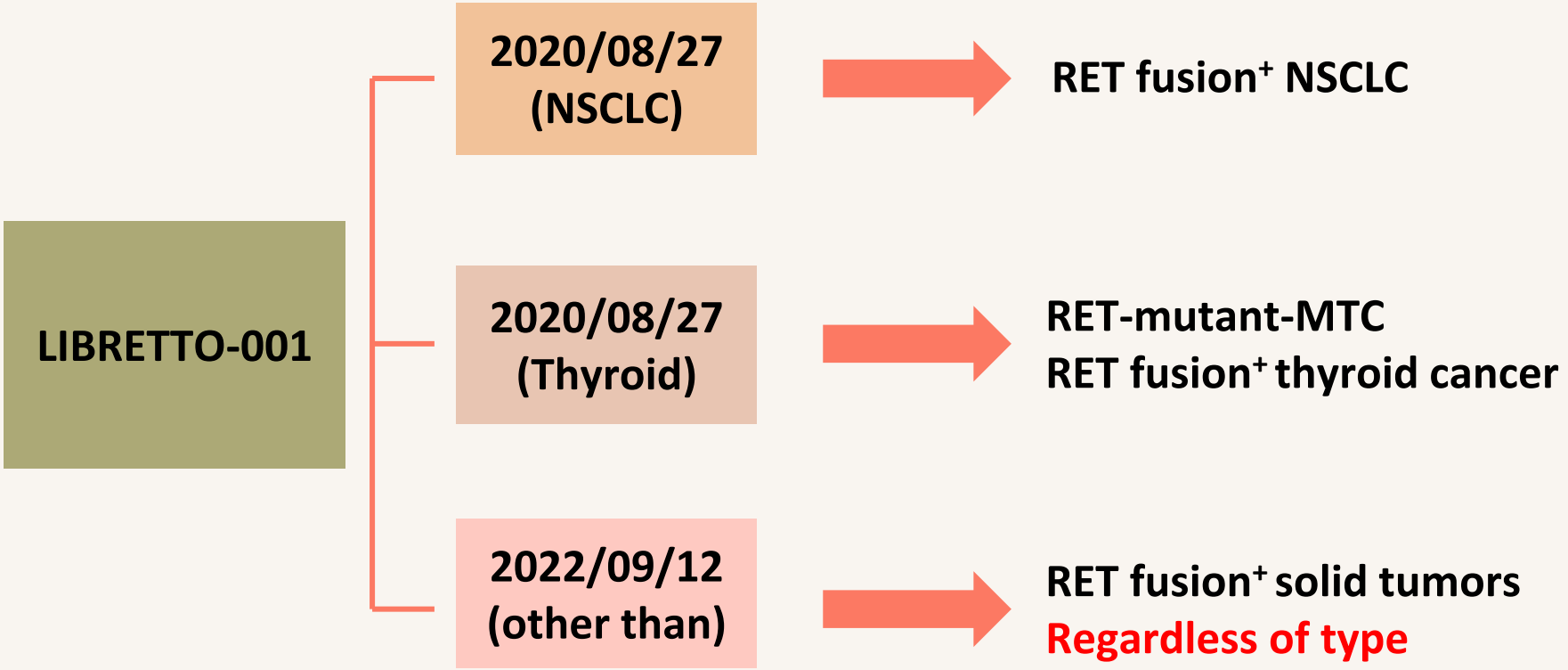


Drusbosky LM, Rodriguez E, Dawar R, Ikpeazu CV. Therapeutic strategies in RET gene rearranged non-small cell lung cancer. J Hematol Oncol.

RET inhibitor

Drug	Selpercatinib (Retevmo, 40mg/80mg)	Pralsetinib (Gavreto®, 100mg)
Indication	① Advanced RET-Driven lung and thyroid cancers — LIBRETTO-001 trial ② Adults with Advanced or Metastatic Solid Tumors with a RET gene fusion, Regardless of type (Only) — LIBRETTO-001 trial	① Adults with Metastatic RET fusion-positive NSCLC — ARROW study ② Advanced or Metastatic RET-Mutant and RET Fusion-Positive Thyroid cancers — ARROW study
Dosing	① Pts ≥ 50 kg: 160mg BID PO ② Pts < 50kg: 120mg BID PO	400mg QD PO
Significant AEs	Hepatotoxicity, Hypertension, QT prolongation Hemorrhage, Hypersensitivity, Wound healing impairment	Hepatotoxicity, Hypertension, Hemorrhage Pulmonary toxicity, Wound healing impairment
Hepatic impairment	① Mild: no dosage adjustment necessary ② Severe: 80mg BID	① Mild: no dosage adjustment necessary ② Moderate: no dosage adjustment provided

LIBRETTO-001 trial



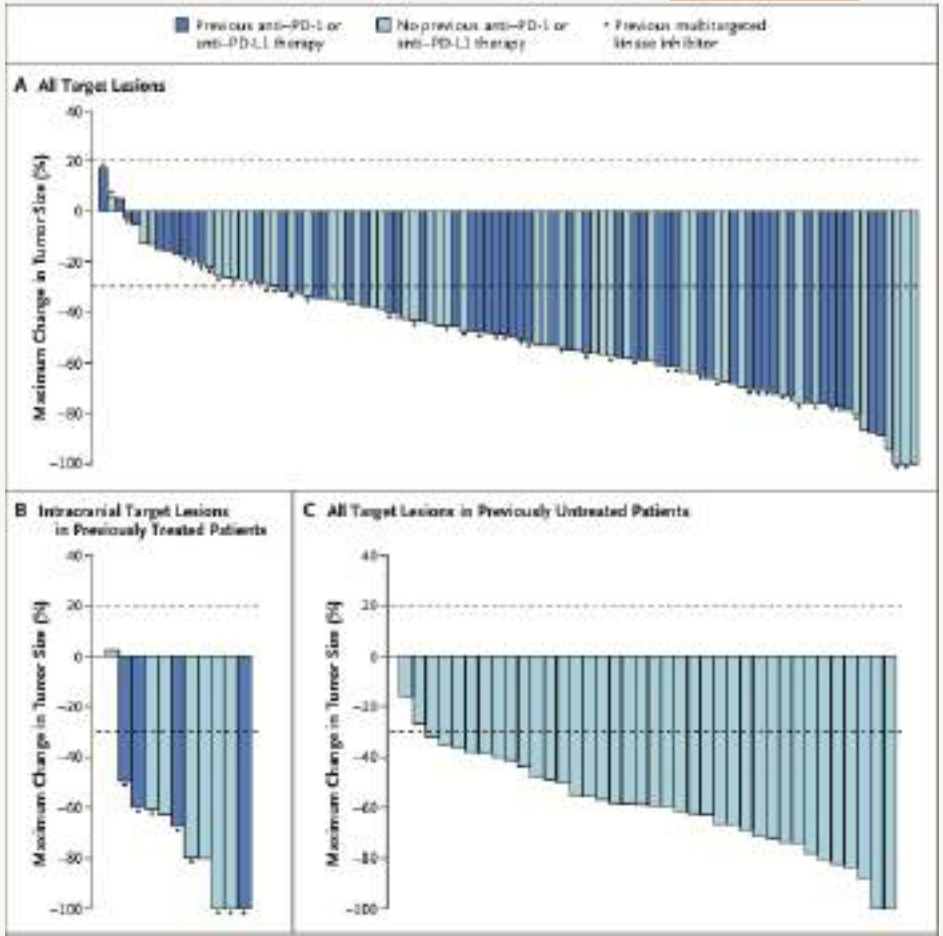
MTC-medullary thyroid cancer

LIBRETTO-001 in NSCLC

Table 2. Efficacy.[a]

Response	Previous Platinum Chemotherapy		Previously Untreated	
	Independent Review (N=105)	Investigator Assessment (N=105)	Independent Review (N=39)	Investigator Assessment (N=39)
Objective response — % (95% CI)	64 (54–73)	70 (60–78)	85 (70–94)	90 (76–97)
Best response — no. (%)				
Complete response	2 (2)	2 (2)	0	1 (3)
Partial response	65 (62)	71 (68)	33 (85)	34 (87)†
Stable disease	30 (29)	25 (24)	4 (10)	2 (5)
Progressive disease	4 (4)	2 (2)	1 (3)	1 (3)
Could not be evaluated	4 (4)	5 (5)	1 (3)	1 (3)
Duration of response				
Patients with a response — no.	67	73	33	33‡
Patients with censored data — no./total no. (%)	44/67 (66)	45/73 (62)	26/33 (79)	26/33 (79)
Median duration of response — mo (95% CI)	17.5 (12.0–NE)	20.3 (15.6–24.0)	NE (12.0–NE)	NE (12.0–NE)
Median follow-up — mo	12.1	14.8	7.4	7.4
Progression-free survival				
Patients with censored data — no. (%)	61 (58)	58 (55)	30 (77)	30 (77)
Median progression-free survival — mo (95% CI)	16.5 (13.7–NE)	18.4 (16.4–24.8)	NE (13.8–NE)	NE (13.8–NE)
Median follow-up — mo	13.9	16.4	9.2	9.2
1-yr progression-free survival — % (95% CI)	66 (55–74)	68 (58–76)	75 (56–87)	75 (55–87)

LIBRETTO-001 in NSCLC



Progressive disease

Partial response

RET fusion % in different cancer type

Cancer type	% of patients with RET fusion-positive
NSCLC	1~2%
Thyroid Cancer	5~10%
Others (Ex. breast, colon, ovary, prostate, pancreas)	<1%

RET fusion % in different cancer type

Cancer type	% of patients with RET fusion-positive
NSCLC	1~2%
Thyroid Cancer	5~10%

Tumour-agnostic efficacy and safety of selpercatinib in patients with *RET* fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial

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02
Methods

LIBRETTO-001 Phase 1

Open-label, Multi-center
Phase1/2 study

Inclusion/Exclusion Criteria:

- **Locally advanced or metastatic solid tumor**

(With or Without RET gene alteration)

- **≥ 18 yrs**
- **ECOG status 0, 1 or 2**
- **Life expectancy ≥ 3 months**
- ✓ **Prior MKIs with Anti-RET activity allowed**
- ✕ **Prior selective RET inhibitor prohibited**

Primary Endpoint:

① MTD
② RP2D

Secondary Endpoint:

① Frequency, severity, and relatedness of TEAEs and SAEs
② PK parameters of selpercatinib
③ ORR based on RECIST 1.1 or RANO, as appropriate to tumor type

MTD-Maximum tolerated dose
RP2D-Recommended Phase 2 dose
ORR-Objective response rate
RECIST-Response Evaluation in Solid Tumors
RANO-Response Assessment in Neuro-Oncology

LIBRETTO-001 Phase 1

Table 1: Actual Dose Escalations for Selpercatinib

Level	Dose	Frequency	Total Daily Dose
1	20 mg	QD	20 mg
2	20 mg	BID	40 mg
3	40 mg		80 mg
4	60 mg		120 mg
5	80 mg		160 mg
6	120 mg		240 mg
7	160 mg		320 mg
8	240 mg		480 mg
9	200 mg		400 mg
Additional potential doses			
10 and higher	Per SRC	TBD	TBD

Abbreviations: BID-twice daily; mg-milligram; QD-once daily; SRC-Safety Review Committee; TBD-to be determined.

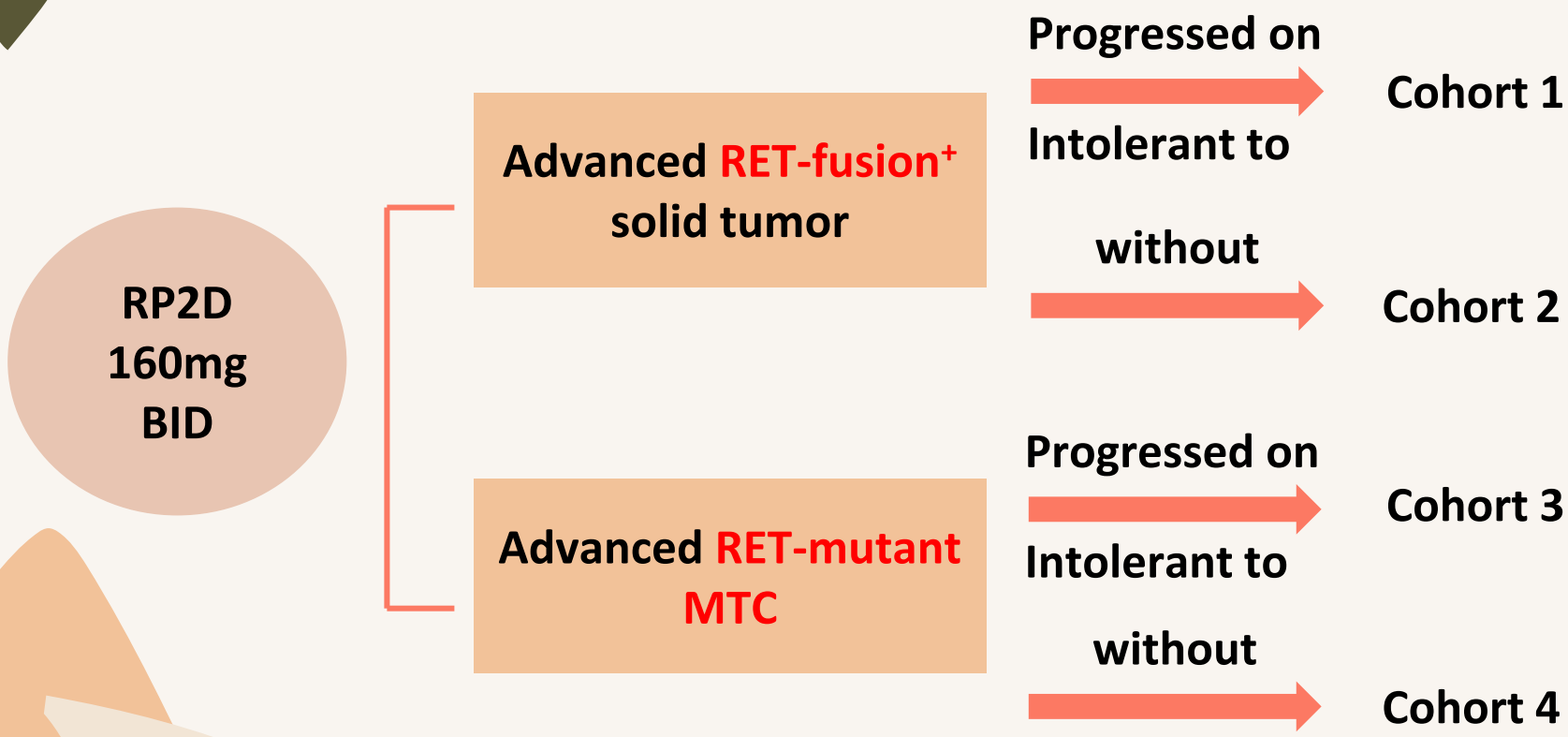
X2

→ **Starting dose**

- BID based on preclinical data
- 3+3 design
- Cycle length: 28 days

→ RP2D: 160mg BID

LIBRETTO-001 Phase 2



MTC-medullary thyroid cancer

LIBRETTO-001 Phase 2

RP2D
160mg
BID

Cohort 5:

- Cohorts 1-4, disease not measurable
- MTC not eligible for Cohort 3 or 4
- MTC syndrome spectrum cancers
- cfDNA^{+} but RET alteration not present in tumor sample

Cohort 6:

Patients not eligible for Cohorts 1-5

＊discontinue another selective RET inhibitor(s) due to intolerance

MTC-medullary thyroid cancer
cfDNA-cell free DNA

LIBRETTO-001 Phase 2

Inclusion/Exclusion Criteria

(same as phase 1, with following modifications):

- ■ Cohorts 1-4: patients with **evidence of a RET gene alteration** in tumor
- ■ Cohorts 1-4: at least one **measurable lesion**
- ✕ Cohorts 1-4: **oncogenic driver** → cause resistance to selpercatinib
- ✕ Prior therapy **≤ 5 half-lives or 2 weeks**

Trial Outcomes

Primary Endpoint:

① Objective response rate*

Secondary Endpoint:

① Objective response rate✦
② Clinical benefit rate
③ Duration of response
④ Time to any and best response
⑤ Progression-free survial
⑥ Overall survival
⑦ Safety
⑧ CNS ORR, CNS DOR

*-by independent review committee
✦-by investigator
ORR-Objective response rate
DOR-Duration of response

Statistical Analysis

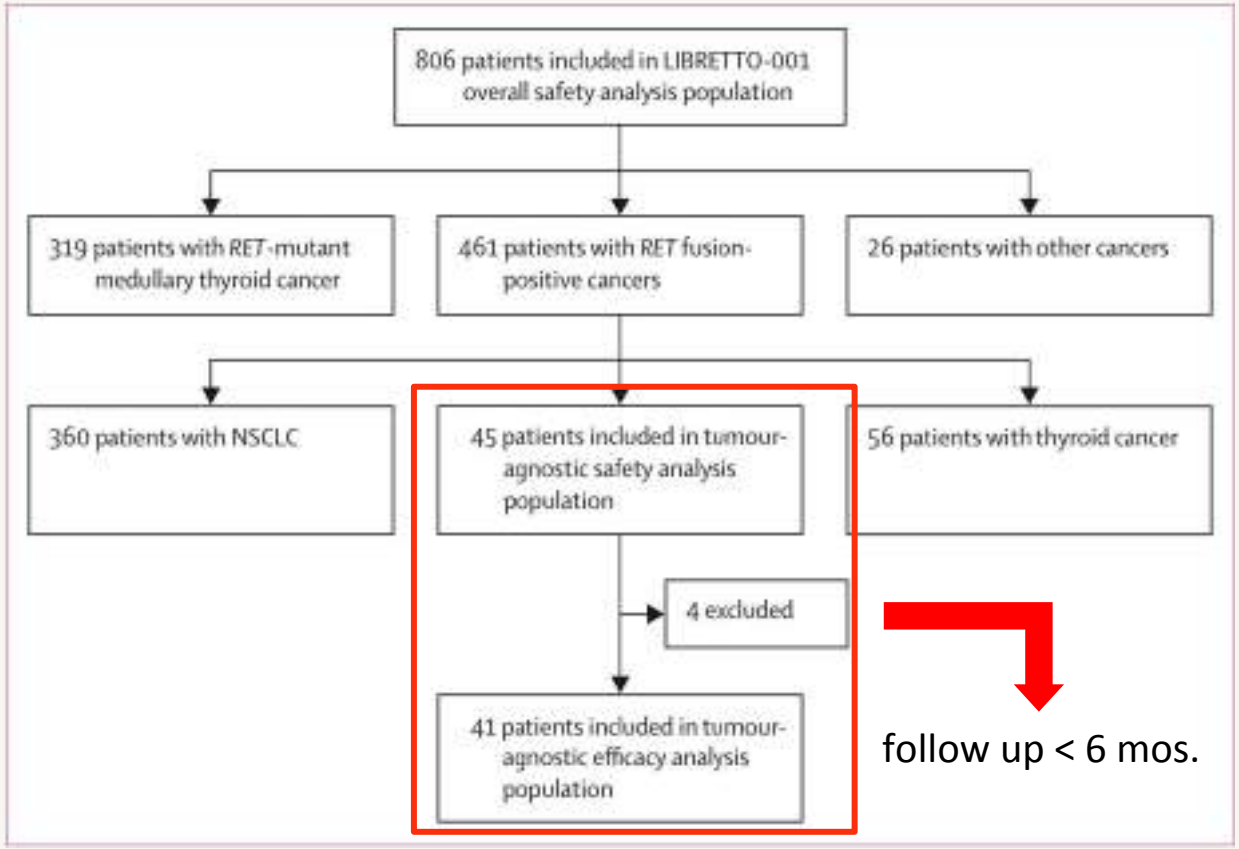
- 40 patients sample size → 79% power
- Efficacy-evaluable: at least 6 months of follow-up
- Safety-evaluable: received selpercatinib before cut off
- 95% CI Response rate: Clopper-Pearson Method
- Time-to-event: Kaplan-Meier method
- **$\alpha = 0.05$**
- Intra-patient sensitivity analysis, McNemar exact test
- Sankey diagram, Growth Modulation Index

Growth Modulation Index (GMI)

- Compare the best overall response between last line of prior systemic therapy and selpercatinib
- GMI = $\frac{Time\ spent\ on\ selpercatinib\ treatment}{Time\ spent\ on\ last\ pervious\ therapy}$
- GMI>1.33→ meaningful clinical activity

03
Results

Trial profile



Baseline characteristics (n=45)

	RET fusion tumour-agnostic population (n=45)
Age, years	53 (41·0–67·0)
Sex	
Female	23 (51%)
Male	22 (49%)
Race*	
White	31 (69%)
Asian	11 (24%)
Black or African American	2 (4%)
Other	1 (2%)
ECOG performance status score	
0	15 (33%)
1	27 (60%)
2	3 (7%)

Baseline characteristics (n=45)

Primary tumour diagnosis	
Pancreatic	12 (27%)
Colon	10 (22%)
Salivary	4 (9%)
Sarcoma	3 (7%)
Unknown primary	3 (7%)
Breast	2 (4%)
Carcinoma of the skin	2 (4%)
Cholangiocarcinoma	2 (4%)
Xanthogranuloma	2 (4%)
Carcinoid	1 (2%)
Ovarian	1 (2%)
Pulmonary carcinosarcoma	1 (2%)
Rectal neuroendocrine	1 (2%)
Small intestine	1 (2%)

Previous lines of systemic therapy	2·0 (1·0–3·0)
0	4 (9%)
1–2	27 (60%)
≥3	14 (31%)
Previous treatment regimen	
Chemotherapy	37 (82%)
Platinum-based chemotherapy	32 (71%)
Taxane chemotherapy	8 (18%)
Immunotherapy	7 (16%)
Anti-PD-1 or anti-PD-L1 therapy	7 (16%)
Multikinase inhibitor†	5 (11%)
Other‡	15 (33%)
Previous radiotherapy	17 (38%)
Previous surgery	27 (60%)

(Table 1 continues in next column)

Baseline characteristics (n=45)

	RET fusion tumour-agnostic population (n=45)
(Continued from previous column)	
Stage at initial diagnosis	
II	1 (2%)
III	3 (7%)
IV	38 (84%)
Missing	3 (7%)
History of metastatic disease	43 (96%)
Fusion partners§	
NCOA4	17 (38%)
CCDC6	7 (16%)
KIF5B	4 (9%)
RET gene rearrangement (FISH)	3 (7%)
Other	14 (31%)
Months since initial diagnosis (IQR)	15·6 (6·3–25·5)
Measurable disease (by investigator assessment)	40 (89%)
Measurable disease (by independent review committee)¶	36 (80%)

In 45 patients:

- **43: starting dose 160mg BID**
- **1: 160mg BID via intra-patient dose escalation**
- **1: starting dose 120mg BID (never escalated)**

Efficacy analysis (n=41)

	Independent review committee assessment	Investigator assessment
Objective response rate (95% CI)	43·9% (28·5–60·3)	43·9% (28·5–60·3)
Best response		
Complete response	2 (5%)	2 (5%)
Partial response	16 (39%)	16 (39%)
Stable disease	14 (34%)	13 (32%)
Progressive disease	3 (7%)	7 (17%)
Not evaluable	6 (15%)	3 (7%)
Duration of response (n=18)		
Median, months (95% CI)	24·5 (9·2–NE)	18·4 (9·2–NE)
Censoring	11 (61%)	9 (50%)
Median duration of follow-up, months (IQR)	14·9 (14·5–28·8)	14·9 (9·2–22·9)
Progression-free survival		
Median, months (95% CI)	13·2 (7·4–26·2)	11·1 (5·6–19·1)
Censoring	21 (51%)	17 (42%)
Median duration of follow-up, months (IQR)	16·4 (5·5–30·2)	16·6 (9·0–30·8)
1-year progression-free survival (95% CI)	53·1% (34·1–68·8)	43·1% (25·5–59·6)
2-year progression-free survival (95% CI)	32·1% (14·0–51·7)	22·4% (8·0–41·2)
Overall survival		
Median, months (95% CI)	..	18·0 (10·7–NE)
Censoring	..	23 (56%)
Median duration of follow-up, months (IQR)	..	18·8 (9·5–26·5)
1-year overall survival (95% CI)	..	66·8% (48·6–79·8)
2-year overall survival (95% CI)	..	47·4% (28·7–64·0)

Data are n (%), unless otherwise stated. Percentages might not total 100 because of rounding. NE=not evaluable.

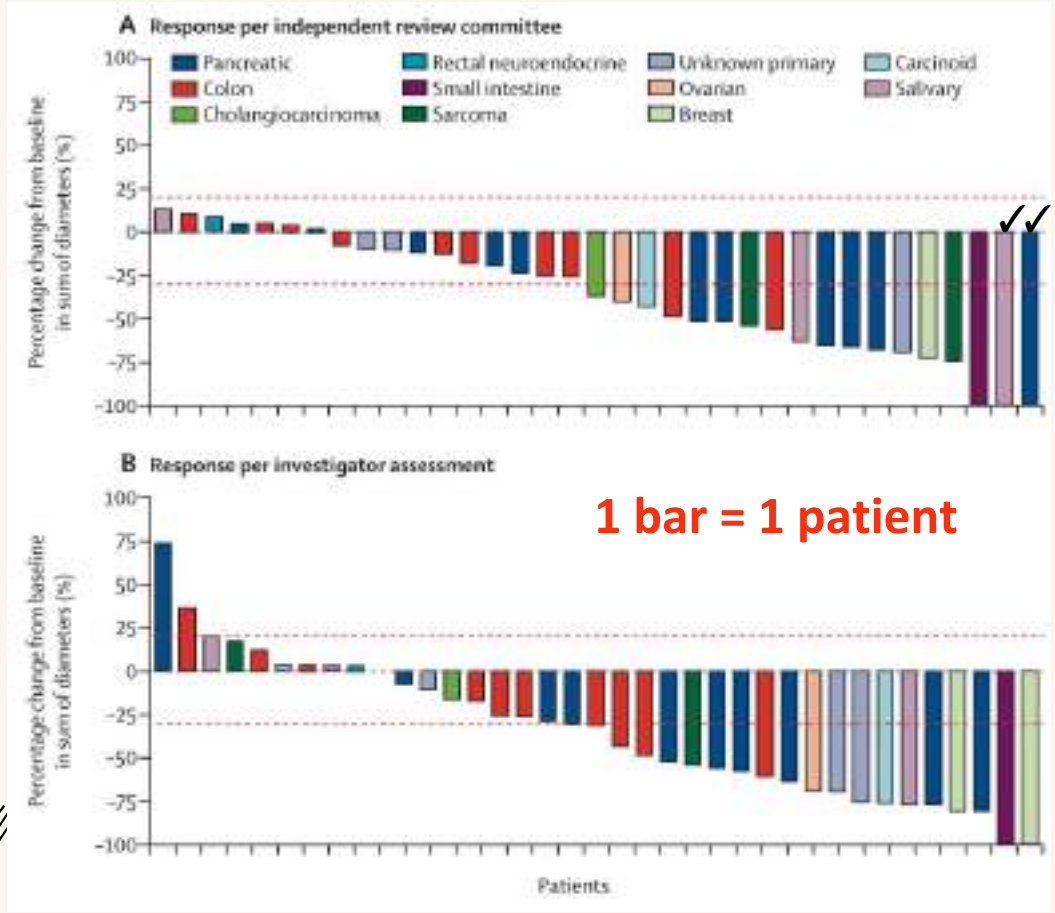
Table 2: Efficacy analysis of patients with RET fusion-positive solid tumours (n=41)

ORR= CR + PR

Better in independent review committee

CR-Complete response
PR-Partial response

Maximum change in tumor size (n=35)

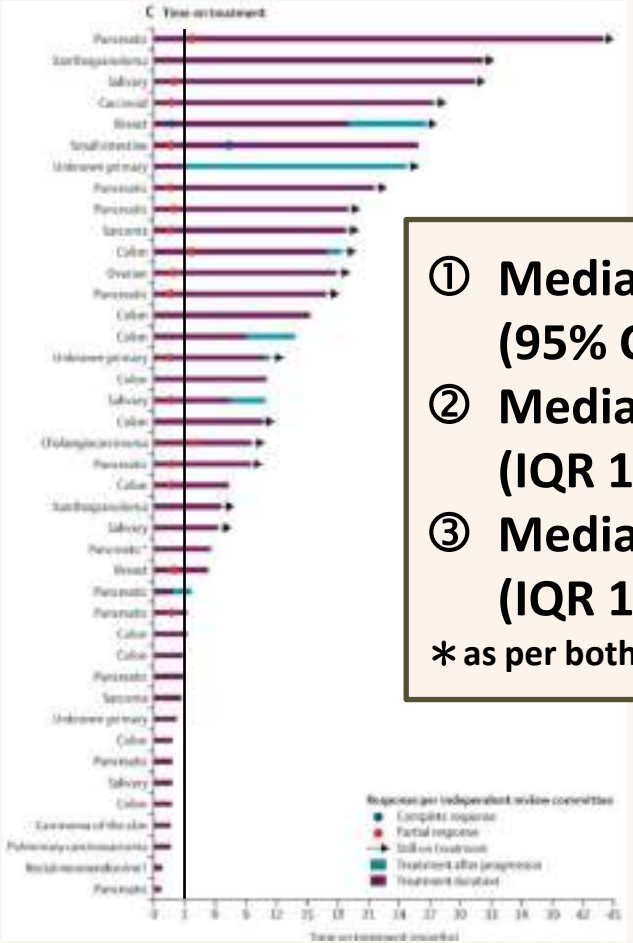


1 bar = 1 patient

Progressive disease

Partial response

Time on treatment (n=35)



① **Median duration of treatment: 11.0 months (95% CI 3.7-NE)**

② **Median time to response: 1.9 months (IQR 1.7-2.0)**

③ **Median time to best response: 1.9 months (IQR 1.8-2.0)**

＊**as per both the independent review committee and investigator**

ORR and DOR by tumour type (n=41)

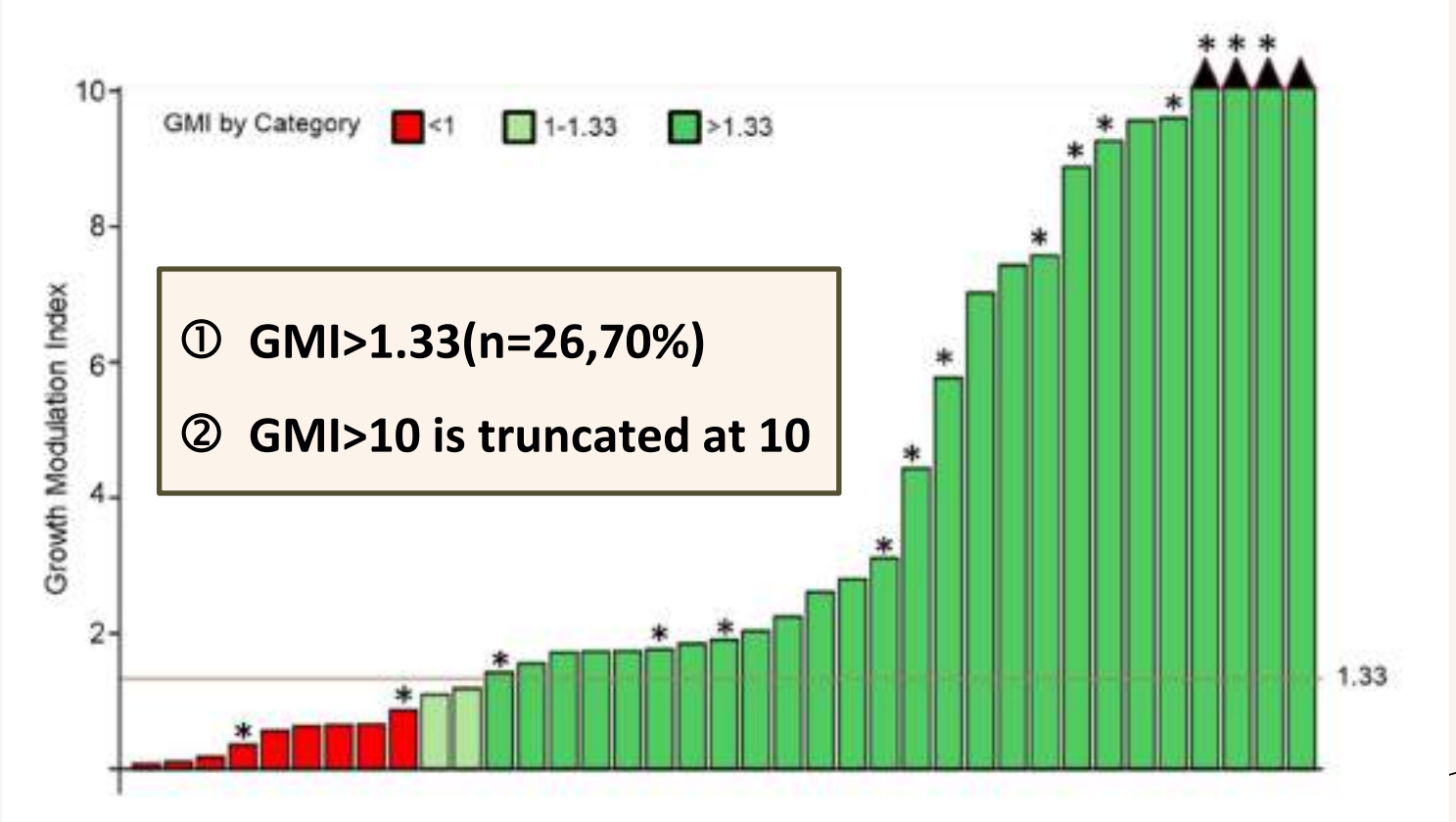
Lower response rate

	Number of patients per primary diagnosis	Independent review committee assessment		Investigator assessment	
		Objective response rate (95% CI)	Median duration of response, months (IQR)	Objective response rate (95% CI)	Median duration of response, months (IQR)
All RET fusion-positive solid tumour types	41	43·9% (28·5–60·3)	24·5 (9·2–NR)	43·9% (28·5–60·3)	18·4 (9·8–22·6)
Pancreatic	11	54·5% (23·4–83·3)	NR (NR–NR)	55·5% (23·4–83·3)	NR (12·0–NR)
Colon	10	20·0% (2·5–55·6)	9·4 (5·6–13·3)	30·0% (6·7–65·3)	9·2 (3·7–9·8)
Salivary	4	50·0% (6·8–93·2)	NR (5·7–NR)	25·0% (0·6–80·6)	5·7 (5·7–5·7)
Unknown primary	3	33·3% (0·8–90·6)	9·2–9·2	33·3% (0·8–90·6)	9·2 (NR–NR)
Breast	2	100·0% (15·8–100·0)	17·3 (17·3–17·3)	100·0% (15·8–100·0)	18·4 (18·4–18·4)
Sarcoma	2	50·0% (1·3–98·7)	14·9 (NR–NR)	50·0% (1·3–98·7)	14·9 (NR–NR)
Xanthogranuloma*	2	NA	NA	50·0% (1·3–98·7)	22·9 (NR–NR)
Carcinoid	1	100·0% (2·5–100·0)	24·1 (NR–NR)	100·0% (2·5–100·0)	18·6 (18·6–18·6)
Ovarian	1	100·0% (2·5–100·0)	14·5 (NR–NR)	100·0% (2·5–100·0)	14·5 (NR–NR)
Small intestine	1	100·0% (2·5–100·0)	24·5 (24·5–24·5)	100·0% (2·5–100·0)	22·6 (22·6–22·6)
Cholangiocarcinoma	1	100·0% (2·5–100·0)	5·6 (NR–NR)	0% (0·0–97·5)	NA
Pulmonary carcinosarcoma	1	0% (0·0–97·5)	NA	0% (0·0–97·5)	NA
Rectal neuroendocrine	1	0% (0·0–97·5)	NA	0% (0·0–97·5)	NA
Carcinoma of the skin	1	0% (0·0–97·5)	NA	0% (0·0–97·5)	NA

NA=not applicable. NR=not reached. *Xanthogranuloma skin cancer could not be evaluated by the independent review committee because of the committee's scope of images not allowing for assessment of skin findings.

Table 3: Objective response rate and duration of response by tumour type

Growth Modulation Index (n=37)



Safety (n=45)

	Adverse events, regardless of attribution				Treatment-related adverse events	
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3
Patients with ≥1 adverse event	16 (36%)	22 (49%)	4 (9%)	3 (7%)	23 (51%)	17 (38%)
ALT increased	12 (27%)	7 (16%)	0	0	8 (18%)	7 (16%)
AST increased	11 (24%)	6 (13%)	0	0	8 (18%)	5 (11%)
Dry mouth	15 (33%)	0	0	0	13 (29%)	0
Hypertension	4 (9%)	10 (22%)	0	0	3 (7%)	6 (13%)
Abdominal pain	8 (18%)	4 (9%)	0	0	2 (4%)	0
Diarrhoea	11 (24%)	1 (2%)	0	0	5 (11%)	0
Fatigue	9 (20%)	3 (7%)	0	0	3 (7%)	3 (7%)
Constipation	10 (22%)	0	0	0	4 (9%)	0
Nausea	8 (18%)	2 (4%)	0	0	4 (9%)	0
Blood alkaline phosphatase increased	3 (7%)	4 (9%)	1 (2%)	0	4 (9%)	1 (2%)
Insomnia	8 (18%)	0	0	0	0	0
Pyrexia	8 (18%)	0	0	0	2 (4%)	0
Back pain	7 (16%)	0	0	0	2 (4%)	0
Decreased appetite	7 (16%)	0	0	0	2 (4%)	0
Dyspnoea	6 (13%)	0	0	1 (2%)	2 (4%)	0
ECG QT prolongation	6 (13%)	1 (2%)	0	0	5 (11%)	0
Headache	7 (16%)	0	0	0	1 (2%)	0
Oedema peripheral	7 (16%)	0	0	0	3 (7%)	0
Thrombocytopaenia	7 (16%)	0	0	0	5 (11%)	0
Vomiting	5 (11%)	2 (4%)	0	0	1 (2%)	0
Anaemia	4 (9%)	2 (4%)	0	0	2 (4%)	0
Blood creatinine increased	6 (13%)	0	0	0	3 (7%)	0
Hypokalaemia	5 (11%)	1 (2%)	0	0	1 (2%)	0
Hyponatraemia	2 (4%)	2 (4%)	2 (4%)	0	0	0
Leucopoenia	6 (13%)	0	0	0	4 (9%)	0
Rash	6 (13%)	0	0	0	2 (4%)	0
Weight increased	6 (13%)	0	0	0	2 (4%)	0
Arthralgia	5 (11%)	0	0	0	2 (4%)	0
Blood bilirubin increased	3 (7%)	2 (4%)	0	0	2 (4%)	1 (2%)
Cough	5 (11%)	0	0	0	0	0
Gastroesophageal reflux disease	5 (11%)	0	0	0	2 (4%)	0
Lymphopenia	4 (9%)	1 (2%)	0	0	2 (4%)	0
Pruritus	5 (11%)	0	0	0	1 (2%)	0
Acute kidney injury	1 (2%)	1 (2%)	0	0	NA	NA
Blood lactate dehydrogenase increased	1 (2%)	1 (2%)	0	0	1 (2%)	1 (2%)
Drug-induced liver injury	1 (2%)	1 (2%)	0	0	1 (2%)	1 (2%)
Neutropenia	1 (2%)	2 (4%)	0	0	0	2 (4%)
Proteinuria	2 (4%)	1 (2%)	0	0	1 (2%)	1 (2%)
Chronic kidney disease	0	1 (2%)	0	0	0	1 (2%)
Hypertonia	0	1 (2%)	0	0	0	1 (2%)
Hyperuricaemia	1 (2%)	1 (2%)	0	0	0	1 (2%)
Aspiration	0	0	0	1 (2%)	NA	NA
Neoplasm progression	0	0	0	1 (2%)	NA	NA

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Headache	7 (16%)	0	0	0	1 (2%)	0
Oedema peripheral	7 (16%)	0	0	0	3 (7%)	0
Thrombocytopaenia	7 (16%)	0	0	0	5 (11%)	0

① **Permanent discontinuation in 1(2%) patients(Hepatotoxicity)**

② **Grade 5 in 3(7%) patients, with no related to treatment**

04

Discussion

① The importance of GMI
② Lower response rate of colon cancer
③ Selpercatinib versus other agents
④ Safety

The importance of Growth Modulation Index

① **Heterogeneously** pretreated patients with mixed tumor histologies

② Represent the total time on treatment

③ Real-world practice for patients with limited treatment options

ORR in different tumor type

- 24(59%) of 41 patients→ Gastrointestinal malignancy

Lower response rate

	Number of patients per primary diagnosis	Independent review committee assessment		Investigator assessment	
		Objective response rate (95% CI)	Median duration of response, months (IQR)	Objective response rate (95% CI)	Median duration of response, months (IQR)
All RET fusion-positive solid tumour types	41	43·9% (28·5–60·3)	14·5 (9·2–NR)	43·9% (28·5–60·3)	18·4 (9·8–22·6)
Pancreatic	11	54·5% (23·4–83·3)	NR (NR–NR)	55·5% (23·4–83·3)	NR (12·0–NR)
Colon	10	20·0% (2·5–55·6)	9·4 (5·6–13·3)	30·0% (6·7–65·3)	9·2 (3·7–9·8)
Salivary	4	50·0% (6·8–93·2)	NR (5·7–NR)	25·0% (0·6–80·6)	5·7 (5·7–5·7)
Unknown primary	3	33·3% (0·8–90·6)	9·2–9·2	33·3% (0·8–90·6)	9·2 (NR–NR)
Breast	2	100·0% (15·8–100·0)	17·3 (17·3–17·3)	100·0% (15·8–100·0)	18·4 (18·4–18·4)
Sarcoma	2	50·0% (1·3–98·7)	14·9 (NR–NR)	50·0% (1·3–98·7)	14·9 (NR–NR)
Xanthogranuloma*	2	NA	NA	50·0% (1·3–98·7)	22·9 (NR–NR)
Carcinoid	1	100·0% (2·5–100·0)	24·1 (NR–NR)	100·0% (2·5–100·0)	18·6 (18·6–18·6)
Ovarian	1	100·0% (2·5–100·0)	14·5 (NR–NR)	100·0% (2·5–100·0)	14·5 (NR–NR)
Small intestine	1	100·0% (2·5–100·0)	24·5 (24·5–24·5)	100·0% (2·5–100·0)	22·6 (22·6–22·6)
Cholangiocarcinoma	1	100·0% (2·5–100·0)	5·6 (NR–NR)	0% (0·0–97·5)	NA
Pulmonary carcinosarcoma	1	0% (0·0–97·5)	NA	0% (0·0–97·5)	NA
Rectal neuroendocrine	1	0% (0·0–97·5)	NA	0% (0·0–97·5)	NA
Carcinoma of the skin	1	0% (0·0–97·5)	NA	0% (0·0–97·5)	NA

NA=not applicable. NR=not reached. *Xanthogranuloma skin cancer could not be evaluated by the independent review committee because of the committee's scope of images not allowing for assessment of skin findings.

Table 3: Objective response rate and duration of response by tumour type

Colorectal cancer in other trials

	Regorafenib (CORRECT)*	Tipiracil (TAS-102) *
Median OS✦	6.4mons (HR=0.77, 95% CI 0.64-0.94, p=0.0052)	7.1mons (HR=0.68, 95% CI 0.58-0.81, p<0.001)
Median PFS✧	1.9mons (HR=0.49, 95% CI 0.42-0.58, p<0.0001)	2.0mons (HR=0.48, 95% CI 0.41-0.57, p<0.001)
ORR✧	**1.0%**	**1.6%**

∗-versus placebo
✦-primary endpoint
✧-secondary endpoint
OS-Overall Survival
PFS-Progression free Survival

Colorectal cancer in other trials

	Regorafenib (CORRECT)*	Tipiracil (TAS-102) *
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ORR✧	**1.0%**	**1.6%**

ORR Appropriate?

∗-versus placebo
✦-primary endpoint
✧-secondary endpoint
OS-Overall Survival
PFS-Progression free Survival

RET fusions in a small subset of advanced colorectal cancers at risk of being neglected

F. Pietrantonio[1,2*], F. Di Nicolantonio[3,4], A. B. Schrock[5], J. Lee[6], F. Morano[1], G. Fucà[1], P. Nikolinakos[7], A. Drilon[8], J. F. Hechtman[9], J. Christiansen[10], K. Gowen[5], G. M. Frampton[5], P. Gasparini[11], D. Rossini[12], C. Gigliotti[3,4], S. T. Kim[6], M. Prisciandaro[1], J. Hodgson[7], A. Zaniboni[13], V. K. Chiu[14], M. Milione[15], R. Patel[10], V. Miller[5], A. Bardelli[3,4], L. Novara[4], L. Wang[16], S. M. Pupa[11], G. Sozzi[11], J. Ross[5], M. Di Bartolomeo[1], A. Bertotti[3,4], S. Ali[5], L. Trusolino[3,4], A. Falcone[12], F. de Braud[1,2] & C. Cremolini[12]

Table 1. Patients' and disease characteristics according to the presence or absence of RET rearrangements

Characteristics		RET negative (*N* = 291) *N* (%)	RET rearranged (*N* = 24) *N* (%)	OR [95% CI]	*P*[a]
Sex	Male	172 (59)	10 (42)	1	0.131
	Female	119 (41)	14 (58)	2.02 [0.87–4.71]	
Age	Median (range)	60 (17–88)	66 (25–80)	–	**0.052**
	<65 years	187 (64)	10 (42)	1	**0.031**
	>65 years	104 (36)	14 (58)	2.52 [1.08–5.87]	
ECOG PS	0	143 (50)	1 (10)	1	**0.020**
	1–2	142 (50)	9 (90)	9.06 [1.13–72.48]	
	NA	6	14		
Primary tumor location	Left colon/Rectum	114/82 (39/28)	9/0 (45/0)	1	
	Right colon	93 (32)	11 (55)	2.58 [1.03–6.43]	**0.049**
	NA	2	4		
Primary tumor resected	Yes	230 (79)	10 (42)	1	**<0.001**
	No	61 (21)	14 (58)	5.28 [2.24–12.46]	
Time to metastases	Synchronous	195 (67)	19 (79)	1	
	Metachronous	96 (33)	5 (21)	0.53 [0.19–1.48]	0.262
RAS and BRAF status	BRAF mutated	26 (10)	0 (0)	–	
	RAS mutated	127 (46)	0 (0)		**<0.001**
	All wild-type	122 (44)	23 (100)		
MSI status	NA	16	0		
	MSS	185 (93)	12 (52)	1	
	MSI-high	14 (7)	11 (48)	12.1 [4.54–32.34]	**<0.001**
	NA	92	1		

All statistical tests were two-sided.

[a]*P* values were based on Fisher's exact test, χ^2, or Mann–Whitney tests, whenever appropriate.

ECOG, Eastern Cooperative Oncology Group; MSI-high, microsatellite instability-high; MSS, microsatellite-stable; NA, not available.

Statistically significant results ($P<0.05$) are highlighted in bold.

Table 2. Association of RET rearrangements and known prognostic baseline characteristics with overall survival

Characteristics		Median	N	Univariable analysis			Multivariable analysis		
				HR	95% CI	P	HR	95% CI	P
RET status	Negative	38.0	236	1	–	–	1	–	–
	Rearranged	14.0	18	4.59	3.64–32.66	**<0.001**	2.97	1.25–7.07	**0.014**
Primary tumor cation	Left colon/Rectum	42.1	203	1	–	–	–	–	–
	Right colon	27.4	99	1.56	1.17–2.3	**0.005**	1.41	0.92–2.15	0.112
Age	<65 years	36.7	195	1	–	–	1	–	–
	>65	33.4	113	1.40	1.04–2.00	**0.030**	1.00	0.65–1.53	0.995
ECOG PS	0	47.5	144	1	–	–	1	–	–
	1–2	33.3	151	1.57	1.17–2.18	**0.034**	1.87	1.24–2.84	**0.003**
Primary resection	Yes	38.9	237	1	–	–	1	–	–
	No	23.0	72	1.70	1.27–2.89	**0.002**	2.18	1.32–3.59	**0.002**
Time to resection	Metachronous	47.1	99	1	–	–	–	–	–
	Synhronous	29.7	210	1.19	0.86–1.63	0.293	–	–	–
RAS and BRAF status	BRAF mutated	18.0	26	1	–		1	–	
	RAS mutated	36.2	127	0.51	0.22–0.82	**0.054**	0.74	0.53–1.04	**0.083**
	All wild-type	38.0	140	0.64	0.33–1.07		0.80	0.50–1.08	
MSI status	MSS	42.1	193	1	–	–	1	–	–
	MSI-high	20.0	23	1.79	1.06–4.36	**0.036**	1.31	0.44–1.69	0.379

All statistical tests were two-sided.

ECOG, Eastern Cooperative Oncology Group; MSI-high, microsatellite instability-high; MSS, microsatellite-stable; NA, not available.

Statistically significant results ($P<0.05$ or $P<0.1$ at multivariable analysis) are highlighted in bold.

Comparisons with other agents' trial

	Larotrectinib	Entrectinib	Dabrafenib + trametinib
Cancer type	TRK fusion^{+} Solid tumor	NTRK fusion^{+} Solid tumor	BRAF V600E mutation Solid tumor
ORR✦	79%	57.7%/61.2%	41%
PFS✧	28.3 months [22.1-NE]	11.7/13.8 months [4.7-30.2]/[10.2-20.8]	-

Thyroid 16%
Lung 8%

Thyroid 10.7%
NSCLC 18.2%

✦-primary endpoint
✧-secondary endpoint

Selpercatinib in different cancer type

	Previously Untreated (%)		Previously treated (%)	
2020/08/27 (NSCLC)	85/90		64/70	
2020/08/27 (Thyroid)	MTC	73/71	MTC	69/62
	Non-MTC	-	Non-MTC	79/58
2022/09/12 (other than)	 43.9/43.9 **without** NSCLC and Thyroid cancer			

★**All numbers represent objective response rate**
/-independent review/investigator assessment

Safety

	Trial (n=45)	LIBRETTO-001 (n=796)
Grade 3 or worse[a]	Hypertension(22%) ALT↑(16%) AST↑(13%)	Hypertension(20%) ALT↑(11%) AST↑(8%)
Grade 5[a]	3(7%)	45(6%)
TRAEs, Grade 5	0	1(<1%)

- Similar safety profile with LIBRETTO-001
- Low percentage of Grade 5 TRAE

a-regardless of attribution
TRAEs-Treatment related adverse events

Limitations

① **Non-randomized**, single group trial with **no comparator**

② **High heterogeneous** population

③ Follow-up times **short**

05
Conclusion

Conclusion

Efficacy

① ORR 43.9%

② Target lesion regression

③ 70% Pts' GMI>1.33

Safety

① Consistent with LIBRETO-001

② Most AEs are low grade

③ TRAEs leading to discontinuation: 2%

Conclusion

Efficacy

① ORR 43.9%

② Target lesion regression

③ 70% Pts' GMI>1.33

Comprehensive Genomic Testing

Safety

① Consistent with LIBRETO-001

② Most AEs are low grade

③ TRAEs leading to discontinuation: 2%

06

Appraisal

-CASP Cohort Study Checklist

Section A:

1. Did the study address a clearly focused issue?

Methods LIBRETTO-001 is an ongoing phase 1/2, single-group, open-label, basket trial of selpercatinib in patients aged 18 years and older (or ≥12 years, where permitted by regulatory authorities) with *RET*-altered cancers. The trial is being conducted at 89 sites in 16 countries; the tumour-agnostic population was enrolled at 30 sites (outpatient and inpatient medical facilities) across eight countries. A prespecified interim analysis of LIBRETTO-001 was planned to investigate the efficacy and safety of selpercatinib in a tumour-agnostic population of patients with *RET* fusion-positive advanced solid tumours; the data cutoff date was Sept 24, 2021. Eligible patients had disease progression on or after previous systemic thera[P] o satisfactory therapeutic options and an Ea[O] operative Oncology Group performance status of 0[I] catinib was orally administered in a conti[O] day cycle. Patients enrolled in the phase 1 dose-esca[O] portion received between 20 mg once daily or [O] mg twice daily; the phase 2 recommended dose was 160 mg twice daily. The primary endpoint was the objective response rate as determined by the independent review committee. The efficacy-evaluable tumour-agnostic population was defined as patients with *RET* fusion-positive cancer, other than non-small-cell lung cancer and thyroid cancer, who had at least 6 months of foll[O] from the first study dose at the time of data cutoff (all responders at the time of data cutoff were followed up f[O] 6 months from the onset of response unless they progressed or died earlier). Safety was analysed in the [O] agnostic population of patients who had been enrolled and received selpercatinib on or before the data cutoff date. This study is registered with ClinicalTrials.gov (NCT03157128) and is still recruiting participants.

C NA

Yes Can't tell No

Section A:

2. Was the cohort recruited in an acceptable way?

Methods LIBRETTO-001 is an ongoing phase 1/2, single-group, open-label, basket trial of selpercatinib in patients aged 18 years and older (or ≥12 years, where permitted by regulatory authorities) with *RET*-altered cancers. The trial is being conducted at 89 sites in 16 countries; the tumour-agnostic population was enrolled at 30 sites (outpatient and inpatient medical facilities) across eight countries. A prespecified interim analysis of LIBRETTO-001 was planned to investigate the efficacy and safety of selpercatinib in a tumour-agnostic population of patients with *RET* fusion-positive advanced solid tumours; the data cutoff date was Sept 24, 2021. Eligible patients had disease progression on or after previous systemic therapies or no satisfactory therapeutic options and an Eastern Cooperative Oncology Group performance status of 0–2. Selpercatinib was orally administered in a continuous 28-day cycle. Patients enrolled in the phase 1 dose-escalation portion received between 20 mg once daily or 20–240 mg twice daily; the phase 2 recommended dose was 160 mg twice daily. The primary endpoint was the objective response rate as determined by the independent review committee. The efficacy-evaluable tumour-agnostic population was defined as patients with *RET* fusion-positive cancer, other than non-small-cell lung cancer and thyroid cancer, who had at least 6 months of follow-up from the first study dose at the time of data cutoff (all responders at the time of data cutoff were followed up for at least 6 months from the onset of response unless they progressed or died earlier). Safety was analysed in the tumour-agnostic population of patients who had been enrolled and received selpercatinib on or before the data cutoff date. This study is registered with ClinicalTrials.gov (NCT03157128) and is still recruiting participants.

Yes Can't tell No

Section A:

3. Was the exposure accurately measured to minimize bias?

Procedures

Selpercatinib was orally administered in a continuous 28-day cycle until disease progression, death, unacceptable toxic effects, or withdrawal of consent. Patients enrolled in the phase 1 dose-escalation cohort received between 20 mg once daily or 20–240 mg twice daily in the following doses: 20 mg, 40 mg, 60 mg, 80 mg, 120 mg, 160 mg, 200 mg, and 240 mg of selpercatinib. The phase 2 recommended dose was 160 mg twice daily. Patients who had a dose reduction (one level to 120 mg twice daily or two levels to 80 mg twice daily) due to an adverse event were permitted to re-escalate upon resolution of the adverse event. Patients with progressive disease could continue treatment per investigator discretion of perceived clinical benefit with sponsor approval.

Yes Can't tell No

Section A:

4. Was the outcome accurately measured to minimize bias?

Radiological tumour assessments were done at baseline, every 8 weeks for 1 year, and every 12 weeks thereafter. Response was determined according to RECIST 1.1, assessed by both the investigator and independent review committee. All responses required a central confirmation of radiological assessment more than 4 weeks after the initial assessment of response. Adverse events were assessed from the first dose of study drug until the safety follow-up visit, 28 days after the last selpercatinib dose. The safety review committee met regularly to review safety data, including serious adverse events, fatal adverse events, and adverse events leading to treatment discontinuation. Adverse events were graded according to Common Terminology Criteria for Adverse Events (version 4.03). Standard

Yes Can't tell No

Section A:

5.(a) Have the authors identified all important confounding factors?

- ORR versus different cancer type
- Genetic diversity
- Subgroup

Yes Can’t tell No

Section A:

5.(b) Have they taken account of the confounding factors in the design and/or analysis?

- Selection criteria: ECOG status 0-2, Life expectancy ≥ 3 mons
- Efficacy evaluable: at least 6 mons of follow up
- Subgroup
- Intra-patient sensitivity analysis, McNemar exact test
- Sankey diagram, Growth Modulation Index

 **Yes**

 Can’t tell

 No

Section A:

6.(a) Was the follow up of subjects complete enough?

Radiological tumour assessments were done at baseline, every 8 weeks for 1 year, and every 12 weeks thereafter. Response was determined according to RECIST 1.1, assessed by both the investigator and independent review committee. All responses required a central confirmation of radiological assessment more than 4 weeks after the initial assessment of response. Adverse events were assessed from the first dose of study drug until the safety follow-up visit, 28 days after the last selpercatinib dose. The safety review committee met regularly to review safety data, including serious adverse events, fatal adverse events, and adverse events leading to treatment discontinuation. Adverse events were graded according to Common Terminology Criteria for Adverse Events (version 4.03). Standard

Yes Can't tell No

Section A:

6.(b) Was the follow up of subjects long enough?

A limitation of the current study is that the patient population was derived from a non-randomised, single-group trial with no comparator. *RET* fusions are relatively rare, resulting in a heterogeneous population with a diversity of tumour types and relatively small numbers of patients with specific types of solid tumours. At this point in the study, follow-up times are also short.

Yes **Can't tell** No

Section B:

7. What are the results of this study?

	Independent review	Investigator review
ORR	43.9 [28.5-60.3]	43.9 [28.5-60.3]
DOR	24.5 [9.2-NE]	18.4 [9.2-NE]
PFS	13.2 [7.4-26.2]	11.1 [5.6-19.1]
OS	-	18.0 [10.7-NE]

ORR-Objective response rate
DOR-Duration of response
NE-not evaluable
PFS-Progression-free survival
OS-Overall Survival

Section B:

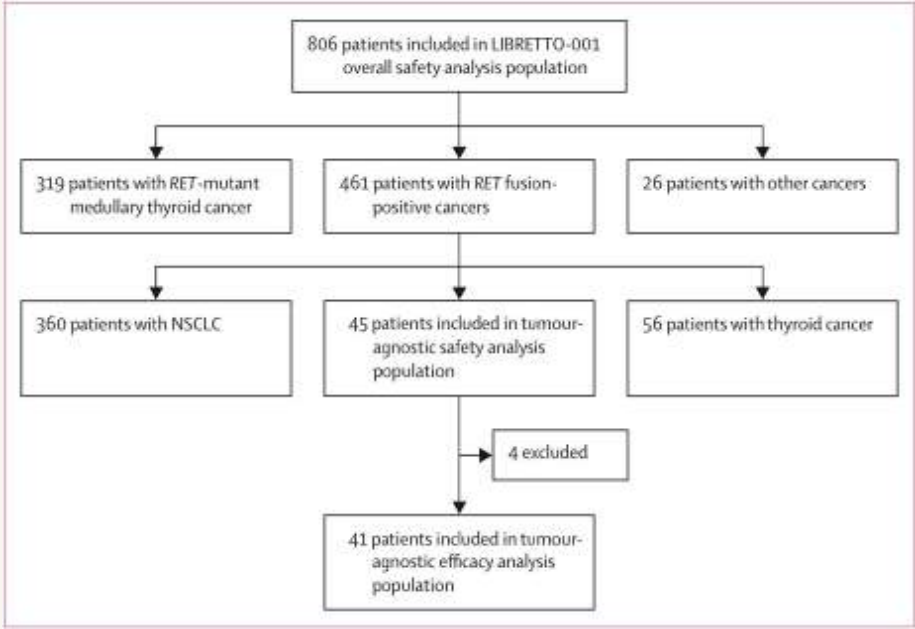
8. How precise are the results?

	Independent review	Investigator review
ORR	43.9 [28.5-60.3]	43.9 [28.5-60.3]
DOR	24.5 [9.2-NE]	18.4 [9.2-NE]
PFS	13.2 [7.4-26.2]	11.1 [5.6-19.1]
OS	-	18.0 [10.7-NE]

→ **Range of CI, Small numbers of patients**

Section B:

9. Do you believe the results?



- ➢ Random error
- X Bradford Hill criteria

Yes **Can't tell** No

Section C:

10. Can the results be applied to the local population?

	RET fusion tumour-agnostic population (n=45)
Age, years	53 (41·0–67·0)
Sex	
Female	23 (51%)
Male	22 (49%)
Race*	
White	31 (69%)
Asian	11 (24%)
Black or African American	2 (4%)
Other	1 (2%)
ECOG performance status score	
0	15 (33%)
1	27 (60%)
2	3 (7%)

Yes Can't tell No

Section C:

11. Do the results of this study fit with other available evidence ?

Selpercatinib, a highly selective RET kinase inhibitor with CNS activity,[16] was developed specifically to treat patients with *RET*-altered cancers. Selpercatinib is active preclinically in several *RET* fusion-positive models of lung, thyroid, and other cancers.[17] Consistent with the hypothesis that *RET* fusions are targetable oncogenic drivers in NSCLC and thyroid cancer, selpercatinib showed notable efficacy in both treatment-naive and pretreated populations in a phase 1/2 study in patients with *RET*-altered advanced solid tumours (LIBRETTO-001).[18–21] These data led to the global regulatory approval of selpercatinib for *RET* fusion-positive lung and thyroid cancers.[22] Concurrently, LIBRETTO-001 enrolled a tumour-agnostic population of patients with *RET* fusion-positive advanced solid tumours. Here, we report the prespecified interim efficacy analyses of this tumour-agnostic population of patients with multiple *RET* fusion-positive cancers. This analysis, as agreed upon with the US Food and Drug Administration for submission for regulatory approval, was done after

Yes Can't tell No

Section C:
12. What are the implication of this study for practice?

Interpretation Selpercatinib showed clinically meaningful activity in the *RET* fusion-positive tumour-agnostic population, with a safety profile consistent with that observed in other indications. Comprehensive genomic testing that includes *RET* fusions will be crucial for identifying patients who might benefit from selpercatinib.

- Consider use selpercatinib in RET-fusion positive solid tumors
- Comprehensive genomic testing

THANKS!

Do you have any question?