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Selpercatinib Efficacy and Safety in Patients with *RET*-Altered Thyroid Cancer: A LIBRETTO-001 Update

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BACKGROUND

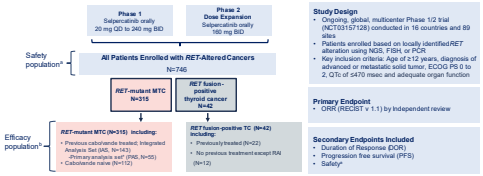
- Selpercatinib is a first-in-class, highly selective, and potent RET inhibitor[1] with CNS activity[2] approved in multiple countries for the treatment of *RET*-altered lung or thyroid cancers
- *RET* mutations are oncogenic drivers in 70% of medullary thyroid cancers (MTC)[3], and *RET*-fusions occur in differentiated thyroid cancers (TC), including up to 10% of papillary thyroid cancers[4]
- In previous analyses of selpercatinib in *RET*-altered thyroid cancers, despite a median follow-up of 14.1 and 17.5 months for previously treated MTC and TC patients, respectively, the majority of which remain progression-free and on therapy; median duration of response and progression-free survival have not yet been defined

OBJECTIVES

- Here we present updated selpercatinib efficacy and safety data from LIBRETTO-001 in patients with *RET*-altered thyroid cancers

STUDY DESIGN

The Phase 1/2 LIBRETTO-001 Trial[5]: Selpercatinib in Patients with RET-altered Cancers



[a] Safety population includes all patients who received at least one selpercatinib dose prior to March 2020 data cutoff

[b] Efficacy population includes all patients enrolled 6 months prior to data cutoff date, to allow adequate follow-up

*The primary analysis set (PAS) is a subset of the integrated analysis set (IAS) and was defined through health authority agreement as the first 55 consecutively enrolled patients with RET-mutant MTC previously treated with cabo/vande and is the more mature dataset. Patients with non-measurable disease enrolled in Phase 1 were included in the PAS.

[c] LIBRETTO-001 trial also included patients with NSCLC and RET mutant cancers, see ASCO 2021 poster 9065[s]

BASELINE CHARACTERISTICS

Characteristic	*RET*-Mutant MTC: Previously Treated (PAS; N=55)	*RET*-Mutant MTC: Cabo/vande Previously Treated (IAS; N=143)	*RET*-Mutant MTC: Cabo/vande naïve (N=112)	*RET* Fusion-Positive TC: Previously Treated (N=22)	*RET* Fusion-Positive TC: Treatment Naïve (N=12)
Median Age (range) — years	57 (17-84)	58 (17-90)	57 (15-82)	54 (25-88)	57 (20-84)
Sex — no. (%)					
Female	19 (35)	51 (36)	44 (39)	12 (55)	5 (42)
Male	36 (66)	92 (64)	68 (61)	10 (46)	7 (58)
Race — no. (%)[a]					
White	49 (89)	128 (90)	97 (87)	16 (73)	9 (75)
Asian	0 (0)	2 (1)	6 (5)	2 (9)	0 (0)
Black	1 (2)	2 (1)	1 (1)	2 (9)	0 (0)
ECOG PS score — no. (%)[b]					
0	11 (20)	37 (26)	56 (50)	7 (32)	5 (42)
1	41 (75)	95 (66)	53 (47)	13 (59)	6 (50)
2	3 (6)	11 (8)	3 (3)	2 (9)	1 (8)
Prior systemic regimens					
Median	2	2	0	4	2
Range	1-8	1-8	0-2	1-7	0-4
Prior Systemic Therapy					
Multitargeted kinase inhibitor therapy [c]	55 (100)	143 (100)	7 (6)	18 (82)	0 (0)
Radioiodine	0 (0)	0 (0)	1 (1)	18 (82)	11 (92)
Anti-PD1/PD-L1 therapy	8 (15)	11 (8)	4 (4)	3 (14)	0 (0)
Disease Stage at Study Entry					
Metastatic	54 (98)	141 (99)	112 (100)	22 (100)	12 (100)

Percentages may add up to greater than 100 due to rounding. [a]Race was reported by the patients. Other races included American Indian or Alaska Native among others (MTC: n=5 [PAS]; n=11 [IAS]; n=8 [cabo/vande naïve]; TC: n=2 [previously treated]; n=2 [treatment naïve]). Missing information for 1 patient (treatment naïve TC). [b]ECOG performance-status scores ranged from 0 to 5, with higher scores indicating greater disability. [c]Multitargeted kinase inhibitors administered included cabozantinib, vandetanib, lenvantinib, and others. Patients may have received more than one multitargeted kinase inhibitor. Treatment naïve *RET*-fusion positive TC are patients with no prior systemic therapy except radioiodine.

BEST OVERALL RESPONSE

Response	*RET*-Mutant MTC: Previously Treated (PAS; N=55)	*RET*-Mutant MTC: Cabo/vande Previously Treated (IAS; N=143)	*RET*-Mutant MTC: Cabo/vande naïve (N=112)	*RET* Fusion-Positive TC: Previously Treated (N=22)	*RET* Fusion-Positive TC: Treatment Naïve (N=12)
Objective response rate by IRC — % (95% CI)	69 (55-81)	69 (61-77)	71 (62-80)	77 (55-92)	92 (62-100)
Best response — no. (%)					
Complete response	6 (11)	6 (4)	10 (9)	2 (9)	4 (33)
Partial response	32 (58)	93 (65)	70 (63)	15 (68)	7 (58)
Stable disease	14 (26)	35 (25)	28 (25)	5 (23)	1 (8)
Duration of response					
Median duration of response — mo (95% CI)	NE (19-NE)	NE (19-NE)	22 (22-NE)	18 (10-NE)	NE (15-NE)
Censoring rate, no. (%)	29 (76)	81 (82)	75 (94)	9 (53)	10 (91)
Median follow -up — mo	17.5	10.1	9.3	20.3	9.1
1-yr progression -free survival — % (95% CI)	82 (69-90)	77 (68-84)	93 (85-97)	69 (43-85)	100 (100 - 100)

Percentages may not total 100 because of rounding. Abbreviations: NE, could not be evaluated; IRC, independent review committee; IAS, integrated analysis set; no, number; mo, months; CI, confidence interval; PAS, primary analysis set.

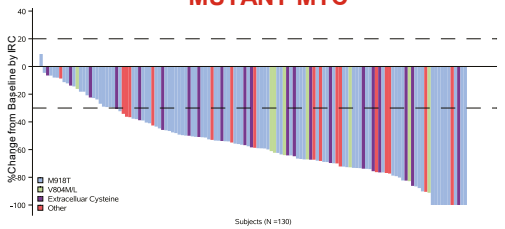
ADVERSE EVENTS

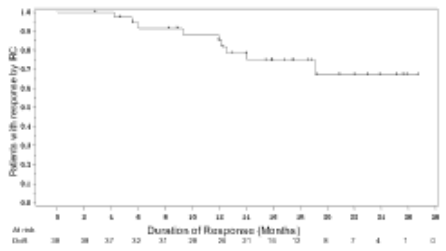
- A total of 2% of patients discontinued selpercatinib due to a treatment related AE

All Patients Enrolled with *RET*-altered Cancers (N=746)	Any causality: Grade 1	Grade 2	Grade 3	Grade 4	Any Grade[s]	Related to treatment: Grade 3	Grade 4	Any Grade*
Patients with ≥1 AE	52 (7)	218 (29)	385 (52)	60 (8)	740 (99)	222 (30)	17 (2)	690 (92)
Dry mouth	266 (36)	34 (5)	0 (0)	0 (0)	300 (40)	0 (0)	0 (0)	265 (36)
Diarrhea	196 (26)	67 (9)	26 (3)	0 (0)	289 (39)	12 (2)	0 (0)	163 (22)
Hypertension	29 (4)	101 (14)	142 (19)	1 (0.1)	273 (37)	92 (12)	1 (0.1)	190 (25)
Increased ALT	127 (17)	43 (6)	66 (9)	7 (0.9)	243 (33)	54 (7)	6 (0.8)	197 (26)
Increased AST	140 (19)	41 (5)	56 (8)	6 (0.8)	243 (33)	42 (6)	5 (0.7)	196 (26)
Fatigue	138 (18)	84 (11)	11 (1)	0 (0)	233 (31)	8 (1)	0 (0)	144 (19)
Constipation	161 (22)	36 (5)	4 (0.5)	0 (0)	202 (27)	2 (0.3)	0 (0)	97 (13)
Peripheral Edema	163 (22)	27 (4)	2 (0.3)	0 (0)	192 (26)	0 (0)	0 (0)	108 (14)
Headache	131 (18)	34 (5)	11 (1)	0 (0)	176 (24)	3 (0.4)	0 (0)	65 (9)
Nausea	133 (18)	37 (5)	5 (0.7)	0 (0)	175 (23)	2 (0.3)	0 (0)	75 (10)
Increased blood creatinine level	121 (16)	32 (4)	0 (0)	1 (0.1)	154 (21)	0 (0)	0 (0)	88 (12)
Abdominal pain	106 (14)	28 (4)	14 (2)	0 (0)	148 (20)	1 (0.1)	0 (0)	45 (6)
Rash	109 (15)	28 (4)	3 (0.4)	0 (0)	140 (19)	3 (0.4)	0 (0)	87 (12)
QT interval prolonged on electro - cardiograph	50 (7)	53 (7)	30 (4)	0 (0)	133 (18)	21 (3)	0 (0)	103 (14)
Cough	101 (14)	20 (3)	0 (0)	0 (0)	121 (16)	0 (0)	0 (0)	9 (1)
Vomiting	91 (12)	23 (3)	7 (0.9)	0 (0)	121 (16)	1 (0.1)	0 (0)	32 (4)
Dyspnoea	68 (9)	28 (4)	17 (2)	2 (0.3)	115 (15)	0 (0)	0 (0)	13 (2)

Safety population (N=746) included all patients with *RET*-altered cancers (includes RET-mutant MTC and *RET*-fusion positive non-small cell lung cancer). [s]In total, 25 of 746 patients had grade 5 TEAEs. *No grade 5 TRAEs were observed. TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events. Safety among the 315 patients with thyroid cancer was consistent with the safety of the overall population.

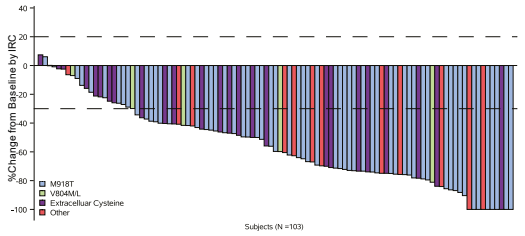
PREVIOUS CABO/VANDE TREATED *RET*-MUTANT MTC

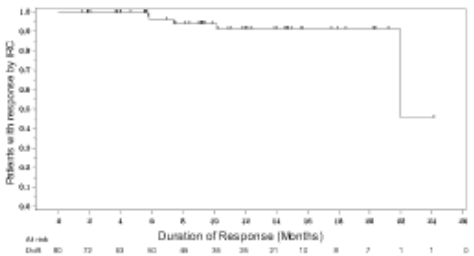




13 previously treated subjects with MTC are not included because they have non target lesion only or do not have post baseline target lesion measurement based on IRC. Baseline is defined as the last available measurement prior to the first dose of selpercatinib. Duration of response graph is based on the PAS population, a subset of the IAS, which is the more mature dataset. The waterfall plot for PAS is available in the supplement via the QR code. Abbreviations: cabo/vande, cabozantinib and/or vandetanib; Integrated Analysis Set, IAS; Primary analysis set, PAS.

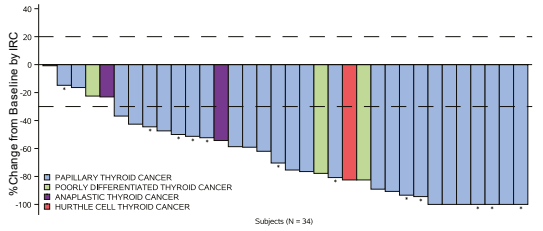
CABO/VANDE NAÏVE *RET*-MUTANT MTC

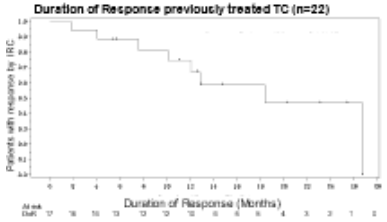


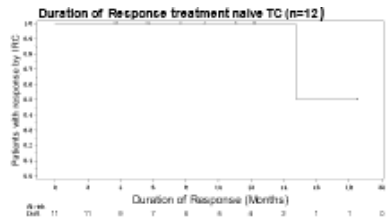


9 cabo/vande treatment naïve subjects are not included because they have non target lesion only or do not have post baseline target lesion measurement based on IRC. Baseline is defined as the last available measurement prior to the first dose selpercatinib. Although a median was estimated, the estimate is not reliable because it can be attributed to a single late event. Therefore, the median should be interpreted as NE/ Abbreviations: cabo/vande, cabozantinib and/or vandetanib; TC, thyroid cancer, Integrated Analysis Set, IAS; Primary analysis set, PAS. Not estimable, NE.

RET-FUSION POSITIVE THYROID CANCER







*Treatment naïve *RET*-fusion positive TC are patients with no prior systemic therapy except radioiodine.

Abbreviations: cabo/vande, cabozantinib and/or vandetanib; TC, thyroid cancer, Integrated Analysis Set, IAS; Primary analysis set, PAS.

CONCLUSIONS

- **Selpercatinib continues to demonstrate robust and durable efficacy in *RET*-altered thyroid cancer**
  - *RET*-mutant MTC:
    - ORR by IRC 69% in patients with previous cabozantinib and/or vandetanib treatment (PAS population)
      - At a median follow-up of 17.5 months, 76% of responses are ongoing and thus a stable median cannot yet be estimated
    - ORR by IRC 71% in patients who were treatment-naïve
      - At a median follow-up of 9.3 months, 94% of responses are ongoing
  - *RET*-fusion positive TC
    - ORR by IRC 77% in patients previously treated
      - At a median follow-up of 20.3 months, 53% of responses are ongoing
    - ORR by IRC 92% treatment naïve patients (except RAI)
      - At a median follow-up of 9.1 months, 91% of responses are ongoing
- **Selpercatinib continues to be well-tolerated with a safety profile consistent to previous reports**
  - Most adverse events were low-grade and included dry mouth, diarrhea, hypertension, increased ALT/AST, peripheral edema, and fatigue
- **This trial update provides larger supportive analysis sets and a longer follow-up than previously reported**
- **LIBRETTO-001 study (NCT03157128) is still enrolling patients with RET fusion-positive non-lung cancers**
- **A global, randomized, phase 3 trial (LIBRETTO-531; NCT04211337) evaluating selpercatinib compared with standard frontline therapy in MTC is ongoing**

References:
[1]Subbiah V, et al, Ann Oncol 2018.
[2] Subbiah V, et al., JCO, 2020.
[3]Ciampi, R., et al, iScience 2019
[4]Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. Cell 2014;
[5]Wirth, L. et al., NEJM 2020.
[s] Besse B. et al.,: Updated Overall Efficacy and Safety of Selpercatinib in Patients with RET Fusion-Positive Non-Small-Cell Lung Cancer (NSCLC): LIBRETTO-001 Study. ASCO 2021., Poster 9065

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Background and Objectives

- Selpercatinib is a first-in-class, highly selective, and potent RET kinase inhibitor[1] with CNS activity[2], approved in multiple countries for the treatment of *RET*-altered lung or thyroid cancers
- *RET* mutations are oncogenic drivers in 70% of medullary thyroid cancers (MTC)[3], and *RET*-fusions occur in differentiated thyroid cancers (TC), including up to 10% of papillary thyroid cancers[4]
- In previous analyses of selpercatinib in *RET*-altered thyroid cancers, despite a median follow-up of 14.1 and 17.5 months for previously treated MTC and TC patients, respectively, the majority of which remain progression-free and on therapy; median duration of response and progression-free survival have not yet been defined

OBJECTIVES

- Here we present updated selpercatinib efficacy and safety data from LIBRETTO-001 in patients with *RET*-altered thyroid cancers

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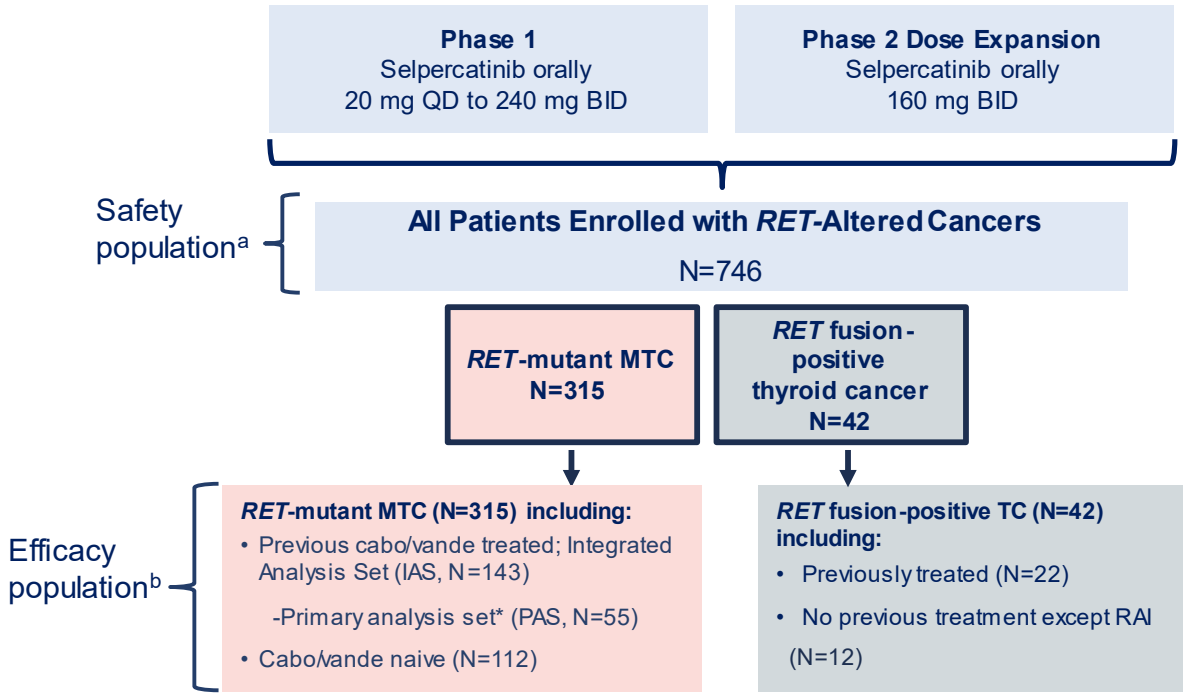
Study Design

The Phase 1/2 LIBRETTO-001 Trial[6]: Selpercatinib in Patients with RET-altered Cancers



Study Design
- Ongoing, global, multicenter Phase 1/2 trial (NCT03157128) conducted in 16 countries and 89 sites
- Patients enrolled based on locally identified *RET* alteration using NGS, FISH, or PCR
- Key inclusion criteria: Diagnosis of advanced or metastatic solid tumor, ECOG PS 0 to 2, QTc of ≤470 msec and adequate organ function

Primary Endpoint
- ORR (RECIST v 1.1) by Independent review

Secondary Endpoints Included
- Duration of Response (DOR)
- Progression free survival (PFS)
- Safety[a]

[a] Safety population includes all patients who received at least one selpercatinib dose prior to March 2020 data cutoff

[b] Efficacy population includes all patients enrolled 6 months prior to data cutoff date, to allow adequate follow-up

*The primary analysis set (PAS) is a subset of the integrated analysis set (IAS) and was defined through health authority agreement as the first 55 consecutively enrolled patients with RET-mutant MTC previously treated with cabo/vande and is the more mature dataset. Patients with non-measurable disease enrolled in Phase 1 were included in the PAS.

[6] LIBRETTO-001 trial also included patients with NSCLC, see ASCO 2021 poster 9065[6]

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Baseline Characteristics

Characteristic	*RET*-Mutant MTC			*RET* Fusion-Positive TC	
	Previously Treated (PAS; N=55)	Cabo/vande Previously Treated (IAS; N=143)	Cabo/vande naive (N=112)	Previously Treated (N=22)	Treatment Naive (N=12)
Median Age (range) — years	57 (17-84)	58 (17-90)	57 (15-82)	54 (25-88)	57 (20-84)
Sex — no. (%)					
Female	19 (35)	51 (36)	44 (39)	12 (55)	5 (42)
Male	36 (66)	92 (64)	68 (61)	10 (46)	7 (58)
Race — no. (%)[a]					
White	49 (89)	128 (90)	97 (87)	16 (73)	9 (75)
Asian	0 (0)	2 (1)	6 (5)	2 (9)	0 (0)
Black	1 (2)	2 (1)	1 (1)	2 (9)	0 (0)
ECOG PS score — no. (%)[b]					
0	11 (20)	37 (26)	56 (50)	7 (32)	5 (42)
1	41 (75)	95 (66)	53 (47)	13 (59)	6 (50)
2	3 (6)	11 (8)	3 (3)	2 (9)	1 (8)
Prior systemic regimens					
Median	2	2	0	4	2
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Metastatic	54 (98)	141 (99)	112 (100)	22 (100)	12 (100)

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Best Overall Response

	RET-Mutant MTC			*RET* Fusion-Positive TC	
Response	Previously Treated (PAS; N=55)	Cabo/vande Previously Treated (IAS; N=143)	Cabo/vande naive (N=112)	Previously Treated (N=22)	Treatment Naive (N=12)
Objective response rate by IRC — % (95% CI)	69 (55-81)	69 (61-77)	71 (62-80)	77 (55-92)	92 (62-100)
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Partial response	32 (58)	93 (65)	70 (63)	15 (68)	7 (58)
Stable disease	14 (26)	35 (25)	28 (25)	5 (23)	1 (8)
Duration of response					
Median duration of response — mo (95% CI)	NE (19-NE)	NE (19-NE)	22 (22-NE)	18 (10-NE)	NE (15-NE)
Censoring rate, no. (%)	29 (76)	81 (82)	75 (94)	9 (53)	10 (91)
Median follow-up — mo	17.5	10.1	9.3	20.3	9.1
1-yr progression-free survival — % (95% CI)	82 (69-90)	77 (68-84)	93 (85-97)	69 (43-85)	100 (100-100)

Percentages may not total 100 because of rounding. Abbreviations: NE, could not be evaluated; IRC, independent review committee; IAS, integrated analysis set; no, number; mo, months; CI, confidence interval; PAS, primary analysis set.

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Adverse Events

- A total of 2% of patients discontinued selpercatinib due to a treatment related AE

All Patients Enrolled with *RET*-altered Cancers (N=746)								
	Any causality					Related to treatment		
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade[§]	Grade 3	Grade 4	Any Grade*
Patients with ≥1 AE	52 (7)	218 (29)	385 (52)	60 (8)	740 (99)	222 (30)	17 (2)	690 (92)
Dry mouth	266 (36)	34 (5)	0 (0)	0 (0)	300 (40)	0 (0)	0 (0)	265 (36)
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QT interval prolonged on electro - cardiograph	50 (7)	53 (7)	30 (4)	0 (0)	133 (18)	21 (3)	0 (0)	103 (14)
Cough	101 (14)	20 (3)	0 (0)	0 (0)	121 (16)	0 (0)	0 (0)	9 (1)
Vomiting	91 (12)	23 (3)	7 (0.9)	0 (0)	121 (16)	1 (0.1)	0 (0)	32 (4)
Dyspnoea	68 (9)	28 (4)	17 (2)	2 (0.3)	115 (15)	0 (0)	0 (0)	13 (2)

Safety population (N=746) included all patients with *RET*-altered cancers (includes RET-mutant MTC and *RET*-fusion positive non-small cell lung cancer). [§]In total, 25 of 746 patients had grade 5 TEAEs. *No grade 5 TRAEs were observed. TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events. Safety among the 315 patients with thyroid cancer was consistent with the safety of the overall population.

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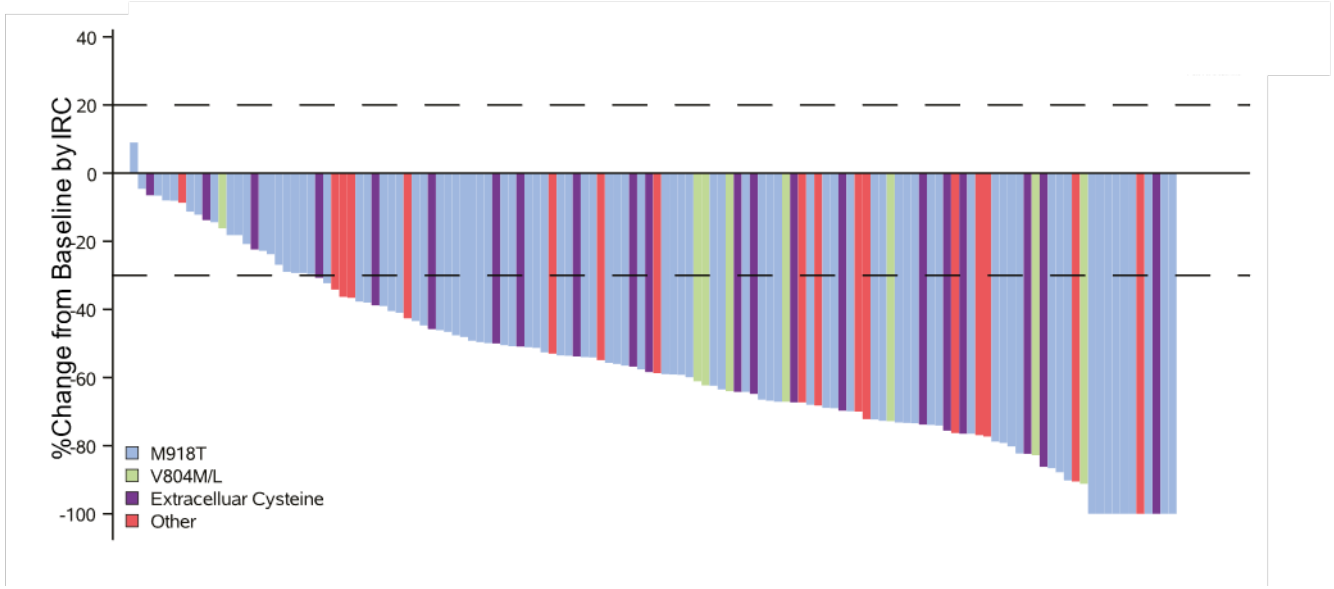
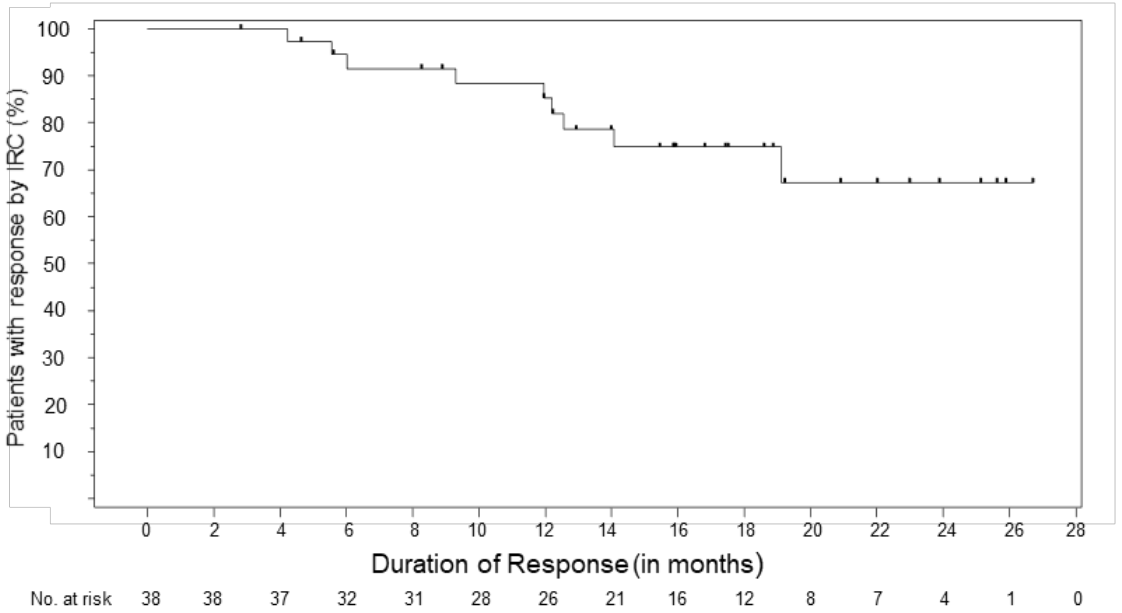
Previous Cabo/Vande Treated *RET*-mutant MTC





13 previously treated subjects with MTC are not included because they have non target lesion only or do not have post baseline target lesion measurement based on IRC. Baseline is defined as the last available measurement prior to the first dose of selpercatinib. Duration of response graph is based on the PAS population, a subset of the IAS, which is the more mature dataset. The waterfall plot for PAS is available in the supplement via the QR code. Abbreviations: cabo/vande, cabozantinib and/or vandetanib; Integrated Analysis Set, IAS; Primary analysis set, PAS.

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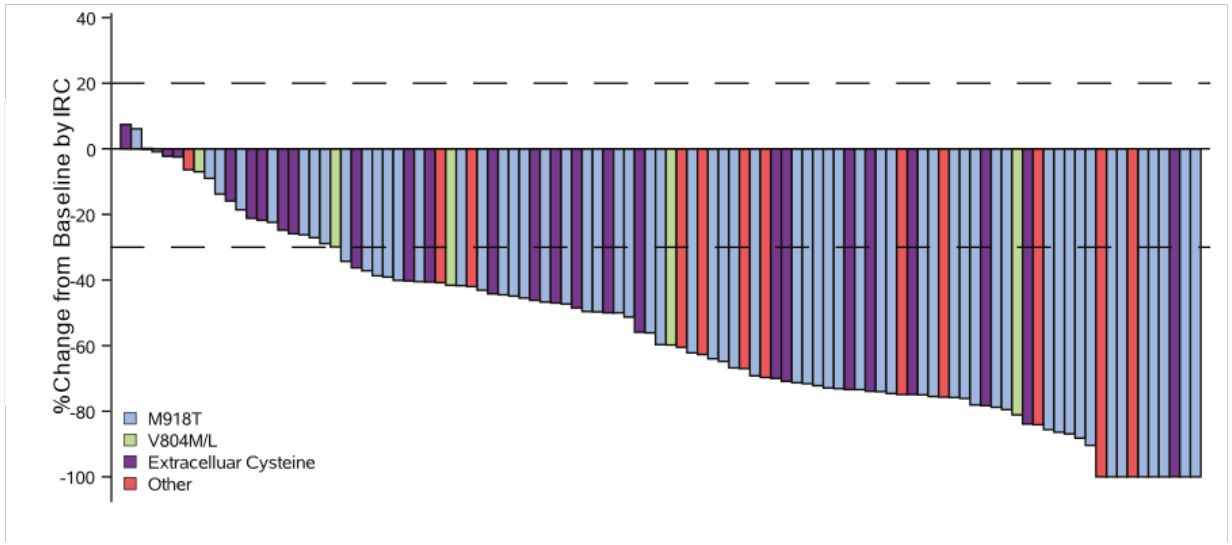
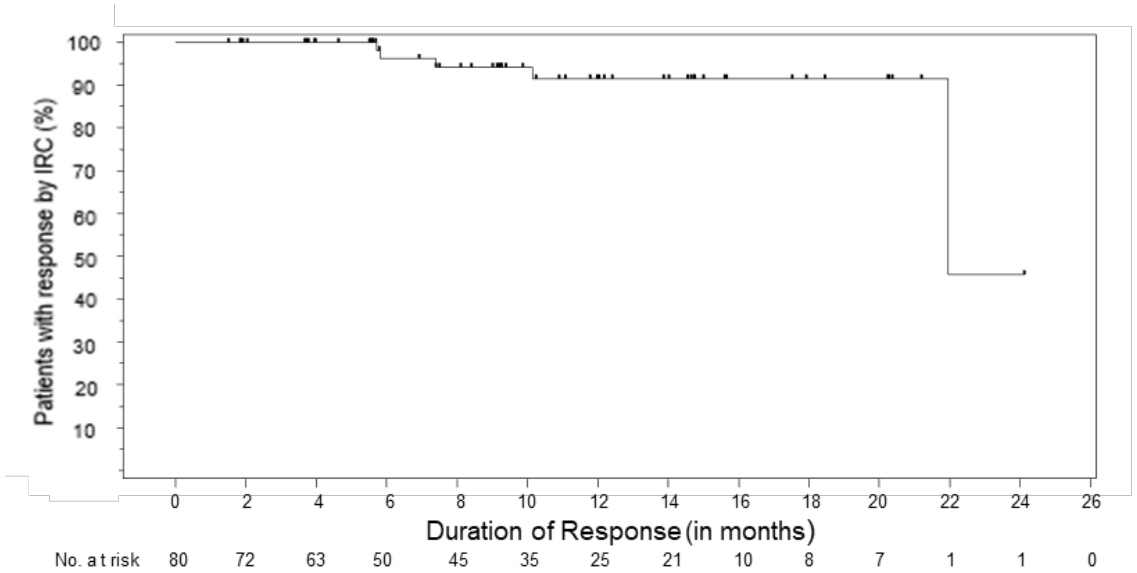
Cabo/Vande Naïve *RET*-mutant MTC





9 cabo/vande treatment naïve subjects are not included because they have non target lesion only or do not have post baseline target lesion measurement based on IRC. Baseline is defined as the last available measurement prior to the first dose selpercatinib. Although a median was estimated, the estimate is not reliable because it can be attributed to a single late event. Therefore, the median should be interpreted as NE/ Abbreviations: cabo/vande, cabozantinib and/or vandetanib; TC, thyroid cancer, Integrated Analysis Set, IAS; Primary analysis set, PAS. Not estimable, NE.

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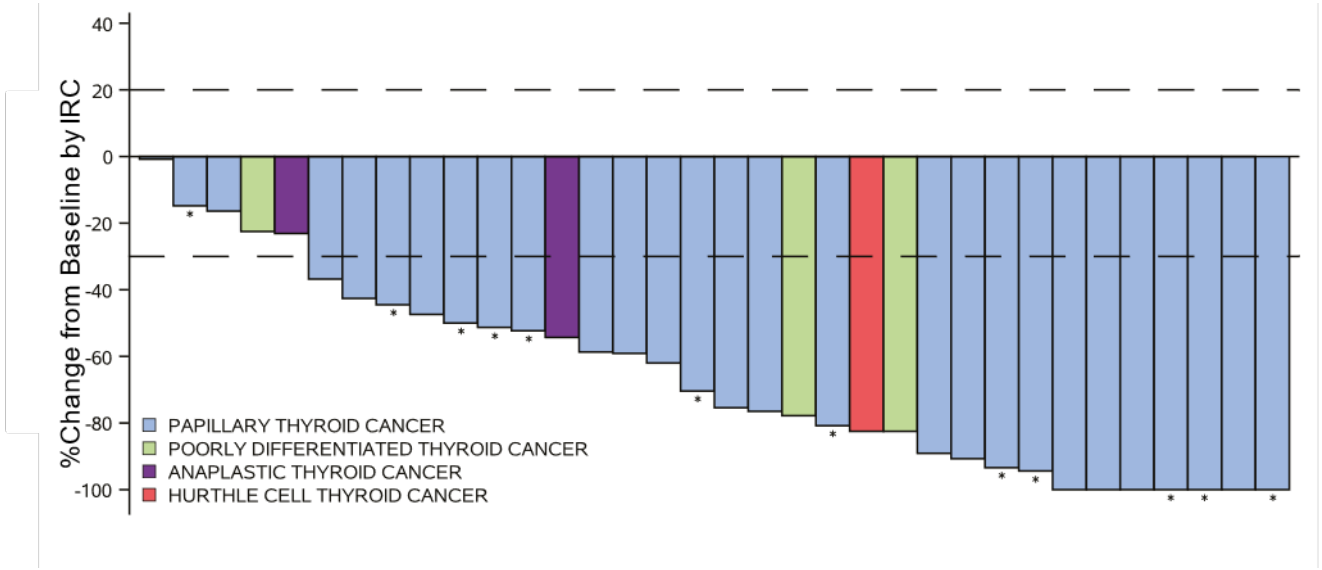
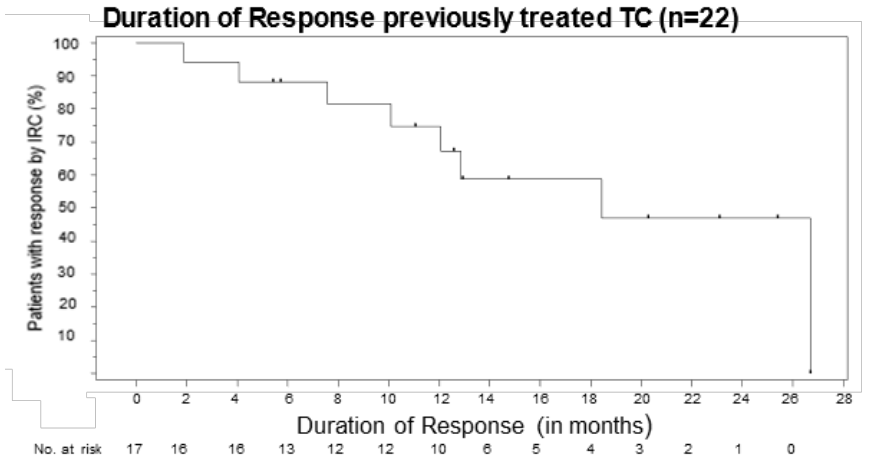
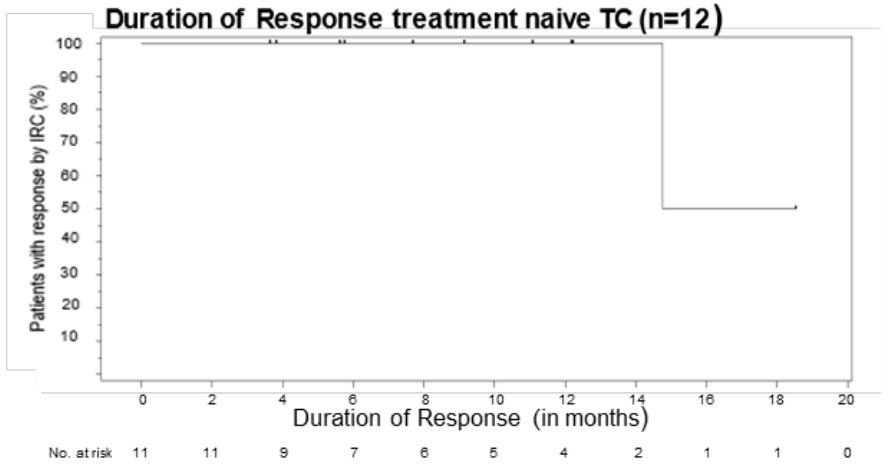
RET-Fusion Positive Thyroid Cancer







*Treatment naïve *RET*-fusion positive TC are patients with no prior systemic therapy except radioiodine.

Abbreviations: cabo/vande, cabozantinib and/or vandetanib; TC, thyroid cancer, Integrated Analysis

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Conclusions

- **Selpercatinib continues to demonstrate robust and durable efficacy in *RET*-altered thyroid cancer**

RET-mutant MTC:

  - ORR by IRC 69% in patients with previous cabozantinib and/or vandetanib treatment (PAS population)
  - At a median follow-up of 17.5 months, 76% of responses are ongoing and thus a stable median cannot yet be estimated
  - ORR by IRC 71% in patients who were treatment-naïve
  - At a median follow-up of 9.3 months, 94% of responses are ongoing

RET-fusion positive TC

  - ORR by IRC 77% in patients previously treated
  - At a median follow-up of 20.3 months, 53% of responses are ongoing
  - ORR by IRC 92% in treatment naïve patients (except RAI)
  - At a median follow-up of 9.1 months, 91% of responses are ongoing

- **Selpercatinib continues to be well-tolerated with a safety profile consistent to previous reports**
  - Most adverse events were low-grade and included dry mouth, diarrhea, hypertension, increased ALT/AST, peripheral edema, and fatigue
- **This trial update provides larger supportive analysis sets and a longer follow-up than previously reported**
- **LIBRETTO-001 study (NCT03157128) is still enrolling patients with *RET* fusion-positive non-lung cancers**
- **A global, randomized, phase 3 trial (LIBRETTO-531; NCT04211337) evaluating selpercatinib compared with standard frontline therapy in MTC is ongoing**

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Acknowledgments and References

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[1]Subbiah V, et al, Ann Oncol 2018
[2] Subbiah V. et al., JCO, 2020
[3]Ciampi, R., et al, iScience 2019
[4]Cancer Genome Atlas Research Network, Cell 2014
[5]Wirth, L. et al., NEJM 2020
[6] Besse B. et al.,: Updated Overall Efficacy and Safety of Selpercatinib in Patients with RET Fusion-Positive Non-Small-Cell Lung Cancer (NSCLC): LIBRETTO-001 Study. ASCO 2021., Poster 9065

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Supplementary Material

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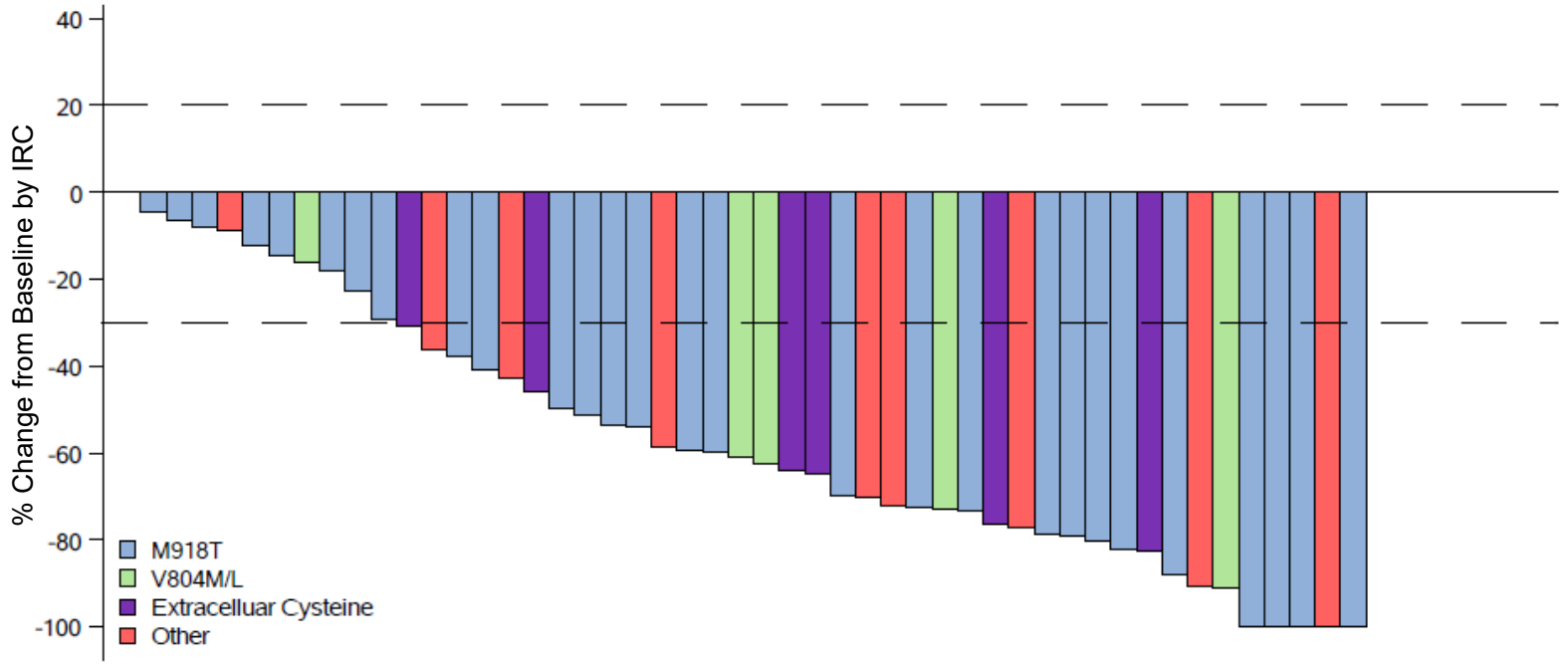
Supplementary Material: MTC
Primary Analysis Set - Antitumor Response by *RET* mutation



Note: The PAS population, a subset of the IAS, is the more mature dataset. Thirteen previously treated subjects with MTC are not included because they have non target lesion only or do not have post baseline target lesion measurement based on IRC.

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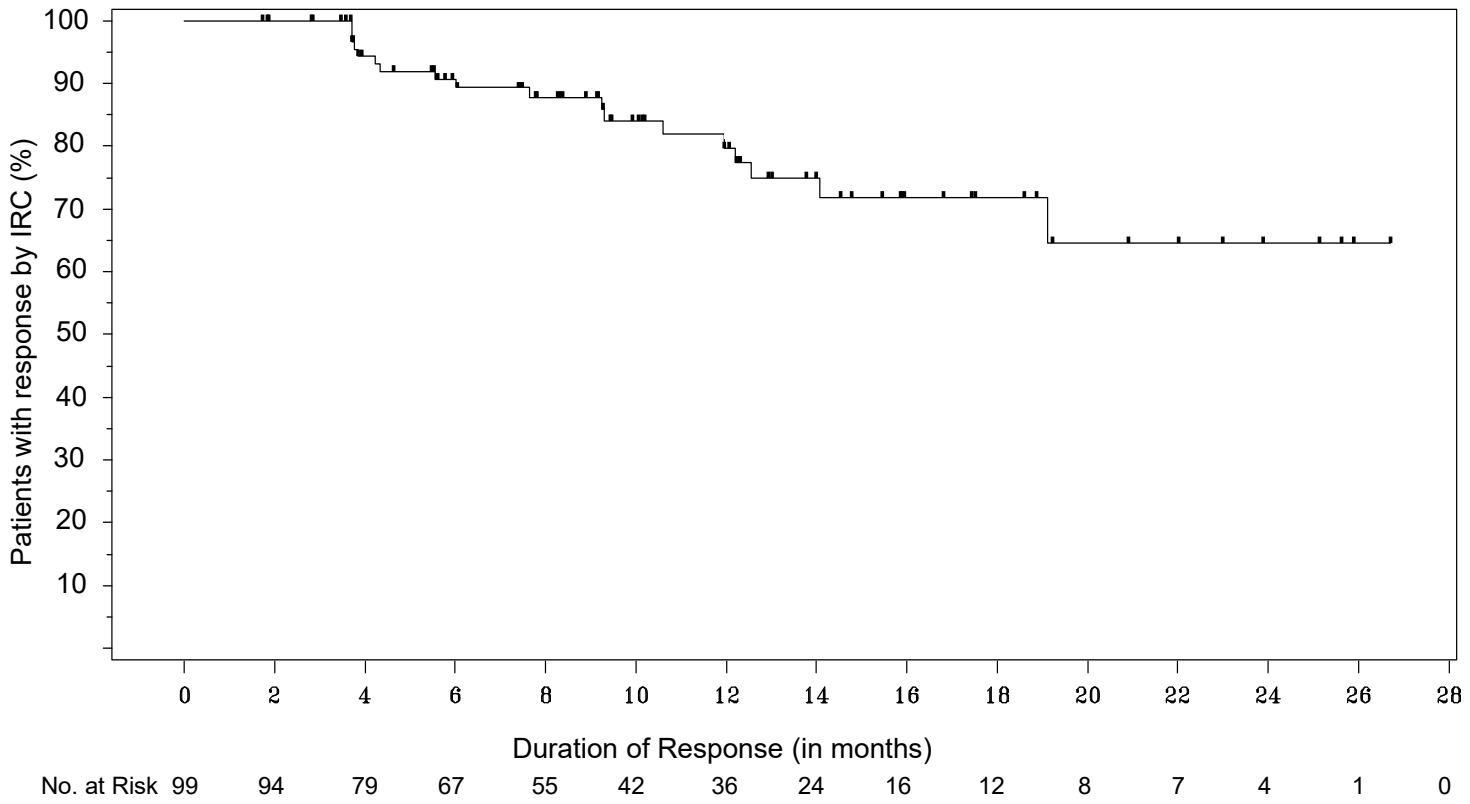
Supplementary Material : *RET*-Mutant MTC Integrated Analysis Set Duration of Response

- With a median follow-up of 10.1 months, 82% (81/99) of responses are ongoing



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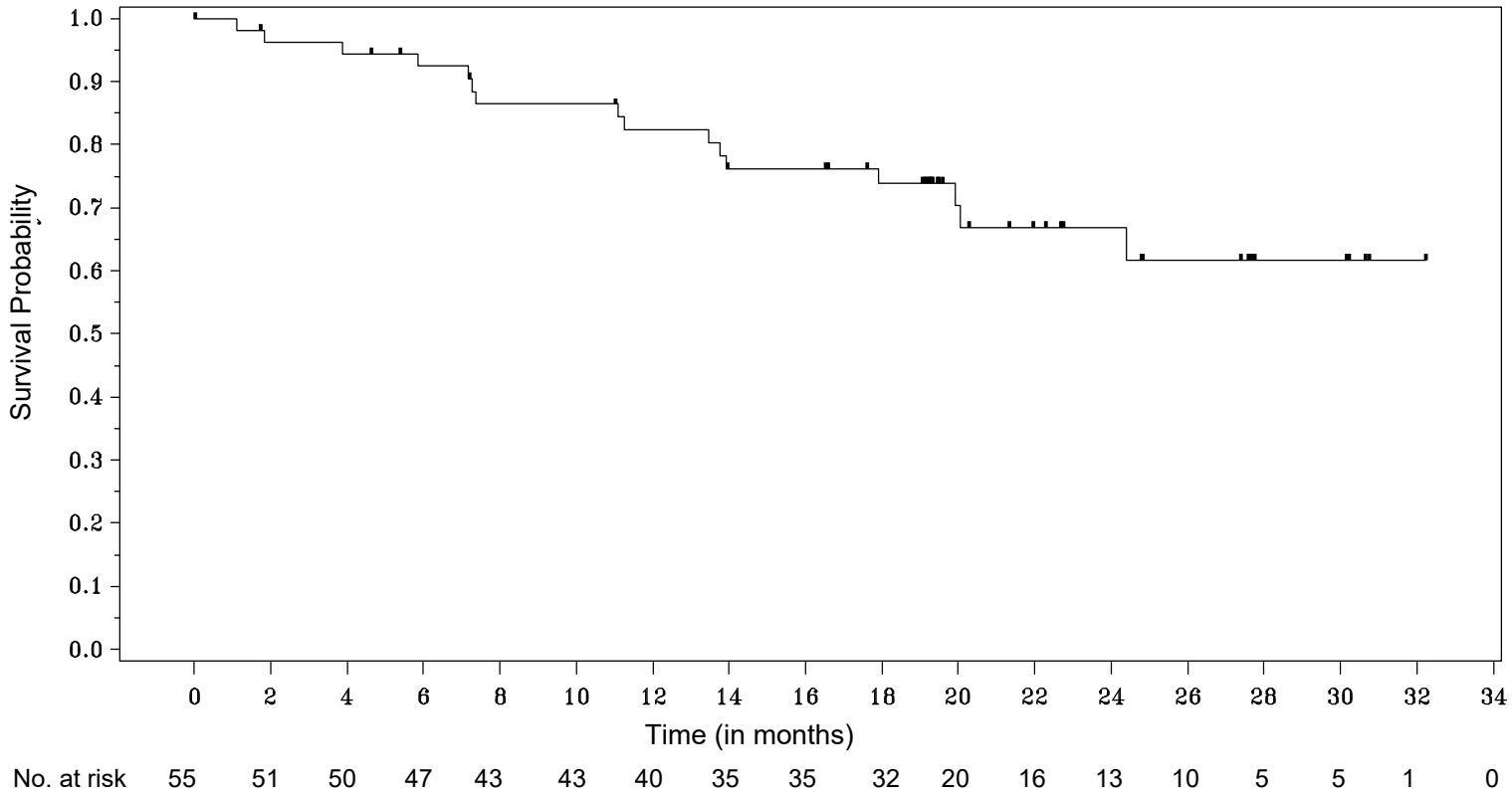
Supplementary Material : *RET*-Mutant MTC Primary Analysis Set Progression-Free Survival

- With a median follow up of 20.3 months, 71% (39/55) of patients remain alive and free from progression



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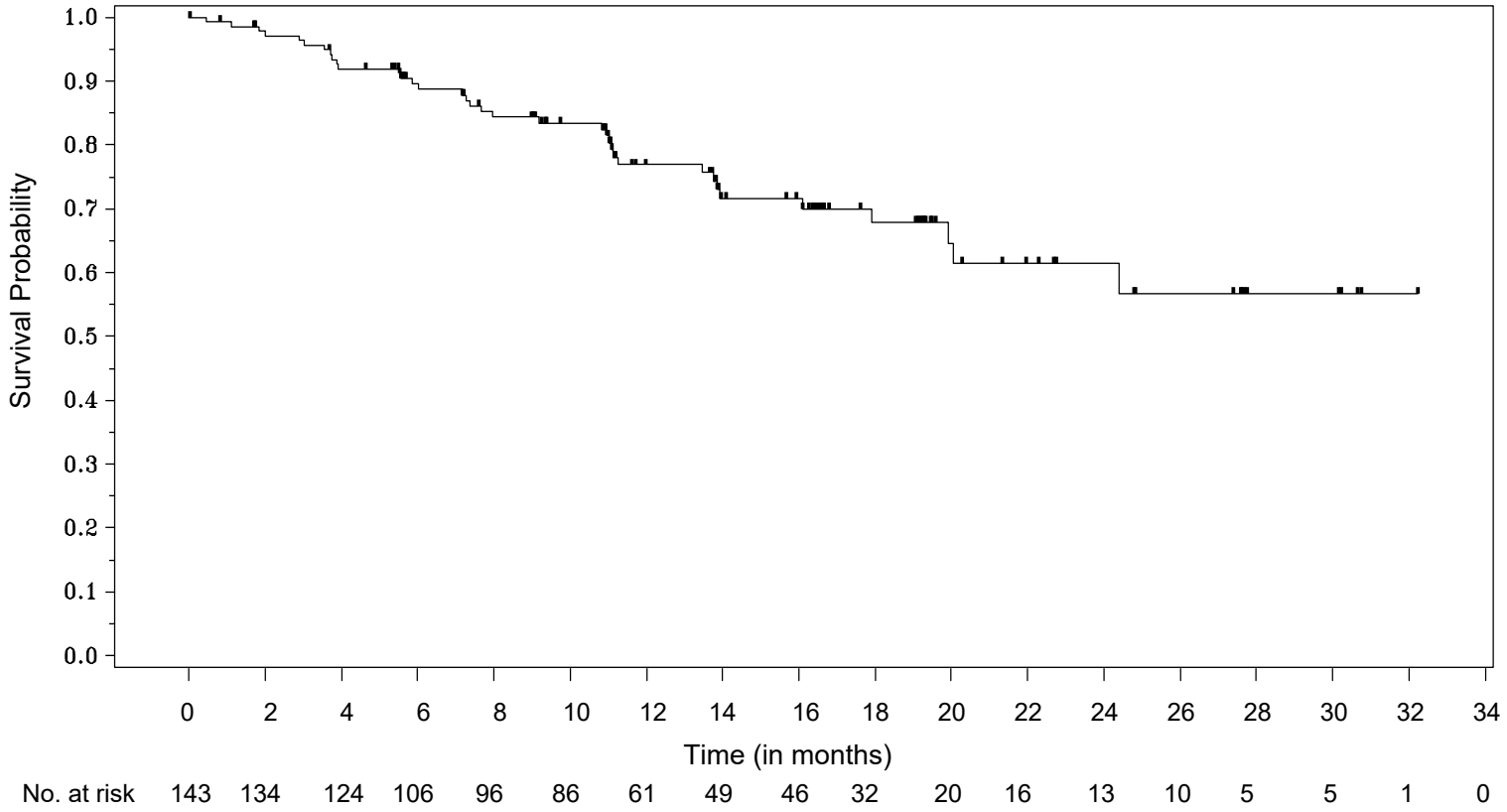
Supplementary Material : *RET*-Mutant MTC Integrated Analysis Set Progression-Free Survival

- With a median follow up of 13.9 months, 75% (107/143) of patients remain alive and free from progression



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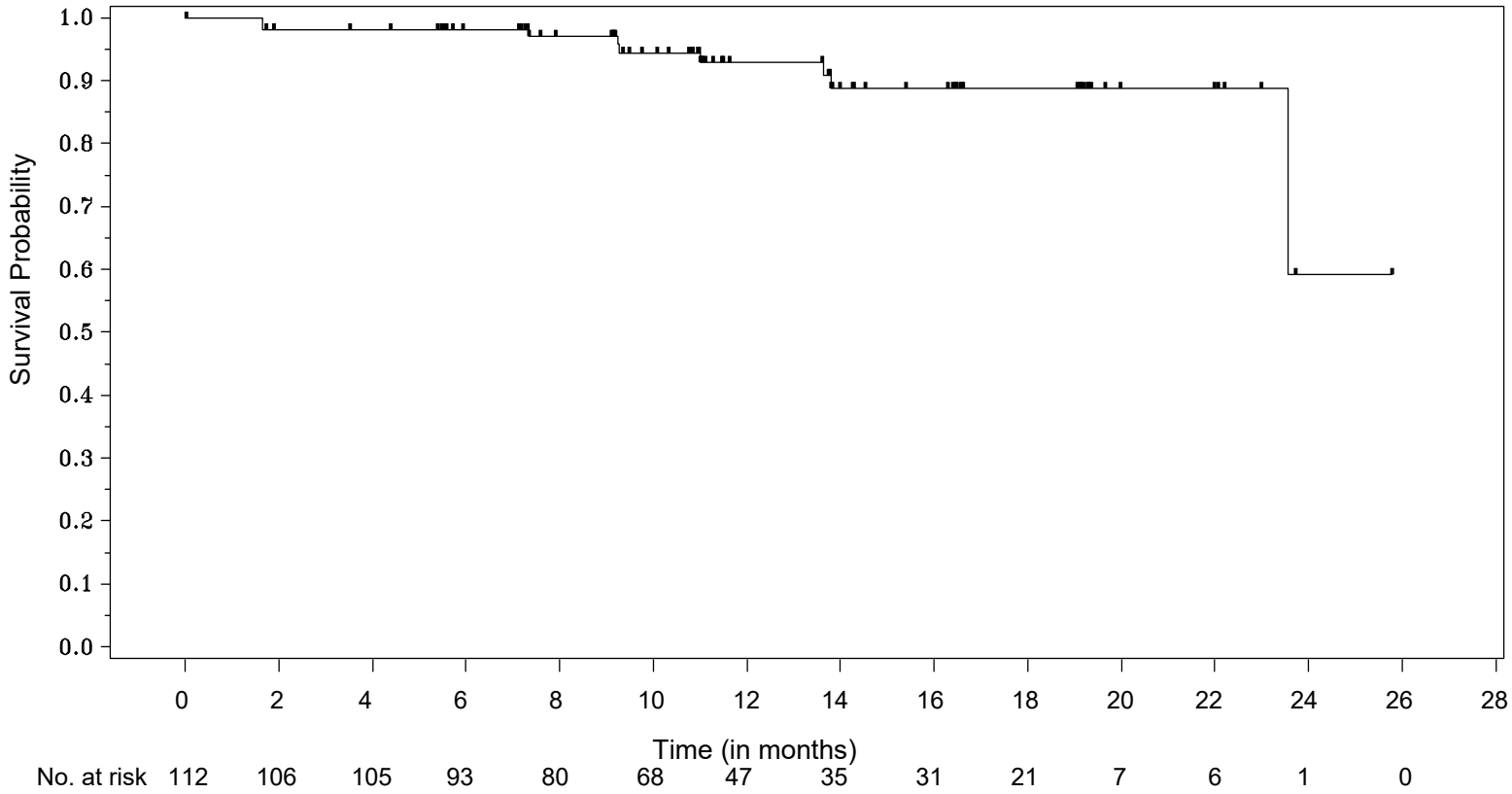
Supplementary Material: *RET*-Mutant MTC Cabo/Vande naïve Progression-Free Survival

- With a median follow up of 11.1 months, 92% (103/112) of patients remain alive and free from progression



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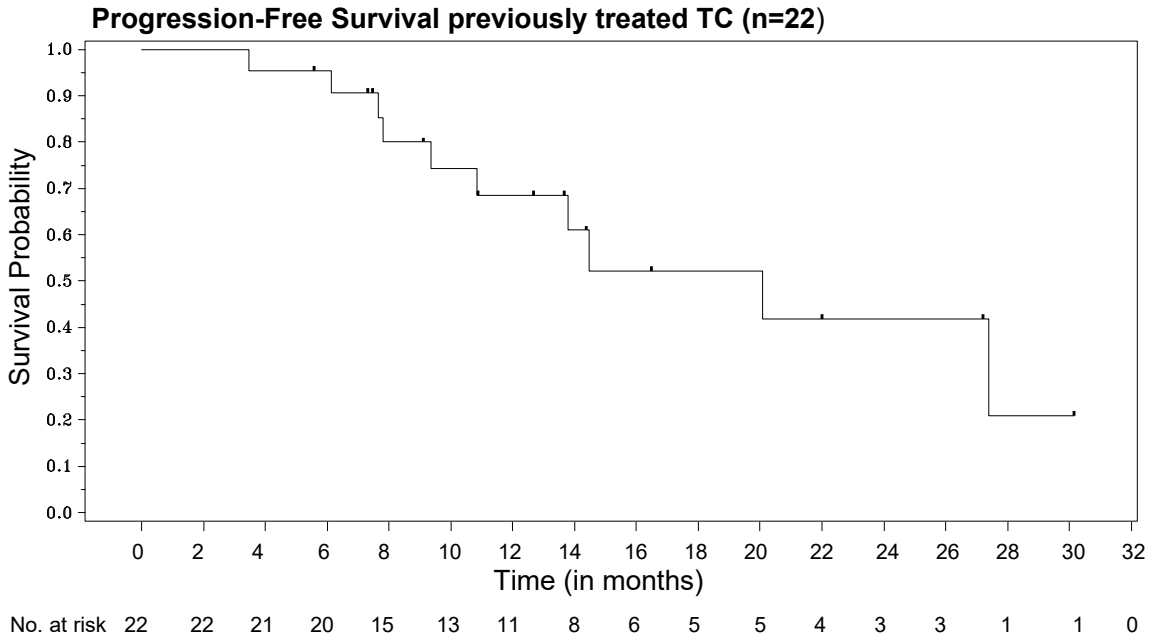
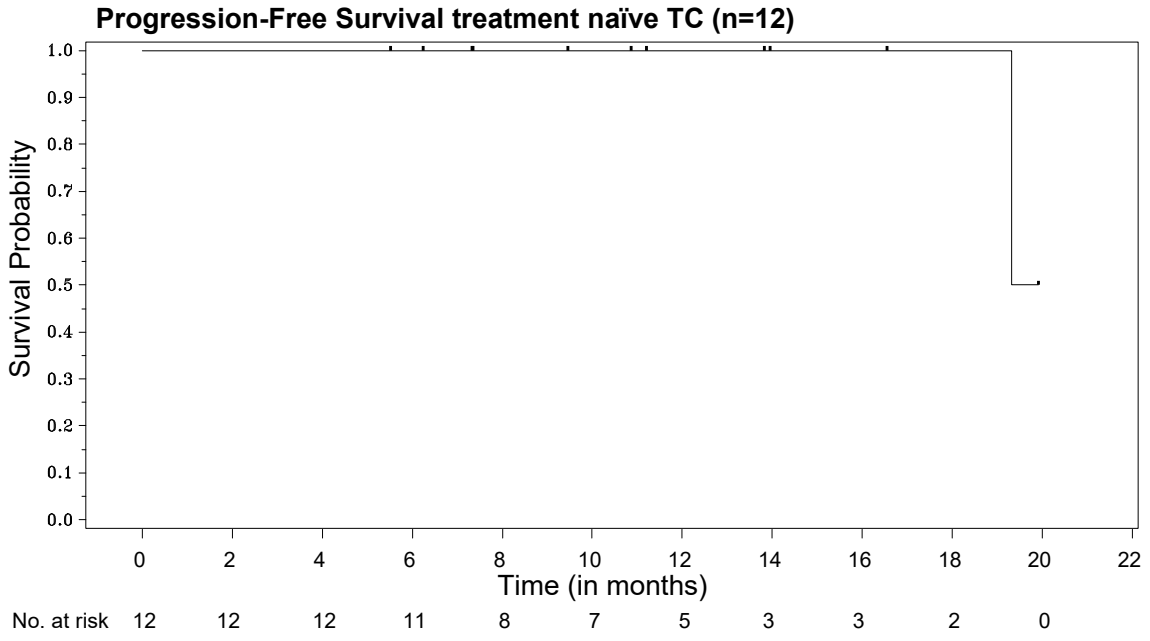
Supplementary Material: *RET*-Fusion positive TC Progression-Free Survival

- With a median follow up of 16.5 months, 55% (12/22) of previously treated patients remain alive and free from progression



- With a median follow up of 11 months, 92% (11/12) of treatment naïve patients remain alive and free from progression



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Supplementary Material: Adverse Events in *RET*-Mutant MTC

- A total of 2% of patients discontinued selpercatinib due to a treatment related AE

RET-mutant MTC (n=315)								
	Any causality					Related to treatment		
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade [5]	Grade 3	Grade 4	Any Grade *
Patients with ≥1 AE	23 (7)	94 (30)	166 (53)	22 (7)	313 (99)	90 (29)	6 (2)	293 (93)
Dry mouth	111 (35)	12 (4)	0 (0)	0 (0)	123 (39)	0 (0)	0 (0)	104 (33)
Diarrhea	68 (22)	28 (9)	13 (4)	0 (0)	109 (35)	4 (1)	0 (0)	55 (18)
Hypertension	16 (5)	42 (13)	61 (19)	1 (0.3)	120 (38)	39 (12)	1 (0.3)	90 (29)
Fatigue	63 (20)	46 (15)	3 (1)	0 (0)	112 (36)	3 (1)	0 (0)	76 (24)
Constipation	83 (26)	17 (5)	1 (0.3)	0 (0)	101 (32)	0 (0)	0 (0)	59 (19)
Increased AST	60 (19)	10 (3)	18 (6)	1 (0.3)	89 (28)	16 (5)	1 (0.3)	71 (23)
Increased ALT	52 (17)	13 (4)	20 (6)	2 (0.6)	87 (28)	18 (6)	2 (0.6)	71 (23)
Headache	63 (20)	19 (6)	7 (2)	0 (0)	89 (28)	3 (1)	0 (0)	41 (13)
Peripheral edema	74 (24)	10 (3)	1 (0.3)	0 (0)	85 (27)	0 (0)	0 (0)	47 (15)
Nausea	55 (18)	22 (7)	1 (0.3)	0 (0)	78 (25)	0 (0)	0 (0)	34 (11)
Increased blood creatinine level	60 (19)	17 (5)	0 (0)	0 (0)	77 (24)	0 (0)	0 (0)	41 (13)
Abdominal pain	51 (16)	17 (5)	6 (2)	0 (0)	74 (24)	1 (0.3)	0 (0)	28 (9)
QT interval prolonged on electro-cardiograph	24 (8)	26 (8)	11 (4)	0 (0)	61 (19)	8 (3)	0 (0)	47 (15)
Arthralgia	47 (15)	13 (4)	0 (0)	0 (0)	60 (19)	0 (0)	0 (0)	19 (6)
Cough	42 (13)	9 (3)	0 (0)	0 (0)	51 (16)	0 (0)	0 (0)	2 (0.6)
Rash	42 (13)	6 (2)	1 (0.3)	0 (0)	49 (16)	1 (0.3)	0 (0)	28 (9)

The adverse events listed for any causality occurred at any grade in at least 15% of the patients, regardless of attribution [5]In total, 8 patients with MTC had grade 5 TEAEs, including general physical health deterioration, septic shock, brain herniation, cardiac arrest, cardia failure, cardio-respiratory arrest, post procedural hemorrhage and haemoptysis. *No grade 5 TRAEs were observed.

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Supplementary Material: Adverse Events in *RET*-Fusion positive TC

- No patients with *RET*-Fusion positive TC discontinued selpercatinib due to a treatment related AE

RET-fusion positive TC (n=42)								
	Any causality					Related to treatment		
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade [δ]	Grade 3	Grade 4	Any Grade *
Patients with ≥1 AE	3 (7)	13 (31)	23 (55)	2 (5)	42 (100)	11 (26)	2 (5)	41 (98)
Dry mouth	17 (41)	1 (2)	0 (0)	0 (0)	18 (43)	0 (0)	0 (0)	15 (36)
Diarrhea	13 (31)	1 (2)	2 (5)	0 (0)	16 (38)	2 (5)	0 (0)	9 (21)
Hypertension	1 (2)	8 (19)	9 (21)	0 (0)	18 (43)	4 (10)	0 (0)	12 (29)
Fatigue	12 (29)	5 (12)	1 (2)	0 (0)	18 (43)	0 (0)	0 (0)	12 (29)
Constipation	13 (31)	4 (10)	0 (0)	0 (0)	17 (41)	0 (0)	0 (0)	5 (12)
Increased AST	5 (12)	1 (2)	3 (7)	0 (0)	9 (21)	2 (5)	0 (0)	5 (12)
Increased ALT	6 (14)	2 (5)	2 (5)	0 (0)	10 (24)	1 (2)	0 (0)	6 (14)
Headache	9 (21)	0 (0)	0 (0)	0 (0)	9 (21)	0 (0)	0 (0)	3 (7)
Peripheral edema	6 (14)	0 (0)	1 (2)	0 (0)	7 (17)	0 (0)	0 (0)	4 (10)
Nausea	10 (24)	1 (2)	0 (0)	0 (0)	11 (26)	0 (0)	0 (0)	3 (7)
Increased blood creatinine level	3 (7)	3 (7)	0 (0)	0 (0)	6 (14)	0 (0)	0 (0)	6 (14)
Abdominal pain	8 (19)	0 (0)	2 (5)	0 (0)	10 (24)	0 (0)	0 (0)	2 (5)
QT interval prolonged on electro-cardiograph	1 (2)	1 (2)	2 (5)	0 (0)	4 (10)	2 (5)	0 (0)	4 (10)
Arthralgia	6 (14)	2 (5)	1 (2)	0 (0)	9 (21)	0 (0)	0 (0)	0 (0)
Cough	7 (17)	1 (2)	0 (0)	0 (0)	8 (19)	0 (0)	0 (0)	2 (5)
Rash	7 (17)	2 (5)	0 (0)	0 (0)	9 (21)	0 (0)	0 (0)	5 (12)

The adverse events listed for any causality occurred at any grade in at least 15% of the patients, regardless of attribution. One patient with TC had a grade 5 sepsis. *No grade 5 TRAEs were observed

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