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Updated Overall Efficacy and Safety of Selpercatinib in Patients with *RET* Fusion-Positive Non-Small-Cell Lung Cancer (NSCLC): LIBRETTO-001 Study

Benjamin Besse[1], Alexander Drilon[2], Benjamin Solomon[3], Vivek Subbiah[4], Daniel Shao-Weng Tan[5], Keunchil Park[6], Filippo de Braud[7], Guzmán Alonso[8], Jürgen Wolf[9], Victoria Soldatenkova[10], Aimee Bence Lin[10], Pearl French[10], Koichi Goto[11], Oliver Gautschi[12]

[1]Gustave Roussy Universite' Paris Sud, Villejuif, France; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Peter MacCallum Cancer Institute, Australia; [4]MD Anderson Cancer Center, Houston, TX; [5]National Cancer Centre Singapore, Singapore; [6]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [7]University of Milan, Italy; [8]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [9]University Hospital of Cologne, Lung Cancer Group Cologne, Department of Internal Medicine, Cologne, Germany; [10]Eli Lilly and Company, Indianapolis, IN; [11]National Cancer Center Hospital East, Kashiwa, Japan;[12]University of Berne and Cantonal Hospital of Lucerne, Switzerland.

BACKGROUND

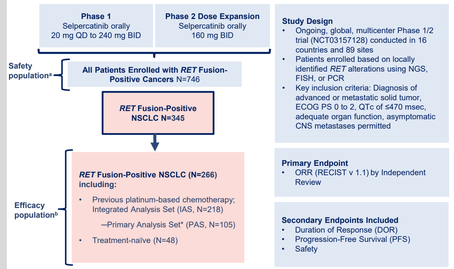
- Selpercatinib is a first-in-class, highly selective and potent RET-inhibitor[1] with CNS activity[2] approved in multiple countries for the treatment of *RET*-altered lung or thyroid cancers
- *RET* fusions are oncogenic drivers in ~2% of patients with NSCLC[3]
- In previous analyses of selpercatinib in *RET* fusion-positive NSCLC, at a median follow up of 12.1 months for patients with previous chemotherapy, the majority remained progression-free and on treatment, with 63% of responses ongoing and thus the estimated median was not yet stable[4]

OBJECTIVES

- Here we present updated selpercatinib efficacy and safety data from LIBRETTO-001 in patients with *RET* fusion-positive NSCLC

STUDY DESIGN

The Phase 1/2 LIBRETTO-001[a] Trial: 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* alterations using NGS, FISH, or PCR
- Key inclusion criteria: Diagnosis of advanced or metastatic solid tumor, ECOG PS 0 to 2, QTc of ≤470 msec, adequate organ function, asymptomatic CNS metastases permitted

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

Secondary Endpoints Included
- Duration of Response (DOR)
- Progression-Free Survival (PFS)
- Safety

- [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 105 consecutively enrolled patients with *RET* fusion-positive NSCLC previously treated with platinum chemotherapy and is the more mature dataset. Patients with non-measurable disease enrolled in Phase 1 were included in the PAS
- [4]LIBRETTO-001 trial also included patients with MTC and *RET* mutant cancers, see ASCO 2021 poster 6073[5]

BASELINE CHARACTERISTICS

	Previous platinum chemotherapy		Treatment-naive
Characteristic	PAS (N=105)	IAS (N=218)	(N=48)
Median Age (range) — years	61 (23-81)	61 (23-81)	64 (23-92)
Sex — no. (%)			
Female	62 (59)	121 (56)	29 (60)
Male	43 (41)	97 (44)	19 (40)
Race — no. (%)[a]			
White	55 (52)	100 (46)	35 (73)
Asian	40 (38)	97 (44)	9 (19)
Black	5 (5)	12 (6)	3 (6)
ECOG PS score — no. (%)[b]			
0	31 (30)	80 (37)	20 (42)
1	72 (69)	133 (61)	25 (52)
2	2 (2)	5 (2)	3 (6)
Median prior systemic lines — no. (range)	3 (1-15)	2 (1-15)	0
1-2 — no. (%)	19 (61)	46 (62)	0
≥3 — no. (%)	12 (39)	28 (38)	0
Previous regimen — no. (%)			
Platinum-based chemotherapy	105 (100)	218 (100)	NA
Anti-PD-1 and anti-PD-L1 therapy	58 (55)	119 (55)	NA
Multitargeted kinase inhibitor[c]	50 (48)	71 (33)	NA
Disease Stage at Study Entry			
Metastatic	103 (98)	213 (98)	47 (98)
Smoking status			
Current	1 (1)	4 (2)	1 (2)
Former	29 (28)	63 (29)	13 (27)
Never	75 (71)	151 (69)	34 (71)

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 (n=3 [PAS]; n=7 [IAS]; n= 1 [treatment-naïve]). Missing information for 2 patients (PAS, IAS). [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.

BEST OVERALL RESPONSE

	Previous platinum chemotherapy		Treatment-naive
Response	PAS (N=105)	IAS (N=218)	(N=48)
Overall response rate by IRC — % (95% CI)	64 (54–73)	57 (50–64)	85 (72–94)
Best response — no. (%)			
Complete response	3 (3)	9 (4)	1 (2)
Partial response	64 (61)	115 (53)	40 (83)
Stable disease	30 (29)	81 (37)	4 (8)
Duration of response			
Median duration of response — mo (95% CI)	17.5 (12.1–NE)	17.5 (12.1–NE)	NE (12.0–NE)
Censoring rate, no. (%)	39 (58)	86 (69)	31 (76)
Median follow-up — mo	15.7	12.0	9.8
Progression-free survival			
Median progression-free survival — mo (95% CI)	19.3 (13.9–NE)	19.3 (16.5–NE)	NE (13.8–NE)
1-yr progression-free survival — % (95% CI)	66 (56–74)	70 (62–76)	68 (50–80)
Censoring rate, no. (%)	55 (52)	144 (66)	34 (71)
Median follow-up — mo	16.8	13.6	10.8
Overall survival			
2-yr overall survival — % (95% CI)	68 (55.3–77.8)	67 (55.4–76.7)	88 (68.6–95.8)
Censoring rate, no. (%)	77 (73)	177 (81)	44 (92)
Median follow-up — mo	19.9	14.3	12.6

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.

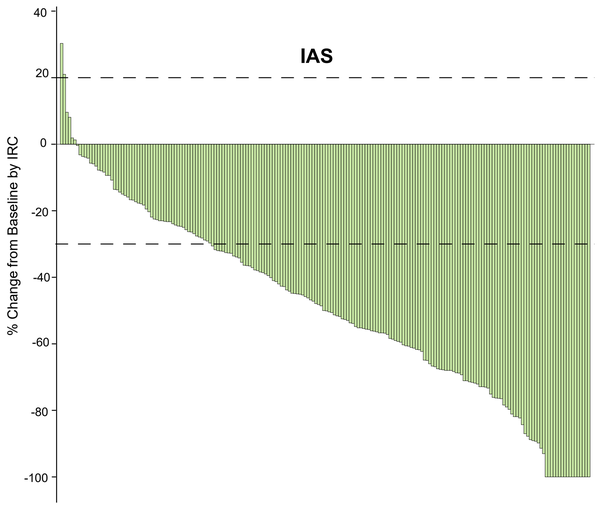
ADVERSE EVENTS

- 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					Related to treatment			
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade[a]	Grade 3	Grade 4	Any Grade[a]
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-cardiogrph	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)

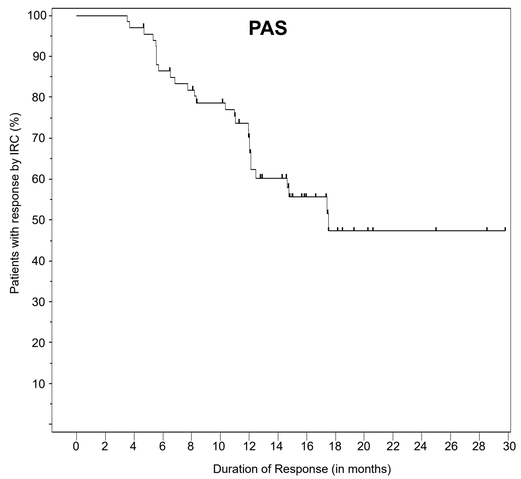
Safety population (N=746) included all patients with *RET*-altered cancers (includes RET-mutant MTC and *RET*-fusion positive non-small cell lung cancer). [a]In total, 25 of 746 patients had grade 5 TEAEs. *No grade 5 TRAEs were observed. TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events. Safety among the 345 patients with NSCLC was consistent with the safety of the overall population.

PLATINUM CHEMOTHERAPY TREATED (PAS or IAS)



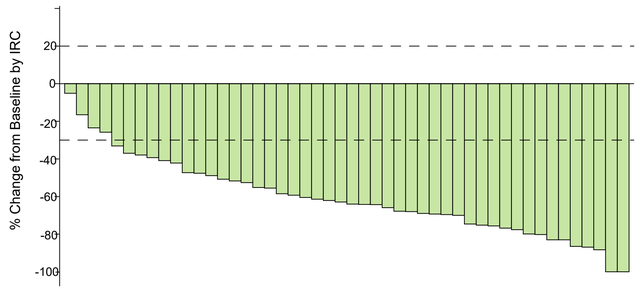
Note: The IAS is a larger population, including the PAS as well as additional patients. Eighteen patients were not included because they had only non-target lesions or did not have a post-baseline target lesion measurement based on IRC. A Kaplan-Meier plot depicting duration of response for IAS is available in the supplement via the QR code.

- With a median follow-up of 15.7 months, 58% (39/67) of responses are ongoing

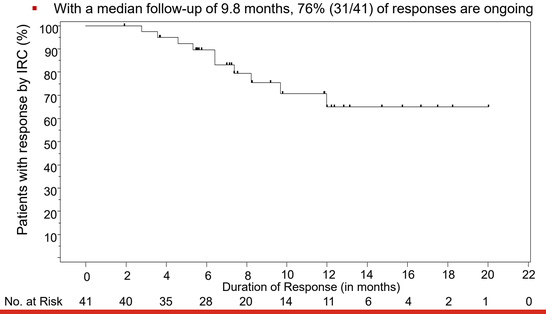


Note: The PAS population, a subset of the IAS, is the more mature dataset. The waterfall plot for PAS is available in the supplement via the QR code.

TREATMENT-NAÏVE



- With a median follow-up of 9.8 months, 76% (31/41) of responses are ongoing



CONCLUSIONS

- **Selpercatinib continues to demonstrate robust and durable efficacy in *RET* fusion-positive NSCLC**
  - ORR by IRC 64% in patients with previous platinum-based chemotherapy (PAS population)
    - At a median follow-up of 15.7 months, 58% of responses are ongoing and thus a stable median cannot yet be estimated
  - ORR by IRC 85% in patients who were treatment-naïve
    - At a median follow-up of 9.8 months, 76% of responses 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-431; NCT04194944) compared selpercatinib to standard frontline chemotherapy-based treatment is ongoing**

References:
1. Goto et. al., *JCO* 2020
2. Subbiah et. al., *JCO* 2020
3. Drilon et. al., *Nat Rev Clin Oncol* 2018
4. Drilon et. al., *NEJM* 2020
5. Sherman et. al., ASCO 2021 Poster Number 6073, "Selpercatinib efficacy and safety in patients with *RET*-altered thyroid cancer: a clinical trial update".

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Background and Objectives

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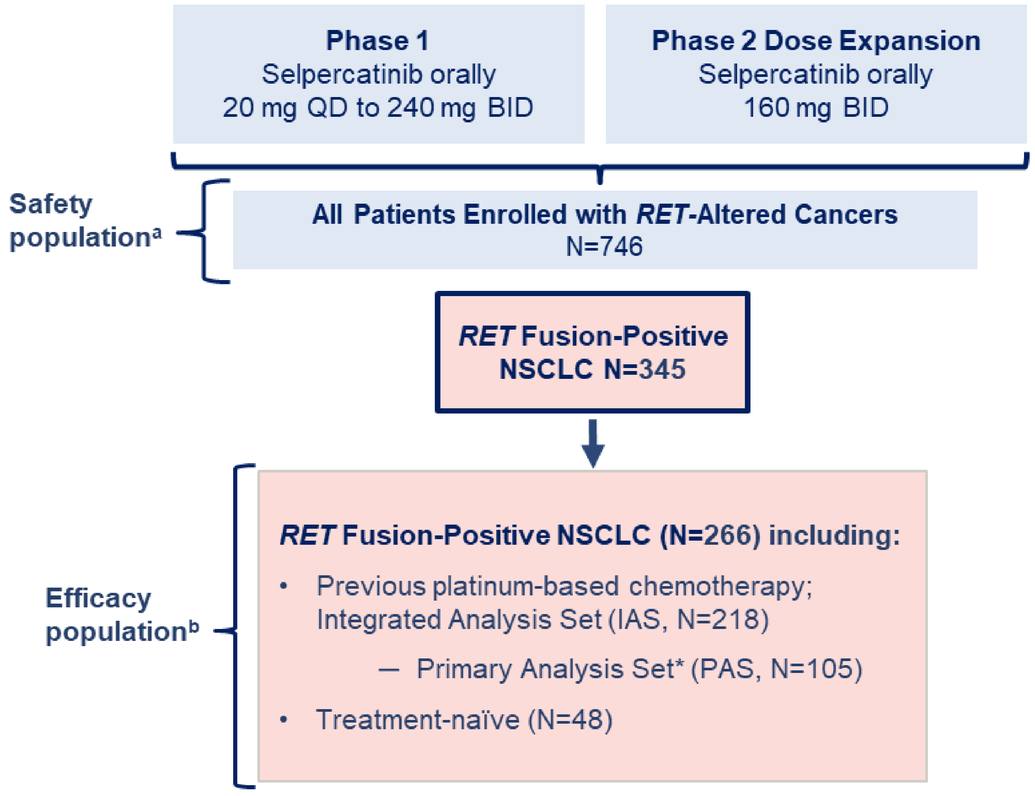
Study Design

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



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- Key inclusion criteria: Diagnosis of advanced or metastatic solid tumor, ECOG PS 0 to 2, QTc of ≤470 msec, adequate organ function, asymptomatic CNS metastases permitted.

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
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Baseline Characteristics

	Previous platinum chemotherapy		Treatment-naive
Characteristic	PAS (N=105)	IAS (N=218)	(N=48)
Median Age (range) — years	61 (23-81)	61 (23-81)	64 (23-92)
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Black	5 (5)	12 (6)	3 (6)
ECOG PS score — no. (%)[b]			
0	31 (30)	80 (37)	20 (42)
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2	2 (2)	5 (2)	3 (6)
Median prior systemic lines — no. (range)	3 (1-15)	2 (1-15)	0
1-2 — no. (%)	19 (61)	46 (62)	0
≥3 — no. (%)	12 (39)	28 (38)	0
Previous regimen — no. (%)			
Platinum-based chemotherapy	105 (100)	218 (100)	NA
Anti-PD-1 and anti-PD-L1 therapy	58 (55)	119 (55)	NA
Multitargeted kinase inhibitor[c]	50 (48)	71 (33)	NA
Disease Stage at Study Entry			
Metastatic	103 (98)	213 (98)	47 (98)
Smoking status			
Current	1 (1)	4 (2)	1 (2)
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Best Overall Response

	Previous platinum chemotherapy		Treatment-naive
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Overall response rate by IRC — % (95% CI)	64 (54–73)	57 (50–64)	85 (72–94)
Best response — no. (%)			
Complete response	3 (3)	9 (4)	1 (2)
Partial response	64 (61)	115 (53)	40 (83)
Stable disease	30 (29)	81 (37)	4 (8)
Duration of response			
Median duration of response — mo (95% CI)	17.5 (12.1–NE)	17.5 (12.1–NE)	NE (12.0–NE)
Censoring rate, no. (%)	39 (58)	86 (69)	31 (76)
Median follow-up — mo	15.7	12.0	9.8
Progression-free survival			
Median progression-free survival — mo (95% CI)	19.3 (13.9–NE)	19.3 (16.5–NE)	NE (13.8–NE)
1-yr progression-free survival — % (95% CI)	66 (56–74)	70 (62–76)	68 (50–80)
Censoring rate, no. (%)	55 (52)	144 (66)	34 (71)
Median follow-up — mo	16.8	13.6	10.8
Overall survival			
2-yr overall survival — % (95% CI)	68 (55.3–77.8)	67 (55.4–76.7)	88 (68.6–95.8)
Censoring rate, no. (%)	77 (73)	177 (81)	44 (92)
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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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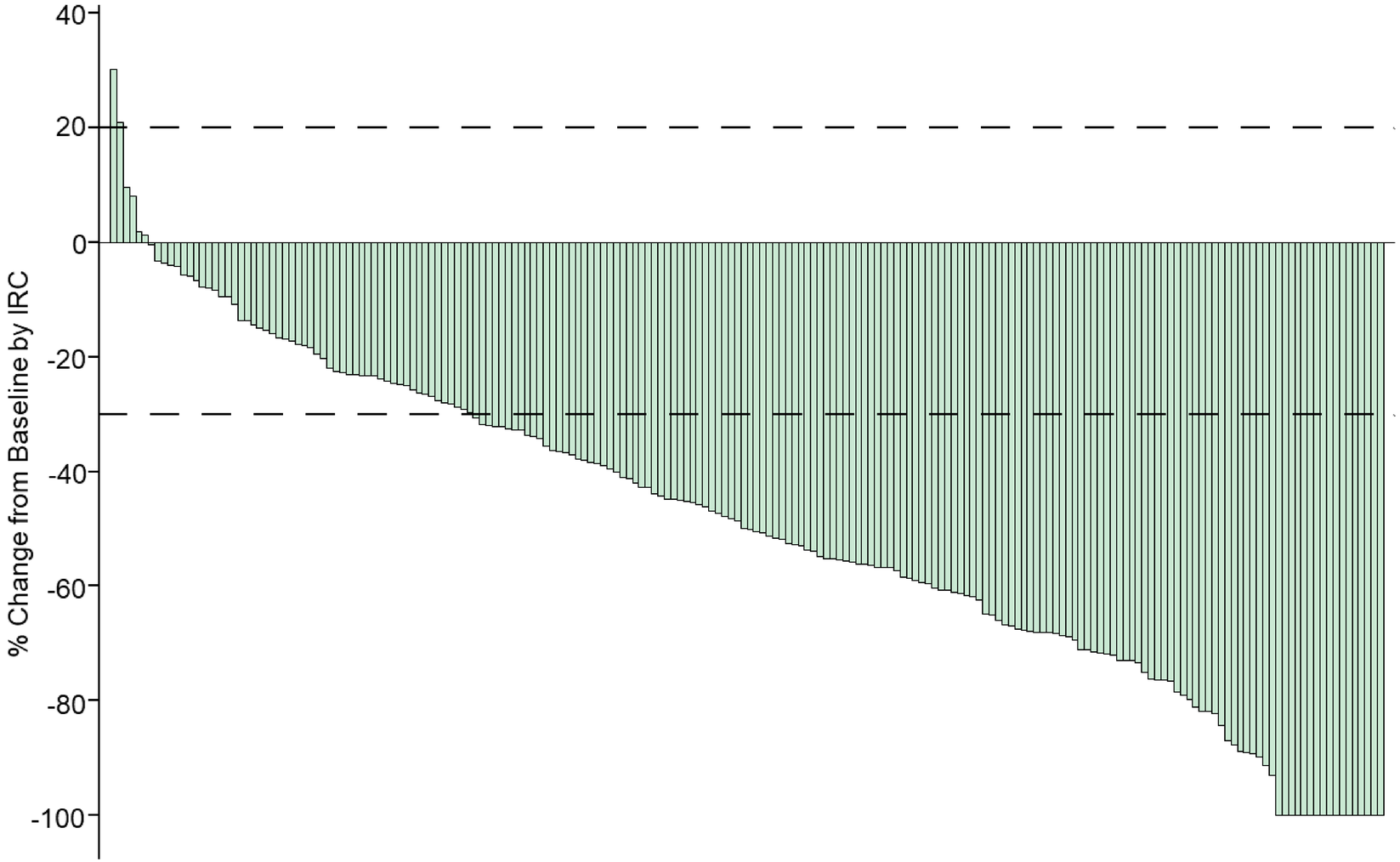
Integrated Analysis Set (IAS) Change in Tumor Size



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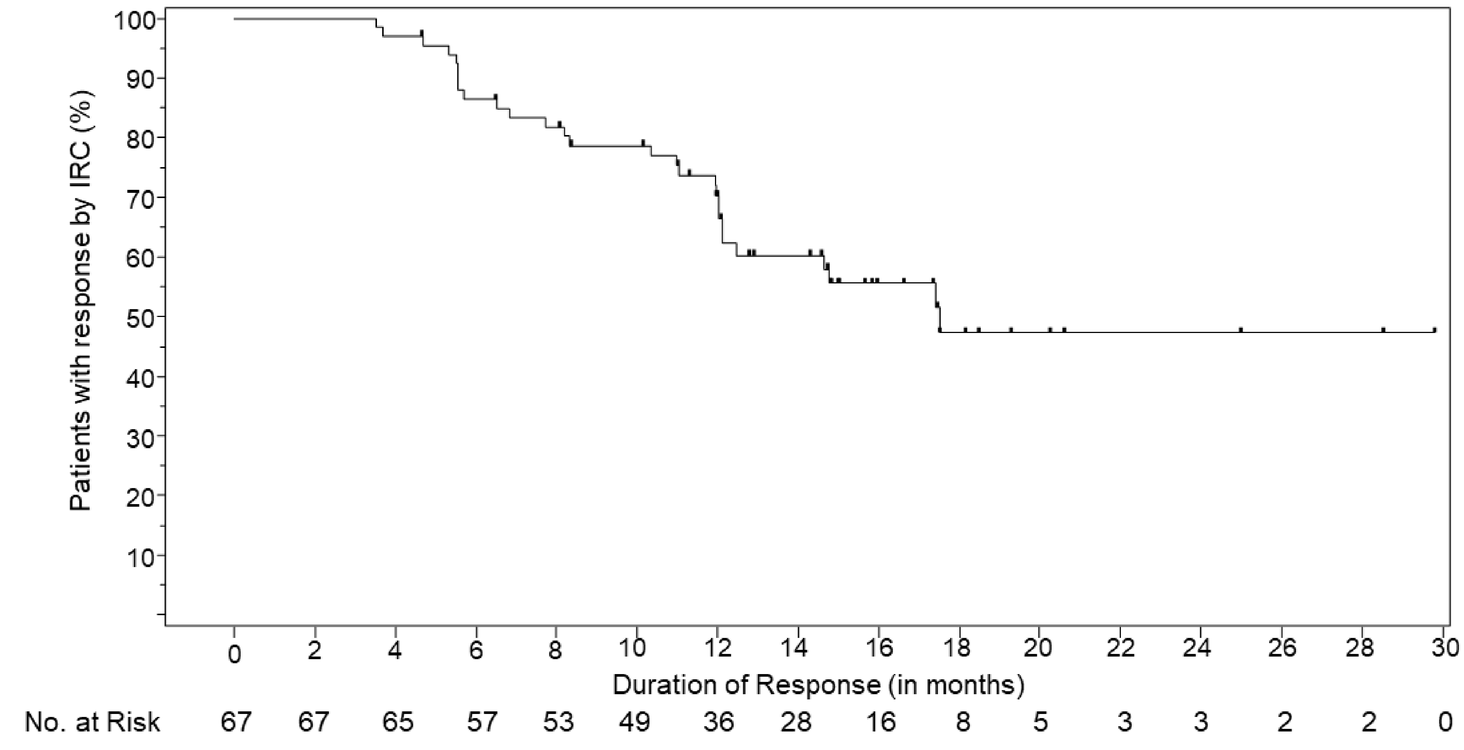
Primary Analysis Set (PAS) Duration of Response

- With a median follow-up of 15.7 months, 58% (39/67) of responses are ongoing



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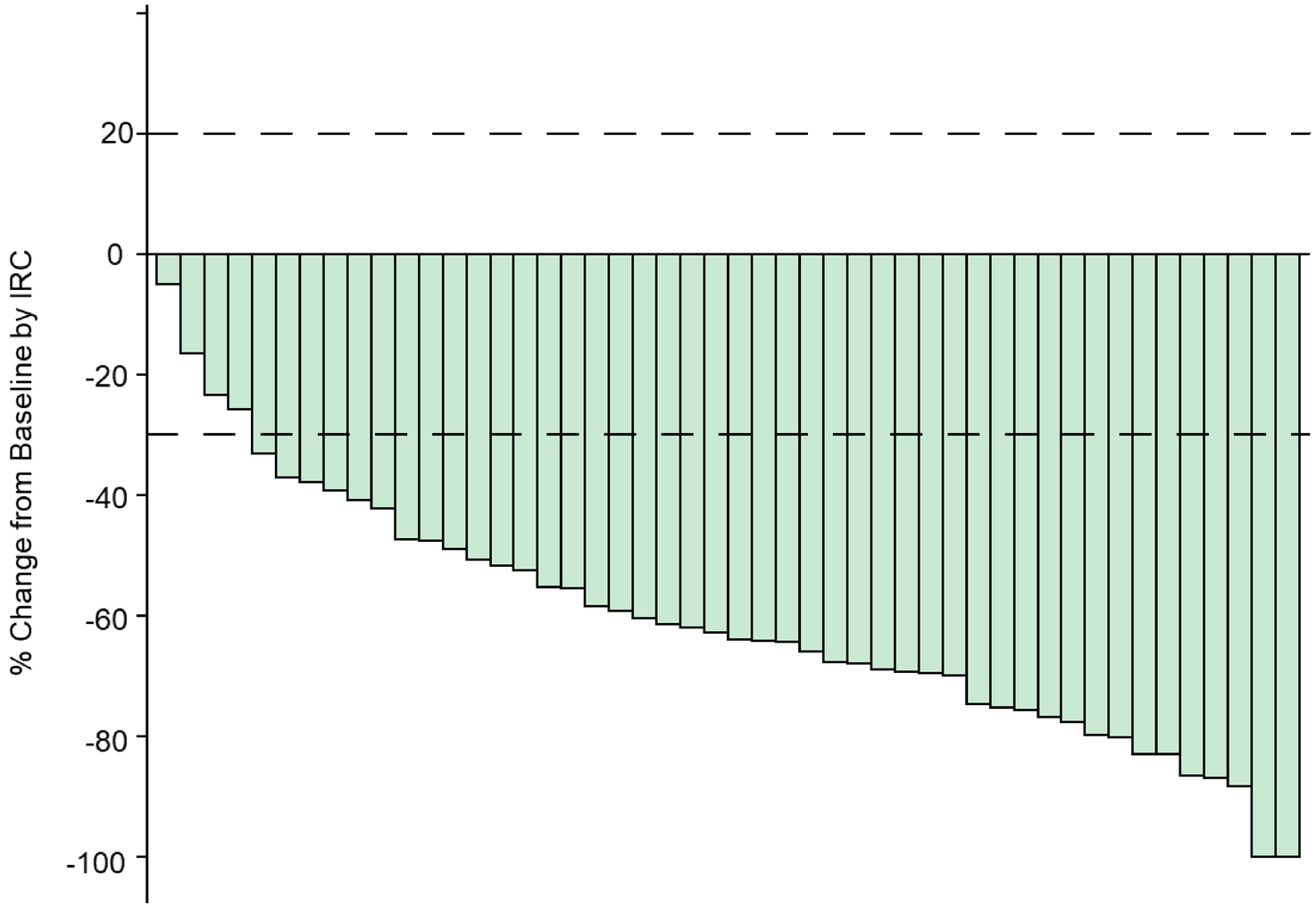
Treatment-Naïve Change in Tumor Size



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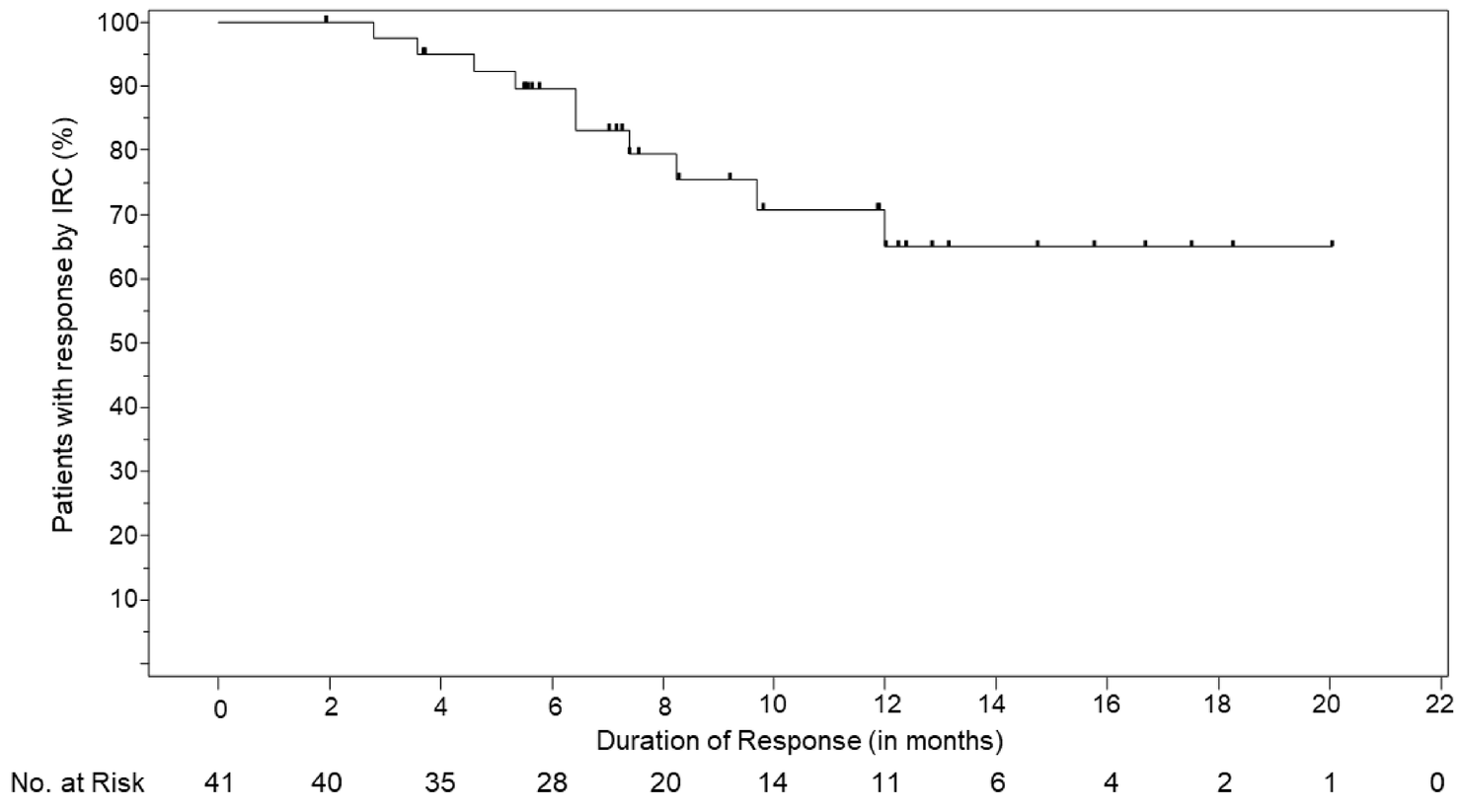
Treatment-Naïve Duration of Response

- With a median follow up of 9.8 months, 76% (31/41) of responses are ongoing



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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)
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)
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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).
[§]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 345 patients with NSCLC was consistent with the safety of the overall population.

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Conclusions

- **Selpercatinib continues to demonstrate robust and durable efficacy in *RET* fusion-positive NSCLC**
  - ORR by IRC 64% in patients with previous platinum-based chemotherapy (PAS population)
    - At a median follow-up of 15.7 months, 58% of responses are ongoing and thus a stable median cannot yet be estimated
  - ORR by IRC 85% in patients who were treatment-naïve
    - At a median follow-up of 9.8 months, 76% of responses 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-431; NCT04194944) compared selpercatinib to standard frontline chemotherapy-based treatment is ongoing**

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Acknowledgments and References

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References:

1. Goto et. al., *JCO* 2020
2. Subbiah et. al., *JCO* 2020
3. Drilon et al. *Nat Rev Clin Oncol* 2018
4. Drilon et. al., *NEJM* 2020
5. Sherman et. al., ASCO 2021 Poster Number 6073, “Selpercatinib efficacy and safety in patients with *RET*-altered thyroid cancer: a clinical trial update”

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Supplementary Material

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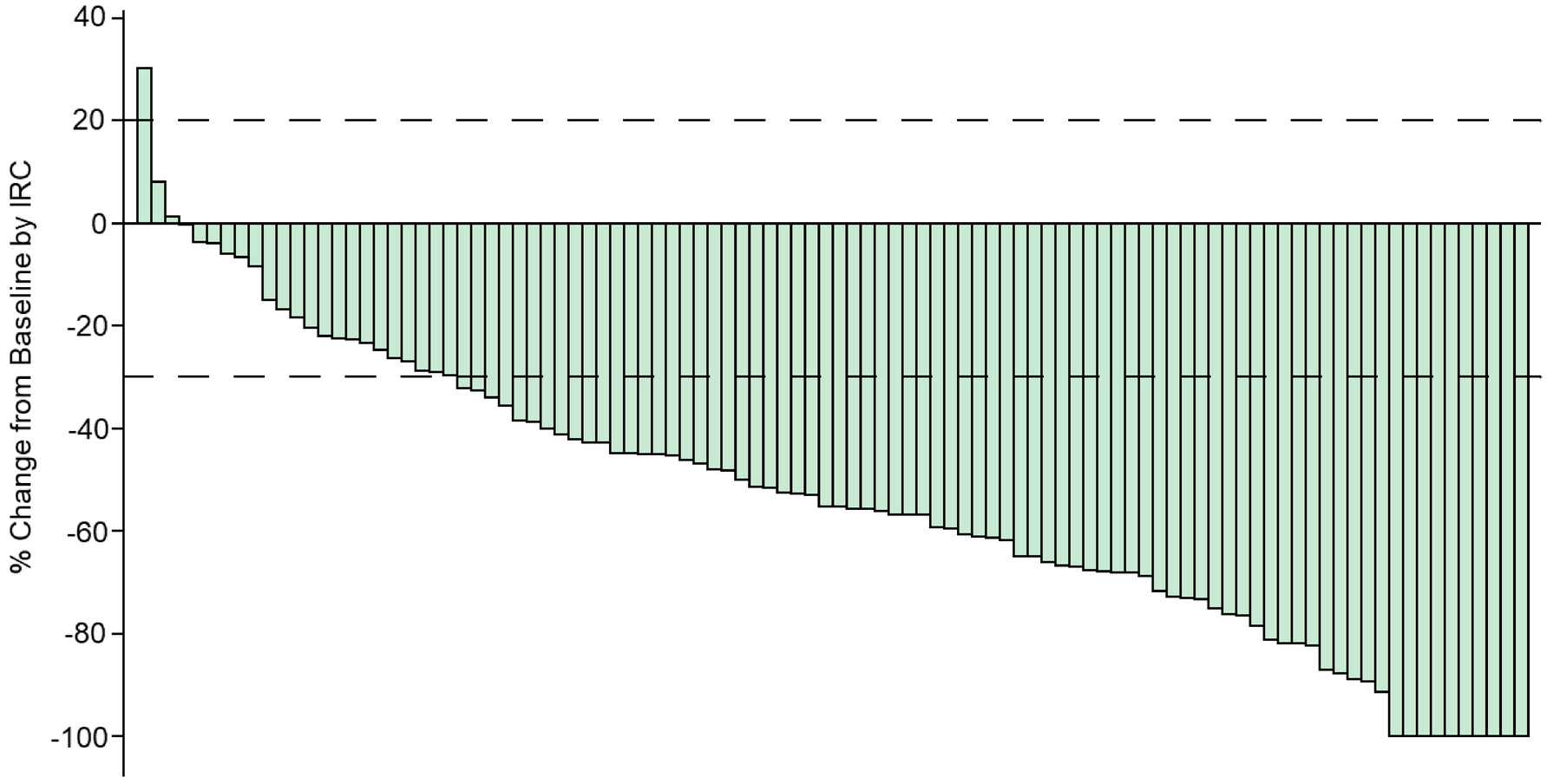
Supplementary Material:
Primary Analysis Set Change in Tumor Size



Note: The PAS population, a subset of the IAS, is the more mature dataset. Five patients were not included because they had only non-target lesions or did not have a post-baseline target lesion measurement based on IRC.

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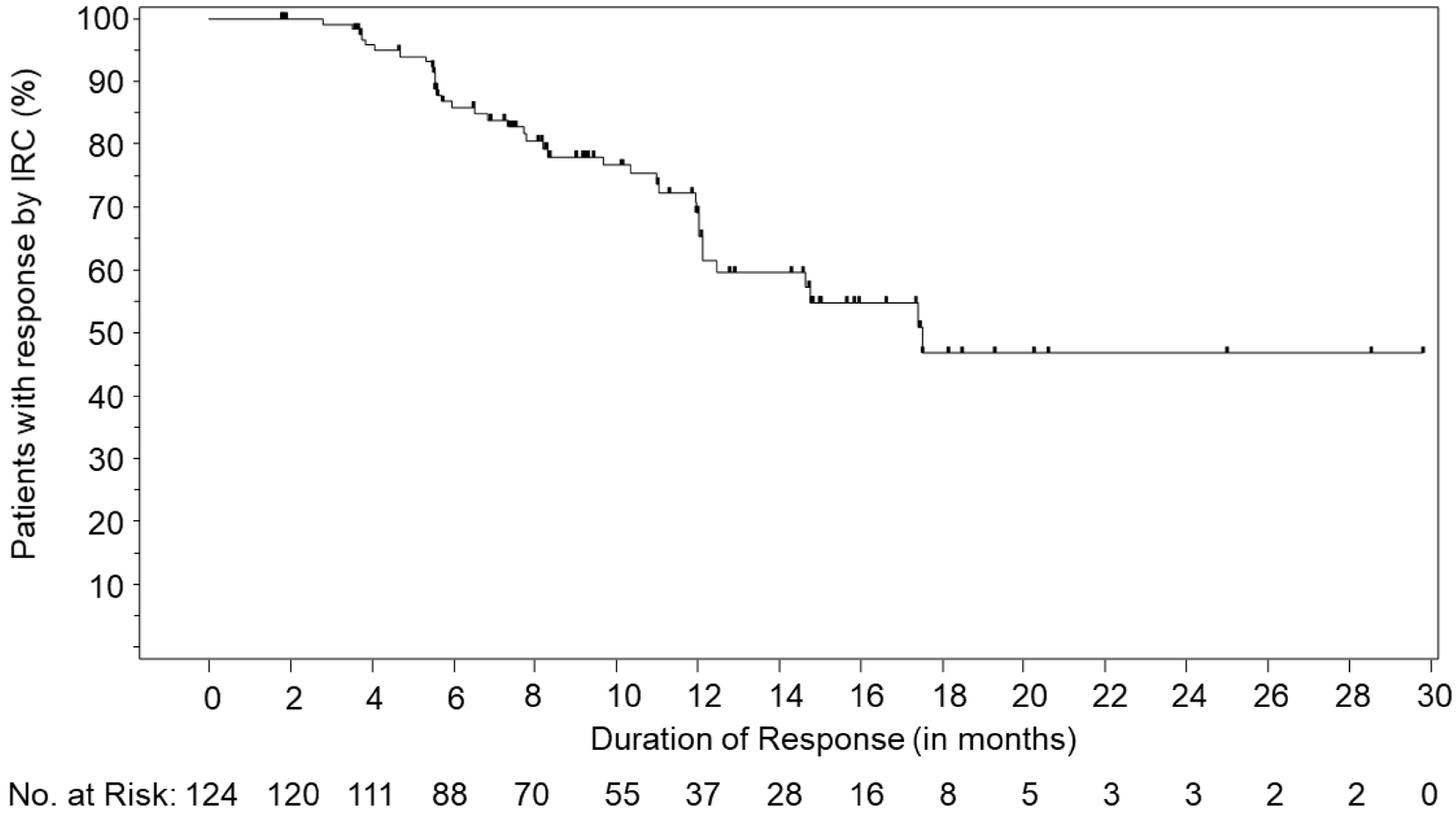
Supplementary Material:
Integrated Analysis Set Duration of Response

- With a median follow up of 12.0 months, 69% (86/124) of responses are ongoing



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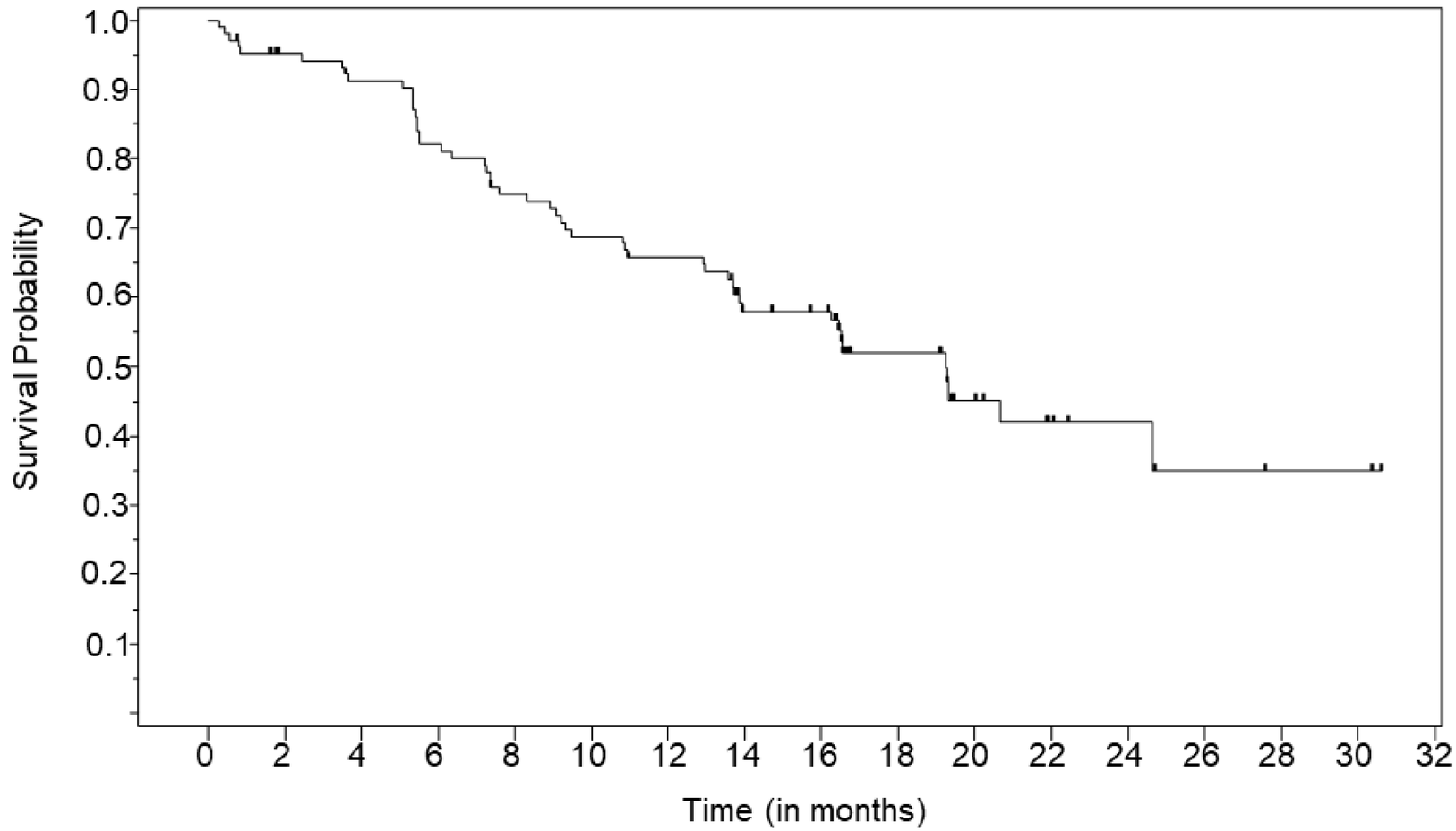
Supplementary Material:
Primary Analysis Set Progression-Free Survival

- With a median follow up of 16.8 months, 52% (55/105) of patients remain alive and free from progression



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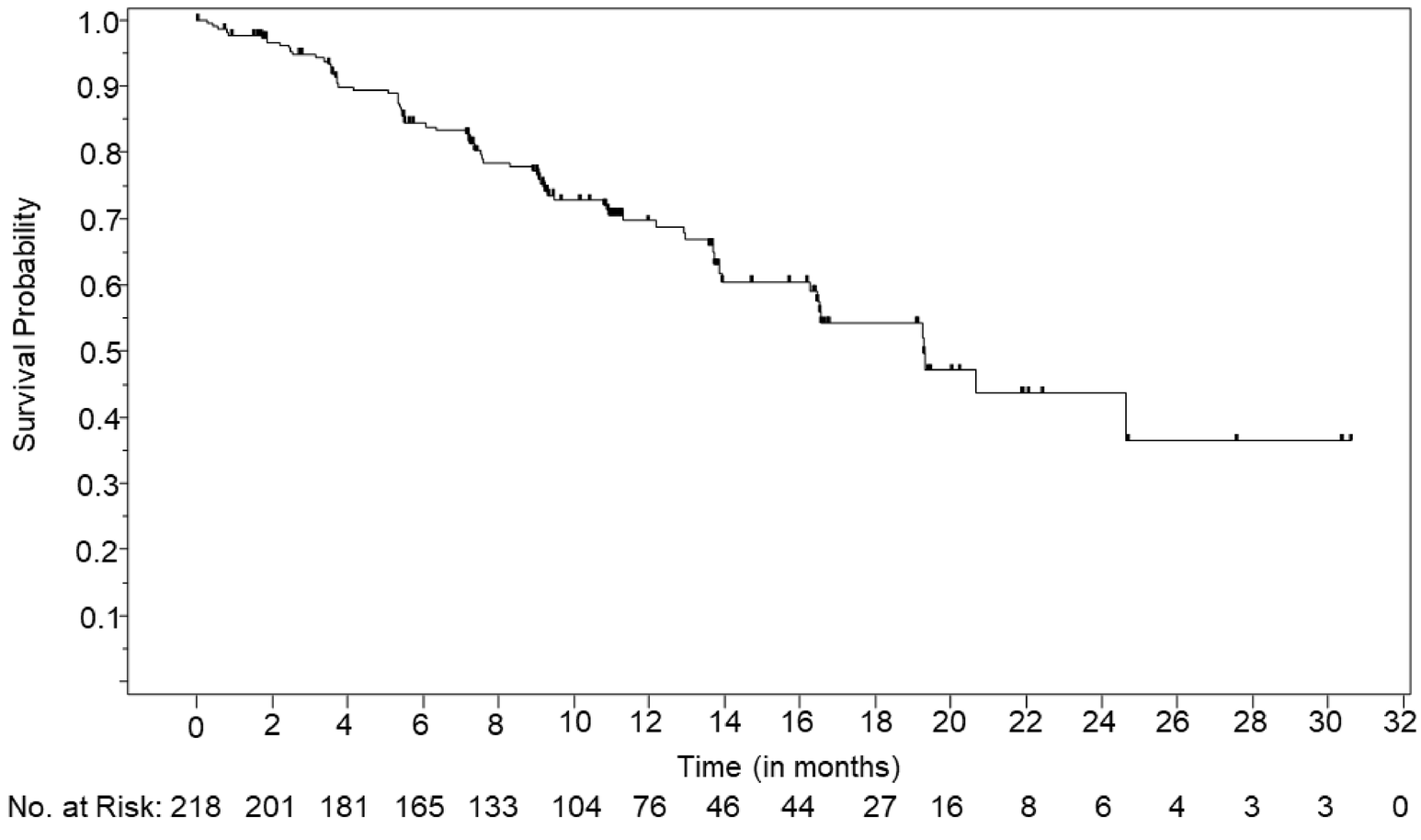
Supplementary Material:
Integrated Analysis Set Progression-Free Survival

- With a median follow up of 13.6 months, 66% (144/218) of patients remain alive and free from progression



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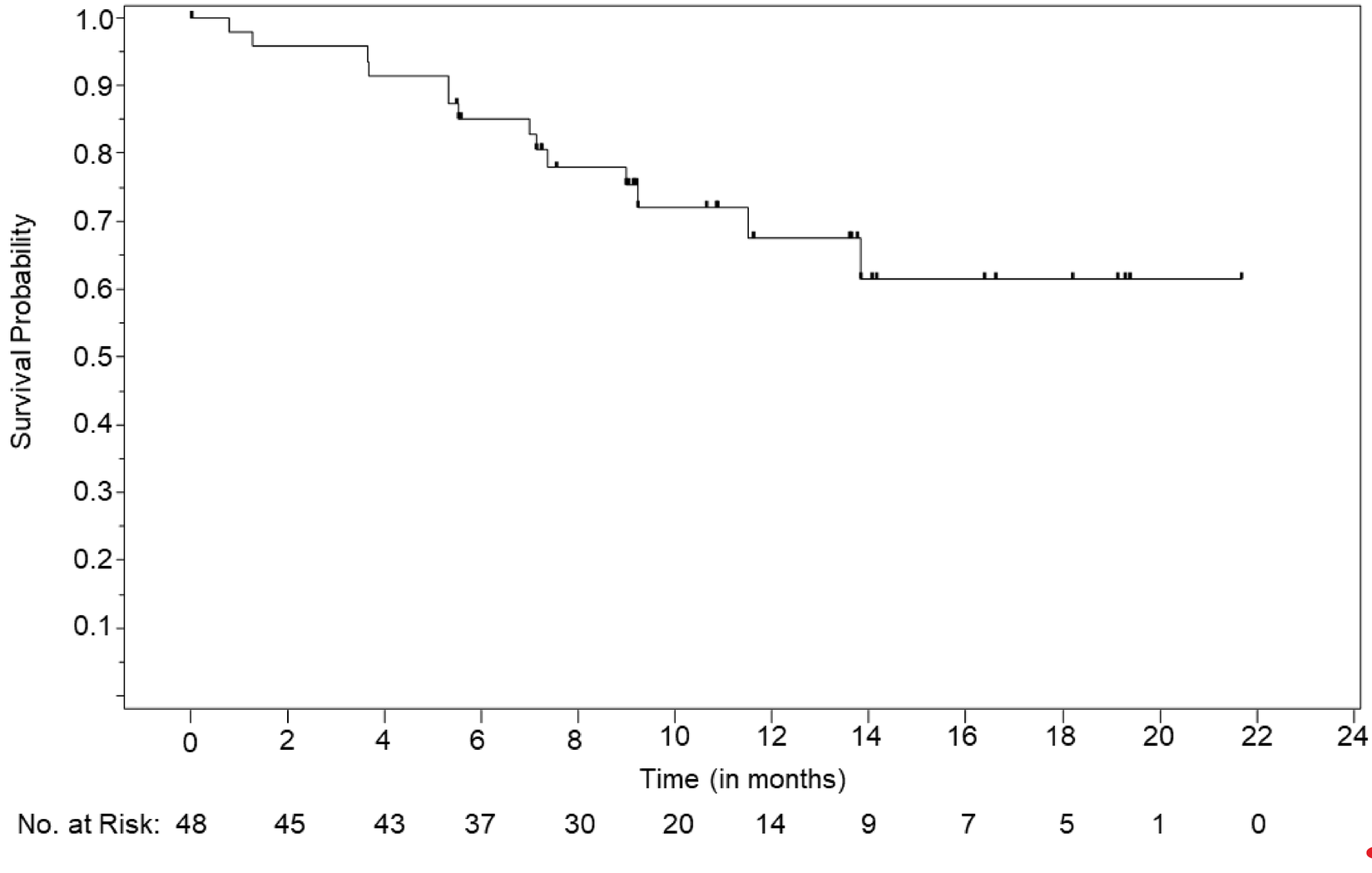
Supplementary Material:
Treatment-Naïve Progression-Free Survival

- With a median follow up of 10.8 months, 71% (34/48) of patients remain alive and free from progression



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Supplementary Material: Adverse Events (≥15% incidence) in NSCLC

- A total of 3% of patients discontinued selpercatinib due to a treatment related AE

	Any causality					Related to treatment*		
N=345, n (%)	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Any Grade§**	**Grade 3**	**Grade 4**	**Any Grade**
Patients with ≥1 AE	20 (6)	100 (29)	179 (52)	32 (9)	344 (100)	110 (32)	9 (3)	322 (93)
Diarrhea	105 (30)	36 (10)	10 (3)	0	151 (44)	6 (2)	0	90 (26)
Dry mouth	129 (37)	19 (6)	0	0	148 (43)	0	0	137 (40)
AST increased	70 (20)	26 (8)	30 (9)	5 (1)	131 (38)	20 (6)	4 (1)	109 (32)
ALT increased	64 (19)	21 (6)	39 (11)	5 (1)	129 (37)	31 (9)	4 (1)	107 (31)
Hypertension	8 (2)	48 (14)	63 (18)	0	119 (35)	45 (13)	0	80 (23)
Edema peripheral	76 (22)	16 (5)	0	0	92 (27)	0	0	54 (16)
Fatigue	58 (17)	29 (8)	4 (1)	0	91 (26)	2 (1)	0	48 (14)
Rash	56 (16)	20 (6)	2 (1)	0	78 (23)	2 (1)	0	52 (15)
Constipation	59 (17)	14 (4)	3 (1)		77 (22)	2 (1)	0	30 (9)
Nausea	61 (18)	12 (4)	2 (1)	0	75 (22)	1 (0.3)	0	32 (9)
Headache	55 (16)	14 (4)	3 (1)	0	72 (21)	0	0	20 (6)
Pyrexia	55 (16)	15 (4)	1 (0.3)	0	71 (21)	1 (0.3)	0	21 (6)
Blood creatinine increased	53 (15)	10 (3)	0	1 (0.3)	64 (19)	0	0	37 (11)
Thrombocytopenia	32 (9)	13 (4)	13 (4)	6 (2)	64 (19)	10 (3)	2 (1)	46 (13)
Electrocardiogram QT prolonged	21 (6)	23 (7)	17 (5)	0	61 (18)	11 (3)	0	46 (13)
Dyspnea	58 (17)	16 (5)	11 (3)	1 (0.3)	58 (17)	0	0	5 (1)
Cough	47 (14)	9 (3)	0	0	56 (16)	0	0	4 (1)
Vomiting	44 (13)	8 (2)	2 (1)	0	54 (16)	1 (0.3)	0	12 (4)
Abdominal pain	40 (12)	11 (3)	2 (1)	0	53 (15)	0	0	13 (4)
Urinary tract infection	12 (4)	32 (9)	8 (2)	0	52 (15)	0	0	1 (0.3)

Safety population (N=345) included all pts with NSCLC who received ≥1 selpercatinib dose by data cutoff (30 Mar 2020). The adverse events listed are those that occurred at any grade in at least 15% of the patients as TEAEs. The total percentage for any given adverse event may be different than the sum of the components for the individual grades because of rounding. Note, hypersensitivity was observed in 9% of patients, all ≤Grade 3. §In total, thirteen patients had grade 5 TEAEs, including pneumonia, respiratory failure, sepsis, cardiac arrest (in 2 each), hypoxia, cerebrovascular accident, cerebral hemmorrhage, cardio-respiratory arrest, and multiple organ dysfunction syndrome (in one each). *No grade 5 TRAEs were observed. TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events.

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