Supplementary Appendix

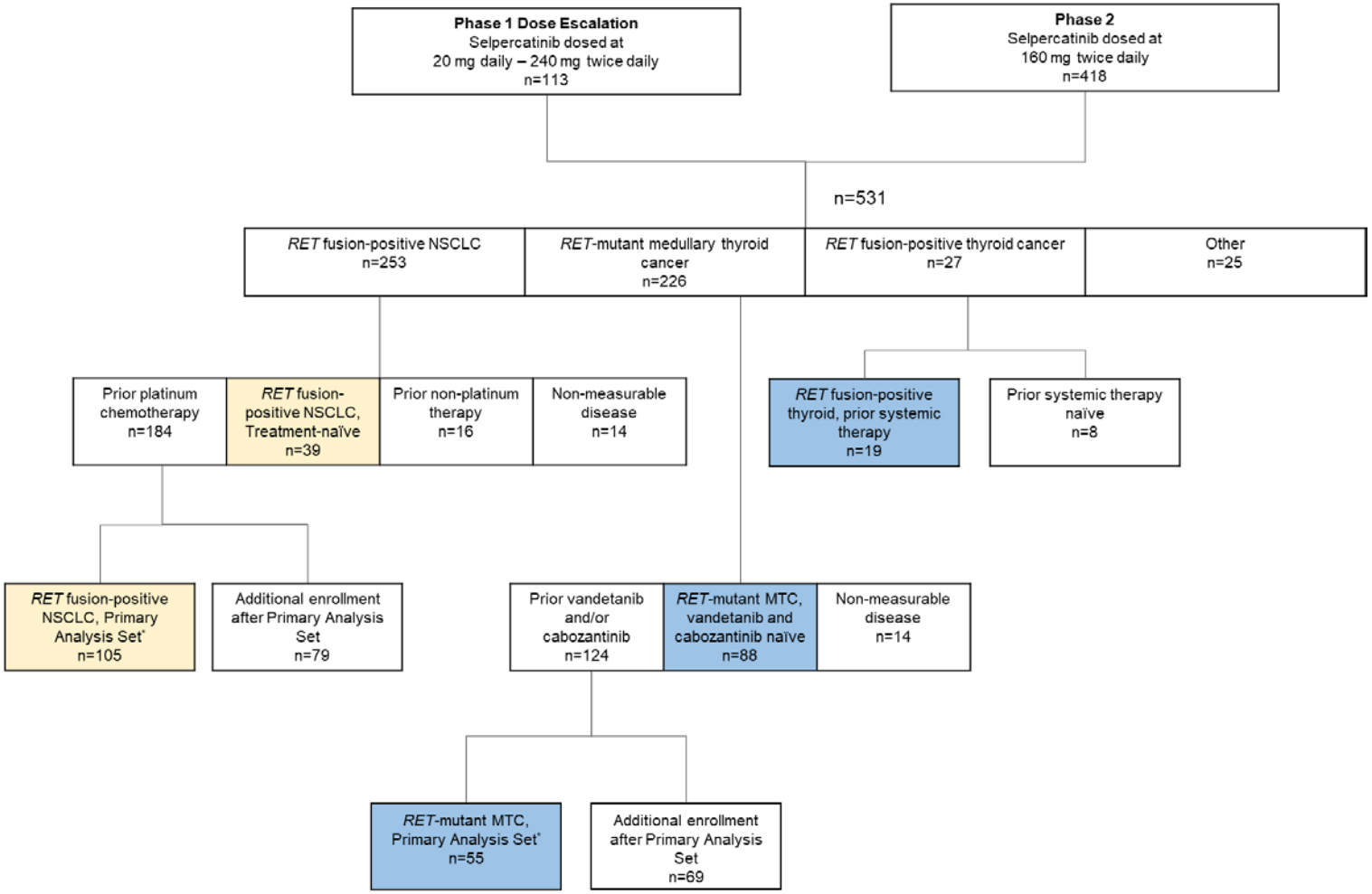
This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Drilon A, Oxnard GR, Tan DSW, et al. Efficacy of selpercatinib in *RET* fusion–positive non–small-cell lung cancer. N Engl J Med 2020;383:813-24. DOI: 10.1056/NEJMoa2005653

Efficacy of Selpercatinib in *RET* Fusion-Positive Non-Small Cell Lung Cancer Drilon A, Oxnard GR, Tan DSW, et al.

SUPPLEMENTARY APPENDIX

Figure S1: LIBRETTO–001 trial profile



*Per agreement with FDA, primary analysis sets defined as first consecutively treated 55 patients with RET-mutant vandetanib and/or cabozantinib previously-treated MTC and first consecutively treated 105 RET fusion-positive platinum-chemotherapy treated NSCLC. Primary analysis set established to ensure adequate selpercatinib treatment follow-up. Per agreement with FDA, patients with non-measurable disease at baseline enrolled during phase 1 dose escalation, but not the phase 2, were eligible for the primary analysis set.

Figure S2: Waterfall Plots of the Maximum Change in Tumor Size in Platinum-chemotherapy Pretreated (n=105) and Treatment-naïve patients (n=39) as assessed by blinded independent review committee. For each patient, the best (minimum) percent change from baseline in the sum of diameters for all target lesions is represented by a vertical bar. (A) platinum-chemotherapy pretreated patients; five patients are not shown as 2 had non-target lesions only, and 3 had no post-baseline target lesion measurement. (B) intracranial tumor response in evaluable platinum-chemotherapy pretreated patients with measurable CNS lesions. (C) treatment naïve patients.

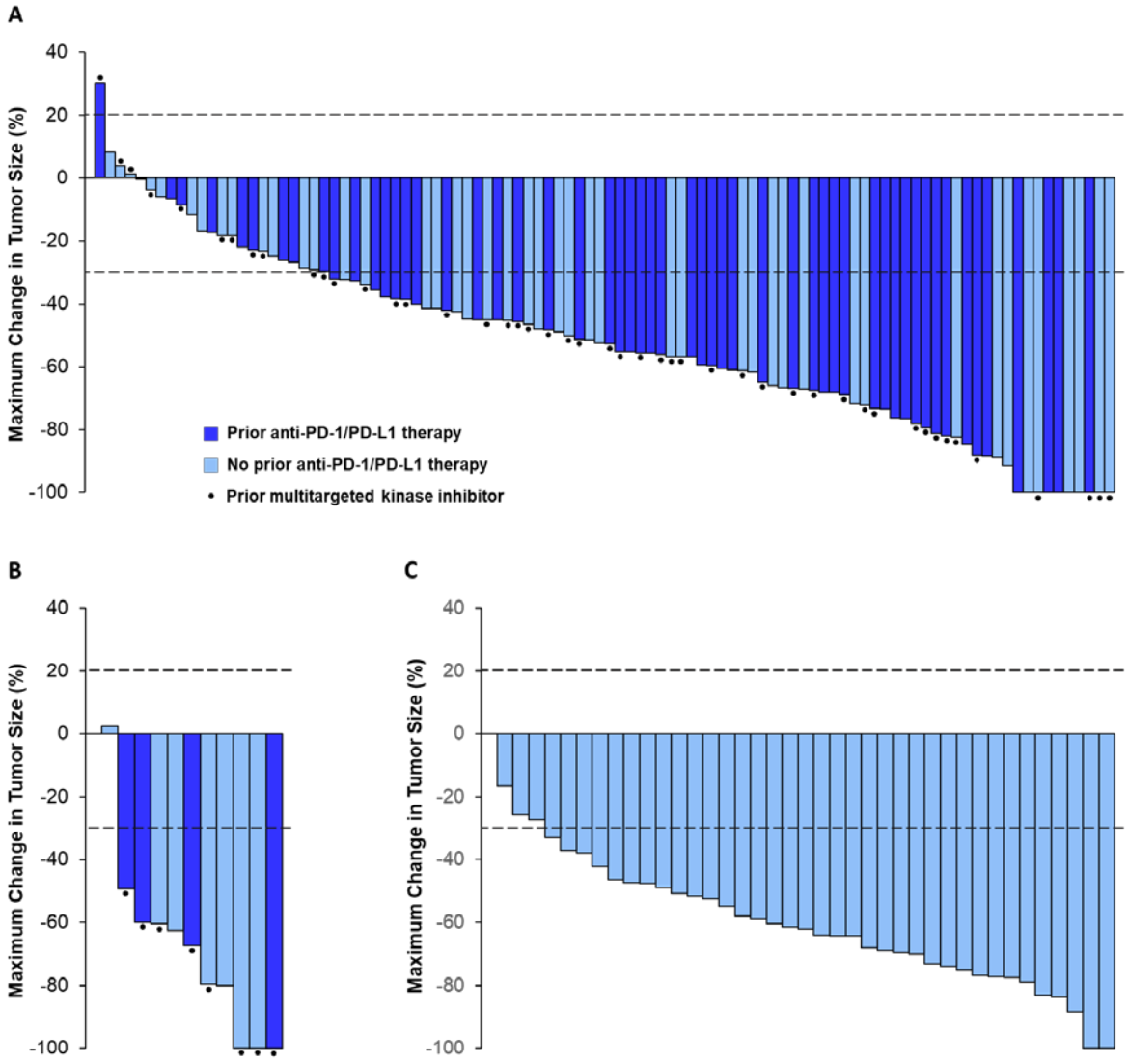
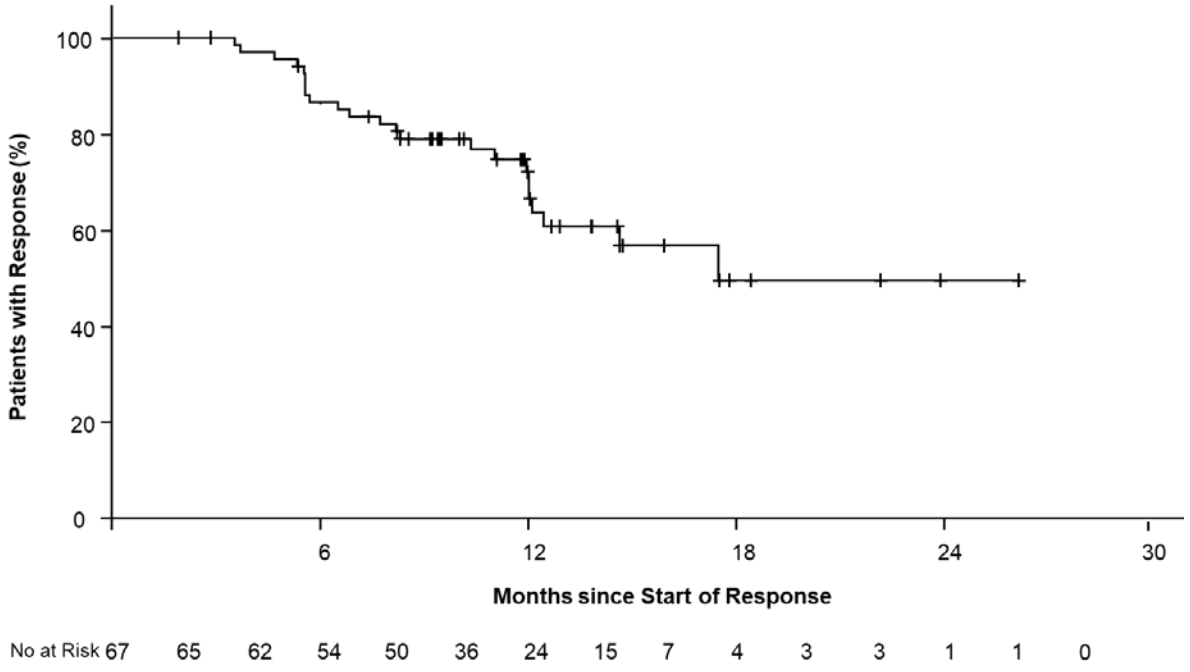


Figure S3: Kaplan-Meier Plots of Duration of Response and Progression-free Survival among Platinum-chemotherapy pretreated Patients as assessed by blinded independent review committee. Kaplan-Meier plots of (A) duration of response among 67 of 105 patients with a confirmed response, and (B) progression-free survival among all 105 patients in the platinum-chemotherapy pretreated group.

A.



B.

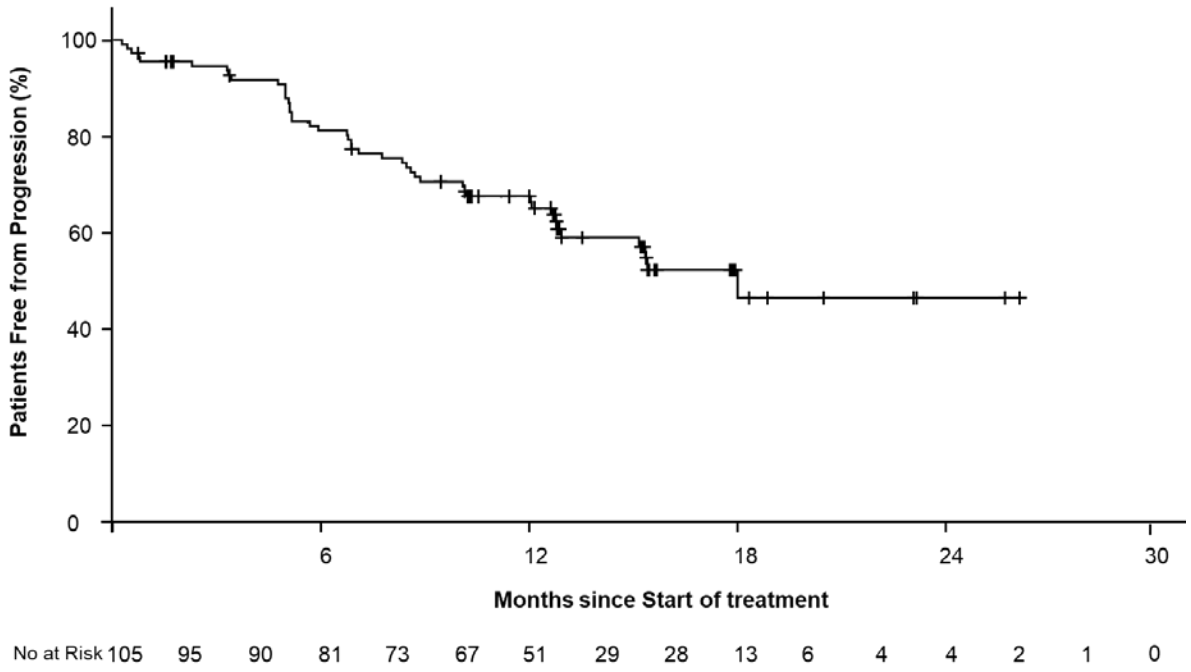


Figure S4: Waterfall Plot of the Maximum Change in Tumor Size in Platinum-chemotherapy Pretreated Patients (n=105) by fusion partner per investigator assessment. For each patient, the best (minimum) percent change from baseline in the sum of diameters for all target lesions is represented by a vertical bar. Data for five patients are not shown as one had non-target lesions only, and four had no post-baseline target lesion measurement.

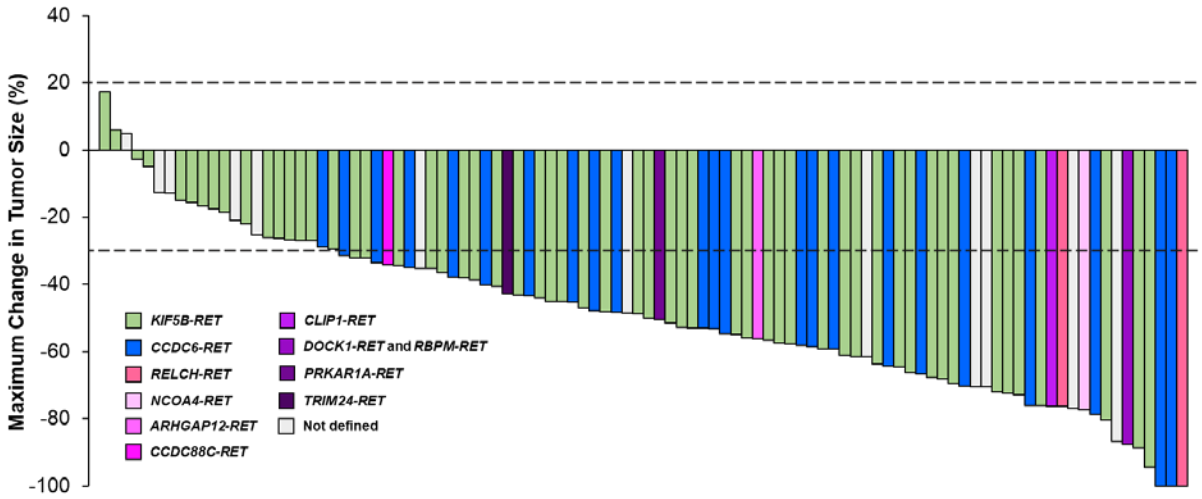


Figure S5: Outcomes in Platinum-chemotherapy Pretreated Patients (n=105).

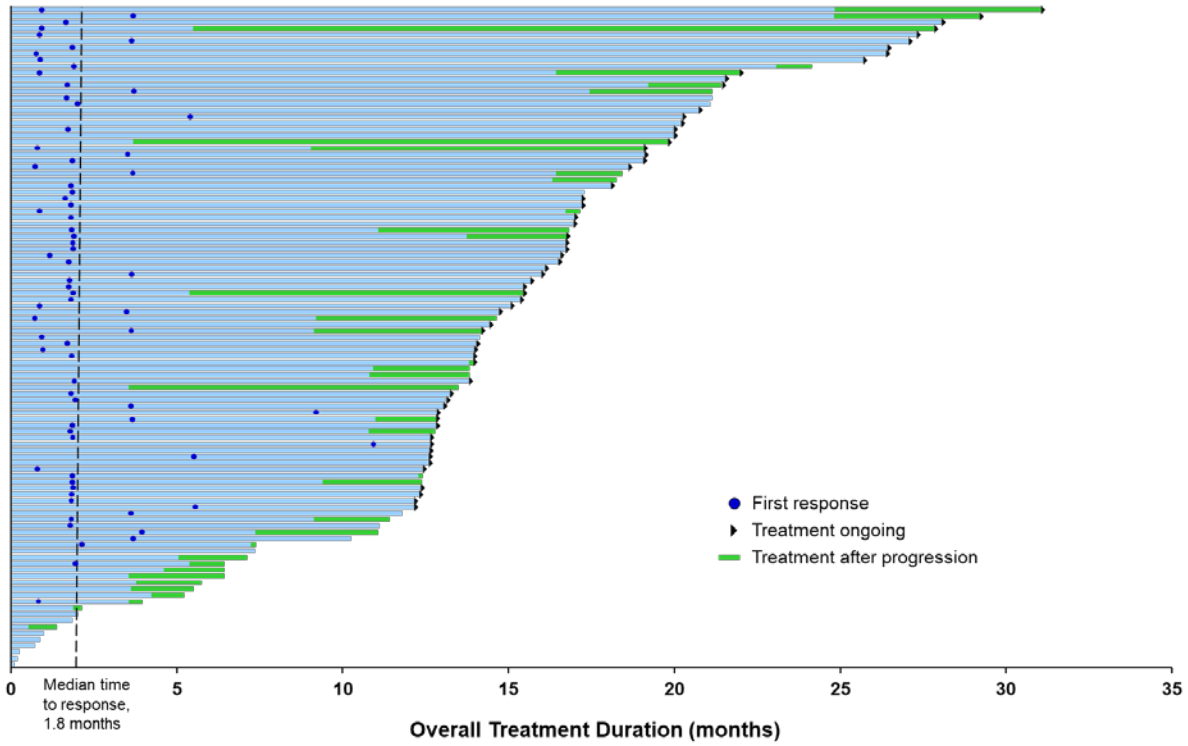


Figure S6: Waterfall Plot of the Maximum Change in Tumor Size in Treatment-naive Patients (n=39) by fusion partner per investigator assessment. For each patient, the best (minimum) percent change from baseline in the sum of diameters for all target lesions is represented by a vertical bar. One patient discontinued treatment prior to any post-baseline imaging assessment and is not shown in the waterfall plot.

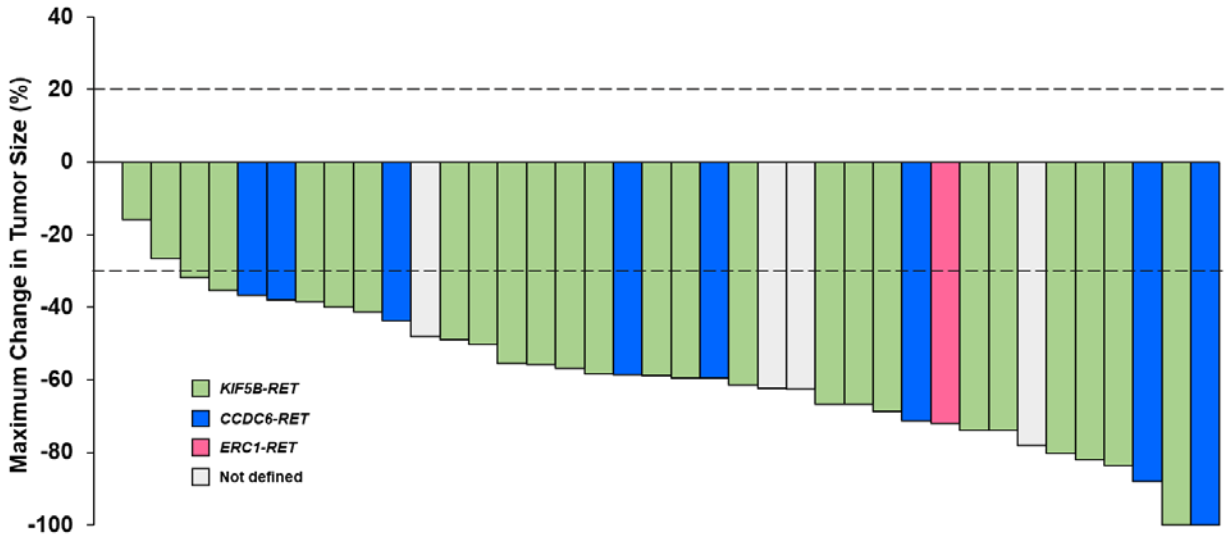


Table S1: LIBRETTO–001 patient enrollment

Country (number of sites)	*RET* Fusion-positive NSCLC (n=253)	*RET*-mutant MTC (n=226)	RET Fusion-positive thyroid cancer (n=27)	Other cancers* (n=25)
United States (32)	138	165	25	19
France (5)	13	26	0	0
Japan (11)	32	0	0	2
Australia (2)	3	26	1	0
South Korea (5)	23	0	0	0
Singapore (1)	13	2	0	0
Switzerland (1)	8	4	0	1
Hong Kong (1)	9	0	1	0
Spain (3)	7	2	0	3
Israel (2)	5	1	0	0
Denmark (1)	1	0	0	0
Italy (1)	1	0	0	0

*Includes other RET-altered cancers or RET alteration unknown/negative

Table S2: Local diagnostic assays used to detect RET alterations in NSCLC patients (n=144) enrolled in LIBRETTO–001		
Laboratory	**Test Name**	**n (%)**
Assistance Publique des Hopitaux de Paris	Somatic lung NGS RNA panel	1 (1)
Basel University Hospital	Oncomine Fusion Panel	2 (1)
Beijing Genome Institute	Oseq	2 (1)
Brigham and Womens Hospital	Oncopanel	4 (3)
Brigham and Womens Hospital	RET FISH	1 (1)
Burning Rock Dx	Burning Rock Langqing Test	1 (1)
Burning Rock Dx	Oncoscreen Plus	1 (1)
Centre Hospitalier Universitaire de Nimes	Oncomine NGS panel	1 (1)
Columbia University Medical Center	Columbia Targeted Fusion Panel	1 (1)
Foundation Medicine	Foundation T5a	2 (1)
Foundation Medicine	FoundationAct	2 (1)
Foundation Medicine	FoundationOne	25 (17)
Foundation Medicine	FoundationOne CDx	9 (6)
Geneseeq	Geneseeq One	1 (1)
Genomics for Life	Somatic DNA Targeted Sequencing Panel TSP22 and RNA Fusion	1 (1)
Guardant Health	Guardant360	13 (9)
Guardant Health	Not provided	1 (1)
Gustave Roussy	Gustave Roussy NGS	1 (1)
Gustave Roussy	Oncomine Comprehensive Assay v3	1 (1)
Gustave Roussy	RET FISH	1 (1)
HaploX	HapOnco 451 Gene Detection	1 (1)
Hong Kong Molecular Pathology Diagnostic Centre	RET FISH	1 (1)
Hopitaux Universitaires Paris Centre	RET FISH	1 (1)
Ignyta	Trailblaze Pharos	2 (1)
Institute for Haemopathology Hamburg	NEOselect	1 (1)
Instituto Nazionale dei Tumori	FusionPlex Lung Panel	1 (1)
Laboratorio de Dianas Terapeuticas	Oncomine Focus Assay	1 (1)
MD Anderson Cancer Center	RET FISH	1 (1)
MD Anderson Cancer Center	Solid Tumor Genomic Assay 2018	2 (1)
Macrogen	Axen Cancer Panel 2	1 (1)
Massachusetts General Hospital	RET FISH	1 (1)
Massachusetts General Hospital	Solid fusion assay	2 (1)
Mayo Clinic Laboratories	Lung Panel Rearrangement Tumor	2 (1)
Mayo Medical Laboratory	RET FISH	1 (1)
Memorial Sloan Kettering Cancer Center	FusionPlex Custom Solid Panel	2 (1)
Memorial Sloan Kettering Cancer Center	MSK IMPACT	12 (8)
NYU Langone Hospitals	Oncomine Focus Assay	1 (1)
Neo New Oncology	NEOliquid	1 (1)
OncoDNA	OncoDeep	1 (1)
Paradigm	FusionPlex Solid Tumor Panel	2 (1)
Pathgroup Oncology	RET FISH	1 (1)
Pathline Emerge	RET FISH	1 (1)
Resolution Bioscience	Resolution ctDx Lung Assay	1 (1)

SRL	Oncomine Cancer Panel	5 (3)
SRL	Oncomine Comprehensive Assay v3	4 (3)
SRL	RET FISH	1 (1)
SRL	RET RTPCR	2 (1)
Samsung Biomedical Research Institute	Not provided	3 (2)
Samsung Genome Institute	CancerSCAN	2 (1)
Sema4	Sema4 Solid Tumor Panel	1 (1)
Seoul National University Bundang Hospital	SNUBH Pan cancer test	3 (2)
Severance Hospital	TST170	1 (1)
Strata Oncology	StrataNGS	2 (1)
UC San Diego Health System	Comprehensive NGS Solid Tumor Mutation Panel	1 (1)
University Hospital	Focused Solid Tumor Assay	1 (1)
University of Bern Institute of Pathology	Oncomine Focus Assay	1 (1)
University of Pennsylvania Center for Personalized Diagnostics	Solid Tumor Genomic Sequencing Panel	1 (1)
University of Pennsylvania Cytogenetics Laboratory	RET FISH	1 (1)
University of Vermont Medical Center	Gene Panel NSCLC	1 (1)
University of Virginia Health System	RET FISH	1 (1)
Yale Pathology Laboratories	Oncomine Gene Panel	1 (1)
Zurich University Hospital	Oncomine Focus Assay	1 (1)

Table S3. Best Overall Response in Platinum Pretreated Patients by Prior Anti-PD-1 or Anti-PD-L1 Therapy		
Response	**Independent Review**	
	Prior Anti-PD-1/PD-L1 (n=58)	Anti-PD-1/PD-L1 Naïve (n=47)
Objective response rate (95% CI) – %	66 (52-78)	62 (46-76)
Best response – no. %		
Complete response	1 (2)	1 (2)
Partial response	37 (64)	28 (60)
Stable disease	13 (22)	17 (36)
Progressive disease	3 (5)	1 (2)
Not evaluable	4 (7)	0
Duration of response		
Median, months (95% CI)	NE (12-NE)	17.5 (10.3-NE)
Median follow-up, months	11.9	12.7

Table S4. Best Overall Response in Platinum Pretreated Patients by Prior Multikinase Inhibitors (MKI)		
Response	**Independent Review**	
	Prior MKI (n=50)	MKI Naïve (n=55)
Objective response rate (95% CI) – %	64 (49-77)	64 (50-76)
Best response – no. %		
Complete response	2 (4)	0
Partial response	30 (60)	35 (64)
Stable disease	13 (26)	17 (31)
Progressive disease	3 (6)	1 (2)
Not evaluable	2 (4)	2 (4)
Duration of response		
Median, months (95% CI)	NE (12-NE)	17.5 (12-NE)
Median follow-up, months	12.7	12.0

Table S5: Adverse Events in All Selpercatinib Treated Patients (N=531)								
Adverse Event	**Adverse Events, Regardless of Attribution**					**Treatment-Related Adverse Events**		
	Percent of patients with event							
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**
Diarrhea	145 (27)	48 (9)	20 (4)	0	213 (40)	9 (2)	0	114 (22)
Dry mouth	177 (33)	25 (5)	0	0	202 (38)	0	0	174 (33)
Hypertension	22 (4)	75 (14)	92 (17)	1 (<1)	190 (36)	56 (11)	1 (<1)	128 (24)
Aspartate aminotransferase increased	100 (19)	29 (6)	36 (7)	5 (1)	170 (32)	27 (5)	4 (1)	136 (26)
Fatigue	96 (18)	60 (11)	5 (1)	0	161 (30)	2 (<1)	0	96 (18)
Alanine aminotransferase increased	80 (15)	25 (5)	47 (9)	6 (1)	158 (30)	38 (7)	5 (1)	130 (25)
Nausea	111 (21)	30 (6)	3 (1)	0	144 (27)	2 (<1)	0	56 (11)
Constipation	113 (21)	25 (5)	3 (1)	0	141 (27)	1 (<1)	0	66 (12)
Edema peripheral	119 (22)	21 (4)	1 (<1)	0	141 (27)	0	0	77 (15)
Headache	94 (18)	26 (5)	9 (2)	0	129 (24)	2 (<1)	0	44 (8)
Blood creatinine increased	81 (15)	27 (5)	0	1 (<1)	109 (21)	0	0	59 (11)
Abdominal pain	72 (14)	24 (5)	11 (2)	0	107 (20)	1 (<1)	0	25 (5)
Rash	78 (15)	18 (3)	3 (1)	0	99 (19)	3 (1)	0	61 (12)
Vomiting	72 (14)	21 (4)	2 (<1)	0	95 (18)	1 (<1)	0	25 (5)
Electrocardiogram QT prolonged	26 (5)	39 (7)	22 (4)	1 (<1)	88 (17)	15 (3)	1 (<1)	65 (12)
Cough	74 (14)	13 (2)	0	0	87 (16)	0	0	6 (1)
Dyspnea	52 (10)	18 (3)	11 (2)	2 (<1)	83 (16)	0	0	7 (1)

*The adverse events listed here are those that occurred at any grade in at least 15% of patients, regardless of attribution. The relatedness of adverse events to treatment was determined by the investigators. Total % for any given AE may be different than the sum of the individual grades, due to rounding. In total, 19 patients experience grade 5 adverse events including cardiac arrest (3), sepsis (3) respiratory failure (2), brain herniation, cardiac failure, cerebral hemorrhage, cerebrovascular accident, general physical health deterioration, hemoptysis, hypoxia, multiple organ dysfunction syndrome, neoplasm progression, pneumonia, and post-procedure hemorrhage (1 each), all grade 5 adverse events deemed unrelated to selpercatinib.