Instituto de Investigación Hospital 12 de Octubre

cnio SPANISH NATIONAL CANCER RESEARCH CENTRE

UNIVERSIDAD COMPLUTENSE MADRID

RET fusion-positive NSCLC

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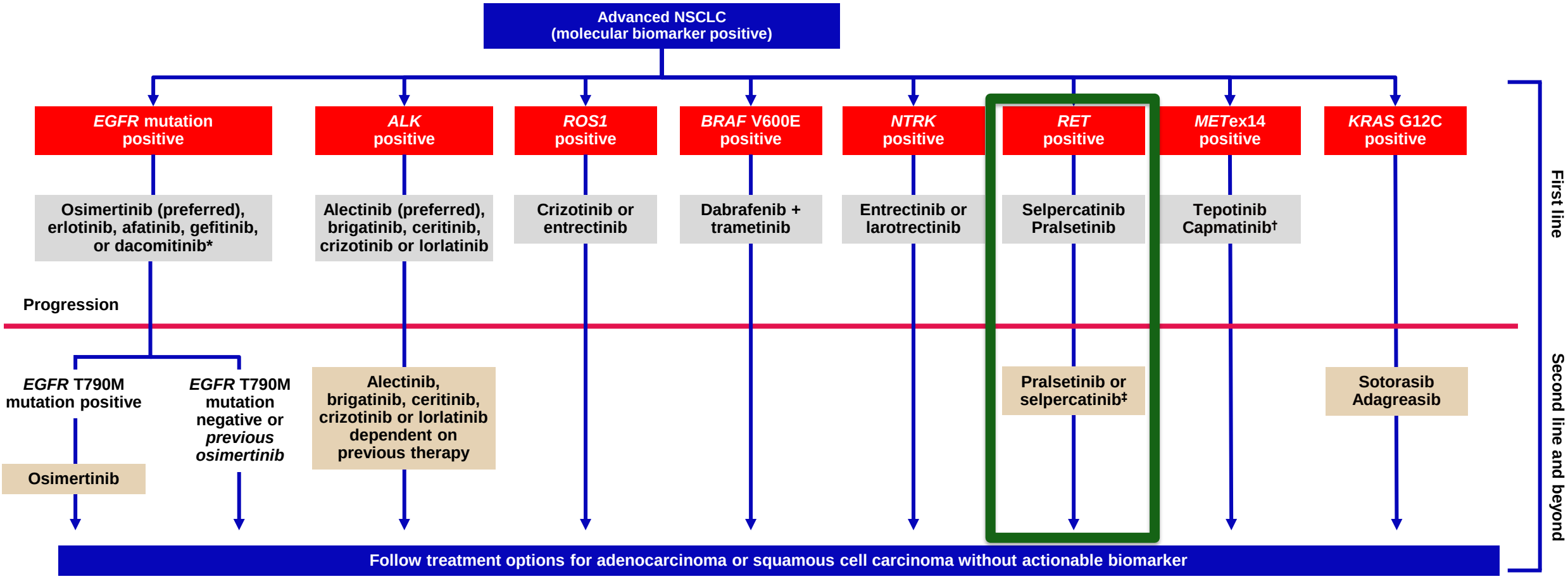
Disclosures

- **Honoraria (self)**: Amgen, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Ipsen, Merck, Merck Sharp & Dohme, Mirati, Novartis, Pfizer, Pharmamar, Roche, Sanofi, Servier, Sysmex, Takeda
- **Speaker Bureau / Expert testimony**: AstraZeneca, Bristol Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Roche
- **Leadership role**: Altum Sequencing, Stab therapeutics
- **Research grant / Funding (self)**: AstraZeneca, Bristol Myers Squibb, Merck Sharp & Dohme
- **Spouse / Financial dependant**: AAA, Advanz Pharma, Bayer, HMP, Ipsen, Merck, Merck, Sharp & Dohme, Midatech Pharma, Novartis, Pfizer, PharmaMar, Pierre Fabre, Roche, Sanofi, Servier

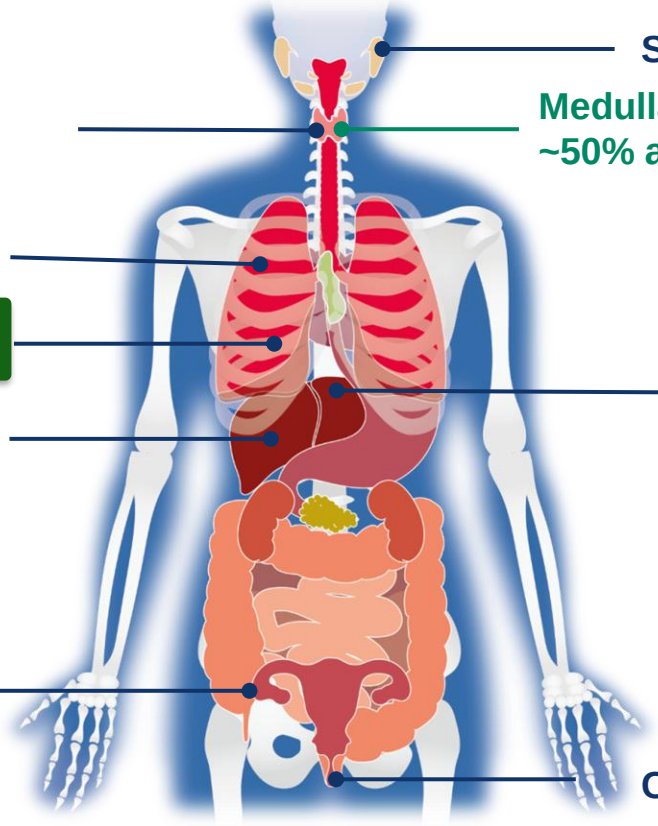
Current Treatment Paradigm for Molecular Biomarker–Positive Advanced NSCLC



*Afatinib, dacomitinib, erlotinib, gefitinib, osimertinib approved for *EGFR* exon19del, exon 21 L858R; afatinib for *EGFR* G719X, S768I, L861Q.
†Capmatinib is not currently approved in Europe. ‡Following prior treatment with immunotherapy and/or platinum-based chemotherapy.

Afatinib SmPC; Alectinib SmPC; Capmatinib PI; Ceritinib SmPC; Crizotinib SmPC; Dabrafenib SmPC; Dacomitinib SmPC; Entrectinib SmPC; Erlotinib SmPC; Gefitinib SmPC; Larotrectinib SmPC; Osimertinib SmPC; Pralsetinib SmPC; Selpercatinib SmPC; Trametinib SmPC; Sotorasib SmPC.

RET Fusions are Oncogenic Drivers in Multiple Tumor Types



Salivary gland (intraductal) including MASC[4,5]

Medullary thyroid cancer (*RET* mutations, sporadic in ~50% and germline as part of MEN2 syndrome in ~100%)[6,7]

Papillary thyroid cancer (~10–20%)[1,2]

Breast (0.1%)[3]

NSCLC (1% to 2%)[1]

Cholangiocarcinoma[2,8]

Pancreatic adenocarcinoma (0.6%)[2]

Ovarian epithelial carcinoma (1.9%)[2]

Colorectal (0.2% to 7.6%)[9–11]

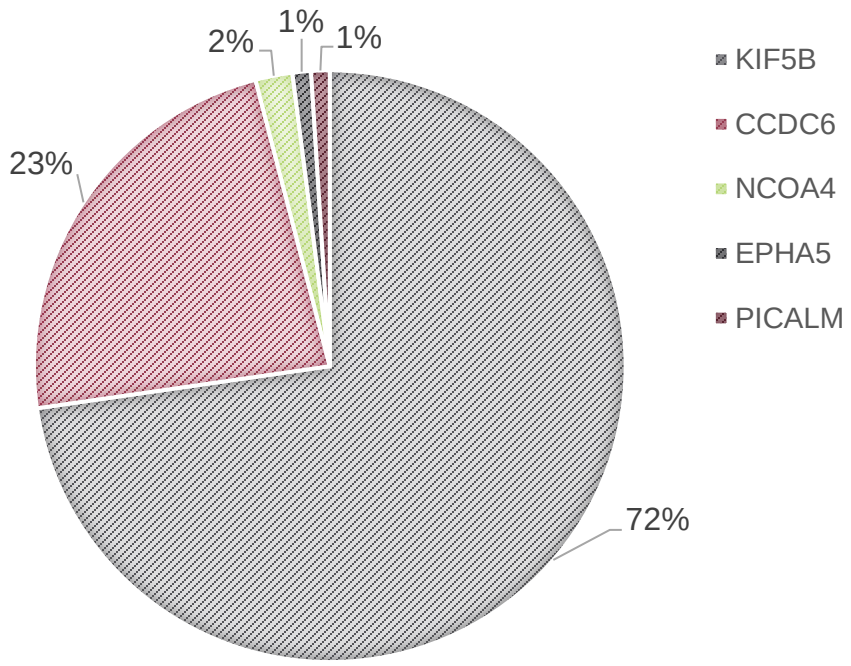
- **Standard therapies provide limited benefit for patients with *RET* fusion-positive tumors[12–16]**
- **Outcomes with immunotherapies in patients with *RET* fusion-positive NSCLC are poor[17–20]**

The prevalence of *RET* fusion is shown. MASC, mammary analog secretory carcinoma of the salivary gland; NSCLC, non-small cell lung cancer; RET, rearranged during transfection.

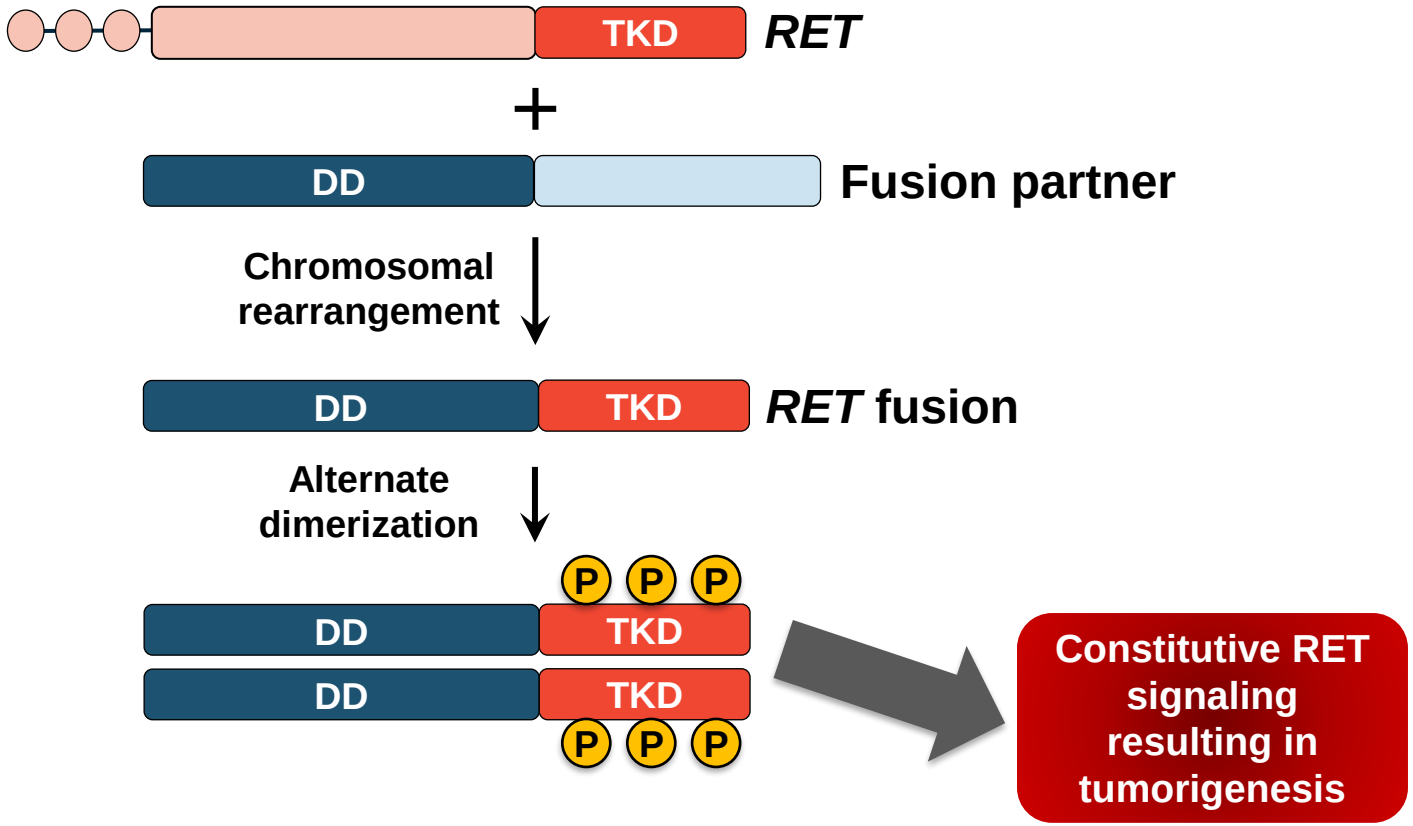
1. Drilon A, et al. *Nat Rev Clin Oncol* 2018;15:151–67; 2. Kato S, et al. *Clin Cancer Res* 2017;23:1988–97; 3. Paratala BS, et al. *Nat Commun* 2018;9:4821; 4. Skalova A, et al. *Am J Surg Pathol* 2018;42:234–46; 5. Skalova A, et al. *Am J Surg Pathol* 2018;42:1445–55; 6. Krampitz GW, et al. *Cancer* 2014;120:1920–31; 7. Subbiah V, et al. *J Clin Oncol* 2020;38:1209–21; 8. Gainor JF, et al. *J Clin Oncol* 2019;37(suppl 15):Abstract 9008; 9. Le Rolle AF, et al. *Oncotarget* 2015;6:28929–37; 10. Cremolini C, et al. *Ann Oncol* 2017;28:3009–14; 11. Pietrantonio F, et al. *Ann Oncol* 2018;29:1394–401; 12. Gandhi L, et al. *N Engl J Med* 2018;378:2078; 13. Hellman MD, et al. *N Engl J Med* 2018;378:2093–104; 14. Mok TSK, et al. *Lancet* 2019;393:1819–30; 15. Sandler A, et al. *N Engl J Med* 2006;355:2542–50; 16. Scagliotti GV, et al. *J Clin Oncol* 2008;26:3543–51; 17. Sabari JK, et al. *J Clin Oncol* 2018;36:9034; 18. Offin M, et al. *JCO Precis Oncol* 2019;3:PO.18.00386; 19. Tufman A, et al. *J Clin Oncol* 2018;36(suppl 15):Abstract e21071; 20. Mazieres J, et al. *Ann Oncol* 2019;30:1321–8.

Pathobiology of *RET* in NSCLC

Common Fusion Partners[1]

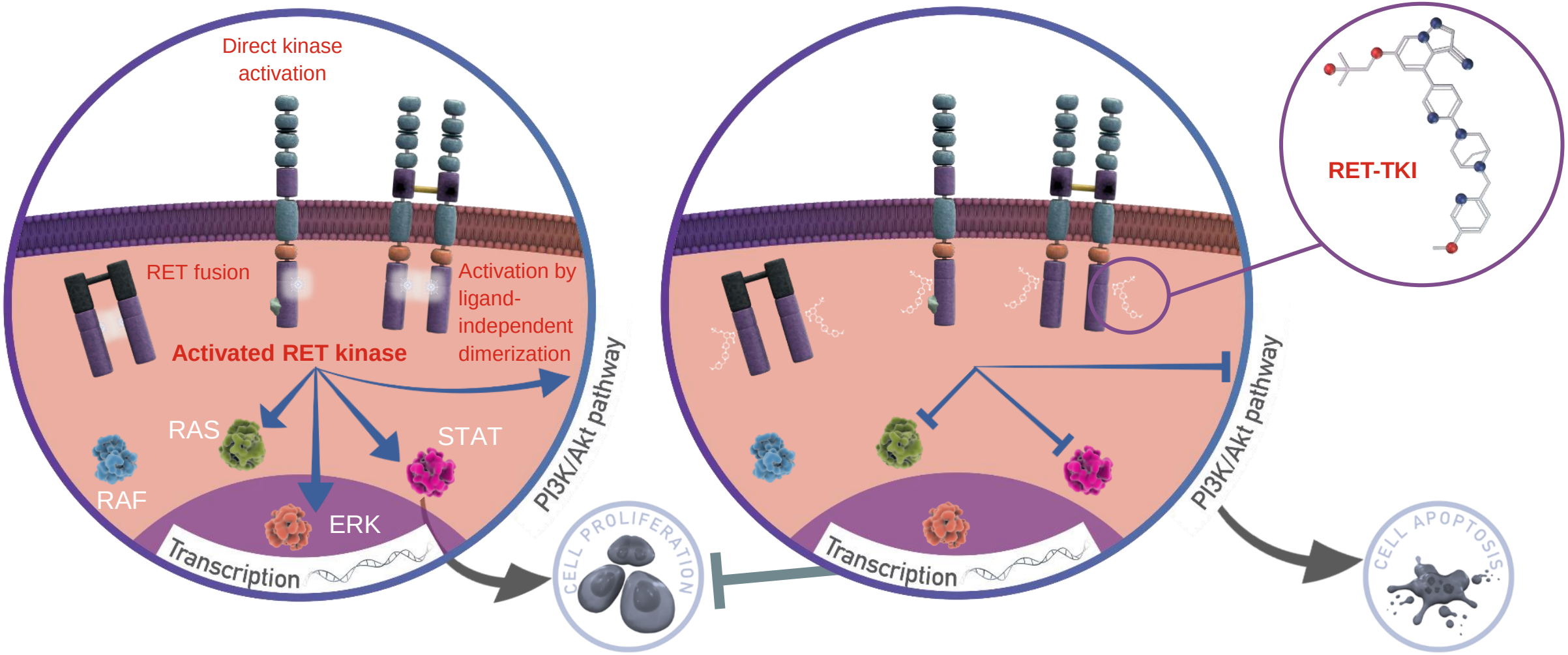


RET Fusions[2]



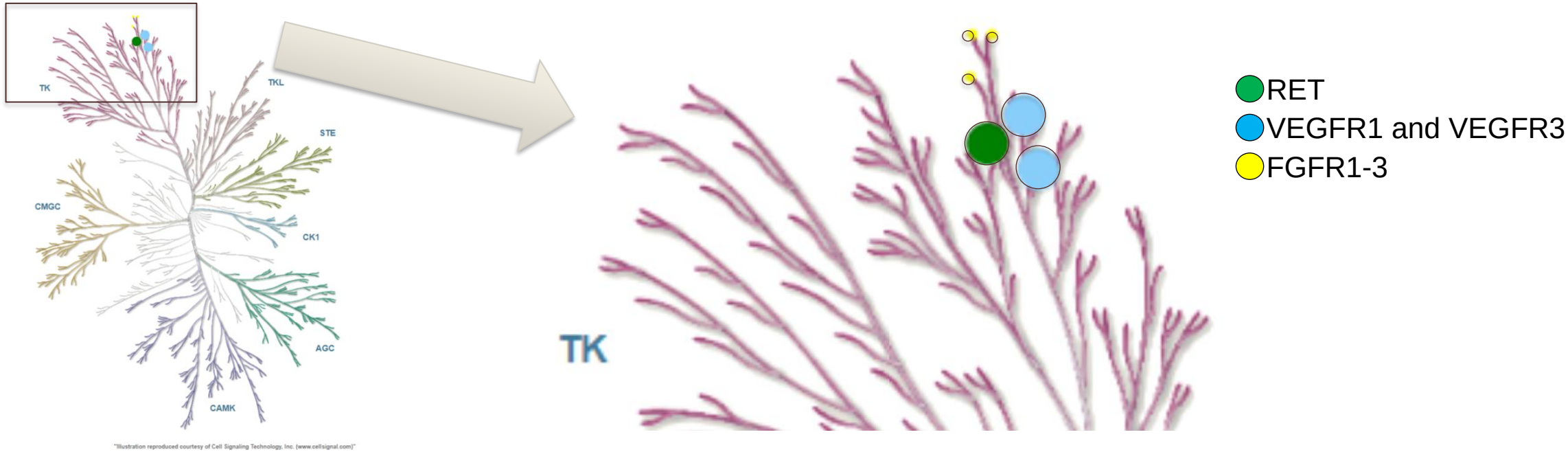
1. Mendoza L. *Oncol Rev* 2018;12:352; 2. Ferrara R, et al. *J Thorac Oncol* 2018;13:27–45.

Mechanism of Action of RET-TKIs



Akt, protein kinase B; ERK, extracellular signal-regulated kinase; PI3K; phosphoinositide 3-kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RET, rearranged during transfection; STAT, signal transducer and activator of transcription.

Selpercatinib is a Highly Selective RET Inhibitor



"Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)"

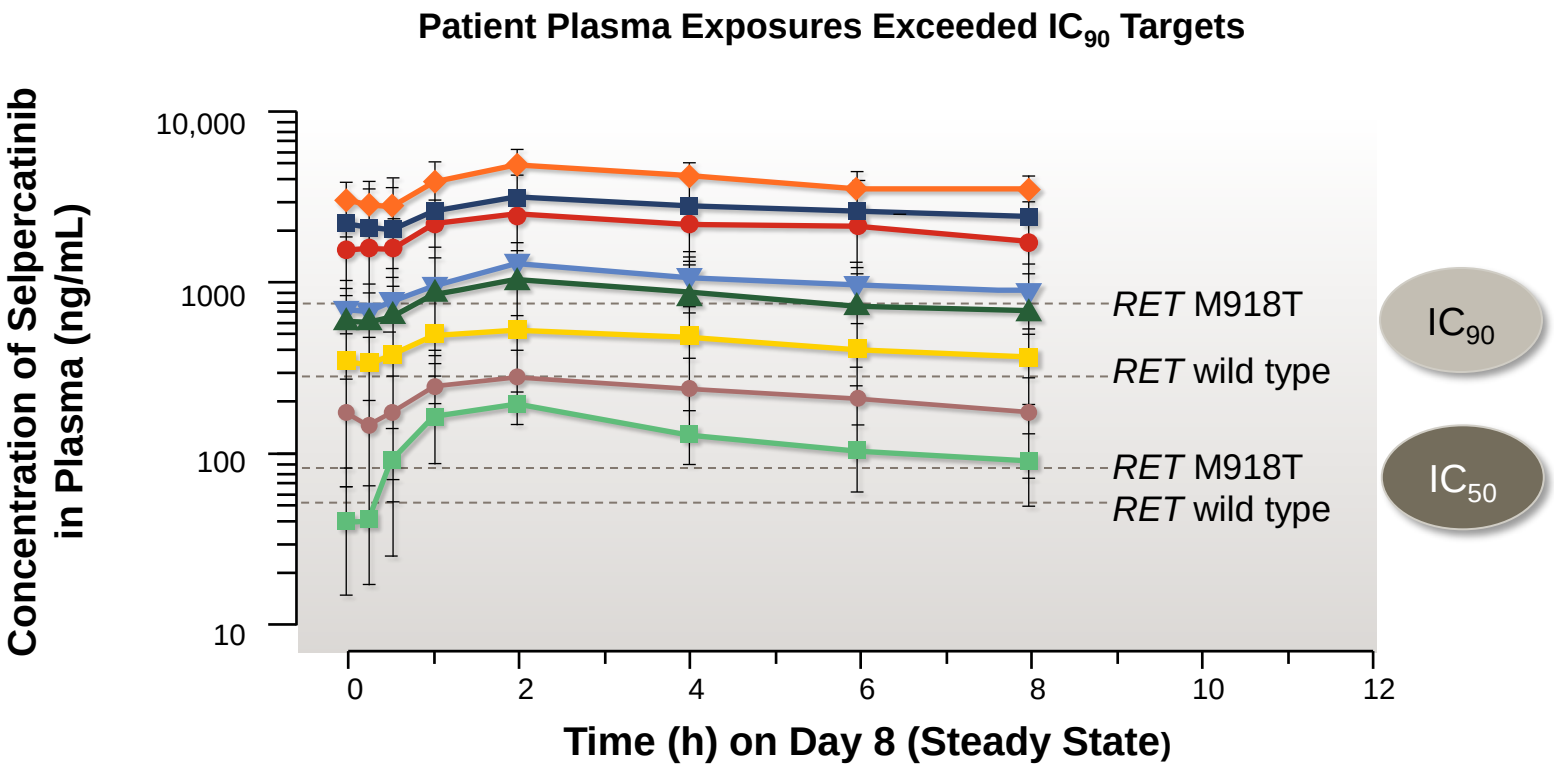
Enzyme Assay 1 mM ATP	RET	RET V804M	RET V804L	RET M918T	RET S891A	RET L790F	RET A883F	VEGFR1	VEGFR3
IC50 (nM)	2.8-17.3	6.4-36.7	30.5	1.5-28.7	32.9	0.92	67.8	27.7	11.9

Cellular Assay	KIF5B-RET	VEGFR2	VEGFR3	FGFR1	FGFR2
IC50 (nM)	3.3-4	683	33	248-1286	242

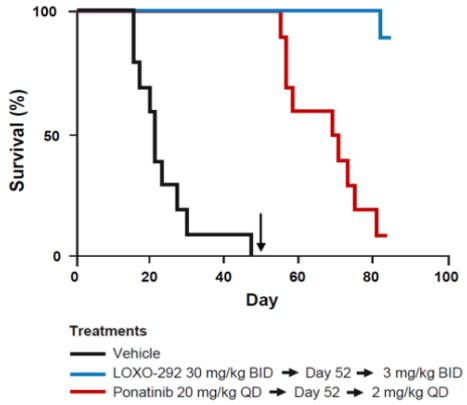
1. Data on File; 2. http://www.kinhub.org/kinmap/. Accessed April 24, 2020.

Selpercatinib is a Potent RET Inhibitor

LIBRETTO-001: Phase 1 Pharmacokinetics



Horizontal lines represent the plasma level at which the unbound selpercatinib concentration corresponds to IC_{50} or IC_{90} of the indicated target based on cellular assays



IC_{90}, inhibitory concentration 90%.

Oxnard GR, et al. *J Thorac Oncol* 2018;13(suppl):Abstract OA12.07.

LIBRETTO-001: Selpercatinib

Key inclusion criteria

- Advanced or metastatic *RET* fusion-positive NSCLC or thyroid cancer or *RET*-mutant medullary thyroid cancer
- ECOG PS 0–2

(n=796)

- *RET* fusion-positive NSCLC (n=356)
- *RET*-mutant MTC (n=319)
- *RET* fusion-positive TC (n=54)
- Other (n=67)

Dose escalation
Selpercatinib
20 mg/day to
240 mg BID

Dose expansion
Selpercatinib
160 mg BID q4w

***RET* fusion-positive NSCLC (n=355)**
[Treatment naïve, n=69
Prior platinum-based chemotherapy, n=247
Prior other systemic therapy, n=19
Non-measurable disease, n=20]

Primary endpoint

- ORR (RECIST v1.1, IRC)

Secondary endpoints

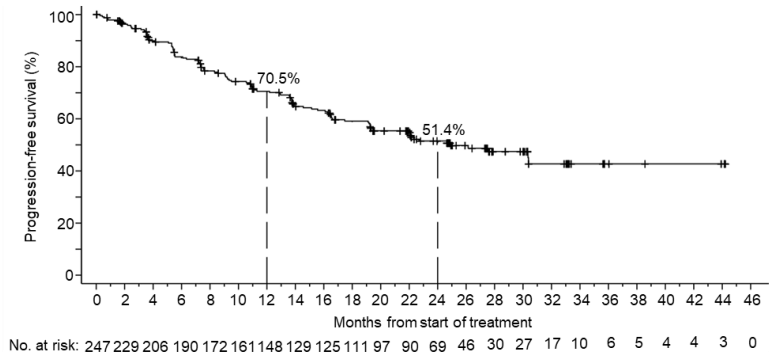
- DoR, PFS, HRQoL, safety

Objective response rate

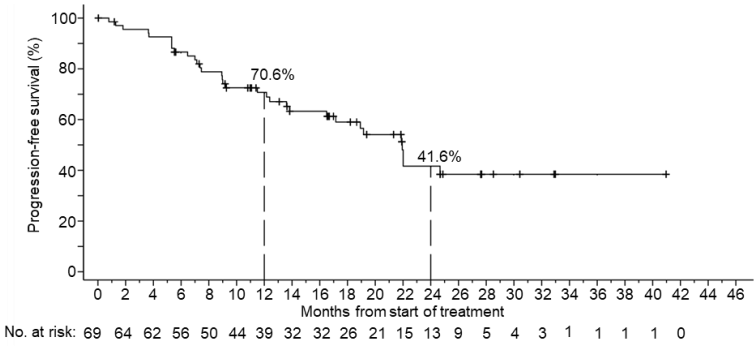
15 June 2021 cut-off	Previously treated (n=247)	Treatment-naïve (n=69)
ORR, n (%) [95%CI]	151 (**61.1**) [54.7, 67.2]	58 (**84.1**) [73.3, 91.8]

Progression-free survival

Previously treated
mPFS 24.9 mo (95%CI 19.3, NE)

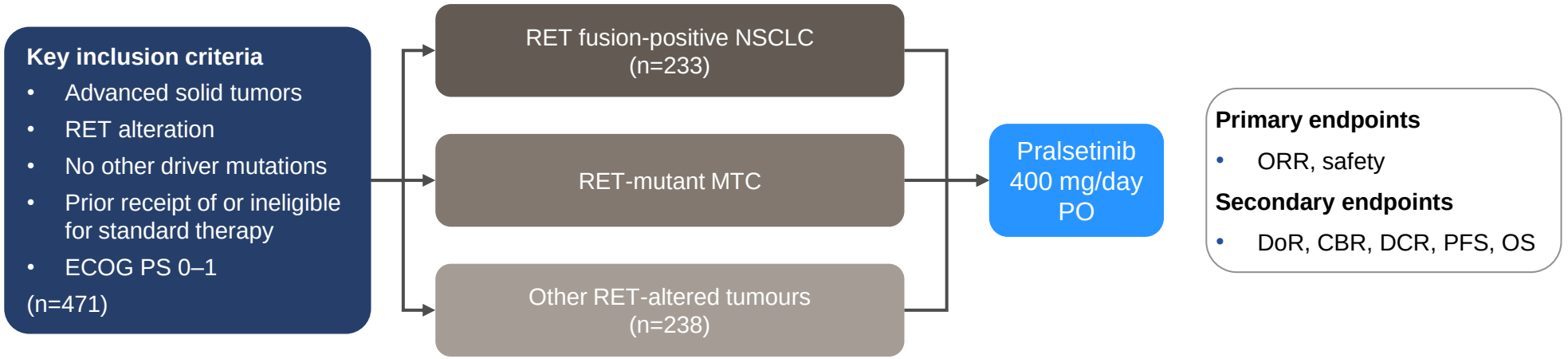


Treatment-naïve
mPFS 22.0 mo (95%CI 13.8, NE)



Drilon A, et al. *Ann Oncol* 2022;33(suppl):Abstract 27P.

ARROW: Pralsetinib



Objective response rate[1]

22 May 2020 cut-off	Previously treated (n=136)	Treatment-naïve (n=75)
ORR, n (%) [95%CI]	80 (**58.8**) [50.1, 67.2]	54 (**72.0**) [60.4, 81.8]
BOR, n (%)		
CR	7 (5.1)	4 (5.3)
PR	73 (53.7)	50 (66.7)

Progression-free survival[2]

22 May 2020 cut-off	Previously treated (n=136)	Treatment-naïve (n=75)
mPFS, months (95%CI)	**16.5** (10.5, 24.1)	**13.0** (9.1, NR)

1. Pralsetinib SmPC 2021; 2. Curigliano G, et al. *J Clin Oncol* 2021;39(suppl 15):Abstract 9089.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

First-Line Selpercatinib or Chemotherapy and Pembrolizumab in *RET* Fusion–Positive NSCLC

Caicun Zhou, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Herbert H. Loong, M.B., B.S., Keunchil Park, M.D., Ph.D., Maurice Pérol, M.D., Edurne Arriola, M.D., Ph.D., Silvia Novello, M.D., Ph.D., Baohui Han, M.D., Ph.D., Jianying Zhou, M.D., Andrea Ardizzoni, M.D., M. Perez Mak, M.D., Ph.D., Fernando C. Santini, M.D., Yasir Y. Elamin, M.D., Alexander Drilon, M.D., Jürgen Wolf, M.D., Nalin Payakachat, Ph.D., Minji K. Uh, Ph.D., Deborah Rajakumar, B.D.S., M.Sc., Hongmei Han, M.S., M.Ap.St., Tarun Puri, M.D., Victoria Soldatenkova, M.S., A. Bence Lin, Ph.D., Boris K. Lin, M.D., Ph.D., and Koichi Goto, M.D., Ph.D., for the LIBRETTO-431 Trial Investigators*

LIBRETTO-431 phase 3 open-label study design

Key Eligibility Criteria

- Stage IIIB-IIIC[1], IV non-squamous NSCLC
- No prior systemic therapy for metastatic disease
- *RET* fusion identified via NGS or PCR
- ECOG PS 0-2
- Symptomatic CNS metastases excluded

Stratification factors:

- Geography (East Asian vs. non-East Asian)
- Brain metastases (present vs. absent/unknown)[2]
- Investigator's choice of treatment with pembrolizumab

R 2:1[3]

Selpercatinib (160 mg BID)
N= 159

Carboplatin (AUC 5) or **Cisplatin** (75 mg/m^2)
+ **Pemetrexed** (500 mg/m^2)
+/- **Pembrolizumab** (200 mg)
N= 102

Optional Crossover

Selpercatinib
(Upon BICR confirmed PD)

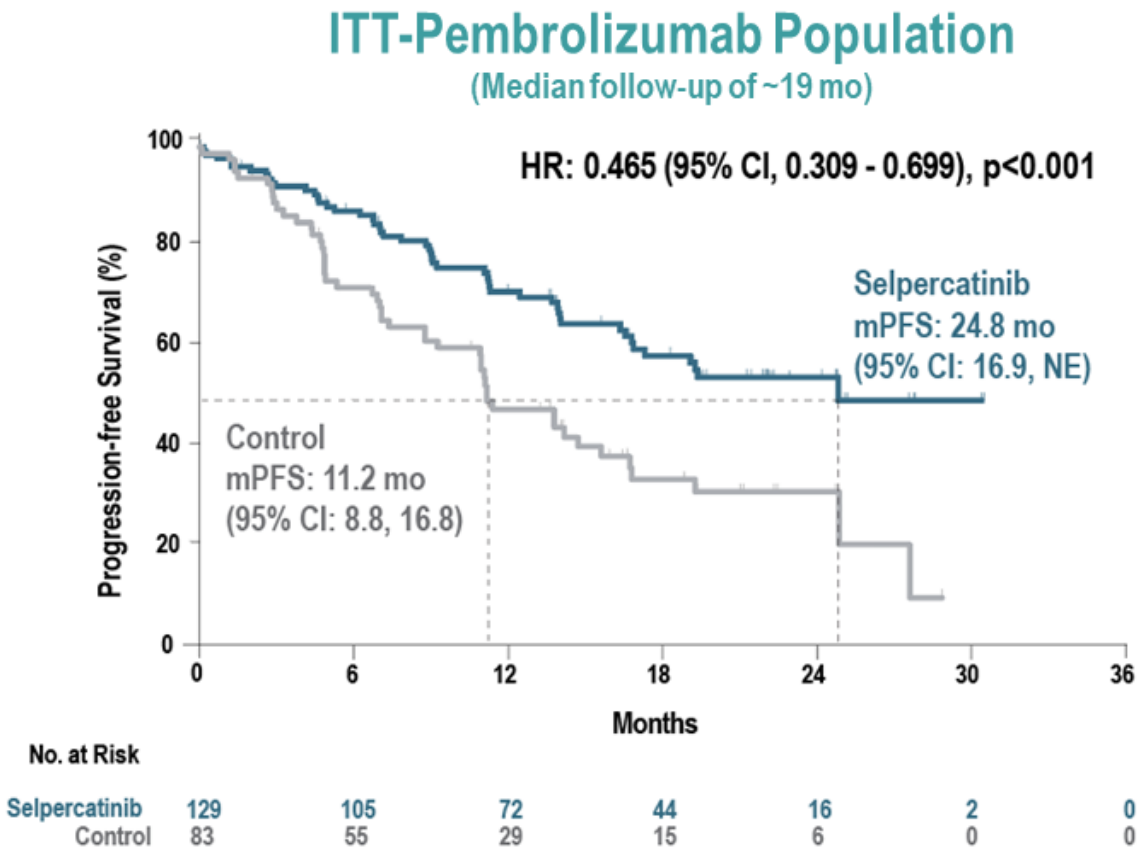
Gated Primary Endpoints: PFS by blinded independent central review (BICR) in ITT-Pembrolizumab[4] and ITT population

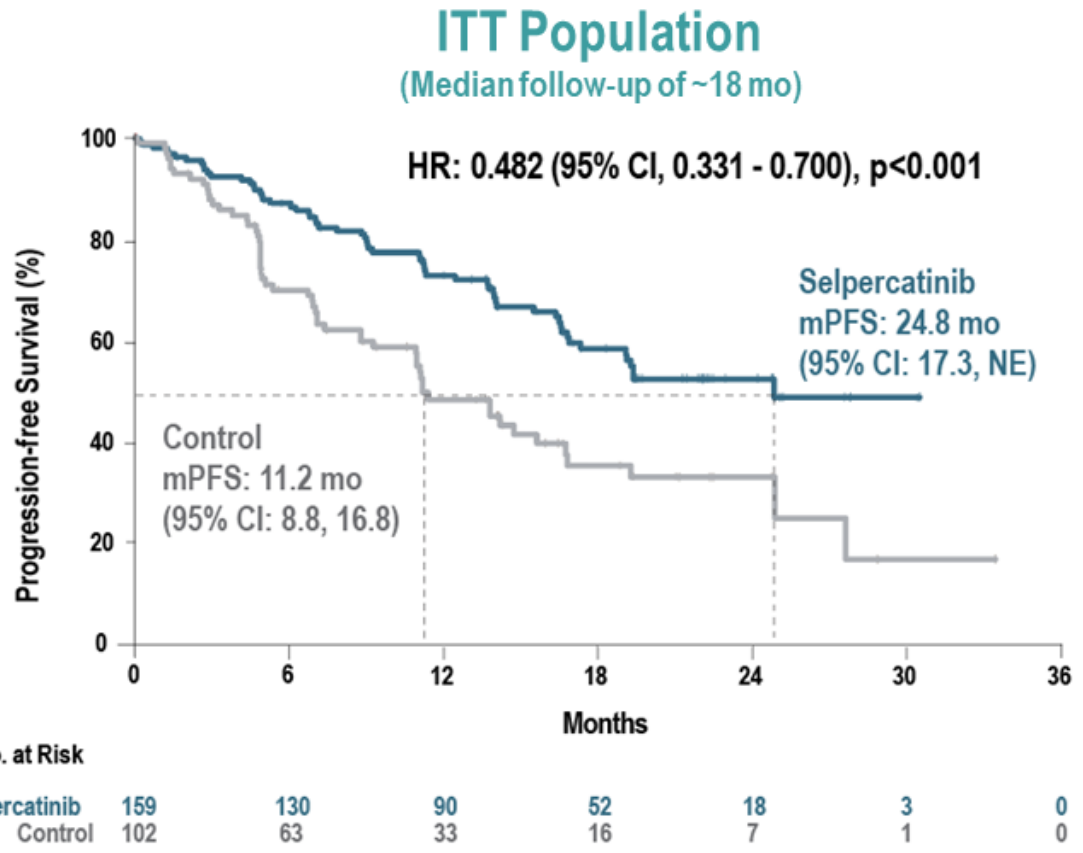
Secondary Endpoints:

- **Efficacy** ([OS, ORR, DOR], CNS [ORR, DOR, time to progression][5])
- **Safety**
- **Patient Reported Outcomes** (NSCLC-SAQ [tertiary endpoint EORTC QLQ-C30])

[1] Not suitable for radical surgery or radiation therapy ; [2] Investigator assessed
[3] The initial randomization ratio was 1:1, but amended to 2:1
[4] ITT-Pembrolizumab are patients stratified with investigator intent to receive chemotherapy with pembrolizumab and per protocol had to be at least 80% of the ITT population
[5] Baseline and longitudinal intracranial scans were required for all patients following an amendment. Prior to the amendment, longitudinal intracranial scans were required if patients had known CNS metastases at baseline

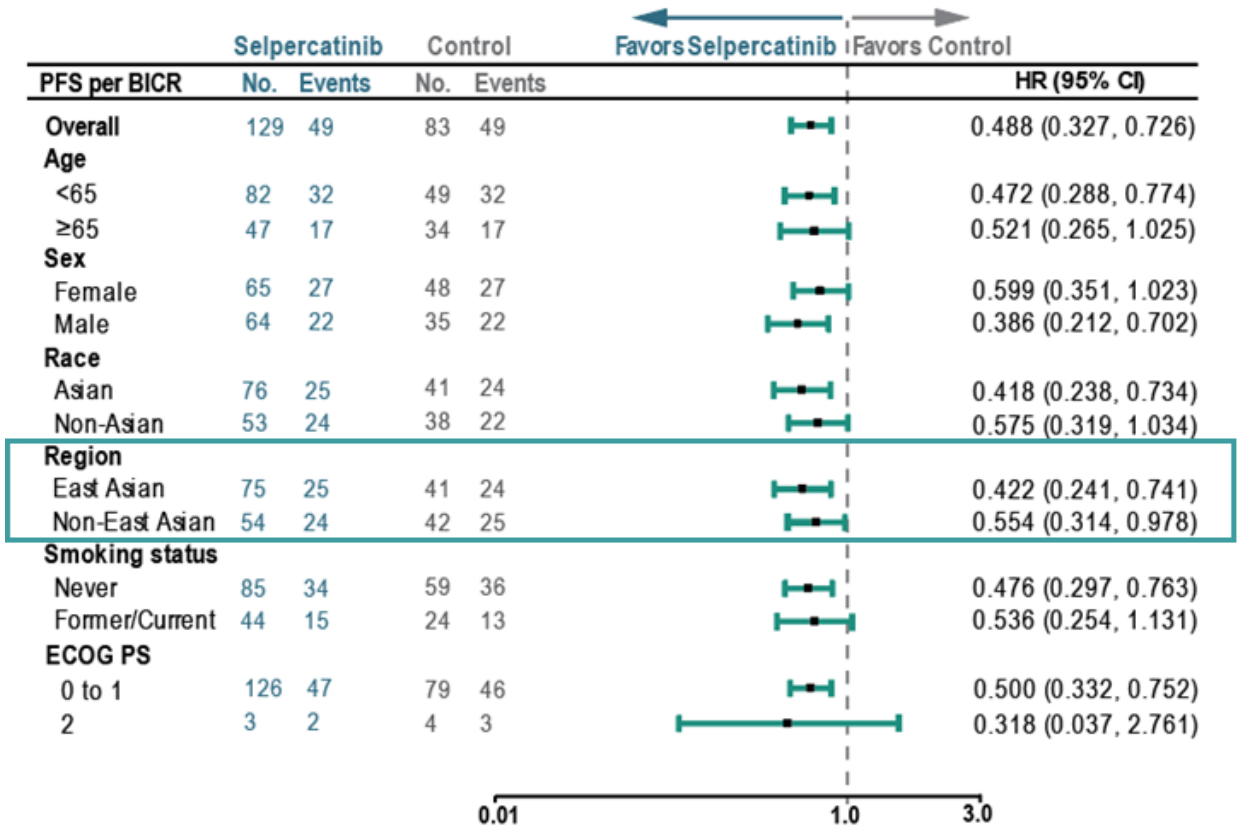
Progression-free survival (PFS) assessed by BICR

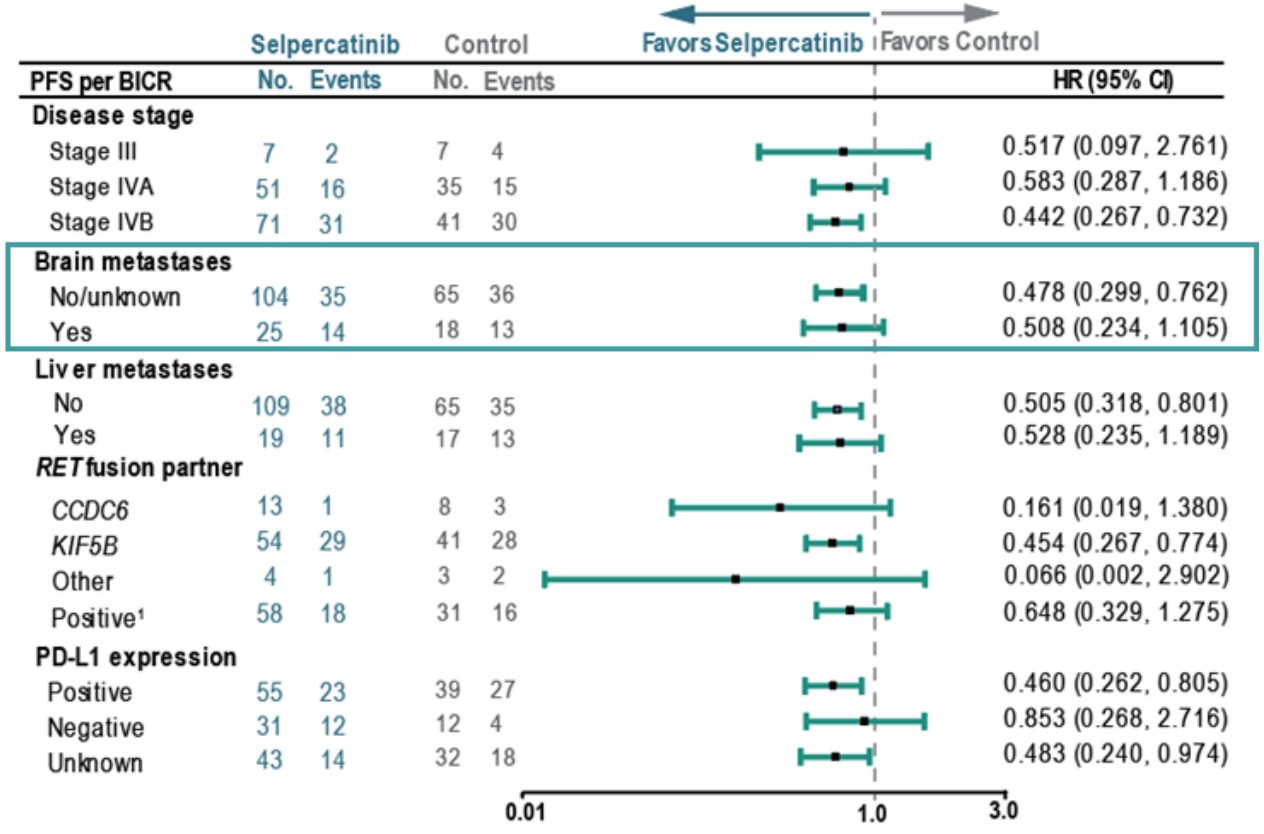




The primary endpoints were met, as selpercatinib resulted in a statistically significant improvement in PFS in both pre-specified populations

Consistent PFS Benefit by BICR – All Preplanned Subgroups





Systemic ORR, DOR, OS and Intracranial ORR and DOR

Systemic Outcomes

	Selpercatinib N= 129	Control N= 83
ORR, %	83.7	65.1
Median DOR, mo (95% CI)	24.2 (17.9, NE)	11.5 (9.7, 23.3)

Overall Survival immature (censoring rate ~80%) and confounded by crossover (75% effective rate)[1]: HR 0.961 (95% CI: 0.503, 1.835)

Overall response rate by RECIST 1.1 was higher and responses were more durable with selpercatinib

Intracranial Outcomes[2]

	Selpercatinib N= 17	Control N= 12
Intracranial ORR, %	82.4	58.3
Intracranial CR, %	35.3	16.7
12-mo Intracranial DOR Rate, % (95% CI)	76.0 (42.2, 91.6)	62.5 (14.2, 89.3)
Median Intracranial PFS, mo (95% CI)	16.1 (8.8, NE)	10.4 (3.8, NE)

In patients with measurable CNS disease at baseline, selpercatinib demonstrated improved outcomes in:

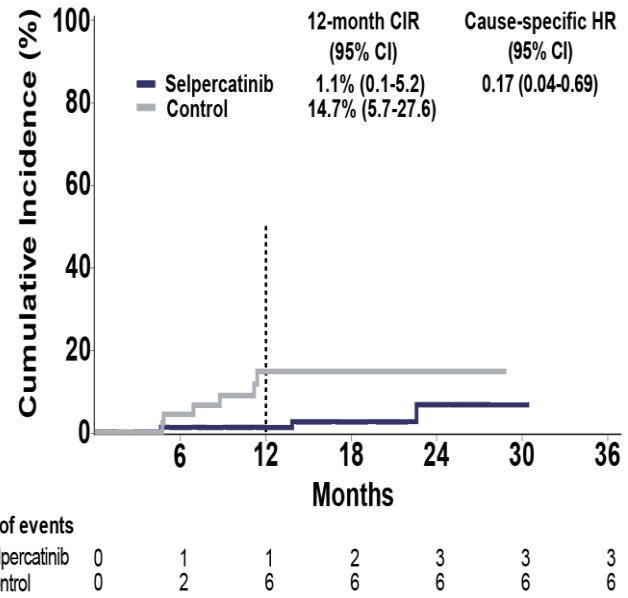
- **intracranial response rate by RECIST 1.1 including complete responses, and DOR**
- **intracranial PFS**

[1] Effective crossover rate: patients who discontinued from control treatment and received a selective RET inhibitor on or off study
[2] In patients with measurable CNS disease at baseline.

Intracranial Outcomes with/without baseline CNS metastasis

Cumulative incidence rates and intracranial PFS in the CNS-pembro population without baseline CNS metastases

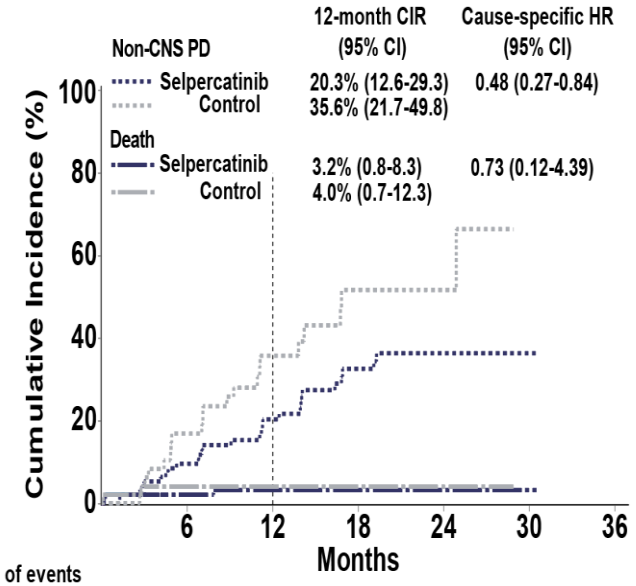
Cumulative Incidence of CNS PD



No. of events

Selpercatinib	0	1	1	2	3	3	3
Control	0	2	6	6	6	6	6

Cumulative Incidence of non-CNS PD or death



No. of events

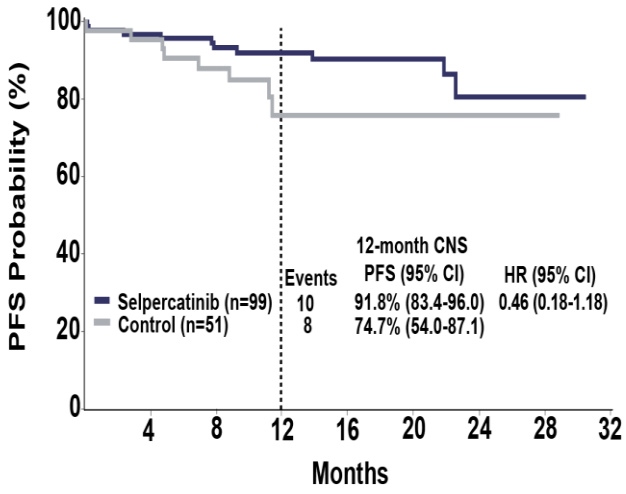
Non-CNS PD

Selpercatinib	0	9	18	26	28	28	28
Control	0	8	16	20	20	21	21

Death

Selpercatinib	0	2	3	3	3	3	3
Control	0	2	2	2	2	2	2

CNS PFS



No. at risk

Selpercatinib	99	86	74	60	44	23	12	2	0
Control	51	39	30	13	11	6	3	1	0

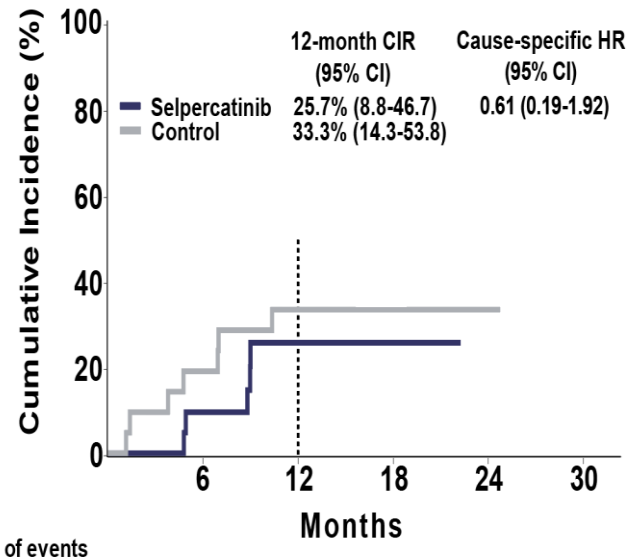
In patients without baseline CNS disease, the 12-mo CIR of CNS PD was 1.1% with selpercatinib vs 14.7% with control (cause-specific HR: 0.17 [95%CI: 0.04-0.69]).

Perol, et al. ASCO 2024

Intracranial Outcomes with/without baseline CNS metastasis

Cumulative incidence rates and intracranial PFS in CNS-pembro population with baseline CNS metastases

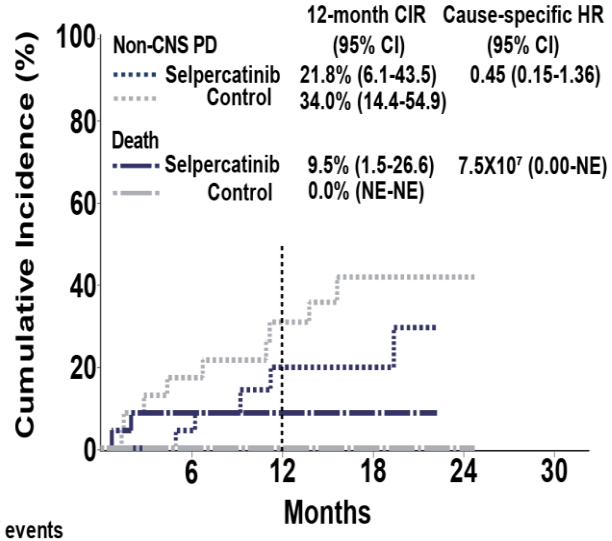
Cumulative Incidence of CNS PD



No. of events

Selpercatinib	0	2	5	5	5	5
Control	0	4	7	7	7	7

Cumulative Incidence of non-CNS PD or death



No. of events

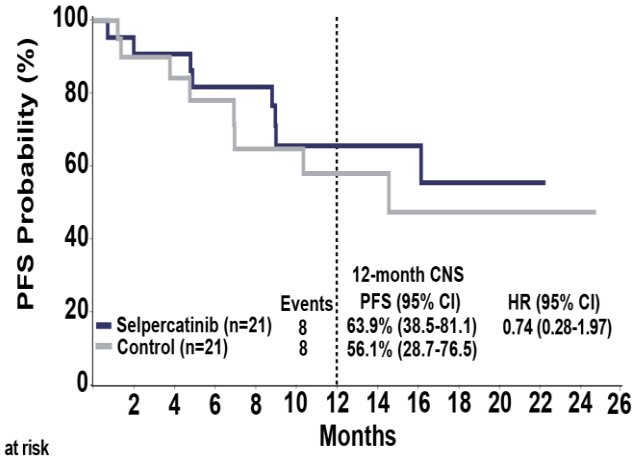
Non-CNS PD

Selpercatinib	0	1	4	4	5	5
Control	0	4	7	9	9	9

Death

Selpercatinib	0	2	2	2	2	2
Control	0	0	0	0	0	0

CNS PFS



No. at risk

Selpercatinib	21	20	19	17	15	10	7	7	6	5	2	2	0	0
Control	21	15	14	12	9	9	6	6	3	1	1	1	1	0

In patients with baseline CNS disease, the 12-mo CIR of CNS PD was 25.7% with selpercatinib vs 33.3% with control (cause-specific HR:0.61 [95%CI:0.19-1.92])

Perol, et al. ASCO 2024

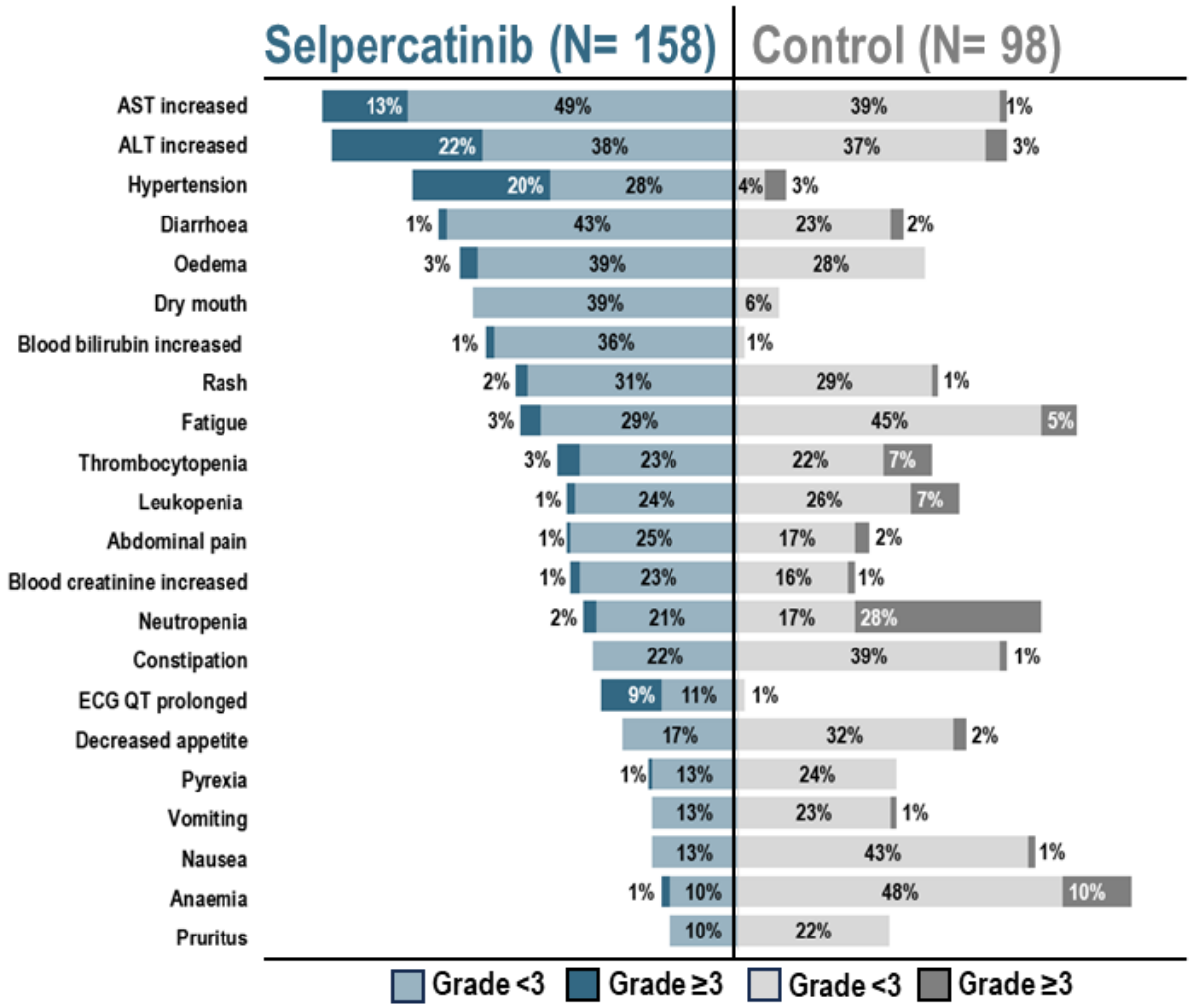
Outcome according to fusion partner

Factors	PFS Hazard Ratio (95% CI)	ORR Odds Ratio (95% CI)
Age (< 65 years vs ≥ 65 years)	**1.10** (0.82-1.48)	**0.99** (0.61-1.58)
Sex (Male vs Female)	**0.96** (0.71-1.30)	**1.44** (0.90-2.33)
Region of Enrollment (East Asian vs non-East Asian)	**0.99** (0.74-1.33)	**0.78** (0.49-1.24)
Smoking Status (Never smoker vs Current/Former smoker)	**1.12** (0.81-1.55)	**0.65** (0.39-1.11)
ECOG PS (0 vs Other)	**0.62** (0.46-0.85)	**1.65** (1.00-2.71)
Liver Metastases (Yes vs No)	**0.51** (0.38-0.67)	**1.37** (0.86-2.19)
***RET* Fusion** (*KIF5B* vs *CCDC6*)	**0.43** (0.29-0.64)	**2.67** (1.41-5.03)

Fusion Partner	mPFS, mo (95%CI)	ORR, [n/N] % (95%CI)			mDOR, mo (95%CI)
	Overall N=415	Overall N=415	Prior Treatment n=263	Treatment Naïve n=152	Overall N=415
KIF5B-RET	**19.4** (17.1-22.7)	[194/297] **65.3** (59.6-70.7)	[96/179] **53.6** (46.0-61.1)	[98/118] **83.1** (75.0-89.3)	**20.3** (17.5-23.9)
CCDC6-RET	**NR** (33.0-NR)	[73/88] **83.0** (73.4-90.1)	[47/61] **77.0** (64.5-86.8)	[26/27] **96.3** (81.0-99.9)	**NR** (28.5-NR)
OTHER-RET	**16.9** (7.5-NR)	[16/30] **53.3** (34.3-71.7)	[10/23] **43.5** (23.2-65.5)	[6/7] **85.7** (42.1-99.6)	**17.6** (5.6-NR)

Solomon et al. WLCC 2024

Safety



Any grade treatment-emergent adverse events (TEAEs) occurring in ≥20% of patients in either study arm

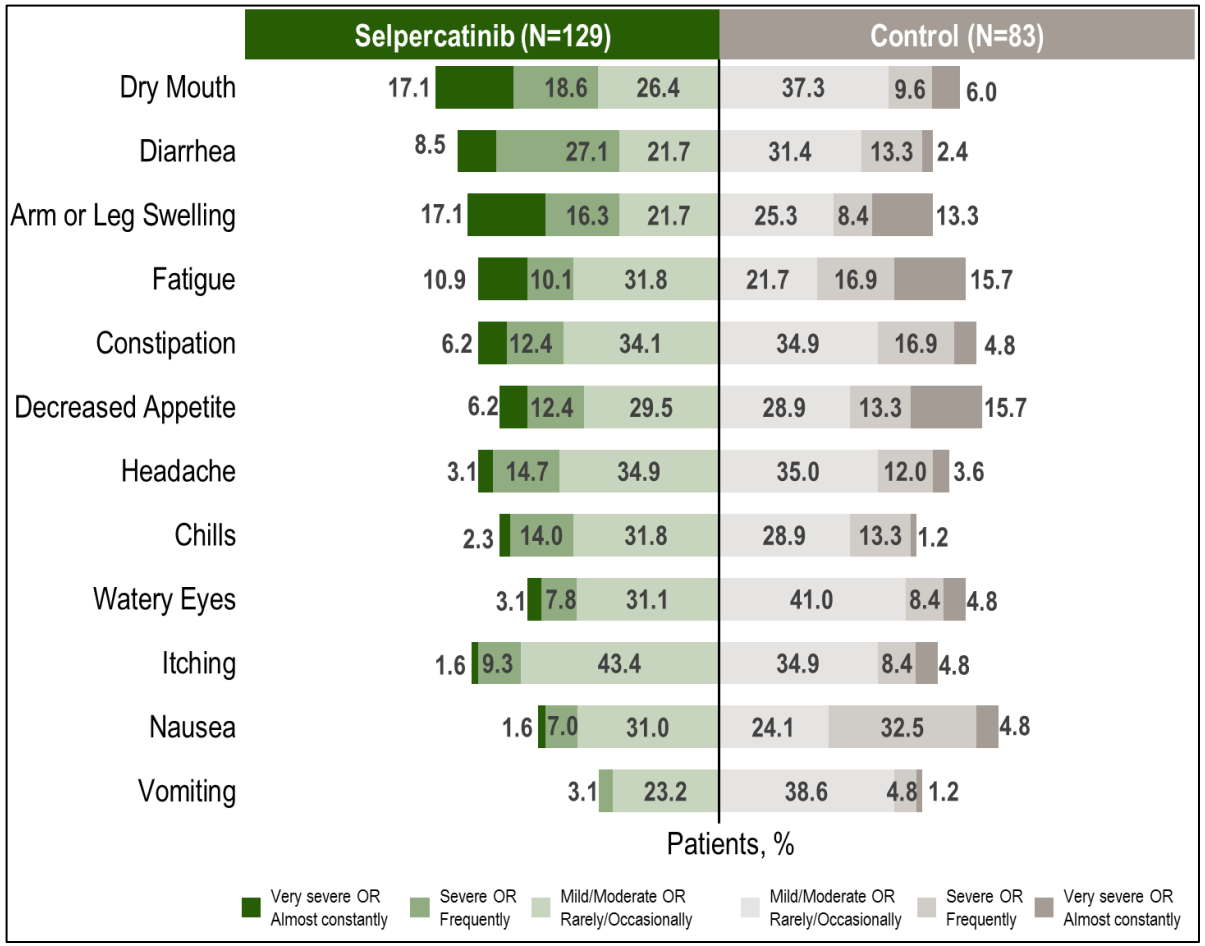
- **Median time on selpercatinib was approximately 70% longer than control (16.7 vs 9.8 months)**
- **TEAEs observed with selpercatinib were generally consistent with those previously reported, and the majority were managed with dose modifications**

	Selpercatinib N= 158	Control N= 98
Median time on treatment, months ± SD	**16.7 ± 8.3**	**9.8 ± 7.2**
Any AE, n (%)	158 (100.0)	97 (99.0)
AE Grade ≥3	111 (70.3)	56 (57.1)
Deaths due to AE, n (%)	7 (4.4)	0
Related AE (malnutrition and sudden death)	2 (1.3)	0
AEs leading to discontinuation, n (%)	16 (10.1)	2 (2.0)
AEs leading to any dose adjustment, n (%)	123 (77.8)	74 (75.5)
AEs leading to dose reduction	81 (51.3)	28 (28.6)

Data shown are from all patients who received at least one dose of study treatment

Patient Reported Adverse Events

PRO-CTCAE: Symptomatic AEs



- **Dry mouth, diarrhea, and arm or leg swelling were reported at a higher level of severity or frequency in the selpercatinib arm.**
- **Fatigue, decreased appetite, and nausea were reported at a higher level of severity or frequency in the control arm.**

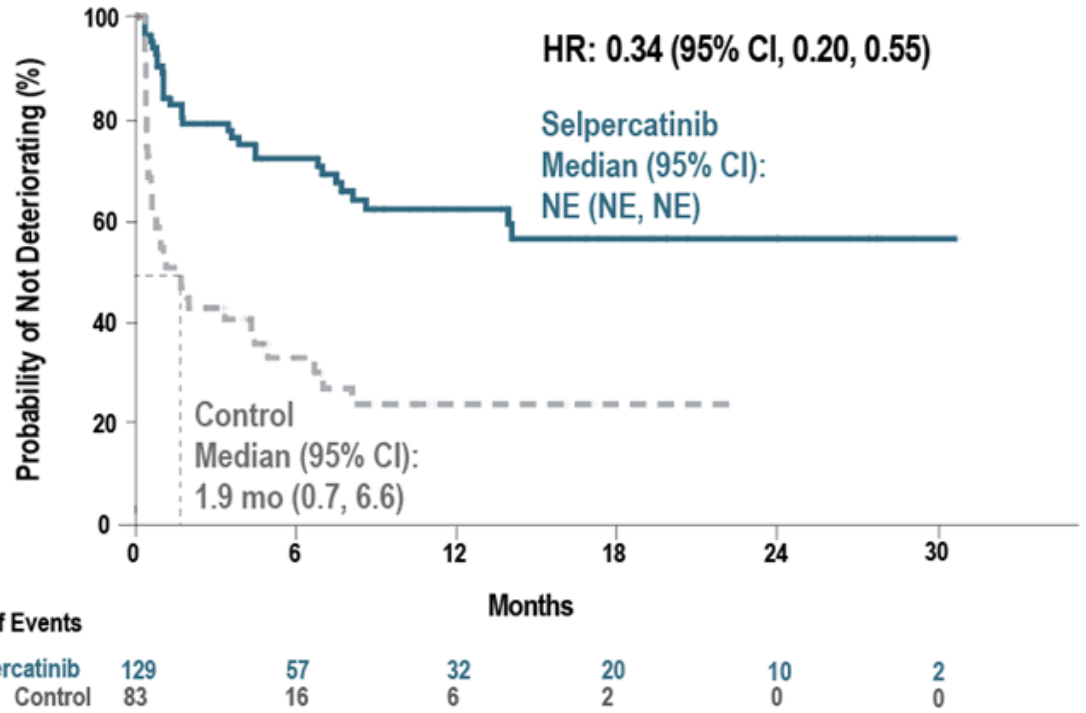
PRO-CTCAE, Patient-Reported Outcomes of Common Terminology Criteria for Adverse Events, data shown as Baseline Adjusted Worst Scores during on-treatment study period

Data shown are from the ITT-Pembrolizumab population

Goto, et al.; ESMO-Asia 2023

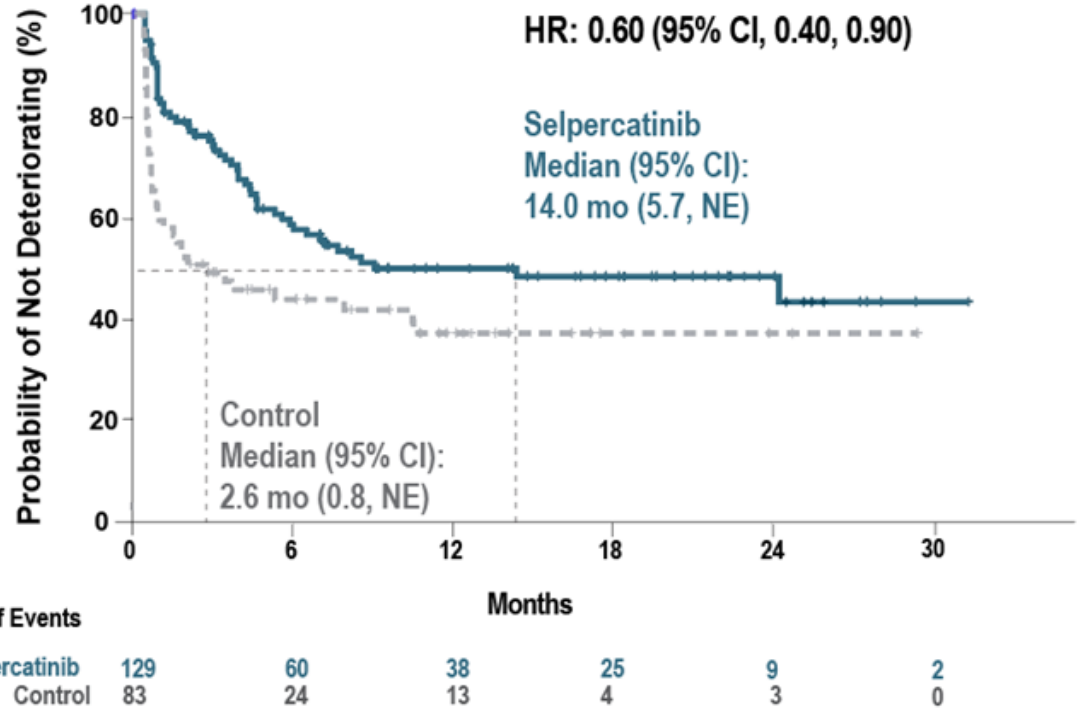
Time to deterioration of pulmonary symptoms and physical function

NSCLC-SAQ - Pulmonary Symptoms[1]



No. of Events						
Selpercatinib	129	57	32	20	10	2
Control	83	16	6	2	0	0

EORTC QLQ-C30 - Physical Function[2]



No. of Events						
Selpercatinib	129	60	38	25	9	2
Control	83	24	13	4	3	0

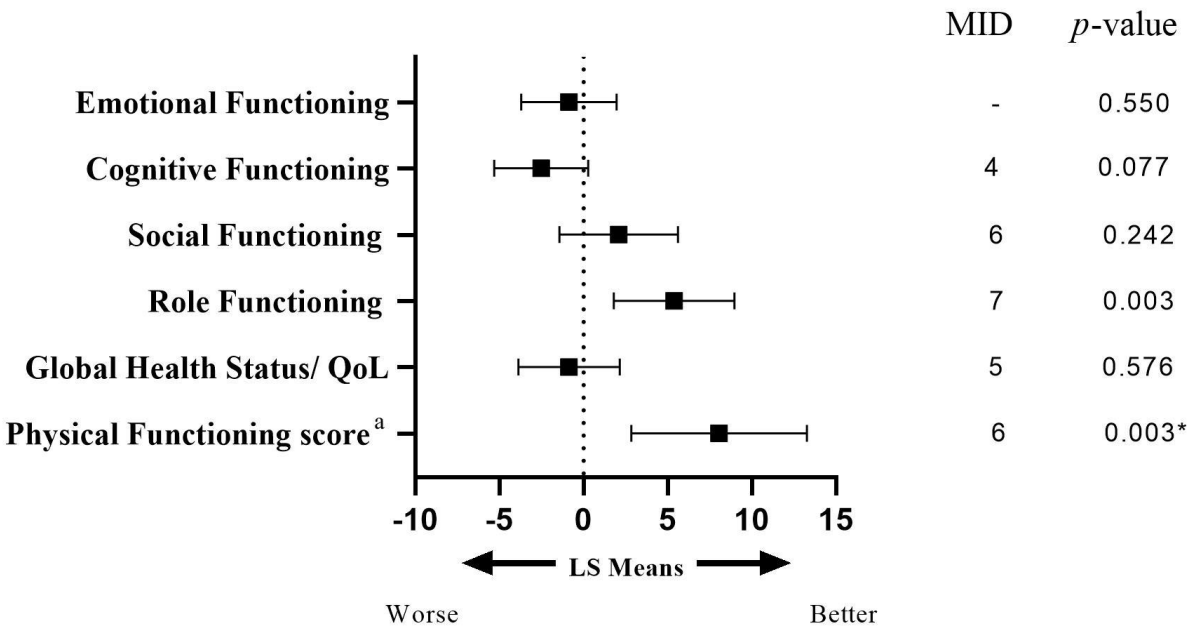
Selpercatinib delayed time to deterioration of pulmonary symptoms and overall physical function

[1]Clinically meaningful change for deterioration of pulmonary symptoms using a ≥2 points increase in NSCLC-SAQ total scores (range from 0 [no symptoms] to 20 [worst symptoms]) from baseline
[2]Clinically meaningful change for deterioration of physical function using a ≥10 points decrease in QLQ-C30 physical functioning scores (range from 0 to 100 [best possible physical function]) from baseline

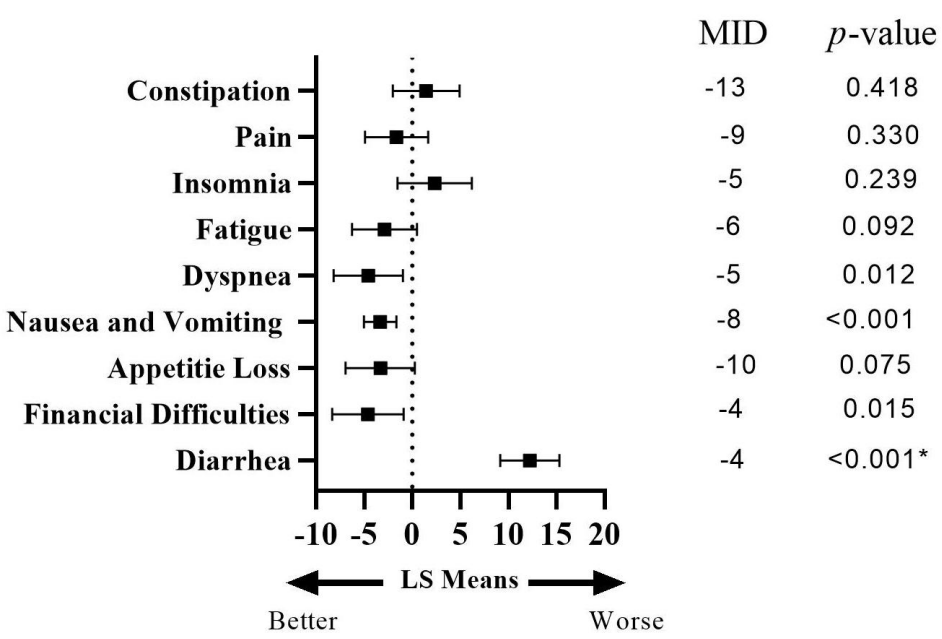
Quality of life

Difference in HRQoL for selpercatinib compared to control from baseline to year 1 as measured by EORTC QLQ-C30

Higher score → Better functioning



Higher score → Worse symptoms



Physical functioning with selpercatinib was clinically and statistically improved from baseline at 1 year, compared to the control group.

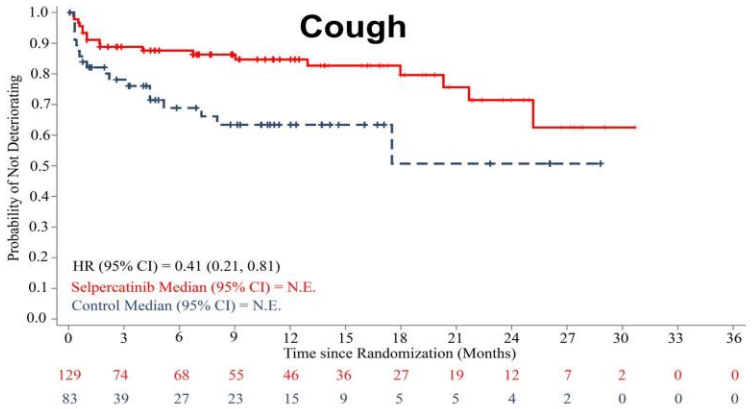
Diarrhea was clinically and statistically worse in the selpercatinib arm compared to the control arm.

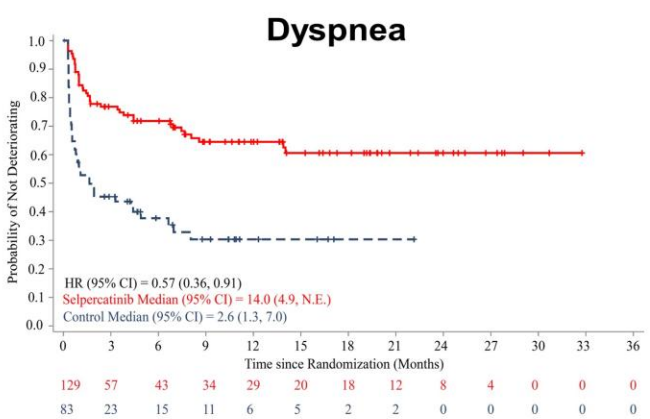
**Clinical and statistical significance.* [a]The estimated score difference for the physical functioning score was from a growth curve model analysis at 49 weeks.
Dyspnea improved but did not reach the clinically meaningful threshold. Role function improved but did not reach the clinically meaningful threshold
EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS/QoL = Global Health Status/Quality of Life; LS Means = least-square means;MID=meaningful important difference; NSCLC-SAQ=NSCLC Symptom Assessment Questionnaire

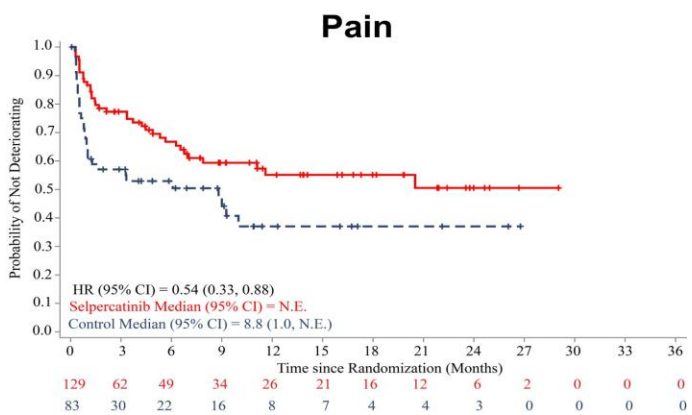
C Zhou , et al.; ESMO-Asia 2023

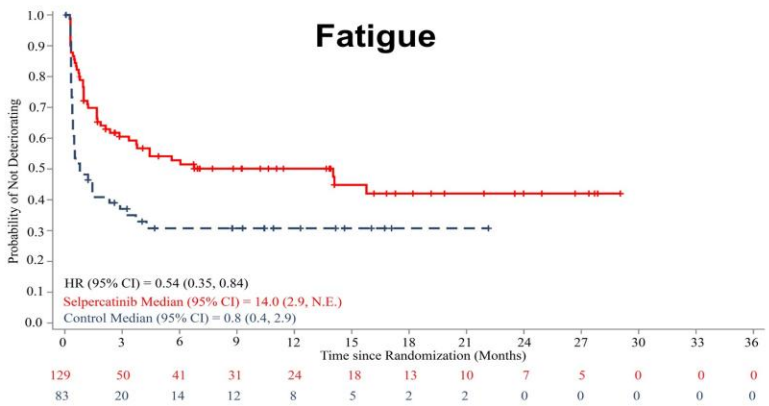
Time to confirmed deterioration

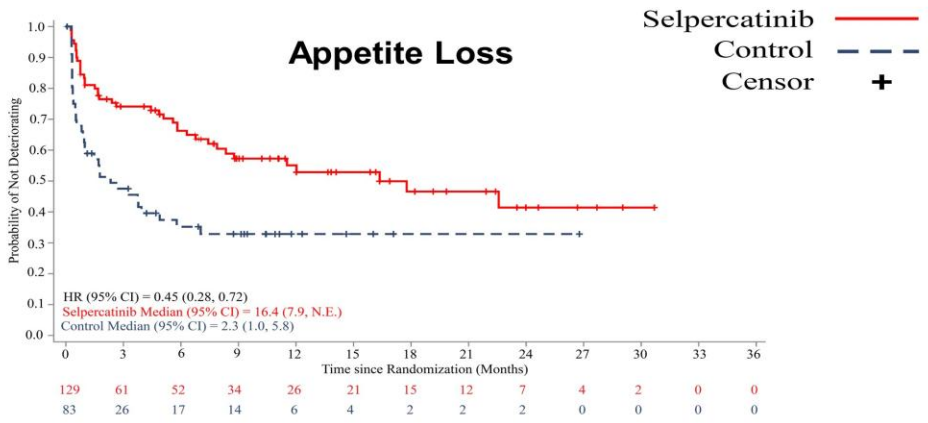
Selpercatinib significantly (p <.05) delayed time to confirmed deterioration* of all individual symptoms





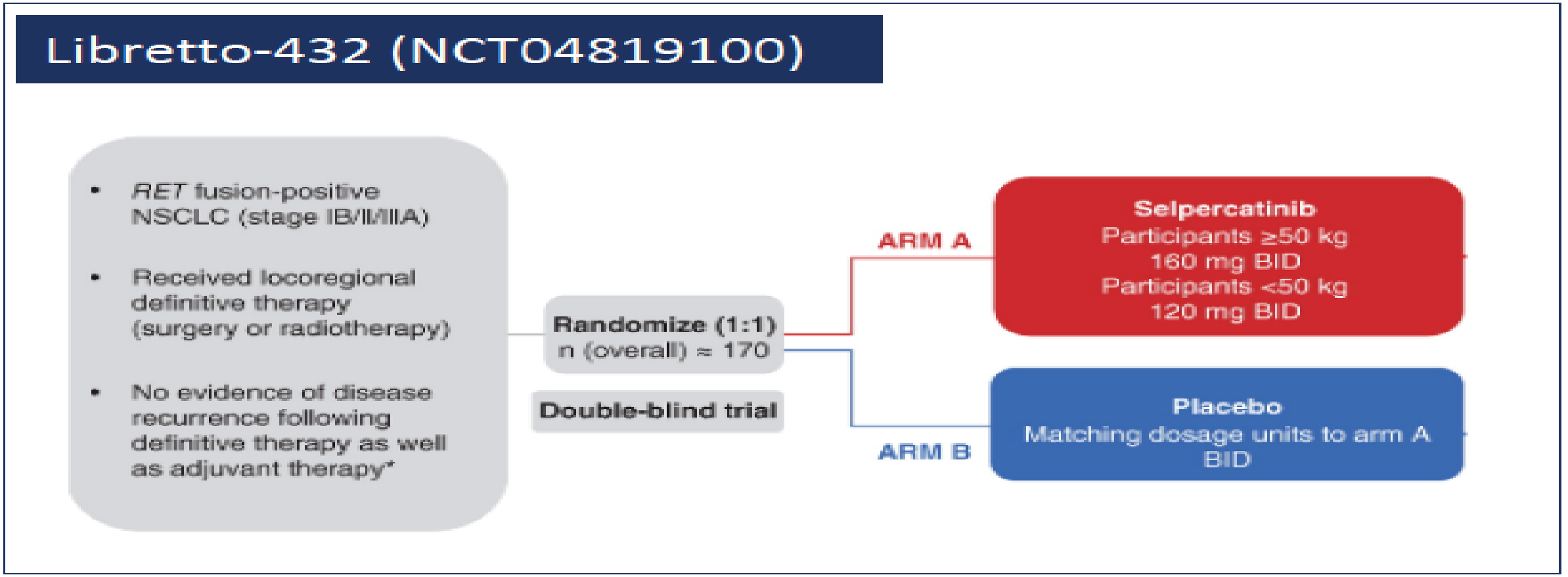






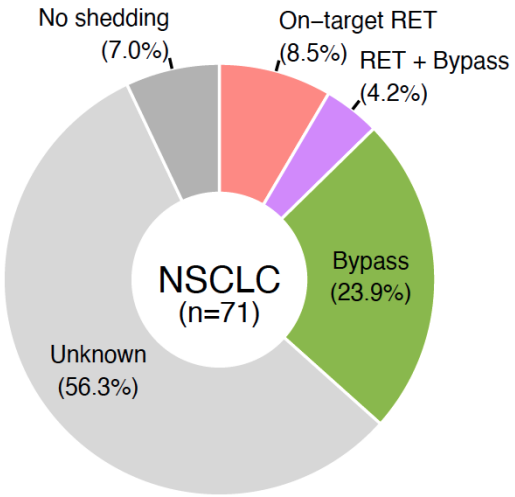
C Zhou , et al.; ESMO-Asia 2023

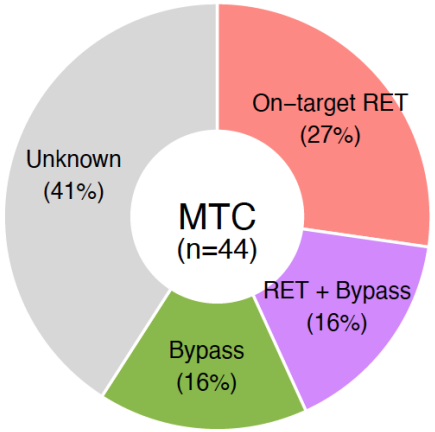
Early stage RET driven NSCLC



Stage IB (3 cm)–IIIA (8th edition)
TKI for 3 years (as Adaura)
No chemotherapy (as Alina)

Acquired mechanism of resistance to Selpercatinib





	NSCLC N (%)	MTC N (%)	All patients N (%)
Resistance mechanism	26 (37)	26 (59)	52 (45)
Unknown/No shedding*	45 (63)	18 (41)	63 (55)
On-target	9 (13)	19 (43)	28 (24)
RET Solvent Front G810C/S/R	8	16	24
RET V804M/L**	1	8	9
RET V804M/L** and G810C/S	0	5	5
Bypass	20 (28)	14 (32)	34 (30)
*BRAF*V600E/Amplification	4	5	9
KRAS G12D/R	1	4	5
MET Amplification	5	2	7
NTRK1 fusion	2	1	3
Other***	8	2	10

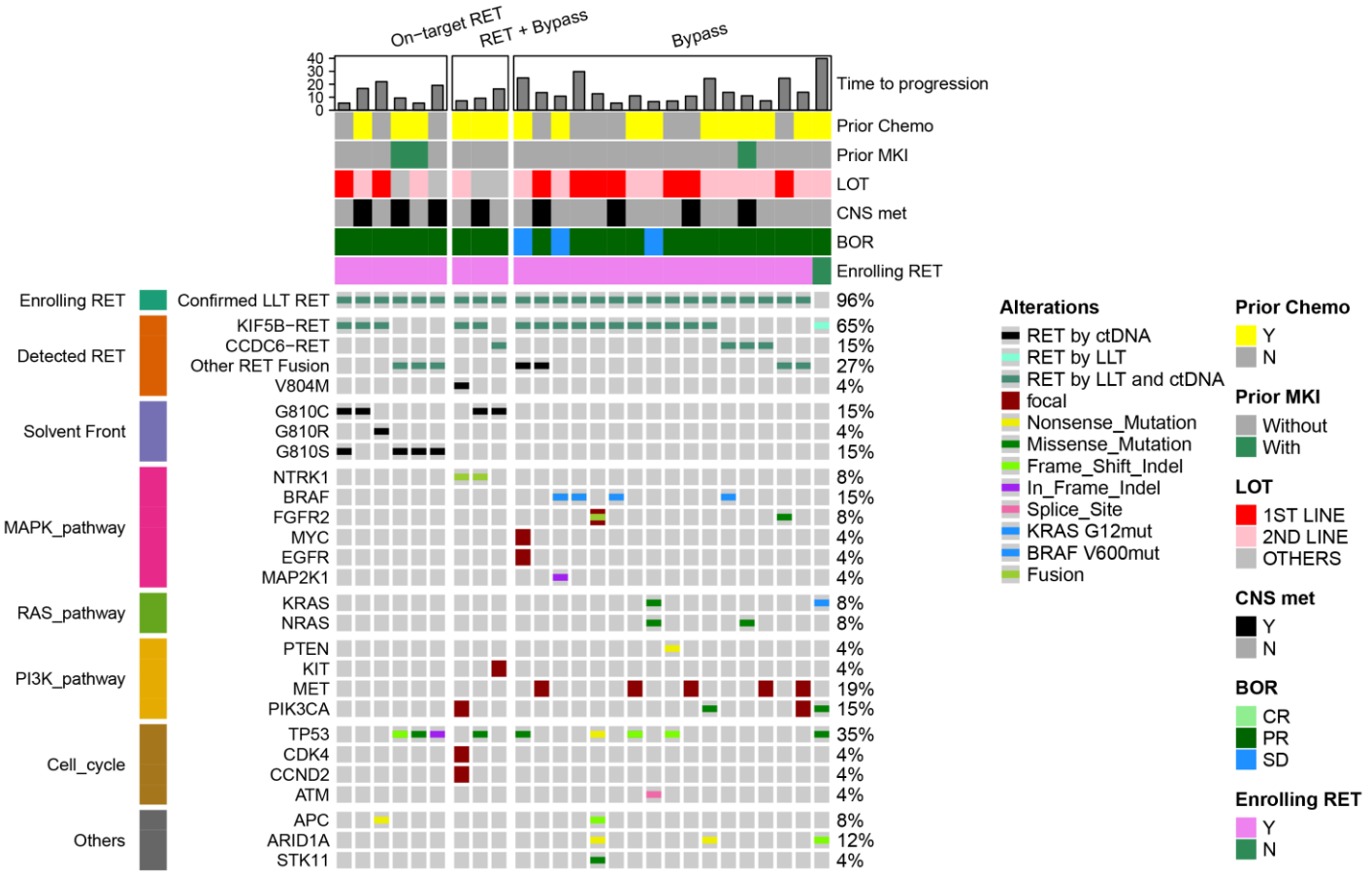
*patients with no oncogenic alterations detected at baseline.
**1 NSCLC and 1 MTC patient acquired *RET* V804M alone; 4 MTC patients had clonal expansion of *RET* V804M/L with other acquired on-target *RET* alterations; 3 MTC patients acquired *RET* V804M with other acquired on-target *RET* alterations;
****EGFR/MYC* amplification, *FGFR2* N82S/ P253L/amplification, *KIT* amplification, *KRAS* Q61H, *PIK3CA* E545K, *NRAS* Q61K/L.

- **On-target resistance mechanisms were identified more frequently in MTC vs NSCLC patients, 43% vs 13%, respectively**

B Solomon, et al.; ESMO 2024

Mechanisms of resistance were identified in 37% (26/71) of NSCLC patients

- Mechanisms of resistance includes both acquired variants at progression and primary variants with clonal expansion at progression

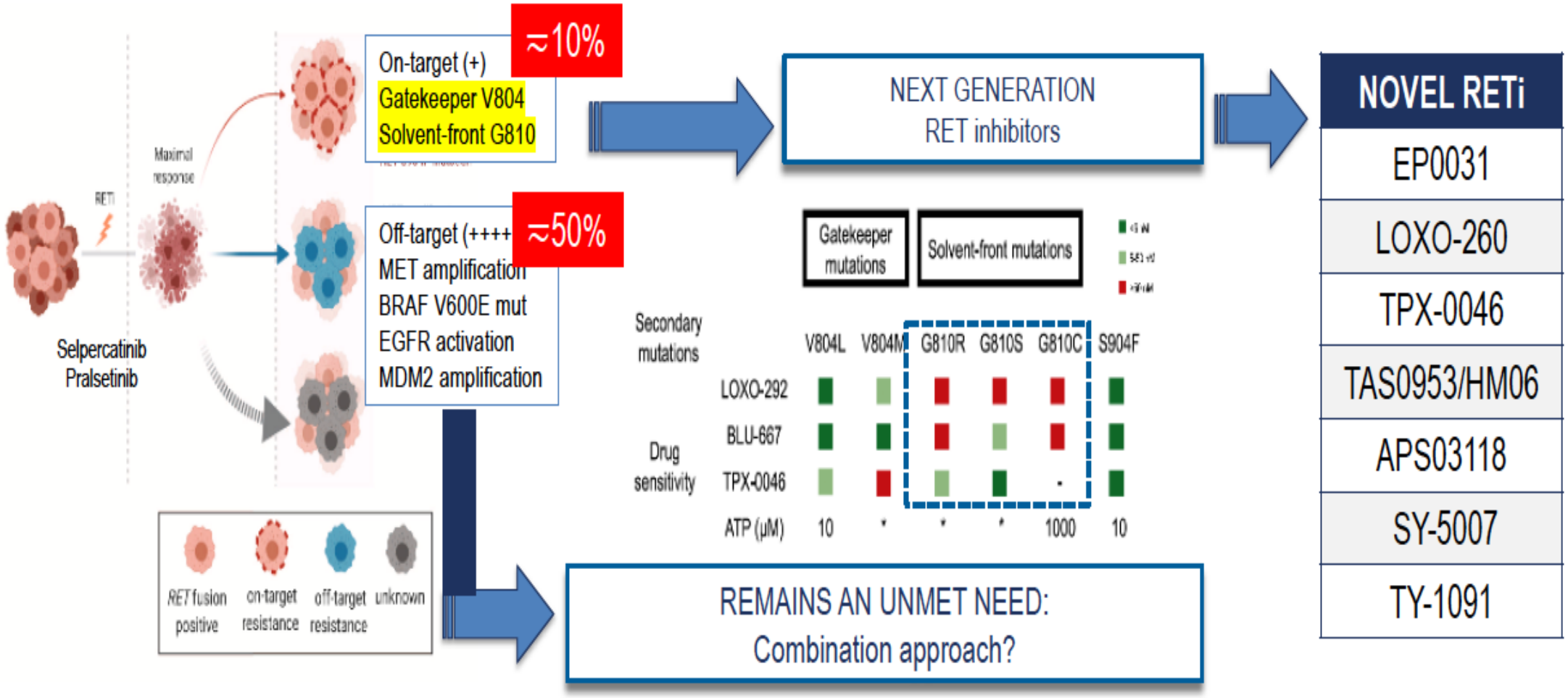


- ***RET* solvent front mutation (12%)** was the most prevalent on-target *RET* alteration:
  - G810C/S/R was found in 11% (8/71)
  - V804M/L was found in 1% (1/71)

- **17% (12/71) had bypass alterations in MAPK/RAS pathway**:
  - *MET* amplification was found in 7% (5/71)
  - *BRAF* V600E was found in 6% (4/71)
  - *NTRK1* fusion was found in 3% (2/71)
  - *KRAS* G12R was found in 1% (1/71)

B Solomon, et al.; ESMO 2024

RET Resistance
Novel Gen RET inhibitors do not cover all needs

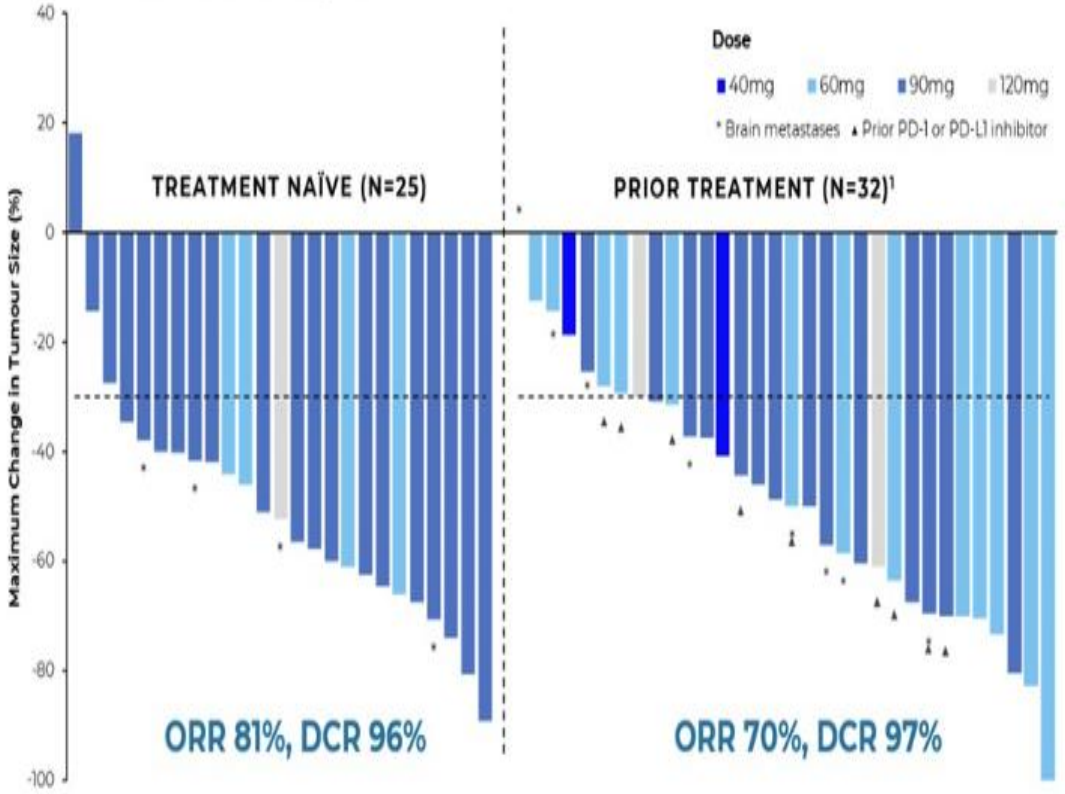


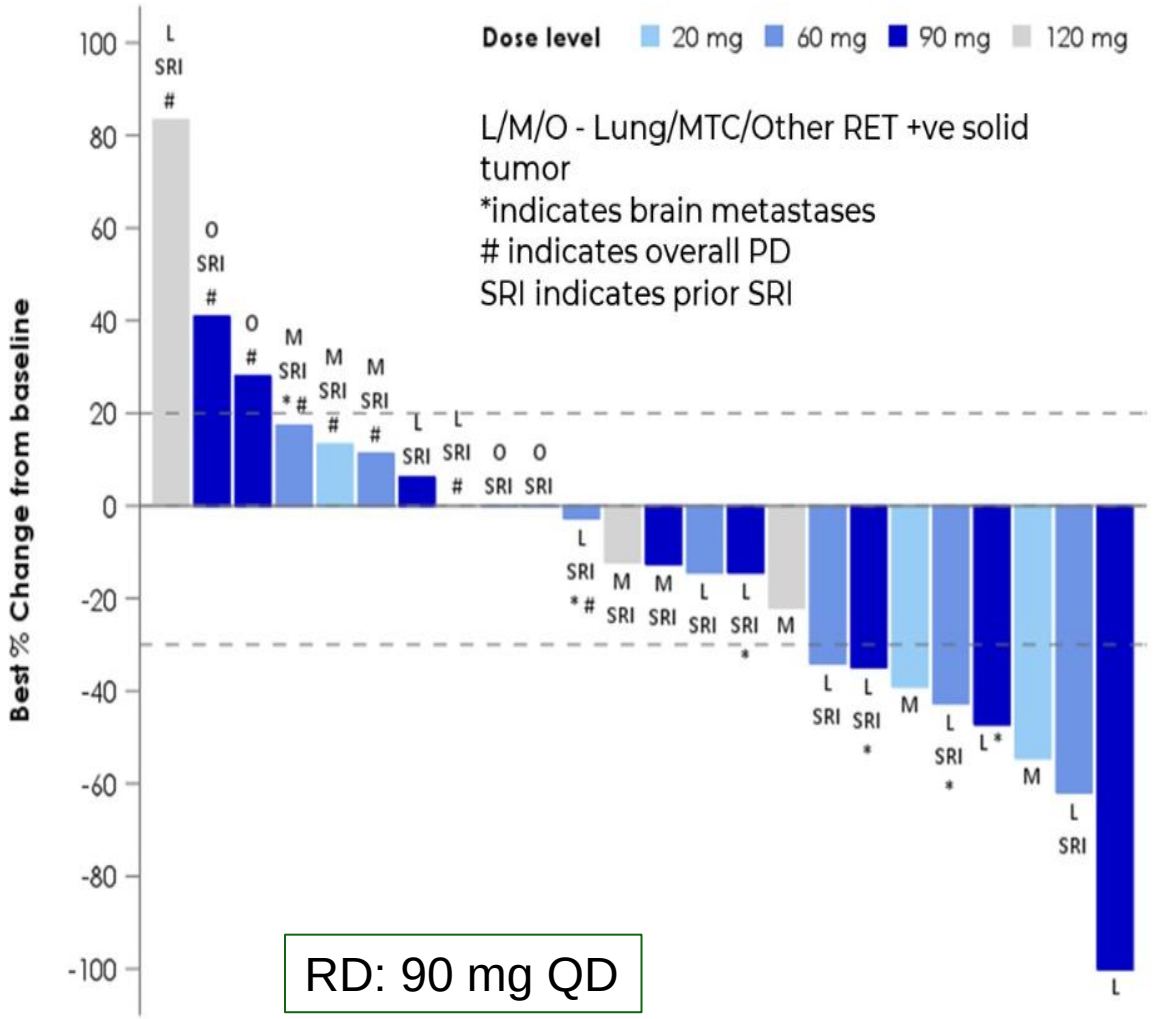
NOVEL RETi
EP0031
LOXO-260
TPX-0046
TAS0953/HM06
APS03118
SY-5007
TY-1091

1.- Figure adapted from Lu C.et al. Cancer Treat Rev 2021;

EP0031 – Phase I Trial

Figure 1: Tumor response from NSCLC SRI-naïve pts in China at doses of EP0031 40-120 mg QD





RD: 90 mg QD

E Garralda, et al.; ASCO 2024

Gracias

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