XXIV Simposio de Revisiones en Cáncer

"Tratamiento médico del cáncer en el año 2022"

Nuevos avances en la medicina de precisión para el tratamiento del cáncer de pulmón. CPCNP con fusión de RET positiva

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ARÁN

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DISCLOSURE INFORMATION

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OUTLINE

- Introduction
- Molecular biology
- Clinical features of RET-rearranged NSCLC
- Diagnosis
- Conventional systemic therapies
- Non-selective RET inhibitors
- Selective RET inhibitors
- Acquired resistance to selective RET-inhibitors
- Next generation RET-inhibitors
- Conclusions

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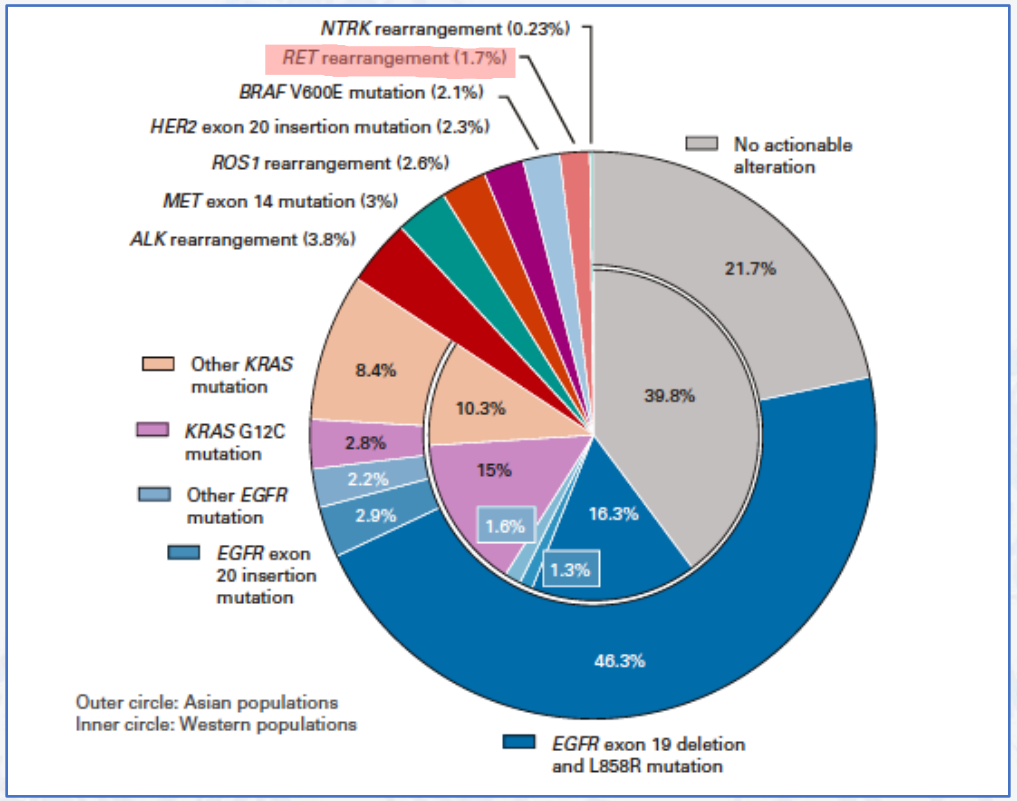
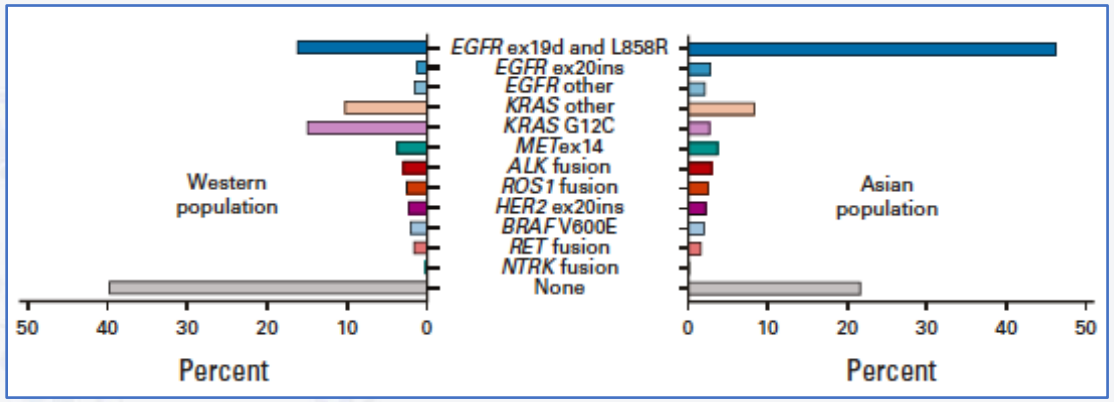
INTRODUCTION

- Diagnosis and treatment approach to advanced NSCLC continues to be refined
- Growing number of genetic and molecular markers guide tailored therapy

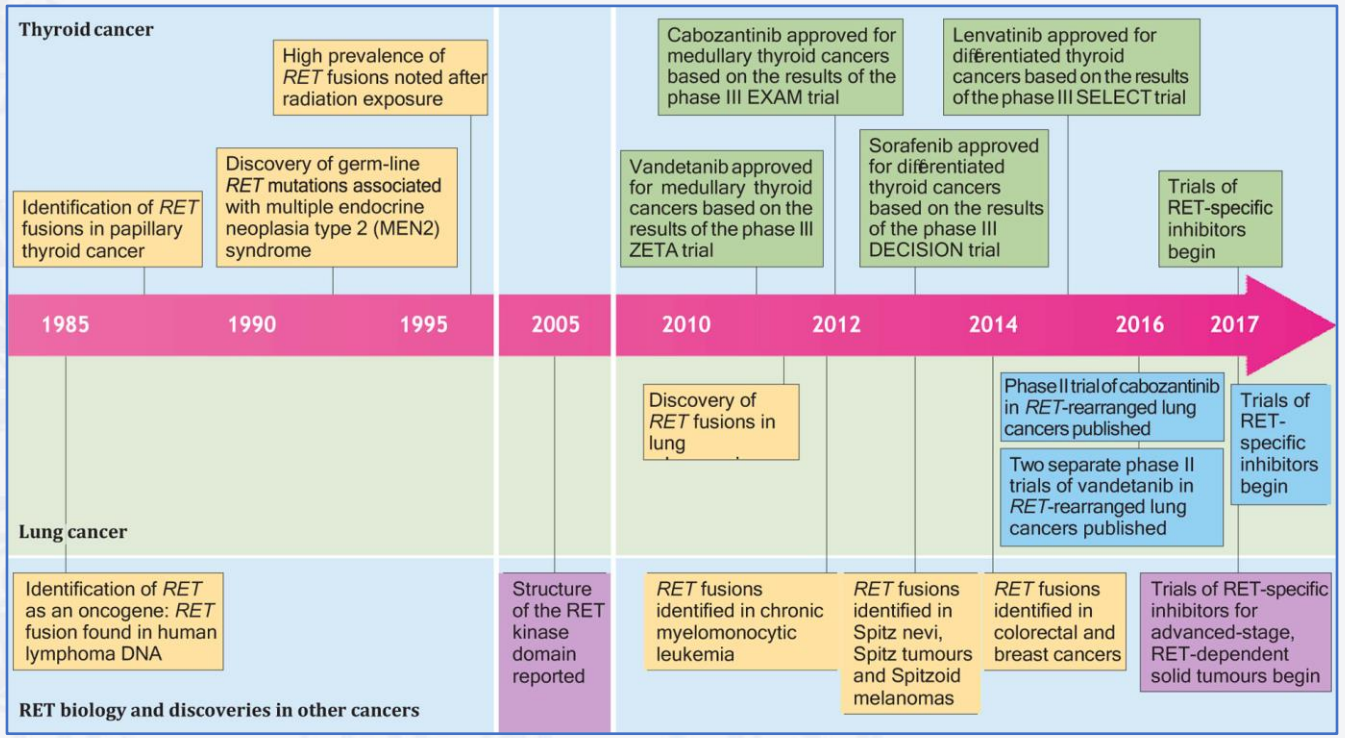




Tan AC, et al. J Clin Oncol Jan 5:JCO2101626

INTRODUCTION

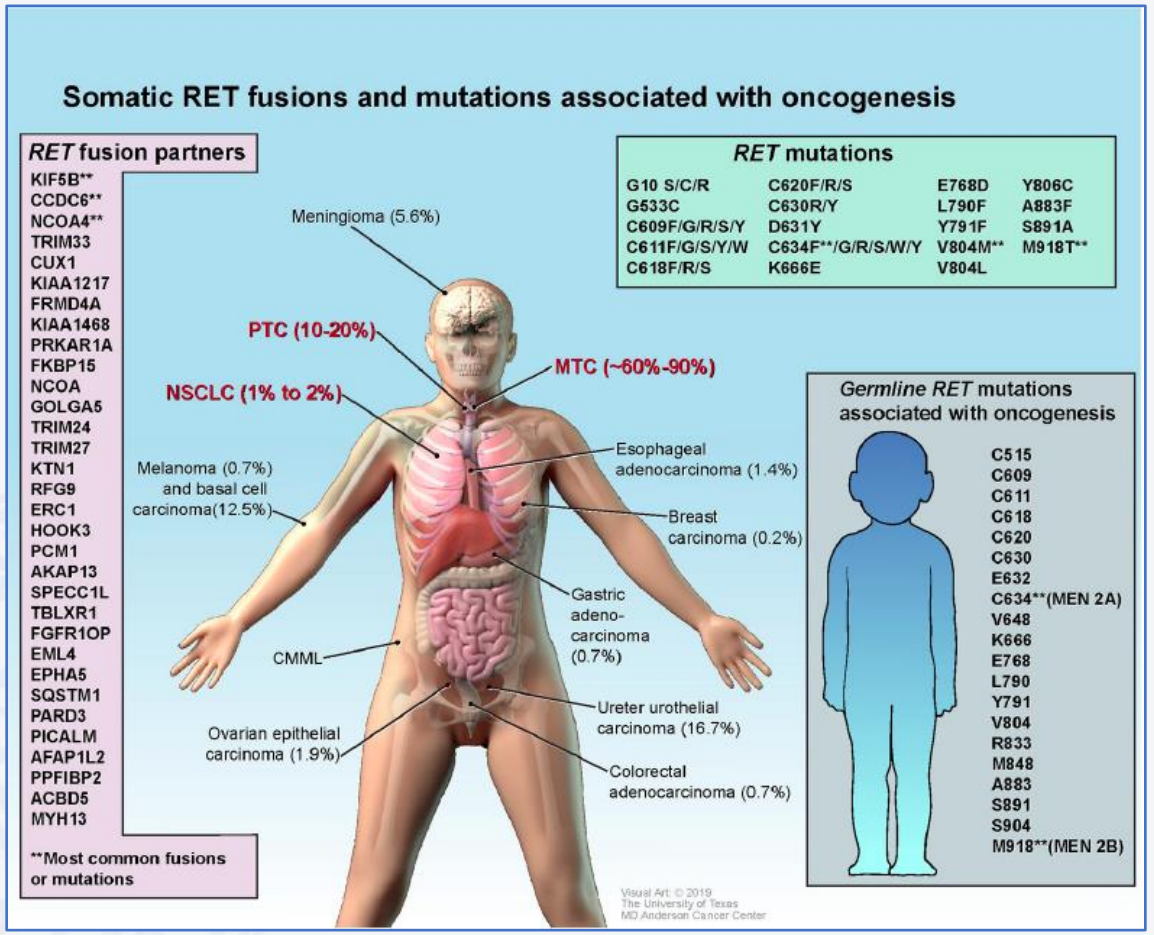
- Timeline of key developments in therapeutically targeting rearranged during transfection (RET)
- RET gene was discovered in 1985
- Oncogenic RET fusions were first identified in NSCLC in 2012



Drilon A, et al. Nat Rev Clin Oncol 2018;15:151-67

INTRODUCTION

- RET gene is a protooncogene that can be present in different types of cancers:
  - Thyroid
  - Lung
  - Colorectal
  - Breast
  - Salivary gland
- The prevalence of RET alterations varies by tumor type
- RET fusions have been reported in 1-2% of NSCLC



Kohno T, et al. Nat Med 2012;18:375-7; Takeuchi K, et al. Nat Med 2012;18:378-81; Lipson D, et al. Nat Med 2012;18:382-4; Ju YS, et al. Genome Res 2012;22:436-45; Wang R, et al. J Clin Oncol 2012;30:4352-9; Subbiah V, et al. Cancer Discov 2020;10:498-505

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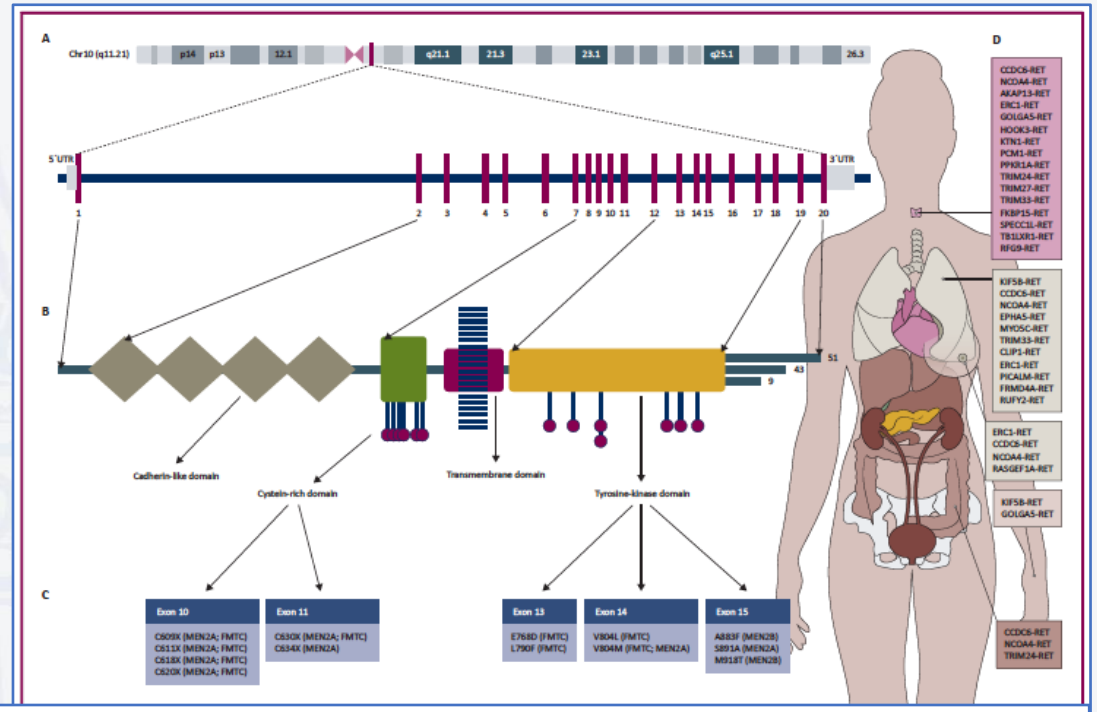
MOLECULAR BIOLOGY

- RET gen location: chromosome 10, and it is composed of 20 exons
- Structure: RET receptor is composed of a large extracellular domain containing cadherine-like domains and cysteine-rich domain and an intracellular tyrosine kinase domain



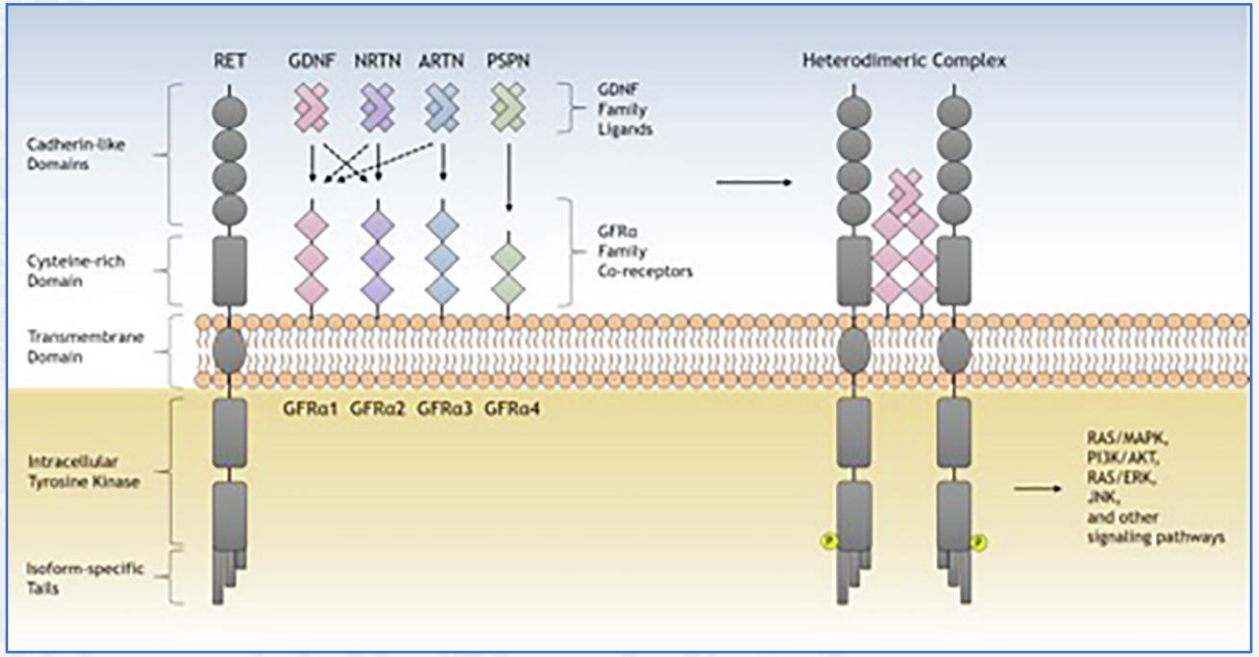
Most commonly identified RET fusions according to cancer site

Most commonly identified RET mutations and associated genetic syndromes occurring in cysteine-rich domain and tyrosine-kinase domain

Belli C, et al. Ann Oncol 2021;32:337-50

MOLECULAR BIOLOGY

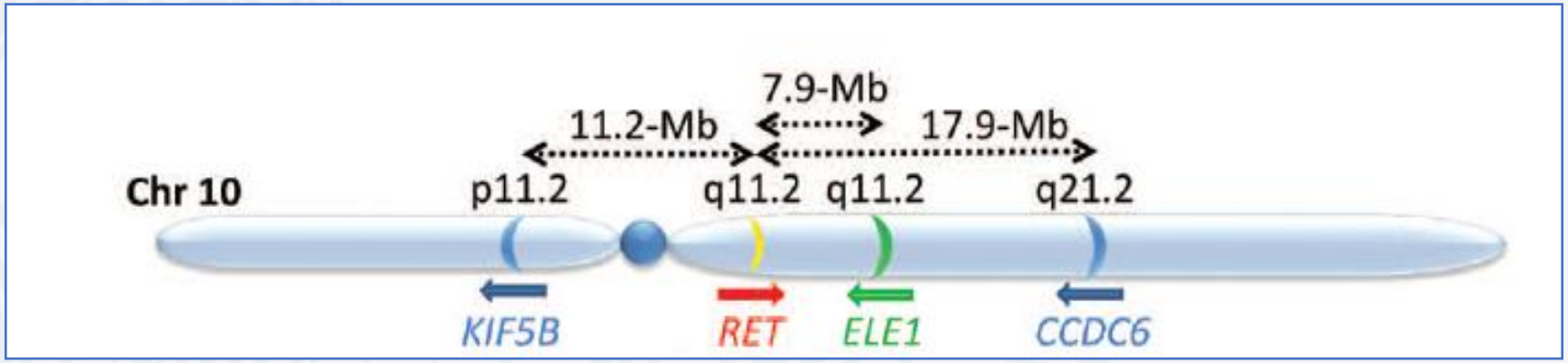
- Encodes the RET transmembrane receptor kinase
- The RET receptor kinase is activated by glial-derived neurotrophic factor (GDNF) family ligands (GFL), and forms a heterocomplex with GDNF-family receptor alpha (GFRA1)
- RET dimerization, autophosphorylation and activation



Mulligan LM, et al. Nat Rev Cancer 2014;14:173-86; Li AY, et al. Cancer Treat Rev 2019;81:101911

MOLECULAR BIOLOGY

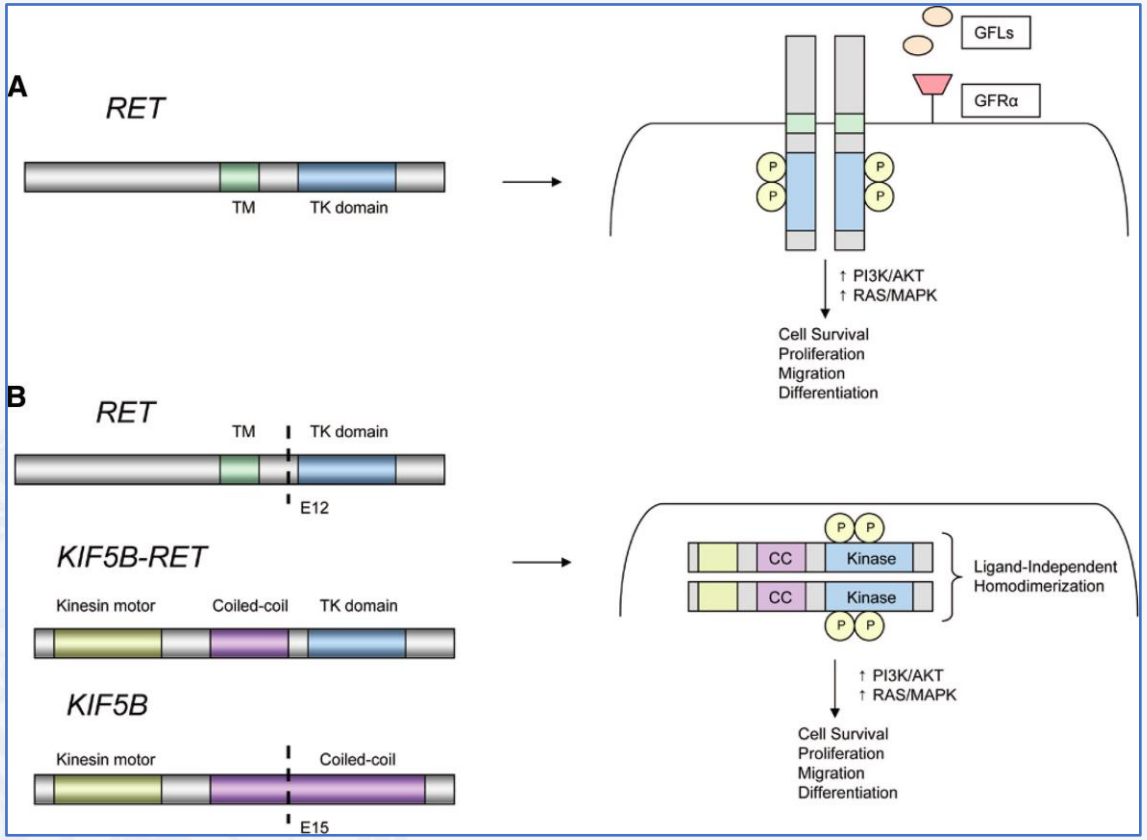
- Chromosomal inversions or translocations involving RET results in a juxtaposition of its kinase domain and the coiled coil domain of the partner
- This coiled coil domain is responsible for the ligand-independent homodimerization and constitutive RET activation



Takahashi M, et al. Cell 1985;42:581-8; Ju YS, et al. Genome Res 2012;22:436-45; Gautschi O, et al. J Clin Oncol 2017;35:1403-10; Takeuchi K. Front Physiol 2019;10:216; Mizukami T, et al. J Thorac Oncol 2014;9:622-30

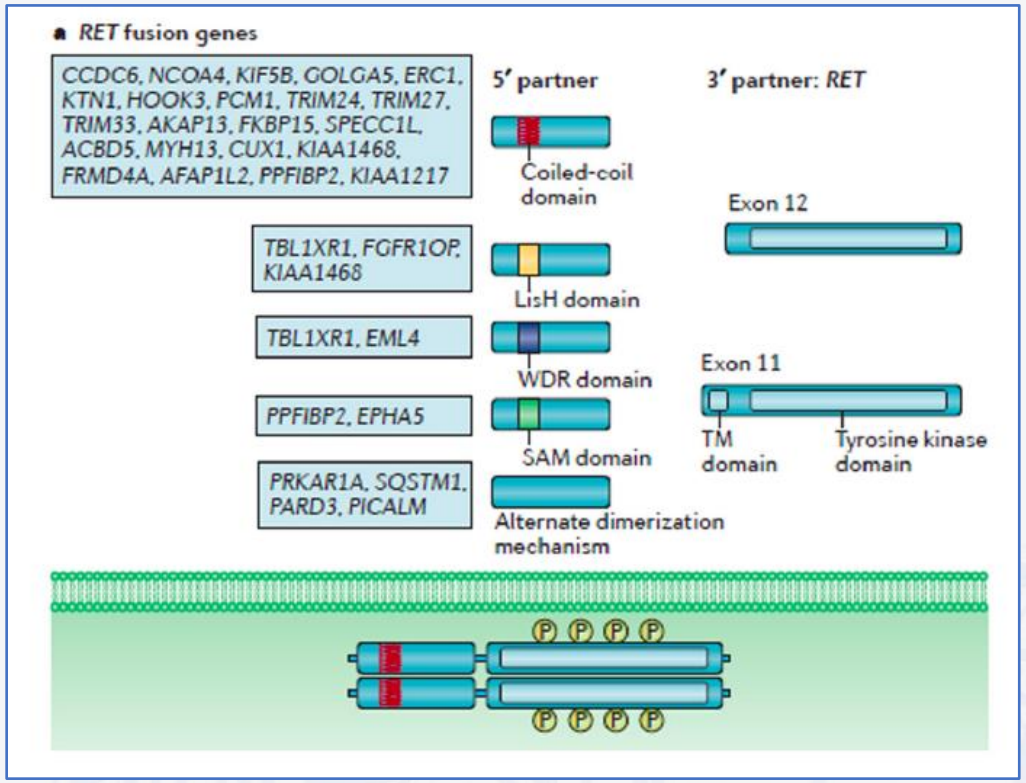
MOLECULAR BIOLOGY

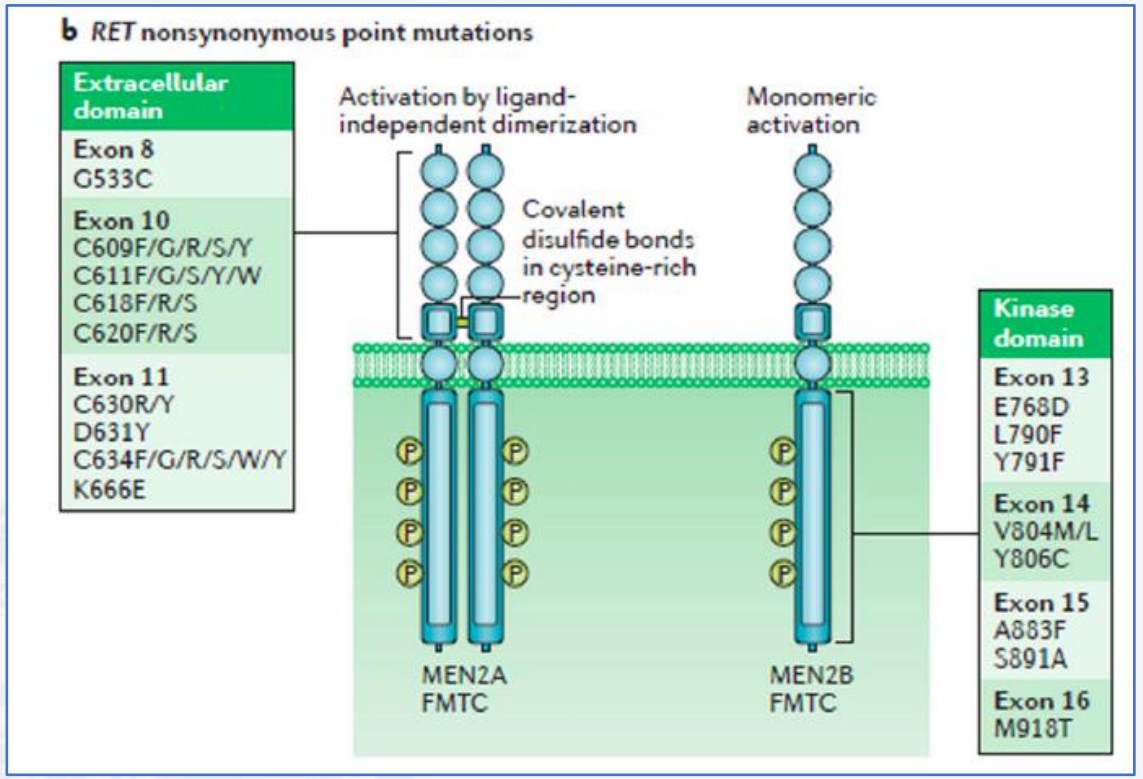
- RET proto-oncogene. RET activation typically involves ligand binding, interactions with a coreceptor, and homodimerization leading to formation of a multiprotein complex
- KIF5B-RET fusion. The coiled-coil domain of KIF5B promotes ligand-independent homodimerization of RET, leading to constitutive activation of downstream growth signaling



Gainor JF et al. The Oncologist 2013;18:865-75

MOLECULAR BIOLOGY





Most common RET fusions partners in:
-NSCLC: KIF5B (75%), CCDC6, NCOA4
-PTC: CCDC6, NCOA4

Most common RET mutations in:
-MTC: C634F/G/R/W/Y, M918T, V804M, L790F, Y791F

Drilon A, et al. Nat Rev Clin Oncol 2018;15:151-67

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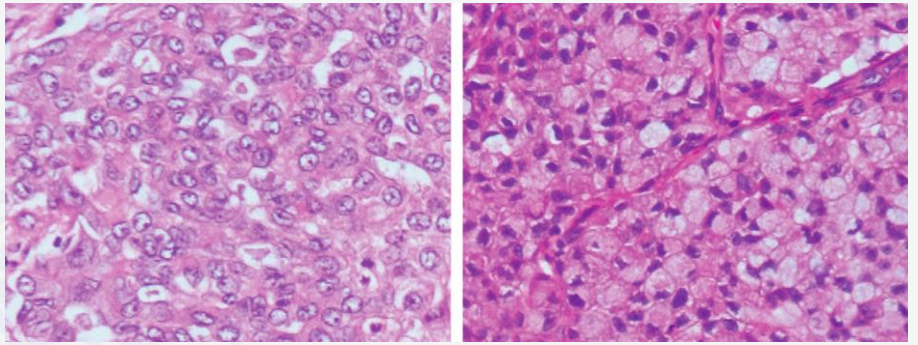
CLINICAL FEATURES OF RET-REARRANGED NSCLC

- RET fusions have been reported in approximately 1-2% of NSCLC
- Adenocarcinoma are the most frequent histology (lepidic, solid and papillary), followed by adeno-squamous, squamous cell, and neuroendocrine cancers
- RET+ patients had higher frequency of neuroendocrine histology (12%)
- Without any other driver mutations
- Relatively younger (<60 years of age)
- Never or light smokers



- More advanced disease at the time of the initial diagnosis (77% stage III/IV)
- Brain metastases at initial diagnosis (32%)

Wang R, et al. J Clin Oncol 2012;30:4352-9; Gainor JF, et al. The Oncologist 2013;18:865-75; Lin C, et al. Cancer Biol Ther 2015;16:1019-28; Michels S, et al. J Thorac Oncol 2016;11:122-7; Gautschi O, et al. J Clin Oncol 2017;35:1403-10; Dugay F, et al. Oncotarget 2017;8:53336-53351

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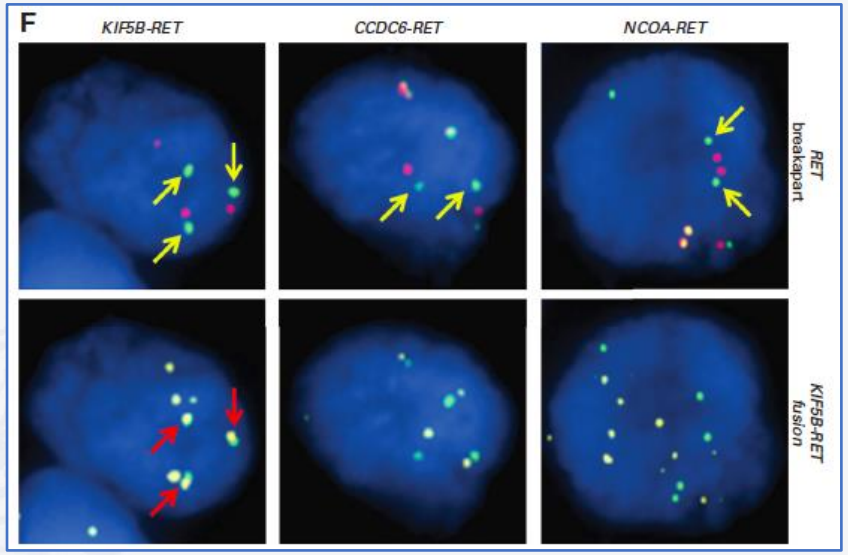
DIAGNOSIS

- RET-fusions are detected via different molecular methods in tissue biopsies, fine-needle aspirates, and even in liquid biopsies
- Immunohistochemistry (or immunocytochemistry) is not yet recommended
  - Low sensitivity and highly variable specificity
- Fluorescence-in-situ-hybridization (FISH) using a specific break-apart probe for RET detects different variants and fusions
  - False-positive
- Real-time PCR
- NGS can validate positive results, has the advantage of parallel testing for other driver mutations and can detect RET-fusions in liquid biopsies



Wang R, et al. J Clin Oncol 2012;30:4352-9; Belli C, et al. Ann Oncol 2021;32:337-50; Yang SR, et al. Clin Cancer Res 2021;27:1316-28

DIAGNOSIS

Table 3. Prevalence of *RET* rearrangements in non-small cell lung cancer screening studies

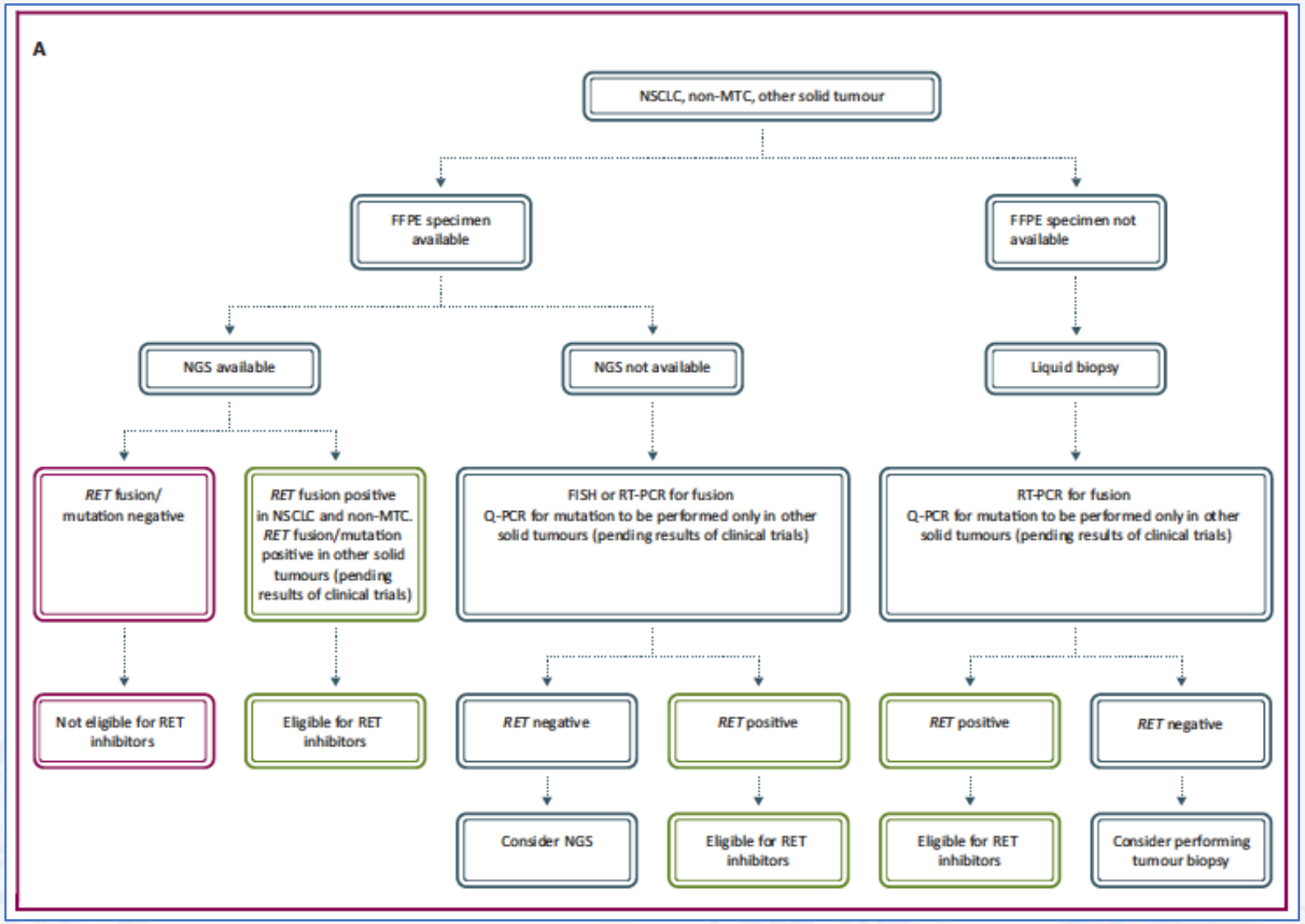
Study	Screening/validation techniques	Prevalence of *RET* rearrangements
Cai et al. [82]	RT-PCR, direct sequencing	6/392 (1.5%)
Ju et al. [38]	Whole-genome sequencing, transcriptome sequencing, RT-PCR	3/21 (14.3%)[a]
Kohno et al. [76]	Whole-transcriptome sequencing, RT-PCR, FISH	7/433 (1.6%)[b]
Li et al. [78]	Exon array analyses, RT-PCR	2/202 (1%)[c]
Lipson et al. [77]	Next-generation sequencing, IHC, RT-PCR	12/667 (1.8%)[d]
Seo et al. [31]	Whole-transcriptome sequencing, whole-exome sequencing	4/200 (2%)[b]
Suehara et al. [32]	Messenger RNA screen, RT-PCR, FISH	1/69 (1.4%)[e]
Takeuchi et al. [33]	FISH, RT-PCR	14/1529 (0.9%)
Wang et al. [79]	RT-PCR, IHC, FISH	13/936 (1.4%)
Yokota et al. [80]	RT-PCR, direct sequencing	3/371 (0.8%)

Table 1. Summary of main features, strengths and weaknesses of all available techniques to detect *RET* rearrangements

Method	Sensitivity	Specificity	Detection of partner	Detection of expression	Screening
IHC	Moderate[a]	Moderate[b]	No	Yes	No
FISH	High	High	No/Yes[c]	No	Rare circumstances
RT-PCR	Moderate/high[d]	High	Yes/No[e]	Yes	Rare circumstances
DNA-seq NGS	Moderate[f]	High/moderate[g]	Yes	No	Yes
RNA-seq NGS	High	High	Yes	Yes[h]	Yes

Gainor JF et al. The Oncologist 2013;18:865-75; Belli C, et al. Ann Oncol 2021;32:337-50

DIAGNOSIS



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CONVENTIONAL SYSTEMIC THERAPIES

- Chemotherapy remains a reasonable choice for the treatment of metastatic lung adenocarcinoma with driver mutations, including RET fusions
- Platinum and pemetrexed was very effective in (ALK, ROS1, RET) fusion-positive lung adenocarcinoma

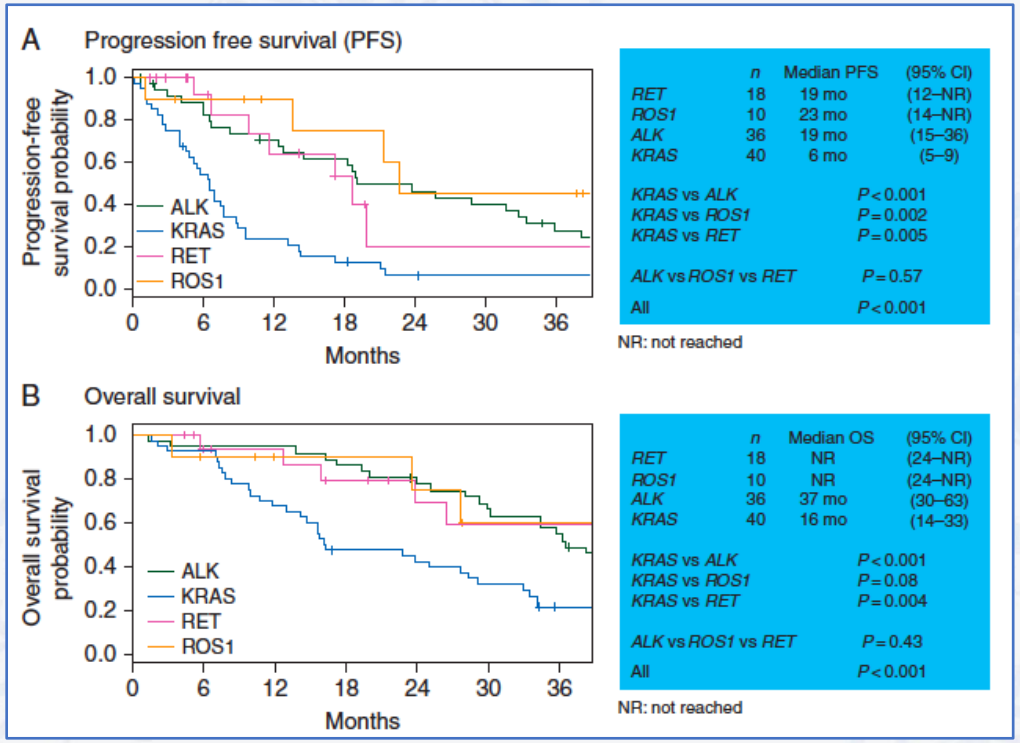


Table 2. Response to pemetrexed-based therapy

Patients	ORR (PR)	DCR (PR + SD)
RET-rearranged	45% ($n = 5/11$)	91% ($n = 10/11$)
ROS1-rearranged	78% ($n = 7/9$)	90% ($n = 8/9$)
ALK-rearranged	50% ($n = 14/28$)	93% ($n = 26/28$)
KRAS-mutant	26% ($n = 9/35$)	86% ($n = 30/35$)
P value	0.02	0.91

Drilon A, et al. Ann Oncol 2016;27:1286-91

CONVENTIONAL SYSTEMIC THERAPIES

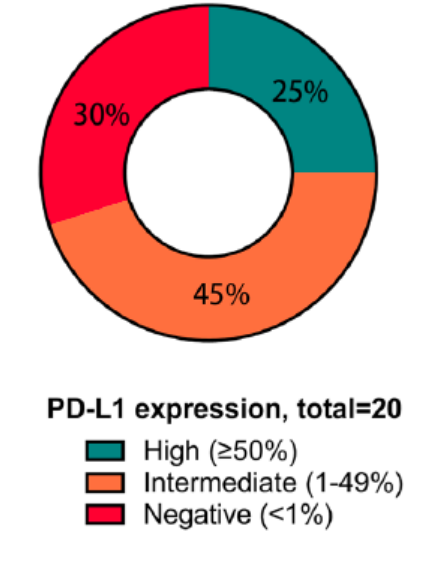
Lu et al. Journal of Hematology & Oncology (2020) 13:37
https://doi.org/10.1186/s13045-020-00866-6

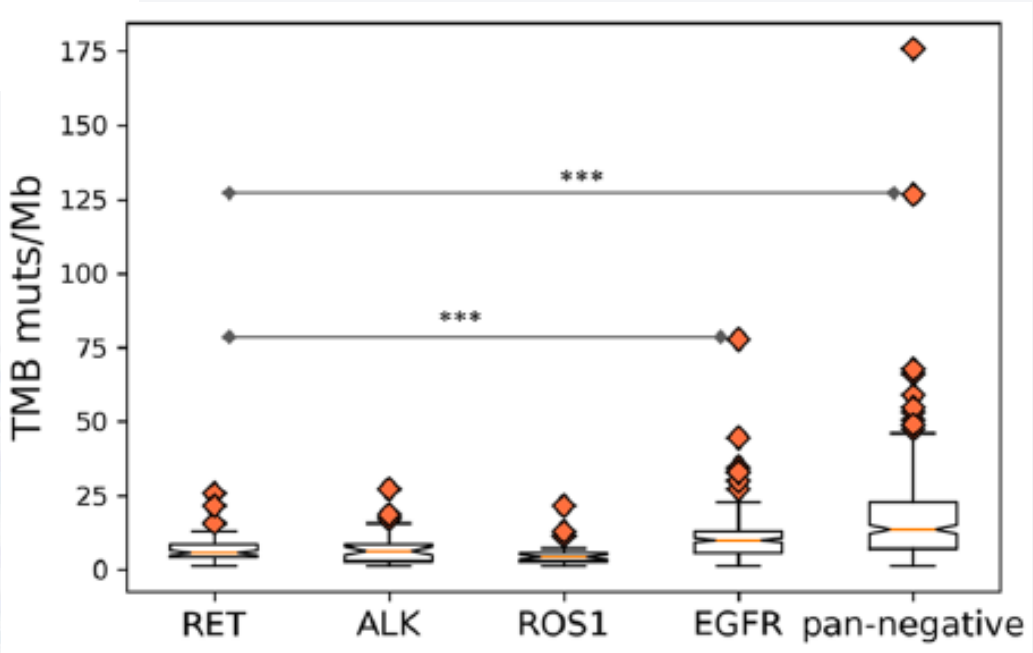
Journal of Hematology & Oncology

RESEARCH Open Access

Association of genetic and immuno-characteristics with clinical outcomes in patients with *RET*-rearranged non-small cell lung cancer: a retrospective multicenter study

- Patients with RET-rearranged NSCLC are characterized by low level of PD-L1 expression, as well as low TMB ("cold tumors")

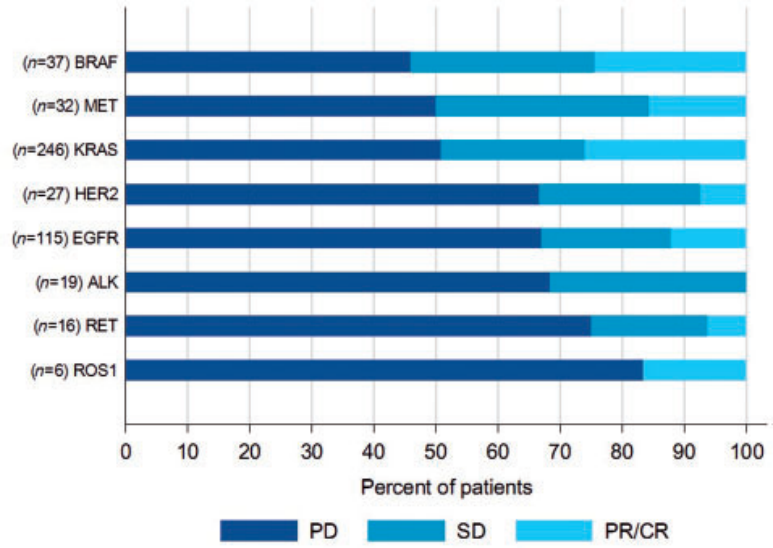




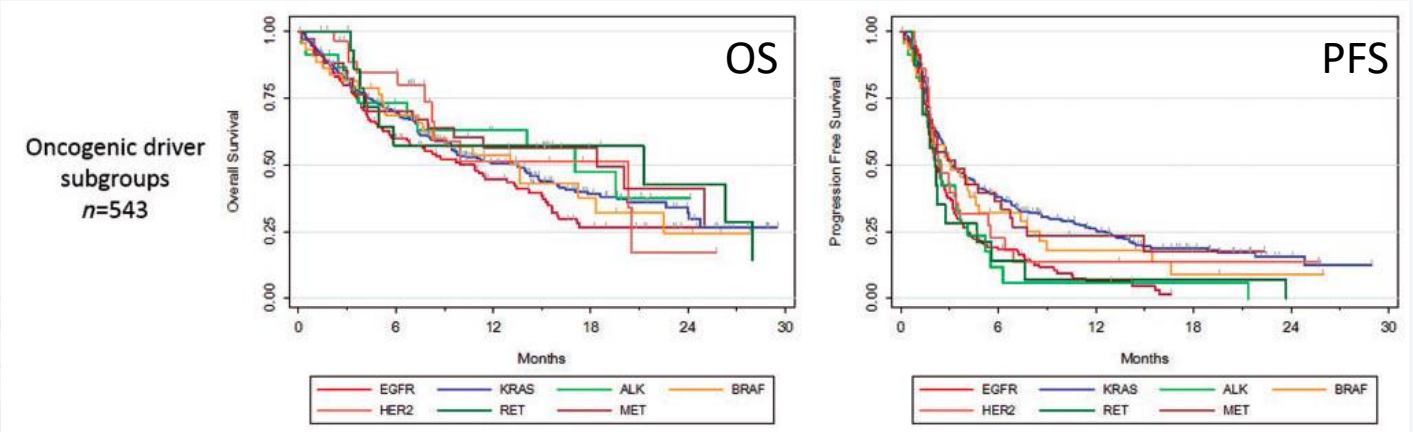
Offin M, et al. JCO Precis Oncol 2019;3:PO.18.00386; Lu C, et al. J Hematol Oncol 2020;13:37

CONVENTIONAL SYSTEMIC THERAPIES

- Immunotherapy (alone or in combination with chemotherapy) is approved for first line therapy, except for EGFR- and ALK-NSCLC
- NSCLC with ALK, ROS1 or RET fusions are associated with poor response to checkpoint inhibitors



IMMUNOTARGET



- Broad use of immunotherapy alone or in combination with chemotherapy for RET-NSCLC cannot be recommended, regardless of the PD-L1 expression level

Mazieres J, et al. Ann Oncol 2019;30:1321-8; Hegde A, et al. ESMO Open 2020;5:e000799

CONVENTIONAL SYSTEMIC THERAPIES

- The retrospective evidence points to poor response to immunotherapy

Table 1. Immune checkpoint inhibitors (ICI) in *RET*-altered cancers[a]

Study	MSKCC retrospective study [63]	MDACC retrospective study [62]	Flatiron Health-Foundation Medicine NSCLC Clinico-Genomic database (CGD) and Guardant Health database (GHD) [64]
Number of patients	74	70	29 in CGD, 40 in GHD
Tumor types	*RET*-rearranged lung cancers	*RET*-altered solid tumors; NSCLC ($n = 29$), MTC ($n = 32$), DTC and other cancers ($n = 9$)	*RET* fusion-positive NSCLC
Smoking history	31% tobacco exposure	29% tobacco exposure	12/29 tobacco exposure
RET fusion partner	*KIF5B* (58%) *CCDC6* (16%)	Fusion (49%) - *KIF5B* (41%) Mutation (51%) - *M918T* (67%)	*KIF5B* (74%) *CCDC6* (14%)
Immune phenotype findings in available population	PD-L1 expression: zero (58%), 1–49% (23%) Tumor mutational burden (TMB) - *RET*-rearranged (1.75 Mut/Mb) versus *RET* wild-type (5.27 Mut/Mb) ($P < 0.0001$)	PD-L1 expression: weak (<1%) (56%), 1–49% (22%) Tumor mutational burden (TMB) - All 15 patients have TMB low (≤5 Mut/Mb)	PD-L1 expression: <1% (7/13), ≥1% (6/13), others missing Tumor mutational burden (TMB) - <6 Mut/Mb (11/14) - ≥6 Mut/Mb (3/14) - Others missing
Response in evaluable patients	Response was not observed ($n = 13$) - SD 3/13 (23%), PD 8/13 (62%), mPFS 3.4 months	Time to treatment discontinuation (TTD) - Non-ICI group (18 months) versus ICI group (5.2 months) ($P = 0.00045$)	Median real-world PFS of 4.2 months and OS of 19.1 months (CGD)

Thein KZ, et al. Trends in Cancer 2021;7:1074-88

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NON-SELECTIVE RET INHIBITORS

- Different multi-kinase inhibitors have been evaluated in RET-rearranged NSCLC

Author	Regimen	Phase	Setting	N	ORR (%)	mPFS, months	mOS, months	Toxicities
Drilon A, et al. Lancet Oncol 2016	**Cabozantinib** 60mg/day	II (MSKCC study)	Pretreated or untreated	26 (25 evaluable)	28	5.5	9.9	>G3AEs: 69% ALT/AST increased
Gautschi O, et al. J Clin Oncol 2017	**Cabozantinib** 60mg/day	Global, Multicenter RET Registry (GLORY)	Pretreated	21	37	3.6	4.9	
Neal JW, et al. Lancet Oncol 2016	**Cabozantinib** 60mg/day vs **Cabozantinib** 40mg/day + **Erlotinib** 150mg/day vs **Erlotinib** 150mg/day	II	Pretreated	125	11 vs 3 vs 3	4.3 vs 4.7 vs 1.8	9.2 vs 13.3 vs 5.1	Cabozantinib or Cabozantinib + Erlotinib were more toxic
Yoh K, et al. Lancet Resp Med 2017	**Vandetanib** 300mg/day	II (LURET)	Pretreated	19	47	4.7	11.1	AEs G3-4: hypertension, diarrhea and rash
Lee SH, et al. Ann Oncol 2017	**Vandetanib** 300mg/day	II	Pretreated	18 (17 evaluable)	18	4.5	11.6	Common AEs: rash, diarrhea and hypertension
Gautschi O, et al. J Clin Oncol 2017	**Vandetanib** 300mg/day	Global, Multicenter RET Registry (GLORY)	Pretreated	11	18	2.9	10.2	
Gautschi O, et al. J Clin Oncol 2017	**Sunitinib** 37,5mg/day	Global, Multicenter RET Registry (GLORY)	Pretreated	10	22	2.2	6.8	
Hida T, et al. Lung Cancer 2019	**Lenvatinib** 24mg/day	II	Pretreated	25	16	7.3	NE	Hypertension, nausea, diarrhea and proteinuria

Drilon A, et al. Lancet Oncol 2016;17:1653-60; Neal JW, et al. Lancet Oncol 2016;17:1661-71; Gautschi O, et al. J Clin Oncol 2017;35:1403-10; Lee SH, et al. Ann Oncol 2017;28:292-7; Yoh K, et al. Lancet Respir Med 2017;5:42-50; Hida T, et al. Lung Cancer 2019;138:124-30

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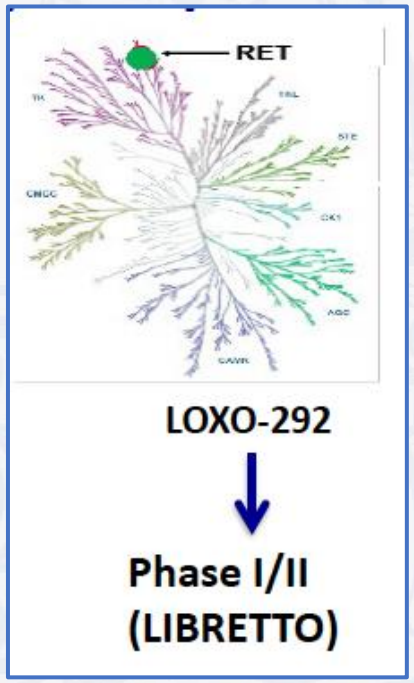
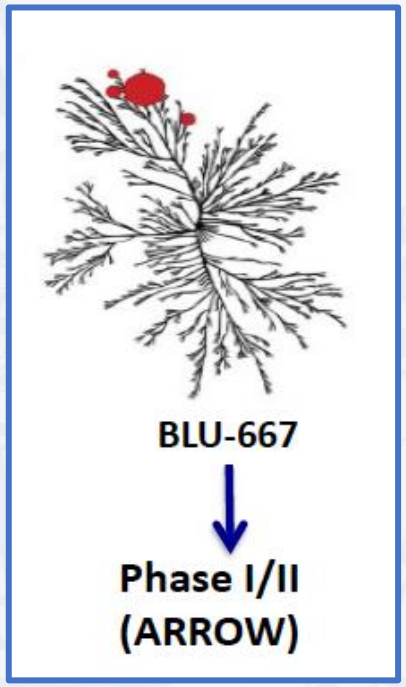
SELECTIVE RET INHIBITORS

- Small, highly selective RET inhibitors have been developed with the aim of:
  - overcoming treatment-related toxicities commonly seen with non-selective RET inhibitors
  - being more specific and potent



SELPERCATINIB

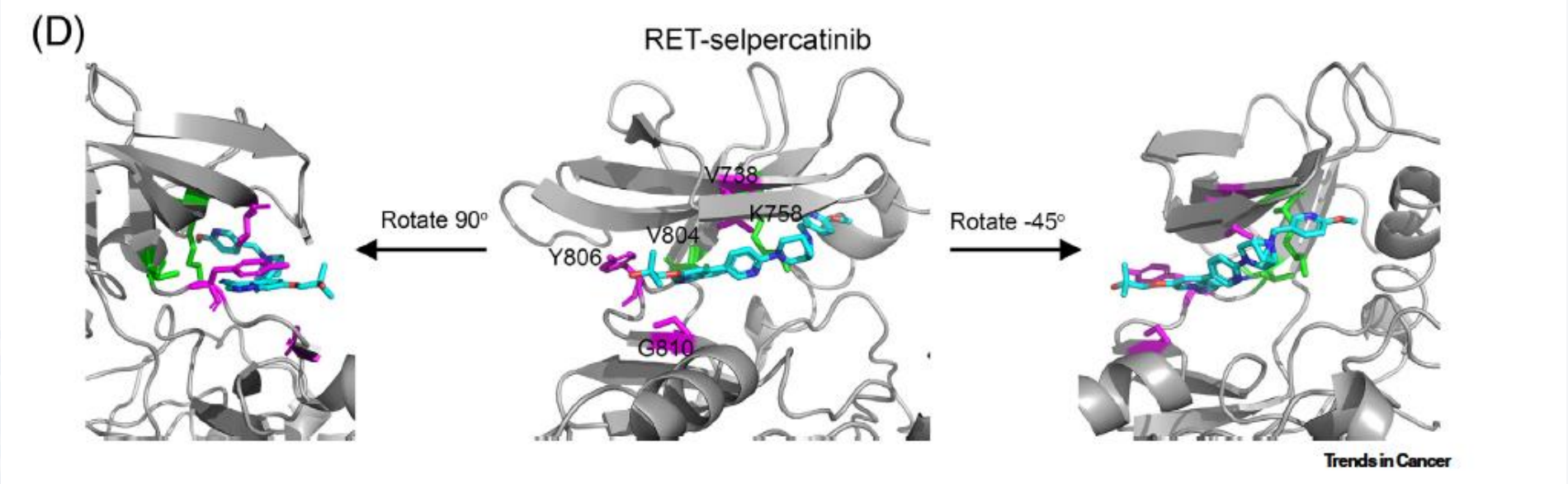


PRALSETINIB

Drug	IC_{50} RET (nM) (cell-free)	IC_{50} VEGFR2 (nM) (cell-free)
Alectinib	4.8[1]	> 100x
Vandetanib	4[2]	4[2]
Lenvatinib	35	4[3]
Sunitinib	224[4]	38[4]
Ponatinib	23	1.5[5]
Sorafenib	43[6]	90[6]
Cabozantinib	11[2]	2.2[2]
Regorafenib	1.5[7]	4.2[7]
LOXO-292	3	> 100x
BLU-667	0.4[2]	35[2]

SELPERCATINIB

- Selpercatinib (LOXO-292) is an oral TKI with potent and specific activity against the RET kinase domain, including multiple RET alterations such as fusions, activating point mutations and predicted acquired resistance mutations



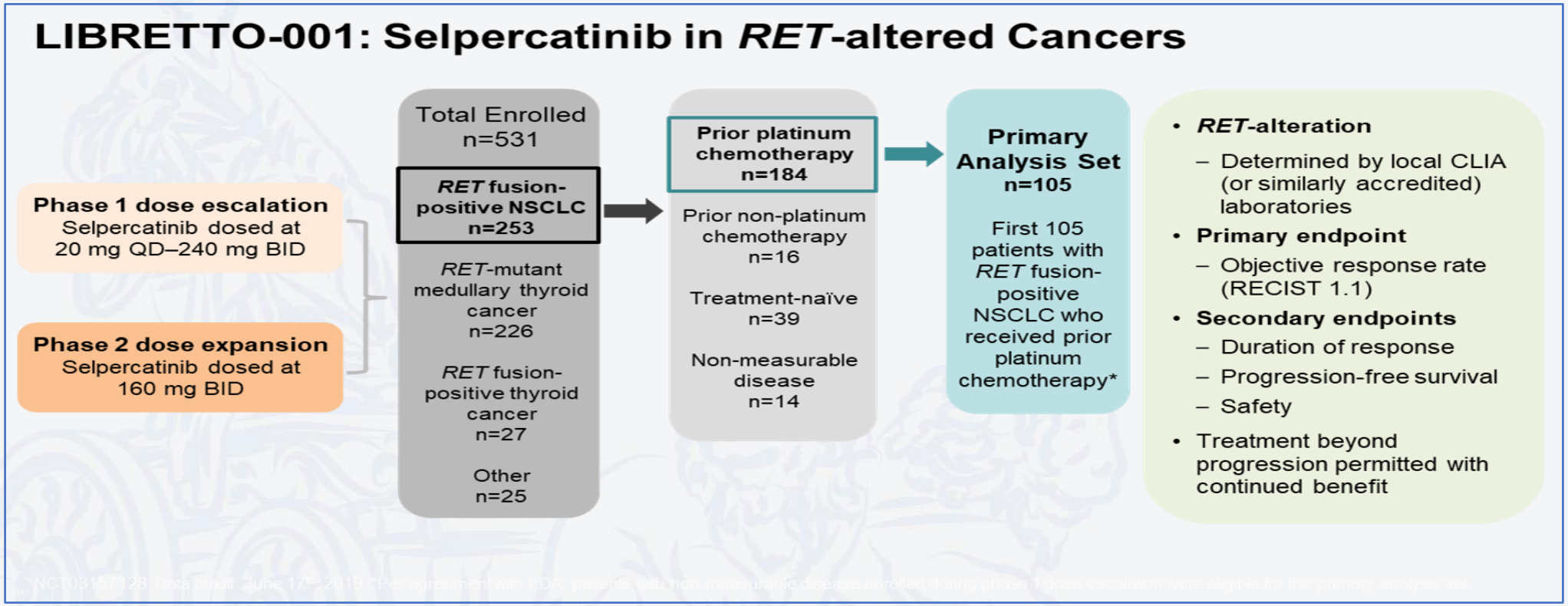
- Selpercatinib (LOXO-292) inhibiting the RET V804M/L gatekeeper mutants, docks one end of the ATP-binding pocket without inserting into the gate and wraps outside the K758

Thein KZ, et al. Trends in Cancer 2021;7:1074-88

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 27, 2020 VOL. 383 NO. 9

Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer

SELPERCATINIB



- LIBRETTO-001: phase I-II, open-label, first-in-human. Clinical safety and its activity profile

Drilon A, et al. N Engl J Med 2020;383:813-24

SELPERCATINIB

- Phase I part:
- 82 RET-driven cancers of different origin were treated with increasing doses of selpercatinib, ranging from 20 mg once daily to 260 mg twice daily
- The maximum tolerated dose was not reached and only two TRAEs G3 were observed (tumor lysis syndrome, ALT increase)
- RR in patients with NSCLC, who were heavily pretreated reached 77% and was independent of the respective RET-fusion-partner and MTK-inhibitor pretreatment
- All 3 patients with pretreatment brain-metastases showed intracranial tumor-shrinkage
- 160mg BID was determined as the recommended phase II-dose and expansion cohort was opened

Drilon A, et al. J Clin Oncol 2018;36(suppl;abstract 102)

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 27, 2020 VOL. 383 NO. 9

Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer

SELPERCATINIB

- Baseline characteristics of the patients

Characteristic	Previous Platinum Chemotherapy (N=105)	Previously Untreated (N=39)
Age — yr		
Median	61	61
Range	23–81	23–86
Sex — no. (%)		
Female	62 (59)	22 (56)
Male	43 (41)	17 (44)
Race — no. (%)†		
White	55 (52)	28 (72)
Asian	40 (38)	7 (18)
Black	5 (5)	3 (8)
Other	3 (3)	1 (3)
Missing data	2 (2)	0
Smoking status — no. (%)		
Never smoked	75 (71)	29 (74)
Former smoker	29 (28)	9 (23)
Current smoker	1 (1)	1 (3)
ECOG performance-status score — no. (%)‡		
0	31 (30)	18 (46)
1	72 (69)	21 (54)
2	2 (2)	0

Characteristic	Previous Platinum Chemotherapy (N=105)	Previously Untreated (N=39)
NSCLC histologic subtype — no. (%)		
Adenocarcinoma	90 (86)	34 (87)
Large-cell neuroendocrine carcinoma	2 (2)	0
Squamous-cell carcinoma	1 (1)	0
NSCLC-NOS	12 (11)	5 (13)
Median previous systemic regimens — no. (range)	3 (1–15)	0
Previous regimen		
Platinum-based chemotherapy — no. (%)	105 (100)	NA
Anti–PD-1 or anti–PD-L1 therapy — no. (%)	58 (55)	NA
Multitargeted kinase inhibitor — no. (%)§	50 (48)	NA
1 — no./total no. (%)	37/50 (74)	NA
≥2 — no./total no. (%)	13/50 (26)	NA
Brain metastases — no. (%)	38 (36)	7 (18)
Measurable disease — no. (%)	104 (99)	39 (100)
RET fusion — no. (%)		
KIF5B-RET	59 (56)	26 (67)
CCDC6-RET	24 (23)	8 (21)
NCOA4-RET	2 (2)	0
RELCH-RET	2 (2)	0
Other¶	6 (6)	1 (3)
Not determined‖	12 (11)	4 (10)

Drilon A, et al. N Engl J Med 2020;383:813-24

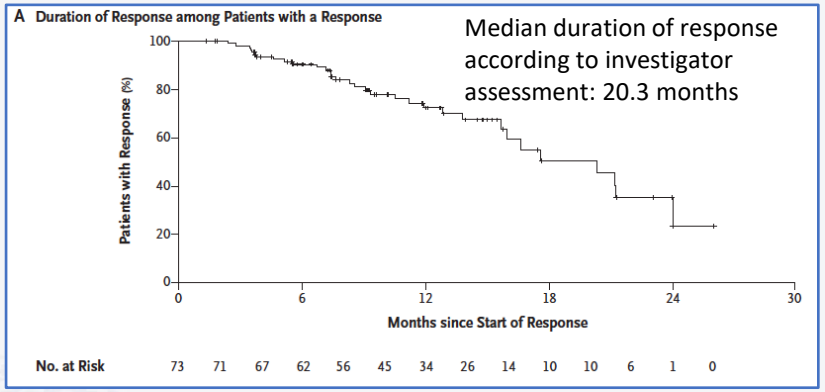
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 27, 2020 VOL. 383 NO. 9

Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer

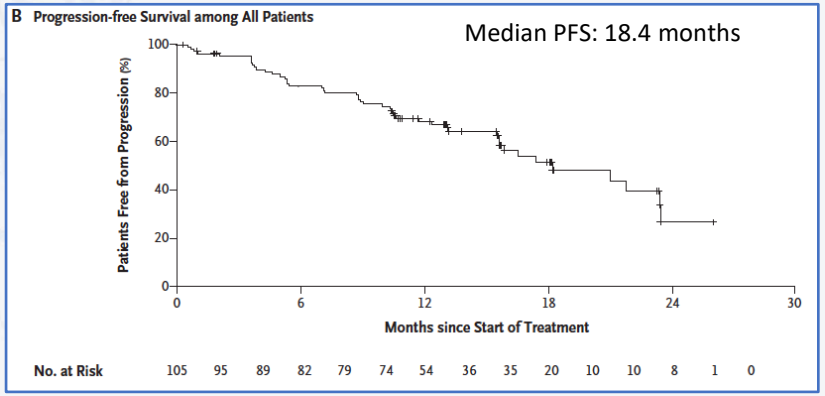
SELPERCATINIB

- Efficacy

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



Median duration of response according to investigator assessment: 20.3 months



Median PFS: 18.4 months

Drilon A, et al. N Engl J Med 2020;383:813-24

The NEW ENGLAND JOURNAL of MEDICINE
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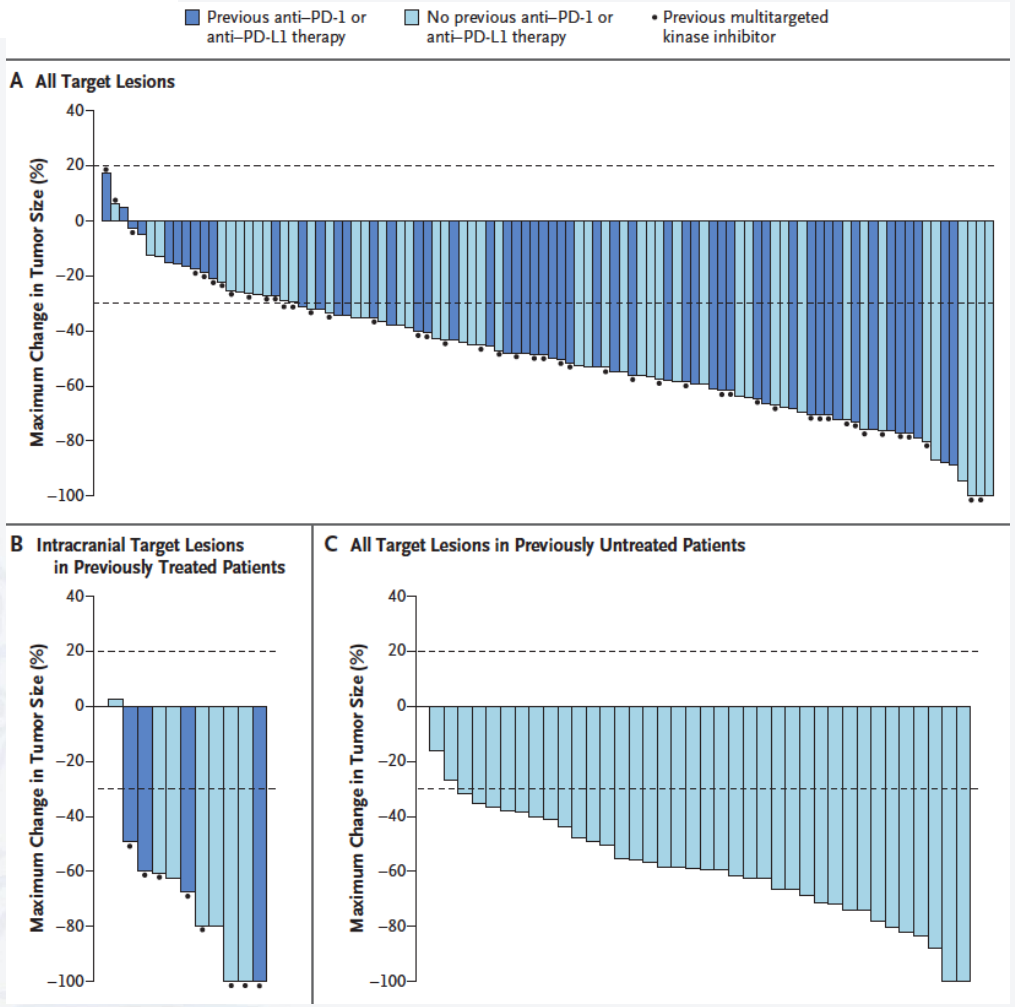
Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer

SELPERCATINIB

- Efficacy:
- Waterfall plots of the maximum change in tumor size in all target lesions, according to investigator assessment: 70%
- Waterfall plots in intracranial target lesions in patients who had previously received platinum-based chemotherapy:
  - 38/105
  - 11/38 were deemed to have measurable lesions
  - Objective intracranial RR was 91% (10/11)
  - 3 complete response (in 27%)



Drilon A, et al. N Engl J Med 2020;383:813-24

The NEW ENGLAND JOURNAL of MEDICINE
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Efficacy of Selpercatinib in *RET* Fusion–Positive Non–Small-Cell Lung Cancer

SELPERCATINIB

- Safety profile:
  - Dose reduction: 160 (30%)
  - Discontinued: 12 (2%)
    - The most common:
      - Increase AST
      - Increase ALT
      - Increase glucose levels

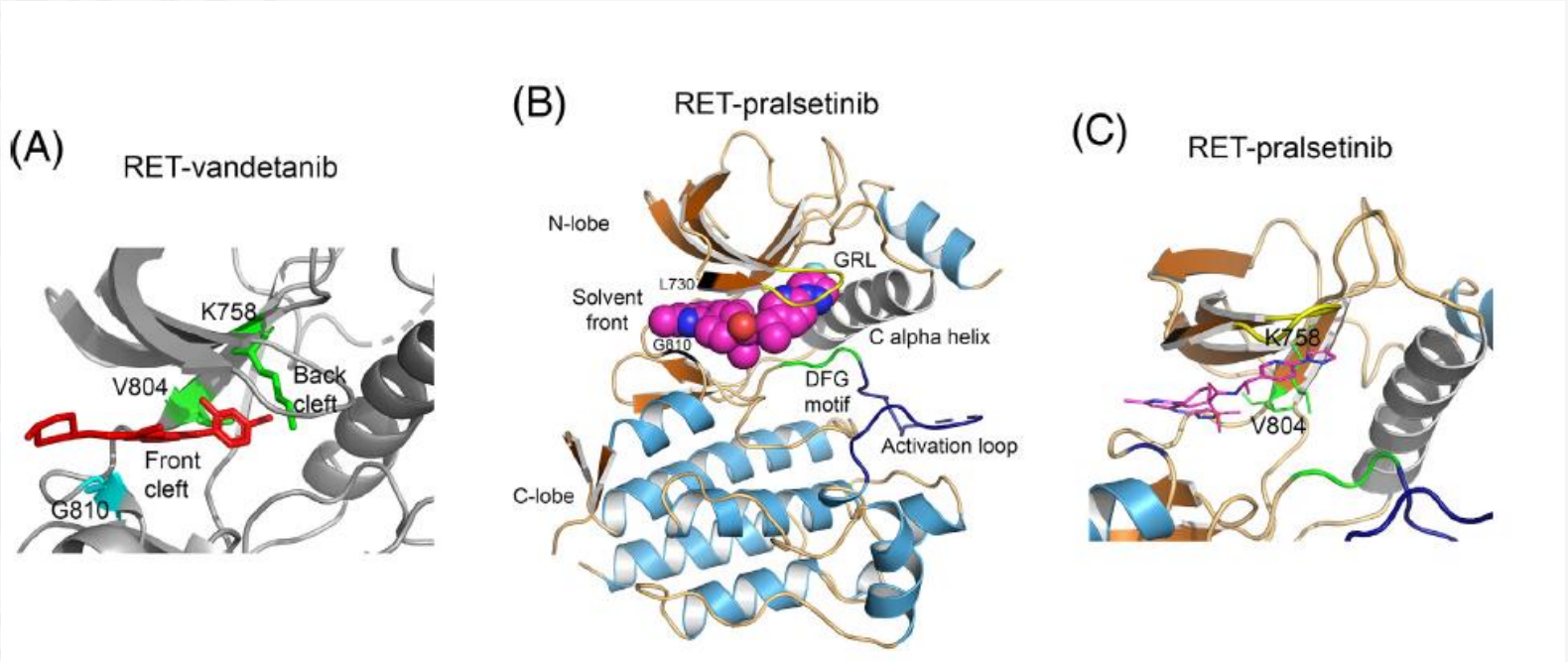
Table 3. Adverse Events in 144 Patients with *RET* Fusion–Positive NSCLC Who Received Selpercatinib.*

Adverse Event	Adverse Events, Regardless of Attribution (N=144)					Treatment-Related Adverse Events (N=144)		
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade
	number of patients (percent)							
Any adverse event	8 (6)	47 (33)	69 (48)	14 (10)	144 (100)	39 (27)	2 (1)	131 (91)
Diarrhea	46 (32)	18 (12)	5 (3)	0	69 (48)	2 (1)	0	36 (25)
Dry mouth	48 (33)	11 (8)	0	0	59 (41)	0	0	52 (36)
Hypertension	3 (2)	22 (15)	20 (14)	0	45 (31)	13 (9)	0	25 (17)
Increased aspartate aminotransferase level	18 (12)	11 (8)	12 (8)	2 (1)	43 (30)	7 (5)	1 (1)	32 (22)
Fatigue	26 (18)	16 (11)	0	0	42 (29)	0	0	19 (13)
Increased alanine aminotransferase level	14 (10)	6 (4)	15 (10)	3 (2)	38 (26)	11 (8)	2 (1)	29 (20)
Constipation	33 (23)	3 (2)	2 (1)	0	38 (26)	1 (1)	0	16 (11)
Nausea	32 (22)	5 (3)	1 (1)	0	38 (26)	0	0	14 (10)
Peripheral edema	29 (20)	6 (4)	0	0	35 (24)	0	0	19 (13)
Urinary tract infection	4 (3)	21 (15)	7 (5)	0	32 (22)	0	0	0
Headache	21 (15)	7 (5)	2 (1)	0	30 (21)	0	0	6 (4)
Rash	20 (14)	6 (4)	2 (1)	0	28 (19)	2 (1)	0	17 (12)
Abdominal pain	18 (12)	8 (6)	1 (1)	0	27 (19)	0	0	5 (3)
Cough	24 (17)	3 (2)	0	0	27 (19)	0	0	3 (2)
Increased blood creatinine level	21 (15)	3 (2)	0	0	24 (17)	0	0	13 (9)
Dyspnea	15 (10)	6 (4)	3 (2)	0	24 (17)	0	0	4 (3)
Vomiting	17 (12)	6 (4)	1 (1)	0	24 (17)	1 (1)	0	5 (3)
Prolonged QT on electrocardiography	9 (6)	7 (5)	7 (5)	0	23 (16)	3 (2)	0	14 (10)
Pyrexia	14 (10)	8 (6)	1 (1)	0	23 (16)	1 (1)	0	8 (6)
Dry skin	19 (13)	3 (2)	0	0	22 (15)	0	0	13 (9)
Thrombocytopenia	13 (9)	6 (4)	3 (2)	0	22 (15)	2 (1)	0	15 (10)

Drilon A, et al. N Engl J Med 2020;383:813-24

PRALSETINIB

- Pralsetinib (BLU-667) is a small molecule that strongly inhibits the RET kinase domain
- Pralsetinib binds to the RET kinase by occupying both the front and back cletfs without passing through the gate like vandetanib
- Pralsetinib is also highly selective against VEGFR2



Subbiah V, et al. Cancer Discov 2018;8:836-49; Thein KZ, et al. Trends in Cancer 2021;7:1074-88

PRALSETINIB

Pralsetinib for *RET* fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study

- Phase I-II ARROW trial: BLU-667 dose-escalation and expansion study

Part 1: Dose-Escalation (N=62; Complete)[1]

RET-altered advanced solid tumors

BLU-667: 30-600 mg by daily oral administration (QD or BID)

Phase 2 dose determined (400 mg QD) →

ARROW is registered with clinicaltrials.gov (NCT03037385)

Part 2: Expansion Cohorts (Ongoing)

BLU-667 400 mg QD

- Unresectable, advanced solid tumor
- RET alteration status by local tumor testing
- No additional driver mutation
- ECOG PS 0-1
- Asymptomatic brain metastases allowed
- Progressive disease or intolerant to SOC therapy, or not a candidate

Primary objectives:

Overall response rate (RECIST 1.1)

Safety

- RET fusion+ NSCLC, prior platinum (n=80)
- RET fusion+ NSCLC, platinum naïve (n=40)
- MTC, prior cabozantinib or vandetanib (n=60)
- MTC, no prior cabozantinib or vandetanib (n=40)
- Other RET fusion+ tumors (n=40)
- Other RET-mutated tumors (n=20)
- RET-altered, prior selective RET inhibitor (n=20)

Gainor J. 2019 ASCO Annual Meeting

Pralsetinib for *RET* fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study

PRALSETINIB

- Baseline characteristics of the patients (N=233)

	Previous platinum-based chemotherapy group (n=92)	No previous systemic treatment group (n=29)
Age, years	60 (63–68)	65 (54–69)
≥65 years	33 (36%)	15 (52%)
Sex		
Female	46 (50%)	15 (52%)
Male	46 (50%)	14 (48%)
Region		
USA	30 (33%)	7 (24%)
Europe	32 (35%)	14 (48%)
Asia	30 (33%)	8 (28%)
Race		
White	49 (53%)	17 (59%)
Asian	32 (35%)	10 (34%)
Other or unknown	11 (12%)	2 (7%)
Smoking history		
Current or former	32 (35%)	13 (45%)
Never or unknown	60 (65%)	16 (55%)
Histology		
Adenocarcinoma	88 (96%)	29 (100%)
Other*	4 (4%)	0
Eastern Cooperative Oncology Group performance status		
0	34 (37%)	11 (38%)
1	53 (58%)	17 (59%)
2†	5 (5%)	1 (3%)
Brain metastases‡	38 (41%)	12 (41%)
RET fusion partner		
KIF5B	69 (75%)	20 (69%)
CCDC6	16 (17%)	3 (10%)
Other	2 (2%)§	0
Unknown	5 (5%)¶	6 (21%)‖

	Previous platinum-based chemotherapy group (n=92)	No previous systemic treatment group (n=29)
(Continued from previous column)		
RET assay**		
Next-generation sequencing -based	41 (45%)	8 (28%)
ctDNA	61 (66%)	16 (55%)
FISH	18 (20%)	9 (31%)
Other	7 (8%)	6 (21%)
Lines of previous therapy	2 (1–3)	0
Previous therapy type		
Chemotherapy	92 (100%)	0
PD-(L)1 inhibitor	41 (45%)	0
Multikinase inhibitor	24 (26%)	0

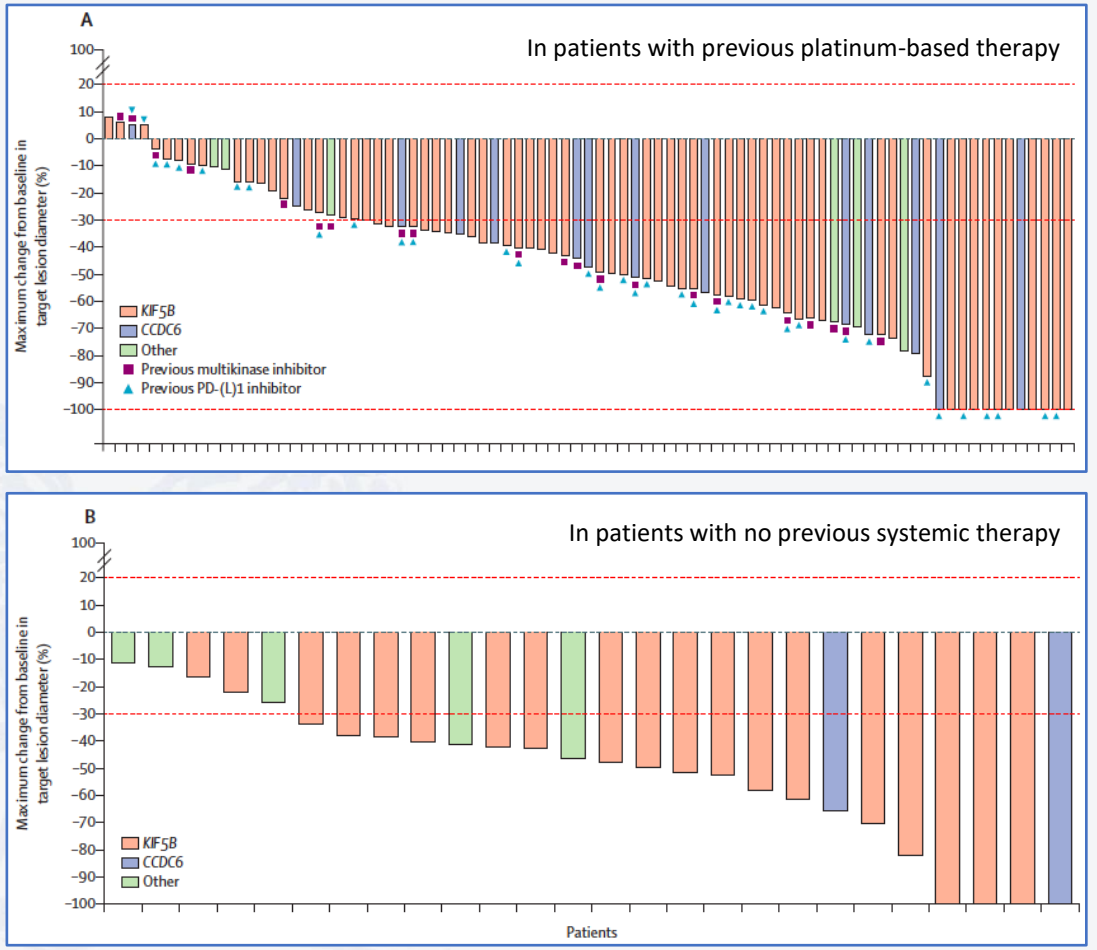
Gainor J. Lancet Oncol 2021;22:959-69

Pralsetinib for *RET* fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study

PRALSETINIB

- Efficacy: clinical activity endpoints in patients with measurable disease

	Previous platinum group (n=87)	No previous systemic treatment group (n=27)†
Overall response rate	53 (61%; 50–71)‡	19 (70%; 50–86)
Disease control rate	79 (91%; 83–96)	23 (85%; 66–96)
Best overall response		
Complete response	5 (6%)	3 (11%)
Partial response	48 (55%)‡	16 (59%)
Stable disease	26 (30%)	4 (15%)
Progressive disease	4 (5%)	3 (11%)
Not evaluable	4 (5%)	1 (4%)
Median duration of response, months	NR (15·2–NE)	9·0 (6·3–NE)
Rate at 6 months	83%; 73–94	74%; 52–96
Rate at 12 months	74%; 61–87	26%; 0–52
Clinical benefit rate§	69% (58–79)	70% (50–86)



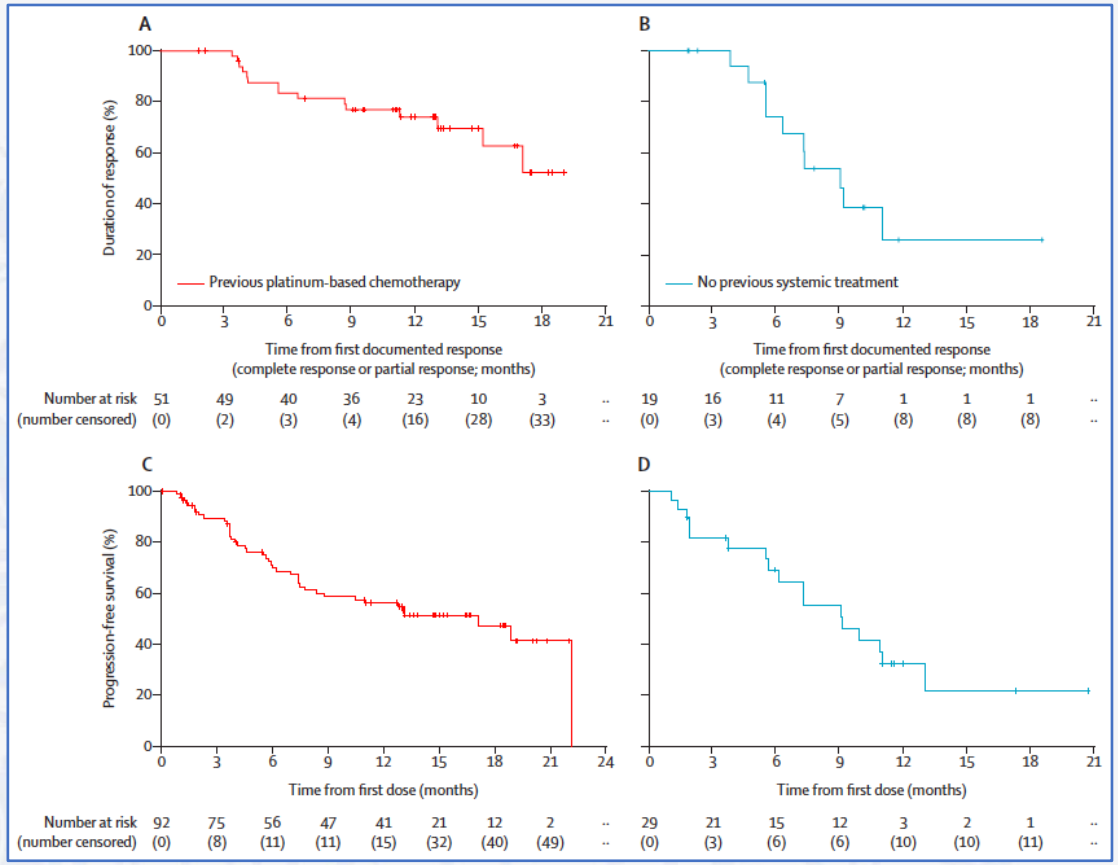
Gainor J. Lancet Oncol 2021;22:959-69

Pralsetinib for *RET* fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study

PRALSETINIB

- Efficacy: duration of response and progression-free survival

Median duration of response was not reached



Median duration of response was in all responders was 9.0 months

Median PFS was 17.1 months

Median PFS was 9.1 months

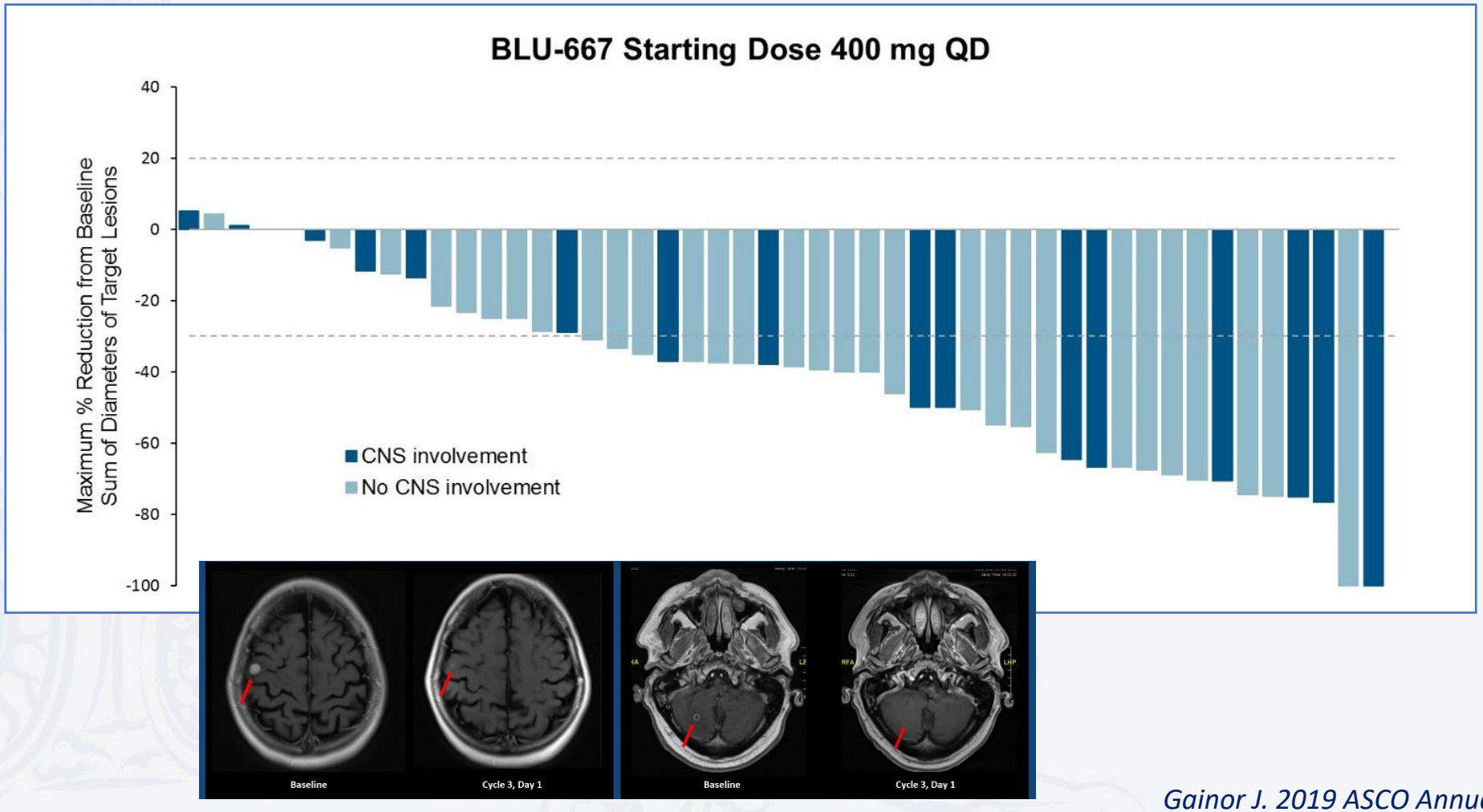
- Efficacy: OS was not reached at a median follow-up of 13.6 months (IQR 13.0-17.6) with 5 deaths

Gainor J. Lancet Oncol 2021;22:959-69

Pralsetinib for *RET* fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study

PRALSETINIB

- BLU-667 is active regardless of CNS involvement

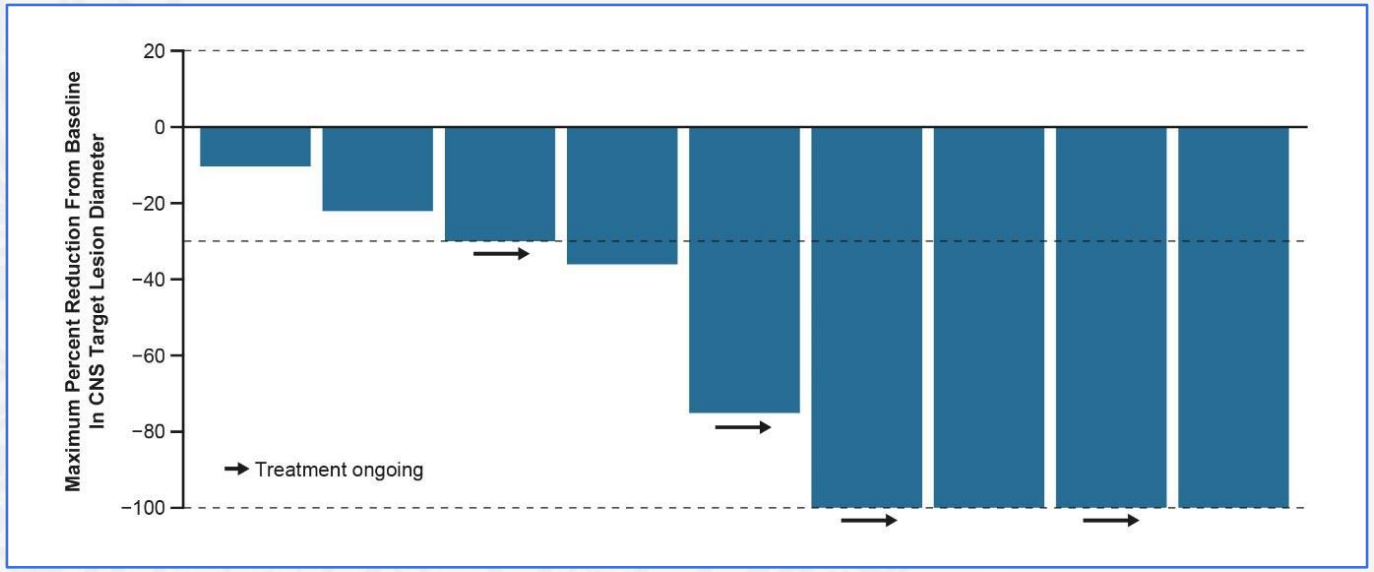


Gainor J. 2019 ASCO Annual Meeting

Pralsetinib for *RET* fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study

PRALSETINIB

- Shrinkage of intracranial metastases was seen in all nine patients with measurable intracranial metastases at baseline and at least one post-baseline intracranial response assessment
- Five of nine (56%; 95% CI 21-86) had an intracranial response, including three complete response (one patient had 100% reduction at one scan only, so was not considered a complete response)
- Median duration of intracranial response was not reached



Gainor J. Lancet Oncol 2021;22:959-69 (appendix p24)

Pralsetinib for *RET* fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study

PRALSETINIB

	Grade 1–2	Grade 3	Grade 4
Neutropenia*	48 (21%)	34 (15%)	9 (4%)
Elevated aspartate aminotransferase	82 (35%)	4 (2%)	2 (1%)
Anaemia*	50 (21%)	24 (10%)	0
Decreased white blood cell count*	50 (21%)	14 (6%)	0
Elevated alanine aminotransferase	56 (24%)	4 (2%)	1 (<1%)
Asthenia*	49 (21%)	4 (2%)	0
Constipation	51 (22%)	2 (1%)	0
Hypertension*	24 (10%)	26 (11%)	0
Dysgeusia	31 (13%)	0	0
Elevated blood creatinine	30 (13%)	0	0
Thrombocytopenia*	23 (10%)	5 (2%)	2 (1%)
Diarrhoea	28 (12%)	1 (<1%)	0
Dry mouth	29 (12%)	0	0
Elevated blood creatine phosphokinase	19 (8%)	8 (3%)	0
Pneumonitis*	22 (9%)	3 (1%)	1 (<1%)
Hyperphosphataemia	25 (11%)	0	0
Lymphopenia*	14 (6%)	9 (4%)	2 (1%)
Oedema*	24 (10%)	0	0
Hypophosphataemia	6 (3%)	5 (2%)	1 (<1%)
Hyponatraemia*	6 (3%)	4 (2%)	1 (<1%)
Stomatitis	6 (3%)	4 (2%)	0

- Safety profile:
  - 216 (93%) patients had TRAEs
  - 111 (48%) patients had TRAEs G3 or worse
  - The most common TRAEs G3 or worse were:
    - NEUTROPENIA (43 (18%) of 233 patients)
    - HYPERTENSION (26 (11%))
    - ANAEMIA (24 (10%))
  - 89 (38%) patients had dose reductions owing to TRAEs
  - 14 (6%) patients discontinued treatment owing to TRAEs
  - There were no deaths considered related to pralsetinib

Gainor J. Lancet Oncol 2021;22:959-69

SELECTIVE RET INHIBITORS

Table 3. Published clinical data of specific RET inhibitors in various stages of development[a,b]

	Selpercatinib (LOXO-292)	Pralsetinib (BLU-667)
Clinical trial	LIBRETTO-001 (NCT03157128)	ARROW (NCT03037385)
Trial setting	Multicenter, multicohort, Phase I/II	Multicenter, multicohort, Phase I/II
RP2D	160 mg orally twice daily	400 mg orally once daily
Published preliminary efficacy in patients with NSCLC and thyroid cancers	*RET* + NSCLC [88] 1. Previously treated (n = 105): ORR 64%, CR 2%, mDOR 17.5 months, mPFS 16.5 months, 1-year PFS 66% 2. Treatment naïve (n = 39): ORR 85%, CR 0%, mDOR NE, mPFS NE, 1-year PFS 75%	*RET* + NSCLC [92] 1. Previously treated (n = 87): ORR 61%, CR 6%, mDOR NR, mPFS 17.1 months 2. Treatment naïve (n = 27): ORR 70%, CR 11%, mDOR 9 months, mPFS 9.1 months
	RET + thyroid cancers [87] 1. Previously treated *RET*-mutant MTC (n = 55): ORR 69%, CR 9%, mDOR NE, mPFS NE, 1-year PFS 82% 2. Treatment naïve *RET*-mutant MTC (n = 88): ORR 73%, CR 11%, mDOR 22 months, mPFS 23.6, 1-year PFS 92% 3. Previously treated *RET* fusion-positive thyroid cancer (n = 19): ORR 79%, CR 5%, mDOR 18.4, mPFS 20.1, 1-year PFS 64%	*RET* + thyroid cancers [93] 1. Previously treated *RET*-mutant MTC (n = 55): ORR 60%, CR 2%, mDOR NR, mPFS NR 2. Treatment naïve *RET*-mutant MTC (n = 21): ORR 71%, CR 5%, mDOR NR, mPFS NR 3. Previously treated *RET* fusion-positive thyroid cancer (n = 9): ORR 89%, CR 0%, mDOR NR, mPFS NR
Activity in *RET* + tumors beyond NSCLC and thyroid	AACR 2021 data https://cancerres.aacrjournals.org/content/81/13_Supplement/CT011	ASCO 2021 data https://meetinglibrary.asco.org/record/197581/abstract
CNS activity	Pre-clinical and clinical data +++/+++	Pre-clinical and clinical data +++/++++
FDA approval timeline	May 8, 2020 1. Adult patients with metastatic *RET* fusion-positive NSCLC; 2. Adult and pediatric patients ≥12 years of age with advanced or metastatic *RET*- MTC who require systemic therapy; 3. Adult and pediatric patients ≥12 years of age with advanced or metastatic *RET* fusion-positive thyroid cancer who require systemic therapy and who are RAI-refractory	September 4, 2020 1. Adult patients with metastatic *RET* fusion-positive NSCLC December 1, 2020 1. Adult and pediatric patients 12 years of age and older with advanced or metastatic *RET*-mutant MTC who require systemic therapy or *RET* fusion-positive thyroid cancer who require systemic therapy and who are RAI-refractory

[a]Clinical trials with TPX-0046 (NCT04161391), BOS 172738 (NCT03780517), and TAS0953/HM06 (NCT04683250) are ongoing. Early nonclinical studies with *BiDAC*™

Thein KZ, et al. Trends in Cancer 2021;7:1074-88

SELECTIVE RET INHIBITORS

- Summary of phase I/II clinical trials of RET inhibitors in RET fusion-positive NSCLC

Study	Agent	Dosing	N	ORR (%)	mPFS, mo	mfollow-up, mo	mDOR, mo	mfollow-up, mo
First-line LIBRETTO-001	Selpercatinib	160 mg orally twice daily	39	85 (70-94)	NE (13.8-NE)	9.2	NE (12.0-NE)	7.4
ARROW	Pralsetinib	400 mg orally once daily	27	70 (50-86)	9.1 (6.1-13-0)	11.6	9.0 (6.3-NE)	10.2
Second-line LIBRETTO-001	Selpercatinib	160 mg orally twice daily	105	64 (54-73)	16.5 (13.7-NE)	13.9	17.5 (12.0-NE)	12.1
ARROW	Pralsetinib	400 mg orally once daily	87	61 (50-72)	17.2 (8.3-22.1)	14.7	NE (15.2-NE)	12.9

Drilon A, et al. N Engl J Med 2020;383:813-24; Gainor J. Lancet Oncol 2021;22:959-69

SELECTIVE RET INHIBITORS

- Ongoing trials on RET-altered tumors

Protocol name	Phase	Patient population	Malignancy	Intervention	Targeted sample size	Primary outcomes	Secondary outcomes[a]	Estimated study completion
Selpercatinib								
NCT03157128 (LIBRETTO-001)	I/II	Adolescent, adult	Advanced solid tumors	Selpercatinib	989	MTD, ORR	DOR, OS, PFS	May 2022
NCT04268550 (A LUNG-MAP)	II	Adolescent, adult	Metastatic or recurrent NSCLC	Selpercatinib	124	RR	DOR, OS, PFS	Feb 2023
NCT04280081 (LIBRETTO-321)	II	Adult	Advanced solid tumors	Selpercatinib	75	ORR	DOR, OS, PFS	Apr 2023
NCT03899792 (LIBRETTO-121)	I/II	Pediatric	Advanced solid or primary CNS tumors	Selpercatinib	100	MTD, ORR	DOR, OS, PFS	Mar 2024
NCT04759911	II	Adolescent, adult	Advanced thyroid cancers	Selpercatinib followed by surgery	30	ORR	OS, R0/R1 resection rates, PFS	Sep 2024
NCT04194944 (LIBRETTO-431)	III	Adult	Advanced NSCLC	Selpercatinib vs. chemotherapy ± pembrolizumab	250	PFS	DOR, ORR, OS	Aug 2025
NCT04211337 (LIBRETTO-531)	III	Adolescent, adult	Advanced MTC	Selpercatinib vs. cabozantinib or vandetanib	400	TFFS	DOR, ORR, OS, PFS	Nov 2026
NCT04320888 (MATCH)	II	Adolescent	Advanced solid tumors, lymphomas, histiocytic disorders	Selpercatinib	49	ORR	PFS	Sep 2027
NCT04819100 (LIBRETTO-432)	III	Adult	Stage IB-IIIA NSCLC	Selpercatinib vs. placebo	170	EFS	OS, PFS	April 2032
Pralsetinib								
NCT04697446	Obser-vational	Adult	Advanced NSCLC	Pralsetinib vs. best available therapy	279	ORR	DOR, OS, PFS	Oct 2021
NCT03037385 (ARROW)	I/II	Adult	Advanced solid tumors	Pralsetinib	647	MTD, ORR	DOR, OS, PFS	Feb 2024
NCT04222972 (AcceleRET Lung)	III	Adult	Advanced NSCLC	Pralsetinib vs. chemotherapy ± pembrolizumab	250	PFS	DOR, ORR, OS	Dec 2024
NCT04760288 (AcceleRET-MTC)	III	Adolescent, adult	Advanced MTC	Pralsetinib vs. cabozantinib or vandetanib	198	PFS	DOR, ORR, OS, TTF	Apr 2028
NCT04302025	II	Adult	Resectable stages II-III NSCLC	Pralsetinib neoadjuvant treatment, followed by resection, pralsetinib, and chemotherapy	60	MPR	DFS, EFS, ORR, OS, pathological regression	Aug 2028

Liu AW, et al. J Oncol Pharm Practice 2022;28:175-84

SELECTIVE RET INHIBITORS

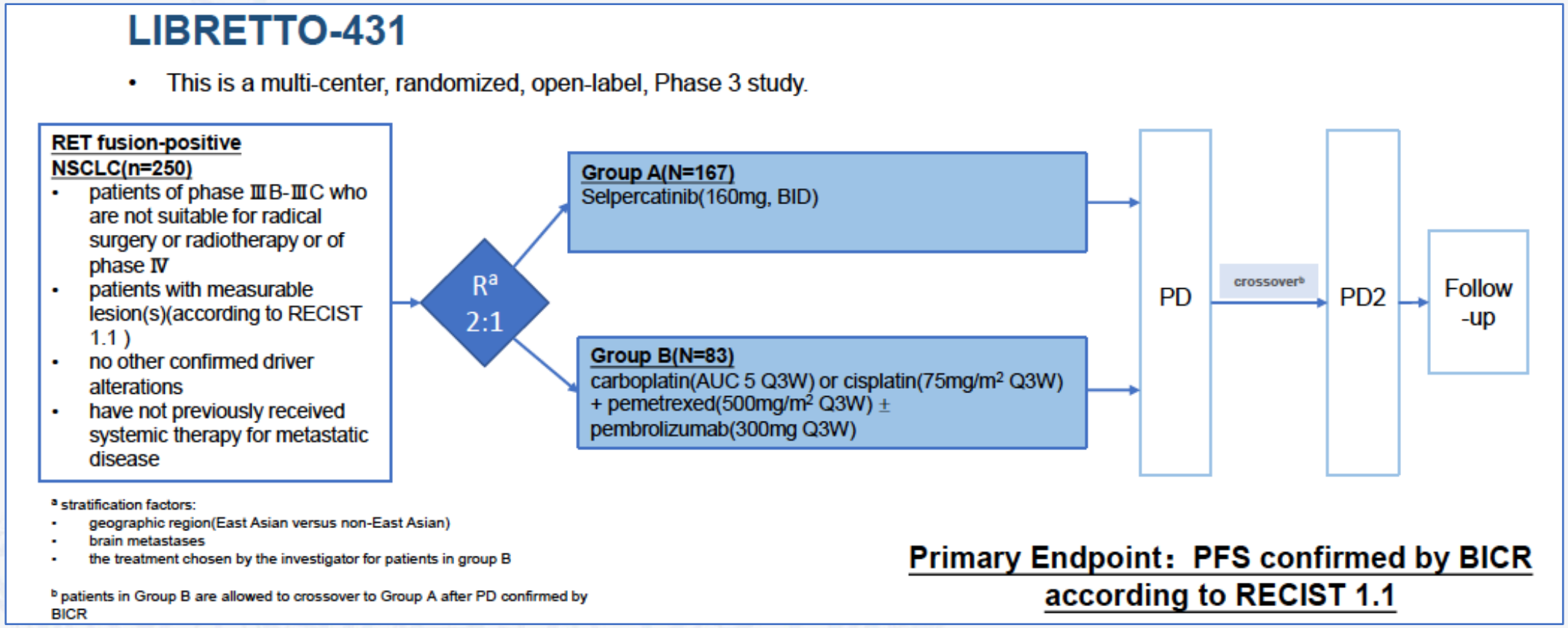
- Ongoing trials on RET-altered tumors

Protocol name	Phase	Patient population	Malignancy	Intervention	Targeted sample size	Primary outcomes	Secondary outcomes[a]	Estimated study completion
BOS172738								
NCT03780517	I	Adult	Advanced solid tumors	BOS172738	114	MTD	DOR, ORR, PFS,	Dec 2021
TAS0953/HM06								
NCT04683250 (MARGARET)	I/II	Adult	Advanced solid tumors	TAS0953/HM06	202	MTD, ORR	DOR, OS, PFS	Aug 2024
TPX-0046								
NCT04161391	I/II	Adult	Advanced solid tumors	TPX-0046	362	MTD, ORR	DOR, OS, PFS	Mar 2025
Cabozantinib								
NCT01639508	II	Adult	Advanced NSCLC	Cabozantinib	68	ORR	OS, PFS	Jul 2021
NCT04131543 (CRETA)	II	Adult	Advanced NSCLC	Cabozantinib	25	RR	DOR, OS, PFS	Aug 2022
PD-1/PD-L1								
NCT04322591 (POSEIDON)	Obser-vational	Adult	Advanced NSCLC	Chemotherapy vs. chemotherapy and PD-1 antibody	70	PFS	ORR, OS	Mar 2022

Liu AW, et al. J Oncol Pharm Practice 2022;28:175-84

SELECTIVE RET INHIBITORS

- Ongoing trials with RET inhibitors in the first-line setting of RET fusion-positive NSCLC patients



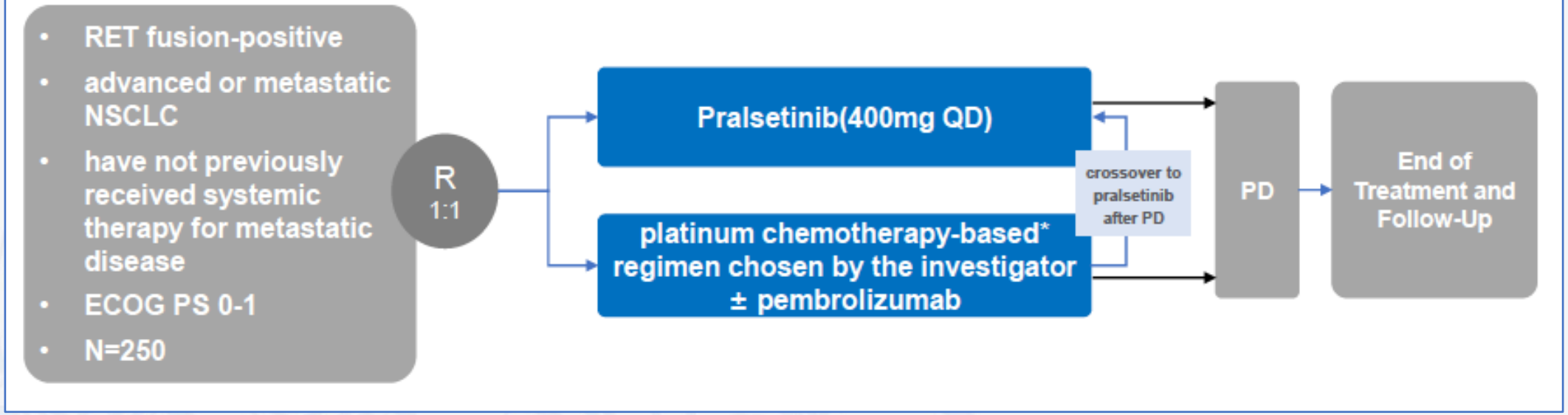
Clinicaltrials.gov: NCT04194944

SELECTIVE RET INHIBITORS

- Ongoing trials with RET inhibitors in the first-line setting of RET fusion-positive NSCLC patients

AcceleRET Lung (NCT04222972)

- This is an international, randomized, open-label, Phase 3 study.
- To compare the efficacy and safety of pralsetinib therapy and a platinum chemotherapy-based regimen chosen by the Investigator from a list of standard of care treatments in in the first-line setting of RET fusion-positive NSCLC.



Clinicaltrials.gov: NCT04222972

OUTLINE

- Introduction
- Molecular biology
- Clinical features of RET-rearranged NSCLC
- Diagnosis
- Conventional systemic therapies
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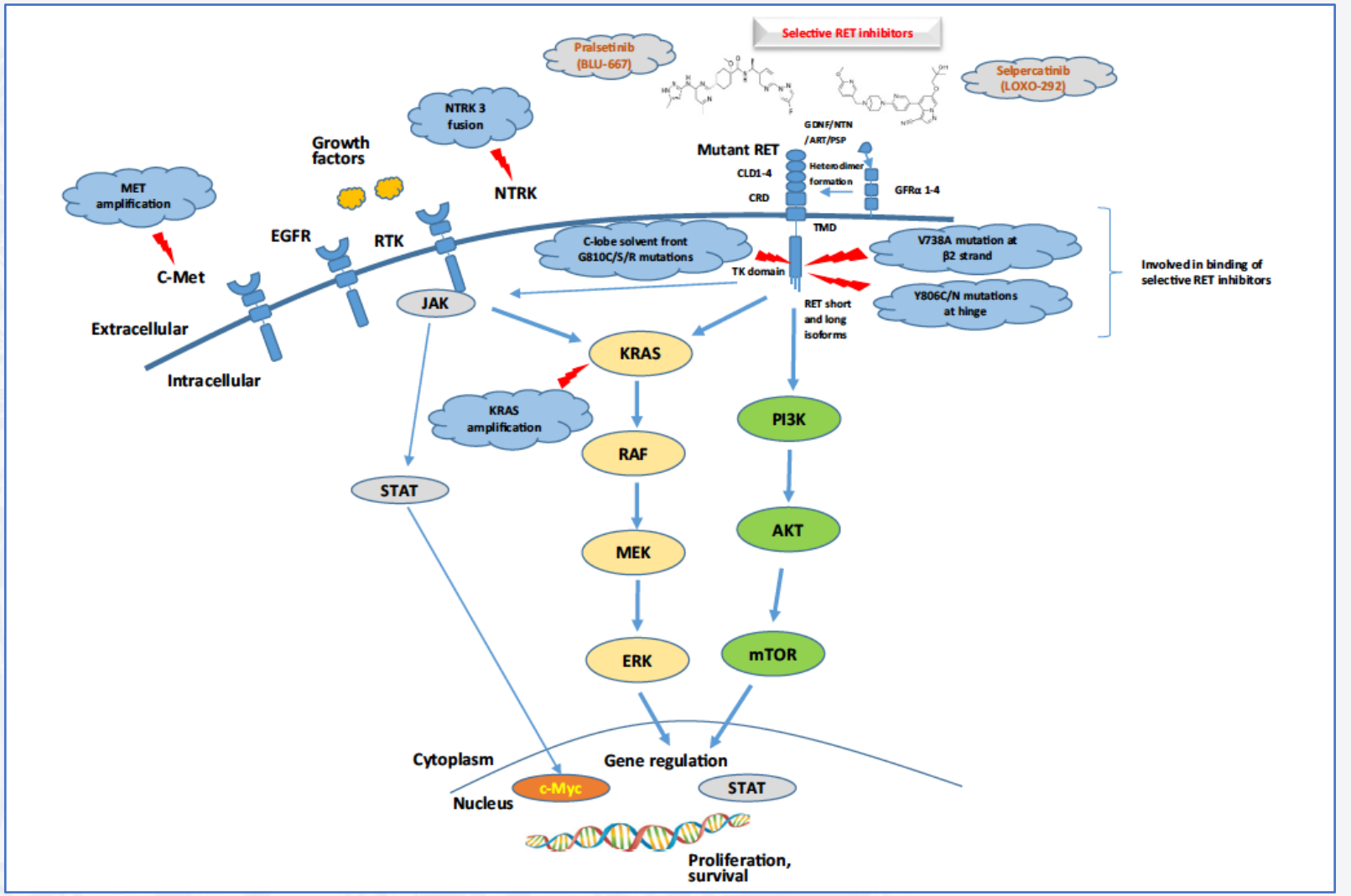
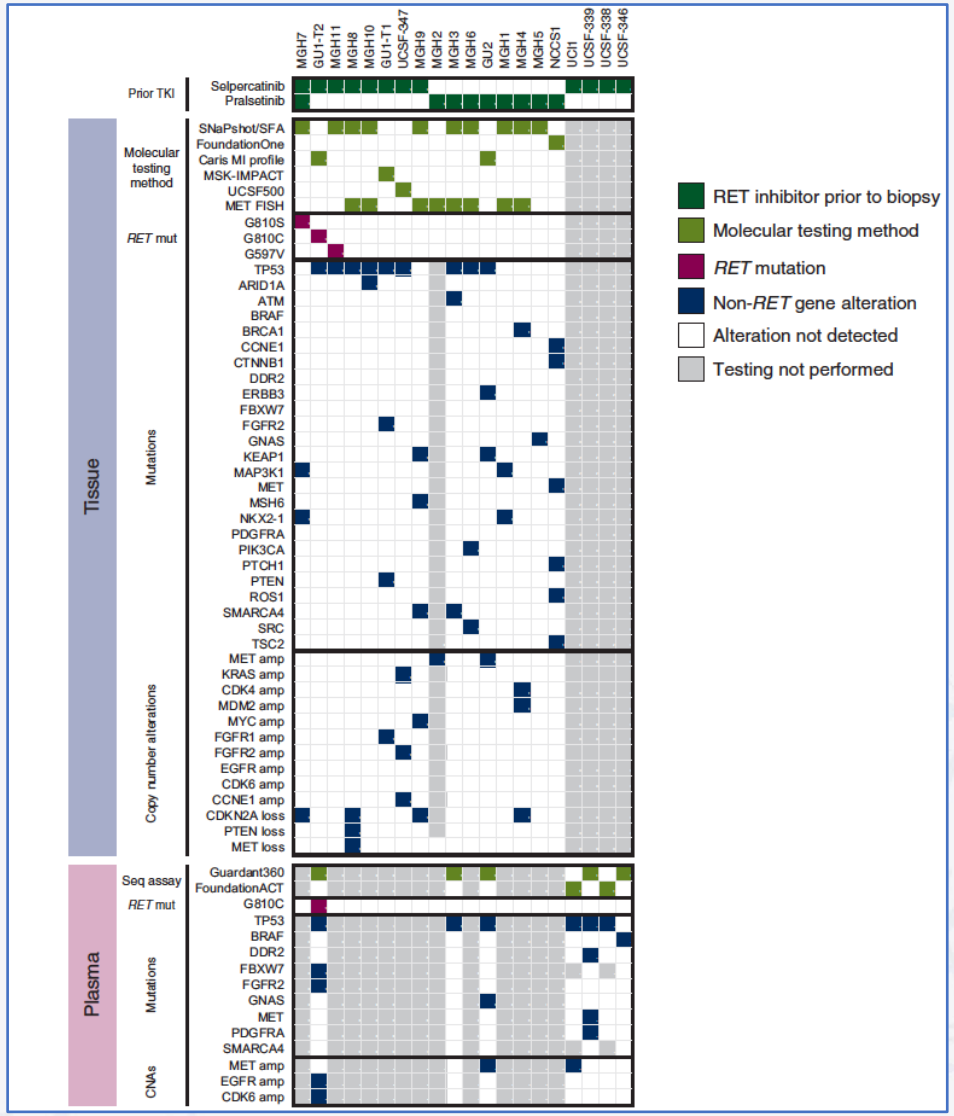
- Selective RET inhibitors
- Acquired resistance to selective RET-inhibitors
- Next generation RET-inhibitors
- Conclusions

ACQUIRED RESISTANCE TO SELECTIVE RET-INHIBITORS



Thein KZ, et al. Trends in Cancer 2021;7:1074-88

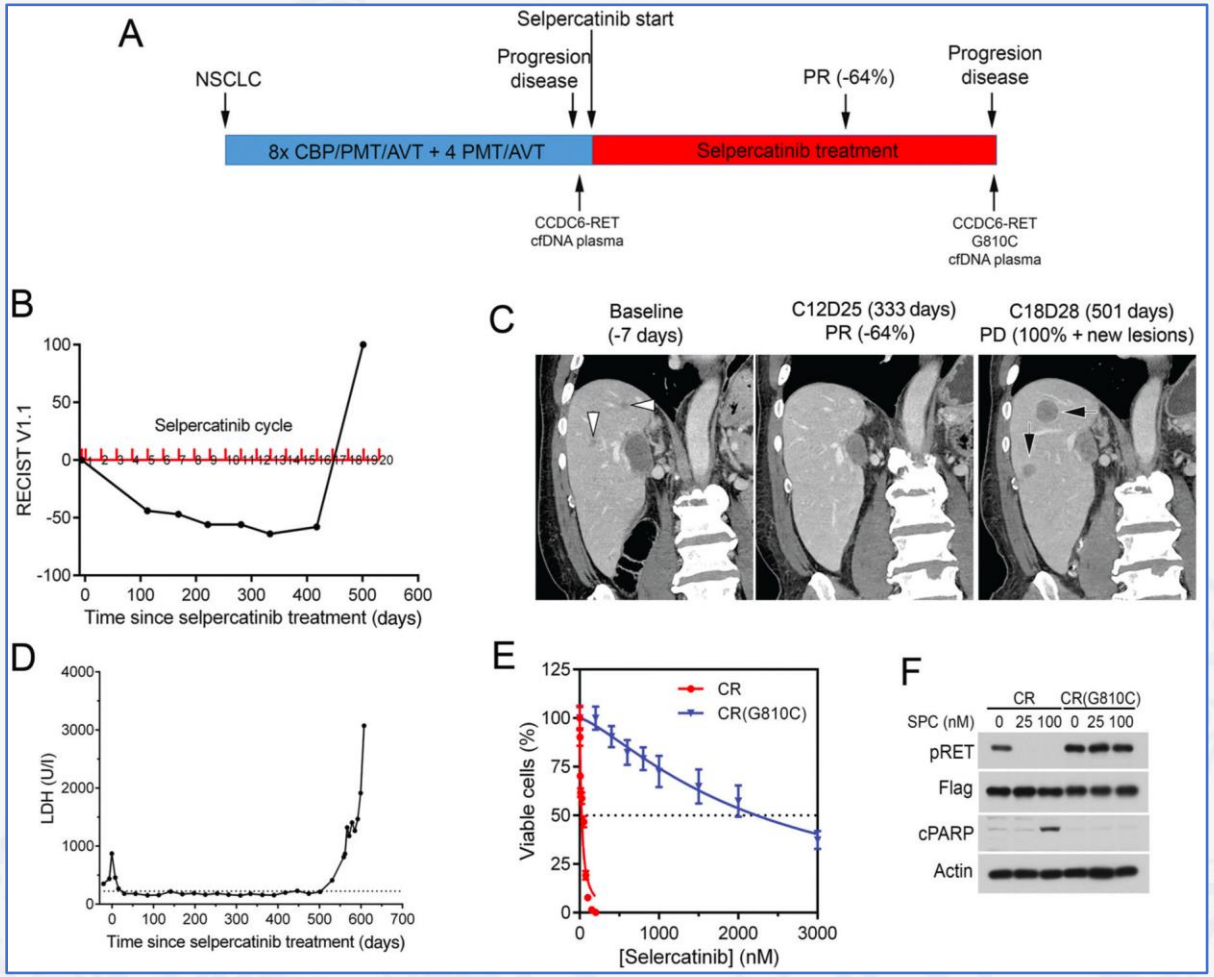
ACQUIRED RESISTANCE TO SELECTIVE RET-INHIBITORS

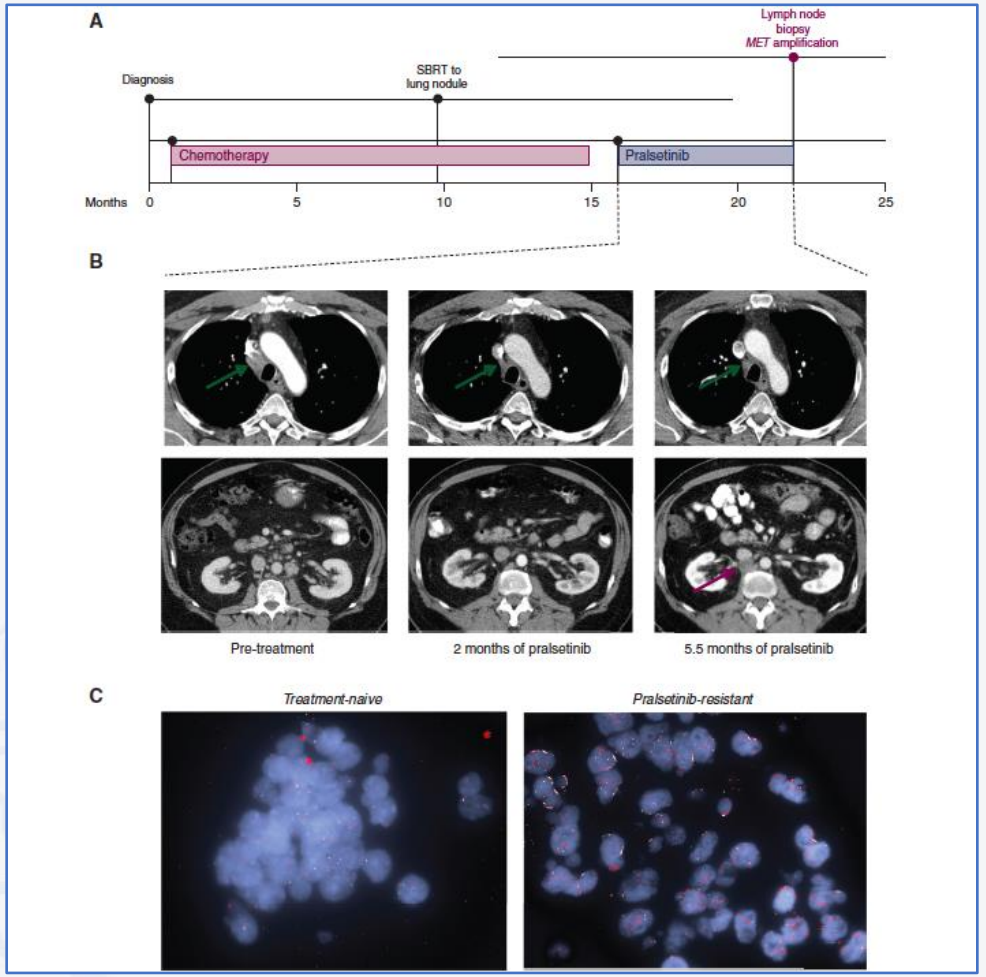


- The occurrence of secondary mutations, leading to sterically hindering of target binding
  - For patients progressing during Selpercatinib treatment, such G810-mutation have been described in a limited number of samples (ctDNA and tissue-rebiopsies)
- In another series of 18 patients treated with selective RET-inhibitors (Selpercatinib and Pralsetinib) RET G810-mutations were also detected in 10%
- Other singular genetic events: KRAS or FGFR-amplification have been described or MET-amplification

Solomon BJ, et al. J Thorac Oncol 2020;15:541-9; Lin JJ, et al. Ann Oncol 2020;31:1725-33

ACQUIRED RESISTANCE TO SELECTIVE RET-INHIBITORS





Lin JJ, et al. Ann Oncol 2020;31:1725-33; Subbiah V, et al. Ann Oncol 2021;32:261-8

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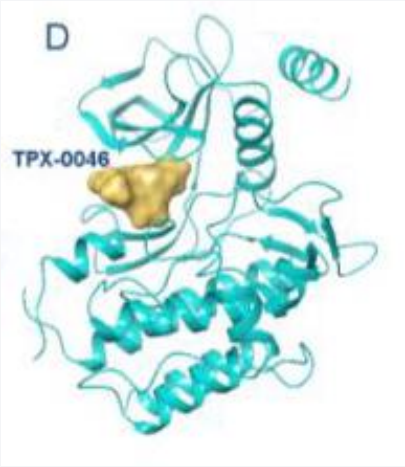
NEXT GENERATION RET-INHIBITORS

- TPX-0046
  - Novel orally bioavailable RET/sarcoma (SRC) kinase inhibitor
  - Preclinical activity against RET-WT and RET-G810-mutated isoforms
  - A phase I/II trial is ongoing (NCT04161391)
- BOS172738
  - Highly potent and selective oral RET inhibitor
  - Showed potency for the wild type RET, RET V804M/L gatekeeper mutations, and the most oncogenic RET mutation M918T
  - Had high selectivity against VEGFR2
  - Phase I (NCT03780517)



Schoffski. ASCO 2021. Abstract 3008; Drilon. ASCO 2020. Abstract 3616

NEXT GENERATION RET-INHIBITORS

- TAS09553/HM06
  - Another RET TKI in preclinical development
  - Phase I/II (NCT04683250)
- LOX-18228
  - In preclinical development
- LOX-19260
  - In preclinical development

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CONCLUSIONS

- RET-fusions can be considered an established therapeutic target in NSCLC
- Testing for RET-fusions should be included in the standard molecular diagnosis of metastatic non-squamous NSCLC
- Selpercatinib and pralsetinib represent the currently most effective treatment options for patients with metastatic RET-fusion positive NSCLC
- Their definitive place within the treatment algorithms, however, remains uncertain
- To better understand and finally overcome acquired resistance to selective RET-inhibitors can be considered one of the most important challenges for the near future

XXIV Simposio de Revisiones en Cáncer

"Tratamiento médico del cáncer en el año 2022"

Gracias

ARÁN