TARGETED THERAPY FOR RET NSCLC

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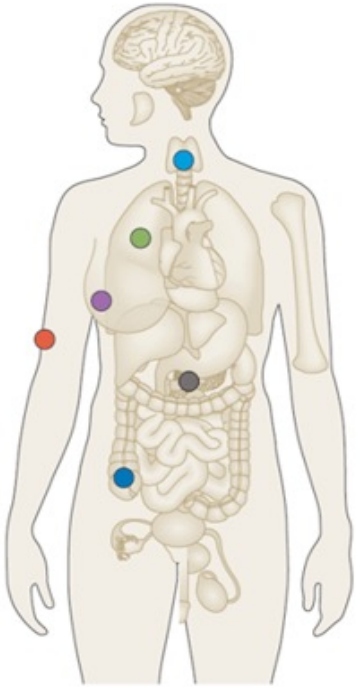
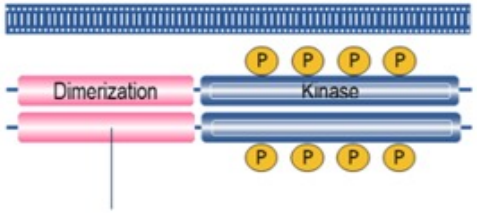
RET Pathway

- *RET* fusions are known oncogenic drivers in NSCLC[1,2]
- Up to half of patients with advanced NSCLC will develop brain metastases[3]
- Multikinase inhibitors
  - Provide a modest clinical benefit
  - Associated with significant toxicity (non-*RET* kinase inhibition)
- Immunotherapy drugs (PD-1/PD-L1 inhibitors) may be less efficacious in patients with driver-positive NSCLC, including *RET* fusion[4,5]

***RET* fusions**



Non-small cell lung cancer (2%)
Thyroid cancers (10–20%)
Pancreatic cancer (<1%)
Salivary gland cancer (<1%)
Spitz tumors (<1%)
Colorectal cancer (<1%)
Ovarian cancer (<1%)
Myeloproliferative disorders (<1%)
Many others (<1%)

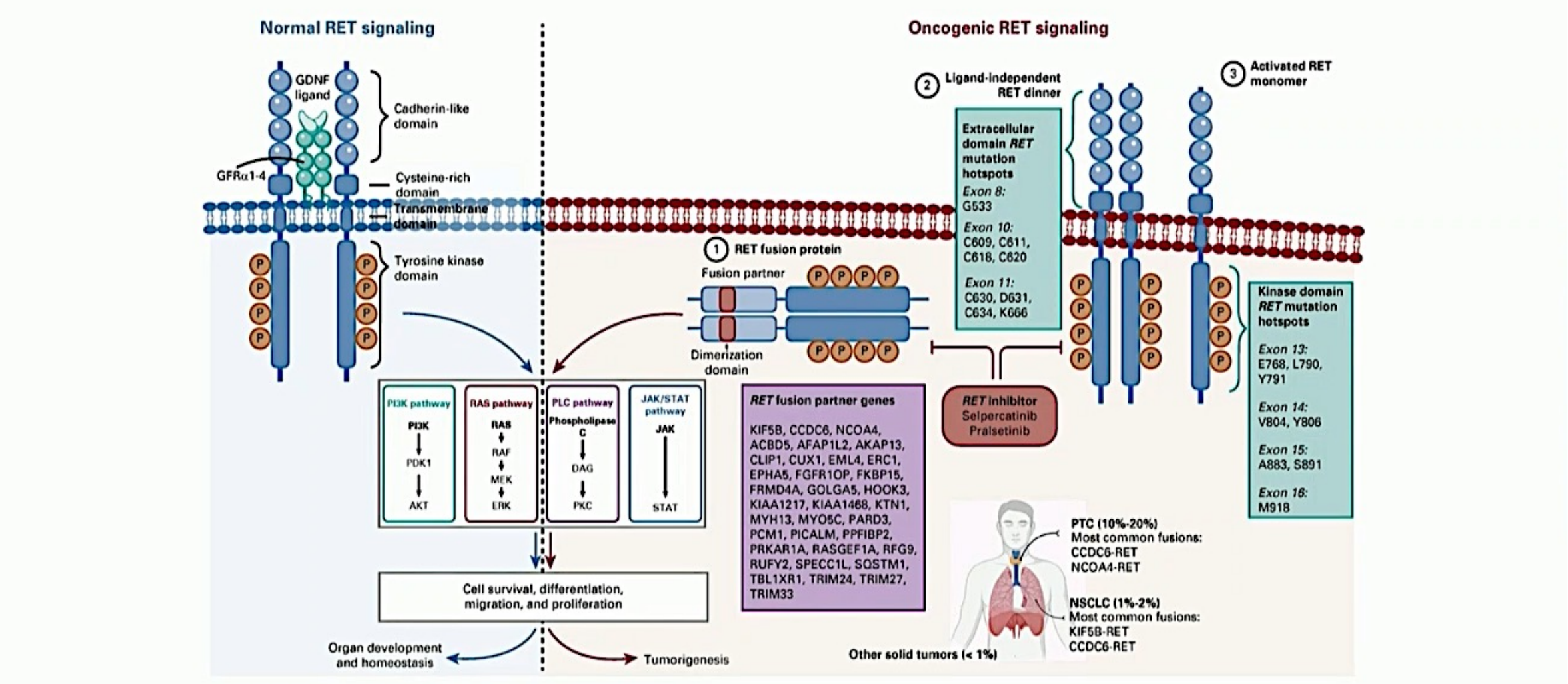


KIF5B (most common in lung cancer)
CCDC6* or *NCOA4 (most common in thyroid cancer)

Presented by Loong HH, et al. ESMO 2021.

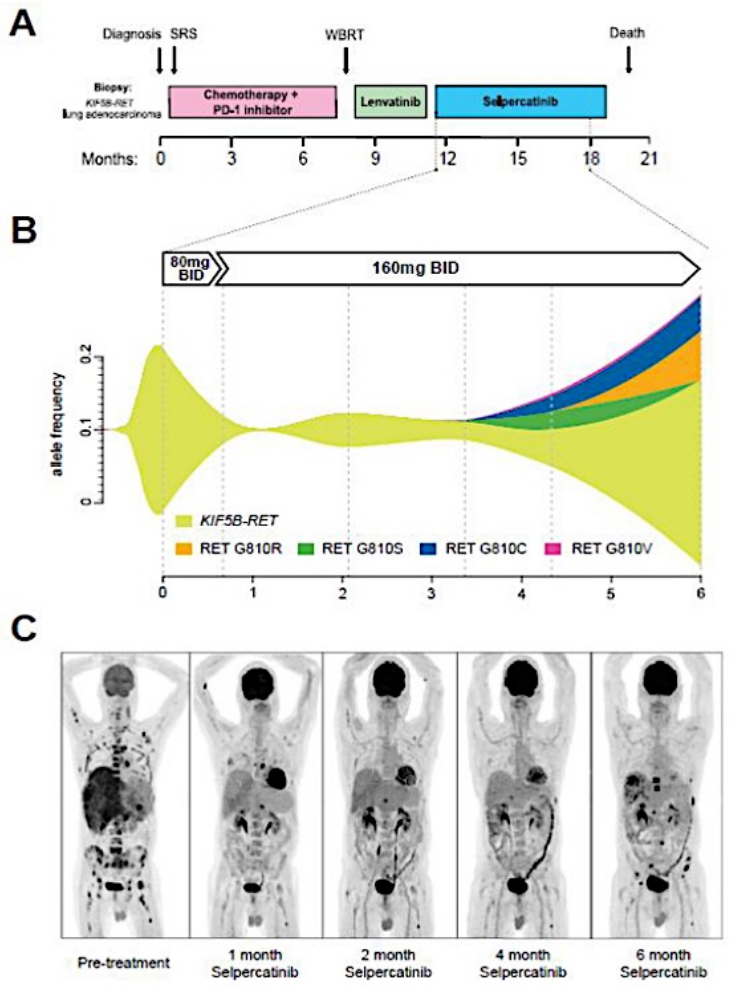
1. Drilon A, et al. *Nat Rev Clin Oncol.* 2018;15(3):151-167. 2. Wang R, et al. *J Clin Oncol.* 2012;30(35):4352-4359.
3. Drilon A, et al. *J Clin Oncol.* 2017;35(Suppl):9069-9069. 4. Sabari JK, et al. *J Clin Oncol.* 2018;36(15 Suppl):9034.
5. Mazieres J, et al. *J Clin Oncol.* 2018;36(15 Suppl):9010.

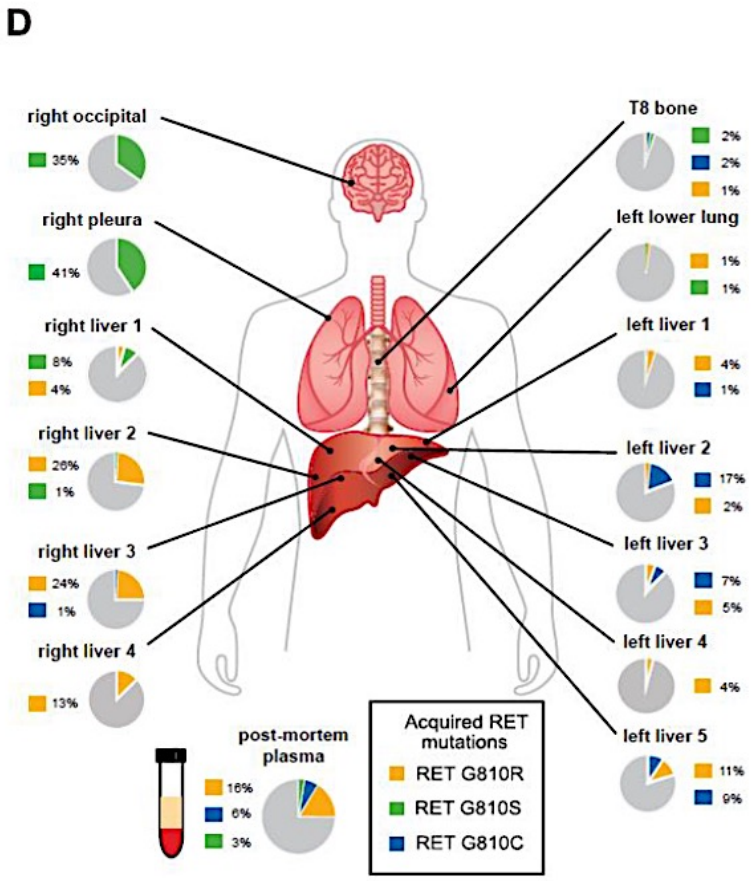
RET biology

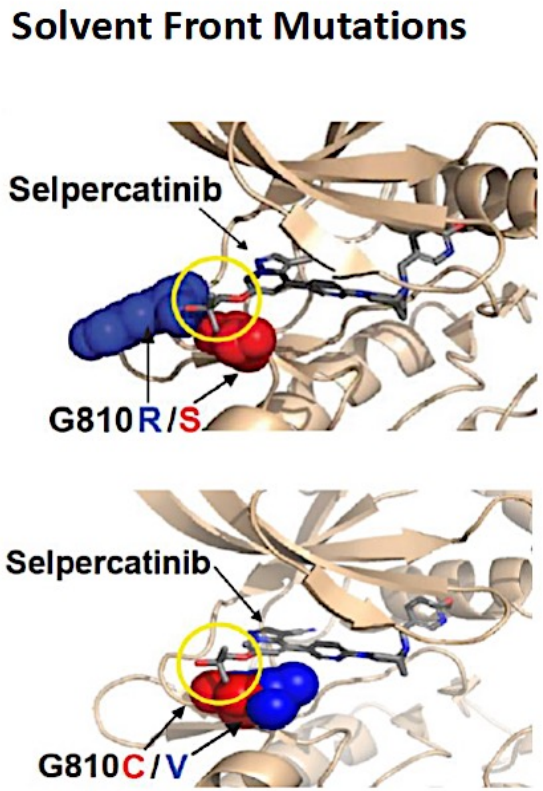


Lin and Gainor, JCO 2023

RET Inhibitor Resistance

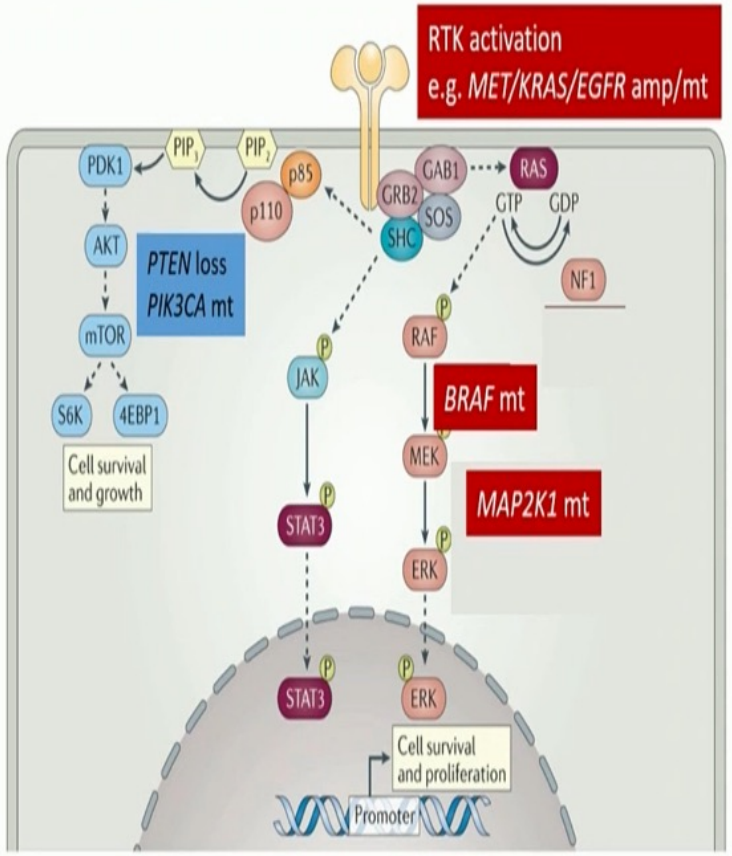


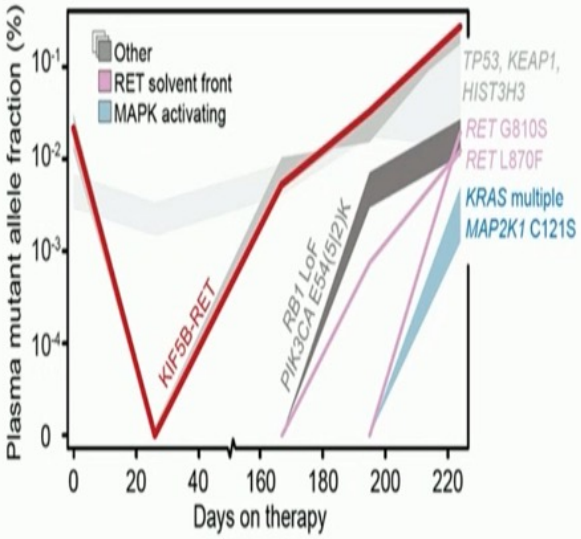




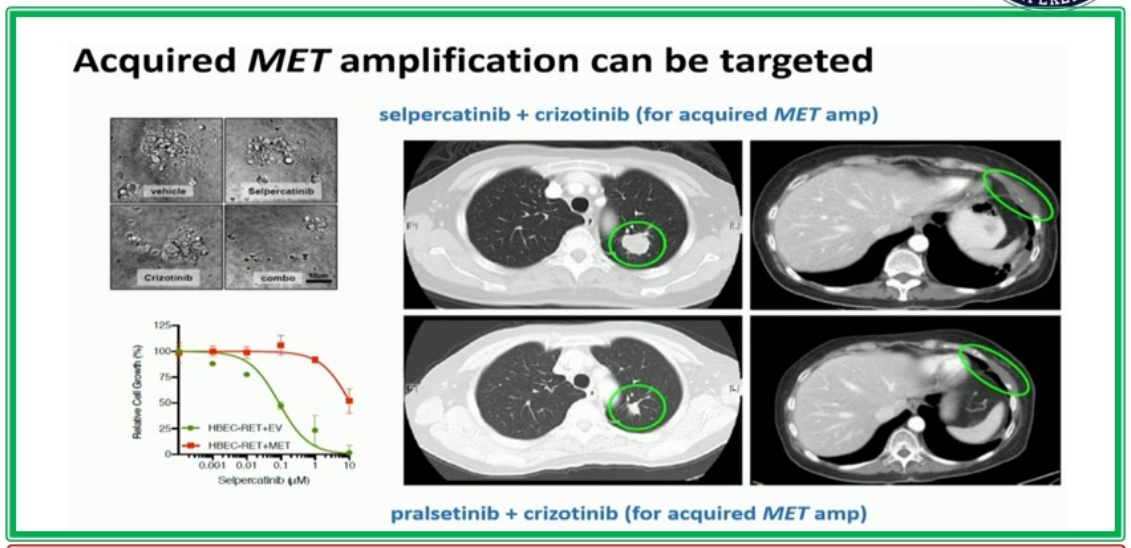
Solomon B, et al J Thorac Oncol 2020

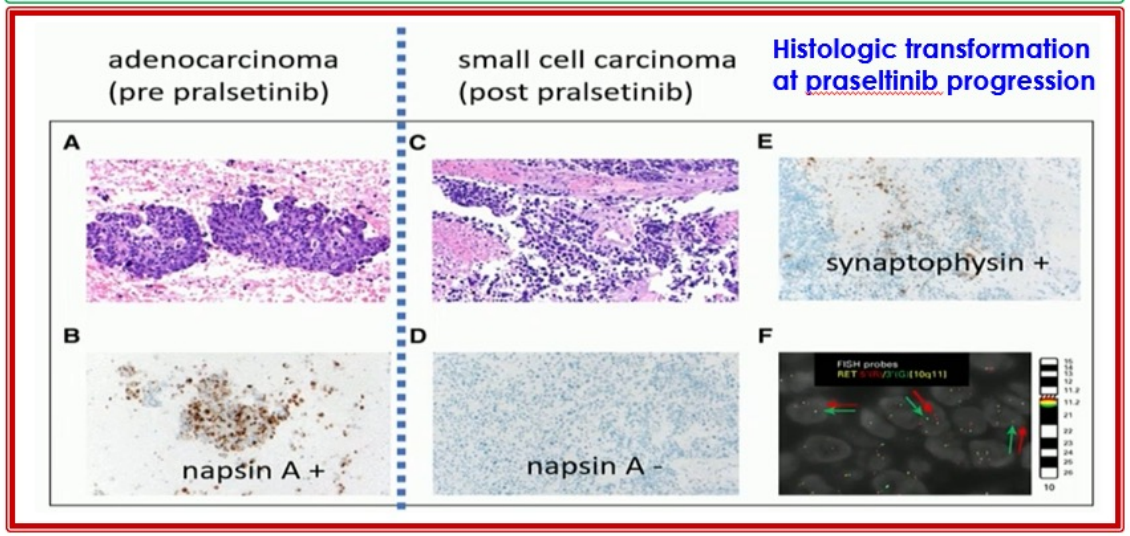
Off-target/polyclonal resistance to selective RET TKI therapy

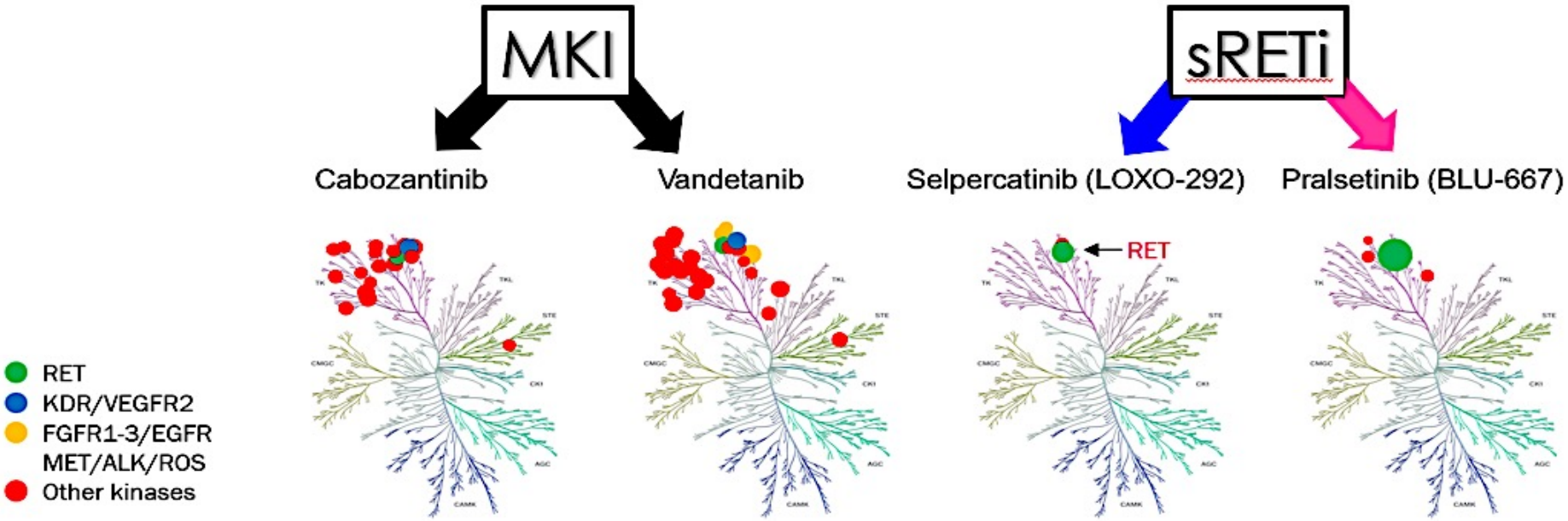




Rosen et al, Nature Comm 2022; Zhu et al, J Thor Oncol 2020; Lin et al, Ann Oncol 2020; Marinello et al, ESMO 2022







Agent	Cabozantinib	Vandetanib	Selpercatinib (LOXO-292)	Pralsetinib (BLU-667)
IC_{50} RET, nM[a]	11	4	3	0.4
ORR, %	37	18	68	58
CR	5	0	2	1

[a] Cell free.

Presented by Loong HH, et al. ESMO 2021.
1. Velcheti V, et al. WCLC 2017. Abstract OA 12.07. 2. Gautschi O, et al. *J Clin Oncol.* 2017;35(13):1403-1410. 3. Drilon A, et al. WCLC 2019. Abstract PL02.08. 4. Gainor JF, et al. ASCO 2019. Abstract 9008. 5. Rahal R, et al. AACR 2017. Abstract B151. 6. Solomon BJ, et al. *J Thorac Oncol.* 2020;15(4):541-549.

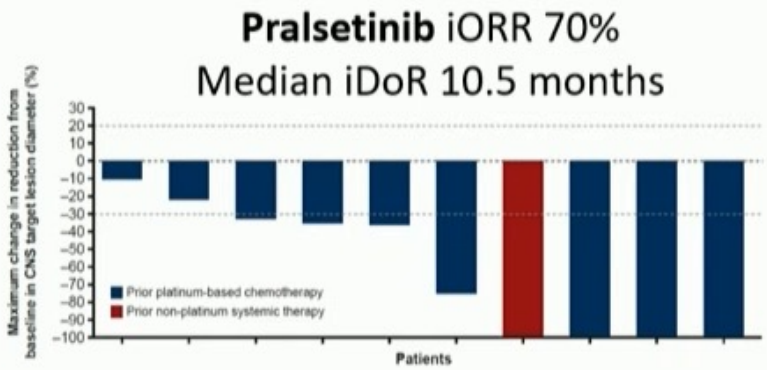
Selective RET TKI's; Efficacy & Safety Data

Agent	Ref	Post-Platinum			Treatment-naïve			Most Common AEs
		N	ORR#	Median PFS	N	ORR#	Median PFS	Treatment-Related^
Selpercatinib	Drilon A et al. NEJM 2020	105	64%	16.5 mo	39	85%	NR	Dry mouth (36%), Diarrhea (22%), HTN (25%), elevated ALT/AST(20-22%), fatigue 19%
	Besse B, et al. ASCO 2021 Update	218	57%	19.3 mo	48	85%	NR	
Pralsetinib	Gainor JF, et al. Lancet Oncol 2021	87	61%	17.1 mo	27	70%	9.1 mo	Neutropenia (42%), AST increase (39%), anemia (38%), WBC decreased (30%), ALT increase (27%) HTN (25%)
	Curigliano G, et al. ASCO 2021 Update	126	62%	16.5 mo	43* 25**	74% 88%	10.9 mo NR	

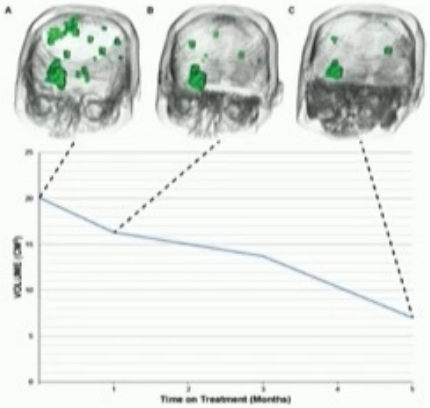
Based upon blinded independent review; ^ Data from most recent report; * Pre-eligibility revision; ** Post-eligibility revision

Selective RET inhibitors are active in the CNS

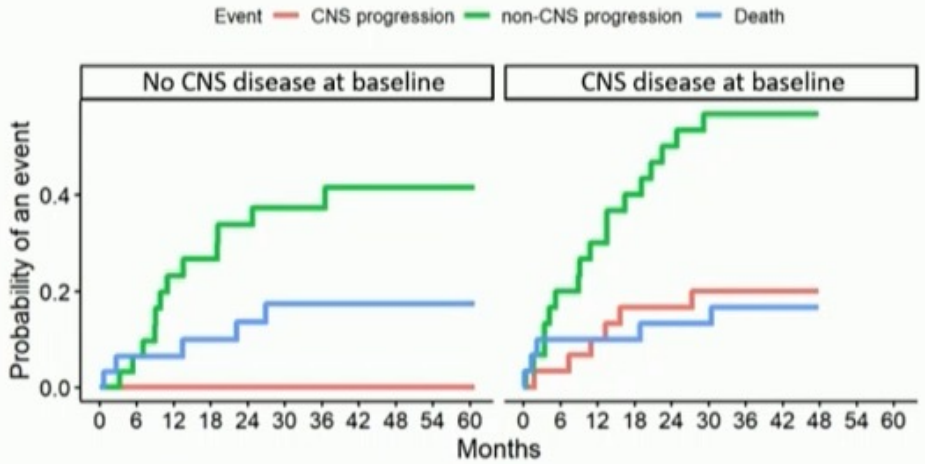
Intracranial response rates are high



Complete resolution of leptomeningeal disease has been observed

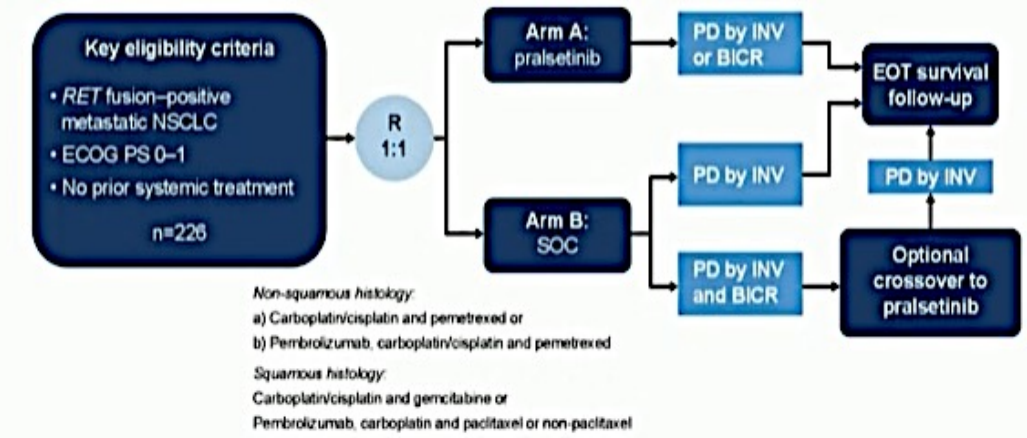


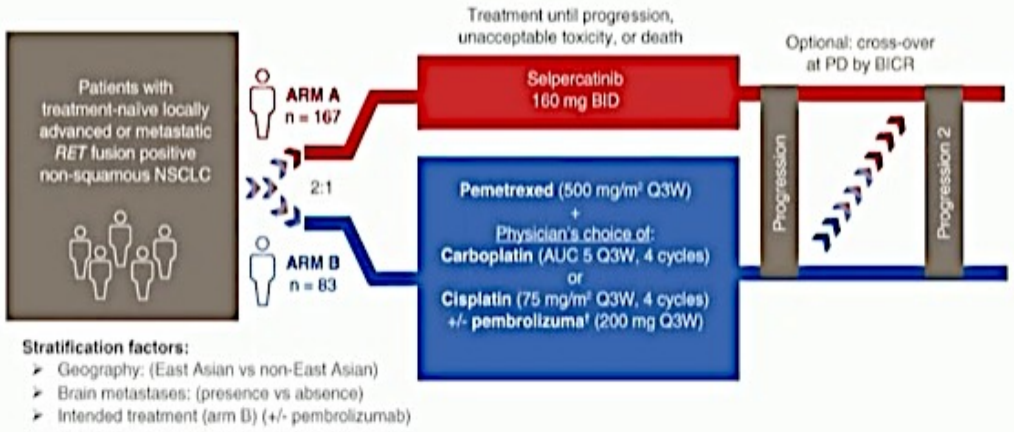
CNS metastases acquisition or progression may be attenuated



Drilon et al, J Clin Oncol 2022; Griesinger et al Ann Oncol 2022; Rosen et al, JCO P) 2019; Murciano-Goroff et al, J Thor Oncol 2023

Targeted therapy versus standard of care chemo+-immunotherapy





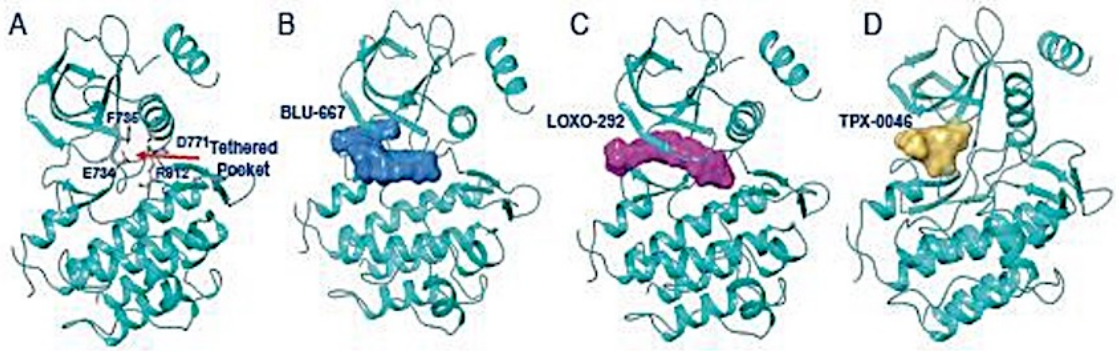
Popat et al, ASCO 2022; Solomon et al, Future Oncol 2021

Novel RET inhibitors in development

Agent	Target(s)	Resistance Coverage	NCT
TPX-0046	RET, SRC	RET G810C/S/R	NCT04161391
Zeteletinib (BOS172738; DS-5010)	RET	RET V804M	NCT03780517
TAS0953/HM06	RET	RET V804M/L & RET G810R/S	NCT04683250
LOXO-260	RET, TrkC	RET V804M/L & RET G810S	N/A

Schoffski P, et al. ASCO 2021. 3. Miyazaki I, et al. Mol Cancer Ther 2021. 4. Kolakowski GR, et al. AACR 2021

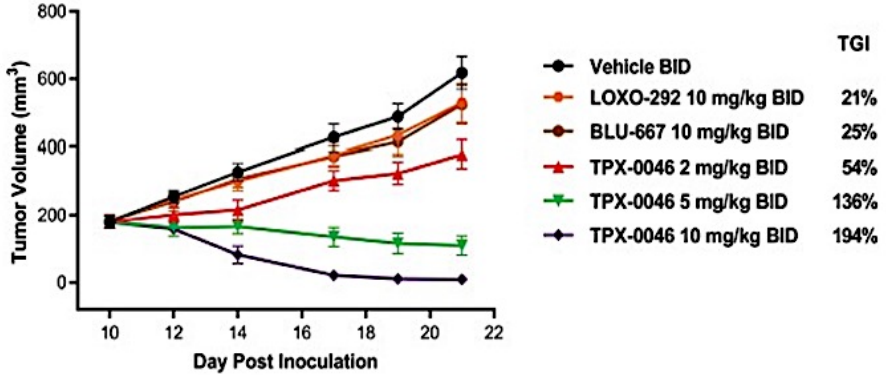
TPX-0046



	TPX-0046	BLU-667[a]	LOXO-292[a]
Ba/F3 KIF5B-RET	0.4	0.7	0.2
Ba/F3 KIF5B-RET Y806N	13.2	22.1	13.5
Ba/F3 KIF5B-RET G810S	0.4	4.9	62.8
Ba/F3 KIF5B-RET G810R	16.9	749	568
Ba/F3 KIF5B-RET G810C	11.2	32.9	426
Ba/F3 KIF5B-RET G810N	17.3	40.9	86.8
Ba/F3 KIF5B-RET V804M	533	1.1	23.4
TT RET C634W	0.9	3.7[b]	1[c]
LC2/ad CCDC6-RET	1.0	15.4[b]	35[c]

[a] Data based on evaluation of comparable proxy chemical reagents purchased from commercial sources
[b] Data based on Subbiah et al. 2018a[4]
[c] Data based on Subbiah et al. 2018b[4]

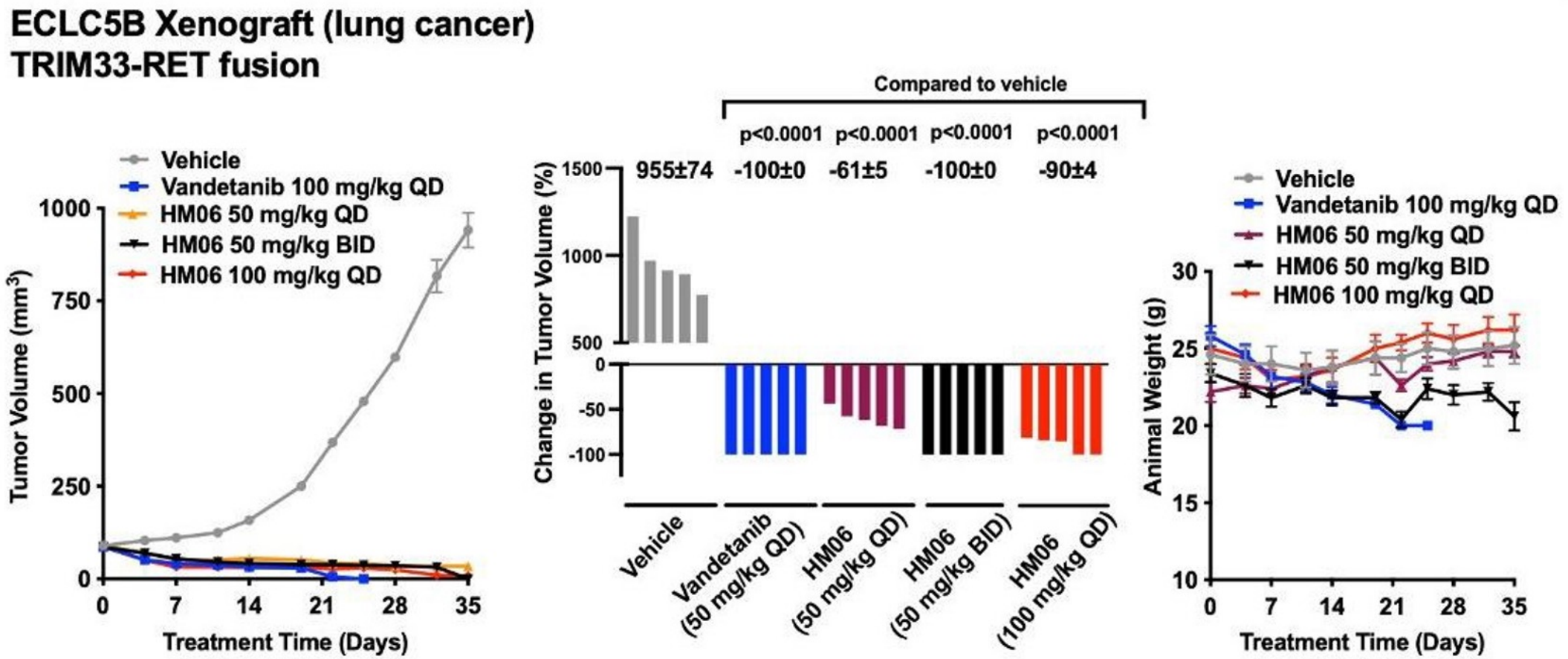
Anti-tumor Effect of TPX-0046 in Ba/F3 Cell-Derived Xenograft Tumors with a KIF5B-RET G810R Fusion



Drilon A, et al. ASCO 2020

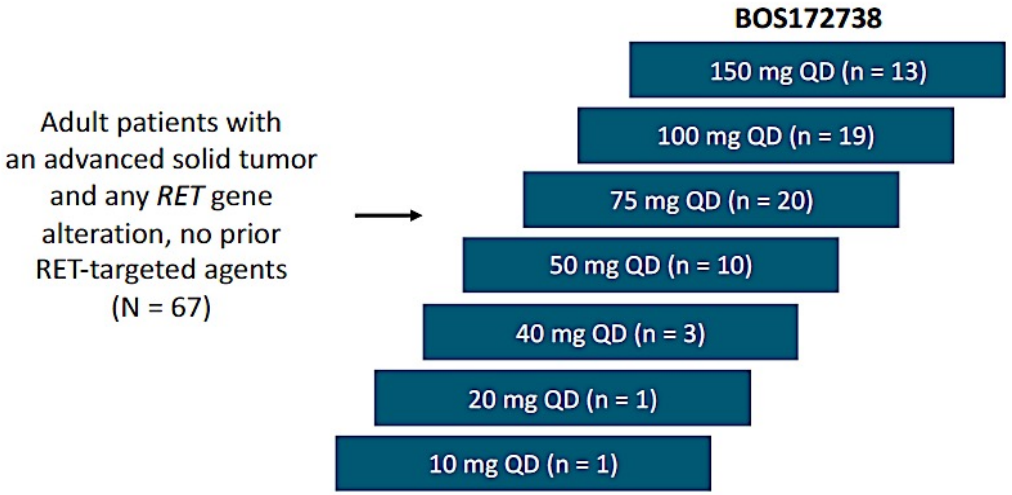
SWORD-1 Phase I/II: 2/5 TKI-naïve pts with PRs, 2/9 RET TKI-pretreated pts with SD.

TASO0953/HM06



Miyazaki I, et al. AACR-NCI-EORTC 2021

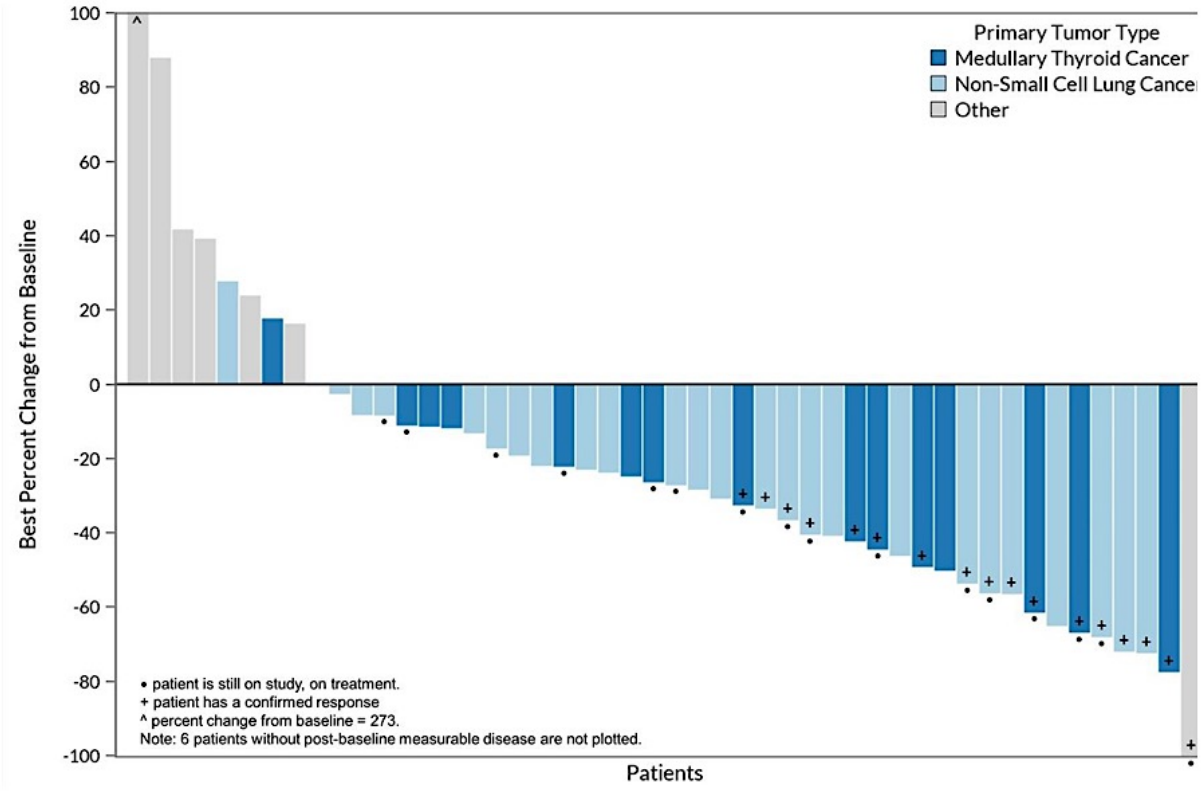
Zeteletinib (BOS172738; DS-5010)



Most Frequent TEAEs in ≥15% of Patients All Grades (N=67)		Related Grade 3 or Higher TEAEs (N=67)
Event	n (%)	n (%)
CPK Increase	40 (60)	17 (25)
Dyspnea	25 (37)	1 (1)
AST Increase	20 (30)	1 (1)
Diarrhea	20 (30)	
Anemia	19 (28)	4 (6)
Face Edema	19 (28)	
Fatigue	18 (27)	
Constipation	15 (22)	
Neutropenia	15 (22)	7 (10)
Asthenia	14 (21)	2 (3)
Hypertension	13 (19)	2 (3)
Muscle Weakness	13 (19)	3 (4)
Cough	12 (18)	
Hypophosphatemia	12 (18)	1 (1)

Schoffski, P et al. ASCO 2021

Zeteletinib (BOS172738; DS-5010)

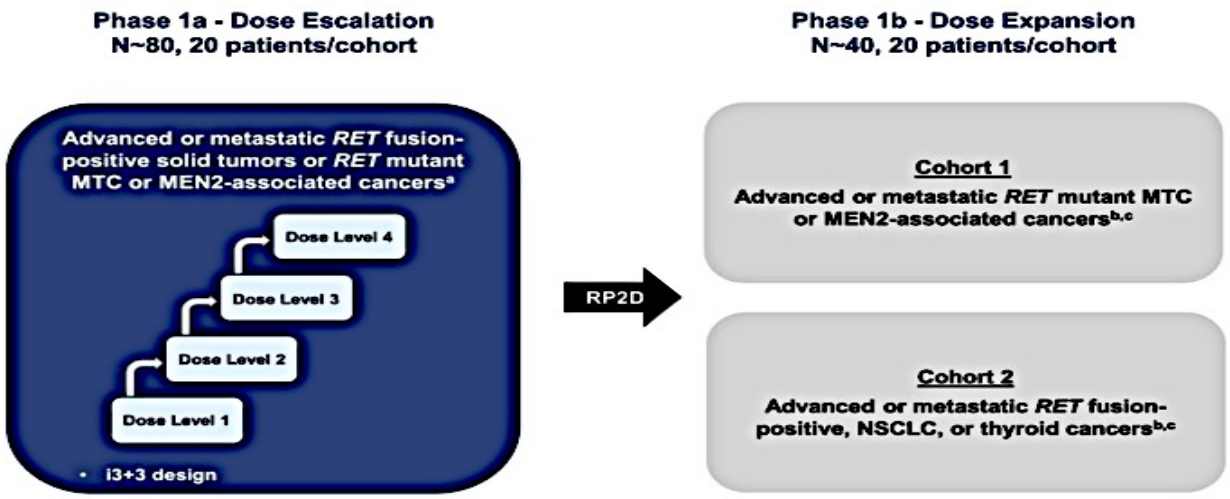


	Overall Cohort (N=54*)
Objective Response Rate	17 (31%)
Best Overall Response	
Confirmed Complete Response (CR)	1 (2%)
Confirmed Partial Response (PR)	16 (30%)
Stable Disease (SD)†	27 (50%)
Progressive Disease	10 (19%)

All RET+ Patients were naïve to selective RET inhibitors

Schoffski, P et al. ASCO 2021

LOXO-260



Objectives

Phase 1a - Dose Escalation	Phase 1b - Dose Expansion
Primary Objectives	
• Determine the safety, tolerability, and RP2D of LOXO-260 monotherapy	• Assess the ORR per RECIST v1.1
Secondary Objectives	
• Characterize the PK properties of LOXO-260 • Evaluate the antitumor activity of LOXO-260 – ORR, DOR	• Assess the PFS, TTR, DOR per RECIST v1.1 • Determine the safety and tolerability of LOXO-260 – AEs, SAEs • Characterize the PK properties of LOXO-260

Pennel N, et al. ASCO 2022

Summary of select next generation KDR sparing RET inhibitors

	RET G810X Solvent Front Coverage	RET V804X Gatekeeper Coverage	Other RET Substitution Coverage	Non-RET kinases inhibited
LOXO-260	✓	✓	G810S + V804M	TRKC (40x selectivity)
HM06/TAS0953	✓	✓		
TPX-0046	✓	less potent		TRKB, FGFR1, JAK2, SRC
APS03118	✓	✓	Y806H (hinge)	
EP0031-101/A400	✓			

Kolakowski et al, AACR 2021; Odintsov et al, AACR-NCI-EORTC 2021; Miyazaki et al, AACR-NCI-EORTC 2021; Drilon et al, AACR 2022, Ellipses.life

Conclusion

- On-target resistance is relatively uncommon with sRETi (selpercatinib and praseltinib)
- Increasingly smaller patient populations to target
- Understand intrinsic and extrinsic mechanisms of resistance
- Multiple RET inhibitors in development for solvent front, hinge and gatekeeper coverages
- Combination approaches to overcome resistance?