



“RARE” FUSIONS IN LUNG CANCER

Alexander Drilon MD

Chief, Early Drug Development Service
Memorial Sloan Kettering Cancer Center, NY

Endorsed by



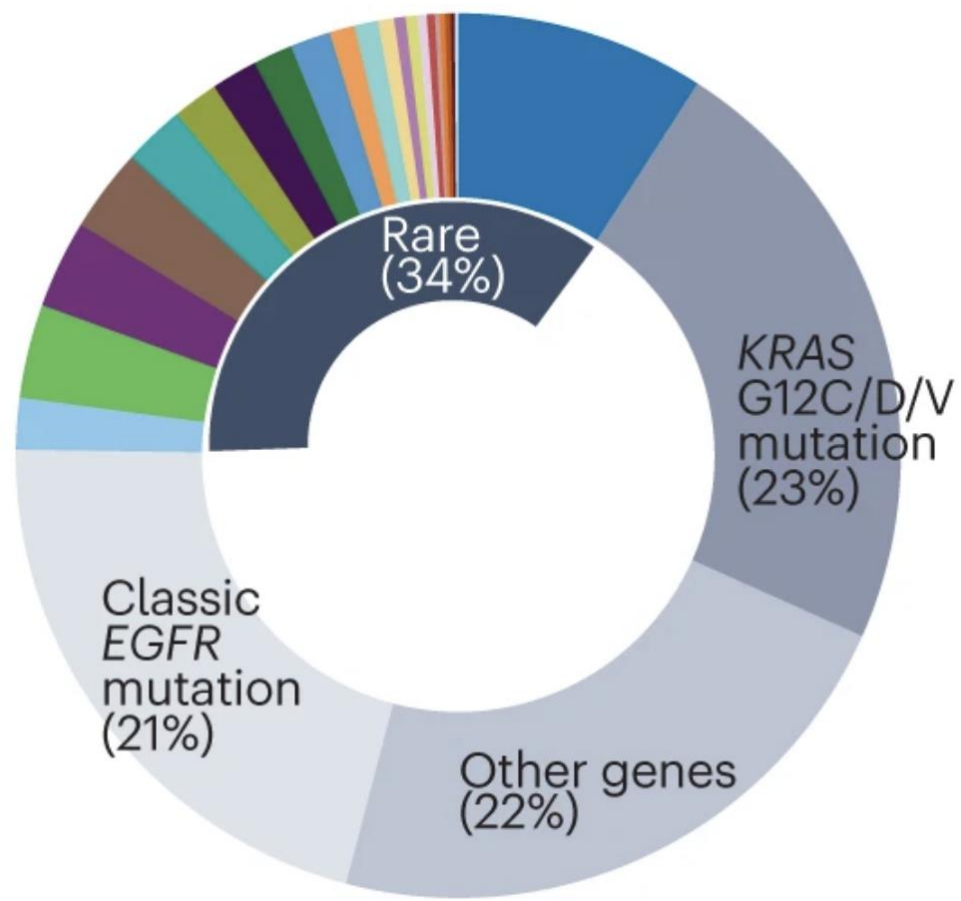
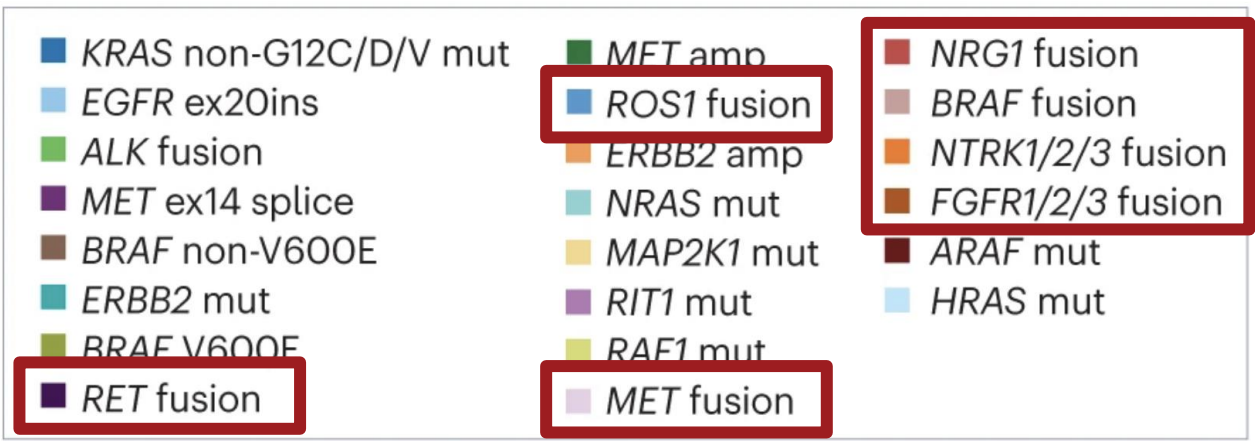
Accredited by



Presented by



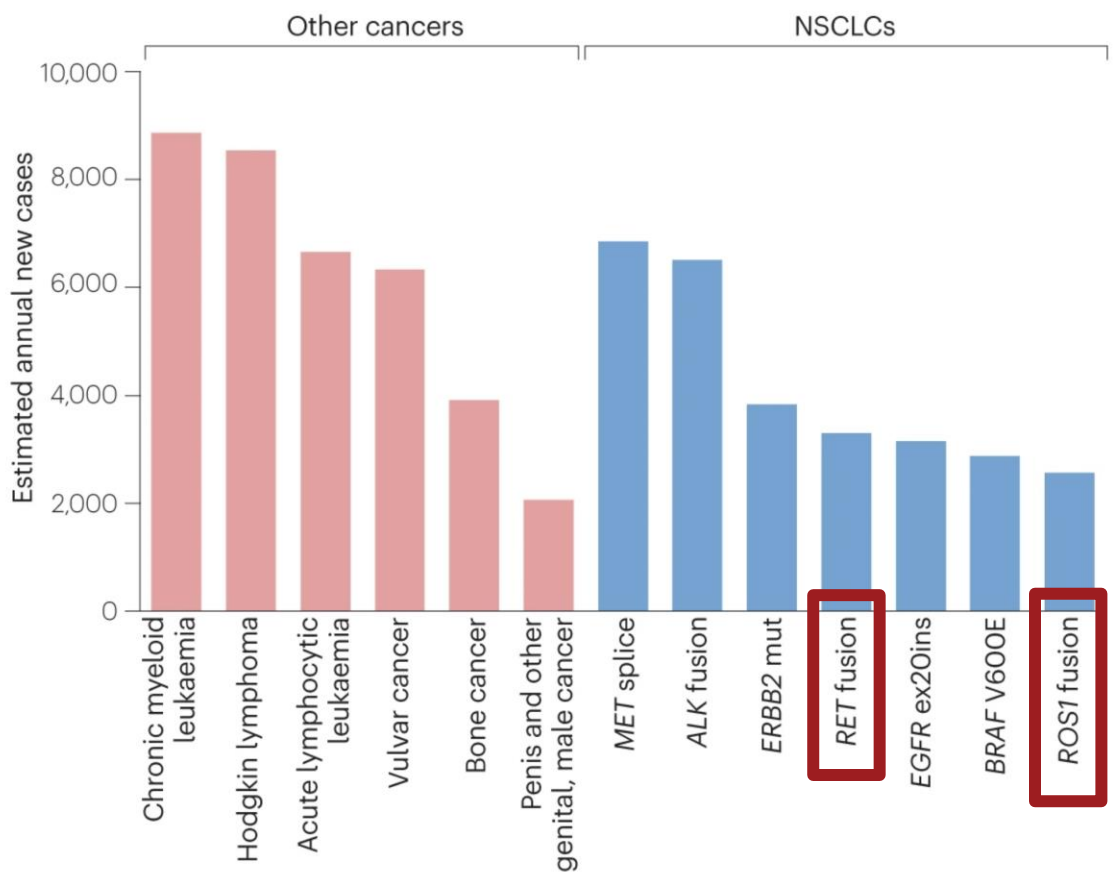
Several fusion-driven lung cancers are technically classified as “rare”



Harada et al, Nat Rev Clin Oncol 2023



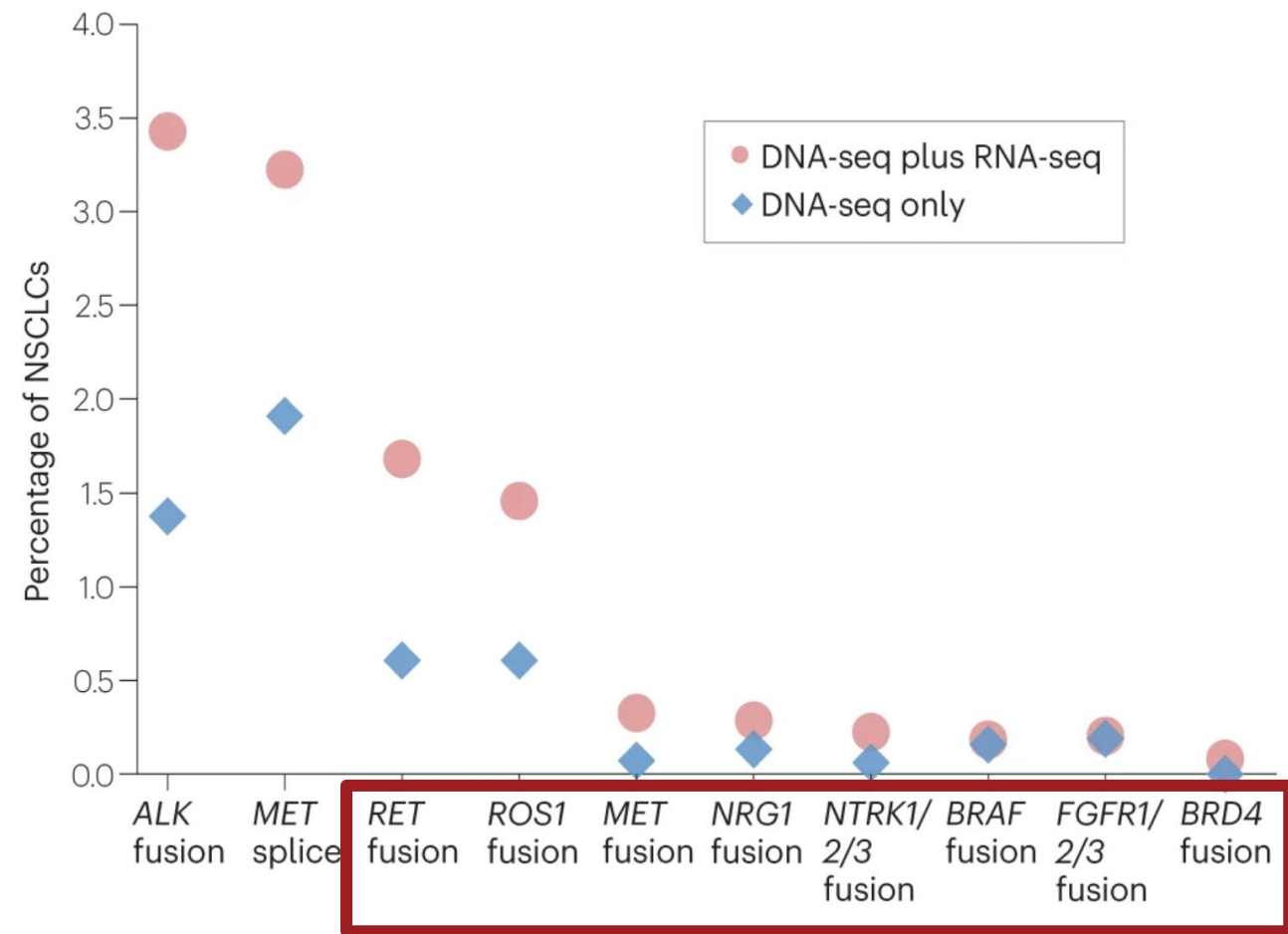
As lung cancer is a common cancer, “rare” subsets are not as uncommon as you think



The estimated incidence of *RET* and *ROS1* fusion-positive lung cancer exceeds 2,000 cases a year.

Harada et al, Nat Rev Clin Oncol 2023

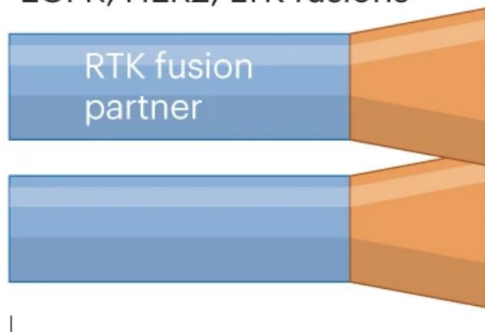
Calling a cancer “rare” may lead to deemphasis of optimal testing strategies



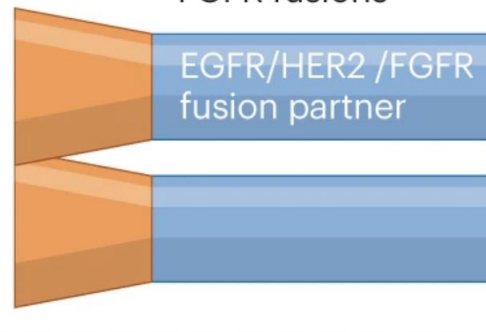
Harada et al, Nat Rev Clin Oncol 2023

Many different oncogenic fusion types exist

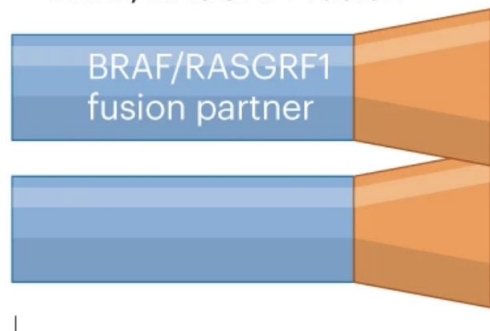
ALK, ROS1, RET, NTRK, MET,
EGFR, HER2, LTK fusions



EGFR, HER2,
FGFR fusions

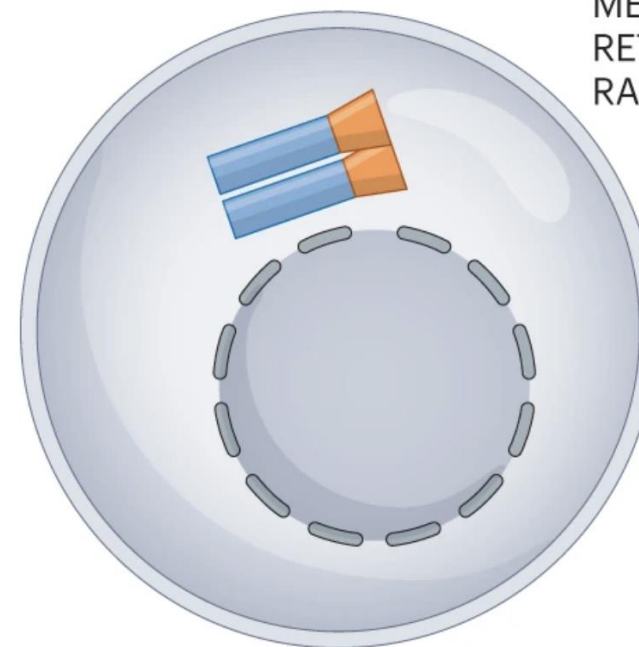


BRAF, RASGRF1 fusion



RASGRF1 fusions

Cytoplasmic



ALK, ROS1, NTRK,
MET, EGFR, HER2,
RET, LTK, BRAF,
RASGRF1 fusions

Harada et al, Nat Rev Clin Oncol 2023

For advanced NSCLCs with *RET*, *ROS1*, and *NTRK* fusions, 1st line TKI therapy is standard

Advanced *RET*,
ROS1, *NTRK* fusion-
positive lung cancer

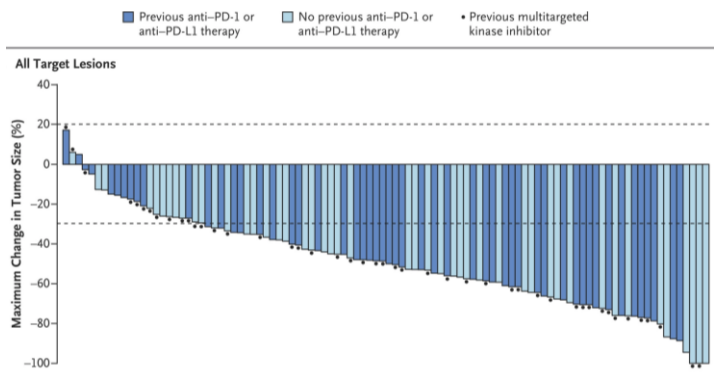


TKI therapy

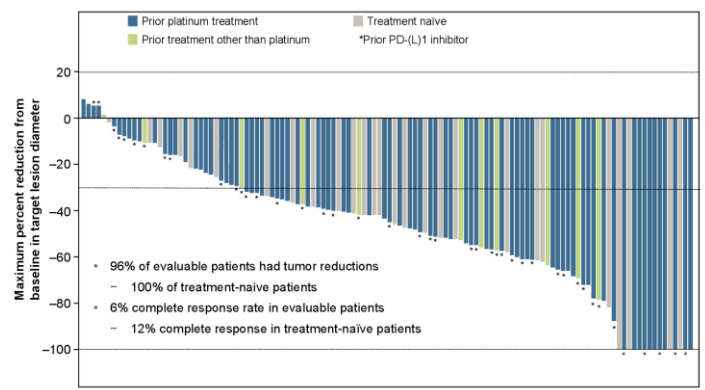
- *RET*: selpercatinib or pralsetinib
- *ROS1*: repotrectinib, entrectinib, or crizotinib
- *NTRK1/2/3*: larotrectinib, or entrectinib

TKI therapy for *RET* fusion-positive lung cancers is highly active

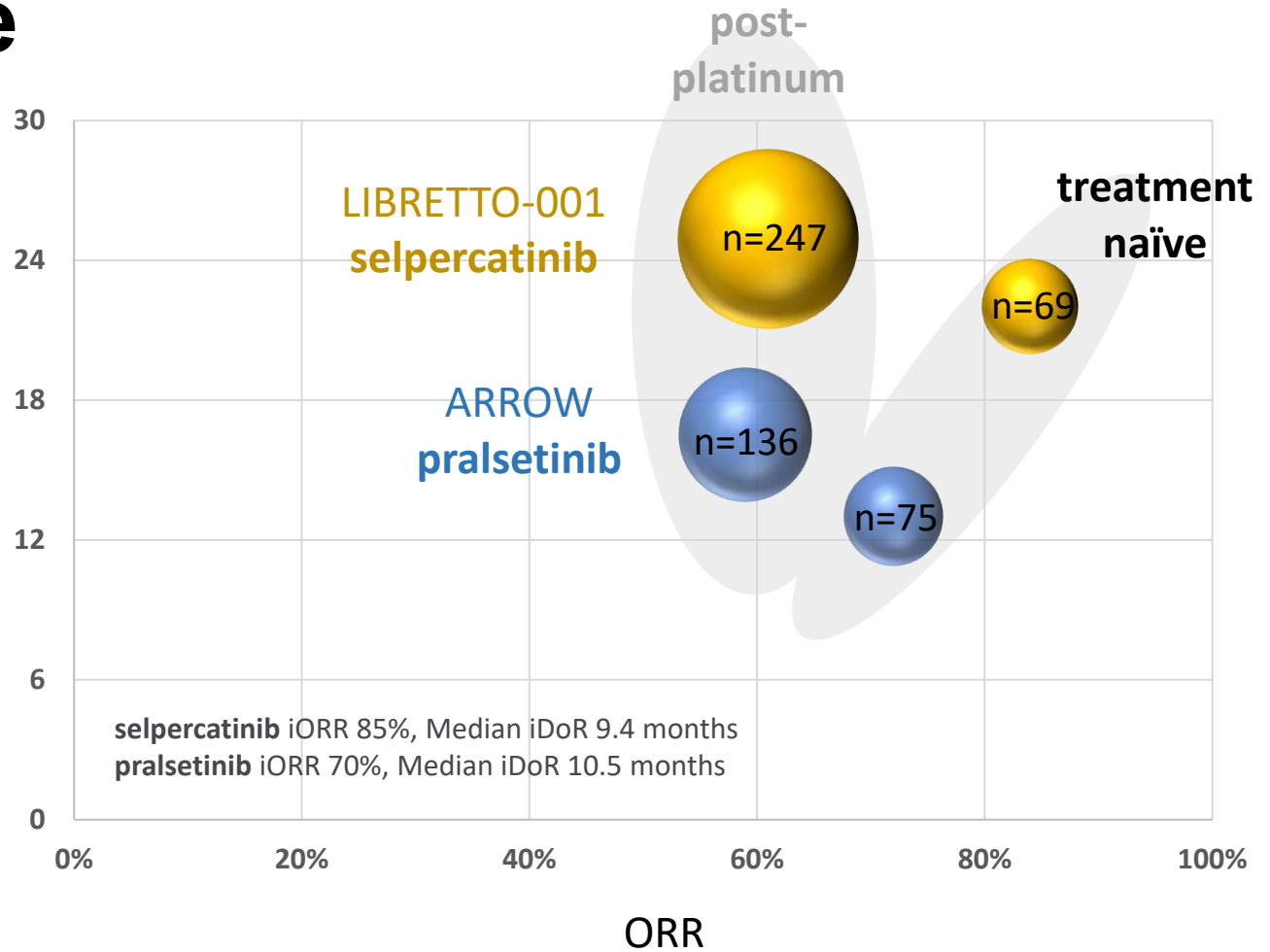
selpercatinib



pralsetinib

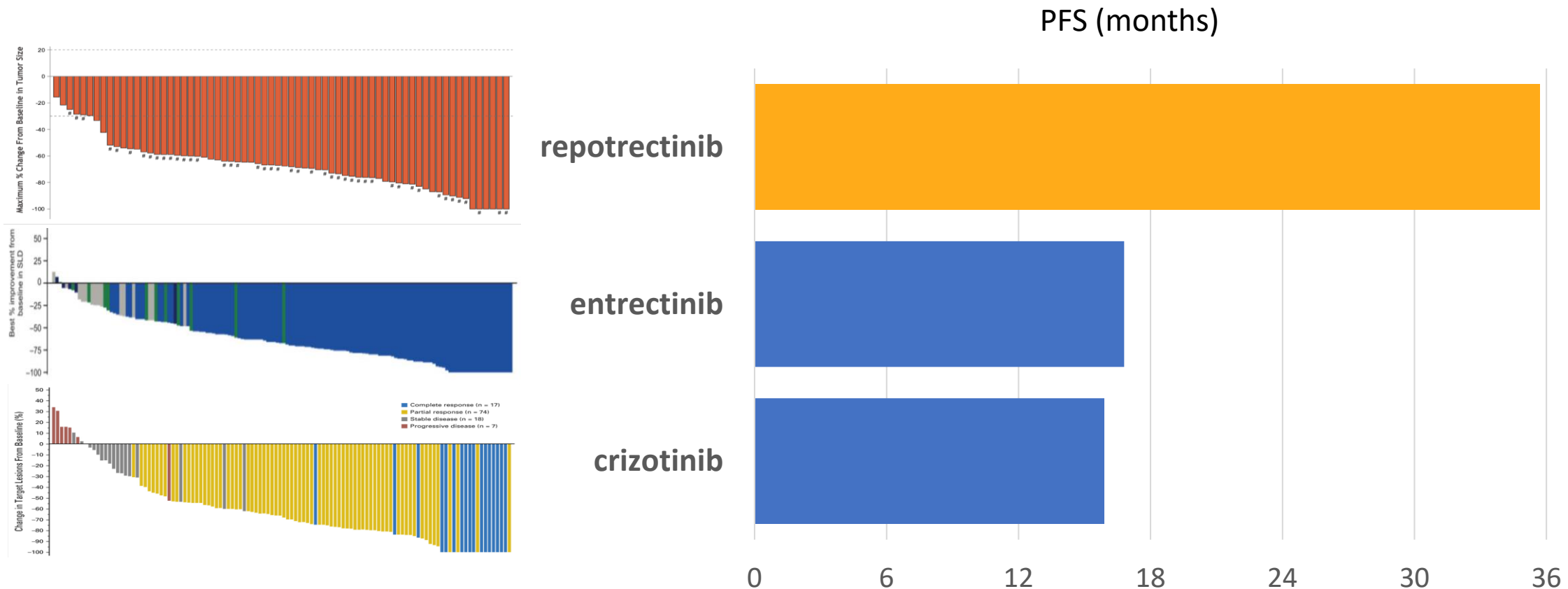


PFS (months)



Drilon et al, NEJM 2020; Gainor et al, ASCO 2020; Drilon et al, J Clin Oncol 2022; Griesinger et al Ann Oncol 2022; *Drilon et al, N Engl J Med 2020; *Gainor et al, Lancet Oncol 2021

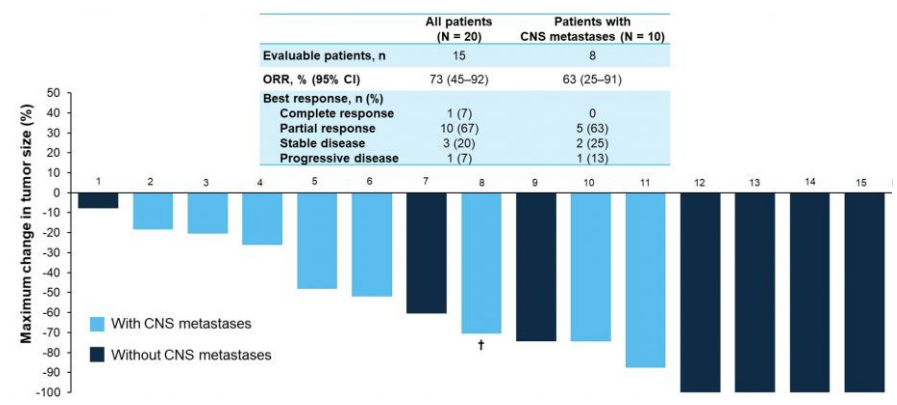
TKI therapy for *ROS1* fusion-positive lung cancers is highly active



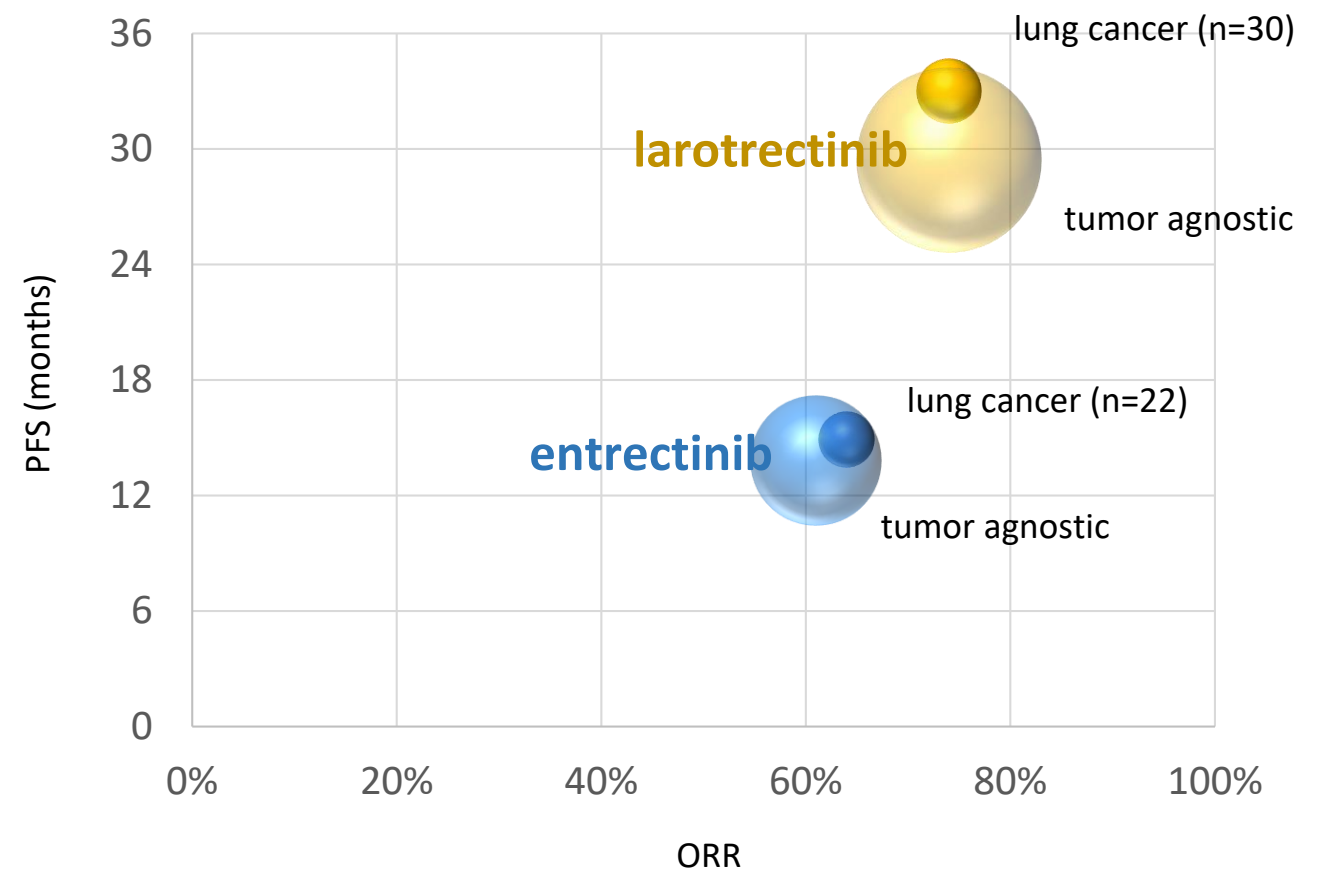
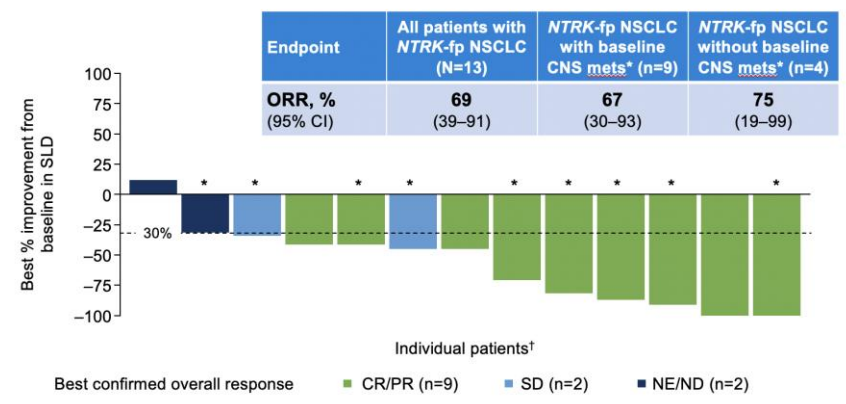
Wu et al JCO 2018, Drilon et al JTO CRR 2022, Drilon et al NEJM 2024

TKI therapy for *NTRK1/2/3* fusion-positive lung cancers is highly active

larotrectinib

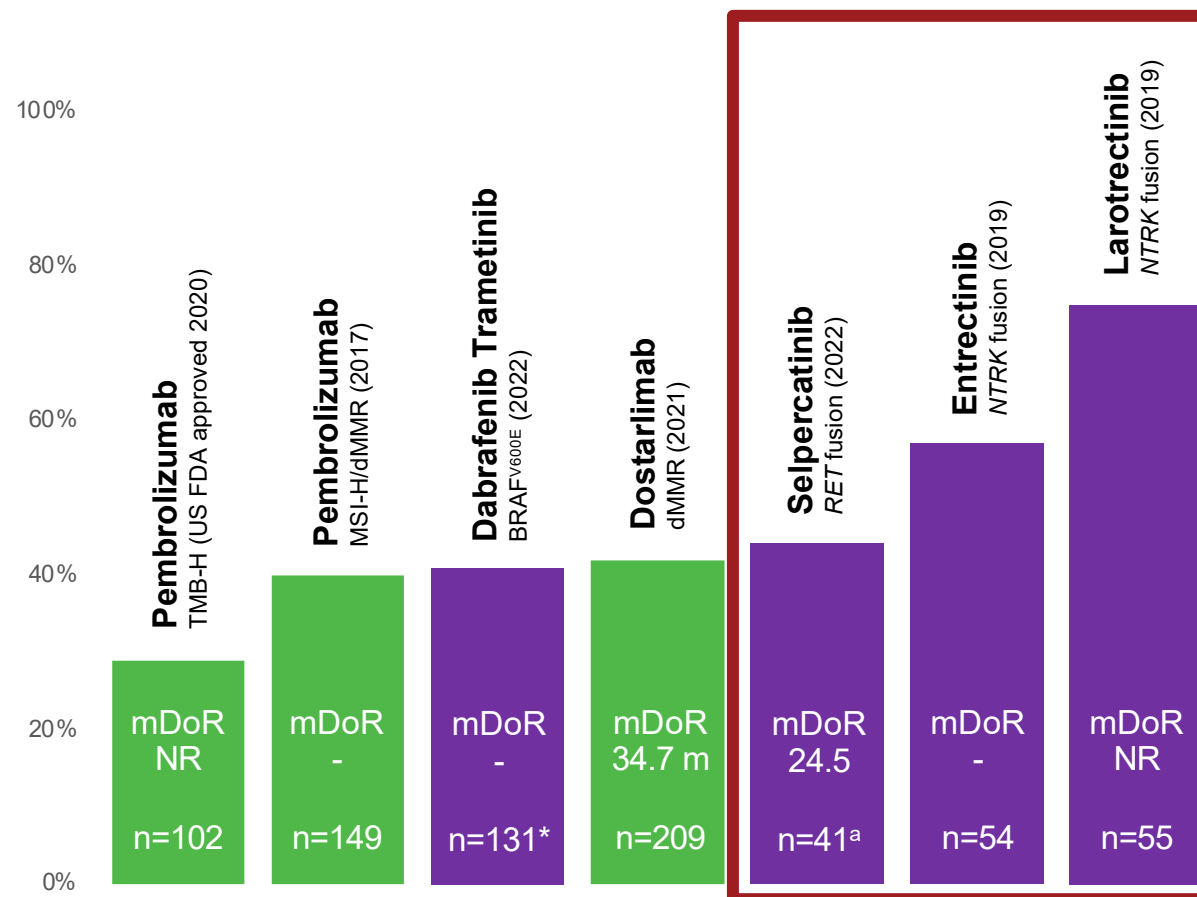


entrectinib

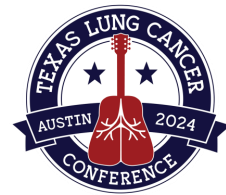


Lin et al, ASCO 2023; Drilon et al, ASCO 2022; Demetri et al, CCR 2022

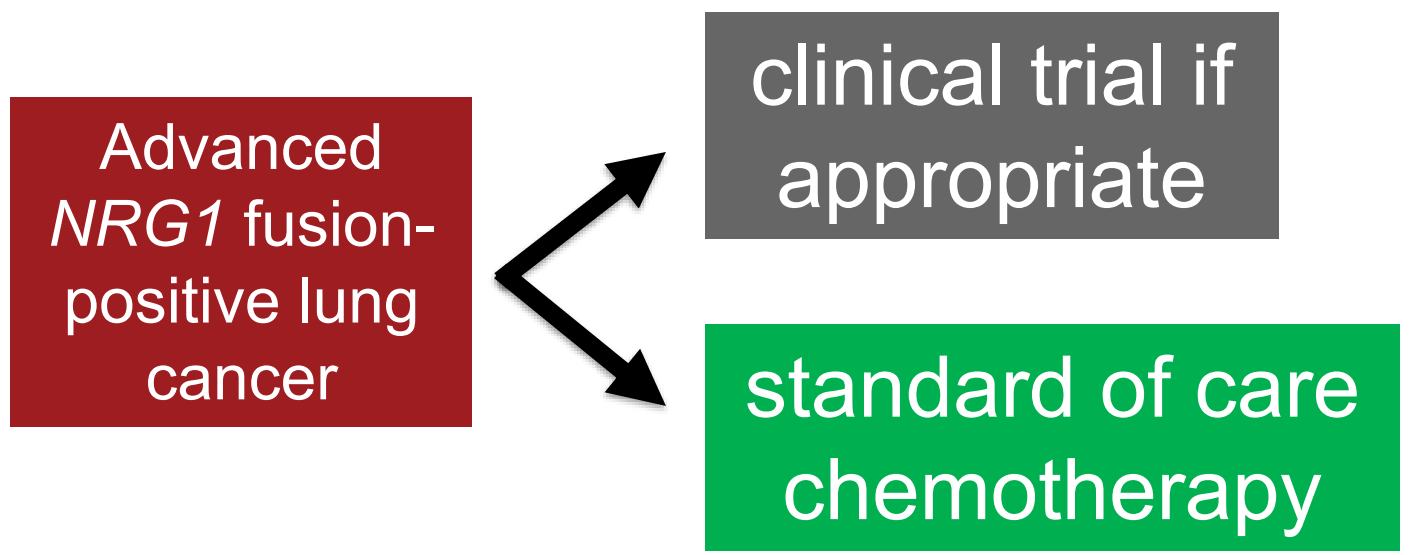
Lung cancer targeted therapy exploration has supported tumor-agnostic drug approvals



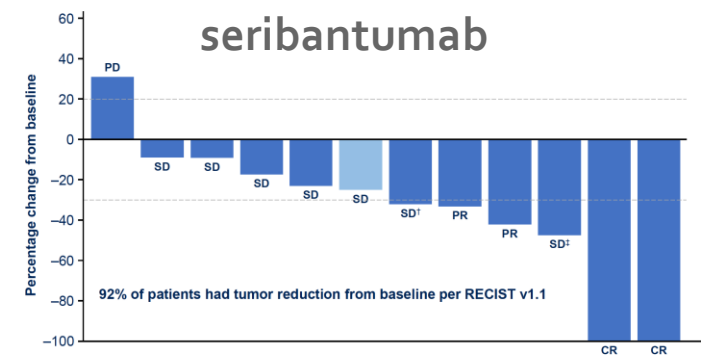
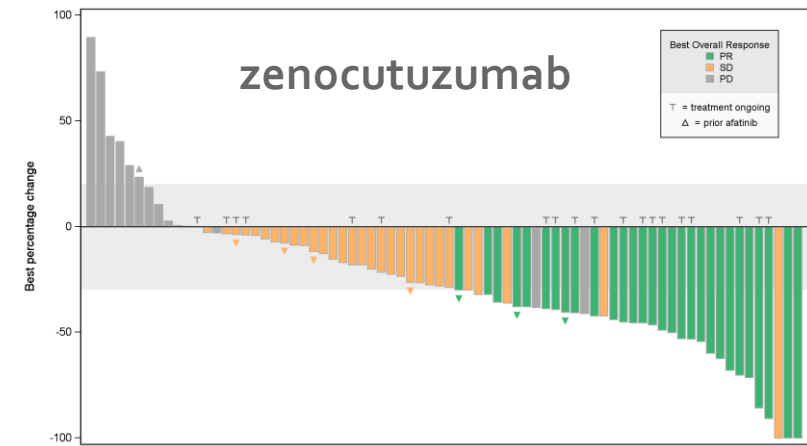
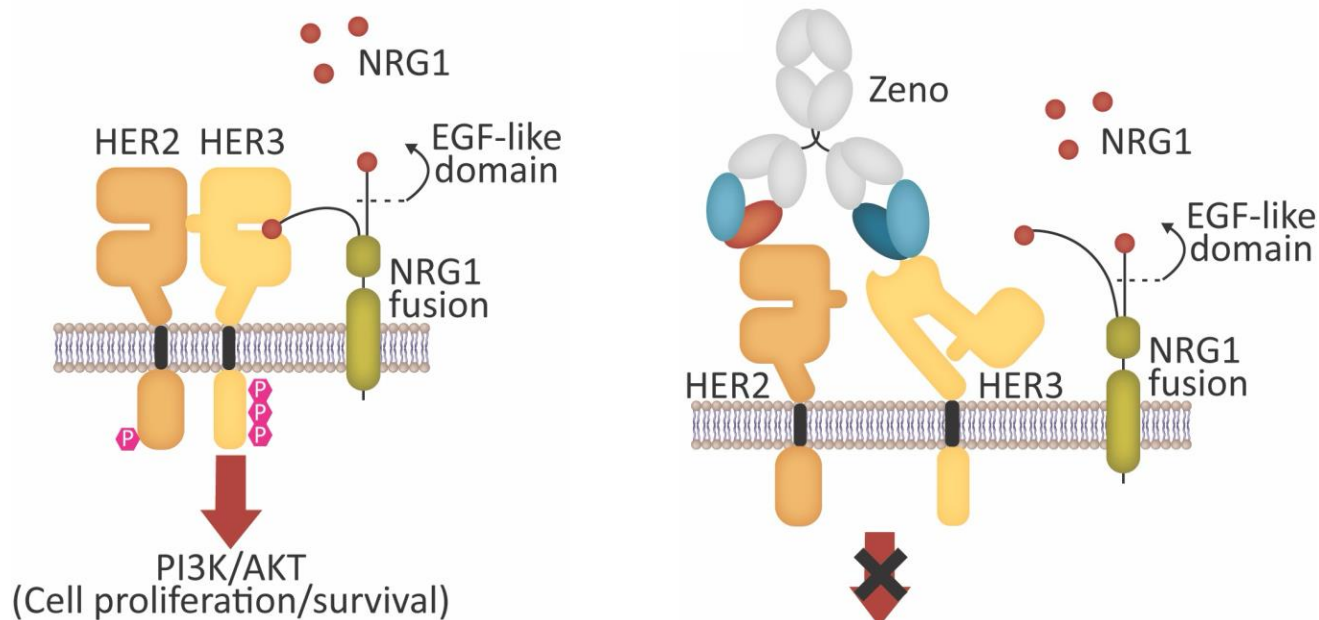
data based on activity that led to initial regulatory approval, www.fda.gov
 *adults, 36 pediatric ORR 25%; ^a supported by 343 thyroid/lung pts; unpublished, do not reproduce



Targeted therapy has not yet been approved for *NRG1* fusion-positive lung cancers

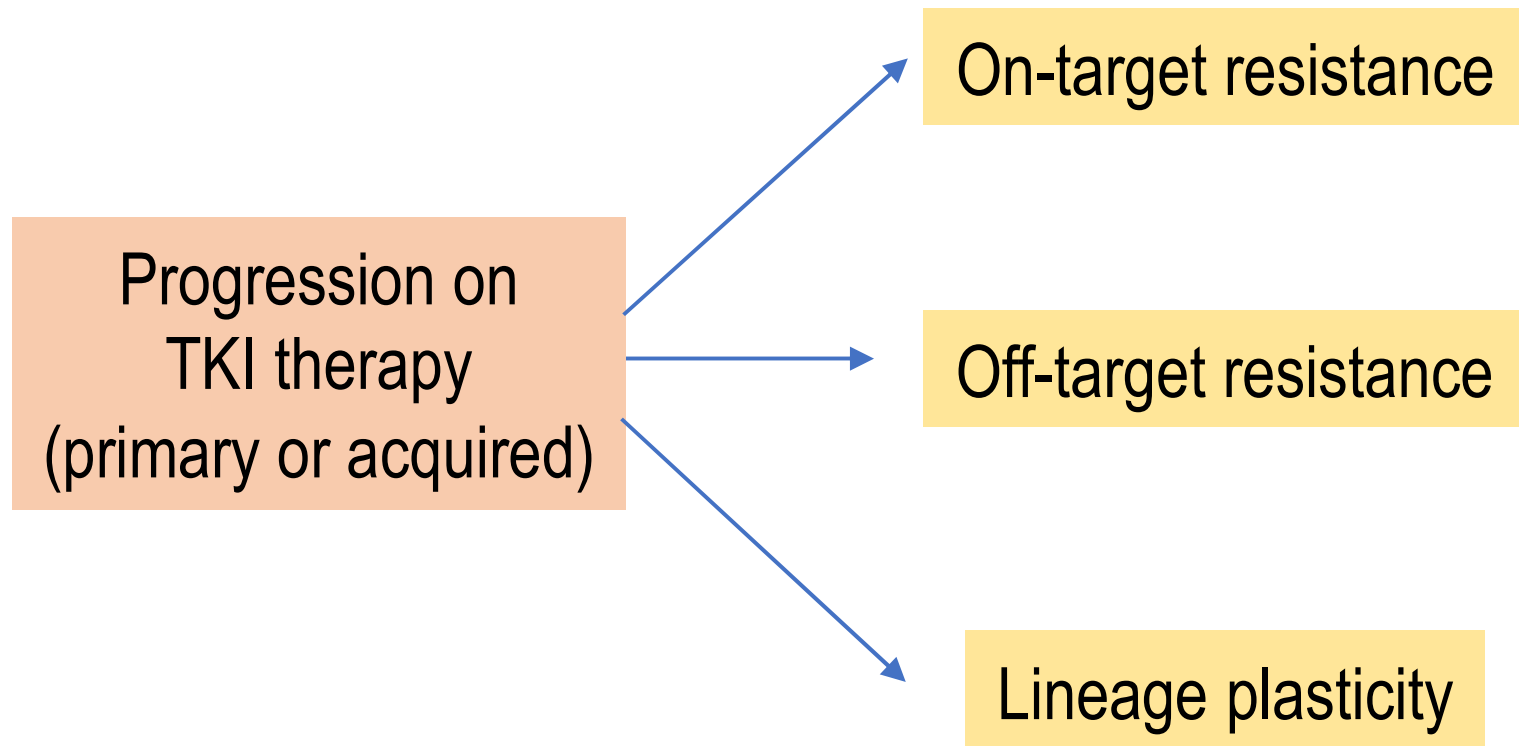


NRG1 fusion-positive lung cancers are biologically distinct, targeted therapy is active



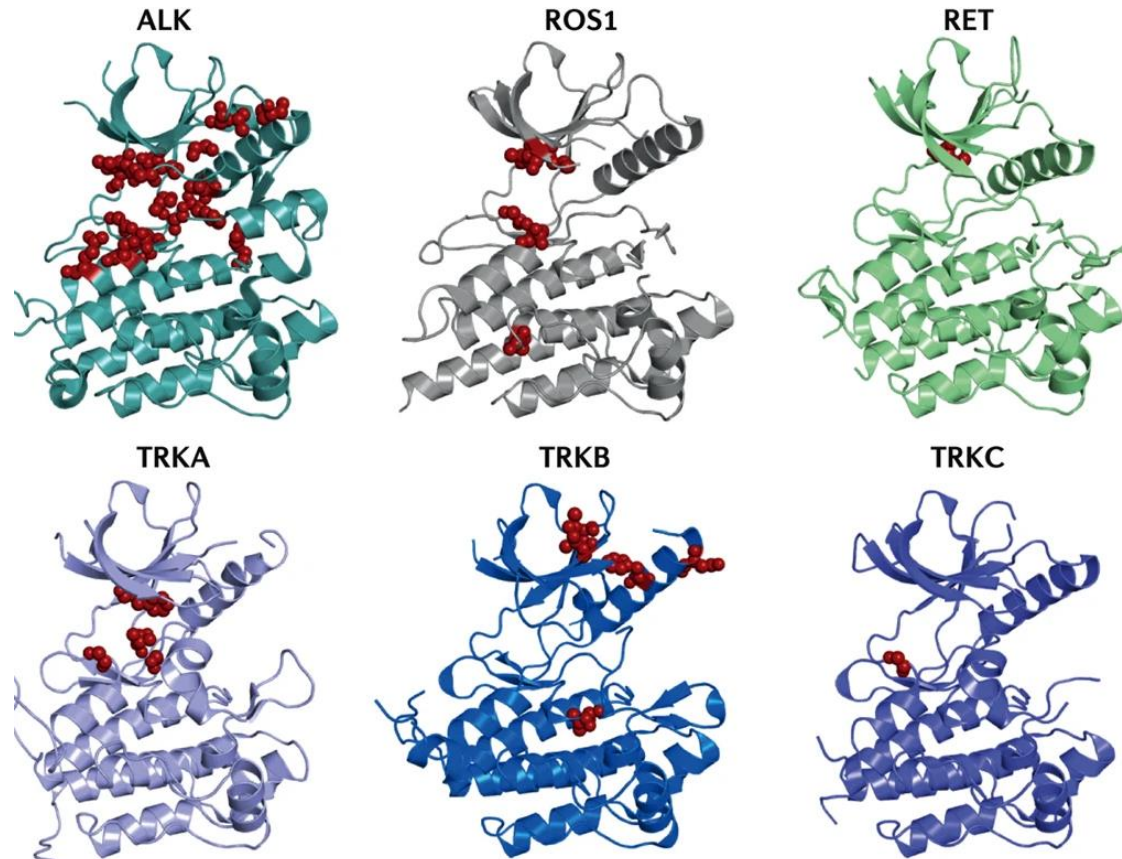
Schram et al ESMO 2023, Carrizosa et al, ASCO 2022

Targeted therapy resistance can take many forms



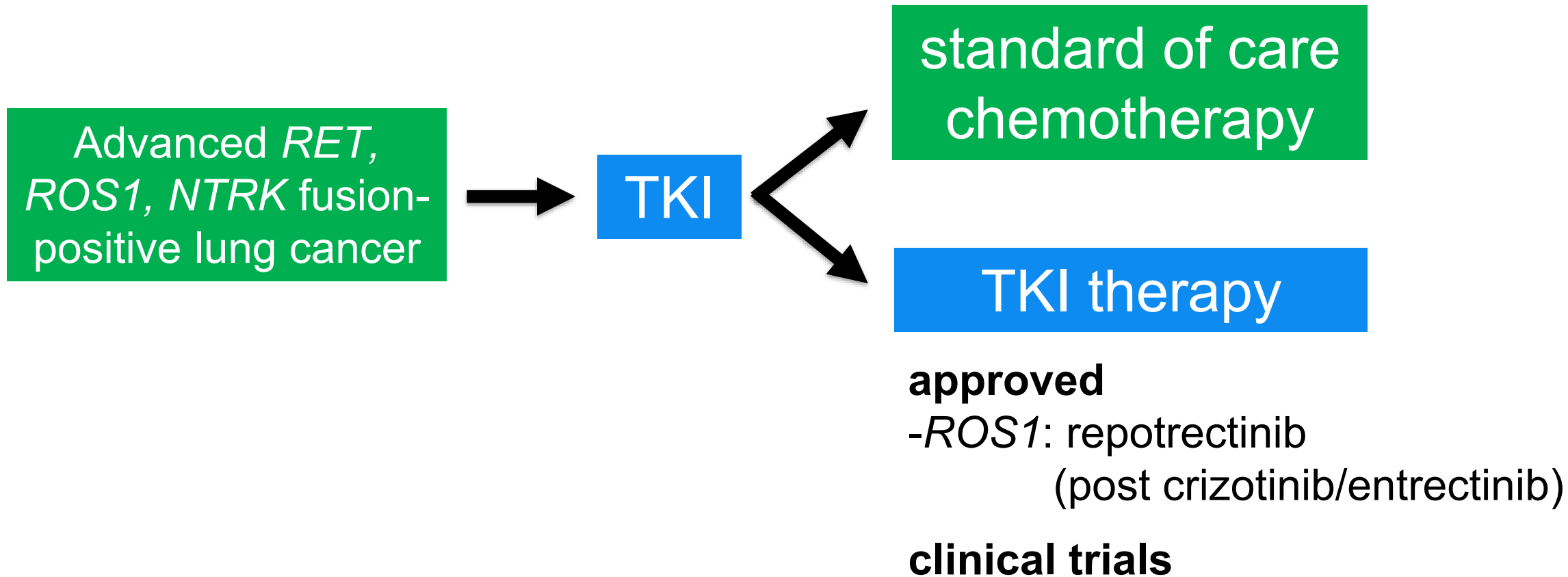
*combinations of the above may occur

Fusion-positive lung cancers can acquire resistance mutations in response to TKI therapy

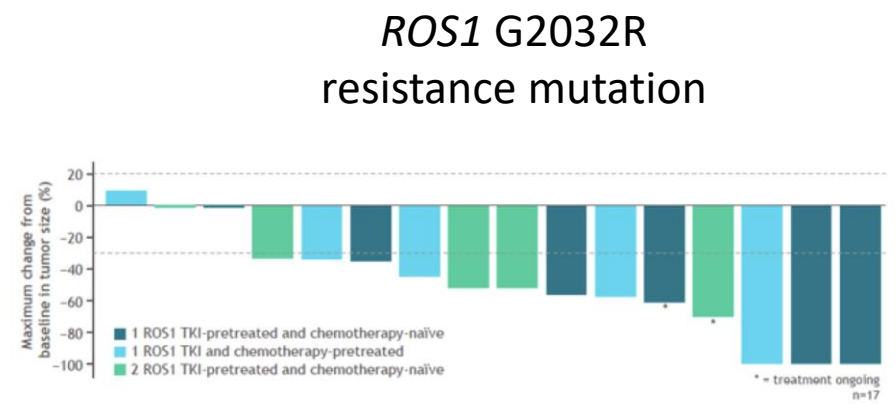
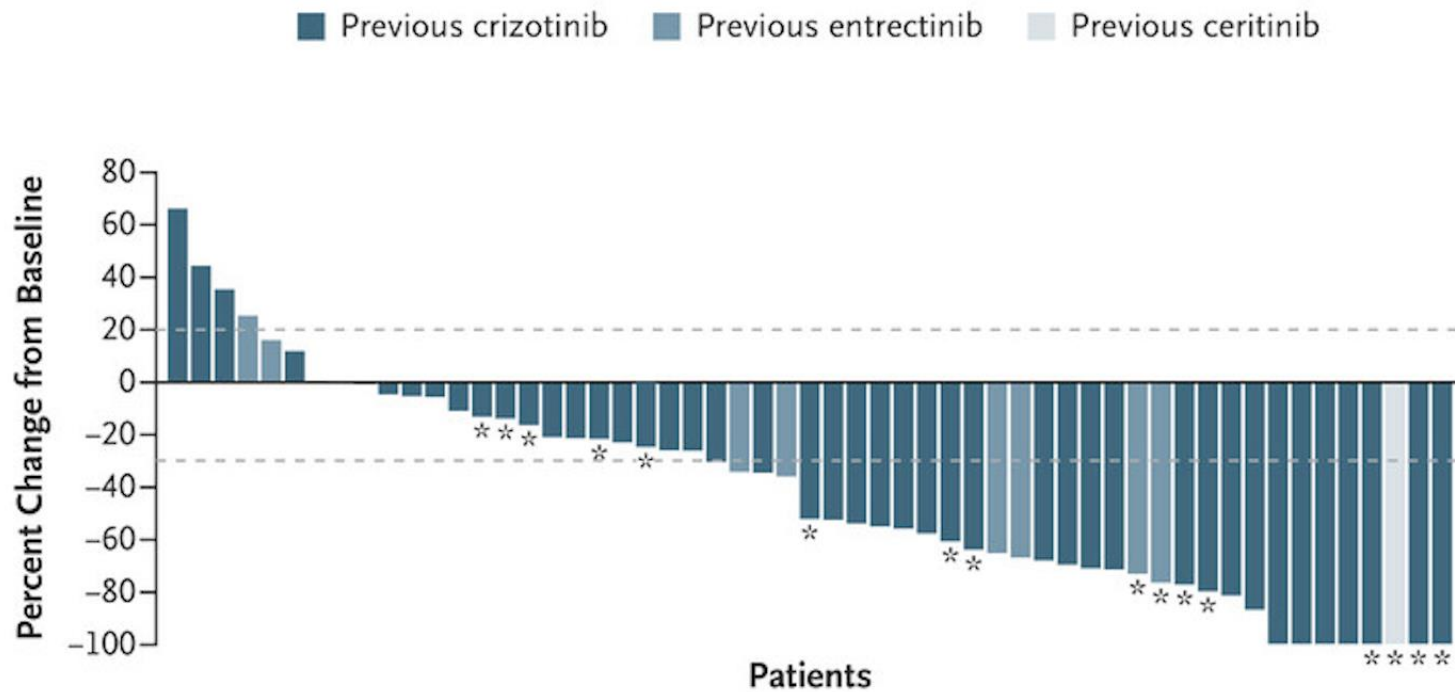


Schram et al, NRCO 2017

Next-generation TKIs are currently approved or in trials for patients with PD on a 1st line TKI

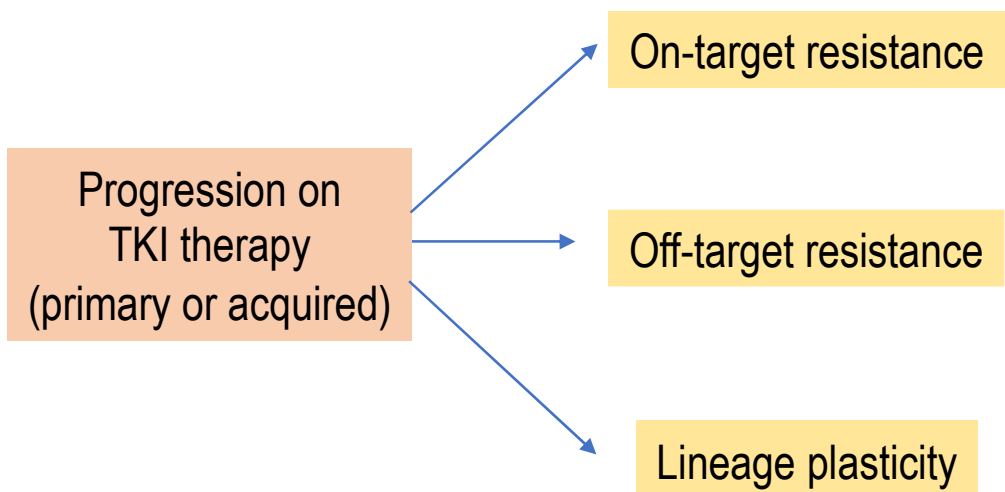


Repotrectinib is active in *ROS1* fusion-positive lung cancers with prior PD on a TKI

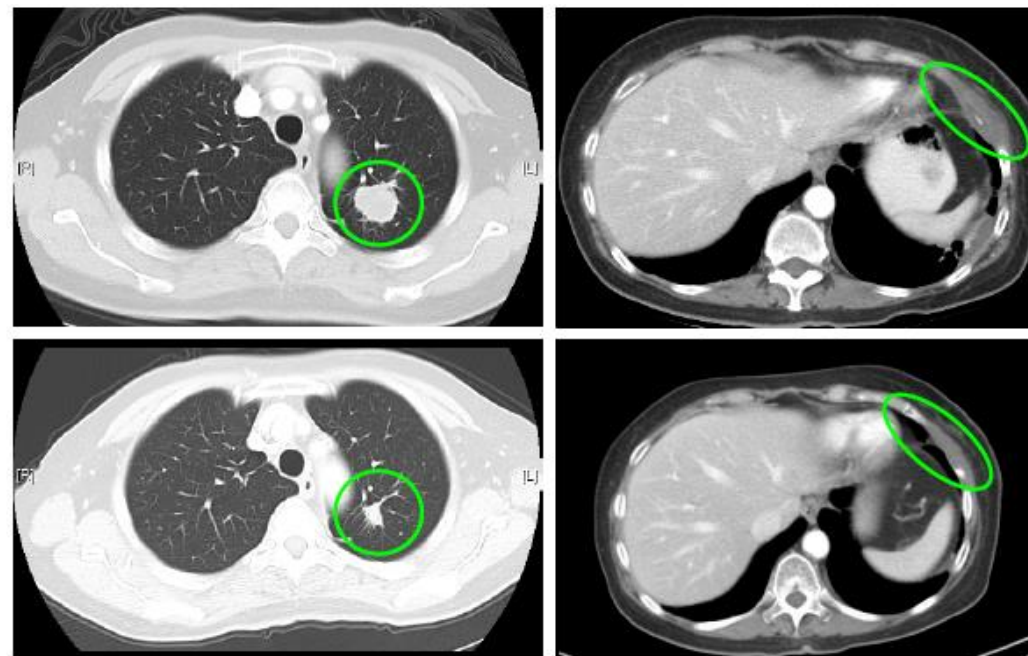


Drilon et al, NEJM 2024

Targeted therapy resistance can take many forms



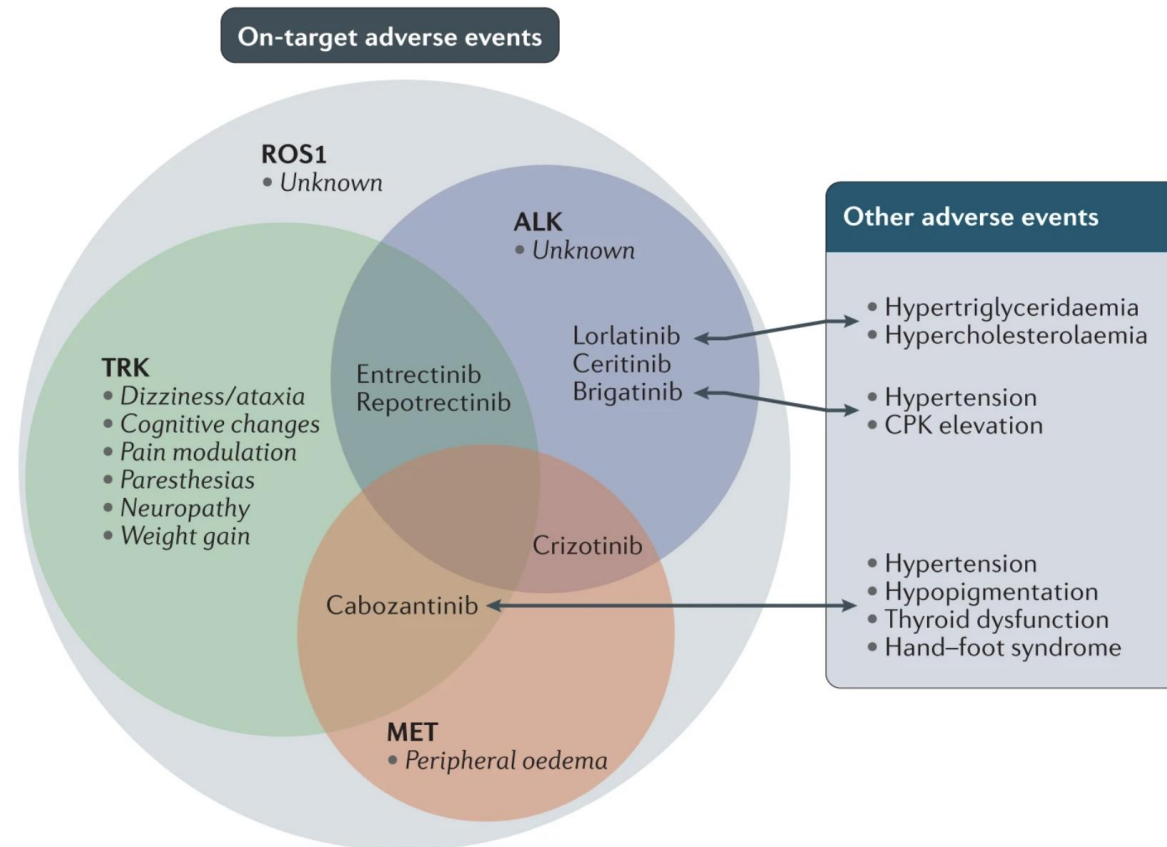
*combinations of the above may occur



Selpercatinib and crizotinib combination rescues *MET* amplification-mediated resistance to selpercatinib in a patient with a *RET* fusion-positive lung cancer

Rosen et al, CCR 2020

Side effects of TKIs for fusion-positive lung cancers depend on the kinases inhibited



Drilon et al NRCO 2021

Summary



Fusion	Choice for 1 st Line Targeted Therapy	Choice for Later Line Targeted Therapy
RET	Selpercatinib Pralsetinib	Clinical trial (e.g., APS03118, EP0031-101)
ROS1	Repotrectinib Entrectinib Crizotinib	Repotrectinib (if not previously received) Lorlatinib (NCCN guidelines) Clinical trial (e.g., taletrectinib, NVL-520)
NTRK	Larotrectinib Entrectinib	Clinical trial (e.g., repotrectinib, zurletrectinib, SIM1803)
NRG1	Clinical trial (e.g., zenocutuzumab, seribantumab)	-