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RET and NTRK: The Good, The Bad, The Ugly….and What's Coming Up?

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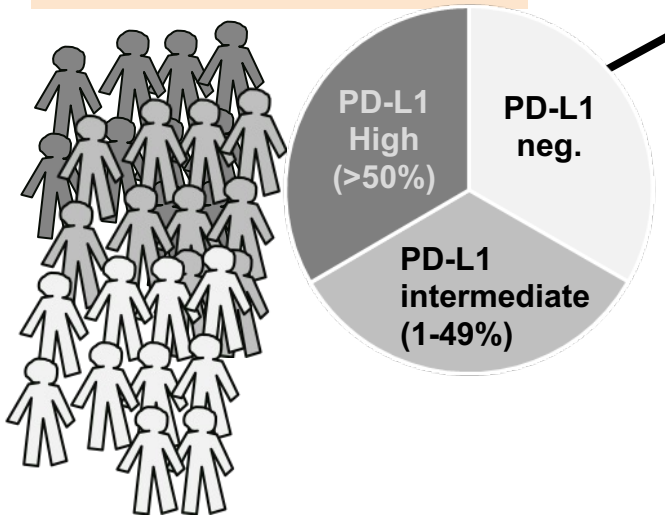
Masters in Thoracic Oncology Summit
Albuquerque, New Mexico
November 17, 2023

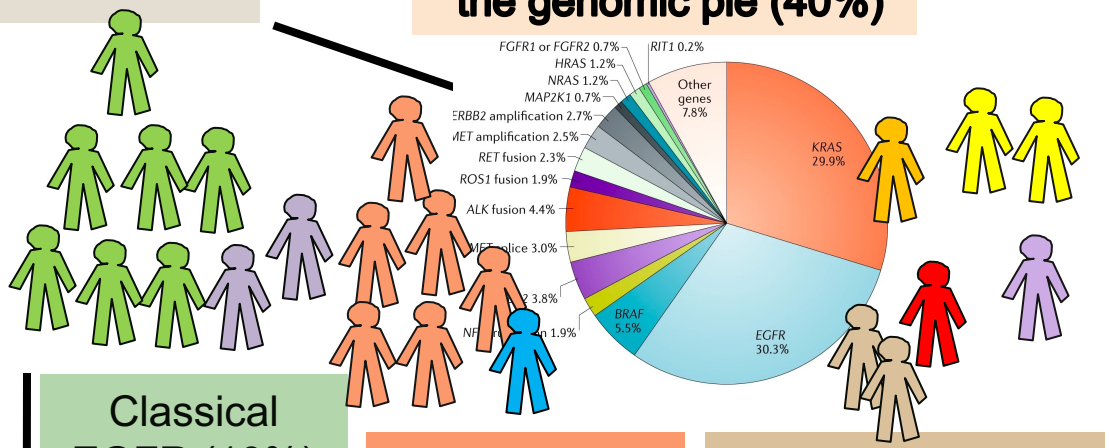
The treatment landscape of NSCLC 2023 (yes, in the near future, this will look ridiculously simple too)

Driver negative: the immune pie (60%)



NSCLC

Driver positive: the genomic pie (40%)



Likely coming soon:
-ADCs (TROP2, CEACAM5, etc)
-more atypical EGFRs (structural)
-KRAS G12D and other alleles
-tailoring based on co-mutations
--TCRs, CAR-Ts, TILs
-vaccines?

Classical EGFR (10%)

EGFR T790M

EGFR Exon20 (2%)

EGFR atypicals (3%)

ALK fusion (4%)

KRAS G12C 12%

HER2 mutant (3%)

BRAF mutant (3%)

ROS-1 mutant (1%)

MET ex14 (3%)

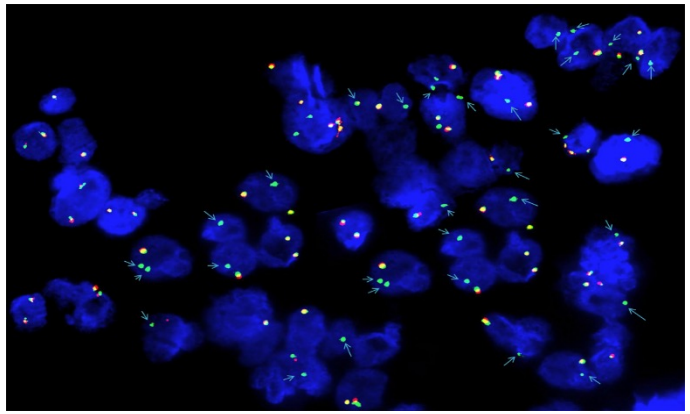
RET fusion (1%)

NTRK mutant (1%)

Skoulidis and Heymach, Nat Rev Cancer 2019

RET fusions define a unique molecular and clinicopathological subtype of NSCLC

- RET normally plays role in enteric nervous system development, kidney morphogenesis, spermatogenesis, other roles
- Germline mutations in MEN 2; sporadic mutations in MTC and PTC
- *RET* rearrangements (*RET*+) with distinct fusion partners have been identified in 1-2% of unselected NSCLC pts, younger<60, never smokers[1-3]
- *KIF5B-RET* and *CCDC6-RET* fusions are the most common variants in NSCLC[1,2], promote cancer cell proliferation and tumor growth[4]

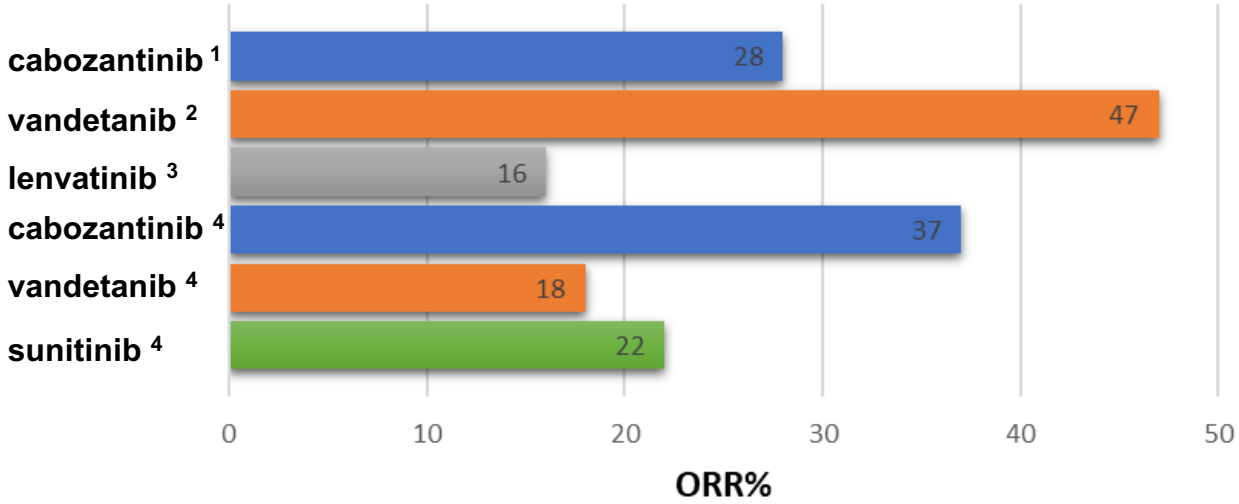


5

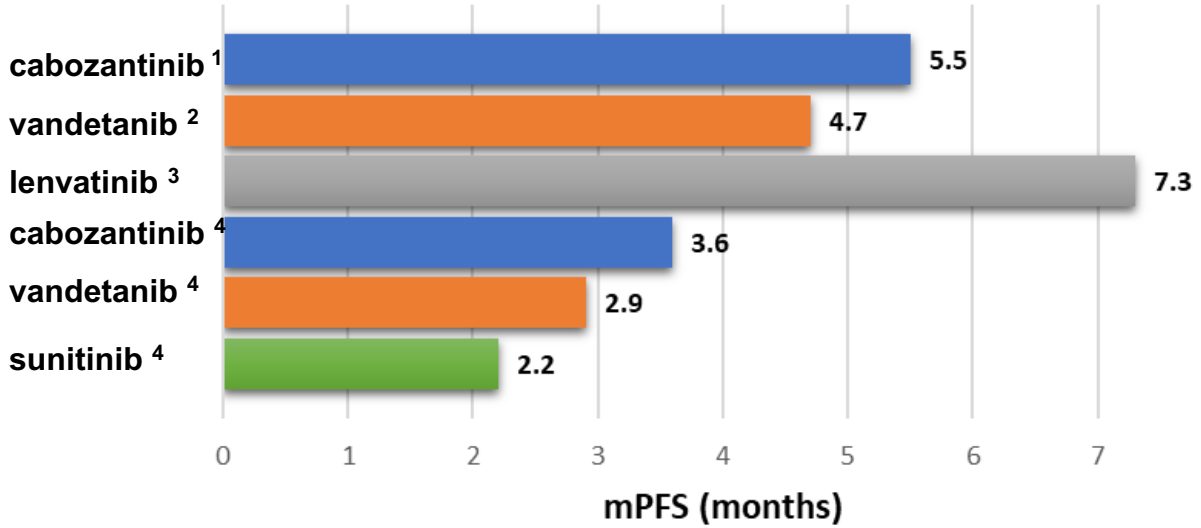
1. Kohno T et al. *Nat Med*. 2012
2. Takeuchi K et al. *Nat Med*. 2012
3. Wang R et al. *JCO* 2012
4. Lipson D et al. *Nat Med*. 2012
5. Subbiah V et al. *Lung Cancer* 2015

Activity of “old” multitargeted TKIs in RET fusion NSCLC: modest ORR and mPFS

ORR 18-47%



mPFS 2.2-7.3 months



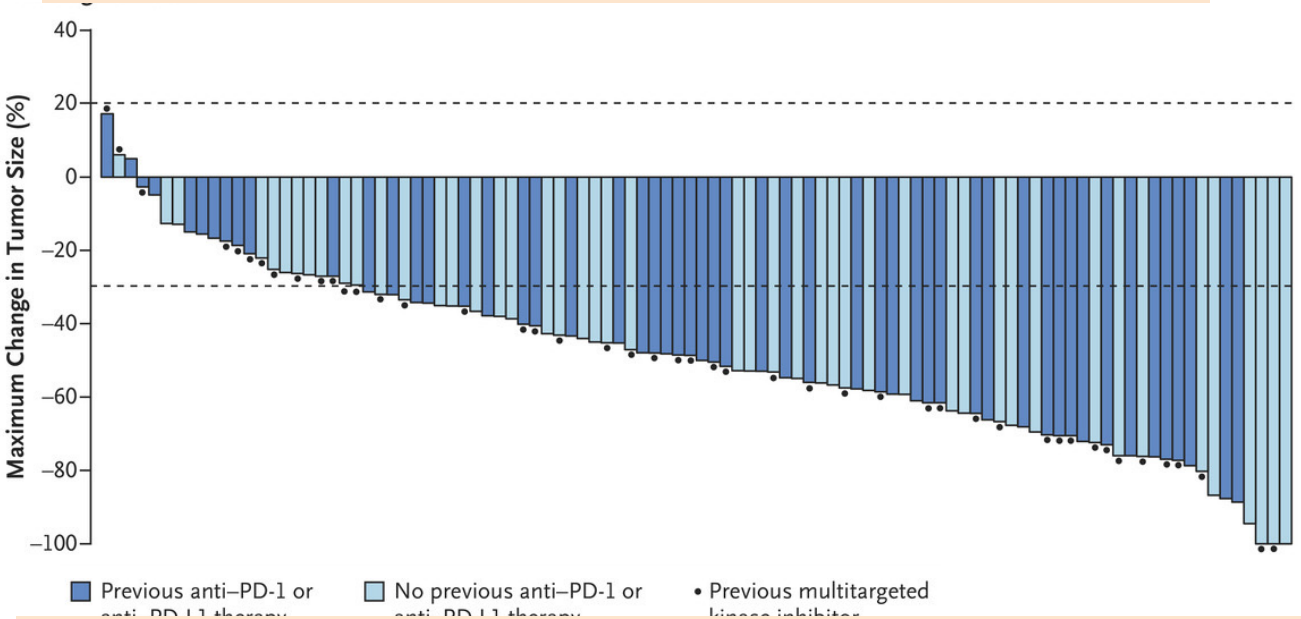
1. Drilon, A. et al. Cabozantinib in patients with advanced RET-rearranged non-small-cell lung cancer: an open-label, single-centre, phase 2, single-arm trial. Lancet Oncol. 17, 1653–1660, 2016
2. Yoh, K. et al. Vandetanib in patients with previously treated RET-rearranged advanced non-small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial. Lancet Respir. Med. 5, 42–50, 2017
3. Hida, T. et al. A phase 2 study of lenvatinib in patients with RET fusion-positive lung adenocarcinoma. Lung Cancer 138, 124–130, 2019
4. Gautschi, O. et al. Targeting RET in patients with RET-rearranged lung cancers: results from the global, multicenter RET registry. J. Clin. Oncol. 35, 1403–1410, 2017

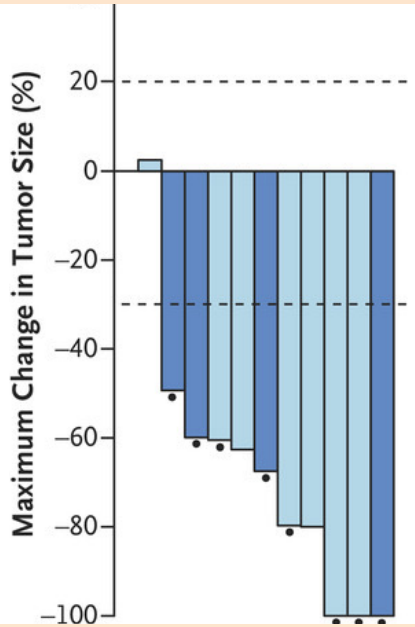
Adapted from Thein KZ et. al. Trends in Cancer 2021

Selpercatinib for RET fusion NSCLC (LIBRETTO-001)

ORR 64% (IRC) overall
ORR 85% in previously untreated
mPFS 16.5 months

Intracranial ORR
91% in platinum treated group

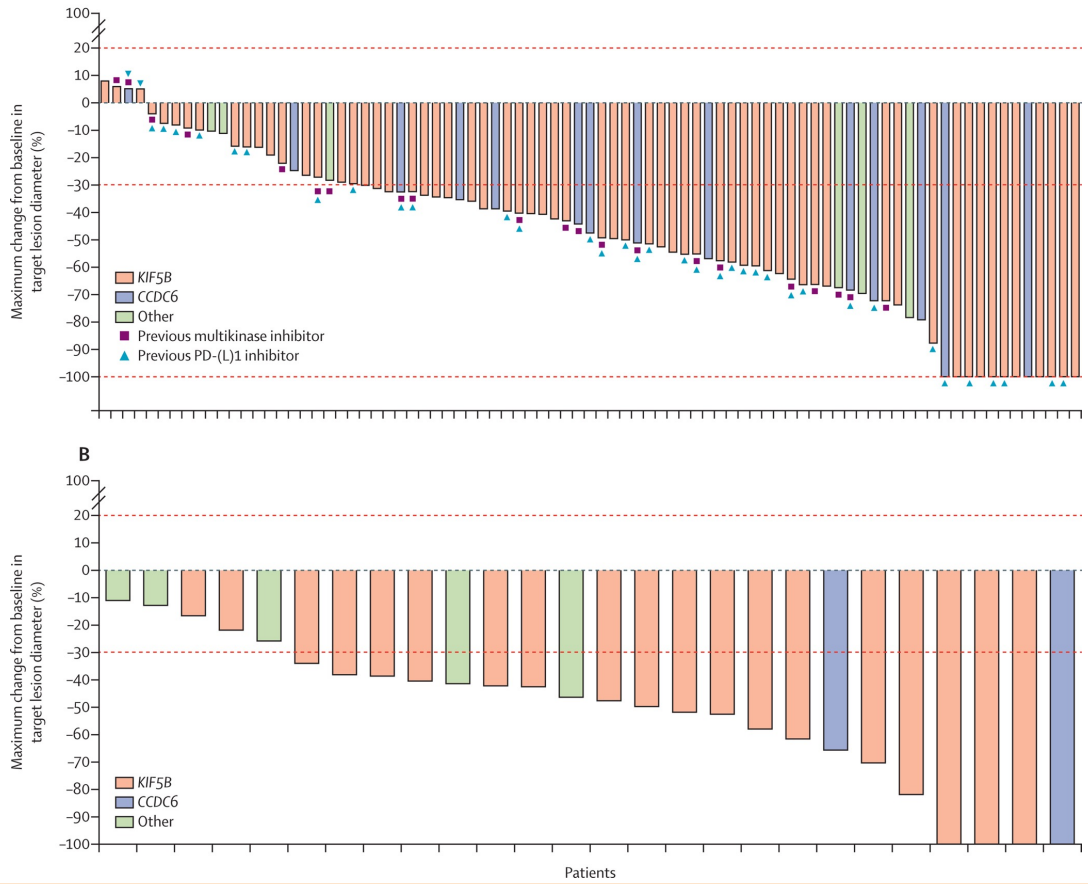




May 8, 2020: FDA granted accelerated approval to selpercatinib for RET fusion NSCLC. Sept. 21, 2022: regular approval

A Drilon et al. N Engl J Med 2020;383:813-824.

Pralsetinib for RET fusion NSCLC (ARROW study)



ORR 61% in prior platinum group (N=87)
mPFS 17.1 months

ORR 70% in treatment naïve (N=27)
mPFS 9.1 months

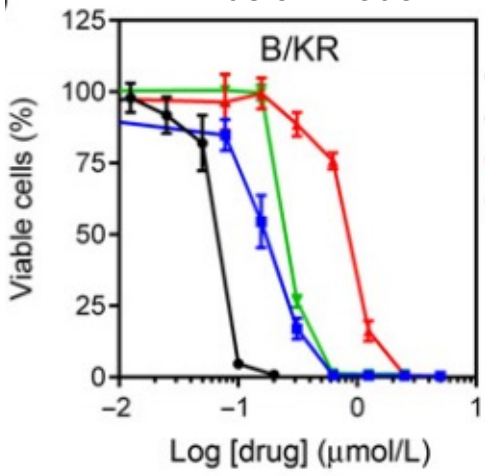
Intracranial ORR 56%

Sept. 4, 2020: FDA granted accelerated approval to pralsetinib for RET fusion NSCLC.

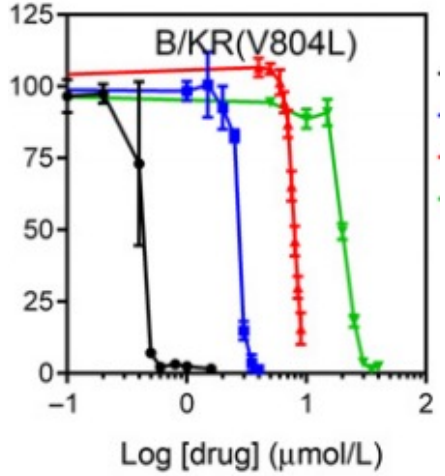
Gainor et al, Lancet Oncology 2021

Resistance to RET inhibitors through gatekeeper mutations

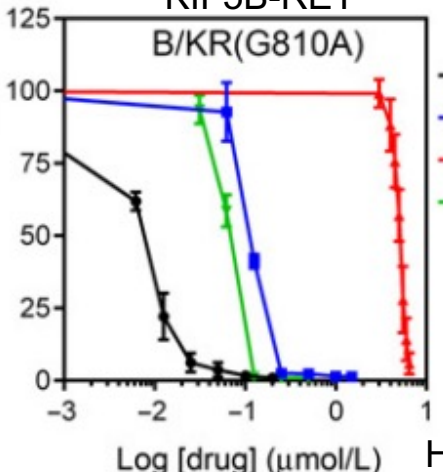
B/KR
RET Fusion Model



Gatekeeper Mutation:
KIF5B-RET^{V804L}



Gatekeeper Mutation:
KIF5B-RET^{G810A}

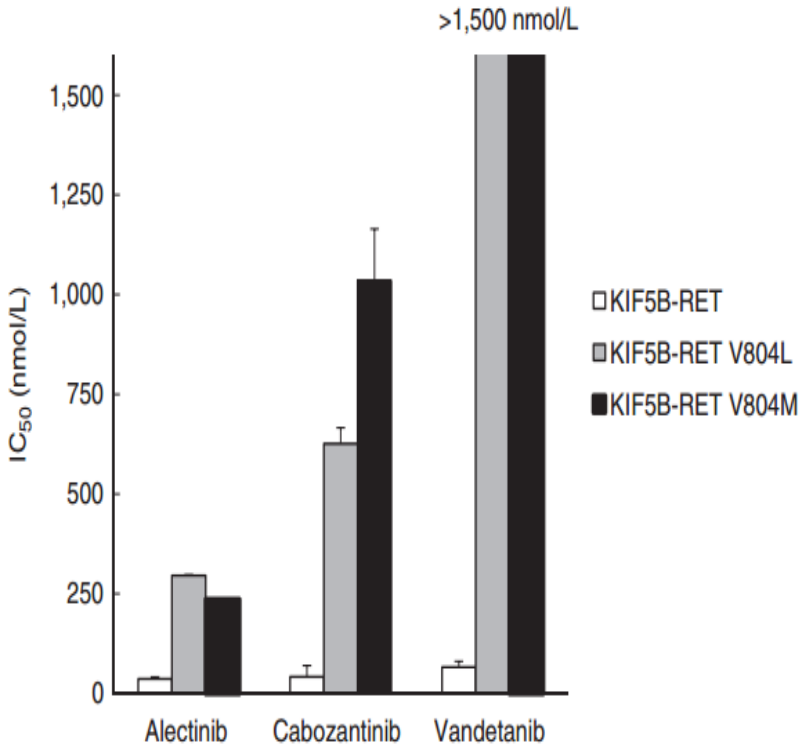


RET TKI

- ponatinib
- cabo
- van
- lenv

Huang, et al. *MCT* 2016

Inhibition of *RET* gatekeeper mutants by alectinib



Kodama, et al. *MCT* 2014

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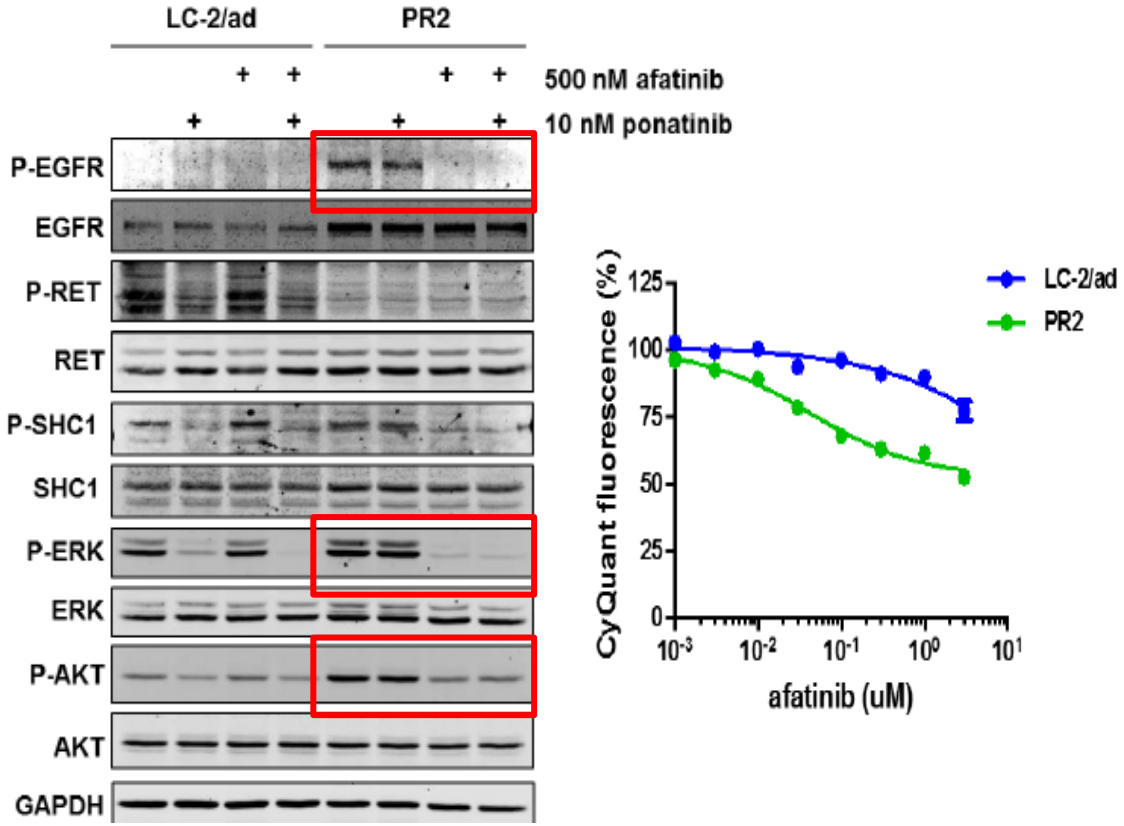
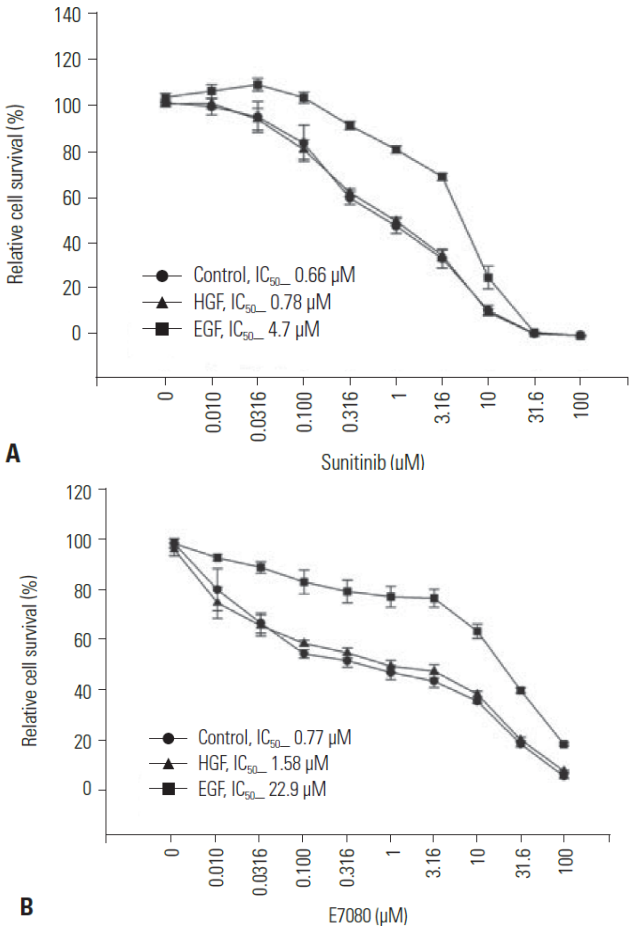
RET inhibitor resistance in *RET*+ NSCLC is mediated by EGFR, MET or PI3K/mTOR bypass signaling



Nelson, et al. et al. *MCT* 2017

EGF reduces sensitivity of LC-2/ad cells (CCDC6-RET) to RET inhibitors *in vitro*



Chang, et al. *Yonsei Med J* 2017

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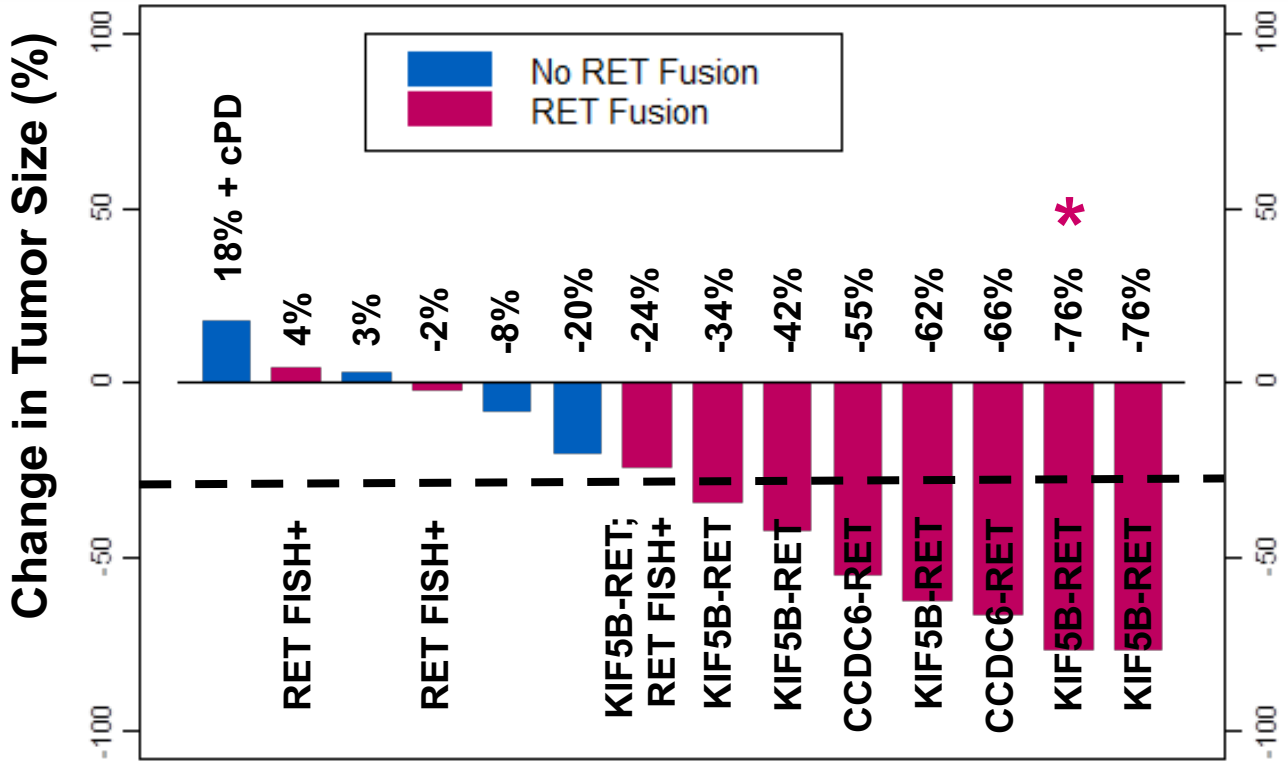
Activity of vandetanib+everolimus in RET fusion NSCLC



***RET*+, NGS and/or FISH (13)**: 7 PR (54%), mPFS 4.4 mon, 95% CI (3.4, NR)

In *RET*+ patients by NGS: **ORR= 70%** (7/10), **PFS=8.0 months,** 95% CI (4.4, NR)

In FISH *RET*+ but NGS patients- patients ORR **= 0/3 (0%)**

% Change in Tumor Size from Baseline: median -29% (-76%, 18%); 5 RECIST NA

% Change in Tumor Size from Baseline by *RET* status:

- *RET*+: median -48% (-76%, 4%); 3 RECIST NA (2 NGS+, 1 FISH+);
- *RET*-/NA: median -2% (-20%,18%); 2 RECIST NA; P = 0.040

Subbiah, Cascone et al, in preparation

*Cabozantinib-progressor

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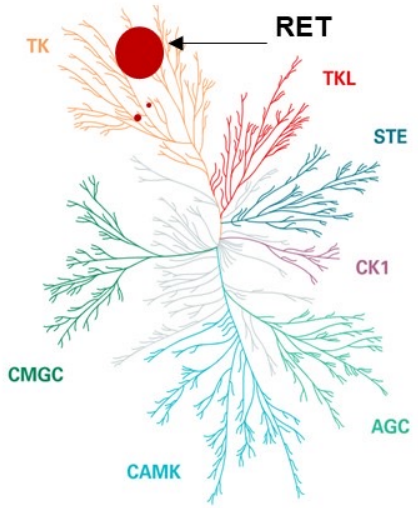
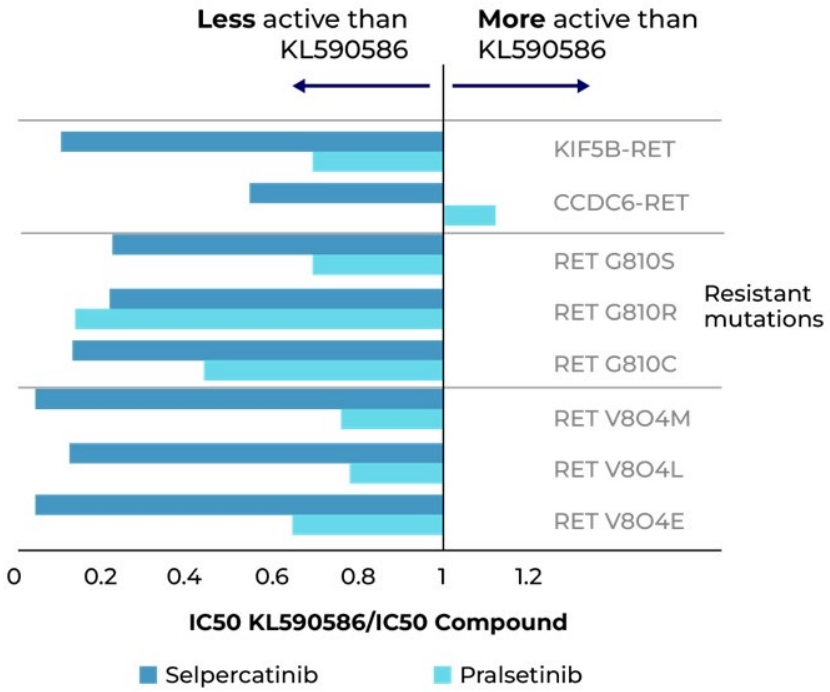
New generation TKIs: EP0031 (A400/KL590586)

01 **HIGHLY SELECTIVE** FOR RET COMPARED WITH VEGFR AND OTHER KINASES



- **93-fold** more selective for RET than VEGFR2
- **10-fold** more selective for RET than JAK1
- **22-fold** more selective for RET than JAK2

02 **GREATER POTENCY** THAN 1ST GEN SRIs AGAINST COMMON AND RESISTANT MUTATIONS



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Zhou et al, ASCO 2023

NTRK1,2,3 (a.k.a. TRK A, TRK B, TRK C): involved in nervous system development

NTRK genes and **TRK** receptors[1]:

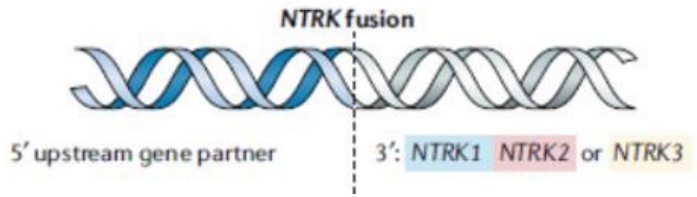
- In normal biology, expressed in neuronal tissue; roles in development, nervous system function via activation by neurotrophins
- Rarely expressed in normal

Receptor	Gene	Function
TRKA	NTRK1	Pain, thermoregulation
TRKB	NTRK2	Movement, memory, mood, appetite
TRKC	NTRK3	Proprioception

NTRK gene fusions and
TRK chimeric fusion proteins[1]:

In-frame rearrangement of any *NTRK* gene links tyrosine kinase domain with upstream fusion partner to generate a chimeric RNA and TRK fusion protein

Uncontrolled TRK kinase function results[5]



.Adapted from Amatu. ESMO Open. 2016;1:e000023. 2. Loewenthal. Pediatr Res. 2005;57:587. 3. Razzoli. Genes Brain Behav. 2011;10:424. 4. Inoue. Blood Cells Mol Dis. 2003;30:157. 5. Adapted from Hyman. ASCO 2017. Abstr LBA2501; Cocco et al. Nature Review 2018

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Slide courtesy of Jyoti Patel

TRK receptors and ligands were even investigated in ancient times! (like 1997)

THE JOURNAL OF BIOLOGICAL CHEMISTRY

Vol. 272, No. 46, Issue of November 14, pp. 29222–29228, 1997
Printed in U.S.A.

The Role of the Nerve Growth Factor Carboxyl Terminus in Receptor Binding and Conformational Stability*

(Received for publication, July 9, 1997, and in revised form, August 25, 1997)

Alex Krüttgen‡, John V. Heymach, Jr., Philipp J. Kahle§, and Eric M. Shooter¶

From the Department of Neurobiology, Stanford University School of Medicine, Stanford, California 94305-5401

1997: studies of binding of NGF (ligand for TRK A)

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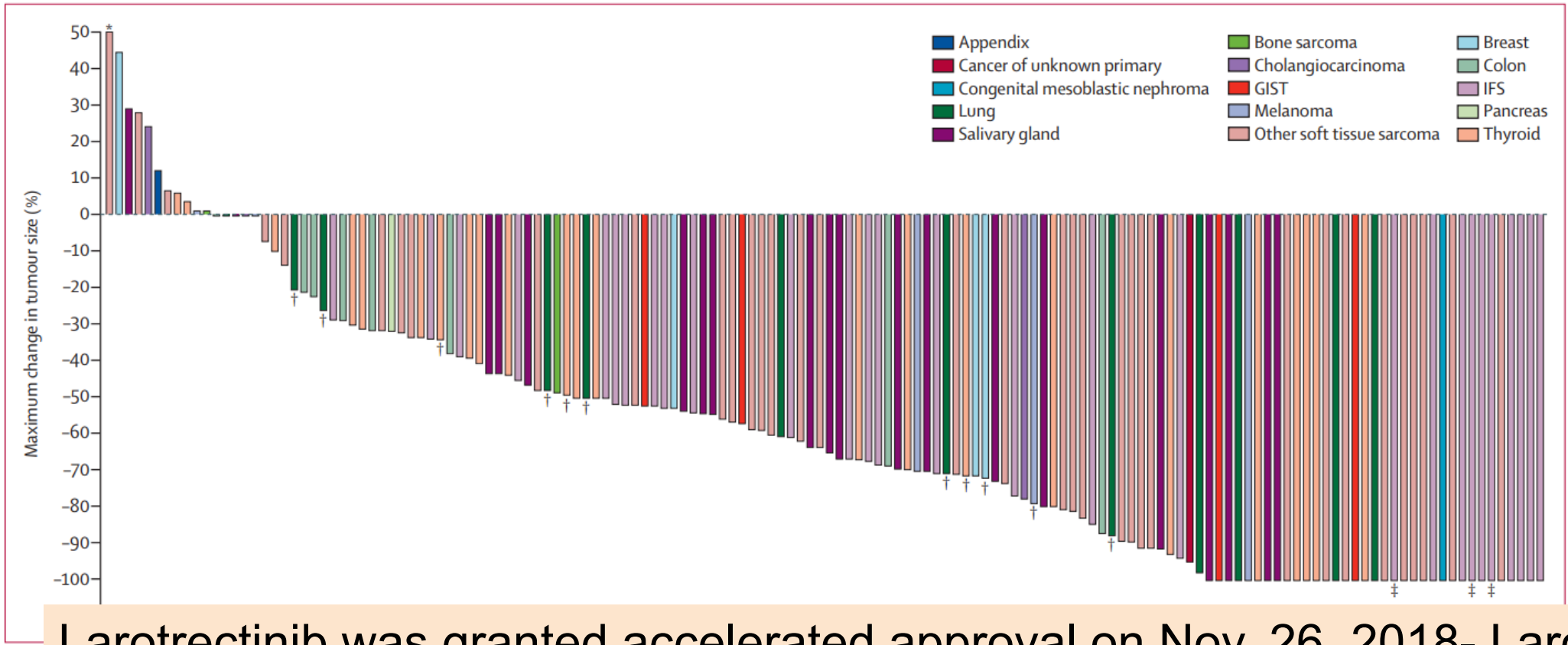
Kruttgen et al, JBC 1997

Larotrectinib is highly active in solid tumors with NTRK fusions including NSCLC



Larotrectinib was granted accelerated approval on Nov. 26, 2018- Larotrectinib granted accelerated FDA approval for adult/pediatric patients with solid tumors that have a *NTRK* gene fusion

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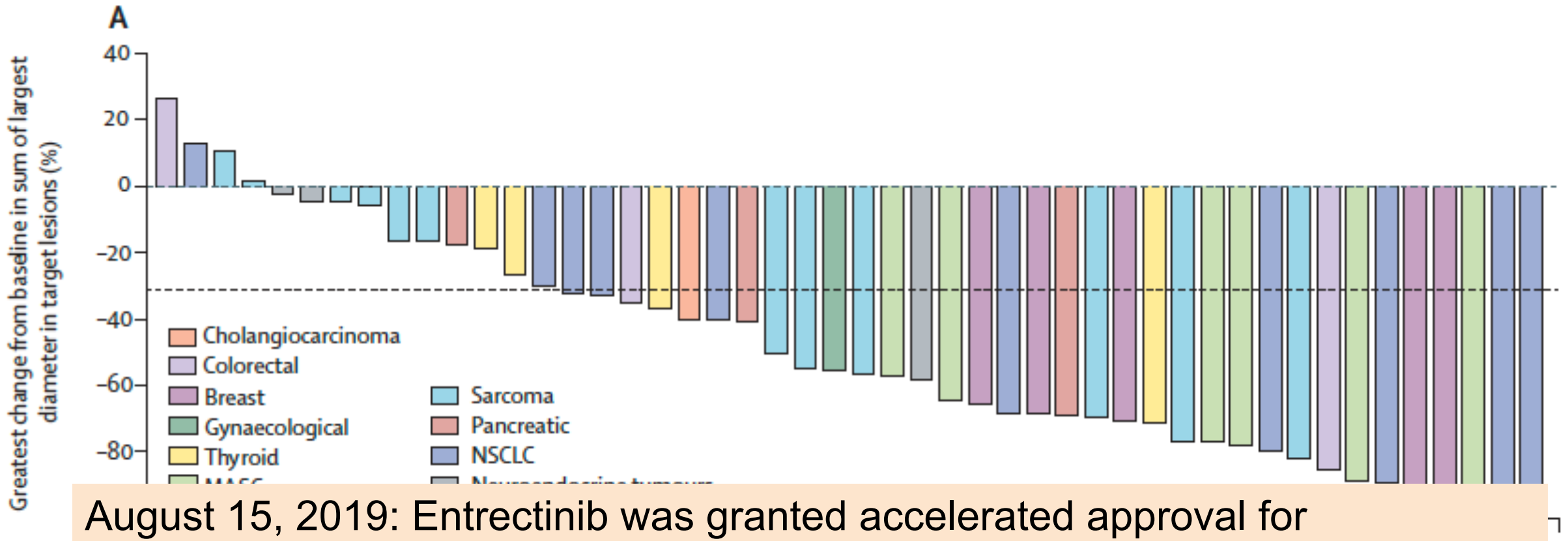
Hong et al, Lancet Oncology 2020

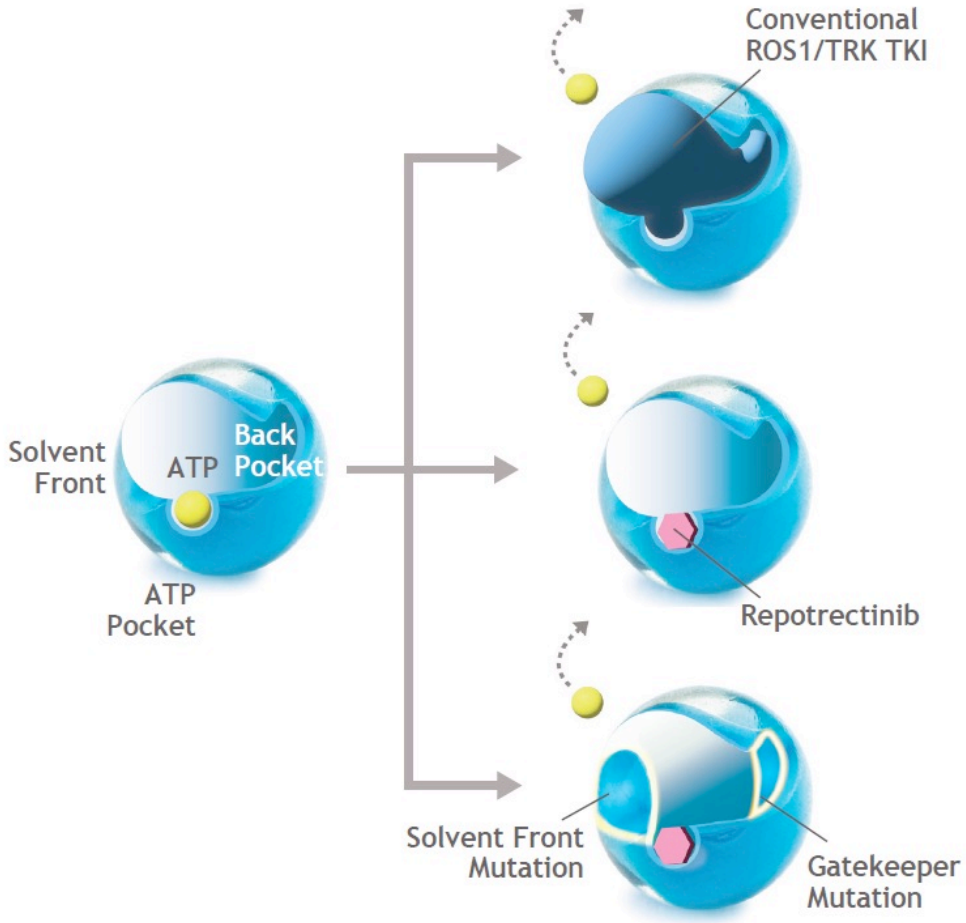
Entrectinib is highly active in solid tumors with NTRK fusions



August 15, 2019: Entrectinib was granted accelerated approval for adult/pediatric patients with solid tumors that have a *NTRK* gene fusion

Doebele et al, Lancet Oncology 2020

TRIDENT study of Repotrectinib for NTRK fusion: mechanism of action

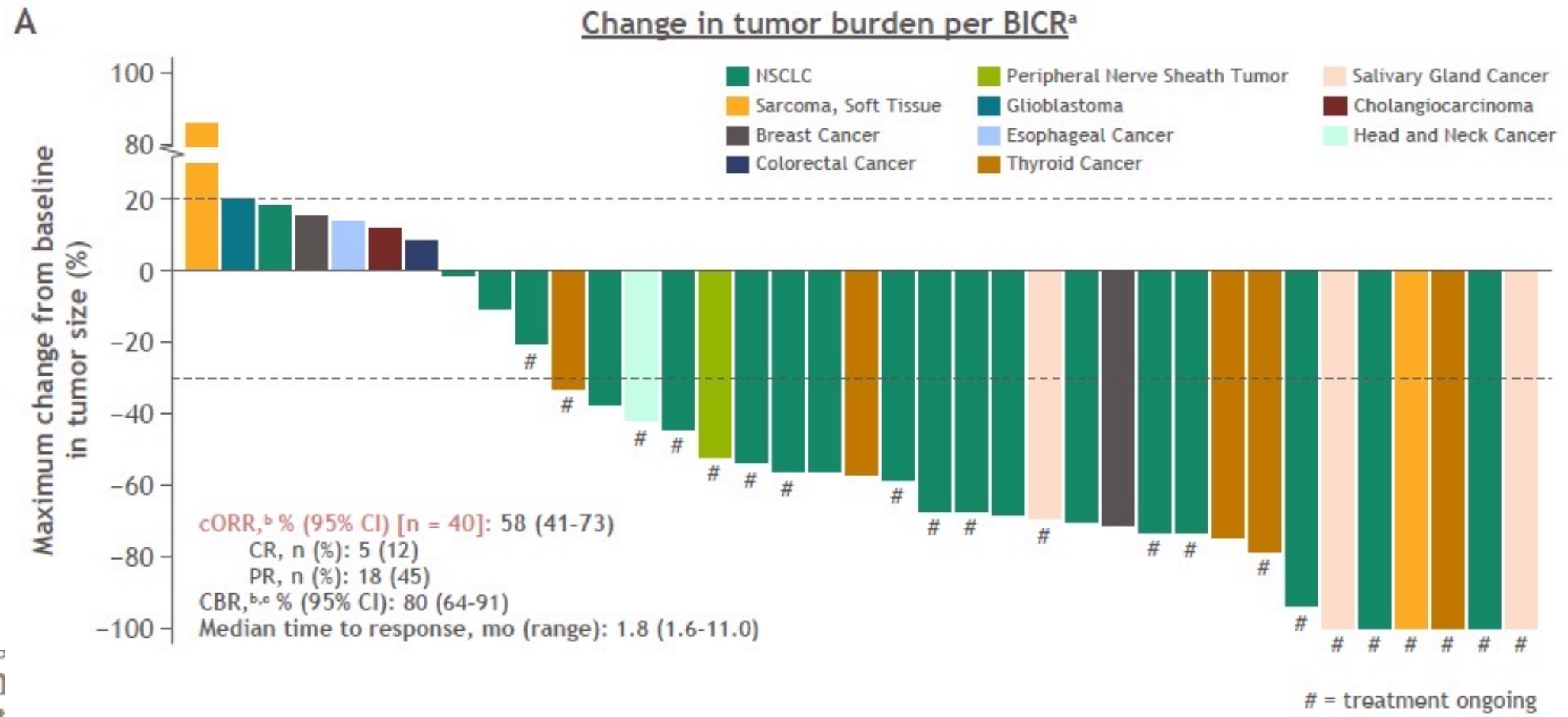


Activity against TRK fusions with solvent front or gatekeeper resistance mutations

B.J. Solomon, et. al., Abstract 1372P, ESMO Congress 2023

Change in tumor burden per BICR in TRK TKI-naïve patients with NTRK+ locally advanced/metastatic solid tumors

ORR 58% in TKI naïve patients (N=40)



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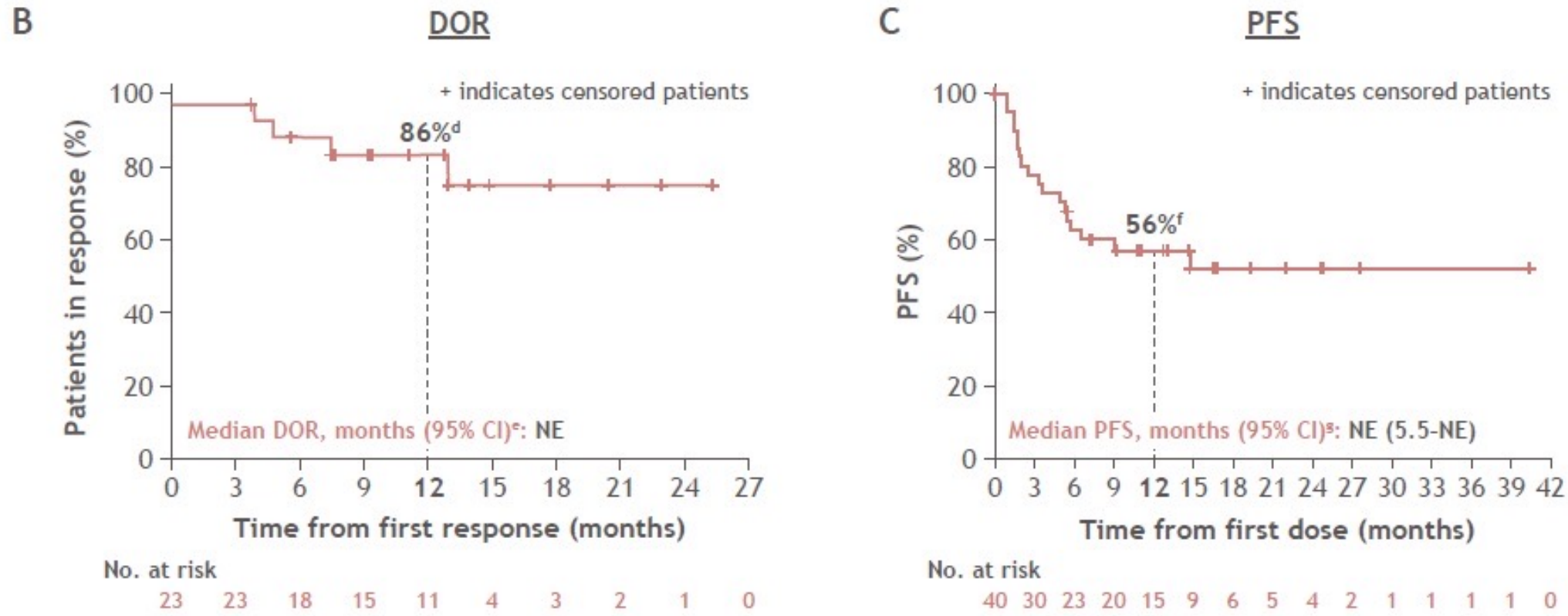
B.J. Solomon, et. al., Abstract 1372P, ESMO Congress 2023

DOR and PFS per BICR in TRK TKI-naïve patients with NTRK+ locally advanced/metastatic solid tumors



Median follow-up: 17.8 months.

[a]Two patients with NSCLC and 1 patient with soft tissue sarcoma had no post-baseline scan. [b]By RECIST v1.1. [c]CBR was defined as CR + PR + SD; 22% (n = 9) and 12% (n = 5) of patients, respectively, had SD or PD. [d]95% CI, 71–100. [e]Number of events/censored, 4/19; DOR range, 3.7+ months to 25.2+ months; 11 (52%) responders remain on treatment. [f]95% CI, 40–72. [g]Number of events/censored, 18/22; PFS range, 0.0+ months to 40.4+ months; 21 (53%) patients remain on treatment.
NE, not estimable.

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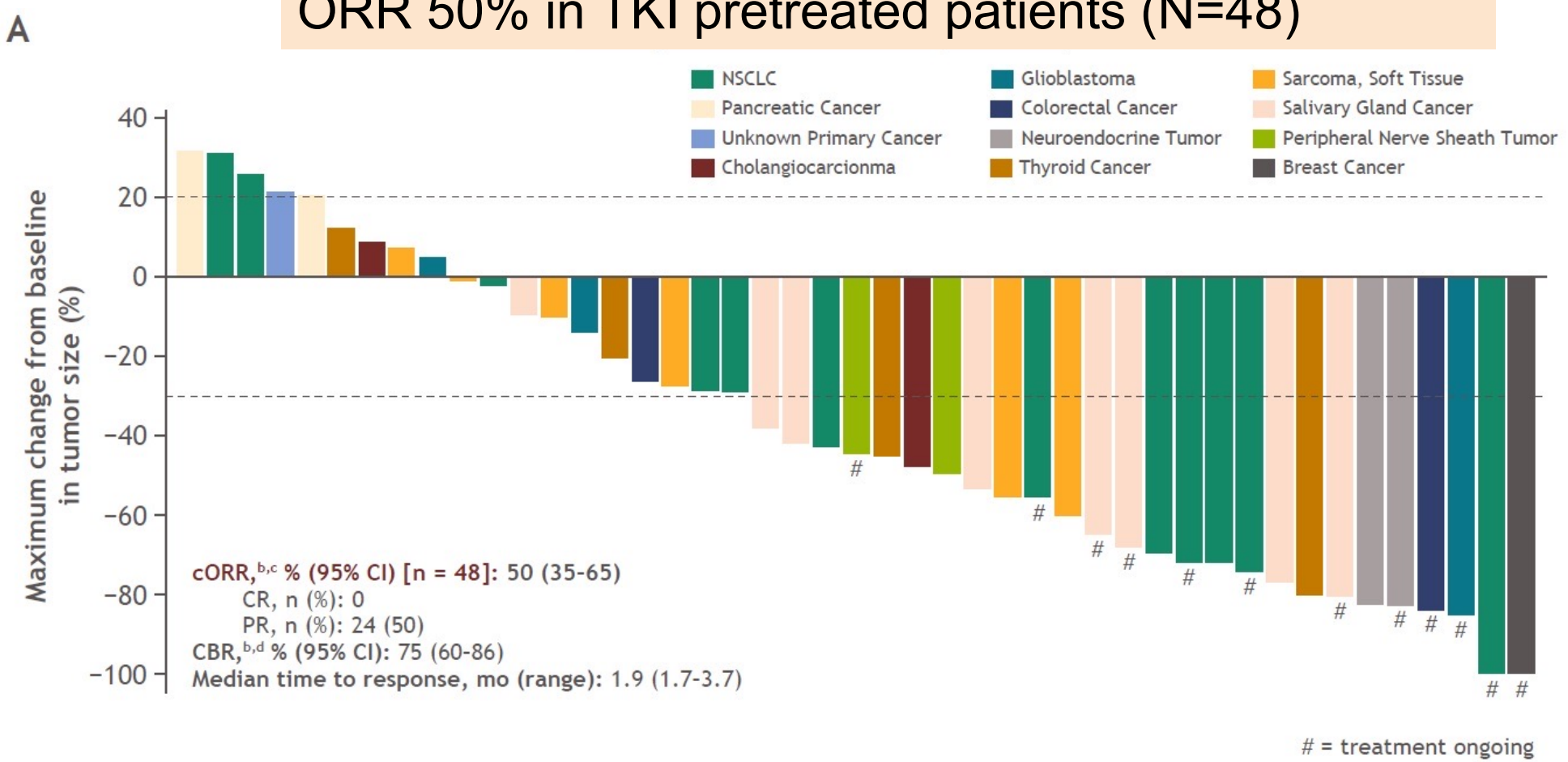
B.J. Solomon, et. al., Abstract 1372P, ESMO Congress 2023

Change in tumor burden per BICR in TRK TKI-pretreated patients with NTRK+ locally advanced/metastatic solid tumors

ORR 50% in TKI pretreated patients (N=48)



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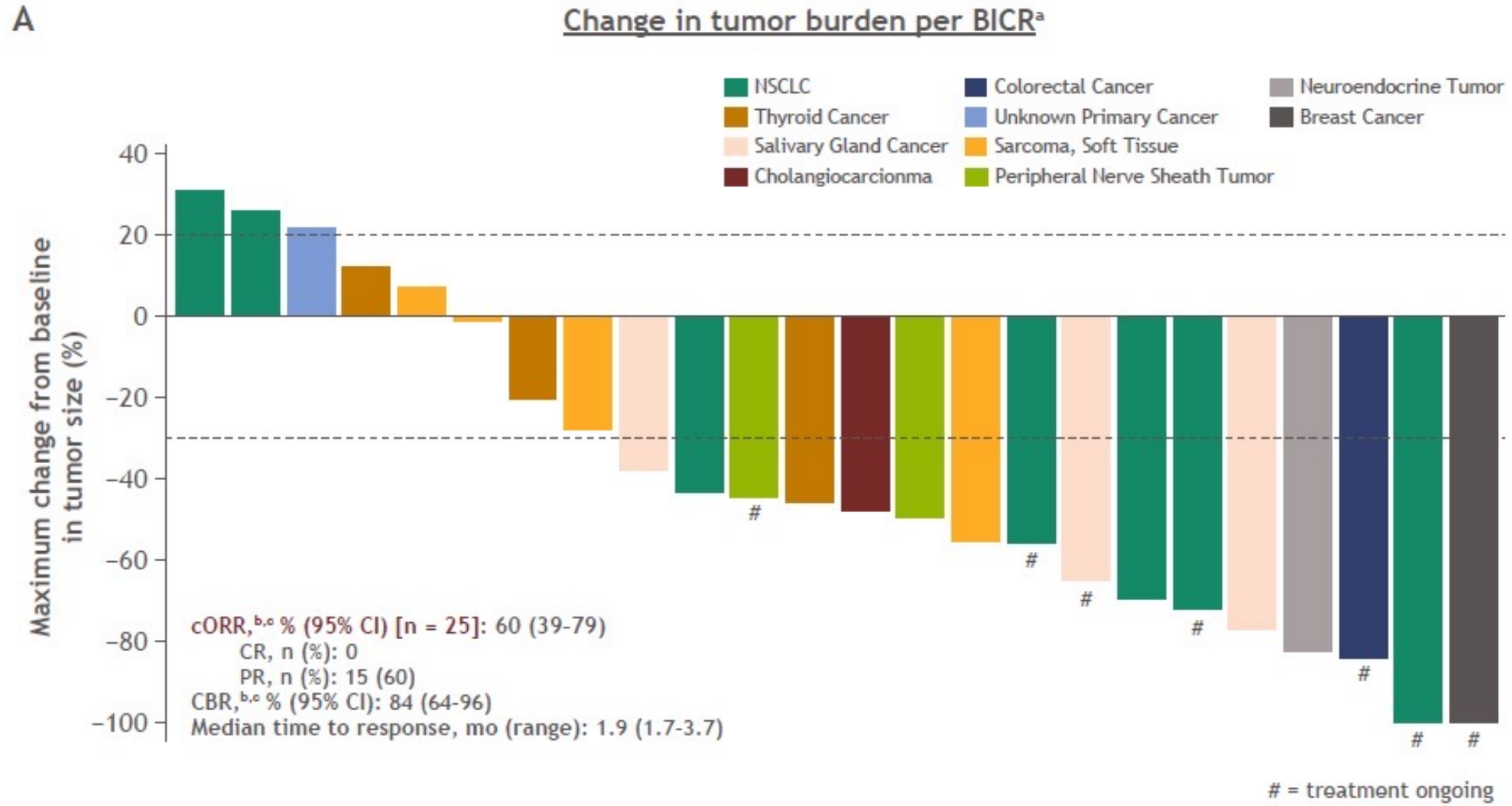
B.J. Solomon, et. al., Abstract 1372P, ESMO Congress 2023

Change in tumor burden per BICR in TRK TKI-pretreated patients with NTRK+ locally advanced/metastatic solid tumors and solvent front mutation



B.J. Solomon, et. al., Abstract 1372P, ESMO Congress 2023

Bottom line: RET and NTRK fusions

- Approved options for both
  - –RET fusions: pralsetinib and selpercatinib
    - New drugs that inhibit resistance mechanisms (e.g. EP0031)
  - –NTRK fusions: Larotrectinib, entrectinib
    - Repotrectinib with high activity in TRIDENT study
- Many new TKIs coming to target on-target resistance
  - –BUT: off-target resistance remains a persistent issue