Understanding Molecular Pathology and Targeting the Bulls Eye in Cancer Therapy: Targeted Therapy for Lung Cancer -Approaches to the Management of Patients with DRIVER Mutations

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Chief, Early Phase Drug Development
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How did we treat advanced cancers like NSCLC before targeted therapy & before immunotherapy ?

Palmistry

Crystal Ball

Evolution in Astronomy

Galileo Telescope to Hubble to James Webb telescope

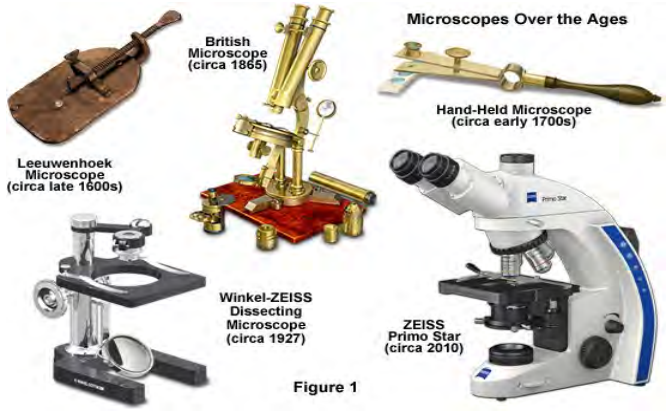
Jupiters moons –Galileo saw using an amateur telescope

1st public image: Cluster of galaxies SMACS 0723,Credit: NASA, ESA, CSA, and STScI

Twitter/X @VivekSubbiah

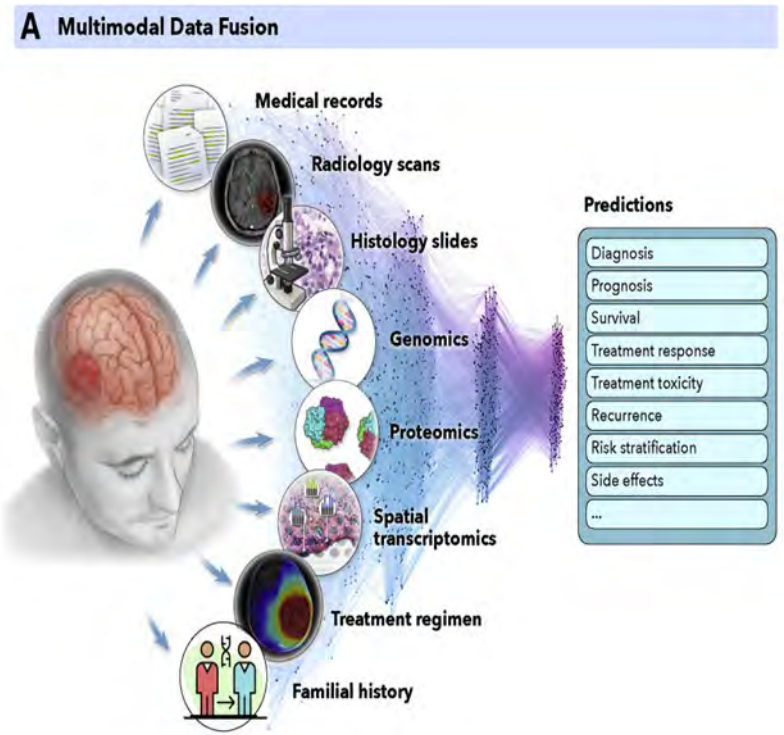
Evolution in Oncology

Light microscope



Molecular microscope

AI era microscope



Twitter/X @VivekSubbiah

Question # 1

- Which is the most common actionable alteration in metastatic advanced Non-small cell lung cancer ?

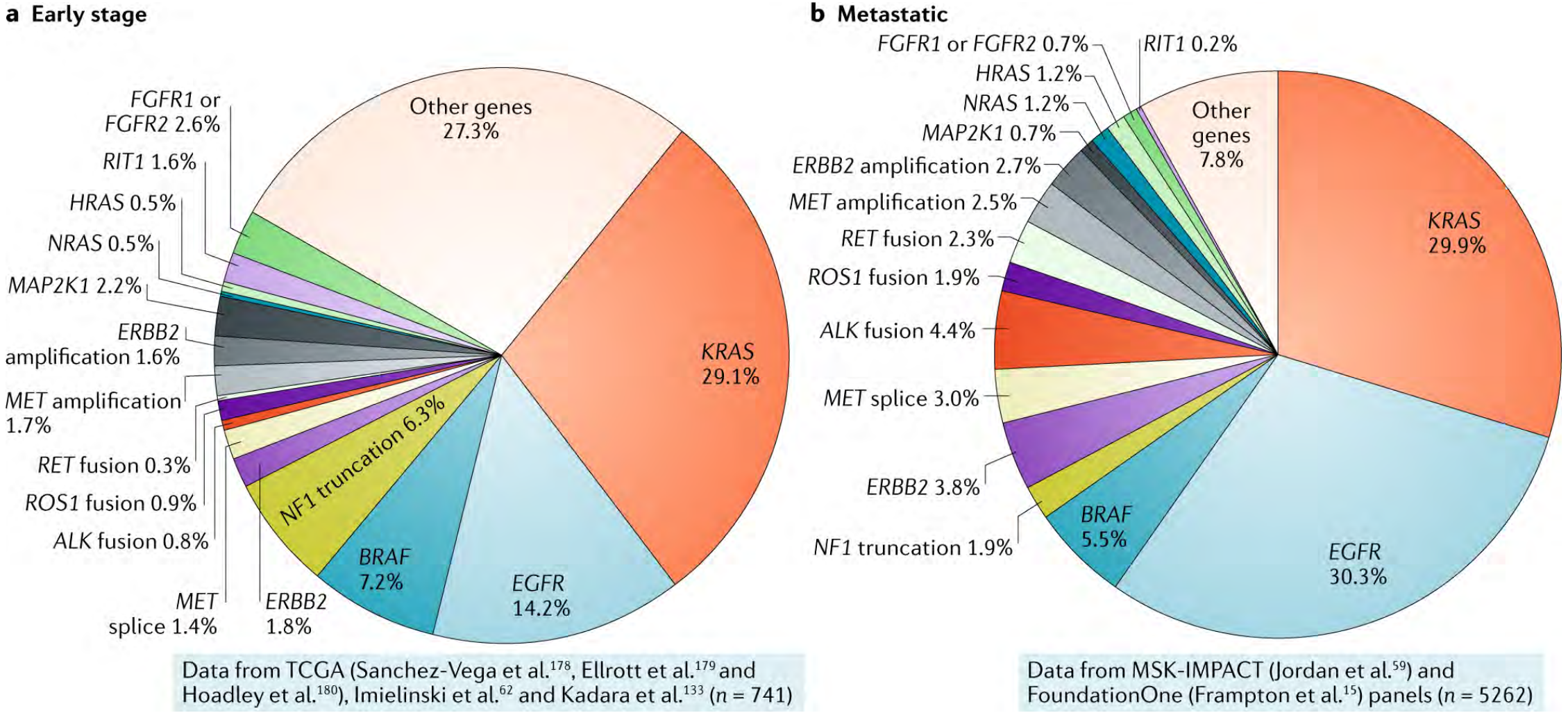
A: KRAS mutation

B: EGFR mutation

C: ALK fusions

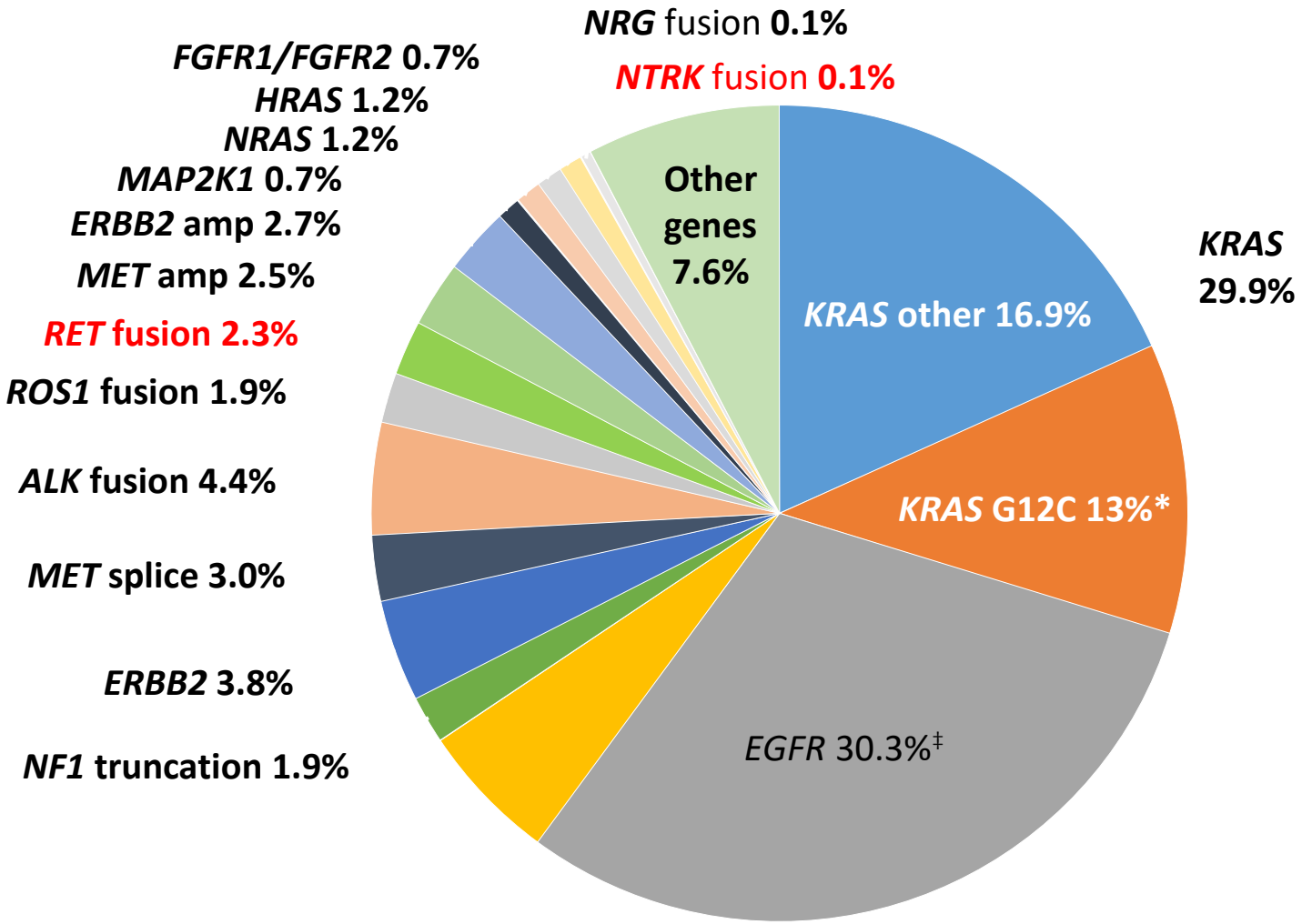
D: RET fusions

Genomics of NSCLC drivers



Skoulidis F. Nat Rev Cancer. 2019

Oncogenic Drivers in Advanced Nonsquamous NSCLC

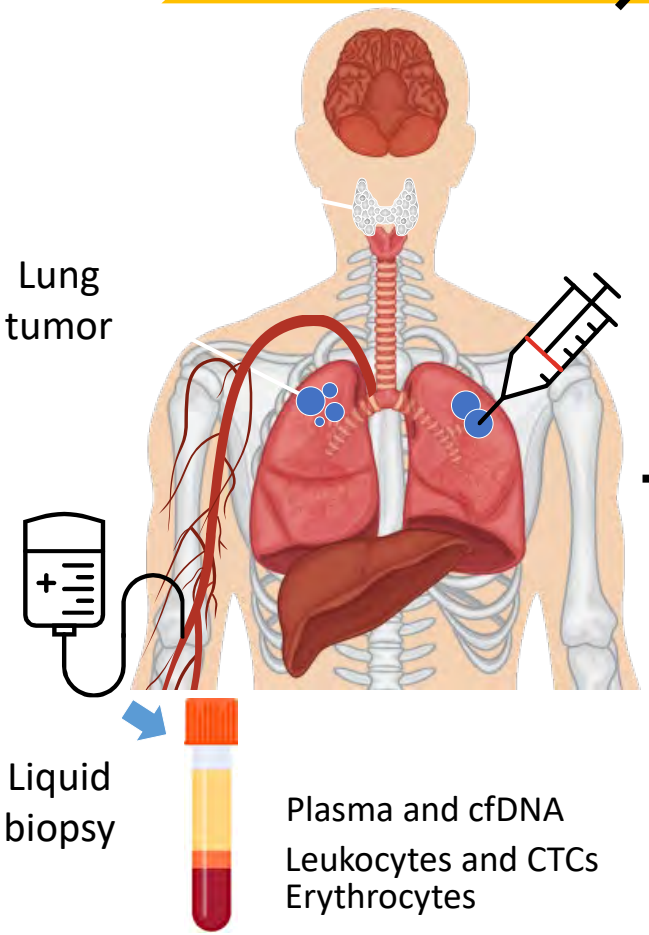


- Actionable biomarkers include *EGFR*‡, *BRAF* V600E, *MET*ex14 skipping, *KRAS* G12C, and *HER2/ERBB2* mutations and *ALK*, *ROS1*, *NTRK*, and *RET* fusions

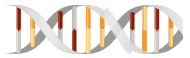
Addeo. Cancer Treat Rev. 2021;96:102179. Palma. NPJ Precis Oncol. 2021;5:98.
NCCN. Clinical practice guidelines in oncology: NSCLC. v.5.2023. nccn.org.

Molecular Testing Techniques

Biopsy → **Sample** → **Analyze** → **Methods**



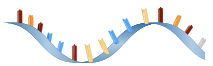
DNA



Single gene
- PCR
- Cancer gene panels
- FISH

Multigene
- NGS

RNA



Single gene
- RT-qPCR
- Gene expression panels

Multigene
- RNA-seq NGS

Protein

Single protein
- IHC

Ascierto. J Mol Diagn. 2019;21:756.

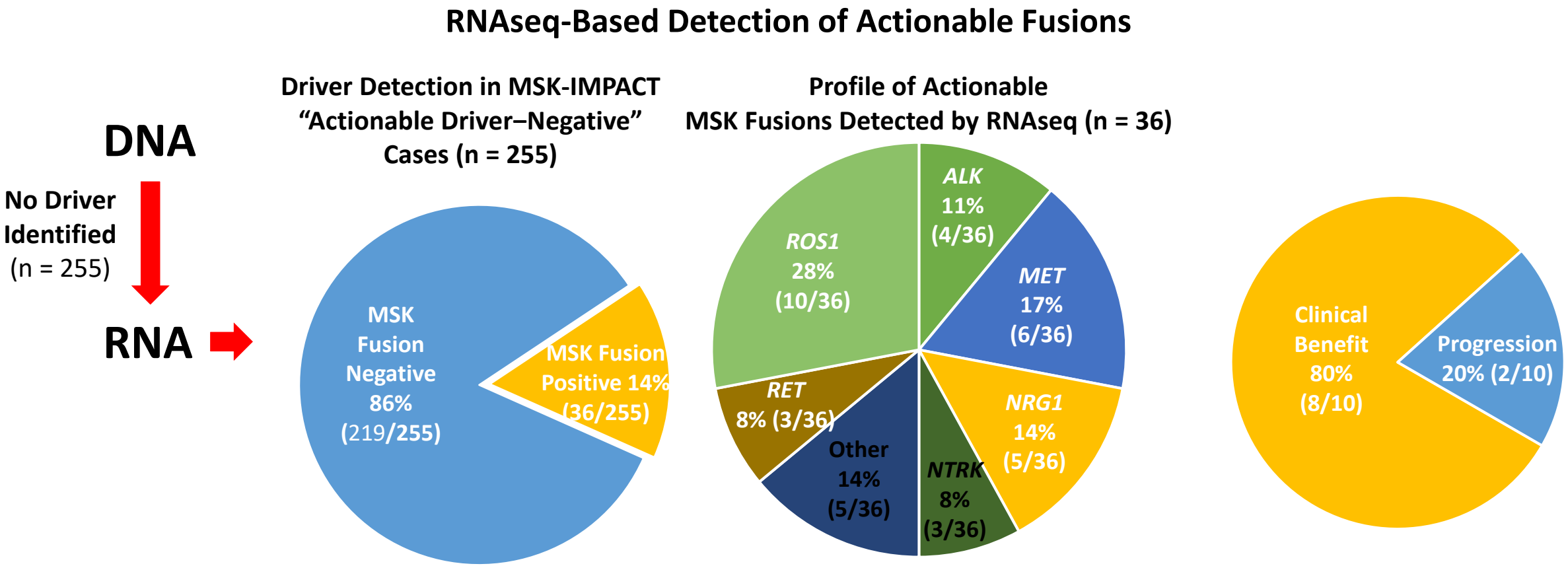
Broad NGS Recommended for Detection of Targetable Driver Alterations in Advanced Lung Cancer

- **All nonsquamous NSCLC:** *EGFR,* including *EGFR* ex20ins, *BRAF* V600E, *MET*ex14, *KRAS* G12C, and *HER2* mutations and ***ALK, ROS1, RET*, and *NTRK* fusions**
  - Important to wait for NGS results before acting on PD-L1 testing for IO
  - For squamous NSCLC, consider testing in young, never/light smokers, and female patients, or if biopsy specimen is of mixed histology
- Tissue biopsy is gold standard; preferred for detection of gene fusions by RNA NGS
  - Liquid biopsy (ie, cfDNA in plasma) useful in NSCLC when inadequate tissue, incomplete results from tissue testing; simultaneous use with tissue testing can increase biomarker detection
  - Limited utility of liquid biopsy in thyroid cancer

NCCN. Clinical practice guidelines in oncology: NSCLC. v.5.2023. nccn.org.
NCCN. Clinical practice guidelines in oncology: thyroid carcinoma. v.4.2023. nccn.org.
Pennell. ASCO Educ Book. 2019;39:351. Lindeman. J Thorac Oncol. 2018;13:323. Rolfo. J Thorac Oncol. 2021;16:1647.

Targeted RNA Sequencing More Sensitive for Detection of Oncogenic Gene Fusions Than DNA-Based NGS

- **RNAseq identified targetable fusions in 14% of driver-negative cases by DNA NGS**



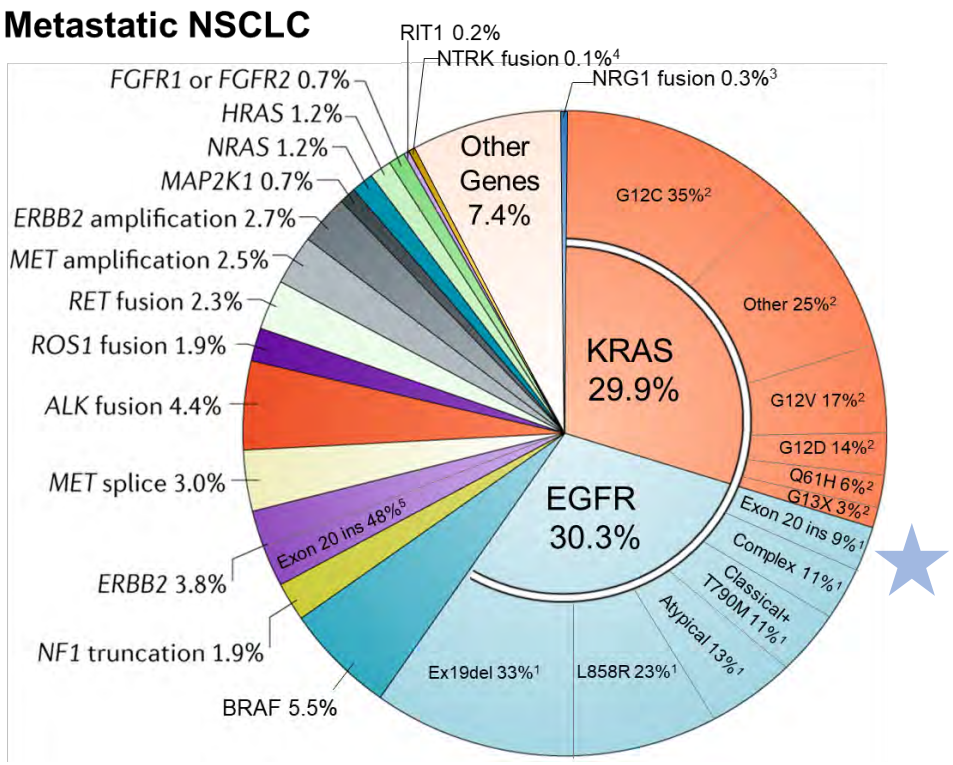
Benayed. ASCO 2018. Abstr 12076. Benayed. Clin Cancer Res. 2019;25:4712.

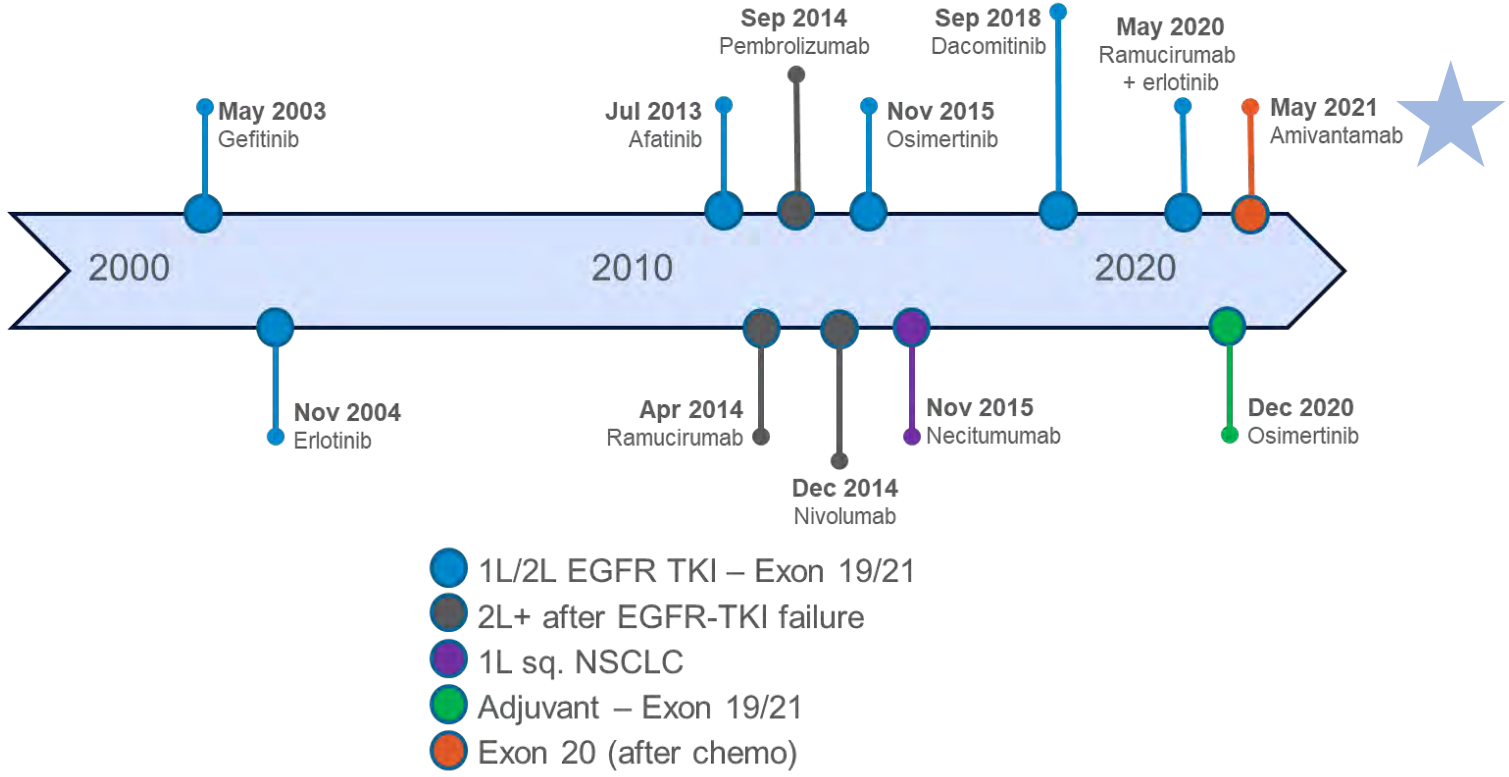
Important Considerations for Biomarker Testing

- Not all alterations listed on NGS report will be actionable (eg, VUS)
- For help interpreting complicated findings on NGS reports:
  - If available, ask to present your case at nearby Molecular Tumor Board
  - Reach out to local or regional experts in field for advice
  - Use virtual options provided by testing vendors
- Communicating with patients about importance of waiting for NGS results
  - Personalize treatment to most efficacious and safe option for their specific tumor profile
  - Potential for oral therapy vs IV infusion
- Potential need for more tissue
- Resources about patient advocacy groups, especially for rare diseases

EGFR

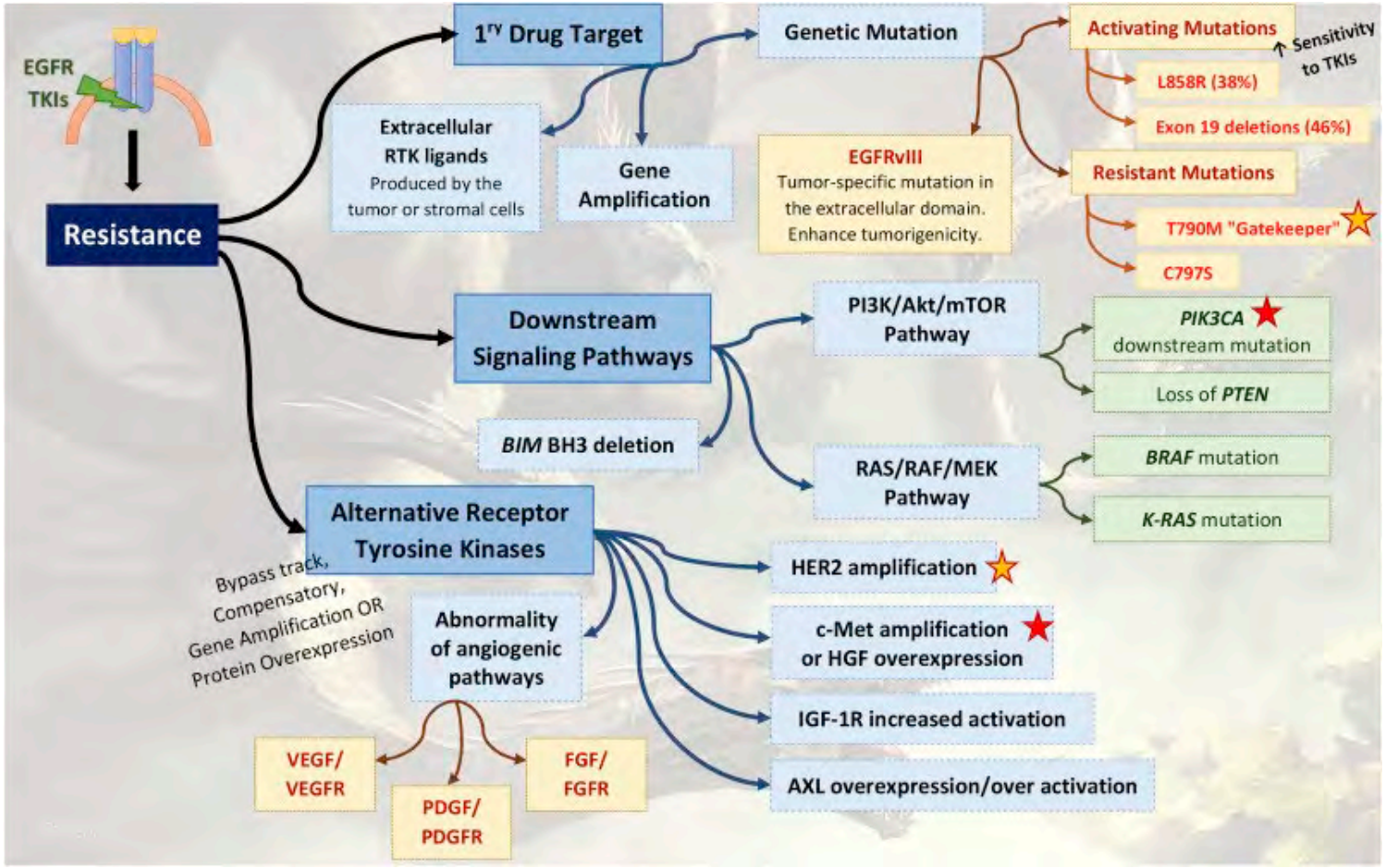
Timeline of EGFR-indicated Treatments





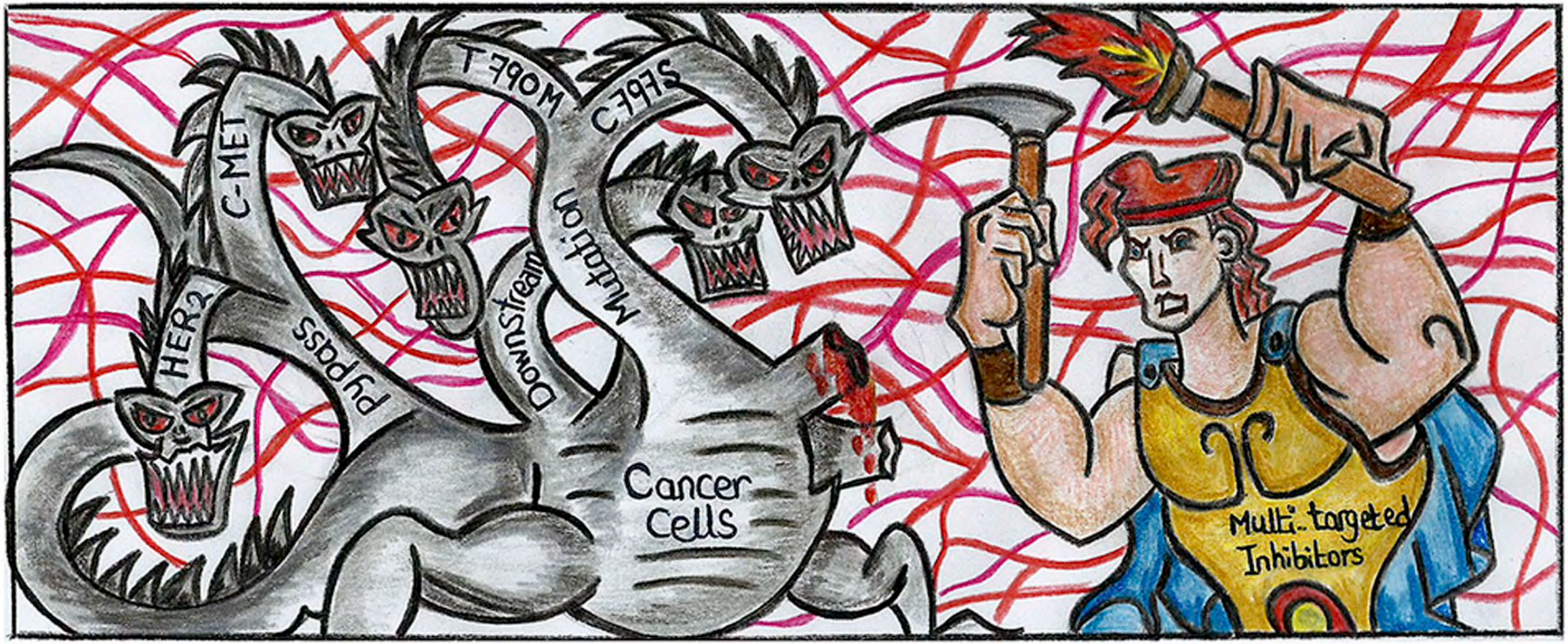
Adapted from Skoulidis and Heymach 2019 Nat Rev Can
[1] Robichaux et al 2020 WCLC
[2] Mack et al 2020 Cancer
[3] Jonna et al 2019 Clin Can Res
[4] Russo et al 2020 Precis Cancer Med
[5] Robichaux et al 2019 Cancer Cell

EGFR resistance mechanisms



Milik SN, Eur J Med Chem. 2017 Dec 15

Combating EGFR resistance mechanisms is a Herculean task

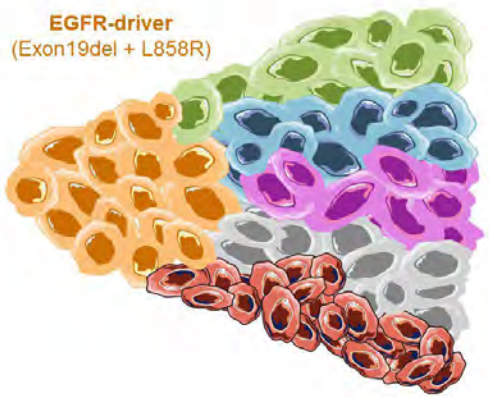


Milik SN, Eur J Med Chem. 2017 Dec 15

Acquired Resistance to Osimertinib in EGFRm NSCLC

Osimertinib → **Platinum Chemotherapy**

Primary Mutations → **Resistance Mutations**



EGFR-driver
(Exon19del + L858R)

EGFR-dependent
(C797S)

MET-dependent
(MET amplification)

Other Pathways
(PIK3CA, RAS/RAF, Fusions, Cell Cycle)

Unknown
(~40-50%)

Transformations

Osimertinib resistance is complex

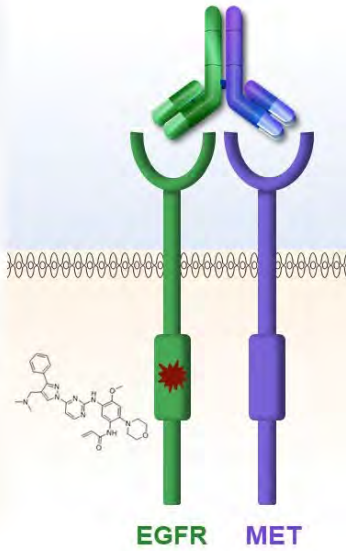
- Heterogenous patterns of resistance
- Co-occurrence of multiple resistance mechanisms
- NGS of ctDNA has been the most frequently used method to characterize osimertinib resistance mechanisms due to difficulties in obtaining tissue[1-2]

Amivantamab (am-e-van-tuh-mab)

- Fully human bispecific antibody that targets EGFR and MET
- Fc portion has immune cell-directing activity[1]
- Demonstrated clinical activity across diverse EGFRm NSCLC[2-4]
- Granted Breakthrough Therapy Designation for EGFRm Exon20ins NSCLC post-chemotherapy in US and China

Lazertinib (la-zer-tin-ib)

- Potent 3rd-gen TKI with efficacy in activating EGFR mutations, T790M, and CNS disease[5-6]
- Low rates of EGFR-related toxicity such as rash and diarrhea[5]
- Low cardiovascular safety risk[7]
- Safety profile that supports combination with other anti-EGFR molecules



DRUG

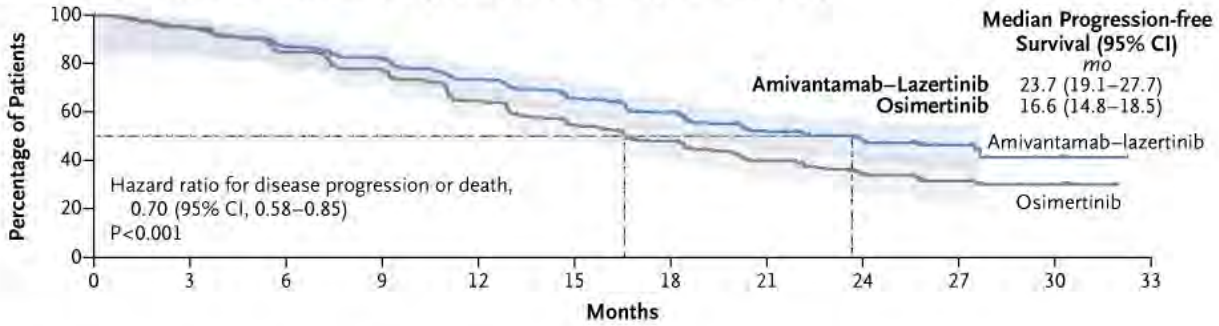
FDA approves lazertinib with amivantamab-vmjw for non-small lung cancer

BREAKING NEWS

ved

On August 19, 2024, the Food and Drug Administration approved lazertinib (Lazcluze, Janssen Biotech, Inc.) in combination with amivantamab-vmjw (Rybrevant, Janssen Biotech, Inc.) for the first-line treatment of locally advanced or metastatic non-small cell

Progression-free Survival in the Amivantamab–Lazertinib Group as Compared with the Osimertinib Group



No. at Risk

Amivantamab–lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Amivantamab plus Lazertinib in Previously Untreated *EGFR*-Mutated Advanced NSCLC

B.C. Cho, S. Lu, E. Felip, A.I. Spira, N. Girard, J.-S. Lee, S.-H. Lee, Y. Ostapenko, P. Danchaivijitr, B. Liu, A. Alip, E. Korbenfeld, J. Mourão Dias, B. Besse, K.-H. Lee, H. Xiong, S.-H. How, Y. Cheng, G.-C. Chang, H. Yoshioka, J.C.-H. Yang, M. Thomas, D. Nguyen, S.-H.I. Ou, S. Mukhedkar, K. Prabhash, M. D'Arcangelo, J. Alatorre-Alexander, J.C. Vázquez Limón, S. Alves, D. Stroyakovskiy, M. Peregudova, M.A.N. Şendur, D. Yazici, R. Califano, V. Gutiérrez Calderón, F. de Marinis, A. Passaro, S.-W. Kim, S.M. Gadgeel, J. Xie, T. Sun, M. Martinez, M. Ennis, E. Fennema, M. Daksh, D. Millington, I. Leconte, R. Iwasawa, P. Lorenzini, M. Baig, S. Shah, J.M. Baum, S.M. Shreeve, S. Sethi, R.E. Knoblauch, and H. Hayashi, for the MARIPOSA Investigators*

ABSTRACT

BACKGROUND
Amivantamab plus lazertinib (amivantamab–lazertinib) has shown clinically meaningful and durable antitumor activity in patients with previously untreated or osimertinib-pretreated *EGFR* (epidermal growth factor receptor)–mutated advanced non–small-cell lung cancer (NSCLC).

METHODS
In a phase 3, international, randomized trial, we assigned, in a 2:2:1 ratio, patients with previously untreated *EGFR*-mutated (exon 19 deletion or L858R), locally advanced or metastatic NSCLC to receive amivantamab–lazertinib (in an open-label fashion), osimertinib (in a blinded fashion), or lazertinib (in a blinded fashion, to assess the contribution of treatment components). The primary end point was progression-free survival in the amivantamab–lazertinib group as compared with the osimertinib group, as assessed by blinded independent central review.

RESULTS
Overall, 1074 patients underwent randomization (429 to amivantamab–lazertinib, 429 to osimertinib, and 216 to lazertinib). The median progression-free survival was significantly longer in the amivantamab–lazertinib group than in the osimertinib group (23.7 vs. 16.6 months; hazard ratio for disease progression or death, 0.70; 95% confidence interval [CI], 0.58 to 0.85; P<0.001). An objective response was observed in 86% of the patients (95% CI, 83 to 89) in the amivantamab–lazertinib group and in 85% of those (95% CI, 81 to 88) in the osimertinib group; among patients with a confirmed response (336 in the amivantamab–lazertinib group and 314 in the osimertinib group), the median response duration was 25.8 months (95% CI, 20.1 to could not be estimated) and 16.8 months (95% CI, 14.8 to 18.5), respectively. In a planned interim overall survival analysis of amivantamab–lazertinib as compared with osimertinib, the hazard ratio for death was 0.80 (95% CI, 0.61 to 1.05). Predominant adverse events were *EGFR*-related toxic effects. The incidence of discontinuation of all agents due to treatment-related adverse events was 10% with amivantamab–lazertinib and 3% with osimertinib.

CONCLUSIONS
Amivantamab–lazertinib showed superior efficacy to osimertinib as first-line treatment in *EGFR*-mutated advanced NSCLC. (Funded by Janssen Research and Development; MARIPOSA ClinicalTrials.gov number, NCT04487080.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Cho can be contacted at cbc1971@yuhs.ac or at the Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea.

*A complete list of the investigators in the MARIPOSA trial is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Cho and Lu contributed equally to this article.

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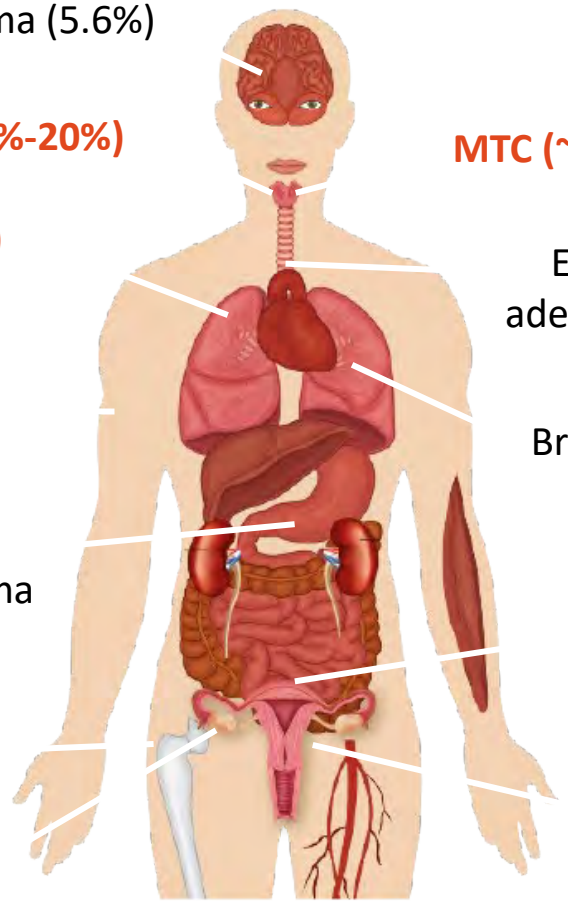
DOI: 10.1056/NEJMoa2403614

Mariposa trial

- MARIPOSA (NCT04487080), a randomized, active-controlled, multicenter trial of 1074 patients with exon 19 deletion or exon 21 L858R substitution mutation-positive locally advanced or metastatic NSCLC and no prior systemic therapy for advanced disease.
- Patients were randomized (2:2:1): Lazertinib+ Amivantamab: Osimertinib monotherapy: Lazertinib monotherapy until disease progression or unacceptable toxicity.
- Lazertinib with amivantamab demonstrated a statistically significant improvement in PFS compared to osimertinib with a hazard ratio of 0.70 (95% confidence interval [CI]: 0.58, 0.85; p-value=0.0002).
- The median PFS=23.7 months (95% CI: 19.1, 27.7) in the lazertinib + amivantamab arm and 16.6 months (95% CI: 14.8, 18.5) in the osimertinib arm.

RET Overview



- Normal role in neural and GU development
- 2 major mechanisms for RET oncogene activation
  - ***RET* gene fusions in NSCLC and DTC (majority in PTC), with many possible fusion partners**
    - KIF5B most common partner in NSCLC, with others including CCDC6, NCOA4, TRIM33
    - CCDC6 and NCOA4 are most common partners in DTC
  - **Gain-of-function *RET* point mutations in MTC**
    - >100 alterations reported

Kato. Clin Cancer Res. 2017;23:1988. Mulligan. Nat Rev Cancer. 2014;14:173. Subbiah. Cancer Discov. 2020;10:498. Thien. Trends Cancer. 2021;7:12. Santoro. Cold Spring Harb Perspect Biol. 2013;5:a009233.

FDA-Approved Selective RET Inhibitors (2023)

Selpercatinib[1]

- Adults with **LA/metastatic NSCLC with *RET* gene fusion**
- Adult/pediatric patients ≥12 yr of age with **advanced/metastatic MTC with *RET* mutation** who require systemic therapy
- Adult/pediatric patients ≥12 yr of age with **advanced/metastatic thyroid cancer with *RET* gene fusion** who require systemic therapy and who are RAI refractory
- Adults with **LA/metastatic solid tumors with *RET* gene fusion** with PD on/following prior systemic therapy or who have no satisfactory alternative treatment options

Pralsetinib[2]

- Adults with metastatic *RET* fusion–positive NSCLC
- Adult/pediatric patients ≥12 yr of age with **advanced or metastatic *RET* fusion–positive thyroid cancer** who require systemic therapy and who are RAI refractory

1. Selpercatinib PI. 2. Pralsetinib PI.

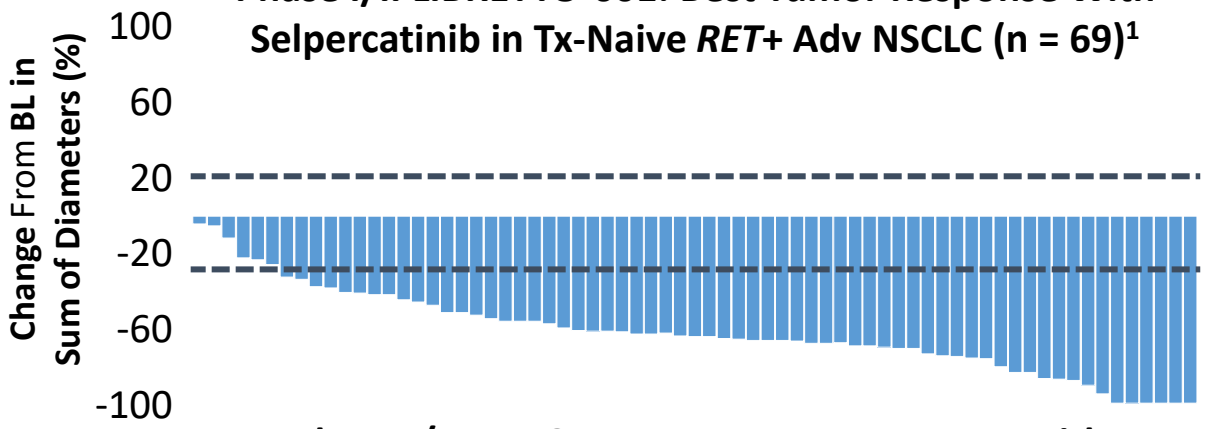
RET Inhibitors in *RET* Fusion–Positive Advanced NSCLC

Selpercatinib[1]	Prior Plt-Based CT (n = 247)	Tx Naive (n = 69)
ORR, %	61	84
Median DoR, mo	28.6	20.2
Median PFS, mo	24.9	22.0

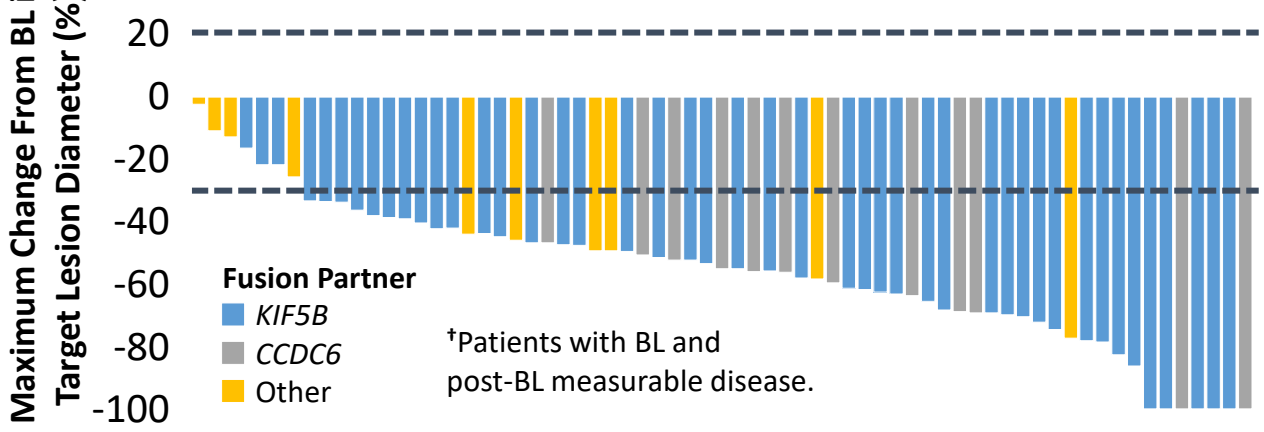
Pralsetinib[2]	Prior Plt-Based CT (n = 136)	Tx Naive* (n = 75)
ORR, %	59	72
Median DoR, mo	22.3	NR
Median PFS, mo	16.5	13.0

*After July 2019, enrollment expanded to include treatment-naive patients eligible for plt-based CT who had not previously been permitted.

Phase I/II LIBRETTO-001: Best Tumor Response With Selpercatinib in Tx-Naive *RET*+ Adv NSCLC (n = 69)[1]



Phase I/II ARROW: Best Tumor Response With Pralsetinib in Tx-Naive *RET*+ Adv NSCLC (n = 67†)[2]

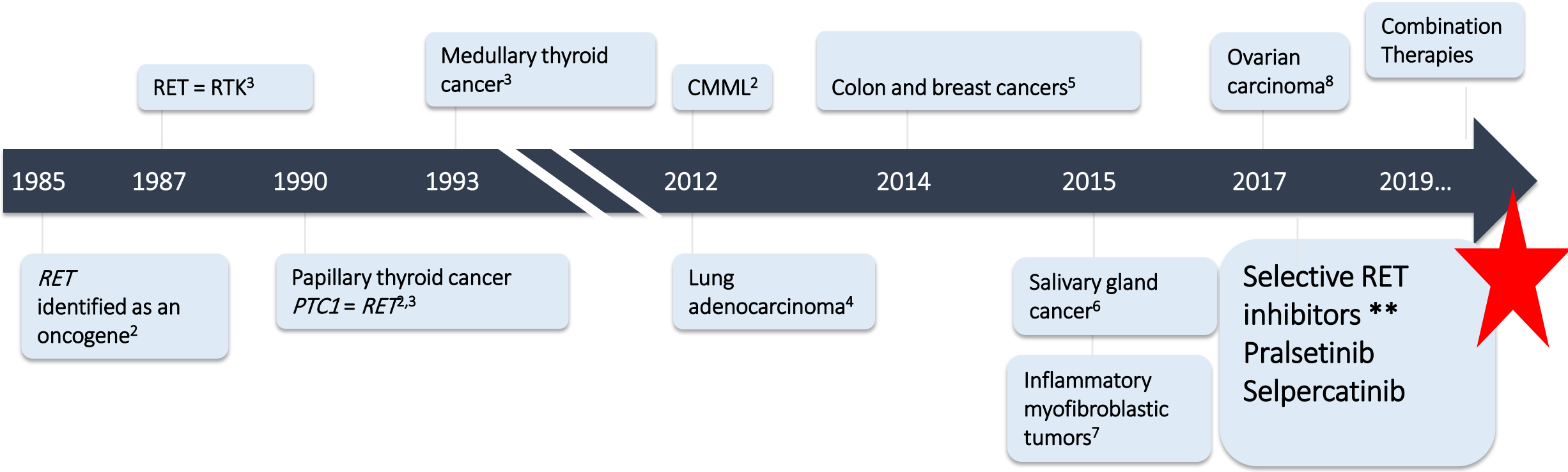


- Intracranial antitumor activity observed in patients with brain metastases at BL[1,2]

1. Drilon. JCO. 2023;41:385. 2. Griesinger. Ann Oncol. 2022;33:1168.

Rapid clinical translation and FDA approval of RET inhibitors

***RET* is one of the first oncogenic kinase fusions cloned from an epithelial tumor, and has since been found to be an oncogenic driver primarily in solid tumors[1,2]**



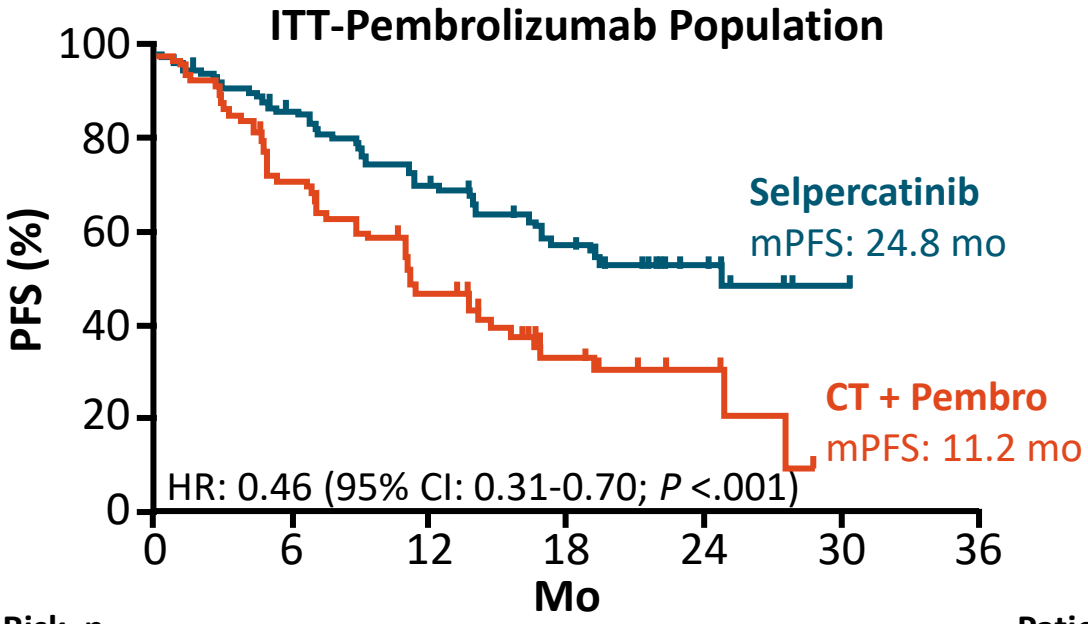
** FDA approval 3 yrs !!!

CMML, chronic myelomonocytic leukemia.

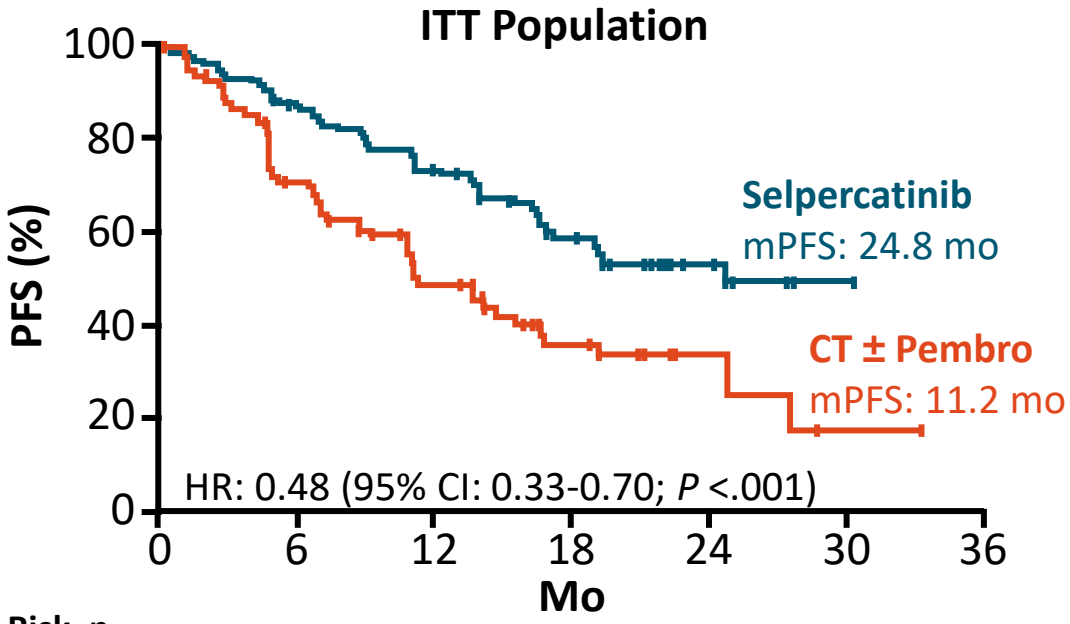
1. Subbiah V et al. *Cancer Discov*. 2018;8(7):836-849. 2. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15(3):151-167. 3. Ibáñez CF. *Cold Spring Harb Perspect Biol*. 2013;5(2):a009134. 4. Ju YS et al. *Genome Res*. 2012;22(3):436-445. 5. Stransky N et al. *Nat Commun*. 2014;5:4846. 6. Grünewald I et al. *Oncotarget.* 2015;6(20):18224-18237.

LIBRETTO-431: Selpercatinib vs Chemotherapy ± Pembrolizumab in *RET* Fusion–Positive NSCLC

- International, randomized, open-label phase III trial



Patients at Risk, n							
Selpercatinib	129	105	72	44	16	2	0
CT + Pembro	83	55	29	15	6	0	0



Patients at Risk, n							
Selpercatinib	159	130	90	52	18	3	0
CT ± Pembro	102	63	33	16	7	1	0

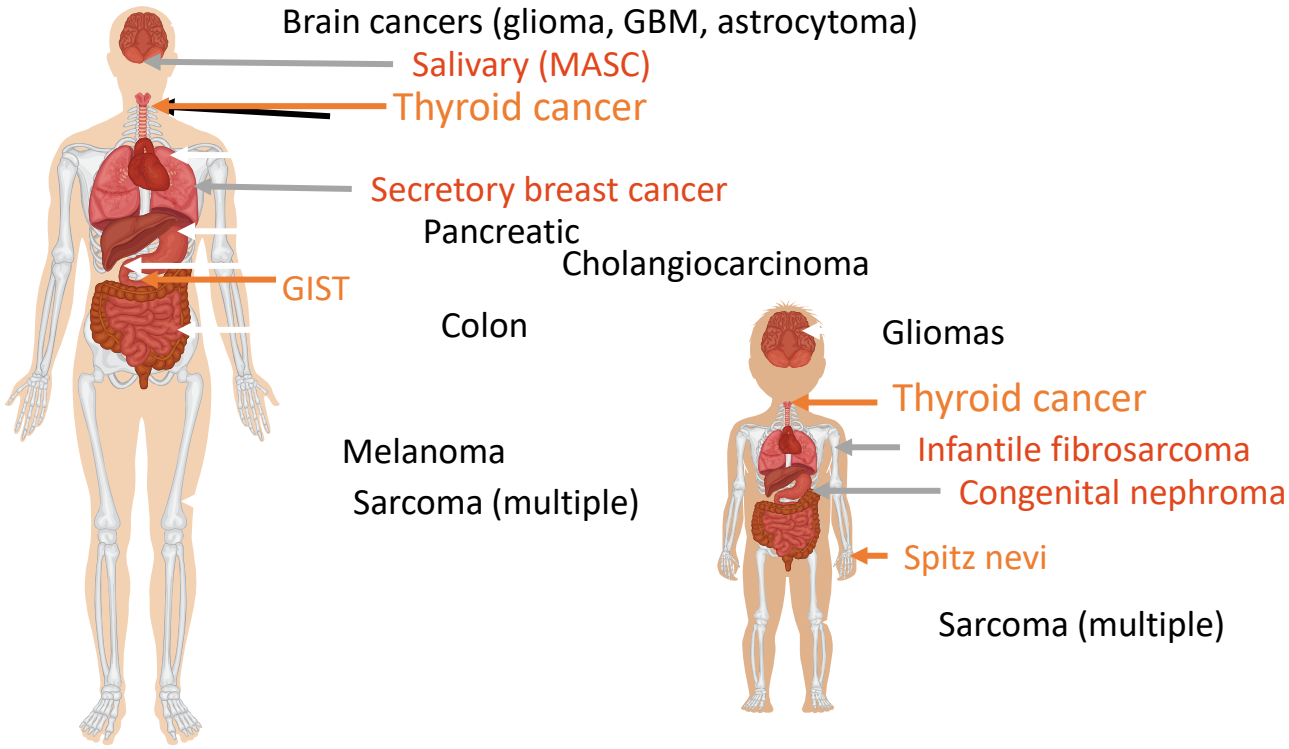
- Selpercatinib yielded statistically significant improvement in PFS vs control in both ITT-pembrolizumab and ITT populations, meeting both primary endpoints

Loong. ESMO 2023. Abstr LBA4. Zhou. NEJM. 2023;[Epub].

NTRK Overview

- Normal role in neuronal development; expression limited to CNS
- For *NTRK* genes, **FUSIONS** are activating, predictive of response to targeted therapy
  - Typically results in intracellular fusion protein with constitutively activated or overexpressed kinase domain
- For *NTRK* genes, **MUTATIONS** do **NOT** appear to be oncogenic driver events
  - Typically results in abnormal protein product

NTRK Fusions Are Rare Events:
0.21% Across >11,000 Patients With Tumors of All Types



Cancer with <5% *NTRK* fusion
Common cancer with 5%-25% *NTRK* fusions
Rare cancer with high incidence of *NTRK* fusions (>90%)

Supek. Cell. 2014;156. Amatu. ESMO Open. 2016;1:e000023. Cocco. Nat Rev Clin Oncol. 2018;15:731. Amatu. ESMO Open. 2016;1:e000023. Watanabe. Cancer Genet Cytogenet. 2002;136:10. Gatalica. AACR-NCI-EORTC 2017. Abstr A047.

FDA-Approved TRK Inhibitors (2023)

Larotrectinib[1]

- Adult and pediatric patients with **solid tumors with *NTRK* gene fusion** without a known acquired resistance mutation who either have **metastatic disease or who are not candidates for surgical resection** due to likely severe morbidity and who have **no satisfactory alternative treatments or whose cancer has progressed following treatment**

Entrectinib[2]

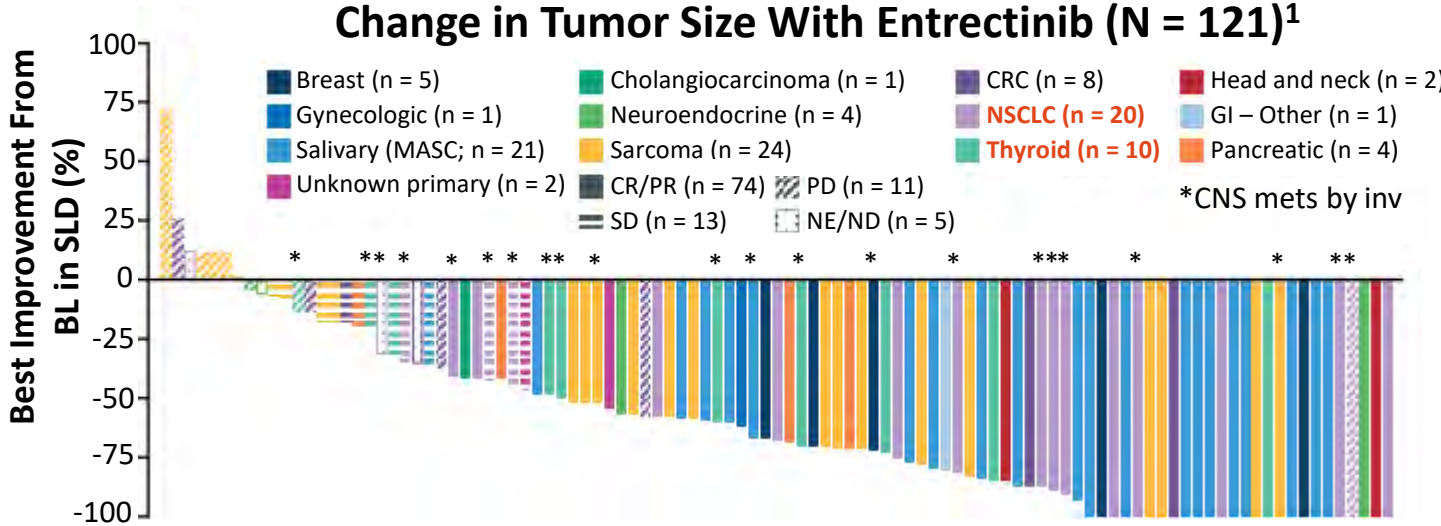
- Adult and pediatric patients ≥1 mo of age with **solid tumors with an *NTRK* gene fusion** without a known acquired resistance mutation who either have **metastatic disease or who are not candidates for surgical resection** due to likely severe morbidity and who have **no satisfactory alternative treatments or whose cancer has progressed following treatment**
- Adult patients with *ROS1*-positive metastatic NSCLC

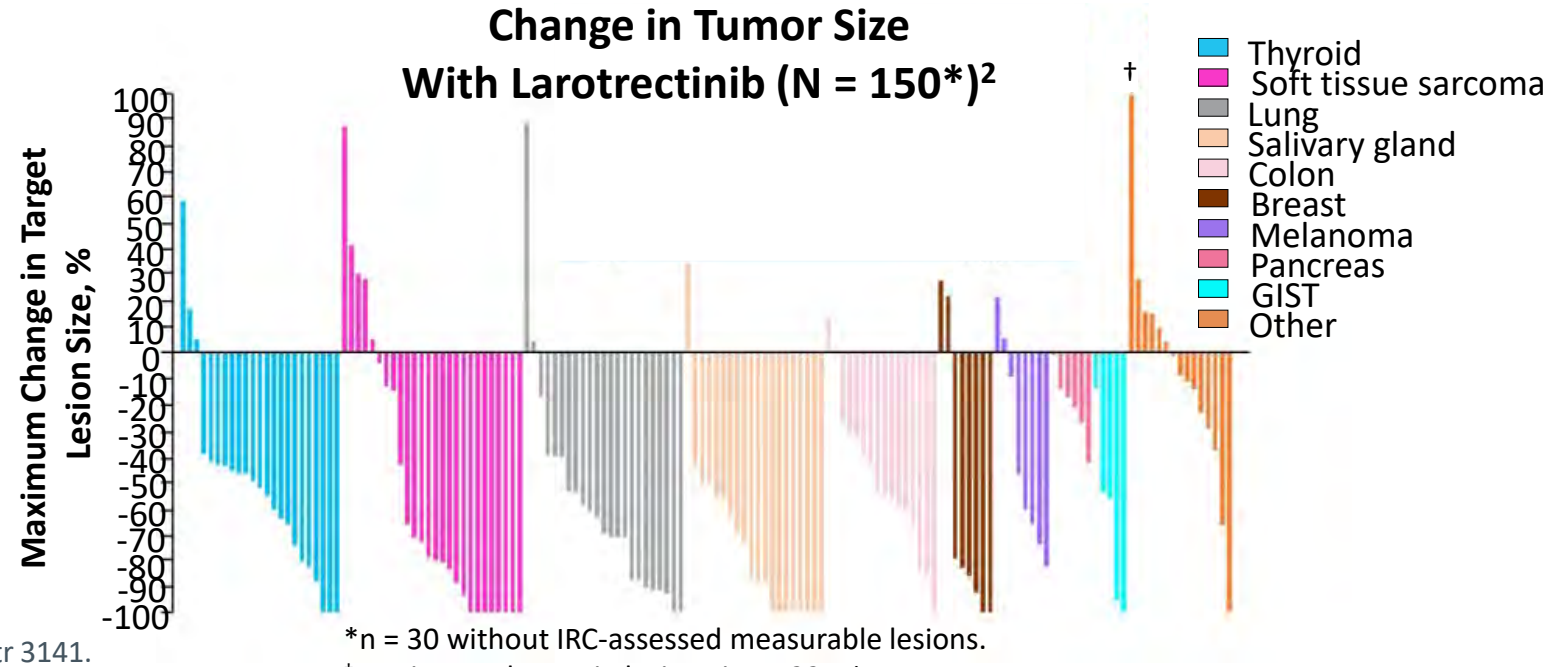
1. Larotrectinib PI. 2. Entrectinib PI.

TRK Inhibitors Are Active in *NTRK* Fusion-Positive Cancers

Entrectinib[1]	N = 121
ORR, % (95% CI)	61.2 (51.9-69.9)
Median DoR, mo	20.0
Median PFS, mo	13.8
Median follow-up, mo	25.8

Larotrectinib[2]	N = 180
ORR, % (95% CI)	57 (50-65)
Median DoR, mo	43.3
Median PFS, mo	24.6
Median follow-up, mo	48.7





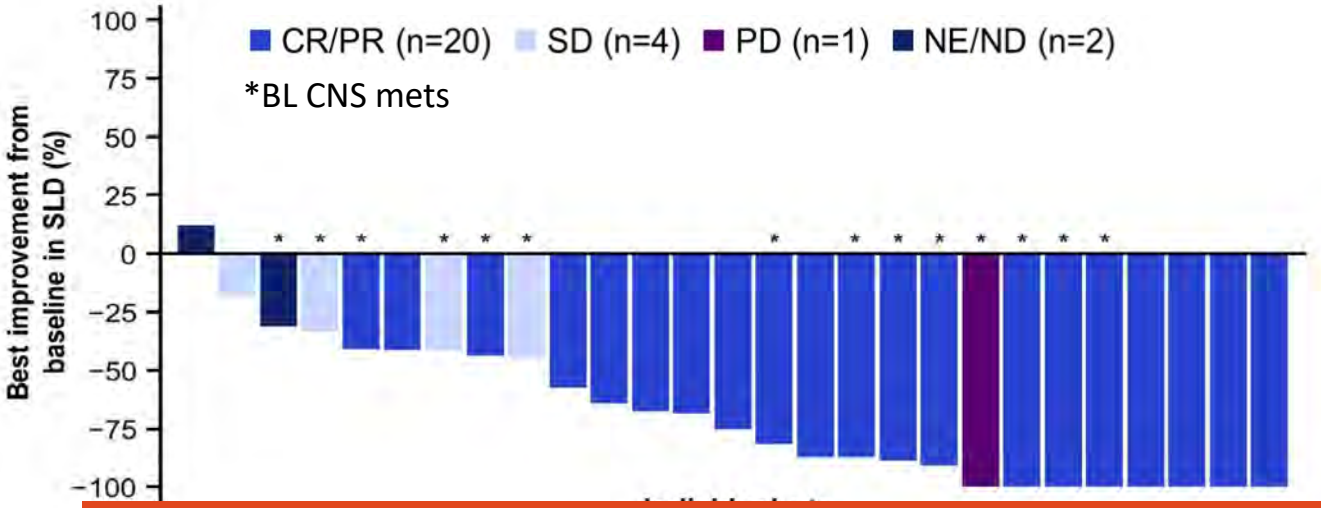
Each is a pooled analysis of 3 studies.

*n = 30 without IRC-assessed measurable lesions.
†Maximum change in lesion size: +227%.

1. Demetri. Clin Cancer Res. 2022;28:1302. 2. Hong. ASCO 2023. Abstr 3141.

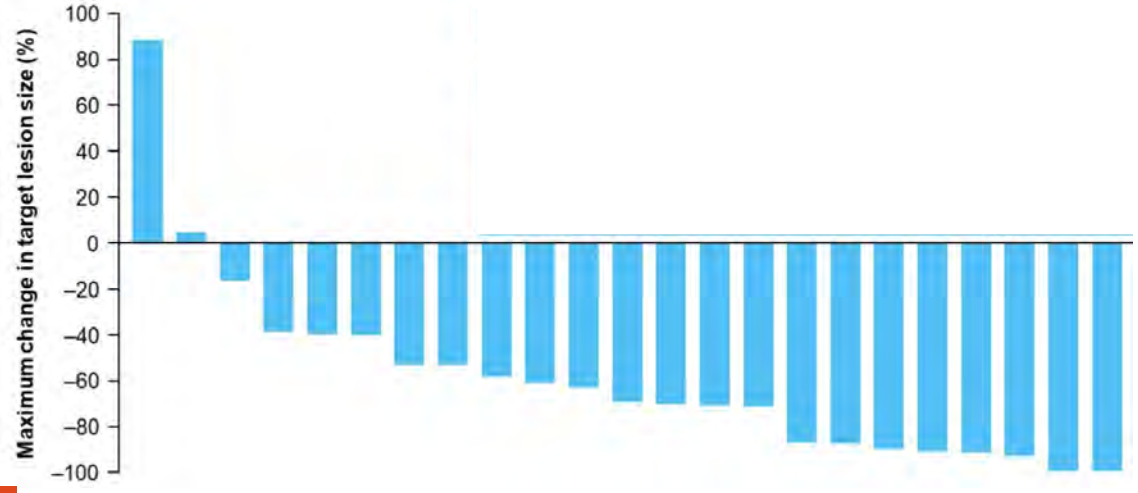
TRK Inhibitors in *NTRK* Fusion–Positive NSCLC

Antitumor Activity with Entrectinib (n = 27)



Efficacy by BICR	Total (N = 31)	BL CNS Mets (n = 15)	No CNS Mets (n = 16)
ORR, %	64.5	60	68.8
mDoR, mo	27.1	29.4	19.9
mPFS, mo	20.8	30.3	20.8
mOS, mo	NE	NR	NR

Antitumor Activity with Larotrectinib (n = 23†)



Efficacy by BICR	Total (N = 30)
ORR, %	74
mDoR, mo	33.9
mPFS, mo	33.0
mOS, mo	39.3

†n = 4 without IRC measurable lesions.

- Intracranial antitumor activity observed in patients with brain metastases at BL[3-5]

1. Cho. ASCO 2023. Abstr 9047. 2. Lin. ASCO 2023. Abstr 9056. 3. Drilon. ASCO 2019. Abstr 2006.
4. Doebele. Lancet Oncol. 2020;21:271. 5. Rosen. JCO Precis Oncol. 2019;3:PO.19.00009

BREAKING NEWS

FDA approval of Repotrectinib in NTRK + cancers

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l to repotrectinib for adult and pediatric patients with NTRK gene fusion-positive solid tumors

FDA grants accelerated approval to repotrectinib for adult and pediatric patients with NTRK gene fusion-positive solid tumors

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On June 13, 2024, the Food and Drug Administration granted accelerated approval to repotrectinib (AUGTYRO, Bristol-Myers Squibb Company) for adult and pediatric patients 12 years and older with solid tumors that have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion, are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and that have progressed following treatment or have no satisfactory alternative therapy.

Full prescribing information for Augtyro will be posted on Drugs@FDA.

Efficacy and Safety

Efficacy was evaluated in TRIDENT-1 (NCT03093116), a multicenter, single-arm, open-label, multi-cohort trial in 88 adult patients with locally advanced or metastatic *NTRK* gene fusion-positive solid tumors who had either received a prior TRK tyrosine kinase inhibitor (TKI) (n=48) or were TKI-naïve (n=40). All patients were assessed for central nervous (CNS) lesions at baseline, and patients with symptomatic brain metastases were excluded. Tumor assessments were performed every 8 weeks.

Content current as of:
06/13/2024

Efficacy and Safety data per FDA label

- Efficacy was evaluated in TRIDENT-1 (NCT03093116), a multicenter, single-arm, open-label, multi-cohort trial in 88 adult patients with locally advanced or metastatic *NTRK* gene fusion-positive solid tumors who had either received a prior TRK tyrosine kinase inhibitor (TKI) (n=48) or were TKI-naïve (n=40).
- **Confirmed ORR:**
- TKI-naïve group= 58% (95% [confidence internal] CI: 41, 73), Med DOR = NE
- TKI-pretreated group= 50% (95% CI: 35, 65) Med DOR =9.9 months (95% CI: 7.4, 13.0)
- Most common (>20%) adverse reactions: Dizziness, dysgeusia, peripheral neuropathy, constipation, dyspnea, fatigue, ataxia, cognitive impairment, muscular weakness, and nausea.

NTRK FDA approvals

On November 26, 2018, the Food and Drug Administration granted accelerated approval to larotrectinib (VITRAKVI, Loxo Oncology Inc. and Bayer) for adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.

On August 15, 2019, the Food and Drug Administration granted accelerated approval to entrectinib (ROZLYTREK, Genentech Inc.) for adults and pediatric patients 12 years of age and older with solid tumors that have a neurotrophic tyrosine receptor kinase (*NTRK)* gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have progressed following treatment or have no satisfactory standard therapy.

On June 13, 2024, the Food and Drug Administration granted accelerated approval to repotrectinib (AUGTYRO, Bristol-Myers Squibb Company) for adult and pediatric patients 12 years and older with solid tumors that have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion, are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and that have progressed following treatment or have no satisfactory alternative therapy.

Question ?

- What is actionable in ALK+ NSCLC ?

- A: ALK mutation
- B: ALK fusion
- C: ALK amplification
- D: All of the above

ALK

Abstract LBA8503

2024 ASCO® ANNUAL MEETING

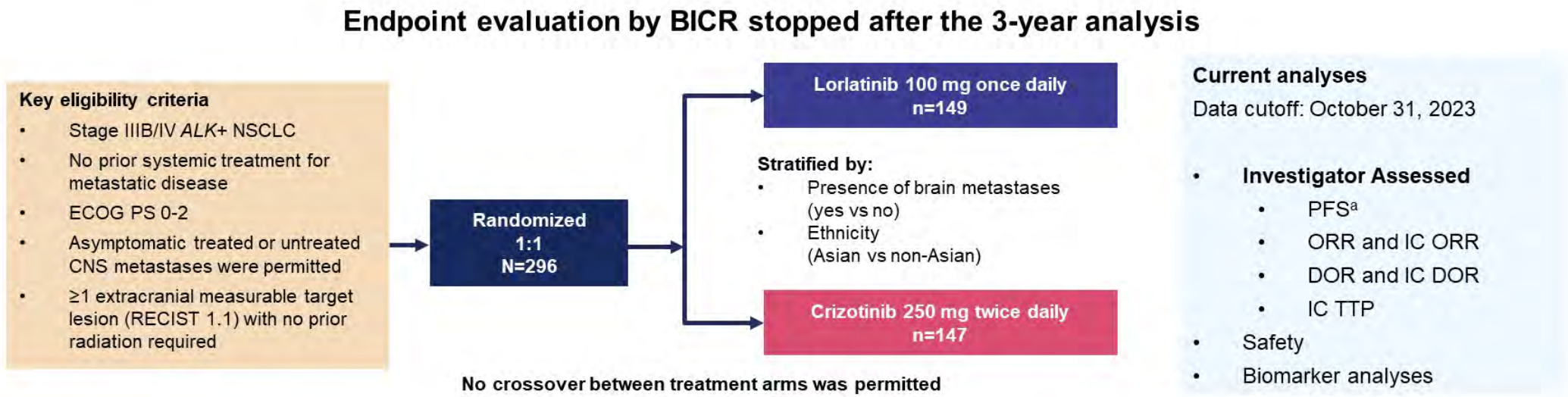
Lorlatinib vs Crizotinib in Treatment-Naive Patients With Advanced *ALK*+ Non-Small Cell Lung Cancer: 5-Year Progression-Free Survival and Safety From the CROWN Study

Key Takeaways

- In this 5-year analysis of the phase 3 CROWN study, median PFS has still not been reached with lorlatinib
- PFS observed with lorlatinib corresponds to the longest PFS reported in advanced NSCLC
- These systemic efficacy results coupled with protection from intracranial progression and absence of new safety signals, indicates that first-line lorlatinib provides an unprecedented improvement in outcomes for patients with advanced *ALK*+ NSCLC

Key Takeaways

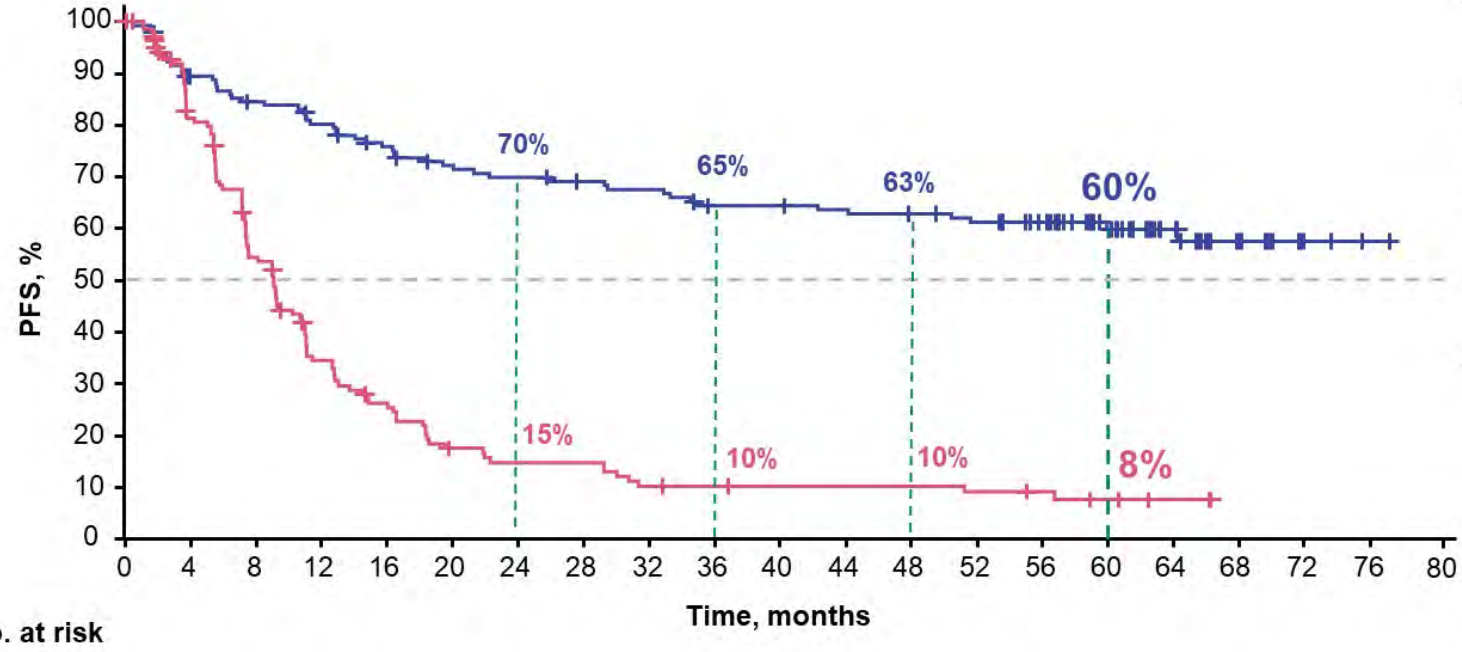
Current Post Hoc Analyses at 5 Years



- The median duration of follow-up for PFS was 60.2 months (95% CI, 57.4-61.6) in the lorlatinib arm and 55.1 months (95% CI, 36.8-62.5) in the crizotinib arm

Current Post Hoc Analyses at 5 Years

At 60.2 Months of Median Follow-Up, Median PFS by Investigator Was Still Not Reached With Lorlatinib



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	55	115
PFS, median (95% CI), months	NR (64.3-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.27)**	

At the time of this analysis, the required number of OS events for a protocol-specified second interim analysis

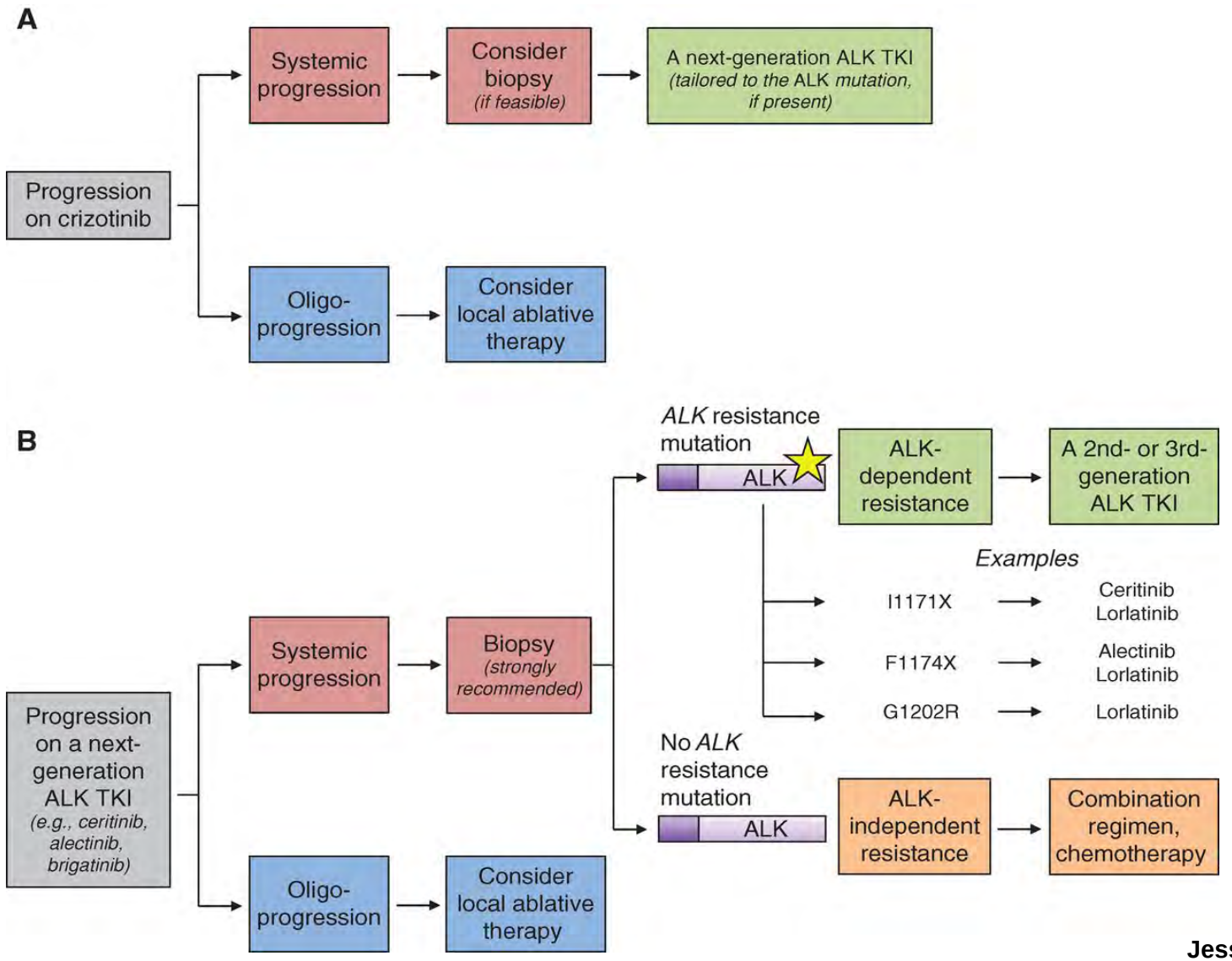
At 60.2 Months of Median Follow-Up, Median PFS by Investigator Was Still Not Reached With Lorlatinib

Conclusions

- After 5 years of follow-up in the CROWN study, with lorlatinib treatment:
  - Median PFS has still not been reached and PFS was 60%
  - The probability of being free of intracranial progression was 92%
  - No new safety signals emerged
  - Efficacy benefit was seen across all subgroups, including patients with poor prognostic biomarkers
- The PFS observed with lorlatinib corresponds to the longest PFS reported in advanced NSCLC
- These systemic efficacy results coupled with protection from intracranial progression and absence of new safety signals, indicates that first-line lorlatinib provides an unprecedented improvement in outcomes for patients with advanced *ALK*+ NSCLC

Conclusions

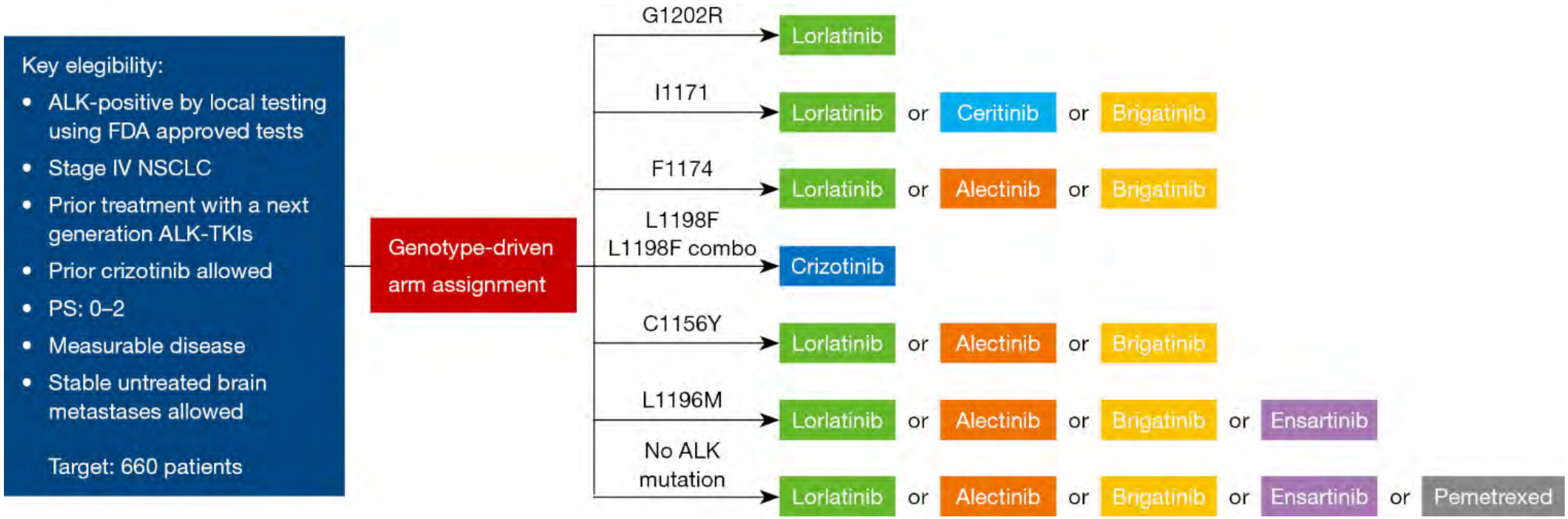
Guidelines for selecting treatment after progression on an ALK TKI. When patients have oligoprogression on an ALK TKI, local ablative therapies can be considered.



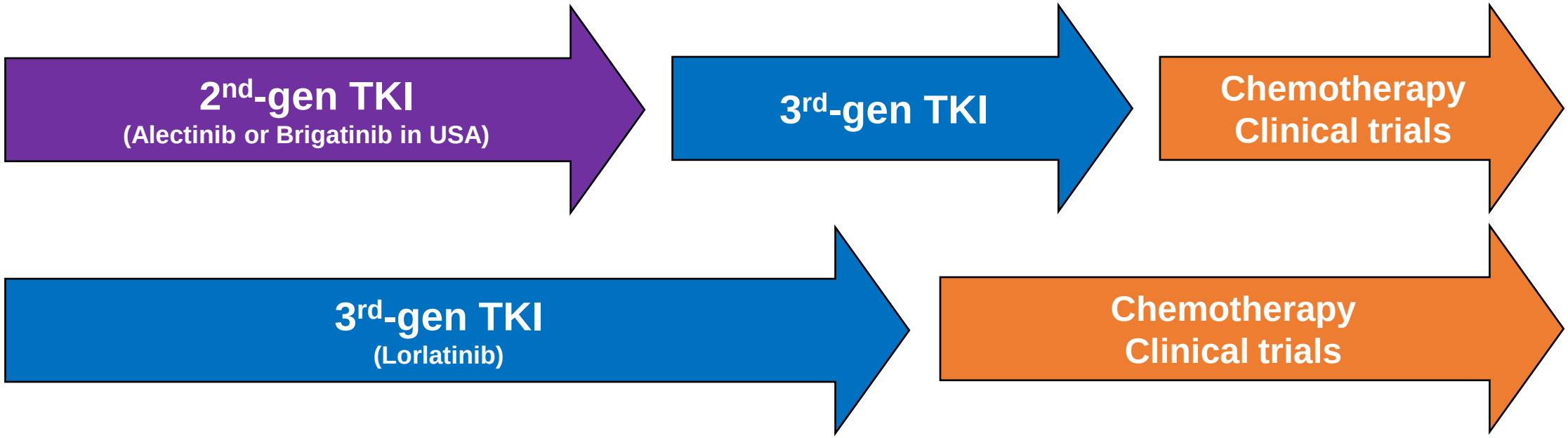
Jessica J. Lin et al. Cancer Discov 2017;7:137-155

AACR American Association for Cancer Research
CANCER DISCOVERY

ALK Master protocol



Advanced ALK+ NSCLC: Current Treatment Paradigm



NOT drawn to scale or to reflect relative median PFS on each treatment option

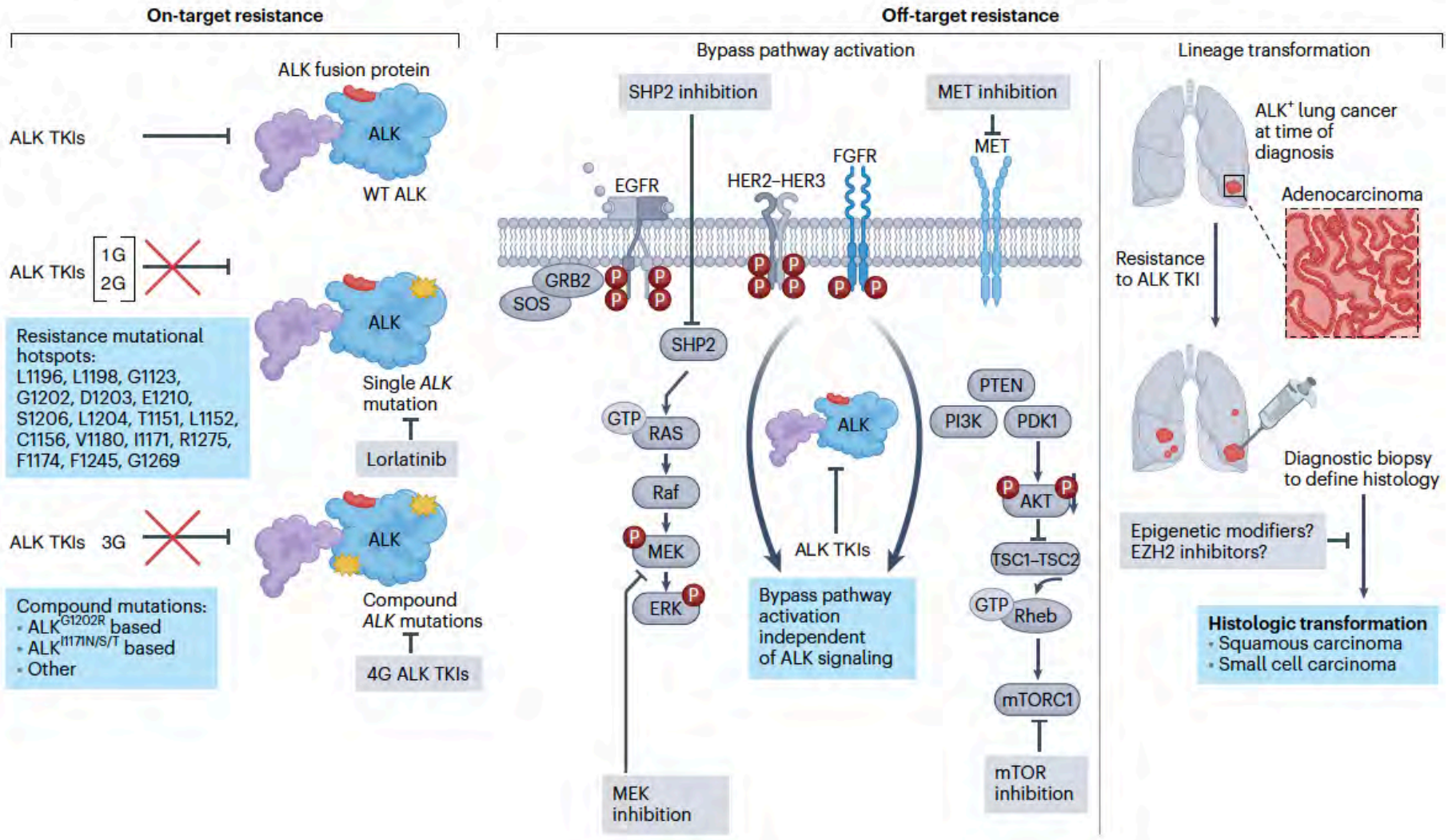
Next-Generation ALK TKI as Standard 1L Therapy

	Crizotinib# (PROFILE 1014[1])	Ceritinib# (ASCEND-4[2])	Alectinib# (Global ALEX[3,4])	Alectinib (ALESIA[5,6])	Alectinib (J-ALEX[7,8])	Brigatinib# (ALTA-1L[9,10])	Ensartinib (eXalt-3[11])	Lorlatinib# (CROWN[12,13])
Comparator	Platinum/pem	Platinum/pem	Crizotinib	Crizotinib	Crizotinib	Crizotinib	Crizotinib	Crizotinib
N	172	189	152	125	103	137	143	149
PFS, median	10.9 mos	16.6 mos	25.7 months HR 0.50 (0.36-0.70)	41.6 mos^ HR 0.33 (0.23-0.49)	34.1 mos HR 0.37 (0.26-0.52)	24.0 mos HR 0.48 (0.35-0.66)	25.8 mos HR 0.51 (0.35-0.72)	NR HR 0.27 (0.18-0.39)
CNS mets at baseline	26% (treated only)	31%	42%	35%	14%	29%	33%	26%
PFS in pts with brain mets	9.0 mos*	10.7 mos	25.4 mos^ (HR 0.37)	42.3 mos^ (HR 0.17)	25.9 mos (HR 0.47) (initial result)	24.0 mos (HR 0.25)	NR	NR (HR 0.21)
ORR	74%	73%	83%^	91%^	92%	74%	75%	77%
Median follow-up	17.4 mos	19.7 mos	18.6 mos (for BIRC)	61 mos	42.4 mos	40.4 mos	23.7 mos	36.7 mos

#Approved by US FDA for 1L indication in advanced ALK+ NSCLC **Pts with stable, treated brain mets allowed* *^By investigator assessment (not BICR)*

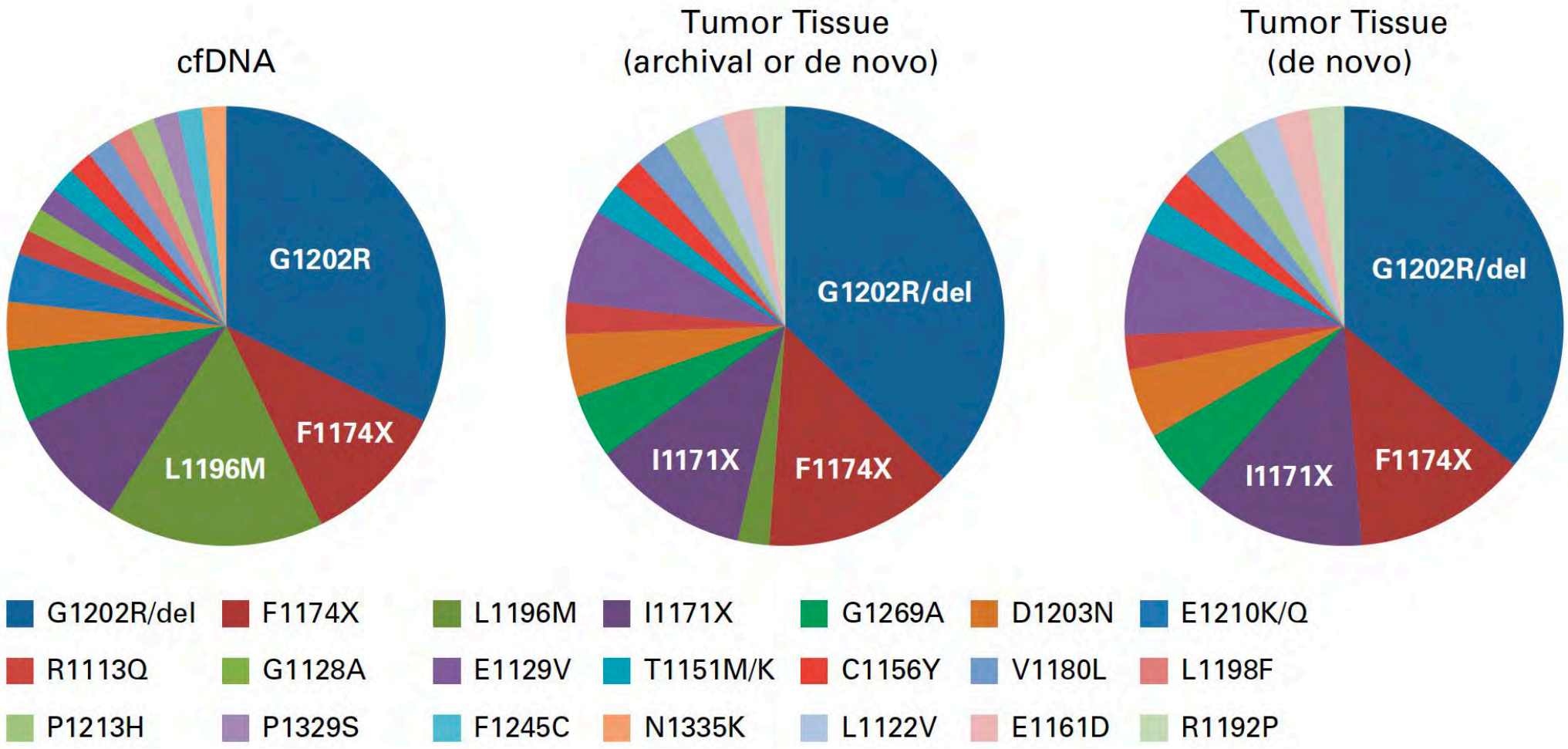
[1]Solomon BJ et al., N Engl J Med 2014; [2]Soria JC et al., Lancet 2017;[3]Peters S et al., N Engl J Med 2017; [4]Mok T et al., Ann Oncol 2020; [5]Zhou C et al., Lancet Respir Med 2019; [6]Zhou C et al., ESMO Asia 2022; [7]Hida T et al., Lancet 2017; [7]Nakegawa K et al., Lung Cancer 2020; [8]Camidge DR et al., NEJM 2018; [9]Camidge DR et al., J Thorac Oncol 2021; [10]Horn L et al., JAMA Oncol 2021; [11]Shaw AT et al., N Engl J Med 2020; [12]Solomon BJ et al., Lancet Respir Med 2022

Broad Framework for Understanding Systemic TKI Failure: Mechanisms of Resistance to ALK Inhibitors



Schneider JL et al. *Nat Cancer* 2023;4(3):330-43

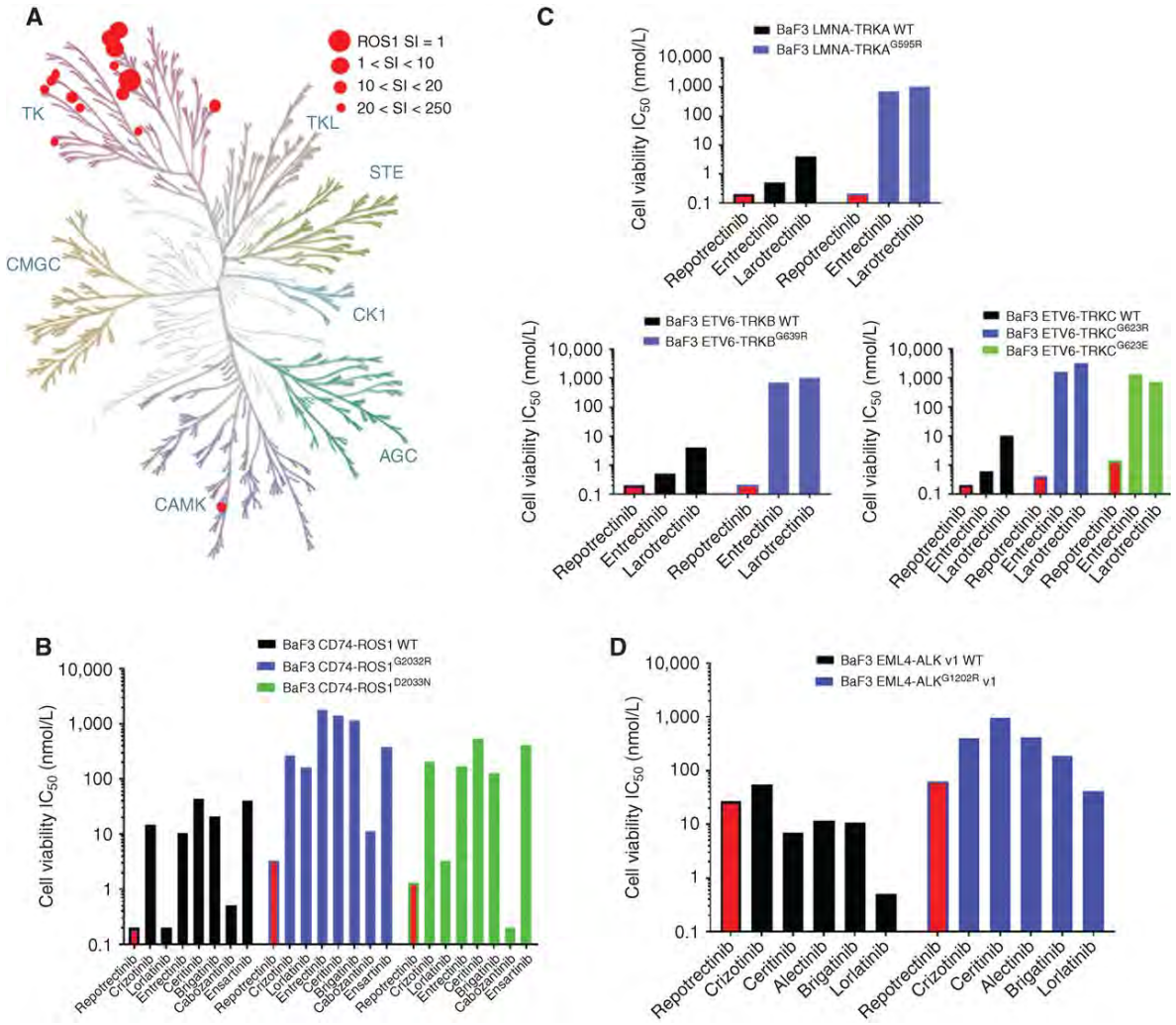
Resistance to 2G ALK TKIs



Shaw AT et al. *J Clin Oncol* 2019;37:1370-9

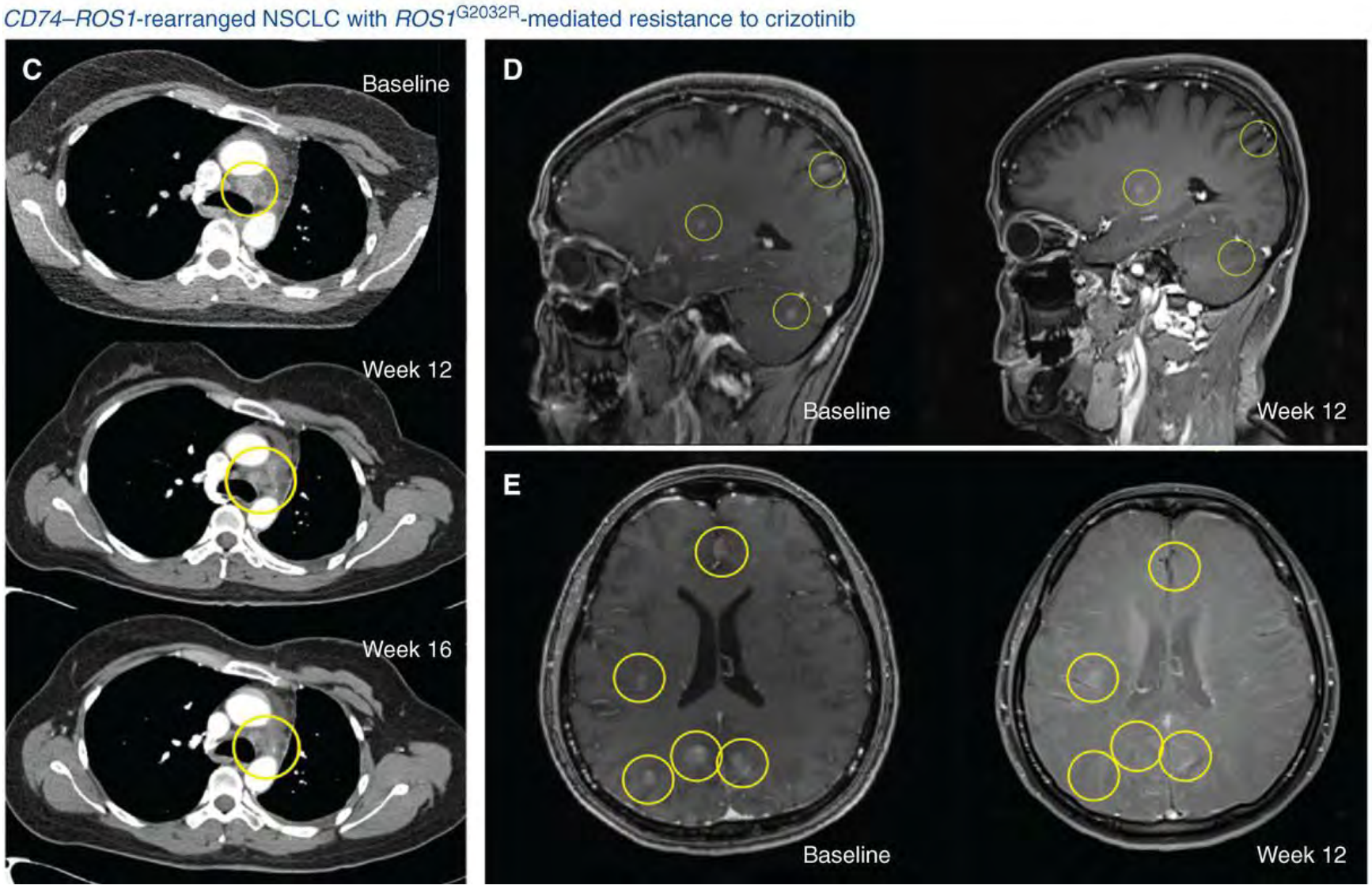
ROS1

Selectivity and in vitro antiproliferative activity of repotrectinib.



Alexander Drilon et al. Cancer Discov 2018;8:1227-1236

Response to repotrectinib in ROS1 solvent-front substitution–containing cancers.

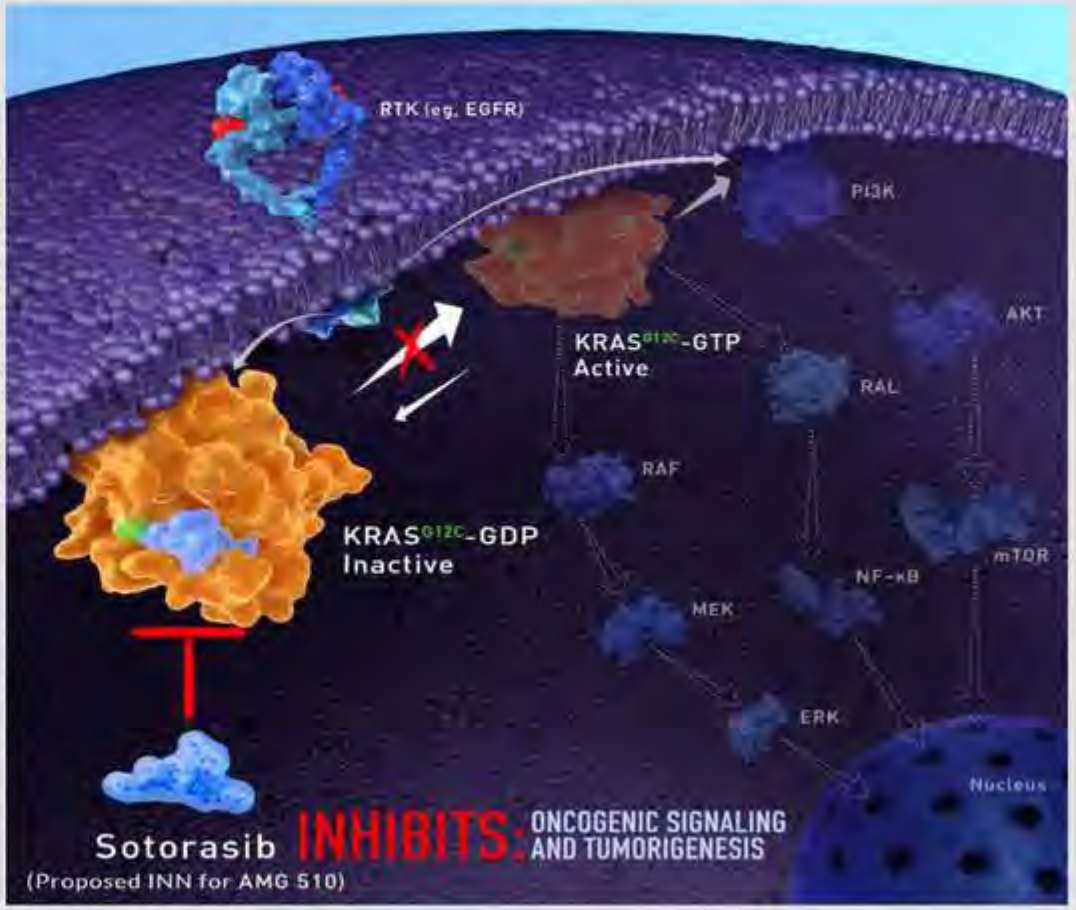


Drilon et al. Cancer Discov 2018;8:1227-1236

KRAS G12 C

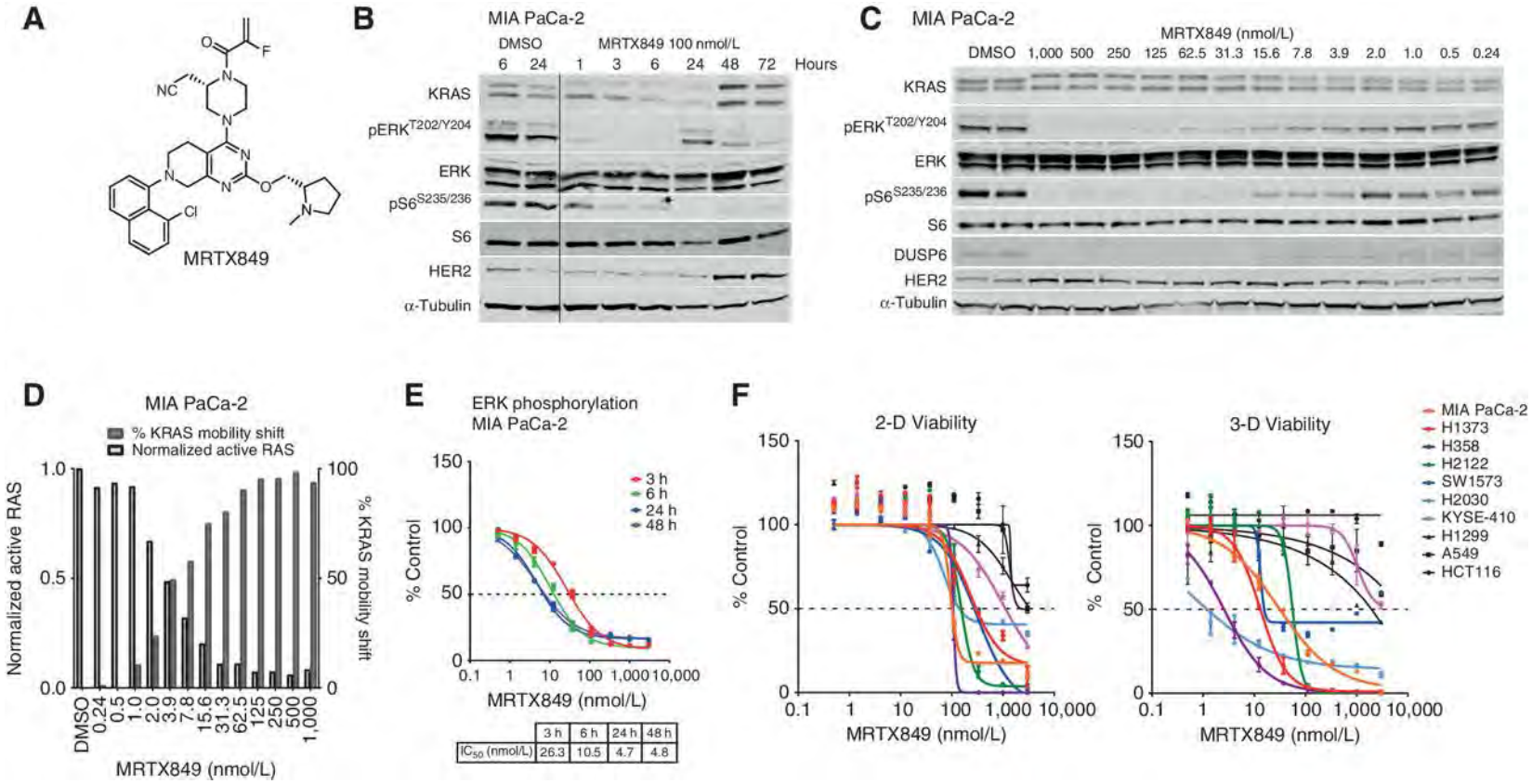
SOTORASIB IS A FIRST-IN-CLASS KRAS^{G12C} INHIBITOR

- ***KRAS*** **p.G12C mutation is found in approximately 13% of NSCLC, 3-5% of colorectal cancer, and 1%-3% of other solid tumors[1-6]**
- **Sotorasib (proposed INN for AMG 510) is a novel, highly selective, first-in-class KRAS^{G12C} inhibitor that has demonstrated anticancer activity and a manageable safety profile in patients with *KRAS* p.G12C mutant solid tumors[5,7]**



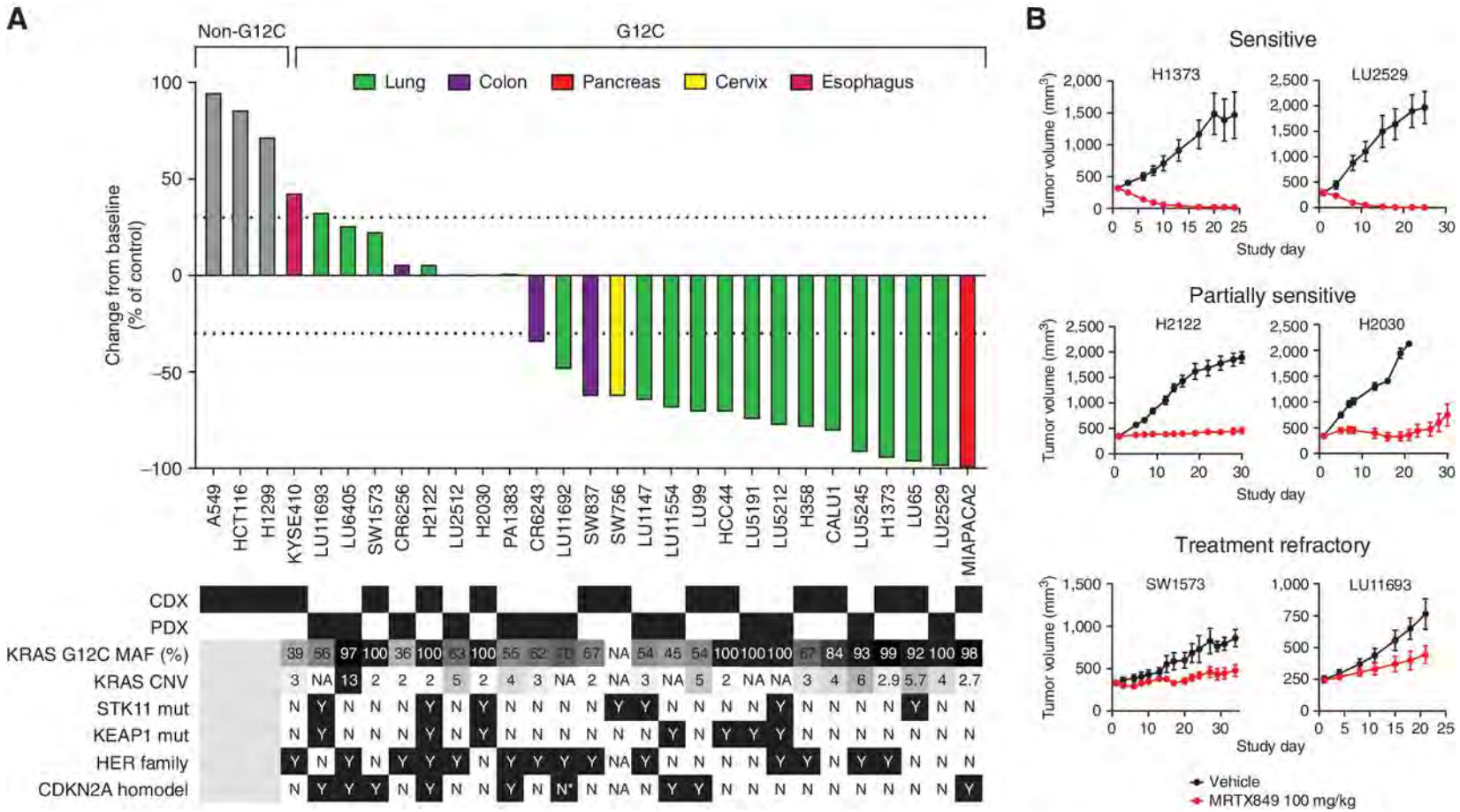
1. Biernacka A, et al. *Cancer Genet.* 2016;209:195-198. 2. Neumann J, et al. *Pathol Res Pract.* 2009;205:858-862. 3. Jones RP, et al. *Br J Cancer.* 2017;116:923-929. 4. Wiesweg M, et al. *Oncogene.* 2019;38:2953-2966. 5. Canon J, et al. *Nature.* 2019;575:217-223. 6. Zhou L, et al. *Med Oncol.* 2016;33:32. 7. Govindan R, et al. Presented at: European Society for Medical Oncology; September 27–October 1, 2019; Barcelona, Spain. Abstract #446PD.

Adagrasib is a potent, covalent KRASG12C inhibitor in vitro.



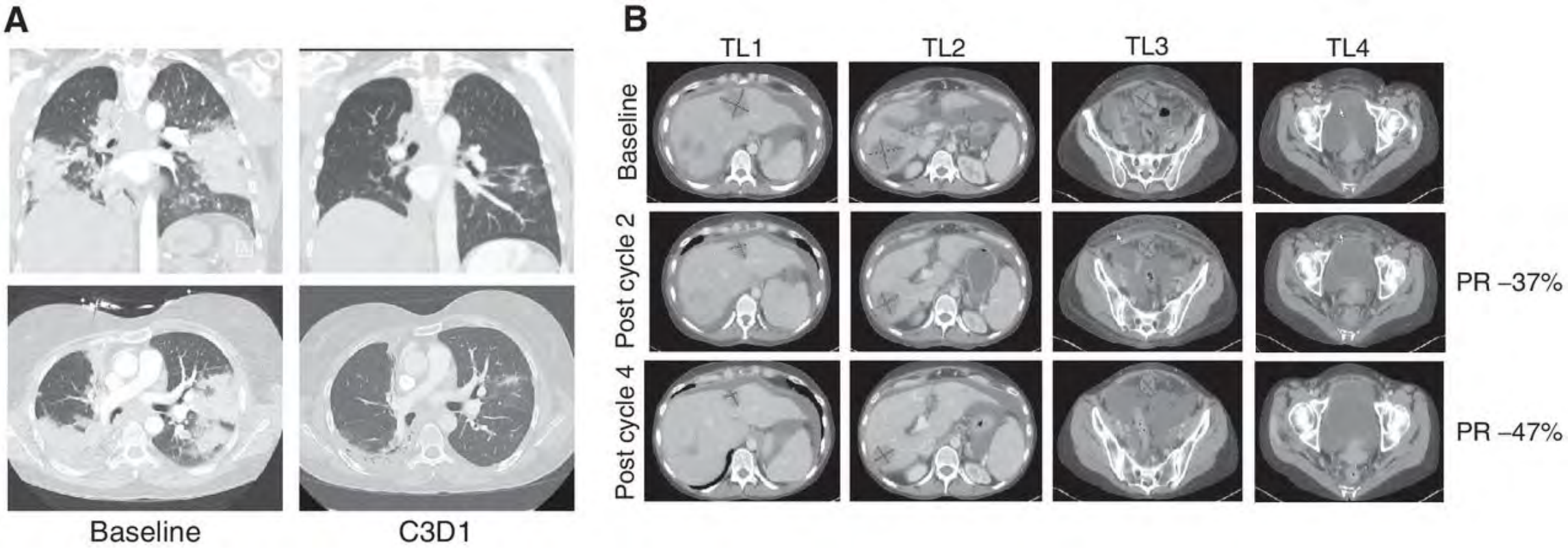
Jill Hallin et al. Cancer Discov 2020;10:54-71

Antitumor activity of MRTX849 in KRASG12C-mutant and non–KRASG12C-mutant human tumor xenograft models.



Jill Hallin et al. Cancer Discov 2020;10:54-71

Activity of MRTX849 in patients with lung and colon cancers.



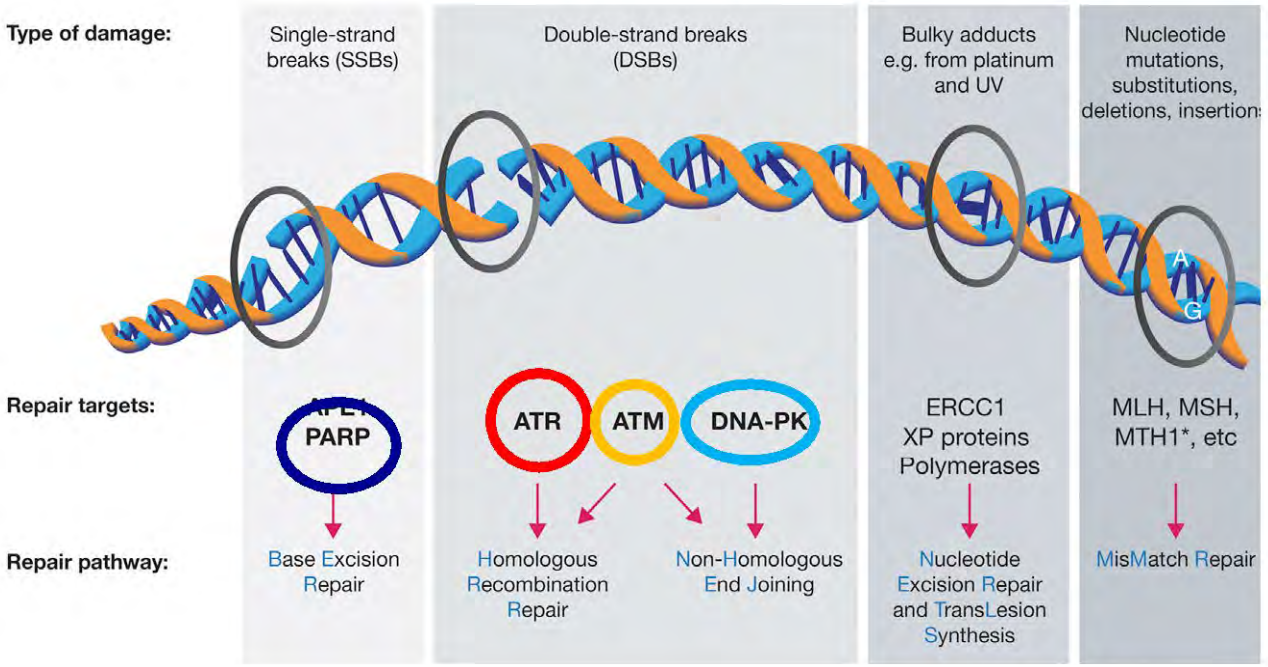
Jill Hallin et al. Cancer Discov 2020;10:54-71

AACR American Association for Cancer Research
CANCER DISCOVERY

DDR

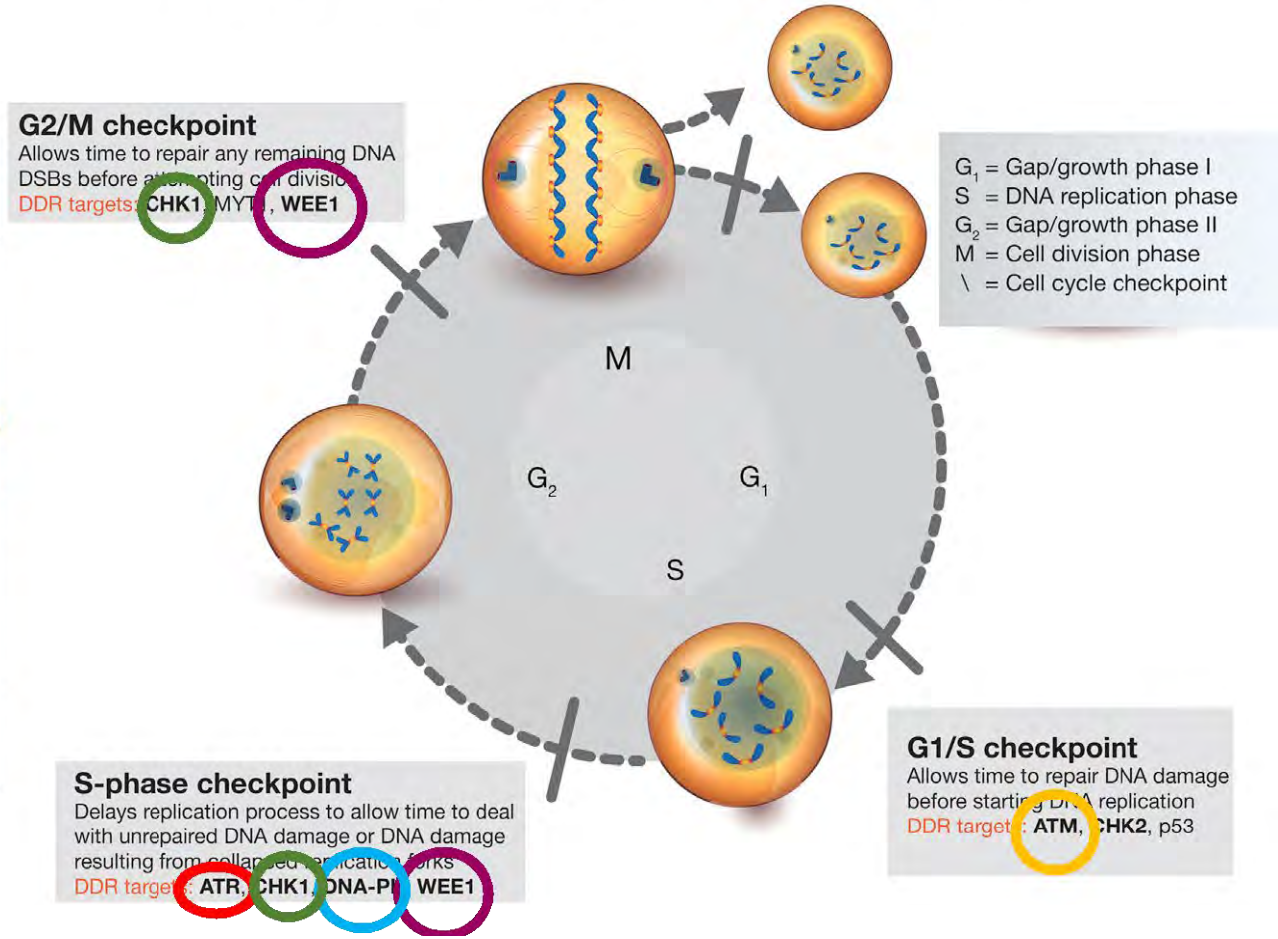
Targeting the DNA damage response (DDR)

DDR pathway targets



DDR Inhibitors
Phase I: ATM, DNA-PK
Phase II: ATR, WEE1, CHK1
FDA Approved: PARP

DDR cell-cycle targets



O'Connor, Molecular Cell 2015

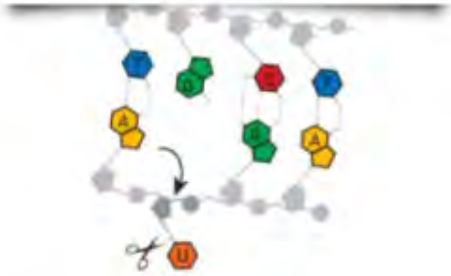
Nobel prize for DNA repair

Tomas Lindahl

- Swedish citizen
- Born 1967
- Emeritus group leader at Francis Crick Institute and Emeritus director of Cancer Research UK

Base excision repair

Constantly counteracts the collapse of our DNA

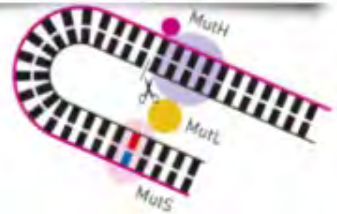


Paul Modrich

- U.S. citizen
- Born 1946
- Howard Hughes Medical Institute and Duke University School of Medicine

Mismatch repair

How the cell corrects errors that occur when DNA is replicated during cell division



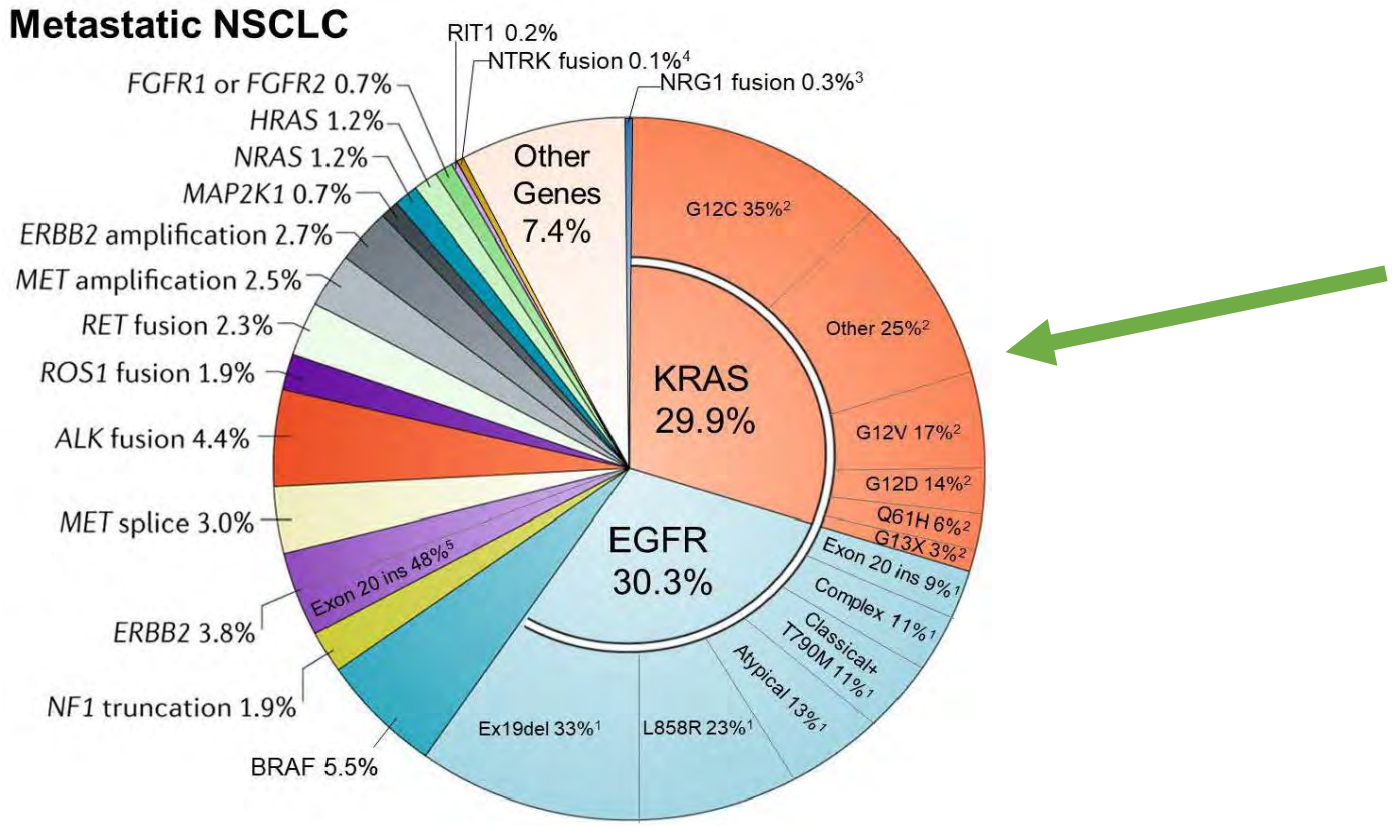
Aziz Sancar

- U.S. and Turkish citizen
- Born 1946
- University of North Carolina School of Medicine

Nucleotide excision repair

The mechanism that cells use to repair UV damage to DNA

~43% of NSCLC patients have mutations that are targetable with approved agents



Adapted from Skoulidis and Heymach 2019 Nat Rev Can

[1] Robichaux et al 2020 WCLC

[2] Mack et al 2020 Cancer

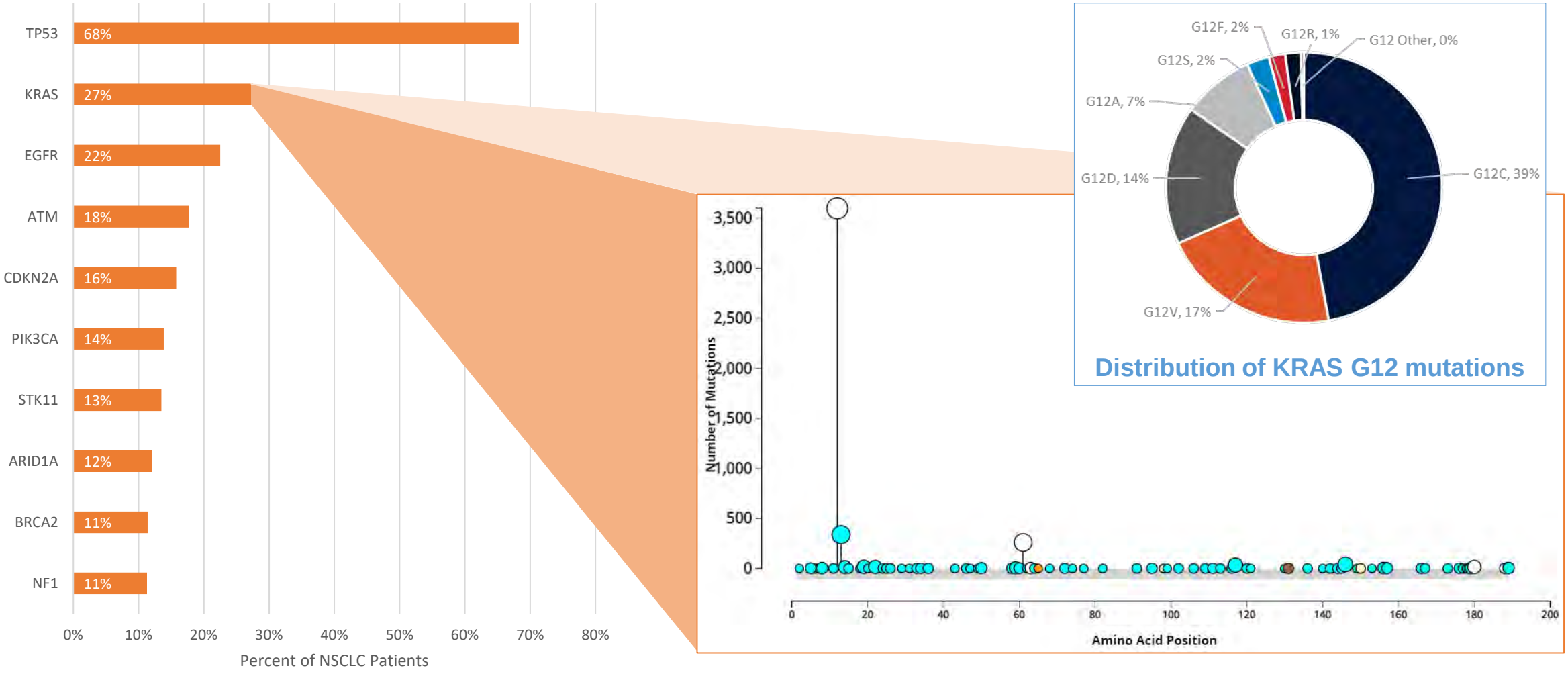
[3] Jonna et al 2019 Clin Can Res

[4] Russo et al 2020 Precis Cancer Med

[5] Robichaux et al 2019 Cancer Cell

Includes FMI, Guardant, and Caris NGS reports within Genospace across the Sarah Cannon network.

Frequency of KRAS Mutations in Lung Cancer

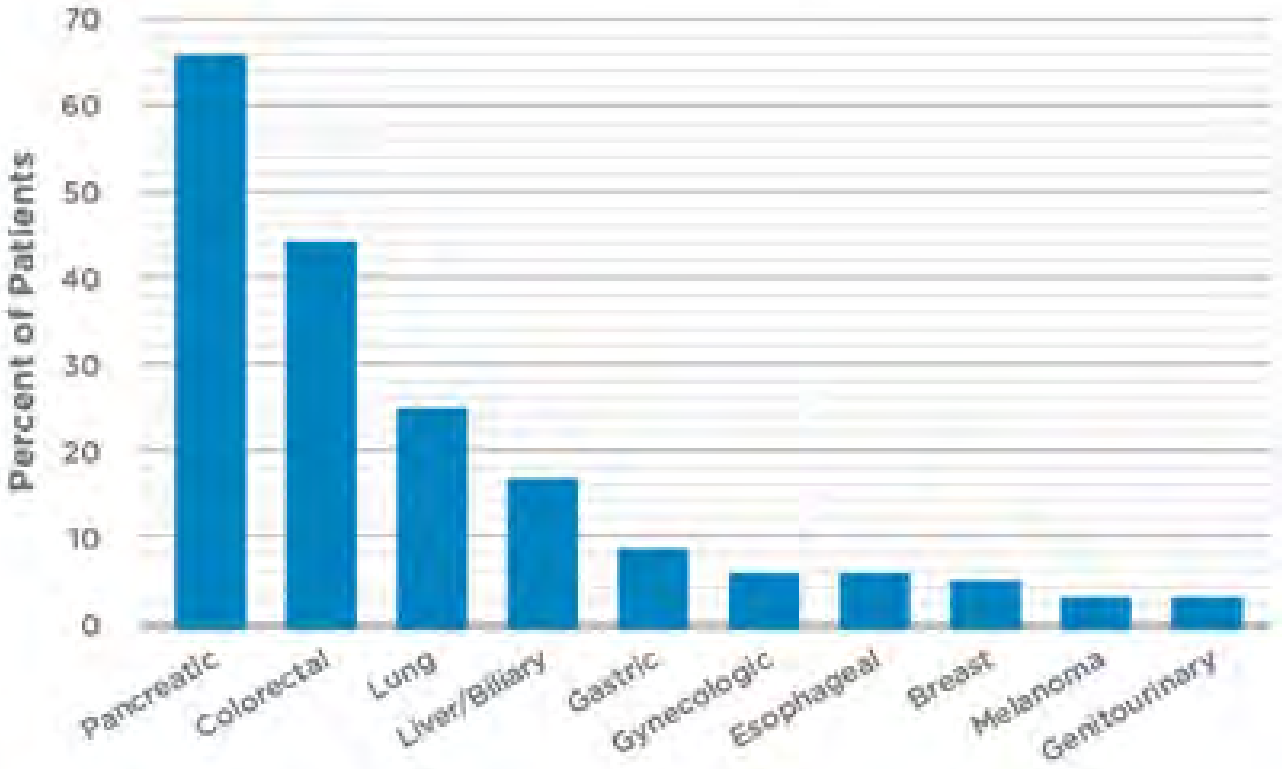


Provided by Sarah Cannon Personalized Medicine

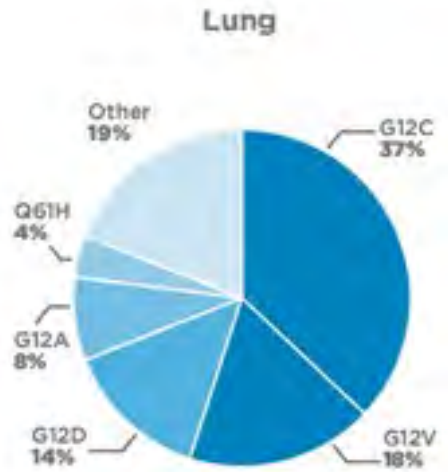
Includes FMI, Guardant, and Caris NGS reports within Genospace across the Sarah Cannon network.

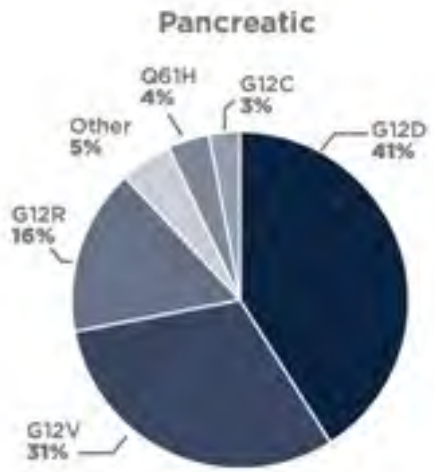
KRAS Mutations Across Tumor Types

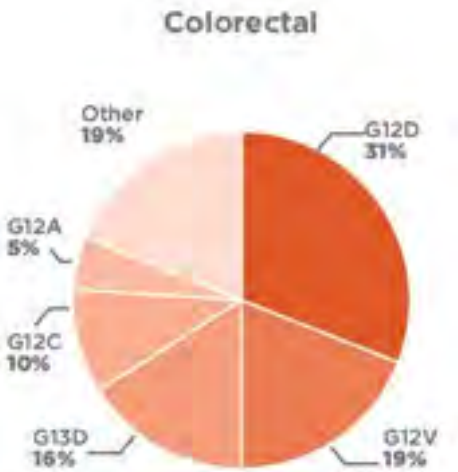
Frequency of activating KRAS mutations across tumor types within the Sarah Cannon network



Breakdown of frequently occurring KRAS mutations in lung, pancreatic, and colorectal cancers within the Sarah Cannon network.



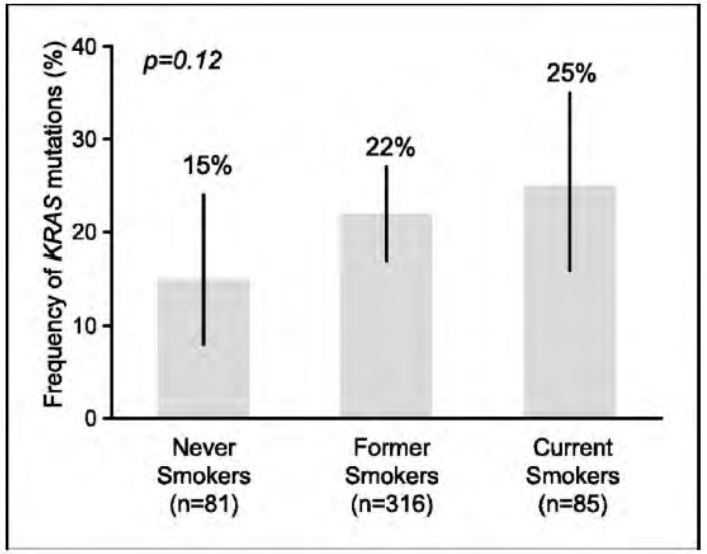


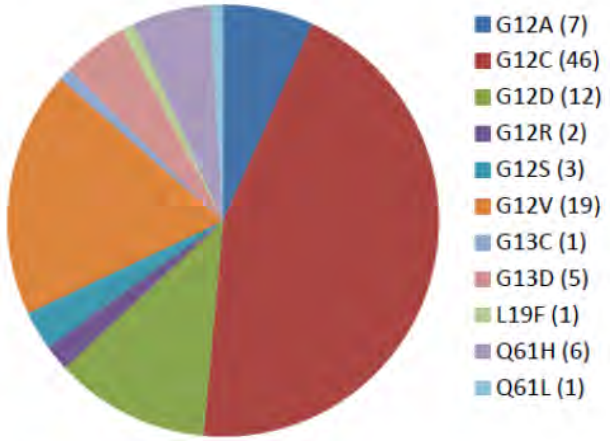


Provided by Sarah Cannon Personalized Medicine

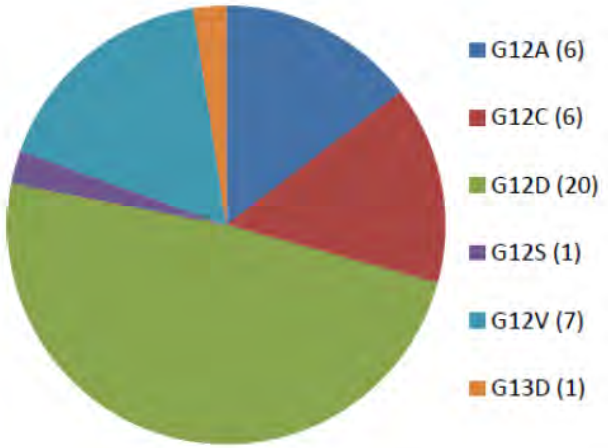
KRAS Mutations in NSCLC

- *KRAS G12C* mutation is found in approximately 13% of lung cancer,[1] 3% of colorectal cancer[2] and appendix cancer, and 1%–3% of other solid tumors[3].





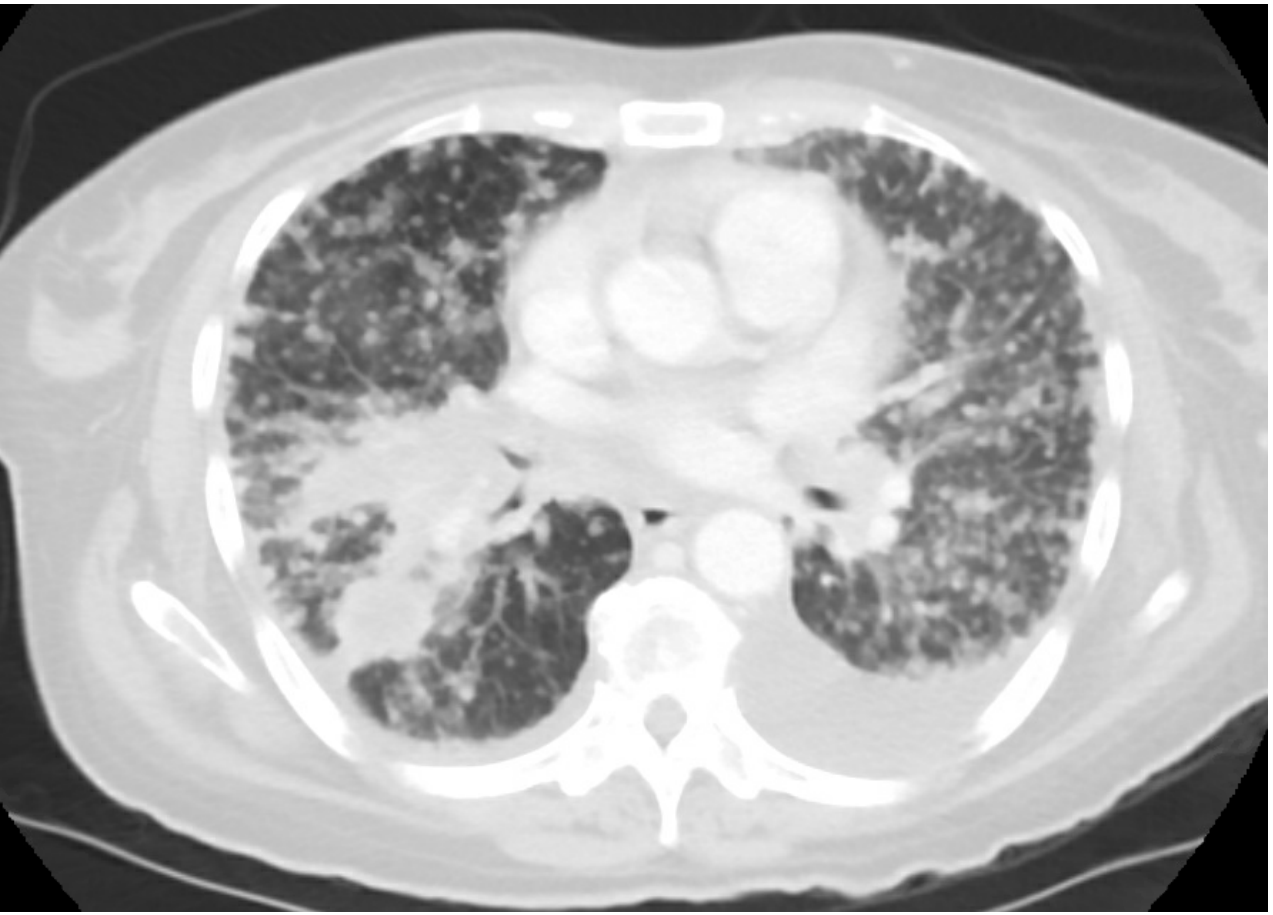
Current/Former Smokers

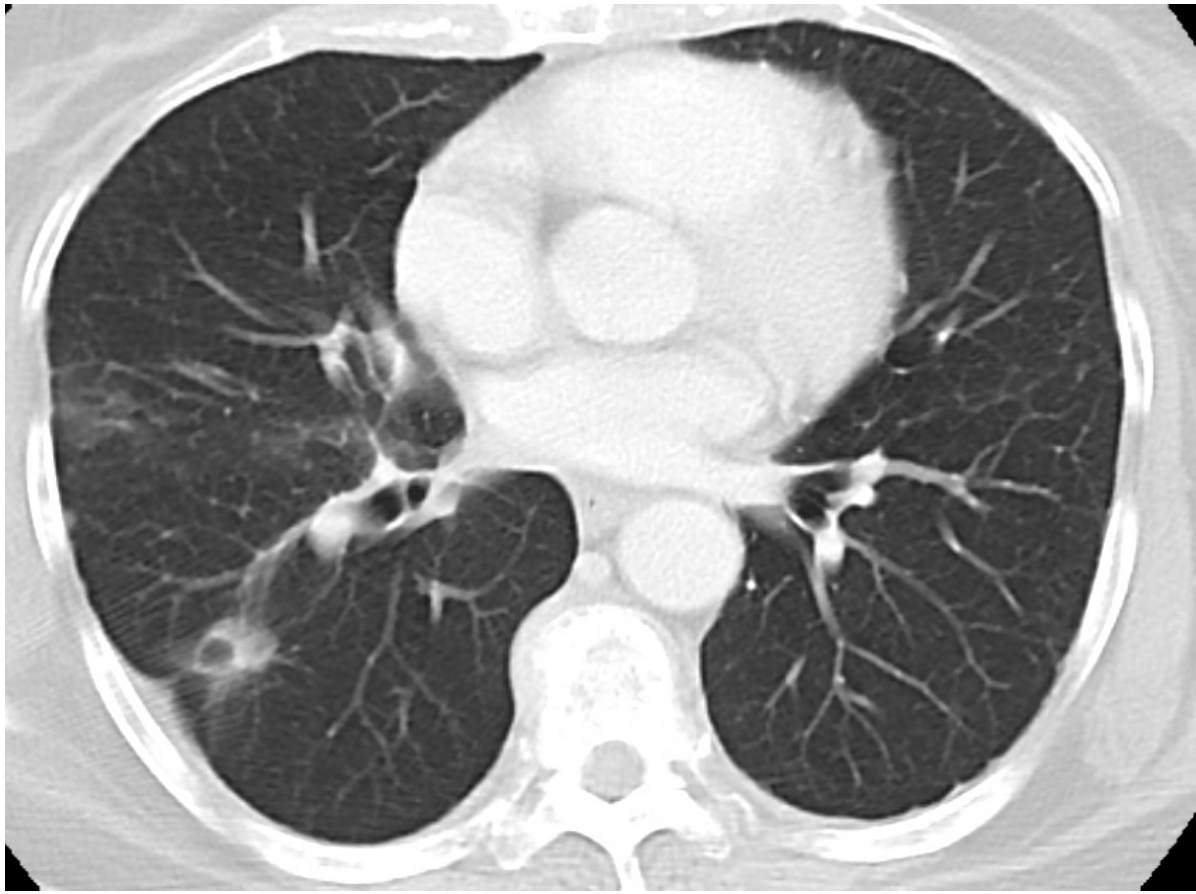


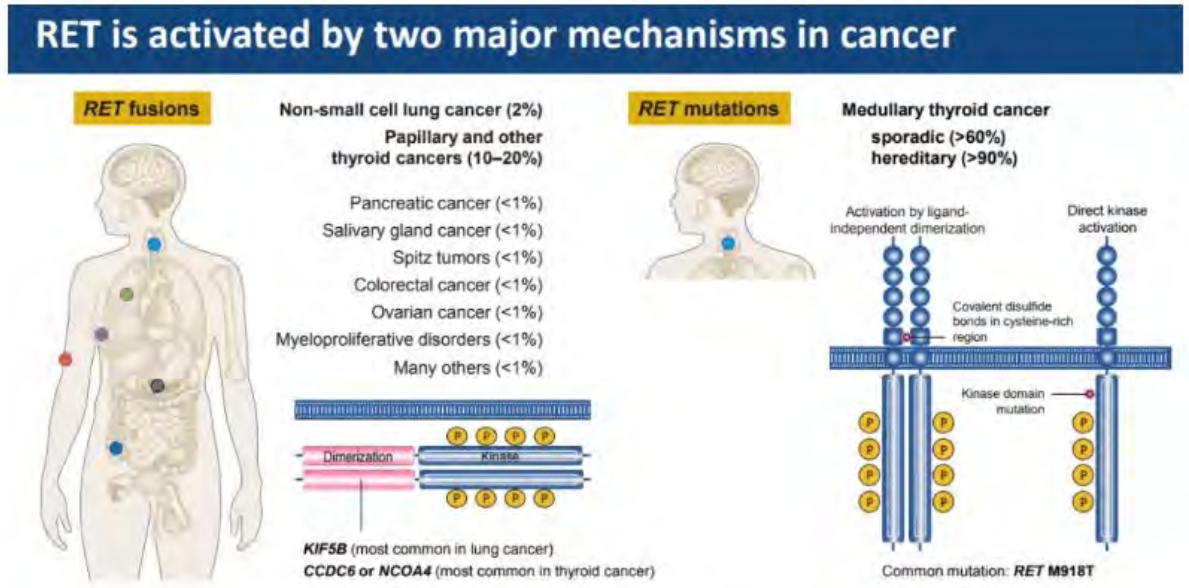
Never Smokers

1. Biernacka A, et al. *Cancer Genet.* 2016;209:195-198. 2. Neumann J, et al. *Pathol Res Pract.* 2009;205:858-862. 3. Zhou L, et al. *Med Oncol.* 2016;33:32, Riely, G. et al. CCR 2008; Rediget al. ASCO 2016
.

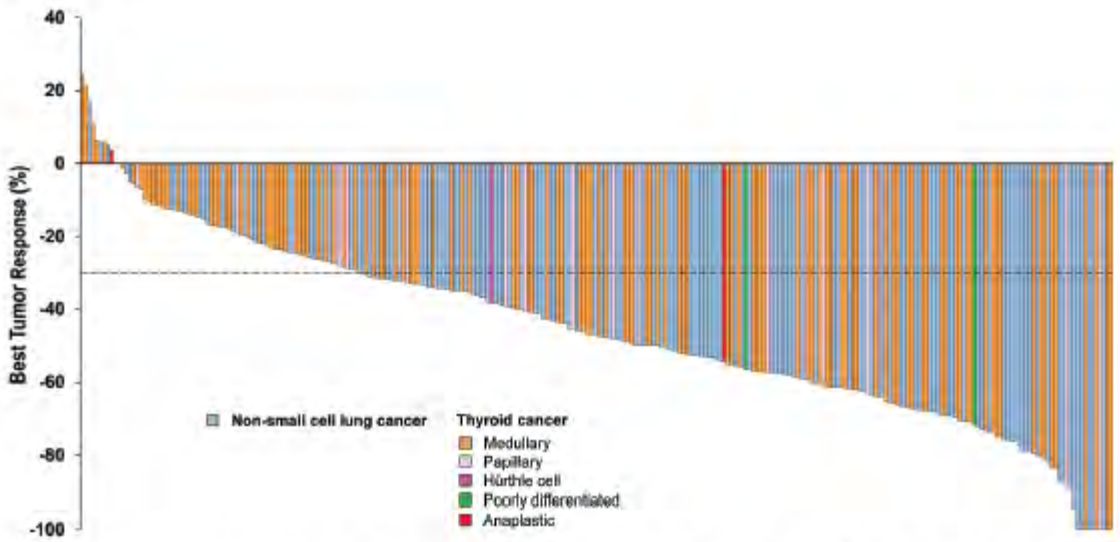
Targeted therapy- when you find RET- nothing to FRET!







Selpercatinib (Loxo-292)

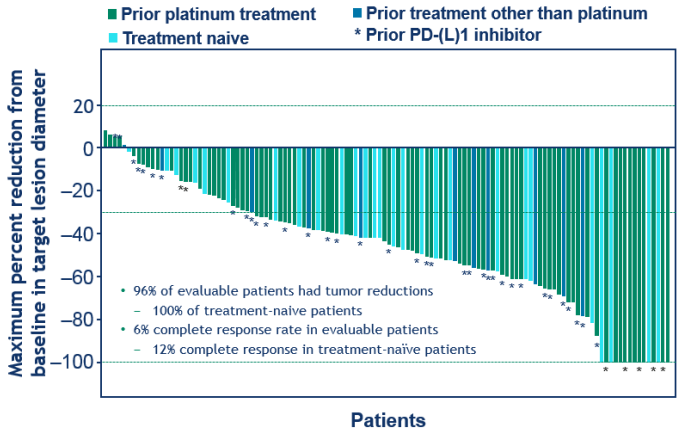


Investigator response assessments as of June 17th, 2019. 16 patients not shown in waterfall plot (discontinued prior to any post-baseline imaging assessments, did not have measurable disease at baseline or deemed not evaluable on study by the investigator). N=296 dataset includes 22 unconfirmed partial responses awaiting confirmatory response assessments

Pralsetinib (Blu-667)

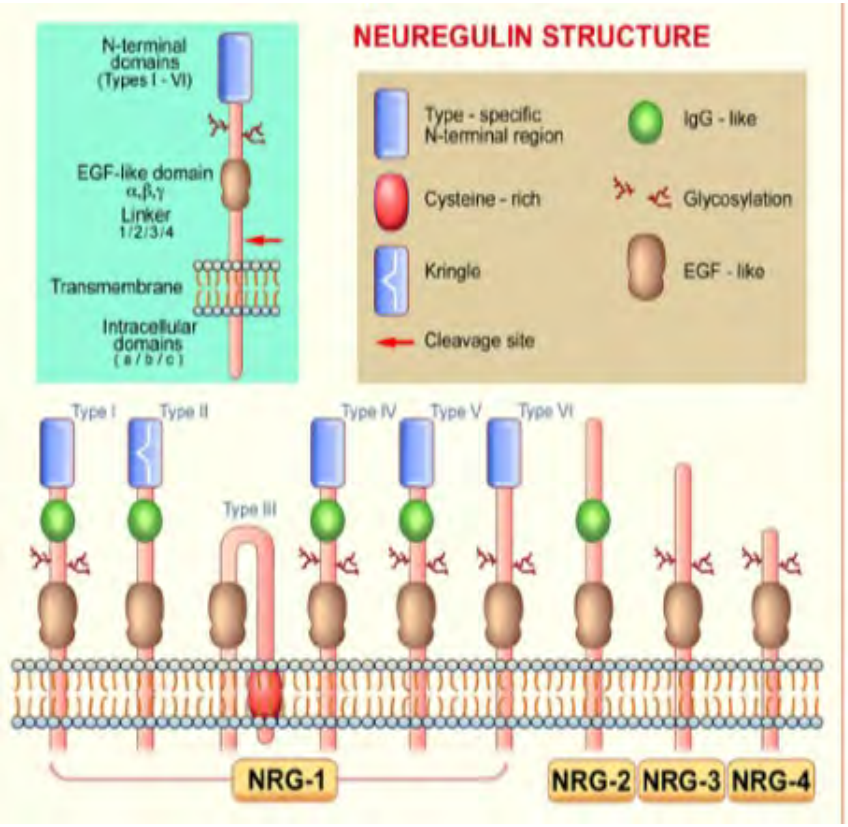
Efficacy results

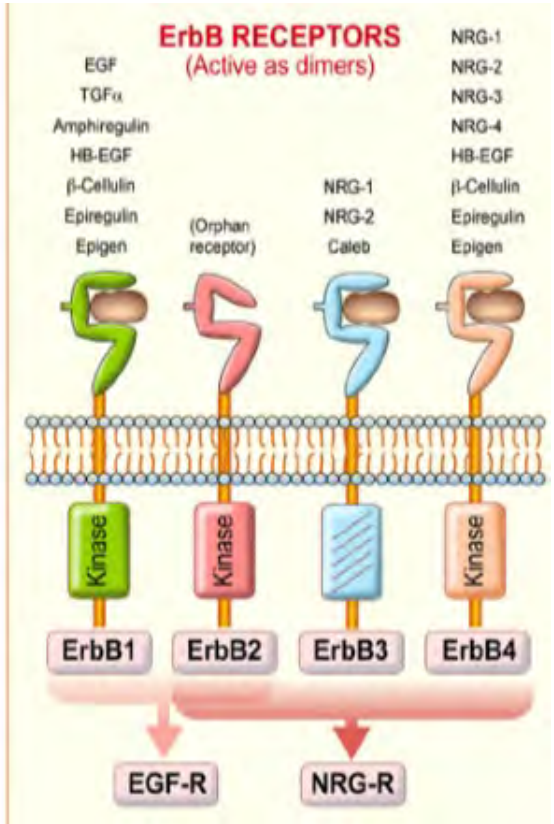
Best Overall Response by Independent Central Radiographic Review	Intent-to-treat efficacy population: All NSCLC (n=132)*	Prior platinum (n=92)	Treatment Naïve (n=29)
ORR	58%†	55%†	66%
95% CI	49–67%	45–66%	46-82%
CR	6%	5%	10%
PR	52%†	50%†	55%
Best Overall Response by Independent Central Radiographic Review	**Response-evaluable population: All NSCLC (n=116)‡**	**Prior platinum (n=80)**	**Treatment Naïve (n=26)**
ORR	65%†	61%†	73%
95% CI	55–73%	50–72%	52–88%
CR	6%	5%	12%
PR	59%†	56%†	62%

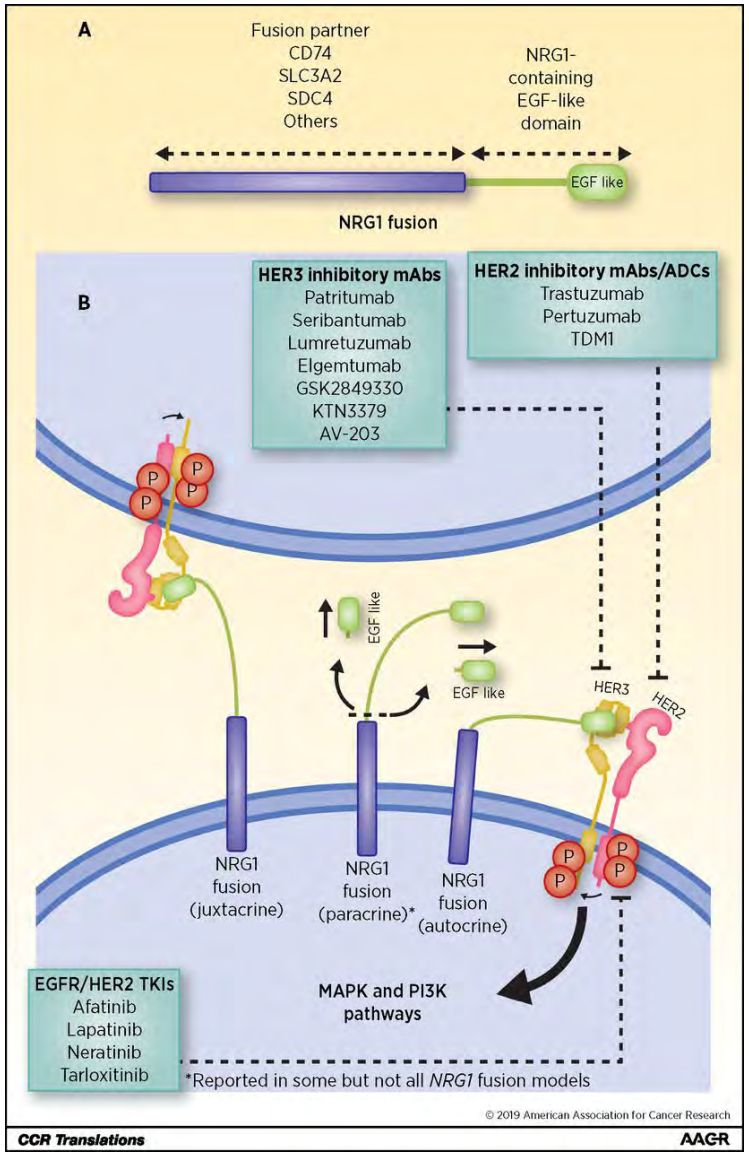


- Median duration of response was not reached (95% CI: 11.3 months to not reached)
- 75% of responding patients continue on treatment
- Intracranial ORR in 9 patients with baseline measurable CNS metastases was 56%, including 3 (33%) CRs

NRG fusions- hope you still have the NRG!

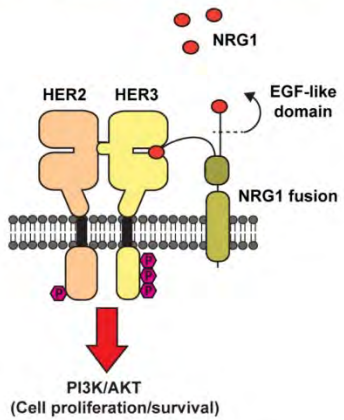


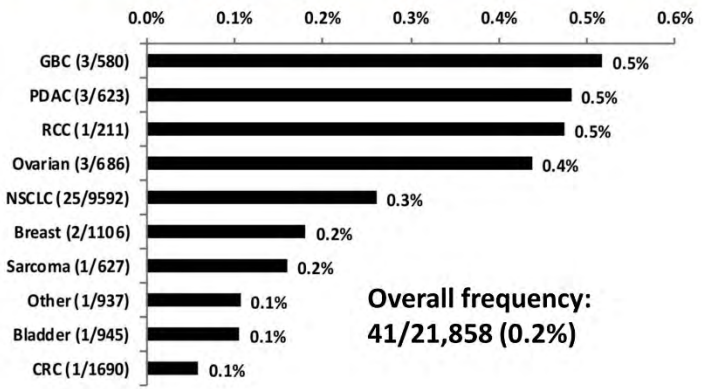




NRG1 Fusions are Clinically Actionable Targets

- Neuregulin 1 (NRG1) is a ligand that binds to HER3, promoting HER2/HER3 heterodimerization and activation of PI3K/AKT/mTOR signaling
- Chromosomal rearrangements involving NRG1 are rare oncogenic drivers in solid tumors, enriched in *KRASwt* PDAC and lung IMA
- Numerous NRG1 fusion partners identified (e.g., CD74, ATP1B1, SDC4)
- NRG1 fusion positive (NRG1+) *in vitro* and *in vivo* models are sensitive to HER2/HER3 directed therapy

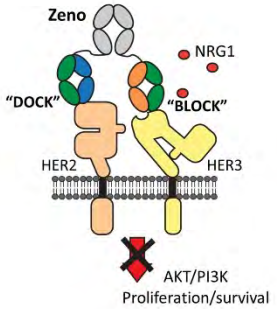


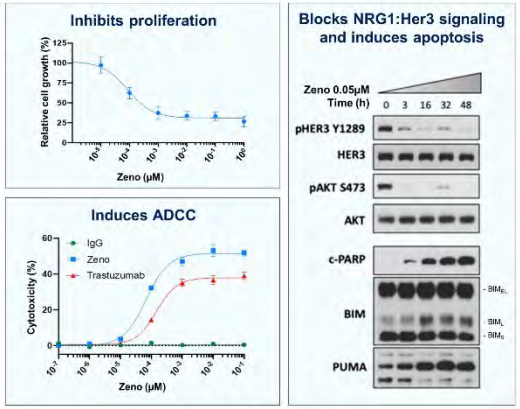


Fernandez-Cuesta et al. Cancer Discov. 2014;4:415-22
Schram et al. J Clin Oncol. 2019;37:3129
Jonna et al. J Clin Oncol. 2020;38:3113
Jonna et al. Clin Cancer Res. 2019;25:4966–7

Zenocutuzumab: A Novel Therapeutic Paradigm for NRG1+ Cancers

- Common light chain bispecific Biclonics® antibody with enhanced ADCC activity
- Docks on HER2 and blocks NRG1 interaction with HER3
- Potent inhibition of cell growth and molecular signaling (pHER3, PI3K) at 0.01 µM
- Orphan drug and fast-track designations were granted





MDA-MB-175-VII (*DOC4-NRG1* fusion)

Geuijen et al. Cancer Cell. 2018;33:922-36
Odintsov et al. AACR. 2021; abstract 956

Zeno NRG1+ Development Program

Phase 1/2 global, open-label clinical trial (eNRGy)
+
Early Access Program (EAP)

- PDAC
- NSCLC
- Other solid tumors

Inclusion criteria

- Locally advanced, unresectable or metastatic solid tumor
- *NRG1* gene fusion
- Previously treated with or unable to receive standard therapy
- ≥ 18 years-old
- ECOG PS ≤ 2

- Zenocutuzumab 750 mg IV Q2W until PD
- Tumor assessment Q8W

Survival follow-up (up to 1 year)

Endpoints and Population

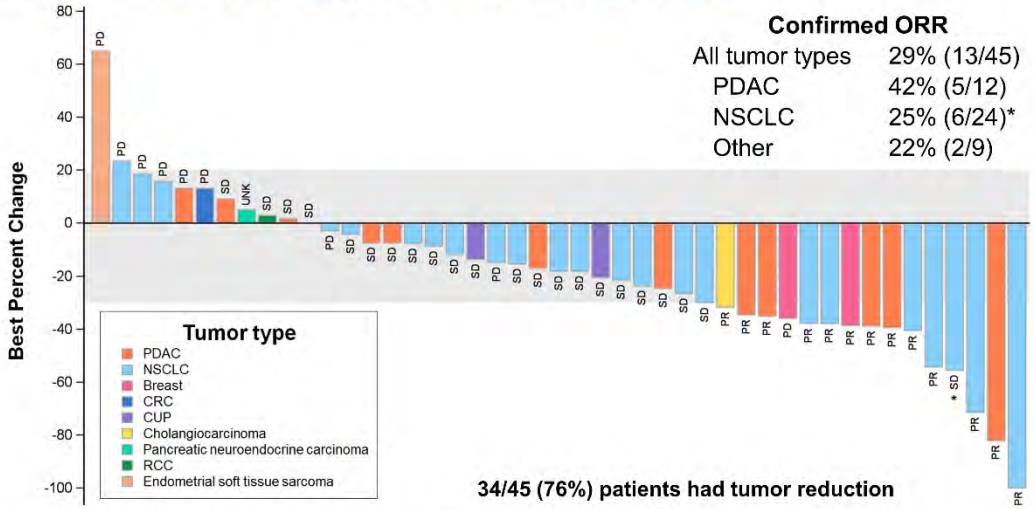
- **Primary endpoint**: Overall response rate (ORR) using RECIST v1.1 per investigator
- **Secondary endpoints**: Duration of response, ORR per central review, safety
- **Primary analysis population:** opportunity for ≥1 post-baseline tumor assessment at the cutoff

Enrollment and Analysis

- **Data cutoff date**: 13-Apr-2021
- **Enrollment:** n = 61
- **Primary analysis population:** n = 47
  Excluded:
  - *10 patients recently enrolled (first dose < 8 weeks from data cutoff date)*
  - *2 patients without baseline scan within 5 weeks of first dose*
  - *1 patient with ECOG 3 received 2 doses on non-standard treatment interval*
  - *1 patient with concomitant KRAS mutation (excluded per SAP)*

Efficacy Regardless of NRG1+ Tumor Type

Best Percent change in Target Lesions from Baseline



Confirmed ORR

All tumor types	29% (13/45)
PDAC	42% (5/12)
NSCLC	25% (6/24)*
Other	22% (2/9)

34/45 (76%) patients had tumor reduction

* One additional PR confirmed after the cutoff date; NSCLC ORR 29% (7/24)

Zenocutuzumab is Well Tolerated

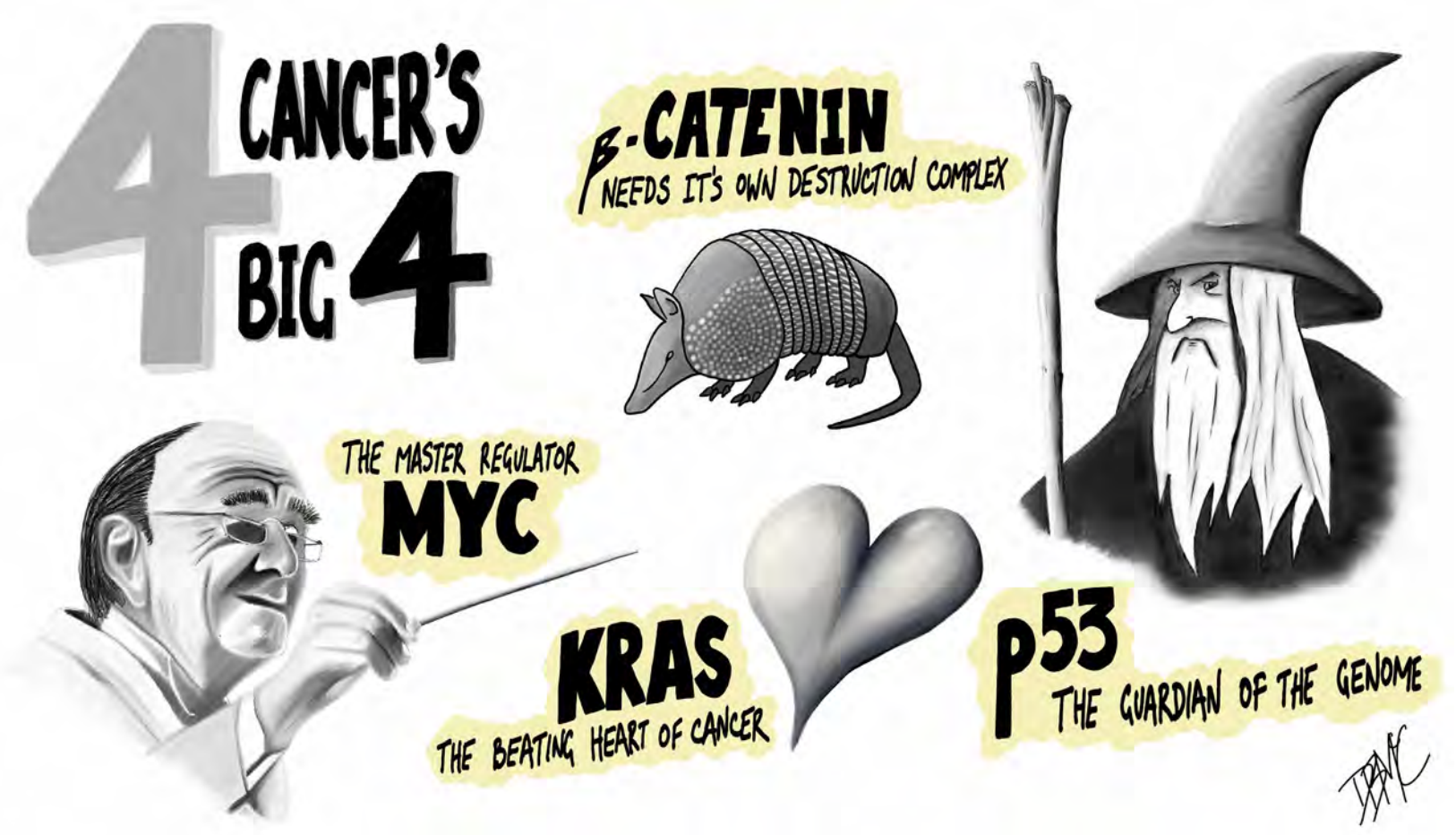
PREFERRED TERM	AEs Irrespective of Causality >10%			Treatment-related AEs >10% and all ≥ Grade 3		
	ALL GRADES	GRADE 3-4	GRADE 5	ALL GRADES	GRADE 3-4*	GRADE 5**
Patients with ≥1 AE	**94%**	**34%**	**4%**	**59%**	**3%**	**<1%**
Asthenia/fatigue	35%	4%	-	13%	<1%	-
Diarrhea	30%	1%	-	20%	-	-
Anemia	20%	4%	-	<1%	-	-
Nausea	18%	-	-	10%	-	-
Dyspnea	13%	5%	-	1%	<1%	-
Vomiting	13%	<1%	-	3%	-	-
Abdominal pain	11%	<1%	-	2%	-	-
Decreased appetite	11%	<1%	-	4%	-	-
Constipation	10%	-	-	1%	-	-
Hypomagnesaemia	10%	<1%	-	<1%	-	-
Infusion-related reaction	7%	1%	-	7%	1%	-
Myalgia	4%	<1%	-	3%	<1%	-
Hypersensitivity**	3%	-	-	3%	-	<1%
Cough	8%	<1%	-	1%	<1%	-
Hypertension	<1%	<1%	-	<1%	<1%	-
Hypoxia	<1%	<1%	-	<1%	<1%	-
Neutropenia	<1%	<1%	-	<1%	<1%	-

*No Grade 4 treatment-related AEs reported
**Grade 5 hypersensitivity in patient with pre-existing severe aortic stenosis (previously reported)
Safety data cut off: 12-Jan-2021.

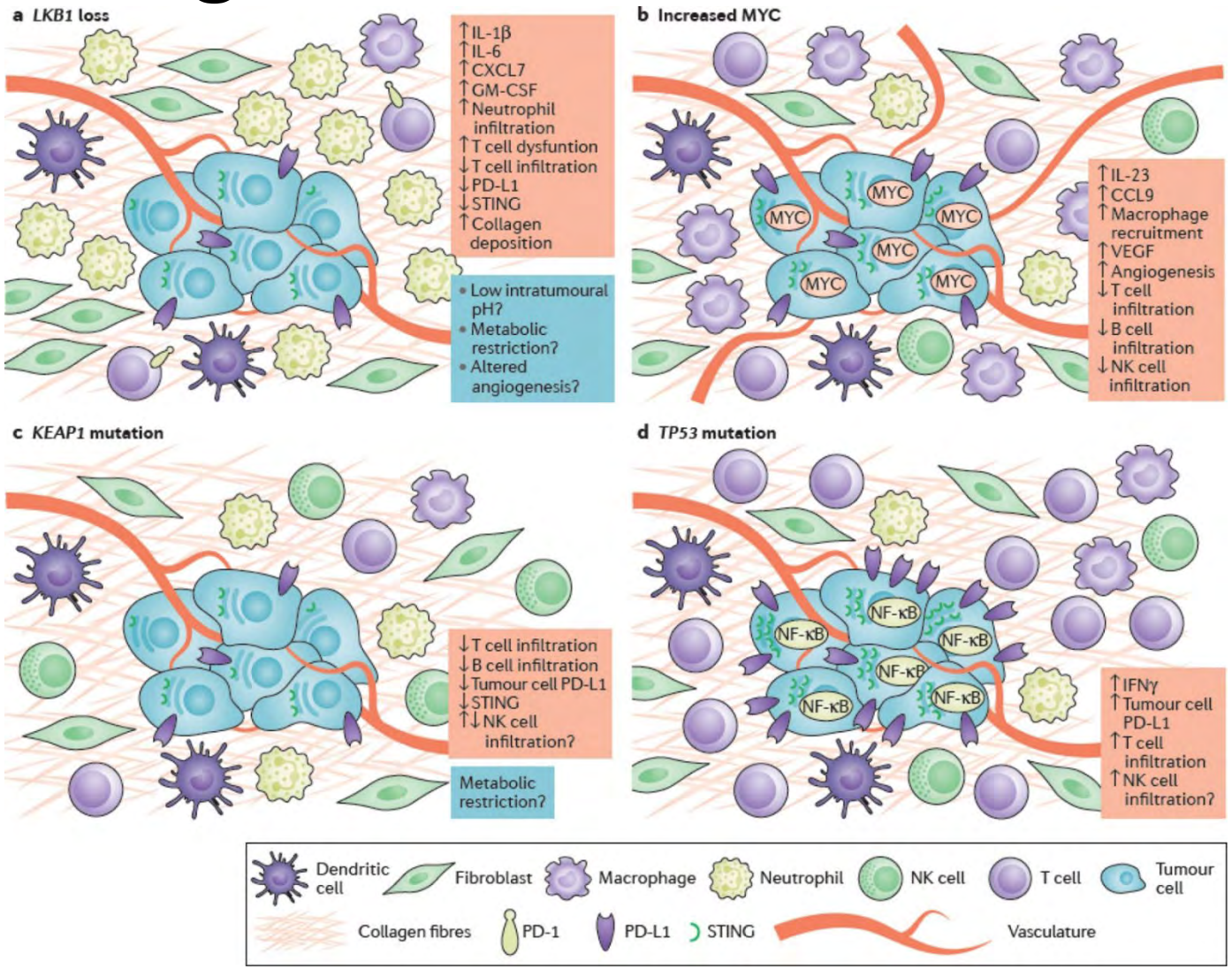
- Safety profile of 157 patients across multiple indications treated with zenocutuzumab at the RP2D in the single agent program
- The majority of AEs were grade 1-2
- Absence of severe gastrointestinal toxicity, skin toxicities and clinical cardiotoxicity

Future strategies for Drug development

Undruggables- the super villians



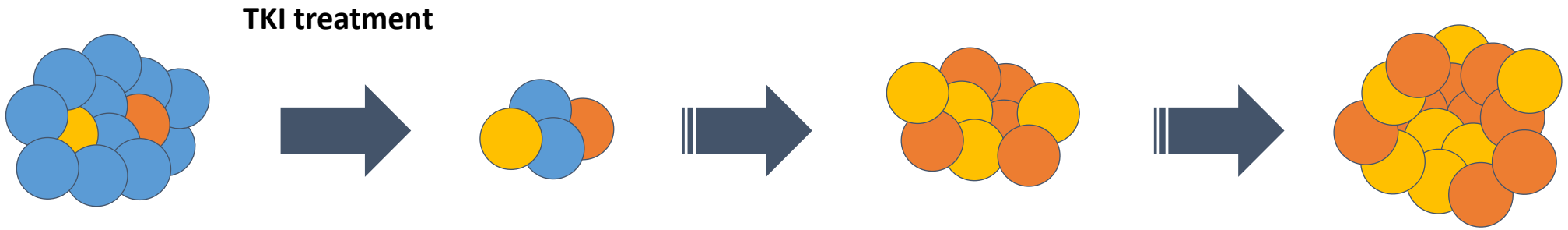
Co-occurring alterations



Skoulidis F, Nat Rev Cancer. 2019

The emergence of resistance mutations severely impacts the durability of TKI's in cancer

Model of the emergence of TKI-resistant mutant clones[1]



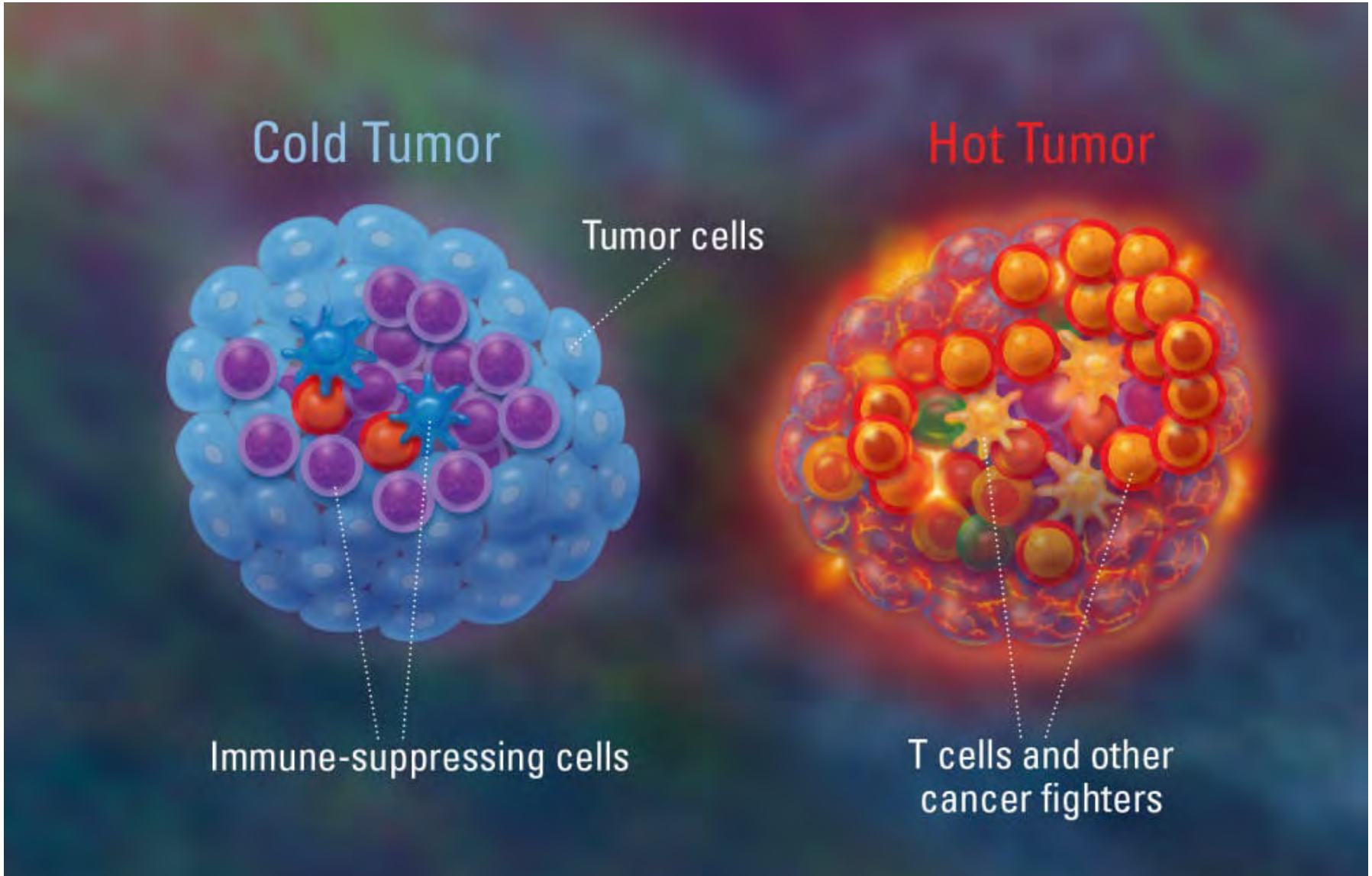
Overcoming resistance mutations in oncogenic drivers is essential for effective precision therapy

Identifying mechanisms of resistance to first generation TKI inhibitors.

Combination therapies, Therapies earlier in the disease course and developing 2nd/3rd/4th generation TKI inbitors

1. Lin JJ, Shaw AT. *Trends Cancer*. 2016;2(7):350-364. 2. Soria J-C et al. *N Engl J Med*. 2018;378(2):113-125.

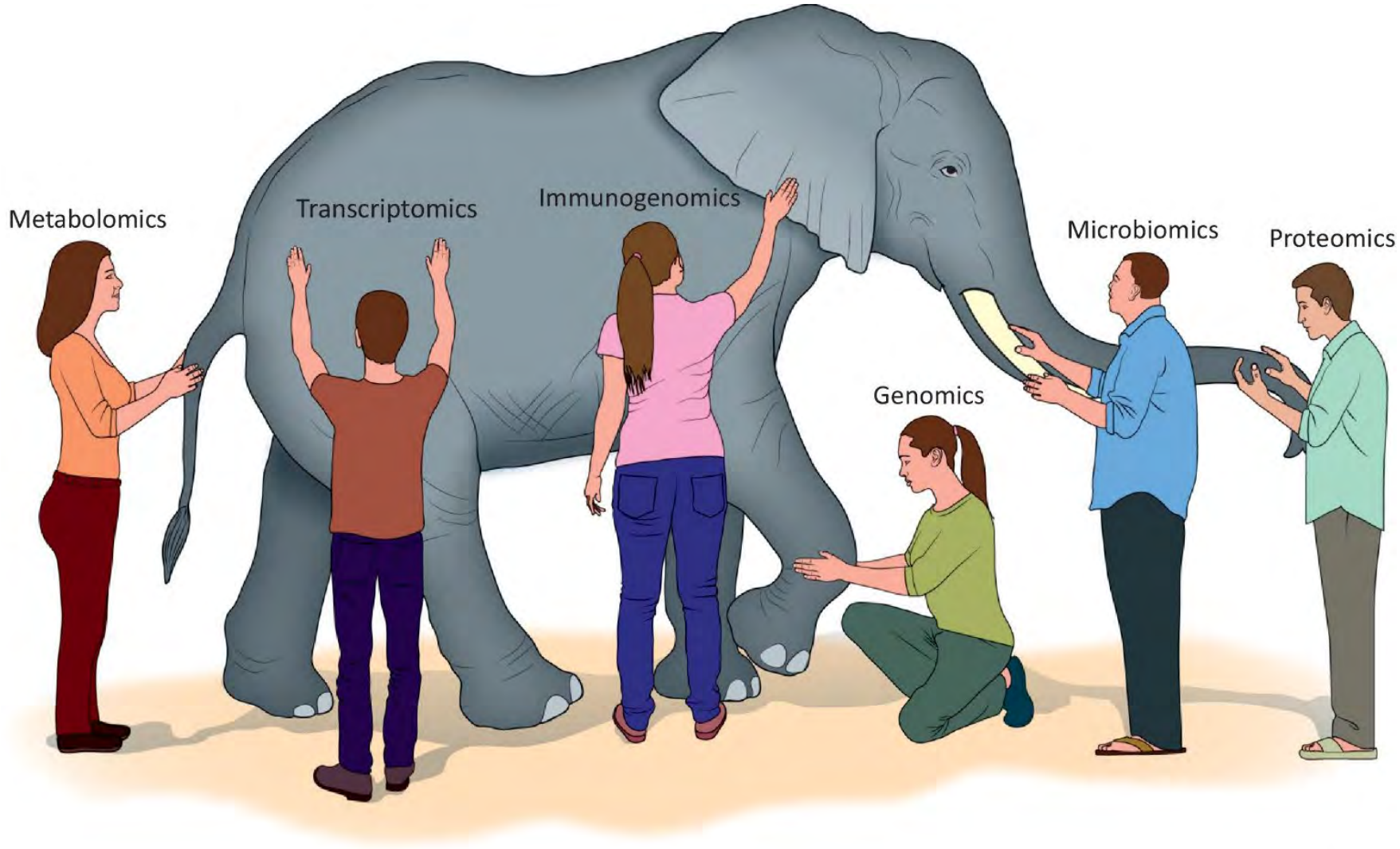
Converting “Cold tumors” to “HOT tumors”



Neoadjuvant therapy in NSCLC

- Surgery is the best option for **Curative intent:**
  - Node-negative pts have residual disease
  - Node-positive pts have residual disease
  - Pts present with distant metastases
  - **Current treatment options are non-curative**
  - ***Neoadjuvant therapy with TKI inhibitor therapy has the potential to improve disease free rates***

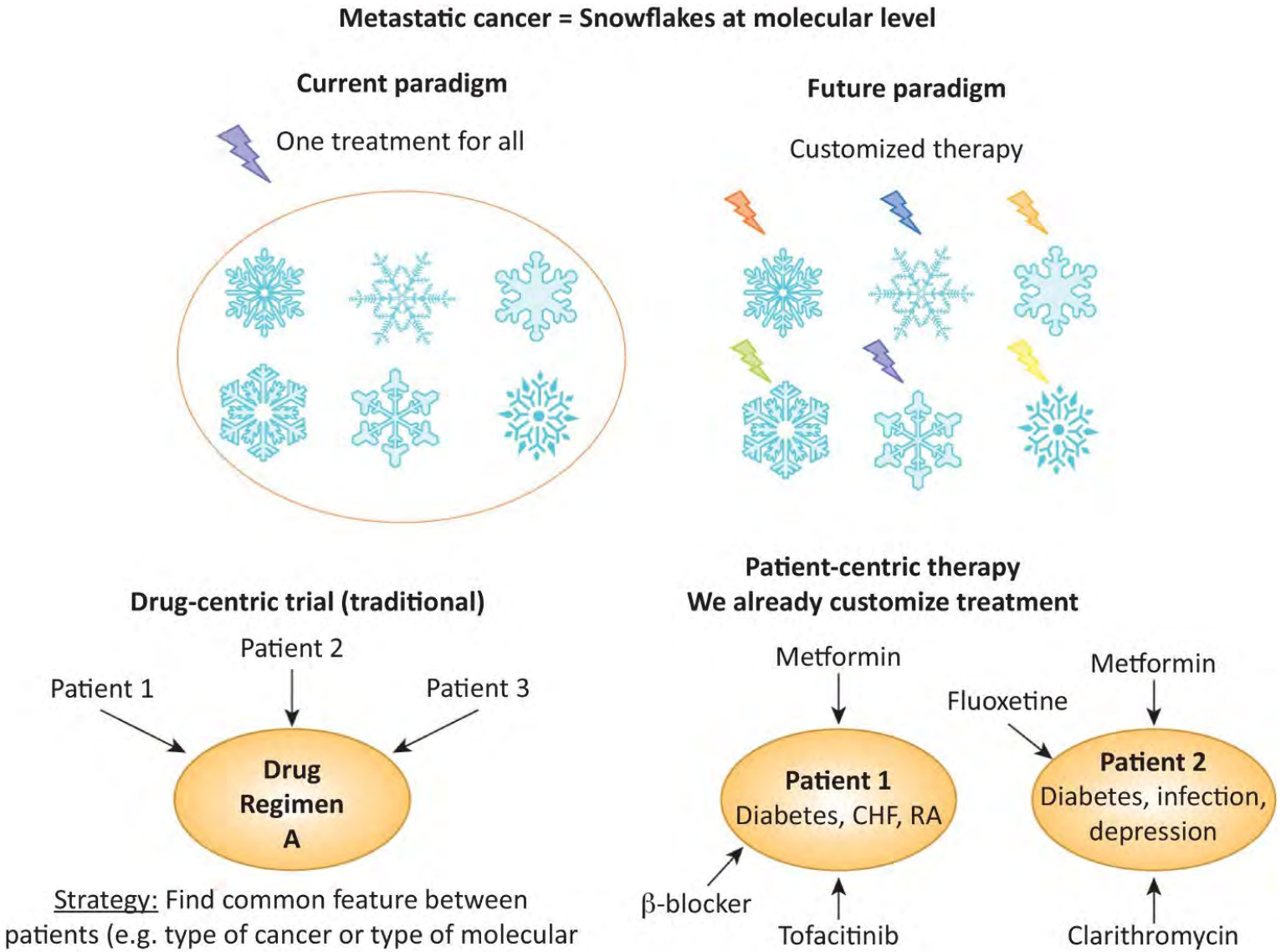
Six Blind Scientists and Elephants



Trends in Cancer

Subbiah V Trends in Cancer 2019

Snowflake Theory and Changing Drug Development Paradigms



Trends in Cancer

Subbiah V et al Trends in Cancer @cellpress

How about an immunotherapy combination?

> 1000 PD-1/L1 inhibitor combo trials

Tang et al,
Annals of Oncology 2018

Throwing spaghetti at the wall to see what sticks

Need to stop serendipitous development of combinations
Biology should be driving development

Strategy for drug development

- **Identifying mechanisms of resistance to first generation TKI inhibitors.**
- **Overcoming resistance mechanisms to first generation TKI drugs.**
- **Development of second generation & beyond TKI's.**
- **Neoadjuvant strategy**
- **Combination therapies: RAS/ RAF/ MTOR/ CDK pathway ?**
- **TKI+ Immunotherapy combinations ?**
- **National and international registry of genomics and beyond**

Acknowledgements

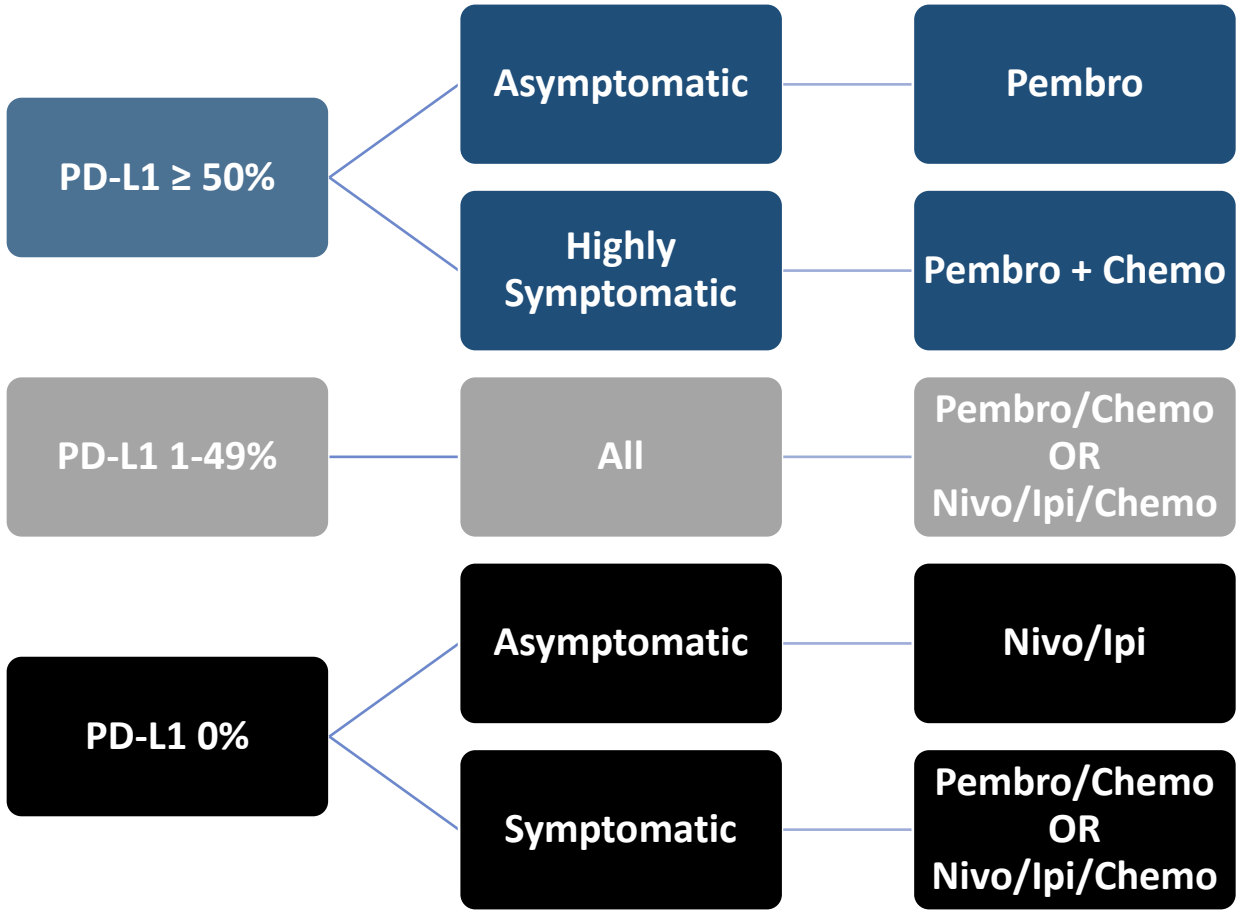
- **Motivated Patients and families who enrolled on the clinical trials**

Email:Vivek.Subbiah@scri.com

Twitter: @VivekSubbiah

tweets(my own)

What do I do?


PD-L1 ≥ 50%
Asymptomatic
Pembro
Highly Symptomatic
Pembro + Chemo
PD-L1 1-49%
All
Pembro/Chemo OR Nivo/Ipi/Chemo
PD-L1 0%
Asymptomatic
Nivo/Ipi
Symptomatic
Pembro/Chemo OR Nivo/Ipi/Chemo