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Masters in Thoracic Oncology Summit
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Deciphering the Mechanism of Resistance to First Generation KRAS Inhibitors

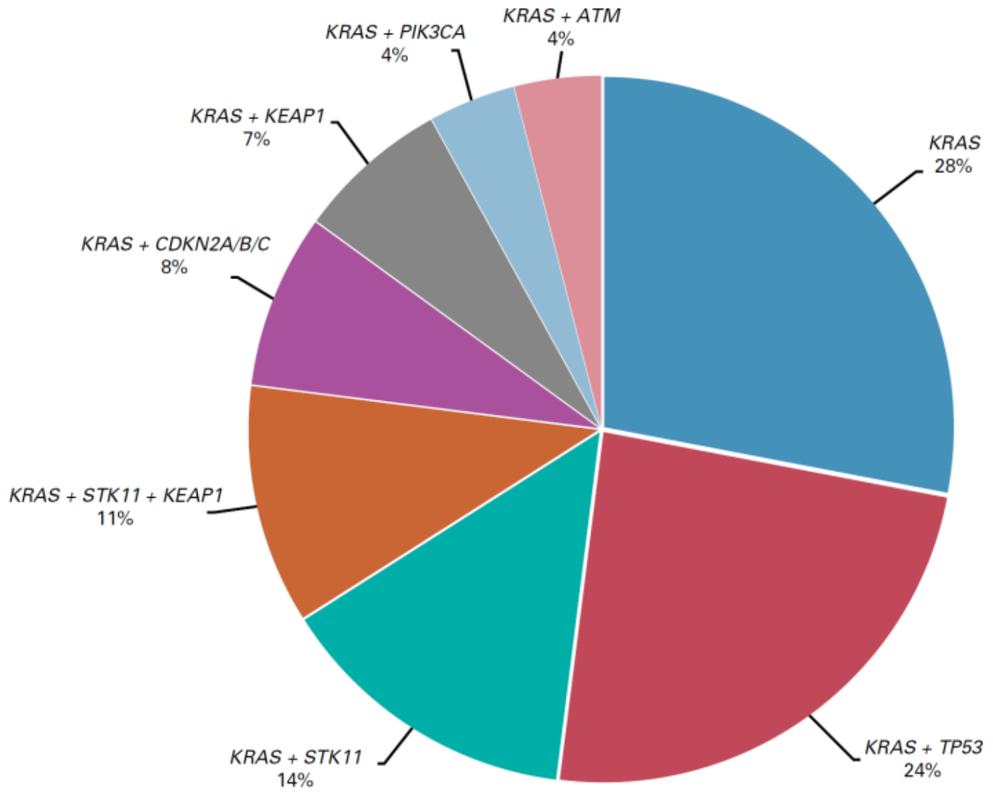
Karen Reckamp, MD, MS

Professor, Department of Medicine
Director, Division of Medical Oncology
Associate Director, Clinical Research
Cedars Sinai Cancer

Co-mutations as potentially predictive markers in *KRAS* mutated NSCLC

- Most common *TP53*, *STK11, KEAP1*
  - Arbour et al (n=330): *TP53* (42%), *STK11* (29%), *KEAP1* (24%)
  - Scheffler et al (n=1078): *TP53* (39%); (n=101 subset): *STK11* (20%), *KEAP1* (13%)
  - Aredo et al (Stanford; $KRAS^{G12C}$ mutation subtype): *TP53* 31% and *STK11* 27%

- Preclinical– differences in signaling, immune features, metabolic programming
- Prognostic
- Potentially predictive with treatment (e.g. immunotherapy)

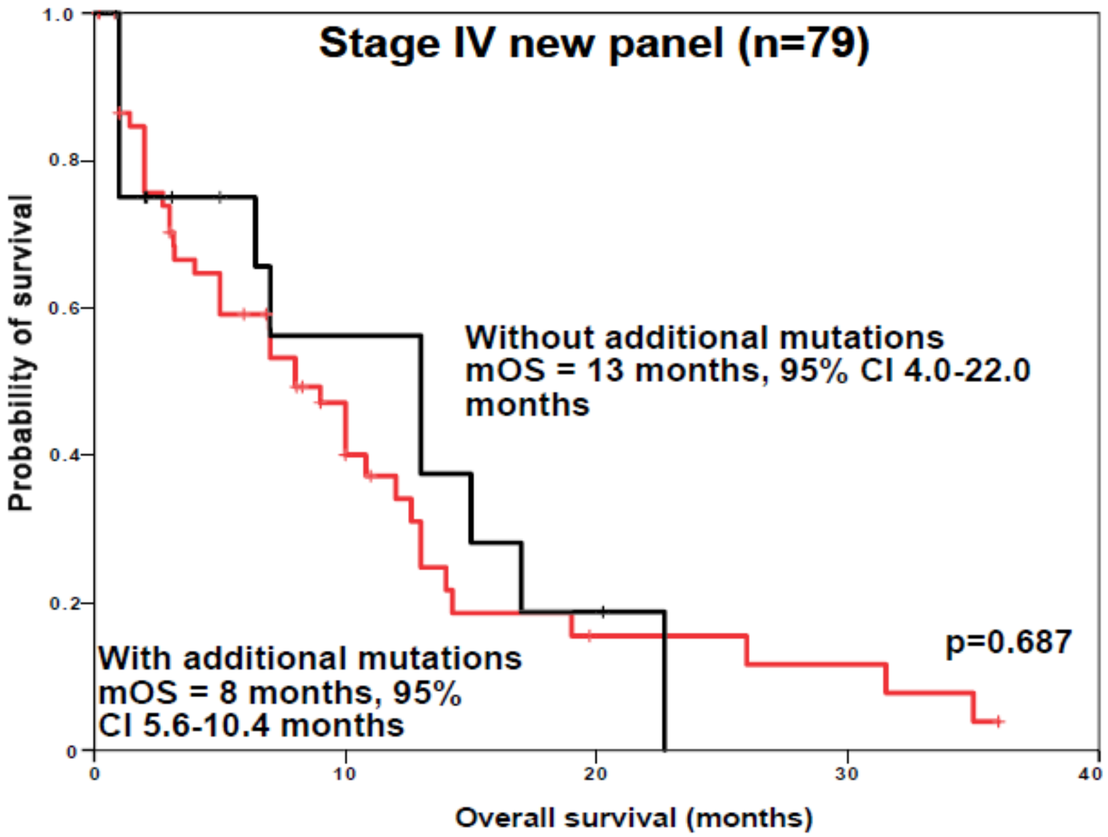


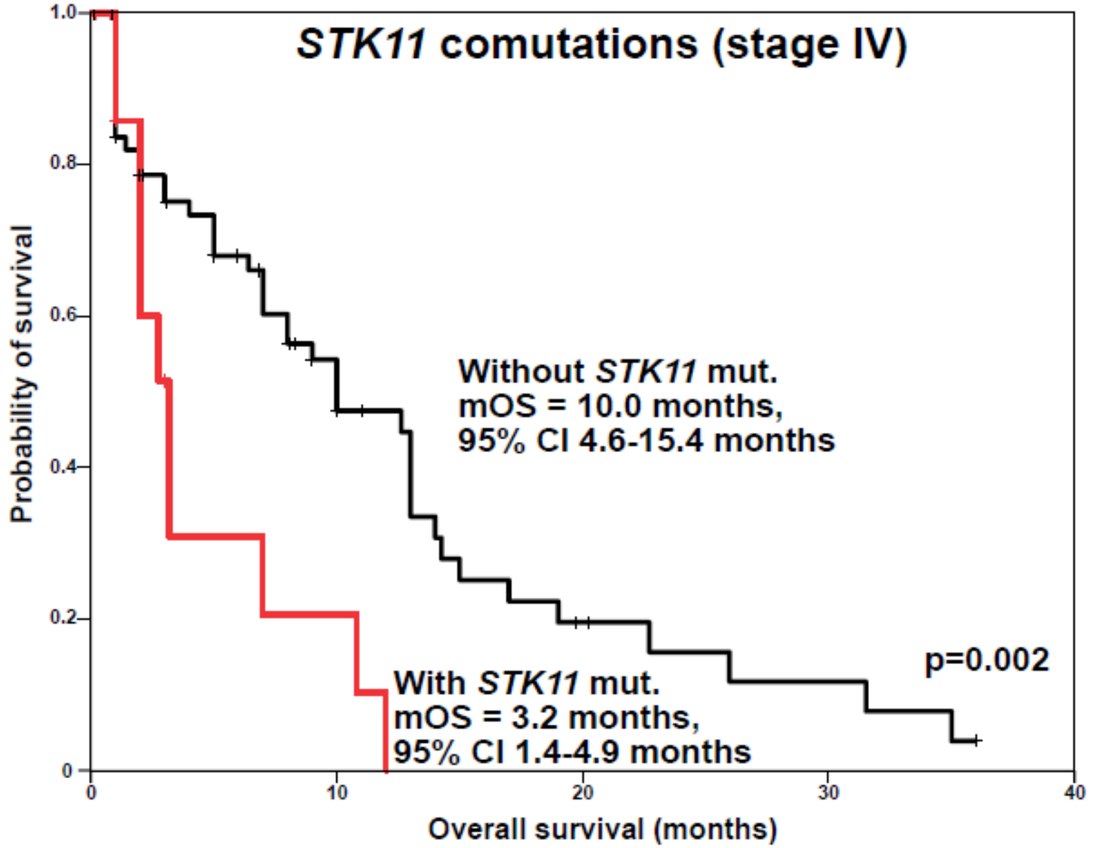
Clustering analysis of 776 cases of *KRAS* mutated NSCLC

Figure from Padda SK et al. JCO Precision Oncology 2021:5, 153-162

Arbour KC et al. Clin Cancer Res, 2018. 24(2): p. 334-340. Scheffler M et al. J Thorac Oncol, 2019. 14(4): p. 606-616. Aredo JV et al Lung Cancer, 2019. 133: p. 144-150. Chen Z et al. Nature. 2012 Mar 18;483(7391):613-7. Skoulidis F et al. Cancer Discovery. 2015 Aug 1;5(8):860-77.; Galan-Cobo et al. Cancer Res. 2019 Jul 1;79(13):3251-3267; Skoulidis F et al. Cancer Discov 2018

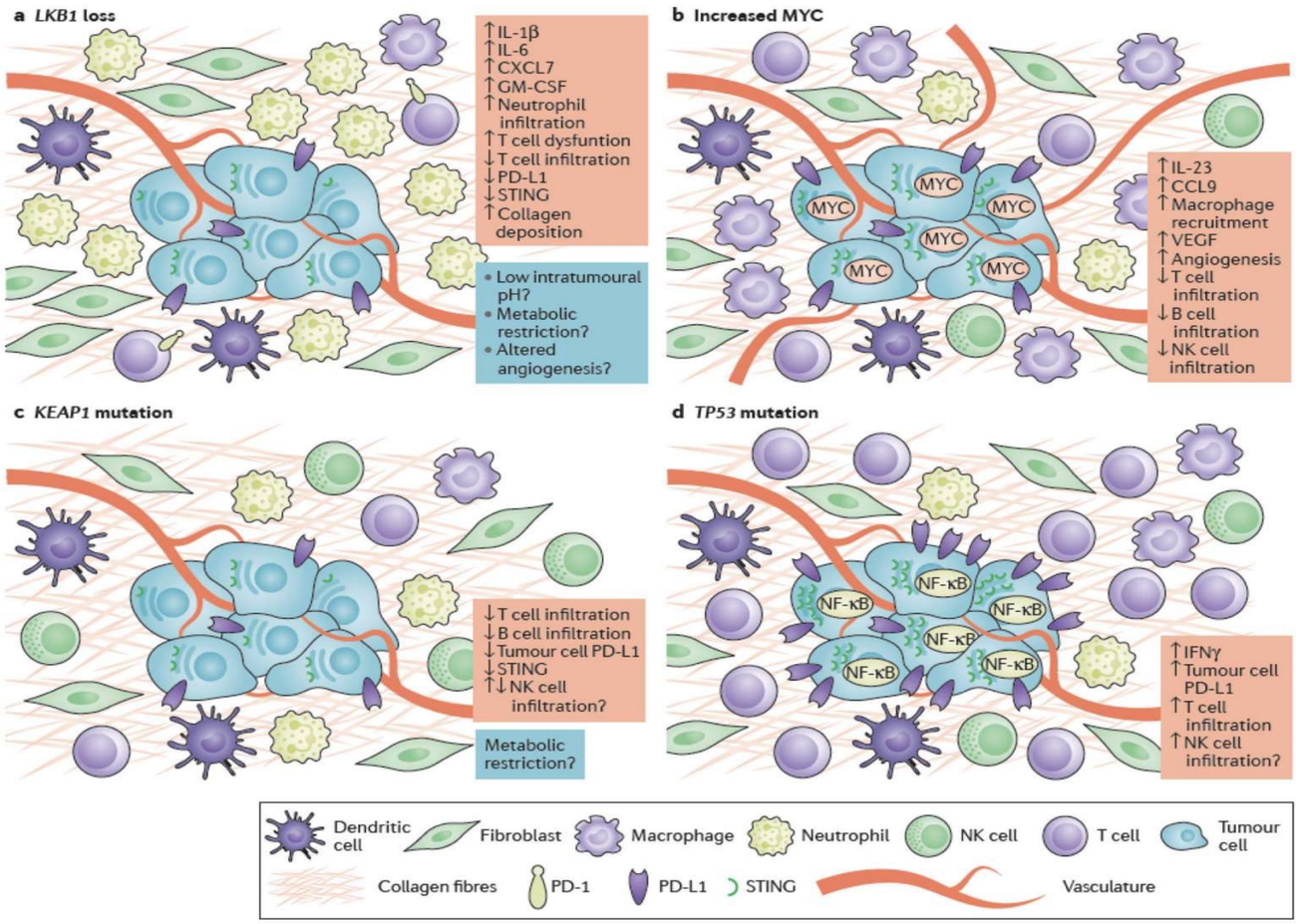
Overall survival in *KRAS* mutant NSCLC by co-mutation

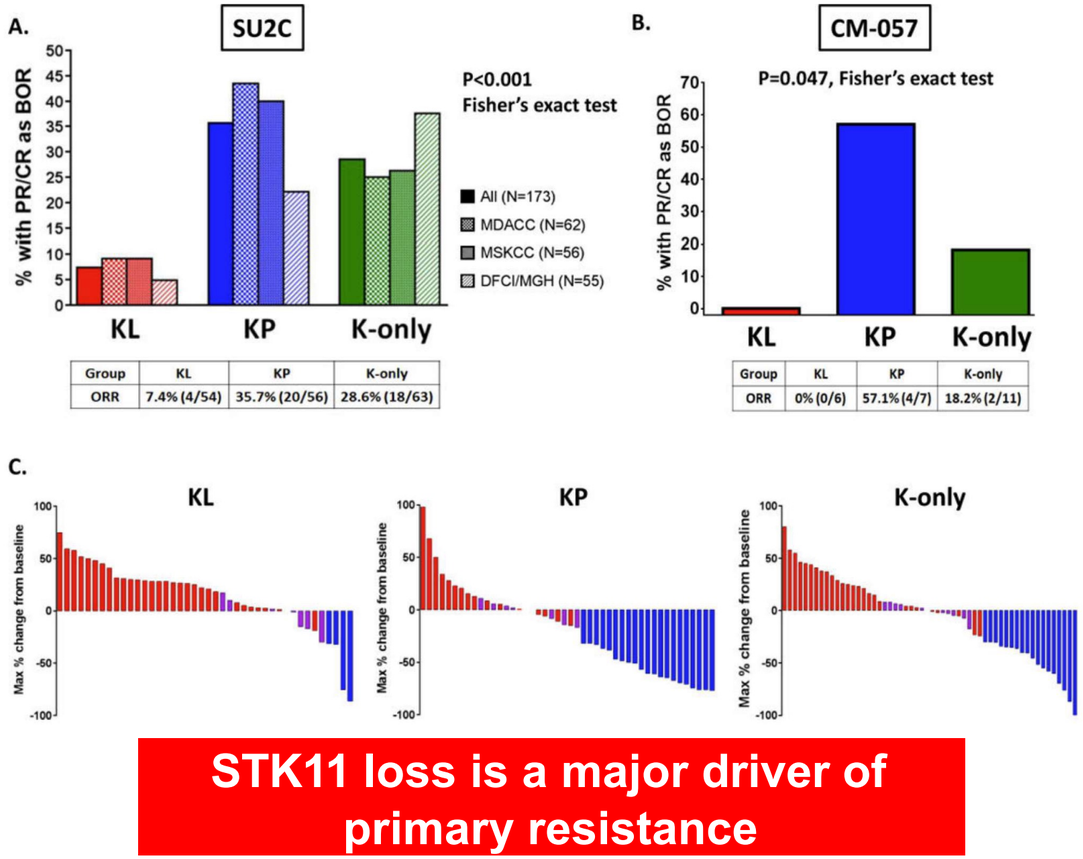




Scheffler et al J Thorac Oncol 2019

Clinical Impact of KRAS co-alterations



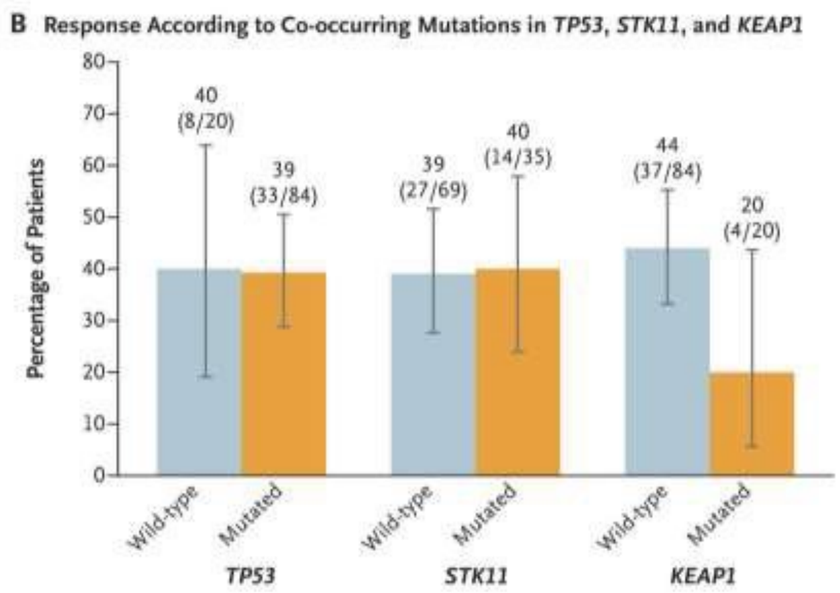


STK11 loss is a major driver of primary resistance

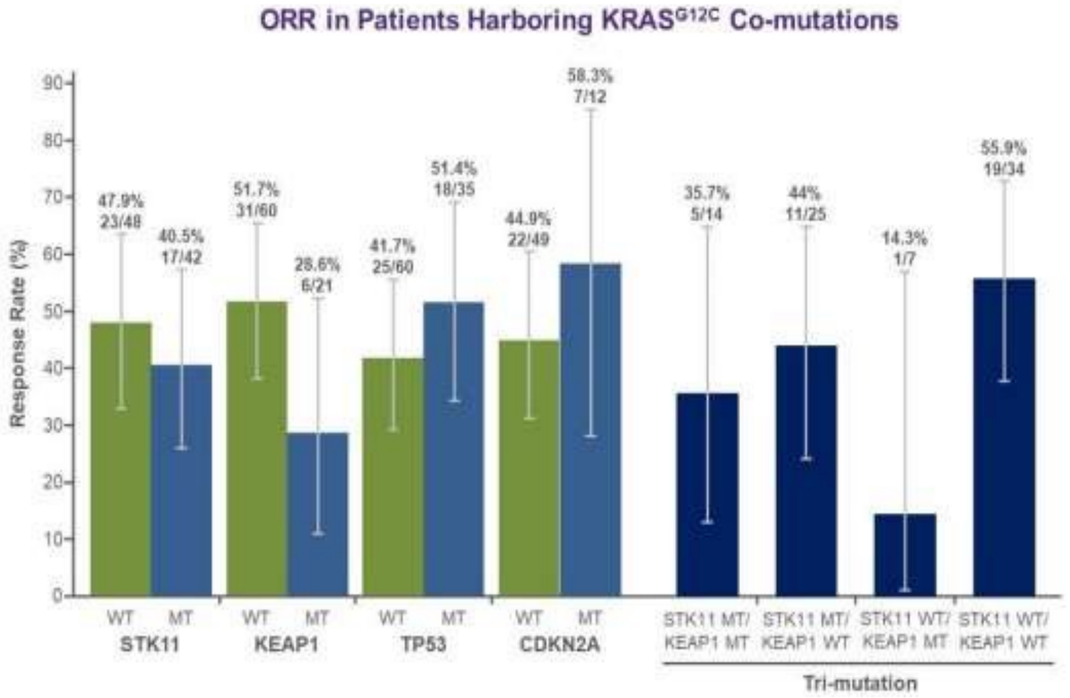
Skoulidis F et al Nat Rev Cancer. 2019 September ; 19(9):495–509.
Skoulidis F et al Cancer Discov. 2018 July ; 8(7):822–835.

Objective Response Rates by KRAS G12C Co-alterations TP53, STK11, KEAP1

Sotorasib

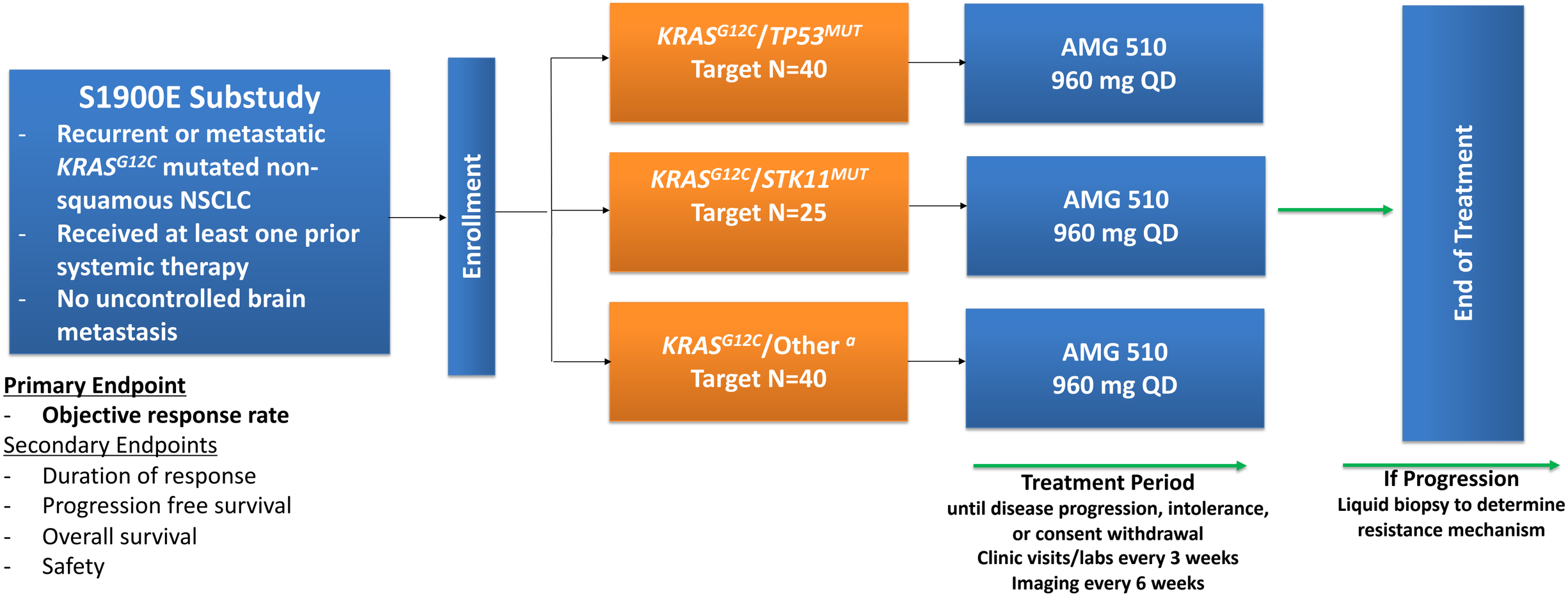


Adagrasib



Skoulidis F, et al, N Engl J Med 2021;384:2371-81. Spira AI, et al, ASCO 2022

Lung-MAP S1900E—Evaluation of sotorasib in *KRAS* G12C mutant NSCLC with specific co-mutations



Primary Endpoint

- **Objective response rate**

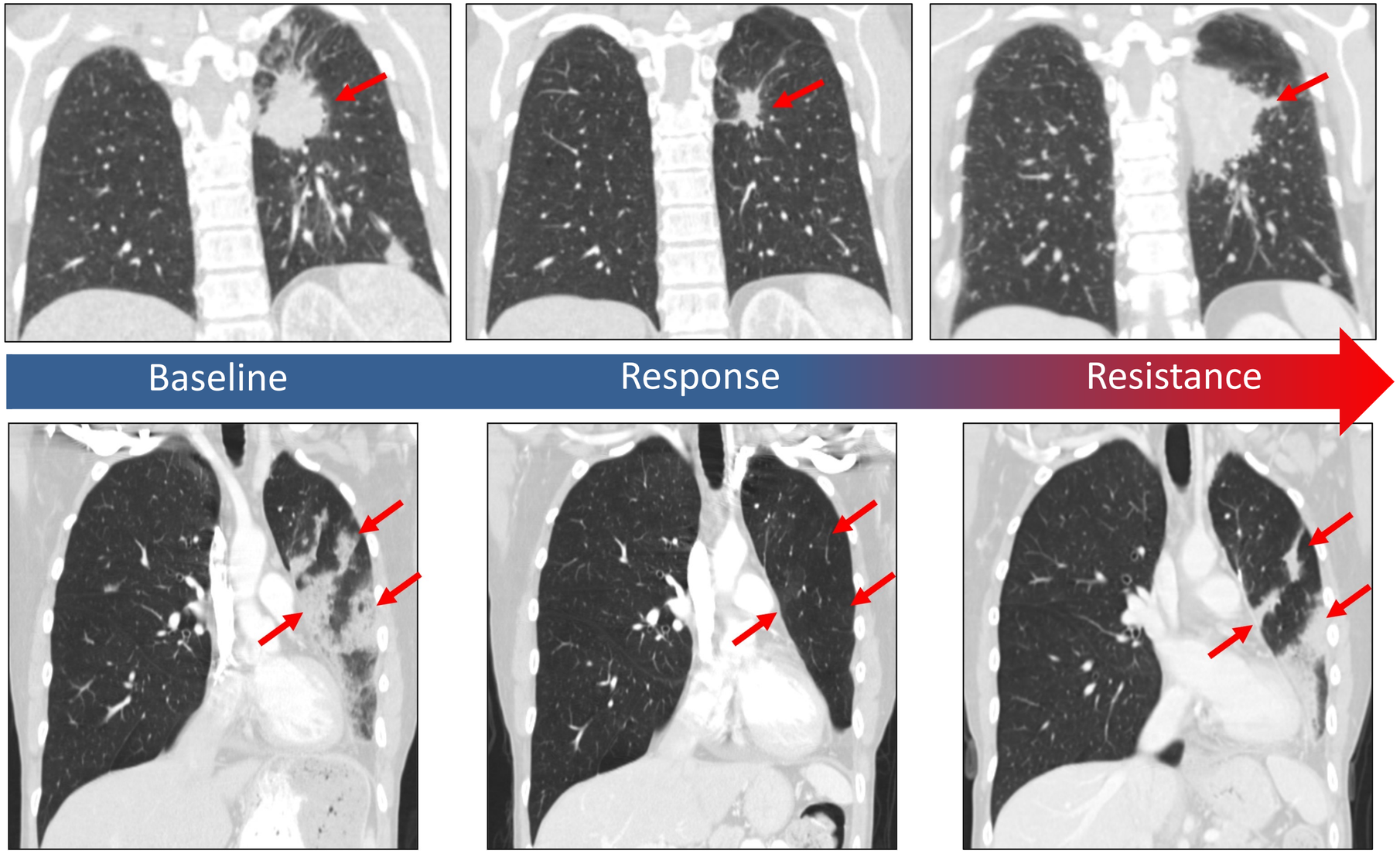
Secondary Endpoints

- Duration of response
- Progression free survival
- Overall survival
- Safety

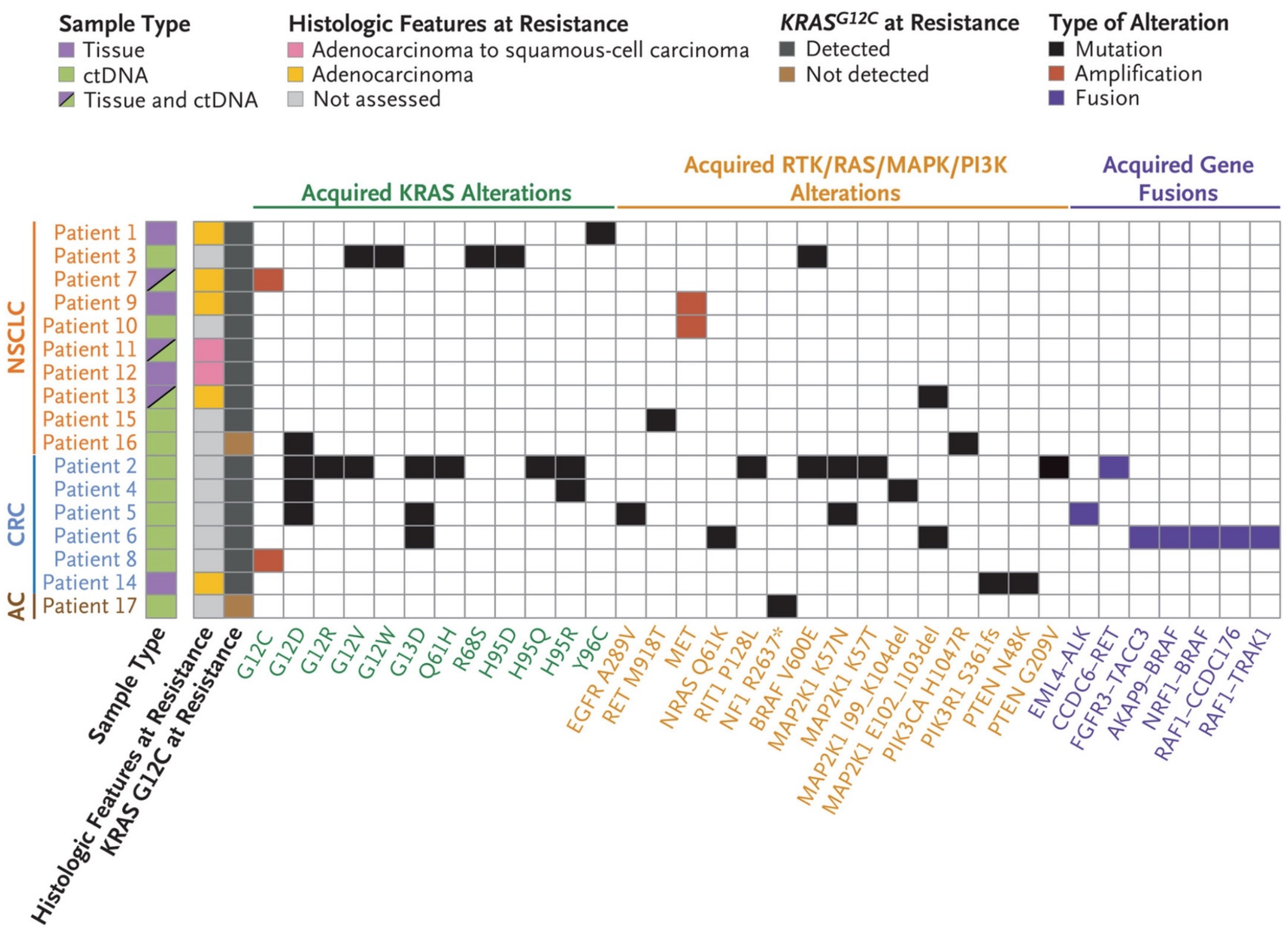
[a]other co-mutations (e.g., *KEAP1, NFE2L2, CUL3*), double or triple co-mutations (e.g., *STK11/TP53, STK11/TP53/KEAP1*), or no co-mutations

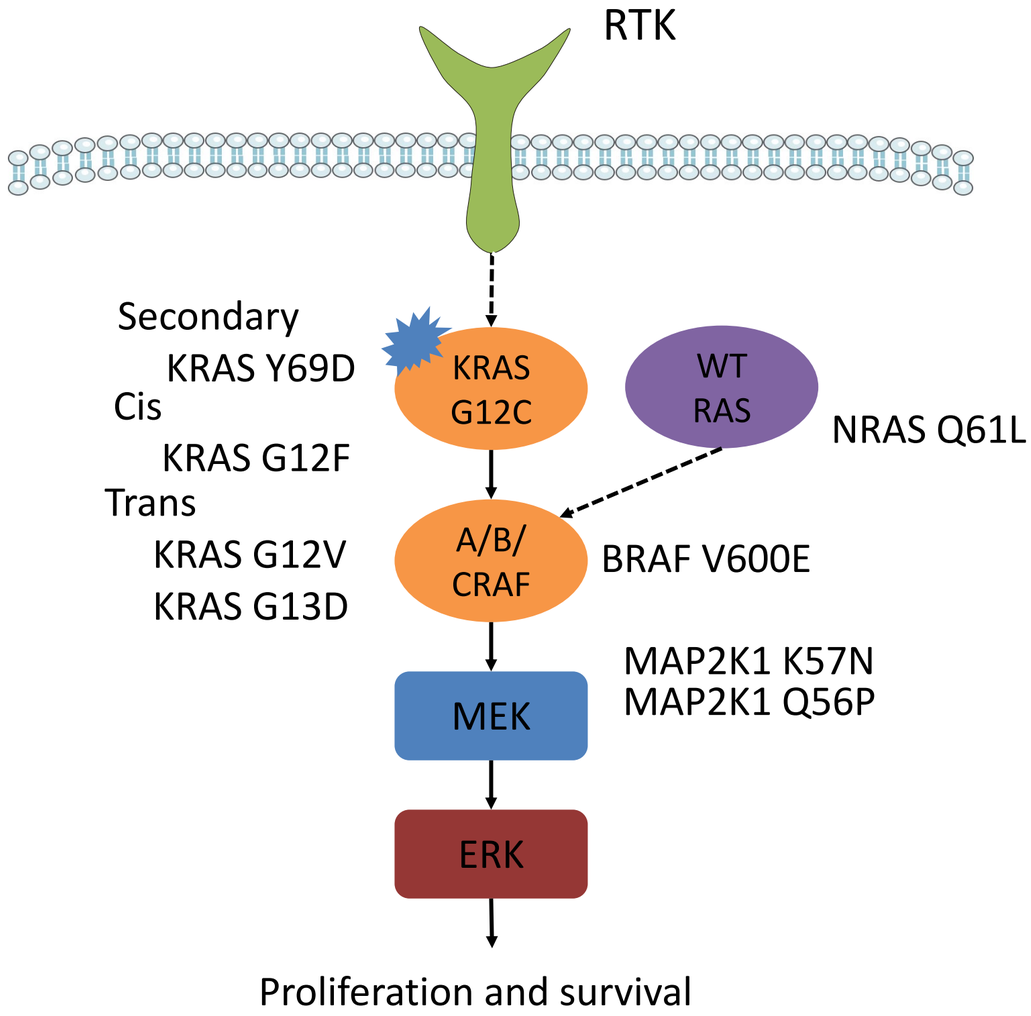
Acquired Resistance

KRAS G12C mutant



Acquired Resistance to *KRAS* G12C Inhibitors





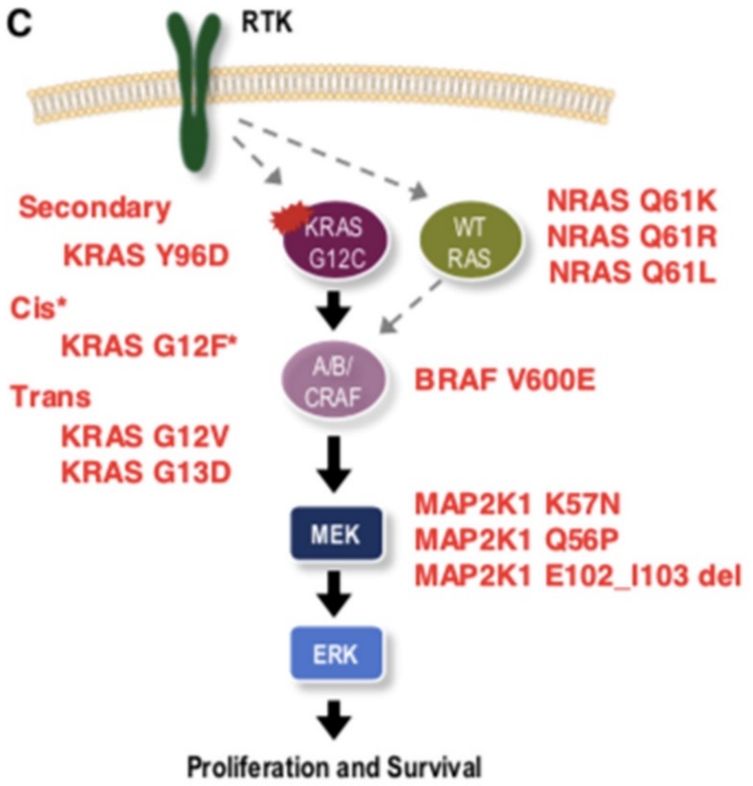
Awad. NEJM. 2021;344:2382. Tanaka. Cancer Discov. 2021:11:1.

Resistance to G12C Inhibitors

B

	Tumor	cfDNA			
	Pre-MRTX849	Pre-MRTX849	Days post-MRTX849 discontinuation: 0	9	51
TP53 F338fs	36.8%	0.22%	8.8%	10.1%	14.3%
KRAS G12C	21.3%	0.12%	31.7%	47.1%	24.9%
KRAS G12V	-	-	-	-	0.09%
KRAS G13D	-	-	-	0.13%†	0.04%
KRAS Y96D	-	-	0.4%	0.2%	-
NRAS Q61L	-	-	-	0.2%	-
NRAS Q61R	-	-	-	-	0.02%
NRAS Q61K	-	-	0.6%	0.6%	0.9%
BRAF V600E	-	-	0.1%	0.1%	0.5%
MAP2K1 K57N	-	-	0.05%†	-	0.3%
MAP2K1 Q56P	-	-	-	-	0.1%
MAP2K1 E102_I103del	-	-	-	0.12%†	0.2%

C

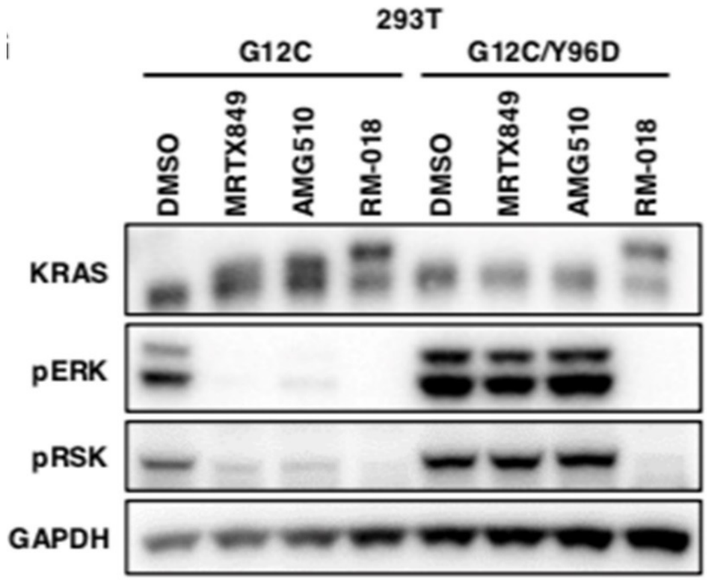


Mechanisms of Resistance

1) Activation of other RAS isoforms (NRAS)
2) Other KRAS activating mutations in trans (G13D, G12V)
3) Loss of G12C thru mutational switch to different KRAS mutation in cis
4) Novel KRAS Y96D alters drug binding

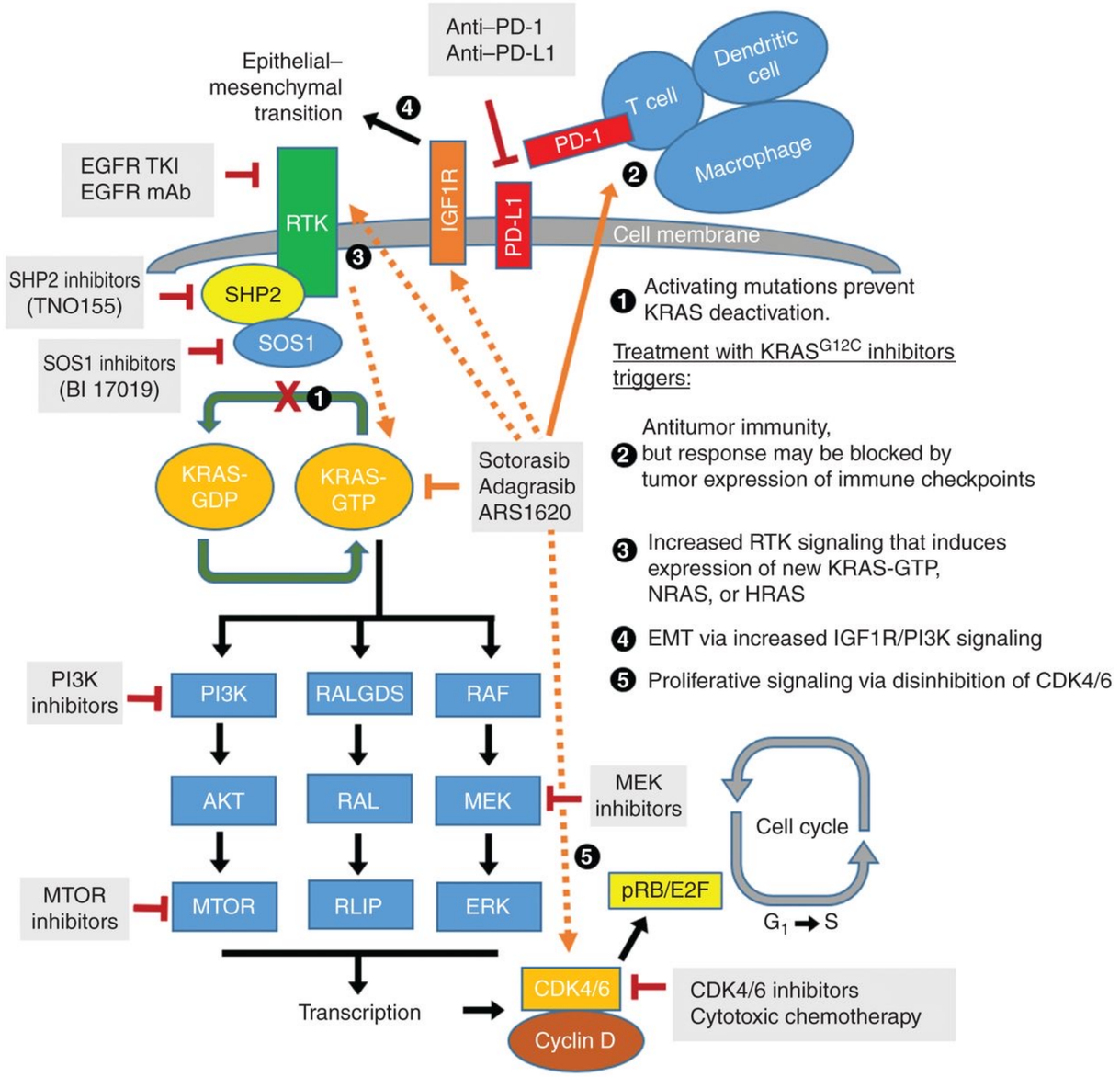
Tanaka N, et al. *Cancer Discov*. 2021;11(8):1913-1922.

Complexity of resistance to G12C inhibitors



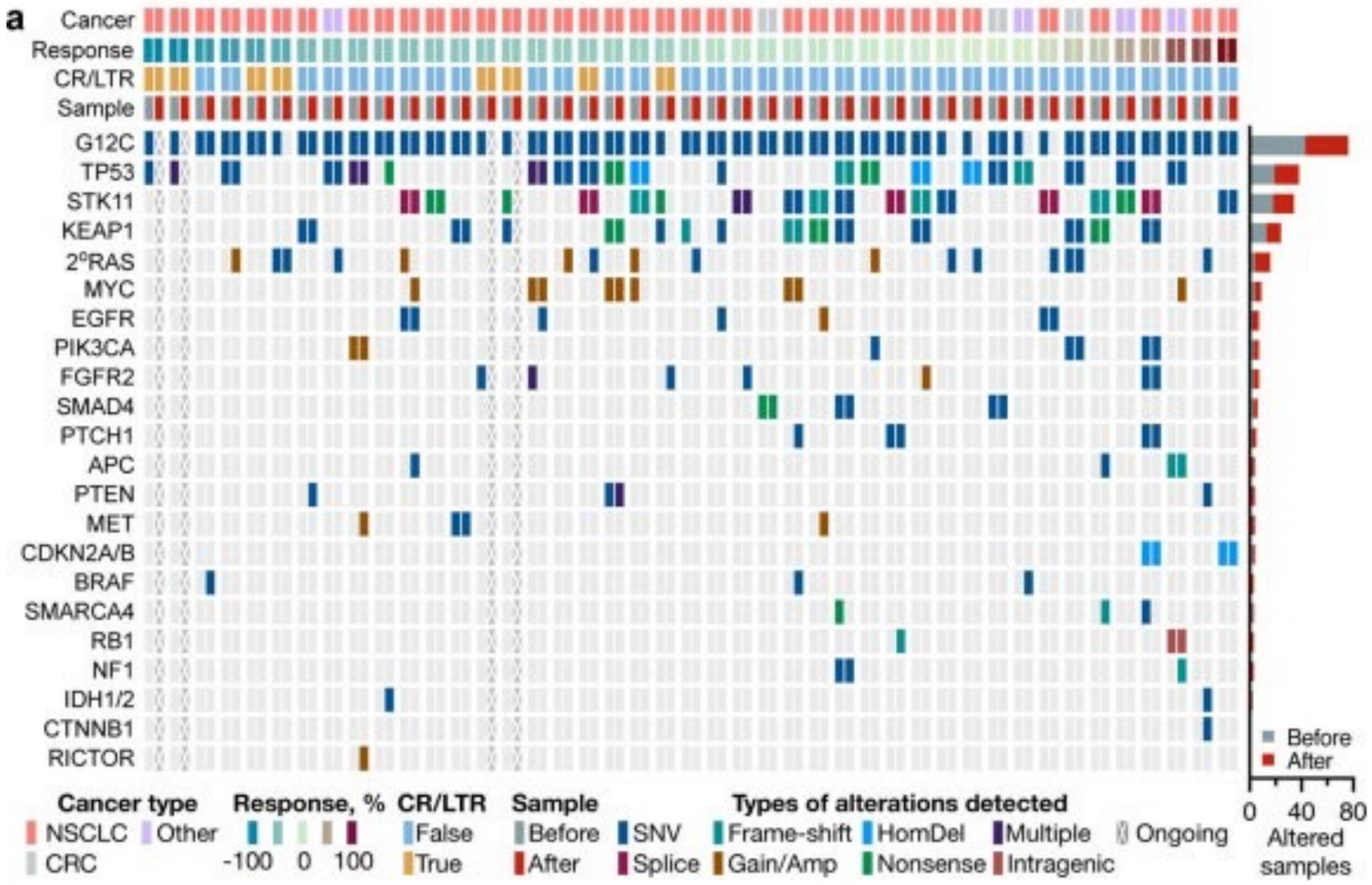
RM-018 blocks downstream signaling in KRAS G12C/Y96D

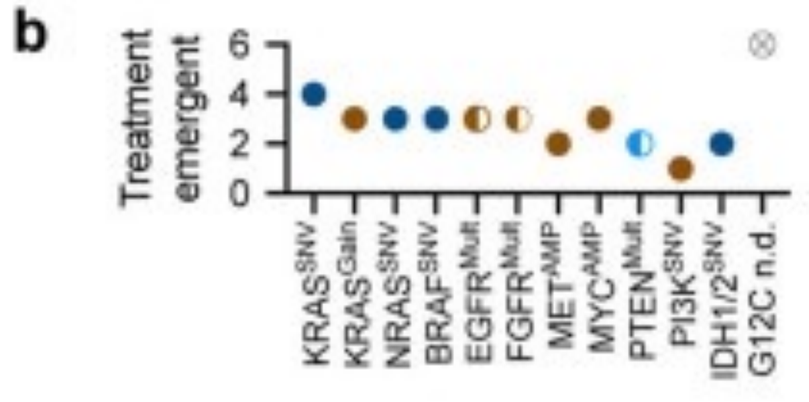
RM-018 = KRAS G12C (ON) inhibitor

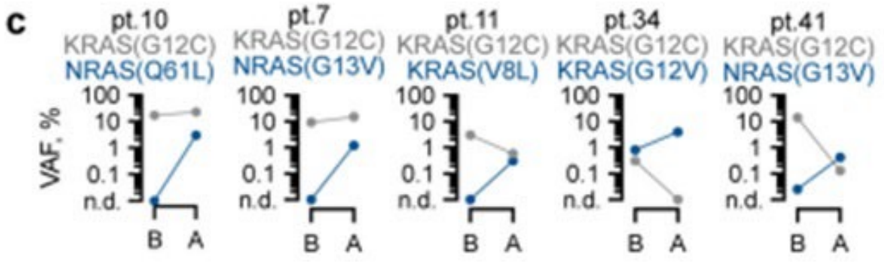


Akhave et al. Cancer Discov 2021

Resistance to G12C inhibitors

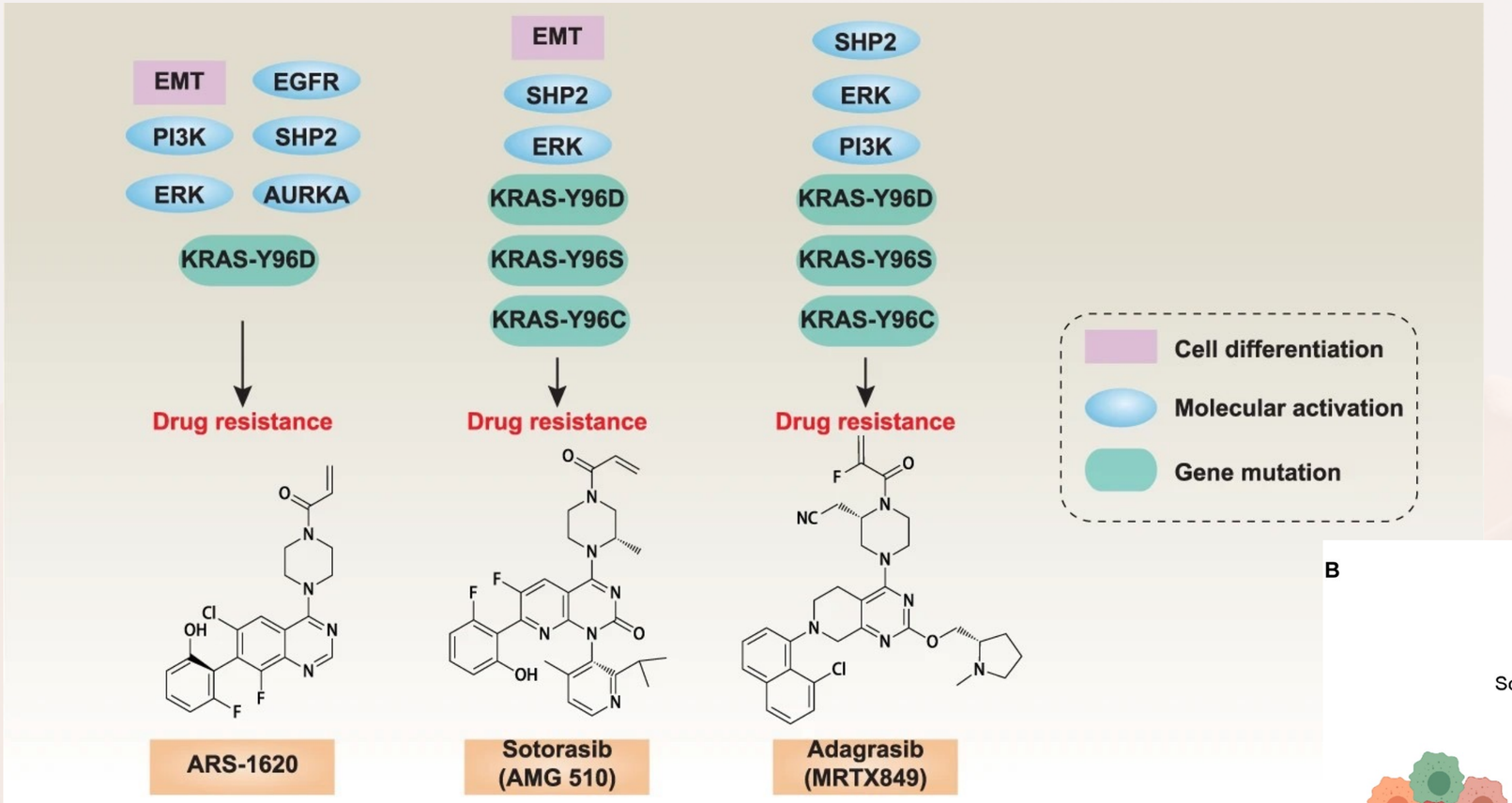




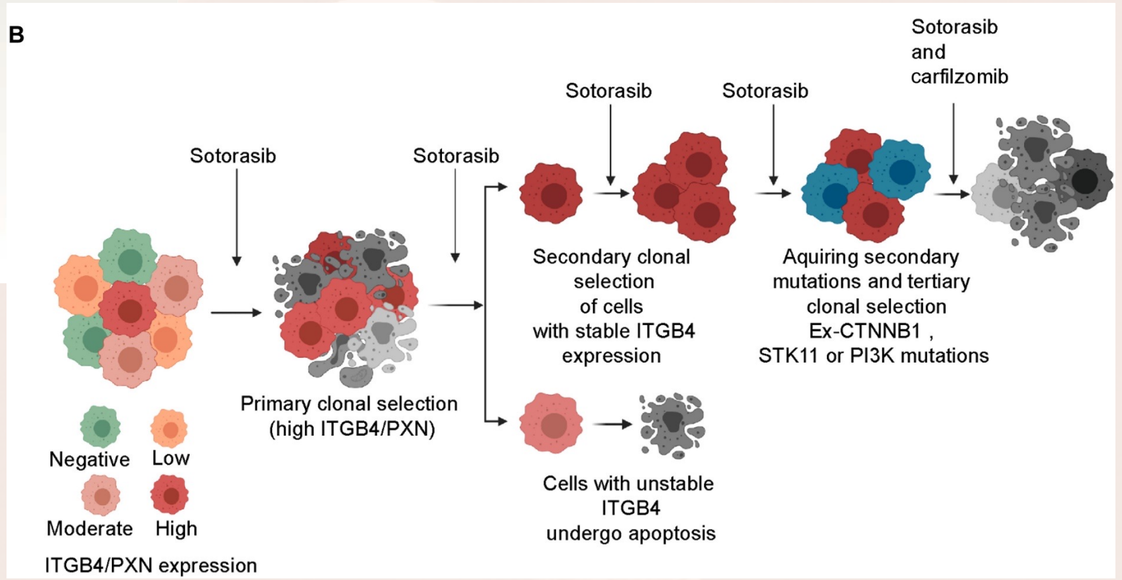


Zhao Y, et al. *Nature*. 2021;599(7886):679-683.

KRAS G12C resistance mechanisms

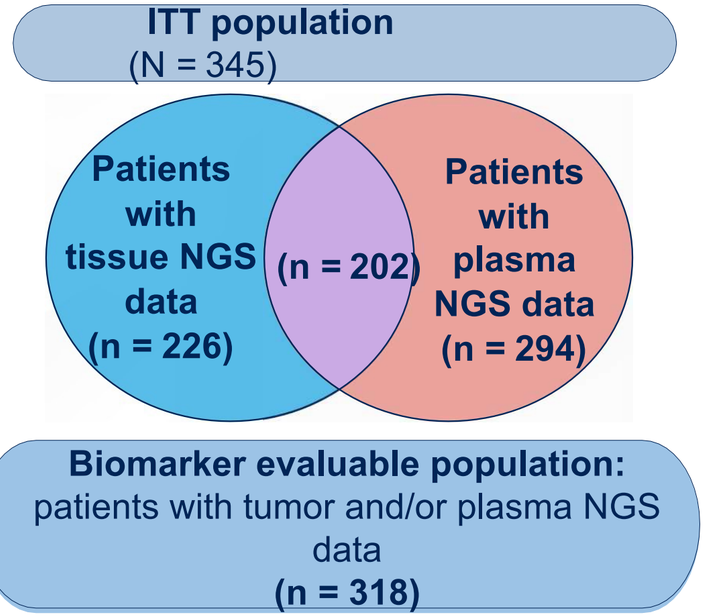


Liu J, Kang R, Tang D. Cancer Gene Ther 2022



Salgia R et al. Science Adv 2023

Biomarker Subgroup Analysis of Codebreak 200

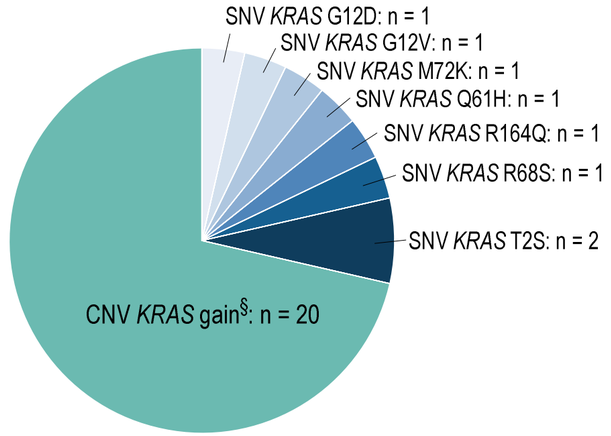


Baseline co-alterations were balanced in the Sotorasib and Docetaxel arms

Sotorasib Retained PFS Benefit Versus Docetaxel Across Key Co-alteration Subgroups

- How to use this information in clinical practice?
  - STK11, KEAP1, TP53 ✓
  - Additional RAS (non-KRAS G12C) alterations X
  - ?NOTCH1 ✓ / X
- Limitations
  - Small numbers
  - Exploratory endpoints
- What about acquired resistance?

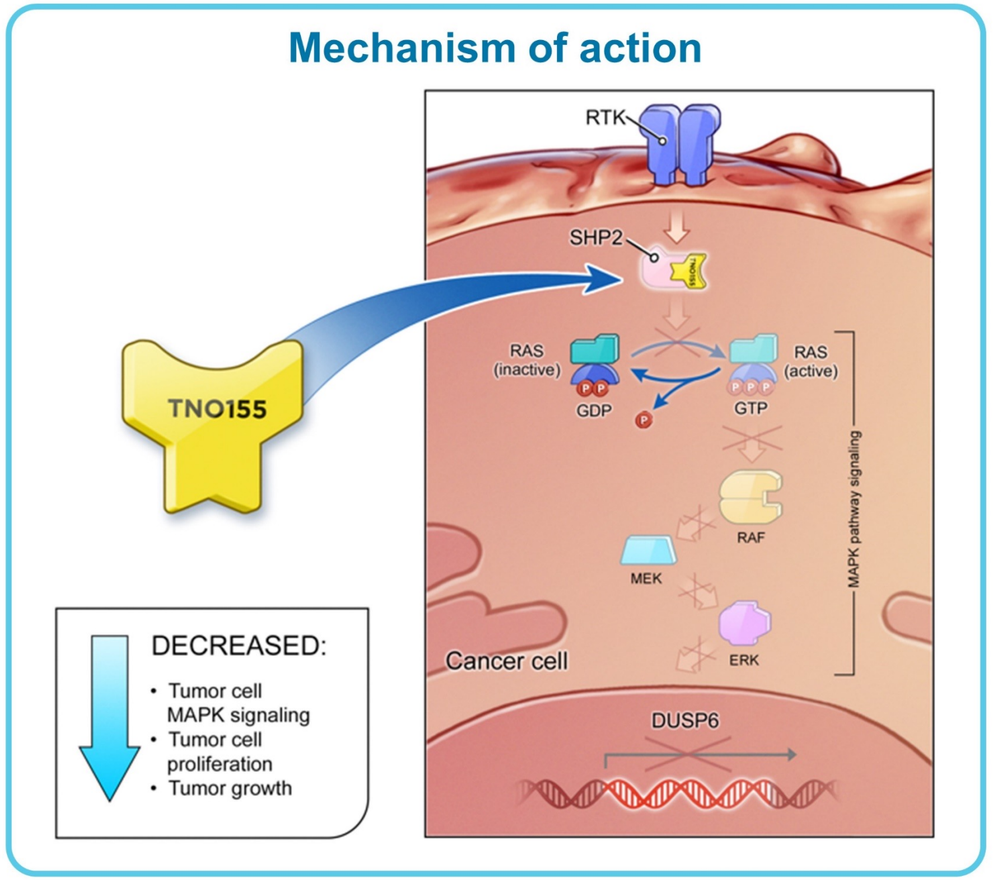
	Sotorasib (n = 164)	Docetaxel (n = 154)	Treatment Difference (*P*-value)
***KRAS* co-alteration*, n (%)**	**9 (5)**	**17 (11)**	
ORR†, n (%)	0	0	–
Median PFS (m)	1.8	2.5	0.016‡
HR (95% CI)‡	1.74 (0.84, 3.58)		



Skoulidis et al ASCO 2023

SHP2 in overcoming KRAS G12C inhibitor resistance

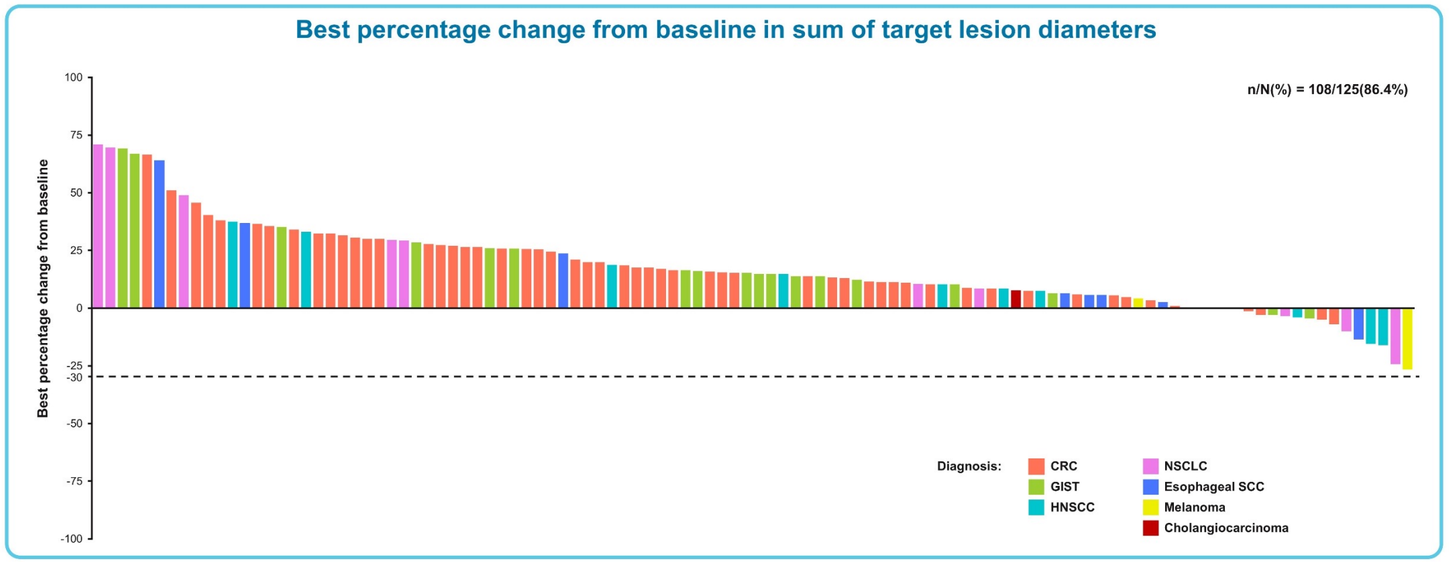
- SHP2 is a cytoplasmic phosphatase that transduces signaling from RTKs, such as EGFR, MET, and HER2[1]
- Upon activation of RTK, SHP2 activates signaling pathways, including the RAS/MAPK pathway[1–3]
- RTK and RAS signaling is frequently deregulated in many cancer types[3]
- Patients with RTK-driven cancers can develop resistance to RTK- and MAPK-targeted agents;[4,5] targeting SHP2 may potentially offer an alternative treatment option for these patients
- TNO155 is an orally bioavailable, selective, first-in-class allosteric inhibitor of wild-type SHP2[6]
- CTNO155X2101 (NCT03114319) is an ongoing first-in-human, open-label dose escalation/expansion trial of TNO155 in adults with select advanced solid tumors; here we describe data from the TNO155 single-agent dose-escalation part



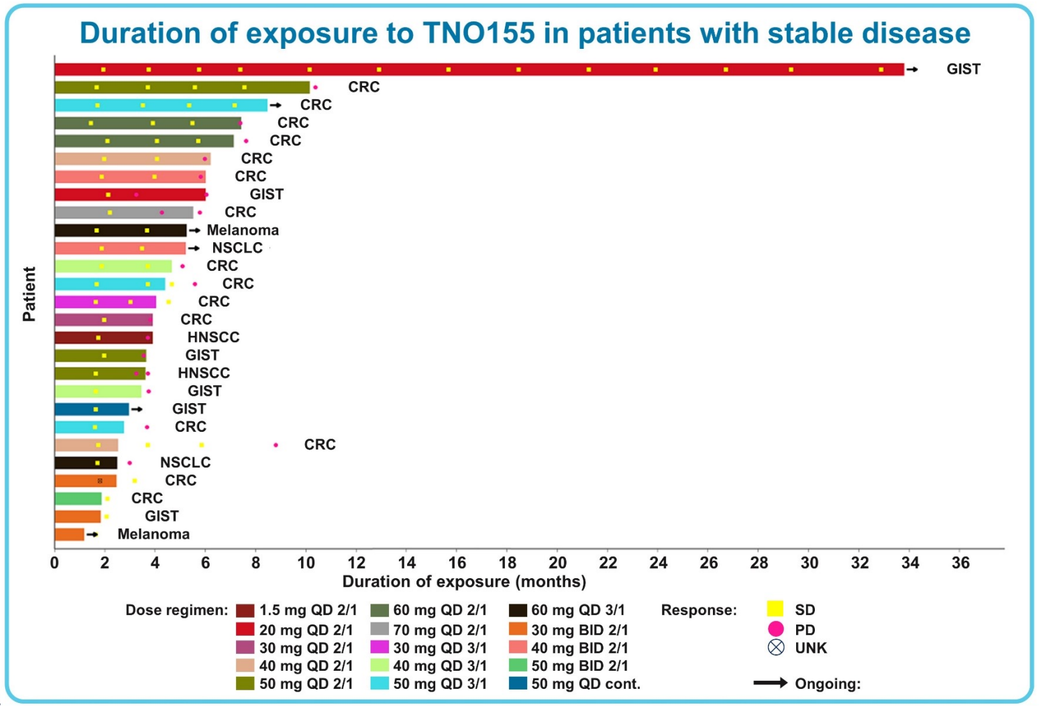
EGFR: epidermal growth factor receptor; HER2: human epidermal growth factor receptor 2; MAPK: mitogen-activated protein kinase; RTK: receptor tyrosine kinase; SHP2: Src homology region 2 domain-containing phosphatase-2.

1. Grossmann KS *et al. Adv Cancer Res.* 2010;106:53–89; 2. Matozaki T *et al. Cancer Sci.* 2009;100:1786–1793; 3. Sanchez-Vega F *et al. Cell.* 2018;173:321–337; 4. van der Wekken AJ *et al. Crit Rev Oncol Hematol.* 2016;100:107–116; 5. Wang WL *et al. Cancer Chemother Pharmacol.* 2011;67(suppl 1):S15–S24; 6. LaMarche MJ *et al. J Med Chem*. 2020;63:13578–13594.

TNO155—Best percentage change in target lesions and duration of response in dose escalation patients



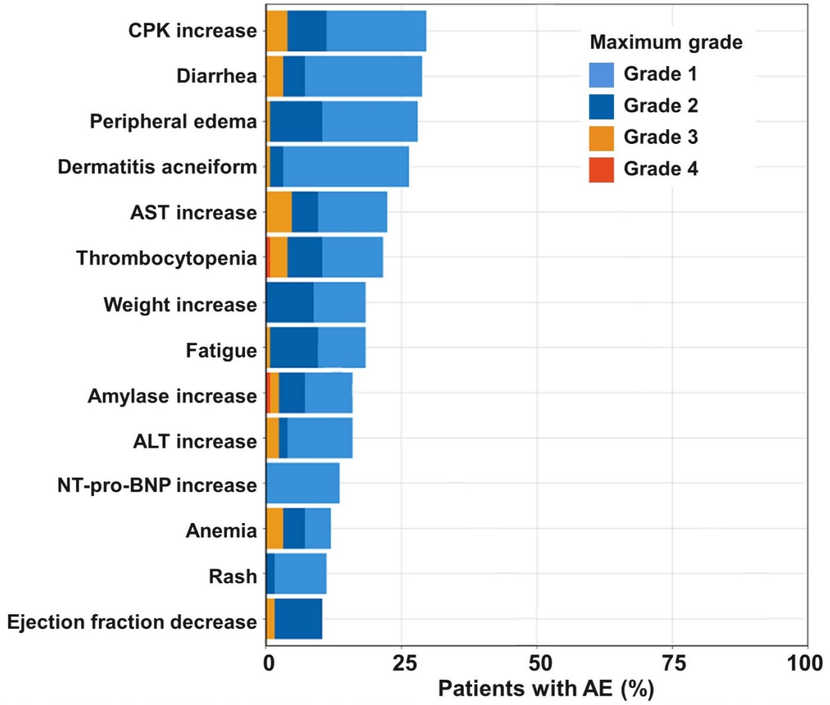
CRC: colorectal cancer; GIST: gastrointestinal stromal tumor; HNSCC: head and neck squamous cell cancer; NSCLC: non-small cell lung cancer; SCC: squamous cell cancer.



- Best response was SD
- Median duration of SD 5.6 months (95% CI: 1.6, 32.9)
- Only 7 *KRAS* mutant patients

Braña et al ASCO 2021

Treatment-related AEs to TNO155, SHP2 inhibition



- Most AEs were Grade 1 or 2 in severity
- There were no suspected-related Grade 5 AEs

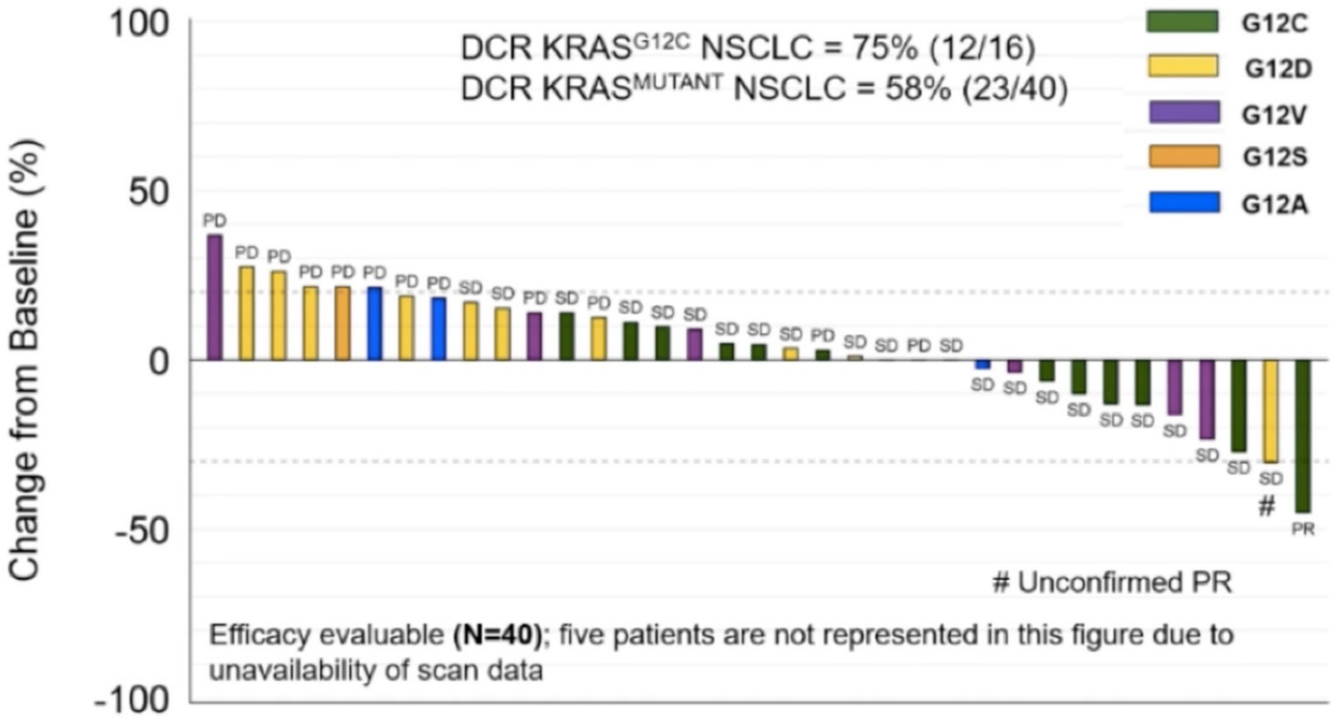
- Ejection fraction decreases/left ventricular dysfunction of any grade were reported in 13/125 (10%) patients
  - Five patients (4%) had LVEF decreases of ≥10% from baseline to a value below 50%, with only one below 40%
    - Four resolved within 7–9 days and one in 23 days
  - The majority of ejection fraction decreases were mild (n=11 Grade 2) and were identified as a result of frequent monitoring*

AE terms which are equivalent are grouped for reporting: rash and maculopapular rash are reported as rash; platelet count decrease and thrombocytopenia are reported as thrombocytopenia; neutrophil count decrease and neutropenia are reported as neutropenia; ejection fraction decrease and left ventricular dysfunction are reported as ejection fraction decrease.
*Cardiac imaging by echocardiogram or MUGA scan was required at baseline, C1D14 (2/1 schedule) or C1D21 (3/1 or continuous schedules), C2D1, C2D14 or C2D21, C3D1, then D1 of every even cycle through C8, then D1 of every third cycle.

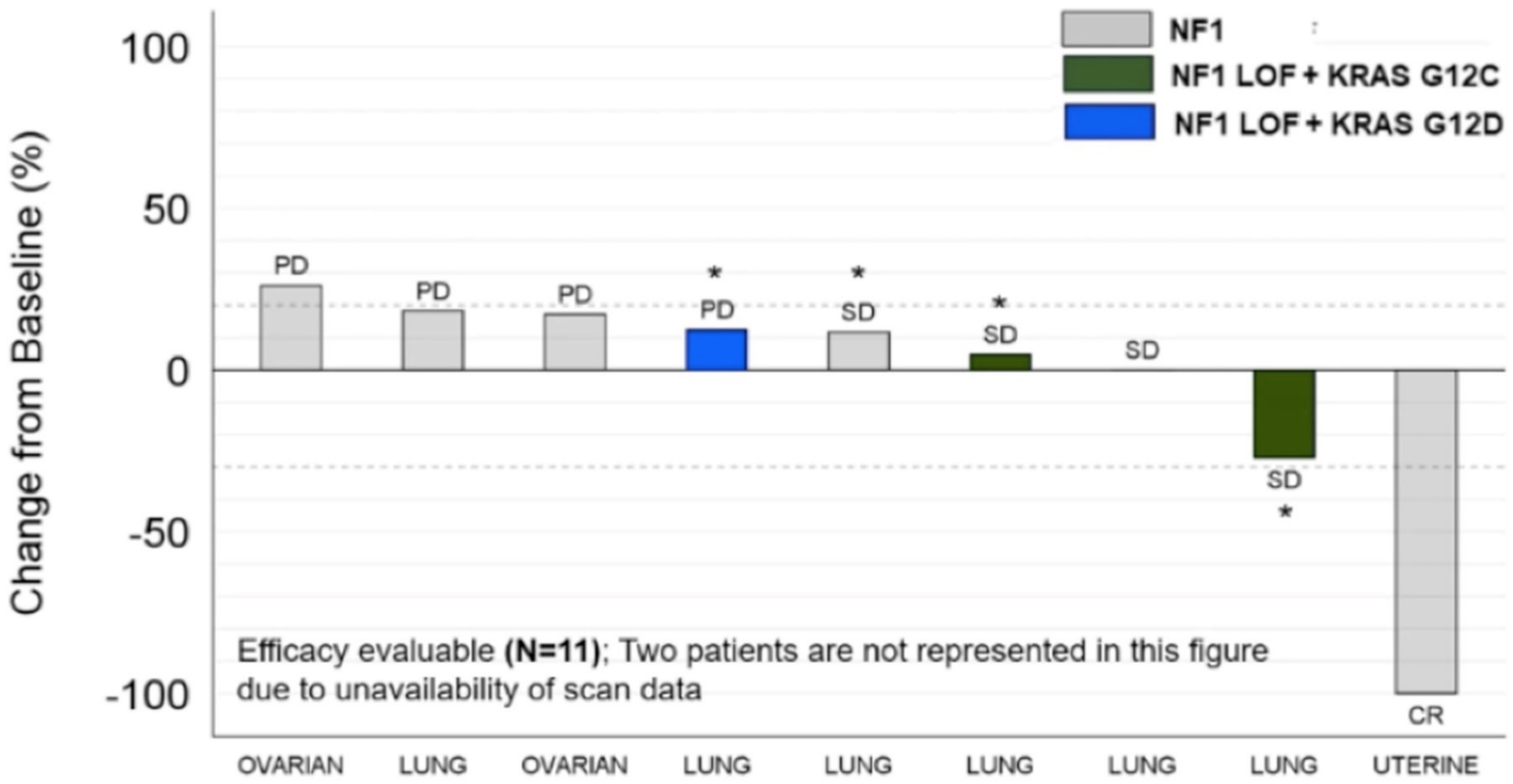
AE: adverse event; ALT: alanine amino transferase; AST: aspartate amino transferase; C: cycle; CPK: blood creatine phosphokinase; D: day; LVEF: left ventricular ejection fraction; MUGA: multiple gated acquisition; NT-pro-BNP: N-terminal prohormone brain natriuretic peptide.

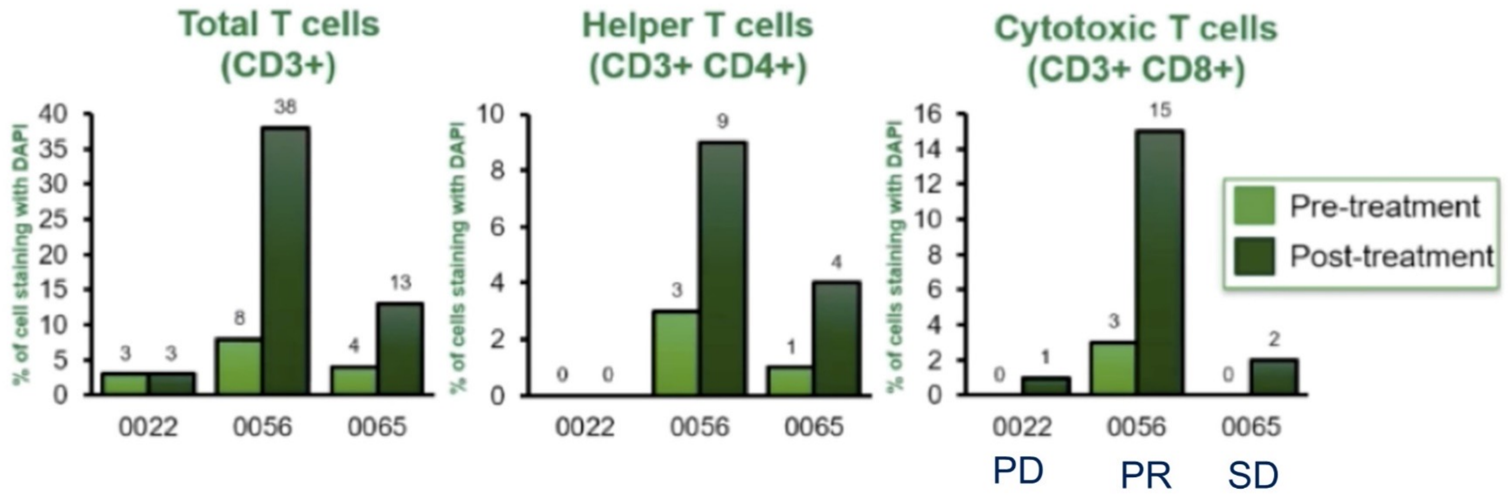
Braña et al ASCO 2021

RMC-4630 (SHP2i) single agent activity—enriched for *KRAS* G12C and *NF1* LOF



NSCLC = Non-small cell lung cancer; DCR = Disease Control Rate (no PD at first response assessment); PD = Progressive Disease; SD = Stable Disease; PR = Partial Response; PD, SD and PR each per RECIST 1.1

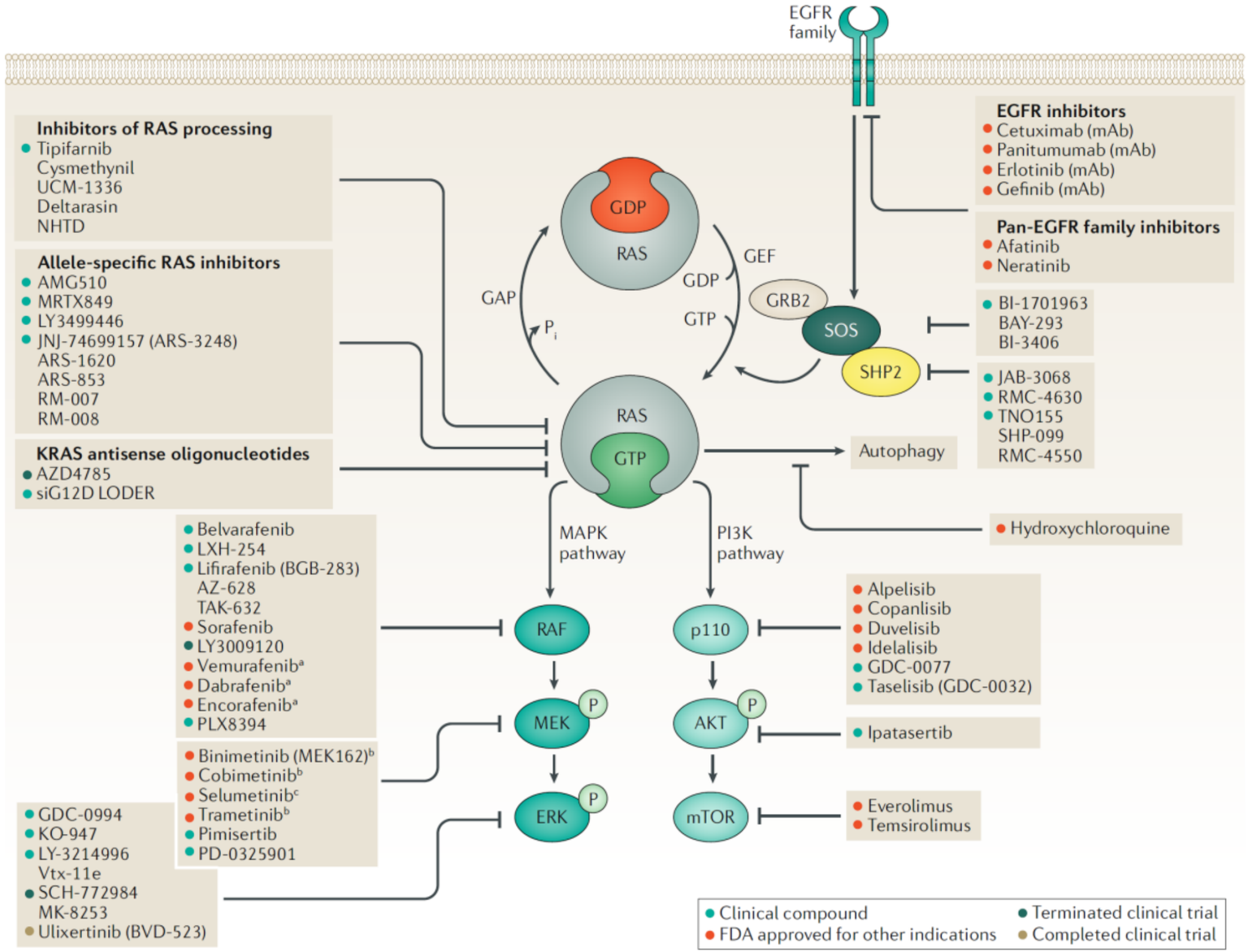




→ Preliminary evidence of increased T cell infiltration

Koczywas et al. AACR 2021 LBA 001

Emerging Treatment Combinations in *KRAS*-Mutant NSCLC



KRAS G12C inhibitor

+

PD-1 inhibitor

Pan-EGFR TKI

SHP2 inhibitor

CDK4/6 inhibitor

FGFR inhibitor

Moore, et al Nature Reviews, Drug Discovery 2020

Thank you!

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QUESTIONS?