Targeting RAS-RAF-MAPK pathway in Solid Tumors

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California Cancer Consortium Conference
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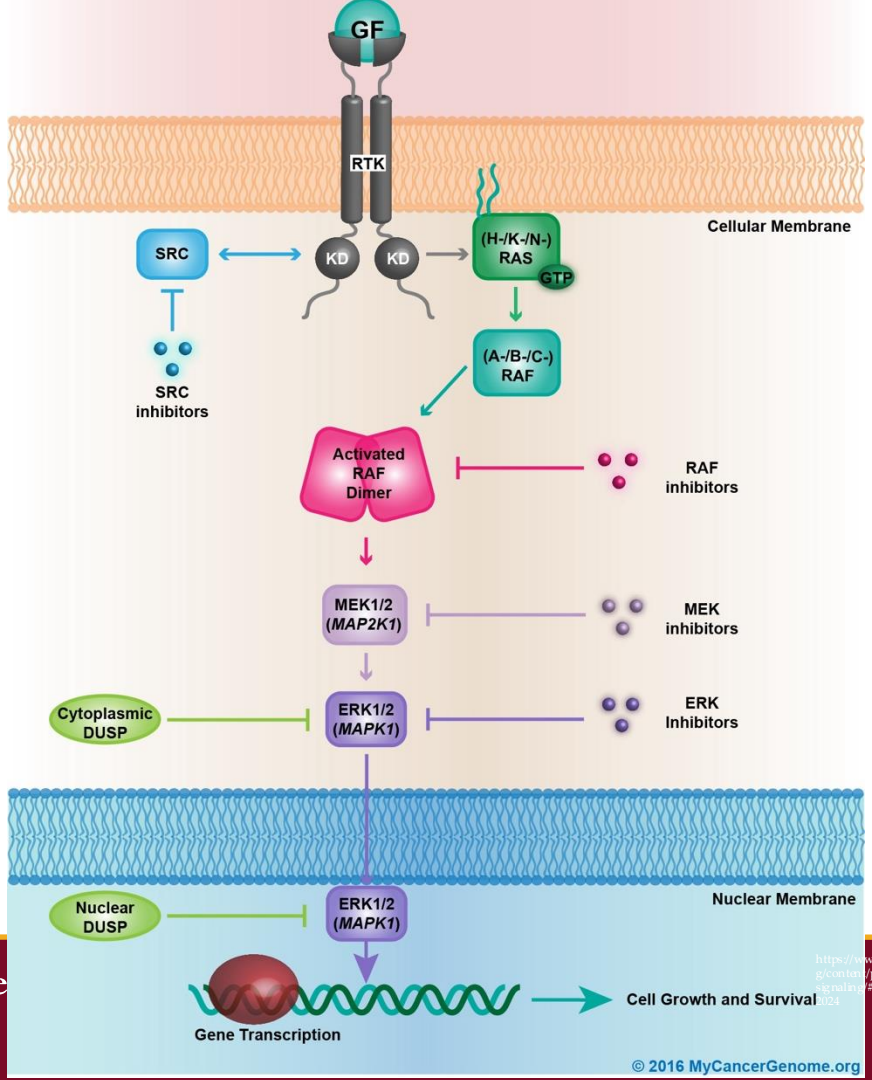
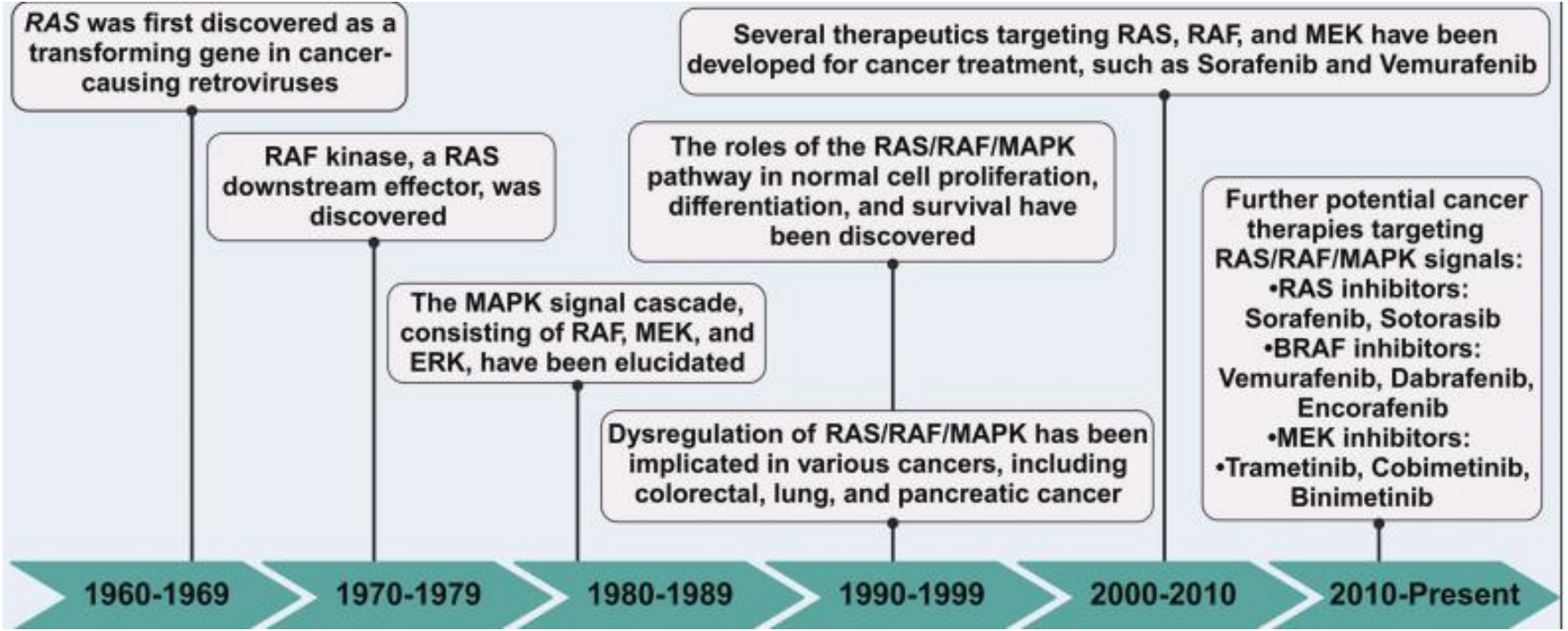


https://www.mycancergenome.org/content/pathways/map-kinase-signaling/#ref-1. Accessed 8-2-2024



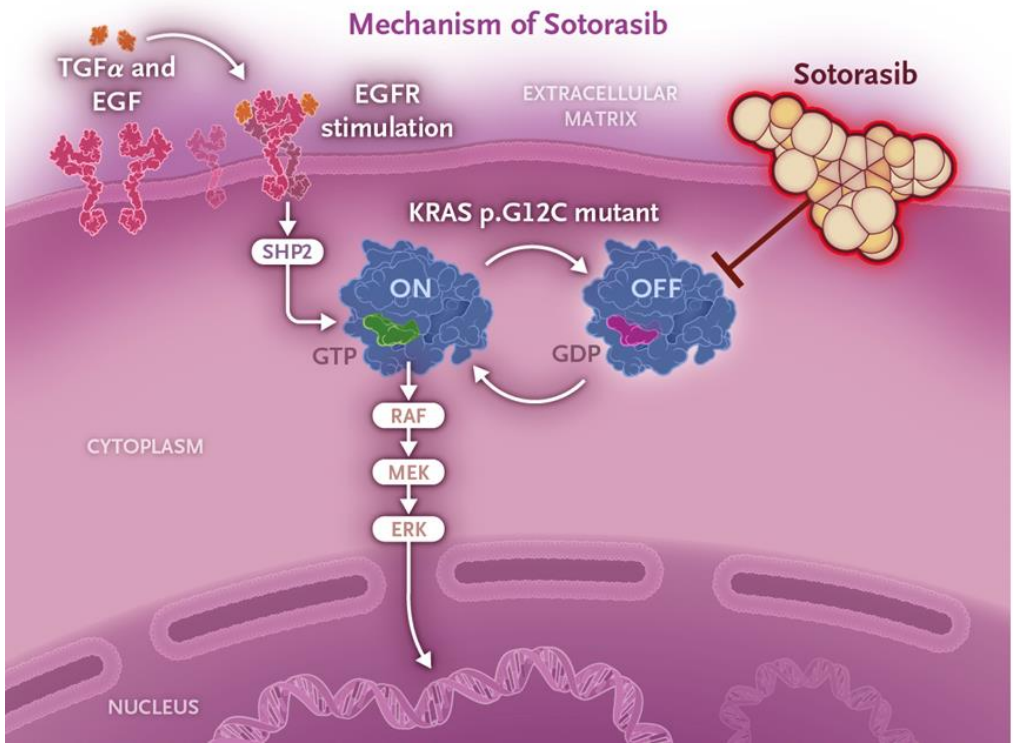
Signal Transduct Target Ther. 2023 Dec 18;8(1):455.

Targeting RAS

- Historic Challenges
  - Lacks deep binding pockets
  - RAS-GTP binding at picomolar level – not possible to drug
- Targeting specific KRAS mutations

KRAS G12C Inhibition

- KRAS G12C mutation favors active form
- KRAS G12C inhibitors bind pocket of switch II region - present only in inactive GDP-bound conformation, trapping KRAS in "OFF" state



KRAS G12C in NSCLC

- KRAS mutations in 25-30% NSCLC
- KRAS G12C in ~ 13% Lung Adenocarcinomas

N Engl J Med. 2021 Jun 24;384(25):2371-2381.

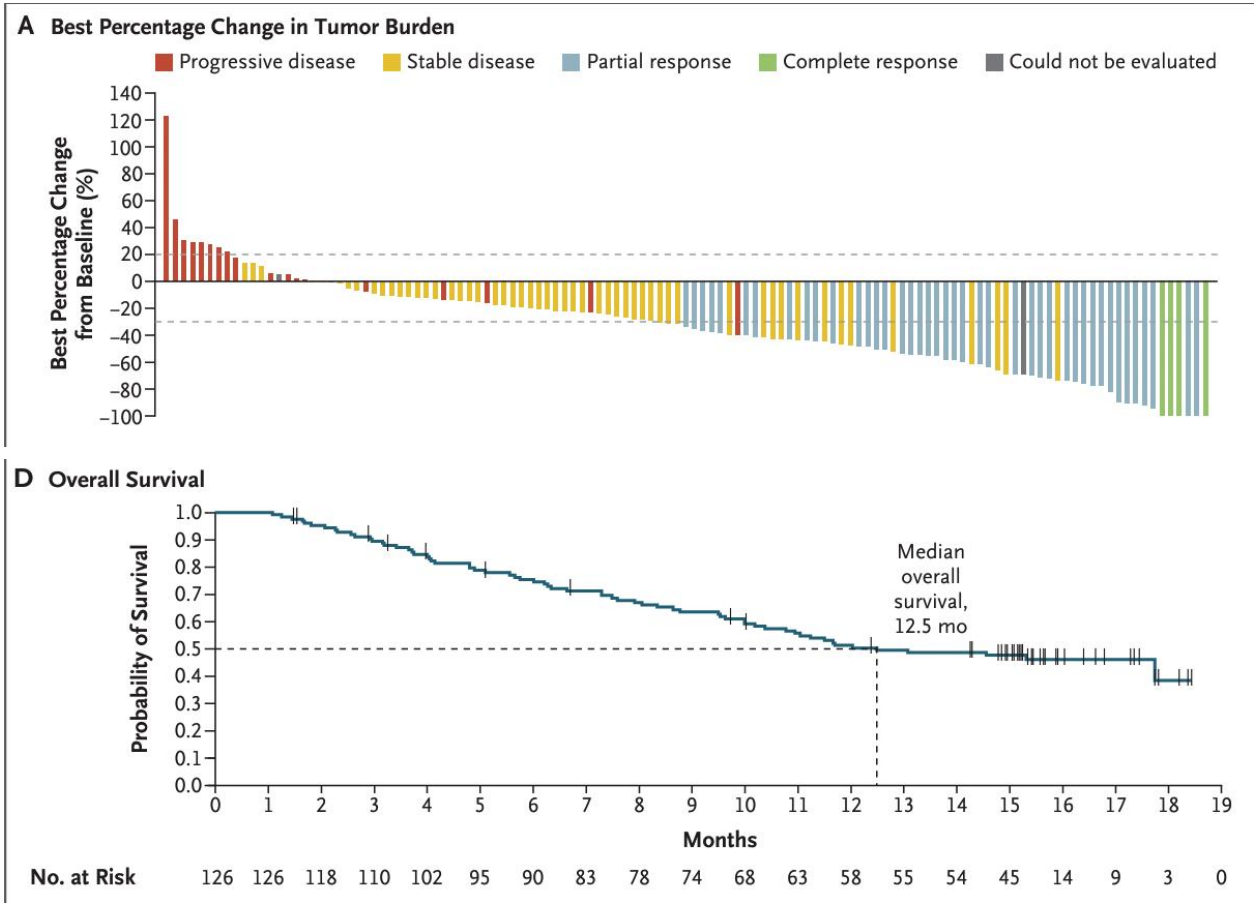
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 24, 2021 VOL. 384 NO. 25

Sotorasib for Lung Cancers with *KRAS* p.G12C Mutation

F. Skoulidis, B.T. Li, G.K. Dy, T.J. Price, G.S. Falchook, J. Wolf, A. Italiano, M. Schuler, H. Borghaei, F. Barlesi, T. Kato, A. Curioni-Fontecedro, A. Sacher, A. Spira, S.S. Ramalingam, T. Takahashi, B. Besse, A. Anderson, A. Ang, Q. Tran, O. Mather, H. Henary, G. Ngarmchamnanrith, G. Friberg, V. Velcheti, and R. Govindan

- 126 patients with KRAS G12Cmt metastatic NSCLC
- All had ≥ 1 line of therapy
- FDA accelerated approval 5/28/2021



N Engl J Med. 2021 Jun 24;384(25):2371-2381.

Event	All Patients (N=126)				
	Any Grade	Grade 1 or 2	Grade 3	Grade 4	Fatal
	number of patients (percent)				
Adverse event	125 (99.2)	48 (38.1)	53 (42.1)	4 (3.2)	20 (15.9)
Treatment-related adverse event	88 (69.8)	62 (49.2)	25 (19.8)	1 (0.8)	0
Treatment-related adverse event leading to dose modification	28 (22.2)	8 (6.3)	20 (15.9)	0	0
Treatment-related adverse event leading to discontinuation of therapy	9 (7.1)	4 (3.2)	4 (3.2)	1 (0.8)	0
Treatment-related adverse event of any grade occurring in >5% of the patients or that was grade ≥3					
Diarrhea	40 (31.7)	35 (27.8)	5 (4.0)	0	0
Nausea	24 (19.0)	24 (19.0)	0	0	0
Alanine aminotransferase increase	19 (15.1)	11 (8.7)	8 (6.3)	0	0
Aspartate aminotransferase increase	19 (15.1)	12 (9.5)	7 (5.6)	0	0
Fatigue	14 (11.1)	14 (11.1)	0	0	0
Vomiting	10 (7.9)	10 (7.9)	0	0	0
Blood alkaline phosphatase increase	9 (7.1)	8 (6.3)	1 (0.8)	0	0
Maculopapular rash	7 (5.6)	7 (5.6)	0	0	0
Hypokalemia	5 (4.0)	4 (3.2)	1 (0.8)	0	0
Drug-induced liver injury	3 (2.4)	1 (0.8)	2 (1.6)	0	0
γ-Glutamyltransferase increase	3 (2.4)	0	3 (2.4)	0	0
Lymphocyte count decrease	3 (2.4)	2 (1.6)	1 (0.8)	0	0
Dyspnea	2 (1.6)	1 (0.8)	0	1 (0.8)	0
Pneumonitis	2 (1.6)	0	1 (0.8)	1 (0.8)	0
Abnormal hepatic function	2 (1.6)	1 (0.8)	1 (0.8)	0	0

N Engl J Med. 2021 Jun 24;384(25):2371-2381.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adagrasib in Non–Small-Cell Lung Cancer Harboring a *KRAS*^{G12C} Mutation

Pasi A. Jänne, M.D., Ph.D., Gregory J. Riely, M.D., Ph.D., Shirish M. Gadgeel, M.D., Rebecca S. Heist, M.D., M.P.H., Sai-Hong I. Ou, M.D., Ph.D., Jose M. Pacheco, M.D., Melissa L. Johnson, M.D., Joshua K. Sabari, M.D., Konstantinos Leventakos, M.D., Ph.D., Edwin Yau, M.D., Ph.D., Lyudmila Bazhenova, M.D., Marcelo V. Negrao, M.D., Nathan A. Pennell, M.D., Ph.D., Jun Zhang, M.D., Ph.D., Kenna Anderes, Ph.D., Hirak Der-Torossian, M.D., Thian Kheoh, Ph.D., Karen Velastegui, B.Sc., Xiaohong Yan, Ph.D., James G. Christensen, Ph.D., Richard C. Chao, M.D., and Alexander I. Spira, M.D., Ph.D.

- 116 patients enrolled
- All had ≥ 1 line of therapy
- Known to penetrate CSF
- Accelerated FDA approval 12/12/2022

N Engl J Med. 2022 Jul 14;387(2):120-131.

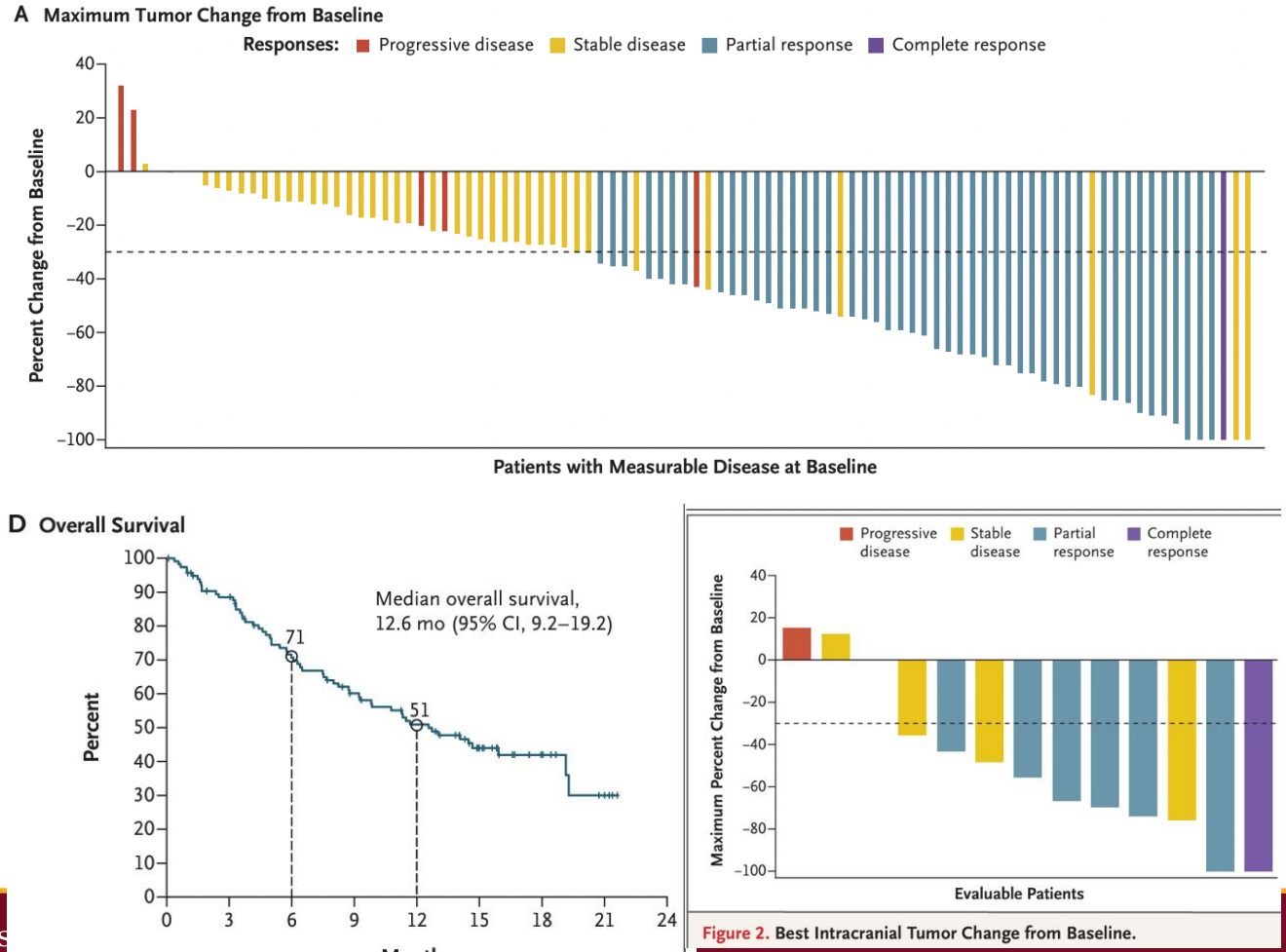


Figure 2. Best Intracranial Tumor Change from Baseline.

N Engl J Med. 2022 Jul 14;387(2):120-131.

Table 3. Adverse Events Reported during Treatment (Safety Population).*

Event	Any Grade	Grade ≥3
	no. of patients (%)	
Any adverse event	116 (100)	95 (81.9)
Adverse event leading to dose reduction or interruption	96 (82.8)	—
Adverse event leading to discontinuation of therapy	18 (15.5)	—
Adverse event of any grade that occurred in >10% of patients or that was grade ≥3 in >1 patient†		
Diarrhea	82 (70.7)	1 (0.9)
Nausea	81 (69.8)	5 (4.3)
Fatigue	69 (59.5)	8 (6.9)
Vomiting	66 (56.9)	1 (0.9)
Anemia	42 (36.2)	17 (14.7)
Dyspnea	41 (35.3)	12 (10.3)
Blood creatinine increased	40 (34.5)	1 (0.9)
Decreased appetite	37 (31.9)	5 (4.3)
ALT increased	33 (28.4)	6 (5.2)
Edema peripheral	33 (28.4)	0
AST increased	31 (26.7)	6 (5.2)
Constipation	27 (23.3)	0

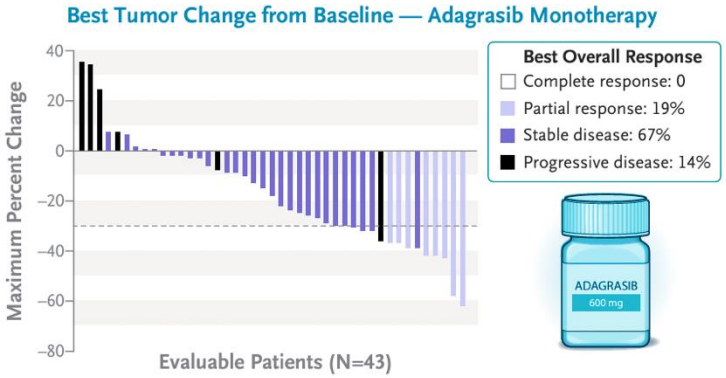
N Engl J Med. 2022 Jul 14;387(2):120-131.

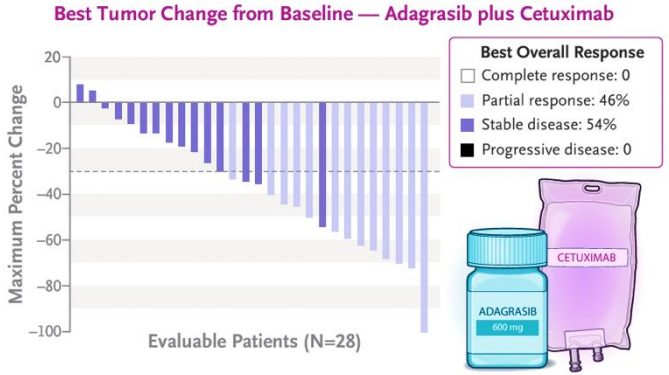
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adagrasib with or without Cetuximab in Colorectal Cancer with Mutated *KRAS* G12C

Rona Yaeger, M.D., Jared Weiss, M.D., Meredith S. Pelster, M.D., Alexander I. Spira, M.D., Ph.D., Minal Barve, M.D., Sai-Hong I. Ou, M.D., Ph.D., Ticiana A. Leal, M.D., Tanios S. Bekaii-Saab, M.D., Cloud P. Paweletz, Ph.D., Grace A. Heavey, B.A., James G. Christensen, Ph.D., Karen Velastegui, B.Sc., Thian Kheoh, Ph.D., Hirak Der-Torossian, M.D., and Samuel J. Klempner, M.D.





- FDA accelerated approval 6/21/24
- Pts had prior FOLFOX / FOLFIRI + VEGF

N Engl J Med. 2023 Jan 5;388(1):44-54.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Acquired Resistance to KRAS^{G12C} Inhibition in Cancer

M.M. Awad, S. Liu, I.I. Rybkin, K.C. Arbour, J. Dilly, V.W. Zhu, M.L. Johnson, R.S. Heist, T. Patil, G.J. Riely, J.O. Jacobson, X. Yang, N.S. Persky, D.E. Root, K.E. Lowder, H. Feng, S.S. Zhang, K.M. Haigis, Y.P. Hung, L.M. Sholl, B.M. Wolpin, J. Wiese, J. Christiansen, J. Lee, A.B. Schrock, L.P. Lim, K. Garg, M. Li, L.D. Engstrom, L. Waters, J.D. Lawson, P. Olson, P. Lito, S.-H.I. Ou, J.G. Christensen, P.A. Jänne, and A.J. Aguirre

- 38 patients with NSCLC, CRC, or appendiceal CA
- All treated with Adagrasib
- 17/38 had resistance mechanism identified

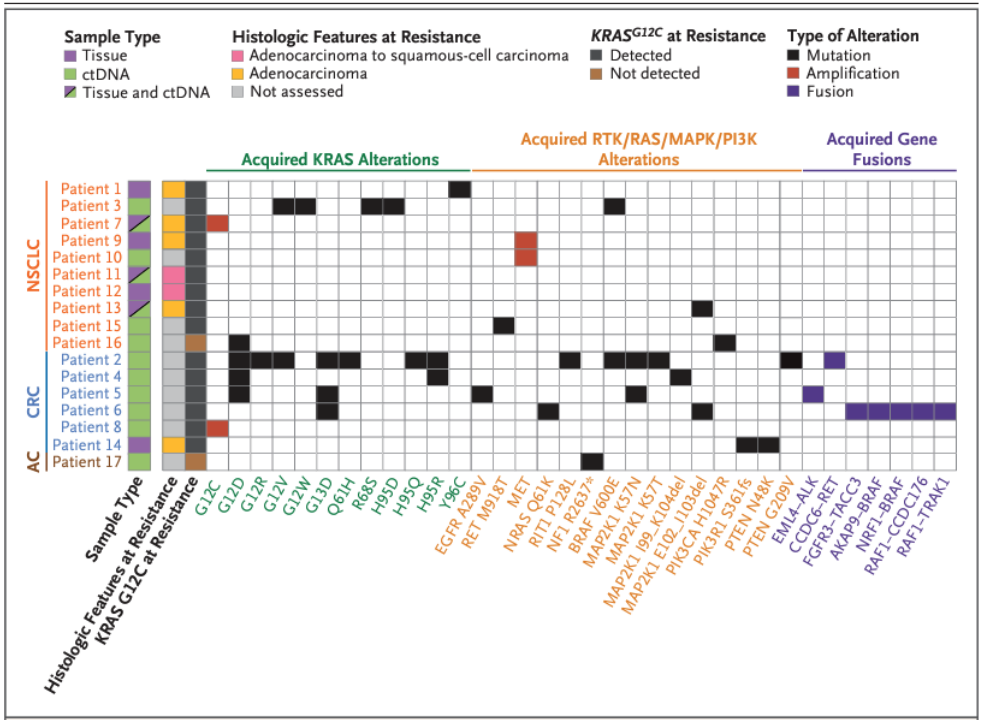
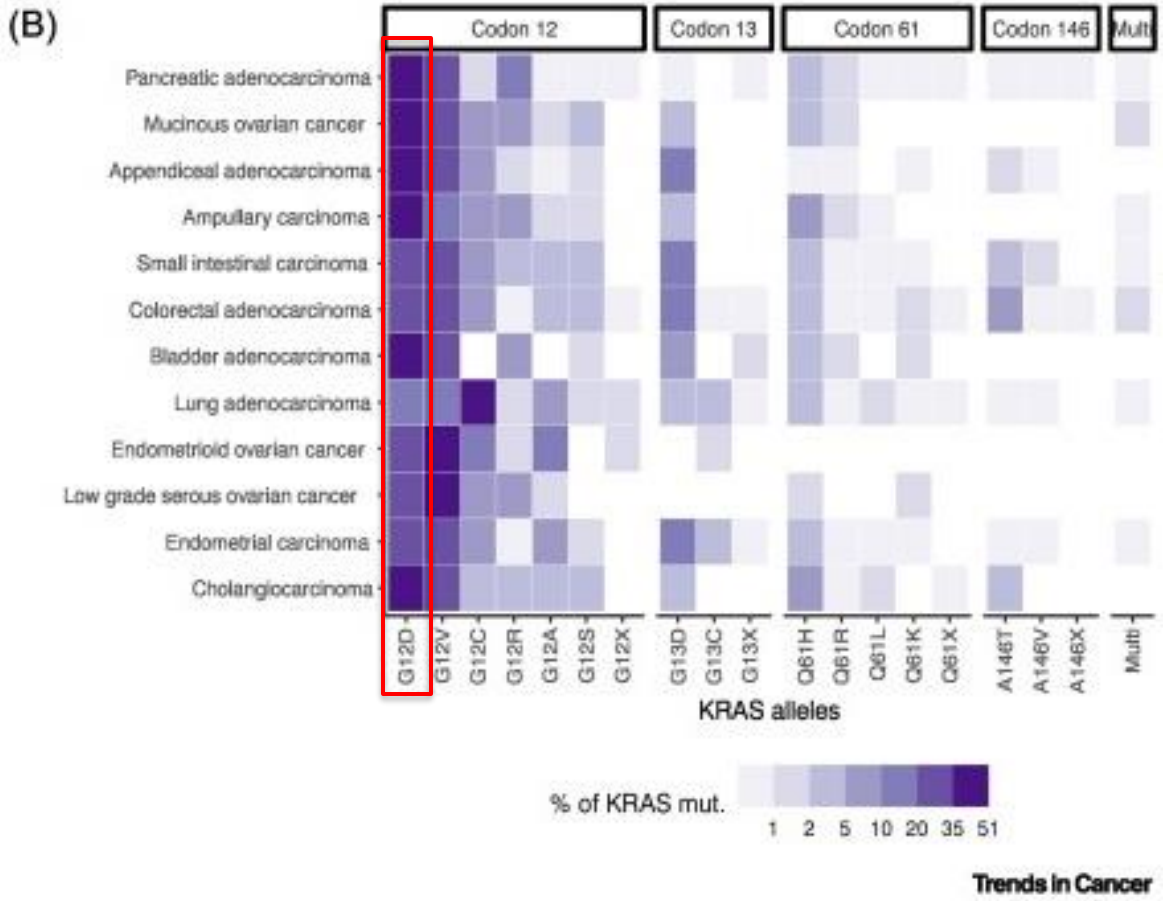


Figure 3. Summary of Putative Mechanisms of Acquired Resistance to Adagrasib Treatment.

Of 38 patients with *KRAS*^{G12C}-mutant cancers, 17 had at least one putative resistance mechanism. A summary of the genomic and histologic mechanisms of resistance among these 17 patients is shown in the comutation plot, with each row indicating a patient and each column indicating a specific acquired alteration. Seven patients had more than one putative resistance mechanism identified. AC denotes appendiceal cancer, CRC colorectal cancer, ctDNA circulating tumor DNA, and NSCLC non–small-cell lung cancer.

Next steps for KRASG12C?

- Next Generation KRASG12C inhibitors
  - Divarasib
    - More potent and selective
    - Phase 3 trial enrolling in 2024. Direct comparison to Sotorasib / Adagrasib in NSCLC
  - Glecirasib
    - Ph2 data in NSCLC reported at ASCO 2024
- Novel combinations
  - Chemotherapy
  - Checkpoint inhibitor (ASCO 2024)
  - VIC-1911 – Aurora Kinase A inhibitor
  - Adagrasib + Palbociclib
  - Adagrasib + Nab-Sirolumus
  - Adagrasib + Olaparib



Trends Cancer. 2023 Nov;9(11):955-967.

KRAS G12D Inhibitors

Drug	Phase	Began Study
TSN1611	1 / 2	2024
MRTX1133	1 / 2	2023
ASP3082	1	2022
RMC-9805	1	2023
QTX3046	1	2024
QTX3034	1	2024
INCB161734	1	2024

Clinicaltrials.gov – Accessed 8/24

Targeting BRAF

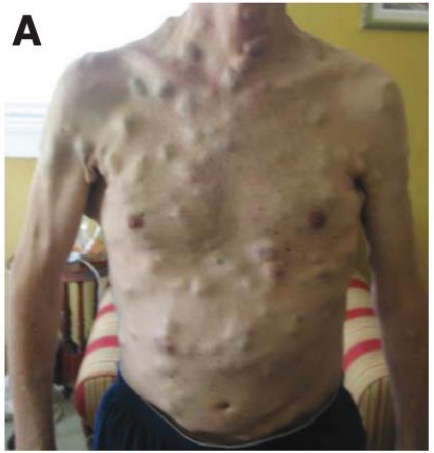
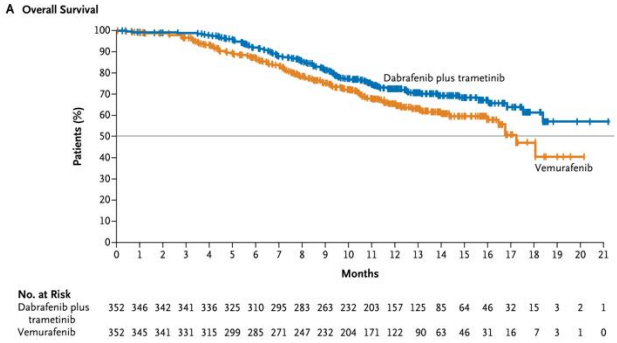


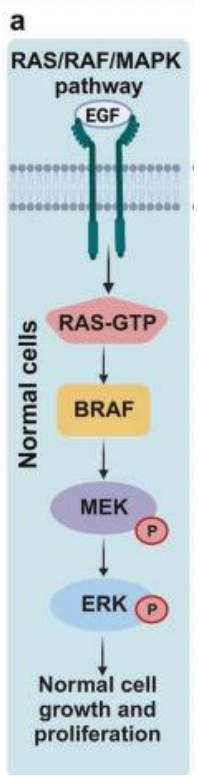
Fig 2. A 38-year-old man with *BRAF*-mutant melanoma and miliary, subcutaneous metastatic deposits. Photographs were taken (A) before initiation of PLX4032, (B) after 15 weeks of therapy with PLX4032, and (C) after relapse, after 23 weeks of therapy.

J Clin Oncol. 2011 Aug 1;29(22):3085-96.

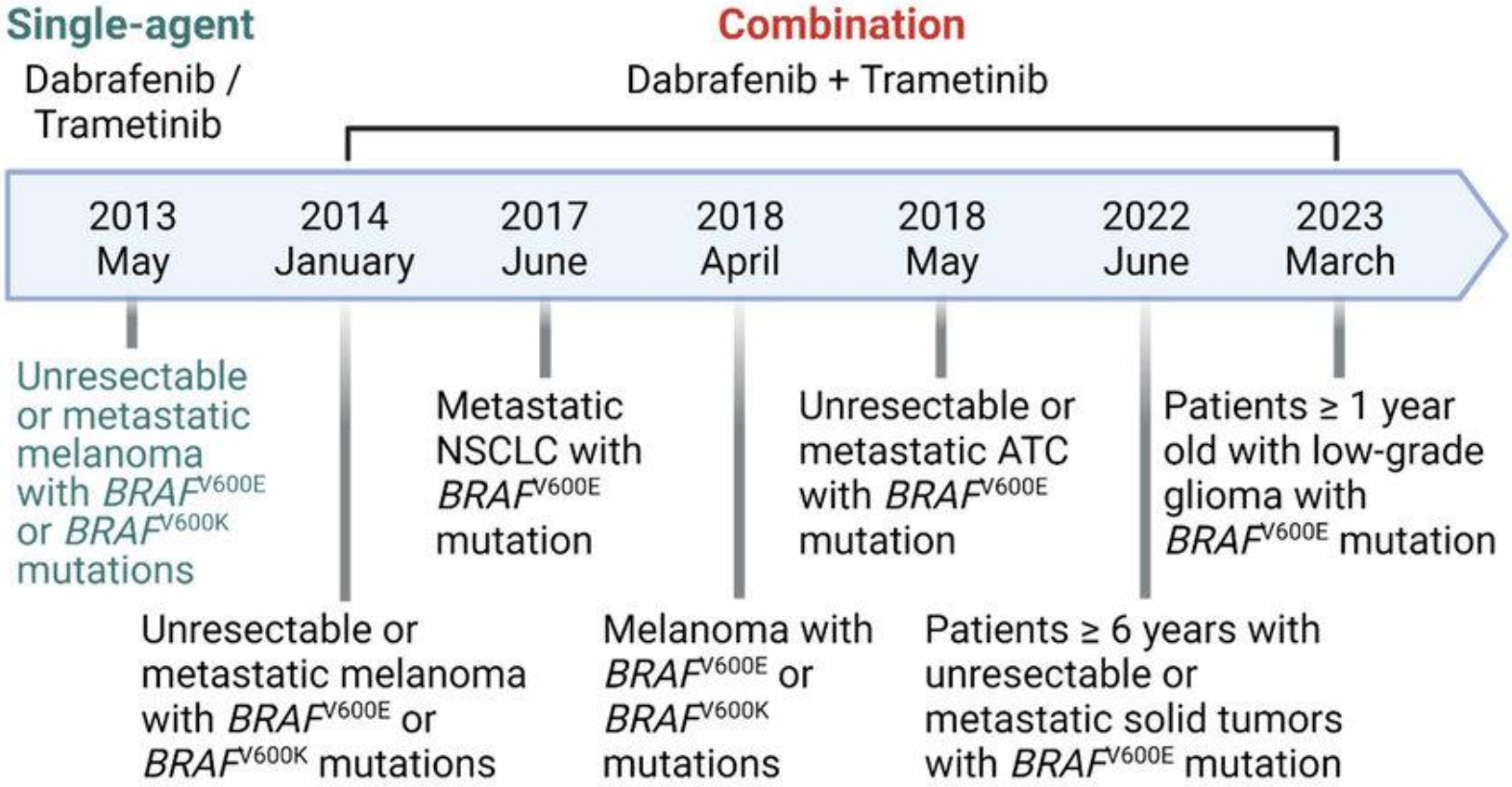
BRAF Inhibition

- Rapid resistance
  - Up-regulation of bypass pathways
  - De novo NRAS or MEK mutations
  - Dimerization or variant splicing of BRAF V600
- Cutaneous SCC due to paradoxical MAPK pathway activation
- Solution: Add MEK inhibitor





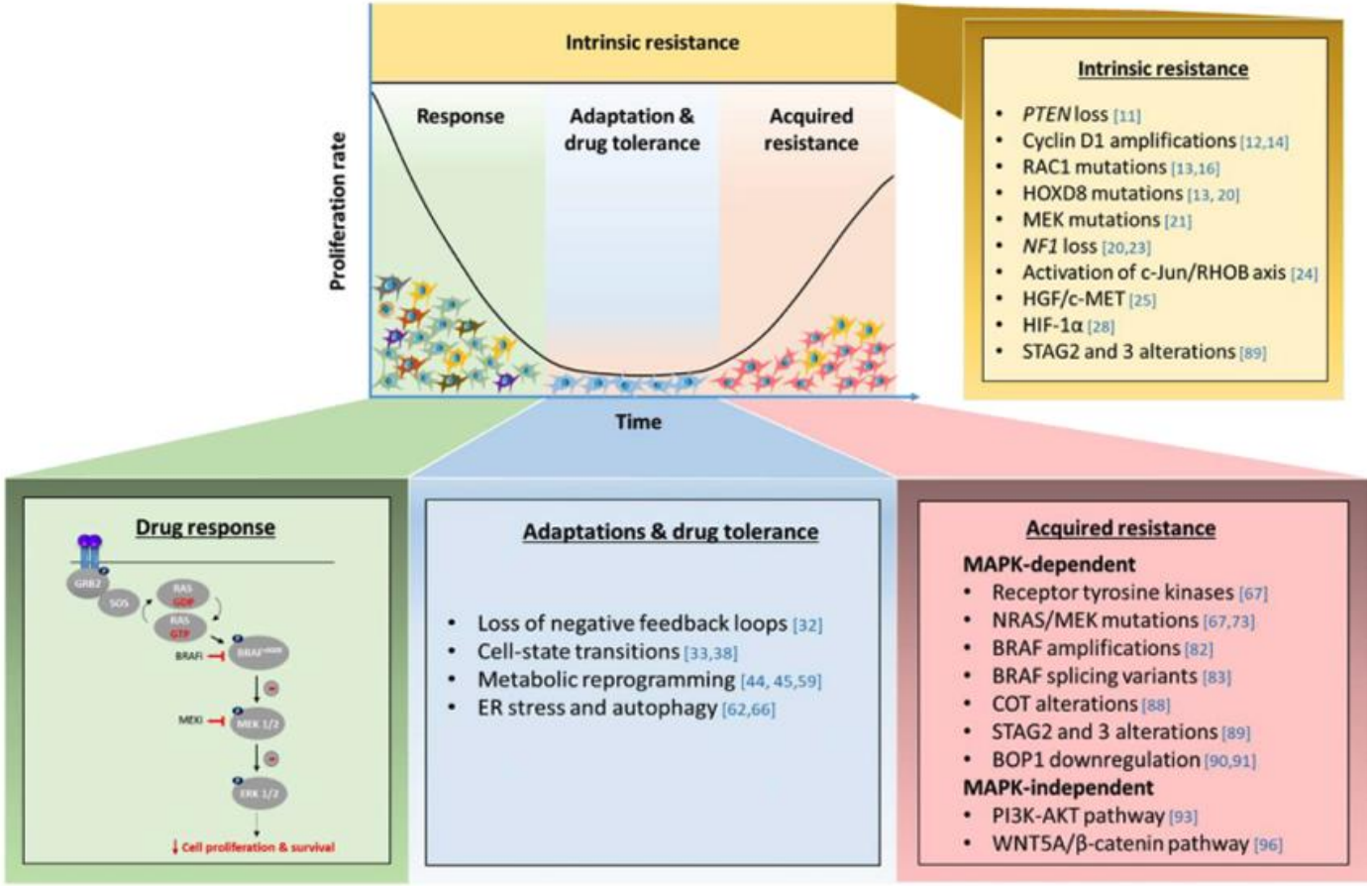
Signal Transduct Target Ther. 2023 Dec 18;8(1):455.
N Engl J Med 2015;372:30-9.



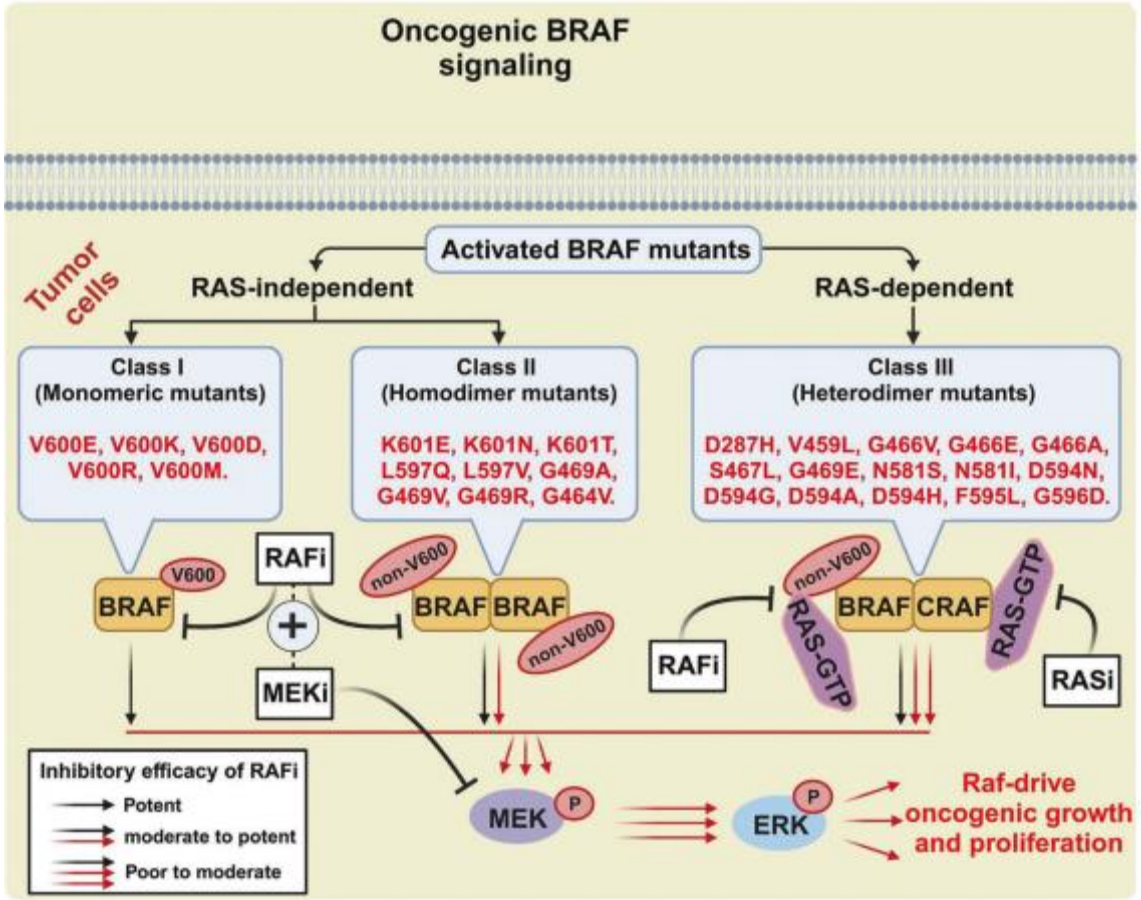
Tumor Cell Resistance to the Inhibition of BRAF and MEK1/2 - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/The-history-of-FDA-approval-of-dabrafenib-and-trametinib-Dabrafenib-and-trametinib-have_fig1_373708629 [accessed 2 Aug 2024]

FDA Approved BRAF / MEKi

Drugs	Indication	Year
Vemurafenib + Cobimetinib	Melanoma with BRAF V600E or V600K	2015
Encorafenib + Binimetinib	Melanoma with BRAF V600E or V600K	2018
Encorafenib + Cetuximab	Metastatic CRC with BRAF V600E	2020
Atezolizumab + Vemurafenib + Cobimetinib	Melanoma with BRAF V600	2020
Encorafenib + Binimetinib	Metastatic NSCLC with BRAF V600E	2023



Biochim Biophys Acta Gen Subj. 2021 Jan;1865(1):129736.



Signal Transduct Target Ther. 2023 Dec 18;8(1):455.

Next steps for targeting RAF

Drug	Phase of Study	Mechanism of Action
Tovorafenib	1	Pan-RAF kinase inhibitor – suppresses both monomeric and dimeric forms
KIN-2787	1	Pan-RAF inhibitor, specifically designed to target class II and III BRAF dimers, in addition to class I monomer.
JZP815	1	Pan-RAF inhibitor – both mono-and dimeric. Active against class I-III as well as BRAF fusion and CRAF mutants.

Clinicaltrials.gov – Accessed 8/24

Summary

- Several FDA approved drugs targeting RAS/RAF
- Numerous mechanisms of resistance to both RAS / RAF inhibitors
- Future directions: Novel combinations as well as improved RAS / RAF inhibitors