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New Developments in Pancreatic Adenocarcinoma

WHAT WE KNOW NOW AND A LOOK TO THE FUTURE

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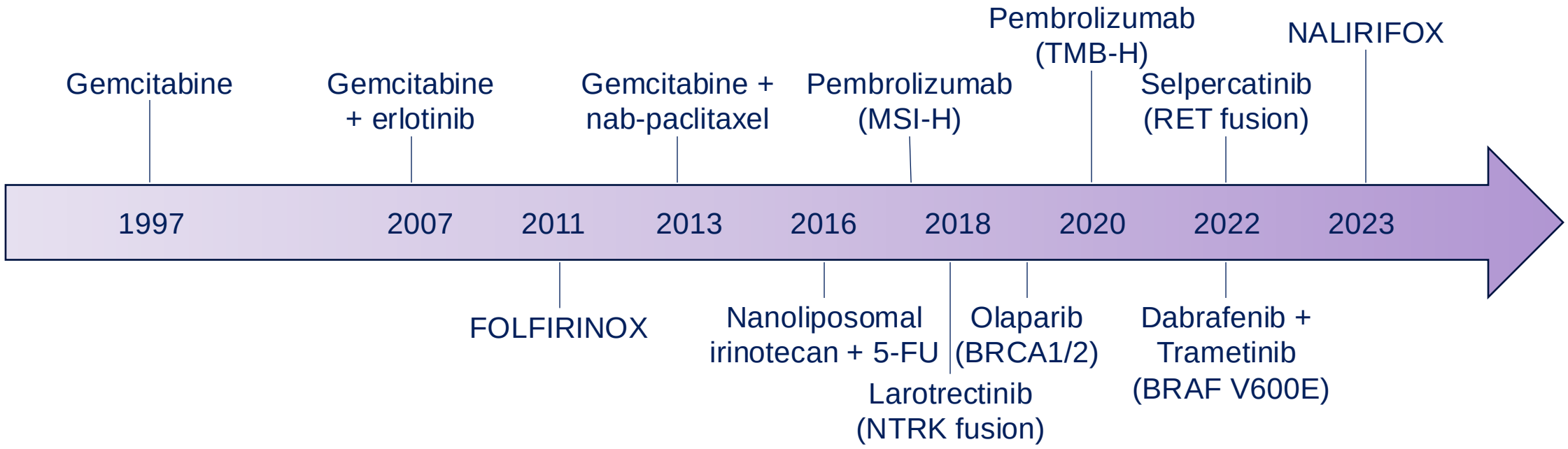
Disclosures

Institutional Grants: Bristol Myers Squibb, Genmab, Akamis, Astra Zeneca, Natera, Elicio, Revolution Medicine, Verastem, Verismo, Geistlich, Arcus, Merck, Celldex, Hibercell

Advisory Board/Consultant: Revolution Medicine, Alligator, Akamis, Merus, Strike

Systemic Therapy for Pancreatic Cancer through the Years



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Outline

- Immunotherapy in pancreatic cancers
  - Vaccine therapy
- Targeted therapy in pancreatic cancer
  - NRG1 fusions
  - KRAS inhibition
- KRAS inhibition and immunotherapy

Immunotherapy in pancreatic cancer

- Single agent and dual immune checkpoint inhibition is ineffective in pancreatic adenocarcinoma
- Most trials of chemotherapy + checkpoint inhibitors are not more effective than chemotherapy alone

Drug	Response rate
Checkpoint inhibitors	
Ipilimumab (n=27)[1]	0%
Pembrolizumab (n=1)[2]	0%
Nivolumab (n=14)[3]	0%
Durvalumab (n=33)[4]	0%
Tremelimumab/durvalumab (n=32)[4]	3%
Chemotherapy + checkpoint inhibitors	
Gem + tremelimumab (n=28)[5]	7.1%
Gem + ipilimumab (n=21)[6]	14%
Gem/nP + pembrolizumab (n=15)[7]	20%
Gem/nP + nivolumab (n=50)[8]	18%
Gem/nP + nivolumab (n=34)[9]	50%
Gem/nP + durva + treme (n=119)[10]	30.3%

[1]Royal RE et al, J immune 2010; [2]Patnaik A. et al, CCR 2015; [3]Brahmer JR et al, NEJM 2012; [4]O'Reilly EM et al, JAMA Oncol 2019; [5]Aglietta M et al, Ann Onc 2014; [6]Kamath SD et al, Oncologist 2020; [7]Weiss GJ et al, Invest New Drugs 2018; [8]Wainberg ZA et al, CCR 2020; [9]Padron L et al, Nat Med 2022; [10]Renouf DJ et al, Nat Commun 2022

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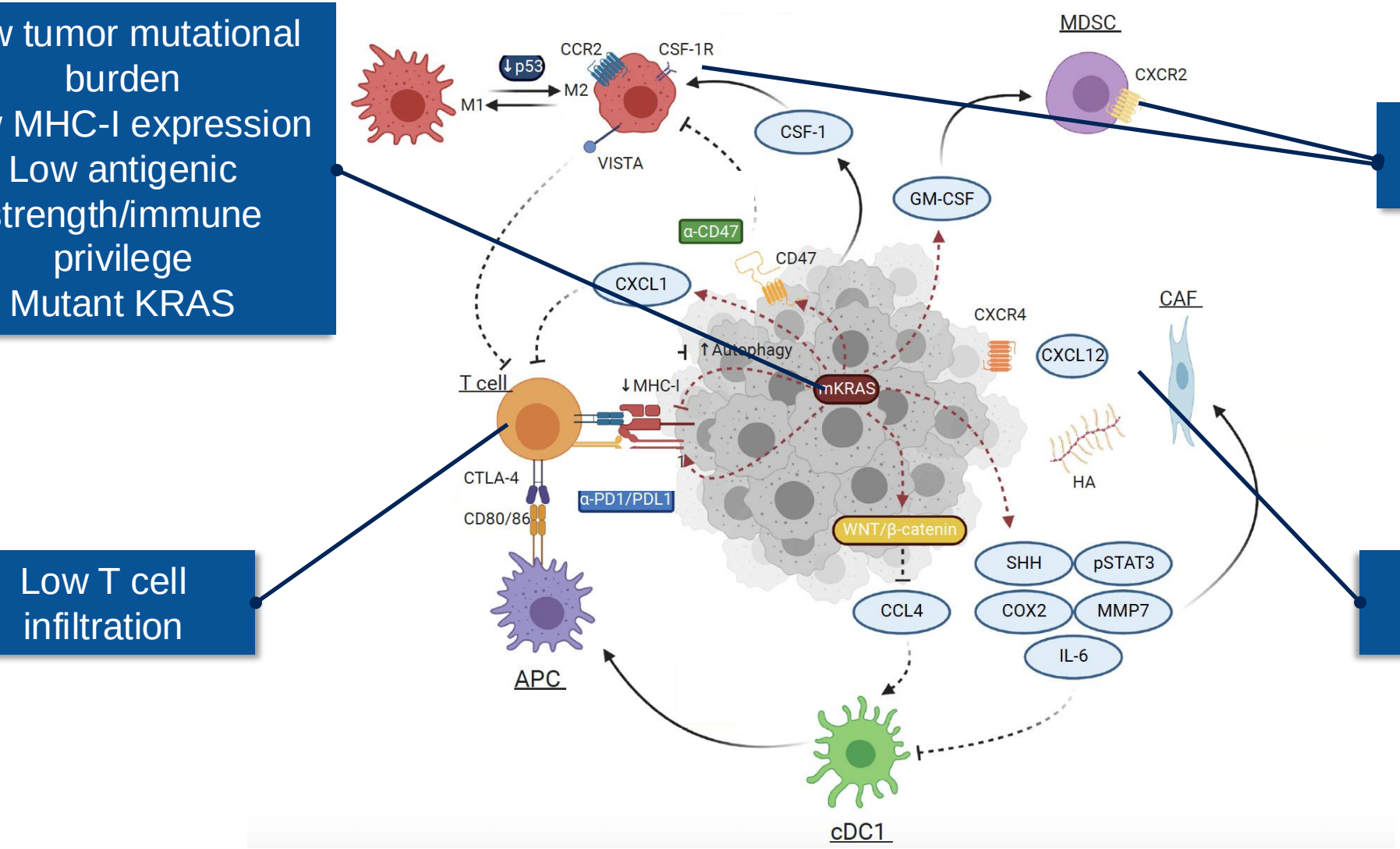
Cold Tumor: Pancreatic Adenocarcinoma

- Low tumor mutational burden
- Low MHC-I expression
- Low antigenic strength/immune privilege
- Mutant KRAS



Immunosuppressive myeloid cells

Low T cell infiltration

Dense desmoplasia

Bear AS et al Cancer Cell 2020

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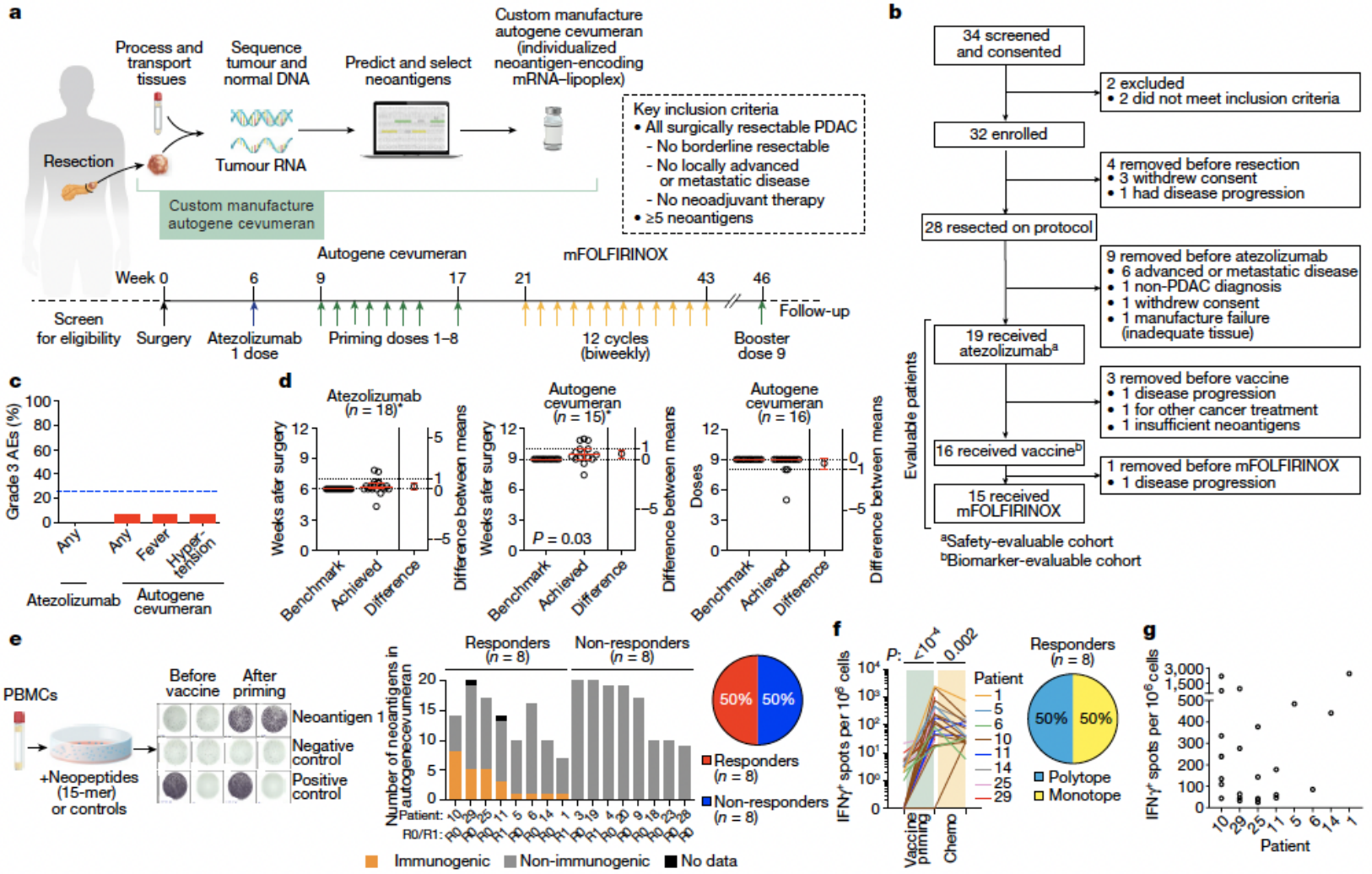
Personalized RNA neoantigen vaccine: autogene cevumaren



Rojas LA et al Nature 2023

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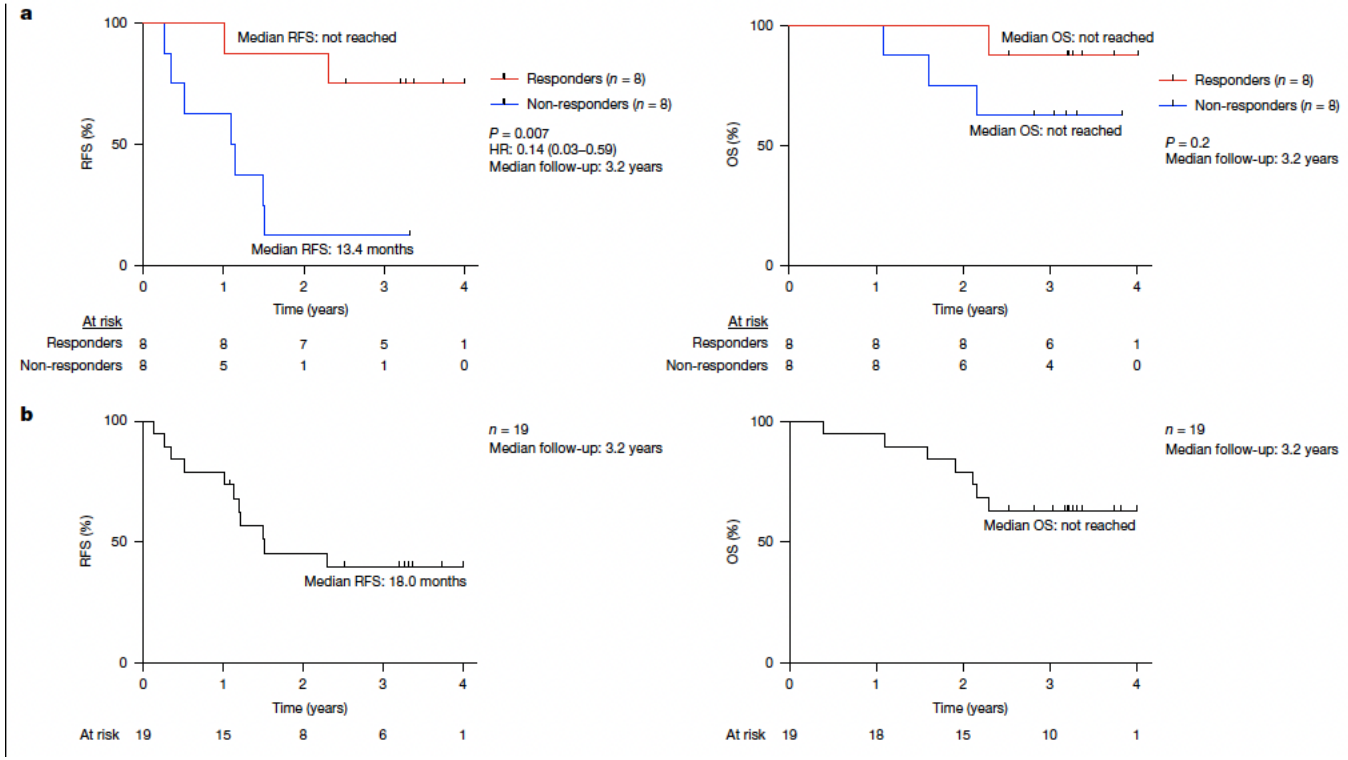
Personalized RNA neoantigen vaccine: autogene cevumaren



- Two responders recurred on trial
  - Fewer vaccine-induced T cells in these patients
- In responders, CD8+ T cell clones have an estimated lifespan of 7.7 years
- 86% of T cell clones per patient persist at high levels even 3 years post-vaccination
- Ongoing randomized phase 2 trial

Sethna Z et al Nature 2025

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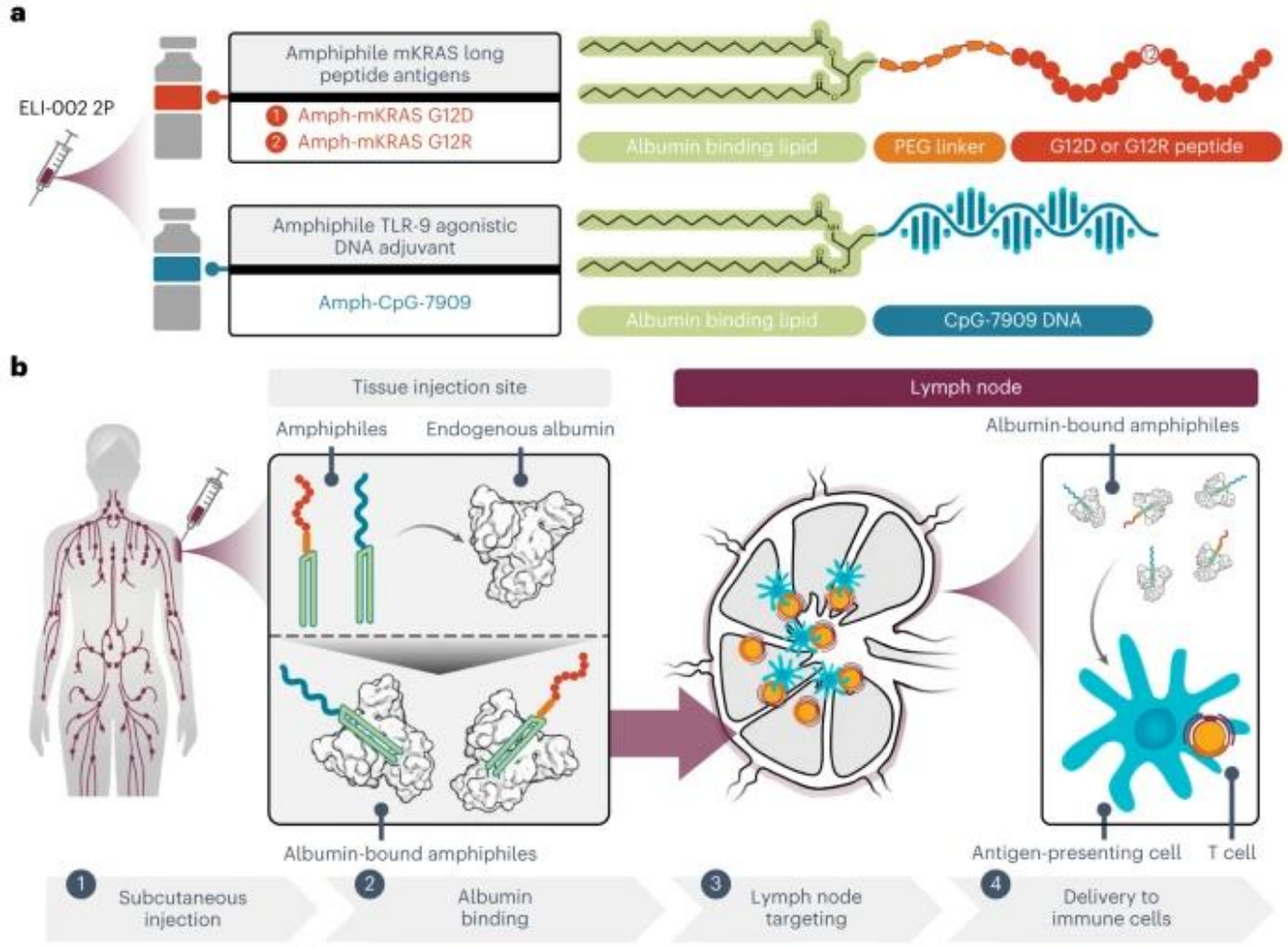
mKRAS-specific Amphiphile Vaccine



Pant S et al Nat Med 2024

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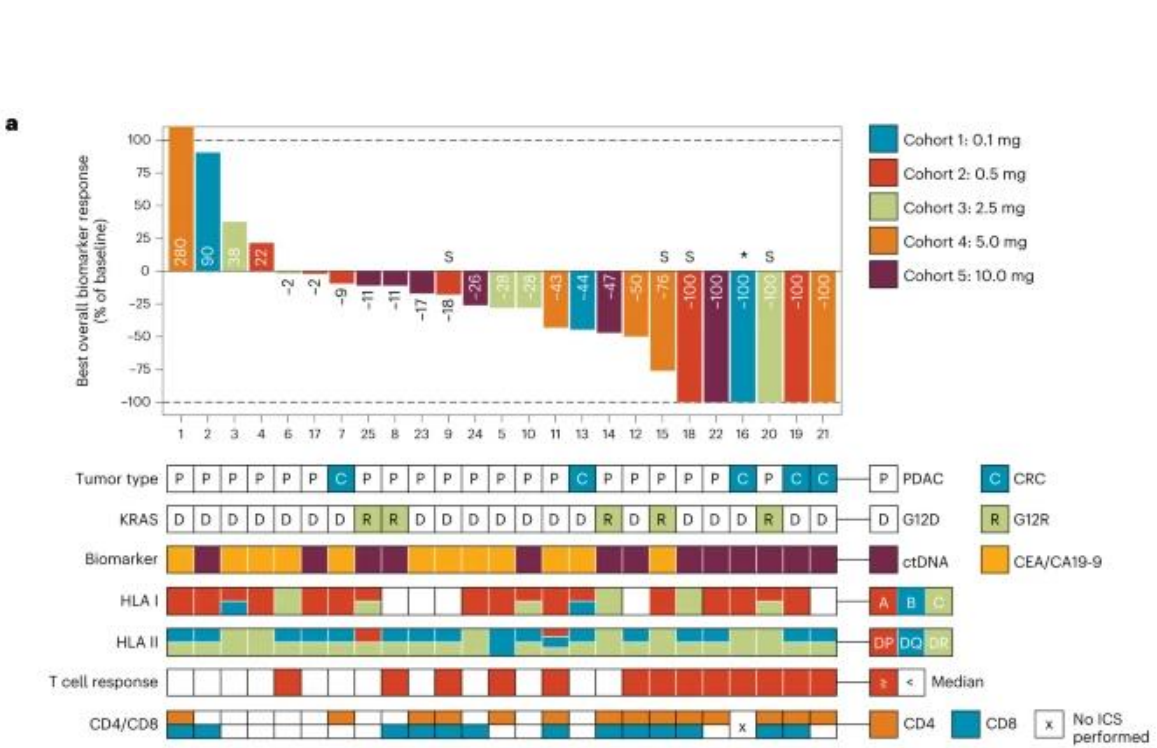
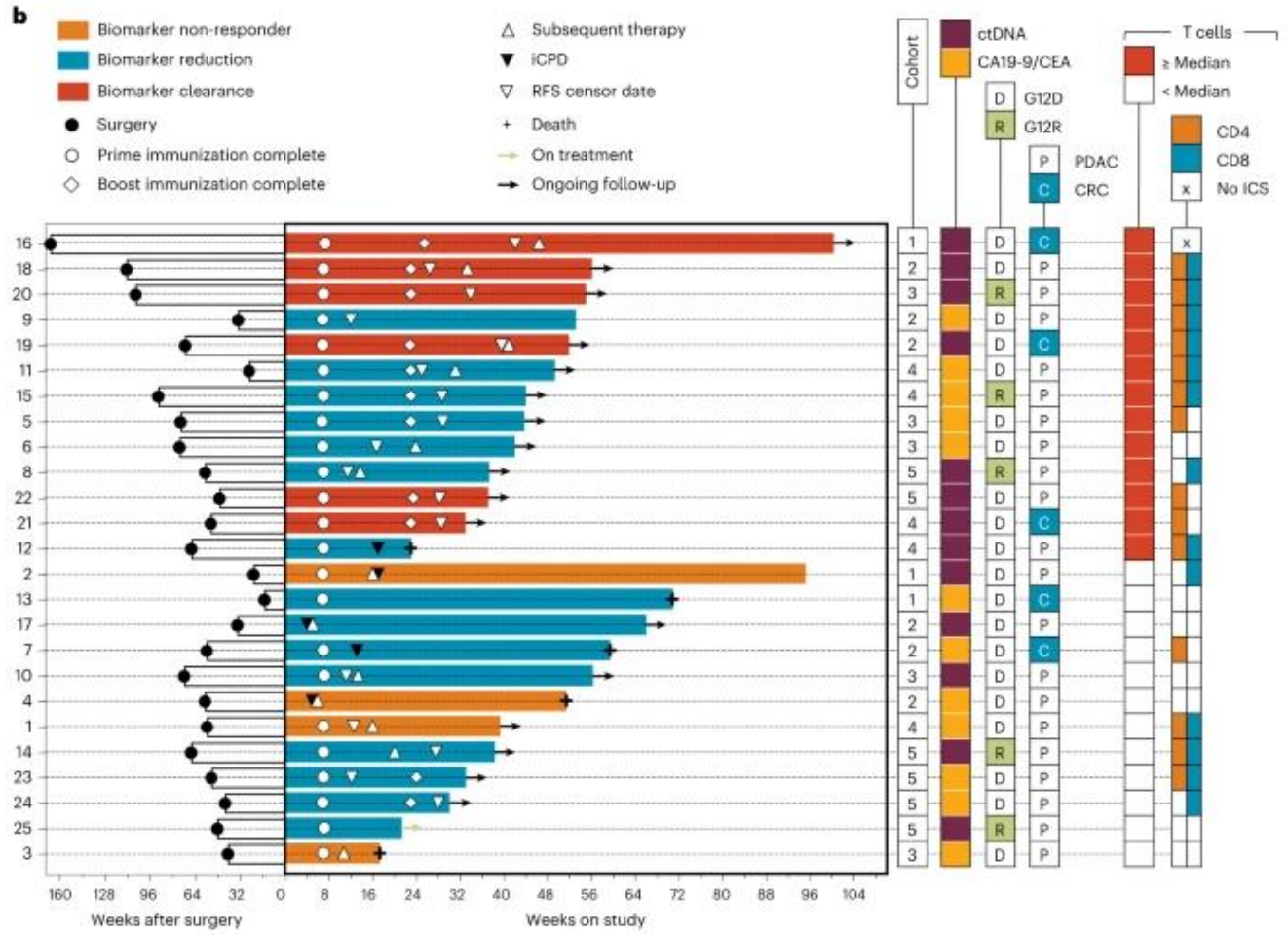
ELI002 2P in Pancreatic Adenocarcinoma





Pant S et al Nat Med 2024

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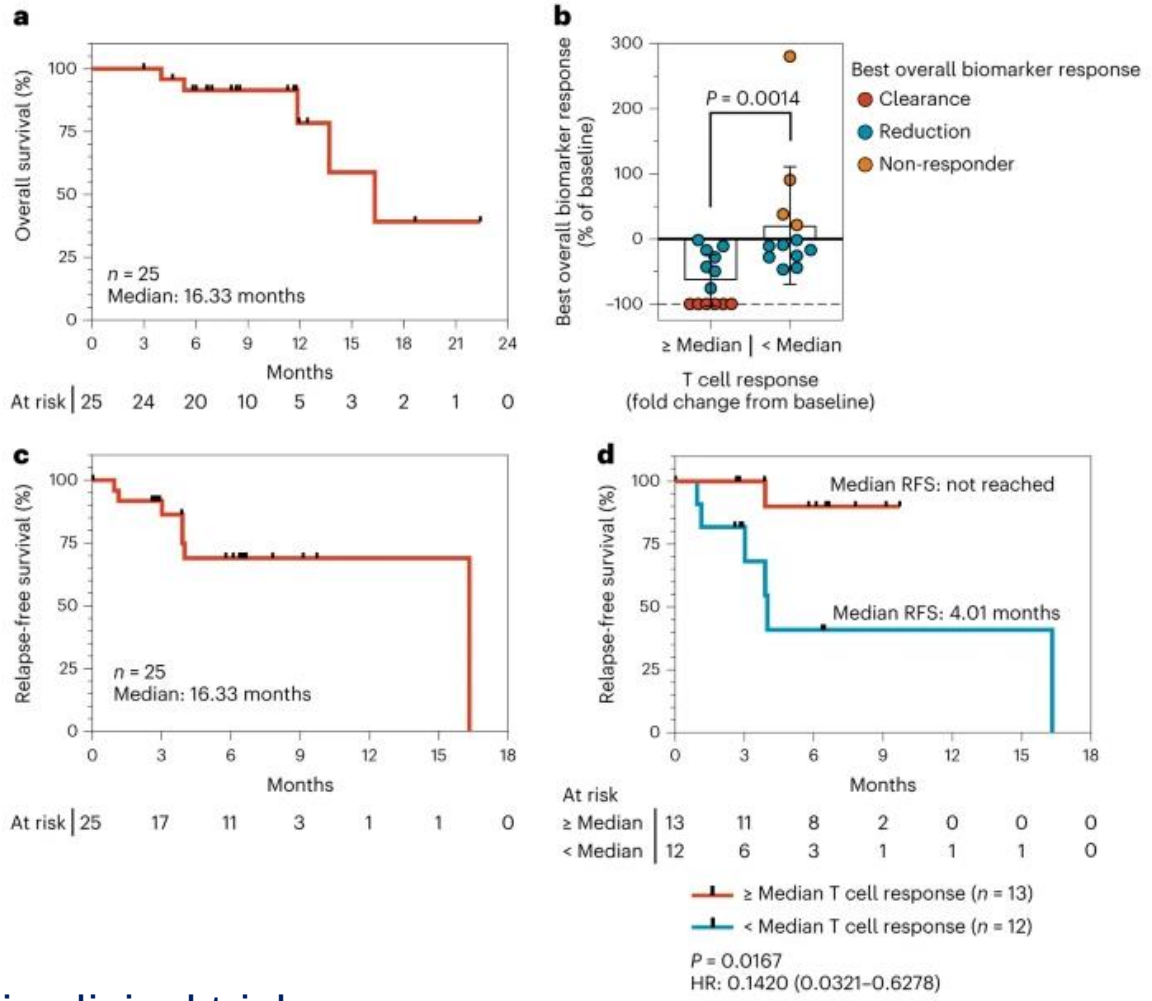
ELI002 2P in Pancreatic Adenocarcinoma



ELI-002 7P is currently in clinical trials

Pant S et al Nat Med 2024

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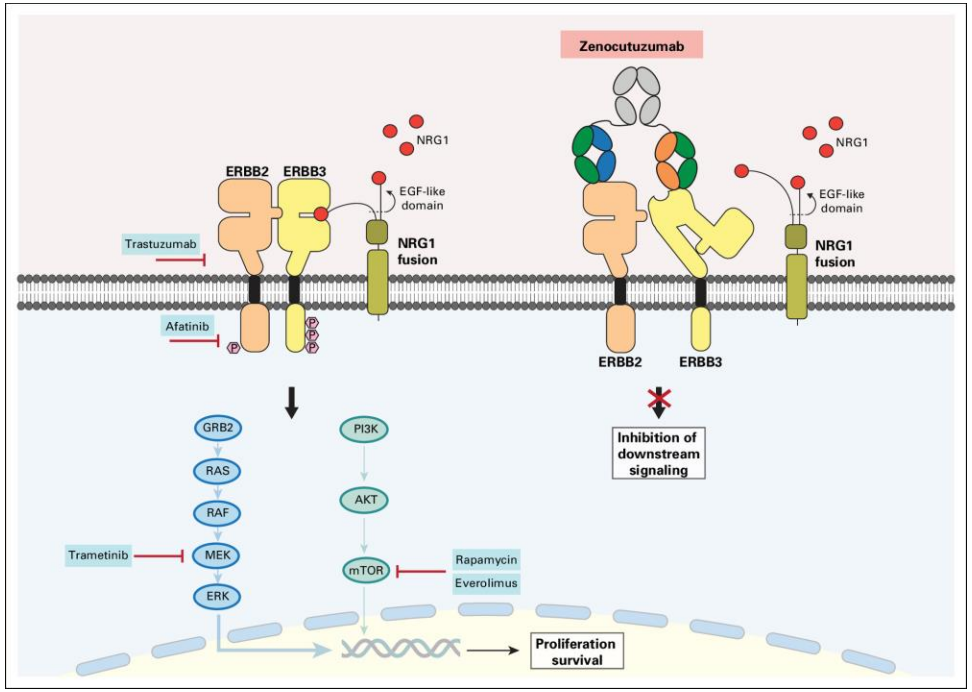
Targeted therapy in pancreatic cancer

Zenocutuzumab in pancreatic cancer with NRG1 fusions

- NRG1 is a epidermal growth factor
- NRG1 fusions bind to HER3 through an EGF like binding domain triggering heterodimerization of HER3 and HER2, resulting in downstream proliferation
- NRG1 fusions are enriched in KRAS wild type pancreatic cancer
- Zenocutuzumab is a bispecific antibody directed against HER2 and HER3



Schram AM et al NEJM 2025; Fontana E et al, JCO Prec Oncol 2022

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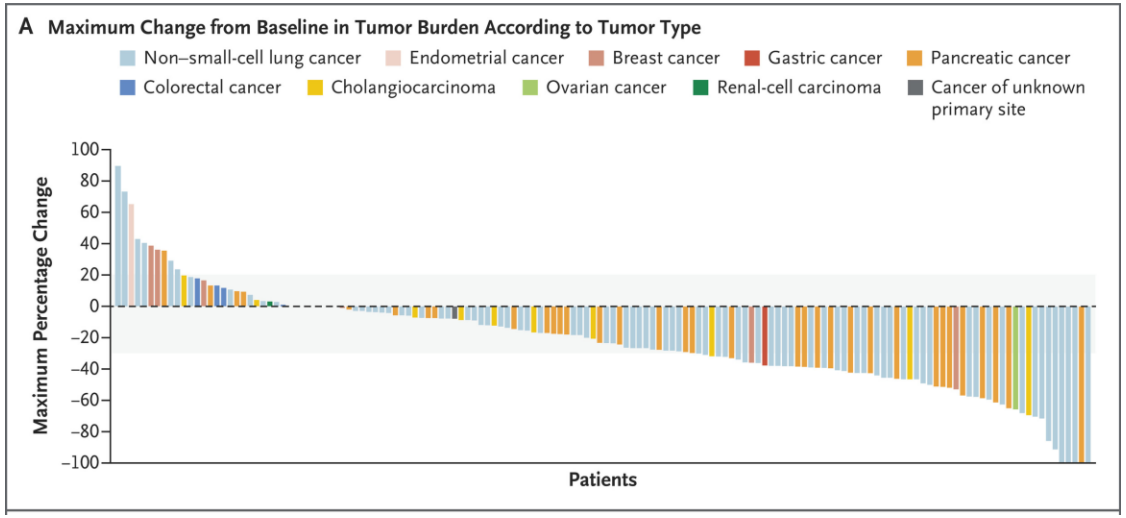
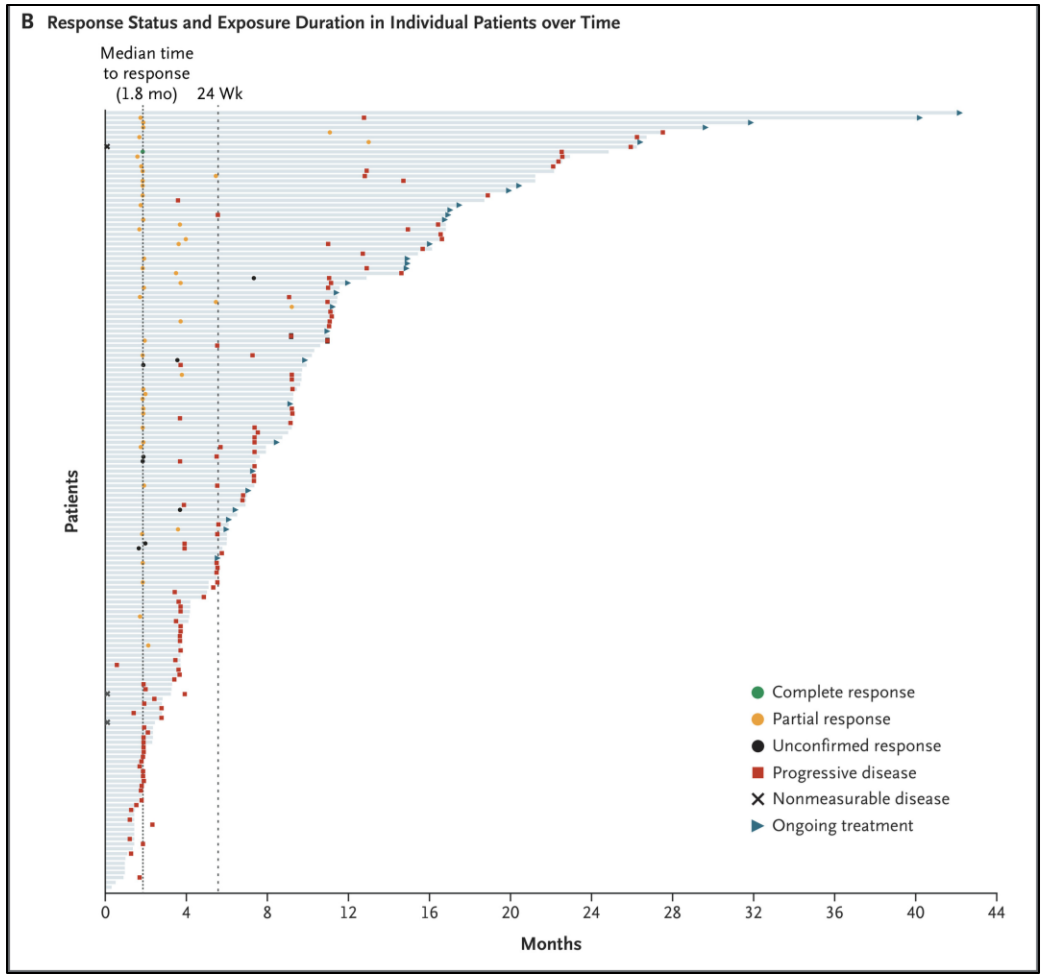
Zenocutuzumab in pancreatic cancer with NRG1 fusions





In pancreatic cancer: 42% ORR, 7.4 month duration of response

Schram AM et al NEJM 2025

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Zenocutuzumab in pancreatic cancer with NRG1 fusions

Table 3. Adverse Events among All the Patients Who Received Zenocutuzumab.*

Event	Regardless of Attribution (N=204)		Treatment-Related (N=204)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Any adverse event	194 (95)	72 (35)	135 (66)	14 (7)
Serious adverse event	49 (24)	33 (16)	4 (2)	2 (1)
Adverse event leading to treatment discontinuation	15 (7)	8 (4)	1 (<1)	0
Adverse event leading to treatment delay	64 (31)	36 (18)	12 (6)	3 (1)
Fatal adverse event	9 (4)	0	0	0
Adverse events occurring in ≥10% of patients				
Diarrhea	60 (29)	4 (2)	37 (18)	3 (1)
Fatigue	42 (21)	5 (2)	24 (12)	0
Nausea	40 (20)	4 (2)	23 (11)	2 (1)
Anemia	34 (17)	10 (5)	9 (4)	3 (1)
Dyspnea†	33 (16)	5 (2)	4 (2)	0
Constipation	28 (14)	0	7 (3)	0
Vomiting	28 (14)	2 (1)	12 (6)	1 (<1)
Abdominal pain‡	26 (13)	4 (2)	3 (1)	1 (<1)
Alanine aminotransferase increased	25 (12)	6 (3)	7 (3)	1 (<1)
Cough§	24 (12)	1 (<1)	3 (1)	0
Hypomagnesemia	23 (11)	4 (2)	5 (2)	0
Covid-19¶	22 (11)	1 (<1)	0	0
Arthralgia	21 (10)	0	7 (3)	0
Aspartate aminotransferase increased	21 (10)	6 (3)	6 (3)	2 (1)
Decreased appetite	20 (10)	2 (1)	5 (2)	1 (<1)

* The investigator-reported adverse events listed are those that occurred at any grade during treatment in at least 10% of the patients treated with zenocutuzumab at a dose of 750 mg every 2 weeks, regardless of attribution. The relatedness of the treatment to adverse events was determined by the investigators. Covid-19 denotes coronavirus disease 2019.
† Dyspnea includes the *Medical Dictionary for Regulatory Activities*, version 26.0 (MedDRA), preferred term exertional dyspnea.
‡ Abdominal pain includes the MedDRA preferred term upper abdominal pain.
§ Cough includes the MedDRA preferred term productive cough.
¶ Covid-19 includes the MedDRA preferred term Covid-19 pneumonia. One patient (<1%) had grade 5 Covid-19.

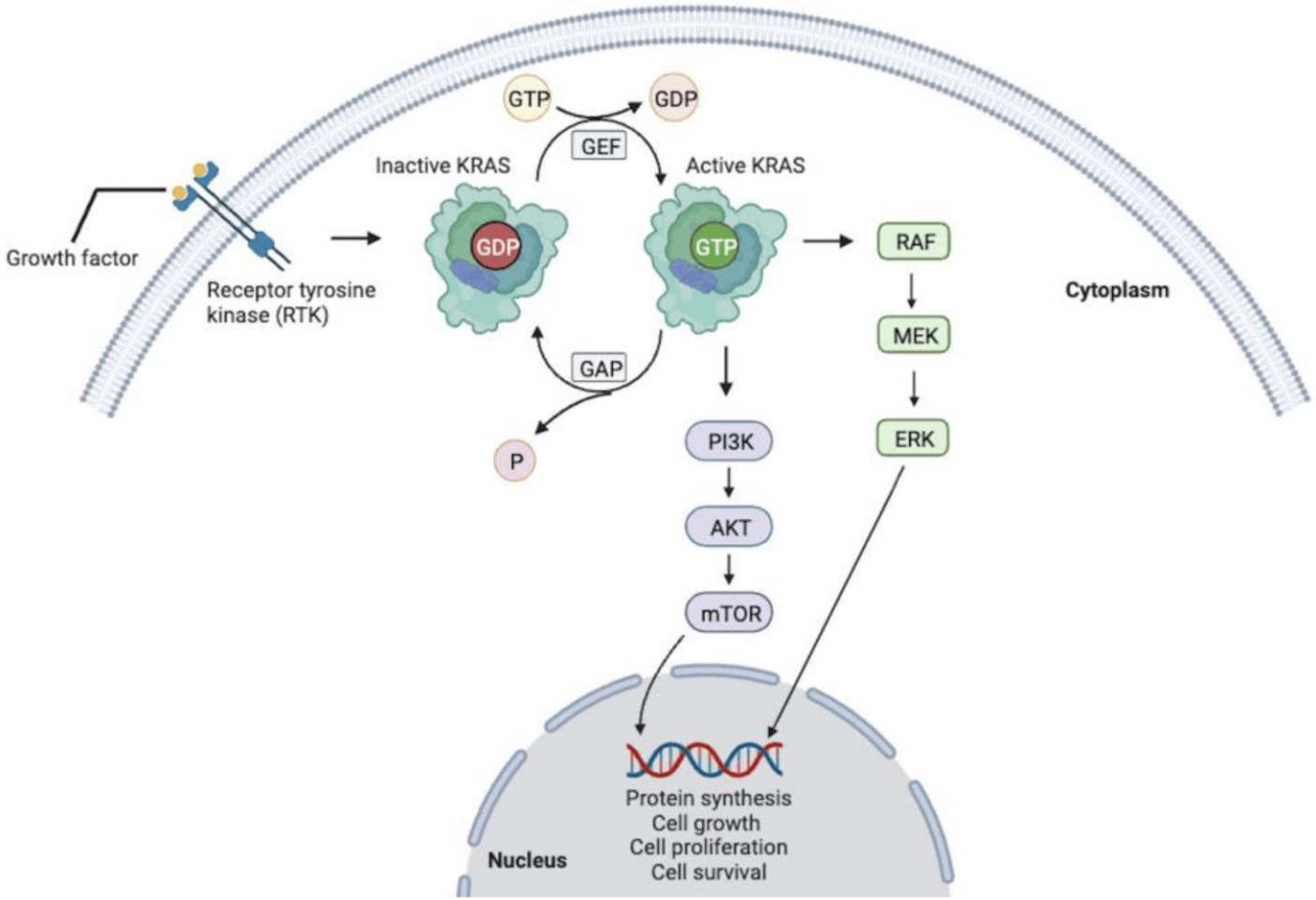
FDA grants accelerated approval to zenocutuzumab-zbco for non-small cell lung cancer and pancreatic adenocarcinoma

On December 4, 2024, the Food and Drug Administration granted accelerated approval to zenocutuzumab-zbco (Bizengri, Merus N.V.) for adults with the following:

- advanced, unresectable, or metastatic non-small cell lung cancer (NSCLC) harboring a neuregulin 1 (*NRG1*) gene fusion with disease progression on or after prior systemic therapy, or
- advanced, unresectable, or metastatic pancreatic adenocarcinoma harboring a *NRG1* gene fusion with disease progression on or after prior systemic therapy.

Schram AM et al NEJM 2025

KRAS Background



Nusrat F, et al J Clin Med 2024

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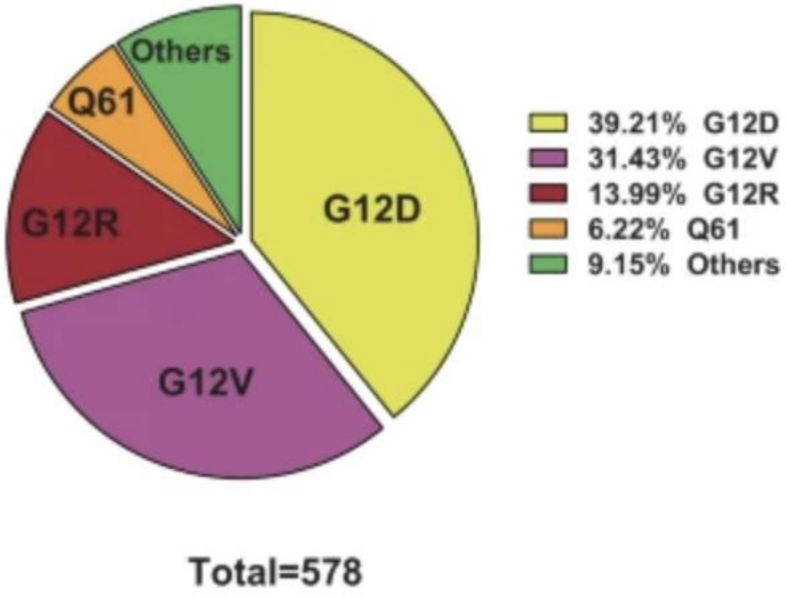
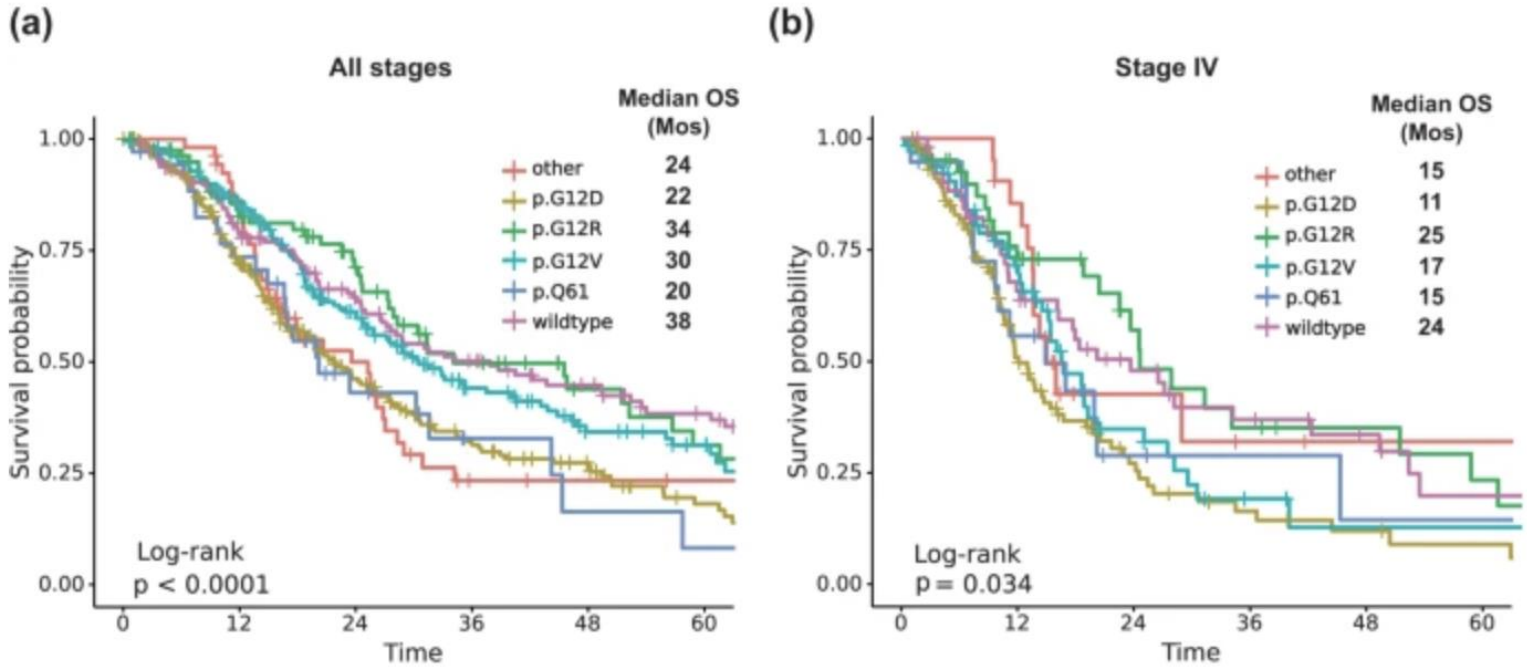
KRAS mutations in PDAC





Yousef A et al, NPJ Prec Oncol 2024

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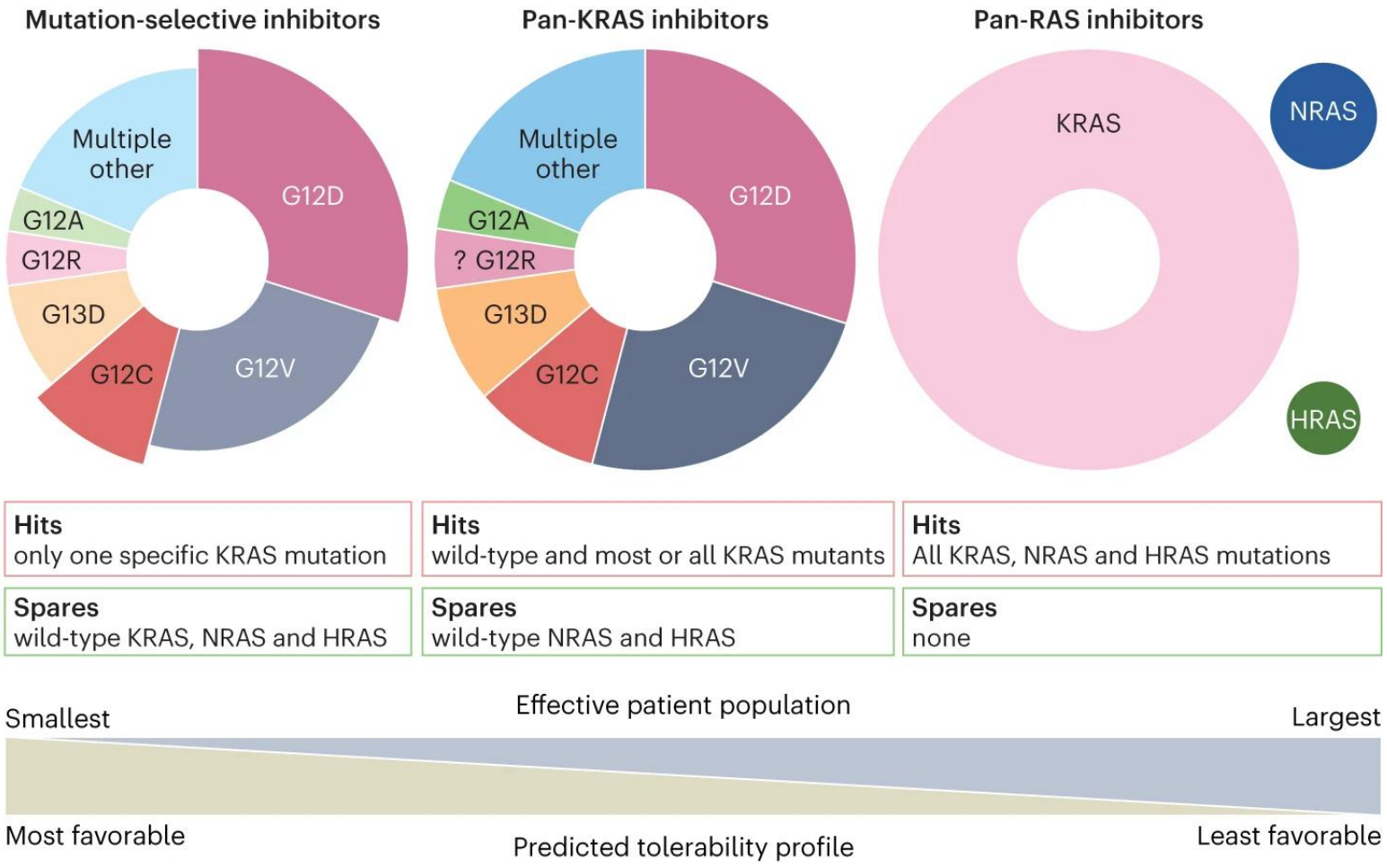
RAS inhibitors



Corcoran RB Nat Cancer 2023

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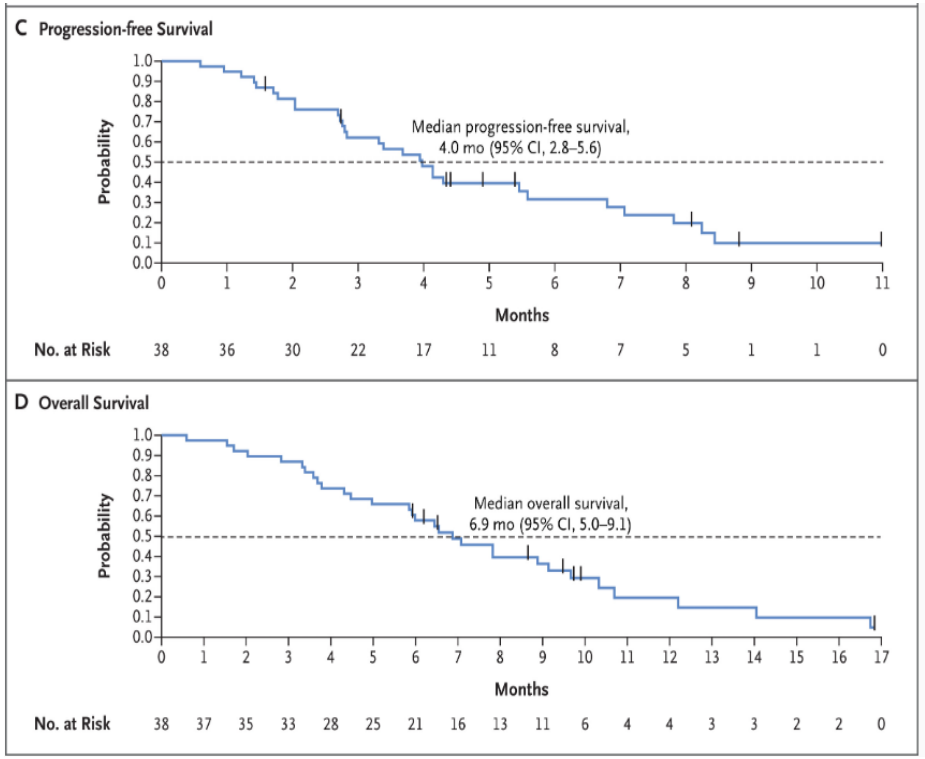
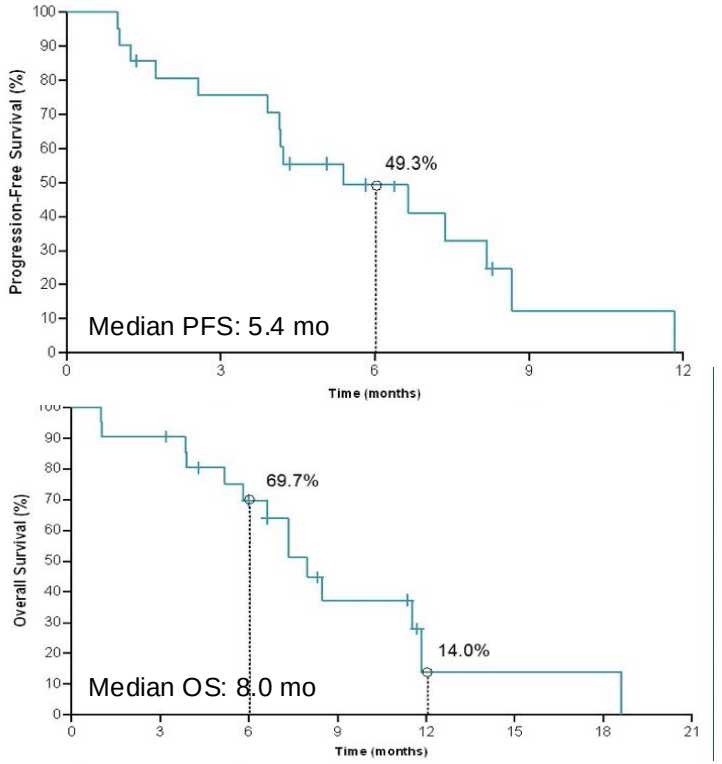
KRAS G12C Inhibition in PDAC

Sotorasib



Strickler JH et al NEJM 2022

Adagrasib



Pant S, ASCO Plenary Series 2023

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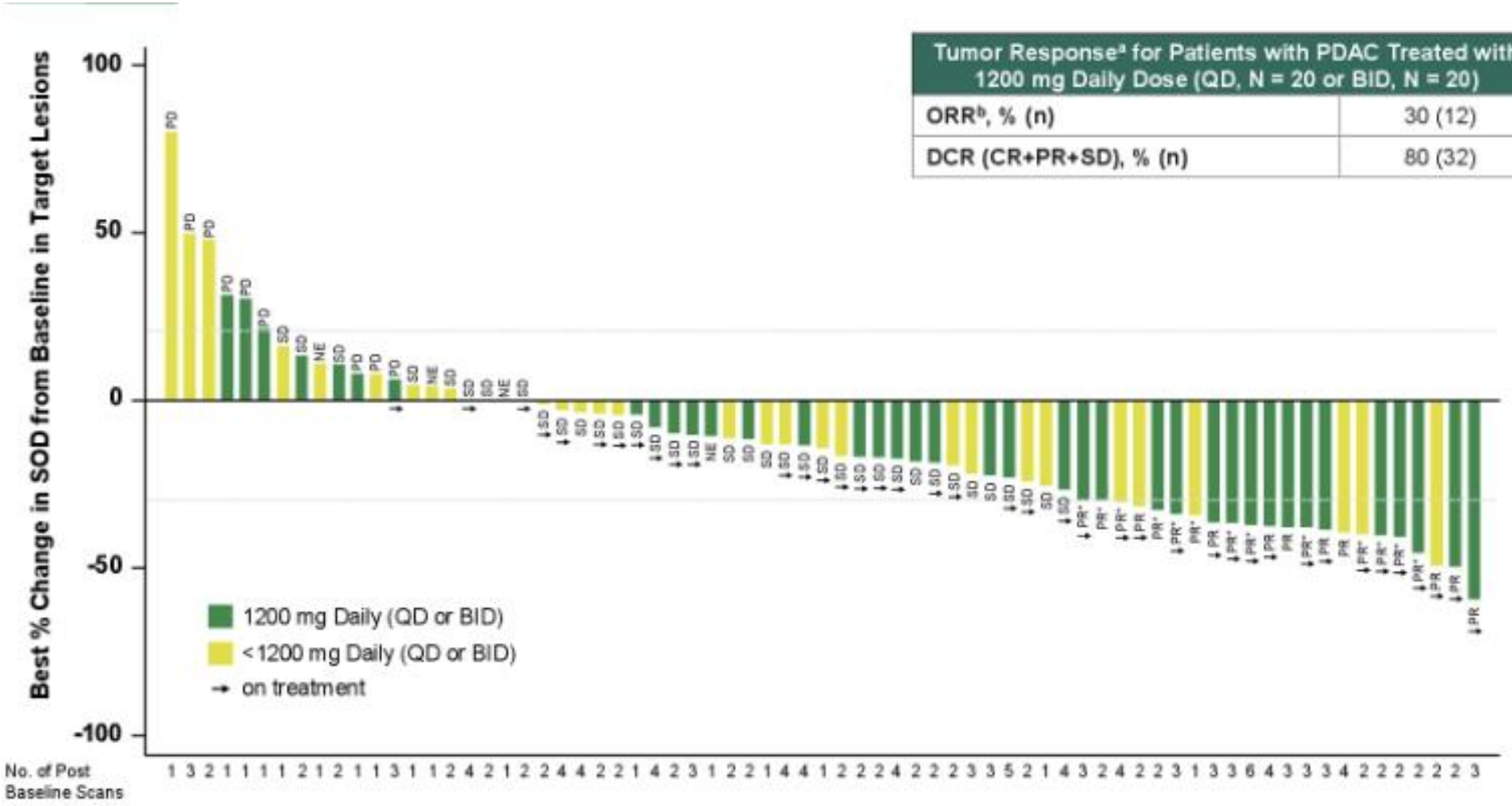
KRAS G12D inhibition: Zoldonrasib (RMC-9805)

Tumor Response[a] for Patients with PDAC Treated with 1200 mg Daily Dose (QD, N = 20 or BID, N = 20)	
ORR[b], % (n)	30 (12)
DCR (CR+PR+SD), % (n)	80 (32)



Spira A et al ASCO GI 2025

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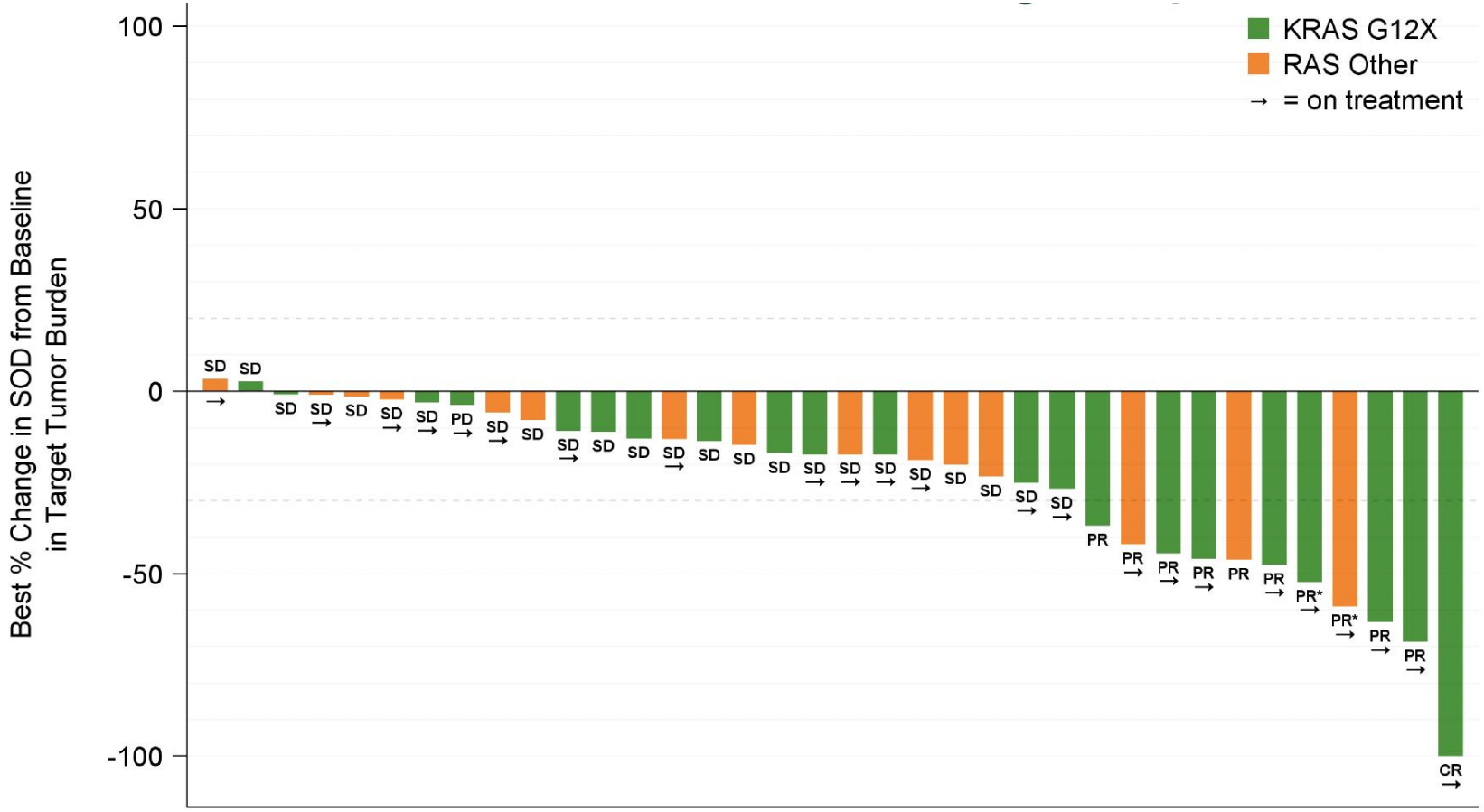
MultiRAS inhibitor in second line treatment of metastatic pancreatic adenocarcinoma



Wolpin BM ENA Symposium 2024

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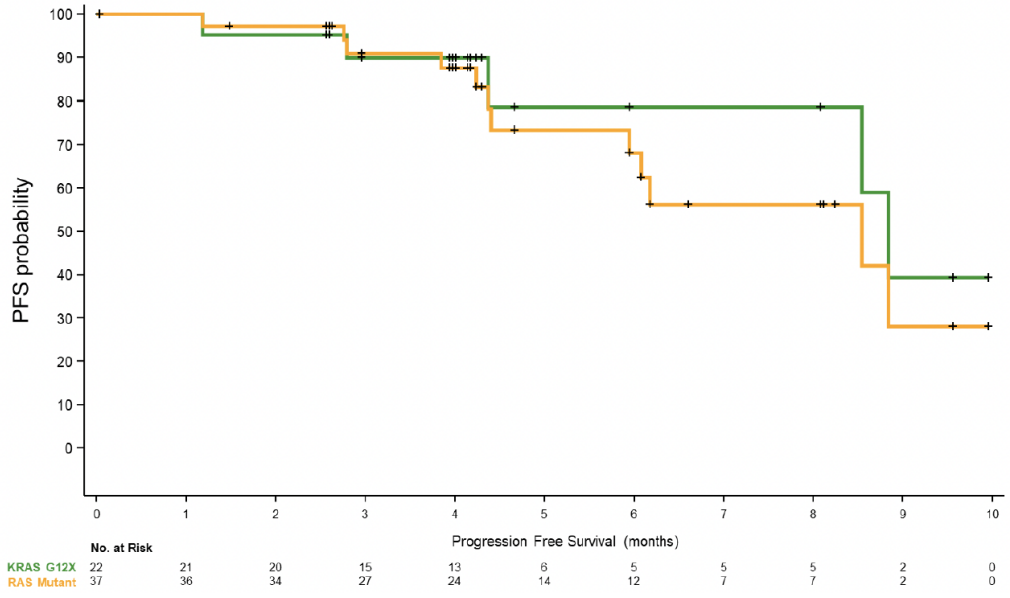
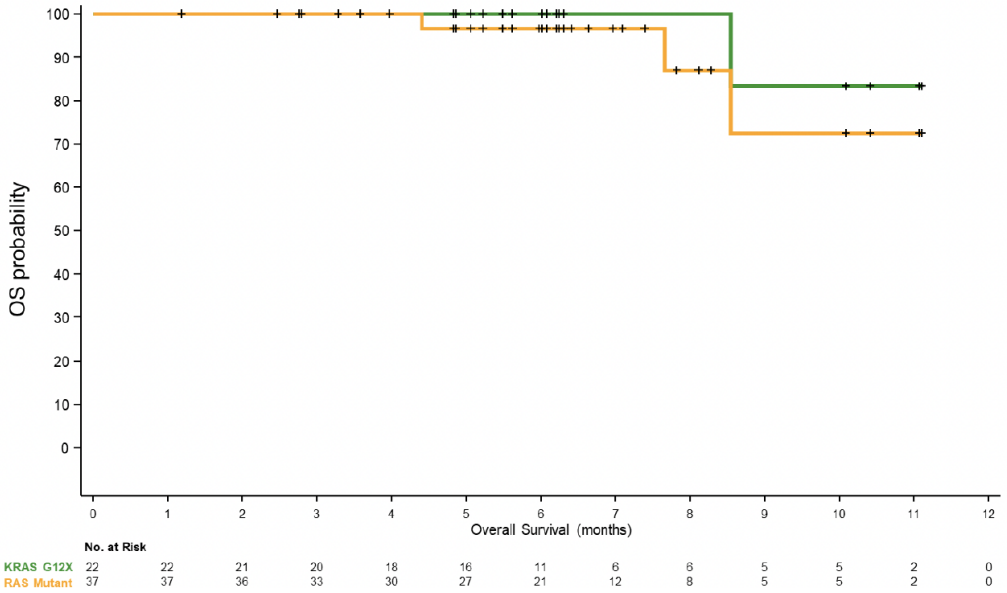
MultiRAS inhibitor in second line treatment of metastatic pancreatic adenocarcinoma

	Median PFS, months (95% CI)	Median OS, Months (95% CI)	OS Rate at 6 months, % (95% CI)
KRAS G12X	**8.8** (8.5, NE)	**NE** (NE, NE)	**100** (100, 100)
RAS Mutant[(1)]	**8.5** (5.9, NE)	**NE** (8.5, NE)	**97** (79, 100)





Wolpin BM ENA Symposium 2024

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Toxicity of MultiRAS- vs RAS Mutation-specific Inhibitors

KRAS G12D (zoldonrasib)

- Most common (G1/2): nausea (30%), diarrhea (16%), vomiting (15%)
- G3: AST increase (3%)
- TRAE leading to dose reduction: 3%
- TRAE leading to discontinuation: 0%

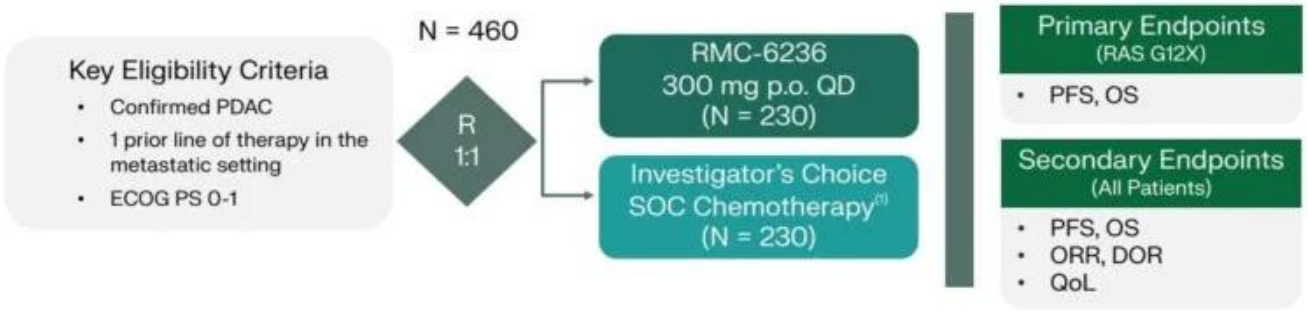
MultiRAS (daraxonrasib)

- Most common: rash (91%), diarrhea (53%), nausea (38%), vomiting 36%, stomatitis (34%)
- G3: rash (8%), diarrhea (4%), stomatitis (4%)
- TRAE leading to dose modification: 42%
- TRAE leading to doe discontinuation: 0%

Spira A et al ASCO GI 2025, Wolpin BM ENA Symposium 2024

Ongoing studies

RASolute 302: Phase 3 trial in second line metastatic pancreatic adenocarcinoma



Study of RAS inhibitors in gastrointestinal malignancies

- RMC-6236 (daraxonrasib) in combination with FOLFIRINOX or Gemcitabine and nab-paclitaxel in 1L mPDAC
- RMC-6236 (daraxonrasib) in combination with cetuximab in 2L mPDAC
- FOLFIRINOX or gemcitabine/nab-paclitaxel + RMC 9805 (Zoldonrasib) +/- RMC-6236 (daraxonrasib) in 1L mPDAC
- Cetuximab + RMC 9805 (Zoldonrasib) +/- RMC-6236 (daraxonrasib) in 2L mPDAC

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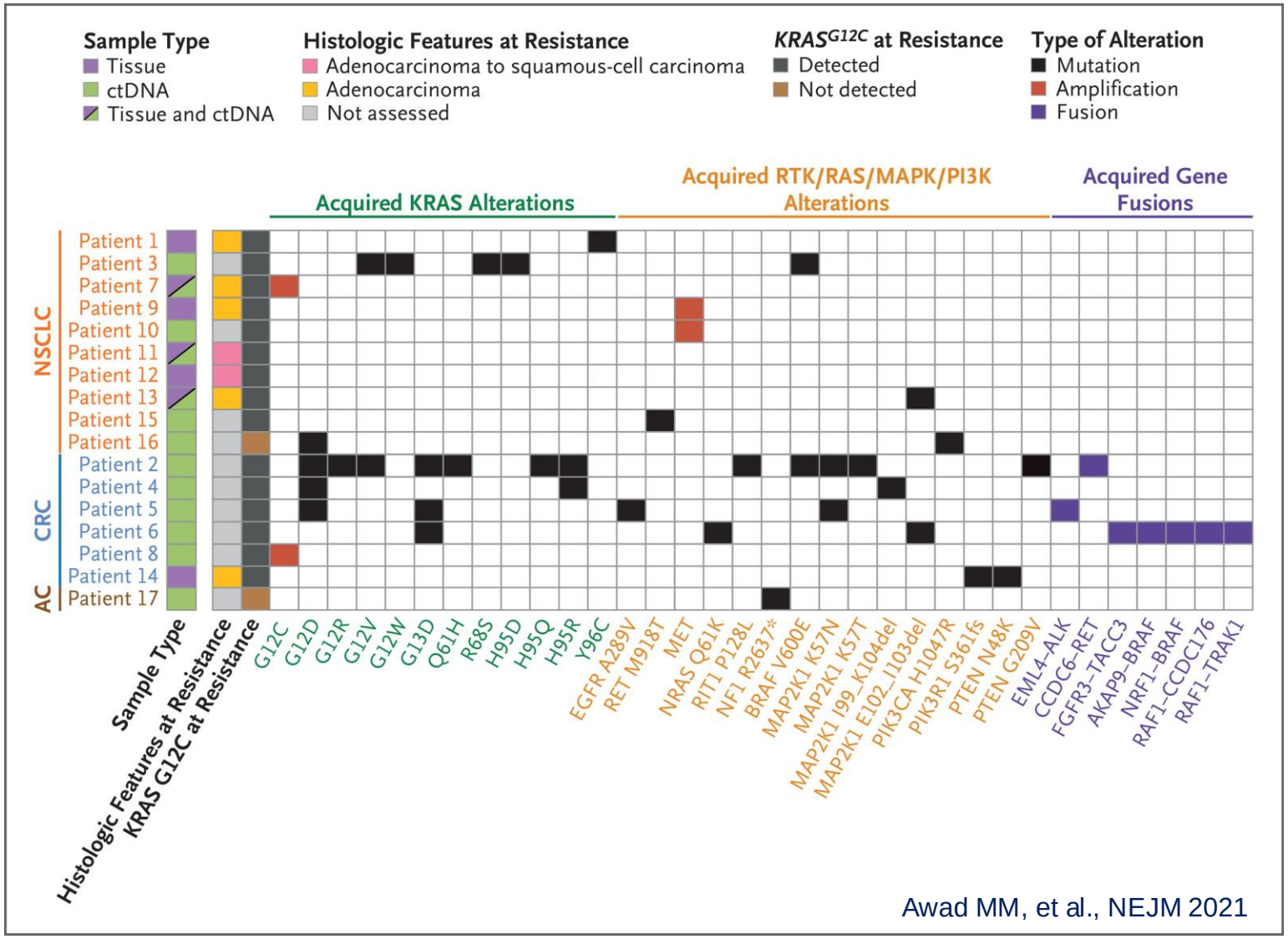
Clinical Trial	Compound (Company)	Phase	Target	Population
Phase 1/2 study of TSN1611 in subjects with KRAS G12D mutant advanced solid tumors	TSN1611 (Tyligand Therapeutics)	I/II	KRAS G12D	Ph1: Solid Tumors Ph2: PDAC, CRC, NSCLC
A Study of the Pan-KRAS Inhibitor LY4066434 in Participants With KRAS Mutant Solid Tumors	LY40664343 (Lilly)	I	Pan-KRAS	Solid Tumors
Study of RMC-9805 in Participants With KRAS G12D Mutant Solid Tumors	RMC9805 (Revolution Medicine)	I	KRAS G12D	Solid Tumors
A Study of LY3962673 in Participants With KRAS G12D Mutant Solid Tumors	LY3962673 (Lilly)	I	KRAS G12D	Solid Tumors
Study of RMC-6236 in Patients With Advanced Solid Tumors Harboring Specific Mutations in RAS	RMC6236 (Revolution Medicine)	I/Ib	Pan-KRAS	Solid Tumors
A First-in-human Study of BGB-53038, a Pan-KRAS Inhibitor, Alone or in Combinations in Participants With Advanced or Metastatic Solid Tumors With KRAS Mutations or Amplification	BGB53038 (Beigene)	Ia/Ib	Pan-KRAS	Solid Tumors
Study of RAS(ON) Inhibitors in Patients with Gastrointestinal Solid Tumors	RMC6236 RMC9805	Platform	Pan-KRAS KRAS G12D	Pancreatic Cancer Colorectal Cancer
A Study to Evaluate INCB161734 in Participants With Advanced or Metastatic Solid Tumors With KRAS G12D Mutation	INCB161734 (Incyte)	I	KRAS G12D	Solid Tumors
Phase 3 Study of RMC-6236 in Patients with Previously Treated Metastatic Pancreatic Ductal Adenocarcinoma (PDAC) (RASolute 302)	RMC6236	III	Pan-KRAS	Pancreatic Cancer
A Phase I/IIa Study of AZD0022 as Monotherapy and in Combination With Anti-cancer Agents in Adult Participants With Tumors Harbouring a KRASG12D Mutation (ALAFOSS-01)	AZD0022 (AstraZeneca)	I/IIa	KRAS G12D	Solid Tumors

KA Reiss

Future Directions with KRAS Inhibitors

KRAS inhibitor resistance mechanisms



Awad MM, et al., NEJM 2021

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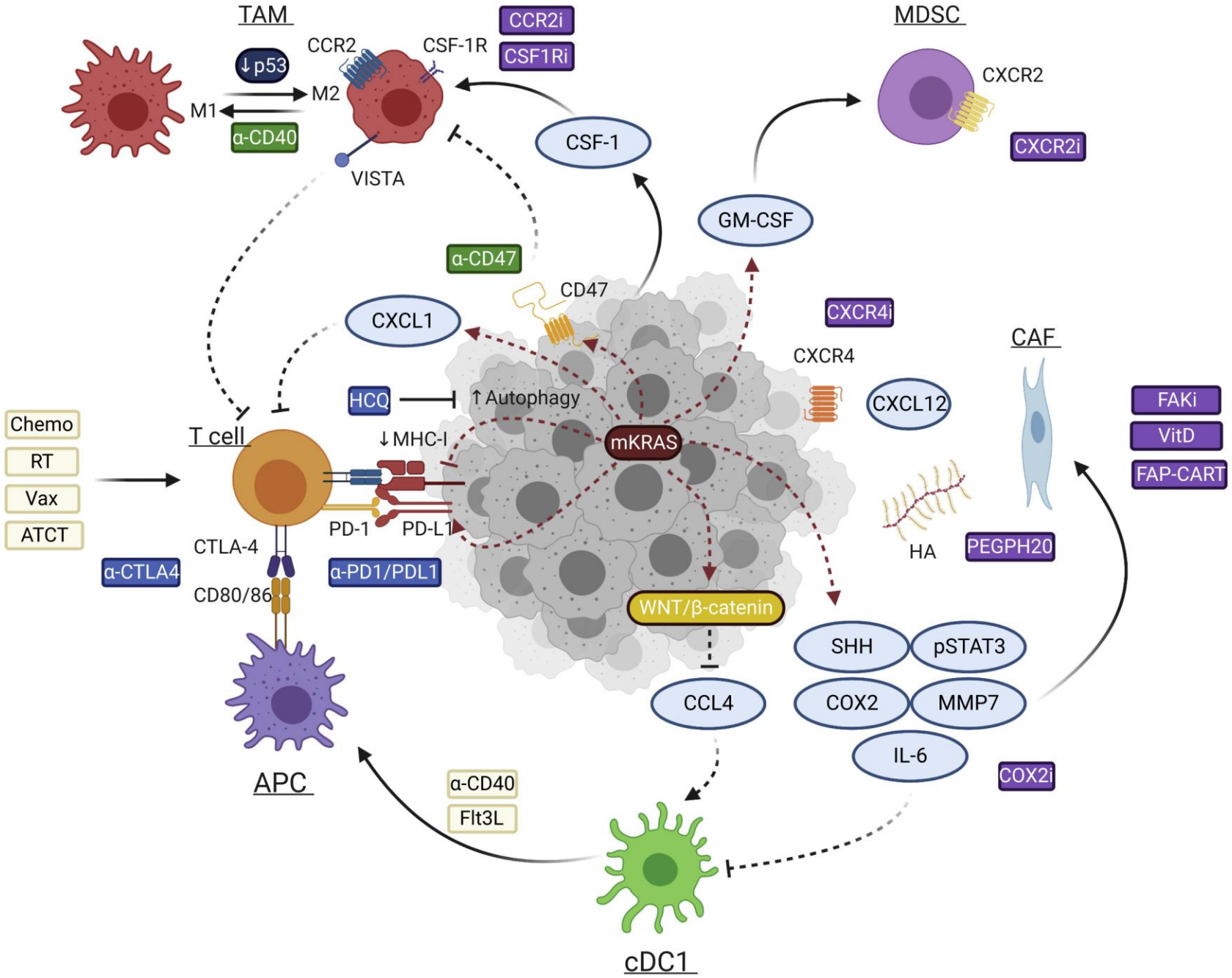
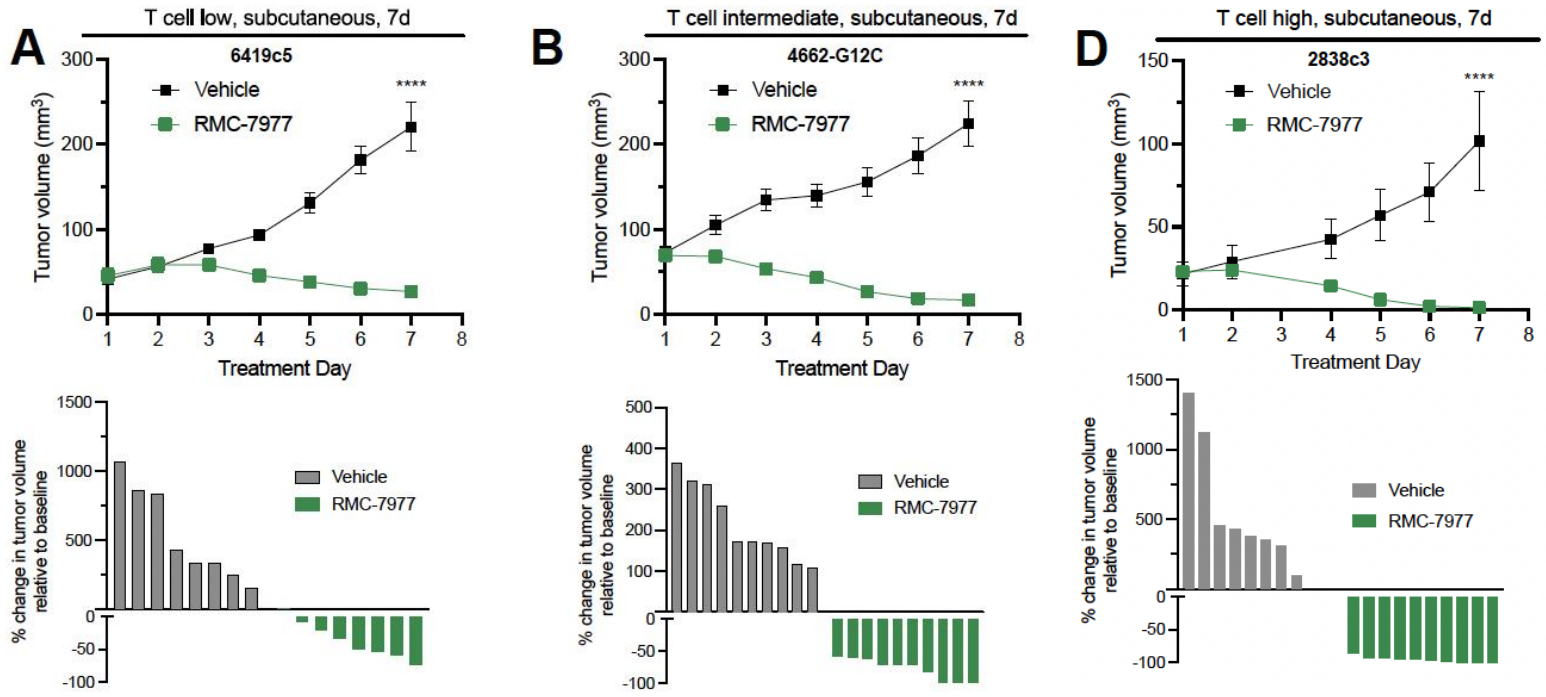


Bear AS et al Cancer Cell 2020

Depth of reponses to panRAS inhibition is dependent on T cell infiltration



Orlen MI et al Cancer Discov 2025

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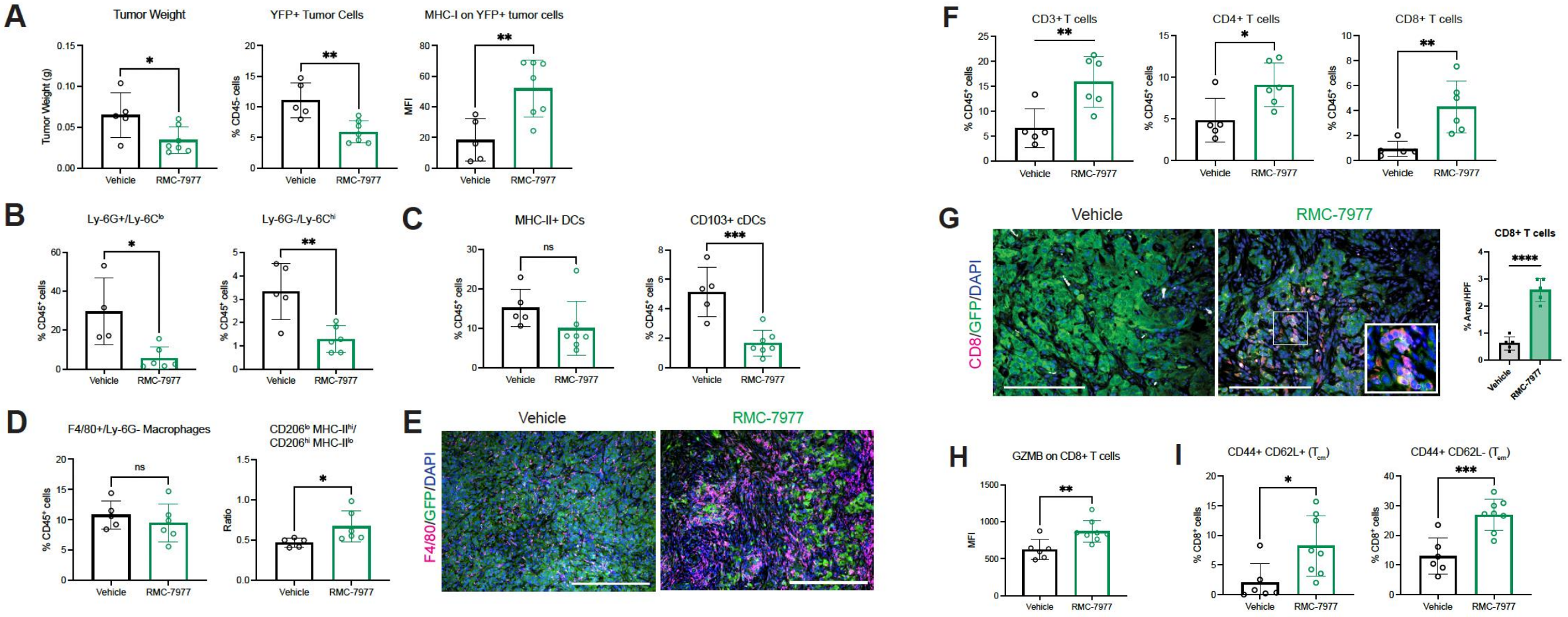
Pan RAS inhibition alters the TME



Orlen MI et al Cancer Discov 2025

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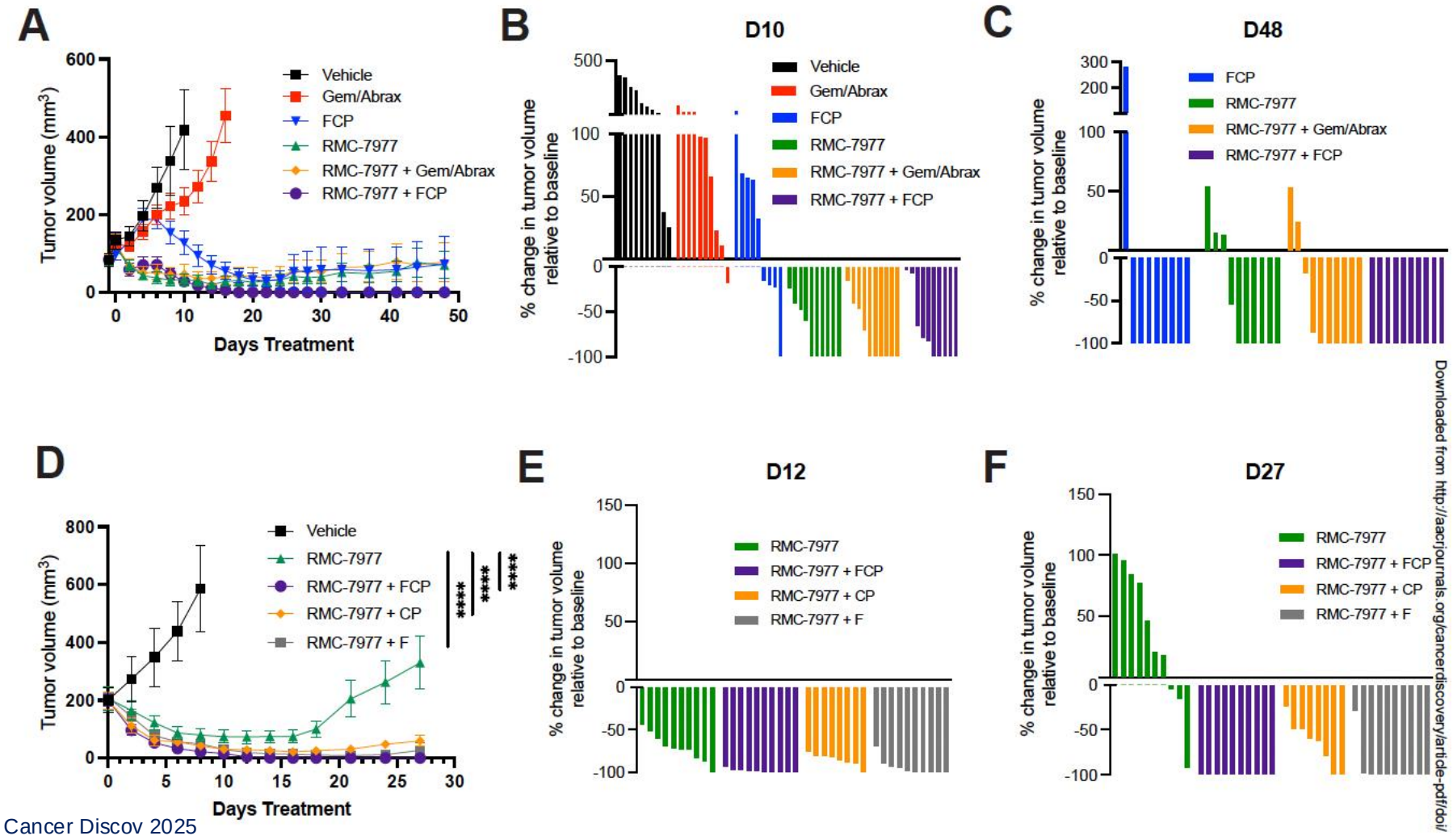
PanRAS inhibitor + immunotherapy

Figure 5

T cell high, 2838c3, subcutaneous



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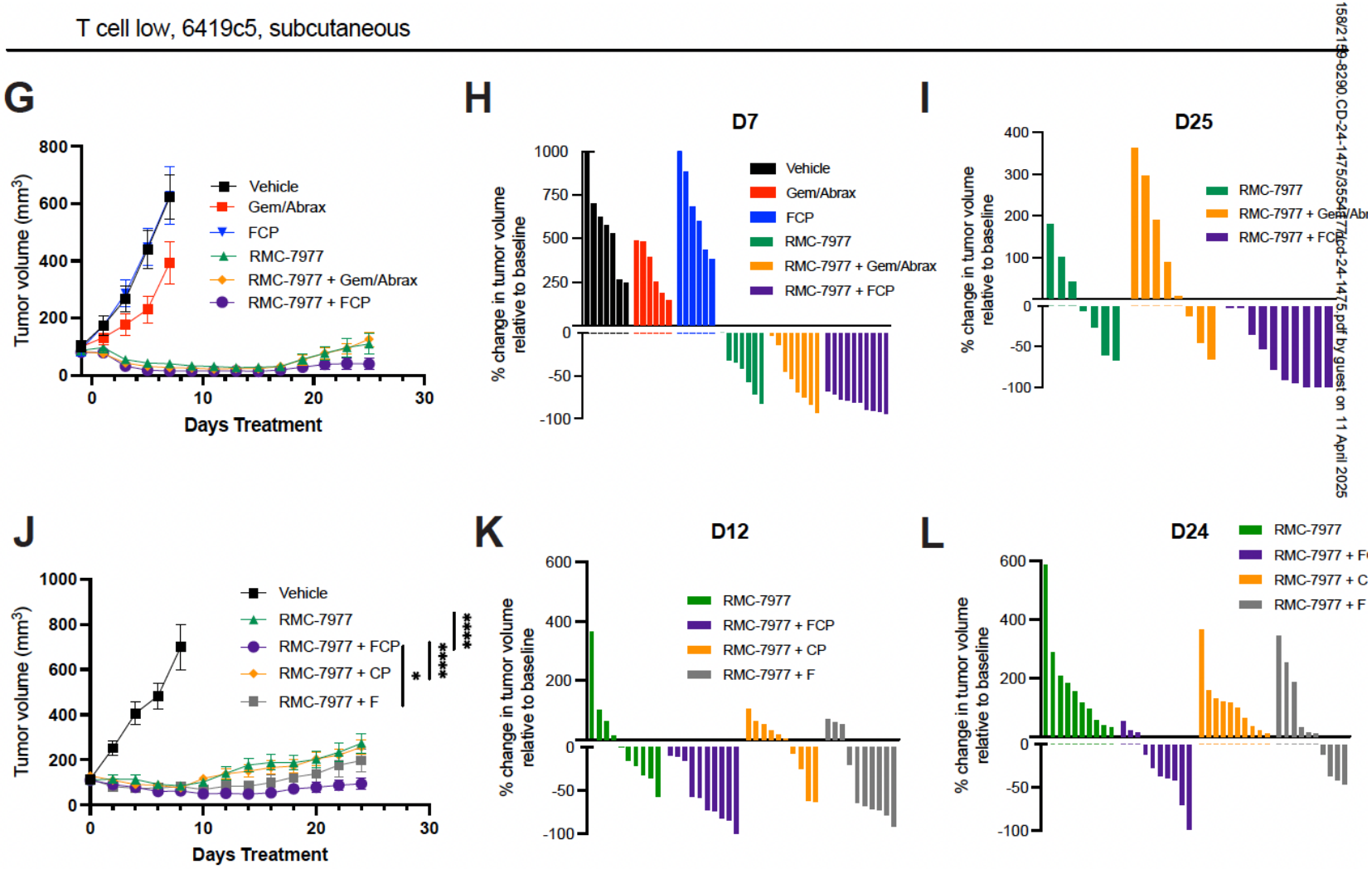
PanRAS inhibitor + immunotherapy



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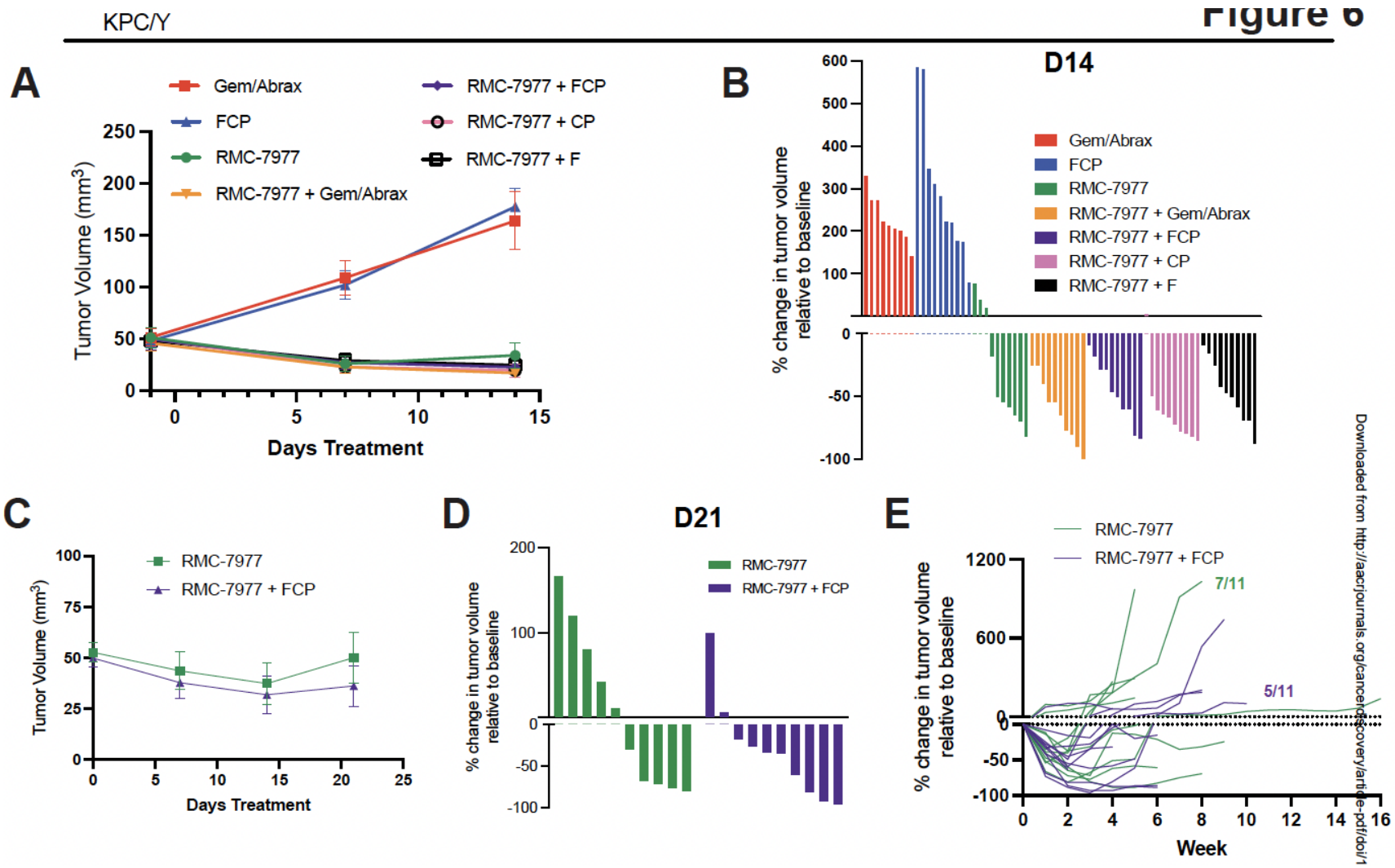
PanRAS inhibitor + immunotherapy



Orlen MI et al Cancer Discov 2025

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Conclusions

- The toolbox of treatments for pancreatic cancer does not only include cytotoxic chemotherapy and is changing
- Immunotherapy continues to have a limited role in pancreatic adenocarcinoma, though vaccination in the adjuvant setting has shown promise
- Targeted therapy options are expanding in pancreatic adenocarcinoma, highlighting the role for next generation sequencing and fusion panel testing
- Zenocutuzumab has accelerated approval for NRG1 fusions
- KRAS inhibitors have shown promise in early trials and phase 3 trials are ongoing
- Future potential to enhance KRAS inhibition with immunotherapy

Thank you

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