Treatment of metastatic pancreatic cancer what direction are we going

Mike Cusnir MD

Division Chief Hematology and Oncology

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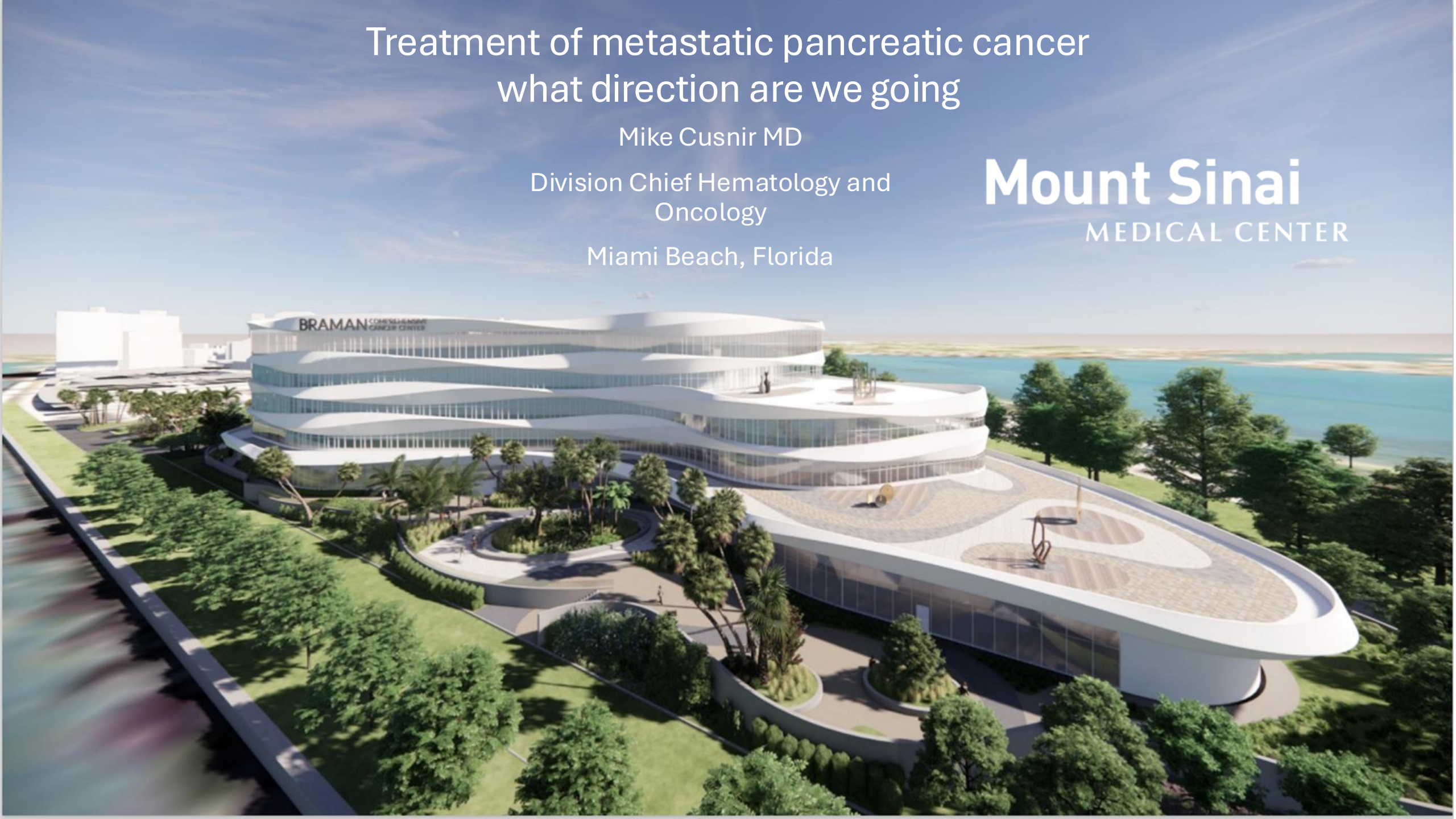
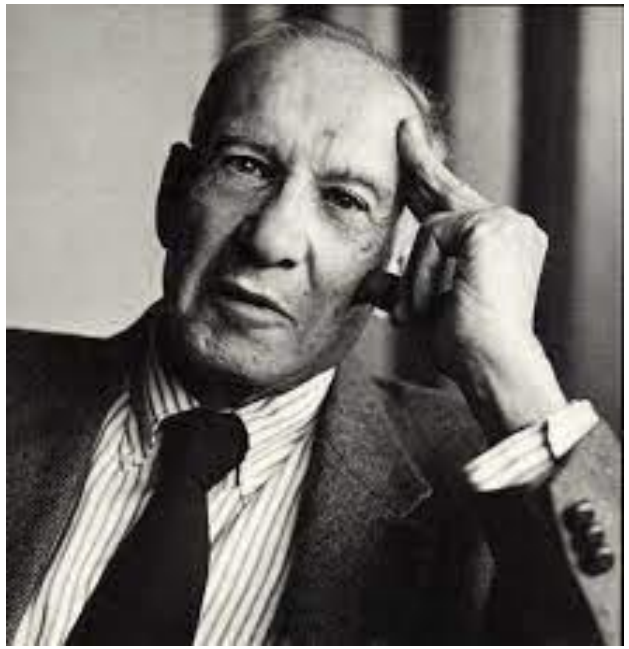


- *Until we can manage time, we can manage nothing else.”*



— Peter F. Drucker

5 year survival is now close to 13% up from 5%

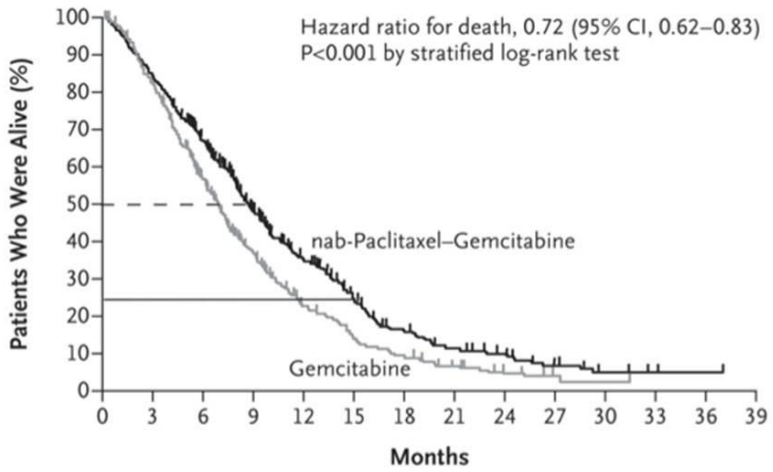
Non-biomarker driven combination chemotherapy is of marginal benefit in pancreatic cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine

Daniel D. Von Hoff, M.D., Thomas Ervin, M.D., Francis P. Arena, M.D., E. Gabriela Chiorean, M.D., Jeffrey Infante, M.D., Malcolm Moore, M.D., Thomas Seay, M.D., Sergei A. Tjulandin, M.D., Wen Wee Ma, M.D., Mansoor N. Saleh, M.D., Marion Harris, M.D., Michele Reni, M.D., Scot Dowden, M.D., Daniel Laheru, M.D., Nathan Bahary, M.D., Ramesh K. Ramanathan, M.D., Josep Tabernero, M.D., Manuel Hidalgo, M.D., Ph.D., David Goldstein, M.D., Eric Van Cutsem, M.D., Xinyu Wei, Ph.D., Jose Iglesias, M.D., and Markus F. Renschler, M.D.

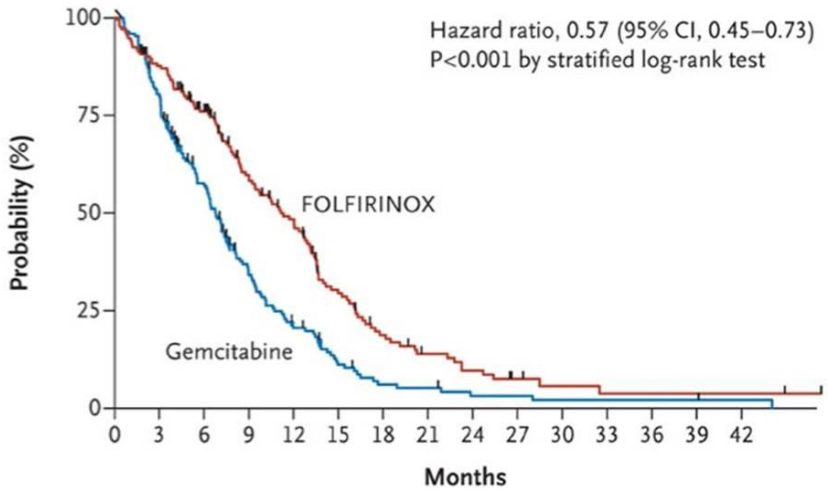


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

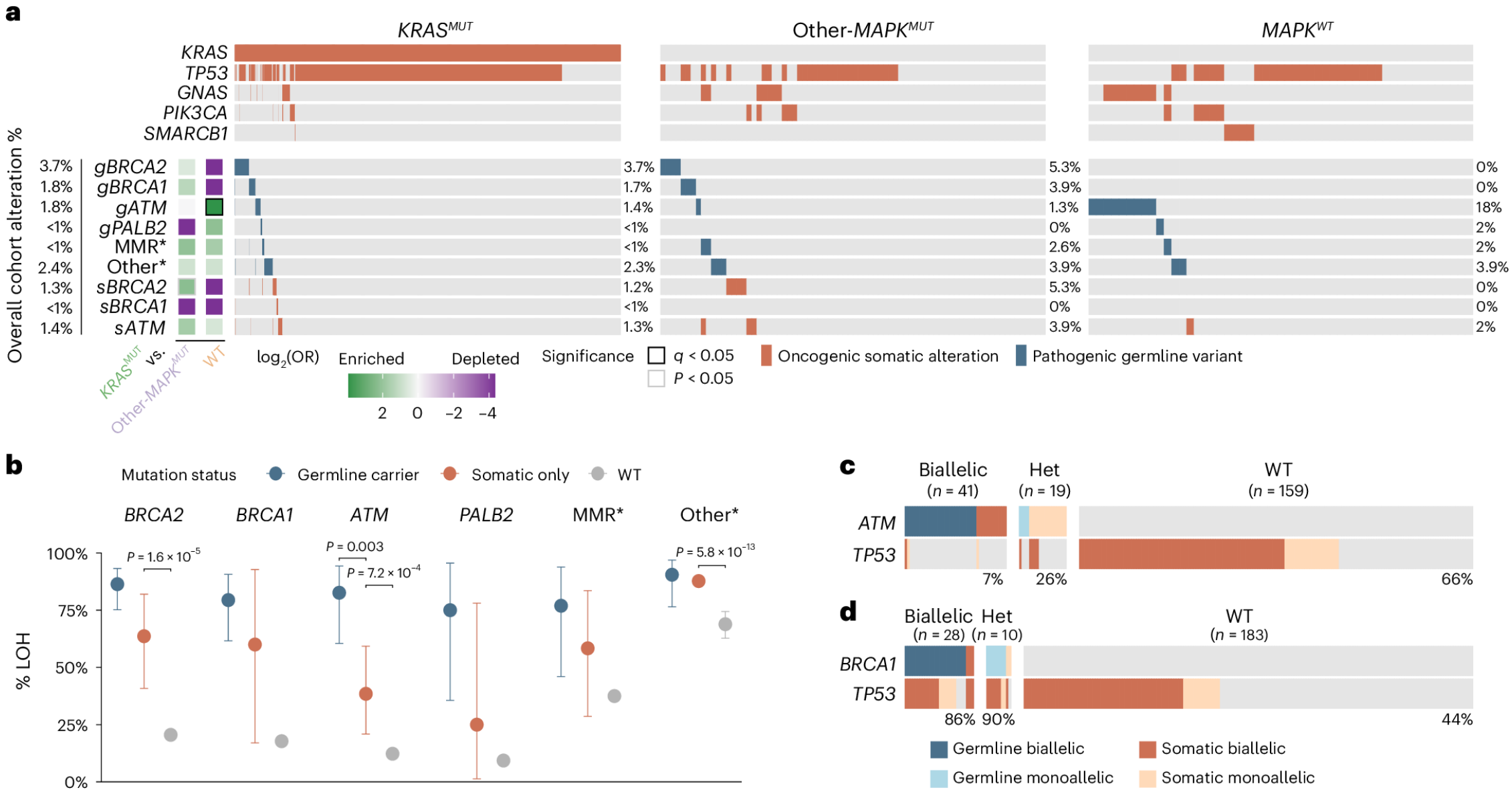
Thierry Conroy, M.D., Françoise Desseigne, M.D., Marc Ychou, M.D., Ph.D., Olivier Bouché, M.D., Ph.D., Rosine Guimbaud, M.D., Ph.D., Yves Bécouarn, M.D., Antoine Adenis, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Sophie Gourgou-Bourgade, M.Sc., Christelle de la Fouchardière, M.D., Jaafar Bennouna, M.D., Ph.D., Jean-Baptiste Bachet, M.D., Faiza Khemissa-Akouz, M.D., Denis Péré-Vergé, M.D., Catherine Delbaldo, M.D., Eric Assenat, M.D., Ph.D., Bruno Chauffert, M.D., Ph.D., Pierre Michel, M.D., Ph.D., Christine Montoto-Grillot, M.Chem., and Michel Ducreux, M.D., Ph.D., for the Groupe Tumeurs Digestives of Unicancer and the PRODIGE Intergroup*



- Time you enjoy wasting is not wasted time.”

Marthe Troly-Curtin

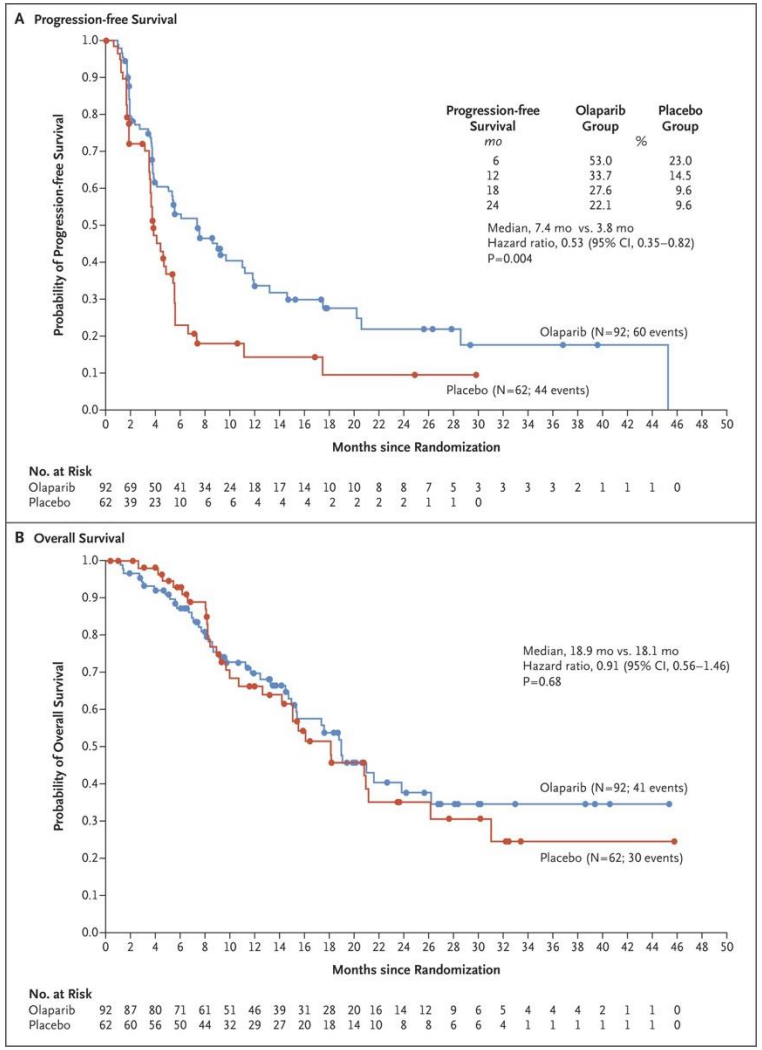
Germline alteration landscape in PDAC



Cancer. 2020 Jun 23;126(17):3939–3949. doi: 10.1002/cncr.33038

Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

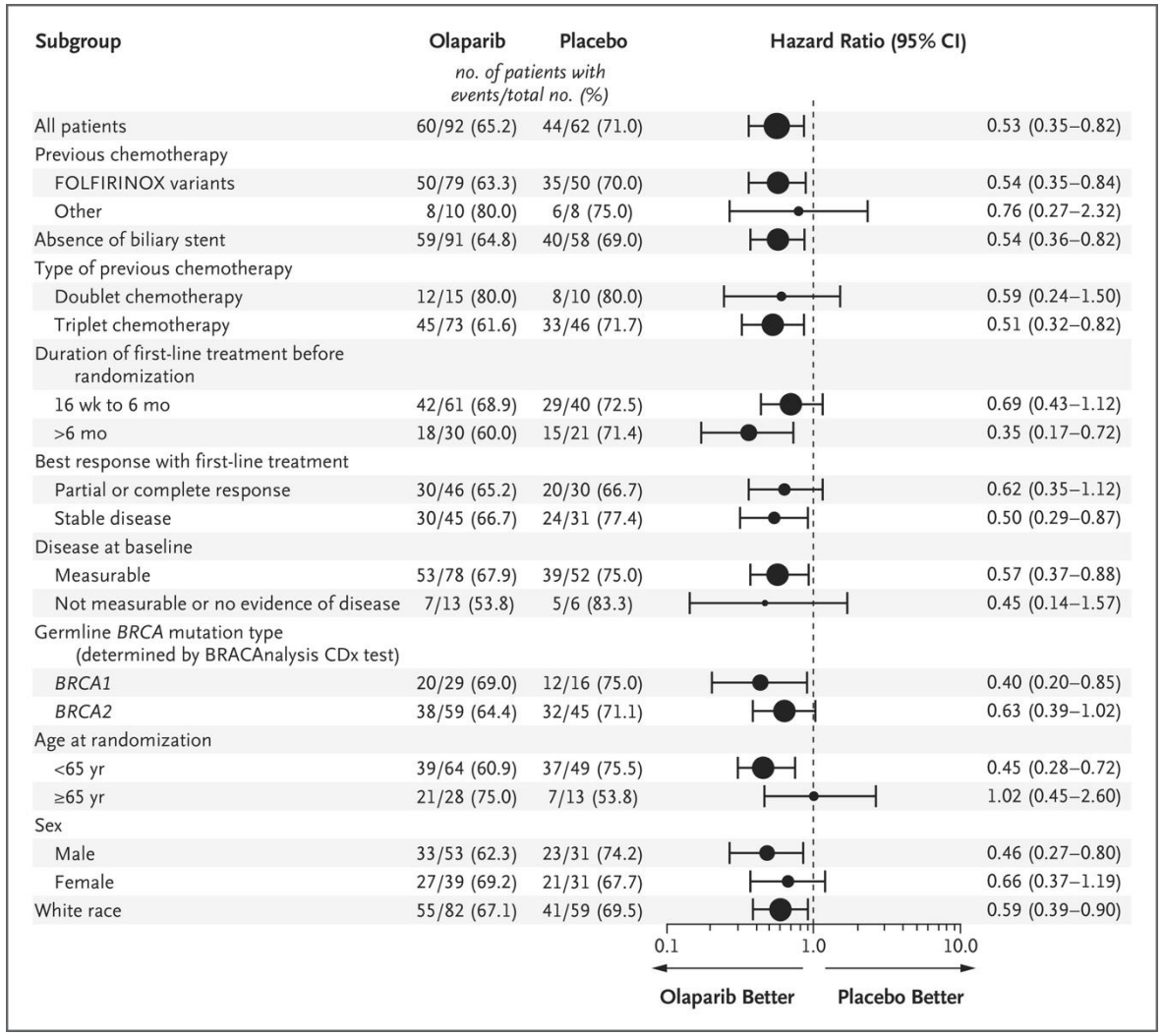
Kaplan–Meier Estimates of Progression-free Survival and Overall Survival.



Golan T et al. N Engl J Med2019;381:317-327

The NEW ENGLAND JOURNAL of MEDICINE

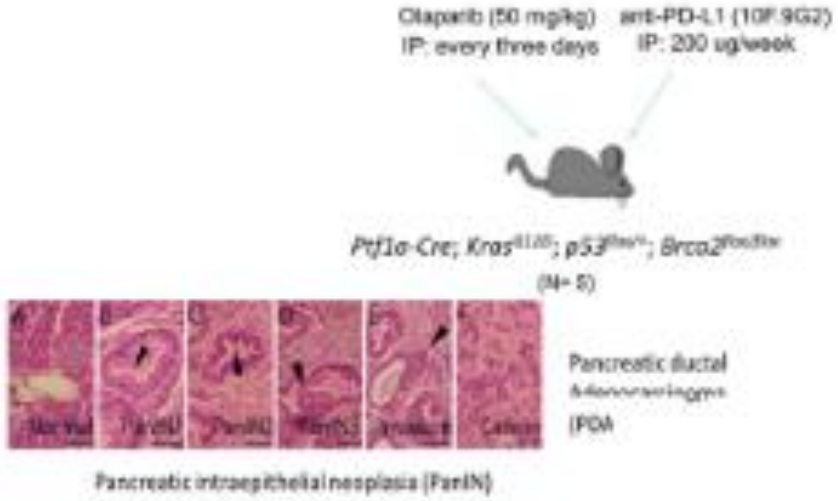
Subgroup Analysis of Progression-free Survival.



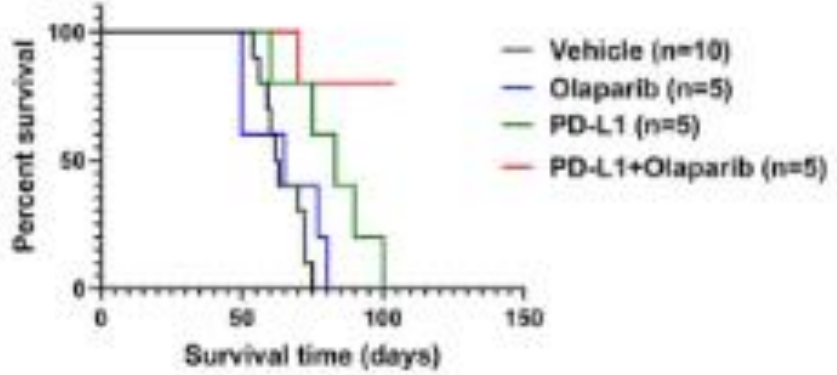
Golan T et al. N Engl J Med2019;381:317-327

The NEW ENGLAND JOURNAL of MEDICINE

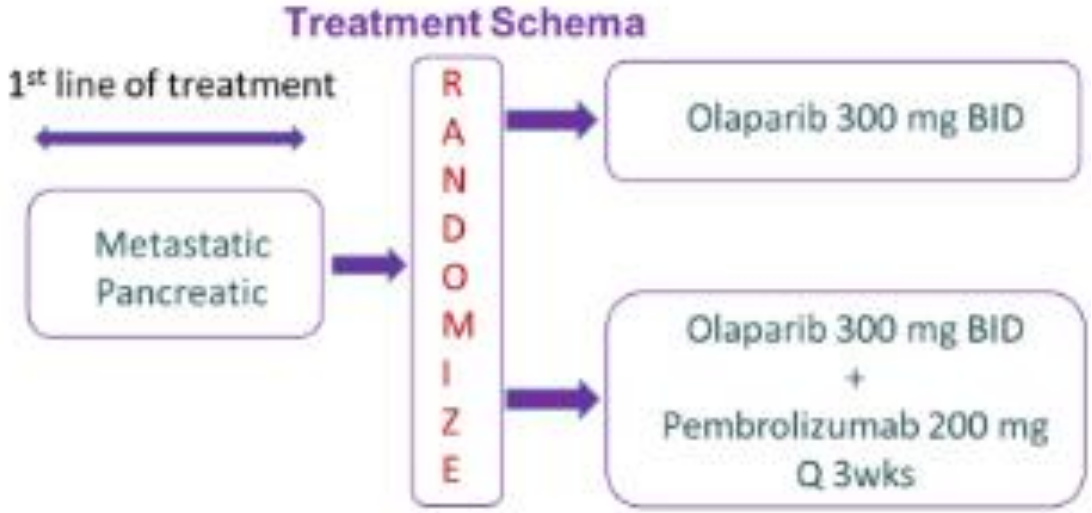
SWOG S2001



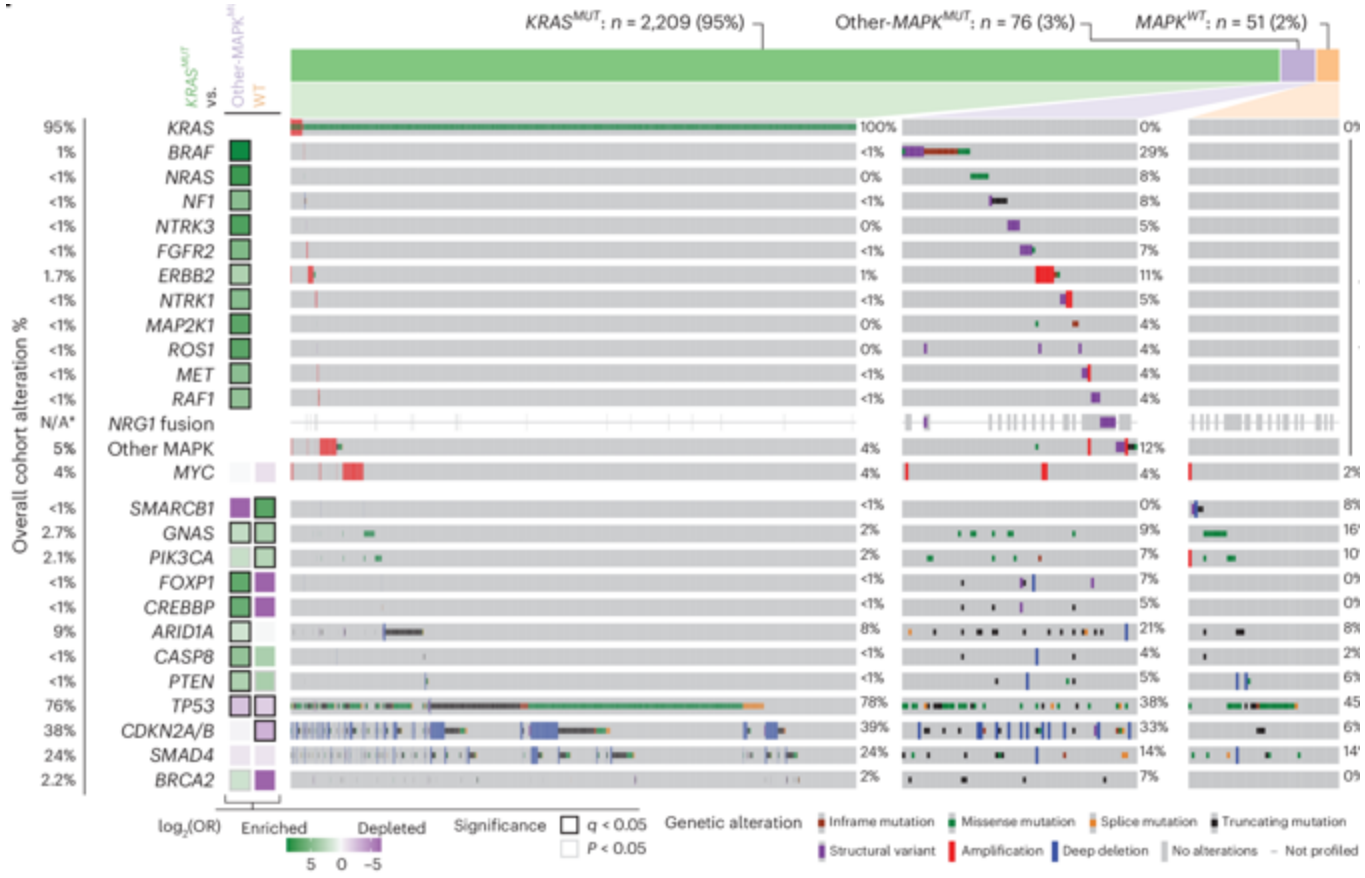
Development of pancreatic cancer in the GEMM

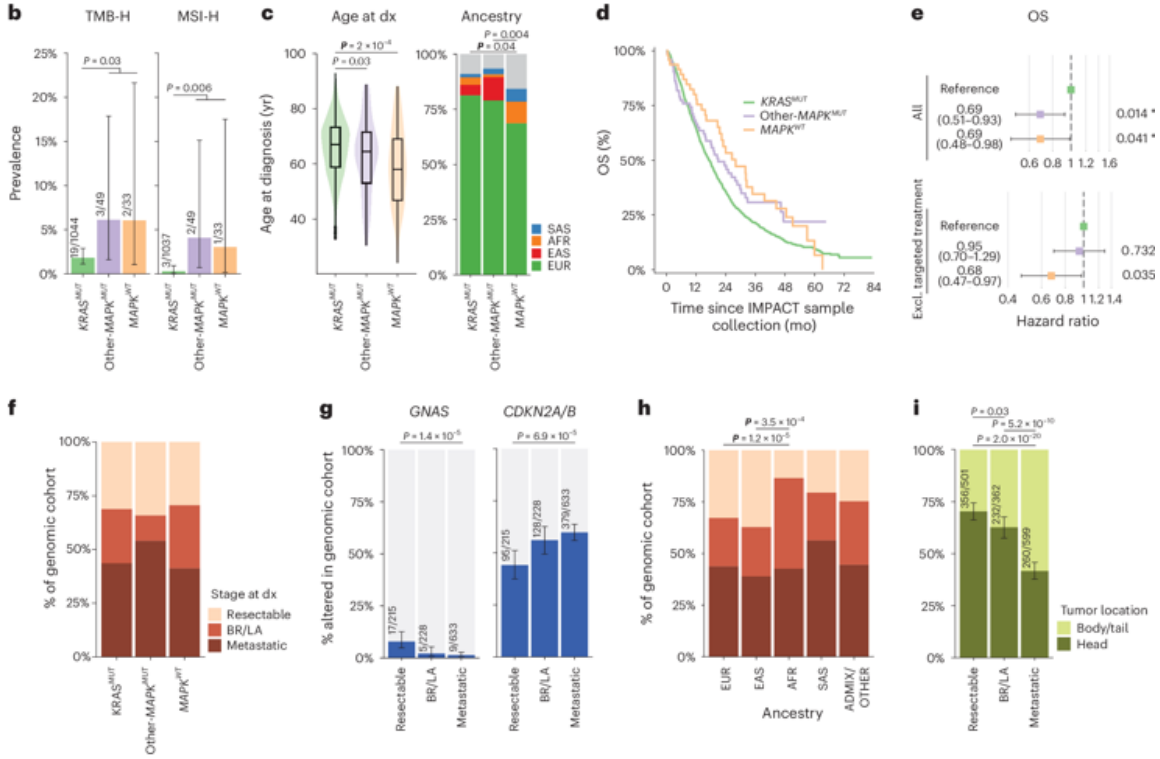


Combination therapy with olaparib and an anti PD-L1 mAb improved survival in mouse models



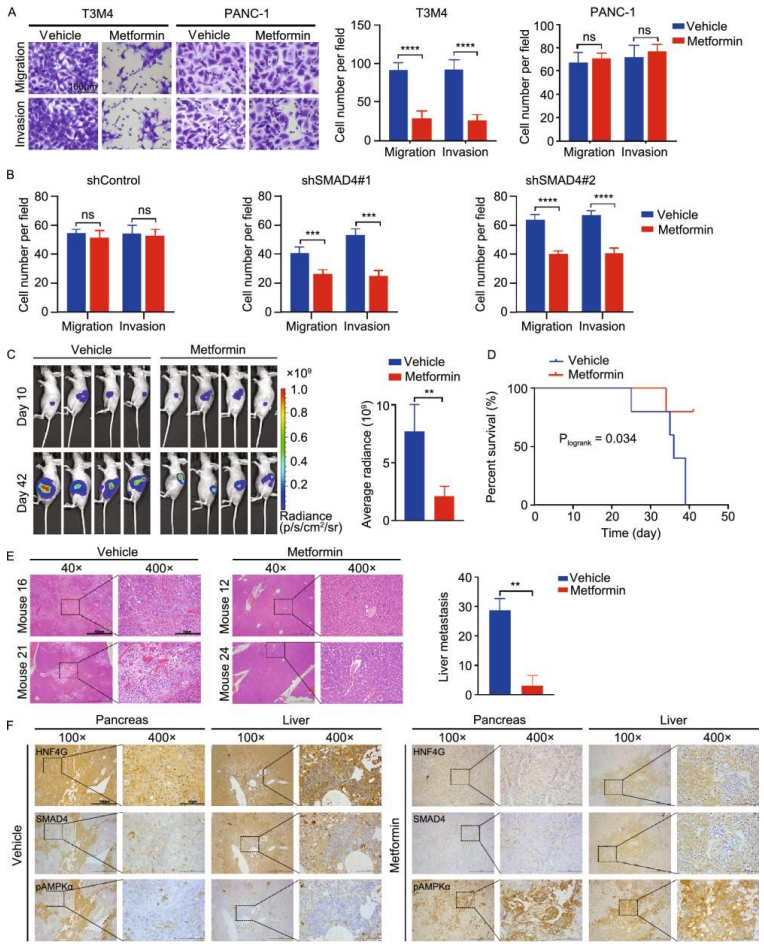
Somatic alteration landscape in PDAC.

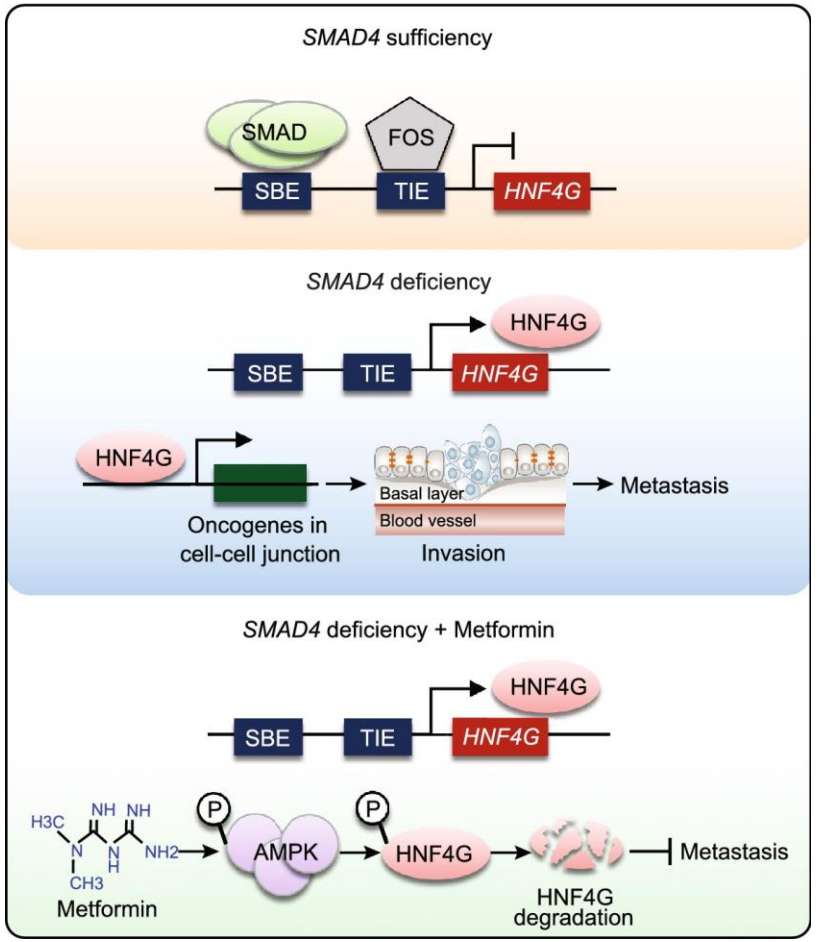




Cancer. 2020 Jun 23;126(17):3939–3949. doi: 10.1002/cncr.33038

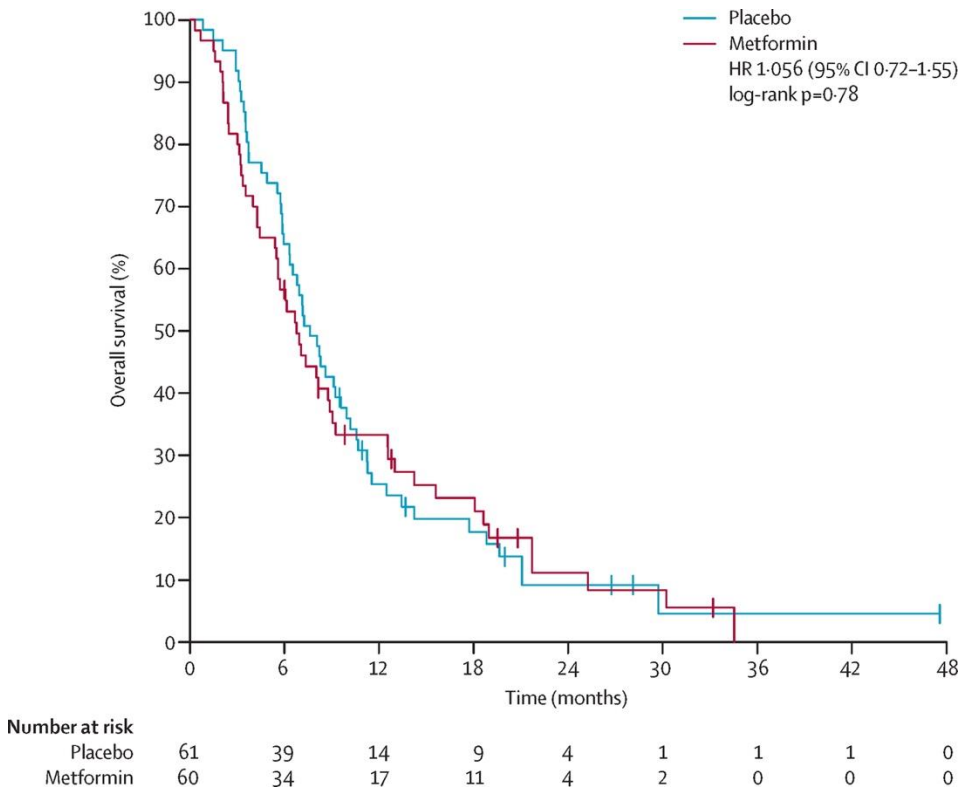
Metformin suppress HNF4G-induced PDAC metastasis depending on SMAD4 status.

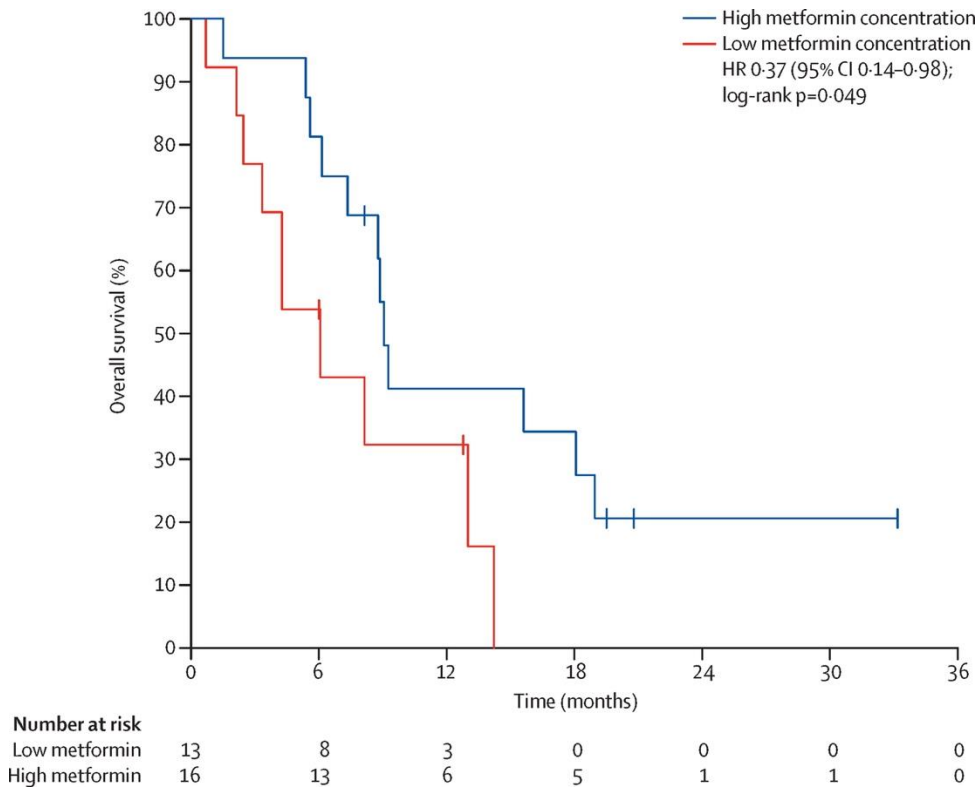




protein. cell., Volume 12, Issue 2, February 2021, Pages 128–144, https://doi.org/10.1007/s13238-020-00760-4

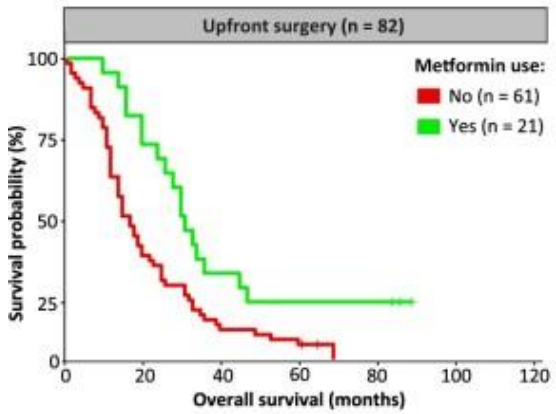
Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial

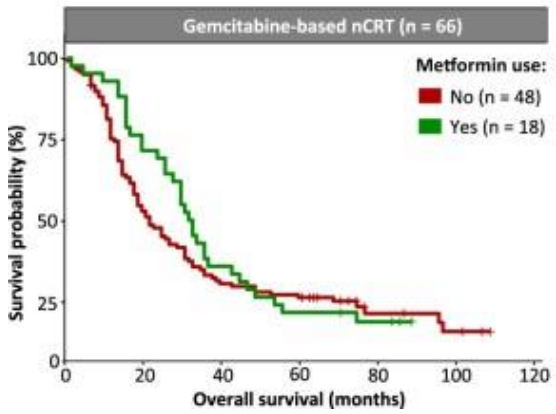




Kordes, Sil et al.The Lancet Oncology, Volume 16, Issue 7, 839 - 847

A Kaplan-Meier curves





B Cox regression models

Upfront surgery (n = 82)

Covariate	No. patients	Univariate hazard ratio (95% CI)	P.adj
Metformin			
No	61	Reference	
Yes	21	0.46 (0.26 to 0.79)	**0.010**
Resection classification (R)			
R1	47	Reference	
R0	35	0.45 (0.28 to 0.72)	**0.014**
Adjuvant gemcitabine cycles	82	0.84 (0.76 to 0.92)	**0.010**

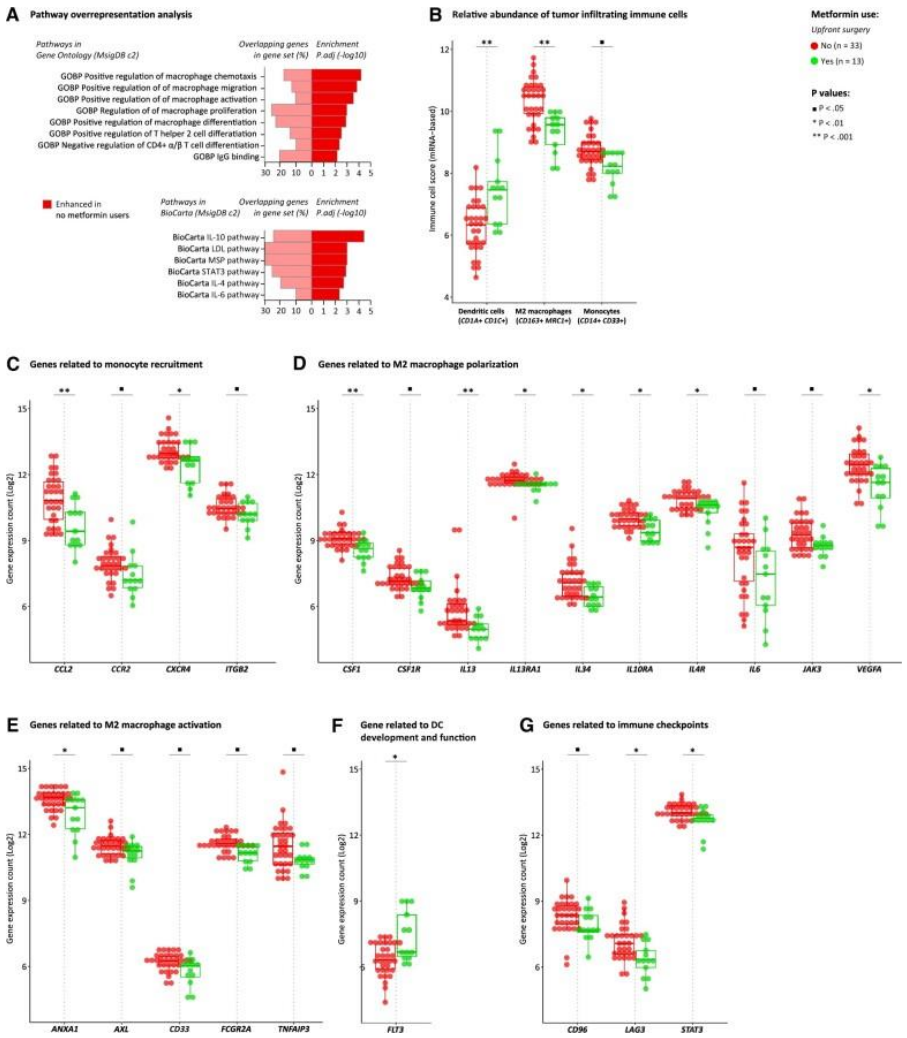
Covariate	No. patients	Multivariate hazard ratio (95% CI)	P.adj
Metformin			
No	61	Reference	
Yes	21	0.56 (0.32 to 0.99)	**0.047**
Resection classification (R)			
R1	47	Reference	
R0	35	0.47 (0.28 to 0.77)	**0.004**
Adjuvant gemcitabine cycles	82	0.83 (0.75 to 0.91)	**< 0.001**

0.5 1 2

Gemcitabine-based nCRT (n = 66)

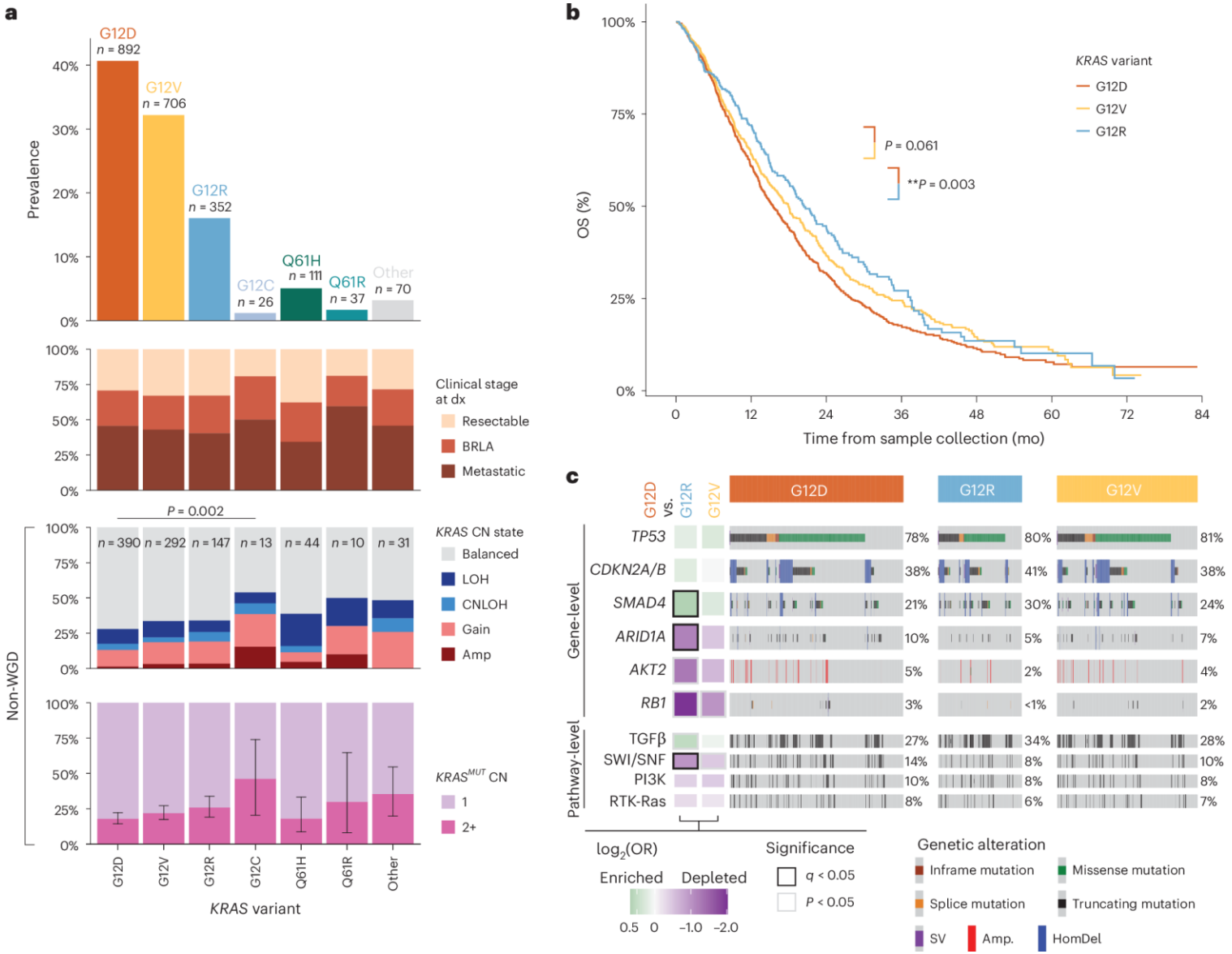
Covariate	No. patients	Univariate hazard ratio (95% CI)	P.adj
Metformin			
No	48	Reference	
Yes	18	1.67 (0.92 to 3.05)	0.53
Sex			
Male	35	Reference	
Female	31	0.44 (0.25 to 0.79)	**0.017**

0.5 1 2



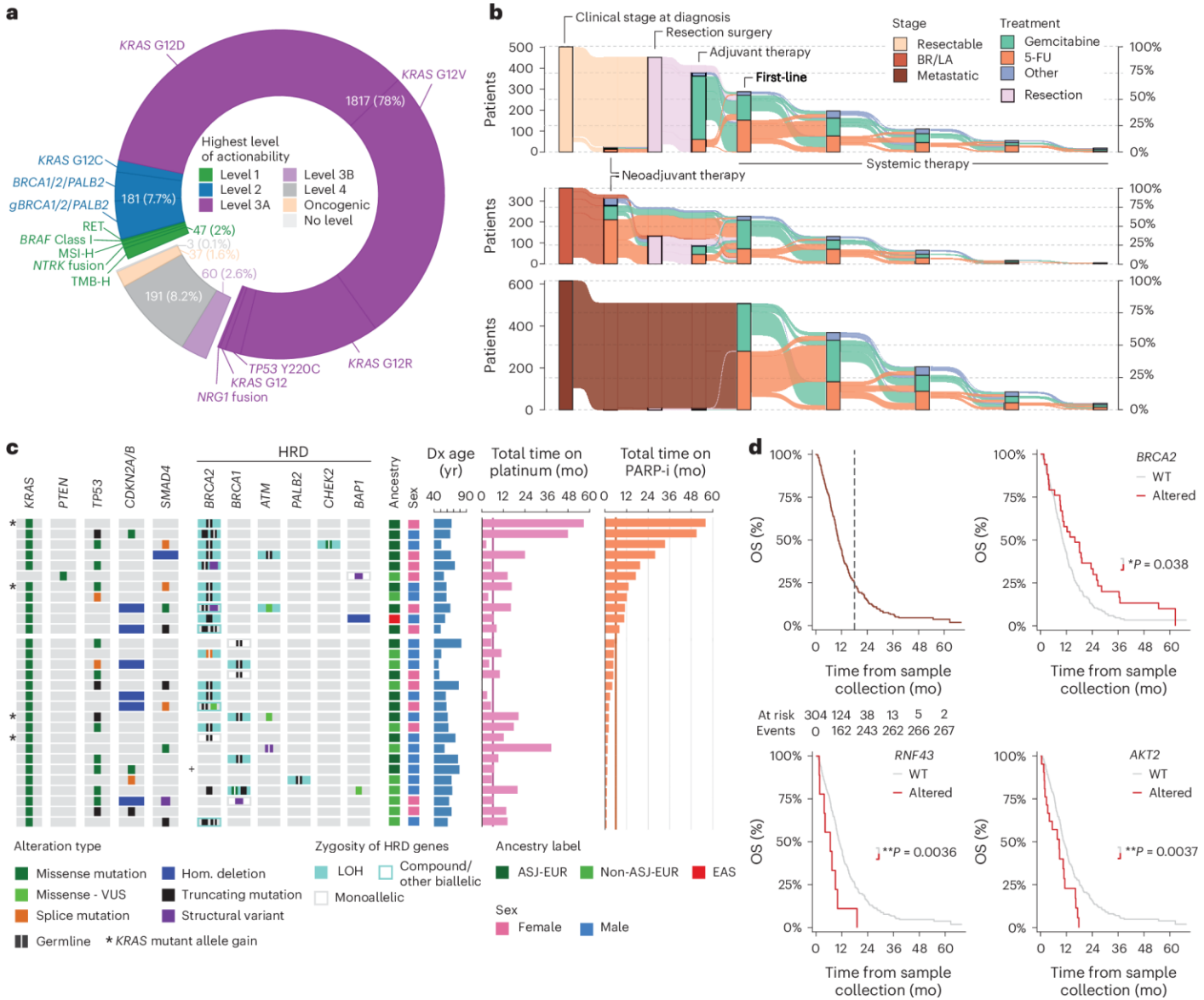
J Natl Cancer Inst. 2024 Mar 26;116(8):1374–1383. doi: 10.1093/jnci/djae070

Differential genomic and prognostic features of *KRAS* variants



Cancer. 2020 Jun 23;126(17):3939–3949. doi: 10.1002/cncr.33038

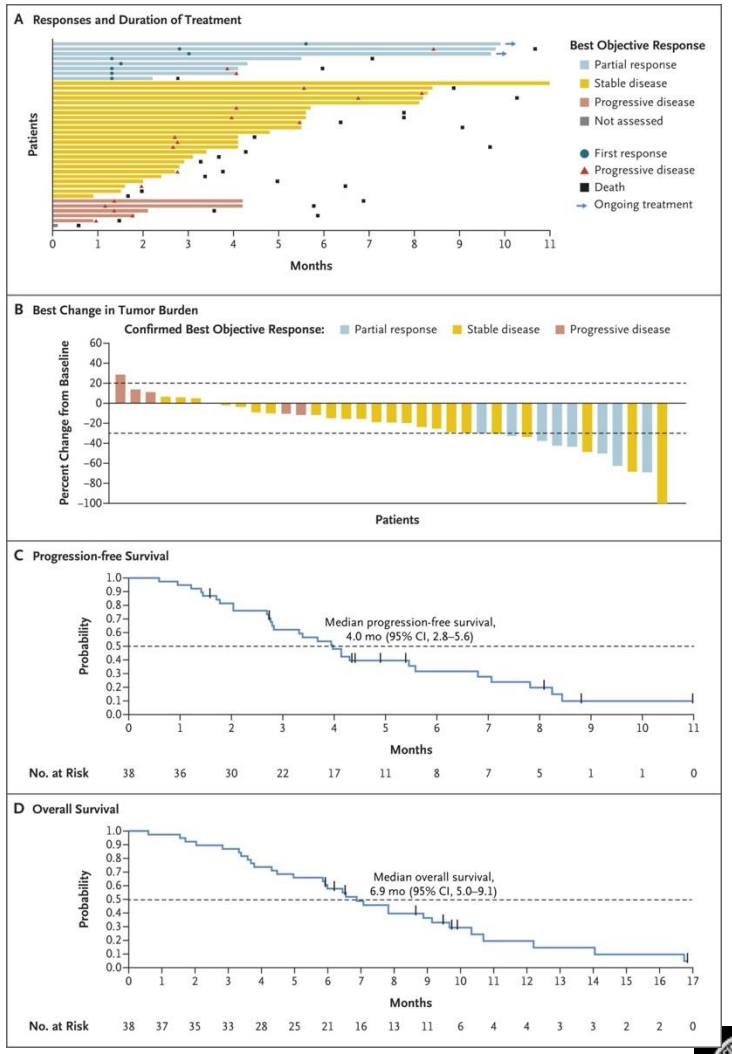
Clinically actionable alterations and treatment landscape.



Cancer. 2020 Jun 23;126(17):3939–3949. doi: 10.1002/cncr.33038

Sotorasib in *KRAS* p.G12C–Mutated Advanced Pancreatic Cancer

Efficacy Analyses of Sotorasib Therapy.



Strickler JH et al. N Engl J Med2023;388:33-43

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Efficacy of Sotorasib Therapy.

Table 2. Efficacy of Sotorasib Therapy.*

Variable	Phase 1 (N = 12)	Phase 2 (N = 26)	Combined Phase 1–2 (N = 38)
Best overall response — no. (%)†			
Confirmed complete response	0	0	0
Confirmed partial response	3 (25)	5 (19)	8 (21)
Stable disease	6 (50)	18 (69)	24 (63)
Progressive disease	2 (17)	3 (12)	5 (13)
Could not be evaluated	0	0	0
Not assessed	1 (8)	0	1 (3)
Percentage of patients with objective response (95% CI) — %	25 (6–57)	19 (7–39)	21 (10–37)
Percentage of patients with disease control (95% CI) — %‡	75 (43–95)	89 (70–98)	84 (69–94)
Median time to objective response (range) — mo§	1.4 (1.3–1.5)	2.8 (1.3–5.6)	1.5 (1.3–5.6)
Median duration of response (95% CI) — mo§¶	—	—	5.7 (1.6–NE)

* An objective response was defined as a complete or partial response. NE denotes could not be evaluated.
† The best overall response was determined by blinded independent central review.
‡ Disease control was defined as an objective response or stable disease.
§ The median time to objective response and the median duration of response were calculated for the patients who had a confirmed objective response.
¶ The median duration of response (Kaplan–Meier estimates) is not provided for individual phases because of the small number of patients.

Strickler JH et al. N Engl J Med2023;388:33-43

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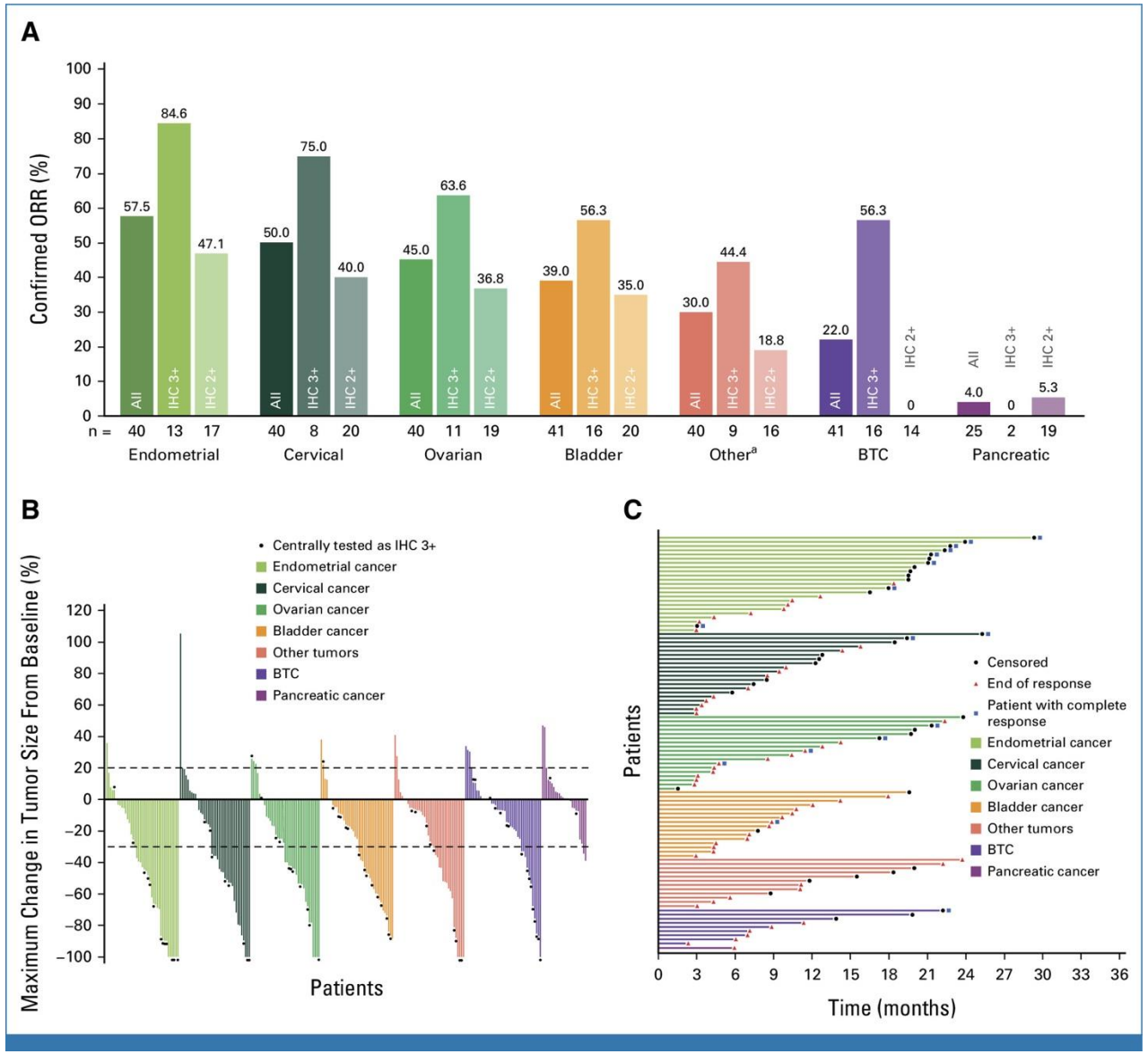
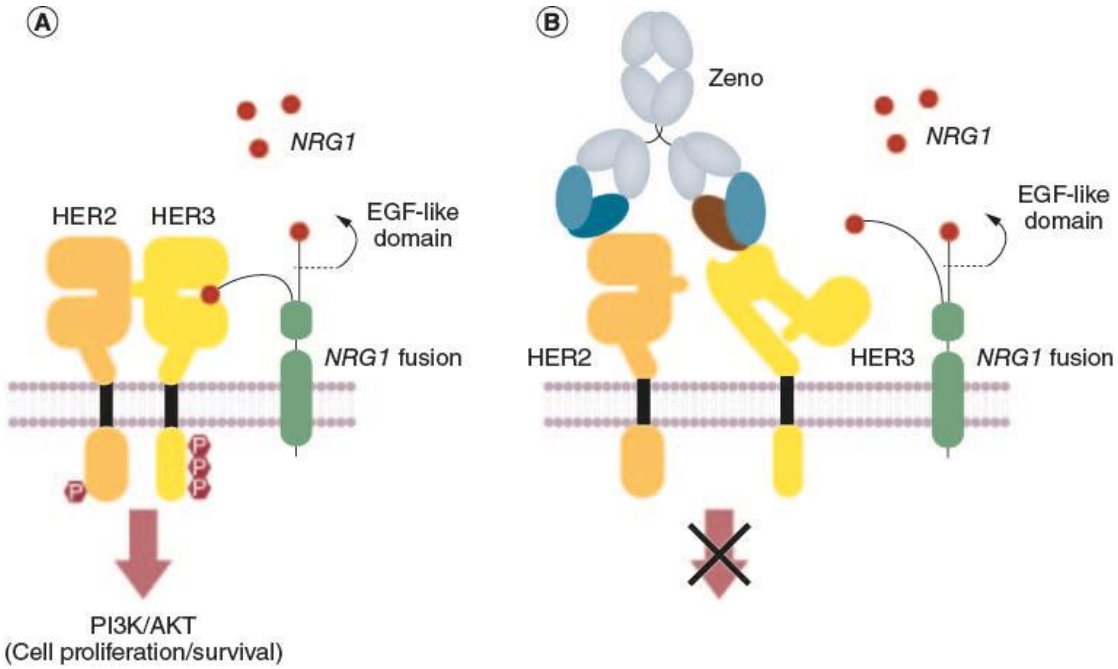
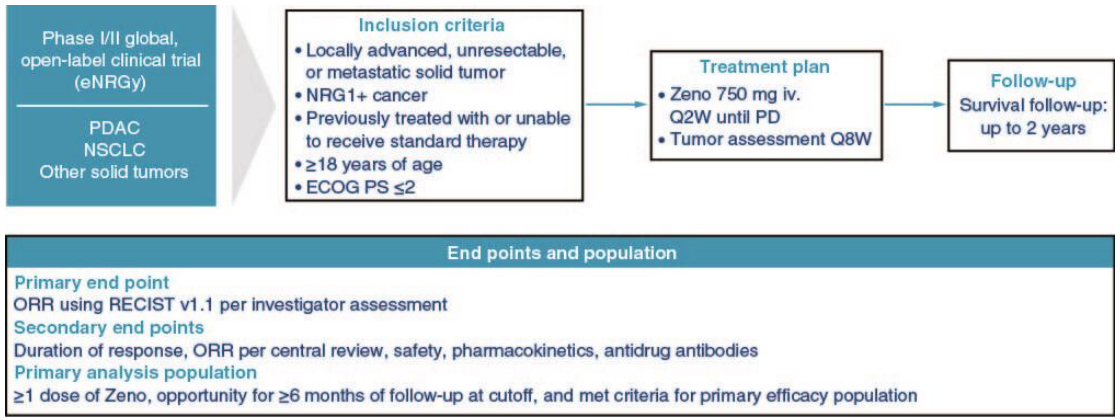

A
Confirmed ORR (%)
100
90
80
70
60
50
40
30
20
10
0
57.5
84.6
47.1
50.0
75.0
40.0
45.0
63.6
36.8
39.0
56.3
35.0
30.0
44.4
18.8
22.0
56.3
0
4.0
0
5.3
All
IHC 3+
IHC 2+
n = 40 13 17 40 8 20 40 11 19 41 16 20 40 9 16 41 16 14 25 2 19
Endometrial
Cervical
Ovarian
Bladder
Other[a]
BTC
Pancreatic
B
Maximum Change in Tumor Size From Baseline (%)
120
100
80
60
40
20
0
−20
−40
−60
−80
−100
Centrally tested as IHC 3+
Endometrial cancer
Cervical cancer
Ovarian cancer
Bladder cancer
Other tumors
BTC
Pancreatic cancer
Patients
C
Patients
Censored
End of response
Patient with complete response
Endometrial cancer
Cervical cancer
Ovarian cancer
Bladder cancer
Other tumors
BTC
Pancreatic cancer
0 3 6 9 12 15 18 21 24 27 30 33 36
Time (months)

Zenocutuzumab in patients with cancers harboring *NRG1* gene fusions

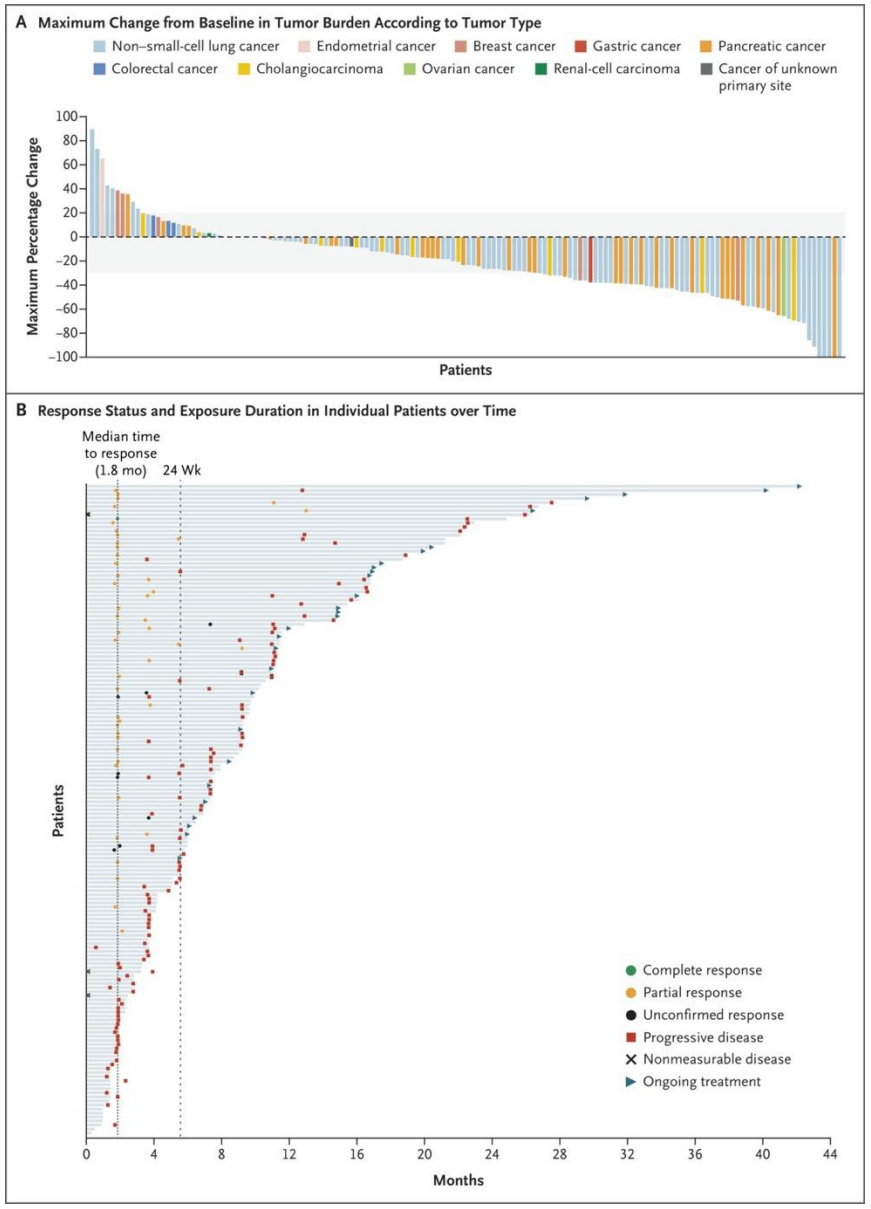




The eNRGy study demonstrated a 40% overall response rate in pancreatic adenocarcinoma, with a median duration of response of 3.7 to 16.6 months in PDAC.

Future Oncol. 2024;20(16):1057-1067. doi: 10.2217/fon-2023-0824. Epub 2024 Feb 13.

Efficacy of Zenocutuzumab in NRG1 Fusion–Positive Cancer.



Schram AM et al. N Engl J Med2025;392:566-576

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Efficacy of Zenocutuzumab in NRG1 Fusion–Positive Cancer across Multiple Tumor Types.

Table 2. Efficacy of Zenocutuzumab in *NRG1* Fusion–Positive Cancer across Multiple Tumor Types.*

Tumor Type	Investigator Assessment			Blinded Independent Central Review		
	Overall Response†		Median Duration of Response (Range)‡	Overall Response†		Median Duration of Response (Range)‡
	no./total no.	*% (95% CI)*	*mo*	*no./total no.*	*% (95% CI)*	*mo*
All *NRG1* fusion–positive tumor types§	47/158	30 (23 to 37)	11.1 (1.7+ to 29.5+)	50/160	31 (24 to 39)	11.5 (1.9+ to 29.5+)
Non–small-cell lung cancer	27/93	29 (20 to 39)	12.7 (1.8+ to 29.5+)	29/94	31 (22 to 41)	13.4 (1.9+ to 29.5+)
Pancreatic cancer	15/36	42 (25 to 59)	7.4 (2.1+ to 20.7)	16/36	44 (28 to 62)	9.1 (1.9+ to 16.6)
Cholangiocarcinoma	2/10	20 (2 to 56)	9.2 (7.4 to 11.1)	2/10	20 (2 to 56)	8.3 (3.7 to 12.9)
Breast cancer	1/7¶	14‖	1.7+	0/8	0	NA
Colorectal cancer	0/6	0	NA	1/6¶	17‖	11.7
Cancer of unknown primary site	0/2	0	NA	0/2	0	NA
Endometrial cancer	0/1	0	NA	0/1	0	NA
Gastric cancer	1/1¶	100‖	1.9+	1/1¶	100‖	1.9+
Ovarian cancer	1/1¶	100‖	12.8	1/1¶	100‖	12.8+
Renal-cell carcinoma	0/1	0	NA	0/1	0	NA

* NA denotes not applicable.
† For investigator assessment, percentages were based on the number of patients with measurable disease at baseline according to the investigator. For blinded independent central review, percentages were based on the number of patients with measurable disease at baseline according to either the investigator or blinded independent central review (i.e., patients were excluded if they had nonmeasurable disease according to both the investigator and blinded independent central review). Analyses were based on confirmed objective responses according to the Response Evaluation Criteria in Solid Tumors, version 1.1. For tumor types with eight or fewer patients, only confirmed objective responses and corresponding duration of response are reported. Table S5 provides details on confirmed objective responses in patients with non–small-cell lung cancer and pancreatic cancer.
‡ Analyses of duration of response were performed in patients with a confirmed objective response. The plus sign (+) indicates that data were censored at the time of the data-cutoff date.
§ One complete response was confirmed by investigator assessment, and three complete responses were observed by blinded independent central review.
¶ The one response was a partial response.
‖ Confidence intervals are not provided because of the small sample size.

Schram AM et al. N Engl J Med2025;392:566-576

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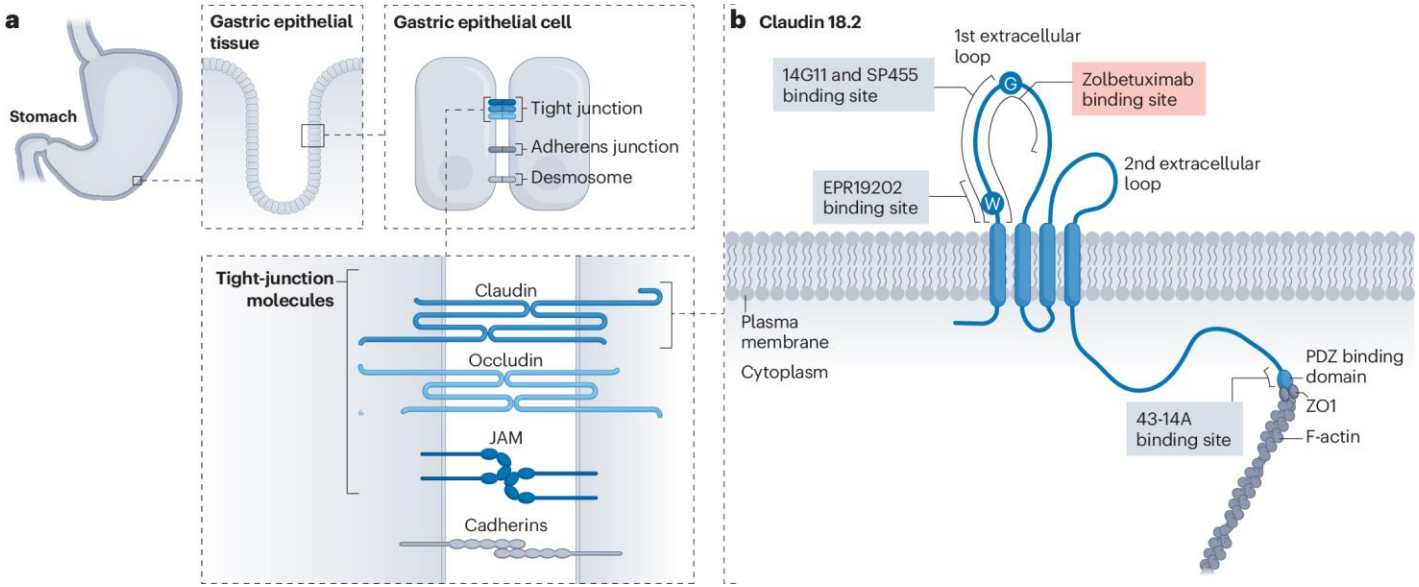
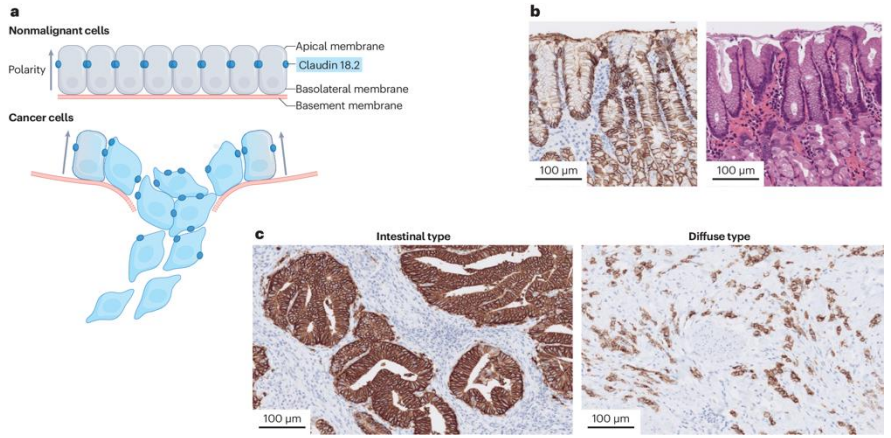
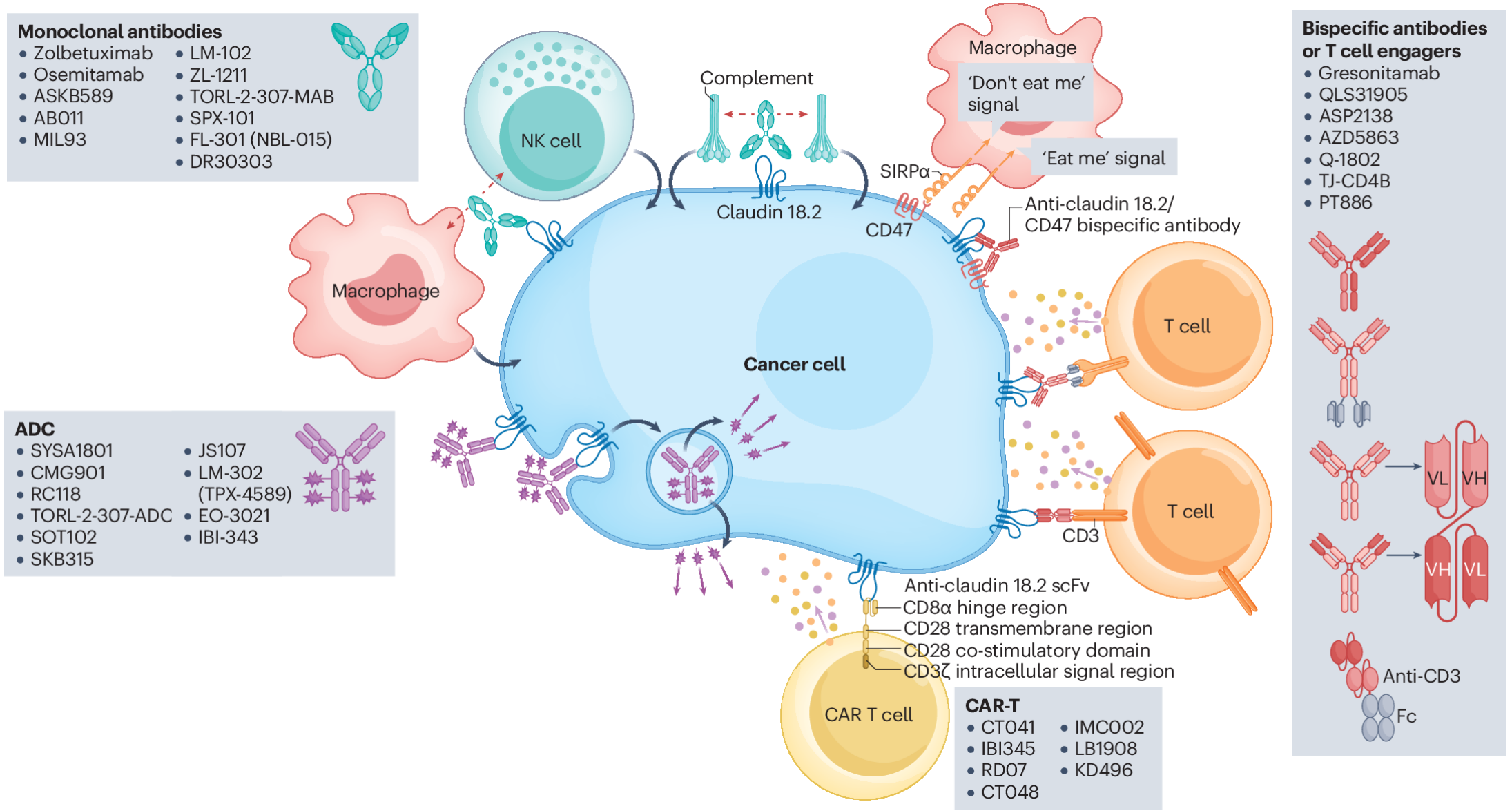




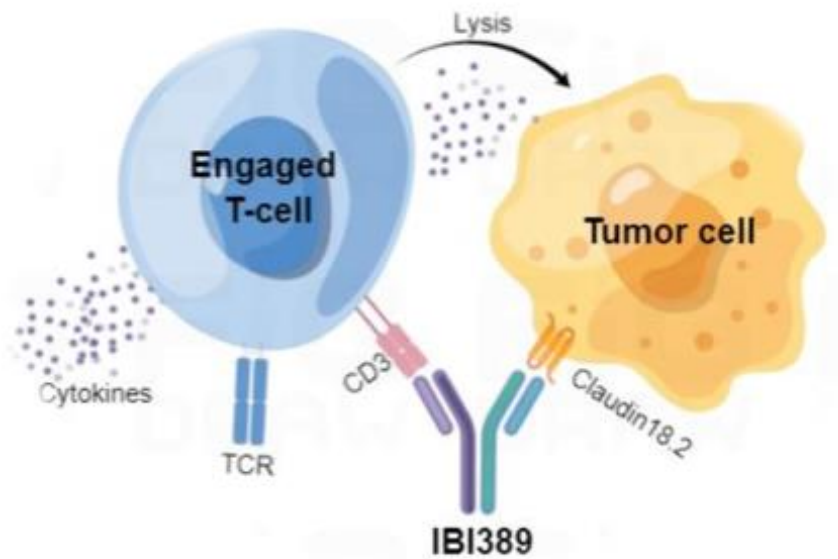
Nature Reviews Clinical Oncology **volume 21**, pages354–369 (2024)



Nature Reviews Clinical Oncology **volume 21**, pages354–369 (2024)

IBI389: an anti-CLDN18.2/CD3 bispecific antibody

- CLDN18.2, a prominent constituent within the tight junction molecule family, typically exhibits robust expression levels within the gastric mucosa. However, the onset of malignancy instigates the breakdown of tight junctions, thereby unveiling CLDN18.2 epitopes on the surface of tumor cells.
- In pancreatic ductal adenocarcinoma (PDAC), approximately 60% of patients showcase positive CLDN18.2 expression, thereby positioning it as a promising frontier for innovative anti-cancer interventions.

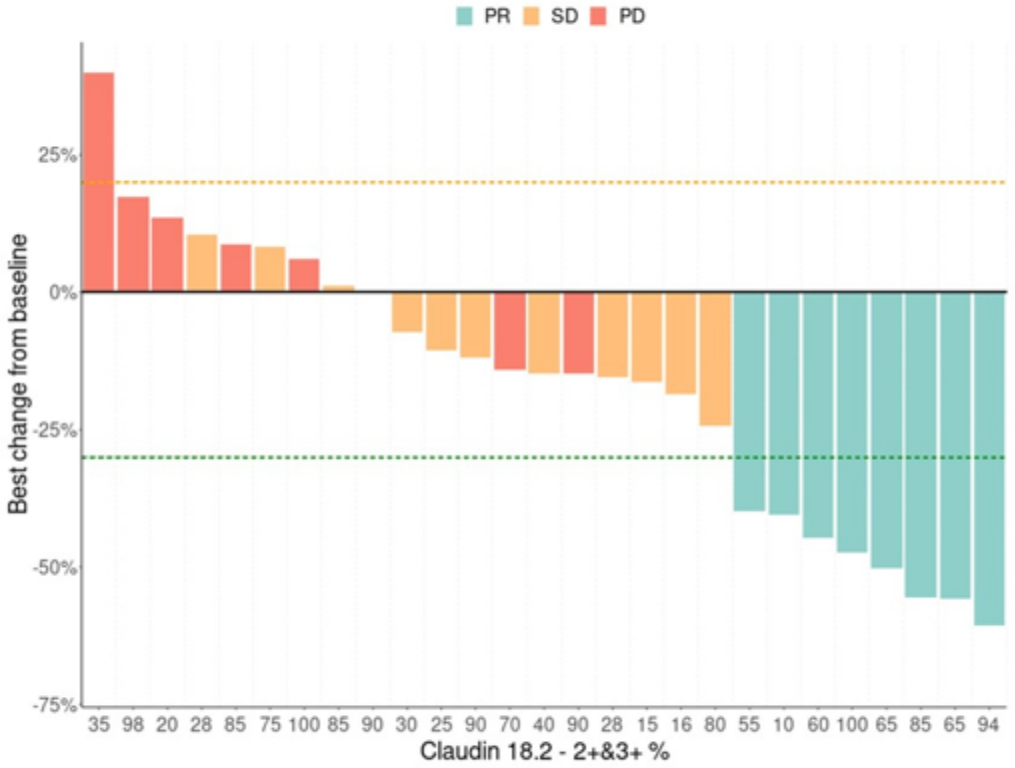


IBI389 induces immune synapse formations by linking CD3 molecules in T-cell receptor complexes and CLDN18.2 antigens on tumor cell membranes.

Yu, et al. ASCO 2024

Response of IBI389 at 600 μg/kg in PDAC

Response assessed by investigators	CLDN18.2 $^{2/3+}$ ≥10%* (^N=27)	CLDN18.2 $^{2/3+}$ ≥40%* (^N=18)
Best overall response, n (%)		
CR	0	0
PR	8 (29.6)	7 (38.9)
SD	11 (40.7)	5 (27.8)
PD	8 (29.6)	6 (33.3)
ORR, % (95% CI)	29.6% (13.8-50.2)	38.9% (17.3-64.3)
cORR, % (95% CI)	25.9% (11.1-46.3)	38.9% (17.3-64.3)
DCR, % (95% CI)	70.4% (49.8-86.2)	66.7% (41-86.7)



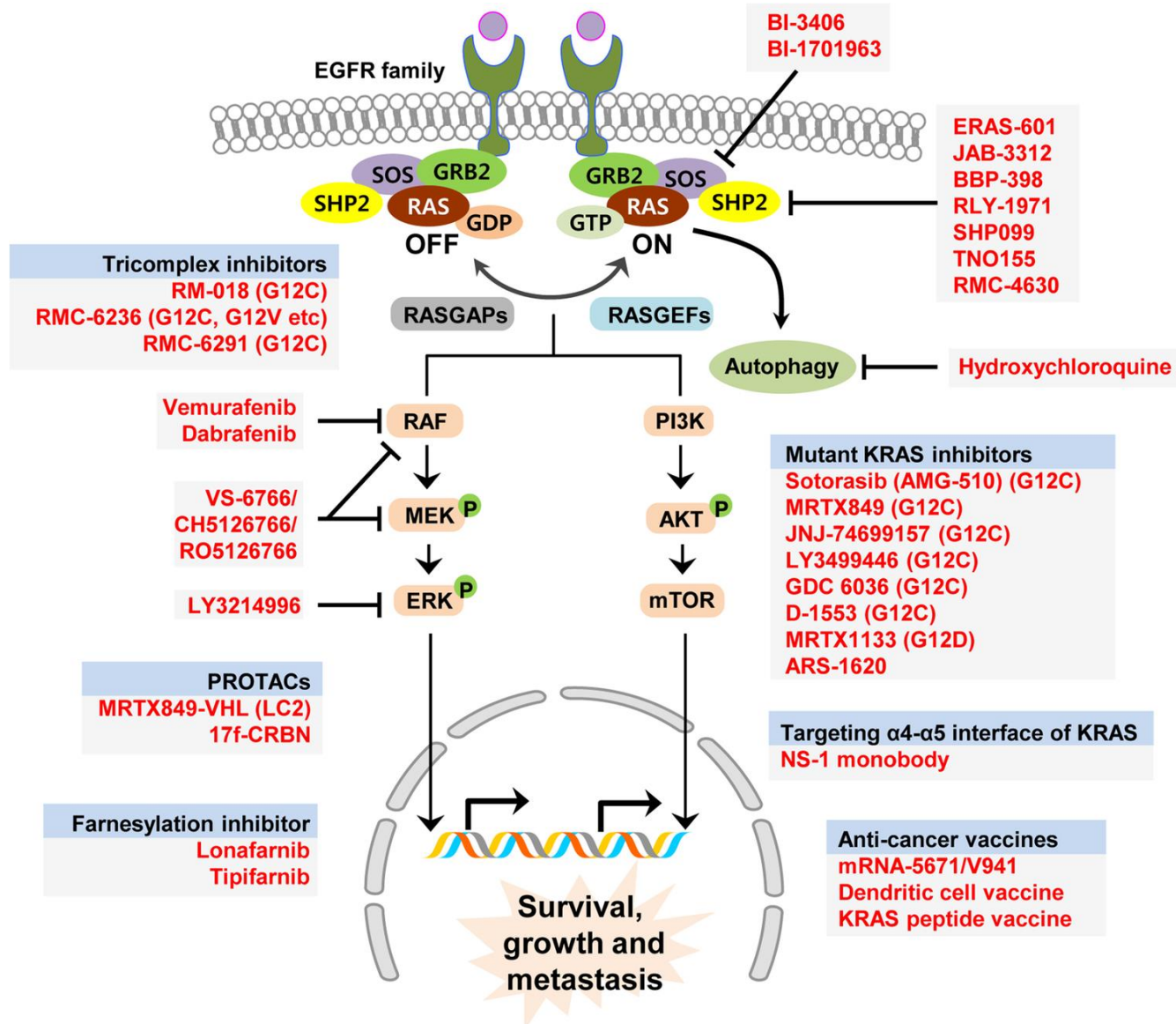
^Patients with at least one post baseline tumor assessment.

* CLDN18.2 $^{2/3+}$: means the proportion of tumor cells demonstrating moderate-to-strong CLDN18 membranous staining.

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: objective response rate; cORR confirmed objective response rate; DCR: disease control rate.

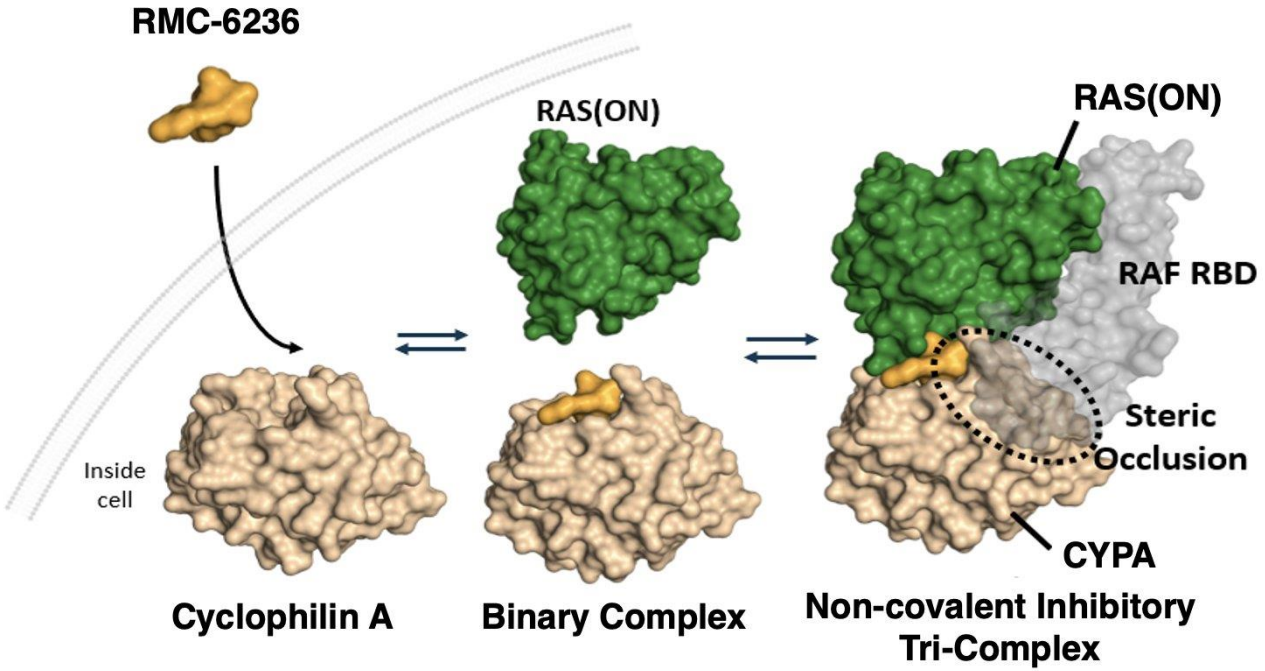
Data cutoff: May 1, 2024

Yu, et al. ASCO 2024


EGFR family
BI-3406
BI-1701963
ERAS-601
JAB-3312
BBP-398
RLY-1971
SHP099
TNO155
RMC-4630
SOS
GRB2
SHP2
RAS
GDP
OFF
GTP
ON
Tricomplex inhibitors
RM-018 (G12C)
RMC-6236 (G12C, G12V etc)
RMC-6291 (G12C)
RASGAPs
RASGEFs
Autophagy
Hydroxychloroquine
Vemurafenib
Dabrafenib
RAF
PI3K
VS-6766/
CH5126766/
RO5126766
MEK
P
AKT
Mutant KRAS inhibitors
Sotorasib (AMG-510) (G12C)
MRTX849 (G12C)
JNJ-74699157 (G12C)
LY3499446 (G12C)
GDC 6036 (G12C)
D-1553 (G12C)
MRTX1133 (G12D)
ARS-1620
LY3214996
ERK
mTOR
PROTACs
MRTX849-VHL (LC2)
17f-CRBN
Targeting α4-α5 interface of KRAS
NS-1 monobody
Farnesylation inhibitor
Lonafarnib
Tipifarnib
Anti-cancer vaccines
mRNA-5671/V941
Dendritic cell vaccine
KRAS peptide vaccine
Survival,
growth and
metastasis

RMC-6236 Is a First-in-Class, RAS^{MULTI}(ON) Inhibitor

- RMC-6236 is a novel, oral, non-covalent, RAS^{MULTI}(ON) inhibitor selective for the active, GTP-bound or ON state of both mutant and wild-type variants of the canonical RAS isoforms
- Preclinical studies have demonstrated deep and sustained regressions across multiple RAS^{MUT} tumor types, particularly those harboring KRAS^{G12X} mutations



KRAS^{G12X} defined as mutation at codon 12, which encodes glycine (G), to X where X = A, D, R, S, or V.
CYPA, cyclophilin A; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma virus; Mut, mutated; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RBD, RAS-binding domain.

Case Report: Patient with KRAS^{G12D} PDAC

Demographics and Baseline Characteristics

- 76-year-old man
- Diagnosed with Stage II PDAC in November 2017
- Metastatic disease to lung in January 2022

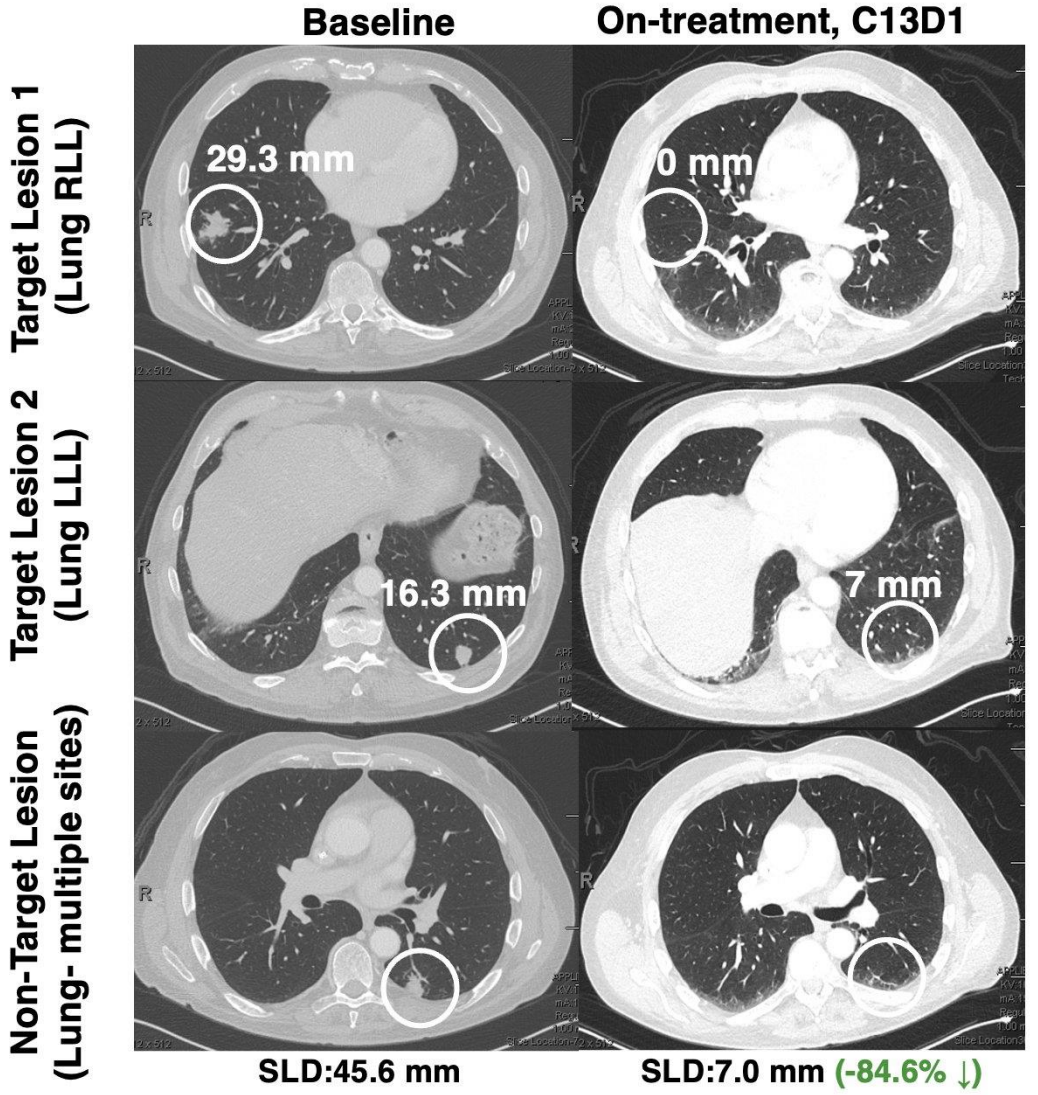
Treatment History

- **Prior surgery:** distal pancreatectomy (March 2018)
- **Prior therapies:**
  - Gemcitabine/nab-paclitaxel (neoadjuvant)
    - Nov 2017–Feb 2018
  - Gemcitabine/capecitabine (adjuvant)
    - Apr 2018–Jun 2018
  - Gemcitabine/nab-paclitaxel/investigational agent
    - Mar 2022–Oct 2022
    - Best response SD with PD Aug 2022

RMC-6236 Treatment Course

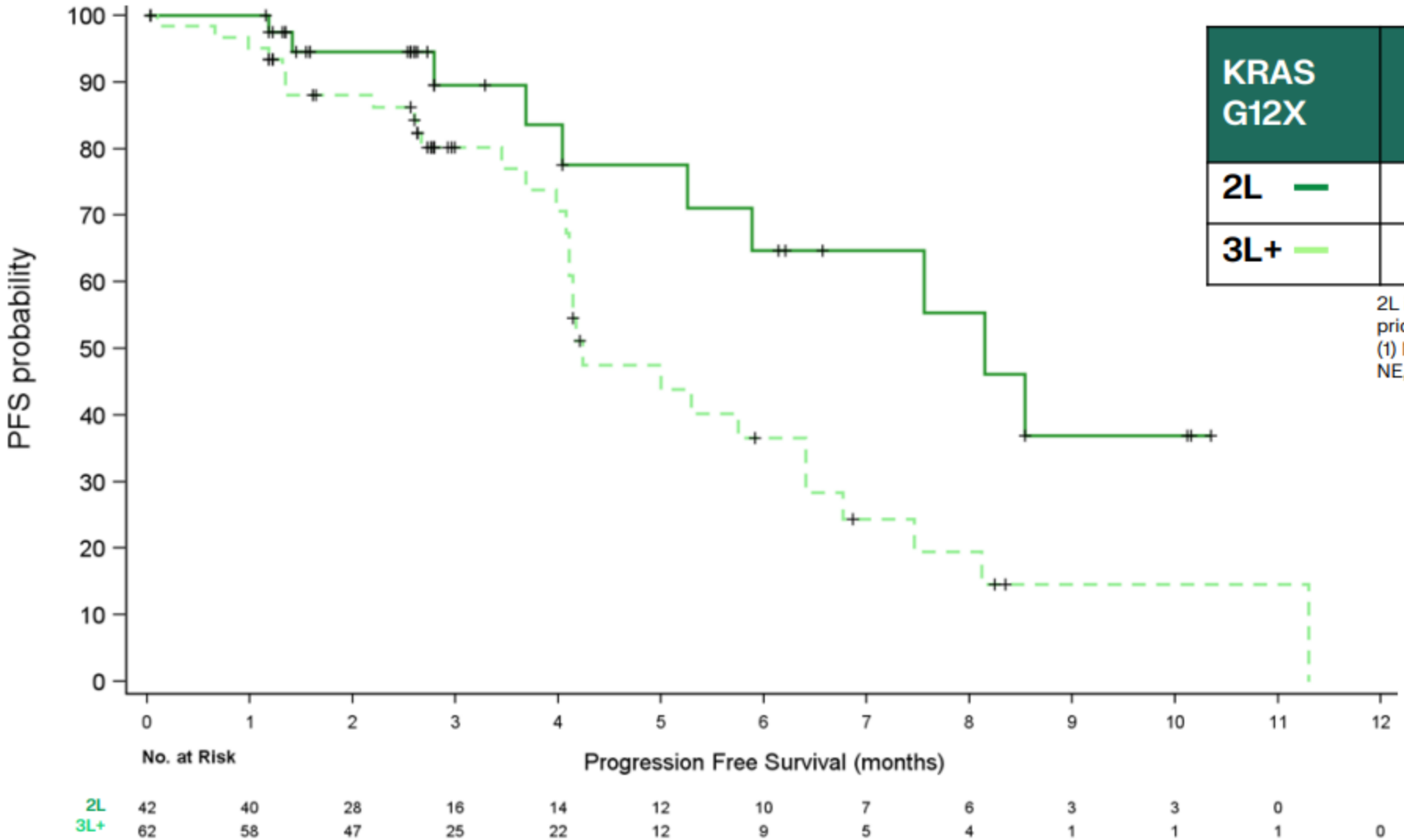
- Started at 80 mg QD
- Baseline ctDNA not detectable
- Confirmed PR at C5; ongoing
- Treatment ongoing for >10 months

LLL, left lower lobe; RLL, right lower lobe.



Data Extracted 11 Sep 2023.

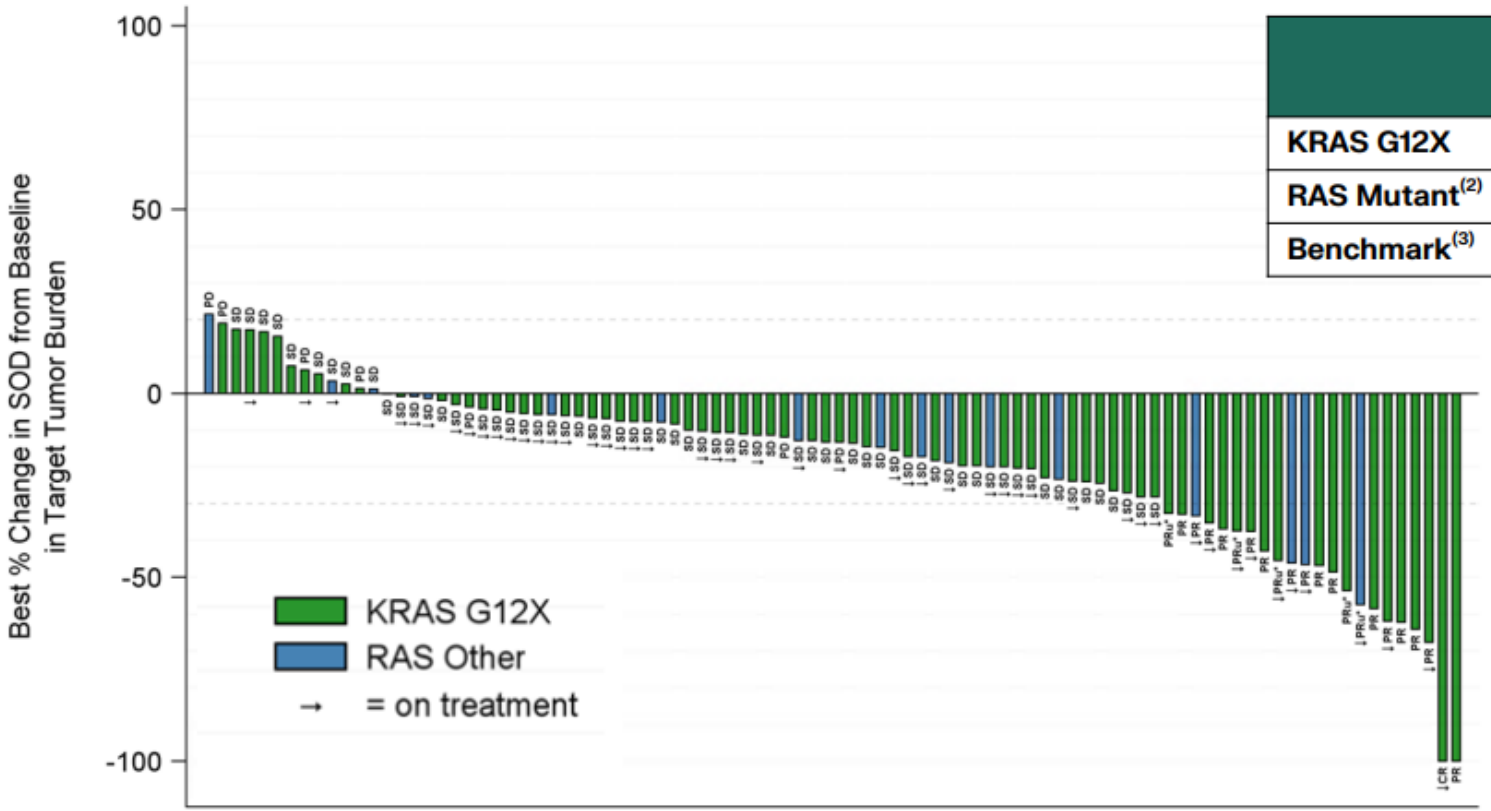
Observed PFS in 2L vs. 3L+ Metastatic PDAC on RMC-6236 (160-300 mg)



KRAS G12X	Median PFS Months (95% CI)	Benchmark Median PFS(1) Months
2L	8.1 (5.9-NE)	2.0-3.5
3L+	4.2 (4.1-6.4)	1.9

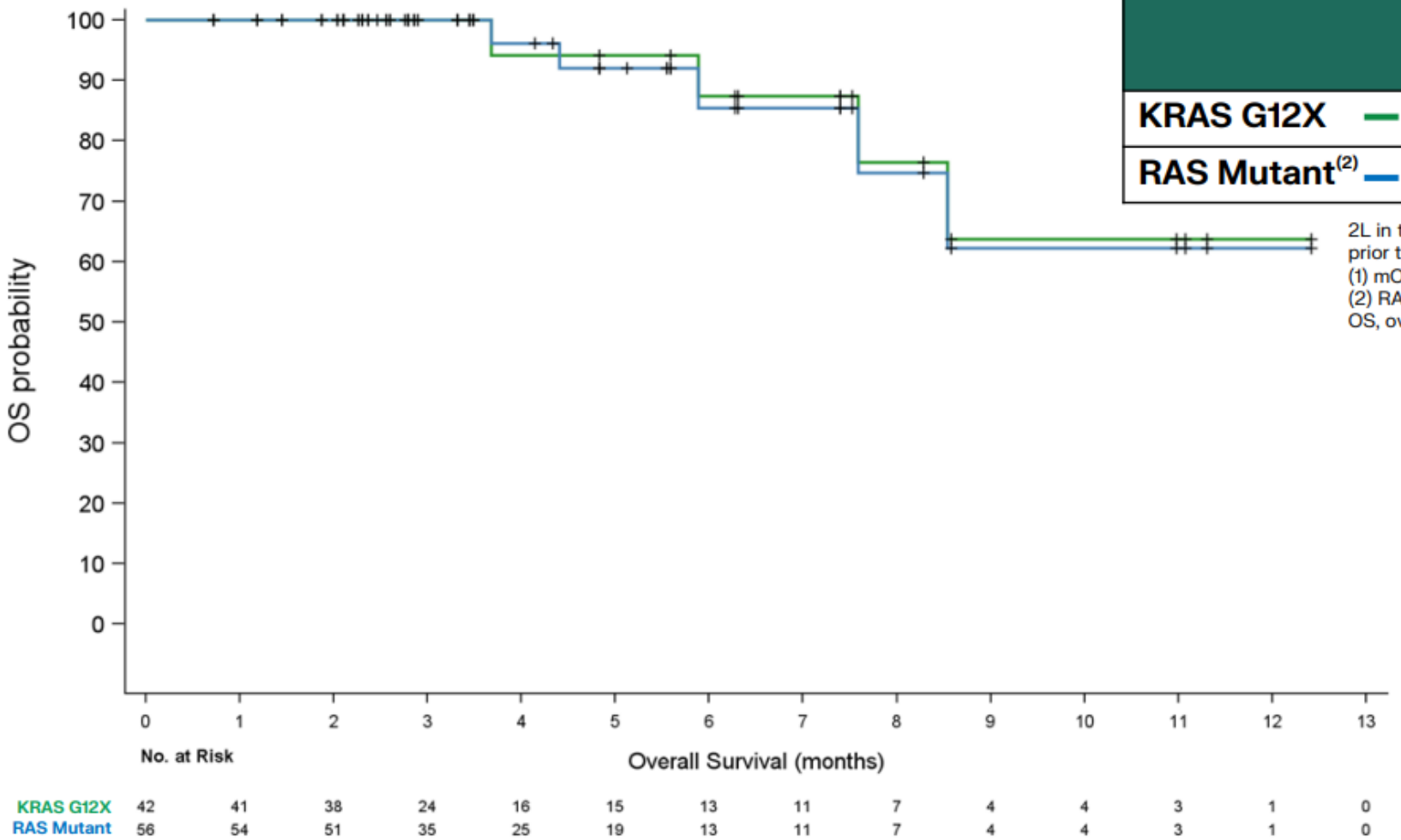
2L in the metastatic setting includes patients who progressed on prior therapy in an earlier setting within 6 months of last dose
(1) Median PFS benchmark from published reports (see slide 7)
NE, not estimable

Best Percentage Change in Tumor Size from Baseline and Objective Response Rate in 2L+ PDAC (RMC-6236 160-300 mg)



	ORR 14+ week[1]	ORR 20+ week[1]	DCR 14+ week[1]
KRAS G12X	20% (16/79)	27% (13/48)	87% (69/79)
RAS Mutant[2]	21% (20/97)	26% (16/61)	88% (85/97)
Benchmark[3]	9%		NA

Interim Observed OS in 2L Metastatic PDAC on RMC-6236 (160-300 mg)



	Median OS Months (95% CI)	Benchmark Median OS[1] Months
KRAS G12X	NE (8.5, NE)	6.1-6.9
RAS Mutant[2]	NE (8.5, NE)	

2L in the metastatic setting includes patients who progressed on prior therapy in an earlier setting within 6 months of last dose
(1) mOS benchmark from published reports (see slide 7)
(2) RAS Mutant defined as patients with G12X, G13X or Q61X PDAC
OS, overall survival; NE, not estimable

Give me six hours to cut down a tree and I'll spend the first four sharpening the axe.

Abraham Lincoln