2025 John Hopkins Updates in Gastrointestinal Cancers

RAS Targeting in Pancreas Cancer

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Memorial Sloan Kettering Cancer Center

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Disclosures: O’Reilly

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Consulting/Data & Safety Monitoring Boards/Steering Committees

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Family: Agios, Genentech-Roche, Eisai, Servier, Abbvie

Off Label/Investigational Use

Sotorasib, adagrasib, RMC-6236, MRTX-1133, olomarasib, glecirasib, ELI-002 2P/7P, ASP-3082, RMC-9085

Agenda

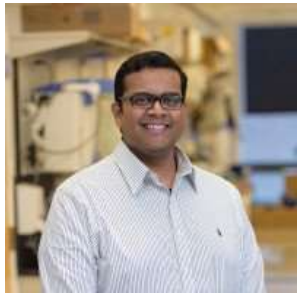
KRAS descriptors and therapeutics

KRAS-directed immunotherapy

MSK PDAC Cohort Descriptors (N= 2,336)





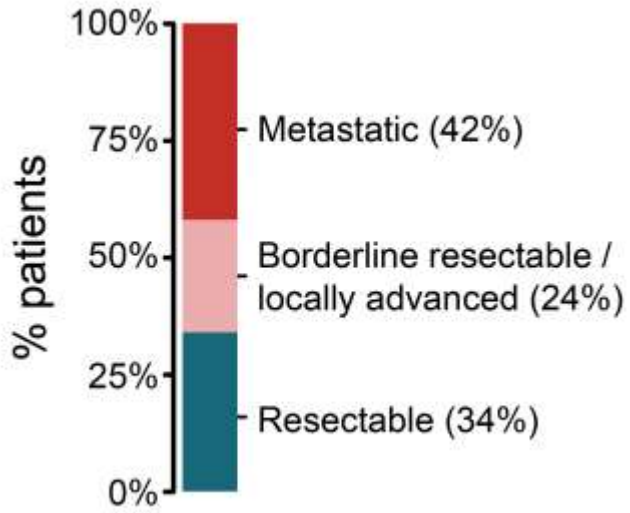
- Integrate histopathologic, somatic, germline features of PDAC with clinical factors, treatment history, response, outcome
- Eligible: Pancreas cancer, consented #12-245; cohort 2014-2021
- Prospectively sequenced MSK IMPACT
  Substitutions, insertions, deletions, copy # amplifications, homozygous deletions, fusions

Perry, M, Varghese, A…..Bandalamudi, C, O'Reilly, EM. Nat Med, 2025

Pancreas Adenocarcinoma Cohorts

Genomics Cohort: N= 2,336

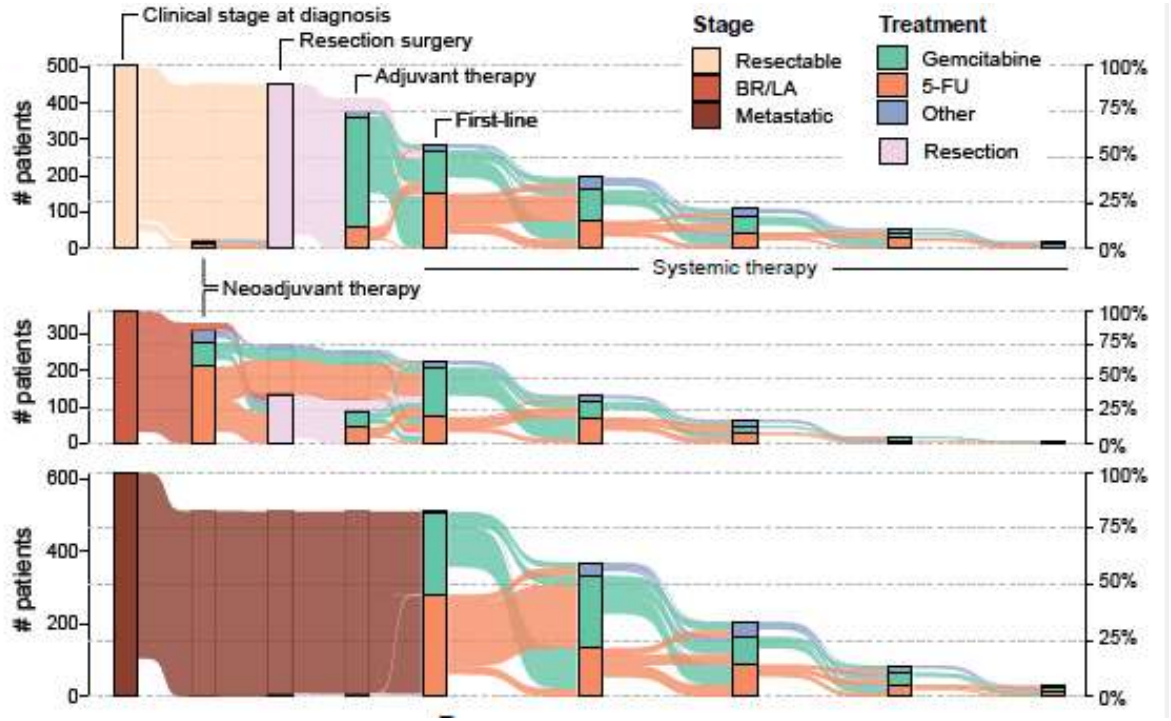
Somatic & germline profiling



Median age 67 years
Median seq. depth 606x MSK IMPACT (341-505 genes)
Median purity (FACETS) 31%
Matched tumor-normal sequencing
OncoKB (precision oncology knowledgebase)

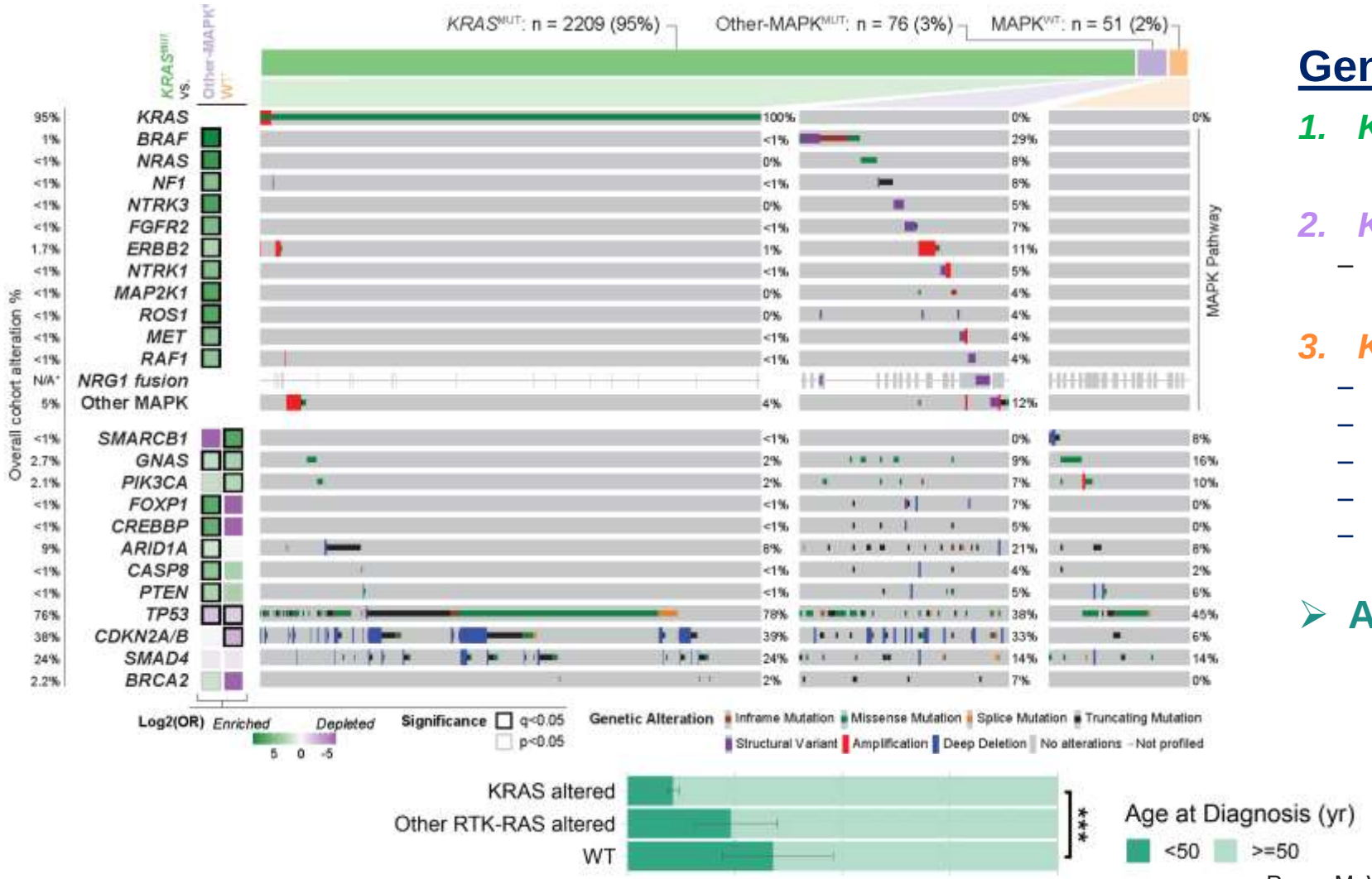
Clinical Cohort: N= 1,480 (63%)

Detailed treatment and clinical histories (350 variables)



Alluvial diagram: Treatment sequencing

Somatic Alteration Landscape in PDAC (N= 2,336)



Genomic Classifiers of PDAC

1. ***KRAS*^{MUT}(+) 95%**

2. ***KRAS*^{WT}, MAPK^{MUT}(+) 3% (Other-MAPK^{MUT})**
   - Enriched other MAPK genes

3. ***KRAS*^{WT} , MAPK^{WT}: 2%**
   - MAPK alterations (15%) (RNA-seq)
   - Enriched *SMARCB1* (7%)
   - Enriched g*ATM* (15%)
   - Enriched early onset
   - Enriched MSI-H, TMB-H

➢ **All *KRAS*^{MUT} are not alike**

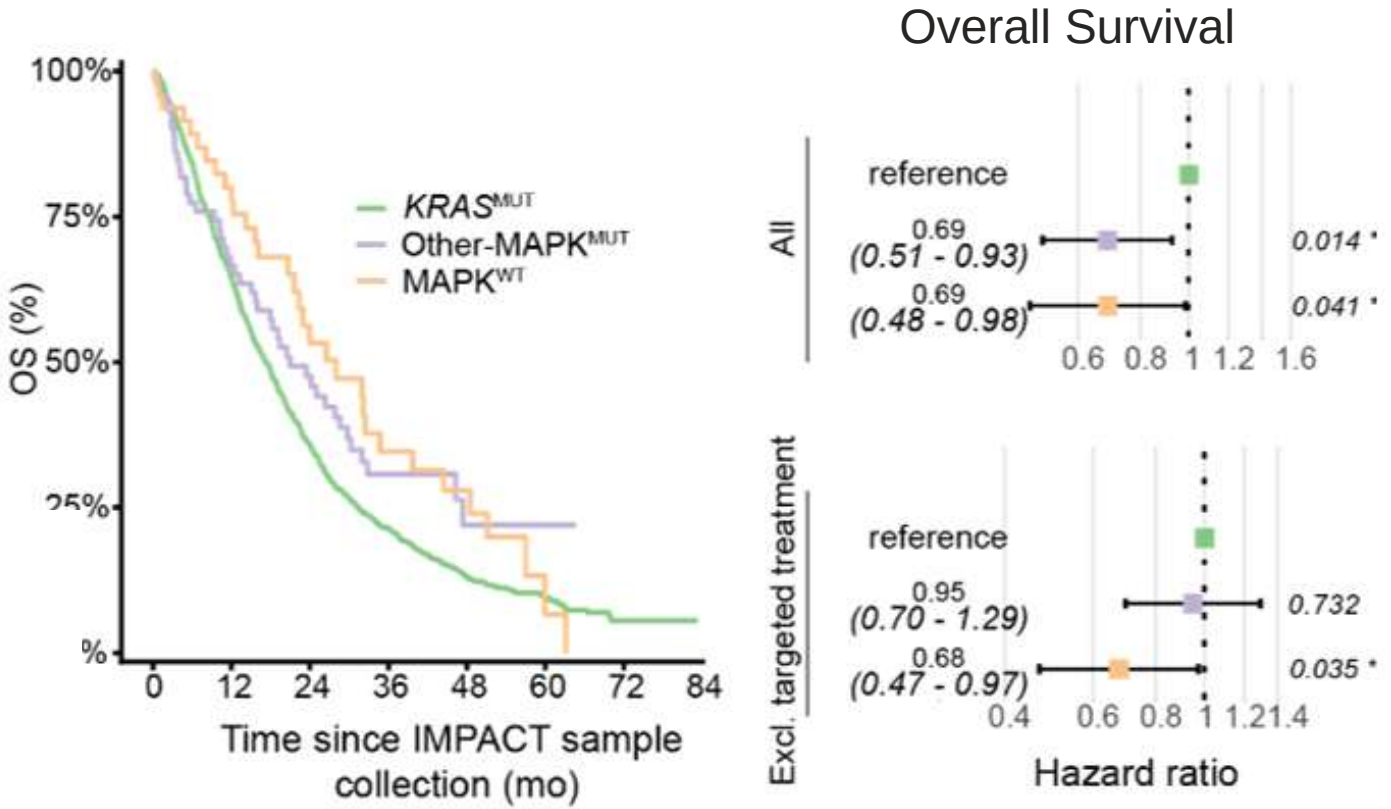
Perry, M, Varghese, A…..Bandalamudi, C, O'Reilly, EM. Nat Med, 2025

Genomic Classifiers of PDAC and Survival

MAPK^{WT} and Other-MAPK^{MUT} Significantly Better OS Compared to *KRAS*^{MUT}

MAPK^{WT}

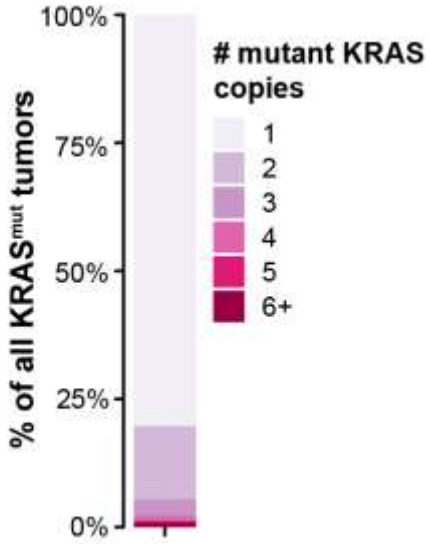
OS benefit not limited to patients treated with targetable alterations



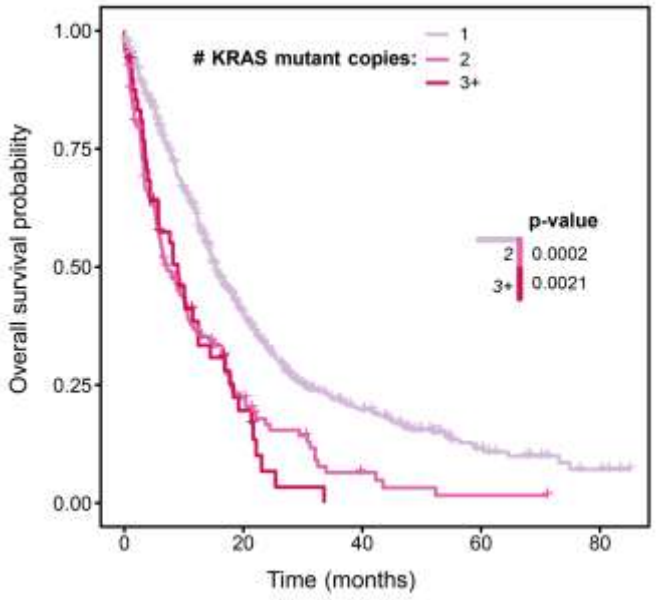
Overall cohort (top) and excluding biomarker directed therapy (bottom)

20% *KRAS*^{MUT} Tumors ≥ 2 Mutated Copies (Dosage Gains)

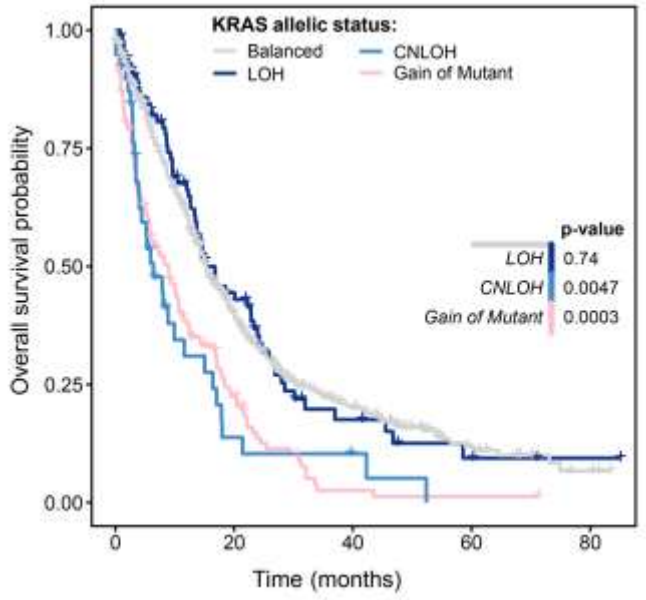
Mutant Allele Gain Prognostic of Survival



Mutant allele gain prognostic** of OS



Prognostic** effect independent of WT allele status (loss/retained)

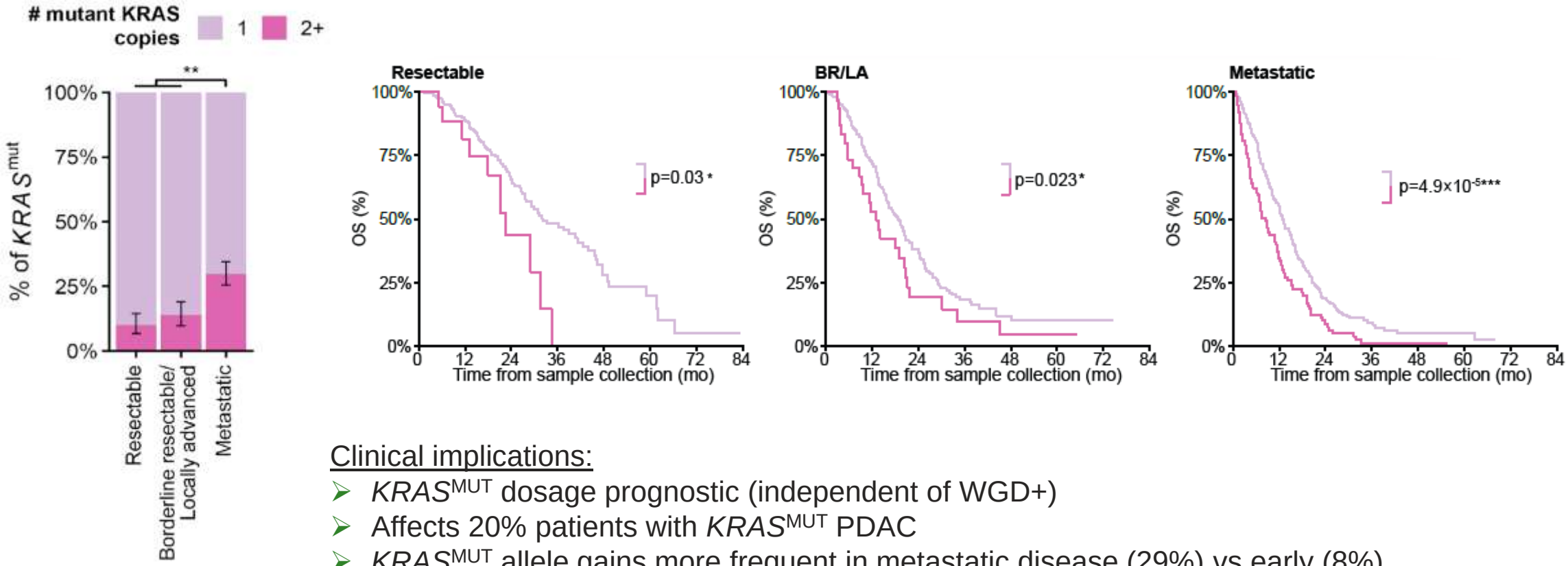


(** adjusted for covariates including stage, sex and genomic instability)

Perry, M, Varghese, A…..Bandalamudi, C, O'Reilly, EM. Nat Med, 2025

KRAS^{MUT} Dosage Gains: Prognostic Across All Stages

Whole Genome Duplication+ Removed; N= 934



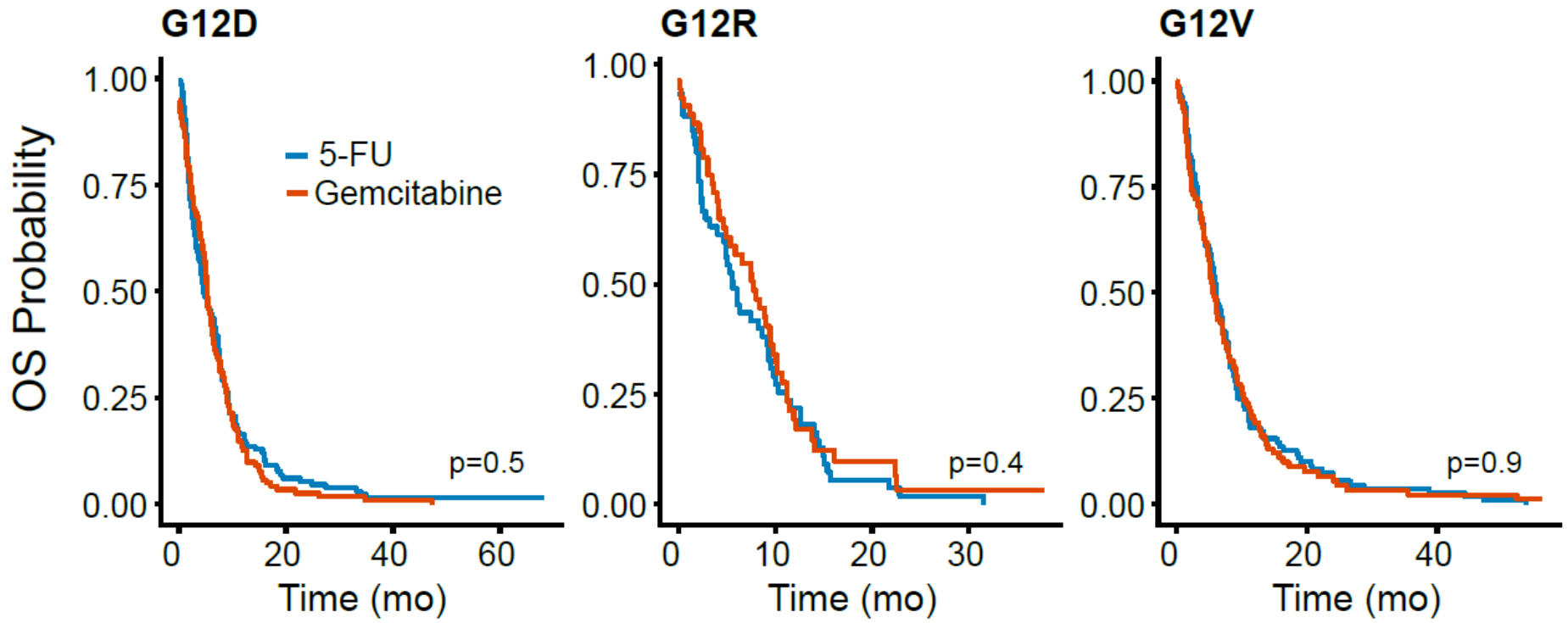
Clinical implications:

- *KRAS*^{MUT} dosage prognostic (independent of WGD+)
- Affects 20% patients with *KRAS*^{MUT} PDAC
- *KRAS*^{MUT} allele gains more frequent in metastatic disease (29%) vs early (8%)
- *KRAS*^{MUT} allele gains 5 m shorter OS in metastatic disease

Perry, M, Varghese, A…..Bandalamudi, C, O'Reilly, EM. Nat Med, 2025

Metastatic Cohort: No Difference in PFS Outcome

Fluoropyrimidine/Combination vs Gem-Based Therapy for *KRAS* G12D, R or V

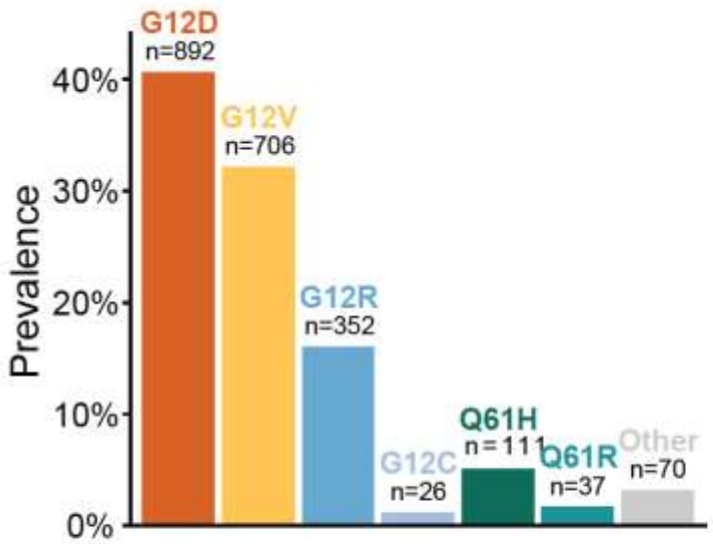


No *KRAS* targeted therapy included

Perry, M, Varghese, A…..Bandalmudi, C, O'Reilly, EM. Nat Med, 2025

Differential Genomic, Prognostic Features of *KRAS* Variants

KRAS G12R Prognostic



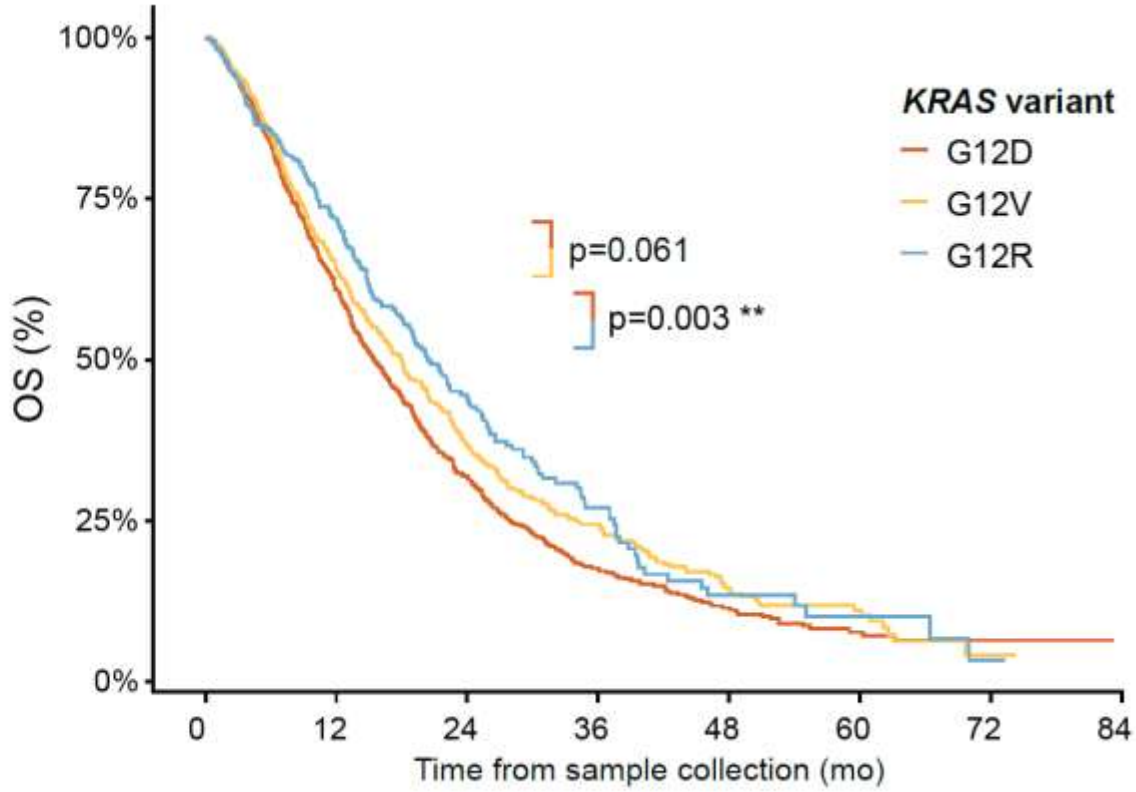
Prevalence *KRAS* variants

98% *KRAS* substitutions G12 (91%), Q61 (7%)

N= 14 (0.6%) multiple hotspot mutations

G12R vs G12D (smoking 40% vs 55%)

Not shown: No difference in allele distribution across stage



Kaplan-Meier of OS among *KRAS* variants

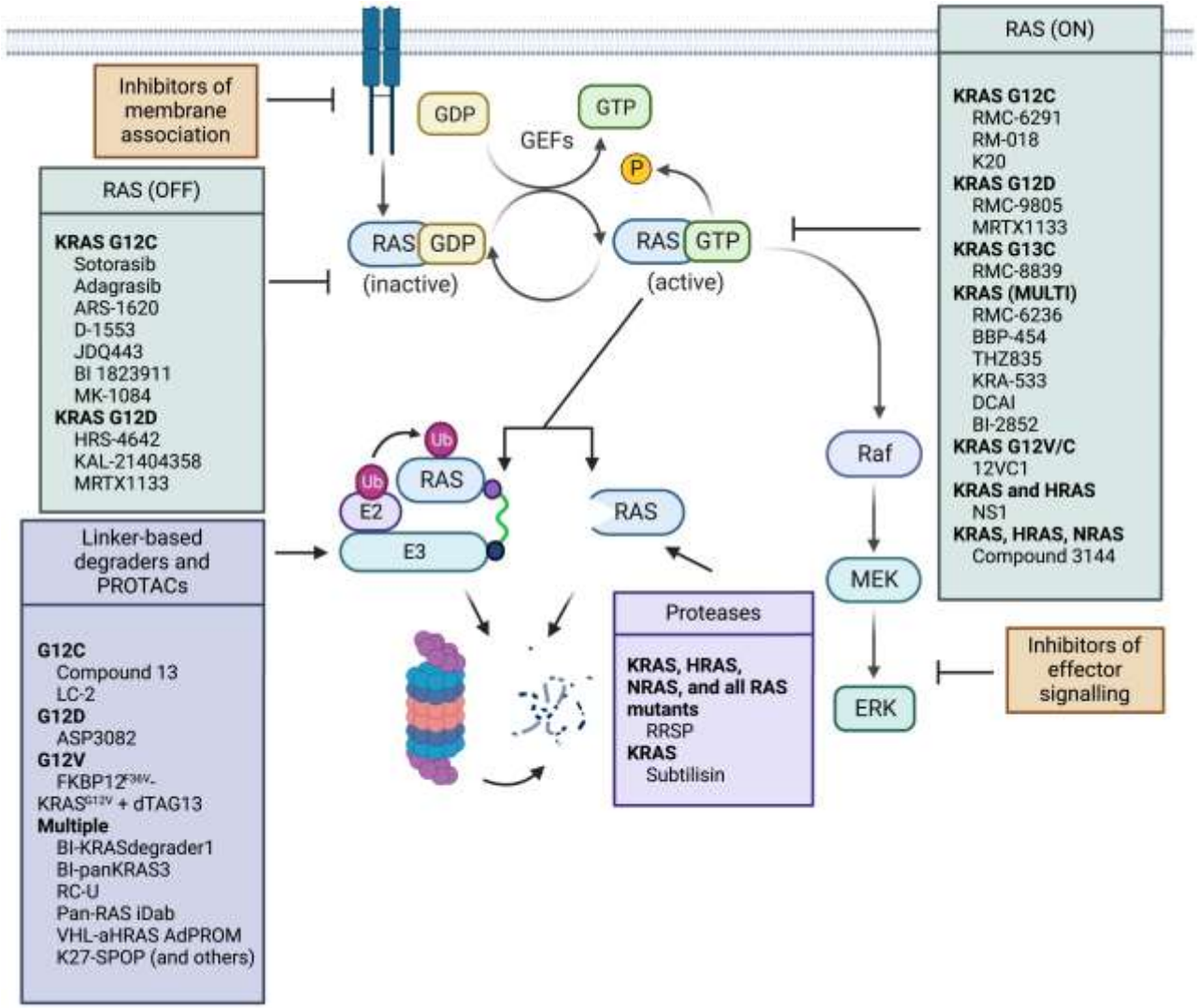
**multivariate Cox proportional hazards model by stage at diagnosis, *KRAS* mutant allele copy #, sex, age, ancestry, time diagnosis to sample collection

Perry, M, Varghese, A…..Bandalmudi, C, O'Reilly, EM. Nat Med, 2025

Johns Hopkins GI Conference

KRAS Therapeutics

- Direct inhibition
  RAS ‘off’ vs ‘on’
- Linker-based degraders
  PROTAC’s
- Proteases
- Indirect downstream inhibitors
  e.g., SOS1, shP2
- *KRAS* vaccines



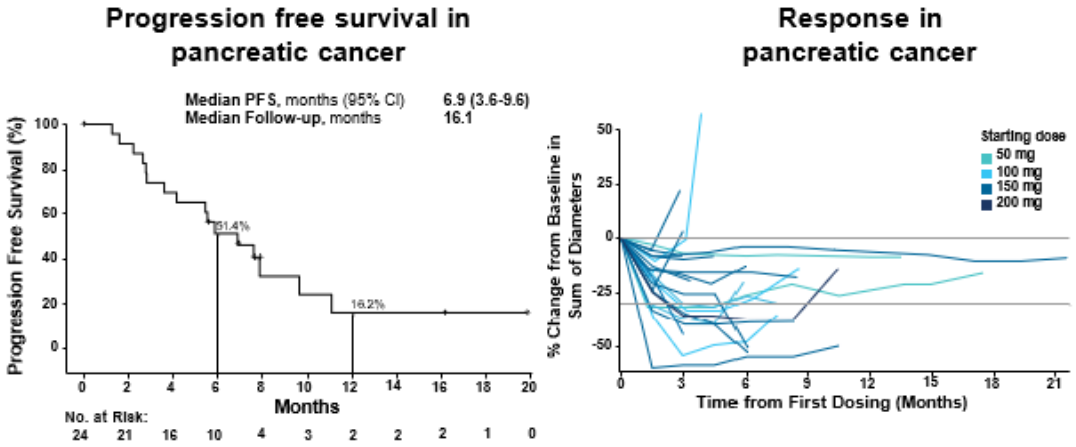
Esacher, TE, Sactchell, KJF. Mol Therapy, 2023

PDAC *KRAS* G12C Inhibitors: Summary

Reference: Chemotherapy 2-3rd Line Median PFS ~ 2-3 m

	N	Response Rate	Disease Control	Median PFS	Median OS
Sotorasib (CodeBreaK 100)	38	21% (8/38)	84% (32/38)	4 m	6.9 m
Adagrasib (KRYSTAL-1)	21	33% (7/21)	81% (17/21)	5.4 m	8 m
Divarasib	7	43% (3/7)	100% (7/7)	-	-
Olomorasib (LY3537982)	24	42% (10/24)	92% (22/24)	6.9 m	-
Glecirasib (JAB-21822)	31	42% (13/31)	93.5% (29/31)	5.6 m	10.7 m

Olomorasib (covalent GDP-G12Ci)

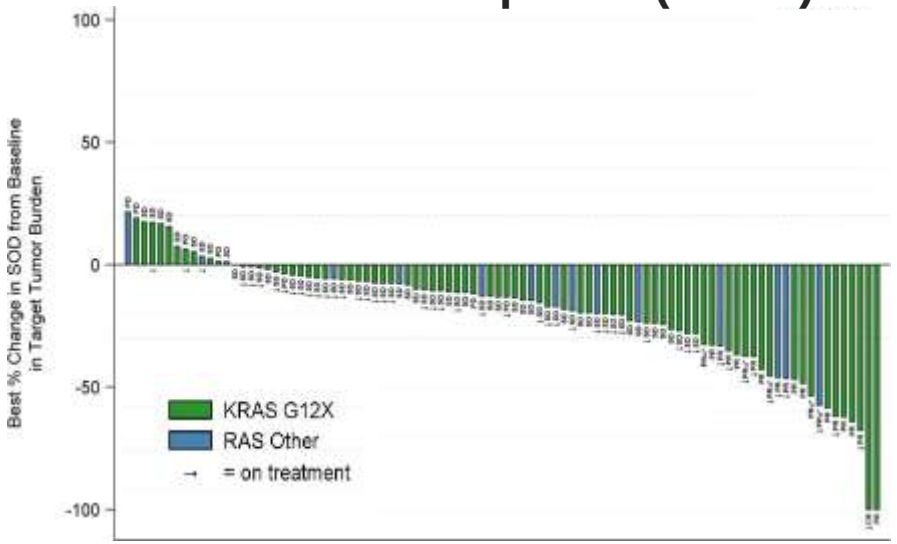


Stickler, J. New Engl J Med, 2023
Bekaii-Saab, T…Pant, S. J Clin Oncol, 2023
Sacher, A. New Engl J Med, 2023
Murciano-Goroff, Y. AACR, 2023
Holebecque, A. Gastrointestinal Cancers Symposium, 2024
Li, J. Gastrointestinal Cancers Symposium, 2024

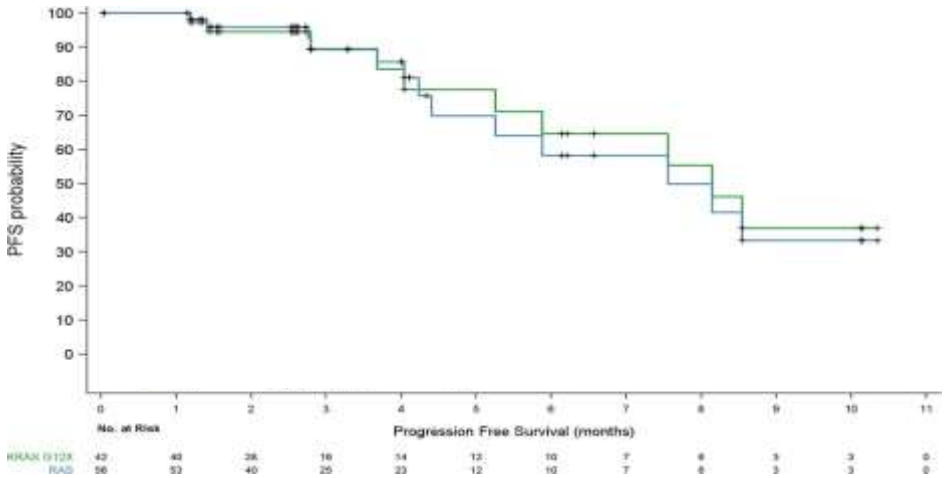
Daraxonrasib* (RAS-ON): Early Outcomes in PDAC

Reversible GTP-Binding Multi-Selective Inhibitor (*KRAS*, H,N, Wild-Type)

Anti-Tumor Response (N= 97)



PFS Second Line (N= 98)



	Response Rate 14+ Week	Disease Control 14+ Week
KRAS G12X	29% (16/79)	87% (69/79)
RAS^{MUT}	21% (20/97)	88% (85/97)

	N	Median PFS	Median OS
KRAS G12X	42	8.5 (5.9-NE)	14.5 (8.8-)
RAS MUT*	56	7.6 (5.3-NE)	14.5 (8.8-)

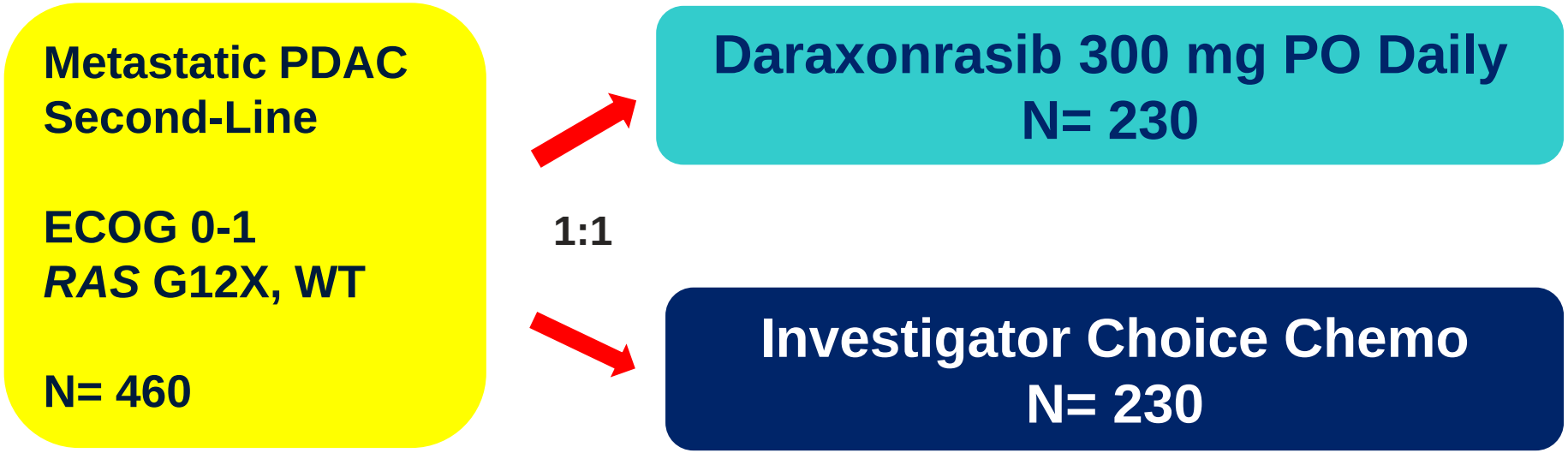
**RAS* mutant: G12X, G13X, Q61X*
Exploratory 3L *RAS* 612X: (N= 62): 4.2 m PFS (historical <2 m)

*Daraxonrasib (RMC-6236)

Courtesy Revolution Medicine public posting 07/14/2024 NCT05379985
Jiang, J. Can Discovery, 2024. Holderfield, M. Nature, 2024
https://ir.revmed.com/press-releases
Wolpin, B. EORTC-NCI-AAACR, 2024

RASolute 302: Phase III Met PDAC 2L RMC-6236 vs Chemo

Ongoing



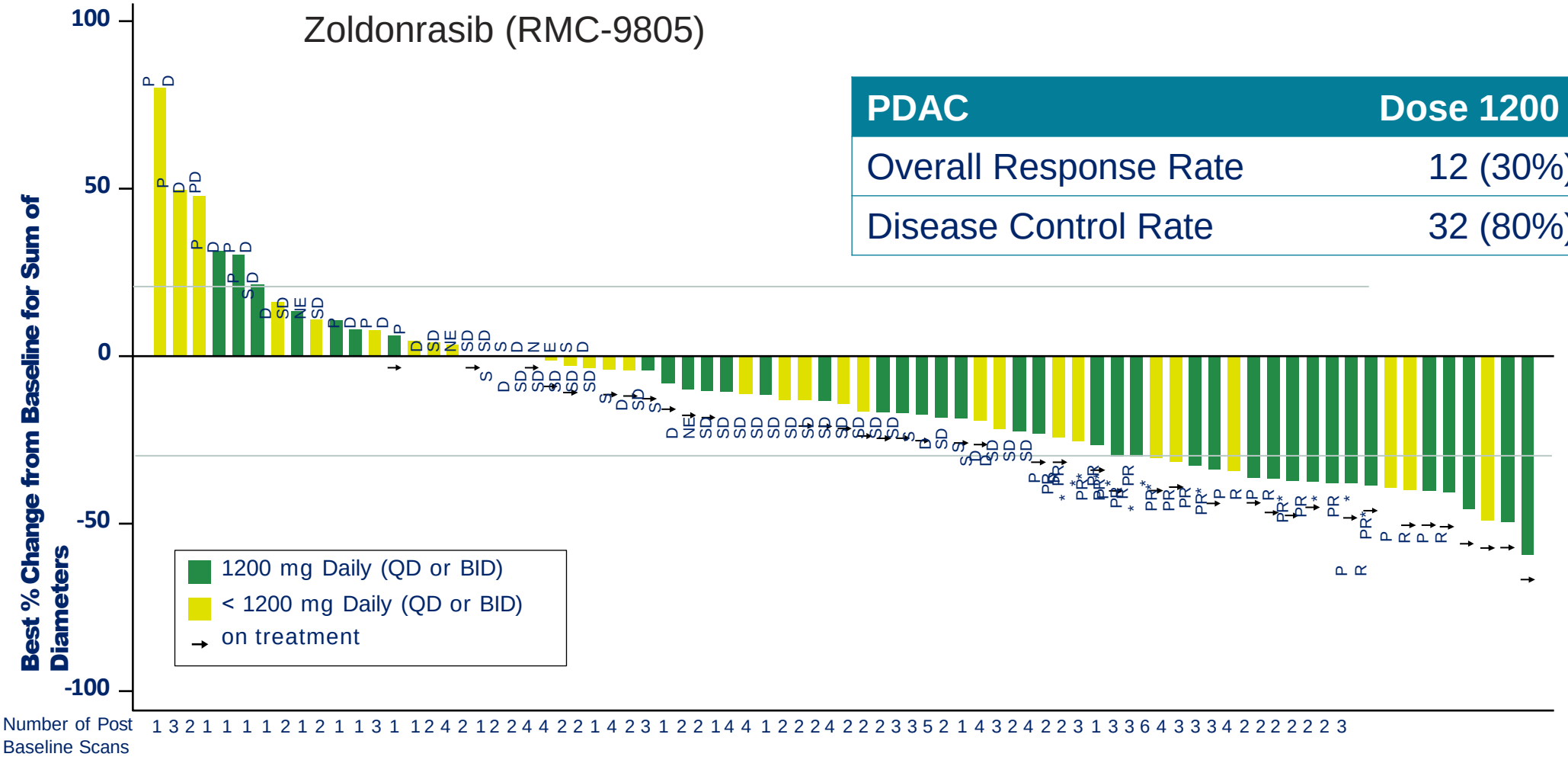
Co-primary endpoints: Progression-free survival; OS (G12X)

Secondary endpoints: PFS, OS (all), Overall response rate, duration of response, QoL

HR 0.7 OS (G12X 7.1 → 10.1 m)
HR 0.54 PFS (G12X 3.5 → 6.5 m)

NCT06625320

Zoldonrasib: Phase G12D RAS-On Allele Specific PDAC



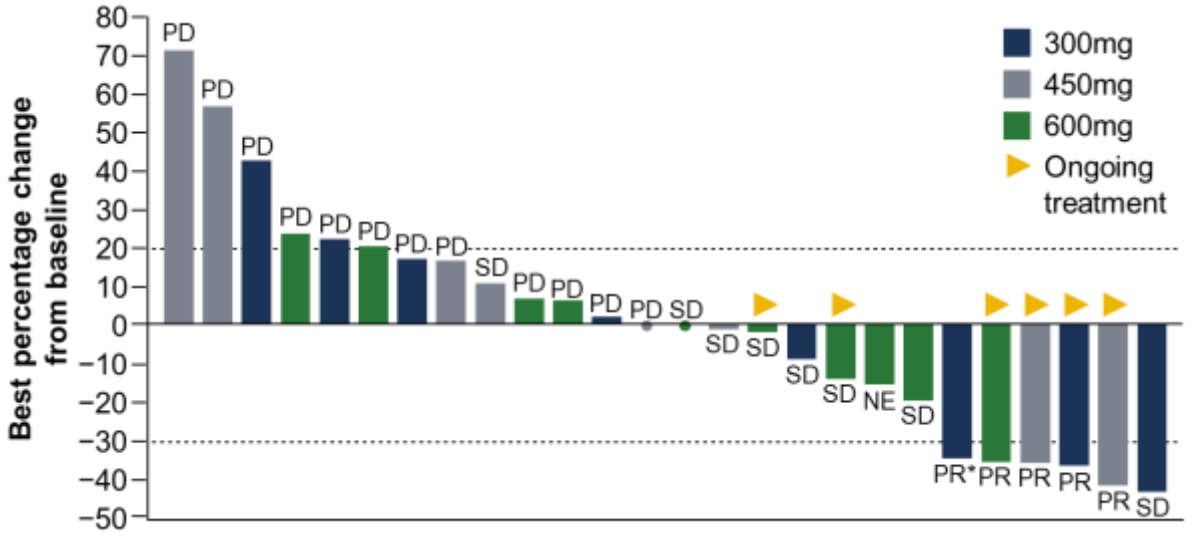
PDAC	Dose 1200 mg
Overall Response Rate	12 (30%)
Disease Control Rate	32 (80%)

Hong, D. EORTC-NCI-AACR, 2024
Spira, A. Gastrointestinal Cancers Symposium, 2025

ASP3082 KRAS G12D Protein Degrader

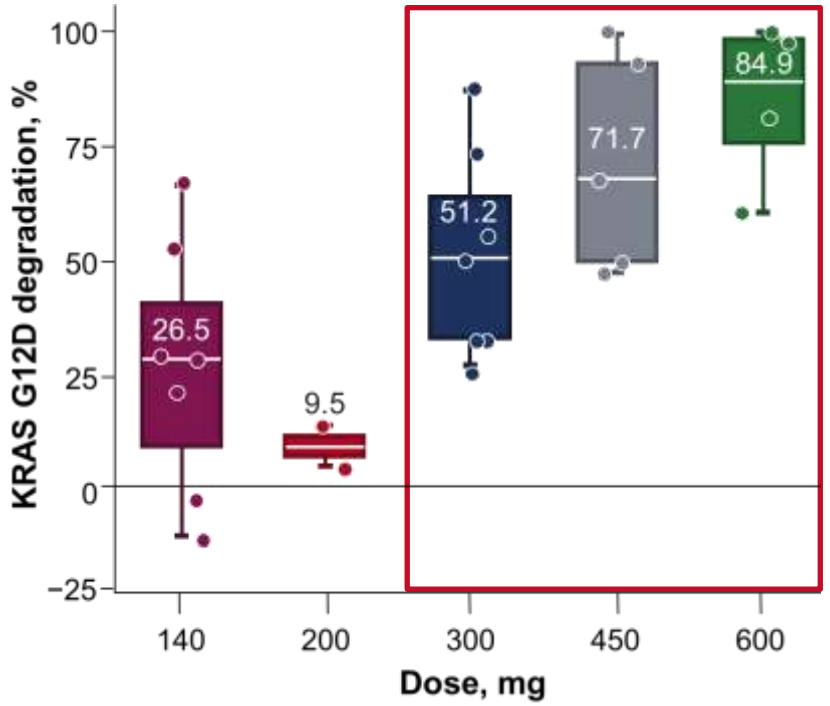
First in Class

Anti-tumor Activity >300 mg PDAC (+NSCLC)



PDAC	Overall N= 27	<2 Lines
Overall RR	5 (18.5%)	4 (23.5%)
Disease Control	13 (48%)	8 (47%)

KRAS G12D Protein Degradation (IHC)



Park, W….Tolcher, A. Abst 608O. ESMO, 2024

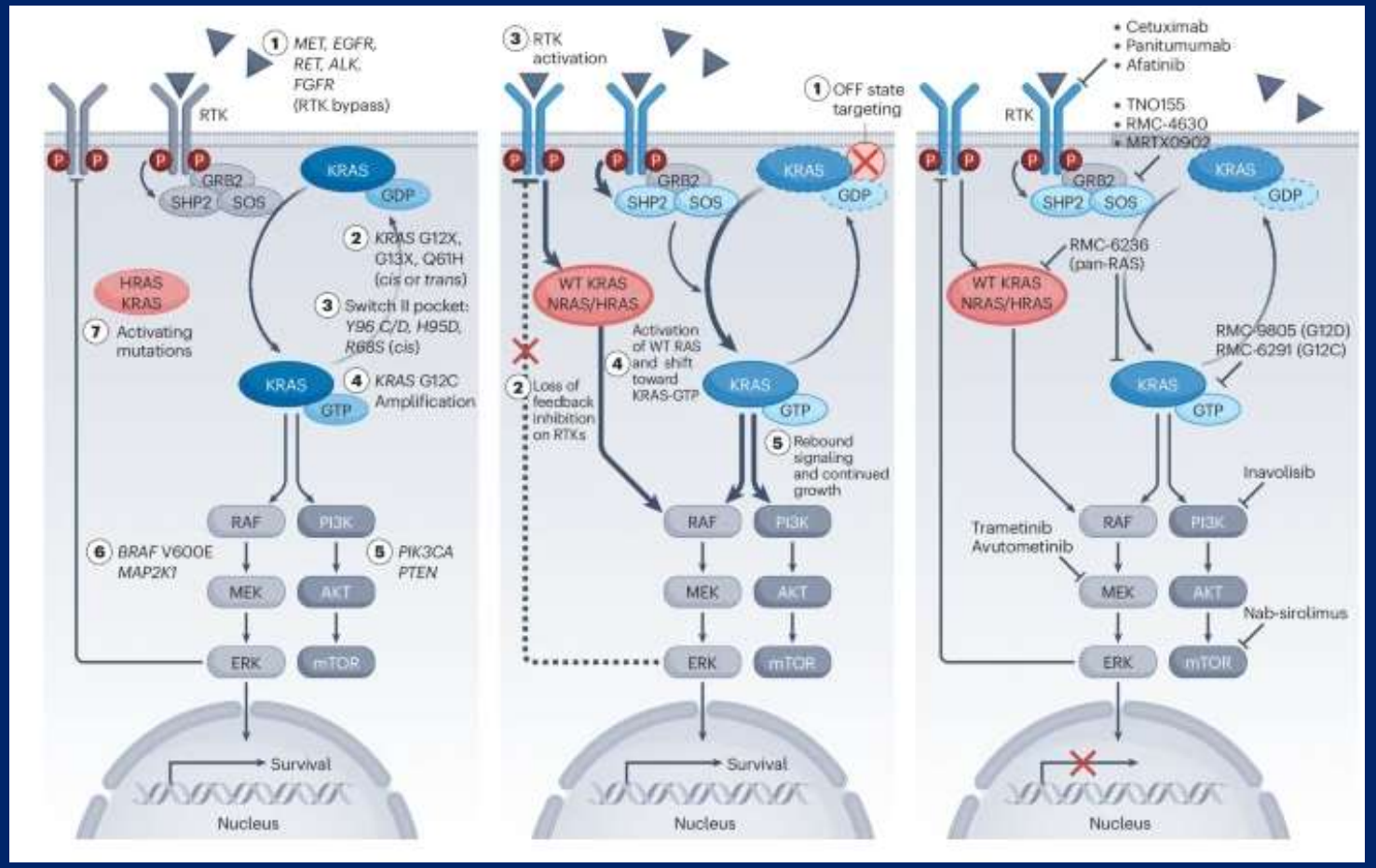
Johns Hopkins GI Conference

RAS Resistance Targeting

Diverse mechanisms
- Genetic
- Non-genetic
- Cell-state transitions

Combination approaches:
Allele specific, pan RAS
+Upstream receptor TKI signaling
+MAPK pathway targeting
+Immunotherapy
+Chemotherapy
+Classical state targeting

Genetic Resistance to G12C | Adaptive Resistance | Addressing Resistance with Combinations



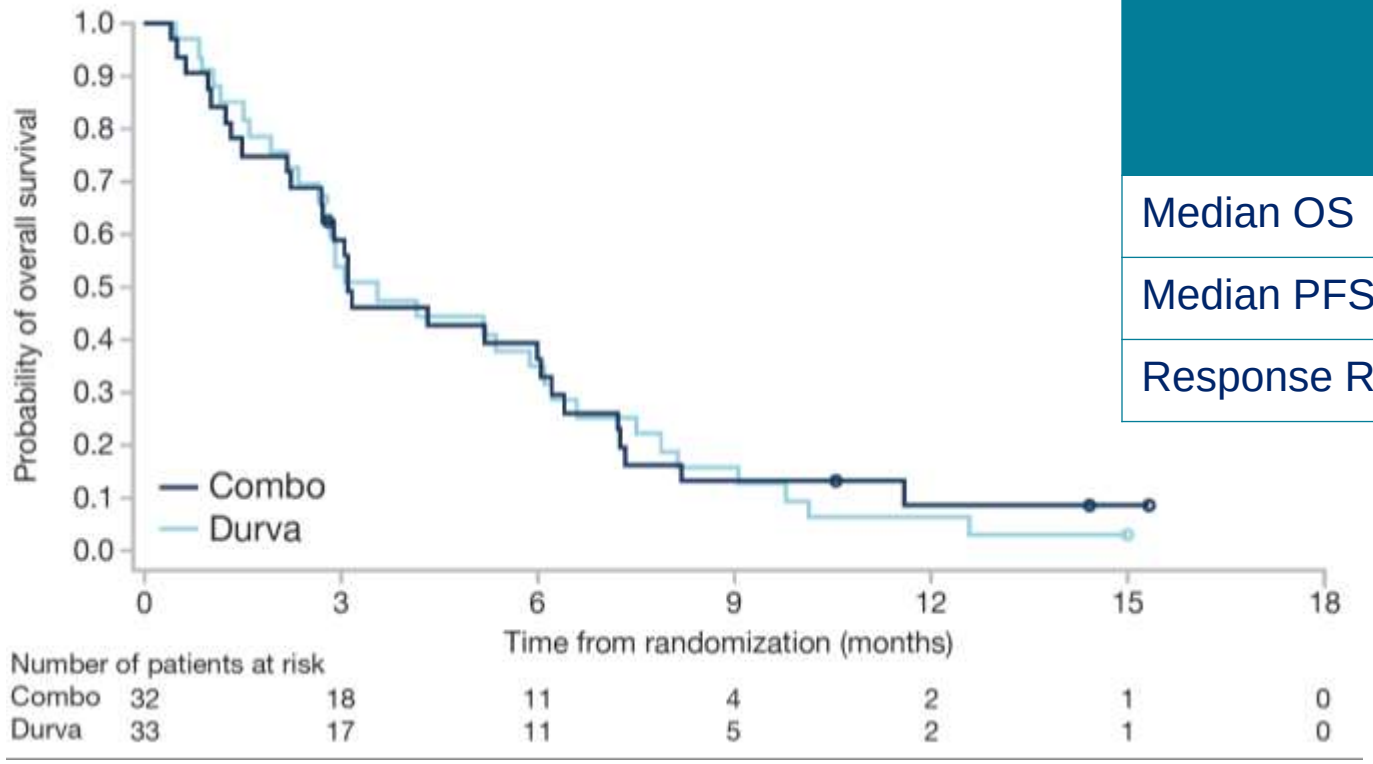
Singhal, A, Li, B, O'Reilly, EM. Nat Med, 2024

Agenda

KRAS descriptors and therapeutics

***KRAS*-directed immunotherapy**

Single vs Double ICB in Unselected PDAC – Ineffective
Rand Ph. II: Durvalumab (D) +/- Tremelimumab (T)



	Durvalumab + Tremelimumab N= 32	Durvalumab N= 33
Median OS	3.1 months	3.6 months
Median PFS	1.5 months	1.5 months
Response Rate	3.1%	0%

- No activity to single agent/double immune checkpoint blockade in unselected PDAC

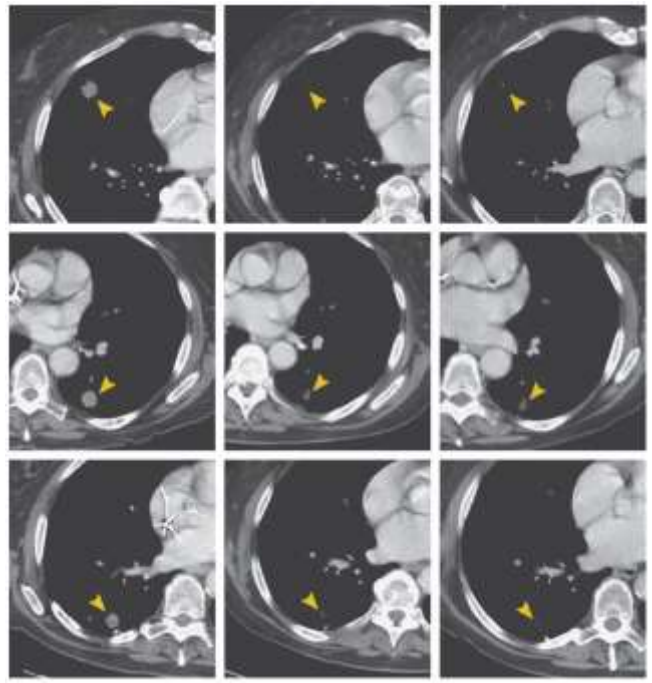
O'Reilly, EM…Philip, PA. JAMA Oncol, 2019

Targeting m*KRAS* in PDAC with T Cell Receptor Therapies

- Mutant *KRAS* promising public neoantigen target in PDAC
- Mutant KRAS peptides presented by MHC-1, recognized cytotoxic CD8+ T cells

- HLA C*08:02 restricted
  G12D *KRAS* TCR → PR in PDAC, CRC
  G12V

- Adoptive therapy challenges:
  - Select HLA's (e.g., HLA-C*08:02, A*11.01)
  - Select mutations
  - Logistics
  - Potential CRS
  - Cost, resources, time

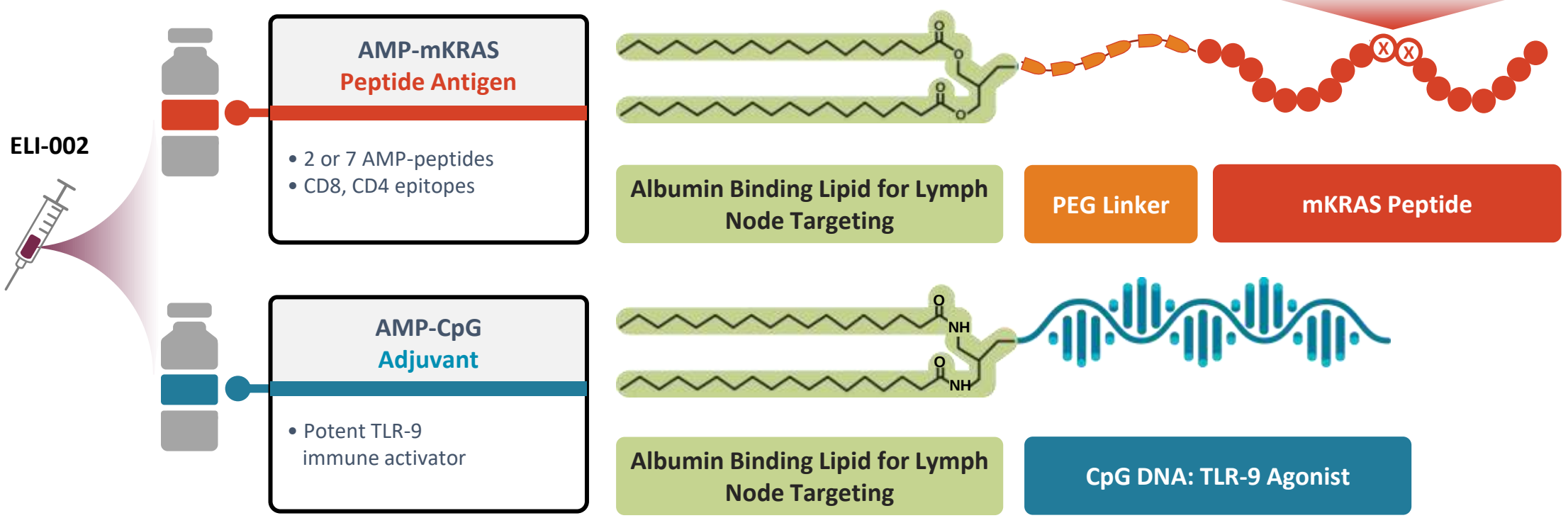


Leidner R. N Engl J Med, 2022
Tran E. N Engl J Med, 2016
Lu, D. Nat Commun, 2023
Poole, A. Nat Commun, 2022
Al, Q, Front Immunol, 2023
NCT03190941
NCT03704532
NCT06105021

ELI-002 2P, 7P Vaccine Composition

Platform for Antigen Presentation

	ELI-002	G12X					G13X
Peptide Composition	2P	D	R				
	7P	D	R	V	C	S	A	D

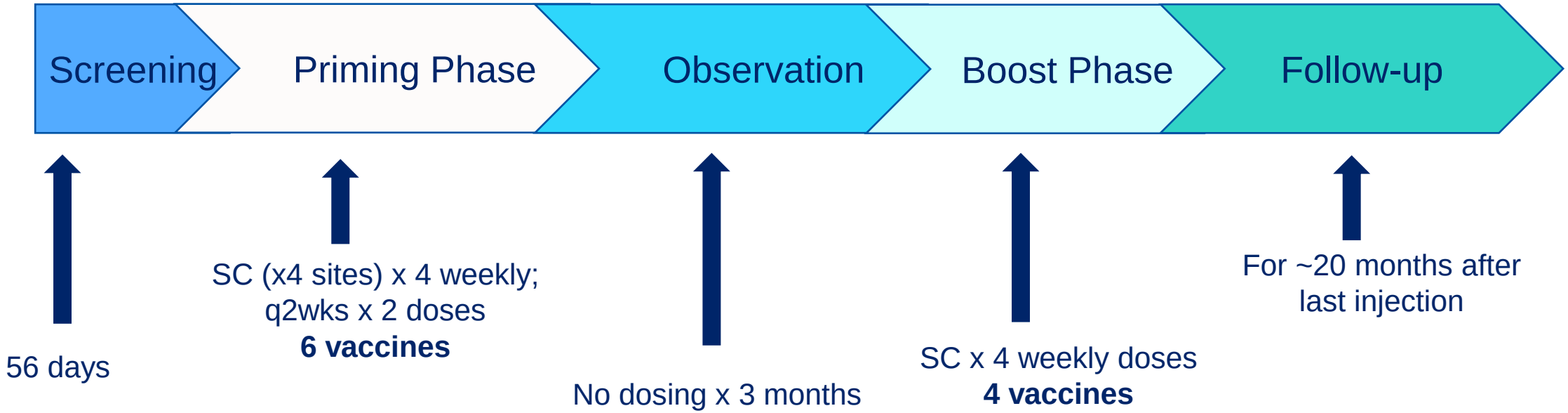


O'Reilly EM…Pant S et al. ASCO 2023. Abstract 2528
Pant, S….O'Reilly, EM. Nature Medicine, 2024

First in Human Phase I-II ELI-002 2P *KRAS* G12D/R

Pancreas, Colon with MRD (+ctDNA or +CEA/Ca 19-9)

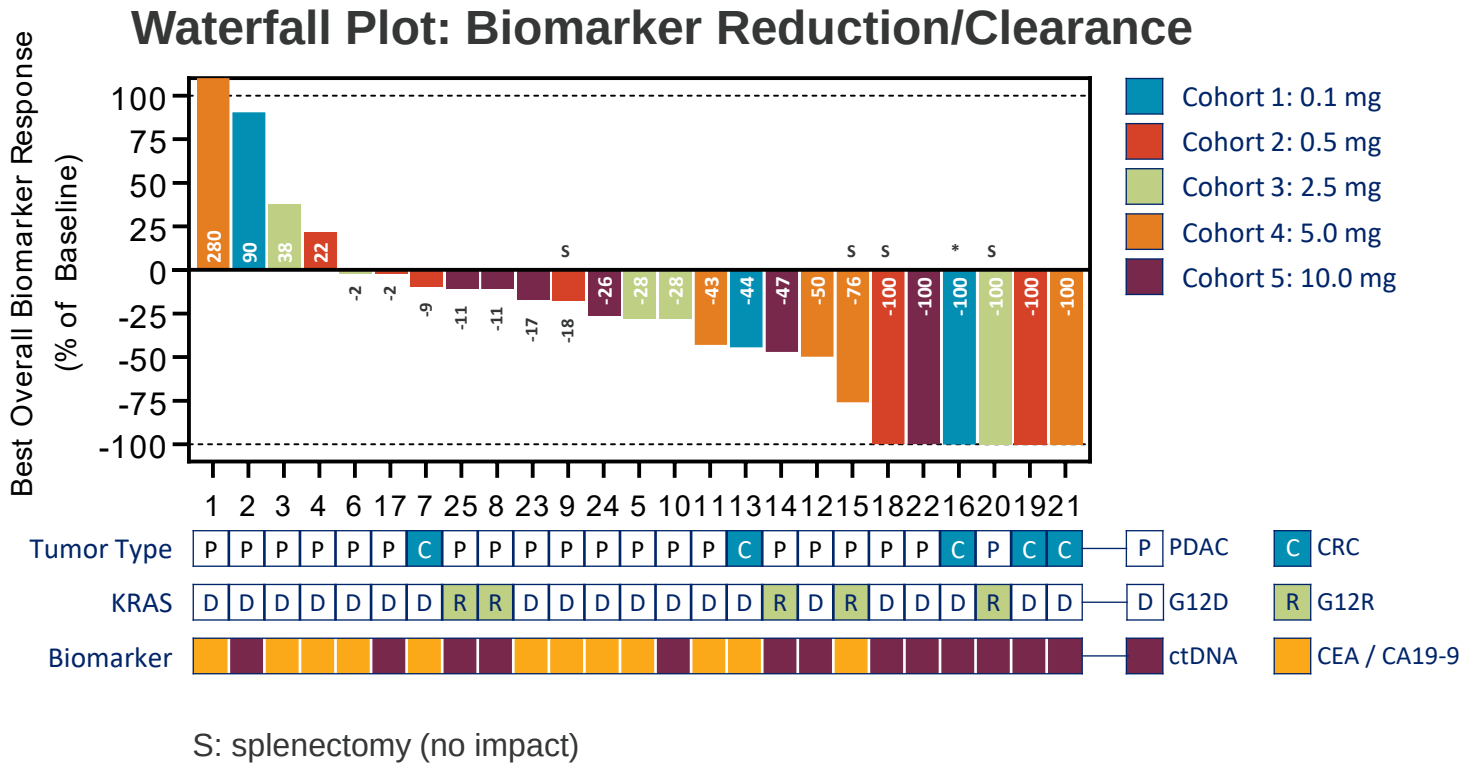
- Determine MTD or RP2D, safety, ctDNA clearance, Immunogenicity, relapse-free survival
- Eligibility: Adjuvant MRD+ resected 'NED', +biomarkers
- Phase IA: Dose-escalation **immune adjuvant** 0.1 mg → 10 mg



Pant, S…Haqq, C, O'Reilly, EM.. Nature Med, 2024

Phase IA: Results ELI 002 2P Pancreas (N= 20), Colon (N= 5)

- All pretreated; stage III/IV NED
- 21/25 (84%) decline ctDNA or CEA/Ca 19-9 from baseline
- 6/25 (24%) ctDNA clearance
- Responses: PDAC, CRC, *KRAS* G12D, G12R
- No DLT; G1-2 side effects

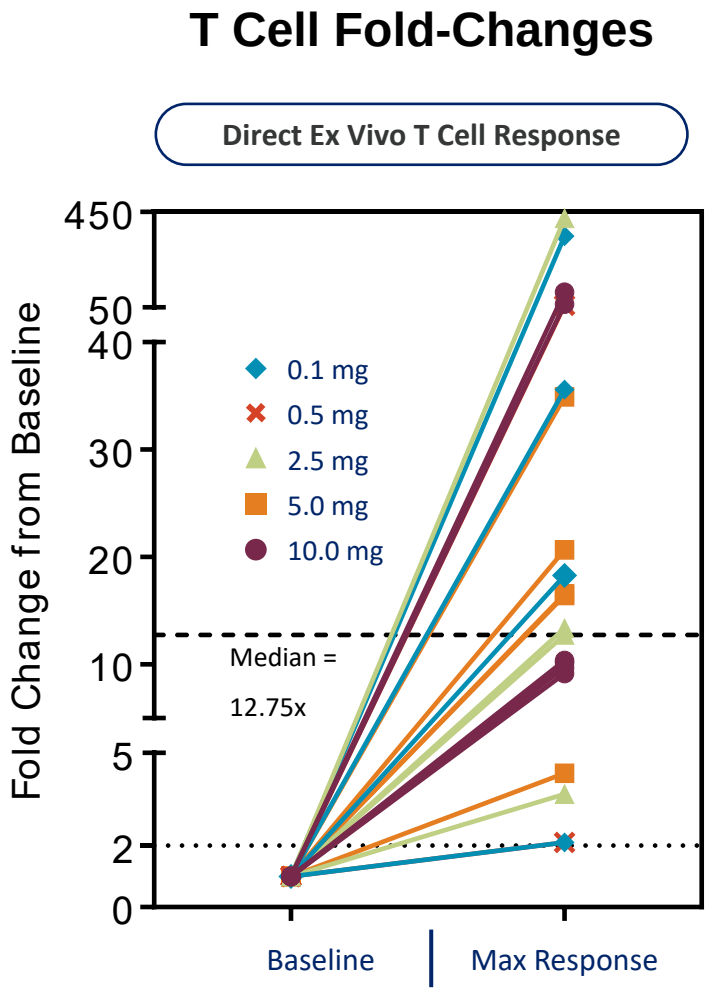


S: splenectomy (no impact)

Pant, S…Haqq, C, O'Reilly, EM.. Nature Med, 2024

Phase IA: 2P Immunogenicity Results

- T cells ex vivo FluoroSpot, flow cytometry
  (no expansion)
- Recommended phase II dose 10 mg TLR9 agonist:
  100% T cell response
  (all cohorts: 84%)
- Average 58x fold-change T cells
  Median 12.75; range 2- 423x
- ~60% both CD4, CD8 T cells
- Strength T cell response correlated to tumor biomarker response



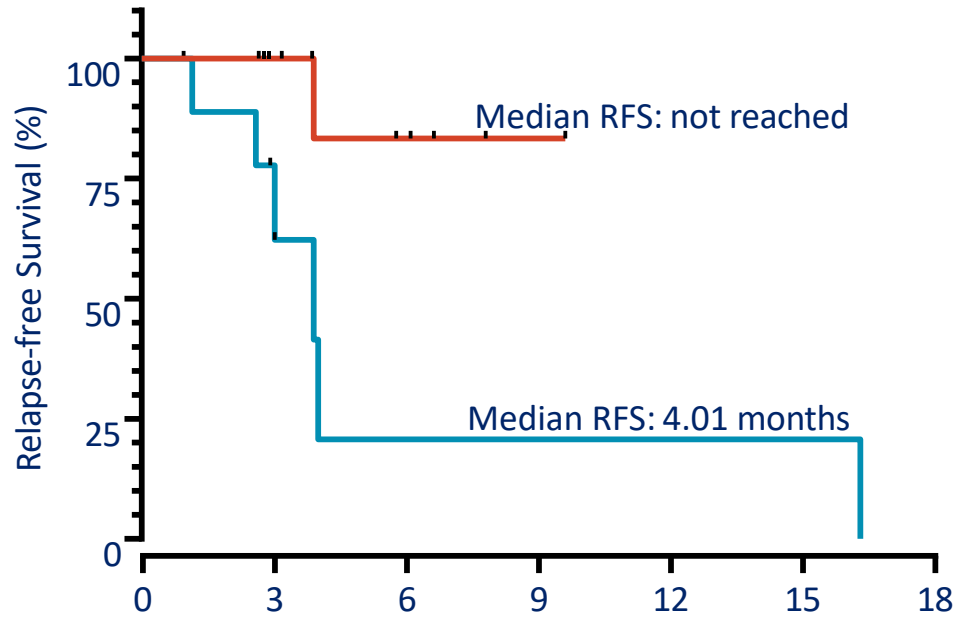
O'Reilly EM…Pant S et al. Abstract 2528, ASCO, 2023
Wainberg, Z…O'Reilly, EM. AACR Pancreas, 2023
Pant, S…Haqq, C, O'Reilly, EM.. Nature Med, 2024

Strength T cell Response Correlates with RFS/Outcomes
Phase 1A ELI-002 2P (Two Peptide Vaccine)

- At median f/up 8.5 m:
  For ≥ median T cell response: med RFS Not Reached
  For < median T cell response: med RFS 4.01 m
  HR 0.14 (0.03 – 0.63)

- Median relapse free survival: 16.3 m

Survival Outcome by T cell Response



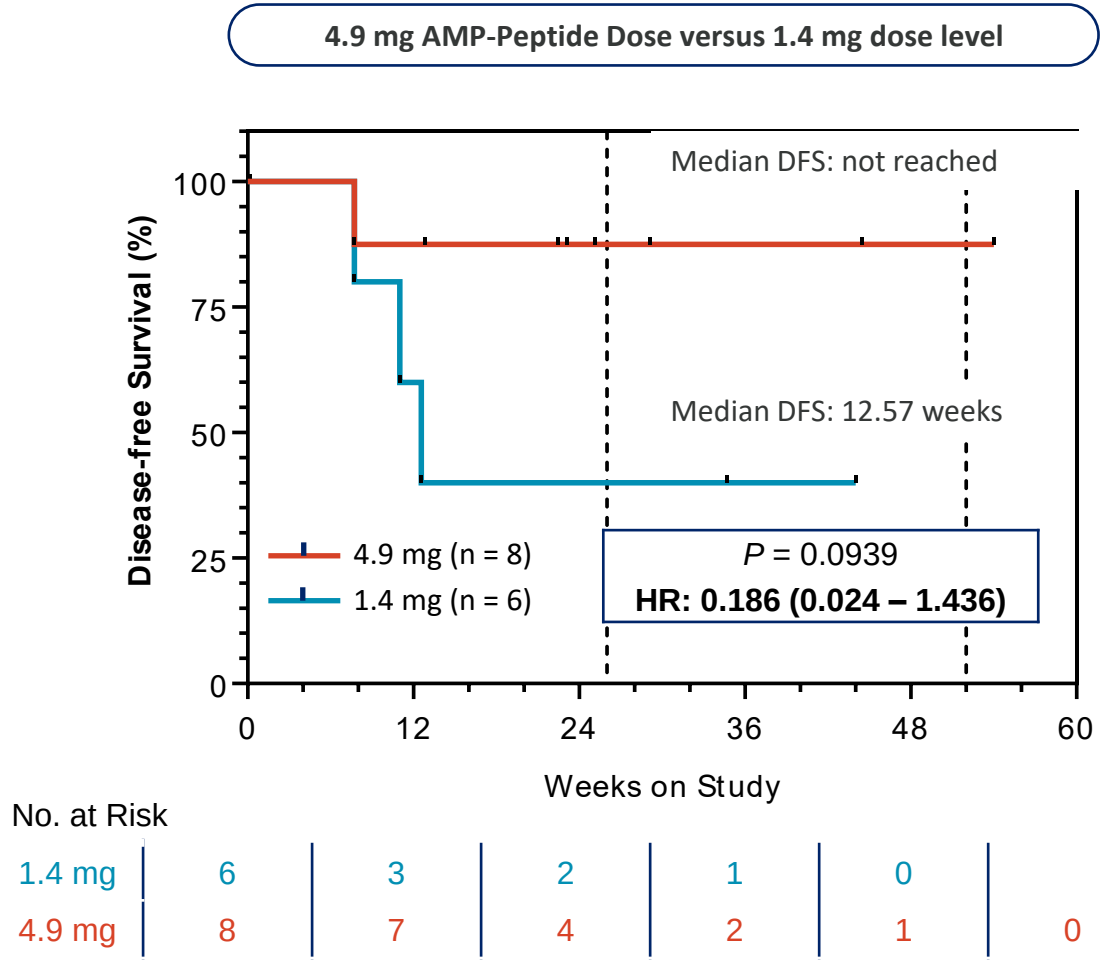
At risk							
≥ Median	12	8	4	1	0	0	0
< Median	10	5	1	1	1	1	0

Pant, S…Haqq, C, O'Reilly, EM.. Nature Med, 2024

Phase IA: ELI-002 7P Disease-Free Survival (Preliminary)

Seven Peptide Similar to 2P – But Better

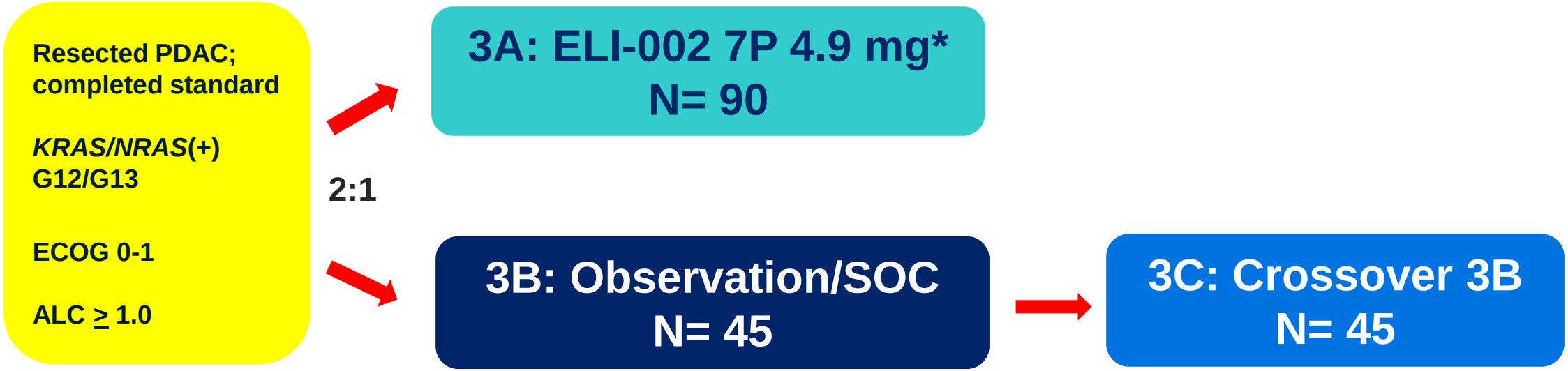
- Improved DFS 4.9 mg vs 1.4 mg peptide dose
- Median DFS not reached for 4.9 mg dose
- Improved DFS also associated with
  - Median T cell fold change
  - Biomarker response



Data cut-off May 2024

AMPLIFY-201 7P: Randomized Phase II Trial PDAC

Accrued



Primary endpoint: Disease-free survival (investigator)
Secondary: Biomarker reduction & clearance, 1-year DFS, median OS, safety, ORR (crossover)
Exploratory: Immunogenicity ELI-002 7P to baseline
Stratification: N0 vs N1
*7-Peptide: G12D, G12V, G12R, G12C, G12A, G12S, G13D

Wainberg, Z…O'Reilly, EM. Trials In Progress, Gastrointestinal Cancers Symposium, 2024
NCT05726864

Other *KRAS* Vaccines (Johns Hopkins Group)

Pooled Long-Peptide *KRAS* vaccine + Ipilimumab, Nivolumab in Resected PDAC

- 6 synthetic (21-mer) peptide G12V,D,C,R,A, G13D + poly-ICLC
- N= 11 resected PDAC post standard therapy
- Co-primary endpoint: Immunogenicity (IFN-producing *KRAS* specific T cells); median 10-fold; 8/11
- Lowest immune response in *KRAS* G12D; 3/3 recurred
- Antigen-specific T cell response associated with DFS (median DFS NR vs 2.8 m; p= 0.045)
- Tolerable, immunogenic

High-Risk Individuals: Germline Cohort; IPMN Cohort

- N= 20 enrolled
- mRNA-based mutant *KRAS*

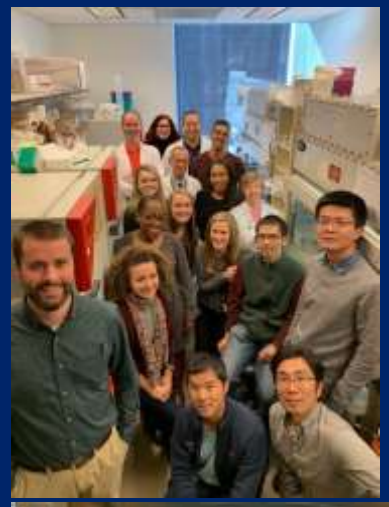
Huff AL , Azad, N, Jaffee, E. et al. AACR 2023. Abstract LB197.
NCT05013216

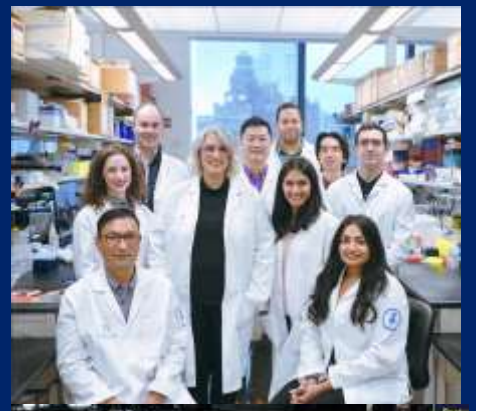
Pancreas Cancer 2025: *RAS* Current and Future…

KRAS Genomics	• 20% of all cancer – *KRAS* mutation – clonal, prevalent, immunogenic • GI Cancers – Pancreas, CRC, Cholangiocarcinoma, Small bowel, others • Testing – tumor, ctDNA; turn around times • Understanding mechanisms of resistance
KRAS Directed Therapy	• Established *KRAS* G12C inhibitor activity (‘off’ state): Sotorasib, Adagrasib • Activity G12Ci – NCCN guidelines • Efficacy panRAS, G12D degrader PDAC • Phase III underway 2L panRASi
Combination Therapies for RAS	• Immunotherapy: +ICB (NSCLC), +vaccines • Combination approaches: +chemotherapy, mutant-selective + panRAS, +EGFRi, +PROTAC’s • Other: indirect inhibitors, iExosomes, siRNA, RAF/MEKi, autophagy

Johns Hopkins GI Cancers

Thank You!





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