Pancreatic Cancer and Molecular/Genetic Testing: Challenges and Opportunities

Supported by RevMed, OMNI Oncology, and The Personalized Medicine Foundation.

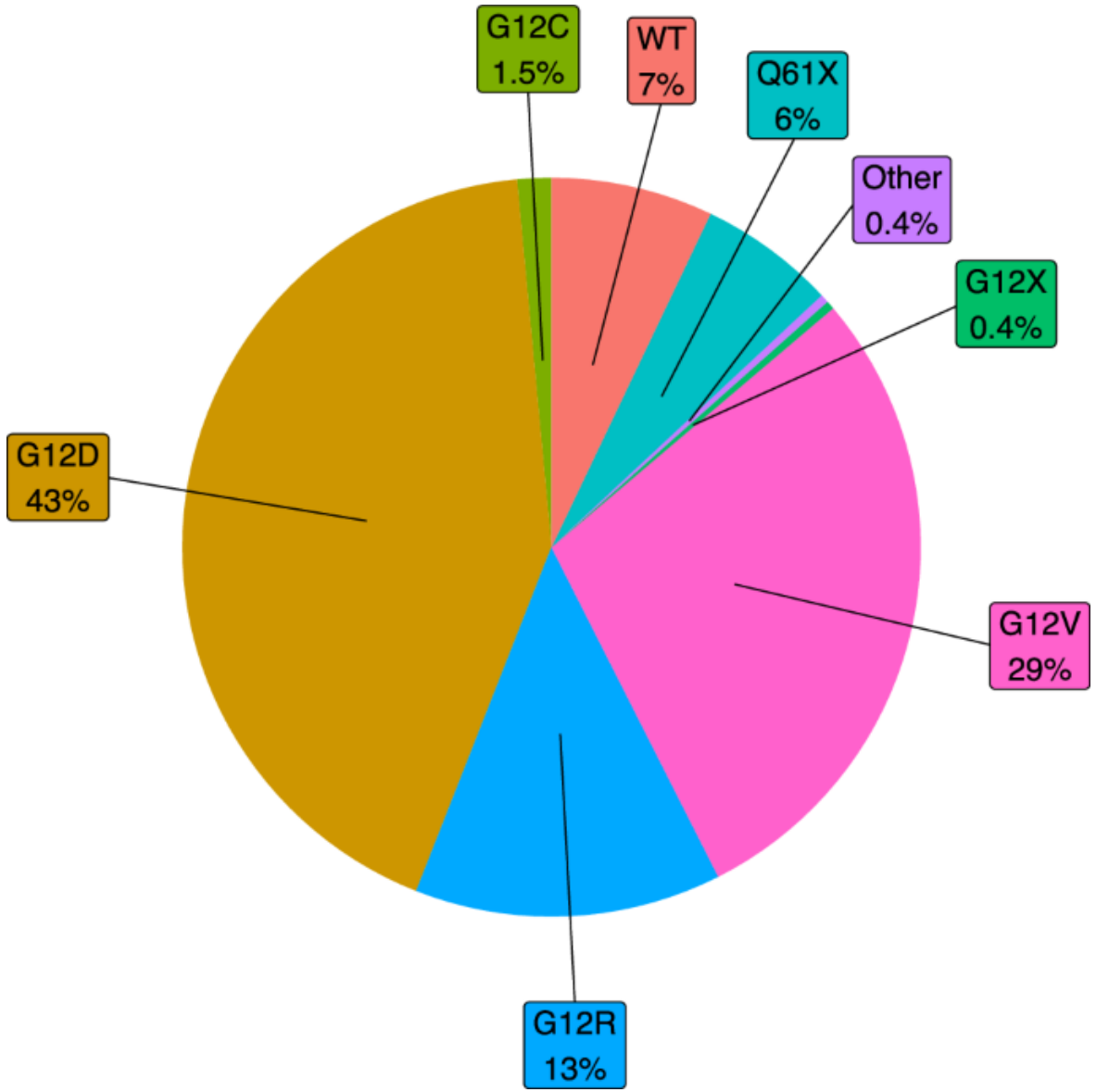
VMTB Chair

John Strickler, MD
Professor of Medicine
Co-leader, Duke Cancer Institute Molecular Tumor Board
Duke University

Panelist

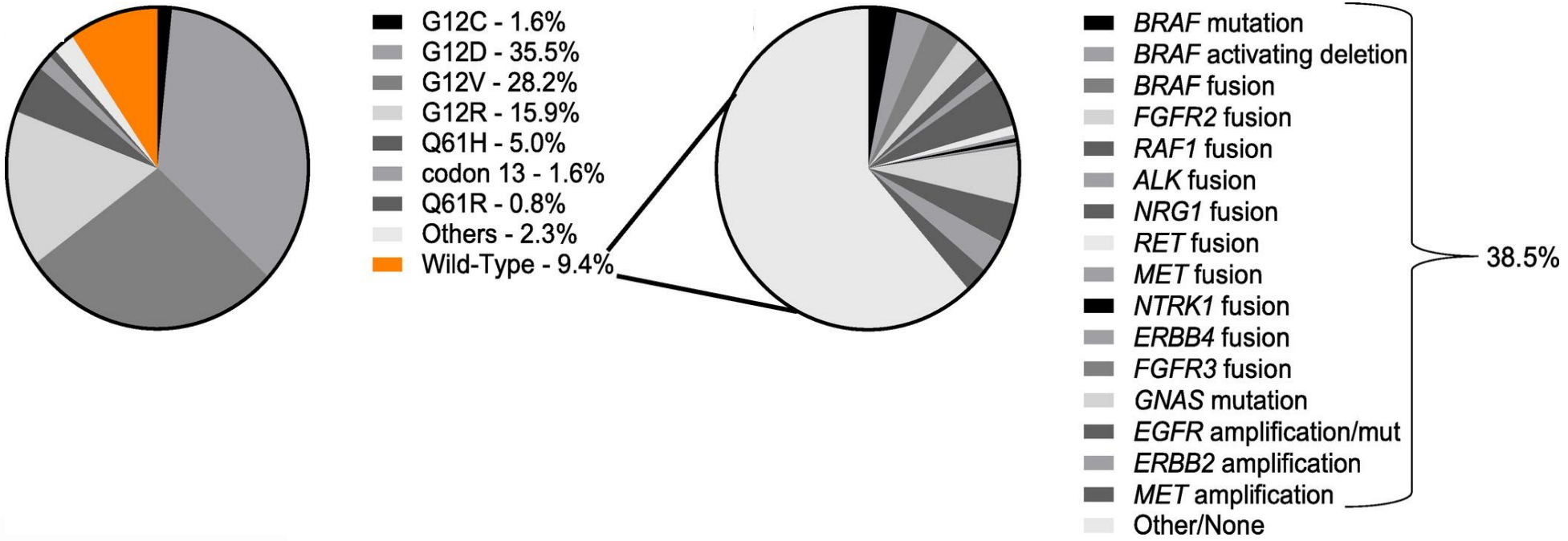
Tanios S. Bekaii-Saab, MD
David F. and Margaret T. Grohne Professsor of Novel Therapeutics for Cancer Research
Chair and Consultant, Division of Hematology and Medical Oncology
Professor, Mayo Clinic College of Medicine and Science
Mayo Clinic in Arizona

KRAS Mutational Spectrum in PDAC



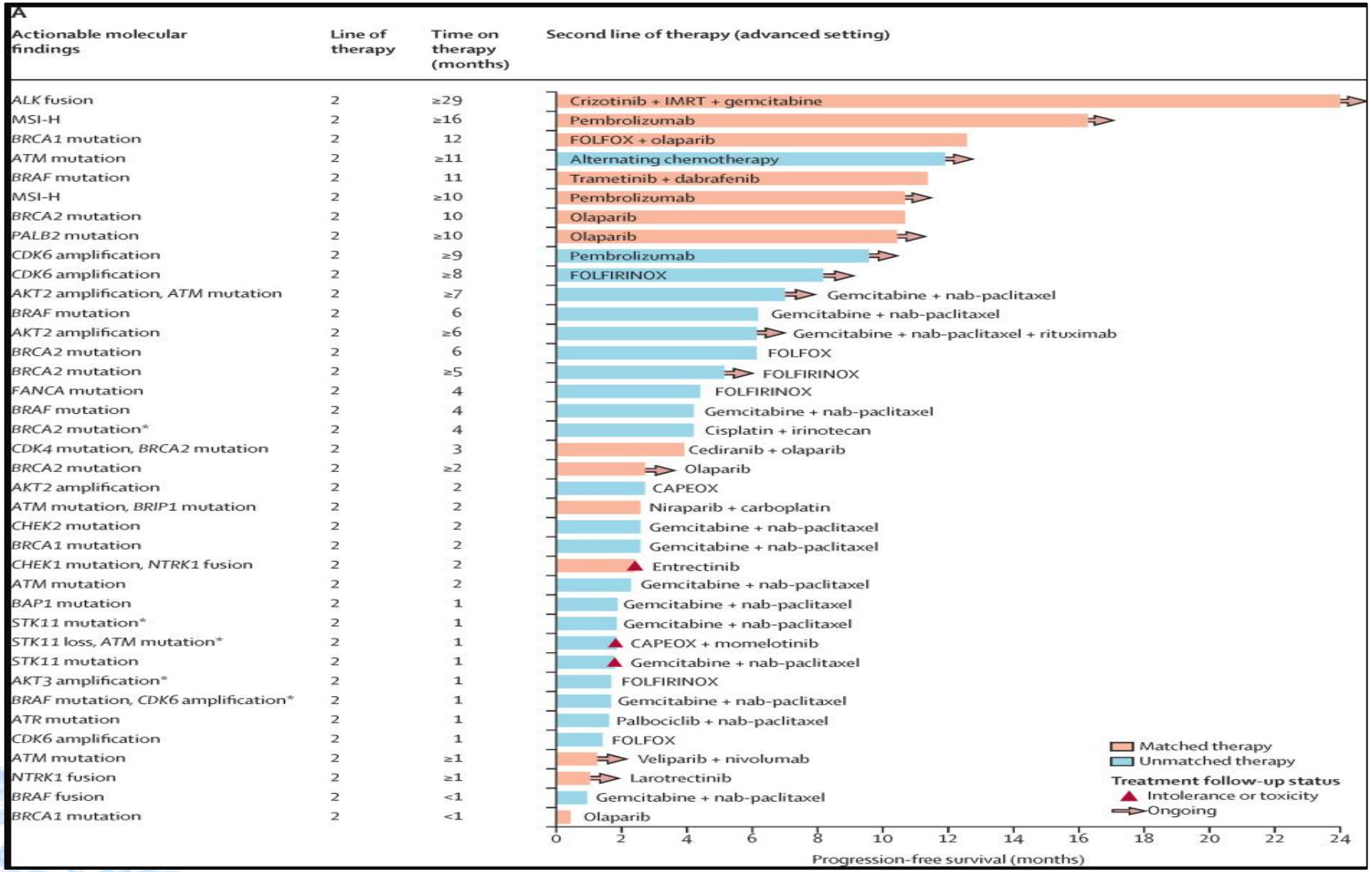
KRAS^{WT} PDAC (~5%-8%)

Rare Important Oncogenic Drivers beyond *RAS*



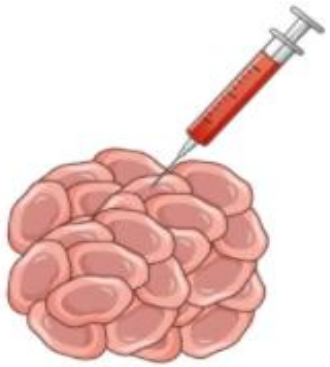
Singhi AD et al. *Gastroenterology*. 2019;156(8):2242-2253.e4;
Varghese AM et al. *J Natl Cancer Inst*. 2021;113(9):1194-1202;
Lee MS and Pant S. *Am Soc Clin Oncol Educ Book*. 2021;41:1-13;
Philip PA et al. *Clin Cancer Res*. 2022;28(12):2704-2714;
Singh H et al. *Clin Cancer Res*. 2023;29(22):4627-4643;
Varghese AM et al. *Nat Med*. 2025;31(2):466-477.

Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor registry trial



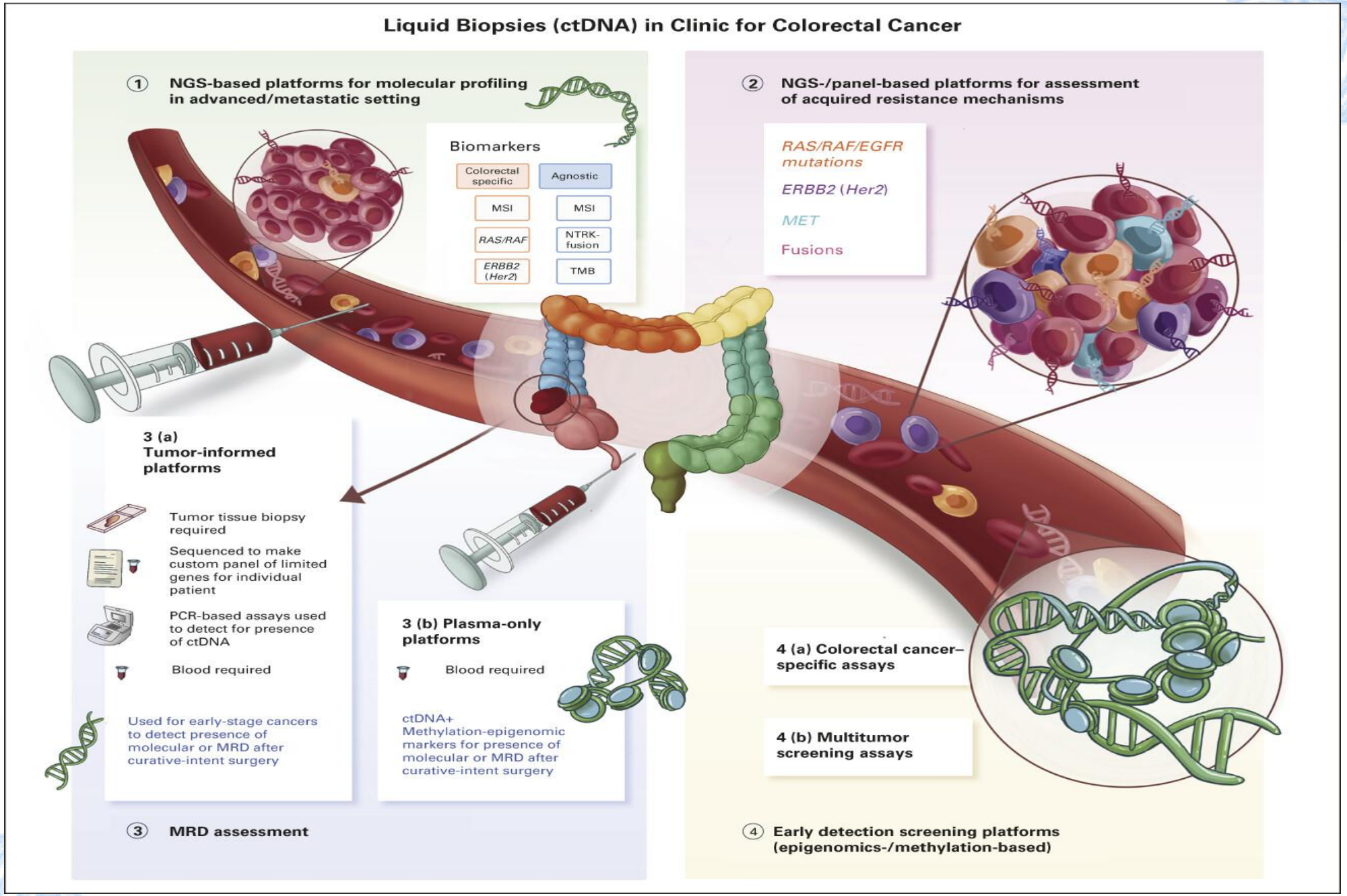
Pishvaian M et al Lancet Oncology , 2020.

Tumor vs. Liquid biopsy

		At metastatic diagnosis	After subsequent lines of therapy
Tumor biopsy 	Advantages	• Key pathological information • Ability to assess non-DNA biomarkers (protein, RNA, etc)	• Important for research and discovery • Critical if assessment of non-DNA biomarkers needed
	Disadvantages	• Longer turnaround time for sequencing limits first-line precision-therapy selection • Limited tissue quantities can constrain breadth of testing or cause assay failure	• Requires repeat invasive procedure • Longer turnaround time for sequencing results may hinder rapid selection of therapy
Liquid-biopsy cfDNA 	Advantages	• High concordance with tissue biopsy • Ready sample availability • Rapid turnaround to facilitate first-line precision-oncology therapies • Baseline for subsequent liquid biopsy	• Non-invasive, easy to obtain serial samples • Captures heterogeneous resistance alterations • Rapid turnaround can enhance clinical-trial enrollment
	Disadvantages	• Parallel assessment with tumor testing increases cost • Cannot assess non-DNA biomarkers	• Cannot assess non-DNA biomarkers

Advantages and disadvantages of tumor biopsy versus liquid biopsy at the time of metastasis diagnosis or after subsequent lines of therapy.

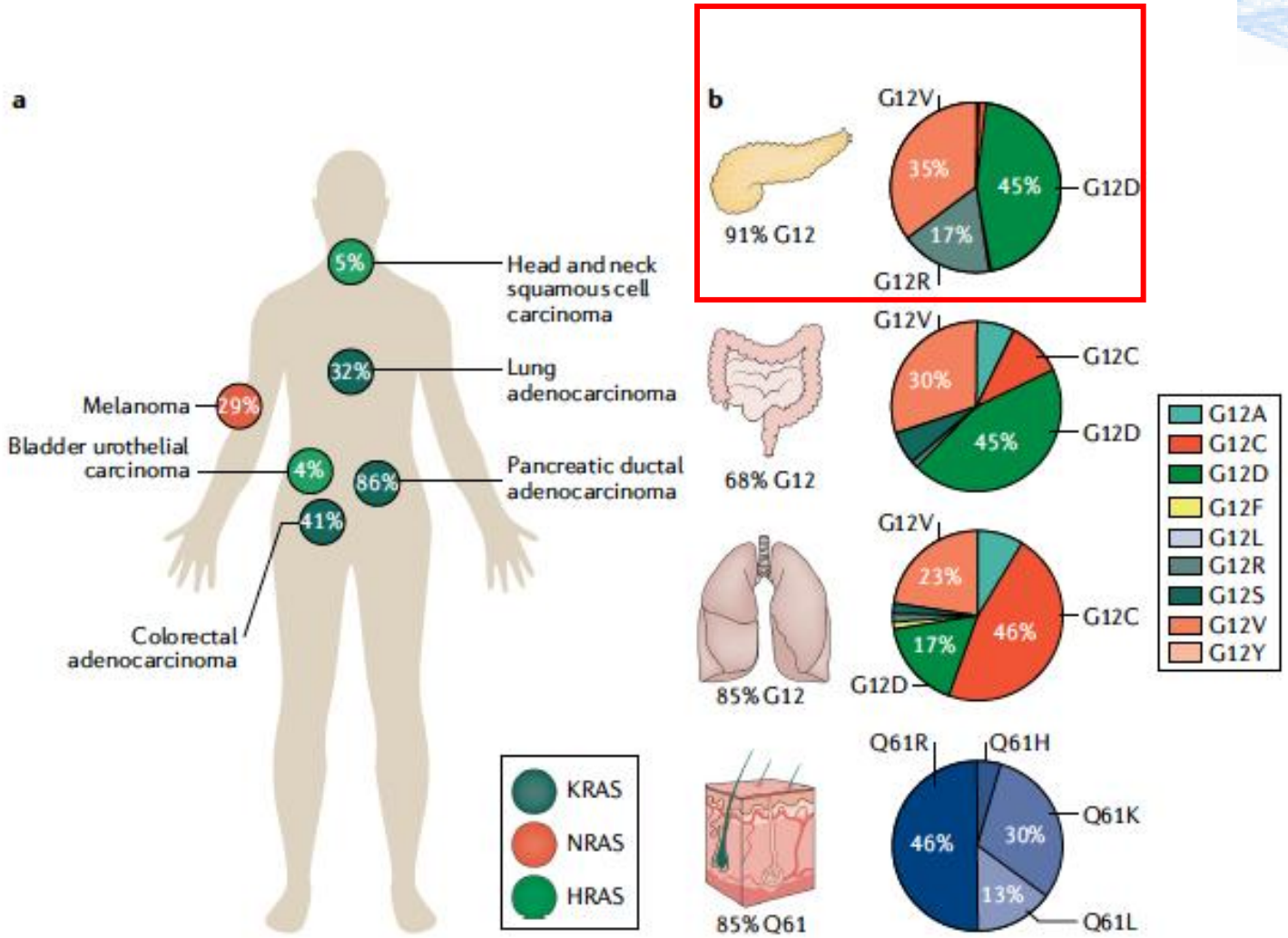
Corcoran RB. *Nature Medicine* , 2020.



Malla et al . JCO 2022

Targeting RAS mutations

Frequency and Distribution of RAS mutations in Cancer

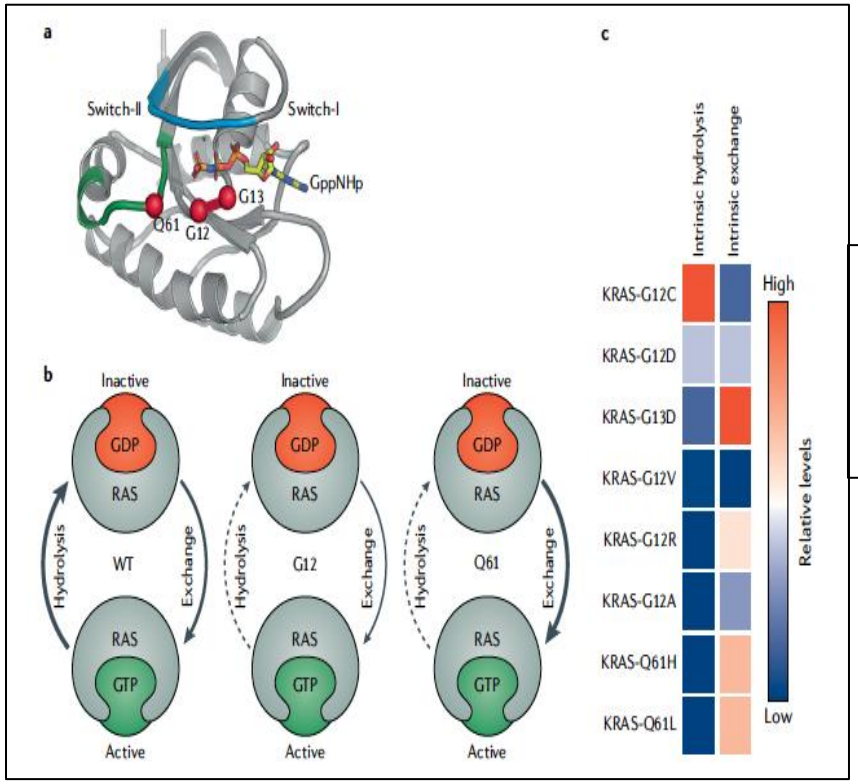


- *KRAS* is the most mutated oncogene in human cancer
- **Directly** inhibiting RAS is a desirable approach for treating RAS- mutant tumors

Moore et al. Nature 2020

Why Has KRAS Been Considered Undruggable?

- Efforts to target KRAS have been unsuccessful due to:
  - Its small binding pocket, high affinity for GTP
  - Redundant mechanisms of posttranslational processing.
- The first signs of the dawn appear on the horizon for one specific mutation, KRAS (G12C).
  - Unlike G12D and G12V, G12C can maintain alternative interactions with its downstream effectors through an active cycle between the GDP-bound and GTP-bound states



Intrinsic GTPase and GDP–GTP exchange rates can vary among the different RAS mutants and this observation may offer insight into how to best target each mutant

Huang L et al, Signal Transduct Target Ther 2021; 6(1):386

Moore et al. Nature 2020

Targeting KRAS G12C mutations in Pancreas cancer

PDAC: *KRAS* G12Ci (Glycine → Cysteine): Summary

	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
Hollebecque, A. Gastrointestinal Cancers Symposium, 2024

Li, J. Gastrointestinal Cancers Symposium, 2024

Extending the breadth of RAS inhibitors

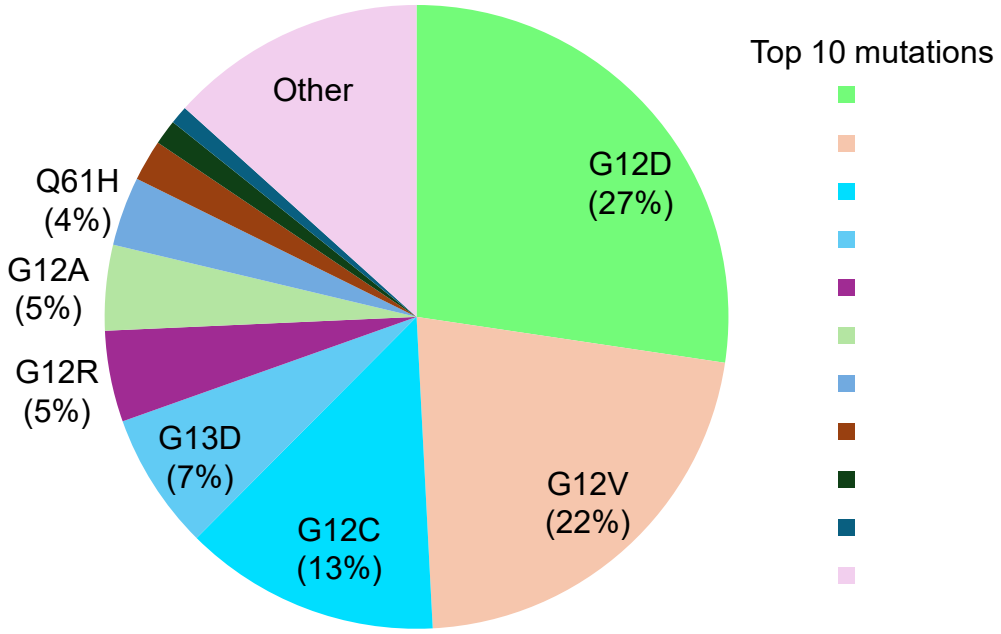
More KRAS Inhibitors in the Pipeline: Beyond $KRAS^{G12C}$

Approved
Recruiting
Active, not recruiting
Completed
Preclinical

Adagrasib/MRTX849
BBO-8520
BI 1823911
BPI-421286
D-1553
D3S-001
Divarasib/GDC-6036
GEC255*
GH35
Glecirasib/JAB-21822
HBI-2438
HS-10370
IBI351/GFH925
JNJ-74699157
LY3537982
MK-1084
Opnurasib/JDQ443
RMC-6291
Sotorasib/AMG520
YL-15293

- $KRAS^{G12C}$
- $KRAS^{G12D}$: ASP3082, BI-2852, ERAS-4, HRS-4642, JAB-22000, MRTX1133, QTX3046, RMC-9805
- $KRAS^{G13C}$: RMC-8839
- $KRAS^{Q61H}$: RMC-0708
- $KRAS^{WT/X}$: BBP-454, BI-2493, BI-2865, JAB-23400, QTX2024, RMC-6236, RSC-1255

KRAS mutations: all cancers



ClinicalTrials.gov

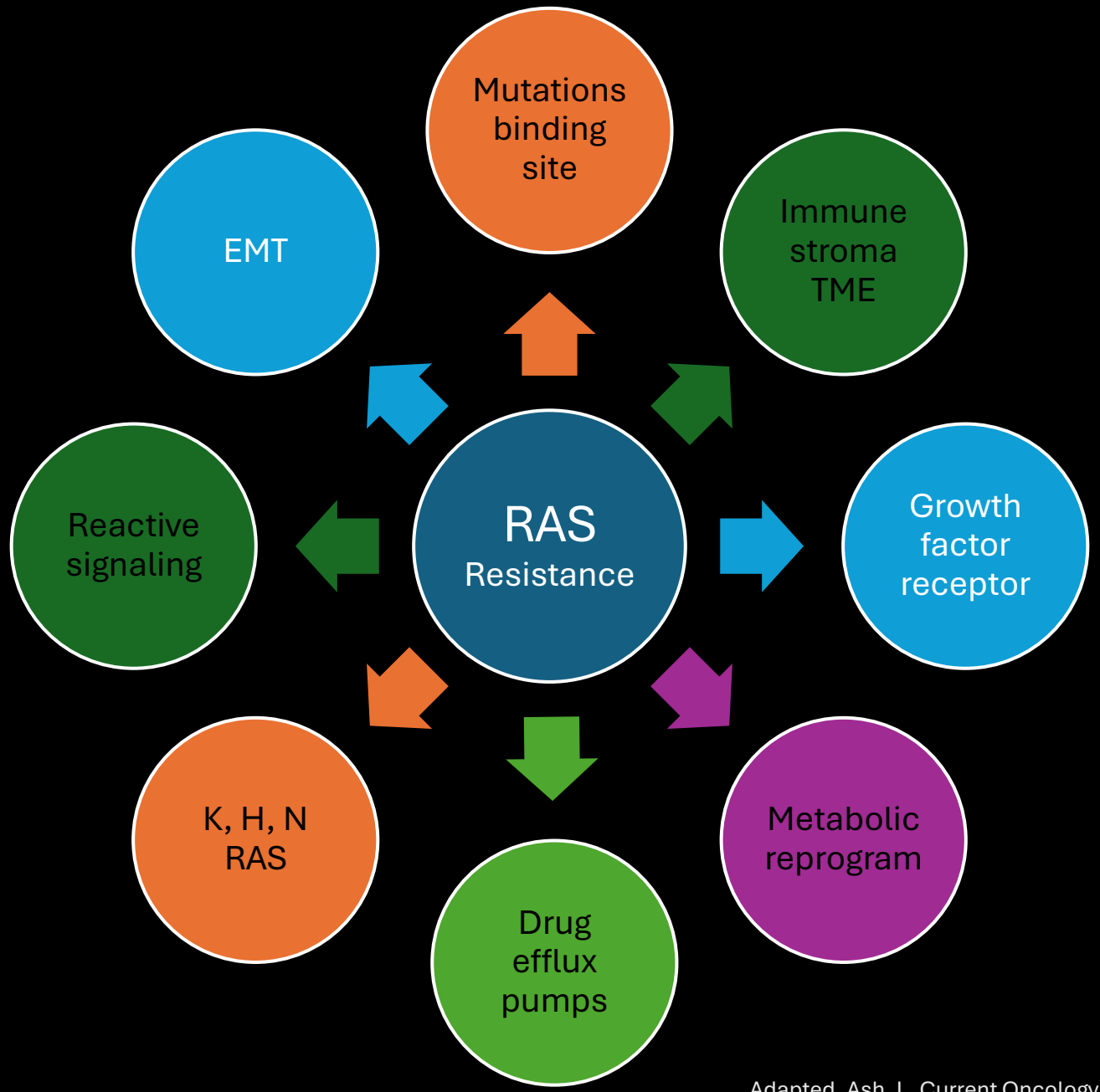
Courtesy: C Der

cBioPortal FOR CANCER GENOMICS GENIE Cohort v13.0

Diverse KRAS Resistance Mechanisms

- Genetic resistance
  - Mutations switch II binding site
  - Copy # alterations in *KRAS*
  - Mutation by cis, trans of *KRAS*
  - Activating mutations downstream *PIK3CA, BRAF, MEK*
  - Activating mutations *NRAS, HRAS*

- Non-mutational resistance
  - Rapid adaptive resistance
  - Reactivation of RAS-MAPK signaling
  - EMT
  - Cell-state transition
  - Tumor microenvironment
  - Drug efflux pumps

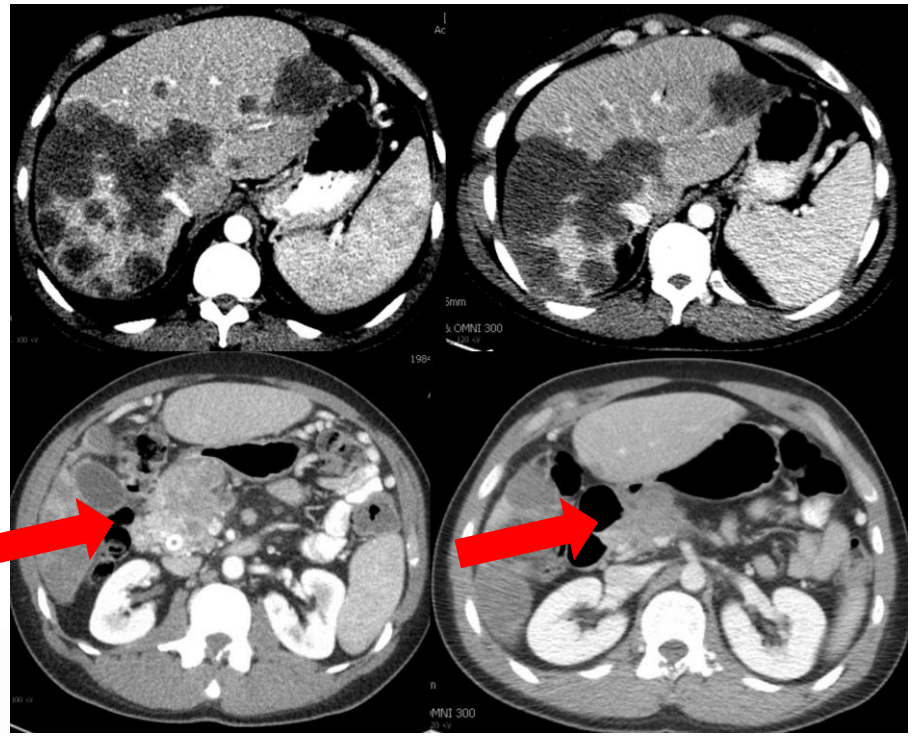


Adapted, Ash, L. Current Oncology, 2024

Targeting the WT and Other

Young Man PDAC *KRAS*-WT *NRG1(+)* Fusion

Bispecific, IgG1 mAb ADCC inhibits HER2, HER3



Baseline
Ca 19-9 ~450

T+ 2 m
Ca 19-9 <50

Features *NRG1*(+) PDAC Tumors

Younger patients/ early onset PDAC
KRAS wild-type
Low Ca 19-9, disease bulk

Can respond well to chemotherapy

Testing methodology key:
DNA, RNA

Schram AM et al. ASCO 2021. Abstract 3003;
Varghese AM et al. *J Natl Cancer Inst*. 2021;113(9):1194-1202;
Singhi AD et al. *Gastroenterology*. 2019;156(8):2242-2253.e4;
Schram AM et al. *Cancer Discov*. 2022;12(5):1233-1247;
Schram AM et al. *N Engl J Med*. 2025;392(6):566-576.

BRAF Alterations, Class, Actionability (2%-3% PDAC)

Enriched *RAS*-Wild Type PDAC, Acinar Cancer

BRAF Alteration/Class	Example	Treatment	Notes
BRAF Exon 15 (Class I; ~20%)	*BRAF* V600E	BRAF inhibitors +/- MEKi	RAS independency
BRAF Exon 11 (Class II; ~50%)	*BRAF* N486-P490del +no other drivers	BRAF inhibitors +/- MEKi	In-frame deletion
BRAF/RAF Fusions (~20%)	*SND1:BRAF* fusion +no other drivers	Pan-RAF inhibitors +/- MEKi	Acinar cancer
Other Alterations (Class III)	+*RAS* drivers	Not actionable; RAS dependency	No kinase activity

<u>Class I V600E</u>

Phase II Basket: Dabrafenib/trametinib
NCI MATCH EAY-131-H (NCT02465060)
ROAR (NCT02034110)
N= 131 /24 cancer types/ PR/CR ~40%

Hyman DM et al. *N Engl J Med.* 2015;373(8):726-236;

Singhi AD et al. *Gastroenterology.* 2019;156(8):2242-2253.e4;

Salama AKS et al. *J Clin Oncol.* 2020;38(33):3895-3904;

Subbiah V et al. *Nat Med.* 2023;29(1):49-58;

Ciner AT et al. *Mol Cancer Res.* 2023;21(4):293-300.

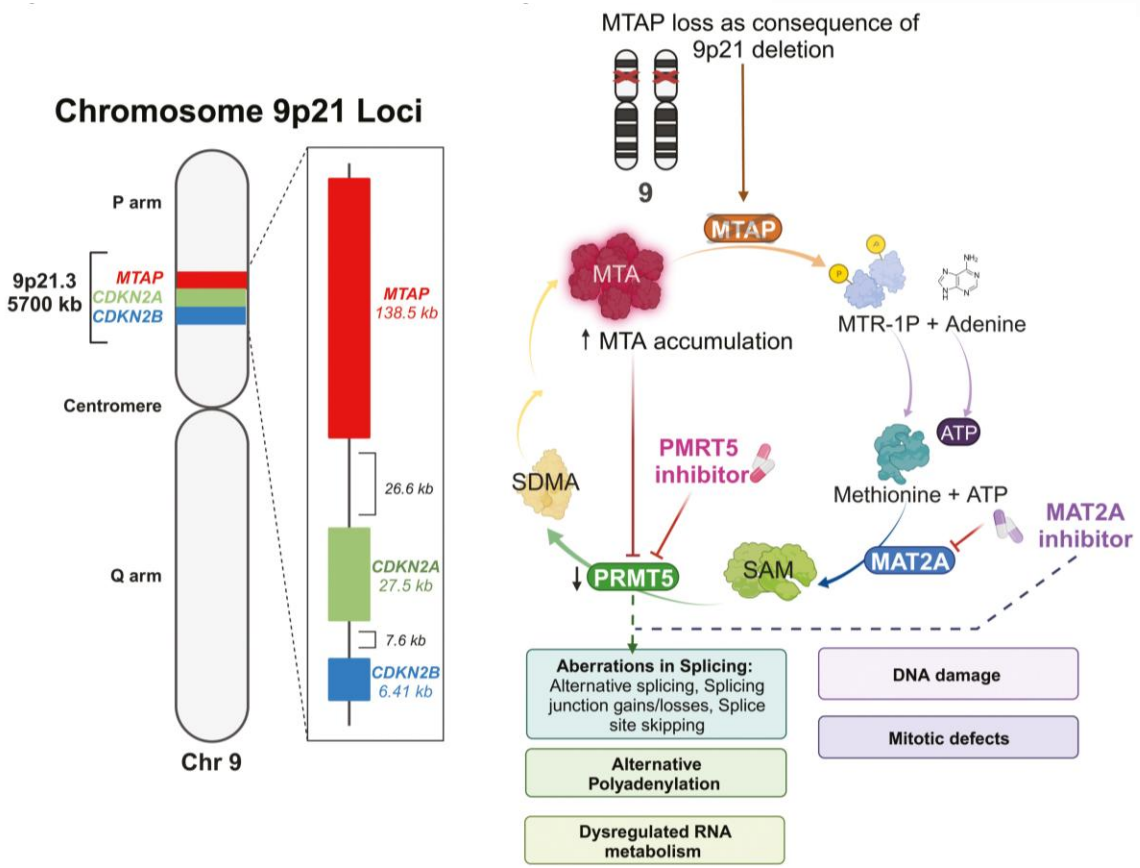
Hendifar A et al. *JCO Precis Oncol.* 2021:5:PO.20.00494.

Singh H et al. *Clin Cancer Res.* 2023;29(22):4627-4643.

Synthetic Lethality: PRMT5, MTA Inhibition

Common Target in GI Cancers

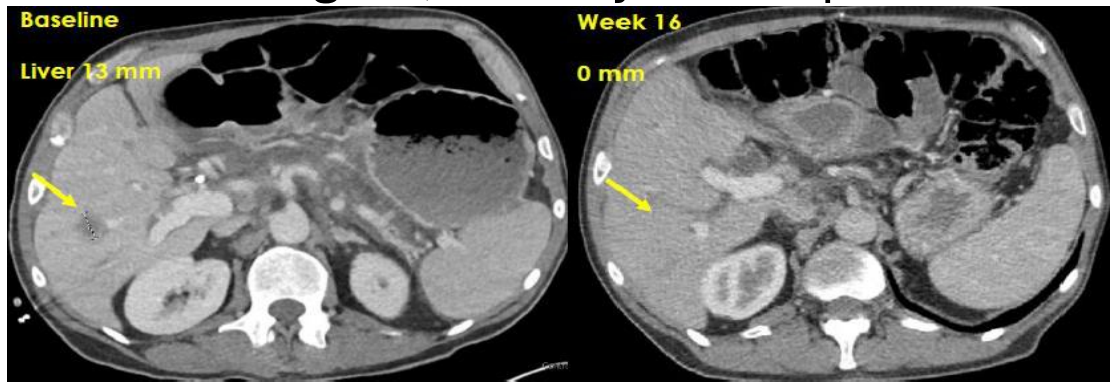
- Methylthioadenosine phosphorylase (*MTAP*)
- *MTAP* deletion/loss ~15% multiple solid tumors; 8% GI cancers; PDAC 15%-25%
- *MTAP* often co-deleted *CDKN2A* (9p21)
- *MTAP, CDKN2A* associated resistance to IO therapies ('cold' TME)
- *MTAP*-loss novel biomarker for agents inhibiting MAT2A and PRMT5



Ngoi NYL...Ahnert JR et al. *Oncologist*. 2024;29(6):493-503;
Stopa N et al. *Cell Mol Life Sci*. 2015;72(11):2041-2059;
Rodon J et al. AACR-EORTC-NCI 2023. Abstract PR006.
Gorboken N et al. *Cancers*. 2025;17(7):1205;
Guo JA...Aguirre AJ et al. *Cell Rep*. 2025;44(9):116191.

MTAP-Deleted Solid Tumors: Phase I AMG 193 (2nd Gen)

MTD 1200 mg PO; Efficacy in Multiple Solid Tumors

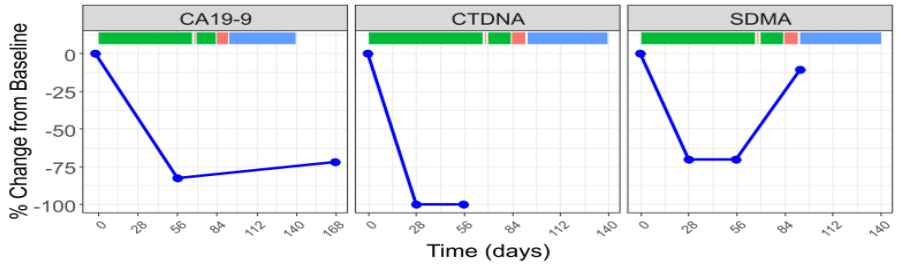


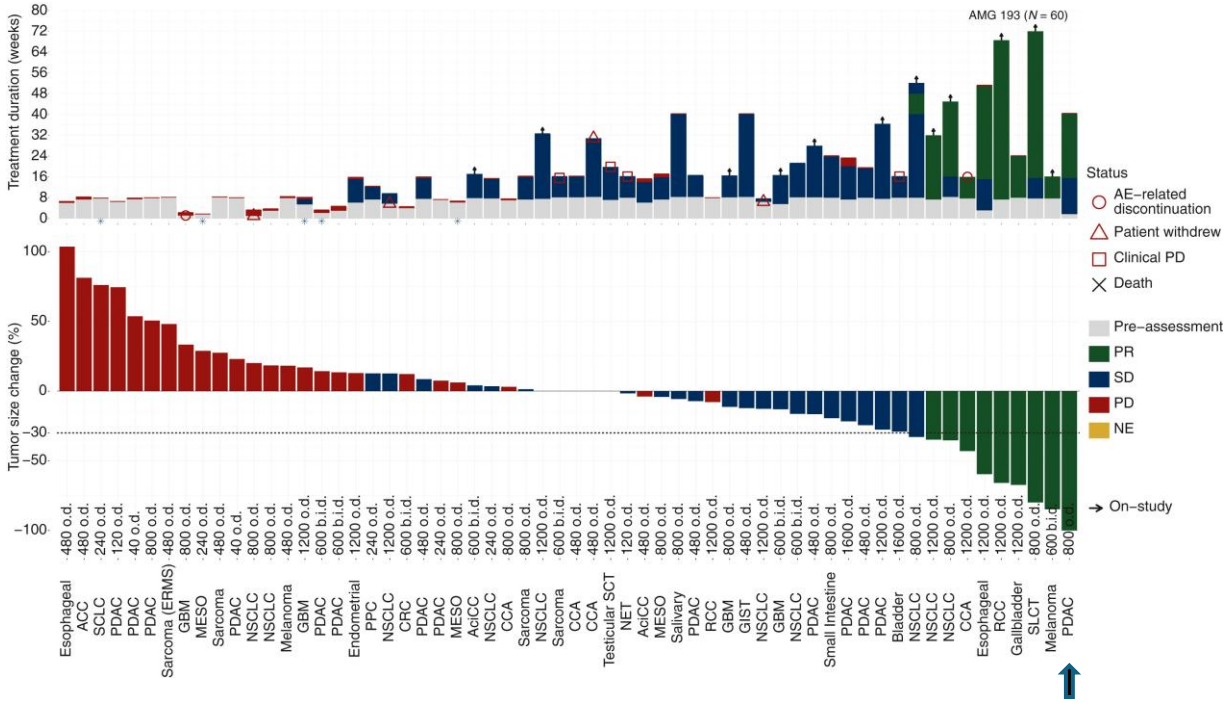
PDAC

65 y/o male

2 prior lines

- *TP53m*
- *CDKN2A/2B*-loss, *MTAP*-loss
- *KRAS*





- ESMO 2024 PDAC sub-cohort N= 23: 5 PR's (2 confirmed); 4 SD
- Multiple PRMT5, MAT2A agents/combinations in development

Rodon J et al. AACR-EORTC-NCI 2023. Abstract PR006;
Sacher A et al. ESMO 2024. Abstract 604O.
Rodon J…O'Neil B et al. *Ann Oncol*. 2024;35(12):1138-1147.

PDAC: Standard Therapy & Genomically Defined 2025 →

All patients: Germline (multigene panel), Somatic testing (+/-ctDNA)

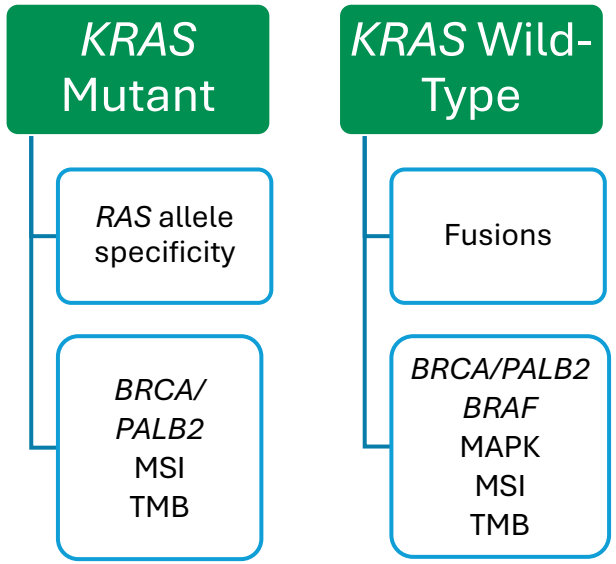
Untreated mPDAC ECOG 0-1	*KRAS* Mutated# (90%+)	*KRAS* Wild-Type (4-8%)	g/s*BRCA1/2* (+*RAD51C/D, PALB2*); MSI-H, TMB ≥10

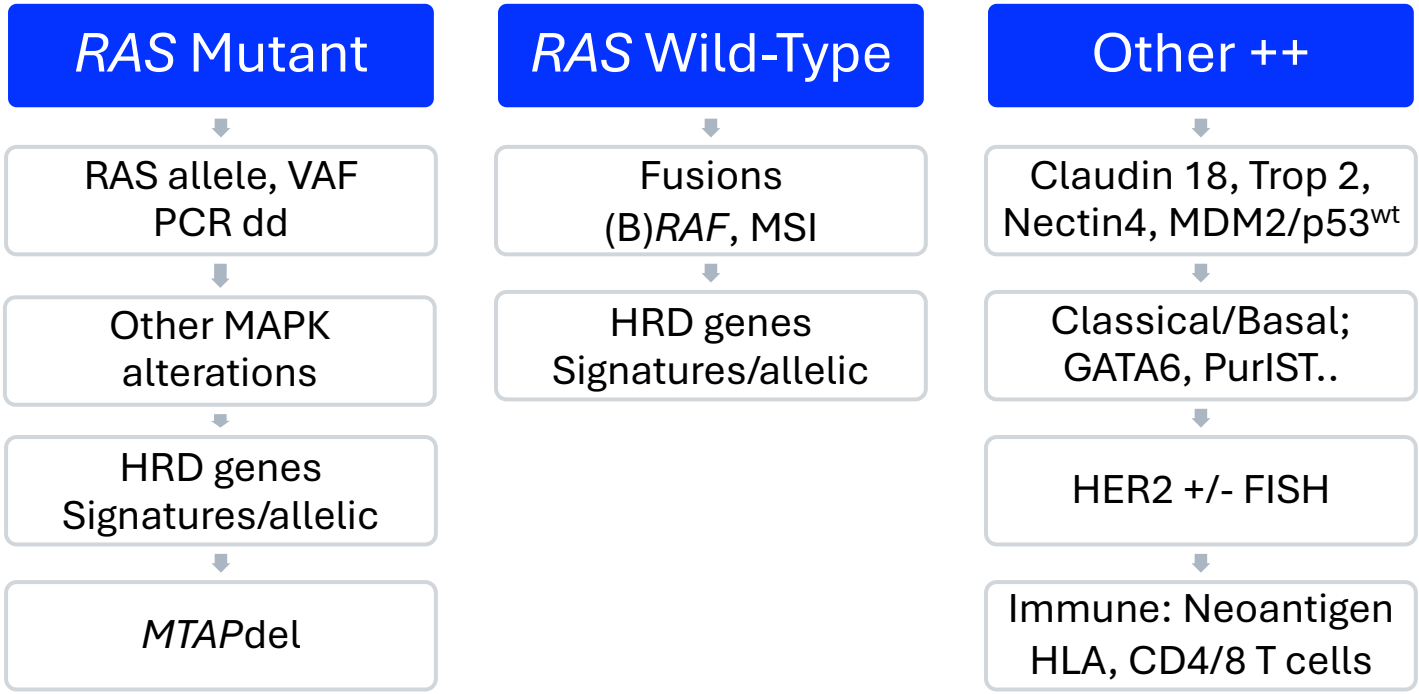
• Clinical trial (preferred)
• (m)FOLFIRINOX
• NALIRIFOX
• Gemcitabine/nab-paclitaxel
 	
• Maintenance
  • FOLFIRI
  • 5-FU/LV
  • Capecitabine
	• G12C (1%)
	Sotorasib*
	Adagrasib*
	
	• G12D (35%), G12V (30%), G12R (15%)
	Allele specific
	Pan RAS/all RASi
	
	Small molecule
	Vaccines
	Protein degraders (PROTACs)
	Other
		• MAPKinase pathway
		BRAF V600E
		HER2
		
		• Fusions (0.3-0.5% each)
		RET, ALK, ROS, FGFR2/3, MET, NRG-1, NTRK*, BRAF*, ERBB4*
		
		Erlotinib#
		Selpercatinib#
		Zenocutuzumab
		Entrectinib#
		Larotrectinib#
		Dabrafenib/trametinib#
		Trastuzumab deruxtecan#
			• (m)FOLFIRINOX#
			• Cisplatin/gemcitabine#
			• NALIRIFOX#
			
			• Maintenance
			Olaparib*
			Rucaparib**
			• Ipilimumab/nivolumab?
			
			• Immune therapy
			Nivolumab#
			Pembrolizumab#
			Dostarlimab#

#Guideline endorsed/not FDA approved; *Disease agnostic approvals; **Guideline endorsed

Maximizing Genomic Data: Tumor + cfDNA… At Diagnosis

- Today: **Minimum** Requirements
- Tomorrow: **Ideal/ Future** State





Germline; Tumor NGS +/- cfDNA;
+/- RNA seq/IHC; TMB
At diagnosis; Stage agnostic