

Hot Topics in Colorectal Cancer: Targeted Therapies and Relevant Clinical Trials

YOCRC Patient Conference

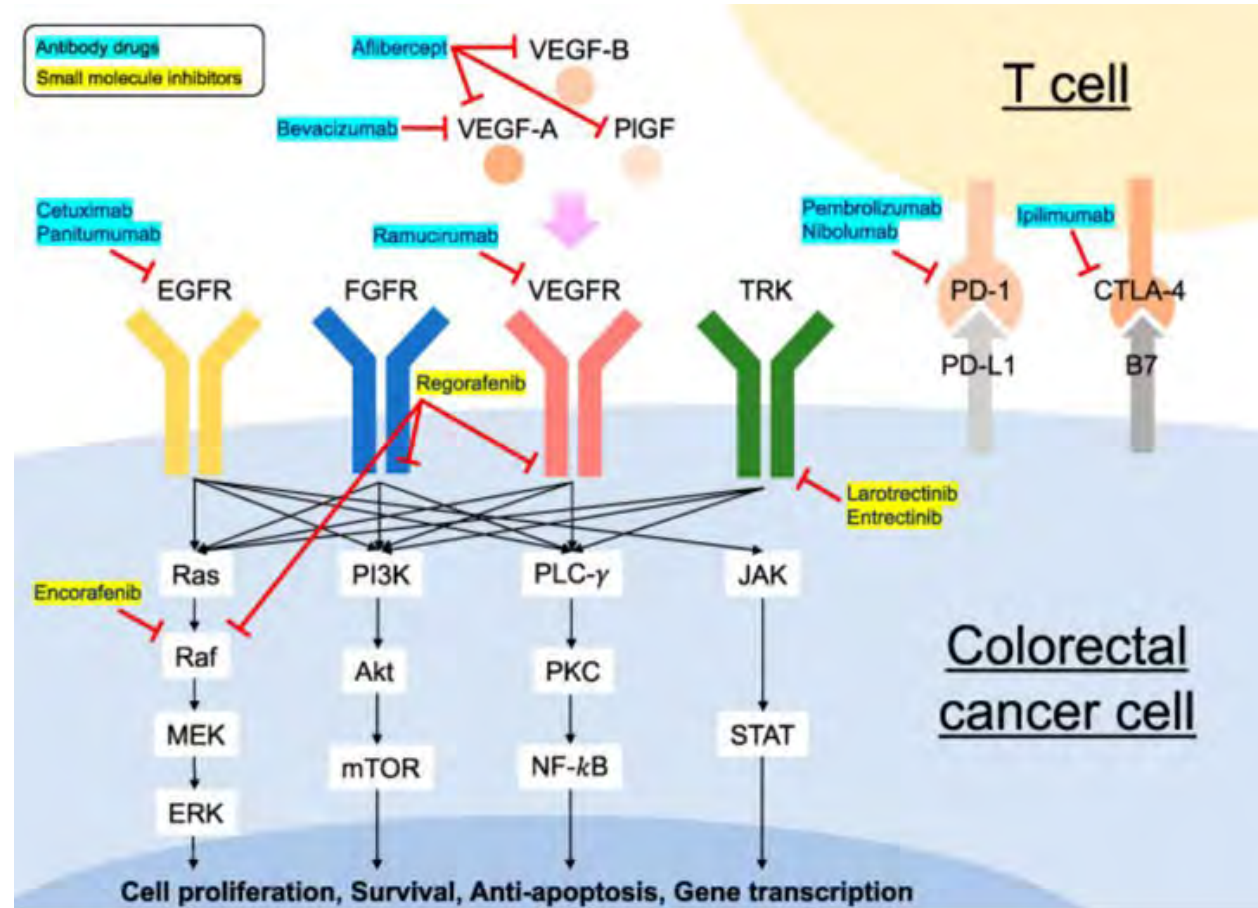
May 3, 2025

Victoria Higbie, MD

Overview

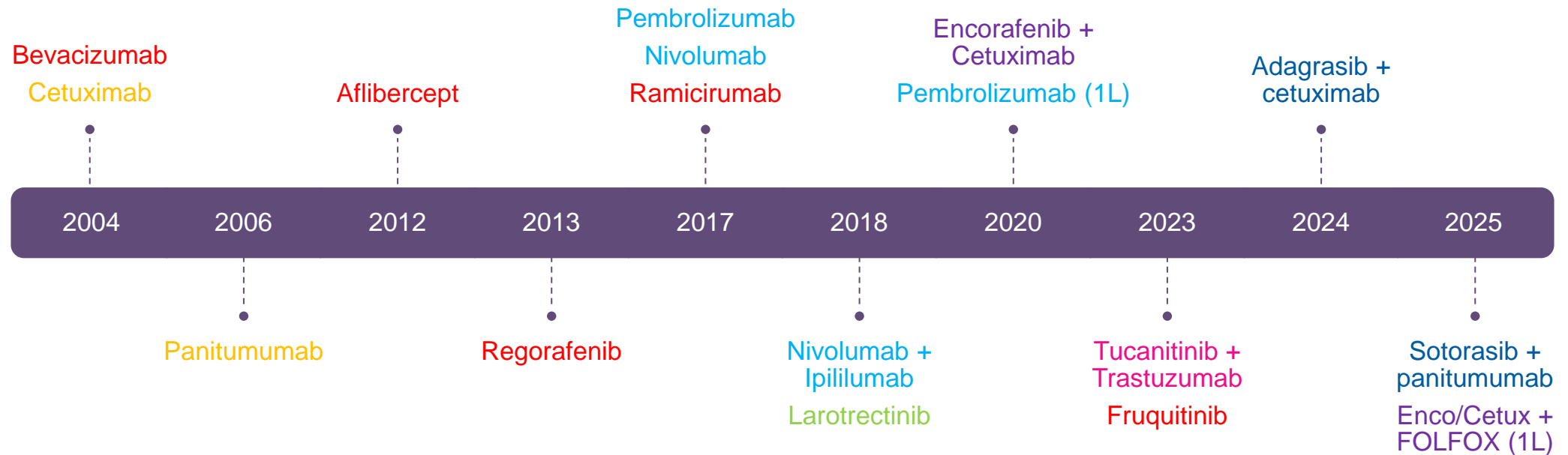
- **Review of molecular testing**
- **Targetable mutations: current therapies & clinical trials**
 - Anti-EGFR
 - MSI-H/dMMR
 - BRAF V600E
 - KRAS mutations: G12C, G12D, and beyond
 - Others
- **Navigating the world of clinical trials**

Targeted Therapies in CRC



• Ohishi et al, Int J Mol Sci, 2023.

Targeted Therapies in CRC- Timeline



- Anti-VEGF
- Anti-EGFR
- Immune Checkpoint Inhibitor
- TRK Inhibitor
- Anti-BRAF
- Anti-Her2
- KRAS G12C Inhibitor

Molecular Testing in CRC

- ALL patients:
 - dMMR/MSI-H
- ALL unresectable/metastatic patients:
 - KRAS/NRAS (expanded panel)
 - BRAF (V600E)
 - dMMR/MSI-H
 - Her2 amplification

Example of Molecular Testing

B. ACTIONABLE FINDINGS (for details, see D. Clinical Interpretation)

Signature	Result	Actionability	Level of Evidence
Tumor mutational burden (TMB)	6 mut/Mb	n/a	n/a
Microsatellite instability (MSI)	MSS	n/a	n/a

Tier 1 – Somatic variants of strong clinical significance (e.g. FDA label or Guideline-recommended in this tumor type):

Gene	Alteration	Type	Location	VAF	Actionability	Evidence
KRAS	p.G12D c.35G>A	Missense	Exon 2	44%	Resistance	FDA

Tier 2 – Somatic variants of potential clinical significance (e.g. FDA label or Guideline-recommended in another tumor type):

None identified

Pertinent Negatives (i.e. ordered genes where Tier 1/2 annotated mutations were *not* detected):

BRAF, NRAS, PIK3CA

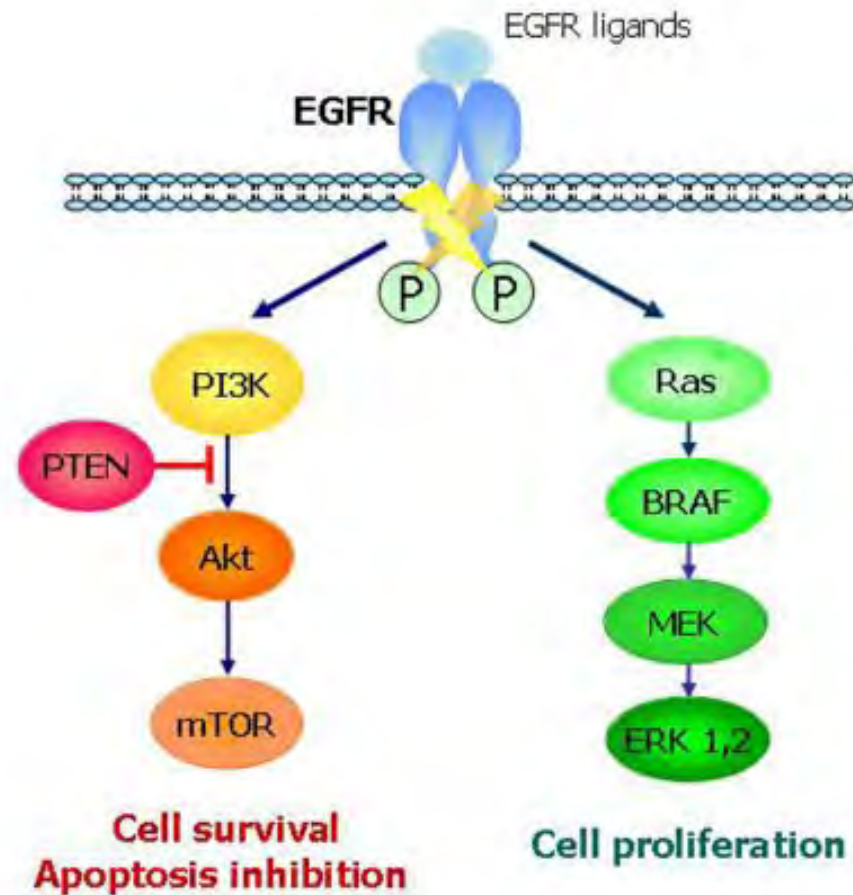
C. ADDITIONAL FINDINGS

Additional somatic variants (e.g. potentially actionable variants, or variants of unknown [Tier 3] or benign [Tier 4] clinical significance):

Gene	Alteration	Type	Location	VAF
ALK	p.R412C c.1234C>T	Missense	Exon 5	51%
CARD11	p.S547Y c.1640C>A	Missense	Exon 12	20%
CCND2	Amplification	CNV	12p13.32	n/a
CTNNB1	p.D583V c.1748A>T	Missense	Exon 11	41%
CTNNB1	p.? c.1955-1G>A	Splice?	Splice? (Intron 12)	43%
ERCC3	p.D25N c.73G>A	Missense	Exon 2	13%
FANCI	p.? c.2623+1G>T	Splice?	Splice? (Intron 24)	26%
FGF6	Amplification	CNV	12p13.32	n/a
H2AX	p.R82C c.244C>T	Missense	Exon 1	18%
KDM5A	Amplification	CNV	12p13.33	n/a
NOTCH4	p.D823Y c.2467G>T	Missense	Exon 16	60%
RAD52	Amplification	CNV	12p13.33	n/a
SOX10	p.T437M c.1310C>T	Missense	Exon 4	26%
SYK	p.Q337H c.1011G>C	Missense	Exon 9	44%
TBX3	p.? c.1040-2A>T	Splice?	Splice? (Intron 5)	24%
TP53	p.R282W c.844C>T	Missense	Exon 8	60%
TSC1	p.G1108D c.3323G>A	Missense	Exon 23	46%
WT1	p.G178R c.532G>A	Missense	Exon 1	44%

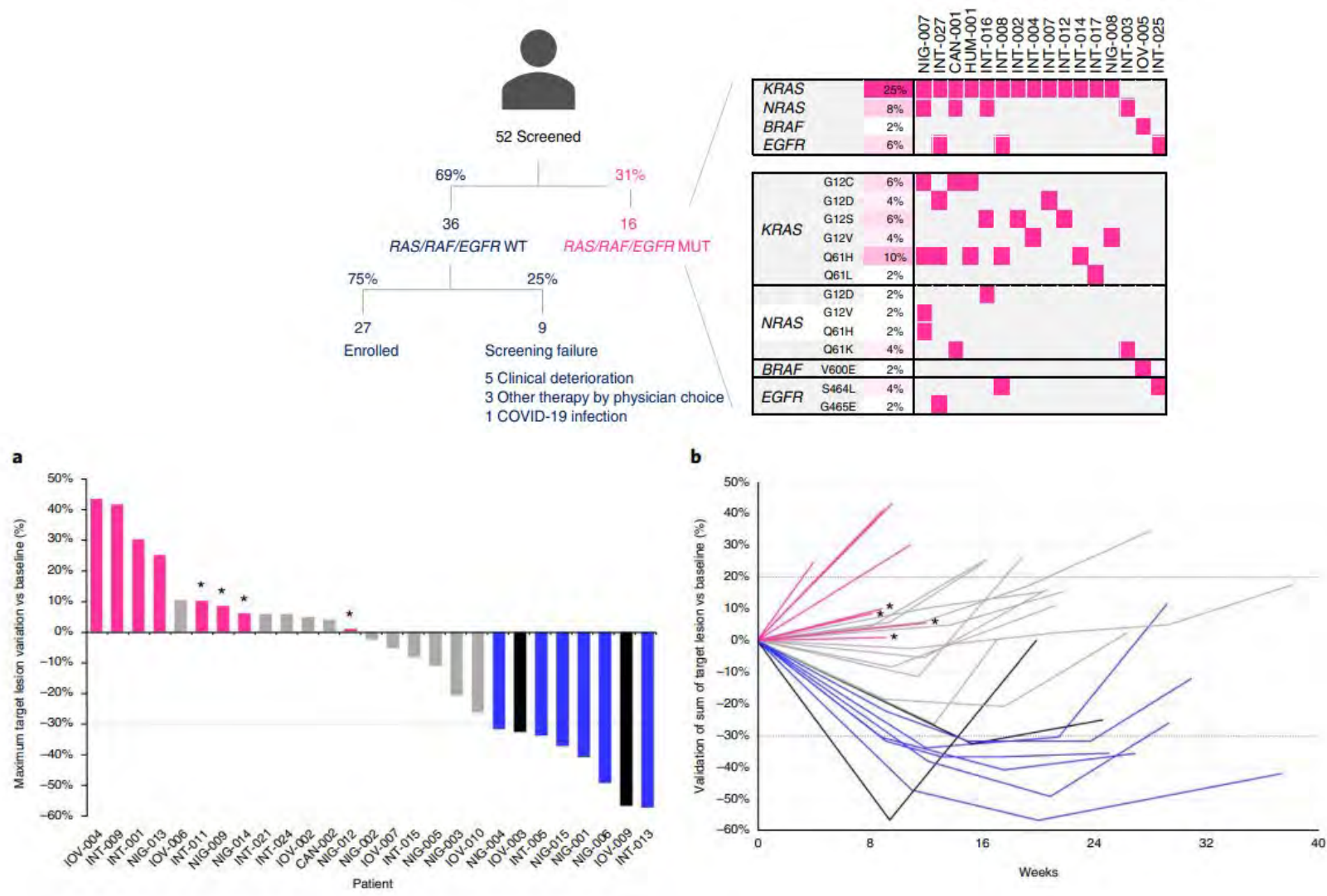
Anti-EGFR Monoclonal Antibodies

- Cetuximab
- Panitumumab
- In combination with chemotherapy
- KRAS/NRAS, BRAF WT
- Left Sided > Right Sided



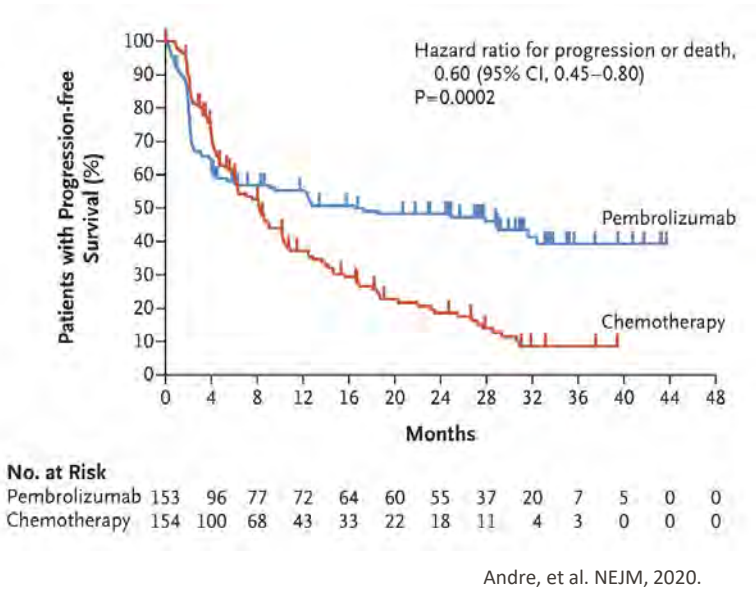
Saletti, et al. GI Cancers: Targets and Therapy. 2015.

Anti-EGFR- Future Directions

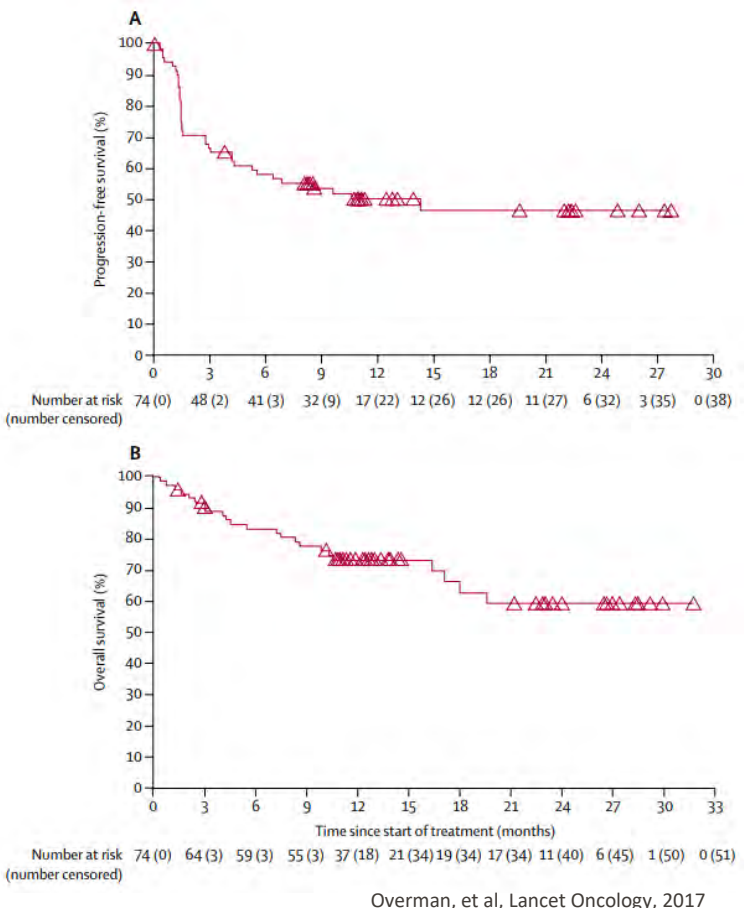


Immunotherapy- MSI-H/dMMR

Keynote 177- Pembrolizumab

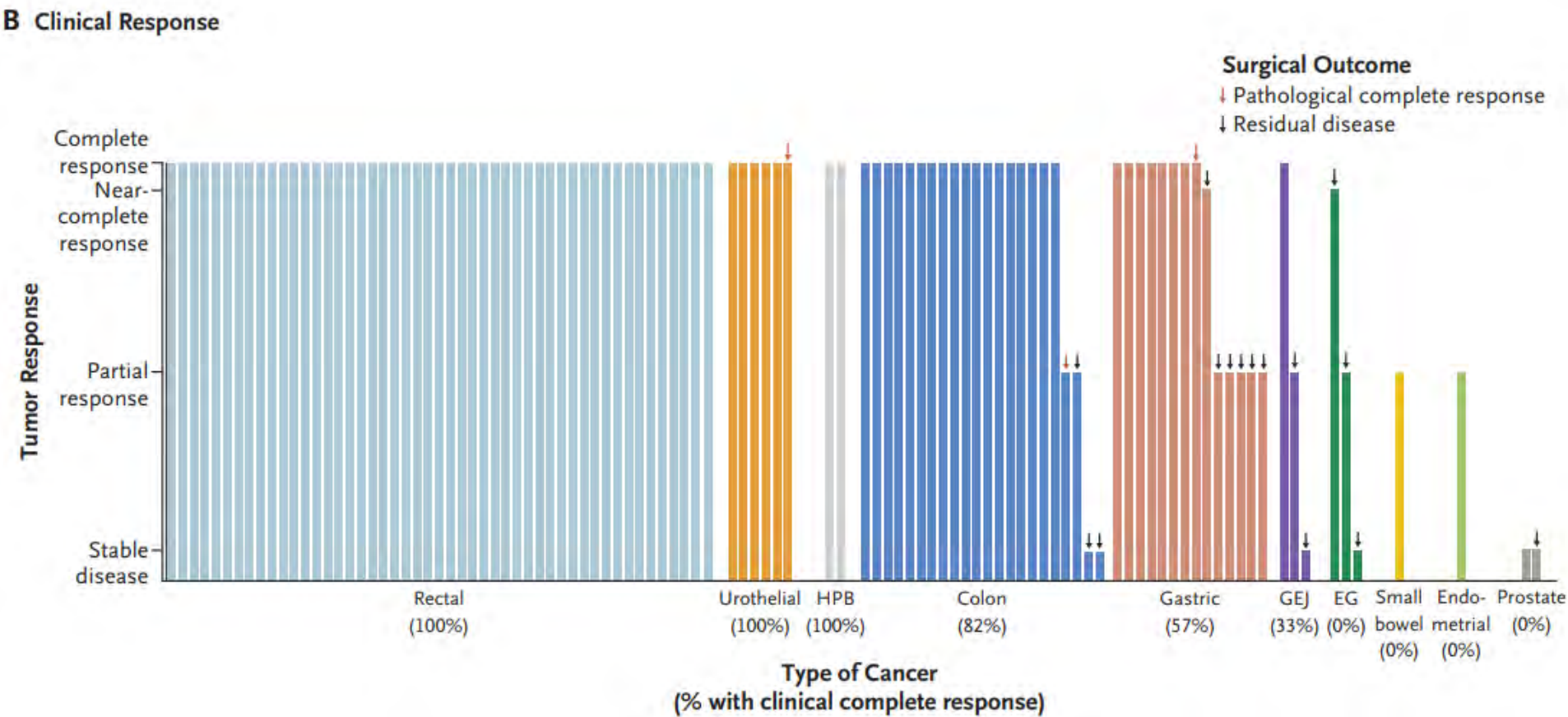


Checkmate 142- Nivolumab +/- Ipililumab





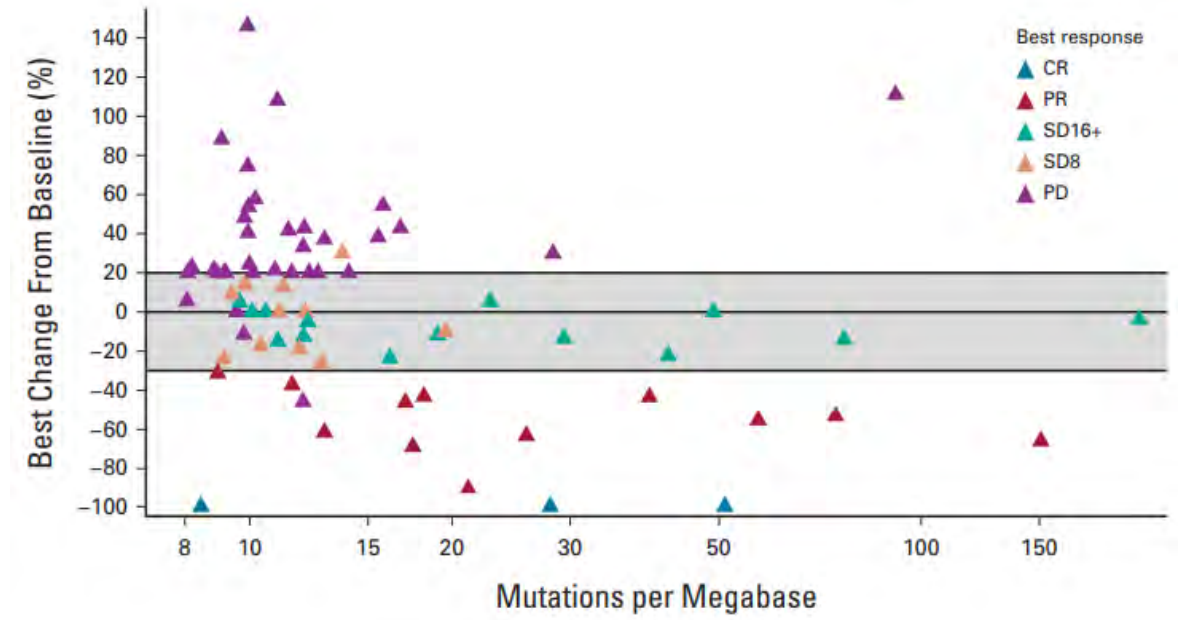
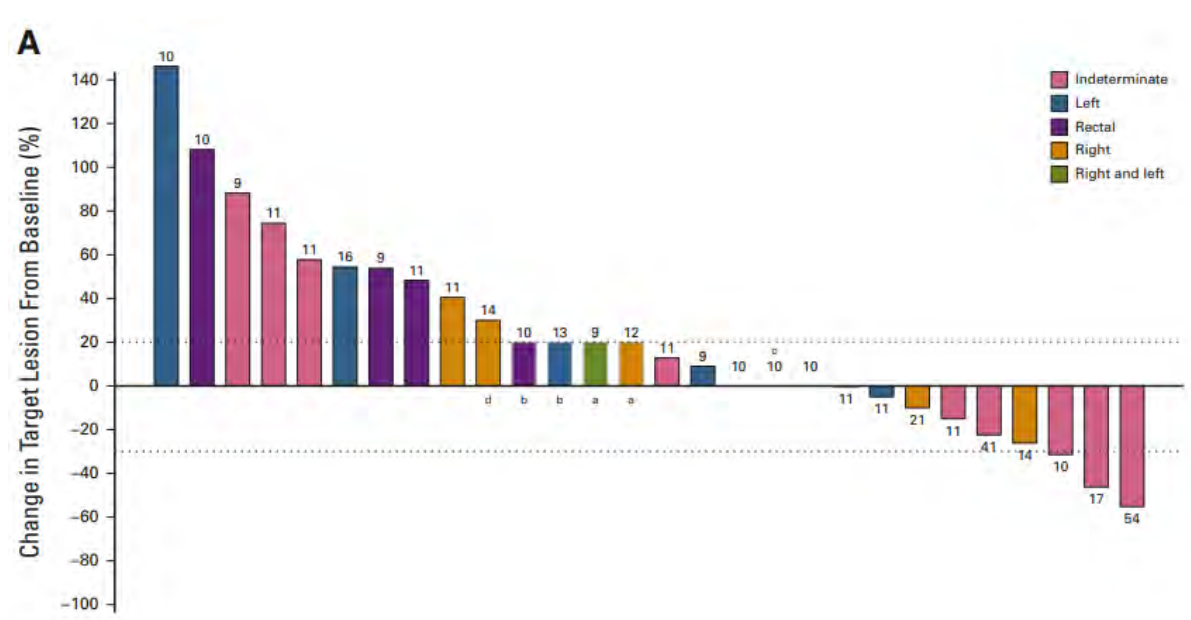
Immunotherapy- Localized MSI-H/dMMR



Cercek, et al. NEJM. 2025.



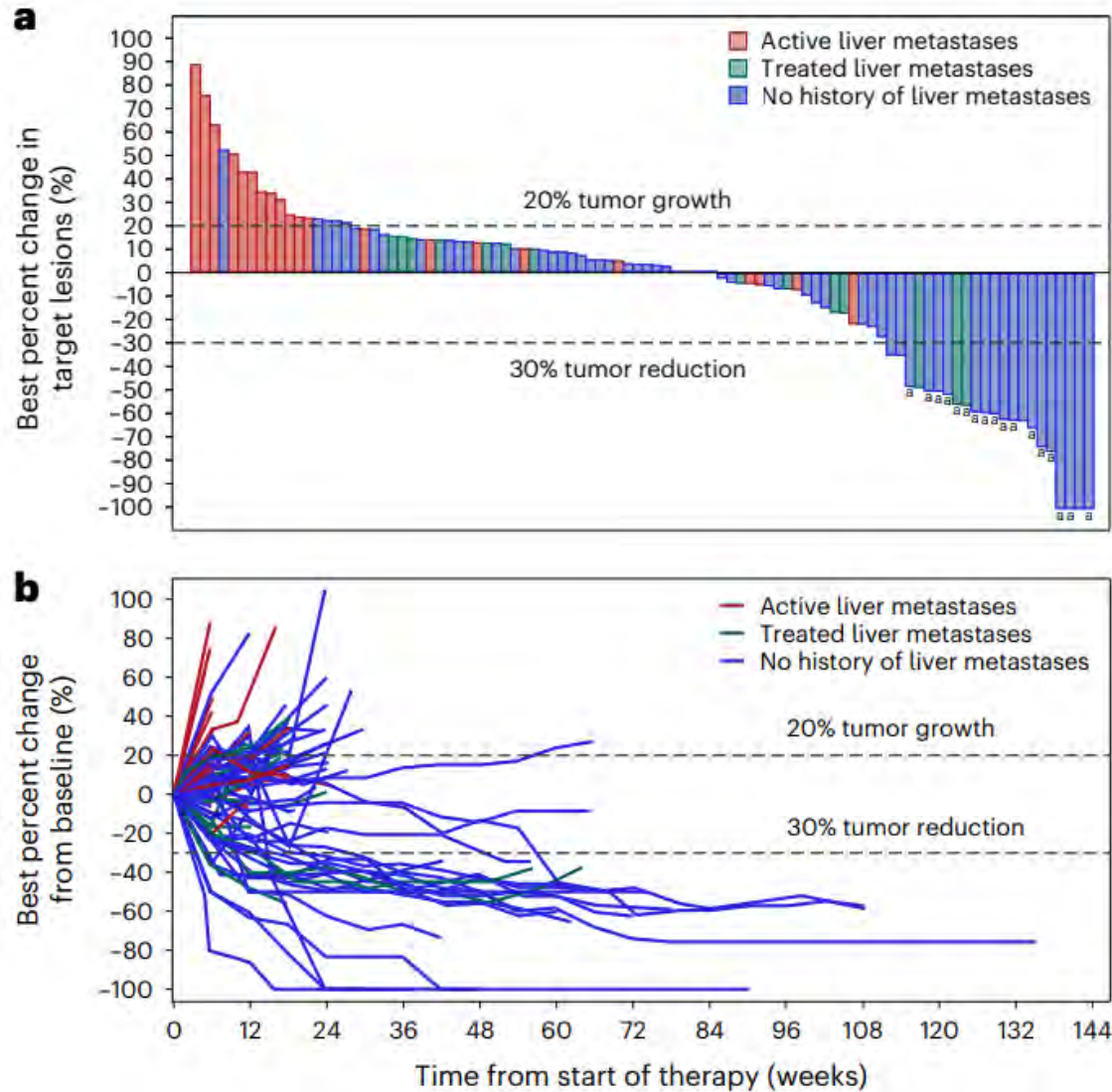
Immunotherapy- High TMB & POLE Mutations



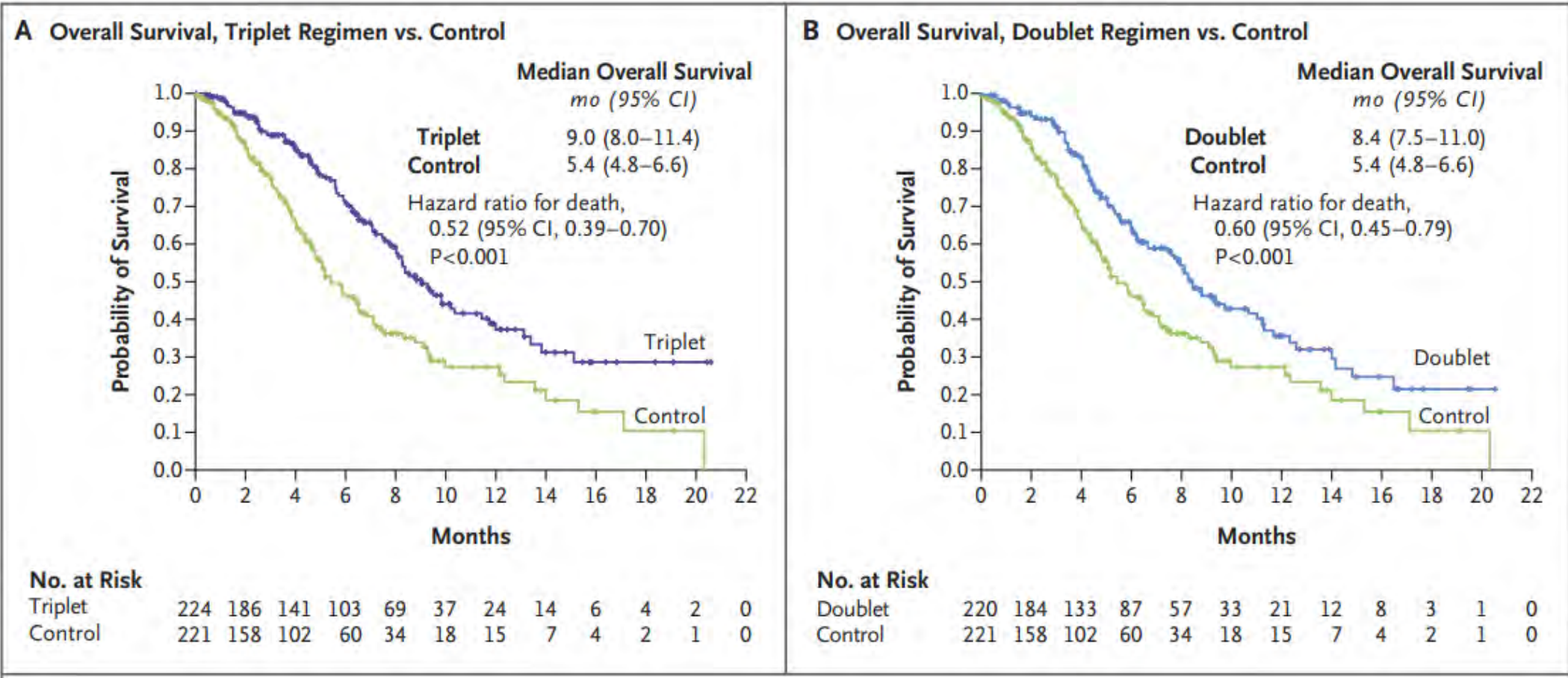
Duvivier, et al. Immunotherapy. 2023.



Immunotherapy- Future Directions



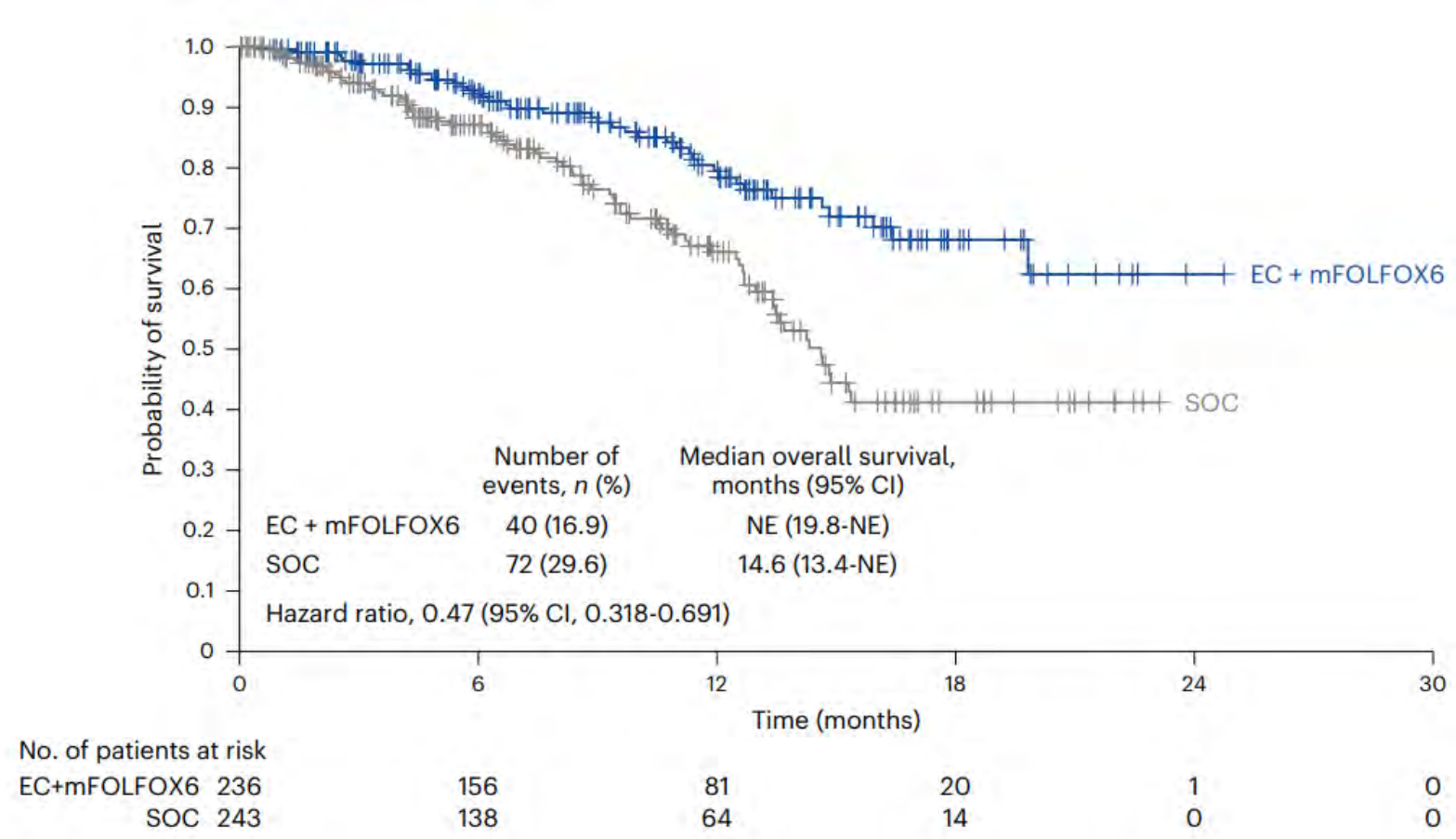
BRAF V600E



Kopetz, et al NEJM. 2019.

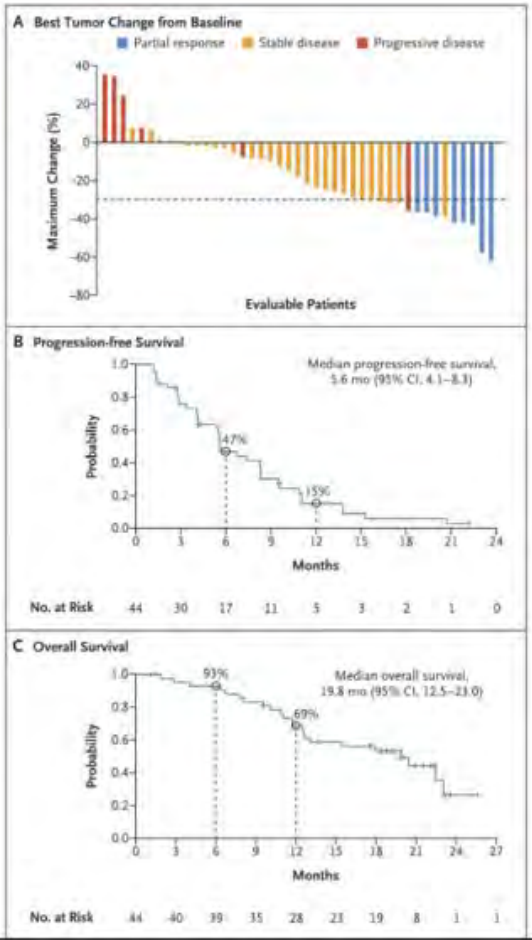


BRAF V600E



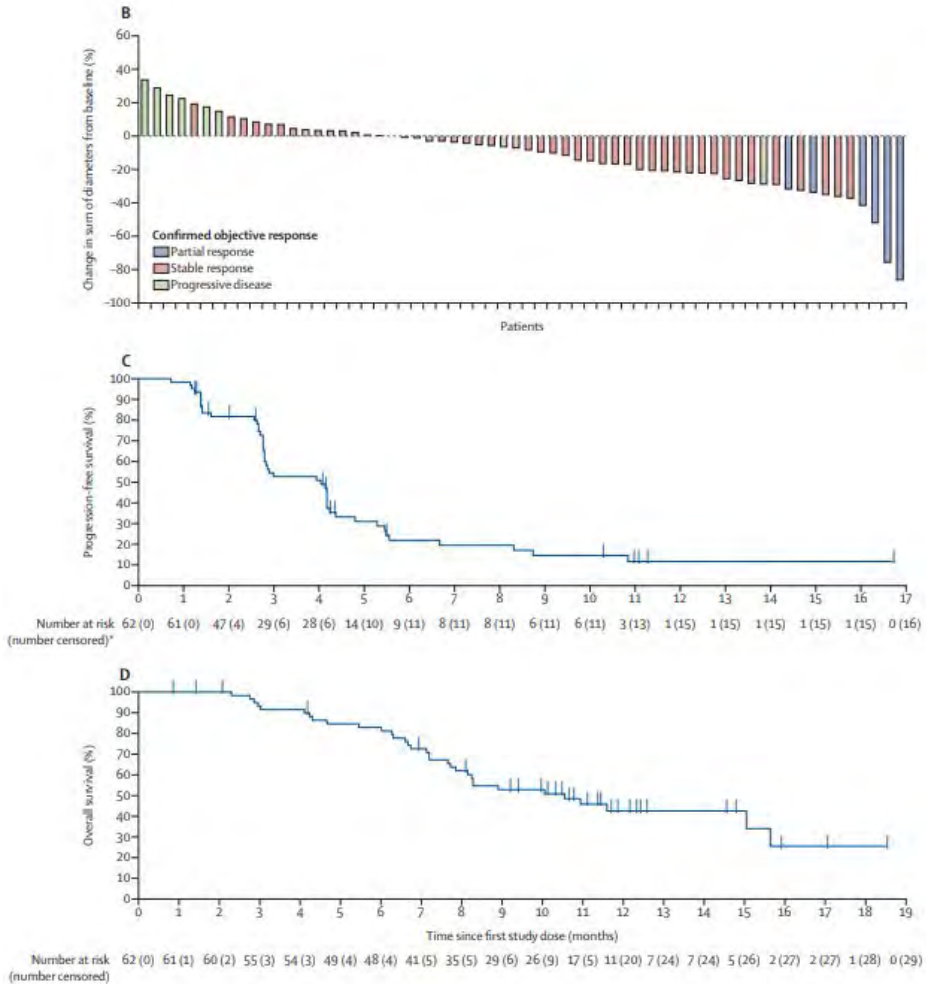
KRAS- G12C

Adagrasib



• Yaeger, et al, NEJM, 2023.

Sotorasib



• Fakih et al, Lancet Oncology, 2022.

KRAS- G12D and beyond

Recruiting ⓘ

A Study of the Pan-KRAS Inhibitor LY4066434 in Participants With KRAS Mutant Solid Tumors

ClinicalTrials.gov ID ⓘ NCT06607185

Sponsor ⓘ Eli Lilly and Company

Information provided by ⓘ Eli Lilly and Company (Responsible Party)

Last Update Posted ⓘ 2025-04-22

Recruiting ⓘ

A Phase 1/2 Study of MRTX0902 in Solid Tumors With Mutations in the KRAS MAPK Pathway

ClinicalTrials.gov ID ⓘ NCT05578092

Sponsor ⓘ Mirati Therapeutics Inc.

Information provided by ⓘ Mirati Therapeutics Inc. (Responsible Party)

Last Update Posted ⓘ 2025-04-08

Recruiting ⓘ

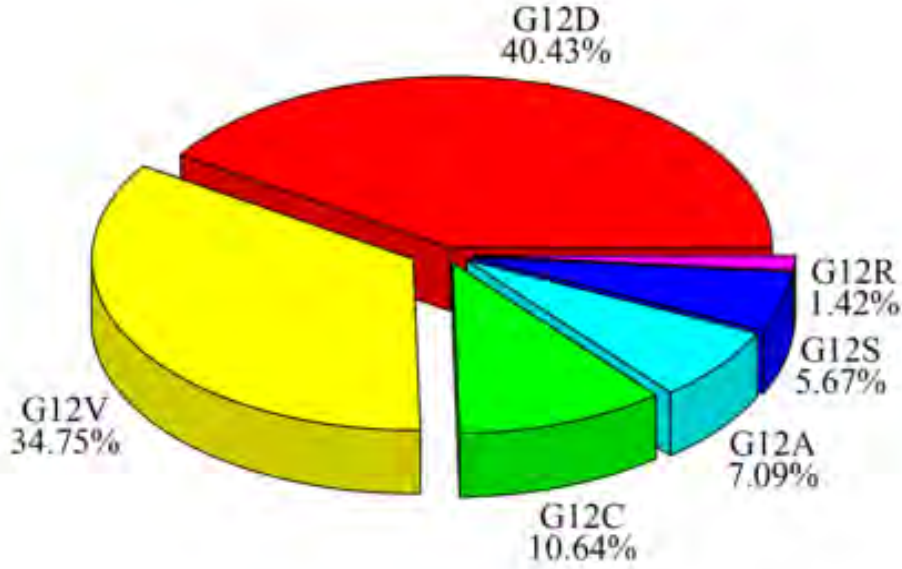
A First-in-human Study of BGB-53038, a Pan-KRAS Inhibitor, Alone or in Combinations in Participants With Advanced or Metastatic Solid Tumors With KRAS Mutations or Amplification

ClinicalTrials.gov ID ⓘ NCT06585488

Sponsor ⓘ BeiGene

Information provided by ⓘ BeiGene (Responsible Party)

Last Update Posted ⓘ 2025-04-16



Zhu, et al. Molecular Cancer. 2021.



Navigating Clinical Trials

- **How do I find clinical trials?**
- **When is the right time for a clinical trial?**
- **What do clinical trials offer me?**



Questions?