

Current and Emerging Role of Immune Checkpoint Inhibitors in the Management of mCRC

Michael J Overman, MD

Professor

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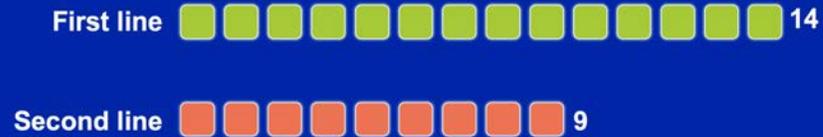
Division of Cancer Medicine

The University of Texas

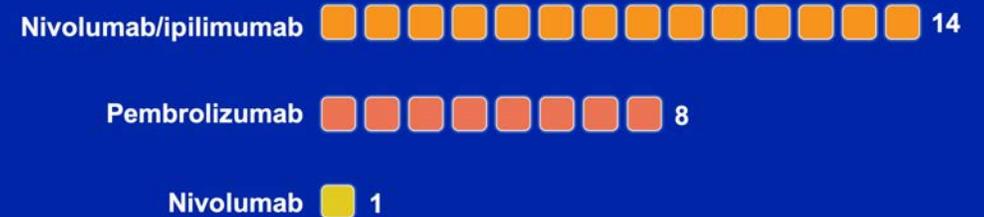
MD Anderson Cancer Center

Houston, Texas

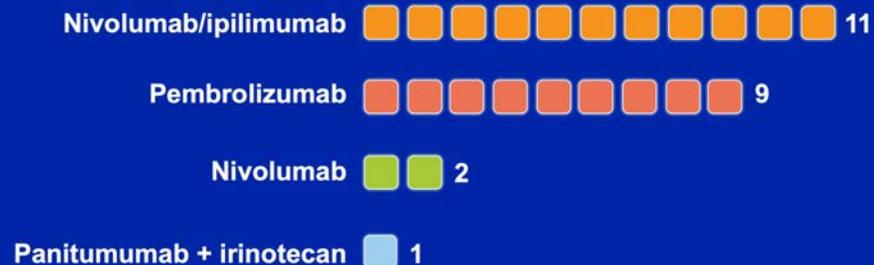
Reimbursement and regulatory issues aside, for a patient with minimally symptomatic, MSI-high mCRC with modest tumor burden, in which line of therapy would you like to use an anti-PD-1/PD-L1 antibody?



For a younger, otherwise healthy patient with MSI-high mCRC for whom you are planning to administer immune checkpoint inhibitor therapy, in general which agent or regimen would you most likely recommend?



A 65-yo patient with right-sided, MSI-high, pan-RAS WT, BRAF WT mCRC who receives FOLFOX/bev then FOLFIRI/bev is now experiencing progression. What would be your most likely third-line treatment?



Immune checkpoint inhibitors MSI-high disease

- Sequencing and selection of treatment
- Autoimmune toxicity
- Treatment discontinuation

Microsatellite-stable disease

- Regorafenib/nivolumab

Regulatory and reimbursement issues aside, what is your likely initial treatment for a younger patient (PS 0) with left-sided, pan-RAS WT, BRAF WT, MSI-high mCRC with liver-only metastases that require shrinkage for potentially curative surgery?

Nivolumab/ipilimumab  7

FOLFOXIRI + bevacizumab  5

FOLFOXIRI + panitumumab  3

FOLFOX/CAPOX + cetuximab  3

FOLFOXIRI (1), FOLFOX/CAPOX (1), FOLFOX + nivolumab or pembrolizumab (1), Pembrolizumab (1), FOLFOX/CAPOX + panitumumab (1)

Regulatory and reimbursement issues aside, what is your likely initial treatment for a patient with right-sided, pan-RAS WT, BRAF WT, MSI-high mCRC with liver-only metastases that require shrinkage for potentially curative surgery?

FOLFOXIRI + bevacizumab  11

Nivolumab/ipilimumab  6

FOLFOXIRI  2

FOLFOX/CAPOX + cetuximab  1

FOLFOX/CAPOX (1), FOLFOX + nivolumab or pembrolizumab (1), Pembrolizumab (1)

In approximately how many patients with MSI-high mCRC who are receiving a checkpoint inhibitor have you observed lack of disease progression after 2 years?

Number of patients (median): 3

Have you or would you discontinue immunotherapy in a patient with MSI-high mCRC who remains in remission?

I have  15

I have not but would for the right patient  6

I have not and would not  2

Immune checkpoint inhibitors

MSI-high disease

- Sequencing and selection of treatment
- Autoimmune toxicity
- Treatment discontinuation

Microsatellite-stable disease

- Regorafenib/nivolumab

A 65-yo patient with right-sided, MSS mCRC with a RAS mutation who receives FOLFOX/bev then FOLFIRI/bev is now experiencing progression (PS 0). What would be your most likely treatment?



Have you or would you use regorafenib in combination with nivolumab for a patient with metastatic colorectal or gastric cancer?



To approximately how many patients with metastatic colorectal or gastric cancer have you administered regorafenib in combination with nivolumab either on or off protocol?

23 patients treated by 9 clinical investigators

Have you observed any objective responses after administering regorafenib in combination with nivolumab for patients with metastatic colorectal or gastric cancer?



Immune checkpoint inhibitors MSI-high disease

- Sequencing and selection of treatment
- Autoimmune toxicity
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Microsatellite-stable disease

- Regorafenib/nivolumab

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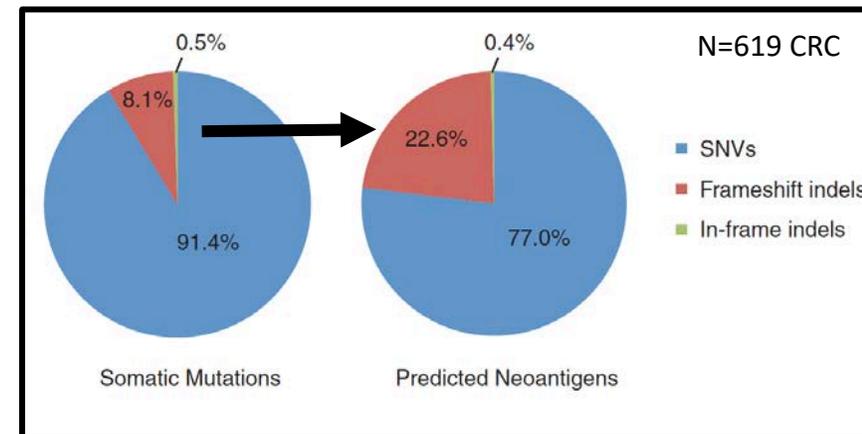
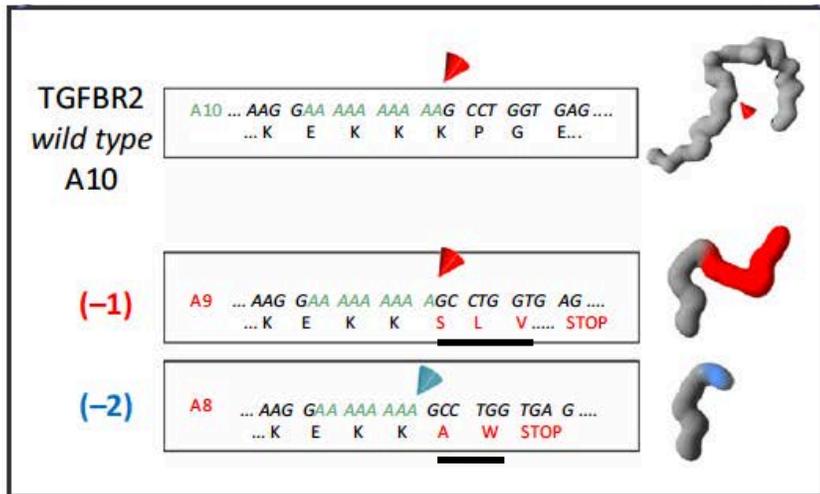
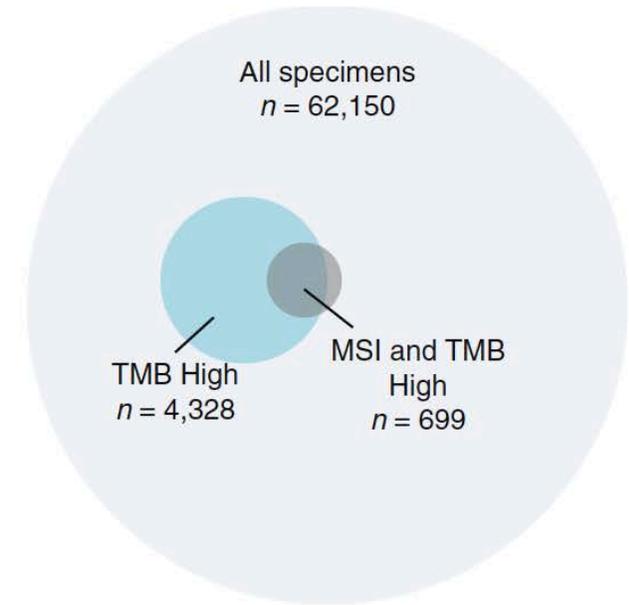
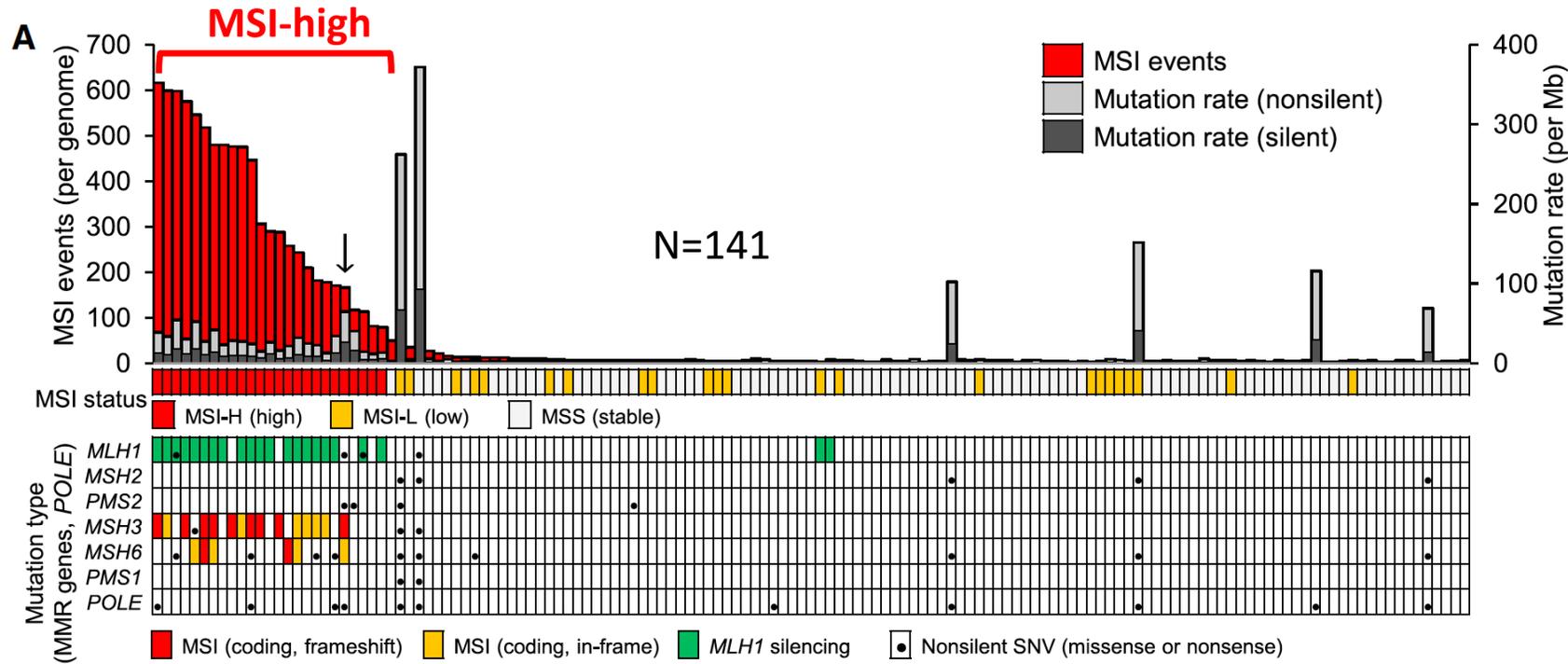
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Disclosures

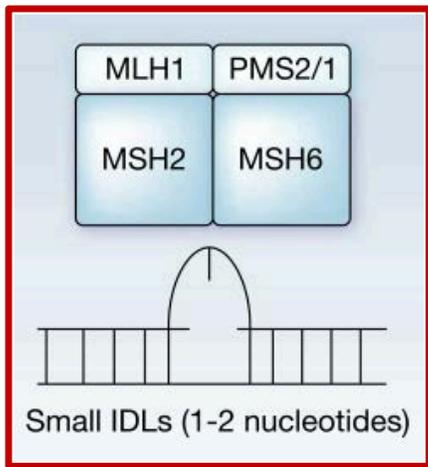
Consulting Agreements	Array BioPharma Inc, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, CatalYm, Gritstone Oncology, Promega Corporation, Roche Laboratories Inc
Contracted Research	Apexigen, AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Merck, Nouscom, Roche Laboratories Inc.

dMMR or MSI-H CRC: Frameshift Neoantigens

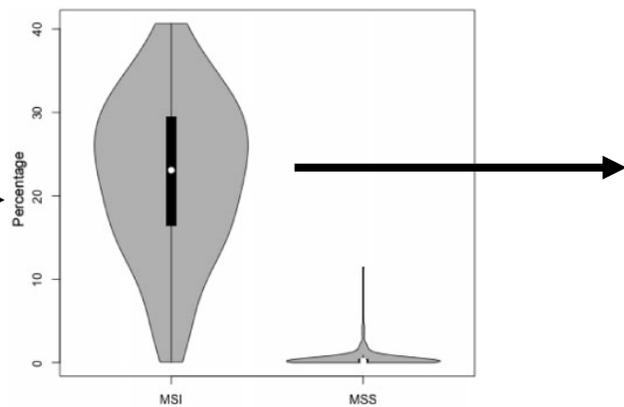


Giannakis et al. Cell Report 2016; Kloor et al. Trends in Cancer 2016; Chalmers et al. Genomic Medicine 2017; 2013 Kim et al. Cell

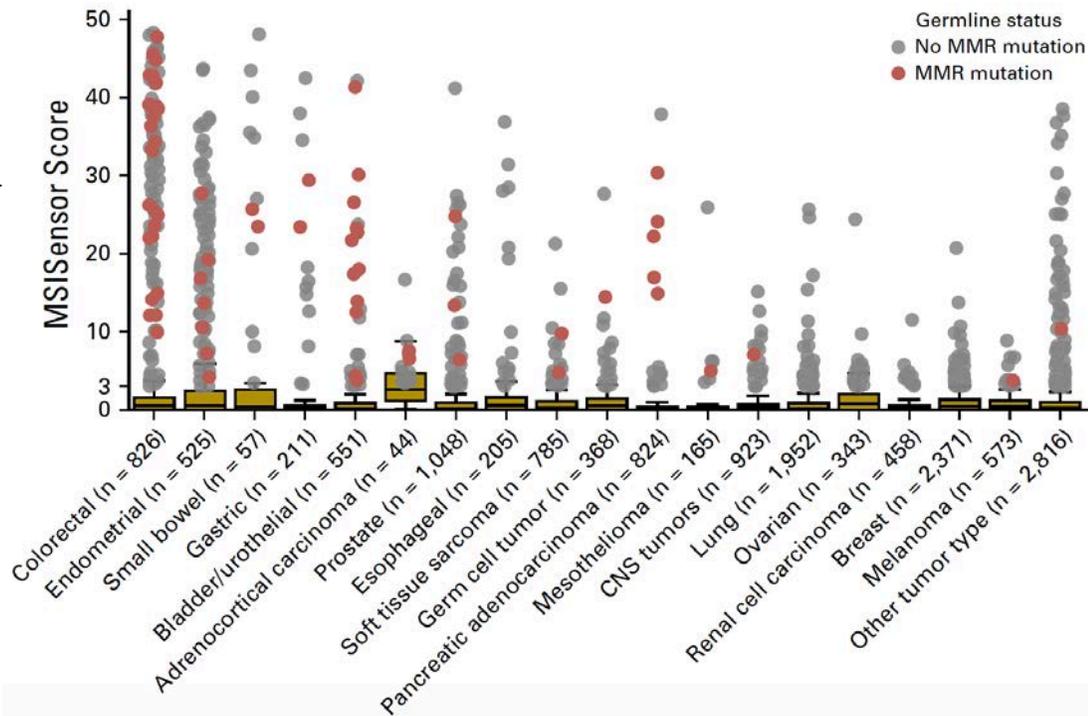
dMMR Testing



Next-generation Sequencing

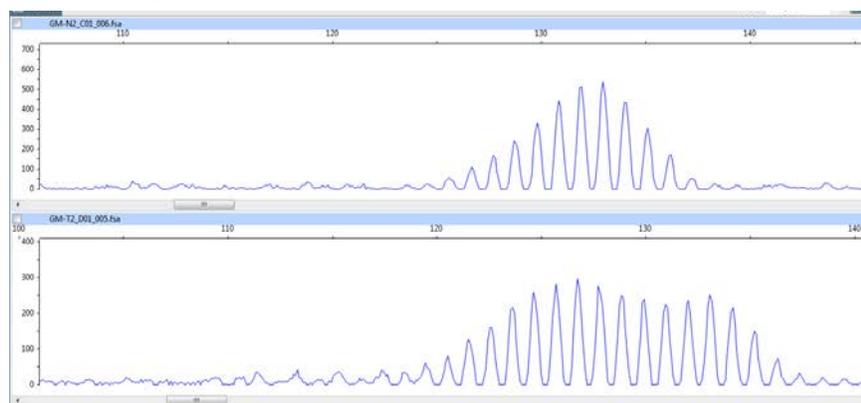
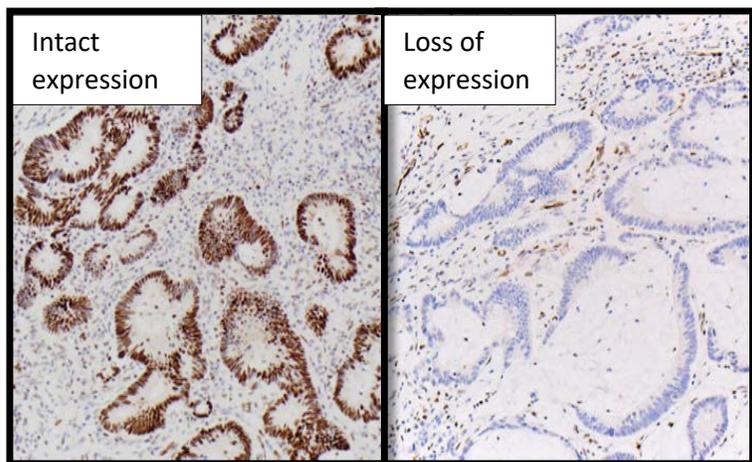


Polymerase Chain Reaction



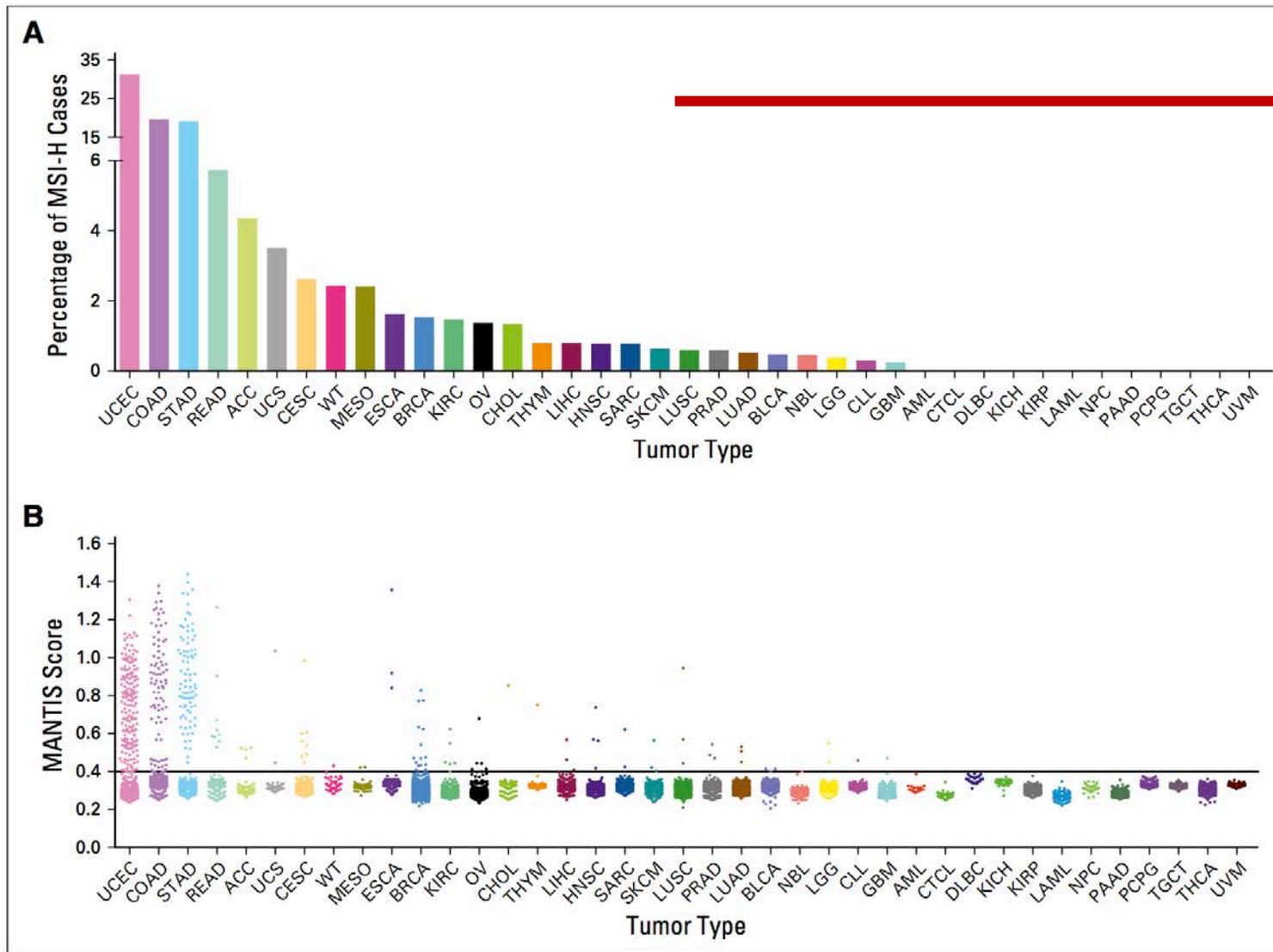
Immunohistochemistry

Complete loss of expression in one of the MMR proteins = MSI-high



Panel of 5 or more microsatellites with allelic shift in 2 (>30%) or more markers = MSI-high

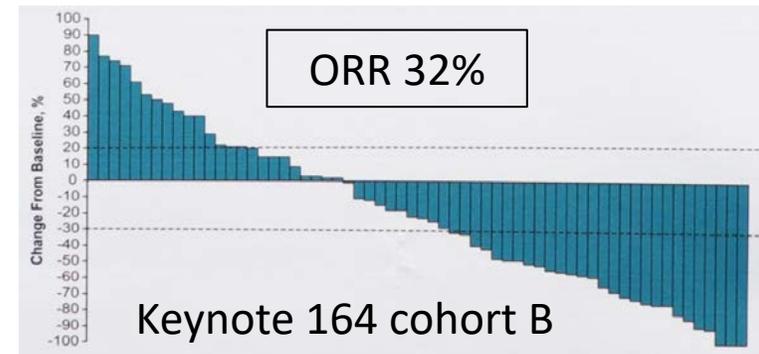
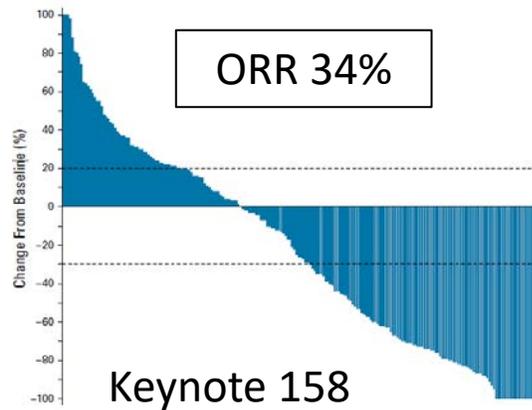
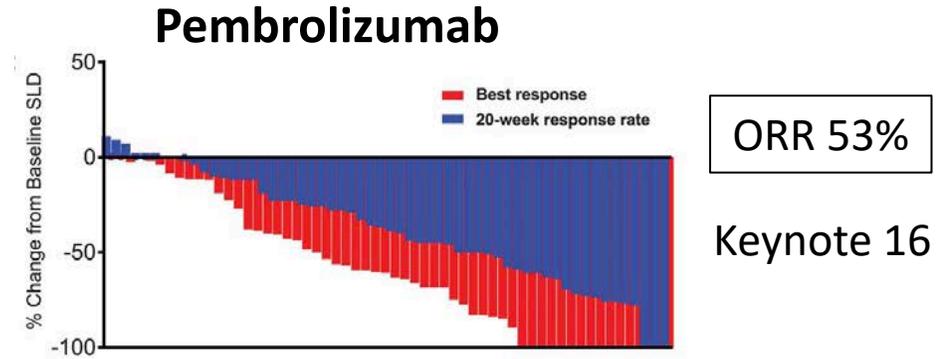
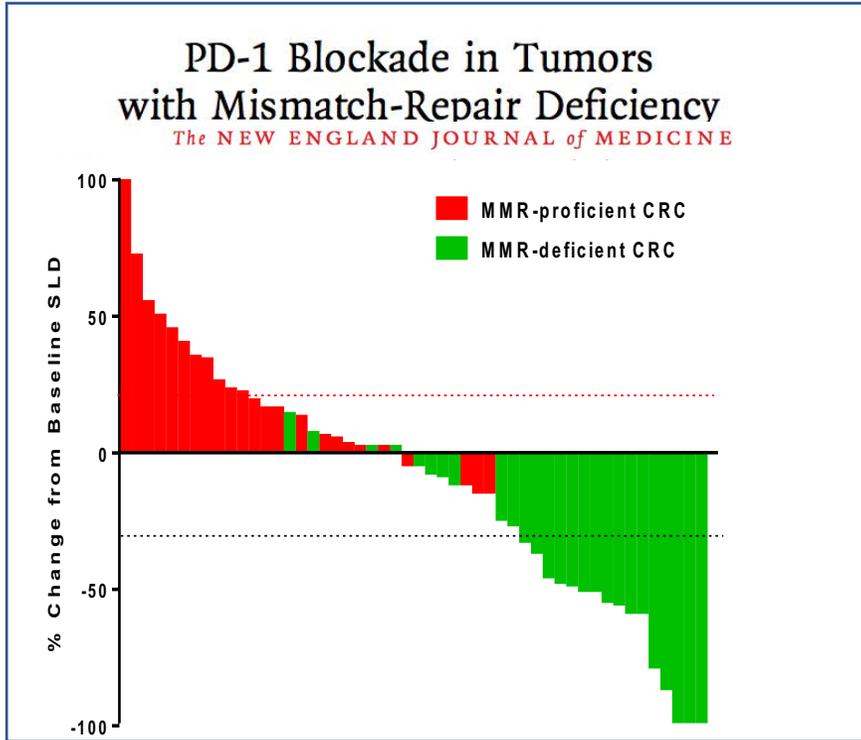
TCGA Analysis: 39 cancer types; 11,139 tumors



TOP 15

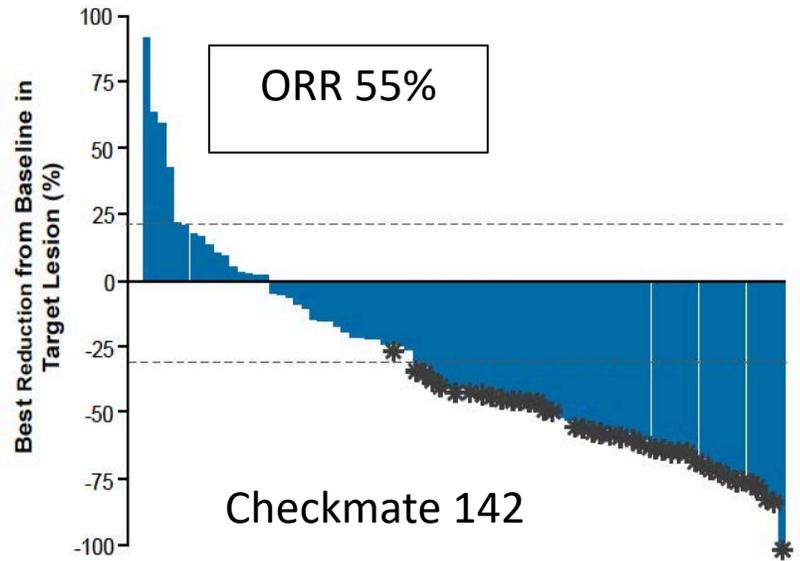
- Uterine Endometrial Carcinoma
- Colon Adenocarcinoma
- Stomach Adenocarcinoma
- Rectal Adenocarcinoma
- Adrenocortical Carcinoma
- Uterine Carcinosarcoma
- Cervical
- Wilms Tumor
- Mesothelioma
- Esophageal Carcinoma
- Breast Carcinoma
- Renal Clear Cell
- Ovarian
- Cholangiocarcinoma
- Thymoma

dMMR and Pembrolizumab

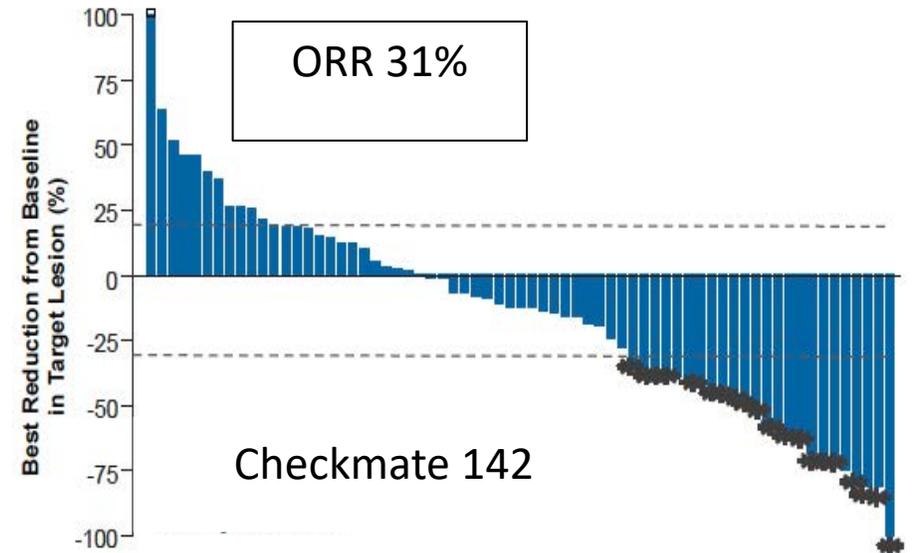


dMMR and Nivolumab, Nivolumab/Ipilimumab

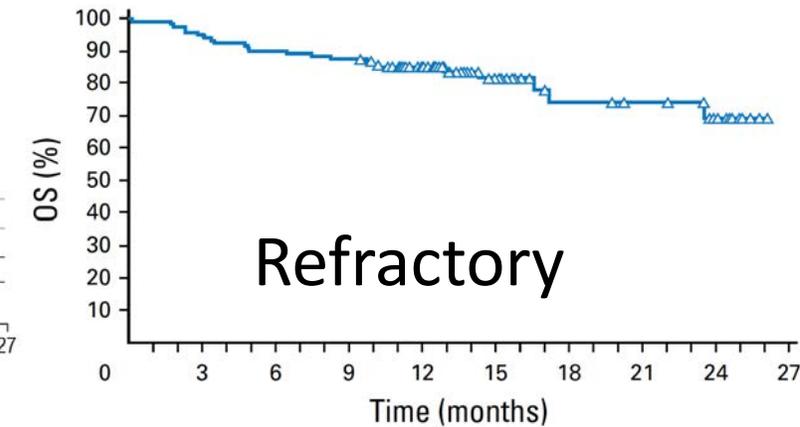
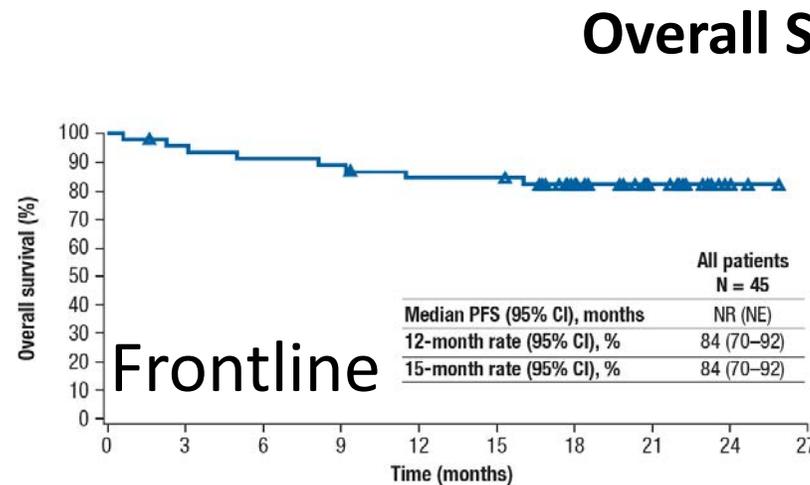
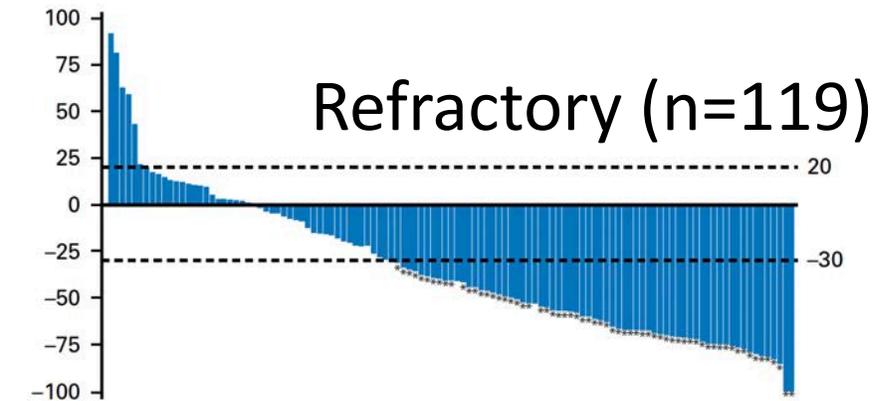
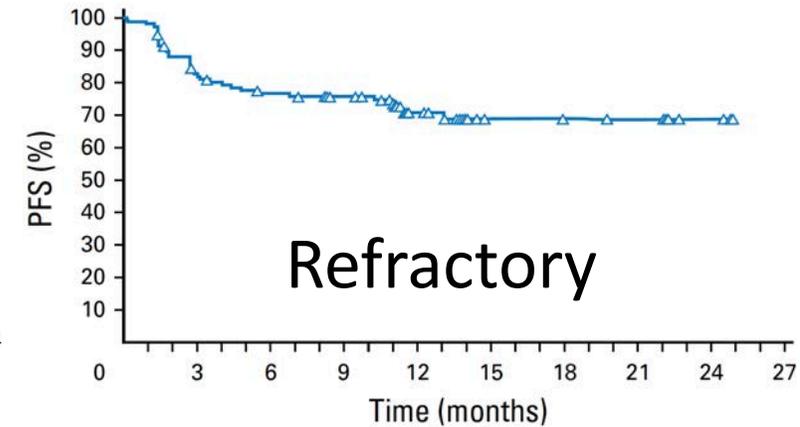
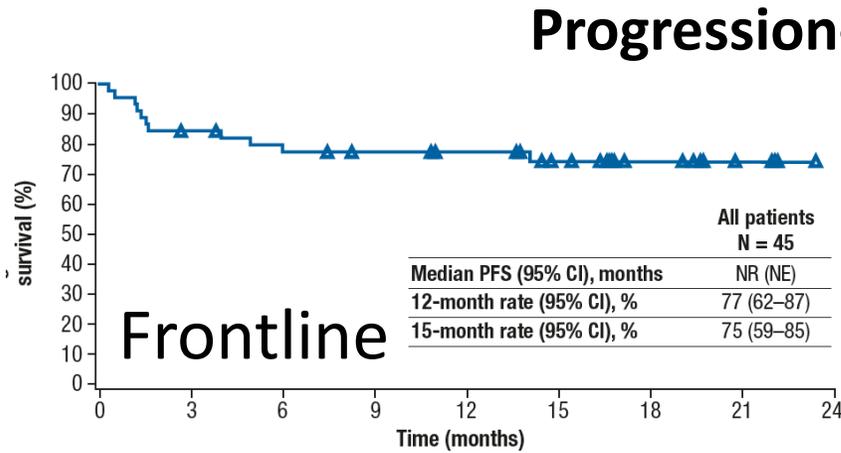
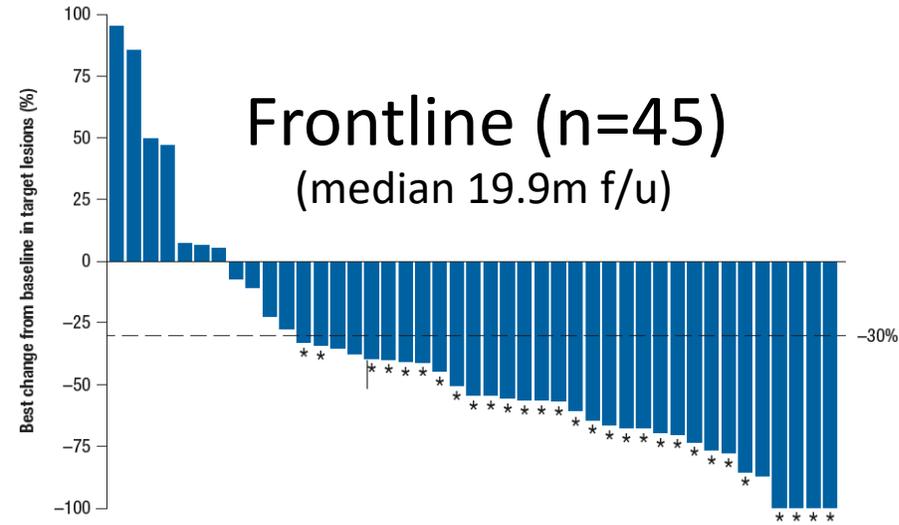
Nivolumab and Ipilimumab



Nivolumab

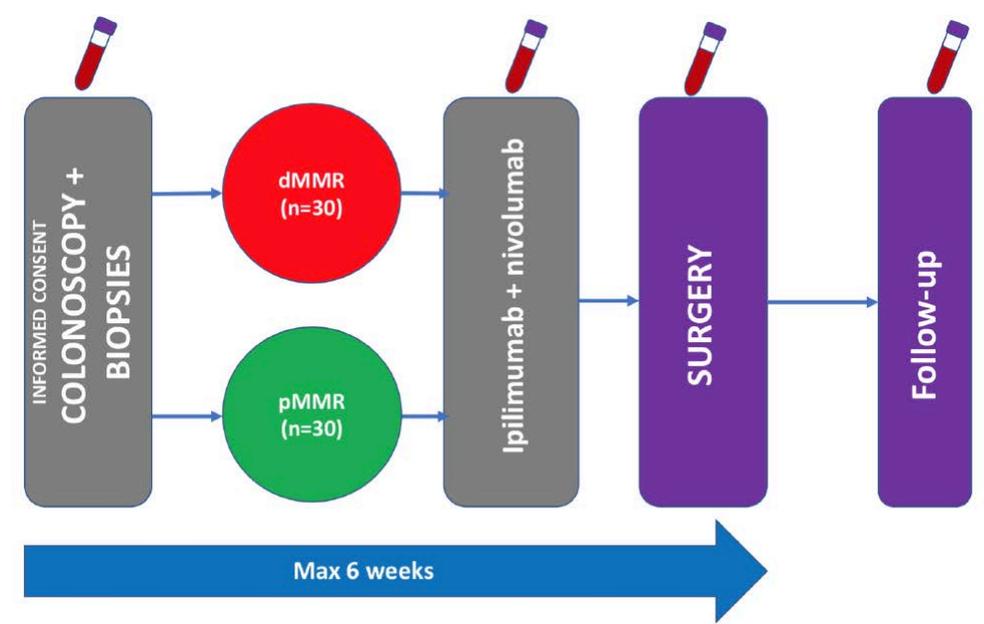


Efficacy for NI Refractory vs Frontline Cohorts



NICHE Clinical Trial

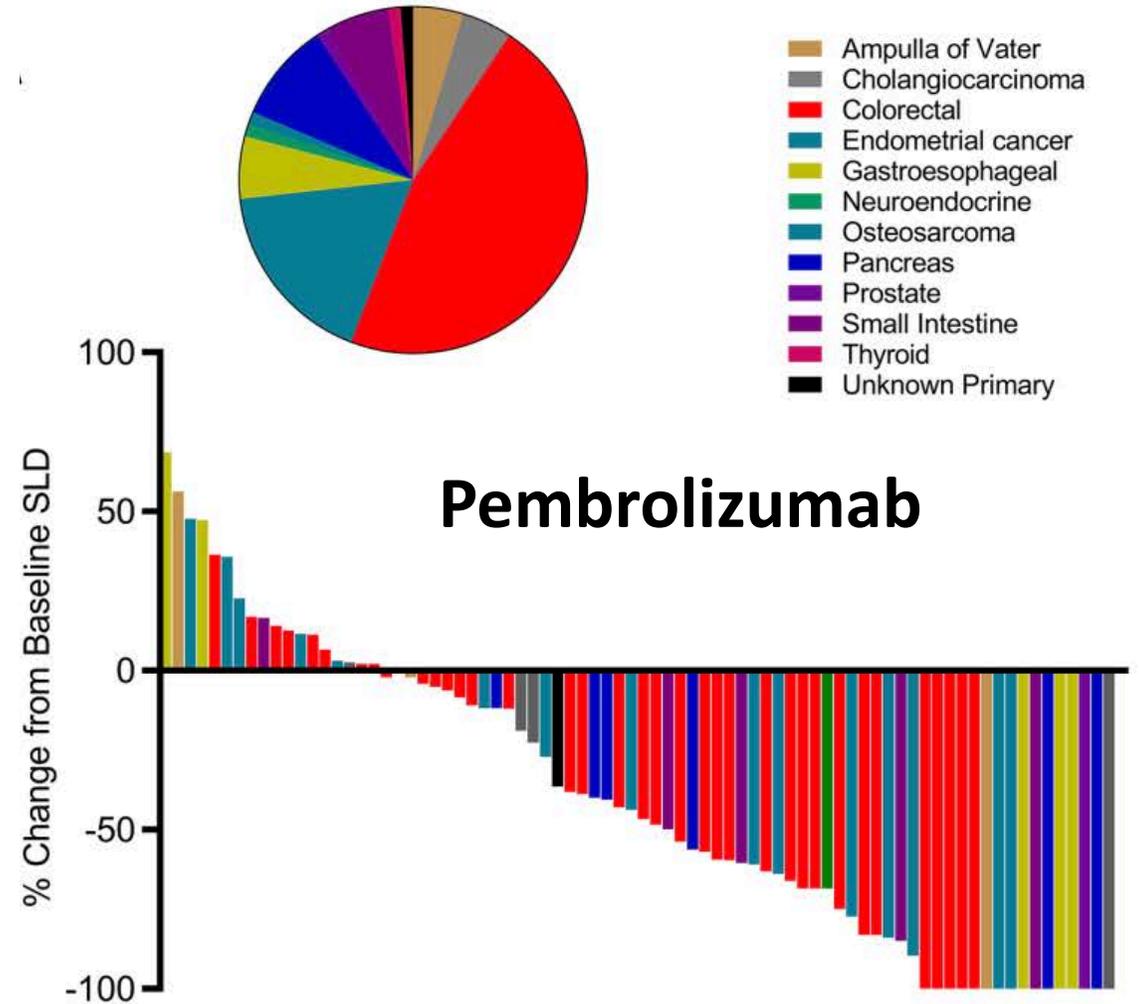
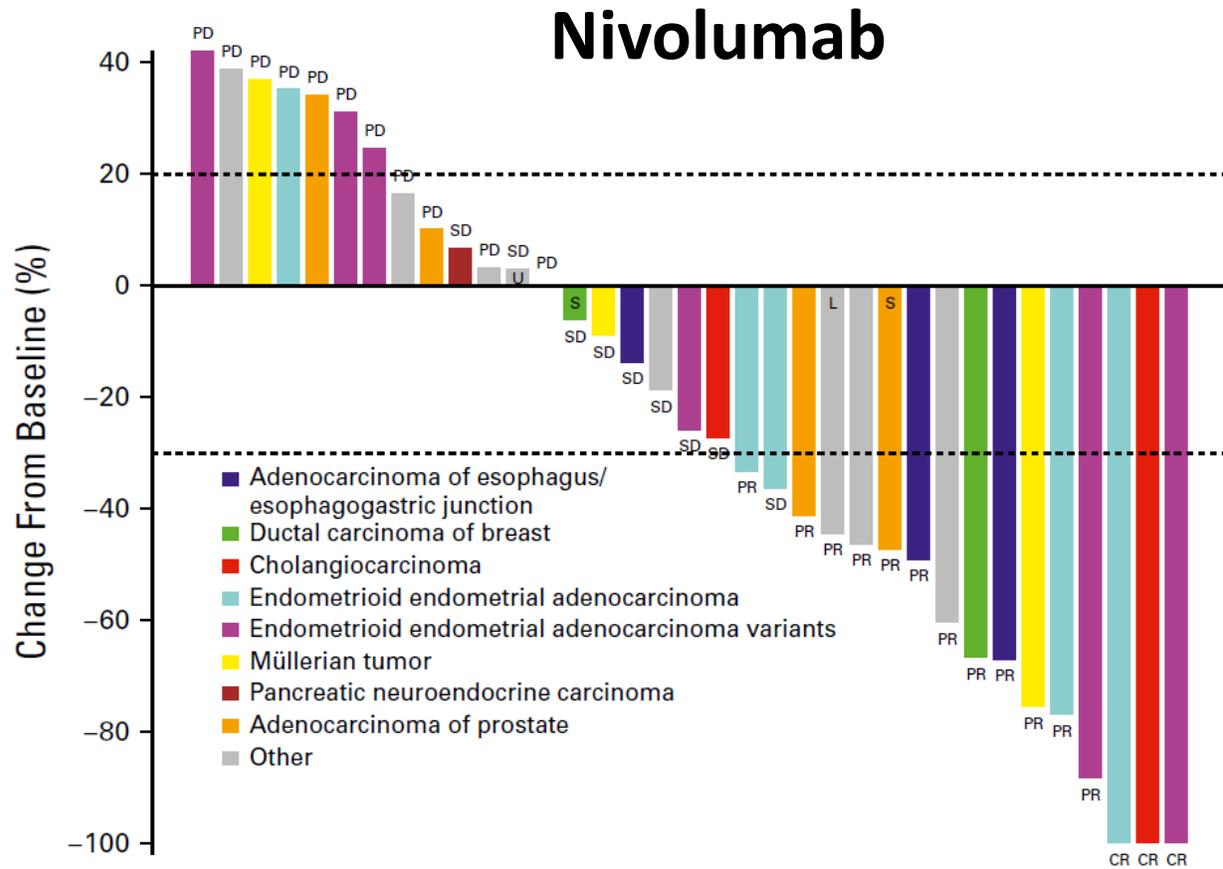
- Ipilimumab 1mg/kg Day1
- Nivolumab 3mg/kg Day 1 + 15
- Median duration from first tx to surgery 32 days (IQR: 28-35)



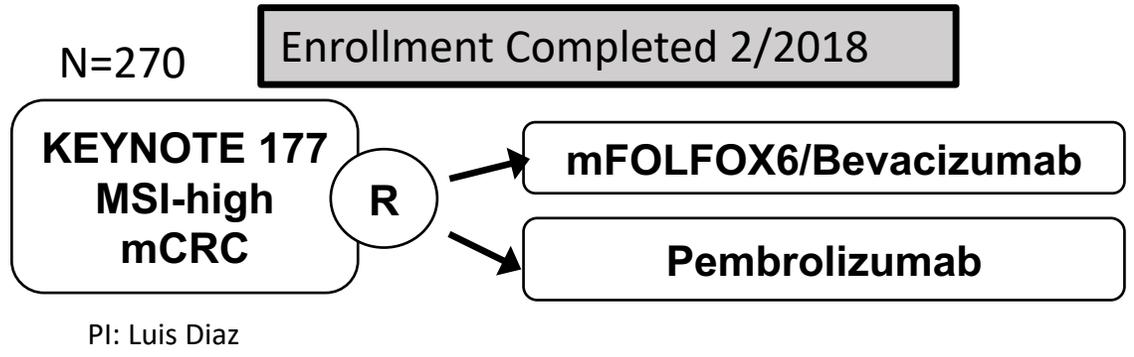
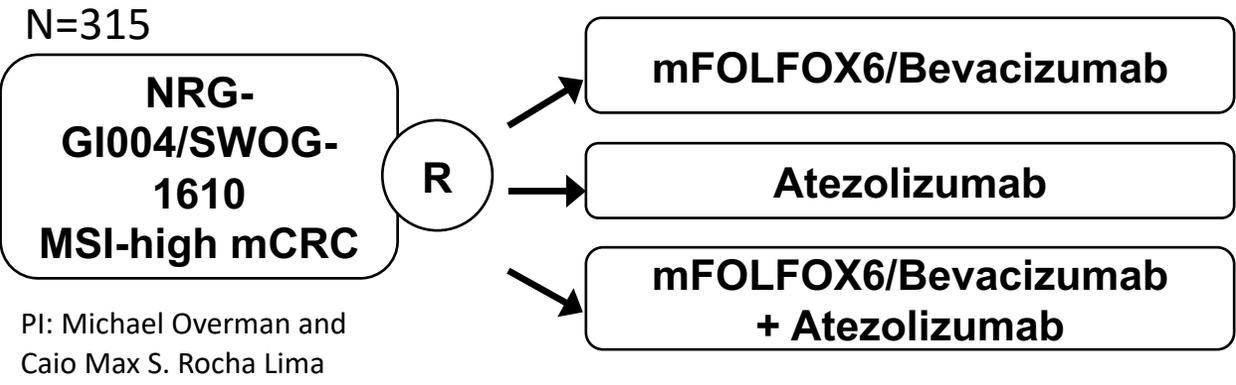
dMMR (n=7)		
Pre-treatment clinical stage	Pathological stage at resection	Residual vital tumor
cT2N2a	ypT0N0	0 %
cT2N0	ypT0N0	0 %
cT2N0	ypT0N0	0 %
cT3N0	ypT0N0	0 %
cT3N2a	ypT1N0	1 %
cT4aN2a	ypT2N0	2 %
cT4aN1a	ypT3N1	2 %

pMMR (n=8)		
Pre-treatment clinical stage	Pathological stage at resection	Residual vital tumor
cT3N1a	ypT3N2	85 %
cT3N0	ypT3N0	90 %
cT2N0	ypT3N1	90 %
cT2N0	ypT3N0	90 %
cT3N1b	ypT3N1	90 %
cT3N1b	ypT3N2	95 %
cT3N0	ypT3N0	100%
cT2N0	ypT2N0	100 %

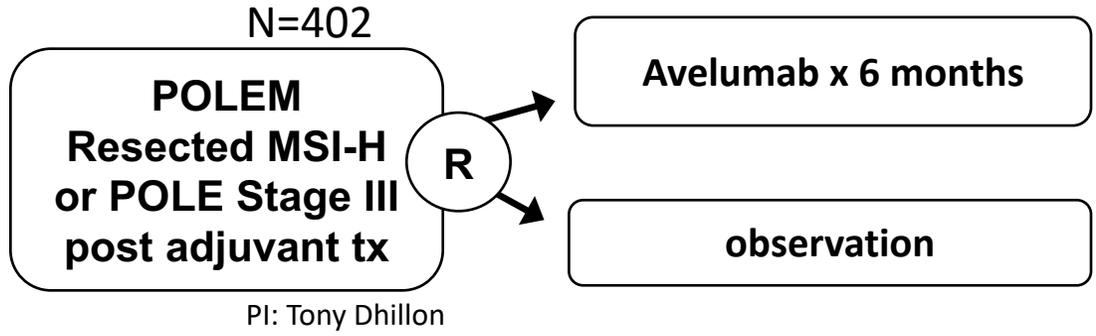
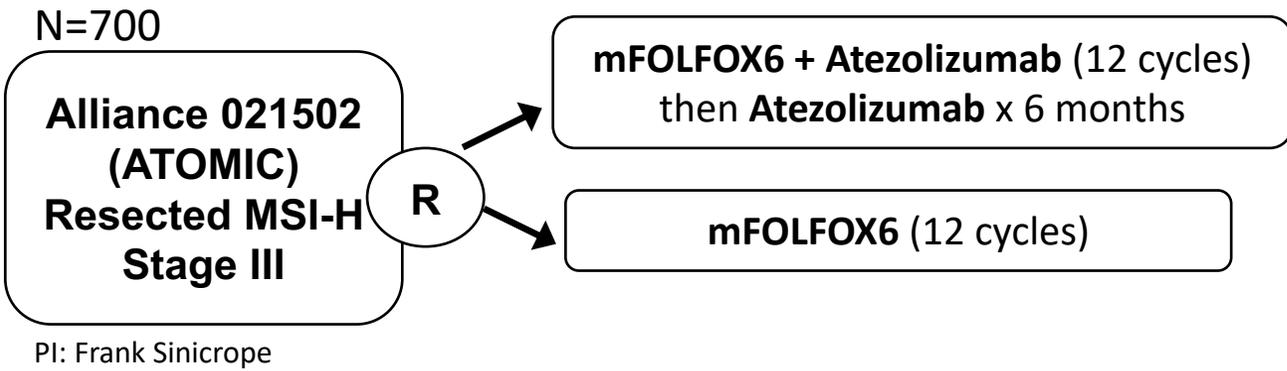
non-CRC dMMR



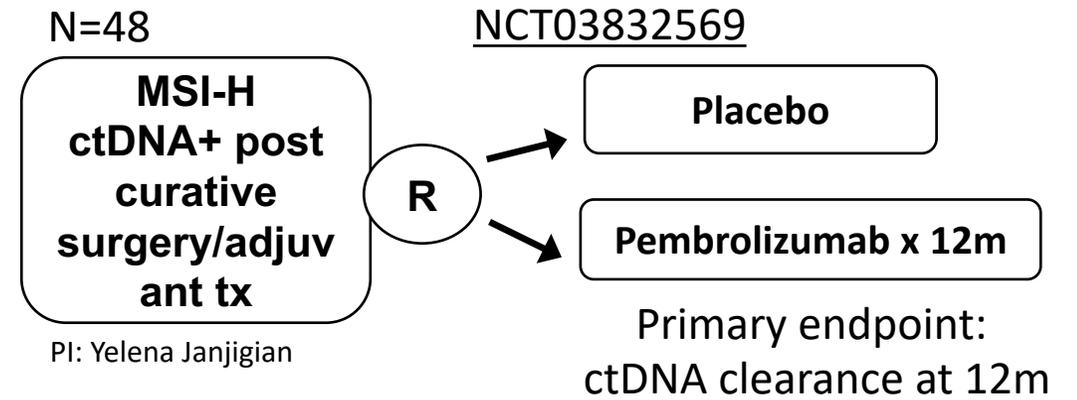
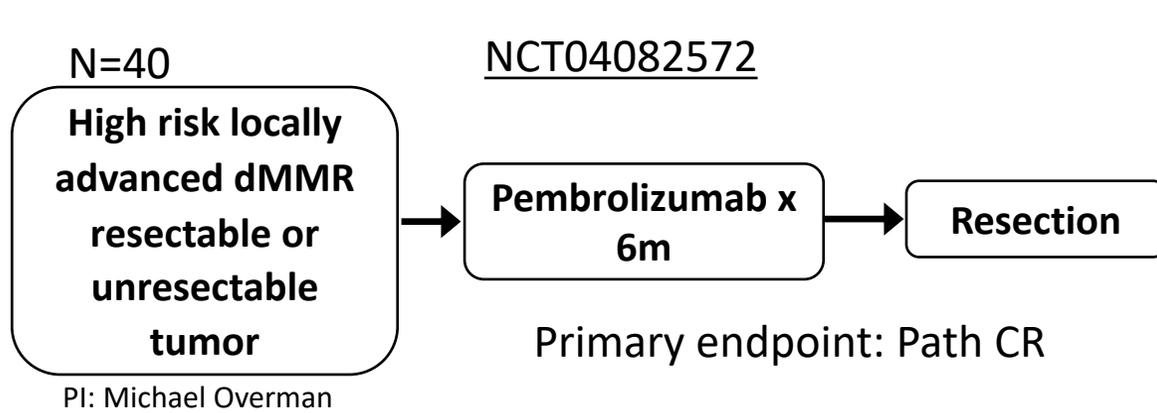
Frontline Metastatic



Stage III Adjuvant



Novel Phase IIs



Are There Response Predictors ?

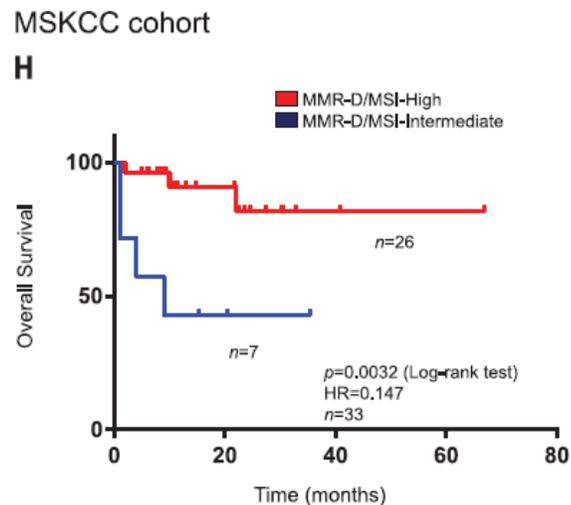
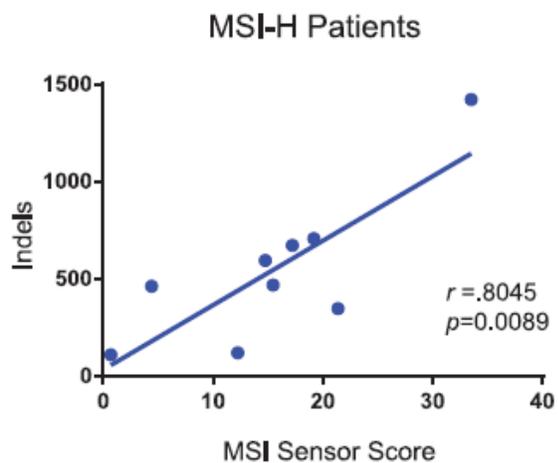
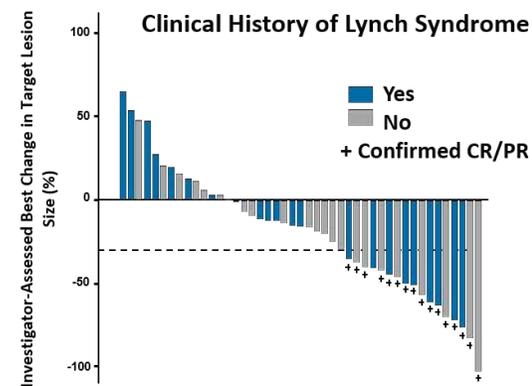
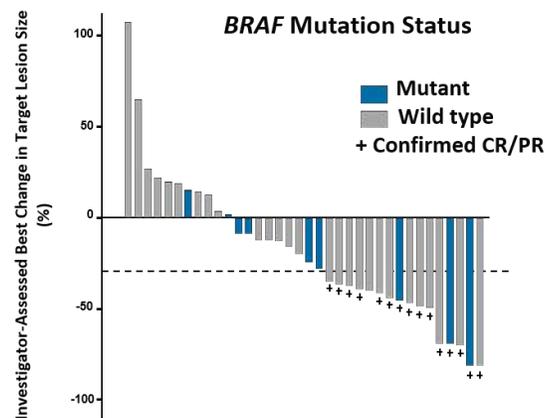
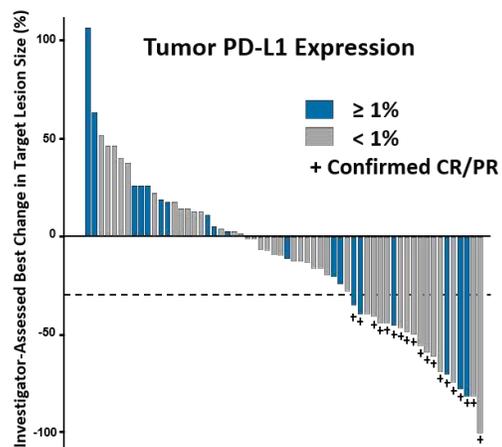


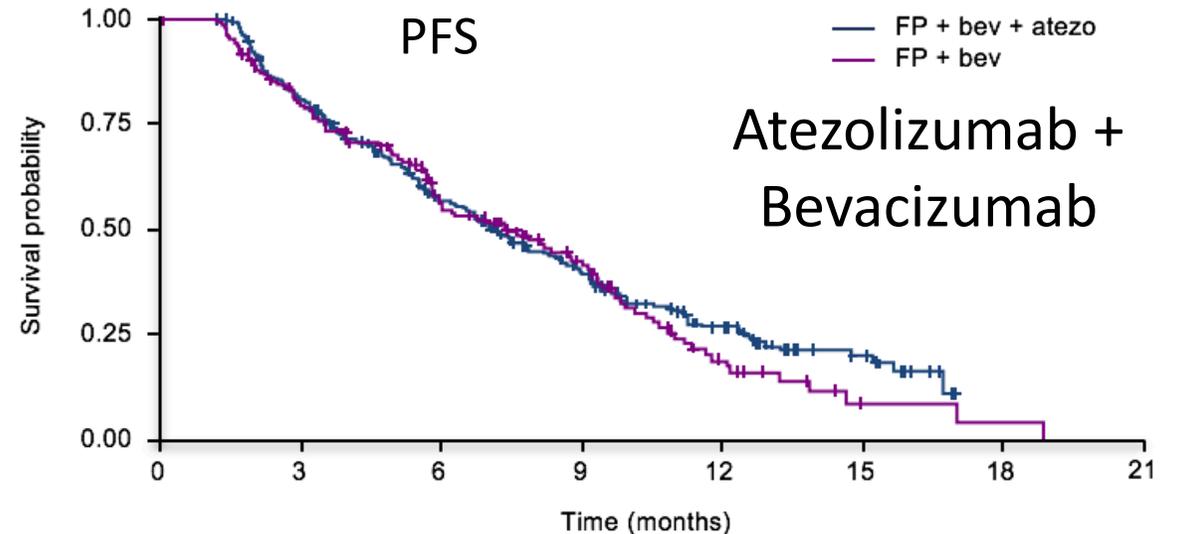
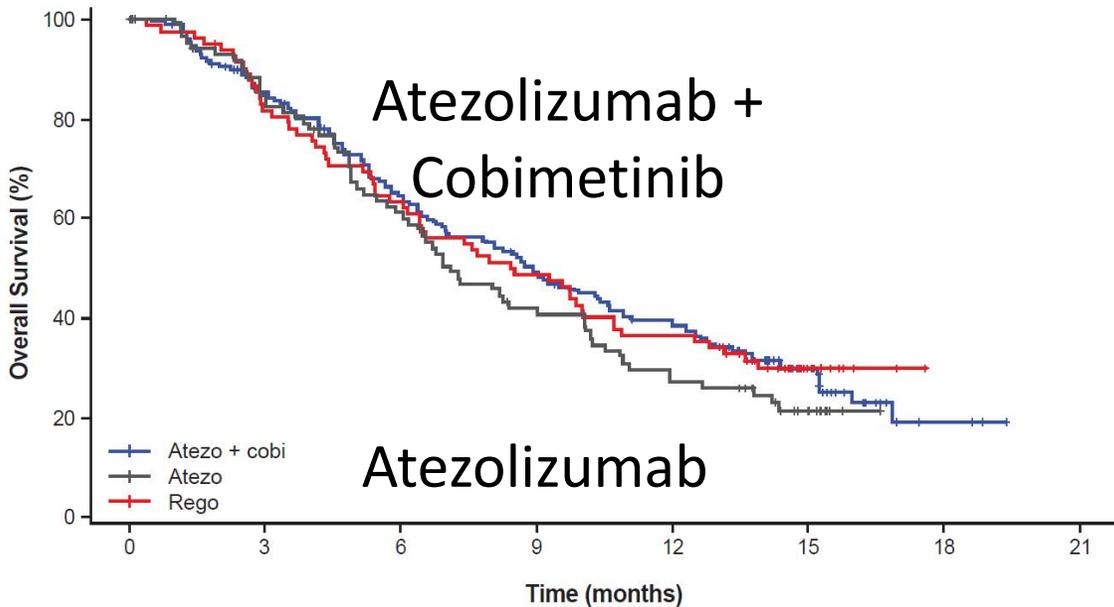
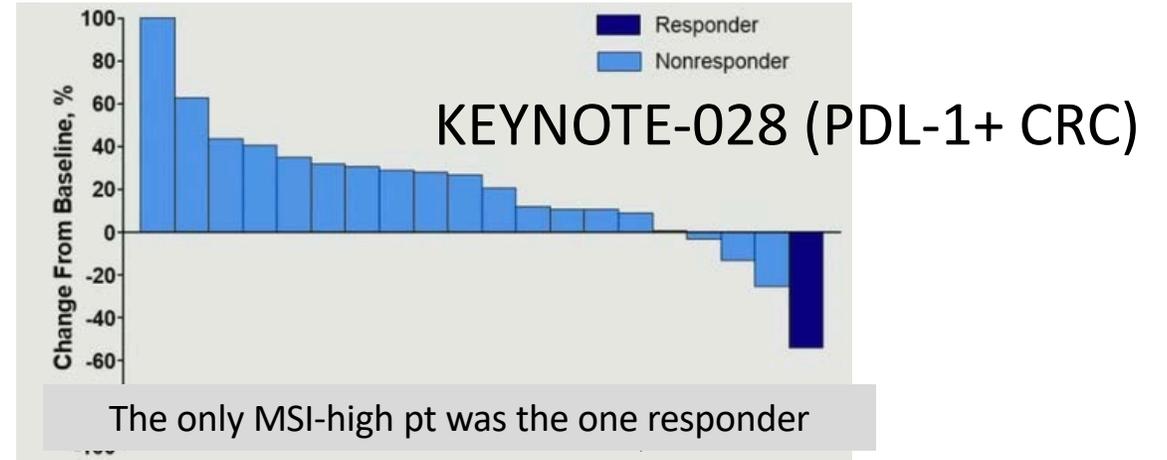
Table. Misdiagnosis of Microsatellite Instability and Mismatch Repair-Deficient Tumors by Local Assessment

Sample No. ^a	Local Assessment		Central Review		Best Response Under Immunotherapy
	IHC	PCR	IHC	PCR	
Patients included in immunotherapy trials (n = 38)					
47	pMMR	MSI	pMMR	MSS	Disease progression
115	NE	MSI	pMMR	MSS	Disease progression
181	dMMR	NE	pMMR	MSS	Disease progression
Retrospective historical cohort (n = 93)					
29	pMMR	MSI	pMMR	MSS	NA ^b
41	NE	MSI	pMMR	MSS	NA
42	NE	MSI	pMMR	MSS	NA
43	NE	MSI	pMMR	MSS	NA
46	NE	MSI	pMMR	MSS	NA
56	NE	MSI	pMMR	MSS	NA
64	pMMR	MSI	pMMR	MSS	NA
94	pMMR	MSI	pMMR	MSS	NA
106	NE	MSI	pMMR	MSS	NA

Negative anti-PD1/PDL1 trials in MSS CRC

CHECKMATE 142 (MSS CRC)

	Nivo 1/ Ipi 3 (n = 10)	Nivo 3/ Ipi 1 (n = 10)
ORR, n (%)	1 (10)	0
Median PFS (95% CI), mo	2.28 (0.62, 4.40)	1.31 (0.89, 1.71)



High TMB as a Marker for Response in MSS CRC?

CO.26 Durvalumab/Tremelimumab in MSS CRC

GuardantOMNI cfDNA panel: 500 genes, 2.1MB

Figure 6. Overall survival for pts with TMB ≥ 28

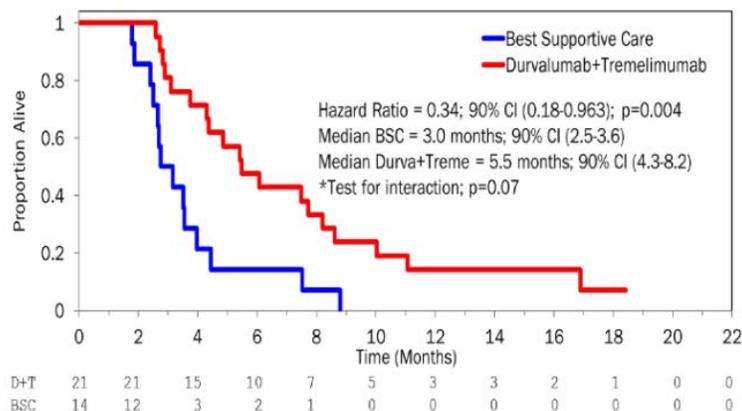
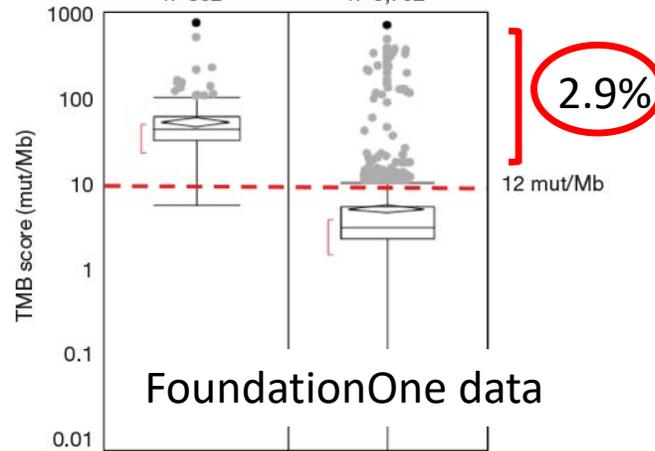
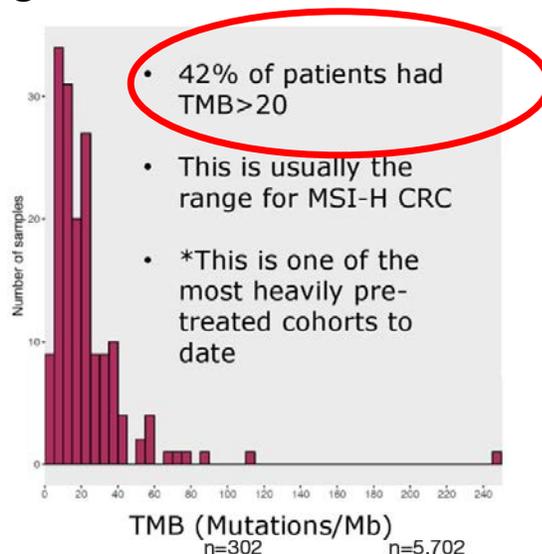
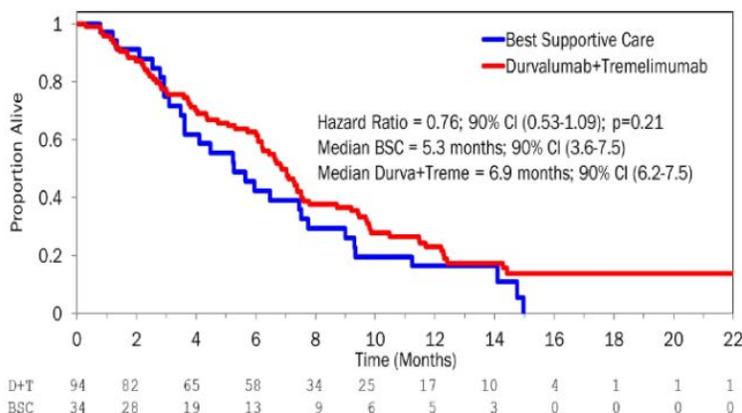


Figure 7. Overall survival for pts with TMB < 28



TAPUR: Pembrolizumab in high TMB (≥9) CRC

Number of pts	27
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Median Age, yrs	59 (34-79)
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≥3 Prior systemic regimens, %	78
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DC rate, % (OR or SD16+) (90% CI)	28 (16, 45)
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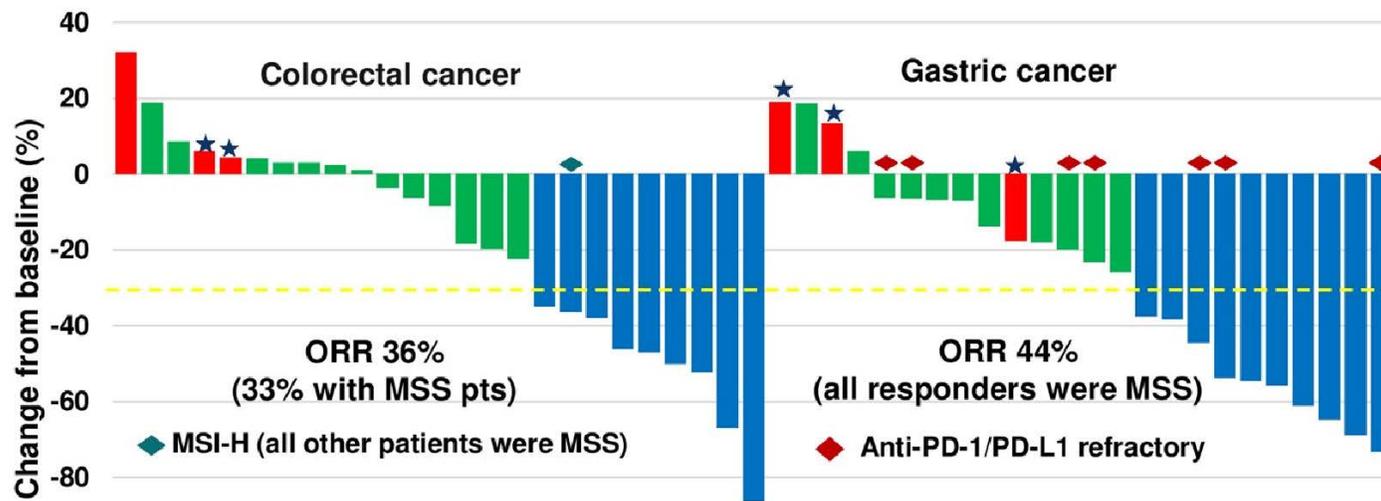
OR rate, % (95%)	4 (0, 19)
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Median PFS, wks (95% CI)	9.3 (7.3, 16.1)
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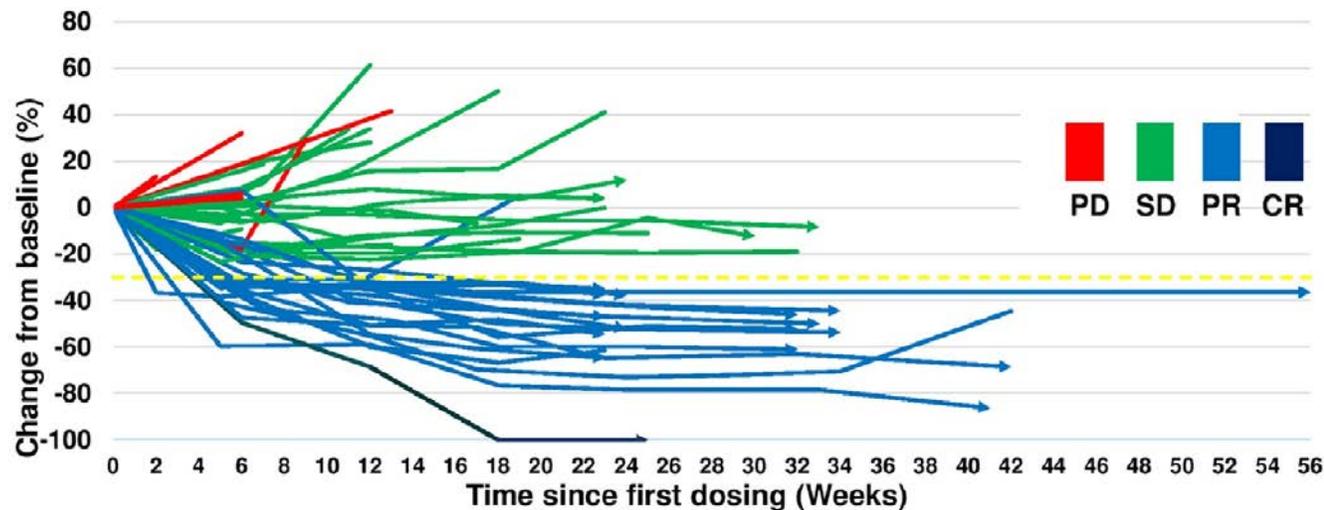
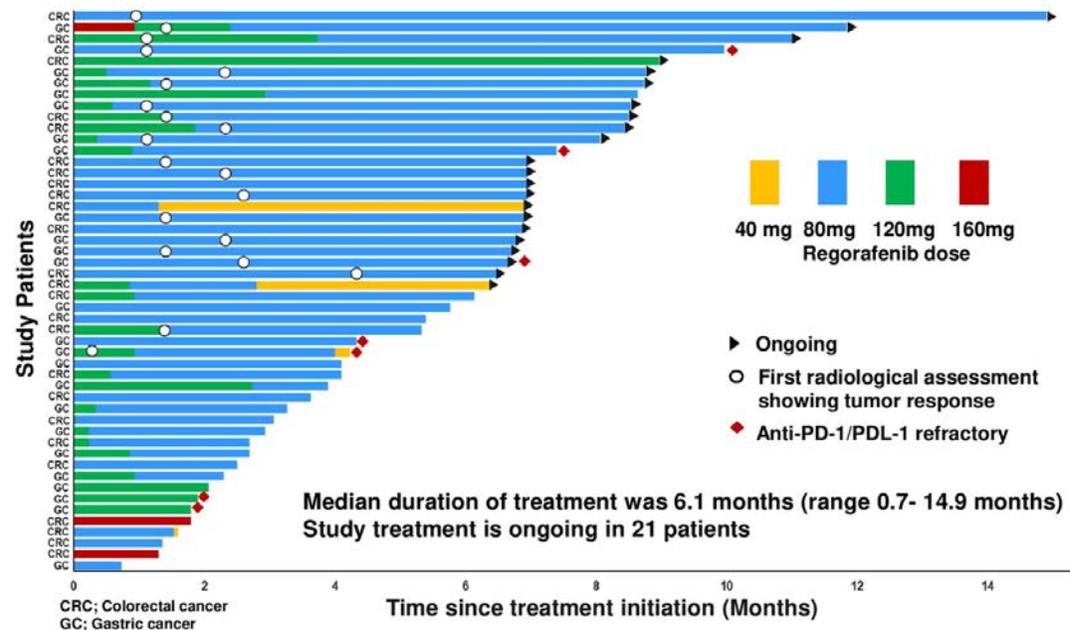
1 year OS, % (95% CI)	45.6 (22.2, 66.3)
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HTMB ranged from 9 to 54 Muts/Mb

Regorafenib and Nivolumab



Regorafenib 80mg/d 21on/7off
Nivolumab 3mg/kd q2wks



Treatment-Related Adverse Events for N/I

	Frontline (N=45)		Refractory (N =119)	
	Nivolumab (3 mg/kg, Q2W) + ipilimumab (1 mg/kg, Q6W)		Nivolumab (3 mg/kg, Q3W) + ipilimumab (1 mg/kg, Q3W x 4 doses) then Nivolumab (3mg/kg, Q2W)	
Patients, n (%)	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE	35 (78)	7 (16)	49 (41)	32 (27)
Any serious TRAE	6 (13)	3 (7)	27 (23)	24 (20)
Any TRAE leading to discontinuation	3 (7)	1 (2)	15 (13)	12 (10)
TRAEs reported in >10% of patients				
Pruritus	11 (24)	0	20 (17)	0
Hypothyroidism	8 (18)	1 (2)	16 (14)	1 (1)
Asthenia	7 (16)	1 (2)	21 (18)	2 (2)
Anthralgia	6 (13)	0	<10%	0
Lipase increased	5 (11)	0	<10%	0
Nausea	5 (11)	0	<10%	0
Rash	5 (11)	0	13 (11)	2 (2)
Diarrhea	<10%	1 (2)	26 (22)	2 (2)