UPMC CancerCenter

Partner with University of Pittsburgh Cancer Institute

Targeted Therapies to Enhance Rectal Preservation

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Available Targets in Rectal cancer

- DNA Changes
  - KRAS
  - BRAF V600E
  - Tumor Mutation Burden
  - **MSI/Lynch**
- IHC
  - MSI
  - HER2

DNA Mismatch Repair Deficiency in CRC

- MSI-H is found in >90% of patients with HNPCC and in only 5%-10% of sporadic CRC.
- MMR deficiency in MSI-H sporadic CRC is mainly due to hypermethylation of the MLH1 promoter, resulting in MLH1 silencing.
- MMR deficiency is observed in 5% of metastatic CRC, stomach, endometrium, bile duct, pancreas, prostate, and brain

MSI

- "Synonymous" terms (but not really): MMR proficient (pMMR) = Microsatellite stable (MSS); MMR deficient (dMMR) = Microsatellite high (MSI-H)

- What is it? Refers to a DNA repair pathway (mismatch repair pathway); inherited deleterious mutations = Lynch Syndrome (or HNPCC)
  - MMR pathway usually corrects mismatches at single nucleotides as well as short insertions/deletions

- Microsatellites: short DNA repeats in the genome; MSI-H refers to the increased frequency of deletions/insertions at microsatellites (don't worry too much about specific gene loci etc., unless you are a pathologist)

- Why do we care?
  - Predictive of immunotherapy response (one of the few times immunotherapy works in CRC)
  - If germline mutation, need to refer to genetic counseling and discuss screening/surveillance

Diagnosis of DNA Mismatch Repair Deficiency

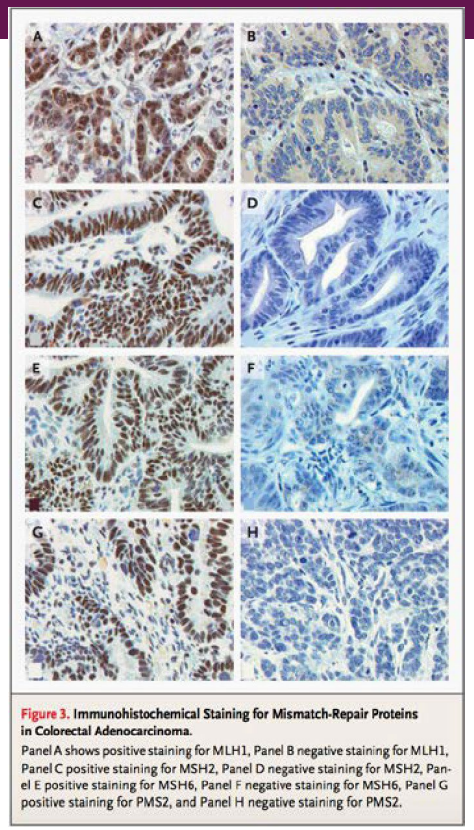
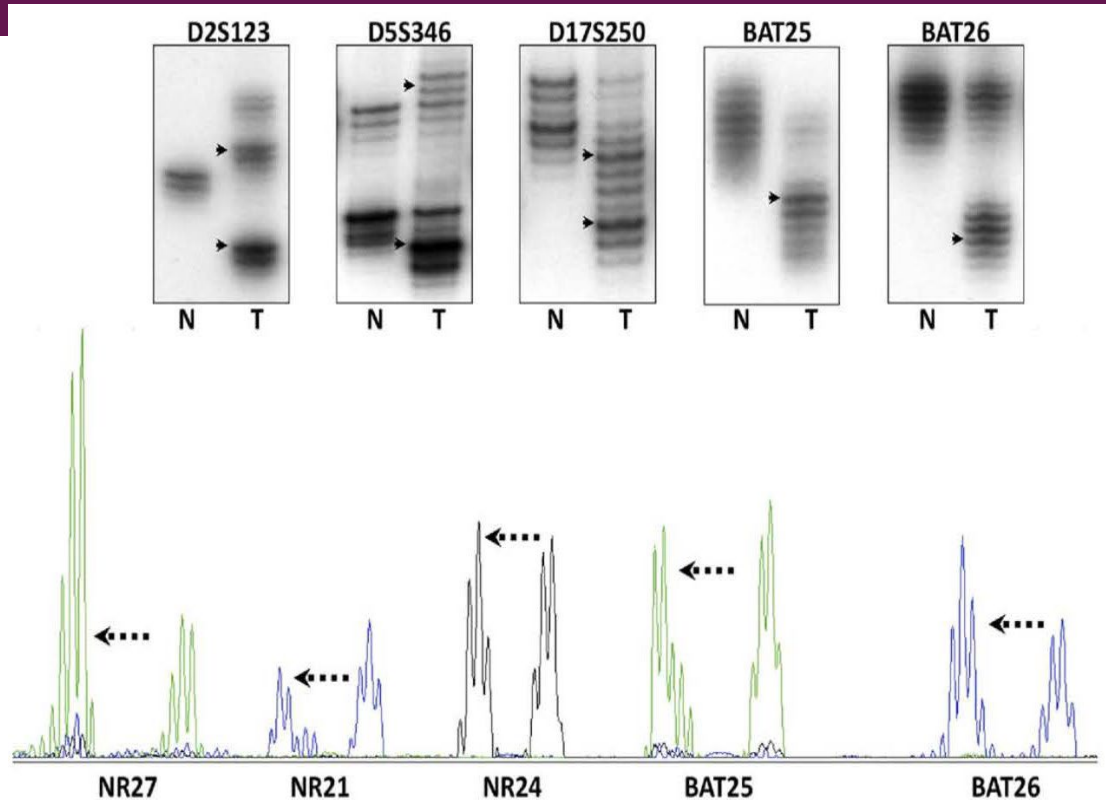


Figure 3. Immunohistochemical Staining for Mismatch-Repair Proteins in Colorectal Adenocarcinoma.
Panel A shows positive staining for MLH1, Panel B negative staining for MLH1, Panel C positive staining for MSH2, Panel D negative staining for MSH2, Panel E positive staining for MSH6, Panel F negative staining for MSH6, Panel G positive staining for PMS2, and Panel H negative staining for PMS2.

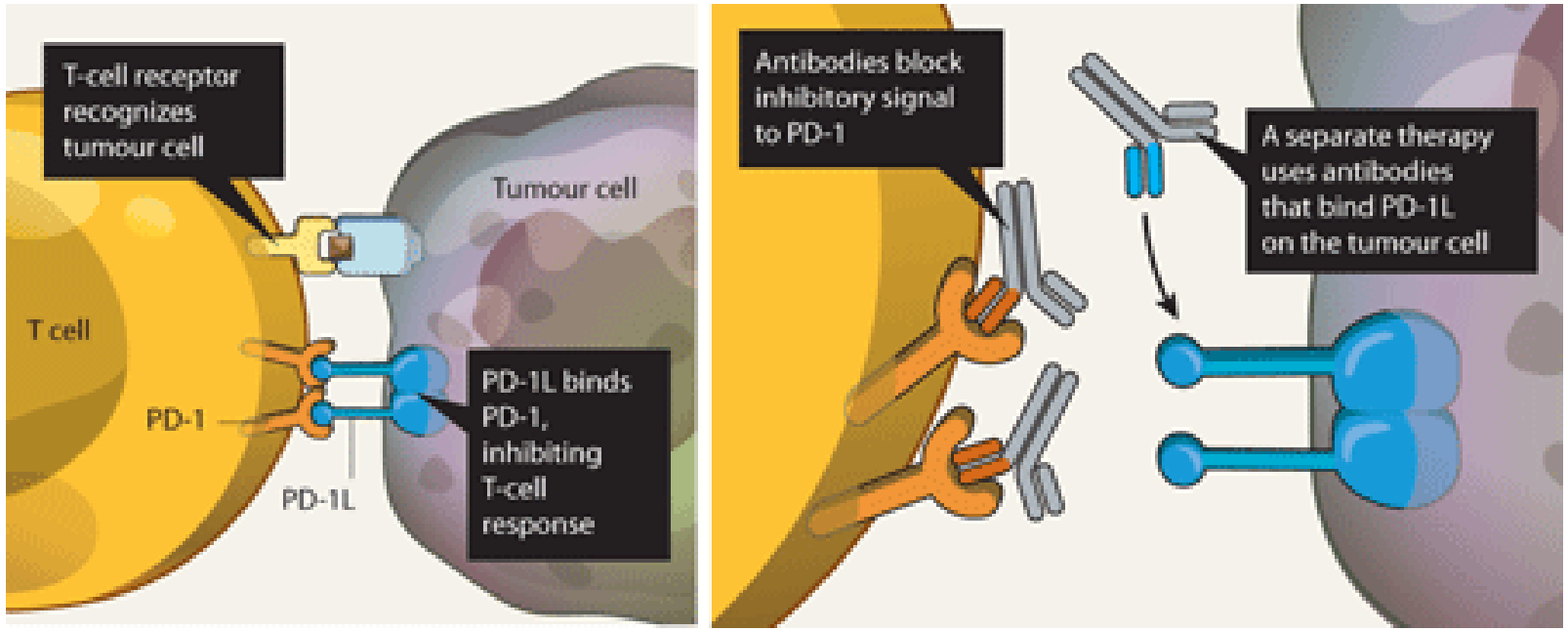


IHC of 4 MMR genes:
MLH1; PMS2; MSH2; MSH6
à dMMR vs. pMMR

PCR of 5 Markers for Microsatellite Instability (MSI) à MSI-high (3-5) vs. MSI-low (1-2) vs. MSS (microsatellite stable)

Hampel H, et al, NEJM 2005; Boland CR et al, Gastroenterology 2010

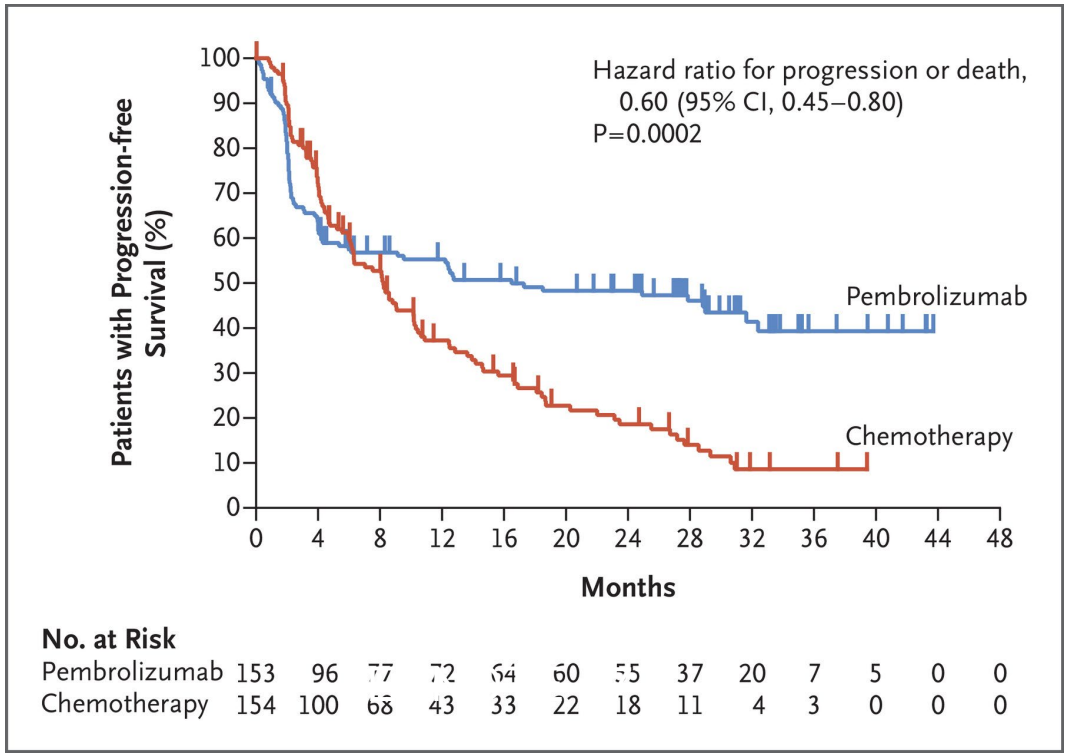
Immunotherapy



Pembrolizumab is an antibody directed at PD-1

- http://www.nature.com/nbt/journal/v30/n8/images/nbt0812-729-I1.gif

Metastatic MSIH Colon Cancer



	Chemo	Pembro
Complete Response	3.9 %	11.1 %
Partial Response	29.2 %	32.7 %
Stable Disease	42.2 %	20.9 %
Progressive disease	12.3 %	29.4 %
NE	12.3 %	5.9 %

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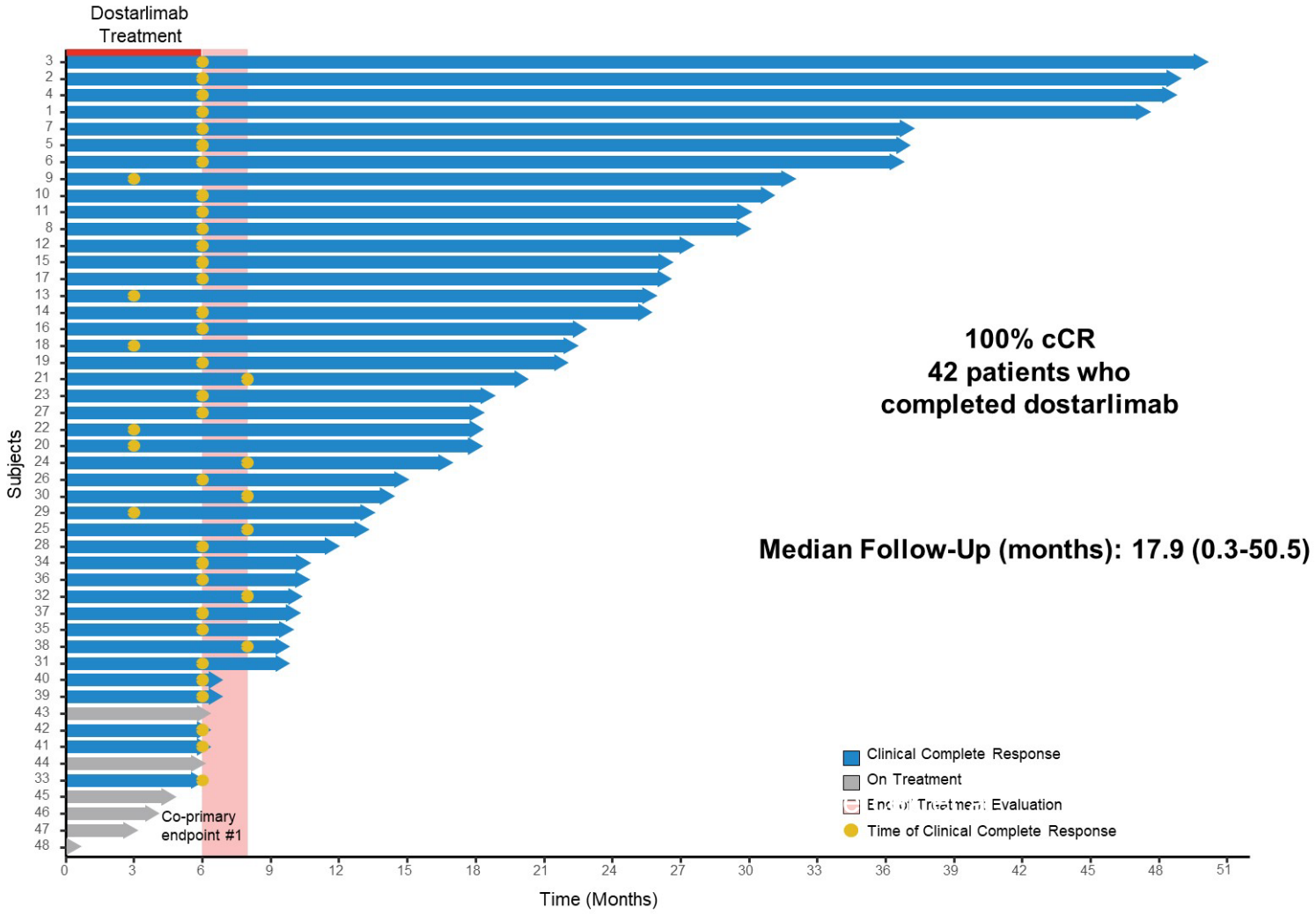
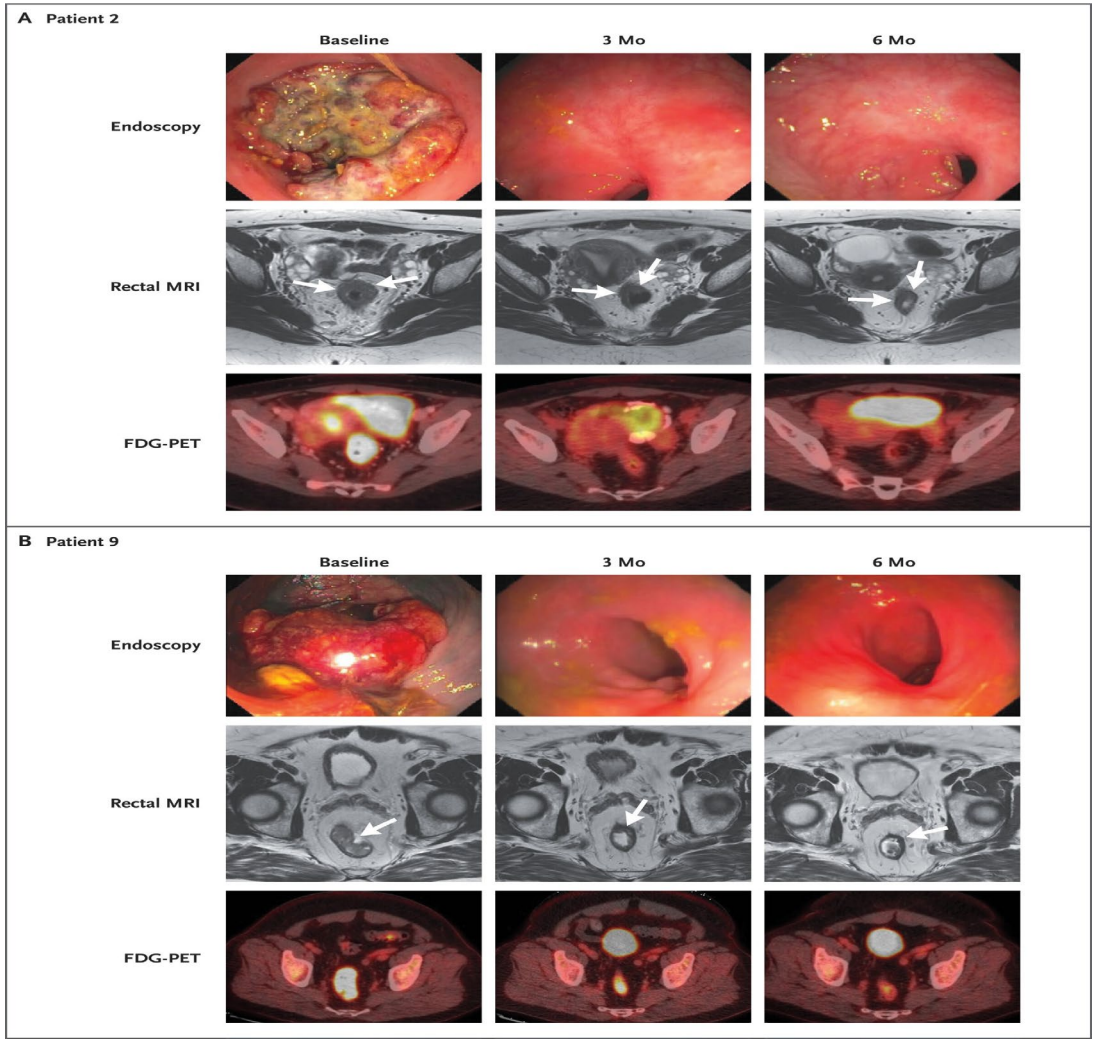
MSI-H rectal cancer: high rates of complete clinical response with immunotherapy alone



Results



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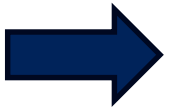
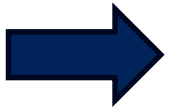
Typical TNT schema for dMMR rectal cancer

Immunotherapy (dostarlimab or pembro or nivo) ~ 6 months



Re-evaluate every 2 months; if persistent disease at 6 months then chemoRT; if no cancer, “watchful



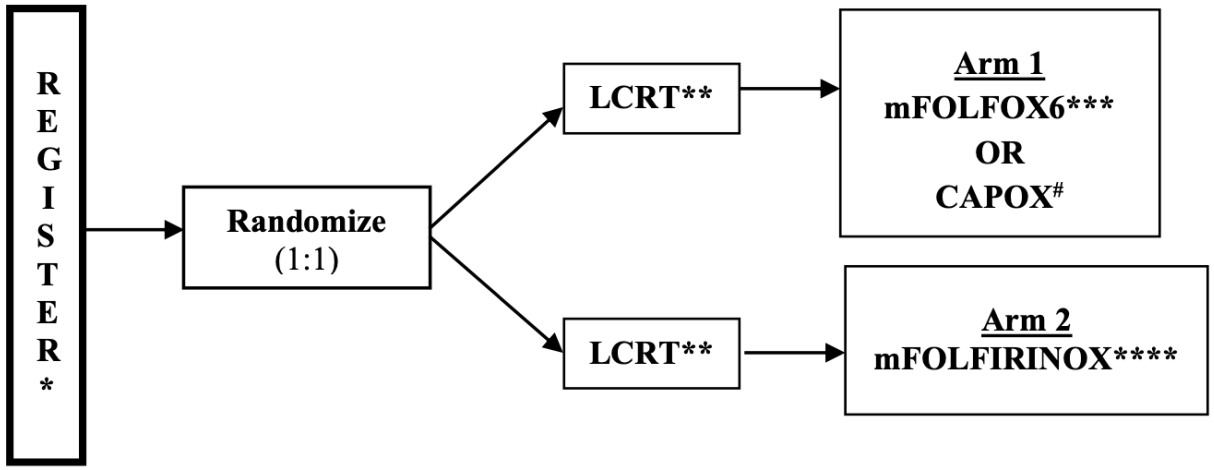
If residual disease after chemoRT, surgery +/- systemic chemo

If complete response, observation is an option +/- systemic chemo

Locally advanced MSS rectal cancer

Locally advanced rectal cancer: JANUS – IRB 22-191

Schema



* Patients with locally advanced rectal cancer: <=12cm, T4N0 OR anyT, N1 OR T3N0 that would require APR or coloanal anastomosis

** LCRT = long-course chemoradiation (5 weeks)

***mFOLFOX6 = 8 cycles (1 cycle = 2 weeks)

****mFOLFIRINOX = 8 cycles (1 cycle = 2 weeks)

CAPOX = 5 cycles (1 cycle = 3 weeks)

Treatment is to continue for the full course of LCRT and Arm 1 or Arm 2 chemotherapy unless there is a clinical reason to stop. Following neoadjuvant chemotherapy, patients will either proceed to surgery (TME) or watch & wait (WW). Patients will be followed for 8 years or until death, whichever comes first.

Conclusions

- MSI testing should be performed on all ColoRectal Cancers.
- If no contraindications to IO, proceed with single agent IO.
- JANUS clinical trial for locally advanced MSS rectal cancer
- MSS Upper and Mid Rectal Cancer, neoadjuvant chemotherapy followed by surgery is an option for pts wishing to avoid radiation.

[1]Kim S-B et al. Lancet Oncol 2017. [2]Schmid P et al. J Clin Oncol 2020