Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

ACI MSI/TMB Case Studies

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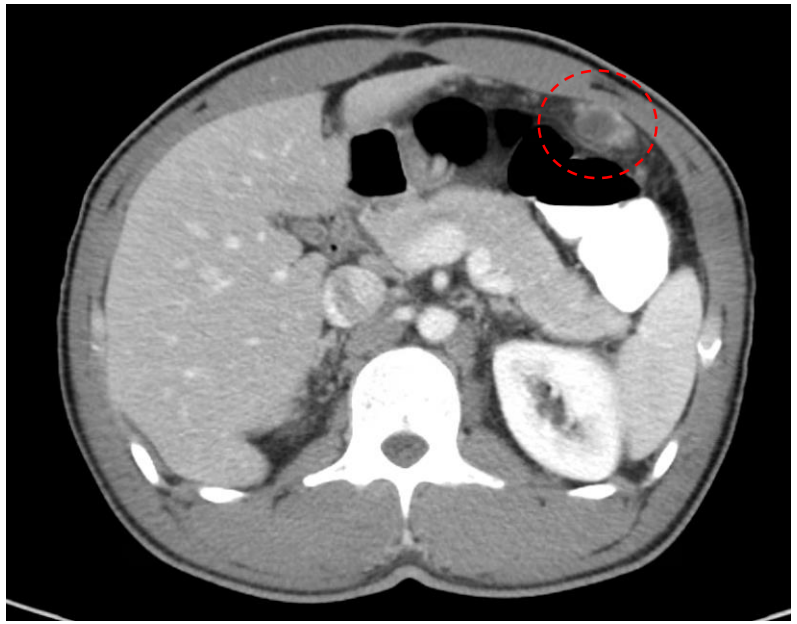
MSI Case Studies

Case 1

Metastatic colon cancer, MSI-H, first line therapy decision

- 38-year-old man presents with periumbilical pain.
  - CT CAP described right-sided colon mass.
  - Colonoscopy identified mass in ascending colon, unable to pass scope beyond, positive for adenocarcinoma.
- Underwent extended right hemicolectomy.
  - Pathology showed poorly differentiated adenocarcinoma, 3/39 LN involved, pT3N1b. MLH1 and PMS2 staining absent.
- Completed 3 months of adjuvant CAPEOX.
  - Noticed an increase in abdominal pain after 4 months.
  - CT CAP showed multiple areas soft tissue nodularity and infiltration suspicious for carcinomatosis (example on right).
  - CEA increased from 7 ng/mL to 89 ng/mL.



What would you do next?

1. Perform Next Generation Sequence analysis
2. FOLFIRI + bevacizumab
3. Pembrolizumab 400 mg every 6 weeks
4. Nivolumab + ipilimumab

Case 2

Metastatic pancreatic cancer, MSI-H, first line therapy decision

- 75 yo otherwise healthy man presented with nodules on scalp and chest;
- Biopsy of skin nodule showed adenocarcinoma (CD20 - CK7+).
- C/A/P CT scans showed pancreatic mass and multiple liver lesions.
- CA19-9: 2806
- Foundation One CDx on skin metastasis biopsy showed:

Microsatellite status MSI-High §
Tumor Mutational Burden 23 Muts/Mb §
ARID1A E1774*
ASXL1 G645fs*58
ATR E3fs*9
KRAS G12D
MLL2 P2354fs*30
MSH2 V686fs*24
MSH2 I770fs*37
MSH6 K693fs*43
PTCH1 L39fs*41
QKI E135fs*5
RNF43 G659fs*41
SMAD4 R361H
TGFBR2 K128fs*3

What would you do next?

1. Chemotherapy with FOLFIRINOX or Gemcitabine/Nab paclitaxel
2. Pembrolizumab 400 mg every 6 weeks
3. Nivolumab + ipilimumab
4. Clinical trial (which requires 300 mile drive)

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TMB Case Studies

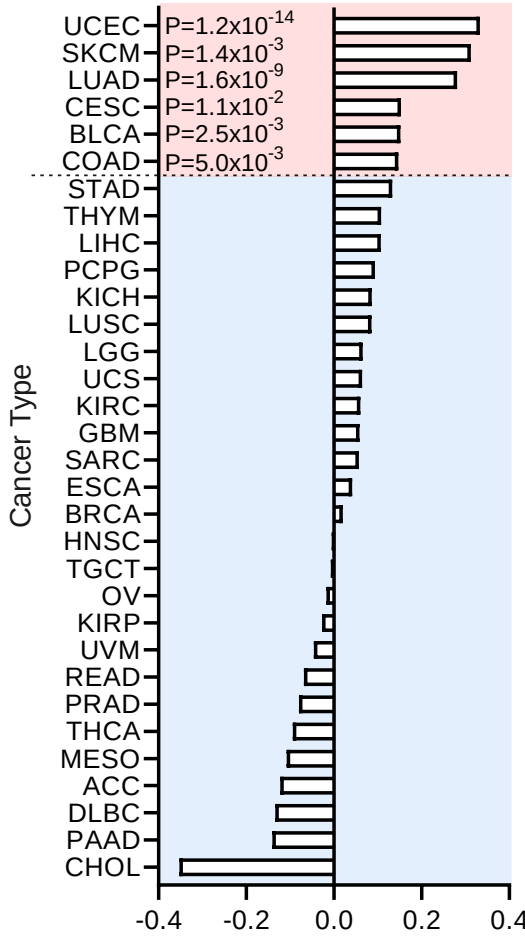
Cancer-type differences in tumor mutation burden as an immune checkpoint biomarker

Daniel McGrail, Ph.D.

The University of Texas MD Anderson Cancer Center

Association of TMB and immunogenicity across cancers

- If mutations/neoantigens promote immunogenicity, more neoantigens should correlate with more T cells
  - **True** for melanoma, lung, and others
    - "**Category I**"
  - **Not detected** for breast, prostate, renal, GBM, and others
    - "**Category II**"
- Implications for immune checkpoint blockade?



Category I: ~27% of new cases
- More neoantigens → more T cells

Category II: ~52% of new cases
- No association of neoantigens and T cells

McGrail et al., *Annals of Oncology* (2021)

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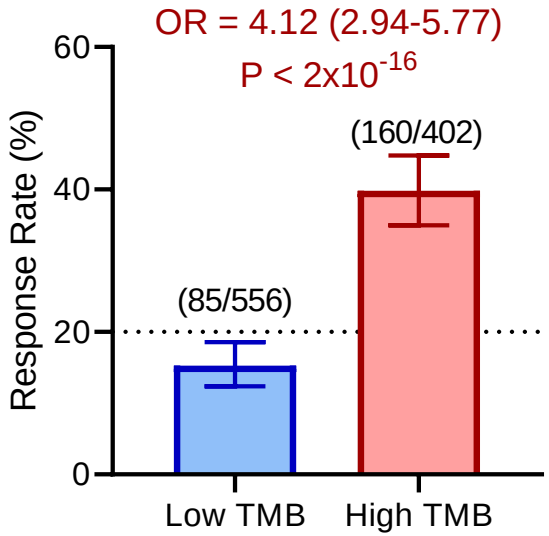
Ability of TMB to predict ICB response varies across cancer types

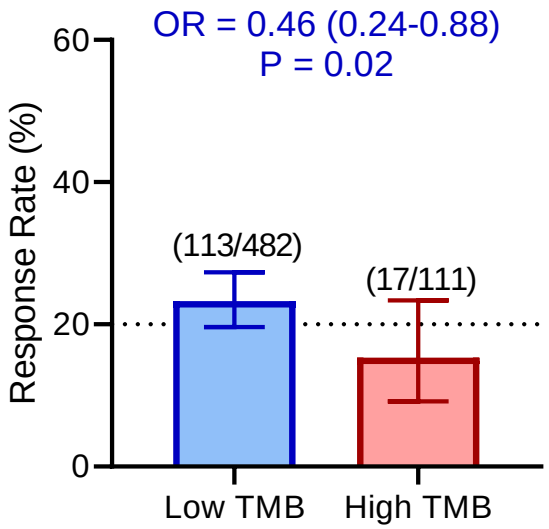
Category I: ~27% of new cases

- More neoantigens → more T cells
- **Improved** ICB response rate in TMB-H



Category II: ~52% of new cases

- No association of neoantigens and T cells
- **Slightly worse** response rate in TMB-H



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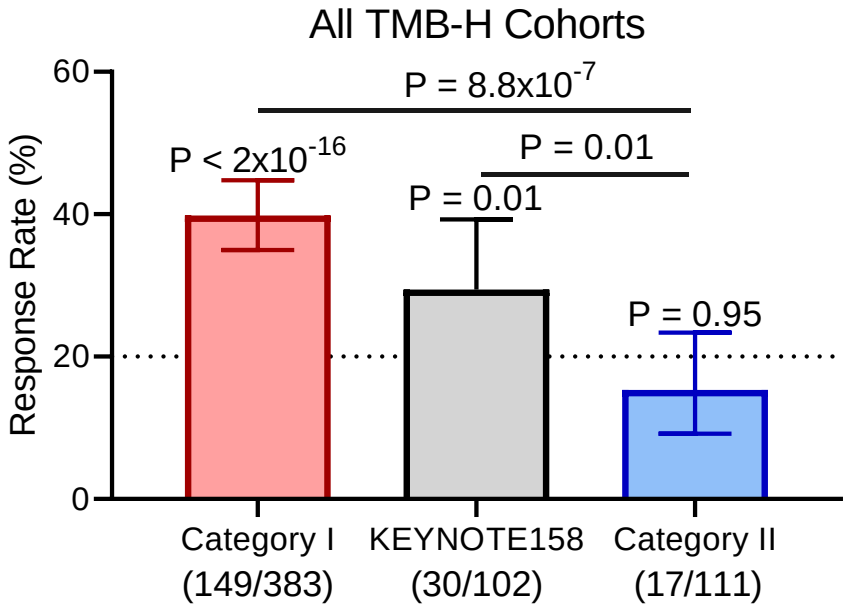
McGrail et al., *Annals of Oncology* (2021)

Ability of TMB to predict ICB response varies across cancer types

- TMB-H predicted ICB response in Category I, but not Category II tumors
- Equivalent results obtained when analyzing:
  - ORR with continuous TMB or varying TMB thresholds
  - Overall survival with binary or continuous TMB
- **Cancer context may be important when considering TMB as an ICB biomarker**



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McGrail et al., *Annals of Oncology* (2021)

Case 3
Durable response to PD-1 inhibitor monotherapy in microsatellite-stable, tumor mutational burden-high colorectal cancer

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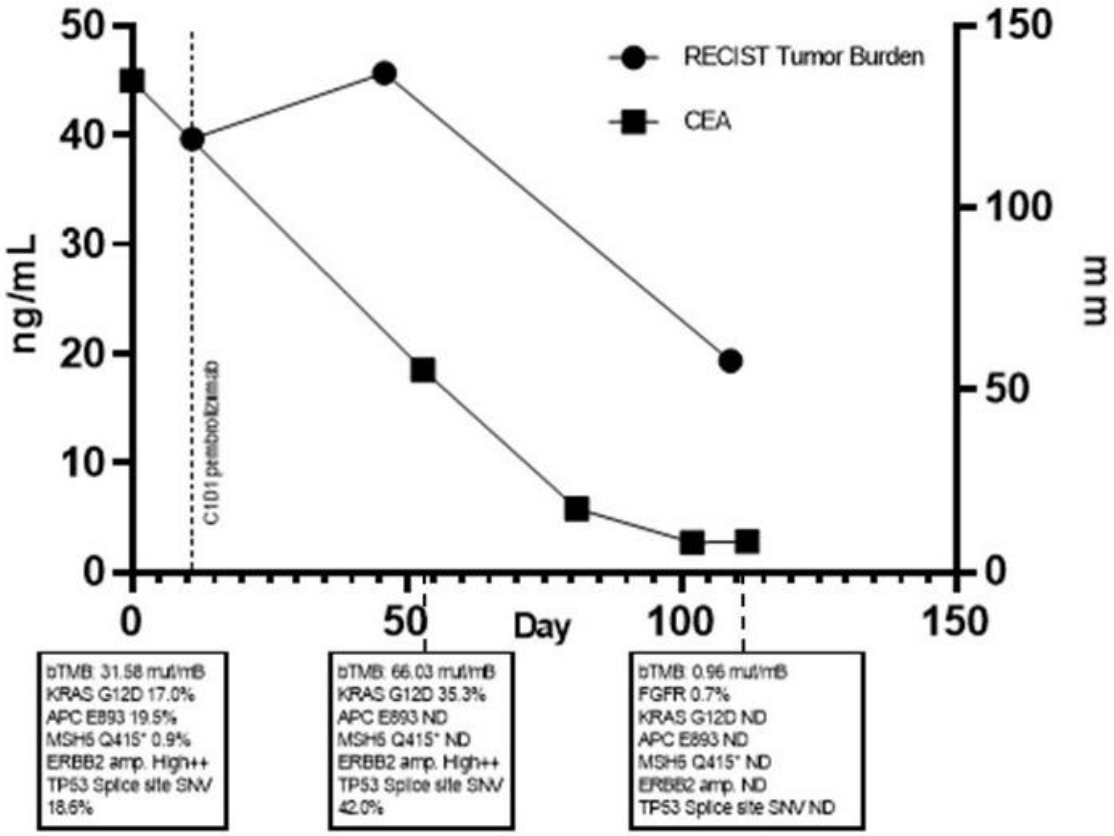
Co-Director, Developmental Therapeutics -Lurie Cancer Center
Associate Professor, Division of Hematology and Oncology, Department of Medicine

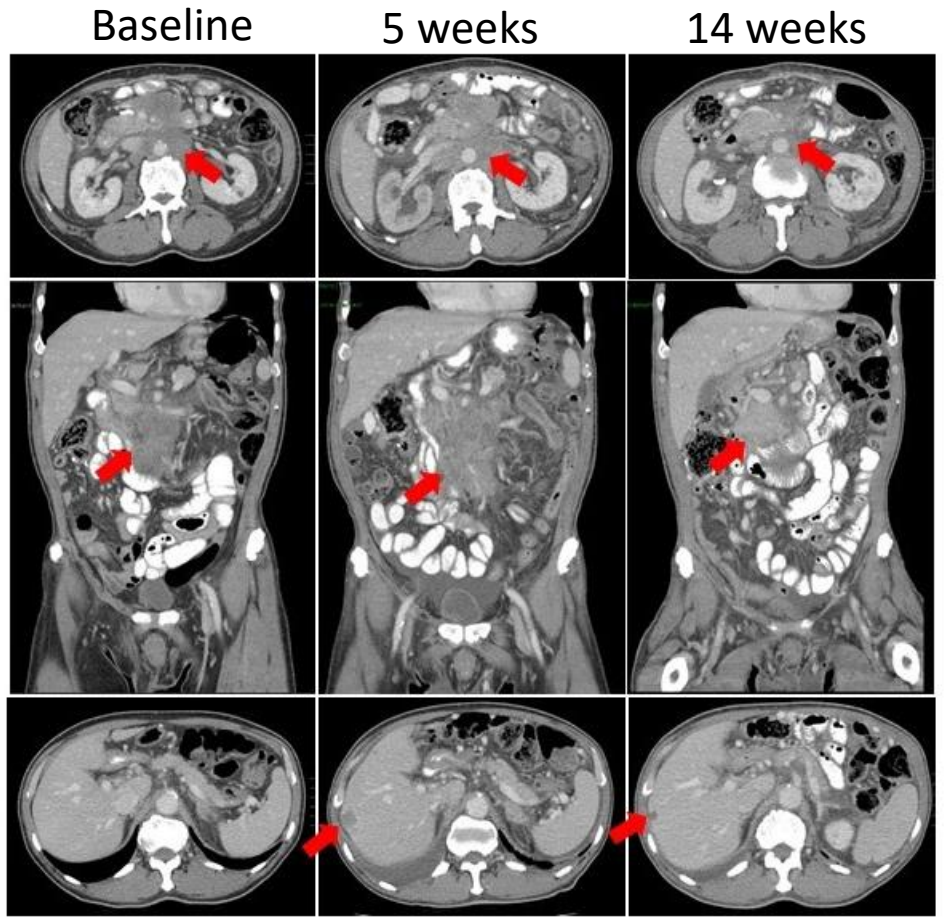
Associate Program Director, Developmental Therapeutics Fellowship
Northwestern University Feinberg School of Medicine
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Case Presentation

- 64-year-old male presented with initial complaint of abdominal, found to be right-sided colorectal cancer (CRC)
- Stage IIIC, MSS, TMB-H (11 mut/mB), with KRASG12D and ERBB2 amplification
- Progression on multiple lines of therapy and put under home hospice
- Started on pembrolizumab monotherapy around 3.5 years after initial presentation

Treatment Response





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Discussion

- Several cases of response to ICI in MSS, TMB-H have been reported
- Most cases involve POLE mutations, known to sensitize to immunotherapy[1,2,3]
- One patient's response was due to germline MSH6 mutations[4]
- Our patient did have an MSH6 null variant found at start of treatment (0.9% VAF), no POLE alteration
- MSH6 may have contributed, but high TMB likely driver of response

1. Gong J et al. *J Natl Compr Canc Netw* 2017.
2. Fabrizio DA et al. *J Gastrointest Oncol* 2018.
3. Keenan BP *et al. Anticancer Res* 2021.
4. Xie T et al.. Hered Cancer Clin Pract 2021.

Conclusions

- MSS, TMB-H colorectal cancer may respond to anti-PD-1 therapy even in the absence of a known sensitizing mutation
- Comprehensive genomic profiling that reports TMB should be utilized in order to not miss this subset of patients
- Further prospective studies should evaluate immunotherapy for MSS, TMB-H CRC

Case 4

Metastatic colon cancer, TMB-H

Metastatic colon cancer, TMB-H

- 65 year old male diagnosed with adenocarcinoma of the proximal transverse colon on screening colonoscopy
- Right hemicolectomy performed. Path- T3N1b, MSS (MMR proficient)
- Received adjuvant FOLFOX
- 3 years later… diagnosed with recurrent/ metastatic disease
- **FoundationOne CDX: *KRAS* G12D mutation, MSS, TMB=11 muts/Mb**
- Progressed on 1st line FOLFIRI/bev, 2nd line FOLFOX/bevacizumab, 3rd line regorafenib

Metastatic colon cancer cancer, TMB-H

- Patient initiated treatment with single-agent pembrolizumab
- No treatment related side effects
- Abdominal pain increased on treatment
- After 3 months of treatment with pembrolizumab
  - CEA increased from 95 at baseline to 1053
  - CT scan - progressive disease with new hepatic metastatic disease and new/increased peritoneal carcinomatosis

Questions

Thoughts on why there was no response and progression of disease occurred?

What would you do next?

Additional cases if time permits

Case 5

Metastatic adenocarcinoma of the GE junction, TMB-H

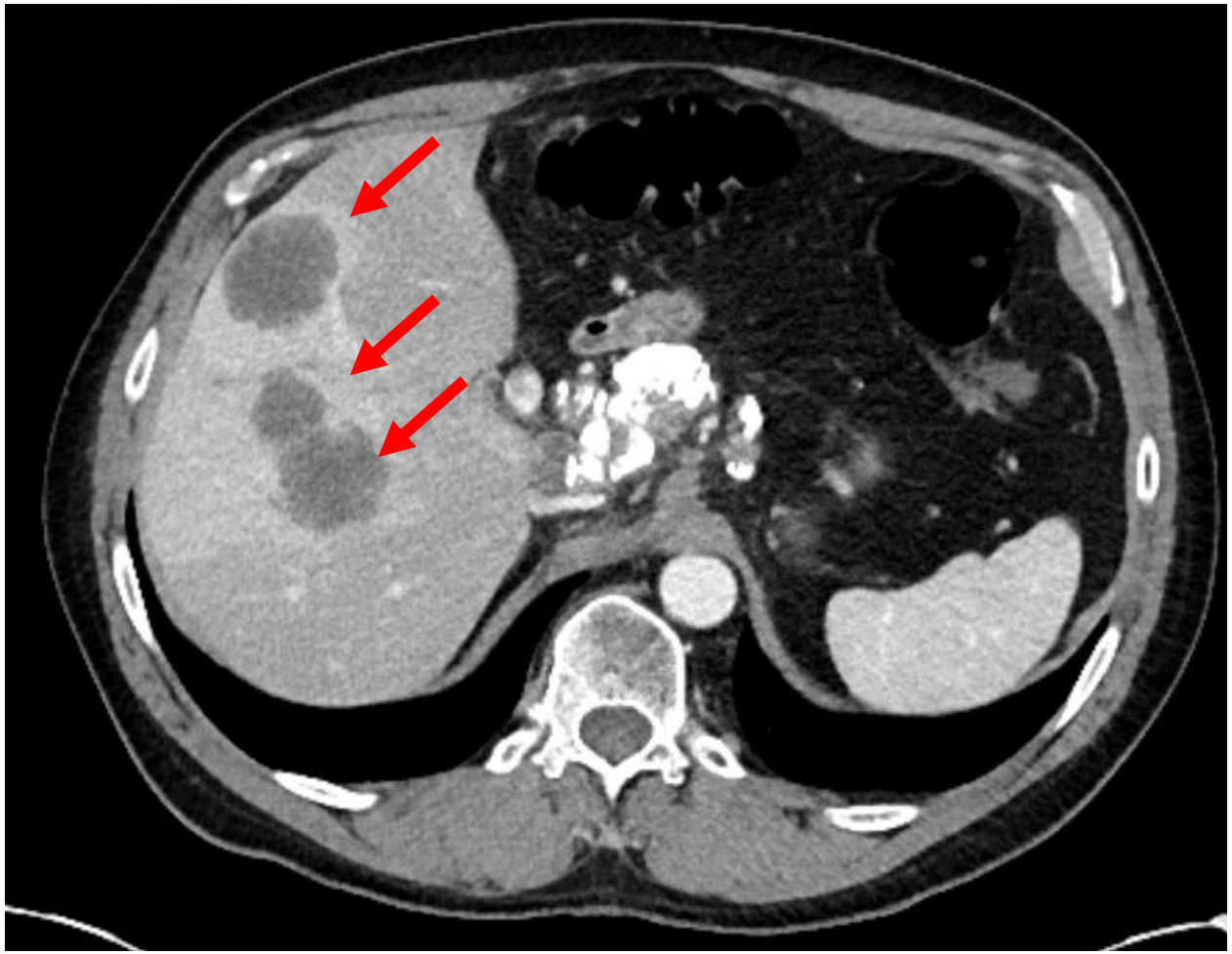
Metastatic esophageal cancer, TMB-H

- 47 year old male presented with dysphagia and upper gi bleed
- 15 years prior was diagnosed with stage III Hodgkin lymphoma
  - Treated with chemotherapy and radiation
  - Complete response to treatment. No evidence of disease since treatment
- Diagnosed with adenocarcinoma of the gastroesophageal junction, with metastases to the liver
- **Biomarkers: HER2 negative, MSS, insufficient tissue for PDL1 testing**
- Progressed on 1st line FOLFOX, 2nd line paclitaxel + ramucirumab, 3rd line irinotecan

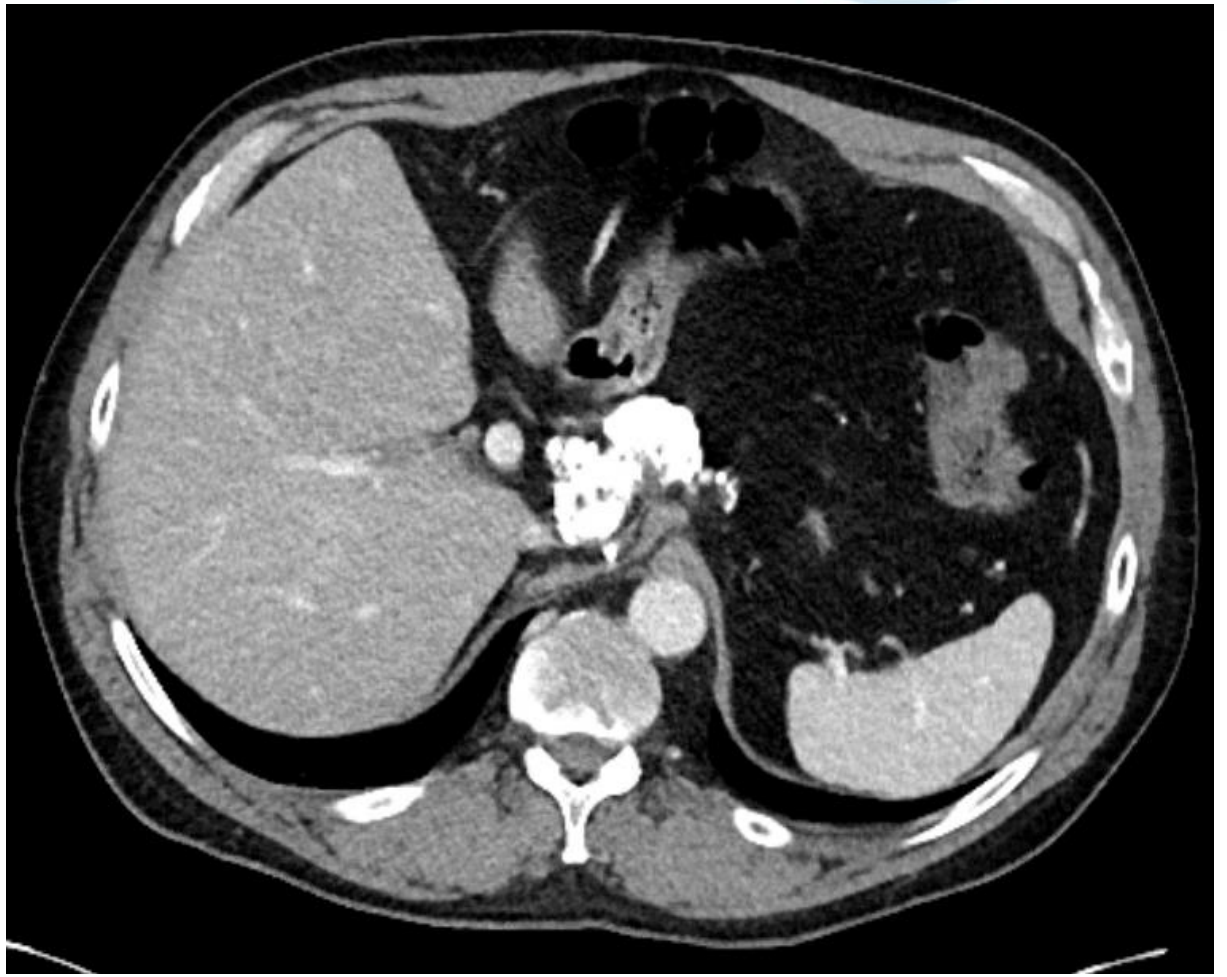
Metastatic esophageal cancer, TMB-H

- Referred for clinical trial
- Symptomatic right upper quadrant pain related to liver metastases
- Biopsy of liver metastasis obtained for additional biomarker testing
- **Biomarker testing:**
  - PDL1 CPS = 8%
  - NGS profiling: Multiple mutations, MSS, *ERBB2* not amplified, **TMB=127**
- Patient initiated treatment with single-agent pembrolizumab
- Rapid resolution of abdominal pain and improvement in QOL
- CEA fell from 643 to 2.0 in first 6 months

Metastatic esophageal cancer, TMB-H



Baseline

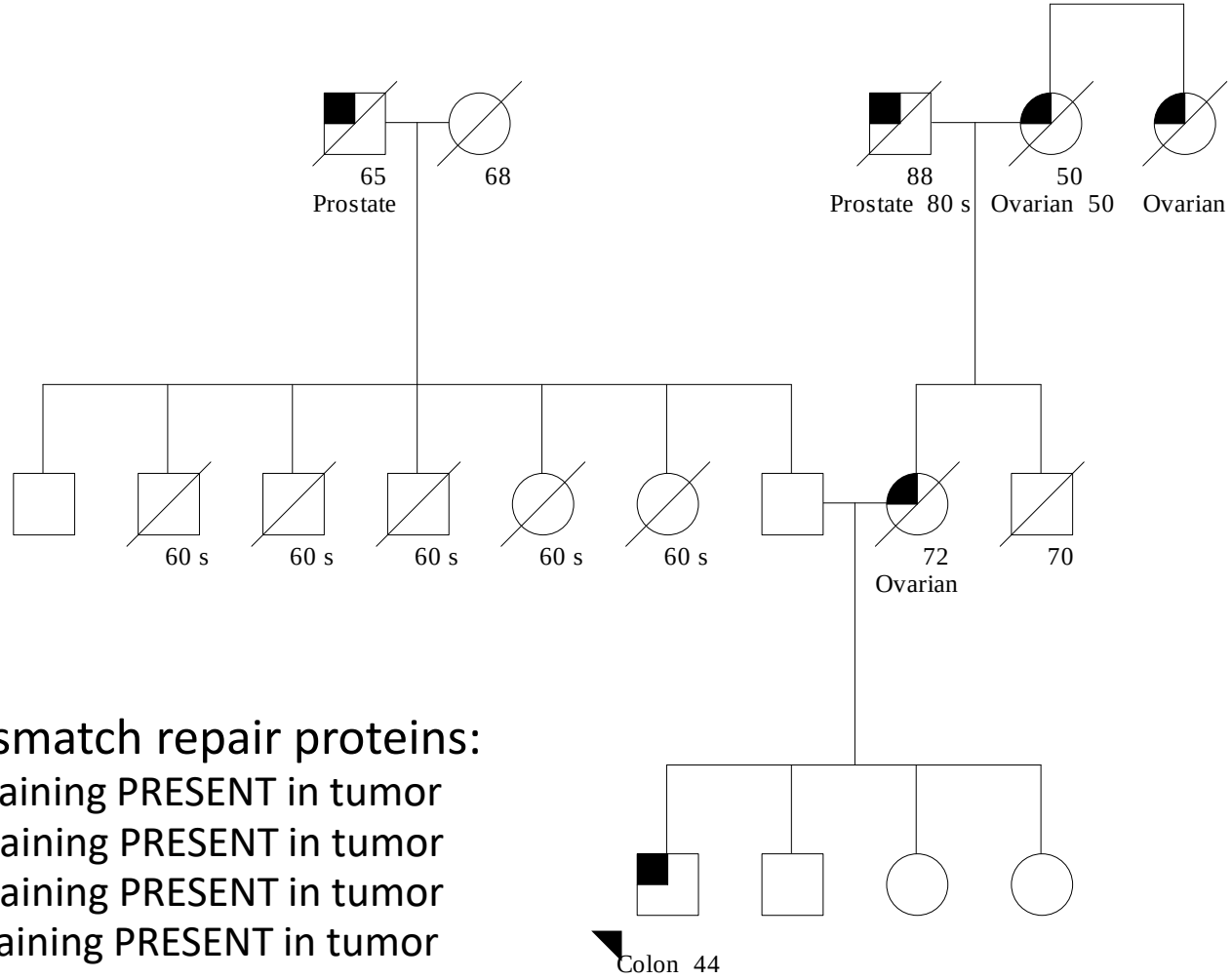


After 2 years

Case 6

Lynch syndrome with sporadic colon cancer

- 44 year-old man with sigmoid colon cancer
  - synchronous metastasis to liver and lung, low-volume disease
  - initiated on systemic chemotherapy



IHC for the mismatch repair proteins:

- MLH1: staining PRESENT in tumor
- MSH2: staining PRESENT in tumor
- MSH6: staining PRESENT in tumor
- PMS2: staining PRESENT in tumor

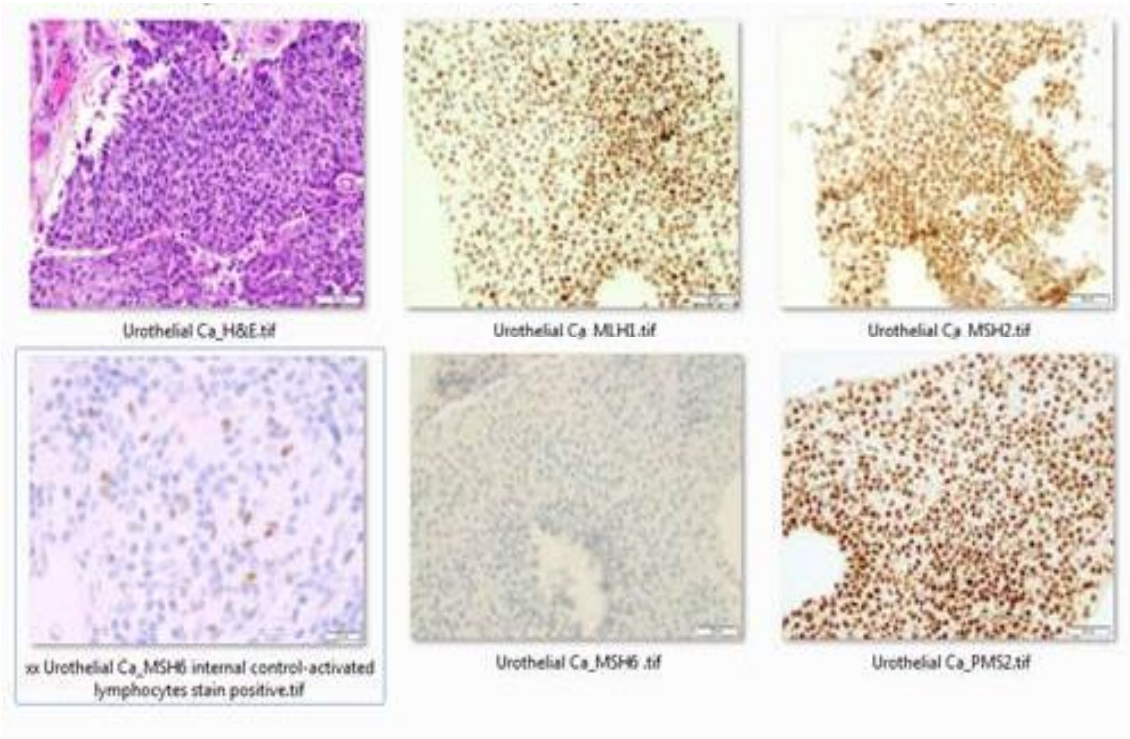
Case #5 Presentation Continued

…..Fast forward 10 years

- Pt now 54 years-old
  - s/p multiple resections for metastatic disease
  - intermittent chemotherapy/targeted therapy; low volume disease
  - KRAS/BRAF wild-type
- Pt develops intermittent hematuria
- CT imaging demonstrates increasing size of a right renal pelvis tumor from 2cm to 3.5cm
- Ureteroscopy biopsy:
  - Superficial fragments of papillary urothelial cancer, high-grade
- Radical nephroureterectomy:
  - pT1N1; high-grade urothelial cancer
  - NGS performed including MSI testing

Case #5 continued…

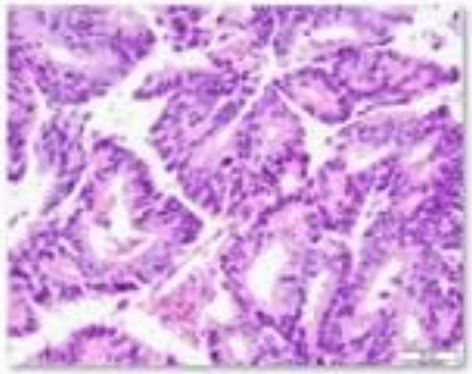
- Renal pelvis tumor evaluated via MSK-IMPACT:
  - MSISensor score: 3.97 (Indeterminate range)
- Immunohistochemical staining:
  - MSH6 protein loss

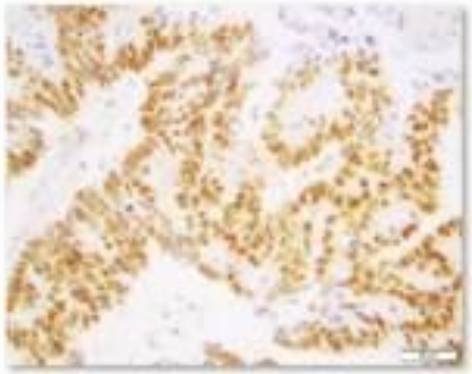


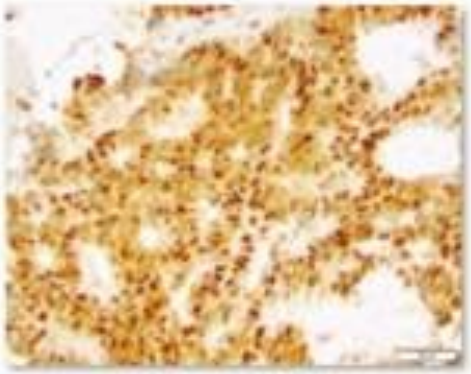
- MSK-IMPACT Germline analysis:
  - *MSH6* c.651dupT (p.Lys218*) exon4 pathogenic variant identified

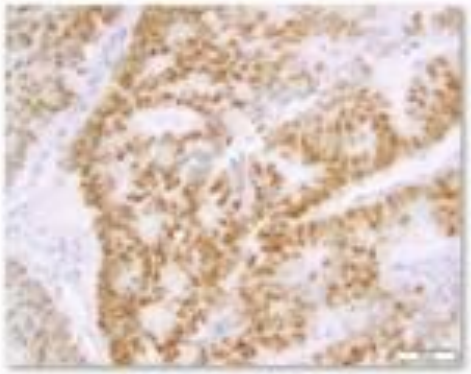
Case #5 continued…

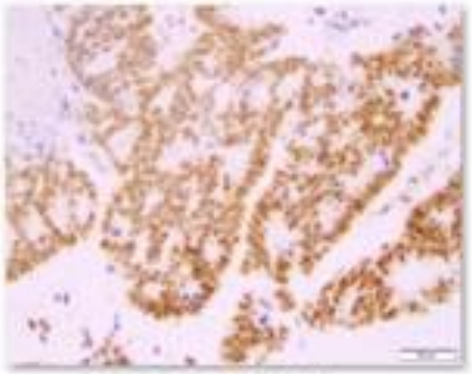
- Based on finding of Lynch syndrome, further analysis of the colorectal tumor was performed including:
  - *Repeat* IHC: NORMAL staining of all 4 MMR proteins
  - MSK-IMPACT: MSISensor score: 0.1 (Microsatellite stable)
  - Tumor signature not consistent with MSI tumor
  - No somatic *MSH6* mutations and no LOH at *MSH6*


Colon Ca_H&E.tif


Colon Ca_MLH1.tif


Colon Ca_MSH2.tif


Colon Ca_MSH6.tif


Colon Ca_PMS2.tif

Case conclusion…

Integration of Tumor/Germline genetics:

- Pt's CRC tumor appears to have developed sporadically
- Pt's UTUC occurred in the setting of Lynch syndrome (*MSH6* germline mutation)