Society for Immunotherapy of Cancer

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Immunotherapy for the Treatment of Microsatellite Instability – High Cancers

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AAEM American Academy of Emergency Medicine — Champion of the Emergency Physician

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

Disclosures

- Research support: Roche/Genentech
- Contracted research: Roche/Genentech, Merck
- Consulting fees: Maze Therapeutics

- I will be discussing non-FDA approved indications during my presentation.

DNA Mismatch Repair

- The presence of microsatellite instability (MSI) represents phenotypic evidence of mismatch repair (MMR) dysfunction.
- MMR dysfunction can be caused by mutations in genes that code for MMR proteins (MLH1, MSH2, MSH6, PMS2)
- Mutations in MMR proteins can result from:
  - Hereditary causes (Lynch syndrome)
  - Somatic mutations
  - Silencing through promoter methylation

Microsatellite Instability

- Microsatellites are stretches of DNA with a repetitive sequence of nucleotides and are susceptible to acquiring errors when defective MMR genes are present.
- MSI is a condition in genetic hypermutability
- Increased somatic mutations → increased neoantigen numbers
- Patients with MSI-H tumors responding to immune checkpoint inhibitors develop rapid expansion of neoantigen-specific T cell clones that are reactive to tumor neoantigens
- The 1997 NCI consensus meeting recommended testing a core panel of five microstatellite markers for MSI (BAT25, BAT26, D2S123, D5S346, and D17S250). MSI-high is defined as 2/5 microsatellite markers that are mutated

References for T-cell clonality

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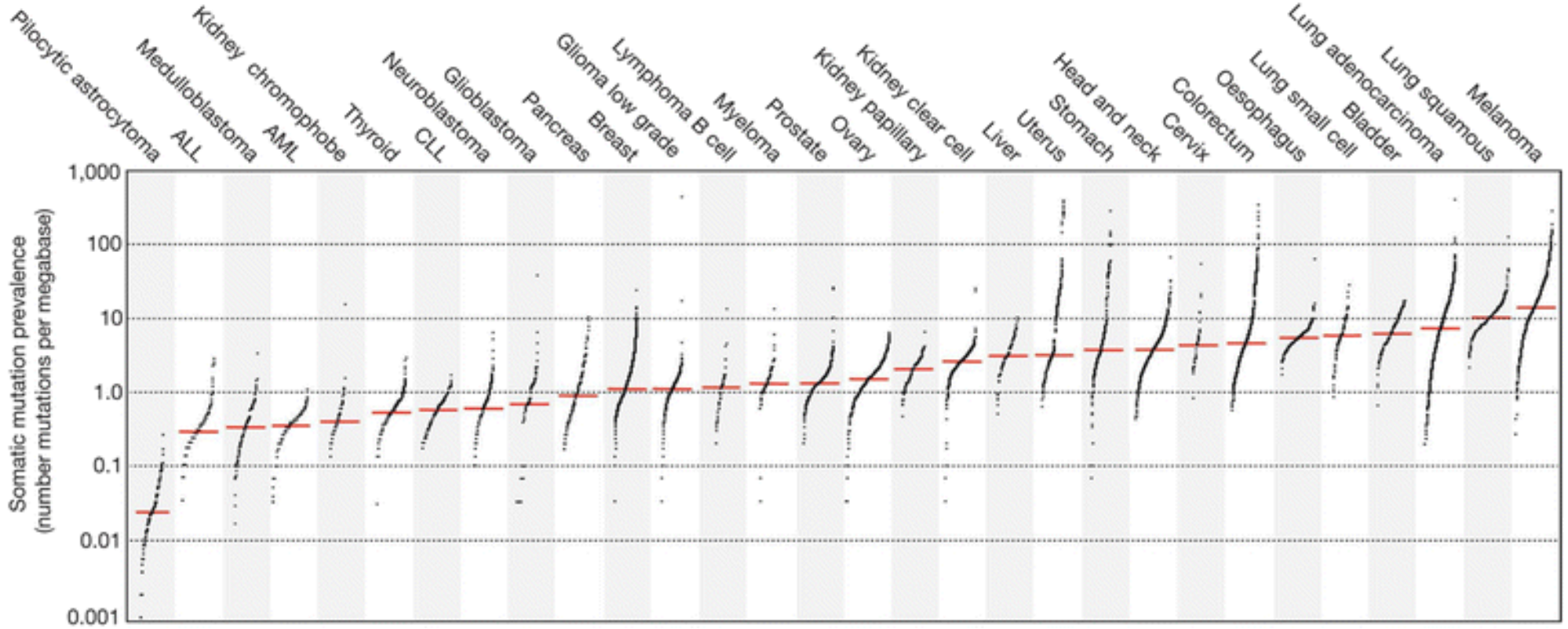
- Riaz N, Havel JJ, Makarov V, et al. Tumor and Microenvironment Evolution during Immunotherapy with Nivolumab. Cell. 2017 Nov 2;171(4):934-949.e16. doi: 10.1016/j.cell.2017.09.028. Epub 2017 Oct 12.
- van Rooij N, van Buuren MM, Philips D, et al. Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma. J Clin Oncol. 2013 Nov 10;31(32):e439-42. doi: 10.1200/JCO.2012.47.7521. Epub 2013 Sep 16.

Somatic mutations by cancer type

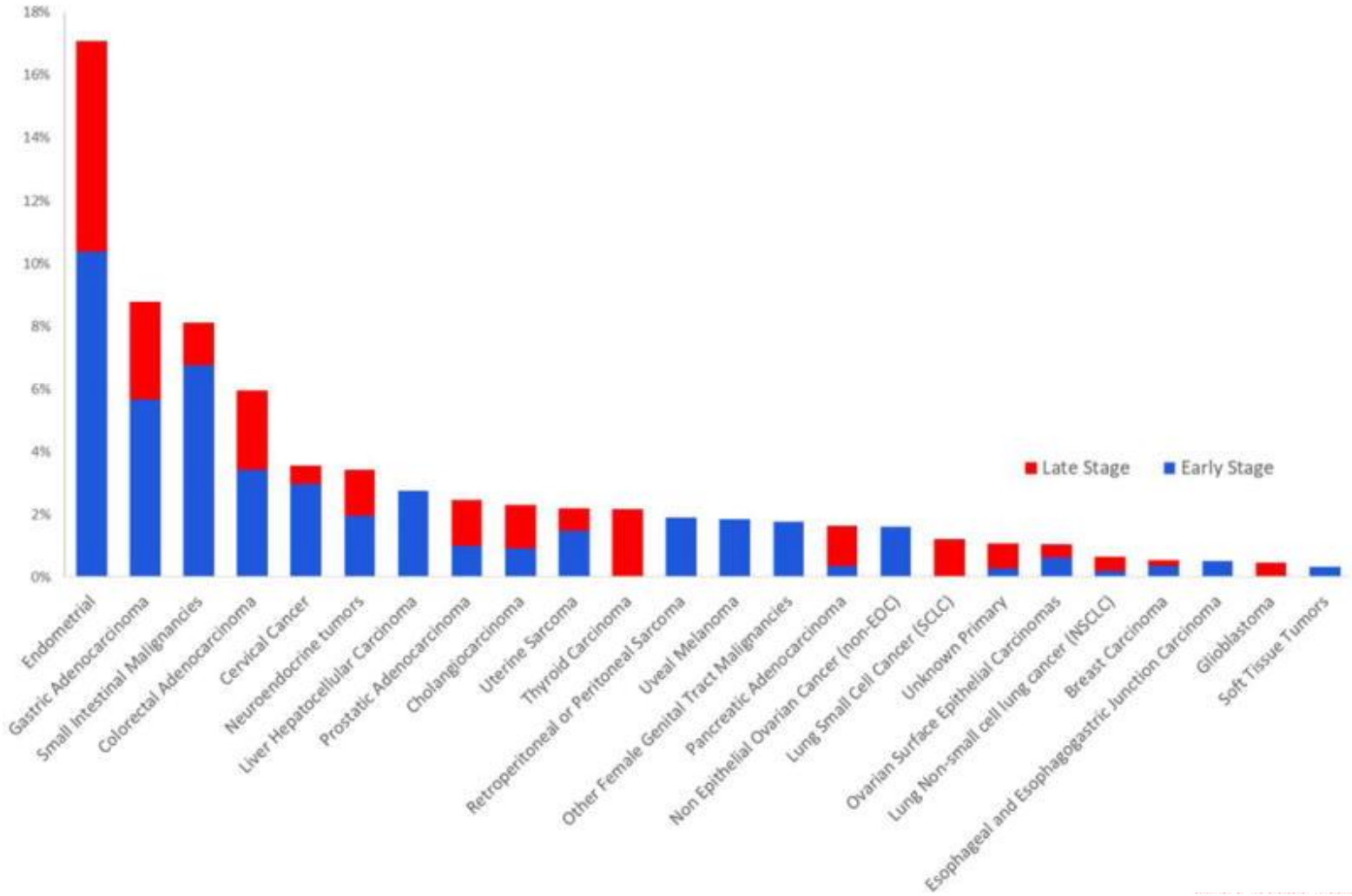


Alexandrov, Nature 2013.

Many tumors are MSI-high or MMR-deficient

- Endometrial cancer (30%)
- Colorectal/gastric cancer (20%, up to 5% of metastatic patients)
- Genitourinary, breast, thyroid, others (<5%)
- Also share histopathological characteristics, like immune cell infiltration, medullary histology, poorly differentiated
- Prognosis with MSI-H appears to be stage-specific
  - Localized, surgically-resected is favorable
  - Metastatic = not favorable

Many tumors are MSI-high or MMR-deficient



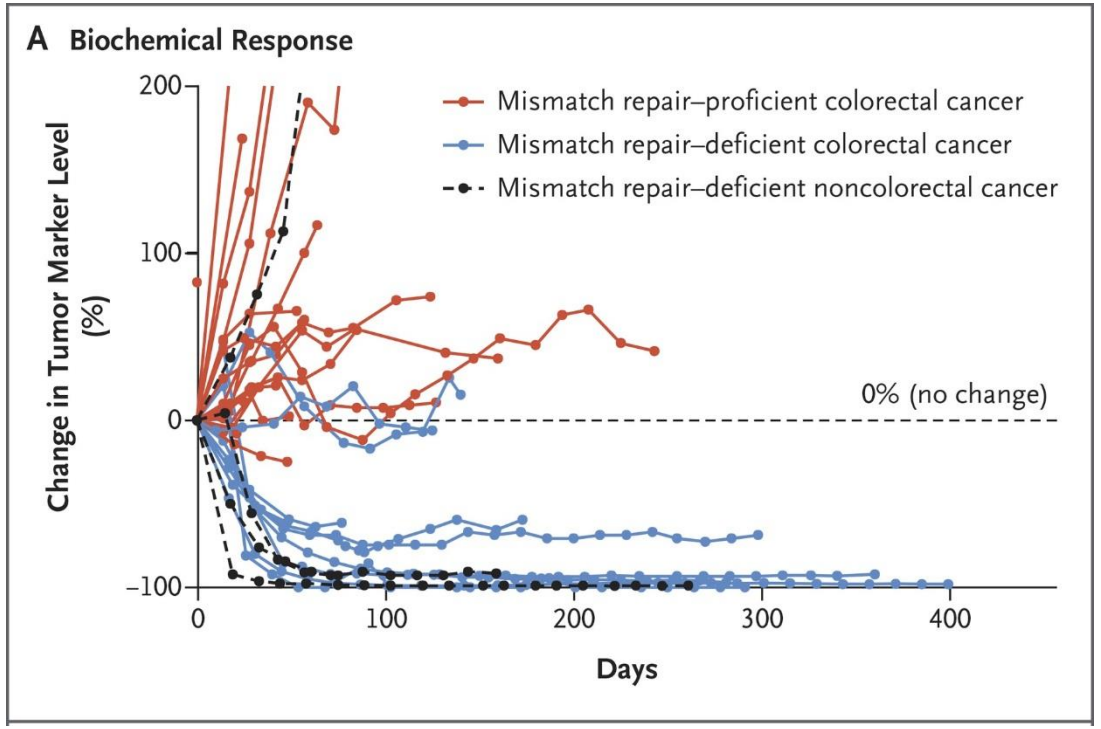
Le, Science 2017.

FDA-approved immunotherapies for MSI-high populations

Drug	Approved	Indication	Dose
Pembrolizumab	2017	Adult/pediatric patients with unresectable/metastatic **MSI-H or dMMR solid tumors** with progression on other treatment **MSI-H or dMMR colorectal cancer** with progression after a fluoropyrimidine, oxaplatin, and irinotecan	Adults: 200 mg Q3W Pediatric: 2 mg/kg (up to 200 mg) Q3W
Nivolumab	2017	Patients >12 yr with **MSI-H/dMMR metastatic CRC** with progression after fluoropyrimidine, oxaplatin, and irinotecan	≥40 kg: 240 mg Q2W or 480 mg Q4W <40 kg: 3 mg/kg Q2W
Ipilimumab + nivolumab	2018	Patients >12 yr with **MSI-H/dMMR metastatic CRC** with progression after fluoropyrimidine, oxaplatin, and irinotecan	≥40 kg: 3 mg/kg nivolumab + 1 mg/kg ipilimumab Q3W for 4 doses, Then nivolumab 240 mg Q2W or 480 mg Q4W

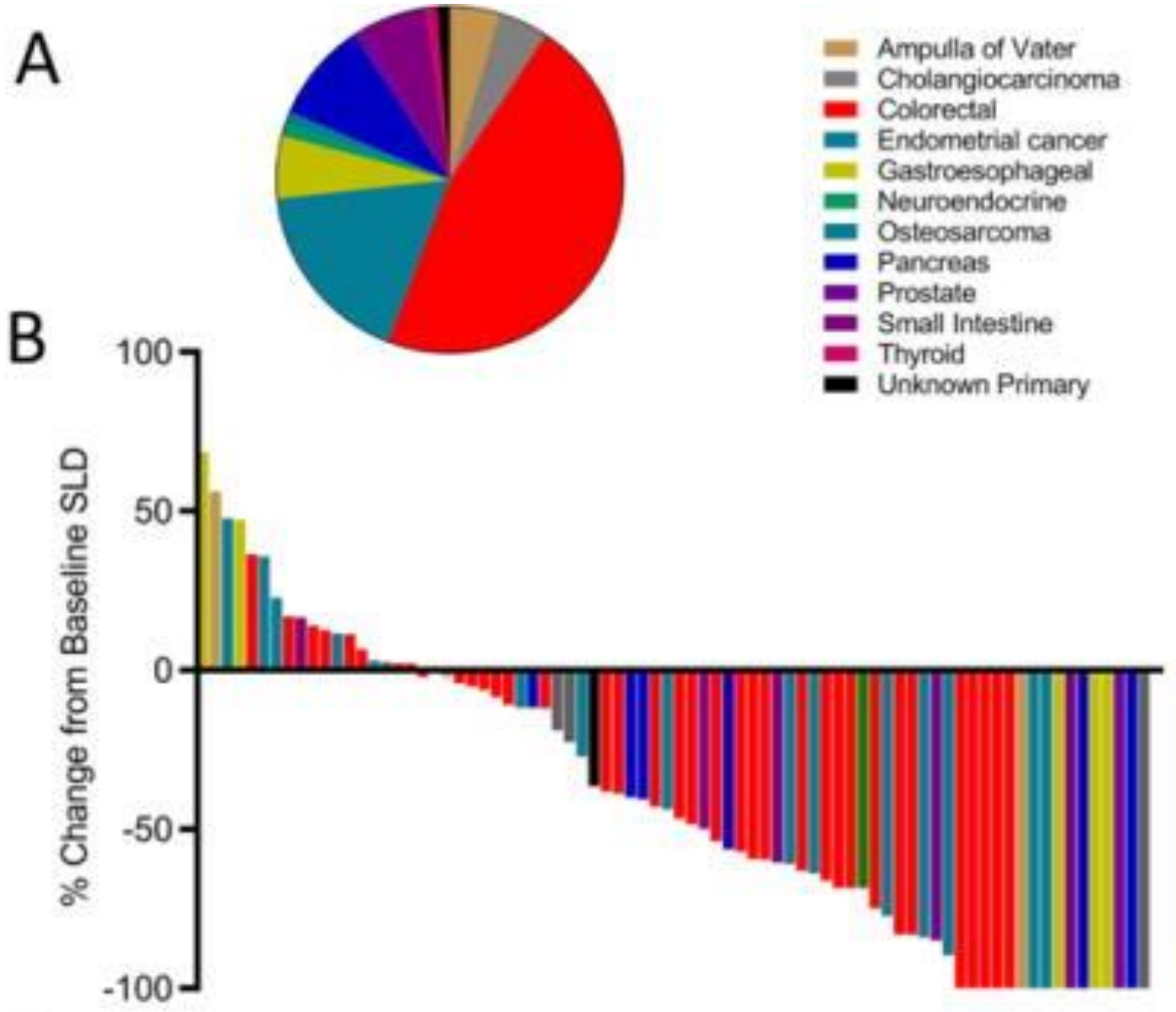
Clinical Data – pembrolizumab studies

- KEYNOTE-016: CRC only
  - no CR in MMR-proficient, 40% in dMMR
- KEYNOTE-164 and 158
  - ORR:
    - 27.9% for MSI-H CRC
    - 37.7% for MSI-H non-CRC
  - At 6 months OS:
    - 87% CRC
    - 73% non-CRC



Le, NEJM 2015.

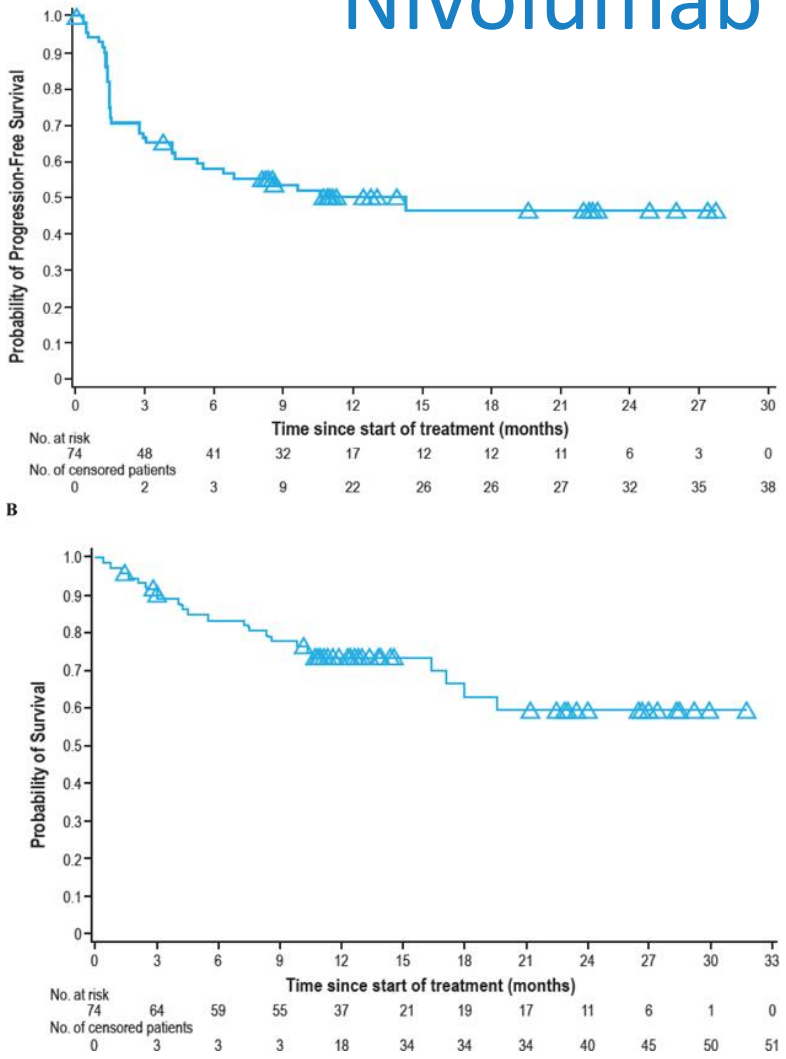
Clinical Data – pembrolizumab studies



- NCT01876511
- 12 cancer types with dMMR
- ORR: 53%
- CR: 21%

Le, Science 2017.

Clinical Data – CheckMate 142
Nivolumab monotherapy



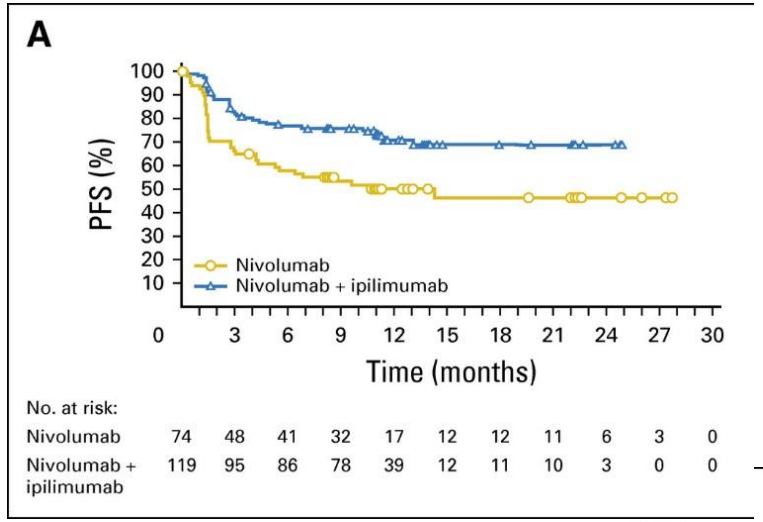
- mCRC with MSI-H, progressed after ≥1 therapy
- Nivolumab 3 mg/kg Q2W
- At 12 months: 31% ORR
- 68.9% disease control >12 weeks
- Median DOR not reached

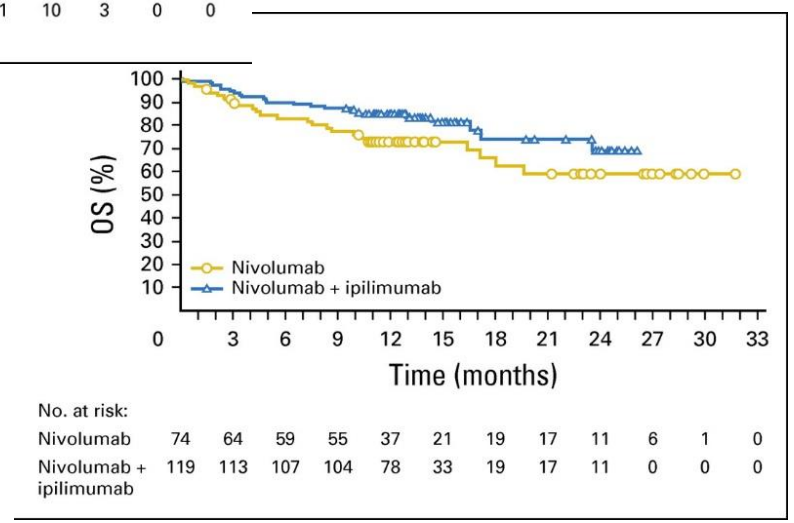
Overman, Lancet Oncol 2017.

Clinical Data – CheckMate 142

Nivolumab + Ipilimumab

- MSI-H/dMMR mCRC
- Nivolumab 3mg/kg + ipilimumab 1 mg/kg Q3W (4 doses), then nivolumab 3 mg/kg Q2W
- At 13.4 months: 55% ORR
- PFS: 76% (9 months); 71% (12 months)





Overman, J Clin Oncol 2018.

In development for MSI-high

- Potential for immunotherapy to impact new disease states
  - Prostate (~3%), pancreatic (~1%)
- Other tissue-agnostic markers:
  - Microbiome
  - POLE mutation
  - Mutational signatures beyond TMB

Resistance in MSI-H tumors

- Loss of β2 Microglobulin, a critical component of the antigen presentation machinery and MHC class I expression.
  - Gurjao C, Liu D, Hofree M, et al. Intrinsic Resistance to Immune Checkpoint Blockade in a Mismatch Repair Deficient Colorectal Cancer. Cancer Immunol Res. 2019 Jun 19. pii: canimm.0683.2018. doi: 10.1158/2326-6066.CIR-18-0683. [Epub ahead of print]
- Other mechanisms are similar to causes of resistance to ICI in any cancer type

Future Directions

- No standard companion diagnostic test yet approved – subjectivity of interpreting results; lack of consistency
- Not every clinic has access to these resources for measuring MSI/MMR (PCR, IHC, NGS) – may limit who can use the treatment
- Laid the groundwork for future biomarker-related drug approvals

Case Study 1

- You are seeing a 71 year-old male in your medical oncology clinic to discuss treatment options for newly metastatic, castration-resistant prostate cancer (mCRPC). He has a history of Gleason 3+4 prostate adenocarcinoma on biopsy with PSA 4.9, status post radical prostatectomy in 2004, who had a detectable PSA post-op and then received salvage XRT to the prostate in 2006 with 3 months of peri-operative Lupron and Casodex. He subsequently had a rising PSA with no metastases with numerous cycles of intermittent androgen-deprivation therapy from 2011-2018. He now has a rising PSA despite ongoing Lupron/Casodex, with newly documented bone metastases on a bone scan, no soft tissue metastases. Family history is not notable for any known cancer history. He remains fit and asymptomatic.

Case Study 1

- Question 1: What is your recommendation for genetic testing of his tumor tissue for microsatellite instability?

  A. Recommend MSI testing, using immunohistochemistry for MLH1/MSH2/MSH6/PMS2

  B. Recommend MSI testing, using commercial next-generation sequencing panels

  C. Do not recommend MSI testing

  D. Don’t know

Case Study 1

- Question 1: What is your recommendation for genetic testing of his tumor tissue for microsatellite instability?

  A. Recommend MSI testing, using immunohistochemistry for MLH1/MSH2/MSH6/PMS2

  Approved indication for immunotherapy for MSI-high tumors is after failing one prior line of therapy

  B. Recommend MSI testing, using commercial next-generation sequencing panels

  As above. Note: assay type is not specified in approval

  C. Do not recommend MSI testing

  Consider MSI testing after an approved line of therapy

  D. Don’t know

Case Study 1

- The patient receives abiraterone with prednisone, which he tolerates well with a prolonged reduction in PSA. However, his PSA then begins to rise on serial tests, with a bone scan confirming 3 new areas of uptake consistent with new skeletal metastases. You send his prior prostatectomy specimen for a commercial next-generation sequencing test, which does not identify actionable mutations, however identifies microsatellite instability. The patient is highly interested in pursuing immunotherapy at this time, and declines chemotherapy. He remains asymptomatic and active.

Case Study 1

- Question 2: Approved immunotherapies in this situation include all of the following EXCEPT:

  A. Nivolumab

  B. Sipuleucel-T (Provenge)

  C. Ipilimumab plus nivolumab

  D. CAR-T therapy

Case Study 1

- Question 2: Approved immunotherapies in this situation include all of the following EXCEPT:

  A. Nivolumab

  FDA approved

  B. Sipuleucel-T (Provenge)

  FDA approved for mCRPC (note: unclear whether MSI-high patients have enhanced responses)

  C. Ipilimumab plus nivolumab

  FDA approved (note: no direct evidence that this combination is superior to anti-PD-1 monotherapy)

  D. CAR-T therapy

  Experimental, trials ongoing

Case Study 2

- You are seeing a 55 year-old female in your clinic for newly diagnosed and recently resected colorectal carcinoma (CRC). Colonoscopy after new-onset melena showed a circumferential mass in the sigmoid colon. Biopsy confirmed adenocarcinoma. Microsatellite instability testing by IHC showed loss of MLH1 expression with intact expression of MSH2, MSH6, PMS2. She undergoes a hemicolectomy, and pathology confirms a resection with clear margins and none of 25 lymph nodes involved by cancer. Observation without further adjuvant chemotherapy is recommended, the patient is concerned and wishes to discuss immunotherapy.

Case Study 2

- Question 1: What is the recommended immunotherapy in this clinical scenario?

  A. Anti-PD-1

  B. Ipilimumab plus nivolumab

  C. No immunotherapy

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- Question 1: What is the recommended immunotherapy in this clinical scenario?

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  B. Ipilimumab plus nivolumab

  C. No immunotherapy

  Adjuvant immunotherapy for MSI-high resected CRC is still experimental

Case Study 2

- The patient is observed post surgery without chemotherapy as recommended. Unfortunately the patient develops new liver metastases during this period. There is no response to FOLFOX and FOLFIRI chemotherapy. She next receives pembrolizumab and tolerates this well, with an initial partial shrinkage on a CT scan after about 12 weeks of therapy. However her subsequent scans at 24 weeks show definite growth of existing liver metastases, and new liver metastases. She does not desire further chemotherapy and remains interested in immunotherapy options.

Case Study 2

- What immunotherapy treatment option would you recommend in this clinical scenario?

  A. Nivolumab

  B. Ipilimumab plus nivolumab

  C. Clinical trial

Case Study 2

- What immunotherapy treatment option would you recommend in this clinical scenario?

  A. Nivolumab

  No evidence that changing to an alternate anti-PD-1 agent will be effective

  B. Ipilimumab plus nivolumab

  No definite evidence that addition of ipilimumab to anti-PD-1 after failing anti-PD-1 will be effective

  C. Clinical trial

  Consider additional approved chemotherapy versus clinical trial if interested in immunotherapy options