Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy for the Treatment of Microsatellite Instability – High Cancers

Osama Rahma, MD

Assistant Professor of Medicine, Harvard Medical School
Center for Immuno-Oncology, Gastrointestinal Cancer Center
Dana-Farber Cancer Institute

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

- I will be discussing non-FDA approved indications during my presentation.
- Receipt of Intellectual Property Rights/Patent Holder: Methods of using pembrolizumab (Merck) and trebananib (Amgen) pending
- Consulting Fees: Merck, Celgene, Five Prime, GSK, GFK, Bayer, Roche/Genentech, Puretech, Imvax

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

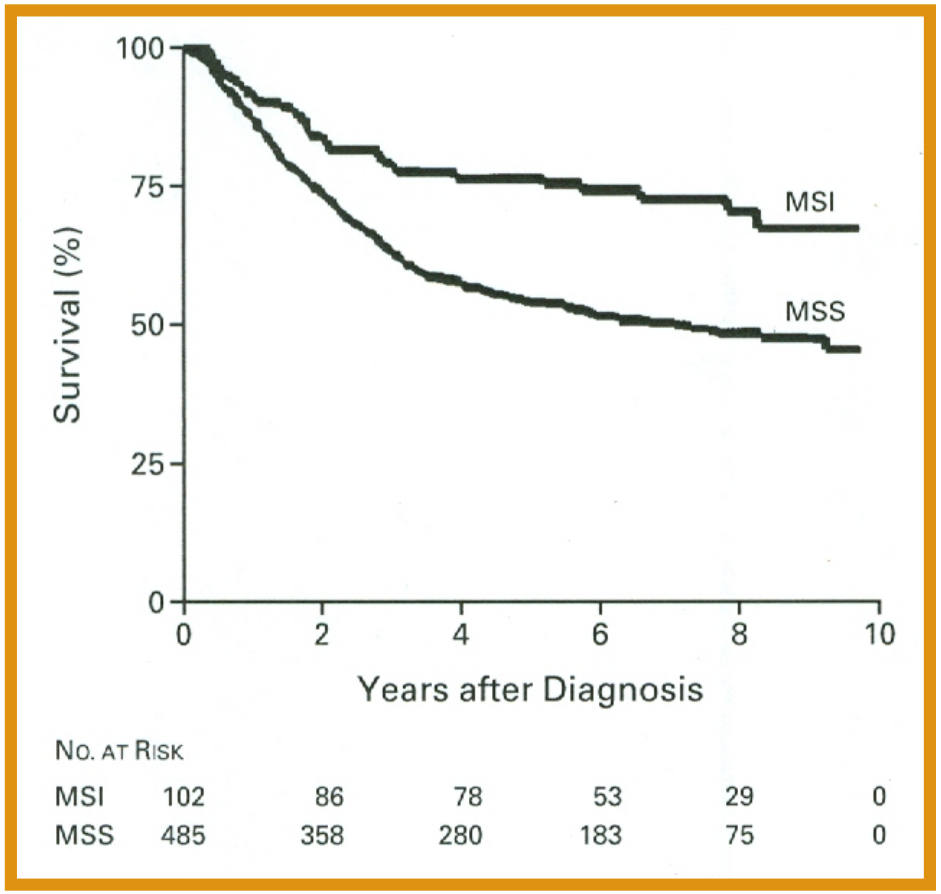
Microsatellite Instability

- 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

Fehlings M et al, Nat Commun. 2017 Sep 15;8(1):562. Le DT et al, Science. 2017 Jul 28;357(6349):409-413. Riaz N et al, Cell. 2017 Nov 2;171(4):934-949.e16. Van Rooij N et al, J Clin Oncol. 2013 Nov 10;31(32)

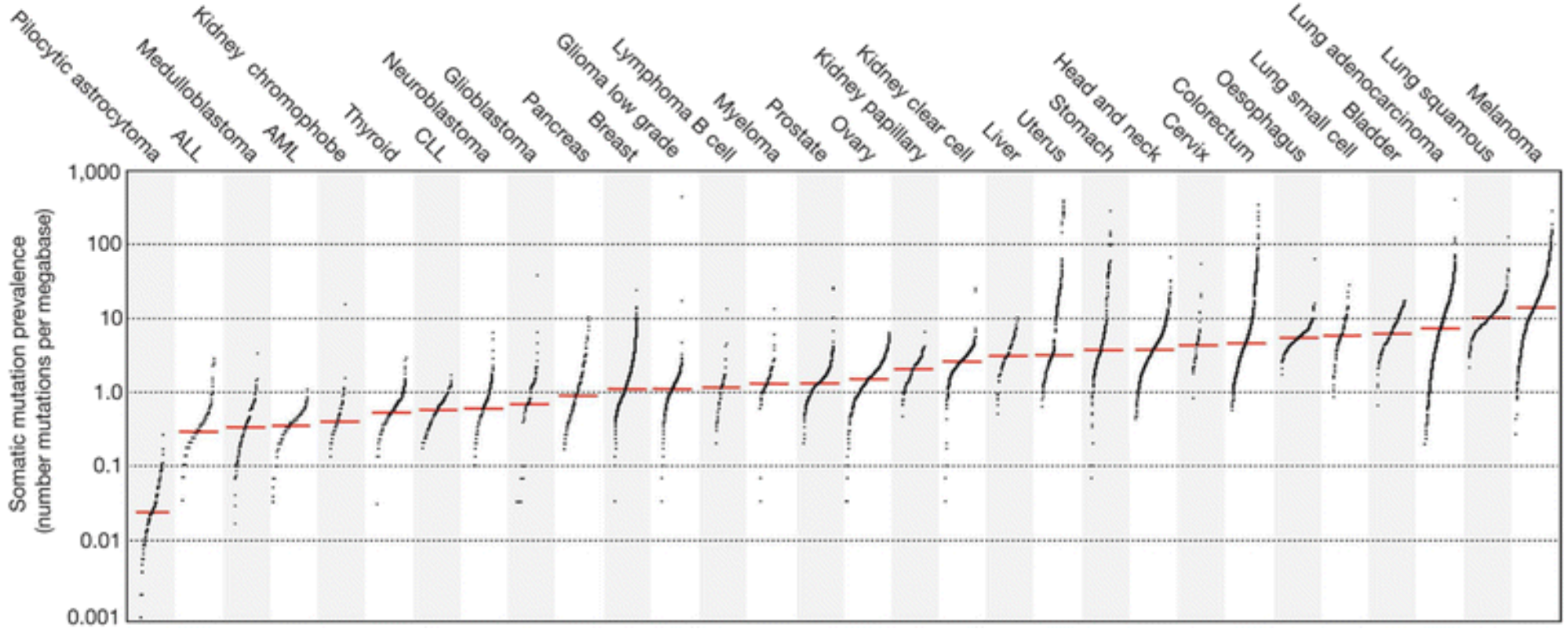
Many tumors are MSI-high or MMR-deficient

- Prognosis with MSI-H appears to be stage-specific
  - Localized, surgically-resected is favorable
  - Metastatic = not favorable



Gryfe R, et. al. N Engl J Med. 2000;342:69-77

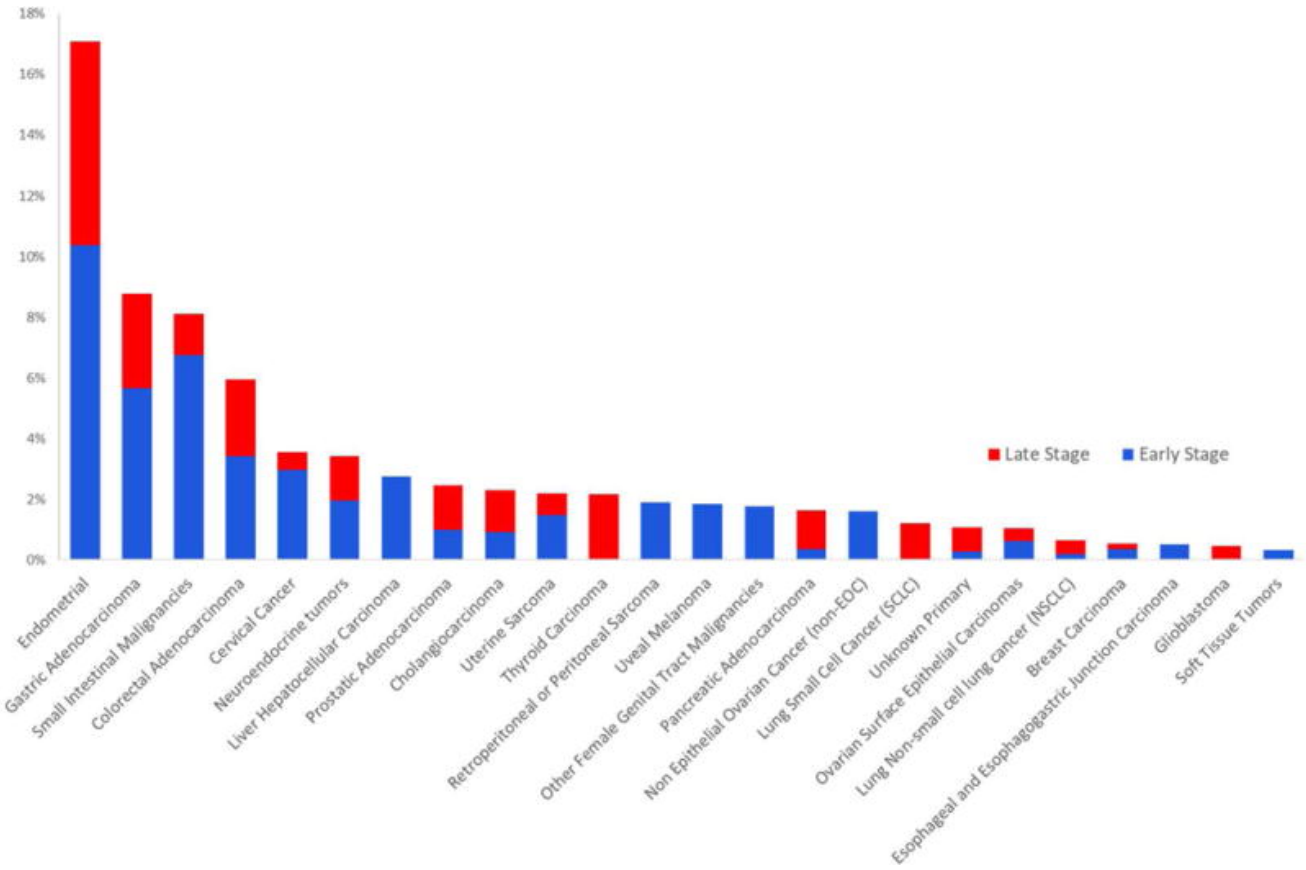
Somatic mutations by cancer type



Alexandrov, Nature 2013.

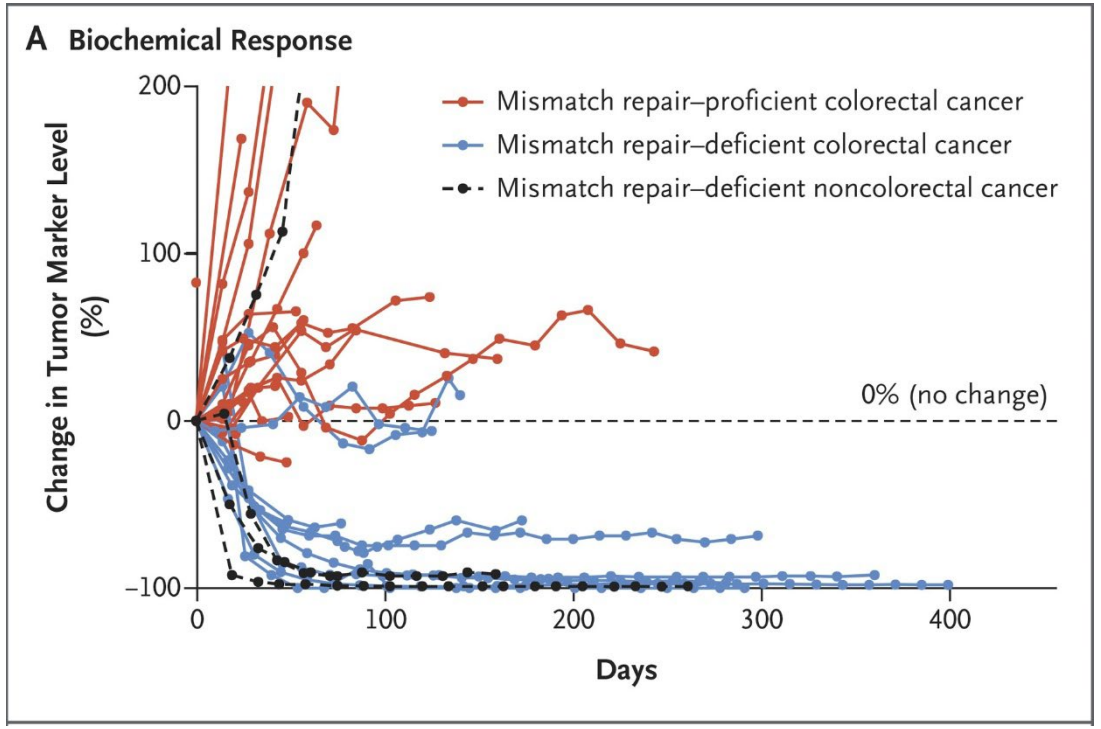
Many tumors are MSI-high or MMR-deficient

- 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



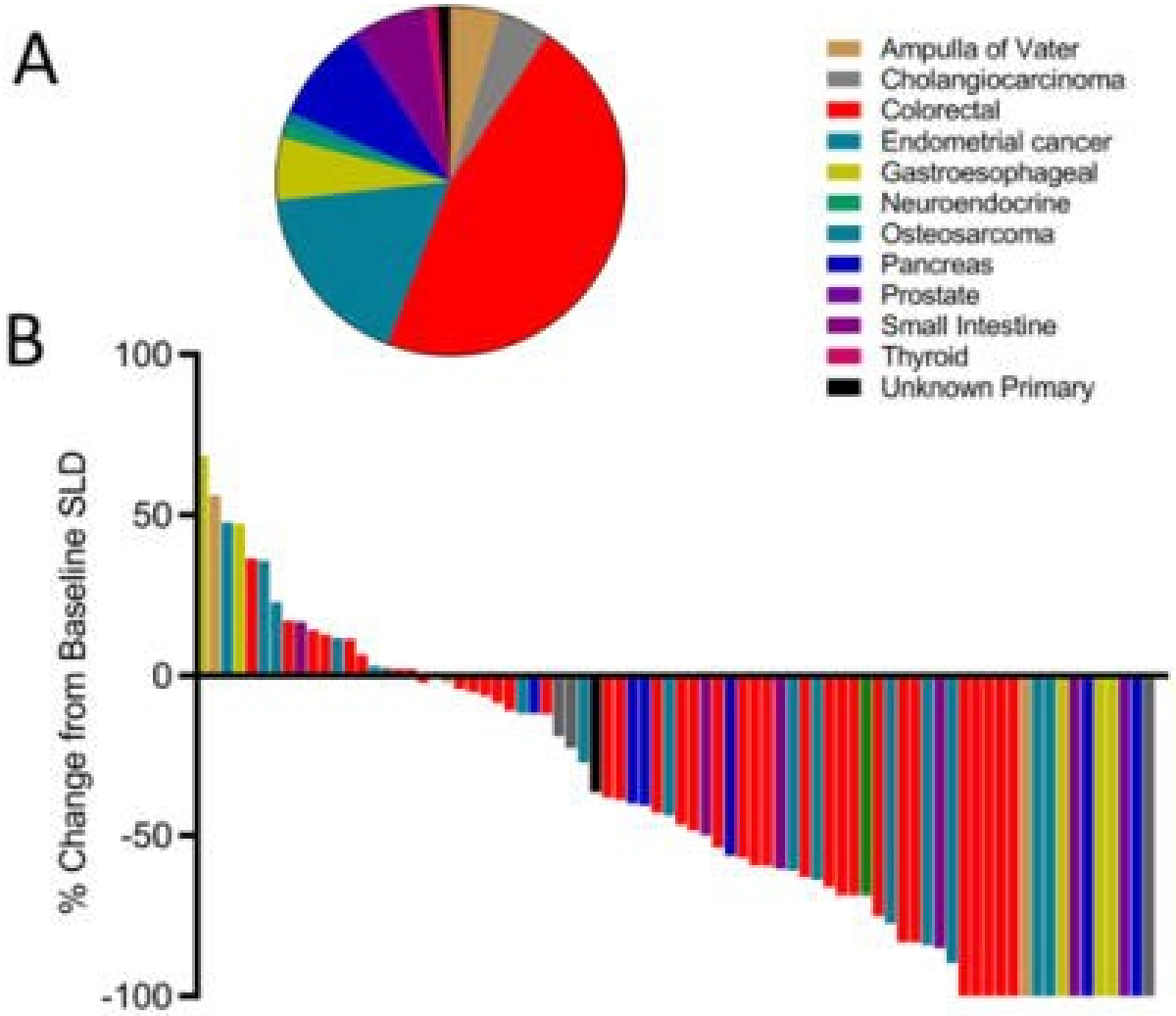
Clinical Data – pembrolizumab studies

- 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.

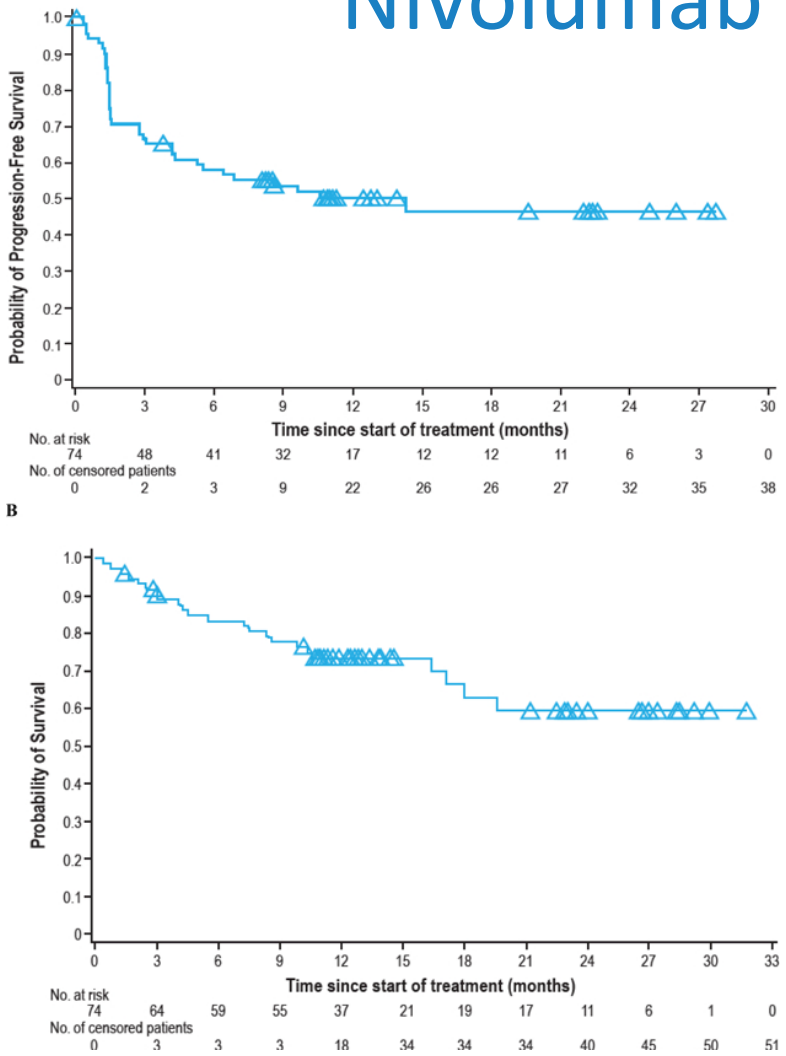
Clinical Data – pembrolizumab studies



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

Le, Science 2017.

Clinical Data – CheckMate 142
Nivolumab monotherapy



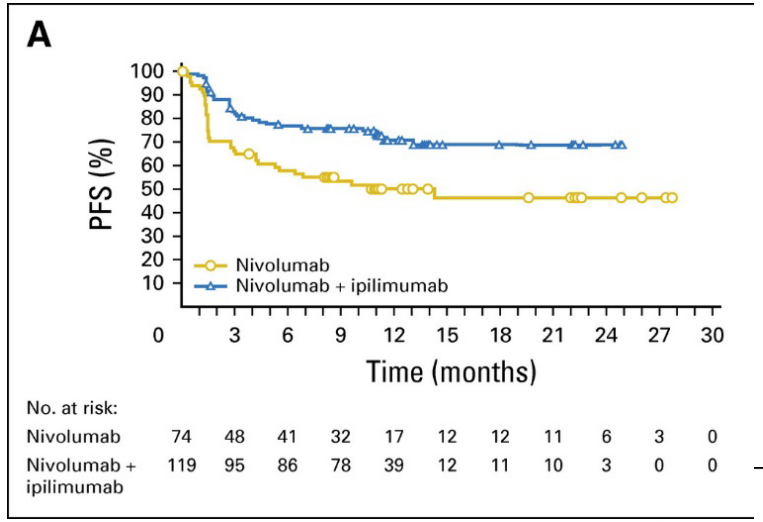
- mCRC with MSI-H, progressed after ≥1 therapy
- Nivolumab 3 mg/kg Q2W
- At 12 months: 31% ORR
- 68.9% disease control >12 weeks
- Median DOR not reached

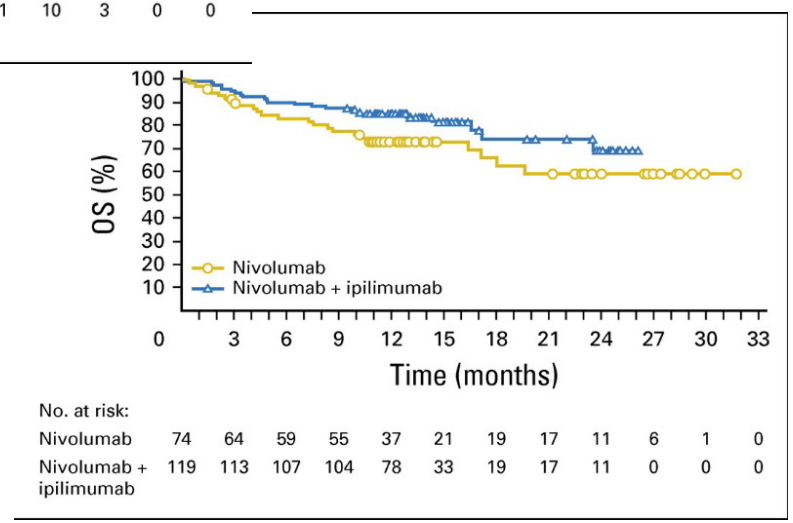
Overman, Lancet Oncol 2017.

Clinical Data – CheckMate 142

Nivolumab + Ipilimumab

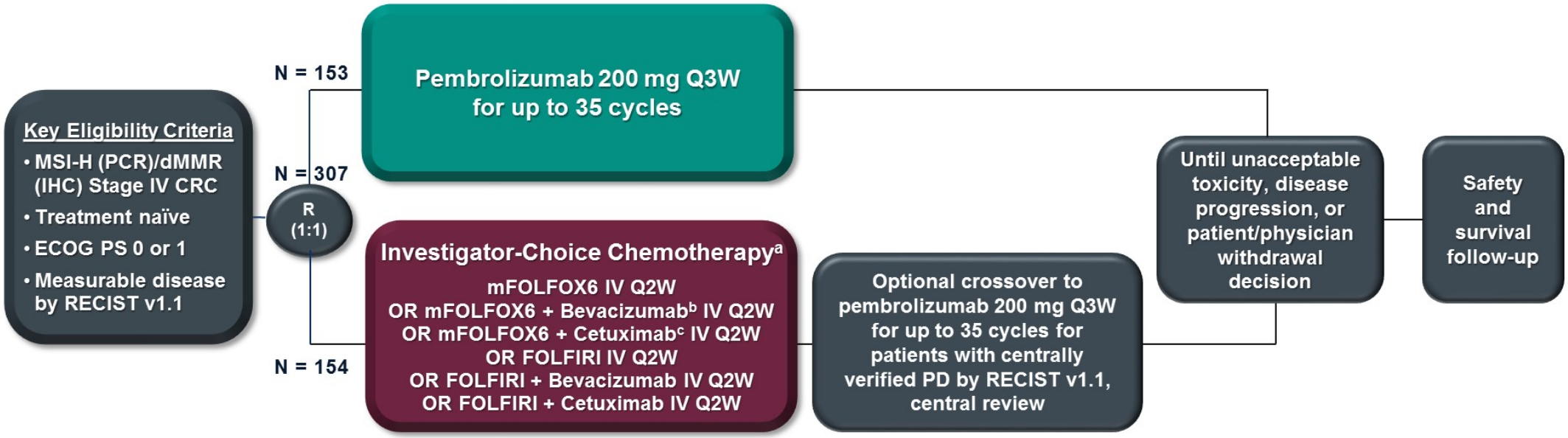
- MSI-H/dMMR mCRC
- Nivolumab 3mg/kg + ipilimumab 1 mg/kg Q3W (4 doses), then nivolumab 3 mg/kg Q2W
- At 13.4 months: 55% ORR
- PFS: 76% (9 months); 71% (12 months)





Overman, J Clin Oncol 2018.

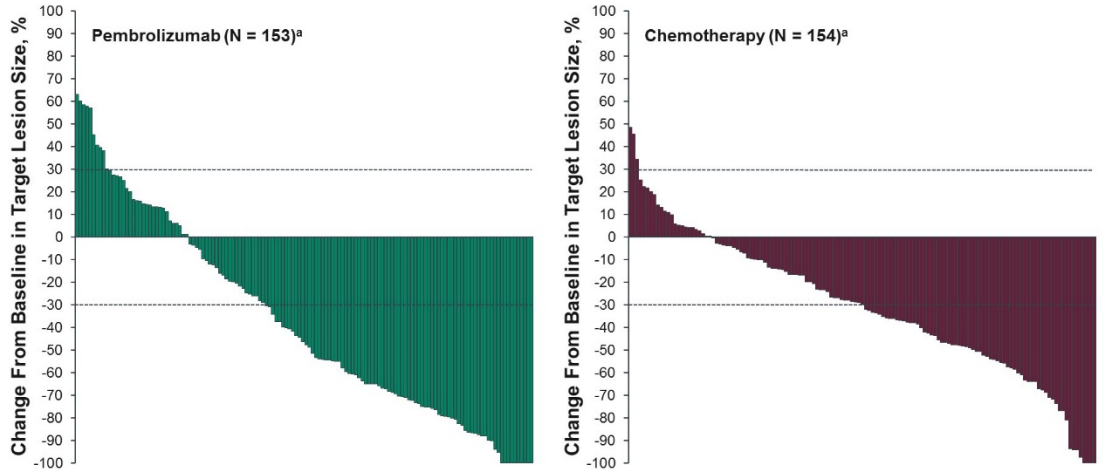
KEYNOTE-177 Study Design (NCT02563002)



- Dual-Primary endpoints: PFS per RECIST v1.1 per blinded independent central review (BICR) and OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

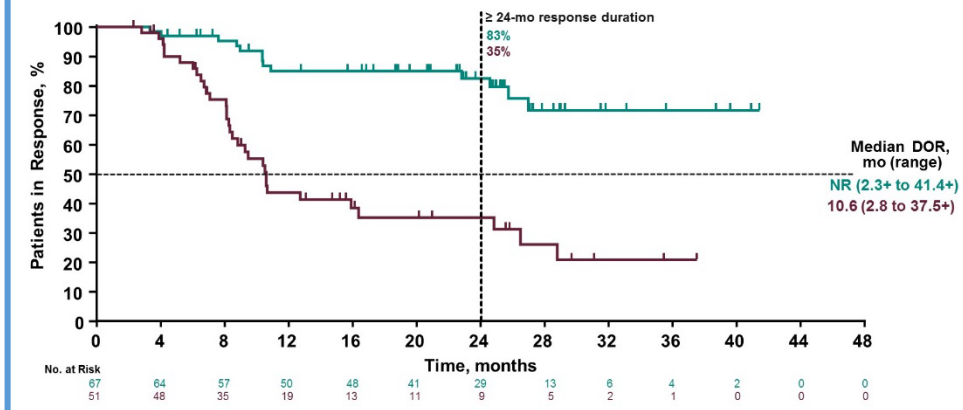
[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

Radiographic Response in Target Lesions



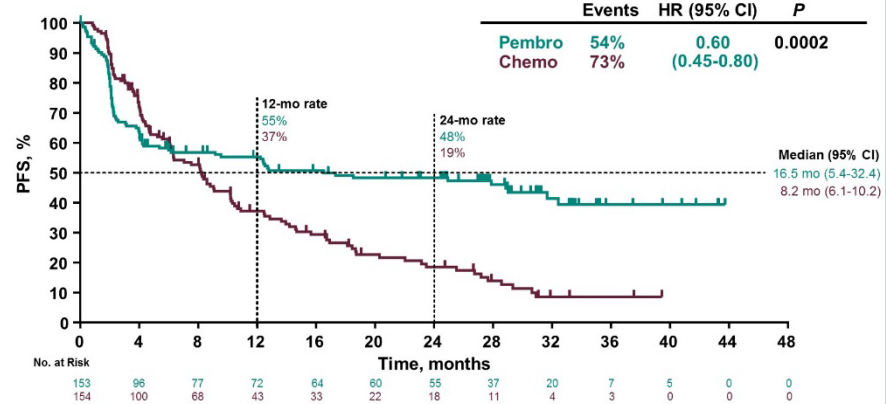
[a]104 of 138 (75%) evaluable patients in the pembrolizumab arm and 111 of 135 (82%) evaluable patients in the chemotherapy arm had a reduction from baseline in target lesion size.
Evaluable patients include those with ≥1 post-baseline target lesion imaging assessment in the intention-to-treat population; Data cut-off: 19Feb2020.

Duration of Response



of Response assessed per RECIST v1.1 by BICR; Data cut-off: 19Feb2020.

Progression-Free Survival



dy follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR.
of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

FDA-approved immunotherapies for MSI-high populations

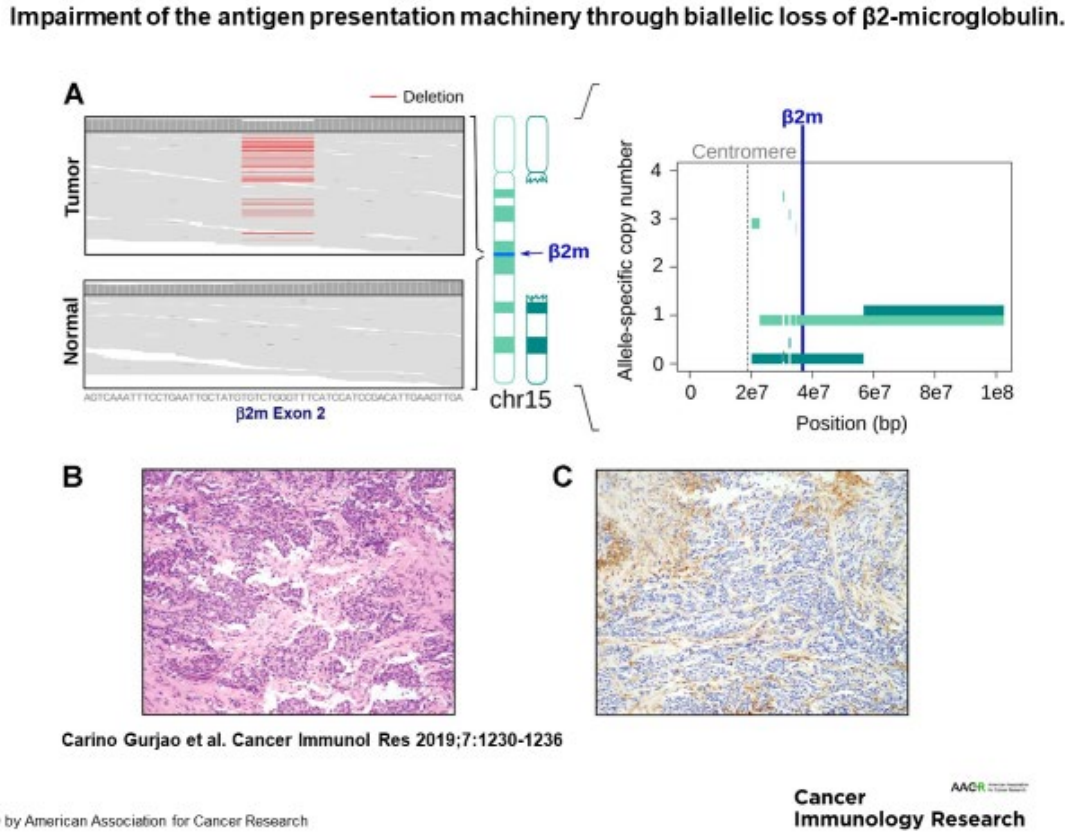
Drug	Approved	Indication	Dose
Pembrolizumab	2017	Adult/pediatric patients with unresectable/metastatic **MSI-H or dMMR solid tumors** with progression on other treatment **MSI-H or dMMR colorectal cancer** with progression after a fluoropyrimidine, oxaplatin, and irinotecan	Adults: 200 mg Q3W Pediatric: 2 mg/kg (up to 200 mg) Q3W
Pembrolizumab	2020	**First-line treatment of MSI-H/dMMR colorectal cancer**	200 mg every 3 weeks or 400 mg every 6 weeks.
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

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

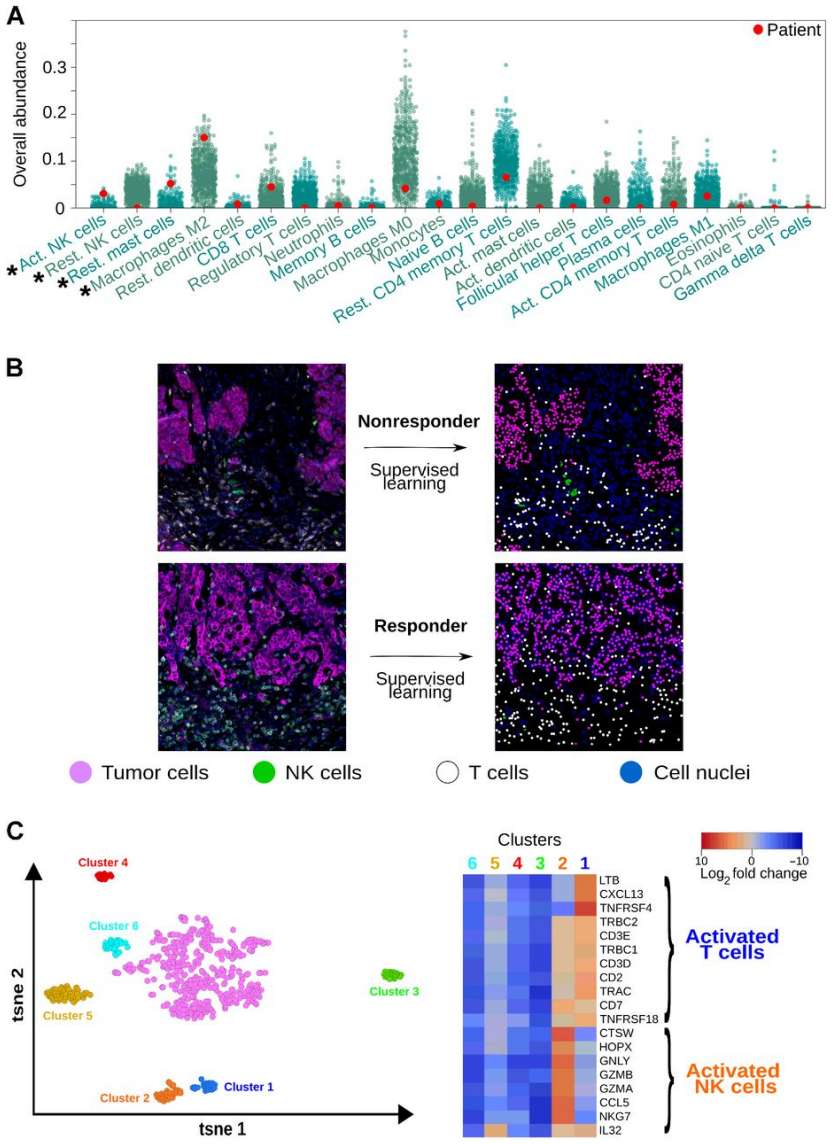
Resistance in MSI-H tumors

- Loss of β2 Microglobulin, a critical component of the antigen presentation machinery and MHC class I expression.
- Other mechanisms could be 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
- Highlight the role of other immune cells such as NK cells for future development



Carino Gurjao et al. Cancer Immunol Res 2019;7:1230-1236

Case Study 1

- 81-year-old women with family history of endometrial cancer in her mother. She was diagnosed with stage II colon cancer in 1975, endometrial cancer 1980, superficial bladder cancer 2006 and 2017, and localized unresectable pancreatic adenocarcinoma in 2019. How would you treat her pancreatic cancer

  - A) Start modified FOLIRINOX or FOLFOX
  - B) Start pembrolizumab
  - C) Start ipilimumab and nivolumab
  - D) Start FOLFIRNIOX+pembrolizumab
  - E) Monitor off therapy

Case Study 1

- 81-year-old women with family history of endometrial cancer in her mother. She was diagnosed with stage II colon cancer in 1975, endometrial cancer 1980, superficial bladder cancer 2006 and 2017, and localized unresectable pancreatic adenocarcinoma in 2019. How would you treat her pancreatic cancer

  - A) Start modified FOLIRINOX or FOLFOX
  - B) Start pembrolizumab
  - C) Start ipilimumab and nivolumab
  - D) Start FOLFIRNIOX+pembrolizumab
  - E) Monitor off therapy

Case Study 1

- 81-year-old women with family history of endometrial cancer in her mother. She was diagnosed with stage II colon cancer in 1975, endometrial cancer 1980, superficial bladder cancer 2006 and 2017, and localized unresectable pancreatic adenocarcinoma in 2019. How would you treat her pancreatic cancer

  - A) Start modified FOLIRINOX or FOLFOX
    - Chemotherapy remains the standard of care for MSI pancreatic tumors
  - B) Start pembrolizumab
    - Pembrolizumab is FDA approved after failing standard of care chemo
  - C) Start ipilimumab and nivolumab
    - Ipilimumab and nivolumab are also approved in second line
  - D) Start FOLFIRNIOX+pembrolizumab
    - There is no evidence that the combination has better activity compared to chemo or pembrolizumab alone
  - E) Monitor off therapy

Case Study 1

- The patient started on FOLFOX then was admitted to the hospital with severe fatigue, nausea and vomiting. She is discharged home and came to your office to discuss next step. What would you do next?

  - A) Modify FOLFOX
  - B) Switch therapy to pembrolizumab
  - C) Switch therapy to ipilimumab and nivolumab
  - D) Add pembrolizumab to FOLFOX
  - E) Referral to HOSPICE

Case Study 1

- The patient started on FOLFOX then was admitted to the hospital with severe fatigue, nausea and vomiting. She is discharged home and came to your office to discuss next step. What would you do next?

  - A) Modify FOLFOX
  - B) Switch therapy to pembrolizumab
  - C) Switch therapy to ipilimumab and nivolumab
  - D) Add pembrolizumab to FOLFOX
  - E) Referral to HOSPICE

Case Study 1

- The patient started on FOLFOX then was admitted to the hospital with severe fatigue, nausea and vomiting. She is discharged home and came to your office to discuss next step. What would you do next:
  - A) Modify FOLFOX
    - Given her age, she is unlikely to tolerate this regimen
  - B) Switch therapy to pembrolizumab
    - It is better tolerated than chemo and FDA approved for second line
  - C) Switch therapy to ipilimumab and nivolumab
    - This regimen is more toxic than pembrolizumab alone
  - D) Add pembrolizumab to FOLFOX
    - She did not tolerate chemotherapy and there is no evidence to support this combination
  - E) Referral to HOSPICE
    - Pembrolizumab has 40% RR and worth considering

Case Study 2

- 40 yo male diagnosed with metastatic MSI colon cancer to the liver. He was treated with pembrolizumab based on Keynote-177 study and had a response for 1 year then recently had restaging scan that showed progression of disease. What would you do next?

  - A) Check b2 Microglobulin
  - B) Switch therapy to FOLFOX/Avastin
  - C) Switch therapy to ipilimumab+nivolumab
  - D) Continue pembrolizumab considering “pseudo-progression”

Case Study 2

- 40 yo male diagnosed with metastatic MSI colon cancer to the liver. He was treated with pembrolizumab based on Keynote-177 study and had a response for 1 year then recently had restaging scan that showed progression of disease. What would you do next?

  - A) Check b2 Microglobulin
  - B) Switch therapy to FOLFOX/Avastin
  - C) Switch therapy to ipilimumab+nivolumab
  - D) Continue pembrolizumab considering “pseudo-progression”

Case Study 2

- 40 yo male diagnosed with metastatic MSI colon cancer to the liver. He was treated with pembrolizumab based on Keynote-177 study and had a response for 1 year then recently had restaging scan that showed progression of disease. What would you do next?

  - A) Check b2 Microglobulin
    - Although there is research evidence to suggest that a defect in antigen presentation could lead to resistance to pembrolizumab this test is not considered a standard of care
  - B) Switch therapy to FOLFOX/Avastin
    - This is a possibility given 30-40% activity of chemo in this setting
  - C) Switch therapy to ipilimumab+nivolumab
    - It is unknow if this regimen is active post-single agent pembrolizumab since it has not been studied in this setting
  - D) Continue pembrolizumab considering “pseudo-progression”
    - This phenomena has been described but difficult to prove in clinical setting

Case Study 2

- The patient was started on FOLFOX/Avastin and had no response after 3 months. His ECOG is 0. What would you do next?

  - A) Switch chemo to FOLFIRI/Avastin
  - B) Switch therapy back to pembrolizumab
  - C) Switch therapy to ipilimumab+nivolumab
  - D) A or C

Case Study 2

- The patient was started on FOLFOX/Avastin and had no response. His ECOG is 0. What would you do next?

  - A) Switch chemo to FOLFIRI/Avastin
  - B) Switch therapy back to pembrolizumab
  - C) Switch therapy to ipilimumab+nivolumab
  - D) A or C

Case Study 2

- The patient was started on FOLFOX and had no response after 3 months of treatment . His ECOG is 0. What would you do next?
  - A) Switch chemo to FOLFIRI/Avastin
    - This is an option, however, his tumor seems to be resistant to chemotherapy
  - B) Switch therapy back to pembrolizumab
    - It is unlikely he would respond considering previous treatment with pembrolizumab
  - C) Switch therapy to ipilimumab+nivolumab
    - This regimen is approved for MSI high CRC but activity is unknown post-pembrolizumab
  - D) A or C

Thank you