Immunotherapy in a patient with mismatch repair deficient metastatic colorectal cancer
Case History

- 69 y/o Female
- 2012 → Hemicolecotomy CRC
  - pT3N1a (1/16 LN+) adenocarcinoma
  - Moderately differentiated
  - Tumor Infiltrating lymphocytes present
  - <10% mucinous
Case History

2012
Adjuvant FOLFOX

2014
KRAS WT
BRAF V600E
Case History

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FOLFIRI + Cetuximab

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Loss of staining:
- MLH1
- PMS2
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Loss of staining:
MLH1
PMS2

KRAS WT
BRAF V600E

Nivolumab 3mg/kg q14
Marked Clinical response
No Grade 3 or 4 toxicity
No dose delays
Molecular Subtyping Colorectal Cancer

- CMS1
  - MSI immune
  - 14%
  - MSI, CIMP high, hypermutation
  - BRAF mutations
  - Immune infiltration and activation
  - Worse survival after relapse

- CMS2
  - Canonical
  - 37%
  - SCNA high

- CMS3
  - Metabolic
  - 13%
  - Mixed MSI status, SCNA low, CIMP low
  - KRAS mutations
  - Metabolic deregulation

- CMS4
  - Mesenchymal
  - 23%
  - SCNA high
  - KRAS mutations
  - Stromal infiltration, TGF-β activation, angiogenesis
  - Worse relapse-free and overall survival

ESMO PRECEPTORSHIP PROGRAM

Nat Med. 2015 Nov;21(11):1350-6
Mismatch Repair Machinery

MLH1  MLH3
MSH2  MSH3
MSH6  PMS1
PMS2

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Nature Reviews Cancer 1, 22-33 (October 2001)
Mismatch Repair Deficiency

Pathways to mismatch repair deficiency in colorectal cancer

- Germline mutation (MLH1, MSH2, MSH6, PMS2)
- Biallelic MLH1 methylation CIMP+

- Lynch syndrome (~3%)
- Sporadic (~12%)

Deficient MMR repair
Hypermethylated

MMR-Deficient CRC

MMR-Proficient CRC

ESMO PRECEPTORSHIP PROGRAM
Science 339 (6127), 1546-1558. [doi: 10.1126/science.1235122]
Tumor Infiltrating Lymphocytes

MMR-deficient CRC

MMR-proficient CRC
Phenotypic Features

- Tumor infiltrating lymphocytes
- Hypermutated
- Proximal colon
- Female
- Mucinous component
- Poorly differentiated
- Less nodal disease
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

PD-1 Blockade in tumors with Mismatch repair deficiency

**Cohort A**
- Mismatch repair (MMR)-deficient Colon Cancers
  - 11 Enrolled
  - 11 Treated
  - 1° Endpoint: immune-related RR and 20 week PFS rate

**Cohort B**
- Mismatch repair (MMR)-proficient Colon Cancers
  - 21 Enrolled
  - 21 Treated
  - 1° Endpoint: immune-related RR and 20 week PFS rate

**Cohort C**
- Mismatch repair (MMR)-deficient Non-Colon Cancers
  - 9 Enrolled
  - 9 Treated
  - 1° Endpoint: immune-related 20 week PFS rate

Pembrolizumab – 10 mg/kg every 2 weeks
# Primary Endpoints

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Progression Free Survival

MMR-P  2.2 months

MMR-D  Not Reached
Overall Survival

- MMR-D: Not Reached
- MMR-P: 5 months
Conclusions

- MMR-Deficient CRC is phenotypically and molecularly distinct
- Hypermutated and high TIL count
- PD-1 Blockade has a promising role in treatment of metastatic disease
Thank You