JADPRO CE Regional Lectures

Clinical Advances and Case Studies in Immune Checkpoint Inhibitors in Oncology

Mismatch Repair Deficient (dMMR) and Microsatellite Instability-High (MSI-H) Tumors

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Faculty Financial Disclosures

- Ms. Hoffner has received consulting fees/honoraria from Abbott, Array BioPharma, and Merck.
- Ms. Zitella has served on the advisory board for Array Biopharma and has equity interests/stock options in Kite Pharma.
- Dr. Lewis has nothing to disclose.

Planning Committee Financial Disclosures

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Learning Objectives

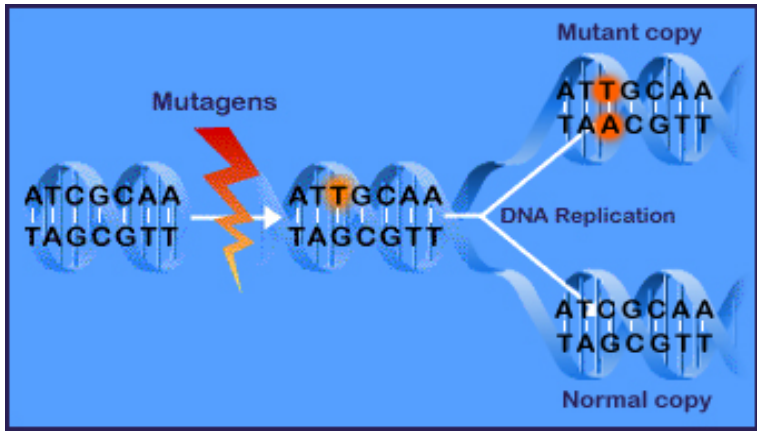
- Differentiate between early and late adverse effects associated with immunotherapeutic agents.
- Recognize the differences between immunotherapeutic agents and chemotherapeutic agents: mechanisms of action, adverse effects, and toxicity management.
- Summarize data on currently available immunotherapeutic agents as they relate to durable treatment responses.
- Explain the utility of biomarker testing in selecting patients for immunotherapy and in predicting clinical outcomes.

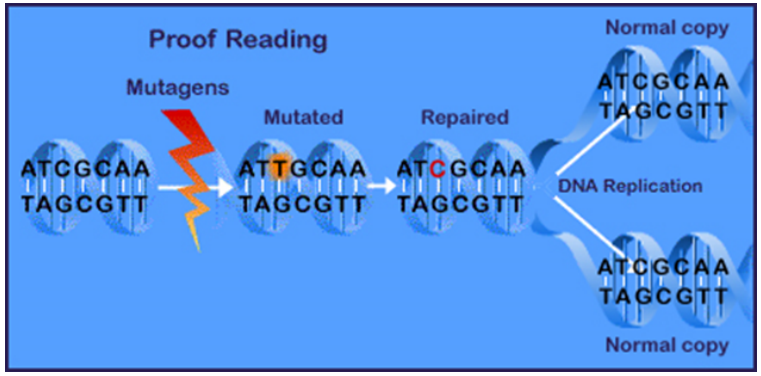
Goals

- Summarize data on currently available immunotherapeutic agents for mismatch repair deficient (dMMR)/microsatellite instability-high (MSI-H) tumors
- Identify appropriate management of immune-related hypothyroidism

Mismatch Repair Genes (MMR): The “spell-checker” for DNA

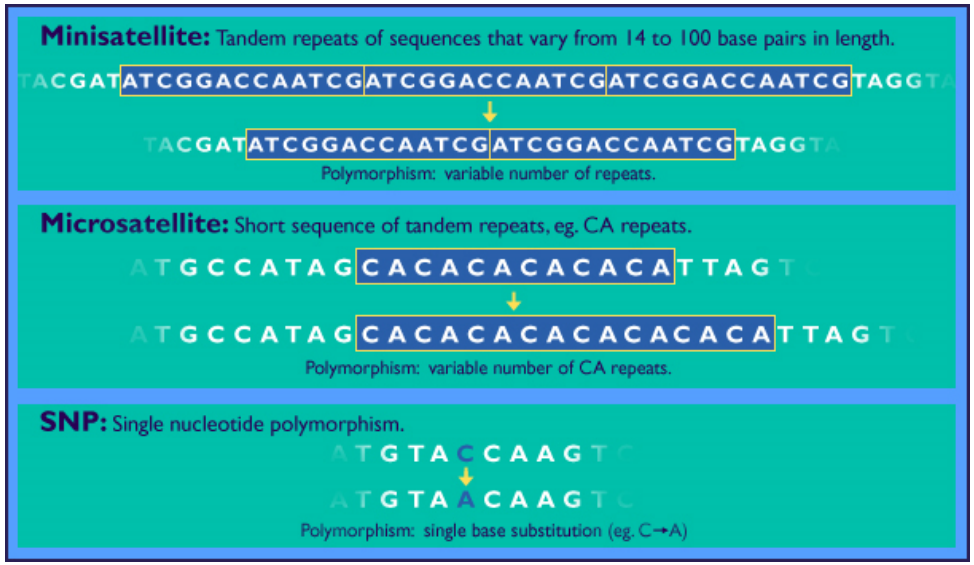
- Mismatch repair genes are error-correction systems that check DNA for damaged or mismatched base pairs
- Mismatch repair deficient (dMMR) cells lack ability to repair mistakes in DNA so they acquire multiple DNA mutations





Naboush, A., et al. . (2017). Journal of Investigative Medicine, 65(4), 754–758. https://doi.org/10.1136/jim-2016-000342 Photo credit: Roche Genetics education CD 2002

Microsatellite Instability

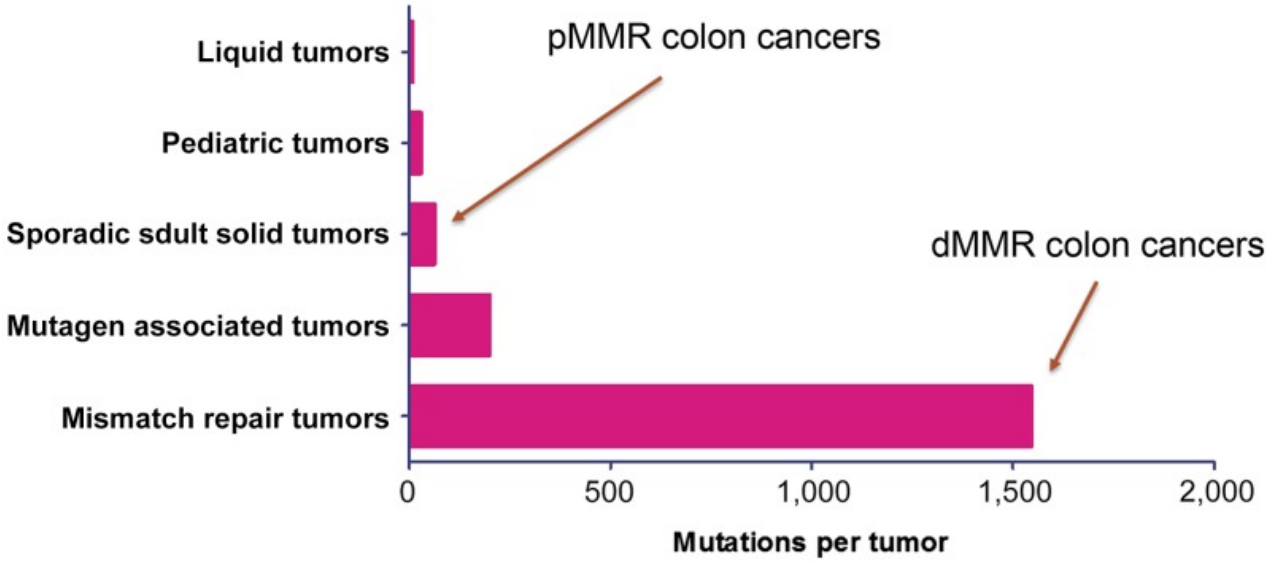


- Microsatellites are units of 1–6 nucleotides tandemly repeated multiple times throughout the genome
- The repetitive nature of the microsatellite sequences make them vulnerable to errors during DNA replication
- Mismatch repair (MMR) machinery detects and repairs mistakes in the microsatellites
- In dMMR cells, the microsatellite errors go unrepaired and cause “microsatellite instability” (MSI)
- Microsatellite instability-high (MSI-H) tumor cells have at least 30% more DNA alterations than normal cells

dMMR = mismatch repair deficiency.

Naboush, A., et al. (2017). Journal of Investigative Medicine, 65(4), 754–758. https://doi.org/10.1136/jim-2016-000342 Photo credit: Roche Genetics education CD 2002

MMR-deficient Cells Have More Than 1000 Mutations, Compared With 50–100 in a Typical Cancer Cell



- These mutations may give rise to tumor “neoantigens”
- Since these neoantigens are unique to the tumor, they can potentially be recognized as “nonself” molecules by the immune system
- MSI-H tumors are highly infiltrated with T cells including cytotoxic T lymphocytes (CTLs)
  - Most likely responding to the tumor neoantigens

Lee, V., et al. (2016). The Oncologist, 21(10), 1200–1211. https://doi.org/10.1634/theoncologist.2016-0046

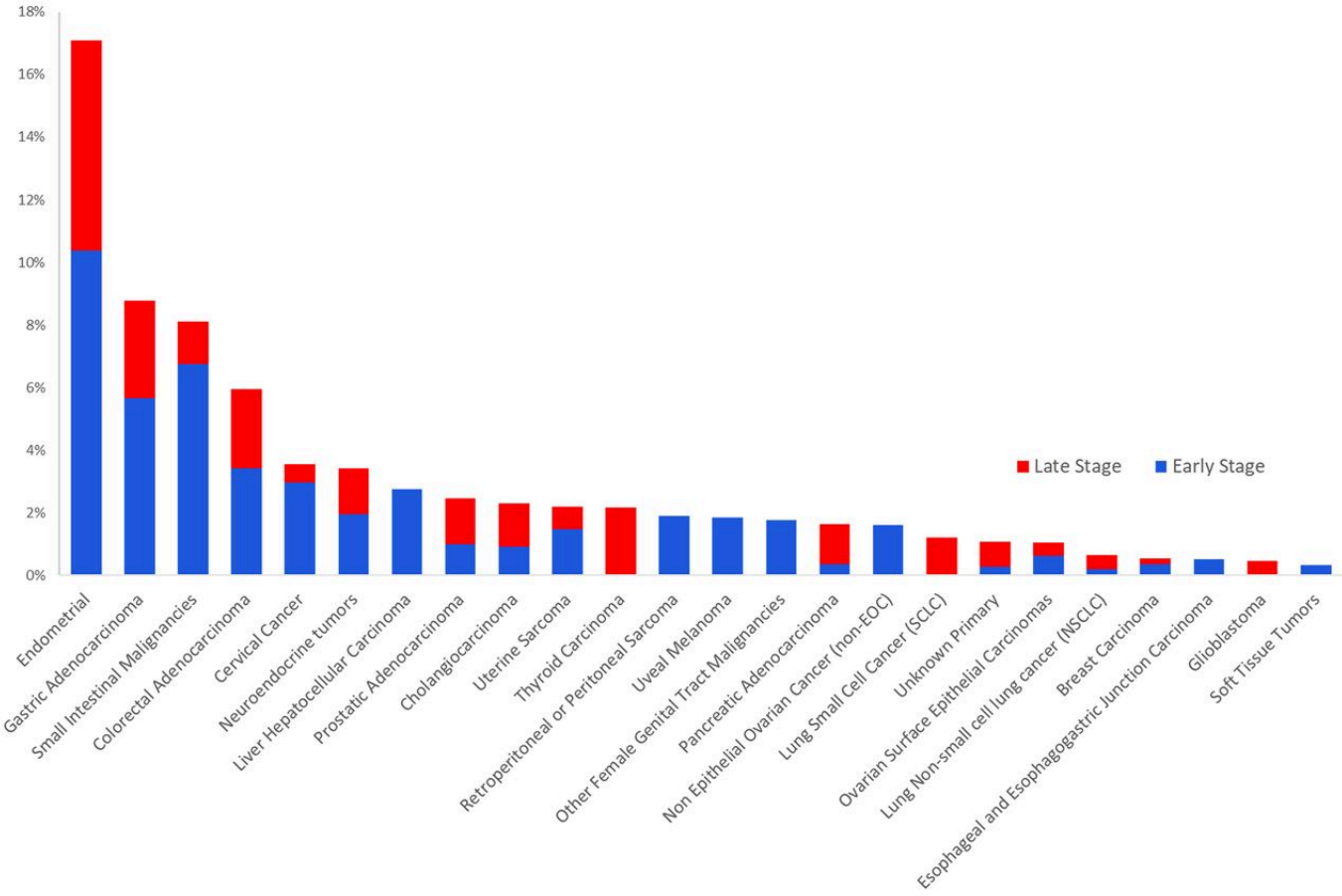
Why Doesn't the Immune System Eradicate dMMR/MSI-H Tumors Since There Is a High Level of Immunogenicity?

- "Adaptive resistance" in which the cytotoxic T-cell response is countered by tumor-induced immune suppressive checkpoints that protect the tumor from killing
- Escape mechanisms include upregulation of
  - PD-1, PD-L1, CTLA-4, lymphocyte activation gene 3, and IDO
- This supports the use of checkpoint blockade inhibitor therapy to reverse tumor immune protection
- MSI is a common mutation driver in many cancers and is emerging as a predictive biomarker for responsiveness to immune checkpoint inhibition

Naboush, A., et al. (2017). Journal of Investigative Medicine, 65(4), 754–758. https://doi.org/10.1136/jim-2016-000342

Mismatch Repair Deficiency (dMMR) Across 12,019 Cases of Cancer

- 24/32 tested tumor types were dMMR
- More common in early stage tumors
- Incidence of dMMR
  - 8% of stage I to stage III cancers
  - 4% of stage IV cancers
  - This represents roughly 40,000 annual stage I–III and 20,000 stage IV diagnoses in the United States alone



Le, D. T., et al. (2017). Science (New York, N.Y.), 357(6349), 409–413. https://doi.org/10.1126/science.aan6733

Microsatellite Instability-High (MSI-H) Colorectal Cancer

- Microsatellite instability (MSI) is present in 10%–20% of colorectal cancer (CRC) cases
  - 15% of early stage CRC
  - 4% of metastatic CRC
  - Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch Syndrome (LS) is characterized by MSI
    - The associated germline mutations in LS are seen in one of the following MMR genes; *MLH1, MSH2, HSH6, PMS2*.
  - However, nearly two-thirds of MSI CRC are sporadic in nature and are associated with an epigenetic modification that leads to the inactivation of the *MLH1* gene.
- NCCN recommends testing all CRC specimens for MMR or MSI
- MSI-H CRC presents with a distinct clinic-pathologic pattern
  - Proximal colon location in younger patients
  - Tend to be early stage
  - Poorly differentiated tumors that exhibit an abundance of tumor infiltrating lymphocytes (TIL)
  - Better overall prognosis compared to patients with microsatellite stable disease (MSS or pMMR).

NCCN = National Comprehensive Cancer Network

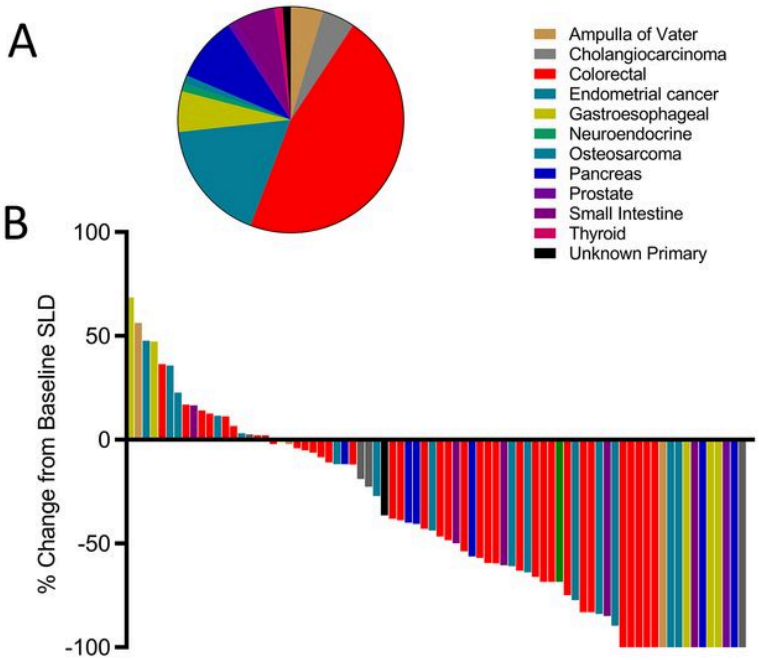
Copija, A., et al. (2017). International Journal of Molecular Sciences, 18(1). https://doi.org/10.3390/ijms18010107; Overman, M. J., et al. (2018). *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *36*(8), 773–779. https://doi.org/10.1200/JCO.2017.76.9901

Pembrolizumab Approval for dMMR/MSI-H Tumors

- First “disease-agnostic” approval and represents major paradigm shift to approve cancer drug based on the presence of a specific biomarker
- FDA approval based on data from five single-arm multicohort trials (n = 149)
  - KEYNOTE-016 (n = 58), KEYNOTE-164 (n = 61), KEYNOTE-012 (n = 6), KEYNOTE-028 (n = 5), and KEYNOTE-158 (n = 19)
  - Pembrolizumab at 200 mg q3w or 10 mg/kg q2w until unacceptable toxicity or either symptomatic disease progression, rapid progression requiring urgent intervention, or progression with a performance status decline. Maximum length of treatment was 24 months.
- Objective response rate: 39.6% (95% CI = 31.7%–47.9%)
  - 48 partial responses and 11 complete responses
  - 78% of responders had responses of > 6 months
- Recommended pembrolizumab dose for this indication
  - Adults: 200 mg IV over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm

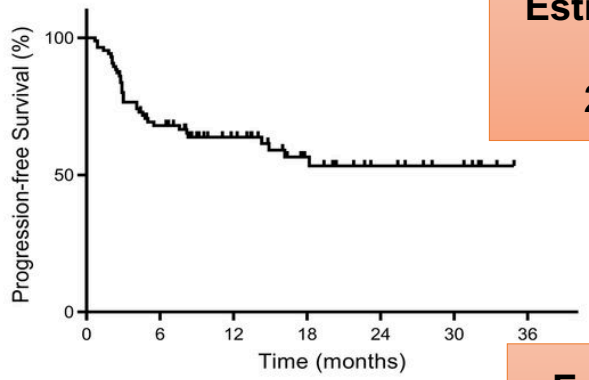
Pembrolizumab in 12 Different Tumor Types With Mismatch Repair Deficiency (n = 78)



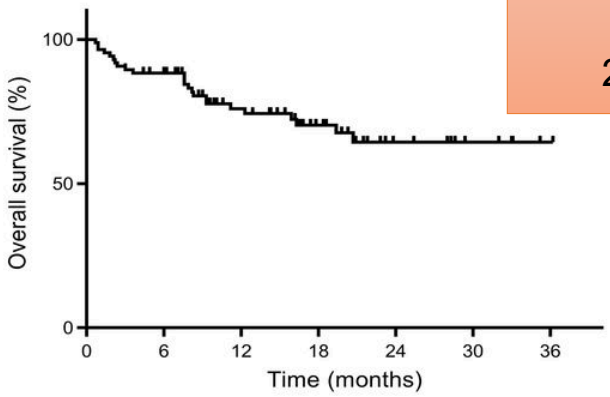
Objective response: 53%

Complete response: 21%

Disease control (CR+PR=SD): 77%



Estimated PFS
1 y: 64%
2 y: 53%



Estimated OS
1 y: 76%
2 y: 64%

CR = complete response; PR = partial response; SD = stable disease.

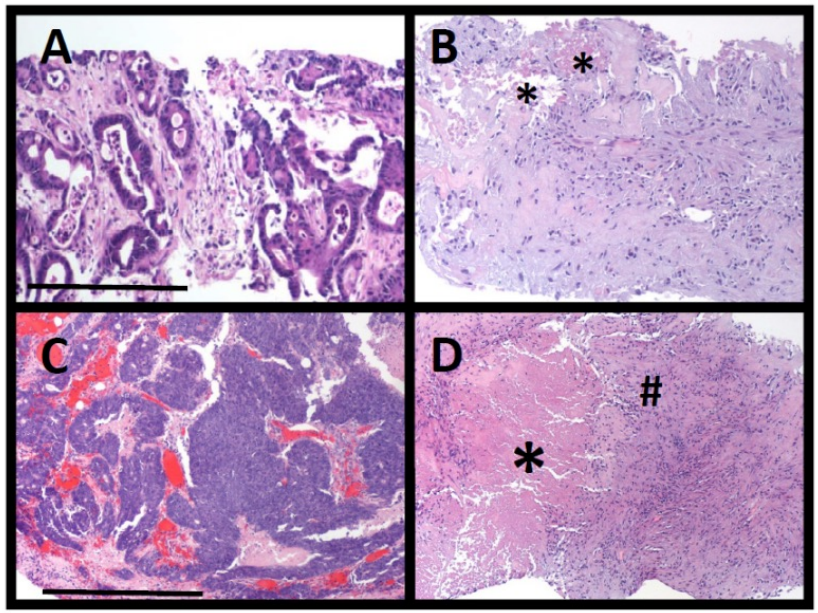
Le, D. T., Durham, J. N., Smith, K. N., Wang, H., Bartlett, B. R., Aulakh, L. K., … Diaz, L. A. (2017). Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science (New York, N.Y.), 357(6349), 409–413. https://doi.org/10.1126/science.aan6733

Biopsies of Residual Radiographic Disease: Evidence Of Cancer in 60% of Cases

- 20 patients with residual radiographic disease had biopsies
  - 12 patients (60%) had negative biopsies
    - No evidence of tumor cells
    - There were varying degrees of inflammation, fibrosis and mucin, consistent with an ongoing immune response
  - 8 cases showed residual tumor cells
- The absence of cancer cells in post-treatment biopsies was a strong predictor of progression-free survival
  - Median PFS: 25.9 months vs. 2.9 months for biopsies with evidence of residual tumor
  - Median OS has not yet been reached in patients with negative biopsies

Le, D. T., Durham, J. N., Smith, K. N., Wang, H., Bartlett, B. R., Aulakh, L. K., … Diaz, L. A. (2017). Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science (New York, N.Y.)*, *357*(6349), 409–413. https://doi.org/10.1126/science.aan6733

Pre-Treatment and Post-Treatment Biopsies



(A) Pre-treatment core biopsies of metastatic colonic adenocarcinoma

(B) Post-therapy demonstrating focal necrosis
(*) mild chronic inflammation, early hyalinizing fibrosis, and resolving granulation tissue.

(C) Pre-treatment biopsy of metastatic colonic adenocarcinoma

(D) Post-treatment biopsy shows prominent necrosis
(*) loose granuloma formation
(#) focal fibrosis, and moderate chronic inflammation. No malignant epithelial (neoplastic) colon cancer cells were identified.

Le, D. T., Durham, J. N., Smith, K. N., Wang, H., Bartlett, B. R., Aulakh, L. K., … Diaz, L. A. (2017). Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science (New York, N.Y.)*, *357*(6349), 409–413. https://doi.org/10.1126/science.aan6733

Pembrolizumab Monotherapy: Adverse Effects

Any grade: 74%

Grade 3/4: 20%

Event-no. (%)	All Grades N=84	Grade 1 or 2	Grade 3 or 4
Any	62 (74%)	62 (74%)	17 (20%)
Generalized Symptoms			
Fatigue	21 (25%)	19 (23%)	2 (2%)
Flu-like symptoms	6 (7%)	6 (7%)	0 (0%)
Infection	5 (6%)	5 (6%)	0 (0%)
Gastrointestinal			
Diarrhea/colitis	19 (23%)	14 (17%)	5 (6%)
Nausea/vomiting	11 (13%)	10 (12%)	1 (1%)
Gastritis/ulcer	4 (5%)	3 (4%)	1 (1%)
Transaminitis	4 (5%)	4 (5%)	0 (0%)
Pancreatitis/Hyperamylasemia	5 (6%)	0 (0%)	5 (6%)
Endocrine Disorders			
Thyroid disease/hypophysitis	18 (21%)	18 (21%)	0 (0%)
Arthritis/arthralgias	14 (17%)	12 (14%)	2 (2%)
Hematologic			
Anemia	6 (7%)	4 (5%)	2 (2%)
Thrombocytopenia	4 (5%)	3 (4%)	1 (1%)
Rash/pruritus	30 (36%)	29 (35%)	1 (1%)
Neuropathy	5 (6%)	4 (5%)	1 (1%)
Acute kidney injury	4 (5%)	3 (4%)	1 (1%)

Le, D. T., Durham, J. N., Smith, K. N., Wang, H., Bartlett, B. R., Aulakh, L. K., … Diaz, L. A. (2017). Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science (New York, N.Y.)*, *357*(6349), 409–413. https://doi.org/10.1126/science.aan6733

Phase III KEYNOTE-177 (NCT02563002) Is Ongoing

- International, randomized, open-label, phase III study of pembrolizumab vs. standard-of-care (SOC) chemotherapy in first-line MMR-deficient or MSI-high metastatic CRC
- ~270 patients will be randomly assigned 1:1 to receive either pembrolizumab at 200 mg every 3 weeks or investigator's choice of SOC chemotherapy (mFOLFOX6 or FOLFIRI alone or in combination with bevacizumab or cetuximab, chosen before randomization)
- Treatment is to continue until progressive disease (PD), unacceptable toxicity, patient/investigator decision, or completion of 35 cycles (pembrolizumab only)
- Response is to be assessed every 9 weeks per RECIST v1.1 by central imaging vendor review and per RECIST adapted for immunotherapy response patterns
- Eligible patients may continue pembrolizumab beyond initial RECIST-defined progression
- Patients in the SOC arm who have PD and meet crossover criteria may be eligible to receive pembrolizumab for up to 17 treatment cycles.
- The primary end point is PFS per RECIST v1.1; secondary end points include OS and ORR.

Diaz, L. A., Le, D. T., Yoshino, T., Andre, T., Bendell, J. C., Koshiji, M., … Jäger, D. (2017). KEYNOTE-177: Randomized phase III study of pembrolizumab versus investigator-choice chemotherapy for mismatch repair-deficient or microsatellite instability-high metastatic colorectal carcinoma. *Journal of Clinical Oncology*, *35*(4_suppl), TPS815-TPS815. https://doi.org/10.1200/JCO.2017.35.4_suppl.TPS815

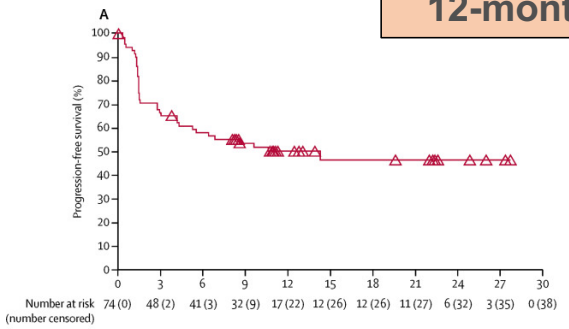
Nivolumab

- FDA approved for
  - Adult and pediatric (12 years and older) patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan
- Based on data from CheckMate 142
- Dose: 240 mg IV over 30 minutes every 2 weeks until disease progression or unacceptable toxicity

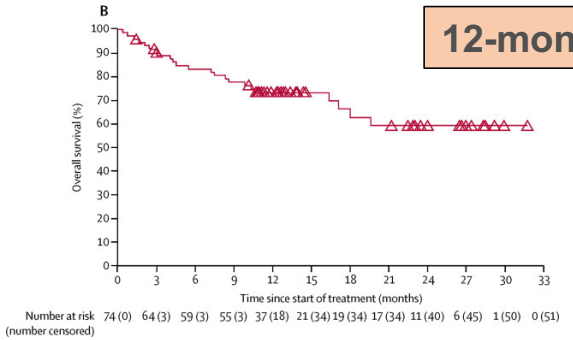
CheckMate 142: Nivolumab Monotherapy for dMMR/MSI-H Metastatic Colorectal Cancer

- 74 patients
- Nivolumab at 3 mg/kg q2wk
- Median follow-up: 12 months
  - Objective response: 31%
  - Disease control: 69%
  - Median time to response: 2.8 months (range 1.4–3.2)
  - Median duration of response: not reached
  - Median PFS: 14.3 months
- Responses were seen irrespective of PD-L1 status, Lynch syndrome, or *KRAS* and *BRAF* mutations.

12-month PFS: 50%



12-month OS: 73%

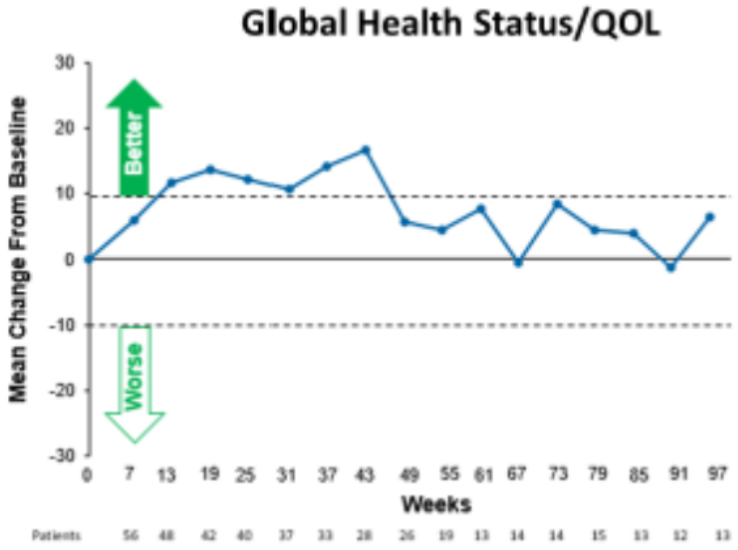


dMMR/MSI-H = DNA mismatch repair deficient/microsatellite instability-high

Overman, M. J., McDermott, R., Leach, J. L., Lonardi, S., Lenz, H.-J., Morse, M. A., … André, T. (2017). Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *The Lancet Oncology*, *18*(9), 1182–1191. https://doi.org/10.1016/S1470-2045(17)30422-9

CheckMate 142: Patient-Reported Outcomes and Adverse Effects

- Any grade: 70%
- Grade 3/4: 20%
- Most adverse events were easily managed
- As early as week 13, clinically meaningful improvements in quality of life

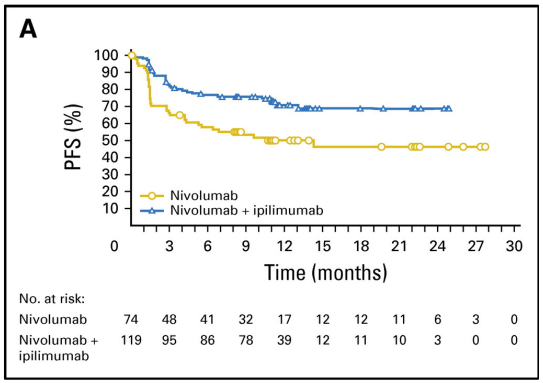


European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30

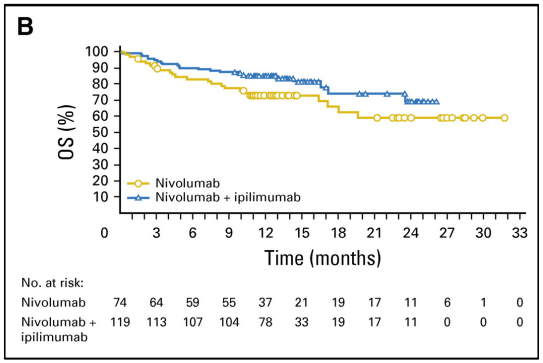
Overman, M. J., McDermott, R., Leach, J. L., Lonardi, S., Lenz, H.-J., Morse, M. A., … André, T. (2017). Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *The Lancet Oncology*, *18*(9), 1182–1191. https://doi.org/10.1016/S1470-2045(17)30422-9

CheckMate 142: Nivolumab/Ipilimumab for dMMR/MSI-H Metastatic Colorectal Cancer

- 119 patients
- Nivolumab at 3 mg/kg plus ipilimumab at 1 mg/kg once every 3 weeks (four doses) followed by nivolumab at 3 mg/kg once every 2 weeks
- Median follow-up: 13.5 months
  - Objective response: 55%
  - Disease control: 80%
  - Median time to response: 2.8 months (range 1–14)
  - Median duration of response: not reached
  - Median PFS: not reached



12-month PFS
Nivo: 50%
Nivo/Ipi: 71%



12-month OS
Nivo: 73%
Nivo/Ipi: 85%

dMMR/MSI-H = DNA mismatch repair deficient/microsatellite instability-high

Overman, M. J., et al. (2018). *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *36*(8), 773–779. https://doi.org/10.1200/JCO.2017.76.9901

CheckMate 142: Nivolumab/Ipilimumab Cohort Adverse Events

- Combination therapy had similar adverse events, but more likely to be grade 3/4 than monotherapy
- Any grade: 73%
- Grade 3/4: 32%
- 13% of patients discontinued therapy due to adverse events
- QOL improved with combination therapy similar to monotherapy

TRAE	No. (%)		
	Grade 1-2	Grade 3	Grade 4
Any TRAE	49 (41)	32 (27)	6 (5)
Diarrhea*	24 (20)	2 (2)	0
Fatigue*	19 (16)	2 (2)	0
Pruritus*	18 (15)	2 (2)	0
Pyrexia*	18 (15)	0	0
Increased AST*	8 (7)	9 (8)	0
Hypothyroidism*	15 (13)	1 (1)	0
Nausea*	14 (12)	1 (1)	0
Increased ALT*	6 (5)	8 (7)	0
Rash*	11 (9)	2 (2)	0
Hyperthyroidism*	13 (11)	0	0

TRAE = treatment-related adverse event.

Overman, M. J., et al. (2018). *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *36*(8), 773–779. https://doi.org/10.1200/JCO.2017.76.9901

Case Study

- EN is a 54-year-old male with CRC (*RAS* and *BRAF* wild type), metastatic to liver and lungs. ECOG PS 1, MSI-high disease, no family history of hereditary nonpolyposis CRC, and negative germline testing for Lynch syndrome.
- Treated with FOLFOX + bevacizumab until progression, then FOLFIRI + panitumumab until progression.
- Most recent scan shows progression in liver and lung.
- He starts treatment with pembrolizumab at 200 mg IV over 30 minutes every 3 weeks.

Audience Response Question

EN is seen in clinic for cycle 5 of pembrolizumab. He mentions that he has been extremely fatigued. TFTs: TSH 23 mIU/L (high) and T4 0.2 µg/dL (low) consistent with primary hypothyroidism. What do you recommend to treat autoimmune hypothyroidism?

A. Treat autoimmune hypothyroidism with prednisone 1 mg/kg for 1 week then taper over 1–2 months
B. Treat with thyroid hormone replacement and expect that thyroid function will recover after completion of pembrolizumab
C. Treat with thyroid hormone replacement; thyroid function unlikely to recover so anticipate lifelong therapy
D. Repeat thyroid function tests in 4–6 weeks. If TSH still elevated, treat with thyroid hormone replacement
E. Unsure

Symptoms of Thyroid Disorders

Hyperthyroidism

- Anxiety
- Irritability
- Increased bowel movements
- Diaphoresis
- Palpitations
- Weight loss

Hypothyroidism

- Fatigue
- Joint pain
- Constipation
- Intolerance to cold
- Decreased heart rate
- Hair loss

Byun DJ, et al. *Nat Rev Endocrinol* 2017;13:195-207.

Management of Immune-Related Hypothyroidism

Monitor TSH and free T4 every 4–6 weeks			
Asymptomatic subclinical hypothyroidism	TSH 4 to < 10 Normal free T4	Repeat TSH, free T4 in 4-6 weeks	Continue IO
	TSH > 10 Normal free T4	Consider thyroid hormone replacement therapy or repeat TFTs in 4 weeks and if persists > 4 weeks, thyroid hormone replacement	Continue IO
Symptomatic subclinical hypothyroidism	TSH > 4 Normal free T4	Thyroid hormone replacement	Continue IO
Primary hypothyroidism	TSH > 10 Low free T4	Thyroid hormone replacement Consider endocrine consult	Continue IO
Central hypothyroidism	Normal or low TSH Low free T4	Thyroid hormone replacement Consider central hypothyroidism Consider endocrine consult	Continue IO
If required, thyroid hormone therapy should be initiated as an initial full replacement (1.6 mcg/kg/d) or as partial replacement in frail/elderly patients (25–50 μg/d). Titrate dose in gradual increments based on TSH assessments every 4–8 weeks to target goal of normal TSH.			

Cukier, P., et al. (2017). *Endocrine-Related Cancer*, *24*(12), T331–T347. https://doi.org/10.1530/ERC-17-0358; NCCN Guidelines Version 1.2018 Management of Immunotherapy-Related Toxicities; Brahmer, J. R., et al. (2018). *Journal of Clinical Oncology*, JCO2017776385. https://doi.org/10.1200/JCO.2017.77.6385

Case Study (cont.)

- Initiate levothyroxine at 1.6 µg/kg orally daily
- Repeat TSH in 6 weeks and titrate levothyroxine to normal serum TSH
- Consider referral to endocrinology
- Counsel EN that this may not be reversible and to anticipate lifelong thyroid replacement therapy
- OK to continue treatment with pembrolizumab

Audience Response Question

EN is seen in clinic for cycle 5 of pembrolizumab. He mentions that he has been extremely fatigued. TFTs: TSH 23 mIU/L (high) and T4 0.2 µg/dL (low) consistent with primary hypothyroidism. What do you recommend to treat autoimmune hypothyroidism?

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C. Treat with thyroid hormone replacement; thyroid function unlikely to recover so anticipate lifelong therapy
D. Repeat thyroid function tests in 4–6 weeks. If TSH still elevated, treat with thyroid hormone replacement
E. Unsure

Immune-Related Hyperthyroidism

- Thyrotoxicosis may be detected in routine blood work or due to symptoms
  - Low TSH and elevated free T4
  - Occurs approximately 3–6 weeks after the first immunotherapy dose
  - Thyroid peroxidase (TPO) antibody and/or thyroid-stimulating hormone receptor antibody (TRAb) generally positive
- May treat symptoms temporarily with β-blocker therapy
  - e.g., Propranolol at 10–20 mg q4–6 hrs prn, atenolol, metoprolol
- Monitor thyroid function every 2 to 3 weeks after diagnosis to catch transition to hypothyroidism
  - Thyrotoxicosis usually resolves spontaneously within ~4 weeks
  - Typically followed by hypothyroidism requiring thyroid hormone replacement (usually lifelong)

NCCN Guidelines Version 1.2018 Management of Immunotherapy-Related Toxicities; Brahmer, J. R., et al. (2018). *Journal of Clinical Oncology*, JCO2017776385. https://doi.org/10.1200/JCO.2017.77.6385

Conclusion

- The use of immune checkpoint inhibitors to treat dMMR/MSI-H tumors is emerging as an effective strategy with durable responses
- dMMR/MSI-H tumors may be particularly susceptible to immune checkpoint therapy due to:
  - High mutation rate: giving rise to tumor-specific neoantigens that the immune system can target
  - High concentration of infiltrating cytotoxic T cells
- Unlike other tumors, responses did not correlate with PD-L1 status
- The side effect profile is similar to other populations with mostly low grade manageable toxicities