SITC Webinar:
2023 Guidelines-GI Case Studies
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Case 2: Colorectal Cancer

• 67 y/o woman with history of Type II DM, HTN, hyperlipidemia, and DJD of the spine with prior laminectomy presents to her new PCP with a 2M history of fatigue, loss of 10 lbs, reduced appetite, LLQ pain (3 out of 10) and hematochezia.

• Her last colonoscopy was in 2015 and she underwent a polypectomy. She reports regular bowel movements until 4 days ago. Her last BM was 2 days ago. She is passing flatus.

• She states her last HgbA1C < 7.0, six months ago.

• PE: No rebound or guarding, good BS, but mild tenderness of LUQ

• Labs drawn today include Hgb = 8.4 and her MCV = 77.

• Diagnostic workup including colonoscopy and a CT scan was completed.
Diagnostic tests:

Colonoscopy:
• An infiltrative partially obstructing large mass was found in the transverse colon/splenic flexure at ~80 cm. The mass was circumferential with biopsy c/w poorly differentiated adenocarcinoma.

CT Scan c/a/p:
• Large transverse colonic mass compatible with colon cancer with evidence of peritoneal and hepatic metastatic disease.
• Peritoneal nodules noted at the left upper quadrant are compatible with peritoneal metastatic disease with for example the largest measuring 2.2 x 2 cm.

December 2020
Multidisciplinary management

• She was evaluated by a CRC surgeon to determine if any concerns for impending obstruction. Agreed no immediate surgical intervention is needed.

• Pathology: Loss of MLH1 by IHC

• NGS ordered:
  • cfDNA: MSI-H and BRAF V600E MT
  • Tumor NGS:
    • MSI-H (dMMR)
    • BRAF V600E MT
    • TMB = 43.7 m/MB
    • RNA: NTRK Fusion not detected

• Conclusion: dMMMR due to hypermethylation of MLH-1
SITC 2023 Guideline for mCRC

Diagnostic Workup

- Disease stage confirmed: Surgically unresectable, metastatic, or stage IV
- Tissue-based biomarkers obtained: NGS (including TMB, MSI*, POLE/D1), KRAS/NRAS/BRAF, HER2 expression
- Immunotherapy-naïve†
- Patient considered for available clinical trials

MSI-H or dMMR?

No

POLE or POLD1 mutation with ultramutated TMB‡

Yes

- Pembrolizumab
- Nivolumab +/- ipilimumab

No

Refer to published guidelines for non-immunotherapeutic treatments

Yes

- Pembrolizumab (preferred)
- Nivolumab + ipilimumab

Kelly et al: JITC, 2023
How do you decide for single agent vs. combination immunotherapy?
KN177: Phase III trial in MSI-H/dMMR mCRC

Key Eligibility Criteria
- MSI-H (PCR)/dMMR (IHC) Stage IV CRC
- Treatment naïve
- ECOG PS 0 or 1
- Measurable disease by RECIST v1.1

N = 153

N = 307

R (1:1)

Pembrolizumab 200 mg Q3W for up to 35 cycles

Investigator-Choice Chemotherapy
- mFOLFOX6 IV Q2W
- OR mFOLFOX6 + Bevacizumab IV Q2W
- OR mFOLFOX6 + Cetuximab IV Q2W
- OR FOLFIRI IV Q2W
- OR FOLFIRI + Bevacizumab IV Q2W
- OR FOLFIRI + Cetuximab IV Q2W

Optional crossover to pembrolizumab 200 mg Q3W for up to 35 cycles for patients with centrally verified PD by RECIST v1.1, central review

Until unacceptable toxicity, disease progression, or patient/physician withdrawal decision

Safety and survival follow-up

- 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
- Exploratory endpoints: DOR per RECIST v1.1 by BICR, PFS2, HRQoL
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

Andre et al: NEJM, 2020
KN177 Results:

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 62 (40.5%)</td>
<td>0.74 (0.53-1.03)</td>
<td>0.0359*</td>
</tr>
<tr>
<td>Chemo 78 (50.6%)</td>
<td></td>
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</tr>
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</table>

Median (95% CI) Not reached (49.2-NR) 36.7 mo (27.6-NR)

André et al: NEJM, 2020
- Median follow-up: 32.4M
- Cross-over:
  - 36% cross-over from control arm
  - 37 additional pts received off protocol PD-1 therapy (total = 60% for ITT)
- Updated RR: 45% vs. 33%
  - CR: 13% vs. 4%
  - PR: 32% vs. 29%
- Median duration of response: NR vs. 10.6M
### KN-177: Treatment related SAE’s

<table>
<thead>
<tr>
<th>Event</th>
<th>Any</th>
<th>Grade ≤3</th>
<th>Any</th>
<th>Grade ≤3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>149 (51)</td>
<td>86 (56)</td>
<td>142 (59)</td>
<td>111 (78)</td>
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<tr>
<td>Diarrhea</td>
<td>68 (44)</td>
<td>9 (6)</td>
<td>89 (62)</td>
<td>16 (11)</td>
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<tr>
<td>Fatigue</td>
<td>58 (38)</td>
<td>6 (4)</td>
<td>72 (50)</td>
<td>13 (9)</td>
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<tr>
<td>Nausea</td>
<td>47 (31)</td>
<td>4 (3)</td>
<td>85 (59)</td>
<td>6 (4)</td>
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<tr>
<td>Abdominal pain</td>
<td>37 (24)</td>
<td>6 (5)</td>
<td>42 (28)</td>
<td>8 (6)</td>
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<tr>
<td>Decreased appetite</td>
<td>36 (24)</td>
<td>5 (4)</td>
<td>58 (41)</td>
<td>7 (5)</td>
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<tr>
<td>Vomiting</td>
<td>31 (21)</td>
<td>7 (5)</td>
<td>51 (36)</td>
<td>7 (5)</td>
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<tr>
<td>Arthralgia</td>
<td>25 (16)</td>
<td>1 (1)</td>
<td>7 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>28 (18)</td>
<td>3 (2)</td>
<td>20 (14)</td>
<td>0</td>
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<tr>
<td>Anemia</td>
<td>27 (18)</td>
<td>8 (5)</td>
<td>32 (23)</td>
<td>15 (10)</td>
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<tr>
<td>Pruritus</td>
<td>25 (16)</td>
<td>0</td>
<td>12 (9)</td>
<td>1 (1)</td>
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<tr>
<td>Back pain</td>
<td>26 (17)</td>
<td>2 (1)</td>
<td>24 (17)</td>
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<tr>
<td>Constipation</td>
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<td>45 (31)</td>
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<td>Cough</td>
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<td>25 (16)</td>
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<td>Aspartate aminotransferase increase</td>
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<td>12 (9)</td>
<td>3 (2)</td>
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<td>Dizziness</td>
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<td>20 (14)</td>
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<td>Alanine aminotransferase increase</td>
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<td>16 (11)</td>
<td>3 (2)</td>
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<td>Blood alkaline phosphatase increase</td>
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<td>10 (8)</td>
<td>2 (1)</td>
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<td>Dyspeps</td>
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<td>Headache</td>
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<td>Dry skin</td>
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<td>Hypertension</td>
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<td>Pain in extremity</td>
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<tr>
<td>Periophthalgia</td>
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<td>12 (8)</td>
<td>2 (1)</td>
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<tr>
<td>Dry mouth</td>
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<td>9 (6)</td>
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<tr>
<td>Upper respiratory tract infection</td>
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<td>Urinary tract infection</td>
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<td>Stevensian</td>
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<td>41 (29)</td>
<td>6 (4)</td>
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</table>
Checkmate 142: Nivo + Ipi MSI-H/ dMMR mCRC

CheckMate 142 is an ongoing, multicohort, nonrandomized phase 2 trial evaluating the efficacy and safety of NIVO-based therapies in patients with mCRC\textsuperscript{a}

- Histologically confirmed metastatic or recurrent CRC
- MSI-H/dMMR per local laboratory
- No prior treatment for metastatic disease

Primary endpoint:
- ORR per investigator assessment (RECIST v1.1)

Other key endpoints:
- ORR per BICR, DCR,\textsuperscript{c} DOR, PFS, OS, and safety

At data cutoff (October 2019), the median duration of follow-up was 29.0 months (range, 24.2-33.7)\textsuperscript{d}

\textsuperscript{a}Lenz et al: JCO, 2021
Checkmate 142: Response Rate

- ORR was generally similar across evaluated subgroups and consistent with that of the overall study population

*Median follow-up, 29.0 months. †Per investigator assessment. ‡Excluded 5 patients with unknown mutation status. §All patients had stage IV disease at study entry. ¶Excluded 4 patients with uncategorized primary tumor location. ‖Error bars and numbers in parentheses indicate 95% CIs; evaluated subgroups had overlapping 95% CIs for ORR.

Lenz et al: JCO, 2021
Checkmate 142: Response and SAE’s

![Graph showing response and SAE's over time](image)

<table>
<thead>
<tr>
<th>TRAEs reported in &gt; 10% of patients</th>
<th>Any grade</th>
<th>Grade 3</th>
<th>Grade 4</th>
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</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>16 (36)</td>
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<tr>
<td>Arthralgia</td>
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<tr>
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</tr>
<tr>
<td>Lipase increased</td>
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</tr>
<tr>
<td>Pyrexia</td>
<td>5 (11)</td>
<td>0</td>
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</tr>
</tbody>
</table>

Lenz et al: JCO, 2021
SITC Panel Recommendations for mCRC

• For all patients with CRC, clinical trial enrollment should be considered at all stages of treatment, when feasible.

• For patients with untreated, metastatic, MSI-H/dMMR CRC, pembrolizumab monotherapy is recommended (LE:2). Treatment with combination nivolumab plus ipilimumab may be considered for this indication as well (LE:3), although there are no randomized data to suggest that this regimen is superior to pembrolizumab monotherapy.

• For patients with untreated, metastatic, MSS/pMMR CRC, treatment with ICIs is not recommended outside of a clinical trial. This applies to patients with tumors that are TMB-H while being MSS/pMMR (LE:3), except for patients with POLE/POLD1 mutations with an associated ultramutated TMB (LE:3).

• For patients with previously treated, metastatic, MSI-H/dMMR CRC who have not received prior ICI therapy, pembrolizumab monotherapy (LE:3) or nivolumab with (LE:3) or without (LE:3) ipilimumab are all recommended options. Dostarlimab monotherapy is a recommended treatment option for dMMR disease only (LE:3).
Case #2 Continued: Outcome

Summer 2022:
• Colonoscopy negative excluding a sessile adenoma s/p polypectomy

Dec 2022:
• CT scan c/a/p: Interval decrease in the size of peritoneal implants. There is new calcification in the left upper quadrant peritoneal implant, decreased soft tissue adjacent to the distal transverse colon
  • The previously described segment five hepatic lesion is less conspicuous on today's exam.
  • No evidence of new adenopathy or new peritoneal deposits
• Surgical follow-up: Patient opted to defer resection of primary at this time and is being followed conservatively.
Case #2: Treatment

• No clinical trial was available at that time
• Discussed with the patient the role of single agent immune checkpoint inhibition in the setting of stage IV, T4NxM1 transverse colon cancer.
• ECOG PS = 1
• Pembrolizumab single agent was provided every q6 weeks with diagnostic imaging offered q3M CT scan c/a/p for restaging.
Case 2: Outcome continued

Feb 2023:

• Pet/CT scan (to rule IO induced fibrosis):
  • Similar region of soft tissue thickening adjacent to the left transverse colon with associated moderate FDG uptake versus background physiologic colonic activity attributed to metformin.
  • No FDG avidity otherwise.

August 2023:

• PET/CT: No convincing FDG avid disease with decrease FDG uptake in the left transverse colon and minimal soft tissue thickening similar to prior exam
• Patient continues to have PS = 1 and continue to defer surgical resection. Patient desires close surveillance only.
Conclusions:

• Multidisciplinary management is highly encouraged early on if appropriate.

• Discussion with the patient regarding pluses or minuses of single agent vs. combined agent is encouraged with the discussion of the level of evidence.

• The patient will be followed by close surveillance only for now.