SITC Webinar:
2023 Guidelines-GI Case Studies
October 2023

Cathy Eng, MD, FACP, FASCO

Vanderbilt-Ingram Cancer Center
David H. Johnson Chair in Surgical and Medical Oncology
Professor of Medicine, Hematology and Oncology
Co-Director, GI Oncology
Co-Leader, Gastrointestinal Cancer Research Program
Director for Strategic Relations
Director, VICC Young Adults Cancer Program
Co-Chair, NCI Gastrointestinal Steering Committee

Contact Info: cathy.eng@vumc.org
Twitter: @cathyengmd;
FB: cathy eng-mdcancer
www.youngadultswithcancer.com

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:

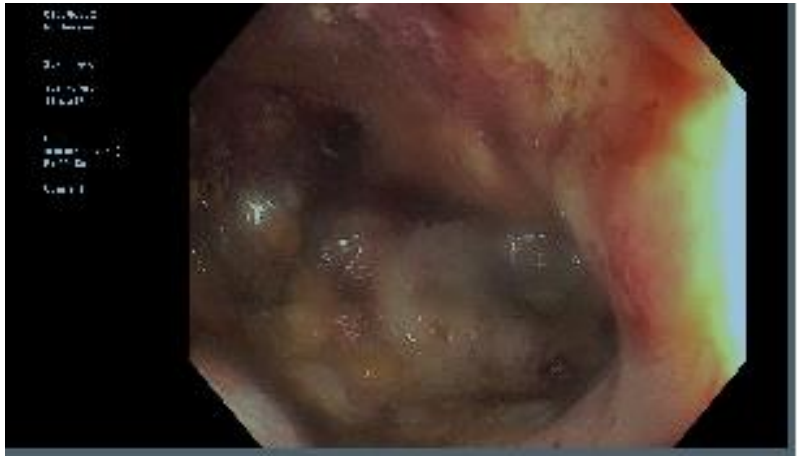
Colonoscopy:

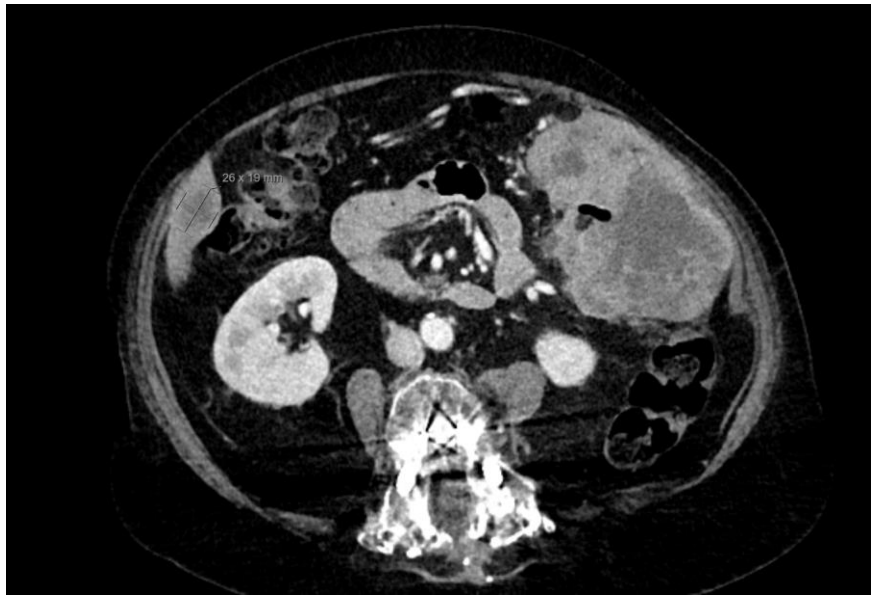
- An infiltrative partially obstructing large mass was found in the transverse colon/splenic flexure at ~80 cm. The mass was circumferential with biopsy c/w poorly differentiated adenocarcinoma.

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

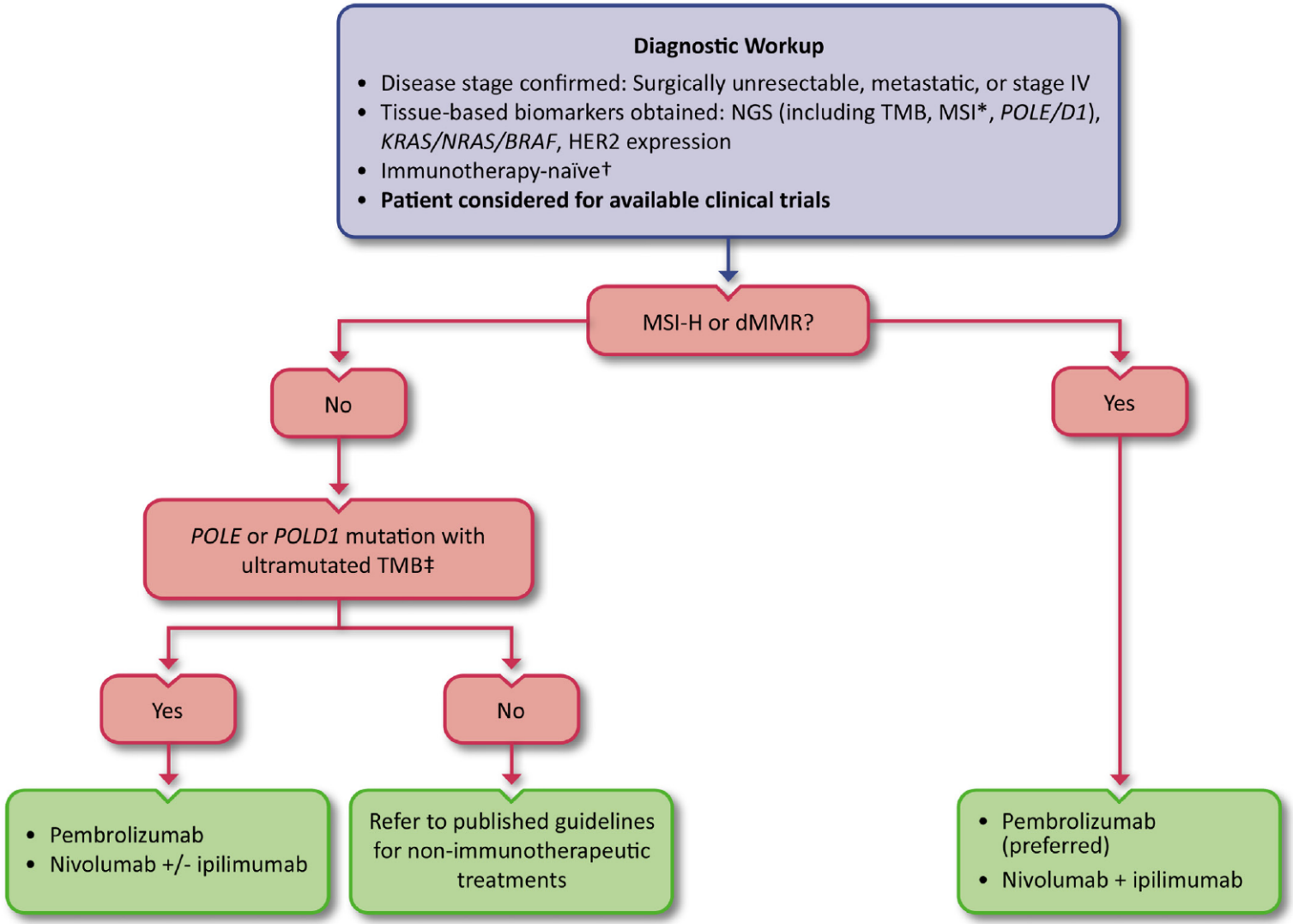




Multidisciplinary management

- 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: dMMR due to hypermethylation of MLH-1

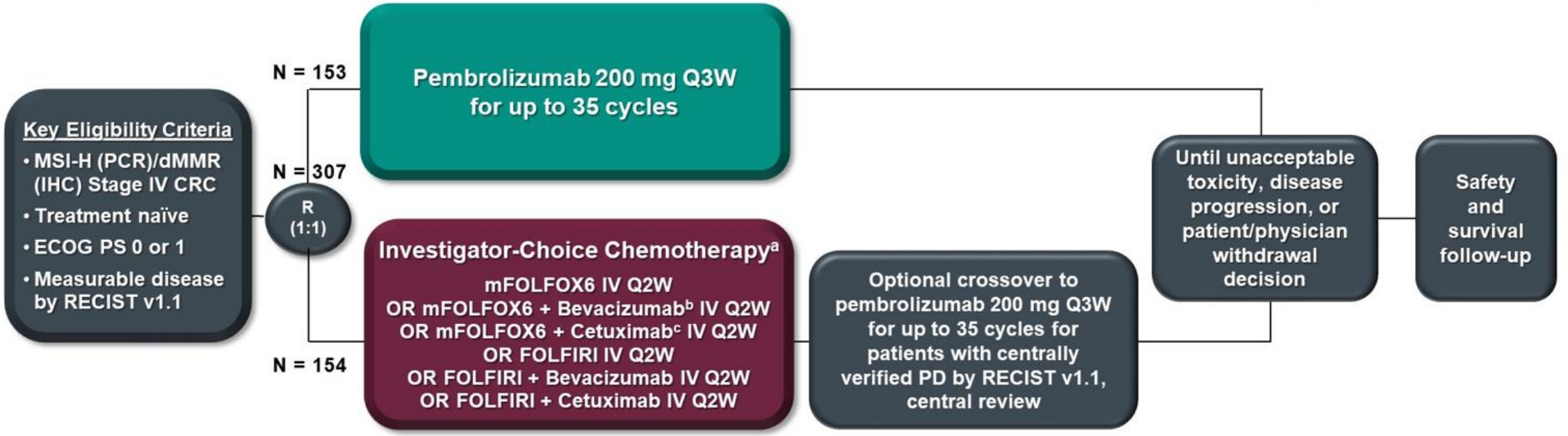
SITC 2023 Guideline for mCRC



Kelly et al: JITC, 2023

How do you decide for single agent vs. combination immunotherapy?

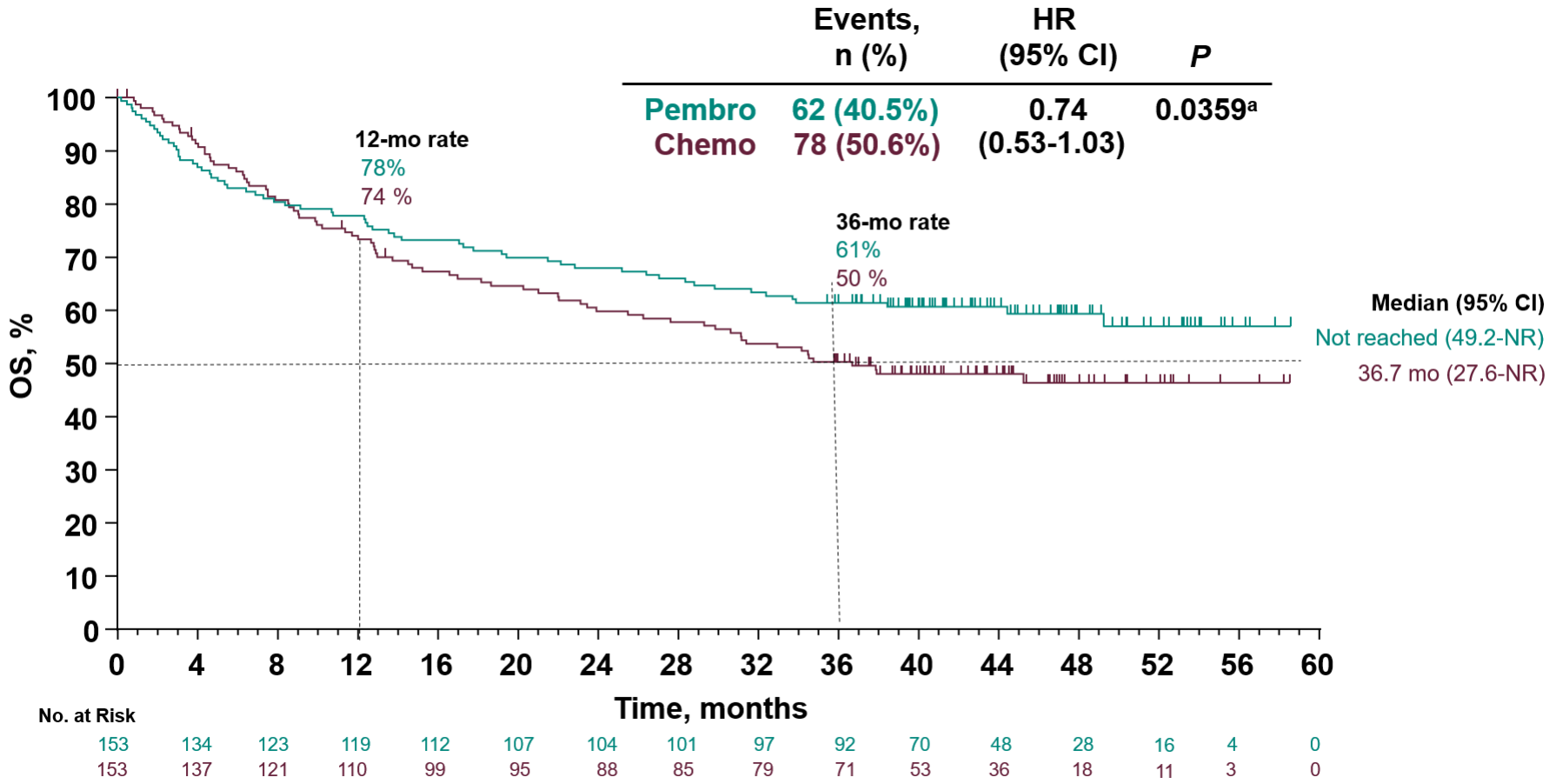
KN177: Phase III trial in MSI-H/dMMR mCRC



- 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

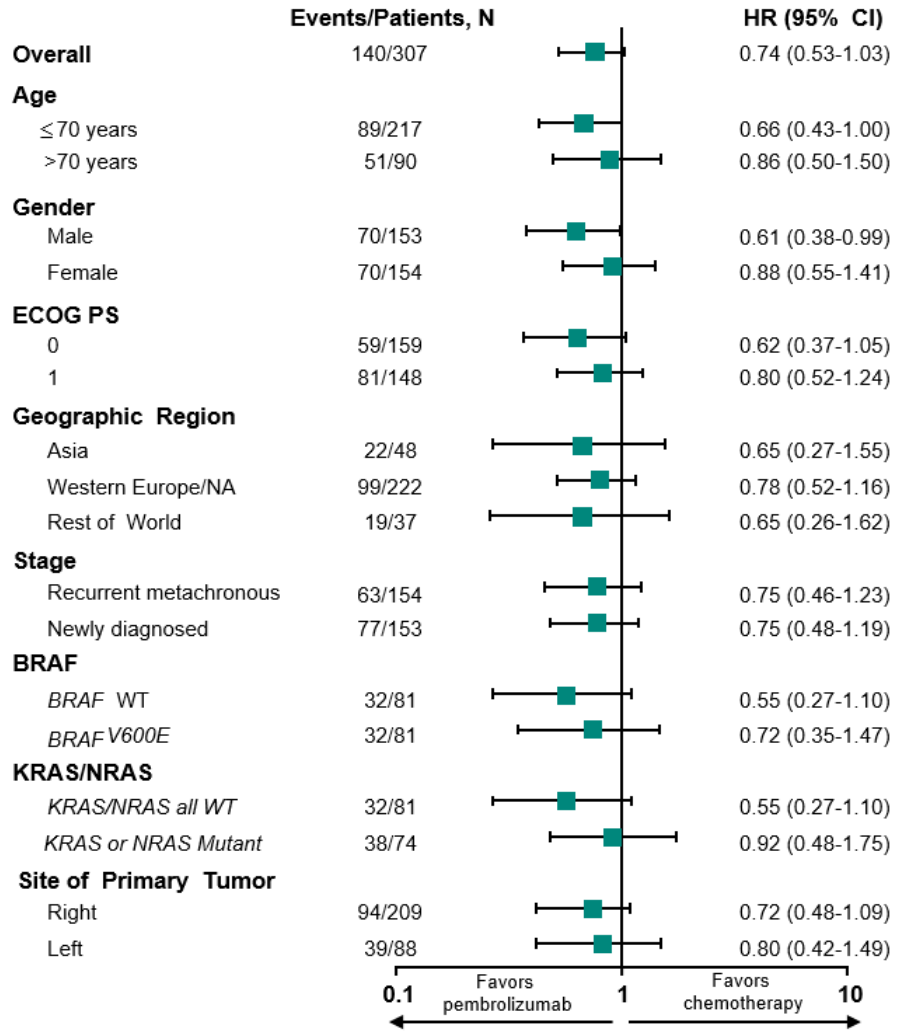
KN177 Results:



Andre et al: NEJM, 2020

KN-177 Response and OS Forest Plot

- 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



Andre et al: NEJM, 2020

KN-177: Treatment related SAE's

Event	Pembrolizumab (N=153)		Chemotherapy (N=143)	
	Any	Grade ≥3	Any	Grade ≥3
	number of patients (percent)			
Any adverse event†	149 (97)	86 (56)	142 (99)	111 (78)
Diarrhea	68 (44)	9 (6)	89 (62)	16 (11)
Fatigue	58 (38)	6 (4)	72 (50)	13 (9)
Nausea	47 (31)	4 (3)	85 (59)	6 (4)
Abdominal pain	37 (24)	8 (5)	42 (29)	8 (6)
Decreased appetite	36 (24)	0	58 (41)	7 (5)
Vomiting	33 (22)	2 (1)	53 (37)	7 (5)
Arthralgia	28 (18)	1 (1)	7 (5)	0
Pyrexia	28 (18)	1 (1)	20 (14)	0
Anemia	27 (18)	8 (5)	32 (22)	15 (10)
Pruritus	25 (16)	0	12 (8)	1 (1)
Back pain	26 (17)	2 (1)	24 (17)	1 (1)
Constipation	26 (17)	0	45 (31)	0
Cough	26 (17)	0	23 (16)	0
Aspartate aminotransferase increase	24 (16)	4 (3)	12 (8)	3 (2)
Dizziness	24 (16)	0	27 (19)	0
Alanine aminotransferase increase	22 (14)	4 (3)	16 (11)	3 (2)
Blood alkaline phosphatase increase	22 (14)	4 (3)	6 (4)	2 (1)
Dyspnea	21 (14)	1 (1)	15 (10)	0
Headache	21 (14)	0	22 (15)	0
Rash	20 (13)	1 (1)	16 (11)	1 (1)
Upper abdominal pain	20 (13)	2 (1)	11 (8)	1 (1)
Nasopharyngitis	20 (13)	0	10 (7)	0
Asthenia	19 (12)	3 (2)	31 (22)	6 (4)
Dry skin	19 (12)	0	13 (9)	0
Hypertension	19 (12)	11 (7)	16 (11)	7 (5)
Hypothyroidism	19 (12)	0	3 (2)	0
Pain in extremity	18 (12)	0	11 (8)	1 (1)
Peripheral edema	18 (12)	0	12 (8)	2 (1)
Dry mouth	17 (11)	0	9 (6)	0
Upper respiratory tract infection	16 (10)	0	8 (6)	0
Urinary tract infection	14 (9)	1 (1)	16 (11)	4 (3)
Hypokalemia	13 (8)	2 (1)	24 (17)	9(6)
Alopecia	11 (7)	0	29 (20)	0
Stomatitis	10 (7)	0	43 (30)	6 (4)

Andre et al: NEJM, 2020

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[a]

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

→ NIVO3 Q2W + IPI1 Q6W[b]

Primary endpoint:

- ORR per investigator assessment (RECIST v1.1)

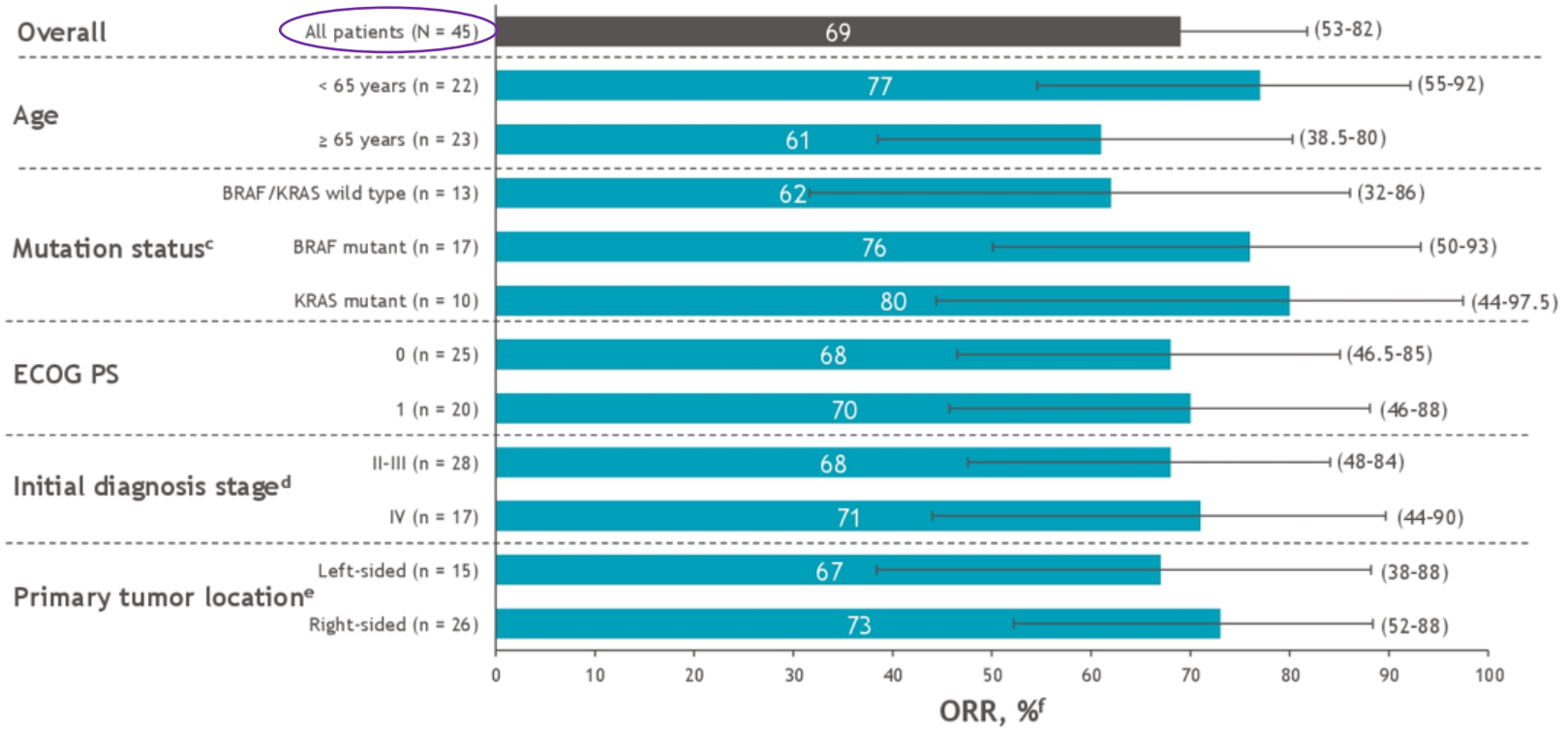
Other key endpoints:

- ORR per BICR, DCR,[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)[d]

Lenz et al: JCO, 2021

Checkmate 142: Response Rate

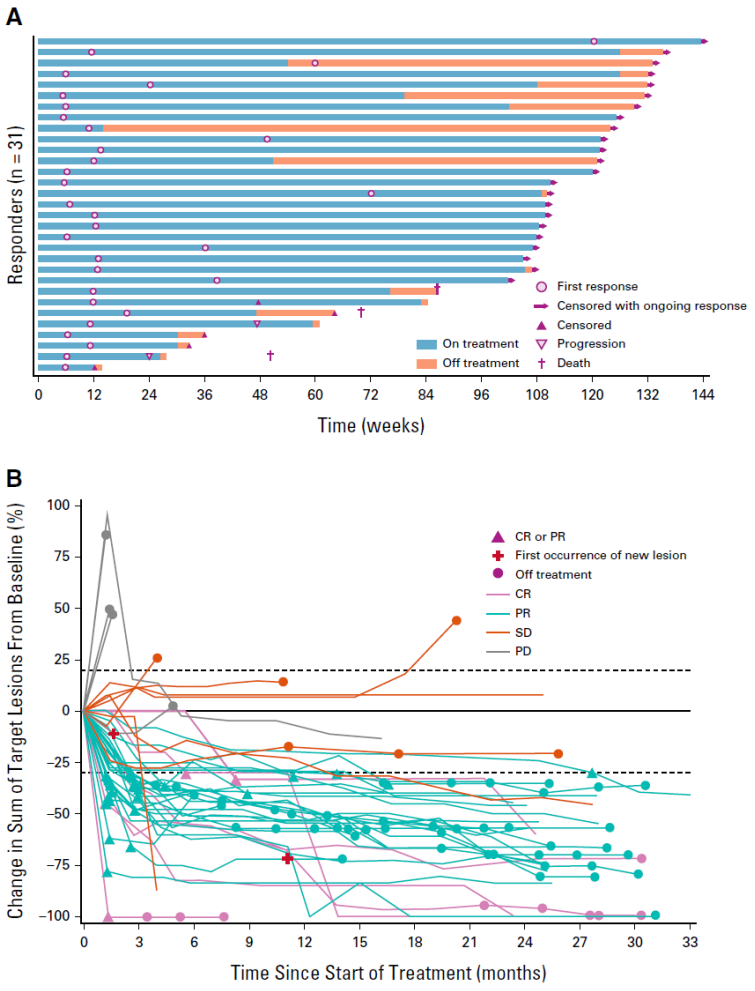


- ORR was generally similar across evaluated subgroups and consistent with that of the overall study population

[a]Median follow-up, 29.0 months. [b]Per investigator assessment. [c]Excluded 5 patients with unknown mutation status. [d]All patients had stage IV disease at study entry. [e]Excluded 4 patients with uncategorized primary tumor location. [f]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



	No. (%)[c]		
TRAE[b]	Any grade	Grade 3	Grade 4
Any TRAE	36 (80)	9 (20)	1 (2)[d]
TRAEs reported in > 10% of patients			
Pruritus	16 (36)	0	0
Arthralgia	9 (20)	0	0
Hypothyroidism	8 (18)	1 (2)	0
Asthenia	7 (16)	1 (2)	0
Rash	7 (16)	0	0
Fatigue	7 (16)	0	0
Diarrhea	7 (16)	0	0
Nausea	6 (13)	0	0
Lipase increased	5 (11)	0	0
Pyrexia	5 (11)	0	0

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).

Kelly et al: JITC, 2023

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.

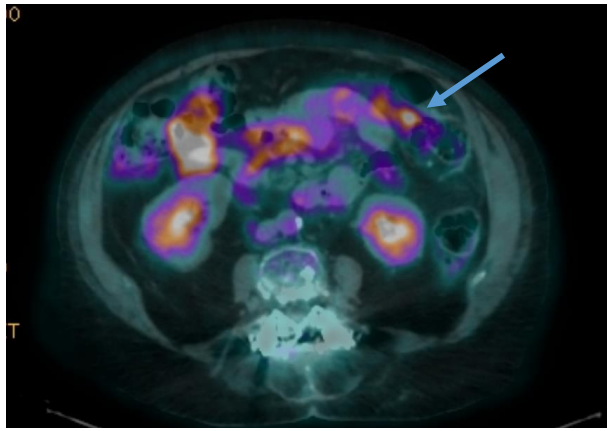
Case #2: Treatment

- 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 transversec 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.