Comparison of real-world later-line treatment outcomes in patients with microsatellite-instability high versus microsatellite-stable metastatic colorectal cancer in the United States

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Background

- Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related deaths[1]
- Approximately 50%–60% of patients diagnosed with CRC develop colorectal metastases[2,3]
- Among patients with metastatic colorectal cancer (mCRC), roughly 90%–95% have microsatellite stability (MSS) and 5%–10% have a high degree of microsatellite instability (MSI-H)[4,5]
- Emerging evidence suggests that patients with mismatch repair-deficient (dMMR)/MSI-H mCRC derive lesser benefit from conventional systemic therapy and have a shorter overall survival (OS) than patients with mismatch repair-proficient (pMMR)/MSS mCRC[6–10]
- Few studies have assessed the impact of MSI status on survival in mCRC, and there are no data available in previously treated patients with mCRC
- Here, we present results assessing treatment patterns and outcomes for patients with later-line mCRC within the Flatiron Health oncology electronic health record (EHR) database

Objectives

Primary

- To describe the demographic and clinical characteristics, treatment patterns, and treatment sequences for patients with mCRC who received ≥1 systemic (non-immuno-oncology [IO]) therapy by MMR/MSI biomarker status (MSI-H/MSS)
- To estimate time-to-next-treatment or death (TTNTd) and OS in patients with mCRC who received ≥1 systemic therapy by MMR/MSI biomarker status and line of therapy

Secondary

- To compare TTNTd and OS between the MSI-H and MSS patient subgroups after controlling for baseline confounding factors

Methods

Study design

- This retrospective analysis included patients from the Flatiron Health oncology EHR database, which compiles data from over 280 cancer clinics representing >3 million patients with cancer in the US
  - Adult patients diagnosed with pathologically confirmed stage IV/recurrent mCRC on or after January 1, 2013, with known MSI/MMR biomarker status, and who received ≥1 prior systemic therapy were included
  - Patients had at least 2 documented clinical visits on or after January 1, 2013, and had medical data for ≥2 months before index date (defined as the start of first-line [1L] treatment on or after January 1, 2013) and for ≥1 month post-index
  - Patients who received IO therapy (second-line [2L] or third-line [3L]) before or at index date were excluded
- Patients were assessed from index date until death, loss to follow-up, or end of study (January 31, 2021)

Endpoints

- Treatment patterns by line of systemic therapy (1L, 2L, 3L, fourth-line [4L], fifth-line [5L], or greater)
- Comparison of TTNTd and OS in the 2L and 3L settings between patients with MSI-H mCRC and MSS mCRC
- Impact of MSI status on TTNTd and OS in the 2L and 3L settings

Statistical analyses

- Demographics and baseline clinical characteristics were described using descriptive statistics
- Systemic treatments and treatment patterns were assessed using summary statistics
- Inverse probability (IP)-weighted Kaplan-Meier estimator was used to estimate median TTNTd and OS
- IP-adjusted Cox proportional hazard regression model was fitted by including MSI-H or MSS status as a covariate to evaluate the association between MMR/MSI status and OS/TTNTd

Results

Baseline characteristics

- Baseline demographic characteristics of IP-weighted patients who received 2L or 3L therapy are summarized in **Table 1**
  - The majority of patients were ≥65 years of age
  - Most patients were male (2L: 55%; 3L: 53%), White (2L: 64%; 3L: 65%), treated in a community-practice setting (2L: 96%; 3L: 97%), and had commercial insurance (2L: 43%; 3L: 44%)
  - A higher number of patients had MSS versus MSI-H disease in both the 2L (2307 vs 110 patients) and 3L (1110 vs 50 patients) therapy settings
  - Patient characteristics were generally similar in the MSI-H and MSS subgroups
  - An imbalance between MSI-H and MSS subgroups after IP-weighting was observed in patients ≥65 years receiving 2L therapy (standardized mean difference [SMD], 0.20), in patients receiving 3L therapy in a community practice setting (SMD, 0.27), and in patients with Medicare (SMD, 0.27) or those with no available data on benefit plan type (SMD, −0.24) receiving 3L therapy

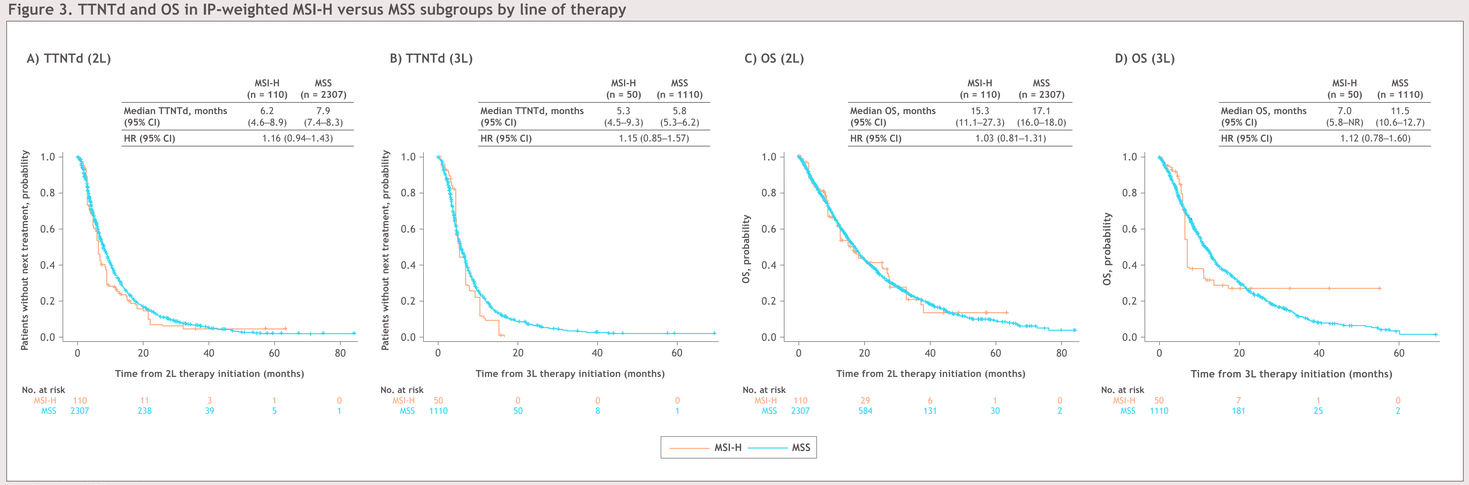
Table 1. Baseline demographic characteristics of IP-weighted patients

Characteristic, n (%)	2L therapy				3L therapy			
	All patients (N = 2417)	MSI-H (n = 110)	MSS (n = 2307)	SMD	All patients (N = 1160)	MSI-H (n = 50)	MSS (n = 1110)	SMD
Age group at therapy start date, years								
<65	1179 (49)	43 (39)	1136 (49)	**0.20**	571 (49)	22 (44)	549 (49)	0.10
≥65	1238 (51)	67 (61)	1171 (51)		588 (51)	28 (56)	561 (51)	
Sex								
Male	1327 (55)	62 (56)	1264 (55)	0.03	618 (53)	27 (54)	591 (53)	0.04
Female	1090 (45)	48 (44)	1042 (45)		541 (47)	22 (44)	519 (47)	
Race								
White	1551 (64)	71 (65)	1480 (64)	0.01	751 (65)	35 (70)	716 (65)	0.12
Non-White	701 (29)	33 (30)	668 (29)	0.02	325 (28)	13 (26)	312 (28)	−0.04
NA	165 (7)	6 (5)	159 (7)	−0.06	83 (7)	2 (4)	82 (7)	−0.18
Practice type								
Community	2328 (96)	108 (98)	2221 (96)	0.09	1119 (96)	50 (100)	1069 (96)	**0.27**
Academic	89 (4)	2 (2)	86 (4)		40 (3)	0 (0)	40 (4)	
Benefit plan type								
Commercial	1040 (43)	49 (45)	991 (43)	0.04	510 (44)	21 (42)	489 (44)	−0.04
Medicare	704 (29)	41 (37)	664 (29)	0.18	372 (32)	22 (44)	350 (32)	**0.27**
Medicaid or other	964 (40)	38 (35)	926 (40)	−0.12	493 (42)	25 (50)	468 (42)	0.17
NA	365 (15)	17 (15)	348 (15)	0	135 (12)	3 (6)	132 (12)	**−0.24**
Length of follow-up from therapy start date, months								
Mean (SD)	15.0 (13.2)	16 (13.7)	15 (13.2)	0.10	11.0 (10.5)	10.0 (8.6)	11.0 (10.6)	−0.14
Median (range)	11 (0–84)	13 (0–63)	11 (0–84)		8 (0–69)	7 (0–55)	8 (0–69)	
Length of potential follow-up from therapy start date, months								
Mean (SD)	34.0 (21.4)	38.0 (21.8)	34 (21.3)	**0.21**	30.0 (20.2)	31.0 (19.9)	30.0 (20.2)	0.04
Median (range)	32 (0–91)	36 (1–90)	31 (0–91)		28 (0–89)	30 (1–84)	28 (0–89)	

Bold values indicate imbalances with an absolute value of SMD ≥0.20 between MSI-H and MSS subgroups. NA, not available; SD, standard deviation.

A trend toward shorter TTNTd and poorer survival outcomes was observed in patients with MSI-H versus MSS mCRC receiving 2L or 3L therapy

Figure 3. TTNTd and OS in IP-weighted MSI-H versus MSS subgroups by line of therapy



CI, confidence interval; HR, hazard ratio.

- Baseline clinical characteristics of IP-weighted patients who received 2L or 3L therapy are summarized in **Table 2**
  - Most patients had stage III disease (~45%); the primary tumor site was the colon
  - Of all tested patients, most had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 (~40%) or 1 (47%); 44% and 43% of all tested patients were Kirsten rat sarcoma viral oncogene homolog (*KRAS*)-positive in the 2L and 3L cohorts, respectively
  - An imbalance between *MSI-H* and MSS subgroups after IP-weighting was observed in patients receiving 3L therapy with colon as the primary tumor site (SMD, −0.39), those with ECOG PS of 0 (SMD, −0.28), and those with *KRAS*-negative (SMD, −0.45), *NRAS*-negative (SMD, 0.25), or *BRAF*-negative status (SMD, 0.20)

Table 2. Baseline clinical characteristics of IP-weighted patients

Characteristic, n (%)	2L therapy				3L therapy			
	All patients (N = 2417)	MSI-H (n = 110)	MSS (n = 2307)	SMD	All patients (N = 1160)	MSI-H (n = 50)	MSS (n = 1110)	SMD
Disease stage at date of initial diagnosis								
Stage I–II	513 (21)	27 (25)	486 (21)	0.10	235 (20)	10 (20)	224 (20)	0
Stage III	1076 (45)	44 (40)	1032 (45)	−0.07	516 (44)	23 (46)	493 (44)	0.04
Stage IV	743 (31)	37 (34)	706 (31)	0.01	364 (31)	16 (32)	348 (31)	0.01
Unknown/ND	85 (4)	2 (2)	82 (4)	−0.09	45 (4)	0 (1)	44 (4)	−0.19
Tumor site								
Colon	1727 (71)	77 (70)	1651 (72)	−0.05	804 (69)	26 (52)	778 (70)	**−0.39**
Rectum or colorectal NOS	690 (29)	34 (31)	656 (28)		356 (31)	24 (48)	332 (30)	
Time from initial to metastatic diagnosis, days								
0	740 (31)	34 (31)	706 (31)	0.01	364 (31)	16 (32)	348 (31)	0.01
0–182	138 (6)	5 (5)	134 (6)	−0.07	59 (5)	2 (4)	57 (5)	−0.06
>182	1538 (64)	71 (65)	1467 (64)	0.02	736 (63)	32 (64)	704 (63)	0.01
ECOG PS[a] closest to therapy start date								
Patients tested	2128 (88)	96 (87)	2032 (88)		1031 (89)	35 (70)	996 (90)	
0	847 (40)	39 (41)	808 (40)	−0.01	397 (39)	11 (31)	386 (39)	**−0.28**
1	997 (47)	48 (50)	949 (47)	0.04	483 (47)	20 (57)	463 (46)	−0.05
≥2	285 (13)	10 (10)	275 (14)	−0.10	151 (15)	4 (11)	147 (15)	−0.17
***KRAS* status[a] closest to therapy start date**								
Patients tested	2280 (94)	103 (93)	2177 (94)		1126 (97)	49 (98)	1077 (97)	
KRAS-negative	1248 (55)	50 (49)	1198 (55)	−0.09	641 (57)	17 (35)	624 (58)	**−0.45**
KRAS-positive[b]	999 (44)	50 (49)	949 (44)	0.08	485 (43)	32 (65)	453 (42)	
Unknown/indeterminate[b]	33 (1)	2 (2)	31 (1)	0.02				
***NRAS* status[a] closest to therapy start date**								
Patients tested	1735 (72)	84 (76)	1650 (72)		868 (75)	45 (90)	823 (74)	
NRAS-negative	1597 (92)	76 (90)	1520 (92)	0.08	793 (91)	39 (87)	754 (92)	**0.25**
NRAS-positive[b]	68 (4)	2 (2)	66 (4)	−0.06	74 (9)	5 (11)	69 (8)	
Unknown/indeterminate[b]	70 (4)	6 (7)	64 (4)	0.14				
***BRAF* status[a] closest to therapy start date**								
Patients tested	1778 (74)	83 (75)	1695 (73)		884 (76)	40 (80)	844 (76)	
BRAF-negative	1574 (89)	73 (88)	1500 (88)	0.04	783 (89)	38 (95)	745 (88)	**0.20**
BRAF-positive[b]	59 (3)	4 (4)	55 (3)	−0.03	101 (11)	2 (5)	99 (12)	
Unknown/indeterminate[b]	145 (8)	6 (7)	139 (8)	0.02				

[a]Data are indicated as n (%) of tested patients; [b]Patients with unknown/indeterminate status in the 3L therapy subgroup are grouped with mutation-positive patients. Percentages may not sum to 100 due to rounding. Bold values indicate imbalances with an absolute value of SMD ≥0.20 between MSI-H and MSS subgroups. *BRAF*, v-Raf murine sarcoma viral oncogene homolog B1; ND, not documented; NOS, not otherwise specified; *NRAS*, neuroblastoma *RAS* viral oncogene homolog.

Treatment patterns

- The 6 most common treatment regimens for 2L and 3L therapy in pre-weighted patients are shown in **Figure 1**
  - The most common 1L treatment of choice was bevacizumab + FOLFOX (leucovorin, 5-fluorouracil, and oxaliplatin) in the MSI-H subgroup (19%), and bevacizumab + FOLFOX and bevacizumab + FOLFIRI (leucovorin, 5-fluorouracil, and irinotecan) in the MSS subgroup (18% each)
  - The most common 2L treatment of choice was bevacizumab + FOLFIRI in both the MSI-H (12%) and MSS (17%) subgroups
  - The most common 3L treatment of choice was trifluridine/tipiracil in both the MSI-H (13%) and MSS (16%) subgroups

Treatment sequences among the top 10 most frequent treatment regimens

- In the 2L MSI-H subgroup, the most common treatment sequence for 1L → 2L was bevacizumab + FOLFOX → bevacizumab + FOLFIRI (7%); the most common 2L → 3L treatment sequence was FOLFIRI → Did not continue (7%) (**Figure 2A**)
  - In the 2L MSS subgroup, the most common 1L → 2L treatment sequence was bevacizumab + FOLFOX → bevacizumab + FOLFIRI (11%); the most common 2L → 3L treatment sequence was bevacizumab + FOLFIRI → Did not continue (10%) (**Figure 2B**)
- In the 3L MSI-H subgroup, the most common 1L → 2L treatment sequence was FOLFOX → bevacizumab + FOLFOX (9%); 5-fluorouracil + leucovorin → bevacizumab + 5-fluorouracil + leucovorin (4%) and cetuximab + FOLFIRI → regorafenib (4%) were among the most common 2L → 3L treatment sequences (**Figure 2C**)
  - In the 3L MSS subgroup, the most common 1L → 2L treatment sequence was bevacizumab + FOLFOX → bevacizumab + FOLFIRI (11%); the most common 2L → 3L treatment sequence was bevacizumab + FOLFIRI → Other (6%) (**Figure 2D**)

Figure 1. Systemic treatment patterns in pre-weighted patients by line of therapy

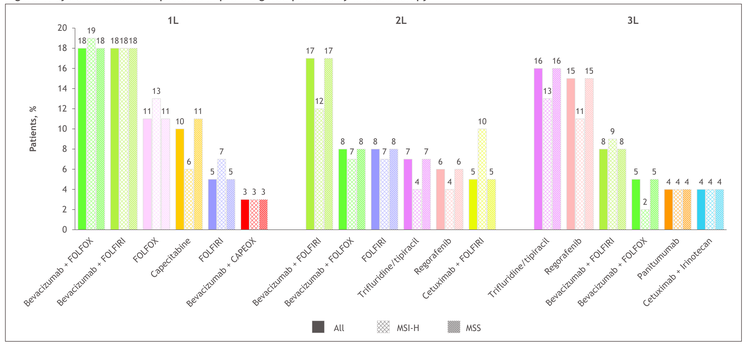
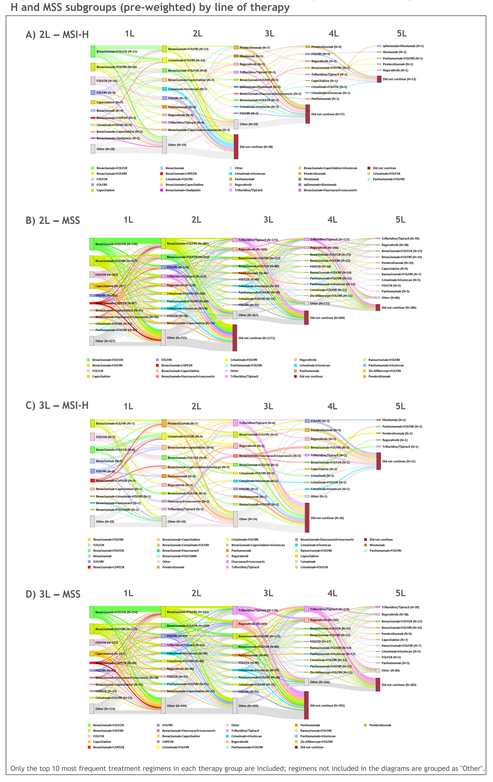


Figure 2. Treatment sequences among the top 10 most frequent treatment regimens in MSI-H and MSS subgroups (pre-weighted) by line of therapy



Only the top 10 most frequent treatment regimens in each therapy group are included; regimens not included in the diagrams are grouped as "Other".

TTNTd and OS

- TTNTd and OS were numerically shorter in the MSI-H versus MSS subgroups of IP-weighted patients (**Figure 3**)
  - In patients who received 2L therapy, median TTNTd was 6.2 versus 7.9 months (HR 1.16, 95% CI 0.94–1.43); median (95% CI) OS was 15.3 (11.1–27.3) versus 17.1 (16.0–18.0) months (HR 1.03, 95% CI 0.81–1.31) (**Figures 3A** and **3C**)
  - In patients who received 3L therapy, median TTNTd was 5.3 versus 5.8 months (HR 1.15, 95% CI 0.85–1.57); median (95% CI) OS was 7.0 (5.8–not reached) versus 11.5 (10.6–12.7) months (HR 1.12, 95% CI 0.78–1.60) (**Figures 3B** and **3D**)

Conclusions

- There was a trend toward poorer clinical outcomes in patients with MSI-H/dMMR mCRC than in those with MSS/pMMR mCRC receiving 2L or 3L therapy
- The results highlight the need for more effective later-line treatment options for mCRC, such as the recently approved IO regimens for patients with MSI-H mCRC[11,12]

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