Outcomes for patients with microsatellite instability-high metastatic colorectal cancer in the real world treated with standard of care versus patients treated with nivolumab plus low-dose ipilimumab in CheckMate 142

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Background

- Optimizing personalized medicine remains a key focus toward improving outcomes in metastatic colorectal cancer (mCRC), one of the leading causes of cancer-related deaths worldwide[1,2]
- The prognostic and predictive value of mismatch repair-deficient/microsatellite instability-high (dMMR/MSI-H) status is becoming increasingly recognized in the mCRC setting[3]
- CheckMate 142 (NCT02060188) is an ongoing single-arm, phase 2, open-label, multicohort study assessing nivolumab monotherapy or nivolumab-based combination therapy in adults with dMMR/MSI-H unresectable mCRC[4-7]
  - Recently published CheckMate 142 cohort 2 results with 5 years of follow-up demonstrated the long-term benefit of nivolumab in combination with low-dose ipilimumab in previously treated dMMR/MSI-H mCRC[8]
  - Nivolumab in combination with low-dose ipilimumab has received approval in the United States (US), European Union, and Japan for the treatment of patients with dMMR/MSI-H mCRC who progressed following treatment with chemotherapy[9]
- To provide additional clinical context to the single-arm CheckMate 142 cohort 2 results, this retrospective study compared outcomes for patients receiving nivolumab in combination with low-dose ipilimumab in CheckMate 142 with real-world outcomes for patients receiving non-immunotherapy (IO)-based historical standard of care (SoC) systemic therapy for dMMR/MSI-H mCRC in the second-line or later (2L+) setting
  - The US-based Flatiron Health oncology electronic health records (EHR) database was used for the real-world cohort

Objectives

- To describe the demographic and clinical characteristics for patients who received ≥ 1 prior line(s) of therapy with at least 1) fluoropyrimidine and 2) oxaliplatin or irinotecan for dMMR/MSI-H mCRC in CheckMate 142 cohort 2 versus the Flatiron Health cohort
- To describe and compare overall survival (OS) in patients who received ≥ 1 prior line(s) of therapy with at least 1) fluoropyrimidine and 2) oxaliplatin or irinotecan for dMMR/MSI-H mCRC in CheckMate 142 cohort 2 versus the Flatiron Health cohort

Methods

- This retrospective analysis included patients ≥ 18 years of age with dMMR/MSI-H mCRC from:
  - CheckMate 142 cohort 2
    - Patients were treated with nivolumab 3 mg/kg + ipilimumab 1 mg/kg once every 3 weeks (total of 4 doses) followed by nivolumab 3 mg/kg every 2 weeks, in the 2L+ setting
    - The 4-year follow-up data (data cutoff: August 2020) were used
    - Patients diagnosed with histologically confirmed recurrent/metastatic disease, with an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1, and who progressed during or after or were intolerant to ≥ 1 prior line of therapy comprising at least a fluoropyrimidine and oxaliplatin/irinotecan were included
    - Patients with active brain or leptomeningeal metastases, autoimmune disease, conditions requiring systemic treatment with corticosteroid/immunosuppressive medications within 14 days of study drug administration, or who received prior treatment with T-cell costimulation or immune checkpoint pathway inhibitors were excluded
  - The US Flatiron Health oncology EHR database
    - The database compiles data from over 280 community cancer centers representing > 3 million patients with cancer in the US
    - Data from patients treated with non-IO-based historical SoC between January 2013 through February 2021 were used
      - Study index date was defined as the date of treatment initiation after ≥ 1 prior line of therapy that included at least a fluoropyrimidine and oxaliplatin/irinotecan
    - Patients diagnosed with stage IV or recurrent mCRC, with ECOG performance status 0–1, and who received ≥ 1 prior line of therapy that included at least a fluoropyrimidine and oxaliplatin/irinotecan were included
    - Patients with active brain or leptomeningeal metastases, autoimmune disease, who received first-line or 2L immunotherapy during the period before the index date, or who received clinical trial drugs during the period before the index date were excluded
- Patients from both CheckMate 142 cohort 2 and the Flatiron Health cohort were followed from their index date until death, loss to follow-up, or the end of study period, whichever occurred first
- Statistical analyses
  - Descriptive statistics were used to assess demographic and patient characteristics in the 2 cohorts
  - Kaplan-Meier estimation was used to analyze OS data, and Cox proportional hazards models were used to generate hazard ratios (HRs) and 95% confidence intervals (CIs)
    - Patients in the Flatiron Health cohort who received IO as subsequent therapy were censored at the time of IO administration
  - Inverse probability of treatment weighting (IPTW) based on a propensity score (PS) model was used to adjust confounders for the indirect comparison of OS outcomes[10]
    - Several sensitivity analyses were conducted, including PS matching based on a greedy algorithm, unadjusted model (univariate regression), complete case analysis, and exploring the censoring of subsequent IO/clinical trial therapy

Results

Patients and baseline characteristics

- Baseline demographic and clinical characteristics of patients from CheckMate 142 cohort 2 (N = 119) and the Flatiron Health cohort (N = 146) included in the primary patient-level adjusted OS analysis before adjustment for trimmed stabilized IPTW are shown in **Table 1**
  - The mean patient age was lower in CheckMate 142 cohort 2 versus the Flatiron Health cohort (56.6 vs 61.8 years)
  - A higher proportion of patients in the CheckMate 142 versus Flatiron Health cohorts were male (58.8% vs 47.3%), White (92.4% vs 73.3%), had stage I-III disease at initial diagnosis (55.5% vs 42.5%), had received ≥ 2 lines of prior therapy (76.5% vs 4.8%), were heavily pretreated (68.9% vs 3.4% previously received oxaliplatin and irinotecan in 1 line or in different lines of therapy), and had *KRAS* mutations (37.0% vs 26.0%)
  - CheckMate 142 cohort 2 had a lower proportion of patients with rectal tumors versus the Flatiron Health cohort (5.0% vs 12.3%)
- Following IPTW, the distributions of the following potential confounders were balanced, with standardized mean differences (SMDs) within the 0.20 threshold: sex (SMD, 0.10), ECOG performance status (SMD, −0.06), primary tumor location (SMD, −0.08), and *BRAF* mutational status (SMD, 0.03) (**Figure 1**)
  - Imbalances (with an absolute value of SMD ≥ 0.20) were still observed for age (SMD, −0.29), race (SMD, 0.37), disease stage at initial diagnosis (SMD, 0.27), number of lines of prior therapy (SMD, 0.80), type of prior therapy (SMD, 0.97), and *KRAS* mutational status (SMD, 0.21)
  - However, despite imbalances, all potential confounders had a smaller absolute SMD after adjustment

Prior therapies received in the metastatic setting

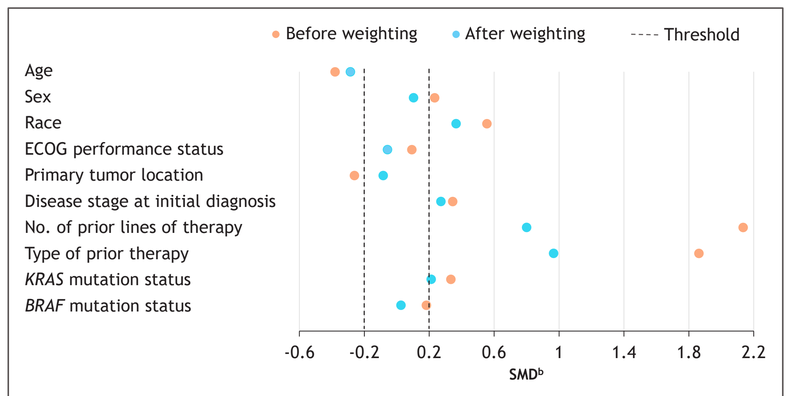
- The types of prior therapy received by patients with mCRC in the metastatic setting in the CheckMate 142 and Flatiron Health cohorts are shown in **Figure 2**
- Patients in CheckMate 142 cohort 2 were more heavily pretreated, with > 40% of patients having received ≥ 3 prior regimens in the metastatic setting versus no patients in the Flatiron Health cohort (**Table 2**)
  - The time from completion of the most recent prior regimen in the metastatic setting to index date was < 3 months for all patients in the Flatiron Health cohort
  - In CheckMate 142 cohort 2, the time from completion period was ≥ 3 months in 28.6% and > 6 months in 14.3% of patients

Table 1. Baseline demographic and clinical characteristics of patients before adjustment for trimmed stabilized IPTW

Characteristic, %	Before weighting: CheckMate 142 cohort 2 (N = 119)	Before weighting: Flatiron Health cohort (N = 146)	SMD[a]
Age, mean, years	56.6	61.8	**−0.38**
Sex			**0.23**
Female	41.2	52.7	
Male	58.8	47.3	
Race			**0.56**
White	92.4	73.3	
Non-White	7.6	19.9	
Not reported	0	6.8	
ECOG performance status			0.09
0	45.4	50.0	
1	54.6	50.0	
Primary tumor location			**−0.26**
Colon	95.0	87.7	
Rectum	5.0	12.3	
Disease stage at initial diagnosis			**0.34**
I/II/III	55.5	42.5	
IV	44.5	55.5	
Unknown	0	2.0	
Number of prior lines of therapy			**2.13**
0–1	23.5	95.2	
≥ 2	76.5	4.8	
Type of prior therapy,[b]			**1.86**
Not heavily pretreated	31.1	96.6	
Heavily pretreated	68.9	3.4	
***KRAS* mutation status**			**0.33**
Wild-type	51.3	67.1	
Mutated	37.0	26.0	
Unknown/no test	11.8	6.8	
***BRAF* mutation status**			0.18
Wild-type	47.1	56.2	
Mutated	25.2	19.9	
Unknown/no test	27.7	24.0	

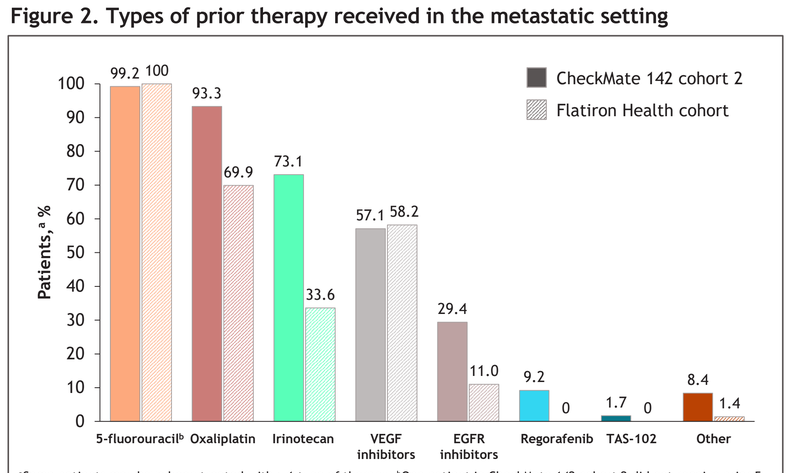
[a]SMD was obtained from the CheckMate 142 cohort 2 minus the Flatiron cohort data using trimmed stabilized weights when combining the mean and standard deviation. Shaded cells with **bold values** indicate potentially important imbalances, with absolute SMD values ≥ 0.20; [b]Heavily pretreated patients were those who had previously received oxaliplatin and irinotecan (in 1 line or in different lines of therapy); not heavily pretreated patients were those who had received only 1 or neither of them.
BRAF, v raf murine sarcoma viral oncogene homolog B1.

Figure 1. Baseline characteristics balance plot before and after trimmed stabilized IPTW[a]



[a]The stabilized IPTWs were trimmed at the maximum of the minimum weight and the minimum of the maximum weight; [b]SMD was obtained from the CheckMate 142 cohort 2 minus the Flatiron cohort data using trimmed stabilized weights when combining the mean and standard deviation. An absolute SMD value of ≥ 0.20 indicated potentially important imbalances.

Figure 2. Types of prior therapy received in the metastatic setting



[a]Some patients may have been treated with > 1 type of therapy; [b]One patient in CheckMate 142 cohort 2 did not receive prior 5-fluorouracil because they had refused chemotherapy with FOLFOX.
EGFR, epidermal growth factor receptor; FOLFOX, folinic acid + fluorouracil + oxaliplatin; TAS-102, trifluridine-tipiracil hydrochloride; VEGF, vascular endothelial growth factor.

Table 2. Summary of prior cancer therapies in the metastatic setting

	CheckMate 142 cohort 2 (N = 119)	Flatiron Health cohort (N = 146)
Number of prior regimens, n (%)		
0	1 (0.8)[a]	0
1	27 (22.7)	139 (95.2)
2	43 (36.1)	7 (4.8)
3	29 (24.4)	0
≥ 4	19 (16.0)	0
Time from completion of most recent prior regimen to index date, n (%)		
< 3 months	84 (70.6)	146 (100)
3–6 months	17 (14.3)	0
> 6 months	17 (14.3)	0
Not reported	1 (0.8)[a]	0

[a]One patient had not received a prior regimen in the metastatic setting because they had refused chemotherapy with FOLFOX.

Duration of observation and treatment

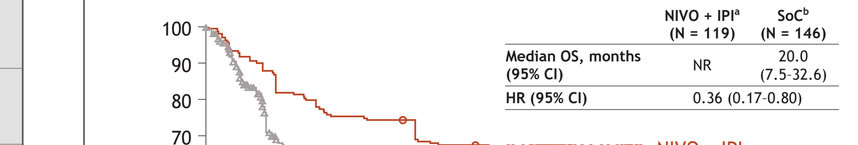
- Median (range) duration of observation (ie, duration of therapy + follow-up) was 49.7 (0.1–63.4) and 8.3 (0–81.2) months in CheckMate 142 cohort 2 and the Flatiron Health cohort, respectively
- Median (range) duration of nivolumab in combination with low-dose ipilimumab in CheckMate 142 cohort 2 was 24.9 (0–58.7) months, and median (range) duration of non-IO-based SoC treatment in the Flatiron Health cohort was 5.55 (0–81.2) months

OS

- In the primary patient-level adjusted analysis (IPTW), median OS was not reached (NR; 95% CI, NR) with nivolumab in combination with low-dose ipilimumab in CheckMate 142 cohort 2 versus 20.0 (95% CI, 7.5–32.6) months in patients receiving non-IO-based SoC in the Flatiron Health cohort; HR, 0.36 (95% CI, 0.17–0.80) (**Figures 3 and 4**)
  - Multiple sensitivity analyses confirmed the robustness of the primary analysis (**Figure 3**)
- OS rates were higher in CheckMate 142 cohort 2 versus the Flatiron Health cohort at all evaluated timepoints (results not shown), including 6, 18, 24, and 36 months (**Table 3**)
  - OS rates plateaued after 36 months with substantial censoring (results not shown)

Figure 3. Treatment effect on OS

	CheckMate 142 cohort 2 (NIVO + IPI) n	CheckMate 142 cohort 2 (NIVO + IPI) Median OS, months (95% CI)	Flatiron Health cohort (SoC) n	Flatiron Health cohort (SoC) Median OS, months (95% CI)	HR (95% CI)
Trimmed stabilized IPTW	119	NR	146	20.0 (7.5-32.6)	0.36 (0.17-0.80)
CheckMate 142 cohort 2 "no progression"[a]	109	NR	146	20.0 (6.6-33.5)	0.33 (0.12-0.91)
Complete case analysis	77	NR	99	36.8 (7.9-65.7)	0.46 (0.21-0.99)
PS matched	29	NR	29	23.9 (6.8-41.0)	0.67 (0.21-2.18)
No censoring for IO/clinical trial therapy					
No adjustment	119	NR	146	20.8 (14.7-27.6)	0.29 (0.20-0.44)
Trimmed stabilized IPTW	119	NR	146	23.8 (18.1-29.4)	0.35 (0.17-0.74)
PS matched	29	NR	29	37.6 (12.4-62.9)	0.51 (0.20-1.30)



[a]Subgroup excludes 10 patients who had received treatment in the adjuvant setting and had tumor progression during or within 6 months of completion of adjuvant therapy.
IPI, ipilimumab; NIVO, nivolumab.

Figure 4. Kaplan-Meier plot of OS adjusted for trimmed stabilized IPTW

[a]CheckMate 142 cohort 2; [b]Flatiron Health cohort. The percentage of deaths was 32.6% in CheckMate 142 cohort 2 and 37.4% in the Flatiron Health cohort; the proportions of censored patients were 67.4% and 62.6%, respectively.

Table 3. OS adjusted for trimmed stabilized IPTW

OS rate, % (95% CI)[a]	CheckMate 142 cohort 2 (N = 119)	Flatiron Health cohort (N = 146)
6-month	92 (87-97)	84 (78-90)
18-month	76 (69-84)	50 (40-64)
24-month	74 (67-82)	44 (33-59)
36-month	67 (60-76)	42 (30-56)

[a]Based on adjusted Kaplan-Meier estimates.

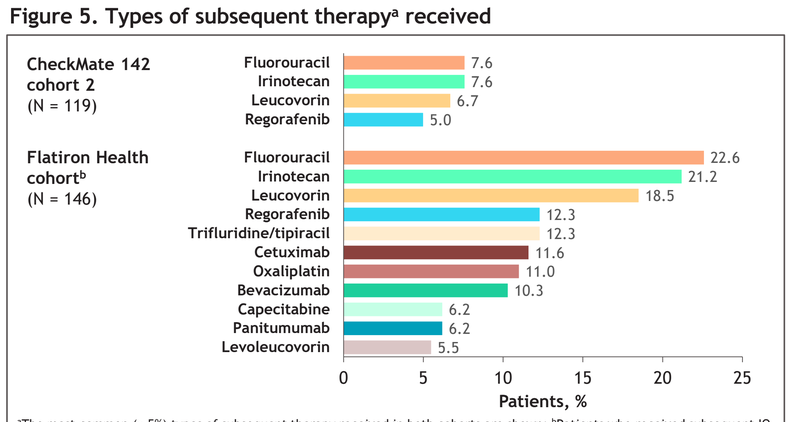
Cancer therapy received on index date

- All patients in CheckMate 142 cohort 2 (N = 119) started nivolumab in combination with low-dose ipilimumab on the index date
- The most common (> 5%) SoC therapies started on the index date in the Flatiron Health cohort (N = 146) were folinic acid, fluorouracil, and irinotecan (FOLFIRI) + bevacizumab (17.8%), FOLFIRI (8.9%), FOLFOX + bevacizumab (6.8%), FOLFIRI + cetuximab (6.2%), and FOLFIRI + panitumumab (5.5%)

Subsequent therapy

- Subsequent systemic therapy was received by a lower proportion of patients in CheckMate 142 cohort 2 (20.2%) versus the Flatiron Health cohort (57.5%) at the time of the analysis
- The most common (≥ 5%) subsequent therapies in CheckMate 142 cohort 2 and the Flatiron Health cohort are shown in **Figure 5**

Figure 5. Types of subsequent therapy[a] received



[a]The most common (≥ 5%) types of subsequent therapy received in both cohorts are shown; [b]Patients who received subsequent IO (pembrolizumab, n = 33; nivolumab, n = 13) were censored at the time of IO administration.

Discussion

- Strengths of the study:
  - Comparative effectiveness methods and the use of an external control arm can help contextualize single-arm trial results, as demonstrated in this study
  - All sensitivity analyses in the study showed consistent results, thus supporting the validity of the findings
- Study limitations:
  - Residual confounding may have remained even after IPTW
  - Some analyses were limited by small sample sizes
  - Unknown or unmeasured confounders may have impacted study results

Conclusions

- OS outcomes were significantly better for patients who received nivolumab in combination with low-dose ipilimumab in CheckMate 142 cohort 2 than for patients who received non-IO-based historical SoC therapy in the Flatiron Health cohort
- This study provides supportive evidence for the effectiveness of nivolumab in combination with low-dose ipilimumab for patients with dMMR/MSI-H mCRC in the 2L+ setting versus non-IO-based historical SoC

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