

Nivolumab plus ipilimumab versus chemotherapy or nivolumab monotherapy for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: expanded analyses from CheckMate 8HW

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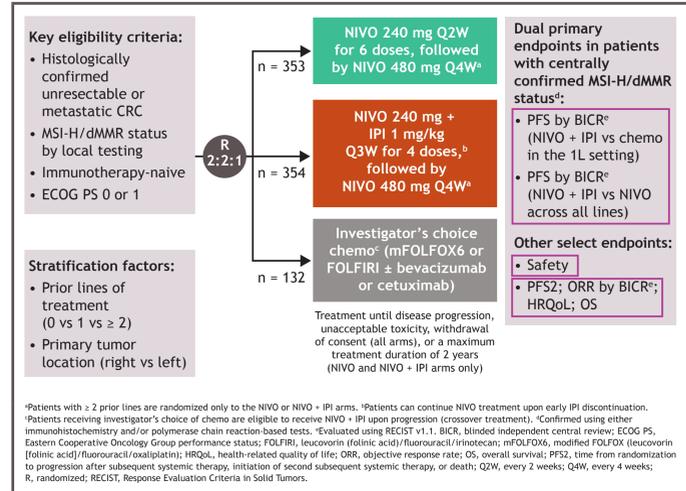
Introduction

- In the phase 3 CheckMate 8HW trial, nivolumab plus ipilimumab (NIVO + IPI) demonstrated superior progression-free survival (PFS) vs chemotherapy (chemo) in the first-line (1L) setting (hazard ratio [HR], 0.21; 95% confidence interval [CI], 0.14-0.32; $P < 0.0001$) and superior PFS vs NIVO across all lines (HR, 0.62; 95% CI, 0.48-0.81; $P = 0.0003$), with no new safety signals in patients with centrally confirmed microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC)¹⁻⁴
- These results led to the approval of NIVO + IPI in the 1L setting in patients with MSI-H/dMMR mCRC in the United States, European Union, and other countries^{5,6}
- Here, we report expanded analyses of NIVO + IPI vs NIVO across all lines and longer follow-up results for NIVO + IPI vs chemo in the 1L setting

Methods

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 trial (NCT04008030; Figure 1)

Figure 1. CheckMate 8HW study design¹



Results

- At data cutoff (August 28, 2024), the median follow-up (time between randomization and data cutoff among all randomized patients across all 3 treatment arms) was 47.0 months (range, 16.7-60.5)
- Baseline characteristics were generally balanced across the treatment arms (Table 1)

Table 1. Baseline characteristics

Characteristic (all randomized patients)	Category	NIVO + IPI (n = 354)	NIVO (n = 353)	Chemo (n = 132)
Age	Median (range), years	62 (21-86)	63 (20-87)	65 (26-87)
Sex	Female	192 (54)	163 (46)	68 (52)
	Male	162 (46)	190 (54)	64 (48)
Region	US/Canada/Europe	251 (71)	246 (70)	95 (72)
	Asia	26 (7)	33 (9)	13 (10)
	Rest of world	77 (22)	74 (21)	24 (18)
ECOG PS	0	192 (54)	183 (52)	61 (46)
Number of prior lines of therapy per IRT	0	202 (57)	201 (57)	101 (77)
	1	67 (19)	67 (19)	31 (23)
	≥ 2	85 (24)	85 (24)	0
Tumor sidedness	Right	244 (69)	244 (69)	89 (67)
Sites of metastases ^{a,c}	Liver	140 (40)	149 (42)	57 (43)
	Peritoneum	143 (40)	126 (36)	59 (45)
Centrally confirmed MSI-H/dMMR status	Yes	296 (84)	286 (81)	113 (86)
	No	58 (16)	67 (19)	19 (14)
	MSS and pMMR	41 (12)	40 (11)	13 (10)
	MSS or pMMR ^d	8 (2)	10 (3)	0
	Not available ^e	9 (3)	17 (5)	6 (5)
BRAF, KRAS, NRAS mutation status ^{a,f}	BRAF/KRAS/NRAS all wild type	83 (23)	103 (29)	34 (26)
	BRAF mutant	106 (30)	85 (24)	34 (26)
	KRAS or NRAS mutant	83 (23)	89 (25)	31 (23)
	Unknown	73 (21)	74 (21)	31 (23)

Data are shown as n (%). ^aPer BICR. ^bPatients may have had more than 1 site of metastases. ^cSites of metastases not reported: NIVO + IPI, n = 3; NIVO, n = 2; chemo = 1. ^dPatients with either centrally confirmed MSS tumors that could not be evaluated or were not tested for MMR status or centrally confirmed pMMR tumors that could not be evaluated or were not tested for MSI status. ^ePatients with tumors that could not be tested for MMR status or were not tested centrally for both MSI and MMR status. Percentages may not add up to 100% due to rounding. ^fBRAF and KRAS/NRAS mutant: NIVO + IPI, n = 9; NIVO, n = 7; chemo, n = 2. BRAF, V-raf murine sarcoma viral oncogene homolog B; IRT, interactive response technology; KRAS, Kirsten rat sarcoma viral oncogene; MSS, microsatellite stable; NRAS, neuroblastoma RAS viral oncogene homolog; PD-L1, programmed death ligand 1; pMMR, mismatch repair-proficient.

- At 47.0 months of median follow-up, 6% of patients in the NIVO + IPI arm, 4% of patients in the NIVO only arm, and no patients in the chemo arm were still on treatment (Table 2)

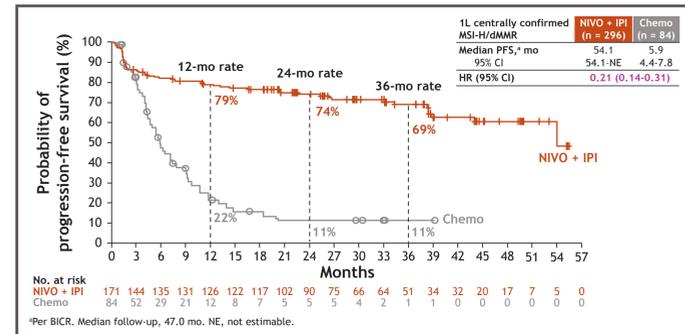
Table 2. Exposure and disposition

Disposition	NIVO + IPI	NIVO	Chemo
All randomized patients, n	354	353	132
All treated patients, n	352	351	115
Ongoing treatment, ^a n (%)	20 (6)	13 (4)	0
Completed treatment, ^{a,b} n (%)	159 (45)	137 (39)	0
Discontinued treatment, ^a n (%)	173 (49)	201 (57)	115 (100)
Median duration of treatment (range), ^c mo	20.5 (0-35.9) ^d	16.4 (0-36.0)	5.1 (0.1-32.8)
Median number of doses (range) ^e	NIVO: 23 (1-41) IPI: 4 (1-4) 288 (82)	NIVO: 21 (1-43)	—
Received all 4 doses of IPI, n (%)	—	—	—
Death, ^a n (%)	103 (29)	149 (42)	54 (47)
Disease progression	74 (21)	122 (35)	37 (32)
Other ^a	29 (8)	27 (8)	17 (15)

^aPercentages shown are based on all treated patients. ^bFor NIVO + IPI and NIVO arms: completed 2 years of treatment. ^cPatients can continue NIVO treatment upon early IPI discontinuation. ^dMedian duration of treatment was 20.5 (range, 0-35.9) mo for NIVO and 2.1 (range, 0-3.7) mo for IPI. ^eOther reasons for death included treatment-related toxicity (n = 3), other reasons (n = 48), and unknown (n = 22).

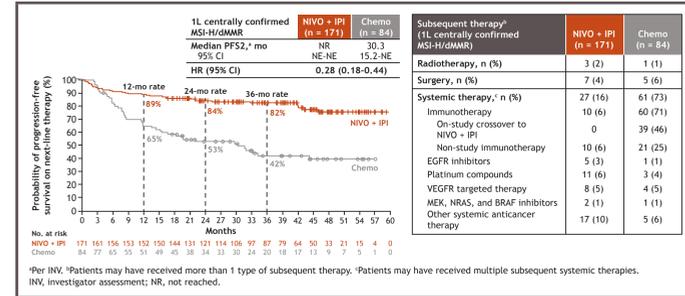
- NIVO + IPI continued to demonstrate clinically meaningful PFS benefit vs chemo with longer follow-up in patients with centrally confirmed MSI-H/dMMR mCRC in the 1L setting (Figure 2)

Figure 2. Progression-free survival: NIVO + IPI vs chemo (1L)



- PF2S continued to favor NIVO + IPI vs chemo with a 72% reduction in the risk of death or disease progression after first subsequent therapy, despite a high rate of subsequent immunotherapy in the chemo group (71%; Figure 3)

Figure 3. PF2S: NIVO + IPI vs chemo (1L)

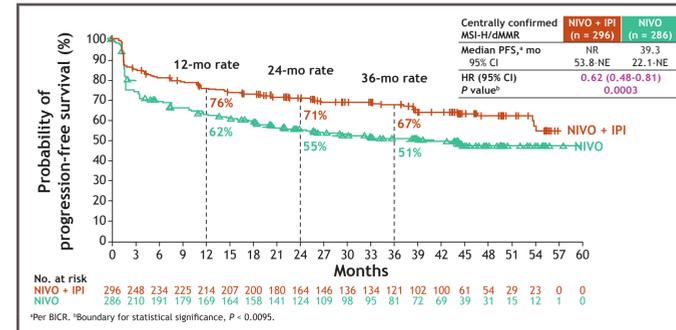


- NIVO + IPI demonstrated statistically significant and clinically meaningful PFS benefit vs NIVO in patients with centrally confirmed MSI-H/dMMR mCRC across all lines of therapy (Figure 4) — PFS benefit with NIVO + IPI vs NIVO was consistent in all randomized patients (mPFS: 54.1 vs 18.4 months; HR, 0.64 [95% CI, 0.52-0.79])

Acknowledgments

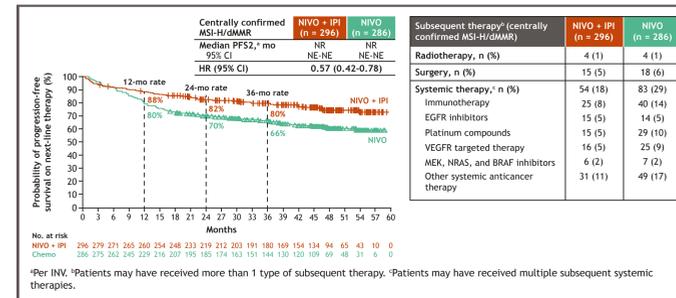
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Figure 4. Progression-free survival: NIVO + IPI vs NIVO (all lines)



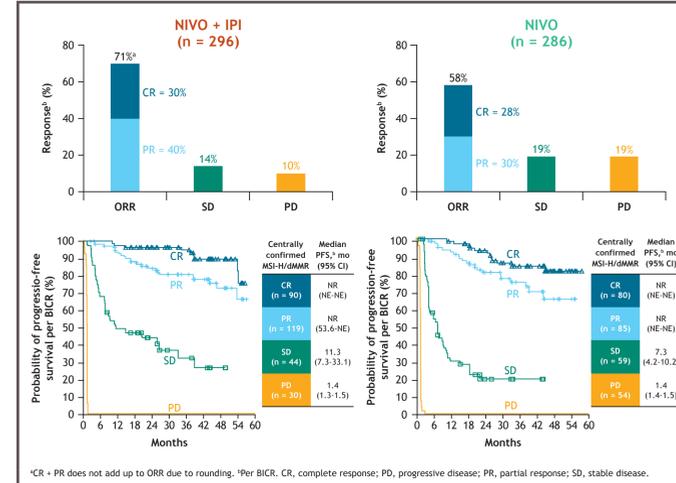
- PF2S favored NIVO + IPI vs NIVO with a 43% reduction in the risk of death or disease progression after first subsequent therapy (Figure 5)

Figure 5. PF2S: NIVO + IPI vs NIVO (all lines)



- Statistically significant and clinically meaningful improvement in ORR was observed with NIVO + IPI vs NIVO (difference in ORR, 13% [95% CI, 5-21]; $P = 0.0011$; Figure 6)

Figure 6. PFS by response: NIVO + IPI vs NIVO (all lines)



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- Treatment-related adverse events (TRAEs) in all treated patients are reported in Table 3

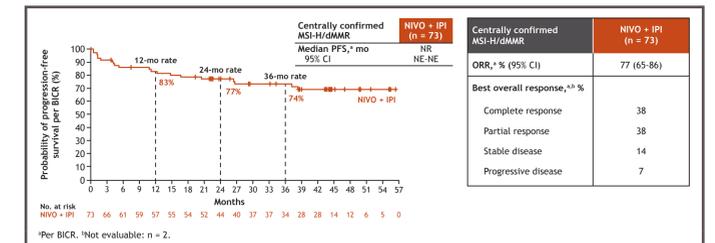
Table 3. Treatment-related adverse events

All treated patients, n (%)	NIVO + IPI (n = 352)		NIVO (n = 351)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs ^a				
Any TRAEs	285 (81)	78 (22)	249 (71)	50 (14)
Serious TRAEs	65 (18)	55 (16)	29 (8)	24 (7)
TRAEs leading to discontinuation ^b	48 (14)	33 (9)	21 (6)	14 (4)
Treatment-related deaths ^c	2 (< 1) ^d		1 (< 1) ^e	
TRAEs ^a reported in ≥ 10% of patients				
Pruritus	91 (26)	0	63 (18)	0
Diarrhea	71 (20)	3 (< 1)	59 (17)	2 (< 1)
Hypothyroidism	61 (17)	2 (< 1)	31 (9)	0
Asthenia	58 (16)	2 (< 1)	44 (13)	2 (< 1)
Fatigue	42 (12)	1 (< 1)	35 (10)	1 (< 1)
Hyperthyroidism	40 (11)	0	16 (5)	0
Arthralgia	38 (11)	1 (< 1)	23 (7)	0
Rash	34 (10)	3 (< 1)	29 (8)	1 (< 1)
Adrenal insufficiency	34 (10)	8 (2)	12 (3)	3 (< 1)

^aIncludes events reported between first dose and 30 days after last dose of study therapy. ^bDiscontinuation of any component of the combination regimen was counted as a drug discontinuation event. ^cTreatment-related deaths were reported regardless of timeframe. ^dIncludes 1 event each of myocarditis and pneumonitis. ^eNo new treatment-related deaths were reported since the previous interim analysis. ^fOne event of pneumonitis.

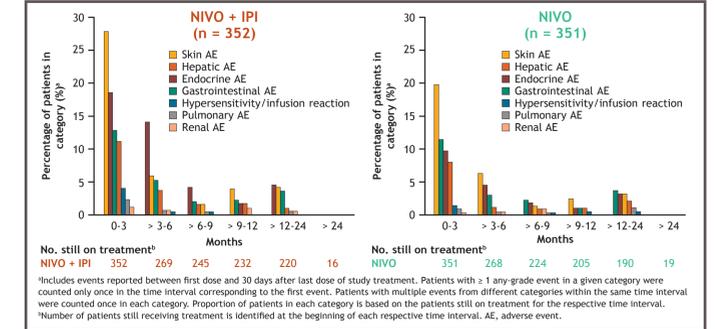
- PFS and response rates with NIVO + IPI in patients with grade 3/4 TRAEs were consistent with the results of the overall study population (Figure 7)

Figure 7. Efficacy in patients with grade 3/4 TRAEs: NIVO + IPI (all lines)



- The majority of any-grade TRAEs with potential immunologic etiology that require frequent monitoring or intervention in the NIVO + IPI and NIVO groups emerged within the first 6 months of treatment across organ categories (Figure 8) — Frequencies were generally comparable between the 2 treatment groups, except skin and endocrine TRAEs were more frequent with NIVO + IPI

Figure 8. Emergence of TRAEs with potential immunologic etiology over time



Conclusions

- 1L NIVO + IPI continued to demonstrate improved PFS (HR, 0.21 [95% CI, 0.14-0.31]) and PF2S (HR, 0.28 [95% CI, 0.18-0.44]) vs chemo with longer follow-up in patients with centrally confirmed MSI-H/dMMR mCRC
- NIVO + IPI demonstrated superior PFS (HR, 0.62 [95% CI, 0.48-0.81]) and improved PF2S (HR, 0.57 [95% CI, 0.42-0.78]) vs NIVO across all lines of therapy in patients with centrally confirmed MSI-H/dMMR mCRC
- No new safety signals were observed with NIVO + IPI, and most TRAEs with potential immunologic etiology emerged within the first 6 months of treatment
- These results provide further evidence to support NIVO + IPI as a standard-of-care treatment option for patients with MSI-H/dMMR mCRC
- NCCN Guidelines[®] include subcutaneous nivolumab and hyaluronidase-nhvy as an alternative route of administration to IV nivolumab during