Immunotherapy as first line treatment for MSI-H/dMMR colorectal cancer

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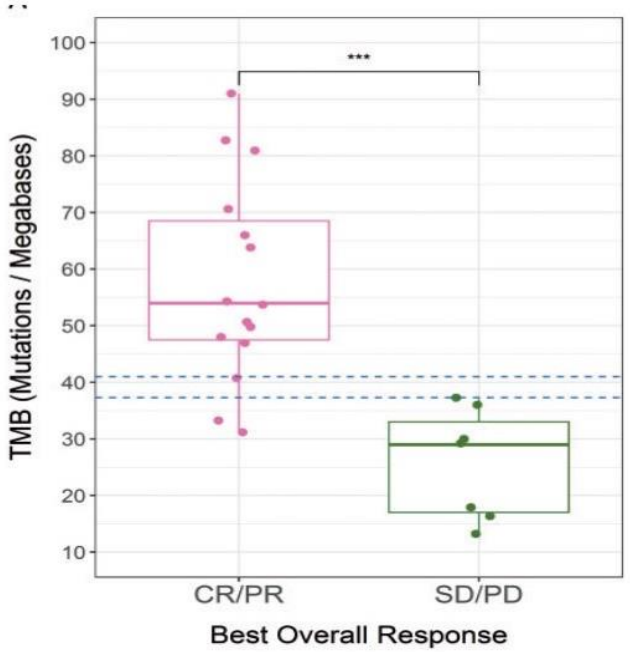
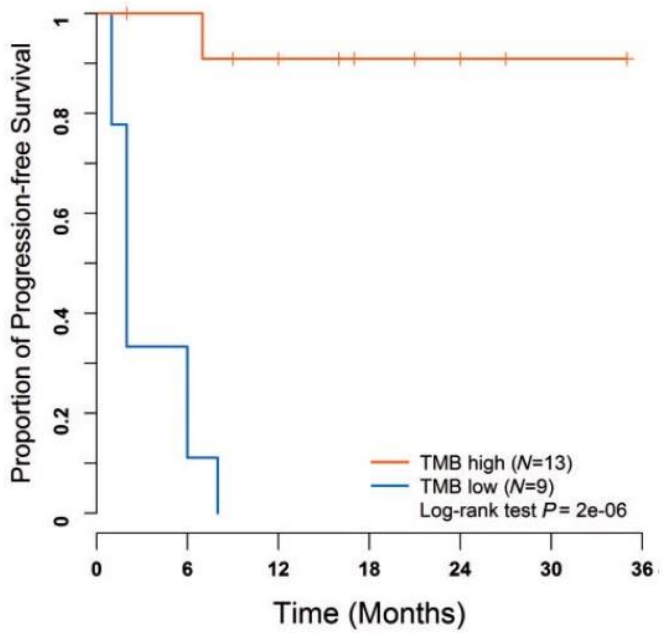
Not all MSI-High/dMMR tumors are created equal

Salem ME, et al. Presented at: ASCO;2022.

TMB as an IO Response Predictor in MSI-H

- 22 pts treated with PD-1 based therapy
- Optimal TMB cut-off point: 37-41 mut/Mb
  - PR/CR vs. SD/PD p = 0.0003 (p = 0.088 for MSI score)
- (foundation medicine 37.4 mut/Mb = 35th percentile)





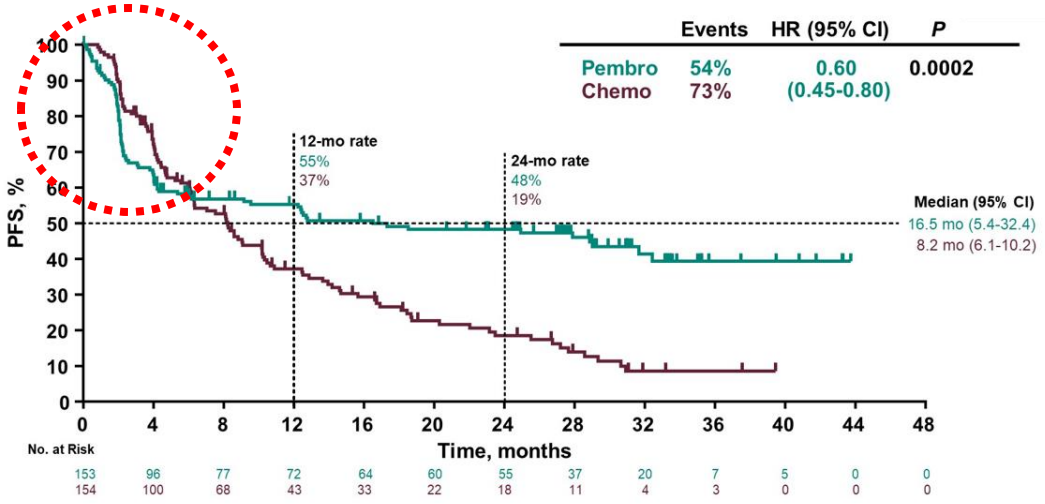
Schrock et la. Ann Oncol. 2019

TMB = tumor mutation burden; IO = immunotherapy.

Salem ME, et al. Presented at: ASCO;2022.

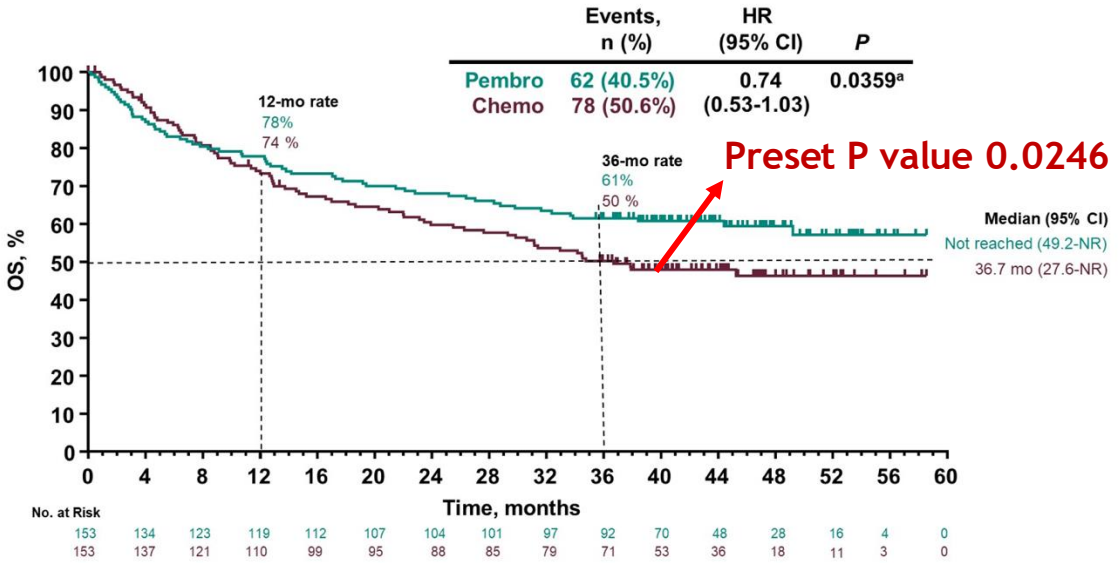
1L StageIV MSI-H/dMMR Colorectal Cancer: KN-177

PFS[1]



Median study follow-up: 32.4 months (range, 24.0 – 48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR. Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the pre-specified one-sided α = 0.0117; Data cut-off: 19Feb2020.

OS[2]

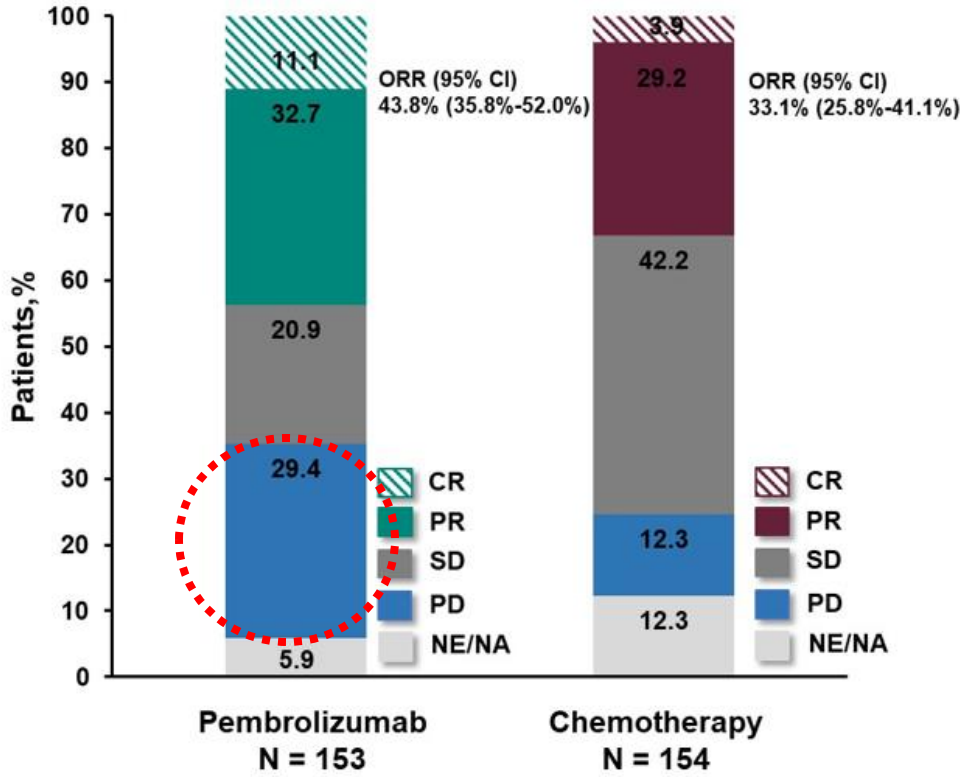


[a]Pembrolizumab was not superior to chemotherapy for OS as one-sided α > 0.0246. Pre-specified sensitivity analyses to adjust for crossover effect by rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38). Data cut-off: 19Feb2021.

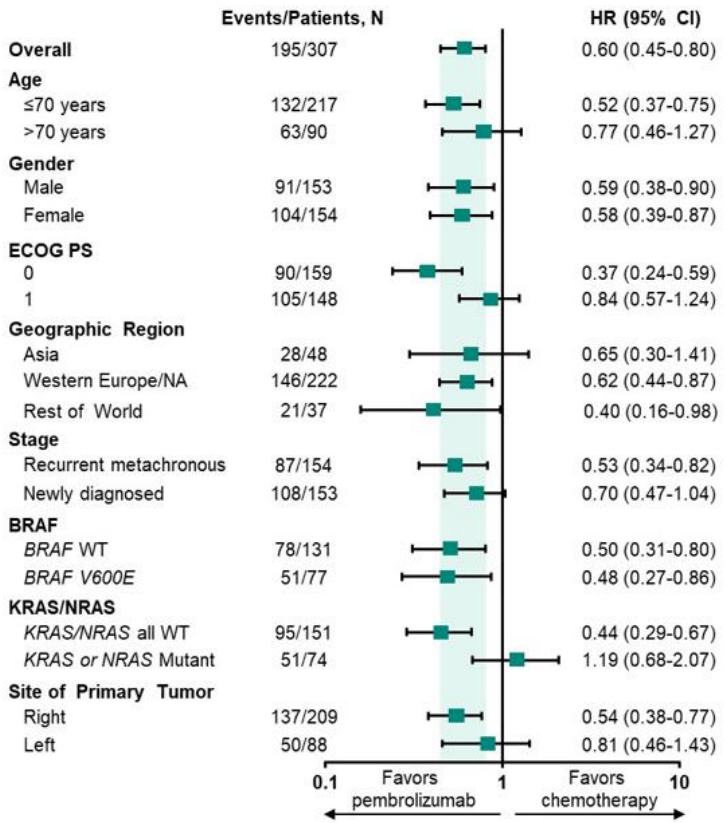
1. Thierry Andre et al 2022, Lancet Oncology.
2. Thierry Andre, et al. 2025 Ann Oncology.
3. Tieery Andre et al 2020, NEJM

1L StageIV MSI-H/dMMR Colorectal Cancer: KN-177

Best Anti-Tumor Response

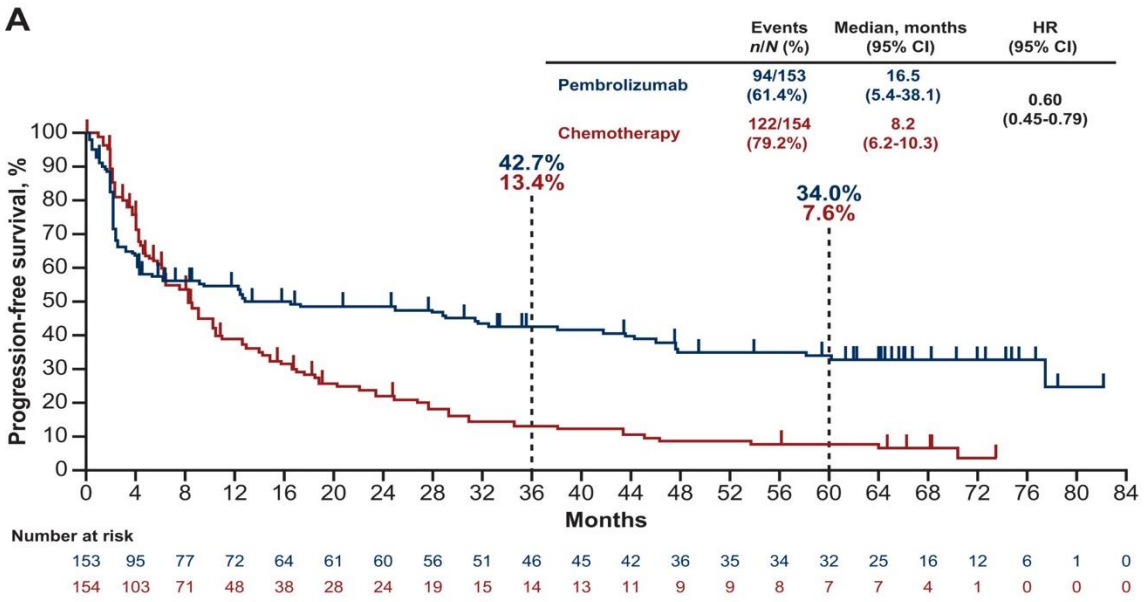


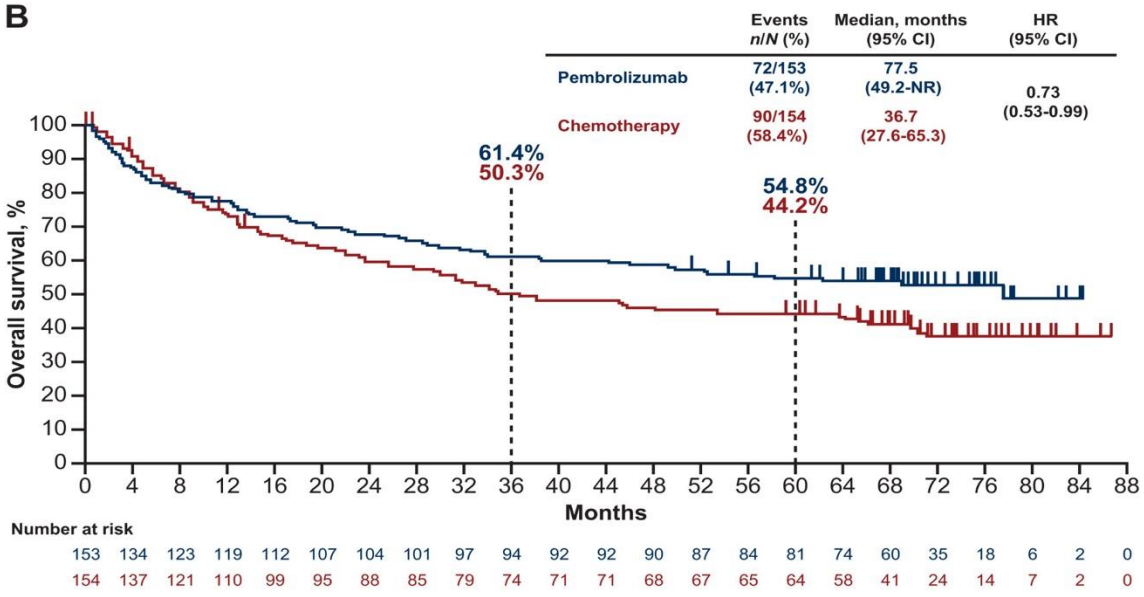
PFS in key subgroup



Kai-Keen Shiu, et al. 2021ASCO. Abstract # 6.

5 Year Follow Up on KN177



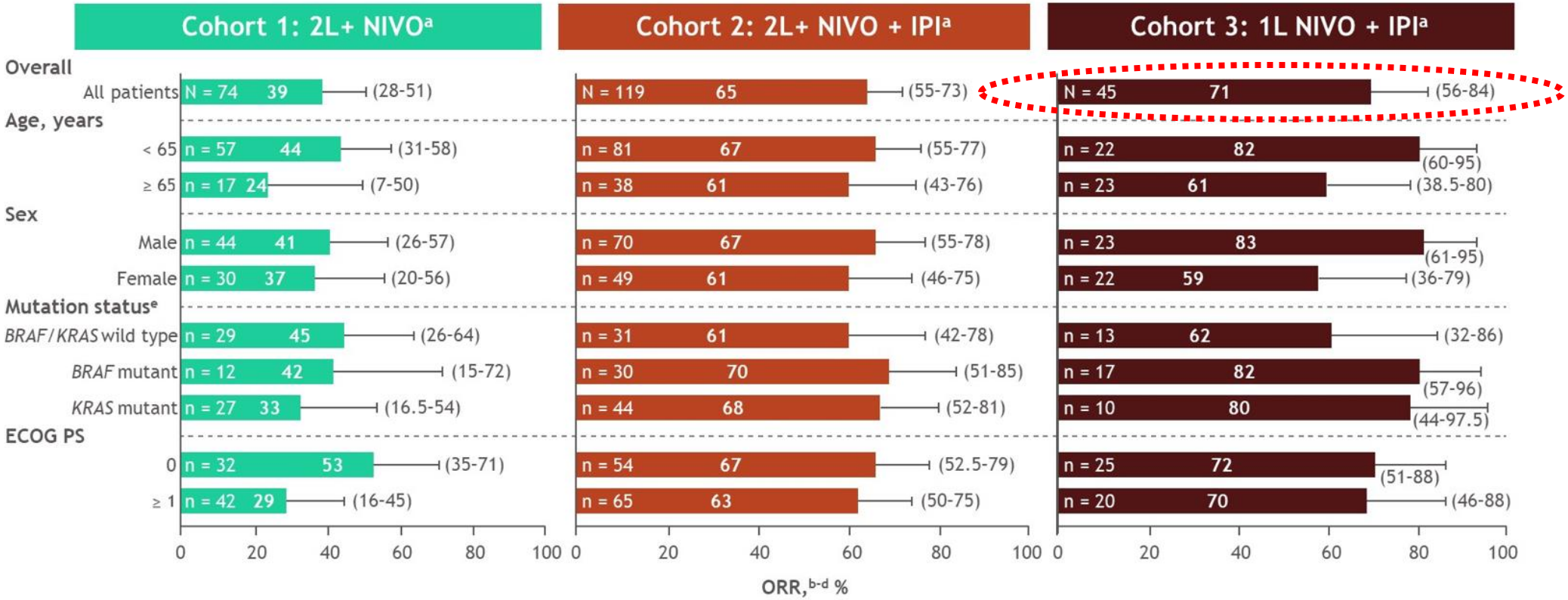


Andre et al Ann Oncology 2025

Questions that arise from IO mono….

- Is single agent anti-PD-1 blockade sufficient?
  - If not, should combine with chemo or IO/IO combinations?

Dual IO: ORR: 71%, CR: 20% (CM-142)



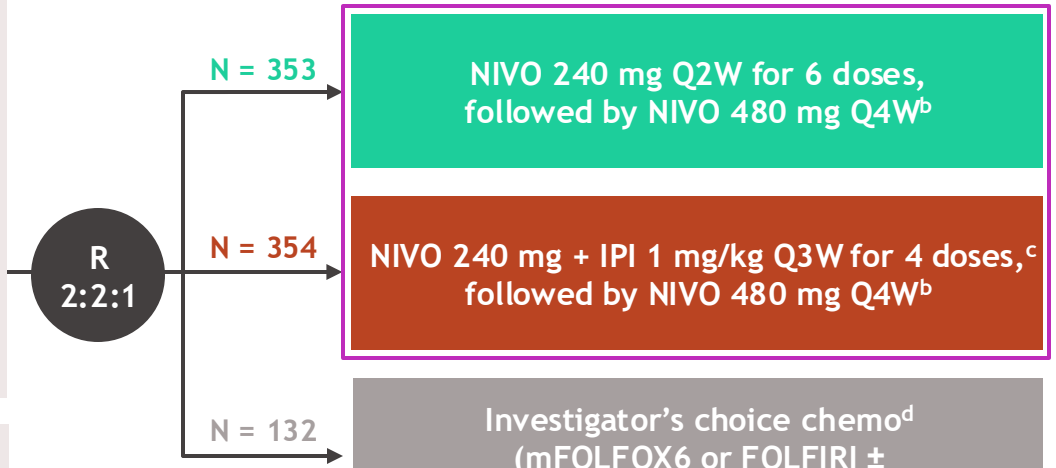
Michael J. Overman, et al. 2022 ASCO. Abatract #3510.

Study design

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]

Key eligibility criteria:
- Histologically confirmed unresectable or metastatic CRC
- MSI-H/dMMR status by local testing
- Immunotherapy-naive
- ECOG PS 0 or 1

Stratification factors:
- Prior lines of treatment (0 vs 1 vs ≥ 2)
- Primary tumor location (right vs left)



Treatment until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (NIVO and NIVO + IPI arms only)

Dual primary endpoints in patients with centrally confirmed MSI-H/dMMR status[e]:
- PFS by BICR[f] (NIVO + IPI vs chemo in the 1L setting)
- PFS by BICR[f] (NIVO + IPI vs NIVO across all lines)

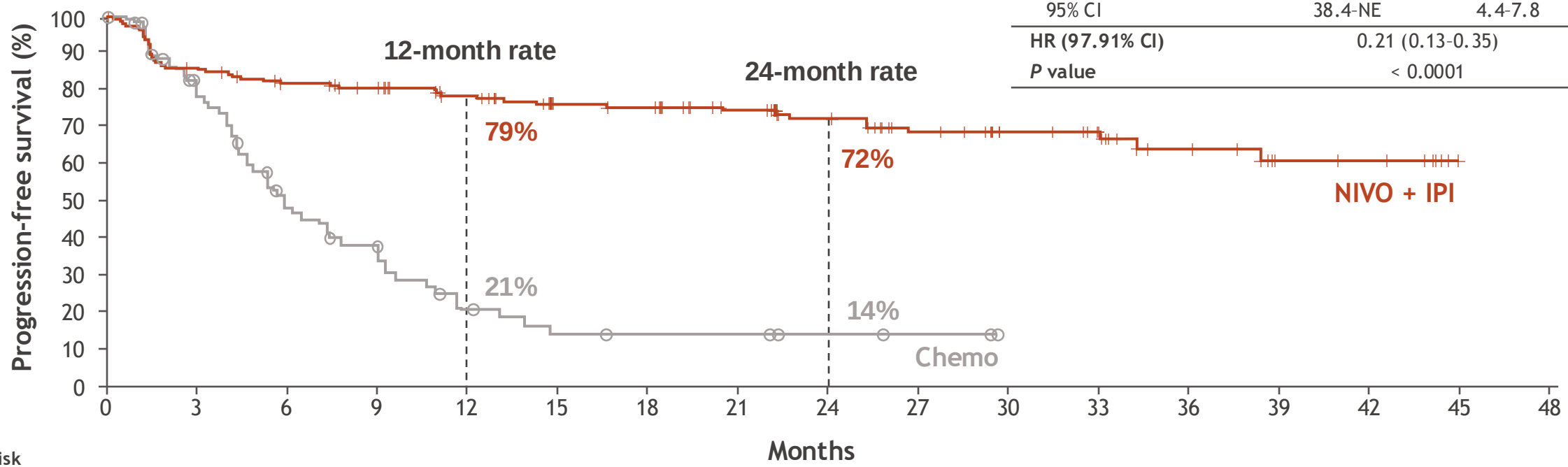
Other select endpoints:
- Safety
- ORR by BICR[f] (NIVO + IPI vs NIVO across all lines)
- HRQoL
- OS

- At data cutoff (August 28, 2024), the median follow-up[g] was 47.0 months (range, 16.7–60.5)

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients can continue NIVO treatment upon early IPI discontinuation. [d]Patients receiving investigator's choice of chemo are eligible to receive NIVO + IPI upon progression (crossover treatment). [e]Confirmed using either IHC and/or polymerase chain reaction-based tests. [f]Evaluated using RECIST v1.1. [g]Time between randomization and data cutoff among all randomized patients across all 3 treatment arms.

CM-8HW: PFS early separation, HR=0.21

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.4-7.8
HR (97.91% CI)	0.21 (0.13-0.35)	
P value	< 0.0001	



No. at risk																	
NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity and supportive analyses, including PFS by BICR in 1L all randomized patients (HR, 0.32; 95% CI, 0.23–0.46)

[a]Per BICR. [b]Median follow-up in patients with centrally confirmed MSI-H/dMMR, 31.6 months.

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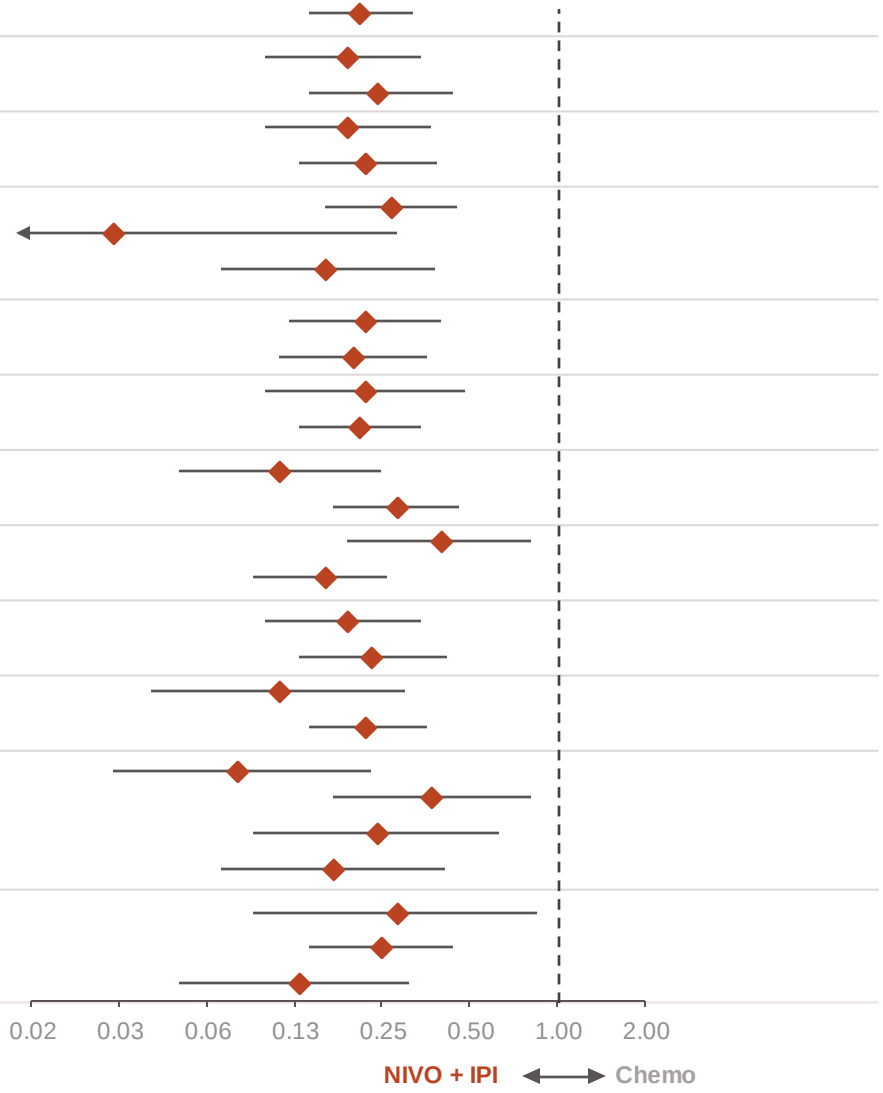
PFS benefits across all subgroup

Category (1L centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo		Unstratified HR
		NIVO + IPI	Chemo	
Overall (N = 255)		NR	5.9	0.21
Age, years	< 65 (n = 138)	NR	5.7	0.19
	≥ 65 (n = 117)	NR	5.9	0.24
Sex	Male (n = 117)	NR	5.9	0.19
	Female (n = 138)	NR	6.2	0.22
Region	US/Canada/Europe (n = 167)	NR	5.7	0.27
	Asia (n = 28)	NR	7.4	0.03
	Rest of world (n = 60)	NR	6.2	0.16
ECOG PS	0 (n = 142)	NR	9.0	0.22
	1 (n = 113)	NR	4.2	0.20
Tumor sidedness	Left (n = 70)	NR	4.4	0.22
	Right (n = 185)	NR	7.1	0.21
Liver metastases[a]	Yes (n = 87)	NR	5.9	0.11
	No (n = 166)	NR	5.4	0.28
Lung metastases[a]	Yes (n = 53)	13.2	4.9	0.40
	No (n = 200)	NR	6.2	0.16
Peritoneal metastases[a]	Yes (n = 115)	NR	4.4	0.19
	No (n = 138)	NR	7.4	0.23
Tumor cell PD-L1 expression	≥ 1% (n = 55)	NR	3.4	0.11
	< 1% (n = 191)	NR	6.5	0.22
BRAF/KRAS/NRAS mutation status	*BRAF/KRAS/NRAS* wild type (n = 58)	34.3	5.4	0.08
	BRAF mutant (n = 72)	NR	9.2	0.37
	KRAS or *NRAS* mutant (n = 45)	NR	5.7	0.24
	Unknown (n = 74)	NR	4.9	0.17
Lynch syndrome	Yes (n = 31)	NR	7.4	0.28
	No (n = 152)	NR	6.2	0.25
	Unknown (n = 66)	NR	5.5	0.13



Andre, Elez, Lenz et al Lancet 2025

[a]Per BICR.

PFS by age

Age < 50 years

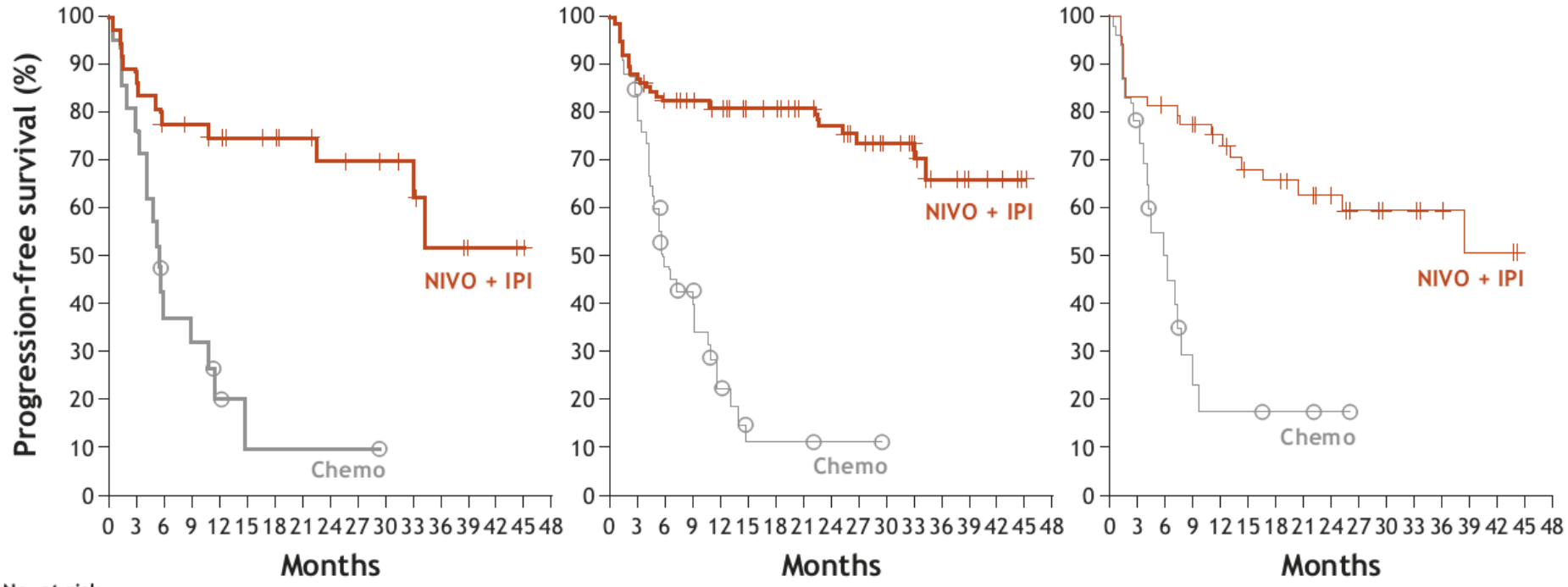
1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 39)	Chemo (n = 23)
Median PFS,[a,b] mo	NR	5.6
95% CI	33.1-NE	3.4-10.9
HR (95% CI)	0.21 (0.10-0.48)	

Age < 70 years

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 117)	Chemo (n = 56)
Median PFS,[a,b] mo	NR	5.7
95% CI	NE	4.4-9.3
HR (95% CI)	0.18 (0.11-0.31)	

Age ≥ 70 years

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 54)	Chemo (n = 28)
Median PFS,[a,b] mo	NR	5.9
95% CI	20.5-NE	3.7-7.8
HR (95% CI)	0.27 (0.14-0.54)	



[a]Median follow-up in patients with centrally confirmed MSI-H/dMMR, 31.6 months. [b]Per BICR.

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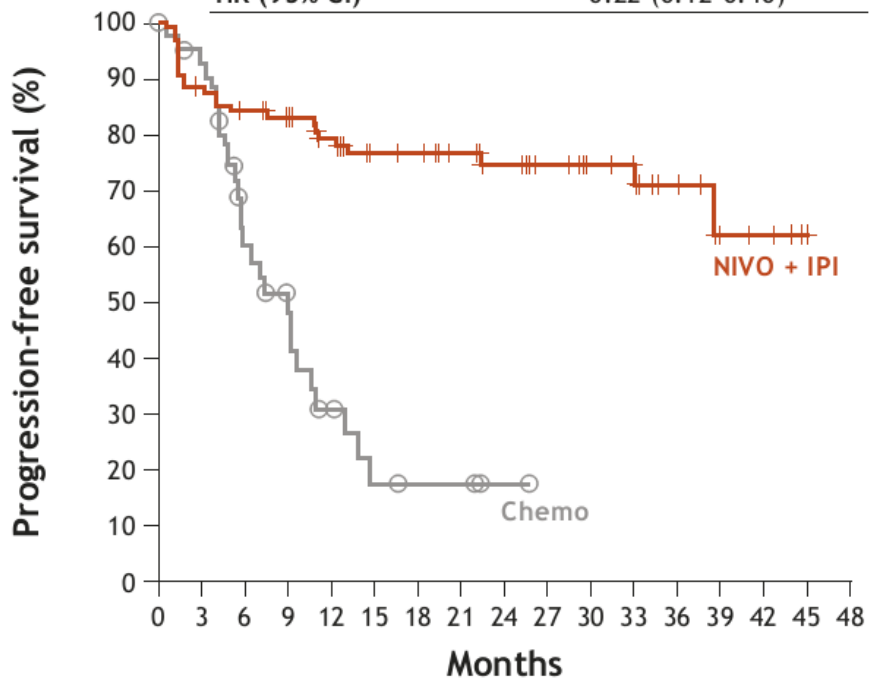
PFS by ECOG PS

ECOG PS 0

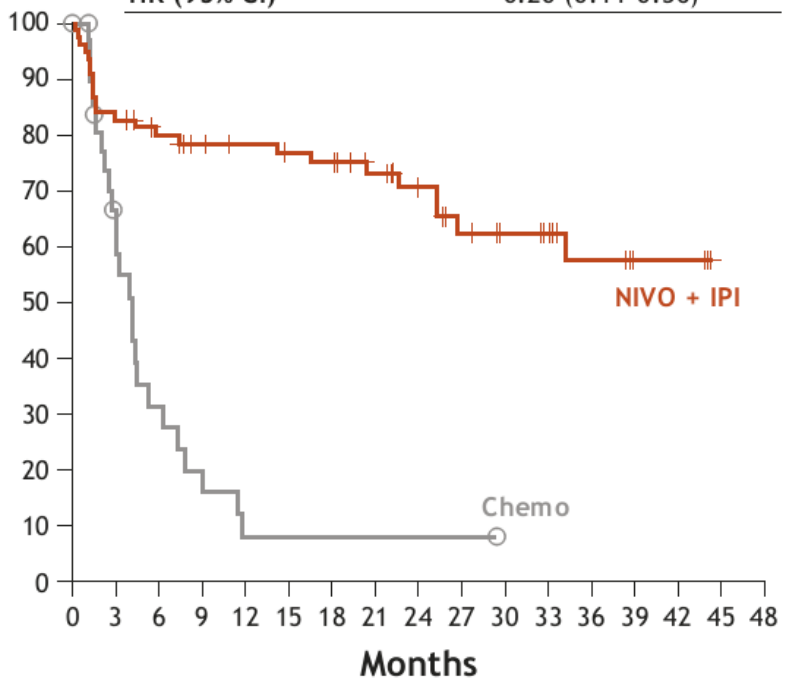
1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 97)	Chemo (n = 45)
Median PFS,[a,b] mo	NR	9.0
95% CI	38.4-NE	5.7-10.9
HR (95% CI)	0.22 (0.12-0.40)	



No. at risk																	
NIVO + IPI	97	82	76	73	62	52	50	43	36	31	24	21	10	5	4	1	0
Chemo	45	37	21	15	8	4	3	3	1	0	0	0	0	0	0	0	0

ECOG PS 1

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 74)	Chemo (n = 39)
Median PFS,[a,b] mo	NR	4.2
95% CI	26.7-NE	2.6-5.4
HR (95% CI)	0.20 (0.11-0.36)	



NIVO + IPI	74	62	56	49	46	43	42	34	28	22	18	16	12	5	5	0	0
Chemo	39	16	8	5	2	2	2	2	2	2	0	0	0	0	0	0	0

[a]Median follow-up in patients with centrally confirmed MSI-H/dMMR, 31.6 months. [b]Per BICR.

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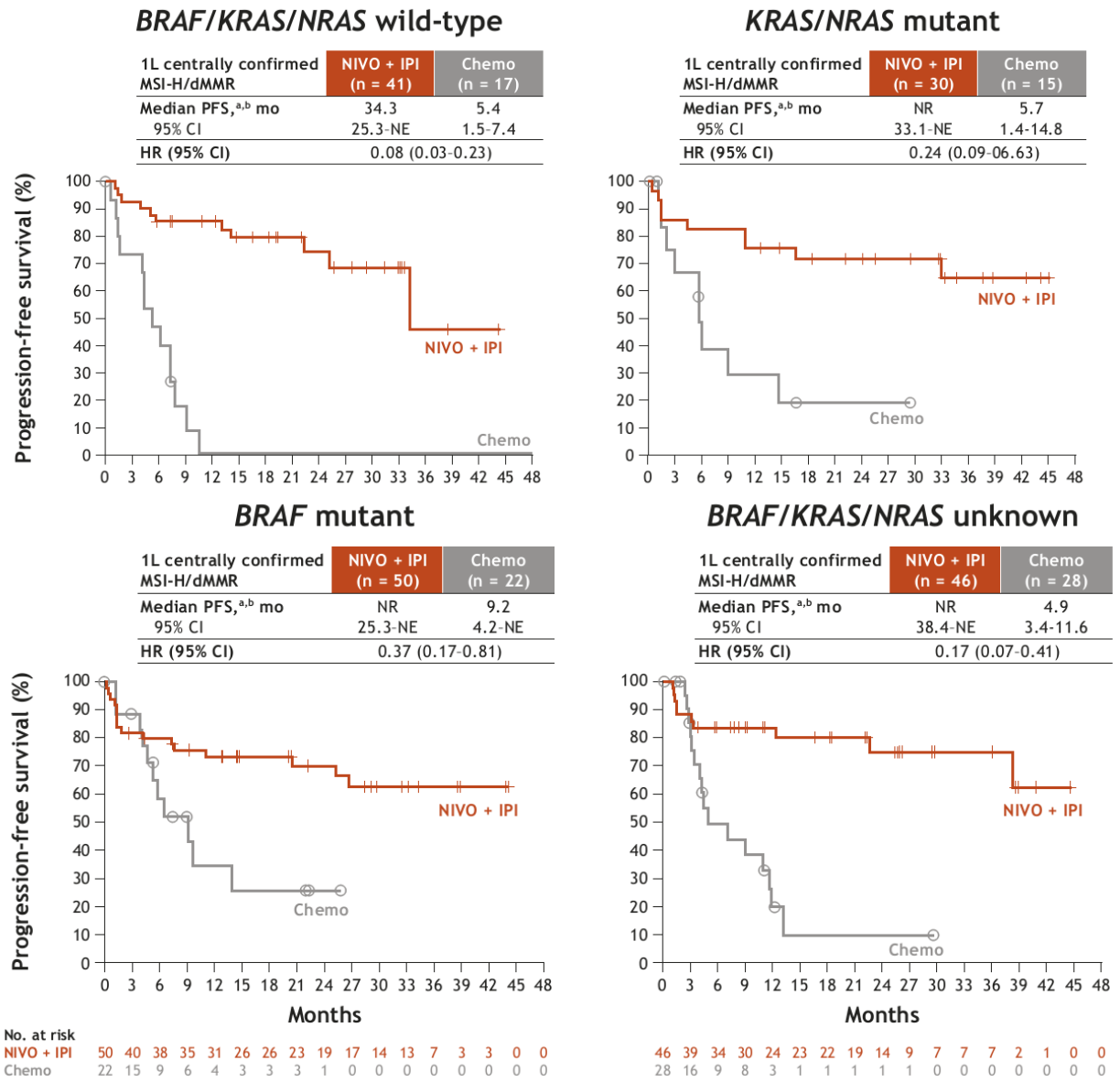
PFS by RAS/BRAF mutation status



[a]Median follow-up in patients with centrally confirmed MSI-H/dMMR, 31.6 months. [b]Per BICR.

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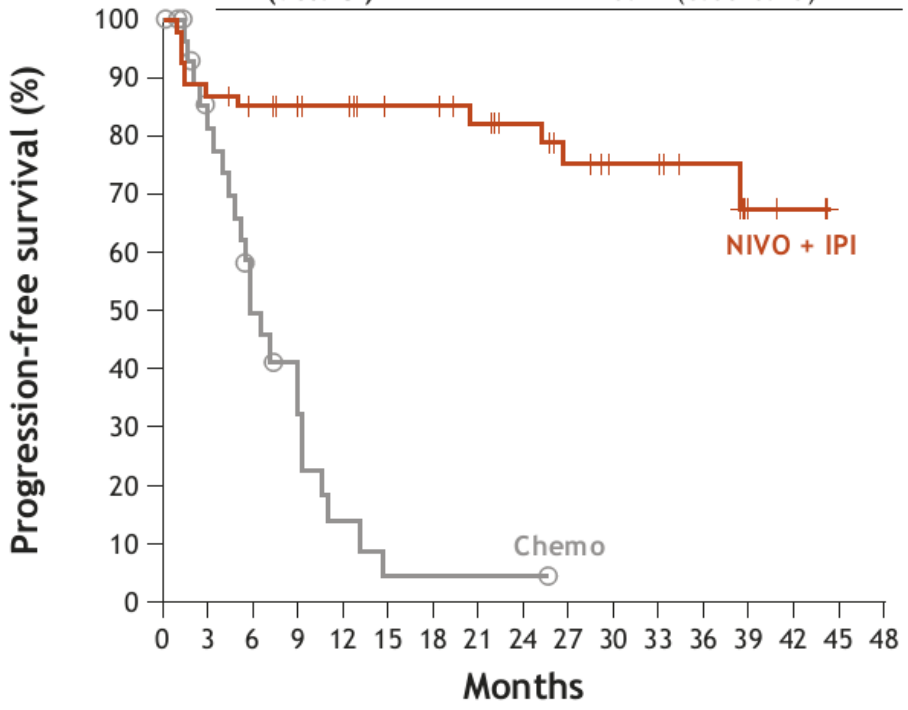
PFS by Liver mets

Liver metastases: Yes

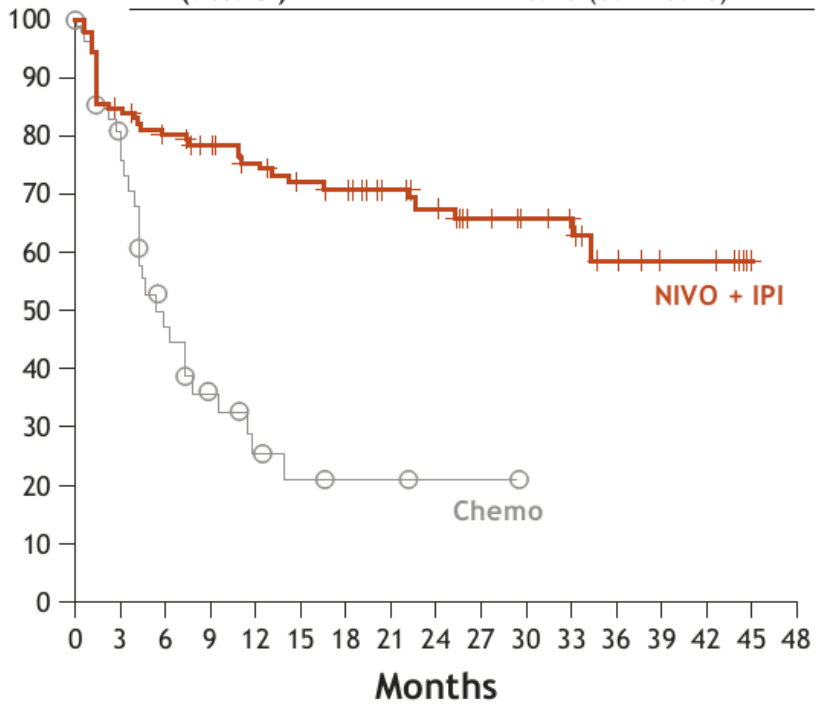
1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 55)	Chemo (n = 32)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.3-9.2
HR (95% CI)	0.11 (0.05-0.25)	



No. at risk																	
NIVO + IPI	55	49	44	41	38	33	33	28	24	20	17	15	10	3	2	0	0
Chemo	32	22	12	9	3	1	1	1	1	0	0	0	0	0	0	0	0

Liver metastases: No

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 114)	Chemo (n = 52)
Median PFS,[a,b] mo	NR	5.4
95% CI	34.3-NE	4.2-9.6
HR (95% CI)	0.28 (0.17-0.46)	



NIVO + IPI	114	95	88	81	70	62	59	49	40	33	25	22	12	7	7	1	0
Chemo	52	31	17	11	7	5	4	4	2	2	0	0	0	0	0	0	0

[a]Median follow-up in patients with centrally confirmed MSI-H/dMMR, 31.6 months. [b]Per BICR.

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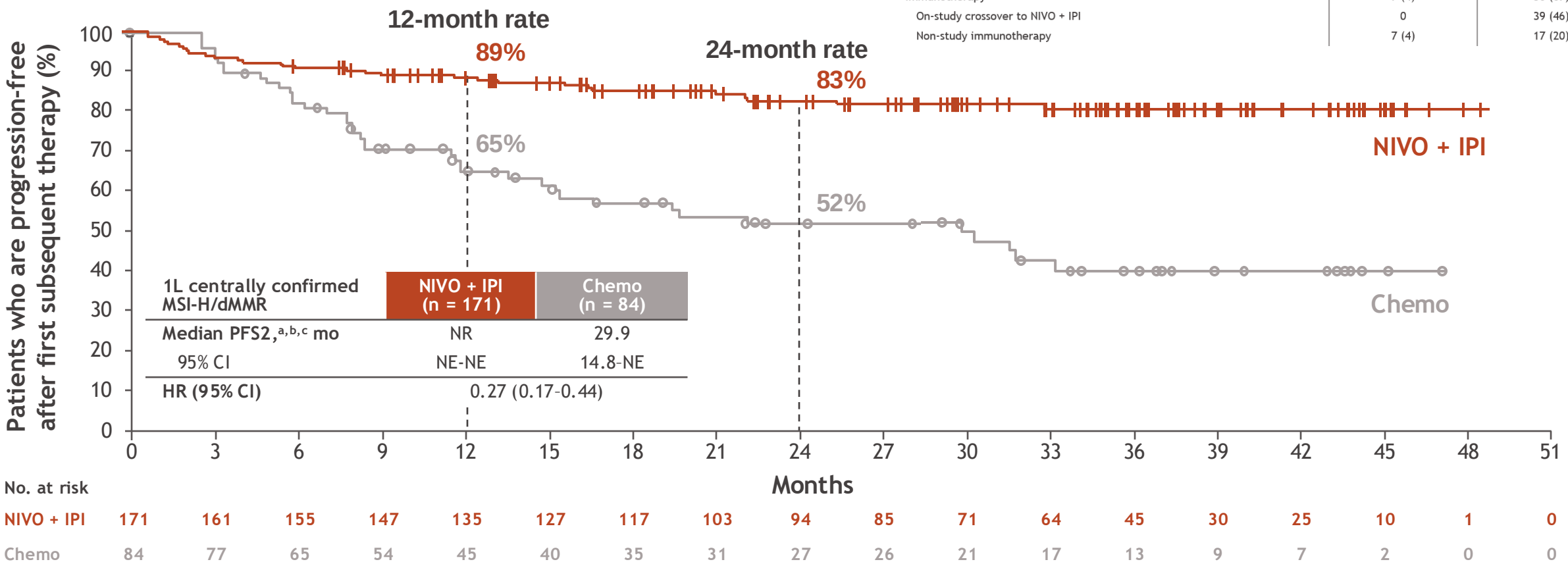
PFS2: progression-free survival after subsequent therapy

Subsequent therapy (1L centrally confirmed MSI-H/dMMR),[a-c] n (%)	NIVO + IPI (n = 171)	Chemo (n = 84)
Immunotherapy	7 (4)	56 (67)
On-study crossover to NIVO + IPI	0	39 (46)
Non-study immunotherapy	7 (4)	17 (20)



- PFS2[a] favored NIVO + IPI vs chemo with a 73% reduction in the risk of death or disease progression after first subsequent therapy

[a]Defined as time from randomization to progression after subsequent systemic therapy, initiation of second subsequent systemic therapy, or death. [b]Per investigator. [c]Median follow-up in patients with centrally confirmed MSI-H/dMMR, 31.6 months.

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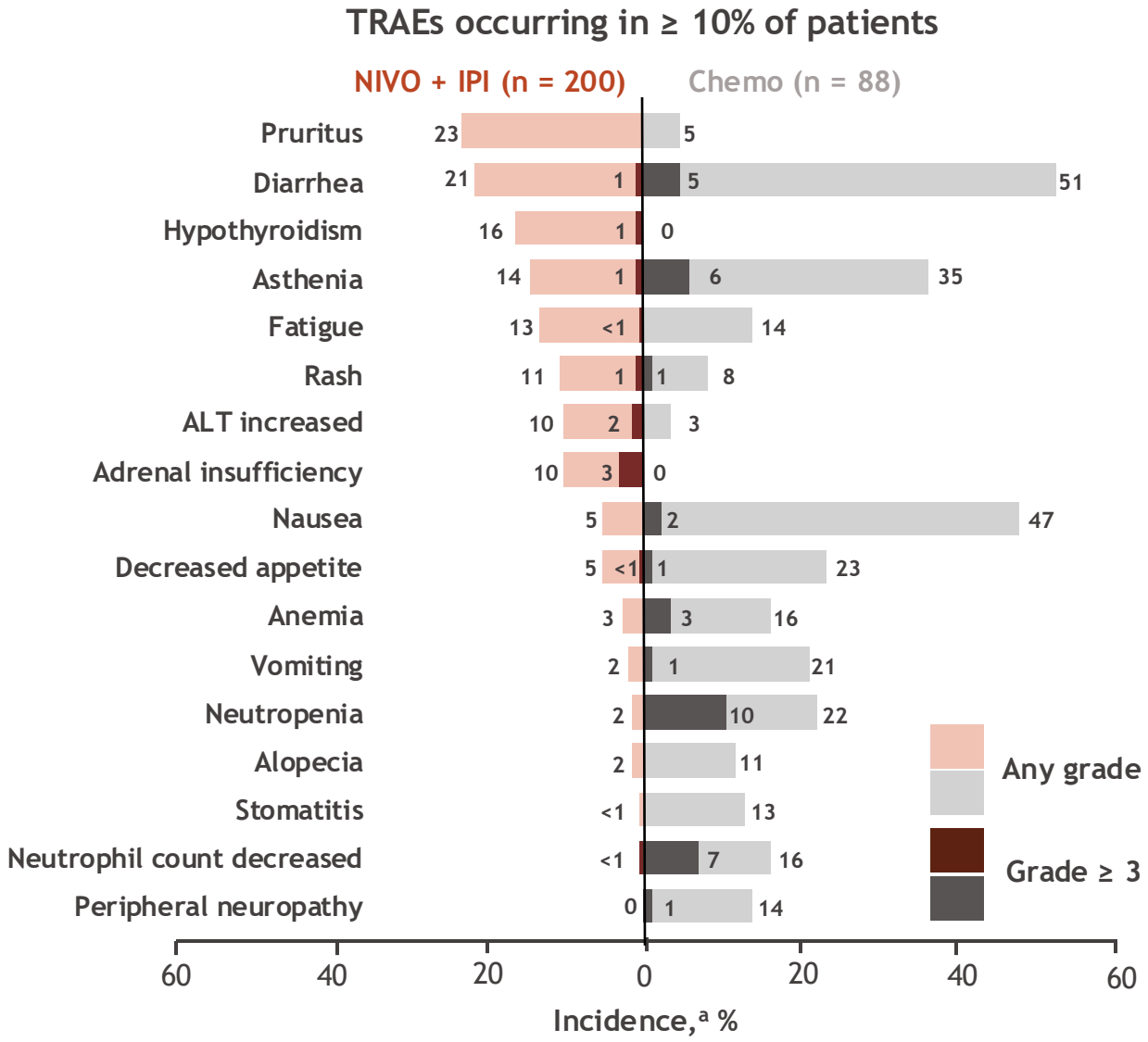
Treatment-related adverse events



1L all treated patients	NIVO + IPI (n = 200)		Chemo (n = 88)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TRAEs,[a] n (%)				
Any TRAEs	160 (80)	46 (23)	83 (94)	42 (48)
Serious TRAEs	38 (19)	32 (16)	17 (19)	14 (16)
TRAEs leading to discontinuation	33 (17)	23 (12)	28 (32)	9 (10)
Treatment-related deaths, n (%)	2 (1)[b]		0 (0)[c]	

- Any-grade and grade 3/4 TRAEs were less frequent in the NIVO + IPI arm than in chemo arm
- The most common any-grade TRAEs occurring in ≥ 10% of patients were:
  - NIVO + IPI: pruritis (23%), diarrhea (21%), and hypothyroidism (16%)
  - Chemo: diarrhea (51%), nausea (47%), and asthenia (35%)

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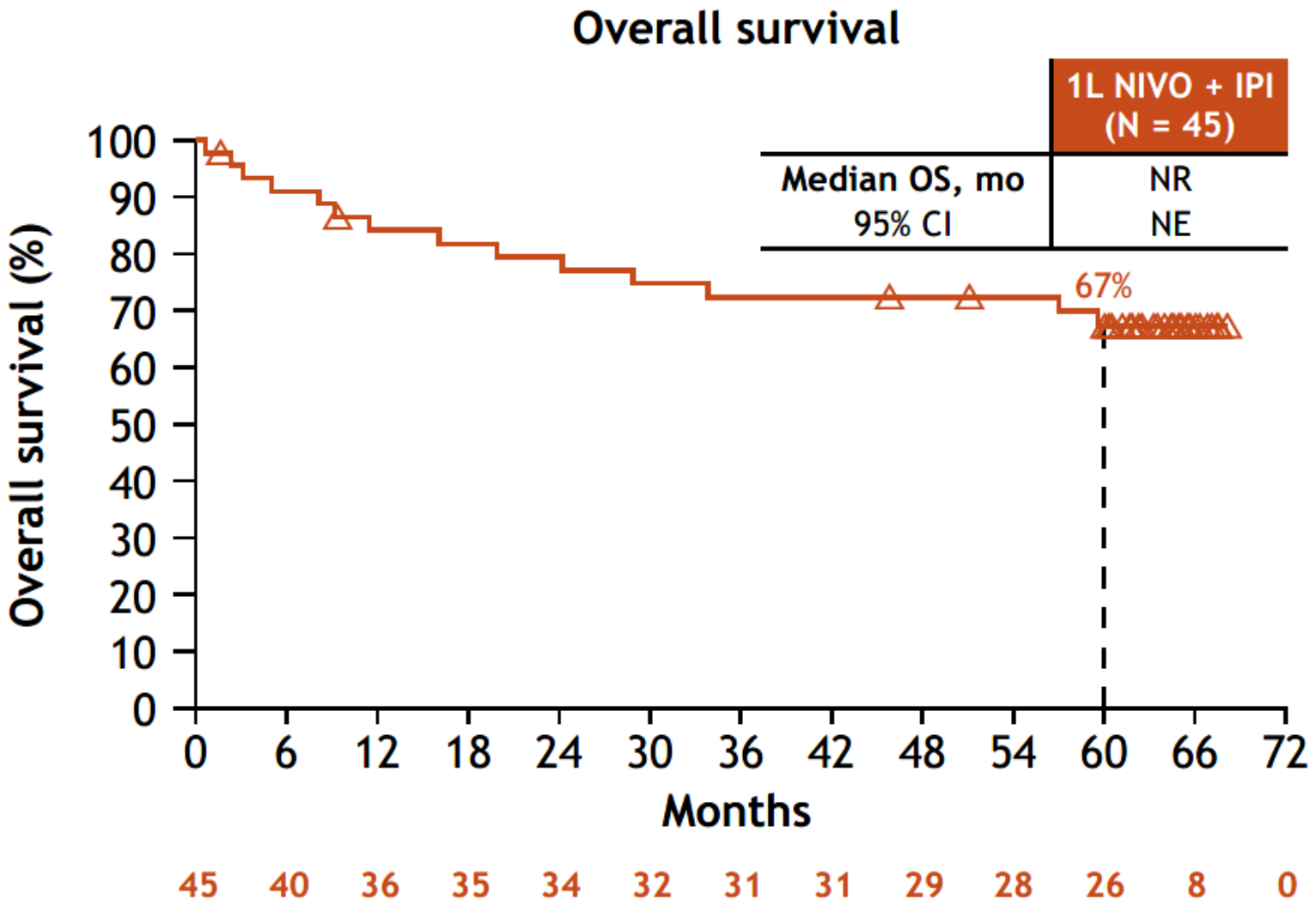
[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Includes 1 event each of myocarditis and pneumonitis. [c]One death (acute myocarditis) was related to crossover treatment.

Overall survival (CM-142: 5 Yr f/u)



Lenz et al JCO 2022

ASCO Gastrointestinal Cancers Symposium

First results of nivolumab plus ipilimumab vs nivolumab monotherapy for microsatellite instability high/ mismatch repair-deficient metastatic colorectal cancer from CheckMate 8HW

Thierry Andre,[1] Elena Elez,[2] Heinz-Josef Lenz,[3] Lars Henrik Jensen,[4] Yann Touchefeu,[5] Eric Van Cutsem,[6] Rocio Garcia-Carbonero,[7] David Tougeron,[8] Guillermo Ariel Mendez,[9] Michael Schenker,[10] Christelle de la Fouchardiere,[11] Maria Luisa Limon Miron,[12] Takayuki Yoshino,[13] Jin Li,[14] Francine Aubin,[15] Elvis Cela,[16] Tian Chen,[16] Ming Lei,[16] Lixian Jin,[16] Sara Lonardi[17]

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Abstract number LBA143

Background

- Tumors with MSI-H/dMMR status are found in 4% to 7% of patients with mCRC and are correlated with poor outcomes with chemo ± targeted therapies[1-3]
- Pembrolizumab monotherapy showed improved PFS vs chemo in MSI-H/dMMR mCRC in the 1L setting; however, primary progressive disease was reported in 29% of patients, and the 2-year and 5-year PFS rates were 48% and 34%, respectively,[4] so an unmet need remains
- In the non-randomized phase 2 CheckMate 142 study, indirect comparisons suggested that NIVO + IPI provided better outcomes than NIVO monotherapy in MSI-H/dMMR mCRC[5,6]
- CheckMate 8HW is a randomized phase 3 study comparing NIVO + IPI with NIVO or chemo in patients with MSI-H/dMMR mCRC across different lines of therapy
- NIVO + IPI demonstrated superior PFS vs chemo in previously untreated patients with centrally confirmed MSI-H/dMMR mCRC (HR, 0.21 [95% CI, 0.14–0.32]; $P < 0.0001$), meeting one of the dual primary endpoints of the CheckMate 8HW study[7,8]
- Here, we report first results from the other dual primary endpoint of PFS for NIVO + IPI vs NIVO across all lines of therapy

1. Venderbosch S, et al. *Clin Cancer Res* 2014;20:5322–5330. 2. Gutierrez C, et al. *JCO Precis Oncol* 2023;7:e2200179. 3. Innocenti F, et al. *J Clin Oncol* 2019;37:1217-1227. 4. Andre T, et al. *N Engl J Med* 2020;383:2207–2218. 5. Overman MJ, et al. *J Clin Oncol* 2018;36:773-779. 6. Overman MJ, et al. *J Clin Oncol* 2022;40:3510. 7. Andre T et al. *J Clin Oncol* 2024 42:3_suppl, LBA768. 8. Andre T, et al. *N Engl J Med* 2024;391:2014-2026.

Study design

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]

Key eligibility criteria:
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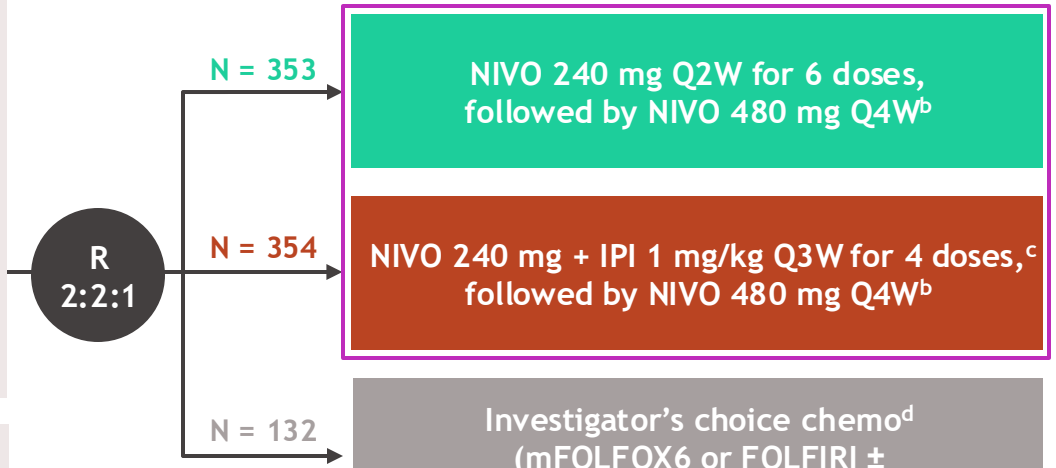

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- PFS by BICR[f] (NIVO + IPI vs NIVO across all lines)

Other select endpoints:
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- ORR by BICR[f] (NIVO + IPI vs NIVO across all lines)
- HRQoL
- OS

- At data cutoff (August 28, 2024), the median follow-up[g] was 47.0 months (range, 16.7–60.5)

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients can continue NIVO treatment upon early IPI discontinuation. [d]Patients receiving investigator's choice of chemo are eligible to receive NIVO + IPI upon progression (crossover treatment). [e]Confirmed using either IHC and/or polymerase chain reaction-based tests. [f]Evaluated using RECIST v1.1. [g]Time between randomization and data cutoff among all randomized patients across all 3 treatment arms.

Baseline characteristics

Characteristic (all randomized patients)	Category	NIVO + IPI (n = 354)	NIVO (n = 353)
Age	Median (range), years	62 (21-86)	63 (20-87)
Sex	Female	192 (54)	163 (46)
	Male	162 (46)	190 (54)
Region	US/Canada/Europe	251 (71)	246 (70)
	Asia	26 (7)	33 (9)
	Rest of world	77 (22)	74 (21)
ECOG PS	0	192 (54)	183 (52)
Disease stage at initial diagnosis[a]	Stage IV	152 (43)	158 (45)
Number of prior lines of therapy per IRT	0	202 (57)	201 (57)
	1	67 (19)	67 (19)
	≥ 2	85 (24)	85 (24)
Tumor sidedness	Right	244 (69)	244 (69)
Sites of metastases[b-d]	Liver	140 (40)	149 (42)
	Peritoneum	143 (40)	126 (36)
Centrally confirmed MSI-H/dMMR status	Yes	296 (84)	286 (81)
	No	58 (16)	67 (19)
	MSS and pMMR	41 (12)	40 (11)
	MSS or pMMR[e]	8 (2)	10 (3)
	Not available[f]	9 (3)	17 (5)
Tumor cell PD-L1[g,h]	< 1%	255 (72)	264 (75)
	≥ 1%	74 (21)	63 (18)
***BRAF*, *KRAS*, *NRAS* mutation status**[g,i]	*BRAF*/*KRAS*/*NRAS* all wild type	83 (23)	103 (29)
	BRAF mutant	106 (30)	85 (24)
	KRAS or *NRAS* mutant	83 (23)	89 (25)
	Unknown	73 (21)	74 (21)
Clinical history of Lynch syndrome[g,j]	Yes	48 (14)	49 (14)
	No	217 (61)	207 (59)
	Reported as unknown	86 (24)	91 (26)

Data are shown as n (%) unless otherwise noted. [a]Disease stage not reported: NIVO + IPI, n = 2; NIVO, n = 1. [b]Per BICR. [c]Patients may have had more than one site of metastasis. [d]Sites of metastases not reported: NIVO + IPI, n = 3; NIVO, n = 2. [e]Patients 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. [f]Patients with tumors that could not be evaluated or were not tested centrally for both MSI and MMR status. [g]Percentages may not add up to 100% due to rounding. [h]Tumor cell PD-L1 expression indeterminate, not evaluable, or not available: NIVO + IPI, n = 25; NIVO, n = 26. [i]*BRAF* and *KRAS*/*NRAS* mutant: NIVO + IPI, n = 9; NIVO, n = 2. [j]Patients with Lynch syndrome not reported: NIVO + IPI, n = 3; NIVO, n = 6.

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Exposure and disposition

Disposition	NIVO + IPI	NIVO
All randomized patients, n	354	353
All treated patients, n	352	351
Ongoing treatment,[a] n (%)	20 (6)	13 (4)
Completed treatment,[a,b] n (%)	159 (45)	137 (39)
Discontinued treatment,[a] n (%)	173 (49)	201 (57)
Disease progression	82 (23)	137 (39)
AE related to treatment	48 (14)	28 (8)
AE not related to treatment	22 (6)	28 (8)
Other[c]	21 (6)	8 (2)
Median duration of treatment (range),[d] mo	20.5 (0–35.9)[e]	16.4 (0–36.0)
Median number of doses (range)[d]	NIVO: 23 (1-41) IPI: 4 (1-4)	NIVO: 21 (1-43)
Received all 4 doses of IPI,[a] n (%)	288 (82)	-
Death,[a] n (%)	103 (29)	149 (42)
Disease progression	74 (21)	122 (35)
Other[f]	29 (8)	27 (8)

[a]Percentages shown are based on all treated patients. [b]Completed 2 years of treatment. [c]Other reasons for discontinuation included death (n = 6), withdrawal of consent (n = 2), pregnancy (n = 1), patient no longer met study criteria (n = 1), maximum clinical benefit (n = 1), and other reasons (n = 18). [d]Patients can continue NIVO treatment upon early IPI discontinuation. [e]Median duration of treatment was 20.5 (range, 0–35.9) months for NIVO and 2.1 (range, 0–3.7) months for IPI. [f]Other reasons for death included treatment-related toxicity (n = 3), other reasons (n = 36), and unknown (n = 17).

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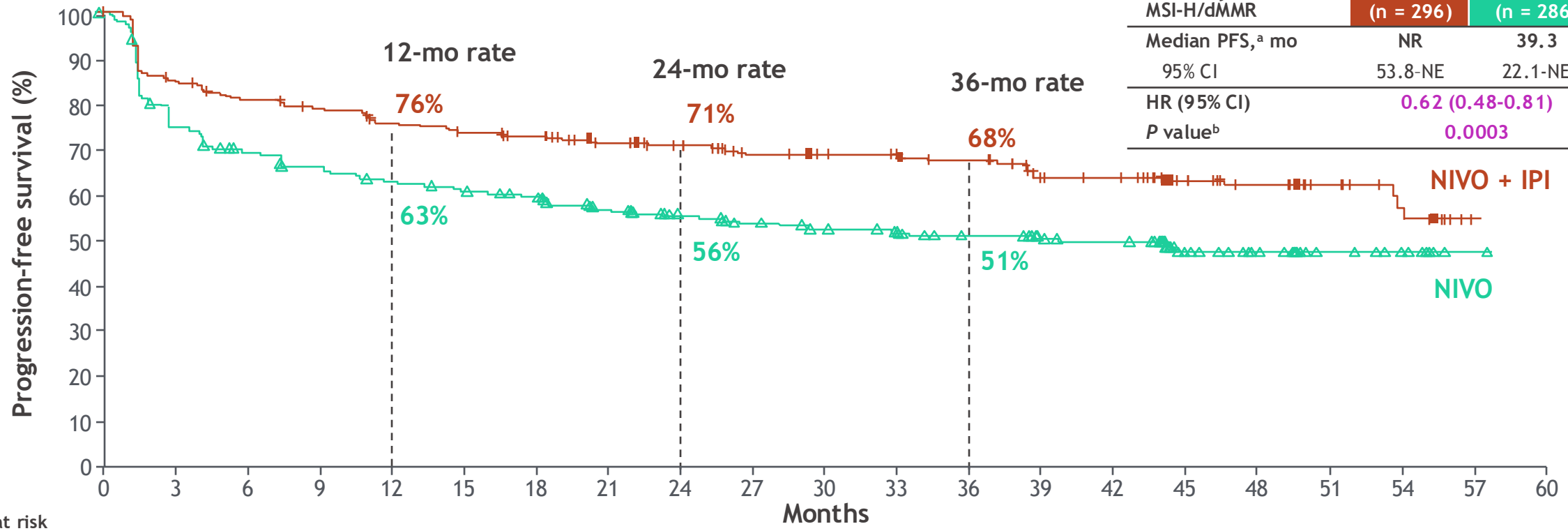
Progression-free survival



Centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 296)	NIVO (n = 286)
Median PFS,[a] mo	NR	39.3
95% CI	53.8-NE	22.1-NE
HR (95% CI)	0.62 (0.48-0.81)	
P value[b]	0.0003	

No. at risk

NIVO + IPI	296	248	234	225	214	207	200	180	164	146	136	134	121	102	100	61	54	29	23	0	0
NIVO	286	210	191	179	169	164	158	141	124	109	98	95	81	72	69	39	31	15	12	1	0

- 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
  - PFS benefit with NIVO + IPI vs NIVO was consistent in all randomized patients (median PFS: 54.1 vs 18.4 months; HR, 0.64 [95% CI, 0.52–0.79])

[a]Per BICR. [b]Boundary for statistical significance, p < 0.0095.

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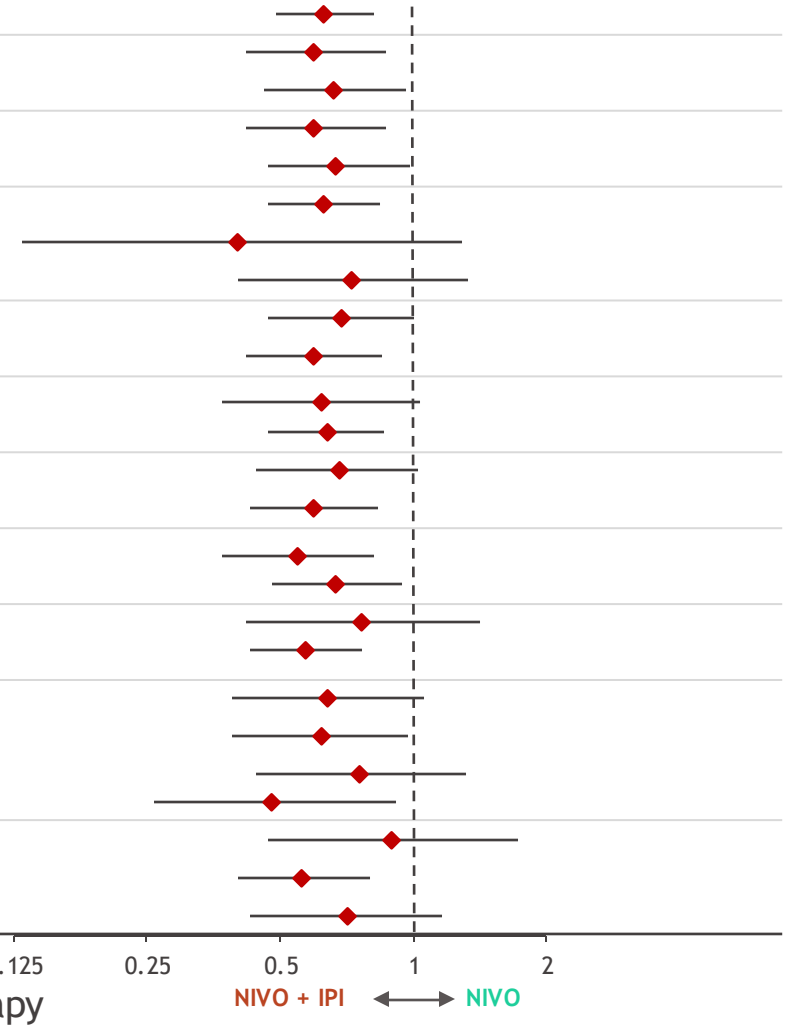
Progression-free survival subgroup analysis

Category (centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo		Unstratified HR
		NIVO + IPI	NIVO	
Overall (N = 582)		NR	39.3	0.63
Age, years	< 65 (n = 321)	NR	NR	0.60
	≥ 65 (n = 261)	NR	29.4	0.66
Sex	Male (n = 284)	NR	28.2	0.60
	Female (n = 298)	NR	NR	0.67
Region	US/Canada/Europe (n = 415)	NR	29.4	0.63
	Asia (n = 52)	NR	NR	0.40
	Rest of world (n = 115)	NR	NR	0.73
ECOG PS	0 (n = 313)	54.1	NR	0.69
	1 (n = 269)	NR	18.2	0.60
Tumor sidedness	Left (n = 152)	NR	NR	0.62
	Right (n = 430)	NR	33.2	0.64
Liver metastases[a,b]	Yes (n = 210)	NR	NR	0.68
	No (n = 368)	NR	33.2	0.60
Peritoneal metastases[a,b]	Yes (n = 226)	54.1	24.8	0.55
	No (n = 352)	NR	NR	0.67
Tumor cell PD-L1 expression	≥ 1% (n = 133)	NR	NR	0.77
	< 1% (n = 427)	NR	24.8	0.57
***BRAF/KRAS/NRAS* mutation status**	*BRAF/KRAS/NRAS* all wild type (n = 156)	NR	44.3	0.64
	BRAF mutant (n = 179)	NR	25.9	0.62
	KRAS or *NRAS* mutant (n = 125)	NR	NR	0.76
	Unknown (n = 114)	54.1	38.1	0.48
Clinical history of Lynch syndrome	Yes (n = 83)	53.8	38.1	0.90
	No (n = 334)	NR	44.3	0.56
	Unknown (n = 156)	NR	33.2	0.71



- PFS consistently favored NIVO + IPI vs NIVO in prespecified subgroups across all lines of therapy

[a]Per BICR. [b]Patients may have had more than one site of metastasis.

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Response and duration of response

Centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 296)	NIVO (n = 286)
ORR,[a] % (95% CI)	**71 (65-76)**	**58 (52-64)**
Difference in ORR,[b] % (95% CI)	13 (5-21)	
P value[c]	0.0011	
Best overall response,[a,d] %		
Complete response	30	28
Partial response	40	30
Stable disease	14	19
Progressive disease	10	19
Median TTR (range),[a,e] mo	2.8 (1.2-44.5)	2.8 (1.2-29.5)
Median DOR (95% CI),[a,e] mo	NR (NE)	NR (NE)

- Statistically significant and clinically meaningful improvement in ORR with NIVO + IPI vs NIVO (71% vs 58%) across all lines of therapy, with complete responses in 30% vs 28% of patients, respectively
  - Progressive disease as best response was reported in 10% and 19% of patients, respectively

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[a]Per BICR. [b]Strata-adjusted difference in ORR (NIVO + IPI arm – NIVO arm) based on Cochran-Mantel-Haenszel method of weighting. [c]Two-sided *P* value from stratified Cochran-Mantel-Haenszel test. Boundary for statistical significance: $P < 0.006$. [d]Not evaluable: NIVO + IPI, n = 17; NIVO, n = 14. [e]In responders only (NIVO + IPI, n = 209; NIVO, n = 165).

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)

[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Discontinuation of any component of the combination regimen was counted as a drug discontinuation event. [c]Treatment-related deaths were reported regardless of timeframe. [d]Includes 1 event each of myocarditis and pneumonitis. No new treatment-related deaths were reported since the previous interim analysis. [e]One event of pneumonitis.

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Immune-mediated adverse events

IMAEs[a] (all treated patients), n (%)	NIVO + IPI (n = 352)		NIVO (n = 351)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Non-endocrine events				
Rash	23 (7)	5 (1)	20 (6)	3 (< 1)
Diarrhea/colitis	21 (6)	12 (3)	13 (4)	8 (2)
Hepatitis	13 (4)	6 (2)	4 (1)	3 (< 1)
Pneumonitis	7 (2)	4 (1)	7 (2)	4 (1)
Nephritis and renal dysfunction	6 (2)	2 (< 1)	1 (< 1)	1 (< 1)
Hypersensitivity	0	0	3 (< 1)	0
Endocrine events				
Hypothyroidism/thyroiditis	62 (18)	3 (< 1)	33 (9)	0
Hyperthyroidism	42 (12)	0	16 (5)	0
Adrenal insufficiency	35 (10)	10 (3)	12 (3)	3 (< 1)
Hypophysitis	23 (7)	11 (3)	4 (1)	4 (1)
Diabetes mellitus	4 (1)	2 (< 1)	2 (< 1)	1 (< 1)

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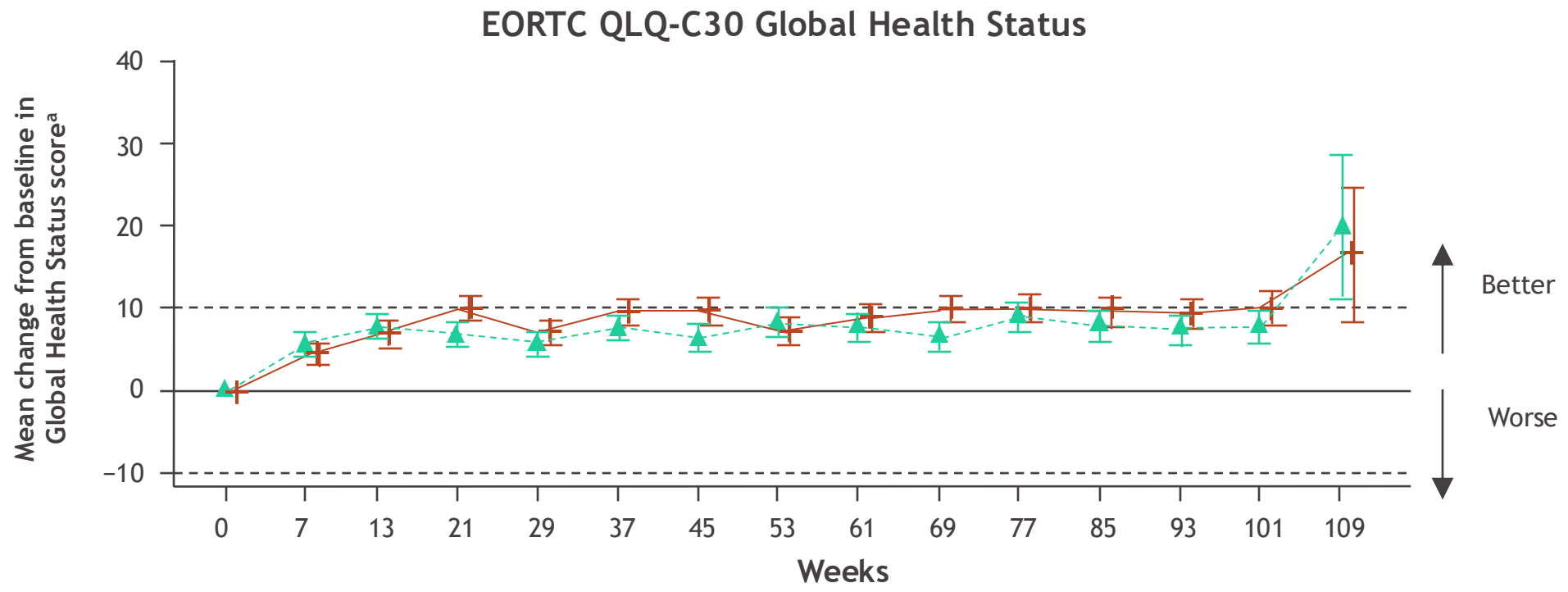
[a]IMAEs are specific events considered as potential immune-mediated events by investigator, occurring within 100 days after the last dose of study treatment, regardless of causality, and, with the exception of endocrine events, are treated with immune-modulating medication.

Health-related quality of life



- HRQoL improvements were observed with NIVO + IPI and NIVO in the EORTC QLQ-C30 Global Health Status subscale
  - Mean change from baseline scores were consistently positive in both arms, with the NIVO + IPI arm reaching the prespecified threshold for meaningful change from baseline starting at week 21

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Error bars represent standard error for the mean. Horizontal reference line indicates minimally important changes from baseline of 10 for improvement and -10 for deterioration. Only time points for which data are available for ≥ 5 patients in each treatment group are plotted. [a]Data are from patients with centrally confirmed MSI-H/dMMR status.

Key takeaways

- NIVO + IPI demonstrated statistically significant and clinically meaningful improvement in PFS vs NIVO in patients with centrally confirmed MSI-H/dMMR mCRC across all lines of therapy (HR, 0.62 [95% CI, 0.48–0.81]; *P* = 0.0003)
  - Early and sustained separation of PFS curves after the first scan
  - 2-year PFS rates: 71% vs 56%; 3-year PFS rates: 68% vs 51%
  - Consistent PFS benefit was observed across subgroups
- Statistically significant and clinically meaningful improvement in ORR was observed with NIVO + IPI vs NIVO (71% vs 58%; *P* = 0.0011), with PD as best response reported in 10% and 19% of patients, respectively
- Grade 3/4 TRAEs were reported in 22% of patients with NIVO + IPI and 14% with NIVO, and no new safety signals were identified
- HRQoL improvements from baseline were observed with both NIVO + IPI and NIVO, and the prespecified threshold for meaningful change was reached with NIVO + IPI starting at week 21
- **These results, combined with the previously reported superior PFS with NIVO + IPI vs chemo in the 1L setting, establish NIVO + IPI as a new standard-of-care treatment for patients with MSI-H/dMMR mCRC**

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We would like to acknowledge the investigators of the CheckMate 8HW study

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