CM9X8: *JITC*

SUPPLEMENTAL MATERIAL

Modified FOLFOX6 plus bevacizumab with and without nivolumab for first-line treatment of metastatic colorectal cancer

Phase 2 results from the CheckMate 9X8 randomized clinical trial

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SUPPLEMENTAL METHODS

Additional outcomes methods

Objective response rate (ORR) was defined as the number of patients with a best overall response of complete response (CR) or partial response (PR), divided by the number of randomized patients; disease control rate (DCR) was defined as the number of patients with a best overall response of CR, PR, or stable disease (SD), divided by the number of randomized patients; duration of response (DOR) was defined as time from first confirmed response to the date of first documented tumor progression or death from any cause, whichever occurred first; time to response (TTR) was defined as time from randomization to the date of the first confirmed CR or PR; TTR and DOR were derived for responders only. Response-evaluable patients had 1) best overall response of CR, PR, stable disease (SD), or progressive disease (PD); 2) target lesion(s) assessed at baseline, and 3) at least 1 post-baseline assessment of all baseline target lesion(s). Overall survival (OS) was defined as time from randomization to death. ORR, DCR, DOR, and TTR were per blinded independent central review (BICR) and investigator assessments.

Treatment-related adverse events (TRAEs) with potential immunologic etiology that required frequent monitoring/intervention were grouped by category (endocrine, gastrointestinal, hepatic, pulmonary, renal, and skin).[1] Immune-modulating medications, including corticosteroids and immunosuppressive agents, were used to manage TRAEs with potential immunologic etiology per protocol-specified algorithms.[2] Time to onset of any-grade TRAEs with potential immunologic etiology was defined as the time between the first dose and the onset date of the earliest adverse event; time to resolution was defined as the longest time from onset to complete resolution or improvement to baseline grade.

Additional biomarker methods

For analysis of biomarkers, baseline peripheral blood and tumor tissue were collected prior to dosing. Peripheral blood samples were also collected at selected timepoints during treatment. Tumor samples were collected at screening, day 1 of cycle 3, and at the time of progression or suspected progression (biopsy or surgical resection).

Baseline consensus molecular subtype (CMS) status and tumor mutational burden (TMB) were evaluated only in patients with sufficient tumor samples for sequencing analyses. CMSclassifier random forest method was used for CMS evaluation.[3] As baseline TMB levels were low in this study, a lower TMB threshold (TMB-bottom: ≤54 mutations/exome; TMB-middle: >54 to ≤74 mutations/exome; TMB-top: >74 mutations/exome) was used for patient subgroup classification.

KRAS mutations in codons 12 and 13 (exon 2), 59 and 61 (exon 3), and 117 and 146 (exon 4) were identified by next-generation sequencing. *KRAS* G12D/V/C mutations were grouped together in this study as these are the most oncogenic and prevalent mutations in CRC.[4] Microsatellite status testing was performed locally by the sites using polymerase chain reaction (PCR) or immunohistochemistry (IHC) techniques. Programmed death ligand 1 (PD-L1) expression was determined using Dako 28-8 pharmDx IHC assay (Dako, Santa Clara, CA, USA). Tumor cell PD-L1 expression was defined as the percentage of viable tumor cells with partial or complete membrane staining for PD-L1 in at least 100 viable tumor cells. PD-L1 expression was also determined using combined positive score (CPS), defined as the number of PD-L1 staining cells (tumor cells, lymphocytes, and macrophages) divided by the total number of viable tumor cells, multiplied by 100.

Statistical methods

Sample size determination for PFS was based on the assumptions that median PFS with SOC was 9.4 months,[5] and with nivolumab plus SOC was 14.4 months (HR, 0.655). If PFS followed

an exponential distribution, approximately 180 randomized patients were estimated to provide about 80% power for treatment comparison between the 2 arms with type I error of 0.20 (2-sided). Clinical data cutoff would occur when at least 114 PFS events by BICR were observed or at a minimum follow-up of approximately 20 months, whichever occurred first. For the final analysis of PFS, an observed HR of ≤0.78 (ie, median PFS improvement of at least 2.7 months) was expected to result in a statistically significant improvement with nivolumab plus SOC at a significance level of 0.2 (2-sided). An HR of 0.678 was proposed to achieve a $P<0.05$; this would be attained with a median PFS improvement of 4.5 months.

Criteria for phase 3 expansion

One interim analysis was planned in phase 2 after approximately 60 patients had valid ORR assessments to guide expansion into phase 3, which would include approximately 330 patients (excluding the randomized patients from the interim analysis). The study would be expanded to phase 3 if a strong efficacy signal was observed among all randomized patients (eg, at least a 10% improvement in ORR per BICR between treatment groups). The expansion criteria would be based on the totality of the benefit/risk assessment at the interim analysis, including safety, ORR, durability of response, PFS, and OS, and no substantial differential effects by subgroups (at least 1 response per CMS subgroup). If the study does not expand to phase 3 at the interim analysis, enrollment continues as planned to approximately 180 patients for final analysis at phase 2.

ADDITIONAL RESULTS

Supplemental table 1. Subsequent therapy in all randomized patients

Patients, No. (%)	NIVO + SOC (n=127)	SOC (n=68)
Any subsequent therapy[a]	76 (60)	39 (57)
Subsequent radiotherapy	2 (2)	1 (1)
Subsequent surgery	10 (8)	12 (18)
Subsequent systemic therapy	73 (57)	36 (53)
Anti–IL-1beta	1 (<1)	0
Gevokizumab	1 (<1)	0
Anti–PD-1	3 (2)	4 (6)
Nivolumab	3 (2)	0
Pembrolizumab	0	4 (6)
BRAF inhibitor	4 (3)	0
Dabrafenib	1 (<1)	0
Encorafenib	3 (2)	0
EGFR targeted therapy	13 (10)	9 (13)
Cetuximab	3 (2)	1 (1)
Panitumumab	10 (8)	8 (12)
Folinic acid	48 (38)	30 (44)
Calcium folinate	7 (6)	3 (4)
Calcium levofolinate	1 (<1)	0
Calcium levofolinate pentahydrate	3 (2)	1 (1)
Folic acid	1 (<1)	0
Folinic acid	33 (26)	24 (35)
Levofolinic acid	4 (3)	4 (6)
Investigational antineoplastic agents	6 (5)	3 (4)
BI 754111	1 (<1)	0
Dilpacimab	0	1 (1)
Investigational antineoplastic drugs	5 (4)	1 (1)

Spartalizumab	0	1 (1)
MEK inhibitors	4 (3)	1 (1)
Binimetinib	3 (2)	1 (1)
Trametinib	1 (<1)	0
Other systemic anti-cancer chemotherapy	67 (53)	34 (50)
Capecitabine	8 (6)	3 (4)
Cisplatin	1 (<1)	0
Docetaxel	1 (<1)	0
Fluorouracil	57 (45)	30 (44)
Gimeracil; Oteracil potassium; Tegafur	1 (<1)	0
Irinotecan	40 (31)	26 (38)
Irinotecan hydrochloride	6 (5)	3 (4)
Mitomycin	1 (<1)	0
Oxaliplatin	17 (13)	9 (13)
Raltitrexed	1 (<1)	0
Tipiracil hydrochloride; Trifluridine	10 (8)	1 (1)
Tipiracil; Trifluridine	3 (2)	1 (1)
VEGFR targeted therapy	39 (31)	22 (32)
Aflibercept	3 (2)	2 (3)
Aflibercept beta	3 (2)	0
Bevacizumab	34 (27)	19 (28)
Ramucirumab	0	1 (1)
Regorafenib	8 (6)	0

Data are No. (%).

[a]Patients may have received more than 1 type of subsequent therapy.

BRAF, V-Raf murine sarcoma viral oncogene homolog B1; *EGFR*, epidermal growth factor receptor; IL-1, interleukin 1; *MEK,* mitogen-activated protein kinase; NIVO, nivolumab; PD-1, programmed death-1; SOC, standard of care; *VEGFR*, vascular endothelial growth factor receptor.

Supplemental table 2. Extent of exposure

All treated patients	NIVO + SOC (n=123)						SOC (n=62)				
	NIVO (n=123)	BEV (n=123)	FU-B (n=122)	FU-C (n=123)	LEU (n =123)	OXA (n=123)	BEV (n=62)	FU-B (n=60)	FU-C (n=62)	LEU (n=62)	OXA (n=62)
Number of doses received	17.0 (1–52)	14.0 (1–70)	13.0 (1–70)	16.0 (1–70)	16.0 (1–70)	11.0 (1–50)	13.0 (1–56)	12.0 (1–58)	14.5 (1–58)	13.5 (1–58)	11.0 (1–31)
Cumulative dose[a]	4080.0 (240.0–12480.0)	72.4 (4.9–346.6)	4860.5 (396.2–20452.4)	36281.9 (2377.4–140173.2)	5358.3 (396.2–20126.1)	797.8 (84.9–3098.3)	64.0 (4.9–270.9)	4806.4 (393.4–23270.5)	30577.5 (2365.5–143203.4)	4805.6 (393.4–22176.7)	883.5 (81.2–2536.2)
Relative dose intensity ≥90%, No. **(%)**	66 (54)	51 (41)	43 (35)	35 (28)	47 (38)	38 (31)	40 (65)	31 (52)	29 (47)	36 (58)	29 (47)
Duration of treatment, months	8.6 (0.0–24.6)	8.0 (0.0–31.7)	6.5 (0.0–31.7)	8.1 (0.1–31.8)	8.0 (0.0–31.7)	5.1 (0.0–24.0)	6.7 (0–26.6)	5.3 (0–26.6)	7.3 (0.1–26.7)	6.7 (0–26.6)	5.0 (0–22.6)
Patients with ≥1 dose delay,[b] No. **(%)**	102 (83)	102 (83)	94 (77)	102 (83)	100 (81)	89 (72)	44 (71)	38 (63)	42 (68)	40 (65)	38 (61)
Patients with ≥1 dose reduction, No. **(%)**	NA	13 (11)	52 (43)	58 (47)	54 (44)	74 (60)	6 (10)	18 (30)	19 (31)	15 (24)	33 (53)

Data are median (range) unless otherwise noted.

[a]Cumulative dose units: NIVO (mg), BEV (mg/kg), OXA (mg/m^2), LEU (mg/m^2), and FU (mg/m^2).

[b]Delay exceeding 3 days.

BEV, bevacizumab; FU, fluorouracil; FU-B, fluorouracil-bolus; FU-C, fluorouracil-continuous; LEU, leucovorin; NA, not available; NIVO, nivolumab; OXA, oxaliplatin; SOC, standard of care.

Supplemental table 3. Concordance between BICR and investigator assessments for progression-free survival in all randomized patients

PFS by investigator	PFS by BICR					
	NIVO + SOC (n=127)			SOC (n=68)		
	Progression	Death	Censored	Progression	Death	Censored
Progression	55 (43)	0	12 (9)	23 (34)	0	3 (4)
Death	3 (2)	8 (6)	0	0	8 (12)	0
Censored	7 (6)	0	42 (33)	5 (7)	0	29 (43)
Agreement between BICR and investigator assessments	108 (85)			60 (88)		

Data are No. (%).

BICR, blinded independent central review; NIVO, nivolumab; PFS, progression-free survival; SOC, standard of care.

Supplemental table 4. Antitumor activity per investigator assessment

All randomized	NIVO + SOC (n=127)	SOC (n=68)
ORR,[a] No. (%) [95% CI]	78 (61) [52 to 70]	35 (51) [39 to 64]
Best overall response, No. (%)		
Complete response	6 (5)	2 (3)
Partial response	72 (57)	33 (49)
Stable disease	38 (30)	18 (26)
Progressive disease	3 (2)	2 (3)
Unable to determine	8 (6)	13 (19)
DCR,[b] No. (%) [95% CI]	116 (91) [85 to 96]	53 (78) [66 to 87]
Median TTR (range),[c] mo	2.8 (2.2 to 12.0)	2.8 (1.8 to 8.3)
Median DOR (95% CI),[c] mo	11.9 (8.8 to 14.8)	10.8 (7.6 to 14.9)
≥12-month rate (95% CI), %	49 (36 to 60)	39 (20 to 58)
≥18-month rate (95% CI), %	34 (22 to 46)	21 (6 to 42)

[a]Patients with best overall response of CR + PR divided by the number of randomized patients.
[b]Patients with best overall response of CR + PR + SD divided by the number of randomized patients.
[c]Evaluated in patients who had an objective response.

CR, complete response; DCR, disease control rate; DOR, duration of response; NIVO, nivolumab; ORR, objective response rate; PR, partial response; SD, stable disease; SOC, standard of care; TTR, time to response.

Supplemental table 5. Summary of treatment-related adverse events

All treated,[a] No. (%)	NIVO + SOC (n=123)		SOC (n=62)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
All TRAEs[b,c]	120 (98)	92 (75)	60 (97)	30 (48)
Serious TRAEs[b,c]	34 (28)	33 (27)	11 (18)	9 (15)
TRAEs leading to discontinuation[b,c]	70 (57)	31 (25)	22 (35)	6 (10)
TRAEs leading to dose delay[b]	89 (72)	55 (45)	30 (48)	13 (21)
Treatment-related deaths[d]	2 (2)[e]		2 (3)[f]	
Any-grade TRAEs occurring in ≥25% of patients in either treatment arm				
Fatigue	56 (46)	1 (<1)	29 (47)	3 (5)
Nausea	57 (46)	2 (2)	23 (37)	0
Peripheral neuropathy	52 (42)	7 (6)	20 (32)	2 (3)
Diarrhea	50 (41)	9 (7)	14 (23)	0
Neutropenia	43 (35)	32 (26)	13 (21)	8 (13)
Peripheral sensory neuropathy	43 (35)	2 (2)	28 (45)	4 (6)
Neutrophil count decrease	36 (29)	25 (20)	11 (18)	8 (13)
Decreased appetite	33 (27)	0	9 (15)	0
Stomatitis	25 (20)	0	16 (26)	0

[a]Patients who received ≥1 dose of study drug.
[b]Includes events reported between first dose and 30 days after last dose of study therapy according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
[c]One grade 5 event (cardiac arrest) in the SOC arm.
[d]Treatment-related deaths were reported regardless of timeframe.
[e]Includes 1 event each of pneumonitis and fulminant type myocarditis.
[f]Includes 1 event each of bowel perforation and cardiac arrest.

NIVO, nivolumab; SOC, standard of care; TRAE, treatment-related adverse event.

Supplemental table 6. Treatment-related adverse events with potential immunologic etiology[a–c]

Organ system[d]	NIVO + SOC (n=123)				SOC (n=62)			
	Any grade/ grade 3-4,[e] n (%)/n (%)	Time to onset, weeks Median (range)	Time to resolution,[f–h] weeks Median (range)	Patients with resolution, n (%)	Any grade/ grade 3-4, n (%)/n (%)	Time to onset, weeks Median (range)	Time to resolution,[f–h] weeks Median (range)	Patients with resolution, n (%)
Endocrine	27 (22)/1 (<1)	9.6 (3.9–47.7)	NR (2.1–134.3+)	7 (26)	0/0	0	0	0
Gastrointestinal	52 (42)/16 (13)	4.3 (0.1–52.0)	4.1 (0.1–138.1+)	40 (77)	14 (23)/0	3.0 (0.1–16.9)	NR (0.3–130.3+)	6 (43)
Hepatic	22 (18)/6 (5)	15.0 (1.7–69.0)	9.1 (1.1–105.3+)	15 (68)	8 (13)/1 (2)	19.5 (2.1–31.0)	14.7 (1.6–99.1+)	5 (63)
Pulmonary	5 (4)/2 (2)	29.0 (14.4–47.6)	13.9 (2.3+ to 22.7)	3 (60)	2 (3)/0	28.7 (22.1–35.3)	14.9 (4.9–25.0)	2 (100)
Renal	5 (4)/0	10.3 (2.6–52.1)	2.0 (1.9–5.1)	5 (100)	0/0	0	0	0
Skin	33 (27)/4 (3)	8.1 (1.1–57.7)	NR (1.0–131.9+)	16 (48)	9 (15)/0	8.1 (0.1–26.7)	NR (1.4–101.3+)	3 (33)

[a]Patients who received ≥1 dose of study drug.
[b]Includes events reported between first dose and 30 days after last dose of study therapy according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
[c]TRAEs with potential immunologic etiology that require frequent monitoring or intervention.
[d]Other events of special interest occurring within 100 days of last dose included iritis (n=1; grade 1-2), myocarditis (n=1; grade 3-4), and acute pancreatitis (n=1; grade 3-4), in the nivolumab plus SOC arm, and none were reported in the SOC arm.
[e]The most common grade 3-4 events (≥2%) in the nivolumab + SOC arm were diarrhea (n=9), colitis (n=8), AST increased (n=5), and pneumonitis (n=2).
[f]Symbol + indicates a censored value.
[g]Based on Kaplan-Meier estimates.
[h]Patients who experienced a TRAE with potential immunologic etiology without worsening from baseline grade were excluded from time-to-resolution analysis; events without a stop date or with a stop date equal to the death, as well as grade 5 events, are considered unresolved.

AST, aspartate aminotransferase; MedDRA, Medical Dictionary for Regulatory Activities; NIVO, nivolumab; NR, not reached; SOC, standard of care; TRAE, treatment-related adverse event.

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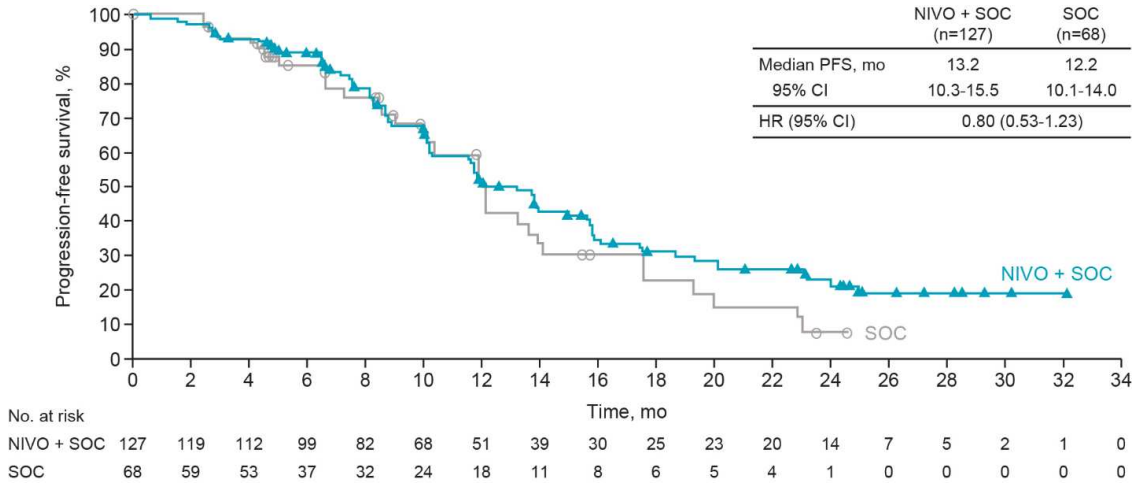
Supplemental figure 1. Kaplan-Meier estimate of progression-free survival per investigator assessment in all randomized patients

HR, hazard ratio; NIVO, nivolumab; PFS, progression-free survival; SOC, standard of care.



Supplemental figure 2. Kaplan-Meier estimate of progression-free survival by BICR in all randomized patients by baseline KRAS mutation status

Progression-free survival in patients with KRAS wild type (A), KRAS G12D/V/C mutation (B), and other KRAS mutations (C). BICR, blinded independent central review; KRAS, Kirsten rat sarcoma viral oncogene homolog; NIVO, nivolumab; PFS, progression-free survival; SOC, standard of care.

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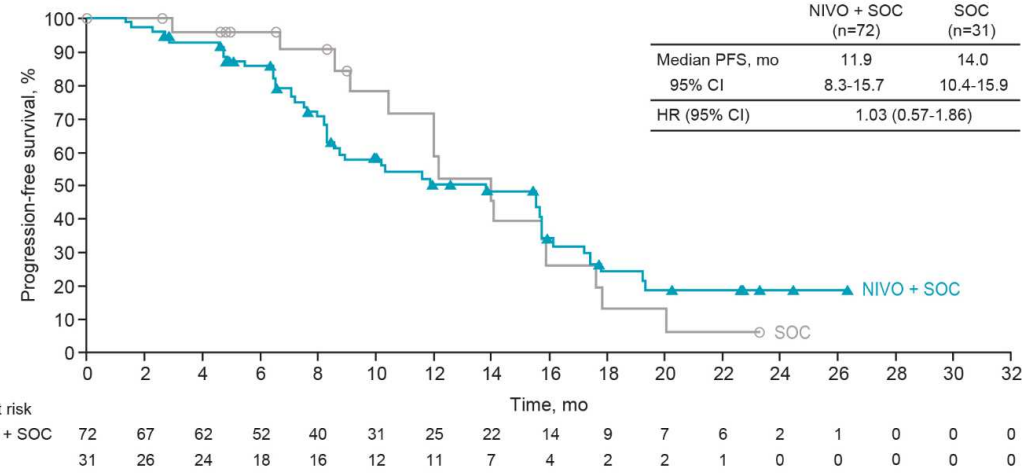
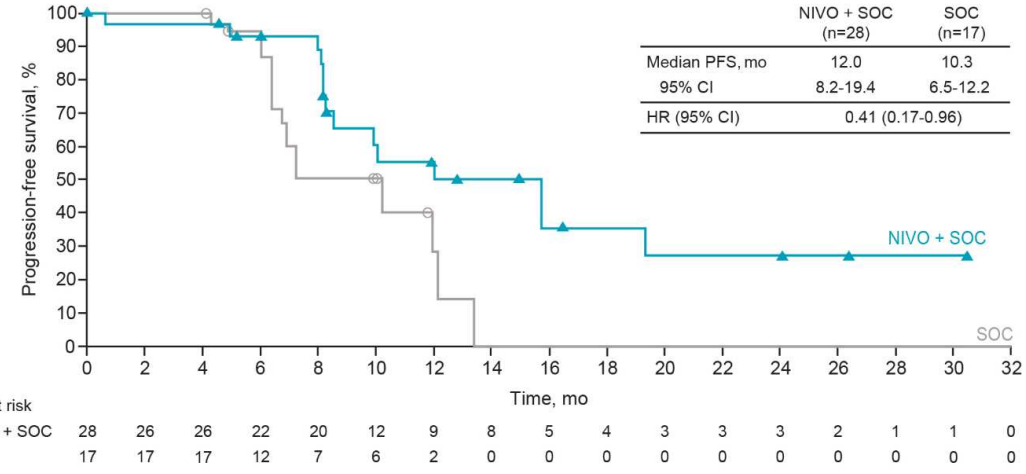
a *KRAS* wild type



	NIVO + SOC (n=72)	SOC (n=31)
Median PFS, mo	11.9	14.0
95% CI	8.3-15.7	10.4-15.9
HR (95% CI)	1.03 (0.57-1.86)	

No. at risk																	
NIVO + SOC	72	67	62	52	40	31	25	22	14	9	7	6	2	1	0	0	0
SOC	31	26	24	18	16	12	11	7	4	2	2	1	0	0	0	0	0

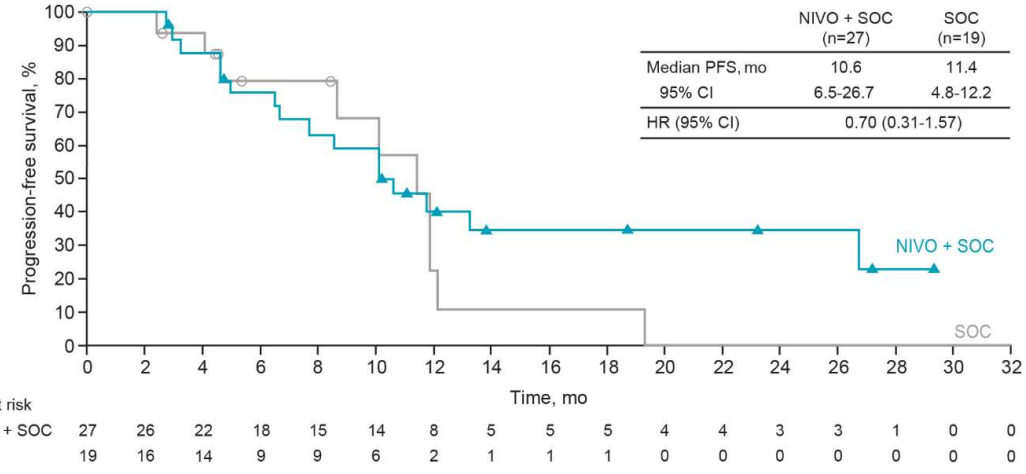
b *KRAS* G12D/V/C mutation



	NIVO + SOC (n=28)	SOC (n=17)
Median PFS, mo	12.0	10.3
95% CI	8.2-19.4	6.5-12.2
HR (95% CI)	0.41 (0.17-0.96)	

No. at risk																	
NIVO + SOC	28	26	26	22	20	12	9	8	5	4	3	3	3	2	1	1	0
SOC	17	17	17	12	7	6	2	0	0	0	0	0	0	0	0	0	0

c Other *KRAS* mutations



	NIVO + SOC (n=27)	SOC (n=19)
Median PFS, mo	10.6	11.4
95% CI	6.5-26.7	4.8-12.2
HR (95% CI)	0.70 (0.31-1.57)	

No. at risk																	
NIVO + SOC	27	26	22	18	15	14	8	5	5	5	4	4	3	3	1	0	0
SOC	19	16	14	9	9	6	2	1	1	1	0	0	0	0	0	0	0

Supplemental figure 3. Progression-free survival and responses by baseline TMB and PD-L1 CPS through BICR assessment

PFS in all treated TMB-evaluable patients (A), TMB levels versus best overall response in all randomized TMB-evaluable patients (B), and PFS in all treated patients with baseline PD-L1 CPS ≥1 (C). [a]TMB-bottom: ≤54 mutations/exome; TMB-middle: >54 to ≤74 mutations/exome; TMB-top: >74 mutations/exome. [b]Horizontal line within each box represents the median, the lower and upper ends of the boxes represent the 25th and 75th percentiles, and whiskers indicate the most extreme points within 1.5 of the interquartile range. Patients with greater than 250 mutations/exome are not shown. BICR, blinded independent central review; CPS, combined positive score; CR, complete response; NE, not evaluable; PD, progressive disease; PD-L1, programed death ligand 1; PFS, progression-free survival; PR, partial response; SD, stable disease; SOC, standard of care; TMB, tumor mutational burden.

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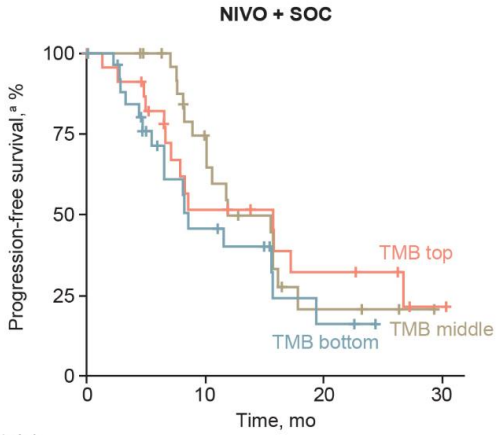
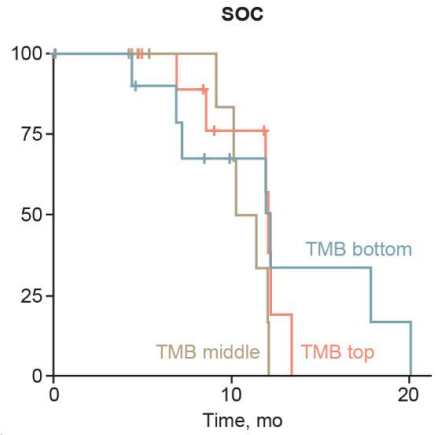
a All treated TMB-evaluable patients





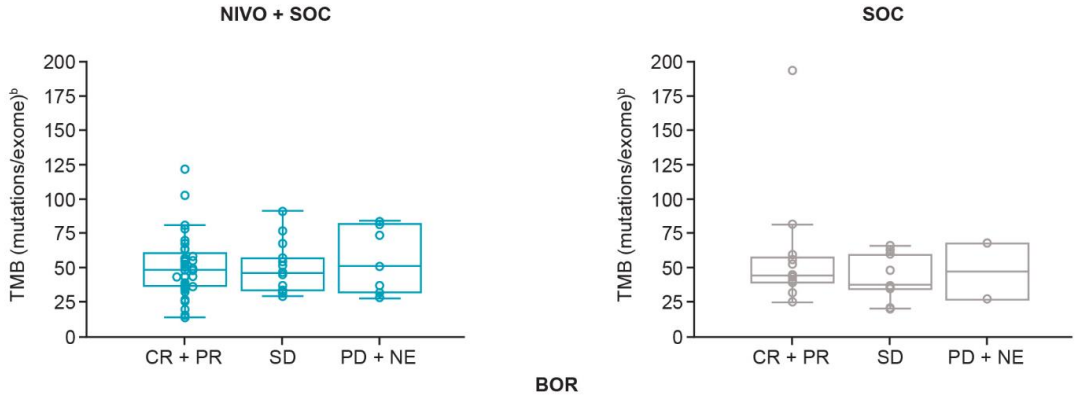
No. at risk				
TMB bottom	27	9	2	0
TMB middle	28	16	3	0
TMB top	24	10	5	1

No. at risk			
TMB bottom	11	4	1
TMB middle	9	5	0
TMB top	13	5	0

	TMB bottom[a]	TMB middle[a]	TMB top[a]
Median PFS, mo	8.5	11.9	15.7
95% CI	6.5-NE	10.1-NE	7.1-NE

	TMB bottom[a]	TMB middle[a]	TMB top[a]
Median PFS, mo	12.2	10.8	12.0
95% CI	7.2-NE	10.1-NE	11.9-NE

b All randomized TMB-evaluable patients



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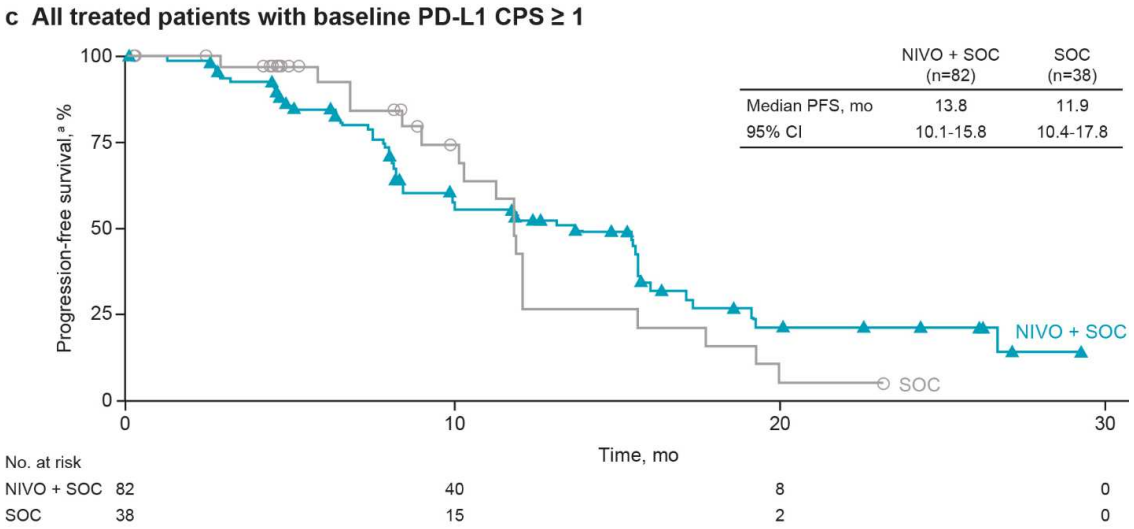
c All treated patients with baseline PD-L1 CPS ≥ 1
Progression-free survival,[a] %
100
75
50
25
0
0
10
20
30
Time, mo
NIVO + SOC
SOC
NIVO + SOC (n=82)
SOC (n=38)
Median PFS, mo 13.8 11.9
95% CI 10.1-15.8 10.4-17.8
No. at risk
NIVO + SOC 82 40 8 0
SOC 38 15 2 0

REFERENCES

1 Brahmer JR, Lacchetti C, Schneider BJ*, et al.* Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2018;36:1714-68. doi: 10.1200/JCO.2017.77.6385.

2 Robert C, Long GV, Brady B*, et al.* Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015;372:320-30. doi: 10.1056/NEJMoa1412082.

3 Guinney J, Dienstmann R, Wang X*, et al.* The consensus molecular subtypes of colorectal cancer. *Nat Med* 2015;21:1350-6. doi: 10.1038/nm.3967.

4 Zhu G, Pei L, Xia H*, et al.* Role of oncogenic KRAS in the prognosis, diagnosis and treatment of colorectal cancer. *Mol Cancer* 2021;20:143. doi: 10.1186/s12943-021-01441-4.

5 Saltz LB, Clarke S, Diaz-Rubio E*, et al.* Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008;26:2013-9. doi: 10.1200/JCO.2007.14.9930.