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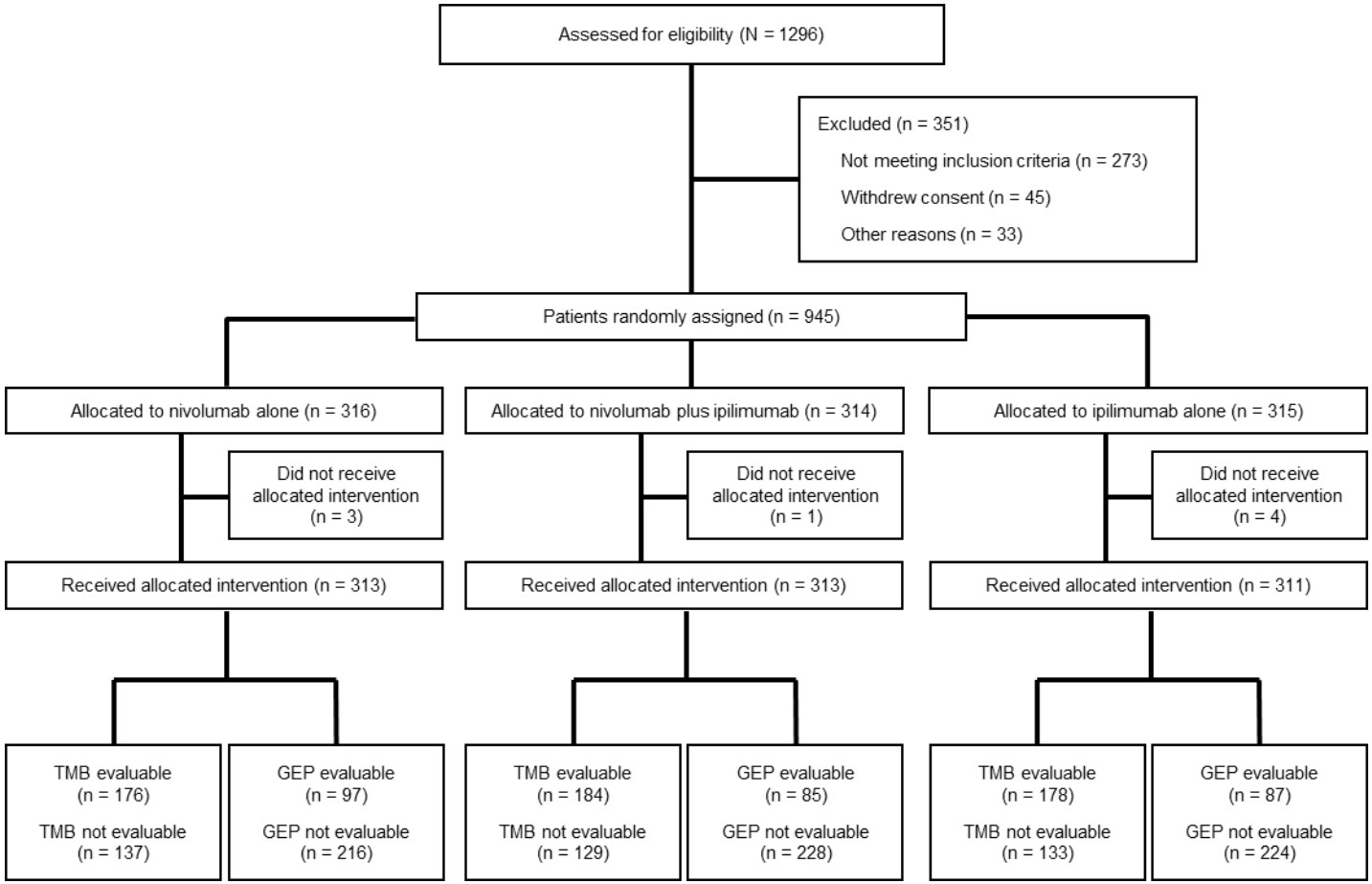
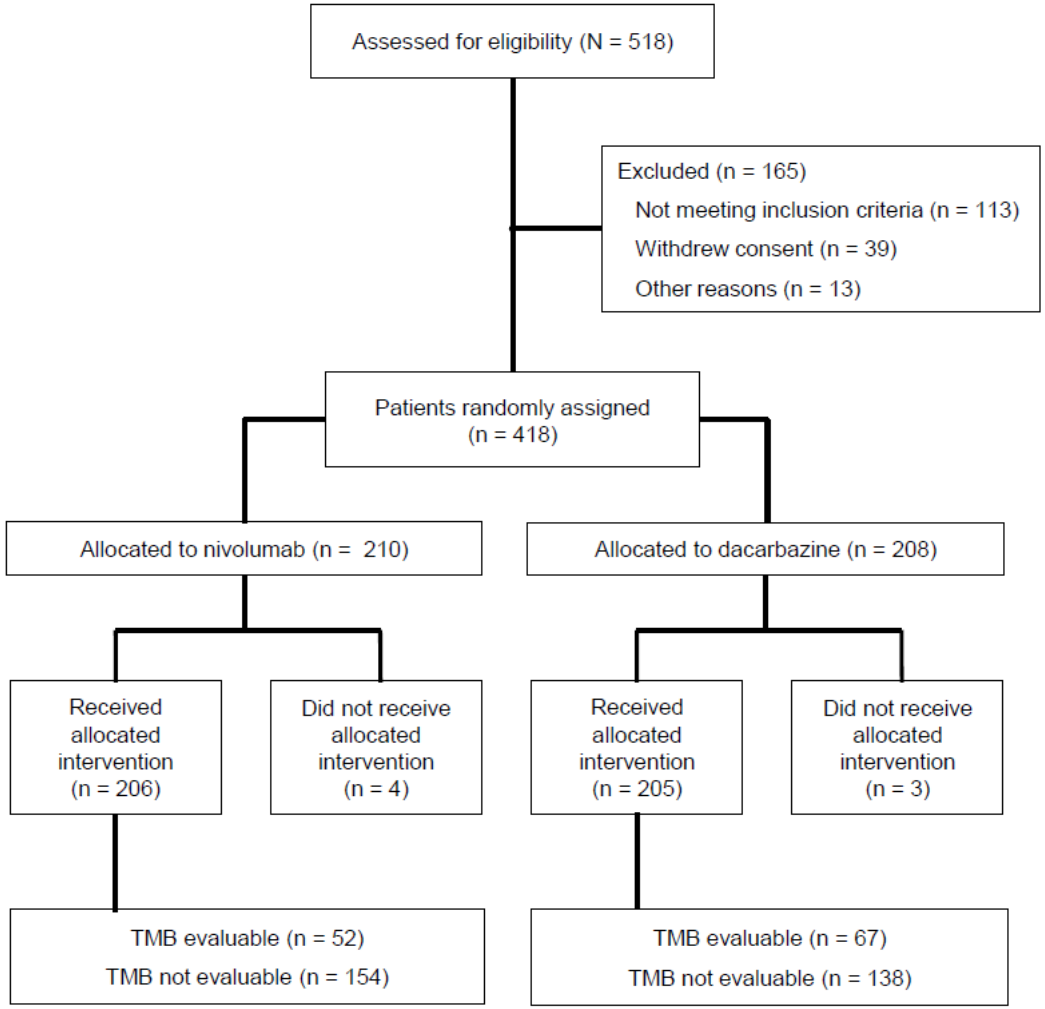
FIGURES

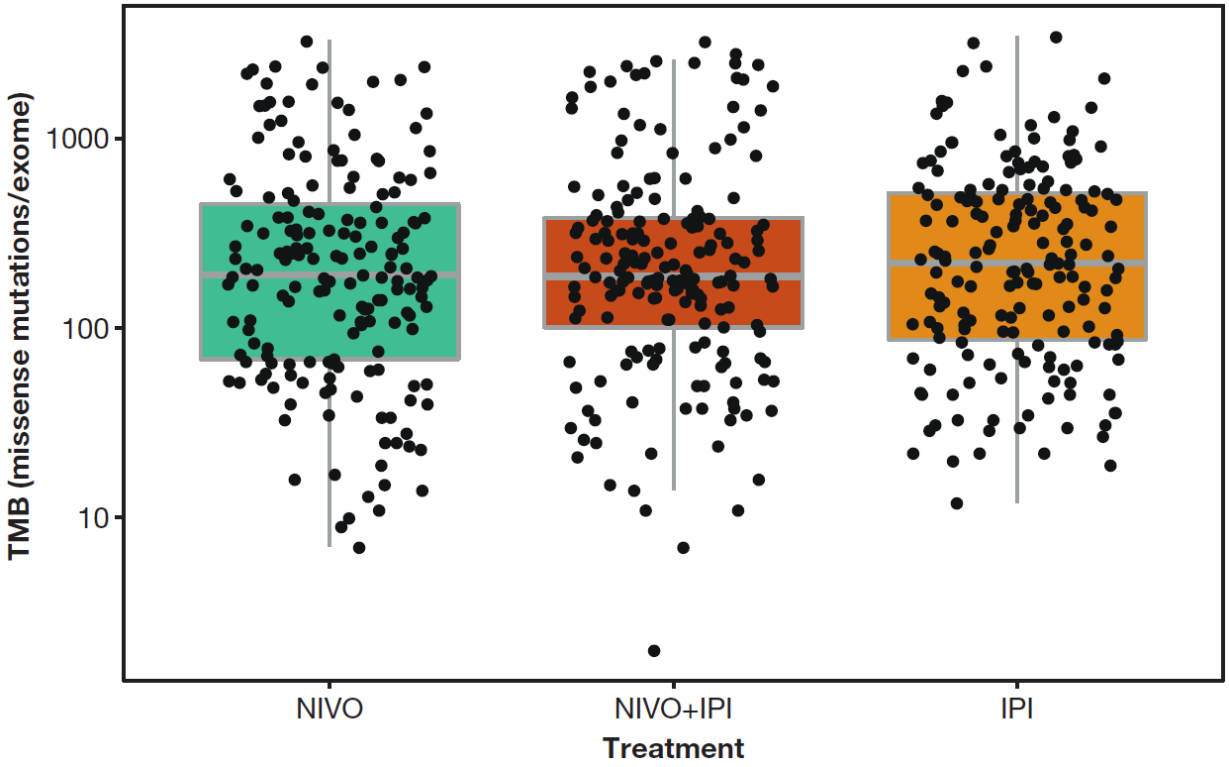
Supplementary Figure 1. CONSORT diagram for CheckMate 067.



Supplementary Figure 2. CONSORT diagram for CheckMate 066.

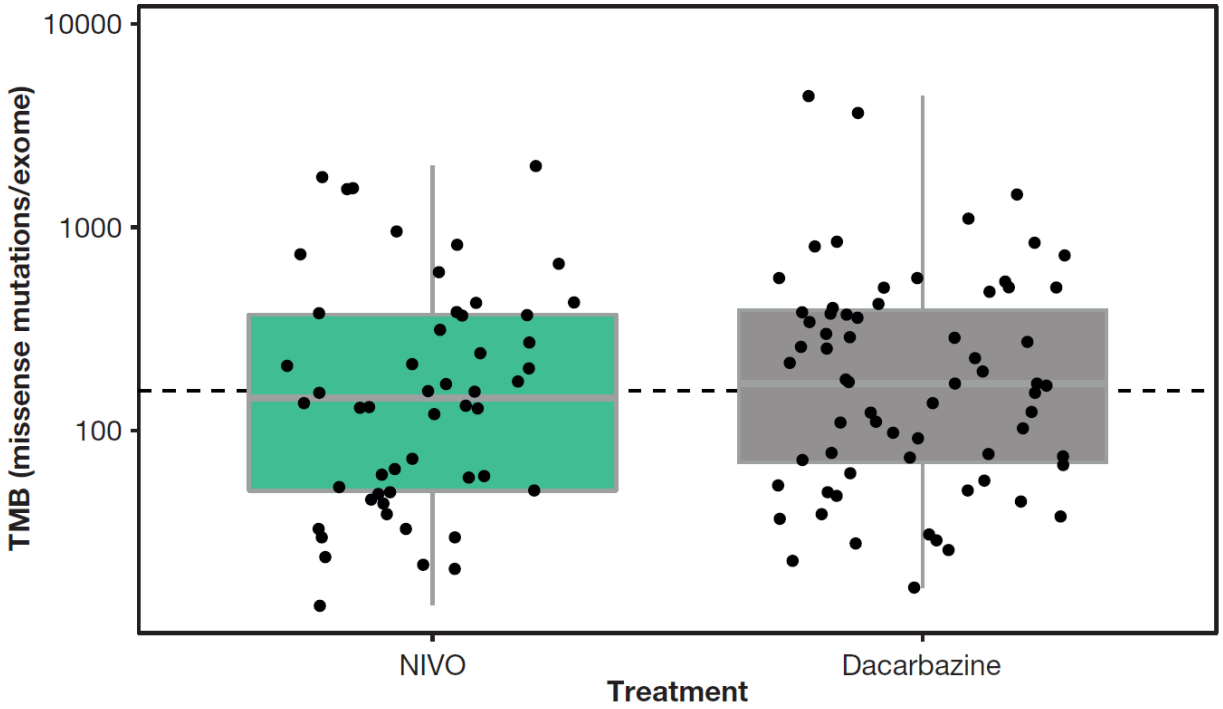


Supplementary Figure 3. TMB for TMB-evaluable patients in the NIVO (n = 176), NIVO+IPI (n = 184), and IPI (n = 178) arms of CheckMate 067. The median TMB for all evaluable patients was 203.5. Boxes extend from the first to third quartiles, the middle line shows the median, and the whiskers extend to the most extreme data point that is no more than 1.5 times the IQR from the box. IPI, ipilimumab; NIVO, nivolumab; TMB, tumor mutational burden.



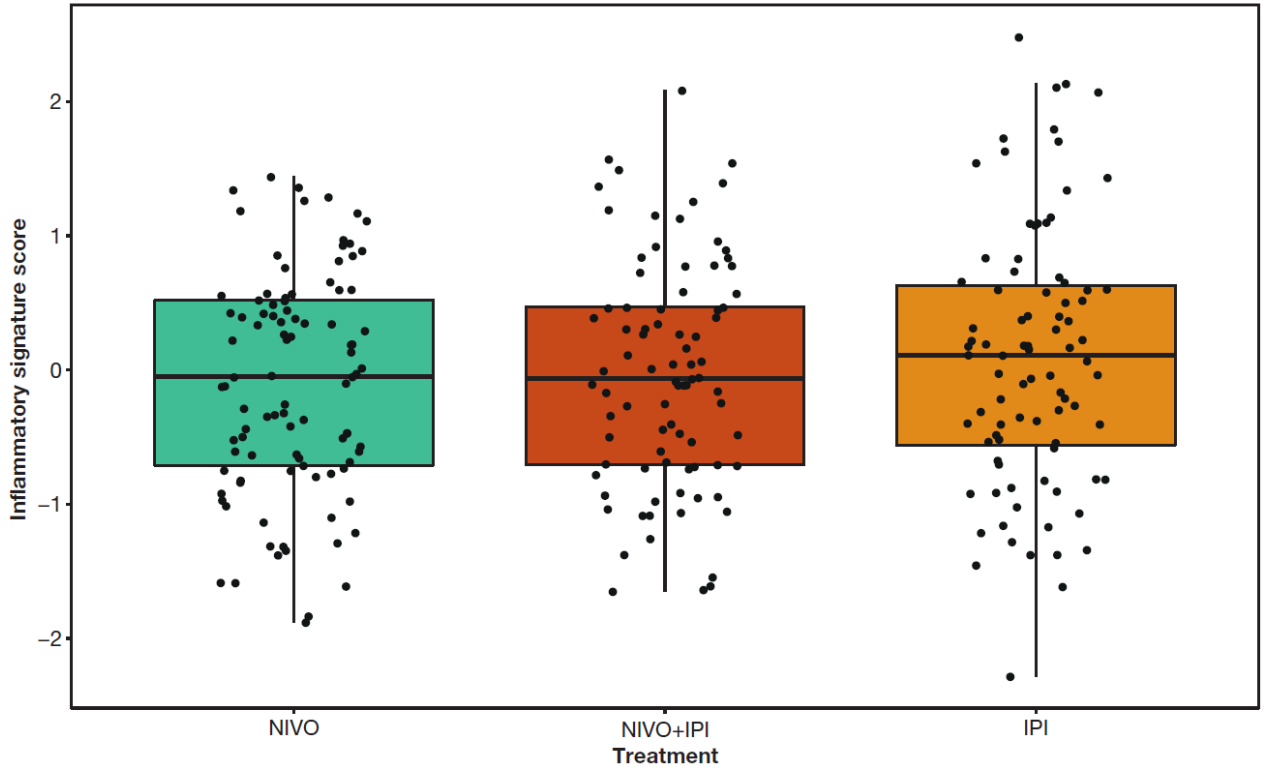
Treatment	Q1	Median	Q3
NIVO	68.5	191.0	449.8
NIVO+IPI	100.8	187.5	382.0
IPI	87.0	220.5	515.5

Supplementary Figure 4. TMB for TMB-evaluable patients in the NIVO (n = 52) and dacarbazine (n = 67) treatment arms of CheckMate 066. Dashed line represents the study median TMB value. The median TMB value for all evaluable patients was 157.0. Boxes extend from the first to third quartiles, the middle line shows the median, and the whiskers extend to the most extreme data point that is no more than 1.5 times the IQR from the box. NIVO, nivolumab; TMB, tumor mutational burden.



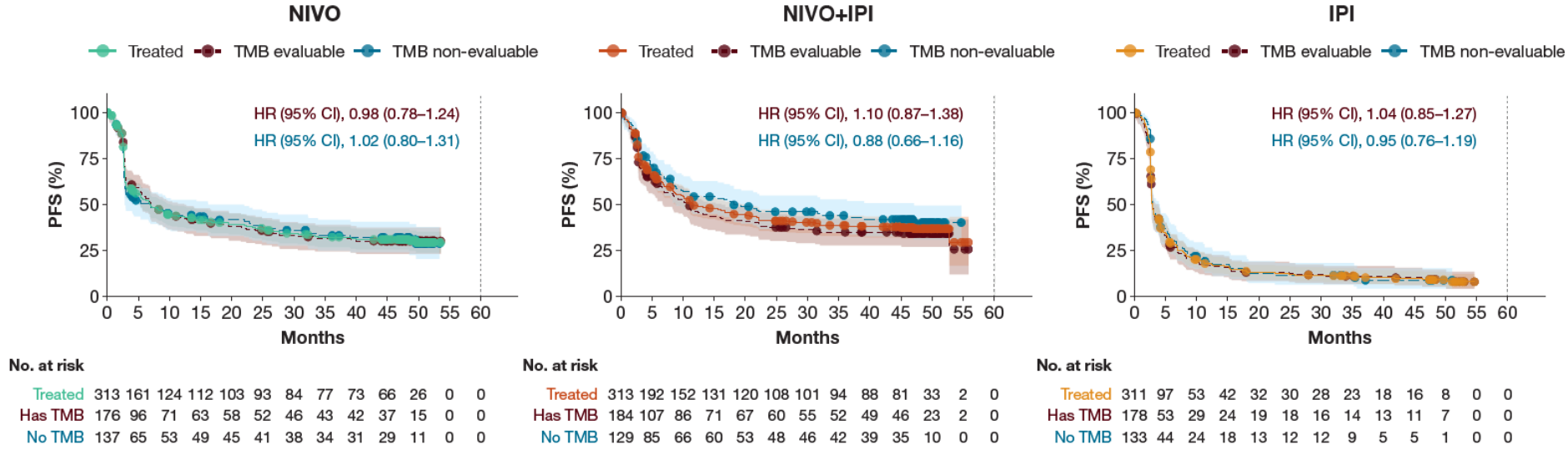
Treatment	Q1	Median	Q3
NIVO	50.8	145.5	373.0
Dacarbazine	70.0	171.0	392.5

Supplementary Figure 5. Distribution of inflammatory signature scores in the NIVO (n = 97), NIVO + IPI (n = 85), and IPI (n = 87) treatment arms of CheckMate 067. The median baseline inflammatory signature score for all evaluable patients was −0.04. Boxes extend from the first to third quartiles, the middle line shows the median, and the whiskers extend to the most extreme data point that is no more than 1.5 times the IQR from the box. IPI, ipilimumab; NIVO, nivolumab.

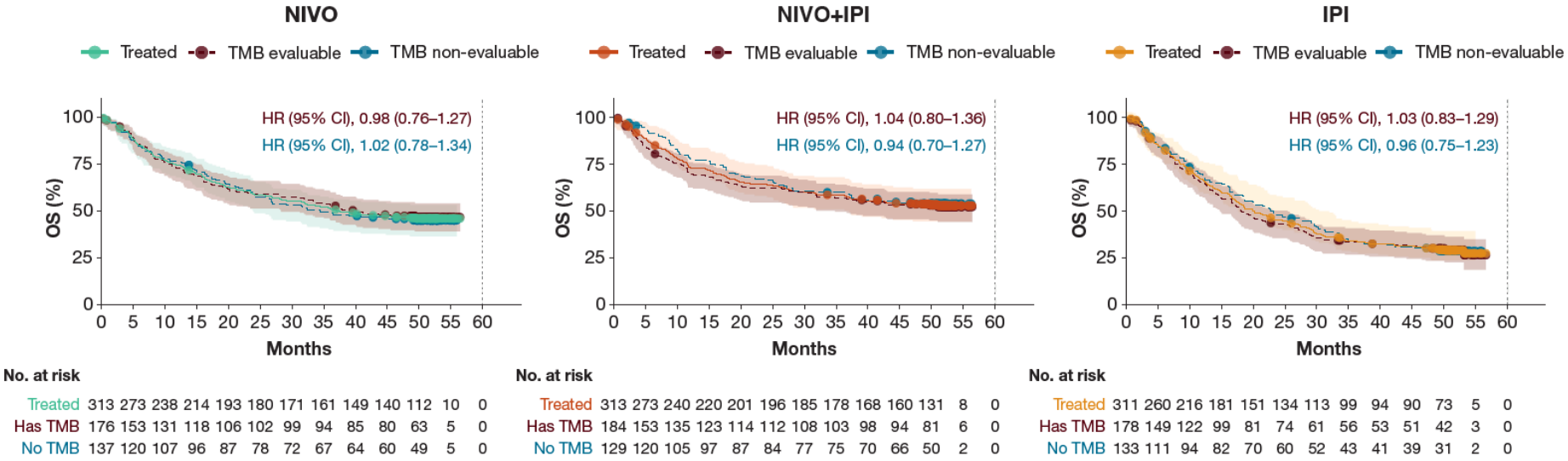


Treatment	Q1	Median	Q3
NIVO	−0.71	−0.05	0.52
NIVO+IPI	−0.70	−0.06	0.47
IPI	−0.56	−0.11	0.63

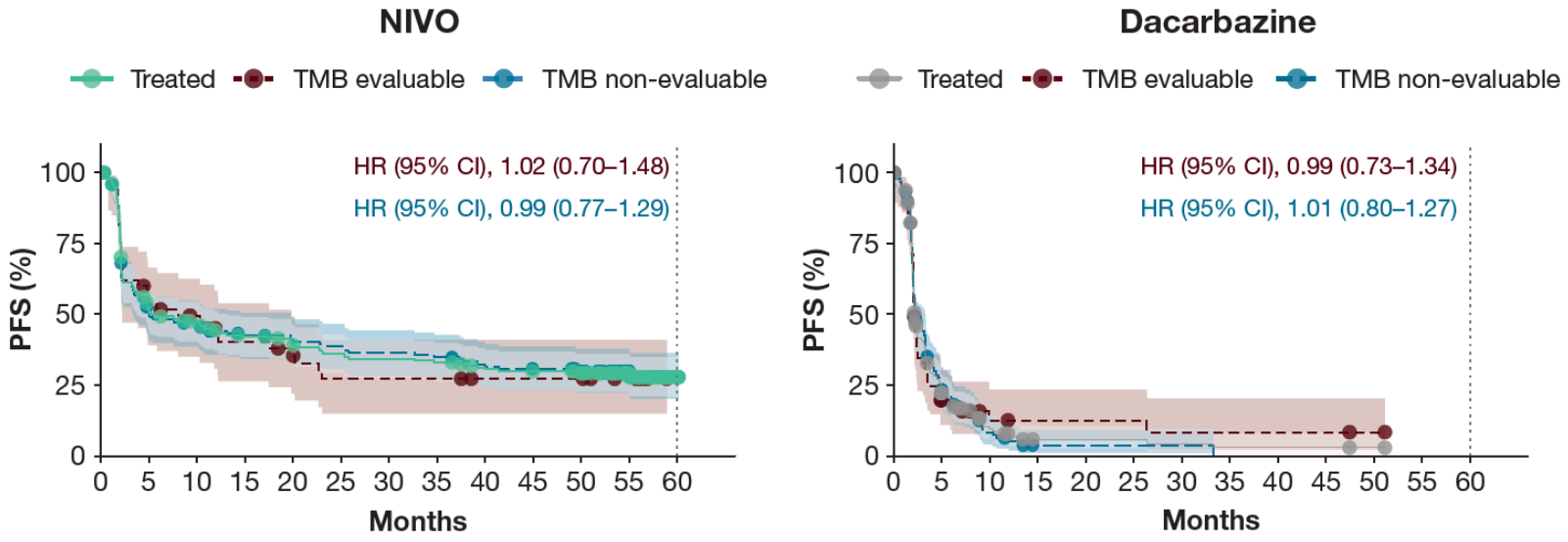
Supplementary Figure 6. Kaplan–Meier curves for PFS versus TMB availability by treatment arm for CheckMate 067. HRs (95% CI) for TMB evaluable versus non-evaluable were obtained with univariate Cox proportional hazards models. CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; PFS, progression-free survival; TMB, tumor mutational burden.



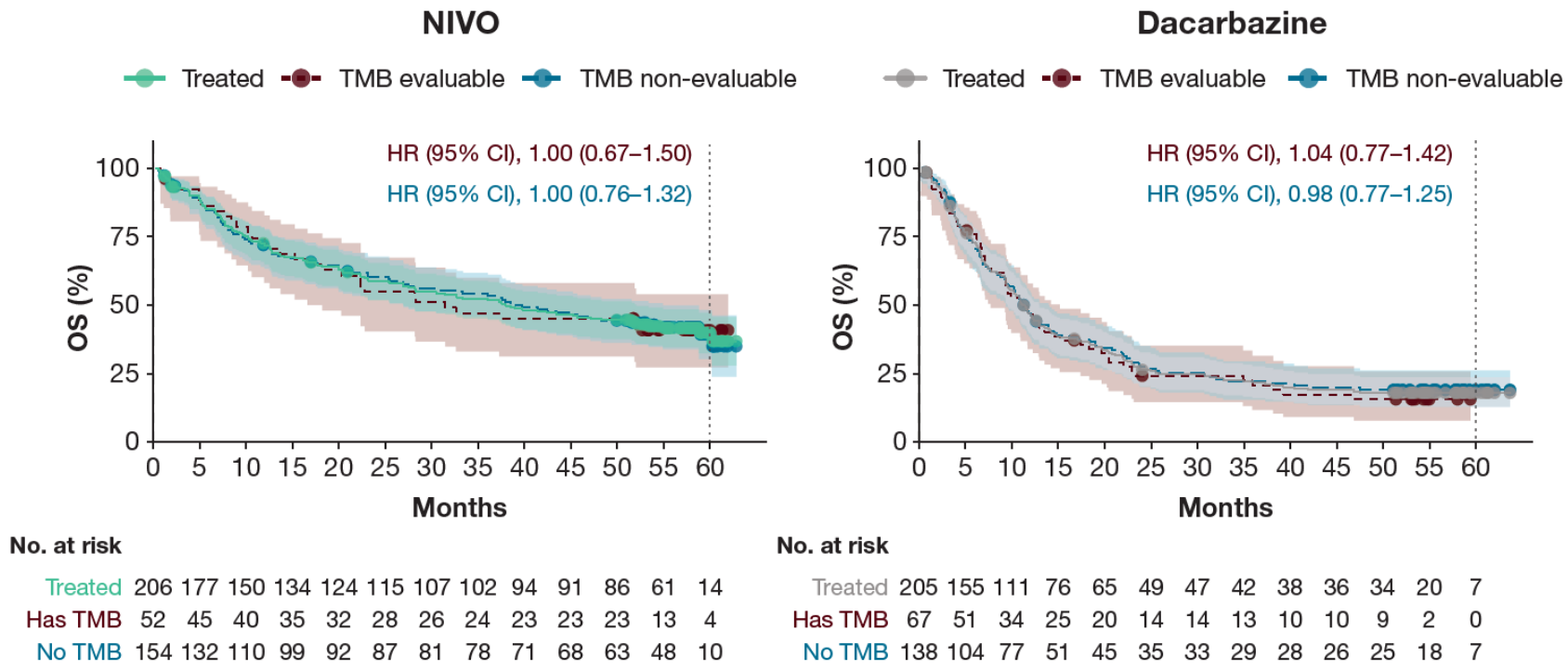
Supplementary Figure 7. Kaplan–Meier curves for OS versus TMB availability by treatment arm for CheckMate 067. HRs (95% CI) for TMB evaluable versus non-evaluable were obtained with univariate Cox proportional hazards models. CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; TMB, tumor mutational burden.



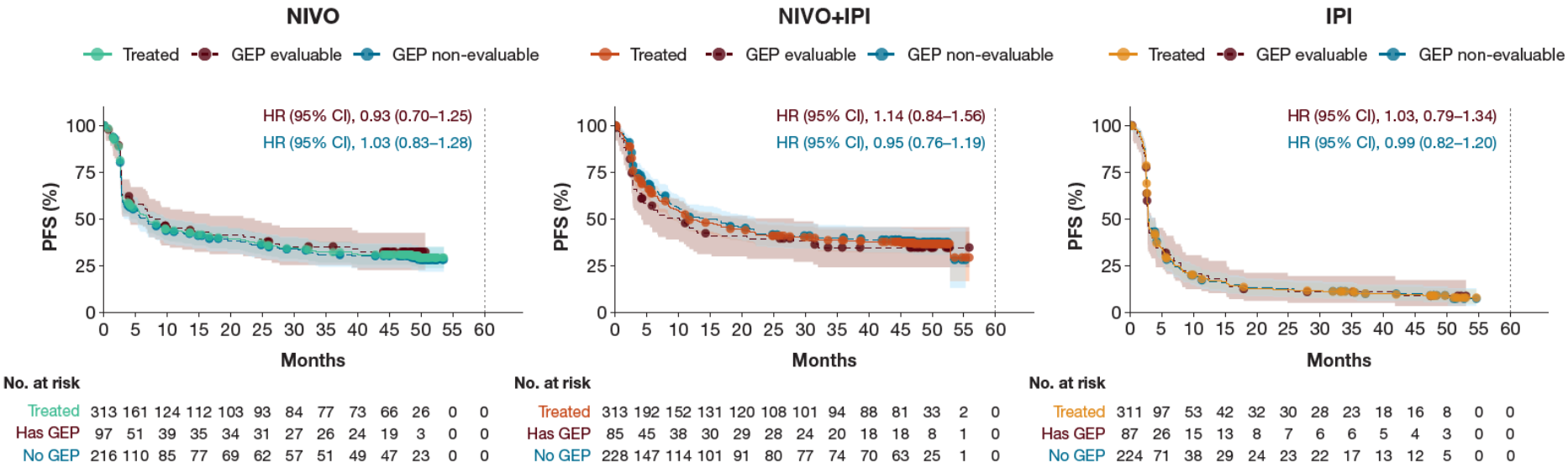
Supplementary Figure 8. Kaplan–Meier curves for PFS versus TMB availability by initial treatment for CheckMate 066. HRs (95% CI) for TMB evaluable versus non-evaluable were obtained with univariate Cox proportional hazards models. CI, confidence interval; HR, hazard ratio; NIVO, nivolumab; PFS, progression-free survival; TMB, tumor mutational burden.



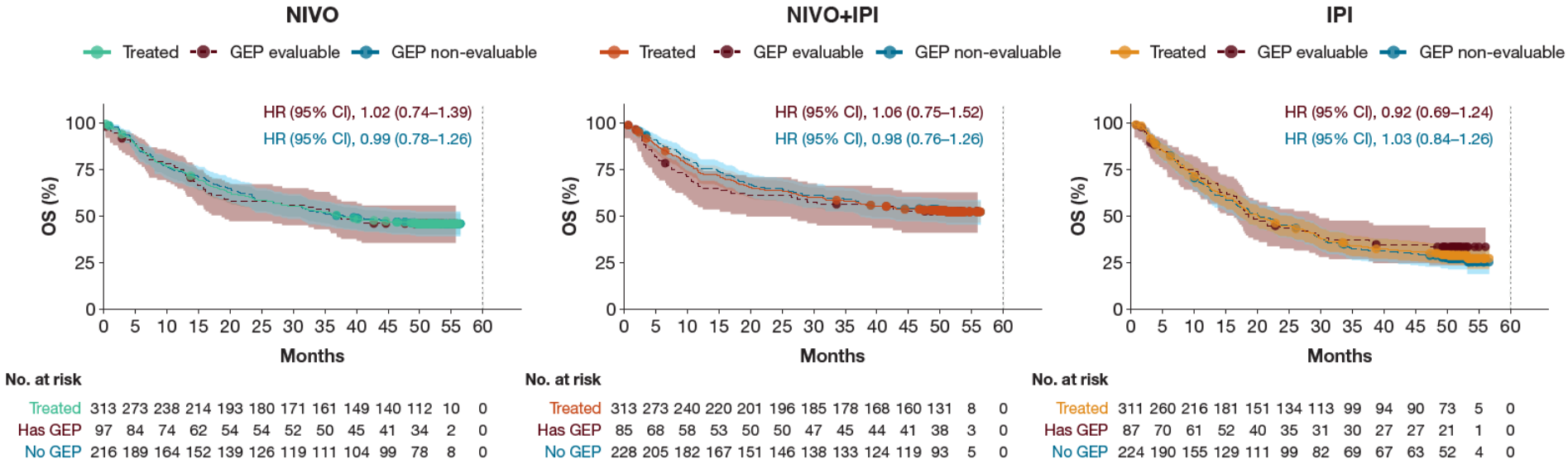
Supplementary Figure 9. Kaplan–Meier curves for OS versus TMB availability by initial treatment for CheckMate 066. HRs (95% CI) for TMB evaluable versus non-evaluable were obtained with univariate Cox proportional hazards models. CI, confidence interval; HR, hazard ratio; NIVO, nivolumab; OS, overall survival; TMB, tumor mutational burden.



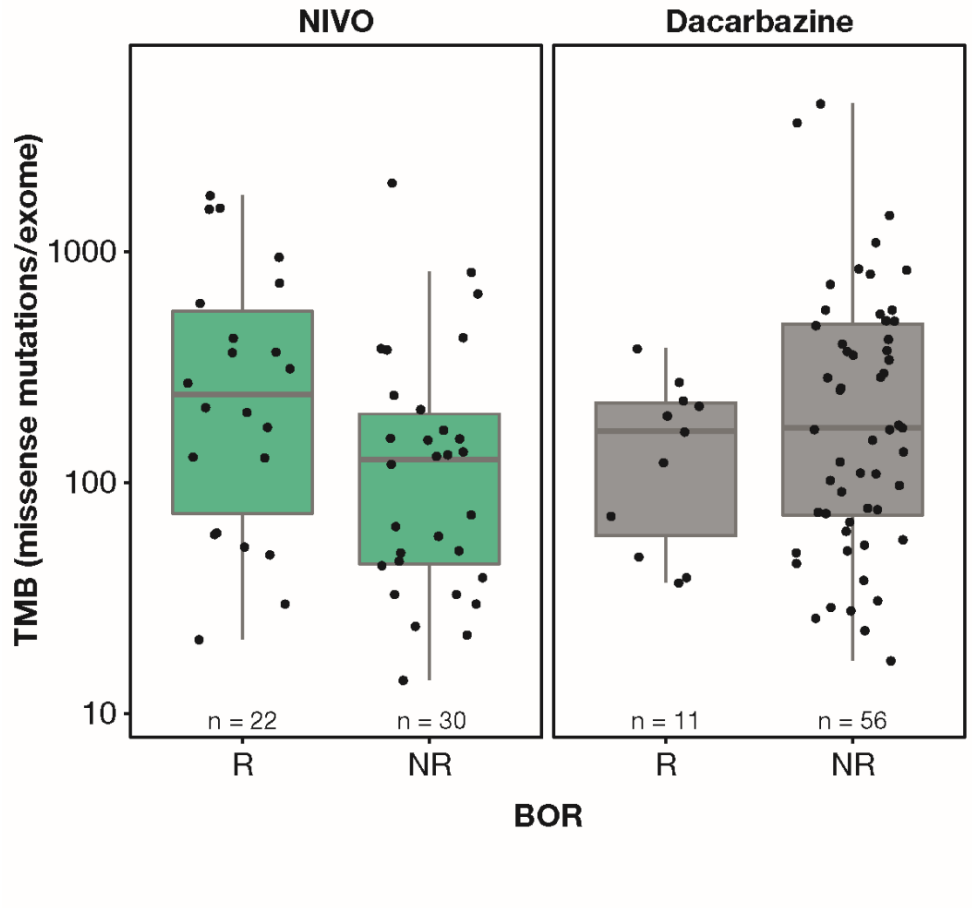
Supplementary Figure 10. Kaplan–Meier curves for PFS versus inflammatory signature score availability by treatment arm for CheckMate 067. HRs (95% CI) for GEP evaluable versus non-evaluable were obtained with univariate Cox proportional hazards models. CI, confidence interval; GEP, gene expression profiling; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; PFS, progression-free survival.



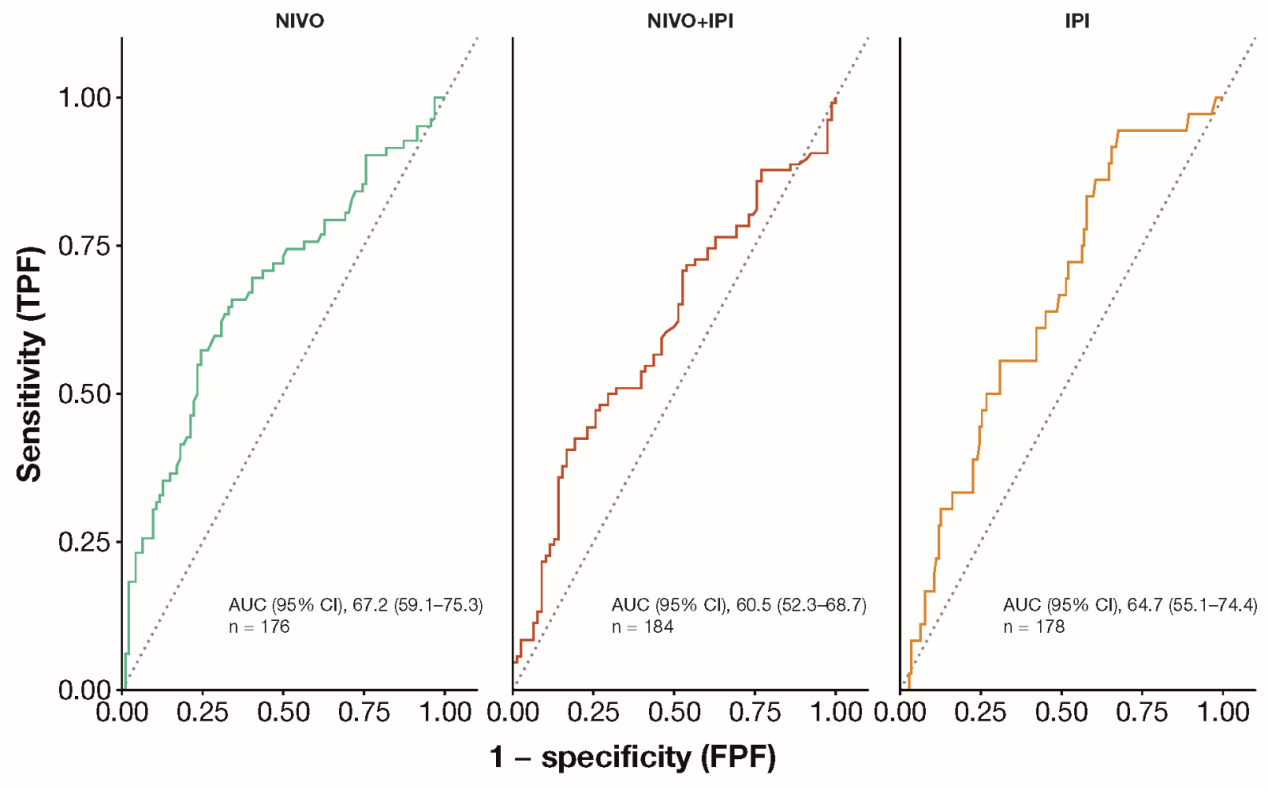
Supplementary Figure 11. Kaplan–Meier curves for OS versus inflammatory signature score availability by treatment arm for CheckMate 067. HRs (95% CI) for GEP evaluable versus non-evaluable were obtained with univariate Cox proportional hazards models. CI, confidence interval; GEP, gene expression profiling; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival.



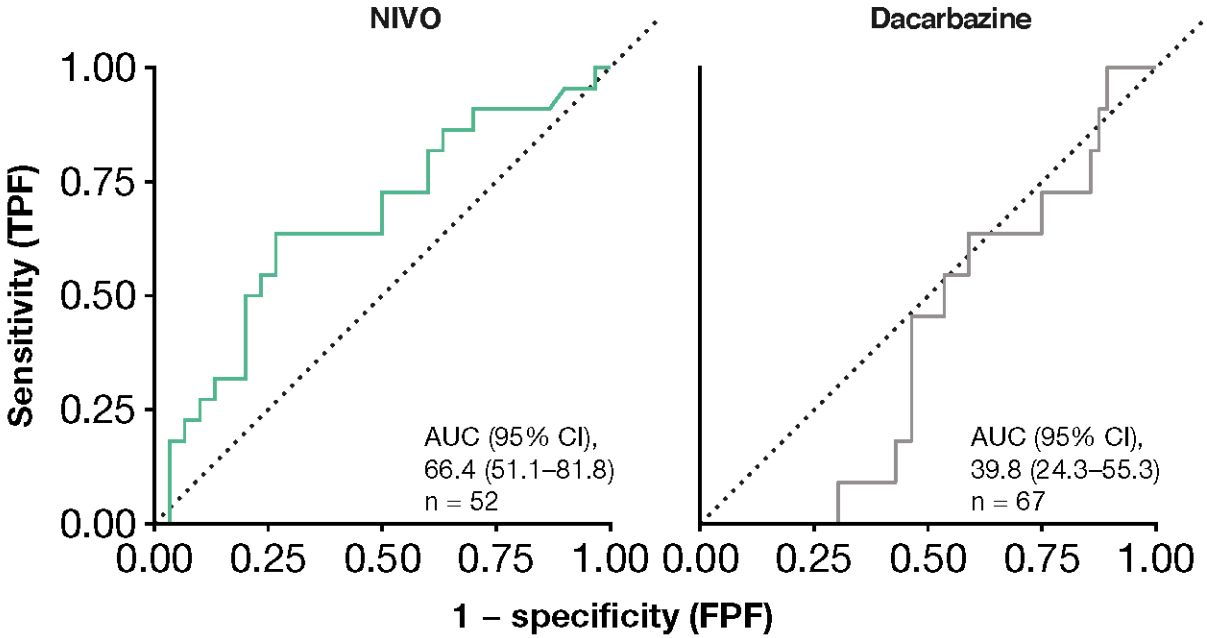
Supplementary Figure 12. Distribution of TMB by BOR with NIVO or dacarbazine in CheckMate 066. Number of responders and nonresponders by treatment arm are indicated on the figure. Boxes extend from the first to third quartiles, the middle line shows the median, and the whiskers extend to the most extreme data point that is no more than 1.5 times the IQR from the box. BOR, best overall response; NIVO, nivolumab; NR, nonresponders; R, responders; TMB, tumor mutational burden.



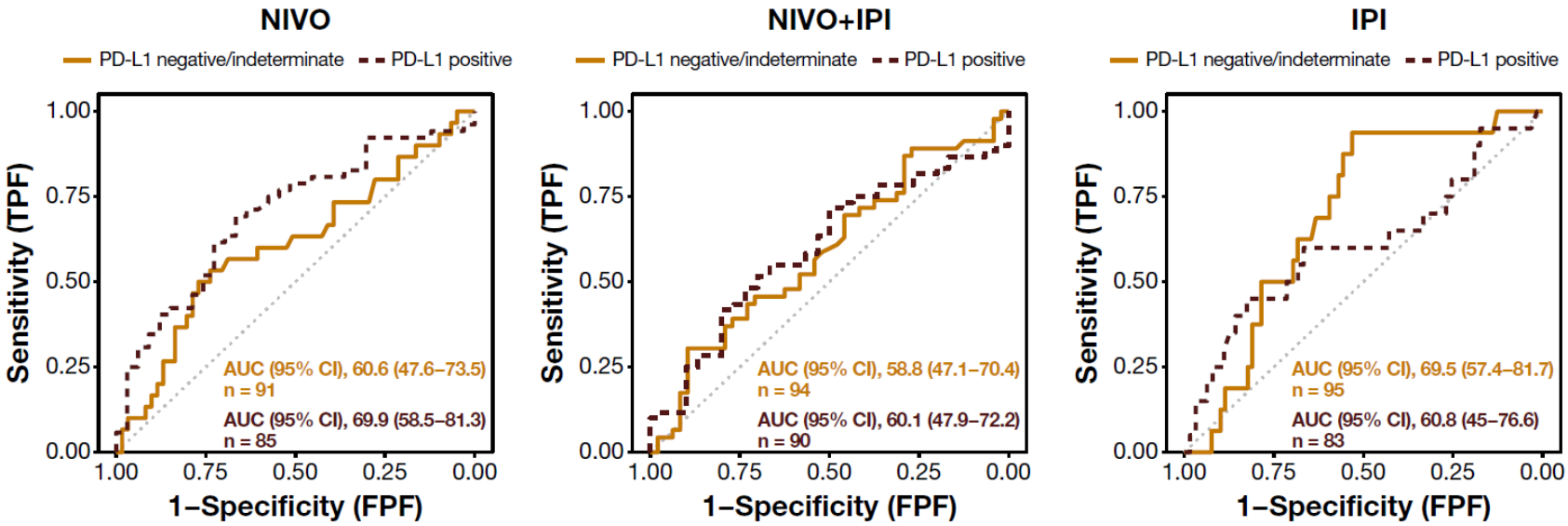
Supplementary Figure 13. ROC curves illustrating the ability of TMB to predict response in CheckMate 067. AUC, area under the curve; CI, confidence interval; FPF, false positive fraction; IPI, ipilimumab; NIVO, nivolumab; ROC, receiver operating characteristic; TMB, tumor mutational burden; TPF, true positive fraction.



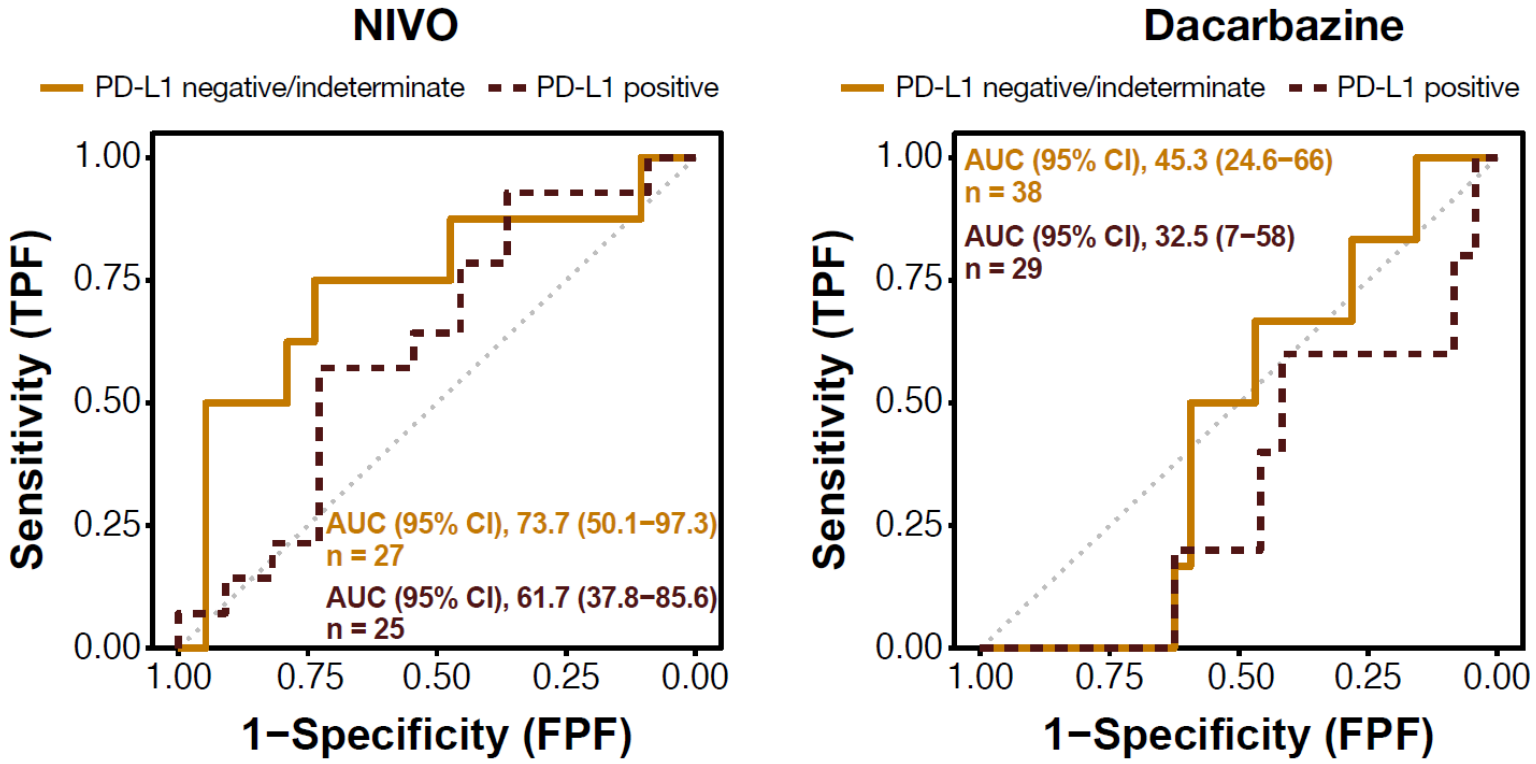
Supplementary Figure 14. ROC curves illustrating the ability of TMB to predict response in CheckMate 066. AUC, area under the curve; CI, confidence interval; FPF, false positive fraction; NIVO, nivolumab; ROC, receiver operating characteristic; TMB, tumor mutational burden; TPF, true positive fraction.



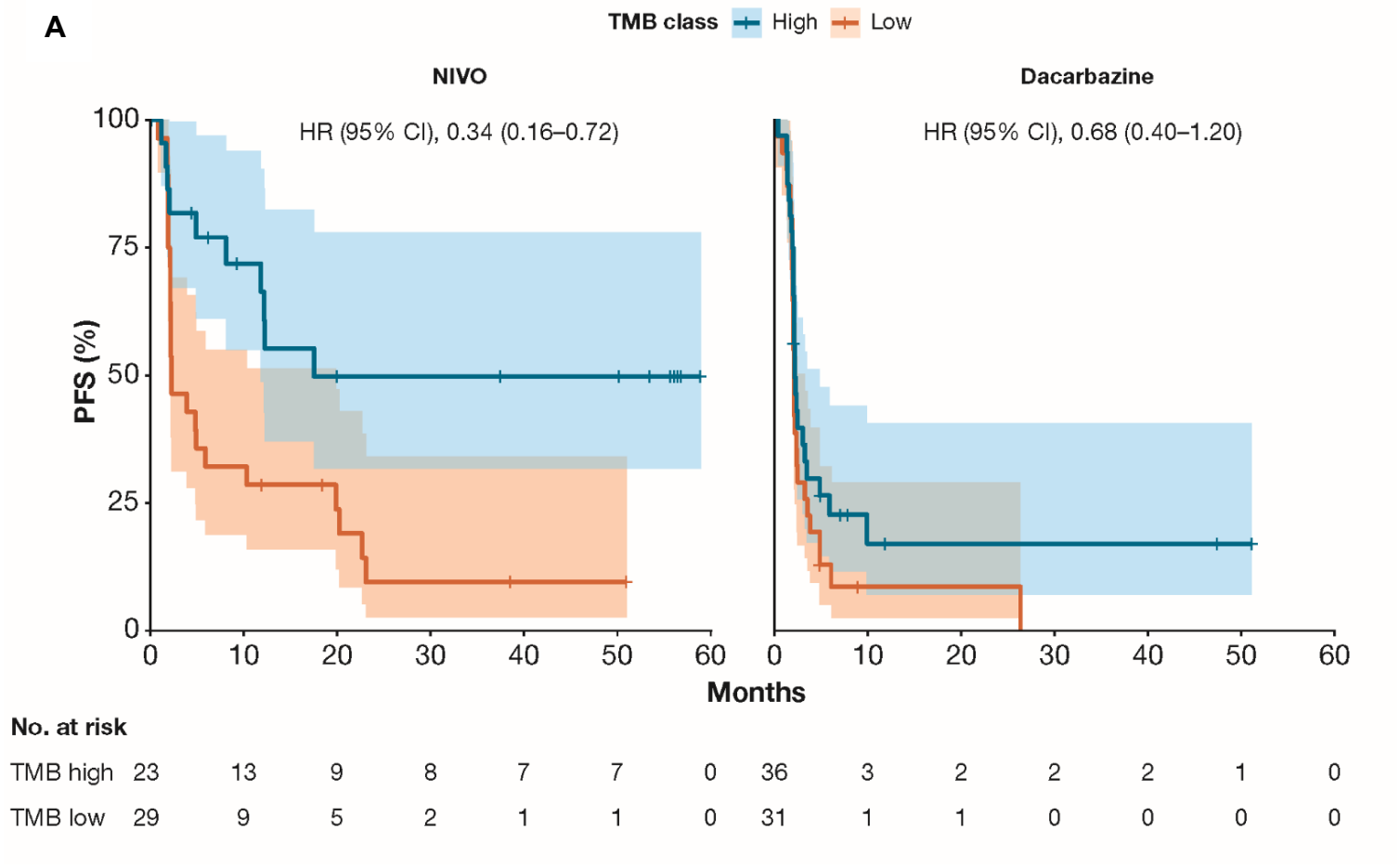
Supplementary Figure 15. ROC curves illustrating the ability of TMB to predict response by ≥ 5% TC PD-L1 versus < 5% TC/indeterminate PD-L1 expression in CheckMate 067. AUC, area under the curve; CI, confidence interval; FPF, false positive fraction; IPI, ipilimumab; NIVO, nivolumab; PD-L1, programmed death ligand 1; ROC, receiver operating characteristic; TC, tumor cell; TMB, tumor mutational burden; TPF, true positive fraction.

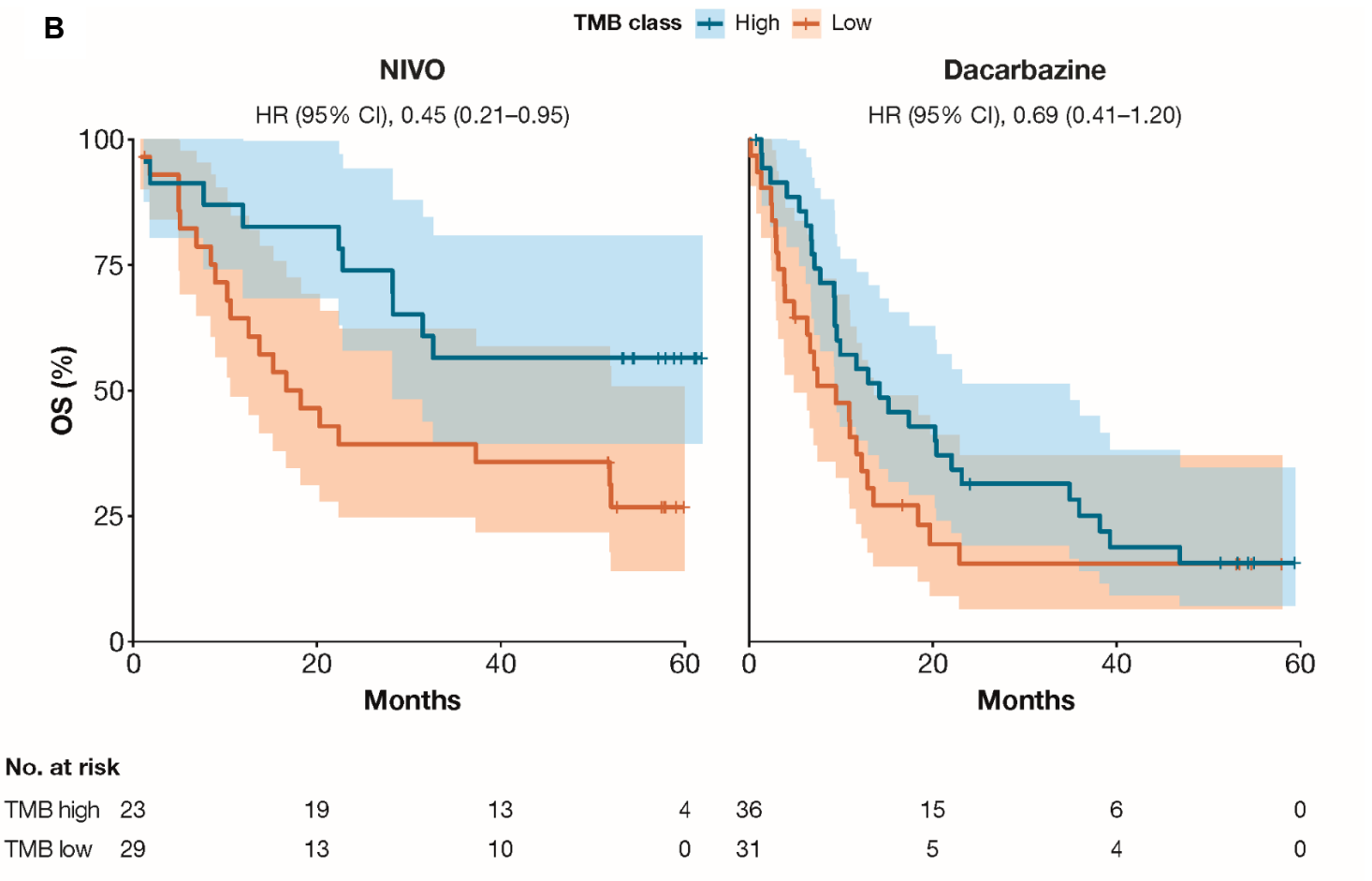


Supplementary Figure 16. ROC curves illustrating the ability of TMB to predict response by ≥ 5% TC PD-L1 versus < 5% TC/indeterminate PD-L1 expression in CheckMate 066. AUC, area under the curve; CI, confidence interval; FPF, false positive fraction; NIVO, nivolumab; PD-L1, programmed death ligand 1; ROC, receiver operating characteristic; TC, tumor cell; TMB, tumor mutational burden; TPF, true positive fraction.

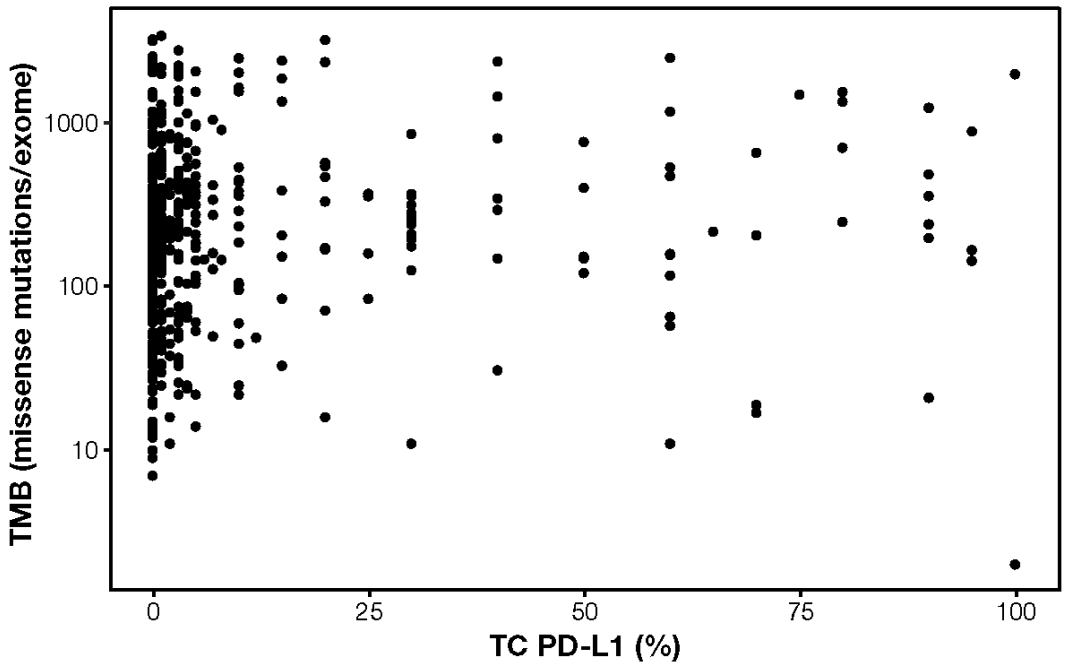


Supplementary Figure 17. Kaplan–Meier curve for (A) PFS and (B) OS comparing TMB-high (> median) or TMB-low (≤ median) status patient subgroups in CheckMate 066. HRs (95% CI) for high versus low TMB were obtained with univariate Cox proportional hazards models. CI, confidence interval; HR, hazard ratio; NIVO, nivolumab; OS, overall survival; PFS, progression-free survival; TMB, tumor mutational burden.

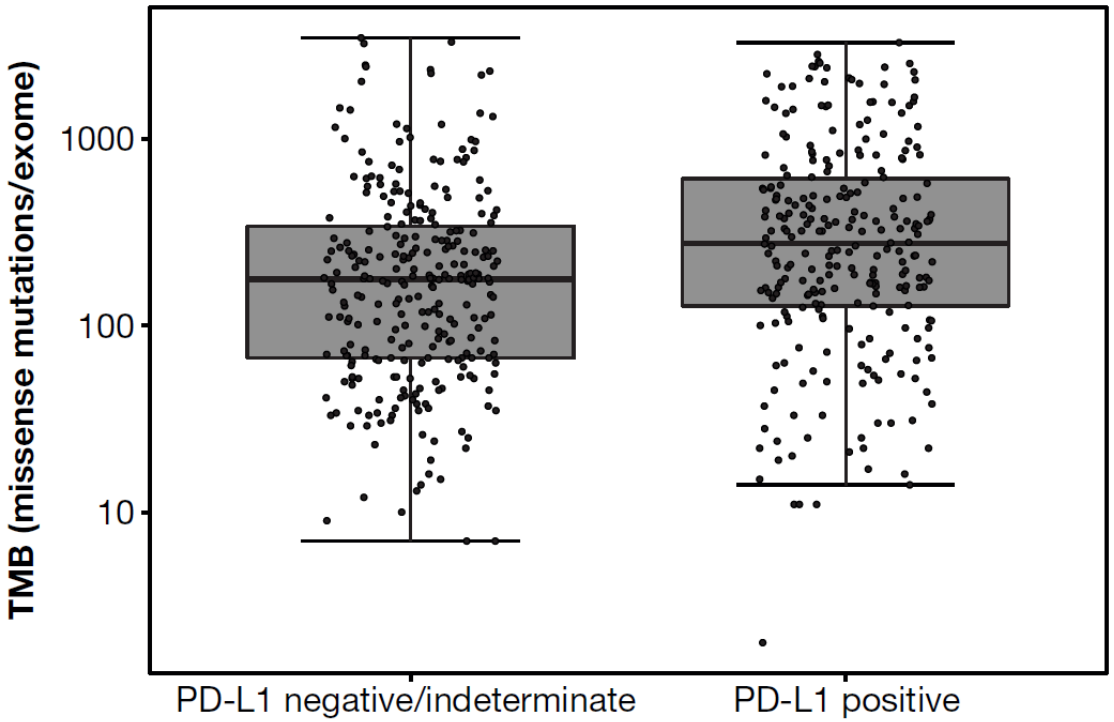




Supplementary Figure 18. Scatter plot illustrating the distribution of TMB versus tumor % PD-L1 expression for TMB-evaluable and PD-L1–evaluable patients from CheckMate 067 (n = 538). PD-L1, programmed death ligand 1; TC, tumor cell; TMB, tumor mutational burden.

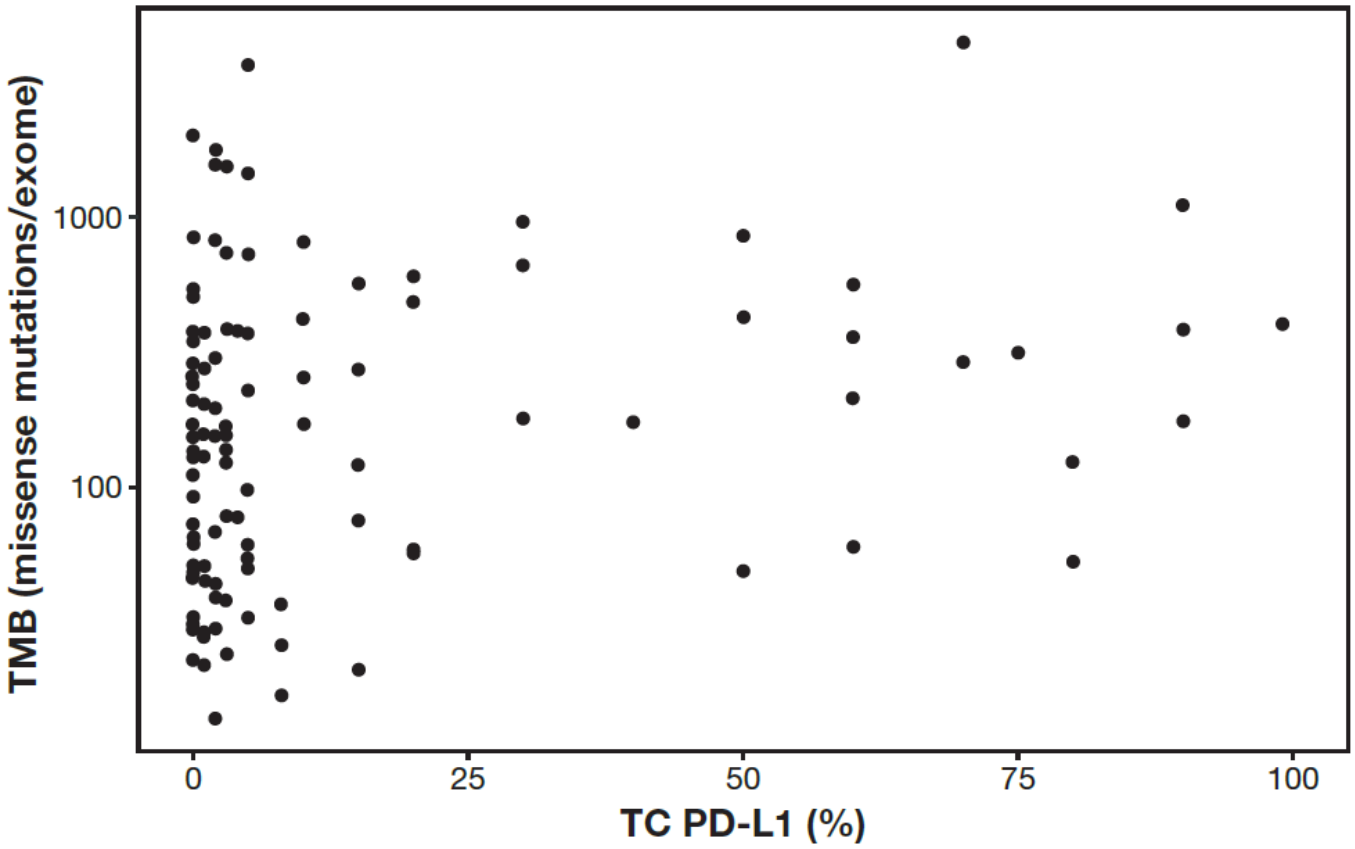


Supplementary Figure 19. Distribution of TMB by ≥ 5% TC PD-L1 (n = 258) versus < 5% TC/indeterminate PD-L1 (n = 280) expression in CheckMate 067. Boxes extend from the first to third quartiles, the middle line shows the median, and the whiskers extend to the most extreme data point that is no more than 1.5 times the IQR from the box. PD-L1, programmed death ligand 1; TC, tumor cell; TMB, tumor mutational burden.

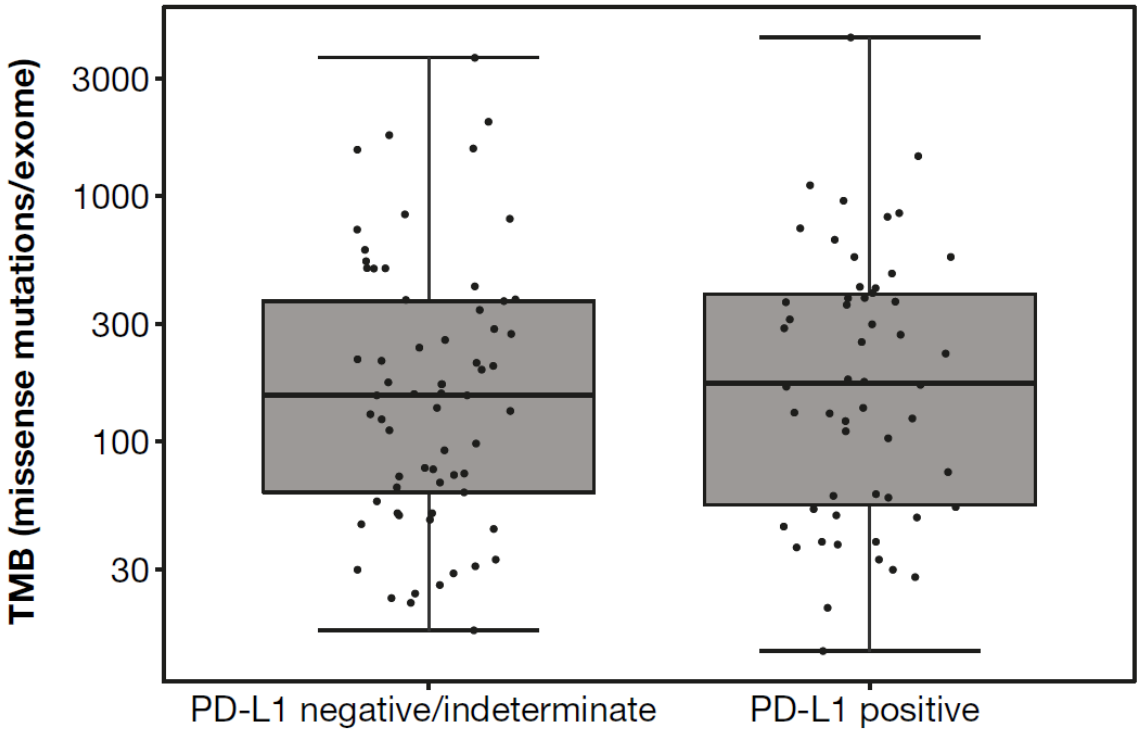


PD-L1	Q1	Median	Q3
Negative/indeterminate	67.0	177.0	340.3
Positive	127.3	275.0	611.3

Supplementary Figure 20. Scatter plot illustrating the distribution of TMB versus tumor % PD-L1 expression for TMB-evaluable and PD-L1–evaluable patients from CheckMate 066 (n = 119). PD-L1, programmed death ligand 1; TC, tumor cell; TMB, tumor mutational burden.

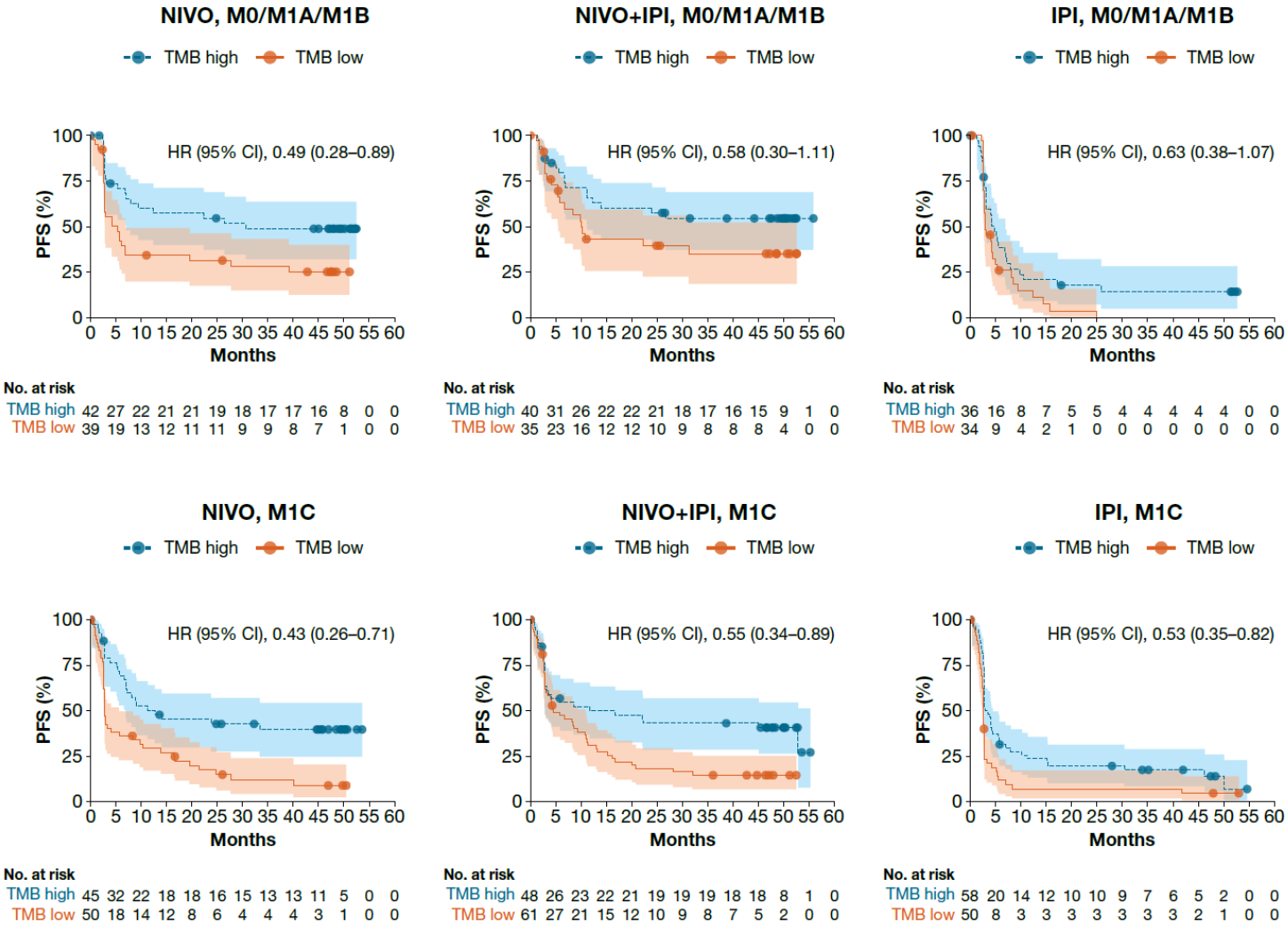


Supplementary Figure 21. Distribution of TMB by ≥ 5% TC PD-L1 (n = 54) versus < 5% TC/indeterminate PD-L1 (n = 65) expression in CheckMate 066. Boxes extend from the first to third quartiles, the middle line shows the median, and the whiskers extend to the most extreme data point that is no more than 1.5 times the IQR from the box. PD-L1, programmed death ligand 1; TC, tumor cell; TMB, tumor mutational burden.

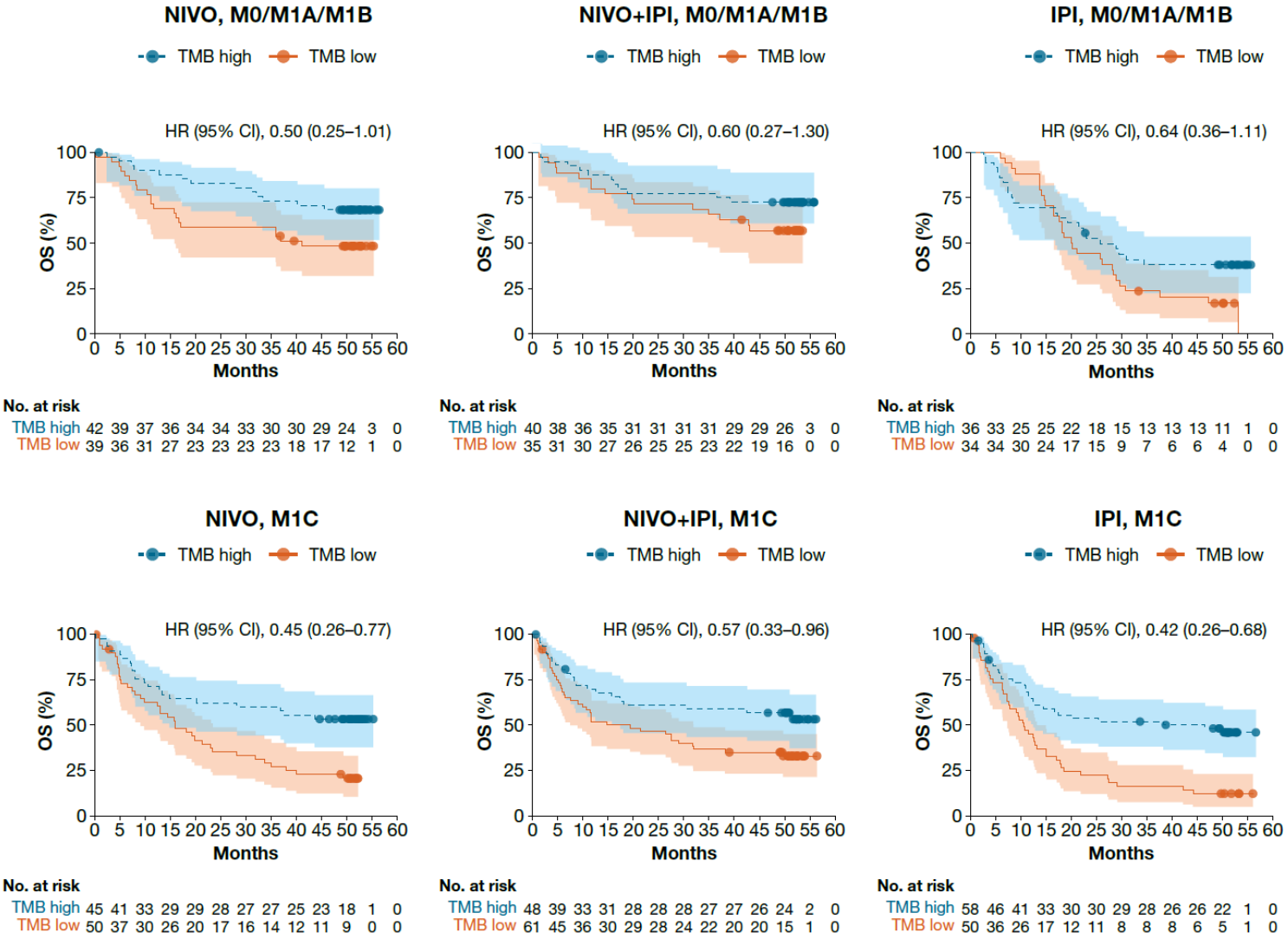


PD-L1	Q1	Median	Q3
Negative/indeterminate	62.0	154.0	373.0
Positive	55.3	172.5	397.5

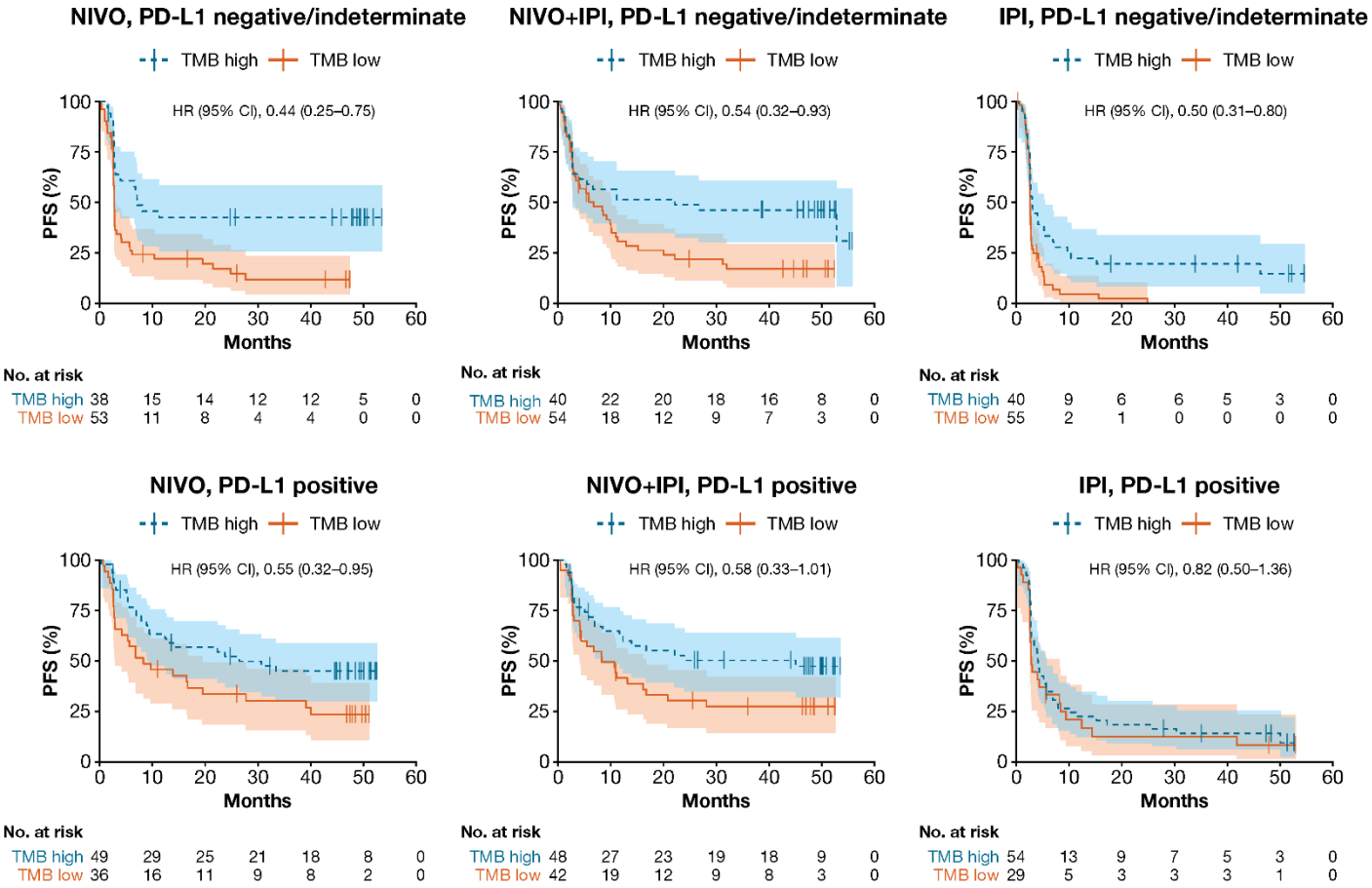
Supplementary Figure 22. Kaplan–Meier curves for PFS by TMB status and metastatic stage in CheckMate 067. HRs (95% CI) for high versus low TMB were obtained with univariate Cox proportional hazards models. CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; PFS, progression-free survival; TMB, tumor mutational burden.



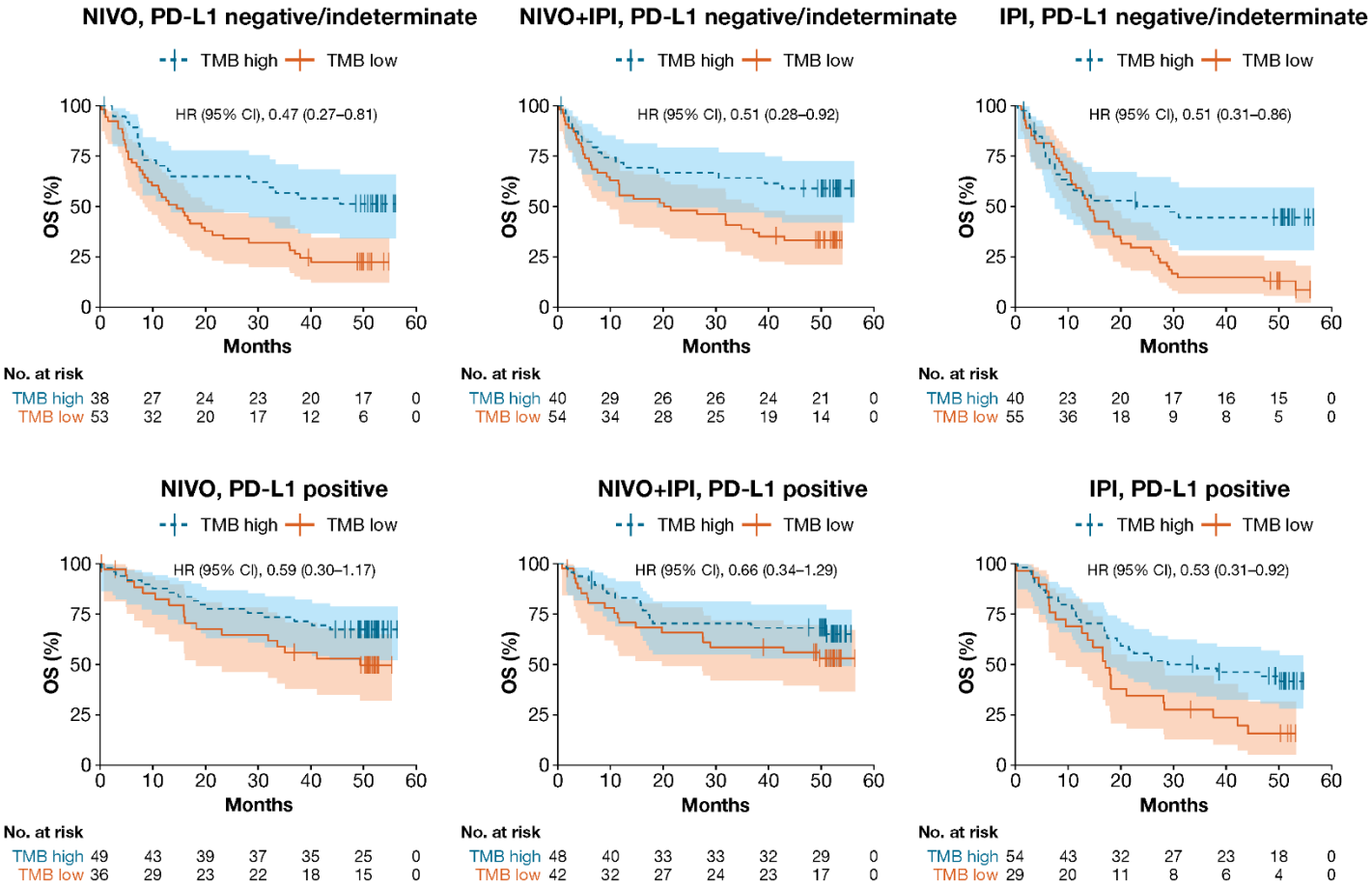
Supplementary Figure 23. Kaplan–Meier curves for OS by TMB status and metastatic stage in CheckMate 067. HRs (95% CI) for high versus low TMB were obtained with univariate Cox proportional hazards models. CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; TMB, tumor mutational burden.



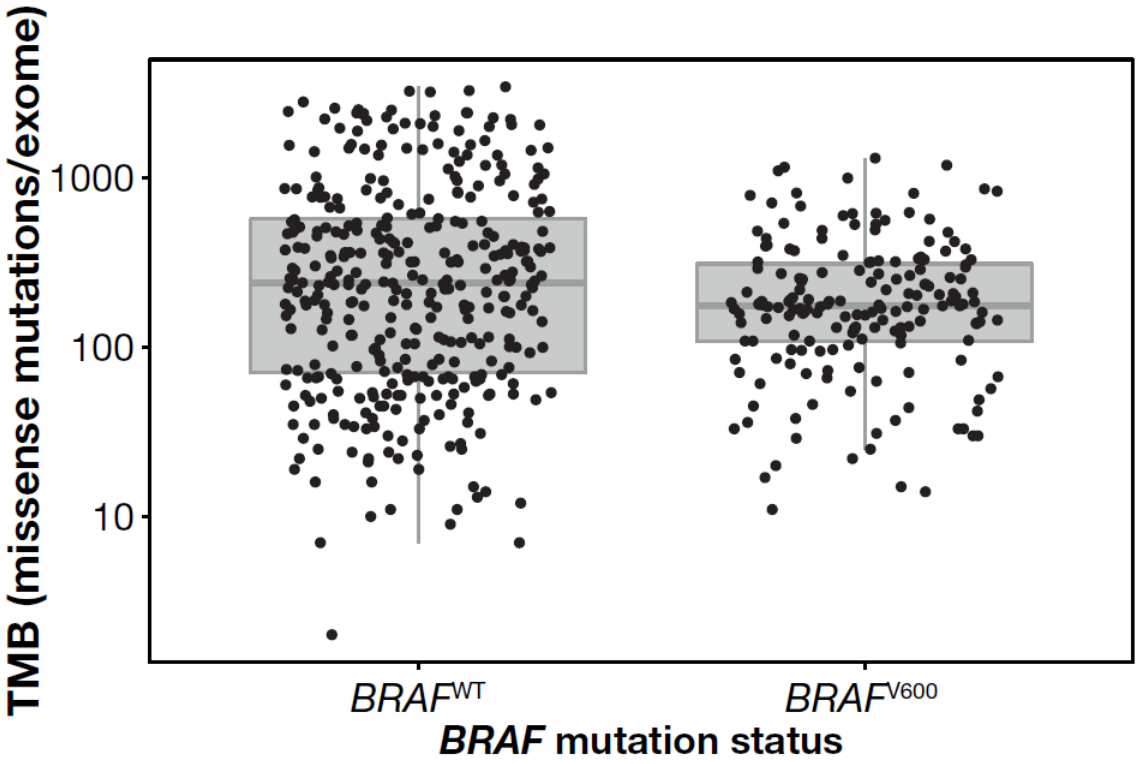
Supplementary Figure 24. Kaplan–Meier curves for PFS by TMB status and PD-L1 expression in CheckMate 067. HRs (95% CI) for high versus low TMB were obtained with univariate Cox proportional hazards models. CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; PD-L1, programmed death ligand 1; PFS, progression-free survival; TMB, tumor mutational burden.



Supplementary Figure 25. Kaplan–Meier curves for OS by TMB status and PD-L1 expression in CheckMate 067. HRs (95% CI) for high versus low TMB were obtained with univariate Cox proportional hazards models. CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death ligand 1; TMB, tumor mutational burden.

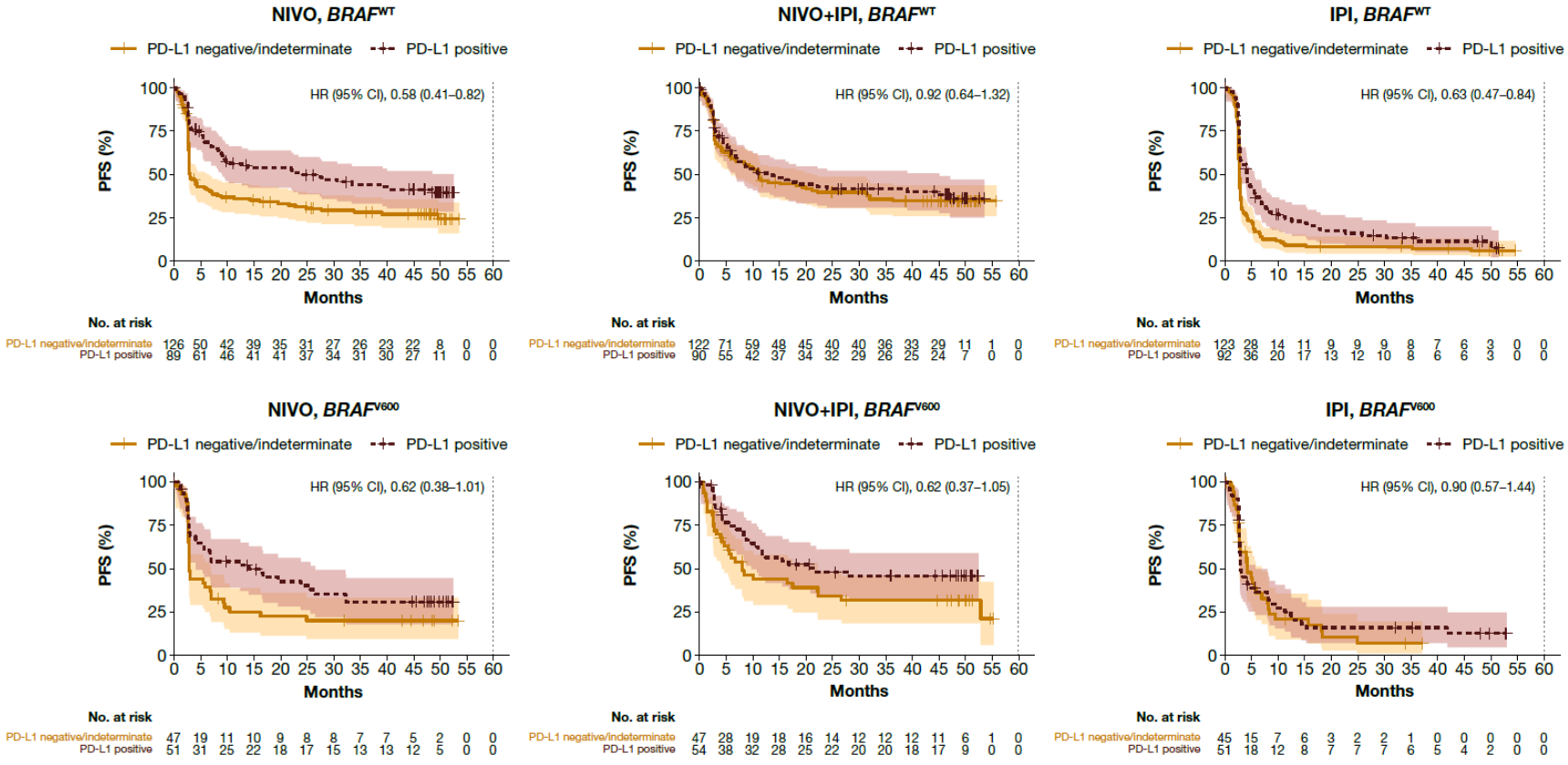


Supplementary Figure 26. Distribution of TMB for patients with *BRAF*^{WT} tumors (n = 359) and *BRAF*^{V600} tumors (n = 179) in CheckMate 067. Boxes extend from the first to third quartiles, the middle line shows the median, and the whiskers extend to the most extreme data point that is no more than 1.5 times the IQR from the box. TMB, tumor mutational burden; WT, wild-type.

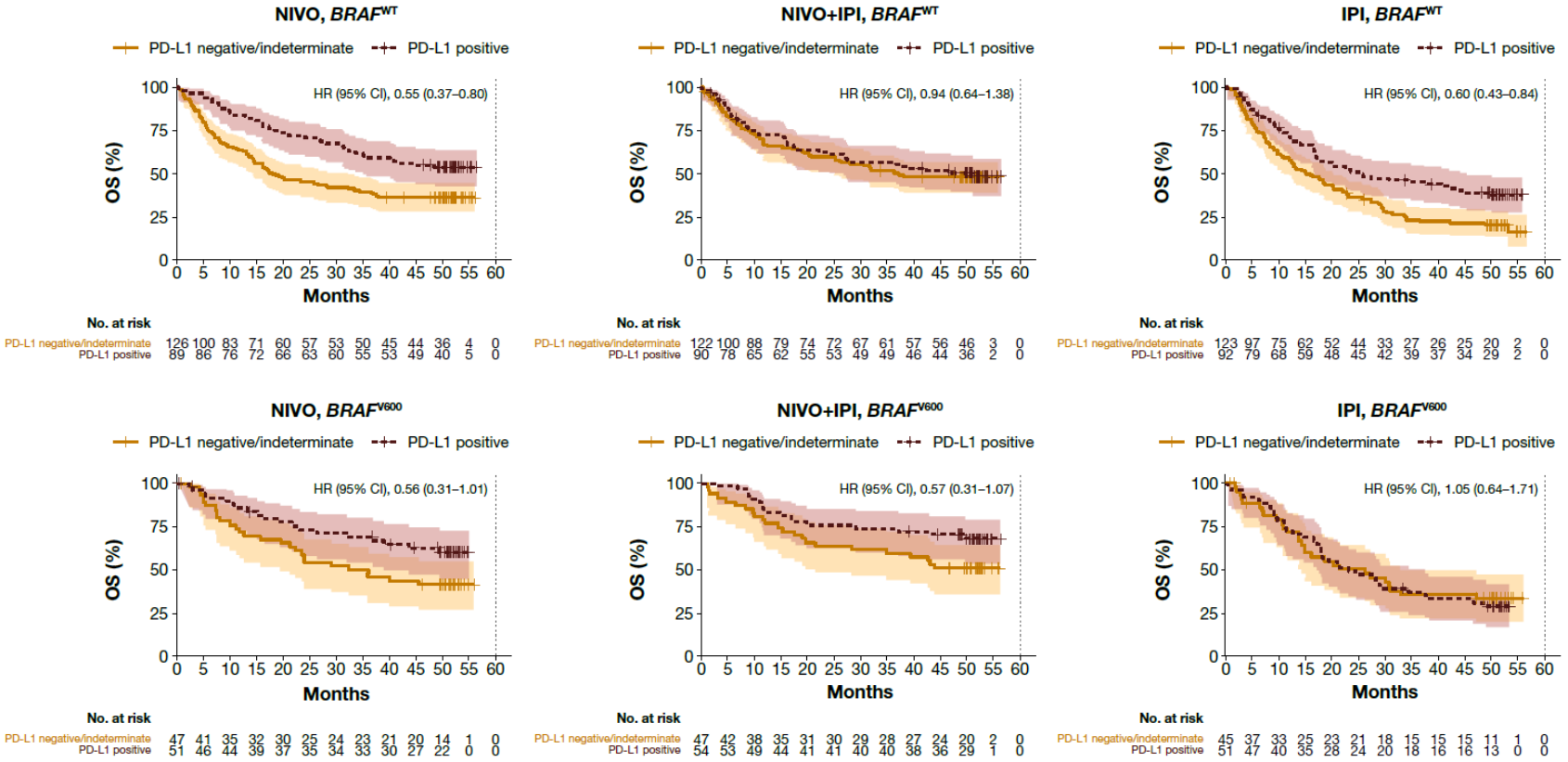


BRAF V600 mutation status	Q1	Median	Q3
BRAF^{WT}	71.0	240.0	573.0
BRAF^{V600}	109.0	176.0	312.5

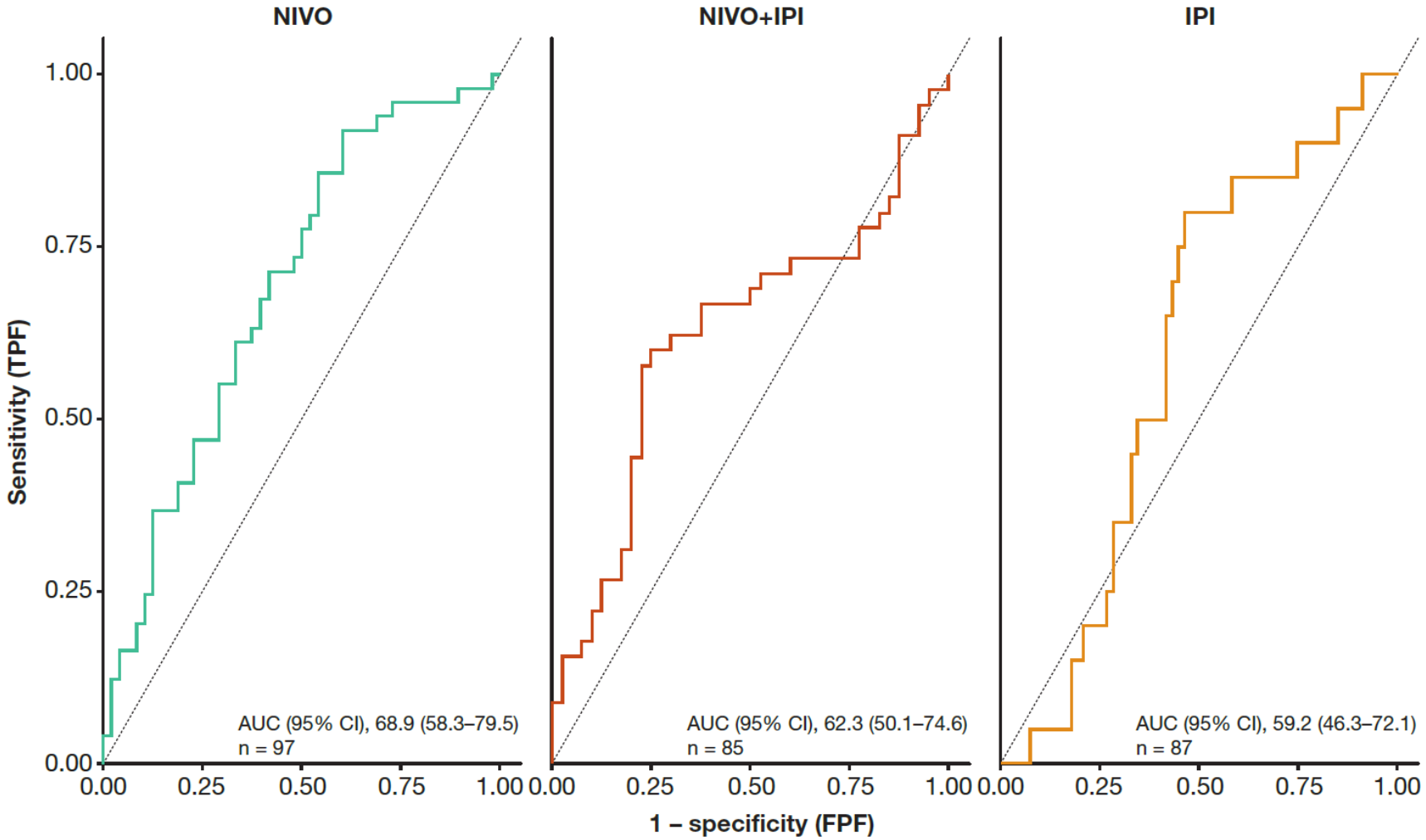
Supplementary Figure 27. Kaplan–Meier curves for PFS by *BRAF* status and by ≥ 5% TC PD-L1 versus < 5% TC/indeterminate PD-L1 expression in CheckMate 067. HRs (95% CI) for PD-L1 negative/indeterminate versus positive were obtained with univariate Cox proportional hazards models. CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; PD-L1, programmed death ligand 1; PFS, progression-free survival; TC, tumor cell; WT, wild-type.



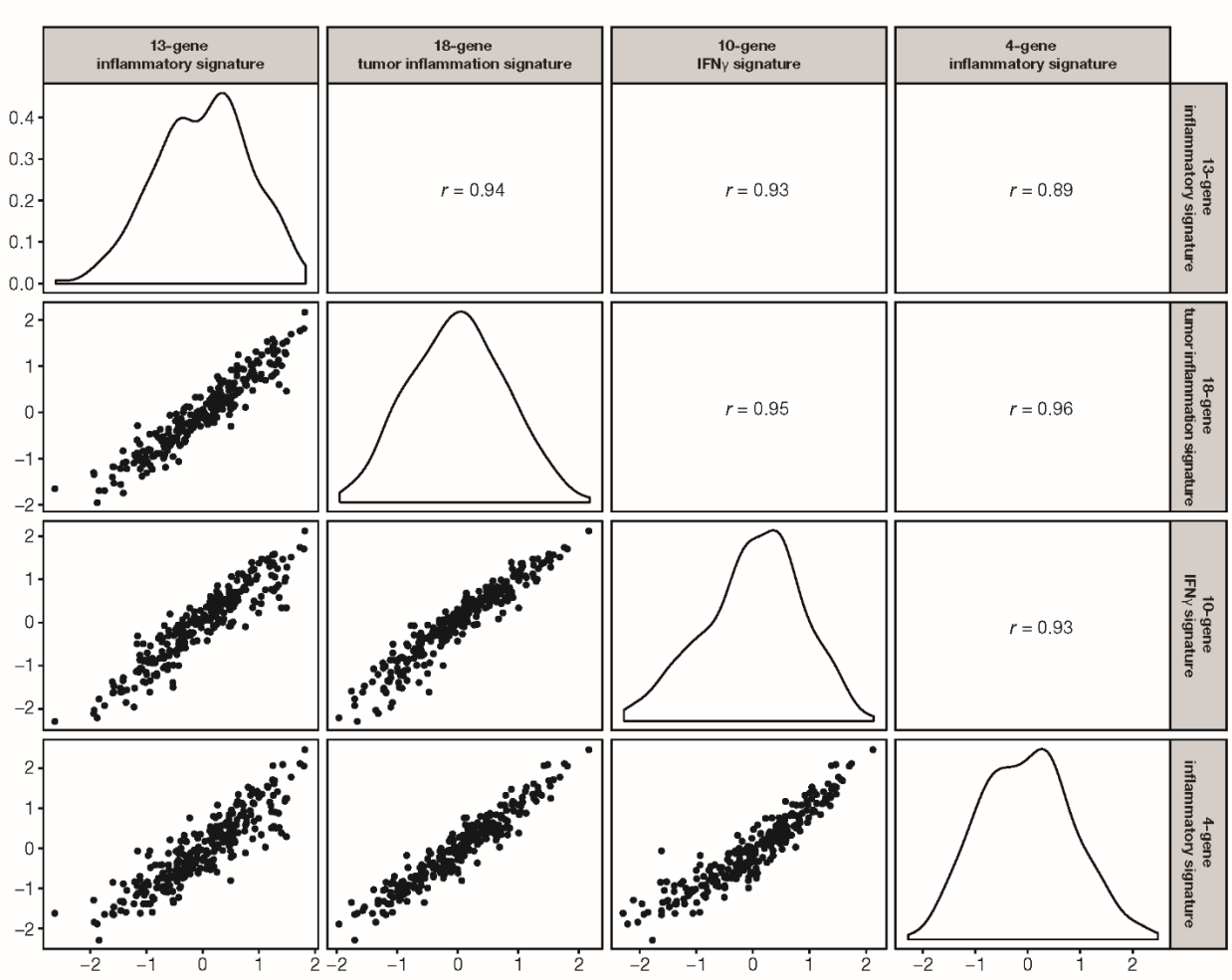
Supplementary Figure 28. Kaplan–Meier curves for OS by *BRAF* status and by ≥ 5% TC PD-L1 versus < 5% TC/indeterminate PD-L1 expression in CheckMate 067. HRs (95% CI) for PD-L1 negative/indeterminate versus positive were obtained with univariate Cox proportional hazards models. CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PD-L1, programmed death ligand 1; TC, tumor cell; WT, wild-type.



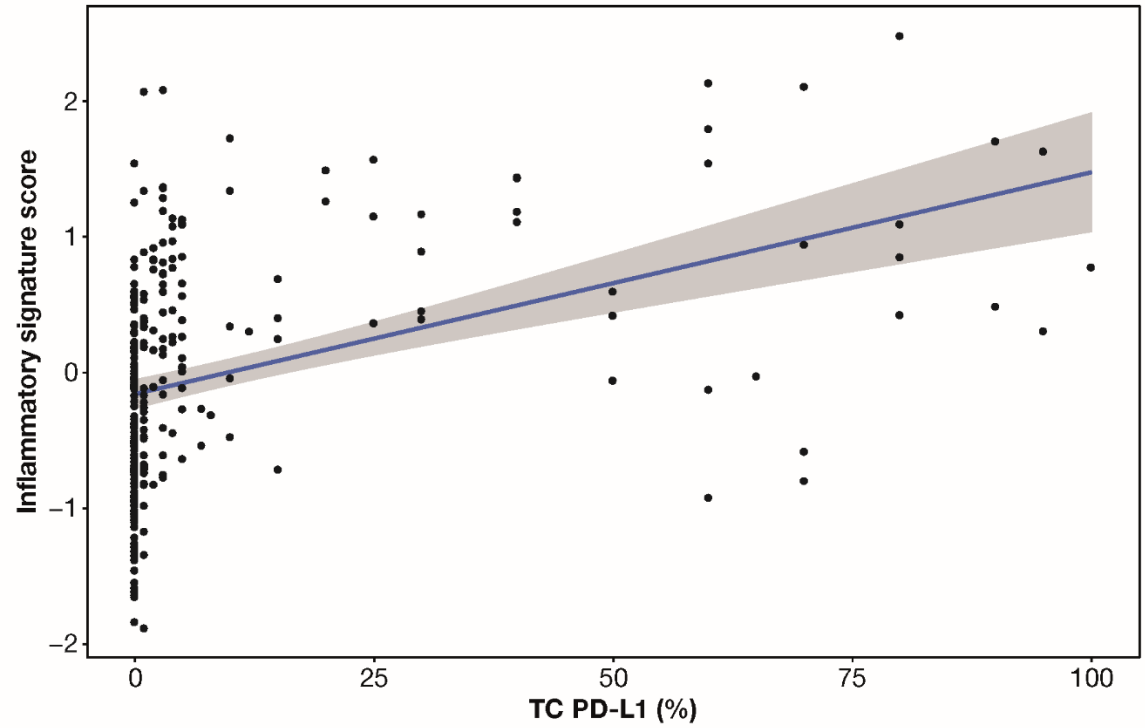
Supplementary Figure 29. ROC curves illustrating the ability of the inflammatory signature to predict response in CheckMate 067. AUC, area under the curve; CI, confidence interval; FPF, false positive fraction; IPI, ipilimumab; NIVO, nivolumab; ROC, receiver operating characteristic; TPF, true positive fraction.



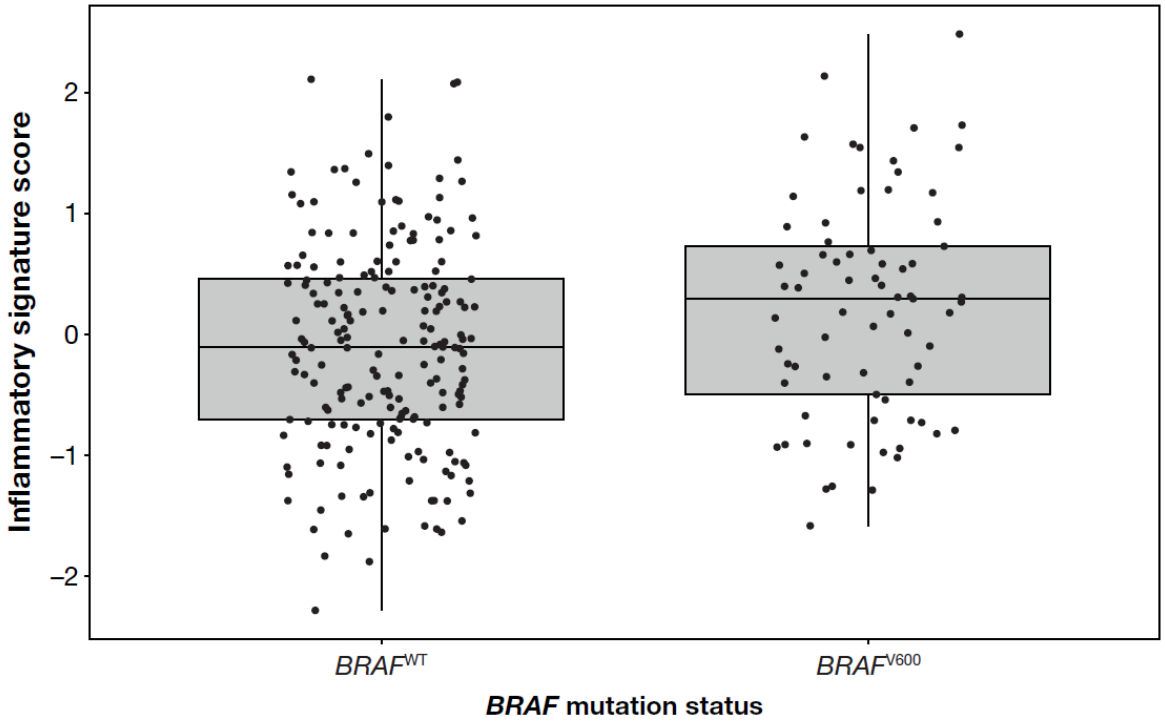
Supplementary Figure 30. Pearson's correlation analysis of the inflammatory signature with other published inflammation signatures in GEP-evaluable patients (n = 269) from CheckMate 067 (1-3).



Supplementary Figure 31. Pearson's correlation analysis of the inflammatory signature versus tumor % PD-L1 expression by IHC in GEP-evaluable patients (n = 269) from CheckMate 067. IHC, immunohistochemistry; PD-L1, programmed death ligand 1; TC, tumor cell.

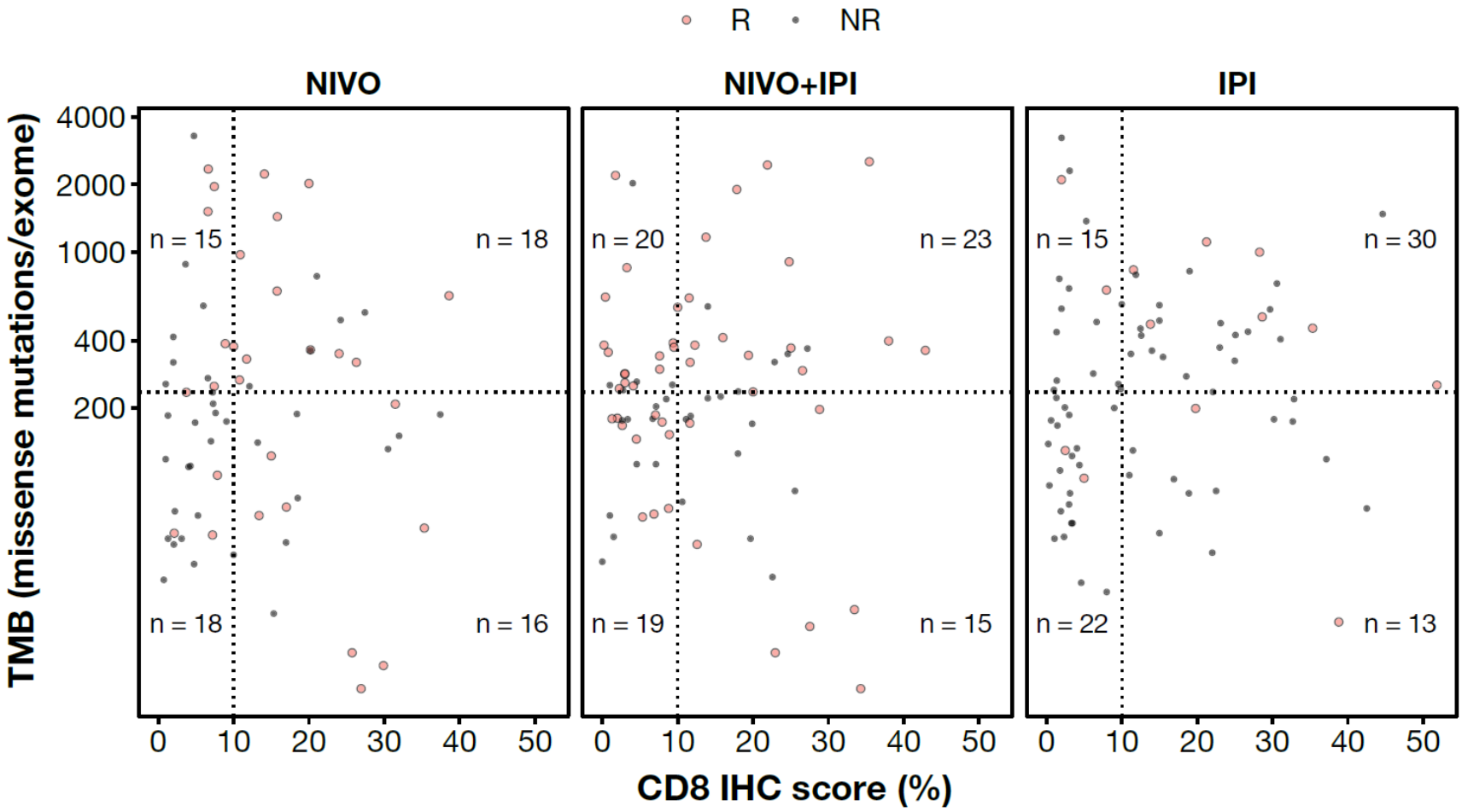


Supplementary Figure 32. Distribution of the inflammatory signature scores for patients with *BRAF*^{WT} tumors (n = 196) and *BRAF*^{V600} tumors (n = 73) in CheckMate 067. Boxes extend from the first to third quartiles, the middle line shows the median, and the whiskers extend to the most extreme data point that is no more than 1.5 times the IQR from the box. WT, wild-type.

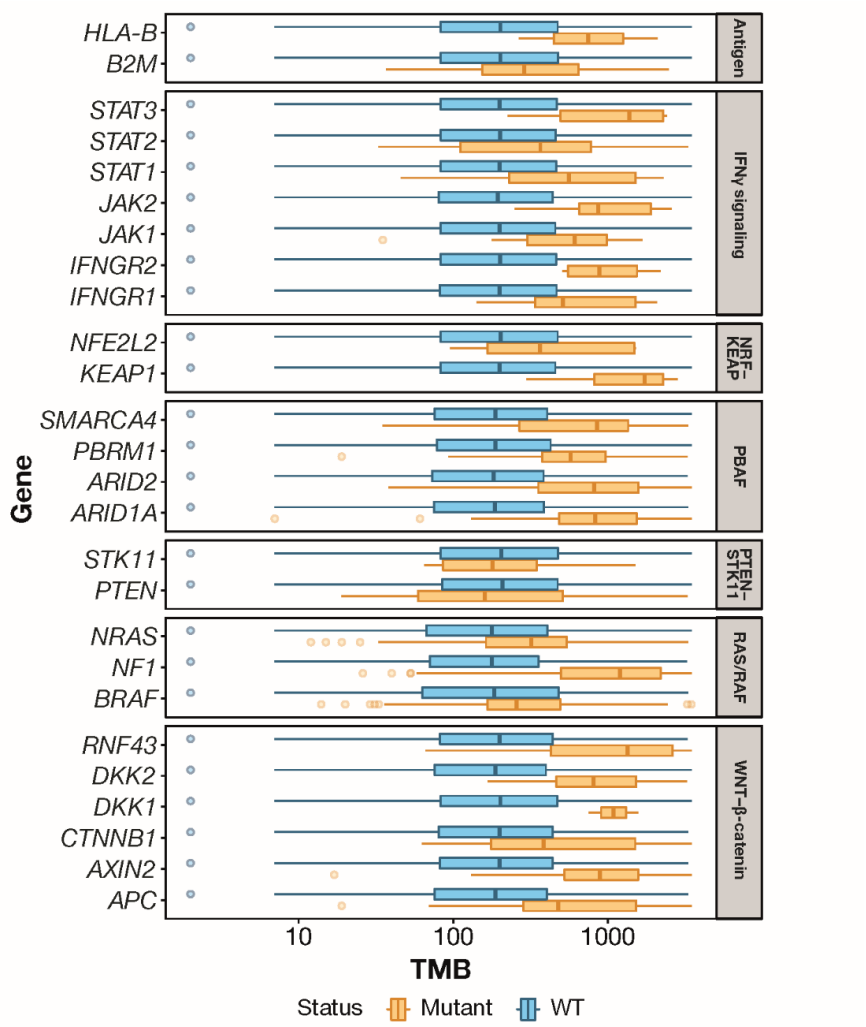


BRAF^{V600} mutation status	Q1	Median	Q3
BRAF^{WT}	–0.71	–0.10	0.46
BRAF^{V600}	–0.50	0.29	0.73

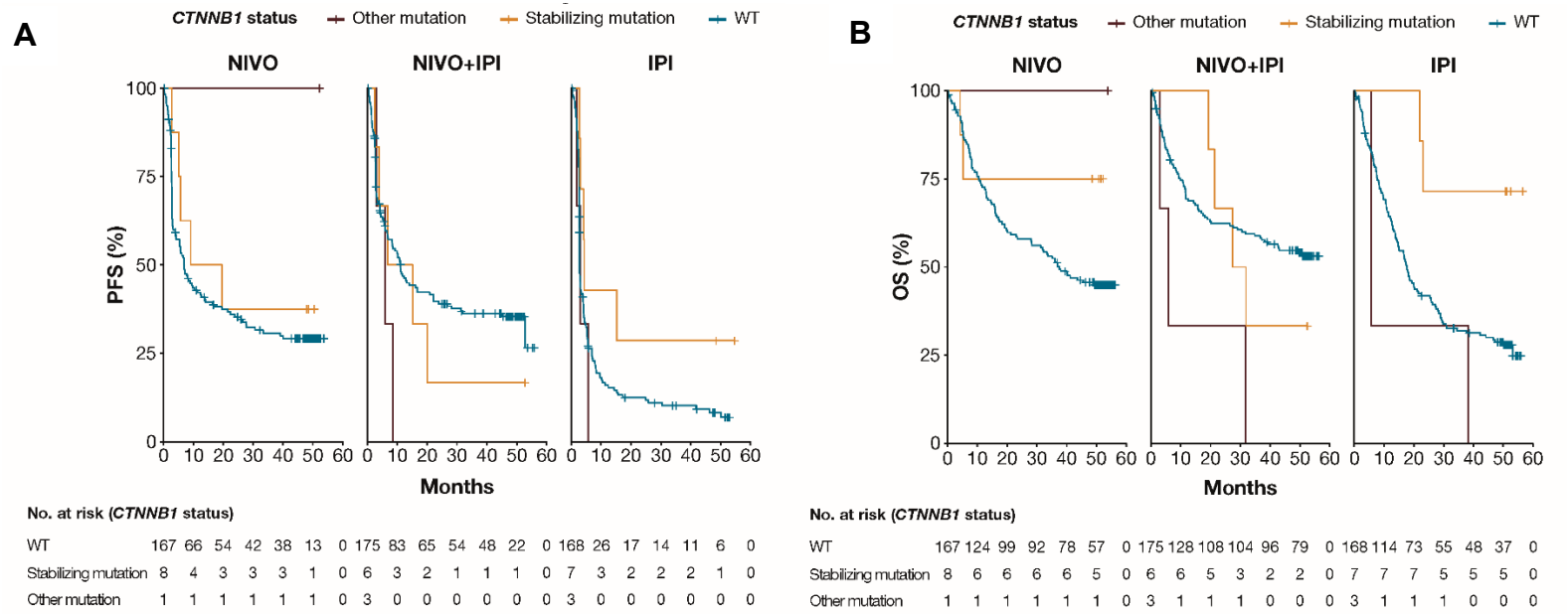
Supplementary Figure 33. Distribution of responders and nonresponders by TMB and CD8 expression by IHC in each treatment arm of CheckMate 067. IHC, immunohistochemistry; IPI, ipilimumab; NIVO, nivolumab; NR, nonresponders; R, responders; TMB, tumor mutational burden.



Supplementary Figure 34. TMB distribution versus mutation status for candidate genes in TMB-evaluable tumors from CheckMate 067 (n = 538). TMB, tumor mutational burden; WT, wild-type.



Supplementary Figure 35. Kaplan–Meier curves for PFS and OS comparing patient subgroups with and without stabilizing mutations in β-catenin in CheckMate 067. IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PFS, progression-free survival; WT, wild-type.



TABLES

Supplementary Table 1. Selected patient characteristics for TMB-evaluable and nonevaluable patients in CheckMate 067

Characteristic		TMB not evaluable	TMB evaluable	ITT population
		Patients, n (%)	Patients, n (%)	Patients, n (%)
Treatment	Not treated	8 (2.0)	0 (0.0)	8 (0.9)
	NIVO	137 (33.7)	176 (32.7)	313 (33.1)
	NIVO+IPI	129 (31.7)	184 (34.2)	313 (33.1)
	IPI	133 (32.7)	178 (33.1)	311 (32.9)
Age, years	< 65	240 (59.0)	325 (60.4)	565 (59.8)
	≥ 65 to < 75	118 (29.0)	144 (26.8)	262 (27.7)
	≥ 75	49 (12.0)	69 (12.8)	118 (12.5)
Metastatic stage	M0/M1A/M1B	171 (42.0)	226 (42.0)	397 (42.0)
	M1C	236 (58.0)	312 (58.0)	548 (58.0)
ECOG performance status	0	303 (74.5)	388 (72.1)	691 (73.1)
	1	103 (25.3)	149 (27.7)	252 (26.7)
	2	0 (0.0)	1 (0.2)	1 (0.1)
	Not available	1 (0.3)	0 (0.0)	1 (0.1)
PD-L1 TC (≥ 5%)	Negative/ indeterminate	234 (57.5)	280 (52.0)	514 (54.4)
	Positive	173 (42.5)	258 (48.0)	431 (45.6)
BRAF status	$BRAF^{V600}$	119 (29.2)	179 (33.3)	298 (31.5)
	$BRAF^{WT}$	288 (70.8)	359 (66.7)	647 (68.5)
Sex	Female	153 (37.6)	182 (33.8)	335 (35.5)
	Male	254 (62.4)	356 (66.2)	610 (64.6)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPI, ipilimumab; ITT, intent-to-treat; NIVO, nivolumab; PD-L1, programmed death ligand 1; TC, tumor cell; TMB, tumor mutational burden; WT, wild-type.

Supplementary Table 2. Selected patient characteristics for TMB-evaluable and nonevaluable patients in CheckMate 066

Characteristic		TMB not evaluable	TMB evaluable	ITT population
		Patients, n (%)	Patients, n (%)	Patients, n (%)
Treatment	**Not treated**	7 (2.3)	0 (0.0)	7 (1.7)
	Dacarbazine	138 (46.2)	67 (56.3)	205 (49.0)
	NIVO	154 (51.5)	52 (43.7)	206 (49.3)
Age, years	**< 65**	146 (48.8)	53 (44.5)	199 (47.6)
	≥ 65 to < 75	108 (36.1)	44 (37.0)	152 (36.4)
	≥ 75	45 (15.1)	22 (18.5)	67 (16.0)
Metastatic stage	**M0/M1A/M1B**	115 (38.5)	54 (45.4)	169 (40.4)
	M1C	184 (61.5)	65 (54.6)	249 (59.6)
ECOG performance status	**0**	189 (63.2)	80 (67.2)	269 (64.4)
	1	107 (35.8)	37 (31.1)	144 (34.5)
	2	2 (0.7)	2 (1.7)	4 (1.0)
	Not available	1 (0.3)	0 (0.0)	1 (0.2)
PD-L1 TC (≥ 5%)	**Negative/ indeterminate**	205 (68.6)	65 (54.6)	270 (64.6)
	Positive	94 (31.4)	54 (45.4)	148 (35.4)
***BRAF* status**	**Not available**	5 (1.7)	3 (2.5)	8 (1.9)
	***BRAF*^{WT}**	294 (98.3)	116 (97.5)	410 (98.1)
Sex	**Female**	125 (41.8)	47 (39.5)	172 (41.2)
	Male	174 (58.2)	72 (60.5)	246 (58.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ITT, intent-to-treat; NIVO, nivolumab; PD-L1, programmed death ligand 1; TC, tumor cell; TMB, tumor mutational burden; WT, wild-type.

Supplementary Table 3. Selected patient characteristics for GEP-evaluable and nonevaluable patients in CheckMate 067

Characteristic		GEP not evaluable	GEP evaluable	ITT population
		Patients, n (%)	Patients, n (%)	Patients, n (%)
Treatment	**Not treated**	8 (1.2)	0 (0.0)	8 (0.9)
	NIVO	216 (32.0)	97 (36.1)	313 (33.1)
	NIVO+IPI	228 (33.7)	85 (31.6)	313 (33.1)
	IPI	224 (33.1)	87 (32.3)	311 (32.9)
Age, years	**< 65**	402 (59.5)	163 (60.6)	565 (59.8)
	≥ 65 to < 75	187 (27.7)	75 (27.9)	262 (27.7)
	≥ 75	87 (12.9)	31 (11.5)	118 (12.5)
Metastatic stage	**M0/M1A/M1B**	288 (42.6)	109 (40.5)	397 (42.0)
	M1C	388 (57.4)	160 (59.5)	548 (58.0)
ECOG performance status	**0**	511 (75.6)	180 (66.9)	691 (73.1)
	1	163 (24.1)	89 (33.1)	252 (26.7)
	2	1 (0.2)	0 (0.0)	1 (0.1)
	Not available	1 (0.2)	0 (0.0)	1 (0.1)
PD-L1 TC (≥ 5%)	**Negative/ indeterminate**	369 (54.6)	145 (53.9)	514 (54.4)
	Positive	307 (45.4)	124 (46.1)	431 (45.6)
***BRAF* status**	***BRAF*^{V600}**	225 (33.3)	73 (27.1)	298 (31.5)
	***BRAF*^{WT}**	451 (66.7)	196 (72.9)	647 (68.5)
Sex	**Female**	236 (34.9)	99 (36.8)	335 (35.5)
	Male	440 (65.1)	170 (63.2)	610 (64.6)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GEP, gene expression profiling; IPI, ipilimumab; ITT, intent-to-treat; NIVO, nivolumab; PD-L1, programmed death ligand 1; TC, tumor cell; WT, wild-type.

Supplementary Table 4. ORR for TMB-evaluable and nonevaluable patients by treatment arm in CheckMate 067

Treatment	TMB evaluable	Nonresponders, n (%)[a]	Responders, n (%)[b]
NIVO	No	78 (57)	59 (43)
	Yes	94 (53)	82 (47)
	As-treated population	172 (55)	141 (45)
NIVO+IPI	No	52 (40)	77 (60)
	Yes	78 (42)	106 (58)
	As-treated population	130 (42)	183 (58)
IPI	No	109 (82)	24 (18)
	Yes	142 (80)	36 (20)
	As-treated population	251 (81)	60 (19)

[a]Nonresponders include patients experiencing stable or progressive disease or those whose best overall response could not be determined.
[b]Responders include patients who achieved complete or partial response.
Abbreviations: IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; TMB, tumor mutational burden.

Supplementary Table 5. ORR for TMB-evaluable and nonevaluable patients by initial treatment in CheckMate 066

Treatment	TMB evaluable	Nonresponders, n (%)[a]	Responders, n (%)[b]
NIVO	No	87 (57)	67 (44)
	Yes	30 (58)	22 (42)
	As-treated population	117 (57)	89 (43)
Dacarbazine	No	119 (86)	19 (14)
	Yes	56 (84)	11 (16)
	As-treated population	175 (85)	30 (15)

[a]Nonresponders include patients experiencing stable or progressive disease or those whose best overall response could not be determined.
[b]Responders include patients who achieved complete or partial response.
Abbreviations: NIVO, nivolumab; ORR, objective response rate; TMB, tumor mutational burden.

Supplementary Table 6. ORR for GEP-evaluable and nonevaluable patients in CheckMate 067

Treatment	GEP evaluable	Nonresponders, n (%)[a]	Responders, n (%)[b]
NIVO	No	124 (57)	92 (43)
	Yes	48 (49)	49 (51)
	As-treated population	172 (55)	141 (45)
NIVO+IPI	No	90 (39)	138 (61)
	Yes	40 (47)	45 (53)
	As-treated population	130 (42)	183 (58)
IPI	No	184 (82)	40 (18)
	Yes	67 (77)	20 (23)
	As-treated population	251 (81)	60 (19)

[a]Nonresponders include patients experiencing stable or progressive disease or those whose best overall response could not be determined.
[b]Responders include patients who achieved complete or partial response.
Abbreviations: GEP, gene expression profiling; IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate.

Supplementary Table 7. ORR by TMB status in CheckMate 066

Treatment	TMB class, N	Nonresponders, n[a]	Responders, n[b]	ORR, %
NIVO	Low, 29	21	8	27.6
	High, 23	9	14	60.9
	As-treated population, 206	117	89	43.2
Dacarbazine	Low, 31	26	5	16.1
	High, 36	30	6	16.7
	As-treated population, 205	175	30	14.6

[a]Nonresponders include patients experiencing stable or progressive disease or those whose best overall response could not be determined.
[b]Responders include patients who achieved complete or partial response.
Abbreviations: NIVO, nivolumab; ORR, objective response rate; TMB, tumor mutational burden.

Supplementary Table 8. ORR for TMB-high versus TMB-low by arm and PD-L1 ≥ 5% TC PD-L1 versus < 5% TC/indeterminate PD-L1 expression in CheckMate 067

Treatment	PD-L1	TMB class	Nonresponders, n[a]	Responders, n[b]	Total, N	ORR, %
NIVO	Positive	High	12	37	49	75.5
	Positive	Low	21	15	36	41.7
	Negative/ indeterminate	High	21	17	38	44.7
	Negative/ indeterminate	Low	40	13	53	24.5
NIVO+IPI	Positive	High	13	35	48	72.9
	Positive	Low	17	25	42	59.5
	Negative/ indeterminate	High	18	22	40	55.0
	Negative/ indeterminate	Low	30	24	54	44.4
IPI	Positive	High	41	13	54	24.1
	Positive	Low	22	7	29	24.1
	Negative/ indeterminate	High	29	11	40	27.5
	Negative/ indeterminate	Low	50	5	55	9.1

[a]Nonresponders include patients experiencing stable or progressive disease or those whose best overall response could not be determined.
[b]Responders include patients who achieved complete or partial response.
Abbreviations: IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; PD-L1, programmed death ligand 1; TC, tumor cell; TMB, tumor mutational burden.

Supplementary Table 9. ORR for TMB-high versus TMB-low by arm and PD-L1 ≥ 5% TC PD-L1 versus < 5% TC/indeterminate PD-L1 expression in CheckMate 066

Treatment	PD-L1	TMB class	Nonresponders, n[a]	Responders, n[b]	Total, N	ORR, %
NIVO	Positive	High	4	8	12	66.7
	Positive	Low	7	6	13	46.2
	Negative/ indeterminate	High	5	6	11	54.5
	Negative/ indeterminate	Low	14	2	16	12.5
Dacarbazine	Positive	High	14	3	17	17.6
	Positive	Low	10	2	12	16.7
	Negative/ indeterminate	High	16	3	19	15.8
	Negative/ indeterminate	Low	16	3	19	15.8

[a]Nonresponders include patients experiencing stable or progressive disease or those whose best overall response could not be determined.
[b]Responders include patients who achieved complete or partial response.
Abbreviations: NIVO, nivolumab; ORR, objective response rate; PD-L1, programmed death ligand 1; TC, tumor cell; TMB, tumor mutational burden.

Supplementary Table 10. PFS and OS HRs for TMB-high versus TMB-low by arm and metastatic stage in CheckMate 067

Treatment	Metastatic stage	PFS HR (95% CI)	OS HR (95% CI)
NIVO	M0/M1A/M1B	0.49 (0.27–0.87)	0.50 (0.25–1.00)
	M1C	0.41 (0.25–0.68)	0.45 (0.26–0.77)
NIVO+IPI	M0/M1A/M1B	0.60 (0.31–1.10)	0.59 (0.27–1.30)
	M1C	0.57 (0.36–0.91)	0.54 (0.32–0.92)
IPI	M0/M1A/M1B	0.69 (0.42–1.10)	0.70 (0.40–1.20)
	M1C	0.51 (0.34–0.78)	0.40 (0.25–0.64)

Abbreviations: CI, confidence interval; HR, hazard ratio; IPI, ipilimumab; NIVO, nivolumab; OS, overall survival; PFS, progression-free survival; TMB, tumor mutational burden.

Supplementary Table 11. ORR by PD-L1 expression (≥ 5% TC PD-L1 versus < 5% TC/indeterminate PD-L1 expression), *BRAF* mutation status, and arm in CheckMate 067

Treatment	PD-L1	*BRAF* status	Nonresponders, n[a]	Responders, n[b]	Total, N	ORR, %
NIVO	Positive	*BRAF*^{WT}	33	56	89	62.9
	Positive	*BRAF*^{V600}	24	27	51	52.9
	Negative/ indeterminate	*BRAF*^{WT}	81	45	126	35.7
	Negative/ indeterminate	*BRAF*^{V600}	34	13	47	27.7
NIVO+IPI	Positive	*BRAF*^{WT}	36	54	90	60.0
	Positive	*BRAF*^{V600}	11	43	54	79.6
	Negative/ indeterminate	*BRAF*^{WT}	61	61	122	50.0
	Negative/ indeterminate	*BRAF*^{V600}	22	25	47	53.2
IPI	Positive	*BRAF*^{WT}	71	21	92	22.8
	Positive	*BRAF*^{V600}	39	12	51	23.5
	Negative/ indeterminate	*BRAF*^{WT}	106	17	123	13.8
	Negative/ indeterminate	*BRAF*^{V600}	35	10	45	22.2

[a]Nonresponders include patients experiencing stable or progressive disease or those whose best overall response could not be determined.
[b]Responders include patients who achieved complete or partial response.
Abbreviations: IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; PD-L1, programmed death ligand 1; TC, tumor cell; WT, wild-type.

Supplementary Table 12. ORR by inflammatory signature score status in CheckMate 067

Treatment	Signature score, N	Nonresponders, n[a]	Responders, n[b]	ORR, %
NIVO	Low, 51	32	19	37.3
	High, 46	16	30	65.2
	As-treated population, 313	172	141	45.0
NIVO+IPI	Low, 44	27	17	38.6
	High, 41	13	28	68.3
	As-treated population, 313	130	183	58.5
IPI	Low, 40	36	4	10.0
	High, 47	31	16	34.0
	As-treated population, 311	251	60	19.3

[a]Nonresponders include patients experiencing stable or progressive disease or those whose best overall response could not be determined.
[b]Responders include patients who achieved complete or partial response.
Abbreviations: IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate.

Supplementary Table 13. ORR by TMB and inflammatory signature score status in CheckMate 067

Treatment	TMB class	Inflammatory signature score	Nonresponders, n[a]	Responders, n[b]	Total, N	ORR, %
NIVO	High	Low	5	6	11	54.6
	High	High	6	18	24	75.0
	Low	Low	21	6	27	22.2
	Low	High	6	7	13	53.9
NIVO+IPI	High	Low	8	8	16	50.0
	High	High	6	12	18	66.7
	Low	Low	15	5	20	25.0
	Low	High	4	13	17	76.5
IPI	High	Low	9	2	11	18.2
	High	High	21	8	29	27.6
	Low	Low	19	2	21	9.5
	Low	High	7	7	14	50.0

[a]Nonresponders include patients experiencing stable or progressive disease or those whose best overall response could not be determined.
[b]Responders include patients who achieved complete or partial response.
Abbreviations: IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; TMB, tumor mutational burden.

Supplementary Table 14. ORR by TMB and CD8 expression status in CheckMate 067

Treatment	TMB class	CD8 IHC score	Nonresponders, n[a]	Responders, n[b]	Total, N	ORR, %
NIVO	High	Low	9	6	15	40.0
	High	High	5	13	18	72.2
	Low	Low	15	3	18	16.7
	Low	High	9	7	16	43.8
NIVO+IPI	High	Low	6	14	20	70.0
	High	High	7	16	23	69.6
	Low	Low	9	10	19	52.6
	Low	High	8	7	15	46.7
IPI	High	Low	13	2	15	13.3
	High	High	23	7	30	23.3
	Low	Low	20	2	22	9.1
	Low	High	11	2	13	15.4

[a]Nonresponders include patients experiencing stable or progressive disease or those whose best overall response could not be determined.
[b]Responders include patients who achieved complete or partial response.
Abbreviations: IHC, immunohistochemistry; IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate; TMB, tumor mutational burden.

Supplementary Table 15. Genes assessed in tumor mutation analysis of WES-evaluable patients in CheckMate 067

Pathway	Gene	Mutant, n	Wild-type, n
Antigen presentation	Any gene	10	528
	B2M	8	530
	HLA-A	0	538
	HLA-B	2	536
	HLA-C	0	538
	HLA-E	0	538
	TAP1	0	538
	TAP2	0	538
IFNγ signaling	Any gene	54	484
	IFNGR1	9	529
	IFNGR2	4	534
	JAK1	10	528
	JAK2	12	526
	STAT1	12	526
	STAT2	11	527
	STAT3	6	532
NRF-KEAP	Any gene	11	527
	KEAP1	6	532
	NFE2L2	5	533
PBAF	Any gene	138	400
	ARID1A	47	491
	ARID2	56	482
	PBRM1	26	512
	SMARCA4	45	493
PTEN-STK11	Any gene	37	501
	PTEN	33	505
	STK11	5	533
RAS/RAF	Any gene	379	159
	BRAF	204	334
	NF1	83	455
	NRAS	144	394
WNT/ β-catenin	Any gene	120	418
	APC	49	489
	AXIN2	13	525
	CTNNB1	28	510
	DKK1	2	536
	DKK2	35	503
	RNF43	16	522

Abbreviation: WES, whole-exome sequencing.

Supplementary Table 16. ORR by pathway-level mutation status of tumors for CheckMate 067

Pathway	Status	NIVO				NIVO+IPI				IPI			
		NR, n[a]	R, n[b]	Total, N	ORR, %	NR, n[a]	R, n[b]	Total, N	ORR, %	NR, n[a]	R, n[b]	Total, N	ORR, %
Antigen presentation	Mutant	1	2	3	66.7	1	2	3	66.7	3	1	4	25.0
	Wild-type	93	80	173	46.2	77	104	181	57.5	139	35	174	20.1
IFNγ signaling	Mutant	7	9	16	56.3	9	13	22	59.1	12	4	16	25.0
	Wild-type	87	73	160	45.6	69	93	162	57.4	130	32	162	19.8
NRF-KEAP	Mutant	0	6	6	100.0	1	3	4	75.0	1	0	1	0.0
	Wild-type	94	76	170	44.7	77	103	180	57.2	141	36	177	20.3
PBAF	Mutant	22	26	48	54.2	14	28	42	66.7	35	13	48	27.1
	Wild-type	72	56	128	43.8	64	78	142	54.9	107	23	130	17.7
PTEN-STK11	Mutant	4	7	11	63.6	1	5	6	83.3	17	3	20	15.0
	Wild-type	90	75	165	45.5	77	101	178	56.7	125	33	158	20.9
RAS/RAF	Mutant	60	62	122	50.8	52	76	128	59.4	100	29	129	22.5
	Wild-type	34	20	54	37.0	26	30	56	53.6	42	7	49	14.3
WNT/ β-catenin	Mutant	18	27	45	60.0	15	25	40	62.5	24	11	35	31.4
	Wild-type	76	55	131	42.0	63	81	144	56.3	118	25	143	17.5

[a]Nonresponders include patients experiencing stable or progressive disease or those whose best overall response could not be determined.
[b]Responders include patients who achieved complete or partial response.
Abbreviations: IPI, ipilimumab; NIVO, nivolumab; NR, nonresponders; ORR, objective response rate; R, responders.

Supplementary Table 17. Response in patients with stabilizing mutations in β-catenin in CheckMate 067

Treatment	β-catenin tumor mutation status	Nonresponders, n[a]	Responders, n[b]	ORR, %
NIVO	Other mutation	0	1	100.0
	Stabilizing mutation	2	6	75.0
	None detected	92	75	44.9
NIVO+IPI	Other mutation	0	3	100.0
	Stabilizing mutation	2	4	66.7
	None detected	76	99	56.6
IPI	Other mutation	3	0	0
	Stabilizing mutation	3	4	57.1
	None detected	136	32	19.0

[a]Nonresponders include patients experiencing stable or progressive disease or those whose best overall response could not be determined.
[b]Responders include patients who achieved complete or partial response.
Abbreviations: IPI, ipilimumab; NIVO, nivolumab; ORR, objective response rate.

Supplementary Table 18. Response in patients with stabilizing mutations in genes of the WNT–β-catenin pathway in CheckMate 067

Gene	Status	NIVO			NIVO+IPI			IPI		
		NR, n[a]	R, n[b]	ORR, %	NR, n[a]	R, n[b]	ORR, %	NR, n[a]	R, n[b]	ORR, %
APC	Mutant	7	7	50.0	9	10	52.6	12	4	25.0
	Wild-type	87	75	46.3	69	96	58.2	130	32	19.8
AXIN2	Mutant	3	3	50.0	3	0	0.0	4	0	0.0
	Wild-type	91	79	46.5	75	106	58.6	138	36	20.7
CTNNB1	Mutant	2	7	77.8	2	7	77.8	6	4	40.0
	Wild-type	92	75	44.9	76	99	56.6	136	32	19.0
DKK1	Mutant	0	1	100.0	0	0	NA	1	0	0.0
	Wild-type	94	81	46.3	78	106	57.6	141	36	20.3
DKK2	Mutant	6	12	66.7	1	8	88.9	3	5	62.5
	Wild-type	88	70	44.3	77	98	56.0	139	31	18.2
RNF43	Mutant	4	4	50.0	0	3	100.0	4	1	20.0
	Wild-type	90	78	46.4	78	103	56.9	138	35	20.2

[a]Nonresponders include patients experiencing stable or progressive disease or those whose best overall response could not be determined.
[b]Responders include patients who achieved complete or partial response.
Abbreviations: IPI, ipilimumab; NIVO, nivolumab; NR, nonresponders; ORR, objective response rate; R, responders.

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