

Supplemental Table 1. Clinical and demographic characteristics of nivolumab training, test, and validation cohorts

	Training (CheckMate 238)	Test (CheckMate 238)	Validation (CheckMate 915)	p-value
<i>N</i>	117	40	190	
Age (years)				0.16
Mean (SD)	54.03 (14.64)	58.30 (11.52)	56.39 (12.92)	
Sex				0.11
Female	45 (38.5)	23 (57.5)	80 (42.1)	
Male	72 (61.5)	17 (42.5)	110 (57.9)	
Race				0.29
White	114 (97.4)	39 (97.5)	189 (99.5)	
Asian	3 (2.6)	1 (2.5)	1 (0.5)	
Disease stage				0.02
IIIB	52 (44.4)	12 (30.0)	58 (30.5)	
IIIC	41 (35.0)	19 (47.5)	97 (51.1)	
IIID	0 (0.0)	0 (0.0)	8 (4.2)	
IV	22 (18.8)	9 (22.5)	27 (14.2)	
Other	1 (0.9)	0 (0.0)	0 (0.0)	
Not reported	1 (0.9)	0 (0.0)	0 (0.0)	
BRAF Mutation Status				0.02
Wild type	55 (47.0)	18 (45.0)	93 (48.9)	
Mutant	49 (41.9)	17 (42.5)	53 (27.9)	
Not reported	13 (11.1)	5 (12.5)	44 (23.2)	
Baseline ECOG				0.03
0	105 (89.7)	35 (87.5)	183 (96.3)	
1	12 (10.3)	5 (12.5)	7 (3.7)	
Baseline LDH (U/L)				0.08
Mean (SD)	220.67 (95.09)	238.68 (104.15)	208.69 (64.23)	
Disease recurrence				0.36
No	71 (60.7)	28 (70.0)	129 (67.9)	
Yes	46 (39.3)	12 (30.0)	61 (32.1)	
Severe toxicity				0.001
No	71 (60.7)	22 (55.0)	148 (77.9)	
Yes	46 (39.3)	18 (45.0)	42 (22.1)	

Supplemental Table 2. Clinical and demographic characteristics of ipilimumab training and test cohorts

	Training (CheckMate 238)	Test (CheckMate 238)	p-value
<i>N</i>	306	102	
Age (years)			0.24
Mean (SD)	54.30 (13.07)	52.49 (14.16)	
Sex			0.45
Female	123 (40.2)	46 (45.1)	
Male	183 (59.8)	56 (54.9)	
Race			0.71
White	294 (96.1)	97 (95.1)	
Asian	11 (3.6)	5 (4.9)	
Other	1 (0.3)	0 (0.0)	
Disease stage			0.64
IIIB	102 (33.3)	35 (34.3)	
IIIC	140 (45.8)	50 (49.0)	
IV	64 (20.9)	17 (16.7)	
BRAF Mutation Status			0.28
Wild type	147 (48.0)	97 (42.2)	
Mutant	130 (42.5)	44 (43.1)	
Not reported	29 (9.5)	15 (14.7)	
Baseline ECOG			1.00
0	272 (88.9)	91 (89.2)	
1	34 (11.1)	11 (10.8)	
Baseline LDH (U/L)			
Mean (SD)	212.35 (85.13)	223.57 (97.24)	0.27
Disease recurrence			0.04
No	173 (56.5)	45 (44.1)	
Yes	133 (43.5)	57 (55.9)	
Severe toxicity			1.00
No	152 (49.7)	50 (49.0)	
Yes	154 (50.3)	52 (51.0)	

Supplemental Table 3. Clinical and demographic characteristics of ipilimumab plus nivolumab training and test cohorts

	Training (CheckMate 915)	Test (CheckMate 915)	p-value
<i>N</i>	146	49	
Age (years)			0.06
Mean (SD)	55.46 (12.82)	50.72 (16.80)	
Sex			0.17
Female	62 (42.5)	27 (55.1)	
Male	84 (57.5)	22 (44.9)	
Race			0.21
White	144 (98.6)	47 (95.9)	
African American	0 (0.0)	1 (2.0)	
Other	2 (1.4)	1 (2.0)	
Disease stage			0.55
IIIB	37 (25.3)	13 (26.5)	
IIIC	85 (58.2)	26 (53.1)	
IIID	7 (4.8)	1 (2.0)	
IV	17 (11.6)	9 (18.4)	
BRAF Mutation Status			0.85
Wild type	62 (42.5)	23 (46.9)	
Mutant	50 (34.2)	16 (32.7)	
Not reported	34 (23.3)	10 (20.4)	
Baseline ECOG			1.00
0	136 (93.2)	45 (91.8)	
1	10 (6.8)	4 (8.2)	
Baseline LDH (U/L)			0.86
Mean (SD)	222.51 (82.57)	225.00 (80.52)	
Disease recurrence			0.71
No	89 (61.0)	32 (65.3)	
Yes	57 (39.0)	17 (34.7)	
Severe toxicity			1.00
No	98 (67.1)	33 (67.3)	
Yes	48 (32.9)	16 (32.7)	

Supplemental Table 4. Summary of common immune-related adverse events in the patients from CheckMate 238 and CheckMate 915.

Event	CheckMate 238				CheckMate 915			
	Ipilimumab (n = 408)		Nivolumab (n = 157)		Nivolumab (n = 190)		Ipilimumab + Nivolumab (n = 195)	
	Total	Severe	Total	Severe	Total	Severe	Total	Severe
	<i>Number of patients with event (percent)</i>							
Cardiac	7 (1.7)	1 (0.2)	5 (3.2)	0 (0)	5 (2.6)	2 (1.1)	7 (3.6)	0 (0)
Endocrine								
Adrenal disorder	20 (4.9)	8 (2.0)	2 (1.3)	1 (0.6)	5 (2.6)	0 (0)	18 (9.2)	3 (1.5)
Pituitary disorder	59 (14.5)	17 (4.2)	4 (2.5)	1 (0.6)	4 (2.1)	1 (0.5)	27 (13.8)	4 (2.1)
Thyroid disorder								
Hyperthyroidism	33 (8.1)	3 (0.7)	24 (15.3)	1 (0.6)	25 (13.2)	0 (0)	62 (31.8)	0 (0)
Hypothyroidism	34 (8.3)	2 (0.5)	22 (14.0)	2 (1.3)	40 (21.1)	1 (0.5)	50 (25.6)	1 (0.5)
Gastrointestinal								
Colitis	67 (16.4)	49 (12.0)	10 (6.4)	4 (2.5)	7 (3.7)	4 (2.1)	17 (8.7)	13 (6.7)
Diarrhea	202 (49.5)	44 (10.8)	49 (31.2)	8 (5.1)	43 (22.6)	3 (1.6)	94 (48.2)	1 (0.5)
Hematologic	22 (5.4)	4 (1.0)	7 (4.5)	0 (0)	9 (4.7)	2 (1.1)	13 (6.7)	1 (0.5)
Hepatic	100 (24.5)	53 (13.0)	32 (20.4)	11 (7.0)	30 (15.8)	9 (4.7)	42 (21.5)	18 (9.2)
Musculoskeletal	98 (24.0)	8 (2.0)	51 (32.5)	8 (5.1)	52 (27.4)	5 (2.6)	51 (26.2)	3 (1.5)
Nervous	121 (30.0)	9 (2.2)	43 (27.4)	2 (1.3)	31 (16.3)	1 (0.5)	44 (22.6)	1 (0.5)
Pulmonary	63 (15.4)	4 (1.0)	20 (12.7)	2 (1.3)	15 (7.9)	1 (0.5)	31 (15.9)	3 (1.5)
Renal	7 (1.7)	0 (0)	5 (3.2)	0 (0)	10 (5.3)	2 (1.1)	12 (6.2)	1 (0.5)
Skin								
Rash	210 (51.5)	28 (6.9)	65 (41.4)	5 (3.2)	60 (31.6)	3 (1.6)	72 (36.9)	4 (2.1)
Pruritus	153 (37.5)	7 (1.7)	36 (22.9)	0 (0)	50 (26.3)	0 (0)	69 (35.4)	1 (0.5)

Supplemental Table 5. Coefficients of the multivariable logistic regression models for severe irAEs

	Nivolumab		Ipilimumab		Ipilimumab plus Nivolumab	
	HR [95% CI]	p-value	HR [95% CI]	p-value	HR [95% CI]	p-value
Age	1.04 [1.00, 1.08]	0.067	0.98 [0.95, 1.02]	0.404	1.01 [0.95, 1.07]	0.767
Gender (ref: male)	0.95 [0.37, 2.45]	0.908	0.94 [0.34, 2.65]	0.910	0.54 [0.07, 3.65]	0.516
BRAF unknown (ref: mutant)	0.15 [0.03, 0.55]	0.009	1.09 [0.23, 5.24]	0.917	NA	NA
BRAF WT (ref: mutant)	0.17 [0.06, 0.45]	0.001	3.46 [1.16, 11.09]	0.030	NA	NA
Stage	0.42 [0.06, 1.79]	0.295	0.64 [0.17, 2.44]	0.505	NA	NA
ECOG = 1 (ref: 0)	1.39 [0.07, 10.71]	0.78	2.19 [0.40, 15.03]	0.388	NA	NA
Baseline LDH	1.00 [0.99, 1.00]	0.409	1.00 [0.99, 1.00]	0.569	NA	NA
PD-L1 <5%	0.60 [0.22, 1.62]	0.312	0.48 [0.16, 1.34]	0.169	0.59 [0.06, 5.24]	0.635
High autoAb severe toxicity score	13.53 [2.59, 86.65]	0.003	11.04 [3.84, 37.25]	<0.001	23.44 [4.10, 212.50]	0.001

HR = hazard ratio; CI = confidence interval

Supplemental Table 6. Coefficients of the multivariable Cox proportional Hazard Models for recurrence free survival.

	Nivolumab		Ipilimumab		Ipilimumab plus Nivolumab	
	HR [95% CI]	p-value	HR [95% CI]	p-value	HR [95% CI]	p-value
Age	1.02 [0.99, 1.04]	0.157	1.00 [0.98, 1.03]	0.716	1.02 [0.97, 1.07]	0.394
Gender (ref: male)	0.86 [0.47, 1.57]	0.633	1.39 [0.69, 2.79]	0.359	1.85 [0.36, 9.67]	0.464
BRAF unknown (ref: mutant)	0.87 [0.38, 2.00]	0.740	0.83 [0.31, 2.23]	0.704	0.90 [0.12, 6.85]	0.919
BRAF WT (ref: mutant)	0.89 [0.45, 1.77]	0.744	0.96 [0.48, 1.95]	0.919	0.75 [0.14, 4.05]	0.739
Stage	1.94 [0.97, 3.89]	0.061	0.74 [0.29, 1.87]	0.523	1.12 [0.16, 8.06]	0.910
Baseline ECOG	0.62 [0.08, 4.63]	0.642	1.23 [0.42, 3.66]	0.705	0.71 [0.09, 5.43]	0.745
Baseline LDH	1.00 [0.99, 1.00]	0.616	1.00 [1.00, 1.00]	0.538	1.00 [0.99, 1.01]	0.407
PD-L1 <5%	2.10 [1.02, 4.30]	0.043	2.15 [1.02, 4.53]	0.045	0.97 [0.15, 6.49]	0.977
High autoAb recurrence score	3.60 [1.98, 6.55]	<0.001	3.21 [1.38, 7.45]	0.007	6.45 [1.48, 28.02]	0.013

HR = hazard ratio; CI = confidence interval