

Supplemental Tables for:
Organ dysfunction in advanced melanoma patients treated with immune checkpoint inhibitors
Susan Spillane et al.

Table S1: Multivariable hazard ratios (HR) and 95% confidence intervals (CI) of associations with rwTTD (top) or OS (bottom) for: baseline renal function, patient characteristics (age and stage at diagnosis), treatment regimen (dichotomized as monotherapy/combination therapy)†,

		Adjusted‡ HR (95% CI)	p-value
rwTTD			
Renal function	Normal	Ref	
	Moderate/severe	1.4 (1.0-2.0)	0.044
Age	<70 years	Ref	
	70 years+	0.9 (0.8-1.1)	0.286
Stage at diagnosis	III/IV	Ref	
	0/I/II	0.9 (0.8-1.0)	0.014
	Unknown	1.0 (0.9-1.1)	0.930
Treatment regimen†	Monotherapy	Ref	-
	Combination therapy	0.8 (0.7-0.9)	<0.001
OS			
Renal function	Normal	Ref	
	Moderate/severe	2.3 (1.6-3.2)	<0.001
Age	<70 years	Ref	
	70 years+	1.3 (1.1-1.5)	<0.001
Stage at diagnosis	III/IV	Ref	-
	0/I/II	0.8 (0.6-0.9)	0.001
	Unknown	1.0 (0.9-1.2)	0.687
Treatment regimen†	Monotherapy	Ref	-
	Combination therapy	0.9 (0.8-1.1)	0.475

†Note: Patients may have received second-line ICI or other relevant treatment subsequent to treatment start and prior to outcome measurement.

‡Models adjusted for all variables listed

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Table S2: Multivariable hazard ratios (HR) and 95% confidence intervals (CI) of associations with rwTTD (top) or OS (bottom) for: baseline hepatic function, patient characteristics (age and stage at diagnosis), treatment regimen (dichotomized as monotherapy/combination therapy)†,

		Adjusted‡ HR (95% CI)	p-value
rwTTD			
Hepatic function	Normal	Ref	
	Moderate/severe	1.6 (1.2-2.3)	0.006
Age	<70 years	Ref	
	70 years+	1.0 (0.9-1.1)	0.813
Stage at diagnosis	III/IV	Ref	
	0/I/II	0.9 (0.8-1.0)	0.054
	Unknown	1.0 (0.9-1.2)	0.972
Treatment regimen†	Monotherapy	Ref	-
	Combination therapy	0.8 (0.7-0.9)	<0.001
OS			
Hepatic function	Normal	Ref	
	Moderate/severe	1.9 (1.3-2.9)	0.001
Age	<70 years	Ref	
	70 years+	1.4 (1.2-1.7)	<0.001
Stage at diagnosis	III/IV	Ref	-
	0/I/II	0.7 (0.6-0.9)	0.002
	Unknown	1.0 (0.9-1.2)	0.787
Treatment regimen†	Monotherapy	Ref	-
	Combination therapy	0.9 (0.8-1.1)	0.502

†Note: Patients may have received second-line ICI or other relevant treatment subsequent to treatment start and prior to outcome measurement.

‡Models adjusted for all variables listed

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Table S3: Multivariable odds ratios (OR) and 95% confidence intervals (CI) for associations between patient characteristics, treatment regimen, and risk of emergent (A) renal dysfunction; (B) hepatic dysfunction in first 90 days following ICI treatment initiation.*

		Total	Events (% total)	Adjusted OR†	(95% CI)	p-value
Emergent renal dysfunction (82 events/1,778 total)						
Age	<70 years	935	36 (3.9%)	<i>Ref</i>		
	70 years+	843	46 (5.5%)	1.71	(1.07, 2.74)	0.027
Sex	Female	569	16 (2.8%)	<i>Ref</i>		
	Male	1,209	66 (5.5%)	1.92	(1.17, 3.15)	0.012
Stage at diagnosis	III/IV	930	41 (4.4%)	<i>Ref</i>	-	
	0/I/II	486	25 (5.1%)	1.13	(0.74, 1.75)	0.569
	Unknown	362	16 (4.4%)	1.00	(0.65, 1.55)	0.999
Practice type	Academic practice	292	14 (4.8%)	<i>Ref</i>		
	Community	1,486	68 (4.6%)	0.79	(0.32, 1.97)	0.621
Treatment regimen† (first regimen received)	ipilimumab monotherapy	558	24 (4.3%)	<i>Ref</i>	-	-
	ipilimumab + nivolumab	376	29 (7.7%)	2.07	(1.10, 3.88)	0.026
	nivolumab monotherapy	338	15 (4.4%)	0.96	(0.51, 1.82)	0.905
	pembrolizumab monotherapy	506	14 (2.8%)	0.57	(0.29, 1.14)	0.114
Emergent hepatic dysfunction (119 events/1,616 total)						
Age	<70 years	831	79 (9.5%)	<i>Ref</i>		
	70 years+	785	40 (5.1%)	0.63	(0.41, 0.97)	0.040
Sex	Female	503	39 (7.8%)	<i>Ref</i>		
	Male	1,113	80 (7.2%)	0.96	(0.66, 1.40)	0.824
Stage at diagnosis	III/IV	836	68 (8.1%)	<i>Ref</i>	-	-
	0/I/II	435	32 (7.4%)	0.95	(0.63, 0.69)	0.824
	Unknown	345	19 (5.5%)	0.68	(0.42, 1.12)	0.136
Practice type	Academic practice	165	10 (6.1%)	<i>Ref</i>		
	Community	1,451	109 (7.5%)	1.08	(0.58, 1.98)	0.816
Treatment regimen† (first regimen received)	ipilimumab monotherapy	512	39 (7.6%)	<i>Ref</i>	-	-
	ipilimumab + nivolumab	328	44 (13.4%)	1.71	(1.12, 2.60)	0.014
	nivolumab monotherapy	317	19 (6.0%)	0.81	(0.44, 1.51)	0.515
	pembrolizumab monotherapy	459	17 (3.7%)	0.49	(0.29, 0.84)	0.011

†Note: Patients may have received second-line ICI or other relevant treatment subsequent to treatment start and prior to identification of emergent dysfunction. ‡Models adjusted for all variables listed

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Table S4: Comparison of characteristics and outcomes for patients with lab values available at baseline, versus unavailable for each of: (A) renal function; (B) hepatic function.

	A. Renal function information, baseline lab			B. Hepatic function information, baseline lab		
	Unavailable N=523	Available N=1,884	<i>p</i> -value	Unavailable N=690	Available N=1,717	<i>p</i> -value
Demographic characteristics						
Sex, n (%):			0.877			0.282
Female	166 (31.7)	589 (31.3)		228 (33.0%)	527 (30.7)	
Male	357 (68.3)	1,295 (68.7)		462 (67.0%)	1,190 (69.3)	
Median age† (years), [IQR]	71.0 (59.0, 78.0)	69.0 (59.0, 78.0)	0.224	70.0 (59.0, 78.0)	69.0 (59.0, 78.0)	0.525
Clinical characteristics, n (%)						
Stage at initial diagnosis:			0.018			0.665
Stage 0	1 (0.2)	8 (0.4)		1 (0.1)	8 (0.5)	
Stage I	35 (6.7)	155 (8.2)		53 (7.7)	137 (8.0)	
Stage II	85 (16.3)	353 (18.7)		117 (17.0)	321 (18.7)	
Stage III	94 (18.0)	423 (22.5)		146 (21.2)	371 (21.6)	
Stage IV	173 (33.1)	555 (29.5)		213 (30.9)	515 (30.0)	
Unknown	135 (25.8)	390 (20.7)		160 (23.2)	365 (21.3)	
ECOG PS†:			0.167			<0.001
0	130 (24.9)	460 (24.4)		141 (20.4)	449 (26.2)	
1	95 (18.2)	381 (20.2)		111 (16.1)	365 (21.3)	
2+	61 (11.7)	163 (8.7)		65 (9.4)	159 (9.3)	
Missing	237 (45.3)	880 (46.7)		373 (54.1)	744 (43.3)	
LDH test result‡:			<0.001			<0.001
Abnormal LDH test result	45 (8.6)	390 (20.7)		78 (11.3)	357 (20.8)	
No LDH test	426 (81.5)	750 (39.8)		467 (67.7)	709 (41.3)	
Normal LDH test result	50 (9.6)	728 (38.6)		143 (20.7)	635 (37.0)	
Not elevated LDH	2 (0.4)	16 (0.8)		2 (0.3)	16 (0.9)	
Tumor characteristics, n (%)						
BRAF:			<0.001			<0.001
Mutation -	268 (51.2)	1,072 (56.9)		357 (51.7)	983 (57.3)	
Mutation +	117 (22.4)	480 (25.5)		160 (23.2)	437 (25.5)	
Not tested pre treatment	120 (22.9)	275 (14.6)		156 (22.6)	239 (13.9)	
Unknown/indeterminate	18 (3.4)	57 (3.0)		17 (2.5)	58 (3.4)	
Treatment characteristics, n (%)						
Practice type:			<0.001			<0.001
Academic	11 (2.1)	302 (16.0)		143 (20.7)	170 (9.9)	
Community	512 (96.7)	1,582 (84.0%)		547 (79.3)	1547 (90.1%)	
Regimen:			0.029			0.084
ipilimumab	151 (28.9)	590 (31.3)		199 (28.8)	542 (31.6)	

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ipilimumab + nivolumab	105 (20.1)	389 (20.6)		143 (20.7)	351 (20.4)	
nivolumab	135 (25.8)	374 (19.9)		168 (24.3)	341 (19.9)	
pembrolizumab	132 (25.2)	531 (28.2)		180 (26.1)	483 (28.1)	
Time to treatment discontinuation						
Median, months (95% CI)	2.5 (2.3, 2.8)	2.1 (1.6, 3.2)	0.033	2.5 (2.3, 2.8)	2.1 (1.6, 3.2)	0.033
Overall survival						
Median months (95% CI)	22.1 (19.9, 25.5)	8.2 (4.2, 12.9)	<0.001	22.1 (19.9, 25.5)	8.2 (4.2, 12.9)	<0.001

ECOG PS: Eastern Cooperative Oncology Group Performance Status

†At index date, defined as first-line therapy start date

§LDH: Lactate dehydrogenase