

## Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

**eTable 1.** OS and PFS Measures by AJCC Eighth Edition M category

	Subjects alive at 1 year (%)	Median Survival (months)	D-Stat (95% CI)
<b>OS</b>			
M1a	91.9	not reached	1.4 (1.1, 1.8)
M1b	76	43.7	
M1c	65	43.9	
M1d	64	32.9	
<b>PFS</b>			
M1a	66.6	25.5	1.3 (1.0, 1.6)
M1b	54.4	23.6	
M1c	44.6	9.1	
M1d	45.2	8.3	

eTable 1. Percent of patients in each AJCC 8<sup>th</sup> edition M category alive (OS) or progressed (PFS) at 1 year and median survival time in months. Royston D statistic (D-Stat) of M staging model determined at the start of immunotherapy (ICB). M1a, patients with non-regional lymph nodes and/or skin/soft tissue lesions; M1b, patients with lung metastases; M1c, patients with all other visceral sites of disease (including liver involvement); M1d, patients with CNS metastases.

**eTable 2.** Pairwise Comparisons of each AJCC Eighth Edition M category

	OS			PFS		
	HR	95% CI	p-value	HR	95% CI	p-value
M1a vs M1b	0.58	[0.30, 1.14]	0.11	0.79	[0.46, 1.36]	0.39
M1a vs M1c	0.57	[0.35, 0.95]	0.03	0.66	[0.44, 1.01]	0.05
M1a vs M1d	0.53	[0.31, 0.91]	0.02	0.62	[0.40, 0.96]	0.03
M1b vs. M1c	0.79	[0.51, 1.22]	0.29	0.79	[0.54, 1.14]	0.21
M1b vs. M1d	0.76	[0.48, 1.22]	0.26	0.74	[0.50, 1.11]	0.14
M1c vs. M1d	0.91	[0.64, 1.30]	0.61	0.92	[0.68, 1.24]	0.57

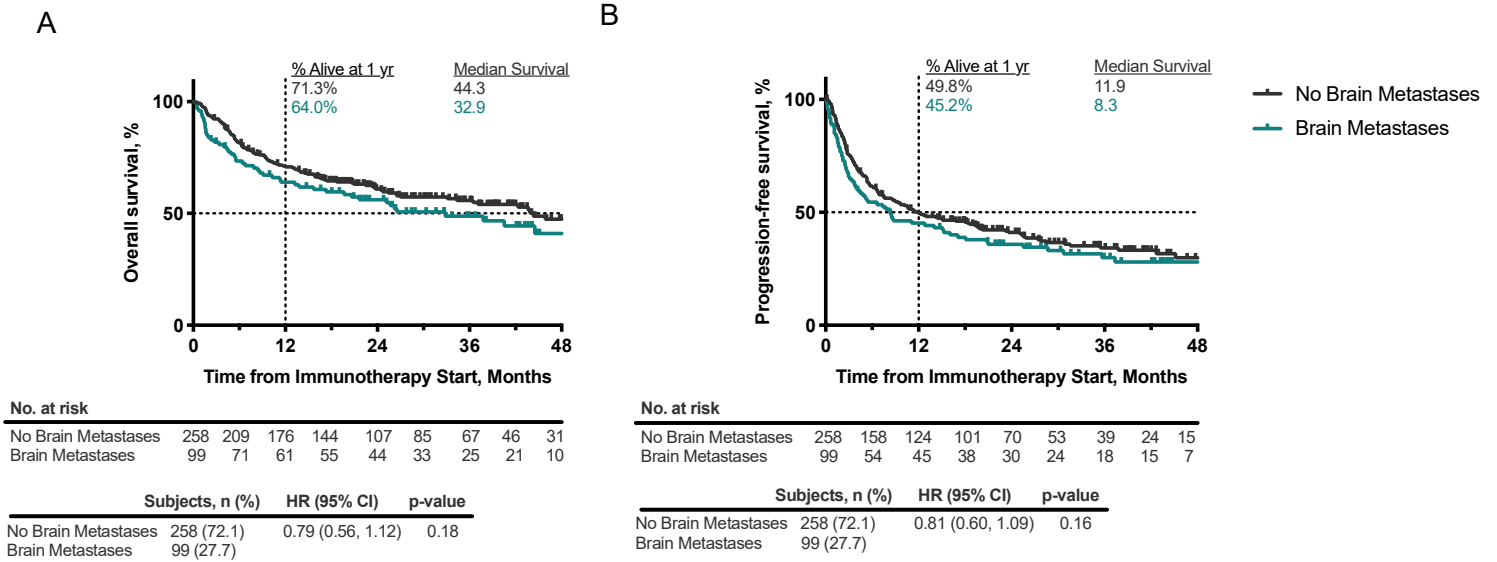
eTable 2. Pairwise comparisons of each AJCC 8<sup>th</sup> edition M category. HR, hazard ratio. CI, confidence interval. M1a, patients with non-regional lymph nodes and/or skin/soft tissue lesions; M1b, patients with lung metastases; M1c, patients with all other visceral sites of disease (including liver involvement); M1d, patients with CNS metastases.

**eTable 3.** Royston D Statistic of M Staging Models

<b>Endpoint</b>	<b>M stage</b>	<b>Royston D-Statistic</b>	<b>95% CI</b>
OS	ICB	1.4	(1.1 ,1.8)
OS	Met Dx	1.3	(0.99 ,1.7)
OS	New	2.4	(1.8 ,3.2)
PFS	ICB	1.3	(1.0 ,1.6)
PFS	Met Dx	1.2	(0.97 ,1.5)
PFS	New	1.7	(1.3 ,2.1)

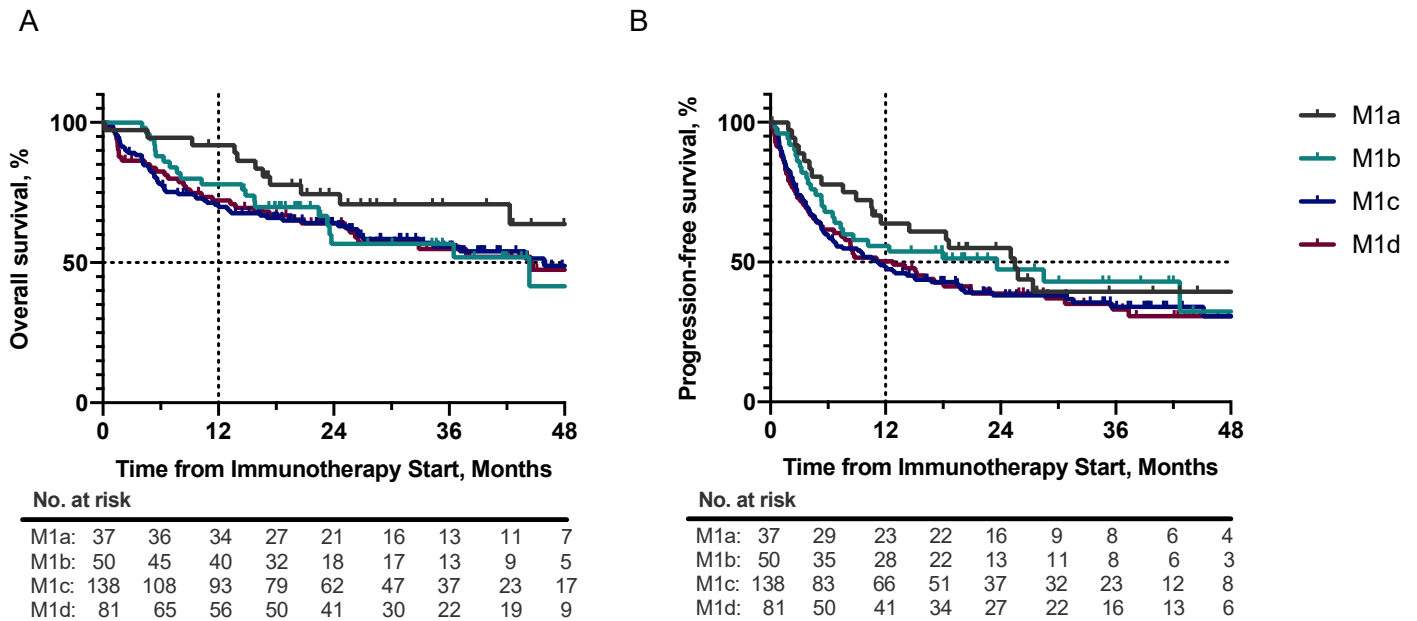
eTable 3. Royston D statistic of AJCC 8<sup>th</sup> edition M stage 1) determined at the start of immunotherapy (ICB), 2) at metastatic diagnosis (Met Dx), and 3) the newly proposed staging model at the start of immunotherapy (New) for both OS and PFS.

**eFigure 1. Kaplan-Meier Analysis of the OS and PFS in Patients With and Without Brain Metastases**



eFigure 1. Kaplan-Meier estimates of **A)** OS and **B)** PFS of patients with and without brain metastases. HR, hazard ratio; CI, confidence interval. Vertical dotted line marks 1-year survival.

**eFigure 2.** Kaplan-Meier Analysis of AJCC Eighth Edition M Category at ICI Initiation in Patients Who Received First-Line ICI



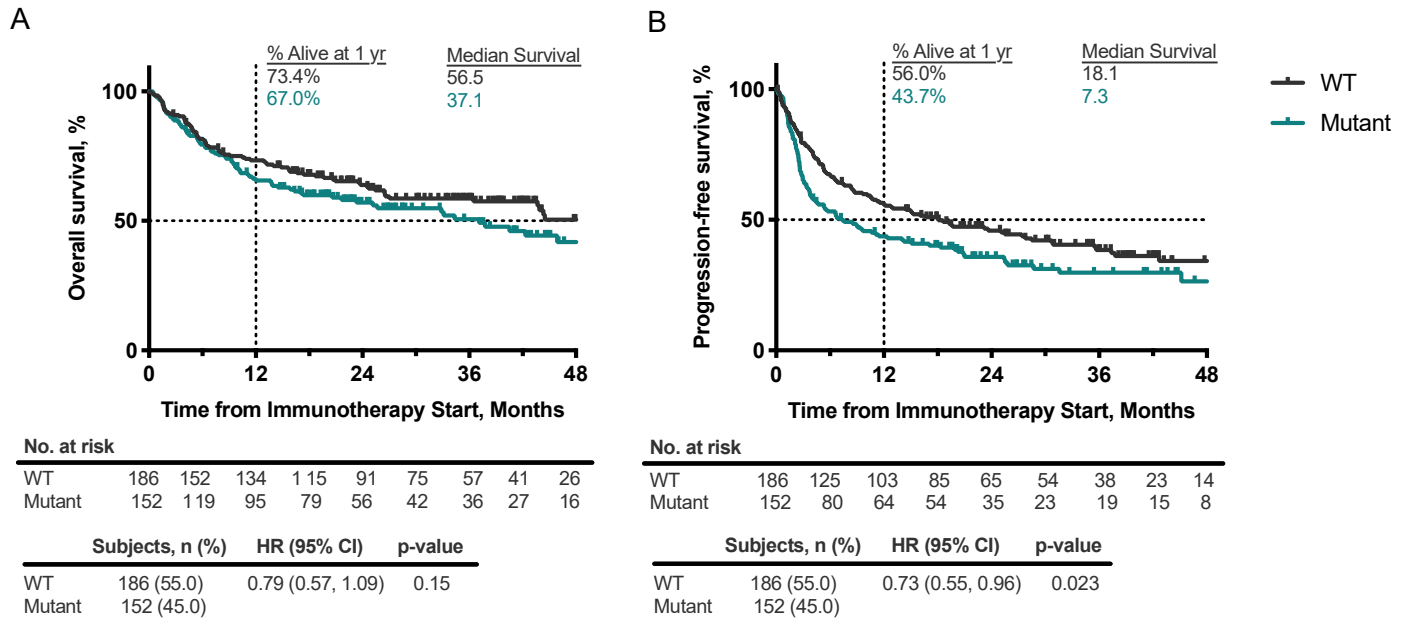
eFigure 2. Kaplan-Meier estimates of A) OS and B) PFS stratified by the AJCC 8<sup>th</sup> edition M category at ICI initiation for patients who received first line ICI. M1a, patients with non-regional lymph nodes and/or skin/soft tissue lesions; M1b, patients with lung metastases; M1c, patients with all other visceral sites of disease (including liver involvement); M1d, patients with CNS metastases. Vertical dotted line marks 1-year survival.

**eTable 4.** Pairwise Comparisons of Each AJCC Eighth Edition M Category for Patients Who Received First-Line ICI

	OS			PFS		
	HR	95% CI	p-value	HR	95% CI	p-value
M1a vs M1b	0.6	[0.30, 1.20]	0.15	0.88	[0.49, 1.56]	0.66
M1a vs M1c	0.58	[0.34, 0.99]	0.05	0.72	[0.47, 1.12]	0.15
M1a vs M1d	0.6	[0.33, 1.10]	0.1	0.7	[0.43, 1.13]	0.14
M1b vs. M1c	0.84	[0.52, 1.35]	0.46	0.78	[0.52, 1.18]	0.25
M1b vs. M1d	0.92	[0.54, 1.57]	0.75	0.77	[0.50, 1.20]	0.25
M1c vs. M1d	1.04	[0.69, 1.56]	0.87	0.97	[0.69, 1.36]	0.85

eTable 4. Pairwise comparisons of each M category for patients who received first line ICI. M1a, patients with non-regional lymph nodes and/or skin/soft tissue lesions; M1b, patients with lung metastases; M1c, patients with all other visceral sites of disease (including liver involvement); M1d, patients with CNS metastases. HR, hazard ratio. CI, confidence interval.

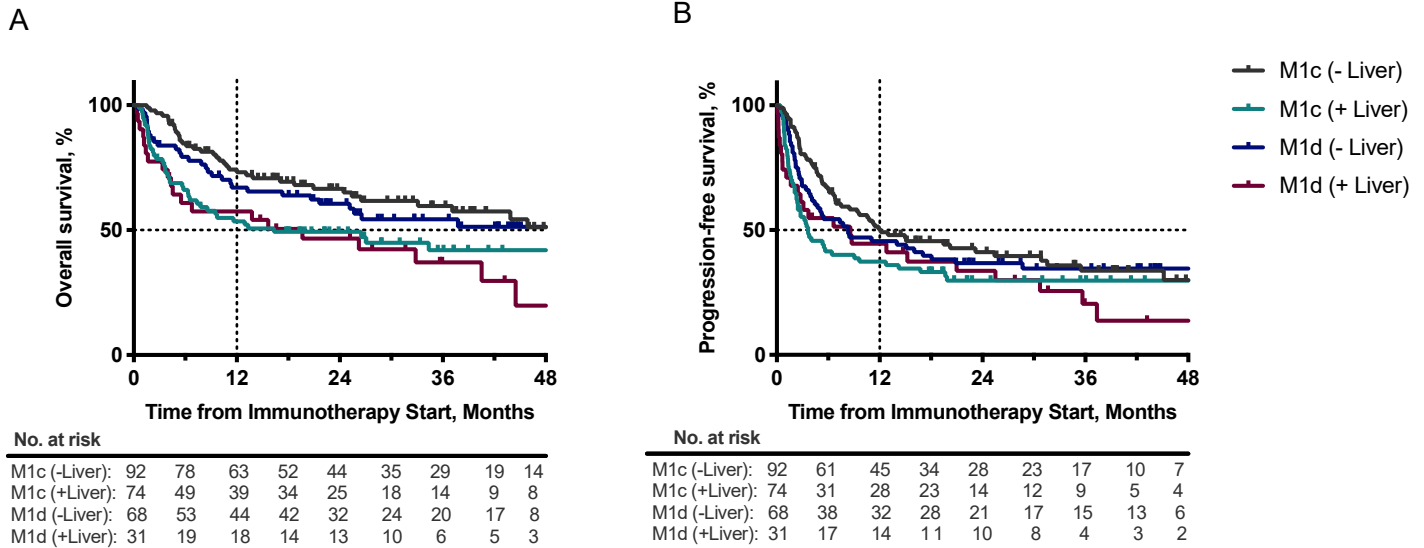
**eFigure 3.** Kaplan-Meier Analysis of Patient OS and PFS by *BRAF* Status



eFigure 3. Kaplan-Meier estimates of patient **A)** OS and **B)** PFS by *BRAF* mutation status. HR, hazard ratio; CI, confidence interval. Vertical dotted line marks 1-year survival.



**eFigure 4.** Kaplan-Meier Analysis Comparing the OS and PFS of Patients With and Without Liver Metastases



eFigure 4. Kaplan-Meier estimates of **A)** OS and **B)** PFS of M1c and M1d cutaneous melanoma patients with and without liver metastases. M1c (- Liver), patients in the M1c category without liver metastases; M1c (+Liver), patients in the M1c category with liver metastases; M1d (-Liver), patients with CNS metastases that do not have liver involvement; M1d (+ Liver), patients with both CNS and liver metastases; HR, hazard ratio; CI, confidence interval. Vertical dotted line marks 1-year survival.

**eTable 5.** OS and PFS Measures for Patients With M1c and M1d Disease With and Without Liver Metastases

	<b>Subjects alive at 1 year (%)</b>	<b>Median Survival (months)</b>
<b>OS</b>		
M1c (-Liver)	73.1	56.5
M1c (+Liver)	54.9	16.3
M1d (-Liver)	66.9	62.0
M1d (+ Liver)	57.5	19.6
<b>PFS</b>		
M1c (-Liver)	50.3	12.1
M1c (+Liver)	37.4	3.7
M1d (-Liver)	45.6	8.3
M1d (+ Liver)	44.6	8.6

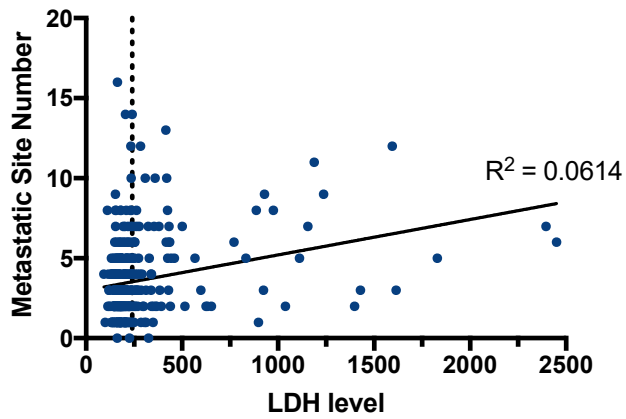
Extended Table 5. Percent of M1c or M1d patients with and without liver metastases alive (OS) or progressed (PFS) at 1 year and median survival time in months. M1c (- Liver), patients in the M1c category without liver metastases; M1c (+Liver), patients in the M1c category with liver metastases; M1d (-Liver), patients with CNS metastases that do not have liver involvement; M1d (+ Liver), patients with both CNS and liver metastases

**eTable 6.** Pairwise Comparisons of Patients With M1c and M1d Disease With and Without Liver Metastases

	OS			PFS		
	HR	95% CI	p-value	HR	95% CI	p-value
M1c (-Liver) vs M1c (+Liver)	0.52	[0.33-0.82]	0.0043	0.64	[0.43-0.95]	0.025
M1c (- Liver) vs M1d (-Liver)	0.86	[0.52-1.36]	0.47	0.83	[0.56-1.23]	0.36
M1c (+ Liver) vs M1d (- Liver)	1.54	[0.97-2.45]	0.065	1.28	[0.86-1.91]	0.23
M1c (+Liver) vs M1d (+ Liver)	0.81	[0.47-1.43]	0.46	0.92	[0.56-1.51]	0.74
M1d (+Liver) vs M1d (-Liver)	0.53	[0.28-0.99]	0.045	0.71	[0.42-1.21]	0.21

Extended Table 6. Pairwise comparisons of M1c and M1d patients with and without liver metastases. M1c (-Liver), patients in the M1c category without liver metastases; M1c (+Liver), patients in the M1c category with liver metastases; M1d (-Liver), patients with CNS metastases that do not have liver involvement; M1d (+ Liver), patients with both CNS and liver metastases; HR, hazard ratio. CI, confidence interval.

**eFigure 5.** Comparison of Number of Metastatic Sites and LDH Level



eFigure 5. Scatter plot of metastatic site number by LDH level. Dotted line is at 240 IU/L which is the upper limit of normal.

**eTable 7.** Pairwise Univariable Analysis of LDH Stratified by Liver Involvement

LDH at Metastatic Diagnosis	Presence of Liver Metastases	OS (months)		PFS (months)	
		HR [95% CI]	p-value	HR [95% CI]	p-value
WNL	No	0.65 [0.39-1.10]	0.096	0.77 [0.51-1.18]	0.23
	Yes				
Elevated (> 240 IU/L)	No	0.42 [0.24-0.71]	0.0014	0.56 [0.34-0.92]	0.021
	Yes				
WNL	No	0.56 [0.33-0.95]	0.032	0.79 [0.52-1.21]	0.28
Elevated					
WNL	Yes	0.32 [0.18-0.56]	<0.0001	0.56 [0.34-0.91]	0.020
Elevated					

eTable 7. Pairwise comparisons of LDH level stratified by liver involvement. LDH, lactate dehydrogenase; WNL, within normal limits,  $\leq 240$  IU/L, elevated,  $>240$  IU/L; HR, hazard ratio; CI, confidence interval.

**eTable 8.** OS and PFS Measures of Patients in the Proposed Staging Model

	<b>Subjects alive at 1 year (%)</b>	<b>Median Survival (months)</b>
<b>OS</b>		
-Liver, LDH (WNL)	79.8	56.5
+Liver OR LDH (Elevated)	63.6	34.4
+Liver AND LDH (Elevated)	34.7	4.2
<b>PFS</b>		
-Liver, LDH (WNL)	55.0	18
+Liver OR LDH (Elevated)	43.7	8.5
+Liver AND LDH (Elevated)	33.2	2.1

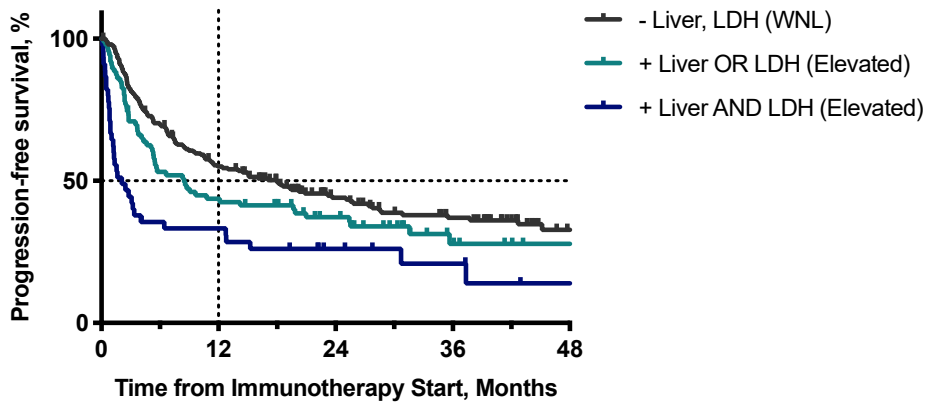
eTable 8. Percent of patients alive at 1 year and median survival in each stratum of the new staging model. - Liver, all patients without liver metastases; + Liver, all patients with liver metastases; LDH, lactate dehydrogenase; WNL, within normal limits,  $\leq 240$  IU/L, elevated,  $>240$  IU/L.

**eTable 9.** Pairwise Comparisons of Each Stratum in the Proposed Staging Model of Patients With Metastatic Cutaneous Melanoma

	OS			PFS		
	HR	95% CI	p-value	HR	95% CI	p-value
+Liver OR LDH (Elevated) vs -Liver, LDH (WNL)	1.79	[1.19-2.67]	0.0049	1.32	[0.95-1.85]	0.10
+Liver AND LDH (Elevated) vs -Liver, LDH (WNL)	9.98	[5.30-18.77]	<0.0001	3.19	[1.93-5.26]	<0.0001
+Liver AND LDH (Elevated) vs +Liver OR LDH (Elevated)	3.01	[1.77-5.12]	<0.0001	1.85	[1.16-2.96]	0.0095

eTable 9. Pairwise comparisons of each stratum. 1) patients with normal LDH levels and no liver metastases (-Liver); 2), patients with either elevated LDH OR liver metastases (+Liver); 3), patients with both elevated LDH and liver metastases. - Liver, all patients without liver metastases; + Liver, all patients with liver metastases; LDH, lactate dehydrogenase; WNL, within normal limits,  $\leq 240$  IU/l, High,  $>240$  IU/L; CI, confidence interval.

**eFigure 6.** Kaplan-Meier Analysis of Progression-Free Survival of the Proposed Staging Model of Patients With Metastatic Cutaneous Melanoma Incorporating LDH Levels and Liver Involvement



**No. at risk**

-Liver, LDH (WNL):	203	141	108	87	62	49	41	29	16
+Liver OR LDH (Elevated):	86	46	38	33	25	17	9	6	4
+Liver AND LDH (Elevated):	45	16	15	12	8	6	5	3	2

eFigure 6. Kaplan-Meier estimates of patient PFS using the proposed staging system for metastatic melanoma. LDH, lactate dehydrogenase; WNL, within normal limits,  $\leq 240$  IU/l, High,  $>240$  IU/L; - Liver, all patients without liver metastases; + Liver, all patients with liver metastases; CI, confidence interval; vertical dotted line marks 1-year survival.



**eTable 10.** Clinical and Disease Characteristics of External Validation Cohort

	<b>Factor</b>	<b>n (%)</b>	
	<b>Overall (n = 652)</b>		
	<b>Age at ICB Start</b>		
	Mean (SD)	67.9 (11.6)	
	Median (IQR)	68.6 (5.3)	
	<b>Gender</b>		
	Female	22 (3.4)	
	Male	630 (96.6)	
	<b>BRAF</b>		
	WT	256 (39.3)	
	MT	179 (27.5)	
	Unknown	217 (33.2)	
	<b>ECOG</b>		
	0	178 (27.3)	
	1	85 (13.0)	
	2+	17 (2.6)	
	Unknown	372 (57.1)	
	<b>ICB Type</b>		
	Dual Agent (Ipilimumab, Nivolumab)	89 (13.7)	
	Single Agent	563 (86.3)	
	<b>Presence of Liver Metastases</b>		
	No	503 (77.1)	
	Yes	149 (22.9)	
	<b>LDH</b>		
	Elevated	203 (31.1)	
	WNL	449 (68.9)	

**eTable 11.** OS Measures of External Validation Cohort

	<b>Subjects alive at 1 year (%)</b>	<b>Median Survival (months)</b>
-Liver, LDH (WNL)	70.1	30.7
+Liver OR LDH (Elevated)	50.6	12.4
+Liver AND LDH (Elevated)	16.9	2.5

eTable 11. OS measures of external validation cohort. - Liver, all patients without liver metastases; + Liver, all patients with liver metastases LDH, lactate dehydrogenase; WNL, within normal limits.

**eTable 12.** Pairwise Comparisons of Each Stratum in the New Staging Model Using an External Validation Cohort

	OS		
	HR	95% CI	p-value
+Liver OR LDH (Elevated) vs -Liver, LDH (WNL)	1.77	[1.40-2.24]	<0.0001
+Liver AND LDH (Elevated) vs -Liver, LDH (WNL)	37.65	[22.69-62.46]	<0.0001
+Liver AND LDH (Elevated) vs +Liver OR LDH (Elevated)	3.96	[2.72-5.78]	<0.0001

eTable 12. Pairwise comparisons of each stratum using a validation cohort. - Liver, all patients without liver metastases; + Liver, all patients with liver metastases; LDH, lactate dehydrogenase; WNL, within normal limits; HR, hazard ratio; CI, confidence interval.