

## Supplemental tables and figure:

**Supplemental Table S1:** Characteristics of the disease before first and second course (ICI rechallenge) of immune checkpoint inhibitor immunotherapy

	First ICI Total, N = 85, 100%	Second ICI Total, N = 85, 100%
<b>AJCC stage</b>		
IIIB (%)	4 (5)	0 (0)
IIIC (%)	15 (18)	7 (8)
IIID (%)	3 (3)	3 (4)
IV (%)	63 (74)	75 (88)
<b>Number of metastatic sites</b>		
≤3 (%)	40 (47)	48 (57)
> 3 (%)	45 (53)	37 (43)
<b>Brain metastasis</b>		
n (%)	16 (19)	22 (26)
<b>Elevated LDH level</b>		
No (%)	47 (55)	55 (65)
Yes (%)	12 (14)	11 (13)
Unknown (%)	26 (31)	19 (22)
<b>Corticosteroids (ICI rechallenge)</b>		9 (11)
> 10 mg/day (%)		6 (7)
≤ 10 mg/day (%)		3 (4)
<b>Immunotherapy (ICI)</b>		
Pembrolizumab (%)	41 (48)	44 (52)
Nivolumab (%)	27 (32)	35 (41)
Ipilimumab (%)	10 (12)	2 (2)
Ipilimumab + Nivolumab (%)	7 (8)	4 (5)
<b>Duration of ICI (months)</b>		
Median [range]	15 [1 – 51]	9 [1 – 72]
<b>Response to ICI</b>		
Complete response (%)	47 (55)	30 (35)
Partial response (%)	28 (33)	16 (19)
Stable disease (%)	10 (12)	18 (21)
Progression (%)	0 (0)	21 (25)
<b>Time to relapse (months)</b>		
Median [range]	14 [2 - 54]	11 [0.1 - 63]
<b>Time to best response to ICI (months)</b>		
Median [range]	11 [0.6 – 48]	3 [0.5 - 34]
<b>Toxicity</b>	43 (51)	23 (27)
Cutaneous (%)	14 (16)	8 (9)
Endocrinal (%)	14 (16)	4 (5)
Digestive (%)	7 (8)	6 (7)
Liver (%)	10 (12)	3 (4)
Respiratory (%)	3 (4)	2 (2)
Hematological (%)	1 (1)	2 (2)
Neuromuscular (%)	3 (4)	0 (0)
Renal	0 (0)	1 (1)
Rheumatological (%)	4 (5)	2 (2)
Cardiac (%)	1 (1)	0
<b>Grade of toxicity</b>		
Grade I (%)	10 (12)	6 (7)
Grade II (%)	15 (18)	7 (8)
Grade III (%)	17 (20)	8 (9)
Grade IV (%)	2 (2)	1 (1)
Grade V (%)	0	0
<b>Time to toxicity (months)</b>		
Median [range]	5 [0.6 – 43]	3 [0.4 – 36]

AJCC: American joint committee on cancer, ECOG: Eastern cooperative oncology group, ICI: Immune checkpoint inhibitor, LDH: Lactate dehydrogenase.

**Supplemental Table S2:** Univariate and multivariate analyses for factors associated with progression free survival during ICI rechallenge

Variable	Univarious model			Multivarious model		
	HR	95% CI	P-value	HR	95% CI	P-value
<b>Age (years)</b>	1.001	0.98, 1.024	0.958			
<b>Gender</b>			0.273			
Male	1	—				
Female	0.702	0.373, 1.321				
<b>ECOG performance status (ICI rechallenge)</b>			0.668			
0/1	1	—				
≥ 2	1.295	0.398, 4.218				
<b>Type of primary melanoma</b>			0.439			
Cutaneous	1	—				
Other	1.330	0.646, 2.737				
<b>BRAFV600 mutation</b>			0.600			
No	—	—				
Yes	1.203	0.603, 2.399				
<b>Response to 1st ICI</b>			0.511			
Complete response + Partial response	1	—				
Stable disease	1.318	0.578, 3.006				
<b>Duration of 1st ICI (months)</b>	1.022	0.99, 1.052	0.139	1.033	1.003, 1.063	0.031
<b>Time to relapse after 1st ICI (months)</b>			0.248			
≤ 6 months	1	—				
> 6 months	0.680	0.353, 1.309				
<b>Systemic treatment between the ICI courses</b>			0.008			0.016
No	1	—		1	—	
Yes	2.548	1.272, 5.104		2.382	1.173, 4.835	
<b>Local treatment between the ICI courses</b>			0.051			
No	1	—				
Yes	1.965	0.997 ; 3.872				
<b>Number of metastatic sites (ICI rechallenge)</b>			0.010			0.007
> 3	1	—		1	—	
≤ 3	0.448	0.243, 0.826		0.421	0.224, 0.793	
<b>Brain metastasis (ICI rechallenge)</b>			0.603			
No	1	—				
Yes	1.192	0.615, 2.312				
<b>Elevated LDH level (ICI rechallenge)</b>			0.312			
No	1	—				
Yes	1.717	0.730, 4.040				
Unknown	1.540	0.763, 3.109				
<b>Corticosteroids (ICI rechallenge)</b>			0.307			
No	1	—				
Yes	1.575	0.658, 3.765				
<b>2<sup>nd</sup> course of ICI (ICI rechallenge)</b>			0.385			
Rechallenge	1	—				
Escalation	1.528	0.364, 6.405				
Switch	0.473	0.143, 1.565				
<b>Toxicity (ICI rechallenge)</b>			0.163			
No	1	—				
Yes	0.599	0.292, 1.230				

CI: Confidence interval, ECOG: Eastern cooperative oncology group, ICI: Immune checkpoint inhibitor, LDH: Lactate dehydrogenase, OR: Odds ratio. Only factors which are significant are shown in multivariate analysis

**Supplemental Table S3:** Univariate and multivariate analyses for factors associated with overall survival during ICI rechallenge

Variable	Univarious model			Multivarious model		
	HR	95% CI	P-value	HR	95% CI	P-value
<b>Age (years)</b>	1.007	0.97, 1.040	0.677			
<b>Gender</b>			0.436			
Male	1	—				
Female	0.711	0.301, 1.679				
<b>Type of primary melanoma</b>			0.252			
Other	1	—				
Cutaneous	0.591	0.270, 3.077				
<b>BRAFV600 mutation</b>			0.971			
No	1	—				
Yes	0.980	0.362, 2.665				
<b>Response to 1st ICI</b>			0.267			
Complete response + Partial response	1	—				
Stable disease	1.770	0.646, 4.852				
<b>Duration of 1st ICI (months)</b>	1.019	0.98, 1.058	0.340			
<b>Time to relapse after 1st ICI (months)</b>			0.039			
≤ 6 months	1	—				
> 6 months	0.419	0.183, 0.96				
<b>Systemic treatment between the ICI courses</b>			0.088			
No	1	—				
Yes	2.259	0.887, 5.755				
<b>Local treatment between the ICI courses</b>			0.100			
No	1	—				
Yes	0.767	0.260, 2.262				
<b>Number of metastatic sites (ICI rechallenge)</b>			0.039			0.020
> 3	1	—		1		
≤ 3	0.413	0.179, 0.96		0.366	0.157, 0.856	
<b>Brain metastasis (ICI rechallenge)</b>			0.283			
No	1	—				
Yes	1.606	0.677, 3.813				
<b>Elevated LDH level (ICI rechallenge)</b>			0.275			
No	1	—				
Yes	2.362	0.828, 6.742				
Unknown	1.297	0.486, 3.462				
<b>Corticosteroids (ICI rechallenge)</b>			0.195			0.007
No	1	—		1	—	
Yes	2.044	0.692, 6.036		5.395	1.578, 18.44	
<b>2<sup>nd</sup> course of ICI (ICI rechallenge)</b>			0.748			
Rechallenge	1	—				
Escalation	1.350	0.179, 10.16				
Switch	0.598	0.138, 2.595				
<b>Toxicity (ICI rechallenge)</b>			0.146			0.025
No	1	—		1	—	
Yes	0.447	0.151, 1.325		0.246	0.072, 0.839	

CI: Confidence interval, ECOG: Eastern cooperative oncology group, ICI: Immune checkpoint inhibitor, LDH: Lactate dehydrogenase, OR: Odds ratio. Only factors which are significant are shown in multivariate analysis

**Supplemental Figure S1:** Efficacy of the repeated courses of immune checkpoint inhibitors

