

**Supplemental Figure Legends:****Figure S1: Association between anti-PD1 regimen and survival in melanoma**

(A) cPFS and (B) OS for the entire cohort of melanoma patients; anti-PD1 (n=172) anti-PD1+ anti-CTLA4 (n=77), Log-rank test P=0.0098 (cPFS); P=0.0132 (OS). Blue line = anti-PD1 monotherapy and Green line = anti-PD1+anti-CTLA4. Tick marks indicate censored patients.

**Figure S2: Survival of BRAF/NRAS wild-type melanoma patients according to anti-PD1 regimen and primary tumor type.**

(A) cPFS and (B) OS for patients with BRAF/NRAS wild-type non-mucosal melanoma; anti-PD1 (n=58) anti-PD1+ anti-CTLA4 (n=15), Log-rank test P=0.9821 (cPFS); P= 0.4338 (OS). (C) cPFS and (D) OS for patients with BRAF/NRAS wild-type mucosal melanoma; anti-PD1 (n=11) anti-PD1+ anti-CTLA4 (n=10), Log-rank test P=0.0007 (cPFS); P= 0.0034 (OS). Tick marks indicate censored patients. Blue line = Anti-PD1 monotherapy and Green line = anti-PD1+anti-CTLA4.

**Figure S3: Survival of BRAF/NRAS wild-type melanoma patients according to the presence or absence of a KIT mutation.**

(A) cPFS and (B) OS for patients with KIT mutant (n=8) or BRAF/NRAS/KIT wildtype (n=71), Log-rank test P=0.8243 (cPFS); P= 0.7868 (OS). The KIT mutant population comprised 7 patients, including: cutaneous melanoma (n=4), mucosal melanoma (n=2) and acral melanoma (n=1). The patient with acral melanoma received 2 lines of anti-PD1 ICI, first ipilimumab + nivolumab which was

discontinued due to toxicity. Then, upon progression they were treated with pembrolizumab, which was discontinued due to progression; both lines of treatment are included in these analyses. Both patients with *KIT* mutant mucosal melanoma received anti-PD1 + anti-CTLA4 ICI. All four patients with *KIT* mutant cutaneous melanoma received anti-PD1 monotherapy. One patient with cutaneous *KIT* mutant melanoma also had a concomitant *NRAS* mutation. Tick marks indicate censored patients. Blue line = *BRAF/NRAS/KIT* wild-type (n=73) and Green line = *KIT* mutant (n=8).

**Table S1: Characteristics in the entire melanoma cohort and according to anti-PD1 treatment regimen**

		Entire cohort (n=249)	Anti-PD1 monotherapy (n=172)	Anti-PD1 + anti-CTLA4 (n=77)	P-value
Genomic subtype					0.472
	<b>BRAF V600E/K</b>	86 (35%)	56 (33%)	30 (39%)	
	<b>NRAS</b>	69 (28%)	47 (27%)	22 (29%)	
	<b>BRAF/NRAS wt</b>	94 (38%)	69 (40%)	25 (32%)	
Primary tumor type					<b>0.022</b>
	<b>Cutaneous</b>	183 (73%)	136 (79%)	47 (61%)	
	<b>Unknown</b>	20 (8%)	10 (6%)	10 (14%)	
	<b>Primary</b>				
	<b>Mucosal</b>	28 (11%)	15 (9%)	13 (17%)	
Age	<b>Acral</b>	18 (7%)	11 (6%)	7 (9%)	
					<b>0.006</b>
	<b>&lt;60</b>	122 (49%)	74 (43%)	48 (62%)	
	<b>≥60</b>	127 (51%)	98 (57%)	29 (38%)	
Gender					<b>0.035</b>
	<b>male</b>	145 (58%)	96 (56%)	53 (69%)	
	<b>female</b>	104 (42%)	76 (44%)	24 (31%)	
# metastatic sites					0.144
	<b>&gt;3</b>	184 (74%)	131 (76%)	53 (69%)	
	<b>≤3</b>	65 (26%)	41 (24%)	24 (31%)	
M-stage					0.066
	<b>M0/M1a/M1b</b>	93 (37%)	71 (41%)	22 (44%)	
	<b>M1c/M1d</b>	156 (63%)	101 (59%)	55 (56%)	
LDH					0.876
	<b>&lt;1.5x ULN</b>	183 (74%)	127 (74%)	56 (73%)	
	<b>≥1.5x ULN</b>	65 (26%)	44 (26%)	21 (27%)	
NLR					0.749
	<b>&lt;5</b>	188 (76%)	131 (76%)	57 (74%)	
	<b>≥5</b>	60 (24%)	40 (24%)	20 (26%)	
Line of therapy					<b>&lt;0.001</b>
	<b>1<sup>st</sup></b>	135 (54%)	72 (58%)	63 (82%)	
	<b>2<sup>nd</sup> or later</b>	114 (46%)	100 (42%)	14 (18%)	

**Table S2: Cox regression analyses for cutaneous melanoma patients (n=183)**

	cPFS - univariable			cPFS - multivariable			OS - univariable			OS - multivariable		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
<b>Anti-PD1 regimen</b> PD1+CTLA4 vs. PD1	0.75	0.48-1.15	0.190	0.66	0.42-1.02	0.063	0.68	0.41-1.14	0.142	0.57	0.33-0.96	0.035
<b>Genomic subtype</b> BRAF or NRAS mt vs. WT	1.70	1.13-2.56	0.011	1.64	1.07-2.49	0.022	1.50	0.96-2.36	0.077	1.65	1.02-2.67	0.043
<b>Line of therapy</b> 1 <sup>st</sup> vs. 2 <sup>nd</sup> or later	0.65	0.46-0.93	0.019	-	-	-	0.62	0.41-0.92	0.019	-	-	-
<b># metastatic sites</b> > 3 vs. ≤ 3	2.50	1.72-3.65	<0.001	2.25	1.53-3.31	<0.001	2.60	1.72-3.95	<0.001	2.24	1.46-3.44	<0.001
<b>M-stage</b> M1c/1d vs. M0/1a/1b	1.50	1.04-2.17	0.028	-	-	-	1.86	1.23-2.82	0.003	-	-	-
<b>LDH</b> ≥1.5X ULN vs. < 1.5x	1.90	1.25-2.89	0.003	1.57	1.03-2.41	0.037	2.42	1.53-3.84	<0.001	1.88	1.16-3.03	0.010
<b>NLR</b> ≥5 vs. <5	1.47	0.98-2.21	0.060	-	-	-	1.82	1.18-2.82	0.007	1.58	0.99-2.53	0.056
<b>Age</b> ≥60 vs. <60	0.84	0.59-1.20	0.329	-	-	-	1.38	0.92-2.07	0.119	-	-	-
<b>Gender</b> male vs. female	0.93	0.65-1.33	0.685	-	-	-	0.96	0.64-1.43	0.824	-	-	-

**Table S3: Cox regression analysis for NRAS mutant melanoma patients (n=69)**

	cPFS - univariable			cPFS - multivariable			OS - univariable			OS - multivariable		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
<b>Anti-PD1 regimen</b> PD1+CTLA4 vs. PD1	0.45	0.23-0.92	0.029	0.34	0.16-0.71	0.004	0.49	0.21-1.13	0.095	0.24	0.10-0.62	0.003
<b>Primary tumor type</b> acral or mucosal vs. cutaneous or UP	1.55	0.77-3.15	0.222	-	-	-	2.01	0.93-4.35	0.076	3.18	1.34-7.51	0.008
<b>Line of therapy</b> 1 <sup>st</sup> vs. 2 <sup>nd</sup> or later	0.82	0.45-1.51	0.525	-	-	-	0.65	0.33-1.27	0.204	-	-	-
<b># metastatic sites</b> > 3 vs. ≤ 3	1.64	0.88-3.09	0.121	2.27	1.17-4.42	0.016	1.69	0.83-3.46	0.152	3.14	1.38-7.16	0.006
<b>M-stage</b> M1c/1d vs. M0/1a/1b	1.96	1.04-3.70	0.037	-	-	-	2.57	1.20-5.53	0.015	-	-	-
<b>LDH</b> ≥1.5X ULN vs. < 1.5x	2.32	1.28-4.21	0.005	2.80	1.52-5.18	0.001	3.23	1.64-6.37	0.001	4.25	2.05-8.78	<0.001
<b>NLR</b> ≥5 vs. <5	1.59	0.82-3.08	0.165	-	-	-	2.30	1.12-4.74	0.024	-	-	-
<b>Age</b> ≥60 vs. <60	1.29	0.69-2.42	0.429	-	-	-	1.74	0.81-3.74	0.152	2.50	1.13-5.52	0.024
<b>Gender</b> male vs. female	0.86	0.48-1.54	0.617	-	-	-	1.05	0.55-2.02	0.881	-	-	-

**Table S4: Cox regression analysis for BRAF V600E/K mutant advanced melanoma patients (n=86)**

	cPFS - univariable			cPFS - multivariable			OS - univariable			OS - multivariable		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
<b>Anti-PD1 regimen</b> PD1+CTLA4 vs. PD1	0.64	0.37-1.09	0.100	-	-	-	0.49	0.25-0.94	0.033	0.47	0.24-0.90	0.024
<b>Primary tumor type</b> acral or mucosal vs. cutaneous or UP	1.17	0.29-4.82	0.824	-	-	-	1.17	0.28-4.85	0.824	-	-	-
<b>Line of therapy</b> 1 <sup>st</sup> vs. 2 <sup>nd</sup> or later	0.61	0.36-1.04	0.070	-	-	-	0.45	0.24-0.87	0.017	-	-	-
<b># metastatic sites</b> > 3 vs. ≤ 3	3.14	1.89-5.25	<0.001	3.48	2.04-5.90	<0.001	2.70	1.53-4.78	0.001	3.24	1.79-5.90	<0.001
<b>M-stage</b> M1c/1d vs. M0/1a/1b	1.92	1.11-3.12	0.019	-	-	-	2.08	1.11-3.89	0.021	-	-	-
<b>LDH</b> ≥1.5X ULN vs. < 1.5x	1.45	0.85-2.48	0.175	-	-	-	1.89	1.03-3.45	0.039	-	-	-
<b>NLR</b> ≥5 vs. <5	1.50	0.83-2.72	0.177	1.88	1.02-3.46	0.041	1.81	0.94-3.50	0.075	2.54	1.28-5.05	0.008
<b>Age</b> ≥60 vs. <60	0.70	0.40-1.22	0.213	-	-	-	1.39	0.77-2.51	0.281	-	-	-
<b>Gender</b> male vs. female	0.63	0.38-1.02	0.064	-	-	-	0.59	0.34-1.04	0.070	-	-	-

**Table S5: Cox regression analysis for BRAF/NRAS wild-type melanoma patients (n=94)**

	cPFS - univariable			cPFS - multivariable			OS - univariable			OS - multivariable		
	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
<b>Anti-PD1 regimen</b> PD1+CTLA4 vs. PD1	0.73	0.40-1.36	0.326	-	-	-	0.80	0.40-1.62	0.540	-	-	-
<b>Primary tumor type</b> acral or mucosal vs. cutaneous or UP	2.21	1.31-3.76	0.003	2.29	1.35-3.91	0.002	2.24	1.25-4.00	0.007	2.29	1.28-4.11	0.005
<b>Line of therapy</b> 1 <sup>st</sup> vs. 2 <sup>nd</sup> or later	0.43	0.25-0.72	0.001	0.42	0.25-0.70	0.001	0.51	0.29-0.90	0.019	0.50	0.28-0.88	0.016
<b># metastatic sites</b> > 3 vs. ≤ 3	1.72	0.96-3.11	0.070	-	-	-	1.96	1.05-3.65	0.035	-	-	-
<b>M-stage</b> M1c/1d vs. M0/1a/1b	0.90	0.54-1.52	0.710	-	-	-	1.17	0.66-2.08	0.583	-	-	-
<b>LDH</b> ≥1.5X ULN vs. < 1.5x	1.79	0.99-3.24	0.051	-	-	-	2.34	1.25-4.38	0.008	-	-	-
<b>NLR</b> ≥5 vs. <5	1.31	0.75-2.29	0.340	-	-	-	1.55	0.85-2.83	0.151	-	-	-
<b>Age</b> ≥60 vs. <60	0.81	0.49-1.37	0.443	-	-	-	1.02	0.58-1.82	0.922	-	-	-
<b>Gender</b> male vs. female	0.86	0.51-1.45	0.578	-	-	-	0.94	0.53-1.68	0.839	-	-	-

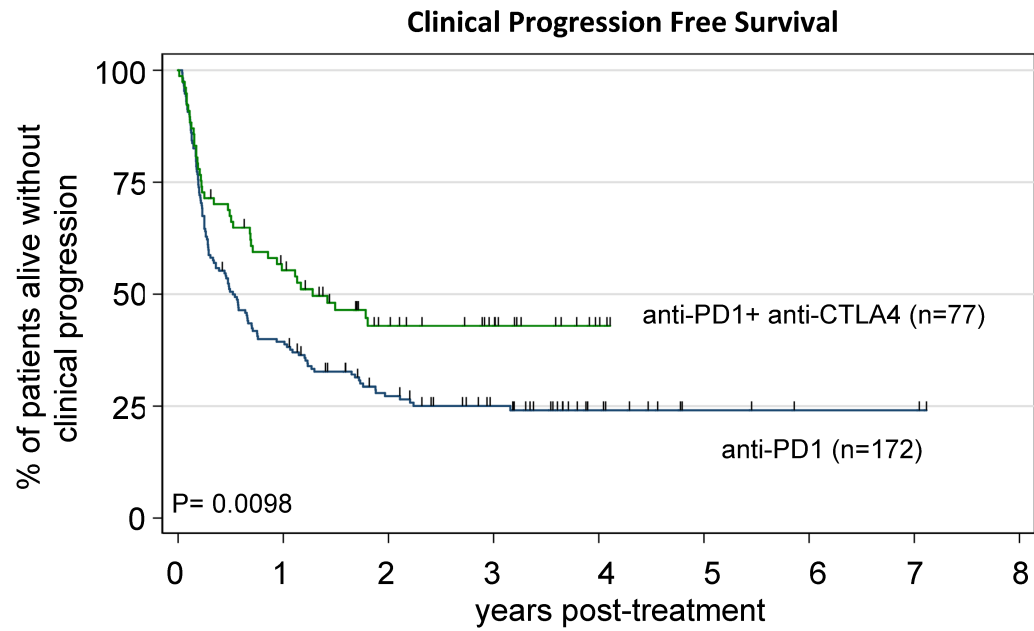
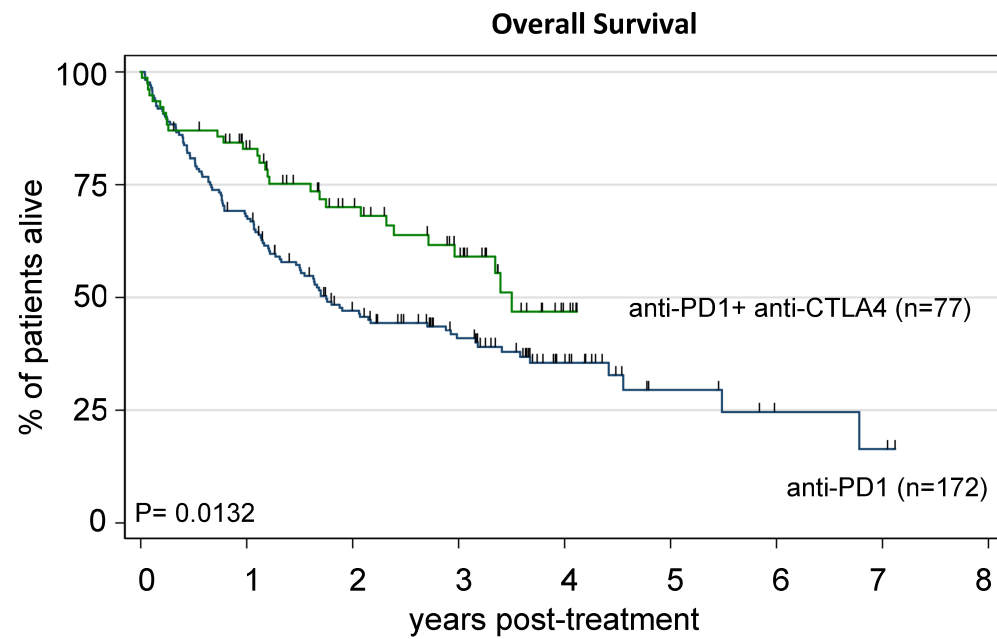
**A****B**

Figure S1



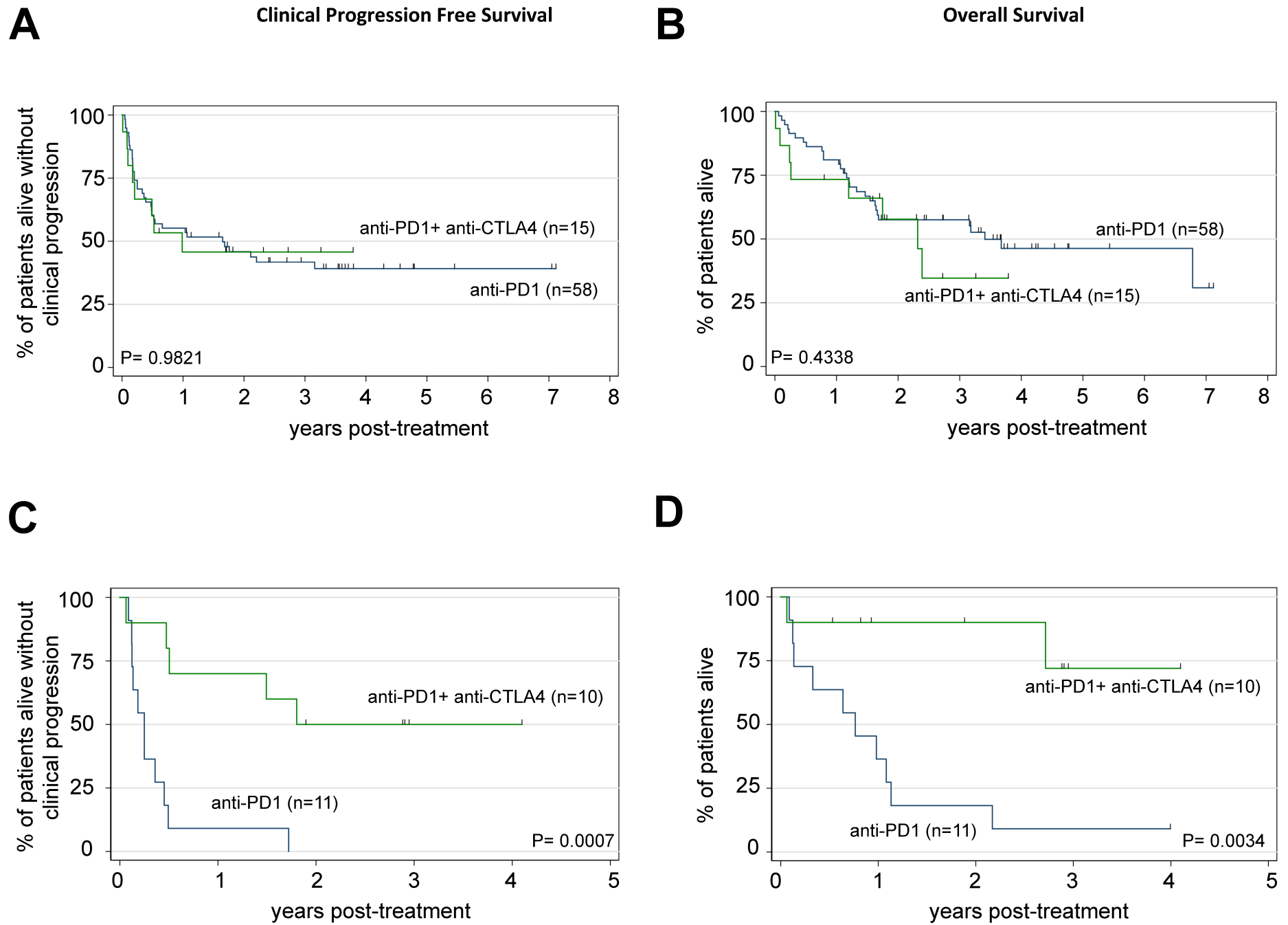


Figure S2

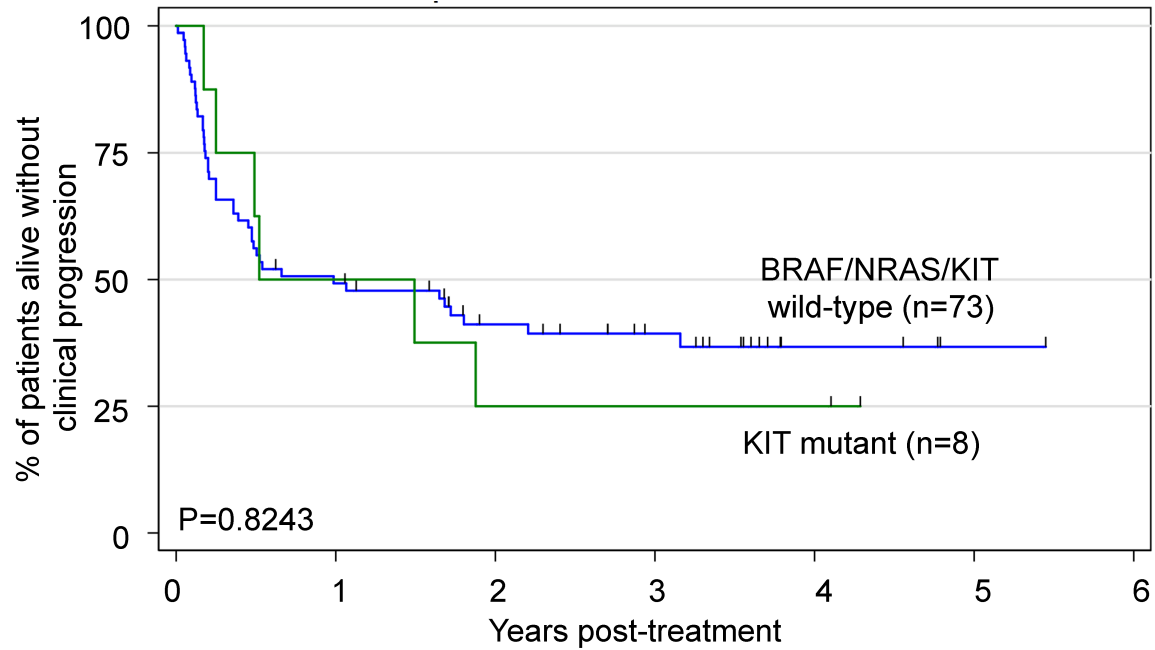
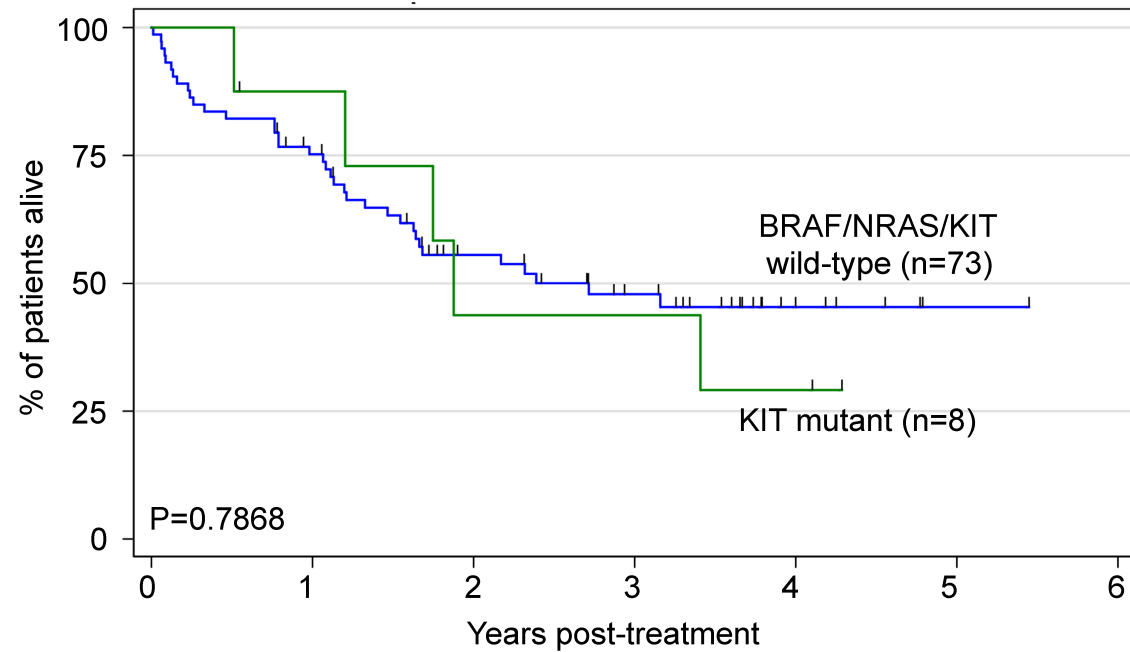
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Figure S3