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Online-Only Supplements

1. **Supplement 1:** Details on 1st exposure CPI combination approaches. TVEC Talimogene laherparepvec.

2. **Supplement 2:** Additional details of patient and disease characteristics at 1st exposure to CPI. CR complete response, ECOG Eastern Cooperative Oncology Group, LDH lactate dehydrogenase.

3. **Supplement 3:** Progression Free Survival (PFS) by best overall RECIST response.

   a. **Supplement 3a:** Progression Free Survival (PFS) for patients who responded to 1st exposure CPI.

   b. **Supplement 3b:** Progression Free Survival (PFS) for patients who responded to 1st exposure CPI, by best RECIST response.

   c. **Supplement 3c:** Progression Free Survival (PFS) for patients who responded to 1st exposure CPI, by treatment received.

   d. **Supplement 3d:** Progression Free Survival (PFS) for patients achieving CR to 1st exposure CPI, by treatment received.

   e. **Supplement 3e:** Progression Free Survival (PFS) for patients achieving PR to 1st exposure CPI, by treatment received.

4. **Supplement 4:** Objective response rate (ORR) to second line therapy, immediately subsequent to 1st CPI exposure. CR complete response; PR partial response; SD stable disease; PD progressive disease.

5. **Supplement 5:** Univariable and Multivariable Cox regression for overall survival (OS) to 1st exposure CPI. HR hazard ratio; CPI checkpoint inhibitor; LDH lactate dehydrogenase; ECOG Eastern Cooperative Oncology Group.

6. **Supplement 6:** Patient and disease characteristics by primary acral melanoma site.

7. **Supplement 7:** Objective response rate (ORR) to 1st exposure CPI, by primary site. CR complete response; PR partial response; SD stable disease; PD progressive disease; OR odds ratio.

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8. **Supplement 8:** Patient and disease characteristics for patients treated with 1st line CPI therapy. ECOG Eastern Cooperative Oncology Group; LDH lactate dehydrogenase.

9. **Supplement 9:** Efficacy of 1st line CPI therapy.

   a. **Supplement 9a:** Objective response rate (ORR) to 1st line CPI therapy. CR complete response; PR partial response; SD stable disease; PD progressive disease.

   b. **Supplement 9b:** Univariable and Multivariable Logistic regression for objective response rate (ORR) to 1st line CPI therapy, excluding 69 patients who received first line non-CPI therapy. OR odds ratio; CPI checkpoint inhibitor; LDH lactate dehydrogenase; ECOG Eastern Cooperative Oncology Group.

10. **Supplement 10:** Progression free survival (PFS) and overall survival (OS) the 1st line CPI therapy.

    a. **Supplement 10a:** Kaplan-Meier curve for progression free survival (PFS) to 1st line CPI therapy (p=0.017).

    b. **Supplement 10b:** Univariable and Multivariable Cox regression for progression free survival (PFS) to 1st line CPI therapy. HR hazard ratio; CPI checkpoint inhibitor; LDH lactate dehydrogenase; ECOG Eastern Cooperative Oncology Group.

    c. **Supplement 10c:** Kaplan-Meier curve for overall survival (OS) to 1st line CPI therapy (p=0.68).

    d. **Supplement 10d:** Univariable and Multivariable Cox regression for overall survival (OS) to 1st line CPI therapy. HR hazard ratio; CPI checkpoint inhibitor; LDH lactate dehydrogenase; ECOG Eastern Cooperative Oncology Group.

11. **Supplement 11:** Patient and disease characteristics of total population, and by 1st CPI exposure (anti-PD1 vs anti-PD1/ipilimumab), before and after propensity score matching.

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13. **Supplement 13:** Progression free survival (PFS), after propensity score matching.

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    d. **Supplement 15d:** Kaplan-Meier curve for overall survival (OS) in BRAF mutant patients (N=38)

Supplement 1: Details on 1st exposure CPI combination approaches. TVEC Talimogene laherparepvec.

1st exposure CPI category	Combination agents	Patient number (N)
PD1 +/- Other	Pembrolizumab + Electrochemotherapy	1
	Pembrolizumab + Epacadostat	6
	Pembrolizumab + Imatinib	1
	Pembrolizumab + IDO inhibitor	2
	Pembrolizumab + TVEC	7
	Nivolumab + Bempegaldesleukin	1
	Pembrolizumab + Interleukin	1
	Pembrolizumab + Lenvatinib	1
CTLA4 +/- Other	Ipilimumab + TVEC	2
	Ipilimumab + Bevacizumab	1

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Supplement 2: Additional details of patient and disease characteristics at 1st exposure to CPI. CR complete response, ECOG Eastern Cooperative Oncology Group, LDH lactate dehydrogenase.

Patient and Disease Characteristic	Total (N=325)	Anti-PD1 (N=184)	Anti-PD1 + Ipilimumab (N=59)	Ipilimumab (N=82)	P-value[a]
Median age at diagnosis of primary acral melanoma, years [range]	63 [20-88]	65 [29-88]	60 [20-81]	59 [28-80]	**0.001**
Mutation- positive/tested (% of tested)					0.07
BRAF	38/312 (12)	21/179 (12)	10/55 (18)	7/78 (9)	
V600E	29	13	9	7	
V600	2	2	-	-	
Other	4	3	1	-	
Unknown	3	3	-	-	
KIT	23/235 (10)	19/140 (14)	1/45 (2)	3/50 (6)	
NRAS	54/264 (21)	29/153 (19)	11/49 (22)	14/62 (23)	
Q61R	20	12	4	4	
Q61K	8	5	1	2	

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G12C/D/K/R/S	6	1	2	3	
Other	4	1	2	1	
Unknown	16	10	2	4	
BRAF/KIT both	1/234 (0.4)	1/139 (0.7)	0	0	
Other	23/93 (25)	14/56 (25)	7/26 (27)	2/11 (18)	
Wild Type	175/314 (56)	96/180 (53)	26/55 (47)	53/78 (67)	
Unknown/Not tested	11/325 (3)	4	4	3	
Treatment discontinuation reason					**<0.0001**
Progressive Disease	197 (61)	126 (69)	32 (54)	39 (48)	
Toxicity	46 (14)	17 (9)	22 (37)	7 (9)	
Complete Response	19 (6)	14 (8)	1 (2)	4 (5)	
Completed therapy	36 (11)	7 (4)	0	29 (35)	
Elective	7 (2)	3 (2)	2 (3)	2 (2)	
Other[b]	9 (3)	7 (4)	1 (2)	1 (1)	
Treatment ongoing	11 (3)	10 (5)	1 (2)	0	

[a]Pearson's Chi-squared test; Fisher's exact test. [b]Other includes death, other medical condition.

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Supplement 3: Progression Free Survival (PFS) by best overall RECIST response.

Supplement 3a: Progression Free Survival (PFS) for patients who responded to 1st exposure CPI.

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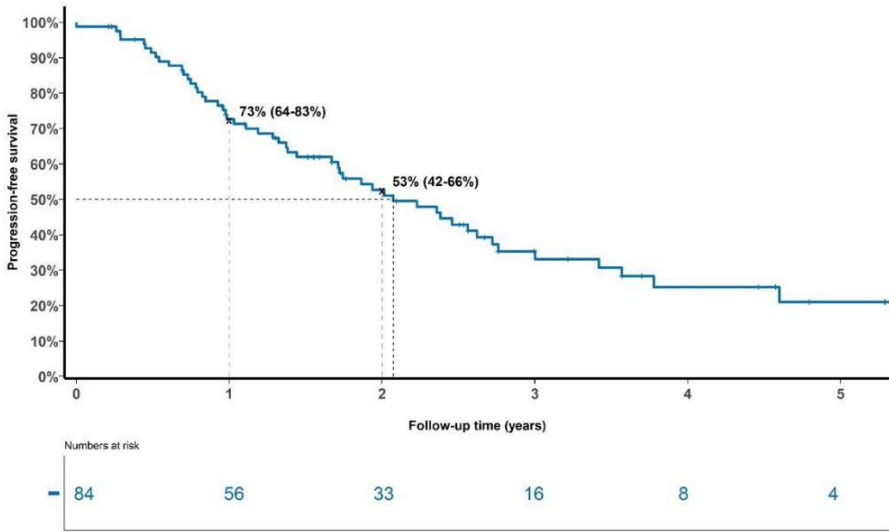
Supplement 3b: Progression Free Survival (PFS) for patients who responded to 1st exposure CPI, by best RECIST response.
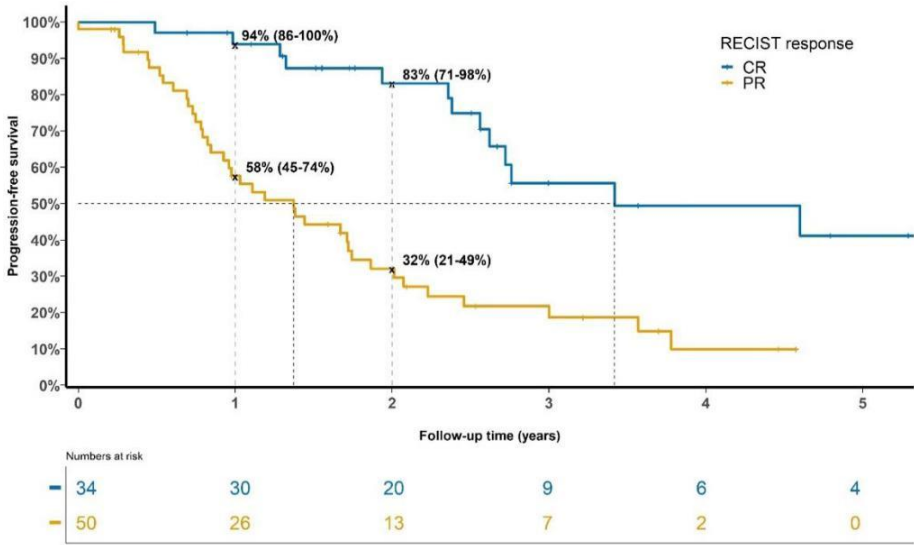
Supplement 3c: Progression Free Survival (PFS) for patients who responded to 1st exposure CPI, by treatment received.
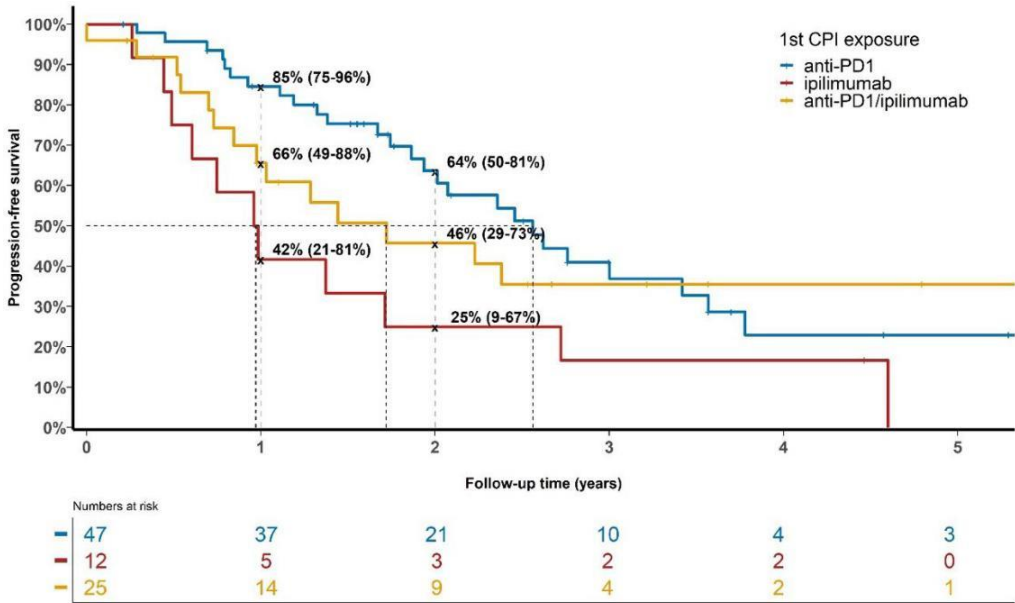
Supplement 3d: Progression Free Survival (PFS) for patients achieving CR to 1st exposure CPI, by treatment received.
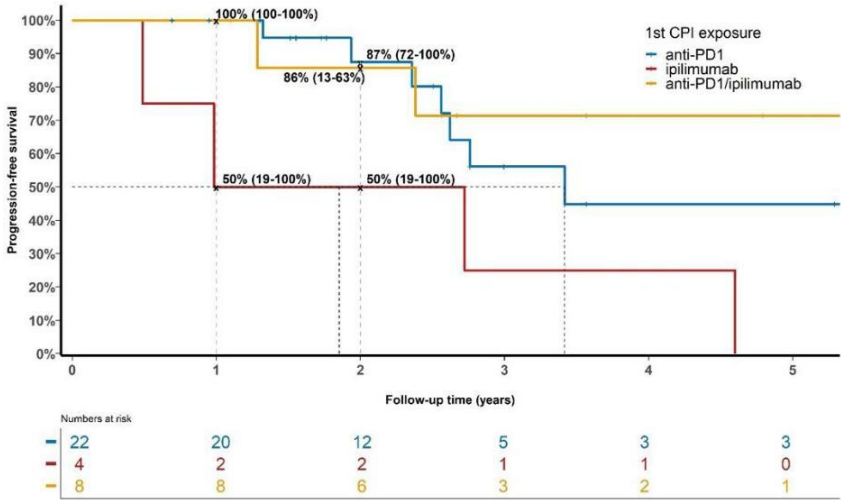
Supplement 3e: Progression Free Survival (PFS) for patients achieving PR to 1st exposure CPI, by treatment received.
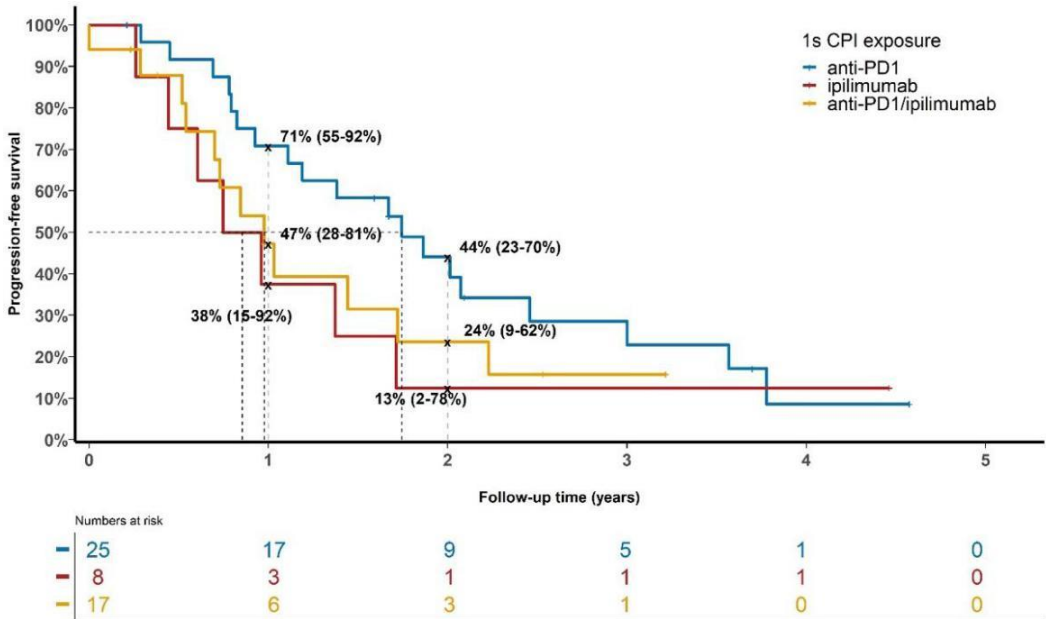
Supplement 4: Objective response rate (ORR) to second line therapy, immediately subsequent to 1st CPI exposure. CR complete response; PR partial response; SD stable disease; PD progressive disease.

N (%)	1st exposure anti-PD1 → anti-PD1 + ipilimumab (N=21)	1st exposure anti-PD1 → ipilimumab (N=37)	1st exposure anti-PD1 → BRAF/MEK (N=8)	1st exposure anti-PD1 + ipilimumab → BRAF/MEK (N=3)
ORR, %	24	14	75	67
CR	2 (10)	1 (3)	3 (38)	1 (33)
PR	3 (14)	4 (11)	3 (38)	1 (33)
SD	3 (14)	11 (30)	1 (13)	0 (0)
PD	13 (62)	21 (57)	1 (13)	1 (33)

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Supplement 5: Univariable and Multivariable Cox regression for overall survival (OS) to 1st exposure CPI. HR hazard ratio; CPI checkpoint inhibitor; LDH lactate dehydrogenase; ECOG Eastern Cooperative Oncology Group.

Variable	Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
1st CPI exposure				
Anti-PD1	1			
Anti-PD1/ipilimumab	1.30 (0.90, 1.87)	0.16	-	-
Ipilimumab	1.11 (0.82, 1.52)	0.50	-	**-**
Stage of advanced disease				
Unresectable IIIB	1		1	
Unresectable IIIC	0.57 (0.22, 1.48)	0.25	0.48 (0.18, 1.25)	0.13
Unresectable IIID	0.69 (0.23, 2.07)	0.51	0.61 (0.20, 1.88)	0.39
M1a	0.68 (0.26, 1.75)	0.42	0.68 (0.26, 1.79)	0.44
M1b	0.90 (0.36, 2.26)	0.82	0.76 (0.30, 1.96)	0.58
M1c	1.02 (0.41, 2.52)	0.97	0.84 (0.33, 2.10)	0.71
M1d	4.49 (1.71, 11.83)	**0.002**	2.96 (1.07, 8.23)	**0.04**
Primary acral melanoma site				

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Subungual	1			
Plantar	0.86 (0.63, 1.18)	0.35	-	-
Palmar	0.58 (0.30, 1.12)	0.11	-	-
Sex				
Female	1			
Male	1.13 (0.86, 1.48)	0.39	-	-
Ethnicity				
Non-Caucasian	1			
Caucasian	0.97 (0.69, 1.36)	0.85	-	-
LDH[a]				
Normal (≤ULN)	1			
Elevated (>ULN)	1.45 (1.02, 2.05)	**0.04**	-	-
ECOG				
0	1		1	
≥1	2.11 (1.57, 2.84)	**<0.0001**	1.75 (1.27, 2.42)	**0.0006**

[a]LDH not included in multivariable analysis due to >20% missing values.

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Supplement 6: Patient and disease characteristics by primary acral melanoma site.

Patient Characteristic	Total (N=325)	Palmar (N=22)	Plantar (N=234)	Subungual (N=69)	P-value[a]
Median age at diagnosis of advanced acral melanoma, years [range]	66 [23- 90]	59 [32-77]	67 [23- 90]	67 [31- 89]	**0.04**
Sex- no. (%)					0.67
Female	154 (47)	10 (46)	108 (46)	36 (52)	
Male	171 (53)	12 (55)	126 (54)	33 (48)	
Ethnicity- no. (%)					0.97
Caucasian	252 (78)	17 (77)	183 (78)	52 (75)	
Non-Caucasian[b]	64 (20)	4 (18)	46 (20)	14 (20)	
Unknown	9 (3)	1 (5)	5 (2)	3 (4)	
Mutation- positive/tested (% of tested)					**0.0004**
BRAF	38/312 (12)	2/20 (10)	32/227 (14)	4/65 (6)	
V600E	29	2	25	2	

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V600	2	0	1	1
Other	4	0	3	1
Unknown	3	0	3	0
KIT	23/235 (10)	5/17 (29)	9/170 (5)	9/48 (19)
NRAS	54/264 (21)	2/18 (11)	47/191 (25)	5/55 (9)
Q61R	20	0	18	2
Q61K	8	0	8	0
G12C/D/K/R/S	6	1	5	0
Other	4	0	4	0
Unknown	16	1	12	3
BRAF/KIT both	1/234 (0.4)	0	0	1/47 (2)
Other	23/93 (25)	0	14/64 (22)	9/24 (38)
Wild Type	175/314 (56)	11/20 (55)	126/228 (55)	33/66 (50)
Unknown/Not tested	11	2	6	3
ECOG- no. (%)				0.78
0	170 (52)	13 (59)	119 (51)	38 (55)
≥1	110 (34)	6 (27)	79 (34)	25 (36)

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Unknown	45 (37)	3 (14)	36 (15)	6 (9)	
LDH					0.37
Normal (≤ULN)	135 (42)	12(55)	93 (40)	30 (44)	
Elevated (>ULN)	69 (21)	4 (18)	54 (23)	11 (16)	
Unknown	121 (37)	6 (27)	87 (37)	28 (41)	
Stage (AJCC 8th ed)- no (%)					0.66
Unresectable III	79 (24)	3 (14)	62 (26)	14 (20)	
IV	246 (76)	19(86)	172 (74)	55 (80)	
M1a	53 (16)	3(14)	39 (16)	11 (16)	
M1b	66 (21)	7(32)	40 (17)	19 (28)	
M1c	103 (32)	7(32)	73 (31)	23 (34)	
M1d	24 (7)	2(9)	20 (9)	2 (2)	
Number of treatment lines for advanced disease prior to 1st CPI exposure					0.18
0	256 (79)	15(68)	181 (77)	60 (87)	
1	62 (19)	6 (27)	47 (20)	9 (13)	

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2	7 (2)	1 (5)	6 (3)	0	
De-novo metastatic disease- no (%)	33 (10)	1 (5)	25 (11)	7 (10)	0.68
Time from primary diagnosis to advanced disease, months [range]	21 [0-261]	27 [0-154]	21 [0-246]	18 [0-261]	0.49

[a]Pearson's Chi-squared test; Fisher's exact test. [b]Non-Caucasian includes: East Asian, South East Asian, Middle Eastern, Hispanic and Black.

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Supplement 7: Objective response rate (ORR) to 1st exposure CPI, by primary site. CR complete response; PR partial response; SD stable disease; PD progressive disease; OR odds ratio.

N (%)	Subungual (N=67)	Plantar (N=232)	Palmar (N=21)
ORR, %	**19**	**27**	**43**
CR	6 (9)	24 (10)	4 (19)
PR	7 (10)	38 (16)	5 (24)
SD	10 (15)	39 (17)	3 (14)
PD	44 (66)	131 (57)	9 (43)

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Supplement 8: Patient and disease characteristics for patients treated with 1st line CPI therapy. ECOG Eastern Cooperative Oncology Group; LDH lactate dehydrogenase.

Patient and Disease Characteristic	Total (N=256)	Anti-PD1 (N=151)	Anti-PD1 + Ipilimumab (N=54)	Ipilimumab (N=51)	P-value[a]
Primary site- no. (%)					0.57
Palmar	15 (6)	10 (7)	3 (6)	2 (4)	
Plantar	181 (71)	111 (74)	36 (67)	34 (67)	
Weight bearing	109	63	24	22	
Non-weight bearing	36	23	8	5	
Subungual	60 (23)	30 (20)	15 (28)	15 (29)	
Toenail	33	17	9	7	
Fingernail	27	13	6	8	
Median age at diagnosis of primary acral melanoma, years [range]	65 [20-87]	67 [30-87]	61 [20-81]	63 [30-80]	**0.001**
Median age at diagnosis of advanced acral melanoma, years [range]	68 [23-90]	70 [31-90]	64 [23-82]	65 [31-85]	**0.001**
Sex- no. (%)					0.80

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Female	121 (47)	69 (46)	26 (48%)	.326 (51)	
Male	135 (53)	82 (54)	28 (52%)	25 (49)	
Ethnicity- no. (%)					0.41
Caucasian	208 (81)	121 (80)	43 (80)	44 (86)	
Non-Caucasian[b]	40 (16)	27 (18)	8 (15)	5 (10)	
Unknown	8 (3)	3 (2)	3 (6)	2 (4)	
Mutation- positive/tested (% of tested)					0.21
BRAF	27/248 (11)	16/148 (11)	8/50 (16)	3/50 (6)	
V600E	21	11	7	3	
V600	1	1	0	0	
Other	3	3	1	0	
Unknown	1	1	0	0	
KIT	19/184 (10)	15/112 (13)	1/42 (2)	3/30 (10)	
NRAS	43/210 (21)	25/125 (20)	10/45 (22)	8/40 (20)	
Q61R	17	10	4	3	
Q61K	6	5	0	1	
G12C/D/K/R/S	5	1	2	2	

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Other	4	1	2	1
Unknown	11	8	2	1
BRAF/KIT both	1/184 (0.5)	1/112 (0.9)	0	0
Other	22/84 (26)	13/50 (26)	7/24 (29)	2/10 (20)
Wild Type	136/248 (55)	78/148 (53)	24/50 (48)	34/50 (68)
Unknown/Not tested	8	3	4	1
ECOG at 1st line systemic therapy- no. (%)				**0.02**
0	139 (54)	85 (56)	24 (44)	30 (59)
≥1	82 (32)	43 (29)	27 (50)	12 (24)
Unknown	35(14)	23 (15)	3 (6)	9 (18)
LDH at 1st line systemic therapy				**0.03**
Normal (≤ULN)	98 (38)	65 (43)	17 (31.5%)	16 (31)
Elevated (>ULN)	50 (20)	23 (15)	18 (33.3%)	9 (18)
Unknown	108 (42)	63 (42)	19 (35.2%)	26 (51)
Stage (AJCC 8th ed)- no (%)				**0.003**
Unresectable III	71 (28)	51 (34)	9 (17)	11 (22)
IV	185 (72)	100 (66)	45 (83)	40 (78)

M1a	41 (16)	25 (17)	6 (11)	10 (20)	
M1b	49 (19)	34 (23)	6 (11)	9 (17)	
M1c	79 (31)	35 (23)	24 (44)	20 (39)	
M1d	16 (6)	6 (4)	9 (17)	1 (2)	
Treatment discontinuation reason					**<.0001**
Progressive Disease	156 (61)	103 (68)	27 (50)	26 (51)	
Toxicity	43 (17)	15 (10)	22 (41)	6 (12)	
Complete Response	15 (6)	13 (9)	1 (2)	1 (2)	
Completed therapy	18 (7)	3 (2)	0	15 (29)	
Elective	6 (2)	2 (1)	2 (4)	2 (4)	
Other[c]	7 (3)	5 (3)	1 (2)	1 (2)	
Treatment ongoing	11 (4)	10 (7)	1 (2)	0	
De-novo metastatic disease- no (%)	24 (10)	14 (10)	7 (13)	3 (6)	0.48
Time from primary diagnosis to advanced disease, months [range]	20 [0-261]	18 [0-261]	22 [0-131]	24 [0-193]	0.12

[a]Pearson's Chi-squared test; Fisher's exact test. [b]Non-Caucasian includes East Asian, South East Asian, Middle Eastern, Hispanic and Black. [c]Other includes death, other medical condition.

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Supplement 9: Efficacy of 1st line CPI therapy.

Supplement 9a: Objective response rate (ORR) to 1st line CPI therapy. CR complete response; PR partial response; SD stable disease; PD progressive disease.

N (%)	Anti-PD1 (N=149)	Anti-PD1 + Ipilimumab (N=54)	Ipilimumab (N=51)
ORR, %	26	45	12
CR	19 (13)	8 (15)	1 (2)
PR	20 (13)	16 (30)	5 (10)
SD	25 (17)	7 (13)	11 (22)
PD	85 (57)	22 (42)	34 (67)

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Supplement 9b: Univariable and Multivariable Logistic regression for objective response rate (ORR) to 1st line CPI therapy, excluding 69 patients who received first line non-CPI therapy. OR odds ratio; CPI checkpoint inhibitor; LDH lactate dehydrogenase; ECOG Eastern Cooperative Oncology Group.

	Univariable		Multivariable	
Variable	**OR (95% CI)**	**P-value**	**OR (95% CI)**	**P-value**
1st line CPI				
Anti-PD1	1		1	
Anti-PD1/ipilimumab	2.33 (1.22, 4.48)	**0.0002**	2.33 (1.20, 4.53)	**0.0002**
Ipilimumab	0.38 (0.15, 0.95)	**0.0026**	0.36 (0.14, 0.91)	**0.0019**
Stage of advanced disease				
Unresectable IIIB	1			
Unresectable IIIC	3.03 (0.33, 27.84)	**0.024**	-	-
Unresectable IIID	2.50 (0.21, 29.25)	0.32	-	-
M1a	1.45 (0.15, 14.07)	0.91	-	-
M1b	1.15 (0.12, 11.12)	0.64	-	-
M1c	2.36 (0.26, 21.27)	0.10	-	-
M1d	0.33 (0.02, 6.37)	0.12	-	-

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Primary acral melanoma site				
Subungual	1			
Plantar	1.73 (0.83, 3.58)	0.59	-	-
Palmar	4.36 (1.27, 15.01)	**0.03**	-	-
Sex				
Female	1		1	
Male	0.51 (0.29, 0.90)	**0.02**	0.49 (0.27, 0.87)	**0.02**
Ethnicity				
Non-Caucasian	1			
Caucasian	1.33 (0.59, 2.96)	0.49	-	-
LDH				
Normal (≤ULN)	1			
Elevated (>ULN)	1.45 (0.69, 3.04)	0.32	-	-
ECOG				
0	1			
≥1	0.72 (0.38, 1.35)	0.31	-	-

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Supplement 10: progression free survival (PFS) and overall survival (OS) the 1st line CPI therapy.

Of the total cohort of 325 patients, 256 (79%) received 1st line CPI: anti-PD1 monotherapy in 151 (46%) patients, anti-PD1/ipilimumab combination in 54 (17%) patients and ipilimumab in 51 (16%) patients. The most common non-CPI 1st line treatment was chemotherapy (43/69 patients, 62%); others treatments included BRAK/MEK inhibitors, cKIT inhibitors, interleukin, intra-tumoural therapies and electrochemotherapy (**Supplement 6**).

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Supplement 10a: Kaplan-Meier curve for progression free survival (PFS) to 1st line CPI therapy (p=0.017).

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Supplement 10b: Univariable and Multivariable Cox regression for progression free survival (PFS) to 1st line CPI therapy. HR hazard ratio; CPI checkpoint inhibitor; LDH lactate dehydrogenase; ECOG Eastern Cooperative Oncology Group.

Variable	Univariable		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
1st line CPI				
Anti-PD1	1		1	
Anti-PD1/ipilimumab	0.81 (0.57, 1.15)	0.23	0.78 (0.53, 1.13)	0.19
Ipilimumab	1.43 (1.03, 1.99)	**0.03**	1.58 (1.09, 2.29)	**0.02**
Stage of advanced disease				
Unresectable IIIB	1		1	
Unresectable IIIC	0.69 (0.27, 1.75)	0.43	0.73 (0.29, 1.88)	0.52
Unresectable IIID	0.89 (0.31, 2.53)	0.82	1.02 (0.35, 2.94)	0.98
M1a	1.14 (0.45, 2.92)	0.78	1.21 (0.47, 3.13)	0.69
M1b	0.98 (0.39, 2.48)	0.97	1.07 (0.42, 2.76)	0.88
M1c	0.87 (0.35, 2.17)	0.77	0.84 (0.33, 2.11)	0.71
M1d	3.32 (1.21, 9.10)	**0.02**	3.30 (1.17, 9.27)	**0.02**

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Primary acral melanoma site				
Subungual	1			
Plantar	0.71 (0.52, 0.96)	**0.03**	-	-
Palmar	0.58 (0.29, 1.13)	0.11	-	-
Sex				
Female	1			
Male	1.11 (0.85, 1.44)	0.46	-	**-**
Ethnicity				
Non-Caucasian	1			
Caucasian	0.99 (0.68, 1.44)	0.94	-	-
LDH				
Normal (≤ULN)	1			
Elevated (>ULN)	1.09 (0.75, 1.58)	0.65	-	-
ECOG				
0	1		1	
≥1	1.36 (1.01, 1.83)	**0.04**	1.33 (0.98, 1.80)	0.07

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Supplement 10c: Kaplan-Meier curve for overall survival (OS) to 1st line CPI therapy (p=0.68).

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Supplement 10d: Univariable and Multivariable Cox regression for overall survival (OS) to 1st line CPI therapy. HR hazard ratio; CPI checkpoint inhibitor;

LDH lactate dehydrogenase; ECOG Eastern Cooperative Oncology Group.

	Univariable		Multivariable	
Variable	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
1st line CPI				
Anti-PD1	1			
Anti-PD1/ipilimumab	1.19 (0.80, 1.76)	0.38	-	-
Ipilimumab	1.03 (0.71, 1.50)	0.87	-	-
Stage of advanced disease				
Unresectable IIIB	1		1	
Unresectable IIIC	0.59 (0.21, 1.68)	0.32	0.48 (0.16, 1.40)	0.18
Unresectable IIID	0.66 (0.20, 2.20)	0.50	0.57 (0.16, 1.94)	0.36
M1a	0.79 (0.27, 2.30)	0.67	0.78 (0.27, 2.29)	0.65
M1b	0.96 (0.34, 2.70)	0.93	0.91 (0.32, 2.60)	0.86
M1c	0.98 (0.35, 2.71)	0.97	0.77 (0.27, 2.16)	0.62
M1d	4.24 (1.41, 12.72)	**0.01**	2.33 (0.74, 7.35)	0.15
Primary acral melanoma site				

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Subungual	1			
Plantar	0.79 (0.56, 1.12)	0.19	-	-
Palmar	0.60 (0.27, 1.34)	0.22	-	-
Sex				
Female	1			
Male	1.22 (0.89, 1.66)	0.22	-	-
Ethnicity				
Non-Caucasian	1			
Caucasian	0.96 (0.63, 1.46)	0.85	-	-
LDH				
Normal (≤ULN)	1			
Elevated (>ULN)	1.09 (0.71, 1.67)	0.69	-	-
ECOG				
0	1		1	
≥1	2.31 (1.64, 3.25)	<.0001	1.99 (1.37, 2.90)	0.0003

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Supplement 11: Patient and disease characteristics of total population, and by 1st CPI exposure (anti-PD1 vs anti-PD1/ipilimumab), before and after propensity

score matching.

	Before matching			After matching		
Characteristics	**Anti-PD1** **(N = 184)**	**Anti-PD1/Ipilimumab** **(N = 59)**	**P-value**	**Anti-PD1** **(N = 51)**	**Anti-PD1/Ipilimumab** **(N = 51)**	**P-value**
Primary site- no. (%)						
Sole of foot	138 (75.0%)	41 (69.5%)	0.42	39 (76.5%)	34 (66.7%)	0.18
Palm of hand	13 (7.1%)	3 (5.1%)		5 (9.8%)	3 (5.9%)	
Nail apparatus (subungual)	33 (17.9%)	15 (25.4%)		7 (13.7%)	14 (27.5%)	
Median age at diagnosis of primary acral melanoma years [range]	65(29, 88)	60.20(20, 81)	**0.02**	64(34, 83)	60.20(20, 81)	0.31
Median age at diagnosis of advanced acral melanoma years [range]	69(31, 90)	64(23, 82)	**0.01**	67(36, 86)	64(23, 82)	0.19
Sex- no. (%)						
Female	82 (44.6%)	29 (49.2%)	0.54	19(37.3%)	23 (45.1%)	0.42

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	Before matching			After matching		
Characteristics	**Anti-PD1** **(N = 184)**	**Anti-PD1/Ipilimumab** **(N = 59)**	**P-value**	**Anti-PD1** **(N = 51)**	**Anti-PD1/Ipilimumab** **(N = 51)**	**P-value**
Male	102 (55.4%)	30 (50.8%)		32 (62.7%)	28 (54.9%)	
Ethnicity- no. (%)						
Non-Caucasian	50 (27.6%)	9 (16.4%)	0.09	11 (21.6%)	7 (14.6%)	0.37
Caucasian	131 (72.4%)	46 (83.6%)		40 (78.4%)	41 (85.4%)	
ECOG at 1st line systemic therapy- no. (%)						
0	99 (62.7%)	27 (49.1%)	0.08	29 (65.9%)	24 (50.0%)	0.12
≥1	59 (37.3%)	28 (50.9%)		15 (34.1%)	24 (50.0%)	
LDH at 1st line systemic therapy[a]						
Normal	86 (73.5%)	19 (48.7%)	**0.004**	17 (56.7%)	17 (53.1%)	0.78
Elevated	31 (26.5%)	20 (51.3%)		13 (43.3%)	15 (46.9%)	
Melanoma stage at treatment start (AJCC 8th ed)- no (%)[a]						
Unresectable IIIB	5 (2.7%)	0 (0.0%)	**<.0001**	8 (15.7%)	8 (15.7%)	0.71

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	Before matching			After matching		
Characteristics	**Anti-PD1** **(N = 184)**	**Anti-PD1/Ipilimumab** **(N = 59)**	**P-value**	**Anti-PD1** **(N = 51)**	**Anti-PD1/Ipilimumab** **(N = 51)**	**P-value**
Unresectable IIIC	42 (22.8%)	9 (15.3%)		1 (2.0%)	1 (2.0%)	
Unresectable IIID	10 (5.4%)	1 (1.7%)		5 (9.8%)	6 (11.8%)	
M1a	33 (17.9%)	6 (10.2%)		7 (13.7%)	6 (11.8%)	
M1b	43 (23.4%)	6 (10.2%)		27 (52.9%)	22 (43.1%)	
M1c	45 (24.5%)	25 (42.4%)		3 (5.9%)	8 (15.7%)	
M1d	6 (3.3%)	12 (20.3%)		3 (5.9%)	8 (15.7%)	
BRAF mutation[a]						
No	163 (88.6%)	49 (83.1%)	0.27	42 (82.4%)	43 (84.3%)	0.79
Yes	21 (11.4%)	10 (16.9%)		9 (17.6%)	8 (15.7%)	
De-novo metastatic disease- no (%)						
No	161 (89.0%)	52 (88.1%)	0.86	46 (90.2%)	44 (86.3%)	0.54
Yes	20 (11.0%)	7 (11.9%)		5 (9.8%)	7 (13.7%)	

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	Before matching			After matching		
Characteristics	**Anti-PD1** **(N = 184)**	**Anti-PD1/Ipilimumab** **(N = 59)**	**P-value**	**Anti-PD1** **(N = 51)**	**Anti-PD1/Ipilimumab** **(N = 51)**	**P-value**
Treatment discontinuation reason						
Progression	126(68.5%)	32 (54.2%)	**<.0001**	35 (68.6%)	25 (49.0%)	**0.01**
Toxicity	17(9.2%)	22 (37.3%)		7 (13.7%)	21 (41.2%)	
Rx ongoing	10(5.4%)	1 (1.7%)		1 (2.0%)	1 (2.0%)	
Completed Rx	7 (3.8%)	0 (0.0%)		1 (2.0%)	0 (0.0%)	
Elective	3 (1.6%)	2 (3.4%)		1 (2.0%)	2 (3.9%)	
Other, specify	7 (3.8%)	1 (1.7%)		1 (2.0%)	1 (2.0%)	
CR	14(7.6%)	1 (1.7%)		5 (9.8%)	1 (2.0%)	
Median time from primary diagnosis to advanced disease months [range]	18.4(-0.13, 260.6)	22.8(0.0, 131.3)	0.81	19.7(0.0, 204.7)	21.3(0.0, 131.3)	0.44

[a]indicates variable is included in the matching process.

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Supplement 12: Univariate Logistic Regression of Objective Response Rate, after propensity score matching.

	Univariate	
Variable	**OR (95% CI)**	**P-value**
1st CPI exposure		
Anti-PD1	1	
Anti-PD1/ipilimumab	2.30 (0.99, 5.33)	0.05
Primary acral melanoma site		
Subungual	1	
Palmar	5.67 (0.89, 36.08)	0.16
Plantar	3.53 (0.95, 13.13)	0.46
Sex		
Female	1	
Male	0.45 (0.20, 1.04)	0.06
Ethnicity		
Non-Caucasian	1	
Caucasian	1.32 (0.43, 4.10)	0.62
Stage of advanced disease		
Unresectable IIIC	1	
Unresectable IIID	0.60 (0.03, 11.47)	0.55
M1a	0.23 (0.04, 1.19)	0.68
M1b	0.27 (0.06, 1.26)	0.87
M1c	0.30 (0.09, 0.97)	0.96
M1d	0.06 (0.01, 0.59)	0.09
LDH		

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	Univariate	
Variable	**OR (95% CI)**	**P-value**
Normal	1	
Elevated	1.20 (0.40, 3.56)	0.74
ECOG		
0	1	
>=1	0.38 (0.14, 0.97)	**0.04**

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Supplement 13: Progression free survival (PFS), after propensity score matching.

Supplement 13a: Kaplan-Meier curve for progression free survival (PFS) by 1st CPI exposure as anti-PD1 vs anti-PD1/ipilimumab after propensity score matching (p = 0.36). Landmark PFS for anti-PD1/ipilimumab vs anti-PD1 at 1 year: 36% (95% CI 24-52) vs 27% (95% CI 17-43); 2 years: 24% (95% CI 14-40) vs 16% (95% CI 8-31).
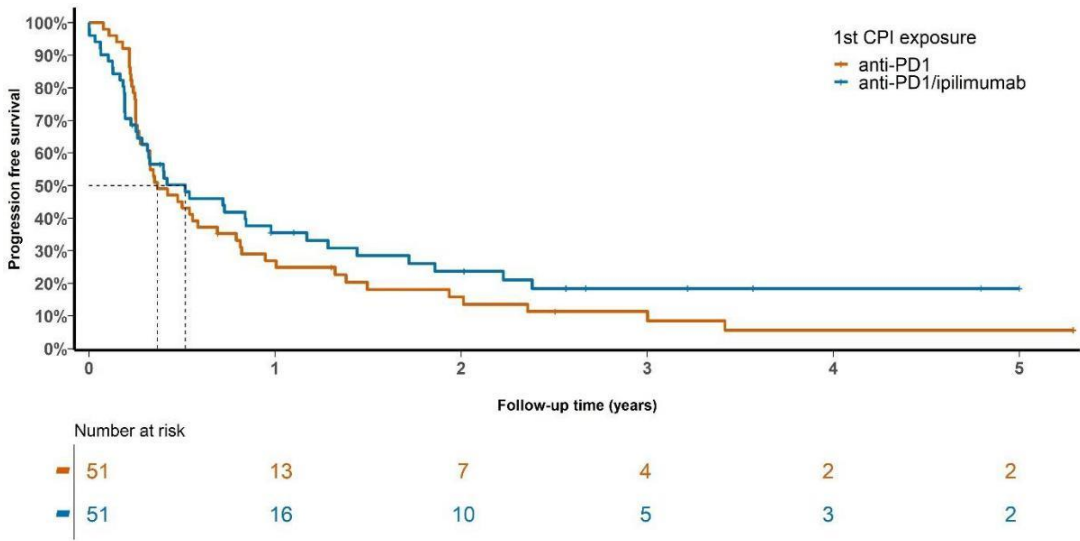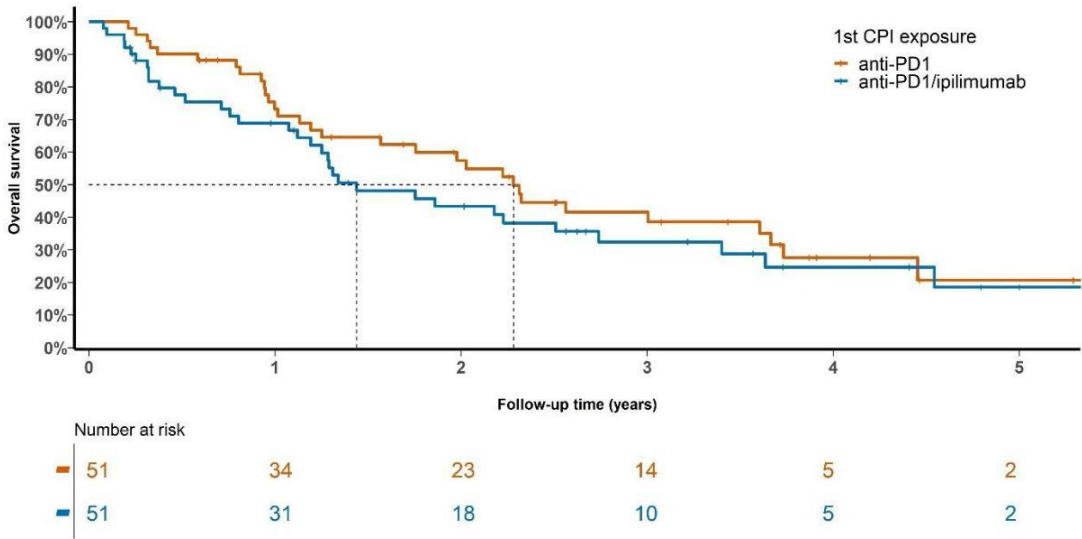
Supplement 13b: Univariable and Multivariable Cox regression of progression free survival (after propensity score matching).

Variable	Univariate HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
1st CPI exposure				
Anti-PD1	1			
Anti-PD1/ipilimumab	0.82 (0.53, 1.26)	0.36		
Stage of advanced disease				
Unresectable IIIC	1		1	
Unresectable IIID	2.39 (0.53, 10.80)	0.26	3.24 (0.68, 15.54)	0.14
M1a	2.52 (1.10, 5.75)	**0.03**	2.95 (1.16, 7.48)	**0.02**
M1b	1.27 (0.56, 2.89)	0.56	1.69 (0.68, 4.23)	0.26
M1c	1.46 (0.76, 2.81)	0.25	1.62 (0.78, 3.37)	0.20
M1d	8.34 (3.54, 19.63)	**<.0001**	6.70 (2.60, 17.28)	**<.0001**
Primary acral melanoma site				
Subungual	1			

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Variable	Univariate		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Palmar	0.52 (0.19, 1.38)	0.19		
Plantar	0.59 (0.35, 0.99)	**0.05**		
Sex				
Female	1			
Male	0.96 (0.63, 1.49)	0.87		
Ethnicity				
Non-Caucasian	1			
Caucasian	1.26 (0.70, 2.28)	0.45		
LDH				
Normal	1			
Elevated	1.06 (0.61, 1.83)	0.84		
ECOG				
0	1		1	
>=1	1.91 (1.20, 3.02)	**0.006**	1.67 (1.01, 2.78)	**0.05**

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Supplement 14: Overall survival (OS), after propensity score matching.

Supplement 14a: Kaplan-Meier curve for overall survival (OS) by 1st CPI exposure as anti-PD1 vs anti-PD1/ipilimumab after propensity score matching (p

= 0.32). Landmark OS for anti-PD1/ipilimumab vs anti-PD1 at 1 year: 69% (95% CI 57-83) vs 73% (95% CI 62-87); 2 years: 43% (95% CI 31-61) vs

57% (95% CI 45-74).

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Supplement 14b: Univariable and Multivariable Cox regression of overall survival, after propensity score matching.

Variable	Univariable		Multivariable	
	HR	P-value	HR (95% CI)	P-value
1st CPI exposure				
Anti-PD1	1			
Anti-PD1/ipilimumab	1.28 (0.78, 2.10)	0.32		
Primary acral melanoma site				
Subungual	1		1	
Palmar	0.29 (0.08, 0.99)	**0.05**	0.15 (0.03, 0.80)	**0.03**
Plantar	0.40 (0.22, 0.71)	**0.002**	0.25 (0.13, 0.49)	**<.0001**
Sex				
Female	1			
Male	1.24 (0.74, 2.08)	0.42		
Ethnicity				
Non-Caucasian	1			
Caucasian	1.19 (0.62, 2.29)	0.60		

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	Univariable		Multivariable	
Variable	**HR**	**P-value**	**HR (95% CI)**	**P-value**
Stage of advanced disease				
Unresectable IIIC	1		1	
Unresectable IIID	0.80 (0.10, 6.29)	0.83	2.13 (0.21, 21.45)	0.52
M1a	1.66 (0.62, 4.48)	0.32	3.23 (1.05, 9.95)	**0.04**
M1b	0.81 (0.29, 2.27)	0.69	0.79 (0.26, 2.43)	0.68
M1c	1.51 (0.71, 3.19)	0.28	1.79 (0.78, 4.14)	0.17
M1d	5.32 (2.19, 12.95)	**0.0002**	6.17 (2.14, 17.83)	**0.0008**
LDH				
Normal	1			
Elevated	1.37 (0.73, 2.55)	0.3230		
ECOG				
0	1		1	
>=1	2.40 (1.41, 4.08)	**0.001**	1.56 (0.85, 2.87)	0.16

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Supplement 15: BRAF mutant subgroup.

Supplement 15a: Objective response rate (ORR) to 1st line CPI or BRAF/MEK inhibitor therapy in BRAF mutant patients (N=38)
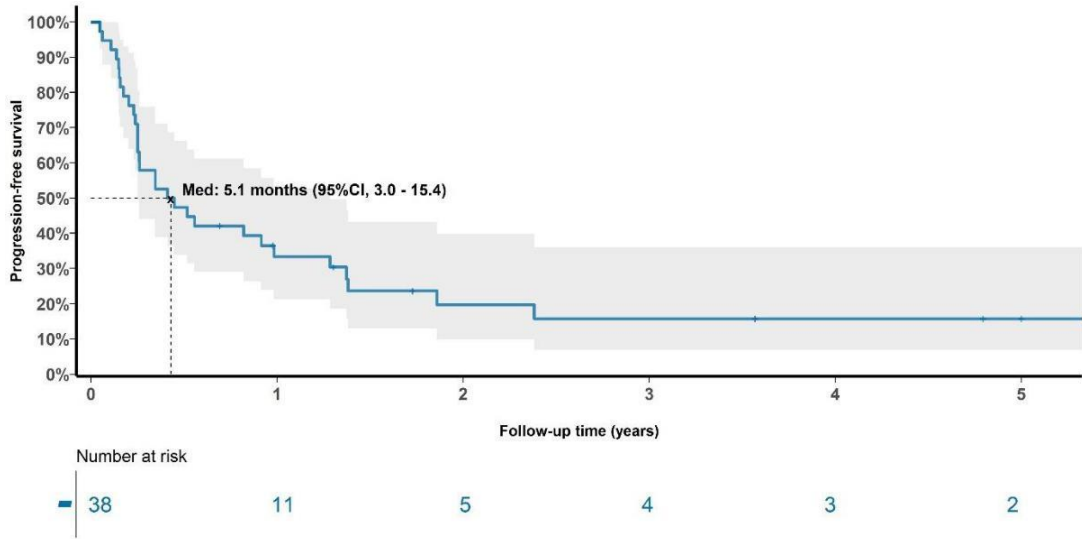
N (%)	Anti-PD1 (N=16)	Anti-PD1 + ipilimumab (N=8)	Ipilimumab (N=3)	Targeted therapy (N=9)
ORR, %	31	63	67	67
CR	4	4	0	1
PR	1	1	2	5
SD	2	2	1	1
PD	9	1	0	2

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Supplement 15b: Univariable Logistic regression for objective response rate (ORR) to 1st line CPI or targeted therapy in BRAF mutation patients (N=38).

	OR (95% CI)	P-value
1st line CPI		
Anti-PD1	1	
Anti-PD1/ipilimumab	3.67 (0.62, 21.73)	0.73
Ipilimumab	4.40 (0.32, 60.61)	0.67
Targeted therapy	4.40 (0.77, 25.15)	0.52
Primary acral melanoma site		
Subungual	1	
Palmar	NA	0.97
Plantar	0.88 (0.11, 7.05)	0.97
Sex		
Female	1	
Male	0.79 (0.20, 3.07)	0.73
Ethnicity		
Non-Caucasian	1	
Caucasian	1.50 (0.22, 10.30)	0.68

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Stage of advanced disease		
Unresectable IIIC	1	
Unresectable IIID	NA	0.97
M1a	1.00 (0.13, 7.57)	0.97
M1b	3.00 (0.19, 47.96)	0.95
M1c	0.83 (0.11, 6.11)	0.97
M1d	1.00 (0.08, 12.56)	0.97
LDH		
Normal (≤ULN)	1	
Elevated (>ULN)	0.13 (0.01, 1.38)	0.09
ECOG		
0	1	
≥1	0.62 (0.15, 2.58)	0.51

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Supplement 15c: Kaplan-Meier curve for progression free survival (PFS) in BRAF mutant patients (N=38).

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Supplement 15d: Kaplan-Meier curve for overall survival (OS) in BRAF mutant patients (N=38).