Duration of Treatment after Partial or Complete Remission in Immunotherapy for Metastatic Melanoma: A EUMelaReg Real World Study

EUROPEAN MELANOMA REGISTRY — EU MELA REG

Abstract: 9531

Nethanel Asher[1], Peter Mohr[2], Eva Ellebaek[3], Marc Bender[2,4], Joanna Mangana[5], Lidija Kandolf[6], Iva Gavrilova[7], Paolo Antonio Ascierto[8], Helen Gogas[9], Piotr Rutkowski[10], Dirk Schadendorf[11], Lars Bastholt[12], Michael Weichenthal[4, 13], EUMelaReg Consortium *

[1]Davidoff Cancer Center, Beilinson Medical Center, Petach Tikva, Israel; [2]Elbe Klinikum Buxtehude, Buxtehude, Germany; [3]National Center for Cancer Immune Therapy (CCIT-DK), Department of Oncology, Copenhagen University Hospital Herlev, Denmark; [4]EUMelaReg, Berlin, Germany; [5]Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland; [6]Medical Faculty, Military Medical Academy, Belgrade, Serbia; [7]National Cancer Center Bulgaria, Sofia, Bulgaria; [8]Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Naples, Italy; [9]National and Kapodistrian University of Athens, Athens, Greece; [10]Maria Skłodowska-Curie National Institute of Oncology Center, Warsaw, Poland; [11]West German Cancer Center, University Hospital Essen, Essen, Germany; [12]Dept of Oncology R, Odense C, Denmark; [13]University of Kiel, Kiel, Germany

Background

- A significant proportion of patients with non-resectable melanoma treated with immune checkpoint inhibitors (ICI) achieve durable remissions, but there is limited data on the optimal duration of ICI therapy in these patients. In clinical trials the duration of ICI treatment was limited to a fixed maximum time regardless of the remission state.
- Therefore, the influence of the duration and maintenance of ICI therapy in patients with a partial (PR) or complete remission (CR) on further outcome is of interest.
- Primary objectives of this study were the progression-free and overall survival outcomes after achieving PR or CR in non-resectable stage III/IV melanoma in relation to the duration of maintenance treatment with ICIs after achieving the respective response.

Material and Methods

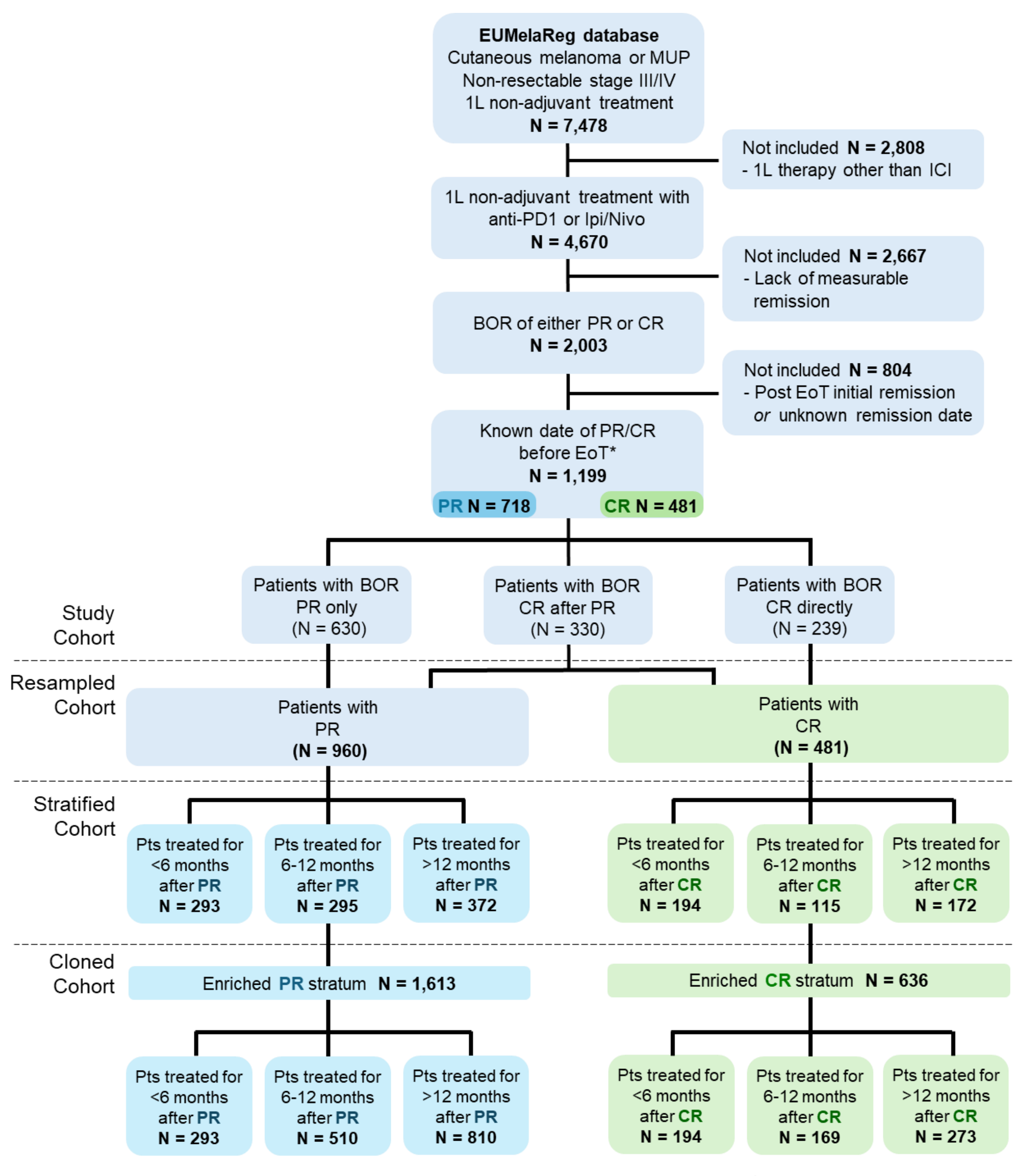


FIG 1: Flowchart of the study population. 1L, first-line; BOR, best overall response; CR, complete response; EoT, end-of-treatment; ICI, immune checkpoint inhibition; MUP, melanoma of unknown primary; Ipi, ipilimumab; Nivo, nivolumab; PR, partial response.

- ➢ The study retrospectively analysed patients with non-resectable stage III/IV cutaneous melanoma or MUP with a best overall response (BOR) of CR or PR with either single agent anti-PD1 or combined anti-PD1/anti-CTLA4 in first-line.
- ➢ Eligible patients were stratified by PR/CR and ICI maintenance therapy post remission of < 6 months, 6-12 months or > 12 months.

STUDY POPULATION
Inherent guaranteed time bias

CLONING
Reduces guaranteed time bias

IPSW MODELLING
Adjustment for baseline imbalances

BOOTSTRAPPING
Obtain adequate estimates

- ➢ To address immortal time bias, cases with PD within 12 months after remission were cloned into all respectively compatible strata resulting in a 'synthetic' study population eliminating immortal time bias.
- ➢ The cloned population was further analyzed and compared by propensity score weighting, and robust confidence intervals were retrieved by bootstrapping techniques.

Results

- For patients achieving PR, adjusted Kaplan-Meier estimates for the synthetic cohort resulted in prolonged PFS for patients with ICI maintenance for >12 months, but also for 6-12 months as compared to <6 months (Fig. 4A)
- Accordingly, this advantage also translated into significantly improved OS with longer maintenance treatment (Fig. 4B)
- For patients achieving a CR, prolonged maintenance treatment only showed non-significant impact on hazard ratios for PFS and OS (Fig. 4C/D).
- Whether subgroups with CR might potentially benefit from prolonged maintenance ICI therapy, could not be evaluated due to low subgroup sample sizes.

TAB 1: Patient characteristics of the basic study population

	CR (N=569)	PR (N=630)	P-value	Overall (N=1,199)
Sex				
Female	212 (37.3%)	239 (37.9%)	0.855	451 (37.6%)
Male	357 (62.7%)	391 (62.1%)		748 (62.4%)
Age (years)				
Mean (SD)	66.3 (14.0)	68.2 (13.4)	0.013	67.3 (13.7)
ECOG performance status				
0	420 (73.8%)	375 (59.5%)	<0.001	795 (66.3%)
1	78 (13.7%)	154 (24.4%)		232 (19.3%)
≥ 2	23 (4.0%)	41 (6.5%)		64 (5.3%)
Missing/Unknown	48 (8.4%)	60 (9.5%)		108 (9.0%)
Charlson comorbidity score				
6	54 (9.5%)	45 (7.1%)	0.0266	99 (8.3%)
7	73 (12.8%)	58 (9.2%)		131 (10.9%)
8	78 (13.7%)	82 (13.0%)		160 (13.3%)
≥ 9	210 (36.9%)	276 (43.8%)		486 (40.5%)
Missing	154 (27.1%)	169 (26.8%)		323 (26.9%)
Type of 1L treatment				
Anti-PD1	417 (73.3%)	434 (68.9%)	0.107	851 (71.0%)
Ipilimumab/Nivolumab	152 (26.7%)	196 (31.1%)		348 (29.0%)
Adjuvant therapy prior to 1L				
No	491 (86.3%)	574 (91.1%)	0.0107	1065 (88.8%)
Yes	78 (13.7%)	56 (8.9%)		134 (11.2%)
Radiotherapy prior to 1L				
No	506 (88.9%)	569 (90.3%)	0.488	1075 (89.7%)
Yes	63 (11.1%)	61 (9.7%)		124 (10.3%)
AJCC stage (8th edition)				
Stage III, non-resectable	67 (11.8%)	34 (5.4%)	<0.001	101 (8.4%)
Stage IV M1a	128 (22.5%)	102 (16.2%)		230 (19.2%)
Stage IV M1b	131 (23.0%)	125 (19.8%)		256 (21.4%)
Stage IV M1c	179 (31.5%)	259 (41.1%)		438 (36.5%)
Stage IV M1d	64 (11.2%)	110 (17.5%)		174 (14.5%)
LDH				
Normal	382 (67.1%)	385 (61.1%)	0.00126	767 (64.0%)
Elevated	108 (19.0%)	175 (27.8%)		283 (23.6%)
Missing	79 (13.9%)	70 (11.1%)		149 (12.4%)
Number of metastatic sites				
1	232 (40.8%)	180 (28.6%)	<0.001	412 (34.4%)
2	180 (31.6%)	184 (29.2%)		364 (30.4%)
≥ 3	157 (27.6%)	266 (42.2%)		423 (35.3%)
Type of melanoma				
Cutaneous	486 (85.4%)	511 (81.1%)	0.0561	997 (83.2%)
MUP	83 (14.6%)	119 (18.9%)		202 (16.8%)
Time to remission (6 months cut-off)				
Early remission	410 (72.1%)	547 (86.8%)	<0.001	957 (79.8%)
Late remission	159 (27.9%)	83 (13.2%)		242 (20.2%)

Age and ECOG are reported at start of 1st line treatment. N, number of patients; SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; 1L, MUP, melanoma of unknow primary; first-line treatment; anti-PD1, PD-1, Programmed cell death protein 1.

TAB 2: End of treatment reasons of the study population

Reason for end of 1L treatment	CR (N=569)	PR (N=630)	P-value	Overall (N=1,199)
Elective discontinuation	308 (54.1%)	177 (28.1%)	<0.001	485 (40.5%)
Toxicity	75 (13.2%)	119 (18.9%)		194 (16.2%)
Disease progression	40 (7.0%)	178 (28.3%)		218 (18.2%)
Ongoing	120 (21.1%)	127 (20.2%)		247 (20.6%)
Other	26 (4.6%)	29 (4.6%)		55 (4.6%)

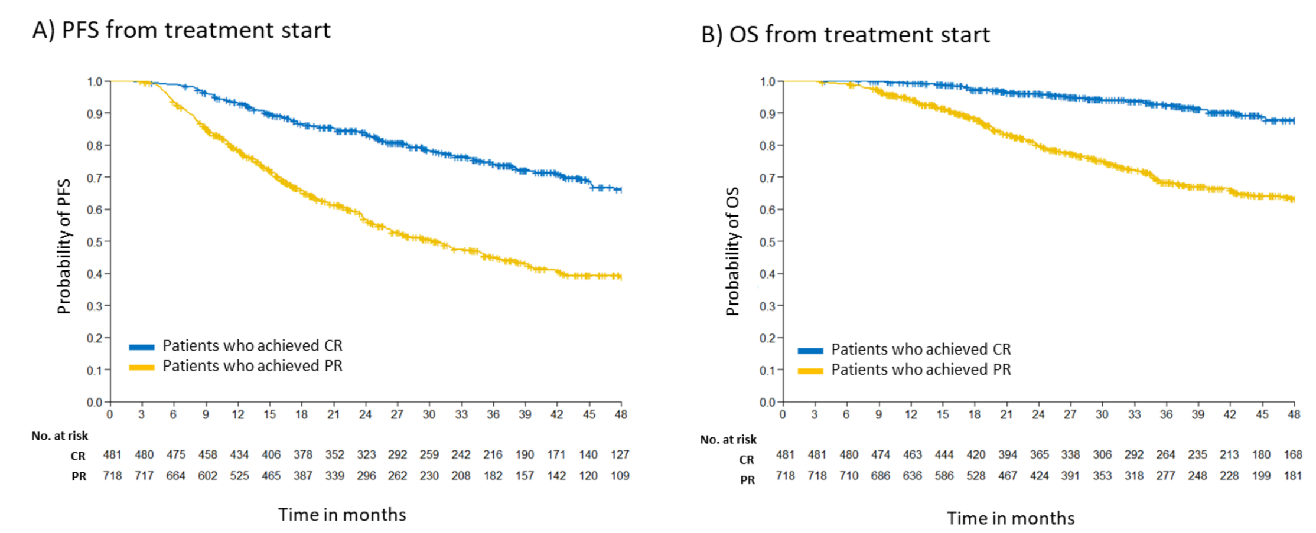


FIG 2: Kaplan-Meier estimates for PFS and OS for study population. Kaplan Meier estimates grouped by BOR: (A) progression-free survival (PFS), and (B) overall survival (OS) from treatment start for patients achieving a CR (blue line) or PR (yellow line).

- ➢ Patients with PR as BOR compared to patients with CR either directly, or when transitioning from a PR show highly significant survival outcomes.
- ➢ Attempts to include BOR as a parametric co-variate in e.g. cox regression models for other prognostic factors fail from high confounding with survival outcomes.
- ➢ Analysing maintenance strategies in BOR subgroups requires stratified analysis.

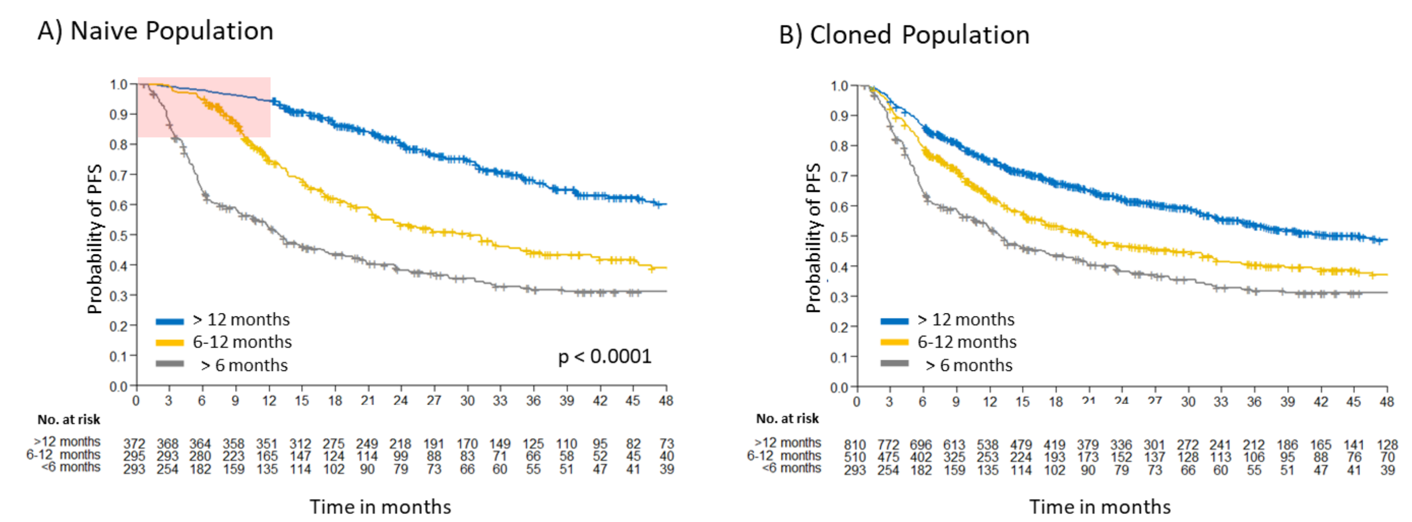
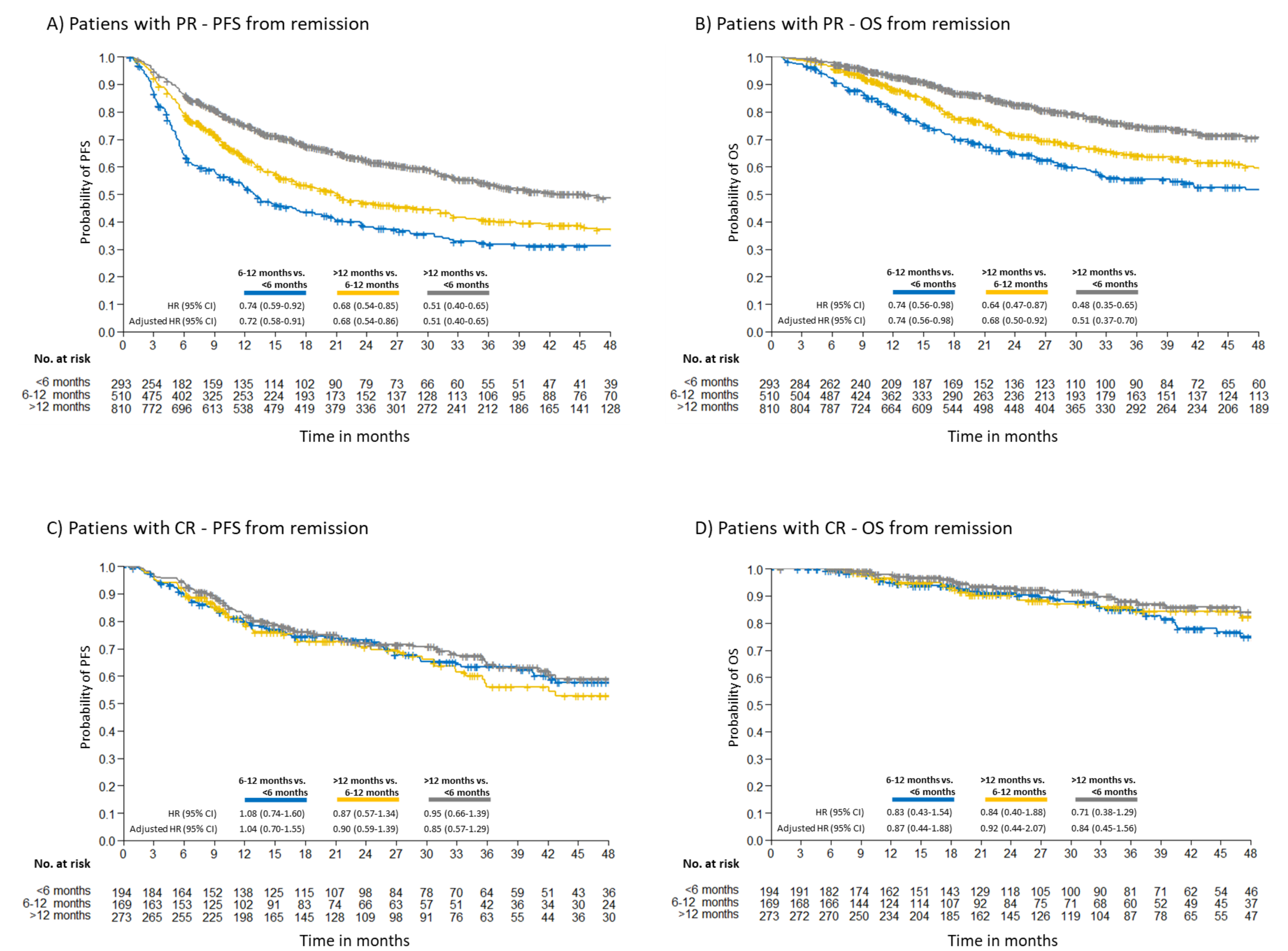


FIG 3: Kaplan Meier estimates for naive (A) and cloned (B) population. Estimates display land-mark PFS rates from time of first remission in patients with PR and stratified by duration of ICI maintenance therapy.

- ➢ Illustration of the cloning procedure eliminating guaranteed time bias (red box).
- ➢ Cases that experience progressive disease (PD) while on maintenance treatment for less than 6 months are duplicated into both other arms.
- ➢ Cases with PD while on treatment for 6–12 months duplicated into the >12 months arm.
- ➢ Guaranteed time bias bias is effectively diminished by the procedure (Fig.3B)



Patients who achieved PR as first remission:

- ➢ Adjustment of survival outcomes for guaranteed time bias demonstrates the impact of ICI maintenance on PFS (A) and OS (B).
- ➢ Hazard ratios (HR) indicate statistically significant gains in PFS (A) and OS (B).
- ➢ Adjusting for other prognostic variables by IPSW (Adjusted HR) demonstrates robust independency of the results over all strata.

Patients who achieved CR w/ or w/o prior PR:

- ➢ After adjustment of guaranteed time bias by the cloning procedure the analysis shows no remaining significant impact of ICI maintenance on PFS (C) and on OS (D).
- ➢ This was also not significantly affected by applying IPSW based weighting of prognostic co-factors.
- ➢ Identifying subgroups within the CR stratum who might potentially benefit from longer ICI maintenance was precluded by the limited effective sample size.

FIG 4: Kaplan-Meier estimates for PFS and OS for bias-adjusted, cloned population. Estimates display outcomes in patients which had achieving a partial remission (A, B), and complete remission (C, D) after ICI maintenance therapy. Hazard ratios (HR) are reported for the synthetic subgroups as observed and after inverse propensity score weighted (IPSW) adjustment (adjusted HR).

TAB 3A: Adjusted survival rates for PFS and OS for patients with PR

Timepoints		>12 months [%] (95% CI)	6-12 months [%] (95% CI)	<6 months [%] (95% CI)
Patients with partial remission (N = 1,613)				
1-year	PFS	75.1 (71.0-79.1)	62.9 (57.2-68.4)	52.5 (44.8-60.2)
2-year	PFS	62.3 (57.5-66.9)	46.7 (40.3-52.9)	38.2 (30.4-46.0)
3-year	PFS	53.7 (48.6-58.8)	40.4 (33.9-46.8)	31.8 (24.3-39.5)
4-year	PFS	48.6 (42.9-54.1)	37.1 (30.5-43.6)	31.1 (23.6-38.9)
1-year	OS	92.9 (90.5-95.1)	88.3 (84.3-91.9)	80.8 (74.5-86.4)
2-year	OS	82.7 (78.9-86.3)	71.7 (65.8-77.2)	64.9 (57.1-72.4)
3-year	OS	74.7 (69.9-79.1)	64.1 (57.6-70.5)	55.4 (47.0-63.8)
4-year	OS	70.7 (65.5-75.8)	59.5 (52.4-66.3)	51.7 (42.9-60.5)

TAB 3B: Adjusted survival rates for PFS and OS for patients with CR

Timepoints		>12 months [%] (95% CI)	6-12 months [%] (95% CI)	<6 months [%] (95% CI)
Patients with complete remission (N = 636)				
1-year	PFS	82.3 (76.8-87.5)	79.3 (71.5-86.6)	80.1 (73.0-86.3)
2-year	PFS	72.2 (65.3-78.6)	70.6 (61.3-79.2)	73.2 (65.5-80.5)
3-year	PFS	64.3 (55.8-72.3)	56.2 (44.8-66.9)	63.4 (54.5-72.2)
4-year	PFS	58.9 (49.2-68.1)	52.9 (41.2-64.2)	57.7 (47.5-67.4)
1-year	OS	98.0 (95.8-99.5)	96.6 (92.5-99.2)	95.1 (90.9-98.5)
2-year	OS	93.0 (88.6-96.6)	90.6 (84.1-96.1)	91.2 (85.8-95.8)
3-year	OS	88.2 (81.8-93.5)	86.0 (77.7-93.2)	85.0 (77.7-91.5)
4-year	OS	84.3 (76.1-91.2)	82.6 (72.4-91.0)	75.2 (65.1-84.4)

- ➢ Following achievement of PR, survival rates for both PFS and OS showed consistent improvement of more than 50% and 37%, respectively, at 4 years for patients remaining on treatment for > 12 months.
- ➢ For patients achieving a CR, prolongation of ICI maintenance for >12 months showed no consistent impact on PFS rates over 4 years.
- ➢ Maintenance treatment > 12 months following CR showed a tendency for slightly improved OS rates over 4 years with overlapping confidence intervals, not allowing for statistical inference.

TAB 3: Adjusted survival rates for PFS and OS OS for patients based on their treatment status at a given landmark timepoint. To this end a "snapshot" of the data was made 3, 6, 9 and 12 months after treatment start and patients were assigned either on treatment or off treatment. Progression or death under treatment or up to 45 days after the specified landmark was counted as event on treatment.

Conclusion

- This study underpins the relevance of the depth of ICI-induced remissions for subsequent patient management.
- Melanoma patients achieving a partial remission from first-line ICI significantly benefit from a continued maintenance treatment after achieving the response in terms of progression-free and overall survival.
- For patients with a complete response there was no significant impact of the duration of maintenance treatment on further outcome. However, sample size restrictions warrant further research on which subgroups can safely been stopped after CR.

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Correspondence: asher.nati@gmail.com