# Efficacy of immune checkpoint inhibition in metastatic or nonresectable melanoma after failure of adjuvant anti PD1 treatment - A EUMelaReg real world evidence study -

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## Background

Adjuvant immune checkpoint inhibition (ICI) with anti-PD1 antibodies in high-risk resected melanoma has improved recurrence-free survival by about 50 percent, but there is still a proportion of patients who develop recurrence despite adjuvant anti-PD1 treatment, many of them unresectable or metastatic disease. Overall, in stage IIIA to IIID around 40% of patients may develop a recurrence according to the long-term result of the KEYNOTE-054 trial. This may occur while still on the 12 months of adjuvant treatment or later in the course of the disease and is referred to as early and late ICI resistance.

Available data on the efficacy of ICI therapy in advanced patients who have relapsed after adjuvant anti-PD1 therapy are sparse, and it is unclear, whether adjuvant pre-treatment with anti-PD1 antibodies would impair response to ICI in patients with metastatic recurrence. This study was performed to evaluate the clinical outcomes of patients with metastatic or non-resectable melanoma treated with or without upfront anti-PD1 monotherapy treatment in the adjuvant setting.

## Methods

Cases with non-resectable stage III or stage IV melanoma who were treated with non-adjuvant immune checkpoint inhibition after failure from adjuvant anti-PD1 treatment were selected from the EUMelaReg database. Patients were excluded if they had a uveal or mucosal type of melanoma, while acral and melanoma of unknown primary were included. Both, 1st line single anti-PD1 therapy (pembrolizumab or nivolumab) and combined anti-PD1/CTLA4 (Ipi/Nivo) therapy were included.

Primary outcomes of interest were (1) the overall response rate (ORR) of 1st line ICI treatment and (2) progression-free survival (PFS) from start of non-adjuvant ICI.

Further analysis included stratifications for the time of the preceding recurrence (‘early’: up to 3 months after end of adjuvant treatment) and the impact of several prognostic covariates.

In order to prevent statistical bias from selection of patients, matching was performed with a nearest neighbour algorithm using mahalanobis distance as distance metric. Samples were matched for ECOG, AJCC stage, baseline serum LDH, number of metastatic sites, sex, BRAF status, age and Charlson comorbidity score. The type of 1st line ICI was included as exact 1:1 match.

## Results

389 cases with 1st line ICI after failure from adjuvant anti-PD1 therapy were successfully matched with metastatic cases receiving 1st line ICI without adjuvant anti-PD1 treatment (anti-PD1 naïve cohort). The goodness of matching is demonstrated by only non-significant differences in key prognostic variables (Table 1) as well as by only small standardized differences in the respective parameters (Figure 3).

Response rates in cases after adjuvant anti-PD1 failure were significantly lower (ORR: 31.6% vs. 49.9%; p<0.0001) than in treatment naïve cases (Table 2), which was also reflected in a shorter PFS (4.0 months vs. 15.5 months; p < 0.0001; Figure 1).

The results were influenced by the time of the preceding recurrence (ORR: 28.8% in early vs. 38.5% in late recurrences; Figure 4A). For the early recurrences, this was most pronounced in recurrence during the first 6 months of adjuvant treatment (Figure 4B).

The effect of decreased response rate in 1st line after failure of adjuvant anti-PD1 could be seen in both, combined anti-PD1/CTLA4 treatment as in single agent anti-PD1 re-treatment (Figure 6).

**Figure 1:** PFS of patients treated with 1st line ICI stratified by adjuvant anti-PD1 pre-treatment

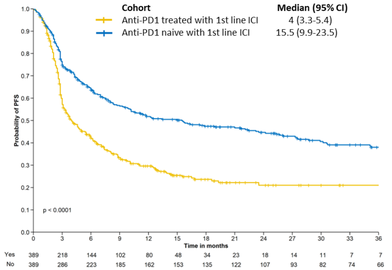



**Table 2:** Response rates with 1st line ICI in stratified by adjuvant anti-PD1 pre-treatment

| | Anti-PD1 treated (N = 389) | Anti-PD1 naïve (N = 389) | P-value |
|---|---|---|---|
| **Best response** | | | |
| CR | 62 (15.9%) | 86 (22.1%) | < 0.0001 |
| PR | 61 (15.7%) | 108 (27.8%) | |
| SD | 54 (13.9%) | 51 (13.1%) | |
| PD | 154 (39.6%) | 93 (23.9%) | |
| Unknown | 58 (14.9%) | 51 (13.1%) | |
| **ORR** | 123 (31.6%) | 194 (49.9%) | < 0.0001 |
| **DCR** | 177 (45.5%) | 245 (63.0%) | < 0.0001 |
| **Survival** | | | |
| **Median PFS (95% CI)** | 4.0 (3.3-5.5) | 15.5 (10.1-24.2) | < 0.0001 |

**PFS was 4.0 months in the adjuvant anti-PD1 pre-treated cohort compared to 15.5 months in anti-PD1 naive patients (p<0.0001; Figure 1; Table 2). Response rates were accordingly lower in patients after adjuvant anti-PD1 failure, affecting both partial responses (PR) and compete responses (CR) (Table 2).**
**The median follow-up time was significantly shorter in pre-treated patients than in anti-PD1 naive cases due to the relative recent introduction of adjuvant anti-PD1 treatment into routine practice (Table 1).**

**Figure 2:** Graphical illustration of the analyzed polulation

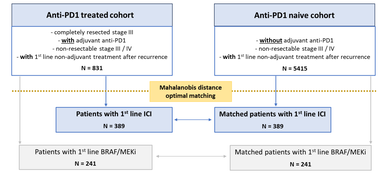
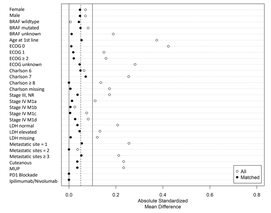



**Figure 3:** Love plot of matched population



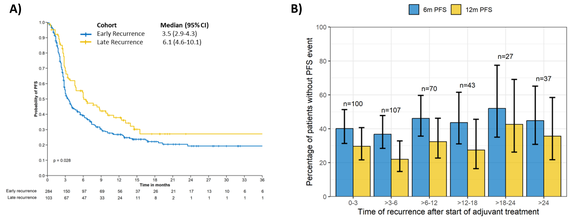

**Matching was performed with an optimal matching algorithm using mahalanobis distance as distance metric. Samples were matched for ECOG, AJCC stage, LDH, Number of metastatic sites, Sex, BRAF status, Age and Charlson comorbidity score. Additionally, an exact matching on the type of immunotherapy was performed. The love plot (Figure 3) shows good matching of all covariates indicated by absolute standardized mean differences below 0.1 (a generally accepted threshold).**

**Table 1:** Clinical characteristics of matched patients treated with ICI in 1st line

| | Anti-PD1 treated (N=389) | Anti-PD1 naive (N=389) | P-value |
|---|---|---|---|
| **Sex** | | | |
| Female | 139 (35.7%) | 148 (38.0%) | 0.552 |
| Male | 250 (64.3%) | 241 (62.0%) | |
| **Age at start of 1st line (years)** | | | |
| Mean (SD) | 61.5 (14.6) | 62.2 (12.5) | 0.442 |
| Median [Min, Max] | 63.0 [19.0, 89.0] | 63.0 [30.0, 93.0] | |
| **BRAF** | | | |
| Wildtype | 241 (62.0%) | 233 (59.9%) | 0.78 |
| Mutated | 112 (28.8%) | 121 (31.1%) | |
| Unknown | 36 (9.3%) | 35 (9.0%) | |
| **ECOG at start of 1st line** | | | |
| 0 | 285 (73.3%) | 283 (72.8%) | 0.798 |
| 1 | 63 (16.2%) | 60 (15.4%) | |
| >= 2 | 10 (2.6%) | 8 (2.1%) | |
| Missing/Unknown | 31 (8.0%) | 38 (9.8%) | |
| **Charlson comorbidity score** | | | |
| 6 | 249 (64.0%) | 258 (66.3%) | 0.872 |
| 7 | 64 (16.5%) | 56 (14.4%) | |
| >=8 | 25 (6.4%) | 25 (6.4%) | |
| Missing/Unknown | 51 (13.1%) | 50 (12.9%) | |
| **AJCC stage at start of 1st line** | | | |
| Stage III, NR | 52 (13.4%) | 48 (12.3%) | 0.987 |
| Stage IV M1a | 54 (13.9%) | 52 (13.4%) | |
| Stage IV M1b | 69 (17.7%) | 70 (18.0%) | |
| Stage IV M1c | 156 (40.1%) | 157 (40.4%) | |
| Stage IV M1d | 58 (14.9%) | 62 (15.9%) | |
| **LDH at start of 1st line** | | | |
| Normal | 260 (66.8%) | 253 (65.0%) | 0.795 |
| Elevated | 87 (22.4%) | 95 (24.4%) | |
| Missing | 42 (10.8%) | 41 (10.5%) | |
| **Number of metastatic sites at start of 1st line** | | | |
| 1 | 174 (44.7%) | 164 (42.2%) | 0.69 |
| 2 | 108 (27.8%) | 108 (27.8%) | |
| >= 3 | 107 (27.5%) | 117 (30.1%) | |
| **Type of melanoma** | | | |
| Cutaneous | 363 (93.3%) | 358 (92.0%) | 0.582 |
| MUP | 26 (6.7%) | 31 (8.0%) | |
| **Type of 1st line therapy** | | | |
| PD1 blockade | 81 (20.8%) | 81 (20.8%) | 1 |
| Ipi/Nivo | 308 (79.2%) | 308 (79.2%) | |
| **Median Follow-up (95% CI)** | 17.5 (15.5-19.3) | 36.5 (32.7-38.9) | < 0.0001 |

N: number of patients, MUP: melanoma with unknown primary, ECOG: Eastern Cooperative Oncology Group, LDH: Lactate dehydrogenase; AJCC: American Joint Committee on Cancer, anti-PD1: PD-1, Programmed cell death protein 1.

**Figure 4:** A) Kaplan Meier curves of PFS of patients treated with 1st line ICI stratified by early and late resistance. B) 6 and 12 months PFS stratified by timing of recurrence after start of adjuvant treatment.




**Progression-free survival (PFS) in metastatic 1st line was significantly longer in patients who had experienced late recurrences from adjuvant treatment (> 3 months after end of adjuvant treatment) than those with early recurrences.**

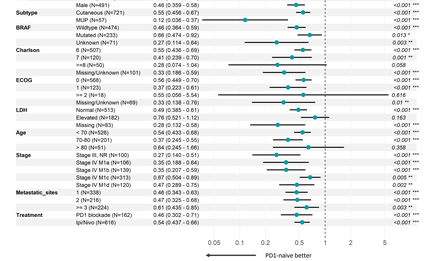
**Six months (6m) and 12 months (12m) PFS for cases treated with anti-PD1 single agent or combined anti-PD1/CTLA4 showing lower progression-survival (PFS) for very early recurrences.**

**Table 3:** Clinical outcome of patients with IO in 1st line grouped by reason for end of adjuvant treatment

| | Disease Progression (N = 231) | Regularly Ended (N = 85) | Toxicity (N = 38) | Other* (N = 35) | Total (N = 389) | P-value |
|---|---|---|---|---|---|---|
| **Best response** | | | | | | |
| CR | 30 (13.0%) | 14 (16.5%) | 10 (26.3%) | 8 (22.9%) | 62 (15.9%) | 0.61 |
| PR | 33 (14.3%) | 19 (22.4%) | 5 (13.2%) | 4 (11.4%) | 61 (15.7%) | |
| SD | 34 (14.7%) | 12 (14.1%) | 4 (10.5%) | 4 (11.4%) | 54 (13.9%) | |
| PD | 97 (42.0%) | 30 (35.3%) | 13 (34.2%) | 14 (40.0%) | 154 (39.6%) | |
| Unknown | 37 (16.0%) | 10 (11.8%) | 6 (15.8%) | 5 (14.3%) | 58 (14.9%) | |
| **ORR** | 63 (27.3%) | 33 (38.8%) | 15 (39.5%) | 12 (34.3%) | 123 (31.6%) | 0.14 |
| **DCR** | 97 (42.0%) | 45 (52.9%) | 19 (50.0%) | 16 (45.7%) | 177 (45.5%) | 0.34 |
| **Survival** | | | | | | |
| **Median PFS (95% CI)** | 3.5 (3-4.4) | 6.0 (3-8.7) | 8.3 (3.4-14.5) | 4 (2.6-8.1) | 4 (3.3-5.5) | 0.1827 |

N: Number of patients; CR: Complete response; PR: Partial remission, SD: Stable disease, PD: Progressive disease, ORR: Overall response rate, DCR: Disease control rate, CI: Confidence interval; PFS: Progression-free survival, FU: follow-up. *Patients ended adjuvant therapy due to investigators decision/patient’s wish/other

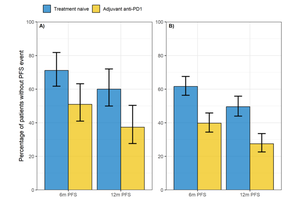
**Figure 5:** Multivariable cox regression for PFS for patients treated with 1st line ICI.




Hazard ratios for PFS grouped by different prognostic covariates and adjusted in a multivariable Cox regression model for the effect of all other covariates showing general homogenous effect of pre-treatment with adjuvant anti-PD1 on PFS outcome in the metastatic situation.

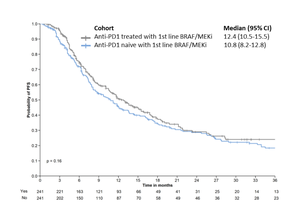
N: number of patients, MUP: melanoma with unknown primary, ECOG: Eastern Cooperative Oncology Group, LDH: Lactate dehydrogenase; Stage: American Joint Committee on Cancer V8 clinical stage.

**Figure 6:** PFS landmark analysis by ICI type and adjuvant pre-treatment




**Six months (6m) and 12 months (12m) PFS for cases treated with anti-PD1 single agent (A) or combined anti-PD1/CTLA4 (B) showing similar PFS decrease for both treatment approaches. PFS: progression-free survival.**

**Figure 7:** Kaplan Meier analysis 1st line BRAF/MEKi therapy after failure of adjuvant anti-PD1




**BRAF-V600 mutated cases matched by the same algorithm as for the main study and comparing PFS for ant-PD1 naive (‘No’) cases vs. those with anti-PD1 failure in adjuvant treatment (‘Yes’) showing no outcome bias from different follow-up times in both cohorts. PFS: progression-free survival.**

## Conclusions

Adjuvant pre-treatment with anti-PD1 antibodies was related to an inferior response and progression-free survival in patients with metastatic or non-resectable melanoma receiving ICI in the 1st line setting after failure from adjuvant anti-PD1 treatment. This effect was seen irrespective of whether combined ICI or single agent anti-PD1 re-treatment was used. While there is no general direct impact of these results on clinical practise, it underscores the need for further developments of immune based treatments but may also impact treatment decisions in BRAF V600 mutated cases.
A major limitation of our study is the observational nature of our database and despite matching a major differences persisted in follow-up times of both cohorts (Figure 1). In order to check whether this difference could introduce bias, we reproduced the procedure for patients with 1st line BRAF/MEKi therapy. Notably, there was no evidence of bias due to different follow-up times as shown by the analogous Kaplan-Meier analysis with unimpaired efficacy of BRAK/MEK inhibition after adjuvant anti-PD1 failure (Figure 7).
In conclusion, the potential of ICI in metastatic disease may be impaired by preceding adjuvant ICI in high-risk melanoma.

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