# Impact of switching from BRAF/MEK inhibition to immune checkpoint inhibition before secondary resistance in metastatic melanoma. A EUMelaReg real-world study.

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## BACKGROUND

- Recent studies have shown that immune checkpoint inhibition (ICI) is a preferable treatment of choice in first-line (1L) in BRAF mutated metastatic melanoma.
- For a variety of reasons, such as poor performance status or rapidly progressive disease, some patients might have immediate benefit from 1L BRAF/MEK inhibitors (BRAF/MEKi).
- However, these patients still have limited progression-free survival (PFS) and poor long-term outcomes, and it is unclear whether a switch to ICI should be considered before secondary resistance develops.

## OBJECTIVES

- Primary objective was overall survival (OS) from 1L BRAF/MEKi treatment in patients switching to ICI before progression.
- As secondary outcome, efficiency of 2L ICI was evaluated for response rates and PFS, calculated from the start of 2L treatment (PFS-2L).

## SUMMARY AND CONCLUSION

- After achieving tumor control from BRAF/MEKi, switching to ICI might improve clinical outcomes including OS.
- This could be considered in the current guideline recommendations in 1L for patients who are not suitable for ICI upfront.

## METHODS

- **Study population:** Patients with BRAF$^{V600}$ mutated non-resectable stage III or metastatic stage IV cutaneous melanoma were retrieved from the **European Melanoma Registry (EUMelaReg)** database. Those who achieved tumor control (complete/partial response or stable disease) from 1L BRAF/MEKi and either received ICI in 2L or no 2L therapy were selected as study population. We compared those who switched to 2L ICI without having progressed (switch cohort) to the remaining cohort (control cohort).
- **Matching:** For adjustment of guaranteed time bias and baseline imbalances a 1:2 optimal matching algorithm (mahalanobis distance as distance metric) for several prognostic factors was performed. Samples were matched for sex, age, ECOG, Charlson comorbidity score, AJCC substage, baseline serum LDH, number of metastatic sites, and prior adjuvant therapy.

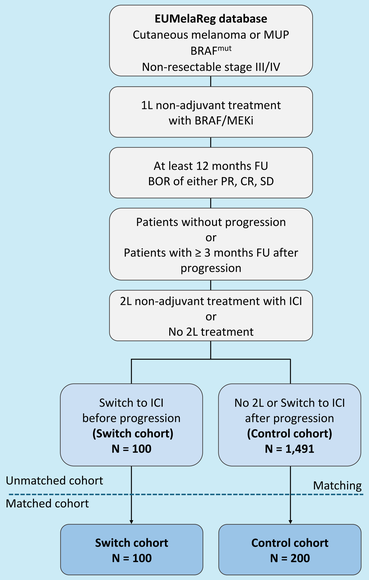


**Figure 1: Flow chart illustrating the selected populations for analysis using real-world data from the EUMelaReg.** BRAF/MEKi, BRAF/MEK inhibitor therapy; FU, follow-up; BOR, best overall response; PR, partial response; CR, complete response; SD, stable disease; ICI, immune checkpoint inhibitor therapy; MUP, melanoma of unknown primary; Mut, mutated; 1L/2L, first/second line. *ICI treatment includes anti-PD1 and/or anti-PD1/anti-CTLA4 antibodies. Matching was performed with an optimal matching algorithm using inverse propensity score matching.

## RESULTS

- We identified 100 patients who switched to 2L ICI treatment electively before progression (switch cohort) and 1,491 in the control cohort. 200 patients in the control group were matched to 100 patients in the switched group (**Table 1**).
- **Median OS** from start of 1L BRAF/MEKi treatment was significantly longer in the switch cohort than in the unmatched control group (42.1 months vs. 23.6 months; p = 0.005; **Table 2**).
- After matching for prognostic baseline factors the benefit for the switch group could be confirmed (OS 42.1 months vs 23.0 months; p=0.017; **Figure 2**).
- 733 patients from the control group received a 2L treatment. **Overall response rate (ORR)** after 2L ICI treatment was lower than in the switch group (24% vs 34%), although not statistically significant (p=0.13; **Table 2**).

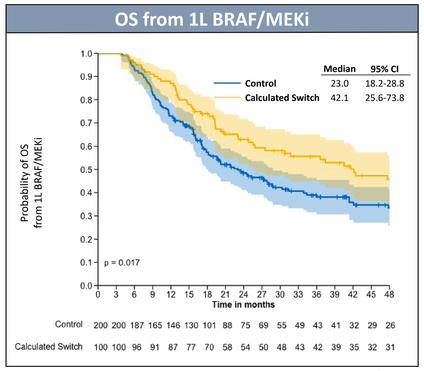


**Figure 2: Kaplan-Meier curves of OS from start of 1L BRAF/MEKi in matched samples for patients who switched to 2L ICI before progression (yellow line) or after disease progression (blue line).** OS, overall survival; BRAF/MEKi, BRAF/MEK inhibitor therapy; 1L, first line; CI, confidence interval.

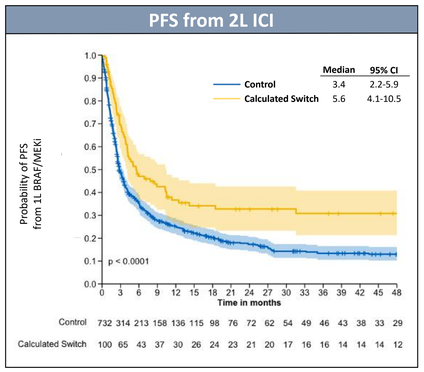


**Figure 3: Kaplan-Meier curves of PFS from start of 2L ICI in unmatched samples for patients who switched to 2L ICI before progression (yellow line) or after disease progression (blue line).** PFS, progression-free survival; ICI, immune checkpoint inhibition; 2L, second line; CI, confidence interval.

| | Control Unmatched | Switch | P-value | Control Matched | Switch | P-value |
|---|---|---|---|---|---|---|
| **Survival, months (95% CI) from 1L** | **(N = 1,491)** | **(N = 100)** | | **(N = 200)** | **(N = 100)** | |
| Median OS from start of 1L BRAF/MEKi | 23.6 (21.0-25.4) | 42.1 (25.6-73.8) | 0.005 | 23.0 (18.2-28.8) | 42.1 (25.6-73.8) | 0.017 |
| Median PFS from start of 1L BRAF/MEKi* | 10.1 (9.5-11.2) | 13.1 (9.6-15.7)* | 0.02 | 11.6 (9.7-13.9) | 13.1 (9.6-15.7)* | 0.11 |
| **Outcomes from 2L** | **(N = 733)** | **(N = 100)** | | **(N = 112)** | **(N = 100)** | |
| CR | 64 (8.7%) | 16 (16.0%) | 0.07 | 10 (8.9%) | 16 (16.0%) | 0.38 |
| PR | 112 (15.3%) | 18 (18.0%) | | 17 (15.2%) | 18 (18.0%) | |
| SD | 138 (18.8%) | 22 (22.0%) | | 22 (19.6%) | 22 (22.0%) | |
| PD | 319 (43.5%) | 32 (32.0%) | | 44 (39.3%) | 32 (32.0%) | |
| Unknown | 100 (13.6%) | 12 (12.0%) | | 19 (17.0%) | 12 (12.0%) | |
| **PFS after 2L ICI, months (95% CI)** | | | | | | |
| Median PFS from start of 2L ICI | 2.8 (2.6-3.4) | 5.6 (4.1-10.5) | < 0.0001 | 3.4 (2.2-5.9) | 5.6 (4.1-10.5) | 0.01 |

**Table 2: Therapy outcome for patients with 1L BRAF/MEKi → 2L ICI sequence.** N, Number of patients; OS, overall survival; PFS, progression-free survival; CR, complete response; PR, partial remission; SD, stable disease; PD, progressive disease; ICI, immune checkpoint inhibition; 1L/2L, first/second line. *For the switch cohort progression after 2L ICI was the event for comparison.

- Elevated serum LDH levels are a predictive and prognostic factor for poor outcomes in patients with metastatic melanoma.
- A subgroup analysis of patients stratified by normal or elevated LDH at 1L indicated, that switching to ICI before progression was even more beneficial in patients with elevated LDH.

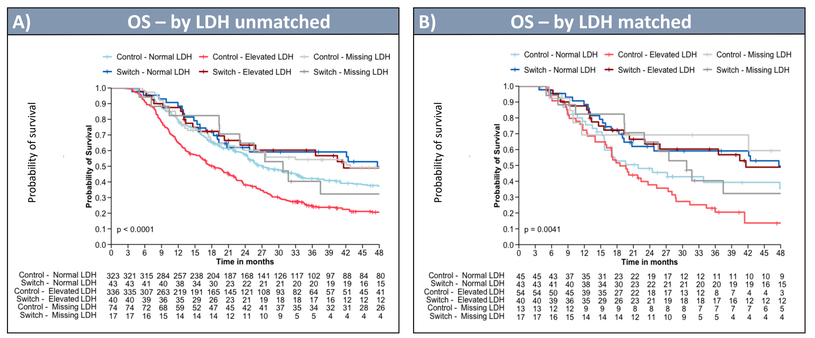


**Figure 5: Kaplan-Meier curves of OS from start of 1L BRAF/MEKi in A) unmatched and B) matched samples for patients stratified by LDH levels at 1L baseline for the following cohorts: control cohort with normal (light blue line), elevated (light red line) and missing (light grey line) LDH levels; switch cohort with normal (blue line), elevated (red line) and missing (grey line) LDH levels.** OS, overall survival; LDH, lactate dehydrogenase.

**Table 1: Demographics and clinical characteristics at 2L treatment in response to progression**

| | Control Unmatched (N = 1,491) | Switch (N = 100) | P-value | Control Matched (N = 200) | Switch (N = 100) | P-value |
|---|---|---|---|---|---|---|
| **Sex** | | | | | | |
| Female | 607 (40.7%) | 45 (45.0%) | 0.46 | 83 (41.5%) | 45 (45.0%) | 0.65 |
| Male | 884 (59.3%) | 55 (55.0%) | | 117 (58.5%) | 55 (55.0%) | |
| **Age (years)** | | | | | | |
| Mean (SD) | 61.5 (13.5) | 58.3 (15.6) | 0.02 | 58.9 (13.5) | 58.3 (15.6) | 0.75 |
| Median [Min, Max] | 62.0 [19.0, 94.0] | 57.0 [19.0, 120] | | 58.0 [26.0, 88.0] | 57.0 [19.0, 120] | |
| **ECOG** | | | | | | |
| 0 | 706 (47.4%) | 62 (62.0%) | 0.005 | 120 (60.0%) | 62 (62.0%) | 0.93 |
| 1 | 410 (27.5%) | 12 (12.0%) | | 29 (14.5%) | 12 (12.0%) | |
| ≥ 2 | 153 (10.3%) | 10 (10.0%) | | 18 (9.0%) | 10 (10.0%) | |
| Missing/Unknown | 222 (14.9%) | 16 (16.0%) | | 33 (16.5%) | 16 (16.0%) | |
| **Charlson comorbidity score** | | | | | | |
| 6 | 208 (14.0%) | 21 (21.0%) | 0.17 | 41 (20.5%) | 21 (21.0%) | 0.99 |
| 7 | 277 (18.6%) | 23 (23.0%) | | 48 (24.0%) | 23 (23.0%) | |
| 8 | 280 (18.8%) | 15 (15.0%) | | 31 (15.5%) | 15 (15.0%) | |
| ≥ 9 | 529 (35.5%) | 28 (28.0%) | | 56 (28.0%) | 28 (28.0%) | |
| Missing/Unknown | 197 (13.2%) | 13 (13.0%) | | 24 (12.0%) | 13 (13.0%) | |
| **AJCC stage** | | | | | | |
| Stage III, NR | 107 (7.2%) | 6 (6.0%) | | 12 (6.0%) | 6 (6.0%) | |
| Stage IV M1a | 201 (13.5%) | 14 (14.0%) | 0.92 | 26 (13.0%) | 14 (14.0%) | 0.99 |
| Stage IV M1b | 204 (13.7%) | 11 (11.0%) | | 24 (12.0%) | 11 (11.0%) | |
| Stage IV M1c | 613 (41.1%) | 42 (42.0%) | | 87 (43.5%) | 42 (42.0%) | |
| Stage IV M1d | 366 (24.5%) | 27 (27.0%) | | 51 (25.5%) | 27 (27.0%) | |
| **LDH** | | | | | | |
| Normal | 690 (46.3%) | 53 (53.0%) | 0.16 | 109 (54.5%) | 53 (53.0%) | 0.89 |
| Elevated | 606 (40.6%) | 40 (40.0%) | | 75 (37.5%) | 40 (40.0%) | |
| Missing | 195 (13.1%) | 7 (7.0%) | | 16 (8.0%) | 7 (7.0%) | |
| **Number of metastatic sites** | | | | | | |
| 1 | 440 (29.5%) | 22 (22.0%) | 0.28 | 45 (22.5%) | 22 (22.0%) | 0.76 |
| 2 | 416 (27.9%) | 31 (31.0%) | | 54 (27.0%) | 31 (31.0%) | |
| ≥ 3 | 635 (42.6%) | 47 (47.0%) | | 101 (50.5%) | 47 (47.0%) | |
| **Prior adjuvant therapy** | | | | | | |
| No | 1122 (75.3%) | 82 (82.0%) | 0.16 | 59 (29.5%) | 48 (48.0%) | NA |
| Yes | 369 (24.7%) | 18 (18.0%) | | 51 (25.5%) | 52 (52.0%) | |

N, number of patients; SD, standard deviation; min, minimum; max, maximum; ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Committee on Cancer staging version 8; NR, non-resectable; LDH, Lactate dehydrogenase.

- Multivariate Cox regression analysis of OS from start of 1L in the unmatched data shows that several variables increased the hazard ratio (HR) for death.
- ECOG PS 1 and ≥2, elevated LDH levels, melanoma stage M1c/d, metastatic sites of 2 or ≥3, best overall response of progressive disease and stable disease and no 2L therapy significantly increased the risk of death, while patients who switched to ICI before progression had a significantly lower risk of death (HR of 0.63 (95% CI: 0.47-0.85)).

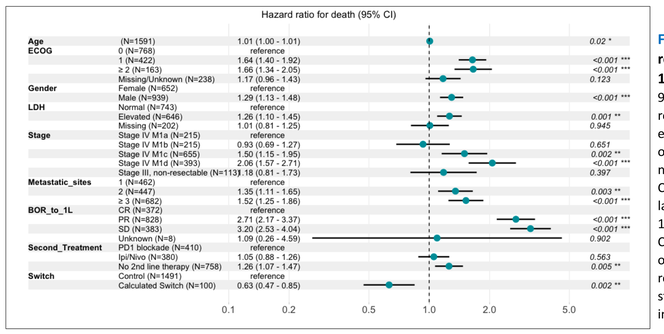


**Figure 4: Multivariate cox regression for OS from start of 1L BRAF/MEKi.** Hazard ratios and 95% CI from a multivariate cox regression model are reported in each category and adjusted for all other variables in the model. N, number of patients; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase at start of 1L; stage, AJCC American Joint Committee on Cancer; BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease; CI, confidence interval.

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**European Melanoma Registry (EUMelaReg**; www.eumelareg.org): This registry is a multi-center database run by a cross-national consortium of academic groups in Europe collecting and evaluating real-world melanoma cases with non-resectable stage III or metastatic stage IV melanoma. Data has been captured since 2018 entered voluntarily into the system by participating centers.