Upfront usage of single agent anti-PD1 antibodies versus combined BRAF and MEK inhibitors in metastatic or unresectable BRAF V600 mutated melanoma
- A EUMelaReg real world evidence study -

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Background

Treatment of BRAF V600 mutated metastatic melanoma patients with either BRAF and MEK inhibitors (BRAF/MEKi) or immune-checkpoint inhibitors (ICI) with anti-PD1 antibodies or anti-PD1/CTLA4 combinations, has improved the outcome of patients significantly compared to former treatment standards. Until recently, there was only sparse evidence on the question of whether any of the approved BRAF/MEKi or anti-PD1 schedules would offer significant advantage over others in patients with BRAF mutated melanoma as upfront treatment for treatment-naïve metastatic disease, and most guidelines did not recommend one of the two strategies to be preferred.

While some evidence is available for advantage of combined anti-PD1/CTLA4 antibody treatment compared to BRAF/MEKi, the role of single agent anti-PD1 antibody treatment is less clear.

The current study analysed patients with metastatic or nonresectable BRAF V600 mutated melanoma, who received either BRAF/MEKi combination, or single agent anti-PD1 antibody treatment in the first-line setting. The aim of this study was to understand the clinical characteristics associated with treatment allocation in first-line unresectable or metastatic BRAF V600-mutated melanoma besides combined ICI with Ipi/Nivo in order to evaluate which treatment choice could be paramount for patient's ineligible for Ipi/Nivo.

Methods

A total of 1,861 patients with BRAF V600 mutated unresectable metastatic melanoma who received for first-line either BRAF/MEKi (n=1,150) or single anti-PD1 ICI (n=711) were evaluated based on data from the EUMelaReg, which is a real-world registry for the treatment of advanced and high-risk melanoma at the European level.

Patients were excluded if they had received previous BRAF/MEKi or anti-PD1 adjuvant treatment or their follow-up after the start of first-line treatment was less than 12 months, except for patients with PFS2 event, including death, within the first 12 months

Primary outcomes of interest were (1) overall survival (OS), (2) time interval until progression after second-line therapy (PFS2) and (3) time to next treatment (TTNT).

In addition, latent class analysis (LCA) was used to identify complex patient profiles and their relation to treatment outcomes. For LCA the study populations data was split into two cohorts. The exploration cohort consisted of those sources that were particularly rich for all potentially important covariates and had a low rate of missing or unknown values for those covariates and potential indicator variables. This cohort consisted of data from 1,065 patients. The remaining data sources were used as a validation cohort and consisted of 793 cases.

Results

Adjusted survival analysis revealed that patients treated with anti-PD1 only had a significant higher overall survival with a median OS (95% CI) of 38.1 (30.4-48.3) months and median PFS2 (95% CI) of 21.7 (19-27.4) months compared to the BRAF/MEKi group with 16.7 (15.5-18.6) months and 12.3 (11.6-13.5) months (p<0.0001 for both), respectively (Table 3, Figure 1A, C).

Median TTNT (95% CI) did not differ significantly between both treatments with 13.7 (10.6-16.8) months for anti-PD1 and 11.8 (11.0-12.8) months for BRAF/MEKi (Table 3, Figure 1D).

Latent class analysis revealed 4 distinct classes of patient profiles showing differential outcomes of anti-PD1 compared to BRAF/MEKi. The advantage of anti-PD1 compared to BRAF/MEKi was most prominent in patients with very high tumor load, symptomatic M1c/M1d disease, and many metastatic sites, and in young patients with average tumor load, while elderly patients with average tumor load, but higher rate of comorbidities showed no significant difference. The same was true for patients with low tumor burden, regardless of age (Figure 2 and 3). The distribution of classes and the respective survival outcomes could generally be confirmed in the validation cohort (data not shown).

Table 1: Baseline Characteristics

	BRAF/MEKi (N=1,150)	Anti-PD1 (N=711)	P-value	Total (N=1,861)
Sex				
Female	476 (41.4%)	292 (41.1%)	0.929	768 (41.3%)
Male	674 (58.6%)	419 (58.9%)		1,093 (58.7%)
Age at treatment start (years)				
< 70	794 (69.0%)	385 (54.1%)	<0.001	1,179 (63.4%)
70-80	267 (23.2%)	222 (31.2%)		489 (26.3%)
> 80	89 (7.7%)	104 (14.6%)		193 (10.4%)
ECOG score				
0	457 (39.7%)	410 (57.7%)	<0.001	867 (46.6%)
1	337 (29.3%)	185 (26.0%)		522 (28.0%)
≥ 2	208 (18.1%)	36 (5.1%)		244 (13.1%)
Missing/Unknown	148 (12.9%)	80 (11.3%)		228 (12.3%)
Charlson comorbidity score				
0	239 (20.8%)	98 (13.8%)	<0.001	337 (18.1%)
1	251 (21.8%)	116 (16.3%)		367 (19.7%)
2	250 (21.7%)	136 (19.1%)		386 (20.7%)
≥ 3	410 (35.7%)	361 (50.8%)		771 (41.4%)
Ipi/Nivo available at therapy start				
Yes	847 (73.7%)	543 (76.4%)	0.353	1,390 (74.7%)
No	139 (12.1%)	82 (11.5%)		221 (11.9%)
Missing	164 (14.3%)	86 (12.1%)		250 (13.4%)

N, number of patients; BRAF/MEKi, therapy with BRAF/MEK inhibitors; anti-PD1: PD-1, Programmed cell death protein 1; ECOG, Eastern Cooperative Oncology Group; Ipi/Nivo, Ipilimumab/nivolumab.

Table 2: Tumor Characteristics

	BRAF/MEKi (N=1,150)	Anti-PD1 (N=711)	P-value	Total (N=1,861)
AJCC Stage				
Stage III, non-resectable	65 (5.7%)	60 (8.4%)	<0.001	125 (6.7%)
Stage IV M1a	111 (9.7%)	155 (21.8%)		266 (14.3%)
Stage IV M1b	117 (10.2%)	150 (21.1%)		267 (14.3%)
Stage IV M1c	489 (42.5%)	261 (36.7%)		750 (40.3%)
Stage IV M1d	368 (32.0%)	85 (12.0%)		453 (24.3%)
LDH at baseline				
Normal	440 (38.3%)	423 (59.5%)	<0.001	863 (46.4%)
Elevated <2.5 x ULN	384 (33.4%)	187 (26.3%)		571 (30.7%)
≥ 2.5 x ULN	153 (13.3%)	21 (3.0%)		174 (9.3%)
Missing	173 (15.0%)	80 (11.3%)		253 (13.6%)
Number of metastatic sites				
1	243 (21.1%)	252 (35.4%)	<0.001	495 (26.6%)
2	272 (23.7%)	225 (31.6%)		497 (26.7%)
≥ 3	635 (55.2%)	234 (32.9%)		869 (46.7%)
Type of melanoma				
Cutaneous	957 (83.2%)	618 (86.9%)	0.037	1575 (84.6%)
MUP	193 (16.8%)	93 (13.1%)		286 (15.4%)
Adjuvant therapy prior to 1L*				
YES	86 (7.5%)	48 (6.8%)	0.619	134 (7.2%)
Radiotherapy prior to 1L				
YES	161 (14.0%)	67 (9.4%)	0.004	228 (12.3%)

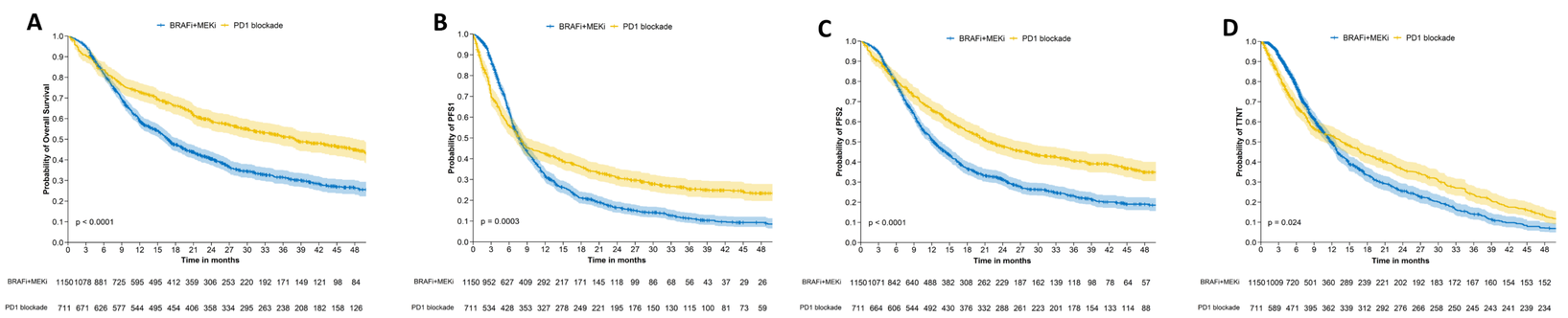
N, number of patients; BRAF/MEKi, therapy with BRAF/MEK inhibitors; anti-PD1, PD-1, Programmed cell death protein 1; AJCC, American Joint Committee on Cancer; LDH, Lactate dehydrogenase; MUP, melanoma with unknown primary. *Adjuvant pre-treatments with interferon.

Table 3: Treatment outcomes

	BRAF/MEKi (N=1,150)	Anti-PD1 (N=711)	Total (N=1,861)	P-value
Best response				
CR	145 (12.6%)	165 (23.2%)	310 (16.7%)	< 0.0001
PR	535 (46.5%)	167 (23.5%)	702 (37.7%)	
SD	234 (20.3%)	135 (19.0%)	369 (19.8%)	
PD	167 (14.5%)	208 (29.3%)	375 (20.2%)	
Unknown	69 (6.0%)	36 (5.1%)	105 (5.6%)	
ORR	680 (59.1%)	332 (46.7%)	1,012 (54.4%)	< 0.0001
DCR	914 (79.5%)	467 (65.7%)	1,381 (74.2%)	< 0.0001
Survival (95% CI)*				
Median OS	16.7 (15.5-18.6)	38.1 (30.4-48.3)	23.8 (21.1-26.8)	< 0.0001
Median PFS1	7.7 (7.3-8.2)	7.8 (6.7-8.8)	7.7 (7.2-8.3)	0.0003
Median PFS2	12.3 (11.6-13.5)	21.7 (19-27.4)	16.1 (14.6-17.5)	< 0.0001
Median TTNT	11.8 (11.0-12.8)	13.7 (10.6-16.8)	12.7 (11.6-13.7)	0.024
Median FU	38.5 (35-40.6)	41.8 (39.9-44.7)	40.3 (38.5-41.8)	0.002

N, number of patients; BRAF/MEKi, therapy with BRAF/MEK inhibitors; anti-PD1, PD-1, Programmed cell death protein 1; CR, complete response; PR, partial remission; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; CI, confidence interval; PFS1, progression-free survival; PFS2: progression-free survival after second line of treatment; TTNT, time to next treatment; FU, follow-up;
*Adjusted with inverse propensity score weighting.

Figure 1: Adjusted survival analysis
Kaplan-Meier survival estimates adjusted by propensity score weighting for overall survival (A), progression free survival PFS1 (B), time to second progression PFS2 (C), and time to next treatment (D). 95 percent confidence intervals of the estimate are denoted by colour shading.



OS, PFS1 and PFS2 estimates adjusted by inverse propensity score weighting were significantly higher in anti-PD1 treated patients compared to BRAF/MEKi (Figure 1A, 1B, 1C).

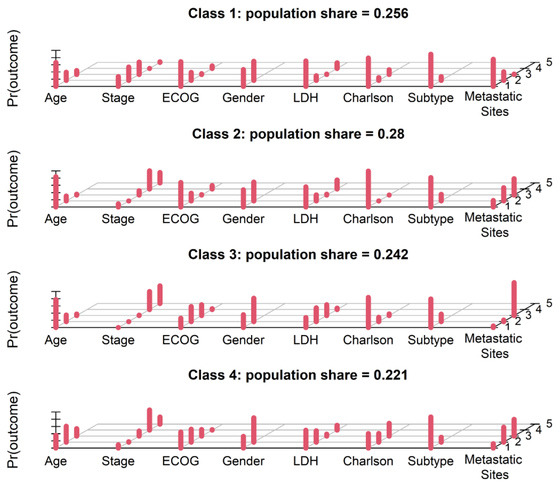
Time to next treatment was comparable between both groups (Figure 1D, p=0.024).

During the first few months, hazards appear worse for anti-PD1, resulting in crossing over of the Kaplan-Meier curves within the first 12 months for all outcomes.

ORR showed a significantly higher percentage of 59.1 for BRAF/MEKi as compared to 46.7% with anti-PD1 (p<0.0001). Likewise, the overall disease control rate was in favour of BRAF/MEKi (79.5% vs. 65.7%; p<0.0001).

The median follow-up time was significantly shorter in BRAF/MEKi treated patients than in anti-PD1 (Table 3).

Figure 2: Latent class analysis
Supervised clustering of patient groups defined by relevant indicator variables (age, AJCC stage, ECOG, gender, LDH, Charlson score (without age), melanoma subtype and number of metastatic sites). Clustering was performed for two, three and four latent classes and the 4-class model was chosen based on optimal AIC. Bars represent the proportion of each factor level within the respective latent class.

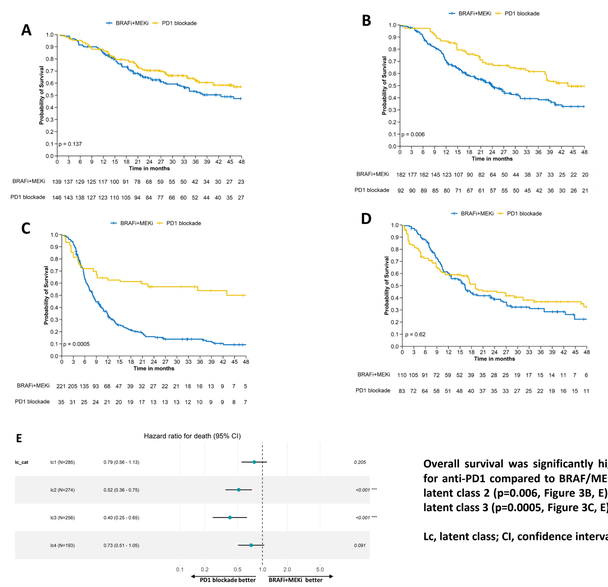


- **Age (years):**
  - 1: < 70
  - 2: 70-80
  - 3: > 80
- **Stage:**
  - 1: Stage III, non-resectable
  - 2: Stage IV M1a
  - 3: Stage IV M1b
  - 4: Stage IV M1c
  - 5: Stage IV M1d
- **ECOG:**
  - 1: 0
  - 2: 1
  - 3: ≥ 2
  - 4: Missing/Unknown
- **Gender:**
  - 1: Female
  - 2: Male
- **LDH:**
  - 1: Normal
  - 2: Elevated
  - 3: ≥ 2.5 ULN
  - 4: Missing
- **Charlson score (without age)**
  - 1: 0
  - 2: 1
  - 3: ≥ 2
- **Melanoma subtype:**
  - 1: Cutaneous
  - 2: MUP
- **Metastatic sites:**
  - 1: 1
  - 2: 2
  - 3: ≥ 3

- **Latent class 1 (lc1)**
  - represents predominantly younger patients in lower stages with ECOG 0 and 1, a balanced gender proportion, low levels of LDH, mostly without comorbidities and 1 or 2 metastatic sites only.
- **Latent class 2 (lc2)**
  - is characterized by similar distribution of covariates except for AJCC stage and a higher number of metastatic sites (predominantly 2 and ≥3).
- **Latent class 3 (lc3)**
  - show young patients without comorbidities but with a high tumor load evidenced by stage IV M1c and M1d, mostly ECOG 1 or ≥2, high rate of LDH elevation, and almost all patients presenting with ≥3 metastatic sites. Additionally, the majority of patients in LC3 was male (67.6%).
- **Latent class 4 (lc4)**
  - has an average distribution for tumor characteristics but contained more elderly and more comorbid patients than in LC2.

ECOG, Eastern Cooperative Oncology Group; LDH, Lactate dehydrogenase; Stage, American Joint Committee on Cancer V8 clinical stage; Charlson, Charlson comorbidity score; MUP, melanoma with unknown primary; AIC, Akaike information criterion.

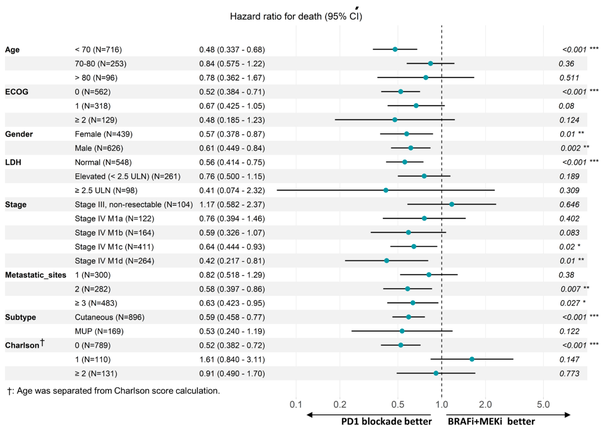
Figure 3: Real-world OS with inverse propensity score weighting for 4 latent classes
Kaplan-Meier curves were obtained from propensity score adjusted estimates for overall survival as described for the total population subdivided for latent classes lc1 (A), lc2 (B), lc3 (C) and lc4 (D). (E) Cox regression analysis for overall survival comparing BRAF/MEKi and anti-PD1 within latent classes.



Overall survival was significantly higher for anti-PD1 compared to BRAF/MEKi in latent class 2 (p=0.006, Figure 3B, E) and latent class 3 (p=0.0005, Figure 3C, E).

Lc, latent class; CI, confidence interval.

Figure 4: Adjusted overall survival by treatment
Forest plot showing stratified hazard ratios for death according to treatment group. Each stratified variable was fully adjusted for all other variables in a multivariable cox regression model.



†: Age was separated from Charlson score calculation.

Multivariable cox regression of OS comparing anti-PD1 with BRAF/MEKi with multiple imputation for missing values and addressing baseline imbalances in treatment groups and in the covariates LDH and ECOG.

Anti-PD1 was better for the majority of examined subgroups with the exception of patients with very high levels of LDH (≥2.5 ULN), patients with non-resectable stage III and patients with an age-excluded Charlson comorbidity score of 1.

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; CI, confidence interval.

Conclusions

In this study, we present real-world data obtained from a European registry of patients with advanced BRAF V600 mutated melanoma who received BRAFi/MEKi or single agent immunotherapy with anti-PD1 antibodies as a first-line treatment. We found that – overall – single agent anti-PD1 ICI seems superior to upfront BRAF/MEK inhibition as upfront treatment with anti-PD1 resulted in better overall and progression free survival compared to BRAF/MEKi (Figure 1).

This finding needs to be interpreted with caution, since various demographic and clinical variables, including higher age, higher ECOG scores, comorbidities, increased LDH levels, AJCC substage as well as the number of metastatic sites were associated with both, treatment assignment and outcome in this population. Still, these results provide additional support for the use of immunotherapy in first-line, and single agent anti-PD1 might be suffice in patients not eligible for combined ICI.

In conclusion, these results suggest that anti-PD1 single agent may be a valuable option for certain patients with BRAF V600 mutated metastatic melanoma.

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