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Treatment patterns using encorafenib plus binimetinib in patients with BRAF mutated melanoma

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BACKGROUND

- Following results of recent clinical studies, the role of BRAF and MEK inhibition in the treatment of BRAF V600 mutated melanoma is under discussion.
- This analysis aims at describing the treatment patterns clinical characteristics, and outcomes in adult patients with unresectable or metastatic melanoma with a $BRAF^{V600}$ mutation who were treated with encorafenib plus binimetinib (E/B) in the real-life setting.

OBJECTIVES

- To describe different sequencing patterns in the clinical usage of encorafenib/binimetinib
- To describe response rates, overall survival (OS) and progression-free survival (PFS) from start of E/B treatment.

SUMMARY AND CONCLUSION

- This study shows different major treatment patterns of E/B use in real-world setting and informs on patient profiles and related outcome variables.
- Overall, E/B shows efficacy for different treatment settings and lines.
- Tolerability was generally well and in the expected range in all treatment sequences and lines.

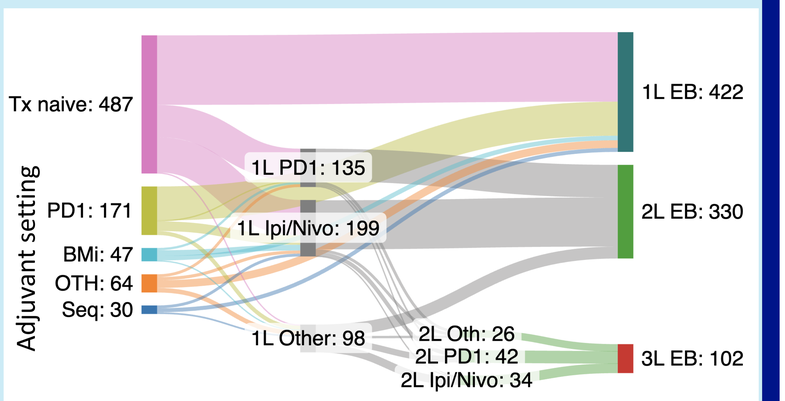

Figure 1: Treatment sequences for Encorafenib Binimetinib (EB) in first (1L), second (2L) and third (3L) line. In the adjuvant setting anti-PD1 antibodies (PD1) were most frequent, followed by combined BRAF/MEK inhibitors (BMi), and various others (OTH; Ipi/Nibo, experimental, interferon etc.), and a proportion of patients got both anti-PD1 antibodies and BRAF/MEKi (Seq). In the advanced setting anti-PD1 and Ipilimumab/Nivolumab (Ipi/Nivo) were most commonly used.

METHODS

- **Study population:** Patients with non-resectable stage III or metastatic stage IV cutaneous melanoma who received E/B between SEP 2018 and JAN 2024 were retrieved from the **European Melanoma Registry (EUMelaReg)** database.
- **Treatment sequences** were based on the line of treatment, and the class of preceding systemic treatments before initiating treatment with combined encorafenib/binimetinib (**Figure 1**).
- **Treatment responses** were evaluated from reported clinical best overall response in routine practice setting.
- **Survival outcomes** were calculated by Kaplan-Meier estimates from start of the respective encorafenib/binimetinib treatment to the event of permanent treatment stop (TTD), documented progression or death (PFS), or death to any cause (OS), otherwise censored for ongoing treatments or loss to follow-up.

RESULTS

- We identified 854 patients who were treated with E/B in any line of treatment. The median age at start of E/B was 62 years and 61.6% were male. Stage IV M1c was diagnosed in 39.1% and M1d in 34.4% at the start of E/B. 52.7% of patients had an elevated LDH and 48.2% had ≥ 3 metastatic sites at baseline (**Table 1**).
- The **overall response rate (ORR)** was 55.3% of the total population and varied from 54% to 64%, with no statistically significant differences between the four major treatment patterns (**Table 2**).
- **Median PFS** showed significant heterogeneity between the groups (p=0.004) with the shortest being 7.2 months in treatment naive patients receiving 1L E/B and the longest being 10.5 months in patients receiving 1L E/B following adjuvant ICI (**Figure 2; Table 2**).
- **Median OS** from initiation of E/B treatment ranged from 15.2 to 20.5 months, without significant variation observed among the groups (**Table 2**).
- **Tolerability** was in the range of the expected rates of severe or clinically relevant side effects.

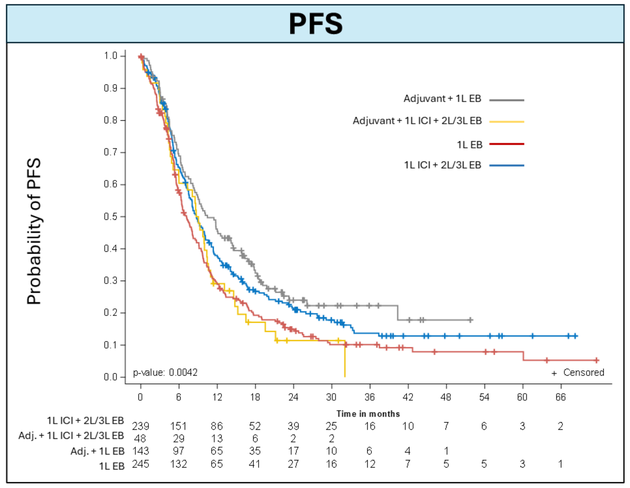

Figure 2: Kaplan-Meier curves of PFS stratified by treatment sequences:

- **Adjuvant + 1 EB (n=143):** 1L E/B following adjuvant ICI.
- **Adjuvant + 1L ICI + 2L/3L EB (n=48):** 2L or 3L E/B following both adjuvant and non-adjuvant ICI.
- **1L EB (n=245):** 1L E/B in treatment naive patients.
- **1L ICI + 2L/3L EB (n=239):** 2L or 3L E/B following 1L ICI without adjuvant therapy.

PFS, progression-free survival; N, number of patients; 1L/2L/3L, first/second/third line; EB, encorafenib/binimetinib; ICI, immune checkpoint inhibition; CI, confidence interval.

Table 2: Treatment outcomes stratified by treatment sequence

	1L E/B post-adjuvant (N = 143)	2L or 3L E/B post-adjuvant + 1L ICI (N = 48)	1L E/B (N = 245)	2L or 3L E/B post 1L ICI (N = 239)
Best response				
CR	36 (25.2%)	7 (14.6%)	25 (10.2%)	27 (11.3%)
PR	56 (39.2%)	19 (39.6%)	114 (46.5%)	114 (47.7%)
SD	13 (9.1%)	7 (14.6%)	33 (13.5%)	36 (15.1%)
PD	20 (14.0%)	10 (20.8%)	44 (18.0%)	44 (18.4%)
Unknown/Missing	18 (12.6%)	5 (10.4%)	29 (11.8%)	18 (7.5%)
ORR	92 (64.3%)	26 (54.2%)	139 (56.7%)	141 (59.0%)
Survival analyses, months (95% CI)				
Median TTD	9.6 (7.5-12.8)	9.5 (7.6-12.2)	5.6 (4.8-6.3)	8.3 (7.0-9.5)
Median OS	20.5 (15.5-28.1)	16.0 (9.9-28.6)	15.2 (11.7-17.7)	17.4 (14.7-21.8)
Median PFS	10.5 (8.4-14.2)	8.9 (5.1-10.4)	7.2 (6.3-8.2)	8.7 (7.6-10.1)

N, Number of patients; CR, complete response; PR, partial remission; SD, stable disease; PD, progressive disease; ORR, overall response rate; TTD, time to treatment discontinuation; OS, overall survival; PFS, progression-free survival.

Table 1: Demographics at baseline stratified by treatment sequence

	1L E/B post-adjuvant (N = 143)	2L or 3L E/B post-adjuvant + 1L ICI (N = 48)	1L E/B (N = 245)	2L or 3L E/B post 1L ICI (N = 239)
Sex				
Male	93 (65.0%)	24 (50.0%)	148 (60.4%)	146 (61.1%)
Female	50 (35.0%)	24 (50.0%)	97 (39.6%)	93 (38.9%)
Age (years)				
Mean (SD)	61.1 (13.5)	57.7 (14.1)	64.0 (14.1)	61.6 (14.3)
Median (min, max)	61 (26.0-84.0)	57 (23.0-86.0)	65 (23.0-91.0)	62 (20.0-91.0)
Melanoma type				
Cutaneous	139 (97.2%)	45 (93.8%)	184 (75.1%)	191 (79.9%)
MUP	4 (2.8%)	3 (6.3%)	61 (24.9%)	48 (20.1%)
BRAF mutation type				
V600D positive	-	-	1 (0.4%)	-
V600E positive	89 (62.2%)	34 (70.8%)	140 (57.1%)	163 (68.2%)
V600K positive	17 (11.9%)	9 (18.8%)	25 (10.2%)	30 (12.6%)
V600R positive	3 (2.1%)	-	1 (0.4%)	1 (0.4%)
Other mutation	4 (2.8%)	2 (4.2%)	8 (3.3%)	7 (2.9%)
Positive, unknown variant	30 (21.0%)	3 (6.3%)	70 (28.6%)	38 (15.9%)
ECOG				
0	98 (68.5%)	23 (47.9%)	91 (37.1%)	109 (45.6%)
1	29 (20.3%)	13 (27.1%)	81 (33.1%)	66 (27.6%)
≥ 2	8 (5.6%)	7 (14.6%)	57 (23.3%)	37 (15.5%)
Missing/Unknown	8 (5.6%)	5 (10.4%)	16 (6.5%)	27 (11.3%)
LDH				
Normal	81 (56.6%)	16 (33.3%)	81 (33.1%)	89 (37.2%)
Elevated	50 (35.0%)	27 (56.3%)	150 (61.2%)	128 (53.6%)
Missing	12 (8.4%)	5 (10.4%)	14 (5.7%)	22 (9.2%)
AJCC stage v8.0				
Stage III – NR	8 (5.6%)	1 (2.1%)	13 (5.3%)	8 (3.3%)
Stage IV - M1a	27 (18.9%)	6 (12.5%)	23 (9.4%)	27 (11.3%)
Stage IV - M1b	23 (16.1%)	3 (6.3%)	22 (9.0%)	22 (9.2%)
Stage IV - M1c	57 (39.9%)	14 (29.2%)	96 (39.2%)	92 (38.5%)
Stage IV - M1d	28 (19.6%)	24 (50.0%)	91 (37.1%)	90 (37.7%)
Number of metastatic sites				
1	63 (44.1%)	10 (20.8%)	60 (24.5%)	60 (25.1%)
2	38 (26.6%)	12 (25.0%)	53 (21.6%)	58 (24.3%)
≥ 3	42 (29.4%)	26 (54.2%)	132 (53.9%)	121 (50.6%)
Brain metastases				
Yes	28 (19.6%)	24 (50.0%)	91 (37.1%)	90 (37.7%)
Liver metastases				
Yes	38 (26.6%)	16 (33.3%)	84 (34.3%)	72 (30.1%)

N, number of patients; E/B, encorafenib/binimetinib; ICI, immune checkpoint inhibition; SD, standard deviation; min, minimum; max, maximum; MUP, melanoma of unknown primary; ECOG, Eastern Cooperative Oncology Group; LDH, Lactate dehydrogenase; AJCC, American Joint Committee on Cancer staging; 1L/2L/3L, first/second/third line.

Table 3: Grade 3/4 or clinically relevant side effects

Preferred Term, %	1L E/B post-adjuvant (N = 143)	2L or 3L E/B post-adjuvant + 1L ICI (N = 48)	1L E/B (N = 245)	2L or 3L E/B post 1L ICI (N = 239)	Other Sequences
Diarrhea	4.2 %	4.2 %	4.5 %	0.8 %	2.8 %
Nausea/Vomiting	1.4 %	6.3 %	1.6 %	2.9 %	4.5 %
Eye disorders	2.8 %	2.1 %	0.8 %	3.3 %	2.2 %
Arthralgia/Arthritis	3.5 %	2.1 %	1.2 %	0 %	2.2 %
Cutaneous/Rash	3.5 %	2.1 %	0.8 %	3.3 %	4.5 %
Increased CK/Myalgia	2.8 %	2.1 %	1.6 %	2.9 %	4.5 %
Hepatic disorders	7.7 %	0 %	2.0 %	2.9 %	6.7 %
Pyrexia	2.1 %	0 %	0.8 %	2.9 %	2.2 %
Rash	3.5 %	2.1 %	0.8 %	3.3 %	3.4 %
Gastrointestinal disorders	0.7 %	0 %	0.8 %	2.5 %	2.2 %
Renal disorders	4.9 %	2.1 %	1.2 %	0.8 %	1.1 %

N, number of patients; E/B, encorafenib/binimetinib; ICI, immune checkpoint inhibition; 1L/2L/3L, first/second/third line. The table contains Recorded event classes with CTCAE severity grades 3 or 4, or ADRs causing changs in treatment schedule, e.g. interruption, dose modification or treatment stop.

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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.