Clinical outcomes in patients with melanoma brain metastases: 1st line treatment options

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BACKGROUND

- Combination immunotherapy with ipilimumab and nivolumab (ipi/nivo) is the current standard of care in patients with asymptomatic melanoma brain metastases (MBM).
- However, optimal strategies for managing symptomatic MBM remain unclear and treatment with BRAF/MEK inhibitors (BRAF/MEKi) is still in common use for symptomatic $BRAF^{V600}$ mutated MBM.
- Triple combination (atezolizumab/vemurafenib/cobimetinib) did not substantially improve efficacy over targeted therapy alone.

OBJECTIVES

- Primary endpoints were overall survival (OS) and melanoma-specific survival (MSS) stratified by 1L treatment.
- Secondary endpoints included progression-free survival (PFS), response rates and stratified analyses for BRAF mutational status and various prognostic factors.

METHODS

- **Study population:** Patients with cutaneous melanoma and MBM who received first-line (1L) systemic treatment were retrieved from the **European Melanoma Registry (EUMelaReg)** database for this analysis. 12 countries contributed to this project.
- Symptomatic patients were defined as those requiring corticosteroids at the initiation of 1L treatment. Patients without corticosteroid documentation were classified as asymptomatic patients (**Figure 1**). Patients who received corticosteroids alongside with radiotherapy were not considered symptomatic.
- Demographics and clinical characteristics at 1L treatment as well as treatment outcome of the study population were analyzed.

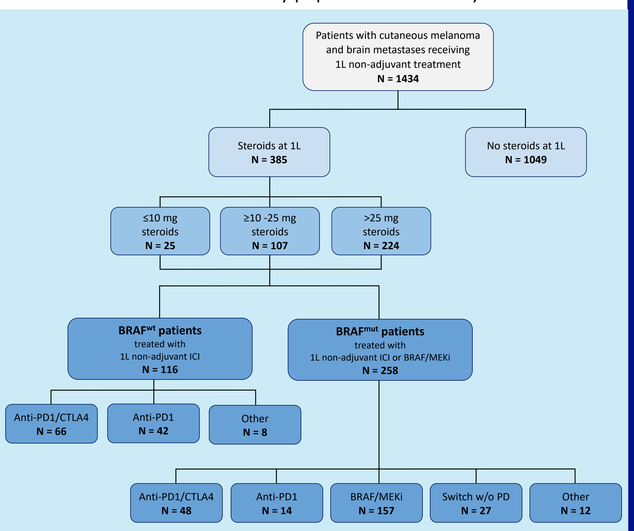

Figure 1. Flow chart illustrating the study population or this multicentre analysis using real-world data from the EUMelaReg. N, number of patients; MUP, melanoma of unknown primary; FU, follow-up; ICI, immune checkpoint inhibitor; wt, wildtyp; mut, mutated; 1L, first line. Other: treatments included mainly study medication, BRAF mono and chemotherapy.

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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.

- We identified a total of 1,434 patients with MBM, of whom 385 (26.8%) required corticosteroids at start of 1L therapy and were classified as symptomatic. 1,049 patients (73.2%) did not require steroids.
- Symptomatic patients had worse baseline prognostic factors, including higher ECOG score, high LDH, and greater intracranial tumor burden.

Table 1: Demographic and clinical characteristics by steroid use at 1L

	With Steroids at 1L (N = 385)	Without Steroids at 1L (N = 1,049)	Total (N = 1,434)
Sex			
Male	237 (61.6%)	659 (62.8%)	896 (62.5%)
Female	148 (38.5%)	390 (37.2%)	538 (37.5%)
Age (years)			
≥ 65 years	182 (47.3%)	497 (47.4%)	679 (47.4%)
> 65 years	203 (52.7%)	552 (52.6%)	755 (52.7%)
Adjuvant treatment			
Yes	55 (14.3%)	180 (17.2%)	235 (16.4%)
No	330 (85.7%)	869 (82.8%)	1199 (83.6%)
Type of adjuvant treatment			
ICI	26 (6.8%)	96 (9.2%)	122 (8.5%)
BRAF/MEKi	8 (2.1%)	22 (2.1%)	30 (2.1%)
Other	21 (5.5%)	62 (5.9%)	83 (5.8%)
BRAF mutation type			
Wild type	116 (30.1%)	362 (34.5%)	478 (33.3%)
Positive	258 (67.0%)	661 (63.0%)	919 (64.1%)
Unknown/Missing/Not tested	11 (2.8%)	26 (2.5%)	37 (2.6%)
ECOG			
0	152 (39.5%)	515 (49.1%)	667 (46.5%)
1	138 (35.8%)	341 (32.5%)	479 (33.4%)
≥2	86 (22.3%)	140 (13.4%)	226 (15.8%)
Missing/Unknown	9 (2.3%)	53 (5.1%)	62 (4.3%)
LDH			
Normal	162 (42.1%)	498 (47.5%)	660 (46.0%)
Elevated	194 (50.4%)	448 (42.7%)	642 (44.8%)
Missing	29 (7.5%)	103 (9.8%)	132 (9.2%)
Extracranial M status			
M0	93 (24.2%)	189 (18.0%)	282 (19.7%)
M1a	26 (6.8%)	99 (9.4%)	125 (8.7%)
M1b	80 (20.8%)	232 (22.1%)	312 (21.8%)
M1c	186 (48.3%)	529 (50.4%)	715 (49.9%)
Number of metastatic sites			
1-2	166 (43.1%)	408 (38.9%)	574 (40.0%)
≥ 3	219 (56.9%)	641 (61.1%)	860 (60.0%)
Number of brain metastases			
1	78 (20.3%)	319 (30.4%)	397 (27.7%)
2-5	98 (25.5%)	303 (28.9%)	401 (28.0%)
>5	155 (40.3%)	297 (28.3%)	452 (31.5%)
Largest diameter of brain metastases			
≤2 cm	109 (28.3%)	508 (48.4%)	617 (43.0%)
>2 cm	180 (46.8%)	262 (25.0%)	442 (30.8%)
Missing/Unknown	96 (24.9%)	279 (26.6%)	375 (26.2%)
Concomitant surgery to therapy start			
Yes	52 (13.5%)	96 (9.2%)	148 (10.3%)
No	333 (86.5%)	953 (90.9%)	1286 (89.7%)
Concomitant radiotherapy to therapy start			
Yes	116 (30.1%)	308 (29.4%)	424 (29.6%)
No	269 (69.9%)	741 (70.6%)	1010 (70.4%)

N, number of patients; ICI, immune checkpoint inhibition; ECOG, Eastern Cooperative Oncology Group; LDH, Lactate dehydrogenase; 1L, first line.

Figure 3: Kaplan-Meier curves of unadjusted OS for symptomatic (A) BRAF mutated and (B) BRAF wildtype patients stratified by 1L therapy. OS, overall survival; mut, mutated; wt, wildtype; w/o: without; PD, progressive disease; CI, confidence interval. Switch w/o PD: patients who switched from BRAF/MEKi to ICI without progression. Other treatments included mainly study medication, BRAF mono and chemotherapy.

- In patients with BRAF mutation and symptomatic MBM, 157 (61.1%) received 1L BRAF/MEKi with an ORR of 60.7%, while 48 (18.7%) received ipi/nivo with an ORR of 32.0%. Median PFS and OS were 5.3 months and 8.5 months with BRAF/MEKi versus 2.7 months and 15.0 months, with ipi/nivo (**Figure 3A**).
- Patients with BRAF wildtype and symptomatic MBM received mainly ipi/nivo (n=64; 54.7%) or anti-PD1 mono (n=40; 34.2%) in 1L. Median OS was longer with ipi/nivo compared to patients treated with anti-PD1 mono (8.1 months vs 4.2 months) (**Figure 3B**).

RESULTS

- Median PFS, OS, and MSS were significantly shorter in symptomatic patients (4.1 months, 9.4 months, and 9.7 months, respectively) compared to asymptomatic patients (6.3 months, 18.9 months, and 19.4 months, respectively) (**Figure 2, Table 2**).
- Median TOT (95% CI) was equal for both cohorts (**Table 2**).
- Stratification of symptomatic patients by steroid dose showed a trend towards better survival outcomes for patients treated with lower steroid doses (≤ 10 mg). Higher steroid doses (>25 mg) correlated with worse outcomes.

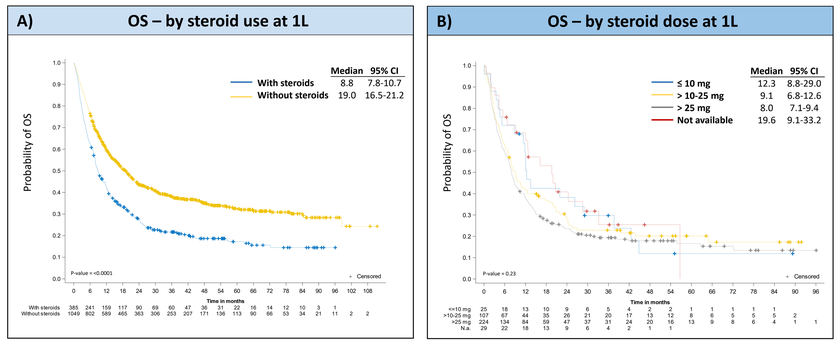

Figure 2: Kaplan-Meier curves of OS stratified by (A) steroid documentation or (B) steroid dose. OS, overall survival; 1L, first line; CI, confidence interval.

	By steroid use at 1L		By steroid dose at 1L		
	With steroids (N = 385)	Without steroids (N = 1,049)	≤ 10 mg (N = 25)	> 10-25 mg (N = 107)	> 25 mg (N = 224)
Best response					
CR	31 (8.1%)	123 (11.7%)	-	8 (7.5%)	21 (9.4%)
PR	138 (35.8%)	375 (35.8%)	12 (48.0%)	36 (33.6%)	81 (36.2%)
SD	58 (15.1%)	180 (17.2%)	4 (16.0%)	15 (14.0%)	32 (14.3%)
PD	131 (34.0%)	323 (30.8%)	7 (28.0%)	45 (42.1%)	75 (33.5%)
Not available	27 (7.0%)	48 (4.6%)	2 (8.0%)	3 (2.8%)	15 (6.7%)
ORR	169 (43.9%)	499 (47.6%)	12 (48.0%)	44 (41.1%)	102 (45.5%)
Intracranial response					
CR	36 (9.4%)	176 (16.8%)	1 (4.0%)	11 (10.3%)	22 (9.8%)
PR	98 (25.5%)	183 (17.5%)	5 (20.0%)	16 (15.0%)	72 (32.1%)
SD	54 (14.0%)	113 (10.8%)	5 (20.0%)	21 (19.6%)	26 (11.6%)
PD	101 (26.2%)	236 (22.5%)	3 (12.0%)	38 (35.5%)	58 (25.9%)
Not available	96 (24.9%)	341 (32.5%)	11 (44.0%)	21 (19.6%)	46 (20.5%)
ORR	134 (34.8%)	359 (34.2%)	6 (24.0%)	27 (25.2%)	94 (42.0%)
Survival (95% CI) months					
Median OS	8.8 (7.8-10.7)	19.0 (16.5-21.2)	12.3 (8.8-29.0)	9.1 (6.8-12.6)	8.0 (6.9-9.4)
Median PFS	4.1 (3.6-4.5)	6.3 (5.7-6.9)	5.4 (2.7-8.4)	3.7 (2.8-4.8)	4.0 (3.3-4.5)
Median TOT	3.7 (3.0-4.1)	4.4 (4.0-4.9)	5.8 (1.4-9.6)	3.6 (2.1-4.6)	3.6 (2.8-4.1)

Table 2: Therapy outcome by steroid documentation and steroid doses. N, Number of patients; CR, complete response; PR, partial remission; SD, stable disease; PD, progressive disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TOT, time on treatment; CI, confidence interval.

	Univariate		Multivariate		Multivariate Backward selection**	
	HR (95% CI)	P-Value	HR (95% CI)	P-Value	HR (95% CI)	P-Value
Age (ref: <65)						
≥65	1.4 (1.2-1.6)	0.0001	1.2 (1.0-1.4)	0.031	1.2 (1.0-1.4)	0.031
Gender (ref: male)						
Female	0.8 (0.7-1.0)	0.009	0.8 (0.6-0.9)	0.0009	0.8 (0.7-0.9)	0.001
ECOG (ref:0)						
1	2.0 (1.7-2.4)	<.0001	1.6 (1.3-1.9)	<.0001	1.6 (1.3-1.9)	<.0001
≥2	3.3 (2.7-4.1)	<.0001	2.3 (1.8-3.0)	<.0001	2.4 (1.9-3.0)	<.0001
LDH (ref: normal)						
Elevated	1.4 (1.2-1.6)	0.0001	1.1 (0.9-1.3)	0.346		
Prior adjuvant therapy (ref: no)						
Yes	0.9 (0.7-1.1)	0.266	1.4 (1.1-1.7)	0.006	1.4 (1.1-1.7)	0.006
Type of therapy (ref: anti- PD1/CTLA4)						
BRAFi/MEKi	3.1 (2.5-3.8)	<.0001	2.3 (1.8-2.9)	<.0001	2.3 (1.8-2.9)	<.0001
anti-PD1 mono	1.8 (1.3-2.4)	0.0001	1.9 (1.4-2.6)	<.0001	1.9 (1.4-2.6)	<.0001
Switch w/o PD	1.0 (0.6-1.7)	0.941	0.8 (0.5-1.3)	0.265	0.7 (0.4-1.2)	0.244
Other*	2.7 (1.9-3.8)	<.0001	2.7 (1.9-3.9)	<.0001	2.7 (1.9-3.9)	<.0001
Steroids (ref: no)						
Yes	1.6 (1.4-1.9)	<.0001	1.4 (1.2-1.7)	0.0003	1.4 (1.2-1.7)	0.0002
Extracranial M status (ref: M0)						
M1a	1.2 (0.8-1.6)	0.375	1.0 (0.7-1.4)	0.977	1.0 (0.7-1.4)	0.941
M1b	1.1 (0.9-1.4)	0.496	1.1 (0.9-1.5)	0.388	1.1 (0.9-1.5)	0.369
M1c	1.4 (1.1-1.7)	0.002	1.4 (1.1-1.7)	0.011	1.4 (1.1-1.7)	0.006
Number of brain metastasis (ref: 1)						
2-5	1.5 (1.2-1.9)	0.0003	1.6 (1.2-2.0)	0.0002	1.6 (1.2-2.0)	0.0002
>5	2.0 (1.6-2.4)	<.0001	1.8 (1.4-2.3)	<.0001	1.8 (1.4-2.3)	<.0001

In multivariate analysis, worse survival outcomes were independently associated with older age, female gender, poor ECOG performance status, prior adjuvant therapy, use of steroids, BRAF/MEKi and a higher number of brain metastases among BRAF mutant patients.

Table 3: Cox regression for OS to 1L of BRAF mutated patients. ECOG, Eastern Cooperative Oncology Group; LDH, Lactate dehydrogenase; w/o: without; PD, progressive disease; ref, reference; HR, hazard ratio; CI, confidence interval. *Other treatments included mainly study medication, BRAF mono and chemotherapy. **Treshold for backward selection was p<0.1.

SUMMARY AND CONCLUSION

- Symptomatic patients with MBM show markedly inferior survival. Despite lower ORR and shorter PFS, symptomatic patients treated with ipi/nivo had notably longer OS than those treated with BRAF/MEKi, supporting the use of 1L immunotherapy even in this high-risk group.
- Due to the small size of the switch w/o PD group and the design of the study, no unbiased conclusions can be drawn about this strategy as 1L option in symptomatic BRAF mutant patients, and prospective trials are needed.