Effectiveness of Dabrafenib plus Trametinib as second-line therapy in comparison to first line in BRAF^{V600} mutated metastatic melanoma patients. A EUMelaReg real-world study

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BACKGROUND

- Treatment with Dabrafenib plus Trametinib (Dabra/Tram) in metastatic melanoma is a well-established treatment option, however its role in second-line (2L) after failure of immune checkpoint inhibitors (ICI) is less well defined.
- Real-world analyses are important to better characterize outcomes in routine clinical practice and to inform on sequencing strategies.
- Our study aimed to evaluate the effectiveness of Dabra/Tram in 2L in a large European real-world population.

OBJECTIVES

- Primary objective was overall survival (OS) from start of 2L Dabra/Tram therapy.
- Secondary objective included OS, progression-free survival (PFS), overall response rate (ORR), and time on treatment (TOT) for 2L compared to first line (1L) Dabra/Tram therapy.

METHODS

- **Study population:** We retrieved BRAF^{V600} mutated patients with non-resectable stage III or metastatic stage IV cutaneous melanoma from the **European Melanoma Registry (EUMelaReg)** database for this analysis.
- Patients who received Dabra/Tram as 2L therapy following progression on 1L ICI were identified and compared with a propensity score-based matched cohort of patients treated with Dabra/Tram in 1L setting. Matching was performed for sex, age, ECOG, baseline serum LDH, Charlson comorbidity score, AJCC stage, and number of metastatic sites to balance baseline prognostic factors.
- Patients pre-treated with adjuvant ICI or Dabra/Tram were excluded.

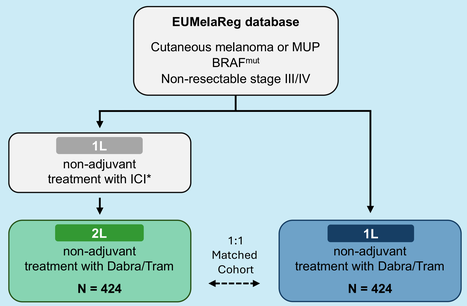


Figure 1: Flow chart illustrating the selected populations for analysis using real-world data from EUMelaReg. MUP: melanoma of unknown primary; mut: mutated; ICI: immune checkpoint inhibitor therapy; Dabra/Tram: Dabrafenib/Trametinib; 1L/2L: first/second line. *ICI treatment includes anti-PD1 and/or anti-PD1/anti-CTLA4 antibodies.

RESULTS

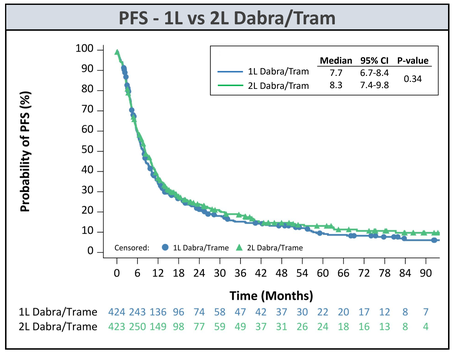
- The matching strategy resulted in well-balanced baseline and clinical characteristics between the two cohorts, with no statistically significant differences observed (**Table 1**).
- Following the matching procedure, we identified 424 patients who received Dabra/Tram in 1L (1L Dabra/Tram cohort), and 424 in 2L (2L Dabra/Tram cohort) after ICI failure.
- Overall, approximately one-third of patients were aged ≥70 years, 53.0% had an ECOG PS of ≥1, and 49.5% had elevated LDH levels.
- 76.6% of patients were diagnosed with stage IV M1c/M1d representing the largest subgroup. Similarly, around 60% of patients in each group had three or more metastatic sites.
- At start of Dabra/Tram treatment, the majority of patients (63.8%) showed no presence of brain metastases.

Table 1: Patient characteristics for 1L and 2L Dabra/Tram cohort

	2L Dabra/Tram N = 424	1L Dabra/Tram N = 424	P-value	Total N = 848
Sex			0.68	
Male	239 (56.4%)	232 (54.7%)		471 (55.5%)
Female	185 (43.6%)	192 (45.3%)		377 (44.5%)
Age			0.57	
< 70 years	268 (63.2%)	277 (65.3%)		545 (64.3%)
≥ 70 years	156 (36.8%)	147 (34.7%)		303 (35.7%)
ECOG			0.98	
0	173 (40.8%)	167 (39.4%)		340 (40.0%)
1	132 (31.1%)	135 (31.8%)		267 (31.5%)
≥ 2	90 (21.2%)	92 (21.7%)		182 (21.5%)
Missing/Unknown	29 (6.9%)	30 (7.1%)		59 (7.0%)
LDH			0.77	
Normal	170 (40.1%)	165 (38.9%)		335 (39.5%)
Elevated	205 (48.3%)	215 (50.7%)		420 (49.5%)
Missing	49 (11.6%)	44 (10.4%)		93 (11.0%)
CCI score			0.75	
≤ 2	197 (46.5%)	213 (50.3%)		410 (48.3%)
3 - 4	127 (29.9%)	117 (27.6%)		244 (28.8%)
≥ 5	51 (12.0%)	48 (11.3%)		99 (11.7%)
Missing/Unknown	49 (11.6%)	46 (10.8%)		95 (11.2%)
AJCC stage			0.79	
Stage III - NR	11 (2.6%)	9 (2.1%)		20 (2.4%)
Stage IV - M1a	43 (10.1%)	52 (12.3%)		95 (11.2%)
Stage IV - M1b	41 (9.7%)	42 (9.9%)		83 (9.8%)
Stage IV - M1c	169 (39.9%)	174 (41.0%)		343 (40.4%)
Stage IV - M1d	160 (37.7%)	147 (34.7%)		307 (36.2%)
No. of metastatic sites			0.84	
1	80 (18.8%)	83 (19.6%)		163 (19.3%)
2	91 (21.5%)	84 (19.8%)		175 (20.6%)
≥ 3	253 (59.7%)	257 (60.6%)		510 (60.1%)
Brain metastases			0.39	
Yes	160 (37.7%)	147 (34.7%)		307 (36.2%)
No	264 (62.3%)	277 (65.3%)		541 (63.8%)

N, number of patients; Dabra/Tram, Dabrafenib/Trametinib; MUP, Melanoma of unknown primary; ECOG, Eastern Cooperative Oncology Group; LDH, Lactate dehydrogenase; CCI, Charlson comorbidity index; AJCC, American Joint Committee on Cancer staging version 8; NR, non-resectable; No, number; 1L/2L, first/second line.

- Survival outcomes were comparable and did not differ significantly between treatment lines.
- Adjusted Kaplan-Meier estimates show a median PFS of 7.7 months vs 8.3 months (p=0.34) and median OS of 16.7 months vs 15.8 months (p=0.42) in the 1L and 2L cohort, respectively (**Figure 2**).
- Similarly, ORR was consistent across both groups (56.6% vs 58.3%; p=0.68), respectively (**Table 2**).



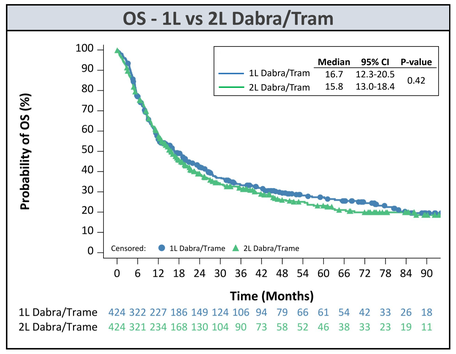


Figure 2: Kaplan-Meier curves of PFS (left) and OS (right) for patients treated with 2L (green line) or 1L Dabra/Tram (blue line). PFS, progression-free survival; OS, overall survival; 1L/2L, first/second line; CI, confidence interval.

	2L Dabra/Tram N = 424	1L Dabra/Tram N = 424	P-value
Best response			0.83
CR	50 (11.8%)	57 (13.4%)	
PR	197 (46.5%)	183 (43.2%)	
SD	76 (17.9%)	74 (17.5%)	
PD	73 (17.2%)	85 (20.0%)	
N.a./Unknown/Missing	28 (6.6%)	25 (5.9%)	
ORR	247 (58.3%)	240 (56.6%)	0.68
DCR	323 (76.2%)	314 (74.1%)	0.53
Survival (95% CI), month			
Median PFS	8.3 (7.4-9.8)	7.7 (6.7-8.4)	0.34
Median OS	15.8 (13.0-18.4)	16.7 (12.3-20.5)	0.42
Median TOT	7.0 (5.5-8.3)	6.4 (5.6-7.4)	0.15

Table 2: Therapy outcome of 2L and 1L Dabra/Tram therapy. N, Number of patients; CR, complete response; PR, partial remission; SD, stable disease; PD, progressive disease; N.a.; not accessible; DCR, disease control rate; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TOT, time on treatment; CI, confidence interval.

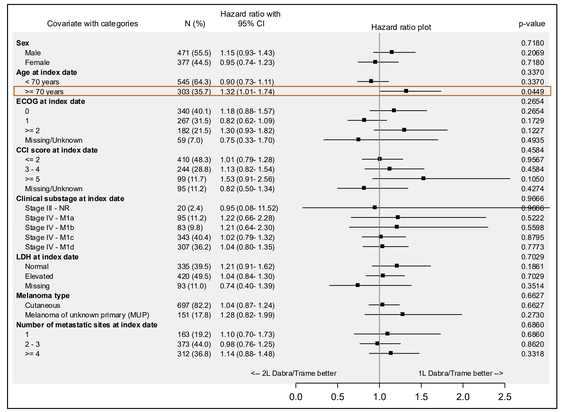
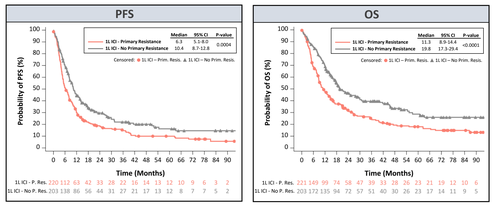


Figure 3: Hazard ratios for OS for patients treated with 1L or 2L Dabra/Tram. HRs and 95% CI from a multivariate cox regression model are reported for various subpopulations in patients treated with 2L in comparison to 1L Dabra/Tram. Stratified analyses in each category are adjusted for all other variables in the model. N: number of patients, ECOG, Eastern Cooperative Oncology Group; CCI, Charlson comorbidity index; NR, non-resectable; LDH, lactate dehydrogenase.

- Subgroup analysis of OS using multivariate Cox regression model showed consistent treatment effects across subgroups.
- However, elderly patients (aged ≥70 years) appeared to benefit less from 2L Dabra/Tram following ICI failure.

- An exploratory stratified analysis evaluated the treatment outcome of 2L Dabra/Tram in patients with primary resistance to 1L ICI (defined as progressive disease in first restaging) versus those without primary resistance.
- Patients with primary resistance to 1L ICI had significantly shorter median OS (11.3 vs 19.8 months; p<0.0001) and PFS (6.3 vs 10.4 months; p=0.0004) following 2L Dabra/Tram compared with patients without primary resistance.



	1L ICI – Primary Resistance N = 221	1L ICI – No Primary Resistance N = 203	P-value
Best response of 2L D/T			0.05
CR	19 (8.6%)	31 (15.3%)	
PR	101 (45.7%)	96 (47.3%)	
SD	36 (16.3%)	40 (19.7%)	
PD	47 (21.2%)	26 (12.8%)	
N.a./Unknown/Missing	18 (8.2%)	10 (4.9%)	
ORR	120 (54.3%)	127 (62.6%)	0.09
DCR	156 (70.6%)	167 (82.3%)	**0.006**
Survival (95% CI; months) from 2L			
Median OS	11.3 (8.9-14.4)	19.8 (17.3-29.4)	**<0.0001**
Median PFS	6.3 (5.1-8.0)	10.4 (8.7-12.8)	**0.0004**
Median TOT	5.5 (4.7-7.4)	8.9 (6.6-10.4)	**0.02**

Figure 4: Subgroup analysis of PFS (left) and OS (right) according to best overall response to 1L ICI therapy in patients with primary resistance (salmon line) vs no primary resistance (grey line). PFS, progression-free survival; OS, overall survival; 1L, first line; ICI, immune checkpoint inhibitors; CI, confidence interval.

Table 3: Outcome of 2L Dabra/Tram stratified by 1L ICI Primary Resistance. N, Number of patients; D/T, Dabrafenib/Trametinib; CR, complete response; PR, partial remission; SD, stable disease; PD, progressive disease; N.a.; not accessible; ORR, overall response rate; DCR, disease control rate; OS, overall survival; PFS, progression-free survival; TOT, time on treatment; 1/2L, first/second line; CI, confidence interval.

SUMMARY AND CONCLUSION

- Our results show that failure of 1L ICI did not adversely affect the effectiveness of subsequent Dabra/Tram therapy in BRAF^{V600} mutated melanoma.
- These findings indicate preserved clinical activity and survival outcomes of Dabra/Tram when used in 2L, supporting its robustness and sequencing flexibility in routine clinical practice.

ACKNOWLEDGEMENTS AND FUNDING

***EUMelaReg Study Group:** **Bosnia and Herzegovina:** Amina Jalovcic Suljevic (Sarajevo); Inga Marijanović (Mostar); Alma Mekic-Abazovic (Zenica). **Bulgaria:** Dimitar Kalev (Varna); Teodora Sotirova Karanikolova (Sofia); Ivan Kazmukov (Burgas); Ahmed Fehimov Kontliev (Sofia); Nevena Nedelcheva (Burgas); Gergana Shalamanova-Deleva (Plovdiv); Aynura Syuleymanova Changalova (Panagyurishte). **Croatia:** Davorin Hercog (Zagreb); Luka Perić (Osijek); Mirna Situm (Zagreb). **Germany:** Ines Bertsch (Heidelberg); Susanne Buder (Berlin-Neukölln); Dirk Debus (Nürnberg); Vasileios Dervenis (Bochum); Nina Devereux (Hamburg-Tabea); Edgar Dippel (Ludwigshafen); Pia Dücker (Dortmund); Jörg Fischer (Augsburg); Julia Friedrich (Berlin-Friedrichshain); Christoffer Gebhardt (Hamburg); Anja Geserich (Würzburg); Ralf Gutzmer (Minden); Axel Hauschild (Kiel); Markus Heppt (Erlangen); Florian Jothe (Quedlinburg); Iris Kamphausen (Duisburg); Alexander Kreuter (Oberhausen); Ulrike Leiter (Tübingen); Kerstin Lommel (Berlin-Buch); Friedegund Meier (Dresden); Mark Meinhold (Bayreuth); Miriam Mengoni (Lübeck); Claudia Pföhler (Homburg/Saar); Michael Sachse (Bremerhaven); Sabine Sell (Gera); Jan Christoph Simon (Leipzig); Henner Stege (Mainz); Gaston Schley (Schwerin); Jochen Utikal (Mannheim); Imke von Wasielewski (Hannover); Carsten Weishaupt (Münster); Fabian Ziller (Chemnitz); Markus Zutt (Bremen). **Greece:** Dimitrios Bafaloukos (Athens). **Israel:** Shaked Levi-Ari (Ramat Gan). **Italy:** Federica De Galitiis (Rome); Alessandro Miniussi (Udine); Luisa Piccin (Padova); Francesco Spagnolo (Genova). **Serbia:** Lidija Kandolf (Belgrade); Jovica Glisic (Kragujevac); Kristina Juskic (Belgrade); Aleksander Popovic (Nis). **Spain:** Enrique Espinosa (Madrid). **Switzerland:** Berna Özdemir (Bern).

COI of the presenting author: P. M. reports consulting/advisory roles: BMS, MSD, Novartis, Pierre Fabre, Sanofi, Sun Pharma; speaker's bureau: Novartis, Roche, BMS, MSD, Sanofi, Sun Pharma, Pierre Fabre; honoraria: BMS, MSD, Novartis, Pierre Fabre, Sanofi, Sun Pharma Advanced Research Company; travel/accommodations/expenses: BMS, MSD, Novartis, Pierre Fabre, Sun Pharma. Research funding: institutional funding from BMS, MSD, Novartis Deutschland Ltd.

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Funding: The study was supported by Novartis AG, Basel, Switzerland.

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.