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EUROPEAN MELANOMA REGISTRY

EU MELA REG

Outcome of PD-1 Inhibitor Therapy of Advanced Melanoma Patients according to Demographic Factors in a Real-World Setting across Europe

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Background and Study objectives

Anti-PD-1 checkpoint inhibitors have shown significant efficacy and durable benefit in clinical trials in metastatic melanoma. They reduce risk of disease progression and death compared to former standard-of-care chemotherapy or CTLA-4 inhibition in both treatment-naive and pretreated patients. We evaluated the anti-PD1 treatment outcome, stratified by BRAF status and line of treatment in cases from the EUMelaReg treatment registry to investigate the translation of clinical trial results into real-world practice.

Methods

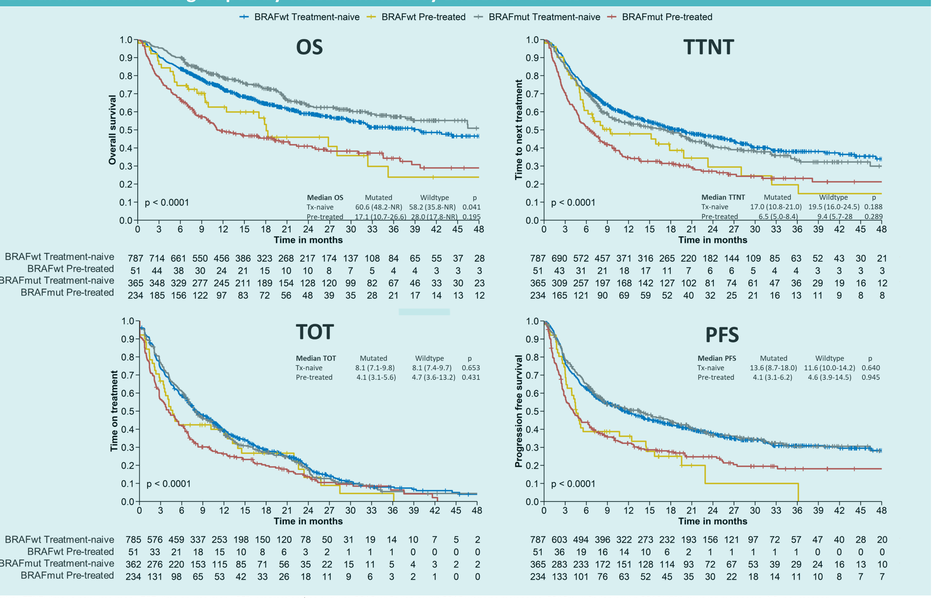
From the EUMelaReg treatment registry, 1,502 patients fulfilling the following inclusion criteria were collected as evaluable cases. 1) Patients with unresectable or metastatic melanoma (first diagnosis after Jan 1st 2016) 2) Application of at least one dose of PD1-monotherapy in the non-adjuvant setting.

Multivariable cox regression analysis as well as multiple imputation were applied to control for bias from baseline imbalances.

Table 3: Clinical outcome

	Treatment-naive (N = 1,210)			Pre-treated (N = 292)			
	Mutated (N = 365)	Wildtype (N = 787)	P-value	Mutated (N = 234)	Wildtype (N = 51)	P-value	Total* (N = 1,502)
ORR							
Overall response	159 (43.6%)	347 (44.1%)	0.84	74 (31.6%)	15 (29.4%)	0.86	621 (41.3%)
Missing	23 (6.3%)	54 (6.9%)		30 (12.8%)	7 (13.7%)		127 (8.5%)
DCR							
Disease control	240 (65.8%)	520 (66.1%)	0.83	118 (50.4%)	29 (56.9%)	0.40	941 (62.6%)
Missing	23 (6.3%)	54 (6.9%)		30 (12.8%)	7 (13.7%)		127 (8.5%)
Survival							
Median OS (95% CI)	60.6 (48.2-NA)	58.2 (35.8-NA)	0.041	17.1 (10.7-26.6)	28 (17.8-NA)	0.195	44.2 (35.6-NA)
Median TTNT (95% CI)	17 (10.8-21)	19.5 (16-24.5)	0.188	6.5 (5-8.4)	9.4 (5.7-28)	0.289	14.9 (12.3-17.3)
Median ToT (95% CI)	8.1 (7.1-9.8)	8.1 (7.4-9.7)	0.653	4.1 (3.1-5.6)	4.7 (3.6-13.2)	0.431	7.3 (6.9-7.8)
Median PFS (95% CI)	13.6 (8.7-18)	11.6 (10-14.2)	0.64	4.1 (3.1-6.2)	4.6 (3.9-14.5)	0.945	10 (8.4-11.4)
OS-Landmarks							
24-months survival	63.4% (58.1%-69.3%)	59% (55.2%-63.1%)		40.9% (34.6%-48.5%)	46% (32.3%-65.5%)		56.5% (53.8%-59.5%)

Figure 1: Survival outcomes grouped by Treatment history and BRAF status



OS: overall survival. TTNT: time to next treatment. TOT: time on treatment. PFS: progression free survival. BRAFwt: Patients with BRAF wildtype melanoma. BRAFmut: Patients with BRAF V600 mutated melanoma. NR: not reached.

Results

In total 1,210 (79.6%) of the patients received anti-PD1 (Pembrolizumab or Nivolumab) monotherapy as 1st line treatment (treatment-naïve) and 292 (20.4%) as ≥2nd line treatment (pre-treated). In the treatment-naïve subgroup the majority of patients had BRAF wildtype melanoma (65.0%), whereas 80.1% of tumors in the pre-treated group were BRAF mutated. For various co-variates there were significant imbalances between strata, including age, comorbidity index and clinical stage, with more favorable prognostic variables for Treatment-naïve patients especially in the BRAF mutated subpopulation. We found that median OS, TTNT, TOT, and PFS were longer in treatment-naïve patients than in pre-treated patients regardless of BRAF status.

In the stratified analysis only OS was significantly altered between BRAF mutated and Wildtype patients [median OS: 60.6 (48.2-NR) mths. vs. 58.2 (35.8-NR) mths. in the treatment-naïve subgroup, however in the adjusted Cox regression, there was no difference. ORR and DCR did not differ between BRAF mutated and Wildtype patients neither in treatment-naïve nor pre-treated patients.

Table 1: Baseline patient characteristics

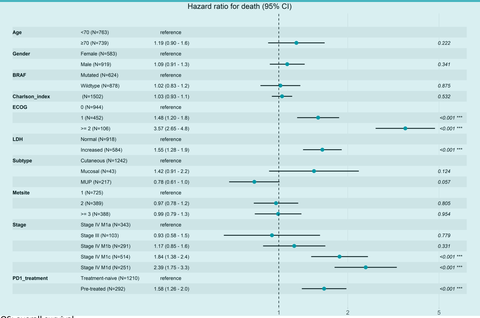
	Treatment-naive (N = 1,210)		Pre-treated (N = 292)		
	Mutated (N=365)	Wildtype (N=787)	Mutated (N=234)	Wildtype (N=51)	Overall* (N=1,502)
Age (years)					
Mean (SD)	63.7 (14.7)	70.5 (12.0)	60.9 (13.2)	63.5 (12.4)	67.1 (13.5)
Median [Min, Max]	65.0 [20.0, 93.0]	73.0 [26.0, 94.0]	62.0 [24.0, 88.0]	66.0 [30.0, 82.0]	69.0 [20.0, 94.0]
Gender					
Female	146 (40.0%)	286 (36.3%)	100 (42.7%)	25 (49.0%)	583 (38.8%)
Male	219 (60.0%)	501 (63.7%)	134 (57.3%)	26 (51.0%)	919 (61.2%)
Charlson comorbidity score					
Mean (SD)	2.15 (1.50)	2.74 (1.34)	1.87 (1.38)	2.33 (1.42)	2.44 (1.43)
Median [Min, Max]	2.00 [0, 7.00]	3.00 [0, 8.00]	2.00 [0, 7.00]	2.00 [0, 6.00]	3.00 [0, 8.00]
ECOG					
0	220 (60.3%)	385 (48.9%)	107 (45.7%)	29 (56.9%)	764 (50.9%)
1	67 (18.4%)	192 (24.4%)	70 (29.9%)	11 (21.6%)	347 (23.1%)
≥ 2	12 (3.3%)	40 (5.1%)	23 (9.8%)	2 (3.9%)	81 (5.4%)
Unknown	63.7 (14.7)	70.5 (12.0)	60.9 (13.2)	63.5 (12.4)	67.1 (13.5)

Table 2: Baseline tumor characteristics

	Treatment-naive (N = 1,210)		Pre-treated (N = 292)		
	Mutated (N=365)	Wildtype (N=787)	Mutated (N=234)	Wildtype (N=51)	Overall* (N=1,502)
LDH					
Normal	188 (51.5%)	385 (48.9%)	93 (39.7%)	20 (39.2%)	705 (46.9%)
Increased	98 (26.8%)	235 (29.9%)	88 (37.6%)	17 (33.3%)	451 (30.0%)
Unknown	79 (21.6%)	167 (21.2%)	53 (22.6%)	14 (27.5%)	346 (23.0%)
AJCC Stage					
Stage III	24 (6.6%)	54 (6.9%)	9 (3.8%)	6 (11.8%)	103 (6.9%)
Stage IV M1a	107 (29.3%)	181 (23.0%)	36 (15.4%)	10 (19.6%)	343 (22.8%)
Stage IV M1b	75 (20.5%)	171 (21.7%)	21 (9.0%)	6 (11.8%)	291 (19.4%)
Stage IV M1c	114 (31.2%)	282 (35.8%)	86 (36.8%)	17 (33.3%)	514 (34.2%)
Stage IV M1d	45 (12.3%)	99 (12.6%)	82 (35.0%)	12 (23.5%)	251 (16.7%)
Number of metastatic sites					
1	191 (52.3%)	369 (46.9%)	102 (43.6%)	24 (47.1%)	725 (48.3%)
2	98 (26.8%)	210 (26.7%)	54 (23.1%)	14 (27.5%)	389 (25.9%)
≥ 3	76 (20.8%)	208 (26.4%)	78 (33.3%)	13 (25.5%)	388 (25.8%)
Type of melanoma					
Cutaneous	316 (86.6%)	626 (79.5%)	200 (85.5%)	40 (78.4%)	1,242 (82.7%)
Mucosal	0 (0%)	38 (4.8%)	1 (0.4%)	3 (5.9%)	43 (2.9%)
MUP	49 (13.4%)	123 (15.6%)	33 (14.1%)	8 (15.7%)	217 (14.4%)

*This column contains 65 patients with unknown BRAF status. AJCC: American Joint Committee on Cancer. ECOG: Eastern Cooperative Oncology Group. LDH: lactate dehydrogenase. MUP: melanoma of unknown primary. Treatment-naïve: Patients who received non-adjuvant anti-PD1 treatment as 1st line therapy. Pre-treated: Patients who received non-adjuvant therapy prior to anti-PD1 application

Figure 2: Multivariable cox regression for OS



OS: overall survival.

Additional information

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Conclusions

PD-1 monotherapy after prior non-adjuvant treatment performed worse than application as 1st line treatment, especially pronounced in patients with BRAF mutated melanoma. This can be partly attributed to baseline imbalances with an unfavorable prognosis in this subgroup. However, after adjustment for confounding variables PD-1 as 1st line treatment was still superior. Additionally, BRAF mutated patients treated with PD-1 inhibitors as 1st line treatment showed favorable prognosis likely due to a viable option as 2nd line treatment. Due to the nature of real-world observational data causing inherent imbalances in the treatments cohorts and being unable to account for potential unknown confounders, outcome parameters may still be biased despite adjustment efforts.