ELSEVIER

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ISSN 0923-7534
Volume 33 Supplement 7 September 2022

ANNALS OF ONCOLOGY

driving innovation in oncology

JSMO Japanese Society of Medical Oncology

Abstract Book of the ESMO Congress 2022
9 - 13 September 2022
Guest Editors: ESMO Congress 2022 Scientific Committee

Financial Interests, Personal, Funding: BMS, MSD; Financial Interests, Personal, Advisory Role: BMs, MSD. P. Rutkowski: Financial Interests, Personal, Invited Speaker, honoraria for lectures: MSD, BMS, Pierre Fabre; Financial Interests, Personal, Advisory Board: MSD, BMS, Pierre Fabre, Merck, Sanofi, Blueprint Medicines, Philogen; Financial Interests, Personal, Invited Speaker: Merck, Sanofi, Novartis; Financial Interests, Institutional, Research Grant, research grant for ISS: Pfzer; Financial Interests, Institutional, Funding, research grant for institution: BMS; Non-Financial Interests, Invited Speaker: Polish Society of Surgical Oncology; Non-Financial Interests, Officer: ASCO; Non-Financial Interests, Invited Speaker, President Elect: Polish Oncological Society. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2022.07.961

836P 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: Treatment with programmed cell death protein (PD-1) blocking antibodies substantially improves prognosis of melanoma patients. However, there is still limited evidence how baseline demographics influence treatment efficacy in real world practice.

Methods: This registry-based observational study evaluated the therapy outcome of 1046 melanoma patients who were treated with single agent PD-1 inhibitors in the advanced setting. Demographic and baseline variables were analysed in respect to differences in overall survival (OS), time to next treatment after PD-1 inhibitor treatment (TTNT) and other outcome variables.

Results: For melanoma-specific OS, many factors were not significantly relevant. However, among the statistically significant factors (age, ECOG, LDH, line of treatment and AJCC stages M1c and M1d) the age effect was of particular interest. When grouping patients into three age groups (<70/70-80/>80) there was a higher risk of melanoma related death for patients aged 70-80 years (multivariable HR (95% CI): 1.51 (1.02-2.2)) and patients older than 80 years (multivariable HR 1.78; 95% CI 1.04-3.0). Median melanoma specific OS was not reached for patients younger than 70 years, 33.6 (31.7—nr) months for patients between 70 and 80 years, and 30.3 (20.4—nr) for patients older than 80 years. For TTNT a significant effect of age could not be observed. Objective response rate (ORR) was slightly elevated in the age group 70-80 years (47%; $p = 0.04$) as compared to younger patients (39.6%) and patients older than 80 years (39.7%). Also, median PFS (95% CI) was 9.9 (7.6-14.1) months for patients younger than 70 years, 12.9 (8.6-18.4) months for patients between 70 and 80 years and 9.3 (6.9-12.3) for patients older than 80 years.

Conclusions: The different survival outcomes showed less benefit of PD-1 inhibitor therapy in patients older than 80 years compared to younger patients. The most likely explanation could be a generally reduced immunoreactivity with increasing age. However, ORR and PFS were slightly higher in the age group of 70-80 years as compared to younger patients. These results suggest a complex relationship between age and response to immune checkpoint inhibition.

Legal entity responsible for the study: EUMelaReg gGmbH, Berlin, Germany.

Funding: Novartis AG; Merck & Co., Inc.; Bristol Myers Squibb.

Disclosure: M. Weichenthal: Financial Interests, Personal, Advisory Board: MSD, BMS, Roche, Novartis, Sanofi. I. Svane: Financial Interests, Personal, Advisory Board: BMS, Pierre Fabre, Novartis; Financial Interests, Personal, Invited Speaker: MSD, Pierre Fabre, Novartis, Roche, BMS, MSD; Financial Interests, Personal, Stocks/Shares, Cofounder and Founder warrents: IO Biotech; Financial Interests, Institutional, Research Grant: Adaptimmune, Enara Bio, Lytix Biopharma, TILT Biotherapeutics; Financial Interests, Institutional, Funding: Evaxion; Non-Financial Interests, Principal Investigator: BMS, Roche, TILT Biotherapeutics, Lytix Biopharma, Novartis. L. Kandolf Sekulovic: Non-Financial Interests, Personal, Invited Speaker: MSD; Financial Interests, Personal, Invited Speaker: Novartis, Roche, BMS, AbbVie. J. Mangana: Financial Interests, Personal, Advisory Board: Merck-Pfizer, Merck Sharp & Dohme, Novartis, Roche, Amgen, Bristol Myers and Squibb, L'oreal, Pierre Fabre; Financial Interests, Personal, Other, Travel grant: Ultrasun, L'oreal, Merck Sharp & Dohme, Bristol Myers and Squibb, Pierre Fabre; Financial Interests, Institutional, Research Grant, The melanoma registry database of the Department of Dermatology has been partially supported by an unrestricted grant to the University of Zurich from Amgen, Novartis, BMS, MSD and Pierre Fabre: Novartis, BMS, Pierre Fabre, Amgen, MSD. I. Lugowska: Financial Interests, Personal, Invited Speaker, The reports of clinical trials: ROCHE, BMS, Macrogenics, Amgen; Financial Interests, Institutional, Other, Research grants: ROCHE; Financial Interests, Institutional, Other, Research grant: Agenus; Financial Interests, Personal and Institutional, Invited Speaker: Agenus, Roche, BMS, Janssen, Astra, Incyte, Macrogenics, Checkpoint Inhibitors, Celon, Pfizer, MSD, Debio; Non-Financial Interests, Project Lead: MSCI; Non-Financial Interests, Advisory Role, Board Member: EORTC. P. Mohr: Financial Interests, Personal, Invited Speaker: BMS, Merck Sharpe & Dohme, Roche, Novartis, Pierre Fabre, Sanofi, Beiersdorf, Amgen; Financial Interests, Personal, Advisory Board: BMS, Merck Sharpe & Dohme, Roche, Amgen, Sanofi, Pierre Fabre; Financial Interests, Institutional, Research Grant: Merck, BMS, Novartis. E. 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R. Dummer: Financial Interests, Personal, Other, Consulting and/or advisory role: Novartis, Merck Sharp & Dohme (MSD), Bristol Myers Squibb (BMS), Roche, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi, Catalym, Second Genome, Regeneron, Alligator, MaviVAX SA, touchIME, T3 Pharma, Pfizer. D. Schadendorf: Financial Interests, Personal, Invited Speaker: BMS, Novartis, MSD, Roche, Merck Serono, Sanofi, Merck, Novartis, BMS, MSD, 4SC, Nektar; Financial Interests, Personal, Advisory Board: BMS, Novartis, MSD, Roche, Merck Serono, Immunocore, 4SC, Pierre Fabre, Sanofi/Regeneron, Array Biopharma, Pfizer, Philogen, NEKTAR, Sandoz, Neracare; Financial Interests, Institutional, Research Grant: Novartis, BMS, MSD, Array/Pfizer; Financial Interests, Institutional, Invited Speaker: Novartis, BMS, MSD, Pierre Fabre, Sanofi, Roche, Philogen, 4SC, Nektar; Non-Financial Interests, Invited Speaker: EORTC-MG. L. Bastholt: Financial Interests, Institutional, Funding: MSD. All other authors have declared no conflicts of interest.

https://doi.org/10.1016/j.annonc.2022.07.962

FPN: 836P

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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%)

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

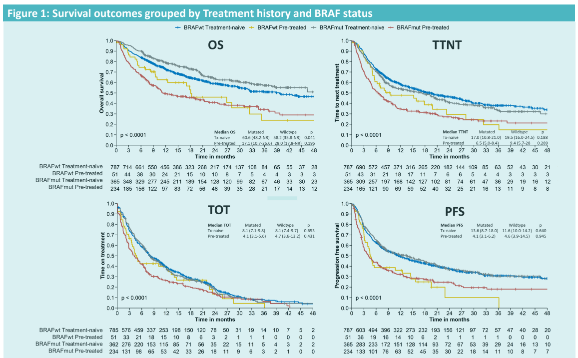
	Treatment-naive (N = 1,210)		Pre-treated (N = 292)		
	Mutated (N=365)	Wildtype (N=787)	Mutated (N=234)	Wildtype (N=51)	Overall* (N=1,502)
LDH					
Normal	188 (51.5%)	385 (48.9%)	93 (39.7%)	20 (39.2%)	705 (46.9%)
Increased	98 (26.8%)	235 (29.9%)	88 (37.6%)	17 (33.3%)	451 (30.0%)
Unknown	79 (21.6%)	167 (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

Conclusions

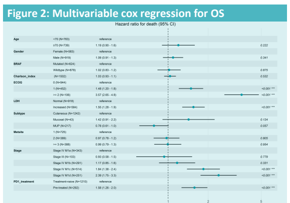
PD-1 monotherapy after prior non-adjuvant treatment performed worse than application as 1st line treatment, especially pronounced in patients with BRAF mutated melanoma. This can be partly attributed to baseline imbalances with an unfavorable prognosis in this subgroup. However, after adjustment for 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.

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.

Figure 2: Multivariable cox regression for OS



OS: overall survival.

Additional information

COI of the presenting author:

M.W. reports honoraria from BMS, MSD, Novartis, Takeda and Kyowa Kirin, advisory roles for Roche, Takeda,, BMS, and Novartis, Takeda, grants or funds from BMS, Millennium, Roche, Novartis, Takeda, and conference travel support from Amgen, MSD, BMS, Pierre Fabre, Novartis, and Beyersdorf.

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