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Original research

Sex-specific survival in advanced metastatic melanoma – a DeCOG study on 2032 patients of the multicenter prospective skin cancer registry ADOREG

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ABSTRACT

Background: Females and males differ in their innate and acquired immune responses. Thus, it is hypothesized that the efficacy of anti-tumor immunotherapies may differ by sex. This study aimed to investigate sex-specific survival differences upon different therapy types in metastatic melanoma.
Patients and Methods: Patients with unresectable metastatic melanoma (stage IV, AJCCv8) of the skin or unknown primary, who had received first-line PD-1-based immune checkpoint inhibition (ICI) or BRAF/MEK-directed targeted therapy (TT) were identified from the prospective multicenter DeCOG skin cancer registry ADOREG. Study endpoints were progression-free survival (PFS) and overall survival (OS).
Results: A total of 2032 patients, 1274 males (62.7 %) and 758 females (37.3 %), received ICI (n = 1484) or TT (n = 548) between May 2010 and December 2020. At median follow-up of 28.6 months, no significant sex-specific differences in survival could be detected, neither in the total cohort nor by treatment type: PFS (total, p = 0.86; ICI, p = 0.46; TT, p = 0.21), OS (total, p = 0.60; ICI, p = 0.20; TT, p = 0.30). Multivariable Cox regression analyses also did not show a relevant prognostic influence by sex. Subgroup analyses were performed according to ICI therapy type. In n = 872 patients treated with PD-1 monotherapy, a survival advantage (PFS, p = 0.041; OS, p = 0.07) could be detected for males by univariable and multivariable analyses, whereas no sex-specific survival differences were found for n = 456 patients who received combination immunotherapy.
Conclusion: No overall sex-specific survival differences were detected for metastatic melanoma patients in the first-line therapy setting. According to subgroup analyses males show a trend towards a survival advantage over females.

1. Introduction

Melanoma is one of the most lethal types of skin cancer and shows early lymphogenic and hematogenic metastatic spread [1]. Although the introduction of modern therapeutic strategies, mainly PD-1-based immune checkpoint inhibition (ICI) and BRAF/MEK-targeted therapy (TT) has improved survival, there still is a high medical need to optimize these existing therapeutic approaches [2–6]. Particularly ICI therapy with PD-1 (programmed cell death protein 1) and/or CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) inhibitors is attributed to lead to durable responses and prolonged survival. However, individual treatment outcomes are very heterogeneous and not all patients benefit equally.

Biodiversity factors such as sex, ethnicity, lifestyle, sporting activity, dietary patterns, and the gut microbiome are becoming increasingly interesting for treatment decision making in the actual era of personalized medicine, as these factors might influence the outcome of cancer therapies. It is known that biological differences exist between males and females in both the innate and acquired immune system, leading to sex-specific differences in prevalence and mortality of autoimmune diseases, infectious diseases, and several types of cancer [7, 8]. This knowledge suggests that the efficacy of anti-tumor therapies may partly rely on the sex of the respective patient, at least in immunologically active cancer entities.

For melanoma the association between sex and treatment outcome is still controversially discussed. With regard to ICI immunotherapy in different cancer entities including melanoma, Botticelli et al. reported in 2017 a better therapy response in males compared to females [9]. In 2018, Conforti et al. confirmed these findings by demonstrating a superior survival upon immunotherapy for males [10]. In contrast, a recent study from Bastholt and colleagues found a strong survival advantage for female melanoma patients treated with ICI [11]. Concerning targeted therapy, a recent study of Vellano et al. showed improved survival outcomes for females in several independent cohorts of melanoma patients treated with BRAF/MEK inhibitors [12].

We aimed to investigate whether the patients' sex has an impact on survival outcomes after first-line ICI or TT therapy in advanced metastatic melanoma. This hypothesized association was analyzed in the total of a large multicenter real-world patient cohort, as well as in subgroups defined by therapy type.

2. Patients and methods

2.1. Study design and patient inclusion

Patients were identified from the prospective multicenter skin cancer registry ADOREG of the German Dermatologic Cooperative Oncology Group (DeCOG) according to the following criteria: Histologically confirmed melanoma of the skin or of unknown primary (mucosal and uveal melanomas were excluded), first-line therapy with either anti-PD-1-based ICI or BRAF/MEK-directed TT for unresectable stage-IV disease (AJCCv8) [9] with all metastatic sites allowed including brain, and at least one follow-up documentation. Study endpoints were progression-free survival (PFS) and overall survival (OS), defined as time from therapy start to disease progression or death, respectively. If no such event occurred, the date of last patient contact was used as endpoint for survival assessment (censored observation). The data cut-off was set close to the application of this study as December 15, 2020. The ADOREG registry was approved by the Ethics Committee of the University of Duisburg-Essen (14–5921-BO); informed consent was obtained from all participating patients.

[1] ASL and TP contributed equally to this work

2.2. Statistics

PFS and OS were analysed using the Kaplan-Meier method for censored failure time data, for the total patient cohort as well as for subgroups defined by type of first-line treatment. The log-rank test was used to assess relevant survival differences between groups. Multivariable analyses were performed using the Cox proportional hazards model, including sex (male versus female) as well as the following prognostic covariates: BRAF status (V600 mutated versus wild type), serum lactate dehydrogenase (LDH) (elevated versus normal), overall performance status by ECOG (0 versus ≥1), age (<65 versus ≥65 years), M stage (M1a/b versus M1c/d), and number of organs involved in metastasis (1–2 versus ≥3). Statistical analyses were performed using SPSSv25 (IBM, Armonk, NY, USA). Exact two-sided significances were calculated; the alpha level was set to 0.05.

3. Results

3.1. Patient characteristics and study flow

A total of 2032 patients, 1274 males (62.7 %) and 758 females (37.3 %), were identified by the above-mentioned selection criteria. Of those, 73.0 % (1484 patients; males=941, 63.4 %; females=543, 36.6 %) had started a PD-1-based ICI therapy, and 27.0 % (548 patients; males=333, 60.8 %; females=215, 39.2 %) a BRAF/MEK-directed TT between May 2010 and December 2020. The median follow-up time was 28.6 months. Regarding baseline parameters at therapy start, mean age was 65.6 years in males and 62.8 years in females, and 60.4 % of patients (n = 1226) had disease stage M1c/d. A detailed overview on patient characteristics is provided in Table 1. The study flow is shown in Fig. 1.

Table 1
Patient characteristics at start of first-line therapy.

	TotalN (%)	MalesN (%)	FemalesN (%)
Total	**2032 (100 %)**	**1274 (100 %)**	**758 (100 %)**
Sex			
male	1274 (62.7 %)	1274 (100 %)	-
female	758 (37.3 %)	-	758 (100 %)
Mean age (range), years	64,5 (19.4–97.2)	65,6 (19.4–97.2)	62,8 (20.4–96.2)
Localisation of primary			
skin	1715 (84.4 %)	1069 (83.9 %)	646 (85.2 %)
unknown primary (MUP)	317 (15.6 %)	205 (16.1 %)	112 (14.8 %)
BRAF V600 mutation			
yes	893 (43.9 %)	548 (43.0 %)	345 (45.5 %)
no	853 (42.0 %)	547 (42.9 %)	107 (14.1 %)
unknown	286 (14.1 %)	179 (14.1 %)	306 (40.4 %)
ECOG overall performance status			
0	678 (33.4 %)	420 (33.0 %)	258 (34.0 %)
≥ 1	336 (16.5 %)	219 (17.2 %)	117 (15.4 %)
unknown	1018 (50.1 %)	635 (49.8 %)	383 (50.5 %)
Sites of metastasis			
skin/subcutaneous and/or lymph node (M1a)	139 (6.8 %)	76 (6.0 %)	63 (8.3 %)
lung (M1b)	363 (17.9 %)	215 (16.9 %)	148 (19.5 %)
liver, bone, other organ (M1c)	719 (35.4 %)	481 (37.8 %)	238 (31.4 %)
brain (M1d)	507 (25.0 %)	318 (25.0 %)	189 (24.9 %)
unknown	304 (15.0 %)	184 (14.4 %)	120 (15.8 %)
Number of organs involved in metastasis			
≤ 2	1084 (53.3 %)	674 (52.9 %)	410 (54.1 %)
≥ 3	644 (31.7 %)	416 (32.7 %)	228 (30.1 %)
unknown	304 (15.0 %)	184 (14.4 %)	120 (15.8 %)
LDH (serum)			
normal (≤ULN)	706 (34.7 %)	438 (34.4 %)	268 (35.4 %)
elevated (>ULN)	699 (34.4 %)	437 (34.3 %)	262 (34.6 %)
unknown	627 (30.9 %)	399 (31.3 %)	228 (30.1 %)
Type of first-line therapy			
immune checkpoint therapy, PD−1 based	1484 (73.0 %)	941 (73.9 %)	543 (71.6 %)
single-agent PD−1 (monotherapy)	872 (42.9 %)	543 (42.6 %)	329 (43.4 %)
PD−1 plus CTLA−4 (combination therapy)	456 (22.4 %)	297 (23.3 %)	159 (21.0 %)
BRAF/MEK-directed targeted therapy	548 (27.0 %)	333 (26.1 %)	215 (28.4 %)

Patient characteristics at start of the first non-adjuvant PD-1-based immune checkpoint inhibition or targeted therapy. AJCCv8 was used for disease classification. LDH, lactate dehydrogenase; ULN, upper limit of normal.

3.2. No relevant sex-specific survival differences for the total of patients receiving immunotherapy or targeted therapy

The median PFS of the total patient cohort after start of any first-line therapy was 6.9 months (95 %CI=6.2–7.7), and the median OS was 32.9 months (95 %CI=29.2–36.6). Analysed separately by sex, no differences could be detected for survival with a median PFS of 6.9 months (95 % CI=5.8–7.9) in males and 6.9 months (95 %CI=5.8–8.1) in females; p = 0.86; Fig. 2A. The median OS stratified by sex was 32.8 months (95 %CI=28.1–37.5) for males and 32.9 months (95 %CI=26.7–39.1) for females; p = 0.60; Fig. 2B.

When grouping the patients by treatment type, no significant sex-specific survival differences were observed. In the anti-PD-1-based immunotherapy cohort the median PFS was 6.2 months (95 % CI=5.3–7.2) and the median OS was 35.4 months (95 %CI=30.3–40.5). Separately analysed for males and females, the median PFS was 6.4 months (95 %CI=4.9–8.0) and 5.7 months (95 %CI=4.4–7.0), respectively; p = 0.46; Fig. 2C. The median OS was 37.0 months (95 % CI=30.6–43.3) in males and 32.0 months (95 %CI=25.0–39.0) in females; p = 0.20; Fig. 2D. Patients treated with BRAF/MEK-directed TT showed a median PFS of 8.3 months (95 %CI=7.2–9.4) and a median OS of 26.9 months (95 %CI=21.0–32.7). Within the TT cohort, the median PFS was 7.6 months (95 %CI=6.2–9.1) in males and 9.1 months (95 % CI=7.5–10.7) in females; p = 0.21; Fig. 2E. The median OS separately analysed for males and females was 24.2 months (95 %CI=19.7–28.7) and 35.6 months (95 %CI=22.0–49.2), respectively; p = 0.30; Fig. 2F. Detailed patient characteristics by therapy type are shown in Suppl Table 1.

3.3. Males show a trend towards a survival advantage over females when treated with anti-PD-1 monotherapy

We subdivided the ICI therapy cohort into patients who received anti-PD-1 monotherapy (n = 872; males=543; females=329), and patients who were treated with anti-PD-1 plus anti-CTLA-4 combination therapy (n = 456; males=297; females=159). For monotherapy, a significant PFS advantage was detected for males with a median PFS of 8.5 months (95 %CI=6.15–10.94) versus 5.98 months (95 %CI=4.51–7.45) in females; p = 0.041; Fig. 3A.

OS showed a favorable trend with improved survival for males (median OS 37.49 months (95 %CI=28.56–46.42) compared to 26.61 months for females (95 %CI=19.53–33.70; p = 0.072), though this difference was not statistically significant; Fig. 3B.

For patients who received anti-PD-1 plus anti-CTLA-4 combination immunotherapy, no sex-specific survival differences could be detected by univariable and multivariable analysis. The median PFS was 8.08 months (95 %CI=4.80–11.36) in males and 6.41 months (95 % CI=3.25–9.56) in females; p = 0.80; Fig. 3C. The median OS was not reached for both groups; p = 0.83; Fig. 3D.

3.4. Multivariable analyses confirm sex-specific survival differences for immunotherapy subtypes

Next, we conducted multivariable analyses, for the total cohort as well as separately for each treatment type and subgroup. Under exclusion of all patients with missing data, 583 ICI patients and 140 TT patients could be selected for multivariable PFS analyses, as well as 581 ICI

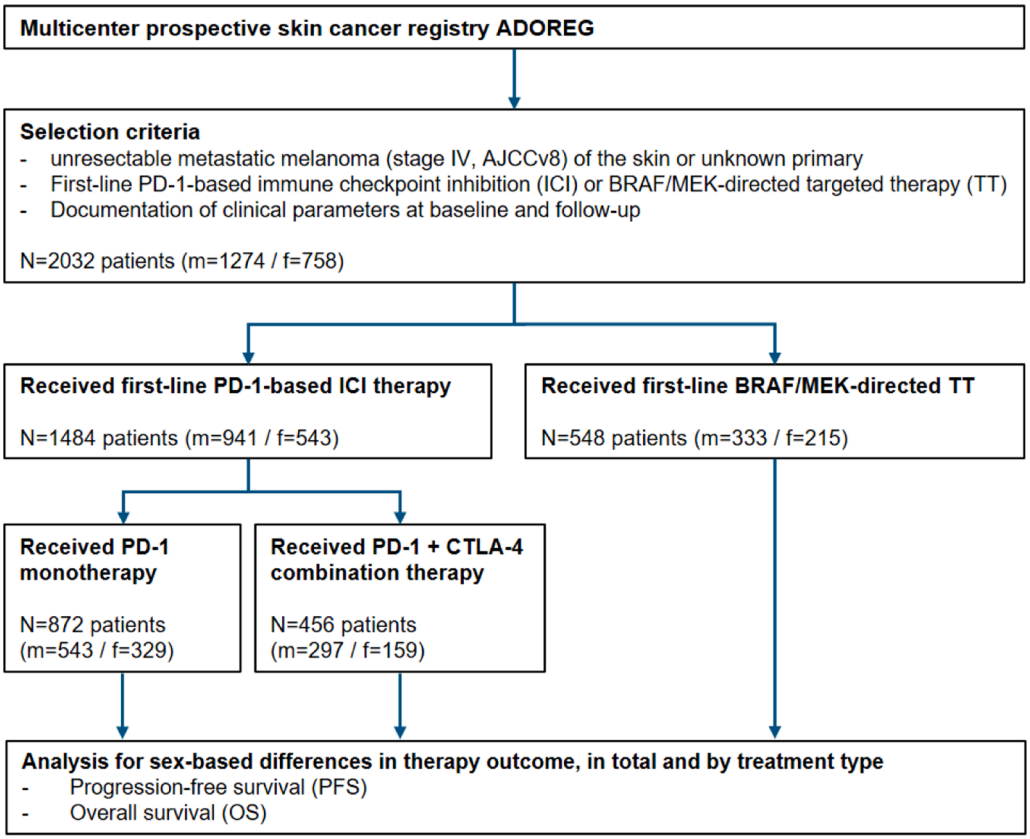

Fig. 1. Schematic presentation of the study flow.

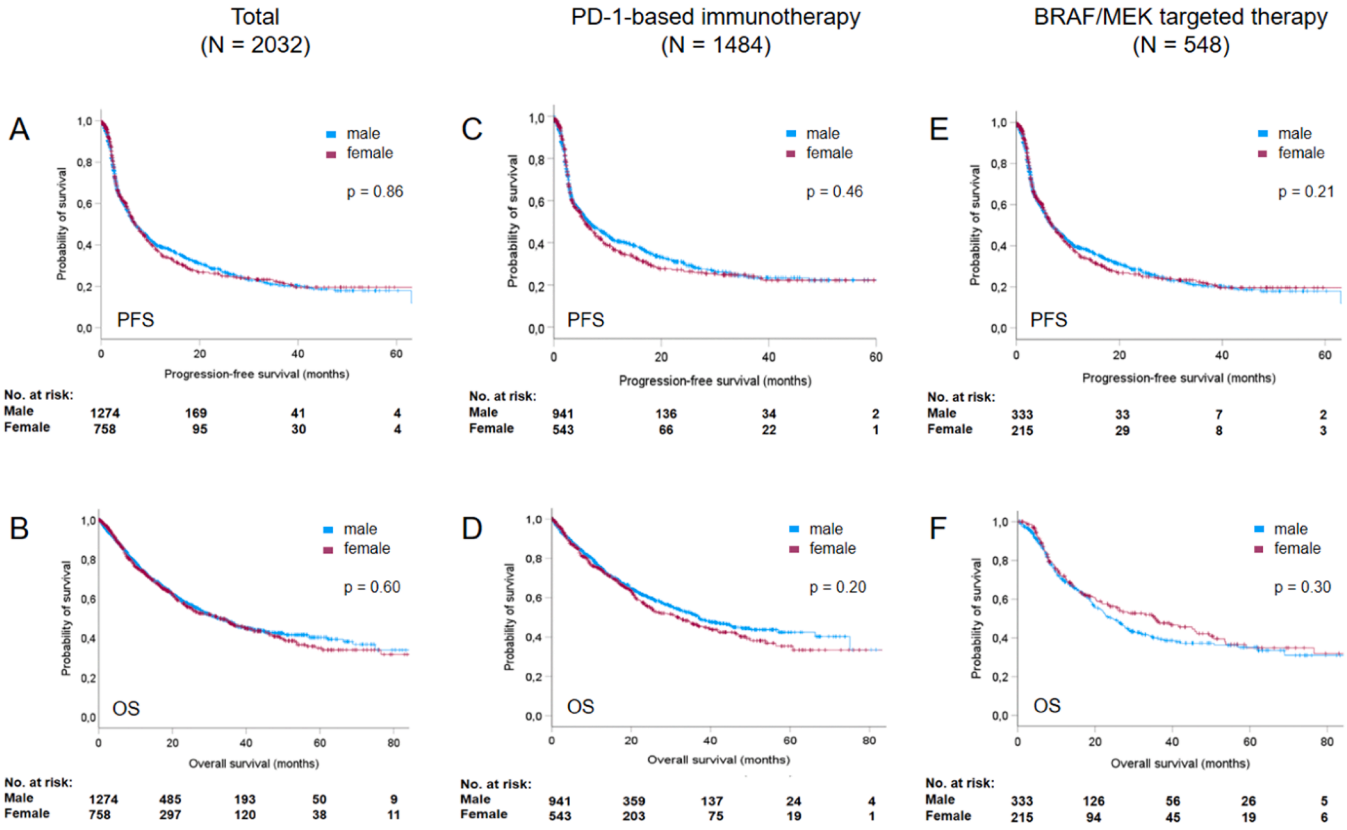

Fig. 2. Kaplan-Meier survival estimates of progression-free (PFS) and overall survival (OS) stratified by patient's sex for the total study cohort (A, B), the immunotherapy cohort (C, D) and the cohort treated with targeted therapy (E, F). P-values calculated by log-rank test.

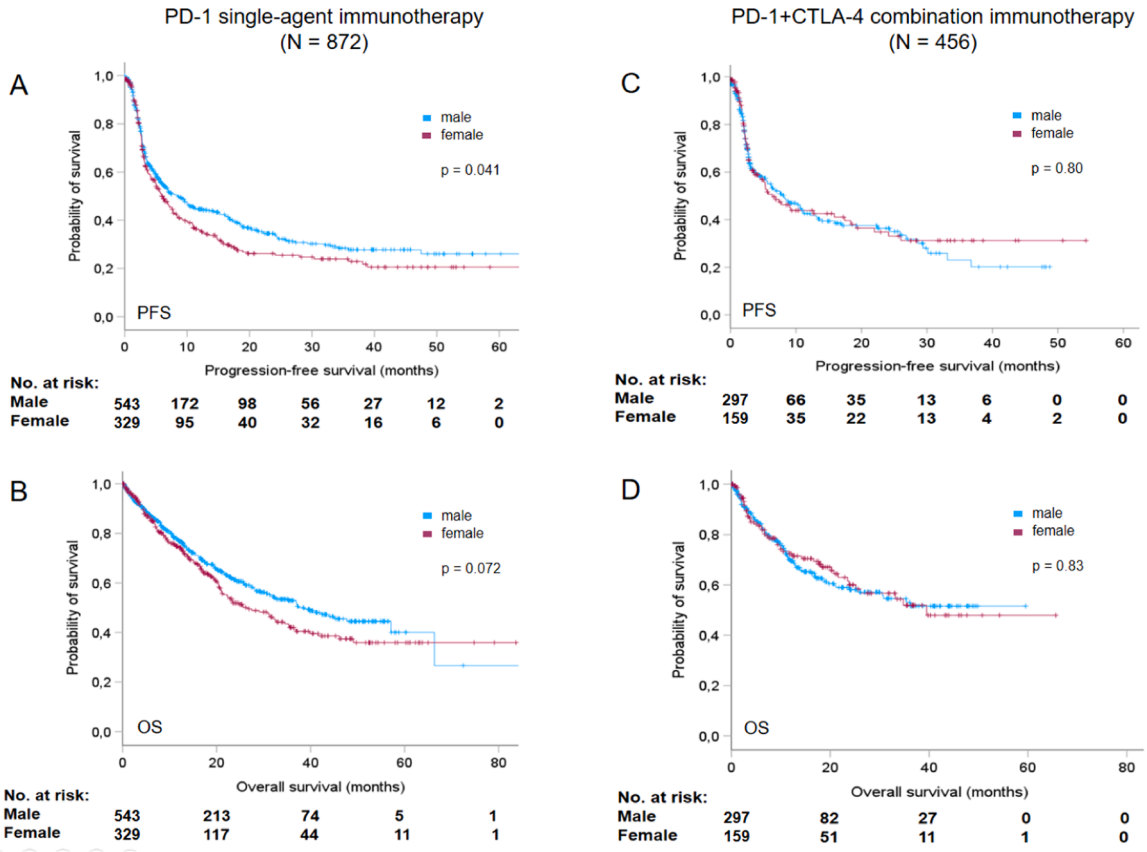

Fig. 3. Kaplan-Meier survival estimates of progression-free (PFS) and overall survival (OS) stratified by patient's sex for different types of immune checkpoint inhibition therapy. PD-1 single-agent therapy (A, B), and PD-1 +CTLA-4 combination therapy (C, D). P-values calculated by log-rank test.

treated and 138 TT treated patients for multivariable OS analyses. Patient's sex was not an independent factor influencing PFS or OS, neither in the total patient cohort, nor in the two subgroups by treatment type. However, serum LDH, ECOG state and M stage were confirmed as significant independent factors impacting PFS; Fig. 4A,C. Concerning OS, for both therapy types serum LDH was a significant independent parameter, whereas ECOG performance state was a significant factor only in patients treated with ICI immunotherapy; Fig. 4B,D.

For multivariable analysis of the immunotherapy subgroups, anti-PD-1 monotherapy and anti-PD-1 plus anti-CTLA-4 combination therapy, after exclusion of all patients with missing data 381 and 175 patients remained for PFS and OS analyses, respectively. Cox regression analysis demonstrated sex as an independent factor impacting OS (HR 1.383, 95 %CI=1.008–1.898; $p = 0.045$), but not PFS (HR 1.136, 95 % CI=0.873–1.479; $p = 0.343$) in patients treated with PD-1 monotherapy, with males showing an OS benefit over females; Fig. 4A,B. The multivariable analysis of PFS in anti-PD-1 monotherapy showed a benefit for patients at younger age; Fig. 4A. No independent prognostic influence of patient's sex could be detected for PFS or OS in combination immunotherapy; Fig. 4C,D.

4. Discussion

Females and males show differences in their innate and acquired immunity due to genetic and hormonal factors. In terms of hormonal regulation, sex hormones such as oestrogen, progesterone and androgens play a crucial role. Depending on age and stage of life, this hormonal regulation differently impacts the immune response. With regard to genetic differences, the X chromosome encodes a large number of genes involved in immune regulation, such as toll-like receptor proteins, cytokine receptor proteins, and transcription factors. In females, incomplete inactivation of the X chromosome may occur during development, leading to an upregulation of X-chromosomal genes in females compared to males [7, 8]. Given these differences, it is reasonable to assume that the response of the immune system is sex-dependent in a way that any further stimulation by ICI might be less effective in females than in males [7].

First meta-analyses of clinical trial data confirmed this hypothesis. In 2017, Botticelli et al. reported a superior treatment response to anti-CTLA-4 or anti-PD-1 ICI therapies for males with various types of cancers [9]. Subsequently, Conforti et al., 2018 performed a meta-analysis including different types of cancers and found a significant difference in the response to ICI immunotherapy between the sexes [10], confirming a significantly better OS for males compared to females. In contrast, a large meta-analysis from 2019 by Wallis et al. on patients with different cancer entities treated with ICI immunotherapy found no significant sex-specific survival differences [13]. The authors examined 23 randomized clinical trials with a total of 13,721 patients. Subgroup analyses according to cancer entity, line of therapy, class of immunotherapy, and study methodology recapitulated these findings.

For melanoma, the data situation is similarly controversial and unclear. A preclinical study by Lin et al. using a melanoma mouse model treated with anti-PD-L1 immunotherapy demonstrated an advantage for female mice [14]. Conforti and coworkers, however, demonstrated a survival benefit for males resulting from a meta-analysis of 7 randomized clinical trials of ICI in metastatic melanoma [10]. In contrast, a recent real-world study from the Danish melanoma registry investigating patients treated with ICI therapy again showed a significant survival advantage for female patients [11]. Here, the research group led by Lars Bastholt was able to demonstrate a significantly improved PFS and OS for females in comparison to males. Nevertheless, the authors pointed out that they were not able to conclude whether these

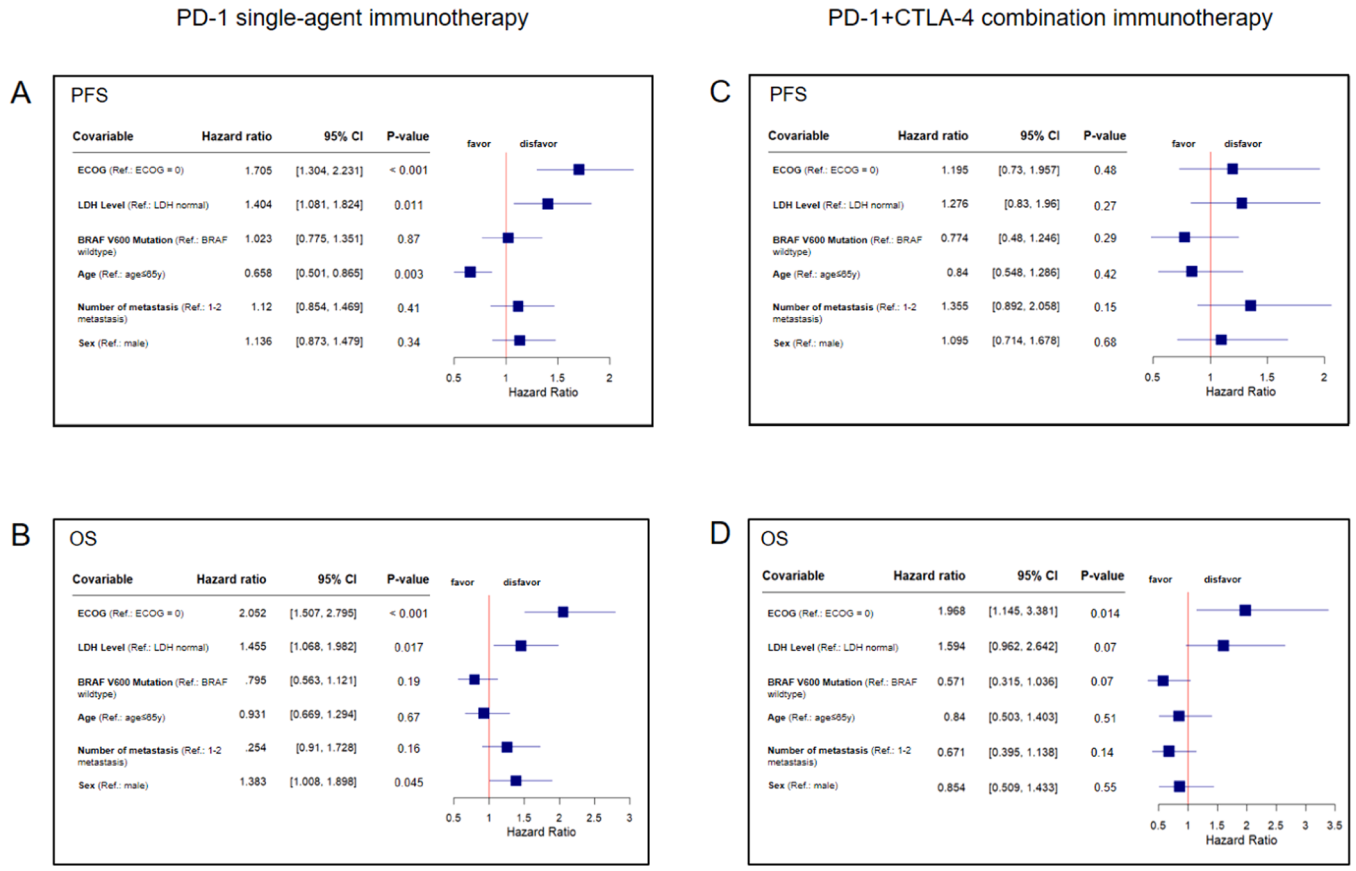

Fig. 4. Forest plots depicting stratified hazard ratios for progression-free survival (PFS) and overall survival (OS) calculated by multivariable Cox regression analysis for different types of immune checkpoint inhibition therapy. Variables were selected in a backward manner with a cut-off $p \leq 0.05$. CI, confidence interval.

associations were attributed to differences in biology or to treatment regimens.

Our results clearly demonstrate that in the German multicenter real-world cohort investigated there is no sex-specific survival benefit for metastatic melanoma patients in the first-line therapy setting, neither in the total cohort of more than 2000 investigated patients, nor in the also sufficiently large cohorts grouped by therapy type, which means ICI immunotherapy or BRAF/MEK-directed TT. This finding is in line with the meta-analysis from Wallis et al., who also detected no survival differences between the sexes in cancer patients under ICI therapy [13]. However, for melanoma patients treated with BRAF/MEK-directed TT, Vellano et al. reported a significantly better treatment outcome in females [12]. Notably, in that study multiple small patient cohorts were used. Importantly, it should be noted that our results are in contrast to the study results from Denmark, showing a better survival upon ICI therapy for females [11]. The Danish study had a similar design to our German study, since also a nation-wide multicenter registry was used, leading to a high number of real-world patients to be analyzed in an unselected manner. As possible reasons for the different results of both studies, we assume the different parameters of biodiversity between the Danish and the German patient cohort, such as genetic background, ethnicity, social status and environmental factors. To further elucidate these differences is a topic of major interest for future studies.

Interestingly, when looking further into our data and building subgroups by type of ICI immunotherapy, we detected a trend towards a survival advantage for males compared to females in patients treated with anti-PD-1 monotherapy. This finding is in line with the results of another meta-analysis performed by Conforti and colleagues in 2019 [15]. Here, the authors investigated sex-based differences in the ICI therapy outcome in lung cancer patients. They were able to show that anti-PD-1 monotherapy led to a better OS in males than in females. This favorable treatment outcome might be related to sex-specific differences in the amount and composition of intratumoral immune infiltrates [16]. An intratumoral immune infiltrate enriched with partially exhausted cytotoxic T lymphocytes expressing high levels of CTLA-4 and PD-1 was described to be present predominantly in male melanoma patients, and to be strongly correlated with an enhanced therapy response [17].

Our results highlight the need to further analyze in depth the biological and genetic disparities in single cancer entities and their response to different treatment types, before we can reasonably provide patients with personalized recommendations for treatment decision making. A study published in 2020 by Castro and colleagues investigated at the molecular level why certain groups of patients respond worse or better to ICI immunotherapy [16]. The authors demonstrated that patients of younger age and female sex accumulated driver mutations in their tumors that were less easily presented by MHC molecules, suggesting a greater burden of immune selection early in tumorigenesis. As a consequence, the authors hypothesized that anti-PD-1 ICI therapy might have a reduced effect in younger female patients [18]. Our findings of poorer survival outcomes in patients of female sex and younger age treated with anti-PD-1 monotherapy confirm this hypothesis (Fig. 4A,B).

The present study has limitations. Due to the real-world setting of the registry, data on covariates such as overall performance status are missing in a relevant number of patients, resulting in a limitation for the multivariable analyses. Due to the retrospective nature of the study, the subgroups by treatment type show a different distribution of possible confounders. As advantages of our study it should be noted that the patient cohort was prospectively and non-selectively collected within a nation-wide multicenter registry. This real-world design of the study diminishes the potential bias generated by patient selection and better reflects other real-world patient cohorts treated at comparable clinical centers, opposite to the highly selected patient cohorts reported from the

majority of randomized clinical trials.

In summary, our study results demonstrate no sex-specific survival differences for metastatic melanoma patients in the first-line therapy setting, neither in the total patient cohort nor in subcohorts grouped by immunotherapy or targeted therapy. Investigating subtypes of immunotherapy revealed a trend towards a survival advantage for males over females in melanoma patients treated first-line with anti-PD-1 monotherapy. Further studies with larger patient collectives, especially within the treatment subgroups, are necessary to further validate this interesting finding for future therapy decision making for melanoma patients.

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Patents

a) intra-tumoral administration of IL-12 encoding nucleic acid molecules; Publication No.: WO/2001/052874; PCT/EP2001/000363;

b) preventing secondary lymphedema with vegf-d DNA; Publication No.: WO/2003/093419; PCT/US2003/013350;

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Appendix A. Supporting information

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