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Original research

Improved survival of advanced melanoma patients receiving immunotherapy with concomitant antithrombotic therapy – A multicenter study on 2419 patients from the prospective skin cancer registry ADOReg

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ABSTRACT

Background: Cancer immunotherapy has revolutionized melanoma treatment, but the high number of non-responders still emphasizes the need for improvement of therapy. One potential avenue for enhancing anti-tumor treatment is through the modulation of coagulation and platelet activity. Both have been found to play an important role in the tumor microenvironment, tumor growth and metastasis. Preclinical studies indicate a beneficial effect, clinical data has been inconsistent.

Methods: We examined a cohort of advanced, non-resectable melanoma patients (n = 2419) derived from the German prospective multicenter skin cancer registry ADOReg, who were treated with immune checkpoint inhibitors (ICI). The patients were classified based on whether it was documented that they received platelet aggregation inhibition (PAI) (n = 137) (acetylsalicylic acid (ASA) or clopidogrel), anticoagulation (AC) (n = 185) (direct oral anticoagulation (DOAC), phenprocoumon, heparins) at the start of ICI or no antithrombotic medication (n = 2097) at any point during ICI treatment. The study endpoints were best overall response (BOR), progression-free survival (PFS) and overall survival (OS).

Results: A significantly improved PFS was observed in patients documented to receive ASA (15.1 vs 6.4 months, HR 0.67, 95 % CI: 0.5 to 0.88, p = 0.0047) as well as in patients to receive AC (15.1 vs. 6.4 months, HR 0.7, 95 % CI: 0.53 to 0.91, p = 0.01) compared to patients for whom no antithrombotic medication was documented. Multivariate analysis of OS showed significant risk reduction in patients who received DOAC (HR 0.68, 95 % CI: 0.49 to 0.92, p = 0.0170) or phenprocoumon (HR: 0.44, 95 % CI: 0.19 to 0.85, p = 0.0301).

Conclusion: Our study indicates a positive prognostic effect of anticoagulant and antiplatelet concomitant medication in melanoma patients receiving ICI. Further studies are needed to confrim the cancer-related benefit of adding anticoagulation or platelet inhibition to ICI treatment.

Key massages

What is already known on this topic

Immune checkpoint inhibition (ICI) is the standard of care for advanced melanoma and has dramatically improved prognosis, but there remains an unmet medical need to improve ICI with concomitant therapy. On the one hand, cancer patients are more frequently affected by thromboembolic events (TEE) and on the other hand, a TEE worsens the prognosis.

What this study adds

The combination of direct oral anticoagulation (DOACs) or phenprocoumon and ICI shows a prolonged overall survival (OS) as assessed in the ADOREG documentation. Additional these anticoagulants and also the platelet aggregation inhibitor (PAI) and

acetylsalicylic acid (ASA) improve progression-free survival (PFS) of advanced melanoma patients (metastatic, non resectable stage III/ IV) treated with ICI.

How this study might affect research, practice or policy

Concomitant antithrombotic therapy, like acetylsalicylic acid (ASA) or anticoagulation, could enhance the therapeutic effect of ICI in advanced melanoma.

1. Background

Over the past decade, immunotherapy has tremendously improved the treatment outcome of various malignancies, including melanoma. Immune checkpoint inhibitors (ICI) are highly effective, leading to

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durable tumor regressions even in advanced cancer stages [1]. However, a significant proportion of patients do not benefit from ICI therapy due to primary or acquired resistance [1,2]. Therefore, there is an urgent need to identify new targets that increase the efficacy of cancer immunotherapy.

On the one hand, thromboembolic events (TEEs) like venous thromboembolism (VTE), pulmonary embolism (PE) or arterial infarcts are more common in tumor patients and on the other hand, they worsen the prognosis when they occur in the context of tumor disease [3]. A direct effect of ICI therapy on platelet activation or via the influence on T cell function on platelet activation however cannot be considered a major factor in the development of thrombotic events [4]. One potential avenue for enhancing cancer therapy is through the modulation of coagulation and platelet activity, which has been found to play an important role in the tumor microenvironment [5].

Several studies suggest that an increased expression of tissue factor (TF) by malignant or myeloid cells may lead to an increase in tumor growth and metastasis formation by inducing thrombin, which promotes coagulation and platelet activation [6–9]. Thrombin can activate platelets and supports tumor immune evasion [6,7,10]. This may mediate an increased release of several factors including vascular endothelial growth factor (VEGF) or VWF [6,7,11,12]. Although ICI do not have a direct effect on platelet activation [4]. The potential inhibition of tumor immune evasion is of special interest in patients treated with ICIs, where many patients lack a lasting therapy response due to the evasion of T-cell-mediated immunosurveillance [13].

Although many of these preclinical findings sound promising, conflicting – depending on the tumor entity – results have been reported on the potential of antithrombotic effects on development of cancer. For example, the CAPP2 study, a large randomized controlled clinical trial, has shown that Lynch syndrome patients who receive acetylsalicylic acid (ASA) are less likely to develop colon cancer [14]. However, data from the ASPREE study did not find a significant reduction of melanoma incidence in patients who received the ASA [15]. Studies investigating the effect of anticoagulation in cancer patients are not consistent – while Johannet *et al.* did not find a significant correlation of neither progression-free survival (PFS) nor overall survival (OS) in various cancer entities, Cortellini *et al.* reported that ICI patients receiving antithrombotic therapy had a higher risk of disease progression [16,17]. In contrast, Haist and Stege *et al.* detected a significant improvement of both PFS and OS in 76 melanoma patients who received concomitant anticoagulation (heparins, direct oral anticoagulation (DOACs) or phenprocoumon) during ICI therapy [18]. Here of course type of anticoagulation, duration and dose as well as timing with respect to ICI therapy have to be taken into account. At this year's ESMO, the randomised SAKK 41/13 study provided the first evidence of a protective effect of adjuvant aspirin in patients with resected, PIK3CA-mutated colorectal cancer in a prospective setting [19].

Notably, cancer patients treated with ICI are at a higher risk of TEEs, such as venous thrombosis and pulmonary embolism, which are often associated with decreased overall survival (OS) [3,20]. Moreover, while effects of ICI on thrombocytes have been characterized and are not pronounced [4]. the proinflammatory state induced by ICI increases the risk of TEE in addition of the already increased risk cancer patients face [21]. Even though not currently recommended in guidelines the evaluation of the risk-benefit ration of antithrombotic therapy in ICI-treated cancer patients should be further investigated.

The conflicting results of clinical data in cancer patients receiving antithrombotic medication together with the results from preclinical research and preclinical data finding a significant role of platelets and coagulation in the tumor microenvironment. They emphasize the urgent need to investigate the impact of concomitant antithrombotic medication in cancer patients who receiving ICI.

In this study, we aimed to examine the effects of concomitant platelet aggregation inhibition or anticoagulation, which was prescribed for medical conditions of the cardiovascular system, in a large multicentric prospectively collected real-world cohort of melanoma patients receiving ICI for advanced non-resectable disease.

2. Methods

2.1. Study design

We identified 2419 patients who had received ICIs for the treatment of advanced, non-resectable melanoma between 2016 and 2022 from the prospective multicenter skin cancer registry ADOReg of the German Dermatologic Cooperative Oncology Group (DeCOG). The two treatment regimens anti-programmed cell death (PD)−1 or anti-PD-1 in combination with anti-cytotoxic T-lymphocyte associated protein (CTLA)−4 antibodies were used. Patients were classified into three groups according to the intake of concomitant antithrombotic medication. The first group, defined as platelet aggregation inhibition (PAI) consisted of patients receiving either ASA or clopidogrel. Factor Xa inhibitors, direct thrombin inhibitors, vitamin K antagonists and low weight molecular heparins (LMWH) were summarized as anticoagulation (AC). Patients who received PAI or AC at any time during ICI therapy were grouped accordingly. PAI and AC groups were merged as antithrombotic treatment (ATT) group. Patients with more than one concomitant antithrombotic medication were counted with the larger group of antithrombotic medication. The third group consisted of patients who did not receive any ATT during the full course of ICI therapy. All patients provided written and informed consent to participate in the ADOReg skin cancer registry. The registry is approved by the Medical Ethics committee of the University Duisburg-Essen (14–5921-BO). Clinical decisions were made independently of this study.

2.2. Definition of clinical outcomes

Best overall response (BOR) was classified according to the revised response evaluation criteria in solid tumors (RECIST) guidelines (version 1.1), with complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) as possible outcomes. Objective response rate (ORR) was defined as patients with CR or PR, while disease control rate (DCR) included patients with CR, PR or SD. PFS was calculated as the duration from the start of treatment until disease progression, death or last time of follow up (censored PFS). Overall survival (OS) was measured as the time from the start of treatment until death or last time of follow up (censored OS). TEEs were defined as venous thrombosis, pulmonary embolism, or stroke.

2.3. Statistical Analysis

Relationships between AC or PAI status and response were examined using the Chi-square test. 95 % confidence intervals were calculated using the Wilson/Brown method. Survival curves were created using the Kaplan-Meier method and compared with the log-rank test. Cox proportional hazards regression models were used for uni- and multivariate analysis, and contained the following parameters due to their potential prognostic value: Concomitant antithrombotic medication, disease stage according to the AJCC classification (8th edition), age, sex, immunotherapy treatment regimen, the presence of brain metastasis at immunotherapy initiation, Eastern Cooperative Oncology Group (ECOG) performance status, and whether the patients have received previous anticancer drug therapy. All parameters that were significant in the univariate Cox proportional hazards regression were included in the multivariate analysis. A two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were performed using GraphPad Prism Version 9.5.1.

3. Results

3.1. Cohort characteristics

Characteristics for the three major patient groups are shown in Table 1. A total of 2419 advanced, non-resectable melanoma patients treated with ICI (anti-PD-1 n = 1400 or anti-PD-1 in combination with anti-CTLA-4 n = 1019) were included in the study. Of these, 2097 (86.7 %) patients were documented to receive no concomitant antithrombotic therapy. A group of 137 (5.7 %) patients was documented to receive PAI, of whom 126 (91.0 %) only received ASA, 7 (5.1 %) only received only clopidogrel, and 4 (2.9 %) were treated with combined PAI (ASA plus clopidogrel). Out of 185 (7.7 %) patients in the AC group, 124 (67.0 %) received a factor Xa inhibitor (rivaroxaban, apixaban or edoxaban), eight (4.3 %) were treated with a direct thrombin inhibitor (dabigatran), 27 (14.6 %) received a vitamin K antagonist (phenprocoumon) and 26 (14.1 %) LMWH (**Suppl.** Table 2). Patients were more likely to be male in the ATT groups (75.9 % (PAI); 67.0 % (AC); p = 0.0011) when compared to those without antithrombotic therapy (61.2 %). Patients receiving antithrombotic therapy were significantly older (74.9 years (PAI); 74.2 years (AC) vs. 64.4 years: p < 0.0001) and had worse ECOG status (ECOG>0: 25.6 % (PAI); 25.4 (AC) vs. 17.5 %). The PAI group included more stage IV patients (87.9 %) than the other two groups (no ATT: 81.8 %, AC: 82.7 %) (Table 1). Melanoma subtypes were mostly nodular (734; 30.3 %) and superficial spreading (468; 19.3 %), while acral lentiginous, mucosal, lentigo maligna, ocular melanoma, and melanomas of unknown primary (MUP) were also included (**Suppl.** Table 2). A total of 47 TEEs were recorded in 42 patients (n = 42, 1.74 %), of which 12 events occurred in 10 patients during ICI treatment. The indications for PAI were mostly unknown (n = 102, 74.5 %) and for AC atrial fibrillation was reported in most cases (n = 76, 41.1 %) (**Suppl.** Table 3).

3.2. Best overall response to treatment

More than one third (n = 752, 35.9 %) of the advanced melanoma patients in the control group (no ATT) showed primary resistance to treatment with anti-PD-1 antibodies or anti-PD-1 in combination with anti-CTLA-4 antibodies (Table 2). In patients with concomitant ATT the number of patients who experienced progression was 26 (19 %) in the PAI-treated group (n = 137), 49 (26.5 %) in the AC group (n = 185) and 833 (39.7 %) in the reference group (no ATT, n = 2097). Treatment responses (PR, CR) were achieved in 27.6 % (n = 578) of patients in the reference group (no ATT), in 25.5 % (n = 35) of PAI patients, and in 31.4 % (n = 58) of AC patients (p = 0.4573). DCR was highest in PAI patients (n = 67, 48.9 %) when compared to AC patients (n = 76, 41.1 %) and those without ATT (n = 842, 40.2 %) (p = 0.13) (Table 2).

3.3. Concomitant platelet aggregation inhibition with ASA is independently prognostic for prolonged PFS

In comparative univariate survival analysis advanced melanoma patients treated with ICI who received concomitant PAI medication had a significantly longer PFS than patients with no concomitant ATT (p = 0.01, 15.13 vs. 6.37 months) (Fig. 1A). Notably, the improved PFS was only observed in patients treated with ASA (n = 130; 15.1 vs 6.4 months, p = 0.0058), while patients who received clopidogrel (n = 7; 3.2 months, p = 0.4808) showed shorter PFS compared to those without concomitant ATT (n = 2097) (Fig. 1B). This finding was confirmed by multivariate cox proportional hazards regression analysis, which showed that patients with concomitant ASA treatment had a 33 % reduced risk of progression compared to patient without concomitant ATT (HR 0.67, 95 % CI: 0.5 to 0.88, p = 0.0047) (Table 3).

Regarding OS, no significant benefit was observed in patients treated with ASA (p = 0.2407, 45.2 vs. 38.8 months) although patients receiving clopidogrel had shown a significantly worse median OS (p = 0.0951, 10.3 months) (Fig. 1C). When adjusting for factors such as age, AJCC stage, ECOG status, and brain metastasis OS was higher, albeit not significant, for patients receiving ASA when compared to those without ATT (HR 0.8; 95 % CI: 0.59 to 1.1, p = 0.1443) (Table 3).

Table 1
Patient characteristics of melanoma ADOReg registry patients by antithrombotic therapy cohort.

	no antithrom-botic therapy	%	platelet aggrega-tion inhibition	%	anticoagu-lation	%	p-value
number of patients	2097		137		185		
sex							**p = 0.0011**
male	1283	61.2 %	104	75.9 %	124	67.0 %	
female	814	38.8 %	33	24.1 %	61	33.0 %	
age							**p < 0.0001**
mean (SD)	64.4 (14.2)		74.9 (8.4)		74.2 (10.3)		
ECOG							**p = 0.0366**
0	982	46.8 %	53	38.7 %	80	43.2 %	
1	291	13.9 %	29	21.2 %	39	21.1 %	
> 1	75	3.6 %	6	4.4 %	8	4.3 %	
not specified	749	35.7 %	49	35.8 %	58	31.4 %	
stage							p = 0.2232
III	382	18.2 %	17	12.4 %	32	17.3 %	
IV	1715	81.8 %	120	87.6 %	153	82.7 %	
brain metastasis							p = 0.8064
yes	371	17.7 %	26	19.0 %	30	16.2 %	
no	1726	82.3 %	111	81.0 %	155	83.8 %	
treatment regimen							p = 0.2985
anti-PD−1	1205	57.5 %	88	64.2 %	107	57.8 %	
anti-PD−1 + anti-CTLA−4	892	42.5 %	49	35.8 %	78	42.2 %	
treatment line							p = 0.4329
1 L	1700	81.1 %	107	78.1 %	155	83.8 %	
2 L or later	397	18.9 %	30	21.9 %	30	16.2 %	
patient status							**p = 0.0122**
alive with disease	1260	60.1 %	82	59.9 %	125	67.6 %	
no evidence of disease	9	0.4 %	3	2.2 %	0	0.0 %	
deceased	828	39.5 %	52	38.0 %	60	32.4 %	

ECOG - Eastern Cooperative Oncology Group performance status scale; 1 L - first line therapy; 2 L – second line therapy.

Table 2
Treatment outcomes of melanoma ADOReg registry patients receiving ICI treatment by antithrombotic therapy cohort.

outcome	no ATT		platelet aggregation inhibition		anticoagulation		p-value
best overall response							**0.0002**
progressive disease	833	39.7 %	32	23.4 %	58	31.4 %	
stable disease	264	12.6 %	32	23.4 %	18	9.7 %	
partial remission	313	14.9 %	20	14.6 %	33	17.8 %	
complete remission	220	10.5 %	14	10.2 %	21	11.4 %	
no evidence of disease	45	2.1 %	1	0.7 %	4	2.2 %	
could not be evaluated	422	20.1 %	38	27.7 %	51	27.6 %	
objective response rate							0.4573
no	578	27.6 %	35	25.5 %	58	31.4 %	
95 % CI of percentage	25.7−29.5		19.0−33.4		25.1−38.4		
disease control rate							0.1292
number	842	40.2 %	67	48.9 %	76	41.1 %	
95 % CI of percentage	38.1−42.3		40.1−57.2		34.2−48.3		

[1]*Objective response rate was defined as the percentage of patients who had CR or PR*
[2]*Disease control rate was defined as the percentage of patients who had CR, PR or SD*
[3]*The 95 % confidence intervals were calculated using the Wilson/Brown method*
No ATT – no antithrombotic therapy

Table 3
Univariate cox proportional hazards regression for melanoma ADOReg registry patients with receiving antithrombotic therapy while on ICIs. Significant values are highlighted in bold.

Variable (reference)	HR (PFS)	95 % CI (profile likelihood)	P value	HR (OS)	95 % CI (profile likelihood)	P value
concomitant ATT (no ATT)						
ASA	**0.67**	**0.50 to 0.88**	**0.0048**	0.8	0.59 to 1.1	0.1461
clopidogrel	1.6	0.50 to 3.8	0.3381	**2.8**	**0.86 to 6.5**	**0.0428**
DOAC	0.78	0.59 to 1.0	0.0597	**0.68**	**0.49 to 0.92**	**0.0170**
phenprocoumon	0.57	0.28 to 1.0	0.0742	**0.44**	**0.19 to 0.85**	**0.0301**
LMWH	0.82	0.45 to 1.4	0.4788	0.93	0.48 to 1.6	0.8026
AJCC Stage (IV)						
III	0.86	0.74 to 1.0	0.0566	**0.75**	**0.62 to 0.91**	**0.0042**
age						
	1	0.99 to 1.0	0.2032	**1**	**1.0 to 1.0**	**< 0.0001**
sex (male)						
female	1.1	0.97 to 1.2	0.1339	1.1	0.94 to 1.2	0.2996
treatment regimen (anti-PD−1)						
anti-CTLA−4 + anti-PD−1	1.1	0.94 to 1.2	0.3278	1	0.87 to 1.2	0.8996
brain metastases (no)						
yes	**1.2**	**1.0 to 1.4**	**0.0143**	**1.3**	**1.1 to 1.6**	**0.0007**
ECOG (0)						
1	**1.2**	**1.0 to 1.4**	**0.0115**	**1.6**	**1.4 to 1.9**	**< 0.0001**
> 1	**1.9**	**1.4 to 2.5**	**< 0.0001**	**3.2**	**2.4 to 4.2**	**< 0.0001**
treatment line (1 L)						
2 L or later	**1.2**	**1.0 to 1.4**	**0.0152**	1	0.86 to 1.2	0.8732

3.4. Concomitant anticoagulation is associated with improved OS and PFS

Melanoma patients who received concomitant anticoagulation during their ICI treatment had a significantly improved outcome when compared to the reference group, with a median time to progression or death of 12.5 month in the univariate analysis (p = 0.0023) (Fig. 2A). The longest median PFS time was observed in patients who received a vitamin K antagonist (24 months, n = 27), followed by LWMH (11.4 months, n = 26) and direct oral anticoagulation (dabigatran or factor Xa inhibitors, 11 months, n = 132) (Fig. 2B). In multivariate analysis including tumor stage, age, sex, ECOG, brain metastasis, treatment regime and previous therapy, patients receiving anticoagulation showed a significantly decreased risk for progression (HR: 0.75, 95 % CI: 0.59 to 0.93) (Table 4). The adjusted hazard ratio for patients who received direct oral anticoagulation (DOAC) was 0.78 (95 % CI: 0.59 to 1.0, p = 0.0597) and 0.57 for those receiving a vitamin K antagonist (phenprocoumon) (95 % CI: 0.28 to 1.0, p = 0.0742), albeit both not significant (Table 3).

In contrast to PAI-treated patients, most patients who received AC showed an increase in OS when compared to those without ATT (p = 0.0715) (Fig. 2C). However, LMWH-treated patients had a decreased OS (32.6 vs. 38.8 months, p = 0,9763) (Fig. 2D). When adjusting for common risk factors in multivariate OS analysis, a significant risk reduction is observed in patients receiving DOAC (HR: 0.68, 95 % CI: 0.49 to 0.92, p = 0.0170) and phenprocoumon (HR: 0.44, 95 % CI: 0.19 to 0.85, p = 0.0301). For patients who received LMWH during ICI therapy, no significant risk change was observed in the multivariate OS analysis (HR: 0.82, 95 % CI: 0.45 to 1.4, p = 0.8026) (Table 3).

4. Discussion

In this multicentric register-based cohort study of 2419 advanced (metastatic, non-resectable) melanoma patients we found a significantly improved PFS in 130 patients who received PAI with ASA, and a significantly increased PFS and OS in159 patients who were anticoagulated with DOACs or phenprocoumon.

Both subgroups, PAI and AC, showed differences depending on the specific types of medication (ASA vs. clopidogrel and DOACs, phenprocoumon vs. heparin). While in the PAI group, an improvement of PFS and a trend towards improved OS is observed in multivariate analysis, a contrary result is found in patients who are treated only with clopidogrel. However, this cohort is too small (7 patients) for reliable analysis.

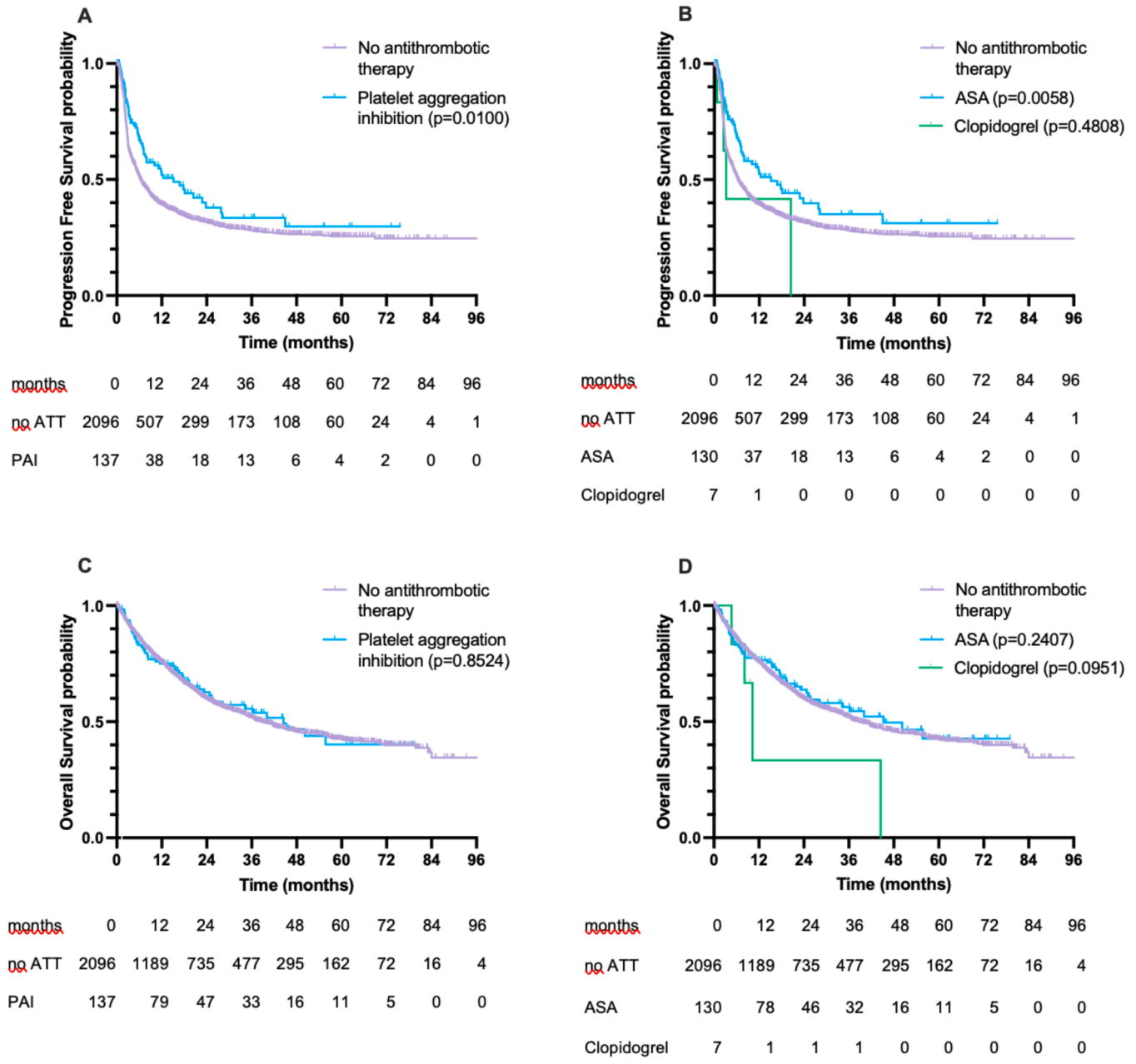

Fig. 1. Kaplan Meier curves showing progression-free survival (PFS) **(A,B)** and overall survival (OS) **(C,D)** of melanoma ADOReg registry patients receiving ICI treatment, stratified based on whether they received any kind of platelet aggregation inhibition (PAI, n = 137) **(A,C)** and type of PAI **(B,D)**. Acetylsalicylic acid (ASA) n = 126, Clopidogrel n = 7, ASA combined with Clopidogrel n = 4, no antithrombotic therapy n = 2097.

In the AC group, patients showed increased PFS and OS when receiving concomitant DOAC or phenprocoumon treatment, while the outcome of patients who received concomitant treatment with LMWH did not significantly improve in multivariate analysis. The lack of survival improvement for patients receiving LMWH may partially be explained by the fact that heparins are often prescribed in cases of specific acute TEEs, which are known to have a negative impact on prognosis in cancer patients [3,22]. Another potential explanation may be that the subcutaneously injected heparins have only been given for a short time according to clinical standards and therefore a possible long-lasting effect did not occur. Additionally, LMWH are more likely to be prescribed in multimorbid patients already receiving various drugs in order to avoid drug interactions, possibly indicating a cohort of patients with a greater underlying risk of tumor progression.

PAI or AC treatment in patients with impaired physical activity as identified by ECOG status could indicate a higher number of comorbidities. Patients with an ECOG performance status of more than 0 points (ECOG ≥ 1) are more likely to have a diminished overall health status (Table 1). Interestingly, the effectiveness of ATT on ICI is improved in these patients with respect to advanced melanoma. This suggests an even greater benefit of ATT as concomitant therapy to ICI and should be investigated in a prospective, placebo-controlled interventional trial. The multivariate Cox regression analysis refutes a possible bias in the group classification due to more restrained use of ATT in patients with brain metastases (Table 4).

Increased expression of tissue factor (TF) by malignant or myeloid cells could lead to metastasis formation and tumor progression by inducing thrombin [6–9]. Thrombin promotes coagulation and activate platelets through protease activated receptors (PARs). This may mediate an increased release of VEGF and vWF, which exerts proangiogenic

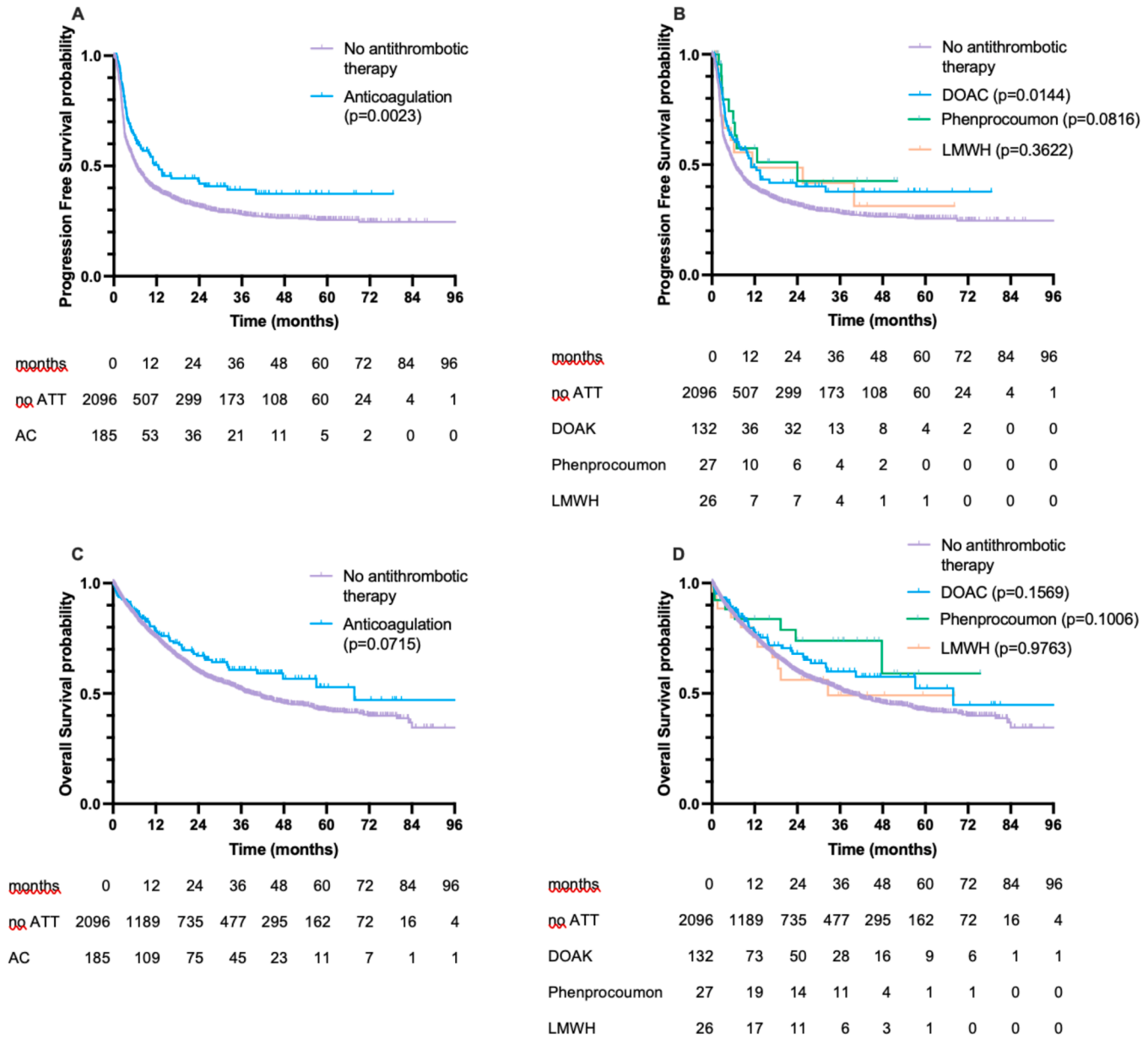

Fig. 2. Kaplan Meier curves showing progression-free survival (PFS) **(A,B)** and overall survival (OS) **(C,D)** of melanoma ADOReg registry patients receiving ICI treatment, stratified based on whether they received any kind of anticoagulation (AC, n = 185) **(A,C)** and type of AC **(B,D)**. Direct oral anticoagulation (DOAC) n = 132, phenprocoumon n = 27, low molecular weight heparin (LMWH) n = 26, no antithrombotic therapy n = 2097.

properties [6,7]. Robador *et al.* and Feinauer *et al.* reported that platelet-derived vWF is involved in cerebral clot formation and in metastatic growth of melanoma in the brain [11,12]. In addition, data from Bauer *et al.* indicate that the VEGF-mediated activation of endothelial cells by melanoma cells leads to the release of vWF fibers and platelet aggregation in tumor microvessels. They showed that blocking this activation by tinzaparin could suppress tumor growth [23]. Subsequently, it has been demonstrated that vWF blood concentrations can predict ICI response in melanoma and other tumor entities [24,25].

Metelli *et al.* found that thrombin supports tumor immune evasion by cleavage of glycoprotein A repetitions predominant (GARP) and the subsequent release of transforming growth factor-ß (TGF-ß). TGF-ß in turn leads to a decrease of CD8 + T-cells, an upregulation of CD4 + T-cells, and an inhibition of immune cell infiltration by increasing the formation of fibroblast barriers and collagen [10]. Additionally, Graf *et al.* suggest that myeloid cell produced factor Xa might promote tumor immune evasion, and that factor Xa inhibitors could support antitumor immunity by enhancing infiltration of dendritic cells and cytotoxic T-cells at the tumor site [9]. These preclinical data may indicate possible mechanisms of an effect of concomitant ATT on ICI.

In contrast to the high incidence of TEE that has been reported in the past for cancer patients [22,26], only 47 TEEs were reported and only 12 of these events during ICI. It is possible that TEEs were not documented in the ADOReg skin cancer registry or not correctly identified as melanoma- or ICI-related and thus missed. It can be assumed that underreporting of TEEs, co-medication and co-morbidities occurs in ADOReg, as this is not a prospective clinical study with on-site monitoring but a registry. However, it is particularly interesting that a beneficial effect of PAI or AC in combination with ICI is shown even in the absence of TEEs.

Increased TEE rates have been observed not only under ICI treatment and in various cancer entities [3,20,22], but also in melanoma patients who have an increased incidence of pulmonary embolism [27]. However, these pulmonary embolisms in melanoma patients are mostly asymptomatic and can only be detected radiologically [27]. D-dimers, a

Table 4
Multivariate cox proportional hazards regression of major subgroups. Significant values are highlighted in bold.

Variable (reference)	HR (PFS)	95 % CI (profile likelihood)	P value	HR (OS)	95 % CI (profile likelihood)	P value
concomitant ATT (no ATT)						
PAI	**0.7**	**0.53 to 0.91**	**0.0092**	0.85	0.63 to 1.1	0.2715
AC	**0.75**	**0.59 to 0.93**	**0.0128**	**0.67**	**0.51 to 0.87**	**0.0035**
AJCC Stage (IV)						
III	**0.86**	**0.74 to 1.0**	**0.0633**	**0,76**	**0.62 to 0.92**	**0.0051**
age						
	1	0.99 to 1.0	0.1892	**1**	**1.0 to 1.0**	**0.0001**
sex (male)						
female	1.1	0.97 to 1.2	0.1369	1.1	0.94 to 1.2	0.3104
treatment regimen (anti-PD−1)						
anti-CTLA−4 + anti-PD−1	1.1	0.94 to 1.2	0.3305	1	0.88 to 1.2	0.8815
brain metastases (no)						
yes	**1.2**	**1.0 to 1.4**	**0.0164**	**1.3**	**1.1 to 1.6**	**0.0008**
ECOG (0)						
1	**1.2**	**1.0 to 1.4**	**0.0133**	**1.6**	**1.4 to 1.9**	**< 0.0001**
> 1	**1.9**	**1.4 to 2.5**	**< 0.0001**	**3.2**	**2.4 to 4.1**	**< 0.0001**
previous drug therapy (no)						
yes	**1.2**	**1.0 to 1.4**	**0.0138**	1	0.85 to 1.2	0.9096

coagulation product and routine marker of TEEs, may therefore represent a prognostic biomarker in melanoma patients to predict TEEs [28].

Bleeding complications under ATT were not documented in this study. However, other studies including a randomized controlled clinical trial, in which the factor Xa inhibitor rivaroxaban was administered to cancer patients with a high risk for venous thromboembolism, did not find a significantly increased bleeding risk [29,30]. While Johann et al. found a significantly increased bleeding risk in patients with concomitant AC without survival benefits, Haist and Stege *et al.* did not observe an increased bleeding risk, but instead an increased PFS and OS in this melanoma cohort [16,18]. Of note, the latter study only reported an improved survival in patients with advanced (metastatic, non resectable) melanoma treated with DOAC, but not in patients treated with phenprocoumon [18]. In a randomized trial Schrag *et al.* recently demonstrated that both DOACs and LMWH had no increased bleeding risk and could be safety administered for TEEs in cancer patients [31].

As a limitation of the ADOReg, a non-pharmacological registry, the rate of 13.3 % (322/2419) with concomitant ATT may be present an underreporting of the true number. Data on dosage and frequency for prescription of concomitant ATT was not included in our study and we have a gap in the indications of the concomitant ATT of 54,0 % (174/322). While it can be assumed that most patients received the medication for primary or secondary prevention of cardiovascular or TEEs, a more detailed analysis of the benefit of antithrombotic therapy in cancer patients would require an analysis of the aforementioned data points and a detailed knowledge of the patients' comorbidities.

Here we show a clinical benefit of ATT in 322 melanoma patients from a real-world registry receiving ICI treatment compared to the control cohort of 2097 patients without anticoagulative therapy (total n = 2419). Our findings may warrant prospective clinical trials to further investigate the role of ATT in cancer patients. However, further translational studies are needed to determine the precise mechanisms of combining PAI or AC with ICIs for the treatment of patients with advanced melanoma.

5. Conclusion

Our study supports preclinical data highlighting the potential cancer-protective and ICI-synergistic effect of concomitant antithrombotic therapy on cancer progression in advanced melanoma patients treated with ICIs. Thus, when prescribing antithrombotic medication for cardiovascular prevention in this patient group, the potential cancer-related benefit might be included in clinical decision making. Prospective randomized trials are needed to confirm this potential effect of anticoagulation or platelet aggregation inhibition on ICI benefit.

Ethics approval and consent to participate

The registry is approved by the Medical Ethics committee of the University Duisburg-Essen (14–5921-BO).

Consent for publication

All authors declare their consent to this publication.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

JK has received honoraria from Bristol-Myers Squibb and Sanofi Genzyme and has received travel support from SUN Pharma and Pierre Fabre, outside the submitted work.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.115159.

Data Availability

The data and further material can be obtained on request from the corresponding authors.

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