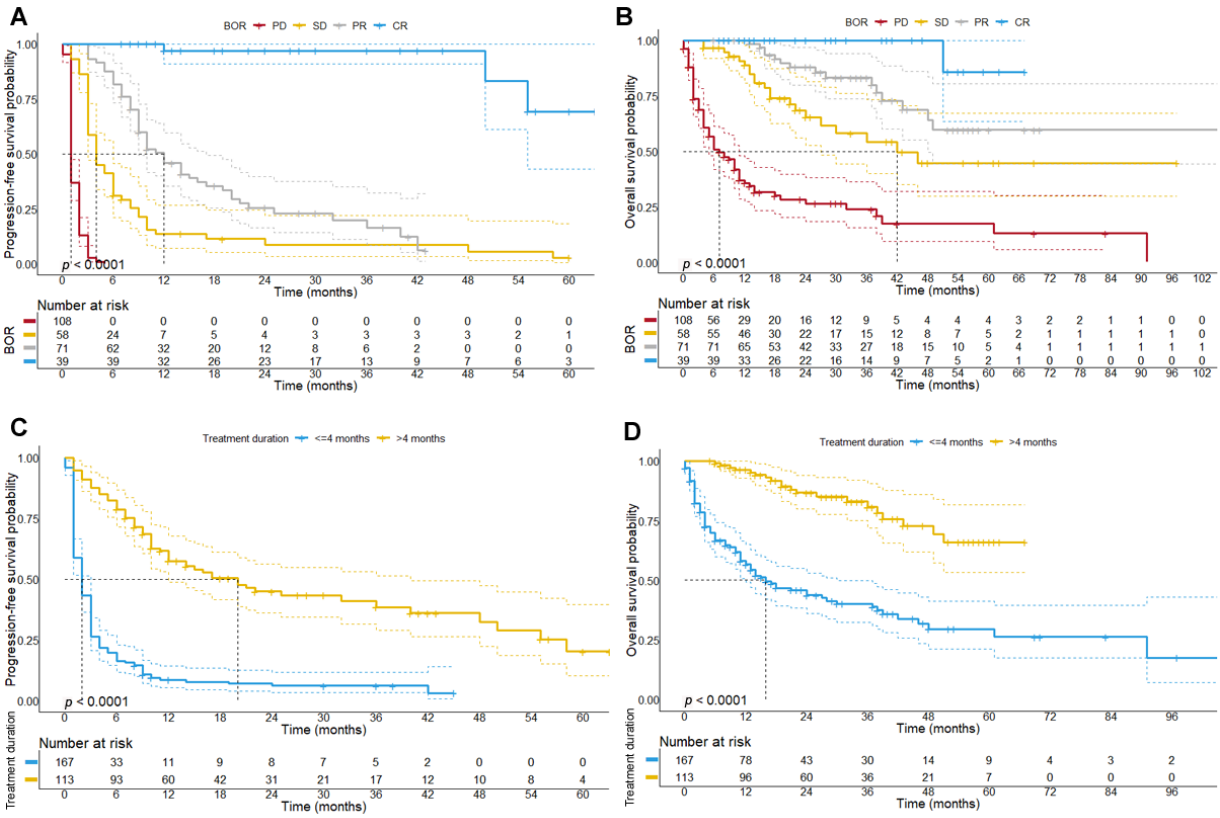
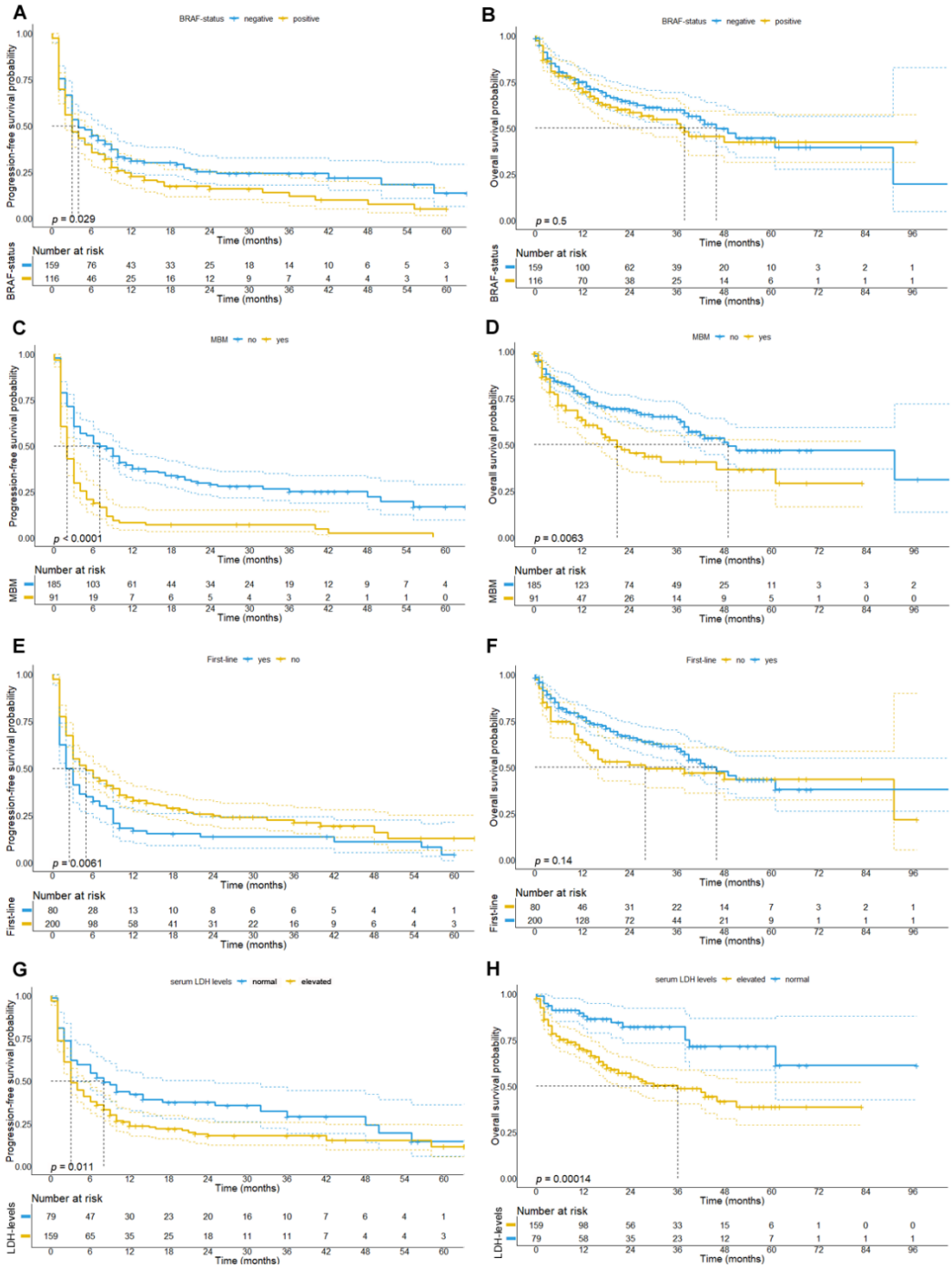
cancers

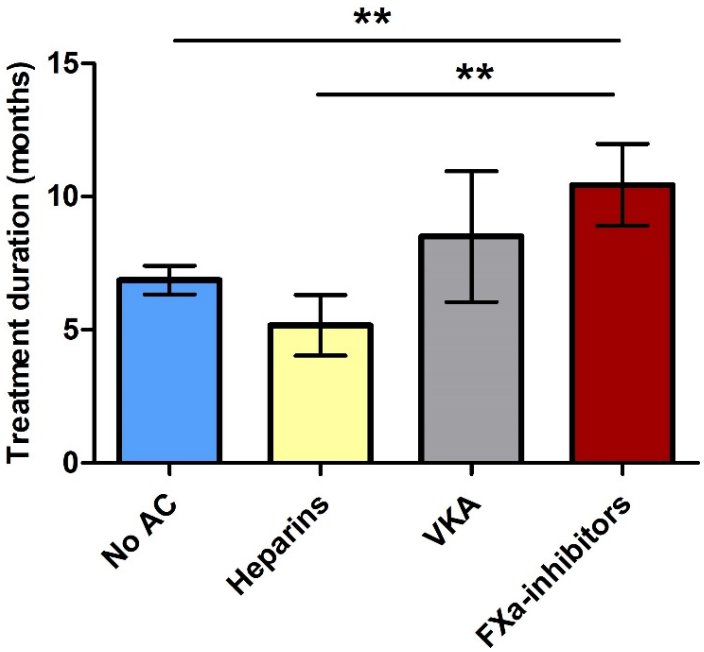
Supplementary Figures and Tables



Supplementary Figure S1: Kaplan Meier plots showing the progression-free (left) and overall survival probabilities of melanoma patients stratified by the BOR to initial ICI (top) and the duration of initial ICI therapy (bottom). Consistent with previous studies BOR has been the best predictor of PFS (median PFS: 0 vs 4 vs 12 months vs not reached, p<0.0001) (**A**) and OS (median OS: 7 vs 42 months vs not reached for PR and CR, p<0.0001) (**B**). It has further been found that patients remaining on initial ICI therapy for at least 5 months had a significantly longer PFS (1 month; 95% CI: 0 – 2.0 months, vs 20 months; 95% CI: 12.2 – 27.8 months; p<0.0001) (**C**) and OS (16 months vs not reached, p<0.0001) (**D**) as compared to patients receiving initial ICI therapy for less than 5 months.



Supplementary Figure S2: Kaplan Meier plots showing the progression-free (left) and overall survival probabilities (right) for melanoma patients stratified by BRAF-status (A,B), the presence of MBM (C,D), the administration of ICI in a first-line setting (E,F) and LDH-serum-levels (G,H). Patients with BRAF-mutated melanoma showed a worse PFS (median: 3 vs 4 months; p=0.032), but not OS (median: 38 vs 46 months; p=0.504) as compared to patients with BRAF-wildtype melanoma. Patients not developing MBM showed a significantly better PFS (median: 7 vs 1 months; p<0.0001) and OS (median: 21 vs 49 months; p=0.006) as compared to patients with MBM. Moreover, patients receiving ICI therapy in a first-line setting showed a significantly better PFS (median: 5 vs 2 months, p=0.006), but not OS (median: 46 vs 28 months, p=0.14) as compared to patients given ICI after systemic pretreatments. Notably, patients with normal serum LDH-levels (<245 U/l) showed a better PFS (median: 8 vs 3 months, p=0.01) and OS (median: not reached vs 36 months, p<0.0001) as compared to patients with elevated LDH-levels at ICI initiation.



Supplementary Figure S3: Treatment duration of initial ICI therapy stratified by the different categories of concomitant AC. Patients receiving concomitant FXa-inhibitors remained significantly longer on initial ICI therapy (mean: 10.4 months; 95% CI: 7.3-13.6 months) as compared to patients not receiving AC (mean: 6.9 months; 95% CI: 5.8-7.9 months) or those with concomitant heparin treatment (mean: 5.2 months; 95% CI: 2.8-7.5 months), whereas patients receiving VKA were heterogeneous in terms of ICI treatment duration (mean: 8.5 months; 95% CI: 3.4-13.6 months). When comparing patients with concomitant FXa-inhibitor therapy to all other subgroups combined, this association was below statistical significance (p=0.063). *Abbreviations: *p<0,05, **p<0,005, ***p<0,001.*

Supplementary Table S1: Univariate Cox proportional hazards model for progression-free survival

Variables	Subgroups	HR	95% CI	*p*-value
Age (years)	>66 vs ≤66	0.91	0.69-1.19	0.47
Gender	Female vs male	0.94	0.72-1.23	0.65
LDH	Elevated vs normal	1.51	1.1-2.08	**0.011**
Ulceration	No vs Yes	0.87	0.62-1.2	0.42
Breslow (mm)	≤2mm vs >2mm	0.89	0.65-1.22	0.46
AC-status	No vs Yes	0.95	0.71-1.28	0.73
AC-category	FXa-i vs other	0.48	0.28-0.81	**0.006**
BRAF status	Pos vs Neg	1.33	1.02-1.74	**0.036**
Brain metastases	Yes vs no	2.39	1.81-3.16	**<0.001**
Pretreatments	Yes vs no	1.17	0.89-1.52	0.26
Line of treatment	First vs other	0.67	0.5-0.89	**0.0056**
BOR to initial ICI	CR, PR vs SD,PD	0.14	0.10-0.19	**<0.001**
Treatment duration (months)	>4 vs ≤4	0.21	0.15-0.29	**<0.001**
Bleeding complications	No vs Yes	0.57	0.36-0.90	**0.016**

The p value is indicated in bold numbers when statistically significant. Abbreviations: AC = anticoagulation, FXai = Factor Xa-inhibitors, CR = complete response, PR = partial response, SD = stable disease, PD = Progressive disease, BOR = best overall response, HR = hazard ratio, CI = confidence interval

Supplementary Table S2: Univariate Cox proportional hazards model for overall survival

Variables	Subgroups	HR	95% CI	*p*-value
Age (years)	>66 vs ≤66	1.03	0.71-1.50	0.88
Gender	Female vs male	0.74	0.49-1.09	0.13
LDH	Elevated vs normal	2.74	1.59-4.71	**<0.001**
Ulceration	Yes vs No	0.91	0.56-1.46	0.68
Breslow (mm)	>2 vs ≤2	0.88	0.65-1.21	0.46
AC-status	No vs Yes	0.81	0.54-1.22	0.32
AC-category	FXa-i vs other	0.49	0.22-1.12	0.09
BRAF status	Pos vs Neg	1.14	0.78-1.65	0.49
Brain metastases	Yes vs no	1.69	1.16-2.45	**0.007**
Pretreatments	Yes vs no	1.07	0.73-1.55	0.73
Line of treatment	First vs other	0.74	0.51-1.1	0.13
BOR to initial ICI	CR, PR vs SD,PD	0.15	0.09-0.25	**<0.001**
Treatment duration (months)	>4 vs ≤4	0.20	0.12-0.32	**<0.001**
Post-ICI treatment lines	=>1 vs 0	0.67	0.43-1.04	0.074
Bleeding complications	No vs Yes	0.42	0.25-0.71	**0.001**

The p value is indicated in bold numbers when statistically significant. Abbreviations: AC = anticoagulation, FXai = Factor Xa-inhibitors, CR = complete response, PR = partial response, SD = stable disease, PD = Progressive disease, BOR = best overall response, HR = hazard ratio, CI = confidence interval

Supplementary Table S3: Multivariate Cox proportional hazards model for progression-free survival.

Variables	Subgroups	HR	95% CI	*p*-value
LDH	Elevated vs normal	1.43	1.03-1.99	**0.035**
BRAF status	Pos vs Neg	1.25	0.90-1.74	0.192
Brain metastases	Yes vs No	2.26	1.62-3.14	**<0.001**
Treatment duration (months)	>4 vs ≤4	0.23	0.16-0.33	**0.003**
BOR to initial ICI	CR, PR vs SD, PD	0.19	0.11-0.33	**<0.001**
AC-category	FXa-i vs other	0.53	0.27-0.81	**0.007**

The p value is indicated in bold numbers when statistically significant. Abbreviations: AC = anticoagulation, FXai = Factor Xa-inhibitors, CR = complete response, PR = partial response, SD = stable disease, PD = Progressive disease, BOR = best overall response, HR = hazard ratio, CI = confidence interval

Supplementary Table S4: Multivariate Cox proportional hazards model for overall survival.

Variables	Subgroups	HR	95% CI	*p*-value
LDH	Elevated vs normal	2.18	1.23-3.87	**0.008**
Brain metastases	Yes vs No	1.95	1.18-3.24	**0.01**
AC-category	FXa-i vs other	0.77	0.32-1.81	0.55
Treatment duration (months)	>4 vs ≤4	0.28	0.14-0.56	**<0.001**
BOR to initial ICI	CR, PR vs SD, PD	0.17	0.10-0.31	**<0.001**
Post-ICI treatment lines	0 vs >=1	0.25	0.15-0.44	**<0.001**
Bleeding complications	No vs Yes	0.52	0.28-0.97	**0.04**

The p value is indicated in bold numbers when statistically significant. Abbreviations: AC = anticoagulation, FXai = Factor Xa-inhibitors, CR = complete response, PR = partial response, SD = stable disease, PD = Progressive disease, BOR = best overall response, HR = hazard ratio, CI = confidence interval

Supplementary Table S5: Patient demographics, tumor characteristics and specifics on concomitant AC treatment stratified by the class of AC received during initial ICI. Chi-square test and ANOVA variance analysis revealed no significant differences between the different subcohorts, except for patients given FXa-inhibitors presented with thicker melanomas at initial diagnosis and patients on concomitant heparin treatment less often received initial ICI in a first-line setting.

	Heparins	**Vit-K Antagonists**	**FXa inhibitors**	*p*-value
Reasons for AC[1]				0.34
- DVT	11	3	9	
- PE	6	12	4	
- AF	1	2	13	
- Other	11	3	1	
Thromboembolic events during ICI	13 (59.3%)	3 (40%)	9 (31.0%)	0.095
PTT	29.2	33.8	30.4	**0.04**
Mean Age at ICI initiation (years)	64.1	70.5	71.0	0.13
Gender (female)	13 (44.8%)	5 (25.0%)	11 (40.7%)	0.35
Mean Breslow thickness (mm)	2.1	3.4	3.4	**0.04**
Ulceration	8 (27.6%)	10 (50.0%)	10 (37.0%)	0.70
BRAF-mutation	12 (41.4%)	7 (35.0%)	9 (33.3%)	0.83
LDH	385.8	322.7	382.0	0.75
Brain metastases	12 (41.4%)	4 (20.0%)	10 (37.0%)	0.27
Pre-treatments	14 (48.3%)	6 (30.0%)	8 (29.6%)	0.27
First	16 (55.2%)	16 (80.0%)	23 (85.2%)	**0.03**
Class of ICI (cICB)	7 (24.1%)	4 (20.0%)	9 (33.3%)	0.61
Post-treatment lines	22 (75.9%)	10 (50.0%)	11 (40.7%)	0.097
ICI-Rechallange	13 (44.8%)	9 (45.0%)	7 (29.6%)	0.44

[1] Reasons for anticoagulation as documented in the medical chart review. For n=7 patients no data on the reasons for AC have been available. The p value is indicated in bold numbers when statistically significant. Abbreviations: DVT= deep vein thrombosis, AF= atrial fibrillation; PE= pulmonary embolism; ICI = immune-checkpoint-inhibitor(s); cICB = combined immune-checkpoint blockade.

Supplementary Table S6: Status of ICI treatment at the time of data cut-off and reasons for treatment discontinuation stratified by the different AC categories.

	No AC	**heparins**	**Vit-K Antagonists**	**FXa inhibitors**
Ongoing	13 (6.4%)	0	2 (10%)	6 (21.4%)
Cessation due to toxicity	51 (25.0%)	5 (17.3%)	3 (15%)	8 (28.6%)
Cessation due to progression	80 (39.4%)	16 (59.3%)	8 (40%)	4 (14.8%)
Other reasons[1]	59 (28.9%)	8 (27.6%)	7 (35%)	10 (37.0%)

Abbreviations: [1] Other reasons include wish of the patient, ongoing subclinical toxicity or regular treatment cessation upon long-term complete response