

Supplementary Table 1 | Detailed summary of included tumor entities in the discovery and validation cohorts. NSCLC – non small cell lung cancer, RCC – renal cell carcinoma, UC – urothelial carcinoma, HNC – head and neck cancer, CRC – colorectal cancer, SCLC – small cell lung cancer, CUP – cancer of unknown primary, HCC – hepatocellular carcinoma

	Discovery cohort 1 (n=562)	Validation cohort 2 (n=474)
Cancer types		
NSCLC	231 (41.1%)	126 (26.6%)
Melanoma	95 (16.9%)	172 (36.3%)
RCC	73 (13%)	38 (8.0%)
UC	46 (8.2%)	21 (4.4%)
HNC	20 (3.6%)	32 (6.8%)
CRC	12 (2.1%)	8 (1.7%)
SCLC	6 (1.1%)	2 (0.4%)
Breast cancer	11 (2%)	
CUP	9 (1.6%)	2 (0.4%)
Prostate cancer	3 (0.5%)	
Esophagus/gastric cancer	12 (2.1%)	1 (0.2%)
Mesothelioma	2 (0.4%)	4 (0.8%)
Small bowel	1 (0.2%)	
Pancreatic cancer	4 (0.7%)	
Merkel cell carcinoma		5 (1.1%)
Anal carcinoma	3 (0.5%)	
Squamous cell (skin)	3 (0.5%)	
Thymic carcinoma	2 (0.4%)	
Thyroid carcinoma	2 (0.4%)	
Bile duct carcinoma	1 (0.2%)	
Cervical cancer	1 (0.2%)	7 (1.5%)
HCC	1 (0.2%)	13 (2.7%)
Sarcoma	2 (0.4%)	14 (3.0%)
Other cancers	22 (3.9%)	29 (6.1%)

Supplementary Table 2 | Uni- and multivariable logistic regression models for the original and refined model for early CRP kinetics in the validation cohort. OR – odds ratio, CI – confidence interval

Variable	Original model				Refined model	
	Univariable analysis		Multivariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (continuously coded)	1.001 (0.987-1.016)	0.851				
Sex						
Male	1 (reference)					
Female	0.893 (0.603-1.324)	0.574				
ECOG						
ECOG 1	1 (reference)		1 (reference)		1 (reference)	
ECOG >1	0.522 (0.319-0.852)	0.009	0.489 (0.273-0.875)	0.016	0.510 (0.285-0.914)	0.024
Charlson Index	1.015 (0.927-1.111)	0.747				
Baseline CRP						
Low (<median)	1 (reference)		1 (reference)		1 (reference)	
High (>=median)	0.616 (0.416-0.912)	0.015	0.699 (0.440-1.109)	0.129	0.733 (0.439-1.225)	0.236
Cancer type						
NSCLC	1 (reference)		1 (reference)		1 (reference)	
Melanoma	1.330 (0.802-2.204)	0.269	1.022 (0.595-1.755)	0.938	0.950 (0.549-1.645)	0.855
RCC	0.840 (0.361-1.955)	0.685	0.765 (0.314-1.862)	0.555	0.781 (0.321-1.900)	0.586
UC	0.637 (0.200-2.027)	0.445	0.648 (0.195-2.155)	0.479	0.611 (0.184-2.033)	0.422
Other	1.843 (1.074-3.164)	0.027	2.022 (1.127-3.626)	0.018	1.941 (1.081-3.486)	0.026
Stage at ICI start						
II+III	1 (reference)				1 (reference)	
IV	1.549 (0.767-3.129)	0.222			0.294 (0.121 -0.716)	0.007
Treatment line						
1 st line	1 (reference)					
2 nd line or higher	0.691 (0.463-1.031)	0.070				
Additional treatments						
No additional treatment	1 (reference)					
Radiotherapy	1.431 (0.831-2.463)	0.196				
Chemotherapy	1.454 (0.620-5.748)	0.264				
Targeted therapy	2.356 (0.292-1.277)	0.191				
CRP response						
CRP non-responder	1 (reference)		1 (reference)			
CRP responder	1.440 (0.940-2.207)	0.094	1.515 (0.963-2.384)	0.072		
CRP flare-responder	2.856 (1.548-5.270)	0.001	3.015 (1.595-5.700)	0.001		

Variable	Original model				Refined model	
	Univariable analysis		Multivariable analysis		Multivariable analysis	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
CRP response						
CRP non-responder	1 (reference)				1 (reference)	
CRP responder	1.729 (1.061-2.819)	0.028			1.792 (1.065-3.017)	0.028
CRP flare-responder	3.073 (1.599-5.907)	0.001			3.045 (1.544-6.003)	0.001
All-normal CRP	2.207 (1.302-3.742)	0.003			1.670 (0.919-3.034)	0.093

Supplementary Table 3 | Uni- and multivariable Cox regression models for PFS for the original and refined model for early CRP kinetics in the validation cohort. HR – hazard ratio, CI – confidence interval

Variable	Original model				Refined model	
	Univariable analysis		Multivariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (continuously coded)	1.00 (0.99-1.01)	0.578				
Sex						
Male	1 (reference)					
Female	1.08 (0.87-1.34)	0.484				
ECOG						
ECOG 1	1 (reference)		1 (reference)		1 (reference)	
ECOG >1	1.83 (1.44-2.33)	<0.001	1.64 (1.22-2.19)	0.001	1.62 (1.21-2.17)	0.001
Charlson Index	1.04 (1.00-1.10)	0.078				
Baseline CRP						
Low (<median)	1 (reference)		1 (reference)		1 (reference)	
High (>=median)	1.95 (1.57-2.42)	<0.001	1.88 (1.47-2.41)	<0.001	1.81 (1.39-2.36)	<0.001
Cancer type						
NSCLC	1 (reference)		1 (reference)		1 (reference)	
Melanoma	0.72 (0.55-0.95)	0.022	1.06 (0.78-1.42)	0.717	1.12 (0.83-1.51)	0.463
RCC	0.79 (0.52-1.22)	0.285	0.79 (0.51-1.22)	0.287	0.78 (0.50-1.21)	0.273
UC	1.81 (1.10-2.97)	0.019	2.18 (1.30-3.64)	0.003	2.36 (1.41-3.95)	0.001
Other	0.81 (0.60-1.08)	0.156	0.79 (0.58-1.08)	0.147	0.80 (0.58-1.09)	0.164
Stage at ICI start						
II+III	1 (reference)					
IV	1.22 (0.87-1.72)	0.254				
Treatment line						
1 st line	1 (reference)					
2 nd line or higher	1.24 (0.99-1.56)	0.060				
Additional treatments						
No additional treatments	1 (reference)					
Radiotherapy	1.08 (0.80-1.46)	0.617				
Chemotherapy	0.91 (0.45-1.84)	0.794				
Targeted therapy	1.12 (0.78-1.59)	0.547				
CRP response						
CRP non-responder	1 (reference)		1 (reference)			
CRP responder	0.92 (0.72-1.16)	0.476	0.76 (0.59-0.98)	0.026		
CRP flare-responder	0.65 (0.43-0.97)	0.034	0.66 (0.44-0.99)	0.044		

Variable	Original model				Refined model	
	Univariable analysis		Multivariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
CRP response						
CRP non-responder	1 (reference)				1 (reference)	
CRP responder	0.79 (0.62-1.02)	0.072			0.64 (0.49-0.83)	0.001
CRP flare-responder	0.59 (0.40-0.89)	0.011			0.63 (0.41-0.95)	0.026
All-normal CRP	0.47 (0.33-0.66)	<0.001			0.62 (0.43-0.90)	0.011

Supplementary Table 4 | Uni- and multivariable Cox regression models for OS for the original and refined model for early CRP kinetics in the validation cohort. HR – hazard ratio, CI – confidence interval

Variable	Original model				Refined model	
	Univariable analysis		Multivariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (continuously coded)	1.01 (1.00-1.02)	0.029	1.00 (0.99-1.02)	0.640	1.002 (0.99-1.01)	0.746
Sex						
Male	1 (reference)					
Female	1.19 (0.90-1.59)	0.207				
ECOG						
ECOG 1	1 (reference)		1 (reference)		1 (reference)	
ECOG >1	2.69 (2.00-3.62)	<0.001	2.09 (1.43-3.06)	<0.001	2.10 (1.43-3.07)	<0.001
Charlson Index	1.05 (0.99-1.12)	0.117			1.07 (1.03-1.11)	<0.001
Baseline CRP						
Low (<median)	1 (reference)		1 (reference)		1 (reference)	
High (>=median)	2.63 (1.99-3.48)	<0.001	2.29 (1.59-3.02)	<0.001	1.86 (1.32-2.61)	<0.001
Cancer type						
NSCLC	1 (reference)		1 (reference)		1 (reference)	
Melanoma	0.51 (0.35-0.73)	<0.001	0.87 (0.58-1.31)	0.503	0.94 (0.62-1.41)	0.749
RCC	0.83 (0.49-1.42)	0.499	0.80 (0.46-1.39)	0.431	0.79 (0.45-1.36)	0.391
UC	1.43 (0.75-2.72)	0.278	1.71 (0.86-3.40)	0.127	1.90 (0.95-3.78)	0.069
Other	0.78 (0.54-1.12)	0.177	0.73 (0.48-1.12)	0.154	0.74 (0.48-1.13)	0.162
Stage at ICI start						
II+III	1 (reference)					
IV	0.95 (0.62-1.45)	0.819				
Treatment line						
1 st line	1 (reference)		1 (reference)		1 (reference)	
2 nd line or higher	1.35 (1.00-1.83)	0.049	1.16 (0.83-1.63)	0.370	1.15 (0.82-1.61)	0.421
Additional treatments						
No additional treatments	1 (reference)					
Radiotherapy	0.84 (0.56-1.25)	0.384				
Chemotherapy	0.56 (0.21-1.51)	0.250				
Targeted therapy	0.93 (0.59-1.46)	0.749				
CRP response						
CRP non-responder	1 (reference)		1 (reference)			
CRP responder	0.99 (0.73-1.34)	0.959	0.82 (0.60-1.13)	0.225		
CRP flare-responder	0.71 (0.43-1.18)	0.187	0.75 (0.44-1.27)	0.289		

Variable	Original model				Refined model	
	Univariable analysis		Multivariable analysis		Multivariable analysis	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
CRP response						
CRP non-responder	1 (reference)				1 (reference)	
CRP responder	0.82 (0.60-0.81)	0.221			0.71 (0.52-0.99)	0.042
CRP flare-responder	0.56 (0.34-0.95)	0.031			0.67 (0.39-1.14)	0.143
All-normal CRP	0.27 (0.17-0.45)	<0.001			0.42 (0.25-0.73)	0.002

Supplementary Table 5: Characteristics of the pooled study cohorts. P-values indicate differences between CRP response groups.

Pooled cohort (n=1036)		Non-CRP responder	CRP responder	CRP flare responder	All-normal CRP		
		N=430 (41.5%)	N=338 (32.6%)	N=117 (11.3%)	N=151 (14.6%)		
	n (%miss.)	Summary measure				p-value	
Sex	1036 (0%)						
---male		635 (61.3%)	265 (61.6%)	216 (63.9)	63 (53.9)	91 (60.3)	0.285
---female		401 (38.7%)	165 (38.4)	122 (36.1)	54 (46.1)	60 (39.7)	
Age (years)		65 [IQR 55.8-72.5]	66.4 [IQR 57-73]	64.5 [IQR 54.7-72.9]	62.5 [55.8 -74.8]	66.3 [51 -72.4]	0.171
ECOG	842 (18.7%)						
---ECOG 0		333 (32.1%)	118 (27.4%)	90 (26.6%)	35 (29.9%)	90 (59.6%)	<0.001
---ECOG >0		509 (49.1%)	128 (50.7%)	179 (53%)	66 (56.4%)	46 (30.5%)	
Charlson Index	1036 (0%)	9 [IQR 8-10]	9 [8-10]	9 [9-10]	9 [9-11]	9 [8-10]	0.011
Cancer types	1036 (0%)						
---NSCLC		357 (34.5%)	160 (37.2%)	122 (36.1%)	48 (41%)	27 (17.9%)	<0.001
---Melanoma		268 (25.9%)	88 (20.5%)	78 (23.1%)	28 (23.9%)	74 (49%)	
---RCC		111 (10.7%)	48 (11.2%)	38 (11.2%)	11 (9.4%)	14 (9.3%)	
---UC		67 (6.5%)	33 (7.7%)	17 (5%)	10 (8.6%)	7 (4.6%)	
---other		223 (22.5%)	101 (23.5%)	83 (24.6%)	20 (17.1%)	29 (19.2%)	
Tumor stage at ICI start	990 (4.4%)						
---II+III		70 (6.8%)	29 (6.7%)	21 (6.2%)	5 (4.3%)	15 (9.9%)	0.375
---IV		920 (88.8%)	386 (89.8%)	302 (89.4%)	104 (88.9%)	128 (84.3%)	
ICI							
Treatment line	1033 (0.3%)						
---1 st line		414 (40%)	149 (34.7%)	139 (41.1%)	55 (47%)	71 (47%)	0.024
---2 nd line or higher		619 (59.8%)	278 (64.7%)	199 (58.9%)	62 (53%)	80 (53%)	
ICI agent	1036 (0%)						
---Nivolumab		438 (42.3%)	185 (43%)	146 (43.2%)	47 (40.2%)	60 (39.4%)	0.003
---Pembrolizumab		435 (42%)	191 (44.4%)	138 (40.8%)	43 (36.8%)	63 (41.7%)	
---Atezolizumab		41 (4%)	22 (5.1%)	13 (3.9%)	5 (4.3%)	1 (0.7%)	
---Durvalumab		4 (0.4%)	0 (0%)	1 (0.9%)	1 (0.9%)	0 (0%)	
---Ipilimumab		54 (5.2%)	14 (3.3%)	19 (5.6%)	5 (4.3%)	16 (10.6%)	
---Avelumab		4 (0.4%)	1 (0.2%)	1 (0.3%)	1 (0.9%)	1 (0.7%)	
---Nivolumab/Ipilimumab		60 (5.8%)	17 (4%)	18 (5.3%)	15 (12.8%)	10 (6.6%)	
Additional treatments	1036 (0%)						
---Chemotherapy		70 (6.8%)	18 (4.2%)	32 (9.5%)	10 (8.6%)	10 (6.6%)	0.029
---Radiotherapy		93 (9%)	26 (6.1%)	31 (9.2%)	16 (13.7%)	20 (13.3%)	0.011
---Targeted therapy		57 (5.5%)	23 (5.4%)	15 (4.4%)	8 (6.8%)	11 (7.3%)	0.556

Supplementary Table 6 | Exploratory uni- and multivariable Cox regression models for PFS in the refined model of early CRP kinetics excluding CRP at baseline. HR – hazard ratio, CI – confidence interval

Variable	Univariable analysis		Refined model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (continuously coded)	0.99 (0.99-1.00)	0.096		
Sex				
Male	1 (reference)			
Female	1.13 (0.94-1.35)	0.202		
ECOG				
ECOG 1	1 (reference)		1 (reference)	
ECOG >1	1.50 (1.12-2.00)	0.007	1.49 (1.10-2.00)	0.009
Charlson Index	1.00 (0.97-1.03)	0.936		
Cancer type				
NSCLC	1 (reference)		1 (reference)	
Melanoma	0.90 (0.70-1.16)	0.426	0.91 (0.70-1.18)	0.465
RCC	0.73 (0.55-0.98)	0.035	0.70 (0.52-0.94)	0.017
UC	1.37 (0.99-1.89)	0.057	1.33 (0.96-1.84)	0.089
Other	1.13 (0.89-1.44)	0.315	1.15 (0.90-1.47)	0.248
Metastatic sites	1.08 (0.99-1.17)	0.076		
Stage at ICI start				
II+III	1 (reference)			
IV	1.57 (1.00-2.49)	0.053		
Treatment line				
1 st line	1 (reference)			
2 nd line or higher	1.20 (1.00-1.44)	0.050		
CRP response				
CRP non-responder	1 (reference)		1 (reference)	
CRP responder	0.59 (0.48-0.73)	<0.001	0.58 (0.47-0.71)	<0.001
CRP flare-responder	0.66 (0.49-0.89)	0.006	0.61 (0.45-0.83)	0.002
All-normal CRP	0.56 (0.40-0.78)	0.001	0.60 (0.43-0.84)	0.003

Supplementary Table 7 | Exploratory uni- and multivariable Cox regression models for OS in the refined model of early CRP kinetics excluding CRP at baseline. HR – hazard ratio, CI – confidence interval

Variable	Univariable analysis		Refined model Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (continuously coded)	1.00 (0.99-1.01)	0.385		
Sex				
Male	1 (reference)			
Female	1.08 (0.87-1.34)	0.477		
ECOG				
ECOG 1	1 (reference)		1 (reference)	
ECOG >1	2.07 (1.39-3.10)	<0.001	1.87 (1.25-2.80)	0.002
Charlson Index	1.10 (1.06-1.14)	<0.001	1.07 (1.03-1.11)	<0.001
Cancer type				
NSCLC	1 (reference)		1 (reference)	
Melanoma	0.76 (0.57-1.02)	0.071	0.71 (0.52-0.95)	0.022
RCC	0.46 (0.31-0.69)	<0.001	0.43 (0.28-0.65)	<0.001
UC	1.66 (1.14-2.41)	0.008	1.63 (1.11-2.39)	0.012
Other	1.11 (0.84-1.47)	0.462	1.01 (0.76-1.34)	0.963
Metastatic sites	1.21 (1.10-1.33)	<0.001	1.24 (1.11-1.38)	<0.001
Stage at ICI start				
II+III	1 (reference)		1 (reference)	
IV	2.03 (1.08-3.80)	0.028	1.55 (0.80-3.01)	0.196
Treatment line				
1 st line	1 (reference)			
2 nd line or higher	1.14 (0.92-1.41)	0.315		
CRP response				
CRP non-responder	1 (reference)		1 (reference)	
CRP responder	0.64 (0.50-0.81)	<0.001	0.57 (0.45-0.73)	<0.001
CRP flare-responder	0.75 (0.54-1.06)	0.104	0.59 (0.42-0.84)	0.004
All-normal CRP	0.46 (0.31-0.69)	<0.001	0.52 (0.34-0.78)	0.002

Supplementary Table 8 | Uni- and multivariable logistic regression models for ORR for the original and refined model for early CRP kinetics -sensitivity analysis including age, cancer type and stage a priori in the multivariable analysis. OR – odds ratio, CI – confidence interval

Variable	Original model				Refined model	
	Univariable analysis	Multivariable analysis		Multivariable analysis		
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (continuously coded)	1.028 (1.003-1.034)	0.022	1.024 (1.004-1.044)	0.017	1.022 (1.002-1.042)	0.027
Sex						
Male	1 (reference)					
Female	0.771 (0.528-1.126)	0.178				
ECOG						
ECOG 1	1 (reference)					
ECOG >1	0.690 (0.395-1.204)	0.191				
Charlson Index	0.995 (0.889-1.026)	0.209				
Baseline CRP						
Low (<median)	1 (reference)		1 (reference)		1 (reference)	
High (≥median)	0.676 (0.465-0.983)	0.040	0.591 (0.383-0.913)	0.018	0.635 (0.397-1.017)	0.059
Cancer type						
NSCLC	1 (reference)		1 (reference)		1 (reference)	
Melanoma	1.270 (0.761-2.120)	0.361	1.108 (0.620-1.981)	0.729	1.105 (0.620-1.971)	0.735
RCC	1.078 (0.606-1.918)	0.797	1.599 (0.838-3.050)	0.155	1.448 (0.757-2.770)	0.263
UC	0.526 (0.233-1.188)	0.122	0.589 (0.245-1.412)	0.234	0.629 (0.263-1.502)	0.296
Other	0.714 (0.424-1.203)	0.206	0.923 (0.509-1.676)	0.793	0.936 (0.516-1.696)	0.826
Metastatic sites	0.988 (0.831-1.175)	0.896				
Stage at ICI start						
II+III	1 (reference)		1 (reference)		1 (reference)	
IV	0.284 (0.126-0.641)	0.002	0.319 (0.130-1.780)	0.012	0.281 (0.113 -0.698)	0.006
Treatment line						
1 st line	1 (reference)		1 (reference)		1 (reference)	
2 nd line or higher	0.448 (0.307-0.655)	<0.001	0.478 (0.313-0.731)	0.001	0.478 (0.313-0.731)	0.001
Additional treatments						
no additional treatment	1 (reference)					
Radiotherapy	1.413 (0.418-4.774)	0.577				
Chemotherapy	1.454 (0.795-2.658)	0.224				
Targeted therapy	2.356 (0.707-7.852)	0.163				

Variable	Original model				Refined model	
	Univariable analysis		Multivariable analysis		Multivariable analysis	
	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value	OR (95% CI)	<i>p</i> -value
CRP response						
CRP non-responder	1 (reference)		1 (reference)			
CRP responder	4.230 (2.714-6.593)	<0.001	4.830 (3.005-7.764)	<0.001		
CRP flare-responder	3.030 (1.639-5.603)	<0.001	3.222 (1.683-6.166)	<0.001		
CRP response						
CRP non-responder	1 (reference)				1 (reference)	
CRP responder	4.385 (2.702-7.117)	<0.001			4.963 (2.959-8.321)	<0.001
CRP flare-responder	3.310 (1.741-6.294)	<0.001			3.382 (1.722-6.641)	<0.001
All-normal CRP	4.992 (2.592-9.614)	<0.001			3.695 (1.825-7.480)	<0.001

Supplementary Table 9 | Uni- and multivariable Cox regression models for PFS for the original and refined model for early CRP kinetics - sensitivity analysis including age, cancer type and stage a priori in the multivariable analysis. OR – odds ratio, CI – confidence interval

Variable	Original model				Refined model	
	Univariable analysis		Multivariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (continuously coded)	0.99 (0.99-1.00)	0.096	0.99 (0.98-0.99)	0.40	0.99 (0.98-0.99)	0.036
Sex						
Male	1 (reference)					
Female	1.13 (0.94-1.35)	0.202				
ECOG						
ECOG 1	1 (reference)		1 (reference)		1 (reference)	
ECOG >1	1.50 (1.12-2.00)	0.007	1.28 (0.95-1.73)	0.103	1.36 (1.01-1.83)	0.046
Charlson Index	1.00 (0.97-1.03)	0.936				
Baseline CRP						
Low (<median)	1 (reference)		1 (reference)		1 (reference)	
High (>=median)	1.46 (1.22-1.75)	<0.001	1.65 (1.36-2.00)	<0.001	1.79 (1.45-2.21)	<0.001
Cancer type						
NSCLC	1 (reference)		1 (reference)		1 (reference)	
Melanoma	0.90 (0.70-1.16)	0.426	1.01 (0.77-1.33)	0.838	1.01 (0.77-1.33)	0.918
RCC	0.73 (0.55-0.98)	0.035	0.63 (0.47-0.85)	0.003	0.66 (0.49-0.89)	0.007
UC	1.37 (0.99-1.89)	0.057	1.38 (0.99-1.91)	0.057	1.30 (0.93-1.81)	0.123
Other	1.13 (0.89-1.44)	0.315	1.13 (0.88-1.45)	0.352	1.16 (0.90-1.49)	0.253
Metastatic sites	1.08 (0.99-1.17)	0.076				
Stage at ICI start						
II+III	1 (reference)		1 (reference)		1 (reference)	
IV	1.57 (1.00-2.49)	0.053	1.45 (0.90-2.31)	0.123	1.47 (0.92-2.36)	0.103
Treatment line						
1 st line	1 (reference)					
2 nd line or higher	1.20 (1.00-1.44)	0.050				
Additional treatments						
no additional treatment	1 (reference)					
Radiotherapy	1.051 (0.592-1.868)	0.864				
Chemotherapy	1.063 (0.777-1.453)	0.703				
Targeted therapy	0.442 (0.183-1.067)	0.070				

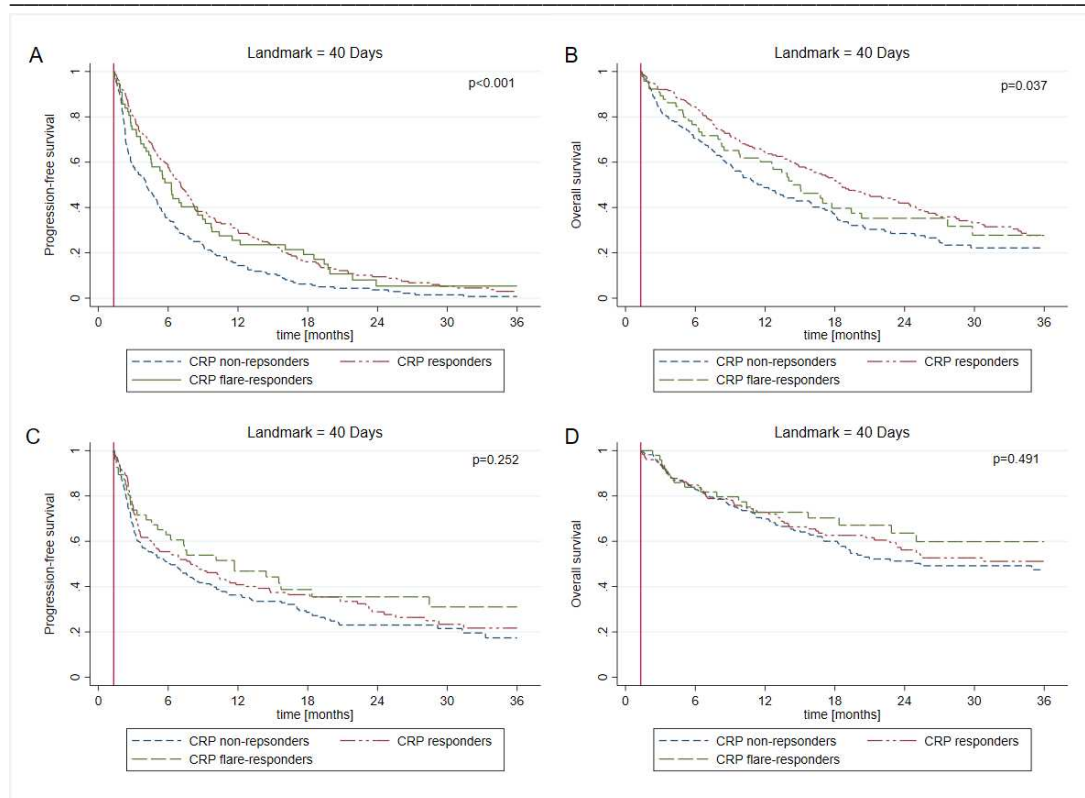
Variable	Original model				Refined model	
	Univariable analysis		Multivariable analysis		Multivariable analysis	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
CRP response						
CRP non-responder	1 (reference)		1 (reference)			
CRP responder	0.63 (0.51-0.77)	<0.001	0.52 (0.42-0.65)	<0.001		
CRP flare-responder	0.68 (0.51-0.92)	0.013	0.61 (0.45-0.83)	0.002		
CRP response						
CRP non-responder	1 (reference)				1 (reference)	
CRP responder	0.59 (0.48-0.73)	<0.001			0.48 (0.38-0.59)	<0.001
CRP flare-responder	0.66 (0.49-0.89)	0.006			0.63 (0.46-0.85)	0.001
All-normal CRP	0.56 (0.40-0.78)	0.001			0.74 (0.52-1.05)	0.078

Supplementary Table 10 | Uni- and multivariable Cox regression models for OS for the original and refined model for early CRP kinetics - sensitivity analysis including age, cancer type and stage a priori in the multivariable analysis. OR – odds ratio, CI – confidence interval

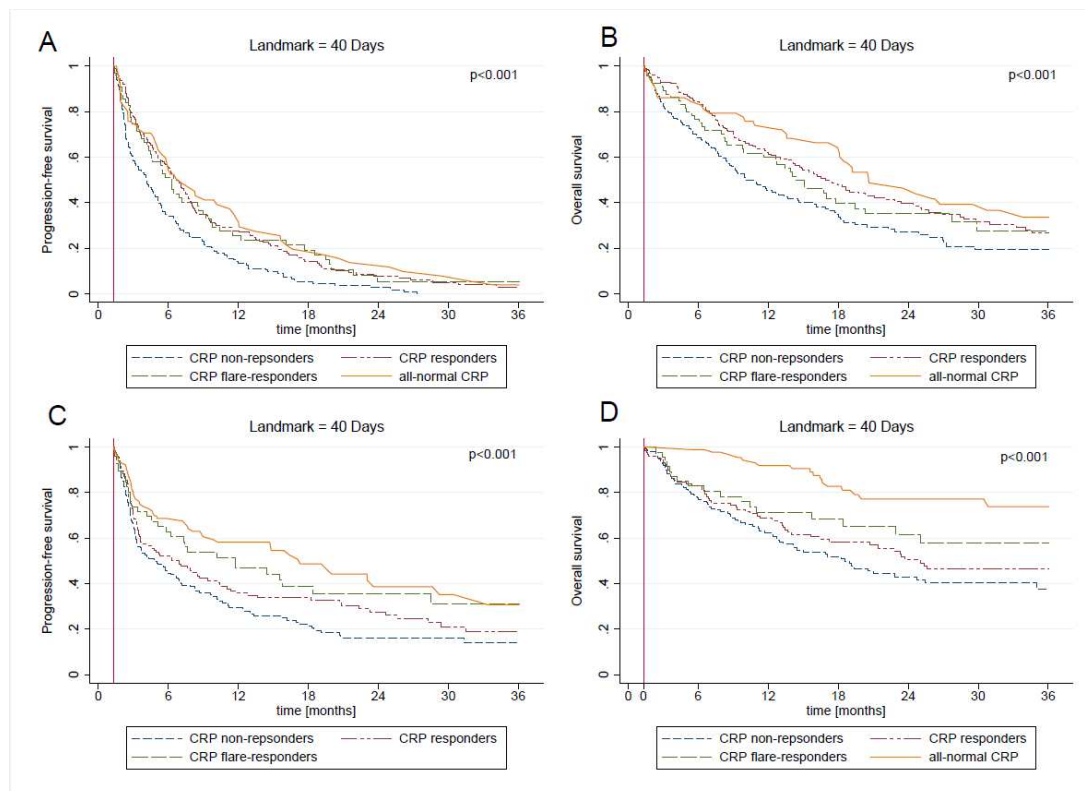
Variable	Original model				Refined model	
	Univariable analysis		Multivariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (continuously coded)	1.00 (0.99-1.01)	0.385	0.99 (0.98-1.00)	0.170	0.99 (0.98-1.00)	0.124
Sex						
Male	1 (reference)					
Female	1.08 (0.87-1.34)	0.477				
ECOG						
ECOG 1	1 (reference)		1 (reference)		1 (reference)	
ECOG >1	2.07 (1.39-3.10)	<0.001	1.74 (1.16-2.62)	0.008	1.78 (1.18-2.68)	0.006
Charlson Index	1.10 (1.06-1.14)	<0.001	1.08 (1.04-1.12)	<0.001	1.08 (1.04-1.13)	<0.001
Baseline CRP						
Low (<median)	1 (reference)		1 (reference)		1 (reference)	
High (>=median)	1.79 (1.45-2.20)	<0.001	1.87 (1.49-2.35)	<0.001	2.00 (1.57-2.55)	<0.001
Cancer type						
NSCLC	1 (reference)		1 (reference)		1 (reference)	
Melanoma	0.76 (0.57-1.02)	0.071	0.84 (0.62-1.14)	0.254	0.85 (0.62-1.15)	0.293
RCC	0.46 (0.31-0.69)	<0.001	0.43 (0.28-0.65)	<0.001	0.44 (0.29-0.66)	<0.001
UC	1.66 (1.14-2.41)	0.008	1.81 (1.24-2.65)	0.002	1.70 (1.16-2.50)	0.007
Other	1.11 (0.84-1.47)	0.462	1.09 (0.81-1.47)	0.560	1.09 (0.81-1.47)	0.560
Metastatic sites	1.21 (1.10-1.33)	<0.001	1.17 (1.05-1.30)	0.005	1.19 (1.07-1.33)	0.001
Stage at ICI start						
II+III	1 (reference)		1 (reference)		1 (reference)	
IV	2.03 (1.08-3.80)	0.028	1.63 (0.84-3.17)	0.149	1.62 (0.83-3.15)	0.155
Treatment line						
1 st line	1 (reference)					
2 nd line or higher	1.14 (0.92-1.41)	0.315				
Additional treatments						
no additional treatment	1 (reference)					
Radiotherapy	1.341 (0.714-2.520)	0.361				
Chemotherapy	1.065 (0.735-1.545)	0.738				
Targeted therapy	0.251 (0.062-1.008)	0.051				

Variable	Original model				Refined model	
	Univariable analysis		Multivariable analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
CRP response						
CRP non-responder	1 (reference)		1 (reference)			
CRP responder	0.73 (0.58-0.92)	0.008	0.57 (0.45-0.73)	<0.001		
CRP flare-responder	0.85 (0.60-1.19)	0.339	0.67 (0.47-0.95)	0.025		
CRP response						
CRP non-responder	1 (reference)				1 (reference)	
CRP responder	0.64 (0.50-0.81)	<0.001	NA	NA	0.46 (0.35-0.59)	<0.001
CRP flare-responder	0.75 (0.54-1.06)	0.104			0.61 (0.43-0.87)	0.006
All-normal CRP	0.46 (0.31-0.69)	<0.001			0.64 (0.42-0.99)	0.042

Supplementary Figures



Supplementary Figure 1 | Landmark analysis showing progression-free survival (PFS) and overall survival (OS) according to previously established CRP response categories for the discovery cohort (A+B) and the validation cohort (C+D)



Supplementary Figure 2 | Landmark analysis showing progression-free survival (PFS) and overall survival (OS) according to CRP response categories including all-normal CRP for the discovery cohort (A+B) and the validation cohort (C+D).