Supplementary Figure 1. Flow diagram

```
┌─────────────────────────────────────────────────────────┐
│  Patients with solid tumors diagnosed between 2015-2018, │
│  who received at least 1 dose of ICI and MSK-IMPACT testing│
│                    (n = 2 827)                          │
└─────────────────────────────────────────────────────────┘
                          │
                          │      ┌────────────────────────────────────────────────┐
                          │      │  Patients with history of > 1 cancer (n = 818) │
                          ├──────│  Patients without CBC within 1 month prior to ICI start (n = 14) │
                          │      │  Patients enrolled in blinded trials (n = 26)  │
                          │      │  Patients with cancer types with <25 cases (n = 115) │
                          │      └────────────────────────────────────────────────┘
                          │
              ┌──────────────────────────────────┐
              │  Patients for whom response to therapy, │
              │      PFS, and OS were analyzed    │
              │            n = 1 854              │
              └──────────────────────────────────┘
                          │
                          │      ┌────────────────────────────────┐
                          │      │  Unevaluable response (n = 40) │
                          ├──────│  Neoadjuvant ICI (n = 44)      │
                          │      │  Adjuvant ICI (n = 56)         │
                          │      └────────────────────────────────┘
                          │
              ┌──────────────────────────────────┐
              │      Included in the analysis     │
              │            n = 1 714              │
              └──────────────────────────────────┘
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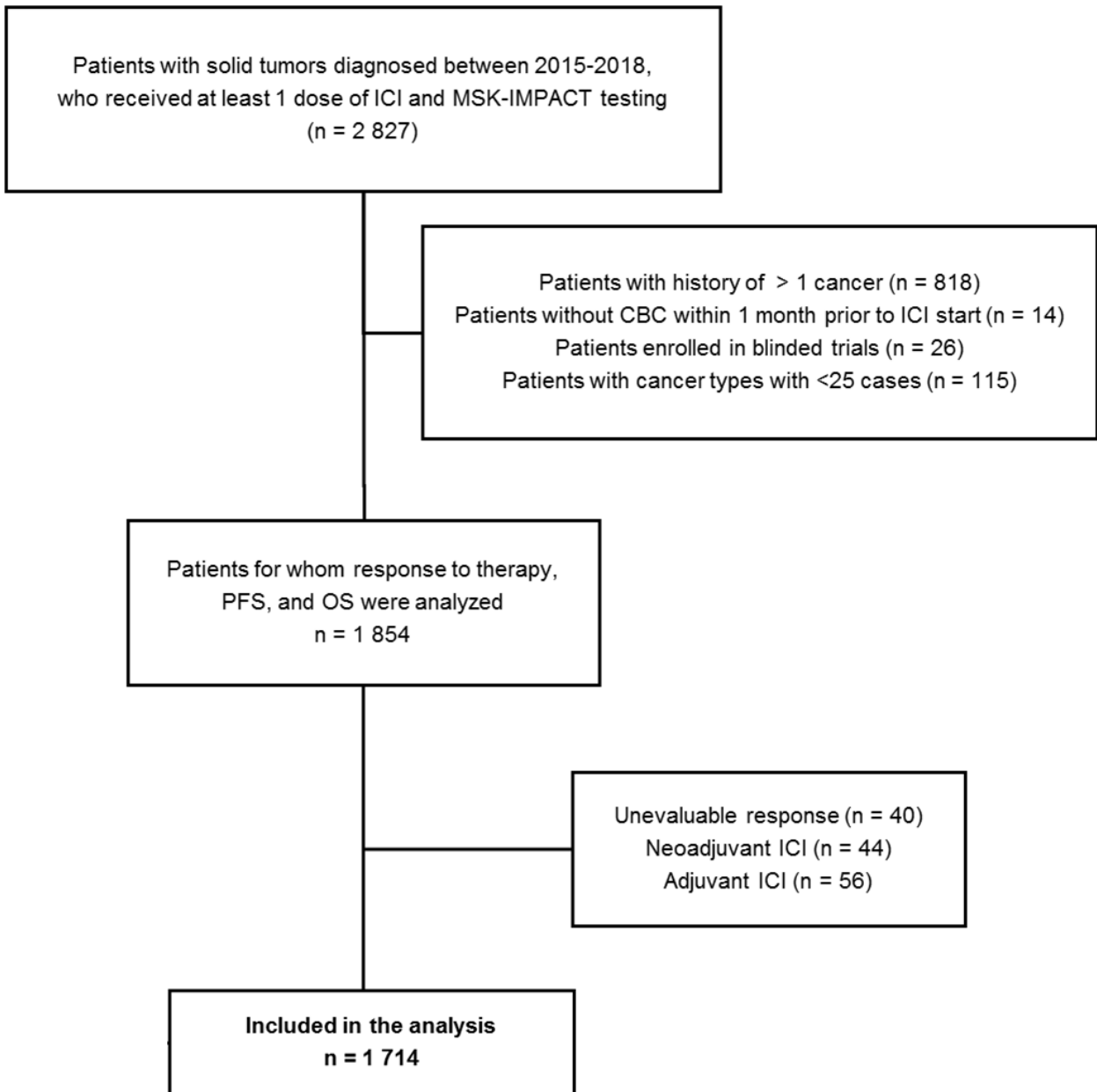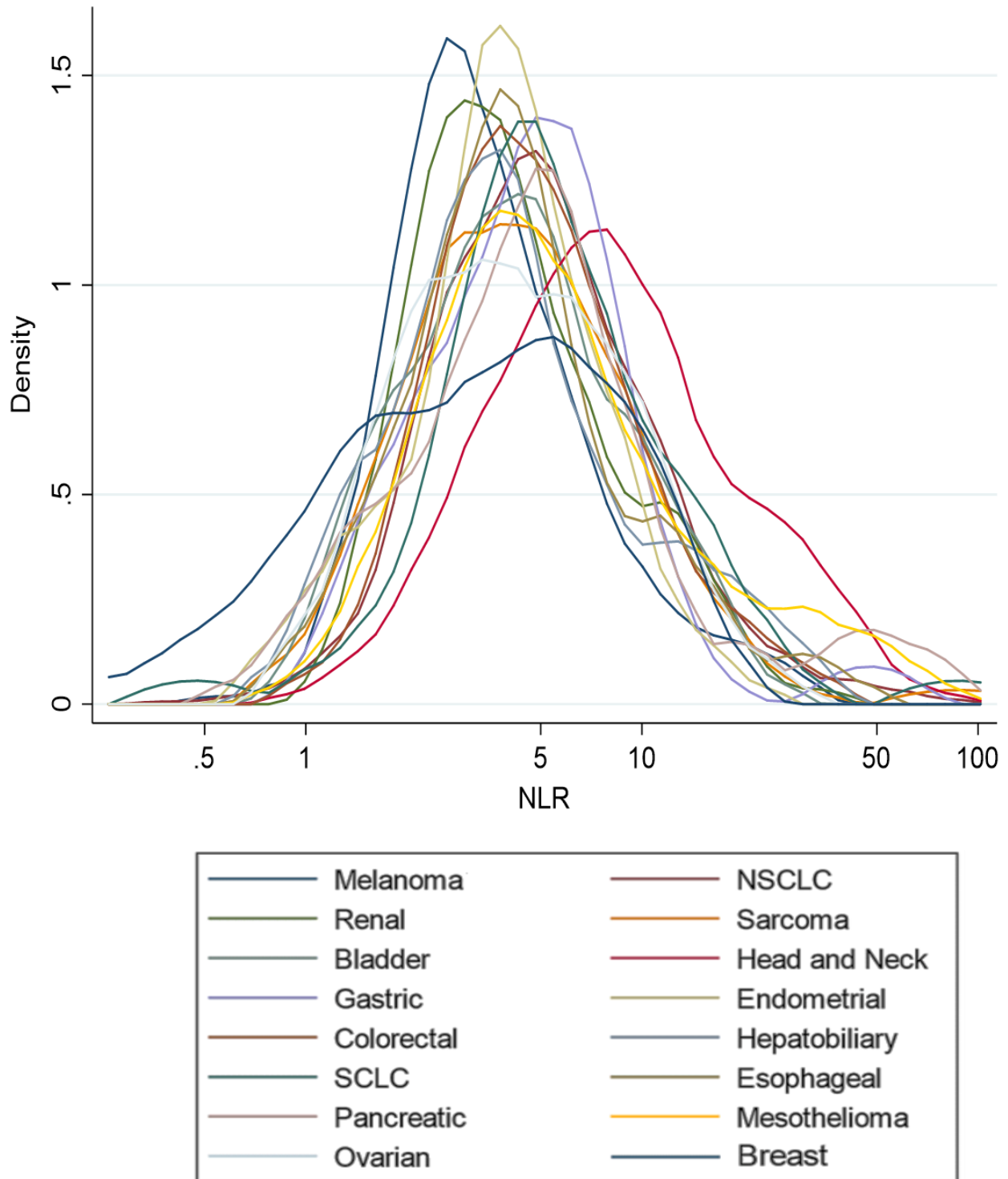
Abbreviations: ICI, Immune checkpoint inhibitors; CBC, complete blood count; PFS, progression-free survival; OS, overall survival

Supplementary Figure 2. Neutrophil-to-lymphocyte ratio (NLR) distribution according to cancer type

Kernel density plots of neutrophil-to-lymphocyte ratio (log scale) across cancer types.

Abbreviations: NSCLC, Non-small cell lung cancer; SCLC, small cell lung cancer

Supplementary Figure 3. Pan-cancer overall survival according to neutrophil-to-lymphocyte ratio (NLR) percentile within cancer type
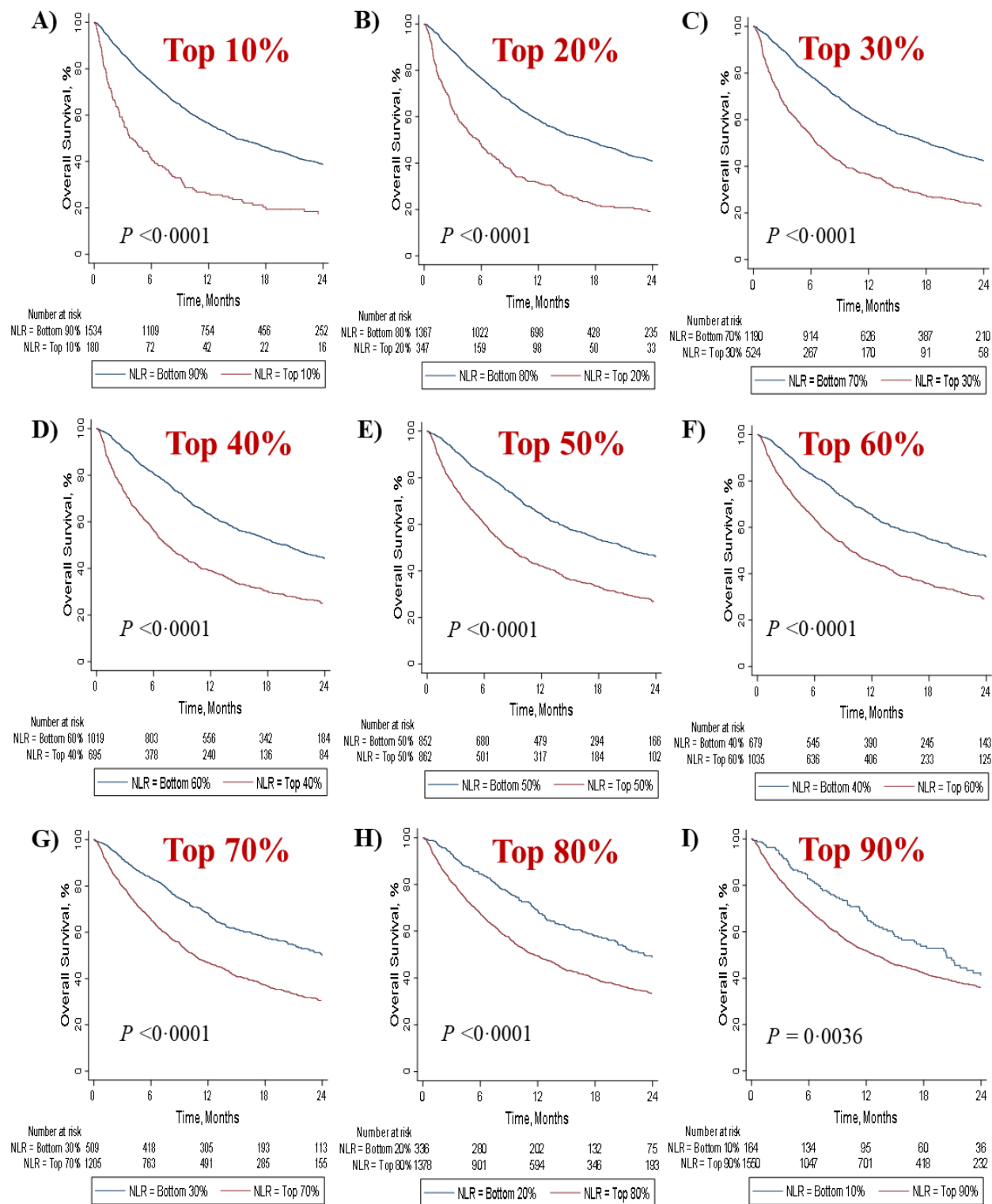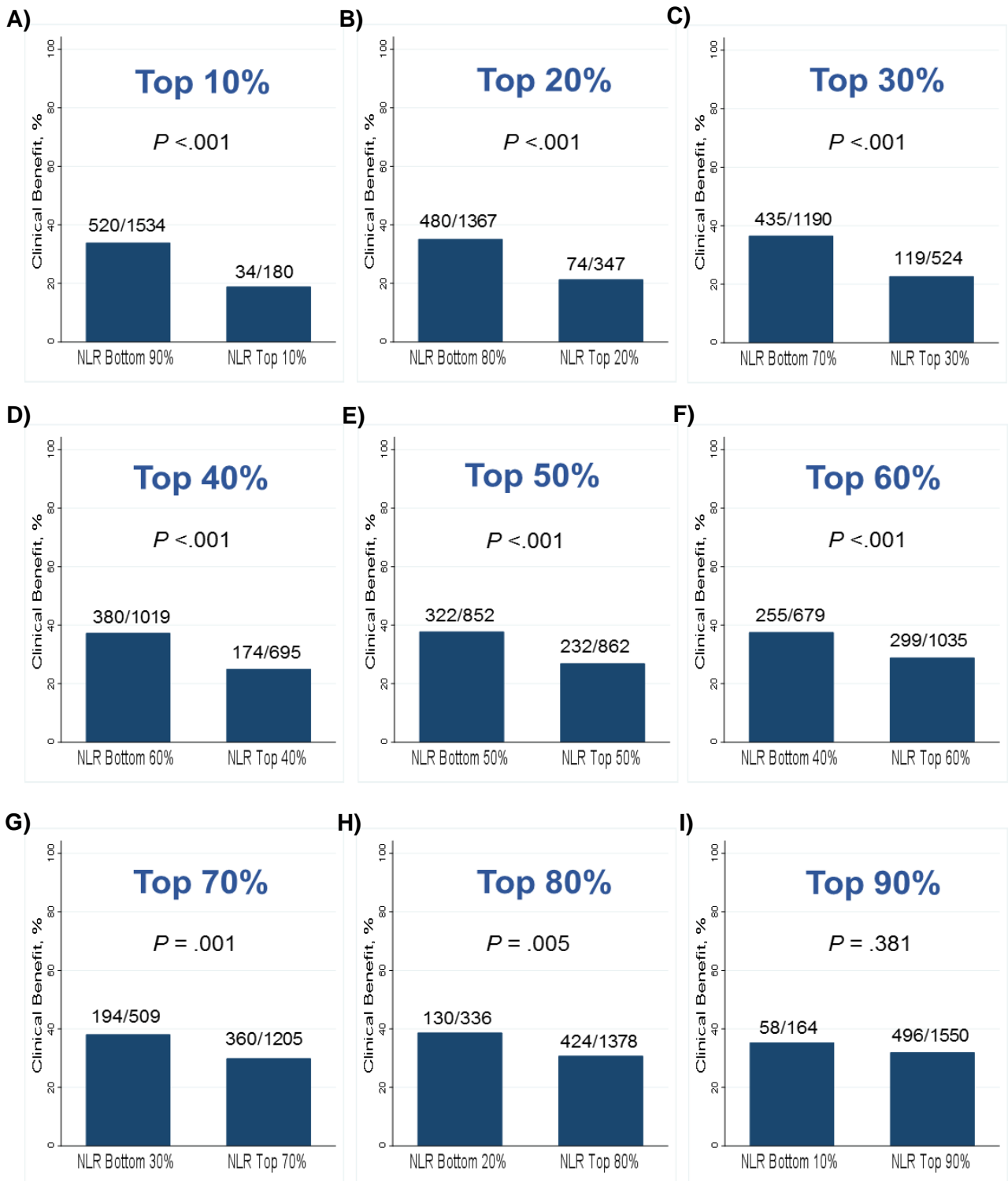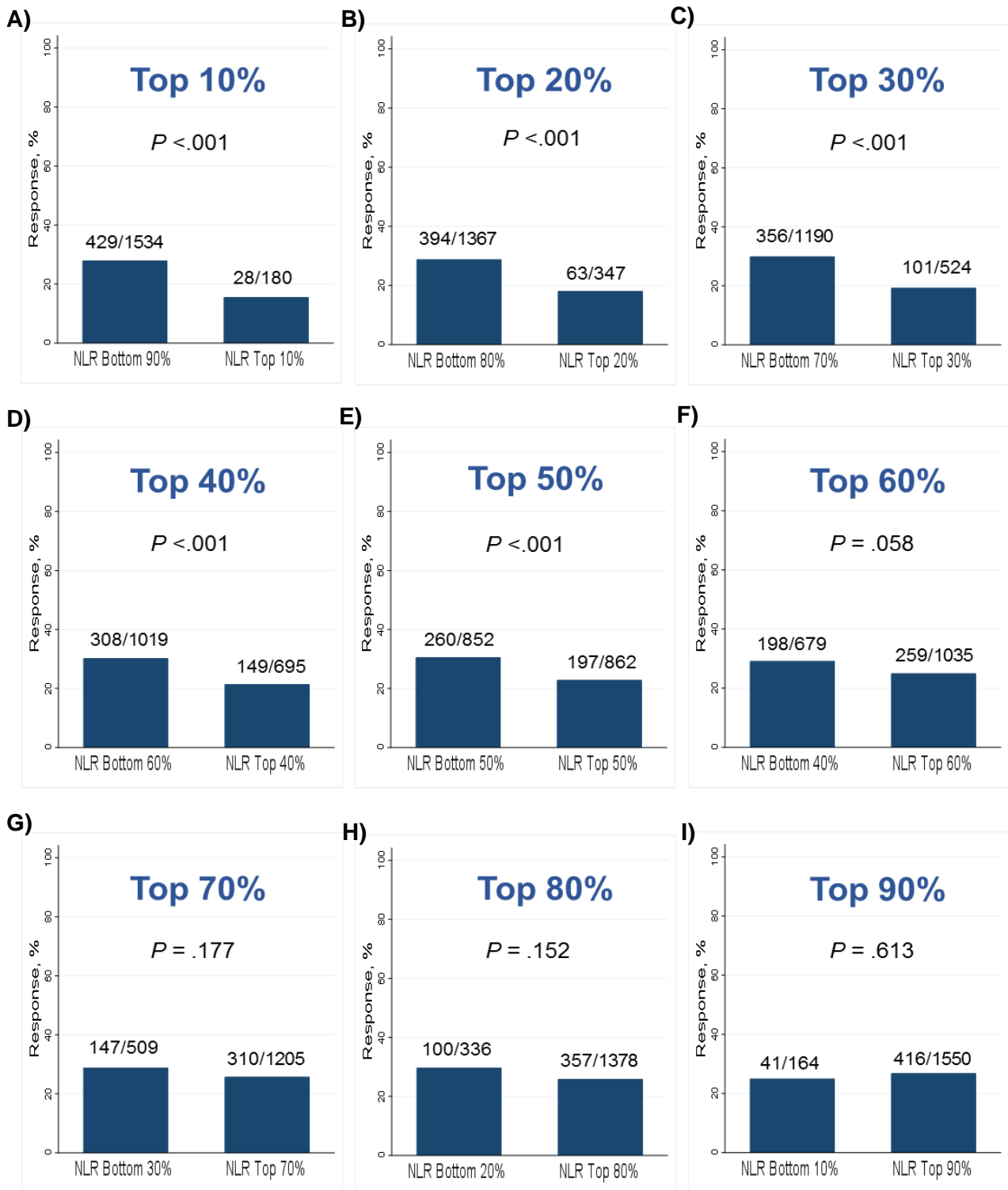

Pan-cancer overall survival comparing NLR high vs low groups, using as cutoff A) top 10th, B) top 20th, C) top 30th, D) top 40th, E) top 50th, F) top 60th, G) top 70th, H) top 80th and I) top 90th percentile within cancer type. P values are according to log-rank test.

Supplementary Figure 4. Pan-cancer progression-free survival according to neutrophil-to-lymphocyte ratio (NLR) percentile within cancer type
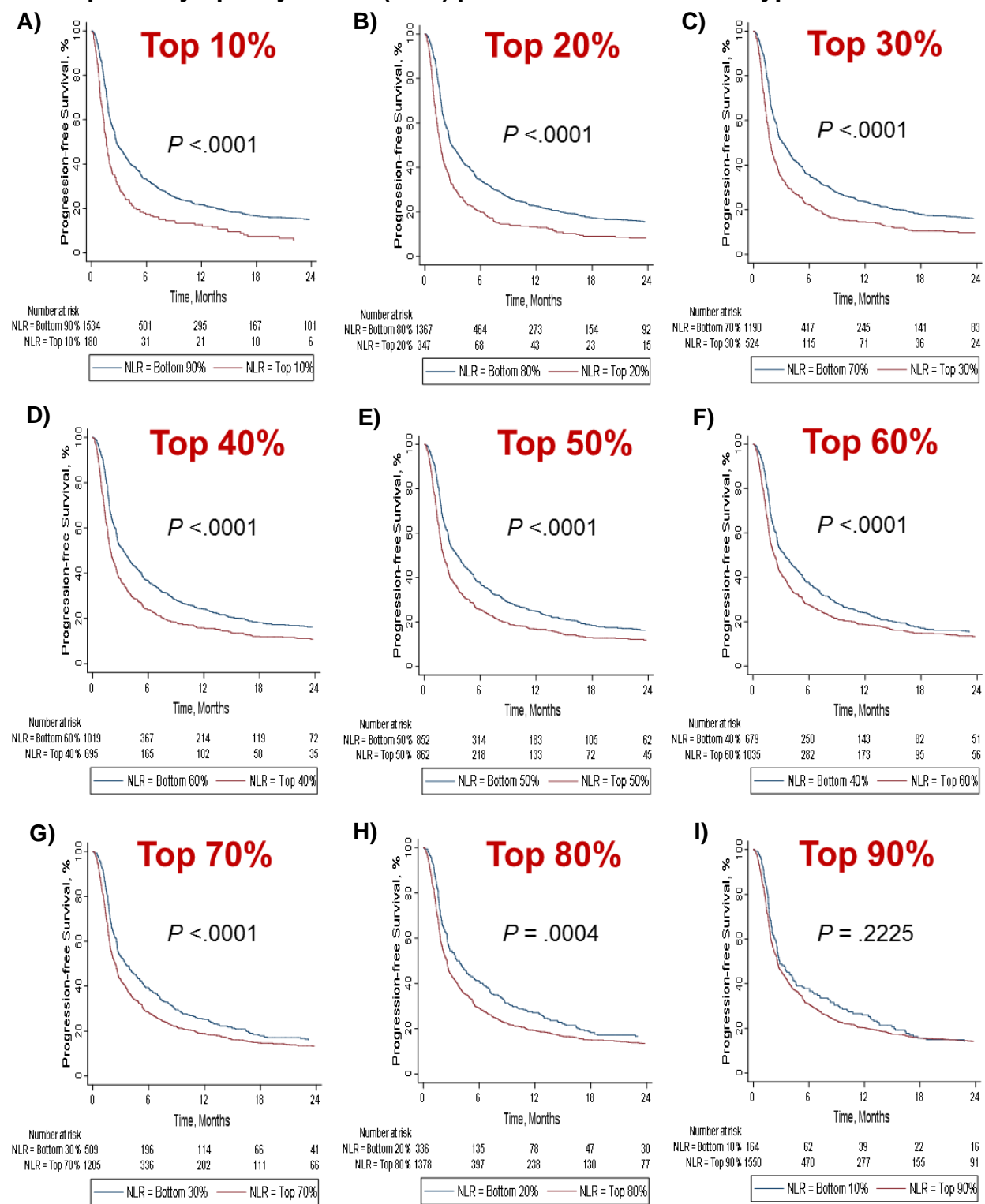
Pan-cancer progression-free survival comparing NLR high vs low groups, using as cutoff A) top 10th, B) top 20th, C) top 30th, D) top 40th, E) top 50th, F) top 60th, G) top 70th, H) top 80th and I) top 90th percentile within cancer type. P values are according to log-rank test.

Supplementary Figure 5. Pan-cancer clinical benefit according to neutrophil-to-lymphocyte ratio (NLR) percentile within cancer type
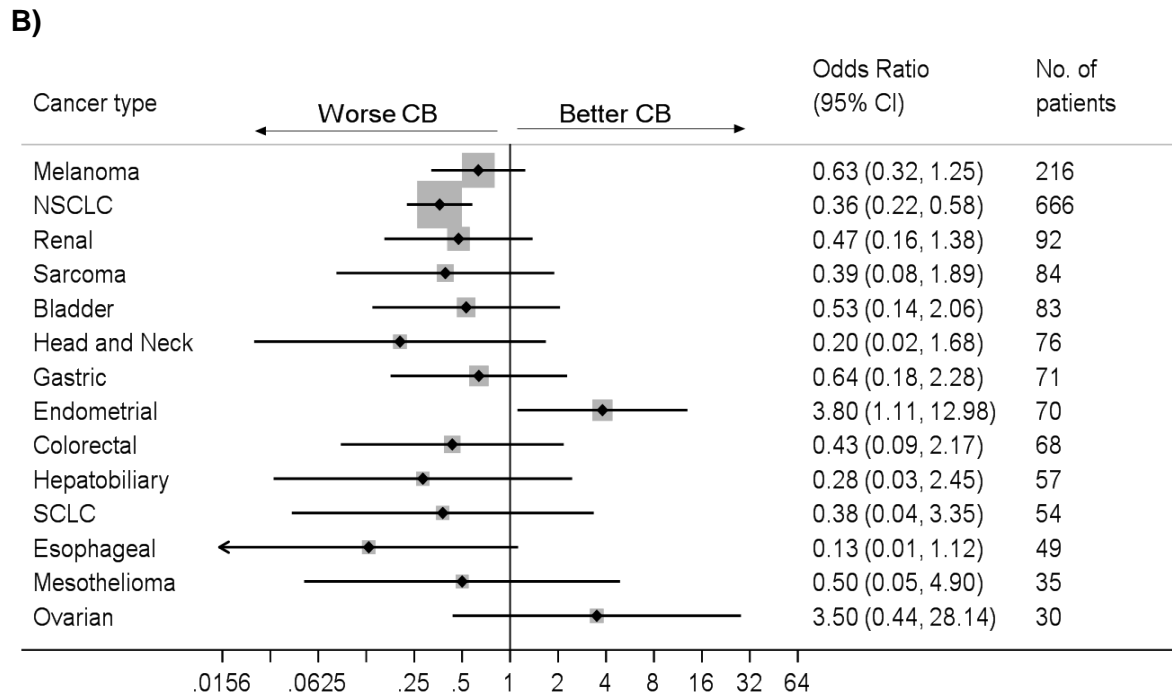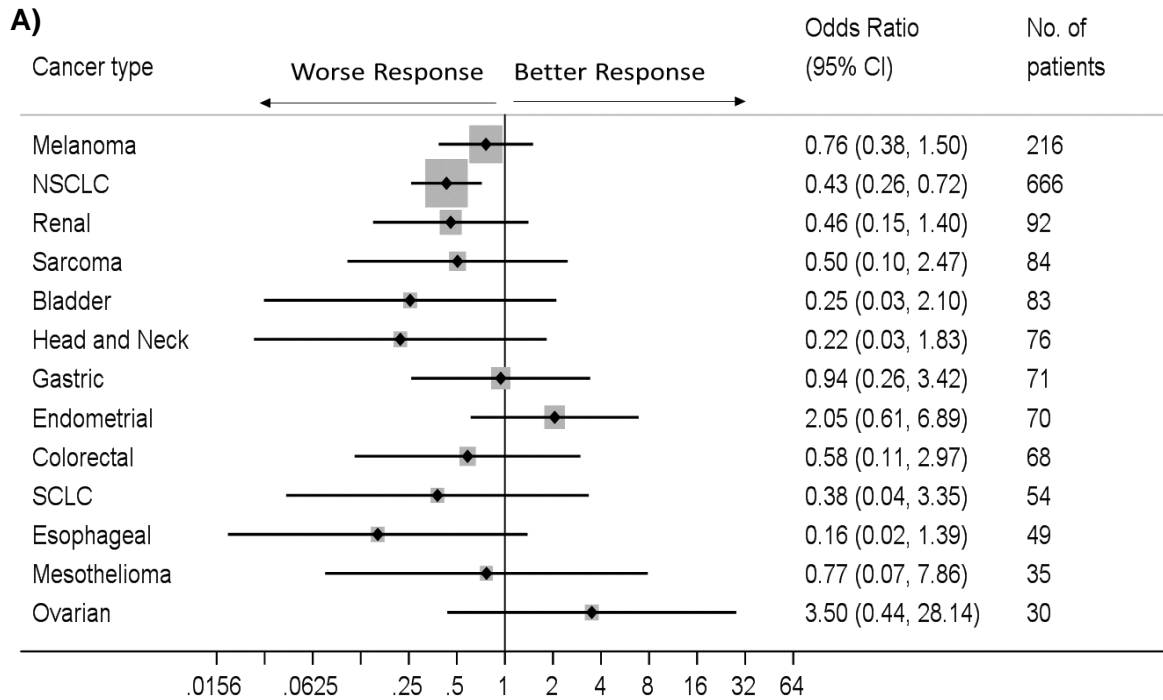

Pan-cancer clinical benefit comparing NLR high vs low groups, using as cutoff A) top 10th, B) top 20th, C) top 30th, D) top 40th, E) top 50th, F) top 60th, G) top 70th, H) top 80th and I) top 90th percentile within cancer type. P values are according to Pearson´s chi-square test.

Supplementary Figure 6. Pan-cancer response according to neutrophil-to-lymphocyte ratio (NLR) percentile within cancer type

Pan-cancer response comparing NLR high vs low groups, using as cutoff A) top 10th, B) top 20th, C) top 30th, D) top 40th, E) top 50th, F) top 60th, G) top 70th, H) top 80th and I) top 90th percentile within cancer type. P values are according to Pearson´s chi-square test.
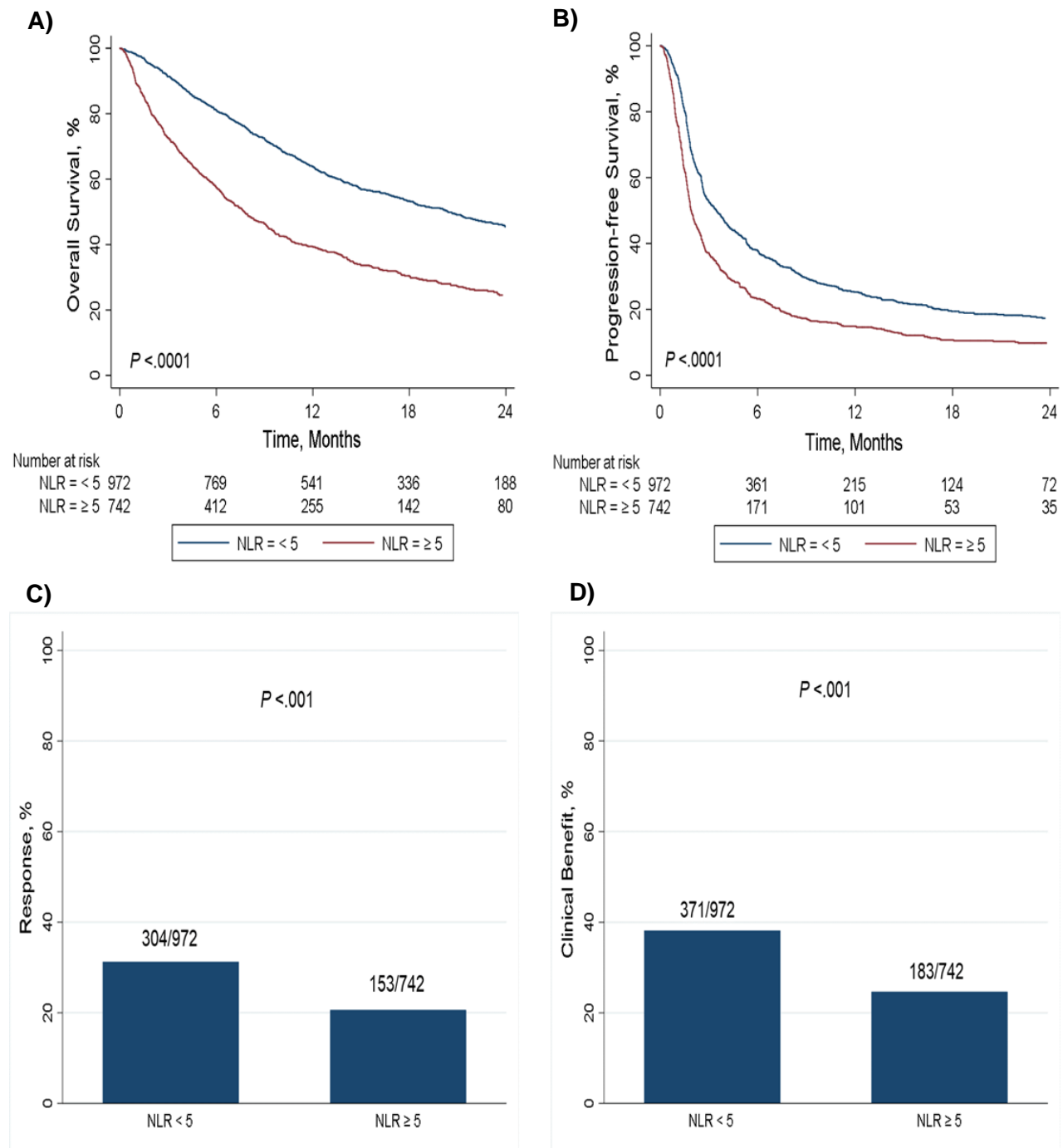
Supplementary Figure 7. Outcomes based on neutrophil-to-lymphocyte ratio (NLR) using top 20th percentile within cancer type as cutoff and stratified by cancer type

A)

Cancer type		Odds Ratio (95% CI)	No. of patients
Melanoma		0.76 (0.38, 1.50)	216
NSCLC		0.43 (0.26, 0.72)	666
Renal		0.46 (0.15, 1.40)	92
Sarcoma		0.50 (0.10, 2.47)	84
Bladder		0.25 (0.03, 2.10)	83
Head and Neck		0.22 (0.03, 1.83)	76
Gastric		0.94 (0.26, 3.42)	71
Endometrial		2.05 (0.61, 6.89)	70
Colorectal		0.58 (0.11, 2.97)	68
SCLC		0.38 (0.04, 3.35)	54
Esophageal		0.16 (0.02, 1.39)	49
Mesothelioma		0.77 (0.07, 7.86)	35
Ovarian		3.50 (0.44, 28.14)	30

Worse Response | Better Response

.0156 .0625 .25 .5 1 2 4 8 16 32 64

B)

Cancer type		Odds Ratio (95% CI)	No. of patients
Melanoma		0.63 (0.32, 1.25)	216
NSCLC		0.36 (0.22, 0.58)	666
Renal		0.47 (0.16, 1.38)	92
Sarcoma		0.39 (0.08, 1.89)	84
Bladder		0.53 (0.14, 2.06)	83
Head and Neck		0.20 (0.02, 1.68)	76
Gastric		0.64 (0.18, 2.28)	71
Endometrial		3.80 (1.11, 12.98)	70
Colorectal		0.43 (0.09, 2.17)	68
Hepatobiliary		0.28 (0.03, 2.45)	57
SCLC		0.38 (0.04, 3.35)	54
Esophageal		0.13 (0.01, 1.12)	49
Mesothelioma		0.50 (0.05, 4.90)	35
Ovarian		3.50 (0.44, 28.14)	30

Worse CB | Better CB

.0156 .0625 .25 .5 1 2 4 8 16 32 64

Forest plots showing odds ratios with 95% CIs for A) response and B) clinical benefit across cancer types comparing top 20th NLR percentile within cancer type to bottom 80th. Odds ratios were calculated with logistic regression. Logistic regression models for response are unstable for hepatobiliary, pancreatic and breast and are not included in figure A. Logistic regression models for clinical benefit are unstable for pancreatic and breast and are not included in figure B.
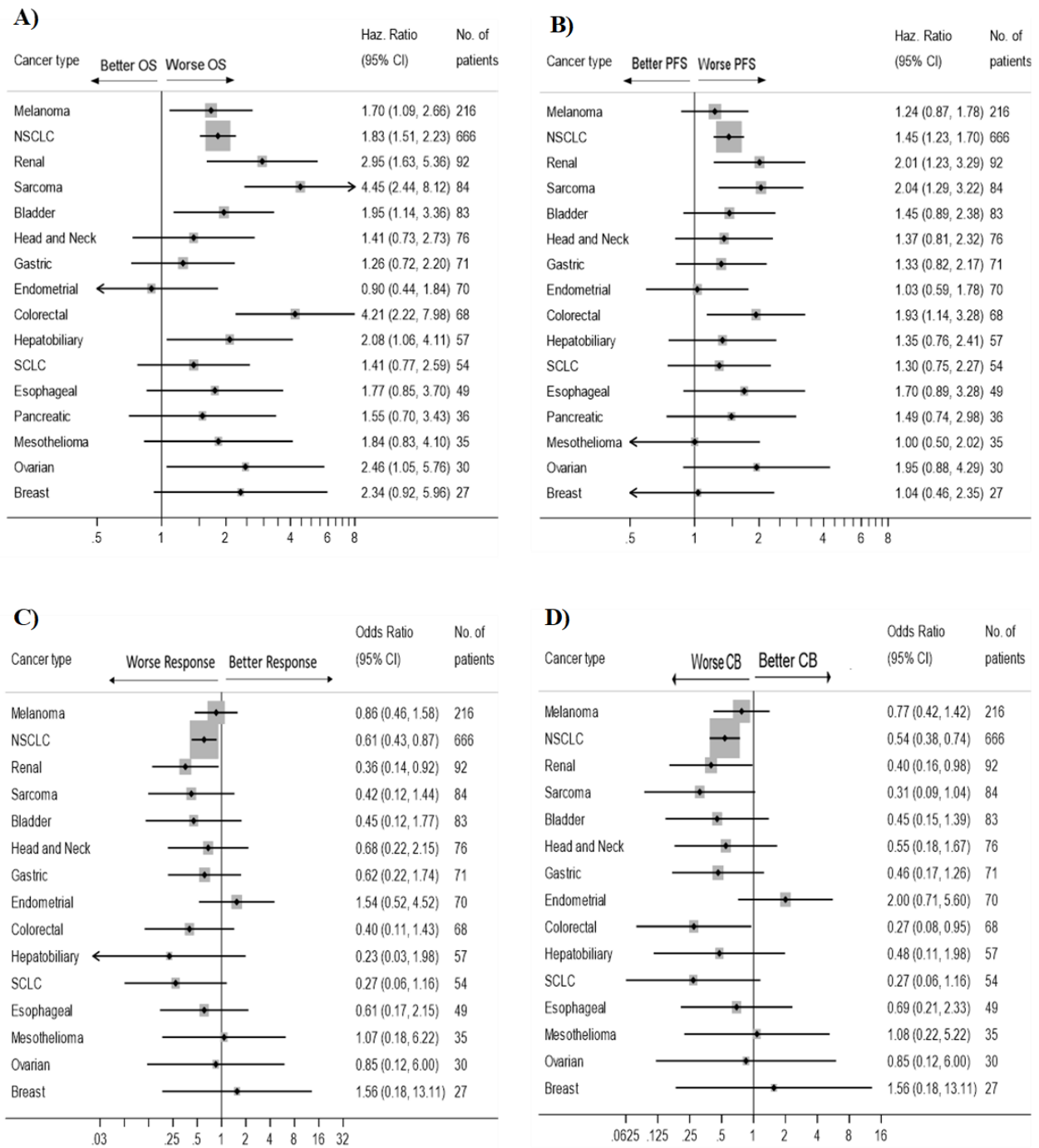
Abbreviations: CI, Confidence interval; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; CB, clinical benefit

Supplementary Figure 8. Pan-cancer outcomes based on neutrophil-to-lymphocyte ratio (NLR) using a universal cutoff (NLR ≥ 5)

A) Overall survival, B) progression-free survival, C) response, and D) clinical benefit at a pan-cancer level based on high vs low NLR. The cutoff was ≥ 5. *P* values are according to log-rank test for A) and B) and Pearson´s chi-square test for C) and D).

Supplementary Figure 9. Outcomes based on neutrophil-to-lymphocyte ratio (NLR) using a universal cutoff (NLR ≥ 5) and stratified by cancer type

Forest plots showing hazard ratios (HRs) with 95% CIs for A) overall survival and B) progression-free survival, and odds ratios (ORs) with 95% CIs for C) response and D) clinical benefit across cancer types using universal cutoff of 5. HRs were calculated with Cox proportional hazard regression. ORs were calculated with logistic regression. Logistic regression models for response and clinical benefit are unstable for pancreatic cancer and are not included in figure C and D.

Abbreviations: CI, Confidence interval; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

Supplementary Figure 10. Pan-cancer outcomes based on neutrophil-to-lymphocyte ratio (NLR) in the validation cohort (n = 323)
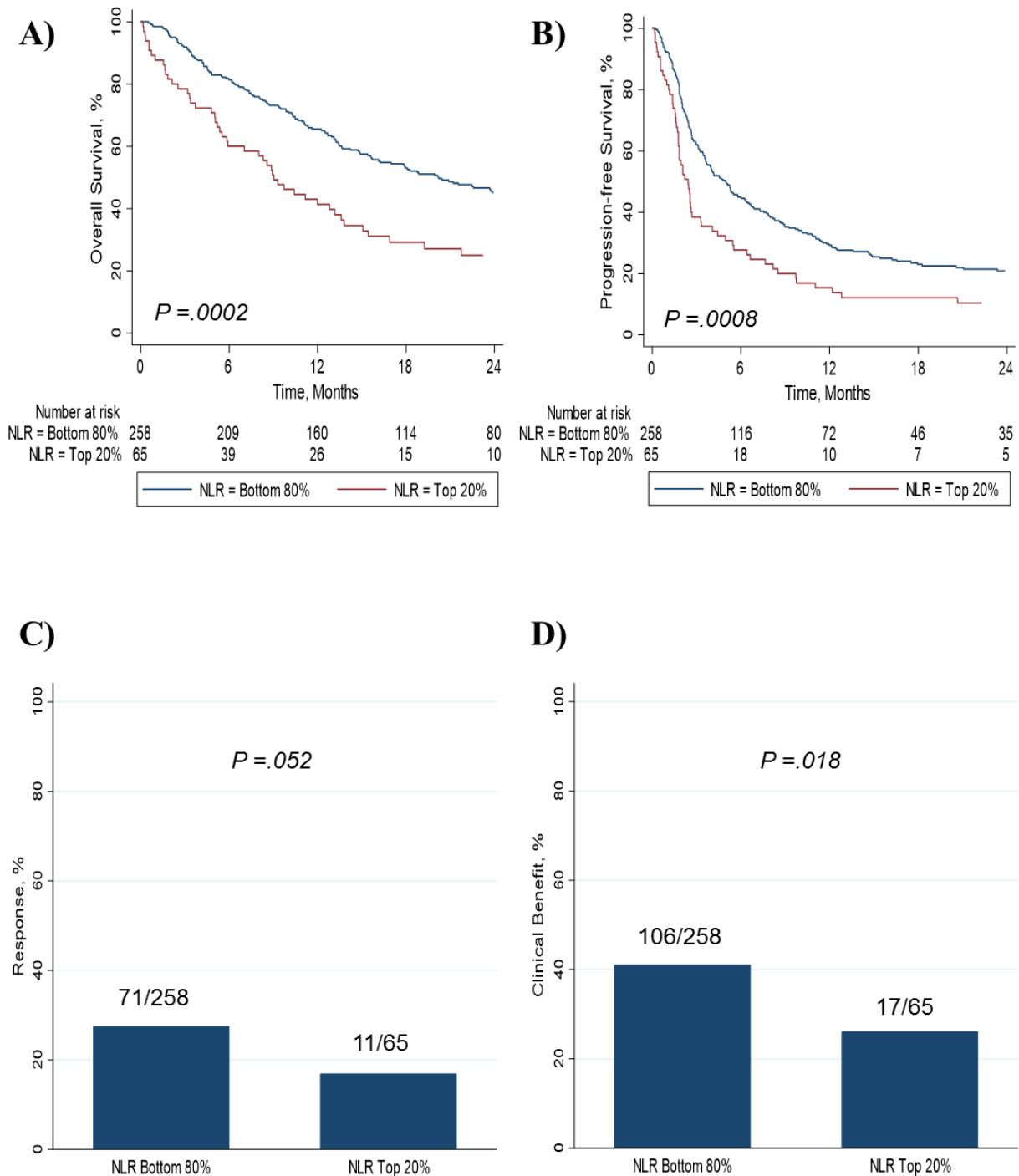

A) Overall survival, B) progression-free survival, C) response, and D) clinical benefit at a pan-cancer level based on high vs low NLR in the validation cohort (n = 323). The cutoff was the top 20th percentile within each cancer type. P values are according to log-rank test for A) and B) and Fisher's exact test for C) and D).

Supplementary Figure 11. Clinical benefit trends based on neutrophil-to-lymphocyte ratio (NLR) and tumor mutational burden (TMB)
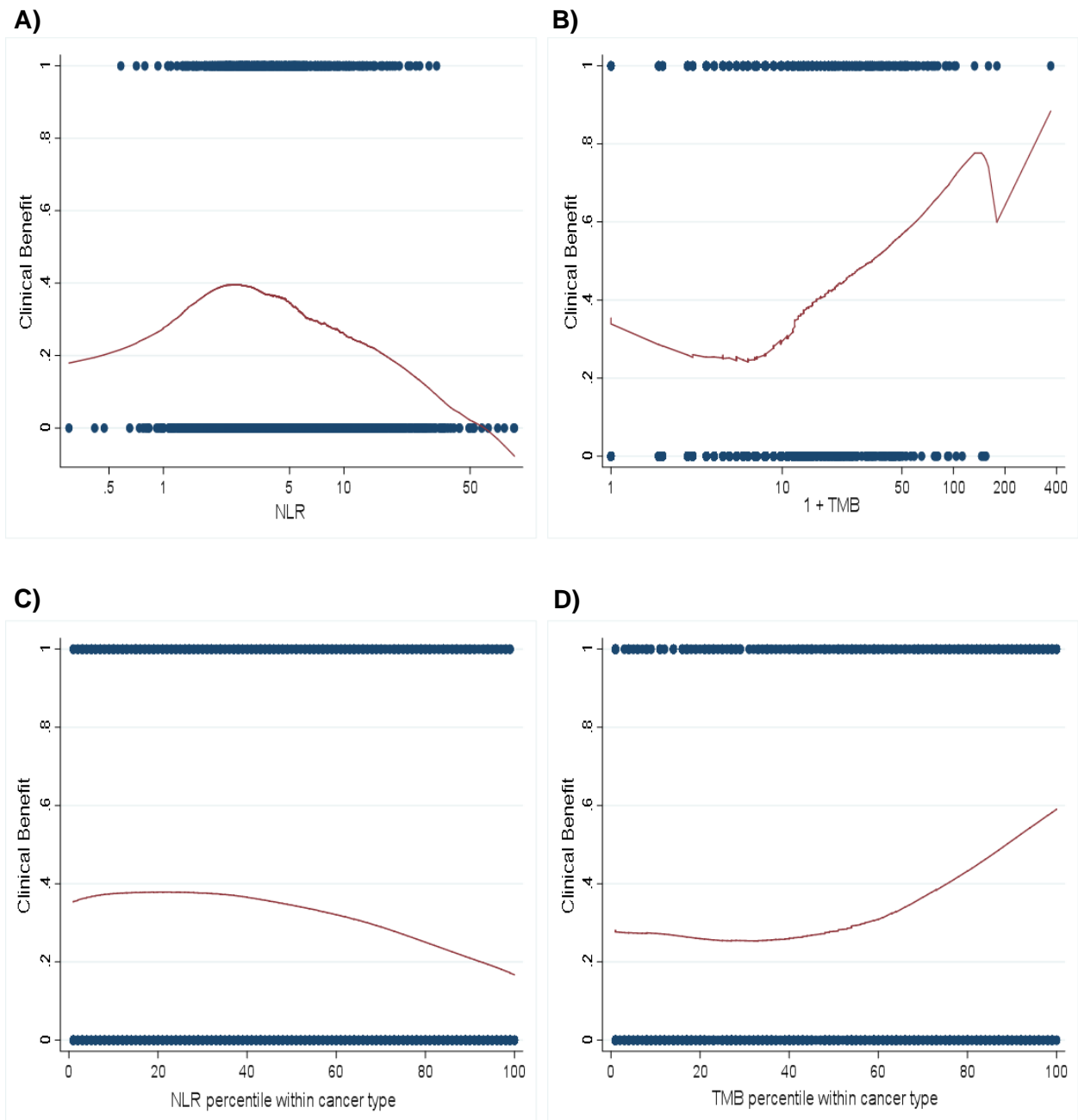

LOWESS plots of clinical benefit based on A) NLR (log scale), B) TMB (log scale), C) NLR percentile within cancer type, and D) TMB percentile within cancer type.

Supplementary Figure 12. Correlation between neutrophil-to-lymphocyte ratio (NLR) and tumor mutational burden (TMB)
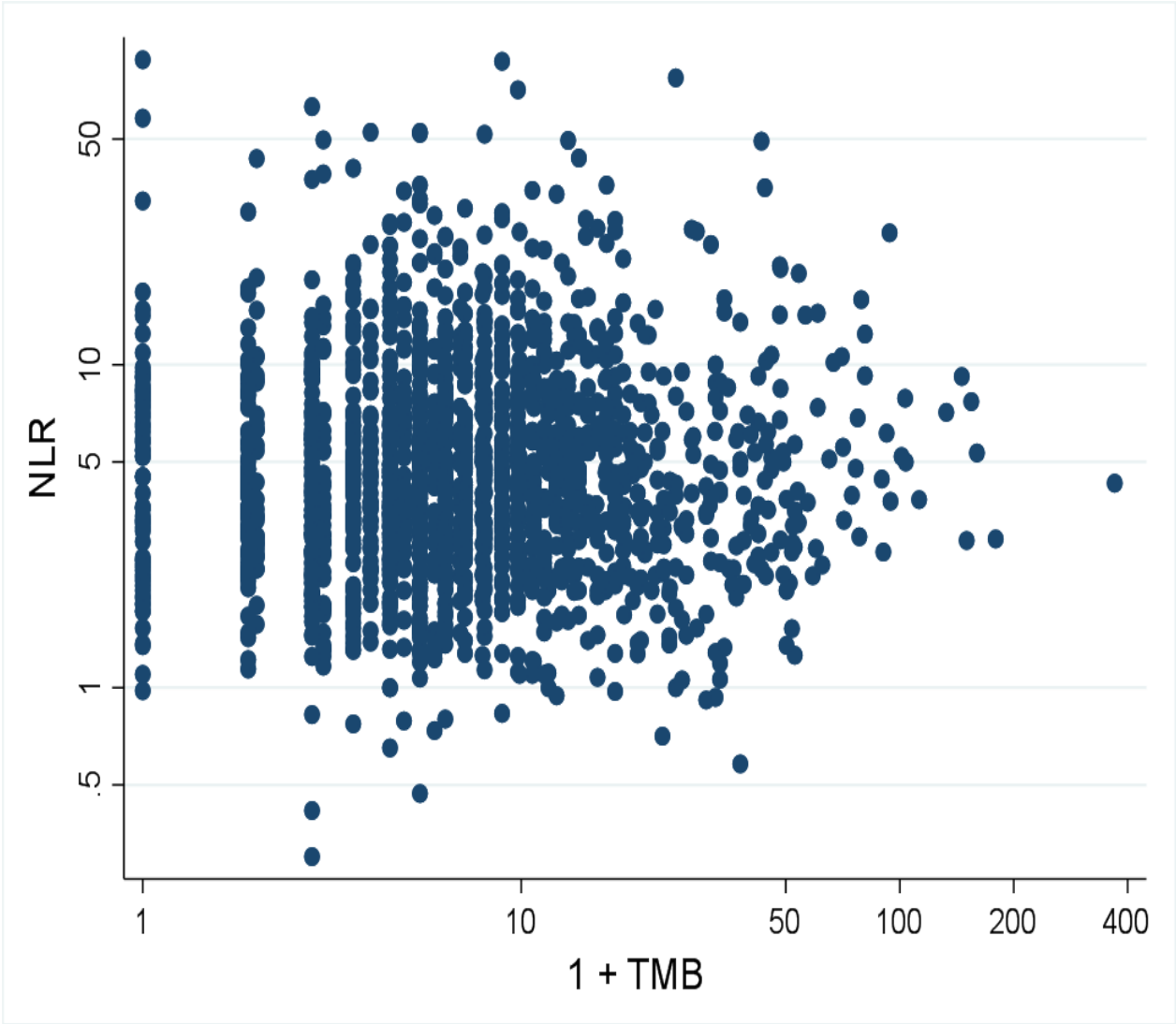
Scatter plot analyzing the correlation between NLR and TMB, both in log scale. Spearman correlation coefficient = 0.048; P = 0.05.

Supplementary Figure 13. Receiver operating characteristic (ROC) curves for neutrophil-to-lymphocyte ratio (NLR) and tumor mutational burden (TMB) with clinical benefit as endpoint
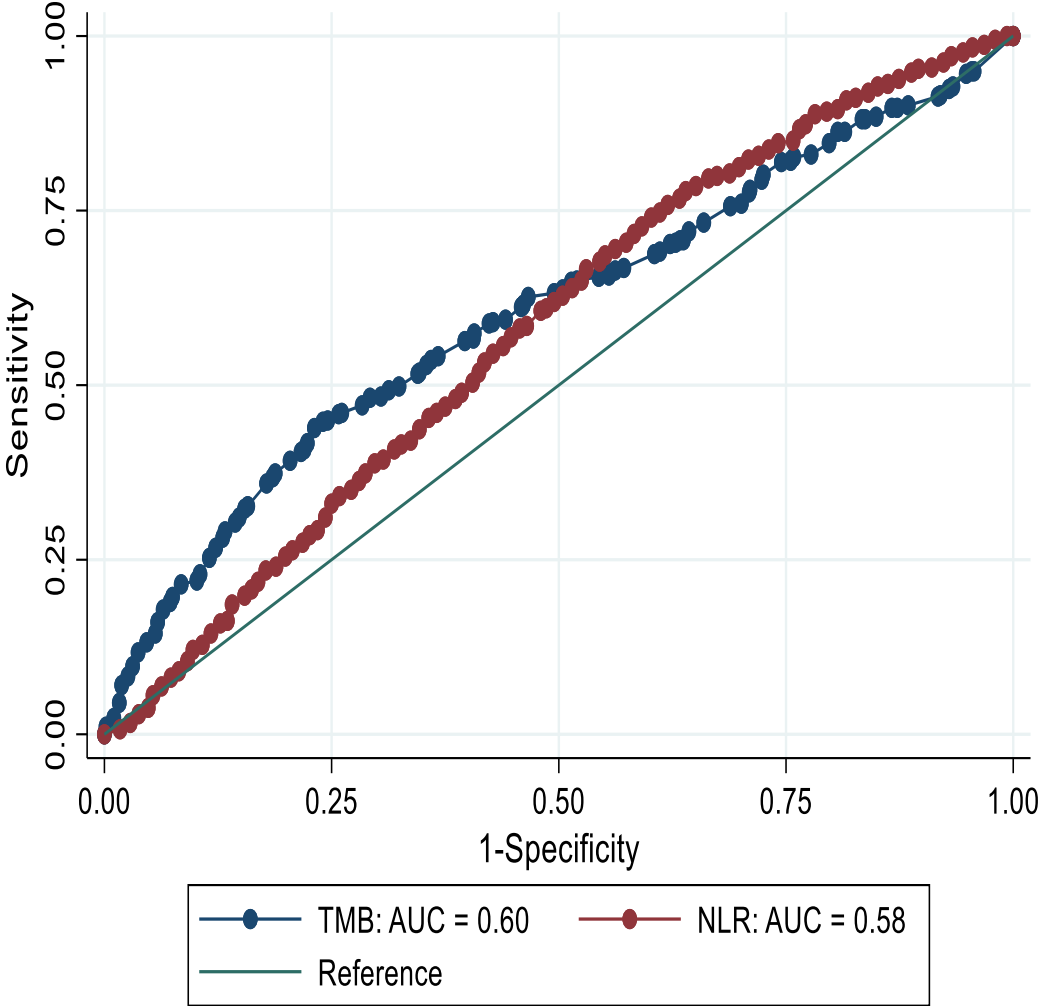
NLR and TMB expressed as percentile within cancer type.

Abbreviations: AUC, Area under the curve

Supplementary Figure 14. Overall survival according to combined neutrophil-to-lymphocyte ratio (NLR) and tumor mutational burden (TMB) categorization for the main cancer types
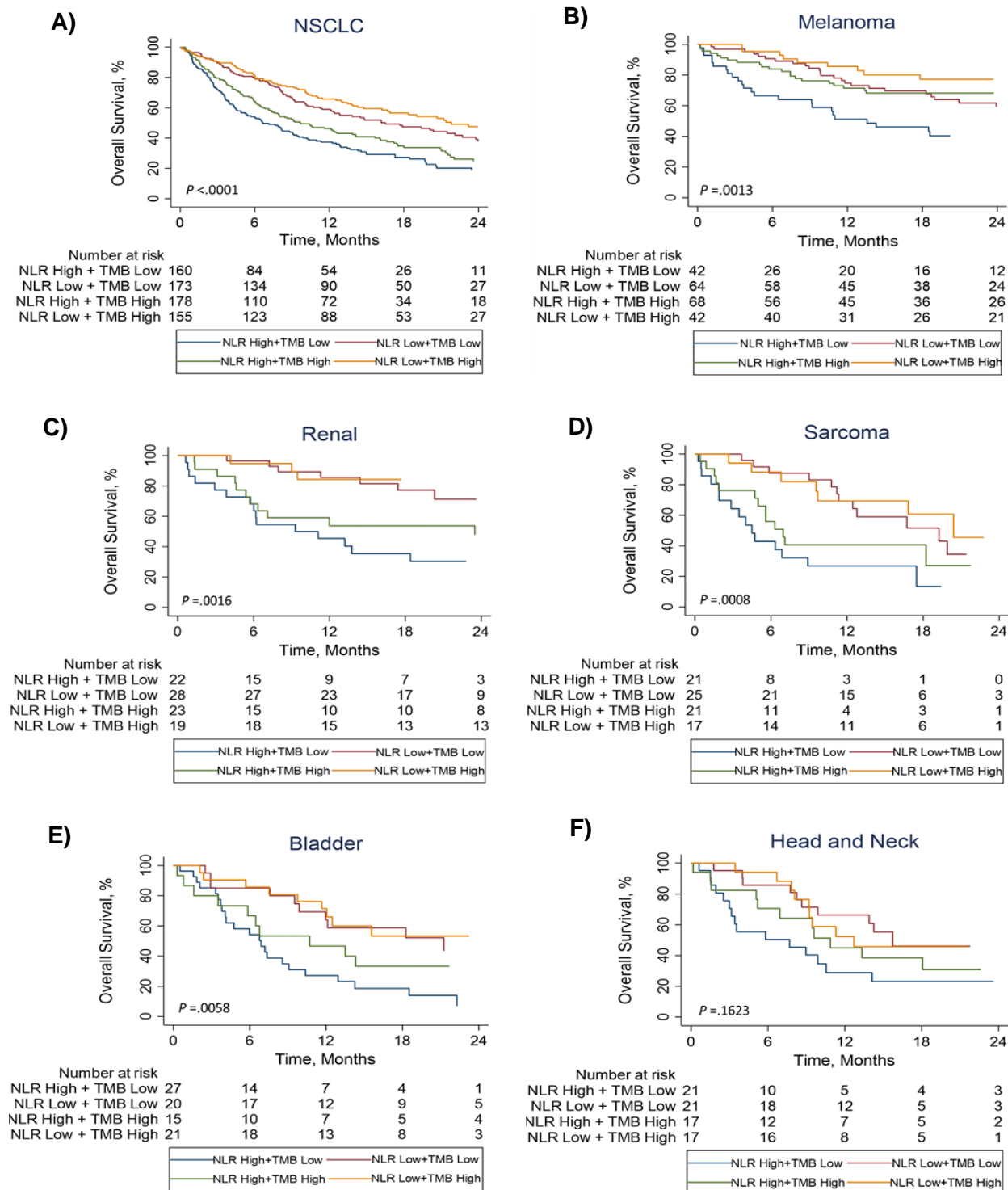
Overall survival based on a combined NLR and TMB variable stratified by cancer type for the main cancer types; A) non-small cell lung cancer (NSCLC), B) melanoma, C) renal, D) sarcoma, E) bladder, F) head and neck. We assigned patients into 4 categories based on NLR low/high and TMB low/high using median within cancer type as cutoff for both variables. P values are according to log-rank test.

Supplementary Figure 15. Progression-free survival according to combined neutrophil-to-lymphocyte ratio (NLR) and tumor mutational burden (TMB) categorization for the main cancer types
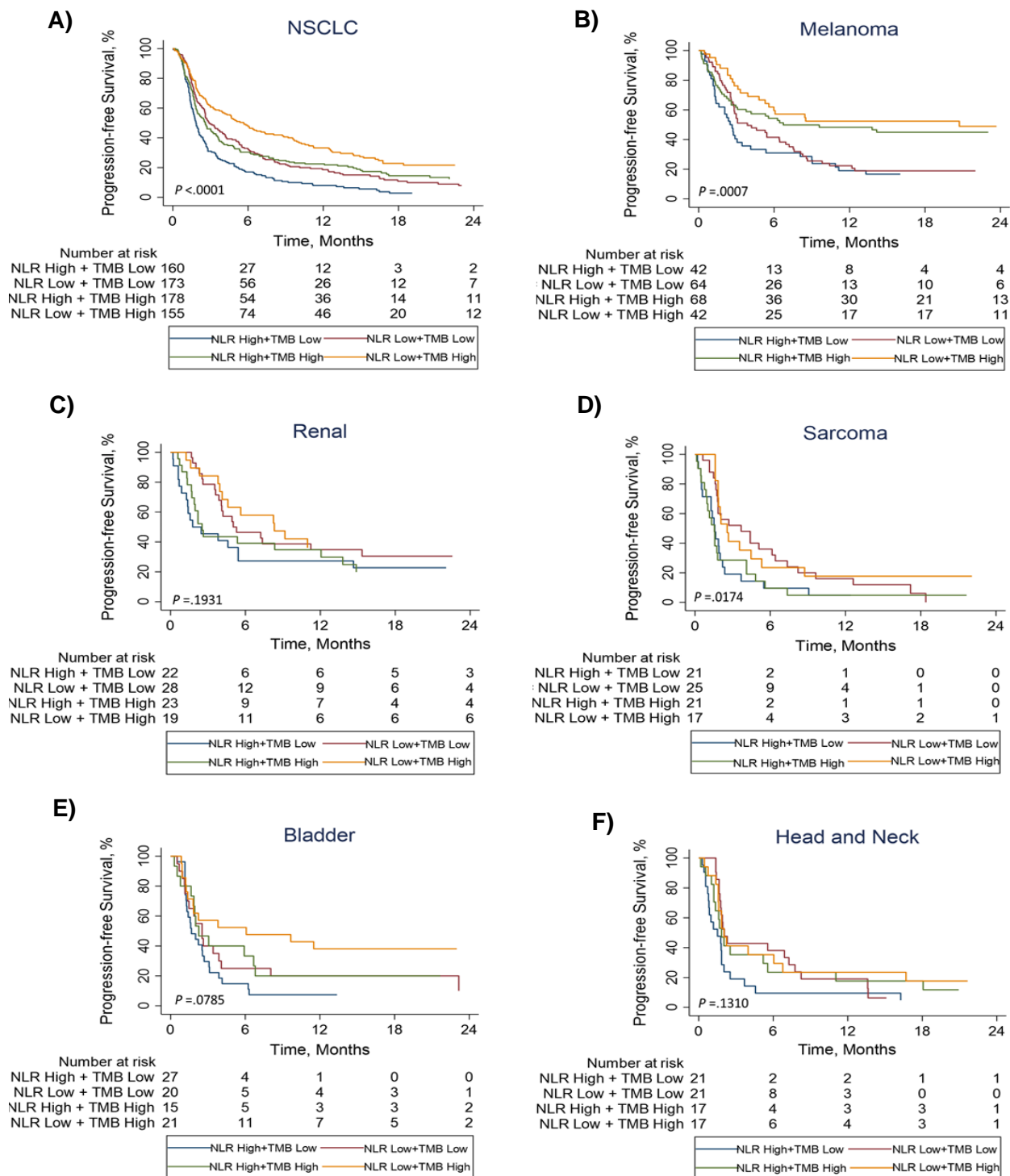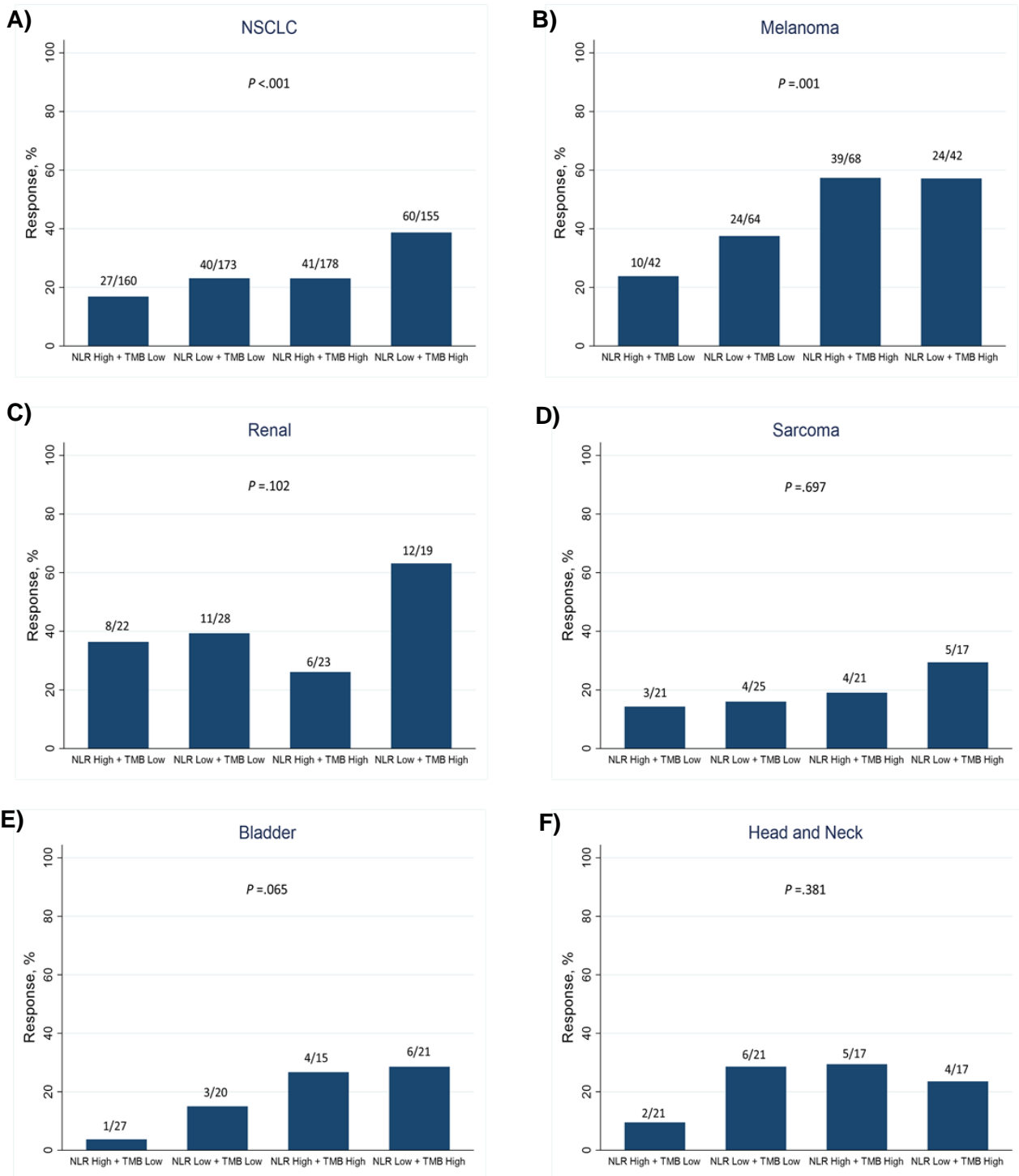

Progression-free survival based on a combined NLR and TMB variable stratified by cancer type for the main cancer types; A) non-small cell lung cancer (NSCLC), B) melanoma, C) renal, D) sarcoma, E) bladder, F) head and neck. We assigned patients into 4 categories based on NLR low/high and TMB low/high using median within cancer type as cutoff for both variables. P values are according to log-rank test.

Supplementary Figure 16. Response according to combined neutrophil-to-lymphocyte ratio (NLR) and tumor mutational burden (TMB) categorization for the main cancer types

Response based on a combined NLR and TMB variable stratified by cancer type for the main cancer types; A) non-small cell lung cancer (NSCLC), B) melanoma, C) renal, D) sarcoma, E) bladder, F) head and neck. We assigned patients into 4 categories based on NLR low/high and TMB low/high using median within cancer type as cutoff for both variables; P values according to Pearson´s chi-square test or Fisher´s exact test when appropriate.

Supplementary Figure 17. Clinical benefit according to combined neutrophil-to-lymphocyte ratio (NLR) and tumor mutational burden (TMB) categorization for the main cancer types

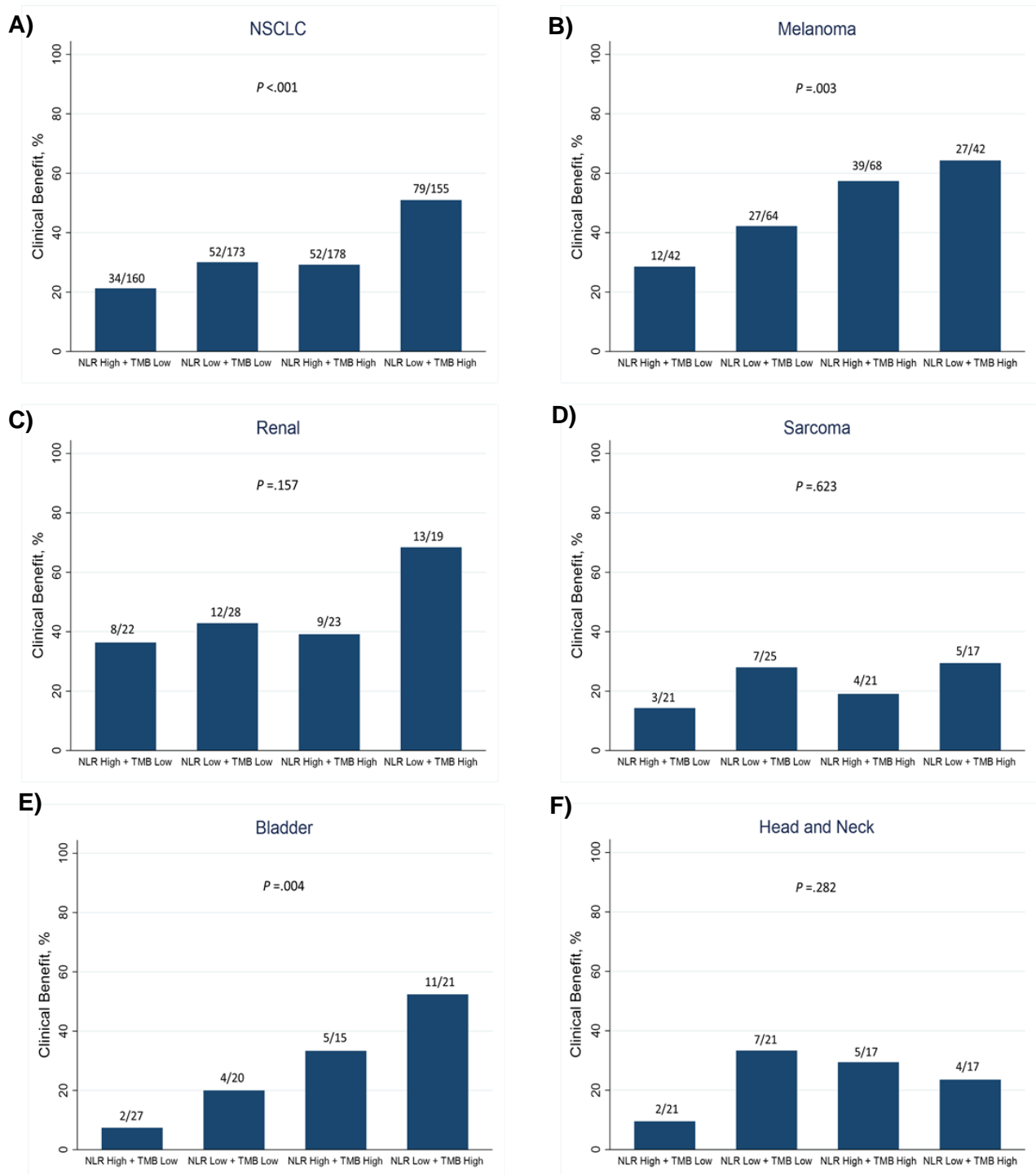Clinical benefit based on a combined NLR and TMB variable stratified by cancer type for the main cancer types; A) non-small cell lung cancer (NSCLC), B) melanoma, C) renal, D) sarcoma, E) bladder, F) head and neck. We assigned patients into 4 categories based on NLR low/high and TMB low/high using median within cancer type as cutoff for both variables; P values according to Pearson´s chi-square test or Fisher´s exact test when appropriate.

Supplementary Table 1. Characteristics of patients in the study

Characteristic	No. patients (%)
Sex	
Female	788 (46.0)
Male	926 (54.0)
Age, median, years (IQR)	64 (55-71)
Cancer type	
NSCLC	666 (38.9)
Melanoma	216 (12.6)
Renal	92 (5.4)
Sarcoma	84 (4.9)
Bladder	83 (4.8)
Head and Neck	76 (4.4)
Gastric	71 (4.1)
Endometrial	70 (4.1)
Colorectal	68 (4.0)
Hepatobiliary	57 (3.3)
SCLC	54 (3.2)
Esophageal	49 (2.9)
Pancreatic	36 (2.1)
Mesothelioma	35 (2.0)
Ovarian	30 (1.8)
Breast	27 (1.6)
Performance status	
ECOG 0	589 (34.4)
ECOG 1	860 (50.2)
ECOG ≥2	138 (8.1)
Unknown	127 (7.4)
Drug class	
PD-1/PD-L1	1422 (83.0)
CTLA-4	7 (0.4)
Combo	285 (16.6)
ICI line of treatment	
First line	522 (30.5)
Subsequent line	1192 (69.5)
Stage	
I-III	105 (6.1)
IV	1577 (92.0)
Unknown	32 (1.9)
Year of treatment	
2015-2016	448 (26.1)
2017-2018	1266 (73.9)
MSI	
Stable	1307 (76.3)
Indeterminate	51 (3.0)
Unstable	57 (3.3)
Unknown	299 (17.4)

Abbreviations: NSCLC, Non-small cell lung cancer; SCLC, small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; Combo, combination of anti-PD-1/PD-L1 and anti-CTLA-4; ICI, immune checkpoint inhibitor; MSI, microsatellite instability

Supplementary Table 2. Characteristics of patients in the validation cohort (n = 323)

Characteristic	No. patients (%)
Sex	
Female	95 (29.4)
Male	228 (70.6)
Age, median, years (IQR)	60 (52-68)
Cancer type	
Renal	136 (42.1)
CNS	75 (23.2)
Head and Neck	55 (17.0)
Unknown primary	29 (9.0)
Bladder	28 (8.7)
Performance status	
ECOG 0	142 (44.0)
ECOG 1	144 (44.6)
ECOG ≥2	26 (8.1)
Unknown	11 (3.4)
Drug class	
PD-1/PD-L1	292 (90.4)
Combo	31 (9.6)
ICI line of treatment	
First line	61 (18.9)
Subsequent line	262 (81.1)
Stage	
I-III	8 (2.5)
IV	240 (74.3)
Non-applicable	75 (23.2)
Year of treatment	
2014-2016	192 (59.4)
2017-2019	131 (40.6)
MSI	
Stable	267 (82.7)
Indeterminate	6 (1.9)
Unstable	3 (0.9)
Unknown	47 (14.6)

Abbreviations: CNS, Central nervous system; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; Combo, combination of anti-PD-1/PD-L1 and anti-CTLA-4; CTLA-4, cytotoxic T-lymphocyte antigen 4; ICI, immune checkpoint inhibitor; MSI, microsatellite instability

Supplementary Table 3. Factors associated with clinical benefit from immune checkpoint inhibitors (ICI) in the validation cohort (n = 323). Multivariable analysis including neutrophil-to-lymphocyte ratio (NLR) and tumor mutational burden (TMB) as continuous variables

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
NLR	0.868 (0.808-0.932)	<.001	0.920 (0.851-0.994)	.035
TMB, Mutations/Mb	1.023 (0.987-1.061)	.21	1.069 (1.021-1.120)	.004
Age, y	1.016 (0.998-1.033)	.08		
Sex				
Female	Ref		Ref	
Male	1.709 (1.023-2.857)	.041	1.447 (0.805-2.599)	.22
Cancer type				
Renal	Ref		Ref	
CNS	0.265 (0.141-0.496)	<.001	0.276 (0.138-0.550)	<.001
Head and Neck	0.314 (0.159-0.622)	.001	0.505 (0.233-1.097)	.08
Unknown primary	0.134 (0.044-0.406)	<.001	0.188 (0.052-0.678)	.011
Bladder	0.628 (0.276-1.428)	.27	0.526 (0.203-1.363)	.19
Performance status				
ECOG 0	Ref		Ref	
ECOG 1	0.471 (0.292-0.761)	.002	0.674 (0.394-1.152)	.15
ECOG ≥2	0.081 (0.018-0.356)	.001	0.144 (0.026-0.795)	.026
Drug class				
PD-1/PD-L1	Ref			
Combo	1.030 (0.481-2.203)	.08		
ICI line of treatment				
First line	Ref		Ref	
Subsequent line	0.409 (0.232-0.720)	.002	0.477 (0.247-0.919)	.027
Stage				
I-III	Ref			
IV	2.255 (0.446-11.404)	.33		
Year of treatment				
2014-2016	Ref			
2017-2019	0.854 (0.539-1.352)	.50		

Odds ratios (ORs) were calculated with logistic regression.

Abbreviations: OR, Odds ratio; CI, confidence interval; Mb, megabase; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; Combo, combination of anti-PD-1/PD-L1 and anti-CTLA-4; CTLA-4, cytotoxic T-lymphocyte antigen 4

Supplementary Table 4. Factors associated with clinical benefit from immune checkpoint inhibitors (ICI). Multivariable analysis including neutrophil-to-lymphocyte ratio (NLR) and tumor mutational burden (TMB) as continuous variables

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
NLR	0.927 (0.904-0.950)	<.001	0.933 (0.906-0.961)	<.001
TMB, Mutations/Mb	1.030 (1.022-1.038)	<.001	1.031 (1.021-1.041)	<.001
Age, y	1.014 (1.006-1.022)	<.001	1.012 (1.002-1.022)	.022
Sex				
Female	Ref			
Male	1.146 (0.935-1.405)	.19		
Cancer type				
Melanoma	Ref		Ref	
NSCLC	0.511 (0.374-0.698)	<.001	1.503 (0.986-2.293)	.058
Renal	0.888 (0.544-1.449)	.63	3.249 (1.769-5.967)	<.001
Sarcoma	0.309 (0.174-0.550)	<.001	1.505 (0.724-3.128)	.27
Bladder	0.381 (0.219-0.665)	.001	1.019 (0.530-1.959)	.96
Head and Neck	0.328 (0.181-0.593)	<.001	2.009 (0.987-4.087)	.054
Gastric	0.611 (0.352-1.060)	.08	2.129 (1.101-4.120)	.025
Endometrial	0.664 (0.383-1.151)	.14	1.980 (1.012-3.876)	.046
Colorectal	0.352 (0.191-0.649)	.001	0.826 (0.373-1.826)	.64
Hepatobiliary	0.312 (0.159-0.613)	.001	1.197 (0.539-2.659)	.66
SCLC	0.270 (0.132-0.552)	<.001	1.165 (0.506-2.679)	.72
Esophageal	0.670 (0.355-1.262)	.22	2.815 (1.341-5.910)	.006
Pancreatic	0.030 (0.004-0.224)	.001	0.160 (0.021-1.232)	.08
Mesothelioma	0.313 (0.136-0.720)	.006	1.503 (0.589-3.833)	.39
Ovarian	0.211 (0.078-0.573)	.002	0.913 (0.307-2.715)	.87
Breast	0.184 (0.062-0.549)	.002	0.798 (0.215-2.963)	.74
Performance status				
ECOG 0	Ref		Ref	
ECOG 1	0.519 (0.416-0.647)	<.001	0.653 (0.504-0.847)	.001
ECOG ≥2	0.203 (0.121-0.343)	<.001	0.244 (0.136-0.440)	<.001
Drug class				
PD-1/PD-L1	Ref			
CTLA-4	0.362 (0.043-3.019)	.35		
Combo	1.268 (0.973-1.654)	.08		
ICI line of treatment				
First line	Ref		Ref	
Subsequent line	0.296 (0.238-0.367)	<.001	0.341 (0.256-0.456)	<.001
Stage				
I-III	Ref		Ref	
IV	0.480 (0.323-0.714)	<.001	0.687 (0.429-1.101)	.12
Year of treatment				
2015-2016	Ref		Ref	
2017-2018	0.792 (0.631-0.993)	.043	0.776 (0.592-1.019)	.07

Odds ratios (ORs) were calculated with logistic regression.

Abbreviations: OR, Odds ratio; CI, confidence interval; Mb, megabase; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; Combo, combination of anti-PD-1/PD-L1 and anti-CTLA-4

Supplementary Table 5. Factors associated with clinical benefit from immune checkpoint inhibitors (ICI). Multivariable analysis including neutrophil-to-lymphocyte ratio (NLR) and tumor mutational burden (TMB) as percentile within cancer type

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
NLR				
Bottom 80%	Ref		Ref	
Top 20%	0.501 (0.379-0.663)	<.001	0.554 (0.400-0.766)	<.001
TMB				
Bottom 80%	Ref		Ref	
Top 20%	2.588 (2.027-3.304)	<.001	3.155 (2.368-4.203)	<.001
Age, y	1.014 (1.006-1.022)	<.001	1.014 (1.004-1.025)	.005
Sex				
Female	Ref			
Male	1.146 (0.935-1.405)	.19		
Cancer type				
Melanoma	Ref		Ref	
NSCLC	0.511 (0.374-0.698)	<.001	0.963 (0.641-1.446)	.86
Renal	0.888 (0.544-1.449)	.63	2.041 (1.121-3.716)	.020
Sarcoma	0.309 (0.174-0.550)	<.001	0.934 (0.454-1.919)	.85
Bladder	0.381 (0.219-0.665)	.001	0.756 (0.394-1.452)	.40
Head and Neck	0.328 (0.181-0.593)	<.001	1.019 (0.509-2.042)	.96
Gastric	0.611 (0.352-1.060)	.08	1.438 (0.746-2.771)	.28
Endometrial	0.664 (0.383-1.151)	.14	1.768 (0.911-3.429)	.09
Colorectal	0.352 (0.191-0.649)	.001	1.084 (0.522-2.250)	.83
Hepatobiliary	0.312 (0.159-0.613)	.001	0.820 (0.373-1.803)	.62
SCLC	0.270 (0.132-0.552)	<.001	0.710 (0.305-1.650)	.43
Esophageal	0.670 (0.355-1.262)	.22	2.067 (0.989-4.321)	.053
Pancreatic	0.030 (0.004-0.224)	.001	0.090 (0.012-0.699)	.021
Mesothelioma	0.313 (0.136-0.720)	.006	0.813 (0.323-2.045)	.66
Ovarian	0.211 (0.078-0.573)	.002	0.597 (0.200-1.783)	.36
Breast	0.184 (0.062-0.549)	.002	0.542 (0.143-2.055)	.37
Performance status				
ECOG 0	Ref		Ref	
ECOG 1	0.519 (0.416-0.647)	<.001	0.597 (0.461-0.772)	<.001
ECOG ≥2	0.203 (0.121-0.343)	<.001	0.208 (0.117-0.370)	<.001
Drug class				
PD-1/PD-L1	Ref			
CTLA-4	0.362 (0.043-3.019)	.35		
Combo	1.268 (0.973-1.654)	.08		
ICI line of treatment				
First line	Ref		Ref	
Subsequent line	0.296 (0.238-0.367)	<.001	0.328 (0.245-0.438)	<.001
Stage				
I-III	Ref		Ref	
IV	0.480 (0.323-0.714)	<.001	0.672 (0.421-1.072)	.10
Year of treatment				
2015-2016	Ref		Ref	
2017-2018	0.792 (0.631-0.993)	.043	0.756 (0.576-0.992)	.04

Odds ratios (ORs) were calculated with logistic regression.

Abbreviations: OR, Odds ratio; CI, confidence interval; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; Combo, combination of anti-PD-1/PD-L1 and anti-CTLA-4

Supplementary Table 6. Factors associated with overall survival from treatment with immune checkpoint inhibitors (ICI)

	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
NLR + TMB[a]				
NLR high + TMB low	Ref		Ref	
NLR low + TMB low	0.493 (0.419-0.582)	<.001	0.586 (0.491-0.699)	<.001
NLR high + TMB high	0.661 (0.562-0.777)	<.001	0.726 (0.613-0.861)	<.001
NLR low + TMB high	0.387 (0.322-0.466)	<.001	0.416 (0.342-0.506)	<.001
Age, y	1.004 (0.999-1.009)	.10		
Sex				
Female	Ref			
Male	0.940 (0.831-1.062)	.32		
Cancer type				
Melanoma	Ref		Ref	
NSCLC	2.227 (1.766-2.808)	<.001	1.326 (0.994-1.768)	.055
Renal	1.208 (0.841-1.737)	.31	0.845 (0.565-1.264)	.41
Sarcoma	2.346 (1.650-3.335)	<.001	1.461 (0.950-2.246)	.08
Bladder	2.303 (1.645-3.225)	<.001	1.308 (0.895-1.909)	.17
Head and Neck	2.240 (1.573-3.190)	<.001	1.066 (0.709-1.602)	.76
Gastric	2.970 (2.094-4.212)	<.001	2.048 (1.400-2.997)	<.001
Endometrial	1.578 (1.064-2.340)	.023	0.896 (0.575-1.397)	.63
Colorectal	2.458 (1.699-3.557)	<.001	1.536 (1.009-2.340)	.045
Hepatobiliary	2.355 (1.583-3.504)	<.001	1.272 (0.814-1.988)	.29
SCLC	3.782 (2.620-5.459)	<.001	2.155 (1.414-3.283)	<.001
Esophageal	2.917 (1.934-4.401)	<.001	1.779 (1.140-2.775)	.011
Pancreatic	4.214 (2.711-6.549)	<.001	2.267 (1.399-3.675)	.001
Mesothelioma	2.828 (1.810-4.418)	<.001	1.488 (0.921-2.405)	.11
Ovarian	2.855 (1.787-4.563)	<.001	1.678 (1.009-2.790)	.046
Breast	2.823 (1.698-4.695)	<.001	1.512 (0.839-2.726)	.17
Performance status				
ECOG 0	Ref		Ref	
ECOG 1	2.032 (1.756-2.350)	<.001	1.677 (1.438-1.954)	<.001
ECOG ≥2	4.655 (3.737-5.798)	<.001	4.040 (3.208-5.088)	<.001
Drug class				
PD-1/PD-L1	Ref		Ref	
CTLA-4	1.351 (0.605-3.016)	.46	1.580 (0.626-3.989)	.33
Combo	0.764 (0.645-0.906)	.002	0.910 (0.747-1.110)	.35
ICI line of treatment				
First line	Ref		Ref	
Subsequent line	2.185 (1.886-2.533)	<.001	1.879 (1.565-2.255)	<.001
Stage				
I-III	Ref		Ref	
IV	2.456 (1.761-3.426)	<.001	1.922 (1.356-2.724)	<.001
Year of treatment				
2015-2016	Ref			
2017-2018	1.092 (0.950-1.255)	.22		

[a]Neutrophil-to-lymphocyte ratio (NLR) and tumor mutational burden (TMB) were stratified into high and low using median within cancer type as cutoff. Hazard ratios (HRs) were calculated with Cox proportional hazard regression.

Abbreviations: HR, Hazard ratio; CI, confidence interval; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; Combo, combination of anti-PD-1/PD-L1 and anti-CTLA-4

Supplementary Table 7. Factors associated with progression-free survival from treatment with immune checkpoint inhibitors (ICI)

	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
NLR + TMB[a]				
NLR high + TMB low	Ref		Ref	
NLR low + TMB low	0.687 (0.597-0.789)	<.001	0.745 (0.641-0.867)	<.001
NLR high + TMB high	0.663 (0.574-0.765)	<.001	0.686 (0.590-0.798)	<.001
NLR low + TMB high	0.475 (0.408-0.554)	<.001	0.504 (0.428-0.594)	<.001
Age, y	0.994 (0.990-0.998)	.004	0.994 (0.989-0.998)	.006
Sex				
Female	Ref			
Male	0.947 (0.854-1.050)	.30		
Cancer type				
Melanoma	Ref		Ref	
NSCLC	1.659 (1.383-1.991)	<.001	1.140 (0.912-1.426)	.25
Renal	1.046 (0.782-1.399)	.76	0.713 (0.518-0.983)	.039
Sarcoma	2.257 (1.715-2.971)	<.001	1.353 (0.972-1.883)	.07
Bladder	1.619 (1.212-2.162)	.001	1.111 (0.809-1.527)	.52
Head and Neck	1.986 (1.489-2.650)	<.001	1.075 (0.775-1.490)	.67
Gastric	1.959 (1.464-2.622)	<.001	1.359 (0.994-1.859)	.055
Endometrial	1.431 (1.055-1.941)	.021	0.900 (0.639-1.267)	.55
Colorectal	1.834 (1.350-2.492)	<.001	1.182 (0.835-1.672)	.35
Hepatobiliary	1.783 (1.293-2.459)	<.001	1.052 (0.738-1.499)	.78
SCLC	2.728 (1.985-3.749)	<.001	1.817 (1.269-2.601)	.001
Esophageal	1.591 (1.117-2.265)	.010	1.038 (0.714-1.510)	.85
Pancreatic	4.147 (2.872-5.988)	<.001	2.529 (1.704-3.754)	<.001
Mesothelioma	1.979 (1.349-2.903)	<.001	1.136 (0.754-1.712)	.54
Ovarian	1.882 (1.239-2.858)	.003	1.162 (0.746-1.809)	.51
Breast	2.043 (1.325-3.148)	.001	1.156 (0.718-1.862)	.55
Performance status				
ECOG 0	Ref		Ref	
ECOG 1	1.523 (1.355-1.711)	<.001	1.363 (1.203-1.545)	<.001
ECOG ≥2	2.764 (2.271-3.364)	<.001	2.536 (3.208-3.122)	<.001
Drug class				
PD-1/PD-L1	Ref			
CTLA-4	1.295 (0.605-2.722)	.50		
Combo	0.933 (0.811-1.074)	.33		
ICI line of treatment				
First line	Ref		Ref	
Subsequent line	1.883 (1.672-2.121)	<.001	1.703 (1.467-1.977)	<.001
Stage				
I-III	Ref		Ref	
IV	1.760 (1.383-2.238)	<.001	1.555 (1.206-2.006)	.001
Year of treatment				
2015-2016	Ref			
2017-2018	1.096 (0.974-1.234)	.13		

[a]Neutrophil-to-lymphocyte ratio (NLR) and tumor mutational burden (TMB) were stratified into high and low using median within cancer type as cutoff. Hazard ratios (HRs) were calculated with Cox proportional hazard regression.

Abbreviations: HR, Hazard ratio; CI, confidence interval; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; Combo, combination of anti-PD-1/PD-L1 and anti-CTLA-4

Supplementary Table 8. Factors associated with response from treatment with immune checkpoint inhibitors (ICI)

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
NLR + TMB[a]				
NLR high + TMB low	Ref		Ref	
NLR low + TMB low	1.578 (1.133-2.198)	.007	1.358 (0.933-1.977)	.11
NLR high + TMB high	1.996 (1.437-2.771)	<.001	1.902 (1.318-2.744)	.001
NLR low + TMB high	3.075 (2.216-4.267)	<.001	2.786 (1.923-4.037)	<.001
Age, y	1.012 (1.004-1.021)	.004	1.014 (1.003-1.024)	.012
Sex				
Female	Ref			
Male	1.171 (0.944-1.453)	.15		
Cancer type				
Melanoma	Ref		Ref	
NSCLC	0.414 (0.300-0.570)	<.001	0.732 (0.483-1.111)	.14
Renal	0.825 (0.503-1.355)	.45	1.653 (0.903-3.024)	.10
Sarcoma	0.289 (0.157-0.530)	<.001	0.734 (0.346-1.559)	.42
Bladder	0.249 (0.132-0.469)	<.001	0.472 (0.230-0.969)	.041
Head and Neck	0.353 (0.194-0.646)	.001	1.112 (0.547-2.260)	.77
Gastric	0.515 (0.290-0.916)	.024	1.085 (0.558-2.109)	.81
Endometrial	0.526 (0.295-0.936)	.029	1.339 (0.675-2.659)	.40
Colorectal	0.318 (0.167-0.607)	.001	0.872 (0.405-1.876)	.73
Hepatobiliary	0.200 (0.091-0.443)	<.001	0.594 (0.247-1.430)	.25
SCLC	0.314 (0.154-0.641)	.001	0.805 (0.349-1.855)	.61
Esophageal	0.652 (0.341-1.244)	.19	1.766 (0.844-3.698)	.13
Pancreatic	0.035 (0.005-0.260)	.001	0.101 (0.013-0.781)	.028
Mesothelioma	0.254 (0.101-0.636)	.003	0.694 (0.258-1.867)	.47
Ovarian	0.245 (0.091-0.665)	.006	0.711 (0.241-2.102)	.54
Breast	0.213 (0.071-0.638)	.006	0.675 (0.178-2.556)	.56
Performance status				
ECOG 0	Ref		Ref	
ECOG 1	0.501 (0.397-0.632)	<.001	0.596 (0.455-0.780)	<.001
ECOG ≥2	0.232 (0.134-0.400)	<.001	0.257 (0.143-0.463)	<.001
Drug class				
PD-1/PD-L1	Ref		Ref	
CTLA-4	-	-	-	-
Combo	1.552 (1.182-2.037)	.002	1.082 (0.765-1.530)	.66
ICI line of treatment				
First line	Ref		Ref	
Subsequent line	0.287 (0.229-0.360)	<.001	0.334 (0.247-0.452)	<.001
Stage				
I-III	Ref		Ref	
IV	0.621 (0.411-0.940)	.024	1.015 (0.619-1.663)	.95
Year of treatment				
2015-2016	Ref		Ref	
2017-2018	0.746 (0.588-0.945)	.015	0.719 (0.541-0.959)	.023

[a]Neutrophil-to-lymphocyte ratio (NLR) and tumor mutational burden (TMB) were stratified into high and low using median within cancer type as cutoff. Odds ratios (ORs) were calculated with logistic regression.

Abbreviations: OR, Odds ratio; CI, confidence interval; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; Combo, combination of anti-PD-1/PD-L1 and anti-CTLA-4

Supplementary Table 9. Factors associated with clinical benefit from treatment with immune checkpoint inhibitors (ICI) in stage III-IV tumors (n = 1,671)

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
NLR + TMB[a]				
NLR high + TMB low	Ref		Ref	
NLR low + TMB low	1.649 (1.206-2.255)	.002	1.516 (1.065-2.157)	.021
NLR high + TMB high	1.946 (1.426-2.656)	<.001	1.888 (1.333-2.674)	<.001
NLR low + TMB high	3.527 (2.579-4.824)	<.001	3.263 (2.289-4.652)	<.001
Age, y	1.015 (1.007-1.023)	<.001	1.014 (1.004-1.024)	.006
Sex				
Female	Ref			
Male	1.147 (0.933-1.410)	.19		
Cancer type				
Melanoma	Ref		Ref	
NSCLC	0.490 (0.355-0.678)	<.001	0.995 (0.665-1.490)	.98
Renal	0.849 (0.516-1.395)	.52	2.059 (1.135-3.734)	.017
Sarcoma	0.307 (0.166-0.565)	<.001	0.901 (0.441-1.841)	.78
Bladder	0.377 (0.214-0.662)	.001	0.836 (0.435-1.606)	.59
Head and Neck	0.314 (0.172-0.571)	<.001	1.079 (0.541-2.152)	.83
Gastric	0.584 (0.334-1.020)	.059	1.486 (0.778-2.840)	.23
Endometrial	0.634 (0.363-1.107)	.11	1.831 (0.949-3.531)	.07
Colorectal	0.317 (0.169-0.594)	<.001	1.024 (0.487-2.154)	.95
Hepatobiliary	0.253 (0.123-0.518)	<.001	0.711 (0.317-1.594)	.41
SCLC	0.258 (0.126-0.531)	<.001	0.759 (0.331-1.738)	.51
Esophageal	0.640 (0.338-1.213)	.17	1.937 (0.934-4.017)	.08
Pancreatic	0.029 (0.004-0.215)	.001	0.092 (0.012-0.707)	.022
Mesothelioma	0.283 (0.117-0.685)	.005	0.829 (0.317-2.166)	.70
Ovarian	0.202 (0.074-0.549)	.002	0.655 (0.222-1.931)	.44
Breast	0.132 (0.038-0.453)	.001	0.571 (0.154-2.120)	.40
Performance status				
ECOG 0	Ref		Ref	
ECOG 1	0.515 (0.411-0.644)	<.001	0.621 (0.480-0.805)	<.001
ECOG ≥2	0.204 (0.121-0.344)	<.001	0.237 (0.135-0.415)	<.001
Drug class				
PD-1/PD-L1	Ref			
CTLA-4	0.436 (0.051-3.739)	.45		
Combo	1.261 (0.960-1.655)	.10		
ICI line of treatment				
First line	Ref		Ref	
Subsequent line	0.283 (0.226-0.353)	<.001	0.323 (0.241-0.431)	<.001
Stage				
III	Ref		Ref	
IV	0.453 (0.299-0.689)	<.001	0.650 (0.400-1.057)	.08
Year of treatment				
2015-2016	Ref		Ref	
2017-2018	0.792 (0.629-0.997)	.047	0.765 (0.583-1.003)	.052

[a]Neutrophil-to-lymphocyte ratio (NLR) and tumor mutational burden (TMB) were stratified into high and low using median within cancer type as cutoff. Odds ratios (ORs) were calculated with logistic regression.

Abbreviations: OR, Odds ratio; CI, confidence interval; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; Combo, combination of anti-PD-1/PD-L1 and anti-CTLA-4

Supplementary Table 10. Factors associated with clinical benefit from treatment with immune checkpoint inhibitors (ICI) in microsatellite stable tumors (n = 1,358)

	Univariate analysis		Multivariable analysis	
	OR (95% CI)	P	OR (95% CI)	P
NLR + TMB[a]				
NLR high + TMB low	Ref		Ref	
NLR low + TMB low	1.492 (1.059-2.100)	.022	1.390 (0.935-2.065)	.10
NLR high + TMB high	1.909 (1.356-2.689)	<.001	1.914 (1.291-2.839)	.001
NLR low + TMB high	3.435 (2.431-4.853)	<.001	3.142 (2.098-4.706)	<.001
Age, y	1.012 (1.003-1.022)	.008	1.012 (1.000-1.024)	.047
Sex				
Female	Ref			
Male	1.118 (0.888-1.408)	.34		
Cancer type				
Melanoma	Ref		Ref	
NSCLC	0.479 (0.335-0.685)	<.001	0.912 (0.568-1.464)	.70
Renal	0.831 (0.486-1.419)	.50	1.907 (0.986-3.686)	.055
Sarcoma	0.298 (0.157-0.565)	<.001	0.845 (0.384-1.858)	.68
Bladder	0.282 (0.144-0.551)	<.001	0.511 (0.232-1.123)	.10
Head and Neck	0.292 (0.146-0.583)	<.001	0.851 (0.379-1.913)	.70
Gastric	0.633 (0.351-1.142)	.13	1.526 (0.756-3.080)	.24
Endometrial	0.463 (0.233-0.920)	.028	1.416 (0.637-3.151)	.39
Colorectal	0.096 (0.033-0.282)	<.001	0.290 (0.091-0.920)	.036
Hepatobiliary	0.219 (0.096-0.501)	<.001	0.614 (0.239-1.576)	.31
SCLC	0.254 (0.115-0.562)	.001	0.686 (0.270-1.744)	.43
Esophageal	0.576 (0.278-1.193)	.14	1.494 (0.648-3.445)	.35
Pancreatic	0.030 (0.004-0.224)	.001	0.084 (0.011-0.660)	.018
Mesothelioma	0.296 (0.113-0.776)	.013	0.769 (0.263-2.246)	.63
Ovarian	0.232 (0.075-0.721)	.012	0.755 (0.222-2.569)	.65
Breast	0.219 (0.071-0.677)	.008	0.632 (0.158-2.524)	.52
Performance status				
ECOG 0	Ref		Ref	
ECOG 1	0.485 (0.378-0.623)	<.001	0.580 (0.433-0.777)	<.001
ECOG ≥2	0.135 (0.067-0.275)	<.001	0.148 (0.070-0.312)	<.001
Drug class				
PD-1/PD-L1	Ref		Ref	
CTLA-4	0.383 (0.046-3.195)	.38	0.388 (0.037-4.039)	.43
Combo	1.435 (1.061-1.941)	.019	1.112 (0.757-1.634)	.59
ICI line of treatment				
First line	Ref		Ref	
Subsequent line	0.277 (0.217-0.355)	<.001	0.325 (0.235-0.450)	<.001
Stage				
I-III	Ref		Ref	
IV	0.491 (0.308-0.782)	.003	0.653 (0.374-1.139)	.13
Year of treatment				
2015-2016	Ref			
2017-2018	0.901 (0.692-1.175)	.44		

[a]Neutrophil-to-lymphocyte ratio (NLR) and tumor mutational burden (TMB) were stratified into high and low using median within cancer type as cutoff. Odds ratios (ORs) were calculated with logistic regression.

Abbreviations: OR, Odds ratio; CI, confidence interval; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; CTLA-4, cytotoxic T-lymphocyte antigen 4; Combo, combination of anti-PD-1/PD-L1 and anti-CTLA-4