Supplemental Online Content

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eFigure 6. (A) Progression-free survival and (B) overall survival in patients with NSCLC from the non-Johns Hopkins cohorts treated with anti-PD(L)1 immunotherapy, with no irAEs, single irAEs, and multi-system irAEs
eFigure 7. (A) Progression-free survival and (B) overall survival in patients with NSCLC treated with anti-PD(L)1 monotherapy, with no irAEs, single irAEs, and multi-system irAEs
eFigure 8. (A) Progression-free survival and (B) overall survival in patients with NSCLC treated with anti-PD(L)1 immunotherapy, who had no irAEs; all <G3 multi-system irAEs; and at least 1 ≥G3 multi-system irAEs

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods

Study Population
Patients with NSCLC and treated with anti-PD(L)1 ICIs between 01/2007-01/2019 at five academic centers (Johns Hopkins Hospital, East Carolina University Hospital, Ohio State University Hospital, University of Perugia, and Sendai Kousei Hospital) were identified. Patients were included if they were ≥ 18 years of age, had pathologically-confirmed advanced NSCLC (stage III/IV), and received ≥ 1 dose of anti-PD-(L)1 monotherapy or anti-PD-(L)1-based 2-drug combinations.

Data Collection
Data were collected retrospectively and stored in institutional IRB-approved databases. Race was classified by the database manager through chart review. Options for race were defined by the investigator. Race data was collected to elucidate a potential association between race and development of multi-system irAEs, as well as to identify race as a potential risk factor for multi-system irAE development. Data from the Johns Hopkins cohort was collected between January 2007 and January 2019, from patients who received treatment between the same dates. Data from the Sendai Kousei cohort was collected between January 2016 and May 2018, from patients who received treatment between January 2016 and January 2018. Data from the East Carolina cohort was collected between June 2018 and January 2019, from patients who received treatment between April 2015 and February 2018. Data from the University of Perugia cohort was collected between October 2017 and March 2018, from patients who received treatment between October 2014 and September 2017. Data from the Ohio State cohort was collected between January 2017 and January 2018, from patients who received treatment between June 2013 and June 2016.

IrAEs were defined by the treating oncologist after alternative diagnoses had been excluded, based on: a) pathologic evidence of irAE, b) multidisciplinary adjudication, or c) clinical improvement with irAE-based management[1-3], in this rank order. Multi-system irAEs were defined as irAEs involving more than one organ system. Tumor response to ICIs was evaluated by investigator clinical assessment or Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (v.4.03) where available, 3 months after ICI start. OS was defined as time from ICI start until death from any cause. PFS was defined as time from ICI start until first radiologic evidence of tumor progression or death from any cause, whichever came first.

Statistical Analysis
Associations between patient features and irAE development were assessed. Multi-system irAEs were characterized by combinations of individual irAE or organ system, and evaluated separately for ICI-monotherapy or combinations. Time to onset of first irAE was compared for patients with single vs. multi-system irAEs using Wilcoxon rank-sum test. Median PFS and OS, and 1-year survival rates were estimated using the Kaplan-Meier method. Differences in PFS and OS between irAE groups were assessed by multivariate proportional hazards regression adjusted for age, gender, race, ECOG performance status (PS), tumor histology, stage, smoking status, ICI-combination, number of doses received, ICI duration, and center. Multivariate proportional hazards regression was used to perform the following sensitivity analysis: 1) development of multi-system irAE as a time-varying covariate, 2) stratified by cohort (Hopkins/non-Hopkins), 3) restricting to patients treated with ICI-monotherapy. The proportional hazards assumption was tested using Schoenfeld residuals. Risk for multi-system irAE was estimated as odds ratios by multivariate logistic regression. Data analysis was performed using R (R Foundation for Statistical Computing, Vienna, Austria), the R circlize package[4], and Stata (v.15, StataCorp, College Station, TX). All P values are two-sided and confidence intervals are at the 95% level, with statistical significance defined as $P \leq 0.05$.

eReferences

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3. Puzanov I, Diab A, Abdallah K et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*. 2017;5(1):95. doi:10.1186/s40425-017-0300-z
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eTable 1. Baseline clinical features of NSCLC patients treated with anti-PD-(L)1 immunotherapy, by cohort.

Characteristic	East Carolina	Ohio State	University of Perugia	Sendai Kousei	Johns Hopkins
N	68	83	158	58	256
Age, median (range)	64.5 (59, 72)	66.9 (58, 72)	63 (55, 71)	67.5 (61, 74)	67 (60, 74.5)
Gender (%)					
Male	40 (58.8)	38 (45.8)	104 (65.8)	44 (75.9)	149 (58.2)
Female	28 (41.2)	45 (54.2)	54 (34.2)	14 (24.1)	107 (41.8)
Race (%)					
African-American	23 (33.8)	11 (13.3)	0 (0.0)	0 (0.0)	45 (17.6)
Caucasian	45 (66.2)	72 (86.7)	158 (100.0)	0 (0.0)	205 (80.1)
Asian	0 (0.0)	0 (0.0)	0 (0.0)	58 (100.0)	6 (2.3)
Smoking status (%)					
Ever	60 (88.2)	76 (91.6)	133 (84.2)	43 (74.1)	201 (78.5)
Never	7 (10.3)	7 (8.4)	25 (15.8)	15 (25.9)	54 (21.1)
N/A	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Stage at diagnosis (%)					
III	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	58 (22.7)
IV	68 (100.0)	83 (100.0)	158 (100.0)	58 (100.0)	198 (77.3)
ECOG PS[a] (%)					
0/1	47 (69.1)	62 (74.7)	128 (81.0)	57 (98.3)	228 (89.1)
2	21 (30.9)	21 (25.3)	30 (19.0)	1 (1.7)	28 (10.9)
Histology (%)					
Adenocarcinoma	37 (54.4)	44 (53.0)	118 (74.7)	43 (74.1)	184 (71.9)
Squamous cell	25 (36.8)	31 (37.3)	35 (22.2)	14 (24.1)	57 (22.3)
NOS[b]	6 (8.8)	8 (9.6)	5 (3.2)	1 (1.7)	15 (5.9)
Treatment received (%)					
Monotherapy	68 (100.0)	83 (100.0)	158 (100.0)	58 (100.0)	160 (62.5)
Combination therapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	96 (37.5)
+CTLA-4[c]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	26 (10.2)
+Chemotherapy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	33 (12.9)
+Other[d]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	37 (14.5)
anti-PD(L)1[e] type (%)					
PD-1	68 (100.0)	83 (100.0)	158 (100.0)	58 (100.0)	226 (88.3)
PD-L1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	30 (11.7)
ICI duration[e], weeks (range)	8.5 (3.28, 14)	11 (4, 30)	12.9 (8.57, 34.3)	15.9 (8.14, 30)	11.4 (4.21, 30)
Best treatment response (%)					
CR, PR, SD	28 (41.2)	0 (0.0)	66 (41.8)	36 (62.1)	105 (41.0)
PD	31 (45.6)	0 (0.0)	92 (58.2)	22 (37.9)	151 (59.0)
N/A	9 (13.2)	83 (100.0)[f]	0 (0.0)	0 (0.0)	0 (0.0)

[a]ECOG PS, Eastern Cooperative Oncology Group performance status
[b]NOS, not otherwise specified
[c]CTLA-4, cytotoxic T-lymphocyte-associated antigen 4
[d]Other= anti-HER2, anti-LAG3, anti-TIM3, anti-KIR therapy; azacitidine/etinostat epigenetic priming
[e]ICI, immune checkpoint inhibitor; PD-(L)1, programmed cell death (ligand) 1
[f]Treatment response data was not collected for this cohort

eTable 2. Multivariate logistic regression of risk factors for developing multi-system irAEs in patients with NSCLC treated with anti-PD(L)1 immunotherapy.

Characteristic	Odds Ratio	P
ECOG PS[a]		
0/1	Ref	
2	0.27	0.037
Age	1.01	0.621
Cohort		
Non-Hopkins	Ref	
Hopkins	0.10	<0.001
Race		
African-American	Ref	
Caucasian	1.03	0.963
Asian/Hispanic	0.80	0.749
Sex		
Male	Ref	
Female	0.99	0.973
Histology		
Adenocarcinoma	Ref	
Squamous cell	0.48	0.080
NOS[b]	1.49	0.481
Smoking Status		
Never	Ref	
Ever	1.01	0.984
Therapy		
Monotherapy	Ref	
Combination	3.01	0.112
ICI duration[c], weeks	1.02	<0.001

[a]ECOG PS, Eastern Cooperative Oncology Group performance status
[b]NOS, not otherwise specified
[c]ICI, immune checkpoint inhibitor

eTable 3. Multivariate Cox regression model of (A) overall and (B) progression-free survival in patients with NSCLC treated with anti-PD(L)1 immunotherapy, utilizing multi-system irAEs as a categorical variable.

A

Characteristic	Hazard Ratio	P
Number of irAEs		
0	Ref	
1	0.86	0.262
≥2	0.57	0.005
Cohort		
East Carolina	Ref	
Ohio State	1.29	0.141
University of Perugia	1.27	0.353
Sendai Kousei	0.78	0.471
Johns Hopkins	0.76	0.317
ECOG PS[a]		
0/1	Ref	
2	1.80	<0.001
Age	1.00	0.702
Race		
African-American	Ref	
Caucasian	1.07	0.867
Asian/Hispanic	1.11	0.615
Sex		
Male	Ref	
Female	0.81	0.116
Histology		
Adenocarcinoma	Ref	
Squamous cell	0.90	0.432
NOS[b]	0.93	0.764
Smoking Status		
Never	Ref	
Ever	1.07	0.646
Therapy		
Monotherapy	Ref	
Combination	0.91	0.627

B

Characteristic	Hazard Ratio	P
Number of irAEs		
0	Ref	
1	0.68	0.01
≥2	0.39	<0.001
Cohort		
East Carolina	Ref	
Ohio State	1.91	<0.001
University of Perugia	1.57	0.006

Sendai Kousei	0.89	0.812
Johns Hopkins	1.10	0.569
ECOG PS		
0/1	Ref	
2	1.26	0.057
Age	0.99	0.037
Race		
African-American	Ref	
Characteristic	**Hazard Ratio**	**P**
Caucasian	0.88	0.391
Asian/Hispanic	1.34	0.510
Sex		
Male	Ref	
Female	1.06	0.540
Histology		
Adenocarcinoma	Ref	
Squamous cell	0.95	0.639
NOS	1.15	0.507
Smoking Status		
Never	Ref	
Ever	1.15	0.238
Therapy		
Monotherapy	Ref	
Combination	0.82	0.186
ICI duration, weeks	0.96	<0.001

[a]ECOG PS, Eastern Cooperative Oncology Group performance status
[b]NOS, not otherwise specified
[c]ICI, immune checkpoint inhibitor

eTable 4. Multivariate Cox regression model of (A) overall and (B) progression-free survival in patients with NSCLC treated with anti-PD(L)1 immunotherapy, utilizing multi-system irAEs as a continuous variable.

A

Characteristic	Hazard Ratio	P
Number of irAEs	0.79	0.003
Cohort		
East Carolina	Ref	
Ohio State	1.27	0.214
University of Perugia	1.25	0.202
Sendai Kousei	0.75	0.705
Johns Hopkins	0.74	0.124
ECOG PS[a]		
0/1	Ref	
2	1.80	<0.001
Age	1.00	0.461
Race		
African-American	Ref	
Caucasian	1.07	0.702
Asian/Hispanic	1.12	0.874
Sex		
Male	Ref	
Female	0.82	0.077
Histology		
Adenocarcinoma	Ref	
Squamous cell	0.90	0.398
NOS[b]	0.90	0.715
Smoking Status		
Never	Ref	
Ever	1.06	0.704
Therapy		
Monotherapy	Ref	
Combination	0.91	0.630
ICI duration[c], weeks	0.95	<0.001

B

Characteristic	Hazard Ratio	P
Number of irAEs	0.67	<0.001
Cohort		
East Carolina	Ref	
Ohio State	1.91	<0.001

University of Perugia	1.58	0.005
Sendai Kousei	0.88	0.788
Johns Hopkins	1.09	0.605
ECOG PS		
0/1	Ref	
2	1.26	0.058
Age	0.99	0.041
Race		
African-American	Ref	
Caucasian	0.88	0.360
Characteristic	**Hazard Ratio**	**P**
Asian/Hispanic	1.32	0.525
Sex		
Male	Ref	
Female	1.07	0.494
Histology		
Adenocarcinoma	Ref	
Squamous cell	0.95	0.611
NOS	1.13	0.545
Smoking Status		
Never	Ref	
Ever	1.14	0.289
Therapy		
Monotherapy	Ref	
Combination	0.81	0.161
ICI duration, weeks	0.96	<0.001

[a]ECOG PS, Eastern Cooperative Oncology Group performance status
[b]NOS, not otherwise specified
[c]ICI, immune checkpoint inhibitor

eTable 5. Multivariate Cox regression model of (A) overall and (B) progression-free survival in patients with NSCLC treated with anti-PD(L)1 immunotherapy, utilizing multi-system IrAEs as a time-varying covariate.

A

Characteristic	Hazard Ratio	P
Multi-system irAEs		
No	Ref	
Yes	0.48	0.001
Cohort		
Non-Hopkins	Ref	
Hopkins	0.57	<0.001
ECOG PS[a]		
0/1	Ref	
2	1.57	0.001
Age	1.00	0.862
Race		
African-American	Ref	
Caucasian	1.19	0.341
Asian/Hispanic	0.74	0.236
Sex		
Male	Ref	
Female	0.86	0.196
Histology		
Adenocarcinoma	Ref	
Squamous cell	0.95	0.715
NOS[b]	0.83	0.523
Smoking Status		
Never	Ref	
Current	1.13	0.464
Former	0.94	0.682
Therapy		
Monotherapy	Ref	
Combination	1.01	0.961

B

Characteristic	Hazard Ratio	P
Multi-system irAEs		
No	Ref	
Yes	0.34	<0.001
Cohort		
Non-Hopkins	Ref	

Hopkins	0.70	0.006
ECOG PS		
0/1	Ref	
2	1.21	0.111
Age	0.99	0.064
Race		
African-American	Ref	
Caucasian	0.89	0.442
Asian/Hispanic	0.84	0.406
Characteristic	**Hazard Ratio**	**P**
Sex		
Male	Ref	
Female	1.07	0.462
Histology		
Adenocarcinoma	Ref	
Squamous cell	0.96	0.725
NOS	1.25	0.300
Smoking Status		
Never	Ref	
Current	1.09	0.545
Former	1.06	0.659
Therapy		
Monotherapy	Ref	
Combination	0.84	0.245
ICI duration, weeks	0.97	<0.001

[a]ECOG PS, Eastern Cooperative Oncology Group performance status
[b]NOS, not otherwise specified
[c]ICI, immune checkpoint inhibitor

eTable 6. Multivariate Cox regression model of (A) overall and (B) progression-free survival in patients with NSCLC treated with anti-PD(L)1 monotherapy, with a sensitivity analysis stratified by cohorts.

A

	Hopkins		Non-Hopkins	
Characteristic	**Hazard Ratio**	**P**	**Hazard Ratio**	**P**
Number of irAEs				
0	Ref		Ref	
1	0.94	0.806	0.83	0.209
≥2	0.15	0.004	0.72	0.130
ECOG PS[a]				
0/1	Ref		Ref	
2	2.00	0.010	1.74	<0.001
Age	1.00	0.859	1.00	0.616
Race				
African-American	Ref		Ref	
Caucasian	1.01	0.984	1.31	0.237
Asian/Hispanic	1.19	0.821	0.86	0.621
Sex				
Male	Ref		Ref	
Female	0.83	0.358	0.84	0.208
Histology				
Adenocarcinoma	Ref		Ref	
Squamous cell	0.64	0.099	0.97	0.809
NOS[b]	0.61	0.410	0.98	0.942
Smoking Status				
Never	Ref		Ref	
Ever	1.09	0.716	1.15	0.463
Therapy				

Monotherapy	Ref		Ref	
Combination	0.83	0.362	n/a[d]	n/a
ICI duration[c], weeks	0.96	<0.001	0.95	<0.001

B

	Hopkins		Non-Hopkins	
Characteristic	**Hazard Ratio**	**P**	**Hazard Ratio**	**P**
Number of irAEs				
0	Ref		Ref	
1	0.75	0.148	0.62	<0.001
≥ 2	0.21	<0.001	0.49	<0.001
ECOG PS				
0/1	Ref		Ref	
2	1.82	0.005	1.11	0.474
	Hopkins		**Non-Hopkins**	
Characteristic	**Hazard Ratio**	**P**	**Hazard Ratio**	**P**
Age	0.99	0.160	0.99	0.183
Race				
African-American	Ref		Ref	
Caucasian	0.76	0.161	1.18	0.415
Asian/Hispanic	1.15	0.758	1.08	0.765
Sex				
Male	Ref		Ref	
Female	0.90	0.468	1.22	0.097
Histology				
Adenocarcinoma	Ref		Ref	
Squamous cell	0.73	0.090	1.03	0.801
NOS	0.96	0.894	1.29	0.346
Smoking Status				
Never	Ref		Ref	
Ever	0.94	0.739	1.32	0.095
Therapy				
Monotherapy	Ref		Ref	
Combination	0.87	0.352	n/a[d]	n/a
ICI duration, weeks	0.96	<0.001	0.96	<0.001

[a]ECOG PS, Eastern Cooperative Oncology Group performance status
[b]NOS, not otherwise specified
[c]ICI, immune checkpoint inhibitor
[d]No patients received combination therapy in the non-Hopkins cohorts.

eTable 7. Multivariate Cox regression model of (A) overall and (B) progression-free survival in patients with NSCLC treated with anti-PD(L)1 monotherapy.

A

Characteristic	Hazard Ratio	P
Number of irAEs		
0	Ref	
1	0.89	0.416
≥2	0.65	0.041
Cohort		
Non-Hopkins	Ref	
Hopkins	0.64	0.007
ECOG PS[a]		
0/1	Ref	
2	1.78	<0.001
Age	1.01	0.376
Race		
African-American	Ref	
Caucasian	1.18	0.390
Asian/Hispanic	0.82	0.460
Sex		
Male	Ref	
Female	0.85	0.181
Histology		
Adenocarcinoma	Ref	
Squamous cell	0.94	0.631
NOS[b]	1.16	0.610
Smoking Status		
Never	Ref	
Ever	1.08	0.652
ICI duration[c], weeks	0.95	<0.001

B

Characteristic	Hazard Ratio	P
Number of irAEs		
0	Ref	
1	0.67	0.001
≥2	0.45	<0.001
Cohort		

Non-Hopkins	Ref	
Hopkins	0.78	0.018
ECOG PS		
0/1	Ref	
2	1.24	0.122
Age	0.99	0.061
Race		
African-American	Ref	
Caucasian	1.04	0.588
Asian/Hispanic	0.99	0.948
Sex		
Male	Ref	
Female	1.18	0.150
Histology		
Adenocarcinoma	Ref	
Squamous cell	0.95	0.830
NOS	1.32	0.171
Smoking Status		
Never	Ref	
Characteristic	**Hazard Ratio**	**P**
Ever	1.21	0.164
ICI duration, weeks	0.96	<0.001

[a]ECOG PS, Eastern Cooperative Oncology Group performance status
[b]NOS, not otherwise specified
[c]ICI, immune checkpoint inhibitor

eTable 8. Multivariate Cox regression model of (A) overall and (B) progression-free survival in patients with NSCLC treated with anti-PD(L)1 immunotherapy, utilizing the four most common single irAEs as binary variables.

A

Characteristic	Hazard Ratio	P
Type of irAE		
Pneumonitis	0.93	0.682
Thyroiditis	0.96	0.829
Dermatitis	0.64	0.059
Colitis/Diarrhea	0.39	0.003
Cohort		
East Carolina	Ref	
Ohio State	1.37	0.109
University of Perugia	1.38	0.073
Sendai Kousei	0.85	0.853
Johns Hopkins	0.80	0.266
ECOG PS[a]		
0/1	Ref	
2	1.80	<0.001
Age	1.00	0.604
Race		
African-American	Ref	
Caucasian	1.08	0.695
Asian/Hispanic	1.13	0.871
Sex		
Male	Ref	
Female	0.84	0.119
Histology		
Adenocarcinoma	Ref	
Squamous cell	0.89	0.381
NOS[b]	0.90	0.717
Smoking Status		
Never	Ref	
Ever	1.16	0.306

Therapy		
Monotherapy	Ref	
Combination	0.97	0.878
ICI duration[c], weeks	0.95	<0.001

B

Characteristic	**Hazard Ratio**	**P**
Type of irAE		
Pneumonitis	0.75	0.047
Thyroiditis	0.94	0.723
Dermatitis	0.48	<0.001
Colitis/Diarrhea	0.38	<0.001
Cohort		
East Carolina	Ref	
Ohio State	2.17	<0.001
University of Perugia	1.80	<0.001
Sendai Kousei	0.99	0.981
Johns Hopkins	1.23	0.217
ECOG PS		
0/1	Ref	
2	1.25	0.061
Characteristic	**Hazard Ratio**	**P**
Age	0.99	0.047
Race		
African-American	Ref	
Caucasian	0.99	0.476
Asian/Hispanic	1.45	0.404
Sex		
Male	Ref	
Female	1.06	0.512
Histology		
Adenocarcinoma	Ref	
Squamous cell	0.95	0.660
NOS	1.16	0.456
Smoking Status		
Never	Ref	
Ever	1.22	0.103
Therapy		
Monotherapy	Ref	
Combination	0.84	0.245
ICI duration, weeks	0.96	<0.001

[a]ECOG PS, Eastern Cooperative Oncology Group performance status
[b]NOS, not otherwise specified
[c]ICI, immune checkpoint inhibitor

eTable 9. Multivariate Cox regression model of (A) overall and (B) progression-free survival in patients with NSCLC treated with anti-PD(L)1 immunotherapy, utilizing the four most common single irAEs as binary variables, and stratified by cohorts.

A

	Hopkins		Non-Hopkins	
Characteristic	**Hazard Ratio**	**P**	**Hazard Ratio**	**P**
Type of irAE				
Pneumonitis	1.69	0.075	0.76	0.172
Thyroiditis	0.52	0.550	0.94	0.766
Dermatitis	0.20	0.032	0.85	0.508
Colitis/Diarrhea	0.13	0.016	0.60	0.122
ECOG PS[a]				
0/1	Ref		Ref	
2	2.55	0.001	1.71	<0.001
Age	1.00	0.822	1.00	0.531
Race				
African-American	Ref		Ref	
Caucasian	0.99	0.983	1.31	0.241
Asian/Hispanic	1.12	0.886	0.87	0.651
Sex				
Male	Ref		Ref	
Female	0.90	0.618	0.85	0.231
Histology				
Adenocarcinoma	Ref		Ref	
Squamous cell	0.63	0.091	0.92	0.584
NOS[b]	0.57	0.355	0.99	0.966
Smoking Status				
Never	Ref		Ref	
Ever	1.17	0.530	1.21	0.308
Therapy				
Monotherapy	Ref		Ref	
Combination	0.90	0.610	n/a[d]	n/a

ICI duration[c], weeks	0.95	<0.001	0.95	<0.001

B

	Hopkins		Non-Hopkins	
Characteristic	**Hazard Ratio**	**P**	**Hazard Ratio**	**P**
Type of irAE				
Pneumonitis	0.85	0.501	0.69	0.041
Thyroiditis	0.22	0.052	0.98	0.921
Dermatitis	0.35	0.022	0.60	0.014
Colitis/Diarrhea	0.23	0.022	0.47	0.006
ECOG PS				
0/1	Ref		Ref	
2	1.89	0.003	1.08	0.616
Age	0.99	0.243	0.99	0.289
Race				
African-American	Ref		Ref	
Caucasian	0.69	0.064	1.24	0.309
Asian/Hispanic	1.06	0.902	1.19	0.524
Sex				
Male	Ref		Ref	
Female	0.94	0.707	1.20	0.129
Histology				
Adenocarcinoma	Ref		Ref	
	Hopkins		**Non-Hopkins**	
Characteristic	**Hazard Ratio**	**P**	**Hazard Ratio**	**P**
Squamous cell	0.72	0.080	0.96	0.736
NOS	0.92	0.791	1.30	0.320
Smoking Status				
Never	Ref		Ref	
Ever	0.92	0.644	1.42	0.039
Therapy				
Monotherapy	Ref		Ref	
Combination	0.85	0.277	n/a[d]	n/a
ICI duration, weeks	0.96	<0.001	0.96	<0.001

[a]ECOG PS, Eastern Cooperative Oncology Group performance status
[b]NOS, not otherwise specified
[c]ICI, immune checkpoint inhibitor
[d]No patients received combination therapy in the non-Hopkins cohorts.

eTable 10. Multivariate Cox regression model of multi-system irAE grade on (A) overall and (B) progression-free survival in patients with NSCLC treated with anti-PD(L)1 immunotherapy.

A

Characteristic	Hazard Ratio	P
Multi-irAE Grade		
No irAE	Ref	
All irAEs <G3	0.50	0.004
At least one irAE ≥ G3	0.75	0.434
Cohort		
East Carolina	Ref	
Ohio State	1.48	0.108
University of Perugia	1.43	0.131
Sendai Kousei	1.31	0.795
Johns Hopkins	0.78	0.306
ECOG PS[a]		
0/1	Ref	
2	1.74	<0.001
Age	1.00	0.927
Race		
African-American	Ref	
Caucasian	1.21	0.388
Asian/Hispanic	0.75	0.782
Sex		
Male	Ref	
Female	0.82	0.126
Histology		
Adenocarcinoma	Ref	
Squamous cell	1.07	0.663

NOS[b]	1.03	0.916
Smoking Status		
Never	Ref	
Ever	1.03	0.881
Therapy		
Monotherapy	Ref	
Combination	0.94	0.790
ICI duration[c], weeks	0.96	<0.001

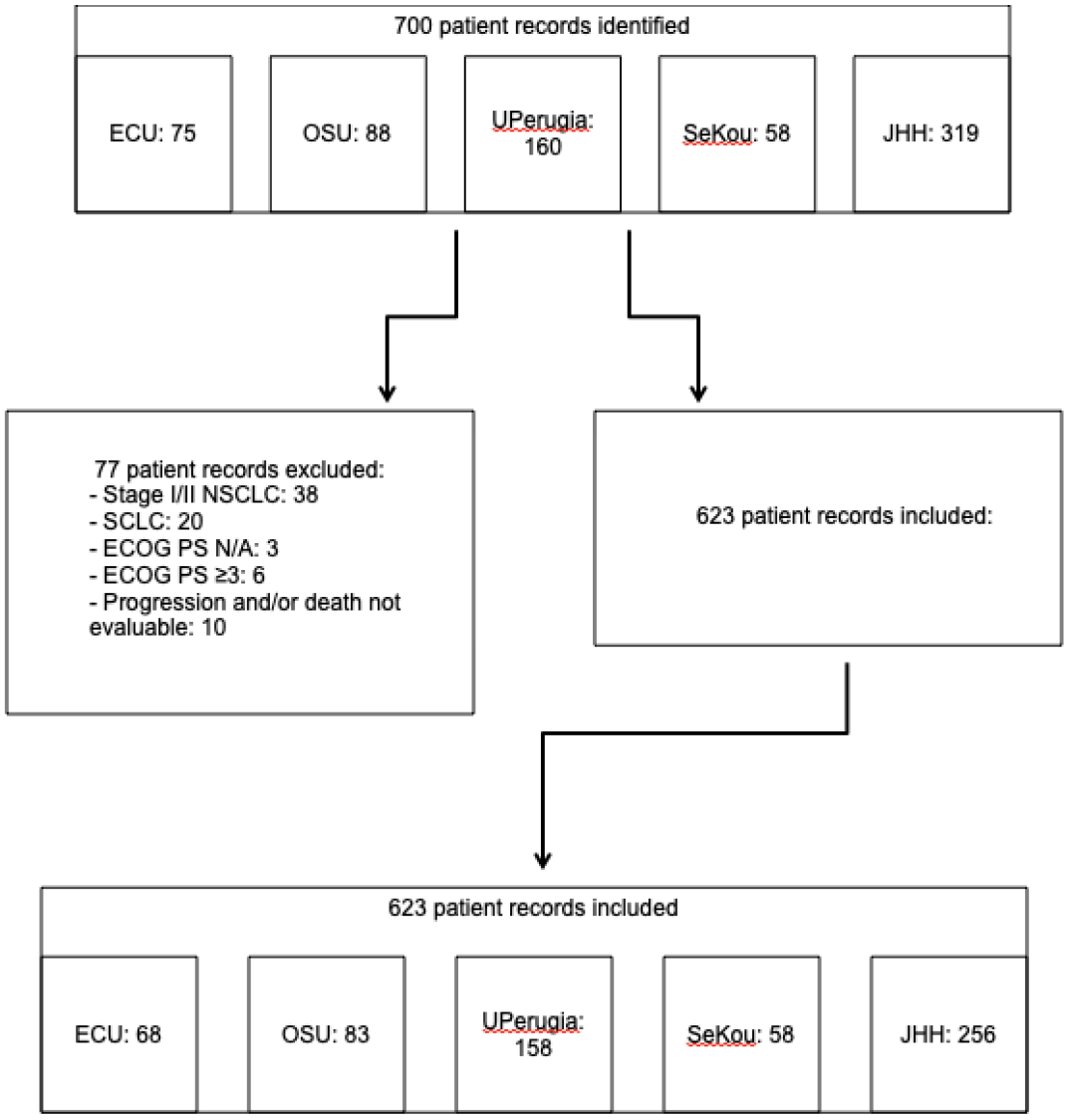
B

Characteristic	**Hazard Ratio**	**P**
Multi-irAE Grade		
No irAE	Ref	
All irAEs <G3	0.40	<0.001
At least one irAE ≥ G3	0.34	0.001
Cohort		
East Carolina	Ref	
Ohio State	2.12	0.001
Characteristic	**Hazard Ratio**	**P**
University of Perugia	1.75	0.009
Sendai Kousei	0.99	0.979
Johns Hopkins	1.16	0.473
ECOG PS		
0/1	Ref	
2	1.24	0.110
Age	0.99	0.018
Race		
African-American	Ref	
Caucasian	0.81	0.205
Asian/Hispanic	1.19	0.721
Sex		
Male	Ref	
Female	1.05	0.655
Histology		
Adenocarcinoma	Ref	
Squamous cell	0.98	0.877
NOS	1.33	0.217

Smoking Status		
Never	Ref	
Ever	1.26	0.103
Therapy		
Monotherapy	Ref	
Combination	0.86	0.359
ICI duration, weeks	0.96	<0.001

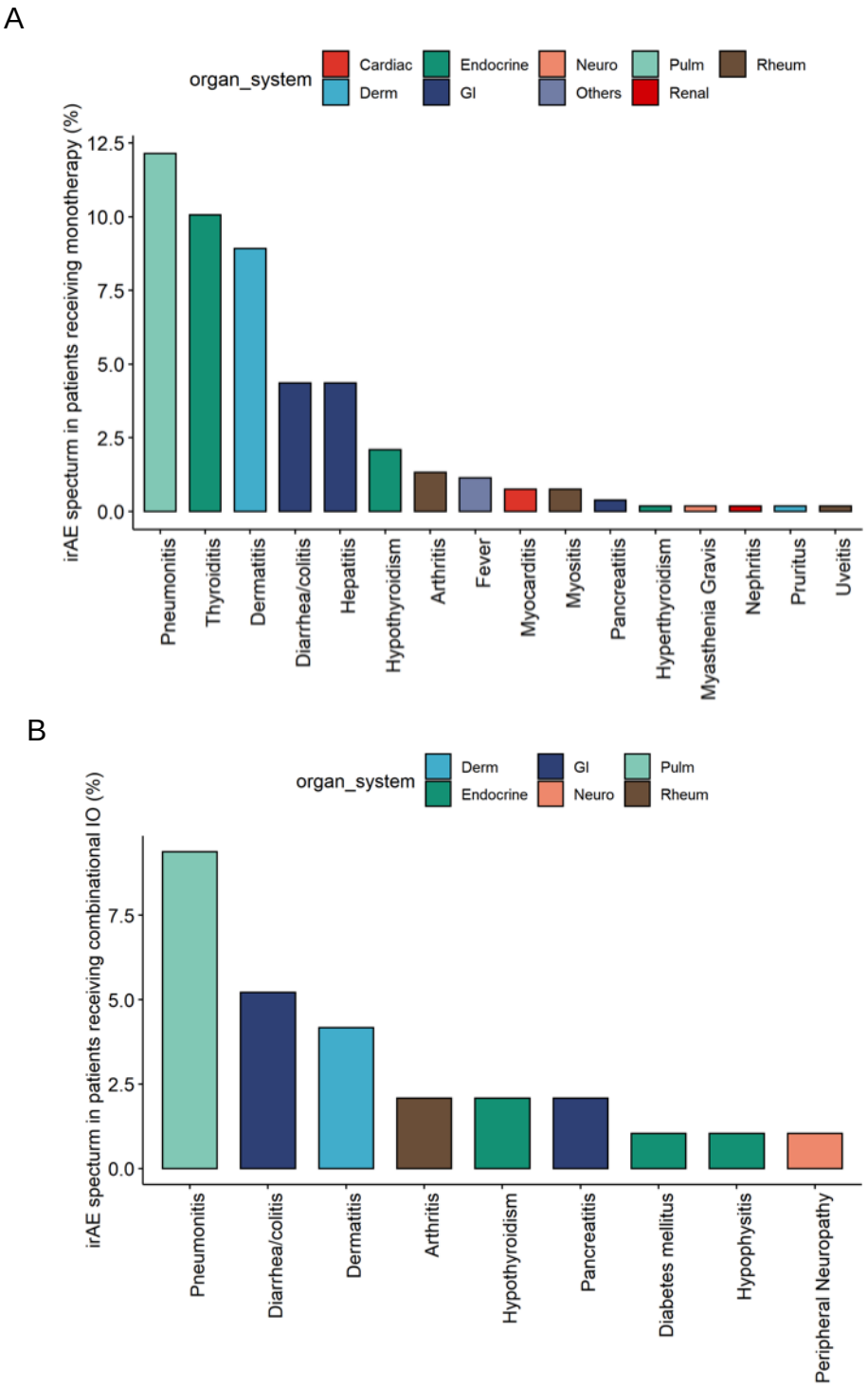
[a]ECOG PS, Eastern Cooperative Oncology Group performance status
[b]NOS, not otherwise specified
[c]ICI, immune checkpoint inhibitor

eFigure 1



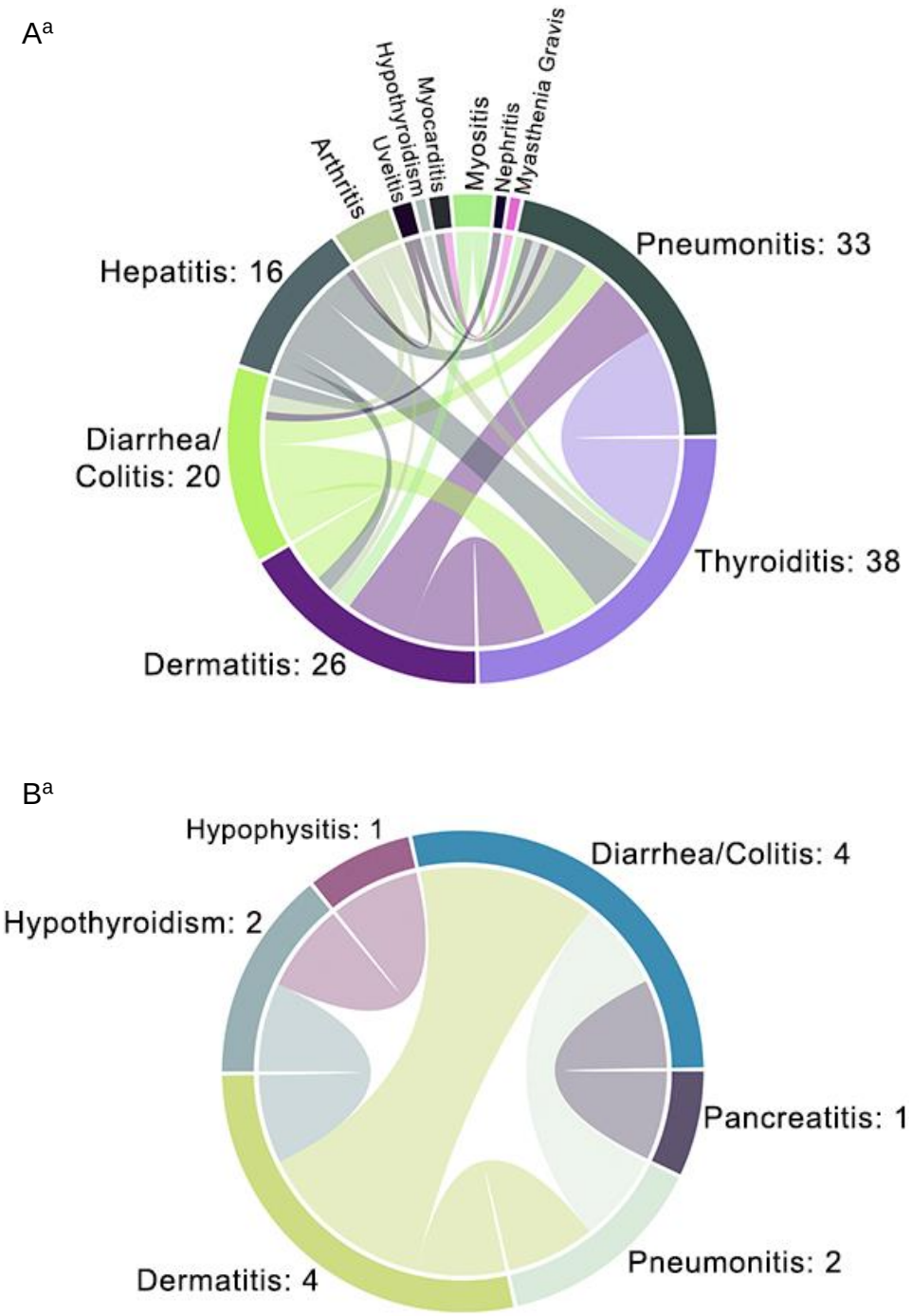
eFigure 1. Study design: inclusion and exclusion criteria.

eFigure 2



eFigure 2. Spectrum of irAEs for patients with NSCLC receiving (A) mono- or (B) combination anti-PD(L)1 immunotherapy.

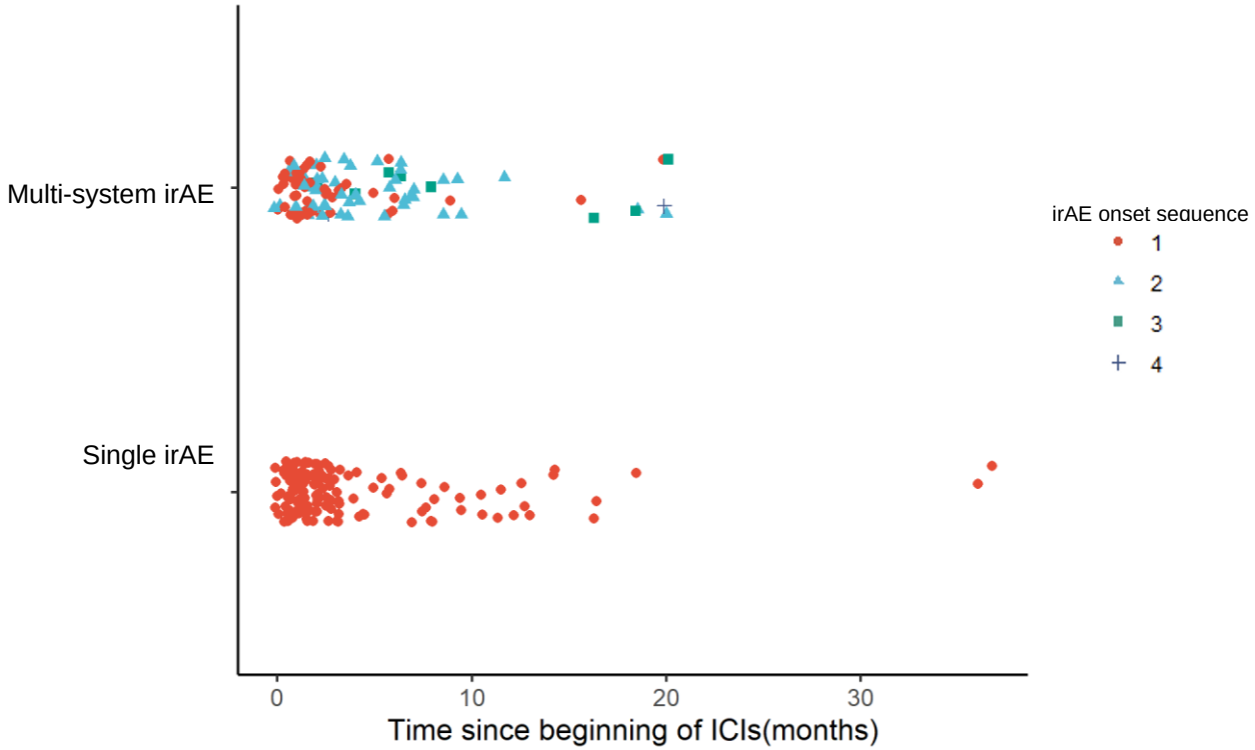
eFigure 3



eFigure 3. Chord diagram displaying the spectrum of multi-system irAEs for patients with NSCLC receiving (A) mono- or (B) combination anti-PD(L)1 immunotherapy.

[a] This figure depicts all possible pairwise combinations of irAEs for patients with multi-system irAEs, regardless of the timing of irAE development.

eFigure 4

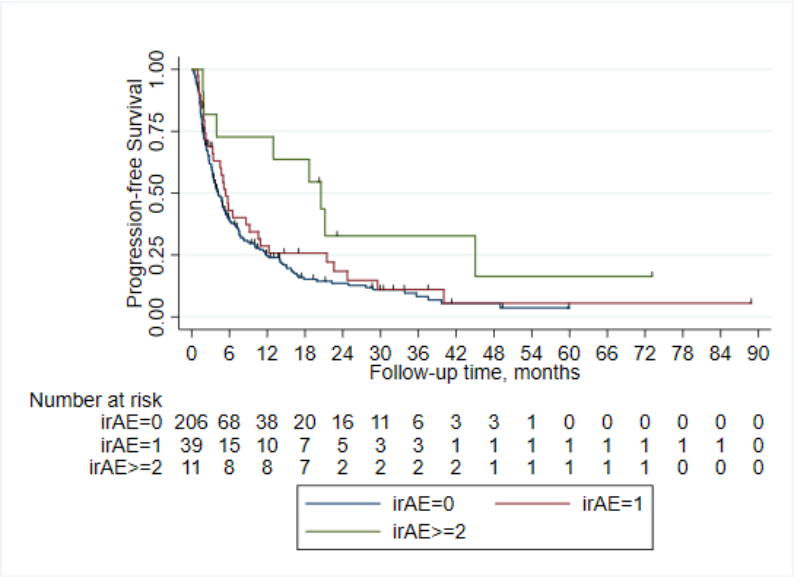


eFigure 4[a]. Time to onset of irAE in all patients with NSCLC after anti-PD(L)1 immunotherapy.

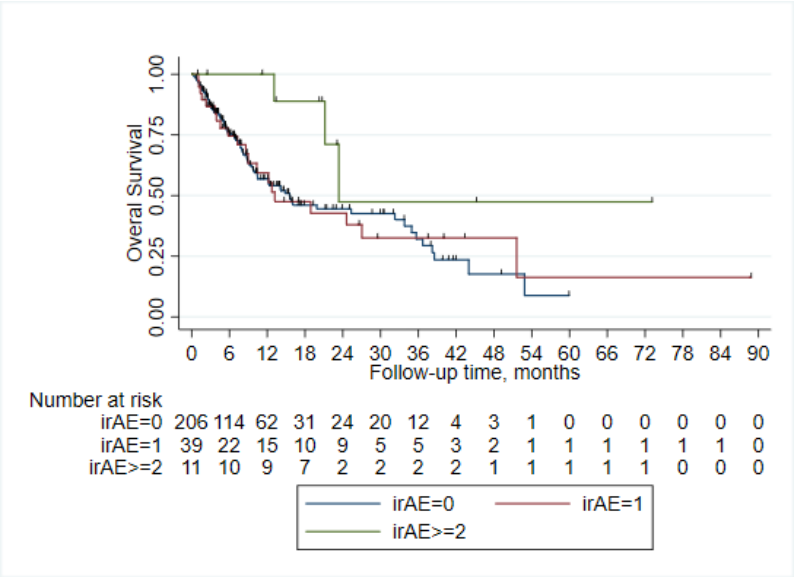
[a] Time of onset data of 7 irAE events (5% of all events) from a total of 7 patients were missing. Only patients with complete onset data for every irAE were included in this analysis (n=199).

eFigure 5

A. Progression-free Survival



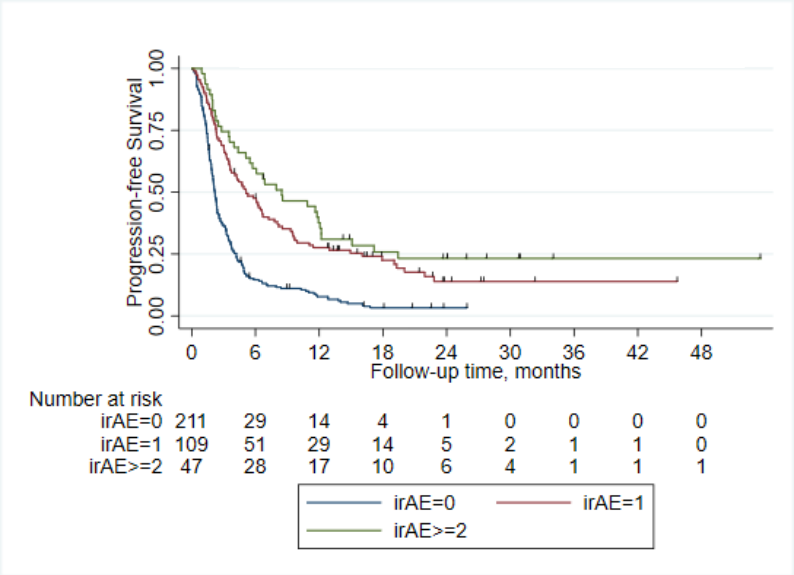
B. Overall Survival



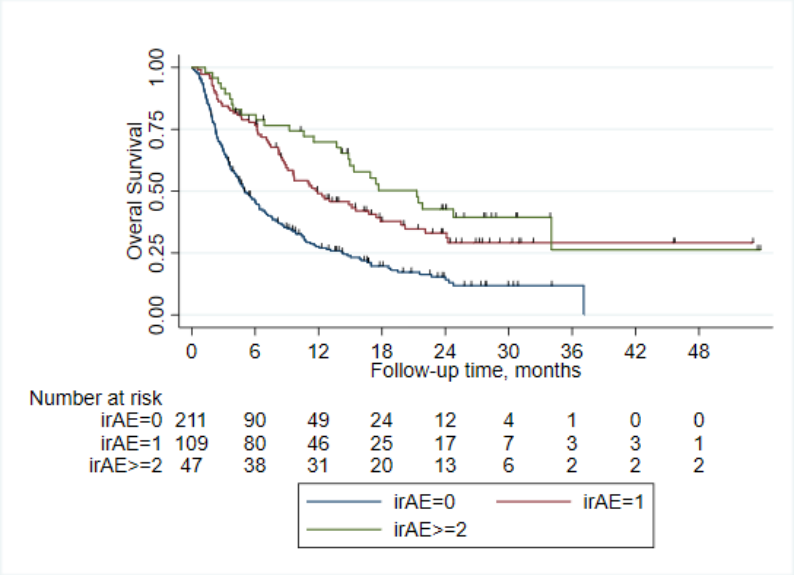
eFigure 5. A) Progression-free survival and (B) overall survival in patients with NSCLC from the Hopkins cohort treated with anti-PD(L)1 immunotherapy, with no irAEs, single irAEs, and multi-system irAEs.

eFigure 6

A. Progression-free Survival



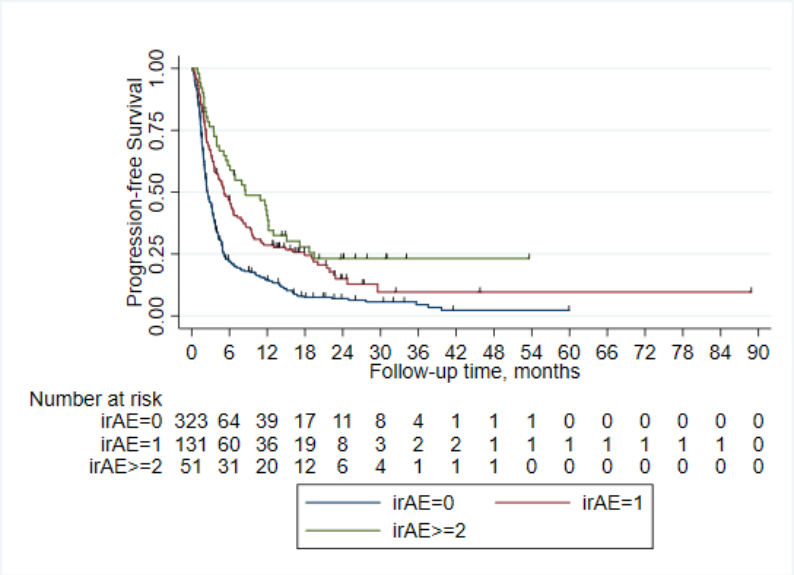
B. Overall Survival



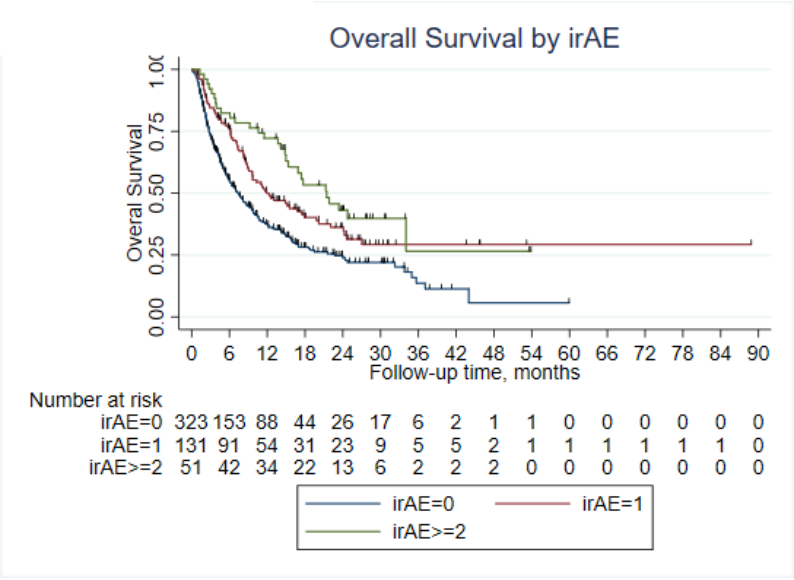
eFigure 6. A) Progression-free survival and (B) overall survival in patients with NSCLC from the non-Hopkins cohorts treated with anti-PD(L)1 immunotherapy, with no irAEs, single irAEs, and multi-system irAEs.

eFigure 7

A. Progression-free Survival



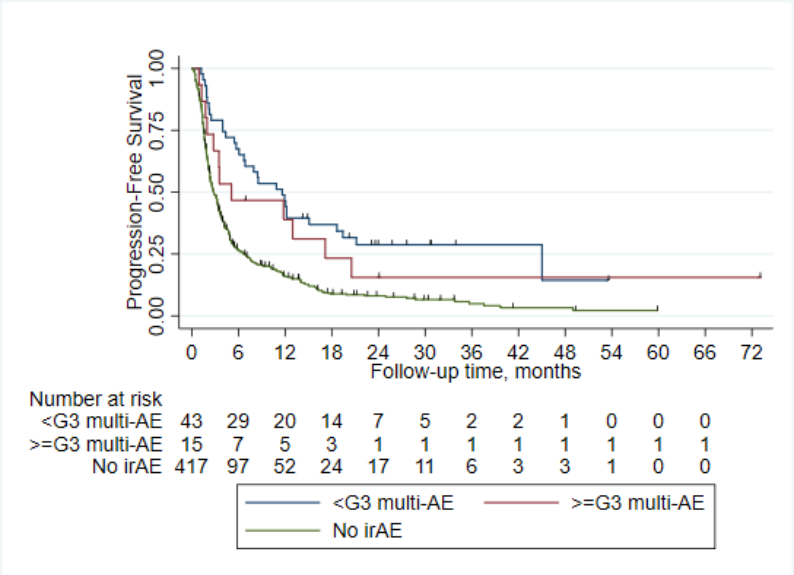
B. Overall Survival



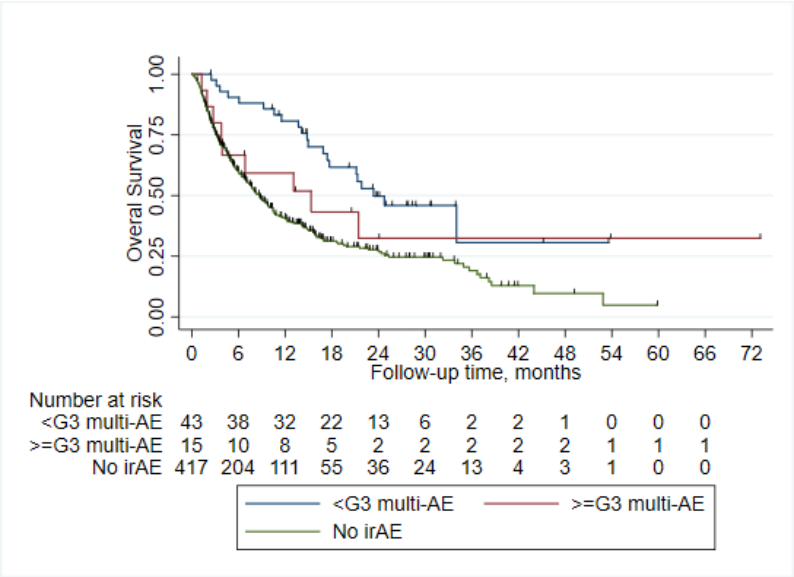
eFigure 7. A) Progression-free survival and (B) overall survival in patients with NSCLC treated with anti-PD(L)1 monotherapy, with no irAEs, single irAEs, and multi-system irAEs.

eFigure 8

A. Progression-free Survival



B. Overall Survival



eFigure 8. A) Progression-free survival and (B) overall survival in patients with NSCLC treated with anti-PD(L)1 immunotherapy, who had no irAEs; all <G3 multi-system irAEs; and at least 1 ≥G3 multi-system irAEs.