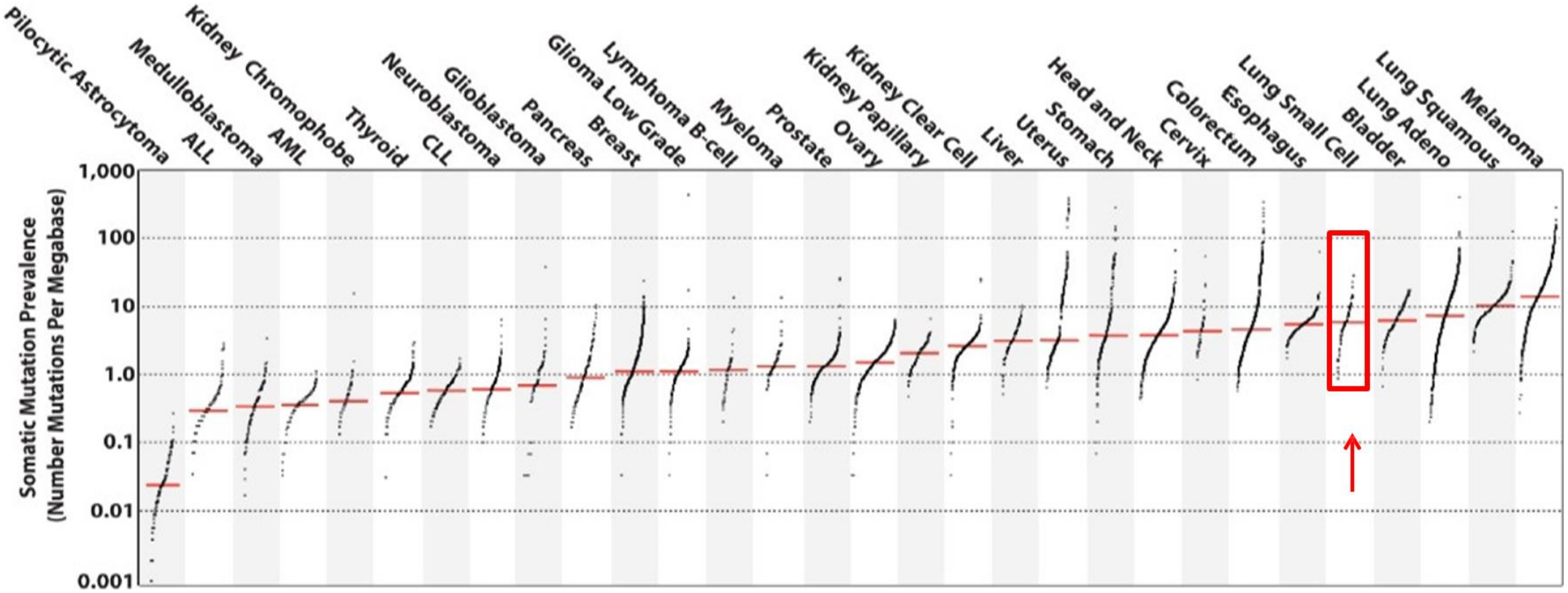
Clinical efficacy of immune checkpoint inhibitors in patients with small cell lung cancer is associated with high tumor mutational burden and development of immune-related adverse events

Biagio Ricciuti[1], Sasha Kravets[2], Suzanne Dahlberg[2], Renato Umeton[3,4], Adem Albayrak[3], Safiya J. Subegdjo[1], Bruce E. Johnson[1], Mizuki Nishino[5], Lynette M. Sholl[6], Mark M. Awad[1]

[1]Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, [2]Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, Boston, MA, [3]Department of Informatics, Dana-Farber Cancer Institute, Boston, MA, [4]Massachusetts Institute of Technology, Cambridge, MA, [5]Department of Radiology, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA. [6]Department of Pathology, Brigham and Women's Hospital, Boston, Harvard Medical School, Boston, MA

Background

- Advanced small cell lung cancer is associated with a dismal prognosis (5yr overall survival = 2%)
- High mutational load

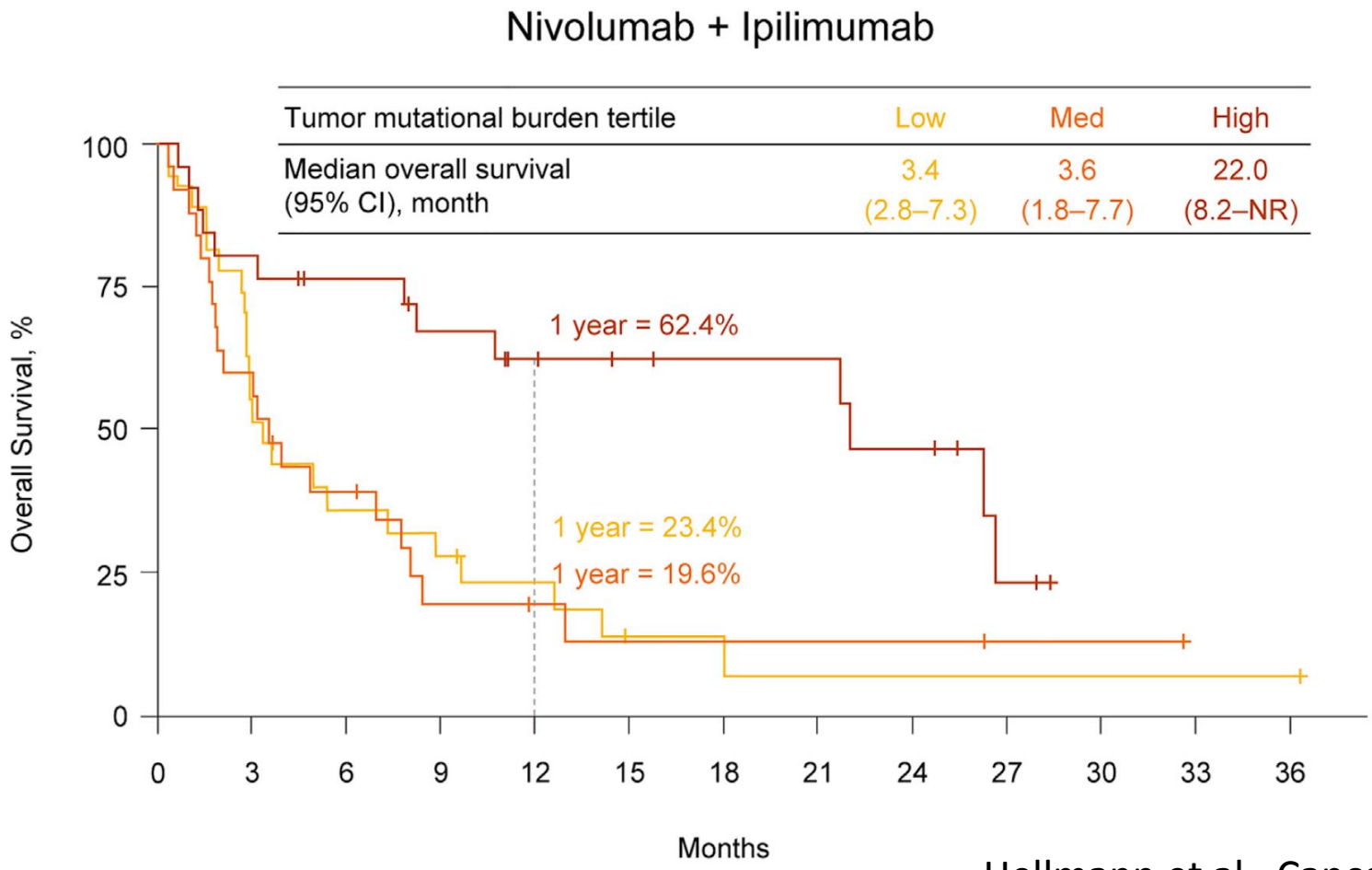


Alexandrov et al., Nature 2013

Background

- Response rates to immunotherapy are low in SCLC (10-20%)
- High tumor mutational load, as determined by whole exome sequencing (WES), correlates with immunotherapy benefit

# mutations	
Low:	0-142
Medium:	143-247
High:	>248



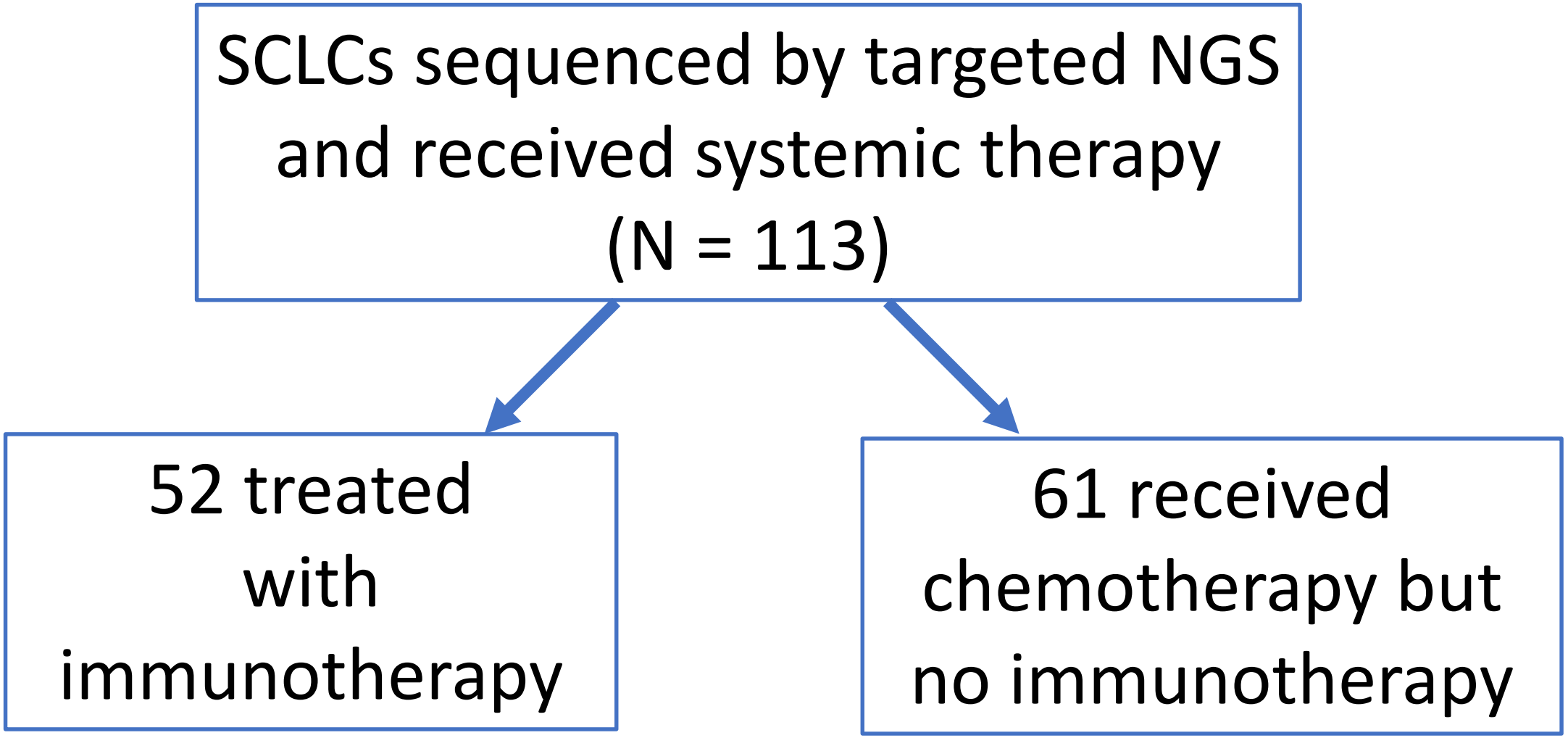
Hellmann et al., Cancer Cell 2017

Hypothesis

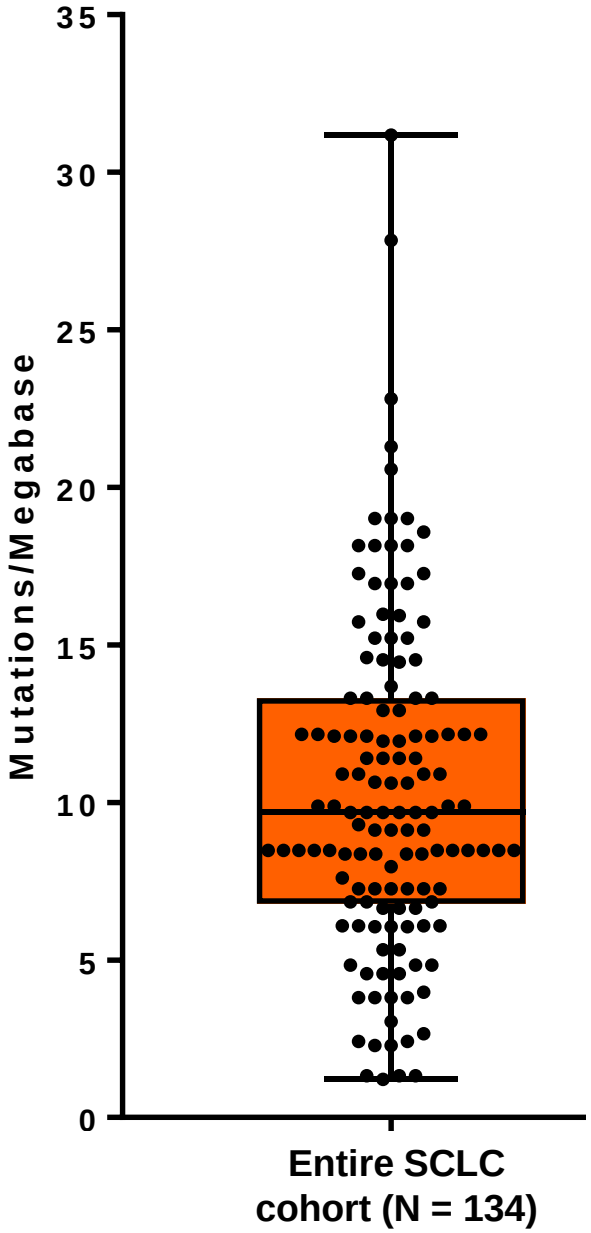
- Do clinically-available targeted next generation sequencing (NGS) panels identify patients with SCLC who benefit from immunotherapy?

- Are immune-related adverse events (irAEs) associated with benefit form immunotherapy?

Results


SCLCs sequenced by targeted NGS and received systemic therapy (N = 113)
52 treated with immunotherapy
61 received chemotherapy but no immunotherapy

TMB distribution in the entire cohort of SCLCs



TMB median: 9.68 mutations/megabase

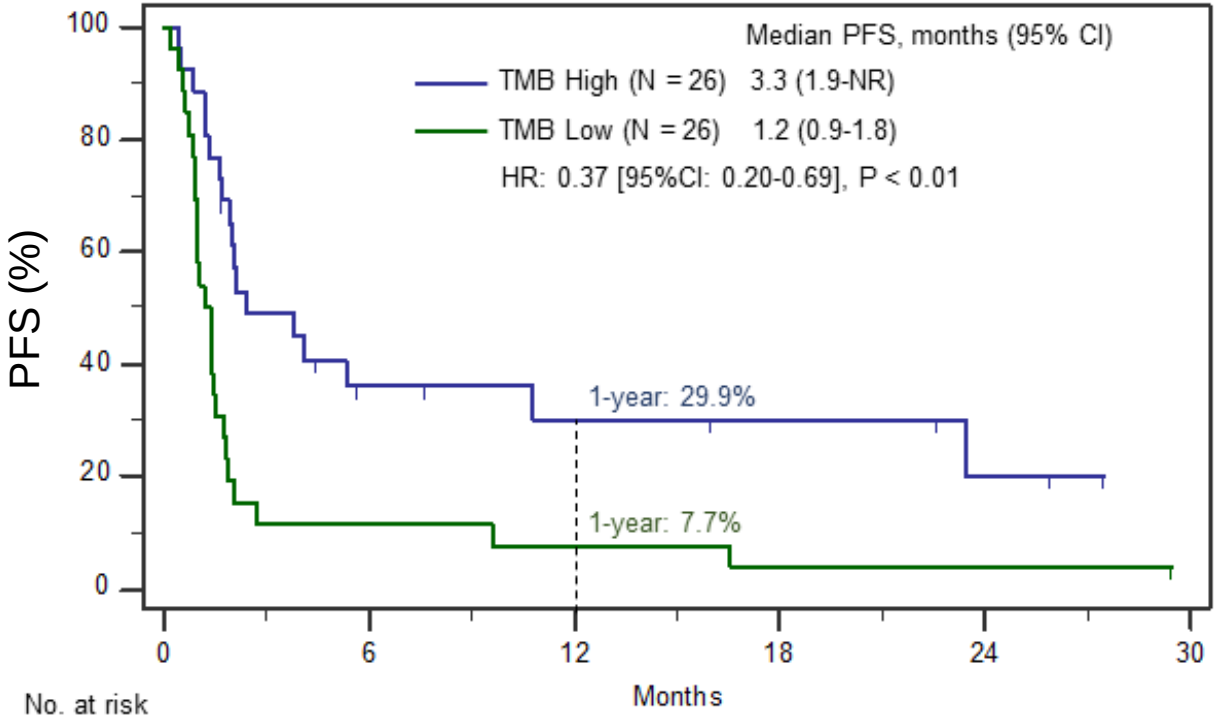
“TMB High” > median
“TMB Low” ≤ median

Baseline clinicopathologic characteristics of patients

		TMB high (> 9.68 mut/Mb) N = 26 (%)	TMB low (≤ 9.68 mut/Mb) N = 26 (%)	P
Age	Median	63.5	67.5	0.18
	Range	47 - 84	43 - 83	
Sex	Male	10 (38.5)	15 (57.7)	0.27
	Female	16 (61.5)	11 (42.3)	
Smoking Status	Current/Former	26 (100)	23 (88.5)	0.24
	Never	0 (0.0)	3 (11.5)	
Stage at Diagnosis	Extensive	15 (57.7)	19 (73.1)	0.38
	Limited	11 (42.3)	7 (26.9)	
ECOG PS	0	3 (11.5)	4 (15.4)	0.24
	1	17 (65.4)	11 (42.3)	
	2	5 (19.2)	10 (38.5)	
	3	1 (3.8)	1 (3.8)	
Platinum sensitivity	Sensitive	15 (57.7)	11 (42.3)	0.41
	Resistant	10 (38.5)	9 (34.6)	
	Refractory	1 (3.8)	6 (23.1)	
Treatment received	PD-1 inhibitor	17 (65.4)	14 (53.8)	0.57
	PD-1 + CTLA-4	9 (34.6)	12 (46.2)	
Line of therapy	2	18 (69.2)	11 (42.3)	0.09
	3	6 (23.1)	9 (34.6)	
	≥ 4	2 (7.7)	6 (23.1)	
Baseline brain metastasis	Yes	7 (26.9)	10 (38.5)	0.56
	No	19 (73.1)	16 (61.5)	

Outcomes on Immunotherapy in TMB high vs TMB low groups

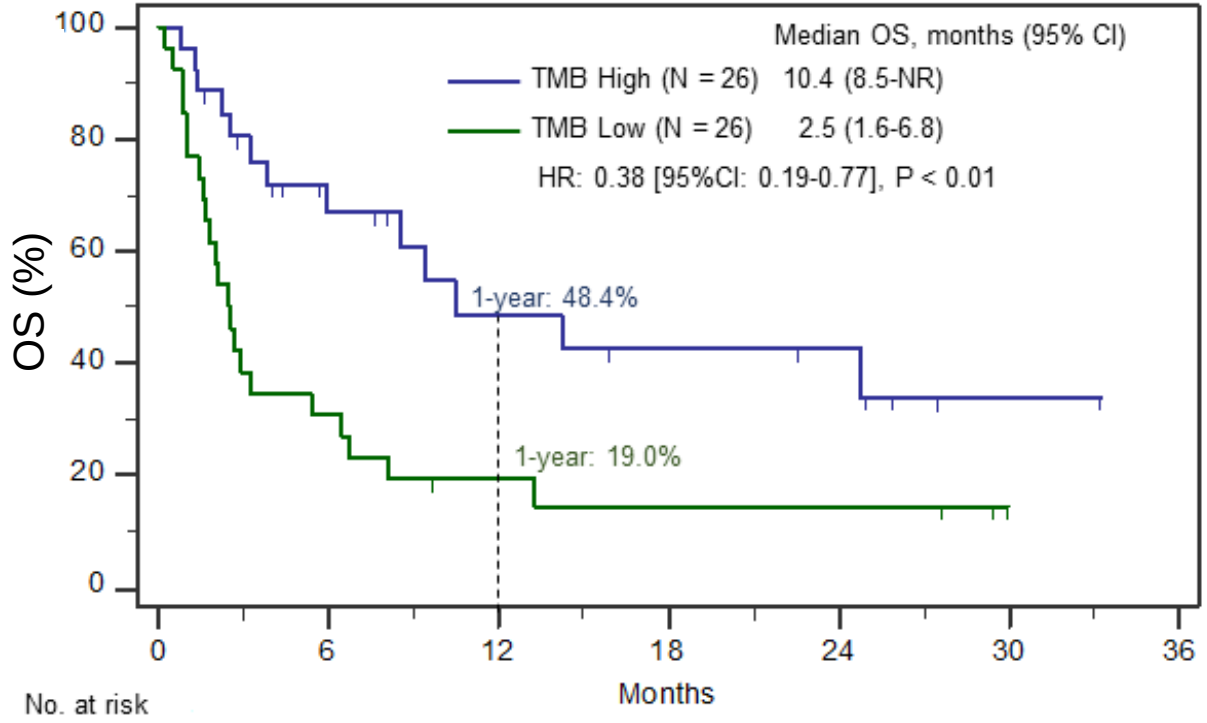
Progression-free survival



No. at risk

TMB High	26	7	5	4	2	0
TMB Low	26	3	2	1	1	0

Overall survival

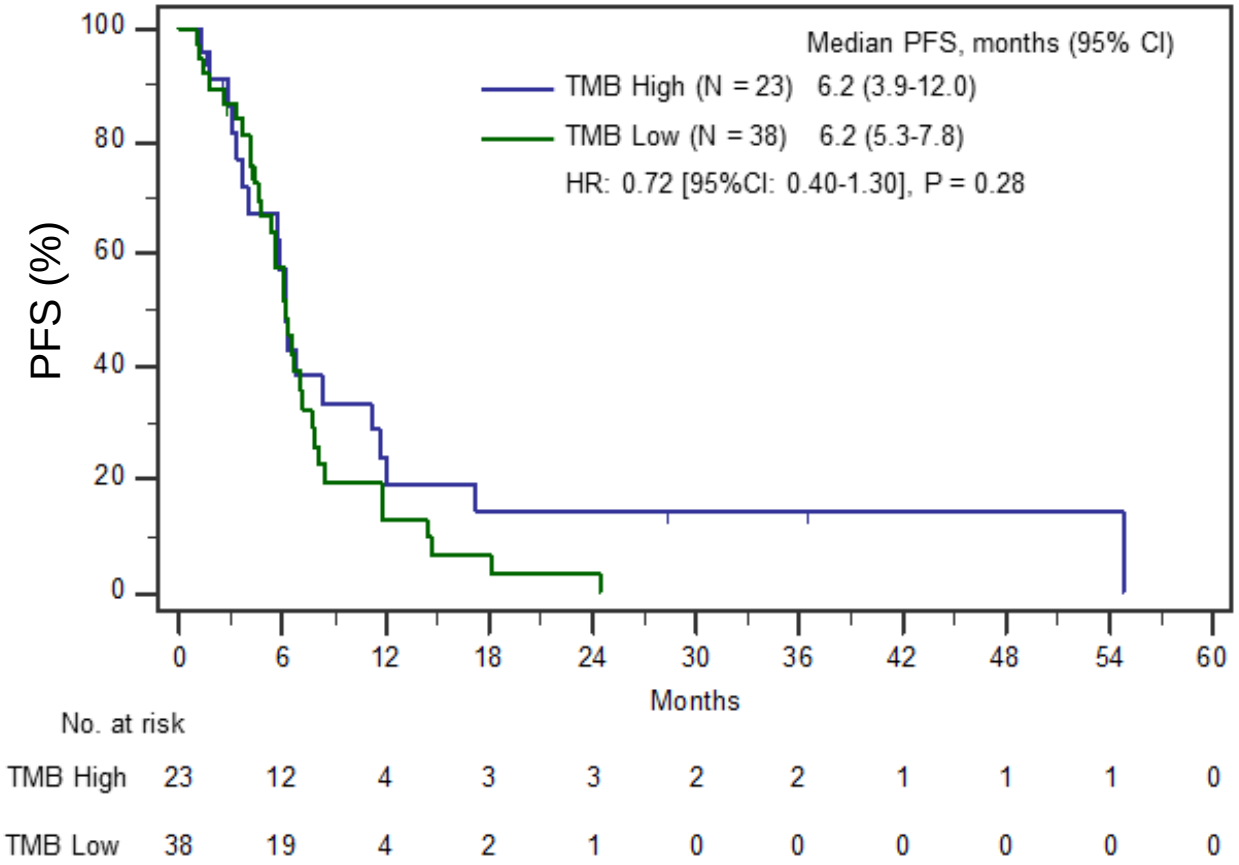


No. at risk

TMB High	26	13	8	6	5	1	0
TMB Low	26	8	4	3	3	0	0

Outcomes on Chemotherapy in TMB high vs TMB low groups

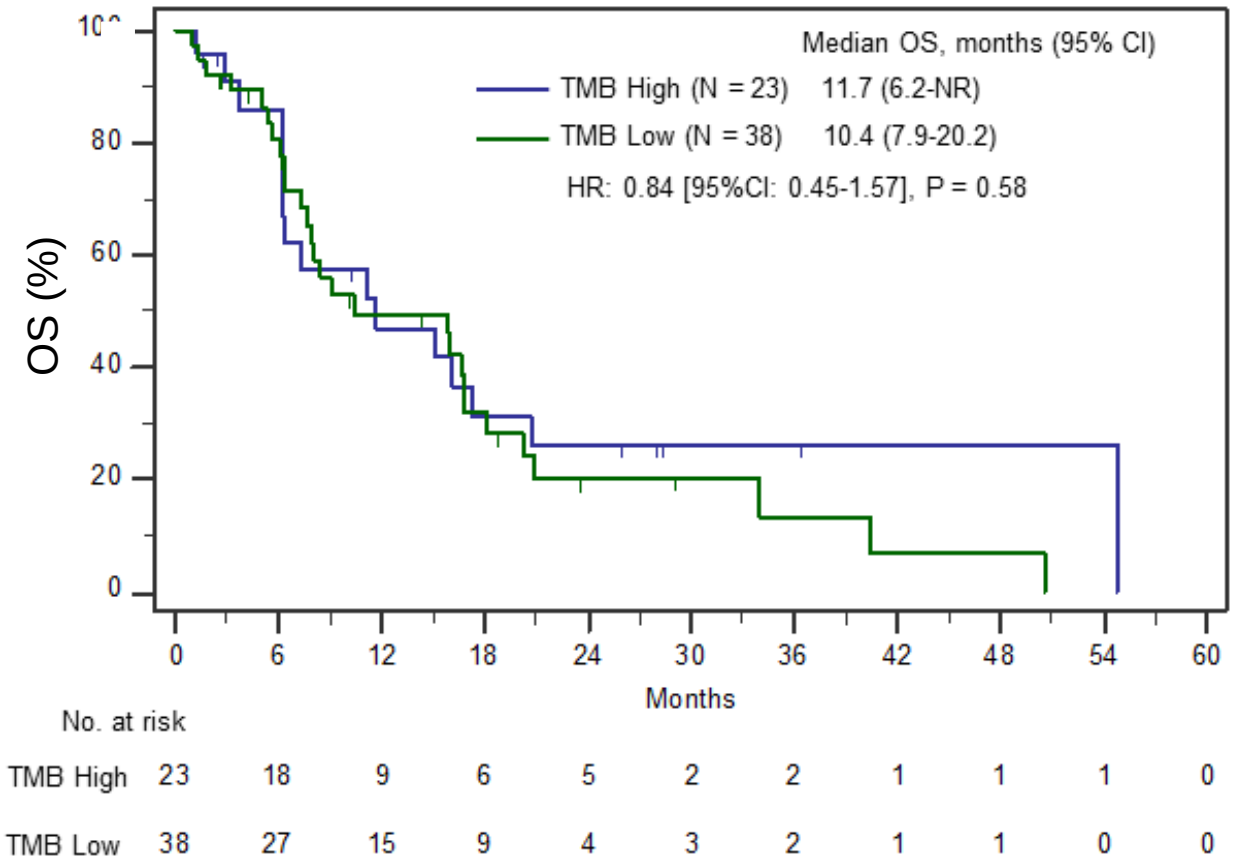
Progression-free survival



No. at risk

TMB High	23	12	4	3	3	2	2	1	1	1	0
TMB Low	38	19	4	2	1	0	0	0	0	0	0

Overall survival



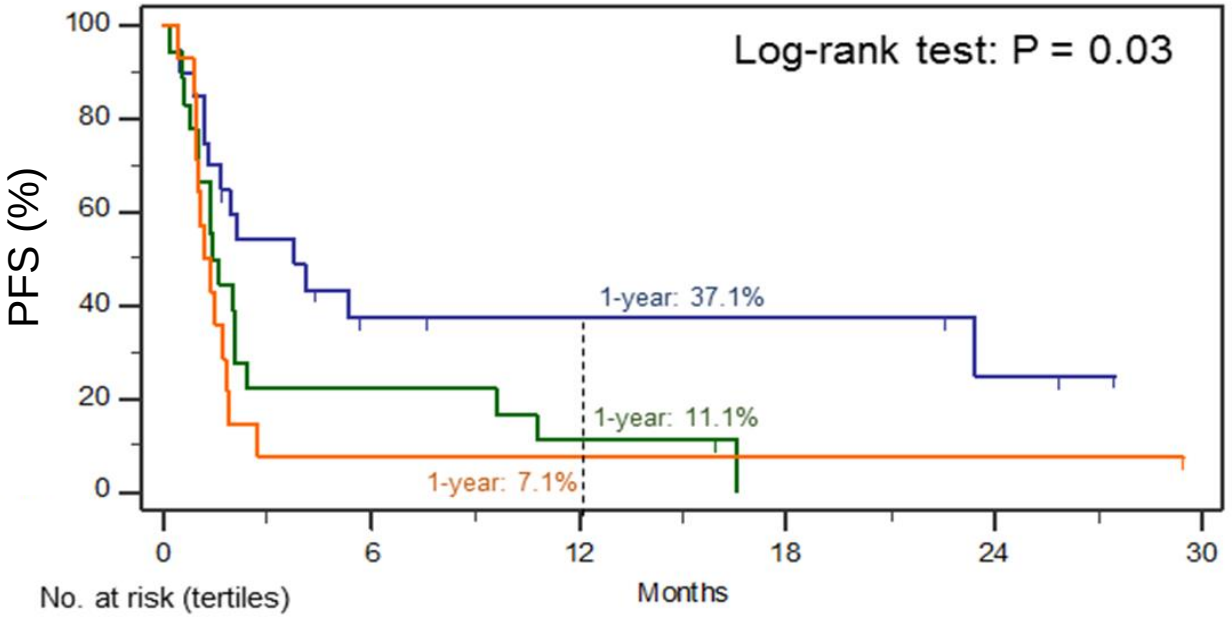
No. at risk

TMB High	23	18	9	6	5	2	2	1	1	1	0
TMB Low	38	27	15	9	4	3	2	1	1	0	0

Outcomes according to TMB tertiles

Progression-free survival

Mutations/Megabase	< 8.36	8.36-12.10	> 12.10
Tumor mutational burden tertile	Lower	Middle	Upper
Median PFS (95% CI)	1.3 (0.9-2.7)	1.5 (1.0-9.6)	3.8 (1.6-NR)

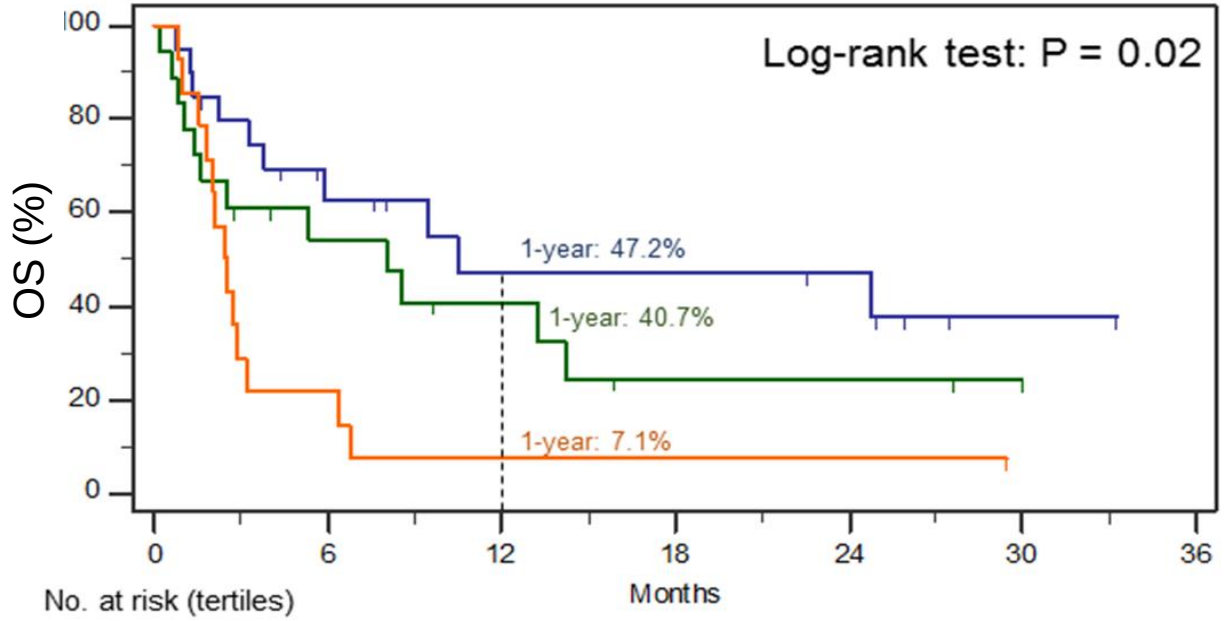


No. at risk (tertiles)

Upper	20	5	4	4	2	0
Middle	18	4	2	0	0	0
Lower	14	1	1	1	1	0

Overall survival

Mutations/Megabase	< 8.36	8.36-12.10	> 12.10
Tumor mutational burden tertile	Lower	Middle	Upper
Median OS (95% CI)	2.5 (2.1-6.8)	8.0 (1.6-14.1)	10.5 (5.9-NR)



No. at risk (tertiles)

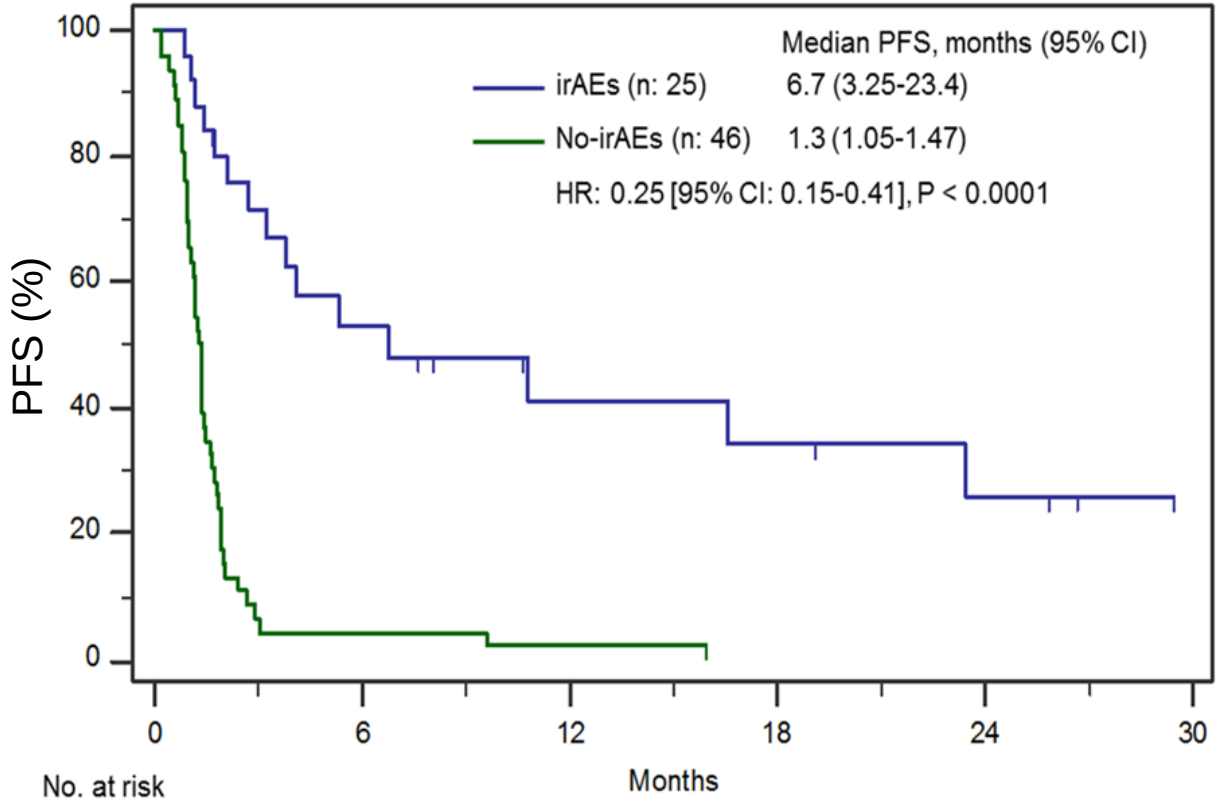
Upper	20	10	6	6	5	1	0
Middle	18	8	5	2	2	0	0
Lower	14	3	1	1	1	0	0

Association between irAEs and clinical outcome

Category	Any grade N = 25	Grade 1-2 N = 17	Grade 3-4 N= 8
Rash	3 (7.8)	3 (10.7)	-
Endocrine:			
• Thyroid disorders	5 (13.1)	5 (17.8)	-
• Hypopituitarism	1 (2.6)	1 (3.5)	-
Colitis	5 (13.1)	2 (7.1)	3 (30.0)
Hepatitis	3 (7.8)	3 (10.7)	-
Pneumonitis	5 (13.1)	2 (7.1)	3 (30.0)
Arthralgias	2 (5.2)	2 (7.1)	-
Hematological:			
• Anemia	2 (5.2)	2 (7.1)	-
• Leukopenia	2 (5.2)	1 (3.5)	1 (10.0)
CNS:			
• Encephalitis	1 (2.6)	-	1 (10.0)
• Peripheral neuropathy	1 (2.6)	1 (3.5)	-
Other:			
• Mesenteric panniculitis	1 (2.6)	-	1 (10.0)
• Lupus flare	1 (2.6)	1 (3.5)	-
• Hypersensitivity reaction	2 (2.6)	1 (3.5)	1 (10.0)
• Atrophic gastritis	1 (2.6)	1 (3.5)	-

Association between irAEs and clinical outcome

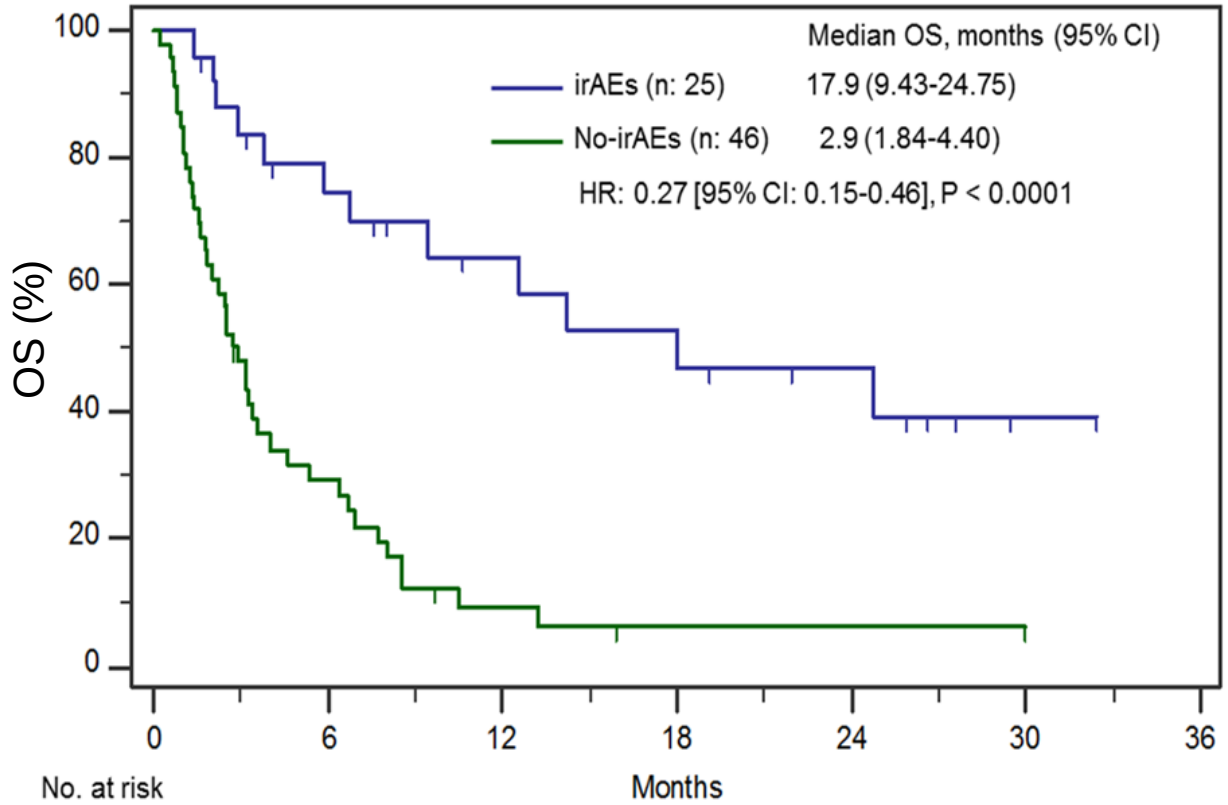
Progression-free survival



No. at risk

irAEs	25	11	6	5	3	0
No- irAEs	46	2	1	0	0	0

Overall survival

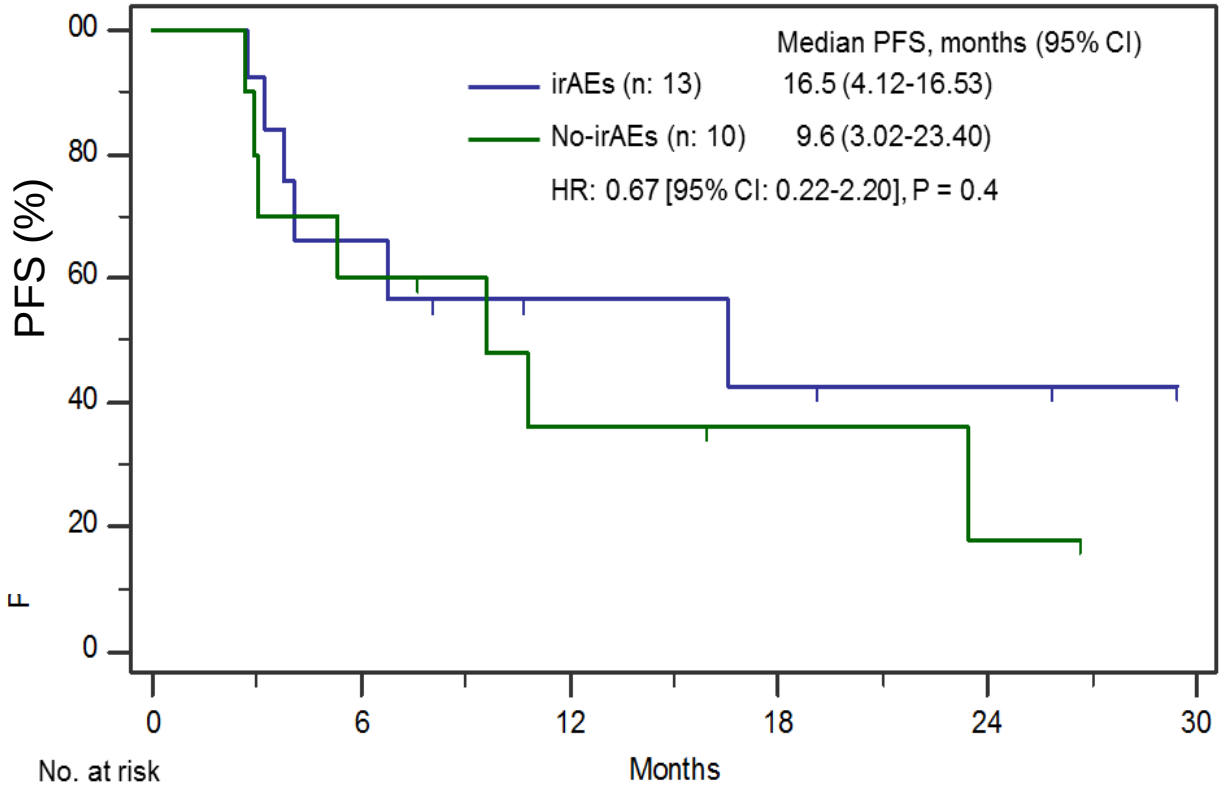


No. at risk

irAEs	25	16	11	8	6	1	0
No-irAEs	46	12	3	1	1	0	0

12-week landmark analysis

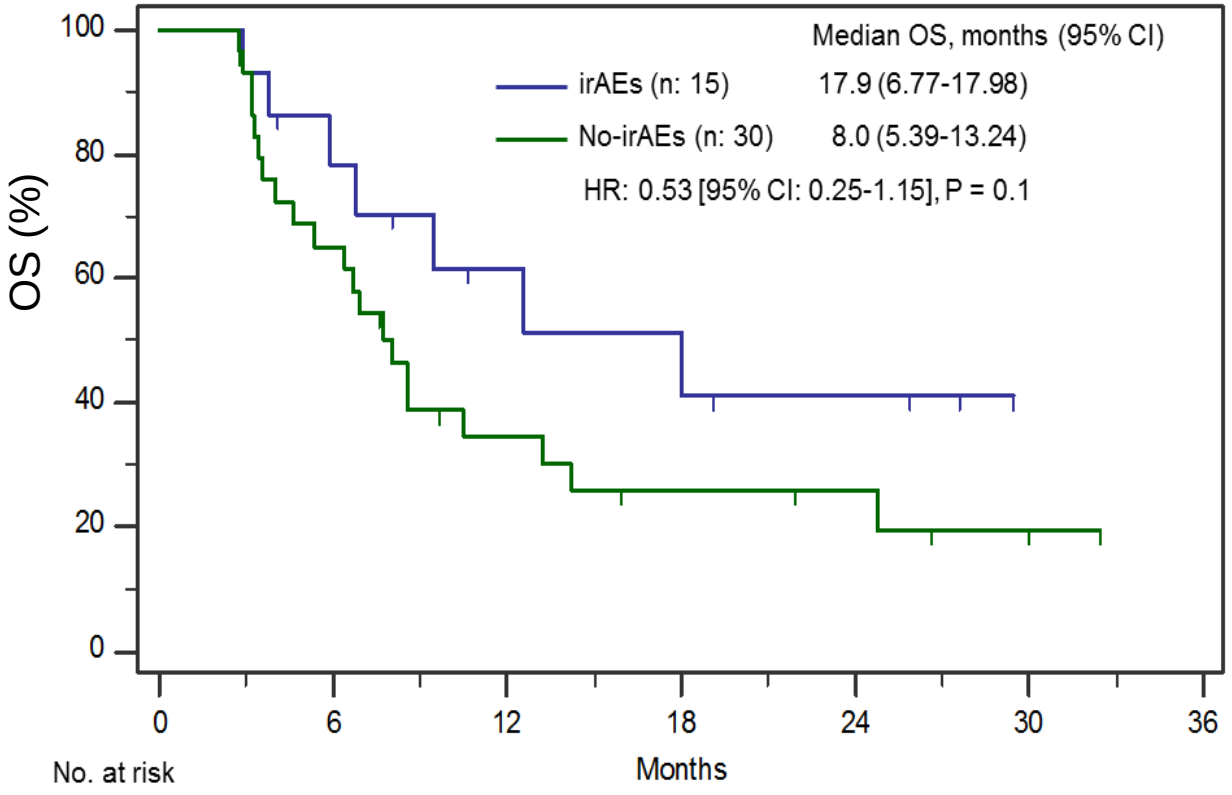
Progression-free survival



No. at risk

irAEs	13	7	4	3	2	0
No-irAEs	10	6	3	2	1	0

Overall survival



No. at risk

irAEs	15	10	6	4	3	0	0
No-irAEs	30	18	8	5	4	1	0

Conclusion

- Our data provide the first evidence for the use of targeted NGS to assess TMB status for the prediction of efficacy of immunotherapy in SCLC
- Compared to WES, TMB estimation using targeted NGS may provide a cost-effective and clinically available tool to optimize SCLC patient selection for ICIs
- irAEs might be associated with improved immunotherapy efficacy. Larger cohort studies with longer follow-up are required to further investigate this association

Acknowledgments

DFCI/BWH

Mark M. Awad

Sasha Kravets

Suzanne Dahlberg

Safiya J. Subegdjo

Bruce E. Johnson

Renato Umeton

Adem Albayrak

Mizuki Nishino

Lynette M. Sholl

DANA-FARBER CANCER INSTITUTE

BRIGHAM HEALTH

BWH BRIGHAM AND WOMEN'S HOSPITAL

Massachusetts Institute of Technology