

	All	Low TMB						High TMB						Low TMB	High TMB
		Wildtype			Altered			Wildtype			Altered				
		STK11/KEAP1/EGFR	STK11 alt	KEAP1 alt	EGFR alt	STK11/KEAP1/EGFR	Altered STK11/KEAP1/EGFR	STK11/KEAP1/EGFR	STK11 alt	KEAP1 alt	EGFR alt	STK11/KEAP1/EGFR	Altered STK11/KEAP1/EGFR		
Patients (n)	169	61 (81.3)	17 (22.7)	14 (18.7)	13 (17.3)	34 (45.3)	40 (53.3)	15 (20.0)	21 (28.0)	4 (5.3)	34 (45.3)				
Age (mean [SD])	66.3 (9.9)	68.0 (9.8)	71.4 (7.0)	66.6 (10.7)	61.2 (7.5)	65.7 (9.3)	66.6 (10.1)	63.5 (11.3)	62.7 (9.6)	63.2 (9.6)	63.6 (10.3)		P=0.23		
Gender (%)															
Male	71 (42.0)	27 (44.3)	7 (41.2)	5 (35.7)	6 (46.2)	15 (44.1)	19 (47.5)	1 (6.7)	8 (38.1)	1 (25.0)	10 (29.4)		P=1.00		
Female	98 (58.0)	34 (55.7)	10 (58.8)	9 (64.3)	7 (53.8)	19 (55.9)	21 (52.5)	14 (93.3)	13 (61.9)	3 (75.0)	24 (70.6)		P=0.15		
Smoking status (n [%])															
Current/former	145 (85.8)	50 (82.0)	15 (88.2)	12 (85.7)	8.0 (61.5)	26 (76.5)	39.0 (97.5)	15.0 (100.0)	19 (90.5)	2.0 (50.0)	30 (88.2)		P=0.59		
Never	21 (12.4)	10 (16.4)	1 (5.9)	1 (7.1)	5.0 (38.5)	7 (20.6)	1.0 (2.5)	0.0 (0.0)	1 (4.8)	2.0 (50.0)	3 (8.8)				
Unavailable	3 (1.8)	1 (1.6)	1 (5.9)	1 (7.1)	0.0 (0.0)	1 (2.9)	0.0 (0.0)	0.0 (0.0)	1 (4.8)	0.0 (0.0)	1 (2.9)				
Pack years (mean [SD])	31.4 (27.5)	29.1 (29.3)	40.6 (38.4)	36.4 (28.4)	13.3 (18.0)	30.5 (33.3)	40.0 (22.7)	28.5 (26.3)	26.7 (16.8)	10.4 (12.3)	26.1 (21.2)		P=0.37		
ECOG (%)															
0	20 (11.8)	9.0 (14.8)	1.0 (5.9)	1.0 (7.1)	2.0 (15.4)	3.0 (8.8)	4.0 (10.0)	1.0 (6.7)	4.0 (19.0)	0.0 (0.0)	4.0 (11.8)		P=0.29		
1	136 (80.5)	46.0 (75.4)	15.0 (88.2)	13.0 (92.9)	11.0 (84.6)	30.0 (88.2)	33.0 (82.5)	13.0 (86.7)	15.0 (71.4)	4.0 (100.0)	27.0 (79.4)				
2	13 (7.7)	6.0 (9.8)	1.0 (5.9)	0.0 (0.0)	0.0 (0.0)	1.0 (2.9)	3.0 (7.5)	1.0 (6.7)	2.0 (9.5)	0.0 (0.0)	3.0 (8.8)				
>2	0 (0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)				
Unavailable	0 (0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)				
Treatment (n [%])															
Nivolumab	70 (41.4)	24 (40.0)	9.0 (52.9)	6.0 (46.2)	6.0 (46.2)	15.0 (45.5)	13.0 (32.5)	6.0 (40.0)	9.0 (42.9)	3.0 (75.0)	16.0 (47.1)		P=0.36		
Pembrolizumab	62 (36.7)	22 (36.7)	2.0 (11.8)	3.0 (23.1)	4.0 (30.8)	8.0 (24.2)	21.0 (52.5)	3.0 (20.0)	8.0 (38.1)	1.0 (25.0)	11.0 (32.4)				
Atezolizumab	35 (20.7)	12 (20.0)	6.0 (35.3)	4.0 (30.8)	3.0 (23.1)	10.0 (30.3)	6.0 (15.0)	6.0 (40.0)	4.0 (19.0)	0.0 (0.0)	7.0 (20.6)				
Durvalumab	2 (1.2)	2 (3.3)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)				
Treatment line (n [%])															
1	50 (29.6)	17.0 (27.9)	6.0 (35.3)	4.0 (28.6)	1.0 (7.7)	8.0 (23.5)	12.0 (30.0)	3.0 (20.0)	12.0 (57.1)	0.0 (0.0)	13.0 (38.2)		P=0.53		
2	98 (58.0)	35.0 (57.4)	10.0 (58.8)	10.0 (71.4)	8.0 (61.5)	21.0 (61.8)	25.0 (62.5)	11.0 (73.3)	7.0 (33.3)	3.0 (75.0)	17.0 (50.0)				
3	15 (8.9)	7.0 (11.5)	0.0 (0.0)	0.0 (0.0)	2.0 (15.4)	2.0 (5.9)	3.0 (7.5)	1.0 (6.7)	2.0 (9.5)	0.0 (0.0)	3.0 (8.8)				
4	5 (3.0)	2.0 (3.3)	1.0 (5.9)	0.0 (0.0)	2.0 (15.4)	3.0 (8.8)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)				
5	1 (0.6)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	1.0 (25.0)	1.0 (2.9)				
Histology (n [%])															
Adenocarcinoma	130 (76.9)	47 (77.0)	14 (82.4)	12.0 (85.7)	10 (76.9)	27 (79.4)	27 (67.5)	14.0 (93.3)	16 (76.2)	4.0 (100.0)	29 (85.3)		P=0.65		
Squamous cell carcinoma	23 (13.6)	10 (16.4)	1 (5.9)	1.0 (7.1)	1 (7.7)	3 (8.8)	8 (20.0)	0.0 (0.0)	2 (9.5)	0.0 (0.0)	2 (5.9)				
NOS	10 (5.9)	2 (3.3)	1 (5.9)	1.0 (7.1)	1 (7.7)	2 (5.9)	4 (10.0)	0.0 (0.0)	2 (9.5)	0.0 (0.0)	2 (5.9)				

Other	6 (3.6)	2 (3.3)	1 (5.9)	0.0 (0.0)	1 (7.7)	2 (5.9)	1 (2.5)	1.0 (6.7)	1 (4.8)	0.0 (0.0)	1 (2.9)	
PD-L1 expression status (n [%])												
<1%	63 (37.3)	20 (32.8)	12 (70.6)	8.0 (57.1)	8.0 (61.5)	20 (58.8)	6 (15.0)	8 (53.3)	10 (47.6)	2.0 (50.0)	17 (50.0)	P=0.020
1-50%	38 (22.5)	16 (26.2)	2 (11.8)	2.0 (14.3)	0.0 (0.0)	3 (8.8)	11 (27.5)	4 (26.7)	3 (14.3)	1.0 (25.0)	8 (23.5)	P=0.0036
>50%	38 (22.5)	15 (24.6)	1 (5.9)	0.0 (0.0)	4.0 (30.8)	5 (14.7)	14 (35.0)	1 (6.7)	4 (19.0)	0.0 (0.0)	4 (11.8)	
Unavailable	30 (17.8)	10 (16.4)	2 (11.8)	4.0 (28.6)	1.0 (7.7)	6 (17.6)	9 (22.5)	2 (13.3)	4 (19.0)	1.0 (25.0)	5 (14.7)	
BOR (n [%])												
PD	92 (54.4)	31 (50.8)	15.0 (88.2)	13.0 (92.9)	12.0 (92.3)	30.0 (88.2)	14.0 (35.0)	8 (53.3)	11 (52.4)	3.0 (75.0)	17 (50.0)	P=0.0014
SD	30 (17.8)	11 (18.0)	1.0 (5.9)	1.0 (7.1)	1.0 (7.7)	3.0 (8.8)	7.0 (17.5)	5 (33.3)	4 (19.0)	1.0 (25.0)	9 (26.5)	P=0.031
PR	42 (24.9)	17 (27.9)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	19.0 (47.5)	1 (6.7)	5 (23.8)	0.0 (0.0)	6 (17.6)	
CR	5 (3.0)	2 (3.3)	1.0 (5.9)	0.0 (0.0)	0.0 (0.0)	1.0 (2.9)	0.0 (0.0)	1 (6.7)	1 (4.8)	0.0 (0.0)	2 (5.9)	
DCB (n [%])												
NO	103 (60.9)	36 (59.0)	16 (94.1)	14.0 (100.0)	13.0 (100.0)	33 (97.1)	15 (37.5)	10 (66.7)	12 (57.1)	3 (75.0)	19 (55.9)	P=0.00027
YES	66 (39.1)	25 (41.0)	1 (5.9)	0.0 (0.0)	0.0 (0.0)	1 (2.9)	25 (62.5)	5 (33.3)	9 (42.9)	1 (25.0)	15 (44.1)	P=0.16

Table S5. Baseline characteristics of patients in the validation cohort, stratified by the TMB and STK11/KEAP1/EGFR alteration status.

Two-sided P-values are shown for between-cohort comparisons of available data and were calculated with Wilcoxon rank-sum test (continuous variables), Fisher's exact test (dichotomous variables), or χ^2 test (discrete variables with >2 levels).