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ARTICLE

Translational Therapeutics

Immune biomarkers and response to checkpoint inhibition of *BRAF*^{V600} and *BRAF* non-V600 altered lung cancers

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BACKGROUND: While 2–4% of lung cancers possess alterations in *BRAF*, little is known about the immune responsiveness of these tumours.
METHODS: Clinical and genomic data were collected from 5945 patients with lung cancers whose tumours underwent next-generation sequencing between 2015 and 2018. Patients were followed through 2020.
RESULTS: In total, 127 patients with metastatic *BRAF*-altered lung cancers were identified: 29 tumours had Class I mutations, 59 had Class II/III alterations, and 39 had variants of unknown significance (VUS). Tumour mutation burden was higher in Class II/III than Class I-altered tumours (8.8 mutations/Mb versus 4.9, $P < 0.001$), but this difference was diminished when stratified by smoking status. The overall response rate to immune checkpoint inhibitors (ICI) was 9% in Class I-altered tumours and 26% in Class II/III ($P = 0.25$), with median time on treatment of 1.9 months in both groups. Among patients with Class I–III-altered tumours, 36-month HR for death in those who ever versus never received ICI was 1.82 (1.17–6.11). Nine patients were on ICI for >2 years (two with Class I mutations, two with Class II/III alterations, and five with VUS).
CONCLUSIONS: A subset of patients with *BRAF*-altered lung cancers achieved durable disease control on ICI. However, collectively no significant clinical benefit was seen.

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BACKGROUND

BRAF alterations have been identified in 2–4% of lung cancers [1–7]. Through the MAP kinase pathway, they can lead to cell proliferation and tumour growth [8, 9]. Three distinct categories of alterations in *BRAF* have been identified: Class I (V600) mutations are the most common *BRAF* alterations in lung cancers in most series [2–4, 8, 10–12], and operate as kinase monomers. Class II alterations, by contrast, promote kinase activity as dimers. Class III alterations have impaired kinase activity and drive signalling in a RAS-dependent, heterodimer-dependent fashion [8, 13–15].

Class I-mutant lung cancers (*BRAF*^{V600}) are clinically distinct from other *BRAF* (non-V600) alterations in several respects [3, 16]. In some studies, *BRAF*^{V600} mutations have been associated with the female sex [4, 6, 17, 18] and with being a never-smoker [1, 17]. Patients with Class I-altered cancers also may benefit from targeted therapies, including BRAF inhibitors and combined BRAF and MEK inhibitors, which have been approved by the FDA and included in national guidelines [19–24]. By contrast, patients with non-V600 mutant lung cancers may have higher rates of brain metastasis and tobacco exposure [4, 16]. Although some patients with non-V600 alterations may respond to combined BRAF and MEK inhibition [25, 26], neither BRAF nor combined BRAF and MEK inhibitors are approved to treat non-V600 mutant lung cancers [20]. Furthermore, patients with non-V600 mutant tumours have shorter survival times [4, 16, 27, 28].

Because of the relative rarity of *BRAF* alterations in lung cancers and with investigations ongoing regarding the biology of different classes of *BRAF*-mutant disease, there is limited information on the immunogenicity of these tumours [27, 29, 30]. Thus, it remains unclear whether *BRAF*-altered lung cancers are similar to other oncogene-addicted lung cancers, including those with *EGFR* and *ALK* mutations, which are generally characterised by lower tumour mutation burden (TMB) and insensitivity to immune checkpoint inhibitors (ICI) [31–37]. The IMMUNOTARGET registry recorded a 24% response rate to ICI among 43 patients with *BRAF*-mutant lung cancers across classes, suggestive of benefit among a subset of patients with the mutation [38]. However, the extent to which responses differ by *BRAF* alteration class remains unknown

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Table 1. Baseline demographic characteristics of patients with *BRAF*-altered lung cancers.

	V600	Non-V600		
	Class I ($n = 29$)	Class II ($n = 36$)	Class III ($n = 23$)	*P* value*
Median age at metastatic diagnosis, years (range)	65 (43–93)	70 (39–88)	59 (46–84)	0.70
Sex				
Female	20 (69%)	20 (56%)	14 (61%)	0.36
Smoking status				
Never	13 (45%)	4 (11%)	2 (9%)	**0.002**
Ever (median pack-years)	16 (20)	32 (30)	21 (30)	—
Histology				
Adenocarcinoma	29 (100%)	30 (83%)	23 (100%)	0.17
Squamous cell	0	3	0	—
Neuroendocrine	0	3	0	—
Co-mutation				
NF1	0	3 (8%)	4 (17%)	0.09
RAS	0	4 (11%)	2 (9%)	0.17
*EGFR***	1 (0.03%)	5 (14%)	2 (9%)	0.26
KEAP1	0	9 (25%)	14 (39%)	**<0.001**
STK11	0	9 (25%)	13 (57%)	**<0.001**
TMB (range)	4.9 (1–19.3)	8.9 (0–82.5)	9.8 (2–32.5)	**<0.001**
PD-L1 status known	11 (38%)	19 (53%)	11 (48%)	0.27
PD-L1 status				**0.039**
0%	3	11	8	
1–49%***	4	6	3	
≥50%	4	2	0	
ICI for metastatic disease (median line)	13 (2)	21 (3)	16 (2.5)	0.17****
Pembrolizumab	4	4	2	—
Nivolumab	6	11	9	—
Ipilimumab/nivolumab	2	2	1	—
Atezolizumab	1	1	0	—
Experimental*****	0	3	4	—

ICI immune checkpoint inhibitors, *TMB* tumour mutation burden.
Bold entries indicate significant *P* values.
**P* values represent comparisons between patients with V600 vs. other *BRAF* mutations.
***Sensitising mutations, including L858R and exon 19 deletion.
****Includes one case of PD-L1 staining called as "<5".
*****P* value refers to the receipt of ICI ever.
******Includes clinical trials of ICI in combination with another agent.

[27, 28, 38]. To determine whether the benefit from ICI for patients differs among classes of *BRAF* alterations, we investigated immune biomarkers as well as response to treatment of a large cohort of patients with lung cancers, with the aim of defining optimal approaches to therapy for different *BRAF* classes.

METHODS

We identified patients with lung cancers who underwent next-generation sequencing (NGS) at our institution using the MSK-IMPACT assay between January 2015 and January 2018 [39]. Data on treatment outcomes and survival were collected through April 2020. To allow sufficient time for follow-up of patients' treatment course in the metastatic setting, patients were considered to have had metastatic disease if their tumours had been found to have recurred/metastasised before June of 2019, with survival defined from the date of metastatic diagnosis. The study was approved by the Institutional Review Board, performed in accordance with the United States Common Rule, and all patients provided written informed consent for data collection.

BRAF alterations were categorised as Class I (V600), Class II or Class III, or as variants of unknown significance (VUS) using standard criteria [13, 14]. For purposes of analysis, patients were grouped into a cohort having cancers with $BRAF^{V600}$ mutant disease or as having either *BRAF* non-V600 alterations (Class II or III alterations) or VUS.

TMB was assessed using previously published methods and reported as mutations/megabase [34, 40–42]. PD-L1 was determined based on institutional standards using the verified E1L3N antibody (Cell Signaling Technology, Danvers, MA) [43].

The overall response rate (ORR) to ICI was assessed by RECIST v1.1 in all evaluable patients by a dedicated study radiologist who was blinded to treatment and mutational status. Some patients were treated with more than one line of ICI. For all patients, data from their first treatment with ICI was analysed.

Categorical variables, including clinicopathologic characteristics, were compared using Fisher's exact test. Differences in TMB were compared using the Mann–Whitney *U* test. A stratified Wilcoxon (Van Elteren) test was used to assess TMB across *BRAF* classes, stratified by smoking status. Overall survival (OS) and time to treat discontinuation (TTD) were computed using Kaplan–Meier estimates, in the former case with adjustment for left truncation to account for the time of sequencing. Patients who were known to have died prior to having available sequencing data were excluded from the survival analyses. Patients who received ICI as part of non-approved experimental combination therapy on a trial were also excluded from survival and time-on-treatment analyses.

Comparisons of survival time with respect to *BRAF* mutation status were computed using the Cox proportional hazards model with left truncation. In addition, the relationship between survival time post-metastatic diagnosis with and without ICI treatment was depicted with smoothed hazard estimates and evaluated as a time-dependent covariate in a Cox proportional hazards model.

Because of the known association between *EGFR* activating mutations (L858R or exon 19 deletions) and lack of benefit from immunotherapy [31], we carried out sensitivity analyses of survival with and without receipt of immunotherapy both including and excluding patients with these tumour mutations.

All statistical analyses were performed using GraphPad Prism version 8 (San Diego, CA), STATA version 16 (College Station, TX), or R version 4.0 (R Project for Statistical Computing, Vienna, Austria)).

RESULTS

Clinical characteristics and immunogenicity of BRAF-altered lung cancers

We identified 5945 patients who were diagnosed with lung cancers and underwent NGS during the study period. Of these, 177 patients had tumours harbouring alterations in *BRAF*, and 127 had the metastatic disease during the study period. Of the patients with metastatic disease, 29 patients had Class I mutant-tumors (22.8%), 36 had Class II-altered cancer (28.3%), 23 had Class III alterations (18.1%) and 39 had VUS (30.7%).

Baseline characteristics of all patients with Class I, II and III *BRAF*-altered lung cancers are shown in Table 1, and of patients with a VUS in Supplementary Table S-1. Across *BRAF* Classes I–III, the median age at diagnosis of metastatic disease was 59–70 years. While more patients with Class I tumours were female as compared to patients with Class II/III-altered cancers, a significant differential effect was not detected (69% versus 58%, $P = 0.36$). More patients with Class I-mutant cancers were never-smokers compared to patients with lung cancers harbouring Class II/III alterations (45% versus 10%, $P = 0.002$).

Fewer patients with *BRAF* Class I mutations than with Class II/III-altered lung cancers had co-mutations in *NF1* (0 versus 7 in Class II/III, $P = 0.09$). Similarly, no patients with Class I mutations had co-mutations in *RAS*, while six with Class II/III alterations had a *RAS* co-mutation ($P = 0.17$). Of patients with *RAS* mutant tumours, three had *KRAS* G12V mutations, and one each had *KRAS* G12D, G13C and G13D-mutant tumours. Eight tumours had activating *EGFR* mutations (L858R or exon 19 deletions); one had a Class I alteration, five had Class II and two had Class III *BRAF* alterations. Seven (87.5%) of the eight patients with tumours harbouring *EGFR* co-mutations had received a prior EGFR-directed TKI, with the *BRAF* alteration found in the setting of resistance in all cases. Seven *BRAF* fusions were detected, with four of these patients having a concomitant sensitising *EGFR* mutation present. All four had received EGFR-directed therapy prior to *BRAF* fusion detection. None of the patients with *BRAF* Class I-mutant tumours had *KEAP1* or *STK11* mutations. Of patients with *BRAF* Class II-altered tumours, eight had mutations in *STK11* and eight had mutations in *KEAP1*. Among patients with Class III-altered tumours, nine had mutations in *STK11* and ten had mutations in *KEAP1*, with four patients with VUS having mutations in *STK11* and six having mutations in *KEAP1*, respectively.

Median TMB was higher in tumours with *BRAF* Class II/III alterations than in those with Class I alterations (median: 8.8 mutations/Mb versus 4.9, $P < 0.001$). However, when differences in TMB between Class I versus II/III-altered tumours were stratified by smoking status (ever versus never-smokers), differences in TMB between Class I versus Class II/III-altered tumours were diminished ($P = 0.09$).

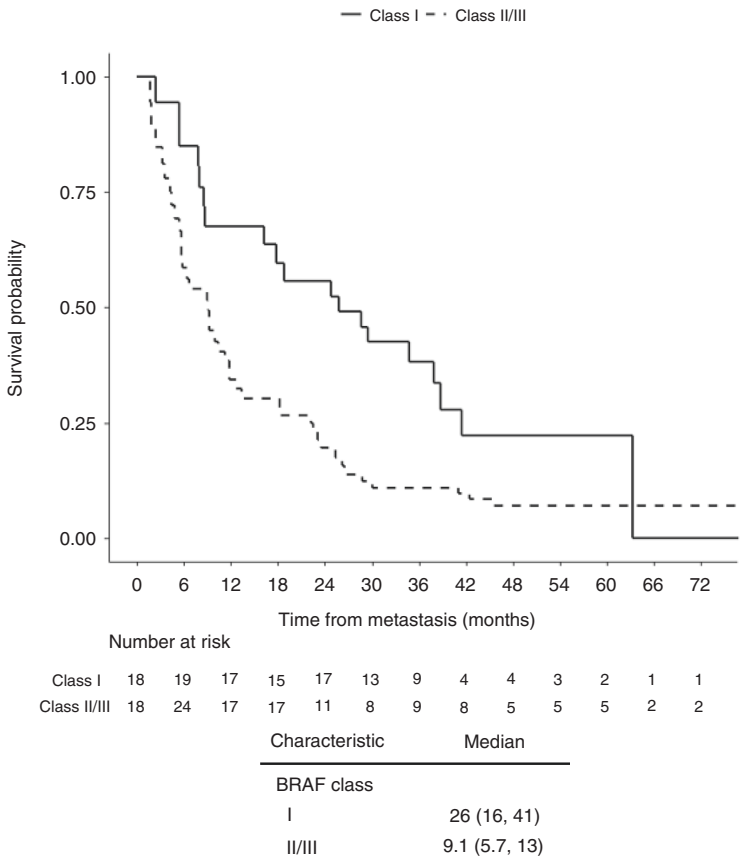

Fig. 1 Overall survival of patients with lung cancers according to the type of *BRAF* alteration. Overall survival in patients with Class I-mutant versus *BRAF* Class II/III lung cancers.

Table 2. Demographic and clinical characteristics of patients who received non-experimental ICI.

Histology	BRAF alteration	BRAF class	Concurrent alterations	TMB	PD-L1 (%)	ICI line of therapy	ICI	Time on ICI (months)	Best RECIST response
Adeno	V600E	I		5	n/a	2	Nivolumab	1.3*	NA
Adeno	p.V600E	I		6	0	2	Nivolumab	0.5	PD
Adeno	p.V600E	I		10	n/a	1	Ipilimumab and Nivolumab	5.5	PD
Adeno	p.V600E	I		5	n/a	2	Nivolumab	27.9	SD
Adeno	p.V600E	I		10	n/a	2	Nivolumab	0.4	PD
Adeno	p.V600E	I		7	99	3	Atezolizumab	1.4	SD
Adeno	p.V600E	I		3	n/a	5	Nivolumab	1.4	SD
Adeno	V600E	I		1	90	3	Pembrolizumab	11.3	NA
Adeno	p.V600E	I		13	n/a	4	Pembrolizumab	1.4	PD
Adeno	p.V600E	I		6	n/a	2	Nivolumab	0.6	PD
Adeno	p.V600E	I		19	70	3	Pembrolizumab	28.2*	PR
Adeno	V600E	I		2	10	1	Ipilimumab and Nivolumab	0.5	SD
Adeno	V600E	I		2	10 to 20	4	Pembrolizumab	11.5*	SD
Adeno	p.G469A	II		7	20	4	Nivolumab	1.8	PD
Adeno	p.T599dup	II		14	n/a	3	Nivolumab	0.04	NA
Adeno	p.G469A	II		10	10	3	Nivolumab	1.4	PD
Squamous Cell	p.G469A	II		1	0	3	Nivolumab	40.1	PR
Adeno	SND1 (NM_014390) - BRAF (NM_004333)	II		4	n/a	4	Nivolumab	0.5	PD
Adeno	BRAF (NM_004333) - MRPS33 (NM_053035)Rearrangement	II		3	n/a	6	nivolumab	0.5	NA
Adeno	p.G469A	II	KRAS G13C	9	n/a	2	Nivolumab	0.06	NA
Adeno	AGAP3 (NM_031946) - BRAF (NM_004333) rearrangement	II		3	0	4	Nivolumab	2.3	PD
Adeno	p.G + AD2:AF121464R	II	KRAS G12V and NF1	10	0	1	Ipilimumab and Nivolumab	3.9	PD
Adeno	AGK (NM_018238) - BRAF (NM_004333) rearrangement	II		0	n/a	3	Nivolumab	0.06	NA
Adeno	p.G464V	II		6	n/a	2	Nivolumab	2.2	PD
Neuroendocrine Tumour	p.G469A	II		19	n/a	2	Ipilimumab and Nivolumab	1.4	PD
Adeno	p.G469A	II		5	0	3	Nivolumab	4.4	SD
Adeno	p.G464V	II	KRAS G13D	8	80	1	Pembrolizumab	0.06	NA
Adeno	p.K601E	II		11	0	2	Pembrolizumab (with chemotherapy)	5.6	CR
Adeno	p.G469S	II	NF1	6	n/a	1	Pembrolizumab	6.0	PR
Large Cell Neuroendocrine	G469A	II		8	1	2	Atezolizumab	1.4	PD
Adeno	p.V600_K601delinsE	II		3	99	1		4.2	PR

Table 2. continued

Histology	BRAF alteration	BRAF class	Concurrent alterations	TMB	PD-L1 (%)	ICI line of therapy	ICI	Time on ICI (months)	Best RECIST response
							Pembrolizumab (with chemotherapy)		
Adeno	p.G596R	III	NF1	22	0	2	Nivolumab	34.8	PD
Adeno	p.G596R	III		11	n/a	3	Nivolumab	0.8	PD
Adeno	p.G466E	III		20	n/a	1	Ipilimumab and Nivolumab	1.9	PD
Adeno	p.D594G	III		6	5	4	Nivolumab	0.9	PD
Adeno	p.D594N	III		7	0	2	Nivolumab	0.04	NA
Adeno	p.G469A	III		14	0	2	Nivolumab	0.9	NA
Adeno	p.V471F	III	NF1	29	n/a	3	Nivolumab	5.8	SD
Adeno	p.G466A	III		4	10	2	Pembrolizumab	18.4	PR
Adeno	p.G596V	III	KRAS G12V	10	5	1	Pembrolizumab	9.2	CR
Adeno	p.S467L	III		33	0	4	Nivolumab	9.7	SD
Adeno	p.N581S	III		11	n/a	3	Nivolumab	1.9	PD
Adeno	p.N581I	III		2	0	4	Nivolumab	1.3	PD
Adeno	p.V168L	U		100	n/a	3	Nivolumab	44.2	PD
Adeno	p.I572F	U	KRAS G12V	21	0	2	Nivolumab	39.8*	PD
Adeno	p.K483E	U		2	0	6	Nivolumab	5.6	PD
Adeno	p.M620I	U		23	5	2	Nivolumab	41.2	SD
Adeno	splicing variant	U		20	n/a	3	Atezolizumab	0.7	NA
Adeno	p.M117L	U		8	60	1	Ipilimumab and Nivolumab	3.7	SD
Small Cell Cancer	p.D40Y	U		17	n/a	2	Nivolumab	0.06	NA
Adeno	p.N412S	U		39	0	7	Nivolumab	7.1	SD
Adeno	E695Q	U		17	0	3	Nivolumab	18.9	PR
Squamous Cell	p.S616Y	U		21	20	2	Nivolumab	41.8*	CR
Adeno	p.T274A	U	KRAS G12D and NF1	16	100	2	Nivolumab	0.9	PD
Adeno	p.R239L	U	KRAS G12C	18	0	2	Nivolumab	35.7*	SD
Adeno	splicing variant p.X380_splice	U	KRAS G12C	14	0	2	Atezolizumab	1.4	PD
Adeno	p.R266T	U		48	0	2	Nivolumab	2.6	PD
Adeno	A404Cfs*9	U	EGFR exon 20 insertion	4	0	2	Nivolumab	0.9	PD
Squamous Cell	p.I556F	U		12	0	2	Atezolizumab	1.4	NA
Small Cell Cancer	p.P152S	U		9	n/a	2	Ipilimumab and Nivolumab	0.06	NA
Adeno	p.A404Cfs*9	U		18	n/a	3	Nivolumab	0.8	PD
Adeno	p.V487L	U	NF1	18	1	2	Pembrolizumab	2.1	PD

Adeno adenocarcinoma, *CR* complete response, *ICI* immune checkpoint inhibitor, *NA* not available/not evaluable, *PD* progressive disease, *PR* partial response, *SD* stable disease, *TMB* tumour mutation burden, *U* variant of unknown significance. *Treatment ongoing.

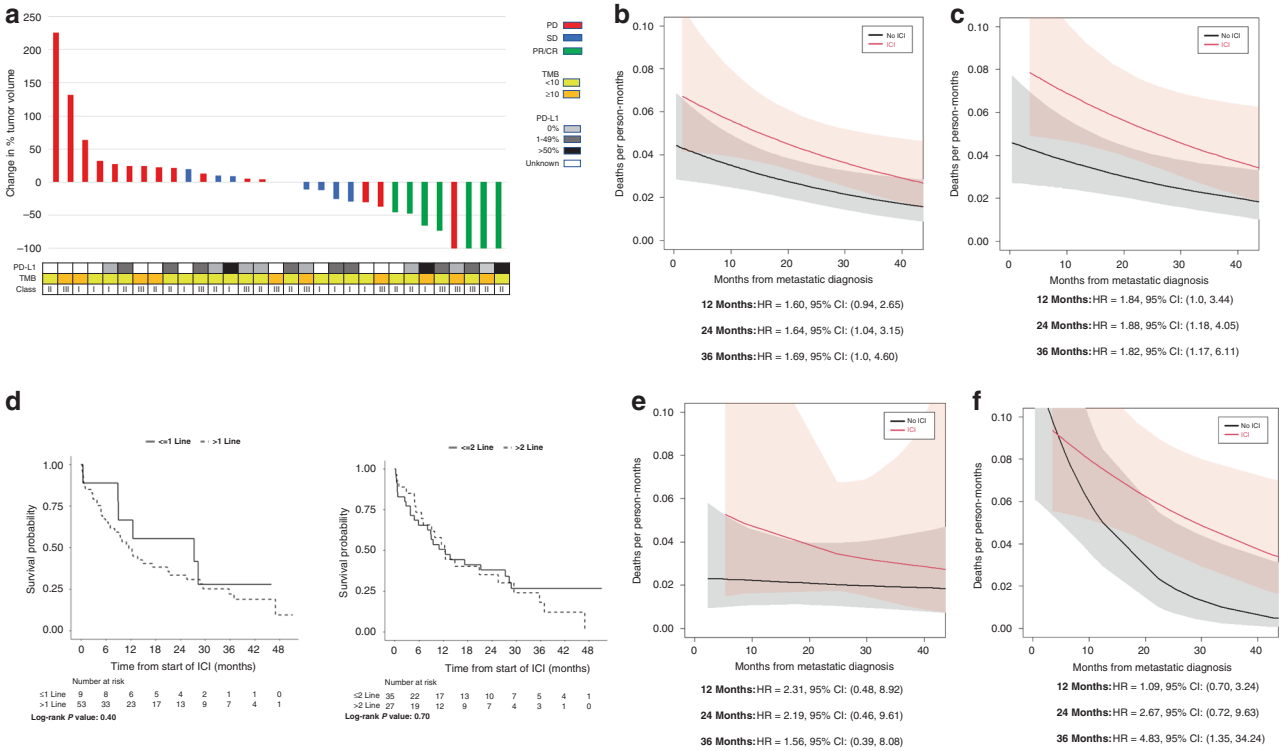

Fig. 2 Response to ICI according to *BRAF* mutation class, TMB and PD-L1 status. a Waterfall plot illustrating individual responses of patients treated with ICI with available scans assessed by RECIST. Boxes below indicate *BRAF* mutation Class (I–III indicates class), PD-L1 expression and tumour mutation burden (TMB). The best overall response was coded as progression of disease (PD), stable disease (SD), partial response (PR) or complete response (CR). **b** Overall survival of patients across all classes of *BRAF*-altered tumours in patients who received ICI versus those who never received ICI. **c** Overall survival of patients with Class I–III *BRAF*-altered tumours who received ICI versus those who never received ICI. **d** Overall survival from the time of first immunotherapy treatment by line of therapy at which ICI was received. **e** Overall survival of patients with Class I-mutant lung cancers who received ICI versus those who never received ICI. **f** Overall survival of patients whose cancers had Class II/III *BRAF* alterations who received ICI versus those who never received ICI.

Data on PD-L1 status were available for 11 tumours in the Class I cohort (38%) and 30 tumours in the Class II/III cohort (51%, $P = 0.27$). The distribution of PD-L1 status (0%, 1–49%, or ≥50%) differed between Class I and Class II/III *BRAF*-altered cancers ($P = 0.04$). Among patients with Class I cancers, 27% (3/11) had PD-L1 negative tumours, compared to 63% (19/30) of patients with Class II/III tumours. Moderate (1–49%) PD-L1 expression was observed in 36% (4/11) of Class I tumours and 30% (9/30) of Class II/III tumours. Four patients with Class I-mutant tumours had high (≥50%) PD-L1 expression (36.4%) versus two (6.7%) with Class II/III-altered lung cancers (Table 1). In all, 13% of patients with VUS mutations had high PD-L1 expression (Supplementary Table S-1).

Patients were followed for a median of 47.9 months (4.0 years) from the date of sequencing (interquartile range: 34.4–55.7). The median OS of patients with Class I-mutant lung cancers was 26 months compared to 9.1 months overall in patients with *BRAF* Class II/III-altered lung cancers (HR = 1.9, $P = 0.02$) (Fig. 1). When patients with Class II and III alterations were compared to those with Class I-mutant lung cancers, a median OS of 8.9 months for Class II and 13 months for Class III alterations was observed (HR 2.27 and 1.52, respectively, $P = 0.03$) (Supplementary Fig. S-1A). Median survival for patients whose tumours had VUS was 16 months (Supplementary Fig. S-1B).

In order to exclude the possibility that concomitant sensitising *EGFR* alterations could be driving the clinical characteristics of those eight patients with Class I–III *BRAF* mutations and a concomitant sensitising *EGFR* alteration, we further assessed survival excluding patients with sensitising *EGFR* alterations. Median survival for patients with Class I-mutant disease was 29, while it remained 9.1 months among those patients with Class II/III-altered disease (HR 1.96, $P = 0.02$).

Response to ICI

Among patients with metastatic disease, 13 patients with Class I-mutant lung cancers and 37 patients with Class II/III *BRAF*-altered lung cancers received ICI. The median line of therapy at which patients received ICI was either the second or third line across all cohorts (Table 1). Eight of the patients who were treated with ICI had received prior BRAF-directed targeted therapy; of these, seven had Class I cancers and one patient had a Class II *AGK-BRAF* rearrangement.

Among patients with Class I–III alterations, nivolumab monotherapy was the most common ICI received ($N = 26$). Five patients received nivolumab with ipilimumab, two received atezolizumab and ten received pembrolizumab. Seven patients with Class I–III alterations were treated on a clinical trial in which ICI was given as part of an experimental combination with a different agent, including with kinase inhibitors, immune-stimulating agents, and angiogenesis modulators; these patients were excluded from further analysis. Demographic and clinical information for patients who received ICI either alone or as part of non-experimental therapies are presented in Table 2.

Among the 34 patients treated with non-experimental ICI with available scans assessed by RECIST, the ORR of patients with Class I tumours was 9% (1/11) as compared to 26% (6/23) in patients with Class II/III-altered disease ($P = 0.25$) (Fig. 2a). The response rate among the 15 patients whose tumours had VUS was 13% (2/15) (Supplementary Fig. S-2). Among patients with an *EGFR* co-alteration,

three received non-experimental ICI, two of whom were evaluable by RECIST and had progression of the disease as their best overall response.

Across all *BRAF* alterations, patients had a higher risk of death if they had received ICI (at 24 months, HR equalled 1.64, 95% CI: 1.04–3.15; at 36 months HR was 1.69, 95% CI: 1.00–4.60) (Fig. 2b). Worse survival was also seen across Class I–III-altered tumours (at 24 months, HR equalled 1.88, 95% CI (1.18–4.05); at 36 months HR was 1.82, 95% CI: 1.17–6.11) (Fig. 2c). There was no evidence of a difference in survival between patients who received ICI as part of first- or second-line therapy versus those who received ICI as part of later lines of therapy (first line: log-rank $P = 0.40$; second line: log-rank $P = 0.70$) (Fig. 2d).

Given that patients with sensitising *EGFR* mutations generally do not benefit from immunotherapy [31], we further analysed differences in survival excluding patients with these alterations who did and did not receive ICI. In the smaller cohort excluding these patients, a trend toward worse survival was seen in patients with any *BRAF* alteration who had received immunotherapy across classes (at 24 months, HR was 1.40, 95% CI 0.87–3.11; at 36 months, HR was 1.18, 95% CI 0.82–4.42). A similar trend was seen in those patients with Classes I–III alterations (at 24 months, HR was 2.29, 95% CI 0.98–3.78; at 36 months HR was 2.21, 95% CI 0.95–6.54).

A trend toward worse survival was also evident among patients with Class I alterations who received ICI versus those who never received ICI (HR at 24 months, 2.19, 95% CI: 0.46–9.61; HR at 36 months 1.56, 95% CI 0.39–8.08) (Fig. 2e). There was a trend toward worse survival in those with Class II/III-altered cancers who received ICI at 24 months of follow-up and this difference was significant at 36 months follow-up (HR at 24 months 2.67, 95% CI 0.72–9.63; HR at 36 months 4.83, 95% CI 1.35–34.24) (Fig. 2f).

Time on ICI therapy

The time on treatment of patients with Class I–III alterations ranged from 1 dose to 3.3 years (Fig. 3). The median time on treatment was 1.9 months in patients with Class I mutations and was also 1.9 months in patients with Class II/III alterations ($P = 0.31$). The median time on treatment of patients with *BRAF* VUS was longer than for patients with Class II/III alterations (2.6 versus 1.9 months, $P = 0.05$) (Supplementary Fig. S-3). One patient in the Class II/III cohort was treated with ICI for >3 years. Four patients were on ICI for >2 years, including two patients with Class I mutations and two patients with Class II/III alterations (one Class II *BRAF* p.G469A and one Class III *BRAF* p.G596R). Five patients with *BRAF* VUS were on therapy for >2 years, and four remained on treatment for >3 years.

Using established cut-offs for TMB (≥10 mutations/Mb) [42], time on treatment did not differ among all patients with high TMB ≥ 10 mutations/Mb or low TMB <10 mutations/Mb (1.9 versus 1.8 months, $P = 0.6$).

Among the eight patients with Class I–III alterations who received BRAF-directed therapy before getting ICI for metastatic disease, time on ICI ranged from 1 day to 2.3 years. While one patient in this group had an OS from metastatic diagnosis of 4.9 months, five patients had an OS greater than 2 years, including three who were alive at the time of data collection.

DISCUSSION

In this study, we analysed data from the largest cohort reported to date of patients with *BRAF*-altered lung cancers treated with ICI. Our study affirms that *BRAF*-altered lung cancers are clinically heterogeneous, with patients with Class I-mutant disease having longer survival than patients whose tumours had Class II/III alterations [4, 16, 27, 28]. While patients with Class I-mutant tumours have options for targeted therapy, our study found no significant clinical benefit from ICI in either the Class I or Class II/III

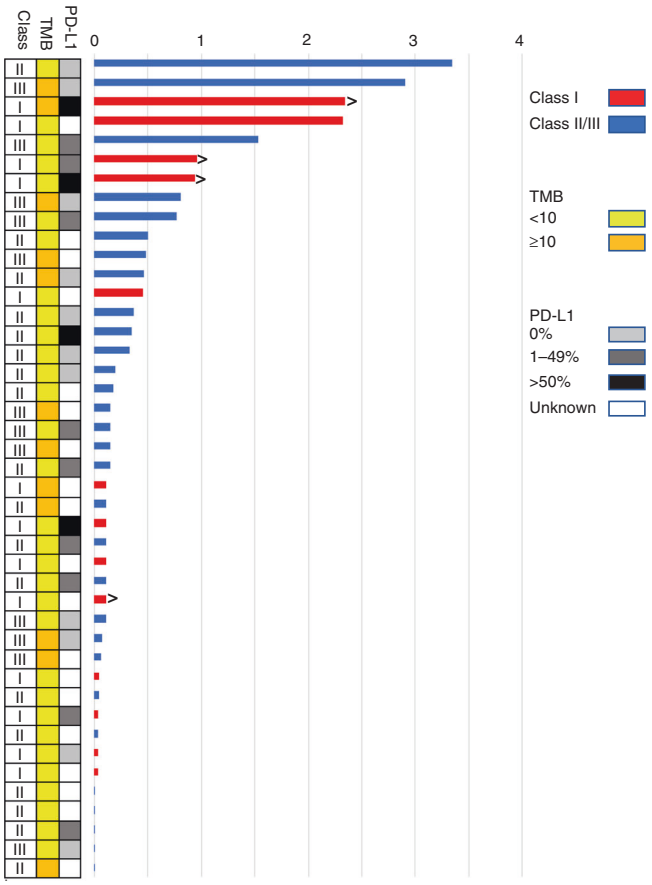

Fig. 3 Time on ICI (in years) among patients with *BRAF*-altered lung cancer. Patients still on treatment are denoted with arrows. Boxes at right indicate *BRAF* mutation Class (I–III indicates class), PD-L1 expression, and tumour mutation burden (TMB).

groups. The median time on treatment of patients with either Class I-mutant or Class II/III-altered disease was just 1.9 months.

Moreover, long-term follow-up of our cohort enabled comparison of overall survival data from patients who had and had not received ICI. The hazard ratio for deaths per person-months comparing patients with Class I–III-altered tumours who ever received ICI versus those who never received ICI at 36 months was 1.82 (1.17–6.11). Our analysis of survival by receipt of ICI was able to account for several clinical factors that can influence treatment outcomes, including *BRAF* class and line of therapy. Notably, there was no difference in survival observed between patients who had received ICI as first- or second-line treatment versus those who had received ICI later on in their disease course. We further analysed differences in survival after receipt of ICI among patients who did not have activating *EGFR* alterations, given the known association of these alterations with lack of ICI benefit [31]. In this smaller cohort of patients who did not have a concomitant *EGFR* alteration, there was still a trend toward worse outcomes with ICI, although this narrowly missed the cut-off for statistical significance.

There are a variety of potential explanations for why we did not see a clear benefit from ICI in most patients with *BRAF* alterations in our cohort. We cannot entirely exclude the possibility that receipt of ICI directly caused harm, such as by delaying more effective treatment. Nonetheless, given the benefit of ICI for other lung cancers [44, 45], we believe this explanation is less likely, especially for those patients who received ICI as second-line or later therapy. We hypothesise that the patients treated with ICI may have been sicker prior to treatment and were therefore

deemed unlikely to tolerate standard chemotherapy. These patients may have had poor baseline expected survival and may have been more likely to come off treatment faster.

The lack of a clear observed benefit with ICI for *BRAF*-altered tumours in our study differs from prior data presented by the Israel Lung Cancer group from Dudnik and colleagues. In this above-mentioned work, which included an investigation of 22 patients with *BRAF*-altered NSCLC, median overall survival was not reached among those patients who had received prior ICI, while it was just 21.1 months in those without prior ICI exposure [27]. Notably, Dudnik et al. did not explicitly differentiate between VUS and other non-V600 *BRAF*-altered tumours. Nonetheless, this difference in methodology alone likely does not account for the disparate results seen in our cohort, as our results were unchanged when patients with VUS were included in our supplementary survival analyses.

Differences in data analysis technique likely is a key factor in the disparate findings of our study and the Israel Lung Cancer investigation. In particular, our analysis took into consideration left truncation to account for differences in the timing at which patients underwent next-generation sequencing. This statistical adjustment can help to account for patients who may not have survived to the time of sequencing [46]. The importance of this adjustment for an aggressive molecular alteration was underscored by the experience of our patients, with at least five patients in the cohort passing away prior to receipt of a sequencing report showing a *BRAF* alteration.

While our results showing a signal of harm with ICI are novel, the lack of benefit from ICI observed does accord with previous data showing low progression-free survival (PFS) among patients with *BRAF*-mutant lung cancers [27, 28, 38]. In the Dudnik study, PFS on ICI was 3.7 months in patients with Class I mutations, as compared to 4.1 months in patients with all other BRAF alterations [27]. Similarly, the IMMUNOTARGET registry included 43 patients with *BRAF*-altered lung cancers, with the Class II/III cohort having a PFS of 4.1 months on ICI as compared to 1.8 months in the Class I cohort [38]. Guisier et al.'s study included 26 patients with Class I-mutant lung cancers and 18 with Class II/III alterations, with a recorded PFS in the former group of 5.3 months compared to 4.9 months in the latter group [28].

While collectively patients in our study did not benefit from ICI, our data did show durable responses in a select group of patients with *BRAF* alterations. These durable responses were observed across *BRAF* classes. In the case of Class I-mutant tumours, our identification of select patients with durable responses to ICI contrasts with the typical finding of a lack of response to ICI among oncogene-addicted tumours [31–37]. Response to ICI among patients with *BRAF* Class I-mutant tumours is not unique to lung cancer. In melanoma, both ICI and targeted therapies are considered first-line options for Class I disease based on robust overall response rates [47, 48]. Given the lack of survival benefit observed in patients with Class I-mutant tumours who received ICI in our study and the response rate of ~64% to targeted therapy in patients with Class I mutations [49], our results affirm a strategy of prioritising BRAF/MEK inhibition for Class I-mutant lung cancers. These data should not be interpreted as precluding immunotherapy in those patients whose tumours progress on *BRAF*-directed therapy, given the durable responses observed in a minority of patients across the *BRAF*-mutant class. Rather, our study may point to the benefits of using BRAF/MEK-directed targeted therapy before ICI in patients with a *BRAF* Class I mutation. Indeed, several patients in our cohort who had received *BRAF*-directed therapy prior to ICI achieved prolonged responses.

Our study also included patients who achieved durable responses with Class II/III-altered tumours. Prior research has shown a trend towards higher TMB, generally a marker of ICI benefit [40, 42], in Class II/III-altered tumours as compared to Class I-altered tumours [27]. In our study, TMB was significantly higher in patients with Class II/III alterations than in patients with Class I-mutant lung cancers. Based on our analyses, this difference could be accounted for by smoking status. Overall survival was ultimately worse in the Class II/III patients who received ICI than in those who had never received ICI despite the higher TMB, and time-on-treatment did not appear to differ by TMB in our study.

Durable responses to ICI were also seen in the cohort of patients with VUS. Interestingly, the largest subset of *BRAF* alterations in our cohort were categorised as VUS using an established, NGS assay [50]. Further multi-centre investigations in additional patients will enable a more granular assessment of whether individual Class II/III alterations and VUS have different sensitivity to ICI.

Our study has several limitations. First, while it represents the largest cohort to date of patients with *BRAF*-mutant disease who received ICI, it is a single-institution study from a tertiary cancer centre. Reassuringly, demographic features of the patients in our study, including higher rates of never-smokers among those with lung cancers possessing Class I alterations, are in agreement with prior investigations [1, 17].

Our analysis is retrospective, and we cannot rule out the possibility that providers may have chosen ICI over chemotherapy for patients with lower performance scores, who would be expected to have a worse prognosis regardless of therapeutic strategy. Our real-world data also includes patients who received different immunotherapy and chemo-immunotherapy regimens. In particular, it is notable that the median line of therapy at which patients in our cohort received ICI was between two and three depending on *BRAF* class. Due to evolving standards of care, current first-line therapy for most patients with lung cancers entails the use of ICI, often in combination with chemotherapy [44, 45]. While no difference in survival was observed between patients who received ICI as first- or second-line therapy and those who received ICI in later lines, further studies will be needed to fully investigate the role of ICI in the early-line setting for patients with *BRAF* alterations, particularly when used as part of combination chemo-immunotherapy.

Finally, not all patients who received ICI had available archival tissue for PD-L1 immunohistochemistry. Previous research on patients with *BRAF*-mutant lung cancers has shown that higher PD-L1 levels correlate with a higher likelihood of response to immunotherapy [27], and future investigations of the PD-L1 positive, *BRAF*-altered cohort are warranted.

Clinically, our study has several advantages, including its analysis of real-world data with long-term follow-up of patients with standardised RECIST measures. This longer-term follow-up enabled the investigation of differences in the durability of responses in both the Class I–III and VUS cohorts. Moreover, a large majority of patients in the study received ICI monotherapy, enabling interrogation of the efficacy of ICI, while minimising the confounding factor of combination therapies.

Overall, our data from a large cohort of patients do not demonstrate an overall survival benefit for ICI among patients with Class I–III disease. Nonetheless, a subset of patients with *BRAF*-altered disease may achieve durable cancer control on ICI. Further investigations into the immunogenicity of individual *BRAF* non-V600 lung cancers, including VUS, are warranted.

DATA AVAILABILITY

All genomic data from sequenced tumours are included in the cBioportal for Cancer Genomics repository (http://cbioportal.org/msk-impact). Relevant clinical data are included in the manuscript.

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AUTHOR CONTRIBUTIONS

MO and BTL conceived of/ designed the study. YRMG, TP, SM, DH, AJP, DL and MO acquired the data. All authors were involved in data analysis and/or interpretation. YRMG and MO drafted the manuscript. All authors approved the final version of the manuscript.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the institutional review board of Memorial Sloan Kettering Cancer Center.

CONSENT TO PUBLISH

Not applicable.

COMPETING INTERESTS

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