ORIGINAL ARTICLE

Real-World Treatment Patterns and Effectiveness of Targeted and Immune Checkpoint Inhibitor-Based Systemic Therapy in *BRAF* Mutation-Positive NSCLC

Amanda J. W. Gibson, BSc (Hons),[a,*] Aliyah Pabani, MD,[a,b] Michelle L. Dean, BSc,[a] Guillermo Martos, MD,[b] Winson Y. Cheung, MD, MPH, FRCPC,[a,b] Vishal Navani, M.B.B.S., MRCP, FRACP[a,b]

[a]*Department of Oncology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada*
[b]*Department of Medical Oncology, Tom Baker Cancer Centre, Alberta Health Services, Calgary, Alberta, Canada*

Received 28 November 2022; revised 28 December 2022; accepted 29 December 2022
Available online - 10 January 2023

ABSTRACT

Introduction: *BRAF* mutations (present in 2%–3% of NSCLC) are a known oncogenic driver and emerging therapeutic target. There is a scarcity of real-world data describing the clinical characteristics, treatment patterns, and effectiveness of targeted *BRAF*-inhibiting and immune checkpoint inhibitor (ICI)-based systemic therapies, yet this is required for appropriate treatment decisions that optimize patient outcome.

Methods: Demographic, clinical, treatment, and outcome data of patients with *BRAF* mutation-positive NSCLC diagnosed between 2018 and 2022 were identified from the Glans-Look Lung Cancer Research database and included in this analysis.

Results: A total of 53 *BRAF* mutation-positive patients were identified (V600E, n = 35; non-V600E, n = 18). Furthermore, 46 patients (87%) were diagnosed with metastatic disease, of whom 61% were treated with systemic anticancer therapy, which significantly improved overall survival (34.1 versus 2.2 mo, $p = 0.01$). ICI-based regimens were found to have effectiveness in the first-line setting for both V600E and non-V600E cohorts (objective response rate: 38%–43%; real-world calculations of median progression-free survival: 10.5–10.8 mo, respectively). Dual-targeted *BRAF*/*MEK* inhibition was also found to have effectiveness in the first-line setting for V600E patients (objective response rate: 33%, real-world calculations of median progression-free survival: 15.2 mo).

Conclusions: This study of real-world patients with *BRAF* mutations confirms the importance of effective systemic therapies. Both dual-targeted *BRAF*/*MEK* inhibition and ICI-based regimens have evidence of benefit in this population revealing that real-world populations can experience similar clinical response and outcome to clinical trial cohorts on these treatment regimens. Future studies to clarify the role of co-mutations on response to both dual-targeted *BRAF*/*MEK* inhibition and ICI-based regimens may be important to treatment selection and optimization of patient outcome.

*Corresponding author.

Disclosure: Dr. Navani reports receiving personal consulting fees from Kwoya Kirin, Novotech PTY, Pfizer, AstraZeneca, EMD Serono, and IPSOS. Dr. Pabani reports receiving grants from Bristol-Myers Squibb; receiving honoraria from AstraZeneca, Bristol-Myers Squibb, Pfizer, Roche, and Novartis; and having advisory board participation with AstraZeneca, Bristol-Myers Squibb, and Novartis. The remaining authors declare no conflict of interest.

Address for correspondence: Amanda J. W. Gibson, BSc (Hons), Department of Oncology, Cumming School of Medicine, University of Calgary, 1331 29th Street Northwest, Calgary, AB T2N 4N2, Canada. E-mail: ajwgibso@ucalgary.ca

Cite this article as: Gibson AJW, Pabani A, Dean ML, Martos G, Cheung WY, Navani V. Real-world treatment patterns and effectiveness of targeted and immune checkpoint inhibitor-based systemic therapy in *BRAF* mutation-positive NSCLC. *JTO Clin Res Rep*. 2023;3:100460.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2022.100460

Keywords: BRAF; Immune checkpoint inhibitor; Targeted therapy; Outcomes; Real-world

Introduction

NSCLC is a genetically heterogeneous disease, of which several distinct oncogene-addicted populations have been identified. One of these lung cancer populations is *BRAF* mutation-positive lung cancer, present in 2% to 3% of patients with advanced NSCLC.[1,2] *BRAF* (v-RAF murine sarcoma viral oncogene homolog B) mutations do not seem to be strongly associated with never-smoking histories, younger age, or Asian ethnicity, as is the case in some other forms of oncogene-driven NSCLC.[3] *BRAF* mutations are categorized into three main classes (I–III) on the basis of RAF kinase activity and signaling. The V600E mutation is synonymous with the class I alteration which functions as a kinase-activated, RAS-independent monomer, whereas classes II and III are known as non-V600E mutations and function as kinase-activated, RAS-independent dimers and kinase-impaired, RAS-dependent heterodimer ERK pathway amplifiers, respectively.[1,4,5] This underlying biological diversity is also reflected in different clinical presentations and outcomes where the V600E subgroup, compared with the non-V600E subgroup, tends to be more often detected in females, never smokers, and those with adenocarcinoma with micropapillary features whereas non-V600E is found almost exclusively in smokers.[1,4,6]

BRAF is a clinically relevant mutation in NSCLC, where the BRAF-V600E (class I) mutation, characterized by a 500-fold increase in kinase activity which mediates cell proliferation,[5] comprises approximately half of all *BRAF* mutations and can be targeted through dual inhibition of the *BRAF* and *MEK* pathways.[1,7] The combination of the *BRAF* inhibitor dabrafenib and the *MEK* inhibitor trametinib was found to have both safety and efficacy in the clinical trial setting, reporting response rates of 63% and progression-free survival (PFS) of 10.9 months. Dual-targeted *BRAF*/*MEK* inhibition is currently the recommended first-line treatment for *BRAF*-V600E–driven advanced NSCLC in Canada,[8] although optimal sequencing has not yet been evaluated in prospective studies.[1,9] Availability of targeted therapies for *BRAF*-V600E is important for optimal patient outcome, as lower-than-expected survival times and response to platinum-based chemotherapy regimens have been noted among patients with V600E mutations.[3,10]

Other *BRAF* mutations in NSCLC, the non-V600E (classes II and III) mutations, currently lack targeted therapy options, although trials investigating *RAS*/*RAF*/*MEK* inhibition for non-V600E *BRAF* are undergoing.[1,7] Current guidelines recommend that *BRAF* non-V600E be managed the same as nononcogene-driven NSCLC, which relies on immune checkpoint inhibitor (ICI) either as a monotherapy (for programmed death-ligand 1 [PD-L1] $\geq$ 50%) or with concurrent platinum-doublet–based cytotoxic chemotherapy (agnostic to PD-L1 expression) in the absence of contraindications.[1] Nevertheless, there is evidence that ICI-based regimens may elicit poor treatment response in oncogene-driven NSCLC,[3] although whether, or to what degree, this is also true for oncogene-driven *BRAF* mutation-positive NSCLC remains unresolved, and more studies are required to move toward understanding the role of ICI in *BRAF*-mutated NSCLC. Granularity about the activity of current standard-of-care chemoimmunotherapy combinations in *BRAF*-mutated contexts is missing from pivotal studies such as KEYNOTE-189 and CheckMate-024.[11,12] Some retrospective reviews have revealed limited response and outcome to ICI among patients with *BRAF* mutations.[7,13,14] Other studies suggest that in *BRAF*-mutated NSCLC—particularly among non-V600E subtypes—higher rates of smoking and smoking-associated upregulation in PD-L1 expression and tumor mutational burden (TMB) may increase sensitivity to ICI and elicit similar response as found in ICI-treated unselected NSCLC populations.[1,15,16]

Clarity regarding the role of both targeted and ICI-based regimens in *BRAF*-mutated NSCLC is of importance to management and subsequent outcome for patients with this form of NSCLC. It is also important to recognize that the data which inform the guideline-recommended treatment regimens for *BRAF*-mutated NSCLC are based on that derived from the clinical trial context where patients may not adequately or accurately represent those encountered in routine, real-world clinical practice. Therefore, an understanding of the characteristics, management, treatment patterns, and response to guideline-recommended therapies for *BRAF*-mutated NSCLC in real world is increasingly important. To help address these knowledge gaps, this study described the clinical characteristics and treatment patterns of patients with *BRAF*-mutated NSCLC in the province of Alberta, Canada. In addition, we investigated the outcomes of *BRAF*-V600E patients treated with dual-targeted *BRAF*/*MEK* inhibition and explored the response to ICI-based systemic therapy regimens in both BRAF-V600E and non-V600E cohorts.

Materials and Methods

This study used the Glans-Look Lung Cancer Research (GLR) database, which captures patient-level demographic, clinical, treatment, response, and outcome data by means of chart reviews of electronic medical records for all patients with a diagnosis of lung

cancer who present for diagnosis and treatment within the Canadian province of Alberta. The data in the GLR used for this analysis were collected under ongoing institutional review board–approved protocol at our institution (HREBA.CC-16-0574), and as a retrospective review, no consent is required. Study data within the GLR database are collected and managed using the Research Electronic Data Capture data capture tools hosted at the University of Calgary.[17,18]

Patient Selection

Included in this retrospective cohort were all adult patients with NSCLC diagnosed with a *BRAF* mutation identified between January 2018 and June 2022, identified according to the International Association for the Study of Lung Cancer/Association for Molecular Pathology/College of American Pathologists biomarker guidelines.[19] In accordance with these guidelines, patients with advanced/metastatic disease, with solid tumor of lung origin amenable for biopsy, and with nonsquamous NSCLC histological subtype were assessed for gene-specific mutations in *BRAF*, identified in tandem with alterations in *EGFR*, *KRAS*, and *PIK3CA* using a DNA-based multigene, Sanger sequencing assay or RNA-based next-generation sequencing, performed by Alberta Precision Laboratories.

Clinical Response and Outcome

The treatment patterns, treatment events, response, and outcomes were calculated using data elements contained in the GLR.

The primary outcome was the difference observed in real-world–assessed clinical response in the following two scenarios:

1. In the context of different types of first-line systemic therapy (ICI-based or targeted) for patients with V600E mutation-positive NSCLC.
2. In the context of ICI-based first-line systemic therapy for different types (V600E or non-V600E) mutations in *BRAF*.

Clinical response was determined using Response Evaluation Criteria in Solid Tumors version 1.1 criteria and described using definitions defined within the literature.[20] As a real-world study, diagnostic imaging reporting did not always include overt calculations of Response Evaluation Criteria in Solid Tumors criteria–based response. In the absence of reporting of actual measurements within the diagnostic imaging report, then response was based on the documented opinion of the reviewing radiologist or medical oncologist, which has been found in other studies, to have good concordance and similar distributions of best overall response.[21] Best overall clinical response was used to categorize patients: those with a partial or complete response were classified as having experienced objective response rate (ORR); those with stable disease, with partial or complete response were considered to have experienced disease control rate (DCR). Patients without diagnostic imaging scans after initiating systemic therapy were recorded with a response of "non-evaluable" and omitted from calculations of ORR and DCR.

Secondary outcomes were time-to-event end points, including real-world calculations of median PFS (RW-mPFS) and median overall survival (mOS), and 6-month PFS, revealed to be a reliable estimate of 12-month mOS.[22] mPFS was calculated as the time from systemic therapy initiation until a definitive progressive disease was detected. Median OS was based on the interval following the diagnosis of advanced disease to death/censored last follow-up, an interval which could be determined for all cases included in the cohort. Advanced disease was considered to be the presence of unresectable (stage IIIB or IIIC not amenable to treatment with definitive-intent, concurrent chemoradiotherapy or the presence of metastatic disease [stage IV]) disease. Staging was based on the American Joint Committee on Cancer eighth edition criteria.[23]

Adverse Events

Occurrence and management of systemic therapy–associated adverse events were derived from the GLR, which identified the occurrence and management of adverse events by retrospective review of the physician progress notes included in the medical record. Adverse events were recorded using Common Terminology Criteria for Adverse Events version 5.0 codes, descriptors, and grades, as standardized and grouped according to Medical Dictionary for Regulatory Activities Primary System Organ Class terms and hierarchy. Adverse events were then further dichotomized into categories denoting low and high severity, where high-severity (serious) adverse events were those of grade 3 or higher, or adverse events of any grade which required intervention (dose reductions, treatment breaks, hospitalization, steroid use, or treatment termination).

Statistical Methods

Demographic and clinical characteristics of the study cohort were summarized using descriptive statistics and univariate methods, including Fisher's exact test for categorical variables and Kruskal-Wallis for continuous events, and time-to-event models which were assessed using the Kaplan-Meier approach. Multivariate methods were precluded owing to small numbers of

events. A two-sided p value less than 0.05 was considered a priori as statistically significant. All statistical analyses were performed using Stata Statistics/Data Analysis version 12.[24]

Results

Baseline Characteristics and Treatment Patterns

A total of 53 patients with *BRAF* mutations were identified: 35 V600E and 18 non-V600E. Non-V600E mutations consisted of the following: G469A (n = 9), G469V (n = 7), and D594G (n = 2). All patients, save for one non-V600E mutation-positive patient, possessed an adenocarcinoma histology rendering the incidence rate at 4.6% among cases with an adenocarcinoma histology; the inclusion of one patient with squamous cell histology was due to initial inconclusive histology classification with molecular testing performed in tandem with a review of pathological findings. At the time of analysis, 66% of the patients were still alive. Baseline demographic and clinical characteristics are summarized in Table 1. There were no significant differences in demographic or clinical characteristics between V600E and non-V600E, with the exception of smoking history and type and frequency of co-mutations. Specifically, 100% of those with a non-V600E mutation had a history of tobacco use, compared with 77% of those with V600E mutation. The non-V600E mutation-positive cohort had a significantly higher rate of *KRAS* co-mutation than the V600E mutation-positive cohort (83% versus 29%), whereas a higher rate of PIK3CA co-mutation (57% versus 0%) was found in the V600E mutation-positive cohort.

The treatment patterns are summarized in Figure 1. Of the cohort, 79% received some type of disease intervention (surgery, thoracic radiotherapy, or systemic therapy). Of those not receiving treatment, 64% had poor performance status or serious comorbidities which precluded treatment, 27% experienced a rapid decline after diagnosis precluding treatment initiation, and 9% refused treatment. Furthermore, 26% of the cohort underwent curative-intent treatments with 57% ultimately developing advanced disease at some point post-diagnosis, resulting in a total of 46 patients identified with advanced disease at the time of data cutoff in September 2022. Most patients with advanced disease underwent palliative systemic anticancer therapy (SACT) (61%), with no significant differences between the proportion of V600E– and non-V600E mutation–positive patients receiving palliative systemic therapy (51% versus 67%, $p = 0.57$). ICI-based systemic therapy was the most common palliative systemic treatment choice in the first-line setting in both V600E (44%) and non-V600E (70%). Among patients with a V600E mutation and advanced disease who received palliative systemic therapy, 49% (n = 7) received dual-targeted *BRAF*/*MEK* inhibition (dabrafenib/trametinib).

For patients with advanced disease, the type of *BRAF* mutation did not seem to significantly affect survival outcomes (log-rank $p = 0.3$; Fig. 2*A*). Receiving palliative-intent SACT had a positive impact on survival outcomes (log-rank $p = 0.01$; Fig. 2*B*), but there was no significant difference in outcome between V600E and non-V600E mutation-positive patients if they had received palliative-intent SACT (log-rank $p = 0.9$; Fig. 2*C*). Similarly, there was no significant difference in survival outcome depending on type of systemic therapy (targeted, concurrent chemoimmunotherapy, or monoimmunotherapy) received for a BRAF mutation (log-rank $p = 0.2$; Fig. 2*D*).

Systemic Treatment Regimens

V600E: Dual *BRAF*/*MEK* Inhibition Versus Immunotherapy-Based Therapy. Among patients with advanced disease and a V600E mutation who received palliative SACT, one patient had a concurrent *EGFR* exon 19 deletion and was treated with *EGFR*-inhibiting therapy; this patient was excluded from the V600E subgroup analysis.

Investigations related to first-line therapy and comparison of dual-targeted *BRAF*/*MEK*-inhibiting therapy and immunotherapy in any line are found in Table 2.

Patients treated with dual-targeted *BRAF*/*MEK* inhibition were similar to those receiving nontargeted systemic therapy (platinum-doublet chemotherapy or ICI-based therapy), although those receiving *BRAF*/*MEK*-inhibiting therapy had a significantly higher rate of distant metastatic disease (66% versus 9%, $p = 0.01$). In comparison with nontargeted options, dual *BRAF*/*MEK*-inhibiting therapy, whether received in the first palliative line or beyond, had good clinical efficacy (DCR: 67%–71%; mPFS: 15.2–16.1 mo, respectively), but had no statistically significant benefit than ICI-based regimens (DCR: 60%; mPFS: 10.4 mo). Rate of adverse events from dual-targeted *BRAF*/*MEK* inhibition was similar to that from ICI-based regimens; serious adverse events associated with dual-targeted *BRAF*/*MEK* inhibition included fatigue, delirium, and vomiting and tended to appear in tandem with discovery of progressive disease and subsequent dual-targeted *BRAF*/*MEK* inhibitor termination. In comparison, serious adverse events associated with ICI (colitis and pneumonitis) necessitated ICI discontinuation in the context of good disease control.

V600E and Non-V600E: ICI. Among patients with advanced disease and a *BRAF* mutation who received palliative ICI-based regimens, two patients had concurrent *EGFR* mutations (BRAF-V600E + EGFR exon 19

Table 1. Demographic and Clinical Characteristics at Diagnosis: BRAF Mutation-Positive Cohort

Demographics

Characteristics	V600E (n = 35), n (%)	Non-V600E (n = 18), n (%)	*p* Value
Sex			$\chi 2$, df(1) = 0.61
Male	16 (46)	11 (61)	$p = 0.29$
Female	19 (54)	7 (39)	
Age (y) median (IQR)	71 (61-80)	67 (65-73)	$\chi 2$, df(1) = 1.1
			$p = 0.44$
Smoking history			$\chi 2$, df(1) = 7.4
Never smoker	8 (23)	0 (0)	$p = 0.007$[a]
Ever smoker	27 (77)	18 (100)	
Smoking pack years			$\chi 2$, df(1) = 1.0
1-20 pack years	8 (30)	3 (17)	$p = 0.313$
20+ pack years	13 (48)	15 (83)	
Unknown	6 (22)	0 (0)	

Clinical Presentation

Characteristics	V600E (n = 35), n (%)	Non-V600E (n = 18), n (%)	*p* Value
Histologic subtype			$\chi 2$, df(1) = 2.2
Adenocarcinoma	35 (100)	17 (94)	$p = 0.14$
Squamous cell carcinoma	0 (0)	1 (6)	
ECOG at diagnosis			$\chi 2$, df(2) = 1.0
ECOG < 2	29 (83)	15 (83)	$p = 0.39$
ECOG ≥ 2	4 (11)	3 (17)	
Unknown	2 (6)	0 (0)	
Stage at diagnosis:			$\chi 2$, df(1) = 0.96
Early stage (I/II/IIIA)	9 (26)	7 (39)	$p = 0.33$
Metastatic (IIIB, IIIC, IV)	26 (74)	11 (61)	
AJCC eighth edition M-stage at diagnosis			$\chi 2$, df(3) = 3.2
M0	11 (31)	10 (56)	$p = 0.36$
M1a	9 (26)	3 (17)	
M1b	5 (14)	1 (5)	
M1c	10 (29)	4 (22)	
Intracranial metastases at diagnosis			
No	32 (91)	14 (78)	$\chi 2$, df(1) = 1.8
Yes	3 (9)	4 (22)	$p = 0.18$
PD-L1 status			$\chi 2$, df(3) = 3.9
Negative (<1%)	2 (6)	3 (17)	$p = 0.27$
Low (1%-49%)	6 (17)	6 (33)	
High (≥50%)	21 (60)	7 (39)	
Unknown/not tested	6 (17)	2 (11)	
Other concurrent mutations			
No	28 (80)	12 (67)	$\chi 2$, df(1) = 1.1
Yes	7 (20)	6 (33)	$p = 0.29$
Type of concurrent mutation	(n = 7)	(n = 6)	
EGFR	1	1	$\chi 2$, df(1) = 0.14
			$p = 0.96$
KRAS	2	5	$\chi 2$, df(1) = 4.2
			$p = 0.04$[a]
PIK3CA	4	0	$\chi 2$, df(1) = 6.5
			$p = 0.01$[a]

Disease Management

Characteristics	V600E (n = 35), n (%)	Non-V600E (n = 18), n (%)	*p* Value
Treatment regimen			
No treatment	9 (26)	2 (11)	$\chi 2$, df(1) = 1.7
Treatment (surgery, systemic therapy, or thoracic RT)	26 (74)	16 (89)	$p = 0.2$

[a]Denotes significant result.

AJCC, American Joint Commission on Cancer; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; PD-L1, programmed death-ligand 1; RT, radiotherapy.

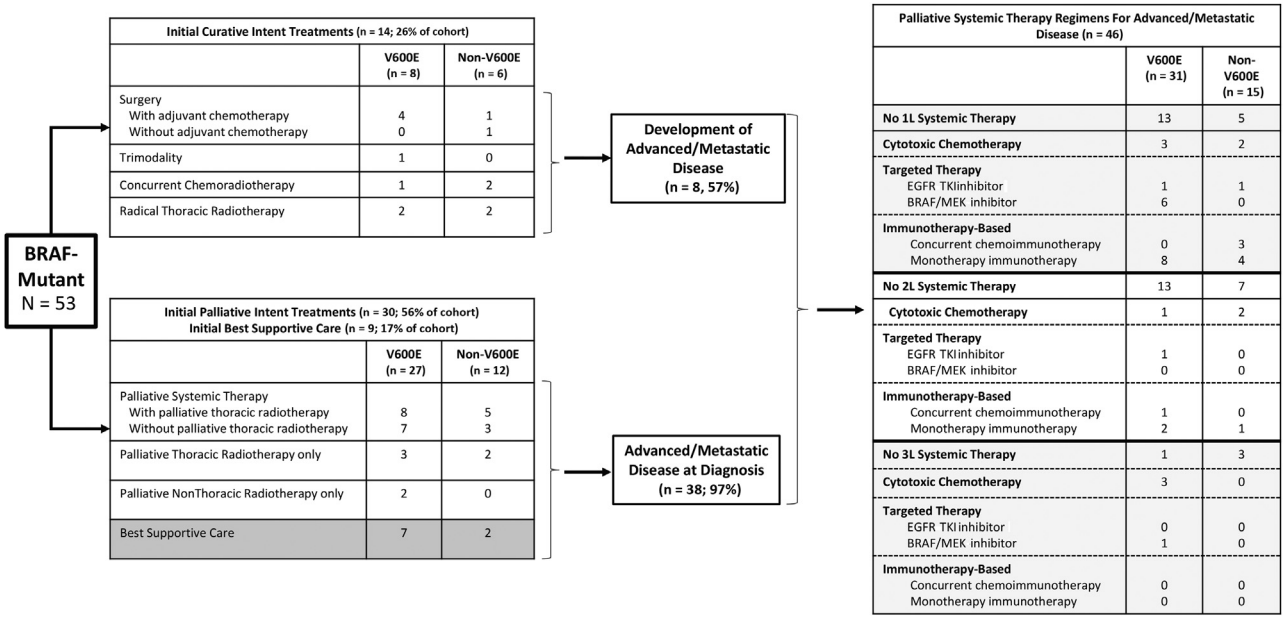

Figure 1. Initial treatment pathways and systemic therapy patterns. 1L, first line; 2L, second line; TKI, tyrosine kinase inhibitor.

deletion; BRAF–non-V600E + EGFR exon 21^{L858R}) and were treated with *EGFR*-inhibiting therapy; these patients were excluded from the ICI subgroup analysis.

Investigations related to ICI-based regimens for V600E and non-V600E mutation-positive groups are found in Table 3.

V600E and non-V600E mutation-positive patients receiving ICI-based therapies did not differ significantly in terms of baseline performance status (Eastern Cooperative Oncology Group), metastatic burden, or PD-L1 status. Similarly, response to ICI-based systemic treatment regimens was not significantly different, where

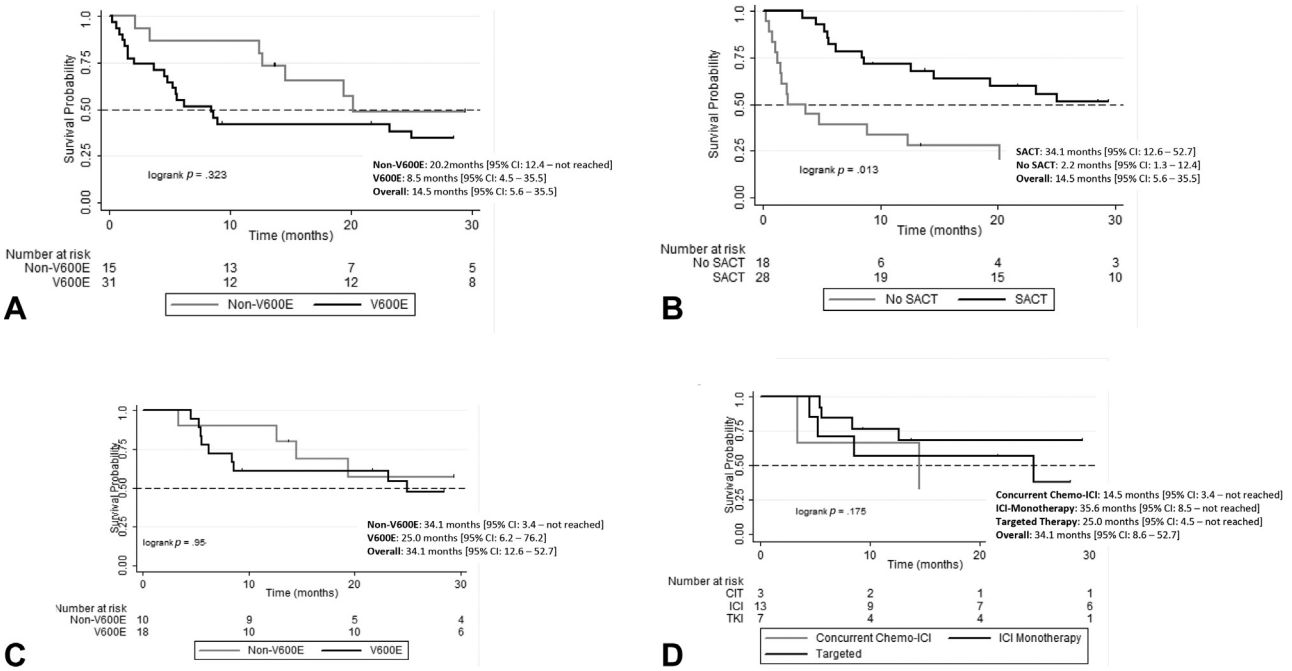

Figure 2. (*A*) Impact of BRAF mutation type on postmetastatic disease survival. (*B*) Impact of systemic anticancer therapy on postmetastatic disease survival. (*C*) Impact of BRAF mutation type on postmetastatic disease survival among patients receiving systemic anticancer therapy. (*D*) Impact of systemic therapy type on postmetastatic disease survival among BRAF mutation-positive patients receiving systemic anticancer therapy. CI, confidence interval; CIT, chemoimmunotherapy; ICI, immune checkpoint inhibitor; SACT, systemic anticancer therapy; TKI, tyrosine kinase inhibitor.

Table 2. Response to Targeted and ICI-Based Systemic Therapies for BRAF-V600E Mutation-Positive Cohort

BRAF-V600E Patients Receiving Systemic Therapy (n = 17)

	1L Therapy			Any Line		
Clinical Data	1L Targeted BRAF/MEK Inhibitors (n = 6), n (%)	Nontargeted Systemic Therapy (n = 11), n (%)	*p* Value	Targeted BRAF/MEK Inhibitors (1L n = 6; 3L n = 1) (n = 7), n (%)	Immune Checkpoint Inhibitor (1L n = 8; 2L n = 2) (n = 10), n (%)	*P* Value
Systemic therapy type	Dabrafenib/trametinib	Cytotoxic chemotherapy (n = 3) Immunotherapy (n = 8)	-	Dabrafenib/trametinib	Monoimmunotherapy: Nivolumab (n = 1) Pembrolizumab (n = 9)	-
ECOG at initiation						
ECOG < 2	5 (83)	7 (64)	$\chi 2$, df(1) = 0.77 $p = 0.4$	6 (86)	6 (60)	$\chi 2$, df(1) = 1.4 $p = 0.2$
ECOG ≥ 2	1 (17)	4 (36)		1 (14)	4 (40)	
AJCC eighth edition M-stage at systemic therapy initiation						
M0	0 (0)	7 (64)	$\chi 2$, df(3) = 10.8 $p = 0.01$[a]	0 (0)	6 (60)	$\chi 2$, df(3) = 9.0 $p = 0.03$[a]
M1a	2 (34)	3 (27)		3 (43)	2 (20)	
M1b	3 (49)	1 (9)		3 (43)	1 (10)	
M1c	1 (17)	0 (0)		1 (14)	1 (10)	
PD-L1 status						
Negative (<1%)	0 (0)	1 (9)	$\chi 2$, df(3) = 3.8 $p = 0.3$	0 (0)	0 (0)	$\chi 2$, df(3) = 3.3 $p = 0.2$
Low (1%-49%)	2 (33)	1 (9)		3 (43)	1 (10)	
High (≥50%)	4 (67)	7 (64)		4 (66)	8 (80)	
Not tested/unknown	0 (0)	2 (18)		0 (0)	1 (10)	
Real-world ORR	33%	36%	$\chi 2$, df(1) = 0.02 $p = 0.9$	43%	50%	$\chi 2$, df(1) = 0.08 $p = 0.8$
Real-world DCR	67%	55%	$\chi 2$, df(1) = 0.2 $p = 0.6$	71%	60%	$\chi 2$, df(4) = 0.24 $p = 0.6$
Real-world primary resistance	33%	18%	$\chi 2$, df(1) = 0.5 $p = 0.5$	29%	20%	$\chi 2$, df(1) = 0.17 $p = 0.7$
Real-world PFS (mo) [95% CI]	15.2 [1.0-not reached]	30.9 [1.9-not reached]	Log-rank $p = 0.09$	16.0 [1.0-not reached]	10.4 [1.9-not reached]	Log-rank $p = 0.9$
6-mo PFS rate [95% CI]	67% [19%-90%]	79% [39%-94%]		71% [26%-92%]	67% [28%-88%]	
1-year survival rate [95% CI] (after detection of advanced/metastatic disease)	50% [11%-80%]	62% [28%-84%]	Log-rank $p = 0.45$	57% [17%-84%]	68% [31%-89%]	Log-rank $p = 0.4$
Reason for termination						
Progressive disease/ death	5 (83)	5 (45)	$\chi 2$, df(5) = 5.9 $p = 0.3$	5 (72)	4 (40)	$\chi 2$, df(4) = 6.0 $p = 0.2$

(continued)

Table 2. Continued

BRAF-V600E Patients Receiving Systemic Therapy (n = 17)

	1L Therapy			Any Line		
Clinical Data	1L Targeted BRAF/MEK Inhibitors (n = 6), n (%)	Nontargeted Systemic Therapy (n = 11), n (%)	*p* Value	Targeted BRAF/MEK Inhibitors (1L n = 6; 3L n = 1) (n = 7), n (%)	Immune Checkpoint Inhibitor (1L n = 8; 2L n = 2) (n = 10), n (%)	*P* Value
Adverse events	0 (0)	2 (18)		0	3 (30)	
Performance status Decline	1 (17)	2 (18)		1 (14)	1 (10)	
Treatment ongoing/ unknown	0 (0)	2 (18)		1 (14)	2 (10)	
Adverse events						
Mild (grade 1 or 2, no dose breaks or modifications)	3 (50)	Not collected	-	4 (57)	5 (50)	$\chi 2$, df(1) = 0.05 $p = 0.8$
Serious (grade 3 or 4 or intervention required)	3 (50)	Not collected	-	4 (57)	3 (30)	$\chi 2$, df(1) = 0.58 $p = 0.5$
2L therapy			$\chi 2$, df(1) = 0.48 $p = 0.5$			
No	4 (66)	9 (82)				
Yes						
Cytotoxic chemotherapy	1 (17)	0 (0)				
Immune checkpoint inhibitor	1 (17)	1 (9)				
Chemoimmunotherapy	0 (0)	1 (9)				

[a]Denotes significance at $\alpha = 0.05$.

1L, first line; AJCC, American Joint Commission on Cancer; CI, confidence interval; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; ORR, objective response rate; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

Table 3. Response to ICI-Based Systemic Therapy for BRAF-V600E and Non-V600E Cohorts

Clinical Data	First-Line Immune Checkpoint Inhibitor-Based Systemic Therapy		
	V600E (n = 8), n (%)	Non-V600E (n = 7), n (%)	*p* Value
Immune checkpoint inhibitor-based systemic therapy type			$\chi 2$, df(1) = 5.5 $p = 0.02$[a]
Concurrent chemoimmunotherapy	0 (0)	3 (43)	
Monoimmunotherapy	8 (100)	4 (57)	
ECOG at systemic therapy initiation	5 (37)	4 (57)	$\chi 2$, df(1) = 0.04
ECOG < 2	3 (63)	3 (43)	$p = 0.8$
ECOG ≥ 2			
M-stage at systemic therapy initiation			$\chi 2$, df(3) = 4.8
M0	6 (76)	3 (43)	$p = 0.2$
M1a	1 (12)	3 (43)	
M1b	1 (12)	0 (0)	
M1c	0 (0)	1 (14)	
PD-L1 status			$\chi 2$, df(2) = 2.5
Negative (<1%)	0 (0)	1 (14)	$p = 0.3$
Low (1%-49%)	1 (12)[b]	2 (29)	
High (≥50%)	7 (88)	4 (57)	
Real-world ORR	38%	43%	$\chi 2$, df(1) = 0.05 $p = 0.8$
Real-world DCR	50%	71%	$\chi 2$, df(1) = 0.7 $p = 0.4$
Real-world primary resistance	25%	0%	$\chi 2$, df(3) = 3.5 $p = 0.3$
Real-world PFS (mo) [95% CI]	10.5 [1.9-not reached]	10.8 [1.4-not reached]	Log-rank $p = 0.8$
6-mo PFS rate [95% CI]	71% [26%-92%]	69% [23%-91%]	
1-y survival rate [95% CI] (after detection of advanced/metastatic disease)	60% [20%-85%]	86% [33%-98%]	Log-rank $p = 0.5$
Reason for termination			$\chi 2$, df(5) = 8.3
Progressive disease/death	3 (38)	1 (14)	$p = 0.1$
Adverse events	2 (25)	0	
Performance status decline	1 (12)	5 (72)	
Treatment ongoing/unknown	2 (25)	1 (14)	
Adverse events			
Mild (grade 1 or 2, no dose breaks or modifications)	5 (63)	3 (43)	$\chi 2$, df(1) = 2.4 $p = 0.1$
Serious (grade 3 or 4 or intervention required)	2 (25)	2 (28)	$\chi 2$, df(1) = 0.03 $p = 0.9$
2L therapy			$\chi 2$, df(1) = 0.01
No	7 (88)	6 (86)	$p = 0.9$
Yes			
Cytotoxic chemotherapy	0 (0)	1 (14)	
Immune checkpoint inhibitor	0 (0)	0 (0)	
Chemoimmunotherapy	1 (12)	0 (0)	

[a]Denotes significance at $\alpha = 0.05$.
[b]Patient-initiated nivolumab outside of Canada and then transferred care to Alberta.
2L, second line; CI, confidence interval; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; ICI, immune checkpoint inhibitor; ORR, objective response rate; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

most patients experienced clinically meaningful disease control on immunotherapy-based regimens (DCR: 50%; 6 mo PFS: 69%). Rates of adverse events were similar between V600E and non-V600E mutation-positive subgroups. Although similar in incidence, the only incidences of immune-related adverse events occurred in ICI-treated V600E subgroup (colitis and pneumonitis) in the absence of preexisting autoimmune disease and required ICI termination, whereas the non-V600E subgroup exhibited non–immune-related serious adverse events that were resolved through short (<14 d) treatment breaks. One instance of dual *BRAF*/*MEK* inhibition after ICI-based regimens was noted; dabrafenib/trametinib received in the third-line setting for a V600E mutation, after ICI-monotherapy in the first-line and concurrent chemoimmunotherapy in the second-line (2L) settings resulted in evidence of clinical benefit (partial response, ongoing dabrafenib/trametinib therapy, and adverse events of grade 2 fatigue managed through a 3-wk treatment break).

Discussion

This retrospective review explored the treatment patterns and outcome of 53 real-world patients with a *BRAF* mutation, with a focus on the management and prognosis of those 46 patients who experienced advanced disease, where *BRAF* mutation type becomes an important factor in the available treatment options (targeted versus ICI based) in the palliative setting. This study plays a role in addressing this evidence gap, by not only exploring the real-world effectiveness of dual-targeted *BRAF*/*MEK* inhibition for V600E mutation-positive patients but also assessing the clinical effectiveness of ICI-based regimens for both patients with non-V600E mutation-positive NSCLC, as standard of care, and a subset of V600E mutations who accessed ICI-based systemic therapy in lieu of targeted treatments, primarily in the first-line setting.

As a real-world study encompassing all cases of NSCLC with a *BRAF* mutation within the southern portion of the Canadian province of Alberta (population approximately 1.5 million),[25] this study was able to capture the diversity inherent among patients with a *BRAF* mutation encountered in routine clinical practice and to reveal the disease management decisions and outcome of a real clinical population. The cohort presented represents a clinically reproducible, real-world population treated in both academic and community centers. The *BRAF* mutation-positive patients in this population possessed similar characteristics to other populations with *BRAF*-mutated NSCLC described in the literature, namely, those with Caucasian ancestry, a history of smoking, and older age at diagnosis,[10,26] and a slight majority of women, particularly among the V600E subgroup.[10,27] Within its geographic context, we observed a marginally higher rate of palliative-intent systemic therapy uptake among the *BRAF*-mutated cohort compared with what has been historically observed within the southern Alberta NSCLC population (61% versus 46%)[28] and a considerably higher survival time (Fig. 2*B*; 34.1 mo) than what was observed among unselected patients with NSCLC receiving cytotoxic chemotherapy in Alberta (11.5 mo).[2,28,29] This suggests increased treatment options for NSCLC in the palliative context as a whole (ICI-based regimens) alongside targeted options for BRAF-V600E mutations which have a positive impact on systemic therapy use and patient prognosis.

Similar to other studies, this study found no significant differences in demographic or clinicopathologic features between those with the V600E and non-V600E mutation, with the exception of differences in smoking history and the rate and type of co-mutated oncodrivers.[6,30] Although rates of concurrent oncodriver mutation were similar between V600E and non-V600E mutation-positive cohorts, the non-V600E subgroup had a higher incidence of concurrent *KRAS* mutations, whereas concurrent *PIK3CA* mutations were more frequently found in association with *V600E* mutations. Smoking history seems a distinctive clinical characteristic in *BRAF*, both in terms of a higher prevalence of smoking history among *BRAF*-mutated populations as a whole compared with several other oncogene-driven forms of NSCLC (*EGFR*, *ALK*, *ROS1*),[6,31] and a further distinction where patients with the V600E mutation tend to possess lower smoking rates than non-V600E mutation-positive patients; the rate of nonsmoking among V600E mutation-positive patients in this Alberta study cohort (23%) was analogous to that of both phase 2 and real-world cohorts.[1,2,4,9] Similarly, this study aligns with other contemporary studies that have found no significant difference in survival between systemically treated V600E and non-V600E mutation-positive cohorts (log-rank $p = 0.9$; Fig. 2*C*),[6,7] although it should be noted that there were no studies to serve as comparator to this real-world *BRAF* mutation-positive population given that the V600E mutation-positive patients within the Alberta cohort were treated with a mix of ICI-based regimens and dual *BRAF*/*MEK* inhibition. Reports suggesting poorer outcome among those cohorts possessing a V600E mutation, in comparison to non-V600E mutations, consisted of V600E mutation-positive cohorts primarily treated with cytotoxic chemotherapy,[4,10] suggesting that in the context of targeted and ICI-based treatments, the previously described poorer outcomes associated with a V600E mutation are diminished.

Exposure to dual-targeted *BRAF*/*MEK* inhibition for V600E mutation-positive patients was observed to produce clinically meaningful disease control in both treatment naive and pretreated V600E mutation-positive patients (DCR: 71%; RW-mPFS: 16 mo, respectively; Table 2). This metric of clinical response compares favorably with the phase 2 clinical trial exploring the use of dabrafenib/trametinib for V600E mutation-positive NSCLC.[9] When compared with the few other real-world V600E mutation-positive cohorts treated with dual *BRAF*/*MEK* inhibition,[6,13,32] the Alberta cohort exhibited a measure of disease control akin to that of a large European real-world retrospective review (mPFS: 17.5 mo).[27] Adverse events in conjunction with dual *BRAF*/*MEK* inhibition within this cohort were experienced by half of the cohort and serious side effects were observed in tandem with progressive disease rending causation of adverse symptoms unclear. This study then adds to the evidence supporting the effectiveness of dual *BRAF*/*MEK* inhibition for V600E mutations and suggests that this therapeutic combination is equally effective for real-

world patients as it is for those treated in the clinical trial setting.

Use of ICI-based regimens was the most frequent first-line palliative treatment for both non-V600E (70%) and V600E (44%) mutation-positive cohorts, reflecting current guidelines which recommend that patients with a *BRAF* mutation be offered ICI-based therapies on the basis of PD-L1 expression in the absence of available targeted options.[1,26]ICI was delivered primarily as pembrolizumab monotherapy among patients with PD-L1 greater than or equal to 50%, reflecting a high rate of PD-L1 up-regulation (69% PD-L1 high) in this study cohort, a phenomenon which has been previously described in another real-world *BRAF* mutation-positive cohort (42% PD-L1-high).[33] Use of pembrolizumab-based ICI—either as a monotherapy for PD-L1 greater than or equal to 50% or in conjunction with concurrent platinum-based chemotherapy for PD-L1 less than 50%—revealed a measure of disease control (ORR: 38%; RW-mPFS: 10.5 mo; Table 3) in treatment-naive V600E and non-V600E mutation-positive patients, respectively, which aligns with the outcomes found among clinical trial patients treated with pembrolizumab monotherapy (KEYNOTE-24: ORR = 45%, mPFS = 10.3 mo) and concurrent pembrolizumab plus chemotherapy (KEYNOTE-189: DCR = 47%, mPFS = 8.8 mo).[11,12] Similarly, severe adverse events were all immune-related events—colitis, pneumonitis, and severe upper respiratory tract infection, requiring hospitalization and ICI termination—and occurred in 27% of the real-world Alberta study cohort, mirroring the types of adverse events (colitis/pneumonitis) observed in KEYNOTE-24 and -189 cohorts,[11,12] and with similar frequency to the KEYNOTE-24 cohort (29%),[12] further supporting the assertion that the outcomes among these real-world *BRAF*-mutated patients are well described by and consistent with BRAF unselected clinical trial cohorts.

The Alberta *BRAF*-mutation positive cohort treated with ICI-based regimens had a longer time to progression (10 mo versus <5 mo) in comparison to other real-world reviews of similarly treated *BRAF* mutation-positive populations.[13–15] Underlying differences among these real-world patient populations, including smoking rates, TMB, or PD-L1 level, could affect response to ICI-based regimens.[2,10,32] Although TMB was not assessed in the context of this study, smoking is a known correlate of both increased TMB through the promotion of somatic mutations[34,35] and up-regulated PD-L1,[36] all of which are associated with improved response to ICI-based therapy. This study cohort consisted predominantly of individuals with a history of smoking and did have high levels of PD-L1 positivity (93% PD-L1 > 1%; 73% PD-L1 ≥ 50%) which could account for the evident benefit of ICI-based regimens in this study cohort. Unique to this study was the ability to compare the responses of ICI-based or targeted therapy in the first-line palliative setting for V600E mutation-positive patients. The dual-targeted *BRAF/MEK* inhibition and ICI-based regimens produced similar clinical response ([DCR: 71%, 60%] and duration of disease control [median PFS, 16.0 and 10.4 mo], respectively) and suggest that both targeted and nontargeted systemic therapy can provide meaningful benefit to V600E mutation-positive patients. Furthermore, survival outcomes do not differ significantly, regardless of category of *BRAF* mutation (V600E or non-V600E) nor type of systemic therapy received (log-rank $p = 0.2$; Fig. 2*D*), although small numbers at risk may decrease the power of statistical detection of differences. Unfortunately, 2L therapy rates among the Alberta patients with a *BRAF* mutation and treated with dual-targeted *BRAF/MEK* inhibition or ICI-based regimens in the first-line setting were low (19%), precluding the opportunity to review the outcomes and safety of sequential use of targeted and nontargeted systemic therapies for V600E mutations, to independently assess the impact of systemic therapy type on outcome, or to add statistically supported evidence to the question of optimal sequencing of *BRAF/MEK* inhibitors and ICI-based systemic therapies in *BRAF* mutation-positive lung cancer. As found in the DREAMseq Trial for V600E mutation-positive melanoma, treatment sequence in the context of multiple lines of systemic therapy has the ability to affect outcome,[37] but it may also pose challenges associated with toxicity, particularly in the context of use of tyrosine kinase inhibitors after ICI-based therapies.[38] Included within the Alberta cohort was a single patient receiving dual *BRAF/MEK* inhibition after exposure to ICI. In this instance, evidence of clinical benefit (partial response, duration of therapy > 18 mo) was observed in the context of minimal side effects managed through a brief treatment break (grade 2 fatigue). Although a reassuring account, the need for clarity regarding treatment sequence and the balance between treatment effectiveness and safety is of upmost importance for V600E mutation-positive NSCLC in light of the apparent benefit of both ICI-based and tyrosine kinase–inhibiting systemic therapies. Low uptake of second-line therapy—either owing to a lack of suitable options or patient performance status precluding further systemic therapy—likely represents an obstacle to improving outcome for patients with a *BRAF* mutation where incremental additions to disease control facilitated through multiple lines of systemic therapy can contribute to improved outcomes.

This study adds some interesting data to the discussion regarding both the existence and incidence of other concurrent oncodrivers in addition to a *BRAF* mutation. Previously believed to be mutually exclusive to other

known oncodrivers such as *KRAS*, *EGFR*, and *ALK*,[1,39] more contemporary studies, including this review of Alberta patients with *BRAF* mutation, suggest that co-mutation of *BRAF* and *EGFR*, *KRAS*, or *PIK3CA* occurs with some frequency, recorded at 25% in this study and identified in 14% to 16% of other reviews, depending on type of co-mutation investigated.[26,32,40] We excluded from the analysis two co-occurring *EGFR*-mutated patients owing to different treatment options available in the context of a canonical *EGFR* mutation, but we made a decision to retain dual *BRAF-KRAS* and *BRAF-PIK3CA* mutation-positive patients within our cohort. Within the context of this study time period, the presence of a co-mutated *KRAS* or *PIK3CA* gene has no impact on treatment options in the first-line setting and thus reflects the real-world management of patients with these co-mutations. Within the remaining study cohort, co-occurring *BRAF* and *KRAS* mutations were most common and more frequently found in association with the non-V600E mutation-positive subgroup, which has also been observed in other studies.[4] *BRAF* detection for the patients in this study was performed using multiplex assays ensuring the simultaneous detection of *BRAF*, *EGFR*, *KRAS*, *PIK3CA*, and *ERBB2* mutations if present; increased use of multiplex testing panels and next-generation sequencing techniques to detect genetic alterations in NSCLC will likely serve to increase the rate at which co-mutations are detected. The presence of other oncodrivers in conjunction with *BRAF* is clinically significant, as it creates both possibilities and challenges: the possibility of using co-inhibition of BRAF and other oncogenic pathways either in tandem or sequentially and the possibility of co-mutations (i.e., *KRAS* and *PIK3CA*) encouraging up-regulation of PD-L1 and subsequent benefit of ICI-based regimens[41,42]; the challenge of co-occurring mutations (specifically *KRAS*) being a mechanism of primary resistance to dual *BRAF/MEK* inhibition.[32] Indeed, in this study, we observed both primary resistance to dabrafenib/trametinib in the context of a dual *BRAF-KRAS* mutation, including a rate of primary resistance double that found within the phase 2 clinical trial of dabrafenib/trametinib (33% versus 14%), which did not include dual *BRAF-KRAS* mutations.[9] Conversely, although the rate of intrinsic *BRAF* mutations is relatively low, *BRAF* mutations may also be acquired, thereby representing one mechanism of resistance to EGFR-inhibiting–targeted therapies. BRAF V600E mutations have been identified in 3% to 10% of patients in the AURA3 and FLAURA clinical trials who exhibited resistance to the third-generation EGFR inhibitor osimertinib.[1] Effective management of *BRAF*-mutated NSCLC is then poised to play an important role in the successful management of oncogene-addicted NSCLC.

There are some limitations to this study: as a retrospective, real-world review, there is a lack of consistency in standardized response assessment because toxicity reporting and patients have variable follow-up schedules. Detailed information regarding *BRAF* functional class, tumor grade, or adenocarcinoma histology patterns was not available for this cohort. In addition, the small size of this cohort and consequent limitations to robust statistical analysis are acknowledged owing to the relative rarity of *BRAF* mutations and presence of co-mutations, so the results should be interpreted cautiously and within this context. To this end, small sample size and proportions of censored end points may have affected statistical significance of univariate measures of outcome and prohibited the use of multivariate Cox regression analysis to assess prognostic factors associated with treatment response or outcome. Low 2L therapy uptake rates render this study unable to add to the literature regarding optimal treatment sequence in the context of targeted and ICI-based treatment options. Despite such limitations, this study does have some distinct strengths: First, as a population-based study, it represents all patients with a *BRAF* mutation within southern Alberta (regional population of approximately 1.5 million). Second, Alberta possesses a single-payer universal health care model that lends equality to care and treatment, irrespective of financial situation or insurance provider, and eliminates potential cohort identification biases. Finally, inclusive and comprehensive real-world data sets are rare, particularly within the North American context, but they are imperative to understand the effectiveness of treatment options for rare molecular subgroups and to determine the experience and outcomes of patients who would not meet clinical trial inclusion criteria.

In summary, to our knowledge, this represents the first single-payer, population-based review of patients with *BRAF* mutations in North America. The results of this study complement the findings of both clinical trials and other real-world reviews in confirming the safety and value of dual *BRAF/MEK* inhibition for a V600E mutation. Importantly, this study was able to reveal the effectiveness of ICI-based regimens in both non-V600E and V600E mutation-positive real-world patients where ICI-based regimens elicited similar clinical response and duration of disease control, irrespective of *BRAF* mutation type, to ICI-treated, *BRAF*-unselected clinical trial cohorts. In addition, of note, this study was able to find a high level of concurrent mutation; the impact of double *BRAF-KRAS* or *BRAF-PIK3CA* mutations on TMB and PD-L1 expression has known implications for ICI response and should be a focus of future investigation to lend clarity to use of ICI for *BRAF* mutations, including the role of ICI-based regimens after targeted *BRAF/MEK* inhibition.

CRediT Authorship Contribution Statement

Amanda J. W. Gibson: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing—original draft.

Michelle L. Dean: Investigation, Resources, Data curation, Writing—review and editing, Project administration.

Guillermo Martos: Investigation, Data curation, Writing—review and editing.

Winson Y. Cheung: Supervision.

Aliyah Pabani: Conceptualization, Validation, Writing—review and editing.

Vishal Navani: Conceptualization, Methodology, Validation, Writing—review and editing, Supervision.

Acknowledgments

This work was supported by a philanthropic donation to the Glans-Look Lung Cancer database. The authors thank and acknowledge Dr. Adrian Box, Medical Lead—Molecular Pathology Program, for his contributions to cohort selection for this project and the donors who continue to support the Glans-Look Lung Cancer Research database.

References

1. Frisone D, Friedlaender A, Malapelle U, Banna G, Addeo A. A BRAF new world. *Crit Rev Oncol Hematol*. 2020;152:103008.
2. Tabbò F, Pisano C, Mazieres J, et al. How far we have come targeting BRAF-mutant non-small cell lung cancer (NSCLC). *Cancer Treat Rev*. 2022;103:102335.
3. Ferrara MG, Di Noia V, D'Argento E, et al. Oncogene-addicted non-small-cell lung cancer: treatment opportunities and future perspectives. *Cancers (Basel)*. 2020;12:1196.
4. Dagogo-Jack I, Martinez P, Yeap BY, et al. Impact of BRAF mutation class on disease characteristics and clinical outcomes in BRAF-mutant lung cancer. *Clin Cancer Res*. 2019;25:158–165.
5. Śmiech M, Leszczyński P, Kono H, Wardell C, Taniguchi H. Emerging *BRAF* mutations in cancer progression and their possible effects on transcriptional networks. *Genes (Basel)*. 2020;11:1342.
6. Perrone F, Mazzaschi G, Minari R, et al. Multicenter observational study on metastatic non-small cell lung cancer harboring *BRAF* mutations: focus on clinical characteristics and treatment outcome of V600E and non-V600E subgroups. *Cancers (Basel)*. 2022;14:2019.
7. Tan I, Stinchcombe TE, Ready NE, et al. Therapeutic outcomes in non-small cell lung cancer with BRAF mutations: a single institution, retrospective cohort study. *Transl Lung Cancer Res*. 2019;8:258–267.
8. CADTH. Dabrafenib and trametinib for non-small cell lung cancer BRAF V600 mutation. https://www.cadth.ca/dabrafenib-and-trametinib-non-small-cell-lung-cancer-braf-v600-mutation. Accessed October 7, 2022.
9. Planchard D, Besse B, Groen HJM, et al. Phase 2 study of dabrafenib plus trametinib in patients with BRAF V600E-mutant metastatic NSCLC: updated 5-year survival rates and genomic analysis. *J Thorac Oncol*. 2022;17:103–115.
10. Leonetti A, Facchinetti F, Rossi G, et al. BRAF in non-small cell lung cancer (NSCLC): pickaxing another brick in the wall. *Cancer Treat Rev*. 2018;66:82–94.
11. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378:2078–2092.
12. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823–1833.
13. Dudnik E, Bar J, Peled N, et al. Efficacy and safety of BRAF inhibitors with or without MEK inhibitors in BRAF-mutant advanced non-small-cell lung cancer: findings from a real-life cohort. *Clin Lung Cancer*. 2019;20:278–286.e1.
14. Mazieres J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol*. 2019;30:1321–1328.
15. Guisier F, Dubos-Arvis C, Viñas F, et al. Efficacy and safety of anti-PD-1 immunotherapy in patients with advanced NSCLC with BRAF, HER2, or MET mutations or RET translocation: GFPC 01-2018. *J Thorac Oncol*. 2020;15:628–636.
16. Abuali I, Lee CS, Seetharamu N. A narrative review of the management of BRAF non-V600E mutated metastatic non-small cell lung cancer. *Precis Cancer Med*. 2022;5:13.
17. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208.
18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42:377–381.
19. Lindeman NI, Cagle PT, Aisner DL, et al. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *Arch Pathol Lab Med*. 2018;142:321–346.
20. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.
21. Izano MA, Tran N, Fu A, et al. Implementing real-world RECIST-based tumor response assessment in patients with metastatic non-small cell lung cancer. *Clin Lung Cancer*. 2022;23:191–194.
22. Kok PS, Cho D, Yoon WH, et al. Validation of progression-free survival rate at 6 months and objective response for estimating overall survival in immune checkpoint inhibitor trials: a systematic review and meta-analysis. *JAMA Netw Open*. 2020;3:e2011809.

23. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. *Chest*. 2017;151:193–203.
24. StataCorp. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP; 2011.
25. Wu JSY, Pinilla J, Watson M, Verma S, Olivotto IA. Medical assistance in dying for cancer patients one year after legalization: a collaborative approach at a comprehensive cancer centre. *Curr Oncol*. 2018;25:486–489.
26. Ding X, Zhang Z, Jiang T, et al. Clinicopathologic characteristics and outcomes of Chinese patients with non-small-cell lung cancer and BRAF mutation. *Cancer Med*. 2017;6:555–562.
27. Auliac JB, Bayle S, Do P, et al. Efficacy of dabrafenib plus trametinib combination in patients with BRAF V600E-mutant NSCLC in real-world setting: GFPC 01–2019. *Cancers (Basel)*. 2020;12:3608.
28. Ko JJ, Tudor R, Li H, et al. Reasons for lack of referral to medical oncology for systemic therapy in stage IV non-small-cell lung cancer: comparison of 2003–2006 with 2010–2011. *Curr Oncol*. 2017;24:e486–e493.
29. Cardarella S, Ogino A, Nishino M, et al. Clinical, pathologic, and biologic features associated with BRAF mutations in non–small cell lung cancer. *Clin Cancer Res*. 2013;19:4532–4540.
30. Litvak AM, Paik PK, Woo KM, et al. Clinical characteristics and course of 63 patients with BRAF mutant lung cancers. *J Thorac Oncol*. 2014;9:1669–1674.
31. Chen D, Zhang LQ, Huang JF, et al. BRAF mutations in patients with non-small cell lung cancer: a systematic review and meta-analysis. *PLoS One*. 2014;9:e101354.
32. Qu J, Shen Q, Li Y, et al. Clinical characteristics, co-mutations, and treatment outcomes in advanced non-small-cell lung cancer patients with the BRAF-V600E mutation. *Front Oncol*. 2022;12:911303.
33. Dudnik E, Peled N, Nechushtan H, et al. BRAF mutant lung cancer: programmed death ligand 1 expression, tumor mutational burden, microsatellite instability status, and response to immune check-point inhibitors. *J Thorac Oncol*. 2018;13:1128–1137.
34. Sun LY, Cen WJ, Tang WT, et al. Smoking status combined with tumor mutational burden as a prognosis predictor for combination immune checkpoint inhibitor therapy in non-small cell lung cancer. *Cancer Med*. 2021;10:6610–6617.
35. Kim J, Ha H, Park J, Cho J, Lim JH, Lee MH. Association of smoking status with efficacy of first-line immune checkpoint inhibitors in advanced non-small cell lung cancers: a systematic review and meta-analysis. *J Cancer*. 2022;13:364–372.
36. Zaleskis G, Pasukoniene V, Characiejus D, Urbonas V. Do the benefits of being a smoker hint at the existence of PD-1/PD-L1 sensitizers for patients on single-agent immunotherapy? *J Immunother Cancer*. 2021;9:e003191.
37. Atkins MB, Lee SJ, Chmielowski B, et al. DREAMseq (Doublet, Randomized Evaluation in Advanced Melanoma Sequencing): a phase III trial—ECOG-ACRIN EA6134. *JCO*. 2021;39(suppl 36):356154–356154.
38. Adderley H, Blackhall FH, Lindsay CR. Toxicity with small molecule and immunotherapy combinations in non-small cell lung cancer. *Cancer Immunol Immunother*. 2021;70:589–595.
39. Bourhis A, Remoué A, Uguen A. KRAS and BRAF double mutations and functional classes of BRAF mutations in non-small-cell lung cancers. *Clin Lung Cancer*. 2020;21:e240–e242.
40. Villaruz LC, Socinski MA, Abberbock S, et al. Clinicopathologic features and outcomes of patients with lung adenocarcinomas harboring BRAF mutations in the Lung Cancer Mutation Consortium. *Cancer*. 2015;121:448–456.
41. Quan Z, Yang Y, Zheng H, et al. Clinical implications of the interaction between PD-1/PD-L1 and PI3K/AKT/mTOR pathway in progression and treatment of non-small cell lung cancer. *J Cancer*. 2022;13:3434–3443.
42. Falk AT, Yazbeck N, Guibert N, et al. Effect of mutant variants of the KRAS gene on PD-L1 expression and on the immune microenvironment and association with clinical outcome in lung adenocarcinoma patients. *Lung Cancer*. 2018;121:70–75.