



Real-world treatment patterns and survival of patients with BRAF V600-mutated metastatic non-small cell lung cancer

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ABSTRACT

Introduction: Clinical outcomes data on BRAF-mutated non-small cell lung cancer (NSCLC) patients treated in routine practice is limited. To address this gap, we described treatment patterns and survival in a cohort of these patients evaluated/treated at 7 US academic cancer centers during 2009–2016.

Methods: This was a retrospective chart review. Patients with BRAF V600-mutated metastatic NSCLC were selected. Current/previous participants in BRAF-related trials were excluded. Onset of metastatic NSCLC defined a patient's index date, which had to occur ≥ 6 months before the chart review date. Analyses were descriptive, including Kaplan-Meier analyses for overall survival (OS).

Results: The study included 72 patients. At index, median age (range) was 65 (44–90) years; 61.1% were female. Fifty-two patients received ≥ 1 line of systemic therapy for metastatic disease. Platinum-based doublet chemotherapy was the most common first-line (1L) regimen (76.9% of 1L recipients); no patient received 1L targeted therapy (TT) with a BRAF/MEK inhibitor. In total, 20 patients received TT in any treatment line (21 or later). At time of review, 38 patients were deceased. Median (95%CI) OS from index for all patients was 31.0 (14.5, 63.8) months. Median (95%CI) OS was 56.5 (13.4, 89.1) months from index for TT recipients and 27.2 (10.6, 64.6) months in patients not treated with TT.

Conclusion: Survival time in BRAF V600-mutated metastatic NSCLC patients studied here was higher than expected based on indirect comparisons with historical NSCLC cohorts for whom no oncogenic driver (BRAF or otherwise) was present. TT recipients had a numerically longer OS from metastatic onset than patients receiving usual care, further highlighting the importance of TT in BRAF V600-mutant NSCLC.

1. Introduction

Ongoing scientific efforts to define the mechanisms driving cancer cell proliferation and survival have led to the classification of non-small cell lung cancer (NSCLC) by the presence of specific genetic aberrations, some of which render tumors actionable for targeted therapy [1–5].

One of the oncogenic drivers under study in NSCLC is mutated BRAF (v-RAF murine sarcoma viral oncogene homolog B), a serine-threonine kinase belonging to the RAF kinase family that directly interacts with the MEK-ERK signaling cascade. BRAF mutations have been reported in 2%–3% of NSCLC cases [5–8], with the BRAF V600 mutation representing approximately half of all BRAF mutations [9,10]. BRAF

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V600 mutations have been observed in former and current smokers as well as those with no smoking history [11,12] and have been identified predominantly in adenocarcinomas. BRAF-mutant NSCLC has been observed in patients with relatively short survival who are not particularly sensitive to platinum-based chemotherapy [10,11], although its natural history has not been clearly elucidated and, in fact, some observational studies [5,13] note prolonged survival in BRAF-mutated NSCLC cases compared to patients with no oncogenic driver.

Ongoing studies to define the pathogenesis of the mutated BRAF gene as an oncogenic driver in NSCLC have strengthened the rationale for the screening and targeting of this pathway in patients with NSCLC. Given the substantial antitumor activity of BRAF inhibition in combination with MEK inhibition in metastatic melanoma with a BRAF V600E or V600K mutation [14], there has been increasing interest in application of these inhibitors to BRAF mutated NSCLC. Clinical trials for patients with BRAF V600E-mutant metastatic NSCLC have shown the combination of BRAF and MEK inhibition with dabrafenib (a BRAF inhibitor [BRAFi]) and trametinib (a MEK inhibitor [MEKi]) to yield an overall response rate that was numerically higher when compared naïvely with a separate trial of dabrafenib monotherapy (overall response: 63% vs. 33%) [15,16]. The median duration of response of approximately 10 months did not differ between the monotherapy and combination therapy cohorts in the noted reports. Median PFS, however, was longer in the combination treatment cohort (10.9 months) than reported for the monotherapy cohort (5.5 months). In both assessments, safety profiles were similar to safety outcomes described in previous studies of these regimens in metastatic melanoma. Based on these data, dabrafenib and trametinib combination treatment was approved for metastatic NSCLC patients with BRAF V600E mutation in February of 2017 by the European Medicines Agency and in June 2017 by United States Food and Drug Administration.

There is limited evidence on clinical outcomes in patients with BRAF-mutated NSCLC treated with standard chemotherapy or other therapies in routine practice outside the highly controlled environs of clinical trials. This is partly because of the rarity of BRAF V600 mutation in NSCLC, the infrequency with which the mutation is tested in NSCLC and the lack of an approved targeted therapy prior to dabrafenib and trametinib combination. Such evidence would be critical to providing an appropriate historical control for retrospective comparison with available trial data. To help address this information gap, we described treatment patterns and survival outcomes of patients with BRAF V600-mutated metastatic NSCLC who were evaluated and treated at selected academic cancer centers across the United States (US). Potential survival differences between patients receiving targeted therapy (BRAFi and/or MEKi) versus usual care were also assessed.

2. Materials and methods

This study (TAF-2015-03) was a collaborative, cross sectional, retrospective, non-interventional medical record review conducted in seven academic oncology centers throughout the US (see Appendix A, Table A1). The study centers were selected based on previous and ongoing participation in prospective trials and observational studies of patients with BRAF-mutated NSCLC and thus the availability of a sufficient pool of BRAF-mutated NSCLC cases for the current review. Patients from these centers who met the following inclusion criteria were selected for study inclusion:

- Confirmed diagnosis of metastatic NSCLC
- BRAF V600-positive (lab confirmed, based on information directly recorded in the patient's medical record; V600E vs. V600 non-E was not distinguished)
- First diagnosis of (or progression to) metastatic NSCLC occurred at least 6 months before the date of medical record abstraction
- Never enrolled in a BRAFi (with or without MEKi) clinical trial (clinicaltrials.gov registration numbers NCT01336634 [dabrafenib]

Table 1
Patient Demographics.

Total Patients, n (%)	72	100.0
Age at Metastatic Diagnosis, Years		
Median	65	
Mean (SD)	64.7	10.4
Range (Min, Max)	44	90
Distribution, n (%)		
36 - 45 years	2	2.8
46 - 55 years	13	18.1
56 - 65 years	22	30.6
≥ 65 years	35	48.6
Sex, n (%)		
Male	28	38.9
Female	44	61.1
Ethnic Origin, n (%)		
White	56	77.8
Black or African American	8	11.1
Asian	5	6.9
Hispanic or Latino	1	1.4
Unknown	2	2.8
Duration (Months) of Follow-Up^a		
From initial NSCLC diagnosis		
Median	16.6	
Mean (SD)	31.9	32.7
Range (Min, Max)	1	133.1
From metastatic diagnosis date		
Median	15.5	
Mean (SD)	27.3	29.3
Min, Max	1	131.8
From date of BRAF identification/positive test result		
Median	9.5	
Mean (SD)	16.0	17.9
Range (Min, Max)	1	81.0

SD = standard deviation, NSCLC = non-small cell lung cancer.

^a Follow-up duration calculated as number of months between date of interest and last available medical record.

or NCT01524978 [vemurafenib]) before the date of medical record abstraction

The date at which a patient was diagnosed with metastatic NSCLC defined the study index date. This included patients diagnosed de novo with stage IV metastatic disease and those who had progression to metastatic disease after an initial diagnosis of early stage (I-IIIb) disease. Data from patients' medical records were abstracted from the date of metastatic diagnosis until death, loss to follow-up, or the database lock date, whichever occurred first. The database lock date, which represents the last date on which medical record reviews were conducted, was set at November 8, 2016. To allow for an adequate potential follow-up duration (retrospectively observed) after the date of metastatic diagnosis, study entry (i.e., first metastatic NSCLC diagnosis) was required to occur at least 6 months prior to the date of medical record abstraction. Although the patients reviewed were required to have not been enrolled in either of the noted targeted therapy clinical trials, off-label treatment with a BRAFi (dabrafenib, vemurafenib, or sorafenib) or MEKi (trametinib, selumetinib) in routine practice outside of a trial setting was permitted. Fig. A1 in Appendix A presents a graphical summary of the study design.

The data collected included baseline patient demographics and clinical characteristics, BRAF test characteristics and date performed, anticancer treatment history prior to first diagnosis of metastatic disease in those patients initially diagnosed with earlier-stage disease, and patients' anticancer treatment from the onset of metastatic NSCLC until the end of follow-up or death. First- and later-line treatment regimens administered in the metastatic setting were analyzed, including the agent composition of each regimen and primary reason for

Table 2
Baseline Clinical Characteristics.

Total Patients, n (%)	72	100.0
Smoking Status at Initial NSCLC Diagnosis^a		
Current smoker, n (%)	7	9.7
Number of years, median (min, max) [n = 6]	42	(25, 50)
Packs per day, median (min, max) [n = 6]	1	(1, 2)
Pack years, median(min, max) [n = 7]	45	(31, 60)
Former smoker, n (%)	41	56.9
Number of years, median (min, max) [n = 32]	30	(7, 60)
Packs per day, median (min, max) [n = 27]	1	(< 1, 3)
Pack years, median (min, max) [n = 40]	30	(3, 90)
Never smoked, n (%)	24	33.3
Disease Stage at Initial NSCLC Diagnosis, n (%)		
Early (Stage IA, IB, IIA, IIB)	5	6.9
Limited Regional (Stage IIIA)	8	11.1
Locally Advanced (Stage IIIB)	6	8.3
Metastatic (Stage IV)	51	70.8
Unknown	2	2.8
Tumor Histology at Initial NSCLC Diagnosis, n (%)		
Adenocarcinoma	65	90.3
Squamous cell carcinoma	1	1.4
Large cell carcinoma	1	1.4
Mixed histology	2	2.8
Other	2	2.8
Unknown	1	1.4
ECOG Status at Initial NSCLC Diagnosis, n (%)^b		
0	16	22.2
1	19	26.4
2	3	4.2
3	2	2.8
4	.	.
Unknown (ECOG not recorded in medical record)	32	44.4
Time (Months) to Progression to Metastatic Disease, Among Patients Initially Diagnosed w/Stage IA-III B Disease (n = 19)		
Median	6.5	
Mean (SD)	15.1	24.3
Range (Min, Max)	1	100.8
Site(s) of Distant Metastases at First Diagnosis of/Progression to Metastatic NSCLC, n (%)		
Lymph nodes	36	50.0
Lung	24	33.3
Pleura	21	29.2
Bone	13	18.1
Brain	8	11.1
Liver	5	6.9
Adrenal	4	5.6
Peritoneal	2	2.8
Other	5	6.9
Unknown	3	4.2
Skin/soft tissue	.	.

SD = standard deviation, NSCLC = non-small cell lung cancer.

^a Data on pack years reported only for patients in which it was available; pack years was recorded both directly and post hoc based on available data on number of years smoked and number of packs per day.

^b ECOG definitions: 0 - Fully active, able to carry on all pre-disease performance without restriction; 1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2 - Ambulatory and capable of all self-care but unable to carry out any work activities; 3 - Capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4 - Completely disabled, cannot carry on any self-care, totally confined to bed or chair.

discontinuation of each treatment regimen. Overall survival (OS) and progression-free survival (PFS) were also assessed. OS was defined as time from the first diagnosis of metastatic disease (and, alternatively, from treatment initiation for first-, second-, and third-line treatment recipients) until death or end of available follow-up. For each treatment line, PFS was defined as time from treatment initiation to the earliest of clinician-documented progression, start of a new treatment line, or

Table 3
BRAF Test Characteristics and History.

Total Patients, n (%)	72	100.0
Time (Months) to BRAF Test Order from Initial NSCLC Diagnosis (n = 46)^a		
Median	2.0	
Mean (SD)	13.0	22.6
Range (Min, Max)	0	100.8
Time (Months) to BRAF Test Procedure from Order Date (n = 46)^a		
Median	0.5	
Mean (SD)	0.6	0.5
Range (Min, Max)	0	2.4
Time (Months) to Receipt of BRAF Test Result from Test Procedure Date (n = 46)^a		
Median	0.2	
Mean (SD)	0.3	0.4
Range (Min, Max)	0	2.1
Disease Stage at Receipt of BRAF Test Result, n (%)		
Early (Stage IA, IB, IIA, IIB)	3	4.2
Limited Regional (Stage IIIA)	5	6.9
Locally Advanced (Stage IIIB)	2	2.8
Metastatic (Stage IV)	59	81.9
Unknown	3	4.2
BRAF Test Method, n (%)		
Sanger sequencing	20	27.8
TaqMan-based allele-specific PCR	2	2.8
Next generation DNA sequencing (NGS)	18	25.0
Multiplex PCR	25	34.7
50 gene Ion Torrent panel	3	4.2
Other	3	4.2
Unknown	1	1.4
Other Biomarkers Tested, n (%)^b		
KRAS	68	94.4
ROS-1	24	33.3
RAS	30	41.7
EGFR	69	95.8
HER-2	40	55.6
ALK translocation	50	69.4
CMet	19	26.4

SD = standard deviation, NSCLC = non-small cell lung cancer.

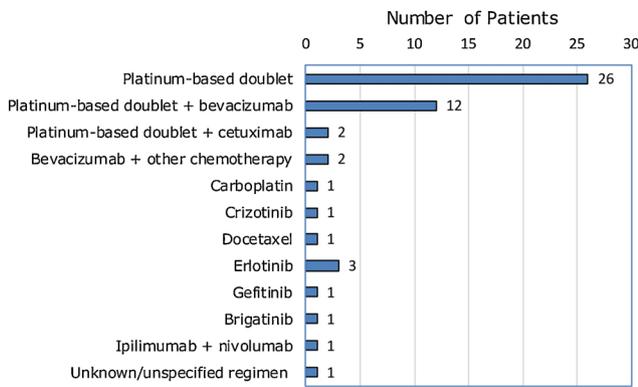
^a Estimate generated only for patients with known (non-missing) BRAF test order date (n = 46).

^b From the noted other biomarker tests, 2 patients were identified as EGFR-positive, 1 patient was HER2-positive, and 1 patient was ALK-positive.

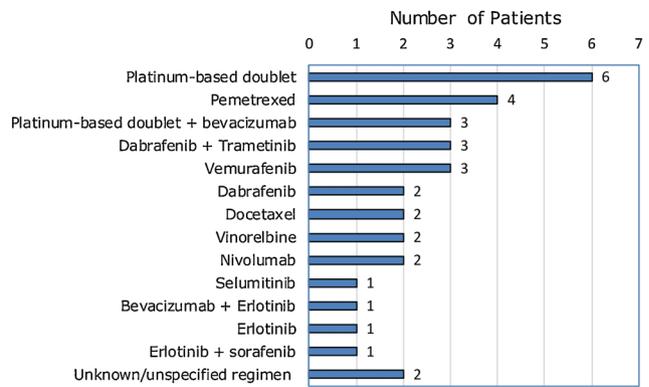
death if no additional treatment line was initiated; patients without a progression event as defined above were censored at the end of available follow-up. Clinical progression during each therapy line was based on documented assessments according to the treating physician's discretion as per routine, site-specific practice; assessments of progression were not protocol driven or based on any predetermined criteria such as RECIST.

All patient data for the study were directly entered by clinical research staff at each site into an electronic data collection form (eDCF) via a secure online portal. Data entry at each site was overseen by the site-specific investigators listed as authors on this study. Based on the exploratory nature of this study, all study measures were analyzed descriptively, using univariate statistics without prespecified power calculations. The event time variables OS and PFS were descriptively analyzed using Kaplan-Meier methods with stratification by BRAFi/MEKi targeted therapy status. Statistical significance of unadjusted, descriptive differences in OS and PFS by targeted therapy status was assessed using generalized Wilcoxon tests. All analyses were carried out using SAS statistical software. The study underwent a project-level institutional review board (IRB) review and clearance by the Research Triangle Institute Committee for the Protection of Human Subjects Research (Federal-Wide Assurance #3331), as well as site-level IRB reviews and clearances.

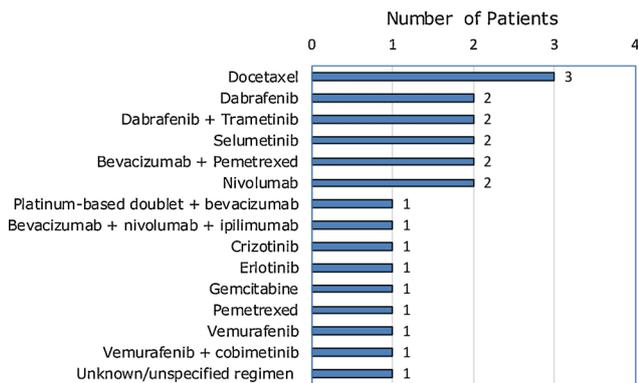
(a) First-Line Treatment Regimens (n = 52)



(b) Second-Line Treatment Regimens (n = 33)



(c) Third-Line Treatment Regimens (n = 22)



(d) Fourth-Line Treatment Regimens (n = 9)

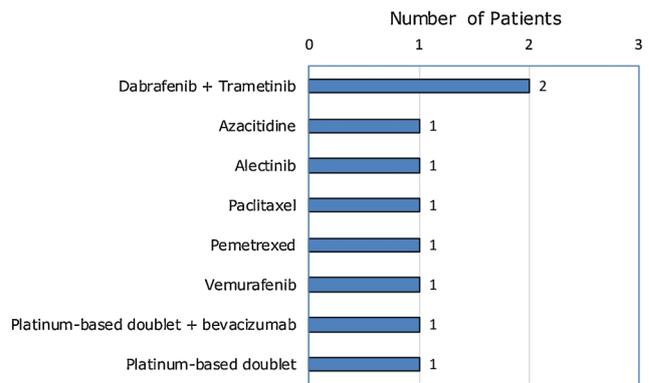


Fig. 1. Distribution of Systemic Treatment Regimens by Line of Therapy in the Metastatic Setting^a.

^a A total of 6 patients progressed to/received fifth-line therapy in the metastatic setting. Observed fifth-line regimens were ceritinib (n = 1), nivolumab (n = 1), selumetinib (n = 1), pemetrexed (n = 1), and vemurafenib (n = 1) monotherapies and bevacizumab + erlotinib (n = 1) combination therapy. A total of 2 patients progressed to/initiated a sixth-line of therapy (platinum-based doublet [n = 1] and vinorelbine monotherapy [n = 1]). No patient received treatment beyond sixth-line.

3. Results

3.1. Demographics

A total of 72 patients were identified who met the study inclusion criteria. Median age at the metastatic diagnosis date was 65 years (range: 44 to 90 years) (Table 1). At the time of chart review, 34 of 72 patients (47.2%) were still alive. A majority of the study cohort was female (44 [61.1%]). Median duration of follow-up per patient from the metastatic diagnosis date until the last available follow-up was 15.5 months; median follow-up duration from the time of BRAF V600 mutation identification was 9.5 months. BRAF tests were performed in the study cohort over the years 2009 to 2016.

3.2. Clinicopathologic characteristics

Two-thirds (66.7%) of patients were current or former smokers at the time of initial NSCLC diagnosis (Table 2). Median number of pack years for current and former smokers at initial NSCLC diagnosis was 42 and 30, respectively. A majority of patients (51 [70.8%]) had stage IV metastatic NSCLC at the time of initial diagnosis; initial disease stage was not recorded for two patients. Among the 19 patients initially diagnosed with earlier-stage disease (stage IA-IIIb), median time to progression from earlier stage disease to metastatic disease was 6.5 months (range: 1 to 100.8 months). Adenocarcinoma tumor histology represented the vast majority (65 [90.3%]) of all cases studied. Sites of metastases at the metastatic diagnosis date were varied, with lymph nodes (36 [50.0%]), lung (24 [33.3%]), pleura (21 [29.2%]), bone (13

[18.1%]), and brain (8 [11.1%]) being the most common. A comprehensive list of comorbidities, based on the Charlson Comorbidity Index [17], was provided to the sites for assessment in each patient. Among the chronic comorbidities assessed at initial NSCLC diagnosis, hypertension was most common (29 [40.3%]). Diabetes without end-organ damage (11 [15.3%]), chronic obstructive pulmonary disease (11 [15.3%]), hyperlipidemia (9 [12.5%]), and depression (8 [11.1%]) were also prevalent. Twelve patients (16.7%) had none of the comorbidities in the Charlson Index at initial NSCLC diagnosis.

3.3. Mutation testing

Table 3 presents summary data describing the method and timing of patients' BRAF test. Although BRAF testing was performed and detection of mutations in V600 were confirmed for all patients, the specific date of the BRAF test order was available for only 46 of the 72 patients reviewed. Among these 46 patients, median time from initial NSCLC diagnosis to BRAF testing was 2 months (range: 0 to 100.8 months). A variety of BRAF testing methods were utilized in clinical practice, with multiplex PCR being the most common (25 [34.7%]), followed by Sanger sequencing (20 [27.8%]) and next generation DNA sequencing (17 [23.6%]). Patients were also commonly evaluated for co-occurring KRAS (68 [94.4%]) mutation, EGFR (69 [95.8%]) mutation, and ALK rearrangements (50 [69.4%]); more than half of all patients (40 [55.6%]) were also tested for HER2 mutations. From these tests, in addition to a BRAF mutation, two patients also had EGFR mutations, one patient also had a HER2 mutation, and one patient also had an ALK rearrangement.

Table 4
Kaplan-Meier Estimates of Overall Survival.

	From First Diagnosis of Metastatic NSCLC		From Start of First-Line Treatment		From Start of Second-Line Treatment		From Start of Third-Line Treatment	
	All Patients (n = 72)	No Targeted Therapy Received ^a (n = 52)	All Patients (n = 52)	Received Targeted Therapy ^b (n = 20)	All Patients (n = 33)	Received Targeted Therapy ^b (n = 20)	All Patients (n = 22)	Received Targeted Therapy ^b (n = 11)
N (% of patients with event)	38 (52.8%)	26 (50%)	29 (55.8%)	12 (60%)	21 (63.6%)	12 (60%)	13 (59.1%)	6 (54.5%)
Median, months (95% CI)	31.0 (14.5, 63.8)	27.2 (10.6, 64.6)	45.9 (16.1, 62.4)	30.1 (14.7, —)	13.9 (8.2, 46.3)	24.9 (8.2, 83.3)	26.5 (4.0, 75.3)	43.8 (4.0, 75.3)
6-Month OS Rate	81.2%	77.3%	86.4%	84.3%	75.0%	73.7%	58.4%	77.8%
12-Month OS Rate	68.1%	63.1%	74.1%	71.0%	50.7%	56.2%	45.5%	27.8%

NSCLC = non-small cell lung cancer, CI = confidence interval, OS = overall survival.

^a For analysis of OS from first diagnosis of metastatic NSCLC, receipt of targeted therapy defined by off-label treatment with a BRAF inhibitor (dabrafenib, vemurafenib, sorafenib) or MEK inhibitor (trametinib, selumetinib) at any point after first diagnosis of (or progression to) metastatic disease.

^b For analysis of OS from start of each respective treatment line, receipt of targeted therapy defined by off-label treatment with a BRAF inhibitor (dabrafenib, vemurafenib, sorafenib) or MEK inhibitor (trametinib, selumetinib) in the current or any subsequent treatment line.

Table 5
Kaplan-Meier Estimates of Progression-Free Survival.

	From Start of First-Line Treatment		From Start of Second-Line Treatment		From Start of Third-Line Treatment	
	All Patients (n = 52)	Received Targeted Therapy ^a (n = 0)	All Patients (n = 33)	Received Targeted Therapy ^a (n = 10)	All Patients (n = 22)	Received Targeted Therapy ^a (n = 8)
N (% of patients with event)	41 (78.8%)	N/A	30 (90.9%)	9 (90.0%)	21 (91.3%)	5 (62.5%)
Median, months (95% CI)	10.9 (5.0, 18.9)	N/A	5.4 (2.8, 8.0)	3.7 (0.9, 5.6)	6.5 (2.8, 13.9)	11.2 (1.8, 11.9)
6-Month PFS Rate	59.3%	N/A	37.6%	12.0%	47.4%	53.6%
12-Month PFS Rate	47.3%	N/A	23.9%	0.0%	28.5%	0.0%

Note: Progression event defined as clinician-documented disease progression during the treatment line, start of a new treatment line, or death during/after the treatment line if no additional treatment lines were initiated. PFS defined as time from treatment line initiation until the earliest of these events or, if no event occurred, last medical record date.

NSCLC = non-small cell lung cancer, CI = confidence interval, OS = overall survival, NA = not applicable.

^a Receipt of targeted therapy defined by off-label treatment with a BRAF inhibitor (dabrafenib, vemurafenib, sorafenib) or MEK inhibitor (trametinib, selumetinib) in the specific treatment line of interest. No patient received targeted therapy as first-line treatment and therefore PFS estimates in first-line for the "no targeted therapy" group are identical to those of the "all patients" group.

3.4. Systemic therapy

Among the 19 patients who were initially diagnosed with earlier-stage NSCLC, approximately half (9 [47.4%]) received adjuvant chemotherapy before first progression to metastatic disease. Two of these patients received more than one line of systemic treatment before first progression to metastatic disease. Cancer-directed surgery and radiotherapy treatments were each administered to 6 patients (31.6%) in the pre-metastatic setting. From the metastatic diagnosis date, 52 of the 72 patients (52 [72.3%]) were treated with at least one line of cancer-directed systemic therapy in the metastatic setting. Approximately one-quarter (19 [26.4]) of all patients in the cohort received a single line of chemotherapy, while nearly half (33 [45.9%]) received at least 2 lines of therapy.

Among the 52 patients initiating a first-line therapy after the metastatic diagnosis date, platinum-based doublet chemotherapy, with or without bevacizumab, was the most common regimen reported (40 [76.9%]). No patient received BRAF-directed therapies in the first-line (Fig. 1a). The median duration of first-line treatment was 5.4 months (range: 1–47.1 months). Twenty-two patients (22 [42.3%]) initiating first-line therapy also received maintenance therapy; 16 of the maintenance therapy recipients were treated with pemetrexed monotherapy, while the remaining 6 patients were treated with bevacizumab alone or in combination with pemetrexed. The most common reason cited for first-line treatment discontinuation was completion of the planned therapy course (24 [46.2%]); one-third of patients (17 [32.7%]) stopped first-line treatment because of disease progression.

Among the 33 patients receiving a second-line regimen in the metastatic setting, second-line chemotherapy regimens were more varied (Fig. 1b). BRAFi and/or MEKi was administered in nearly one-third (10 [30.3%]) of second-line treatment recipients. The next most common regimens were platinum-based doublets (6 [18.2%]) and pemetrexed monotherapy (4 [12.1%]). Among second-line treatment recipients, median time to initiation of second-line therapy following completion or discontinuation of first-line treatment was 1 month (range: < 1 to 37.4 months). Median duration of second-line therapy was 2.3 months (range: < 1–29 months). Disease progression was the primary reason for second-line discontinuation (19 [72.7%] of the 33 s-line recipients). Additional data on later therapy lines is presented in Fig. 1c and d.

Among the 52 patients receiving at least one line of systemic therapy for metastatic disease, a total of 20 unique patients (38.5% of the study cohort) were treated with targeted therapy using a BRAFi and/or MEKi in at least one treatment line, although as noted no patient received these treatments in first-line. Of these 20 patients, 3 received BRAFi and/or MEKi in multiple lines; of those 3 patients, 1 patient received it in both second- and third-line, and the other 2 patients received it in both third- and fourth-line. By line of treatment, median duration of targeted therapy was 4 months (range: 1–29 months) in second-line (n = 10), 2.5 months (range: 2–11 months) in third-line (n = 8), 5 months (range: 3–25 months) in fourth-line (n = 3), and 8 months (range: 8 months for both patients) in fifth-line (n = 2); no patient received targeted therapy beyond fifth-line treatment.

3.5. Overall and progression free survival

More than half of the study cohort (38 [52.8%]) was deceased at the time of the medical record review (Table 4). Median (95% CI) OS from the metastatic diagnosis date was 31.0 (14.5, 63.8) months for all patients combined; for patients who received BRAFi/MEKi targeted therapy in any treatment line in the metastatic setting, median (95% CI) OS from onset of metastatic NSCLC was 56.5 (13.4, 89.1) months, versus 27.2 (10.6, 64.6) months in patients who did not receive targeted therapy. Median OS from the start of first-line treatment, among first-line treatment recipients, was 45.9 (16.1, 62.4) months for all patients combined. By targeted therapy status, median first-line OS was 55.9 (12.5, 87.4) months in patients who received BRAFi/MEKi

targeted therapy in first or any subsequent line of therapy, versus 30.1 (14.7, —) months in patients who did not receive targeted therapy. OS was similarly longer from second- and third-line treatment initiation for targeted therapy recipients as compared with patients receiving usual care. Appendix B provides Kaplan-Meier survival functions for all OS estimates.

Several patients with extended OS times, many of whom were still alive and were therefore censored at the time of data collection, appear to skew the tails of the survival distribution resulting in a later intersection of the curve with the median point of the survival distribution. To gain better insight into the unusually long survival times observed for some patients in this review, potentially resulting from selection bias, we assessed OS by time from diagnosis of metastatic disease to receipt of BRAF test results (< 3 months versus ≥ 3 months) in patients for whom specific test result dates were known (Appendix E, Table E2). Patients who had a BRAF test result within less than 3 months (n = 26) from metastatic diagnosis generally had substantially shorter survival than those with a BRAF test result three or more months (n = 21) from metastatic diagnosis (median [mean]: 14.1 [15.9] months versus 52.7 [52.3] months).

A majority of first-line treatment recipients (41/52 [78.8%]) had a progression event during follow-up; patients without an event were lost to follow-up and therefore censored in the PFS analyses. Among the 52 patients treated with systemic chemotherapy, median (95% confidence interval [CI]) PFS from first-line treatment initiation was 10.9 (5.0, 18.9) months (Table 5). No patient was treated with BRAFi/MEKi targeted therapy as first-line treatment for metastatic NSCLC; therefore, PFS was estimated only for the pooled sample (n = 52) of first-line treatment recipients. In the 33 patients who received second-line treatment, 30 had a progression event. Median (95% CI) second-line PFS was shorter (5.4 [2.8, 8.0] months) as compared with first-line. By targeted therapy status, median (95% CI) second-line PFS was numerically (but not statistically significantly) shorter in the 10 patients who received BRAFi/MEKi in second-line (3.7 [0.9, 5.6] months) as compared with the 23 patients who did not receive BRAFi/MEKi in second-line (6.5 [2.8, 13.9] months). In the 22 patients who received third-line treatment, however, median (95% CI) third-line PFS was longer in the 8 patients who received BRAFi/MEKi therapy (11.2 [1.8, 11.9] months) as compared with the 14 patients who did not receive BRAFi/MEKi (3.2 [1.0, 11.1] months). Kaplan-Meier survival functions for all PFS estimates are provided in Appendix B.

4. Discussion

Consistent with a previous report by Barlesi et al. [8] our study found platinum-based doublet regimens to be the predominant first-line treatment (76.9% of patients receiving first-line therapy) for metastatic disease in the BRAF V600-positive NSCLC patients examined here in this cohort. As expected, with no approved BRAFi/MEKi indication available in NSCLC at the time of data collection, no patient reviewed in the current study was treated with targeted therapy as the first-line systemic treatment. All use of BRAFi/MEKi regimens (20 patients in total) was observed in later lines of treatment. We further documented that 20 patients (28% of the study sample) had no documented evidence of a first-line systemic therapy (i.e., possibly received best supportive care only), which is consistent with the 23% non-treatment rate reported by Barlesi et al. [8]. Although patients not receiving first-line treatment had a similar baseline ECOG distribution versus those receiving treatment, patients who were not treated were somewhat older, with 55% of non-treated patients being > 65 years versus 46% of those who received first-line treatment; older age and resulting reduced fitness for treatment may partially explain the lack of treatment in these patients. The lack of universal treatment after metastatic diagnosis may also be due in part to a short follow-up duration and data censoring for these patients, as median survival duration from metastatic diagnosis for those not receiving first-line treatment was 2.3 months as compared

with 20.3 months in patients who received treatment. It is unclear, however, whether a short survival duration resulted in a limited opportunity to receive treatment or, conversely, whether non-treatment precipitated a short survival duration. In either case, these findings suggest that additional first-line treatment options may be needed in this population.

Evidence on survival outcomes in BRAF V600 mutant NSCLC patients treated outside of clinical trials remains limited to only a few studies based on small biomarker-related registries and other stand-alone medical record reviews. A wide range of OS estimates (9 to 56 months) have been reported in these studies, with those estimates on the lower end being in concordance with survival expectations for metastatic NSCLC in general regardless of BRAF status. Other estimates suggest longer survival in BRAF-positive cases. To provide further context around our findings reported here in a series of 72 BRAF V600-positive patients treated in seven academic institutions across the US, we summarize in Appendix D (Table D1) previous observational studies of BRAF-positive NSCLC patients. Our estimate of median OS from the onset of metastatic disease (31 months) falls within the upper end of the range of estimates available from other observational studies. This survival duration is consistent with the prolonged survival observed in other studies (Villaruz et al. [13] and Kris et al. [5], for example, from the Lung Cancer Mutation Consortium [LCMC] registry) of patients undergoing multiplex genotyping which showed that patients with documented BRAF mutations live longer than typically observed in population-based studies. Kris et al. [5] suggest that the prolonged survival is in part driven by selection bias whereby patients selected for multiplex testing must survive long enough to receive a test assessing BRAF mutations as the BRAF testing was introduced as targeted drugs directed against BRAF first became available in the 2000s. However, our estimate is closer to that of Litvak et al. [18] (19 months), an intermediate estimate within the reported range, than to that of Villaruz et al. [13], which exceeded the median OS reported in our study by 24 months despite our study having a substantially higher proportion of patients receiving targeted therapy. We recognize, however, that accurate comparisons cannot be made given the heterogeneity of these studies, particularly with respect to clinical characteristics of patients and their respective treatments.

Our data showed that patients that had a BRAF test result within less than three months from metastatic diagnosis generally had substantially shorter survival than those with BRAF test result in three or more months. Whereas it is possible that BRAF testing may in some cases have been delayed for patients with less indolent disease, it is also possible that any differences noted in survival times by timing of BRAF testing are spurious.

Our data show a numerically longer OS in patients who received targeted therapy with a BRAFi/MEKi-based regimen as compared with patients who did not receive targeted therapy. Although no differences were statistically significant due to relatively small sample sizes, the numerical differences were substantial: +29.3 months from metastatic diagnosis in patients who received BRAFi/MEKi in any subsequent treatment line, +25.8 months from first-line initiation, +13.4 months from second-line initiation, and +28.3 months from third-line initiation. However, considering that the use of BRAFi/MEKi-based regimens was only observed in the second and subsequent lines of treatment, OS in these data might be biased towards patients that received targeted therapy post-first line, since they had to be alive long enough to use targeted therapy in the subsequent lines. Nevertheless, these OS findings are concordant with the previous controlled trials [14–16] demonstrating improved outcomes in patients receiving BRAF-targeted therapies.

This study was subject to limitations inherent in retrospective medical record reviews. First, the study captures a convenience sample of BRAF V600-positive NSCLC patients from seven academic institutions in the US, which may not be generalizable to the broader population of BRAF V600-positive NSCLC patients treated in other settings

such as standalone community cancer centers. Patients managed in referral centers may have better performance status and access to the most current and comprehensive genomic testing capabilities and cancer treatment resources; as shown in previous research, cancer patients treated at such centers tend to have better survival outcomes as compared with patients treated in community clinics [19]. These factors may have contributed to OS times that were higher than expected relative to metastatic NSCLC cases without BRAF mutations. Second, data were not available in our registry on BRAF V600 mutational subtype (V600E vs. non-E). Although the prognostic value of V600 subtype in BRAF-positive tumors has yet to be thoroughly described, such information may have provided additional context to our findings. However, at present there are no approved BRAF inhibitors for advanced NSCLC that are targeted towards a specific BRAF V600 mutation subtype. As such, during the period covered in this analysis, treatment selections were not driven by patients' V600 mutational subtype. Third, assessments of PFS were not protocol driven in this retrospective study, particularly with regard to the timing of progression evaluations. It is possible that PFS was assessed for some patients at less frequent intervals than would otherwise be required in a clinical trial, and progression events may have been identified somewhat later than they would have otherwise; any potential latency in these assessments would lead to upwardly biased estimates of PFS. For these reasons, findings on PFS may not be directly comparable to those observed in clinical trials. Finally, although no formal hypotheses were tested with regard to clinical outcomes for patients treated with differing therapy regimens (including BRAFi/MEKi targeted therapy), any comparison of outcomes between naturally occurring treatment groups in this study must be made with caution as treatment assignment was not randomized and therefore may be confounded by uncontrolled and unobserved factors. This study was not designed to formally assess comparative effectiveness of alternative treatments. Furthermore, the study is limited by a small sample size and is, in addition, not statistically powered for such comparisons.

5. Conclusion

Although based on a small sample size, this study represents one of the larger ($n = 72$) available real-world assessments of patients with BRAF V600-positive metastatic NSCLC. Although platinum-based doublet chemotherapy was, as expected, the predominant first-line treatment for metastatic disease, the lack of universal systemic treatment (20 of 72 patients did not receive a first-line therapy for metastatic disease) indicates that additional first-line treatment options are needed in this population. Our findings indicate that survival expectations of patients with BRAF-mutated metastatic NSCLC may be higher than in a general metastatic NSCLC population without an oncogenic driver (BRAF or otherwise) based on indirect comparisons with historical controls. However, in one previous study designed to assess this difference, no statistical difference in OS was observed in BRAF-mutated patients versus patients with no oncogenic driver after several confounders were controlled (Villaruz et al. [13]). Additional studies including patients from a more diverse set of treatment settings may help clarify the issue of whether the longer survival times observed here are due to the previously noted selection biases or to BRAF being an inherently positive prognostic factor. Finally, our data showed that patients who received BRAFi/MEKi targeted therapy in later treatment lines had a numerically longer OS as compared with patients receiving usual care, which is consistent with previously reported observations [5]. This finding provides additional evidence from real-world practice settings on the potential importance of targeted therapies as a treatment option in NSCLC patients harboring BRAF mutation.

Acknowledgements

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Appendix A

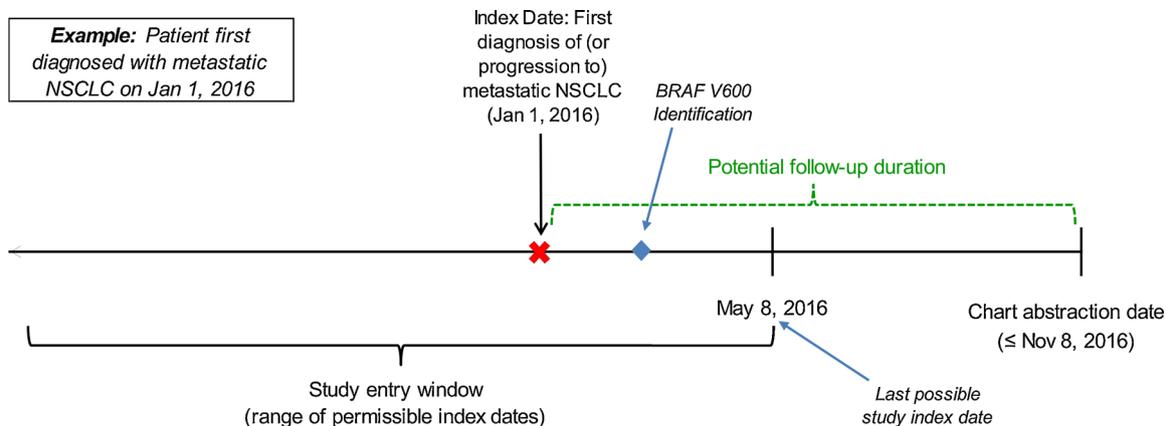


Fig. A1. Study Design. Note: Depicted time intervals not to scale.

Table A1 Study Sites.

Institution	Location	No. Cases Contributed
Dana-Farber Cancer Institute	Cambridge, MA	23
Stanford University Medical Center	Stanford, CA	9
Vanderbilt-Ingram Cancer Center	Nashville, TN	14
Johns Hopkins University	Baltimore, MD	11
University of Pennsylvania	Philadelphia, PA	9
Karmanos Cancer Center	Detroit, MI	3
University of Washington	Seattle, WA	3

Appendix B

See Figs. B1–B4.

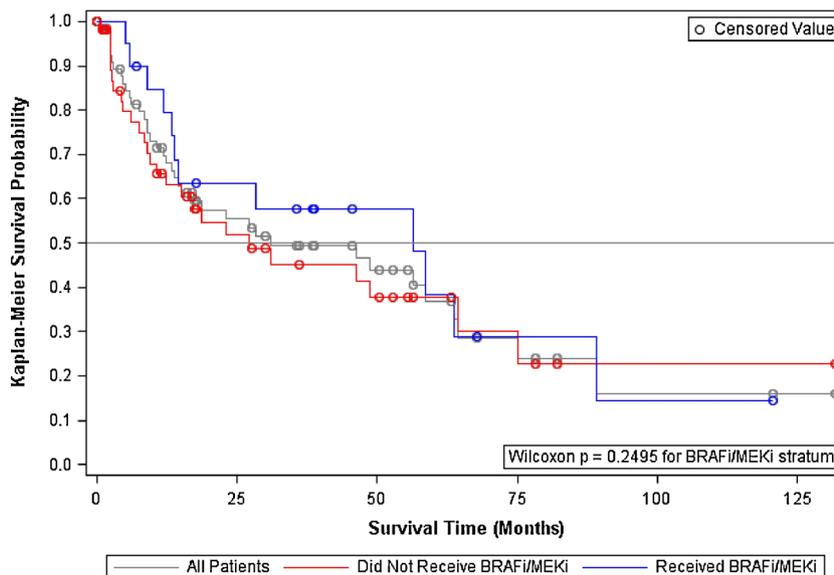


Fig. B1. Overall Survival From First Diagnosis of Metastatic NSCLC, by Targeted Therapy Status.

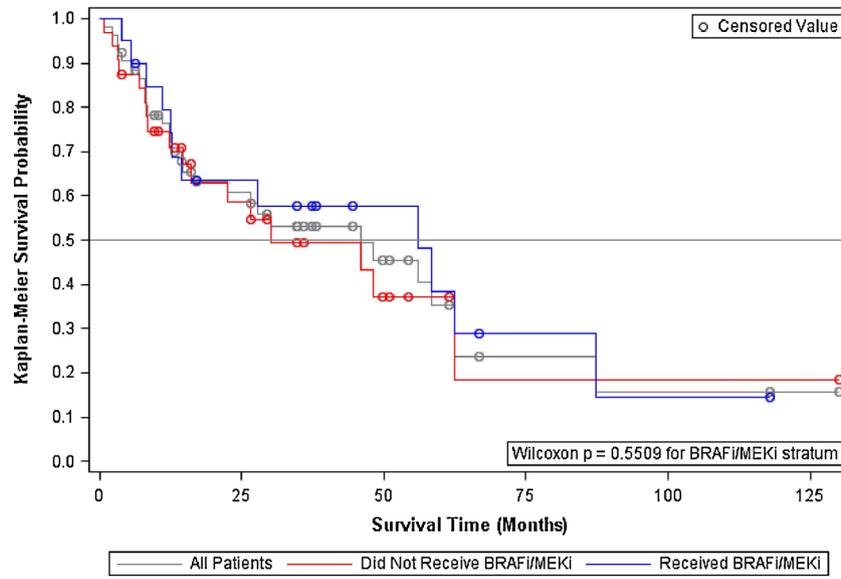


Fig. B2. Overall Survival From Start of First-Line Treatment, by Targeted Therapy Status.

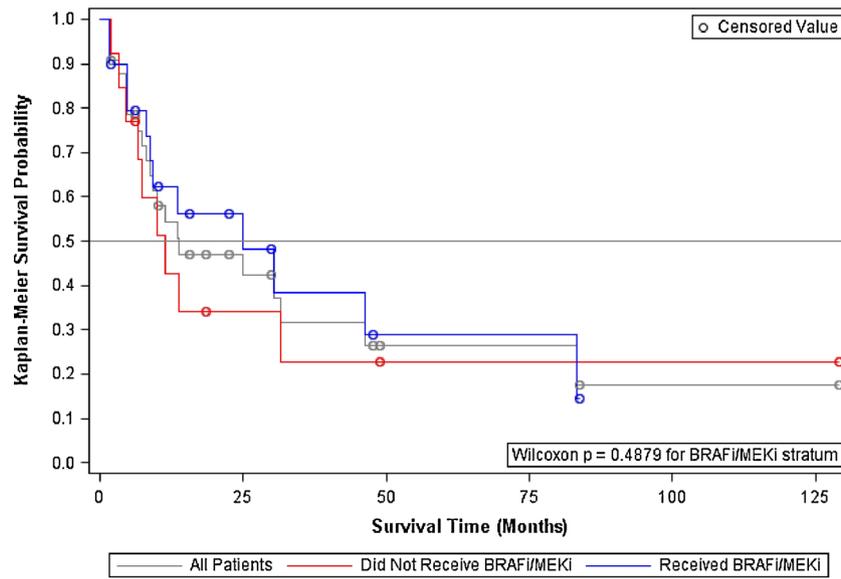


Fig. B3. Overall Survival From Start of Second-Line Treatment, by Targeted Therapy Status.

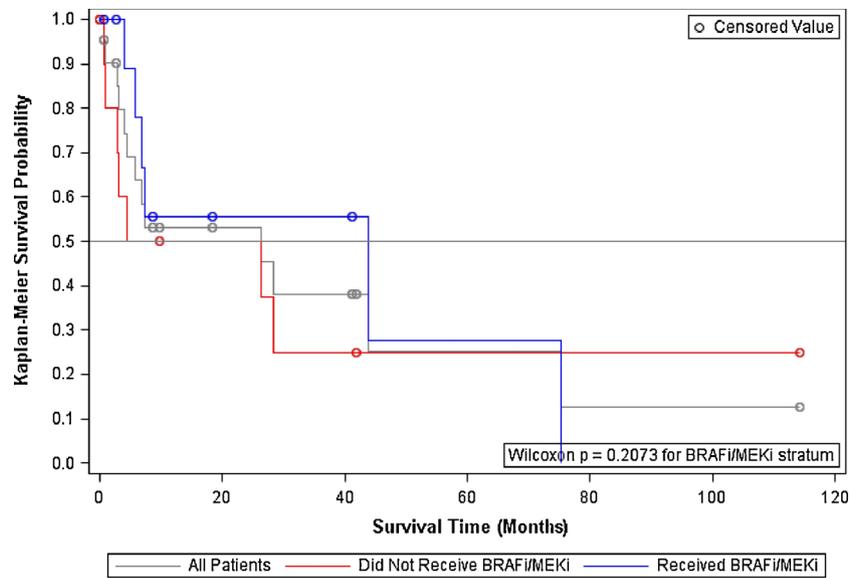


Fig. B4. Overall Survival From Start of Third-Line Treatment, by Targeted Therapy Status.

Appendix C

See Figs. C1–C3.

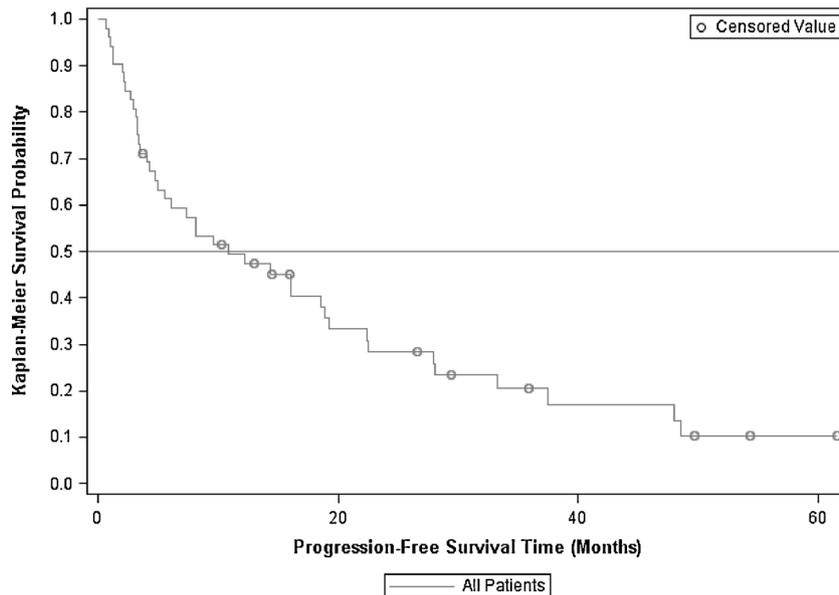


Fig. C1. Progression-Free Survival From Start of First-Line Treatment.

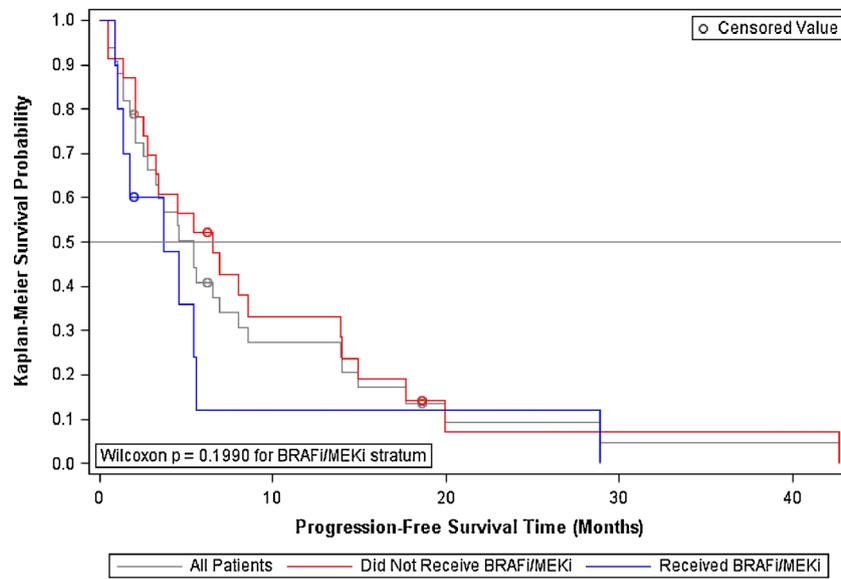


Fig. C2. Progression-Free Survival From Start of Second-Line Treatment, by Targeted Therapy Status.

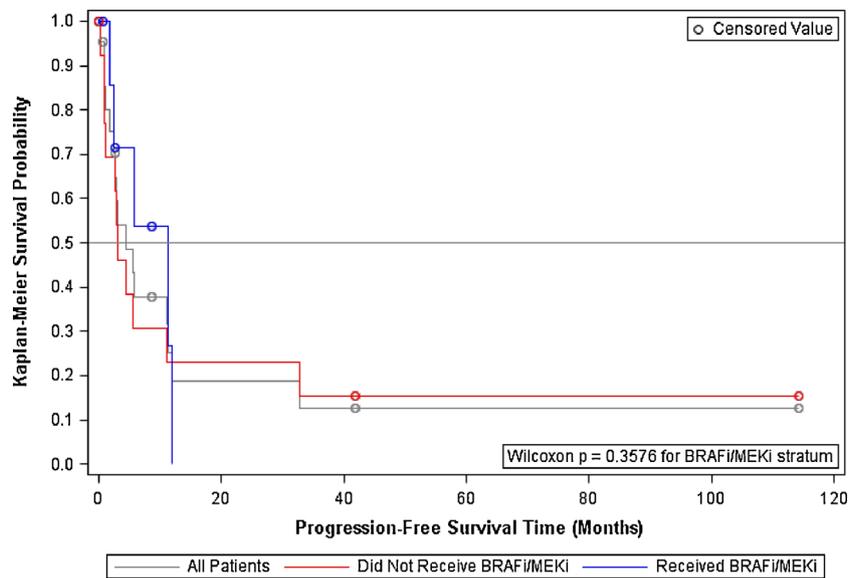


Fig. C3. Progression-Free Survival From Start of Third-Line Treatment, by Targeted Therapy Status.

Appendix D

Table D1

Overall Survival in Previous Observational Studies of Patients with BRAF-Positive Advanced or Metastatic NSCLC.

Study	Setting	Country	Sample Size ^a	OS Starting Point	% Receiving BRAFi/MEKi	Median OS (Months)
Villaruz et al. [13] ^b	Multi-center registry	US	17	Metastatic diagnosis	12%	56
Kris et al. [5] ^b	Multi-center registry	US	16	Metastatic diagnosis	13%	55
TAF-2015-03	Multi-center chart review	US	72	Metastatic diagnosis	28%	31
Litvak et al. [18]	Single-center chart review	US	27	Metastatic diagnosis	50%	19
Tissot et al. [12]	Single-center chart review	France	46	Metastatic diagnosis	11%	16
Cardarella et al. [10]	Single-center chart review	US	24	1 st treatment initiation for metastatic disease	Not reported	15.2
Ding et al. (2017)	Single-center chart review	China	28	Metastatic diagnosis	0%	14.7
Barlesi et al. [8]	Multi-center registry	France	132	Date of BRAF test	48%	13.8
TAF-2015-03	Multi-center chart review	US	46 ^c	Date of BRAF test	28%	13.6
Brustugun et al. (2014)	Single-center chart review	Norway	6	Metastatic diagnosis	0%	9.3

NSCLC = non-small cell lung cancer, US = United States, 1 L = first-line.

Citations (in order presented in table): Villaruz et al. *Cancer* 2015;121(3):448-56; Kris et al. *JAMA* 2014;311:1998-2006; Litvak et al. *J Thorac Oncol* 2014;9(11):1669-74; Tissot et al. *Lung Cancer* 2016;91:23-8. Cardarella et al. *Cancer Res* 2013;19(16):4532-40; Ding et al. *Cancer Medicine* 2017;6(3):555–62; Barlesi et al. *Lancet* 2016;387(10,026):1415-26; Brustugun et al. *Lung Cancer* 2014;84:36–8.^a Indicates number of patients analyzed with locally advanced unresectable or metastatic NSCLC.^b Villaruz et al. and Kris et al. studies based on data from same BRAF mutated NSCLC cohort captured in the Lung Cancer Mutation Consortium study.^c In the current study (TAF-2015-03), specific date of BRAF testing was known for only 46 of the 72 patients reviewed.

Appendix E

See [Table E1](#).

Table E1
Patient-Level Demographics, Clinical Characteristics, and Overall Survival Times.

Patient	Age at Metastatic Diagnosis (Years)	Sex	Smoking Status at Initial NSCLC Diagnosis	Disease Stage at Initial NSCLC Diagnosis	Received ≥ 1 Line of Systemic Therapy for Metastatic Disease	Received BRAF/MEK1 Targeted Therapy in Any Treatment Line	Vital Status at Last Available Medical Record	Overall Survival from Metastatic Diagnosis (Months)
1	58	Female	Former	Locally Advanced (Stage IIIB)	No	No	Deceased	18.6
2	50	Male	Never	Metastatic (Stage IV)	Yes	Yes	Deceased	56.5
3	67	Female	Former	Early (Stage IA, IB, IIA, IIB)	Yes	Yes	Deceased	89.1
4	90	Male	Former	Limited Regional (Stage IIIA)	No	No	Deceased	2.3
5	55	Female	Current	Metastatic (Stage IV)	Yes	Yes	Alive	35.7+
6	77	Male	Never	Metastatic (Stage IV)	Yes	Yes	Alive	38.5+
7	45	Female	Former	Metastatic (Stage IV)	Yes	No	Alive	36.0+
8	46	Female	Never	Metastatic (Stage IV)	Yes	No	Deceased	46.4
9	70	Male	Former	Early (Stage IA, IB, IIA, IIB)	Yes	No	Deceased	22.9
10	58	Male	Never	Metastatic (Stage IV)	Yes	Yes	Deceased	11.9
11	76	Female	Former	Metastatic (Stage IV)	Yes	No	Deceased	9.1
12	69	Female	Former	Metastatic (Stage IV)	Yes	No	Deceased	2.9
13	77	Female	Former	Metastatic (Stage IV)	Yes	No	Deceased	8.5
14	64	Male	Former	Metastatic (Stage IV)	Yes	No	Alive	55.5+
15	55	Female	Former	Limited Regional (Stage IIIA)	Yes	No	Deceased	2.5
16	56	Male	Former	Metastatic (Stage IV)	Yes	Yes	Deceased	28.3
17	61	Male	Current	Metastatic (Stage IV)	Yes	No	Deceased	7.5
18	69	Female	Never	Metastatic (Stage IV)	Yes	No	Deceased	6.1
19	75	Male	Never	Metastatic (Stage IV)	Yes	No	Deceased	31.0
20	59	Female	Current	Metastatic (Stage IV)	No	No	Alive	78.2+
21	59	Female	Former	Metastatic (Stage IV)	No	No	Deceased	82.2+
22	76	Female	Former	Metastatic (Stage IV)	Yes	No	Deceased	9.5
23	62	Male	Former	Locally Advanced (Stage IIIB)	No	No	Deceased	2.3
24	47	Female	Never	Locally Advanced (Stage IIIB)	Yes	No	Alive	56.6+
25	55	Female	Former	Metastatic (Stage IV)	Yes	No	Deceased	27.2
26	61	Female	Current	Metastatic (Stage IV)	Yes	Yes	Deceased	14.5
27	57	Male	Current	Unknown	Yes	No	Deceased	64.6
28	69	Female	Former	Metastatic (Stage IV)	Yes	Yes	Alive	67.8+
29	51	Female	Former	Metastatic (Stage IV)	Yes	No	Alive	17.1+
30	68	Male	Former	Metastatic (Stage IV)	Yes	No	Alive	16.0+
31	82	Female	Former	Metastatic (Stage IV)	No	No	Deceased	2.6
32	89	Female	Never	Metastatic (Stage IV)	No	No	Deceased	0.9
33	66	Male	Current	Locally Advanced (Stage IIIB)	No	No	Alive	1.5+
34	66	Male	Former	Metastatic (Stage IV)	Yes	Yes	Deceased	13.8
35	77	Female	Former	Metastatic (Stage IV)	No	No	Alive	1.7+
36	60	Male	Former	Metastatic (Stage IV)	Yes	Yes	Alive	17.7+
37	62	Male	Never	Metastatic (Stage IV)	Yes	Yes	Alive	38.8+
38	76	Female	Never	Metastatic (Stage IV)	Yes	Yes	Alive	7.0+
39	49	Female	Never	Metastatic (Stage IV)	Yes	Yes	Deceased	13.4
40	75	Male	Never	Metastatic (Stage IV)	Yes	Yes	Alive	120.5+
41	74	Male	Never	Metastatic (Stage IV)	Yes	No	Alive	52.7+
42	49	Male	Never	Metastatic (Stage IV)	Yes	Yes	Alive	48.5+
43	73	Female	Never	Metastatic (Stage IV)	Yes	No	Deceased	4.4
44	68	Male	Never	Metastatic (Stage IV)	Yes	Yes	Deceased	5.0
45	68	Female	Never	Metastatic (Stage IV)	Yes	No	Alive	63.1+

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Table E1 (continued)

Patient	Age at Metastatic Diagnosis (Years)	Sex	Smoking Status at Initial NSCLC Diagnosis	Disease Stage at Initial NSCLC Diagnosis	Received ≥ 1 Line of Systemic Therapy for Metastatic Disease	Received BRAF/MEK1 Targeted Therapy in Any Treatment Line	Vital Status at Last Available Medical Record	Overall Survival from Metastatic Diagnosis (Months)
46	64	Female	Never	Metastatic (Stage IV)	Yes	No	Deceased	48.6
47	44	Female	Former	Metastatic (Stage IV)	Yes	No	Alive	11.7+
48	51	Female	Former	Unknown	No	No	Alive	0.1+
49	51	Female	Never	Metastatic (Stage IV)	Yes	Yes	Deceased	58.6
50	58	Male	Former	Limited Regional (Stage IIIA)	No	No	Deceased	4.5
51	63	Female	Never	Metastatic (Stage IV)	Yes	Yes	Deceased	9.0
52	65	Female	Former	Limited Regional (Stage IIIA)	Yes	Yes	Deceased	63.8
53	65	Female	Never	Limited Regional (Stage IIIA)	Yes	No	Alive	131.8+
54	64	Female	Former	Metastatic (Stage IV)	Yes	Yes	Deceased	5.9
55	71	Female	Former	Limited Regional (Stage IIIA)	Yes	No	Deceased	12.3
56	72	Male	Former	Metastatic (Stage IV)	No	No	Alive	1.0+
57	76	Female	Former	Early (Stage IA, IB, IIA, IIB)	No	No	Alive	0.1+
58	74	Female	Former	Limited Regional (Stage IIIA)	Yes	No	Alive	50.4+
59	55	Male	Former	Metastatic (Stage IV)	No	No	Deceased	10.6
60	67	Male	Former	Metastatic (Stage IV)	No	No	Deceased	2.5
61	65	Female	Former	Metastatic (Stage IV)	No	No	Deceased	75.0
62	71	Female	Former	Early (Stage IA, IB, IIA, IIB)	No	No	Alive	1.1+
63	62	Female	Former	Locally Advanced (Stage IIB)	No	No	Alive	1.4+
64	80	Female	Former	Early (Stage IA, IB, IIA, IIB)	No	No	Alive	1.3+
65	81	Female	Former	Metastatic (Stage IV)	No	No	Alive	17.4+
66	66	Male	Never	Metastatic (Stage IV)	Yes	No	Deceased	17.2
67	48	Female	Former	Metastatic (Stage IV)	Yes	No	Alive	29.9+
68	57	Male	Never	Locally Advanced (Stage IIB)	Yes	No	Alive	27.7+
69	70	Male	Former	Limited Regional (Stage IIIA)	Yes	No	Alive	4.1+
70	73	Female	Former	Metastatic (Stage IV)	Yes	No	Alive	17.7+
71	67	Male	Never	Metastatic (Stage IV)	Yes	No	Alive	10.6+
72	63	Female	Current	Metastatic (Stage IV)	Yes	No	Deceased	15.0

NSCLC = non-small cell lung cancer.

Table E2
Patient-Level Overall Survival Times, by Time to BRAF Testing from First Diagnosis of Metastatic Disease.

Patient	Age at Index Date (Years)	Disease Stage at Initial NSCLC Diagnosis	Vital Status at Last Available Medical Record	Index Date (Metastatic Diagnosis Date)	Date of BRAF Test Result	Time (Months) from Metastatic Diagnosis to BRAF Test Result	Time (Months) from Metastatic Result to Death/Follow-Up End	Time (Months) from Index Date to Death/Follow-Up End
Patients With ≥ 3 Months Time from Metastatic Diagnosis to BRAF Result								
A	75	Metastatic (Stage IV)	Alive	5/25/2006	2/23/2013	80.9	39.7	120.5
B	65	Limited Regional (Stage IIIA)	Alive	9/26/2005	12/27/2011	74.9	56.9	131.8
C	57	Unknown	Deceased	10/8/2009	9/11/2014	59.0	5.6	64.6
D	51	Metastatic (Stage IV)	Deceased	9/7/2006	5/5/2011	55.8	2.9	58.6
E	68	Metastatic (Stage IV)	Alive	5/12/2011	11/12/2015	53.9	9.2	63.1
F	69	Metastatic (Stage IV)	Alive	11/22/2010	12/5/2014	48.3	19.5	67.8
G	67	Early (Stage IA, IB, IIA, IIB)	Deceased	3/24/2006	3/2/2010	47.2	41.9	89.1
H	46	Metastatic (Stage IV)	Deceased	10/17/2011	4/26/2015	42.2	4.2	46.4
I	49	Metastatic (Stage IV)	Alive	9/18/2012	9/16/2015	35.8	9.6	45.5
J	65	Limited Regional (Stage IIIA)	Deceased	11/2/2007	8/20/2010	33.5	30.3	63.8
K	56	Metastatic (Stage IV)	Deceased	11/18/2008	11/12/2010	23.7	4.6	28.3
L	62	Metastatic (Stage IV)	Alive	3/5/2013	1/28/2015	22.8	16.1	38.8
M	47	Locally Advanced (Stage IIIB)	Alive	9/26/2011	6/26/2013	21.0	35.6	56.6
N	74	Metastatic (Stage IV)	Alive	4/21/2010	4/8/2011	11.5	41.2	52.7
O	50	Metastatic (Stage IV)	Deceased	10/11/2008	9/24/2009	11.4	45.1	56.5
P	58	Metastatic (Stage IV)	Deceased	4/3/2009	3/16/2010	11.4	0.5	11.9
Q	49	Metastatic (Stage IV)	Deceased	3/16/2014	10/22/2014	7.2	6.2	13.4
R	76	Metastatic (Stage IV)	Deceased	6/13/2012	12/6/2012	5.8	3.8	9.5
S	55	Metastatic (Stage IV)	Alive	11/6/2012	3/22/2013	4.5	31.2	35.7
T	76	Metastatic (Stage IV)	Alive	10/23/2015	3/7/2016	4.5	2.6	7.0
U	45	Metastatic (Stage IV)	Alive	5/31/2013	9/30/2013	4.0	32.0	36.0
		PERCENT DECEASED	47.6%		MEDIAN	23.7	16.1	52.7
					MEAN	31.4	20.9	52.3
Patients With < 3 Months Time from Metastatic Diagnosis to BRAF Result								
V	63	Metastatic (Stage IV)	Deceased	10/31/2014	1/28/2015	2.9	6.0	9.0
W	68	Metastatic (Stage IV)	Deceased	1/28/2016	4/12/2016	2.5	2.6	5.0
X	76	Metastatic (Stage IV)	Deceased	3/29/2010	6/11/2012	2.4	6.7	9.1
Y	69	Metastatic (Stage IV)	Deceased	3/29/2010	6/11/2010	2.4	3.6	6.1
Z	61	Metastatic (Stage IV)	Deceased	8/14/2010	10/19/2010	2.2	5.3	7.5
AA	77	Metastatic (Stage IV)	Alive	2/28/2013	4/30/2013	2.0	36.5	38.5

(continued on next page)

Table E2 (continued)

Patient	Age at Index Date (Years)	Disease Stage at Initial NSCLC Diagnosis	Vital Status at Last Available Medical Record	Index Date (Metastatic Diagnosis Date)	Date of BRAF Test Result	Time (Months) from Metastatic Diagnosis to BRAF Test Result	Time (Months) from BRAF Test Result to Death/Follow-Up End	Time (Months) from Index Date to Death/Follow-Up End
BB	69	Metastatic (Stage IV)	Deceased	12/2/2011	1/31/2012	2.0	0.9	2.9
CC	64	Metastatic (Stage IV)	Alive	8/10/2011	10/6/2011	1.9	53.6	55.5
DD	55	Metastatic (Stage IV)	Deceased	7/22/2013	9/10/2013	1.6	25.6	27.2
EE	60	Metastatic (Stage IV)	Alive	3/25/2014	5/14/2014	1.6	16.1	17.7
FF	64	Metastatic (Stage IV)	Deceased	9/2/2011	10/20/2011	1.6	4.3	5.9
GG	77	Metastatic (Stage IV)	Deceased	11/15/2011	12/22/2011	1.2	7.3	8.5
HH	51	Metastatic (Stage IV)	Alive	3/23/2015	4/27/2015	1.1	15.9	17.1
II	71	Limited Regional (Stage IIIA)	Deceased	3/20/2012	4/20/2012	1.0	11.3	12.3
JJ	73	Metastatic (Stage IV)	Alive	4/15/2015	5/15/2015	1.0	16.7	17.7
KK	61	Metastatic (Stage IV)	Deceased	4/15/2014	5/9/2014	0.8	13.7	14.5
LL	66	Metastatic (Stage IV)	Deceased	5/6/2014	5/30/2014	0.8	13.0	13.8
MM	68	Metastatic (Stage IV)	Alive	5/1/2015	5/24/2015	0.8	15.3	16.0
NN	70	Early (Stage IA, IB, IIA, IIB)	Deceased	5/2/2014	5/23/2014	0.7	22.2	22.9
OO	66	Metastatic (Stage IV)	Deceased	7/24/2013	8/13/2013	0.7	16.6	17.2
PP	48	Metastatic (Stage IV)	Alive	4/11/2014	4/24/2014	0.4	29.5	29.9
QQ	67	Metastatic (Stage IV)	Alive	12/7/2015	12/16/2015	0.3	10.3	10.6
RR	63	Metastatic (Stage IV)	Deceased	10/30/2013	11/7/2013	0.3	14.8	15.0
SS	55	Limited Regional (Stage IIIA)	Deceased	5/15/2012	5/17/2012	0.1	2.5	2.5
TT	57	Locally Advanced (Stage IIIB)	Alive	7/3/2014	7/3/2014	0.0	27.7	27.7
UU	70	Limited Regional (Stage IIIA)	Alive	4/20/2016	4/15/2016	-0.2	4.3	4.1
		PERCENT DECEASED	61.5%		MEDIAN	1.1	13.3	14.1
					MEAN	1.2	14.7	15.9

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