Original Study

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

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Abstract

Little is known regarding the performance of *BRAF* inhibitors (BRAFi) and BRAFi + *MEK* inhibitor (MEKi) combination in the real-life setting. A real-life cohort of *BRAF*-mutant (BRAFm) non–small-cell lung cancer (NSCLC) patients (n = 58) was analyzed, focusing on comparative efficacy and safety of BRAFi and BRAFi + MEKi combination. In V600E BRAFm NSCLC, BRAFi + MEKi are effective, well tolerated, and superior to BRAFi. Non–V600E kinase-active BRAFm NSCLC may respond to BRAFi + MEKi.

Background: Real-life comparative data on *BRAF* inhibitors (BRAFi) and BRAFi + *MEK* inhibitors (MEKi) combination in *BRAF*-mutant (BRAFm) non–small-cell lung cancer (NSCLC) is lacking. **Patients and Methods:** Consecutive BRAFm advanced NSCLC patients (n = 58) treated in 9 Israeli centers in 2009-2018 were identified. These were divided according to mutation subtype and treatment into groups A1 (V600E, BRAFi; n = 5), A2 (V600E, BRAFi + MEKi; n = 15), A3 (V600E, no BRAFi; n = 7), B1 (non-V600E, BRAFi ± MEKi; n = 7), and B2 (non-V600E, no BRAFi; n = 23); one patient received both BRAFi and BRAFi + MEKi. Safety, objective response rate, progression-free survival with BRAFi ± MEKi, and overall survival were assessed. **Results:** Objective response rate was 40%, 67%, and 33% in groups A1, A2, and B1, respectively ($P = .5$ for comparison between groups A1 and A2). In group B1, G469A and L597R mutations were associated with response to BRAFi + MEKi. Median progression-free survival was 1.2 months (95% confidence interval [CI], 0.5-5.3), 5.5 months (95% CI, 0.7-9.3), and 3.6 months (95% CI, 1.5-6.7) for groups A1, A2, and B1, respectively (log-rank for comparison between groups A1 and A2, $P = .04$). Median overall survival with BRAFi ± MEKi was 1.7 months (95% CI, 0.5-NR), 9.5 months (95% CI, 0.2-14.9), and 7.1 months (95% CI, 1.8-NR) in groups A1, A2, and B1, respectively (log-rank for comparison between groups A1 and A2, $P = .6$). Safety profiles differed slightly, and similar treatment discontinuation rates were observed with BRAFi and BRAFi + MEKi.

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Conclusion: In the real-life setting, activity and safety of BRAFi + MEKi in V600E BRAFm NSCLC are comparable to those observed in prospective clinical trials; the combination of BRAFi + MEKi is superior to monotherapy with a BRAFi. Further research should be done to explore the impact of BRAFi + MEKi treatment on the natural history of BRAFm NSCLC.

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Introduction

Activating mutations in the *BRAF* (v-Raf murine sarcoma viral oncogene homolog B) gene promote cancer cell proliferation and survival by triggering *MEK1/2* activation and *ERK1/2* phosphorylation, and they therefore represent an oncogenic driver; these occur in 2% to 4% of non−small-cell lung cancer (NSCLC) patients.[1-4] Activating V600E mutations (V600E amino acid substitution in exon 15) comprise half of these cases, whereas non-V600E mutations (distributed in exons 11 and 15), comprising the other half, have variable degrees of *BRAF* kinase activity but may result in *MEK* activation through transactivation of *CRAF*.[3,5]

BRAF-mutant (BRAFm) NSCLC are susceptible to *BRAF* inhibition.[6] In fact, in the V600E BRAFm NSCLC, therapy with an anti-*BRAF* agent is associated with objective response rate (ORR) of 33% to 53% and median progression-free survival (PFS) of 5.0 to 7.3 months.[6-9] Combining *BRAF* inhibitors (BRAFi) with *MEK* inhibitors (MEKi) achieves even better results (ORR of 63%-64% and median PFS of 8.6-10.9 months[10,11]). However, the two strategies have never been compared in a randomized study. The effect of *BRAF* inhibition on survival has also never been evaluated.[6-11] Indeed, the rarity of *BRAF* mutations in NSCLC makes conducting a randomized study in this patient population difficult.

The existing data with BRAFi ± MEKi have many caveats with regard to their effects in the elderly, patients with poor Eastern Cooperative Oncology Group performance status (ECOG PS), patients with brain metastases. For instance, the proportion of ECOG PS 2-4 patients being enrolled onto these studies ranges between 3% and 20%, and the proportion of patients with brain metastases is less than 10%, making it difficult to extrapolate results in the general population.[7-11] The data on efficacy of biologic agents in non-V600E tumors are limited to 6 cases, although some of these mutations (eg, G596V) might confer sensitivity to BRAFi and/or MEKi.[6]

We analyzed a real-life cohort of patients with BRAFm advanced NSCLC, focusing on comparative efficacy and safety of monotherapy with BRAFi and combination treatment with BRAFi + MEKi. We also explored the effect of BRAFi ± MEKi on survival of patients with BRAFm advanced NSCLC. *BRAF* V600E and *BRAF* non−V600E-mutant tumors were analyzed separately.

Patients and Methods

Patient Selection

Patients with histologically confirmed BRAFm advanced NSCLC were identified through internal databases of oncologic centers or departments of 9 participating Israeli medical centers: Davidoff Cancer Center, Rabin Medical Center; Oncology Department, Rambam Health Care Campus; Institute of Oncology, Sheba Medical Center; Cancer Institute, Soroka University Medical Center; Oncology Department, Hadassah Hebrew University Medical Center; Oncology Department, Bney Zion Medical Center; Oncology Department, Meir Medical Center; Oncology Department, Lin Medical Center; and Oncology Department, Wolfson Medical Center. All of the patients receiving BRAFi ± MEKi were treated outside a clinical trial because there was no clinical trial evaluating BRAFi ± MEKi in BRAFm NSCLC available in Israel.

Study Design

The patients were divided into groups as follows: group A1, patients with *BRAF* V600E mutation treated with a BRAFi; group A2, patients with *BRAF* V600E mutation treated with a combination of BRAFi + MEKi; group A3, patients with *BRAF* V600E mutation not receiving a BRAFi; group B1, patients with *BRAF* non-V600E mutation treated with a BRAFi or a combination of BRAFi + MEKi; and group B2, patients with *BRAF* non-V600E mutation not receiving a BRAFi.

Baseline demographic, clinical, and pathologic characteristics were collected. Systemic treatment characteristics, with a focus on BRAFi and MEKi, were collected. In groups A1, A2, and B1, ORR, PFS and overall survival (OS) with BRAFi ± MEKi were assessed and compared. Comparative safety of BRAFi and BRAFi + MEKi was analyzed. For the safety analysis, the cohort was regrouped into patients receiving the BRAFi monotherapy, and patients receiving the combined treatment with BRAFi and MEKi. Finally, in order to evaluate the effect of treatment with BRAFi and BRAFi + MEKi on survival, OS since the date of diagnosis of advanced disease was assessed and compared between groups A1, A2, and A3 and between groups B1 and B2. Univariate OS analysis was performed.

PFS was calculated from the date of BRAFi ± MEKi initiation until disease progression by Response Evaluation Criteria in Solid Tumors, version 1.1,[12] death, or start of another systemic treatment. The outcome was censored if a patient was alive without known progression of disease at the time of last follow-up. OS was calculated from the date of BRAFi ± MEKi initiation or the date of advanced disease diagnosis until death; the outcome was censored if a patient was alive at the time of last follow-up. Adverse events were graded according to Common Terminology Criteria for Adverse Events, version 4.03.[13]

The study was conducted in accordance with the principles of good clinical practice, and institutional review board approval was obtained at each participating oncologic center or department before study initiation.

Table 1 Baseline and Treatment Characteristics of Patients According to *BRAF* Mutation Subtype and Treatment Delivered

Characteristic	Group A1[a]	Group A2[a]	Group A3	Group B1	Group B2
N	6	16	7	7	23
Age (years), median (range)	71 (55-93)	67 (54-88)	68 (61-88)	61 (42-78)	65 (40-75)
Sex					
Female	2 (33)	8 (50)	4 (57)	0 (0)	11 (48)
Male	4 (67)	8 (50)	3 (43)	7 (100)	12 (52)
Smoking History					
Current/past smoker	2 (33)	8 (50)	5 (71)	6 (86)	17 (74)
Never smoker	4 (67)	7 (44)	2 (29)	1 (14)	5 (22)
NA		1 (6)			1 (4)
Histology					
Adenocarcinoma	5 (83)	16 (100)	5 (71)	6 (86)	18 (78)
Other histology	1 (17)	0 (0)	2 (29)	1 (14)	5 (22)
ECOG PS at Diagnosis					
0/1	3 (50)	10 (63)	4 (57)	5 (72)	14 (61)
2/3/4	2 (33)	6 (37)	2 (29)	1 (14)	4 (17)
NA	1 (17)		1 (14)	1 (14)	5 (22)
Brain metastases at diagnosis	1 (17)	5 (31)	0 (0)	1 (14)	7 (30)
ECOG PS at BRAFi ± MEKi Initiation					
0/1	3 (50)	10 (63)	NA	0 (0)	NA
2/3/4	3 (50)	5 (31)	NA	2 (29)	NA
NA		1 (6)	NA	5 (71)	NA
No. Previous Systemic Treatment Lines Before BRAFi ± MEKi Administration					
0	4 (66)	5 (31)	NA	0 (0)	NA
1	1 (17)	9 (56)	NA	3 (43)	NA
2+	1 (17)	2 (13)	NA	4 (57)	NA
Chemotherapy administration	3 (50)	10 (62)	3 (43)	7 (100)	11 (48)
ICPi administration	2 (33)	10 (62)	4 (57)	3 (43)	13 (56)
No. Systemic Treatment Lines Administered					
0	0 (0)	0 (0)	2 (28)	0 (0)	4 (17)
1	2 (33)	4 (25)	3 (44)	0 (0)	13 (57)
2+	4 (67)	12 (75)	2 (28)	7 (100)	6 (26)

Data are presented as n (%) unless otherwise indicated. Group A1, *BRAF* V600E BRAFi; group A2, *BRAF* V600E BRAFi + MEKi; group A3, *BRAF* V600E, no BRAFi; group B1, *BRAF* non-V600E BRAFi ± MEKi; group B2, *BRAF* non-V600E, no BRAFi.
Abbreviations: BRAFi = *BRAF* inhibitor; ECOG PS = Eastern Cooperative Oncology Group performance status; ICPi = immune checkpoint inhibitor; MEKi = *MEK* inhibitor; NA = not available/not applicable.
[a]One patient with *BRAF* V600E mutation received both monotherapy and combined treatment sequentially.

Statistical Analysis

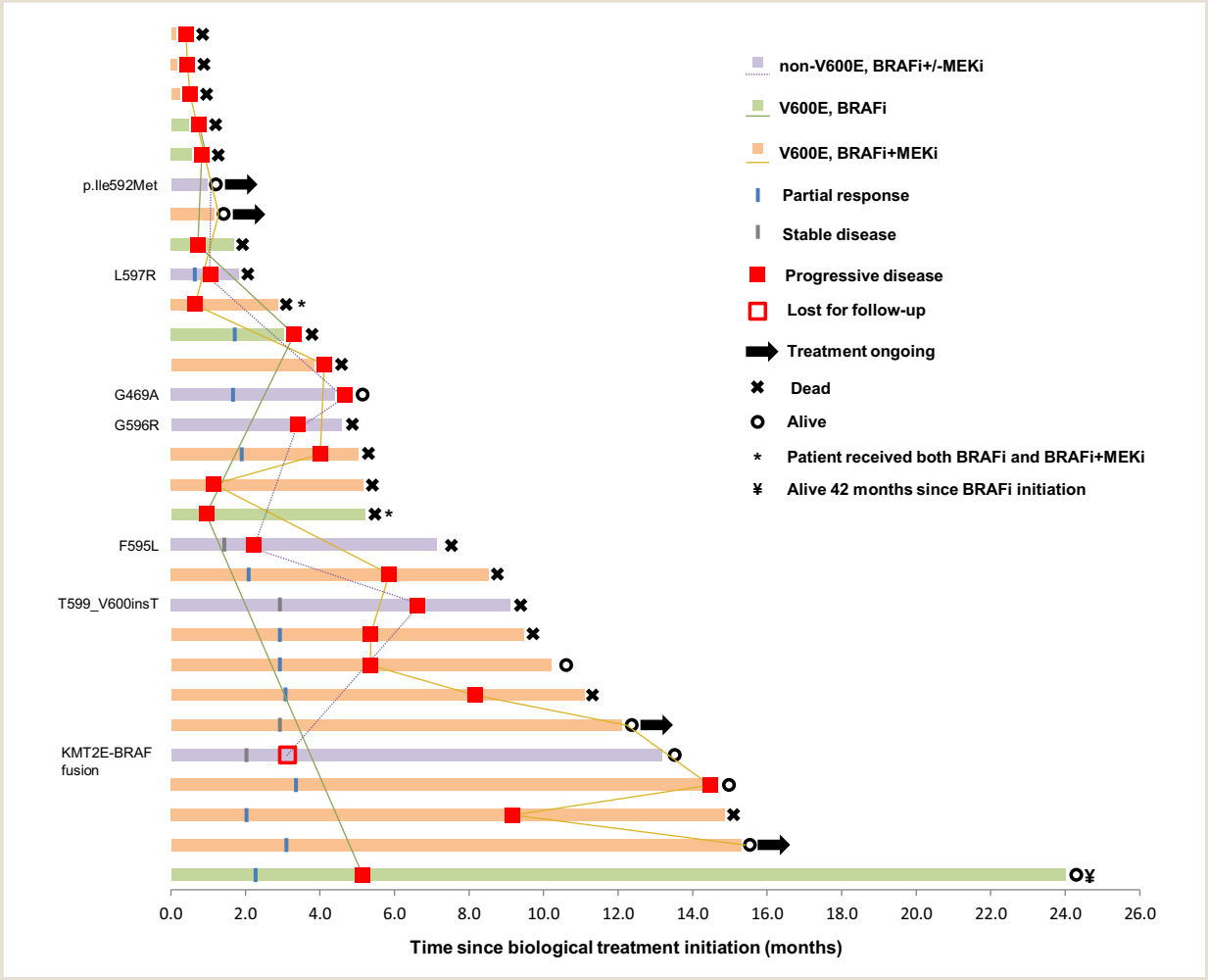
The sample size was determined by the available patients meeting the inclusion criteria. Categorical variables were presented by numbers and percentiles; medians and ranges were reported for continuous variables. The Fisher exact test was used to compare ORR. PFS and OS were assessed by the Kaplan-Meier method, with the log-rank test for the comparison. Response, PFS, and OS with BRAFi ± MEKi were analyzed by swimmer plot. The Cox proportional-hazards regression model was used for univariate OS analysis. All reported *P* values are based on 2-sided hypothesis tests. Statistical analysis was performed by SAS 9.4 software.[14]

Results

Demographics and Clinical Patient Characteristics

Fifty-nine cases of histologically confirmed BRAFm-mutant NSCLC, treated at one of the 9 participating Israeli oncologic

Figure 1 Swimmer Plot for Response, PFS, and OS With BRAFi ± MEKi in BRAFm Advanced NSCLC. Each Bar Represents Survival Since BRAFi ± MEKi Initiation. Thin Lines Connect Points Corresponding to Progression While Receiving BRAFi ± MEKi. For Non-V600E BRAFm, Mutation Types Are Specified



Abbreviations: BRAFi = *BRAF* inhibitors; BRAFm = *BRAF* mutant; MEKi = *MEK* inhibitors; NSCLC = non–small-cell lung cancer; OS = overall survival; PFS = progression-free survival.

centers or departments and diagnosed between February 2009 and June 2018, were identified. One patient with early-stage disease was excluded from the analysis.

Of 58 patients included, 25 patients were diagnosed by hot-spot panel testing, and 33 tumors were profiled by commercially available next-generation sequencing assays using FoundationOne (n = 22), Oncomine Comprehensive Assay (n = 6), Guardant360 (n = 4), and PGDx (n = 1).

Patient group allocation as well as demographic and clinical characteristics are presented in Table 1. One patient with *BRAF* V600E mutation received BRAFi + MEKi after receipt of BRAFi; this patient's data were excluded from the OS analysis but were included in the analysis of ORR, PFS, and safety of BRAFi ± MEKi.

Among the patients with *BRAF* V600E mutations, patients receiving monotherapy (group A1), as opposed to patients receiving combined treatment (group A2), had higher ECOG PS at the time of treatment initiation. Group A2, as opposed to group A1, included a higher proportion of patients with brain metastases and patients with heavily pretreated disease. In addition, there were imbalances in terms of the proportion of patients with brain metastases and patients not receiving systemic treatment between groups that were and were not exposed to BRAFi (groups A1, A2, and B1 as opposed to groups A3 and B2).

Treatment Characteristics of Patients Receiving BRAFi or BRAFi + MEKi

Of 58 patients included in the analysis, 28 patients received targeted treatment: 5 patients with *BRAF* V600E were treated with a BRAFi (group A1; dabrafenib = 3, vemurafenib = 2), 15 patients with *BRAF* V600E were treated with BRAFi + MEKi (group A2; dabrafenib + trametinib = 15), 3 patients with *BRAF* non-V600E were treated with a BRAFi (group B1; dabrafenib = 2, vemurafenib = 1), 4 patients with *BRAF* non-V600E were treated with a combination of BRAFi + MEKi

Table 2 AEs of Any Grade With BRAFi and BRAFi + MEKi

AE	BRAFi (N = 9)		BRAFi + MEKi (N = 20)	
AE leading to BRAFi dose reduction	22		30	
AE leading to MEKi dose reduction	NA		20	
AE leading to BRAFi discontinuation	22		25	
AE leading to MEKi discontinuation	NA		25	
Fatal AE	0		5	
	All Grades AE	**Grade 3-5 AE**	**All Grades AE**	**Grade 3-5 AE**
AE	78	33	75	40
Fatigue	44	22	35	15
Pyrexia	11	0	50	15
Infection	11	11	15	0
Anorexia	22	0	20	10
Nausea	22	0	15	5
Diarrhea	22	11	10	5
Rash	44	0	10	0
Peripheral edema	33	0	0	0
Peripheral neuropathy	22	0	0	0
Arthralgia	22	11	5	0
Bleeding	0	0	5	5
Thrombosis	0	0	15	15
Leukopenia	11	0	20	10
Lymphopenia	0	0	20	10
Thrombocytopenia	0	0	25	5
Anemia	44	0	30	0
ALT/AST elevation[a]	33	11	25	5
Total bilirubin elevation	0	0	15	0
Creatinine elevation	11	0	15	0
CPK elevation	11	0	0	0

Data are presented as percentages.
Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BRAFi = *BRAF* inhibitor; CPK = creatine phosphokinase; MEKi = *MEK* inhibitor; NA = not applicable.
[a]Whichever was higher grade.

(group B1; dabrafenib + trametinib = 4), and one patient with *BRAF* V600E received the combined treatment with vemurafenib and trametinib after receipt of vemurafenib. This patient's data were excluded from OS analysis but were included in ORR, PFS, and safety analyses.

Of patients in group A1, 4 (66%), 1 (17%), and 1 (17%) received BRAFi as a first, second, and third line of treatment. Of patients in group A2, 5 (31%), 9 (56%), and 2 (13%) received BRAFi + MEKi as a first, second, and third or higher line of treatment. Of patients in group B1, 3 (43%) and 4 (57%) received BRAFi ± MEKi as a second or third or higher line of treatment.

Group B1 was composed of patients with tumors harboring the following *BRAF* mutations: G469A, L597R, T599_V600insT (mutations with high kinase activity[3,15-17]), G596R (mutation with impaired kinase activity[15]), F595L, p.Ile592Met, and *KMT2E-BRAF* fusion (mutations with unknown kinase activity).

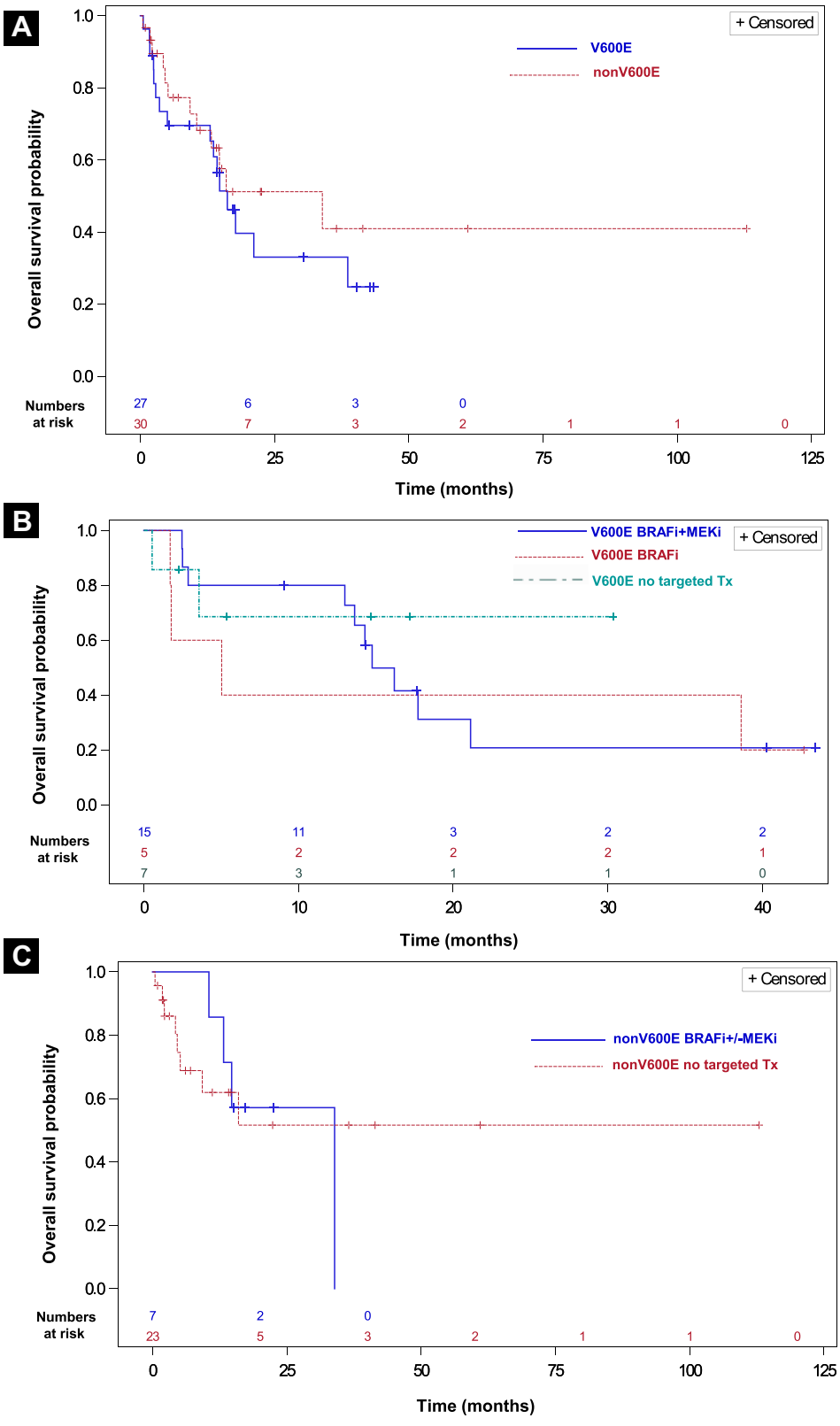
Efficacy of BRAFi and BRAFi + MEKi

Five, 12, and 6 patients in groups A1, A2, and B1, respectively, had data that could be evaluated for response assessment; 1 and 3 patients in groups A1 and A2, respectively, died before radiologic response assessment was performed. Response assessment is pending in one patient each in group A2 and group B1. ORR with BRAFi comprised 40% and 33% in groups A1 and B1, respectively; ORR with BRAFi + MEKi comprised 67% in group A2 ($P = .5$ for comparison between groups A1 and A2; Figure 1).

At a median follow-up since start of BRAFi ± MEKi of 3.6 months (interquartile range, 1.2-6.0), 100%, 81%, and 71% of patients in groups A1, A2, and B1, respectively, experienced disease progression or died (Figure 1). Median PFS comprised 1.2 months (95% confidence interval [CI], 0.5-5.3), 5.5 months (95% CI, 0.7-9.3), and 3.6 months (95% CI, 1.5-6.7) in groups A1, A2, and B1, respectively (log-rank test, $P = .03$; log-rank test for comparison between groups A1 and A2, $P = .04$; log-rank test for comparison between groups A1 and B1, $P = .4$; log-rank test for comparison between groups A2 and B1, $P = .5$) (Supplemental Figure 1A in the online version).

With median follow-up since start of BRAFi ± MEKi of 5.0 months (interquartile range, 1.2-11.1), 80%, 67%, and 57% of patients in groups A1, A2, and B1, respectively, had died (Figure 1). Median OS was 1.7 months (95% CI, 0.5-NR), 9.5 months (95% CI, 0.2-14.9), and 7.1 months (95% CI, 1.8-NR) in groups A1, A2, and B1, respectively (log-rank test, $P = .5$; log-rank test for comparison between groups A1 and A2, $P = .6$; log-rank test for comparison between groups A1 and B1, $P = .8$; log-rank test for

Figure 2 Kaplan-Meier Curves for OS since Diagnosis of Advanced Disease. Curves According to *BRAF* Mutation Type (A) and Treatment With BRAFi ± MEKi (B, C)



Abbreviations: BRAFi = *BRAF* inhibitors; MEKi = *MEK* inhibitors; OS = overall survival; Tx = treatment.

comparison between groups A2 and B1, $P = .9$) (Supplemental Figure 1B in the online version).

BRAF non-V600E mutations associated with response in group B1 were G469A (BRAFi + MEKi delivered as a second line of treatment) and L597R (BRAFi + MEKi delivered as a third line of treatment). Tumors harboring G596R *BRAF* mutation did not respond to combined treatment with BRAFi + MEKi; tumors harboring T599_V600insT *BRAF* mutation, F595L *BRAF* mutation, and *KMT2E-BRAF* fusion resulted in disease stabilization for 6.7, 2, and 3 months with therapy with dabrafenib, dabrafenib and vemurafenib, respectively (Figure 1).

Safety of BRAFi and BRAFi + MEKi

For the comparative safety assessment, the cohort was regrouped into patients treated with a BRAFi and patients treated with BRAFi + MEKi. The median duration of treatment with BRAFi and BRAFi + MEKi was 2.6 months (range, 0.5-6.7 months) and 4.3 months (range, 1.8-14.5 months), respectively. Adverse events that occurred during treatment are listed in Table 2.

Overall, no significant differences (of more than 10 points) in the rates of all-grade or high-grade adverse events between the patients treated with a BRAFi and patients treated with BRAFi + MEKi were seen. Patients receiving the combined treatment were more likely to develop pyrexia, infection, anorexia, diarrhea, thromboembolism, leukopenia, lymphopenia, thrombocytopenia, and bilirubin elevation. Patients treated with the monotherapy more frequently developed rash, peripheral edema, peripheral neuropathy, arthralgia, anemia, and creatine phosphokinase elevation. No cases of hypertension or left ventricle ejection fraction decrease were observed. One patient died of pulmonary embolism 5 days after the initiation of therapy with dabrafenib and trametinib; relation to treatment in this case could not be excluded.

No major differences in the BRAFi dose reduction or BRAFi discontinuation rate were observed between patients receiving combined treatment and those receiving BRAFi monotherapy. In patients who received the combined treatment, MEKi dose reduction and MEKi discontinuation were required in 20% and 25% of patients, respectively.

OS Since Diagnosis of Advanced Disease

With median follow-up since diagnosis of advanced disease of 13.2 months (interquartile range, 3.1-17.6), 59% and 40% patients with *BRAF* V600E mutations and *BRAF* non-V600E mutations, respectively, have died. Median OS was 16.2 months (95% CI, 5.0-38.6) and 33.9 months (95% CI, 10.5-NR) in patients with *BRAF* V600E mutations and *BRAF* non-V600E mutations, respectively (log-rank test, $P = .63$ and .4, respectively) (Figure 2A).

Among the patients with *BRAF* V600E mutations, 80% of patients treated with a BRAFi (group A1), 67% of patients treated with a combination of BRAFi + MEKi (group A2), and 29% of patients not receiving a BRAFi (group A3) have died. Median OS was 5.0 months (95% CI, 1.7-NR), 14.8 months (95% CI, 2.9-21.1), and was not reached (95% CI, 0.5-NR) in groups A1, A2, and A3, respectively (log-rank test for the comparison between groups A1 and A3, $P = .7$, log-rank test for the comparison between groups A2 and A3, $P = .9$, log-rank test for the comparison between groups A1 and A2, $P = .9$) (Figure 2B). In the univariate analysis of OS since advanced disease diagnosis in patients with *BRAF* V600E mutations, none of the parameters examined demonstrated a significant correlation with survival, including age ($P = .1$), gender ($P = .1$), ECOG PS ($P = .2$), presence of brain metastases ($P = .5$), administration of chemotherapy ($P = .4$), administration of immunotherapy ($P = .3$), administration of a BRAFi as opposed to no administration of targeted therapy ($P = .4$), administration of BRAFi + MEKi as opposed to no administration of targeted therapy ($P = .6$), and number of systemic treatment lines ($P > .1$).

Among the patients with *BRAF* non-V600E mutations, 57% treated with BRAFi or BRAFi + MEKi (group B1) and 30% of patients not receiving a BRAFi (group B2) have died. Median OS was 33.9 months (95% CI, 10.5-33.9), and was not reached (95% CI, 4.6-NR) in groups B1 and B2, respectively (log-rank test, $P = .9$), (Figure 2C). In the univariate analysis of OS since advanced disease diagnosis in patients with *BRAF* non-V600E mutations, ECOG PS (ECOG PS 2-4 vs. 0/1, hazard ratio = 6.4, 95% CI, 1.4-29.3; $P = .02$) and number of systemic treatment lines (administration of one line of systemic therapy as opposed to no systemic therapy: hazard ratio = 0.08, 95% CI, 0.01-0.7; $P = .02$) were related to survival, whereas age ($P = .09$), gender ($P = .7$), presence of brain metastases ($P = .5$), administration of chemotherapy ($P = .9$), administration of immunotherapy ($P = .5$), administration of a BRAFi as opposed to no administration of targeted therapy ($P = .8$), and administration of BRAFi + MEKi as opposed to no administration of targeted therapy ($P = .8$) did not demonstrate a significant correlation.

Discussion

In our poor-prognosis cohort of patients with heavily pretreated disease, ECOG PS 2-4, brain metastases, and treatment with BRAFi + MEKi in *BRAF* V600E tumors was associated with ORR of 67%, median PFS of 5.5 months, and median OS since treatment initiation of 9.5 months. These findings are only slightly inferior to the results observed in prospective clinical trials, which found ORR ranging 63% to 64%, median PFS ranging 8.6 to 10.9 months, and 6-month OS of 82%.[10,11] However, ORR of 40%, median PFS of 1.2 months, and median OS of 1.7 months, as demonstrated with BRAFi administered as a monotherapy in *BRAF* V600E tumors, compares unfavorably with the previously reported results, with ORR ranging 33% to 53%, median PFS ranging 5.0 to 7.3 months, and median OS ranging 10.8 to 12.7 months,[6-9] thus hardly justifying their routine clinical use in this setting. Importantly, the results obtained with BRAFi + MEKi therapy were significantly superior to those with BRAFi monotherapy with regard to median PFS (log-rank test, $P = .03$) and were numerically superior with regard to ORR (67% vs. 40%, $P = .5$).

Both the monotherapy and the combined treatment were well tolerated, with safety profiles and discontinuation rates similar to those previously reported.[8-11] As expected, the incidences of pyrexia and myelosuppression were higher with combination therapy than with monotherapy, and cutaneous toxicity was more frequently observed with monotherapy. Importantly, treatment discontinuation rates with BRAFi and BRAFi + MEKi were comparable.

We attempted to explore the effect of BRAFi ± MEKi on OS by comparing the OS rates of patients who were and were not exposed

to BRAFi ± MEKi. Unfortunately, such an effect was not observed in either mutation subgroup, most probably as a result of insufficient follow-up, small sample size, and major imbalances in baseline and treatment characteristics between the cohorts of patients who were and were not exposed to BRAFi ± MEKi. Overall, no firm conclusions can be drawn on the subject.

Interestingly, 2 of 3 patients with non-V600E *BRAF* mutations treated with BRAFi + MEKi experienced partial response; importantly, mutations in both patients with response—G469A and L597R—are associated with high *BRAF* kinase activity,[16] whereas mutation in the patient without response—G596R—is associated with impaired *BRAF* kinase activity.[16] In another study evaluating BRAFi in BRAFm NSCLC, none of the 3 tumors harboring non-V600E *BRAF* mutations associated with high *BRAF* kinase activity responded to monotherapy with BRAFi.[6] This supports the hypothesis of sensitivity to *MEK* inhibition in non-V600E BRAFm tumors associated with high *BRAF* kinase activity,[16] and it adds to the scarce clinical data regarding non-V600E BRAFm NSCLC potentially sensitive to targeted treatment.

We acknowledge the limitations of this study, specifically its retrospective nature, which may introduce biases (eg, absence of a routine *BRAF* testing for all NSCLC patients, resulting in selection bias), the small size of the cohort, and insufficient follow-up, which precluded drawing conclusions about the effect of treatment on OS. Absence of central radiologic review introduced further uncertainties into PFS assessment. However, our cohort had many patients with poor ECOG PS and patients with brain metastases, which allowed us to assess the efficacy and safety of BRAFi + MEKi in a patient population that is generally underrepresented in clinical trials.

Conclusion

In a real-life cohort comprising patients with adverse prognostic features, activity and safety of BRAFi + MEKi in V600E BRAFm NSCLC are comparable to the results observed in prospective clinical trials. In these tumors, the combination of BRAFi + MEKi is clearly superior to monotherapy with a BRAFi. Some non-V600E BRAFm NSCLCs associated with high *BRAF* kinase activity may respond to combined treatment with BRAFi + MEKi, whereas *MEK* inhibition seems to represent the necessary treatment component. Further research should be done to explore the effect of BRAFi + MEKi treatment on OS of BRAFm NSCLC.

Clinical Practice Points

- BRAFm NSCLC is characterized by marked sensitivity to BRAFi. Combining BRAFi with MEKi may achieve even better results; however, the two strategies have never been compared in a randomized fashion. Data on their efficacy in non-V600E BRAFm tumors is limited, and the effect of BRAFi ± MEKi on the natural history of the disease is unknown.
- Analyzing a real-life cohort of BRAFm advanced NSCLC patients, and focusing on comparative efficacy and safety of BRAFi and BRAFi + MEKi, we demonstrated that the combination of BRAFi + MEKi is superior to monotherapy with a BRAFi.
- Some non-V600E kinase-active BRAFm NSCLC may respond to a BRAFi + MEKi combination, whereas *MEK* inhibition here represents the necessary treatment component.
- Although we were unable to demonstrate the impact of BRAFi ± MEKi administration on OS, this could not be excluded, given the small sample size of our cohort, major imbalances in baseline and treatment characteristics between groups with and without exposure to BRAFi ± MEKi, and insufficient follow-up. Evaluation of the BRAFi ± MEKi effect on the natural history of advanced NSCLC will require larger patient cohorts.

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Disclosure

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Supplemental Data

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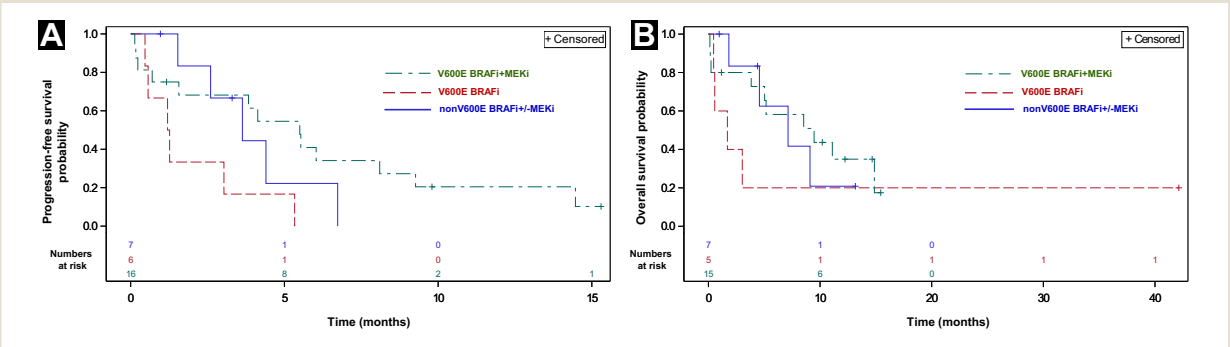
Supplemental Figure 1 **Kaplan-Meier Survival Curves by Group. Curves for PFS (A) and OS (B) With BRAFi ± MEKi in BRAFm Advanced NSCLC**



Abbreviations: BRAFi = *BRAF* inhibitors; BRAFm = *BRAF* mutant; MEKi = *MEK* inhibitors; NSCLC = non–small-cell lung cancer; OS = overall survival; PFS = progression-free survival.