BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-021642
Article Type:	Research
Date Submitted by the Author:	09-Jan-2018
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Keywords:	post-progression survival, time to progression, dabrafenib, trametinib, BRAF V600E NSCLC

Time to progression and post-progression survival in previously treated metastatic non-small cell lung cancer with BRAF V600E mutation

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Word Count: 3118 (excluding title page, abstract, references, figures and tables)
Tables: 2
Figures: 2

ABSTRACT

Objective: Longer time to progression (TTP) is associated with prolonged post-progression survival (PPS) in ALK+ non-small cell lung cancer (NSCLC). This study evaluated the TTP-PPS association among previously treated patients with metastatic BRAF V600E NSCLC receiving dabrafenib as monotherapy or in combination with trametinib.

Methods: Patients who experienced disease progression treated with dabrafenib monotherapy or in combination with trametinib as second-line or later in an open-label, non-randomized, Phase II study were included. PPS was assessed with Kaplan-Meier analysis among patients with shorter versus longer TTP (< or ≥6 months). The TTP-PPS association was quantified in the Cox models adjusting for clinical covariates.

Results: Of the 84 included patients who progressed on dabrafenib monotherapy (N=57) or combination therapy (N=27), 60 (71%) died during post-progression follow-up. Patients with TTP ≥6 months experienced significantly longer PPS compared to those with TTP <6 months (median PPS: 9.5 vs. 2.7 months, log-rank p<0.001). Each 3 months of longer TTP was associated with a 32% lower hazard of death following progression (hazard ratio [95% confidence interval]: 0.68 [0.52-0.88]) in the multivariable Cox model. Similar associations were seen in each treatment arm.

Conclusion: A longer TTP duration after treatment with dabrafenib monotherapy or combination therapy was associated with significantly longer PPS duration.

Keywords: post-progression survival, time to progression, dabrafenib, trametinib, BRAF V600E NSCLC

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The relationship between TTP and PPS has not yet been assessed among patients with BRAF V600E mutant NSCLC receiving the newer generation of targeted therapies. A major strength of this retrospective study is that it quantified the association between time to progression (TTP) and post-progression survival (PPS) among previously treated patients with metastatic, BRAF V600E mutant non-small cell lung cancer (NSCLC) receiving dabrafenib monotherapy or in combination with trametinib who experienced disease progression using existing patient-level data from the ongoing dabrafenib targeted therapy clinical trial.
- A limitation of the present study is that it only included patients who had disease progression observed before death in a clinical trial setting and these results may not fully generalize to other patient populations.
- This study should be considered an interim analysis of the association of TTP with PPS in previously treated patients with metastatic, BRAF V600E mutant NSCLC as collection of the progression and survival data in the dabrafenib targeted therapy clinical trial is ongoing.

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for 80–85% of all lung cancers globally,[1] and is the leading cause of cancer-related mortality in the United States (US).[2] In advanced stages, NSCLC is aggressive. For example, patients with stage IIIB cancer have an estimated 5-year survival rate of 5%; this rate is estimated to be about 1% for patients in stage IV or with confirmed metastatic disease.[3] Treatment for NSCLC has traditionally consisted of cytotoxic chemotherapy, although recent advances in cancer biology have led to the development of targeted anti-cancer agents that modulate specific oncogenic molecular pathways.[4]

NSCLC is a heterogeneous cancer, and molecular diagnostic testing can be used to inform treatment choice for patients with metastatic or relapsing disease. For example, mutations in BRAF (v-Raf murine sarcoma viral oncogene homolog B), which encodes the protein B-Raf involved in cell growth signaling, are present in 1–5% of NSCLC.[5,6] Constitutively active B-Raf mutants can prompt tumorigenesis by excessively signaling cells to divide, often via the MAP kinase (MAPK) pathway.[7] In particular, BRAF V600E mutations account for about 50% of BRAF mutant NSCLC and 2% of all NSCLC, and are usually associated with a history of smoking and with adenocarcinoma.[8] Patients with BRAF V600E mutant NSCLC have poorer clinical outcomes and lower response to platinum-based chemotherapy compared with patients without this mutation.[6,9] Thus, targeted therapies that modulate BRAF kinase signaling or downstream MAPK signaling to slow tumor growth are promising alternatives to effectively treat BRAF-mutant NSCLC.[10]

Dabrafenib is a potent and selective reversible BRAF kinase inhibitor, which has previously demonstrated efficacy and tolerability in clinical trials of patients with BRAF V600 mutant melanoma, including those with metastatic disease.[11] Trametinib, an allosteric inhibitor of mitogen-activated extracellular signal regulated kinase (MEK) 1 and 2, has synergistic anti-oncogenic activity with BRAF inhibition. The efficacy and tolerability profiles of dabrafenib as a single agent and in combination with

trametinib have been assessed among patients with BRAF V600E mutation positive metastatic (stage IV) NSCLC in a recent multicenter, non-randomized, open-label, Phase II trial (ClinicalTrials.gov: NCT01336634).[12,13] For example, among patients who received at least one prior platinum-based chemotherapy regimen for metastatic disease, patients treated with dabrafenib monotherapy (Cohort A) reported an investigator-assessed overall confirmed response rate of 33% and median progression-free survival (PFS) of 5.5 months. The overall confirmed response rate was 63% and median PFS was 9.7 months for patients who received dabrafenib and trametinib in combination (Cohort B).[12,13]

The overarching goals of NSCLC treatment are to prolong overall survival (OS), manage symptoms, and improve patients' quality of life.[14] However, there are practical challenges to directly assess the effects of treatment on long-term survival in clinical trials of late-stage cancer patients who have already failed multiple lines of therapy.[15,16] Clinical trials and meta-analyses of other advanced NSCLC treatments have demonstrated that time to progression (TTP) can be predictive of long-term clinical benefits in patient survival.[17-19] For example, a longer duration of TTP was demonstrated to be significantly associated with a longer duration of post-progression survival (PPS) among NSCLC patients with anaplastic lymphoma kinase (ALK) gene rearrangement[19] and mutations in the epidermal growth factor receptor (EGFR) gene.[20]

To the best of our knowledge, the relationship between TTP and PPS has not yet been assessed among patients with BRAF V600E mutant NSCLC receiving the newer generation of targeted therapies. It is of great clinical interest to determine whether any improvement in TTP is offset by loss of survival time in the post-progression period. To address this question, the current study evaluated the association between TTP and the duration of PPS among adult, previously treated, metastatic NSCLC patients with BRAF V600E mutation who experienced disease progression while receiving dabrafenib monotherapy or in combination with trametinib.

MATERIAL AND METHODS

Study design and population

The study is a secondary analysis of data from metastatic NSCLC patients with BRAF V600E mutation included in the non-randomized, open-label, Phase II trial BRF113928 (NCT01336634; data cut: October 7, 2015, trial ongoing). Written informed consent was obtained from each subject prior to the performance of any study-specific procedures in BRF113928; de-identified patient-level data were used in this retrospective analysis. The current analysis included chemotherapy-experienced patients who were assigned to receive either dabrafenib monotherapy (150 mg twice daily [BID]; Cohort A) or combination therapy of dabrafenib (150 mg BID) and trametinib (2 mg once daily; Cohort B) as second- or later-line and experienced disease progression during the trial's study period. The disease progression was determined based on radiological response as per investigator assessment and Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.[21] For patients in Cohort B, the study treatment could have been up to the fourth-line of systemic anti-cancer therapy for metastatic disease. The full methodology of this trial has been previously published.[12,13]

A diagram of the patient selection process in the current study is shown in **Figure 1**. Patients who were previously untreated, or did not experience observed disease progression (either due to censoring or death before progression) during the original trial's study period, were excluded from the final analytical sample in this study.

Outcomes and Variables

The primary outcome of interest in the current analysis was PPS, which was defined as the time from the date of disease progression after starting the study treatment (dabrafenib monotherapy or combination therapy with dabrafenib and trametinib) until death due to any cause. Patients without an observed death were censored at the date of last contact they were known to be alive. Disease progression was based on radiological response as per investigator assessment and RECIST v1.1.[21]

The primary independent variable was TTP, which was defined as the time from the date of study treatment initiation until the first date of disease progression after treatment initiation. In addition, the following patient characteristics were assessed at baseline: demographics (age, sex, and race), history of tobacco use, disease characteristics (Eastern Cooperative Oncology Group [ECOG] performance status before or at the time of progression and time since diagnosis to study treatment initiation), and prior anti-cancer treatment and response (number of prior regimens for metastatic disease, prior radiotherapy, prior maintenance therapy, and response to most recent anti-cancer therapy for metastatic disease).

Statistical Analyses

The association between TTP and PPS was assessed using Kaplan-Meier analysis and a Cox proportional hazards regression analysis. The analyses were conducted in the combined cohort of patients that received dabrafenib monotherapy (Cohort A) or in combination with trametinib (Cohort B). Sensitivity analyses were conducted in each individual cohort. All analyses were conducted using the statistical software R (version 3.3.2, the R Foundation for Statistical Computing), and statistical significance was assessed at the 5% level.

Kaplan-Meier Analyses

To assess the association between TTP and PPS, patients were first categorized into two subgroups based on length of TTP (≥6 months vs. <6 months) and Kaplan-Meier curves for PPS were then estimated in each subgroup. The 6-month cutoff in TTP was selected based on the median PFS observed in the combined cohort (i.e., 5.3 months), as well as the "efficacy plateau" observed in median TTP across systemic therapies for advanced NSCLC.[9]

In each subgroup defined by TTP, the number of events (i.e., number of patients who died following progression) was summarized, and the median PPS and corresponding 95% confidence interval (CI) were estimated using the Kaplan-Meier method. The log-rank test was used to compare PPS between

the two subgroups defined by TTP. The primary analysis was performed in the combined cohort, while sensitivity analyses were conducted within each cohort (Cohort A and B).

Cox Regression Analyses

To further quantify the association between TTP and PPS, a Cox proportional hazards model was implemented. PPS was the time-to-event outcome in the Cox models and TTP was the main independent variable of interest. In this analysis, TTP was a continuous variable as every patient included had progressed on the assigned treatment. Both univariable and multivariable Cox regression analyses were conducted. Prior to analysis, the proportional hazards assumption was tested to ensure the validity of the Cox model. The hazard ratios (HR) and corresponding 95% CIs are reported. For clinical relevance, results of the HR associated with TTP are presented for each three-month increase in TTP.

In the combined cohort, stratified Cox models with cohort as the stratification variable (i.e., Cohort A [monotherapy] and Cohort B [combination therapy]) were conducted as univariable and multivariable regression analyses. The univariable model included TTP as the only independent variable; the multivariable Cox model was further adjusted for the following patient demographics and disease characteristics: age group, sex, race, time since diagnosis to study treatment initiation, history of tobacco use, number of prior regimens for metastatic disease, prior radiotherapy, prior maintenance therapy, response to the most recent prior anti-cancer therapy, and ECOG status before or at progression.

In the sensitivity analyses within each cohort, unstratified univariable and multivariable Cox models were used to quantify the TTP-PPS association. The Cohort A multivariable Cox model adjusted for the same patient characteristics as those considered in the combined cohort. However, due to a limited sample size and the high proportions of patients in Cohort B that were White and had an ECOG score ≤1 before or at progression, these two covariates were not included in the multivariable model for Cohort B.

RESULTS

Sample Selection

A total of 143 patients with BRAF V600E mutation positive metastatic NSCLC were assigned to receive dabrafenib monotherapy (N = 84, Cohort A) or in combination with trametinib (N = 59, Cohort B) as second-line or above in the BRF113928 trial (**Figure 1**). The final analytic sample was comprised of 84 patients (57 in Cohort A and 27 in Cohort B) who actually received the study treatment as second-line or above and experienced disease progression during the original trial's study period. The follow-up status of the 51 patients who did not experience disease progression is listed in **Supplemental Table 1**.

Patient characteristics

Of the patients in the combined cohort, 50.0% were male, 48.8% were under 65 years of age, and 79.8% were White. The majority of patients (63.1%) were current or former tobacco smokers. The mean (standard deviation) time period between diagnosis to the initiation of the study treatment was 21.7 (18.7) months, and 16.7% of patients had ECOG performance status scores >1 before or at progression. The proportions of patients who had received prior radiotherapy or maintenance therapy were 34.5% and 22.6%, respectively, and 45.2% of patients had received more than one prior systemic regimen for metastatic disease. The proportion of patients that had achieved either complete or partial response with prior therapy for metastatic disease was 21.4% (**Table 1**). The patient characteristics for each cohort (Cohort A and B) are listed in **Supplemental Table 2**.

Kaplan-Meier Analysis of the Association between PPS and TTP

The Kaplan-Meier analysis to assess the association between TTP and PPS among patients in the combined cohort is presented in **Figure 2**. Patients who progressed ≥6 months following treatment initiation experienced significantly prolonged PPS compared with those who progressed before 6 months (log-rank p <0.001). In the combined cohort, 19 post-progression deaths were observed among 35 patients

with TTP ≥6 months, while 41 post-progression deaths were observed among 49 patients with TTP <6 months. In addition, these patients with TTP ≥6 months had longer median PPS (9.5 months; 95% CI: 6.6-20.2 months) compared with patients with TTP <6 months (median PPS: 2.7 months; 95% CI: 1.6-4.8 months).

In the sensitivity analysis, a similar association was observed between TTP duration and PPS among Cohorts A and B (**Supplemental Table 3** and **Supplemental Figure 1a and 1b**). Specifically, TTP of ≥6 months was associated with fewer deaths and significantly prolonged subsequent survival among patients in each individual cohort (log-rank p <0.001 in Cohort A; log-rank p =0.026 in Cohort B).

Univariable and Multivariable Cox Regression Analyses of the Association between PPS and TTP

In both the univariable and multivariable Cox regression analyses of the association between TTP and PPS, increased duration of TTP was associated with significant reductions in the hazard of post-progression death in the combined cohort. Specifically, each three-month increase in TTP was associated with a 32% lower risk of death post-progression in the combined cohort (HR: 0.68; 95% CI: 0.57-0.83; p <0.001) in the univariable analysis. A similar trend was observed in the multivariable Cox regression analyses conducted to control for patient characteristics that could potentially confound the relationship between TTP and PPS (**Table 2**). In the combined cohort, each three-month increase in TTP was associated with a 32% reduction in the risk of post-progression death (HR: 0.68; 95% CI: 0.52-0.88; p =0.003). In addition to TTP, an ECOG performance score >1 before or at progression (HR: 3.89; 95% CI: 1.62-9.32; p =0.002) was also found to be significantly associated with the risk of post-progression death.

Consistent positive TTP and PPS association was demonstrated in each individual cohort in the sensitivity analysis. In the univariable Cox analysis, each three-month increase in TTP was associated with a 30% lower risk of post-progression death in Cohort A (HR: 0.70; 95% CI: 0.57-0.88; p =0.001) and a 43% lower risk in Cohort B (HR: 0.57; 95% CI: 0.34-0.97; p =0.035). Each three-month increase in

the duration of TTP was associated with a reduction in the risk of post-progression death by 32% in Cohort A (HR: 0.68; 95% CI: 0.51-0.91; p =0.010) and 65% in Cohort B (HR: 0.35; 95% CI: 0.14-0.88; p =0.025) in the multivariable analysis.

DISCUSSION

This study addressed the knowledge gap regarding the relationship between TTP and PPS among previously treated patients with metastatic, BRAF V600E mutant NSCLC receiving dabrafenib monotherapy or in combination with trametinib who experienced disease progression. The study quantified the association using existing patient-level data from the ongoing dabrafenib targeted therapy clinical trial.[12,13] The current results indicate the longer a patient objectively benefited from dabrafenib monotherapy or in combination with trametinib (i.e., the longer the duration of TTP), the longer the survival period was after objective failure of the targeted therapy (i.e., PPS). For every three-month increase in duration of TTP following treatment initiation with dabrafenib monotherapy or in combination with trametinib, patients experienced a 32% reduction in the hazard of subsequent death after progression when controlling for patient characteristics. This result indicates that prolonging TTP with dabrafenib monotherapy or in combination with trametinib is associated with prolongation of OS over and above the longer duration of TTP itself.

The relationship between TTP and OS in NSCLC has been evaluated and demonstrated to be a moderate to strong association in several studies.[22-24] However, rather than further explore OS, this study considered the association between TTP and PPS as the primary research question. TTP and PPS were chosen as the measures refer to non-overlapping periods of time and yield prognostic information that can be applied at the time of progression. Also, PPS has been supported as a clinically-relevant outcome measure and a valid surrogate endpoint for OS in advanced NSCLC, particularly in evaluations of later-line therapies.[25] In addition, TTP has been shown to influence PPS in secondary analyses of patients with advanced NSCLC who received first-line chemotherapy or bevacizumab in two clinical trials and an observational cohort study; patients with longer first-line TTP also experienced longer PPS.[26]

With the development of newer therapies for NSCLC, such as targeted therapies that modulate oncogenic molecular pathways active in individuals' tumors, the relationship between TTP and PPS has become a clinically important question for the care of patients with genetic variations. As the first to address this question, Liu et al. studied the association between TTP and PPS among patients with advanced NSCLC and ALK mutations who progressed on the targeted therapy of ceritinib. Similar to the results from the current study, a positive association was revealed; every three months of longer duration of TTP after initiating ceritinib was associated with a 21% lower hazard of death following disease progression. It also found that ECOG performance score was another significant predictor for risk of post-progression death, consistent with the finding of the current analysis.[19] The present study contributes to the evidence that longer duration of TTP is associated with PPS among patients with NSCLC and BRAF V600E mutations receiving targeted therapy who experienced disease progression, and that this association may be a useful to indicate OS in future clinical trials in this patient population.

This retrospective analysis is subject to several limitations. First, this study should be considered an interim analysis of the association of TTP with PPS in previously treated patients with metastatic, BRAF V600E mutant NSCLC. Collection of the progression and survival data in the BRF113928 trial is ongoing. Secondly, unmeasured patient characteristics could potentially confound the association between TTP and PPS. Other factors such as the use of treatments after progression were not directly included in the present study, and could further affect the TTP-PPS association. In addition, limited sample size within each cohort in the sensitivity analyses may not provide sufficient statistical power to the association assessment. Finally, as the present study only included patients who had disease progression observed before death in a clinical trial setting, these results may not fully generalize to other patient populations.

CONCLUSIONS

In conclusion, a positive relationship between TTP and PPS was demonstrated among adults previously treated for advanced, BRAF V600E mutant NSCLC who received BRAF-specific targeted

therapies and experienced disease progression. This relationship was consistent across cohorts with similar patient populations who were treated with dabrafenib monotherapy or in combination with trametinib. This study enriched the understanding and interpretation of TTP-PPS association among metastatic BRAF V600E mutant NSCLC patients, who were previously treated with at least one platinum-based chemotherapy regimen. Patients who have experienced longer TTP during treatment of dabrafenib monotherapy or in combination with trametinib can expect to experience longer subsequent survival than patients with shorter TTP.

Acknowledgements

Medical writing assistance was provided by Shelley Batts, PhD, an employee of Analysis Group, Inc.

Competing Interests

Jie Zhang and Suman Redhu are employees of Novartis Pharmaceuticals Corporation and own stock/stock options. Medha Sasane was a previous employee of Novartis. Junlong Li, Jing Zhao, Marie Louise Ricculli, Zhiwen Yao, and James Signorovitch are employees of Analysis Group, Inc., which has received consultancy fees from Novartis Pharmaceuticals Corporation.

Author Contributions

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All authors had, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval and consent

This study is a secondary analysis of previously-published information; no institutional board review was required.

Consent for publication

N/A

Data sharing statement

The datasets generated during and/or analyzed during the current study are not publicly available due to clinical trial confidentiality agreement.

Funding

This work was supported by Novartis Pharmaceuticals Corporation. The sponsor was involved in all stages of the study and manuscript preparation.

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TABLES

Table 1. Summary of Patient Characteristics: Combined Cohort

Patient characteristic	Combined Cohort N = 84
Demographics, N (%)	
Age <65 years	41 (48.8)
Male	42 (50.0)
Race (White)[i]	67 (79.8)
History of tobacco use, N (%)	
Current or former smoker	53 (63.1)
Disease and treatment characteristics	
ECOG performance status score >1 before or at progression, N (%)	14 (16.7)
Time since diagnosis to study treatment initiation (months), mean ± SD	21.7 ± 18.7
Prior anti-cancer therapy, N (%)	
Number of prior systemic regimens for metastatic disease >1	38 (45.2)
Radiotherapy	29 (34.5)
Maintenance therapy	19 (22.6)
Response to the most recent prior therapy for metastatic disease, N (%)[ii]	
Complete or partial response	18 (21.4)

Caption

Abbreviations: ECOG = Eastern Cooperative Oncology Group; N = number; SD = standard deviation.

Notes:

[i] Other reported races included Asian, Black or African American, and Mixed.

[ii] Response to the most recent prior anti-cancer therapy included complete response, partial response, stable disease, and progressive disease. Seven patients in Cohort A (including one patient with a non-evaluable response) and one patient in Cohort B had an unknown response. These patients were imputed as non-complete or partial responders.

Table 2. The Multivariable Cox Model of the Association between TTP and PPS in the Combined Cohort

	Combined Cohort		
	HR	**95% CI**	***P***
Time to progression in three-month increment(s)	0.68	(0.52-0.88)	0.003*
Age <65 years Yes vs. No	1.28	(0.70-2.36)	0.420
Male Yes vs. No	0.74	(0.38-1.42)	0.365
Race (White) Yes vs. No	1.44	(0.55-3.76)	0.462
Current or former smoker Yes vs. No	1.07	(0.50-2.31)	0.855
ECOG performance status before or at progression >1 Yes vs. No	3.89	(1.62-9.32)	0.002*
Time since diagnosis to study treatment initiation in 1-month increment(s)	0.98	(0.96-1.00)	0.058
Number of prior systemic regimens for metastatic disease >1 Yes vs. No	1.22	(0.51-2.93)	0.658
Prior radiotherapy Yes vs. No	0.88	(0.46-1.70)	0.701
Prior maintenance therapy Yes vs. No	0.50	(0.23-1.08)	0.078
Complete or partial response to most recent prior therapy for metastatic disease Yes vs. No	0.47	(0.22-1.02)	0.056

Caption

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; PPS = post-progression survival; TTP = time to progression. *$p<0.05$

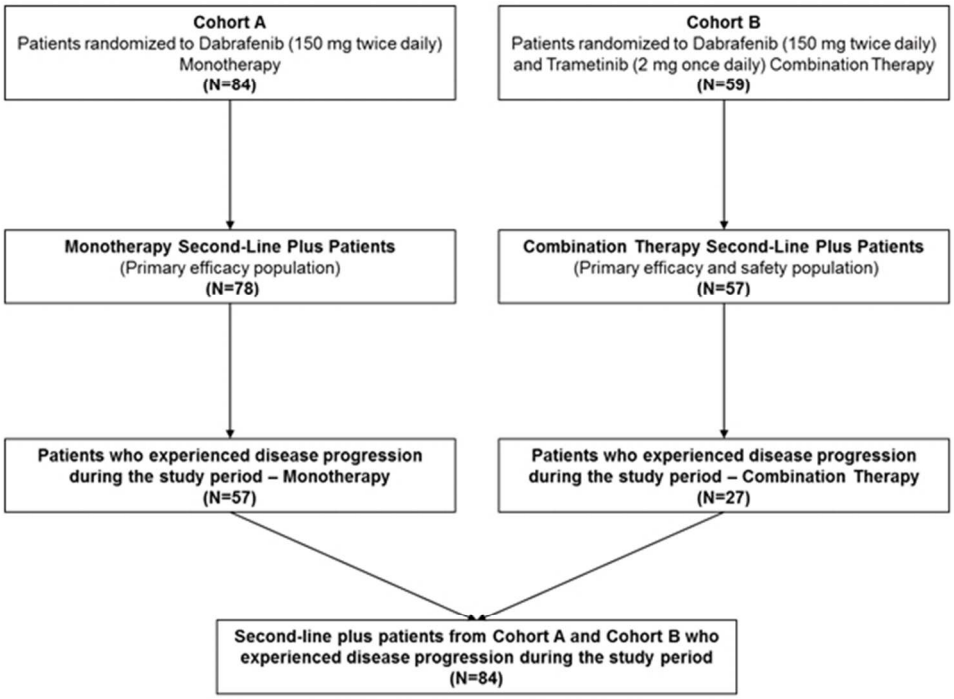


Figure 1. Sample selection flowchart
Patient-level data were used from the non-randomized, open-label, Phase II trial BRF113928 (data cut: October 7, 2015, trial ongoing). Abbreviations: mg = milligrams; N = number.

55x41mm (300 x 300 DPI)

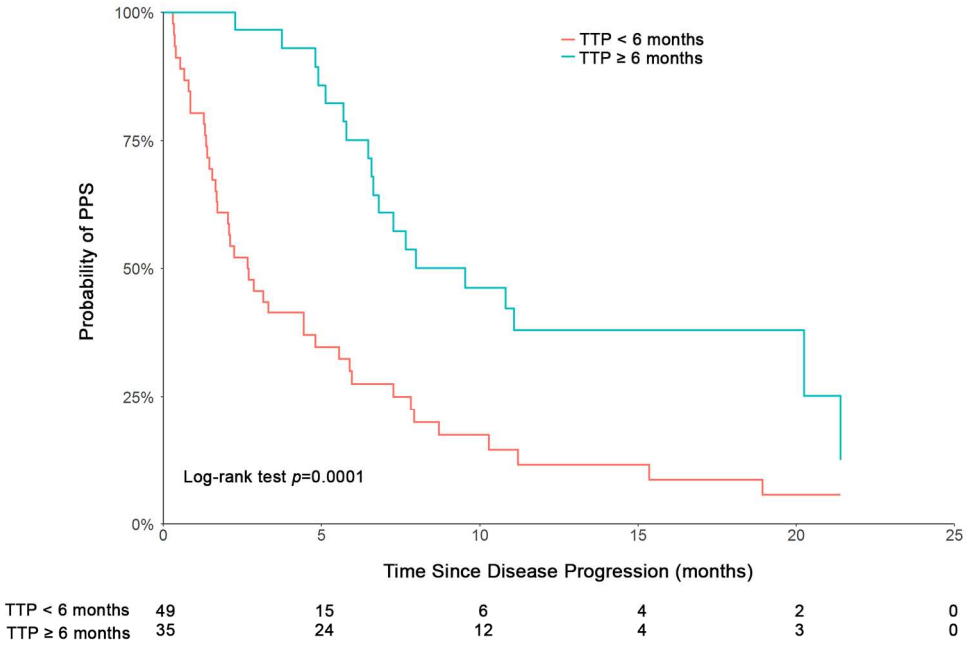


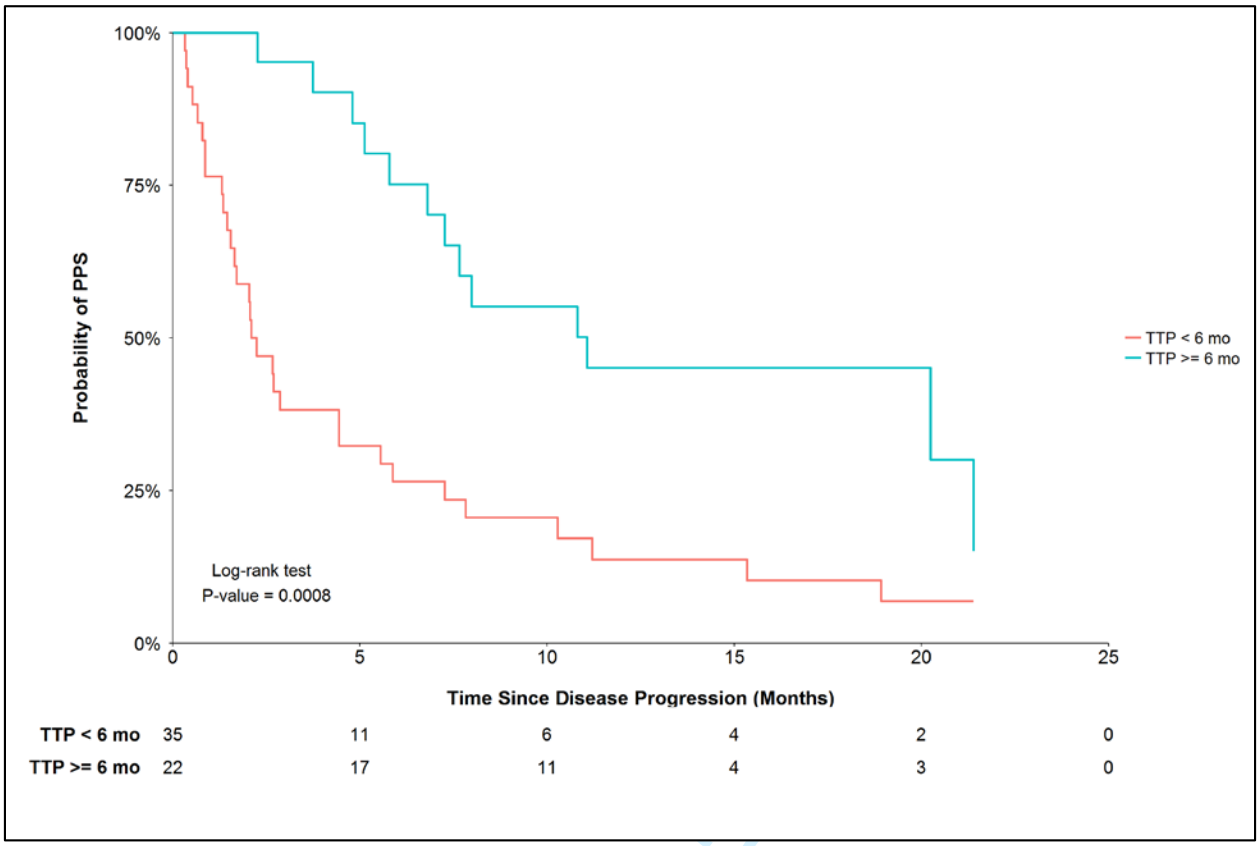
Figure 2. Kaplan-Meier Analysis of PPS in the Combined Cohort, stratified by duration of TTP
Abbreviations: PPS = post-progression survival; TTP = time to progression.

169x123mm (300 x 300 DPI)

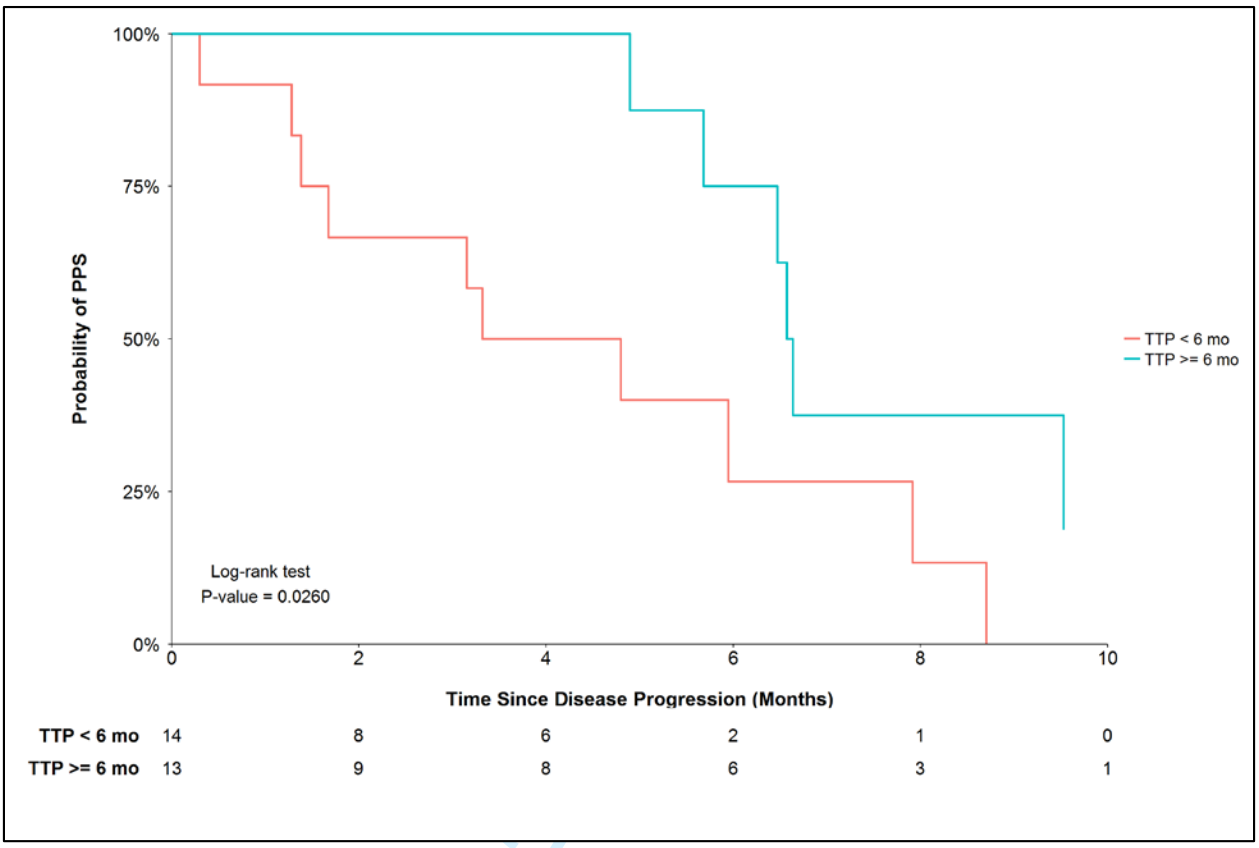
Supplemental Figures and Tables

Supplemental Figure 1. Kaplan-Meier Analysis of PPS in patients stratified by duration of TTP: Cohorts A (A) and B (B)

A. Cohort A



B. Cohort B



Legend

Abbreviations: PPS = post-progression survival; TTP = time to progression.

Supplemental Table 1. Status of Patients Excluded from the Analysis who did not Experience Disease Progression

Patient Status, N (%)	Combined Cohort N = 51	Cohort A N = 21	Cohort B N = 30
Censored, follow-up ended	14 (27.5)	11 (52.4)	3 (10.0)
Censored, follow-up ongoing	28 (54.9)	6 (28.6)	22 (73.3)
Died	9 (17.6)	4 (19.0)	5 (16.7)

Caption

Abbreviations: N = number.

Supplementary Table 2. Summary of Patient Characteristics: Cohorts A and B

Patient characteristic	Cohort A N = 57	Cohort B N = 27
Demographics, N (%)		
Age < 65 years	27 (47.4)	14 (51.9)
Male	29 (50.9)	13 (48.1)
Race (White)[i]	43 (75.4)	24 (88.9)
History of tobacco use, N (%)		
Current or former smoker	34 (59.6)	19 (70.4)
Disease and treatment characteristics,		
ECOG performance status score >1 before or at progression, N (%)	12 (21.1)	2 (7.4)
Time since diagnosis to study treatment initiation (months), mean ± SD	22.1 ± 20.0	21.0 ± 15.9
Prior anti-cancer therapy, N (%)		
Number of prior systemic regimens for metastatic disease >1	27 (47.4)	11 (40.7)
Radiotherapy	22 (38.6)	7 (25.9)
Maintenance therapy	11 (19.3)	8 (29.6)
Response to the most recent prior therapy for metastatic disease, N (%)[ii]		
Complete or partial response	11 (19.3)	7 (25.9)

Caption

Abbreviations: ECOG = Eastern Cooperative Oncology Group; mg = milligrams; N = number; SD = standard deviation.

Notes:

[i] Other reported races included Asian, Black or African American, and Mixed.

[ii] Response to the most recent prior anti-cancer therapy included complete response, partial response, stable disease, and progressive disease. Seven patients in Cohort A (including one patient with a non-

evaluable response) and one patient in Cohort B had an unknown response. These patients were imputed as non-complete or partial responders.

Supplemental Table 3. Summary of PPS, Stratified by Duration of TTP: Cohorts A and B

Cohort	N	Number of post-progression deaths	Median PPS (months)	95% CI
Cohort A				
TTP ≥ 6 months	22	13	11.1	(6.8-21.4)
TTP < 6 months	35	31	2.2	(1.4-4.4)
Cohort B				
TTP ≥ 6 months	13	6	6.6	(4.9-NR)
TTP < 6 months	14	10	4.1	(1.3-7.9)

Caption

Abbreviations: CI = confidence internal; N = number; NR = not reached; PPS = post-progression survival; TTP = time to progression.

BMJ Open

Is time to progression associated with post-progression survival in previously treated metastatic non-small cell lung cancer with BRAF V600E mutation? A secondary analysis of Phase II clinical trial data

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-021642.R1
Article Type:	Research
Date Submitted by the Author:	03-Apr-2018
Complete List of Authors:	Li, Junlong; Analysis Group Inc Boston Sasane, Medha; Novartis Pharmaceuticals Corp Zhang, Jie; Novartis Pharmaceuticals Corp Zhao, Jing; Analysis Group Inc Boston Ricculli, Marie Louise ; Analysis Group Inc New York Yao, Zhiwen; Analysis Group Inc Boston Redhu, Suman; Novartis Pharmaceuticals Corp Signorovitch, James; Analysis Group Inc Boston
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology
Keywords:	post-progression survival, time to progression, dabrafenib, trametinib, BRAF V600E NSCLC, ONCOLOGY

Is time to progression associated with post-progression survival in previously treated metastatic non-small cell lung cancer with BRAF V600E mutation? A secondary analysis of Phase II clinical trial data

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ABSTRACT

Objective: Longer time to progression (TTP) is associated with prolonged post-progression survival (PPS) in ALK+ non-small cell lung cancer (NSCLC). This study evaluated whether TTP is associated with PPS among previously treated patients with metastatic BRAF V600E NSCLC receiving dabrafenib as monotherapy or in combination with trametinib.

Design: Secondary analysis of Phase II clinical trial data (NCT01336634).

Setting: Patients who experienced disease progression treated with dabrafenib monotherapy or in combination with trametinib as second-line or later in an open-label, non-randomized, Phase II study.

Primary outcome measures: The primary outcome was the TTP-PPS association. PPS was assessed with Kaplan-Meier analysis among patients with shorter versus longer TTP (< or ≥6 months). The TTP-PPS association was quantified in the Cox models adjusting for clinical covariates.

Results: Of the 84 included patients who progressed on dabrafenib monotherapy (N=57) or combination therapy (N=27), 60 (71%) died during post-progression follow-up. Patients with TTP ≥6 months experienced significantly longer PPS compared to those with TTP <6 months (median PPS: 9.5 vs. 2.7 months, log-rank p<0.001). Each 3 months of longer TTP was associated with a 32% lower hazard of death following progression (hazard ratio [95% confidence interval]: 0.68 [0.52-0.88]) in the multivariable Cox model. Similar associations were seen in each treatment arm.

Conclusion: A longer TTP duration after treatment with dabrafenib monotherapy or combination therapy was associated with significantly longer PPS duration.

Keywords: post-progression survival, time to progression, dabrafenib, trametinib, BRAF V600E NSCLC

STRENGTHS AND LIMITATIONS OF THIS STUDY

- A major strength of this retrospective study is that it quantified the association between time to progression (TTP) and post-progression survival (PPS) among previously treated patients with metastatic, BRAF V600E mutant non-small cell lung cancer (NSCLC) receiving dabrafenib monotherapy or in combination with trametinib who experienced disease progression using existing patient-level data from the ongoing dabrafenib targeted therapy clinical trial. The relationship between TTP and PPS had not yet been assessed among patients with metastatic, BRAF V600E mutant NSCLC receiving the newer generation of targeted therapies in previous studies.
- One limitation of the present study is that it only included patients who had disease progression observed before death in a clinical trial setting and these results may not fully generalize to other patient populations.
- Another limitation of the present study is that patient characteristics that were unmeasured in the clinical trial could potentially confound the association between TTP and PPS.
- Finally, the present study is limited in that it used data from a clinical trial in which the collection of the progression and survival data is ongoing. As such, this study should be considered an interim analysis of the association of TTP with PPS in previously treated patients with metastatic, BRAF V600E mutant NSCLC.

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for 80–85% of all lung cancers globally,[1] and is the leading cause of cancer-related mortality in the United States (US).[2] In advanced stages, NSCLC is aggressive. For example, patients with stage IIIB cancer have an estimated 5-year survival rate of 5%; this rate is estimated to be about 1% for patients in stage IV or with confirmed metastatic disease.[3] Treatment for NSCLC has traditionally consisted of cytotoxic chemotherapy, although recent advances in cancer biology have led to the development of targeted anti-cancer agents that modulate specific oncogenic molecular pathways.[4]

NSCLC is a heterogeneous cancer, and molecular diagnostic testing can be used to inform treatment choice for patients with metastatic or relapsing disease. For example, mutations in BRAF (v-Raf murine sarcoma viral oncogene homolog B), which encodes the protein B-Raf involved in cell growth signaling, are present in 1–5% of NSCLC.[5,6] Constitutively active B-Raf mutants can prompt tumorigenesis by excessively signaling cells to divide, often via the MAP kinase (MAPK) pathway.[7] In particular, BRAF V600E mutations account for about 50% of BRAF mutant NSCLC and 2% of all NSCLC, and are usually associated with a history of smoking and with adenocarcinoma.[8] Patients with BRAF V600E mutant NSCLC have poorer clinical outcomes and lower response to platinum-based chemotherapy compared with patients without this mutation.[6,9] Thus, targeted therapies that modulate BRAF kinase signaling or downstream MAPK signaling to slow tumor growth are promising alternatives to effectively treat BRAF-mutant NSCLC.[10]

Dabrafenib is a potent and selective reversible BRAF kinase inhibitor, which has previously demonstrated efficacy and tolerability in clinical trials of patients with BRAF V600 mutant melanoma, including those with metastatic disease.[11] Trametinib, an allosteric inhibitor of mitogen-activated extracellular signal regulated kinase (MEK) 1 and 2, has synergistic anti-oncogenic activity with BRAF inhibition. The efficacy and tolerability profiles of dabrafenib as a single agent and in combination with

trametinib have been assessed among patients with BRAF V600E mutation positive metastatic (stage IV) NSCLC in a recent multicenter, non-randomized, open-label, Phase II trial (ClinicalTrials.gov: NCT01336634).[12,13] For example, among patients who received at least one prior platinum-based chemotherapy regimen for metastatic disease, patients treated with dabrafenib monotherapy (Cohort A) reported an investigator-assessed overall confirmed response rate of 33% and median progression-free survival (PFS) of 5.5 months. The overall confirmed response rate was 63% and median PFS was 9.7 months for patients who received dabrafenib and trametinib in combination (Cohort B).[12,13]

The overarching goals of NSCLC treatment are to prolong overall survival (OS), manage symptoms, and improve patients' quality of life.[14] However, there are practical challenges to directly assess the effects of treatment on long-term survival in clinical trials of late-stage cancer patients who have already failed multiple lines of therapy.[15,16] Clinical trials and meta-analyses of other advanced NSCLC treatments have demonstrated that time to progression (TTP) can be predictive of long-term clinical benefits in patient survival.[17-19] For example, a longer duration of TTP was demonstrated to be significantly associated with a longer duration of post-progression survival (PPS) among NSCLC patients with anaplastic lymphoma kinase (ALK) gene rearrangement[19] and mutations in the epidermal growth factor receptor (EGFR) gene.[20]

To the best of our knowledge, the relationship between TTP and PPS has not yet been assessed among patients with BRAF V600E mutant NSCLC receiving the newer generation of targeted therapies. It is of great clinical interest to determine whether any improvement in TTP is offset by loss of survival time in the post-progression period. To address this question, the current study evaluated the association between TTP and the duration of PPS among adult, previously treated, metastatic NSCLC patients with BRAF V600E mutation who experienced disease progression while receiving dabrafenib monotherapy or in combination with trametinib.

MATERIAL AND METHODS

Study design and population

The study is a secondary analysis of data from metastatic NSCLC patients with BRAF V600E mutation included in the non-randomized, open-label, Phase II trial BRF113928 (NCT01336634; data cut: October 7, 2015, trial ongoing). Written informed consent was obtained from each subject prior to the performance of any study-specific procedures in BRF113928; de-identified patient-level data were used in this retrospective analysis. The current analysis included chemotherapy-experienced patients who were assigned to receive either dabrafenib monotherapy (150 mg twice daily [BID]; Cohort A) or combination therapy of dabrafenib (150 mg BID) and trametinib (2 mg once daily; Cohort B) as second- or later-line and experienced disease progression during the trial's study period. The disease progression was determined based on radiological response as per investigator assessment and Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.[21] For patients in Cohort B, the study treatment could have been up to the fourth-line of systemic anti-cancer therapy for metastatic disease. The full methodology of this trial has been previously published.[12,13]

A diagram of the patient selection process in the current study is shown in **Figure 1**. Patients who were previously untreated, or did not experience observed disease progression (either due to censoring or death before progression) during the original trial's study period, were excluded from the final analytical sample in this study.

Outcomes and Variables

The primary outcome of interest in the current analysis was PPS, which was defined as the time from the date of disease progression after starting the study treatment (dabrafenib monotherapy or combination therapy with dabrafenib and trametinib) until death due to any cause. Patients without an observed death were censored at the date of last contact they were known to be alive. Disease progression was based on radiological response as per investigator assessment and RECIST v1.1.[21]

The primary independent variable was TTP, which was defined as the time from the date of study treatment initiation until the first date of disease progression after treatment initiation. In addition, the following patient characteristics were assessed at baseline: demographics (age, sex, and race), history of tobacco use, disease characteristics (Eastern Cooperative Oncology Group [ECOG] performance status before or at the time of progression and time since diagnosis to study treatment initiation), and prior anti-cancer treatment and response (number of prior regimens for metastatic disease, prior radiotherapy, prior maintenance therapy, and response to most recent anti-cancer therapy for metastatic disease).

Statistical Analyses

The association between TTP and PPS was assessed using Kaplan-Meier analysis and a Cox proportional hazards regression analysis. The analyses were conducted in the combined cohort of patients that received dabrafenib monotherapy (Cohort A) or in combination with trametinib (Cohort B). Sensitivity analyses were conducted in each individual cohort. All analyses were conducted using the statistical software R (version 3.3.2, the R Foundation for Statistical Computing), and statistical significance was assessed at the 5% level.

Kaplan-Meier Analyses

To assess the association between TTP and PPS, patients were first categorized into two subgroups based on length of TTP (≥6 months vs. <6 months) and Kaplan-Meier curves for PPS were then estimated in each subgroup. The 6-month cutoff in TTP was selected based on the median PFS observed in the combined cohort (i.e., 5.3 months), as well as the "efficacy plateau" observed in median TTP across systemic therapies for advanced NSCLC.[9]

In each subgroup defined by TTP, the number of events (i.e., number of patients who died following progression) was summarized, and the median PPS and corresponding 95% confidence interval (CI) were estimated using the Kaplan-Meier method. The log-rank test was used to compare PPS between

the two subgroups defined by TTP. The primary analysis was performed in the combined cohort, while sensitivity analyses were conducted within each cohort (Cohort A and B).

Cox Regression Analyses

To further quantify the association between TTP and PPS, a Cox proportional hazards model was implemented. PPS was the time-to-event outcome in the Cox models and TTP was the main independent variable of interest. In this analysis, TTP was a continuous variable as every patient included had progressed on the assigned treatment. Both univariable and multivariable Cox regression analyses were conducted. Prior to analysis, the proportional hazards assumption was tested to ensure the validity of the Cox model. The hazard ratios (HR) and corresponding 95% CIs are reported. For clinical relevance, results of the HR associated with TTP are presented for each three-month increase in TTP.

In the combined cohort, stratified Cox models with cohort as the stratification variable (i.e., Cohort A [monotherapy] and Cohort B [combination therapy]) were conducted as univariable and multivariable regression analyses. The univariable model included TTP as the only independent variable; the multivariable Cox model was further adjusted for the following patient demographics and disease characteristics: age group, sex, race, time since diagnosis to study treatment initiation, history of tobacco use, number of prior regimens for metastatic disease, prior radiotherapy, prior maintenance therapy, response to the most recent prior anti-cancer therapy, and ECOG status before or at progression.

In the sensitivity analyses within each cohort, unstratified univariable and multivariable Cox models were used to quantify the TTP-PPS association. The Cohort A multivariable Cox model adjusted for the same patient characteristics as those considered in the combined cohort. However, due to a limited sample size and the high proportions of patients in Cohort B that were White and had an ECOG score ≤1 before or at progression, these two covariates were not included in the multivariable model for Cohort B.

Sensitivity analysis: Landmark analyses

Landmark analyses were conducted to evaluate the potential for guarantee-time bias in creating the cohorts based on TTP. Two landmark analyses were conducted, one excluding patients who died or were censored prior to 3 months after disease progression (i.e., 3-month landmark analysis) and the other excluding patients who died or were censored prior to 6 months after disease progression (i.e., 6-month landmark analysis). In each landmark analysis, patients were further classified based on their outcome as pre-progression or post-progression at 6 months of follow-up. Baseline characteristics and results from multivariable Cox regression models were summarized as described above.

Patient Involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design or conduct of the study. No patients were asked to advise on interpretation or writing up of the results. There are no plans to disseminate the results of the research to study participants.

RESULTS

Sample Selection

A total of 143 patients with BRAF V600E mutation positive metastatic NSCLC were assigned to receive dabrafenib monotherapy (N = 84, Cohort A) or in combination with trametinib (N = 59, Cohort B) as second-line or above in the BRF113928 trial (**Figure 1**). The final analytic sample was comprised of 84 patients (57 in Cohort A and 27 in Cohort B) who actually received the study treatment as second-line or above and experienced disease progression during the original trial's study period. The follow-up status of the 51 patients who did not experience disease progression is listed in **Supplemental Table 1**.

Patient characteristics

Of the patients in the combined cohort, 50.0% were male, 48.8% were under 65 years of age, and 79.8% were White. The majority of patients (63.1%) were current or former tobacco smokers. The mean (standard deviation) time period between diagnosis to the initiation of the study treatment was 21.7 (18.7) months, and 16.7% of patients had ECOG performance status scores >1 before or at progression. The proportions of patients who had received prior radiotherapy or maintenance therapy were 34.5% and 22.6%, respectively, and 45.2% of patients had received more than one prior systemic regimen for metastatic disease. The proportion of patients that had achieved either complete or partial response with prior therapy for metastatic disease was 21.4% (**Table 1**). The patient characteristics for each cohort (Cohort A and B) are listed in **Supplemental Table 2**.

Kaplan-Meier Analysis of the Association between PPS and TTP

The Kaplan-Meier analysis to assess the association between TTP and PPS among patients in the combined cohort is presented in **Figure 2**. Patients who progressed ≥6 months following treatment initiation experienced significantly prolonged PPS compared with those who progressed before 6 months (log-rank p <0.001). In the combined cohort, 19 post-progression deaths were observed among 35 patients with TTP ≥6 months, while 41 post-progression deaths were observed among 49 patients with TTP <6 months. In addition, these patients with TTP ≥6 months had longer median PPS (9.5 months; 95% CI: 6.6-20.2 months) compared with patients with TTP <6 months (median PPS: 2.7 months; 95% CI: 1.6-4.8 months).

In the sensitivity analysis, a similar association was observed between TTP duration and PPS among Cohorts A and B (**Supplemental Table 3** and **Supplemental Figure 1a and 1b**). Specifically, TTP of ≥6 months was associated with fewer deaths and significantly prolonged subsequent survival among patients in each individual cohort (log-rank p <0.001 in Cohort A; log-rank p =0.026 in Cohort B).

Univariable and Multivariable Cox Regression Analyses of the Association between PPS and TTP

In both the univariable and multivariable Cox regression analyses of the association between TTP and PPS, increased duration of TTP was associated with significant reductions in the hazard of post-progression death in the combined cohort. Specifically, each three-month increase in TTP was associated with a 32% lower risk of death post-progression in the combined cohort (HR: 0.68; 95% CI: 0.57-0.83; p <0.001) in the univariable analysis. A similar trend was observed in the multivariable Cox regression analyses conducted to control for patient characteristics that could potentially confound the relationship between TTP and PPS (**Table 2**). In the combined cohort, each three-month increase in TTP was associated with a 32% reduction in the risk of post-progression death (HR: 0.68; 95% CI: 0.52-0.88; p =0.003). In addition to TTP, an ECOG performance score >1 before or at progression (HR: 3.89; 95% CI: 1.62-9.32; p =0.002) was also found to be significantly associated with the risk of post-progression death.

Consistent positive TTP and PPS association was demonstrated in each individual cohort in the sensitivity analysis. In the univariable Cox analysis, each three-month increase in TTP was associated with a 30% lower risk of post-progression death in Cohort A (HR: 0.70; 95% CI: 0.57-0.88; p =0.001) and a 43% lower risk in Cohort B (HR: 0.57; 95% CI: 0.34-0.97; p =0.035). Each three-month increase in the duration of TTP was associated with a reduction in the risk of post-progression death by 32% in Cohort A (HR: 0.68; 95% CI: 0.51-0.91; p =0.010) and 65% in Cohort B (HR: 0.35; 95% CI: 0.14-0.88; p =0.025) in the multivariable analysis.

Sensitivity analysis: Landmark analysis

After excluding patients who died or were censored prior to 3 months and 6 months after disease progression, the sample size decreased from 84 patients in the main analysis to 75 and 59 patients, respectively. Results from the landmark analyses were consistent with those in the main analysis. In the 3-month landmark analysis, significant and positive TTP and PPS association was observed (TTP in 3-

month increment results from the multivariable cox analysis: HR: 0.68; 95% CI: 0.52-0.88; *p*=0.004; **Supplementary Tables 4 and 5 and Supplementary Figure 2**). Positive TTP-PPS association was also detected in the 6-month landmark analysis, but no statistical significance was observed due to limited sample size (HR: 0.82; 95% CI: 0.62-1.07; *p*=0.148; **Supplementary Tables 6 and 7 and Supplementary Figure 3**).

DISCUSSION

This study addressed the knowledge gap regarding the relationship between TTP and PPS among previously treated patients with metastatic, BRAF V600E mutant NSCLC receiving dabrafenib monotherapy or in combination with trametinib who experienced disease progression. The study quantified the association using existing patient-level data from the ongoing dabrafenib targeted therapy clinical trial.[12,13] The current results indicate the longer a patient objectively benefited from dabrafenib monotherapy or in combination with trametinib (i.e., the longer the duration of TTP), the longer the survival period was after objective failure of the targeted therapy (i.e., PPS). For every three-month increase in duration of TTP following treatment initiation with dabrafenib monotherapy or in combination with trametinib, patients experienced a 32% reduction in the hazard of subsequent death after progression when controlling for patient characteristics. This result indicates that prolonging TTP with dabrafenib monotherapy or in combination with trametinib is associated with prolongation of OS over and above the longer duration of TTP itself. A consistent positive association between TTP and PPS is observed in the landmark analyses in which patients who died or censored prior to 3 months and 6 months after disease progression were excluded, although the small sample size may limit the interpretation of these results.

The relationship between TTP and OS in NSCLC has been evaluated and demonstrated to be a moderate to strong association in several studies.[22-24] However, rather than further explore OS, this study considered the association between TTP and PPS as the primary research question. TTP and PPS were

chosen as the measures refer to non-overlapping periods of time and yield prognostic information that can be applied at the time of progression. Also, PPS has been supported as a clinically-relevant outcome measure and a valid surrogate endpoint for OS in advanced NSCLC, particularly in evaluations of later-line therapies.[25] In addition, TTP has been shown to influence PPS in secondary analyses of patients with advanced NSCLC who received first-line chemotherapy or bevacizumab in two clinical trials and an observational cohort study; patients with longer first-line TTP also experienced longer PPS.[26]

With the development of newer therapies for NSCLC, such as targeted therapies that modulate oncogenic molecular pathways active in individuals' tumors, the relationship between TTP and PPS has become a clinically important question for the care of patients with genetic variations. As the first to address this question, Liu et al. studied the association between TTP and PPS among patients with advanced NSCLC and ALK mutations who progressed on the targeted therapy of ceritinib. Similar to the results from the current study, a positive association was revealed; every three months of longer duration of TTP after initiating ceritinib was associated with a 21% lower hazard of death following disease progression. It also found that ECOG performance score was another significant predictor for risk of post-progression death, consistent with the finding of the current analysis.[19] The present study contributes to the evidence that longer duration of TTP is associated with PPS among patients with NSCLC and BRAF V600E mutations receiving targeted therapy who experienced disease progression, and that this association may be a useful to indicate OS in future clinical trials in this patient population.

This retrospective analysis is subject to several limitations. First, this study should be considered an interim analysis of the association of TTP with PPS in previously treated patients with metastatic, BRAF V600E mutant NSCLC. Collection of the progression and survival data in the BRF113928 trial is ongoing. Secondly, unmeasured patient characteristics could potentially confound the association between TTP and PPS. Other factors such as the use of treatments after progression were not directly included in the present study, and could further affect the TTP-PPS association observed in the multivariable Cox regression analyses. In addition, limited sample size within each cohort in the sensitivity analyses may not

provide sufficient statistical power to the association assessment. Finally, as the present study only included patients who had disease progression observed before death in a clinical trial setting, these results may not fully generalize to other patient populations.

CONCLUSIONS

In conclusion, a positive relationship between TTP and PPS was demonstrated among adults previously treated for advanced, BRAF V600E mutant NSCLC who received BRAF-specific targeted therapies and experienced disease progression. This relationship was consistent across cohorts with similar patient populations who were treated with dabrafenib monotherapy or in combination with trametinib. This study enriched the understanding and interpretation of TTP-PPS association among metastatic BRAF V600E mutant NSCLC patients, who were previously treated with at least one platinum-based chemotherapy regimen. Patients who have experienced longer TTP during treatment of dabrafenib monotherapy or in combination with trametinib can expect to experience longer subsequent survival than patients with shorter TTP.

Acknowledgements

Medical writing assistance was provided by Shelley Batts, PhD, an employee of Analysis Group, Inc.

Competing Interests

Jie Zhang and Suman Redhu are employees of Novartis Pharmaceuticals Corporation and own stock/stock options. Medha Sasane was a previous employee of Novartis. Junlong Li, Jing Zhao, Marie Louise Ricculli, Zhiwen Yao, and James Signorovitch are employees of Analysis Group, Inc., which has received consultancy fees from Novartis Pharmaceuticals Corporation.

Author Contributions

Conception or design of the work: Junlong Li, Jing Zhao, Medha Sasane, Jie Zhang, James Signorovitch

Data analysis and interpretation: Junlong Li, Jing Zhao, Marie Louise Ricculli, Zhiwen Yao

Drafting and critical revision of the manuscript: Junlong Li, Medha Sasane, Jie Zhang, Jing Zhao, Marie Louise Ricculli, Suman Redhu, James Signorovitch

Final approval of the version to be published: Junlong Li, Medha Sasane, Jie Zhang, Jing Zhao, Marie Louise Ricculli, Zhiwen Yao, Suman Redhu, James Signorovitch

All authors had, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval and consent

This study is a secondary analysis of previously-published information; no institutional board review was required.

Consent for publication

N/A

Data sharing statement

The sponsor of the present study, Novartis Pharmaceuticals Corporation, granted permission of the secondary analysis of anonymized clinical trial data. The data were anonymized prior to receipt for the secondary analysis. The datasets generated during and/or analyzed during the current study are not publicly available due to clinical trial confidentiality agreement.

Funding

This work was supported by Novartis Pharmaceuticals Corporation. The sponsor was involved in all stages of the study and manuscript preparation.

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TABLES

Table 1. Summary of Patient Characteristics: Combined Cohort

	Combined Cohort N = 84	Time to progression ≥ 6 months N = 35	Time to progression < 6 months N = 49	P-value[iii]
Demographics, n(%)				
Age < 65 years	41 (48.8%)	15 (42.9%)	26 (53.1%)	0.48
Male	42 (50.0%)	18 (51.4%)	24 (49.0%)	1.00
Race (White)[i]	67 (79.8%)	29 (82.9%)	38 (77.6%)	0.75
History of tobacco use, n(%)				
Current or former smoker	53 (63.1%)	19 (54.3%)	34 (69.4%)	0.24
Disease characteristics, n(%)				
ECOG performance status before or at progression > 1	14 (16.7%)	1 (2.9%)	13 (26.5%)	0.01 *
Time since diagnosis to study treatment initiation (month)	21.7 ± 18.7	21.4 ± 16.4	22.0 ± 20.2	0.75
Prior anti-cancer therapy, n(%)				
Number of prior systemic regimens for metastatic disease > 1	38 (45.2%)	14 (40.0%)	24 (49.0%)	0.55
Radiotherapy	29 (34.5%)	10 (28.6%)	19 (38.8%)	0.46
Maintenance therapy	19 (22.6%)	8 (22.9%)	11 (22.4%)	1.00
Response to the most recent prior therapy for metastatic disease, n(%)[ii]				
Complete or partial response	18 (21.4%)	5 (14.3%)	13 (26.5%)	0.28

Caption

Abbreviations: ECOG = Eastern Cooperative Oncology Group; N = number; SD = standard deviation.

Notes:

[i] Other reported races included Asian, Black or African American, and Mixed.

[ii] Response to the most recent prior anti-cancer therapy included complete response, partial response, stable disease, and progressive disease. Seven patients in Cohort A (including one patient with a non-evaluable response) and one patient in Cohort B had an unknown response. These patients were imputed as non-complete or partial responders.

[iii] Statistical comparisons were conducted using Wilcoxon rank-sum tests for continuous characteristics and chi-squared tests for categorical characteristics.

Table 2. The Multivariable Cox Model of the Association between TTP and PPS in the Combined Cohort

	Combined Cohort		
	HR	**95% CI**	***P***
Time to progression in three-month increment(s)	0.68	(0.52-0.88)	0.003*
Age <65 years Yes vs. No	1.28	(0.70-2.36)	0.420
Male Yes vs. No	0.74	(0.38-1.42)	0.365
Race (White) Yes vs. No	1.44	(0.55-3.76)	0.462
Current or former smoker Yes vs. No	1.07	(0.50-2.31)	0.855
ECOG performance status before or at progression >1 Yes vs. No	3.89	(1.62-9.32)	0.002*
Time since diagnosis to study treatment initiation in 1-month increment(s)	0.98	(0.96-1.00)	0.058
Number of prior systemic regimens for metastatic disease >1 Yes vs. No	1.22	(0.51-2.93)	0.658
Prior radiotherapy Yes vs. No	0.88	(0.46-1.70)	0.701
Prior maintenance therapy Yes vs. No	0.50	(0.23-1.08)	0.078
Complete or partial response to most recent prior therapy for metastatic disease Yes vs. No	0.47	(0.22-1.02)	0.056

Caption

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; PPS = post-progression survival; TTP = time to progression. *p<0.05

FIGURE LEGENDS

Figure 1. Sample selection flowchart

Legend**:** Patient-level data were used from the non-randomized, open-label, Phase II trial BRF113928 (data cut: October 7, 2015, trial ongoing). Abbreviations: mg = milligrams; N = number.

Figure 2. Kaplan-Meier Analysis of PPS in the Combined Cohort, stratified by duration of TTP

Legend**:** Abbreviations: PPS = post-progression survival; TTP = time to progression.

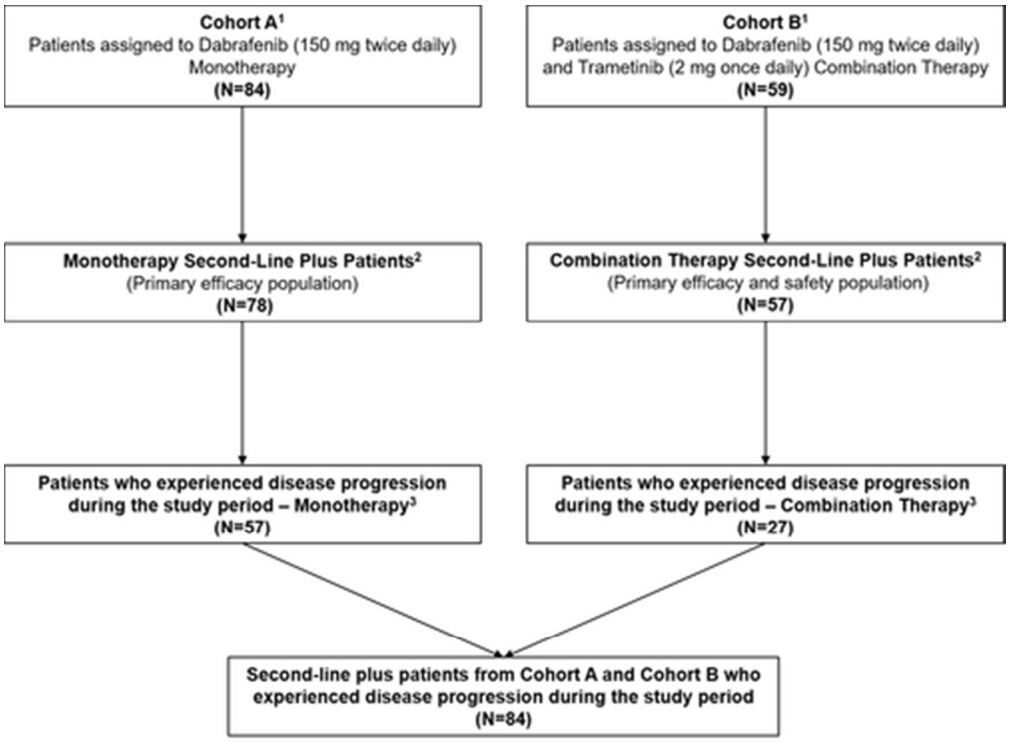

Figure 1. Sample selection flowchart
Legend: Patient-level data were used from the non-randomized, open-label, Phase II trial BRF113928 (data cut: October 7, 2015, trial ongoing). Abbreviations: mg = milligrams; N = number.

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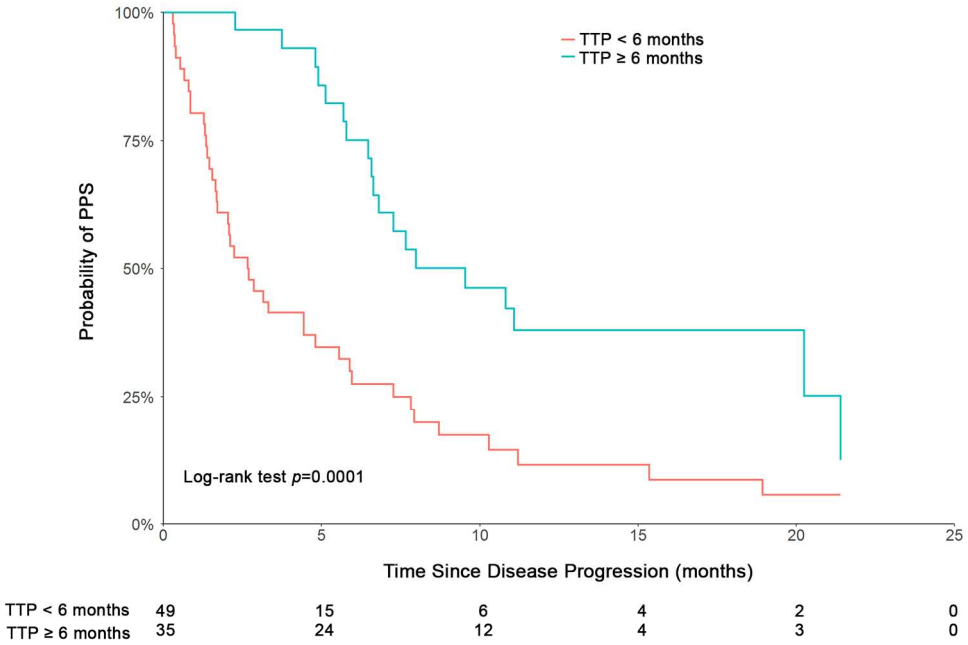
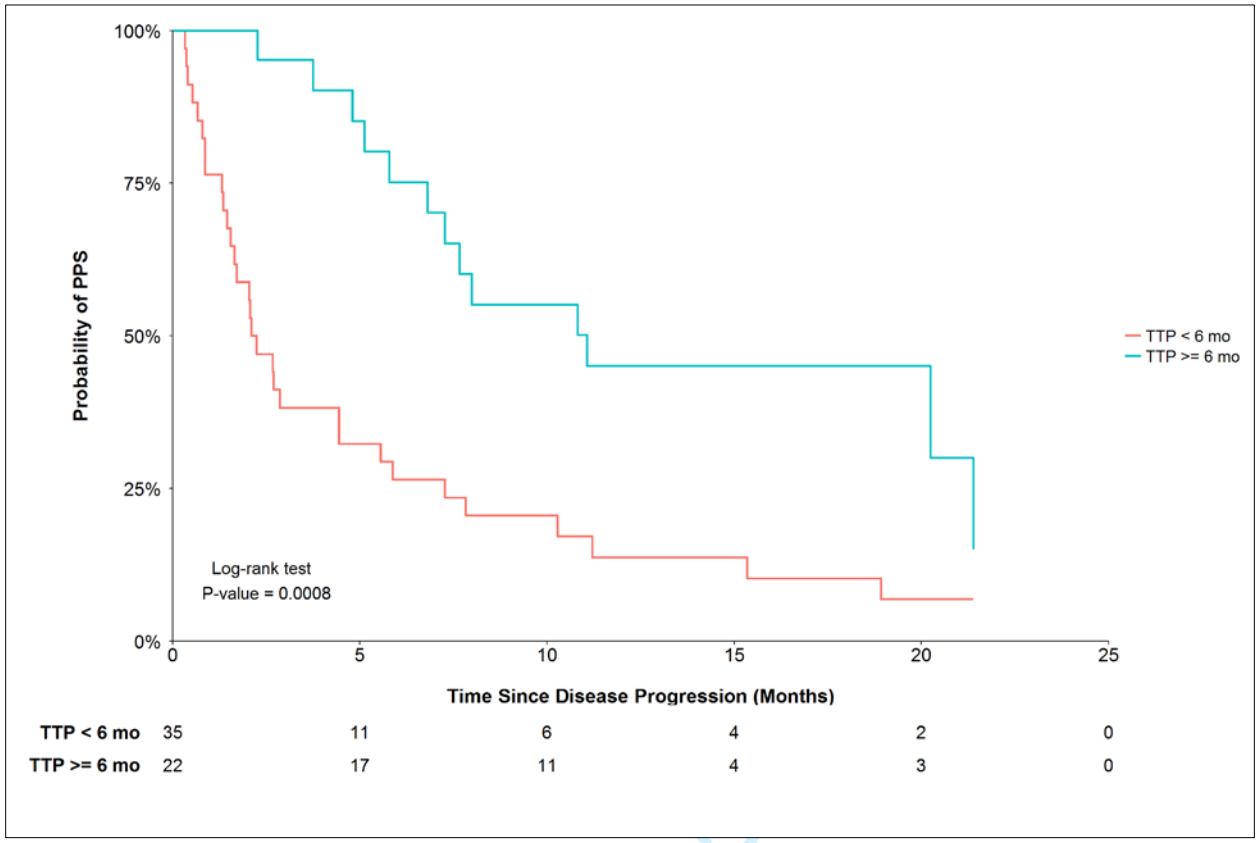


Figure 2. Kaplan-Meier Analysis of PPS in the Combined Cohort, stratified by duration of TTP
Legend: Abbreviations: PPS = post-progression survival; TTP = time to progression.

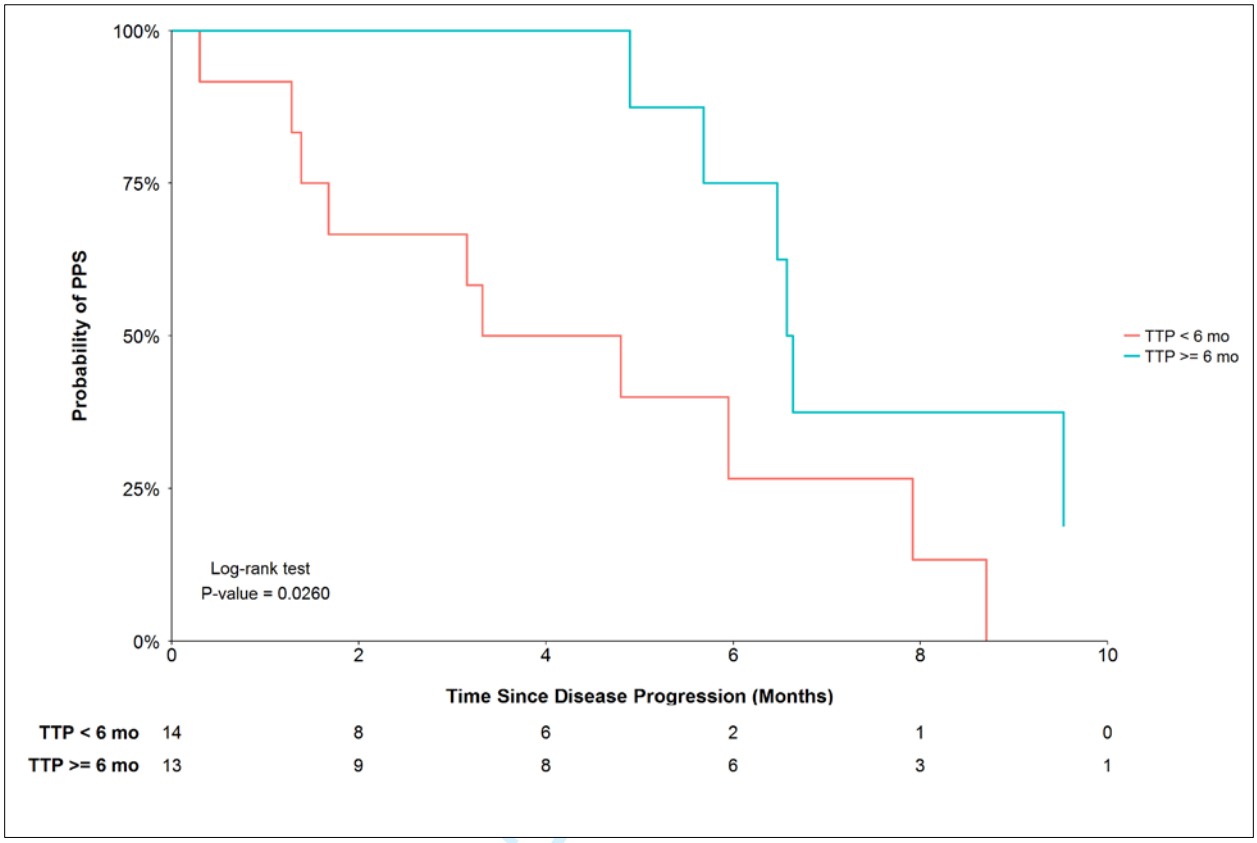
169x123mm (300 x 300 DPI)

Supplemental Figure 1. Kaplan-Meier Analysis of PPS in patients stratified by duration of TTP: Cohorts A (A) and B (B)

A. Cohort A



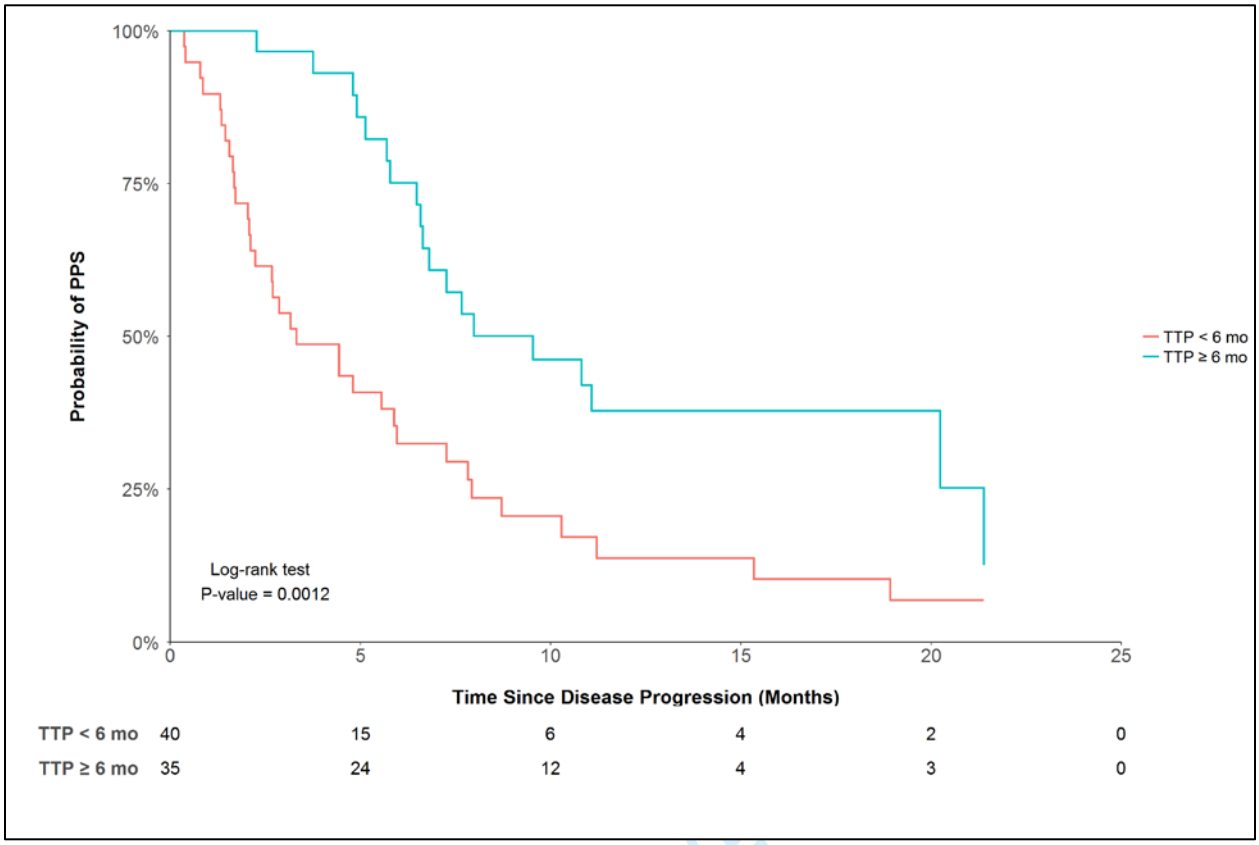
B. Cohort B



Legend

Abbreviations: PPS = post-progression survival; TTP = time to progression.

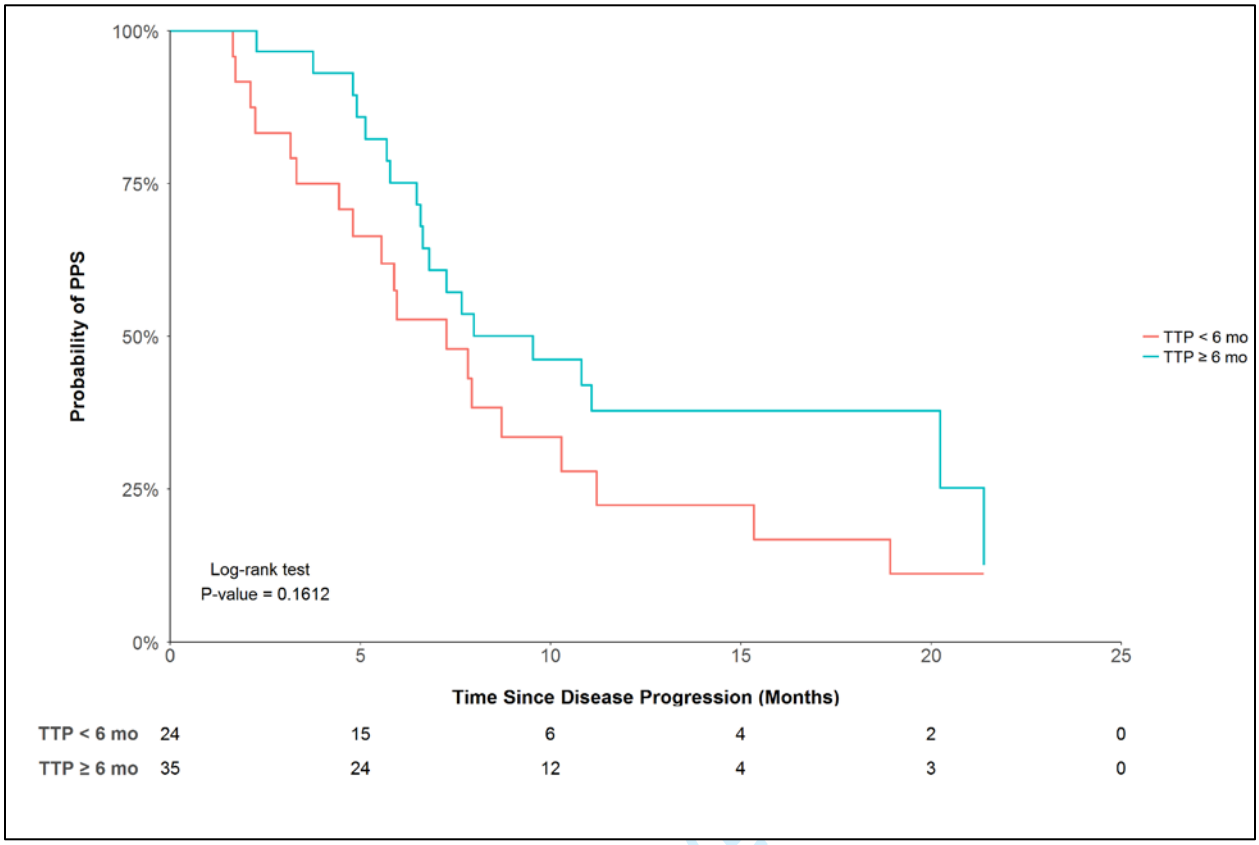
Supplemental Figure 2. Kaplan-Meier Analysis of PPS in patients stratified by duration of TTP: Landmark Analysis (excluding patients who died/were censored prior to 3 months after disease progression)



Legend

Abbreviations: PPS = post-progression survival; TTP = time to progression.

Supplemental Figure 3. Kaplan-Meier Analysis of PPS in patients stratified by duration of TTP: Landmark Analysis (excluding patients who died/were censored prior to 6 months after disease progression)



Legend

Abbreviations: PPS = post-progression survival; TTP = time to progression.

Supplemental Table 1. Status of Patients Excluded from the Analysis who did not Experience Disease Progression

Patient Status, N (%)	Combined Cohort N = 51	Cohort A N = 21	Cohort B N = 30
Censored, follow-up ended	14 (27.5)	11 (52.4)	3 (10.0)
Censored, follow-up ongoing	28 (54.9)	6 (28.6)	22 (73.3)
Died	9 (17.6)	4 (19.0)	5 (16.7)

Caption

Abbreviations: N = number.

Supplementary Table 2. Summary of Patient Characteristics: Cohorts A and B

Patient characteristic	Cohort A N = 57	Cohort B N = 27
Demographics, N (%)		
Age < 65 years	27 (47.4)	14 (51.9)
Male	29 (50.9)	13 (48.1)
Race (White)[i]	43 (75.4)	24 (88.9)
History of tobacco use, N (%)		
Current or former smoker	34 (59.6)	19 (70.4)
Disease and treatment characteristics,		
ECOG performance status score >1 before or at progression, N (%)	12 (21.1)	2 (7.4)
Time since diagnosis to study treatment initiation (months), mean ± SD	22.1 ± 20.0	21.0 ± 15.9
Prior anti-cancer therapy, N (%)		
Number of prior systemic regimens for metastatic disease >1	27 (47.4)	11 (40.7)
Radiotherapy	22 (38.6)	7 (25.9)
Maintenance therapy	11 (19.3)	8 (29.6)
Response to the most recent prior therapy for metastatic disease, N (%)[ii]		
Complete or partial response	11 (19.3)	7 (25.9)

Caption

Abbreviations: ECOG = Eastern Cooperative Oncology Group; mg = milligrams; N = number; SD = standard deviation.

Notes:

[i] Other reported races included Asian, Black or African American, and Mixed.

[ii] Response to the most recent prior anti-cancer therapy included complete response, partial response, stable disease, and progressive disease. Seven patients in Cohort A (including one patient with a non-

evaluable response) and one patient in Cohort B had an unknown response. These patients were imputed as non-complete or partial responders.

Supplemental Table 3. Summary of PPS, Stratified by Duration of TTP: Cohorts A and B

Cohort	N	Number of post-progression deaths	Median PPS (months)	95% CI
Cohort A				
TTP ≥ 6 months	22	13	11.1	(6.8-21.4)
TTP < 6 months	35	31	2.2	(1.4-4.4)
Cohort B				
TTP ≥ 6 months	13	6	6.6	(4.9-NR)
TTP < 6 months	14	10	4.1	(1.3-7.9)

Caption

Abbreviations: CI = confidence internal; N = number; NR = not reached; PPS = post-progression survival; TTP = time to progression.

Supplementary Table 4. Summary of Patient Characteristics in Landmark Analysis (excluding patients who died/were censored prior to 3 months after disease progression)

Patient characteristic	Total	Time to progression ≥ 6 months	Time to progression < 6 months	
	N = 75	N = 35	N = 40	P-value
Demographics, N (%)				
Age < 65 years	36 (48.0%)	15 (42.9%)	21 (52.5%)	0.55
Male	36 (48.0%)	18 (51.4%)	18 (45.0%)	0.75
Race (White)[i]	59 (78.7%)	29 (82.9%)	30 (75.0%)	0.58
History of tobacco use, N (%)				
Current or former smoker	46 (61.3%)	19 (54.3%)	27 (67.5%)	0.35
Disease and treatment characteristics				
ECOG performance status before or at progression > 1, N (%)	9 (12.0%)	1 (2.9%)	8 (20.0%)	0.05
Time since diagnosis to study treatment initiation (month), mean ± SD	22.2 ± 19.3	21.4 ± 16.4	22.8 ± 21.5	0.80
Prior anti-cancer therapy, N (%)				
Number of prior systemic regimens for metastatic disease > 1	34 (45.3%)	14 (40.0%)	20 (50.0%)	0.53
Radiotherapy	23 (30.7%)	10 (28.6%)	13 (32.5%)	0.91
Maintenance therapy	18 (24.0%)	8 (22.9%)	10 (25.0%)	1.00
Response to the most recent prior therapy for metastatic disease, N (%)[ii]				
Complete or partial response	16 (21.3%)	5 (14.3%)	11 (27.5%)	0.27

Caption

Abbreviations: ECOG = Eastern Cooperative Oncology Group; N = number; SD = standard deviation.

Notes:

[i] Other reported races included Asian, Black or African American, and Mixed.

[ii] Response to the most recent prior anti-cancer therapy included complete response, partial response, stable disease, and progressive disease.

Supplementary Table 5. The Multivariable Cox Model of the Association between TTP and PPS in the Combined Cohort: Landmark Analysis (excluding patients who died/were censored prior to 3 months after disease progression)

	Combined Cohort		
	HR	**95% CI**	***P***
Time to progression in 3-month increment(s)	0.68	(0.52-0.88)	0.004 *
Age < 65 years Yes vs. No	1.25	(0.67-2.36)	0.483
Male Yes vs. No	0.65	(0.32-1.33)	0.237
Race (White) Yes vs. No	1.73	(0.60-4.97)	0.311
Current or former smoker Yes vs. No	1.05	(0.47-2.34)	0.913
ECOG performance status before or at progression > 1 Yes vs. No	3.42	(1.23-9.53)	0.019 *
Time since diagnosis to study treatment initiation in 1-month increment(s)	0.98	(0.96-1.00)	0.059
Number of prior systemic regimens for metastatic disease > 1 Yes vs. No	1.28	(0.50-3.26)	0.611
Prior radiotherapy Yes vs. No	0.74	(0.36-1.52)	0.417
Prior maintenance therapy Yes vs. No	0.46	(0.20-1.04)	0.063
Complete or partial response to most recent prior therapy for metastatic disease Yes vs. No	0.39	(0.17-0.91)	0.030 *

Caption

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; PPS = post-progression survival; TTP = time to progression. *p<0.05

Supplementary Table 6. Summary of Patient Characteristics in Landmark Analysis (excluding patients who died/were censored prior to 6 months after disease progression)

Patient characteristic	Total	Time to progression ≥ 6 months	Time to progression < 6 months	
	N = 59	N = 35	N = 24	P-value
Demographics, N (%)				
Age < 65 years	28 (47.5%)	15 (42.9%)	13 (54.2%)	0.56
Male	28 (47.5%)	18 (51.4%)	10 (41.7%)	0.64
Race (White)[i]	45 (76.3%)	29 (82.9%)	16 (66.7%)	0.26
History of tobacco use, N (%)				
Current or former smoker	35 (59.3%)	19 (54.3%)	16 (66.7%)	0.50
Disease and treatment characteristics				
ECOG performance status before or at progression > 1, N (%)	3 (5.1%)	1 (2.9%)	2 (8.3%)	0.74
Time since diagnosis to study treatment initiation (month), mean ± SD	20.5 ± 15.8	21.4 ± 16.4	19.2 ± 15.1	0.64
Prior anti-cancer therapy, N (%)				
Number of prior systemic regimens for metastatic disease > 1	26 (44.1%)	14 (40.0%)	12 (50.0%)	0.62
Radiotherapy	19 (32.2%)	10 (28.6%)	9 (37.5%)	0.66
Maintenance therapy	14 (23.7%)	8 (22.9%)	6 (25.0%)	1.00
Response to the most recent prior therapy for metastatic disease, N (%)[ii]				
Complete or partial response	12 (20.3%)	5 (14.3%)	7 (29.2%)	0.29

Caption

Abbreviations: ECOG = Eastern Cooperative Oncology Group; N = number; SD = standard deviation.

Notes:

[i] Other reported races included Asian, Black or African American, and Mixed.

[ii] Response to the most recent prior anti-cancer therapy included complete response, partial response, stable disease, and progressive disease.

Supplementary Table 7. The Multivariable Cox Model of the Association between TTP and PPS in the Combined Cohort: Landmark Analysis (excluding patients who died/were censored prior to 6 months after disease progression)

	Combined Cohort		
	HR	**95% CI**	***P***
Time to progression in three-month increment(s)	0.82	(0.62-1.07)	0.148
Age < 65 years Yes vs. No	1.59	(0.71-3.57)	0.261
Male Yes vs. No	0.71	(0.31-1.60)	0.409
Race (White) Yes vs. No	1.00	(0.29-3.52)	0.996
Current or former smoker Yes vs. No	1.33	(0.52-3.41)	0.556
ECOG performance status before or at progression > 1 Yes vs. No	3.67	(0.71-19.06)	0.122
Time since diagnosis to study treatment initiation in 1-month increment(s)	0.96	(0.93-1.00)	0.027 *
Number of prior systemic regimens for metastatic disease > 1 Yes vs. No	1.42	(0.48-4.21)	0.532
Prior radiotherapy Yes vs. No	1.00	(0.43-2.31)	0.996
Prior maintenance therapy Yes vs. No	0.45	(0.17-1.19)	0.107
Complete or partial response to most recent prior therapy for metastatic disease Yes vs. No	0.50	(0.19-1.30)	0.153

Caption

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; PPS = post-progression survival; TTP = time to progression. *p<0.05

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-021642.R2
Article Type:	Research
Date Submitted by the Author:	29-Jun-2018
Complete List of Authors:	Li, Junlong; Analysis Group Inc Boston Sasane, Medha; Novartis Pharmaceuticals Corp Zhang, Jie; Novartis Pharmaceuticals Corp Zhao, Jing; Analysis Group Inc Boston Ricculli, Marie Louise ; Analysis Group Inc New York Yao, Zhiwen; Analysis Group Inc Boston Redhu, Suman; Novartis Pharmaceuticals Corp Signorovitch, James; Analysis Group Inc Boston
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology
Keywords:	post-progression survival, time to progression, dabrafenib, trametinib, BRAF V600E NSCLC, ONCOLOGY

Is time to progression associated with post-progression survival in previously treated metastatic non-small cell lung cancer with BRAF V600E mutation? A secondary analysis of Phase II clinical trial data

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ABSTRACT

Objective: Longer time to progression (TTP) is associated with prolonged post-progression survival (PPS) in ALK+ non-small cell lung cancer (NSCLC). This study evaluated whether TTP is associated with PPS among previously treated patients with metastatic BRAF V600E NSCLC receiving dabrafenib as monotherapy or in combination with trametinib.

Design: Secondary analysis of Phase II clinical trial data (NCT01336634).

Setting: Patients who experienced disease progression treated with dabrafenib monotherapy or in combination with trametinib as second-line or later in an open-label, non-randomized, Phase II study.

Primary outcome measures: The primary outcome was the TTP-PPS association. PPS was assessed with Kaplan-Meier analysis among patients with shorter versus longer TTP (< or ≥6 months). The TTP-PPS association was quantified in the Cox models adjusting for clinical covariates.

Results: Of the 84 included patients who progressed on dabrafenib monotherapy (N=57) or combination therapy (N=27), 60 (71%) died during post-progression follow-up. Patients with TTP ≥6 months experienced significantly longer PPS compared to those with TTP <6 months (median PPS: 9.5 vs. 2.7 months, log-rank p<0.001). Each 3 months of longer TTP was associated with a 32% lower hazard of death following progression (hazard ratio [95% confidence interval]: 0.68 [0.52-0.88]) in the multivariable Cox model. Similar associations were seen in each treatment arm.

Conclusion: A longer TTP duration after treatment with dabrafenib monotherapy or combination therapy was associated with significantly longer PPS duration.

Keywords: post-progression survival, time to progression, dabrafenib, trametinib, BRAF V600E NSCLC

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This retrospective study is the first to quantify the association between TTP and PPS among previously treated patients with metastatic BRAF V600E NSCLC receiving a new generation of targeted therapies, dabrafenib monotherapy or in combination with trametinib.
- TTP and PPS were chosen as these measures refer to non-overlapping periods of time and yielded prognostic information relevant for physicians considering later-line therapies in advanced NSCLC.
- The TTP-PPS association was estimated using patient-level data from an ongoing pivotal trial via a Cox model, adjusting for multiple patient demographics and disease characteristics.
- The present analysis only included patients who had disease progression observed before death in a clinical trial setting, which may limit the generalizability to other populations.
- The association between TTP and PPS may be confounded by patient characteristics unmeasured in the clinical trial.

INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for 80–85% of all lung cancers globally,[1] and is the leading cause of cancer-related mortality in the United States (US).[2] In advanced stages, NSCLC is aggressive. For example, patients with stage IIIB cancer have an estimated 5-year survival rate of 5%; this rate is estimated to be about 1% for patients in stage IV or with confirmed metastatic disease.[3] Treatment for NSCLC has traditionally consisted of cytotoxic chemotherapy, although recent advances in cancer biology have led to the development of targeted anti-cancer agents that modulate specific oncogenic molecular pathways.[4]

NSCLC is a heterogeneous cancer, and molecular diagnostic testing can be used to inform treatment choice for patients with metastatic or relapsing disease. For example, mutations in BRAF (v-Raf murine sarcoma viral oncogene homolog B), which encodes the protein B-Raf involved in cell growth signaling, are present in 1–5% of NSCLC.[5,6] Constitutively active B-Raf mutants can prompt tumorigenesis by excessively signaling cells to divide, often via the MAP kinase (MAPK) pathway.[7] In particular, BRAF V600E mutations account for about 50% of BRAF mutant NSCLC and 2% of all NSCLC, and are usually associated with a history of smoking and with adenocarcinoma.[8] Patients with BRAF V600E mutant NSCLC have poorer clinical outcomes and lower response to platinum-based chemotherapy compared with patients without this mutation.[6,9] Thus, targeted therapies that modulate BRAF kinase signaling or downstream MAPK signaling to slow tumor growth are promising alternatives to effectively treat BRAF-mutant NSCLC.[10]

Dabrafenib is a potent and selective reversible BRAF kinase inhibitor, which has previously demonstrated efficacy and tolerability in clinical trials of patients with BRAF V600 mutant melanoma, including those with metastatic disease.[11] Trametinib, an allosteric inhibitor of mitogen-activated extracellular signal regulated kinase (MEK) 1 and 2, has synergistic anti-oncogenic activity with BRAF inhibition. The efficacy and tolerability profiles of dabrafenib as a single agent and in combination with

trametinib have been assessed among patients with BRAF V600E mutation positive metastatic (stage IV) NSCLC in a recent multicenter, non-randomized, open-label, Phase II trial (ClinicalTrials.gov: NCT01336634).[12,13] For example, among patients who received at least one prior platinum-based chemotherapy regimen for metastatic disease, patients treated with dabrafenib monotherapy (Cohort A) reported an investigator-assessed overall confirmed response rate of 33% and median progression-free survival (PFS) of 5.5 months. The overall confirmed response rate was 63% and median PFS was 9.7 months for patients who received dabrafenib and trametinib in combination (Cohort B).[12,13]

The overarching goals of NSCLC treatment are to prolong overall survival (OS), manage symptoms, and improve patients' quality of life.[14] However, there are practical challenges to directly assess the effects of treatment on long-term survival in clinical trials of late-stage cancer patients who have already failed multiple lines of therapy.[15,16] Clinical trials and meta-analyses of other advanced NSCLC treatments have demonstrated that time to progression (TTP) can be predictive of long-term clinical benefits in patient survival.[17-19] For example, a longer duration of TTP was demonstrated to be significantly associated with a longer duration of post-progression survival (PPS) among NSCLC patients with anaplastic lymphoma kinase (ALK) gene rearrangement[19] and mutations in the epidermal growth factor receptor (EGFR) gene.[20]

To the best of our knowledge, the relationship between TTP and PPS has not yet been assessed among patients with BRAF V600E mutant NSCLC receiving the newer generation of targeted therapies. It is of great clinical interest to determine whether any improvement in TTP is offset by loss of survival time in the post-progression period. To address this question, the current study evaluated the association between TTP and the duration of PPS among adult, previously treated, metastatic NSCLC patients with BRAF V600E mutation who experienced disease progression while receiving dabrafenib monotherapy or in combination with trametinib.

MATERIAL AND METHODS

Study design and population

The study is a secondary analysis of data from metastatic NSCLC patients with BRAF V600E mutation included in the non-randomized, open-label, Phase II trial BRF113928 (NCT01336634; data cut: October 7, 2015, trial ongoing). Written informed consent was obtained from each subject prior to the performance of any study-specific procedures in BRF113928; de-identified patient-level data were used in this retrospective analysis. The current analysis included chemotherapy-experienced patients who were assigned to receive either dabrafenib monotherapy (150 mg twice daily [BID]; Cohort A) or combination therapy of dabrafenib (150 mg BID) and trametinib (2 mg once daily; Cohort B) as second- or later-line and experienced disease progression during the trial's study period. The disease progression was determined based on radiological response as per investigator assessment and Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.[21] For patients in Cohort B, the study treatment could have been up to the fourth-line of systemic anti-cancer therapy for metastatic disease. The full methodology of this trial has been previously published.[12,13]

A diagram of the patient selection process in the current study is shown in **Figure 1**. Patients who were previously untreated, or did not experience observed disease progression (either due to censoring or death before progression) during the original trial's study period, were excluded from the final analytical sample in this study.

Outcomes and Variables

The primary outcome of interest in the current analysis was PPS, which was defined as the time from the date of disease progression after starting the study treatment (dabrafenib monotherapy or combination therapy with dabrafenib and trametinib) until death due to any cause. Patients without an observed death were censored at the date of last contact they were known to be alive. Disease progression was based on radiological response as per investigator assessment and RECIST v1.1.[21]

The primary independent variable was TTP, which was defined as the time from the date of study treatment initiation until the first date of disease progression after treatment initiation. In addition, the following patient characteristics were assessed at baseline: demographics (age, sex, and race), history of tobacco use, disease characteristics (Eastern Cooperative Oncology Group [ECOG] performance status before or at the time of progression and time since diagnosis to study treatment initiation), and prior anti-cancer treatment and response (number of prior regimens for metastatic disease, prior radiotherapy, prior maintenance therapy, and response to most recent anti-cancer therapy for metastatic disease).

Statistical Analyses

The association between TTP and PPS was assessed using Kaplan-Meier analysis and a Cox proportional hazards regression analysis. The primary analyses were conducted in the combined cohort of patients that received dabrafenib monotherapy (Cohort A) or in combination with trametinib (Cohort B). Sensitivity analyses were conducted in each individual cohort and in a subgroup of patients who survived and remained in the trial at 3 months post disease progression. All analyses were conducted using the statistical software R (version 3.3.2, the R Foundation for Statistical Computing), and statistical significance was assessed at the 5% level.

Kaplan-Meier Analyses

To assess the association between TTP and PPS, patients were first categorized into two subgroups based on the length of TTP (≥6 months vs. <6 months) and Kaplan-Meier curves for PPS were then estimated in each subgroup. The 6-month cutoff in TTP was selected based on the median PFS observed in the combined cohort (i.e., 5.3 months), as well as the "efficacy plateau" observed in median TTP across systemic therapies for advanced NSCLC.[9]

In each subgroup defined by TTP, the number of events (i.e., number of patients who died following progression) was summarized, and the median PPS and corresponding 95% confidence interval

(CI) were estimated using the Kaplan-Meier method. The log-rank test was used to compare PPS between the two subgroups defined by TTP.

Cox Regression Analyses

To further quantify the association between TTP and PPS, a Cox proportional hazards model was implemented. PPS was the time-to-event outcome in the Cox models and TTP was the main independent variable of interest. In this analysis, TTP was a continuous variable as every patient included had progressed on the assigned treatment. Both univariable and multivariable Cox regression analyses were conducted. Prior to analysis, the proportional hazards assumption was tested to ensure the validity of the Cox model. The hazard ratios (HR) and corresponding 95% CIs are reported. For clinical relevance, results of the HR associated with TTP are presented for each three-month increase in TTP.

In the combined cohort, stratified Cox models with cohort as the stratification variable (i.e., Cohort A [monotherapy] and Cohort B [combination therapy]) were conducted as univariable and multivariable regression analyses. The univariable model included TTP as the only independent variable; the multivariable Cox model was further adjusted for the following patient demographics and disease characteristics: age group, sex, race, time since diagnosis to study treatment initiation, history of tobacco use, number of prior regimens for metastatic disease, prior radiotherapy, prior maintenance therapy, response to the most recent prior anti-cancer therapy, and ECOG status before or at progression. ECOG performance was assessed on the date closest to progression to best understand the patients' health status entering into the post-progression period, due to its potential impact on the TTP-PPS association.

In the sensitivity analyses within each cohort, unstratified univariable and multivariable Cox models were used to quantify the TTP-PPS association. The Cohort A multivariable Cox model adjusted for the same patient characteristics as those considered in the combined cohort. However, due to a limited sample size and the high proportions of patients in Cohort B that were White and had an ECOG score ≤1 before or at progression, these two covariates were not included in the multivariable model for Cohort B.

Landmark analysis

A landmark analysis was conducted as a sensitivity analysis to evaluate the potential for guarantee-time bias in creating the cohorts based on TTP. Patients who died or were censored prior to 3 months after disease progression were excluded. A landmark of 3 months was determined based on a median PPS of 2.7 months among all patients. For patients who were included in the landmark analysis, a Kaplan-Meier analysis and a multivariable Cox regression analysis were conducted using the same approach as described above.

Patient Involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design or conduct of the study. No patients were asked to advise on interpretation or writing up of the results. There are no plans to disseminate the results of the research to study participants.

RESULTS

Sample Selection

A total of 143 patients with BRAF V600E mutation positive metastatic NSCLC were assigned to receive dabrafenib monotherapy (N = 84, Cohort A) or in combination with trametinib (N = 59, Cohort B) as second-line or above in the BRF113928 trial (**Figure 1**). The final analytic sample was comprised of 84 patients (57 in Cohort A and 27 in Cohort B) who actually received the study treatment as second-line or above and experienced disease progression during the original trial's study period. The follow-up status of the 51 patients who did not experience disease progression is listed in **Supplemental Table 1**.

Patient characteristics

Of the patients in the combined cohort, 50.0% were male, 48.8% were under 65 years of age, and 79.8% were White. The majority of patients (63.1%) were current or former tobacco smokers. In addition, the mean (standard deviation) time period between diagnosis to the initiation of the study treatment was 21.7 (18.7) months. The proportion of patients with ECOG performance status scores >1 before or at progression was 16.7% overall. It is noteworthy that the ECOG performance status before or at progression was significantly different among patients stratified by TTP (e.g., only one patient [2.9%] with TTP ≥6 months had a score >1, while 13 patients [26.5%] with TTP <6 months had a score >1 [p= 0.01]). In the combined cohort, the proportions of patients who had received prior radiotherapy or maintenance therapy were 34.5% and 22.6%, respectively, and 45.2% of patients had received more than one prior systemic regimen for metastatic disease. The proportion of patients that had achieved either complete or partial response with prior therapy for metastatic disease was 21.4% (**Table 1**). The patient characteristics for each cohort (Cohort A and B) are listed in **Supplemental Table 2**.

Kaplan-Meier Analysis of the Association between PPS and TTP

The Kaplan-Meier analysis to assess the association between TTP and PPS among patients in the combined cohort is presented in **Figure 2**. Patients who progressed ≥6 months following treatment initiation experienced significantly prolonged PPS compared with those who progressed before 6 months (log-rank p <0.001). In the combined cohort, 19 post-progression deaths were observed among 35 patients with TTP ≥6 months, while 41 post-progression deaths were observed among 49 patients with TTP <6 months. In addition, these patients with TTP ≥6 months had longer median PPS (9.5 months; 95% CI: 6.6-20.2 months) compared with patients with TTP <6 months (median PPS: 2.7 months; 95% CI: 1.6-4.8 months).

In the sensitivity analysis, a similar association was observed between TTP duration and PPS among Cohorts A and B (**Supplemental Table 3** and **Supplemental Figure 1a and 1b**). Specifically,

TTP of ≥6 months was associated with fewer deaths and significantly prolonged subsequent survival among patients in each individual cohort (log-rank p <0.001 in Cohort A; log-rank p =0.026 in Cohort B).

Univariable and Multivariable Cox Regression Analyses of the Association between PPS and TTP

In both the univariable and multivariable Cox regression analyses of the association between TTP and PPS, increased duration of TTP was associated with significant reductions in the hazard of post-progression death in the combined cohort. Specifically, each three-month increase in TTP was associated with a 32% lower risk of death post-progression in the combined cohort (HR: 0.68; 95% CI: 0.57-0.83; p <0.001) in the univariable analysis. A similar trend was observed in the multivariable Cox regression analyses conducted to control for patient characteristics that could potentially confound the relationship between TTP and PPS (**Table 2**). In the combined cohort, each three-month increase in TTP was associated with a 32% reduction in the risk of post-progression death (HR: 0.68; 95% CI: 0.52-0.88; p =0.003). In addition to TTP, an ECOG performance score >1 before or at progression (HR: 3.89; 95% CI: 1.62-9.32; p =0.002) was also found to be significantly associated with the risk of post-progression death.

Consistent positive TTP and PPS association was demonstrated in each individual cohort in the sensitivity analysis. In the univariable Cox analysis, each three-month increase in TTP was associated with a 30% lower risk of post-progression death in Cohort A (HR: 0.70; 95% CI: 0.57-0.88; p =0.001) and a 43% lower risk in Cohort B (HR: 0.57; 95% CI: 0.34-0.97; p =0.035). Each three-month increase in the duration of TTP was associated with a reduction in the risk of post-progression death by 32% in Cohort A (HR: 0.68; 95% CI: 0.51-0.91; p =0.010) and 65% in Cohort B (HR: 0.35; 95% CI: 0.14-0.88; p =0.025) in the multivariable analysis.

Landmark analysis

Among 84 patients included in the primary analyses, 50 patients who survived and were uncensored from the trial 3 months after their disease progression, were included in the landmark analysis. Using both the Kaplan Meier approach and the multivariable regression model, results were similar to the primary analysis **(Supplementary Tables 4 and 5, and Supplementary Figure 2**). The association between TTP and PPS was still positive but not statistically significant due to limited sample size in the landmark analysis (e.g., TTP in 3-month increments from the multivariable cox analysis: HR: 0.84; 95% CI: 0.63-1.13; p=0.242).

DISCUSSION

This study addressed the knowledge gap regarding the relationship between TTP and PPS among previously treated patients with metastatic, BRAF V600E mutant NSCLC receiving dabrafenib monotherapy or in combination with trametinib who experienced disease progression. The present study quantified the association of TTP-PPS, based on existing patient-level data from the ongoing dabrafenib targeted therapy clinical trial, using a Cox regression model while adjusting for multiple patient demographics and disease characteristics (e.g., ECOG score) that may potentially confound the association.[12,13] The current results indicate the longer a patient objectively benefited from dabrafenib monotherapy or in combination with trametinib (i.e., the longer the duration of TTP), the longer the survival period was after objective failure of the targeted therapy (i.e., PPS). For every three-month increase in duration of TTP following treatment initiation with dabrafenib monotherapy or in combination with trametinib, patients experienced a 32% reduction in the hazard of subsequent death after progression when controlling for patient characteristics. In addition, ECOG performance status before or at progression was found to be associated with a significant impact on the association both in the stratified analysis and in the multivariable Cox regression analysis. This result indicates that prolonging TTP with

dabrafenib monotherapy or in combination with trametinib is associated with prolongation of OS over and above the longer duration of TTP itself. A consistent positive association between TTP and PPS is observed in the landmark analysis in which patients who died or censored prior to 3 months after disease progression were excluded, although the small sample size may limit the interpretation of these results.

The relationship between TTP and OS in NSCLC has been evaluated and demonstrated to be a moderate to strong association in several studies.[22-24] However, rather than further explore OS, this study considered the association between TTP and PPS as the primary research question. TTP and PPS were chosen as these measures refer to non-overlapping periods of time and yield prognostic information that can be applied at the time of progression. Also, PPS has been supported as a clinically-relevant outcome measure and a valid surrogate endpoint for OS in advanced NSCLC, particularly in evaluations of later-line therapies.[25] In addition, TTP has been shown to influence PPS in secondary analyses of patients with advanced NSCLC who received first-line chemotherapy or bevacizumab in two clinical trials and an observational cohort study; patients with longer first-line TTP also experienced longer PPS.[26]

With the development of newer therapies for NSCLC, such as targeted therapies that modulate oncogenic molecular pathways active in individuals' tumors, the relationship between TTP and PPS has become a clinically important question for the care of patients with genetic variations. As the first to address this question, Liu et al. studied the association between TTP and PPS among patients with advanced NSCLC and ALK mutations who progressed on the targeted therapy of ceritinib. Similar to the results from the current study, a positive association was revealed; every three months of longer duration of TTP after initiating ceritinib was associated with a 21% lower hazard of death following disease progression. It also found that ECOG performance score was another significant predictor for risk of post-progression death, consistent with the finding of the current analysis.[19] The present study contributes to the evidence that longer duration of TTP is associated with PPS among patients with NSCLC and BRAF V600E mutations receiving targeted therapy who experienced disease progression, and that this association may be a useful way to indicate OS in future clinical trials in this patient population.

This retrospective analysis is subject to several limitations. First, this study should be considered an interim analysis of the association of TTP with PPS in previously treated patients with metastatic, BRAF V600E mutant NSCLC. Collection of the progression and survival data in the BRF113928 trial is ongoing. Secondly, unmeasured patient characteristics could potentially confound the association between TTP and PPS. Other factors such as the use of treatments after progression were not directly included in the present study, and could further affect the TTP-PPS association observed in the multivariable Cox regression analyses. In addition, limited sample size within each cohort in the sensitivity analyses may not provide sufficient statistical power to the association assessment. Finally, as the present study only included patients who had disease progression observed before death in a clinical trial setting, these results may not fully generalize to other patient populations.

CONCLUSIONS

In conclusion, a positive relationship between TTP and PPS was demonstrated among adults previously treated for advanced, BRAF V600E mutant NSCLC who received BRAF-specific targeted therapies and experienced disease progression. This relationship was consistent across cohorts with similar patient populations who were treated with dabrafenib monotherapy or in combination with trametinib. This study enriched the understanding and interpretation of TTP-PPS association among metastatic BRAF V600E mutant NSCLC patients, who were previously treated with at least one platinum-based chemotherapy regimen. Patients who have experienced longer TTP during treatment of dabrafenib monotherapy or in combination with trametinib can expect to experience longer subsequent survival than patients with shorter TTP.

Acknowledgements

Medical writing assistance was provided by Shelley Batts, PhD and Gloria DeWalt, PhD, employees of Analysis Group, Inc.

Competing Interests

Jie Zhang and Suman Redhu are employees of Novartis Pharmaceuticals Corporation and own stock/stock options. Medha Sasane was a previous employee of Novartis. Junlong Li, Jing Zhao, Marie Louise Ricculli, Zhiwen Yao, and James Signorovitch are employees of Analysis Group, Inc., which has received consultancy fees from Novartis Pharmaceuticals Corporation.

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All authors had, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval and consent

This study is a secondary analysis of previously-published information; no institutional board review was required.

Consent for publication

N/A

Data sharing statement

The sponsor of the present study, Novartis Pharmaceuticals Corporation, granted permission of the secondary analysis of anonymized clinical trial data. The data were anonymized prior to receipt for the secondary analysis. The datasets generated during and/or analyzed during the current study are not publicly available due to clinical trial confidentiality agreement.

Funding

This work was supported by Novartis Pharmaceuticals Corporation. The sponsor was involved in all stages of the study and manuscript preparation.

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TABLES

Table 1. Summary of Patient Characteristics: Combined Cohort

	Combined Cohort N = 84	Time to progression ≥ 6 months N = 35	Time to progression < 6 months N = 49	P-value[iii]
Demographics, n(%)				
Age < 65 years	41 (48.8%)	15 (42.9%)	26 (53.1%)	0.48
Male	42 (50.0%)	18 (51.4%)	24 (49.0%)	1.00
Race (White)[i]	67 (79.8%)	29 (82.9%)	38 (77.6%)	0.75
History of tobacco use, n(%)				
Current or former smoker	53 (63.1%)	19 (54.3%)	34 (69.4%)	0.24
Disease characteristics, n(%)				
ECOG performance status before or at progression > 1	14 (16.7%)	1 (2.9%)	13 (26.5%)	0.01 *
Time since diagnosis to study treatment initiation (month)	21.7 ± 18.7	21.4 ± 16.4	22.0 ± 20.2	0.75
Prior anti-cancer therapy, n(%)				
Number of prior systemic regimens for metastatic disease > 1	38 (45.2%)	14 (40.0%)	24 (49.0%)	0.55
Radiotherapy	29 (34.5%)	10 (28.6%)	19 (38.8%)	0.46
Maintenance therapy	19 (22.6%)	8 (22.9%)	11 (22.4%)	1.00
Response to the most recent prior therapy for metastatic disease, n(%)[ii]				
Complete or partial response	18 (21.4%)	5 (14.3%)	13 (26.5%)	0.28

Caption

Abbreviations: ECOG = Eastern Cooperative Oncology Group; N = number; SD = standard deviation.

Notes:

[i] Other reported races included Asian, Black or African American, and Mixed.

[ii] Response to the most recent prior anti-cancer therapy included complete response, partial response, stable disease, and progressive disease. Seven patients in Cohort A (including one patient with a non-evaluable response) and one patient in Cohort B had an unknown response. These patients were imputed as non-complete or partial responders.

[iii] Statistical comparisons were conducted using Wilcoxon rank-sum tests for continuous characteristics and chi-squared tests for categorical characteristics.

Table 2. The Multivariable Cox Model of the Association between TTP and PPS in the Combined Cohort

	Combined Cohort		
	HR	**95% CI**	***P***
Time to progression in three-month increment(s)	0.68	(0.52-0.88)	0.003*
Age <65 years Yes vs. No	1.28	(0.70-2.36)	0.420
Male Yes vs. No	0.74	(0.38-1.42)	0.365
Race (White) Yes vs. No	1.44	(0.55-3.76)	0.462
Current or former smoker Yes vs. No	1.07	(0.50-2.31)	0.855
ECOG performance status before or at progression >1 Yes vs. No	3.89	(1.62-9.32)	0.002*
Time since diagnosis to study treatment initiation in 1-month increment(s)	0.98	(0.96-1.00)	0.058
Number of prior systemic regimens for metastatic disease >1 Yes vs. No	1.22	(0.51-2.93)	0.658
Prior radiotherapy Yes vs. No	0.88	(0.46-1.70)	0.701
Prior maintenance therapy Yes vs. No	0.50	(0.23-1.08)	0.078
Complete or partial response to most recent prior therapy for metastatic disease Yes vs. No	0.47	(0.22-1.02)	0.056

Caption

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; PPS = post-progression survival; TTP = time to progression. *p<0.05

FIGURE LEGENDS

Figure 1. Sample selection flowchart

Legend**:** Patient-level data were used from the non-randomized, open-label, Phase II trial BRF113928 (data cut: October 7, 2015, trial ongoing). Abbreviations: mg = milligrams; N = number.

Figure 2. Kaplan-Meier Analysis of PPS in the Combined Cohort, stratified by duration of TTP

Legend**:** Abbreviations: PPS = post-progression survival; TTP = time to progression.

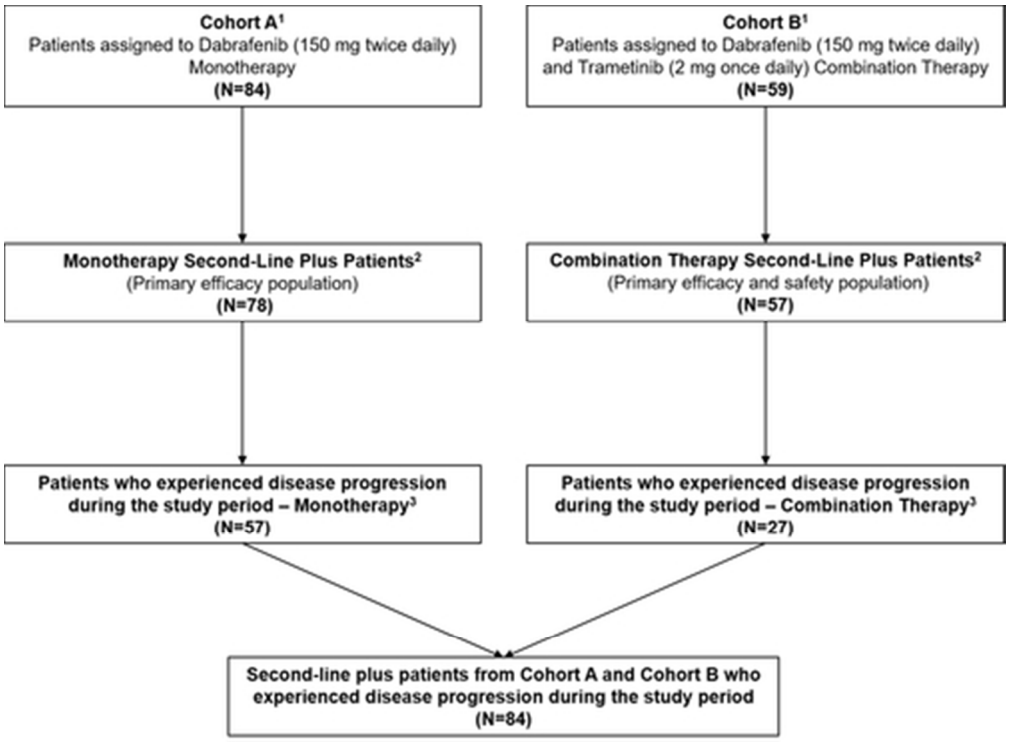


Figure 1. Sample selection flowchart
Legend: Patient-level data were used from the non-randomized, open-label, Phase II trial BRF113928 (data cut: October 7, 2015, trial ongoing). Abbreviations: mg = milligrams; N = number.

21x15mm (600 x 600 DPI)

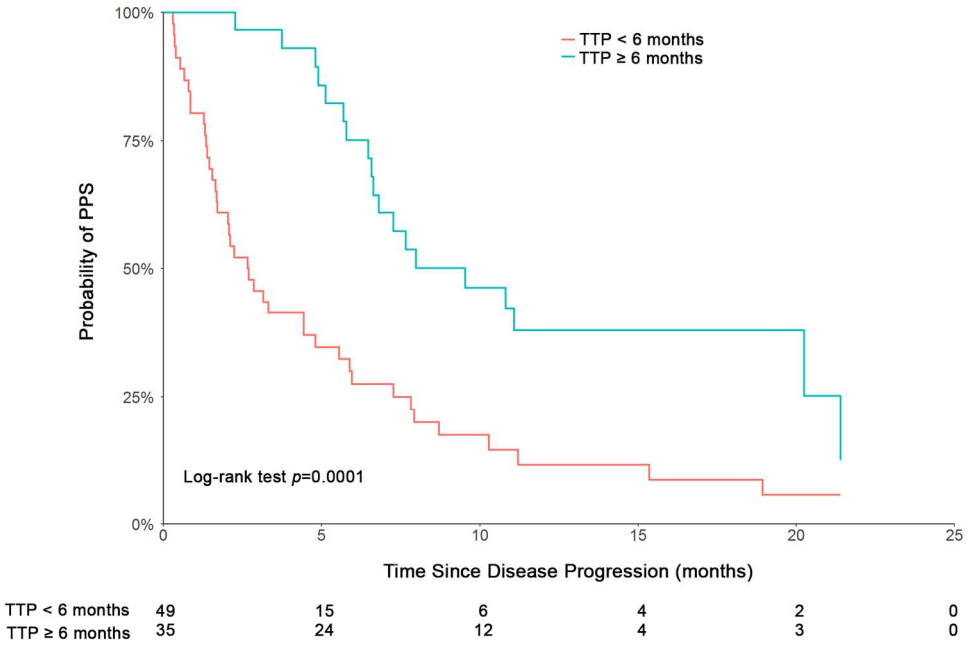
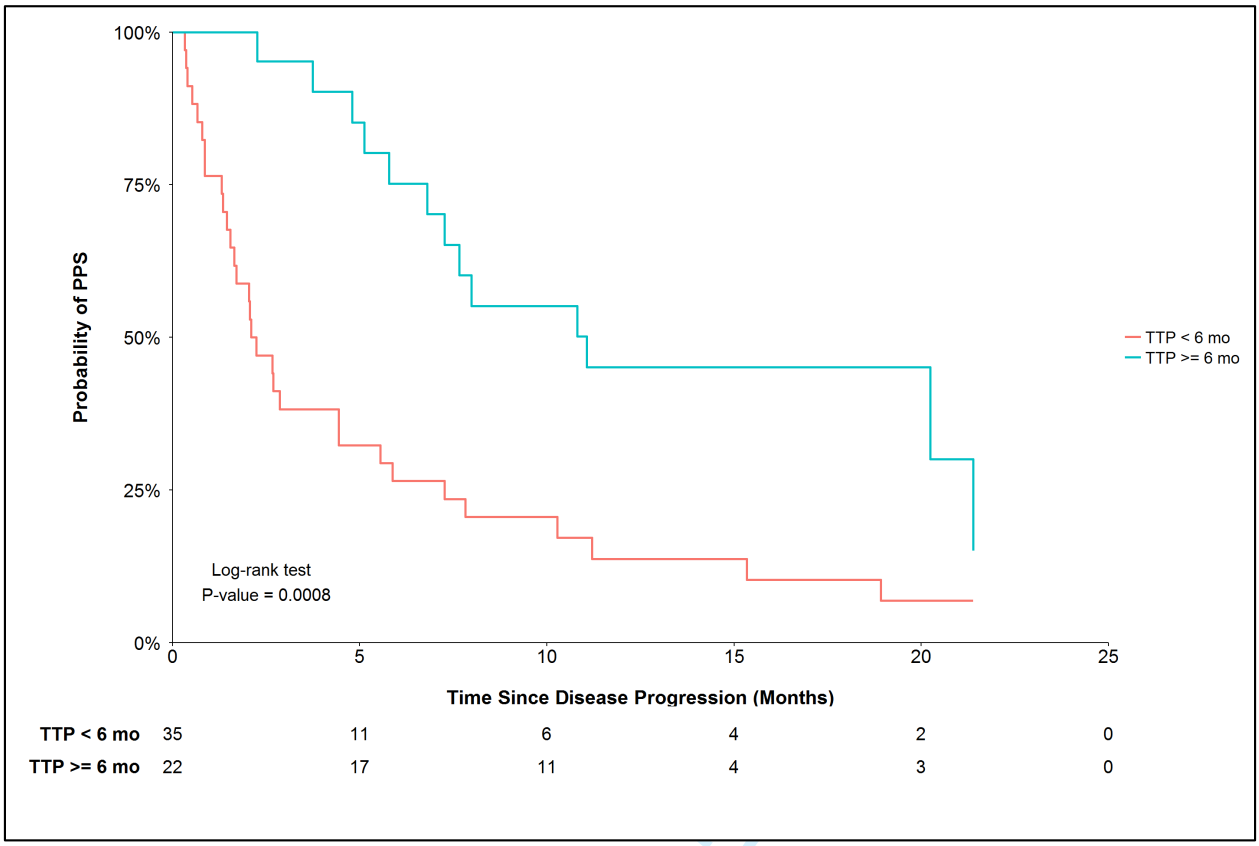


Figure 2. Kaplan-Meier Analysis of PPS in the Combined Cohort, stratified by duration of TTP
Legend: Abbreviations: PPS = post-progression survival; TTP = time to progression.

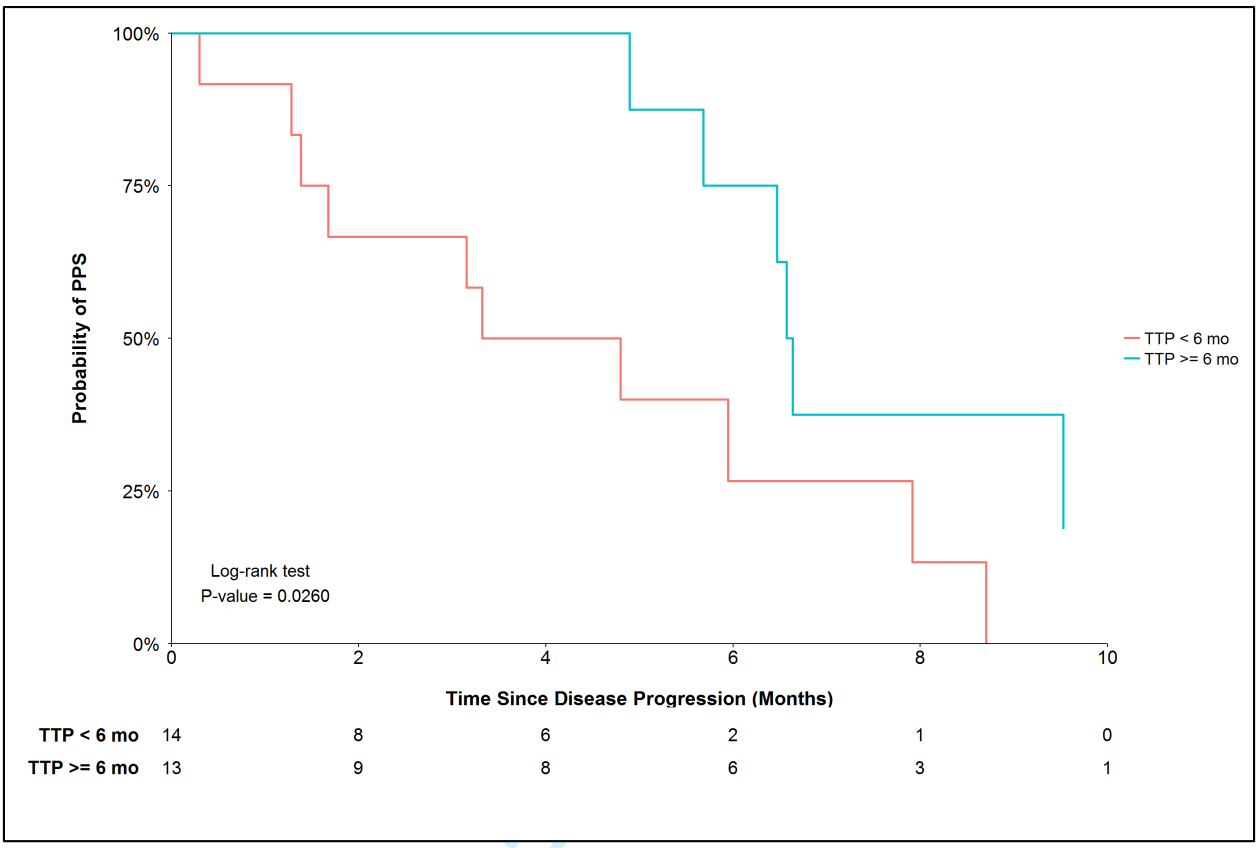
169x123mm (300 x 300 DPI)

Supplemental Figure 1. Kaplan-Meier Analysis of PPS in patients stratified by duration of TTP: Cohorts A (A) and B (B)

A. Cohort A



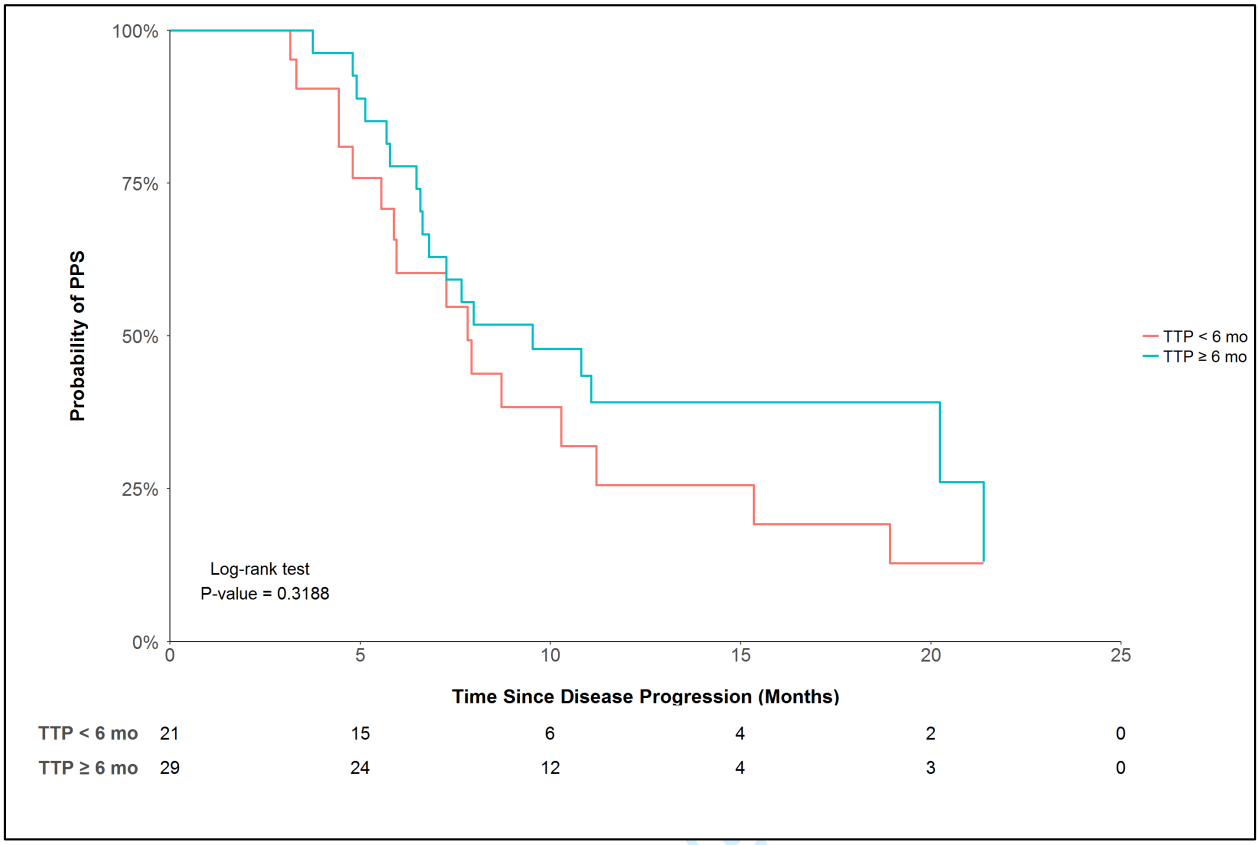
B. Cohort B



Legend

Abbreviations: PPS = post-progression survival; TTP = time to progression.

Supplemental Figure 2. Kaplan-Meier Analysis of PPS in patients stratified by duration of TTP: Landmark Analysis (excluding patients who died/were censored prior to 3 months follow-up)



Legend

Abbreviations: PPS = post-progression survival; TTP = time to progression.

Supplemental Table 1. Status of Patients Excluded from the Analysis who did not Experience Disease Progression

Patient Status, N (%)	Combined Cohort N = 51	Cohort A N = 21	Cohort B N = 30
Censored, follow-up ended	14 (27.5)	11 (52.4)	3 (10.0)
Censored, follow-up ongoing	28 (54.9)	6 (28.6)	22 (73.3)
Died	9 (17.6)	4 (19.0)	5 (16.7)

Caption

Abbreviations: N = number.

Supplementary Table 2. Summary of Patient Characteristics: Cohorts A and B

Patient characteristic	Cohort A N = 57	Cohort B N = 27
Demographics, N (%)		
Age < 65 years	27 (47.4)	14 (51.9)
Male	29 (50.9)	13 (48.1)
Race (White)[i]	43 (75.4)	24 (88.9)
History of tobacco use, N (%)		
Current or former smoker	34 (59.6)	19 (70.4)
Disease and treatment characteristics,		
ECOG performance status score >1 before or at progression, N (%)	12 (21.1)	2 (7.4)
Time since diagnosis to study treatment initiation (months), mean ± SD	22.1 ± 20.0	21.0 ± 15.9
Prior anti-cancer therapy, N (%)		
Number of prior systemic regimens for metastatic disease >1	27 (47.4)	11 (40.7)
Radiotherapy	22 (38.6)	7 (25.9)
Maintenance therapy	11 (19.3)	8 (29.6)
Response to the most recent prior therapy for metastatic disease, N (%)[ii]		
Complete or partial response	11 (19.3)	7 (25.9)

Caption

Abbreviations: ECOG = Eastern Cooperative Oncology Group; mg = milligrams; N = number; SD = standard deviation.

Notes:

[i] Other reported races included Asian, Black or African American, and Mixed.

[ii] Response to the most recent prior anti-cancer therapy included complete response, partial response, stable disease, and progressive disease. Seven patients in Cohort A (including one patient with a non-

evaluable response) and one patient in Cohort B had an unknown response. These patients were imputed as non-complete or partial responders.

Supplemental Table 3. Summary of PPS, Stratified by Duration of TTP: Cohorts A and B

Cohort	N	Number of post-progression deaths	Median PPS (months)	95% CI
Cohort A				
TTP ≥ 6 months	22	13	11.1	(6.8-21.4)
TTP < 6 months	35	31	2.2	(1.4-4.4)
Cohort B				
TTP ≥ 6 months	13	6	6.6	(4.9-NR)
TTP < 6 months	14	10	4.1	(1.3-7.9)

Caption

Abbreviations: CI = confidence internal; N = number; NR = not reached; PPS = post-progression survival; TTP = time to progression.

Supplementary Table 4. Summary of Patient Characteristics in Landmark Analysis (excluding patients who died/were censored prior to 3 months follow-up)

Patient characteristic	Total N = 50	Time to progression ≥ 6 months N = 29	Time to progression < 6 months N = 21	P-value
Demographics, N (%)				
Age < 65 years	20 (40.0%)	10 (34.5%)	10 (47.6%)	0.52
Male	20 (40.0%)	12 (41.4%)	8 (38.1%)	1.00
Race (White)[i]	39 (78.0%)	24 (82.8%)	15 (71.4%)	0.54
History of tobacco use, N (%)				
Current or former smoker	27 (54.0%)	13 (44.8%)	14 (66.7%)	0.21
Disease and treatment characteristics				
ECOG performance status before or at progression > 1, N (%)	3 (6.0%)	1 (3.4%)	2 (9.5%)	0.77
Time since diagnosis to study treatment initiation (month), mean ± SD	23.1 ± 17.3	22.3 ± 16.8	24.1 ± 18.4	0.81
Prior anti-cancer therapy, N (%)				
Number of prior systemic regimens for metastatic disease > 1	23 (46.0%)	11 (37.9%)	12 (57.1%)	0.29
Radiotherapy	16 (32.0%)	8 (27.6%)	8 (38.1%)	0.63
Maintenance therapy	14 (28.0%)	8 (27.6%)	6 (28.6%)	1.00
Response to the most recent prior therapy for metastatic disease, N (%)[ii]				
Complete or partial response	12 (24.0%)	5 (17.2%)	7 (33.3%)	0.33

Caption

Abbreviations: ECOG = Eastern Cooperative Oncology Group; N = number; SD = standard deviation.

Notes:

[i] Other reported races included Asian, Black or African American, and Mixed.

[ii] Response to the most recent prior anti-cancer therapy included complete response, partial response, stable disease, and progressive disease.

Supplementary Table 5. The Multivariable Cox Model of the Association between TTP and PPS in the Combined Cohort: Landmark Analysis (excluding patients who died/were censored prior to 3 months follow-up)

	Combined Cohort		
	HR	**95% CI**	***P***
Time to progression in 3-month increment(s)	0.84	(0.63-1.13)	0.242
Age < 65 years Yes vs. No	1.46	(0.59-3.61)	0.411
Male Yes vs. No	0.59	(0.25-1.41)	0.236
Race (White) Yes vs. No	1.17	(0.31-4.41)	0.814
Current or former smoker Yes vs. No	1.25	(0.46-3.41)	0.662
ECOG performance status before or at progression > 1 Yes vs. No	6.50	(1.02-41.50)	0.048 *
Time since diagnosis to study treatment initiation in 1-month increment(s)	0.97	(0.94-1.01)	0.115
Number of prior systemic regimens for metastatic disease > 1 Yes vs. No	1.69	(0.56-5.16)	0.355
Prior radiotherapy Yes vs. No	0.90	(0.37-2.18)	0.809
Prior maintenance therapy Yes vs. No	0.44	(0.16-1.22)	0.114
Complete or partial response to most recent prior therapy for metastatic disease Yes vs. No	0.56	(0.20-1.59)	0.279

Caption

Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; PPS = post-progression survival; TTP = time to progression. *p<0.05