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A Phase 1/1b Study Evaluating Trametinib Plus Docetaxel or Pemetrexed in Patients With Advanced Non-Small Cell Lung Cancer

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Trial Registration: Safety and Tolerability Study of GSK1120212, a MEK Inhibitor, in Combination With Docetaxel, Erlotinib, Pemetrexed, Pemetrexed Plus Carboplatin, Pemetrexed Plus Cisplatin, or Nab-Paclitaxel. NCT01192165.

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ABSTRACT

Objectives: This two-part study evaluated trametinib, a MEK1/2 inhibitor, in combination with anticancer agents. Inhibition of MEK, a downstream effector of KRAS, demonstrated preclinical synergy with chemotherapy in KRAS-mutant NSCLC cell lines. Part 1 of this study identified recommended phase 2 doses of trametinib combinations. Part 2, reported herein, evaluated the safety, tolerability, pharmacokinetics, and efficacy of trametinib combinations in patients with NSCLC with and without KRAS mutations.

Methods: Phase 1b evaluated trametinib plus docetaxel with growth factor support (trametinib, 2.0 mg once daily, and docetaxel, 75 mg/m² every 3 weeks) or pemetrexed (trametinib, 1.5 mg once daily, and pemetrexed, 500 mg/m² every 3 weeks). Eligibility criteria for the expansion cohorts included metastatic NSCLC with measurable disease, known KRAS mutation status, Eastern Cooperative Oncology Group performance status of 1 or lower, and no more than two prior regimens.

Results: The primary end point of overall response rate (ORR) was met for both combinations. A confirmed partial response (PR) was observed in 10 of the 47 patients with NSCLC who received trametinib plus docetaxel (21%). The ORR was 18% (four PRs in 22 patients) in those with KRAS wild-type NSCLC versus 24% (six PRs in 25 patients) in those with KRAS-mutant NSCLC. Of the 42 patients with NSCLC treated with trametinib plus pemetrexed, six (14%) had a PR; the ORR was 17% (four of 23) in patients with KRAS-mutated NSCLC versus 11% (two of 19) in KRAS wild-type NSCLC. Adverse events—most commonly diarrhea, nausea, and fatigue—were manageable.

Conclusions: Trametinib-plus-chemotherapy combinations were tolerable. Clinical activity exceeding the ORRs previously reported with docetaxel or pemetrexed alone in KRAS-mutated NSCLC and meeting prespecified criteria was observed.

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Keywords: Trametinib; MEK inhibitor; NSCLC; KRAS mutations

Introduction

Lung cancer is the leading cause of death from cancer in both men and women worldwide. Despite recent advances, the overall 5-year survival rate remains low,

estimated at only 18%.¹ Lung cancers are highly genetically diverse, with mutations occurring in common oncogenic pathways.² NSCLC makes up 85% of all lung cancers, with the most common histological subtype being adenocarcinoma.³

KRAS is a frequently mutated oncogene in NSCLC, with a mutation rate of approximately 25% in lung adenocarcinomas.^{4,5} Many KRAS mutation subtypes are found in NSCLC, and most, such as the common G12C subtype, are highly associated with tobacco carcinogenesis.⁶ The presence of KRAS mutations in NSCLC is prognostic of poor survival.^{4,7} Efforts to target mutant KRAS directly have been challenging owing to its tight binding affinity to guanosine triphosphate/guanosine diphosphate.^{6,8} Although cytotoxic chemotherapy remains the standard of care for patients with KRAS-mutated NSCLC, response and survival rates are modest.^{4,9} The presence of KRAS mutations has also been reported to be predictive of a lack of benefit from platinum and antimetabolic therapy and EGFR tyrosine kinase inhibitor therapy.^{9,10} Hence, NSCLC with KRAS mutations represents an unmet need for targeted therapy.

Data suggest that inhibition of the mitogen-activated protein kinase enzymes MEK1 and MEK2, which are downstream effectors of KRAS, could be a clinically relevant approach for the treatment of patients with KRAS-positive NSCLC.^{11,12} Trametinib (GSK1120212) is a reversible and highly selective allosteric inhibitor of MEK1 and MEK2 activation and kinase activity.¹³ It has been shown to have clinical activity in a variety of malignancies, including NSCLC.^{14,15} Because of the presence of compensatory signaling pathways, targeting of MEK alone may not achieve a significant antitumor effect.¹⁶ In a randomized phase 2 study, trametinib monotherapy was not found to be significantly better than docetaxel in KRAS-mutant NSCLC.¹⁴ However, in preclinical studies, trametinib-based combinations with other anticancer agents demonstrated enhanced efficacy compared with either drug alone.¹²

This study was conducted to assess the safety and tolerability of trametinib in combination with chemotherapy or erlotinib in patients with advanced solid tumors. In phase 1,¹⁷ combinations of trametinib with docetaxel with growth factor support and with pemetrexed demonstrated acceptable tolerability, with only one dose-limiting toxicity (mucositis) observed at the recommended phase 2 dose (RP2D) of trametinib plus

docetaxel (trametinib, 2.0 mg once daily, and docetaxel, 75 mg/m² every 3 weeks) and no dose-limiting toxicities observed at the RP2D of trametinib plus pemetrexed (trametinib, 1.5 mg once daily, and pemetrexed, 500 mg/m² every 3 weeks) in patients with advanced solid tumors. In both combinations, the pharmacokinetic profile of each agent was similar to that of monotherapy, suggesting no drug-drug interactions. Notably, both combinations showed clinical activity, particularly in patients with NSCLC, with a partial response (PR) in three of seven patients with NSCLC in the trametinib-plus-docetaxel cohort and two of seven patients with NSCLC in the trametinib-plus-pemetrexed cohort. Phase 1b, reported herein, aimed to evaluate trametinib in combination with docetaxel or pemetrexed at the RP2D in an expansion cohort of patients with advanced NSCLC, with or without *KRAS* mutations. The primary objective was to assess safety and tolerability. Secondary objectives included characterizing the population pharmacokinetics (PK) of trametinib in combination with the selected anticancer agents and evaluating the clinical activity on the basis of tumor response in patients with different *KRAS* mutation subtypes.

Materials and Methods

Patient Eligibility

Inclusion criteria were patient age at least 18 years, Eastern Cooperative Oncology Group performance status of 1 or lower, and adequate organ function. Patients had a histologically or cytologically confirmed diagnosis of metastatic NSCLC, measurable disease per the Response Evaluation Criteria in Solid Tumors, version 1.1,¹⁸ and no more than two prior anticancer treatment regimens. Mutations in the *KRAS* gene were determined locally by a Clinical Laboratory Improvement Amendments–certified laboratory or equivalent at the time of screening. The main exclusion criteria were prior anticancer therapy within 3 weeks of first study dose; symptomatic or untreated leptomeningeal or brain metastases; history or current evidence/risk of retinal vein occlusion or central serous retinopathy; history of interstitial lung disease or pneumonitis; and evidence of severe or uncontrolled systemic diseases. This study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the institutional review board at each institution. All patients provided written informed consent.

Study Design

This was a phase 1/1b open-label, multicenter, non-randomized study evaluating the safety and tolerability of trametinib dosed in combination with different

anticancer agents. The phase 1 component, a standard three-plus-three dose escalation design, determined the RP2D of trametinib given in combination with chemotherapy or erlotinib; results are discussed elsewhere.¹⁷ The phase 1b component, reported herein, further explored the safety and antitumor activity of trametinib in combination with either docetaxel plus growth factor (granulocyte colony-stimulating factor [G-CSF]) or pemetrexed at the RP2D in expansion cohorts of patients with NSCLC with and without *KRAS* mutations. Each expansion cohort was designed to enroll up to 40 patients, including 20 with *KRAS*-mutated NSCLC and 20 with *KRAS* wild-type NSCLC or unknown mutation status. Patients were stratified on the basis of *KRAS* mutation status for entry into treatment cohorts.

Statistical Considerations. The primary objective of this study was to determine the RP2D of trametinib administered in combination with selected anticancer agents. Analyses were descriptive and exploratory, focusing on comparisons between dosing cohorts within treatment groups. Efficacy was evaluated to decide whether to stop a trametinib-based treatment arm for futility (i.e., the antitumor activity was no better than the prespecified historical response rate) or proceed with further development if there were sufficient signs of clinical activity. In the expansion cohort portion of the trial, overall response rate (ORR) was the primary end point for this assessment. For the trametinib-plus-docetaxel cohort, the historical reference ORR for docetaxel alone was 3.7% in *KRAS*-mutated NSCLC and 11.7% in *KRAS* wild-type NSCLC. The minimum acceptable ORRs for the combination warranting further study were 15% and 20%, respectively.¹⁹ For the trametinib-plus-pemetrexed combination, the historical reference ORR for pemetrexed alone was 10%, with insufficient data to distinguish between *KRAS*-mutated and *KRAS* wild-type subgroups.²⁰ The minimum acceptable ORRs for the combination warranting further study were 15% and 20%, respectively. Each NSCLC-based expansion cohort was to enroll up to 40 patients, including up to 20 with previously documented *KRAS*-positive disease.

This sample size was chosen on the basis of a reasonable no-go decision rule as determined by the Bayesian posterior probability that response rates after trametinib-based combination therapy are greater than or equal to the lowest acceptable response rates.²¹ With a sample size of 20 patients, the treatment cohort would be considered as not showing sufficient clinical activity if the Bayesian posterior probability of response rate greater than or equal to the lowest acceptable response rate was very low (i.e., ≤ 0.05). If the Bayesian posterior probability of response rate greater than or equal to the

lowest acceptable response rate was relatively high (i.e., ≥ 0.6), further development of the treatment was warranted.

Dosing and Administration

The combinations of trametinib with docetaxel or pemetrexed were administered at the RP2D. Docetaxel (75 mg/m²) was given every 3 weeks intravenously over a 1-hour infusion with oral corticosteroid premedication. Growth factor support (G-CSF) was given at the beginning of the first cycle of treatment and continued in all subsequent cycles to reduce the risk of febrile neutropenia according to recommendations for the use of myeloid growth factors by the National Comprehensive Cancer Network.²² Intravenous pemetrexed (500 mg/m²) was given every 3 weeks over a 10-minute infusion with vitamin B₁₂ and folic acid supplementation. Patients received trametinib orally once daily, either 2 mg with docetaxel or 1.5 mg with pemetrexed.

Assessments

A safety analysis, including but not limited to monitoring of adverse events (AEs), serious AEs (SAEs), clinical laboratory test results, vital signs, electrocardiogram results, and physical examination results, was performed in all patients. AEs and SAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The investigator or site staff was responsible for detecting, documenting, and reporting events that met the definition of an AE or SAE. Safety and baseline characteristics are reported for all patients treated at the RP2D.

PK

Blood samples for trametinib were taken after 14 days of consecutive dosing to ensure achievement of a steady state and for docetaxel/pemetrexed on the same day as the infusion. Hence, blood samples for all PK analyses were collected on day 22 both before administration of the dose and 60 minutes after the dose or start of infusion. Plasma samples for the trametinib determinations were analyzed by GlaxoSmithKline (Collegeville, PA) using a validated analytical method based on liquid-liquid extraction followed by high-performance liquid chromatography-tandem mass spectrometry analysis. Docetaxel and pemetrexed samples were analyzed by Pharmanet Canada, Inc. (Quebec City, Ontario, Canada) using validated high-performance liquid chromatography-tandem mass spectrometry and automated liquid-liquid extraction.

PK parameters for docetaxel were derived from both the dose escalation (n = 22) and dose expansion

(n = 17) cohorts. The addition of G-CSF was not expected to influence the PK on the basis of its mechanism of action. Therefore, data were pooled across cohorts (with and without G-CSF). PK parameters for pemetrexed were derived from 13 patients treated in the dose escalation cohort and 20 patients treated in the dose expansion cohort. All unscheduled visits were excluded from the analysis. As several patients did not continue to receive the study treatment beyond cycle 1, only PK data from week 3 of cycle 1 are presented.

Population PK

The population PK aspects of this study were conducted within GlaxoSmithKline. Previously, a population PK model was established and validated in patients with *BRAF*-mutated melanoma and NSCLC.¹⁴ The trametinib exposure and demographics of patients with NSCLC from a previous study were similar to those in this study, and data were pooled across studies.²³ The final analysis contained 1826 observations.^{14,15,24} The population PK database included trametinib plasma concentration versus time data and covariates such as age, race, sex, and ethnicity. Data evaluation was performed by using a combination of exploratory data analysis and nonlinear mixed effects modeling implemented in NONMEM 7.1.2 (ICON Development Solutions, Ellicott City, MD). The final model was evaluated by using a visual predictive check.

Efficacy

Efficacy is summarized for all patients who received at least one dose of combination treatment (trametinib plus docetaxel or trametinib plus pemetrexed) at the RP2D. Tumor response and disease progression were determined on the basis of the Response Evaluation Criteria in Solid Tumors. Response assessments were conducted every 6 weeks. Confirmed ORR was defined as the percentage of patients achieving a confirmed complete response or PR from the start of treatment until disease progression. Confirmation of response occurred no earlier than 4 weeks after the criteria for response were first met. Disease control rate (DCR) was defined as complete response rate plus PR rate plus stable disease rate.

Results

Baseline Characteristics

A total of 95 patients received the RP2D across both treatment combinations. Baseline characteristics are summarized in Table 1. Of the 49 patients who received trametinib plus docetaxel with G-CSF and were treated at the RP2D, six were in the dose escalation

Table 1. Baseline Characteristics of All Patients Treated at the Recommended Phase 2 Doses

Characteristic	Trametinib + Docetaxel ^a (n = 49)	Trametinib + Pemetrexed (n = 46)
Median age (range), y	60 (30-82)	62.5 (37-81)
Sex, n (%)		
Male	29 (59)	17 (37)
Female	20 (41)	29 (63)
Race, n (%)		
White	42 (86)	39 (85)
East Asian	2 (4)	2 (4)
Black	1 (2)	2 (4)
Other	1 (2)	1 (2)
Unknown	3 (6)	2 (4)
Primary tumor type, n (%)		
NSCLC	47 (96)	42 (91)
Head and neck cancer	1 (2)	0
Breast cancer	1 (2)	0
Melanoma	0	2 (4)
Ocular melanoma	0	1 (2)
Mesothelioma	0	1 (2)
Histological subtype, n (%)		
Adenocarcinoma	34 (69)	31 (67)
Squamous	7 (14)	4 (9)
Large cell carcinoma	1 (2)	0
Adenosquamous carcinoma	1 (2)	1 (2)
Other ^b	6 (12)	10 (22)
History of brain metastases, n (%)		
Yes	6 (12)	7 (15)
No	43 (88)	39 (85)
Prior chemotherapy, n (%)		
0 regimens	0	3 (7)
1 regimen	27 (55)	18 (39)
2 regimens	20 (41)	18 (39)
3 regimens	0	2 (4)
≥4 regimens ^c	2 (4)	5 (11)

Note: All patients, including those with non-NSCLC, during the dose escalation phase.

^aDocetaxel administered with growth factor.

^bIncludes (but not limited to) poorly differentiated adenocarcinoma, mucinous adenocarcinoma, bronchoalveolar carcinoma, and unknown histological subtype.

^cPatients enrolled before protocol amendment restricting number of previous chemotherapies.

cohort and 43 were in the dose expansion cohort. Of all the patients enrolled at the RP2D, one patient had head and neck cancer, one had breast cancer, and 47 had NSCLC. Most of the patients were white (86%), 41% were women, and their median age was 60 years.

Of the patients who received trametinib plus pemetrexed, a total of 46 received the RP2D; six of these were in the dose escalation cohort (two with melanoma, one with mesothelioma, one with ocular melanoma, and two with NSCLC), and the remaining 40, who had NSCLC, were in the dose expansion cohort. Most patients treated at the RP2D (85%) were white, approximately

two-thirds (63%) were women, and their median age was 62.5 years.

Safety

In all patients who received the RP2D, the most frequently reported AEs of any grade considered by investigators to be related to study treatments were diarrhea, nausea, and fatigue (Table 2). A median of four cycles were administered in both cohorts.

In the trametinib-plus-docetaxel with G-CSF cohort, the most common grade 3 AEs were neutropenia (five patients [10%]), hyponatremia (seven patients [14%]), and anemia (six patients [14%]). Neutropenia was the most common grade 4 AE; it was seen in six patients (12%). Febrile neutropenia occurred in only two patients (4%). Two patients experienced grade 5 AEs. One patient with a history of hypertension and coronary artery calcification reported grade 2 generalized weakness on study day 6 but did not seek medical attention. On study day 7 the patient was hospitalized with grade 4 cardiogenic shock and grade 4 respiratory failure and had a cardiac arrest that was considered possibly related to the study treatment. A second patient, with a history of hypertension, hyperlipidemia, and a past stroke, experienced a cerebrovascular accident considered unrelated to study treatment. Dose reduction due to AEs was reported in 21 patients (43%), and 39 (80%) had a dose interruption or delay; 13 patients (27%) discontinued treatment on account of AEs. Fatigue (6%), dyspnea (4%), and neutropenia (4%) were the most common (occurring in ≥2 patients) AEs leading to permanent discontinuation. The median rate of adherence to trametinib dose administration was 83% (range 34%–105%) in the cohort that received trametinib plus docetaxel with G-CSF. One patient accidentally took more medication than was prescribed for a period, which led to the overall adherence rate of 105%. Dose interruption of trametinib and docetaxel occurred in 41 patients (84%) and 18 patients (37%), respectively. Patients required dose reductions for both trametinib (37%) and docetaxel (27%).

In the trametinib-plus-pemetrexed cohort, all patients reported AEs, and nearly all patients (44 [96%]) had AEs that the investigators considered related to study treatment. The most common AEs in this cohort were nausea (30 patients [65%]) and fatigue (26 patients [57%]) (Table 2). The most common grade 3 AEs were neutropenia, hyponatremia, and anemia. Neutropenia was also the most common grade 4 AE. Four patients in this cohort had grade 5 AEs. Eight patients (17%) were reported to have SAEs, and four deaths were due to SAEs; of these, two deaths, caused by cardiogenic shock and lung infection, were considered to be related to study treatment. The other two deaths resulted from acute cardiac arrest in patients with a history of hypertension, atrial

Table 2. Summary of All Treatment-Associated Adverse Events Reported in at Least 20% of Patients Who Received the Recommended Phase 2 Doses

Adverse Event, n (%)	Trametinib + Docetaxel ^a (n = 49)		Trametinib + Pemetrexed (n = 46)	
	Any Grade ^b	Grade 3 or 4 ^c	Any Grade ^b	Grade 3 or 4 ^c
Alopecia	11 (22)	0	0	0
Anemia	22 (45)	8 (16)	19 (41)	6 (13)
AST increased	0	0	13 (28)	2 (4)
Asthenia	20 (41)	2 (4)	9 (20)	4 (9)
Constipation	11 (22)	0	15 (33)	0
Cough	12 (24)	0	0	0
Decreased appetite	19 (39)	0	15 (33)	2 (4)
Dermatitis acneiform	17 (35)	0	9 (20)	0
Diarrhea	33 (67)	5 (10)	20 (43)	2 (4)
Dry skin	10 (20)	0	11 (24)	0
Dyspnea	15 (31)	2 (4)	16 (35)	3 (7)
Fatigue	25 (51)	5 (10)	26 (57)	0
Hypoalbuminemia	15 (31)	2 (4)	13 (28)	0
Hyponatremia	0	0	9 (20)	7 (15)
Mucosal inflammation	16 (33)	2 (4)	10 (22)	0
Nausea	22 (45)	0	30 (65)	3 (7)
Neutropenia	12 (24)	11 (22)	16 (35)	9 (20)
Peripheral edema	16 (33)	0	24 (52)	0
Pyrexia	10 (20)	0	0	0
Stomatitis	10 (20)	2 (4)	0	0
Rash	18 (37)	0	20 (43)	0
Vomiting	18 (37)	0	15 (33)	0
Any SAE	18 (37)		16 (35)	

Note: All patients, including those with non-NSCLC, during the dose escalation phase.

^aDocetaxel administered with growth factor.

^bReported in more than 20% of patients.

^cReported in at least two patients.

AST, aspartate aminotransferase; SAE, serious adverse event.

fibrillation, and hyperlipidemia and a family history of coronary artery disease and pneumonia. Both were considered unrelated to study treatment.

Of the patients who received the RP2D of trametinib plus pemetrexed, 13 (28%) discontinued treatment on account of AEs. The most common (occurring in ≥ 2 patients) AEs leading to treatment discontinuation in this cohort were peripheral edema (7%), left ventricular dysfunction (4%), and pneumonia (4%). Dose interruptions of trametinib occurred in 37 patients (80%). Pemetrexed dose was delayed at least once in 17 patients (37%). Dose reductions of trametinib and pemetrexed were required in 23 patients (50%) and seven patients (15%), respectively.

Efficacy

Trametinib-Plus-Docetaxel Cohort. Of the 49 patients who received trametinib plus docetaxel plus G-CSF, 10 (20%) had a PR and 21 (43%) had stable disease, for a DCR of 63%. Among 47 patients with NSCLC, 10 (21%) had a confirmed PR and an additional 20 (43%) had stable disease, for a DCR of 64%; the median progression-free survival (PFS) was 3.5 months

(95% confidence interval [CI]: 2.6–6.3) (Table 3). Of the six patients in this cohort with the squamous cell carcinoma histological subtype, one had a confirmed PR, three had stable disease, one had progressive disease, and one was not evaluable for a response.

Patients with *KRAS*-mutated NSCLC had an ORR of 24% (six patients had a PR) and a DCR of 60% (nine patients had stable disease) (Table 3); the median PFS was 3.4 months (95% CI: 1.5–6.3) (Fig. 1). Four of 10 patients with the G12C mutation achieved a PR and four had stable disease, for a DCR of 80% (eight of 10) (Fig. 2A). This favorable trend was not observed for any other *KRAS* mutation subtype, nor was it seen in the G12C subgroup that received trametinib plus pemetrexed. In patients with NSCLC with *KRAS* wild-type or unknown mutation status, the ORR was 18% (four patients had a PR), 11 patients (50%) had stable disease, the DCR was 68% and the median PFS was 4.2 months (95% CI: 2.2–11.0) (Table 3).

Trametinib-Plus-Pemetrexed Cohort. Of the 46 patients who received trametinib plus pemetrexed, six (13%) had a confirmed PR and 25 (54%) had stable

Table 3. Investigator-Assessed Best Confirmed Response to Therapy for Patients With NSCLC Who Received the Recommended Phase 2 Dose, by *KRAS* Mutation Status

Clinical Activity Endpoint	Trametinib + Docetaxel ^a (n = 47)			Trametinib + Pemetrexed (n = 42)		
	<i>KRAS</i> WT/Unknown (n = 22)	<i>KRAS</i> Mutant (n = 25)	Total (n = 47)	<i>KRAS</i> WT/Unknown (n = 19)	<i>KRAS</i> Mutant (n = 23)	Total (n = 42)
CR, n (%)	0	0	0	0	0	0
PR, n (%)	4 (18)	6 (24)	10 (21)	2 (11)	4 (17)	6 (14)
ORR, n (%) ^b	4 (18)	6 (24)	10 (21)	2 (11)	4 (17)	6 (14)
(95% CI)	(5.2-40.3)	(9.4-45.1)	(10.7-35.7)	(1.3-33.1)	(5.0-38.8)	(5.4-28.5)
Stable disease, n (%)	11 (50)	9 (36)	20 (43)	12 (63)	11 (48)	23 (55)
PD, n (%)	4 (18)	6 (24)	10 (21)	1 (5)	7 (30)	8 (19)
NE, n (%)	3 (14)	4 (16)	7 (15)	4 (21)	1 (4)	5 (12)
Median PFS, mo	4.2	3.4	3.5	5.8	4.0	5.1
(95% CI)	(2.2-11.0)	(1.5-6.3)	(2.6-6.3)	(2.8-7.1)	(1.3-8.4)	(2.8-7.1)

Note: Responses confirmed no earlier than 4 weeks after criteria for response were first met.

^aDocetaxel administered with growth factor.

^bORR was CR plus PR.

WT, wild type; CR, complete response; PR, partial response; ORR, overall response rate; CI, confidence interval; PD, progressive disease; NE, not evaluable; PFS, progression-free survival.

disease, for a DCR of 67%. Among the 42 patients in the cohort with NSCLC, the ORR and DCR were 14% (six patients with PR) and 69% (23 patients with stable disease), respectively. None of the four patients in this cohort with the squamous cell carcinoma histological subtype had a confirmed response (two patients each had a best response of stable disease and progressive disease). The median PFS was 5.1 months

(95% CI: 2.8–7.1) (Table 3 and Fig. 1). Patients with *KRAS*-mutated NSCLC had a response rate of 17% versus 11% in those with *KRAS* wild-type NSCLC (Table 3 and Fig. 2B). The estimated median PFS was 4.0 months (95% CI: 1.3–8.4) in patients with *KRAS*-mutated NSCLC and 5.8 months (95% CI: 2.8–7.1) in those with *KRAS* wild-type or unknown mutation status (see Table 3).

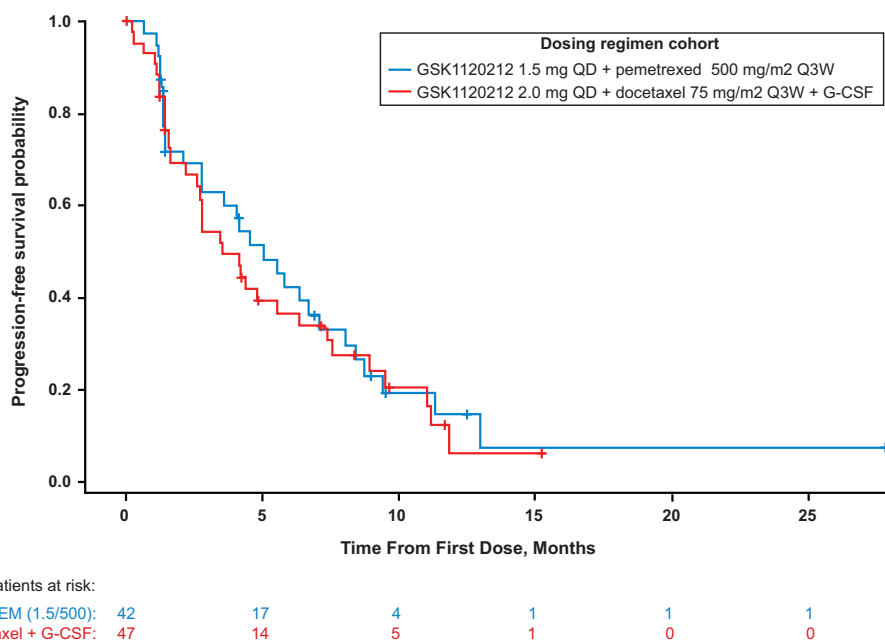


Figure 1. Kaplan-Meier plot of progression-free survival in patients with NSCLC treated with trametinib plus docetaxel (red line) and trametinib plus pemetrexed (blue line). +, censored; G-CSF, granulocyte colony-stimulating factor; PEM, pemetrexed; QD, once daily; Q3W, every 3 weeks; T, trametinib.

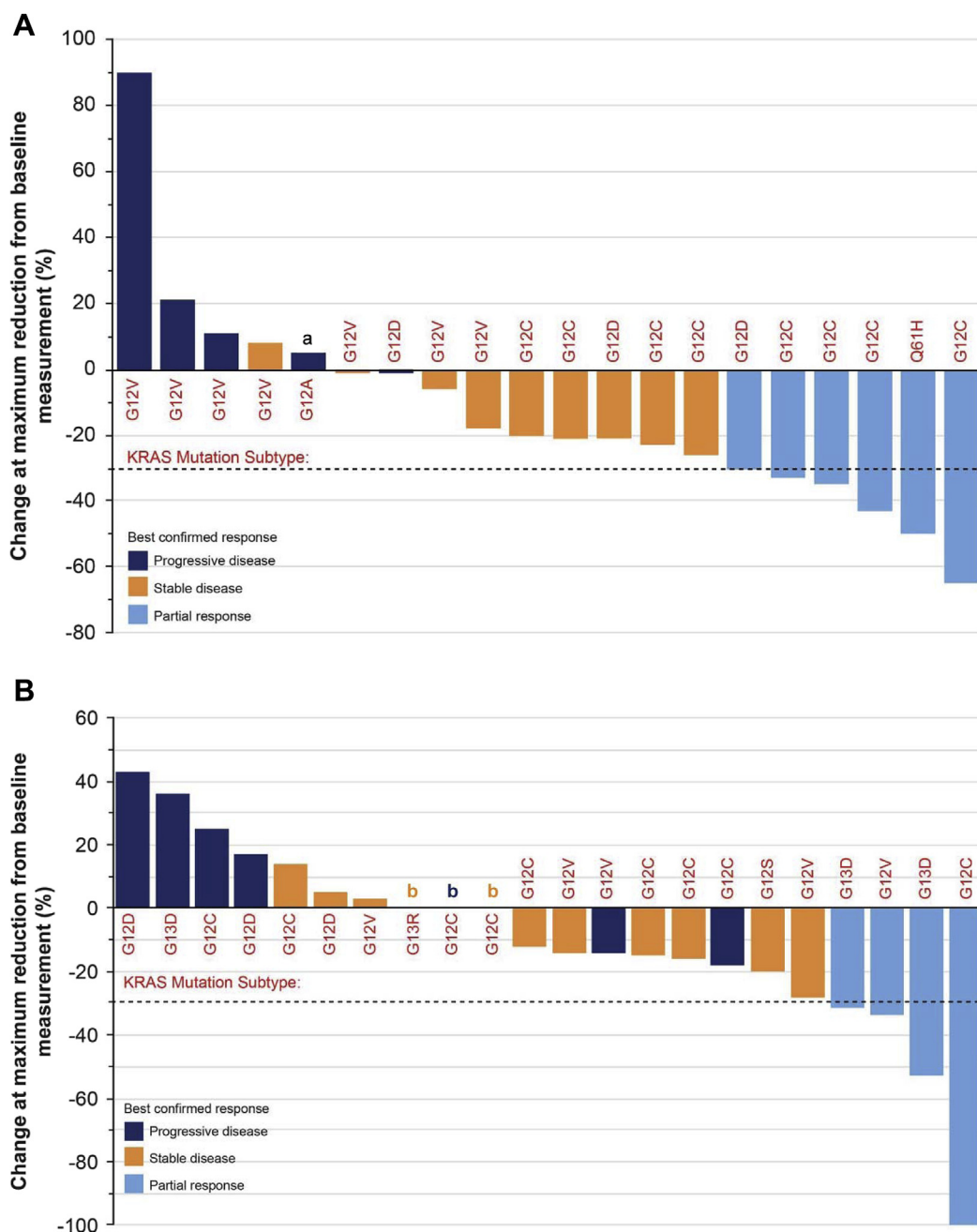


Figure 2. Investigator-assessed percent change at maximum reduction from baseline in tumor measurement in the trametinib-plus-docetaxel cohort (A) and trametinib-plus-pemetrexed cohort (B). In the trametinib-plus-docetaxel cohort of patients with *KRAS*-mutant NSCLC, five patients had no postbaseline evaluation of the target lesion (one patient had progressive disease and a *KRAS* G12D mutation; four patients were not evaluable for response, two with *KRAS* G12C and two with *KRAS* G12V). In the trametinib-plus-pemetrexed cohort of patients with *KRAS*-mutant NSCLC, one patient had no postbaseline evaluation of the target lesion (the patient was not evaluable for response and had a *KRAS* G12C mutation). ^aSquamous cell histological subtype. ^bMaximum change from baseline is 0%.

PK and Population PK

For docetaxel (with or without G-CSF), the mean area under the curve was 1847 ng•h/mL, the mean maximum plasma drug concentration was 1802 ng/mL, and steady-state clearance was 72.8 L/h. For pemetrexed, the mean area under the curve, mean maximum plasma drug

concentration, and steady-state clearance were 117,717 ng•h/mL, 44,152 ng/mL, and 6.62 L/h, respectively.

The population PK analysis suggested a two-compartment model with first-order absorption and elimination, including the following: dual absorption rate constants (K_{a1} and K_{a2}); trametinib apparent total

clearance of the drug from plasma after oral administration (CL/F); apparent volumes of distribution for central and peripheral compartments (V₂/F and V₃/F); intercompartmental clearance with interindividual variability in CL/F, V₂/F, V₃/F, intercompartmental clearance, and Ka₁; and a correlation between CL/F and V₂/F. The covariates assessed did not explain additional variability. The final model provided reasonable population mean PK parameter estimates with relatively good precision (<28% relative SE). The mean population CL/F and V₂/F were 4.63 L/h and 128 L, respectively (Table S1). Interindividual variability was less than 40% for all parameters, with the exception of V₂/F and Ka₁. Random residual variability was best described by an additive error model, and the final model was validated by using a visual predictive check. The observed trametinib concentrations fell within the predicted mean 95% CIs, suggesting that the model adequately described the observed data (Supplementary Fig. S1). The mean population clearance in patients from the current study was within 5% of the mean population clearance from a phase 2 study in patients with NSCLC. The current population PK model can be used in future exposure-response analyses and in possible combination studies.

Discussion

Despite recent advances in personalized therapy for NSCLC with EGFR- or ALK-targeting agents, attempts at targeted inhibition of KRAS have been unsuccessful.^{6,8} Cytotoxic chemotherapy remains the standard of care for patients with KRAS-mutant disease. Although several trials have reported lower rates of response to chemotherapy in patients with KRAS-mutated lung cancer, the role of KRAS mutation status as a predictive marker to therapy is controversial. Demonstrating the low ORRs observed with chemotherapy as second-line therapy for KRAS-mutated NSCLC, Douillard et al. reported differing response rates with docetaxel: 3.7% and 11.9% in patients with NSCLC harboring KRAS-mutant and KRAS wild-type NSCLC, respectively.¹⁹ In a large randomized phase 2 trial comparing docetaxel alone with the MEK inhibitor selumetinib plus docetaxel, no responses in the docetaxel arm versus 37% in the combination arm were observed, as further discussed later.²⁵ Because of the poor outcomes seen in patients with KRAS-mutant NSCLC, there is an unmet need to improve treatment outcomes in this population.⁵

Direct targeting of KRAS itself has thus far not been possible, although recent studies suggest that small molecule inhibitors with potent antitumor activity against specific KRAS subtypes (G12C) are feasible.²⁶ Therefore, the focus has been to target downstream effectors of KRAS, such as the MEK proteins, and

combine these agents with chemotherapy. In particular, combinations of MEK inhibitors with taxanes such as docetaxel have demonstrated marked enhancement of cytotoxic activity against KRAS-mutated lung cancer in vivo and in clinical trials.^{25,27} Trametinib is a reversible MEK1/2 inhibitor active in cancers with RAS-RAF-MEK pathway alterations.¹³ The current study explored the safety and tolerability of combining trametinib with either docetaxel plus G-CSF or pemetrexed and demonstrated that these combinations were tolerable, with safety profiles that were consistent with previously published data for either drug alone.¹⁴ Fatal cardiac events occurred in a total of four patients across both cohorts; of these, two were suspected to be related to treatment. In trials evaluating trametinib monotherapy in patients with BRAF-mutant metastatic melanoma, the rate of cardiomyopathy is 11%. Therefore, because of the risk of cardiac events, assessment of left ventricular ejection fraction before initiation of trametinib, 1 month after initiation, and then every 2 to 3 months is recommended.²⁸

Clinical activity was observed in patients in both cohorts. In the trametinib-plus-docetaxel cohort, the ORR was 21% in patients with NSCLC, 24% in those with KRAS-mutated disease, and 18% in those without the KRAS mutation. Although the ORR was higher in patients with KRAS-mutant NSCLC, the median PFS was numerically longer in patients with wild-type KRAS. One potential explanation for this discrepancy is that NSCLC harboring KRAS mutation may be more aggressive and patients without a response progress more rapidly. This is potentially suggested by a meta-analysis demonstrating poor prognosis in patients with KRAS-mutant NSCLC.²⁹ However, because of the limited patient numbers in our cohort, these data should be interpreted cautiously. Of note, a prior randomized phase 2 study assessing single-agent trametinib versus docetaxel in previously treated KRAS-mutant NSCLC reported an ORR of 12% in the trametinib group.¹⁴ Although a comparison between studies must be taken with caution, these data and others suggest that combinations of MEK inhibitors with docetaxel are more efficacious in KRAS-mutated NSCLC than either drug used as a single agent.³⁰ For example, a randomized phase 2 study in patients with KRAS-mutated NSCLC showed that a combination of docetaxel and the MEK inhibitor selumetinib improved ORR (37% versus 0%) and PFS (5.3 versus 2.1 months) compared with docetaxel alone. However, more patients who received combination selumetinib plus docetaxel were reported to have had SAEs, in particular, myelosuppression and febrile neutropenia (14%).²⁵ On the basis of this observation, in our study we used G-CSF prophylactically in the docetaxel cohort. This strategy proved effective, as febrile neutropenia was observed in

only two patients (4%). Notably, selumetinib plus docetaxel failed to significantly improve PFS, overall survival, or ORR versus placebo plus docetaxel in the phase 3 SELECT-1 trial.³¹

Interestingly, an exploratory subpopulation analysis of our study showed that in the group of patients with *KRAS* G12C mutations, four of 10 patients achieved a confirmed response and eight of 10 had disease control, which is consistent with preclinical observations as well as with data suggesting different downstream signaling depending on the subtype of mutation.^{32,33} Clinical activity greater than that previously reported with single-agent pemetrexed was observed. (To our knowledge, results of studies of combinations of MEK inhibitors with pemetrexed have not been previously reported.)

One limitation of the current study is the lack of a concurrent control arm, precluding direct comparisons of efficacy and safety with those of cytotoxic chemotherapy alone. Although the patient sample size in this study was relatively small, the activity in patients with *KRAS*-mutated disease and in patients with cancers harboring the G12C *KRAS* mutation is intriguing. Recently, the biological importance of co-mutations in patients with *KRAS*-mutated NSCLC has been reported. To this end, additional study may help to determine optimal regimens for *KRAS*-mutated NSCLC harboring key co-mutations such as tumor protein p53 gene (*TP53*) or liver kinase B1 gene (*LKB1*) mutations.³⁴ In summary, this study demonstrated activity and manageable toxicity of these trametinib-chemotherapy combinations, warranting further investigation in larger clinical trials.

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the initial draft. All authors contributed to subsequent drafts and made the decision to submit for publication. Drs. Gandara, Leighl, Barlesi, Zalcman, Reckamp, Shepherd, and Janku provided study materials or patients. The authors affirm the accuracy of the data and fidelity of the study to the protocol.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at <http://dx.doi.org/10.1016/j.jtho.2016.11.2218>.

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