ORIGINAL ARTICLE

A Phase 1/2 Study to Evaluate the Safety and Activity of Nivolumab in Combination With Vorolanib, a Vascular Endothelial Growth Factor Tyrosine Kinase Inhibitor, in Patients With Refractory Thoracic Tumors

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ABSTRACT

Introduction: Targeting the tumor microenvironment may enhance response to immunotherapy (immune checkpoint inhibitors) and improve outcomes for patients. This study tested the safety and efficacy of vorolanib, a novel tyrosine kinase inhibitor of vascular endothelial growth factor, platelet-derived growth factor, and c-KIT, in combination with programmed cell death protein 1 blockade using nivolumab for refractory thoracic malignancies.

Methods: This single-arm multicenter study enrolled patients with extensive-stage SCLC, thymic carcinoma, and NSCLC, either naive or had progressed on previous chemotherapy or immune checkpoint inhibitors (either primary or acquired resistance). The primary objective of phase 1 was to determine the maximum tolerated dose, and the primary end point for each dose-expansion cohort was the objective response rate.

Results: A total of 88 patients were enrolled in phase 1 (n = 11) and dose expansion (n = 77) cohorts. Transaminitis was dose-limiting and expansion proceeded with oral vorolanib 200 mg daily combined with intravenous nivolumab 240 mg every 2 weeks. The objective response rate per cohort were as follows: NSCLC naive 33% (five of 15, 95% confidence interval [CI]: 13%–60%), NSCLC primary refractory 5.9% (one of 17, 95% CI: 0%–17.6%), NSCLC acquired resistance 11.1% (two of 18, 95% CI: 0%–27.8%); SCLC 0% (zero of 18), and thymic carcinoma 11% (one of nine, 95% CI: 0%–33%). Disease control rate ranged from 11.1% in SCLC (two of 18, 0%–27.8%) to 66.7 % in thymic carcinoma (six of nine, 95% CI: 33.3%–100%). The most common adverse events were fatigue (32%), aspartate transaminase (27%) and alanine transaminase elevation

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(25%), and diarrhea (19%). Transaminitis was more common in patients with thymic carcinoma than other tumors.

Conclusions: Vorolanib plus nivolumab had a manageable safety profile and may have clinical benefits in various thoracic malignancies. The disease control rate in thymic malignancies warrants further assessment.

Keywords: Lung cancer; Thymic; Small cell; Anti-angiogenic; Nivolumab; PD-1

Introduction

Thoracic malignancies account for 21% of all cancer-related deaths in the United States, with a 5-year expected survival of 22% (Surveillance, Epidemiology, and End Results, 2022). Blockade of programmed cell death protein 1 (PD-1) relieves negative regulatory input on T cells and allows for immune activation against cancer cells. The development of agents exploiting this pathway has had a profound impact on outcomes for many patients with lung cancer and other malignancies.[1,2] Although immune checkpoint inhibitors (ICIs) have yielded impressive long-term durable control and potentially even a cure, there remains an unmet need for patients with refractory thoracic malignancies. The standard of care for both metastatic SCLC and NSCLC without a driver mutation includes ICI with or without cytotoxic chemotherapy. Thymic carcinoma is a rare tumor type with aggressive biology. PD-1 blockade can be considered in later lines of therapy in this patient population, balanced with potentially higher rates of immune-related adverse events (irAE).[3] Most patients with these thoracic malignancies will ultimately progress on systemic treatment and die of their disease. The mechanisms of resistance to ICI are not largely understood but lack of access by means of the vasculature, an immune suppressive tumor microenvironment, and lack of antigen-presenting cells may contribute.[4]

Angiogenesis contributes to tumor development and has been a target of systemic therapy through antibody blockade such as bevacizumab and ramucirumab, which block vascular endothelial growth factor (VEGF)-A or its receptor. These agents have exhibited clinical benefit in NSCLC and are approved for use by the U.S. Food and Drug Administration in combination with cytotoxic chemotherapy.[5] In addition, the use of sunitinib, a multitargeted tyrosine kinase inhibitor (TKI) that inhibits vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and c-KIT, has exhibited efficacy in patients with refractory thymic carcinoma (TC). In one study, six out of 23 assessable patients exhibited a partial response (PR), and another 15 achieved stable disease.[6] Similarly, a phase 2 study testing lenvatinib after progression after chemotherapy in thymic malignancies revealed a 38% objective response rate (ORR) and 57% achieving stable disease.[7]

The synergistic activity of VEGF blockade with ICI attempts to modulate the tumor microenvironment, decreasing immune suppressive cells and normalizing the vasculature to deliver additional immune-activating cells. Combinations of VEGF inhibitors and ICI have proven efficacious, and are approved in frontline treatment of hepatocellular carcinoma and metastatic clear cell renal cell carcinoma using either pembrolizumab or nivolumab in varying combinations with axitinib, lenvatinib, and cabozantinib, with ORR ranging from 55% to 71% that has translated to improved the median overall survival (mOS).[8–11] Some combinations of nivolumab with sunitinib or pazopanib exhibited significant toxicity, with a 70% grade 3/4 AE rate and up to 40% rates of drug discontinuation of the drug.[12]

Vorolanib is an oral multikinase inhibitor of VEGFR, PDGFR, CSF1R, c-Kit, and FMS-like tyrosine kinase 3. Vorolanib is structurally related to sunitinib and has been designed to improve the safety profile with continuous daily dosing without compromising efficacy. Vorolanib has been tested for safety and early efficacy across solid tumors in a phase 1 clinical trial, which concluded a 400 mg daily dose was tolerable as monotherapy.[13]

This multisite, phase 1/ 2 study sought to combine vorolanib with nivolumab to identify a safe combinatorial dose and test efficacy in patients with refractory thoracic malignancies. This study specifically seeks to understand whether targeting VEGF, PDGFR and the other targets of vorolanib can overcome primary or acquired resistance to checkpoint inhibition theoretically through modulation of the tumor microenvironment.

Materials and Methods

Study Design and Clinical End Points

This clinical trial was conducted in accordance with institutional review board approval (under IRB180403). This study consists of a phase 1 portion to determine the recommended combination dose of vorolanib with nivolumab, followed by a phase 2 expansion conducted in histologically confirmed, metastatic, refractory thoracic tumors (ClinicalTrials.gov identifier NCT03583086). Cohorts included patients with NSCLC naive to checkpoint inhibition, patients with NSCLC who

had progressed on previous immunotherapy with primary or acquired resistance, SCLC who had progressed on previous treatment, and TC who had progressed on previous treatment. Primary refractory is defined as radiographic progression of disease within 12 weeks after initiation of ICI treatment with a 2-week window permitted for radiograph scheduling. Acquired resistance is defined as having achieved Response Evaluation Criteria in Solid Tumors (RECIST) defined by complete or PR, or stable disease for at least 12 weeks, ultimately followed by radiographic progression of disease.

The primary end point of the phase 1 study was the recommended phase 2 dose (RP2D) of the combination, determined by a three-plus-three dose escalation design monitoring for dose-limiting toxicities experienced by Common Terminology Criteria for Adverse Events (CTCAE) criteria version 5.0. In phase 1, three patients were enrolled at dose level 1 of 200 mg vorolanib orally daily in combination with 240 mg intravenous nivolumab every 2 weeks. Dose escalation occurred by 100-mg increments of vorolanib while maintaining a flat 240 mg intravenous dosing of nivolumab. Three patients were enrolled in each cohort for assessment of treatment-related AE (TRAE) and when one patient experienced dose-limiting toxicity (DLT) as defined by CTCAE version 5, another three patients were enrolled; and when two or more of the six patients experienced DLT defined by the investigators, then stepdown in drug dose occurred.

The phase 2 portion of this trial enrolled expansion cohorts of the aforementioned groups to test efficacy in each biological setting. Patients were treated at the RP2D with vorolanib 200 mg orally daily and nivolumab 240 mg intravenously over a 30-minute infusion every 2 weeks. The primary end point of the phase 2 expansion cohorts was the ORR as measured by RECIST version 1.1. Secondary end points included progression-free survival (PFS), OS, duration of response, and disease control rate (DCR). Exploratory end points included assessment of pharmacodynamic correlates from peripheral blood to correlate with treatment response and will be reported separately.

Eligibility Criteria

Patients were at least 18 years of age and able to engage in informed consent. An Eastern Cooperative Oncology Group performance status of 0 or 1, at least one measurable lesion as defined by RECIST version 1.1, and adequate organ function were necessary for enrollment. Patients with nonhealing wounds suspected of active bleeding, significant cardiovascular disease, active autoimmune disease if requiring greater than 10 mg of prednisone, uncontrolled diabetes, human immunodeficiency virus/ acquired immunodeficiency syndrome, or active hepatitis B or C were not eligible. Patients also were not eligible when they had treatment with bevacizumab or major surgery within 28 days before starting the trial. Similarly, patients were not eligible when, within a 14-day window, they had previous anticancer treatment, radiation, or infection requiring antibiotics, or within 7 days had received granulocyte macrophage cytokine stimulating factor or granulocyte stimulating factor. Specific inclusion criteria as they varied by biological cohort include the following:

1. Patients with checkpoint inhibitor–naive NSCLC must have progressed on frontline cytotoxic chemotherapy or have refused chemotherapy and may have received up to three previous treatment regimens for stage IV disease provided no previous regimens included checkpoint inhibition or oral TKI, though previous bevacizumab or ramucirumab was allowed. This cohort closed early because of challenges with enrollment after the approval of frontline carboplatin, pemetrexed, and pembrolizumab.
2. Patients with NSCLC with progression on ICI may have received up to three previous treatment regimens for stage IV disease provided none included oral VEGFR TKI, though previous bevacizumab or ramucirumab was allowed. Patients in this cohort could have EGFR, ALK, ROS1, and BRAF-mutated NSCLC, but must have progressed on appropriately targeted TKI and could have received an unlimited number of previous regimens. The patients with NSCLC having acquired and primary resistance cohort closed at interim analysis owing to failure of meeting efficacy end point.
3. Patients with TC who were not eligible for surgical resection and could have received any number of previous lines of therapy provided none included checkpoint inhibition or oral VEGFR TKI, though previous bevacizumab or ramucirumab was allowed. Because of the potential for increased incidence of AE during the enrollment of this trial, the cohort was closed early.
4. Patients with SCLC must have progressed on platinum-based chemotherapy and may have received up to three previous lines of therapy for stage IV disease provided none included checkpoint inhibition or oral TKI. This cohort completed enrollment before ICI became a standard addition to first-line chemotherapy for SCLC. It did not meet the efficacy end point to pass interim analysis.

Statistical Design

The sample size for the phase 2 dose-expansion portion was up to 159 patients across four cohorts treated at the RCD using a two-stage MinMax design described by Simon et al.[14] Statistical planning was

individualized on the basis of historical controls in each specific biological cohort. In the NSCLC naive to checkpoint inhibitor cohort, there was 90% power to detect a difference of 45% versus 25% with a type I error rate of 10% and interim stopping point of efficacy if less than six of the first 23 patients responded. In the NSCLC with disease primarily refractory to checkpoint inhibition cohort, a 90% power to detect response of 40% versus 15% at the one-sided type 1 error rate of 10% required at least three of 15 patients to achieve response to accrue a total of 21 patients. In the cohort of patients with NSCLC with acquired resistance to checkpoint inhibitor therapy, there was a 90% power to detect a response rate of 40% versus 15% at the one-sided 10% level. In this cohort, response from at least three patients in the first 15 was needed to pass interim analysis to enroll a total of 21 patients. For patients with SCLC progressing on previous chemotherapy, for an 80% power to detect 30% versus the null hypothesis of 15% (with one-sided 10% type 1 error), at least three responses were required in the first 18 patients to continue enrollment up to 37 total patients. The thymic cohort had 80% power to detect a response rate of 35% versus 20% at the one-sided 10% level with an interim stopping point if less than five responses were seen in 22 patients or continuation to 41 assessable patients.

Descriptive statistics, including medians and interquartile ranges for continuous parameters, and percentages and frequencies for categorical parameters, were presented. The ORR and DCR with 95% confidence intervals (CIs) for each tumor type were calculated by the Clopper-Pearson method.

The PFS and OS rates, including the PFS rates at 6 months and the OS rates at 12 months, with the 95% CIs were estimated using the Kaplan-Meier method with the log transformation. The medians of PFS and OS with 95% CIs were estimated by the Brookmeyer-Crowley method. The log-rank test was used to compare the equality of survival curves between tumor types. The duration of response, a defined secondary end point, could not be analyzed because of the lack of patients experiencing a PR. All analyses mentioned above were performed using R software version 4.0.3, and the R packages survival 3.2-7 and survminer 0.4.9. AEs are tabulated. The National Cancer Institute toxicity grade 3 and grade 4 laboratory abnormalities were listed, and summary statistics were provided for all laboratory values. Frequencies and proportions of TRAE levels by cohorts were presented and compared between cohorts by Fisher's exact test.

Role of the Funding Source

Bristol-Myers Squibb provided nivolumab for this trial; Xcovery Holdings provided funding and vorolanib for the conduct of this investigator-initiated clinical trial. These funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The principal investigators had full access to all data in the study and were responsible for data analysis, article preparation, and submission.

Results

Patient Demographics

Between April 2018 and July 2022, 119 patients were screened at seven medical centers in the United States and 88 patients were enrolled (Fig. 1). A total of 88 patients received at least one dose of nivolumab and vorolanib. The screen failures were primarily because of disease progression requiring immediate therapy. The baseline characteristics of the 88 enrolled patients are presented in Table 1 for all patients and by biological cohort, including the 10 patients from the phase 1 portion. The median age was 66 years (range: 58–71) with most being male patients 57% and current or previous smokers (79%). Most patients (67%) with TC had never smoked whereas 89% of those with SCLC were actively smoking or had a history of smoking. Of the enrolled patients, 76% were White, 11% African American, 3% Asian, and 9% not reported. Patients across biological subgroups had a median of two previous lines of therapy. Patients enrolled with refractory thoracic malignancies had stage IV disease with metastasis to the lung (88%), bone (33%), liver (32%), and brain (20%) at the time of enrollment. At the time of the data cutoff of Aug 2022, 68 patients discontinued treatment because of disease progression, and 16 patients discontinued because of AEs. Three patients were still on treatment at the time of the data cutoff.

Determination of Maximum Tolerated Dose and Recommended Phase 2 Dose

In total, 11 patients were enrolled in the phase 1 portion of dose escalation; one patient was nonassessable requiring replacement. Patients enrolled in the phase 1 portion of the study included eight patients with NSCLC and two patients with TC. No patients ($n = 3$) experienced DLT at level 1 vorolanib 200 mg orally daily. Two patients with NSCLC experienced DLT of grade 3 transaminitis at dose level 2 ($n = 6$) at 300 mg vorolanib orally daily. The RP2D, on the basis of predefined criteria, was, therefore, 200 mg vorolanib daily with nivolumab 240 mg every 2 weeks.

Safety

Any grade TRAEs as determined by CTCAE version 5.0 were reported in 75% of patients (Table 2). The most common TRAEs were fatigue (32%), aspartate

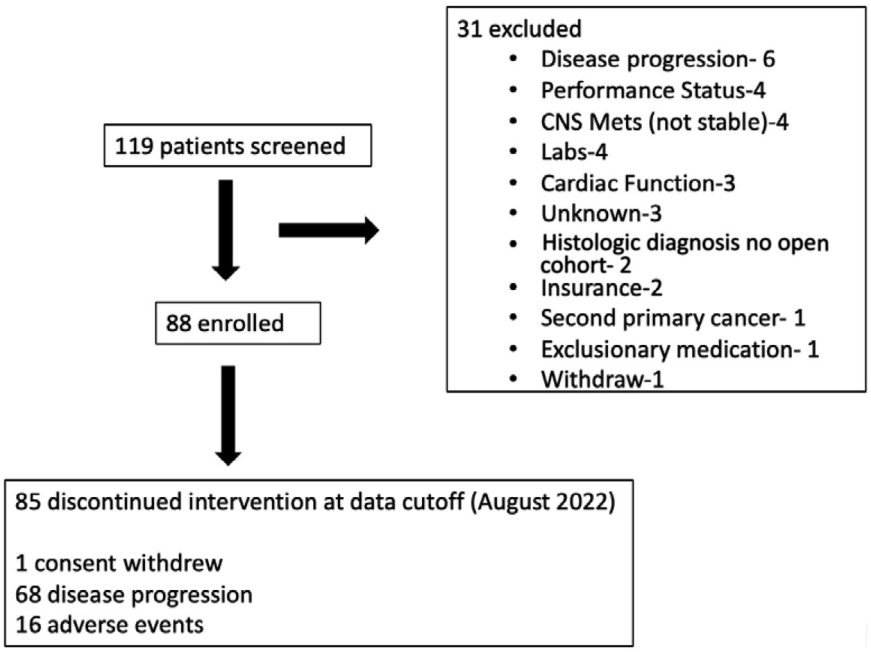

Figure 1. CONSORT diagram outlining patient screening, enrollment, and treatment. CNS mets, central nervous system metastasis; labs, laboratory.

transaminase elevation (27%), alanine transaminase elevation (25%), and diarrhea (19%). Grade 3/4 AEs occurred in 43% of patients and included alanine transaminase elevation (8%), aspartate transaminase elevation (7%), hypertension (5%), and fatigue (3%). No treatment-related deaths occurred in the study.

TRAEs leading to dose interruption of nivolumab occurred in 17% of patients. Dose interruption of vorolanib occurred in 20% of patients and 11% of patients required dose reduction of vorolanib for TRAEs. The safety profile was consistent with known combinations of VEGF and anti–PD-1 therapy in other tumor types. irAEs as assessed by the investigator occurred in 59% of TRAEs. Notably, patients with TC had a statistically significant higher incidence of treatment-related liver function test elevation compared with the other cohorts combined (78%, p value $= 0.004$). In the thymic cohort, seven of nine patients experienced at least grade 1 transaminitis, with two patients experiencing grade 3 transaminitis, four patients required a dose hold of nivolumab, two patients required prednisone for investigator-assessed irAE, and one patient had a dose reduction in vorolanib with transaminitis resolving in all patients with TC after dose hold.

Efficacy

The NSCLC cohort naive to checkpoint inhibitor therapy was closed early after enrollment of 15 patients because of changing standards of care and challenges with enrollment. This cohort had an ORR of 33% (five of 15, 95% CI: 13%–60%) with a 6-month PFS rate of 53% and median (mPFS) of 7.16 months (95% CI: 1.38–not assessable [NA]) (Table 3). The DCR was 53.3% (eight of 15, 95% CI: 26.7%–80.0%). The 12-month OS rate was 33%, with mOS not yet reached (95% CI: 8.77–NA). Tumor shrinkage was highest in this cohort who had not experienced previous ICI therapy, with a median of 30.4% tumor shrinkage.

Patients with NSCLC who had previously been treated with an ICI and were primary refractory had an ORR of 5.9% (one of 17, 95% CI: 0%–17.6%) (Table 3) with a 6-month PFS rate of 9% and mPFS of 3.22 months (95% CI: 1.84–4.60). The DCR was 52.9% (nine of 17, 95% CI: 29.4%–76.5%). The 12-month OS rate was 35%, and the mOS was 16.27 months (95% CI: 5.98– NA).

Those patients with NSCLC who had previously experienced clinical benefit from ICI for a minimum of 12 weeks had an ORR of 11.1% (two of 18, 95% CI: 0%–27.8%) (Table 3). In this cohort, 11% of patients achieved a 6-month PFS and the mPFS was 1.97 months (95% CI: 1.54–4.60). The DCR was 44.4% (eight of 18, 95% CI: 22.3%–66.7%), 12-month OS was 38%, and mOS was 10.81 months (95% CI: 4.60–NA).

In the SCLC cohort, there were no objective responses. The DCR was 11.1% (two of 18, 0%–27.8%) (Table 3), the mPFS was 1.36 months (95% CI: 0.92 – 1.81), and the mOS was 4.5 months (3.75– NA).

Whereas enrollment in the TC cohort was closed early because of limited enrollment and possible increased incidence of AE compared with the other cohorts, patients with TC experienced the longest clinical

Table 1. Baseline Characteristics of all Enrolled Patients

Baseline characteristics	Combined (N=88)	Phase 1 (N=11)	NSCLC-naive (N=15)	NSCLC-AR (N=18)	NSCLC-PR (N=17)	SCLC (N=18)	Thymic (N=9)
Sex							
Female	43% (38)	55% (6)	60% (9)	28% (5)	53% (9)	39% (7)	22% (2)
Male	57% (50)	45% (5)	40% (6)	72% (13)	47% (8)	61% (11)	78% (7)
Age, median (IQR)	66 (58.4-71.1)	69.1 (58.7-72.0)	68.4 (60.6-75.7)	65.2 (60.5-68.2)	66.8 (62.0-69.0)	65.5 (58.7-69.1)	54.4 (43.7-66.0)
Race							
White	76% (67)	100% (11)	60% (9)	83% (15)	76% (13)	78% (14)	56% (5)
Black or African American	11% (10)	0% (0)	27% (4)	11% (2)	6% (1)	11% (2)	11% (1)
Asian	3% (3)	0% (0)	7% (1)	0% (0)	0% (0)	0% (0)	22% (2)
Unknown or not reported	9% (8)	0% (0)	7% (1)	6% (1)	18% (3)	11% (2)	11% (1)
Smoking History							
Former smoker	68% (60)	64% (7)	60% (9)	78% (14)	88% (15)	67% (12)	33% (3)
Current smoker	11% (10)	18% (2)	7% (1)	17% (3)	0% (0)	22% (4)	0% (0)
Never smoker	20 % (18)	18% (2)	33% (5)	6% (1)	12% (2)	11% (2)	67% (6)
Number of Pack Years, median (IQR)	31 (19.8-46.8)	37 (17.0-53.0)	25 (19.0-36.0)	32.5 (23.6-40.0)	30 (16.0-40.0)	40 (27.5-55.5)	30 (16.0-51.5)
Number of Prior Treatments							
0	11% (10)	9% (1)	20% (3)	6% (1)	18% (3)	6% (1)	11% (1)
1	20% (18)	36% (4)	27% (4)	11% (2)	12% (2)	17% (3)	33% (3)
2	28% (25)	18% (2)	33% (5)	22% (4)	41% (7)	28% (5)	22% (2)
>=3	40% (35)	35% (4)	21% (3)	61% (11)	30% (5)	50% (9)	33% (3)
PD-L1 expression (>10%)							
Negative	33% (29)	27% (3)	40% (6)	50% (9)	47% (8)	6% (1)	22% (2)
Positive	12% (11)	18% (2)	13% (2)	17% (3)	24% (4)	0% (0)	0% (0)
Unknown	55% (48)	55% (6)	47% (7)	33% (6)	29% (5)	94% (17)	78% (7)
Sites of Metastasis							
Lung	88% (77)	100% (11)	100% (15)	83% (15)	88% (15)	89% (16)	56% (5)
Adrenal Gland	10% (9)	9% (1)	7% (1)	17% (3)	12% (2)	11% (2)	0% (0)
Bone	33% (29)	36% (4)	13% (2)	28% (5)	41% (7)	50% (9)	22% (2)
Brain	20% (18)	18% (2)	20% (3)	28% (5)	12% (2)	28% (5)	11% (1)
Liver	32% (28)	9% (1)	20% (3)	22% (4)	35% (6)	67% (12)	22% (2)

IQR, interquartile range; NSCLC-AR, NSCLC acquired resistance having experienced clinical benefit to previous checkpoint inhibitors and then progressed on therapy; NSCLC-PR, NSCLC primary refractory to a previous checkpoint inhibitor; PD-L1, programmed death-ligand 1.

benefit and the longest time on treatment (Fig. 2). The ORR was 11% (one of nine, 95% CI: 0%–33%), and they notably experienced the longest mPFS across biological subtypes at 9.10 months (95% CI: 1.81–NA) with a 6-month 67% PFS rate. The mOS of 21.06 months (95% CI: 13.54–NA) and the 12-month OS rate was 88%.

The maximum changes in tumor size for all cohorts are illustrated in Figure 3. Overall, nine patients achieved a PR, of which five were naive to previous checkpoint inhibition, and two had acquired resistance to previous checkpoint inhibition (one with TC, one with NSCLC primary refractory to checkpoint inhibition) (Supplementary Fig. 1). No complete responses were seen.

Discussion

In this phase 1/2 study of refractory patients with various histologic thoracic malignancies, vorolanib and nivolumab exhibited an acceptable safety profile and suggested clinical benefit in select patients. The phase 1 dose escalation portion of this trial identified an RP2D dosing strategy of 200 mg vorolanib daily with 240 mg nivolumab infusion every 2 weeks. At dose level 2, dose-limiting toxicities, specifically transaminitis, led to the RP2D at dose level one 200 mg vorolanib with standard nivolumab dosing.

AEs across expansion cohorts in patients with refractory NSCLC, SCLC, and TC were consistent with other anti–PD-1 and VEGF-TKI combinations. The most common AEs were fatigue (32%), transaminitis (27%), diarrhea (19%), and nausea (19%). These AEs were mostly manageable with dose interruptions or dose reductions of vorolanib. Patients who required dose reduction of vorolanib for toxicity in many instances continued to have clinical benefit. This was particularly true in patients with TC who experienced transaminitis requiring a dose interruption or reduction but were able to remain on treatment for continued clinical benefit. Increased incidence of irAE in patients with TC has previously been reported and was noted in this trial, but

Table 2. Treatment-Related Adverse Disorders

Treatment related adverse events	Vorolanib plus Nivolumab (N = 88), # (%)
Patients with treatment-related AEs	66 (75)
Grade 3	33 (38)
Grade 4	5 (6)
Serious Adverse Events	12 (14)
Patients with treatment-related AEs leading to	
Nivolumab dose hold	11 (17)
Vorolanib dose hold	13 (20)
Vorolanib dose reduction	7 (11)

Patients with treatment-related AEs (Any grade > 10%, Grade 3 > 2%, or all grade 4)	Any Grade	Grade 3	Grade 4
Fatigue	28 (32)	3 (3)	2 (2)
Aspartate aminotransferase increased	24 (27)	6 (7)	0 (0)
Alanine aminotransferase increased	22 (25)	7 (8)	0 (0)
Diarrhea	17 (19)	0 (0)	0 (0)
Nausea	17 (19)	1 (1)	0 (0)
Hypertension	11 (12)	4 (5)	0 (0)
Anorexia	10 (11)	0 (0)	0 (0)
Dyspnea	10 (11)	1 (1)	0 (0)
Neutrophil count decreased	10 (11)	3 (3)	1 (1)
Anemia	9 (10)	1 (1)	0 (0)
White blood cell decreased	8 (9)	2 (2)	0 (0)
Hyperglycemia	7 (8)	0 (0)	1 (1)
Lipase increased	4 (5)	1 (1)	1 (1)
Pneumonitis	3 (3)	3 (3)	0 (0)
Dehydration	3 (3)	0 (0)	1 (1)
Other hepatobiliary disorder	2 (2)	2 (2)	0 (0)
Other general disorder or administration site condition	7 (8)	2 (2)	0 (0)

#, number; AE, adverse event.

with transaminitis as the predominant toxicity, whereas other trials in thymic malignancies have seen an increased incidence of myositis and myocarditis to ICI.[15,16]

Across the entire study, the ORR was 12% and another 31% of patients had stable disease with a median of 3.3 months. There was no clinical benefit seen in

Table 3. Efficacy outcomes

Efficacy outcomes	NSCLC-naive (N=15)	NSCLC-AR (N=18)	NSCLC-PR (N=17)	SCLC (N=18)	thymic (N=9)
Best Overall Response					
Complete Response	0	0	0	0	0
Partial Response	33% (5)	11% (2)	6% (1)	0% (0)	11% (1)
Stable Disease	20% (3)	33% (6)	47% (8)	11% (2)	56% (5)
Progressive Disease	46% (7)	55% (10)	48% (8)	89% (16)	33% (3)
ORR	33.3% (5)	11.1% (2)	5.9% (1)	0% (0)	11.1% (1)
(95% CI)	13.3%-60.0%	0%-27.8%	0%-17.6%	0%-0%	0%-33.3%
DCR	53.3% (8)	44.4% (8)	52.9% (9)	11.1% (2)	66.7% (6)
(95% CI)	26.7%-80.0%	22.2%-66.7%	29.4%-76.5%	0%-27.8%	33.3%-100.0%
mPFS, months (95% CI)	7.16 (1.38-NA)	1.97 (1.54-4.60)	3.22 (1.84-4.60)	1.36 (0.92-1.81)	9.1 (1.81-NA)
mOS, months (95% CI)	NA (8.77-NA)	10.81 (4.60-NA)	16.27 (5.98-NA)	4.5 (3.75-NA)	21.06 (13.54-NA)

CI, confidence interval; DCR, disease control rate; mOS, median overall survival; mPFS, median progression-free survival; NA, not assessable; NSCLC-AR, NSCLC acquired resistance having experienced clinical benefit to previous checkpoint inhibitors and then progressed on therapy; NSCLC-PR, NSCLC primary refractory to a previous checkpoint inhibitor; ORR, objective response rate.

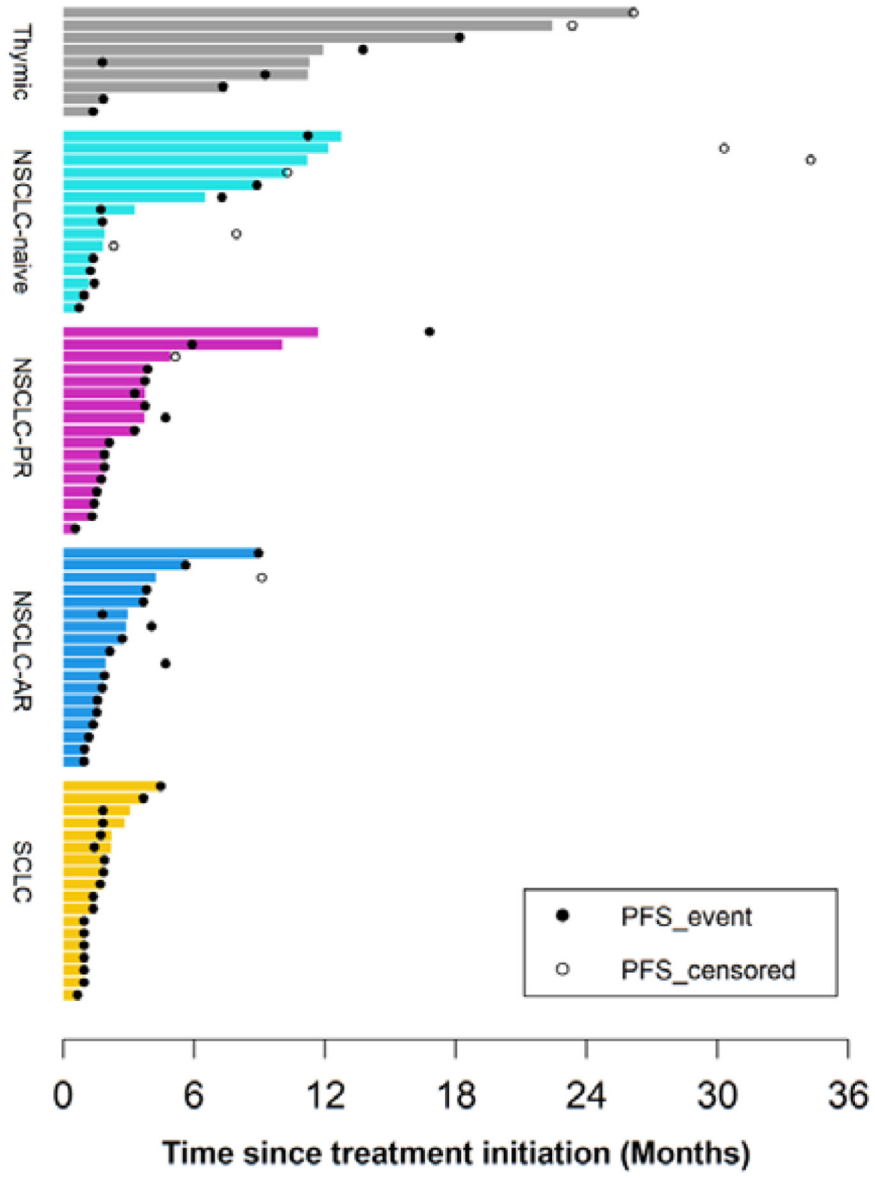

Figure 2. Time on treatment arranged histologic cohort. PFS events assessed per investigator assessment by RECIST version 1.1. NSCLC-AR, NSCLC acquired resistance having experienced clinical benefit to previous checkpoint inhibitors and then progressed on therapy; NSCLC-PR, NSCLC primary refractory to a previous checkpoint inhibitor; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

patients with refractory SCLC, in which most patients experienced primary disease progression as the best response. The combination therapy produced the greatest tumor response in patients with NSCLC who were naive to checkpoint inhibition, suggesting that, perhaps, this combination approach may be useful for those who may not be chemotherapy candidates or who refuse chemotherapy. This trial also sought to understand whether vorolanib, perhaps by modulation of the immune suppressive tumor microenvironment, could overcome resistance to previous ICI therapy either from patients who previously had clinical benefit (acquired resistance) or never previously benefited from ICI treatment. A total of three patients across the acquired and primary refractory NSCLC cohorts achieved an objective response, 94% of the patients experienced disease progression by 6 months, suggesting that the addition of vorolanib to PD-1 inhibition is not able to overcome treatment resistance.

This study is limited by its small size across a diverse group of biologically driven thoracic malignancies. Enrollment was particularly limited in the NSCLC cohort of patients who were previously naive to ICI therapy. Similarly, soon after the opening of this trial, other studies reported the benefit of checkpoint inhibition in TC, which led to enrollment challenges for this study. It is also

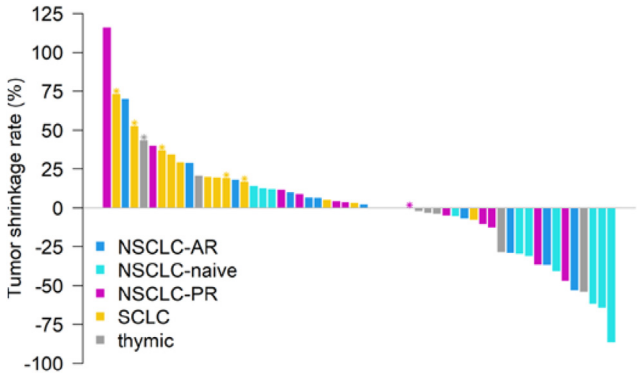

Figure 3. Tumor shrinkage waterfall plot across all expansion cohorts as assessed per investigator calculated as the sum of target lesions per participant. *Clinical progression. NSCLC-AR, NSCLC acquired resistance having experienced clinical benefit to previous checkpoint inhibitors and then progressed on therapy; NSCLC-PR, NSCLC primary refractory to a previous checkpoint inhibitor.

possible that the response rate was not the appropriate end point for the expansion cohort, and that OS may have been a better end point on the basis of previous ICI trials. Interpretation of available response data in this combination of vorolanib and nivolumab is limited with a lack of available programmed death-ligand 1 status across cohorts. Lastly, patients with NSCLC who had progressed on previous PD-1 were included regardless of previous mutational status and it is possible that this underlying biology could have contributed.

Vorolanib and nivolumab combination had an expected safety profile for VEGFR TKI and anti–PD-1 therapy, though higher than anticipated transaminitis was seen in the TC cohort. Efficacy was most intriguing in patients with TC but this was limited to small patient numbers. Because of the initiation of this trial, there have been reports of other VEGFR TKI and ICI combination trials ongoing in NSCLC and thymic malignancies (Immunotherapy-Lung-MAP S1800A, PICATI, and CAVEATT).[17–19] In light of other recent trials of VEGFR TKI plus ICI with a published response rate of 34% with the combination of avelumab and axitinib and the ongoing PECATI trial of lenvatinib and pembrolizumab in TC, it is not clear whether there is a future to evaluate vorolanib and nivolumab combination, though the relative tolerability of the combination is encouraging.

CRediT Authorship Contribution Statement

Kathryn E. Beckermann: Conception and design, Provision of study materials or patients, Collection and assembly of data, Data analysis and interpretation, Manuscript writing, Final approval of manuscript, Accountable for all aspects of the work.

Christine M. Bestvina: Provision of study materials or patients, Data analysis and interpretation, Manuscript writing, Final approval of manuscript, Accountable for all aspects of the work.

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Rachel E. Sanborn: Provision of study materials or patients, Data analysis and interpretation, Manuscript writing, Final approval of manuscript, Accountable for all aspects of the work.

Hossein Borghaei: Provision of study materials or patients, Data analysis and interpretation, Manuscript writing, Final approval of manuscript, Accountable for all aspects of the work.

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Giovanni Selvaggi: Data analysis and interpretation, Manuscript writing, Final approval of manuscript, Accountable for all aspects of the work.

Jennifer G. Whisenant: Data analysis and interpretation, Manuscript writing, Final approval of manuscript, Accountable for all aspects of the work.

Ellen Heimann-Nichols: Data analysis and interpretation, Manuscript writing, Final approval of manuscript, Accountable for all aspects of the work.

Lynne Berry: Collection and assembly of data, Data analysis and interpretation, Manuscript writing, Final approval of manuscript, Accountable for all aspects of the work.

Chih-Yuan Hsu: Collection and assembly of data, Data analysis and interpretation, Manuscript writing, Final approval of manuscript, Accountable for all aspects of the work.

Yu Shyr: Collection and assembly of data, Data analysis and interpretation, Manuscript writing, Final approval of manuscript, Accountable for all aspects of the work.

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Heather Wakelee: Conception and design, Provision of study materials or patients, Collection and assembly of data, Data analysis and interpretation, Manuscript writing, Final approval of manuscript, Accountable for all aspects of the work.

Disclosure

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submitted work; received consulting fees from Aravive, Alpine Bioscience, Aveo, AstraZeneca, Exelixis, Bristol-Myers Squibb, Merck, Sanofi, and Seagen. Dr. Bestvina reports receiving consulting fees from AstraZeneca, Bristol-Myers Squibb, CVS, Daiichi Sankyo, EMD, Serono, Genentech, Gilead, Jazz, JNJ, Mirati, Novartis, Novocure, Pfizer, Regeneron, Sanofi, Takeda, and Tempus; and support for attending meetings from Bristol-Myers Squibb. Dr. Selvaggi is the Chief Medical Officer of Xcovery Holding, Inc. Dr. Sanborn reports receiving consulting fees from GlaxoSmithKline, AstraZeneca, Janssen Oncology, Macrogenics, Daiichi Sankyo, Sanofi Aventis, BeiGene, Gilead, Illumina, Targeted Oncology, Regeneron, G1 Therapeutics, GE HealthCare, Amgen, Abbvie, and Eli Lilly Oncology; and reports receiving payment or honoraria for presentations for EMD-Serono, GameOn!, Illumina, Binay Foundation, OncLive, and Meeting Events and Conference Coordinators, Inc. Dr. Berry reports receiving institutional funding from Xcovery. Dr. Borghaei reports receiving grants from Bristol-Myers Squibb, Eli Lilly, and Amgen; consulting fees from Bristol-Myers Squibb, Eli Lilly, Genentech, Pfizer, Merck, EMD-Serono, Boehringer Ingelheim, AstraZeneca, Novartis, Genmab, Regeneron, BioNTech, Amgen, Axiom, PharmaMar, Takeda, Mirati, Daiichi, Guardant, Natera, Oncocyte, Beigene, iTEO, Jazz, Janssen, Puma, BerGenBio, Bayer, Iobiotech, and Grid Therapeutics; honoraria from Amgen, Pfizer, Daiichi, and Regeneron; support for attending meetings from Amgen, Bristol-Myers Squibb, Merck, Eli Lilly, EMD-Serono, Genentech, Regeneron, and Mirati; and participated on a Data Safety Monitoring Board or Advisory Board for the University of Pennsylvania CAR T Program, Takeda, Incyte, Novartis, and Springworks. The remaining authors declare no conflict of interest.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100619.

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