ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

SAPPHIRE: phase III study of sitravatinib plus nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer

H. Borghaei[1]*, F. de Marinis[2], D. Dumoulin[3], C. Reynolds[4], W. S. M. E. Theelen[5], I. Percent[6], V. Gutierrez Calderon[7], M. L. Johnson[8], A. Madroszyk-Flandin[9], E. B. Garon[10], K. He[11], D. Planchard[12], M. Reck[13], S. Popat[14], R. S. Herbst[15], T. A. Leal[16], R. L. Shazer[17], X. Yan[17], R. Harrigan[17] & S. Peters[18], on behalf of the SAPPHIRE Investigators†

[1]Hematology and Oncology Department, Fox Chase Cancer Center, Philadelphia, USA; [2]Division of Thoracic Oncology, European Institute of Oncology, IRCCS, Milan, Italy; [3]Department of Pulmonary Medicine, Erasmus Medisch Centrum, Rotterdam, the Netherlands; [4]Ocala Cancer Center, Florida Cancer Specialists and Research Institute – North Region (SCRI), Ocala, USA; [5]Department of Thoracic Oncology, The Netherlands Cancer Institute, Amsterdam, the Netherlands; [6]North Port Cancer Center, Florida Cancer Specialists and Research Institute – South Region (SCRI), Port Charlotte, USA; [7]Department of Medical Oncology, Hospital Regional Universitario de Málaga, Málaga, Spain; [8]Department of Medical Oncology, Sarah Cannon Research Institute, Tennessee Oncology, Nashville, USA; [9]Department of Medicine, Institut Paoli-Calmettes, Marseille, France; [10]Division of Hematology-Oncology, David Geffen School of Medicine, University of California, Los Angeles; [11]Comprehensive Cancer Center, Pelotonia Institute for Immuno-Oncology, The Ohio State University, Columbus, USA; [12]Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France; [13]Department of Thoracic Oncology, LungenClinic, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [14]Lung Unit, Department of Medicine, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, UK; [15]Section of Medical Oncology, Yale University, New Haven; [16]Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta; [17]Department of Clinical Research and Development, Mirati Therapeutics, Inc., San Diego, USA; [18]Department of Oncology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

Available online XXX

Background: Checkpoint inhibitor (CPI) therapy revolutionized treatment for advanced non-small-cell lung cancer (NSCLC); however, most patients progress due to primary or acquired resistance. Sitravatinib is a receptor tyrosine kinase inhibitor that can shift the immunosuppressive tumor microenvironment toward an immunostimulatory state. Combining sitravatinib with nivolumab (sitra + nivo) may potentially overcome initial CPI resistance.

Patients and methods: In the phase III SAPPHIRE study, patients with advanced non-oncogenic driven, nonsquamous NSCLC who initially benefited from (≥4 months on CPI without progression) and subsequently experienced disease progression on or after CPI combined with or following platinum-based chemotherapy were randomized 1 : 1 to sitra (100 mg once daily administered orally) + nivo (240 mg every 2 weeks or 480 mg every 4 weeks administered intravenously) or docetaxel (75 mg/m^2 every 3 weeks administered intravenously). The primary endpoint was overall survival (OS). The secondary endpoints included progression-free survival (PFS), objective response rate (ORR), clinical benefit rate (CBR), duration of response (DOR; all assessed by blinded independent central review), and safety.

Results: A total of 577 patients included randomized: sitra + nivo, $n = 284$; docetaxel, $n = 293$ (median follow-up, 17.1 months). Sitra + nivo did not significantly improve OS versus docetaxel [median, 12.2 versus 10.6 months; hazard ratio (HR) 0.86, 95% confidence interval (CI) 0.70-1.05; $P = 0.144$]. The median PFS was 4.4 versus 5.4 months, respectively (HR 1.08, 95% CI 0.89-1.32; $P = 0.452$). The ORR was 15.6% for sitra + nivo and 17.2% for docetaxel ($P = 0.597$); CBR was 75.5% and 64.5%, respectively ($P = 0.004$); median DOR was 7.4 versus 7.1 months, respectively ($P = 0.924$). Grade ≥3 treatment-related adverse events were observed in 53.0% versus 66.7% of patients receiving sitra + nivo versus docetaxel, respectively.

Conclusions: Although median OS was numerically longer with sitra + nivo, the primary endpoint was not met in patients with previously treated advanced nonsquamous NSCLC. The safety profiles demonstrated were consistent with previous reports.

Key words: sitravatinib, nivolumab, NSCLC

*Correspondence to: Prof. Hossein Borghaei, Hematology and Oncology Department, Fox Chase Cancer Center, 333 Cottman Ave, Philadelphia, PA, 19111 USA. Tel: +1-484-343-5668

E-mail: Hossein.Borghaei@fccc.edu (H. Borghaei).

†The individual names of the SAPPHIRE study investigators who are not listed as authors are provided in the Supplementary Appendix S1, available at https://doi.org/10.1016/j.annonc.2023.10.004.

INTRODUCTION

The treatment landscape for advanced non-small-cell lung cancer (NSCLC) has been transformed by checkpoint inhibitor (CPI) therapy, such as programmed cell death protein 1 (PD-1) or programmed-death ligand 1 (PD-L1) inhibitors. CPI therapy with or without platinum-based chemotherapy

(PBC) is currently the standard frontline treatment for patients with advanced NSCLC with no actionable driver mutations.[1] However, the majority of patients with advanced NSCLC do not experience long-term benefit from CPI therapy due to primary or acquired resistance.[2] For patients who have received prior CPI and PBC, treatment options are limited and mainly involve docetaxel, which is associated with poor survival outcomes [median overall survival (OS), ~10-12 months][3-6] and severe toxicities, including neutropenia, febrile neutropenia, anemia, and neuropathy.[7,8] Therefore, there is a need to develop novel therapeutic strategies with better tolerability and improved outcomes for patients who develop CPI resistance.

One of the key mechanisms of CPI resistance involves the immunosuppressive tumor microenvironment (TME), which is driven by both tumor and immune cells.[9,10] Tumor cells can create an immunosuppressive TME by releasing vascular endothelial growth factor (VEGF), which can increase the number of immunosuppressive cells, such as regulatory T cells and myeloid-derived suppressor cells.[10,11] Immune cells, such as tumor-associated macrophages, can also contribute to the immunosuppressive TME by releasing GAS6, which can bind to TYRO3, AXL, and MERTK receptors, also known as TAM receptors.[11] Activation of these receptors inhibits proinflammatory cytokines and stimulates the release of immunosuppressive cytokines, as well as inducing immunosuppressive M2-polarized macrophages.[11] Therefore targeting VEGF and TAM receptors may be a strategy to overcome CPI resistance by shifting the immunosuppressive TME to an immunostimulatory state,[12] and several TAM receptor inhibitors are being investigated in combination with CPIs.[10]

Sitravatinib (MGCD516) is a receptor tyrosine kinase inhibitor with targets that include TAM receptors and VEGF receptor 2 (VEGFR2).[13] By inhibiting these receptors, sitravatinib can modulate the immunosuppressive TME by decreasing regulatory T cells and increasing the ratio of M1 : M2-polarized macrophages, and enhance the efficacy of PD-L1 blockade, as shown in preclinical and clinical studies.[13,14] Sitravatinib, as monotherapy or in combination with nivolumab, has been evaluated in single-arm studies in patients with advanced nonsquamous NSCLC, advanced clear cell renal cell carcinoma, oral cavity carcinoma, and advanced urothelial carcinoma, with variable levels of activity observed.[14-18]

Sitravatinib in combination with nivolumab was further evaluated in the phase II MRTX-500 study enrolling patients with nonsquamous NSCLC with disease progression on or after prior CPI and/or PBC.[19] This combination demonstrated a manageable safety profile and promising antitumor activity in patients who had initially benefited from, and subsequently experienced disease progression on, prior CPI.[19] Among all CPI-experienced patients with a prior clinical benefit, the most common treatment-related adverse events (TRAEs) of any grade were diarrhea (60%), fatigue (45%), nausea (40%), and decreased appetite (34%); the most common grade 3-4 TRAEs were hypertension (18%) and diarrhea (16%).[19] The median OS for all CPI-experienced patients with a prior clinical benefit was 13.6 months; notably, in patients with one or two prior lines of therapy, the median OS was 14.9 months.[19]

Here, we report the results of the phase III SAPPHIRE study evaluating sitravatinib plus nivolumab (sitra + nivo) versus docetaxel in patients with advanced nonsquamous NSCLC who initially benefited from, and subsequently developed progression on, prior CPI with or after PBC as first- or second-line treatment.

PATIENTS AND METHODS

Study oversight

The study was designed by the investigators and employees of Mirati Therapeutics, Inc. (the sponsor). The data were collected by the investigators and analyzed by sponsor-employed statisticians. The study was conducted in accordance with the principles of the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the Declaration of Helsinki, and the International Council for Harmonisation Good Clinical Practice guidelines.[20-22] The protocol was approved by the relevant institutional review boards or ethics committees. All the patients provided written informed consent. Trial oversight was provided by the sponsor, the investigators, the institutional review board, the ethics committee, the research ethics board, and an independent data monitoring committee (IDMC). The trial is registered at ClinicalTrials.gov (NCT03906071).

Patients

Eligible patients were aged ≥18 years, with a histologically or cytologically confirmed diagnosis of unresectable, locally advanced, or metastatic nonsquamous NSCLC, who were not suitable for treatment with curative intent, including concurrent chemoradiotherapy, and who had a life expectancy of ≥3 months and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Patients must have been treated with one or two prior regimens, with the most recent treatment regimen including a CPI for ≥4 months (120 days), in combination with or following PBC, before radiographic disease progression on or after treatment.

The key exclusion criteria included discontinuation of prior CPI >90 days before the date of randomization; treatment with systemic cancer therapy since discontinuation of CPI (maintenance chemotherapy was allowed); prespecified immune-related toxicities on prior CPI; previous treatment with anticancer therapy with the same mechanism of action as sitravatinib; presence of EGFR, ROS1, or ALK mutations; active brain metastases (treated and/or stable brain metastases were allowed); and the presence of another active primary cancer. Full eligibility criteria are provided in the protocol, in Supplementary file, available at https://doi.org/10.1016/j.annonc.2023.10.004.

Study design and endpoints

SAPPHIRE was an open-label, randomized, multicenter, phase III study evaluating the efficacy and safety of sitra +

nivo compared with docetaxel in patients with advanced nonsquamous NSCLC who had previously developed disease progression on or after treatment with CPI and PBC. Patients were randomized 1 : 1 to receive either sitra + nivo (nivo, 240 mg every 2 weeks or 480 mg every 4 weeks administered intravenously) or docetaxel monotherapy (75 mg/m^2 every 3 weeks administered intravenously) until disease progression, unacceptable AEs, investigator decision, withdrawal of consent, or death. Sitravatinib was administered orally as malate capsules at 100 mg once daily (QD); patients enrolled in the United States who initiated treatment with the free-base capsule formulation administered at 120 mg QD (which is equivalent to 100 mg QD of the malate capsule formulation) remained on this formulation throughout the study. Randomization of patients was stratified based on prior treatment regimens in the advanced setting (1 versus 2); ECOG performance status at baseline (0 versus 1); and presence of treated and/or stable brain metastases at baseline (presence versus absence).

The primary endpoint was OS. The secondary endpoints included efficacy endpoints assessed by blinded independent central review and safety. The secondary efficacy endpoints included objective response rate (ORR) per RECIST version 1.1, duration of response (DOR), clinical benefit rate (CBR; defined as the percentage of patients with a confirmed complete response, partial response, or stable disease on one or more on-study assessment and including $\geq$8 weeks on study), progression-free survival (PFS), and 12-month survival rate. Further endpoint definitions and details on tumor assessments are provided in Supplementary Appendix S1, available at https://doi.org/10.1016/j.annonc.2023.10.004.

Statistical analyses

The assumption for sample size calculation was based on a hazard ratio (HR) for OS of 0.73 (which assumed a median OS of 13.0 months in the sitra + nivo arm and 9.5 months in the docetaxel arm). Approximately 372 total OS events were required to detect the assumed HR at a two-sided alpha of 0.05 and a power of 85%. An interim analysis based on OS was planned when ~70% of the events (~260 events) had been observed. The efficacy boundary was constructed using the O'Brien—Fleming boundary implemented by the Lan—DeMets alpha spending method. A nonbinding futility analysis was also planned at the time of the interim analysis. The futility boundary was constructed based on 2% conditional power, and the study would be declared futile if the estimated HR at interim was >0.913.

The intent-to-treat (ITT) population included all patients who were randomized and was used for OS and PFS analyses. The modified ITT population included all patients who were randomized and had measurable disease at baseline (per RECIST version 1.1); this population was used for ORR, CBR, and DOR analyses. The median OS, PFS, and DOR with 95% confidence intervals (CIs; calculated using the Brookmeyer and Crowley method) were estimated using the Kaplan—Meier method, and the unstratified log-rank test was used to compare the two treatment arms. The treatment effect on OS was also evaluated in prespecified subgroup analyses (further details are provided in Supplementary Appendix S1, available at https://doi.org/10.1016/j.annonc.2023.10.004). The HR and 95% CIs were calculated using an unstratified Cox proportional hazard model with Efron's method of tie handling. ORR and CBR were categorized in accordance with RECIST version 1.1 and were presented as frequency and percentage; the 95% CIs were calculated using the Clopper—Pearson method. A chi-square test was used to compare response rates between the two treatment arms. Safety analyses were carried out in patients who received any dose of study treatment (i.e. sitravatinib, nivolumab, or docetaxel).

RESULTS

Patients

A total of 577 patients with advanced nonsquamous NSCLC were enrolled and randomized to receive either sitra + nivo (n = 284) or docetaxel (n = 293) (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.10.004). Patient demographics and baseline characteristics are presented in Table 1 and were well balanced between the groups. Overall, the median age was 65 years and most patients had received one prior line of treatment (74.7%), with the most common prior treatments being carboplatin (84.9%) and pembrolizumab (83.4%) (Table 1).

Efficacy

On 30 November 2022, the IDMC was convened to review the safety and efficacy data for the interim futility analysis, which was based on 279 OS events (75% of the total expected events) as of 15 August 2022 (median follow-up, 10.8 months). The futility analysis resulted in a HR for OS of 0.80; because this did not reach the adjusted futility boundary of HR >0.90 for stopping the trial early, the IDMC recommended the continuation of the study to final analysis.

As of 20 March 2023, a total of 377 OS events had been observed. The median follow-up was 17.1 months (range, 16.0-18.4 months), with 46.1% of patients in both treatment arms receiving subsequent anticancer therapy. The median OS was 12.2 months (95% CI 10.4-13.9 months) and 10.6 months (95% CI 9.4-12.3 months) in the sitra + nivo and docetaxel arms, respectively, with an HR of 0.86 (95% CI 0.70-1.05; P = 0.144; Figure 1A). The alpha boundary at the interim and final analyses for OS was 0.019 and 0.044, respectively. Therefore, the OS endpoint did not meet statistical significance in the final analysis. The estimated proportion of patients who were alive at 12 months was 50.2% (95% CI 44.1% to 56.0%) in the sitra + nivo arm and 44.1% (95% CI 38.0% to 50.1%) in the docetaxel arm. In prespecified subgroup analyses, the HRs for OS with sitra + nivo versus docetaxel were generally consistent with that seen for the overall population and numerically favored

Table 1. Demographics and baseline characteristics

Characteristics	Sitravatinib plus nivolumab (n = 284)	Docetaxel monotherapy (n = 293)	Overall (N = 577)
Age (years), median (range)	65.0 (35.0-85.0)	65.0 (23.0-86.0)	65.0 (23.0-86.0)
Sex, *n* (%)			
Male	170 (59.9)	168 (57.3)	338 (58.6)
Female	114 (40.1)	125 (42.7)	239 (41.4)
Race, *n* (%)			
White	211 (74.3)	198 (67.6)	409 (70.9)
Black or African American	8 (2.8)	14 (4.8)	22 (3.8)
Asian	7 (2.5)	9 (3.1)	16 (2.8)
Other	5 (1.8)	4 (1.4)	9 (1.6)[a]
Not reported/unknown/missing	53 (18.7)	68 (23.2)	121 (21.0)
ECOG PS, *n* (%)			
0	101 (35.6)	102 (34.8)	203 (35.2)
1	183 (64.4)	191 (65.2)	374 (64.8)
Smoking status, *n* (%)			
Never smoker	33 (11.6)	31 (10.6)	64 (11.1)
Current smoker	50 (17.6)	75 (25.6)	125 (21.7)
Former smoker	201 (70.8)	186 (63.5)	387 (67.1)
Unknown	0 (0)	1 (0.3)	1 (0.2)
Tumor PD-L1 expression, *n* (%)			
High	48 (16.9)	47 (16.0)	95 (16.5)
No/low	169 (59.5)	175 (59.7)	344 (59.6)
Missing	67 (23.6)	71 (24.2)	138 (23.9)
Presence of brain metastases, *n* (%)			
Yes	58 (20.4)	62 (21.2)	120 (20.8)
No	226 (79.6)	231 (78.8)	457 (79.2)
Prior treatment regimens in the advanced setting, *n* (%)[b]			
1	213 (75.0)	218 (74.4)	431 (74.7)
2	54 (19.0)	58 (19.8)	112 (19.4)
Prior platinum-based chemotherapy and CPI, *n* (%)			
Concurrent	247 (87.0)	260 (88.7)	507 (87.9)
Sequential	37 (13.0)	33 (11.3)	70 (12.1)
Prior platinum-based chemotherapy, *n* (%)[c]			
Cisplatin	66 (23.2)	61 (20.8)	127 (22.0)
Carboplatin	240 (84.5)	250 (85.3)	490 (84.9)
Median duration of prior CPI, months	8.5	8.3	8.3
Prior CPI, *n* (%)[c]			
Pembrolizumab	235 (82.7)	246 (84.0)	481 (83.4)
Nivolumab	20 (7.0)	13 (4.4)	33 (5.7)
Atezolizumab	21 (7.4)	23 (7.8)	44 (7.6)
Durvalumab	12 (4.2)	15 (5.1)	27 (4.7)
Ipilimumab	4 (1.4)	2 (0.7)	6 (1.0)
Other[d]	2 (0.7)	4 (1.4)	6 (1.0)
Best response to prior CPI, *n* (%)			
Complete response	3 (1.1)	2 (0.7)	5 (0.9)
Partial response	129 (45.4)	122 (41.6)	251 (43.5)
Stable disease	141 (49.6)	151 (51.5)	292 (50.6)
Progressive disease	3 (1.1)	6 (2.0)	9 (1.6)
Unknown	8 (2.8)	12 (4.1)	20 (3.5)

CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed-death ligand 1.
[a]Includes one American Indian or Alaska native patient and one native Hawaiian or other Pacific Islander patient.
[b]Thirty-four patients randomized under an early version of the protocol using a different stratification factor are not included here.
[c]Patients may be counted toward more than one regimen and percentages may add up to more than 100%.
[d]Other CPIs include blinded therapy, combinations of antineoplastic agents, investigational antineoplastic drugs, and monoclonal antibodies.

sitra + nivo in most subgroups, except in patients with ECOG PS 0 (sitra + nivo, $n = 101$; docetaxel, $n = 102$; HR 1.03, 95% CI 0.71-1.48), never smokers (sitra + nivo, $n = 33$; docetaxel, $n = 31$; HR 1.77, 95% CI 0.87-3.61), and those who had previously received sequential PBC followed by CPI (sitra + nivo, $n = 37$; docetaxel, $n = 33$; HR 1.27, 95% CI 0.70-2.29; Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2023.10.004).

The median PFS was 4.4 months (95% CI 3.9-5.4 months) and 5.4 months (95% CI 3.9-5.8 months) in the sitra + nivo and docetaxel arms, respectively, with an HR of 1.08 (95% CI 0.89-1.32; $P = 0.452$; Figure 1B). The estimated proportion of patients who were alive and progression free at 6 months was 35.7% (95% CI 29.7% to 41.8%) in the sitra + nivo group and 40.3% (95% CI 33.8% to 46.8%) in the docetaxel group.

ORR and CBR were analyzed in the modified ITT population, comprising 282 patients in the sitra + nivo arm and 290 patients in the docetaxel arm. The ORR was similar with sitra + nivo (15.6%; 95% CI 11.6% to 20.4%) and with docetaxel (17.2%; 95% CI 13.1% to 22.1%; $P = 0.597$), while the CBR was significantly improved with sitra + nivo (75.5%; 95% CI 70.1% to 80.4%) compared with docetaxel (64.5%; 95% CI 58.7% to 70.0%; $P = 0.004$; Table 2). The

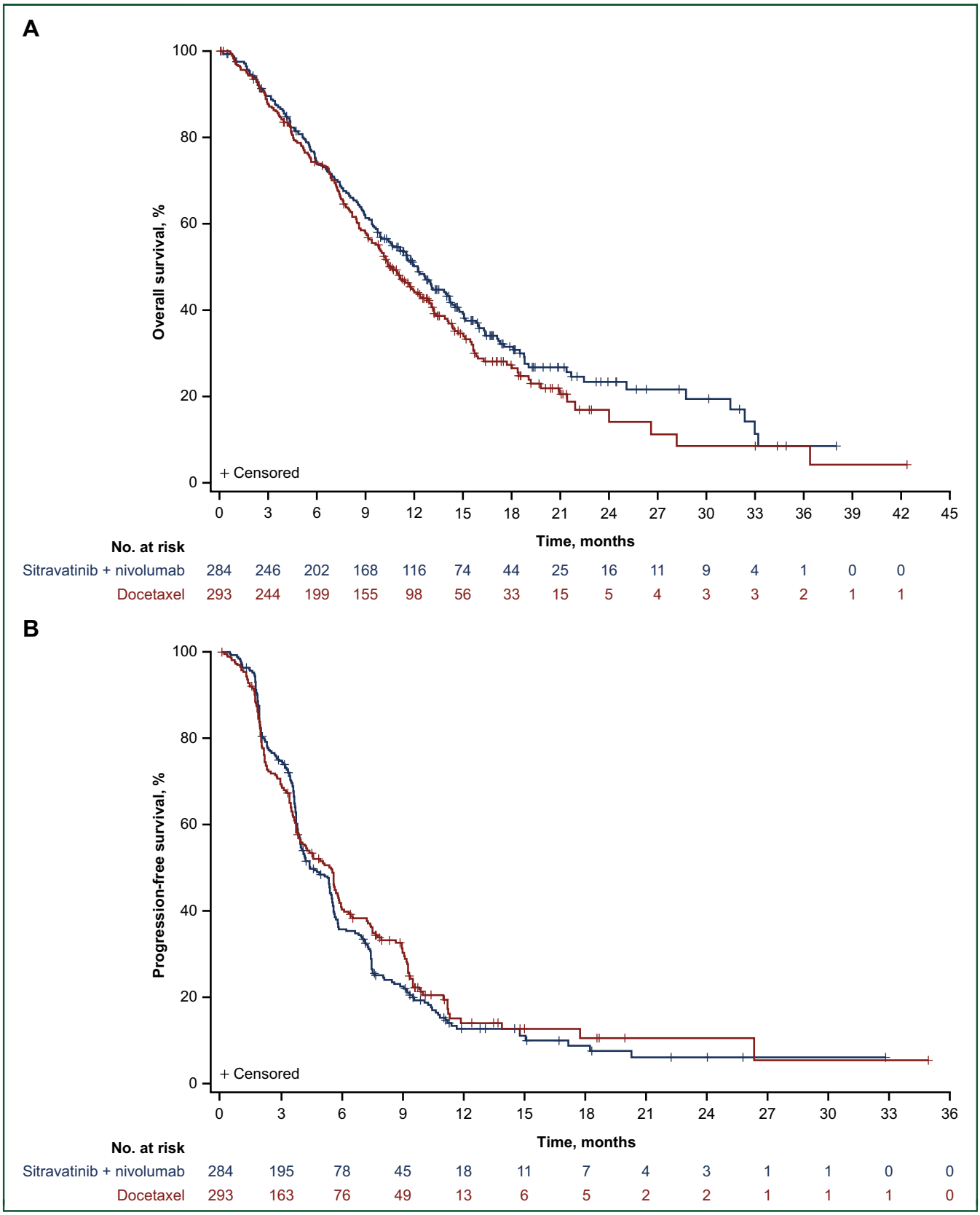

Figure 1. **(A) Overall survival and (B) progression-free survival (assessed by blinded independent central review) in patients with nonsquamous non-small-cell lung cancer treated with sitravatinib plus nivolumab versus docetaxel monotherapy who experienced disease progression on or after prior checkpoint inhibitor therapy with or following platinum-based chemotherapy (intent-to-treat population, *N* = 577).**

Table 2. Objective response rate and clinical benefit rate assessed by blinded independent central review

Efficacy outcome	Sitravatinib plus nivolumab ($n = 282$)	Docetaxel monotherapy ($n = 290$)
Objective response rate, *n* (%)	44 (15.6)	50 (17.2)
95% CI	11.6-20.4	13.1-22.1
P value	0.597	
Best overall response, *n* (%)		
Complete response	1 (0.4)	2 (0.7)
Partial response	43 (15.2)	48 (16.6)
Stable disease	169 (59.9)	137 (47.2)
Progressive disease	44 (15.6)	56 (19.3)
Not evaluable	25 (8.9)	47 (16.2)
Clinical benefit rate, *n* (%)	213 (75.5)	187 (64.5)
95% CI	70.1-80.4	58.7-70.0
P value	0.004	

CI, confidence interval.

median DOR was 7.4 months (95% CI 5.4-13.1 months) in the sitra + nivo arm versus 7.1 months (95% CI 5.9-11.8 months) in the docetaxel arm (HR 1.03, 95% CI 0.58-1.82; $P = 0.924$).

Safety

Overall, 281 patients were treated with sitra + nivo and 273 patients with docetaxel. The median duration of treatment was 4.1 months with sitravatinib, 4.6 months with nivolumab, and 3.5 months with docetaxel. Among 281 patients treated with sitra + nivo, 95.4% experienced TRAEs of any grade and 53.0% grade ≥3 TRAEs, with grade 3 TRAEs occurring in 48.8% of patients, grade 4 TRAEs in 3.9%, and a grade 5 TRAE in one patient (0.4%; acute pancreatitis; Table 3). The most common (≥25%) TRAEs of any grade were diarrhea (56.2%), nausea (31.3%), decreased appetite (28.5%), hypothyroidism (28.1%), and fatigue (26.3%); the most common (≥5%) grade ≥3 TRAEs were hypertension (13.5%), diarrhea (7.5%), and fatigue (6.8%). Immune-related (ir)AEs of any grade occurred in 45.9% of patients treated with sitra + nivo; the most frequent irAEs were hypothyroidism (13.9%) and diarrhea (11.7%). Grade ≥3 irAEs occurred in 14.2% of patients, with grade 3 irAEs in 13.5% of patients [including in two or more patients diarrhea (3.2%), and pneumonitis (2.1%), and two cases each (0.7%) of fatigue, hypoxia, colitis, palmar–plantar erythrodysesthesia syndrome, and increased alanine aminotransferase], grade 4 irAE (pneumonitis) in one patient, and grade 5 irAE (acute pancreatitis) in one patient.

Among 273 patients treated with docetaxel, 94.9% experienced any grade TRAEs and 66.7% grade ≥3 TRAEs, with grade 3 TRAEs occurring in 24.2% of patients, grade 4 TRAEs in 41.4%, and grade 5 TRAEs in three patients (1.1%; arrhythmia, respiratory failure, death; $n = 1$ each; Table 3). The most common (≥25%) TRAEs of any grade were diarrhea (35.5%), fatigue (35.5%), nausea (32.2%), decreased neutrophil count (31.9%), alopecia (30.8%), and neutropenia (26.0%); the most common (≥5%) grade ≥3 TRAEs were decreased neutrophil count (29.3%), neutropenia (23.1%), decreased white blood cell count (10.6%), fatigue (8.4%), febrile neutropenia (7.0%), asthenia (6.6%), and leukopenia (5.1%).

Overall, 18.5% of patients discontinued sitra and/or nivo treatment due to TRAEs, including diarrhea (2.5%), fatigue (1.1%), pneumonitis (1.1%), and stomatitis (1.1%). In the docetaxel arm, TRAEs led to treatment discontinuation in 11.7% of patients, with the most common being fatigue (1.8%) and asthenia (1.8%). TRAEs led to dose reduction or interruption of sitra and/or nivo in 65.5% of patients and of docetaxel in 40.3% of patients (Table 3). Further details on treatment discontinuation and dose reduction or interruption are provided in the Supplementary Appendix S1, available at https://doi.org/10.1016/j.annonc.2023.10.004 (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.10.004). Treatment-emergent AEs for both treatment arms are shown in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.10.004.

DISCUSSION

In this study, sitra + nivo was compared with docetaxel to assess whether this combination could overcome resistance to prior CPI in patients with advanced nonsquamous NSCLC who initially benefitted from (≥4 months on CPI without progression) and subsequently experienced disease progression on or after CPI in combination with or following PBC. In the phase II MRTX-500 study of patients with nonsquamous NSCLC, sitra + nivo demonstrated a manageable safety profile and promising clinical activity in patients who experienced disease progression on prior CPI, especially in patients with one or two prior lines of therapy, with a median OS of 14.9 months.[19] In the present phase III study, the median OS was numerically longer with sitra + nivo compared with docetaxel (12.2 versus 10.6 months, respectively), although this difference was not statistically significant (HR 0.86; $P = 0.144$). Sitra + nivo did not improve PFS (median, 4.4 versus 5.4 months, respectively) or ORR (15.6% versus 17.2%, respectively) compared with docetaxel; however, CBR was significantly improved with sitra + nivo compared with docetaxel (75.5% versus 64.5%, respectively; $P = 0.004$).

The safety profile of sitra + nivo was consistent with that previously observed in the MRTX-500 study, with common TRAEs including diarrhea, fatigue, nausea, and decreased appetite.[19] The frequency of grade ≥3 TRAEs was similar between the SAPPHIRE and MRTX-500 studies (53% and 58%, respectively), as was the frequency of irAEs (46% and 44%, respectively), with hypothyroidism being the most common in both studies.[19] TRAEs leading to sitra + nivo discontinuation were also similar between both studies (19% and 14%, respectively).[19] Compared with docetaxel in this present study, treatment with sitra + nivo resulted in a lower frequency of grade ≥3 TRAEs, but a higher rate of TRAEs leading to dose reduction or interruption.

Treatment options are limited for patients with advanced NSCLC who have previously received CPI and PBC. Docetaxel and docetaxel-based regimens are the current standard of

Table 3. Summary of treatment-related adverse events

Treatment-related adverse events, *n* (%)	Sitravatinib plus nivolumab (*n* = 281)					
	Any grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any event[a]	**268 (95.4)**	**15 (5.3)**	**104 (37.0)**	**137 (48.8)**	**11 (3.9)**[b]	**1 (0.4)**[c]
Most frequent events[d]						
Diarrhea	158 (56.2)	84 (29.9)	53 (18.9)	21 (7.5)	0 (0)	0 (0)
Nausea	88 (31.3)	53 (18.9)	31 (11.0)	4 (1.4)	0 (0)	0 (0)
Decreased appetite	80 (28.5)	34 (12.1)	41 (14.6)	5 (1.8)	0 (0)	0 (0)
Hypothyroidism	79 (28.1)	24 (8.5)	54 (19.2)	1 (0.4)	0 (0)	0 (0)
Fatigue	74 (26.3)	27 (9.6)	28 (10.0)	19 (6.8)	0 (0)	0 (0)
Hypertension	70 (24.9)	5 (1.8)	26 (9.3)	38 (13.5)	1 (0.4)	0 (0)
Vomiting	57 (20.3)	36 (12.8)	19 (6.8)	2 (0.7)	0 (0)	0 (0)
Weight decreased	53 (18.9)	23 (8.2)	25 (8.9)	5 (1.8)	0 (0)	0 (0)
Stomatitis	50 (17.8)	23 (8.2)	20 (7.1)	7 (2.5)	0 (0)	0 (0)
PPE syndrome	49 (17.4)	21 (7.5)	20 (7.1)	8 (2.8)	0 (0)	0 (0)
Asthenia	40 (14.2)	16 (5.7)	20 (7.1)	4 (1.4)	0 (0)	0 (0)
ALT increased	36 (12.8)	25 (8.9)	6 (2.1)	5 (1.8)	0 (0)	0 (0)
AST increased	33 (11.7)	24 (8.5)	7 (2.5)	2 (0.7)	0 (0)	0 (0)
Abdominal pain	30 (10.7)	15 (5.3)	12 (4.3)	3 (1.1)	0 (0)	0 (0)
Dysphonia	30 (10.7)	25 (8.9)	4 (1.4)	1 (0.4)	0 (0)	0 (0)
Leading to treatment discontinuation	52 (18.5)	—	—	—	—	—
Sitravatinib	44 (15.7)	—	—	—	—	—
Nivolumab	18 (6.4)	—	—	—	—	—
Leading to dose reduction or interruption	184 (65.5)	—	—	—	—	—
Sitravatinib reduction or interruption	175 (62.3)	—	—	—	—	—
Dose reduction	137 (48.8)	—	—	—	—	—
Dose interruption	152 (54.1)	—	—	—	—	—
Nivolumab interruption	55 (19.6)	—	—	—	—	—
Treatment-related adverse events, *n* (%)	**Docetaxel monotherapy (*n* = 273)**					
	Any grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Any event[a]	**259 (94.9)**	**19 (7.0)**	**58 (21.2)**	**66 (24.2)**	**113 (41.4)**[e]	**3 (1.1)**[f]
Most frequent events[d]						
Diarrhea	97 (35.5)	58 (21.2)	30 (11.0)	9 (3.3)	0 (0)	0 (0)
Fatigue	97 (35.5)	33 (12.1)	41 (15.0)	23 (8.4)	0 (0)	0 (0)
Nausea	88 (32.2)	52 (19.0)	29 (10.6)	7 (2.6)	0 (0)	0 (0)
Neutrophil count decreased	87 (31.9)	4 (1.5)	3 (1.1)	17 (6.2)	63 (23.1)	0 (0)
Alopecia	84 (30.8)	42 (15.4)	41 (15.0)	1 (0.4)	0 (0)	0 (0)
Neutropenia	71 (26.0)	2 (0.7)	6 (2.2)	19 (7.0)	44 (16.1)	0 (0)
Decreased appetite	68 (24.9)	36 (13.2)	28 (10.3)	4 (1.5)	0 (0)	0 (0)
Asthenia	65 (23.8)	13 (4.8)	34 (12.5)	18 (6.6)	0 (0)	0 (0)
Anemia	57 (20.9)	16 (5.9)	29 (10.6)	12 (4.4)	0 (0)	0 (0)
Stomatitis	53 (19.4)	27 (9.9)	21 (7.7)	5 (1.8)	0 (0)	0 (0)
Vomiting	44 (16.1)	24 (8.8)	16 (5.9)	4 (1.5)	0 (0)	0 (0)
Dysgeusia	42 (15.4)	31 (11.4)	11 (4.0)	0 (0)	0 (0)	0 (0)
Peripheral edema	35 (12.8)	24 (8.8)	6 (2.2)	5 (1.8)	0 (0)	0 (0)
White blood cell count decreased	35 (12.8)	2 (0.7)	4 (1.5)	21 (7.7)	8 (2.9)	0 (0)
Constipation	29 (10.6)	22 (8.1)	6 (2.2)	1 (0.4)	0 (0)	0 (0)
Leading to treatment discontinuation	32 (11.7)	—	—	—	—	—
Leading to dose reduction or interruption	110 (40.3)	—	—	—	—	—
Dose reduction	85 (31.1)	—	—	—	—	—
Dose interruption	45 (16.5)	—	—	—	—	—

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; PPE, palmar—plantar erythrodysesthesia.
[a]For each category, patients are included only once at the maximum severity.
[b]Grade 4 treatment-related adverse events included lipase increased ($n = 2$), colitis, intestinal perforation, amylase increased, GGT increased, skin ulcer, hyponatremia, hyperlipasemia, hyperkalemia, hypertension, pneumonitis, and acute myocardial infarction ($n = 1$ each).
[c]One patient experienced grade 5 acute pancreatitis.
[d]Any grade treatment-related adverse events occurring in >10% of patients.
[e]Other grade 4 treatment-related adverse events included leukopenia ($n = 7$), febrile neutropenia ($n = 6$), hypomagnesemia, acute respiratory failure, respiratory tract infection, colonic abscess, and sepsis ($n = 1$ each).
[f]Grade 5 treatment-related adverse events observed in three patients (arrhythmia, respiratory failure, death; $n = 1$ each).

care after CPI and PBC, but docetaxel is associated with poor survival outcomes and severe toxicities, such as neutropenia, fatigue, and febrile neutropenia,[3-6] as observed in our study. The median OS with docetaxel in patients previously treated with CPI and PBC in recent phase III studies ranges between 10.5 and 12.1 months,[3-6] which is in line with the 10.6 months reported in the present study. Several investigational agents, alone or in combination with docetaxel, have been evaluated in phase III studies to assess whether they could improve survival outcomes compared with docetaxel monotherapy; most of these trials have not shown survival benefits compared with docetaxel in patients with NSCLC previously treated with CPI and PBC.[3-6]

Other studies are evaluating docetaxel compared with combinations of CPIs and agents targeting TAM receptors and/or VEGFR2 with the aim of modulating the

immunosuppressive TME and overcoming CPI resistance.[10,23] Similar to sitravatinib, cabozantinib is another multikinase inhibitor targeting TAM receptors and VEGFR2, among other targets.[10] In the phase III CONTACT-01 trial, cabozantinib plus atezolizumab was compared with docetaxel in patients with NSCLC previously treated with CPI and PBC; however, in line with the present study, results showed that this combination was not superior to docetaxel monotherapy in this patient population, with a median OS of 10.7 versus 10.5 months, respectively (HR 0.88; $P = 0.367$).[5] Lenvatinib, a multikinase inhibitor targeting VEGF and other growth factor receptors, in combination with pembrolizumab, was compared with docetaxel in the phase III LEAP-008 study enrolling patients with NSCLC who experienced disease progression on prior CPI and PBC,[24] following promising results from a phase Ib/II study in advanced solid tumors.[25] However, similar to the results from SAPPHIRE and CONTACT-01,[5] the LEAP-008 study did not meet its dual primary endpoint of OS and PFS; no improvement was seen with lenvatinib plus pembrolizumab compared with docetaxel.[26] Unlike these multitargeted tyrosine kinase inhibitors, ramucirumab is a monoclonal antibody only targeting VEGFR2. In a randomized phase II study, patients with NSCLC previously treated with CPI and PBC received either ramucirumab plus pembrolizumab or other standard of care treatments, including docetaxel monotherapy, docetaxel plus ramucirumab, gemcitabine, or pemetrexed.[27] The median OS was significantly improved with ramucirumab plus pembrolizumab compared with standard of care (HR 0.69, 80% CI 0.5-0.9; $P = 0.05$),[27] and this combination is being further investigated in the phase III Pragmatica-Lung study.[28] Additional studies are investigating other combinations of TAM receptor inhibitors with CPIs, such as sitravatinib plus tislelizumab compared with docetaxel in a phase III trial (NCT04921358)[29] and bemcentinib (an AXL inhibitor) plus pembrolizumab in the phase II BGBC008 trial (NCT03184571).[30] Nevertheless, further research is required to identify improved treatment options compared with docetaxel for patients with NSCLC after CPI and PBC.

Resistance to CPI therapy is a complex process associated with various mechanisms, not only related to an immunosuppressive TME and TAM receptor activation, but also with co-inhibitory checkpoints, defects in antigen processing or neoantigen loss, and tumor-mediated immune suppression.[9,10] Therefore overcoming CPI resistance in patients with NSCLC remains challenging, with many novel targets being explored. Future studies should incorporate standardized, consensus-based definitions of CPI resistance, ideally from a large international oncology society, such as the Society for Immunotherapy of Cancer.[10,31] CPI resistance should be clarified both for patients who received prior CPI as monotherapy and for those who received it as part of combination therapy, such as in combination with PBC, because the presence or absence of chemotherapy with CPI may influence the nature of resistance (i.e. primary versus secondary resistance) and sensitivity to subsequent treatment.[10] The timing of PBC and CPI administration, either concurrently or sequentially, should also be further evaluated in future studies because this may affect the response to subsequent CPI treatment. For example, subgroup analyses in the present study suggested that patients who received prior PBC and CPI concurrently had longer OS compared with those who received PBC followed by CPI sequentially. Another important area of research is the evaluation of potential biomarkers to identify patients most likely to benefit from subsequent therapy after developing CPI resistance. In the present study, there were some patients who benefitted from sitra + nivo by potentially modulating the immunosuppressive TME. However, identifying biomarkers to select these patients is challenging due to an incomplete biological understanding of all the factors involved in the TME and CPI resistance, as well as a lack of adequate animal models. A limitation of this study, and of biomarker research in this context, is that sample collection was based on archived tissue samples, and the collection of fresh samples at progression to assess the dynamic nature of PD-L1 expression was not required. Further research is needed in this field to assess the potential use and predictive ability of novel immune biomarkers following the development of CPI resistance. Evaluation of future potential drugs within this framework and additional prospective biomarker analyses may allow the identification of patients more likely to benefit from treatment after developing CPI resistance.

Conclusion

In patients with advanced nonsquamous NSCLC who had experienced disease progression on prior CPI with or after PBC, treatment with sitra + nivo demonstrated a numerical improvement in OS compared with docetaxel, although this difference was not statistically significant, and hence the study did not meet its primary endpoint. Overall, a higher proportion of patients in the docetaxel arm developed grade $\geq$3 TRAEs than patients treated with sitra + nivo, and the safety profiles of both regimens were consistent with previous reports.

ACKNOWLEDGEMENTS

We thank the patients, their families, and their caregivers, as well as the study investigators and their team members at each site for participation in the SAPPHIRE trial. All authors reviewed, revised, and approved the final manuscript. This study was sponsored by Mirati Therapeutics, Inc. Medical writing support under the direction of the authors was provided by Tamsyn Mamotte, MSc, and Flaminia Fenoaltea, MSc, of Ashfield MedComms, an Inizio Company, and funded by Mirati Therapeutics, Inc.

FUNDING

This work was supported by Mirati Therapeutics, Inc., and Bristol Myers Squibb (no grant number).

DISCLOSURE

HB reports honoraria for lectures for Amgen, Pfizer, Daiichi, and Regeneron; writing engagements (nonfinancial) with

Amgen, BMS, and AstraZeneca; advisory board participation with BMS, Lilly, Genentech, Inc., Pfizer, Merck, EMD-Serono, Boehringer Ingelheim, AstraZeneca, Novartis, Genmab, Regeneron, BioNTech, Amgen, Axiom, PharmaMar, Takeda, Mirati Therapeutics, Inc., Daiichi, Guardant, Natera, Oncocyte, BeiGene, iTEO, Jazz Pharmaceuticals, Janssen, Da Volterra, Puma, and BerGenBio; full or part-time employment at Fox Chase Cancer Center; stock options from Sonnet Bio, Inspirna (formerly Rgenix) and Nucleai; research grants from BMS and Lilly; principal investigator (nonfinancial) for AstraZeneca, Mirati Therapeutics, Inc., and BMS; data and safety monitoring board for the University of Pennsylvania: CAR T Program, Takeda, Incyte, Novartis, and Springworks; and travel support from Amgen, BMS, Merck, Lilly, EMD-Serono, Genentech, Inc., and Regeneron. FdM reports speaker's bureau and advisory board participation with AstraZeneca, F. Hoffmann-La Roche Ltd, BMS, and Novartis. DD reports institutional funding from BMS; principal investigator (nonfinancial) for BMS, F. Hoffmann-La Roche Ltd, Mirati Therapeutics, Inc., and MSD; and an advisory role (nonfinancial) for Amgen, BMS, and MSD. CR reports advisory board fees from AstraZeneca; and stocks from Gilead. WSMET reports research grants from MSD, AstraZeneca, and Sanofi/Regeneron; principal investigator (non-financial) for Roche, Mirati Therapeutics, BeiGene, and Genmab. MLJ reports research funding (institutional) from AbbVie, Acerta, Adaptimmune, Amgen, Apexigen, Arcus Biosciences, Array BioPharma, Artios Pharma, AstraZeneca, Atreca, BeiGene, BerGenBio, BioAtla, Black Diamond, Boehringer Ingelheim, BMS, Calithera Biosciences, Carisma Therapeutics, Checkpoint Therapeutics, City of Hope National Medical Center, Corvus Pharmaceuticals, Curis, CytomX, Daiichi Sankyo, Dracen Pharmaceuticals, Dynavax, Lilly, Elicio Therapeutics, EMD Serono, EQRx, Erasca, Exelixis, Fate Therapeutics, Genentech, Inc./F. Hoffmann-La Roche Ltd, Genmab, Genocea Biosciences, GSK, Gritstone Oncology, Guardant Health, Harpoon, Helsinn Healthcare SA, Hengrui Therapeutics, Hutchison MediPharma, IDEAYA, Biosciences, IGM Biosciences, Immunitas Therapeutics, Immunocore, Incyte, Janssen, Jounce Therapeutics, Kadmon Pharmaceuticals, Kartos Therapeutics, Loxo Oncology, Lycera, Memorial Sloan-Kettering, Merck, Merus, Mirati Therapeutics, Inc., Mythic Therapeutics, NeoImmuneTech, Neovia Oncology, Novartis, Numab Therapeutics, Nuvalent, OncoMed Pharmaceuticals, Palleon Pharmaceuticals, Pfizer, PMV Pharmaceuticals, Rain Therapeutics, RasCal Therapeutics, Regeneron Pharmaceuticals, Relay Therapeutics, Revolution Medicines, Ribon Therapeutics, Rubius Therapeutics, Sanofi, Seven and Eight Biopharmaceuticals/Birdie Biopharmaceuticals, Shattuck Labs, Silicon Therapeutics, Stemcentrx, Syndax Pharmaceuticals, Takeda Pharmaceuticals, Tarveda, TCR2 Therapeutics, Tempest Therapeutics, Tizona Therapeutics, TMUNITY Therapeutics, Turning Point Therapeutics, University of Michigan, Vyriad, WindMIL Therapeutics, and Y-mAbs Therapeutic; consulting/advisory role feed (institutional) from AbbVie, Amgen, Arcus Biosciences, ArriVent, Astellas, AstraZeneca, Axelia Oncology, Black Diamond, Calithera Biosciences, Daiichi Sankyo, EcoR1, Genentech, Inc./F. Hoffmann-La Roche Ltd, Genmab, Genocea Biosciences, GSK, Gritstone Oncology, IDEAYA Biosciences, Immunocore, iTeos, Janssen, Jazz Pharmaceuticals, Merck, Mirati Therapeutics, Inc., Molecular Axiom, Novartis, Oncorus, Pyramid Biosciences, Regeneron Pharmaceuticals, Revolution Medicines, Sanofi-Aventis, Seagen, Synthekine, Takeda Pharmaceuticals, Turning Point Therapeutics, and VBL Therapeutics. EBG reports research grants from ABL-Bio, AstraZeneca, BMS, Dynavax, Technologies, Eli Lilly, EMD Serono, Genentech, Inc., Iovance Biotherapeutics, Merck, Mirati Therapeutics, Inc., Neon, and Novartis; an advisory role for AbbVie, ABL-Bio, AstraZeneca, Boehringer Ingelheim, BMS, Dracen Pharmaceuticals, EMD Serono, Eisai, Eli Lilly, Gilead, GSK, Ipsen, Merck, Natera, Novartis, Personalis, Regeneron, Sanofi, Shionogi, and XILO. KH reports financial interests (personal) and advisory board participation with Mirati Therapeutics, Inc., Perthera, BMS, BeiGene, Iovance Biotherapeutics, Lyell, BioNTech, and AstraZeneca; and an institutional research grant or contract with OncoC4. DP reports to be an invited speaker for AstraZeneca, Novartis, priME Oncology, Peer CME, Samsung, AbbVie, Janssen, GSK, Pfizer; advisory board fees from AstraZeneca, BMS, Merck, Novartis, Pfizer, F. Hoffmann-La Roche Ltd, Samsung, Celgene, AbbVie, Daiichi Sankyo, Janssen, Sanofi-Aventis, GSK, Seagen, Pierre Fabre, and Gilead; principal investigator for AstraZeneca, BMS, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Pfizer, F. Hoffmann-La Roche Ltd, Medimmune, Sanofi-Aventis, Taiho Pharma, Novocure, Daiichi Sankyo, Janssen, AbbVie, and GSK. MR reports to be an invited speaker for Amgen, AstraZeneca, BMS, Boehringer Ingelheim, GSK, Lilly, Mirati Therapeutics, Inc., MSD, Merck, Novartis, Regeneron, Sanofi, and F. Hoffmann-La Roche Ltd; speaker's bureau fees from Amgen, AstraZeneca, BMS, Boehringer Ingelheim, GSK, Lilly, Mirati Therapeutics, Inc., MSD, Merck, Novartis, Regeneron, Sanofi, and F. Hoffmann-La Roche Ltd; advisory board fees from Amgen, AstraZeneca, BMS, BioNTech, Boehringer Ingelheim, Daiichi Sankyo, Gilead, GSK, MSD, Mirati Therapeutics, Inc., Pfizer, Regeneron, Sanofi, and F. Hoffmann-La Roche Ltd; and is a member of the data and safety monitoring board for Daiichi Sankyo and Sanofi. SPo reports consulting fees (personal) from Amgen, AstraZeneca, Bayer, Blueprint Medicines, BMS, Boehringer Ingelheim, Daiichi Sankyo, GSK, Guardant Health, Incyte, Janssen, Lilly, Merck Serono, MSD, Novartis, F. Hoffmann-La Roche Ltd, Takeda, Pfizer, Seattle Genetics, Turning Point Therapeutics, and EQRx; honoraria for lectures, presentations or speakers bureaus (personal) from AstraZeneca, Bayer, Guardant Health, Janssen, Merck Serono, F. Hoffmann-La Roche Ltd, and Takeda; payment for expert testimony (personal) from F. Hoffmann-La Roche Ltd and Merck Serono; support for attending meetings and/or travel from Janssen and F. Hoffmann-La Roche Ltd; and leadership or fiduciary role in other board, society, committee, or advocacy group (nonfinancial) for the British Thoracic Oncology Group, ALK Positive UK, Lung Cancer Europe, Ruth Strauss Foundation, Mesothelioma Applied Research Foundation, and ETOP-IBCSG Partners Foundation Board. RSH reports

consulting fees from DynamiCure Biotechnology, eFFECTOR Therapeutics, Eli Lilly, Genentech, Inc., Gilead, HiberCell, Janssen, Johnson and Johnson, Loxo Oncology, Merck, Mirati Therapeutics, Inc., NextCure, Novartis, Oncocyte Corp, Oncternal Therapeutics, Pfizer, Regeneron Pharmaceuticals, F. Hoffmann-La Roche Ltd, Sanofi, Seattle Genetics, and AbbVie; advisory board fees from AstraZeneca, Bolt Therapeutics, BMS, Candel Therapeutics, Cybrexa Therapeutics, EMD Serono, I-Mab Biopharma, Immune-Onc Therapeutics, Normunity, Ocean Biomedical, Revelar Biotherapeutics, Ribbon Therapeutics, Xencor; stock options from Normunity, Immunocore, and Checkpoint Therapeutics; member of the board of directors for Junshi Pharmaceuticals, American Association for Cancer Research, Immunocore, International Association for the Study of Lung Cancer, Society for Immunotherapy of Cancer, and Southwest Oncology Group; full-time employment at Yale Cancer Center; and research support from AstraZeneca, Eli Lilly, Genentech, Inc./F. Hoffmann-La Roche Ltd, and Merck. TAL reports consulting fees from Catalyst, Eisai, Jazz, Janssen, and F. Hoffmann-La Roche Ltd; and advisory board participation with GI Therapeutics, Pfizer, Regeneron, Amgen, AstraZeneca, Novocure, Takeda, Merck, and Jazz Pharmaceuticals. RLS reports full- or part-time employment with Mirati Therapeutics, Inc.; and stocks/shares from Mirati Therapeutics, Inc. XY reports full or part-time employment with Mirati Therapeutics, Inc.; and stocks/shares from Mirati Therapeutics, Inc. RH reports full- or part-time employment with Mirati Therapeutics, Inc.; and stocks/shares from Mirati Therapeutics, Inc. SPe reports honoraria (institutional) from AiCME, AstraZeneca, Boehringer Ingelheim, BMS, ecancer, Eli Lilly, Foundation Medicine, GSK, Illumina, Imedex, Ipsen, Medscape, Merck Sharp, and Dohme, Mirati Therapeutics, Inc., Novartis, PER, PeerView, Pfizer, F. Hoffmann-La Roche Ltd/Genentech, Inc., RTP, Sanofi, Takeda, and Galencia; financial support (institutional) from Amgen, Arcus, AstraZeneca, BeiGene, BMS, GSK, iTeos, Merck Sharp and Dohme, Mirati Therapeutics, Inc., Pharma Mar, Promontory Therapeutics, F. Hoffmann-La Roche Ltd/Genentech, Inc., and Seattle Genetics; and is a member of ESMO, ASCO, AACR, IASLC, SSOM, SAKK, and ETOP; Other: Vice President of Swiss Cancer League, past President of ESMO, Strategic Advisory board SPCC (Paris-Saclay) Chair, and ETOP scientific chair. All other authors have declared no conflicts of interest.

DATA SHARING

At Mirati Therapeutics, Inc. we are committed to patient care, advancing scientific understanding, and enabling the scientific community to learn from and build upon the research we have undertaken. To that end, we will honor legitimate requests for our clinical trial data from qualified researchers and investigators for conducting methodologically sound research. We will share clinical trial data, clinical study reports, study protocols, and statistical analysis plans from clinical trials for which results have been posted on clinicaltrials.gov for products and indications approved by regulators in the United States and/or European Union. Sharing is subject to the protection of patient privacy and respect for the patient's informed consent. In general, data will be made available for specific requests ~24 months after clinical trial completion from our in-scope interventional trials. For additional information on proposals with regard to data-sharing collaborations with Mirati Therapeutics, Inc., please email us at medinfo@mirati.com.

REFERENCES

1. Hendriks L, Kerr K, Menis J, et al. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34:358-376.
2. Schoenfeld AJ, Hellmann MD. Acquired resistance to immune checkpoint inhibitors. *Cancer Cell*. 2020;37:443-455.
3. de Langen AJ, Johnson ML, Mazieres J, et al. Sotorasib versus docetaxel for previously treated non-small-cell lung cancer with KRASG12C mutation: a randomised, open-label, phase 3 trial. *Lancet*. 2023;401:733-746.
4. Han B, Shi Y, Feinstein T, et al. DUBLIN-3 (BPI-2358-103): a global phase (Ph) III trial with the plinabulin/docetaxel (Plin/Doc) combination vs. Doc in 2nd/3rd line NSCLC patients (pts) with EGFR-wild type (wt) progressing on a prior platinum-based regimen. *Ann Oncol*. 2021;32:S1326.
5. Neal J, Pavlakis N, Kim S, et al. CONTACT-01: efficacy and safety from a phase III study of atezolizumab (atezo) + cabozantinib (cabo) vs docetaxel (doc) monotherapy in patients (pts) with metastatic NSCLC (mNSCLC) previously treated with checkpoint inhibitors and chemotherapy. *J Thorac Oncol*. 2023;18:S39-S40.
6. Paz-Ares L, Goto Y, Lim W, et al. Canakinumab (CAN)+ docetaxel (DTX) for the second-or third-line (2/3L) treatment of advanced non-small cell lung cancer (NSCLC): CANOPY-2 phase III results. *Ann Oncol*. 2021;32:S953-S954.
7. Du Q, Jiang G, Li S, et al. Docetaxel increases the risk of severe infections in the treatment of non-small cell lung cancer: a meta-analysis. *Oncoscience*. 2018;5:220.
8. Garon EB, Ciuleanu T-E, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384:665-673.
9. Aldea M, Andre F, Marabelle A, et al. Overcoming resistance to tumor-targeted and immune-targeted therapies. *Cancer Discov*. 2021;11:874-899.
10. Peters S, Paz-Ares L, Herbst RS, et al. Addressing CPI resistance in NSCLC: targeting TAM receptors to modulate the tumor microenvironment and future prospects. *J Immunother Cancer*. 2022;10:e004863.
11. Bergerot P, Lamb P, Wang E, et al. Cabozantinib in combination with immunotherapy for advanced renal cell carcinoma and urothelial carcinoma: rationale and clinical evidence. *Mol Cancer Ther*. 2019;18:2185-2193.
12. Akalu YT, Rothlin CV, Ghosh S. TAM receptor tyrosine kinases as emerging targets of innate immune checkpoint blockade for cancer therapy. *Immunol Rev*. 2017;276:165-177.
13. Du W, Huang H, Sorrelle N, et al. Sitravatinib potentiates immune checkpoint blockade in refractory cancer models. *JCI Insight*. 2018;3:e124184.
14. Oliva M, Chepeha D, Araujo DV, et al. Antitumor immune effects of preoperative sitravatinib and nivolumab in oral cavity cancer: SNOW window-of-opportunity study. *J Immunother Cancer*. 2021;9:e003476.
15. Bauer T, Cho BC, Heist R, et al. First-in-human phase 1/1b study to evaluate sitravatinib in patients with advanced solid tumors. *Invest New Drugs*. 2022;40:990-1000.
16. Karam JA, Msaouel P, Haymaker CL, et al. Phase II trial of neoadjuvant sitravatinib plus nivolumab in patients undergoing nephrectomy for

locally advanced clear cell renal cell carcinoma. *Nat Commun*. 2023;14:2684.
17. Msaouel P, Goswami S, Thall PF, et al. A phase 1-2 trial of sitravatinib and nivolumab in clear cell renal cell carcinoma following progression on antiangiogenic therapy. *Sci Transl Med*. 2022;14:eabm6420.
18. Msaouel P, Siefker-Radtke A, Sweis R, et al. 705MO Sitravatinib (sitra) in combination with nivolumab (nivo) demonstrates clinical activity in checkpoint inhibitor (CPI) naïve, platinum-experienced patients (pts) with advanced or metastatic urothelial carcinoma (UC). *Ann Oncol*. 2020;31:S556.
19. He K, Berz D, Gadgeel SM, et al. MRTX-500 phase 2 trial: sitravatinib with nivolumab in patients with nonsquamous NSCLC progressing on or after checkpoint inhibitor therapy or chemotherapy. *J Thorac Oncol*. 2023;18:907-921.
20. Council for International Organizations of Medical Sciences. International ethical guidelines for biomedical research involving human subjects. *Bull Med Ethics*. 2002:17-23.
21. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;20:2194.
22. Food and Drug Administration. International Conference on Harmonization. Integrated addendum to ICH E6(R1): guideline for Good Clinical Practice E6(R2). 2016. Available at https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf. Accessed July 1, 2023.
23. Frisone D, Friedlaender A, Addeo A, et al. The landscape of immunotherapy resistance in NSCLC. *Front Oncol*. 2022;12:817548.
24. Leighl NB, Hui R, Rodríguez-Abreu D, et al. Pembrolizumab plus lenvatinib vs docetaxel in patients with previously treated metastatic non-small-cell lung cancer (NSCLC) and PD after platinum-doublet chemotherapy and immunotherapy: phase 3, randomized, open-label LEAP-008 trial. *Cancer Res*. 2020;80:CT289.
25. Taylor MH, Lee C-H, Makker V, et al. Phase IB/II trial of lenvatinib plus pembrolizumab in patients with advanced renal cell carcinoma, endometrial cancer, and other selected advanced solid tumors. *J Clin Oncol*. 2020;38:1154.
26. Merck. Merck and Eisai Provide Update on Two Phase 3 Trials Evaluating KEYTRUDA® (pembrolizumab) Plus LENVIMA® (lenvatinib) in Patients With Certain Types of Metastatic Non-Small Cell Lung Cancer. 2023. Available at https://www.merck.com/news/merck-and-eisai-provide-update-on-two-phase-3-trials-evaluating-keytruda-pembrolizumab-plus-lenvima-lenvatinib-in-patients-with-certain-types-of-metastatic-non-small-cell-lung-cancer/. Accessed October 2, 2023.
27. Reckamp KL, Redman MW, Dragnev KH, et al. Phase II randomized study of ramucirumab and pembrolizumab versus standard of care in advanced non—small-cell lung cancer previously treated with immunotherapy—Lung-MAP S1800A. *J Clin Oncol*. 2022;40:2295-2307.
28. ClinicalTrials.gov. Ramucirumab plus pembrolizumab vs usual care for treatment of stage IV or recurrent non-small cell lung cancer following immunotherapy, Pragmatica-Lung study. 2023. Available at https://clinicaltrials.gov/ct2/show/NCT05633602. Accessed June 20, 2023.
29. ClinicalTrials.gov. Tislelizumab in combination with sitravatinib in patients with locally advanced or metastatic non-small cell lung cancer. 2023. Available at https://clinicaltrials.gov/ct2/show/NCT04921358. Accessed May 19, 2023.
30. ClinicalTrials.gov. Bemcentinib (BGB324) in combination with pembrolizumab in patients with advanced NSCLC. 2022. Available at https://clinicaltrials.gov/ct2/show/NCT03184571. Accessed May 19, 2023.
31. Kluger HM, Tawbi HA, Ascierto ML, et al. Defining tumor resistance to PD-1 pathway blockade: recommendations from the first meeting of the SITC immunotherapy resistance Taskforce. *J Immunother Cancer*. 2020;8:e000398.