MRTX-500: Phase 2 trial of sitravatinib (sitra) + nivolumab (nivo) in patients (pts) with non-squamous (NSQ) non-small cell lung cancer (NSCLC) progressing on or after prior checkpoint inhibitor (CPI) therapy

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Background

Sitravatinib

- Checkpoint inhibitor therapy (CPI) has dramatically changed the treatment landscape for various cancer types, including NSCLC[1–3]
- Many patients experience disease progression and develop CPI resistance through various mechanisms, including an immunosuppressive tumor microenvironment (TME)[3,4]
- Sitravatinib is a receptor tyrosine kinase inhibitor (TKI) that targets TAM receptors (TYRO3, AXL, MERTK) and VEGFR2 which have been shown to modulate the immune TME[5,6]
  - Targeting TAM: macrophages shift from (type) M2 to M1, resulting in production of immuno-stimulating cytokines, which enhances innate and adaptive immune response[5,7]
  - Targeting VEGFR2: reduces regulatory T cells and myeloid-derived suppressor cells (MDSCs), which releases brakes for expansion of CD8+ T cells via PD-1 inhibition[8]
- Preliminary data from a Phase 1 window-of-opportunity trial in oral cavity cancer demonstrated sitravatinib resulted in a less immunosuppressive TME and was associated with a reduction in MDSCs and repolarization of macrophages toward the M1 type[6,9]
- Combination of sitravatinib with nivolumab is a rational approach to augmenting the antitumor immune response and extending long term benefit to patients[5,6,9,10]

Methods

Study Design

- MRTX-500 (NCT02954991) is a Phase 2 open-label trial evaluating sitravatinib + nivolumab in patients with non-squamous NSCLC with prior clinical benefit from CPI therapy

Figure 1. MRTX-500 Study Design.

Key Eligibility Criteria (n=68)

- Advanced/metastatic non-squamous NSCLC
- No actionable driver mutations
- Anti–PD-1/L1 must be the most recent line of therapy
- Prior clinical benefit to CPI: CR, PR, or SD ≥12 weeks from prior CPI therapy[a]
- No uncontrolled brain metastases
- ECOG PS 0–2

→ **Sitravatinib** 120 mg QD + nivolumab 240 mg Q2W or 480 mg Q4W

AE, adverse event; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PR, partial response; Q2W, every 2 weeks; Q4W, every 4 weeks; QD, once daily; SD, stable disease.
[a]Additional cohorts included a CPI-experienced cohort of patients who did not receive prior clinical benefit from CPI therapy (documented radiographic progression of disease ≤12 weeks after initiation of treatment with CPI) and a CPI-naive cohort in patients who were previously treated with platinum-based chemotherapy. Dosing: sitravatinib free base formulation. Treatment discontinuation could be due to (but is not limited to) disease progression, global health deterioration, AEs, protocol violation, lost to follow-up, refusal of further treatment, study termination, or death.

Primary Endpoint

- Objective response rate (ORR), as defined by RECIST 1.1, based on investigator assessment

Secondary Endpoints

- Safety and tolerability; duration of response (DOR); clinical benefit rate (CBR); progression-free survival (PFS); overall survival (OS); 1-year survival rate

Results

Sitravatinib + Nivolumab in Patients With Non-squamous NSCLC

- Here we report updated efficacy and safety with sitravatinib + nivolumab in the 2L or 3L setting in patients with non-squamous NSCLC who have experienced clinical benefit on a prior CPI and subsequent disease progression (**Figure 1** and **Table 1**)
- Data cut-off June 1, 2021

Results

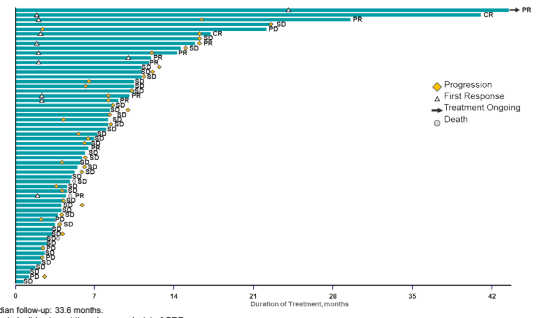
Table 1. Patient Demographics and Baseline Characteristics.

	2L/3L sitravatinib + nivolumab (n=68)
Median age, years (range)	66.0 (37–87)
Sex, n (%)	
Male	29 (43)
Female	39 (57)
Race, n (%)	
Caucasian	58 (85)
Other	10 (15)
ECOG PS, n (%)	
0 / 1 / 2	18 (27) / 45 (66) / 5 (7)
Smoking status	
Never smoker	12 (18)
Current smoker	9 (13)
Prior smoker	47 (69)
Prior platinum-based chemotherapy, n (%)	50 (73)
Cisplatin	5 (7)
Carboplatin	45 (66)
Prior PD-1/L1 checkpoint inhibitor, n (%)	68 (100)
Nivolumab	19 (28)
Pembrolizumab	45 (66)
Durvalumab	1 (2)
Atezolizumab	3 (4)
Best response to checkpoint inhibitor, n (%)	
CR	2 (3)
PR	30 (44)
SD	36 (53)

Efficacy

- ORR was 18% (12/68), including 2 CRs (3%) and 10 PRs (15%); DCR was 78% (53/68)
  - In total, 10 (14.7%) patients were not evaluable (NE) for ORR: 8 patients without post-baseline scan, 1 patient without measurable disease at baseline, and 1 patient for whom all post-baseline scans were NE
- Median DOR was 12.8 months (**Figure 2**)
- Median duration of treatment was 4.8 months (range, 0–40) for sitravatinib and 5.2 months (range, 0–41) for nivolumab
- Median PFS was 5.7 months (95% CI 4.9–7.6) (**Figure 3A**) and median OS was 14.9 months (95% CI 9.3–21.1) (**Figure 3B**)

Figure 2. Duration of Treatment in Patients With Prior Clinical Benefit From CPI Therapy (n=58).

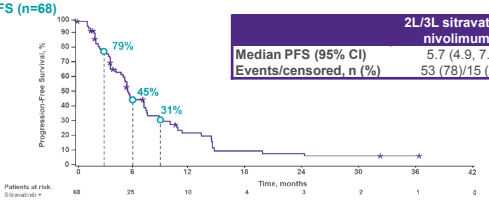


Median follow-up: 33.6 months.
The study did not meet the primary endpoint of ORR.

Results

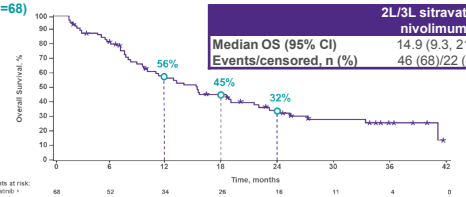
Figure 3 Efficacy in Patients With Prior Clinical Benefit From CPI Therapy.

A PFS (n=68)



	2L/3L sitravatinib + nivolumab
Median PFS (95% CI)	5.7 (4.9, 7.6)
Events/censored, n (%)	53 (78)/15 (22)

B OS (n=68)



	2L/3L sitravatinib + nivolumab
Median OS (95% CI)	14.9 (9.3, 21.1)
Events/censored, n (%)	46 (68)/22 (32)

Data as of June 1, 2021. Median follow-up: 33.6 months.
CI, confidence interval.

Safety

- Overall, 93% of patients reported a treatment-related adverse event (TRAE; any grade); the most frequent were diarrhea, fatigue, nausea, and hypertension (**Table 2**)
- The most frequent immune-related TRAE as assessed by the investigator were hypothyroidism, diarrhea, alanine transaminase (ALT) increase, aspartate aminotransferase (AST) increase, thyroid stimulating hormone increase, maculopapular rash, and pancreatitis
- No grade 5 events were observed in the CPI-experienced cohort
- Discontinuation, dose reduction, and dose interruption rates:
  - Overall, 22% of patients discontinued treatment due to TRAEs; discontinuation rates due to TRAEs were 21% for sitravatinib and 9% for nivolumab
  - Overall, 60% of patients had dose reductions due to AEs; dose reductions of sitravatinib due to AEs were 31% (80 mg), 22% (60 mg) and 7% (40 mg), with a median time from first dose to first dose reduction of 1.4 months
  - At least 1 dose interruption (defined as any gap in the dosing record that is ≥1 day) of sitravatinib due to AEs was reported in 81% of patients, with a median time to first dose interruption of 1 month

Table 2. Incidence of TRAEs.

Most frequent (≥15%) TRAEs (n=68)	2L/3L sitravatinib + nivolumab	
TRAEs, %	**Any Grade**	**Grade 3–4**
Any TRAEs	93	66
Most frequent TRAEs, %		
Diarrhea	62	16
Fatigue	52	4
Nausea	44	2
Hypertension	40	22
Decreased appetite	35	0
Weight decreased	31	9
Vomiting	31	0
Hypothyroidism	22	0
Dysphonia	19	0
ALT increase	18	2
AST increase	16	0
Stomatitis	15	2
PPE syndrome	15	3
Dehydration	15	3

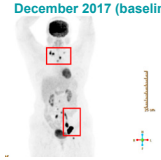
One grade 5 TRAE (cardiac arrest) occurred in the CPI-naive cohort.

Results

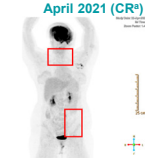
Patient Case: Patient With >3-Year Survival and CR

- 37-year-old female non-smoker with metastatic NSCLC
- Diagnosis of metastatic NSCLC in March 2015
- Treatment history and response:
  - Carboplatin + pemetrexed (March–July 2015)
  - Chest radiotherapy (September 2015)
  - Nivolumab (July 2015–April 2017)
  - Progressive disease (PD; March 2017)
- MRTX-500 trial:
  - Enrolment (January 2018); treated with sitravatinib + nivolumab
  - Dose reduction to 60 mg (May 2018)
  - Confirmed CR (November 2018)
  - Study completed; patient alive (March 2021)
- TRAEs: Grade 3 diarrhea; Grade 2 bottom lip sore; Grade 2 hypothyroidism and palmar-plantar erythrodysesthesia syndrome

December 2017 (baseline)



April 2021 (CR[a])



Positron emission tomography/computed tomography scan. [a]Post-COVID vaccine with some axillary lymphadenopathy was observed.

Summary

- Sitravatinib is a spectrum-selective TKI targeting TAM (TYRO3, AXL, MERTK) receptors and VEGFR2 that can potentially overcome an immunosuppressive TME[5,6]
- Sitravatinib + nivolumab demonstrated antitumor activity, encouraging OS, and durable responses in patients with non-squamous NSCLC with prior clinical benefit from a CPI
  - Median DOR was 12.8 months; ORR was 18% (12/68)
  - 1- and 2-year OS were 56% and 32%, respectively
- No unexpected safety signals with the combination were observed, and AEs were manageable
- These results support the ongoing Phase 3 SAPPHIRE study (NCT03906071), evaluating sitravatinib + nivolumab in patients with non-squamous NSCLC who received clinical benefit from and subsequently experienced PD on a prior CPI

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