MRTX-500: Phase 2 Trial of Sitravatinib + Nivolumab in Patients With Nonsquamous Non–Small-Cell Lung Cancer Progressing on or After Prior Checkpoint Inhibitor Therapy


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Disclosures

Ticiana A. Leal

- **Advisory Board:**
  - Blueprint, Merck, AstraZeneca, Jazz, Boehringer-Ingelheim, Bayer, Mirati

- **Consulting:**
  - Jazz, Boehringer-Ingelheim, Genentech, Lilly, Janssen
Background

- Checkpoint inhibitor therapy (CPI) has dramatically changed the treatment landscape for various cancer types, including NSCLC\(^1,2\)
- Many patients experience disease progression and develop CPI resistance through various mechanisms, including an immunosuppressive 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\(^5-9\)
- 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\(^6\)
- Combination of sitravatinib with nivolumab is a rational approach to augmenting the antitumor immune response and extending long term benefit to patients

Presented at the European Society for Medical Oncology (ESMO) Congress, 18 September 2021
Sitravatinib Is a TKI That Targets TAM Receptors (TYRO3, AXL, MERTK) and Split-Family Receptors (eg, VEGFR2)

Rationale for Targeting TAM and Split RTKs to Enhance Immune Response to CPIs

- Targeting VEGFR2 reduces Tregs and MDSCs
- Targeting KIT also depletes MDSCs
- Releases brakes for expansion of CD8+ T cells via PD-1 inhibition
- Increase dendritic cell maturity and antigen presentation capacity
- Increase NK cell response
- Increase T-cell expansion and trafficking into tumors

Both TAM and Split RTKs cooperate to:

- Macrophages shift from (type) M2 to M1, resulting in production of immuno-stimulating cytokines
- Enhances innate and adaptive immune response

Sitravatinib shifts tumor macrophage polarization toward an immune-stimulating state in patients with HNSCC

MRTX-500: Sitravatinib + Nivolumab in Nonsquamous NSCLC After CPI Therapy

Presented at the European Society for Medical Oncology (ESMO) Congress, 18 September 2021
MRTX-500: Phase 2, Open-Label Study of Sitravatinib + Nivolumab in Patients With Nonsquamous NSCLC With Prior Clinical Benefit From Checkpoint Inhibitor Therapy

Key Eligibility Criteria

- Advanced/metastatic nonsquamous NSCLC
- No actionable driver mutations
- Anti–PD-1/L1 must be the most recent line of therapy
- Prior Clinical Benefit (PCB) to CPI: CR, PR, or SD ≥12 weeks from prior CPI therapy
- No uncontrolled brain metastases
- ECOG PS 0-2

Primary Endpoint:
- Objective Response Rate (ORR), as defined by RECIST 1.1

Secondary Endpoints:
- Safety and tolerability
- DOR
- CBR
- PFS
- OS
- 1-year survival rate

Here we report updated efficacy and safety with sitravatinib + nivolumab in the 2L or 3L setting in patients with nonsquamous NSCLC who have experienced clinical benefit on a prior CPI and subsequent disease progression.

Data as of 1 June 2021

- Additional cohorts included a CPI-experienced cohort that did not receive prior clinical benefit from CPI therapy (radiographic progression of disease ≤12 weeks after initiation of treatment with CPI) and a CPI-naive cohort in patients that were previously treated with platinum-based chemotherapy.
- Objective response rate based on investigator assessment. Dosing: sitravatinib free base formulation: nivolumab, 240 mg Q2W or 480 mg Q4W. 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.

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### Patient Demographics and Baseline Characteristics

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

Data as of 1 June 2021.

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**Duration of Treatment With Sitravatinib + Nivolumab in Patients With Nonsquamous NSCLC With Prior Clinical Benefit From CPI Therapy**

- ORR was 18% (12/68), including 2 CRs (3%) and 10 PRs (15%)\(^a\)
  - DCR was 78% (53/68)
- Median DOR was 12.8 months
- Median duration of treatment:
  - Sitravatinib: 4.8 months (range: 0, 40)
  - Nivolumab: 5.2 months (range: 0, 41)

\(^a\) 10 (14.7%) patients were not evaluable 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. The study did not meet the primary endpoint of ORR.

Median follow-up in the PCB cohort was 33.6 months. Data as of 1 June 2021.

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Progression-Free Survival With Sitravatinib + Nivolumab in Patients With Nonsquamous NSCLC With Prior Clinical Benefit From CPI Therapy

Median follow-up in PCB cohort: 33.6 months.
Data as of 1 June 2021.

Presented at the European Society for Medical Oncology (ESMO) Congress, 18 September 2021
Overall Survival With Sitravatinib + Nivolumab in Patients With Nonsquamous NSCLC With Prior Clinical Benefit From CPI Therapy

**Overall Survival in Patients With NSCLC (n=68)**

- **Sitravatinib + Nivolumab (n=68)**
  - Median OS (95% CI): 14.9 (9.3, 21.1)
  - Events/censored, n (%): 46 (68)/22 (32)

**Patients at risk:**
- Sitravatinib + nivolumab
  - 68 at baseline
  - 52 at 12 months
  - 34 at 18 months
  - 26 at 24 months
  - 16 at 30 months
  - 11 at 36 months
  - 4 at 42 months

Median follow-up in PCB cohort: 33.6 months.
Data as of 1 June 2021.

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Incidence of Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>TRAEs</th>
<th>2L/3L Sitra + Nivo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
</tr>
<tr>
<td>Any TRAEs</td>
<td>93%</td>
</tr>
<tr>
<td>Most frequent TRAEs, %</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>62%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>52%</td>
</tr>
<tr>
<td>Nausea</td>
<td>44%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>35%</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>31%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>31%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>22%</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>19%</td>
</tr>
<tr>
<td>ALT increase</td>
<td>18%</td>
</tr>
<tr>
<td>AST increase</td>
<td>16%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>15%</td>
</tr>
<tr>
<td>PPE syndrome</td>
<td>15%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>15%</td>
</tr>
</tbody>
</table>

• The most frequent immune-related TRAEs included hypothyroidism, diarrhea, ALT increase, AST increase, TSH increase maculopapular rash, and pancreatitis\(^a\)

• No grade 5 events occurred in the CPI-experienced cohort\(^b\)

\(^a\)Investigator-assessed AE causality as immune-related. \(^b\)1 grade 5 TRAE (cardiac arrest) occurred in the CPI-naive patient population.

Data as of 1 June 2021.

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### Sitravatinib Discontinuation, Dose Reduction, and Dose Interruption Rates

<table>
<thead>
<tr>
<th></th>
<th>2L/3L Sitra + Nivo (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuation due to TRAEs, %</td>
<td></td>
</tr>
<tr>
<td>Sitravatinib</td>
<td>22</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>9</td>
</tr>
<tr>
<td>Dose reduction of sitravatinib due to AEs&lt;sup&gt;a&lt;/sup&gt;, %</td>
<td>60</td>
</tr>
<tr>
<td>80 mg</td>
<td>31</td>
</tr>
<tr>
<td>60 mg</td>
<td>22</td>
</tr>
<tr>
<td>40 mg</td>
<td>7</td>
</tr>
<tr>
<td>≥1 dose interruption of sitravatinib due to AEs&lt;sup&gt;b,c&lt;/sup&gt;, %</td>
<td>81</td>
</tr>
</tbody>
</table>

<sup>a</sup> Median time from first dose to first dose reduction: 1.4 months.  
<sup>b</sup> Dose interruption is defined as any gap in the dosing record that is ≥1 day.  
<sup>c</sup> Median time to first dose interruption: 1 month  
Data as of 1 June 2021.

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

Treatment History: 37-Year-Old Female Who Doesn’t Smoke Diagnosed With Metastatic NSCLC

- Mar 2015: Metastatic NSCLC diagnosis
- Mar-July 2015: Carboplatin + pemetrexed
- Sept 2015: Chest radiotherapy
- Enrollment Jan 2018: Sitravatinib + nivolumab (dose reduction 60 mg, May 2018)
- Nov 2018: Confirmed CR
- Mar 2021: Study completed; patient alive

December 2017
Baseline

April 2021
CR

TRAEs
- Grade 3 diarrhea
- Grade 2 bottom lip sore
- Grade 2 hypothyroidism and PPE syndrome

* PET/CT scan
  * Post-COVID vaccine with some axillary lymphadenopathy was observed

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Summary

• Sitravatinib is a spectrum-selective TKI targeting TAM (TYRO3, AXL, MERTK) receptors and VEGFR2 that can potentially overcome an immunosuppressive TME\textsuperscript{5}

• Sitravatinib + nivolumab demonstrated antitumor activity, encouraging OS, and durable responses in patients with nonsquamous 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 SAPHIRE study (NCT03906071), evaluating sitravatinib + nivolumab in patients with nonsquamous NSCLC who received clinical benefit from and subsequently experienced progressive disease on a prior CPI

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Presented at the European Society for Medical Oncology (ESMO) Congress, 18 September 2021
SAPPHIRE: Phase 3, Randomized, Open-Label Trial of 2L/3L Sitravatinib + Nivolumab vs Docetaxel After Progression on or Following CPI in Advanced NSCLC

Key Eligibility Criteria (n=532)
- Advanced, nonsquamous NSCLC
- Prior PD-1/L1 therapy for ≥4 months (prior anti–CTLA-4 therapy allowed)
- Progression on or following PD-1/L1 inhibitor in combination with or following chemotherapy
- Excludes patients with known driver mutations

Primary Endpoint:
- OS

Secondary Endpoints:
- PFS
- ORR
- Safety

Sitravatinib 100 mg QD<sup>a</sup> + nivolumab 240 mg Q2W or 480 mg Q4W (n=266)

Docetaxel 75 mg/m<sup>2</sup> Q3W (n=266)

<sup>a</sup>Newly randomized patients will receive sitravatinib malate capsule formulation administered orally at starting dose of 100 mg once daily (QD). Patients enrolled in the United States who began treatment with the sitravatinib free-base capsule formulation will remain on the free-base capsule formulation throughout the duration of the study; the starting dose of sitravatinib free-base capsule formulation is 120 mg QD.

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References


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**Abbreviations**

2L, second line  
3L, third line  
AE, adverse event  
ALT, alanine aminotransferase  
AST, aspartate aminotransferase  
CBR, clinical benefit rate  
CI, confidence interval  
CPI, checkpoint inhibitor  
CR, complete response  
DCR, disease control rate  
DOR, duration of response  
ECOG, Eastern Cooperative Oncology Group  

HNSCC, head and neck squamous cell carcinoma  
iDC, immature dendritic cells  
irAEs, immune-related adverse events  
mDC, myeloid dendritic cells  
MDSCs, myeloid-derived suppressor cells  
NSCLC, non–small-cell lung cancer  
ORR, objective response rate  
OS, overall survival  
PCB, prior clinical benefit  
PD, progressive disease  
PFS, progression-free survival  
PPE, palmar-plantar erythrodyesthesia  
PR, partial response  
PS, performance status  
QD, once daily  
Q2W, every 2 weeks  
RTK, receptor tyrosine kinase  
SD, stable disease  
TKI, tyrosine kinase inhibitor  
TME, tumor microenvironment  
TSH, thyroid-simulating hormone  
Tregs, T regulatory cells  
TRAEs, treatment-related adverse events  
VEGFR, vascular endothelial growth factor receptor