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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

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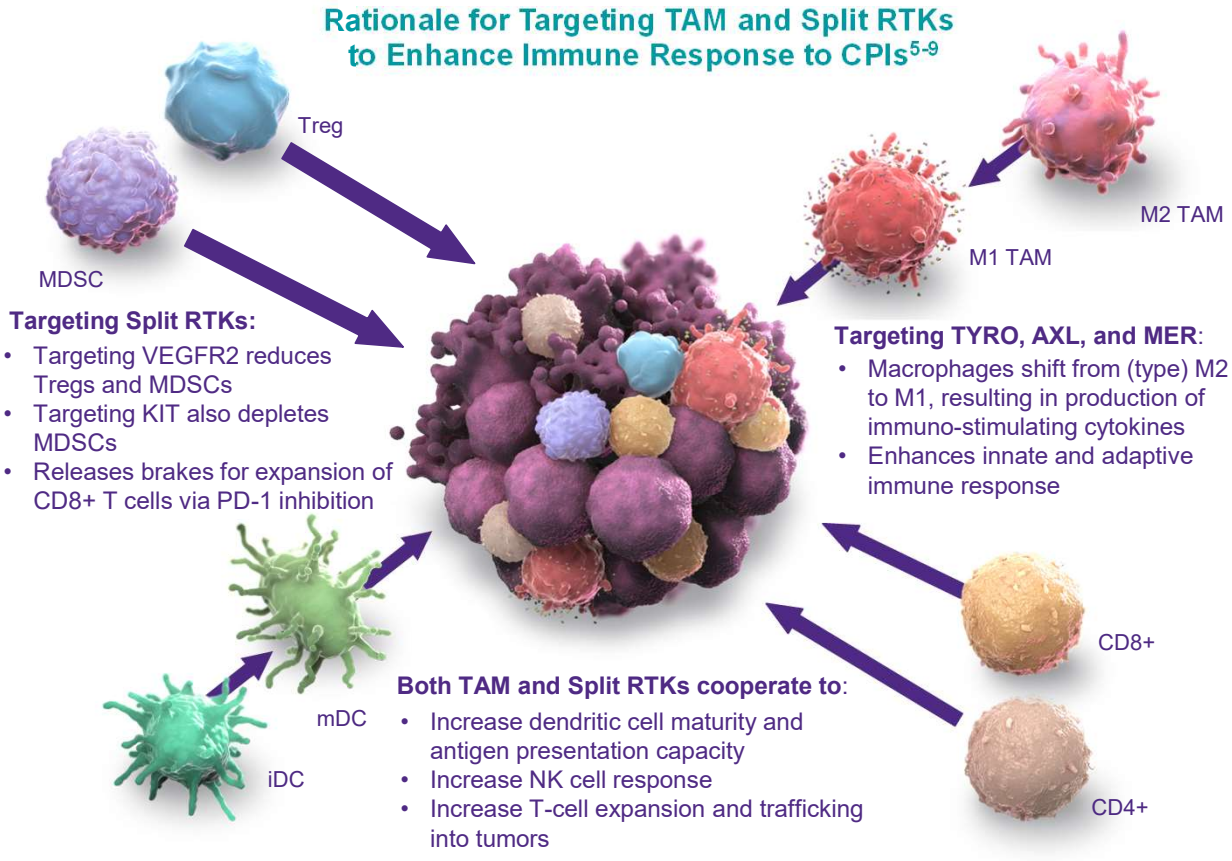
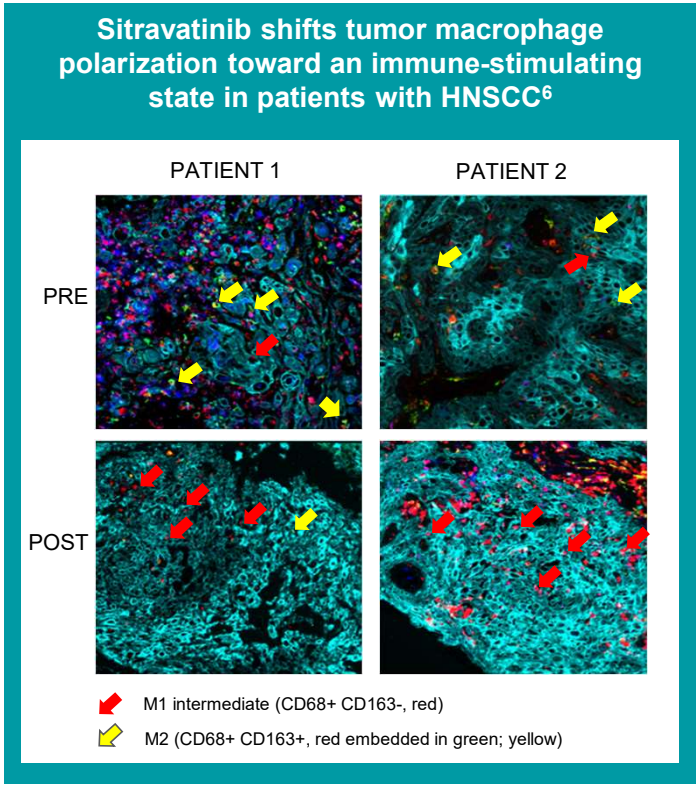
Background

- 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

Sitravatinib Is a TKI That Targets TAM Receptors (TYRO3, AXL, MERTK) and Split-Family Receptors (eg, VEGFR2)





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
(n=68)

- Advanced/metastatic nonsquamous NSCLC[a]
- 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

Sitravatinib 120 mg QD + nivolumab

Primary Endpoint:
- Objective Response Rate[b] (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

[a] 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. [b]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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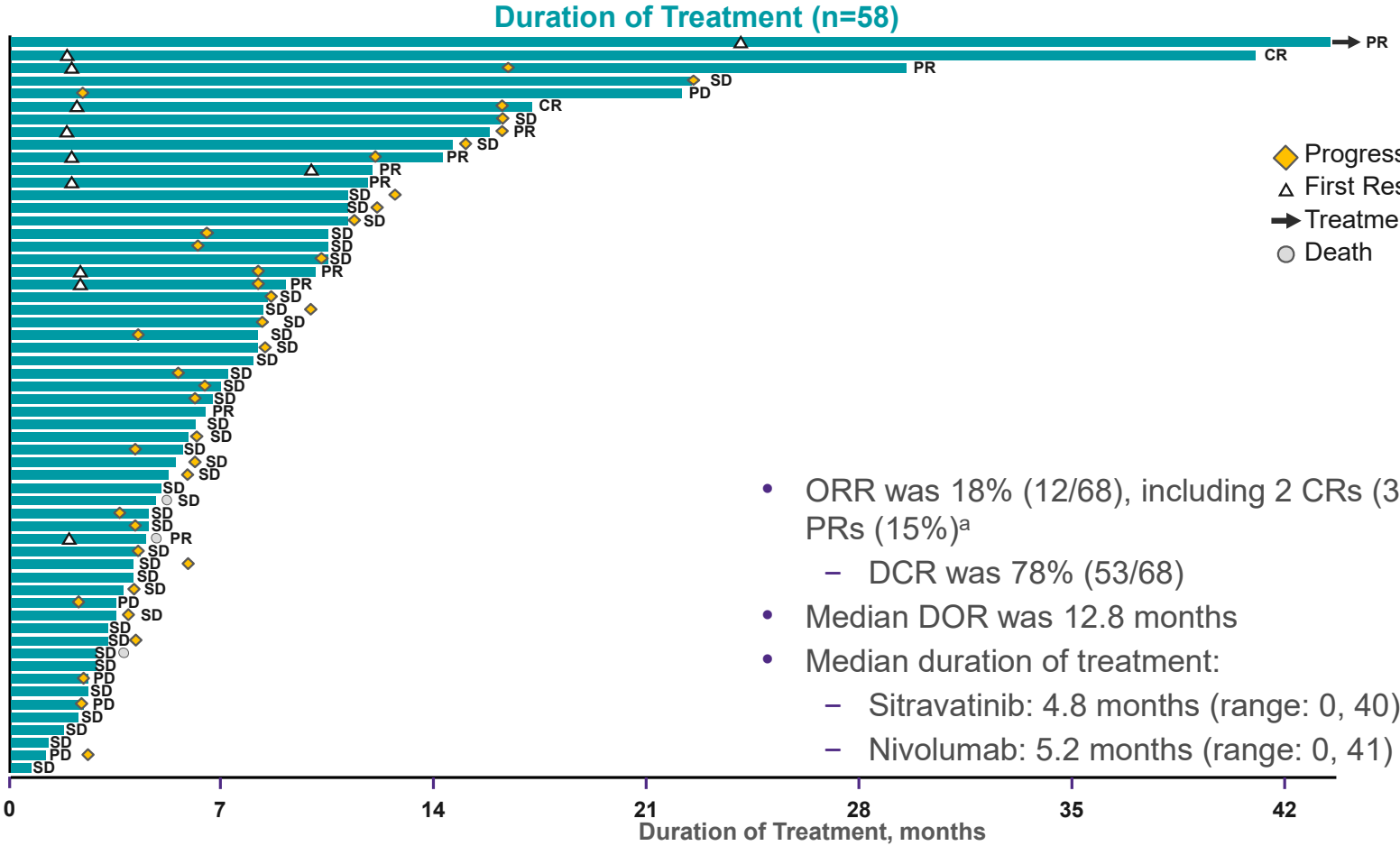
Patient Demographics and Baseline Characteristics

	2L/3L Sitra + Nivo (n=68)
Age, years	
Median	66.0
Range	37–87
Sex, n (%)	
Male	29 (43)
Female	39 (57)
Race, n(%)	
Caucasian	58 (85)
Other	10 (15)
ECOG PS, n (%)	
0	18 (27)
1	45 (66)
2	5 (7)
Smoking status, n (%)	
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)

Data as of 1 June 2021.

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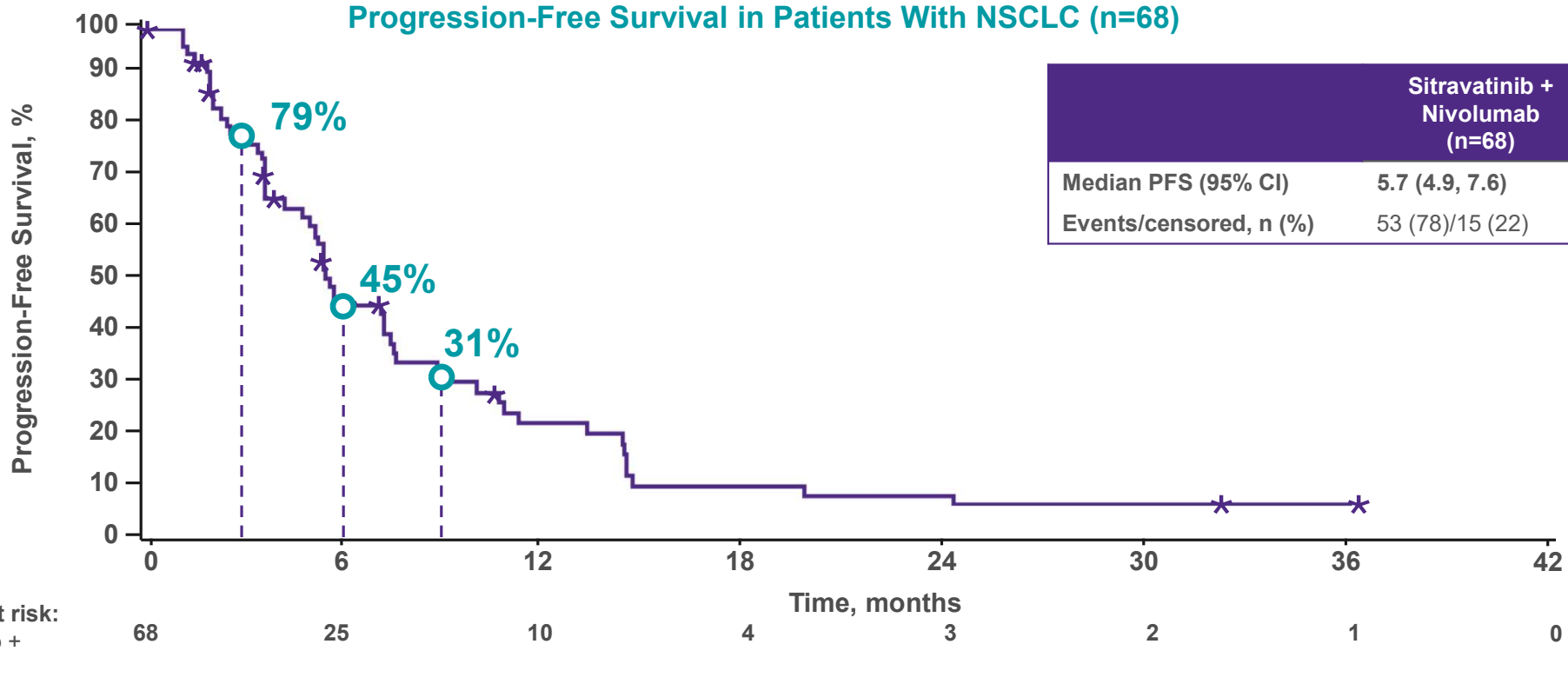
Progression-Free Survival With Sitravatinib + Nivolumab in Patients With Nonsquamous NSCLC With Prior Clinical Benefit From CPI Therapy



	Sitravatinib + Nivolumab (n=68)
Median PFS (95% CI)	5.7 (4.9, 7.6)
Events/censored, n (%)	53 (78)/15 (22)

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

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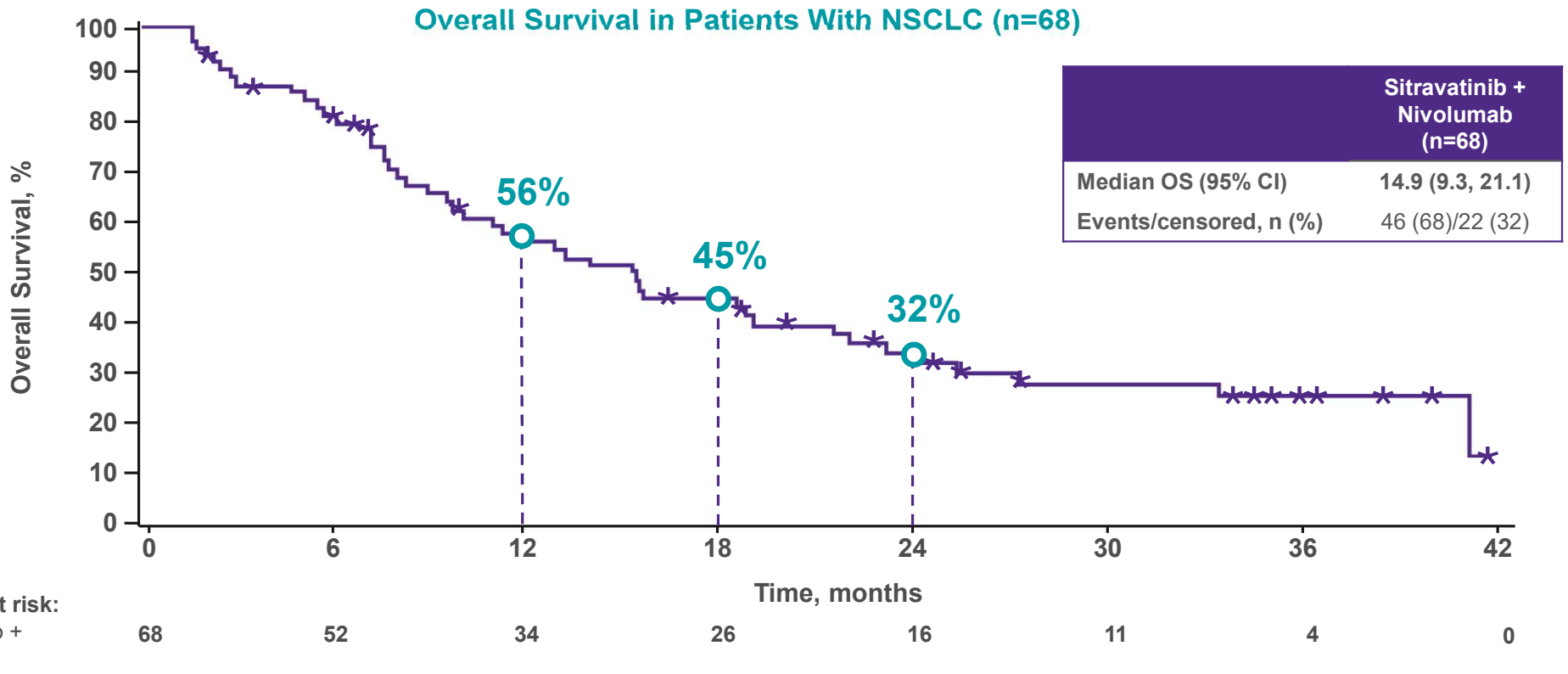
Overall Survival With Sitravatinib + Nivolumab in Patients With Nonsquamous NSCLC With Prior Clinical Benefit From CPI Therapy



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

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

Most Frequent (≥15%) TRAEs (n=68)	2L/3L Sitra + Nivo	
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%

- 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.

Sitravatinib Discontinuation, Dose Reduction, and Dose Interruption Rates

	2L/3L Sitra + Nivo (n=68)
Discontinuation due to TRAEs, %	22
Sitravatinib	21
Nivolumab	9
Dose reduction of sitravatinib due to AEs[a], %	60
80 mg	31
60 mg	22
40 mg	7
≥1 dose interruption of sitravatinib due to AEs[b,c], %	81

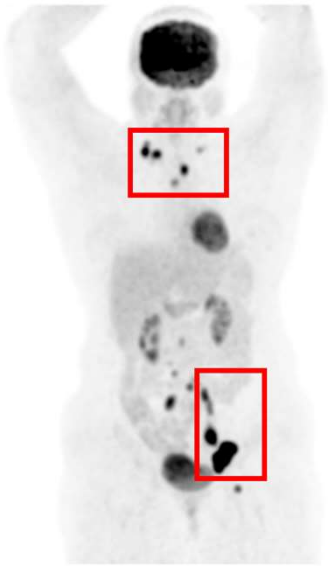
[a] Median time from first dose to first dose reduction: 1.4 months. [b] Dose interruption is defined as any gap in the dosing record that is ≥1 day. [c] Median time to first dose interruption: 1 month
Data as of 1 June 2021.

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

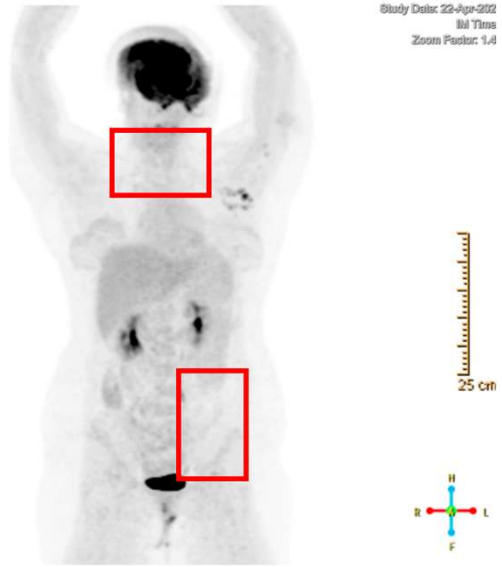
Treatment History: 37-Year-Old Female Who Doesn't Smoke Diagnosed With Metastatic NSCLC

Mar 2015	Metastatic NSCLC diagnosis
Mar-July 2015	Carboplatin + pemetrexed
Sept 2015	Chest radiotherapy
Jul 2015-Apr 2017	Nivolumab (PD, Mar 2017)
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[a]



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

PET/CT scan

[a] Post-COVID vaccine with some axillary lymphadenopathy was observed

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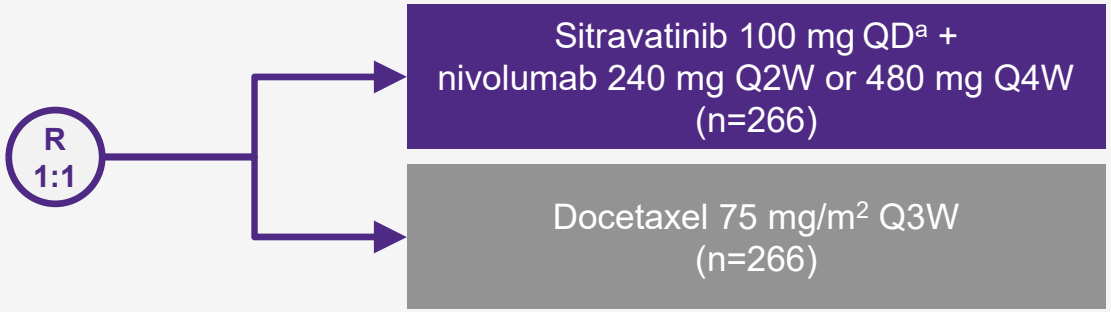
Summary

- Sitravatinib is a spectrum-selective TKI targeting TAM (TYRO3, AXL, MERTK) receptors and VEGFR2 that can potentially overcome an immunosuppressive TME[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 SAPPHIRE study (NCT03906071), evaluating sitravatinib + nivolumab in patients with nonsquamous NSCLC who received clinical benefit from and subsequently experienced progressive disease on a prior CPI

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

[a]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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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