MUNICH 2018 ESMO congress

Stage 2 Enrollment Complete: Sitravatinib in Combination with Nivolumab in NSCLC Patients Progressing on Prior Checkpoint Inhibitor Therapy

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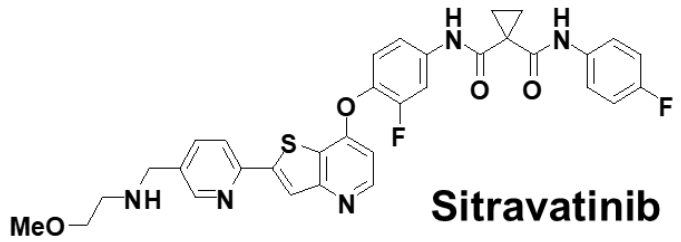
Ticiana Leal, MD – disclosures

- Consultant Advisory Board: Takeda, AstraZeneca, Novartis, AbbVie, BMS.
- Study Sponsored by Mirati Therapeutics, Inc.

MRTX-500 Background

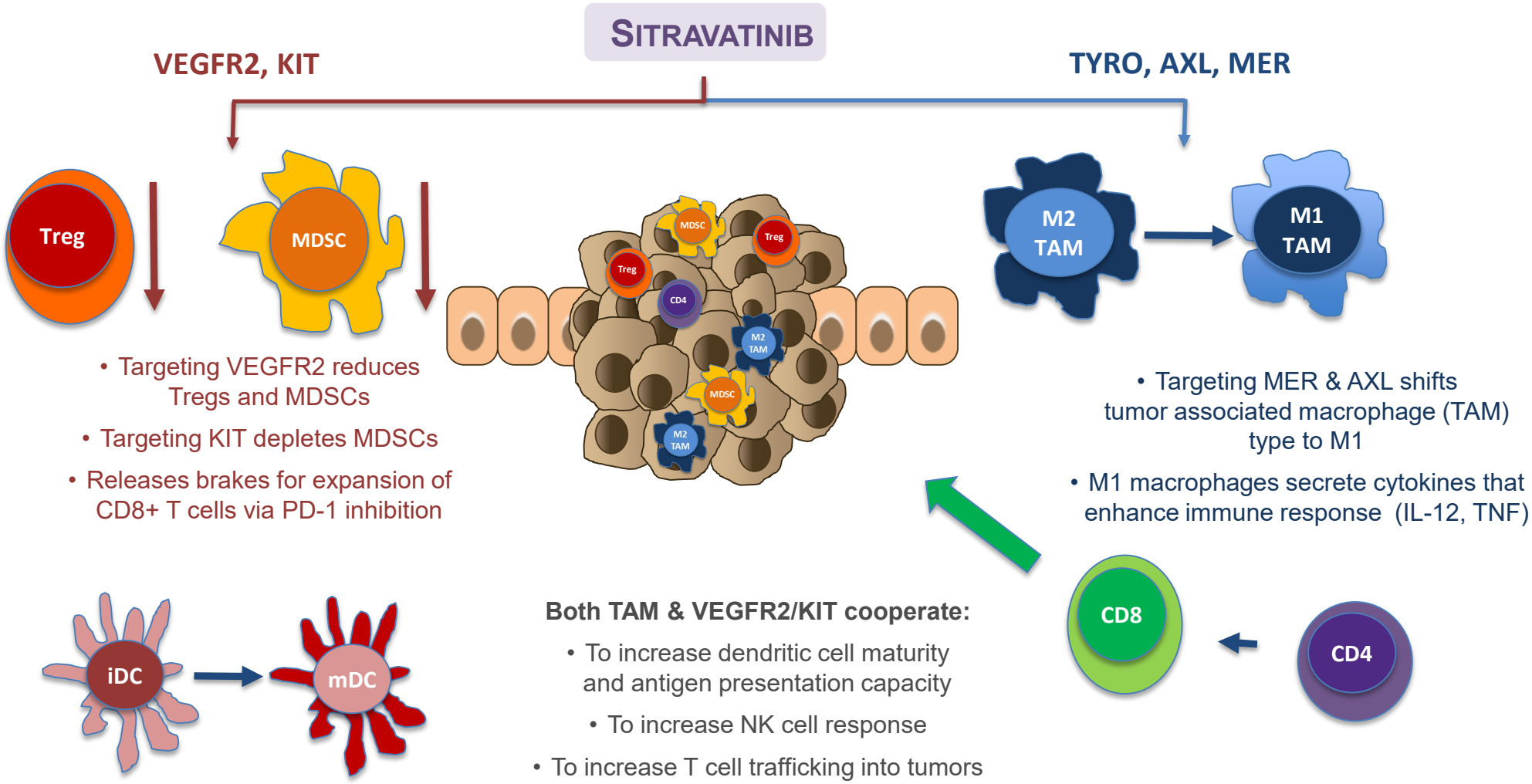
- Sitravatinib (MGCD516) is an orally available, small molecule inhibitor of a spectrum of related receptor tyrosine kinases (RTKs) including:
  - TAM family (AXL and MER):
    - Target cellular IC50: 1nM.
  - Split family RTKs (VEGFR2,PDGFRA and KIT):
    - Target cellular IC50: 5-10 nM.
  - RET, MET, DDR2, TrkA:
    - Target cellular IC50: 10-25 nM.



Sitravatinib

- Combination therapy with agents that target the molecular and cellular mechanisms of resistance to checkpoint inhibitor therapy (CIT) is a rational approach to restoring or improving the efficacy of CIT in patients with immunotherapy resistant non-small cell lung cancer (NSCLC).

MRTX-500 Rationale



- Targeting VEGFR2 reduces Tregs and MDSCs
- Targeting KIT depletes MDSCs
- Releases brakes for expansion of CD8+ T cells via PD-1 inhibition

- Targeting MER & AXL shifts tumor associated macrophage (TAM) type to M1
- M1 macrophages secrete cytokines that enhance immune response (IL-12, TNF)

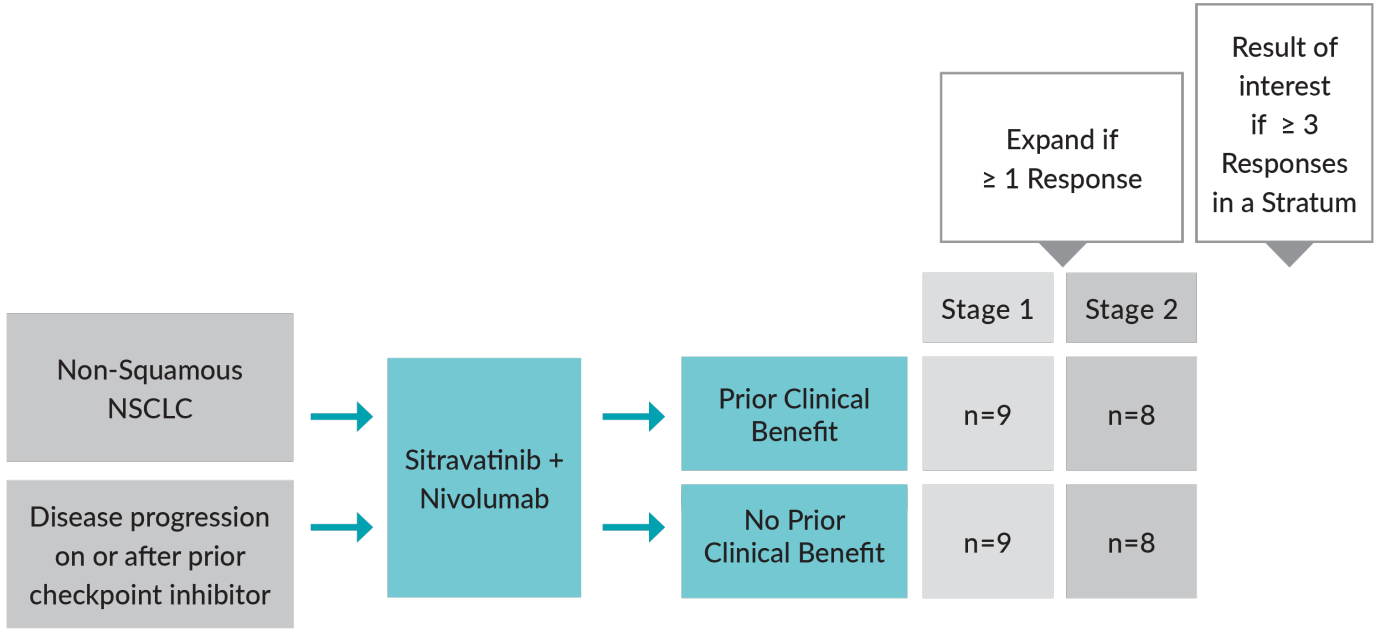
Both TAM & VEGFR2/KIT cooperate:

- To increase dendritic cell maturity and antigen presentation capacity
- To increase NK cell response
- To increase T cell trafficking into tumors

MRTX-500 Study Design

- Phase 2 study evaluating the tolerability and clinical activity of sitravatinib in combination with nivolumab in patients with non-squamous NSCLC who have experienced progression of disease on or after treatment with CIT.

- Patients receive oral sitravatinib once daily (QD) in combination with nivolumab 240/480 mg intravenously every 2/4 weeks, as continuous 28 day cycles.



MRTX-500 Study Eligibility

Key Objectives:

- The primary objective is to assess Objective Response Rate (ORR) by RECIST 1.1.
  - Investigator assessed
- Other objectives include safety, tolerability, pharmacokinetics and changes in circulating and tumor cell PD-L1, circulating and tumor infiltrating immune cell populations, cytokines and gene expression signatures.

Key Eligibility Criteria:

- Non-squamous NSCLC, metastatic or unresectable, locally advanced
- Treatment with at least one prior therapy
  - CIT-experienced patients: Most recent treatment must have included a checkpoint inhibitor with the result of progression of disease on or after treatment.
  - CIT-naïve patients: Receipt of prior platinum-based doublet chemotherapy
- No active brain metastases
- No history of tumors positive for EGFR, ROS1, ALK mutations
- No prior immunotherapies or combo therapies with similar mechanism of action

MRTX-500 Characteristics

Baseline Demographics N=78 All Patients – CIT-Experienced and CIT-Naïve Cohorts*		
Age, years	Median (range)	65.7 (37-89)
Sex, n (%)	Male	35 (45)
	Female	43 (55)
Race, n (%)	Caucasian	64 (82)
	Black	7 (9)
	Asian	2 (3)
	Other	5 (7)
Ethnicity, n (%)	Hispanic/Latino	4 (5)
	Not Hispanic/Latino	73 (94)
Smoking, n (%)	Lifetime Non-smoker	18 (23)
	Current Smoker	9 (12)
	Former Smoker	51 (65)
ECOG PS, n (%)	0	18 (23)
	1	58 (74)
	2	2 (3)
Lines of prior therapy, n (%)	One	25 (32)
	Two	31 (40)
	Three +	22 (28)

*CIT-Experienced Cohort N=70; CIT-Naïve Cohort N=8
Data as of 27-Aug-2018

MRTX-500 Safety: Most Frequent (≥10%) Treatment-Related (Sitravatinib and/or Nivolumab)*

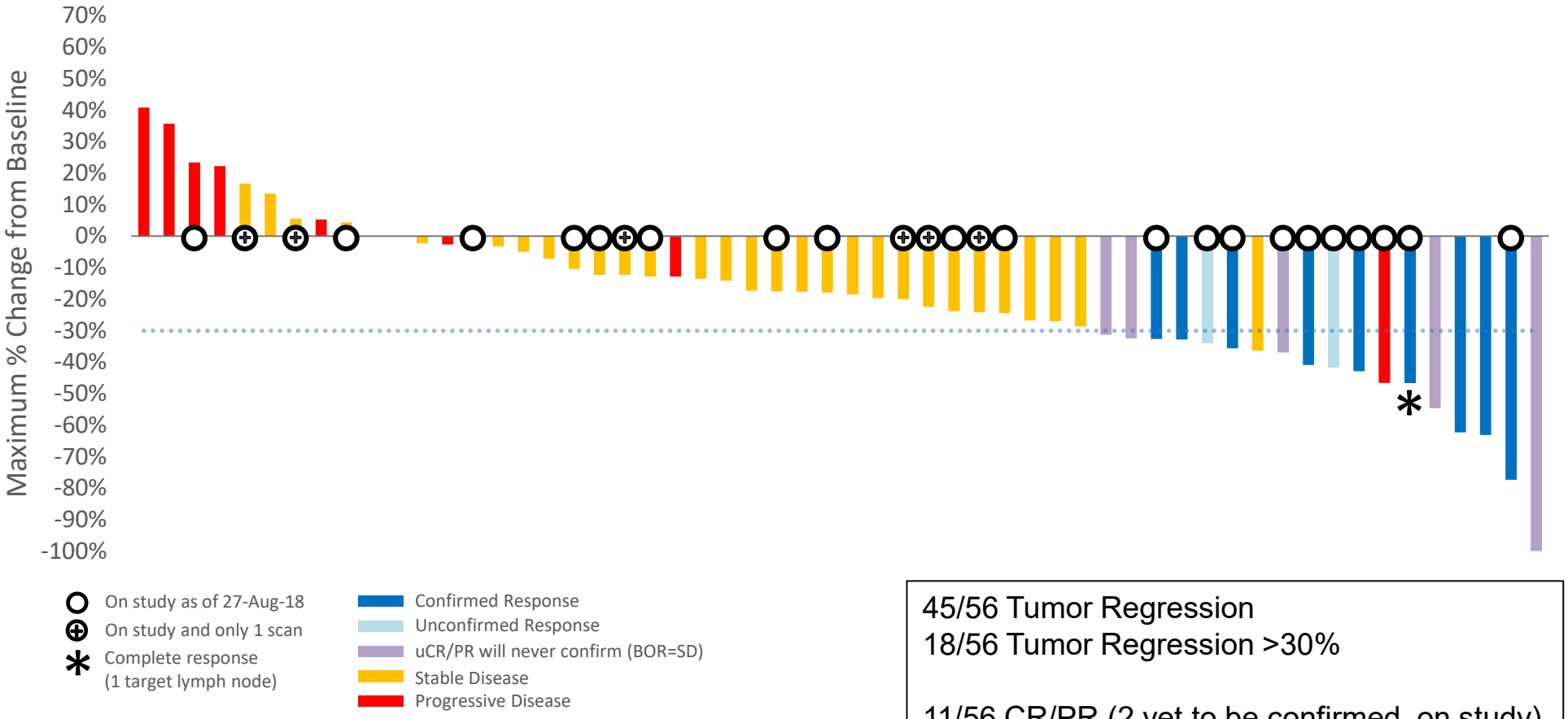
Adverse Event (Preferred Term)	N=70	
	All Grades n (%)	Grade ≥3 n (%)**
Diarrhea	31 (44)	8 (11)
Nausea	28 (40)	0
Fatigue	27 (39)	2 (3)
Decreased appetite	18 (26)	0
Vomiting	18 (26)	1 (1)
Dysphonia	17 (24)	0
Weight decrease	16 (23)	1 (1)
Hypertension	16 (23)	9 (13)
Alanine aminotransferase increase	12 (17)	0
Aspartate aminotransferase increase	10 (14)	0
Stomatitis	10 (14)	1 (1)
Palmar-plantar erythrodysaesthesia	10 (14)	1 (1)
Hypothyroidism	10 (14)	0
Mucosal Inflammation	8 (11)	3 (4)
Lipase increase	4 (6)	2 (3)
Hyponatremia	5 (7)	2 (3)

*Data as of 26-Jun-2018 (Investigators Brochure) – all patients CIT-Experienced and CIT-Naïve Cohorts
-12 patients (17%) discontinued study treatment due to treatment toxicity

MRTX-500 Clinical Activity

Preliminary Maximum Response in NSCLC Patients Who Failed Prior Checkpoint Therapy by Best Response

(CIT-Experienced Cohorts – Clinical Activity Evaluable Patients, N=56)



45/56 Tumor Regression
18/56 Tumor Regression >30%

11/56 CR/PR (2 yet to be confirmed, on study)
5/56 CR/PR will not be confirmed (off study)

Study cycles of 28 days, with disease assessment scans every 2 cycles
Data as of 27-Aug-2018

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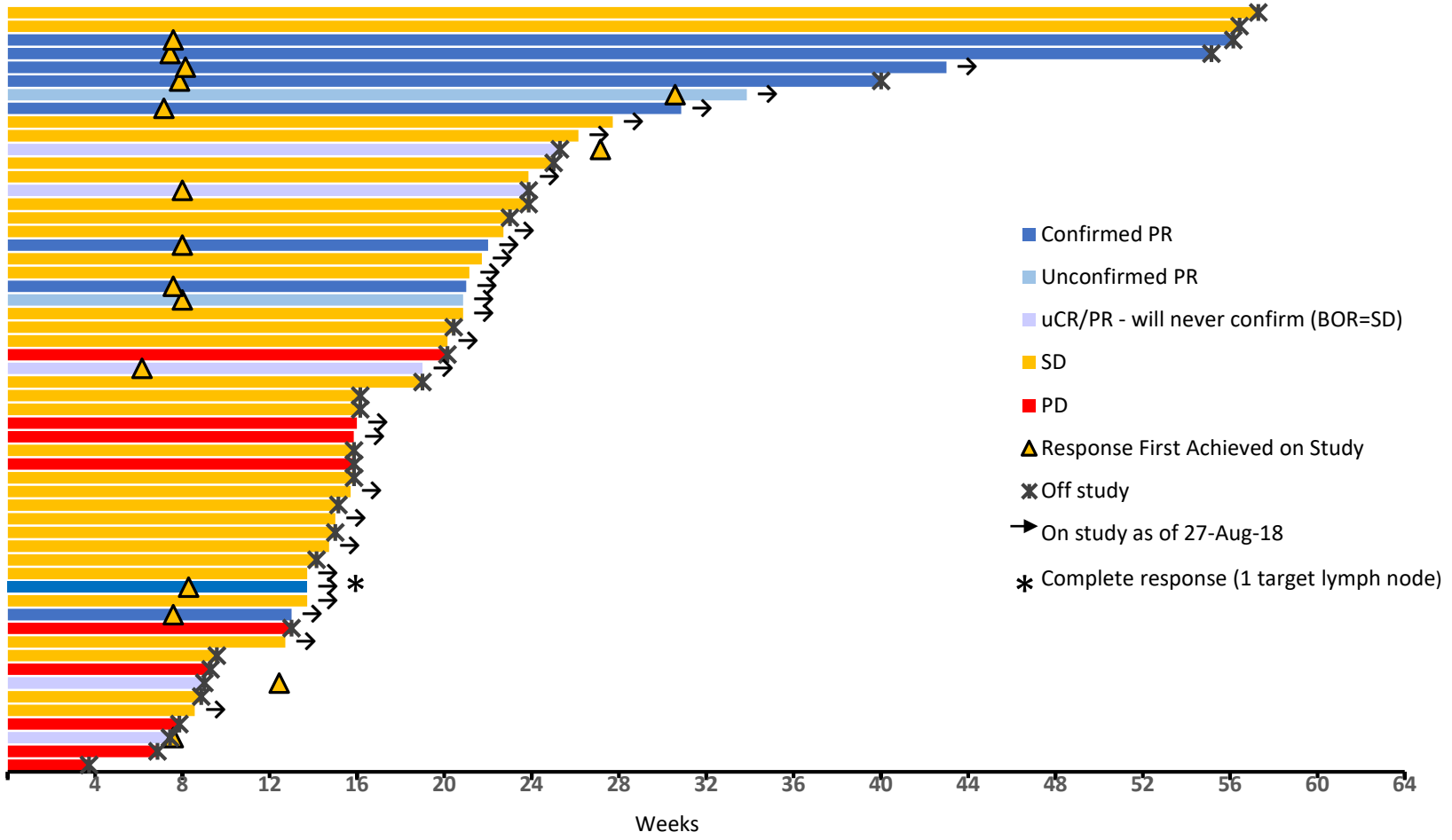
MRTX-500 Clinical Activity
Duration on Treatment

Preliminary Duration of Treatment in NSCLC Patients Who Failed Prior Checkpoint Therapy by Best Response

(CIT-Experienced Cohorts - Clinical Activity Evaluable Patients, N=56)



Study cycles of 28 days, with disease assessment scans every 2 cycles
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MRTX-500 Correlative Biomarkers

Key Objectives:

- Investigate biomarkers from baseline samples predictive of drug response
- Explore pharmacodynamic biomarkers modulated by drug treatment to inform mechanism of action

Baseline and pharmacodynamic biomarkers:

- PD-L1 IHC (28-8 assay (nivolumab); prior PD-L1 assay data)
- Total mutation burden (TMB) – Guardant Omni plasma ctDNA assay for 500+ genes and TMB
- Flow cytometry and cytokines
- Gene expression (HTG EdgeSeq) and multi-plex immunofluorescence

Results:

- Preliminary analysis of PD-L1 status at baseline indicates a nonsignificant trend towards high PD-L1 staining and clinical benefit
- Additional biomarker analyses will be presented at a conference later this year

MRTX-500 Summary

- The combination of sitravatinib with nivolumab is a rational approach to restoring or enhancing the clinical activity of CIT in patients with immunotherapy resistant NSCLC
- The combination has an acceptable toxicity profile with manageable AE's
- This ongoing study continues to show promising clinical activity, including tumor regression and prolonged duration on treatment
- Preliminary analysis of PD-L1 status at baseline indicates a nonsignificant trend towards high PD-L1 staining and clinical benefit
- The study is open at 25 sites in the US and recruitment is ongoing