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Preliminary Biomarker Analysis of Sitravatinib in Combination with Nivolumab in NSCLC Patients Progressing on Prior Checkpoint Inhibitor

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Presenter Disclosure Information

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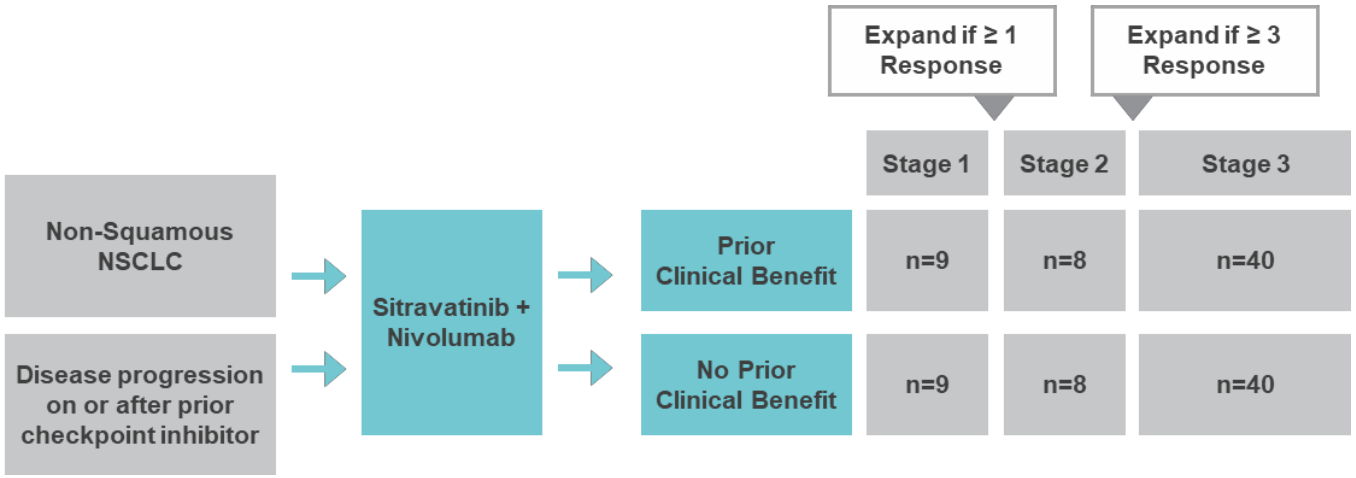
There will be discussion about the use of products for non-FDA approved indications in this presentation.

MRTX-500 Background and Study Design

- Sitravatinib (MGCD516) is an orally available, small molecule inhibitor of a spectrum of related receptor tyrosine kinases (RTKs) including TAM family, VEGFR2 and KIT.
- MRTX-500 is a 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.



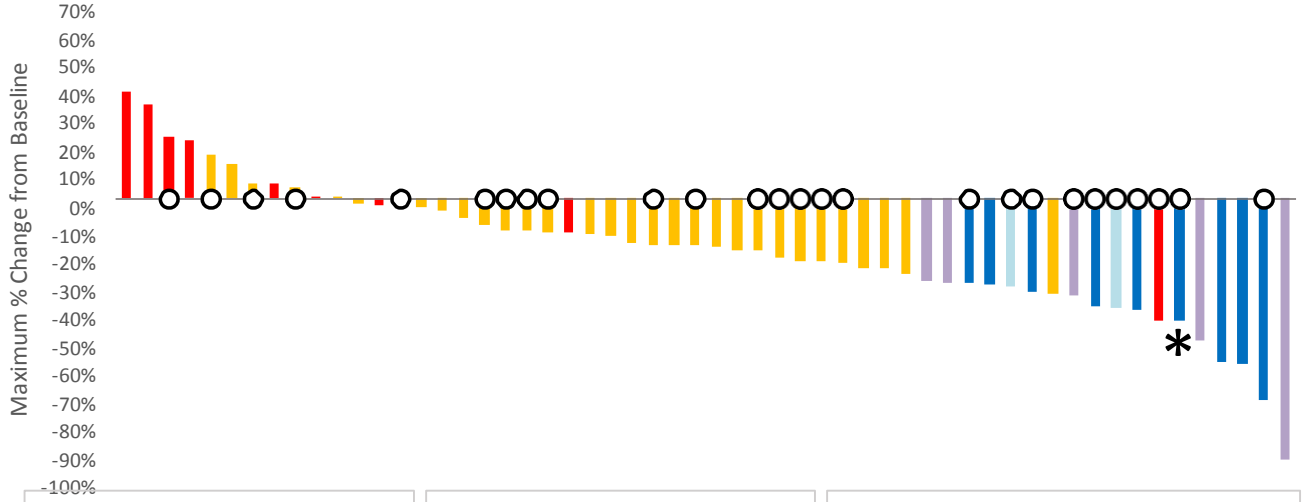
Key Objectives:

- Objective Response Rate (ORR) by RECIST 1.1.
- Safety, tolerability, pharmacokinetics
- Investigate baseline biomarkers for correlation with clinical outcome parameters including clinical benefit (CR, PR, stable disease > 14 wks) vs no clinical benefit (stable disease < 14 wks, PD):
  - Circulating & tumor cell PD-L1
  - Mutation profile/TMB in ctDNA
  - Circulating & tumor infiltrating immune cell populations & cytokines
  - Gene expression signatures

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)



○ On study as of 27-Aug-18
✱ Complete response (1 target lymph node)

Confirmed Response
Unconfirmed Response
uCR/PR will never confirm
Stable Disease
Progressive Disease

45/56 Tumor Regression
18/56 Tumor Regression >30%
16/56 CR/PR
9 confirmed
2 yet to be confirmed and on study
5 will not be confirmed

Preliminary Kaplan-Meier estimate of median Duration of Response > 9 months

Data as of 27-Aug-2018; 28 day cycle, with disease assessment scans every 2 cycles

MRTX-500 Safety

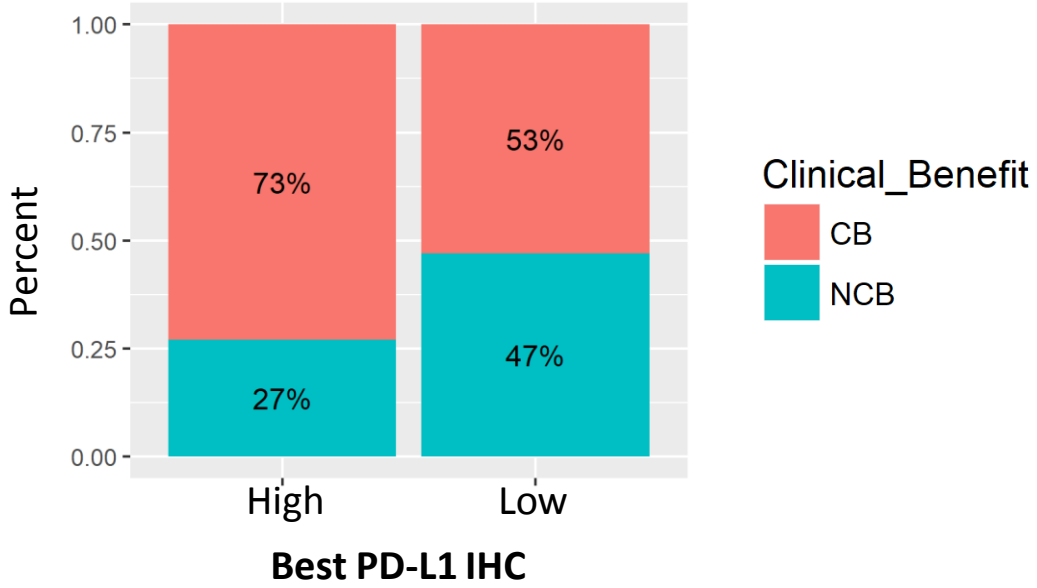
Most Frequent (≥10%) Treatment-Related AE (Sitravatinib and/or Nivolumab)*

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 & CIT-Naïve Cohorts**
-12 patients (17%) discontinued study treatment due to treatment toxicity

MRTX-500 PD-L1 Preliminary Data

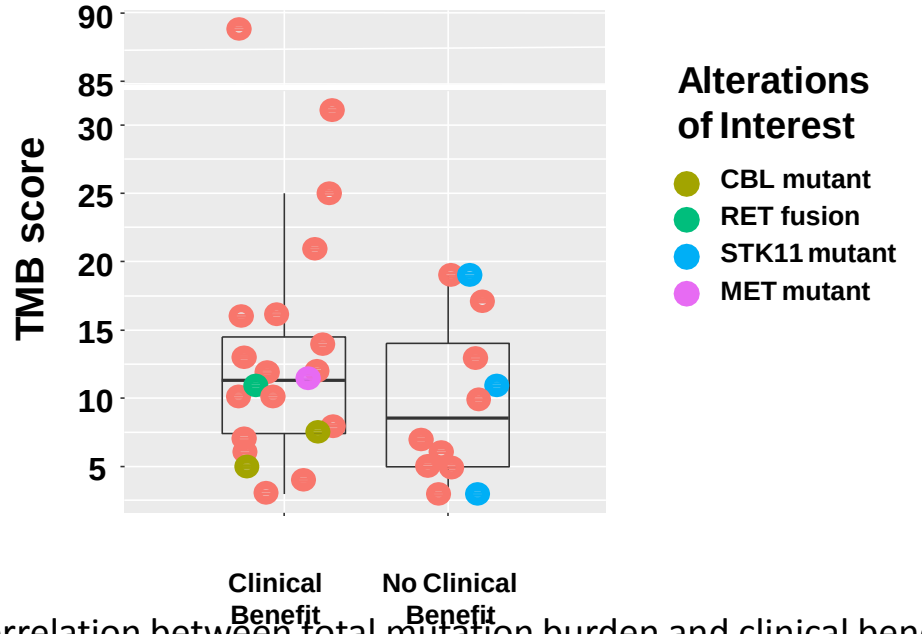
Clinical Benefit – Best PD-L1 IHC



- Highest PD-L1 result from previous testing (any test) or from the central lab (DAKO 28-8) was compared to response.
- A non-significant trend between PD-L1 high staining and clinical benefit was observed (p-value = 0.45).
- Clinical benefit, including PRs, still observed in PD-L1 low pts and some PD-L1 high pts did not respond.

MRTX-500 Circulating Biomarkers

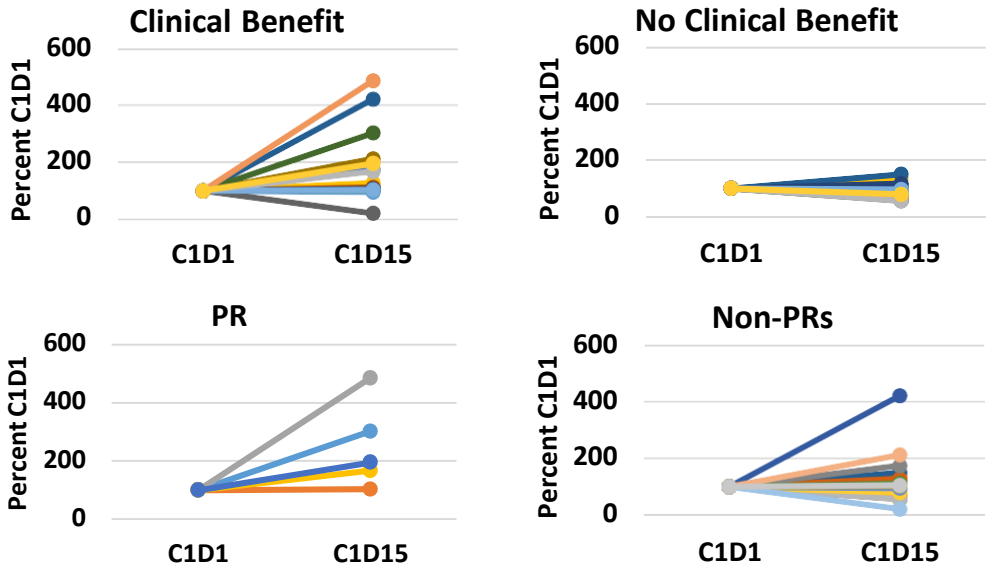
Total Mutation Burden



- No correlation between total mutation burden and clinical benefit.
- Four patients with clinical benefit harbored alterations hypothesized to be sensitive to single agent sitravatinib (MET or CBL mutation, RET fusion); All 3 STK11 mutant pts experienced no clinical benefit.

Cell-free DNA (cfDNA) from baseline patient blood samples was sequenced using the Guardant OMNI assay to estimate total mutation burden (TMB) and detect sitravatinib-sensitizing mutations. TMB was calculated for 33 patients.

Circulating Effector T Cells



- An increase in the fold change of circulating T effector cells (CD3+CD4-CD8+CD45RA+CD62L-) between C1D15 and C1D1 was observed in PRs and patients with clinical benefit vs the rest of the cohort. Clinical benefit vs no clinical benefit p-value = 0.003 and PR vs Non-PRs p-value = 0.012; Kruskal-Wallis test.

Blood was collected before and after treatment and immune cell populations were analyzed by flow cytometry using multi-marker panels at a central lab.

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
- Early signs of clinical activity have been observed in patients who have progressed following prior CIT
- Preliminary Kaplan-Meier estimate of median Duration of Response > 9 months
- Preliminary analysis of PD-L1 status at baseline indicates a nonsignificant trend towards high PD-L1 staining and clinical benefit
- CD8+ T effector cell response evident in patients achieving clinical benefit from the combination
- The study is ongoing and actively accruing patients