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Sitravatinib in Combination with Nivolumab Demonstrates Clinical Activity in Checkpoint Inhibitor-Naïve, Platinum-Experienced Patients with Advanced or Metastatic Urothelial Carcinoma (a/mUC)

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Disclosure Information

The Presenter has the Following Relationships to this Presentation:

Advisory Boards / Honoraria:
Mirati Therapeutics, Bristol-Myers Squibb, Exelixis

Non-branded educational programs:
Exelixis, Pfizer

Clinical Trials with Grant Support:
Mirati Therapeutics, Bristol-Myers Squibb, Takeda Pharmaceutical Company

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

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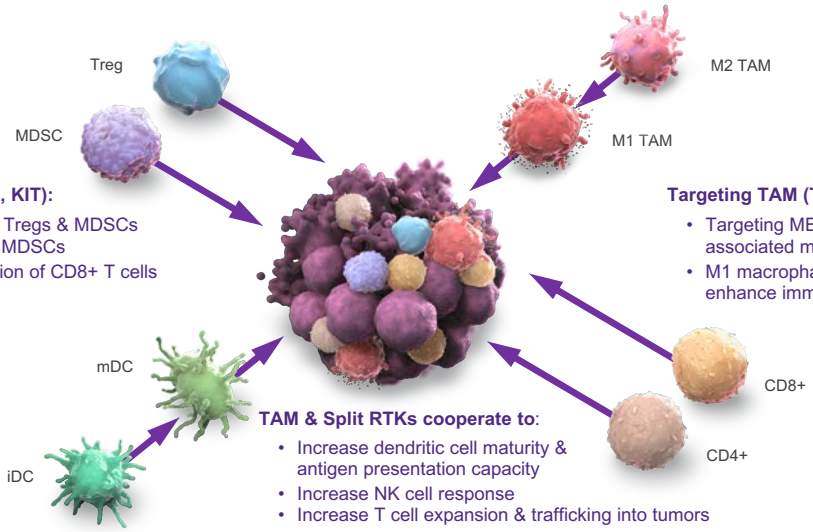
Sitravatinib Inhibits TAM, VEGFR2, and KIT Receptors and May Augment Immune Response



Targeting Split RTKs (VEGFR2, KIT):

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

Targeting TAM (TYRO3, AXL, MER):

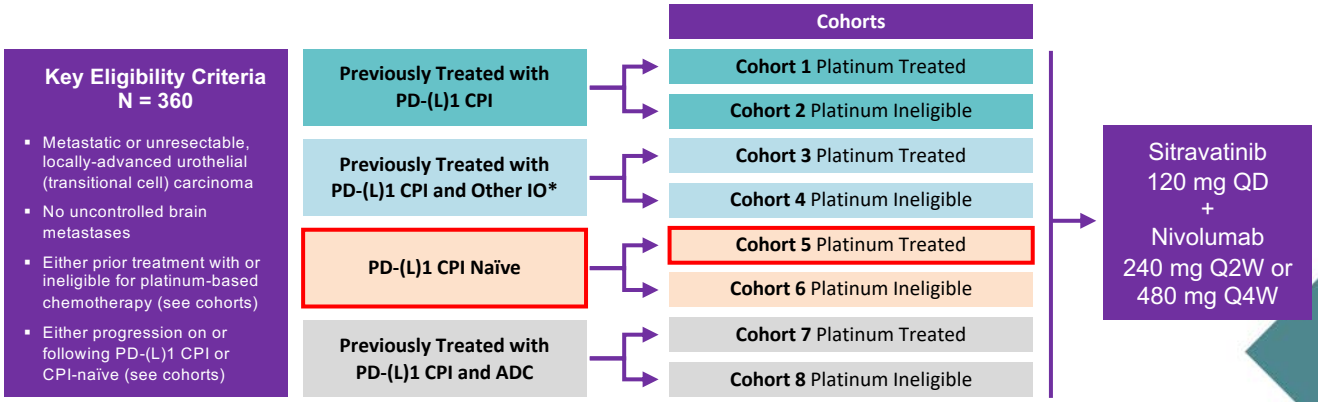
- Targeting MERTK & AXL shifts tumor associated macrophage (TAM) type to M1
- M1 macrophages secrete cytokines that enhance immune response (IL-12, TNF)

TAM & Split RTKs cooperate to:

- Increase dendritic cell maturity & antigen presentation capacity
- Increase NK cell response
- Increase T cell expansion & trafficking into tumors

Pircher et al., Synergies of Targeting Tumor Angiogenesis and Immune Checkpoints. Int J Mol Sci, 2017. 18(11); Garton et al., Anti-KIT Monoclonal Antibody Treatment Enhances the Antitumor Activity of Immune Checkpoint Inhibitors by Reversing Tumor-Induced Immunosuppression. Mol Cancer Ther, 2017. 16(4); Akalu, Y.T., C.V. Rothlin, and S. Ghosh, *TAM receptor tyrosine kinases as emerging targets of innate immune checkpoint blockade for cancer therapy.* Immunol Rev, 2017. **276**(1); Graham, D.K., D. DeRyckere, K.D. Davies, and H.S. Earp, *The TAM family.* Nat Rev Cancer, 2014. **14**(12); Du, W., Huang, H., Sorrelle, N., & Brekken, R. A. (2018). Sitravatinib potentiates immune checkpoint blockade in refractory cancer models. *JCI Insight*, *3*(21).

Study 516-003: Open-Label Phase 2 Trial of Sitravatinib and PD-(L)1 CPIs in Urothelial Carcinoma



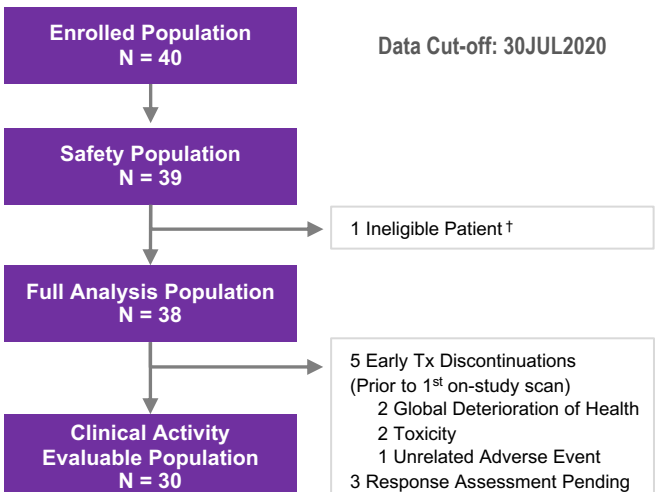
Start Date: September 11, 2018
Status: Enrolling
Sponsor: Mirati Therapeutics

Outcome Measures
Primary: ORR
Secondary: AEs, CBR, DOR, PFS, OS, PK
Exploratory: Circulating and tissue biomarkers

* Other IOs including but not limited to DNA vaccines, anti-CTLA-4, anti-OX40, anti-CD137 therapy or anti-IDO1 therapies, or recombinant IL-2 (CD-122) or IL-7 therapies
Abbreviations: ADC, antibody drug conjugate; AEs, adverse events; CBR, clinical benefit rate; CPI, checkpoint inhibitor; DOR, duration of response; IO, immune-based therapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q2/4W, every 2/4 weeks; QD, once daily
ClinicalTrials.gov. NCT03606174. Accessed August 17, 2020.

Sitravatinib + Nivolumab in Plat-Refractory, CPI-Naïve UC

Patient Disposition



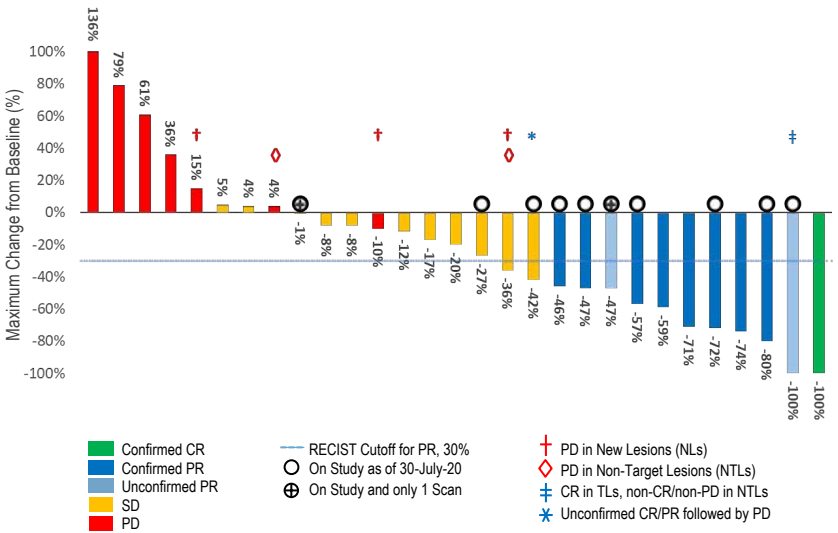
† 1 enrolled subject with histologically confirmed mUC was subsequently found to have a concurrent second primary tumor (HCC). The patient was thus excluded from the Full Analysis Population (for efficacy) but included in the Safety Population. The subject experienced Stable Disease as best response on study.
* 1 patient received both prior cisplatin and carboplatin

Demographics and Disease Characteristics

Safety Population, N		39
Age (years)	Median (range)	66 (38, 81)
Gender, n (%)	Male Female	30 (77) 9 (23)
Race, n (%)	Caucasian Other	34 (87) 5 (13)
ECOG PS, n (%)	0 1 Missing	20 (51) 17 (44) 2 (5)
Prior Platinum, n (%)	Cisplatin* Carboplatin*	38 (97) 2 (5)
Disease Stage – Screening, n (%)	Metastatic Advanced Unresectable	38 (97) 1 (3)
Disease Sites – Screening, n (%)	Lymph Node only Visceral Disease Including Liver	4 (10) 35 (90) 14 (36)
Bellmunt Score, n (%)	≥2 adverse factors Missing	11 (28) 2 (5)

Sitravatinib + Nivolumab in Plat-Refractory, CPI-Naïve UC

Maximal Target Lesion Reduction and Objective Response per Investigator by RECIST v1.1



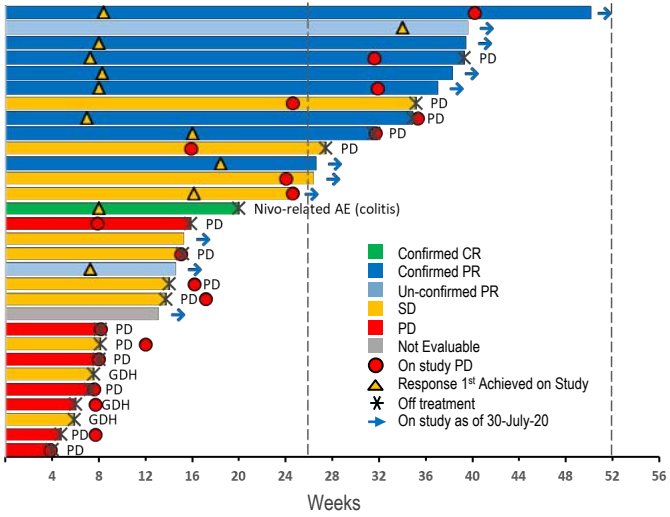
Clinical Activity Evaluable, N	30
Objective Response Rate*, n (%)	**11 (37)**
Best Overall Response, n (%)	
Complete Response Confirmed	**1 (3)**
Partial Response Confirmed Unconfirmed*	**8 (27) 2 (7)**
Stable Disease	11 (37)
Progressive Disease	7 (23)
Not Evaluable**	1 (3)
Clinical Benefit Rate (CR/PR/SD)	**22 (73)**

* 2 unconfirmed PRs have since confirmed as PRs on post-cutoff scans;
** Best overall response for 1 subject is Not Evaluable due to imaging quality (patient remains on study)

Data Cut-off: 30JUL2020

Sitravatinib + Nivolumab in Plat-Refractory, CPI-Naïve UC

Treatment Duration and Preliminary Secondary Efficacy Endpoints



Full Analysis Population, N	38
Follow Up (months), median	8.7
PFS (months), median (95% CI) Events, n	4.0 (1.9, 7.3) 25
OS (months), median (95% CI) Events, n	9.2 (5.1, 11.6) 15
Confirmed Responders (CR/PR), N	**9**
DOR (months), median (95% CI) Events, n	5.6 (3.7, 7.3) 5

DOR = Duration of Response; GDH = Global Deterioration of Health; OS = Overall Survival; PD = Progressive Disease; PFS = Progression-Free Survival

Data Cut-off: 30JUL2020

516-003: Sitravatinib and Nivolumab Safety in UC

Most Frequent (≥20%) Related Treatment-Emergent AEs (Sitravatinib and/or Nivolumab)

Adverse Event (Preferred Term)	Safety Population (N = 39 in Cohort 5) – (N = 151 in Sitravatinib + Nivolumab Cohorts 1-8)			
	Cohort 5 All Grades n (%)	Cohorts 1-8 All Grades n (%)	**Cohort 5 Grade 3/4 n (%)**	Cohorts 1-8 Grade 3/4 n (%)
Fatigue	**21 (54%)**	85 (56%)	**2 (5%)**	12 (8%)
Diarrhea	**17 (44%)**	72 (48%)	**3 (8%)**	13 (9%)
Decreased appetite	**17 (44%)**	62 (41%)	**0**	0
Dysphonia	**14 (36%)**	54 (36%)	**1 (3%)**	1 (1%)
Alanine aminotransferase increased	**14 (36%)**	41 (27%)	**1 (3%)**	3 (2%)
Hypertension	**11 (28%)**	42 (28%)	**5 (13%)**	27 (18%)
Nausea	**9 (23%)**	45 (30%)	**0**	2 (1%)
Hypothyroidism	**9 (23%)**	36 (24%)	**0**	0
Palmar-plantar erythrodysesthesia syndrome	**9 (23%)**	32 (21%)	**1 (3%)**	3 (2%)
Aspartate aminotransferase increased	**9 (23%)**	32 (21%)	**0**	1 (1%)

No treatment-related Grade 5 AEs were reported

4 (10%) subjects discontinued treatment due to AEs: pulmonary embolism/hyperthyroidism (both), skin rash/skin burning sensation (sitra), colitis (nivo), acidosis (unrelated)

Data Cut-off: 30JUL2020

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Summary and Conclusion

Sitravatinib and Nivolumab in CPI-Naïve Platinum-Refractory Urothelial Carcinoma

- Sitravatinib + nivolumab showed promising clinical activity in CPI-naïve, platinum-refractory UC
  - Consistent with previously presented activity in platinum- and CPI-refractory UC *
- ORR with combination was higher than with either monotherapy in this setting †
  - Secondary efficacy continue to mature
- Acceptable toxicity profile with manageable AEs
- Sitravatinib + nivolumab is a rational approach to augmenting the clinical activity of PD-(L)1 CPIs in patients with CPI-naïve, platinum-refractory UC
- The trial (NCT03606174) is ongoing at 26 sites in the US

* 516-003 Cohort 1 (SITC 2019); † CheckMate 275 (Lancet Oncol 2020), KEYNOTE-045 (Ann Onc 2019), Study 1108 UC Cohort (JAMA Oncol), JAVELIN Solid Tumor Trial UC Cohorts (GU ASCO 2019); NCT01688999 Cohort 1 (Lancet Oncol 2020)

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