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

Msaouel, Siefker-Radtke, Sweis, Mao, Rosenberg, Vaishampayan, Rezazadeh Kalebasty, Pili, Bupathi, Nordquist, Shaffer, Davis, Zhang, Gandhi, Christensen, Shazer, Yan, Winter, Der-Torossian, Iyer

Pavlos Msaouel, MD, PhD
Assistant Professor, Department of Genitourinary Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX
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.
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

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

Key Eligibility Criteria N = 360
- Metastatic or unresectable, locally-advanced urothelial (transitional cell) carcinoma
- No uncontrolled brain metastases
- Either prior treatment with or ineligible for platinum-based chemotherapy (see cohorts)
- Either progression on or following PD-(L)1 CPI or CPI-naïve (see cohorts)

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

Cohorts
- Cohort 1 Platinum Treated
- Cohort 2 Platinum Ineligible
- Cohort 3 Platinum Treated
- Cohort 4 Platinum Ineligible
- Cohort 5 Platinum Treated
- Cohort 6 Platinum Ineligible
- Cohort 7 Platinum Treated
- Cohort 8 Platinum Ineligible

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

Cohorts
- Previously Treated with PD-(L)1 CPI
- Previously Treated with PD-(L)1 CPI and Other IO*
- PD-(L)1 CPI Naïve
- Previously Treated with PD-(L)1 CPI and ADC

Sitravatinib 120 mg QD + Nivolumab 240 mg Q2W or 480 mg Q4W

* 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
### Patient Disposition

- **Enrolled Population**
  - N = 40

- **Safety Population**
  - N = 39
  - 1 Ineligible Patient †

- **Full Analysis Population**
  - N = 38
  - 5 Early Tx Discontinuations (Prior to 1st on-study scan)
    - 2 Global Deterioration of Health
    - 2 Toxicity
    - 1 Unrelated Adverse Event
    - 3 Response Assessment Pending

- **Clinical Activity Evaluable Population**
  - N = 30

### Demographics and Disease Characteristics

**Data Cut-off: 30JUL2020**

<table>
<thead>
<tr>
<th>Safety Population, N</th>
<th>39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Median (range)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>Male</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>Caucasian</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Prior Platinum, n (%)</td>
<td>Cisplatin*</td>
</tr>
<tr>
<td>Disease Stage – Screening, n (%)</td>
<td>Metastatic</td>
</tr>
<tr>
<td>Disease Sites – Screening, n (%)</td>
<td>Lymph Node only</td>
</tr>
<tr>
<td>Bellmunt Score, n (%)</td>
<td>≥2 adverse factors</td>
</tr>
</tbody>
</table>

† 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

---

Sitravatinib + Nivolumab in Plat-Refractory, CPI-Naïve UC
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 | 8 (27)
Unconfirmed* | 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)**

<table>
<thead>
<tr>
<th>Adverse Event (Preferred Term)</th>
<th>Safety Population (N = 39 in Cohort 5) – (N = 151 in Sitravatinib + Nivolumab Cohorts 1-8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohort 5 All Grades n (%)</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (54%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17 (44%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>17 (44%)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>14 (36%)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>14 (36%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11 (28%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (23%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>9 (23%)</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia syndrome</td>
<td>9 (23%)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>9 (23%)</td>
</tr>
</tbody>
</table>

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**
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)