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Society for Immunotherapy of Cancer
Sitravatinib + Nivolumab Demonstrates Clinical Activity in Platinum-Experienced Urothelial Carcinoma Patients Who Progressed on Prior Checkpoint Inhibitor

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Presenter Disclosure Information

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MD Anderson Cancer Center
Houston, TX, USA

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Takeda Pharmaceutical Company

There will be discussion about the use of products for non-FDA approved indications in this presentation
Sitravatinib (MGCD516): A Spectrum-Selective Kinase Inhibitor

- Sitravatinib is an orally available small molecule that inhibits a spectrum of related receptor tyrosine kinases (RTKs) including:
  - TAM family (Tyro3, Axl, MerTK)
  - Split family (VEGFR2/PDGFR and c-Kit)
  - c-Met

- Inhibition of these target classes may enhance anti-tumor activity through:
  - Modulation of the immunogenic status of tumors
  - Improvement of tumor perfusion by reducing intratumoral pressure
  - Modulating subsets of immune cells
Sitravatinib in the Tumor Microenvironment (TME)

Tyro, Axl, Mer
- Macrophages shift to Type 1 resulting in production of immune stimulating cytokines
- Enhances innate and adaptive immune response

VEGFR2, KIT + Tyro, Axl, Mer
Increase:
- Dendritic cell dependent antigen presentation
- NK cell response
- T cell trafficking

VEGFR2 & KIT
- Reduction in Tregs and MDSCs
- Enhance CD8+ T-cell response

Immuno-suppressive Pre-Treatment

Immuno-responsive Post-Treatment

References:
- Gatenby et al., Anti-KIT Monoclonal Antibody Treatment Enhances the Antitumor Activity of Immune Checkpoint Inhibitors by Reversing Tumor-Induced Immunosuppression. J Natl Cancer Inst. 2017; 109(4)
- Akatsuka, T., Y. Kushida, and S. Okuhira. TAM receptor-positive tissues as emerging targets of innate immune checkpoint blockade for cancer therapy. Immunol Rev. 2017; 279(1)
Sitravatinib Inhibits Immunosuppressive Immune Populations and Augments Checkpoint Inhibitor Therapy

Inhibition of M2 macrophage polarization by sitra or MERTK KO ex vivo

Sitravatinib decreases M2 MΦs, M-MDSCs and increases CD4 and CD8 cells in a syngeneic model

Sitravatinib augments PD-1 therapy in CPI refractory models


- Sitravatinib shifts macrophage polarization M2 → M1, depletes MDSCs and increases CD8+ T cells in tumor-bearing syngeneic mice
- Sitravatinib augments PD-1 therapy in CPI-refractory models and in mice with complete responses to sitravatinib + PD-1 therapy, tumors do not form upon re-innoculation, confirming an adaptive immunity-based mechanism
Urothelial Carcinoma Background

• Results in approximately 165,000 deaths per year worldwide

• Platinum-based chemotherapy is the cornerstone of first-line therapy
  ▪ Most patients experience treatment resistance or intolerance

• Since 2016, treatment options for platinum-refractory or platinum-ineligible advanced UC have been expanded to include anti-PD-1 and anti-PD-L1 checkpoint inhibitors (CPI)
  ▪ Single agent CPI response rates in UC are relatively low (around 20%)
  ▪ Durable clinical responses in a subset of patients

• Strategies to improve clinical efficacy and overcome acquired or primary resistance to CPI therapy are needed
  ▪ Combine an anti-PD-1 or anti-PD-L1 CPI with an agent that has both immune modulatory and antitumor properties
516-003 Study Design

Open-label, multi-center Phase 2 Study to evaluate sitravatinib + nivolumab in patients with locally-advanced or metastatic UC

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Platinum Treated</td>
<td>≥1 PR</td>
<td>n=9</td>
<td>n=8</td>
</tr>
<tr>
<td>2 Platinum Ineligible</td>
<td>n=9</td>
<td>n=8</td>
<td>n=23</td>
</tr>
<tr>
<td>3 Platinum Treated</td>
<td>n=9</td>
<td>n=8</td>
<td>n=23</td>
</tr>
<tr>
<td>4 Platinum Ineligible</td>
<td>n=9</td>
<td>n=8</td>
<td>n=23</td>
</tr>
<tr>
<td>5 Platinum Treated</td>
<td>≥6 PR</td>
<td>n=24</td>
<td>n=21</td>
</tr>
<tr>
<td>6 Platinum Ineligible</td>
<td>n=24</td>
<td>n=21</td>
<td></td>
</tr>
<tr>
<td>7 Platinum Treated</td>
<td>n=9</td>
<td>n=8</td>
<td>n=23</td>
</tr>
<tr>
<td>8 Platinum Ineligible</td>
<td>n=9</td>
<td>n=8</td>
<td>n=23</td>
</tr>
</tbody>
</table>

Previously Treated with PD-(L)1 & another I/O

Previously Treated with PD-(L)1 & an ADC (e.g. enfortumab, sacituzumab)

PD-(L)1 Naïve

≥1 PR

≥3 PR

≥6 PR

Radiographic Progression

n=9

n=8

n=23

n=24

n=21

n=21

n=9

n=8

n=23

n=9

n=8

n=23

n=9

n=8

n=23

n=9

n=8

n=23

预备治疗的PD-(L)1

预备治疗的PD-(L)1和另一个I/O

PD-(L)1 Naïve
Hypothesized that the combination of sitravatinib + nivolumab will restore or enhance CPI clinical activity in pts with immunotherapy-refractory UC
  • Could enhance the antitumor activity observed with either agent alone
  • Sitravatinib + nivolumab has also been shown to be well-tolerated in other indications, including NSCLC and RCC

Cohort 1 patients (data cut-off of 17 October 2019)
  • UC patients who have progressed on or after treatment with a CPI, as the most treatment prior to the study
  • AND were previously treated with platinum-based chemotherapy

Completed enrollment into the expansion phase

Continuous 28-day Cycles
Sitravatinib 120 mg QD orally
+ Nivolumab 240 mg IV Q2W or 480 mg IV Q4W
Tumor Assessments performed Q8W
OBJECTIVES/ENDPOINTS

• PRIMARY
  • Clinical activity by ORR per RECIST Version 1.1

• SECONDARY
  • Safety & tolerability
  • Secondary efficacy endpoints including DOR, CBR, PFS & OS
  • Pharmacokinetics (PK) of sitravatinib
  • PK of sitravatinib in patients with renal impairment

• EXPLORATORY
  • Circulating PD-L1, immune cell populations and cytokines
  • Tumor cell PD-L1 expression, tumor infiltrating immune cell populations & gene expression signatures
  • Tumor gene alterations in circulation & in tumor tissue

KEY ELIGIBILITY CRITERIA

• Histologically-confirmed transitional cell UC that is locally advanced or metastatic & is unresectable
• Most recent treatment must have included anti-PD-1 or anti-PD-L1 CPI with radiographic PD on or after the CPI
  ▪ No prior treatment with other immunotherapies (e.g. anti-CTLA-4, anti-OX40 and anti–CD137)
• Received prior platinum-based chemotherapy
  ▪ If peri-operative setting, must have PD ≤ 1 yr of last dose
• Measurable disease, as per RECIST Version 1.1
• ECOG 0-1
• GFR ≥ 30 mL/min per CKD-EPI
• No active brain metastases, unless adequately treated & neurologically-stable off treatment
# 516-003 Cohort 1 Patient Disposition

<table>
<thead>
<tr>
<th>Enrolled Population</th>
<th>33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety Population (received ≥1 dose)</td>
<td>33 (100%)</td>
</tr>
<tr>
<td>Early treatment discontinuations (prior to 1st tumor assessment)</td>
<td>4</td>
</tr>
<tr>
<td>• Unrelated AE</td>
<td>2</td>
</tr>
<tr>
<td>• Global deterioration of health</td>
<td>1</td>
</tr>
<tr>
<td>• Withdrew consent</td>
<td>1</td>
</tr>
<tr>
<td>Too early for 1st tumor assessment (&lt;8 wks on study)</td>
<td>7</td>
</tr>
<tr>
<td>Evaluable Population (≥1 on-study tumor assessment)</td>
<td>22 (67%)</td>
</tr>
</tbody>
</table>
### 516-003 Cohort 1 Safety Population Characteristics (N=33)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (range)</th>
<th>≥75 years, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>68 (47, 83)</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23 (70)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (30)</td>
<td></td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>30 (91)</td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Other (refused to provide)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>15 (45)</td>
<td></td>
</tr>
<tr>
<td>1+</td>
<td>18 (55)</td>
<td></td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>17 (52)</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>14 (42)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>2 (6)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease stage at study entry, n (%)</th>
<th>Metastatic</th>
<th>Locally advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 (91)</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metastasis sites at baseline, n (%)</th>
<th>Visceral disease</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>23 (70)</td>
<td>10 (30)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymph node only</td>
<td>7 (21)</td>
</tr>
<tr>
<td></td>
<td>Lymph node + brain/bone</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hemoglobin at baseline, n (%)</th>
<th>&lt;10 g/dL</th>
<th>7 (21)</th>
</tr>
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<tbody>
<tr>
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</table>

<table>
<thead>
<tr>
<th>Bellmunt prognostic factors, n (%)</th>
<th>≥2 adverse factors</th>
<th>8 (24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of prior systemic therapy in advanced/metastatic setting, n (%)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 (1, 4)</td>
</tr>
<tr>
<td></td>
<td>1 (3)</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>27 (82)</td>
</tr>
<tr>
<td></td>
<td>2 (6)</td>
</tr>
<tr>
<td></td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

* Patients with 1 prior therapy had a platinum-based chemotherapy and a PD-(L)1 inhibitor in combination
516-003 Preliminary Sitravatinib Pharmacokinetics

• The PK exposure values attained in UC patients Cohort 1 are consistent with the PK levels historically observed.

• In the current study, limited exposure parameters were derived due to the sparse sampling collections (0, 2 and 4hrs on C1D1 and C1D15).

• The 120 mg QD dose resulted in a single dose geometric mean Cmax of 21 ng/mL reached after approximately 3 hrs. At steady state the geometric mean Ctrough and Cmax values were 50 and 72.5 ng/mL, respectively.

• A renal impairment sub-study is ongoing to compare PK in patients with mild or moderate renal impairment to patients with no renal impairment.
### 516-003 Safety

**Most Frequent (>15%) Related Treatment-Emergent Adverse Events (Sitravatinib and/or Nivolumab)**

<table>
<thead>
<tr>
<th>Adverse Event (Preferred Term)</th>
<th>Safety Population (N=67, Cohorts 1-6; N=33, Cohort 1 only)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cohorts 1-6 All Grades  n (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>36 (54%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>33 (49%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22 (33%)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>20 (30%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (24%)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>16 (24%)</td>
</tr>
<tr>
<td>Palmar-planter erythrodysesthesia syndrome (PPE)</td>
<td>14 (21%)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>12 (18%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (18%)</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>11 (16%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (16%)</td>
</tr>
</tbody>
</table>

**No treatment-related Grade 4 or Grade 5 AEs were reported**
516-003 Cohort 1: Efficacy

BEST RESPONSE (Evaluable Patients, N=22)

21/22 (95%) CR+PR+SD
19/22 (86%) CR+PR+SD>12wks
8/22 (36%) Tumor Regression >30%
6/22 (27%) Confirmed Response (CR+PR)

Abbreviations: At=atezolizumab; Du=durvalumab; Ni=nivolumab; Pe=pembrolizumab

PD-(L)1-Refractory Platinum-Experienced
Cohort 1: Case Study #1

- 10/2017: metastatic UC of bladder
- 10/2017: neoadjuvant ddMVAC x 4 cycles
- 2/2018: cystectomy

- 1/2019: disease progression
  → 2/2019: nivolumab + sitravatinib

1/11/2019 (Baseline)

9/15/2019 (Wk16): confirmatory PR scan (-50%)
Cohort 1: Case Study #2

- 5/2018: metastatic UC of urethra/prostatic duct
- 7/2018: carboplatin/gemcitabine x 6 cycles
- 1/2019: progression in bone and LNs
  → 11/2018: pembrolizumab

- 5/2019: progression in bone, LNs and innumerable new liver metastases
  → 5/2019: nivolumab + sitravatinib

5/2/2019 (Baseline)

9/17/2019 (Wk16): confirmatory PR scan (-50%) – remains in PR (-54%)
516-003 Cohort 1 Conclusion

• The combination of sitravatinib with nivolumab is a rational approach to restoring or enhancing the clinical activity of anti-PD-(L)1 CPI in patients with immunotherapy resistant UC

• The combination has an acceptable toxicity profile with manageable AEs

• This ongoing study continues to show promising clinical activity, including tumor regression & prolonged duration on treatment in patients who have progressed following prior CPI

• The study is open at 25 sites in the US & recruitment is ongoing in 7 Cohorts

• Preliminary clinical activity has been seen in several other cohorts, with decisions regarding expansion awaiting for additional enrollment & maturing data
Acknowledgements

• Thank you to all the patients and their families
• Participating study investigators and clinical sites
• This study is sponsored by Mirati Therapeutics, Inc.