Sitravatinib Demonstrates Activity in Patients with Novel Genetic Alterations that Inactivate CBL

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Lyudmila Bazhenova, MD – disclosures

- Consultant Advisory Board: Ariad, Astra Zeneca, Eli Lilly, Genentech, Novartis
- Study sponsored by Mirati Therapeutics, Inc.
Sitravatinib (MGCD516)
Spectrum-selective RTK Inhibitor Profile

- Sitravatinib is an oral drug that inhibits a spectrum of related receptor tyrosine kinases (RTKs) including:
  - TAM Family (AXL and MER): 1 nM cellular IC$_{50}$
  - VEGFR2/PDGFRA/KIT: 5-10 nM cellular IC$_{50}$
  - RET, MET, DDR2, TRKA: 10-25 nM cellular IC$_{50}$
- Sitravatinib doesn't inhibit >150 serine threonine kinases at <1000 nM
Sitravatinib: Rationale for Targeting CBL Mutations

• CBL mutation correlated with activity in a 500 cancer cell line screen designed to identify sitravatinib response biomarkers

• CBL is an E3-ubiquitin ligase that regulates the internalization and degradation of multiple activated RTKs including PDGFRA, MET, KIT, & TYRO/AXL/MER as a normal signaling attenuation mechanism

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1 Research Collaboration with University of California Los Angeles, Translational Oncology Research Lab (TORL)/Mirati
Sitravatinib: Rationale For Targeting CBL Mutations

Inhibiting hyperactivated PDGFR, KIT, MET, TYRO/AXL/MER

• Loss of function (LOF) mutations in CBL result in increased target RTK activation in tumor cells that may act as oncogenic drivers

* Adapted from B. Mohapatra et al. 2013, Biochim Biophys Acta 1833:122-39.
• CBL is commonly inactivated by gene deletions, nonsense or hotspot mutations in up to 1.5% of NSCLC and 3.5% of melanoma

• Sitravatinib may be an effective therapy against tumors with CBL inactivation through RTK inhibition that counterbalances loss of signal attenuation
Sitravatinib Induces Significant Tumor Regression in Genetically Defined Cancer Models

CBL loss of function mutant models

A549 NSCLC CDX
CBL p.R585C/ hemizygous deletion

NCI-H2073 NSCLC CDX
CBL homozygous deletion

LU11713 NSCLC PDX Crown
CBL R420Q (RING domain)

Graphs showing tumor volume over study days for different cancer models treated with Vehicle or MGCD516 20mg/kg QD.
516-001 Study Design

A multi-center, open label Phase 1/1b Study of MGCD516 in Patients with Advanced Solid Tumor Malignancies

- Phase 1: Determine the MTD and Recommended Dose
- Phase 1b: Evaluate the Clinical Activity of Sitravatinib and Potential Genetic Biomarkers for Patient Selection

**IP administration:**

- Patients receive oral sitravatinib once daily (QD) in continuous cycles of 21 days.

**Primary Objectives:**

- Characterize the safety profile, PK and signs of clinical activity of sitravatinib

**Key Phase1b Eligibility Criteria:**

- Advanced metastatic or unresectable solid tumor malignancy
- Adequate bone marrow and organ function
- No symptomatic or uncontrolled brain metastases
- Malignancy harboring tumor genetic alteration of sitravatinib RTK targets or LOF mutations in CBL
Phase 1b Basket Cohorts: Molecularly Selected Patients

- Basket cohorts designed to explore the use of molecular markers for selection of patients with increased potential for response to sitravatinib.
- Each basket cohort evaluated using Simon’s Optimal Two-Stage Design
- Statistical assumptions:
  - ORR of 35% is considered interesting
  - ORR of 15% is considered uninteresting (and may be observed with currently available treatment)

Stage 1:
- 8 pts
- 0-1 Response
- 2-6 Responses

Stage 2:
- 16 pts (24 total)
- ≥2 Responses
- ≥7/24 Responses

Limited Treatment Effect

Promising Treatment Effect

Phase 1 Dose Escalation

Phase 1b Evolving Basket Cohorts

- CBL LOF
- NSCLC – RET-KIF5B
- NSCLC – RET rearrangement (other)
- Other RET
- Chr4q12 amp (PDGFRA, KIT, KDR)
- Other (MET, AXL, NTRK, DDR2)
Study 516-001 Update

- Phase 1, Dose escalation complete:
  - 32 pts enrolled over 7 dose levels (10mg-200mg). MTD at 150mg QD

- Phase 1b, Currently enrolling at 120mg QD, continuous cycles of 21 days
  - As of 4 Sep 2018, 132 pts (72 men/60 women; median age 66 years; range 36-84) with advanced solid tumors were enrolled in Phase 1b cohorts
  - 16 pts were enrolled in Phase 1b CBL Loss of Function Cohort.

### Baseline Characteristics (CBL LOF Cohort)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=16 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (Median (range))</td>
<td>60 (45-83)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (62.5%)</td>
</tr>
<tr>
<td>Male</td>
<td>6 (37.5%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>13 (81%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Black</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>2 (13%)</td>
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<tr>
<td>Performance status</td>
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<tr>
<td>ECOG 0/1/2</td>
<td></td>
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<tr>
<td>ECOG 0</td>
<td>6 (38%)</td>
</tr>
<tr>
<td>ECOG 1</td>
<td>9 (56%)</td>
</tr>
<tr>
<td>ECOG 2</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Primary Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Non-small Cell Lung Cancer</td>
<td>3 (19%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (31%)</td>
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</tbody>
</table>
# Study 516-001 Safety

<table>
<thead>
<tr>
<th>Treatment-Related Adverse Events (≥10% of pts)</th>
<th>Phase1/1b N=153*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>All Grades n (%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>74 (48)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>65 (42)</td>
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<tr>
<td>Hypertension</td>
<td>56 (37)</td>
</tr>
<tr>
<td>Nausea</td>
<td>45 (29)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40 (26)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>38 (25)</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysaesthesia</td>
<td>28 (18)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>26 (17)</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>25 (16)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>22 (14)</td>
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<tr>
<td>Weight decreased</td>
<td>21 (14)</td>
</tr>
<tr>
<td>Dysphonia</td>
<td>18 (12)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>18 (12)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>16 (10)</td>
</tr>
<tr>
<td>Rash</td>
<td>15 (10)</td>
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</tbody>
</table>

*Safety data available for 153 patients, cut-off 26June2018
Sitravatinib Activity in Advanced Malignancies with Loss of Function Mutations in CBL (Stage 1 of Simon’s Optimal Two-Stage design)

Clinical Activity Evaluable Population:
- Received at least 1 cycle of sitravatinib (≥ 80% of assigned total dose)
- At least 1 on-study disease assessment
Activity of Sitravatinib in *CBL*-mutant NSCLC

Case Study #1

**Confirmed PR with 77% decrease in Target lesions**

- 77 yo female, lifelong non-smoker with adenocarcinoma of the lung characterized by *EGFR* exon19del
- Initial PR of 9 months with erlotinib, then developed resistance with *EGFR* T790M, treated with rociletinib with SD of 11 months duration followed by osimertinib and carboplatin/pemetrexed
- NGS at progression showed persistence of *EGFR* exon19del, loss of *EGFR* T790M, and a new *CBL* mutation (p.C384R), which is located in the RING domain and is predicted to result in loss of CBL ligase adaptor function
- Enrolled into Study 516-001 on 15 March 2017, treated with sitravatinib at 150mg QD in continuous cycles of 21 days
Case Study #2

- 45 yo female, past smoker with UC, SLE, and sinonasal melanoma
- Initially underwent resection and radiation treatment of the primary disease site
- Three months later she presented with local recurrence of disease as well as metastases to the liver, lymph node, and bone
- Received 3 doses of pembrolizumab which was discontinued due to colitis requiring steroids; then treated with carboplatin/paclitaxel x 6 with response
- Imaging 2 months later revealed disease progression. NGS of archival tissue demonstrated a CBL (p.Y368C) loss of function mutation, and she was enrolled into Study 516-001 and treated with sitravatinib at 150mg QD

PR first observed after 4 weeks on treatment, decrease of 43% in target lesions noted at Week 43. Subject remains on study.

Courtesy of Dr. Theresa Werner, Huntsman Cancer Institute, Study 516-001, Subject 105-016
Conclusions

• Loss of function mutations in CBL serve as potentially targetable oncogenic drivers

• Sitravatinib demonstrated clinical activity in Stage 1 of Simon’s optimal two-stage design with responses observed in NSCLC and melanoma, each characterized by a loss of function mutation located in the CBL linker / ring finger domain, a mutation hotspot region

• Sitravatinib activity provides evidence for the potential oncogenic role of RTK activity in tumors with loss of function mutations in CBL

• Further evaluation is warranted, including clinical activity of sitravatinib in patients with different classes of CBL mutations and with different tumor types
Acknowledgements

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