Phase 1 study of CB-839, a small molecule inhibitor of glutaminase (GLS), in combination with paclitaxel (Pac) in patients (pts) with triple negative breast cancer (TNBC)

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INTRODUCTION

Altered Glutamine Metabolism of Cancer Cells

- Tumor cells require glutamine for growth and survival
- Glutaminolysis (GLS) controls the first step in glutamine metabolism and is highly expressed in triple negative breast cancer (TNBC)
- CB-839 is an orally active, highly selective inhibitor of GLS with preclinical and clinical activity in TNBC

BACKGROUND AND RATIONALE

CB-839 Sensitivity Correlates With Glutaminolysis Activity

- Tumor resistance to Paclitaxel is strongly correlated with high baseline levels of glutamate
- Paclitaxel + CB-839 strongly sensitizes mitotically arrested breast cancer cells

CB-839 Enhances the Anti-Tumor Activity of Paclitaxel in Vivo

- CB-839 ≥ 839 mg BID can increase the efficacy of paclitaxel
- One DLT during dose escalation:
  - Grade 3 neutropenia
  - Subject tolerated a reduced dose of paclitaxel
- CB-839 800 mg BID selected as dose for expansion (R20)

RESULTS

Demographics

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<th>Race</th>
<th>N (%)*</th>
<th>American</th>
<th>African</th>
<th>Total</th>
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<tr>
<td>Age: 0 80</td>
<td>Evaluable (N)</td>
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<td>40 40</td>
<td>40 40</td>
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<tr>
<td>Advanced/</td>
<td>Dose Escalation</td>
<td></td>
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<tr>
<td>metastatic</td>
<td>30 10</td>
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Safety

<table>
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<th>N (%)</th>
<th>3 (38)</th>
<th>0 (0)</th>
<th>3 (38)</th>
</tr>
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</table>
| 38% ORR and 50% DCR in patients refractory to prior given in the advanced/metastatic setting
| 50% ORR in African American patients, all of whom were taxane refractory
| Consistent with higher glutamine utilization in tumors of African American patients
| Additional clinical development with CB-839 + paclitaxel is warranted
| Response in relation to genetic background, molecular subtype of TNBC and glutamine biology is being studied

SUMMARY AND CONCLUSIONS