**Efficacy and Safety of CB-839, a Small Molecule Inhibitor of Glutaminase, in Combination With Paclitaxel in Patients With Advanced Triple Negative Breast Tumor (TNBC): Initial Findings from a Multicenter, Open-Label Phase II Study**

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**INTRODUCTION**

Glutaminase (GLS) is a key enzyme that can convert glutamine into glutamate and other metabolic intermediates. In this study, we evaluated the clinical benefit of CB-839 in metastatic triple-negative breast cancer (mTNBC) patients.

**METHODS**

- **Study design**: Open-label, multicenter, phase II study with patients randomized to 1L or 3L+ cohorts.
- **Patient selection**: Advanced mTNBC patients with lactate dehydrogenase levels ≥ 1.5× upper limit of normal.
- **Treatment arms**: 1L (n = 22) or 3L+ (n = 26) at 410 mg twice daily.
- **Endpoints**: Primary endpoint: Overall Response Rate (ORR) and Duration of Clinical Benefit (DCB) in 1L and 3L+ cohorts.

**RESULTS**

- **ORR**: 50% in 1L and 46% in 3L+.
- **DCB**: 100% and 55% for 1L and 3L+, respectively.
- **Clinically Relevant Changes**: Significant improvements in tumor burden and clinical benefit were observed across treatment arms.

**CONCLUSIONS**

- CB-839 plus paclitaxel was well tolerated in this study.
- The combination of CB-839 + paclitaxel had a 41% ORR in 1L mTNBC patients and OCR of 86%.
- In 3L mTNBC patients who had previously progressed on a taxane, the ORR was 12% and OCR was 30%.
- A trend toward improved clinical benefit was noted in patients with IHC-documented AR disease compared to AR null.
- Previously identified signal of improved activity in patients of AA was not confirmed in this study.

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**BIOMARKER ANALYSIS**

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>1L (n = 22)</th>
<th>3L+ (n = 26)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSL</td>
<td>62 (28)</td>
<td>55 (26)</td>
<td>0.05</td>
</tr>
<tr>
<td>LAR subtype</td>
<td>BL1</td>
<td>BL2</td>
<td>ND</td>
</tr>
<tr>
<td>Clinical benefit</td>
<td>100</td>
<td>55</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**SAFETY**

- Grade ≥ 3 adverse events: 2% and 4% in 1L and 3L+ groups, respectively.
- No high-grade treatment-related abnormalities were observed.

**CONCLUSIONS**

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**TUMOR RESPONSE (MOSL)**

- 68% in 1L and 62% in 3L+.
- 3PR and 3SD were observed in 1L, with full dose weekly paclitaxel well tolerated.
- 1L patients who did not respond to taxane had increased severity or frequency of toxicities expected for paclitaxel.
- No events of Grade ≥ 3 peripheral neuropathy.

**CLINICAL OUTCOMES**

- **ORR**: 50% in 1L and 46% in 3L+.
- **DCB**: 100% and 55% for 1L and 3L+, respectively.

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**Key Eligibility Criteria**

- ≥ 18 years
- mTNBC (AA and/or PI [PR, BR] and/or HR [ER, Her2] negative)
- ECOG PS ≤ 2
- Measurable disease (MOSL ≥ 1), *AA or non-AA Genetics: Self-identified
- ≥ 12 weeks from prior systemic therapy for mTNBC

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**Data cutoff**: October 31, 2018