Background

• Colorectal cancers (CRCs) are standardly treated with fluoropyrimidine based therapy but ultimately resistance develops.

• Approximately 15-20% of CRCs harbor a PIK3CA mutation.

• PIK3CA mutated CRCs demonstrate glutamine dependency in both in vitro and in vivo models, including those known to be fluoropyrimidine (FP) resistant while PIK3CA wild-type CRCs do not (Jiao et al., Nature Communications, 7:11971).

• CB-839 is an oral inhibitor of glutaminase, a key enzyme in glutamine metabolism.

• Preclinical CRC studies, in vitro and in vivo, show that the combination of CB-839 and a fluoropyrimidine is superior to either as a single agent and can overcome FP resistance.

Objective

• We conducted a phase I study to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of oral CB-839 when administered with oral capecitabine.

Methods

Eligibility Criteria

• Advanced solid tumor malignancy with progression on all standard therapies or for whom capecitabine is an acceptable option.

• At least 4 weeks since prior chemotherapy or 2 weeks since prior radiation therapy with recovery to ≤ grade 1 heme toxicity per CTCAE v4.0.

• ECOG performance status of ≤ 1.

• Ability to understand and provide written informed consent.

Dose Levels

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>CB-839 (mg) orally twice daily x 21 days</th>
<th>Capcitabine (mg/m²) orally twice daily for 14/21 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>400</td>
<td>500</td>
</tr>
<tr>
<td>Level 2</td>
<td>450</td>
<td>750</td>
</tr>
<tr>
<td>Level 3</td>
<td>600</td>
<td>1000</td>
</tr>
<tr>
<td>Level 4</td>
<td>800</td>
<td>1000</td>
</tr>
</tbody>
</table>

Median age: 69.5 years (43-80) Mean number of cycles received: 5.4 (1-14)

Select PIK3CA Genomic Subset Analysis

• PIK3CA mutated: 7 patients

• RAS mutated: 9 patients

• Dual PIK3CA/RAS mutated: 5 patients

Study Schema and Administration Schedule

• CB-839 orally twice daily continuously Capecitabine twice daily on days 1-14 Treatment cycle x 21 days

• Standard 3+3 dose escalation strategy used.

• Blood collected once for pharmacokinetic analysis.

• CT chest, abdomen and pelvis obtained every 9 weeks to assess response to treatment.

• CB-839 administered orally twice daily with food continuously.

Results

Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender Male</td>
<td>6 (38)</td>
</tr>
<tr>
<td>Gender Female</td>
<td>10 (62)</td>
</tr>
<tr>
<td>Race White</td>
<td>15 (94)</td>
</tr>
<tr>
<td>Race African American</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

PFS Analysis

Median PFS PIK3CA mutant CRC: 26 weeks (4-46 wks)

All grade 3/4 AEs and grade 1/2 AEs seen in ≥ 10% of patients

Dose Limiting Toxicities

- Dose Limiting Toxicity (DLT) period—21 days
- Patients must receive at least 75% of planned CB-839 and capecitabine during the first cycle to be evaluable for DLT

- DLT—any grade 3 non-hematologic toxicity per CTCAE v4 (treatment related), grade 3 febrile neutropenia, grade 3 thrombocytopenia associated with grade 3 bleeding, grade 4 neutropenia or thrombocytopenia occurring during the DLT period

- One patient in dose level 4 replaced as did not receive enough study drug.

- No DLTs observed through DL4, DL3A not evaluated

Conclusions

• CB-839 800 mg orally twice daily may be safely administered with capecitabine 1000 mg/m² orally twice daily for 14/21 days with minimal toxicity and is the recommended phase II dose.

• No patients experienced a partial or complete response but prolonged stable disease was observed.

• Among colorectal cancer patients, those with a PIK3CA mutation had a longer PFS than those with wild-type PIK3CA.

• The phase II portion of this trial assessing this combination in PIK3CA mutant colorectal cancer patients is ongoing (NCT02861300).

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