**Study Objectives:**
- Pharmacokinetics in combination with CZT
- Safety and tolerability of AT13387 with CZT (250 mg BID)
- Delays the onset of resistance
- Displays potent antitumor activity

**Study Methodology:**
- AT13387 is administered intravenously (IV) Day 1, 8, and 15 of a 28-Day dosing cycle.
- PK & PD results support weekly dosing
- PK & PD results support weekly dosing

**Pharmacokinetic Summary:**
- AT13387 dose level, CZT 250 mg PO BID at escalating doses of 150, 180, and 220 mg/m².
- Dose escalation is

**Safety:**
- The most common AE's related to AT13387 treatment, independent of grade, reported in >10% of subjects (cohorts combined) were as follows:
- Dihydroxy (75%), Fatigue (63%), Nausea (59%), Decreased Appetite (38%), Vomiting (25%), Diarrhea (19%), Weight decreased (19%), Dry Mouth (16%), Dysgeusia (16%), Oedema peripheral (16%), ALT increased (13%), AST increased (13%)

**Dose Escalation & Dose Limiting Toxicities:**
- AT13387 dosing was initiated at 150 mg/m² and escalated to 220 mg/m².
- No dose limiting toxicities were observed at the doses investigated.
- All CTCAE grade 3 or higher events related to AT13387 treatment are

**Results:**
- The incidence of DLTs for AT13387 in combination with standard dose CZT
- Primary: The incidence of DLTs for AT13387 in combination with standard dose CZT
- Secondary: The incidence of DLTs for AT13387 in combination with standard dose CZT
- Efficacy: Assessment of ORR and PFS by RECIST every 2 cycles
- PK: Blood samples at various timepoints Day 1 for AT13387 and CZT
- Safety:
- Standard dose CZT
- Primary: The incidence of DLTs for AT13387 in combination with standard dose CZT
- Secondary: The incidence of DLTs for AT13387 in combination with standard dose CZT
- Efficacy: Assessment of ORR and PK by RECIST every 2 cycles

**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dosing Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs) median (range)</td>
<td>65 (21-83)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>71/110</td>
</tr>
<tr>
<td>Histology (Adenocarcinoma/Other)</td>
<td>4/4</td>
</tr>
</tbody>
</table>

**Table 2. AT13387 PK Parameters**

<table>
<thead>
<tr>
<th>Timepoint (hr)</th>
<th>AT13387 (ng/mL)</th>
<th>CZT (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>3.3</td>
<td>2923</td>
</tr>
<tr>
<td>0.8</td>
<td>3.3</td>
<td>8</td>
</tr>
<tr>
<td>1.7</td>
<td>3.3</td>
<td>13</td>
</tr>
<tr>
<td>3.5</td>
<td>3.3</td>
<td>20.8</td>
</tr>
</tbody>
</table>

**Figure 5. Waterfall plot of subjects with measurable disease and at least 1 follow up scan**

**Figure 6. Serial CT Scans from one subject**

**Table 3. AT13387 PK Parameters at 220 mg/m²**

<table>
<thead>
<tr>
<th>Timepoint (hr)</th>
<th>AT13387 (ng/mL)</th>
<th>CZT (ng/mL)</th>
</tr>
</thead>
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<td>3.5</td>
<td>3.3</td>
<td>20.8</td>
</tr>
</tbody>
</table>

**Table 4. Responses by RECIST**

<table>
<thead>
<tr>
<th>Dose Escalation &amp; Dose Limiting Toxicities</th>
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</tr>
</thead>
</table>
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| No dose limiting toxicities were observed at the doses investigated. | No dose limiting toxicities were observed at the doses investigated.
| All CTCAE grade 3 or higher events related to AT13387 treatment are listed in Table 5. | All CTCAE grade 3 or higher events related to AT13387 treatment are listed in Table 5.

**Summary/Conclusions:**
- AT13387 is well tolerated at a dose up to 220 mg/m² in combination with full dose CZT.
- Administration of the agents in combination does not appear to change the pharmacokinetics of either agent.
- Encouraging activity has been seen in the dose-escalation part of the study.
- The incidence of DLTs for AT13387 in combination with standard dose CZT
- Primary: The incidence of DLTs for AT13387 in combination with standard dose CZT
- Secondary: The incidence of DLTs for AT13387 in combination with standard dose CZT
- Efficacy: Assessment of ORR and PK by RECIST every 2 cycles

**References:**
- Dose Escalation & Dose Limiting Toxicities
- Summary/Conclusions
- AT13387 dosing was initiated at 150 mg/m² and escalated to 220 mg/m².
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