**Background**

- Acute Myeloid Leukemia (AML) is an aggressive hematologic disease that is characterized by the accumulation of immature myeloid precursor cells. Treatment options for patients are selected based on factors such as age, comorbidities, and cytogenetics. For patients deemed ineligible for standard intensive induction chemotherapy (~40%), treatments include either low dose cytarabine (LDAC) or hypomethylating agents (e.g., azacitidine and decitabine) but when used as single agents, relapses are inevitable.

- First generation FLT3 inhibitors have been useful in treating AML (sorafenib, midostaurin) and recently the FDA approved midostaurin (Rydapt), Novartis Pharmaceuticals Corp.) for the treatment of adult patients with newly diagnosed AML, who are FLT3 mutation-positive in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. Second generation inhibitors with more selectivity are currently in Phase 3 trials in AML (gilteritinib, gilteritinib). Resistance to FLT3 inhibitors and disease progression while on FLT3 inhibitors remains an important problem for patient care.

- Polo-like Kinase 1 (PLK1), a serine/threonine kinase that is a master regulator of cell-cycle progression, is overexpressed in a number of cancer types including AML. Depletion of PLK1 preferentially induces cell death in tumor versus normal cells. PCM-075 is a potent, highly-selective adenosine triphosphate competitive inhibitor of PLK1. PCM-075 is highly active in blocking proliferation and inducing G2/M arrest in multiple AML cell lines. In a therapeutic model, PCM-075 was capable of inducing significant tumor growth inhibition (TGI), and increasing survival in an in vivo disseminated leukemia model (AML-3858 Cells).

- Synergistic interactions between PCM-075 and either the FLT3 tyrosine kinase inhibitor sorafenib or chemotherapeutic agents were examined in cell culture models. In AML models, we analyzed the activity of PCM-075 both alone and in combination with various chemotherapies and targeted therapeutics, including FLT3 inhibitors.

- Orally administered PCM-075 is currently in clinical trials for the treatment of AML (NCT03303339) and Metastatic Castration-Resistant Prostate Cancer (NCT03414034).

**Results**

In Vitro, PCM-075 Exhibits Synergistic Anti-Proliferative Effects When Combined with Chemotherapy Agents and the FLT3 Inhibitor Sorafenib

- Cell lines were treated with PCM-075 in combination therapy with several anti-cancer drugs. The combining agent was given simultaneously with PCM-075 or 24 hours prior to PCM-075.

- Cell proliferation inhibition was determined 72h after treatment (CellTiter Glo, Promega) and the combination index was calculated using the equation of Chou-Talalay method for mutually non-exclusive drugs.

- PCM-075 was found to have synergistic antiproliferative effects (combination index: 0.3-0.8) when combined with DNA replication inhibitors, proteasome inhibitors, mitotic inhibitors, and kinase inhibitors (some data not shown).

**Evaluation of the In Vivo Efficacy of PCM-075 in the Treatment of Subcutaneous MV-4-11 Human AML Xenograft Model in NOD.Scid Mice**

MV-4-11 cells in an exponential growth phase were harvested and counted for tumor inoculation. The treatments were started when the mean tumor size reached approximately 200 mm³. Each mouse was inoculated subcutaneously at the right flank region with MV-4-11 tumor. The date of tumor cell inoculation was denoted as day 0. Tumor volumes were measured twice weekly. Mouse weight was recorded daily.

**Dosing Schedule**

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Oral/IV</th>
<th>Weight (g)</th>
<th>Dosing Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vehicle</td>
<td>oral</td>
<td>Daily (Days 0-21)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>PCM-075</td>
<td>oral</td>
<td>Daily (Days 0-21)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Quizartinib (AC220)</td>
<td>oral</td>
<td>Daily (Days 0-21)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>PCM-075 + Quizartinib</td>
<td>oral</td>
<td>Daily (Days 0-21)</td>
<td></td>
</tr>
</tbody>
</table>

**Mouse weight did not go below the 20% reduction threshold**

Based on the Bias independence model, if the Tumor/Control ratio for the combination is less than the product of the two individual drugs, the effect of the combination is supra-additive. Therefore, the PCM-075/Quizartinib drug combination is supra-additive effect (e.g. shows synergy).

**Conclusions**

- The combination of PCM-075 and Quizartinib resulted in 97% tumor growth inhibition and regression in FLT3 AML xenograft model
- Combination therapies targeting PLK1 and FLT3 could extend the duration of response to FLT3 inhibitors prior to developing resistance
- This data warrants future investigation of the combination of PCM-075 with FLT3 inhibitors in clinical studies