For Patients with Advanced Intrahepatic Cholangiocarcinoma

EA2187 Available Through ECOG-ACRIN Cancer Research Group
A Phase II Study of Pevonedistat in Combination with Carboplatin and Paclitaxel in Advanced Intrahepatic Cholangiocarcinoma

**Patient Population**
See Section 3.0 for Complete Eligibility Details

- ≥ 18 years of age, ECOG PS 0-1, life expectancy ≥ 12 weeks, and adequate lab values
- Must have histologically confirmed intrahepatic cholangiocarcinoma or biphasic hepatocellular carcinoma and cholangiocarcinoma that is metastatic or unresectable and who have progressed on or been intolerant of 1 prior line of systemic gemcitabine containing chemotherapy regimen (prior immunotherapy/targeted therapies are allowed and will not be considered a line of therapy unless administered with cytotoxic chemotherapy)
- Must have measurable disease defined per protocol
- No major surgery within 14 days of randomization; patients with planned surgery during the study are ineligible
- HIV/HBV/HVC patients must meet criteria per protocol
- No persistent ≥ grade 2 diarrhea lasting more than 3 days within 14 weeks of randomization
- No known CNS involvement
- Patients with known history/current symptoms of cardiac disease/history of treatment with cardiotoxic agents should have a clinical risk assessment of cardiac function using NYHA; to be eligible, patients should be class 2B or better; patients with known cardiopulmonary disease are ineligible (see protocol for details)
- Must not have received chemotherapy/radiotherapy within 2 weeks of randomization; must not have received immunotherapy within 8 weeks of randomization
- No history of allergic reaction attributed to compounds of similar chemical/biologic composition to pevonedistat, carboplatin, or paclitaxel
- No treatment with clinically significant metabolic enzyme inducers within 14 days of the first dose of study drug
- No uncontrolled intercurrent illness/coagulopathy or bleeding disorder; no active, uncontrolled infection/severe infectious disease
- No known moderate chronic obstructive pulmonary disease/interstitial lung disease/pulmonary fibrosis

**Treatment Plan**
See Section 5.0 for Complete Treatment Details

1 cycle = 21 days

**Arm A—Pevonedistat Monotherapy**
- Pevonedistat 50 mg/m² IV over 60 mins (+/- 10) on days 1, 3, 5
- Repeat cycles until disease progression, unacceptable toxicity, or patient desire to discontinue

**Arm B—Pevonedistat in Combination with Carboplatin and Paclitaxel**
- Pevonedistat 20 mg/m² IV over 60 mins (+/- 10) on days 1, 3, 5 every cycle followed by
- Paclitaxel 175 mg/m² IV over 3 hrs or utilizing local standard procedures, on day 1 of every cycle x4, followed by
- Carboplatin AUC 5 IV over 30 mins on day 1 of every cycle x4
- At any time after 4 cycles of combination therapy, the treating physician is given discretion whether to continue with:
  - **OPTION A:** Pevonedistat 50 mg/m² days 1, 3, 5 every cycle OR
  - **OPTION B:** Pevonedistat 20 mg/m² IV days 1, 3, 5, every cycle followed by Paclitaxel 175 mg/m² day 1 every cycle followed by Carboplatin AUC 5 IV day 1 every cycle
- Both options will continue until disease progression, unacceptable toxicity, or patient desire to discontinue; patient can switch from option A to B

**Notes:**
- Treatment is administered on an outpatient basis
- Doses are based on actual body weight
- See protocol for premedications
- If the patient required a dose reduction attributable to pevonedistat, then the patients should be maintained at the single agent dose that they were reduced to

**Patient Enrollment**
All Sites: Oncology Patient Enrollment Network (OPEN), https://open.ctsu.org

**Protocol Information**

Please Enroll Your Eligible Patients!
1. Continue treatment until progression or unacceptable toxicity.

2. Refer to Section 5.1.2 for capecitabine dose reduction.

3. If anyumor < 4 cycles of combination therapy, the treating physician is given discretion whether to continue with combination therapy (amB) or switch to monotherapy (amA).

Accrual (C6671): 52
Cyc cf 21 days

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<th>Schema</th>
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<tbody>
<tr>
<td>1. 5 mg/m² IV on day 1; every cycle x4</td>
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<tr>
<td>2. 250 mg/m² IV on days 1, 3, 5 of every cycle</td>
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Procedure X: 5 + Capecitabine X: Paclitaxel

OR 5% of every cycle

Armor X: 5 mg/m² IV on days 1, 3, 5 of every cycle

Zalando X: 0.6 mg/m² IV on day 1; every cycle x4