

FAST FACTS

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**EA2187 - A Phase 2 Study of Pevonedistat in Combination with Carboplatin and Paclitaxel in Advanced Intrahepatic Cholangiocarcinoma**

**Eligibility Criteria**

1. Patient must be  $\geq 18$  years of age
2. Patient must have an ECOG Performance Status 0-1.
3. Patient must have a life expectancy  $\geq 12$  weeks
4. Patient 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 one prior line of systemic gemcitabine containing chemotherapy regimen.  
NOTE: Prior immunotherapy or targeted therapies are allowed and will not be considered a line of therapy unless administered with cytotoxic chemotherapy.
5. Patient must have measurable disease as defined in Section 6.1.2. For patients who have received localized therapy (embolization, chemoembolization, radiofrequency ablation or radiation) are eligible if measurable disease is not within the treatment field or the treated disease has clearly progressed since last localized therapy.
6. Patients must not have had major surgery within 14 days before randomization. Patients with surgery planned during study period are ineligible
7. Women must not be pregnant or breast-feeding due to the potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used. All females of childbearing potential must have a blood test or urine study within 14 days prior to randomization to rule out pregnancy. A female of childbearing potential is defined as any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).  
Female of child bearing potential? \_\_\_\_\_ (Yes or No) Date of blood test or urine study:  
\_\_\_\_\_
8. Women of childbearing potential and sexually active males must not expect to conceive or father children by using accepted and effective method(s) of contraception or by abstaining from sexual intercourse for the duration of their participation in the study and continue for at least 4 months after the last dose of protocol treatment.
9. Male patients must not donate sperm during the course of this study or within 4 months after receiving their last dose of protocol treatment.
10. Female patients must not donate eggs (ova) during the course of this study or within 4 months after receiving their last dose of protocol treatment.
11. Patients must have adequate organ and marrow function, as defined below, obtained within 14 days prior to randomization.  
Leukocytes  $\geq 3,000/\text{mCL}$   
Leukocytes: \_\_\_\_\_ Date of Test: \_\_\_\_\_  
Absolute neutrophil count  $\geq 1,500/\text{mCL}$   
ANC: \_\_\_\_\_ Date of Test: \_\_\_\_\_

Platelets  $\geq 100,000/\text{mcl}$

Platelet: \_\_\_\_\_ Date of Test: \_\_\_\_\_

Total bilirubin  $\leq$  institutional upper limit of normal (ULN) except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin  $\leq 1.5 \times$  ULN of the direct bilirubin

Bilirubin: \_\_\_\_\_ Institutional ULN: \_\_\_\_\_

Date of Test: \_\_\_\_\_

Patient with Gilbert's syndrome: \_\_\_\_\_ (Yes or No)

Hemoglobin  $\geq 9\text{g/dL}$

Hgb: \_\_\_\_\_ Date of Test: \_\_\_\_\_

AST(SGOT)/ALT(SGPT)  $\leq 2.5 \times$  institutional ULN

ALT: \_\_\_\_\_ Institutional ULN: \_\_\_\_\_

Date of Test: \_\_\_\_\_

AST: \_\_\_\_\_ Institutional ULN: \_\_\_\_\_

Date of Test: \_\_\_\_\_

Creatinine  $\leq$  institutional ULN, OR

Glomerular filtration rate (GFR)  $\geq 40 \text{ mL/min/1.73 m}^2$

Please refer to Appendix VII for the formula to estimate renal function using serum creatinine.

Serum creatinine \_\_\_\_\_ Date of Test: \_\_\_\_\_

GFR: \_\_\_\_\_ Date of Test: \_\_\_\_\_

12. Patient must not have a prolonged rate corrected QT (QTc) interval  $\geq 480$  msec calculated according to institutional guidelines.
13. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial. Known HIV positive patients who meet the following criteria will be considered eligible:
  - CD4 count  $\geq 350\text{cells/mm}^3$
  - Undetectable viral load
  - Maintained on modern therapeutic regimens utilizing non-CYP interactive agents (i.e. excluding ritonavir)
  - No history of AIDS-defining opportunistic infections
14. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
15. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
16. Patients who have not recovered from adverse events due to prior anti-cancer therapy (i.e. have residual toxicities  $>$  grade 1) are ineligible with the exception of alopecia.
17. Patients with persistent  $\geq$  grade 2 diarrhea lasting more than 3 days within 14 weeks of randomization are ineligible.
18. Patients who received prior platinum or taxane chemotherapy are eligible
19. Patients with known central nervous system (CNS) involvement are ineligible.
20. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
21. Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be

class 2B or better. In addition, patients with any of the known cardiopulmonary disease, defined as follows, would be ineligible for this trial:

- a. Unstable angina
  - b. Congestive heart failure (New York Heart Association [NYHA] Class III or IV);
  - c. Myocardial infarction within 6 months prior to randomization (patients who had ischemic heart disease such as acute coronary syndrome [ACS], myocardial infarction, and/or revascularization greater than 6 months before randomization and who are without cardiac symptoms may enroll)
  - d. Symptomatic cardiomyopathy
  - e. Clinically symptomatic pulmonary hypertension requiring pharmacologic therapy
  - f. Clinically significant arrhythmia, defined as:
    - i. History of polymorphic ventricular fibrillation or torsade de pointes,
    - ii. Permanent atrial fibrillation, defined as continuous atrial fibrillation for  $\geq 6$  months,
    - iii. Persistent atrial fibrillation, defined as sustained atrial fibrillation lasting  $> 7$  days and/or requiring cardioversion in the 4 weeks before randomization,
    - iv. Grade 3 atrial fibrillation defined as symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation
    - v. Patients with paroxysmal atrial fibrillation or Grade  $< 3$  atrial fibrillation for period of at least 6 months are permitted to enroll provided that their rate is controlled on a stable regimen.
22. Patients must not be receiving any other investigational agents.
  23. Patients must not have received chemotherapy or radiotherapy within 2 weeks prior to randomization. Prior treatment with radiation therapy involving  $\geq 25\%$  of hematopoietically active bone marrow will be ineligible.
  24. Patients must not have received immunotherapy within 8 weeks prior to randomization.
  25. Patients must not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to pevonedistat, carboplatin, or paclitaxel.
  26. Patients must not be receiving any treatment with clinically significant metabolic enzyme inducers within 14 days before the first dose of the study drug as below. Clinically significant metabolic enzyme inducers are not permitted during the study. Patients must not be receiving any medications or substances that are strong inducers of CYP3A4/5 (i.e. phenytoin, rifampin, St. Johns wort) or inhibitors of BCRP (i.e. cyclosporine). Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if a new medication need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Inhibitors of CYP3A4/5 are allowed.
  27. Patients must not have uncontrolled intercurrent illness.
  28. Patients must not have uncontrolled coagulopathy or bleeding disorder.
  29. Patients must not have active, uncontrolled infection or severe infectious disease such as severe pneumonia, meningitis, or septicemia.
  30. Patients with known moderate chronic obstructive pulmonary disease, interstitial lung disease, and pulmonary fibrosis are ineligible.
  31. Patients must not have psychiatric illness/social situations that would limit compliance with study requirements.
  32. Patients must have the ability to understand and the willingness to sign a written informed consent document.

33. Patients with impaired decision-making capacity (IDMC) who have a legally authorized representative (LAR) or caregiver and/or family member available will also be considered eligible.
34. Patient must not have had prior pevonedistat treatment.

