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Pharmacokinetic and Safety Study of Nab®-Paclitaxel (ABI-007) Plus Gemcitabine in Subjects With Advanced Pancreatic Cancer Who Have Cholestatic Hyperbilirubinemia

Purpose

The purpose of this study is to determine the safety and pharmacokinetic profile of nab®-paclitaxel (ABI-007) plus gemcitabine in subjects with advanced pancreatic cancer who have cholestatic hyperbilirubinemia secondary to bile duct obstruction.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic Neoplasms</td>
<td>Drug: nab-paclitaxel</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>Drug: Gemcitabine</td>
<td></td>
</tr>
</tbody>
</table>

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Endpoint Classification: Safety Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title:
A PHASE 1, MULTICENTER, OPEN-LABEL, DOSE-ESCALATION STUDY TO INVESTIGATE THE SAFETY AND PHARMACOKINETICS OF Nab®-PA CLITAXEL (ABI-007) PLUS GEMCITABINE IN SUBJECTS WITH ADVANCED PANCREATIC CANCER WHO HAVE CHOLESTATIC HYPERBILIRUBINEMIA SECONDARY TO BILE DUCT OBSTRUCTION

Resource links provided by NLM:

- MedlinePlus related topics: Cancer, Jaundice, Pancreatic Cancer
- Drug Information available for: Paclitaxel, Gemcitabine, Gemcitabine hydrochloride
- Genetic and Rare Diseases Information Center resources: Pancreatic Cancer
- U.S. FDA Resources

Further study details as provided by Celgene Corporation:

Primary Outcome Measures:

- Maximum Tolerated Dose [Time Frame: Up to 20 months] [Designated as safety issue: No]
  
  Determination of Maximum Tolerated Dose which is defined as the highest dose which induced a dose limiting toxicity in 0 or 1 out of 6 subjects during their first cycle of treatment.

- Pharmacokinetics - Cmax [Time Frame: Days 1 and 3] [Designated as safety issue: No]
  
  Maximum observed concentration in plasma
Pharmacokinetics - AUC [ Time Frame: Days 1 and 3 ] [ Designated as safety issue: No ]
Area under the plasma concentration-time curve

Pharmacokinetics - T1/2 [ Time Frame: Days 1 and 3 ] [ Designated as safety issue: No ]
Terminal half-life (T1/2)

Pharmacokinetics - Vss [ Time Frame: Days 1 and 3 ] [ Designated as safety issue: No ]
Apparent volume of distribution at the steady state

Pharmacokinetics - CL [ Time Frame: Days 1 and 3 ] [ Designated as safety issue: No ]
Apparent total body clearance

Secondary Outcome Measures:

- Tumor response [ Time Frame: Up to 28 months ] [ Designated as safety issue: No ]
  Objective tumor response based on computed tomography (CT)/ Magnetic Resonance Imaging (MRI) scan according to Response Evaluation Criteria in Solid Tumors (RECIST Version) 1.1 guidelines per Investigator assessment

- Progression-free survival [ Time Frame: Up to 28 months ] [ Designated as safety issue: No ]
  Progression-free survival according to RECIST Version 1.1 guidelines per investigator assessment

- Overall survival [ Time Frame: Up to 28 months ] [ Designated as safety issue: No ]
  Number of participants who are alive or dead

- Adverse Events [ Time Frame: Up to 28 months ] [ Designated as safety issue: No ]
  Incidence of treatment-emergent adverse events (TEAE) and serious adverse events. TEAE are defined as any event that begins or worsens in grade after the start of Investigational Product through 28 days after the last does of Investigational Product.

- Gemcitabine PK profile [ Time Frame: Up to 28 months ] [ Designated as safety issue: No ]
  Evaluate the pharmacokinetic profile of gemcitabine

Estimated Enrollment: 40
Study Start Date: November 2014
Estimated Study Completion Date: October 2018
Estimated Primary Completion Date: March 2018 (Final data collection date for primary outcome measure)

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experimental: Cohort 1 - Bilirubin level &gt; 1.5 x ULN to 3 x ULN 4 dose levels may be given in this arm as follows: nab-paclitaxel 75 mg/m2; gemcitabine 600 mg/m2 nab-paclitaxel 100 mg/m2; gemcitabine 800 mg/m2 nab-paclitaxel 125 mg/m2; gemcitabine 800 mg/m2 nab-paclitaxel 125 mg/m2; gemcitabine 1000 mg/m2</td>
<td>Drug: nab-paclitaxel  Subjects will receive nab-paclitaxel as an intravenous infusion over approximately 30 minutes on Days 1, 8 and 15 of a 28-day cycle. Other Name: Abraxane, ABI-007 Drug: Gemcitabine  Gemcitabine will be administered immediately after nab-paclitaxel as an intravenous infusion over approximately 30 minutes on Days 1, 8 and 15 of a 28-day cycle. Other Name: Gemzar</td>
</tr>
<tr>
<td>Experimental: Cohort 2 - Bilirubin level &gt; 3 x ULN to 5 x ULN 6 dose levels may be given in this arm as follows: nab-paclitaxel 75 mg/m2 nab-paclitaxel 75 mg/m2; gemcitabine 600 mg/m2 nab-paclitaxel 100 mg/m2; gemcitabine 600 mg/m2 nab-paclitaxel 125 mg/m2; gemcitabine 600 mg/m2 nab-paclitaxel 125 mg/m2; gemcitabine 800 mg/m2 nab-paclitaxel 125 mg/m2; gemcitabine 1000 mg/m2</td>
<td>Drug: nab-paclitaxel  Subjects will receive nab-paclitaxel as an intravenous infusion over approximately 30 minutes on Days 1, 8 and 15 of a 28-day cycle. Other Name: Abraxane, ABI-007 Drug: Gemcitabine  Gemcitabine will be administered immediately after nab-paclitaxel as an intravenous infusion over approximately 30 minutes on Days 1, 8 and 15 of a 28-day cycle. Other Name: Gemzar</td>
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after nab-paclitaxel as an intravenous infusion over approximately 30 minutes on Days 1, 8 and 15 of a 28-day cycle. 

Other Name: Gemzar

**Detailed Description:**

There are 2 treatment cohorts in this study based on the predose total bilirubin levels on Cycle 1 Day 1 (Cohort 1 > 1.5 x Upper Limit of Normal [ULN] to 3 x ULN bilirubin and Cohort 2 > 3 x ULN to 5 x ULN). Enrollment of subjects into Cohort 2 will only proceed after a review of the safety and pharmacokinetic (PK) data for all subjects in Cohort 1 has been completed by the Safety Monitoring Committee. The study is following a 3+3 dose escalation scheme within each dose level cohort group. A total of 3 subjects will initially be enrolled to the starting dose level in each cohort. The dose of the study regimen in each cohort will be escalated (or reduced) according to tolerability.

**Eligibility**

**Ages Eligible for Study:** 18 Years and older  
**Genders Eligible for Study:** Both  
**Accepts Healthy Volunteers:** No

**Criteria**

**Inclusion Criteria:**

1. Subject has definitive histologically or cytologically confirmed locally advanced unresectable or metastatic pancreatic adenocarcinoma (islet cell neoplasms are excluded) that is measurable by RECIST Version 1.1 guidelines.

2. Initial diagnosis of advanced stage disease must have occurred ≤ 6 weeks prior to starting Cycle 1 Day 1. NOTE: The clock for this time interval starts with the date of last evaluation confirming advanced disease (either biopsy or imaging results).

3. Subject has confirmed cholestatic hyperbilirubinemia due to bile duct obstruction. Subjects who have liver dysfunction due to metastasis alone are excluded.

4. Subject must have received no prior therapy for the treatment of metastatic disease. Prior treatment with 5-FU or gemcitabine administered as a radiation sensitizer during and up to 4 w eeks after radiation therapy is allowed. If a subject received gemcitabine in the adjuvant setting, tumor recurrence must have occurred at least 6 months after completing the last dose of gemcitabine.

5. For those patients who had a biliary stent inserted, 2 stable bilirubin readings within 48 to 72 hours of each other taken at least 5 days and not more than 14 days post-stenting must be obtained. In addition, there should be no complications (eg, infection) present and bilirubin levels should have stabilized (2 readings with total bilirubin within 20% of each other) before administering first treatment.

6. Males and females ≥ 18 years of age at the time of signing the informed consent document (ICD).

7. Subject has adequate biological parameters as demonstrated by the following blood counts at screening (obtained ≤ 14 days prior to starting Cycle 1 Day 1):
   - Absolute neutrophil count (ANC) ≥ 1500 (1.5 × 10^9/L) cells/mm³;
   - Platelet count ≥ 100,000 (100 × 10^9/L) cells/mm³;
   - Hemoglobin (Hgb) ≥ 9 g/dL.

8. Subject has the following blood chemistry levels at screening (obtained ≤ 14 days prior to starting Cycle 1 Day 1):
   - AST (SGOT), ALT (SGPT) ≤ 5 x ULN is allowed:
   - Serum creatinine within normal limits or calculated clearance ≥ 50 mL/min/1.73 m² for subjects with serum creatinine levels above or below the institutional normal value. If using creatinine clearance, actual body weight should be used for calculating creatinine clearance (eg, using the Cockroft-Gault formula). For subjects with a body mass index (BMI) > 30 kg/m², lean body weight should be used instead.
   - Subject has acceptable coagulation studies (obtained ≤ 14 days prior to starting Cycle 1 Day 1): partial thromboplastin time (PTT) < 1.2 x ULN and INR ≤ 1.5 x ULN.

9. Subject has no clinically significant abnormalities in urinalysis results (obtained ≤ 14 days prior to starting Cycle 1 Day 1).

10. Subject has a Karnofsky performance status (KPS) ≥ 70%.

11. Significant or symptomatic amounts of ascites should be drained prior to Cycle 1 Day 1. Pain symptoms should be stable and should not require modifications in analgesic management prior to Cycle 1 Day 1.

12. Females of childbearing potential (FCBP) (defined as a sexually mature woman who (1) has not undergone hysterectomy [the surgical removal of the uterus] or bilateral oophorectomy [the surgical removal of both ovaries] or (2) has not been naturally postmenopausal for at least 24 consecutive months [i.e., has had menses at any time during the preceding 24 consecutive months]) must:
   a. Either commit to true abstinence* from heterosexual contact (which must be review ed on a monthly basis), or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting IP therapy (including dose interruptions), and while on study medication or for a longer period if required by local regulations following the last dose of IP; and
   b. Have a negative serum pregnancy test (β-hCG) result at screening and agree to ongoing pregnancy testing during the course of
the study, and after the end of study therapy. This applies even if the subject practices true abstinence* from heterosexual contact.

14. Male subjects must practice true abstinence* or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for 6 months following IP discontinuation, even if he has undergone a successful vasectomy. * True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Note: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

15. Understand and voluntarily sign an informed consent document prior to any study related assessments/procedures being conducted.

16. Able to adhere to the study visit schedule and other protocol requirements.

Exclusion Criteria:

1. Subject has known brain metastases.

2. Any other active malignancy. Any other previous malignancy is allowed providing that the tumor was curatively resected and there is no evidence of recurrence within 12 months prior to enrolment to the study. In addition, adequately treated in-situ carcinoma of the cervix, uteri, or non-melanotic skin cancer are allowed provided that all treatment was completed 6 months prior to enrollment.

3. Subject has active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy.

4. Subject has known historical or active infection with HIV (human immunodeficiency virus), hepatitis B, or hepatitis C or subject receiving immunosuppressive or myelosuppressive medications that would, in the opinion of the investigator, increase the risk of serious neutropenic complications.

5. Subject has undergone major surgery for any reason, other than diagnostic surgery (ie, surgery done to obtain a biopsy for diagnosis without removal of an organ), within 4 weeks prior to Cycle 1 Day 1 of treatment in this study.

6. Subject has a history of a myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, New York Heart Association (NYHA) Class II-IV heart failure, uncontrolled hypertension, clinically significant cardiac dysrhythmia or electrocardiogram (ECG) abnormality, cerebrovascular accident, seizure disorder or clinically significant cardiac dysrhythmia or electrocardiogram (ECG) abnormality, within 6 months prior to Cycle 1 Day 1.

7. Subject has a history of allergy or hypersensitivity to nab-paclitaxel or gemcitabine or any of their excipients.

8. Subject uses medication known to be strong inducers of CYP3A4 and CYP2C8 (Section 9.2).

9. History of connective tissue disorders (eg, lupus, scleroderma, arteritis nodosa).

10. Subjects with a history of interstitial lung disease, history of slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies.

11. History of chronic leukemias (eg, chronic lymphocytic leukemia).

12. Subject is enrolled in any other clinical protocol or investigational trial with an interventional agent or assessments that may interfere with study procedures.

13. Subject is unwilling or unable to comply with study procedures.

14. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.

15. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.

16. Any condition that confounds the ability to interpret data from the study.

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT02267707

Contacts

Contact: Associate Director, Clinical Trial Disclosure  1-888-260-1599  clinicaltrialdisclosure@celgene.com

Locations

United States, Arizona
Mayo Clinic Arizona Recruiting
Scottsdale, Arizona, United States, 85259

United States, Michigan
Barbara Ann Karmanos Cancer Center Recruiting
Sponsors and Collaborators
Celgene Corporation

Investigators
Study Director: Alfredo Romano, MD  Celgene Corporation

More Information

Key words provided by Celgene Corporation:
nab®-paclitaxel  Cholestatic Hyperbilirubinemia
ABI-007  Bile Duct Obstruction
Abraxane  Pancreatic Cancer
Advanced Pancreatic Cancer

Additional relevant MeSH terms:
Cholestasis  Anti-Infective Agents
Hyperbilirubinemia  Antimetabolites
Pancreatic Neoplasms  Antimetabolites, Antineoplastic
Bile Duct Diseases  Antimitotic Agents
Biliary Tract Diseases  Antineoplastic Agents
Digestive System Diseases  Antineoplastic Agents, Phytogenic
Digestive System Neoplasms  Antiviral Agents
Endocrine Gland Neoplasms  Enzyme Inhibitors
Endocrine System Diseases  Immunologic Factors
Neoplasms  Immunosuppressive Agents
Neoplasms by Site  Mitosis Modulators
Pancreatic Diseases  Molecular Mechanisms of Pharmacological Action
Pathologic Processes  Pharmacologic Actions
Gemcitabine  Physiological Effects of Drugs
Paclitaxel  Radiation-Sensitizing Agents

ClinicalTrials.gov processed this record on October 08, 2015