A Randomized, Double Blind, Placebo Controlled, Phase II Study Evaluating the Efficacy and Safety of RP101 in Combination with Gemcitabine Administered as First-Line Treatment to Subjects with Unresectable, Locally Advanced, or Metastatic Pancreatic Adenocarcinoma

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Objectives:Primary Objective:* To compare the overall survival (OS) distributions of RP101 and gemcitabine to placebo and gemcitabine in subjects with unresectable, locally advanced or metastatic pancreatic adenocarcinomaSecondary Objectives:* To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON31980

Source
ToetsingOnline

Brief title
SCI-RP-Pan-P2-001

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
Pancreatic Adenocarcinoma

Research involving
Human

Sponsors and support

Primary sponsor: SciClone Pharmaceuticals, Inc.
Source(s) of monetary or material Support: SciClone Pharmaceuticals Inc.

Intervention

Keyword: chemotherapy, Pancreatic Adenocarcinoma, Phase II, RP101 - Gemcitabine

Outcome measures

Primary outcome

The primary efficacy endpoint will be overall survival defined as the time from

randomization to death from any cause or last contact if alive.

Secondary outcome

The secondary efficacy endpoints are as follows:

- Progression-free survival (PFS), determined as the time from

randomization to the first observation of disease progression or death from any

cause or last tumor evaluation if free of progression

- Overall tumor response rate (ORR) defined as the sum of the complete

(CR) and partial (PR) response rates

- Disease control rate defined as the sum of CR, PR and SD where SD is

the stable disease rate

- CR rate

The above rates will be determined using RECIST criteria for complete response (CR), partial response (PR), progressive disease (PD), or stable disease (SD). Measurable disease at study entry is not mandatory, but to be considered evaluable for CR or PR at least one measurable lesion must be present as follows:

* X-ray *20 mm

* Conventional CT scan *20 mm

* Spiral CT scan *10 mm

Measurable lesions must be outside a previous radiotherapy field if they are the sole site of disease, unless disease progression is documented.

Target tumor lesions will be measured at baseline and at the end of every other study treatment cycle (or at early termination)

- Duration of response determined as the time when criteria for CR/PR/SD are first met until the first date that recurrent or progressive disease or death occur

- Longitudinal changes in CA 19-9 levels, measured Day 1 of each treatment cycle, EOT, and at 1 month follow-up after EOT

- ECOG performance status grade reflecting changes in the subject*s daily living abilities

Study description

Background summary

RP101 is a nucleoside analog known as (E)-5-(2-bromovinyl)-deoxyuridine (BVDU) and was originally developed as an antiviral drug and is an effective treatment against herpes zoster. Recent studies have identified RP101 as an effective agent in combating chemoresistance, in which tumor cells become resistant to chemotherapy. When RP101 was combined with various chemotherapeutic agents the in vitro growth of tumor cells was inhibited to a greater extent than with the chemotherapeutic agents alone. This effect was confirmed in in vivo studies with tumor bearing rats. Rats given RP101 co-treatment had significantly less tumor growth than untreated control rats or rats treated with a cytotoxic drug alone. In toxicology studies, RP101 has been carefully studied in several animal species in acute and chronic studies. In murine studies using RP101 at 20-1000 mg/kg/day there was some delay in growth, an effect on maturation of spermatocytes and a modest increase in amyloid deposition. In dogs that received 5-30 mg/kg/day RP101 (BVDU) orally for 52 weeks there was no effect on feed consumption, respiration, body temperature, or heart rate but high doses of RP101 (30 mg/kg/day) caused degenerative and proliferative hepatobiliary damage.
RP101 has been studied in several early stage clinical studies in oncology. In a pilot study of 13 patients with late stage pancreatic cancer patients received 500 mg RP101 for 10 days each 28 day cycle with gemcitabine and cisplatin. Median survival was 447 days. This compares favorably with a median survival of 186 days for a historical control group treated with chemotherapy only.
Based on the promising results of this pilot study a dose ranging study was conducted to determine the optimal dose of RP101 to be used to treat pancreatic cancer with gemcitabine. Gemcitabine was administered at the recommended dose of 1,000 mg/m2 on days 1, 8, and 15 of each 28-day cycle and RP101 was given concomitantly in four doses/day for 4 days per each gemcitabine dose. The first dose group received 500 mg/day RP101 and subsequent dose groups received 625, 750, 875, and 1000mg/day for 12 days of each 28-day cycle.
The most common adverse events were nausea, fatigue, vomiting, neutropenia, anorexia, and fever, toxicities consistent with those expected for gemcitabine alone. Approximately half the patients had grade 3 or 4 neutropenia while anemia and thrombocytopenia were predominantly grade 2. There was no obvious increase in adverse events with increasing doses of RP101. Patients who were treated with 500 - 750 mg/day of RP101 were able to receive a mean of 5 cycles of chemotherapy and were able to receive 91% of the planned dose of gemcitabine. Patients in the 875 mg RP101 dose group received less gemcitabine than other dose groups and patients treated in either the 875 or 1000 mg/day dose groups, in general, had fewer cycles than patients treated in the lower dose groups. Data on ECOG status, monitored throughout the study, showed

minimal to no change in most patients. Doses of RP101 up to 750 mg/day were well tolerated for multiple cycles.
Pharmacokinetic analyses suggested that the mean RP101 levels appeared to increase (Cmax increased approximately 5 fold) disproportionately when the dose was doubled and that gemcitabine blood levels may increase with the increase in RP101 dose.
When all dose groups are combined, the 6-month survival rate was 68% and the 12-month survival rate was 39%. The median survival for all 22 patients in this study was 9.3 months, which compares favorably with that observed in patients treated with gemcitabine alone, which is typically 6 months. The combination of RP101 and gemcitabine warrants further evaluation for the treatment of advanced pancreatic cancer.

Study objective

Objectives:

Primary Objective:
* To compare the overall survival (OS) distributions of RP101 and gemcitabine to placebo and gemcitabine in subjects with unresectable, locally advanced or metastatic pancreatic adenocarcinoma

Secondary Objectives:
* To compare progression-free survival (PFS) between the two treatment arms
* To compare the two treatment groups with respect to overall tumor response rates (ORR) which is the sum of the complete response [CR] and partial response [PR] rates as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) in subjects with measurable disease at baseline
* To compare the two treatment arms with respect to disease control rates (DCR) which is the sum of CR, PR and stable disease (SD) rates as assessed by RECIST in subjects with measurable disease at baseline
* To compare the CR rates between the two treatment arms
* To evaluate CA 19-9 levels as a marker of disease response
* To compare changes in ECOG performance status between the two treatment arms
* To evaluate the safety of RP101

Study design

This is a Phase II, randomized, double blind, placebo controlled study for subjects with unresectable, locally advanced or metastatic pancreatic adenocarcinoma.
The study will be conducted with 153 subjects, at approximately 55 sites located in the North America, Western Europe, Eastern Europe and Latin America.
The patients will be randomized 2:1 to receive gemcitabine +RP101 or gemcitabine + placebo.

Intervention

Refer to study flowchart in the protocol pages 8, 9, 10 and 11.

Study burden and risks

Taking regular medicines or supplements together with the study tablets and gemcitabine may increase the chance of unwanted side effects, change how the study tablets and gemcitabine work, or change how your regular medications and supplements work. The risk will depend on the dose of the regular medicine taken every day, and on how long take the study tablets and gemcitabine with regular medications are taken.
Blood samples will be collected during this study. A needle is inserted into a vein in the arm and a blood sample is withdrawn. Although one blood draw is usually enough, a second one may be needed if the first is not successful. Collecting blood samples may cause fainting or dizziness, and some pain and/or bruising may occur at the site on the arm where the blood was taken. On rare occasions, infection may occur.
There can be risks of radiation from the x-ray or CT scan. The radiation from this study is not expected to greatly increase these risks, but the exact increase of such risks is unknown.
For most people, there is no danger associated with having an MRI scan. However, an MRI could be very dangerous if certain objects or devices are implanted in the body, such as a pacemaker, insulin pump, ear implant, joint replacement, permanent dentures, or shrapnel.
There may be risks or side effects related to RP101 and gemcitabine that are unknown at this time. In previous studies with RP101 and gemcitabine, the most common side effects were nausea, vomiting, fatigue (tiredness), fever, decreased appetite, and weight loss. These drugs may also cause changes in the blood (reduced white blood cells, red blood cells, and platelets). Reduction in white blood cells may increase the risk of getting infections. Other side effects of gemcitabine include swelling of face, hands, and feet; flu-like symptoms; drowsiness; sore mouth; diarrhea; constipation; and thinning of hair.
Because of possible drug reactions, the patient cannot enter this study if he is allergic or sensitive to gemcitabine or TP101. Some things that happen during an allergic reaction are:
* a rash
* having a hard time breathing
* wheezing when you breathe
* sudden drop in blood pressure
* swelling around the mouth, throat, or eyes
* fast pulse
* sweating

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion Criteria:
1. Male or female subjects 18 years of age and older
2. Subjects with a histologically or cytologically confirmed diagnosis of adenocarcinoma of the pancreas that is unresectable, locally advanced or metastatic
3. ECOG performance status 0 or 1
4. Life expectancy of at least 3 months
5. Documentation of all sites of pancreatic cancer disease within 28 days prior to treatment start by MRI or CT or spiral CT scan of chest, abdomen, brain (only if clinical suspicion of metastasis), and other scans as necessary. Negative scans performed within 35 days of randomization do not need to be repeated.
6. Adequate hematological, renal, and hepatic function within 14 days prior to treatment start defined as follows:

- Hemoglobin * 9.0 gm/dL (prior transfusion and/or support with erythropoietin-based products is acceptable)
- Absolute granulocyte count * 1.5 x 109/L (1500 cells/mm3) unsupported for 1 week by growth factors
- Platelet count * 100 x 109/L (100,000/mm3) and non-platelet transfusion dependent
- Serum creatinine < 1.5 times the upper limit of normal
- Total bilirubin < 2.0 times the upper limit of normal
- ALT (SGPT) < 2.0 times the upper limit of normal and/or AST (SGOT) < 2.0 times the upper limit of normal. If clearly attributable to liver metastasis, ALT and/or AST < 5.0 times the upper limit of normal is permitted.
7. Capability of understanding the objectives of the study and giving written informed consent
8. Willingness and ability to comply with the study protocol for the duration of the study
9. Capability to have sufficient oral caloric and fluid intake and to take oral study medications
10. If subject is female and of child-bearing potential she must have a negative *-HCG urine test within 72 hours prior to receiving treatment. Being of child bearing potential is defined as any female subject who does not meet at least one of the following criteria: a) has undergone bilateral salpingo-oophorectomy and/or hysterectomy; b) is greater than age 50 years and has not had a menstrual period for at least 24 months
11. All potentially fertile subjects, both female and male, must practice a medically approved method of contraception or agree to abstinence for the duration of participation in the active treatment phase of the study and for a period of 4 weeks after the last administration of either study drug

Exclusion criteria

Exclusion Criteria:
1. Prior history of other malignant tumors, except non-melanoma skin cancer or in situ cervical carcinoma curatively excised. Subject may be included if disease-free of cancers other than pancreatic cancer for 5 years
2. Major surgery within 2 weeks prior to treatment start
3. Any prior cytotoxic chemotherapy other than 5-FU (+/- folinic acid) or gemcitabine given concurrently with radiation treatment as a *radiosensitizer*. 5-FU must not have been given within 21 days prior to randomization.
4. Radiation treatment within 4 weeks of treatment start. Prior radiation treatment for management of local disease is allowed, provided that local disease progression or progression by new measurable metastasis outside of the radiation portal is documented by imaging procedure, all toxicities resolved, and the last fraction of radiation treatment was completed at least 4 weeks prior to treatment start
5. Uncontrolled cardiac atrial or ventricular arrhythmias (New York Heart Association (NYHA) congestive heart failure * class 2; uncontrolled hypertension; pulmonary embolism or cerebrovascular accident (CVA) within 6 months
6. Neurologic: symptomatic motor or sensory neurotoxicity grade * 2 of National Cancer Institute Common Toxicity Criteria (NCI-CTC)
7. Central nervous system metastasis

8. Psychiatric disabilities, seizures or central nervous system disorders thought to be clinically significant in the opinion of the Investigator that could interfere with informed consent or compliance with the protocol
9. Active bleeding Grade > 2 of NCI-CTC
10. Serious (Grade 3-4 of NCI-CTC) active infections at time of treatment start
11. Subjects with known allergies or intolerance to RP101 or similar compounds
12. Subjects with known allergies or intolerance to gemcitabine
13. Participation in any investigational drug study with investigational drug exposure within 4 weeks prior to treatment start
14. Pregnant or breast feeding women
15. Gastrointestinal (GI) tract disease such resulting in an inability to take oral medication, such as uncontrolled inflammatory GI diseases (e.g., Crohn*s disease, ulcerative colitis) or post-surgical malabsorption characterized by uncontrolled diarrhea that results in weight loss and vitamin deficiency or requires IV hyperalimentation (however, use of pancreatic enzyme supplementation is allowed provided that the above criteria are not met) resulting in an inability to take oral medication
16. Known to be HIV-, HBV-, or HCV- positive. Testing is not required in the absence of clinical signs and symptoms suggestive of HIV infection or acute or chronic hepatitis
17. Any condition which in the judgment of the Investigator would place the subject at undue risk or interfere with the results of the study (e.g., low medical risks because of non malignant organ or systemic disease, or secondary effects of cancer)
18. Uncontrolled cancer pain.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-10-2008

Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gemzar
Generic name:	Gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nog niet beschikbaar
Generic name:	nog niet beschikbaar

Ethics review

Approved WMO Date:	10-03-2008
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	14-04-2008
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	08-08-2008
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2007-004102-27-NL
CCMO	NL21627.096.08