A randomized, double-blind phase 3 study of gemcitabine plus AG-013736 versus gemcitabine plus placebo for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer

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Ethical review	Approved WMO
Status	Pending
Health condition type	Endocrine neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON33926

Source
ToetsingOnline

Brief title
Gemcitabine versus AG-013736 with pancreascancer

Condition

- Endocrine neoplasms malignant and unspecified

Synonym
Pancreatic cancer

Research involving

Human

Sponsors and support

Primary sponsor: PRA International
Source(s) of monetary or material Support: Pfizer

Intervention

Keyword: AG-013736, First-Line, Gemcitabine, Metastatic Pancreascancer

Outcome measures

Primary outcome

Primary Objective: Compare the overall survival (OS) of patients receiving gemcitabine plus AG-013736 versus gemcitabine plus placebo.

Secondary outcome

Secondary Objectives: 1. Compare the progression free survival (PFS) of patients in each arm;2. Compare the objective response rate (ORR) of patients in each arm;3. Estimate the duration of response (DR) of patients in each arm; 4. Evaluate the safety and tolerability of AG-013736 plus gemcitabine; 5.Compare the health-related quality of life (HRQOL), pain ratings, and health status of patients in each arm; 6. Conduct population pharmacokinetic analysis using AG-013736 plasma concentrations.

Study description

Background summary

Pancreatic cancer is diagnosed in over 30,000 people in the United States each year and ranks as the fourth leading cause of cancer death in the United States with an overall survival (OS) rate of <4%. The highest cure rate occurs if the tumor is truly localized to the pancreas; however, this stage of disease accounts for fewer than 20% of cases. For those patients with localized

disease and small tumors (<2 cm) with no lymph node metastases and no extension beyond the capsule of the pancreas, complete surgical resection can yield actuarial 5 year survival rates of 18 24%. For patients with advanced cancers, the OS rate of all stages is <1% at 5 years with most patients dying within 1 year. Compare the overall survival of patients receiving gemcitabine plus AG 013736 versus gemcitabine plus placebo is the main objective in this clincial trial.

On 21 January 2009 the safety and efficacy data were reviewed by an external, independent Data Monitoring Committee (DMC) and recommended stopping the study because adding AG-013736 to gemcitabine did not offer any advantage over gemcitabine alone.The DMC concluded that it was futile to continue the study. Amendment 5 contains a revised schedule of activities, instructions to investigators regardin unblinding patients, a description of how patients may continue to access AG-013736 (in an unblinded fashion and if deemed appropriate) and patient follow-up (including safety reporting).

Study objective

Primary Objective: Compare the overall survival (OS) of patients receiving gemcitabine plus AG-013736 versus gemcitabine plus placebo.
Secondary Objectives: 1. Compare the progression free survival (PFS) of patients in each arm;2. Compare the objective response rate (ORR) of patients in each arm;3. Estimate the duration of response (DR) of patients in each arm; 4. Evaluate the safety and tolerability of AG-013736 plus gemcitabine; 5.Compare the health-related quality of life (HRQOL), pain ratings, and health status of patients in each arm; 6. Conduct population pharmacokinetic analysis using AG-013736 plasma concentrations.

Study design

This is a 2-arm, randomized, double-blind, multi-center Phase 3 study of gemcitabine plus AG-013736 versus gemcitabine plus placebo in patients with chemotherapy-naïve advanced pancreatic cancer. Five hundred and ninety-six (596) patients will be randomized in a 1:1 ration between gemcitabine plus AG-013736 versus gemcitabine plus placebo. Randomization will be stratified by extent of disease (metastatic vs locally advanced). Overall survival will be the primary endpoint. Patients will have tumor assessments performed approximately every 8. Crossover of patients from one arom to the other will not be allowed.

Intervention

No additional invasive interventions are needed as archived tumor samples,

taken in pre-study period, will be used.

Study burden and risks

Weekly visits to hospital

- Efficacy assessments (baseline tumor assessment followed by 8-weekly tumor assessments)
- Physical exam
- Blood pressure assessments (daily home BP measurements)
- Urinalysis (monthly)
- Hematology
- Clinical Chemistry (bi-weekly)
- AG-013736/Placebo population pharmacokinetics assessments - monthly
- Pharmacogenomics for Drug metabolizing Enzymes including UGT1A1 (whole-blood)
- once at baseline
- Patient reported outcomes (monthly - 4 Quesionnaires: EORTC QLQ-C30; QLQ-PAN26; Brief Pain Inventory-Short Form; EQ-5D)

Dose interruption and reductions schedules are foreseen in protocol for adverse events with specific dose reductions rules provided for hypertension, hemoptysis and proteinuria.(protocol p 33)

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

Histologically or cytologically confirmed, metastatic or locally-, advanced pancreatic adenocarcinoma not amenable to curative resection; Adequate coagulation, hepatic and renal function documented within 14 days prior to treatment; Adequate bone marrow function; Male or female, age 18 years or older; ECOG performance status of 0 or 1; Life expectancy of *12 weeks; Resolution of all acute toxic effects of prior therapies, or surgical procedure to NCI CTCAE Grade < or equal to 1; No evidence of preexisting uncontrolled hypertension; negative pregnancy test; Signed and dated informed consent. See also protocol page 27

Exclusion criteria

Prior treatment with any systemic chemotherapy for metastatic disease; Prior adjuvant chemotherapy or radiotherapy <4 weeks before starting study treatment; Prior treatment with gemcitabine, AG-013736 or other VEGF inhibitors; Gastrointestinal abnormalities; central lung lesions involving major blood vessels; history of hemoptysis; current or recent use of a thrombolytic agent; Current use or anticipated use for treatment with potent CYP3A4 inhibitors/CYP1A2 or CYP3A4 inducers; active seizure disorder; serious uncontrolled medical disorder or active infection; Dementia or significantly altered mental status; Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS) related illness; pregnancy or breastfeeding

Study design

Design

Study phase:	3
Study type:	Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2008
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	/
Generic name:	AG-013736
Product type:	Medicine
Brand name:	Gemzar
Generic name:	Gemcitabine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-11-2007
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-04-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2008
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-12-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-02-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2007-001568-66-NL
CCMO	NL19140.018.07