A PHASE 1 STUDY OF CC-486 AS A SINGLE AGENT AND IN COMBINATION WITH CARBOPLATIN OR ABI-007 IN SUBJECTS WITH RELAPSED OR REFRACTORY SOLID TUMORS

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Primary objective:the primary objective of the study is to evaluate the safety and to define the maximal tolerated dose or the maximal administered dose of CC-486 as a single agent, in combination with CBDCA or ABI-007 in subjects with relapsed or...

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

Summary

ID

NL-OMON39682

Source
ToetsingOnline

Brief title
AZA-ST-001

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
relapsed or refractory solid tumors. Tumors that did not respond to treatment or have returned after treatment

Research involving

Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: het onderzoek wordt gefinancieerd door Celgene Corporation

Intervention

Keyword: Abraxane, carboplatin, oral azacitidine, phase 1

Outcome measures

Primary outcome

The nature, incidence and severity of AEs will be evaluated using the National

Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

criteria, Version 4.0.

Secondary outcome

For CC-486 (administered alone and in combination), CBDCA, ABI-007 , the

following plasma PK parameters will be assessed:

* maximum observed concentration in plasma (Cmax);

* area under the concentration-time curve (AUC);

* time to maximum concentration (tmax);

* terminal half-life (t1/2);

* apparent total body clearance (CL/F); and,

* apparent volume of distribution (Vz/F).

To evaluate the PD effects of CC-486 in blood, plasma, and tumor tissue, the

following molecular characterizations will be performed;

* Change from baseline (Cycle 1 Day 1 pre-dose) in DNA methylation (global and

gene-specific assays) in whole blood and tumor

tissue (as available in Part 1); and,

* Reduction from baseline (Cycle 1 Day 1 predose) in DNMT1 protein levels in

tumor tissue (as available in Part 1).

Anti-tumor activity endpoints using tumor-specific response criteria for each

tumor type will include:

* Response rate and duration of response;

* Progression-free survival (PFS); and,

* See definition of response in statistical analysis section.

Exploratory Endpoints - CC-486 Response

Molecular characteristics of the blood and tumor, potentially including, but

not limited to, DNA/RNA methylation, gene sequence and mRNA/miRNA expression

may be evaluated at baseline and post-therapy for examination in relation to

tumor responses.

Study description

Background summary

The hypothesis underlying the combination of a DNA hypomethylating agent with Standard of Care (SoC) cytotoxic chemotherapy is that methylation-based silencing of specific genes limits the anti-tumor effects of cytotoxic agents. Testing this hypothesis rigorously will ultimately require a randomized trial of a SoC agent versus that agent combined with CC-486. The long term goal of the current study is to enable such a study by identifying a dose and schedule of CC-486 that can be safely administered with a cytotoxic agent and that consistently demonstrates pharmacologic activity. Pre-clinical data suggest that platins and taxanes are 2 classes of SoC cytotoxic agents that synergize with CC-486. By examining combinations with both agents each with its own distinct single agent safety profile, this study increases the likelihood of identifying at least one safe combination. If both combinations are found to be

safe, the divergent mechanisms of action of CBDCA and ABI-007 and Gemcitabine increase the spectrum of tumor types that can be explored for activity.
Finally, a single-agent Arm will enable the testing of the hypothesis that sustained daily dosing of CC-486 can have anti-tumor effects in specific tumor types. Since a continuous dosing schedule has not been explored in the AZA PH US 2007 CL 005 CC-486 study, the current study will determine whether such a schedule is tolerated by subjects with solid tumors.

Study objective

Primary objective:
the primary objective of the study is to evaluate the safety and to define the maximal tolerated dose or the maximal administered dose of CC-486 as a single agent, in combination with CBDCA or ABI-007 in subjects with relapsed or refractory solid tumors
Secondary objectives:
* to examine the impact (if any) of CBDCA or ABI-007 on the pharmacokinetics (PK) of CC-486;
* to examine the impact (if any) of CC-486 on the PK of CBDCA or ABI-007
* to evaluate the pharmacodynamic (PD) effects of CC-486 as a single agent and in combination with CBDCA and ABI-007
* to make a preliminary assessment of the anti-tumor activity of CC-486 as a single agent and in combination with CBDCA and ABI-007
Exploratory Objective:
The exploratory objective of the study is to determine whether there is any relationship among baseline tumor molecular characteristics (genetic or epigenetic), PD effects, and anti-tumor activity.

Study design

This will be a phase 1, open-label, 3-arm, multi-center dose-escalation study of CC-486 in combination with CBDCA (Arm A) or ABI-007 (Arm B), or as a single agent (Arm C) in subjects with relapsed or refractory solid tumors (Part 1), followed by expansion cohorts at the Recommended Part 2 Dose (RP2D) of CC-486 in specific tumor types in Part 2.
In part 2, expansion cohorts of up to 20 subjects for each of the following relapsed or refractory tumor types will be enrolled at the RP2D for each Arm:
*Arm A: CC-486 plus CBDCA:
- urothelial carcinoma of the bladder, renal pelvis, ureter, or urethra (mixed histologies are permitted provided
a component of urothelial carcinoma is present)
- epithelial ovarian, fallopian tube, or primary peritoneal carcinoma
*Arm B: CC-486 plus ABI-007:
- NSCLC
- Pancreatic carcinoma
*Arm C: CC-486 single agent

- Virally associated tumors (tumor types known to be driven by Epstein-Barr virus, Human Papilloma Virus (HPV) and Merkel cell carcinoma of the skin (MC polomavirus):
- Nasopharyngeal carcinoma (a minimum of 5 subjects)
- Cervical carcinoma
- Anal carcinoma
- Merkel cell carcinioma (MCc)
Note: hepatitis B virus (HBV) and hepatitis C virus (HCV) -associated tumors (hepatocellular cancers) are not eligible.
Note: head and neck squamous cell cancers (HNSCC) must have HPV-positive status documented to be eligible.
Subjects in Part 2 of the study will receive CC-486 alone (Arm C) or in combination with CBDCA (Arm A) or ABI-007 (Arm B) according to the RP2D established for each Arm in Part 1. All treatment Cycles in Part 2 will be 21 days in duration.

Intervention

Subjects enrolled in the study will be assigned treatment as outlined by the following relapsed or refractory tumor types:
* CC-486 plus carboplatin (CBDCA) (Arm A):
* Urothelial carcinoma of the bladder, renal pelvis, ureter, or urethra (mixed histologies are permitted provided a component of urothelial carcinoma is present)
* Epithelial ovarian, fallopian tube, or primary peritoneal carcinoma
* CC-486 plus ABI-007 (arm B)
* NSCLC
* Pancreatic carcinoma
* CC-486 as a single agent (Arm C):
* Virally associated tumors (tumor types known to be driven by Epstein-Barr virus, Human Papilloma Virus (HPV) and Merkel cell carcinoma of the skin (MC polomavirus):
- Nasopharyngeal carcinoma (a minimum of 5 subjects)
- Cervical carcinoma
- Anal carcinoma
- Merkel cell carcinioma (MCc)
Note: hepatitis B virus (HBV) and hepatitis C virus (HCV) -associated tumors (hepatocellular cancers) are not eligible.
Note: head and neck squamous cell cancers (HNSCC) must have HPV-positive status documented to be eligible.

All cycles in arm A, B and C are 21 days in duration. In arm D, the first cycle is 22 days in duration, all other cycles are 21 days.
Arm A patients take CC-486 orally on day 1-14 and receive CBDCA as an iv infusion over 1 hour on day 8 of each cycle
Arm B patients take CC-486 orally on day 1-14 and receive ABI-007 as an iv

infusion over 30 minutes on day 8 and day 15 of each cycle
Arm C patients take CC-486 orally on day 1-14 of each cycle

Study burden and risks

- Patients have to complete a diary in which they write down for example the time of medication intake.
- Patients will come to the hospital 3 x per cycle
- During visits, physical examination is performed.
- During the study an ECG is done 3x
- The patient has to be fasting on PK days 2 hours before and 2 hours after CC-486 intake
- There are pregnancy tests for women of childbearing potential
- Patients have to use anticonception which is approved by the study doctor
- Blooddraws on day 1 and 15 of every cycle (in cycle 1 also on day 8) of about 15 ml
- On PK days (cycle 1, day 1 and 8, and on day 1 of cycle 2,3 and 6) 2 bloodsamples will be taken of about 5 ml each
-- On PD days (cycle 1 day 1,8 and 15 and on day 1 of cycle 2,3 and 6) about 60 to 70 ml of blood will be taken (2 times 8.5 ml paxgene and 4 times 10 ml biomarkers).
- if the dosis of CC-486 is reduced , there will be 2 extra PK samples and 1 extra PD sample (in total about 30 ml)
- The tumor is measured using scans at screening, cycle 2,4 6 and every 3rd cycle after that
- ABI-007 and Carboplatine are administered via an iv infusion
- There will be a tumorbiopsy twice

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

1.Men and women, 18 years or older
2. Understand and voluntarily sign an ICD prior to any study-related assessments or procedures are conducted
3. Able to adhere to the study visit schedule and other protocol requirements
4. Histological or cytological confirmation of relapsed or refractory advanced unresectable solid tumors as listed below for each Arm, including those who have progressed on (or not been able to tolerate) standard anti-cancer therapy
* Arm A: CC-486 plus CBDCA:
- Urothelial carcinoma of the bladder, renal pelvis, ureter, or urethra (mixed histologies are permitted provided a component of urothelial carcinoma is present)
- Epithelial ovarian, fallopian tube, or primary peritoneal carcinoma
* Arm B: CC-486 plus ABI-007:
- NSCLC
- Pancreatic carcinoma
* Arm C: CC-486 as a single agent:
- Virally associated tumors (tumor types known to be driven by Epstein-Barr virus, Human Papilloma Virus (HPV) and Merkel cell carcinoma of the skin (MC polomavirus):
- Nasopharyngeal carcinoma (a minimum of 5 subjects)
- cervical carcinoma
- Anal carcinoma
- Merkel cell carcinioma (MCc)
Note: hepatitis B virus (HBV) and hepatitis C virus (HCV) -associated tumors (hepatocellular cancers) are not eligible.
Note: head and neck squamous cell cancers (HNSCC) must have HPV-positive status documented to be eligible.
5. Consent to screening tumor biopsy (prior to the first dose of CC-486) and at cycle 1 day 15
6. Eastern Cooperative Oncology Group (ECOG) Performance Status of * 2.

7. Absolute neutrophil count (ANC) * 1.5 x 109/L;
Hemoglobin (Hgb) * 90 g/L;
Platelets (plt) * 100 x 109/L;
Potassium within normal range, or correctable with supplements;
AST and ALT * 2.5 x Upper Limit of Normal (ULN) or * 5.0 x ULN if liver tumor is present;
Serum total bilirubin * 1.5 x ULN;
Serum creatinine * 1.5 x ULN, or 24-hr clearance * 60 mL/min; and,
Negative serum pregnancy test within 72 hours before starting study treatment in females of childbearing potential (FCBP).
8. Females of child-bearing potential (defined as a sexually mature woman who 1) has not undergone a 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 (ie, has had menses at any time during the preceding 24 consecutive months).must:
* Agree to the use of a physician-approved contraceptive method (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) while on CC-486; and for 3 months following the last dose of study medication; and
* Have a medically supervised serum pregnancy test with sensitivity of at least 25mIU/mL is to be obtained in FCBP at Screening. A serum pregnancy test should be done within 72 hours prior to Day 1 of starting study therapy (note that the screening serum pregnancy test can be used as the test prior to Day 1 study therapy if it is performed within the 72-hour timeframe). A serum pregnancy test should be done within 72 hours prior to Day 1 of every cycle, and at the Treatment Discontinuation visit. The subject may not receive investigational product until the investigator has verified that the result of the pregnancy test is negative.
9. Male subjects with a female partner of childbearing potential must agree to the use of a physician-approved contraceptive method throughout the course of the study and avoid fathering a child during the course of the study and for 6 months following the last dose of CC-486.
10. Subjects with documented liver metastases must have serum albumin * 3 g/dL;
11.Sites of disease (primary or metastatic) that are, in the opinion of the investigator, accessible for biopsy without undue risk to the subject
12.Measurable or evaluable disease according to RECIST v1.1.

Exclusion criteria

1. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study.
2. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study.
3. Any condition that confounds the ability to interpret data from the study.
4. Symptomatic central nervous system metastases. Subjects with brain metastases that have been previously treated and are stable for 6 weeks are allowed.
5. Known acute or chronic pancreatitis.
6. Any peripheral neuropathy * NCI CTCAE grade 2.

7. Persistent diarrhea or malabsorption * NCI CTCAE grade 2, despite medical management.
8. Impaired ability to swallow oral medication.
9. Unstable angina, significant cardiac arrhythmia, or New York Heart Association (NYHA) class 3 or 4 congestive heart failure.
10. Prior systemic cancer-directed treatments or investigational modalities * 5 half lives or 4 weeks, whichever is shorter, prior to starting study drug or who have not recovered from side effects of such therapy.(except alopecia).
11. Major surgery * 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy.
12. Pregnant or breast feeding.
13. Known HIV infection.
14. Known chronic hepatitis B or C virus (HBV/HCV) infection, unless this is a comorbidity in subjects with HCC.
15. Liver metastases with serum albumin lower or equal to 3 g/dL.
16. Other prior cancers within previous 5 years except adequately treated in situ carcinoma cervix, basal or squamous carcinoma of the skin.
17. Subjects with >4 prior systemic chemotherapy regimens will require approval by the Celgene medical monitor prior to enrollment.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-05-2013
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Abraxane

Generic name:	paclitaxel protein-bound particles for injectable suspension
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	NA
Generic name:	Carboplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	NA
Generic name:	oral azacitidine

Ethics review

Approved WMO Date:	05-10-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-12-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-01-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-02-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-07-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-10-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-03-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-03-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-06-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-06-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-10-2014

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-10-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-03-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	28-10-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-11-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2012-001295-11-NL
CCMO	NL42064.031.12