A Phase 2, Randomized, Open-Label, Controlled Study to Evaluate the Efficacy and Safety of Ampligen® Compared to Control Group / No Treatment Following FOLFIRINOX in Subjects with Locally Advanced Pancreatic Adenocarcinoma

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This study has been transitioned to CTIS with ID 2024-518627-29-00 check the CTIS register for the current data. PRIMARY OBJECTIVE• To compare the efficacy of Ampligen® versus control group / no treatment following FOLFIRINOX in subjects with...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Exocrine pancreas conditions
Study type	Interventional

Summary

ID

NL-OMON56480

Source
ToetsingOnline

Brief title
AMP-270

Condition

- Exocrine pancreas conditions
- Gastrointestinal neoplasms malignant and unspecified

Synonym
Locally Advanced Pancreatic Adenocarcinoma, Pancreas cancer

Research involving
Human

Sponsors and support

Primary sponsor: AIM ImmunoTech Inc.
Source(s) of monetary or material Support: industry/AIM sponsored

Intervention

Keyword: Adenocarcinoma, Ampligen, FOLFIRINOX, Pancreatic

Outcome measures

Primary outcome

Progression Free Survival (PFS) [Time Frame: Visit 2/ First Treatment until disease progression, death, or end of study up to 42 months]

PFS is defined as the time, in months, from date of Visit 2/ First Treatment to date of the first documentation of definitive disease progression as per RECIST v1.1 (the initial progressive disease (PD)) or death due to any cause. Patients will be classified by the investigator as having disease progression at the time of initial imaging that meets RECIST version 1.1 criteria for disease progression.

Secondary outcome

• Overall Survival (OS)

OS is defined as the time from date of Visit 2/ First Treatment to death due to any cause.

• Overall Survival (OS) at 1 year

• Objective Response Rate (ORR) [Time Frame: Visit 2/ First Treatment until disease progression per RECIST v.1.1, death, or end of study up to 42 months]

ORR is defined as the proportion of subjects who achieve a Complete Response

(CR) or Partial Response (PR) as assessed by RECIST v1.1.

• Duration of Response (DoR) [Time Frame: Visit 2/ First Treatment until

disease progression per RECIST v.1.1, death, or end of study up to 42 months]

DoR is defined as the time from the date of the first documentation of

objective tumor response (CR or PR) to the date of the first documentation of

objective tumor progression or death due to any cause, whichever occurs first.

Study description

Background summary

Pancreatic cancer is associated with an overall five-year survival of 5% and thus contributes significantly to cancer-related mortality. A recent paper predicted that pancreatic cancer will be the second leading cause of cancer-related deaths before 2030 (Ansari, et. al. 2015). Currently surgery is the only potentially curative option, but only around 15% of patients are eligible at initial diagnosis since most pancreatic cancers are detected in an advanced stage of the disease. Around 20% of patients are diagnosed with locally advanced pancreatic cancer and the remaining 30-50% present with metastatic disease (Oettle, 2014). It is clear that new treatment options are desperately needed for this devastating malignancy.
One of these novel therapeutic options is immunotherapy which has shown to be a promising treatment strategy. Essential in this therapeutic strategy is to boost the patient*s immune system, by reversing the tumor-antigen specific T-cell tolerance induced by their tumor. Toll-like receptor (TLR) agonists such as Ampligen® (rintatolimod) are currently under investigation as adjuvants in cancer immunotherapy clinical trials due to their ability to activate immune cells and selectively promote inflammation. In depth analysis of the immune parameters in patients with pancreatic cancer reveal new insights in the interplay of these immune mechanism and survival and provide a basis/rationale for new (immuno)therapeutic approaches and combination therapies (Vaz, et. al. 2014).
The TLR3 receptor is the primary natural danger signal for cancer and viral infection. It is highly conserved in mammals and accordingly Ampligen® has demonstrated its broad spectrum of both antitumor and antiviral activity across many animal species (Strayer, et. al. 2014). The broad-spectrum anticancer activities include complete responses in human clinical trials as a single agent in renal cell carcinoma, melanoma, and lung cancer (NSCLC).

Study objective

This study has been transitioned to CTIS with ID 2024-518627-29-00 check the CTIS register for the current data.

PRIMARY OBJECTIVE
• To compare the efficacy of Ampligen® versus control group / no treatment following FOLFIRINOX in subjects with Locally Advanced Pancreatic Adenocarcinoma.

SECONDARY OBJECTIVE
• To evaluate safety and tolerability of Ampligen® following FOLFIRINOX in subjects with Locally Advanced Pancreatic Adenocarcinoma.

EXPLORATORY OBJECTIVES
• To explore Systemic Immune-Inflammation Index (SII) as a potential biomarker for overall survival.
• To explore associations between subject reported symptoms, functioning and global health status/Quality of Life (QoL) using EORTC QLQ-C30 questionnaire as well as current health status and the EQ-5D Index used in the economic evaluation of health care using the EQ-5D-5L questionnaire.
• Evaluation of lymphocyte profile by flow cytometry in patients with pancreatic cancer.
• To evaluate levels of tumor marker CA19-9 in patients with pancreatic cancer.
• To explore immune cell composition including B-cell and T-cell receptor diversity, blood biomarkers including circulating tumor DNA and antibodies against childhood immunogens, and T-cell responses to known childhood antigens such as MMR, which may predict and/or act as pharmacodynamic indicators of pharmacologic activity of Ampligen®.

Study design

This is a Phase 2 (proof of concept) randomized, open label, controlled, parallel arm study to compare the safety and efficacy of Ampligen® versus Control group / no treatment for subjects with locally advanced pancreatic carcinoma recently completing treatment with FOLFIRINOX chemotherapy regimen*.
*Note: To be eligible for participation in this study, subjects must have completed at least 4 months of treatment with FOLFIRINOX as part of first line standard of care four (4) to six (6) weeks prior to screening and have not shown evidence of disease progression per RECIST v.1.1 on CT scans, X-rays, or MRI since last treatment.
There will be two parallel arms and approximately 90 eligible subjects will be randomized to Ampligen® or Control/No treatment group with a 2:1 allocation.

Control Arm
The parallel control arm will be followed/no treatment until evidence of

disease progression per RECIST v.1.1. In the event of disease progression per RECIST v.1.1, subjects in both arms can receive any standard of care treatment option as determined by the Investigator.
The subjects will continue to be followed in this study for OS until death or 182 weeks, whichever comes first.
Subjects in both arms may continue study until they experience unacceptable toxicity, withdraw consent, or their physician feels it is no longer in their best interest to continue on study.

Ampligen® Arm
In this arm Ampligen® will be administered via twice weekly intravenous (IV) infusions (e.g., Monday/Thursday or Tuesday/Friday schedule**) and subjects will be monitored for disease progression while receiving the Ampligen® infusions.
**Note: Schedules may be switched during a holiday/vacation week to reduce the incidence of missed doses. The original schedule should be resumed during the following week. At least 48 hours between doses is to be maintained. Infusions are to be spaced with a minimum of two and a maximum of three days between infusion days.
Subjects will continue to receive twice weekly Ampligen® treatments throughout the duration of the study until disease progression per RECIST v.1.1 or death, or Ampligen® is discontinued because of a safety issue or best interest of the subject. In the event of disease progression per RECIST v.1.1, Ampligen® will be discontinued. In the event of disease progression per RECIST v.1.1, subjects in both arms can receive any standard of care treatment option as determined by the Investigator.
If Ampligen® is discontinued for any reason, subjects will continue to be followed in this study for OS until death or 182 weeks, whichever comes first.

Intervention

Please refer to study design.

Study burden and risks

RISKS / BENEFITS ASSESSMENT
Ampligen® lacks the potent toxicities seen with most chemotherapeutic cancer drugs. In placebo-controlled Phase II/III clinical trials using the same Ampligen® dosing schedule in patients with Chronic Fatigue Syndrome (CFS) the incidence of Serious Adverse Events (SAEs) was the same in the placebo arm as in the Ampligen® arm. There is no evidence of any cumulative toxicities.
This patient group has a limited life expectancy, despite the patient's burden in the form of time investment and blood tests, we believe that finding a possible new treatment for this patient group justifies this burden.
Furthermore, the design of the study is such that feasibility and safety are of great importance during the implementation of the study. This reduces the

possible side effects and the safety risk to a minimum. Furthermore, the inclusion and exclusion criteria have been designed accordingly.

Anaphylaxis/Allergic Reaction
Ampligen® is contraindicated for patients who have potentially severe allergic reactions to any of the components of the formulation.
Administration of Ampligen® may lead to hypersensitivity reactions, including anaphylaxis. Ampligen® contains trace quantities of protein, and although only one possible "anaphylactic-type" reaction has been noted in over 800 patients treated with the drug, the possibility of allergic reactions including anaphylaxis exists. Mild rashes have been reported in several patients, although the relationship to Ampligen® is not clear. Anaphylaxis is a serious, acute allergic reaction requiring immediate medical attention. Thus, patients will be closely monitored following administration and protocols will be in place to manage should such a reaction occur.

Hepatotoxicity
A non-rintatolimod, but chemically related double-stranded RNA material, poly I : poly C, has caused hepatotoxicity. In view of these observations, patients on rintatolimod should be carefully observed and LFT*s will be monitored throughout the study.

Coagulopathy
Coagulopathy, including intravascular coagulation, has been observed in a non-rintatolimod, but chemically related double-stranded RNA material, poly I : poly C. In view of these observations, patients on rintatolimod should be carefully observed and Prothrombin time (PT) and activated partial thromboplastin time (APTT) and, International Normalized Ratio (INR) will be monitored throughout the study.

Autoimmune Disorders
Since rintatolimod is an inducer of interferons, there is the theoretical potential that it might induce or potentiate autoimmune disease. The following autoimmune diseases have been associated with the various interferons or poly I : poly C, another interferon inducer of similar structure to rintatolimod: thrombocytopenia (low platelet counts), psoriasis (skin disorder), rheumatoid arthritis (joint disorder), hyperthyroidism (increased metabolism), hypothyroidism (decreased metabolism), vasculitis and Raynaud*s phenomenon (disorders of blood vessels), rhabdomyolysis and myositis (muscle disorders), nephritis (kidney disorders), systemic lupus erythematosus and sarcoidosis (disorders involving almost any body organ or tissue), hepatitis (liver disorder), hemolytic anemia (red blood cell disorder), and diabetes (increased blood sugar).

Infusion-Related Reactions
Mild and moderate reactions will be monitored more frequently and in severe and life-threatening situations the treatment will be stopped and appropriately

treated with corticosteroids and epinephrine. Specific signs and symptoms observed during administration will be recorded, including timing and duration.

Pregnancy/Lactation
Preliminary data suggest that rintatolimod may exert an embryotoxic effect in rabbits and rats at doses which are below the projected therapeutic doses. In rabbits there were dose-dependent embryotoxic effects, while in rats, the fetal body weight was reduced. No studies have been done on the effects of rintatolimod on pregnant or nursing women; therefore, treatment of these individuals should not be considered. Females of childbearing potential must have a negative pregnancy test prior to enrollment. Both male and female patients and their partners of childbearing potential must agree to use appropriate birth control methods throughout the study duration (excluding women who are not of childbearing potential and men who have been sterilized).

Hormonal Replacement Therapy
One CFS patient on hormonal estradiol replacement experienced a thrombosis of the superior vena cava (SVC) at the location of an implanted mediport catheter.

Unknown Risks
Research inherently carries the possibility of risks that are unknown or that cannot be foreseen based on current information.

Benefits
Anticipated benefits for subjects participating in the research may include increase in overall survival time and improvement of quality of life.

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

Subjects will be eligible for enrollment in the study only if they meet ALL the following criteria at time of Screening:
1. Histological diagnosis of pancreatic adenocarcinoma confirmed pathologically: Unresectable pancreatic cancer; locally advanced pancreatic cancer.
2. Measurable disease per RECIST v.1.1.
3. Completion of at least four (4) months of first line FOLFIRINOX treatment and no disease progression per RECIST v.1.1 as confirmed by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scan 4 to 6 weeks after last FOLFIRINOX treatment.
4. Male or non-pregnant, non-lactating female, >=18 years or age.
5. Negative pregnancy test for female subjects. Women of child-bearing potential (WOCBP) and Women not of child-bearing potential are eligible to participate. Both women of child-bearing potential and women of non-child-bearing potential should use an approved method of birth control and agrees to continue to use this method for the duration of the study and for 90 days after last treatment.
Acceptable methods of contraception include abstinence, female subject/partner*s use of hormonal contraceptive (oral, implanted, or injected) in conjunction with a barrier method (WOCBP only), female subject/partner*s use of an intrauterine device (IUD), or if the female subject/partner is surgically sterile or two years post-menopausal. All male subjects/partners must agree to use a condom consistently and correctly for the duration of the study and for 90 days after last treatment. In addition, subjects may not donate sperm for the duration of the study and for 90 days after last treatment.
Females who are less than two (2) years post-menopausal, those with tubal ligations and those using contraception must have a negative serum pregnancy test at baseline within the one (1) week prior to the first study medication infusion. Every six weeks, and at study termination a pregnancy test should be

performed, either serum or urine stick test. However, if the urine result is positive, a serum pregnancy test will be performed.
Any pregnancy that occurs while taking Ampligen® should be recorded using a Pregnancy Report Form and reported immediately to AIM ImmunoTech, Inc.
6. Provide signed written informed consent and willingness, ability to comply with study requirements.
7. Minimum weight of 40kg at baseline.
8. Karnofsky Performance Status of 80 or higher at baseline.
9. Subject must have a projected life expectancy of >= 3 months in the opinion of the Investigator.
10. Subject has adequate organ function by the following laboratory assessments at baseline (obtained <= 28 days prior to V2 / First treatment):
Hematologic
Platelets >= 100×109/L
Hemoglobin >= 9.0 g/dL
Absolute Neutrophil Count (ANC) >= 1.5×109/L
Absolute lymphocyte count >= 3 x 109/L
Hepatic
AST/ALT <= 3×ULN (if liver metastases are present, <= 5×ULN)
Alkaline phosphatase <= 2.0×ULN (if liver metastases are present, <= 5×ULN)
Total bilirubin <= 1.5×ULN
Albumin >= 3.0 g/dL
Renal
Creatinine clearance >= 60 mL/min using the Cockcroft-Gault formula. .
Coagulation
PT-INR and APTT within normal limits

Exclusion criteria

meeting ANY of the following criteria at time of Screening will be excluded from enrollment:
1. Diagnosis of islet neoplasm acinar cell carcinoma, non-adenocarcinoma (i.e., lymphoma, sarcoma), adenocarcinoma originating from the biliary tree, or cystadenocarcinoma.
2. Subjects who have surgically resectable locally advanced pancreatic adenocarcinoma following treatment with FOLFIRINOX.
3. Subject has received prior treatment with Ampligen®.
4. Therapy with investigational drugs within 6 weeks of beginning study medication.
5. History of prior malignancy, except for adequately treated in situ cancer, basal cell, squamous cell skin cancer, or other cancers (e.g., breast, prostate) for which the subject has been disease-free for at least 3 years. Subjects with prior cancer that is adequately controlled per the judgement of the Investigator will not be excluded from the study.
6. Any serious medical condition, laboratory abnormality, psychiatric illness,

or comorbidity that, in the judgment of the Investigator, would make the subject inappropriate for the study.
7. Serious systemic fungal, bacterial, viral, or other infection that is not controlled or requires intravenous (IV) treatment for infection(s).
8. Known history of positivity (regardless of immune status) for human immunodeficiency virus (HIV).
9. Known history of, chronic active, or active viral hepatitis A, B, or C infection
10. Clinically significant bleeding within 2 weeks prior to Randomization (e.g., gastrointestinal [GI] bleeding, intracranial hemorrhage).
11. Pregnant or lactating women.
12. Myocardial infarction within the last 6 months prior to Randomization, symptomatic congestive heart failure (New York Heart Association Classification > Class II), unstable angina, or unstable cardiac arrhythmia requiring medication.
13. Subjects with abnormal electrocardiogram (ECG) at baseline QTc interval >470 ms. Both Bazett*s and Fridericia*s corrections need to be applied; if either is >470 ms; subject is not eligible.
14. Subjects with positive germline BRCA (gBRCA) mutations.
15. Clinically significant ascites defined as requiring >= 1 paracentesis every 2 weeks.
16. Major surgery, defined as any surgical procedure that involves general anesthesia and a significant incision (i.e., larger than what is required for placement of central venous access, percutaneous feeding tube, or biopsy), within 28 days prior to Randomization or anticipated surgery during the study period.
17. Prior history of receiving immune checkpoint inhibitors (anti-CTLA4, anti-PD1, anti-PD- L1).
18. Inability to return for scheduled treatment and assessments.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-01-2024
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ampligen
Generic name:	Rintatolimod

Ethics review

Approved WMO Date:	09-03-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-05-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-12-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-01-2024
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-06-2024

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-09-2024
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
EU-CTR	CTIS2024-518627-29-00
EudraCT	EUCTR2022-002383-68-NL
ClinicalTrials.gov	NCT05494697
CCMO	NL83776.078.23