A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of PEGylated Recombinant Human Hyaluronidase (PEGPH20) in Combination With nab-Paclitaxel Plus Gemcitabine Compared With Placebo Plus nab-Paclitaxel and Gemcitabine in Subjects with Hyaluronan-High Stage IV Previously Untreated Pancreatic Ductal Adenocarcinoma

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Primary objective is: * To determine the overall survival (OS) benefit of PAG treatment, compared with AG treatment, in subjects with HA-high Stage IV previously untreated PDA.Secundary objectives are:* To determine the PFS benefit of PAG treatment...

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

Summary

ID

NL-OMON47683

Source
ToetsingOnline

Brief title
HALO

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
carcinoma of the pancreas, pancreatic cancer

Research involving
Human

Sponsors and support

Primary sponsor: Halozyme, Inc
Source(s) of monetary or material Support: Halozyme;Inc

Intervention

Keyword: gemcitabine, nab-paclitaxel, Pancreatic cancer, PEGPH20

Outcome measures

Primary outcome

* Overall survival

Secondary outcome

* Progression-free survival

* Objective response rate

* Duration of response

* Incidence of adverse events (AEs), changes in clinical safety laboratory

values, and changes in cardiovascular parameters (ECG and vital signs)

Exploratory outcomes are:

* Change in serum CA19-9 levels

* Change in plasma and tumor biopsy (when available) HA levels and other

potential biomarkers

* Pharmacokinetics of PEGPH20 in combination with NAB plus GEM

* Pharmacokinetics of NAB and GEM in the PAG group versus the AG group

* Patient-reported outcome measures including the EORTC QLQ-C30, EQ-5D, and NRS

Study description

Background summary

The incidence of pancreatic cancer has continued to increase during the past several decades. Pancreatic cancer currently ranks as the seventh leading cause of cancer death globally. In Europe, pancreatic cancer is the seventh most frequent cancer and the fifth leading cause of cancer-related death and is predicted to take fourth place within the decade. Adenocarcinoma of pancreatic ductal (PDA) origin accounts for approximately 90% of all pancreatic cancers. Due to a lack of specific symptoms and limitations in diagnostic methods, more than 50% of patients with PDA are diagnosed at Stage IV, resulting in poor prognosis with limited options for surgical resection. For most PDA patients, a late stage diagnosis results in a median survival time of less than 1 year following diagnosis.

The past few decades have brought few treatment advances for patients with Stage IV PDA, and the number of treatment options approved remain limited.

Study objective

Primary objective is:
* To determine the overall survival (OS) benefit of PAG treatment, compared with AG treatment, in subjects with HA-high Stage IV previously untreated PDA.

Secundary objectives are:
* To determine the PFS benefit of PAG treatment, compared with AG treatment, in subjects with HA-high Stage IV previously untreated PDA
* To determine the objective response rate (ORR) and duration of response (DOR) of PAG treatment, compared with AG treatment, in subjects with HA-high Stage IV previously untreated PDA.
* To assess the safety and tolerability of PAG treatment in subjects with HA-high Stage IV previously untreated PDA.

Exploratory objectives are:
* To assess the treatment effect of PAG on serum levels of cancer antigen 19-9 (CA19-9).
* To assess the treatment effect of PAG on HA levels and other potential

biomarkers in plasma and tumor biopsies (when available).
* To assess the pharmacokinetics (PK) of PEGPH20 in combination with NAB plus GEM.
* To assess the potential effect of PEGPH20 on the PK of NAB and GEM.
* To assess the impact of PAG treatment on patient-reported outcomes (PROs) including health-related quality of life using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30); other health outcomes using the European Quality of Life-5 Dimensions Scale (EQ-5D); and symptoms related to pancreatic cancer and to treatment-associated toxicities using a
Numerical Rating Scale (NRS).

Study design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study to compare the efficacy and safety of PAG versus AG treatment in subjects with Stage IV previously untreated PDA whose tumors are HA-high. For the purposes of this study, randomized study medication is defined as PEGPH20 or placebo and study medication is defined as PEGPH20, placebo, NAB, and GEM. The study will start with a Screening Period. The Treatment Period will consist of 4-week treatment cycles (28 days); Week 4 of every cycle
will be a rest week (i.e., no treatment will be given).

Intervention

Eligible subjects will be randomized in a double-blind fashion to 1 of 2 treatment groups in a 2:1 ratio as follows:
* PAG group: PEGPH20 (3.0 *g/kg) + NAB (125 mg/m2) + GEM (1000 mg/m2)
* AG group: Placebo + NAB (125 mg/m2) + GEM (1000 mg/m2)

Randomized study medication will be administered as an intravenous (IV) infusion twice weekly for Weeks 1 to 3 of Cycle 1, then once weekly for Weeks 1 to 3 of Cycle 2 and beyond; NAB and GEM will be administered as IV infusions once weekly for Weeks 1 to 3 of all treatment cycles. Treatment will continue until disease progression, unacceptable toxicity, death, or withdrawal of consent.

Study burden and risks

The patient will be asked to visit the hospital seven times in the first cycle, and four times per cycle in the following cycles. The visits can take up to 5 hours depending on the assessments done and if study medication is administered during the visit. Several procedures will take place during the visits, for a schedule please have a look at pages 21-25 of the Protocol AM 2.1. Blood samples will be taken several times every cycle and at the start of each cycle a physical examination will take place and patients are asked to complete the

questionnaires (questionnaires also on day 15 of each cycle). During treatment the patients will also receive dexamethasone and enoxaparin for respectively better chemotherapy tolerability + to lessen muscle and/or jointpain and to avoid blood clots. Besides this the study medication could have harmful side effects to the patient (please refer to section 7 and appendix 3 of the Patient Information Sheet and Consent Form v1.0, 29Jan2016).

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. Signed, written Institutional Review Board/Ethics Committee-approved Informed Consent Form(s).
2. Stage IV pancreatic ductal adenocarcinoma (PDA) with histological or cytological confirmation of PDA

3. Subjects must be determined to be HA-high based on archived or fresh tumor core biopsy or sample obtained after the subject has documented metastatic disease. Biopsies/samples must meet the following requirements:
a. Pancreas tumor biopsies/samples obtained on or after the date that metastatic disease is documented or tumor biopsies/samples from a metastatic lesion are acceptable
b. Tumor biopsies or sample must meet the requirements provided in the study laboratory manual with regard to tumor tissue architecture. Note: cytology samples from fine needle aspirates without maintained tissue architecture or brushing biopsies are not acceptable.
c. Tumor tissue (formalin-fixed paraffin-embedded [FFPE] block preferred) must include enough tumor to make a minimum of 5-10 unstained, consecutive FFPE slides (10 slides are preferred) of 1 archival block that meet specific tissue sample requirements (see study laboratory manual).
requirements noted in the previous inclusion criterion (see Study Laboratory Manual).
4. Radiographic confirmation of stage IV PDA with at least 1 tumor metastasis measurable on computed tomography (CT) scan and/or magnetic resonance imaging (MRI) per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, excluding the primary pancreatic lesion.
5. If a subject has had adjuvant/neoadjuvant therapy and/or therapy for locally advanced disease (chemotherapy for non-metastatic pancreatic cancer in combination with or without radiation therapy), tumor recurrence or disease progression must have occurred no sooner than 6 months after completing the last dose of the aforementioned therapies, provided all toxicities have returned to baseline or * Grade 1.
6. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
7. Life expectancy *3 months.
8. Age *18 years.
9. A negative urine or serum pregnancy test within 7 days before Cycle 1, Day 1 (C1D1; first dose of study medication) if female subject is of childbearing potential.
10. Screening clinical laboratory values as follows (Section 8.2.7)
c. Total bilirubin *1.5 times upper limit of normal (ULN) (subjects with Gilbert syndrome are eligible independent of bilirubin levels).
d. Aspartate aminotransferase (serum glutamic oxaloacetic transaminase) and alanine aminotransferase (serum glutamic pyruvate transaminase) *2.5 times ULN, (if liver metastases are present, then *5 times ULN is allowed).
e. Serum creatinine *2.0 mg/dL or calculated creatinine clearance *40 mL/min.
f. Serum albumin *2.5 g/dL.
g. Prothrombin time or international normalized ratio (INR) within normal limits (±15%), unless subject takes warfarin, in which case prothrombin time or INR result must be within therapeutic range.
h. Partial thromboplastin time (PTT) within normal limits (±15%).
i. Hemoglobin *9 g/dL (transfusion and erythropoietic agents allowed).
j. Absolute neutrophil count *1,500 cells/mm3.
k. Platelet count *100,000/mm3.
11. For women of childbearing potential (WOCBP) and for men, agreement to use a highly effective contraceptive method from the time of screening throughout the study until 1 month (WOCBP) or 6 months (men) after administration of the last dose of any study medication. Highly effective contraceptive methods consist of prior sterilization, intra-uterine device (IUD), intrauterine hormone-releasing system (IUS), oral or injectable contraceptives,

barrier methods, and/or true sexual abstinence (Section 8.2.9).

Exclusion criteria

1. Clinical evidence of deep vein thrombosis (DVT), pulmonary embolism (PE) or other known TE event present during the screening period (see Section 8.2.11.1 and Section 8.2.12).
l. Subjects with superficial vein thrombosis are eligible.
m. Subjects with visceral/splanchnic vein thrombosis are still eligible if, in the opinion of the Investigator, the visceral/splanchnic vein thrombosis is primarily associated with the anatomic location of the underlying disease of metastatic pancreatic cancer. (i.e., there must be primary or metastatic disease in reasonable proximity to the thrombosis, and the Investigator determines that the thrombosis is due to a local tumor event and not a coagulation issue).'
2. Previous radiotherapy, surgery, chemotherapy, or investigational therapy for the treatment of metastatic disease.
a. Palliative radiotherapy for pain control of metastatic bone lesions is allowed.
3. Known central nervous system involvement or brain metastases.
4. New York Heart Association Class III or IV cardiac disease (Appendix C) or myocardial infarction within the past 12 months.
5. History of cerebrovascular accident or transient ischemic attack.
6. Clinically significant pre-existing carotid artery disease.
7. Known infection with human immunodeficiency virus, or active infection with hepatitis B or hepatitis C within the past 12 months.
8. Known allergy to hyaluronidase.
9. Current use of megestrol acetate or megestrol acetate-containing drugs (use within 10 days of Day 1).
10. Contraindication to heparin as per institutional guidelines.
11. Women currently pregnant or breastfeeding.
12. Intolerance to dexamethasone.
13. History of another primary cancer within the last 3 years with the exception of non-melanoma skin cancer, early-stage prostate cancer, or curatively treated cervical carcinoma in-situ.
14. Any other disease, active, uncontrolled bacterial, viral or fungal infection requiring systemic therapy, metabolic dysfunction, physical examination finding or clinical laboratory finding that leads to reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug, or that may affect the interpretation of the results, or that may render the subject at high risk for treatment complications.
15. Immunization with a live vaccine up to 2 weeks prior to Day 1.
16. Hypersensitivity to the active substance or ingredients of PEGPH20, gemcitabine, and nab-paclitaxel.
17. Inability to comply with study and follow-up procedures as judged by the Investigator.

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:	Recruitment stopped
Start date (anticipated):	27-03-2017
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Abraxane
Generic name:	nab-paclitaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Gemzar
Generic name:	gemcitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	not yet available
Generic name:	Pegylated recombinant human hyaluronidase

Ethics review

Approved WMO Date:	07-03-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-06-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-08-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-10-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-06-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-06-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	23-08-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-08-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-05-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-06-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-08-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-08-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-10-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-10-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	28-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-08-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2015-004068-13-NL
ClinicalTrials.gov	NCT02715804
CCMO	NL55923.091.16