A Phase III, Open Label, Randomized, Parallel Group Study to Evaluate the Efficacy and Safety of Intrapleural Administration of Adenovirus-Delivered Interferon Alpha-2b (rAd-IFN) in Combination with Celecoxib and Gemcitabine in Patients with Malignant Pleural Mesothelioma

Published: 11-10-2019
Last updated: 09-04-2024

The primary objective of this study is to compare the overall survival (OS) associated with rAd-IFN, when administered with celecoxib and gemcitabine, versus that associated with celecoxib and gemcitabine alone for the treatment of patients with MPM…

Ethical review	Not approved
Status	Will not start
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON48042

Source
ToetsingOnline

Brief title
INFINITE

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Malignant pleural mesotheliona, pleural cancer

Research involving
Human

Sponsors and support

Primary sponsor: Trizell Ltd
Source(s) of monetary or material Support: Trizell Ltd.

Intervention

Keyword: Gene Therapy, Malignant Pleural Mesothelioma

Outcome measures

Primary outcome

The primary endpoint is OS, defined as time to death (from any cause) from randomization.

Secondary outcome

The secondary efficacy endpoints are:

* To evaluate survival rate at 12 months, defined as the number of deaths (from any cause) at 12 months from randomization, and every 6 months thereafter;

* To evaluate PFS, defined as the time from randomization to the time when the modified Response Evaluation Criteria in Solid Tumor criteria for disease progression are first met, or when death from any cause occurs; and

* To evaluate best response, defined as the best response after randomization (complete response, partial response, or stable disease).

The secondary safety endpoints are:

* To evaluate the number of patients with Common Terminology Criteria for Adverse Events Grade 3 or 4; and

* To evaluate post-treatment levels of rAd-IFN-related viral DNA in biological samples collected up to 28 days after Study Day 1 in a sub-set of patients.

The exploratory efficacy endpoints are:

* Change in total score and individual components of the EQ-5D-5L and Lung Cancer Symptom Scale-mesothelioma from baseline (randomization) to each successive cycle of gemcitabine,

* Correlation between the presence of adenovirus type 5 neutralizing antibodies prior to treatment and survival (death from any cause),

* Correlation between pre- and post-treatment levels of serum mesothelin and treatment outcomes, and

* Correlation between pre- and post-treatment levels of serum fibulin-3 and treatment outcomes.

Study description

Background summary

Trizell*s recombinant adenovirus vector containing the human interferon (IFN) alpha-2b gene (rAd-IFN) is a replication deficient adenovirus-based IFN alpha-2b (IFN-*2b) gene transfer vector that is being developed for the treatment of MPM and other malignancies. When administered locally to the pleural space, the vector transfects both normal mesothelial and malignant mesothelioma cells, resulting in the production of high and sustained local concentrations of IFN-*2b protein within the pleural space and tumor. Mesothelioma cell transduction with rAd-IFN results in tumor cell death and a powerful stimulus to the immune system, as Type 1 IFNs augment tumor neo-antigen presentation/processing in dendritic cells, induce T helper type 1 (Th1) polarization, and augment cytotoxic cluster of differentiation (CD)8+ T cell function, as well as that of natural killer cells and M1 phenotype macrophages. The inflammatory response to the adenovirus viral vector itself also elicits additional *danger signals,* further potentiating anti-tumor immune responses.This multi-modal approach alters the tumor microenvironment, kills tumor cells, and stimulates the innate and adaptive immune systems. (pages 18-19, protocol V3, dated 10 September 2018)

Study objective

The primary objective of this study is to compare the overall survival (OS) associated with rAd-IFN, when administered with celecoxib and gemcitabine, versus that associated with celecoxib and gemcitabine alone for the treatment of patients with MPM who have failed a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen.

The secondary objectives of this study are:

* To compare between rAd-IFN, when administered with celecoxib and gemcitabine, versus that associated with celecoxib and gemcitabine alone for the treatment of patients with MPM who have failed a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen, with respect to:

o Survival rate at 12 months and every 6 months thereafter;
o Progression-free survival (PFS);
o Best response (complete response, partial response, or stable disease); and
o Safety of rAd-IFN; and

* To evaluate rAd-IFN, when administered with celecoxib and gemcitabine, in a sub-set of patients with MPM who have failed a minimum of 1 treatment regimen

and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen, with respect to viral shedding and biodistribution.

Study design

The study is an open-label, randomized, parallel group study conducted in patients with histologically confirmed MPM of epithelioid or biphasic (predominantly [³50%] epithelioid) histology who have failed a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, 1 of which must have been an anti-folate and platinum combination regimen.

Intervention

STUDY DRUGS: Nadofaragene firadenovec (Recombinant adenovirus vector containing the human interferon alpha-2b gene: rAd-IFN), celecoxib, and gemcitabine

Study burden and risks

Frequent hospital visits, blood draws, CT scans, possible side effects of rAd-IFN, possible side effects of celecoxib and gemcitabine.

Contacts

Public
Trizell Ltd

Sanderum House, Oakley Road Chinnor
Oxon OX39 4TW
GB
Scientific
Trizell Ltd

Sanderum House, Oakley Road Chinnor
Oxon OX39 4TW
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Aged 18 years or older and able to give informed consent;
2. Confirmed histological diagnosis of MPM with histological type epithelioid or biphasic (predominantly [*50%] epithelioid);
3. Measurable disease, per modified RECIST for pleural mesothelioma;
4. Has failed a minimum of 1 treatment regimen and a maximum of 2 treatment regimens, which may have been chemotherapeutic and/or immunotherapeutic treatment regimens for MPM which included at least 1 anti-folate and platinum combination regimen;
5. Has a pleural space accessible for pleural catheter insertion. Patients with a previously inserted pleural catheter may enroll, and the pre-existing catheter can be used for vector administration as long as it is functional and has no evidence of local infection;
6. Life expectancy *12 weeks in the judgement of the Investigator;
7. ECOG status of 1 or 0;
8. Female and male patients:
- Female patients must be either postmenopausal (no menstrual period for a minimum of 12 months) or surgically sterile upon entry into the study. Female patients of childbearing potential must have a negative pregnancy test upon entry into this study and agree to use a highly effective method of contraception from Screening until 1 month following administration of gemcitabine;
- Male patients must be either surgically sterile or agree to use a double-barrier contraception method from Screening until 1 month post-gemcitabine administration;
9. Adequate laboratory values at screening

Exclusion criteria

1. Is *treatment-naïve* (i.e., has not received at least 1 anti-folate and platinum combination regimen);
2. Has previously received 3 or more lines of systemic chemotherapeutic or

immunotherapeutic treatment;
3. Has previously received treatment with gemcitabine;
4.Has stage IV extrathoracic metastatic disease;
5.Inadequate pulmonary function of clinical significance as per Investigator review;
6.Clinically significant pericardial effusion at Screening;
7.Prior therapy(ies), if applicable, must be completed according to the protocol-specified criteria
8.Patient previously treated with IFNs (e.g., for chronic active hepatitis);
9.Suspected/known hypersensitivity to IFN-*2b;
10. Known hypersensitivity to celecoxib or sulfonamides;
11. Impaired cardiac function or clinically significant cardiac disease;
12. Women who are pregnant or breastfeeding;
13. Uncontrolled intercurrent illness
14. Patients with active, known, or suspected auto-immune disease or a syndrome that requires systemic or immunosuppressive agents (oral prednisolone or equivalent at a dose of <=10 mg per day is permitted);
15. History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs;
16. History of ulcer disease or gastrointestinal bleeding;
17. Uncontrolled or poorly controlled hypertension requiring 3 or more anti-hypertensive drugs;
18. Patients receiving lithium;
19. Any significant disease which, in the opinion of the Investigator, would place the patient at increased risk of harm if he/she participated in the study;
20. History of malignancy of other organ system within the past 5 years, except treated basal cell or squamous cell carcinoma of the skin, or early stage prostate cancer (stage T2a or smaller, prostate specific antigen <=10 ng/mL, Gleason score <=6); or
21. Has a congenital or acquired immunodeficiency, including patients with known history of infection with human immunodeficiency virus.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	11
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Celecoxib
Generic name:	Celecoxib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Gemcitabine
Generic name:	Gemcitabine Hydrochloride
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Nadofaragene firadenovec
Generic name:	rAd-IFN□2b

Ethics review

Not approved

Date:	23-07-2019
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2017-003169-82-NL
CCMO	NL67688.000.19