Actuate 1801: Phase 1/2 Study of 9-ING-41, a Glycogen Synthase Kinase-3 Beta (GSK-3β) Inhibitor, as a Single Agent and Combined with Chemotherapy, in Patients with Refractory Hematologic Malignancies or Solid Tumors

Published: 30-10-2019
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Primary ObjectivesParts 1 and 2: To evaluate the safety and tolerability, describe any dose-limiting toxicity (DLT), determine the maximum tolerated dose (MTD) or highest protocol-defined doses (in the absence of exceeding the MTD) and the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55073

Source
ToetsingOnline

Brief title
Actuate 1801: Phase 1/2 of 9-ING-41 in Refractory Malignancies

Condition

- Other condition

Synonym
Refractory Hematologic Malignancies or Solid Tumors

Health condition

Patients with Refractory Hematologic Malignancies or Solid Tumors

Research involving
Human

Sponsors and support

Primary sponsor: Actuate Therapeutics, Inc. (Actuate)
Source(s) of monetary or material Support: Actuate Therapeutics Inc.

Intervention

Keyword: 9-ING-41, Phase 1/2, Refractory Malignancies, Single or combined therapy

Outcome measures

Primary outcome

The efficacy endpoints are the following:

• Objective response rate (ORR), defined as the percent of patients with Complete Response (CR) or Partial Response (PR) according to RECIST 1.1 criteria or other standard malignancy-specific response criteria, relative to the efficacy population.

• Duration of Response (DoR), defined as the time from documentation of tumor response to disease progression

• Progression-Free Survival (PFS), defined as the time from study enrolment until objective tumor progression or death

• Overall survival (OS), defined as the time from study entry to death from any cause

Adverse events will be monitored during the period starting on the date of receipt of first administration of 9-ING-41 and ending 30 days after

the final administration of 9 ING-41. All patients who receive any dose (any amount) of 9-ING-41 or combination regimen will be included in the summaries and listings of safety data. Overall safety profile and tolerability will be characterized by type, frequency, severity, timing, duration and relationship of study drug to adverse events and laboratory abnormalities.

Secondary outcome

Specific secondary end points for patients with GBM or other CNS malignancies will include progression free survival, landmark analyses for progression free and overall survival, response rates according to the Response Assessment in NeuroOncology (RANO) criteria, neurologic deterioration-free survival (defined as the time from study entry to documentation of neurologic deterioration or death), clinical or neurologic deterioration-free survival, glucocorticoid use, the development of symptoms of neurocognitive deterioration, and assessments of predictive factors.

Study description

Background summary

9-ING-41 is a first-in-class, intravenously (IV) administered, maleimide-based small molecule potent selective GSK-3β inhibitor with significant pre-clinical antitumor activity that involves G0-G1 and G2-M phase arrest. 9-ING-41 was identified as a candidate therapeutic agent in chemoresistant human breast cancer.

GSK-3 is a serine/threonine kinase initially described as a key regulator of metabolism, specifically glycogen biosynthesis. It has a role in diverse disease processes including cancer, immune disorders, metabolic disorders, and neurological disorders through modulation of a large number of substrates.

GSK-3 has two ubiquitously expressed and highly conserved isoforms, GSK-3α and GSK-3β, with both shared and distinct substrates and functional effects.

GSK-3β is particularly important in tumor progression and modulation of oncogenes (including beta-catenin, cyclin D1 and c-Myc), cell cycle regulators (e.g. p27Kip1) and mediators of epithelial-mesenchymal transition (e.g. zinc finger protein SNAI1, Snail). Aberrant overexpression of GSK-3β has been shown to promote tumor growth and chemotherapy resistance in various solid tumors including colon, ovarian, and pancreatic cancers and glioblastoma through differential effects on the pro-survival nuclear factor kappa-light-chain-enhancer of activated B cells (NF-*B) and c-Myc pathways as well on tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and p53-mediated apoptotic mechanisms.
NF-*B is one of the most important transcription factors. Its activation is essential in promoting human cancer progression, metastasis, and chemoresistance. Among other relevant activities, GSK-3β helps maintain malignant cell survival and proliferation, particularly in terms of mediating resistance to standard anti-cancer therapies, through the NF-*B pathway.
GSK-3β has been established as a potential anticancer target in human bladder, breast, colorectal, glioblastoma, lung, neuroblastoma, ovarian, pancreatic, prostate, renal and thyroid cancers as well as chronic lymphocytic leukemia and lymphomas.
GSK-3β is a potentially very important therapeutic target in human malignancies. This Phase 1/2 study is designed to evaluate the safety and efficacy of 9-ING-41, a potent GSK-3β inhibitor, as a single agent and in combination with cytotoxic agents, in patients with refractory cancers.

Study objective

Primary Objectives

Parts 1 and 2: To evaluate the safety and tolerability, describe any dose-limiting toxicity (DLT), determine the maximum tolerated dose (MTD) or highest protocol- defined doses (in the absence of exceeding the MTD) and the recommended Phase 2 study dose (RP2D) for 9-ING-41 as monotherapy (Study Part 1) and in combination with chemotherapies (Study Part 2) in patients with relapsed or refractory malignancies.
Part 3: To assess clinical benefit in patients with relapsed or refractory malignancies treated with 9-ING-41-based combinations at the RP2D established in Part 2.

Secondary Objectives

1. To correlate response rates with specific molecular tumor profile(s) in a descriptive fashion

Study design

Open label, non-randomized, international, multi-center, Phase 1/2.

Intervention

9-ING-41 is administered by intravenous infusion twice weekly. Cycle duration is 21 days when administered as a single agent. When administered following a companion chemotherapy agent, cycle duration is 21, 28 or -84 days depending upon the chemotherapy agent.
In Parts 2 (RP2D finding) and 3 (Simon 2-Stage Phase 2 at the RP2D), 9-ING-41 will be administered following separate administration of the following:
• Gemcitabine 1250 mg/m2 as a 30-minute IV infusion on Days 1 and 8 of a 21-day cycle
• Doxorubicin 75 mg/m2, IV bolus on Day 1 of a 21-day cycle up to a maximum lifetime dose of 550 mg/m2
• Lomustine 30 mg/m² orally (PO) as a single dose, weekly for twelve weeks
• Carboplatin AUC 6 IV over 1 hour on Day 1 of a 21-day cycle
• Irinotecan 350 mg/m2 as a 90-minute IV infusion on Day 1 of a 21-day cycle
• Nab-paclitaxel 125 mg/m2 IV over 30-minutes immediately followed by gemcitabine 1000 mg/m2 IV over 30-minutes on Days 1, 8 and 15 of a 28-day cycle
• Paclitaxel 175 mg/m2 IV over 3 hours immediately followed by carboplatin AUC 6 IV over 1 hour on Day 1 of a 21-day cycle

Study burden and risks

9-ING-41 is being tested in this clinical trial to explore if, when used alone or in combination with chemotherapy there is an extension in the period where the patient*s cancer is free of progression, and if the patient*s life is extended. These benefits are possible but cannot be guaranteed. It is possible that patient will receive no benefit from participating in the study.

Disadvantages of participation in the study may be:
• possible side effects/complications of the intervention
• possible adverse effects/discomforts of the evaluations in the study. Please refer to section E9 "what risks does participation involve for human subjects" for a detailed overview of the risks associated with the study drug or the study procedures.

Participation in the study also means:
• additional time;
• additional or longer hospital stays;
• additional tests;
• instructions you need to follow;
• the study drug/study approach may not be better, and could possibly be worse,

than a different therapy for cancer treatment.

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

- Is able to understand and voluntarily sign a written informed consent and is willing and able to comply with the protocol requirements including scheduled visits, treatment plan, laboratory tests and other study procedures.
- Is aged >= 18 years
- Part 1&2: Has pathologically confirmed advanced or metastatic malignancy characterized by one or more of the following:
a. Patient is intolerant of existing therapy(ies) known to provide clinical benefit for their condition
b. Malignancy is refractory to existing therapy(ies) known to potentially

provide clinical benefit
c. Malignancy has relapsed after standard therapy
d. Malignancy for which there is no standard therapy that improves survival by at least 3 months
- Part 3: Has pathologically confirmed advanced, recurrent, or metastatic pancreatic cancer AND is previously untreated with systemic agents in the advanced/metastatic setting.
- Has laboratory function within specified parameters (may be repeated):
a. Adequate bone marrow function: absolute neutrophil count (ANC) >= 500/mL; hemoglobin >= 8.5 g/dL, platelets >= 50,000/mL (75,000/mL in Part 3)
b. Adequate liver function: transaminases (aspartate aminotransferase/ alanine aminotransferase, AST/ALT) and alkaline phosphatase <= 3 (<= 10 X the upper limit of normal (ULN) in the setting of liver metastasis or infiltration with malignant cells) x ULN; bilirubin <= 1.5 x ULN
c. Adequate renal function: creatinine clearance >= 30 mL/min (Cockcroft and Gault), except for carboplatin/pemetrexed arm, which should be >= 45 mL/min
d. Serum amylase and lipase <= 1.5 x ULN
- Has adequate performance status (PS): Eastern Co-operative Oncology Group (ECOG) PS 0-3
- Has received the final dose of any of the following treatments/ procedures with the specified minimum intervals before first dose of study drug (unless in the opinion of the investigator and the study medical coordinator the treatments/ procedures will not compromise patient safety or interfere with study conduct:
• Chemotherapy, immunotherapy, or systemic radiation therapy - 14 days, or >= 5 half-lives (whichever is shorter) - Part 1&2
• Focal radiation therapy - 7 days
• Systemic and topical corticosteroids - 7 days - Part 1&2
• Surgery with general anesthesia - 7 days
• Surgery with local anesthesia - 3 days
- May continue endocrine therapies (e.g. for breast or prostate cancer) and/or anti-human epidermal growth factor (Her2) therapies while on this study - Part 1&2
- May have received treatment with fluorouracil or gemcitabine as a radiation sensitizer in the adjuvant setting if the treatment was received at least 6 months before study enrollment - Part 3
- May have received neoadjuvant chemotherapy with FOLFIRINOX if given at least 6 months before study enrollment - Part 3
- May have received prior cytotoxic doses of systemic chemotherapy in the adjuvant setting if given at least 6 months before study enrollment - Part 3
- Women of childbearing potential must have a negative baseline blood or urine pregnancy test within 72 hours of first study therapy. Women may be neither breastfeeding nor intending to become pregnant during study participation and must agree to use effective contraceptive methods (hormonal or barrier method of birth control, or true abstinence) for the duration of study participation and in the following 90 days after discontinuation of study treatment
- Male patients with partners of childbearing potential must take appropriate

precautions to avoid fathering a child from screening until 90 days after discontinuation of study treatment and use appropriate barrier contraception or true abstinence
- Must not be receiving any other investigational medicinal product
- For Part 1: Has as most recent prior anticancer therapy an immune checkpoint agent (anti-PD-1, anti-PD-L1 or anti-CTLA-4), including, but not limited to: pembrolizumab, nivolumab, atezolizumab, durvalumab, avelumab, ipilimumab) and had an inadequate response to that immune checkpoint therapy and/or Has a DNA Repair Deficiency mutation confirmed by NGS in either tumor or blood.
and/or
Has acute T-cell leukemia/lymphoma (ATLL)
12. See Appendix Section 8.7 for details regarding Part 3 Arm B eligibility.

Exclusion criteria

- Is pregnant or lactating
- Is known to be hypersensitive to any of the components of 9-ING-41 or to the excipients used in its formulation
- Has endocrine or acinar pancreatic carcinoma - Part 3
- Has not recovered from clinically significant toxicities as a result of prior anticancer therapy, except alopecia and infertility. Recovery is defined as <= Grade 1 severity per Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (v 4.03)
- Has significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, unstable angina, or stroke within 6 months of the first dose of 9-ING-41, or cardiac arrhythmia requiring medical treatment detected at screening
- Has had a myocardial infarction within 12 weeks of the first dose of 9-ING-41 or has electrocardiogram (ECG) abnormalities that are deemed medically relevant by the investigator or study medical coordinator
- Has symptomatic rapidly progressive brain metastases or leptomeningeal involvement as assessed by CT scan or MRI. Patients with stable brain metastases or leptomeningeal disease or slowly progressive disease are eligible provided that they have not required new treatments for this disease in a 28-day period before the first dose of study drug, and anticonvulsants and steroids are at a stable dose for a period of 14 days prior to the first dose of study drug
- Has had major surgery (not including placement of central lines) within 7 days prior to study entry or is planned to have major surgery during the course of the study (major surgerymay be defined as any invasive operative procedure

in which an extensive resection is performed, e.g. a body cavity is entered, organs are removed, or normal anatomy is altered. In general, if a mesenchymal barrier is opened (pleural cavity, peritoneum, meninges), the surgery is consideredmajor)
- Has any medical and/or social condition which, in the opinion of the investigator or study medical coordinator would preclude study participation
- Has received an investigational anti-cancer drug in the 14-day period before the first dose of study drug (or within 5 half-lives if longer) or is currently participating in another interventional clinical trial
- Has a current active malignancy other than the target cancer
- Is considered to be a member of a vulnerable population (for example, prisoners)

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-06-2020
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Not applicable
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Doxorubicin
Generic name:	Not applicable
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Gemcitabine
Generic name:	Not applicable
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lomustine
Generic name:	Not applicable
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Not applicable
Generic name:	Not applicable

Ethics review

Approved WMO Date:	30-10-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	28-02-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	28-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-06-2020

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-09-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-11-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-09-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-11-2021
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2018-003739-32-NL
ClinicalTrials.gov	NCT03678883
CCMO	NL71462.031.19