A Phase 1/2 Dose Escalation and Dose Expansion Study of ZN-c3 in Combination with Gemcitabine in Adult and Pediatric Subjects with Relapsed or Refractory Osteosarcoma.

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Primary:Phase 1: • To investigate the safety and tolerability, including identification of the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of ZN-c3 in combination with gemcitabinePhase 2: • To evaluate the clinical activity of...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Soft tissue neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54108

Source
ToetsingOnline

Brief title
ZN-c3 with Gemcitabine in Subjects with Relapsed or Refractory Osteosarcoma

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
relapsed or refractory osteosarcoma

Research involving
Human

Sponsors and support

Primary sponsor: K-Group Beta, Inc
Source(s) of monetary or material Support: K-Group Beta;Inc.

Intervention

Keyword: Gemcitabine, relapsed or refractory osteosarcoma, WEE1 inhibitor, ZN-c3

Outcome measures

Primary outcome

Primary:

• Incidence and severity of dose-limiting toxicities (DLTs) in DLT-evaluable subjects during Cycle 1 of Phase 1

• EFS at 18 weeks (Phase 2)

Secondary outcome

Secondary:

• Clinical activity:

According to RECIST v1.1 and clinical criteria:

- *FS

- OS (median and at 12 months)

• Incidence and severity of adverse events (AEs) graded according to National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE), version 5.0

• Plasma PK parameters of ZN-c3 (and its potential metabolites as applicable), including but not limited to maximum concentration (Cmax), time to maximum concentration (Tmax), and area under the concentration-time curve over the dosing interval (AUC0-24h).

Study description

Background summary

The medicinal product ZN-c3 has been tested for its antitumor activity in a laboratory and in animals. It has a novel mechanism of action and results show that this could be a potential treatment for solid tumors like osteosarcoma. It is expected that together with the use of Gemcitabine the antitumor activity can be increased. ZN-c3 is currently being studied in humans but the use of ZN-c3 in combination with gemcitabine has not been studied in humans before.

Study objective

Primary:
Phase 1:
• To investigate the safety and tolerability, including identification of the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of ZN-c3 in combination with gemcitabine

Phase 2:
• To evaluate the clinical activity of WEE1 inhibition by ZN-c3 in combination with gemcitabine in subjects with relapsed/refractory osteosarcoma as assessed by the event-free survival (EFS) at 18 weeks, per the revised Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

Secondary:
• To further evaluate the clinical activity based on EFS according to RECIST v1.1 and to determine median overall survival (OS) and OS at 12 months of ZN-c3 in combination with gemcitabine
• To further investigate the safety and tolerability of ZN-c3 in combination with gemcitabine
• To investigate the plasma pharmacokinetics (PK) of ZN-c3 (and its potential metabolites as applicable) when given in combination with gemcitabine

Study design

This is a Phase 1/2 dose escalation and dose expansion study, evaluating the clinical activity and safety, pharmacodynamics, and pharmacokinetics of ZN c3 in combination with gemcitabine in adults and pediatric patients with relapsed or refractory osteosarcoma.

Intervention

starting at day 2 Daily intake of 2 to 3 ZN-c3 tablets

Infusions of chemotherapy on Day 1 and 8 each cycle

Study burden and risks

At least 11 visits to the hospital (screening, Day 1, 2, 3, 8, 15 and 16 for Cycle 1, Day 1 and day 8 for all other cycles, 1 End of study and 1 FU visit).
Daily intake of 2 to 3 Zn-c3 tablets
Infusions of chemotherapy on Day 1 and 8 each cycle.
CT/MRI scan every 6 weeks
Blood collection at all visits including abbreviated PK, with a total amount of 156 ml (+27ml for each additional cycle)
Blood collection at all visits including full PK, with total amount of 240 ml (+27ml for each additional cycle)
Completion of dosing diary every day (IMP intake, timing, missed dose) which should be brought to each visit
Completion of questionnaires on Day 1, 8 of each cycle and End of study (this will take 10 minutes)

Contacts

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US
Scientific
K-Group Beta, Inc

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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

An individual must meet all the following criteria to participate in this study:
1. Provision of written informed consent by subjects and/or their parents or legally authorized representatives; assent, when appropriate, will be obtained according to institutional guidelines.
2. Age >=12 years old at the time of informed consent.
3. Body weight >=40 kg.
4. Histologically documented relapsed or metastatic osteosarcoma, as confirmed at the local study site.
a) The disease must have failed standard therapy and there is no known curative therapy available, or any available standard of care therapy was not tolerated.
b) The Investigator must confirm that gemcitabine is an appropriate treatment approach.
c) Subjects may have had any number of prior therapies and prior treatment with gemcitabine is allowed.
5. Must have measurable disease according to RECIST v1.1 criteria.
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) <=2 for subjects >=16 years of age or Lansky PS >=50 for subjects <16 years of age.
7. Adequate hematologic and organ function.
8. Ability and willingness to take oral medication.
9. Willingness to release archival tissue (less than 2 years old and of adequate tumor cellularity as described in Laboratory Manual; other cases may be considered after discussion with the Sponsor) for research purposes and/or to undergo a tumor tissue biopsy prior to dosing on Cycle 1 Day 1 if >=18 years old.
Biopsy samples of tumor tissue should be obtained if, in the judgment of the Investigator, the procedure is considered to be free of unacceptable risk. If in the opinion of the investigator a tumor tissue biopsy is not freeof unacceptable risk and archival tissue is not available, eligible patients may be allowed onto the trial on a case-by-case basis after consultation with the sponsor.
10. Female subjects of childbearing potential must have a negative

serum beta human chorionic
gonadotropin (β-hCG) test.
11. Female subjects of childbearing potential and male subjects must agree to use a highly effective method of contraception from the start of Screening period and for 6 months after the last dose of ZN-c3 and/or gemcitabine.
12. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion criteria

Individuals meeting any of the following criteria will be excluded from this study:
1. Any of the following treatment interventions within the specified timeframe prior to Cycle 1 Day 1:
a. Major surgery <28 days (the surgical incision should be fully healed prior to study drug administration).
b. Any chemotherapy <21 days or 5 half-lives (whichever is shorter).
c. Prior radiotherapy <14 days.
d. Any investigational drug therapy <28 days or 5 half-lives (whichever is shorter).
e. Inability to discontinue treatment with prescription or non-prescription drugs, or to discontinue consumption of food and herbal supplements, that are strong and moderate CYP3A inhibitors and inducers, or P-gp inhibitors at least 14 days prior to Cycle 1 Day1.
2. Unresolved toxicity of Grade >1 attributed to any prior therapies (excluding Grade neuropathy, alopecia, or skin pigmentation).
3. Prior therapy with a WEE1 inhibitor.
4. Known hypersensitivity to gemcitabine or its excipients.
5. Known hypersensitivity to any drugs similar to ZN-c3 in class.
6. A serious illness or medical condition(s) including, but not limited to, the following:
a. Brain metastases that require immediate treatment or are clinically orradiologically unstable (i.e., have been stable for <1 month). If receivingsteroids, subjects must be receiving a stable dose or a decreasing corticosteroid dose during at least 1 week before enrollment.
b. Leptomeningeal disease that requires or is anticipated to require immediate treatment.
c. Myocardial impairment of any cause (e.g., cardiomyopathy, ischemic heart disease, significant valvular dysfunction, hypertensive heart disease, and congestive heart failure) resulting in heart failure by New York Heart Association Criteria (Class III or IV).
d. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the

interpretation of study results, and in the judgment of the Investigator would make the subject inappropriate for entry into this study.
e. Significant gastrointestinal abnormalities, requirement for IV alimentation, active peptic ulcer, chronic diarrhea, or vomiting considered to be clinically significant in the judgment of the Investigator, or prior surgical procedures affecting absorption.
f. Active or uncontrolled infection. Subjects with an infection receiving treatment (antibiotic, antifungal, or antiviral treatment) must have completed such treatment and the infection must be considered controlled/resolved by the investigator before enrollment.
7. Pregnant or lactating females or females of childbearing potential who have a positive serum pregnancy test within 14 days prior to Cycle 1Day 1.
8. Subjects with active (uncontrolled, metastatic) second malignancies or requiring therapy.
9. Individuals who are judged by the Investigator to be unsuitable as study subjects.
10. 12-lead ECG demonstrating a corrected QT interval using Fridericia s formula (QTcF) of
>470 ms, except for subjects with atrioventricular pacemakers or other conditions (e.g., right bundle branch block) that render the QT measurement invalid.
11. History or current evidence of congenital or family history of long QT syndrome or Torsades de Pointes (TdP).

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Gemcitabine
Generic name:	Gemcitabine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-01-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	28-10-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-02-2023
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	EUCTR2021-000021-27-NL
ClinicalTrials.gov	NCT04833582
CCMO	NL77680.041.21