A Phase 1b/2 Study of the Dual MDMX/MDM2 Inhibitor, ALRN-6924, for the Prevention of chemotherapy-induced Myelosuppression

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Phase 1b:Primary:- To evaluate the safety and tolerability and determine the recommended Phase 2 dose (RP2D) and schedule of ALRN-6924 when administered to patients with TP53-mutated extensive disease (ED) small cell lung cancer (SCLC) receiving...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Anaemias nonhaemolytic and marrow depression
Study type	Interventional

Summary

ID

NL-OMON49367

Source
ToetsingOnline

Brief title
ALRN-6924

Condition

- Anaemias nonhaemolytic and marrow depression
- Respiratory tract neoplasms

Synonym
Myelopreservation during myelosuppressive chemotherapy with Topotecan

Research involving
Human

Sponsors and support

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

Intervention

Keyword: myeloprotective/preservative effects, prevention, small lung cancer, topotecan

Outcome measures

Primary outcome

Phase 1b

Primary endpoint:

- Proportion of patients with National Cancer Institute (NCI) Common

Terminology Criteria for Adverse Events (CTCAE) Grade 3/4 treatment

emergent adverse events (TEAEs)

Phase 2

Primary endpoint:

- Proportion of patients with Grade * 3 neutropenia in Cycle 1

Secondary outcome

Phase 1b:

Key secondary endpoint:

- Proportion of patients with Grade * 3 neutropenia in Cycle 1

Other secondary endpoints:

- Proportion of patients with Grade * 3 neutropenia in Cycle 2 and beyond

- Time to first incidence of Grade * 3 neutropenia

- Duration of Grade * 3 neutropenia

- Proportion of patients with Grade * 3 thrombocytopenia

- proportion of patients with Grade * 3 anemia

- Proportion of patients with febrile neutropenia

- Proportion of planned treatment cycles delayed due to toxicity

- Overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors

(RECIST) 1.1

- Progression free survival (PFS)

- Overall survival (OS)

- PK parameters (e.g., area-under-the-curve [AUC], maximum concentration

[Cmax], time of Cmax [tmax], half-life [t1/2]) of ALRN-6924

Phase 2:

Secondary endpoints:

- Proportion of patients with Grade * 3 neutropenia in Cycle 2 and beyond

- Time to first incidence of Grade * 3 neutropenia

- Duration of Grade * 3 neutropenia

- Proportion of patients with Grade * 3 thrombocytopenia

- Proportion of patients with febrile neutropenia

- Proportion of planned treatment cycles delayed due to toxicity

- Proportion of patients with NCI CTCAE Grade 3/4 TEAEs

- ORR

- PFS

- OS

- PK parameters (e.g., AUC, Cmax, tmax, t1/2) of ALRN-6924

Study description

Background summary

ALRN-6924 is a synthetic, cell-permeating, stapled peptide designed to disrupt the interaction between the p53 tumor suppressor protein and its predominant endogenous inhibitors, murine double minute X (MDMX) and murine double minute 2 (MDM2). ALRN-6924 is being developed by Aileron Therapeutics, Inc. (Aileron) as a potential treatment for patients with advanced cancers with wild-type (WT) TP53 tumor suppressor protein and for the supportive care of patients with TP53-mutant tumors, but an intact p53 pathway in their non-malignant tissues. The present protocol is designed to evaluate the myelopreservation effects of ALRN-6924 when administered as supportive treatment during myelosuppressive chemotherapy; specifically, during 2nd-line treatment with topotecan in patients with TP53-mutated extensive disease (ED) small cell lung cancer (SCLC).

Study objective

Phase 1b:
Primary:
- To evaluate the safety and tolerability and determine the recommended Phase 2 dose (RP2D) and schedule of ALRN-6924 when administered to patients with TP53-mutated extensive disease (ED) small cell lung cancer (SCLC) receiving topotecan as 2nd-line treatment.

Secondary
- To evaluate the preliminary myelopreservation effects of ALRN-6924 when administered to patients with TP53-mutated ED SCLC undergoing 2nd-line treatment with topotecan
- To evaluate the efficacy of topotecan when administered as 2nd-line treatment for patients with TP53-mutated ED SCLC who are receiving supportive treatment with ALRN-6924
- To evaluate the pharmacokinetic (PK) profile of ALRN 6924 when administered with topotecan

Phase 2:
Primary
- To evaluate the myelopreservation effects of ALRN-6924 when administered at the RP2D and schedule to patients with TP53-mutated ED SCLC undergoing 2nd-line treatment with topotecan

Secondary
- To further evaluate the safety and tolerability of ALRN-6924 as supportive care during treatment with topotecan
- To further evaluate the efficacy of topotecan when administered as 2nd-line treatment for patients with TP53-mutated ED SCLC who are receiving supportive treatment with ALRN-6924
- To further evaluate the PK profile of ALRN 6924 when administered with topotecan

Study design

This is a Phase 1b/2, open-label, multicenter study of ALRN-6924 for the prevention of topotecan-induced myelosuppression during 2nd-line treatment for ED SCLC harboring TP53 mutations. During the Phase 1b portion of the study, chemotherapy-induced myelosuppression in patients with TP53-mutated ED SCLC undergoing 2nd-line treatment with topotecan. The Phase 1b part of the study will consist of a dose optimization stage, a schedule optimization stage, and a dose expansion stage. Two schedules of ALRN-6924 administration (either 24 hours or 6 hours prior to every topotecan infusion) will be evaluated. The RP2D and recommended schedule of ALRN-6924 in combination with topotecan will be determined in the Phase 1b dose optimization and schedule optimization stages of the trial. This dose and schedule will be utilized in the Phase 1b dose expansion and Phase 2 parts of the trial.
During the Phase 1b dose optimization stage, topotecan will be administered per standard practice on Days 1-5 of 21-day cycles. Patients will be randomized to receive 1 of 2 initial ALRN-6924 dose levels, to be administered on Days 0-4 of each cycle, approximately 24 hours prior to each planned topotecan dose.
The severity of hematologic toxicities, particularly neutropenia, thrombocytopenia, anemia and febrile neutropenia, will be determined and compared to the severity of these toxicities when topotecan is administered alone, based on historical controls.

If pre-determined criteria for safety and myelopreservation are met, an additional 8 patients at each of these two dose levels will be evaluated, for a total of 14 patients at each of the two dose levels. If pre-determined criteria for safety and myelopreservation are not met, up to 6 additional (nonrandomized) dose levels may be evaluated. The safety and tolerability of each ALRN-6924 dose level will be assessed during Phase 1b and a Data Review Committee (DRC) will assess these data and the hematologic toxicity data at the end of Phase 1b, in order to select a recommended Phase 2 dose. This committee will also review safety data on a regular basis and will review each ALRN-6924 dose level after 6 patients enrolled to that dose level have completed one full cycle of ALRN-6924 supportive therapy, in order to assess the safety and tolerability of that dose level, before additional patients are enrolled.
If pre-determined criteria for safety and myelopreservation activity are met and the DRC identifies an RP2D, the Phase 2 portion of the study will be triggered.

RP2D. During the Phase 1b schedule optimization stage of the study, topotecan will be administered as described for the dose optimization stage. Patients will receive 1 of 2 dose levels of ALRN-6924, to be administered on Days 1-5 of each cycle, approximately 6 hours prior to each planned topotecan dose. The 2 dose levels ALRN-6924 to be evaluated with this alternative schedule will be determined based on results from the Phase 1b dose optimization stage. Following completion of the Phase 1b schedule optimization evaluation, a recommended schedule for ALRN-6924 (either 24 hours or 6 hours prior to every topotecan infusion) will be determined.

Following identification of the recommended dose and schedule of ALRN-6924, the DRC will make a recommendation regarding initiation of the Phase 1b expansion and/or the Phase 2 portion of the study. Based on the DRC recommendation, the Sponsor will determine which of these cohorts to open first. It is possible that not all study sites will participate in the Phase 1b dose expansion cohort.

In the randomized Phase 1b expansion stage, 20 patients with ED SCLC harboring p53 loss of function mutations and requiring 2nd-line treatment with topotecan will be randomized in a 1:1 ratio to receive:
- Treatment with topotecan + ALRN-6924 per RP2D and recommended schedule during Cycle 1; and topotecan alone during Cycle 2.
- Treatment with topotecan alone during Cycle 1; and topotecan + ALRN-6924 during Cycle 2 per RP2D and recommended schedule.
In all subsequent treatment cycles(Cycles *3), all patients will receive treatment with topotecan + ALRN-6924.

In Phase 2, patients with ED SCLC harboring p53 loss of function mutations requiring 2nd-line treatment with topotecan will be randomized 1:1 to either receive topotecan alone or topotecan with supportive ALRN-6924 treatment. Monitoring of hematologic toxicities will proceed as in Phase 1b.

Intervention

All patients will be treated with Topotecan and a dose of ALRN 6924
During the Phase 1b portion of the study,topotecan will be administered per standard practice on Days 1-5 of 21-day cycles.Patients will be randomized to receive 1 of 2 initial ALRN-6924 dose levels, to be administered on Days 0-4 of each cycle, approximately 24 hours prior to each planned topotecan dose.

During the Phase 1b schedule optimization stage of the study, topotecan will be administered per standard practice on Days 1-5 of 21-day cycles. ALRN-6924 will be administered at 1 of 2 dose levels on Days 1-5 of each cycle approximately 6 hours prior to each planned topotecan dose. The 2 dose levels of ALRN-6924 to be evaluated with this alternative schedule will be determined based on results from the dose optimization stage of the Phase 1b trial. Patients will be enrolled at Dose Level 1 initially followed by enrolment in Dose Level 2. Six

patients will initially be enrolled at each dose level; if pre-determined criteria for safety and myelopreservation are met, an additional 8 patients at each of these 2 dose levels will be evaluated, for a total of 14 patients at each of the 2 dose levels. Following completion of the Phase 2 portion of the study will be triggered. In Phase 2, 1b schedule optimization evaluation, a recommended schedule for ALRN-6924 (either 24 hours or 6 hours prior to every topotecan infusion) will be determined.

During Phase 2, patients randomly assigned to the experimental arm will receive ALRN-6924 as an IV infusion over 1 hour at the RP2D on Days 0-4 of every 21-day cycle and topotecan at a dose of 1.5 mg/m2 on Days 1-5 of each cycle. Patients randomly assigned to the control arm will receive topotecan per the same dose and schedule but will not receive any administrations of ALRN-6924.

Study burden and risks

The patients will be treated with Topotecan and ALRN-6924 for a maximum of 6 cycles the total duration for phase Ib will be 5 months. During each cycle the patient will visit the hospital 6-7 times. With the maximum nr of cycles 44 visits are performed.
- Possible side effects of the treatment.
- Possible adverse effects/discomforts of the evaluations in the study e.g. venapuction or CT scans.
- Incidental findings: participation in the study may lead to additional findings about your health eg. HIV HBV HCV.

Contacts

Public
Aileron Therapeutics, Inc.

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US
Scientific
Aileron Therapeutics, Inc.

Arsenal Way 490
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria:
1. Males and females age 18 years or older.
2. Ability to understand the requirements of this clinical trial and willingness to provide written informed consent
3. Histopathological confirmation of ED SCLC that has recurred or been refractory to one line of treatment with standard platinum-based chemotherapy or immuno-chemotherapy. Patients who received immunotherapy after platinum-based chemotherapy remain eligible.
4. Mutated TP53: no wild type (WT) TP 53 gene copies within the tumor (i.e., biallelic mutation, biallelic deletion, or mutation/deletion), as assessed by next generation sequencing (NGS)
5. Measurable disease using RECIST 1.1
6. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2
7. Adequate hematological status:
a. absolute neutrophil count (ANC) *1500/*L
b. platelet count *100,000/*L
c. hemoglobin *9.0 g/dL
8. Adequate hepatic and renal function:
a. total bilirubin *1.5 X upper limit of normal (ULN) or * 3 X ULN in the presence of Gilbert syndrome or liver metastases
b. alkaline phosphatase (ALP), aspartate aminotransferase (AST [SGOT]), and alanine aminotransferase (ALT [SGPT]) * 2.5 X ULN in the absence of liver metastases
c. ALP, AST (SGOT), and ALT (SGPT) *5 X ULN in the presence of liver metastases
d. serum creatinine <1.5 X ULN or calculated creatinine clearance * 40 mL/min (C&G or EDTA)
9. Recovery from the acute toxic effects of all prior therapies to Grade *1
10. The shorter of 5 half-lives or 4 weeks must have elapsed since any prior

systemic therapy, unless no drug-drug interactions with study treatment would be anticipated and the patient had unequivocal radiologic disease progression during the prior line of therapy.
11. Males and female patients of child-bearing potential must agree to use an acceptable method of birth control for the duration of study treatment and for 3 months (male patients with female partner of child-bearing potential) or 6 months (female patients of child-bearing potential) following the last dose of study treatment.

Exclusion criteria

Exclusion Criteria:
1. Known hypersensitivity to any component of study treatment including mannitol, which is an excipient in topotecan.
2. More than one line of prior chemotherapy for ED SCLC (prior immunotherapy is permitted, concurrent with or subsequent to firstline chemotherapy). Previous treatment with platinum-based chemotherapy concomitant with radiotherapy for limited disease is allowed if completed at least 6 months prior to enrolment into the current trial.
3. Presence of active central nervous system metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable, with no evidence of radiographic or neurologic progression during the screening period and no requirement for steroids for at least 15 days before enrolment.
4. Uncontrolled intercurrent illness including but not limited to:
a. Clinically significant, active, uncontrolled infection including human immunodeficiency virus (HIV), or hepatitis B or C
i. Patients with HIV must be on effective antiretroviral therapy for * 4 weeks prior to enrollment and have HIV viral load < 400 copies/mL, have had no acquired immunodeficiency syndrome (AIDS)-defining opportunistic infections in the past 12 months, and have CD4+ count * 350 cells/*L.
ii. Patients with chronic hepatitis B virus (HBV) must be on antiviral therapy and have HBV viral load below the limits of detection.
iii. Patients with hepatitis C virus (HCV) must be on or have completed antiviral therapy and have an HCV viral load below the limits of detection.
b. Uncontrolled hypertension
c. Uncontrolled diabetes mellitus
5. Clinically significant electrolyte abnormalities
6. Clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active myocardial ischemia, or indwelling temporary pacemaker
7. History of prior malignancy; patients with a known malignancy that does not affect overall well-being and ability to participate in the study can be considered in consultation with the Medical Monitor.
8. Pregnant or lactating women

9. Hereditary angioedema of any severity or severe or life-threatening angioedema due to any cause.
10. Major surgery (e.G. opening up a mesenchymal barrier) within 28 days of enrolment. Please consult Medical monitor as needed
11. Significant weight loss (*15% body weight) within the 4 weeks prior to enrolment.
12. Treatment with an investigational agent for any indication within the shorter of 14 days or 5 half-lives, if the half-life is known
13. The required use of any concomitant medications that are predominantly cleared by hepatobiliary transporters, organic anion transporter polypeptide [OATP] members OATP1B1 and OATP1B3 on the day of the first ALRN-6924 infusion to within 48 hours after the last ALRN-6924 infusion in a treatment cycle (see Appendix A)
14. Other medications, severe acute/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 patient inappropriate for entry into this study

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-09-2019
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ALRN-6924

Generic name:	ALRN-6924
Product type:	Medicine
Brand name:	Potactasol
Generic name:	topotecan
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-10-2019
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-06-2020
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-07-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-07-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-11-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2019-001848-21-NL
ClinicalTrials.gov	NCT04022876
CCMO	NL70430.031.19