Phase III Randomized Clinical Trial of Lurbinectedin (PM01183)/Doxorubicin (DOX) versus Cyclophosphamide (CTX), Doxorubicin (DOX) and Vincristine (VCR) (CAV) or Topotecan as Treatment in Patients with Small-Cell Lung Cancer (SCLC) Who Failed One Prior Platinum-containing Line (ATLANTIS Trial).

Published: 20-07-2016
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Primary objective:To determine whether there is a difference in overall survival (OS) between lurbinectedin (PM01183)/doxorubicin (DOX) and a control armconsisting of best Investigator's choice between cyclophosphamide (CTX), doxorubicin (DOX)…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON46847

Source
ToetsingOnline

Brief title
Atlantis

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
Small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Pharma Mar
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Control arm: CAV or topotecan, Lurbinectedin plus doxorubincin, Phase III, Small cell lung cancer (SCLC)

Outcome measures

Primary outcome

Primary endpoint:

* Overall survival (OS) will be calculated from the date of randomization to

the date of death (death event) or last contact (in this case, survival will be

censored on that date).

Secondary outcome

secondary endpoints:

* Difference in OS between PM01183/DOX and CAV, in patients with CAV as best

Investigator's choice.

* Overall survival (OS)/progression-free survival (PFS) per RECIST v.1.1 in

patients with and without baseline CNS involvement. Subgroup analyses

restricted to the sensitive and resistant populations will also be performed

* Progression-free survival (PFS) by IRC

* Best antitumor response by IRC

* Duration of response (DR) by IRC

* Treatment safety profile

Study description

Background summary

Patients with relapsed SCLC have the worst prognosis among lung cancer patients, with usually a life expectancy of less than six months and few therapeutic options. New treatment options are eagerly needed, particularly agents with novel mechanisms of action and no cross-resistance with prior platinum-regimens.
No new treatment has been approved in Western countries over the last 15 years. In particular, almost none of the randomized clinical trials done over the last 30 years have shown a positive outcome improvement in this setting.

PM01183 is a new chemical entity that binds the DNA leading to the formation of DNA double strand breaks. The binding to the DNA is likely occurring in the minor groove region and induces apoptosis and delayed progression through the phase S/G2. PM01183 also induces the specific degradation of transcribing RNA Pol II in several human tumor cell lines. According to a COMPARE analysis, it does not have an overlapping mechanism of action with other 98 standard cytotoxic agents.
Data from the cohort of 21 second-line SCLC patients treated in the Phase Ib study with the DOX combination showed a confirmed and remarkably high activity consistent with the synergistic effects found in vitro/in vivo, which resulted in an ORR of 67%, with approximately 10% of CRs. This activity is unprecedented, whereas historical data on an anthracycline-containing combination used in a similar setting show ORRs usually in the 20-30% range. Four patients were still ongoing treatment at the cutoff of January 2015; the median PFS observed was 4.7 months (95%CI: 3.5-not reached). The lower boundary of this 95%CI is in fact 3.5 months, which is usually the median PFS obtained with the standard topotecan treatment. The preliminary results of this uncontrolled cohort showed myelosuppression to be of potential concern in an unselected phase III population. Thus, the DOX dose has been adapted to this setting by a 20% reduction in addition to the G-CSF primary prophylaxis implementation to effectively reduce the FN risk associated with the use of this combination.
A new cohort is ongoing, and although results are not available yet, the aforementioned promising results warrant further study in a well-designed, prospective, larger, randomized study to better define the role of this combination in the treatment of relapsed SCLC patients.

Study objective

Primary objective:
To determine whether there is a difference in overall survival (OS) between lurbinectedin (PM01183)/doxorubicin (DOX) and a control arm consisting of best Investigator's choice between cyclophosphamide (CTX), doxorubicin (DOX) and vincristine (VCR) (CAV) or topotecan, as treatment in SCLC patients after failure of one prior platinum-containing line.

Key secondary objectives:

* Difference in OS between PM01183/DOX and CAV, in patients with CAV as best Investigator's choice.
* OS/PFS in patients with and without baseline CNS involvement. Subgroup analyses restricted to the sensitive and resistant populations (i.e., chemotherapy-free interval [CTFI] *90 days and CTFI <90 days) will also be performed.
* PFS by an Independent Review Committee (IRC)
* Antitumor activity by IRC according to the RECIST v.1.1
* Safety profile

Study design

Multicenter, open-label, randomized, controlled phase III clinical trial to evaluate and compare the activity and safety of an Experimental Arm consisting of PM01183 + DOX combination followed by PM01183 alone if applicable vs. CAV or topotecan as a control arm in SCLC patients who failed one prior platinum-containing line.

Central randomization will be implemented; patients will be assigned to each arm at a 1:1 ratio.
If the patient is randomized to the control arm, the assigned treatment will be based on the reported Investigator*s preference between CAV or topotecan. However, whenever the number of patients randomized to either CAV or topotecan reaches 55% of the total number of patients expected in the control arm (i.e., 165 patients), then the assigned treatment will be restricted to the remaining option (i.e., that which has not reached 165 patients) until the end of accrual. Stratification will be performed according to the chemotherapy-free interval (CTFI) after first line [*180 days (very sensitive, VS) vs. 90-179 days (sensitive; S) vs. <90 days (resistant; R)], Eastern Cooperative Oncology Group performance status (ECOG PS) (0 vs. 1-2), baseline central nervous system (CNS) involvement vs. no involvement, and prior immunotherapy against either programmed cell death protein-1 (PD-1) or programmed death ligand-1 (PD-L1) (Yes vs. No).

An Independent Review Committee (IRC) will determine the best patient response and assign the date of objective response or progression/censoring according to RECIST v.1.1. An Independent Data Monitoring Committee (IDMC) will oversee the conduct of the study.

An interim safety analysis is planned after the recruitment of 150 patients (i.e., ~75 patients into each arm). Recruitment will not be put on hold while the interim safety analysis is being performed. The IDMC may also review preliminary efficacy parameters (as per IA) at this time.
Crossover is not allowed.

Intervention

ROUTE OF ADMINISTRATION
Experimental arm:
Doxorubicin: a short i.v. bolus/infusion over a total volume of 20 to 50 ml dilution on 0.9% saline or 5% dextrose (as per institutional practice), via a central or peripheral venous catheter after appropriate visual confirmation of effective venous blood return through the line, followed by:
PM01183: i.v. infusion over one hour over a minimum of 100 ml dilution on 5% glucose or 0.9% sodium chloride (at a fixed rate) via a central line (or a minimum of 250 ml dilution if a peripheral line is used).

Control arm:
- Topotecan: i.v. as a 30-min infusion daily through peripheral or central lines.
- CAV: a short i.v. infusion of CTX over a total volume of 100 to 500 ml dilution on 0.9% saline or 5% dextrose (as per institutional practice), via a central or peripheral venous catheter, followed by,
DOX as a short i.v. bolus/infusion over a total volume of 20 to 50 ml dilution on 0.9% saline or 5% dextrose (as per institutional practice), via a central or peripheral venous catheter, followed by,
VCR as a i.v. bolus over a total volume of 10 to 30 ml dilution on 0.9% saline or 5% dextrose (as per institutional practice), via a central or peripheral venous catheter.

STARTING DOSE AND SCHEDULE
Experimental arm:
- DOX at 40.0 mg/m2 on Day 1, immediately followed by:
- PM01183 at 2.0 mg/m2 on Day 1 q3wk (three weeks = one treatment cycle).
for a maximum of 10 cycles. Then, if applicable, DOX will be withdrawn definitively and remaining patients will continue on maintenance until disease progression (PD), patient refusal or unacceptable toxicity despite applicable dose reductions, at:
- PM01183 at 3.2 mg/m2 on Day 1 q3wk. (if not more than one dose reduction applied while on combination therapy), or:
- PM01183 at 2.6 mg/m2 on Day 1 q3wk. (if more than one dose reduction applied while on combination therapy).

Control arm:
- Topotecan at 1.50 mg/m2 daily on Days 1-5 q3wk (three weeks = one treatment

cycle) for patients with calculated CrCL * 60 ml/min.
- Topotecan at 1.25 mg/m2 daily on Days 1-5 q3wk (three weeks = one treatment cycle) for patients with calculated CrCL between 40 and 59 ml/min.
- Topotecan at 0.75 mg/m2 daily on Days 1-5 q3wk (three weeks = one treatment cycle) for patients with calculated CrCL between 30 and 39 ml/min.

CAV:
- CTX at 1000 mg/m2 on Day 1, immediately followed by,
- DOX at 45.0 mg/m2 on Day 1, immediately followed by,
- VCR at 2.0 mg total flat dose on Day 1 q3wk (three weeks = one treatment cycle).
Up to a maximum of 10 cycles. Then, if applicable, DOX will be discontinued definitively and the remaining patients will continue on maintenance until progressive disease, patient refusal or unacceptable toxicity despite applicable dose reductions.

Doses in both arms, Experimental and Control, will be capped at a body surface area (BSA) of 2.0 m2 for individuals exceeding this BSA value. Doses will have to be recalculated for patients showing a * 10% variation from baseline in total body weight. PM01183 total doses in mg will be rounded to the first decimal, if necessary. DOX, CTX or topotecan total doses will be rounded, if applicable, according to institutional guidelines/standard practice.

Study burden and risks

The patient may or may not receive any direct medical benefit from being in this study. The illness can improve, become worse or remain the same.

Patients with relapsed SCLC have the worst prognosis among lung cancer patients, with usually a life expectancy of less than six months and few therapeutic options. New treatment options are eagerly needed, particularly agents with novel mechanisms of action and no cross-resistance with prior platinum-regimens.
No new treatment has been approved in Western countries over the last 15 years. In particular, almost none of the randomized clinical trials done over the last 30 years have shown a positive outcome improvement in this setting.
PM01183 is a new chemical entity that induces double-strand DNA breaks through binding to the DNA minor groove. According to a COMPARE analysis, it does not have an overlapping mechanism of action with other 98 standard cytotoxic agents.
The promising results in other research warrant further study in a well-designed, prospective, larger, randomized study to better define the role of this combination in the treatment of relapsed SCLC patients.
Considering all the data currently available for PM01183 suggests an acceptable risk-benefit ratio. (Please refer to section J)

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) Voluntary written informed consent of the patient obtained before any study-specific procedure.
2) Adult patients aged * 18 years.
3) Histologically or cytologically confirmed diagnosis of limited or extensive stage SCLC which failed one prior platinum-containing regimen (CTFI, time from the last dose of first-line chemotherapy to the occurrence of progressive disease) * 30 days. Small-cell carcinoma of unknown primary site with or without neuroendocrine features confirmed in histology test(s) performed on metastatic lesion(s) are eligible, if Ki-67/MIB-1 is expressed in >50% of tumor cells.
4) ECOG PS * 2.
5) Adequate hematological, renal, metabolic and hepatic function in an assessment performed within 7 days (+ 3 day window) of randomization:

a) Hemoglobin * 9.0 g/dl [patients may have received prior red blood cell (RBC) transfusion, if clinically indicated]; absolute neutrophil count (ANC) * 2.0 x 109/l, and platelet count * 100 x 109/l.
b) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) * 3.0 x upper limit of normal (ULN).
c) Total bilirubin * 1.5 x ULN or direct bilirubin * ULN.
d) Albumin * 3.0 g/dl.
e) Calculated creatinine clearance (CrCL) * 30 ml/minute (using Cockcroft and Gault*s formula).
f) Left ventricular ejection fraction (LVEF) by echocardiogram (ECHO) or multiple-gated acquisition (MUGA) scan within normal range (according to institutional standards).
g) Creatine phosphokinase (CPK) * 2.5 x ULN (* 5.0 x ULN is acceptable if elevation is disease-related).
6) At least three weeks since last prior anticancer treatment and recovery to grade * 1 from any adverse event (AE) related to previous anticancer treatment (excluding sensory neuropathy, anemia, asthenia and alopecia, all grade * 2) according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v.4).
7) Prior radiotherapy (RT): At least four weeks since completion of whole-brain RT (WBRT), at least two weeks since completion of prophylactic cranial irradiation (PCI), and to any other site not previously specified.
8) Evidence of non-childbearing status for women of childbearing potential (WOCBP). WOCBP must agree to use a highly effective contraceptive measure up to six weeks after treatment discontinuation. Valid methods to determine the childbearing potential, adequate contraception and requirements for WOCBP partners are described in the appendix 2 of the protocol. Fertile male patients with WOCBP partners should use condoms during treatment and for four months following the last IMP dose.

Exclusion criteria

1) More than one prior CHT-containing regimen (including patients re-challenged with same initial regimen).
2) Patients who never received any platinum-containing regimen for SCLC treatment.
3) Prior treatment with PM01183, topotecan or anthracyclines.
4) Limited-stage patients who are candidates for local or regional therapy, including PCI, thoracic RT or both, must have been offered that option and completed treatment or refused it prior to randomization.
5) Impending need for palliative RT or surgery for pathological fractures and/or for medullary compression within four weeks prior to randomization.
6) Symptomatic, or steroid-requiring, or progressing CNS disease involvement during at least four weeks prior to randomization (asymptomatic, non-progressing patients taking steroids in the process of already being tapered within two weeks prior to randomization are allowed).
7) Concomitant diseases/conditions:
a) History (within one year prior to randomization) or presence of unstable angina, myocardial infarction, congestive heart failure or clinically significant valvular heart disease.
b) Symptomatic or uncontrolled arrhythmia despite ongoing treatment.

c) Patients with any immunodeficiency, including those known to be or have been infected by human immunodeficiency virus (HIV).
d) Ongoing, treatment-requiring, non-neoplastic chronic liver disease of any origin. For hepatitis B, this includes positive tests for both Hepatitis B surface antigen (HBsAg) and quantitative Hepatitis B polymerase chain reaction (PCR). For hepatitis C, this includes positive tests for both Hepatitis C antibody and quantitative Hepatitis C PCR.
e) Active infection or increased risk due to external drainages.
f) Intermittent or continuous oxygen requirement within two weeks prior to randomization. Patients with confirmed or suspected diagnosis of diffuse interstitial lung disease (ILD) or pulmonary fibrosis.
g) Patients with a second invasive malignancy treated with CHT and/or RT. Patients with a previous malignancy that was completely resected with curative intention three or more years prior to randomization, and who has been continuously in remission since then will be permitted.
h) Limitation of the patient*s ability to comply with the treatment or to follow the protocol.
i) Documented or suspected invasive fungal infections requiring systemic treatment within 12 weeks of randomization.
8) Pregnant or breast feeding women

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:	Recruitment stopped
Start date (anticipated):	09-08-2017
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CAV (Cyclophosphamide, Doxorubicin, Vincristin)
Generic name:	CAV (Cyclophosphamide, Doxorubicin, Vincristin)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Doxorubicin- Aurobindo
Generic name:	Doxorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lurbinectedin
Generic name:	Lurbinectedin
Product type:	Medicine
Brand name:	Topotecan
Generic name:	Topotecan
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	20-07-2016
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-03-2017
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-05-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	18-07-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-04-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2015-001641-89-NL
ClinicalTrials.gov	NCT02566993
CCMO	NL55383.100.16

Study results