An Open-Label, Multicenter, Randomized Phase Ib/II Study of Eribulin Mesylate Administered in Combination with Gemcitabine Plus Cisplatin Versus Gemcitabine Plus Cisplatin Alone as First-Line Therapy for Locally Advanced or Metastatic Bladder Cancer

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Objectives:Primary* Phase Ib: to determine the maximum tolerated dose (MTD) recommended for Phase II of eribulin mesylate (eribulin), administered in combination with gemcitabine plus cisplatin in patients with locally advanced or metastatic bladder...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON39526

Source
ToetsingOnline

Brief title
Eribulin Mesylate study for Bladder Cancer

Condition

- Renal and urinary tract neoplasms malignant and unspecified
- Therapeutic procedures and supportive care NEC

Synonym

cancer in the bladder, neoplasia

Research involving
Human

Sponsors and support

Primary sponsor: Eisai
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: Bladder Cancer, Open-Label, Phase Ib/II, Randomized

Outcome measures

Primary outcome

Phase Ib

The maximum tolerated dose (MTD) of eribulin administered in combination with gemcitabine and cisplatin will be determined as follows: If 2 dose limiting toxicities (DLTs) occur at any dose level, that dose will be defined as not tolerated and the MTD will either be defined as the preceding dose or an intermediate dose. To evaluate an intermediate dose, additional dosing cohorts may be added to more accurately define the MTD.

Phase II

Safety parameters will include: AEs; vital signs; ECOG PS; clinical laboratory evaluations; physical examinations; and 12 lead electrocardiograms (ECGs).
All AE data will be collected at each visit using Common Terminology Criteria for Adverse Events (CTCAE) v.4.0.

Preliminary Efficacy:

The primary exploratory efficacy endpoint will be the median progression-free survival (PFS) defined as the time from the date of randomization of a patient until the sooner of (1) the date of first documented progression of such patient*s disease based on Investigator assessments according to RECIST (version 1.1) or (2) the date of such patient*s death due to any cause.

Auxiliary Efficacy:

Secondary exploratory efficacy endpoints include proportion of PFS at Week 12, median time to progression (TTP), overall survival (OS), and objective response rate (ORR).

Subgroup summaries will be carried out for the metastatic disease status strata (visceral metastases stratum, and non-visceral metastases stratum).

Secondary outcome

Not applicable

Study description

Background summary

To determine if eribulin makes a good candidate for the combination therapy with gemcitabine and cisplatin in advanced stage, inoperable bladder cancer.

Study objective

Objectives:
Primary
* Phase Ib: to determine the maximum tolerated dose (MTD) recommended for Phase II of eribulin mesylate (eribulin), administered in combination with gemcitabine plus cisplatin in patients with locally advanced or metastatic bladder cancer;
* Phase II: to evaluate the safety and tolerability of eribulin administered

in combination with gemcitabine plus cisplatin in patients with locally advanced or metastatic bladder cancer.

Secondary
* Phase II: to make a preliminary assessment of the efficacy of eribulin administered in combination with gemcitabine plus cisplatin in patients with locally advanced or metastatic bladder cancer.

Study design

This open-label, multicenter, randomized study will consist of 2 phases:
* Phase Ib: a safety run-in period with 3 ascending doses of eribulin;
* Phase II: a randomized 2-arm design.
Patients will only participate in either the Phase Ib or Phase II portion of the study.

Phase Ib
Patients will be recruited into cohorts, with a minimum of 3 and a maximum of 6 patients per cohort. All patients will receive the same dose of gemcitabine (1000 mg/m2 on Days 1 and 8 of a
21-day cycle) and cisplatin (70 mg/m2 on Day 1) in combination with eribulin (administered on Days 1 and 8 of the cycle). All patients in a cohort will receive the same dose level of eribulin.
The dose level of eribulin will be escalated for additional cohorts unless *2 dose limiting toxicities (DLTs) are reported at the lower dose level(s) prior to enrollment of the next dose level. Dose limiting toxicities are defined as clinically significant adverse events (AEs) occurring *21 days after commencing study treatment and considered by the Investigator to be possibly, probably, or definitely related to study treatment.
If one DLT occurs at any dose level, the cohort will be expanded to include up to a maximum of 6 patients.
If 2 DLTs occur at any dose level, that dose will be defined as not tolerated and the MTD/dose recommended for Phase II, hereafter referred to as the MTD, will either be defined as the preceding dose, or an intermediate dose. To evaluate an intermediate dose, additional dose cohorts may be added to more accurately define the MTD.
A Dose Escalation Committee will determine when no further dose escalation is appropriate and whether the MTD will be defined as a preceding dose or an intermediate dose.

Phase II
Patients will be randomized in a 1:1 ratio to receive either eribulin in combination with gemcitabine plus cisplatin (Arm 1) or gemcitabine plus cisplatin alone (Arm 2). The eribulin dose will be 1 mg/m2 when administered in combination with gemcitabine plus cisplatin, as determined in the Phase Ib portion of the study.
Allocation of patients will be stratified based on metastatic disease status

(patients with visceral metastases versus patients with non-visceral metastases). This stratified randomization will be centrally allocated across all centers via an Interactive Voice Activated Response System (IVRS).
For both the Phase Ib and Phase II portions, 1 cycle of therapy will last 21 days, with a maximum number of 6 cycles. Radiologic examinations including a computed tomography (CT) scan of the chest, abdomen, and pelvis as appropriate (and CT or magnetic resonance imaging [MRI] scan as appropriate), will be performed during Screening and after every 2 cycles (phase 1b) or 6 weeks (phase II) until disease progression. Radiographic assessments should be repeated at withdrawal if the last assessment was obtained >3 weeks from withdrawal of therapy.

Intervention

Not applicable

Study burden and risks

The patients physical situation is assessed by examinations, blood draws during visits and the progress of the disease is measured by radiological assessment. Patients will be asked to complete a bowel movement diary every day, from ~ 14 days before their first treatment until the end of their 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

Inclusion Criteria
Patients may be entered in the study only if they meet all of the following criteria:
1. Male or female patient at least 18 years of age;
2. Histologically or cytologically confirmed, locally advanced Stage 4 (eg., T4b) or metastatic transitional cell cancer of the bladder, including other transitional cell cancers of the urothelium (prostate, urethra, ureter, and renal pelvis);
3. Not previously treated with systemic chemotherapy for metastatic bladder cancer (one regimen of adjuvant or neoadjuvant chemotherapy is permitted). Patients must have a disease-free interval of 6 months after adjuvant therapy;
4. At least 1 site of measurable disease by the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST version 1.1) guidelines;
5. Life expectancy of *3 months;
6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1;
7. Patients must have active bowel function defined as at least 3 bowel movements per week according to subject history and must be willing to maintain a diary of bowel function prior to dosing and continuing through completion of study treatment. Laxatives may be used to maintain adequate bowel function;
8. Patients must have adequate renal function as evidenced by calculated creatinine clearance *55 mL/min per the Cockcroft and Gault formula;
9. Patients must have adequate bone marrow function as evidenced by absolute neutrophil count (ANC) *1.5 X 109/L, hemoglobin *10.0 g/dL (a hemoglobin <10.0 g/dL at Screening is acceptable if it is corrected to *10 g/dL by growth factor or transfusion prior to first dose), and platelet count *100 X 109/L;
10. Patients must have adequate liver function as evidenced by bilirubin *1.5 times the upper limit of the normal range (ULN), and alkaline phosphatase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) *3 X ULN (in the case of liver metastases, *5 X ULN). If there are bone metastases, liver-specific alkaline phosphatase may be separated from the total and used to assess liver function instead of total alkaline phosphatase;
11. Male or female patients of child-producing potential must agree to use double barrier contraception, oral contraceptives, or avoidance of pregnancy measures during the study and for 90 days after the last day of treatment;
12. Females of childbearing potential must have a negative serum pregnancy test at

screening;
13. Females may not be breastfeeding; and
14. Ability to understand and willingness to sign a written informed consent.

Exclusion criteria

Exclusion Criteria
Patients will not be entered in the study for any of the following reasons:
1. Prior treatment with epothilone, ixabepilone, patupilone, vinflunine, halichondrin B, and/or halichondrin B chemical derivatives;
2. History of other malignancies except: (1) adequately treated basal or squamous cell carcinoma of the skin; (2) curatively treated, a) in situ carcinoma of the uterine cervix, or b) prostate cancer, or c) superficial bladder cancer; or (3) other curatively treated solid tumor with no evidence of disease for at least 3 years;
3. Presence of brain metastases, unless the patient has received adequate treatment at least 4 weeks prior to randomization, and is stable, asymptomatic, and off steroids for at least 4 weeks prior to randomization;
4. Received an investigational agent, chemotherapy, biological therapy, hormonal therapy, targeted therapy, or radiotherapy within 30 days prior to commencing study treatment, or have not recovered from all treatment-related toxicities to Common Toxicity Criteria (CTC) Grade less than or equal to 1, except for alopecia;
5. Are currently receiving an investigational agent or any other systemic anticancer treatment, including palliative radiotherapy;
6. Significant cardiovascular impairment (history of congestive heart failure New York Heart Association [NYHA] Grade >2, unstable angina or myocardial infarction within the past 6 months, or serious cardiac arrhythmia);
7. Subjects with a high probability of Long QT Syndrome;
8. Patients with organ allografts requiring immunosuppression;
9. Known active infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV);
10. Hypersensitivity to halichondrin B and/or halichondrin B chemical derivative;
11. Prior pelvic radiation;
12. History of known or suspected peritoneal carcinomatosis with risk of bleeding or perforation, or intraluminal or serosal metastatic lesions with risk of bleeding or perforation of any lesions;
13. History of abdominal adhesions, fistula, diverticulitis, gastrointestinal perforation, intra-abdominal abscess, documented peptic ulcer disease (active gastroesophageal reflux disease/dyspepsia are allowed), or other gastrointestinal conditions with increased risk of perforation;
14. Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v.4.0) Grade * 2 constipation;
15. CTCAE v.4.0 Grade *2 peripheral neuropathy;
16. Have any medical condition that would interfere with the conduct of the study.

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:	Recruitment stopped
Start date (anticipated):	01-08-2010
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	E7389
Generic name:	Eribulin Mesylate

Ethics review

Approved WMO Date:	19-04-2010
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-07-2010
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Approved WMO Date:	03-11-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	18-11-2010
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-07-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	14-07-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-11-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	09-11-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-12-2011
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-12-2011
Application type:	Amendment

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	17-04-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-04-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	20-08-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	22-08-2012
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-03-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	15-05-2013
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO	

Date:	07-07-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-08-2014
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	EUCTR2009-015915-42-NL
CCMO	NL32059.068.10