A multicenter, randomized, open-label Phase 2 study evaluating the safety and efficacy of three different regimens of oral panobinostat in combination with subcutaneous bortezomib and oral dexamethasone in patients with relapsed or relapsed/refractory multiple myeloma who have been previously exposed to immunomodulatory agents

Published: 12-05-2016
Last updated: 17-04-2024

Primary: To assess best overall response rate (ORR) up to 8 cycles. Secondary: ORR, complete response (CR), very good partial response (VGPR), progression free survival (PFS), overall survival (OS), safety, PK, exposure-response (efficacy and safety...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON50473

Source
ToetsingOnline

Brief title
CLBH589D2222

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Kahler's disease, Multiple Myeloma

Research involving
Human

Sponsors and support

Primary sponsor: Secura Bio
Source(s) of monetary or material Support: Novartis Pharma

Intervention

Keyword: BTZ - bortezomib, DACi-Pan-deacetylase inhibitor, multiple myeloma, PAN - panobinostat

Outcome measures

Primary outcome

ORR up to cycle 8.

Secondary outcome

ORR, CR, VGPR, PFS, OS, safety, PK, exposure-response relationship, TTP, TTR,

DOR, QoL.

Study description

Background summary

Multiple myeloma (MM) is a malignant proliferation of plasma cells which accounts for 10% to 15% of all hematologic malignancies and 20% of deaths related to cancers of the blood and bone marrow in adults. Despite a survival improvement from 45 to 60 months after the introduction of new therapies in the past decade (proteasome inhibitors and immunomodulatory drugs, often used in combination with dexamethasone), all patients ultimately progress. The hallmarks of MM are bone marrow failure, renal failure, and bone disease. Panobinostat (PAN) (trade name Farydak) is a histone deacetylase (HDAC)

inhibitor that inhibits the enzymatic activity of HDACs. HDACs catalyse the removal of acetyl groups from the lysine residues of histones and some non-histone proteins. Inhibition of HDAC activity results in increased acetylation of histone proteins, an epigenetic alteration that results in a relaxing of chromatin, leading to transcriptional activation. In vitro, PAN caused the accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Increased levels of acetylated histones were observed in xenografts from mice that were treated with PAN. PAN shows more cytotoxicity towards tumour cells compared to normal cells. PAN has received approval from the FDA and in the EU in 2015 for the treatment of patients with MM who have received at least 2 prior regimens, including bortezomib (BTZ, a proteasome inhibitor) and an immunomodulatory agent.
Results of a pivotal study (study code D2308) demonstrated superiority of the combination of PAN + i.v. BTZ + dexamethasone (DEX) compared to placebo + iv BTZ + DEX in patients with MM who progressed on at least one line of prior therapy. Despite observing efficacy benefit, safety concerns were noted as the most frequent AEs included thrombocytopenia and neutropenia, GI toxicities (primarily diarrhea, nausea and vomiting), and fatigue/asthenia, which were more frequent in the PAN arm compared to the placebo arm. Therefore, further evaluation to improve the safety and tolerability of this combination is needed. At the time of conduct, the study used the intravenous formulation of BTZ but today, the subcutaneous formulation of BTZ has become standard of care as this formulation has been shown to be associated with less GI toxicity and peripheral neuropathy compared to the i.v. formulation, albeit without compromising efficacy.
The purpose of the present study is to investigate the safety and efficacy of three different regimens of PAN (20 mg 3 times per week, 20 mg two times per week, and 10 mg 3 times per week) in combination with s.c. BTZ and DEX and to identify the optimal regimen of PAN.

Study objective

Primary:
To assess best overall response rate (ORR) up to 8 cycles.
Secondary:
ORR, complete response (CR), very good partial response (VGPR), progression free survival (PFS), overall survival (OS), safety, PK, exposure-response (efficacy and safety) relationship, time to progression (TTP), time to response (TTR), duration of response (DOR), quality of life (QoL).

Study design

Multicenter phase II open-label study. 3 regimens of oral panobinostat (PAN) in combination with subcutaneous bortezomib and oral dexamethasone. Cycles of 3 weeks. No treatment in week 3.

Randomization 1:1:1 to:
• PAN 20 mg 3 times per week
• PAN 20 mg 2 times per week
• PAN 10 mg 3 times per week.
BTZ injections (1.3 mg/m2): First 4 cycles: twice per week, thereafter: once per week (if age <=75 years) of once per week from the start onwards (if age >75 years).
DEX tablets (10 [>75 y] -20 [<=75 y] mg/day): on the day of and the day after an BTZ injection.
Treatment until disease progression or unacceptable side effects.
Follow-up for survival.
240 subjects

Intervention

Treatment with PAN, BTZ and DEX.

Study burden and risks

Risk: Adverse effects of the combination of PAN, BTZ and DEX.
Burden: Cycles of 3 weeks. Cycle 1-4: 4 visits per cycle, from cycle 5 onwards: 2 visits per cycle. Duration mostly 2 hours.
S.c. injections (1 ml): once or twice per week during cycles 1-4 (age dependent), thereafter once per week for all subjects.
Physical examination: once per cycle.
Blood tests (up to 40 ml/occasion): every visit.
collection of urine during 24 h: every cycle.
ECG: once per cycle.
Questionnaires (QLQ-C30 and FACT/GOG): day 1 of cycle 1, 3, 5 and 7 and every 4th cycle thereafter.
CT-/MRI scan: at baseline, more frequently if needed.
Electronic diaries for diarrhea management and medication intake at home.
Bone marrow puncture: twice, more frequently if needed.

Contacts

Public
Secura Bio

1995 Village Center Cir -
Las Vegas NV 89134
US
Scientific
Secura Bio

1995 Village Center Cir -
Las Vegas NV 89134
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Previous diagnosis of Multiple Myeloma based on IMWG 2014 definition, see protocol page 36 for details
- Measurable disease based on protein assessment. Definition see protocol page 37.
- 1 to 4 prior lines of therapy. Present requirement for re-treatment of relapsed myeloma or relapsed-and-refractory myeloma. Definitions: see protocol page 36
- Prior IMiD exposure (thalidomide, lenalidomide and/or pomalidomide)
- ECOG performance status 0-1-2.
- >= 18 years old
- Measurable disease based on central lab assessment at screening
- Acceptable lab values prior to starting study treatment, see protocol page 37 for details

Exclusion criteria

• Primary refractory myeloma. See protocol page 38 for details.
• Refractory to bortezomib.
• Any concomitant anti-cancer therapy (other than BTZ/Dex; bisphosphonates are permitted
only if commenced prior to the start of screening period).
• Unresolved diarrhea >= CTCAE grade 2 or presence of medical condition associated with

chronic diarrhea.
• Allogeneic stem cell transplantation with graft versus host disease either active or requiring immunosuppression.
• Grade >= 2 peripheral neuropathy or grade 1 peripheral neuropathy with pain on clinical examination at screening.
• Prior treatments: see protocol page 38-39 for details (DAC inhibitors, anti-myeloma chemotherapy, biologicals, stem cell transplantation).
• Major surgery within 2 weeks.
• Uncontrolled heart disease and recent cardiac events. Other uncontrolled conditions. See protocol page 39 for details.
• HIV, hepatitis B-C: activity or history.
• Pregnancy, lactation, insufficient contraception for females of childbearing potential.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-02-2017
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Farydak

Generic name:	panobinostat
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	NVT
Generic name:	dexamethasone
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Velcade
Generic name:	bortezomib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-05-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-06-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-08-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-02-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-04-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2015-001564-19-NL
CCMO	NL56070.029.16

Study results

Results posted: 02-02-2024

First publication
15-12-2023