Phase 3 Study of Ibrutinib in Combination with Venetoclax in Subjects with Mantle Cell Lymphoma

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Primary Objective: Safety Run-in Period:To evaluate the occurrence of tumor lysis syndrome (TLS) and doselimiting toxicities (DLTs) with the concurrent administration of ibrutinib and venetoclax.Randomization Phase:To evaluate whether the...

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

Summary

ID

NL-OMON52949

Source
ToetsingOnline

Brief title
PCYC-1143-CA

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Mantle Cell lymphoma, Non-Hodgkin lymphoma

Research involving
Human

Sponsors and support

Primary sponsor: Pharmacyclics

Source(s) of monetary or material Support: pharmaceutical company

Intervention

Keyword: Mantle Cell Lymphoma, Non Hodgkins lymphoma

Outcome measures

Primary outcome

Randomization Phase:

To evaluate whether the combination of ibrutinib and venetoclax will result in prolongation of PFS compared to ibrutinib and placebo in subjects with relapsed or refractory MCL.

Treatment-naive Open-label Arm Primary Endpoint

The primary efficacy endpoint of the treatment-naive open-label arm is the complete response (CR) rate based on the best overall response according to the Revised Response Criteria for Malignant Lymphoma

(Cheson 2014) - every 3 months for the first year starting with week 13; every 4 months during the second and third years, and every 6 months thereafter until PD

Secondary outcome

Secondary Objective:

Safety Run-in Period: To evaluate response (partial and complete response), progression-free survival (PFS), duration of response (DOR), and overall survival (OS).

Randomization Phase:

• To evaluate whether the combination of ibrutinib and venetoclax will increase the complete response (CR) rate, the overall response rate (ORR), the minimal residual disease (MRD) negative remission rate in subjects who were MRD positive at screening and achieve CR, OS, DOR, and time-to-next treatment (TTNT) compared to ibrutinib and placebo.

• To evaluate the frequency, severity, and relatedness of adverse events (AEs); frequency, severity and management of TLS; AEs requiring dose reductions and/or discontinuation of study drug, or leading to death.

• To determine the pharmacokinetics (PK) of ibrutinib and venetoclax.

• To evaluate whether the combination of ibrutinib and venetoclax will improve quality of life using a Health-related quality of life questionnaire (FACT-Lym) compared to ibrutinib and placebo.

Treatment-Naive Open-Label Arm Secondary Endpoints

•Overall response rate (ORR), defined as CR or PR according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2014) - every 3 months for the first year starting with week 13; every 4 months during the second and third years, and every 6 months thereafter until PD

•Duration of Response (DOR), defined for subjects who achieve an overall response as the time from the first occurrence of response (CR or PR) to disease progression or death, whichever occurs first - every 3 months for the first year starting with week 13; every 4 months during the second and third years, and every 6 months thereafter until PD

•Duration of CR, defined for subjects who achieve CR as the time from the first

occurrence of CR to disease progression or death, whichever occurs first - every 3 months for the first year starting with week 13; every 4 months during the second and third years, and every 6 months thereafter until PD

•MRD-negative remission rate in subjects who achieve CR. MRD-negative remission is defined the same as described in Section 10.2.3 of the Protocol - every 3 months for the first year starting with week 13; every 4 months during the second and third years, and every 6 months thereafter until PD

•PFS, defined as the time from the date of the first dose of study treatment to the date of disease progression using the Revised Response Criteria for Malignant Lymphoma (Cheson 2014), or death from any cause, whichever occurs first - every 3 months for the first year starting with week 13; every 4 months during the second and third years, and every 6 months thereafter until PD

•OS, defined as the time from the date of the first dose of study treatment to death from any cause - after progression every 12 weeks until death

•TTNT, defined as the duration from the date of the first dose of study treatment to the start date of any anti-lymphoma treatment subsequent to study treatment - after progression every 12 weeks until death

Study description

Background summary

Mantle cell lymphoma (MCL) accounts for about 6-9% of all non-Hodgkin lymphoma (NHL) cases in the Western world. The annual incidence of MCL has increased during recent decades to 1-2/100,000. MCL occurs more frequently in older adults. Most patients with MCL are men (median age: 65 years) who present with advanced stage disease (ie, Stage III or IV). Though the clinical course of MCL may be somewhat indolent at diagnosis, the course invariably becomes aggressive

over time. Unlike other NHLs, MCL is considered incurable with standard therapies and is associated with a poor prognosis and a relatively short median overall survival.

Current initial therapy for the treatment of MCL includes cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (Hyper-CVAD), often in combination with rituximab (R-CHOP or R-Hyper CVAD). In recent years, treatment with bendamustine and rituximab has gained increasing use following studies showing that this combination significantly prolongs PFS, while maintaining a favorable safety profile among patients with previously untreated MCL.

In cases of early relapses or in patients with refractory disease, newer targeted approaches should be strongly considered. Three non-cytotoxic drugs, ibrutinib, bortezomib and lenalidomide, are FDA approved for previously treated patients with MCL in the US. In the European Union, approved treatment in the relapsed and refractory MCL setting was limited to temsirolimus until the approval of ibrutinib in 2014. Based on registration trials, the ORR for these drugs are 68% (21% CR) with ibrutinib, 33% (8% CR) with bortezomib, 28% (8% CR) with lenalidomide, and 22% (2% CR) with temsirolimus.

These drugs are being combined with rituximab and incorporated into standard therapeutic and maintenance regimens showing some improved efficacy. Despite the fact that results from ibrutinib showed marked improvement over temsirolimus, the median PFS of approximately 14 months underscores the need to improve further on the dismal outcome for relapsed MCL patients, with a median PFS of 13.9, 6.5, 4 and
4.8 months, respectively.

Based on the preliminary data showing a CR rate of 70% with an acceptable safety profile observed in an ongoing study of ibrutinib and venetoclax in patients with relapsed or refractory MCL (Tam 2016) coupled with the durability of responses observed with ibrutinib monotherapy and venetoclax monotherapy in patients with relapsed or refractory MCL who achieved CR observed with each (Rule 2016, Gerecitano 2015), the combination of ibrutinib and venetoclax is expected to induce deep and durable responses in patients with relapsed/refractory MCL.

In treatment-naive MCL, the standard of care for patients that
are >=65 years of age and transplant-ineligible is BR or a variety of other options based on fitness
level. The reported overall response rates with different therapeutic approaches for treatment naive
MCL patients with varying fitness levels vary from 75 - 94%, the corresponding CR rates vary from 35 - 72% and for BR, one of the most commonly used therapies used in the transplant-ineligible and less fit treatment-naive MCL population,

are
approximately around 50%. Patients with a TP53 mutation are chemo-insensitive and therefore have limited treatment
options.

Based on recent encouraging results in a study of ibrutinib and venetoclax including 24 patients, with a median age of 68 years (CR rate of 71% overall and CR rate of 50% in patients with a TP53 mutation), among which 1 treatment-naive MCL patient with a TP53 mutation who responded (Tam2018), it is of interest to explore the combination of ibrutinib and venetoclax in treatment-naive MCL in patients that are >=65 years of age and transplant-ineligible and in
patients with a TP53 mutation.

Study objective

Primary Objective:
Safety Run-in Period:
To evaluate the occurrence of tumor lysis syndrome (TLS) and doselimiting toxicities (DLTs) with the concurrent administration of ibrutinib and venetoclax.
Randomization Phase:
To evaluate whether the combination of ibrutinib and venetoclax will result in prolongation of PFS compared to ibrutinib and placebo in subjects with relapsed or refractory MCL.

Treatment-naive Open-label Arm:
To evaluate the complete response (CR) rate with the combination of ibrutinib and venetoclax in subjects with treatment-naive MCL

Study design

This Phase 3 multinational, randomized, double-blind study is designed to compare the efficacy and safety of the combination of ibrutinib and venetoclax vs. ibrutinib and placebo in subjects with MCL.

A separate open-label arm is designed to explore the efficacy and safety of the combination of
ibrutinib and venetoclax in subjects with treatment-naive MCL. Approximately 50 subjects >=65 years and approximately 25 subjects less than 65 years of age with a TP53 mutation will be enrolled.

Intervention

Ibrutinib
• 560 mg of ibrutinib dosed orally once daily. Ibrutinib may be supplied either

as 560 mg tablet (1 tablet dosed once daily) or as 140 mg capsules (4 capsules dosed once daily)
Venetoclax
• Orally once daily venetoclax at a target dose of 400 mg (4 X 100 mg).
Placebo (only in Safety Run-in and Randomization Phase)
• Oral once daily matching placebo for venetoclax at a target dose of 400 mg (4 X 100 mg).

Ibrutinib 560 mg (4 x 140-mg capsules) is administered orally once daily. The ibrutinib capsules are to be taken with venetoclax(/placebo tablets) at approximately the same time each day with a meal and water.

In order to assess tumor lysis syndrome (TLS) and dose limiting toxicity (DLT), 6 patients will initially be treated with ibrutinib at 560 mg daily and venetoclax starting at 20 mg and gradually ramped up to a target dose of 400 mg once daily over a 5-week period.

Study burden and risks

Several in vitro studies have shown ibrutinib and venetoclax to be an active combination. In one study, MCL cell lines and leukemic patient cells were exposed to ibrutinib, venetoclax and the combination for 72 hours. The combination substantially increased induction of apoptosis compared to each agent alone (combo: 23%, ibrutinib: 3.8%, venetoclax: 3.0%).
A separate study using MCL cell lines confirmed the synergistic effect of ibrutinib and
venetoclax on proliferation inhibition and apoptosis through perturbation of the BTK, AKT and
BCL2 pathways providing further mechanistic rationale for co-targeting of these two oncogenic pathways.

Supportive in vivo data is derived from a CCMCL1/NSG mouse model where the ibrutinib and
venetoclax combination was tested. The combination produced apoptosis of MCL tumor cells, which was associated with a down-regulation of SOX11 and PAX5. Simultaneous downregulation of MCL1 via ibrutinib and targeting of BCL2 was hypothesized to contribute to the in vitro synergism and in vivo activity observed in this report.
With respect to venetoclax monotherapy activity, in clinical trial M12-175, venetoclax was tested in 28 subjects with relapsed/refractory MCL at target doses of 200 to 1200 mg. The ORR was found to be 75% with a CR rate of 21% (Gerecitano 2015). Based on these data and prior
ibrutinib studies, the ongoing AIM Trial (ABT-199 and ibrutinib in MCL) is evaluating the combination of ibrutinib at 560 mg and venetoclax at a target dose of 400 mg in subjects with relapsed and refractory MCL. This study is using a 4-week venetoclax ramp-up after 4 weeks of
ibrutinib monotherapy. Twenty-one subjects have completed response assessments

at the
primary endpoint landmark of 16 weeks; 10 subjects achieved confirmed CR (including MRD
clearance), 4 subjects achieved unconfirmed CR, and 4 subjects achieved PR (Tam 2017). These results display a high initial response rate for the ibrutinib and venetoclax combination.

Contacts

Public
Pharmacyclics

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US
Scientific
Pharmacyclics

1000 Gateway Boulevard .
South San Francisco CA 94080
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

For SRI and Randomization Phase
Disease-Related
• Pathologically confirmed MCL (in tumor tissue), with documentation of either overexpression of cyclin D1 in association with other relevant markers (eg,

CD19, CD20, PAX5, CD5) or evidence of t(11;14) as assessed by cytogenetics, fluorescent in situ hybridization (FISH), or polymerase chain reaction (PCR).
• At least 1 measurable site of disease on cross-sectional imaging that is >=2.0 cm in the longest diameter and measurable in 2 perpendicular dimensions per CT
• At least 1, but no more than 5, prior treatment regimens for MCL including at least 1 prior rituximab/anti-CD20 containing regimen
• Failure to achieve at least partial response (PR) with, or documented disease progression after, the most recent treatment regimen
• Subjects must have adequate fresh or paraffin embedded tissue., Laboratory
• Adequate hematologic function
• Adequate hepatic and renal function, Demographic
• Men and women >= 18 years of age
• Eastern Cooperative Oncology Group (ECOG) performance status (PS) of <=2.

For Treatment-naive Open-label Arm:
1. Pathologically confirmed treatment-naive MCL (tumor tissue), with documentation of either
overexpression of cyclin D1 in association with other relevant markers (eg, CD19, CD20,
PAX5, CD5) or evidence of t(11;14), as assessed by cytogenetics, fluorescent in situ
hybridization (FISH), or polymerase chain reaction (PCR)
• A report from the local laboratory is acceptable if available; however, it must be reviewed
and approved by the central pathology laboratory to verify the above criteria prior to
enrollment
• If the report from the local laboratory is not available, a tumor block or slides must be sent
to the central pathology laboratory for confirmation of the MCL diagnosis prior to
enrollment.
2. Men and women >=18 years of age, with a TP53 mutation
3. At least 1 measurable site of disease that is >=2.0 cm in the longest diameter and measurable in
2 perpendicular dimensions per CT
4. Subjects must have adequate fresh or paraffin-embedded tissue
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of <= 2
6. Adequate hematologic function independent of transfusion and growth factor support for at
least 7 days prior to first dose, with the exception of pegylated G-CSF (pegfilgrastim) and
darbepoeitin which require at least 14 days prior to the first dose defined as:
• Absolute neutrophil count (ANC) >1000 cells/mm3 (1.0 x 109/L)
• Platelet count >50,000 cells/mm3 (50 x 109/L)
• Hemoglobin >8.0 g/dL
7. Adequate hepatic and renal function defined as:

• Serum aspartate transaminase (AST) or alanine transaminase (ALT) <=3.0 x upper limit of
normal (ULN)
• Estimated Creatinine Clearance (CrCl) >=30 mL/min (Cockcroft-Gault)
• Bilirubin <=1.5 x ULN (unless bilirubin rise is due to Gilbert*s syndrome or of non-hepatic
origin)
8. Prothrombin time (PT) or International normal ratio (INR) <1.5 x upper limit of normal
(ULN) and PTT (activated partial thromboplastin time [aPTT]) <1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder). When treated with warfarin
or other vitamin K antagonists, then INR <=3.0
9. Male and female subjects of reproductive potential who agree to use both a highly effectivemethod of birth control (eg, implants, injectables, combined oral contraceptives, some
intrauterine devices [IUDs], complete abstinence5, or sterilized partner) and a barrier method
(eg, condoms, cervical ring, sponge, etc) during the period of therapy and for 90 days after the
last dose of study drug

Exclusion criteria

For SRI and Randomization Phase
Disease-Related
• History or current evidence of central nervous system lymphoma Concurrent Conditions
• Concurrent enrollment in another therapeutic investigational study or prior therapy with ibrutinib or other BTK inhibitors
• Prior treatment with venetoclax or other BCL2 inhibitors
• Anticancer therapy including chemotherapy, radiotherapy, small molecule and investigational agents <=21 days prior to receiving the first dose of study drug
• Treatment with any of the following within 7 days prior to the first, dose of study drug:
• moderate or strong cytochrome P450 3A (CYP3A) inhibitors
• moderate or strong CYP3A inducers

For Treatment-naive Open-label Arm:
1. Blastoid variant of MCL
2. History or current evidence of central nervous system lymphoma
3. Concurrent enrollment in another therapeutic investigational study or prior therapy, including
ibrutinib or other BTK inhibitors
4. Prior treatment with venetoclax or other BCL2 inhibitors

5. History of other malignancies, except:
• Malignancy treated with curative intent and with no known active disease present for
>=3 years before the first dose of study drug and felt to be at low risk for recurrence by
treating physician
• Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of
disease.
• Adequately treated carcinoma in situ without evidence of disease.
6. Vaccinated with live, attenuated vaccines within 4 weeks of the first dose of study drug
7. Clinically significant infection requiring IV systemic treatment that was completed <=14 days
before the first dose of study drug
8. Any uncontrolled active systemic infection
9. Known bleeding disorders (eg, von Willebrand*s disease or hemophilia)
10. History of stroke or intracranial hemorrhage within 6 months prior to enrollment
11. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus
(HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, or
hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before
enrollment. Those who are hepatitis B surface antigen (HBsAg) or PCR positive will be
excluded.
12. Major surgery within 4 weeks of the first dose of study drug.
13. Any life-threatening illness, medical condition, or organ system dysfunction that, in the
investigator*s opinion, could compromise the subject*s safety or put the study outcomes at
undue risk
14. Currently active, clinically significant cardiovascular disease, such as uncontrolled
arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart
Association Functional Classification; or a history of myocardial infarction, unstable angina, or
acute coronary syndrome within 6 months prior to randomization
15. Unable to swallow capsules or tablets, or malabsorption syndrome, disease significantly
affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic
inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction

16. Treatment with any of the following within 7 days prior to the first dose of study drug:
• Moderate or strong cytochrome P450 3A (CYP3A) inhibitors
• Moderate or strong CYP3A inducers
17. Administration or consumption of any of the following within 3 days prior to the first dose
of study drug:
• grapefruit or grapefruit products
• Seville oranges (including marmalade containing Seville oranges)
• star fruit
18. Known allergy to xanthine oxidase inhibitors and/or rasburicase for subjects with known
risk factors (as defined by high tumor burden and/or diminished renal function, as detailed in
Study Design section above) for TLS
19. Subjects with chronic liver disease with hepatic impairment Child-Pugh class B or C
20. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during
the study or for approximately 90 days after the last dose of study drug
21. Male subject who is considering fathering a child or donating sperm during the study or for
approximately 90 days after the last dose of study drug
22. Unwilling or unable to participate in all required study evaluations and procedures
23. Unable to understand the purpose and risks of the study and to provide a signed and dated
informed consent form (ICF) and authorization to use protected health information
(in accordance with national and local subject privacy regulations)
24. Known hypersensitivity to the active ingredient or other components of one or more study
Drugs

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-11-2018
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Imbruvica
Generic name:	Ibrutinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Venclexta
Generic name:	Venetoclax
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-01-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-07-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-08-2018

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-10-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-11-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	22-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-01-2021
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Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Application type:	Amendment
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Application type:	Amendment
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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Approved WMO Date:	16-05-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2017-000129-12-NL
ClinicalTrials.gov	NCT03112174
CCMO	NL63543.078.17