A PHASE IB/II STUDY OF COBIMETINIB ADMINISTERED AS SINGLE AGENT AND IN COMBINATION WITH VENETOCLAX, WITH OR WITHOUT ATEZOLIZUMAB, IN PATIENTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA

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Primary ObjectiveTo evaluate the preliminary safety and tolerability and the preliminary efficacy of cobimetinib administered as single agent (Arm A), cobimetinib + venetoclax (Arm B), and cobimetinib + venetoclax + atezolizumab (Arm C)Secondary...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Plasma cell neoplasms
Study type	Interventional

Summary

ID

NL-OMON44406

Source
ToetsingOnline

Brief title
Cobimetinib in Patients with Relapsed and Refractory Multiple Myeloma

Condition

- Plasma cell neoplasms

Synonym
multiple myeloma

Research involving

Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: F. Hoffman - La Roche Ltd.

Intervention

Keyword: Atezolizumab, Cobimetinib, multiple myeloma, Venetoclax

Outcome measures

Primary outcome

• Incidence, nature, and severity of adverse events, graded according to NCI CTCAE, v4.0; laboratory data

• ORR (sCR, CR, VGPR, PR) as determined by the investigator using the IMWG response criteria (Kumar et al. 2016) in the safety population and biomarker-selected population

Secondary outcome

• CBR defined as MR or better

• PFS defined as the time from randomization to the first occurrence of disease progression or relapse as determined by the investigator using the IMWG criteria or death from any cause during the study, whichever occurs first

• DOR applies to patients achieving at least a PR, and is measured from the first observation of PR to the time of disease progression; deaths not due to progression will be censored

• OS defined as the time from randomization until death from any cause

Study description

Background summary

Multiple myeloma (MM) is a B-cell neoplasm characterized by the clonal expansion of malignant plasma cells in the bone marrow leading often to an excessive production of monoclonal proteins (M-proteins). The expansion of malignant plasma cells and the accumulation of the M-protein lead to the end-organ damage that characterizes evolution of the disease. MM represents 15% of all hematologic cancers. There are approximately 86,000 new cases of MM annually worldwide.
Treatment of MM consists of combination regimens based on proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and corticosteroids administered in different lines of therapy. Recent advances in the treatment of MM have included a new generation of PIs (e.g., carfilzomib) and IMiDs (e.g., pomalidomide), and more recently, monoclonal antibodies such as daratumumab and elotuzumab, which target the CD38 and the signaling lymphocytic activation molecule F7 (SLAMF7).

Cobimetinib is a potent and selective inhibitor of MEK1 and MEK2. Cobimetinib (Cotellic®) is approved for use with vemurafenib for the treatment of advanced BRAF V600 mutated melanoma in the European Union, United States, and Switzerland, as well as other countries

Study objective

Primary Objective
To evaluate the preliminary safety and tolerability and the preliminary efficacy of cobimetinib administered as single agent (Arm A), cobimetinib + venetoclax (Arm B), and cobimetinib + venetoclax + atezolizumab (Arm C)

Secondary Efficacy Objective
To further evaluate the efficacy of cobimetinib administered as single agent (Arm A), cobimetinib + venetoclax (Arm B), and cobimetinib + venetoclax + atezolizumab (Arm C)

Exploratory Efficacy Objective
To evaluate the time elapsed before requiring the start of further anti-myeloma treatment

Pharmacokinetic Objective
To characterize the pharmacokinetics of cobimetinib (Arm A), to characterize the pharmacokinetics of cobimetinib and venetoclax when administered together (Arm B), and to characterize the pharmacokinetics of cobimetinib, venetoclax, and atezolizumab when administered together (Arm C)

Immunogenicity Objective
To evaluate the immune response to atezolizumab administered in Arm C

Exploratory Immunogenicity Objective
To evaluate the potential effects of ADAs

Exploratory Biomarker Objectives
• To identify biomarkers that are predictive of response to cobimetinib, venetoclax, and atezolizumab, such as RAS mutation, t(11;14) translocation, Bcl-2 family proteins, and pretreatment immune contexture
• Identification and profiling of biomarkers associated with disease biology; the mechanisms of action of cobimetinib alone (Arm A), cobimetinib + venetoclax (Arm B), or cobimetinib + venetoclax + atezolizumab (Arm C); mechanism of resistance to drugs in all the arms; pharmacodynamics; prognosis and improvement of diagnostic assays
• Determine impact of MRD measurements with patient response and survival

Study design

This is an open-label, randomized, multicenter, triple-arm Phase Ib/II study designed to assess the efficacy, safety, tolerability, and pharmacokinetics of cobimetinib administered as a single agent (Arm A), cobimetinib plus venetoclax (Arm B), and cobimetinib plus venetoclax plus atezolizumab (Arm C) in patients with R/R MM.
Two successive cohorts will evaluate the safety of cobimetinib plus venetoclax (n = 6) and that of cobimetinib plus venetoclax plus atezolizumab (n = 6) in the selected population during the safety run-in phase of the study. Once the dose levels have demonstrated acceptable safety during this phase, randomization will begin for all treatment arms (Arms A, B, and C).

Intervention

there are 3 treatment arms is the study
Arm A: administration of cobimetinib as monotherapy
Arm B: cobimetinib plus venetoclax
Arm C: cobimetinib plus venetoclax plus atezolizumab

Study burden and risks

There can be side effects from the drugs or procedures used in this study . Side effects can vary from mild to very serious and may vary from person to person. Everyone taking part in the study will be watched carefully for any side effects. However, Roche, the study doctor, and other doctors do not know all of the side effects that could occur.

Please refer to Appendix D and E for side effects known to be associated with

study drugs and risks associated with study design and medical procedures.

Contacts

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Scientific
Hoffmann-La Roche

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Age >= 18 years
- Eastern Cooperative Oncology Group Performance Status of 0, 1, or 2
- Life expectancy of at least 12 weeks
- Documented MM as defined by criteria such as monoclonal plasma cells in the bone marrow >= 10% or presence of a biopsy-proven plasmacytoma and Measurable disease such as Serum M-protein level >= 1.0 g/dL or urine monoclonal protein (M-protein) level >= 200 mg/24 hours or light chain MM as serum Ig free light chain (FLC) >=10 mg/dL and abnormal serum Ig kappa/lambda FLC ratio
- Received 3 to 5 prior lines of therapy for MM, including a proteasome inhibitor (PI) and an

immunomodulatory drug (IMiD)
- Achieved a response to at least one prior regimen
- Documented evidence of progressive disease on or after their last prior therapy, or patients who were intolerant to their last prior therapy
- Toxicities resulting from previous therapy that must be resolved or stabilized to Grade 1
- Laboratory values such as hemoglobin level >= 7.5 g/dL (>= 5 mmol/L), platelet count >= 50,000/mm3 or >= 30,000 if bone marrow plasma cell >= 50%, absolute neutrophil count >= 1000/mm3, AST and ALT >= 2.5 × the upper limit of normal (ULN), total bilirubin = 40 mL/min; determined via urine collection for 24-hour creatinine clearance or by the Cockcroft-Gault formula
- For women of childbearing potential: agreement to remain abstinent or use two contraceptive methods with a failure rate of < 1% per year during the treatment period and for at least 3 months after the last dose of cobimetinib, 1 month after the last dose of venetoclax, and 5 months after the last dose of atezolizumab
- For men, agreement to remain abstinent or use a condom, and agreement to refrain from donating sperm during the treatment period and for at least 3 months after the last dose of cobimetinib

Exclusion criteria

- Anti-myeloma treatment within 14 days or 5 PK half-lives of the treatment, whichever is longer, before the date of randomization
- Completion of autologous stem cell transplant within 100 days prior to the date of randomization
- Prior allogeneic stem cell transplant as well as prior solid organ transplant
- Spinal cord compression not definitively treated with surgery and/or radiation
- Prior treatment with MEK inhibitors, Bcl-2 inhibitors, or immune checkpoint inhibitor therapies including anti*CTLA-4, anti*PD-1 or anti*PD-L1
- Treatment with systemic immunostimulatory agents within 28 days or 5 half-lives of the drug (whichever is longer) prior to initiation of study treatment
- Treatment with systemic immunosuppressive medication within 14 days prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study with the exceptions as patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication are eligible for the study after Medical Monitor approval has been obtained
- Surgical procedure or significant traumatic injury within 28 days prior to enrollment, or anticipation of need for major surgical procedure during the course of the study and minor surgical procedure within 7 days
- Prior radiation therapy within 14 days prior to study enrollment and/or persistence of radiation-related adverse effects
- History or evidence of retinal pathology on ophthalmic examination that is considered a risk factor for neurosensory retinal detachment/central serous chorioretinopathy, retinal vein occlusion (RVO), or neovascular macular degeneration, serous retinopathy, Evidence of ongoing serous retinopathy or RVO at baseline

- Left ventricular ejection fraction below institutional lower limit of normal
- History of clinically significant cardiovascular dysfunction
- Any previous venous thromboembolism > Grade 3 within 12 months of study enrollment
- INR > 1.5 and aPTT > 1.5 × ULN within 7 days prior to study enrollment.
- History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding, severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins (for patients in Arm C only), history of other malignancy that could affect compliance with the protocol or interpretation of results and history of malabsorption or other condition that would interfere with absorption of study drugs
- Active or history of autoimmune disease or immune deficiency
- Positive test results for hepatitis B (hepatitis B surface antigen [HBsAg] and/or total hepatitis B core antibody [HBcAb]) or hepatitis C virus (HCV) antibody
- Treatment with a live, attenuated influenza vaccine (e.g., FluMist) within 28 days prior to Cycle 1 Day 1, at any time during the study, and for at least 5 months after the last dose of study drug (for patients in Arm C only)
- Received strong CYP3A inhibitors, moderate CYP3A inhibitors strong CYP3A inducers, and moderate CYP3A inducers within 7 days prior to the initiation of study treatment
- Foods/supplements are prohibited at least 7 days prior to initiation of and during study treatment in St John*s wort or hyperforin, Grapefruit juice
- Pregnant or lactating, or intending to become pregnant during the study

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine

Brand name:	ABT-199 (A-1195425.0)
Generic name:	venetoclax, Venclyxto
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Cobimetinib (GDC-0973)
Generic name:	Cotellic
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	RO5541267
Generic name:	Atezolizumab

Ethics review

Approved WMO Date:	24-08-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-03-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-05-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-06-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-07-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-10-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2019
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	EUCTR2017-000830-68-NL
CCMO	NL62064.018.17