A Study of the Bruton's Tyrosine Kinase Inhibitor Ibrutinib Given in Combination With Bendamustine and Rituximab in Patients With Newly Diagnosed Mantle Cell Lymphoma

Purpose

The purpose of this study is to evaluate the efficacy and safety of ibrutinib given in combination with bendamustine and rituximab in patients 65 years of age or older with newly diagnosed mantle cell lymphoma.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantle Cell Lymphoma</td>
<td>Drug: Bendamustine</td>
<td>Phase 3</td>
</tr>
<tr>
<td></td>
<td>Drug: Rituximab</td>
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<tr>
<td></td>
<td>Drug: ibrutinib</td>
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<td></td>
<td>Drug: Placebo</td>
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</table>

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator)
Primary Purpose: Treatment

Official Title: A Randomized, Double-blind, Placebo-controlled Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor, PCI-32765 (ibrutinib), in Combination With Bendamustine and Rituximab (BR) in Subjects With Newly Diagnosed Mantle Cell Lymphoma

Resource links provided by NLM:

MedlinePlus related topics: Lymphoma

Drug Information available for: Tyrosine, Bendamustine hydrochloride, Bendamustine, Rituximab, ibrutinib

Genetic and Rare Diseases Information Center resources: Lymphosarcoma, Mantle Cell Lymphoma

U.S. FDA Resources

Further study details as provided by Janssen Research & Development, LLC:

Primary Outcome Measures:
- Progression-free survival [Time Frame: Up to the end-of-study visit until 265 progression-free survival events have been observed (up to
Secondary Outcome Measures:

- Overall survival [Time Frame: Up to the end-of-study visit until 60% of all enrolled patients have died (up to 7 years after the last patient is randomized)] [Designated as safety issue: No]
- Overall response rate [Time Frame: Up to the end-of-study visit up to 7 years after the last patient is randomized] [Designated as safety issue: No]
- Number of participants with change in Lym subscale scores of the Functional Assessment of Cancer Therapy-Lymphoma (FACT Lym) [Time Frame: Screening, 1 of the first 6 cycles, then every 12 weeks in the first 12 months, thereafter every 16 weeks up to 7 years after the last patient is randomized] [Designated as safety issue: No]
- Minimal residual disease negative rate [Time Frame: For participants with complete response, every 12 weeks in the first 12 months, thereafter every 16 weeks and at disease progression or up to the end-of-study visit (up to 7 years after the last patient is randomized)] [Designated as safety issue: No]
- Duration of response [Time Frame: Up to the end-of-study visit up to 7 years after the last patient is randomized] [Designated as safety issue: No]
- Time-to-next treatment [Time Frame: Up to the end-of-study visit up to 7 years after the last patient is randomized] [Designated as safety issue: No]
- Number of participants affected by an adverse event [Time Frame: Up to 30 days after the last dose of any study treatment] [Designated as safety issue: Yes]
- Oral plasma clearance of ibrutinib as derived from population pharmacokinetics [Time Frame: Predose on Day 2 Cycles 1-3, postdose on Day 2 Cycles 1 and 2 at 1, 2, and 4 hours after administration of ibrutinib study dose] [Designated as safety issue: No]
- Oral volume of distribution at steady state of ibrutinib as derived from population pharmacokinetics [Time Frame: Predose on Day 2 Cycles 1-3, postdose on Day 2 Cycles 1 and 2 at 1, 2, and 4 hours after administration of ibrutinib study dose] [Designated as safety issue: No]
- Area under the concentration curve of ibrutinib as derived from population pharmacokinetics [Time Frame: Predose on Day 2 Cycles 1-3, postdose on Day 2 Cycles 1 and 2 at 1, 2, and 4 hours after administration of ibrutinib study dose] [Designated as safety issue: No]
- Minimum observed plasma concentration of ibrutinib as derived from population pharmacokinetics [Time Frame: Predose on Day 2 Cycles 1-3, postdose on Day 2 Cycles 1 and 2 at 1, 2, and 4 hours after administration of ibrutinib study dose] [Designated as safety issue: No]
- Maximum observed plasma concentration of ibrutinib as derived from population pharmacokinetics [Time Frame: Predose on Day 2 Cycles 1-3, postdose on Day 2 Cycles 1 and 2 at 1, 2, and 4 hours after administration of ibrutinib study dose] [Designated as safety issue: No]

Enrollment: 523
Study Start Date: May 2013
Estimated Study Completion Date: October 2019
Estimated Primary Completion Date: March 2018 (Final data collection date for primary outcome measure)

<table>
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<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
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| Placebo Comparator: Treatment Arm A | Drug: Bendamustine  
90 mg/m² administered intravenously on Days 1-2, Cycles 1-6  
Drug: Rituximab  
375 mg/m² administered intravenously on Day 1, Cycles 1-6; if complete response or partial response is achieved, 375 mg/m² is administered on Day 1 of every second cycle for a maximum of 12 additional doses  
Drug: Placebo  
4 capsules administered orally once daily continuously starting on Day 1, Cycle 1 until disease progression, or unacceptable toxicity, or the final analysis of progression-free survival |
| Experimental: Treatment Arm B | Drug: Bendamustine  
90 mg/m² administered intravenously on Days 1-2, Cycles 1-6  
Drug: Rituximab  
375 mg/m² administered intravenously on Day 1, Cycles 1-6; if complete response or partial response is achieved, 375 mg/m² is administered on Day 1 of every second cycle for a maximum of 12 additional doses  
Drug: Ibrutinib  
560 mg (4 x 140 mg capsules) administered orally once daily continuously starting on Day 1, Cycle 1 until disease progression, or unacceptable toxicity, or study end |

Detailed Description:
This is a randomized (individuals assigned to study treatment by chance), double blind (neither physician nor participant knows the treatment that the participant receives), placebo (an inactive substance that is compared with a drug to test whether the drug has a real effect in a clinical trial)-controlled study to compare the efficacy and safety of ibrutinib given in combination with bendamustine and rituximab (BR) with
BR alone in participants newly diagnosed with mantle cell lymphoma (MCL) who are 65 years of age or older. Approximately 520 participants will be randomly assigned in a 1:1 ratio and stratified by simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) score (low risk [0-3] versus intermediate risk [4-5] versus high risk [6-11]). The treatment phase will extend from randomization until discontinuation of all study treatment or the clinical cutoff for the end of study. A cycle is defined as 28 days. All participants will receive open-label (identity of assigned study drug will be known) BR background therapy for a maximum of 6 cycles; participants with a complete response or partial response will continue to receive open-label background therapy with rituximab maintenance every second cycle for a maximum of 12 additional doses. In addition to the background therapy, all participants will receive blinded study drug (ibrutinib or placebo). Participants randomized to treatment Arm A will receive placebo capsules and participants randomized to treatment Arm B will receive ibrutinib capsules. Study drug will be administered daily and continuously until disease progression, unacceptable toxicity, or study end. Participants with stable disease after initial chemomunotherapy (BR-ibrutinib/placebo) should continue treatment with ibrutinib/placebo until disease progression, unacceptable toxicity, or study end. Participants with progressive disease must discontinue all study treatment. For participants who discontinue background therapy and do not have progressive disease, treatment with study drug will continue until disease progression or unacceptable toxicity or the clinical cutoff for the final analysis of progression-free survival (PFS). Participants receiving BR, rituximab, or ibrutinib at the clinical cutoff for the final analysis of PFS will continue open-label treatment until disease progression or unacceptable toxicity. Placebo will be stopped when the study is unblinded for the clinical cutoff for the final analysis of PFS. The posttreatment follow-up phase will begin once a participant discontinues bendamustine and rituximab and study drug. Participants who discontinue for reasons other than disease progression must continue to have disease evaluations as outlined in the protocol. Participants who discontinue due to disease progression will be followed for survival and subsequent anti-MCL therapy. The posttreatment follow-up phase will continue until death, lost to follow up, consent withdrawal, or study end, whichever occurs first. Three clinical cutoffs are planned. The first 2 clinical cutoffs will occur when approximately 134 and 265 PFS events have been observed, respectively. The interim analysis and the final analysis of PFS will take place at these 2 clinical cutoffs, respectively; participant treatment assignment will be unblinded at the clinical cutoff for the final analysis of PFS. The last cutoff will occur at the end of study, when 60% of the randomized participants have died or the Sponsor terminates the study, whichever comes first. Efficacy assessments will be conducted in accordance with the Revised Response Criteria for Malignant Lymphomas. Safety will be monitored throughout the study and summarized. Blood samples will be drawn for assessment of pharmacokinetic parameters. Blood and bone marrow will be collected for assessment of minimal residual disease and biomarker studies.

Eligibility

Ages Eligible for Study: 65 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:
- Diagnosis of mantle cell lymphoma (MCL) reviewed and approved by central laboratory: diagnosis must include morphology and expression of either cyclin D1 in association with other relevant markers (e.g., CD19, CD20, PAX5 and CD5) or evidence of t(11;14) as assessed by cytogenetics, fluorescent in situ hybridization (FISH), or polymerase chain reaction (PCR)
- Clinical Stage II, III, or IV by Ann Arbor Classification
- At least 1 measurable site of disease according to Revised Response Criteria for Malignant Lymphoma
- No prior therapies for MCL
- Eastern Cooperative Oncology Group (ECOG) performance status grade 0 or 1
- Hematology and biochemical laboratory values within protocol-defined limits
- Agrees to protocol-defined use of effective contraception
- Negative blood or urine pregnancy test at screening

Exclusion Criteria:
- Major surgery within 4 weeks of random assignment
- Known central nervous system lymphoma
- Diagnosed or treated for malignancy other than MCL, except: malignancy treated with curative intent and with no known active disease present for ≥3 years before random assignment; adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease; adequately treated cervical carcinoma in situ without evidence of disease
- Patients for whom the goal of therapy is tumor debulking prior to stem cell transplant
- History of stroke or intracranial hemorrhage within 6 months prior to random assignment
- Requires anticoagulation with warfarin or equivalent vitamin K antagonists
- Requires treatment with strong CYP3A inhibitors
- Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of Screening, or any Class 3 (moderate) or Class 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification
- Vaccinated with live, attenuated vaccines within 4 weeks of random assignment
- Known history of human immunodeficiency virus (HIV) or active hepatitis C virus or active hepatitis B virus infection or any uncontrolled active systemic infection requiring intravenous antibiotics
• Any life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the patient's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk

Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.

Please refer to this study by its ClinicalTrials.gov identifier: NCT01776840

Show 196 Study Locations

Sponsors and Collaborators

Janssen Research & Development, LLC
Pharmacyclics

Investigators

Study Director: Janssen Research & Development, LLC Clinical Trial Janssen Research & Development, LLC

More Information

No publications provided

Responsible Party: Janssen Research & Development, LLC
ClinicalTrials.gov Identifier: NCT01776840 History of Changes
Other Study ID Numbers: CR100967, PCI-32765, MCL3002, U1111-1137-0389, 2012-004056-11
Study First Received: January 24, 2013
Last Updated: December 18, 2014
Health Authority: United States: Food and Drug Administration

Australia: Department of Health and Ageing Therapeutic Goods Administration

Germany: Ethics Commission

Czech Republic: State Institute for Drug Control

China: Food and Drug Administration

Japan: Pharmaceuticals and Medical Devices Agency

Korea: Food and Drug Administration

Taiwan: Department of Health

Belgium: Federal Agency for Medicinal Products and Health Products

France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis)

Hungary: Institutional Ethics Committee

Ireland: Irish Medicines Board

Italy: The Italian Medicines Agency

Israel: Ministry of Health

Netherlands: The Central Committee on Research Involving Human Subjects (CCMO)

Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products

Russia: Ministry of Health of the Russian Federation

Slovakia: State Institute for Drug Control

Spain: Comité Ético de Investigación Clínica

Sweden: Medical Products Agency

Turkey: Ministry of Health

Ukraine: State Pharmacological Center - Ministry of Health

Argentina: Administracion Nacional de Medicamentos, Alimentos y Tecnologia Medica

Brazil: National Health Surveillance Agency

United Kingdom: Medicines and Healthcare Products Regulatory Agency

Canada: Health Canada

Great Britain: Medicines and Healthcare Products Regulatory Agency

Germany: Federal Institute for Drugs and Medical Devices

Great Britain: Research Ethics Committee

Keywords provided by Janssen Research & Development, LLC:
Mantle cell lymphoma
Ibrutinib
Bruton's tyrosine kinase inhibitor
Bendamustine hydrochloride
Rituximab

Additional relevant MeSH terms:
Lymphoma
Lymphoma, Mantle-Cell
Immune System Diseases
Immunoproliferative Disorders
Lymphatic Diseases
Lymphoma, Non-Hodgkin
Lymphoproliferative Disorders
Neoplasms
Neoplasms by Histologic Type
Bendamustine

Rituximab
Alkylating Agents
Antineoplastic Agents
Antineoplastic Agents, Alkylating
Antirheumatic Agents
Immunologic Factors
Molecular Mechanisms of Pharmacological Action
Pharmacologic Actions
Physiological Effects of Drugs
Therapeutic Uses

ClinicalTrials.gov processed this record on February 01, 2015