ClinicalTrials.gov Protocol and Results Registration System (PRS) Receipt
Release Date: 11/28/2012

Grantor: CDER IND/IDE Number: 7023 Serial Number: 921

# A Study of Bevacizumab (Avastin) in Combination With Rituximab (MabThera) and CHOP (Cyclophosphamide, Hydroxydaunorubicin [Doxorubicin], Oncovin [Vincristine], Prednisone) Chemotherapy in Patients With Diffuse Large B-cell Lymphoma

This study has been terminated.
(Due to an unfavorable benefit/risk ratio.)

| | |
|---|---|
| Sponsor: | Hoffmann-La Roche |
| Collaborators: | Genentech, Inc. |
| Information provided by (Responsible Party): | Hoffmann-La Roche |
| ClinicalTrials.gov Identifier: | NCT00486759 |

## Purpose

This 2-arm study was designed to compare the efficacy and safety of bevacizumab (Avastin) in combination with rituximab (MabThera) and CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], prednisone) chemotherapy (R-CHOP) versus rituximab plus CHOP chemotherapy (R-CHOP) in previously untreated patients with CD20-positive diffuse large B-cell lymphoma (DLBCL). Patients were randomized to receive 8 cycles of treatment with R-CHOP plus bevacizumab or R-CHOP plus placebo. Treatment with bevacizumab/placebo and R-CHOP was given either on a 2-week or 3-week schedule and bevacizumab was given at a weekly average dose of 5 mg/kg (10 mg/kg for 2-week cycles and 15 mg/kg for 3-week cycles).

| Condition | Intervention | Phase |
|---|---|---|
| B-cell Lymphoma | Drug: Bevacizumab<br>Drug: Rituximab<br>Drug: CHOP<br>Drug: Placebo | Phase 3 |

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Investigator), Randomized, Safety/Efficacy Study
Official Title: A Multicenter, Randomized, Double-blind, Placebo-controlled Phase III Trial Comparing the Efficacy of Bevacizumab in Combination With Rituximab and CHOP (R-CHOP + Bevacizumab) Versus Rituximab and CHOP (R-CHOP) in Previously Untreated Patients With CD20-positive Diffuse Large B-cell Lymphoma (DLBCL)

Further study details as provided by Hoffmann-La Roche:

Primary Outcome Measure:

- Progression-free Survival (PFS) [Time Frame: Baseline to end of the study (up to 4 years, 4 months)] [Designated as safety issue: No]
  PFS was defined as the time from the date of randomization to the date of disease progression (PD)/relapse, as determined by the investigator, or death from any cause, whichever occurred earlier. A patient with PD/relapse must meet at least 1 of the following criteria: (1) Appearance of any new lesion > 1.0 cm in the short axis during or at the end of therapy. (2) ≥ 50 % increase from nadir in the sum of the products of diameters (SPD, maximum diameter of a tumor x largest diameter perpendicular to the maximum diameter) of any previously involved nodes, in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis < 1.0 cm must increase by ≥ 50% to a size of 1.5 x 1.5 cm or > 1.5 cm in the long axis. (3) ≥ 50 % increase in the greatest diameter of any previously identified node > 1.0 cm in its short axis or in the SPD of more than 1 node.

Secondary Outcome Measures:

- Overall Survival [Time Frame: Baseline to end of the study (up to 4 years, 4 months)] [Designated as safety issue: No]
  Overall survival was defined as the time from the date of randomization to the date of death due to any cause.
- Overall Response (OR) Assessed According to the Revised Response Criteria for Malignant Lymphoma [Time Frame: At the end of treatment (Cycle 8, up to 12 months)] [Designated as safety issue: No]
  OR = a complete response (CR), an unconfirmed CR, or a partial response (PR). CR = Complete disappearance of disease and disease-related symptoms. All lymph nodes and nodal masses regressed on computed tomography (CT) to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm prior to therapy and ≤ 1.0 cm in their short axis for nodes 1.1-1.5 cm in their long axis and > 1.0 cm in their short axis prior to therapy). Spleen and/or liver not palpable on physical examination, normal size by imaging, and disappearance of nodules related to lymphoma. If bone marrow was involved prior to therapy, infiltrate must have cleared on repeat biopsy. PR = ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. No increase in the size of the other nodes, liver, or spleen. Splenic and hepatic nodules regressed by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter. No new sites of disease.

Enrollment: 787
Study Start Date: July 2007
Primary Completion Date: November 2011
Study Completion Date: November 2011

| Arms | Assigned Interventions |
|---|---|
| Experimental: Bevacizumab + rituximab + CHOP<br>Patients received bevacizumab 5 mg/ kg/week on Day 1 of each cycle + rituximab 375 mg/m^2 intravenously (IV) on Day 1 of each cycle + CHOP (cyclophosphamide, hydroxydaunorubicin | Drug: Bevacizumab<br>Bevacizumab was administered at a dose of 15 mg/kg IV on Day 1 of each 21-day cycle for 8 cycles or at a dose 10 mg/kg IV on Day 1 of each 14-day cycle for 8 cycles. The cycle duration (14- or 21-day) was chosen by each center prior to initiation of the study and was the same for all patients enrolled at that center.<br>Other Names: |

| Arms | Assigned Interventions |
| --- | --- |
| [doxorubicin], Oncovin [vincristine], prednisone). | Avastin<br>Drug: Rituximab<br>Rituximab was administered at a dose of 375 mg/m^2 IV on Day 1 of each 14- or 21-day cycle for 8 cycles. The cycle duration (14- or 21-day) was chosen by each center prior to initiation of the study and was the same for all patients enrolled at that center.<br>Other Names:<br>MabThera<br>Drug: CHOP<br>Cyclophosphamide was administered at a dose of 750 mg/m^2 IV on Day 1 of each cycle. Doxorubicin was administered at a dose of 50 mg/m^2 IV on Day 1 of each cycle. Vincristine was administered at a dose of 1.4 mg/m^2 IV (maximum of 2 mg) on Day 1 of each cycle. Prednisone was administered at a dose of 100 mg orally on Days 1-5 of each cycle. All 4 drugs were administered either every 21 days for 8 cycles or every 14 days for 6 cycles. The cycle duration (14- or 21-day) was chosen by each center prior to initiation of the study and was the same for all patients enrolled at that center. |
| Active Comparator: Placebo + rituximab + CHOP<br>Patients received placebo to bevacizumab on Day 1 of each cycle + rituximab 375 mg/m^2 intravenously (IV) on Day 1 of each cycle + CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], prednisone). | Drug: Rituximab<br>Rituximab was administered at a dose of 375 mg/m^2 IV on Day 1 of each 14- or 21-day cycle for 8 cycles. The cycle duration (14- or 21-day) was chosen by each center prior to initiation of the study and was the same for all patients enrolled at that center.<br>Other Names:<br>MabThera<br>Drug: CHOP<br>Cyclophosphamide was administered at a dose of 750 mg/m^2 IV on Day 1 of each cycle. Doxorubicin was administered at a dose of 50 mg/m^2 IV on Day 1 of each cycle. Vincristine was administered at a dose of 1.4 mg/m^2 IV (maximum of 2 mg) on Day 1 of each cycle. Prednisone was administered at a dose of 100 mg orally on Days 1-5 of each cycle. All 4 drugs were administered either every 21 days for 8 cycles or every 14 days for 6 cycles. The cycle duration (14- or 21-day) was chosen by each center prior to initiation |

| Arms | Assigned Interventions |
|---|---|
| | of the study and was the same for all patients enrolled at that center.<br><br>Drug: Placebo<br>Placebo to bevacizumab was administered on Day 1 of each 14- or 21-day cycle for 8 cycles. The cycle duration (14- or 21-day) was chosen by each center prior to initiation of the study and was the same for all patients enrolled at that center. |

Detailed Description:

An independent Data and Safety Monitoring Board (DSMB) was established to review safety data collected during the study on an ongoing basis. At its meeting in December 2009, the DSMB noted a trend for increased cardiac toxicity in the experimental arm (R-CHOP + bevacizumab) compared with the control arm (R-CHOP + placebo). Additional efficacy analyses of data from 720 randomized patients were presented at a DSMB meeting on May 22, 2010; they indicated no improvement in efficacy with the addition of bevacizumab to R-CHOP. It was noted, however, that there was an apparent increase in the risk of cardiotoxicity, premature treatment withdrawal, serious adverse events (SAEs), fatal adverse events (AEs), and perforation/ulcer in the experimental arm. Based on its assessment of an increased risk with unlikely benefit for patients randomized to the experimental arm, the DSMB recommended that further enrollment in the study be permanently halted and that bevacizumab be discontinued for any patients randomized to the experimental arm. On May 31, 2010, the sponsor took the decision to stop enrollment into the study and the bevacizumab treatment was terminated with immediate effect as recommended by the DSMB.

The study protocol was amended. The primary objective of the study was changed from evaluation of efficacy to evaluation of safety and the study was extended to include an 18-month safety follow-up period. Because enrollment was terminated prematurely resulting in fewer enrolled patients than planned, the outcome measure data are premature due to fewer than expected events.

The time frame for the reporting of serious adverse events was modified. Serious adverse events (SAE) unrelated to study treatment were reported until 1 year post-treatment or until new anti-lymphoma treatment was initiated. SAEs judged to be related to study treatment and congestive heart failure events were reported at any time during the study.

## Eligibility

Ages Eligible for Study: 18 Years to 79 Years
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

### Criteria

Inclusion Criteria:

- Adult patients, ≥ 18 and < 80 years of age.
- CD20-positive diffuse large B-cell lymphoma.
- Low-intermediate, high-intermediate, or high risk disease and/or bulky tumor (largest diameter ≥ 7.5 cm).
- Eastern Cooperative Oncology Group (ECOG) performance status 0-2.

Exclusion Criteria:

- Prior treatment for diffuse large B-cell lymphoma.
- Types of non-Hodgkin's lymphoma other than diffuse large B-cell lymphoma (DLBCL).
- Central nervous system (CNS) involvement of lymphoma.

## Contacts and Locations

Locations

United States, California
La Jolla, California, United States, 92093
Los Angeles, California, United States, 90057
United States, Colorado
Aurora, Colorado, United States, 80045
United States, Florida
Jacksonville, Florida, United States, 32207
West Palm Beach, Florida, United States, 33401
United States, Georgia
Marietta, Georgia, United States, 30060
United States, Kansas
Kansas City, Kansas, United States, 66160
United States, Michigan
Ann Arbor, Michigan, United States, 48106
United States, North Carolina
Concord, North Carolina, United States, 28025
Winston-salem, North Carolina, United States, 27103
United States, Oregon
Portland, Oregon, United States, 97213
United States, South Carolina
Charleston, South Carolina, United States, 29406
United States, Texas
Dallas, Texas, United States, 75390-9063
San Antonio, Texas, United States, 78229
United States, Washington
Federal Way, Washington, United States, 98003
Puyallup, Washington, United States, 98372
Tacoma, Washington, United States, 98405
Argentina
Buenos Aires, Argentina, C1114AAN
Buenos Aires, Argentina, 1425
Buenos Aires, Argentina, C1280AEB
Córdoba, Argentina, 5016
Australia
Adelaide, Australia, 5000
Frankston, Australia, 3199
Fremantle, Australia, 6160

Greenslopes, Australia, 4120
Kurralta Park, Australia, 5037
Melbourne, Australia, 3181
Melbourne, Australia, 3002
Wodonga, Australia, 3690
Woolloongabba, Australia, 4102

Austria

Graz, Austria, 8036
Salzburg, Austria, 5020
Wien, Austria, 1070

Brazil

Campinas, Brazil, 13083-970
Goiânia, Brazil, 74140-050
Ijuí, Brazil, 98700-000
Porto Alegre, Brazil, 90035-903
Porto Alegre, Brazil, 91350-200
Santo Andre, Brazil, 09060-870
Sao Paulo, Brazil, 05403-000
Sao Paulo, Brazil, 01221-020

Canada, Alberta

Calgary, Alberta, Canada, T2N 4N2
Edmonton, Alberta, Canada, T6G 1Z2

Canada, Manitoba

Winnipeg, Manitoba, Canada, R3E 0V9

Canada, New Brunswick

Moncton, New Brunswick, Canada, E1C 6Z8

Canada, Newfoundland and Labrador

St. John's, Newfoundland and Labrador, Canada, A1B 3V6

Canada, Nova Scotia

Halifax, Nova Scotia, Canada, B3H 2Y9

Canada, Ontario

Kingston, Ontario, Canada, K7L 5P9
Mississauga, Ontario, Canada, L5M 2N1
Toronto, Ontario, Canada, M4N 3M5
Toronto, Ontario, Canada, M5G 2M9
Windsor, Ontario, Canada, N8W 2X3

Canada, Quebec

Greenfield Park, Quebec, Canada, J4V 2H1
Montreal, Quebec, Canada, H3A 1A1
Montreal, Quebec, Canada, H3T IE2
Quebec City, Quebec, Canada, G1J 1Z4
Quebec City, Quebec, Canada, G1R 2J6

Canada, Saskatchewan

Regina, Saskatchewan, Canada, S4T 7T1
Saskatoon, Saskatchewan, Canada, S7N 4H4

China
- Beijing, China, 100021
- Beijing, China, 100036
- Beijing, China, 100730
- Beijing, China, 100853
- Fuzhou, China, 350014
- Shanghai, China, 200433
- Shanghai, China, 200032
- Shanghai, China, 200127
- Suzhou, China, 215006
- Suzhou, China, 215004
- Tianjin, China, 300020
- Xi'an, China, 710032

Colombia
- Bogota, Colombia
- Medellin, Colombia, 2A-80
- Medellin-antioquia, Colombia
- Pereira, Colombia

Czech Republic
- Brno, Czech Republic, 639 00
- Hradec Kralove, Czech Republic, 500 05
- Olomouc, Czech Republic, 775 20
- Plzen - Lochotin, Czech Republic, 304 60
- Praha, Czech Republic, 100 34
- Praha 2, Czech Republic, 128 08

Ecuador
- Guayaquil, Ecuador
- Quito, Ecuador, 2569
- Quito, Ecuador

France
- Albi, France, 81030
- Angers, France, 49033
- Bordeaux, France, 33076
- Bordeaux, France, 33077
- Caen, France, 14076
- Clermont Ferrand Cedex 1, France, 63003
- Dijon, France, 21079
- La Roche Sur Yon, France, 85925
- La Tronche, France, 38700
- Le Mans, France, 72015
- Lille, France, 59037
- Limoges, France, 87042
- Lyon, France, 69373
- Marseille, France, 13273
- Montauban, France, 82017

Montpellier, France, 34295
Nice, France, 06202
Nimes, France, 30900
Paris, France, 75231
Paris, France, 75475
Paris, France, 75651
Perpignan, France, 66046
Pessac, France, 33604
Pierre Benite, France, 69495
Poitiers, France, 86021
Rodez, France, 12027
Salouel, France, 80480
St Prient En Jarez, France, 42271
Toulouse, France, 31076
Toulouse, France, 31059
Tours, France, 37044
Vandoeuvre Les Nancy, France, 54511
Villejuif, France, 94805

Germany

Amberg, Germany, 92224
Berlin, Germany, 13353
Berlin, Germany, 10117
Bremen, Germany, 28239
Cottbus, Germany, 03048
Dortmund, Germany, 44137
Dortmund, Germany, 44137
Eschweiler, Germany, 52249
Frankfurt, Germany, 60488
Fulda, Germany, 36043
Greifswald, Germany, 17475
Göttingen, Germany, 37075
Hagen, Germany, 58095
Hamburg, Germany, 20099
Hamburg, Germany, 20249
Hamm, Germany, 59071
Hamm, Germany, 59063
Hannover, Germany, 30449
Hildesheim, Germany, 31134
Homburg/saar, Germany, 66241
Homburg/saar, Germany, 66424
Karlsruhe, Germany, 76133
Karlsruhe, Germany, 76137
Landshut, Germany, 84028
Leipzig, Germany, 04129
Leipzig, Germany, 04103

Ludwigshafen, Germany, 67063
Lübeck, Germany, 23562
Lüdenscheid, Germany, 58515
Magdeburg, Germany, 39120
Magdeburg, Germany, 39130
Mannheim, Germany, 68167
Muenster, Germany, 48149
München, Germany, 81377
Münster, Germany, 48149
Oldenburg, Germany, 26133
Recklinghausen, Germany, 45659
Siegen, Germany, 57072
Trier, Germany, 54290
Trier, Germany, 54292
Tübingen, Germany, 72076
ULM, Germany, 89081
Wiesbaden, Germany, 65199
Wuppertal, Germany, 42283
Wuppertal, Germany, 42283

Greece

Thessaloniki, Greece, 57010

Hong Kong

Hong Kong, Hong Kong
Hong Kong, Hong Kong

Hungary

Budapest, Hungary, 1097
Budapest, Hungary, H-1122
Debrecen, Hungary, 4032

Italy

Ascoli Piceno, Italy, 63100
Aviano, Italy, 33081
Bari, Italy, 70124
Bologna, Italy, 40138
Campobasso, Italy, 86100
Catania, Italy, 95124
Monza, Italy, 20052
Orbassano, Italy, 10043
Parma, Italy, 43100
Pavia, Italy, 27100
Pisa, Italy, 56100
Reggio Emilia, Italy, 42100
Roma, Italy, 00161
Torino, Italy, 10126
Udine, Italy, 33100

Korea, Republic of

Seoul, Korea, Republic of, 135-170
Seoul, Korea, Republic of
Seoul, Korea, Republic of, 139-709
Seoul, Korea, Republic of, 138-736

Lithuania
Klaipeda, Lithuania, 92288
Vilnius, Lithuania, 08661

Malaysia
Penang, Malaysia, 10990

Mexico
Aguascalientes, Mexico, 20127
Mexico City, Mexico, 11520
Monterrey, Mexico, 64460
Monterrey, Mexico, 00000

New Zealand
Auckland, New Zealand
Auckland, New Zealand
Christchurch, New Zealand

Panama
Panama City, Panama

Peru
Chiclayo, Peru, CIX
Lima, Peru, 11
Lima, Peru, 13
Lima, Peru, 41
Lima, Peru, Lima11

Philippines
Cebu, Philippines, 6000
Diliman, Quezon City, Philippines, 1100
Quezon City, Philippines, 1102

Poland
Brzozów, Poland, 36-200
Krakow, Poland, 31-501
Lodz, Poland, 93-510
Lublin, Poland, 20-081
Olsztyn, Poland, 10-228
Warszawa, Poland, 02-097
Warszawa, Poland, 02-781
Warszawa, Poland, 02-507

Portugal
Coimbra, Portugal, 3000-075
Lisboa, Portugal, 1099-166
Porto, Portugal, 4200-319

Russian Federation
Kazan, Russian Federation, 420029

Moscow, Russian Federation, 115478
Moscow, Russian Federation, 125167
Moscow, Russian Federation, 129128
St Petersburg, Russian Federation, 191024

Slovakia

Bratislava, Slovakia, 833 10

Spain

Barcelona, Spain, 08036
Barcelona, Spain, 08035
Barcelona, Spain, 08025
Bilbao, Spain, 48013
Galdakano, Spain, 48690
Hospitalet de Llobregat, Spain, 08907
Jaen, Spain, 23007
La Coruna, Spain, 15006
La Laguna, Spain, 38320
Madrid, Spain, 28046
Madrid, Spain, 28040
Málaga, Spain, 29010
Salamanca, Spain, 37007
Santander, Spain, 39008
Sevilla, Spain, 41013
Terrassa, Spain, 08221
Valencia, Spain, 46010
Valencia, Spain, 46009
Zaragoza, Spain, 50009

Sweden

Lund, Sweden, 22185
Malmo, Sweden, 205 02
Sundsvall, Sweden, 85186
Uppsala, Sweden, 751 85

Switzerland

Zürich, Switzerland, 8091

Taiwan

Taipei, Taiwan, 112
Taipei, Taiwan, 105
Taipei, Taiwan, 112

Thailand

Bangkok, Thailand, 10330
Bangkok, Thailand, 10700
Bangkok, Thailand, 10400
Bangkok, Thailand, 10400
Chiang Mai, Thailand, 50200
Khon Kaen, Thailand, 40002

United Kingdom

Birmingham, United Kingdom, B9 5SS
Bradford, United Kingdom, BD9 6RJ
Hampshire, United Kingdom, RG24 9NA
Harlow, United Kingdom, CM20 1QX
Leicester, United Kingdom, LE1 5WW
Liverpool, United Kingdom, L7 8XP
London, United Kingdom, SW17 0QT
Middx, United Kingdom, UB8 3NN
Oxford, United Kingdom, OX3 7LJ
Sheffield, United Kingdom, S10 2SJ
Sheffield, United Kingdom, S10 2JF
Wolverhampton, United Kingdom, WV10 0QP

Investigators

| | | |
|---|---|---|
| Study Director: | Clinical Trials | Hoffmann-La Roche |

## More Information

Responsible Party: Hoffmann-La Roche
Study ID Numbers: BO20603
Health Authority: United States: Food and Drug Administration

# Study Results

## Participant Flow

Reporting Groups

| | Description |
|---|---|
| Bevacizumab + Rituximab + CHOP | Patients received bevacizumab 5 mg/kg/week on Day 1 of each cycle + rituximab 375 mg/m^2 intravenously (IV) on Day 1 of each cycle + CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], prednisone). |
| Placebo + Rituximab + CHOP | Patients received placebo to bevacizumab on Day 1 of each cycle + rituximab 375 mg/m^2 intravenously (IV) on Day 1 of each cycle + CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], prednisone). |

Treatment

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| Started | 390 | 397 |

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| Completed | 203 | 260 |
| Not Completed | 187 | 137 |
| Adverse event/intercurrent illness | 86 | 39 |
| Insufficient therapeutic response | 37 | 39 |
| Death | 17 | 10 |
| Withdrew consent | 15 | 12 |
| Administrative/reason not specified | 17 | 21 |
| Refused treatment | 10 | 7 |
| Violation of selection criteria at entry | 3 | 3 |
| Other protocol violation | 1 | 5 |
| Failure to return | 1 | 1 |

Safety Follow-up

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| Started | 203 | 260 |
| Completed | 64 | 142 |
| Not Completed | 139 | 118 |
| Insufficient therapeutic response | 40 | 50 |
| Death | 40 | 29 |
| Withdrew consent | 32 | 23 |
| Failure to return | 9 | 6 |
| Administrative/not specified | 8 | 6 |
| Refused treatment/did not cooperate | 6 | 4 |
| Adverse event/intercurrent illness | 4 | 0 |

## Baseline Characteristics

Reporting Groups

| | Description |
|---|---|
| Bevacizumab + Rituximab + CHOP | Patients received bevacizumab 5 mg/kg/week on Day 1 of each cycle + rituximab 375 mg/m^2 intravenously (IV) on Day 1 of each cycle + CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], prednisone). |
| Placebo + Rituximab + CHOP | Patients received placebo to bevacizumab on Day 1 of each cycle + rituximab 375 mg/m^2 intravenously (IV) on Day 1 of each cycle + CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], prednisone). |

Baseline Measures

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP | Total |
|---|---|---|---|
| Number of Participants | 390 | 397 | 787 |
| Age, Continuous<br>[units: years]<br>Mean (Standard Deviation) | 57.89 (14.256) | 56.98 (15.399) | 57.44 (14.841) |
| Gender, Male/Female<br>[units: participants] | | | |
| Female | 207 | 193 | 400 |
| Male | 183 | 204 | 387 |

## Outcome Measures

1. Primary Outcome Measure:

| | |
|---|---|
| Measure Title | Progression-free Survival (PFS) |
| Measure Description | PFS was defined as the time from the date of randomization to the date of disease progression (PD)/relapse, as determined by the investigator, or death from any cause, whichever occurred earlier. A patient with PD/relapse must meet at least 1 of the following criteria: (1) Appearance of any new lesion > 1.0 cm in the short axis during or at the end of therapy. (2) ≥ 50 % increase from nadir in the sum of the products of diameters (SPD, maximum diameter of a tumor x largest diameter perpendicular to the maximum diameter) of any previously involved nodes, in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis < 1.0 cm must increase by ≥ 50% to a size of 1.5 x 1.5 cm or > 1.5 cm in the long axis. (3) ≥ 50 % increase in the greatest diameter of any previously identified node > 1.0 cm in its short axis or in the SPD of more than 1 node. |
| Time Frame | Baseline to end of the study (up to 4 years, 4 months) |

| | |
|---|---|
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized patients, regardless whether or not they had actually received the assigned treatments.

Reporting Groups

| | Description |
|---|---|
| Bevacizumab + Rituximab + CHOP | Patients received bevacizumab 5 mg/kg/week on Day 1 of each cycle + rituximab 375 mg/m^2 intravenously (IV) on Day 1 of each cycle + CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], prednisone). |
| Placebo + Rituximab + CHOP | Patients received placebo to bevacizumab on Day 1 of each cycle + rituximab 375 mg/m^2 intravenously (IV) on Day 1 of each cycle + CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], prednisone). |

Measured Values

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| Number of Participants Analyzed | 390 | 397 |
| Progression-free Survival (PFS)<br>[units: Months]<br>Median (Inter-Quartile Range) | 40.2 (12.1 to NA) [1] | 42.9 (13.6 to NA) [1] |

[1] The 75th percentile could not be estimated due to a lack of events.

2. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Overall Survival |
| Measure Description | Overall survival was defined as the time from the date of randomization to the date of death due to any cause. |
| Time Frame | Baseline to end of the study (up to 4 years, 4 months) |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized patients, regardless whether or not they had actually received the assigned treatments.

Reporting Groups

| | Description |
|---|---|
| Bevacizumab + Rituximab + CHOP | Patients received bevacizumab 5 mg/kg/week on Day 1 of each cycle + rituximab 375 mg/m^2 intravenously (IV) on Day 1 of each cycle + CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], prednisone). |
| Placebo + Rituximab + CHOP | Patients received placebo to bevacizumab on Day 1 of each cycle + rituximab 375 mg/m^2 intravenously (IV) on Day 1 of each cycle + CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], prednisone). |

Measured Values

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| Number of Participants Analyzed | 390 | 397 |
| Overall Survival<br>[units: Months]<br>Median (Inter-Quartile Range) | NA (34.0 to NA) [1] | NA (42.9 to NA) [1] |

[1] The median and 75th percentile could not be estimated due to a lack of events,

3. Secondary Outcome Measure:

| | |
|---|---|
| Measure Title | Overall Response (OR) Assessed According to the Revised Response Criteria for Malignant Lymphoma |
| Measure Description | OR = a complete response (CR), an unconfirmed CR, or a partial response (PR). CR = Complete disappearance of disease and disease-related symptoms. All lymph nodes and nodal masses regressed on computed tomography (CT) to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm prior to therapy and ≤ 1.0 cm in their short axis for nodes 1.1-1.5 cm in their long axis and > 1.0 cm in their short axis prior to therapy). Spleen and/or liver not palpable on physical examination, normal size by imaging, and disappearance of nodules related to lymphoma. If bone marrow was involved prior to therapy, infiltrate must have cleared on repeat biopsy. PR = ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or nodal masses. No increase in the size of the other nodes, liver, or spleen. Splenic and hepatic nodules regressed by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter. No new sites of disease. |
| Time Frame | At the end of treatment (Cycle 8, up to 12 months) |
| Safety Issue? | No |

Analysis Population Description

Intent-to-treat population: All randomized patients, regardless whether or not they had actually received the assigned treatments.

Reporting Groups

| | Description |
|---|---|
| Bevacizumab + Rituximab + CHOP | Patients received bevacizumab 5 mg/kg/week on Day 1 of each cycle + rituximab 375 mg/m^2 intravenously (IV) on Day 1 of each cycle + CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], prednisone). |
| Placebo + Rituximab + CHOP | Patients received placebo to bevacizumab on Day 1 of each cycle + rituximab 375 mg/m^2 intravenously (IV) on Day 1 of each cycle + CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], prednisone). |

Measured Values

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| Number of Participants Analyzed | 390 | 397 |
| Overall Response (OR) Assessed According to the Revised Response Criteria for Malignant Lymphoma [units: Percentage of patients] | 63.1 | 70.5 |

## Reported Adverse Events

| | |
|---|---|
| Time Frame | All adverse events (AE) were reported starting from the first dose up to 92 days after the last dose of study drug. AEs of special interest were reported up to 6 months after the last dose. |
| Additional Description | Safety analysis population: All patients who received at least 1 dose of study drug whether withdrawn prematurely or not. Bevacizumab (B) 395=390 randomized-2 no treatment+7 randomized to placebo who received B. Placebo to B 386=397 randomized-5 no treatment-7 received B+1 randomized to B who received placebo but no B. |

Reporting Groups

| | Description |
|---|---|
| Bevacizumab + Rituximab + CHOP | Patients received bevacizumab 5 mg/kg/week on Day 1 of each cycle + rituximab 375 mg/m^2 intravenously (IV) on Day 1 of each cycle + CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], prednisone). |
| Placebo + Rituximab + CHOP | Patients received placebo to bevacizumab on Day 1 of each cycle + rituximab 375 mg/m^2 intravenously (IV) on Day 1 of each cycle + CHOP (cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], prednisone). |

Serious Adverse Events

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) |
| Total | 224/395 (56.71%) | 173/386 (44.82%) |
| Blood and lymphatic system disorders | | |
| Agranulocytosis [A] † | 3/395 (0.76%) | 2/386 (0.52%) |
| Anaemia [A] † | 8/395 (2.03%) | 1/386 (0.26%) |
| Febrile bone marrow aplasia [A] † | 0/395 (0%) | 3/386 (0.78%) |
| Febrile neutorpenia [A] † | 63/395 (15.95%) | 48/386 (12.44%) |
| Leukopenia [A] † | 6/395 (1.52%) | 5/386 (1.3%) |
| Lymphopenia [A] † | 2/395 (0.51%) | 0/386 (0%) |
| Neutropenia [A] † | 12/395 (3.04%) | 17/386 (4.4%) |
| Pancytopenia [A] † | 2/395 (0.51%) | 1/386 (0.26%) |
| Splenic vein thrombosis [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Splenomegaly [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Thrombocytopenia [A] † | 5/395 (1.27%) | 4/386 (1.04%) |
| Cardiac disorders | | |
| Angina pectoris [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| Angina unstable [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Arrhythmia [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Atrial fibrillation [A] † | 2/395 (0.51%) | 4/386 (1.04%) |
| Atrioventricular block complete [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Cardiac disorder [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Cardiac failure [A] † | 6/395 (1.52%) | 4/386 (1.04%) |
| Cardiac failure congestive [A] † | 5/395 (1.27%) | 2/386 (0.52%) |

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) |
| Cardiomyopathy [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Cardiotoxicity [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Cardiovascular disorder [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| Congestive cardiomyopathy [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Left ventricular dysfunction [A] † | 15/395 (3.8%) | 5/386 (1.3%) |
| Restrictive cardiomyopathy [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| Sick sinus syndrome [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Sinus tachycardia [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Supraventricular tachycardia [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Tachyarrhythmia [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Ventricular hypokinesia [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Congenital, familial and genetic disorders | | |
| Aplasia [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Endocrine disorders | | |
| Hyperthyroidism [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Toxic nodular goitre [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Eye disorders | | |
| Retinal detachment [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Retinal haemorrhage [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Retinal vein thrombosis [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Gastrointestinal disorders | | |
| Abdominal pain [A] † | 4/395 (1.01%) | 5/386 (1.3%) |
| Abdominal pain lower [A] † | 1/395 (0.25%) | 0/386 (0%) |

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) |
| Abdominal pain upper [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| Anal fissure [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Ascites [A] † | 4/395 (1.01%) | 0/386 (0%) |
| Constipation [A] † | 2/395 (0.51%) | 2/386 (0.52%) |
| Diarrhoea [A] † | 6/395 (1.52%) | 3/386 (0.78%) |
| Enteritis [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Gastric perforation [A] † | 3/395 (0.76%) | 0/386 (0%) |
| Gastrointestinal haemorrhage [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| Gastrointestinal hypomotility [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Haemorrhoidal haemorrhage [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Haemorrhoids [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Ileal perforation [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Ileus paralytic [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Impaired gastric emptying [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Inguinal hernia [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Inguinal hernia, obstructive [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Intestinal perforation [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Melaena [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Nausea [A] † | 3/395 (0.76%) | 0/386 (0%) |
| Periodontitis [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Rectal ulcer [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Small intestinal obstruction [A] † | 0/395 (0%) | 1/386 (0.26%) |

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) |
| Small intestinal perforation [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Stomatitis [A] † | 2/395 (0.51%) | 1/386 (0.26%) |
| Subileus [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Upper gastrointestinal haemorrhage [A] † | 2/395 (0.51%) | 0/386 (0%) |
| Volvulus [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Vomiting [A] † | 1/395 (0.25%) | 0/386 (0%) |
| General disorders | | |
| Asthenia [A] † | 4/395 (1.01%) | 2/386 (0.52%) |
| Catheter site haemorrhage [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Chest pain [A] † | 0/395 (0%) | 3/386 (0.78%) |
| Death [A] † | 1/395 (0.25%) | 2/386 (0.52%) |
| Effusion [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Fatigue [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| General physical health deterioration [A] † | 3/395 (0.76%) | 0/386 (0%) |
| Hyperthermia [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Impaired healing [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Influenza like illness [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Local swelling [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Medical device complication [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Mucosal inflammation [A] † | 2/395 (0.51%) | 0/386 (0%) |
| Multi-organ failure [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Oedema peripheral [A] † | 0/395 (0%) | 1/386 (0.26%) |

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) |
| Pain [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Pyrexia [A] † | 14/395 (3.54%) | 15/386 (3.89%) |
| Hepatobiliary disorders | | |
| Acute hepatic failure [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Bile duct stone [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Cholangitis [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Cholecystitis acute [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Hepatitis [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Jaundice cholestatic [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Immune system disorders | | |
| Anaphylactic reaction [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Hypersensitivity [A] † | 1/395 (0.25%) | 2/386 (0.52%) |
| Infections and infestations | | |
| Abdominal abscess [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Acute tonsillitis [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Amoebiasis [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Anal abscess [A] † | 2/395 (0.51%) | 0/386 (0%) |
| Appendiceal abscess [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Appendicitis [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| Bronchitis [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| Bronchitis bacterial [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Bronchopneumonia [A] † | 2/395 (0.51%) | 6/386 (1.55%) |

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) |
| Bronchopulmonary aspergillosis [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Cellulitis [A] † | 0/395 (0%) | 2/386 (0.52%) |
| Cystitis [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| Device related infection [A] † | 2/395 (0.51%) | 1/386 (0.26%) |
| Enterococcal infection [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Erysipelas [A] † | 0/395 (0%) | 2/386 (0.52%) |
| Escherichia sepsis [A] † | 0/395 (0%) | 2/386 (0.52%) |
| Fungal oesophagitis [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Gastroenteritis [A] † | 2/395 (0.51%) | 4/386 (1.04%) |
| Gastroenteritis norovirus [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Gastrointestinal fungal infection [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Gastrointestinal infection [A] † | 1/395 (0.25%) | 0/386 (0%) |
| H1N1 influenza [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Herpes zoster [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| Infection [A] † | 3/395 (0.76%) | 6/386 (1.55%) |
| Infectious peritonitis [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Influenza [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Localised infection [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Lower respiratory tract infection [A] † | 1/395 (0.25%) | 2/386 (0.52%) |
| Lung infection [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Lymph gland infection [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Lymphadenitis bacterial [A] † | 0/395 (0%) | 1/386 (0.26%) |

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) |
| Meningitis cryptococcal [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Mucosal infection [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Neutropenic infection [A] † | 1/395 (0.25%) | 4/386 (1.04%) |
| Neutropenic sepsis [A] † | 5/395 (1.27%) | 1/386 (0.26%) |
| Oesophageal candidiasis [A] † | 2/395 (0.51%) | 0/386 (0%) |
| Oral candidiasis [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Oral infection [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Orchitis [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Otitis media [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Paronychia [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Perirectal abscess [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Pharyngitis [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| Pneumocystis jiroveci infection [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Pneumocystis jiroveci pneumonia [A] † | 0/395 (0%) | 2/386 (0.52%) |
| Pneumonia [A] † | 22/395 (5.57%) | 16/386 (4.15%) |
| Pneumonia viral [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Pulmonary sepsis [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Pyelonephritis [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Pyelonephritis acute [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Respiratory syncytial virus infection [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Respiratory tract infection [A] † | 2/395 (0.51%) | 0/386 (0%) |
| Sepsis [A] † | 2/395 (0.51%) | 4/386 (1.04%) |

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) |
| Septic shock [A] † | 6/395 (1.52%) | 4/386 (1.04%) |
| Sinusitis [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Splenic abscess [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Staphylococcal infection [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Systemic candida [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Tooth abscess [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Tuberculous pleurisy [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Upper respiratory tract infection [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Urinary tract infection [A] † | 6/395 (1.52%) | 3/386 (0.78%) |
| Urosepsis [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Injury, poisoning and procedural complications | | |
| Cervical vertebral fracture [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Chemical injury [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Fall [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Femoral neck fracture [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Head injury [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Injury [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Laceration [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Lower limb fracture [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Lumbar vertebral fracture [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Post lumbar puncture syndrome [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Road traffic accident [A] † | 1/395 (0.25%) | 0/386 (0%) |

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) |
| Spinal compression fracture [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Subdural haematoma [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Traumatic lung injury [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Ulna fracture [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Investigations | | |
| Alanine aminotransferase increased [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Aspartate aminotransferase increased [A] † | 1/395 (0.25%) | 0/386 (0%) |
| C-reactive protein increased [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| Ejection fraction decreased [A] † | 4/395 (1.01%) | 3/386 (0.78%) |
| General physical condition abnormal [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Hepatic enzyme increased [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Multiple gated acquisition scan abnormal [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Metabolism and nutrition disorders | | |
| Dehydration [A] † | 2/395 (0.51%) | 4/386 (1.04%) |
| Diabetes mellitus inadequate control [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Hyperglycaemia [A] † | 3/395 (0.76%) | 1/386 (0.26%) |
| Hypoglycaemia [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Hypokalaemia [A] † | 1/395 (0.25%) | 3/386 (0.78%) |
| Musculoskeletal and connective tissue disorders | | |
| Arthralgia [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Back pain [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| Bone pain [A] † | 1/395 (0.25%) | 0/386 (0%) |

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) |
| Muscle atrophy [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Myofascial pain syndrome [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Osteoporosis [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Spinal osteoarthritis [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | |
| Gastrointestinal stromal tumour [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Infected neoplasm [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Thyroid cancer [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Tumour associated fever [A] † | 2/395 (0.51%) | 0/386 (0%) |
| Nervous system disorders | | |
| Cerebrovascular accident [A] † | 1/395 (0.25%) | 2/386 (0.52%) |
| Convulsion [A] † | 2/395 (0.51%) | 0/386 (0%) |
| Dizziness [A] † | 2/395 (0.51%) | 0/386 (0%) |
| Extrapyramidal disorder [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Haemorrhage intracranial [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Headache [A] † | 2/395 (0.51%) | 3/386 (0.78%) |
| Lethargy [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Loss of consciousness [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Nervous system disorder [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Neuralgia [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Partial seizures [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Peripheral motor neuropathy [A] † | 0/395 (0%) | 1/386 (0.26%) |

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) |
| Polyneuropathy [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Syncope [A] † | 0/395 (0%) | 4/386 (1.04%) |
| Transient ischaemic attack [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| Psychiatric disorders | | |
| Confusional state [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Major depression [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Suicidal ideation [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Suicide attempt [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Renal and urinary disorders | | |
| Proteinuria [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Renal colic [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Respiratory, thoracic and mediastinal disorders | | |
| Acute pulmonary oedema [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Acute respiratory distress syndrome [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Bronchiectasis [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Bronchospasm [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Cough [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Dyspnoea [A] † | 4/395 (1.01%) | 3/386 (0.78%) |
| Haemoptysis [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Interstitial lung disease [A] † | 3/395 (0.76%) | 2/386 (0.52%) |
| Lung disorder [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| Organising pneumonia [A] † | 0/395 (0%) | 1/386 (0.26%) |

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) |
| Pleural effusion [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Pleuritic pain [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Pneumonitis [A] † | 1/395 (0.25%) | 1/386 (0.26%) |
| Pulmonary embolism [A] † | 4/395 (1.01%) | 4/386 (1.04%) |
| Pulmonary oedema [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Respiratory failure [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Skin and subcutaneous tissue disorders | | |
| Hidradenitis [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Skin ulcer [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Vascular disorders | | |
| Circulatory collapse [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Deep vein thrombosis [A] † | 2/395 (0.51%) | 4/386 (1.04%) |
| Haematoma [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Hypertension [A] † | 6/395 (1.52%) | 1/386 (0.26%) |
| Hypertensive crisis [A] † | 2/395 (0.51%) | 0/386 (0%) |
| Jugular vein thrombosis [A] † | 0/395 (0%) | 1/386 (0.26%) |
| Shock haemorrhagic [A] † | 1/395 (0.25%) | 0/386 (0%) |
| Thrombosis [A] † | 1/395 (0.25%) | 0/386 (0%) |

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (14.1)

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) |
| Total | 346/395 (87.59%) | 331/386 (85.75%) |
| Blood and lymphatic system disorders | | |
| Anaemia [A] † | 66/395 (16.71%) | 96/386 (24.87%) |
| Leukopenia [A] † | 42/395 (10.63%) | 49/386 (12.69%) |
| Neutropenia [A] † | 88/395 (22.28%) | 119/386 (30.83%) |
| Thrombocytopenia [A] † | 24/395 (6.08%) | 30/386 (7.77%) |
| Gastrointestinal disorders | | |
| Abdominal pain [A] † | 32/395 (8.1%) | 25/386 (6.48%) |
| Abdominal pain upper [A] † | 17/395 (4.3%) | 32/386 (8.29%) |
| Constipation [A] † | 88/395 (22.28%) | 70/386 (18.13%) |
| Diarrhoea [A] † | 95/395 (24.05%) | 81/386 (20.98%) |
| Dyspepsia [A] † | 23/395 (5.82%) | 35/386 (9.07%) |
| Haemorrhoids [A] † | 23/395 (5.82%) | 12/386 (3.11%) |
| Nausea [A] † | 107/395 (27.09%) | 106/386 (27.46%) |
| Stomatitis [A] † | 33/395 (8.35%) | 36/386 (9.33%) |
| Vomiting [A] † | 56/395 (14.18%) | 70/386 (18.13%) |
| General disorders | | |
| Asthenia [A] † | 59/395 (14.94%) | 60/386 (15.54%) |
| Fatigue [A] † | 71/395 (17.97%) | 71/386 (18.39%) |
| Mucosal inflammation [A] † | 61/395 (15.44%) | 45/386 (11.66%) |
| Oedema peripheral [A] † | 24/395 (6.08%) | 29/386 (7.51%) |

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) |
| Pyrexia [A] † | 71/395 (17.97%) | 55/386 (14.25%) |
| Infections and infestations | | |
| Nasopharyngitis [A] † | 30/395 (7.59%) | 22/386 (5.7%) |
| Upper respiratory tract infection [A] † | 25/395 (6.33%) | 17/386 (4.4%) |
| Urinary tract infection [A] † | 24/395 (6.08%) | 23/386 (5.96%) |
| Investigations | | |
| Weight decreased [A] † | 24/395 (6.08%) | 21/386 (5.44%) |
| Metabolism and nutrition disorders | | |
| Decreased appetite [A] † | 60/395 (15.19%) | 46/386 (11.92%) |
| Hypokalaemia [A] † | 21/395 (5.32%) | 17/386 (4.4%) |
| Musculoskeletal and connective tissue disorders | | |
| Arthralgia [A] † | 35/395 (8.86%) | 19/386 (4.92%) |
| Back pain [A] † | 37/395 (9.37%) | 37/386 (9.59%) |
| Bone pain [A] † | 23/395 (5.82%) | 17/386 (4.4%) |
| Pain in extremity [A] † | 22/395 (5.57%) | 19/386 (4.92%) |
| Nervous system disorders | | |
| Dizziness [A] † | 24/395 (6.08%) | 21/386 (5.44%) |
| Headache [A] † | 59/395 (14.94%) | 59/386 (15.28%) |
| Neuropathy peripheral [A] † | 38/395 (9.62%) | 38/386 (9.84%) |
| Paraesthesia [A] † | 42/395 (10.63%) | 31/386 (8.03%) |
| Peripheral sensory neuropathy [A] † | 25/395 (6.33%) | 28/386 (7.25%) |
| Psychiatric disorders | | |
| Insomnia [A] † | 29/395 (7.34%) | 30/386 (7.77%) |

| | Bevacizumab + Rituximab + CHOP | Placebo + Rituximab + CHOP |
|---|---|---|
| | Affected/At Risk (%) | Affected/At Risk (%) |
| Respiratory, thoracic and mediastinal disorders | | |
| Cough [A] † | 52/395 (13.16%) | 43/386 (11.14%) |
| Dysphonia [A] † | 29/395 (7.34%) | 7/386 (1.81%) |
| Dyspnoea [A] † | 19/395 (4.81%) | 27/386 (6.99%) |
| Epistaxis [A] † | 47/395 (11.9%) | 10/386 (2.59%) |
| Oropharyngeal pain [A] † | 27/395 (6.84%) | 19/386 (4.92%) |
| Rhinorrhoea [A] † | 24/395 (6.08%) | 14/386 (3.63%) |
| Skin and subcutaneous tissue disorders | | |
| Alopecia [A] † | 96/395 (24.3%) | 80/386 (20.73%) |
| Rash [A] † | 22/395 (5.57%) | 23/386 (5.96%) |
| Vascular disorders | | |
| Hypertension [A] † | 54/395 (13.67%) | 12/386 (3.11%) |

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (14.1)

## Limitations and Caveats

Due to premature termination of the study, the efficacy results should be interpreted with caution.

## More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The Study being conducted under this Agreement is part of the Overall Study. Investigator is free to publish in reputable journals or to present at professional conferences the results of the Study, but only after the first publication or presentation that involves the Overall Study. The Sponsor may request that Confidential Information be deleted and/or the publication be postponed in order to protect the Sponsor's intellectual property rights.

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