Zytux™ (rituximab)

Health Care Professional Information

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Warnings: fatal infusion reactions, severe mucocutaneous reactions,

Hepatitis B virus reactivation and progressive multifocal

Leukoencephalopathy

infusion reactions

Rituximab administration can result in serious, including fatal infusion reactions. Deaths within 24 hours of rituximab infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Monitor patients closely. Discontinue Zytux™ infusion for severe reactions and provide medical treatment for grade 3 or 4 infusion reactions.

severe mucocutaneous reactions

Severe, including fatal, mucocutaneous reactions can occur in patients receiving rituximab.

hepatitis b virus (HBV) reactivation

HBV reactivation can occur in patients treated with rituximab, in some cases resulting in fulminant hepatitis, hepatic failure, and death. Screen all patients for HBV infection before treatment initiation, and monitor patients during and after treatment with Zytux™. Discontinue Zytux™ and concomitant medications in the event of HBV reactivation.

Progressive multifocal leukoencephalopathy (pPML), including fatal PML, can occur in patients receiving rituximab.

1. Indications and usage

1.1 non–Hodgkin’s lymphoma (NHL)

Zytux™ (rituximab) is indicated for the treatment of patients with:

Relapsed or refractory, low-grade or follicular, CD20-positive, b-cell NHL as a single agent

previously untreated follicular, CD20-positive, b-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to Zytux™ in combination with chemotherapy, as single-agent maintenance therapy.

Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy

Previously untreated diffuse large b-cell, CD20-positive NHL in combination with chop or other anthracycline-based chemotherapy regimens

1.2 chronic lymphocytic leukemia (CLL)

Zytux™ (rituximab) is indicated, in combination with fludarabine and cyclophosphamide (fc), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

1.3 rheumatoid arthritis (RA)

Zytux™ (rituximab) in combination with methotrexate is indicated for the treatment of adult patients with moderately- to severely- active rheumatoid arthritis who have had an inadequate response to one or more tnf antagonist therapies.

1.4 granulomatosis with polyangiitis (GPA) (Wegener’s granulomatosis) and microscopic polyangiitis (MPA)

Zytux™ (rituximab), in combination with glucocorticoids, is indicated for the treatment of adult patients with granulomatosis with polyangiitis (GPA) (wegener's granulomatosis) and microscopic polyangiitis (MPA).

1.5 limitations of use

Zytux™ is not recommended for use in patients with severe, active infections.

2. Dosage and administration

2.1 administration

Administer only as an intravenous infusion.

Do not administer as an intravenous push or bolus.

premedicate before each infusion.

Zytux™ should only be administered by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur.

First infusion: initiate infusion at a rate of 50 mg/hr. in the absence of infusion toxicity, increase infusion rate by 50 mg/hr. increments every 30 minutes, to a maximum of 400 mg/hr.

subsequent infusions:

standard infusion: initiate infusion at a rate of 100 mg/hr. in the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.

for previously untreated follicular NHL and DLBCL patients:

if patients did not experience a grade 3 or 4 infusion related adverse event during cycle 1, a 90-minute infusion can be administered in cycle 2 with a glucocorticoid-containing chemotherapy regimen.

Initiate at a rate of 20% of the total dose given in the first 30 minutes and the remaining 80% of the total dose given over the next 60 minutes. If the 90-minute infusion is tolerated in cycle 2, the same rate can be used when administering the remainder of the treatment regimen (through cycle 6 or 8).

Patients who have clinically significant cardiovascular disease or who have a circulating lymphocyte count ≥5000/mm3 before cycle 2 should not be administered the 90-minute infusion.

Interrupt the infusion or slow the infusion rate for infusion reactions. Continue the infusion at one-half the previous rate upon improvement of symptoms.

2.2 recommended dose for non-Hodgkin's lymphoma (NHL)

The recommended dose is 375 mg/m^2 as an intravenous infusion according to the following schedules:

Relapsed or refractory, low-grade or follicular, CD20-positive, b-cell NHL administer once weekly for 4 or 8 doses.

Retreatment for relapsed or refractory, low-grade or follicular, CD20-positive, b-cell NHL administer once weekly for 4 doses.

Previously untreated, follicular, CD20-positive, b-cell NHL

administer on day 1 of each cycle of chemotherapy, for up to 8 doses. in patients with complete or partial

response, initiate Zytux™ maintenance eight weeks following completion of Zytux™ in combination with chemotherapy. Administer Zytux™ as a single-agent every 8 weeks for 12 doses.

Non-progressing, low-grade, CD20-positive, b-cell NHL, after first-line CVP chemotherapy following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.

Diffuse large b-cell NHL

administer on day 1 of each cycle of chemotherapy for up to 8 infusions.

2.3 recommended dose for chronic lymphocytic leukemia (CLL)

The recommended dose is:

375 mg/m^2 the day prior to the initiation of fc chemotherapy, then 500 mg/m^2 on day 1 of cycles 2–6 (every 28 days).

2.4 recommended dose as a component of Zytux™ for treatment of NHL

Infuse rituximab 250 mg/m^2 within 4 hours prior to the administration of indium-111-(in-111-) Zytux™ and within 4 hours prior to the administration of yttrium-90- (y-90-) Zytux™™.

Administer Zytux™ and in-111-Zytux™7–9 days prior to Zytux™ and y-90- Zytux™.

Refer to the Zytux™ package insert for full prescribing information regarding the Zytux™ therapeutic regimen.

2.5 recommended dose for rheumatoid arthritis (RA)

Administer Zytux™ as two-1000 mg intravenous infusions separated by 2 weeks.

Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions.

Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks.

Zytux™ is given in combination with methotrexate.

2.6 recommended dose for granulomatosis with polyangiitis (GPA) (wegener's granulomatosis) and microscopic polyangiitis (MPA)

Administer Zytux™ as a 375 mg/m^2 intravenous infusion once weekly for 4 weeks.

glucocorticoids administered as methylprednisolone 1000 mg intravenously per day for 1 to 3 days followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day and tapered per clinical need) are recommended to treat severe vasculitis symptoms. This regimen should begin within 14 days prior to or with the initiation of Zytux™ and may continue during and after the 4 week course of rituximab treatment.

safety and efficacy of treatment with subsequent courses of Zytux™ have not been established.

2.7 recommended concomitant medications

premedicate before each infusion with acetaminophen and an antihistamine. For patients administered Zytux™ according to the 90-minute infusion rate, the glucocorticoid component of their chemotherapy regimen should be administered prior to infusion.

For RA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion.

For GPA and MPA patients, glucocorticoids are given in combination with Zytux™.

Pneumocystis jiroveci pneumonia (PCP) and anti-herpetic viral prophylaxis is recommended for patients with CLL during treatment and for up to 12 months following treatment as appropriate.

PCP prophylaxis is also recommended for patients with GPA and MPA during treatment and for at least 6 months following the last Zytux™ infusion.

2.8 preparation for administration

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use vial if particulates or discoloration is present. Withdraw the necessary amount of Zytux™ and dilute to a final concentration of 1 mg/ml to 4 mg/ml in an infusion bag containing either 0.9% sodium chloride, USP, or 5% dextrose in water, USP. Gently invert the bag to mix the solution. Do not mix or dilute with other drugs. Discard any unused portion left in the vial.

Zytux™ solutions for infusion may be stored at 2°c–8°c for 24 hours. Zytux™ solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since Zytux™ solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°c–8°c). No incompatibilities between Zytux™ and polyvinylchloride or polyethylene bags have been observed.

3. Dosage forms and strengths

Injection:

100 mg/10 ml in a single-use vial

500 mg/50 ml in a single-use vial

4. Contraindications

none.

5. Warnings and precautions

5.1 infusion reactions

Rituximab can cause severe, including fatal, infusion reactions. Severe reactions typically occurred during the first infusion with time to onset of 30–120 minutes. Rituximab-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

premedicate patients with an antihistamine and acetaminophen prior to dosing. For RA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion. Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed. Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue Zytux™. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (≥ 25,000/mm3).

5.2 severe mucocutaneous reactions

mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Zytux™™. These reactions include paraneoplastic pemphigus, stevens-johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of rituximab exposure. Discontinue Zytux™in patients who experience a severe mucocutaneous reaction. The safety of read ministration of Zytux™to patients with severe mucocutaneous reactions has not been determined.

5.3 hepatitis b virus reactivation

hepatitis b virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including Zytux™. Cases have been reported in patients who are hepatitis b surface antigen (HBSAG) positive and also in patients who are HBSAG negative but are hepatitis B core antibody (anti-HBC) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis b infection (i.e., HBSAG negative, anti-HBC positive and hepatitis b surface antibody [anti-HBC] positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBSAG in a person who was previously HBSAG negative and anti-HBC positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur.

Screen all patients for HBV infection by measuring HBSAG and anti-HBC before initiating treatment with Zytux™. for patients who show evidence of prior hepatitis b infection (HBSAG positive [regardless of antibody status] or HBSAG negative but anti-HBC positive), consult with physicians with expertise in managing hepatitis b regarding monitoring and consideration for HBV antiviral therapy before and/or during Zytux™ treatment.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following Zytux™therapy. HBV reactivation has been reported up to 24 months following completion of rituximab therapy.

In patients who develop reactivation of HBV while on Zytux™, immediately discontinue Zytux™ and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming Zytux™ in patients who develop HBV reactivation. Resumption of Zytux™ in patients whose HBV reactivation resolves should be discussed with physicians with expertise in managing hepatitis B.

5.4 progressive multifocal leukoencephalopathy (PML)

JC virus infection resulting in PML and death can occur in Zytux™ treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of rituximab.

Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain mri, and lumbar puncture. Discontinue Zytux™ and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

5.5 tumor lysis syndrome (TLS)

acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12–24 hours after the first infusion of Zytux™in patients with NHL. a high number of circulating malignant cells ($\geq$ 25,000/mm3) or high tumor burden, confers a greater risk of tls.

administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for tls. correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

5.6 infections

serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of rituximab-based therapy. infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia >11 months after rituximab exposure). new or

reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus b19, varicella zoster virus, west nile virus, and hepatitis b and c. discontinue Zytux™for serious infections and institute appropriate anti-infective therapy.

5.7 Cardiovascular

Discontinue infusions for serious or life-threatening cardiac arrhythmias. perform cardiac monitoring during and after all infusions of Zytux™ for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina.

5.8 Renal

Severe, including fatal, renal toxicity can occur after Zytux™ administration in patients with NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant Cisplatin therapy during clinical trials. The combination of Cisplatin and Zytux™ is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue Zytux™ in patients with a rising serum creatinine or oliguria.

5.9 bowel obstruction and perforation

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving Zytux™ in combination with chemotherapy. In post marketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1–77) days in patients with NHL. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur.

5.10 immunization

The safety of immunization with live viral vaccines following Zytux™ therapy has not been studied and vaccination with live virus vaccines is not recommended.

For RA patients, physicians should follow current immunization guidelines and administer non-live vaccines at least 4 weeks prior to a course of Zytux™™.

5.11 laboratory monitoring

In patients with lymphoid malignancies, during treatment with Zytux™ monotherapy, obtain complete blood counts (CBC) and platelet counts prior to each Zytux™ course. During treatment with Zytux™and chemotherapy, obtain CBC and platelet counts at weekly to monthly intervals and more frequently in patients who develop cytopenias. in patients with ra, GPA or MPA, obtain CBC and platelet counts at two to four month intervals during Zytux™ therapy. the duration of cytopenias caused by rituximab can extend months beyond the treatment period.

5.12 concomitant use with biologic agents and DMARDs other than methotrexate in RA, GPA and MPA

limited data are available on the safety of the use of biologic agents or DMARDs other than methotrexate in ra patients exhibiting peripheral b-cell depletion following treatment with rituximab. observe patients closely for signs of infection if biologic agents and/or DMARDs are used concomitantly. use of concomitant immunosuppressants other than corticosteroids has not been studied in GPA or MPA patients exhibiting peripheral b-cell depletion following treatment with Zytux™.

5.13 use in RA patients who have not had prior inadequate response to tumor necrosis factor (TNF) antagonists

The use of rituximab in patients with RA who have not had prior inadequate response to one or more TNF antagonists is not recommended

5.14 retreatment in patients with granulomatosis with polyangiitis (GPA) (wegener's granulomatosis) and microscopic polyangiitis (MPA)

limited data are available on the safety and efficacy of subsequent courses of Zytux™ in patients with GPA and MPA. The safety and efficacy of retreatment with Zytux™ have not been established.

6. Adverse reactions

Note: patients treated with rituximab for rheumatoid arthritis (ra) may experience fewer adverse reactions.

>10%:

Cardiovascular: peripheral edema (8% to 16%), hypertension (6% to 12%)

Central nervous system: fever (5% to 53%), fatigue (13% to 39%), chills (3% to 33%),

Headache (17% to 19%), insomnia (≤14%), pain (12%)

Dermatologic: rash (10% to 17%; grades 3/4: 1%), pruritus (5% to 17%), angioedema (11%;

Grades 3/4: 1%)

Gastrointestinal: nausea (8% to 23%), diarrhea (10% to 17%), abdominal pain (2% to 14%),

Weight gain (11%)

Hematologic: cytopenias (grades 3/4: ≤48%; may be prolonged), lymphopenia (48%; grades

3/4: 40%; median duration 14 days), anemia (8% to 35%; grades 3/4: 3%), leukopenia

(NHL: 14%; grades 3/4: 4%; CLL: grades 3/4: 23%; GPA/MPA: 10%), neutropenia (NHL:

14%; grades 3/4: 4% to 6%; median duration 13 days; CLL: grades 3/4: 30% to 49%),

neutropenic fever (CLL: grades 3/4: 9% to 15%), thrombocytopenia (12%; grades 3/4: 2%

To 11%)

Hepatic: alt increased (≤13%)

Neuromuscular & skeletal: neuropathy (≤30%), weakness (2% to 26%), muscle spasm (≤17%), arthralgia (6% to 13%)

Respiratory: cough (13%), rhinitis (3% to 12%), epistaxis (≤11%)

Miscellaneous: infusion-related reactions (lymphoma: first dose 77%; decreases with Subsequent infusions; may include angioedema, bronchospasm, chills, dizziness, fever, Headache, hyper-/hypotension, myalgia, nausea, pruritus, rash, rigors, urticaria, and Vomiting; reactions reported are lower [first infusion: 32%] in RA; CLL: 59%; grades 3/4: 7% to 9%; GPA/MPA: 12%); infection (19% to 62%; grades 3/4: 4%; bacterial: 19%; viral 10%; fungal: 1%), human antichimeric antibody (haca) positive (1% to 23%), night Sweats (15%)

1% to 10%:

Cardiovascular: hypotension (10%; grades 3/4: 2%), flushing (5%)

Central nervous system: dizziness (10%), anxiety (2% to 5%), migraine (ra: 2%)

Dermatologic: urticaria (2% to 8%)

Endocrine & metabolic: hyperglycemia (9%)

Gastrointestinal: vomiting (10%), dyspepsia (RA: 3%)

Neuromuscular & skeletal: back pain (10%), myalgia (10%), and paresthesia (2%)

Respiratory: dyspnea (≤10%), throat irritation (2% to 9%), bronchospasm (8%), dyspnea (7%), upper respiratory tract infection (RA: 7%), sinusitis (6%)

Miscellaneous: LDH increased (7%)

post marketing and/or case reports: acute renal failure, anaphylactic reaction/anaphylaxis, angina, aplastic anemia, ards, arrhythmia, bowel obstruction/perforation, bronchiolitis obliterans, cardiac failure, cardiogenic shock, encephalomyelitis, fatal infusion-related reactions, fulminant hepatitis, gastrointestinal perforation, hemolytic anemia, hepatic failure, hepatitis, hepatitis b reactivation, hyperviscosity syndrome (in waldenström's macroglobulinemia), hypogammaglobulinemia (prolonged), hypoxia, interstitial pneumonitis, laryngeal edema, lichenoid dermatitis, lupus-like syndrome, marrow hypoplasia, mi, mucositis, mucocutaneous reaction, neutropenia (late-onset occurring >40 days after last dose), optic neuritis, pancytopenia (prolonged), paraneoplastic pemphigus (uncommon), pleuritis, pneumonia, pneumonitis, polyarticular arthritis, polymyositis, posterior reversible encephalopathy syndrome (PRES), progressive multifocal leukoencephalopathy (PML), pure red cell aplasia, renal toxicity, reversible posterior leukoencephalopathy syndrome (RPLS), serum sickness, stevens-johnson syndrome, supraventricular arrhythmia, systemic vasculitis, toxic epidermal necrolysis, tuberculosis reactivation, tumor lysis syndrome, uveitis, vasculitis with rash, ventricular fibrillation, ventricular tachycardia, vesiculobullous dermatitis, viral

reactivation (includes JC virus, cytomegalovirus, herpes simplex virus, parvovirus b19, varicella zoster virus, west nile virus, and hepatitis c), wheezing

7. Drug interactions

Formal drug interaction studies have not been performed with Zytux™. In patients with CLL, rituximab did not alter systemic exposure to fludarabine or cyclophosphamide. in clinical trials of patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the pharmacokinetics of rituximab.

8. use in specific populations

8.1 pregnancy

Pregnancy category C

Risk summary

There are no adequate and well-controlled studies of rituximab in pregnant women. Women of childbearing potential should use effective contraception while receiving Zytux™ and for 12 months following treatment. Zytux™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human data

Post marketing data indicate that b-cell lymphocytopenia generally lasting less than six months can occur in infants exposed to rituximab in-utero. Rituximab was detected postnatally in the serum of infants exposed in-utero.

Animal data

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received rituximab via the intravenous route during early gestation (organogenesis period; post-coitum days 20 through 50). rituximab was administered as loading doses on postcoitum (pc) days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on pc days 29, 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased lymphoid tissue b cells.

a subsequent pre-and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of b cells and immune function in infants exposed to rituximab in utero. Animals were treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days, followed by weekly dosing with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were treated from pc day 20 through postpartum day 78, pc day 76 through pc day 134, and from pc day 132 through delivery and postpartum day

28. Regardless of the timing of treatment, decreased b cells and immunosuppression were noted in the offspring of rituximab-treated pregnant animals. The b-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

8.2 nursing mothers

It is not known whether Zytux™ is secreted into human milk. However, rituximab is secreted in the milk of lactating cynomolgus monkeys, and igg is excreted in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. The unknown risks to the infant from oral ingestion of Zytux™ should be weighed against the known benefits of breastfeeding.

8.3 pediatric use

FDA has not required pediatric studies in polyarticular juvenile idiopathic arthritis (PJIA) patients ages 0 to 16 due to concerns regarding the potential for prolonged immunosuppression as a result of b-cell depletion in the developing juvenile immune system. hypogammaglobulinemia has been observed in pediatric patients treated with Zytux™.

the safety and effectiveness of Zytux™ in pediatric patients have not been established.

8.4 geriatric use

Diffuse large B-cell NHL

Cardiac adverse reactions, mostly supraventricular arrhythmias, occurred more frequently among elderly patients. Serious pulmonary adverse reactions were also more common among the elderly, including pneumonia and pneumonitis.

Low-grade or follicular non-hodgkin's lymphoma

No overall differences in safety or effectiveness were observed between these patients and younger patients

Chronic lymphocytic leukemia

The brand study:

Among patients with CLL evaluated in two randomized active-controlled trials, 243 of 676 rituximab-treated patients (36%) were 65 years of age or older; of these, 100 rituximab -treated patients (15%) were 70 years of age or older.

In exploratory analyses defined by age, there was no observed benefit from the addition of rituximab to fludarabine and cyclophosphamide among patients 70 years of age or older in Study 11 or in Study 12; there was also no observed benefit from the addition of rituximab to fludarabine and cyclophosphamide among patients 65 years of age or older in Study 12 .Patients 70 years or older received lower dose intensity of fludarabine and cyclophosphamide compared to younger patients, regardless of the addition of rituximab. In Study 11, the dose intensity of rituximab was similar in older and younger patients, however in Study 12 older patients received a lower dose intensity of rituximab.
The incidence of Grade 3 and 4 adverse reactions was higher among patients receiving R-FC who were 70 years or older compared to younger patients for neutropenia [44% vs. 31% (Study 11); 56% vs. 39% (Study 12)], febrile neutropenia [16% vs. 6% (Study 10)], anemia [5% vs. 2% (Study 11); 21% vs. 10% (Study 12)], thrombocytopenia

[19% vs. 8% (Study 12)], pancytopenia [7% vs. 2% (Study 11); 7% vs. 2% (Study 12)] and infections [30% vs. 14% (Study 12)].

Rheumatoid arthritis

The incidences of adverse reactions were similar between older and younger patients. The rates of serious adverse reactions, including serious infections, malignancies, and cardiovascular events were higher in older patients.

granulomatosis with polyangiitis (GPA) (wegener's granulomatosis) and microscopic polyangiitis

No overall differences in efficacy were observed between patients that were 65 years old and over and younger patients. The overall incidence and rate of all serious adverse events was higher in patients 65 years old and over.

9. over dosage

There has been no experience of overdosage with Zytux™.

10. Description

Zytux™ (rituximab) is a genetically engineered chimeric murine/human monoclonal igg1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kd. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nm.

Rituximab is produced by mammalian cell (chinese hamster ovary) sUSPension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Zytux™ is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous administration. Zytux™ is supplied at a concentration of 10 mg/ml in either 100 mg/10 ml or 500 mg/50 ml single-use vials. the product is formulated in polysorbate 80 (0.7 mg/ml), sodium chloride (9 mg/ml), sodium citrate dihydrate (7.35 mg/ml), and water for injection. the ph. is 6.5.

11. Clinical pharmacology

mechanism of action

Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-b and mature b-lymphocytes. Upon binding to CD20, rituximab mediates b-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC) and antibody dependent cell mediated cytotoxicity (ADCC). The antibody induced apoptosis in the dhl 4 human b cell lymphoma cell line.

B cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis. in this setting, b cells may be acting at multiple sites in the autoimmune/inflammatory process,

including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, t-cell activation, and/or proinflammatory cytokine production.

12. Nonclinical toxicology

12.1 carcinogenesis, mutagenesis, impairment of fertility

No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of Zytux™ or to determine potential effects on fertility in males or females.

13. Clinical studies

a trial was designed as a non-inferiority clinical trial with two parallel arms and random group assignment. the comparator medicine and the control were Zytux™ and mabthera®, respectively. Patients also received fludarabine and cyclophosphamide as part of the FCR regimen. patients and assessors were blinded to administered brand of rituximab (double blind). a non-inferiority margin of 20% for primary outcome was selected by principal investigator (licensed oncologist) as an acceptable estimated difference between the comparator and the control.

a total of 82 patients were assessed and 70 eligible patients underwent randomization. of randomized patients, 14 subjects were not able to finish treatment cycles as scheduled. the number of dropouts difference was not significant between intervention groups.

baseline and demographic data analysis demonstrated adequate homogeneity between treatment arms. the mean±SD of age were 57.94±8.44 and 59.24±8.16 years, for Zytux™ and mabthera® groups, respectively. majority of patients were males (28/7 male/female in Zytux™ group and 29/6 male/female for mabthera® group). baseline lab tests including WBCs, plt, Hg, liver and renal function tests were comparable among treatment groups. Demographic information is summarized in table 1. as shown in table 1 no differences in cd counts (5, 19, 20 and 23) were detected considering treatment groups at baseline.

Table 1 baseline demographic data

variable		Zytux™ group (n=35)	mabthera® group (n=35)	p-value
baseline demographic	age (years)	57.94±8.44	59.24±8.16	0.52
	sex (m/f)	28/7	29/6	0.76
	weight (kg)	71.06±11.40	69.45±11.47	0.69
	body mass index (kg/m^2)	24.44±4.04	25.33±4.60	0.51

	respiratory rate (breaths/ minute)	15.23±1.96	15.27±2.01	0.92
	pulse rate (beats/minute)	77.66±5.24	77.06±4.49	0.19
	systolic blood pressure (mmhg)	120.86±10.67	122.35±11.30	0.57
	diastolic blood pressure (mmhg)	76.32±7.31	76.91±6.96	0.74
	body temperature (° c)	36.82±.31	36.83±.30	-
	body surface area (m^2)	1.83±0.16	1.78±0.16	0.21
baseline laboratory data	wbc × 10^3 (cells/mm^3)	69.34±54.81	52.88±53.73	0.19
	hb (gram/dl)	12.05±2.18	12.20±2.45	0.79
	plt × 10^3 /microliter	128.63±66.55	139.40±52.54	0.45
	lymphocyte %	84.07±14.56	77.67±13.27	0.05
	PMN %	9.14±7.39	16.36±10.11	0.01
	monocyte %	2.60±1.97	3.83±2.52	0.15
	eosinophil %	0.44±0.61	0.74±0.82	-
	reticulocyte × 10^6 /microliter	0.89±0.39	0.82±0.46	0.43
	SGOT (units/liter)	20.41±7.33	19.22±5.71	0.58
	SGPT (units/liter)	16.48±6.92	15.64±4.76	0.57
	alkp (units/liter)	226.40±80.78	224.26±73.45	0.91
	bun (mg/dl)	36.09±12.79	32.05±10.96	0.17
	creatinine (mg/dl)	1.06±0.23	1.11±0.22	0.32
	bilirubin (mg/dl)	0.77±0.36	0.68±0.35	0.17

the primary outcome for which the non-inferiority margin was defined is orr. regarding results of current study, cr rates of 60% and 58% and pr of 28% and 31% were obtained which contributed to 88% and 89% orr for Zytux™ and mabthera® groups, respectively. the predefined margin for acceptable difference between treatment effects of Zytux™ and mabthera® was 20%. as the results of this study confirmed the efficacy of Zytux™in terms of orr, it is shown to be non-inferior to mabthera® by the defined margin (figure 1). It is worth

to mention that the obtained results for orr in our trial were in agreement with various studies in the literature in which the efficacy of rituximab was assessed along with fcr regimen in similar study populations.

Table 2 clinical response rates

response	Zytux™ group (n=27)	mabthera® group (n=29)	p-value*
overall	22 (88%)	23 (89%)	1
complete	15 (60%)	15 (58%)	1
partial	7 (28%)	8 (31%)	1

as for the secondary outcome, flow cytometric assays on lymphocyte surface antigens of interest, including cd5, cd19, CD20 and cd22 demonstrated significant drop off in the percentage of cells expressing these antigens from baseline following administration of fcr regimen. the rates and magnitude of effects with Zytux™resembled that of mabthera® supporting the results obtained from the primary outcome.

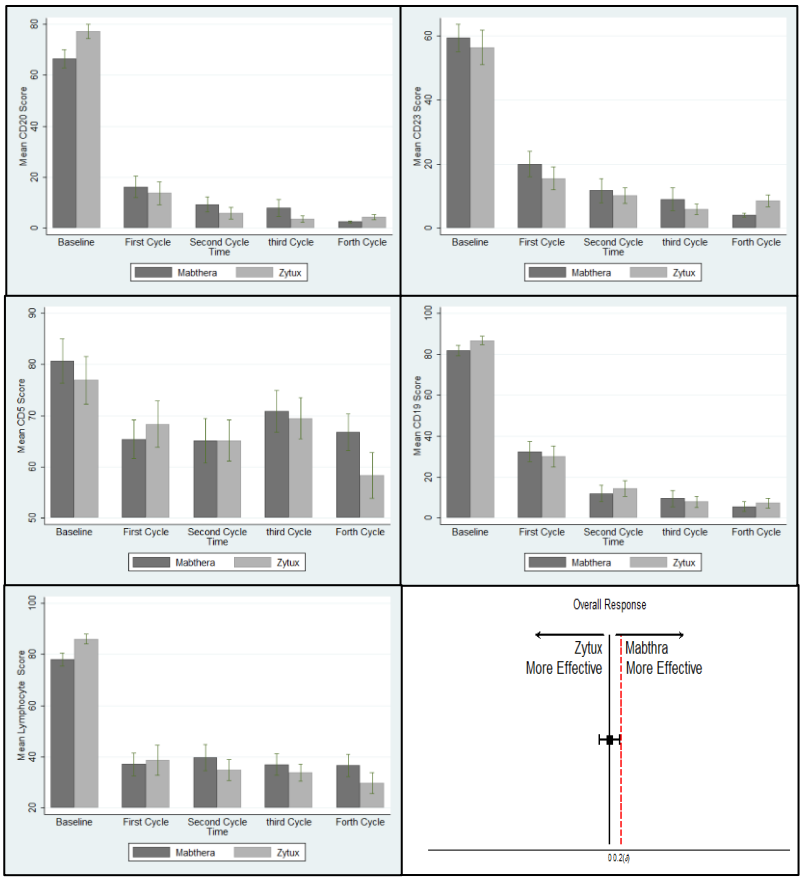

figure 1 lymphocyte and cd counts and non-inferiority plot

infusion reactions are the most anticipated adverse effects associated with rituximab administration especially during first cycle of treatment. it has been reported that infusion reactions occur in more than 50% of patients at early stages of first cycle of infusion but decrease in subsequent cycles. the rates reported in this trial were remarkably lower than the literature, which could be due to exact implementation of infusion protocol and close monitoring applied in our setting. infusion reactions were more common at first cycles with Zytux™ but this was not consistent in subsequent cycles and the overall number of infusion reactions were almost similar for both treatment groups. nausea, urticaria and chest pain occurred in mabthera® groups and were not reported with Zytux™ while headache, hypertension, hot flash and pruritus were reported only in Zytux™ group. other types of infusion reactions were alike for both groups. none of the infusion related events led to therapy discontinuation.

Table 2 incidence of infusion-related reactions

	infusion cycle	Zytux™ group (n=35)	mabthera® group (n=35)	total
incidence	cycle 1	9 (26%)	5 (14%)	14 (20%)
	cycle 2	3 (8.6%)	2 (5.7%)	5 (7.14%)
	cycle 3	2 (5.7%)	3 (8.6%)	5 (7.14%)

	cycle 4	1 (2.9%)	1 (2.9%)	2 (2.86%)
	overall	15 (25.7%)	11 (20%)	26 (22.86%)
type	type			
	shortness of breath	5	3	8
	palpitation	3	3	6
	rigors	3	3	6
	asthenia	3	1	4
	vertigo	1	1	2
	nausea	0	2	2
	urticaria	0	2	2
	chest pain	0	1	1
	headache	1	0	1
	hypertension	1	0	1
	hot flash	1	0	1
	skin rash	1	0	1
	pruritus	1	0	1

hematologic adverse reactions induced by chemotherapy regimens are of particular importance as they are directly associated with patient's quality of life and treatment outcomes. regarding these facts, the safety profile of biosimilar products concerning hematologic toxicities, have to be closely considered. the results of the current study demonstrated that there were no statistically or clinically meaningful diversity between Zytux™and mabthera® according hematologic toxicities. neutropenia was the most influential adverse reaction seen in both treatment groups, considering the fact that CLL patient are susceptible for this condition. the majority of neutropenic events were grade i and ii (28/33 and 29/36 for Zytux™ and mabthera®, respectively). grade iii/iv events were uncommon among treatment groups, 5/33 and 7/36 patients experienced grade iii/iv neutropenia in Zytux™and mabthera® groups, respectively. despite the slightly higher rate of neutropenia in mabthera® group, the difference was not significant (*p* value: 0.92). analysis of anemia as the most frequent hematologic adverse reaction, showed no remarkable difference between two groups; numerically more patients in Zytux™ group had experienced this adverse effect (41 vs 38) although this was not statistically significant (*p* value: 0.95). thrombocytopenia, another hematologic adverse effect, occurred in 54 patients including 29 and 25 patients in Zytux™and mabthera® group, respectively. stage i/ii thrombocytopenia incidence was similar in both groups, more patients in Zytux™group had experienced stage iii/iv thrombocytopenia than in mabthera® group (7 patients compared to 1 patient, respectively) though the difference did not achieve statistical significance (*p* value: 0.18). the hematologic events were in line with literature in terms of frequency and intensity and none of the events led to therapy discontinuation.

Table 4 hematologic adverse reactions

	Zytux™group (n=35) (122 exposures)	mabthera® group (n=35) (115 exposures)	total	*p* value
thrombocytopenia	no. (%)	no. (%)	no. (%)	
grade i (<lln* to 75,000/mm ^{3})	13 (11)	17 (15)	30 (13)	
grade ii (50,000 to 75,000/mm ^{3})	9 (7)	7 (6)	16 (7)	
grade iii (25,000 to 50,000/mm ^{3})	4 (3)	1 (1)	5 (2)	
grade iv (<25,000/mm ^{3})	3 (2)	0 (0)	3 (1)	
total	29 (24)	25 (22)	54 (23)	0.18
anemia (hemoglobin level)				
grade i (<lln* to 10 g/dl)	18 (15)	18 (16)	36 (15)	
grade ii (8.0 to 10.0 g/dl)	18 (15)	16 (14)	34 (14)	
grade iii (<8.0 g/dl)	5 (4)	4 (4)	9 (4)	
total	41 (34)	38 (33)	79 (33)	0.95
neutropenia				
grade i (<lln* to 1500/mm ^{3})	11 (9)	13 (11)	24 (10)	
grade ii (1000 to 1500/mm ^{3})	17 (14)	16 (14)	33 (14)	
grade iii (500 to 1000/mm ^{3})	4 (3)	6 (5)	10 (4)	
grade iv (<500/mm ^{3})	1 (1)	1 (1)	2 (1)	
total	33 (27)	36 (31)	69 (30)	0.92

* lln: lower limit of normal

the non-hematologic adverse reactions seen in this study were generally mild except for one case of tumor lysis syndrome which occurred in mabthera® group and also there was one case of hospitalization due to infection in Zytux™ group. in line with literature the most common non-hematologic adverse reactions observed were chills, nausea, fatigue, pain and flu-like syndrome and except for one case of tumor lysis syndrome, other events were mild to moderate and no therapy interruptions were indicated. the profile of these reactions for Zytux™ were corresponding to that of mabthera®.

Table 5 type of non-hematologic adverse reactions

type	Zytux™group (n=35)	mabthera® group (n=35)	total
chills	7	12	19
nausea	8	5	13
hot flashes	4	4	8

weight loss	4	1	5
fever	2	2	4
infection	3	1	4
asthenia	2	1	3
shortness of breath	1	2	3
pruritus	1	2	3
arthralgia	1	1	2
body pain	1	1	2
chest pain	0	2	2
headache	1	1	2
lumbar pain	1	1	2
night sweats	0	2	2
sweating	2	0	2
decreased appetite	1	0	1
apnea	1	0	1
bradycardia	1	0	1
flu-like syndrome	0	1	1
chemotherapy delay	0	1	1
delirium	1	0	1
hiccups	1	0	1
hospitalization	1	0	1
limb coldness	1	0	1
incontinence	1	0	1
mouth ulcer	0	1	1
rhinitis	0	1	1
rhinorrhea	0	1	1
sore throat	0	1	1
epiphora	0	1	1
tumor lysis syndrome	0	1	1
vertigo	1	0	1
dysphonia	0	1	1

the limitations of this study include rather small sample size and the patient survival information is unavailable because the complete follow-up was not performed. also, we only investigated the role of the biosimilar in CLL treatment. although, according to concerned guidelines, the efficacy or safety of biosimilar needs to be established in at least one of the indications, and if so, it can be generalized to the other uses of the reference drug.

according to the results of the current study, Zytux™(rituximab, AryoGen Pharmed) administration has been associated with coMPArable outcomes in terms of efficacy and safety in coMPArison to mabthera® and as a result the non-inferiority of Zytux™to mabthera® is established.

14. how supplied/storage and handling

Zytux™ vials (100 mg/10 ml single-use vials and 500 mg/50 ml single-use vials) are stable at 2°c–8°c .Zytux™ vials should be protected from direct sunlight. Do not freeze or shake.

Patients can be advised to get in touch with OrchidPharmed Patient Support Center for any question or report any Adverse Drug event.

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