PACK INSERT FOR MALAYSIA

MabThera®

Rituximab

1. DESCRIPTION

1.1 Therapeutic / Pharmacologic Class of Drug

Antineoplastic agent
ATC Code: L01XC02

1.2 Type of Dosage Form

Concentrate for solution for infusion.

1.3 Route of Administration

Intravenous (i.v.) infusion.

1.4 Sterile / Radioactive Statement

Sterile product.

1.5 Qualitative and Quantitative Composition

Active ingredient: rituximab
MabThera/Rituxan is a clear, colorless liquid supplied in sterile, preservative-free, non-pyrogenic single-dose vials.
Single-dose vials. Vials contain 100 mg/10 mL and 500 mg/50 mL.
Excipients: Sodium citrate, polysorbate 80, sodium chloride, sodium hydroxide, hydrochloric acid, water for injections.

2 CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Non-Hodgkin's Lymphoma:
MabThera/Rituxan is indicated for the treatment of:

- patients with relapsed or chemoresistant low-grade or follicular, CD20-positive, B-cell non-Hodgkin's lymphoma;
- previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy;
- patients with follicular lymphoma as maintenance treatment, after response to induction therapy.
- patients with CD20-positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP *(cyclophosphamide, doxorubicin, vincristine and prednisone)* chemotherapy.

Chronic Lymphocytic Leukemia (CLL):
MabThera/Rituxan is indicated, in combination with chemotherapy, for the treatment of patients with previously untreated and relapsed/refractory CD20-positive Chronic Lymphocytic Leukemia.
Rheumatoid Arthritis:
MabThera/Rituxan in combination with methotrexate is indicated for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to one or more tumor necrosis factor (TNF) inhibitor therapies.
Mabthera has been shown to reduce the rate of progression of joint damage as measured by X-ray when given in combination with methotrexate.
Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA)
MabThera in combination with glucocorticoids is indicated for the treatment of adult patients with severe, active granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis) and microscopic polyangiitis (MPA).

2.2 Dosage and Administration

General
Substitution by any other biological medicinal product requires the consent of the prescribing physician.
It is important to check the product labels to ensure that the appropriate formulation (IV or SC) and strength is being given to the patient, as prescribed.
MabThera/Rituxan should always be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced physician.

Premedication and Prophylactic Medications
Premedication consisting of an analgesic/anti-pyretic (e.g., paracetamol /acetaminophen) and an anti-histaminic drug (e.g., diphenhydramine) should always be given before each administration of MabThera/Rituxan.

Premedication with glucocorticoids should also be considered, particularly if MabThera/Rituxan is not given in combination with steroid-containing chemotherapy (see section 2.4 Warnings and Precautions).

In adult patients with non-Hodgkin's lymphoma and CLL, premedication with glucocorticoids should be considered if MabThera is not given in combination with glucocorticoid-containing chemotherapy.

Prophylaxis with adequate hydration and administration of uricostatics starting 48 hours prior to start of therapy is recommended for CLL patients to reduce the risk of tumour lysis syndrome. For CLL patients whose lymphocyte counts are > 25 X 10^9/L it is recommended to administer prednisone/prednisolone 100 mg intravenously shortly before infusion with MabThera/Rituxan to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

In patients with rheumatoid arthritis, GPA or MPA or pemphigus vulgaris, premedication with 100 mg intravenous methylprednisolone should be completed 30 minutes prior to each infusion of MabThera to decrease the incidence and severity of infusion related reactions (IRRs).

In adult patients with GPA or MPA, methylprednisolone given intravenously for 1 to 3 days at a dose of 1000 mg per day is recommended prior to the first infusion of MabThera (the last dose of methylprednisolone may be given on the same day as the first infusion of MabThera). This should be followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day, and tapered as rapidly as possible based on clinical need) during and after the 4 week induction course of MabThera treatment.

Dosage adjustments during treatment:
No dose reductions of MabThera/Rituxan are recommended. When MabThera/Rituxan is given in combination with chemotherapy, standard dose reductions for the chemotherapeutic drugs should be applied.
MabThera/Rituxan IV formulation is not intended for subcutaneous administration (see section 4.2 Special Instructions for Use, Handling and Disposal).
Do not administer the prepared infusion solutions as a push or bolus (see section 4.2 Special Instructions for Use, Handling and Disposal).

Intravenous Formulation Infusion Rate
First intravenous infusion:
The recommended initial infusion rate is 50 mg/hour; after the first 30 minutes, the rate can be escalated in 50 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

Subsequent intravenous infusions:
Subsequent infusions of MabThera/Rituxan IV can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

Standard dosage
Low-grade or follicular non-Hodgkin's lymphoma
Initial treatment
• Intravenous monotherapy
The recommended dosage of MabThera/Rituxan IV used as monotherapy for adult patients is 375 mg/m^2 body surface area (BSA), administered as an intravenous infusion (see "Intravenous Formulation Infusion Rate" sub-section, above) once weekly for 4 weeks.
The recommended dosage of MabThera/Rituxan IV (R-IV) in combination with any chemotherapy is 375 mg/m^2 body surface area per cycle for a total of:
- 8 cycles R-IV with CVP (21 days/cycle)
- 8 cycles R-IV with MCP (28 days/cycle)
- 8 cycles R-IV with CHOP (21 days/cycle); 6 cycles if a complete remission is achieved after 4 cycles
- 6 cycles with R-CHVP-Interferon (21 days/cycle)

MabThera/Rituxan IV should be administered on day 1 of each chemotherapy cycle after intravenous administration of the glucocorticoid component of the chemotherapy, if applicable.

Re-treatment following relapse
Patients who have responded to MabThera/Rituxan IV initially may receive MabThera/Rituxan at a dose of 375 mg/m^2 BSA, administered as an i.v. infusion once weekly for 4 weeks (see section 3.1.2 Clinical/Efficacy Studies, Re-treatment, weekly for 4 doses).

Maintenance treatment
Previously untreated patients after response to induction treatment may receive maintenance therapy with MabThera/Rituxan given at 375mg/m^2 once every 2 months until disease progression or for a maximum period of two years (12 infusions in total).
Relapsed/refractory patients after response induction treatment may receive maintenance therapy with MabThera/Rituxan given at 375 mg/m^2 once every 3 months until disease progression or for a maximum period of two years (8 infusions in total).

Diffuse large B-cell non-Hodgkin's lymphoma
In patients with diffuse large B cell non-Hodgkin's lymphoma MabThera/Rituxan should be used in combination with CHOP (cyclophosphamide, doxorubicin, prednisone and vincristine) chemotherapy. The recommended dosage of MabThera/Rituxan is 375 mg/m^2 BSA, administered on day 1 of each chemotherapy cycle for 8 cycles after i.v. administration of the glucocorticoid component of CHOP (see "Intravenous Formulation Infusion Rate" sub-section, above).

Chronic Lymphocytic Leukemia
The recommended dosage of MabThera/Rituxan in combination with chemotherapy for previously untreated and relapsed/refractory CLL patients is 375 mg/m^2 BSA administered on day 1 of the first treatment cycle followed by 500 mg/m^2 BSA administered on day 1 of each subsequent cycle for 6 cycles in total (see section 3.1.2 Clinical/Efficacy Studies). The chemotherapy should be given after the MabThera/Rituxan IV infusion (see "Intravenous Formulation Infusion Rate" sub-section, above).

Rheumatoid arthritis
A course of MabThera/Rituxan consists of two 1000 mg i.v. infusions. The recommended dosage of MabThera/Rituxan is 1000 mg by i.v. infusion followed two weeks later by the second 1000 mg i.v. infusion (see "Intravenous Formulation Infusion Rate" sub-section, above).
The need for further courses should be evaluated 24 weeks following the previous course with retreatment given based on residual disease or disease activity returning to a level above a DAS28-ESR of 2.6 (treatment to remission) (see section 3.1.2 Clinical/Efficacy Studies, Rheumatoid Arthritis). Patients may receive further courses no sooner than 16 weeks following the previous course.

Alternative 120-minute subsequent infusions with the concentration of 4 mg/mL in a 250 mL volume:
If patients did not experience a serious infusion-related adverse event with their previous infusion administered over the original administration schedule, a 120-minute infusion can be administered for subsequent infusions. Initiate at a rate of 250mg/hour for the first 30 minutes and then 600 mg/hour for the next 90 minutes. If the 120-minute infusion is tolerated, the same alternative 120-minute infusion rate can be used when administering subsequent infusions and courses.
Patients who have clinically significant cardiovascular disease including arrhythmias or previous serious infusion reactions to any prior biologic therapy or to MabThera/Rituxan, should not be administered the 120-minute infusion.

Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)
The recommended dosage of MabThera/Rituxan for treatment of GPA and MPA is 375 mg/m^2 BSA, administered as an IV infusion (see "Intravenous Formulation Infusion Rate" sub-section, above) once weekly for 4 weeks.
Methylprednisolone 1000 mg IV per day for 1 to 3 days is recommended in combination with MabThera/Rituxan to treat severe vasculitis symptoms, followed by oral prednisone 1 mg/kg/day (not to exceed 80mg/day, and tapered as rapidly as possible per clinical need) during and after MabThera/Rituxan IV treatment.
Pneumocystis jiroveci pneumonia (PCP) prophylaxis is recommended for patients with GPA and MPA prior to and following MabThera/Rituxan IV treatment, as appropriate according to local clinical practice guidelines..

2.2.1 Special Dosage Instructions
Pediatric use:
The safety and efficacy of MabThera/Rituxan in children and adolescents (<18 years) have not been established.
Geriatric use:
No dose adjustment is required in patients aged ≥65 years of age.

2.3 Contraindications

MabThera/Rituxan is contraindicated in patients with known hypersensitivity to rituximab, to any component of the product or to murine proteins.

2.4 Warnings and Precautions

2.4.1 General

In order to improve the traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly recorded (or stated) in the patient file.

Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukemia Patients

Infusion-related reactions

MabThera/Rituxan is associated with infusion-related reactions, which may be related to release of cytokines and/or other chemical mediators. Cytokine release syndrome may be clinically indistinguishable from acute hypersensitivity reactions.

Severe infusion-related reactions (IRRs) with fatal outcome have been reported during post-marketing use. Severe IRRs usually manifested within 30 minutes to 2 hours after starting the first MabThera/Rituxan infusion, were characterized by *pulmonary events* and included, in some cases, *rapid tumor lysis* and *features of tumor lysis syndrome* in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms (see section 2.6 Undesirable Effects). Patients with a high tumor burden or with a high number (>25 x 10^9/L) of circulating malignant cells such as patients with CLL and mantle cell lymphoma may be at higher risk of developing IRRs reactions. Infusion reaction symptoms are usually reversible with interruption of the infusion. Treatment of infusion-related symptoms with diphenhydramine and paracetamol/acetaminophen is recommended. Additional treatment with bronchodilators or i.v. saline may be indicated. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/hour to 50 mg/hour) when symptoms have completely resolved. Most patients who have experienced non-life threatening IRRs have been able to complete the full course of MabThera/Rituxan therapy. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe IRRs.

Patients with a high number (>25 x 10^9/L) of circulating malignant cells or high tumor burden such as patients with CLL and mantle cell lymphoma, who may be at higher risk of especially severe IRRs, should only be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle and any subsequent cycles if the lymphocyte count is still > 25 x 10^9/L.

Hypersensitivity reactions / Anaphylaxis

Anaphylactic and other hypersensitivity reactions have been reported following the intravenous administration of proteins to patients. Epinephrine, antihistamines and glucocorticoids should be available for immediate use in the event of a hypersensitivity reaction to MabThera/Rituxan IV.

Pulmonary events

Pulmonary events have included hypoxia, lung infiltration, and acute respiratory failure. Some of these events have been preceded by severe bronchospasm and dyspnea. In some cases, symptoms worsened over time, while in others initial improvement was followed by clinical deterioration. Therefore, patients experiencing pulmonary events or other severe infusion-related symptoms should be closely monitored until complete resolution of their symptoms occurs. Patients with a history of pulmonary insufficiency or those with pulmonary tumour infiltration may be at greater risk of poor outcome and should be treated with increased caution. Acute respiratory failure may be accompanied by events such as pulmonary interstitial infiltration or edema, visible on a chest X-ray. The syndrome usually manifests itself within one or two hours of initiating the first infusion. Patients who experience severe pulmonary events should have their infusion interrupted immediately (see section 2.2 Dosage and Administration) and should receive aggressive symptomatic treatment.

Rapid tumor lysis

MabThera/Rituxan mediates the rapid lysis of benign and malignant CD20-positive cells. Signs and symptoms (e.g., hyperuricemia, hyperkalemia, hypocalcemia, hyperphosphataemia, acute renal failure, elevated LDH) consistent with tumour lysis syndrome (TLS) have been reported to occur after the first MabThera/Rituxan infusion in patients with high numbers of circulating malignant lymphocytes. Prophylaxis for TLS should be considered for patients at risk of developing rapid tumour lysis (e.g., patients with a high tumor burden or with a high number [>25 x 10^9/L] of circulating malignant cells such as patients with CLL or mantle cell lymphoma). These patients should be followed closely and appropriate laboratory monitoring performed.

Appropriate medical therapy should be provided for patients who develop signs and symptoms consistent with rapid tumour lysis. Following treatment and complete resolution of signs and symptoms, subsequent MabThera/Rituxan therapy has been administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Cardiovascular
Since hypotension may occur during MabThera/Rituxan infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to and throughout MabThera/Rituxan infusion. Angina pectoris or cardiac arrhythmia, such as atrial flutter and fibrillation, heart failure or myocardial infarction have occurred in patients treated with MabThera/Rituxan. Therefore, patients with a history of cardiac disease should be monitored closely.

Monitoring of blood counts
Although MabThera/Rituxan is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophil counts of $<1.5 \times 10^9$/L and/or platelet counts of $<75 \times 10^9$/L, as clinical experience with such patients is limited. MabThera/Rituxan has been used in patients who underwent autologous bone marrow transplantation and in other risk groups with a presumable reduced bone marrow function without inducing myelotoxicity.

Consideration should be given to the need for regular full blood counts, including platelet counts, during monotherapy with MabThera/Rituxan. When MabThera/Rituxan is given in combination with CHOP or CVP chemotherapy, regular full blood counts should be performed according to usual medical practice.

Infections
MabThera/Rituxan treatment should not be initiated in patients with severe active infections.

Hepatitis B Infections
Cases of hepatitis B reactivation, including reports of fulminant hepatitis, some of which were fatal, have been reported in subjects receiving MabThera/Rituxan IV, although the majority of these subjects were also exposed to cytotoxic chemotherapy. The reports are confounded by both the underlying disease state and the cytotoxic chemotherapy.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera/Rituxan. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guideline. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Progressive Multifocal Leukoencephalopathy
Cases of progressive multifocal leukoencephalopathy (PML) have been reported during use of MabThera/Rituxan IV in NHL and CLL (see section 2.6 Undesirable Effects, Post Marketing). The majority of patients had received MabThera/Rituxan IV in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Physicians treating patients with NHL and CLL should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a Neurologist should be considered as clinically indicated.

Skin reactions
Severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 2.6. Undesirable Effects, Post Marketing). In case of such an event with a suspected relationship to MabThera/Rituxan, treatment should be permanently discontinued.

Immunization
The safety of immunization with live viral vaccines, following MabThera/Rituxan therapy has not been studied and vaccination with live virus vaccines is not recommended.

Patients treated with MabThera/Rituxan may receive non-live vaccinations. However, with non-live vaccines response rates may be reduced. In a non-randomized study, patients with relapsed low-grade NHL who received MabThera/Rituxan monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 76% when assessed for >2-fold increase in antibody titer).

Mean pre-therapeutic antibody titers against a panel of antigens (Streptococcus pneumoniae, influenza A, mumps, rubella, varicella) were maintained for at least 6 months after treatment with MabThera/Rituxan.

Rheumatoid Arthritis (RA), Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA) Patients:
The efficacy and safety of MabThera/Rituxan for the treatment of autoimmune disease other than rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis have not been established.

Infusion-related reactions
MabThera/Rituxan is associated with infusion-related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators. Premedication consisting of an analgesic/anti-pyretic and an anti-histaminic, should always be administered before each infusion of MabThera/Rituxan.
For RA patients, premedication with IV glucocorticoids should also be administered before each infusion of MabThera/Rituxan, in order to reduce the frequency and severity of IRRs (see section 2.2 Dosage and Administration and section 2.6 Undesirable Effects).
For RA patients, most infusion-related events reported in clinical trials were mild to moderate in severity. Severe IRRs with fatal outcome have been reported in the post-marketing setting (see section 2.6. Undesirable Effects, Post Marketing). Closely monitor patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions. The most common symptoms were headache, pruritus, throat irritation, flushing, rash, urticaria, hypertension, and pyrexia. In general, the proportion of patients experiencing any infusion reaction was higher following the first infusion of any treatment course than following the second infusion. Subsequent MabThera/Rituxan infusions were better tolerated by patients than the initial infusion. Less than 1% of patients experienced serious IRRs, with most of these reported during the first infusion of the first course (see section 2.6 Undesirable Effects). The reactions reported were usually reversible with a reduction in rate or interruption of MabThera/Rituxan infusion, and administration of an anti-pyretic, an antihistamine, and occasionally; oxygen, i.v. saline, bronchodilators, or glucocorticoids as required. Depending on the severity of the IRRs and the required interventions, temporarily or permanently discontinue MabThera/Rituxan. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hour to 50 mg/hour) when symptoms have completely resolved.

Infusion-related reactions in GPA and MPA patients were similar to those seen in RA patients in clinical trials and in the post-marketing setting (see section 2.6 Undesirable Effects). For GPA and MPA patients, MabThera IV was given in combination with high doses of glucocorticoids (see section 2.2 Dosage and Administration), which may reduce the incidence and severity of these events (see information for Rheumatoid Arthritis patients, above)

Hypersensitivity reactions/Anaphylaxis:
Anaphylactic and other hypersensitivity reactions have been reported following the i.v. administration of proteins to patients. Medicinal products for the treatment of hypersensitivity reactions, (e.g., epinephrine, antihistamines and glucocorticoids), should be available for immediate use in the event of an allergic reaction during administration of MabThera/Rituxan.

Cardiovascular
Since hypotension may occur during MabThera/Rituxan infusion, consideration should be given to withholding anti-hypertensive medications 12 hours prior to the MabThera/Rituxan infusion.

Angina pectoris, cardiac arrhythmias such as atrial flutter and fibrillation heart failure or myocardial infarction have occurred in patient treated with MabThera/Rituxan. Therefore patients with a history of cardiac disease should be monitored closely (see Infusion-related reactions sub-section, above).

Infections
Based on the mechanism of action of MabThera/Rituxan and the knowledge that B cells play an important role in maintaining normal immune response, patients may have an increased risk of infection following MabThera/Rituxan therapy. MabThera/Rituxan should not be administered to patients with an active infection or severely immunocompromised patients (e.g. where levels of CD4 or CD8 are very low). Physicians should exercise caution when considering the use of MabThera/Rituxan in patients with a history of recurring or chronic infections or with underlying conditions which may further predispose patients to serious infection (see section 2.6 Undesirable Effects). Patients who develop infection following MabThera/Rituxan therapy should be promptly evaluated and treated appropriately.

Hepatitis B infections:
Cases of hepatitis B reactivation including those with a fatal outcome, have been reported in RA, GPA and MPA patients receiving MabThera/Rituxan IV.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera/Rituxan IV. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guideline. Patients with active hepatitis B disease should not be treated with MabThera. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis B reactivation.

Skin reactions
Severe skin reactions such as toxic epidermal necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported (see section 2.6 Undesirable Effects, Post Marketing). In case of such an event, with a suspected relationship to MabThera/Rituxan IV, treatment should be permanently discontinued.

Progressive multifocal leukoencephalopathy
Cases of fatal progressive multifocal leukoencephalopathy (PML) have been reported following use of MabThera/Rituxan for the treatment of autoimmune diseases including RA. Several, but not all of the reported cases had potential risk factors for PML, including the underlying disease, long-term immunosuppressive therapy or chemotherapy. PML has also been reported in patients with autoimmune disease not treated with MabThera/Rituxan. Physicians treating patients with autoimmune diseases should consider PML in the differential diagnosis of patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Immunization
The safety of immunization with live viral vaccines following MabThera/Rituxan IV therapy has not been studied. Therefore. vaccines with live virus vaccines is not recommended whilst receiving MabThera/Rituxan IV or whilst peripherally B-cell depleted. Patients treated with MabThera/Rituxan IV may receive non-live vaccinations. However, response rates to non-live vaccines maybe reduced.
For patients treated with Mabthera/Rituxan IV, physicians should review the patient's vaccination status and patients should, if possible, be brought up-to-date with all immunizations in agreement with current immunization guidelines prior to initiating MabThera/Rituxan IV therapy. Vaccinations should be completed at least 4 weeks prior to first administration of MabThera/Rituxan.

In a randomized study, patients with RA treated with MabThera/Rituxan and methotrexate had comparable response rates to tetanus recall antigen (39% vs. 42%), reduced rates to pneumococcal polysaccharide vaccine (43% vs. 82% to at least 2 pneumococcal antibody serotypes), and KLH neoantigen (34% vs. 80%), when given at least 6 months after MabThera/Rituxan as compared to patients only receiving methotrexate.
Should non-live vaccinations be required whilst receiving MabThera/Rituxan therapy, these should be completed at least 4 weeks prior to commencing the next course of MabThera/Rituxan.

In the overall experience of MabThera/Rituxan repeat treatment in RA patients over one year, the proportions of patients with positive antibody titers against S. pneumonia, influenza, mumps, rubella, varicella and tetanus toxoid were generally similar to the proportions at baseline.

Methotrexate-naïve RA populations
The use of MabThera/Rituxan is not recommended in methotrexate-naïve patients since a favourable benefit risk relationship has not been established.

2.4.2 Ability to Drive and Use Machines
No studies on the effects of MabThera on the ability to drive and use machines have been performed, although the pharmacological activity and adverse reactions reported to date suggest that MabThera would have no or negligible influence on the ability to drive and use machines.

2.5 Use in Special Populations
2.5.1 Females and Males of Reproductive Potential
Fertility
No preclinical fertility studies have been conducted.
Animal data

Developmental toxicity studies performed in cynomolgus monkeys revealed no evidence of embryotoxicity in utero. Newborn offspring of maternal animals exposed to MabThera/Rituxan were noted to have depleted B-cell populations during the post-natal phase

Contraception

Women of childbearing age must employ effective contraceptive methods during and for 12 months after treatment with MabThera/Rituxan.

2.5.2 Pregnancy

IgG immunoglobulins are known to cross the placental barrier.

B cell levels in human neonates following maternal exposure to MabThera/Rituxan have not been studied in clinical trials. There are no adequate and well-controlled data from studies in pregnant women, however transient B-cell depletion and lymphocytopenia have been reported in some infants born to mothers exposed to rituximab during pregnancy. For these reasons MabThera/Rituxan should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

2.5.3 Lactation

Limited data on rituximab excretion into breast milk suggest very low milk levels (relative infant dose less than 0.4%). Few cases of follow-up of breastfed infants describe normal growth and development up to 1.5 years. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breastfeeding is not recommended while being treated with rituximab and optimally for 12 months following rituximab treatment.

2.5.4 Pediatric Use

The safety and efficacy of MabThera/Rituxan in pediatric patients have not been established. Hypogammaglobulinaemia has been observed in pediatric patients treated with MabThera IV, in some cases severe and requiring long-term immunoglobulin substitution therapy (see section 2.6 Undesirable Effects, Clinical Trails). The consequences of long term B cell depletion in pediatric patients are unknown.

2.5.5 Geriatric Use

The safety and efficacy of MabThera/Rituxan in geriatric patients has not been established.

2.5.6 Renal Impairment

The safety and efficacy of renal impairment in MabThera/Rituxan patients has not been established.

2.5.7 Hepatic Impairment

The safety and efficacy of hepatic impairment in MabThera/Rituxan patients has not been established.

2.6 Undesirable Effects

2.6.1 Clinical Trials

Experience from Clinical Trials in Hemato-Oncology

The frequencies of adverse drug reactions (ADRs) reported with MabThera/Rituxan IV alone or in combination with chemotherapy are summarized in the tables below and are based on data from clinical trials. These ADRs had either occurred in single arm studies or had occurred with at least a 2% difference compared to the control arm in at least one of the major randomized clinical trials. ADRs are added to the appropriate category in the tables below according to the highest incidence seen in any of the major clinical trials. Within each frequency grouping ADRs are listed in descending order of severity. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), and uncommon (≥ 1/1,000 to < 1/100).

MabThera/ Rituxan IV Monotherapy/Maintenance Therapy

The ADRs in the Table 1 below are based on data from single-arm studies including 356 patients with low-grade or follicular lymphoma, treated with MabThera/Rituxan IV weekly as single agent for the treatment or re-treatment of non-Hodgkin's lymphoma (see section 3.1.2 Clinical/Efficacy Studies). The table also contains ADRs based on data from 671 patients with follicular lymphoma who received MabThera/Rituxan IV as maintenance therapy for up to 2 years following response to initial induction with CHOP, R-CHOP, R-CVP or R-FCM (see section 3.1.2 Clinical/Efficacy Studies). The ADRs were reported up to 12 months after treatment with monotherapy and up to 1 month after treatment with MabThera/Rituxan IV maintenance.

Table 1 Summary of ADRs Reported in Patients with Low-Grade or Follicular Lymphoma Receiving MabThera/Rituxan IV Monotherapy (n=356) or MabThera/Rituxan IV Maintenance Treatment (n=671) in Clinical Trials.

System Organ Class	Very Common (≥ 10%)	Common (≥1% - < 10%)	Uncommon (≥0.1% - < 1%)
Infections and infestations	bacterial infections, viral infections	sepsis, [+]pneumonia, [+]febrile infection, [+]herpes zoster, [+]respiratory tract infection, fungal infections, infections of unknown aetiology	
Blood and lymphatic system disorders	neutropenia, leucopenia	anaemia, thrombocytopenia	coagulation disorders, transient aplastic anaemia, haemolytic anaemia, lymphadenopathy
Immune system disorders	angioedema	hypersensitivity	
Metabolism and nutrition disorders		hyperglycaemia, weight decrease, peripheral edema, face edema, increased LDH, hypocalcemia	
Psychiatric disorders			depression, nervousness,
Nervous system disorders		paresthesia, hypoesthesia, agitation, insomnia, vasodilatation, dizziness, anxiety	dysgeusia
Eye disorders		lacrimation disorder, conjunctivitis	
Ear and labyrinth disorders		tinnitus, ear pain	
Cardiac disorders		[+]myocardial infarction, arrhythmia , [+]atrial fibrillation, tachycardia, [+]cardiac disorder	[+]left ventricular failure, supraventricular tachycardia, [+]ventricular tachycardia, [+]angina, [+]myocardial ischaemia, bradycardia,
Vascular disorders		hypertension, orthostatic hypotension, hypotension	
Respiratory, thoracic and mediastinal disorders		bronchospasm , respiratory disease, chest pain, dyspnoea , cough , rhinitis	asthma , bronchiolitis obliterans, lung disorder, hypoxia
Gastrointestinal disorders	nausea	vomiting , diarrhea, abdominal pain , dysphagia , stomatitis, constipation,	abdominal enlargement

		dyspepsia, anorexia, throat irritation	
Skin and subcutaneous tissue disorders	pruritus, rash	urticaria , +alopecia, sweating, night sweats	
Musculoskeletal, connective tissue and bone disorders		hypertonia, myalgia , arthralgia , back pain , neck pain, pain	
General disorders and administration site conditions	fever , chills , asthenia , headache	tumour pain, flushing, malaise, cold syndrome	infusion site pain
Investigations	decreased IgG levels		

For each term, the frequency count was based on reactions of all grades (from mild to severe), except for terms marked with "+" where the frequency count was based only on severe (≥ grade 3 NCI common toxicity criteria) reactions. Only the highest frequency observed in either trial is reported.

MabThera/Rituxan IV in Combination with Chemotherapy in NHL and CLL

The ADRs listed in Table 2 are based on MabThera/Rituxan IV arm data from controlled clinical trials that occurred in addition to those seen with monotherapy / maintenance therapy and/or at a higher frequency grouping: 202 patients with diffuse large B-cell lymphoma (DLBCL) treated with R-CHOP, and from 234 and 162 patients with follicular lymphoma treated with R-CHOP or R-CVP, respectively and from 397 previously untreated CLL patients and 274 relapsed/refractory CLL patients, treated with MabThera/Rituxan IV in combination with fludarabine and cyclophosphamide (R-FC) (see section 3.1.2 Clinical/Efficacy Studies).

Table 2 Summary of Severe ADRs Reported in Patients Receiving R-CHOP in DLBCL (n=202), R-CHOP in Follicular Lymphoma (n=234), R-CVP in Follicular Lymphoma (n=162), R-FC in Previously Untreated (n=397) or Relapsed/Refractory (n=274) Chronic Lymphocytic Leukaemia

System Organ Class	Very Common (≥ 10%)	Common (≥ 1% - <10%)
Infections and infestations	bronchitis	acute bronchitis, sinusitis hepatitis B*,
Blood and the lymphatic system disorders	neutropenia# febrile neutropenia, thrombocytopenia	pancytopenia, granulocytopenia
Skin and subcutaneous tissue disorders	alopecia	skin disorder
General disorders and administration site conditions		fatigue, shivering,

*includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL

Frequency count was based on only severe reactions defined in clinical trials as ≥ grade 3 NCI common toxicity criteria

Only the highest frequency observed in any trial is reported

prolonged and/or delayed onset neutropenia after completion of an R-FC course in previously untreated or relapsed/refractory CLL

The following terms have been reported as adverse events, however, were reported at a similar (<2% difference between the groups) or lower incidence in the MabThera/Rituxan IV-arms compared to control arms: Haematotoxicity, neutropenic infection, urinary tract infection, septic shock, superinfection lung, implant infection, septicaemia staphylococcal, lung infection, rhinorrheoa, pulmonary oedema, cardiac failure, sensory disturbance, venous thrombosis, mucosal inflammation nos, influenza-like illness, oedema lower limb,

abnormal ejection fraction, pyrexia, general physical health deterioration, fall, multi-organ failure, venous thrombosis deep limb, positive blood culture, diabetes mellitus inadequate control.

The safety profile for MabThera/Rituxan IV in combination with other chemotherapies (e.g. MCP, CHVP-IFN) is comparable to the safety profile as described for the combination of MabThera/Rituxan IV and CVP, CHOP or FC in equivalent populations.

Further information on selected, serious adverse drug reactions

Administration-related reactions

Monotherapy - 4 weeks treatment

Signs and symptoms suggestive of an infusion-related reaction (IRR) were reported in more than 50% of patients in clinical trials, and were predominantly seen during the first infusion. Hypotension, fever, chills, rigors, urticaria, bronchospasm, sensation of tongue or throat swelling (angioedema), nausea, fatigue, headache, pruritus, dyspnea, rhinitis, vomiting, flushing, and pain at disease sites have occurred in association with MabThera/Rituxan infusion as part of infusion-related symptom complex. Some features of tumor lysis syndrome have also been observed.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)

Severe IRRs occurred in up to 12% of all patients at the time of the first treatment cycle with MabThera/Rituxan IV in combination with chemotherapy. The incidence of infusion-related symptoms decreased substantially with subsequent infusion and in <1% of patients by the eighth cycle. Additional reactions reported were dyspepsia, rash, hypertension, tachycardia, and features of tumour lysis syndrome. Isolated cases of mycocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia were also reported.

Infections

Monotherapy 4 weeks treatment

MabThera/Rituxan IV induced B-cell depletion in 70% to 80% of patients but was associated with decreased serum immunoglobulins in only a minority of patients. Bacterial, viral, fungal and unknown etiology infections, irrespective of causal assessment, occurred in 30.3% of 356 patients. Severe infectious events (Grade 3 or 4), including sepsis occurred in 3.9% of patients

Maintenance Treatment (NHL) up to 2 years

Higher frequencies of infections overall, including Grade 3 and 4 infections, were observed during MabThera/Rituxan IV treatment. There was no cumulative toxicity in terms of infections reported over the 2-year maintenance period.

Data from clinical trials included cases of fatal PML in NHL patients that occurred after disease progression and retreatment (see section 2.4 Warnings and Precautions).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)

No increase in the frequency of infections or infestations was observed. The most common infections were upper respiratory tract infections which were reported for 12.3% patients on R-CVP and 16.4% patients receiving CVP. Serious infections were reported in 4.3% of the patients receiving R-CVP and 4.4% of the patients receiving CVP. No life-threatening infections were reported during this study.

In the R-CHOP study the overall incidence of Grade 2 to 4 infections was 45.5% in the R-CHOP group and 42.3% in the CHOP group. Grade 2 to 4 fungal infections were more frequent in the R-CHOP group (4.5% vs. 2.6% in the CHOP group); this difference was due to a higher incidence of localized Candida infections during the treatment period. The incidence of Grade 2 to 4 herpes zoster was higher in the R-CHOP group (4.5%) than in the CHOP group (1.5%). The proportion of patients with grade 2 to 4 infections and/or febrile neutropenia was 55.4% in the R-CHOP group and 51.5% in the CHOP group.

In patients with CLL, the incidence of Grade 3 and 4 hepatitis B infection (reactivation and primary infection) was 2% in the R-FC group vs. 0% in the FC group.

Hematologic events

Monotherapy 4 weeks treatment

Severe (Grade 3 and 4) neutropenia was reported in 4.2% of patients, severe anemia was reported in 1.1% of patients and severe thrombocytopenia was reported in 1.7% of patients.

Maintenance Treatment (NHL) up to 2 years

There was a higher incidence of Grade 3 and 4 leucopenia (observation 2%, vs. MabThera/Rituxan IV 5%) and neutropenia (observation 4% vs. MabThera/Rituxan IV 10%) in the MabThera/Rituxan IV arm compared to the observation arm. The incidence of Grade 3 and 4 thrombocytopenia (observation 1% vs. MabThera/Rituxan IV <1%) was low. In approximately half of the patients with available data on B-cell recovery after end of MabThera/Rituxan IV induction treatment, it took 12 months or more for their B-cell levels return to normal values.

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)
During treatment course in studies with MabThera/Rituxan in combination with chemotherapy, Grade 3 and 4 leucopenia (R-CHOP 88% vs. CHOP 79%, R-FC 23% vs. FC 12%) and neutropenia (R-CVP 24% vs. CVP 14%, R-CHOP 97% vs. CHOP 88%, R-FC 30% vs. FC 19% in previously untreated CLL), were usually reported with higher frequencies when compared to chemotherapy alone. However, the higher incidence of neutropenia in patients treated with MabThera/Rituxan IV and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone. Studies in previously untreated and relapsed/refractory CLL have established that in some cases neutropenia was prolonged or with a late onset following treatment in the MabThera/Rituxan IV plus FC group.

No relevant difference between the treatment arms was observed with respect to Grade 3 and 4 anaemia or thrombocytopenia. In the CLL first-line study Grade 3 and4 anaemia was reported by 4% of patients treated with R-FC compared to 7% of patients receiving FC, and Grade 3 and 4 thrombocytopenia was reported by 7% of patients in the R-FC group compared to 10% of patients in the FC group. In the relapsed/refractory CLL study, adverse events of Grade 3 and 4 anaemia were reported in 12% of patients treated with R-FC compared to 13% of patients receiving FC and Grade 3 and 4 thrombocytopenia was reported by 11% of patients in the R-FC group compared to 9% of patients in the FC group.

Cardiovascular events
Monotherapy 4 weeks treatment
Cardiovascular events were reported in 18.8% of patients during the treatment period. The most frequently reported events were hypotension and hypertension. Cases of Grade 3 and 4 arrhytmia (including ventricular and supraventricular tachycardia) and angina pectoris during a MabThera/Rituxan IV infusion were reported.

Maintenance Treatment (NHL) up to 2 years
The incidence of Grade 3 and 4 cardiac disorders was comparable between the two treatment groups. Cardiac events were reported as serious adverse event in <1% of patients on observation and in 3% of patients on MabThera/Rituxan IV: atrial fibrillation (1%), myocardial infarction (1%), left ventricular failure (<1%), myocardial ischemia (<1%).

Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)
In the R-CHOP study the incidence of Grade 3 and 4 cardiac arrhythmias, predominantly supraventricular arrhythmias such as tachycardia and atrial flutter/fibrillation, was higher in the R-CHOP group (6.9%) as compared to the CHOP group (1.5%). All arrhythmias either occurred in the context of a MabThera/Rituxan IV infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease (see section 2.4 Warnings and Precautions). No difference between the R-CHOP and CHOP group was observed in the incidence of other Grade 3 and 4 cardiac events including heart failure, myocardial disease and manifestations of coronary artery disease.
In CLL, the overall incidence of Grade 3 and 4 cardiac disorders was low both in the first-line study (4% R-FC, vs 3% FC) and in the relapsed/refractory study (4% R-FC, vs 4% FC).

IgG levels
Maintenance Treatment (NHL) up to 2 years
After induction treatment, median IgG levels were below the lower limit of normal (LLN) (<7 g/L) in both the observation and the MabThera/Rituxan IV groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant during MabThera/Rituxan IV treatment. The proportion of patients with IgG levels below the LLN was about 60% in the MabThera/Rituxan IV group throughout the 2 years treatment period, while it decreased in the observation group (36% after 2 years).

Neurologic events
Combination Therapy (R-CVP in NHL; R-CHOP in DLBCL, R-FC in CLL)
During the treatment period, four patients (2%) in the R-CHOP group, all with cardiovascular risk factors, experienced thromboembolic cerebrovascular accidents during the first treatment cycle. There was no difference between the treatment groups in the incidence of other thromboembolic events. In contrast, three

patients (1.5%) had cerebrovascular events in the CHOP group, all of which occurred during the follow-up period.

In CLL, the overall incidence of Grade 3 and 4 nervous system disorders was low both in the first-line study (4% R-FC vs. 4% FC) and in the relapsed/refractory study (3% R-FC vs. 3% FC).

Subpopulations
Monotherapy 4 weeks treatment
Elderly patients (≥65 years)
The incidence of any ADR and of Grade 3 and 4 ADRs was similar in elderly (≥ 65 years of age) and younger patients (88.3% vs. 92.0% for any ADR and 16.0% vs. 18.1% for Grade 3 and 4 ADRs).
Combination Therapy
Elderly patients (≥ 65 years):
The incidence of Grade 3 and 4 blood and lymphatic adverse events was higher in elderly patients (≥ 65 years of age) compared to younger patients, with previously untreated or relapsed/refractory CLL.
Bulky disease
Patients with bulky disease had a higher incidence of Grade 3 and 4 ADRs than patients without bulky disease (25.6% vs. 15.4%). The incidence of any ADR was similar in these two groups (92.3% in bulky disease vs. 89.2% in non-bulky disease).
Re-treatment with monotherapy
The percentage of patients reporting any ADR and Grade 3 and 4 ADRs upon re-treatment with further courses of MabThera/Rituxan IV was similar to the percentage of patients reporting any ADR and Grade 3 and 4 ADRs upon initial exposure (95.0% vs. 89.7% for any ADR and 13.3% vs. 14.8% for Grade 3 and 4 ADRs).

Experience from Rheumatoid Arthritis Clinical Trials
The safety profile for MabThera/Rituxan in the treatment of patients with moderate to severe RA is summarized below. In the exposure population more than 3000 patients received at least one treatment course were followed for periods ranging from 6 months to over 5 years with an overall exposure equivalent to 7198 patient years; approximately 2300 patients received two or more courses of treatment during the follow up period.

The ADRs listed in Table 3 are based on data from placebo-controlled periods of four multicenter, RA clinical trials. The patient populations receiving MabThera/Rituxan IV differed between studies, ranging from early active RA patients who were methotrexate (MTX) naïve, through MTX inadequate responders (MTX-IR) to patients who had inadequate response to anti-tumour necrosis factor (TNF) therapies (TNF-IR) (see section 3.1.2 Clinical/Efficacy Studies).

Patients received 2 x 1000 mg or 2 x 500 mg of MabThera/Rituxan separated by an interval of two weeks, in addition to methotrexate (10 to 25 mg/week) *(see section 2.2 Dosage and Administration, Rheumatoid Arthritis).*

The ADRs listed in Table 3 are those which occurred at a rate of at least 2 % difference compared to the control arm and are presented regardless of dose. Frequencies in Table 3 and the corresponding footnote are defined as very common (≥1/10), common (≥1/100 to <1/10) and uncommon ((≥1/1000 to <1/100).

Table 3 Summary of ADRs Reported in Patients with Rheumatoid Arthritis–within Control Period of Clinical Trials †

System Organ Class	Very Common	Common
Infections and Infestations	Upper respiratory tract infection, Urinary tract infection	Bronchitis, Sinusitis, Gastroenteritis, Tinea pedis
Immune System Disorders/General disorders and administration site conditions	Infusion related reactions	*****Infusion related reactions: (Hypertension, Nausea, Rash, Pyrexia, Pruritus, Urticaria, Throat irritation, Hot flush, Hypotension, Rhinitis, Rigors, Tachycardia, Fatigue, Oropharyngeal pain, Peripheral Oedema, Erythema)
Metabolism and Nutritional Disorders		Hypercholesterolemia

Nervous Systems disorders	Headache	Paraesthesia, Migraine, Dizziness, Sciatica
Skin & Subcutaneous Tissue disorders		Alopecia
Psychiatric Disorders		Depression, Anxiety
Gastrointestinal Disorders		Dyspepsia, Diarrhoea, Gastrooesophageal reflux, Mouth ulceration, Abdominal pain upper
Musculoskeletal and connective tissue disorders		Arthralgia/Musculoskeletal pain, Osteoarthritis, Bursitis

† This table includes all events with an incidence difference of ≥ 2 % for Mabthera/Rituxan IV compared to placebo
* In addition, medically significant events reported uncommonly associated with IRRs include: generalized oedema, bronchospasm, wheezing, laryngeal oedema, angioneurituc oedema, generalized pruritus, anaphylaxis, anaphylactoid reaction.

In the all-exposure population, the safety profile was consistent with that seen in the controlled period of the clinical trials with no new ADRs identified.

Multiple courses:
Multiple courses of treatment are associated with a similar ADR profile to that observed following first exposure. The safety profile improved with subsequent courses due to a decrease in IRRs, RA exacerbation and infections, all of which were more frequent in the first 6 months of treatment.

Further information on selected, serious adverse drug reactions:
Infusion-related reactions:
The most frequent ADRs following receipt of MabThera/Rituxan IV in RA clinical studies were IRRs clinical studies were infusion-related reactions. Among the 3095 patients treated with MabThera/Rituxan, 1077 (35%) experienced at least one IRR. The vast majority of IRRs were CTC Grade 1 or 2. In clinical studies less than 1% (14/3095 patients) of patients with RA who received an infusion of MabThera/Rituxan at any dose experienced a serious IRR. There were no CTC Grade 4 IRRs and no deaths due to IRRs in the clinical studies (see section 2.6 Undesirable Effects, Post-Marketing). The proportion of CTC Grade 3 events and IRRs leading to withdrawal decreased by course and were rare from course 3 onwards.
Signs and/or symptoms suggesting an IRR (i.e., nausea, pruritus, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic oedema, throat irritation, cough and bronchospasm, with or without associated hypotension or hypertension) were observed in 720/3095 (23%) patients following the first infusion of the first exposure to MabThera/Rituxan. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events (see section 2.4 Warnings and Precautions).
In a study designed to evaluate the safety of a 120-minute MabThera/Rituxan IV infusion in patients with RA, patients with moderate-to-severe active RA who did not experience a serious IRR during or within 24 hours of their first studied infusion were allowed to receive a 120-minute infusion of MabThera/Rituxan IV. Patients with a history of a serious infusion reaction to a biologic therapy for RA were excluded from entry. The incidence, types and severity of IRRs were consistent with that observed historically. No serious IRRs were observed (see section 3.1.2 Clinical/Efficacy Studies).

Infections:
The overall rate of infection was approximately 97 per 100 patient years in MabThera/Rituxan treated patients. The infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections and urinary tract infections. The rate of serious infections was approximately 4 per 100 patient years, some of which were fatal. In addition to the ADRs in Table 3, medically serious events reported also include pneumonia at a frequency of 1.9%.
Malignancies:
The incidence of malignancy following exposure to rituximab in RA clinical studies (0.8 per 100 person years) lies within the range expected for an age- and gender-matched population.

Clinical Trial Experience in Granulomatosis with polyangiitis (Wegener's) (GPA) and Microscopic polyangiitis (MPA)
In the GPA and MPA clinical study 99 patients were treated with MabThera/Rituxan (375 mg/m^2, once weekly for 4 weeks) and glucocorticoids (see section 3.1.2 Clinical/Efficacy Studies).

The ADRs listed in Table 4 were all adverse events which occurred at an incidence of ≥ 10% in the MabThera/Rituxan-treated group. Frequencies in Table 4 are defined as very common (≥1/10).

Table 4 Incidence of Very Common (≥ 10%) ADRs for MabThera/Rituxan-treated GPA and MPA Patients in Clinical Study up to Month 6*

Adverse reactions	Rituximab n = 99	Cyclophosphamide n = 98
Infections and infestations		
Infections[a]	61 (61.6%)	46 (46.9%)
Gastrointestinal disorders		
Nausea	18 (18.2%)	20 (20.4%)
Diarrhea	17 (17.2%)	12 (12.2%)
Nervous system disorders		
Headache	17 (17.2%)	19 (19.4%)
Musculoskeletal and connective tissue disorders		
Muscle spasm	17 (17.2%)	15 (15.3%)
Arthralgia	13 (13.1%)	9 (9.2%)
Blood and lymphatic system disorders		
Anemia	16 (16.2%)	20 (20.4%)
Leukopenia	10 (10.1%)	26 (26.5%)
General disorders and administration site conditions		
Peripheral edema	16 (16.2%)	6 (6.1%)
Fatigue	13 (13.1%)	21 (21.4%)
Psychiatric disorders		
Insomnia	14 (14.1%)	12 (12.2%)
Investigations		
Increased ALT	13 (13.1%)	15 (15.3%)
Respiratory, thoracic and mediastinal disorders		
Cough	13 (13.1%)	11 (11.2%)
Epistaxis	11 (11.1%)	6 (6.1%)
Dyspnea	10 (10.1%)	11 (11.2%)
Vascular disorders		
Hypertension	12 (12.1%)	5 (5.1%)
Immune system disorders		
Infusion related reactions[b]	12 (12.1%)	11 (11.2%)
Skin and subcutaneous tissue disorders		
Rash	10 (10.1%)	17 (17.3%)

*The study design allowed for crossover or treatment by best medical judgment, and 13 patients in each treatment group received a second therapy during the 6 month study period.

[a]Most common infections in the rituximab group included upper respiratory tract infections, urinary tract infections, and herpes zoster.

[b]Most common terms reported in the rituximab group included cytokine release syndrome, flushing, throat irritation, and tremor.

Further information on selected adverse drug reactions:

Infusion-related reactions:

Infusion-related reactions (IRRs) in the GPA and MPA clinical study were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators in the safety population. Ninety-nine patients were treated with MabThera/Rituxan and 12% experienced at least one IRR. All IRRs were CTC Grade 1 or 2. The most common IRRs included cytokine release syndrome, flushing,

throat irritation, and tremor. MabThera/Rituxan was given in combination with intravenous glucocorticoids which may reduce the incidence and severity of these events.
Infections:
In the clinical trial studying induction of remission, 99 patients with severe GPA/MPA MabThera/Rituxan IV patients, the overall rate of infection was approximately 210 per 100 patient years (95% CI 173-256). Infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections, herpes zoster and urinary tract infections. The rate of serious infections was approximately 25 per 100 patient years. The most frequently reported serious infection in the MabThera/Rituxan IV group was pneumonia at a frequency of 4%.
Malignancies:
The incidence of malignancy in MabThera/Rituxan treated patients in the clinical study was 2.05 per 100 patient years. On the basis of standardized incidence ratios, this malignancy rate appears to be similar to rates previously reported in GPA and MPA populations.

2.6.1 Laboratory Abnormalities
Hypogammaglobulinaemia (IgG or IgM below the lower limit of normal) has been observed in RA and GPA/MPA patients treated with MabThera/Rituxan IV. There was no increased rate in overall infections or serious infections after the development of low IgG or IgM

Rheumatoid Arthritis Patients
Events of neutropenia associated with MabThera/Rituxan IV treatment, the majority of which were transient and mild or moderate in severity, were observed in clinical trials in RA patients after the first course of treatment. Neutropenia can occur several months after the administration of MabThera/Rituxan IV.

In placebo-controlled periods of clinical trials, 0.94% (13/1382) of MabThera/Rituxan IV related patients and 0.27% (2/731) of placebo patients developed severe (Grade 3 or 4) neutropenia. In these studies, rates of severe neutropenia were 1.06 and 0.53 per 100 patient years, respectively after the first treatment course, and 0.97 and 0.88 per 100 patient years, respectively after multiple courses. Therefore, neutropenia can be considered an ADR for the first course only. Time to onset of neutropenia was variable. In clinical trials neutropenia was not associated with an observed increase in serious infection and most patients continued to receive additional courses of MabThera/Rituxan IV after episodes of neutropenia.

Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA) Patients

At 6 months, in the MabThera/Rituxan IV group, 27%, 58% and 51% of patients with normal immunoglobulin levels at baseline, had low IgA, IgG and IgM levels, respectively compared to 25%, 50% and 46 %, respectively in the cyclophosphamide group. There was no increased rate in overall infections or serious infections in patients with low IgA, IgG or IgM.
In the active-controlled, randomized, double-blind, multicenter, non-inferiority study of MabThera/Rituxan IV in GPA and MPA, 24% of patients in the MabThera/Rituxan IV group (single course) and 23% of patients in the cyclophosphamide group developed CTC Grade 3 or greater neutropenia. Neutropenia was not associated with an observed increase in serious infection in MabThera/Rituxan IV-treated patients. The effect of multiple rituximab courses on the development of neutropenia in GPA and MPA patients has not been studied in clinical trials.

2.6.2 Post Marketing Experience
Non-Hodgkin's Lymphoma and Chronic Lymphocytic Leukaemia Patients
The reporting frequencies in this section (rare, very rare) are based on estimated marketed exposures and data largely derived from spontaneous reports.
Additional cases of severe IRRs have been reported during post-marketing use of MabThera/Rituxan (see section 2.4 Warnings and Precautions).
As part of the continuing post-marketing surveillance of MabThera/Rituxan IV safety, the following serious adverse reactions have been observed:
Cardiovascular system:
Severe cardiac events, including heart failure and myocardial infarction have been observed, mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and mostly associated with IRRs. Vasculitis, predominantly cutaneous, such as leukocytoclastic vasculitis, has been reported very rarely.
Respiratory system:
Respiratory failure/insufficiency and lung infiltration in the context of IRRs have been observed (see section 2.4 Warnings and Precautions). In addition to pulmonary events associated with infusions, interstitial lung disease, some with fatal outcome, have been reported.

Blood and lymphatic system:
Cases of infusion-related acute reversible thrombocytopenia have been reported.
Skin and appendages:
Severe bullous skin reactions including some fatal cases of toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported rarely.
Nervous system:
Cases of posterior reversible encephalopathy syndrome (PRES)/reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms included visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including the patients' underlying disease, hypertension, immunosuppressive therapy and/or chemotherapy.
Cases of cranial neuropathy with or without peripheral neuropathy have been reported rarely. Signs and symptoms of cranial neuropathy, such as severe vision loss, hearing loss, loss of other senses and facial nerve palsy, occurred at various times up to several months after completion of MabThera/Rituxan IV therapy.
Body as a whole:
Serum sickness-like reactions have been reported rarely.
Infections and infestations:
Cases of hepatitis B reactivation have been reported, the majority of which were in subjects receiving MabThera/Rituxan IV in combination with cytotoxic chemotherapy (see section 2.4 Warnings and *Precautions*).Other serious viral infections, either new, reactivation or exacerbation, some of which were fatal, have been reported with MabThera/Rituxan IV treatment. The majority of patients had received MabThera/Rituxan IV in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Examples of these serious viral infections are infections caused by the herpes viruses (cytomegalovirus [*CMV*], *varicella zoster* virus *and h*erpes simplex virus), JC virus (progressive multifocal leukoencephalopathy [*PML*] see section 2.4 Warnings and Precautions) and hepatitis C virus.
Progression of Kaposi's sarcoma has been observed in MabThera/Rituxan IV-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.
Gastro-intestinal system:
Gastrointestinal perforation, in some cases leading to death, has been observed in patients receiving MabThera/Rituxan IV in combination with chemotherapy for non-Hodgkin's lymphoma.

Rheumatoid Arthritis (RA), Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA) Patients
As part of the continuing post-marketing surveillance of MabThera/Rituxan IV safety, the following have been observed in the RA setting and are also expected, if not already observed, in GPA/MPA patients:

Infections and Infestations:
Progressive multifocal leukoencephalopathy (PML) and reactivation of hepatitis B infection have been reported.
Body as a whole:
Serum sickness-like reaction has been reported.
Skin and subcutaneous tissue disorders:
Toxic epidermal necrolysis and Stevens-Johnson syndrome some with fatal outcome have been reported very rarely.
Blood and lymphatic system disorders:
Neutropenic events, including severe late onset and persistent neutropenia, have been reported rarely, some of which were associated with fatal infections.
Nervous system:
Cases of posterior reversible encephalopathy syndrome (PRES) / reversible posterior leukoencephalopathy syndrome (RPLS) have been reported. Signs and symptoms include visual disturbance, headache, seizures and altered mental status, with or without associated hypertension. A diagnosis of PRES/RPLS requires confirmation by brain imaging. The reported cases had recognized risk factors for PRES/RPLS, including hypertension, immunosuppressive therapy and/or other concomitant therapies.
General disorders and administration site conditions:
Severe IRRs some with fatal outcome have been reported (see section 2.6 Undesirable Effects, Clinical Trials).

2.6.2.1 Laboratory Abnormalities
Non-Hodgkin's Lymphoma
Blood and lymphatic system:

Rarely the onset of neutropenia has occurred more than four weeks after the last infusion of MabThera/Rituxan IV.
In studies of MabThera/Rituxan IV in patients with Waldenstrom's macroglobulinemia, transient increases in serum IgM levels have been observed following treatment initiation, which may be associated with hyperviscosity and related symptoms. The transient IgM increase usually returned to at least baseline level within 4 months.

2.7 Overdose
Limited experience with doses higher than the approved intravenous doses of MabThera/Rituxan IV is available from clinical trials in humans. The highest IV dose tested in humans to date is 5000mg (2250 mg/m2), tested in a dose escalation study in patients with chronic lymphocytic leukaemia. No additional safety signals were identified. Patients who experience overdose should have immediate interruption of their infusion and be closely monitored.
Three patients in the MabThera/Rituxan SC SABRINA (BO22334) study were inadvertently administered the SC formulation through the IV route up to a maximum rituximab dose of 2780 mg, with no untoward effect. Patients who experience overdose or medication error with MabThera/Rituxan SC should be closely monitored..
Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell-depleted

2.8 Interactions with other Medicinal Products and other Forms of Interaction
At present, there are limited data on possible drug interactions with MabThera.

In CLL patients, co-administration with MabThera IV did not appear to have an effect on the pharmacokinetics of fludarabine or cyclophosphamide, in addition; there was no apparent effect of fludarabine and cyclophosphamide on the pharmacokinetics of MabThera.
Co-administration with methotrexate had no effect on the pharmacokinetics of MabThera IV in RA patients.

Patients with human anti-mouse antibody (HAMA) or human anti-chimeric antibody (HACA) titers may develop allergic or hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.

In the RA clinical trial program, 373 MabThera IV-treated patients received subsequent therapy with other disease-modifying antirheumatic drugs (DMARDs), of whom 240 received a biologic DMARD. In these patients the rate of serious infection while on MabThera IV (prior to receiving a biologic DMARD) was 6.1 per 100 patient years compared to 4.9 per 100 patient years following subsequent treatment with the biologic DMARD.

3 PHARMACOLOGICAL PROPERTIES AND EFFECTS

3.1 Pharmacodynamic Properties

3.1.1 Mechanism of Action

Rituximab is a chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20. This antigen is located on pre-B- and mature B-lymphocytes, but not on hemopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. The antigen is expressed on >95% of all B-cell non-Hodgkin's lymphomas (NHLs). Following antibody binding, CD20 is not internalized or shed from the cell membrane into the environment. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding.
Rituximab binds to the CD20 antigen on B-lymphocytes and initiates immunologic reactions that mediate B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and induction of apoptosis. Finally, in vitro studies have demonstrated that rituximab sensitizes drug-resistant human B-cell lymphoma lines to the cytotoxic effects of some chemotherapeutic agents.
Peripheral B-cell counts declined to levels below normal following the first dose of MabThera/Rituxan. In patients treated for hematological malignancies, B cell recovery began within 6 months of treatment and generally returning to normal levels within 12 months after completion of therapy, although in some patients this may take longer (see section 2.6 Undesirable Effects, Clinical Trials, Experience from Clinical Trials in Hemato-Oncology).
In patients with rheumatoid arthritis, the duration of peripheral B-cell depletion was variable. The majority of patients received further treatment prior to full B-cell repletion. A small proportion of patients had prolonged peripheral B-cell depletion lasting 2 years or more after their last dose of MabThera/Rituxan IV.

In GPA and MPA patients, peripheral blood CD19 B-cells depleted to less than 10 cells/µl following the first two infusions of rituximab and remained at that level in most patients through month 6.
Of 67 patients evaluated for human anti-mouse antibody (HAMA), none were positive. Of 356 non-Hodgkin's lymphoma patients evaluated for human anti-chimeric antibody (HACA) 1.1% (4 patients) were positive.

3.1.2 Clinical / Efficacy Studies

Low-grade or Follicular Non-Hodgkin's Lymphoma

MabThera/Rituxan IV Monotherapy

Initial treatment, weekly for 4 doses

In the pivotal study, 166 patients with relapsed or chemoresistant low-grade or follicular B-cell NHL received 375 mg/m^2 of MabThera/Rituxan as an i.v. infusion weekly for four doses. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48% ($CI_{95\%}$ 41% – 56%) with a 6% complete response (CR) and a 42% partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months.
In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histologic subtypes as compared to IWF A subtype (58% vs. 12%), higher in patients whose largest lesion was <5 cm vs >7 cm in greatest diameter (53% vs. 38%), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response <3 months) relapse (50% vs. 22%). ORR in patients previously treated with autologous bone marrow transplant (ABMT) was 78% *vs.* 43% in patients with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically significant effect (Fisher's exact test) on response to MabThera/Rituxan IV.
A statistically significant correlation was noted between response rates and bone marrow involvement. Forty percent of patients with bone marrow involvement responded compared to 59% of patients with no bone marrow involvement (p=0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histologic type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Initial treatment, weekly for 8 doses

In a multi-center, single-arm study, 37 patients with relapsed or chemoresistant, low grade or follicular B-cell NHL received 375 mg/m^2 of MabThera/Rituxan as i.v. infusion weekly for eight doses. The ORR was 57% ($CI_{95\%}$ 41% – 73%; CR 14%, PR 43%) with a projected median TTP for responding patients of 19.4 months (range 5.3 to 38.9 months).

Initial treatment, bulky disease, weekly for 4 doses

In pooled data from three studies, 39 patients with relapsed or chemoresistant, bulky disease (single lesion ≥10 cm in diameter), low grade or follicular B-cell NHL received 375 mg/m^2 of MabThera/Rituxan as i.v. infusion weekly for four doses. The ORR was 36% ($CI_{95\%}$ 21% – 51%; CR 3%, PR 33%) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Re-treatment, weekly for 4 doses

In a multi-center, single-arm study, 58 patients with relapsed or chemoresistant low grade or follicular B-cell NHL, who had achieved an objective clinical response to a prior course of MabThera/Rituxan IV were re-treated with 375 mg/m^2 of MabThera/Rituxan as i.v. infusion weekly for four doses. Three of the patients had received two courses of MabThera/Rituxan IV before enrollment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38% ($CI_{95\%}$ 26% – 51%; 10% CR, 28% PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favorably with the TTP achieved after the prior course of MabThera/Rituxan IV (12.4 months).

MabThera/Rituxan IV in Combination with Chemotherapy

Initial treatment

In an open-label randomized trial, a total of 322 previously untreated patients with follicular lymphoma were randomized to receive either CVP chemotherapy (cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1-5) every 3 weeks for 8 cycles or MabThera/Rituxan 375 mg/m^2 in combination with CVP (R-CVP). MabThera/Rituxan IV was administered on the first day of each treatment cycle. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analyzed for efficacy.

The median follow-up of patients was 53 months. R-CVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (27 months vs. 6.6 months, $p < 0.0001$, log-rank test). The proportion of

patients with a tumor response (CR, CRu, PR) was significantly higher (p< 0.0001 Chi-Square test) in the R-CVP group (80.9%) than the CVP group (57.2%). Treatment with R-CVP significantly prolonged the time to disease progression or death compared to CVP, 33.6 months and 14.7 months, respectively (p < 0.0001, log-rank test). The median duration of response was 37.7 months in the R-CVP group and was 13.5 months in the CVP group (p < 0.0001, log-rank test). The difference between the treatment groups with respect to overall survival showed a strong clinical benefit (p=0.029, log-rank test stratified by center): survival rates at 53 months were 80.9% for patients in the R-CVP group compared to 71.1% for patients in the CVP group.

Results from three other randomized trials using MabThera/Rituxan in combination with chemotherapy regimen other than CVP (CHOP, MCP, CHVP/Interferon-α) also demonstrated significant improvements in response rates, time-dependent parameters as well as in overall survival. Key results from all four studies are summarized in table 5 below.

Table 5 Summary of Key Results from Four Phase III Randomized Studies Evaluating the Benefit of MabThera/Rituxan IV with Different Chemotherapy Regimens in Follicular Lymphoma

Study	Treatment, n	Median FU, months	ORR, %	CR, %	Median TTF/PFS/ EFS months	OS rates, %
M39021	CVP, 159 R-CVP, 162	53	57 81	10 41	Median TTP: 14.7 33.6 P<0.0001	53-months 71.1 80.9 p=0.029
GLSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 2.6 years Not reached p < 0.001	18-months 90 95 p = 0.016
OSHO-39	MCP, 96 R-MCP, 105	47	75 92	25 50	Median PFS: 28.8 Not reached p < 0.0001	48-months 74 87 p = 0.0096
FL2000	CHVP-IFN, 183 R-CHVP-IFN, 175	42	85 94	49 76	Median EFS: 36 Not reached p < 0.0001	42-months 84 91 p = 0.029

TTP – Time to progression or death
PFS – Progression-Free Survival
TTF – Time to Treatment Failure
OS rates – survival rates at the time of the analyses

MabThera/Rituxan IV Maintenance Therapy

Previously untreated follicular NHL

In a prospective, open label, international, multi-center, phase III trial 1193 patients with previously untreated advanced follicular lymphoma received induction therapy with R-CHOP (n=881), R-CVP (n=268) or R-FCM (n=44), according to the investigators' choice. A total of 1078 patients responded to induction therapy, of which 1018 were randomized to MabThera/Rituxan IV maintenance therapy (n=505) or observation (n=513). The two treatment groups were all well balanced with regards to baseline characteristics and disease status. MabThera/Rituxan IV maintenance treatment consisted of a single infusion of MabThera/Rituxan at 375 mg/m^2 BSA given every 2 months until disease progression or for a maximum period of two years.

The pre-specified primary analysis was conducted at a median observation time of 25 months from randomization, maintenance therapy with MabThera/Rituxan IV resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator assessed progression-free survival (PFS) as compared to observation in patients with previously untreated follicular NHL(see Table 6 below). This improvement in PFS was confirmed by an independent review committee (IRC).

Significant benefit from maintenance treatment with MabThera/Rituxan IV was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) (see Table 6 below).

Data from extended follow-up of patients in the study (median follow-up 9 years) confirmed the long-term benefit of MabThera/Rituxan IV maintenance therapy in terms of PFS, EFS, TNLT and TNCT (see Table 6 below).

Table 6 Overview of Efficacy Results for Maintenance MabThera/Rituxan IV vs. Observation (25 Months and 9 Years Median Follow-up Final Analysis)

	Primary analysis (median FU: 25 months)		**Final analysis (median FU: 9.0 years)**	
	Observation N=513	**MabThera/Rituxan N=505**	**Observation N=513**	**MabThera/Rituxan N=505**
Primary efficacy				
Progression-free survival (median)	NR	NR	4.06 years	10.49 years
log-rank p value	<0.0001		<0.0001	
hazard ratio (95% CI)	0.50 (0.39, 0.64)		0.61 (0.52, 0.73)	
risk reduction	50%		39%	
Secondary efficacy				
Overall survival (median)	NR	NR	NR	NR
log-rank p value	0.7246		0.7953	
hazard ratio (95% CI)	0.89 (0.45, 1.74)		1.04 (0.77, 1.40)	
risk reduction	11%		-6%	
Event-free survival (median)	38 months	NR	4.04 years	9.25 years
log-rank p value	<0.0001		<0.0001	
hazard ratio (95% CI)	0.54 (0.43, 0.69)		0.64 (0.54, 0.76)	
risk reduction	46%		36%	
TNLT (median)	NR	NR	6.11 years	NR
log-rank p value	0.0003		<0.0001	
hazard ratio (95% CI)	0.61 (0.46, 0.80)		0.66 (0.55, 0.78)	
risk reduction	39%		34%	
TNCT (median)	NR	NR	9.32 years	NR
log-rank p value	0.0011		0.0004	
hazard ratio (95% CI)	0.60 (0.44, 0.82)		0.71 (0.59, 0.86)	
risk reduction	40%		39%	
Overall response rate*	55%	74%	61%	79%
chi-squared test p value	<0.0001		<0.0001	
odds ratio (95% CI)	2.33 (1.73, 3.15)		2.43 (1.84, 3.22)	
Complete response (CR/CRu) rate*	48%	67%	53%	67%
chi-squared test p value	<0.0001		<0.0001	
odds ratio (95% CI)	2.21 (1.65, 2.94)		2.34 (1.80, 3.03)	

* at end of maintenance/observation; final analysis results based on median follow-up of 73 months.

FU: follow-up; NR: not reached at time of clinical cut off, TNCT: time to next chemotherapy treatment; TNLT: time to next anti lymphoma treatment.

MabThera/Rituxan IV maintenance treatment provided consistent benefit in all subgroups tested: gender (male, female), age (<60 years, ≥ 60 years), FLIPI score (1, 2 or 3), induction therapy (R-CHOP, R-CVP or R-FCM) and regardless of the quality of response to induction treatment (CR or PR).

Relapsed/Refractory follicular NHL

In a prospective, open label, international, multi-centre, phase III trial, 465 patients with relapsed/refractory follicular NHL were randomized in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or MabThera/Rituxan IV plus CHOP (R-CHOP, n=234). The two treatment groups were well balanced with regard to baseline characteristics and disease status. A total of 334 patients achieving a complete or partial remission following induction therapy were randomized in a

second step to MabThera/Rituxan IV maintenance therapy (n=167) or observation (n=167). MabThera/Rituxan IV maintenance treatment consisted of a single infusion of MabThera/Rituxan at 375 mg/m^2 BSA given every 3 months until disease progression or for a maximum period of two years.
The final efficacy analysis included all patients randomized–to both parts of the study. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular NHL when compared to CHOP (see Table 7 below).

Table 7 – Induction Phase: Overview of Efficacy Results for CHOP vs. R-CHOP (31 Months Median Observation Time)

	CHOP	R-CHOP	p-value	Risk Reduction[1)]
Primary Efficacy				
ORR[2)]	74%	87%	0.0003	na
CR[2)]	16%	29%	0.0005	na
PR[2)]	58%	58%	0.9449	na
Secondary Efficacy				
OS (median)	NR	NR	0.0508	32%
PFS(median)	19.4 mo.	33.2 mo.	0.0001	38%

[1)] Estimates were calculated by hazard ratios
[2)] Last tumor response as assessed by the investigator. The "primary" statistical test for "response" was the trend test of CR versus PR versus non-response ($p < 0.0001$)
Abbreviations: NA, not available; NR, not reached; mo, months; ORR: overall response rate; CR: complete response; PR: partial response; OS: overall survival: PFS: progression free survival

For patients randomized to the maintenance phase of the trial, the median observation time was 28 months from maintenance randomization. Maintenance treatment with MabThera/Rituxan IV led to a clinically relevant and statistically significant improvement in the primary endpoint, PFS, (time from maintenance randomisation to relapse, disease progression or death) when compared to observation alone ($p<0.0001$ log-rank test). The median PFS was 42.2 months in the MabThera/Rituxan IV maintenance arm compared to 14.3 months in the observation arm. Using a cox regression analysis, the risk of experiencing progressive disease or death was reduced by 61% with MabThera/Rituxan IV maintenance treatment when compared to observation (95% CI; 45%-72%). Kaplan-Meier estimated progression-free rates at 12 months were 78% in the MabThera/Rituxan IV maintenance group vs. 57% in the observation group. An analysis of overall survival confirmed the significant benefit of MabThera/Rituxan IV maintenance over observation ($p=0.0039$ log-rank test). MabThera/Rituxan IV maintenance treatment reduced the risk of death by 56% (95% CI; 22%-75%).
The median time to new anti-lymphoma treatment was significantly longer with MabThera/Rituxan IV maintenance treatment than with observation (38.8 months vs. 20.1 months, $p<0.0001$ log-rank test). The risk of starting a new treatment was reduced by 50% (95% CI; 30%-64%). In patients achieving a CR/CRu (complete response unconfirmed) as best response during induction treatment, MabThera/Rituxan IV maintenance treatment significantly prolonged the median disease free survival (DFS) compared to the observation group (53.7 vs 16.5 months, $p=0.0003$) log-rank test (see Table 8 below). The risk of relapse in complete responders was reduced by 67% (95% CI; 39%-82%).

Table 8 Maintenance Phase: Overview of Efficacy Results MabThera/Rituxan IV vs. Observation (28 Months Median Observation Time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Risk Reduction
	Observation (n = 167)	MabThera (n =167)	Log-Rank p value	
Progression-free survival (PFS)	14.3	42.2	<0.0001	61%
Overall Survival	NR	NR	0.0039	56%
Time to new lymphoma treatment	20.1	38.8	<0.0001	50%
Disease-free survivala	16.5	53.7	0.0003	67%
Subgroup Analysis				

PFS				
CHOP	11.6	37.5	<0.0001	71%
R-CHOP	22.1	51.9	0.0071	46%
CR	14.3	52.8	0.0008	64%
PR	14.3	37.8	<0.0001	54%
OS				
CHOP	NR	NR	0.0348	55%
R-CHOP	NR	NR	0.0482	56%

NR: not reached; a: only applicable to patients achieving a CR

The benefit of MabThera/Rituxan IV maintenance treatment was confirmed in all subgroups analyzed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (see Table 8). MabThera/Rituxan IV maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months vs. 11.6 months, p<0.0001) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs. 22.1 months, p=0.0071). MabThera/Rituxan IV maintenance treatment also provided a clinically meaningful benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP in the induction phase of the study.

MabThera/Rituxan IV maintenance treatment provided consistent benefit in all subgroups tested [gender (male, female), age (≤60 years, > 60 years), stage (III, IV), WHO performance status (0 vs. >0), B symptoms (absent, present), bone marrow involvement (no vs. yes), IPI (0-2 vs. 3-5), FLIPI score (0-1 vs. 2 vs. 3-5), number of extra-nodal sites (0-1 vs. >1), number of nodal sites (< 5 vs. ≥ 5), number of previous regimens (1 vs. 2), best response to prior therapy (CR/PR vs. NC/PD), hemoglobin (< 12 g/dL vs. ≥12 g/dL), β2-microglobulin (< 3mg/L vs. ≥3 mg/L), LDH (elevated, not elevated) except for the small subgroup of patients with bulky disease.

Diffuse Large B-cell Non-Hodgkin's Lymphoma

In a randomized, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B-cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/m2, doxorubicin 50 mg/m2, vincristine 1.4 mg/m^2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m^2/day on days 1 - 5) every 3 weeks for eight cycles, or MabThera/Rituxan 375 mg/m^2 plus CHOP (R-CHOP). MabThera/Rituxan IV was administered on the first day of the treatment cycle.

The final efficacy analysis included all randomized patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months. The two treatment groups were well balanced in baseline characteristics and disease status. The final analysis confirmed that R-CHOP significantly increased the duration of event-free survival (the primary efficacy parameter, where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment) (p=0.0001). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41%. At 24 months, estimates for overall survival were 68.2% in the R-CHOP arm compared to 57.4% in the CHOP arm. A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32%.

The analysis of all secondary parameters (response rates, progression-free survival, disease-free survival, duration of response) verified the treatment effect of R-CHOP compared to CHOP. The complete response rate after Cycle 8 was 76.2% in the R-CHOP group and 62.4% in the CHOP group (p=0.0028). The risk of disease progression was reduced by 46% and the risk of relapse by 51%.

In all patient subgroups (gender, age, age-adjusted IPI, Ann Arbor stage, ECOG, Beta 2 Microglobulin, LDH, Albumin, B-symptoms, Bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95; respectively. R-CHOP was associated with improvements in outcome for both high- and low-risk patients according to age-adjusted IPI.

Previously Untreated and Relapsed/Refractory Chronic Lymphocytic Leukemia

In two open-label randomized trials, a total of 817 previously untreated patients and 552 patients with relapsed/refractory CLL were randomized to receive either FC chemotherapy (fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2, day 1-3) every 4 weeks for 6 cycles or MabThera/Rituxan in combination with

FC (R-FC). MabThera/Rituxan was administered at a dosage of 375 mg/m^2 during the first cycle one day prior to chemotherapy and at a dosage of 500 mg/m^2 on day 1 of each subsequent treatment cycle. A total of 810 patients (403 R-FC, 407 FC) in the first line study (see Table 9 and Table 10 below) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study (see Table 11) were analyzed for efficacy.
In the first line study, after a median observation time of 20.7 months, study the median progression-free survival (primary endpoint) was 40 months in the R-FC group and 32 months in the FC group ($p < 0.0001$, log rank test). The analysis of overall survival showed an improved survival in favour of the R-FC arm ($p = 0.0427$, log-rank test). These results were confirmed with longer follow-up: after a median observation time of 48.1 months, the median PFS was 55 months in the R-FC group and 33 months in the FC group ($p < 0.0001$, log-rank test) and overall survival analyses continued to show a significant benefit of R-FC treatment over FC chemotherapy alone ($p = 0.0319$, log-rank test). The benefit in terms of PFS was consistently observed in most patient subgroups analyzed according to disease risk at baseline (i.e., Binet stages A-C) and was confirmed with longer follow-up (see Table 10).

Table 9 First-line Treatment of Chronic Lymphocytic Leukaemia - Overview of Efficacy Results for MabThera IV Plus FC vs. FC Alone (20.7 Months Median Observation Time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Hazard Ratio
	FC (*n* = 407)	R-FC (*n* = 403)	Log-Rank p value	
Progression-free survival (PFS)	32.2 (32.8)***	39.8 (55.3)***	<0.0001 (<0.0001)***	0.56 (0.55)***
Overall Survival	NR (NR)***	NR (NR)***	0.0427 (0.0319)***	0.64 (0.73)***
Event Free Survival	31.1 (31.3)***	39.8 (51.8)***	<0.0001 (<0.0001)***	0.55 (0.56)***
Response rate (CR, nPR, or PR)	72.7%	86.1%	<0.0001	n.a.
CR rates	17.2%	36.0%	<0.0001	n.a.
Duration of response*	34.7 (36.2)***	40.2 (57.3)***	0.0040 (<0.0001)***	0.61 (0.56)***
Disease free survival (DFS)**	NR (48.9)***	NR (60.3)***	0.7882 (0.0520)***	0.93 (0.69)***
Time to new CLL treatment	NR (47.2)***	NR (69.7)***	0.0052 (<0.0001)***	0.65 (0.58)***

Response rate and CR rates analyzed using Chi-squared Test.
***Values in parentheses correspond to 48.1 months median observation time (ITT population: 409 FC, 408 R-FC).
NR: not reached n.a: not applicable
*: only applicable to patients with CR, nPR or PR as end-of-treatment response;
**: only applicable to patients with CR as end-of-treatment response;

Table 10 Hazard Ratios of Progression-Free Survival According to Binet Stage (ITT) (20.7 Months Median Observation Time)

Progression-free survival (PFS)	Number of patients		Hazard Ratio (95% CI)	Log-Rank p value
	FC	R-FC		
Binet Stage A	22 (22)*	18 (18)*	0.13 (0.03; 0.61) (0.39 (0.15; 0.98))*	0.0025 (0.0370)*
Binet Stage B	257 (259)*	259 (263)*	0.45 (0.32; 0.63) (0.52 (0.41; 0.66))*	<0.0001 (<0.0001)*
Binet Stage C	126 (126)*	125 (126)*	0.88 (0.58; 1.33) (0.68 (0.49; 0.95))*	0.5341 (0.0215)*

CI: Confidence Interval
******Values correspond to 48.1 months median observation time (ITT population: 409 FC, 408 R-FC)***.**
In the relapsed/refractory study, the median progression-free survival (primary endpoint) was 30.6 months in the R-FC group and 20.6 months in the FC group ($p = 0.0002$, log-rank test). The benefit in terms of PFS was

observed in almost all patient subgroups analyzed according to disease risk at baseline. A slight but not significant improvement in overall survival was reported in the R-FC compared to the FC arm.

Table 11 Treatment of Relapsed/Refractory Chronic Lymphocytic Leukaemia - Overview of Efficacy Results for MabThera/Rituxan IV Plus FC vs. FC Alone (25.3 Months Median Observation Time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Risk Reduction
	FC (*n* = 276)	R-FC (*n* = 276)	Log-Rank p value	
Progression-free survival (PFS)	20.6	30.6	0.0002	35%
Overall Survival	51.9	NR	0.2874	17%
Event Free Survival	19.3	28.7	0.0002	36%
Response rate (CR, nPR, or PR)	58.0%	69.9%	0.0034	n.a.
CR rates	13.0%	24.3%	0.0007	n.a.
*Duration of response**	27.6	39.6	0.0252	31%
*Disease free survival (DFS)***	42.2	39.6	0.8842	-6%
Time to new CLL treatment	34.2	NR	0.0024	35%

Response rate and CR rates analysed using Chi-squared Test
NR: not reached n.a. not applicable
*only applicable to patients with CR, nPR or PR as best overall response
**: only applicable to patients with CR as best overall response

Results from other supportive studies using MabThera/Rituxan IV in combination with other chemotherapy regimens (including CHOP, FCM, PC, PCM, bendamustine and cladribine) for the treatment of CLL patients have also demonstrated high overall response rates with benefit in terms of PFS rates, albeit with modestly higher toxicity (especially myelotoxicity).

Rheumatoid Arthritis

The efficacy of MabThera/Rituxan IV in rheumatoid arthritis has been demonstrated in three pivotal, phase III, randomized, placebo-controlled, double-blind, multi-center studies. Eligible patients had severe active RA, diagnosed according to the criteria of the American College of Rheumatology (ACR). MabThera/Rituxan IV was administered as two IV infusions separated by an interval of 15 days. Each course was preceded by an IV infusion of 100 mg methylprednisolone. All patients received concomitant oral methotrexate. In addition, in Study WA17042, all patients received concomitant oral glucocorticoids on days 2 to 7 and on days 8 to 14 following the first infusion.

The retreatment criteria differed between the studies using one of two approaches*:* 'Treatment to Remission' whereby patients were treated no more frequently than every 6 months if not in DAS28 remission (i.e., DAS28-ESR ≥2.6) and 'Treatment as Needed' strategy ('Treatment PRN'), based on disease activity and/or return of clinical symptoms (swollen and tender joint counts ≥ 8) and treated no sooner than every 16 weeks.

Study WA17042 (REFLEX) included 517 patients that had experienced an inadequate response or intolerance to one or more tumour necrosis factor (TNF) inhibitor therapies (TNF-IR). The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 24. Patients received 2 x 1000 mg MabThera/Rituxan or placebo. Patients were followed beyond Week 24 for long-term endpoints, including radiographic assessment at 56 weeks. During this time patients could receive further courses of MabThera/Rituxan IV under an open label extension study protocol. In the open-label protocol patients received further courses based on the 'Treatment PRN' criteria.

Study WA17045 (SERENE) included 511 patients that had experienced an inadequate response to methotrexate (MTX-IR) and had not received prior biologic therapy. The primary endpoint was the proportion of patients who achieved an ACR20 response at Week 24. Patients received placebo, 2 x 500 mg or 2 x 1000 mg MabThera/Rituxan infusion. Patients were followed beyond Week 24 for long term endpoints and could receive further courses of MabThera/Rituxan based on the 'Treatment to Remission' criteria. An active dose comparison was made at Week 48.

Disease Activity Outcomes

In all three studies, MabThera/Rituxan (Rituximab 2 x 1000 mg) significantly increased the proportion of patients achieving at least a 20% improvement in ACR score compared with patients treated with methotrexate alone (see Table 12). Across all development studies the treatment effect was similar in patients independent of age, gender, body surface area, race, number of prior treatments or disease status. Patients seropositive for disease related auto-antibodies (RF and/or anti CCP) demonstrated consistently high efficacy compared to MTX alone across studies. Efficacy in seropositive patients was higher than observed in seronegative patients in whom efficacy was modest.
Clinically and statistically significant improvement was also noted on all individual components of the ACR response (tender and swollen joint counts, patient and physician global assessment, disability index scores (HAQ), pain assessment and *CRP*-[*mg/dL*].

Table 12 Cross-Study Comparison of ACR Responses (ITT Population)

	Timepoint	**ACR Response**	**Placebo+MTX**	**RTX+MTX** *(2 x 1000 mg)*
Study WA17042 **(TNF-IR)**	*Week 24*		*n = 201*	*n = 298*
		ACR20	36 (18%)	153 (51%)***
		ACR50	11 (5%)	80 (27%)***
		ACR70	3 (1%)	37 (12%)***
Study WA17045 **(MTX-IR)**	*Week 24*		*n = 172*	*n =170*
		ACR20	40 (23%)	86 (51%)***
		ACR50	16 (9%)	44 (26%)***
		ACR70	9 (5%)	17 (10%)

Significant difference from placebo at the primary timepoint: * $p < 0.05$, ** $p < 0.001$ *** $p \leq 0.0001$

Patients treated with MabThera/Rituxan had a significantly greater reduction in disease activity score (DAS28) than patients treated with methotrexate alone. A good to moderate EULAR response was achieved by significantly more MabThera/Rituxan treated patients compared to patients treated with methotrexate alone (**see** Table 13).

Table 13 Cross-Study Comparison of DAS28-ESR and EULAR Responses (ITT Population)

	Placebo+MTX	**RTX+MTX** *(2 × 1000mg)*
Study WA17042 (TNF-IR)		
Change in DAS28 at Week 24		
n	***n = 201***	***n = 298***
Mean Change	-0.4	-1.9***
EULAR response (Week 24)		
n	**n = 201**	**n = 298**
Moderate	20%	50%***
Good	2%	15%***
Study WA17045 (MTX-IR)		
Change in DAS28 at Week 24		
n	***n = 171***	***n = 168***
Mean Change	–0.8	–1.7***
EULAR response (Week 24)		
n	***n = 172***	***n = 170***
Moderate	29%	51%***
Good	5%	12%***

Significant difference from placebo at the primary timepoint: * $p \leq 0.05$, ** $p \leq 0.001$ *** $p \leq 0.0001$

Inhibition of Joint Damage
In Studies WA17042 and WA17047 structural joint damage was assessed radiographically and expressed as change in modified Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score.
In Study WA17042, conducted in TNF-IR patients receiving MabThera/Rituxan in combination with methotrexate, demonstrated significantly less radiographic progression at 56 weeks than patients from the methotrexate alone group. A higher proportion of patients receiving MabThera/Rituxan also had no erosive progression over 56 weeks.

Study WA17047, conducted in methotrexate-naïve patients (755 patients with early RA of between 8 weeks to four years duration), assessed the prevention of structural joint damage as its primary objective (*see section 2.4 Warnings and Precautions*). Patients received placebo, 2 x 500mg or 2 x 1000mg MabThera/Rituxan infusion. From Week 24 patients could receive further courses of MabThera/Rituxan (or placebo to Week 104) based on the 'Treatment to Remission' criteria. The primary endpoint of change in modified Total Sharp Score (TSS) demonstrated that only treatment with MabThera/Rituxan at a dose of 2 x 1000 mg in combination with methotrexate significantly reduced the rate of progression of joint damage (PJD) at 52 weeks compared with placebo + methotrexate (see Table 14). The reduction in PJD was driven mainly by a significant reduction in the change in Erosion Score.

Inhibition of the rate of progressive joint damage was also observed long term. Radiographic analysis at 2 years in *S*tudy WA17042demonstrated significantly reduced progression of structural joint damage in patients receiving MabThera/Rituxan (2 x 1000mg) + methotrexate–compared to methotrexate alone as well as a significantly higher proportion of patients with no progression of joint damage over the 2 year period.

Table 14 Radiographic Outcomes at 1 Year in Studies WA17042 and WA17047 (MITT Population)

	Placebo+MTX	**RTX+MTX** *(2 ×1000 mg)*
Study WA17042 (TNF-IR)	***n=184***	***n=273***
Mean Change from Baseline:		
Modified Total Sharp Score	2.30	1.01*
Erosion Score	1.32	0.60*
Joint Space Narrowing Score	0.98	0.41**
Proportion of patients with no radiographic change	46%	53% NS
Proportion of patients with no erosive change	52%	60% NS
Study WA17047 (MTX- naïve)	***n=232***	***n=244***
Mean Change from Baseline:		
Modified Total Sharp Score	1.079	0.359**
Erosion Score	0.738	0.233***
Joint Space Narrowing Score	0.341	0.126
Proportion of patients with no radiographic change	53%	64%*
Proportion of patients with no erosive change	55%	67%*

Radiographic outcomes were assessed at Week 52 in Study WA17047 and Week 56 in Study WA17042
150 patients originally randomized to placebo + MTX in WA17042 received at least one course of RTX + MTX by one year
* p <0 05, ** p < 0.001, *** p < 0.0001, NS Non Significant

Quality of Life Outcomes

MabThera/Rituxan treated patients reported an improvement in all patient-reported outcomes (HAQ-DI, FACIT-Fatigue and SF-36 questionnaires). Significant reductions in disability index (HAQ-DI), fatigue (FACIT-Fatigue), and improvement in the physical health domain of the SF-36 were observed in patients treated with MabThera/Rituxan compared to patients treated with methotrexate alone.

Table 15 Cross Study Comparison of HAQ-DI and FACIT–Fatigue responses

	Placebo+MTX[1]	**RTX+MTX[1]** ***(2 × 1000mg)***
Study WA17042 (TNF-IR)	***n=201***	***n=298***
- *Mean change in HAQa at Week 24*	-0.1	-0.4***
- *% patients with HAQ MCID at Week 24*	20%	51%
- *Mean change in FACIT-Fatigue[b] at Week 24*	-0.5	-9.1***
Study WA17045 (MTX-IR)	***n=172[a] (170)[b]***	***n=170[a] (168)[b]***
- *Mean change in HAQ[a] at Week 24*	-0.21	-0.42***
- *% patients with HAQ MCID at Week 24*	48%	58%*
- *Mean change in FACIT-Fatigue[b] at Week 24*	2.7	6.4***

[a] Health assessment questionnaire (HAQ),[b] Functional assessment of chronic illness therapy (FACIT-Fatigue)
Significant difference from placebo at the primary timepoint: * p < 0.05, **p < 0.001 ***p ≤ 0.0001
(CMH test for categorical change, ANOVA for mean change, note that the unadjusted mean changes are displayed)

Table 16 Cross-study comparisons of Short Form Health Survey (SF-36).

	Placebo+MTX	**RTX +MTX** *(2 × 1000 mg)*
Study WA17042 (TNF-IR)	***n=197***	***n=294***
Physical Health		
Mean change at Week 24	0.9	5.8***
% patients with MCID at Week 24	13%	48%***
Mental Health		
Mean change at Week 24	1.3	4.7**
% patients with MCID at Week 24	20%	38%**
Study WA17045 (MTX-IR)	***n=147***	***n=155***
Physical Health		
Mean change at Week 24	2.7	5.9***
% patients with MCID at Week 24	31%	48%
Mental Health		
Mean change at Week 24	2.1	4.4**
% patients with MCID at Week 24	24%	35%*

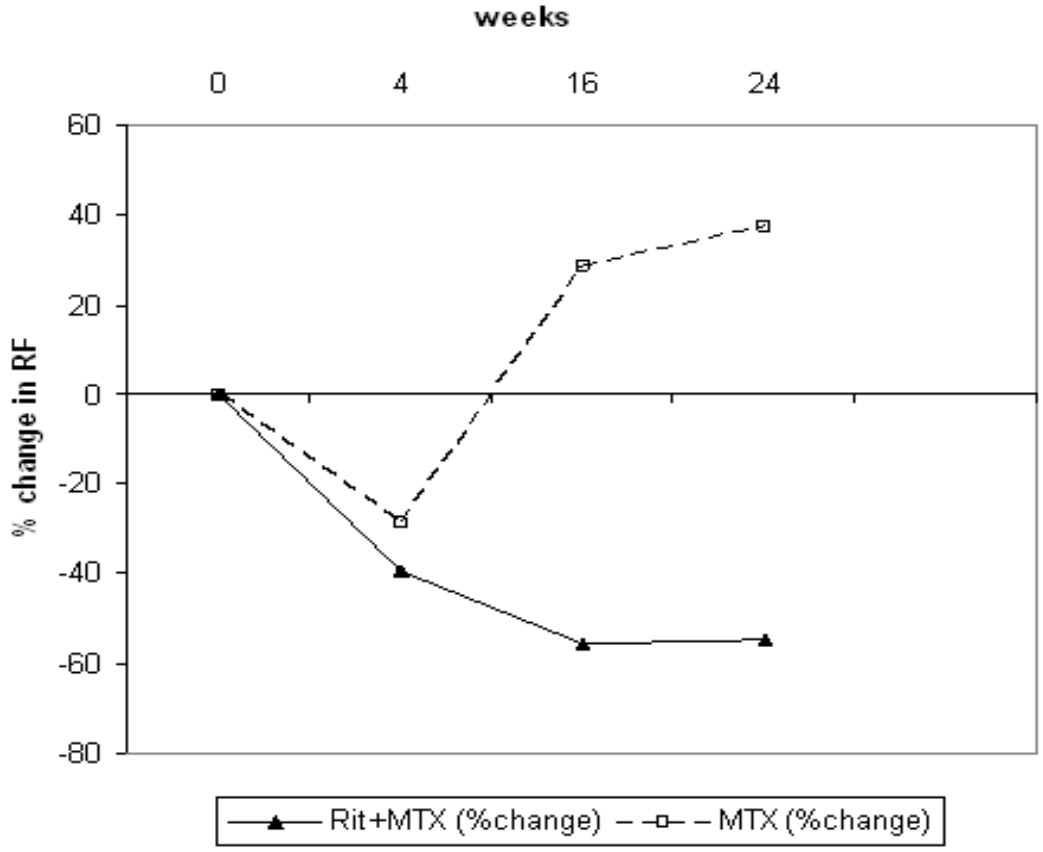
MCID = minimum clinically important difference defined as an increase of: >6.33 for mental health score and >5.42 for physical health score, % of patients based on number of patients assessable (N)
Significant difference from placebo at the primary timepoint: * $p \leq 0.05$, ** $p \leq 0.001$, *** $p \leq 0.0001$ (CMH test for categorical change, ANOVA for mean change - note that unadjusted mean changes are displayed)

Laboratory Evaluations

Approximately 10% of patients with rheumatoid arthritis tested positive for HACA in clinical studies. The emergence of HACA was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions in the majority of patients. The presence of HACA may be associated with worsening of infusion or allergic reactions after the second infusion of subsequent courses, and failure to deplete B cells after receipt of further treatment courses has been observed rarely.

In rheumatoid factor (RF) positive patients, marked decreases were observed in rheumatoid factor concentrations following treatment with rituximab in all three studies (range 45-64%, Figure 1).

Figure 1 Percentage Change in Total RF Concentration Over Time in Study 1 (ITT Population, RF-Positive Patients)



Plasma total immunoglobulin concentrations, total lymphocytes counts, and white cell counts generally remained within normal limits following MabThera/Rituxan treatment, with the exception of a transient drop in white cell counts over the first four weeks following therapy. Titers of Ig G antigen specific antibody to mumps, rubella, varicella, tetanus toxoid, influenza and streptococcus pneumococci remained stable over 24 weeks following exposure to MabThera/Rituxan in rheumatoid arthritis patients.

Effects of rituximab on a variety of biomarkers were evaluated in patients enrolled into a clinical study. This sub-study evaluated the impact of a single treatment course of rituximab on levels of biochemical markers, including markers of inflammation [Interleukin 6, C Reactive protein, Serum amyloid type A protein, Protein S100 isotypes A8 and A9], autoantibody (RF and anti-cyclic citrullinated peptide immunoglobulin) production and bone turnover [osteocalcin and procollagen 1 N terminal peptide (P1NP). Rituximab treatment, whether as monotherapy or in combination with methotrexate or cyclophosphamide reduced the levels of inflammatory markers significantly, relative to methotrexate alone, over the first 24 weeks of follow-up. Levels of markers of bone turnover, osteocalcin and P1NP, increased significantly in the rituximab groups compared to methotrexate alone.

Long Term Efficacy with Multiple Course Therapy

In clinical studies patients were retreated based on either a 'Treatment to Remission' or a 'Treatment PRN' strategy. Repeat courses of MabThera/Rituxan maintained or improved treatment benefit, irrespective of the treatment strategy (*Treatment to Remission or Treatment PRN*) (Figure 2). However, Treatment to Remission generally provided better responses and tighter control of disease activity as indicated by ACRn, DAS28-ESR and HAQ-DI scores over time. Patients treated PRN also experienced returning disease symptoms between courses, as evidenced by DAS28-ESR scores which were close to pre-treatment levels prior to each course (Table 17).

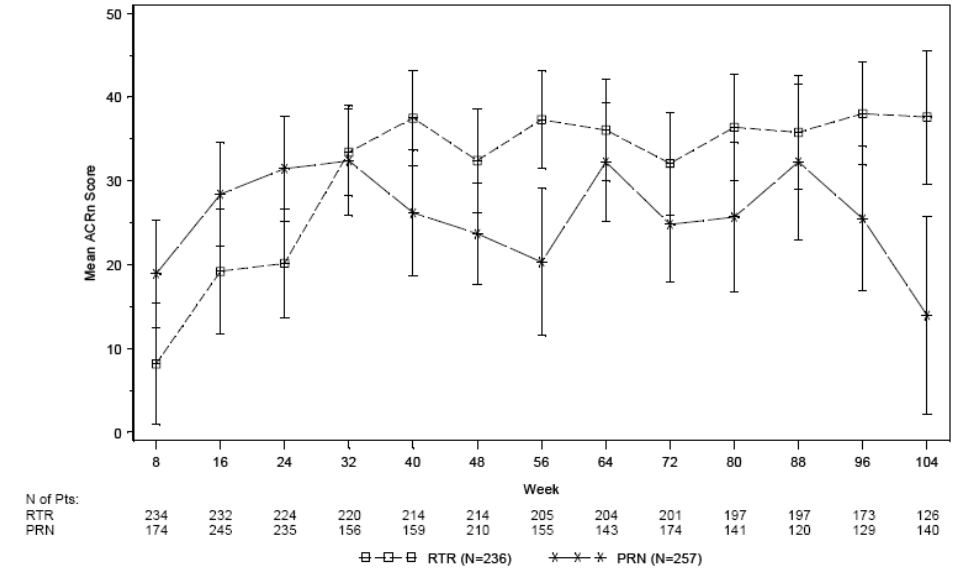
Table 17 Baseline Values Prior to Each Course for Parameters of Disease Activity

Population	**Parameter**	**C1**	**C2**	**C3**	**C4**	**C5**
Treatment To Remission		***N=236***	***N=218***	***N=198***	***N=156***	***N=83***
	Mean BL DAS	6.6	4.9	4.6	4.6	4.7

	Median BL ACRn	-	22.7	25.5	26.5	26.3
Treatment PRN		***N=257***	***N=182***	***N=139***	***N=85***	***N=39***
	Mean BL DAS	6.7	6.2	6.2	5.9	6.0
	Median BL ACRn	-	-5.3	-11.1	-10.9	-4.2

Positive change in ACRn = improvement
BL=Baseline

Figure 2 Plot of Mean ACRn Over Time by Treatment Criteria (MTX-IR Population)



Error bars displayed are 95% confidence intervals about the mean.
No imputation made for missing data
RTR = Re-treat to Remission

120-minute infusion rate study (ML25641)

In a multi-center, open-label single-arm trial, 351 patients with moderate-to-severe, active RA, who had an inadequate response to at least one tumor necrosis factor-inhibitor and were receiving methotrexate, were to receive 2 courses of MabThera/Rituxan IV treatment. Patients who were naïve to prior MabThera/Rituxan IV therapy (n=306) and those who had received 1 to 2 prior courses of MabThera/Rituxan IV 6 to 9 months prior to baseline (n=45), were eligible for enrollment.

Patients received 2 courses of MabThera/Rituxan IV (2 x 1000 mg) + methotrexate treatment with the first course administered on Days 1 and 15 and the second course six-months later on Days 168 and 182. The first infusion of the first course (Day 1 infusion) was administered over a 4.25-hour (255 minutes) period. The second infusion of the first course (Day 15 infusion) and both infusions in the second course (Day 168 and 182 infusions) were administered over a 2-hour (120 minutes) period. Any patient experiencing a serious IRR with any infusion was withdrawn from the study.

The primary objective of the study was to assess the safety of administering the second infusion of the first study course of MabThera/Rituxan IV over a 2-hour (120 minutes) period.

The incidence of IRRs at Day 15 was 6.5% (95% CI [4.1%-9.7%]) consistent with the rate observed historically. There were no serious IRRs observed. Data observed for the infusions on Days 168 and 182 (120-minute infusion) demonstrates a low incidence of IRRs, similar to the rate observed historically, with no serious IRRs occurring. (see section 2.6 Undesirable Effect, Clinical Trials).

Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA):

A total of 197 patients with severely, active granulomatosis with polyangiitis (Wegener's) (GPA) and microscopic polyangiitis (MPA) were enrolled and treated in an active-controlled, randomized, double-blind, multicenter, non-inferiority study. Patients were 15 years of age or older, diagnosed with severely, active granulomatosis with polyangiitis (Wegener's) (75% of patients) or microscopic polyangiitis (MPA) (24% of patients) according to the Chapel Hill Consensus Conference Criteria. One percent of patients had unknown GPA and MPA type).

Patients were randomized in a 1:1 ratio to receive either oral cyclophosphamide daily (2mg/kg/day) for 3 to 6 months, followed by azathioprine or MabThera/Rituxan (375 mg/m^2) once weekly for 4 weeks. Patients in both arms received 1000 mg of pulse methylprednisolone (or another equivalent-dose glucocorticoid) per day for 1 to 3 days, followed by oral prednisone (1 mg/kg/day, not exceeding 80 mg/day). Prednisone tapering was to be completed by 6 months from the start of study treatment.

The primary outcome measure was achievement of complete remission at 6 months defined as a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) of 0, and off glucocorticoid therapy. The prespecified non-inferiority margin for the treatment difference was 20%. The study demonstrated non-inferiority of MabThera/Rituxan IV to cyclophosphamide for complete remission at 6 months (see Table 18). In addition, the complete remission rate in the MabThera/Rituxan IV arm was significantly greater than the estimated complete remission rate in patients with severe GPA and MPA not treated or treated only with glucocorticoids, based on historical control data.
Efficacy was observed both for patients with newly diagnosed GPA and MPA and for patients with relapsing disease.

Table 18 Percentage of Patients Who Achieved Complete Remission at 6 Months (Intent-to-Treat Population)

	MabThera (n = 99)	Cyclophosphamide (n = 98)	Treatment Difference (MabThera-Cyclophosphamide)
Rate	63.6%	53.1%	10.6%
95.1%[b] CI	(54.1%, 73.2%)	(43.1%, 63.0%)	(-3.2%, 24.3%)[a]

CI = confidence interval.

[a] Non-inferiority was demonstrated since the lower bound (– 3.2%) was higher than the pre-determined non-inferiority margin (– 20%).

[b.] The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy

3.1.3 Immunogenicity

As with all therapeutic proteins, there is the potential for an immune response in patients treated with MabThera/Rituxan. The data reflects the number of patients whose test results were considered positive for antibodies to rituximab using an enzyme-linked immunosorbent assay (ELISA). Immunogenicity assay results may be influenced by several factors including assay sensitivity and specificity, sample handling, timing of sample collection, concomitant medicinal products and underlying disease. For these reasons, comparison of incidence of antibodies to rituximab with the incidence of antibodies in other studies or to other products may be misleading.

Rheumatoid Arthritis:

Approximately 10% of patients with rheumatoid arthritis tested positive for anti-drug antibodies (ADA) in the RA clinical studies. The emergence of ADA was not associated with clinical deterioration or with an increased risk of reactions to subsequent infusions in the majority of patients. The presence of ADA may be associated with worsening of infusion or allergic reactions after the second infusion of subsequent courses, and failure to deplete B cells after receipt of further treatment courses has been observed rarely.

Granulomatosis with Polyangiitis (Wegener's) (GPA) and Microscopic Polyangiitis (MPA):

Twenty-three percent (23/99) of MabThera/Rituxan IV-treated patients from GPA and MPA induction of remission trial and 18% (6/34) of MabThera/Rituxan IV-treated patients in the maintenance therapy clinical trial developed ADA.
There was no apparent trend or negative impact of the presence of ADA on safety or efficacy in the adult GPA and MPA clinical trials

3.2 Pharmacokinetic Properties

3.2.1 Distribution

Non-Hodgkin's Lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of Mabthera/Rituxan IV as a single agent or in combination with
CHOP therapy, the typical population estimates of nonspecific clearance (CL_1), specific clearance (CL_2) likely contributed by B cells or tumor burden, and central compartment volume of distribution (V_1) were 0.14 L/day, 0.59 L/day, and 2.7 L, respectively. The estimated median terminal elimination half-life of Rituximab was 22 days (range, 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumor lesions contributed to some of the variability in CL_2 of Rituximab in data from 161 patients given 375 mg/m^2 as an i.v. infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumor lesions had a higher CL_2. However, a large component of inter-individual variability remained for CL_2 after correction for CD19-positive cell counts and tumor lesion size. V_1 varied by body surface area (BSA) and CHOP therapy. This variability in V_1 (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m^2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender, race, and WHO performance status had no effect on the pharmacokinetics of Rituximab. This analysis suggests that dose adjustment of Rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.
Mabthera/Rituxan IV at a dose of 375 mg/m^2 was administered as an i.v. infusion at weekly intervals for 4 doses to 203 patients with NHL naive to Rituximab. The mean C_{max} following the fourth infusion was

486 µg/mL (range, 77.5 to 996.6 µg/mL). The peak and trough serum levels of Rituximab were inversely correlated with baseline values for the number of circulating CD19-positive B-cells and measures of disease burden. Median steady-state serum levels were higher for responders compared with non-responders. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A. Rituximab was detectable in the serum of patients 3 – 6 months after completion of last treatment.
Mabthera/Rituxan IV at a dose of 375 mg/m^2 was administered as an i.v. infusion at weekly intervals for 8 doses to 37 patients with NHL. The mean C_{max} increased with each successive infusion, spanning from a mean of 243 µg/mL (range, 16 – 582 µg/mL) after the first infusion to 550 µg/mL (range, 171 – 1177 µg/mL) after the eighth infusion.
The pharmacokinetic profile of Mabthera/Rituxan IV when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with Mabthera/Rituxan IV alone.

Chronic Lymphocytic Leukemia
Rituximab was administered as an i.v infusion at a first-cycle dose of 375 mg/m^2 increased to 500 mg/m^2 each cycle for 5 doses in combination with fludarabine and cyclophosphamide in CLL patients. The mean C_{max} (n=15) was 408 µg/mL (range, 97-764 µg/mL) after the fifth 500 mg/m^2 infusion.

Rheumatoid Arthritis
Following two intravenous infusions of rituximab at a dose of 1000 mg, two weeks apart, the mean terminal half-life was 20.8 days (range, 8.58 to 35.9 days), mean systemic clearance was 0.23 L/day (range, 0.091 to 0.67 L/day), and mean steady-state distribution volume was 4.6 L (range, 1.7 to 7.51 L). Population pharmacokinetic analysis of the same data gave similar mean values for systemic clearance and half-life, 0.26 L/day and 20.4 days, respectively. Population pharmacokinetic analysis revealed that BSA and gender were the most significant covariates to explain inter-individual variability in pharmacokinetic parameters. After adjusting for BSA, male subjects had a larger volume of distribution and a faster clearance than female subjects. The gender- related pharmacokinetic differences are not considered to be clinically relevant and dose adjustment is not required.
The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1000 mg on Days 1 and 15 in four studies. In all these studies, rituximab pharmacokinetics were dose proportional over the limited dose range studied. Mean C_{max} for serum rituximab following first infusion ranged from 157 to 171 µg/mL for 2 x 500 mg dose and ranged from 298 to 341 µg/mL for 2 x 1000 mg dose. Following second infusion, mean C_{max} ranged from 183 to 198 µg/mL for the 2×500 mg dose and ranged from 355 to 404 µg/mL for the 2×1000 mg dose. Mean terminal elimination half-life ranged from 15 to 16.5 days for the 2 x 500 mg dose group and 17 to 21 days for the 2×1000 mg dose group. Mean C_{max} was 16 to 19% higher following second infusion compared to the first infusion for both doses.
The pharmacokinetics of rituximab were assessed following two IV doses of 500 mg and 1000 mg upon re-treatment in the second course. Mean C_{max} for serum rituximab following first infusion was 170 to 175 µg/mL for 2 x 500 mg dose and 317 to 370 µg/mL for 2 x 1000 mg dose. C_{max} following second infusion, was 207 µg/mL for the 2 x 500 mg dose and ranged from 377 to 386 µg/mL for the 2 x 1000 mg dose. Mean terminal elimination half-life after the second infusion, following the second course, was 19 days for 2 x 500 mg dose and ranged from 21 to 22 days for the 2 x 1000 mg dose. PK parameters for rituximab were comparable over the two treatment courses. The pharmacokinetic parameters in the anti-TNF inadequate responder population, following the same dosage regimen (2 x 1000 mg, i.v., 2 weeks apart), were similar with a mean maximum serum concentration of 369 µg/mL and a mean terminal half-life of 19.2 days.

Granulomatosis with* Polyangiitis *(Wegener's) (GPA) and Microscopic* Polyangiitis *(MPA)
The PK parameters in adult and pediatric patients with GPA/MPA receiving 375 mg/m2 MabThera/Rituxan IV once weekly for four doses are summarized in Table 19.

Parameter	Statistic	Study Adult GPA/MPA
N	Number of Patients	97
Terminal Half-life (days)	Median (Range)	23 (9 to 49)
Clearance (L/day)	Mean (Range)	0.313 (0.116 to 0.726)
Volume of Distribution (L)	Mean (Range)	4.50 (2.25 to 7.39)

The PK parameters of rituximab in adult GPA/MPA patients appear similar to what has been observed in RA patients (*see section 3.2 Pharmacokinetic Properties, Distribution*).

3.2.2 Elimination

See section 3.2.1 Distribution.

3.2.3 Pharmacokinetics in Special Populations

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Renal impairment

No pharmacokinetic data are available in patients with renal impairment.

Hepatic impairment

No pharmacokinetic data are available in patients with hepatic impairment.

4 PHARMACEUTICAL PARTICULARS

4.1 Storage

Intravenous and Subcutaneous Formulation

This medicine should not be used after the expiry date (EXP) shown on the pack.

Store vials at 2°C - 8°C (in a refrigerator). Keep the container in the outer carton in order to protect from light.

After aseptic dilution in 0.9% aqueous saline solution:

The prepared infusion solution of MabThera/Rituxan IV in 0.9% aqueous saline solution is physically and chemically stable for 30 days at 2°C - 8°C plus an additional 24 hours at room temperature.

After aseptic dilution in 5% aqueous dextrose solution:

The prepared infusion solution of MabThera/Rituxan IV in 5% aqueous dextrose solution is physically and chemically stable for 24 hours at 2°C - 8°C plus an additional 12 hours at room temperature.

From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

4.2 Special Instructions for Use, Handling and Disposal

Use sterile needle and syringe to prepare MabThera/Rituxan. Withdraw the required amount of MabThera/Rituxan under aseptic conditions and dilute to a calculated rituximab concentration of 1 – 4 mg/mL in an infusion bag containing sterile, non-pyrogenic 0.9%, aqueous saline solution or 5% aqueous dextrose solution. To mix the solution, gently invert the bag to avoid foaming. . Care must be taken to ensure the sterility of prepared solutions. Since the medicinal product does not contain any anti-microbial preservative or bacteriostatic agents, aseptic technique must be observed. Parenteral medications should be inspected visually for particulate matter or discoloration prior to administration.

The prepared infusion solution of MabThera/Rituxan is physically and chemically stable for 24 hours at 2°C - 8°C and subsequently 12 hours at room temperature.

Incompatibilities

No incompatibilities between MabThera/Rituxan IV and polyvinyl chloride or polyethylene bags or infusion sets have been observed.

Disposal of unused/expired medicines

The release of pharmaceuticals in the environment should be minimized. Medicines should not be disposed via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location

4.3 Packs

Vial of 10 ml (10 mg/mL)	2
Vial of 50 ml (10 mg/mL)	1

Medicine: keep out of reach of children

Revision Date: December 2021

Made for F.Hoffmann-La Roche Ltd, Basel, Switzerland
By Roche Diagnostics GmbH, Mannheim Germany
and
By Genentech Inc., Hillsboro, Oregon, USA
and
By Genentech Inc., South San Franciso, California, USA