Please visit www.roche.com.sg/pharma/mabthera for a printable version of this leaflet.

INF/INJ-MAB-2025 07-0

MabThera®

Rituximab

1. DESCRIPTION

1.1 Therapeutic/Pharmacologic Class of Drug

Antineoplastic agent.
ATC Code: L01FA01

1.2 Type of Dosage Form

Intravenous (IV) formulation: concentrate for solution for infusion
Subcutaneous (SC) formulation: solution for subcutaneous injection

1.3 Route of Administration

Intravenous formulation: intravenous infusion
Subcutaneous formulation: subcutaneous injection

1.4 Sterile/Radioactive Statement

Sterile product.
The content of the vial is a clear to opalescent liquid, colorless to pale yellow.

1.5 Qualitative and Quantitative Composition

Active ingredient: rituximab.

Intravenous Formulation
MabThera IV is a clear, colourless liquid supplied in sterile, preservative-free, non-pyrogenic single-dose vials.
Excipients: Sodium citrate, Polysorbate 80, Sodium chloride, Water for injection
Single-dose vials contain 100 mg/10 ml and 500 mg/50 ml.

Subcutaneous Formulation
MabThera SC is a clear to opalescent, colourless to yellowish liquid supplied in sterile, preservative-free, non-pyrogenic, single use vials.
MabThera SC contains recombinant human hyaluronidase (rHuPH20), an enzyme used to increase the dispersion and absorption of co-administered substances when administered subcutaneously.
Excipients: Recombinant human hyaluronidase (rHuPH20), L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate, L-methionine, Polysorbate 80, Water for injection

Subcutaneous formulation for non-Hodgkin's lymphoma:
Single dose vials contain 1400 mg/11.7 mL rituximab.

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

MabThera IV and MabThera SC
Non-Hodgkin's Lymphoma:
MabThera IV and MabThera SC are indicated for the treatment of:

- patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma (DLCL) in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) chemotherapy.
- previously untreated patients with stage III-IV follicular lymphoma in combination with CVP chemotherapy.

MabThera IV and MabThera SC maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

MabThera IV only
Non-Hodgkin's Lymphoma:
MabThera IV is indicated for the treatment of patients with relapsed or chemoresistant indolent B-cell non-Hodgkin's lymphomas.

Chronic Lymphocytic Leukaemia:
MabThera IV is indicated in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

Rheumatoid Arthritis:
MabThera IV 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 tumour necrosis factor (TNF) inhibitor therapies.

2.2 Dosage and Administration

General
Intravenous and Subcutaneous Formulations
Substitution by any other biological medicinal product requires the consent of the prescribing physician.

It is important to check the medicinal product labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) and strength is being given to the patient, as prescribed.

MabThera should always be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced physician.

The safety and efficacy of alternating or switching between MabThera and products that are biosimilar but not deemed interchangeable to MabThera has not been established. Therefore, the benefit/risk of alternating or switching need to be carefully considered.

Premedication and Prophylactic Medications:
Premedication consisting of an analgesic/anti-pyretic (e.g. paracetamol) and an antihistaminic drug (e.g. diphenhydramine), should always be given before each administration of MabThera. Premedication with corticosteroids should also be considered.

Premedication with glucocorticoids should be considered if MabThera is not given in combination with glucocorticoid-containing chemotherapy for treatment of non-Hodgkin's lymphoma.

Patients should be closely monitored for the onset of cytokine release syndrome (*see section 2.4 Warnings and Precautions*). Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm and hypoxia should have the infusion interrupted immediately. The patient should then be evaluated for evidence of tumour lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest x-ray. The infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest x-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same severe adverse reactions occur for a second time the decision to stop the treatment should be seriously considered on a case by case basis.

Mild or moderate infusion-related reactions (*see section 2.6 Undesirable effects*) usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.

Dosage adjustments during treatment
No dose reductions of MabThera are recommended. When MabThera is given in combination with CVP chemotherapy, standard dose reductions for the chemotherapeutic medicinal products should be applied.

Intravenous Formulation
MabThera IV formulation is not intended for subcutaneous administration (*see section 4.2 Special Instructions for Use, Handling and Disposal*).

MabThera should be administered as an IV infusion through a dedicated line. The prepared infusion solution must not be administered as an IV injection or bolus infusion.

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

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

Subcutaneous Formulation
MabThera SC formulation is not intended for intravenous administration and should be given via subcutaneous injection only (*see section 4.2 Special Instructions for Use, Handling and Disposal*).

The 1400 mg strength is intended for subcutaneous use in non-Hodgkin's lymphoma (NHL) only.

MabThera subcutaneous formulation should be injected subcutaneously into the abdominal wall and never into areas where the skin is red, bruised, tender, hard or areas where there are moles or scars. No data are available on performing the injection in other sites of the body, therefore injections should be restricted to the abdominal wall.

During the treatment course with MabThera subcutaneous formulation, other medicinal products for subcutaneous administration should preferably be given at different sites.

MabThera subcutaneous formulation should be administered as subcutaneous injection only, over approximately 5 minutes. The hypodermic injection needle must only be attached to the syringe immediately prior to administration to avoid potential needle clogging.

If an injection is interrupted it can be resumed at the same site or another location may be used, if appropriate.

Standard dosage
Low-grade or follicular non-Hodgkin's lymphoma
Intravenous Formulation
Initial treatment:

- *Intravenous monotherapy*

The recommended dosage of MabThera IV used as monotherapy for adult patients is 375 mg/m^2 body surface area, administered as an IV infusion once weekly for 4 weeks.

- *Intravenous combination therapy*

The recommended dosage of MabThera IV in combination with CVP chemotherapy is 375 mg/m^2 body surface area for 8 cycles (21 days/cycle), administered on day 1 of each chemotherapy cycle after IV administration of the corticosteroid component of CVP. MabThera has shown acceptable safety in combination with other chemotherapies e.g. CHOP.

Re-treatment following relapse
Patients who have responded to MabThera IV initially have been treated again with MabThera IV at a dose of 375 mg/m^2 body surface area, administered as an IV infusion once weekly for 4 weeks (see *Re-treatment, weekly for 4 doses*).

Maintenance treatment

Previously untreated follicular lymphoma
The recommended dose of MabThera IV used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m^2 body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

Relapsed/refractory follicular lymphoma
Patients who have responded to induction treatment may receive maintenance therapy with MabThera IV given at 375 mg/m^2 body surface area once every 3 months until disease progression or for a maximum period of two years.

Subcutaneous Formulation
The recommended dose of MabThera subcutaneous formulation used for adult patients is a subcutaneous injection at a fixed dose of 1400 mg irrespective of the patient's body surface area.

Before starting MabThera subcutaneous injections, all patients must always receive beforehand, a full dose of MabThera by intravenous infusion, using MabThera intravenous formulation. During their first cycle the patient is at the highest risk of experiencing an infusion/administration related reaction. Beginning therapy with MabThera IV infusion allows management of infusion/administration related reactions by slowing or stopping the intravenous infusion (*see section 2.4 Warnings and Precautions*).

If patients were not able to receive one full MabThera intravenous infusion dose prior to the switch, they should continue the subsequent cycles with MabThera intravenous formulation until a full intravenous dose is successfully administered.
Therefore, the switch to MabThera subcutaneous formulation can only occur at the second or subsequent cycles of treatment.

Initial therapy
The recommended dose of MabThera in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: first cycle with MabThera intravenous formulation 375 mg/m^2 body surface area, followed by subsequent cycles with MabThera subcutaneous formulation injected at a fixed dose of 1400 mg per cycle. In total: 8 cycles.

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

Maintenance therapy

- *Previously untreated follicular lymphoma*

The recommended dose of MabThera subcutaneous formulation used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is:
1400 mg once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

- *Relapsed/refractory follicular lymphoma*

The recommended dose of MabThera subcutaneous formulation used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is:
1400 mg once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

Diffuse Large B-cell Non-Hodgkin's Lymphoma
Intravenous Formulation
MabThera IV should be used in combination with CHOP chemotherapy. The recommended dosage of MabThera IV is 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle after IV administration of the corticosteroid component of CHOP. The other components of CHOP (cyclophosphamide, doxorubicin and vincristine) should be given after the administration of MabThera IV. Safety and efficacy of Mabthera have not been established in combination with other chemotherapies.

Subcutaneous Formulation
The recommended dose of MabThera subcutaneous formulation used for adult patients is a subcutaneous injection at a fixed dose of 1400 mg irrespective of the patient's body surface area.

Before starting MabThera subcutaneous injections, all patients must always receive beforehand, a full dose of MabThera by intravenous infusion, using MabThera intravenous formulation. During their first cycle the patient is at the highest risk of experiencing an infusion/administration related reaction.

Beginning therapy with MabThera IV infusion allows management of infusion/administration related reactions by slowing or stopping the intravenous infusion (*see section 2.4 Warnings and Precautions*).

If patients were not able to receive one full MabThera intravenous infusion dose prior to the switch, they should continue the subsequent cycles with MabThera intravenous formulation until a full intravenous dose is successfully administered.
Therefore, the switch to MabThera subcutaneous formulation can only occur at the second or subsequent cycles of treatment.

MabThera should be used in combination with CHOP chemotherapy. The recommended dose is: first cycle, MabThera intravenous formulation: 375 mg/m^2 body surface area, followed by subsequent cycles with MabThera subcutaneous formulation injected at a fixed dose of 1400 mg per cycle. In total: 8 cycles.

MabThera is administered on day 1 of each chemotherapy cycle after intravenous infusion of the glucocorticoid component of CHOP.
Safety and efficacy of MabThera have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma.

Chronic Lymphocytic Leukaemia
Intravenous Formulation
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 x10^9/L it is recommended to administer prednisone/prednisolone 100 mg IV shortly before infusion with MabThera IV to decrease the rate and severity of acute infusion reactions and/or cytokine release syndrome.

The recommended dosage of MabThera IV for CLL is 375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2−6, in combination with FC, administered every 28 days *(see "Intravenous Formulation Infusion Rate" sub-section above*).

Rheumatoid arthritis
Intravenous Formulation
A course of MabThera IV consists of two 1000 mg IV infusions. The recommended dosage of MabThera is 1000 mg by IV infusion followed two weeks later by the second 1000 mg IV infusion *(see "Intravenous Formulation Infusion Rate" sub-section above*).

Patients may receive further courses of treatment, based on signs and symptoms of disease. In clinical studies, no patient received a second course of rituximab treatment within 16 weeks of the first infusion of the first course. The time interval between courses was variable, with the majority of patients receiving further therapy 6-12 months after the previous course. Some patients required even less frequent retreatment. The efficacy and safety of further courses is comparable to the first course (*see sections 2.6.1 Clinical trials, Experience from Rheumatoid Arthritis and 3.1.2 Clinical/Efficacy Studies, Chronic lymphocytic leukemia*).

Rheumatoid arthritis patients should receive treatment with 100 mg IV methylprednisolone 30 minutes prior to MabThera IV to decrease the rate and severity of acute infusion reactions (*see section 2.4 Warnings and Precautions*).

Rheumatoid Arthritis Only
Alternative subsequent, faster, infusions schedule:
In RA, with a dose of 1000 mg MabThera IV, if there are no infusion related reactions or other reasons to slow or cease the infusion, the standard infusion schedules shown above result in an estimated duration of infusion of 4h 15 minutes for the first infusion and 3h 15 minutes for the second infusion in each course.

If patients did not experience a serious infusion-related adverse event with their first or subsequent infusions of a dose of 1000 mg MabThera IV administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using the same concentration as in previous infusions (4 mg/ml in a 250 ml volume). Initiate at a rate of 250mg/hour for the first 30 minutes and then 600 mg/hour for the next 90 minutes. If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions. With this infusion schedule, the 1000 mg/250 ml infusion will generally be completed in 2 h.

Patients who have clinically significant cardiovascular disease including arrhythmias or previous serious infusion reactions to any prior biologic therapy or to rituximab, should not be administered the more rapid infusion.

2.2.1 Special Dosage Instructions

Pediatric use:
The safety and efficacy of MabThera in children and adolescents (<18 years) have not been established.
Hypogammaglobulinaemia has been observed in pediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in pediatric patients are unknown.

Geriatric use:
No dose adjustment is required in patients aged ≥65 years of age.

2.3 Contraindications

MabThera is contraindicated in patients with known hypersensitivity to rituximab, to any of its excipients or to murine proteins.

Active, severe infections (*see section 2.4 Warnings and Precautions*).

Patients in a severely immunocompromised state.

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.The use of MabThera subcutaneous formulation as monotherapy in patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy cannot be recommended as the safety of the once weekly subcutaneous administration has not been established.

The following Warnings and Precautions apply to MabThera IV as well as SC unless otherwise specified, based on the events observed in clinical trials, post-marketing surveillance and spontaneous reports.

Non-Hodgkin's Lymphoma Patients and Chronic Lymphocytic Leukaemia Patients
Infusion/administration-related reactions:
MabThera is associated with infusion/administration-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.

This set of reactions which includes syndrome of cytokine release, tumor lysis syndrome and anaphylactic and hypersensitivity reactions are described below. They are not specifically related to the route of administration of MabThera and can be observed with both formulations.

Severe infusion-related reactions (IRRs) with fatal outcome have been reported during post-marketing use of the MabThera intravenous formulation. Severe IRRs usually manifested within 30 minutes to 2 hours after starting the first MabThera IV infusion. They were characterized by pulmonary events and included, in some cases, rapid tumour lysis and features of tumour lysis syndrome in addition to fever, chills, rigors, hypotension, urticaria, angioedema and other symptoms (*see sections 2.4 Warnings and Precautions and 2.6 Undesirable Effects*).

Severe cytokine release syndrome is characterised by severe dyspnea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. This syndrome may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, hyperphosphaetemia, acute renal failure, elevated lactate dehydrogenase (LDH) and may be associated with acute respiratory failure and death.

Patients with a high tumour 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 severe infusion-related reactions. Infusion reaction symptoms are usually reversible with interruption of the infusion. Treatment of infusion-related symptoms with diphenhydramine and acetaminophen is recommended. Additional treatment with bronchodilators or IV

saline may be indicated. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved. Most patients who have experienced non-life-threatening infusion-related reactions have been able to complete the full course of MabThera IV therapy. Further treatment of patients after complete resolution of signs and symptoms has rarely resulted in repeated severe infusion-related reactions.

Patients with a high number (>25 x 10^9/L) of circulating malignant cells or high tumour burden such as patients with CLL and mantle cell lymphoma, who may be at higher risk of especially severe infusion-related reactions, should only be treated with extreme caution and when other therapeutic alternatives have been exhausted. 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. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. Medicinal products for the treatment of hypersensitivity reactions, e.g., epinephrine (adrenaline), antihistamines and glucocorticoids, should be available for immediate use in the event of a hypersensitivity reaction to MabThera. Clinical manifestations of anaphylaxis may appear similar to clinical manifestations of the cytokine release syndrome (described above). Reactions attributed to hypersensitivity have been reported less frequently than those attributed to cytokine release.

Infusion related adverse reactions of all kinds have been observed in 77% of patients treated with MabThera intravenous formulation (including cytokine release syndrome accompanied by hypotension and bronchospasm in 10 % of patients) see section 4.8. These symptoms are usually reversible with interruption of MabThera infusion and administration of an anti-pyretic, an antihistaminic, and, occasionally, oxygen, intravenous saline or bronchodilators, and glucocorticoids if required. Please see cytokine release syndrome above for severe reactions.

- *Administration-related reactions for MabThera SC*

Administration related reactions have been observed in up to 50% of patients treated with Mabthera subcutaneous formulation in clinical trials. The reactions occurring within 24 hours of the subcutaneous injection consisted primarily of erythema pruritus, rash and injections site reactions such as pain, swelling and redness and were generally of mild or moderate (grade 1 or 2) and transient nature.

Local cutaneous reactions were very common in patients receiving MabThera subcutaneous in clinical trials; reported in up to 50% of patients at some time during treatment. Symptoms included pain, swelling, induration, haemorrhage, erythema, pruritus and rash (*see section 2.6 Undesirable Effects*). Some local cutaneous reactions occurred more than 24 hours after the MabThera subcutaneous administration. The majority of local cutaneous reactions seen following administration of MabThera subcutaneous formulation was mild or moderate and resolved without any specific treatment.

Before starting MabThera subcutaneous injections, all patients must always receive beforehand, a full dose of MabThera by intravenous infusion, using MabThera intravenous formulation. The highest risk of experiencing an administration related reaction is generally observed at cycle one. Beginning the therapy with MabThera intravenous infusion would allow a better handling of the administration reactions by slowing or stopping the intravenous infusion. If patients were not able to receive one full MabThera intravenous infusion dose prior to the switch, they should continue the subsequent cycles with MabThera intravenous formulation until a full intravenous dose is successfully administered. Therefore, the switch to MabThera subcutaneous formulation can only occur at the second or subsequent cycles of treatment.

As with the intravenous formulation, MabThera subcutaneous formulation should be administered in an environment where full resuscitation facilities are immediately available and under the close supervision of an experienced healthcare professional. Premedication consisting of an analgesic/antipyretic and an antihistamine should always be administered before each dose of MabThera subcutaneous formulation. Premedication with glucocorticoids should also be considered.

Patients should be observed for at least 15 minutes following MabThera subcutaneous administration. A longer period may be appropriate in patients with an increased risk of hypersensitivity reactions.
Patients should be instructed to contact their treating physician immediately if symptoms that are suggestive of severe hypersensitivity or cytokine release syndrome occur at any time after medicinal product administration.

Pulmonary events:
Pulmonary events have included hypoxia, pulmonary infiltrates, 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 tumour lysis:
MabThera 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 IV 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 tumour burden or with a high number (>25 x 10^9/L) of circulating malignant cells such as patients with CLL and 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 for and complete resolution of signs and symptoms, subsequent MabThera therapy has been administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

MabThera IV infusions should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of an experienced oncologist/ hematologist.

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

Monitoring of blood counts:
Although MabThera is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophil counts of < 1.5 x 10^9/L and/or platelet counts of < 75 x 10^9/L, as clinical experience with such patients is limited. MabThera 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. When MabThera is given in combination with CHOP or CVP chemotherapy, regular full blood counts should be performed according to usual medical practice.

Infections:
Serious infections, including fatalities, can occur during therapy with MabThera. MabThera should not be administered to patients with an active, severe infection (e.g. tuberculosis, sepsis and opportunistic infections, *see section 2.3 Contraindications*).

Physicians should exercise caution when considering the use of MabThera 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*).

Hepatitis B Infections:
Cases of hepatitis B reactivation, some of which were fatal, including reports of fulminant hepatitis, have been reported in subjects receiving MabThera, 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. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera. Reactivation of HBV infection is a well-known complication in patients with chronic hepatitis B, especially in those receiving cytotoxic or immunosuppressive therapy. In addition, hematological malignancies may be a risk factor for HBV reactivation. 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.

The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or post-marketing reports. The majority of patients were profoundly immune-suppressed. These viral infections included JC virus [progressive multifocal leucoencephalopathy (PML)], cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of MabThera and have resulted in death.

Very rare cases of progressive multifocal leukoencephalopathy (PML) have been reported during post-marketing use of MabThera in NHL and CLL (*see section 2.6 Undesirable Effects*). The majority of patients had received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant.

Progressive multifocal leukoencephalopathy
Use of MabThera may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. The clinician should evaluate the patient to determine if the symptoms are indicative of neurological dysfunction, and if so, whether these symptoms are possibly suggestive of PML. Consultation with a neurologist should be considered as clinically indicated.

If any doubt exists, further evaluation, including MRI scan preferably with contrast, cerebrospinal fluid (CSF) testing for JC Viral DNA and repeat neurological assessments, should be considered.

The physician should be particularly alert to symptoms suggestive of PML that the patient may not notice (e.g. cognitive, neurological or psychiatric symptoms). Patients should also be advised to inform their partner or caregivers about their treatment, since they may notice symptoms that the patient is not aware of.

If a patient develops PML, the dosing of MabThera must be permanently discontinued.
Following reconstitution of the immune system in immunocompromised patients with PML, stabilisation or improved outcome has been seen. It remains unknown if early detection of PML and suspension of MabThera therapy may lead to similar stabilisation or improved outcome.

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).* In case of such an event with a suspected relationship to MabThera, treatment should be permanently discontinued.

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

Patients treated with MabThera 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 IV 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 IV.

Rheumatoid Arthritis Patients
Infusion-related Reactions:
MabThera IV is associated with infusion-related reactions (IRRs), which may be related to release of cytokines and/or other chemical mediators. Premedication with IV glucocorticoid significantly reduced the incidence and severity of these events and should be administered prior to MabThera IV treatment (*See section 2.2 Dosage and Administration and section 2.6 Undesirable Effects*).

Most infusion events reported were mild to moderate in severity. 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 infusions were better tolerated by patients than the initial infusion. Fewer 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 infusion and administration of an anti-pyretic, an antihistamine, and, occasionally, oxygen, IV saline or bronchodilators, and glucocorticoids if required. In most cases, the infusion can be resumed at a 50% reduction in rate (e.g. from 100 mg/h to 50 mg/h) when symptoms have completely resolved.

Hypersensitivity Reactions / Anaphylaxis:
Anaphylactic and other hypersensitivity reactions have been reported following the intravenous 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 IV.

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

Angina pectoris, or cardiac arrhythmias such as atrial flutter and fibrillation heart failure or myocardial infarction have occurred in patients with non-Hodgkin's lymphoma treated with MabThera IV. Therefore patients with a history of cardiac disease and/or those receiving cardiotoxic drug therapy should be monitored closely during infusions.

Infections:
Based on the mechanism of action of MabThera 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 therapy. MabThera 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 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 therapy should be promptly evaluated and treated appropriately.

In patients with non-Hodgkin's Lymphoma receiving rituximab in combination with cytotoxic chemotherapy, very rare cases of hepatitis B reactivation have been reported (*see 2.4 Warnings and Precautions*).

Hepatitis B Infections:
Cases of hepatitis B reactivation including those with a fatal outcome, have been reported in RA patients receiving MabThera IV.

Hepatitis B virus (HBV) screening should be performed in all patients before initiation of treatment with MabThera IV. At minimum this should include HBsAg-status and HBcAb-status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with MabThera IV. 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).* In case of such an event with a suspected relationship to MabThera IV, treatment should be permanently discontinued.

Progressive Multifocal Leukoencephalopathy:
Cases of fatal progressive multifocal leukoencephalopathy (PML) have been reported following use of MabThera IV for the treatment of autoimmune diseases (including RA). Several, but not all of the reported cases had potential multiple 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 IV. 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.

The efficacy and safety of MabThera for the treatment of autoimmune diseases other than rheumatoid arthritis has not been established.

Immunization:
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 IV therapy and follow local/national guidance for adult vaccination against infectious disease. Vaccinations should be completed at least 4 weeks prior to first administration of MabThera IV.

The safety of immunization with live viral vaccines following MabThera therapy has not been studied. Therefore vaccination with live virus vaccines is not recommended whilst receiving MabThera or whilst peripherally B cell depleted.

Patients treated with MabThera may receive non-live vaccinations. However, response rates to non-live vaccines may be reduced. In a randomized study, patients with RA treated with MabThera IV 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 IV as compared to patients only receiving methotrexate. Should non-live vaccinations be required whilst receiving MabThera therapy, these should be completed at least 4 weeks prior to commencing the next course of MabThera IV.
In the overall experience of MabThera IV repeat treatment over one year, the proportions of patients with positive antibody titers against S. pneumoniae, influenza, mumps, rubella, varicella and tetanus toxoid were generally similar to the proportions at baseline.

Methotrexate (MTX) naïve populations:
The use of MabThera is not recommended in MTX-naïve patients since a favourable benefit risk relationship has not been established.

Concomitant/sequential use of other DMARDs:
The concomitant use of MabThera and antirheumatic therapies other than those specified under the rheumatoid arthritis indication and posology is not recommended.

There are limited data from clinical trials to fully assess the safety of the sequential use of other DMARDs (including TNF inhibitors and other biologics) following MabThera. The available data indicate that the rate of clinically relevant infection is unchanged when such therapies are used in patients previously treated with MabThera, however patients should be closely observed for signs of infection if biologic agents and/or DMARDs are used following MabThera therapy.

Malignancy:
Immunomodulatory drugs may increase the risk of malignancy. On the basis of limited experience with MabThera in rheumatoid arthritis patients a possible risk for the development of solid tumours cannot be excluded at this time, although present data do not seem to suggest any increased risk.

2.4.2 Ability to Drive and Use Machines
MabThera has no or negligible effect on the ability to drive and use machines.

2.5 Use in Special Populations
2.5.1 Females and Males of Reproductive Potential
Intravenous and Subcutaneous Formulations
Fertility
No preclinical fertility studies have been conducted

Contraception
Due to the long retention time of rituximab in B cell depleted patients, women of childbearing age must employ effective contraceptive methods during and for 12 months after treatment with MabThera.

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

Subcutaneous Formulation
Pharmacokinetic and toxicology studies in animals demonstrate reduction in foetal weight and increase in the number of resorptions following injection of rHuPH20 at maternal systemic exposure levels comparable to those that could occur after accidental bolus IV administration of a single vial of the MabThera SC formulation in humans, based on the most conservative assumptions possible (*see section 3.3 Nonclinical Safety*).

2.5.2 Pregnancy
Intravenous and Subcutaneous Formulations
IgG immunoglobulins are known to cross the placental barrier.

B-cell levels in human neonates following maternal exposure to MabThera 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 MabThera during pregnancy. For these reasons MabThera should not be administered to pregnant women unless the possible benefit outweighs the potential risk.

Subcutaneous Formulation
The subcutaneous formulation contains recombinant human hyaluronidase (rHuPH20).

2.5.3 Lactation
Maternal IgG enters breast milk, and rituximab has been reported to be excreted at low concentrations in human breast milk. Given that the clinical significance of this finding for infants is not known, MabThera should not be administered to nursing mothers.

Limited data on rituximab excretion into breast milk suggest very low rituximab concentrations in milk (relative infant dose less than 0.4%). Few cases of follow-up of breastfed infants describe normal growth and development up to 2 years. However, as these data are limited and the long-term outcomes of breastfed infants remain unknown, breast-feeding is not recommended while being treated with rituximab and optimally for 6 months following rituximab treatment.

2.5.4 Pediatric Use
The safety and efficacy of MabThera in children and adolescents (<18 years) have not been established.

Hypogammaglobulinaemia has been observed in pediatric patients treated with MabThera, in some cases severe and requiring long-term immunoglobulin substitution therapy. The consequences of long term B cell depletion in pediatric patients are unknown.

2.5.5 Geriatric Use
No dose adjustment is required in patients aged ≥65 years of age.

2.5.6 Renal Impairment
The safety and efficacy of renal impairment in MabThera patients has not been established.

2.5.7 Hepatic Impairment
The safety and efficacy of hepatic impairment in MabThera patients has not been established.

2.6 Undesirable Effects
2.6.1 Clinical Trials
Experience from non-Hodgkin's lymphoma and chronic lymphocytic leukaemia
Intravenous Formulation
The overall safety profile of MabThera in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia is based on data from patients from clinical trials and from post-marketing surveillance. These patients were treated either with MabThera monotherapy (as induction treatment or maintenance treatment following induction treatment) or in combination with chemotherapy.

The most frequently observed adverse drug reactions (ADRs) in patients receiving MabThera were infusion-related reactions which occurred in the majority of patients during the first infusion. The incidence of infusion-related symptoms decreases substantially with subsequent infusions and is less than 1 % after eight doses of MabThera.

Infectious events (predominantly bacterial and viral) occurred in approximately 30-55 % of patients during clinical trials in patients with NHL and in 30-50 % of patients during clinical trial in patients with CLL.
The most frequent reported or observed serious adverse drug reactions were:

- Infusion-related reactions (including cytokine-release syndrome, tumour-lysis syndrome), *see section 2.4 Warnings and Precautions.*
- Infections, *see section 2.4 Warnings and Precautions.*
- Cardiovascular events, *see section 2.4 Warnings and Precautions*.

Other serious ADRs reported include hepatitis B reactivation and PML (*see section 2.4 Warnings and Precautions*).
The frequencies of ADRs reported with MabThera alone or in combination with chemotherapy are summarised in Table 1 below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1000), very rare (< 1/10,000) and not known (cannot be estimated from the available data). The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under "not known".

Table 1 ADRs reported in clinical trials or during postmarketing surveillance in patients with NHL and CLL disease treated with MabThera monotherapy/maintenance or in combination with chemotherapy

System Organ Class	Very Common	Common	Uncommon	Rare	Very Rare	Not known[8]
Infections and infestations	Bacterial infections, viral infections, +bronchitis	Sepsis, +pneumonia, +febrile infection, +herpes zoster, +respiratory tract infection, fungal infections, infections of unknown aetiology, +acute bronchitis, +sinusitis, hepatitis B[1]		Serious viral infection[2]		
Blood and the lymphatic system disorders	Neutropenia, leucopenia, +febrileneutropenia, +thrombocytopenia	Anaemia, pancytopenia, +granulocytopenia	Coagulation disorders, aplastic anaemia, haemolytic anaemia, lymphadenopathy		Transient increase in serum IgM levels[3]	Late neutropenia[3]
Immune system disorders	Infusion related reactions[4], angioedema	Hypersensitivity		Anaphylaxis	Tumour lysis syndrome, cytokine release syndrome[4], serum sickness	infusion-related acute reversible thrombocytopenia [4]
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		peripheral neuropathy, facial nerve palsy[5]	Cranial neuropathy, loss of other senses[5]
Eye disorders		Lacrimation disorder, conjunctivitis			Severe vision loss[5]	
Ear and labyrinth disorders		Tinnitus, ear pain				Hearing loss[5]
Cardiac disorders		+Myocardial infarction[4 and 6], arrhythmia, +atrial fibrillation, tachycardia, +cardiac disorder	+Left ventricular failure, +supraventricular tachycardia, +ventricular tachycardia, +angina, +myocardial ischaemia, bradycardia	severe cardiac events[4 and 6]	Heart failure[4 and 6]	
Vascular disorders		Hypertension, orthostatic hypotension, hypotension			Vasculitis (predominately cutaneous), leukocyte-clastic vasculitis	
Respiratory, thoracic and mediastinal disorders		Bronchospasm[4], respiratory disease, chest pain, dyspnoea, increased cough, rhinitis	Asthma, bronchiolitis obliterans, lung disorder, hypoxia	Interstitial lung disease[7]	Respiratory failure[4]	lung infiltration
Gastrointestinal disorders	Nausea	Vomiting, diarrhea, abdominal pain , dysphagia , stomatitis, constipation, dyspepsia, anorexia, throat irritation	Abdominal enlargement		Gastrointestinal perforation[7]	
Skin and subcutaneous tissue disorders	Pruritis, rash, +alopecia	Urticaria, sweating, night sweats, +skin disorder			Severe bullous skin reactions, toxic epidermal necrolysis[7], Stevens-Johnson syndrome	
Musculoskeletal, connective tissue and bone disorders		Hypertonia, myalgia, arthralgia, back pain, neck pain, pain				
Renal and urinary disorders					Renal failure[4]	
General disorders and administration site conditions	Fever, chills , asthenia , headache	Tumour pain, flushing, malaise, cold syndrome, +fatigue, +shivering, +multi-organ failure[4]	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 the trials is reported.
[1] includes reactivation and primary infections; frequency based on R-FC regimen in relapsed/refractory CLL
[2] see also section infection below
[3] see also section haematologic adverse reactions below
[4] see also section infusion-related reactions below. Rarely fatal cases reported
[5] signs and symptoms of cranial neuropathy. Occurred at various times up to several months after completion of MabThera therapy
[6] observed mainly in patients with prior cardiac condition and/or cardiotoxic chemotherapy and were mostly associated with infusion-related reactions
[7] includes fatal cases
[8] frequency not known (cannot be estimated from the available data)

The following terms have been reported as adverse events during clinical trials, however, were reported at a similar or lower incidence in the MabThera-arms compared to control arms: haematotoxicity, neutropenic infection, urinary tract infection, sensory disturbance, pyrexia.

Subcutaneous Formulation
During the development programme, the safety profile of MabThera subcutaneous formulation was comparable to that of the intravenous formulation with the exception of local injection site reactions.

Local cutaneous reactions, including injection site reactions were very common (≥ 1/10) in patients receiving MabThera subcutaneous formulation. In the phase 3 SABRINA (BO22334), local cutaneous reactions were reported in up to 23% of patients receiving subcutanous MabThera. The most common local cutaneous reactions in the subcutaneous arm were injection erythema (13%), injection site pain (8%) and injection site oedema (4%). Events seen following subcutaneous administration were mild or moderate, apart from one patient who reported a local cutaneous reaction of Grade 3 intensity (injection site rash) following the first MabThera subcutaneous administration (Cycle 2). Local cutaneous reactions of any grade in the MabThera subcutaneous arm were most common during the first subcutaneous cycle (Cycle 2), followed by the second, and the incidence decreased with subsequent injections.

Further information on selected, serious adverse drug reactions
Intravenous Formulation
Administration-related reactions
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, usually in the first one to two hours. These symptoms mainly comprised fever, chills and rigors. Other symptoms included flushing, angioedema, bronchospasm, vomiting, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, pruritus, pain, tachycardia, hypertension, hypotension, dyspnoea, dyspepsia, asthenia and features of tumour lysis syndrome.

Severe IRRs (such as bronchospasm, hypotension) occurred in up to 12 % of the cases. Additional reactions reported in some cases were myocardial infarction, atrial fibrillation, pulmonary oedema and acute reversible thrombocytopenia. Exacerbations of pre-existing cardiac conditions such as angina pectoris or congestive heart failure or severe cardiac events (heart failure, myocardial infarction, atrial fibrillation), pulmonary oedema, multi-organ failure, tumour lysis syndrome, cytokine release syndrome, renal failure, and respiratory failure were reported at lower or unknown frequencies. The incidence of infusion-related symptoms decreased substantially with subsequent infusions and is < 1% of patients by the eighth cycle of MabThera (-containing) treatment.

Subcutaneous Formulation
The risk of acute administration-related reactions associated with the subcutaneous formulation of MabThera was assessed in two open-label trials involving patients with follicular lymphoma during induction and maintenance (SABRINA BO22334) and during maintenance only (SparkThera BP22333).

In trial SABRINA BO22334, severe administration-related reactions (grade≥3) were reported in two patients (1%) following administration of MabThera subcutaneous formulation (one patient reporting grade 3 injection site rash, and one patient reporting grade 3 dry mouth), both occurring after induction cycle 2 i.e. the first MabThera subcutaneous formulation dose given to each patient.

In trial SparkThera BP22333, no severe administration-related reactions were reported.

Intravenous Formulation
Infections
MabThera IV induces B-cell depletion in about 70-80% of patients, but was associated with decreased serum immunoglobulins only in a minority of patients.

Localized candida infections as well as Herpes zoster were reported at a higher incidence in the MabThera-containing arm of randomized studies. Severe infections were reported in about 4% of patients treated with MabThera monotherapy. Higher frequencies of infections overall, including grade 3 or 4 infections, were observed during MabThera maintenance treatment up to 2 years when compared to observation. There was no cumulative toxicity in terms of infections reported over a 2-year treatment period. In addition, other serious viral infections either new, reactivated or exacerbated, some of which were fatal, have been reported with MabThera treatment. The majority of patients had received MabThera 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, Varicella Zoster Virus and Herpes Simplex Virus), JC virus (progressive multifocal leukoencephalopathy (PML)) and hepatitis C virus. Cases of fatal PML that occurred after disease progression and retreatment have also been reported in clinical trials. Cases of hepatitis B reactivation, have been reported, the majority of which were in subjects receiving MabThera in combination with cytotoxic chemotherapy. In patients with relapsed/refractory CLL, the incidence of grade 3/4 hepatitis B infection (reactivation and primary infection) was 2 % in R-FC vs 0 % FC. Progression of Kaposi's sarcoma has been observed in MabThera-exposed patients with pre-existing Kaposi's sarcoma. These cases occurred in non-approved indications and the majority of patients were HIV positive.

Maintenance Treatment (NHL) up to 2 years
Data from a phase III clinical trial included 2 cases of fatal PML in NHL patients that occurred after disease progression and retreatment (*see section 2.4 Warnings and Precautions*).

Hematologic events
In clinical trials with MabThera monotherapy given for 4 weeks, haematological abnormalities occurred in a minority of patients and were usually mild and reversible. Severe (grade 3/4) neutropenia was reported in 4.2%, anaemia in 1.1% and thrombocytopenia in 1.7% of the patients. During MabThera maintenance treatment for up to 2 years, leucopenia (5% vs. 2%, grade 3/4) and neutropenia (10 % vs. 4 %, grade 3/4) were reported at a higher incidence when compared to observation. The incidence of thrombocytopenia was low (<1%, grade 3/4) and was not different between treatment arms.

During the treatment course in studies with MabThera in combination with chemotherapy, grade 3/4 leucopenia (R-CHOP 88 % vs. CHOP 79 %, R-FC 23 % vs. FC 12 %), neutropenia (R-CVP 24 % vs. CVP 14 %; R-CHOP 97 % vs. CHOP 88%, R-FC 30% vs. FC 19% in previously untreated CLL), pancytopenia (R-FC 3% vs. FC 1% 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 and chemotherapy was not associated with a higher incidence of infections and infestations compared to patients treated with chemotherapy alone and the neutropenia was not prolonged in the MabThera group plus chemotherapy group. There were no differences reported for the incidence of anaemia. Some cases of late neutropenia occurring more than four weeks after the last infusion of MabThera were reported. In the CLL first-line study, Binet stage C patients experienced more adverse events in the R-FC arm compared to the FC arm (R-FC 83% vs. FC 71%). In the relapsed/refractory CLL study, grade 3/4 thrombocytopenia was reported in 11 % of patients in the R-FC group compared to 9 % of patients in the FC group.

In studies of MabThera in patients with Waldenstrom's macroglobulinaemia, 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.

Cardiovascular events
Cardiovascular reactions during clinical trials with MabThera monotherapy were reported in 18.8 % of patients with the most frequently reported events being hypotension and hypertension. Cases of grade 3 or 4 arrhythmia (including ventricular and supraventricular tachycardia) and angina pectoris during infusion were reported.

During maintenance treatment, the incidence of grade 3/4 cardiac disorders was comparable between patients treated with MabThera and observation. Cardiac events were reported as serious adverse events (including atrial fibrillation, myocardial infarction, left ventricular failure, myocardial ischemia) in 3 % of patients treated with MabThera compared to <1 % on observation.

In studies evaluating MabThera in combination with chemotherapy, 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 (14 patients, 6.9 %) as compared to the CHOP group (3 patients, 1.5 %). All of these arrhythmias either occurred in the context of a MabThera infusion or were associated with predisposing conditions such as fever, infection, acute myocardial infarction or pre-existing respiratory and cardiovascular disease. 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 or 4 cardiac disorders was low both in the first-line study (4 % R-FC, 3 % FC) and in the relapsed/refractory study (4 % R-FC, 4 % FC).

IgG levels
In the clinical trial evaluating MabThera maintenance treatment in relapsed/refractory follicular lymphoma, median IgG levels were below the lower limit of normal (LLN) (< 7 g/L) after induction treatment in both the observation and the MabThera groups. In the observation group, the median IgG level subsequently increased to above the LLN, but remained constant in the MabThera group. The proportion of patients with IgG levels below the LLN was about 60 % in the MabThera group throughout the 2 year treatment period, while it decreased in the observation group (36 % after 2 years).

Neurologic events
During the treatment period, four patients (2 %) treated with R-CHOP, 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 or 4 nervous system disorders was low both in the first-line study (4 % R-FC, 4 % FC) and in the relapsed/refractory study (3 % RFC, 3 % FC).

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.

Respiratory system
Respiratory failure/insufficiency and pulmonary infiltrates in the context of infusion-related reactions (*see section 2.4 Warnings and Precautions*). In addition to pulmonary events associated with infiltrates outside of infusions-related reactions and interstitial lung disease, pneumonitis have some with fatal outcome, has been reported rarely.

Gastrointestinal disorders
Gastrointestinal perforation in some cases leading to death has been observed in patients receiving MabThera for treatment of Non-Hodgkin's lymphoma (NHL). In the majority of these cases, MabThera was administered with chemotherapy.

Skin and subcutaneous tissue disorders
Toxic Epidermal Necrolysis and Stevens-Johnson syndrome, some with fatal outcome, have been reported very rarely.

Subpopulations
Monotherapy
Elderly patients (≥ 65 years):
The incidence of ADRs of all grades and grade 3 /4 ADR was similar in elderly patients compared to younger patients (<65 years).

Combination Therapy
Elderly patients (≥ 65 years):
The incidence of grade 3/4 blood and lymphatic adverse events was higher in elderly patients compared to younger patients (<65 years), with previously untreated or relapsed/refractory CLL.

Bulky disease:
There was a higher incidence of grade 3/4 ADRs in patients with bulky disease than in patients without bulky disease (25.6 % vs. 15.4 %). The incidence of ADRs of any grade was similar in these two groups.

Re-treatment with monotherapy:
The percentage of patients reporting ADRs upon re-treatment with further courses of MabThera was similar to the percentage of patients reporting ADRs upon initial exposure (any grade and grade 3/4 ADRs).

Experience from Rheumatoid Arthritis
Intravenous Formulation
The overall safety profile of MabThera IV in rheumatoid arthritis is based on data from patients from clinical trials and from post-marketing surveillance. The safety profile of MabThera IV in patients with severe rheumatoid arthritis (RA) is summarized in the sections below. In clinical trials more than 3100 patients received at least one treatment course and were followed for periods ranging from 6 months to over 5 years; approximately 2400 patients received two or more courses of treatment with over 1000 having received 5 or more courses. The safety information collected during post marketing experience reflects the expected adverse reaction profile as seen in clinical trials for MabThera (*see section 2.4 Warnings and Precautions*)
Patients received 2 x 1000 mg of MabThera separated by an interval of two weeks; in addition to methotrexate (10-25 mg/week). MabThera infusions were administered after an intravenous infusion of 100 mg methylprednisolone; patients also received treatment with oral prednisone for 15 days. Events are listed in Table 2. Frequencies are defined as very common (≥1/10) and common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
The most frequent adverse reactions considered due to receipt of MabThera were infusion related reactions. The overall incidence of IRRs in clinical trials was 23% with the first infusion and decreased with subsequent infusions. Serious IRRs were uncommon (0.5% of patients) and were predominantly seen during the initial course. In addition to adverse reactions seen in RA clinical trials for rituximab, progressive multifocal leukoencephalopathy (PML) (*see section 2.4 Warnings and Precautions*) and serum sickness-like reaction have been reported during post marketing experience.

Table 2 Summary of Adverse Drug Reactions Reported in Clinical Trials or During Postmarketing Surveillance Occurring in Patients with Rheumatoid Arthritis receiving MabThera

System Organ Class	Very Common	Common	Uncommon	Rare	Very rare	Not known
Infections and Infestations	Upper respiratory tract infection, urinary tract infection	Bronchitis, sinusitis, gastroenteritis, tinea pedis			PML, reactivation of hepatitis B	serious viral infection[1]
Blood and lymphatic system disorders		neutropenia[2]		late neutropenia[3]	Serum sickness-like reaction	
Cardiac Disorders				Angina pectoris, atrial fibrillation, heart failure, myocardial infarction	Atrial flutter	
Immune System Disorders	[4]Infusion related reactions (hypertension, nausea, rash, pyrexia, pruritus, urticaria, throat irritation, hot flush, hypotension rhinitis, rigors, tachycardia, fatigue, oropharyngeal pain, peripheral oedema, erythema		[4]Infusion related reactions (generalized oedema, bronchospasm wheezing, laryngeal oedema, angioneurotic oedema, generalized pruritis, anaphylaxis, anaphylactoid reaction			
General disorders and administration site conditions						
Metabolism and Nutritional Disorders		Hypercholesterolemia				
Nervous System disorders	Headache	Paraesthesia, migraine,				

System Organ Class	Very Common	Common	Uncommon	Rare	Very rare	Not known
		dizziness, sciatica				
Skin and subcutaneous tissue disorders		Alopecia			Severe bullous skin reactions, toxic epidermal necrolysis, Stevens-Johnson syndrome[6]	
Psychiatric disorders		Depression, anxiety				
Gastrointestinal Disorders		Dyspepsia, diarrhoea, gastro-oesophageal reflux, mouth ulceration, upper abdominal pain				
Musculoskeletal disorders		Arthralgia/ musculoskeletal pain, osteoarthritis, bursitis				
Investigations	decreased IgM levels[5]	decreased IgG levels[5]				

[1]See also section infections below.
[2]Frequency category derived from laboratory values collected as part of routine laboratory monitoring.in clinical trials
[3] Frequency category derived from post-marketing data.
[4] Reactions occurring during or within 24 hours of infusion. See also infusion-related reactions below. Infusion related reactions may occur as a result of hypersensitivity and/or to the mechanism of action.
[5]Includes observations collected as part of routine laboratory monitoring.
[6] includes fatal cases

Multiple Courses:
Multiple courses of treatment are associated with a similar ADR profile to that observed following first exposure. The rate of all ADRs following first MabThera exposure was highest during the first 6 months and declined thereafter. This is mostly accounted for by infusion-related reactions (most frequent during the first treatment course), RA exacerbation and infections, all of which were more frequent in the first 6 months of treatment.

Further information on selected adverse drug reactions:
Infusion-related reactions:
The most frequent ADRs following receipt of MabThera IV in RA clinical studies were infusion-related reactions (IRRs) (refer to Table 2). Among the 3189 patients treated with MabThera, 1135 (36%) experienced at least one IRR with 733/3189 (23%) of patients experiencing an IRR following first infusion of the first exposure to MabThera. The incidence of IRRs decline for all subsequent infusions.

In clinical studies fewer than 1% (17/3189) of patients experienced a serious IRR. There were no CTC Grade 4 IRRs and no deaths due to IRRs. The proportion of CTC Grade 3 events, and of IRRs leading to withdrawal decreased by course and were rare from course 3 onwards.

Signs and or symptoms suggesting an infusion-related reaction (e.g. nausea, pruritis, fever, urticaria/rash, chills, pyrexia, rigors, sneezing, angioneurotic edema, throat irritation, cough and bronchospasm, with or without associated hypotension or hypertension) were observed in 720/3095 (23%) patients following first infusion of the first exposure to MabThera; Premedication with intravenous 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 infusion in patients with rheumatoid arthritis, patients with moderate-to-severe active RA who did not experience a serious infusion-related reaction (IRR) during or within 24 hours of their first studied infusion were allowed to receive a 120-minute infusion of MabThera 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 infusion-related reactions (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 reported from clinical trials was approximately 94 per 100 patient years in MabThera treated patients. The infections were predominately mild to moderate and consisted mostly of upper respiratory tract infections and urinary tract infections. The incidence of infections that were serious or required IV antibiotic was approximately 4 per 100 patient years. The rate of serious infections did not show any significant increase following multiple courses of MabThera. Lower respiratory tract infections (including pneumonia) have been reported during clinical trials, at a similar incidence in the Mabthera arms compared to control arms.

In the post marketing setting, serious viral infections have been reported in RA patients treated with rituximab.

Cases of Progressive Multifocal Leukoencephalopathy with fatal outcome have been reported following use of MabThera for the treatment of autoimmune diseases. This includes Rheumatoid Arthritis and off-label autoimmune diseases, including Systemic Lupus Erythematosus (SLE) and Vasculitis. All the reported cases had multiple risk factors for PML, including either the underlying disease and or long-term immunosuppressive therapy or chemotherapy.

Malignancies:
In RA clinical studies, the incidence of malignancy following exposure to rituximab is 0.8 per 100 patient years, which is within the range expected for an age- and gender- matched population.

Cardiovascular:
Cardiac events were observed in 11 % patients in clinical studies with MabThera. In placebo controlled studies, serious cardiac events were reported equally in MabThera and placebo treated patients (2 %).

Neurologic events:
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

2.7 Overdose
Intravenous and Subcutaneous Formulations
Limited experience with doses higher than the approved intravenous doses of MabThera is available from clinical trials in humans. The highest IV dose of MabThera tested in humans to date is 5000 mg (2250 mg/m^2), 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. 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.

Three patients in the MabThera subcutaneous SABRINA BO22334 study were inadvertently administered the subcutaneous formulation through the intravenous route up to a maximum rituximab dose of 2780 mg with no untoward effect. Patients who experience overdose or medication error should be closely monitored.

In the post-marketing setting five cases of MabThera overdose have been reported. Three cases had no reported adverse event. The two adverse events that were reported were flu-like symptoms, with a dose of 1.8 g of rituximab and fatal respiratory failure, with a dose of 2 g of rituximab.

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 rheumatoid arthritis 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 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) and 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. In patients treated for hematological malignancies, B cell repletion began within 6 months of treatment returning to normal levels between 9 and 12 months after completion of therapy. 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 of more after their last dose of MabThera.

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
Intravenous Formulation
Low-grade or follicular non-Hodgkin's lymphoma
MabThera 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 as an IV 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% versus 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.

A statistically significant correlation was noted between response rates and bone marrow involvement. 40% 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 as IV 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 as IV 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, were re-treated with 375 mg/m^2 of MabThera as IV infusion weekly for four doses. Three of the patients had received two courses of MabThera 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 (12.4 months).

MabThera IV in combination with CVP chemotherapy
Initial treatment
In an open-label randomized trial, a total of 322 previously untreated patients with follicular lymphoma patients 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 375 mg/m^2 in combination with CVP (R-CVP). MabThera 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 tumour 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 significant clinical difference (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 IV in combination with chemotherapy regimen other than CVP (CHOP, MCP, CHVP/Interferon-α) have also demonstrated significant improvements in response rates, time-dependent parameters as well as in overall survival. Key results from all four trials are summarized in table 3.

Table 3 Summary of key results from four phase III randomized trials evaluating the benefit of MabThera with different chemotherapy regimens in follicular lymphoma

Trial	Treatment, N	Median FU, months	ORR, %	CR, %	Median TTF/PFS/ EFS mo	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

EFS – Event Free Survival
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 IV Maintenance Therapy
Previously untreated follicular lymphoma
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 maintenance therapy (n=505) or observation (n=513). The two treatment groups were well balanced with regards to baseline characteristics and disease status. MabThera maintenance treatment consisted of a single infusion of MabThera at 375 mg/m^2 body surface area 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 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 lymphoma (Table 4).

Significant benefit from maintenance treatment with MabThera 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) (Table 4).Data from extended follow-up of patients in the study (median follow-up 9 years) confirmed the long-term benefit of MabThera maintenance therapy in terms of PFS, EFS, TNLT and TNCT(Table 4).

Table 4 Overview of Efficacy results for Maintenance MabThera 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 N=505**	**Observation N=513**	**MabThera 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%	72%
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 IV maintenance treatment provided consistent benefit in all predefined 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/CRu or PR). Exploratory analyses of the benefit of maintenance treatment showed a less pronounced effect in elderly patients (> 70 years of age), however sample sizes were small.

Relapsed/Refractory follicular NHL
In a prospective, open label, international, multi-centre, phase III trial, 465 patients with relapsed/refractory follicular NHL were randomised in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or MabThera 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 randomised in a second step to MabThera IV maintenance therapy (n=167) or observation (n=167). MabThera IV maintenance treatment consisted of a single infusion of MabThera at 375 mg/m^2 body surface area 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 5).

Table 5 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 tumour 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 randomisation. Maintenance treatment with MabThera 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 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 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 IV maintenance group vs. 57% in the observation group. An analysis of overall survival confirmed the significant benefit of MabThera IV maintenance over observation ($p=0.0039$ log-rank test). MabThera 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 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 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 (table 6). The risk of relapse in complete responders was reduced by 67% (95% CI; 39%-82%).

Table 6 Maintenance phase: overview of efficacy results MabThera 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 survival[a]	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 IV maintenance treatment was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (table 6). MabThera 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, $p=0.0071$). Although subgroups were small, MabThera IV maintenance treatment provided a significant benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP, although longer follow-up is required to confirm this observation.

MabThera maintenance treatment provided consistent benefit in all subgroups tested [gender (male, female), age (≤60 years, > 60 years), stage (III, IV), WHO performance status (0 versus >0), B symptoms (absent, present), bone marrow involvement (no versus yes), IPI (0-2 versus 3-5), FLIPI score (0-1, versus 2 versus 3-5), number of extra-nodal sites (0-1 versus >1), number of nodal sites (< 5 versus ≥ 5), number of previous regimens (1 versus 2), best response to prior therapy (CR/PR versus NC/PD), hemoglobin (< 12 g/dL versus ≥12 g/dL), β_2-microglobulin (< 3mg/L versus ≥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/m^2, doxorubicin 50 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 eight cycles, or MabThera 375 mg/m^2 plus CHOP (R-CHOP). MabThera 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, β2 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.

Chronic lymphocytic leukaemia
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 25mg/m^2, cyclophosphamide 250 mg/m^2, days 1-3) every 4 weeks for 6 cycles or MabThera in combination with FC (R-FC). MabThera 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. Patients were excluded from the study in relapsed/refractory CLL if they had previously been treated with monoclonal antibodies or if they were refractory (defined as failure to achieve a partial remission for at least 6 months) to fludarabine or any nucleoside analogue. A total of 810 patients (403 R-FC, 407 FC) the first line study (Table 7a and 7b) and 552 patients (276 R-FC, 276 FC) for the relapsed/refractory study Table 8 were analyzed for efficacy.

In the first line 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), however longer follow-up is needed to confirm this observation. The benefit in terms of PFS was consistently observed in most patient subgroups analyzed according to disease risk at baseline.

Table 7a First-line treatment of chronic lymphocytic leukaemia - overview of efficacy results for MabThera plus FC vs. FC alone (20.7 months median observation time)

Efficacy Parameter	Kaplan-Meier Estimate of Median Time to Event (Months)			Risk Reduction
	FC (N = 407)	R-FC (N=403)	Log-Rank p value	
Progression-free survival (PFS)	*32.2*	*39.8*	*<0.0001*	*44%*
Overall Survival	*NR*	*NR*	*0.0427*	*36%*
Event Free Survival	*31.1*	*39.8*	*<0.0001*	*45%*
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*	*40.2*	*0.0040*	*39%*
*Disease free survival (DFS)***	*NR*	*NR*	*0.7882*	*7%*
Time to new CLL treatment	*NR*	*NR*	*0.0052*	*35%*

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

Table 7b First-line treatment of chronic lymphocytic leukaemia
Progression-free survival according to Binet stage (ITT)

Progression-free survival (PFS)	Number of patients		Hazard Ratio (95% CI)	p-value (Wald test, not adjusted)
	FC	R-FC		
Binet A	22	18	0.13 (0.03; 0.61)	0.0093
Binet B	257	259	0.45 (0.32; 0.63)	<0.0001
Binet C	126	125	0.88 (0.58; 1.33)	0.5406

CI: Confidence Interval

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 8 Treatment of relapsed/refractory chronic lymphocytic leukaemia - overview of efficacy results for MabThera 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 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 promising PFS rates without adding relevant toxicity to the treatment.

Subcutaneous Formulation
Non-Hodgkin's lymphoma
The clinical experience of MabThera subcutaneous formulation in Non-Hodgkin's lymphoma is based on data from a phase III clinical trial (SABRINA BO22334) in patients with follicular lymphoma (FL) and a phase Ib dose-finding/dose-confirmation trial (SparkThera BP22333) in patients with FL. Results from trial BP22333 are presented in section 3.2 Pharmacokinetic Properties.

Trial BO22334 (SABRINA)

A two-stage phase III, international, multi-centre, randomised, controlled, open-label trial was conducted in patients with previously untreated follicular lymphoma, to investigate the non-inferiority of the pharmacokinetic profile, together with efficacy and safety of MabThera subcutaneous formulation in combination with CHOP or CVP versus MabThera intravenous formulation in combination with CHOP or CVP.

The objective of the first stage was to establish the MabThera subcutaneous dose that resulted in comparable rituximab serum C_{trough} levels compared with MabThera intravenous formulation, when given as part of induction treatment every 3 weeks for 8 cycles (*see section 3.2 Pharmacokinetic Properties*). Stage 1 enrolled previously untreated patients with CD20-positive, follicular lymphoma (FL) Grade 1, 2 or 3a (n=127). Patients with a response at the end of induction therapy received maintenance therapy with the corresponding formulation (intravenous or subcutaneous) used in the induction treatment, every 8 weeks for 24 months.

The objective of Stage 2 was to provide additional efficacy and safety data for subcutaneous MabThera compared with MabThera IV using the 1400 mg subcutaneous dose established in stage 1. Previously untreated patients with CD20-positive, follicular lymphoma Grade 1, 2 or 3a (n=283) were enrolled in the Stage 2.

The overall trial design was identical across Stage 1 and Stage 2. Patients were randomized into the following two treatment groups:

- MabThera subcutaneous formulation arm (n= 205): first cycle MabThera intravenous formulation plus 7 cycles of MabThera subcutaneous formulation in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks.
  MabThera intravenous formulation was used at the standard dose of 375 mg/m^2 body surface area.
  MabThera subcutaneous formulation was given at a fixed dose of 1400 mg.
  Patients achieving at least partial response (PR) at the end of induction treatment were entered on to MabThera subcutaneous formulation maintenance therapy administered once every 8 weeks for 24 months.
- MabThera intravenous formulation arm (n= 205): 8 cycles of MabThera intravenous formulation in combination with up to 8 cycles of CHOP or CVP chemotherapy administered every 3 weeks.
  MabThera intravenous formulation was used at the standard dose of 375 mg/m^2.
  Patients achieving at least PR at the end of induction were entered on to MabThera intravenous formulation maintenance therapy administered once every 8 weeks for 24 months.

Overall response rate (ORR, comprising complete response [CR], unconfirmed response [CRu], and partial response [PR]) at the end of induction treatment was calculated using investigator assessment of response in the ITT population based on pooled data from Stages 1 and 2. Additionally, ORR and complete response rate (CRR, comprising CR and CRu) at the end of maintenance treatment and time-to-event endpoints (progression-free survival [PFS] and overall survival [OS]) were analyzed. Key efficacy results are presented in Table 9 based on a median follow-up of 58 months

Table 9 Efficacy Results for Study SABRINA/BO22334

	MabThera SC N=205	MabThera IV N=205
Overall Response Rate at End of Induction[a]		
Number of responders (CR/CRu, PR)	173	174
Overall response (CR/CRu, PR) rate (%, [95% CI])	84.4% [78.7;89.1]	84.9% [79.2;89.5]
Number of complete responders (CR/CRu)	66	65
Complete response (CR/CRu) rate (%, [95% CI])	32.2% [25.9;39.1]	31.7% [25.4;38.6]
Overall Response Rate at End of Maintenance		
Number of patients treated in maintenance (n)	172	178
Number of responders (CR/CRu, PR)	134	139
Overall response (CR/CRu, PR) rate (%, [95% CI])	77.9% [71.0;83.9]	78.1% [71.3;83.9]
Number of complete responders (CR/CRu)	87	103
Complete response (CR/CRu) rate (%, [95% CI])	50.6% [42.9;58.3]	57.9% [50.3;65.2]
Progression-free survival[b]		
Number of patients with event	65 (31.7%)	71 (34.6%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.90 [0.64%, 1.26%]	
Overall survival[b]		
Number of patients with event	18 (8.8%)	26(12.7%)
Hazard Ratio [95% CI] (unstratified Cox model)	0.70[0.38;1.27]	

[a] at end of Induction
[b] at time of final analysis (median follow-up 58 months)
Stage 2 primary efficacy endpoint was ORR at the end of induction, however pooled results which were preplanned are presented in this Table.
Response rates based on investigator assessment.
Response rates at end of maintenance based on patients who received at least one cycle of maintenance treatment (n).

Exploratory analyses showed response rates among BSA, chemotherapy and gender subgroups were not notably different from the overall ITT population.

Intravenous Formulation
Rheumatoid arthritis
The efficacy and safety of MabThera IV in alleviating the symptoms and signs of rheumatoid arthritis was demonstrated in three randomized, controlled, double-blind, multicenter studies.

Study 1 was a double blind comparative study which included 517 patients that had experienced an inadequate response or intolerance to one or more TNF inhibitor therapies. Eligible patients had severe active rheumatoid arthritis, diagnosed according to the criteria of the American College of Rheumatology (ACR). The primary endpoint was the percent of patients who achieved an ACR20 response at week 24. Patients received two 1000 mg IV infusions of MabThera, each following an IV infusion of 100 mg methylprednisolone and separated by an interval of 15 days. All patients received concomitant oral methotrexate (10-25 mg/week) and 60 mg oral prednisolone on days 2-7 and 30 mg on days 8-14 following the first infusion.

Study 2 was a randomized, double-blind, double-dummy, controlled, 3 x 3 multifactorial study which compared two different dose levels of rituximab given with or without one of two per infusional corticosteroid regimens in combination with weekly methotrexate in patients with active rheumatoid arthritis which had not responded to treatment with at least 5 other DMARDs.

Study 3 was a double-blind, double-dummy, controlled study evaluating rituximab monotherapy, and rituximab in combination with either cyclophosphamide or methotrexate in patients with active rheumatoid arthritis which had not responded to one or more prior DMARDs.
The comparator group in all three studies was weekly methotrexate (10-25mg weekly).

Disease Activity Outcomes
In all three studies, MabThera 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 (Table 10). The treatment effect was similar in patients independent of age, gender, body surface area, race, number of prior treatments or disease status.

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 10 Cross-Study Comparison of ACR Responses at Week 24 (ITT Population)

	ACR Response	Placebo+MTX	Rituximab+MTX
Study 1		N= 201	N= 298
	ACR20	36 (18%)	153 (51%)[1 ***]
	ACR50	11 (5%)	80 (27%)[1 ***]
	ACR70	3 (1%)	37 (12%)[1 ***]
Study 2		N= 143	N= 185
	ACR20	45 (31%)	96 (52%)[2]
	ACR50	19 (13%)	61 (33%)[2]
	ACR70	6 (4%)	28 (15%)[2]
Study 3		N= 40	N= 40
	ACR20	15 (38%)	28 (70%)[3]
	ACR50	5 (13%)	17 (43%)[3]
	ACR70	2 (5%)	9 (23%)[3]

[1] $p \le 0.0001$; [2] $p \le 0.001$; [3] $p < 0.05$

Patients treated with MabThera in combination with methotrexate had a significantly greater reduction in disease activity score (DAS28) than patients treated with methotrexate alone (Table 11). Similarly, a good to moderate EULAR response was achieved by significantly more MabThera treated patients treated with MabThera and methotrexate compared to patients treated with methotrexate alone (Table 11).

Table 11 Cross-Study Comparison of DAS and EULAR Responses at Week 24 (ITT Population)

	Placebo+MTX	Rituximab +MTX (2 × 1g)
Study 1	(n = 201)	(n = 298)
Change in DAS28 [Mean (SD)]	-0.4 (1.2)	-1.9 (1.6)*
EULAR Response (%)		
None	78%	35%
Moderate	20%	50%*
Good	2%	15%
Study 2	(n = 143)	(n = 185)
Mean change in DAS28 (SD)	–0.8 (1.4)	–2.0 (1.6)
EULAR response		
None	61%	37%
Moderate	35%	40%
Good	4%	23%
Study 3	N=40	N=40
Change in DAS [Mean (SD)]	-1.3 (1.2)	-2.6 (1.3)
EULAR response		
None	50%	18%
Moderate	45%	63%
Good	5%	20%

*p value <0.0001. p values not calculated for studies 2 and 3.

Radiographic Response
Structural joint damage was assessed radiographically and expressed as change in modified total Sharp score and its components, the erosion score and joint space narrowing score.

In Study 1, conducted in patients with inadequate response or intolerance to one or more TNF inhibitor therapies, receiving MabThera in combination with methotrexate demonstrated significantly less radiographic progression than patients originally receiving methotrexate alone at 56 weeks. Of the patients originally receiving methotrexate alone, 81 % received rituximab either as rescue between weeks 16-24 or in the extension trial, before week 56. A higher proportion of patients receiving MabThera/MTX also had no erosive progression over 56 weeks (Table 12)

Table 12 Radiographic outcomes at 1 year (mITT population)

	Placebo+MTX	Rituximab +MTX (2 × 1000mg)
Study 1	(n = 184)	(n = 273)
Mean Change from Baseline:		
Modified Total Sharp score	2.31	1.00*
Erosion Score	1.32	0.59*
Joint Space narrowing score	0.99	0.41**
Proportion of patients with no radiographic change	46%	53%
Proportion of patients with no erosive change	52%	61%*

150 patients originally randomized to placebo + MTX in Study 1 received at least one course of RTX + MTX by one year * p <0 05, ** p < 0.001,
Inhibition of the rate of progressive joint damage was also observed long term. Radiographic analysis at 2 years in study 1 demonstrated significantly reduced progression of structural joint damage in patients receiving MabThera in combination with 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.

Physical function and quality of life outcomes
Significant reductions in disability index (HAQ-DI) and fatigue (FACIT-Fatigue) scores were observed in patients treated with MabThera compared to patients treated with methotrexate alone. The proportions of rituximab treated patients showing a minimal clinically important difference (MCID) in HAQ-DI (defined as an individual total score decrease of >0.22) was also higher than among patients receiving methotrexate alone (Table 13).

Significant improvement in health related quality of life was also demonstrated with significant improvement in both the physical health score (PHS) and mental health score (MHS) of the SF-36.

Further, a significantly higher proportion of patients achieved MCIDs for these scores (Table 13).

Table 13 Physical Function and Quality of Life outcomes at week 24 in study 1

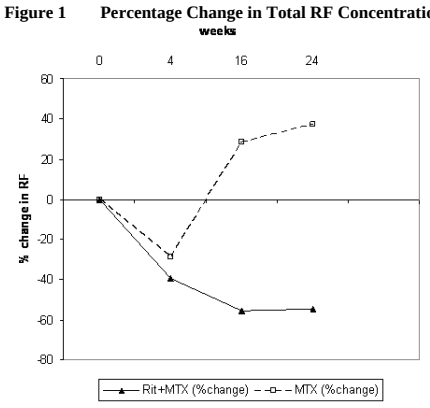
Outcome†	Placebo+MTX	Rituximab+MTX *(2 x 1000 mg)*
	n=201	n=298
Mean change in HAQ-DI	0.1	-0.4***
% HAQ-DI MCID	20%	51%
Mean change in FACIT-T	-0.5	-9.1***
	n=197	n=294
Mean Change in SF-36 PHS	0.9	5.8***
% SF-36 PHS MCID	13%	48%***
Mean Change in SF-36 MHS	1.3	4.7**
% SF-36 MHS MCID	20%	38%*

† Outcome at 24 weeks
Significant difference from placebo at the primary time point: * $p < 0.05$, ** $p < 0.001$ *** $p \leq 0.0001$
MCID HAQ-DI ≥0.22, MCID SF-36 PHS >5.42, MCID SF-36 MHS >6.33

Laboratory Evaluations
A total of 54/990 (5.5%) 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 these patients.

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)

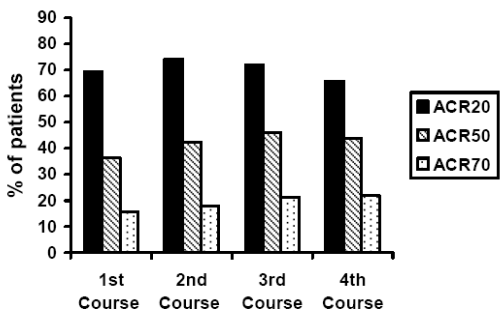


Plasma total immunoglobulin concentrations, total lymphocytes counts, and white cells generally remained within normal limits following MabThera treatment, with the exception of a transient drop in white cells counts over the first four weeks following therapy. Titers of Ig G antigen specific antibody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

Effects of rituximab on a variety of biomarkers was evaluated in patients enrolled into Study 3. This substudy 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 cyclophophamide 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
Treatment with MabThera in combination with methotrexate over multiple courses resulted in sustained improvements in the clinical signs and symptoms of RA, as indicated by ACR, DAS28-ESR and EULAR responses which was evident in all patient populations studied (Figure 2). Sustained improvement in physical function as indicated by the HAQ-DI score and the proportion of patients achieving MCID for HAQ-DI were observed.

Figure 2: ACR responses for 4 treatment courses (24 weeks after each course (within patient, within visit) in patients with an inadequate response to TNF-inhibitors (n=146)



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 TNF inhibitor and were receiving MTX, were to receive 2 courses of MabThera treatment. Patients who were naïve to prior MabThera therapy (n=306) and those who had received 1 to 2 prior courses of rituximab 6-9 months prior to baseline (n=45), were eligible for enrollment.

Patients received 2 courses of MabThera 2 x 1000mg + MTX 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 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 120 minutes. Any patient experiencing a serious infusion-related reaction (IRR) with any infusion was withdrawn from the study. In this study, an infusion-related reaction (IRR) was defined as any adverse event that occurred during or within 24 hours following the infusion of MabThera and met pre-specified criteria for adverse event terms for IRRs. IRRs were defined as serious if they met one of the following seriousness criteria: fatal, life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, were medically significant.

The primary objective of this study was to assess the safety of administering the second infusion of the first study course of MabThera over 120 minutes.

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 Effects*)

3.1.3 Immunogenicity
Subcutaneous Formulation
Data from the subcutaneous formulation development program indicate that the formation of anti-rituximab antibodies (HACAs) after subcutaneous administration is comparable with that observed after IV administration. In the SABRINA study (BO22334) the incidence of treatment-induced/enhanced anti-rituximab antibodies in the subcutaneous group was low and similar to that observed in the IV group (1.9% IV vs. 2% SC). The incidence of treatment-induced/enhanced anti-rHuPH20 antibodies was 8% in the IV group compared with 15% in the subcutaneous group, and none of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies. The overall proportion of patients found to have anti-rHuPH20 antibodies remained generally constant over the follow-up period in both cohorts.

3.2 Pharmacokinetic Properties
3.2.1 Absorption
Intravenous Formulation
Not applicable.

Subcutaneous Formulation
Rituximab pharmacokinetics following single dose administration of MabThera subcutaneous 375 mg/m^2, 625 mg/m^2 and 800 mg/m^2 were compared with MabThera intravenous 375 mg/m^2 in FL patients. Following subcutaneous administration, the absorption of rituximab is slow, reaching maximal concentrations about 3 days after administration. Based on popPK analysis an absolute bioavailability of 64.6% (95% CI: 63.4 – 65.9) was estimated. Rituximab exposure increased dose proportional over the 375 mg/m^2 to 800 mg/m^2 subcutaneous dose range. Pharmacokinetic parameters such as clearance, distribution volume, and elimination half-life were comparable for both formulations.

Trial BP22333 (SparkThera)
A two-stage phase Ib trial to investigate the pharmacokinetics, safety and tolerability of MabThera subcutaneous formulation in patients with follicular lymphoma (FL) as part of maintenance treatment.

In stage 2, MabThera subcutaneous formulation at a fixed dose of 1400 mg was administered as subcutaneous injection during maintenance treatment, after at least one cycle of MabThera intravenous formulation at a dose of 375 mg/m^2 to FL patients who had previously responded to MabThera intravenous formulation in induction.
The comparison of predicted median C_{max} data for MabThera subcutaneous formulation and intravenous formulation are summarized in Table 14.

Table 14 Trial BP22333 (SparkThera): Absorption – Pharmacokinetic parameters of MabThera SC compared to MabThera IV

	MabThera subcutaneous	MabThera intravenous
Predicted median C_{max} (q2m) µg/mL	201	209
Predicted median C_{max} (q3m) µg/mL	189	184

The median T_{max} in the MabThera subcutaneous formulation group was approximately 3 days as compared to the T_{max} occurring at or close to the end of the infusion for the intravenous formulation group.

Trial BO22334 (SABRINA)
MabThera subcutaneous formulation at a fixed dose of 1400 mg was administered for 6 cycles subcutaneously during induction at 3-weekly intervals, following a first cycle of MabThera intravenous formulation at a dose of 375 mg/m^2, in previously untreated FL patients in combination with chemotherapy. The serum rituximab C_{max} at cycle 7 was similar between the two treatment arms, with geometric mean (CV%) values of 250.63 (19.01) µg/mL and 236.82 (29.41) µg/mL for the intravenous and the subcutaneous formulations respectively, with the resulting geometric mean ratio ($C_{max, SC}/C_{max, IV}$) of 0.941 (90% CI: 0.872, 1.015).

3.2.2 Distribution and Elimination
Non-Hodgkin's Lymphoma
Intravenous Formulation
Pharmacokinetic studies performed in a phase I study in which patients (N=15) with relapsed B–cell lymphoma were given single doses of rituximab at 10, 50, 100 or 500 mg/m^2 indicated that serum levels and half-life of rituximab were proportional to dose.

In a cohort of 14 patients among the 166 patients with relapsed or chemoresistant low-grade or follicular non-Hodgkin's lymphoma enrolled in the phase III pivotal trial and given rituximab 375 mg/m^2 as an IV infusion for 4 weekly doses, the mean serum half-life was 76.3 hours (range, 31.5 to 152.6 hours) after the first infusion and 205.8 hours (range, 83.9 to 407.0 hours) after the fourth infusion. The mean C_{max} after the first and fourth infusion were 205.6 ± 59.5 µg/ml and 464.7 ± 119.0 µg/ml, respectively. The mean plasma clearance after the first and fourth infusion was 0.0382 ± 0.0182 l/h and 0.0092 ± 0.0033 l/h, respectively.

However, variability in serum levels was large. Rituximab serum concentrations were statistically significantly higher in responding patients than in non-responding patients just prior to and after the fourth infusion and post-treatment. Serum concentrations were negatively correlated with tumor burden and the number of circulating B cells at baseline. Typically, rituximab was detectable for 3 – 6 months after administration of the last infusion.

Distribution and elimination have not been extensively studied in patients with DLCL, but available data indicate that serum levels of rituximab in DLCL patients are comparable to those in patients with low-grade or follicular NHL following treatment with similar doses.

Subcutaneous Formulation
Geometric mean C_{trough} and geometric mean AUCτ from the BP22333 and BO22334 trials are summarized in Table 15.

Table 15 Distribution/Elimination - Pharmacokinetic parameters of MabThera subcutaneous compared to MabThera intravenous

Trial BP22333 (SparkThera)				
	Geometric mean C_{trough} (q2m) µg/mL	Geometric mean C_{trough} (q3m) µg/mL	Geometric mean $AUC\tau_{cycle\ 2\ (q2m)}$ µg.day/mL	Geometric mean $AUC\tau_{cycle\ 2\ (q3m)}$ µg.day/mL
MabThera subcutaneous formulation	32.2	12.1	5430	5320
MabThera intravenous formulation	25.9	10.9	4012	3947
Trial BO22334 (SABRINA)				
	Geometric mean C_{trough} values at pre-dose cycle 8 µg/mL		Geometric mean AUC values at cycle 7 µg.day/mL	
MabThera subcutaneous formulation	134.6		3778.9	
MabThera intravenous formulation	83.1		2734.2	

In a population pharmacokinetic analysis in follicular lymphoma patients who received subcutaneous and/or intravenous MabThera, single or multiple infusions of MabThera as a single agent or in combination with chemotherapy, the population estimates of nonspecific clearance (CL_1), initial specific clearance (CL_2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V_1) were 0.200 L/day, 0.398 L/day, and 4.54 L/day, respectively. The estimated median terminal elimination half-life of MabThera subcutaneous formulation was 34 days (range, 18.9 to 87.1 days). The analysis data set contained samples from 399 patients administered SC and/or IV rituximab in Study BO22334.

Special populations
In clinical trial BO22334, an effect was observed between body size and exposure ratios reported in cycle 7, between rituximab subcutaneous formulation 1400 mg q3w and rituximab intravenous formulation 375 mg/m2 q3w with C_{trough} ratios of 2.29, 1.31, and 1.41 in patients with low, medium and high BSA, respectively (low BSA ≤ 1.70 m^2; 1.70 m^2 < medium BSA < 1.90 m^2; high BSA < 1.90 m^2). The corresponding AUCτ ratios were 1.66, 1.17 and 1.32.

There was no evidence of clinically relevant dependencies of rituximab pharmacokinetics on age and sex.

Anti-rituximab antibodies were detected in only 13 patients and did not result in any clinically relevant increase in steady-state clearance.

Chronic Lymphocytic Leukaemia
Intravenous Formulation
Rituximab was administered as an IV 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
Intravenous Formulation
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 Cmax 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 Cmax 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 days for the 2 x 500 mg dose group and 17 to 21 days for the 2 × 1000 mg dose group. Mean Cmax 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 Cmax 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. Cmax 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.

3.2.3 Pharmacokinetics in Special Populations
No pharmacokinetic data are available in patients with hepatic or renal impairment.

3.3 Nonclinical Safety
3.3.1 Other
Subcutaneous Formulation
Rituximab has shown to be highly specific to the CD20 antigen on B cells. Toxicity studies in cynomolgus monkeys have shown no other effect than the expected pharmacological depletion of B cells in peripheral blood and in lymphoid tissue.

Developmental toxicity studies have been performed in cynomolgus monkeys at doses up to 100 mg/kg (treatment on gestation days 20-50) and have revealed no evidence of toxicity to the foetus due to rituximab. However, dose-dependent pharmacologic depletion of B cells in the lymphoid organs of the foetuses was observed, which persisted post natally and was accompanied by a decrease in IgG level in the newborn animals affected. B cell counts returned to normal in these animals within 6 months of birth and did not compromise the reaction to immunization.

Standard tests to investigate mutagenicity have not been carried out, since such tests are not relevant for this molecule. No long-term animal studies have been performed to establish the carcinogenic potential of rituximab.

Specific studies to determine the effects of rituximab or rHuPH20 on fertility have not been performed. In general toxicity studies in cynomolgus monkeys no deleterious effects on reproductive organs in males or females were observed. Additionally, no effects on semen quality were shown for rHuPH20.

In embryofetal developmental studies in mice, rHuPH20 caused reduced fetal weight and loss of implantations at systemic exposures sufficiently in excess of human therapeutic exposure.

There is no evidence of dysmorphogenesis (i.e. teratogenesis) resulting from systemic exposure to rHuPH20.

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.

Intravenous Formulation
Store vials at 2 - 8 °C. Protect vials from direct sunlight.

Prepared infusion solutions of MabThera are stable for 12 hours at room temperature. If necessary, the prepared solutions may be stored in the refrigerator (at 2 - 8 °C) and are then chemically stable for up to 24 hours. As MabThera contains no antimicrobial preservative, it is essential to ensure that the prepared solutions remain sterile.

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.

Subcutaneous Formulation
Store in a refrigerator (2 °C – 8 °C). Keep the container in the outer carton in order to protect from light.

Once transferred from the vial into the syringe, the solution of MabThera subcutaneous formulation is physically and chemically stable for 48 hours at 2°C – 8°C and subsequently for 8 hours at 30°C in diffuse daylight.

From a microbiological point of view, the product should be used immediately. If not used immediately, preparation should take place in controlled and validated aseptic conditions. In-use storage times and conditions prior to use are the responsibility of the user.

4.2 Special Instructions for Use, Handling and Disposal
Intravenous Formulation
Use sterile needle and syringe to prepare MabThera. Withdraw the required amount of MabThera 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. Case 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.

Prepared infusion solutions of MabThera are stable for 12 hours at room temperature. If necessary, the prepared solutions may be stored in the refrigerator (at 2 - 8 °C) and are then chemically stable for up to 24 hours.

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

Subcutaneous Formulation

Once transferred from the vial into the syringe, the solution of MabThera subcutaneous formulation is physically and chemically stable for 48 hours at 2°C – 8°C and subsequently for 8 hours at 30°C in diffuse daylight.

MabThera SC is provided in sterile, preservative-free, non-pyrogenic, single use vials. Use a sterile needle and syringe to prepare MabThera.

Incompatibilities
No incompatibilities between MabThera subcutaneous formulation and polypropylene or polycarbonate syringe material or stainless steel transfer and injection needles and polyethylene Luer cone stoppers have been observed.

4.3 Nature and contents of container

Intravenous Formulation
100mg/10ml
Colourless type I glass vial with butyl rubber stopper, containing 10ml/vial of rituximab
Each carton contains two vials

500mg/50ml
Colourless type I glass vial with butyl rubber stopper, containing 50ml/vial of rituximab.
Each carton contains one vial.

Subcutaneous Formulation
Colourless type I glass vial with butyl rubber stopper with aluminium over seal and a pink plastic flip-off disk, containing 1400 mg/11.7 mL of rituximab.
Each carton contains one vial.

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

The following points should be strictly adhered to regarding the use and disposal of syringes and other medicinal sharps:
- Needles and syringes should never be reused
- Place all used needles and syringes into a sharps container (puncture-proof disposable container).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

5. PACKS

Mabthera IV

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

Mabthera SC

Vial of 11.7 ml	1

Medicine: keep out of reach of children

Current at July 2025

F. Hoffmann-La Roche Ltd, Basel, Switzerland