

SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 January 2005. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

Mabthera contains as active substance, rituximab, which is a chimeric mouse/human monoclonal antibody (mAb), consisting of a glycosylated IgG₁ kappa immunoglobulin with murine light- and heavy-chain variable regions (Fab domain) and human kappa and gamma-1 constant regions (Fc domain). Rituximab binds to CD20; a transmembrane phosphorylated protein, located on pre-B and matures B-lymphocytes (B-cell lineage-restricted pan-B cell antigen). The antigen is found on both normal B-cells and malignant B-cells (except from myeloma cells and most precursor B cell ALL). The CD20 antigen has characteristics that render it a suitable target for treatment: CD20 does not circulate freely in the plasma, CD20 does not shed from the surface of B-cells after binding of anti-CD20 antibodies, and CD20 does not internalise upon antibody binding. The potential therapeutic advantage of chimeric antibodies as compared with pure murine mAbs is the reduction of immunogenicity thereby permitting repeated administration. Other important features of chimeric mAbs are their ability of binding human complement (C1q), and the mediation of human effector functions such as complement fixation and antibody-dependent cellular cytotoxicity resulting in a potentially more effective destruction of tumour cells.

MabThera is intended for use in the treatment of patients with relapsed or chemoresistant follicular B-cell non-Hodgkin's lymphoma (NHL) and for the treatment of patients with CD20 positive diffuse large B-cell NHL in combination with CHOP chemotherapy.

Non-Hodgkin's lymphoma (NHL) is the most common of the malignant lymphoid neoplasms. The incidence in western countries varies in reports from 6 to 16/100,000 and in the EU an estimated number of approximately 50,000 new cases are diagnosed each year. NHL is the common name for a cluster of related but individual diseases, which have neoplastic transformation of a lymphoid cell as the common denominator. Eighty five percent of the NHLs are derived from a B-lymphocyte and 15% of the NHLs from a T-lymphocyte. The many classification schemes have built first on histopathology and cytopathology, then supplemented with immunopathology and more recently molecular biology and pathology. The use of the new DNA-chips should lead to a further refinement in classification within the next few years. The International Working Formulation (IWF) and the Kiel classification have in recent years been substituted by the REAL classification and later by its slightly modified version, the WHO classification. Translation of diagnoses within the systems is possible for most but not all classes. The WHO classification recognizes 13 individual B-cell lymphomas (with several further subdivisions), which form a clinical spectrum from the low-grade lymphocytic and follicular lymphomas with a medium survival of 10-15 years at one end, and the high grade lymphoblastic lymphomas with a medium survival of months at the other end of the spectrum.

Monoclonal antibodies (mAbs) specific for lymphoma antigens have been developed in the past, but the results to date have been somewhat disappointing. Anti-idiotype antibodies were impractical for broad clinical use. The use of murine antibodies targeted to tumours was limited by the lack of efficacy, the induction of neutralising antibodies HAMA (human anti-murine antibodies) or "allergic-like" reactions. Radiolabeled mAbs may be more active than their unlabeled counterparts but the toxicities appear to be more severe. Objective response rates of over 60% (in some studies, up to 90%) with 44% CR were reported in patients with recurrent indolent B-cell NHLs. Dose limiting toxicities have included severe and often serious cardiopulmonary and hepatic toxicities, myelosuppression, due to the radiosensitivity of the bone marrow. Most trials have used radiolabeled murine antibodies, which often induce HAMA; in addition, their use is likely to be restricted by environmental issues.

For several decades it has been recognised that low-grade NHL, and in particular follicular lymphomas are incurable diseases in spite of their high sensitivity to both radiotherapy and chemotherapy. Combination chemotherapy of the CHOP-type has no clear advantage over single

agent chemotherapy with chlorambucil with regards to prognosis. Although the majority of the patients will exhibit relapse or persistent lymphoma, this event is not the major prognostic determinant. The 10-year disease-free survival is 20-30% compared with an overall survival of about 8-10 years for patients with follicular lymphoma. The course of disease often contains several relapses that are manageable but ultimately most patients will develop chemoresistant lymphoma often with a transformation to a large cell more malignant NHL. Neither the use of interferon-alfa or autologous bone marrow transplantation have convincingly changed the outcome for these patients. The combination of interferon-alfa and chemotherapy was shown to be better than chemotherapy alone both in terms of tumour progression free survival and overall survival in a controlled trial.

Rituximab has now been proven to have a consistent antineoplastic effect in patients with follicular lymphomas.

Diffuse large cell NHL is a group of intermediate –high-grade malignant lymphomas which account for 30-40% of all newly diagnosed NHL. They have an aggressive and rapidly fatal course unless treated with relatively intensive combination chemotherapy, which however cures less than half of the patients. Thus, the four-drug regimen CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) consistently has produced a CR rate of 50%-60% in patients with large cell lymphomas and about 30%-40% of the patients remained continuously disease-free. The CHOP regimen has for decades been the most widely used chemotherapy for large cell lymphoma. The results of SWOG-8516 (Intergroup 0067), the so-called US National High-Priority Lymphoma Study comparing standard CHOP with m-BACOD or ProMACE-CytaBOM or MACOP-B in a prospective, randomised phase III trial enrolling approximately 1200 patients, led to the conclusion that CHOP remains the standard chemotherapy for patients with advanced-stage, intermediate- or high-grade non-Hodgkin's lymphoma.

Rituximab added to CHOP now seems able not only to increase the response rate, but also to improve the survival of patients with DLCL.

MabThera was granted a marketing authorisation on 2 June 1998 for the indication: "treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy". On <date of Commission Decision> this indication was extended through a type II variation to "treatment of patients with CD20 positive diffuse large B-cell Non-Hodgkin's lymphoma in combination with CHOP chemotherapy".

2. Chemical, pharmaceutical, and biological aspects

MabThera contains the active ingredient rituximab which is a chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG₁ kappa constant regions (Fc domain), and a murine light- and heavy-chain variable regions (Fab domain).

Part II of the dossier is of a good standard. The Notice to Applicants is strictly followed and the EU guidelines are fulfilled in general.

Composition

MabThera is a sterile, clear, colourless, preservative-free liquid concentrate for intravenous (IV) administration. MabThera is supplied at a concentration of 10 mg/ml in either 100 mg (10 ml) or 500 mg (50 ml) single-use vials. The product is formulated for intravenous administration in 9.0 mg/ml sodium chloride, 7.35 mg/ml sodium citrate dihydrate, 0.7 mg/ml polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5.

The container is a type I glass vial with rubber stopper.

Method of preparation

The manufacture of rituximab begins with a thoroughly characterised Chinese Hamster Ovary master cell bank that contains the integrated gene coding for expression of the product.

The purification process is based on two chromatographic techniques: protein an affinity chromatography and anion exchange chromatography. The anion exchange steps are designed to remove impurities such as protein A, host cell DNA, host cell impurity proteins as well as endogenous

and putative adventitious viruses. Following production of the formulated bulk drug substance at IDEC Pharmaceuticals, San Diego, CA, and the product is shipped to Genentech, Inc., South San Francisco, CA, for final aseptic filling into 100 mg and 500 mg glass vials.

Based on recent concerns over both the continued supply and safety issues related to bovine and human raw materials, a number of process changes were implemented. These changes included autoclaving media components at 121°C or higher and removal of the human transferrin. A replacement master cell bank (MCB) was developed because of an inadequate supply of initial cell bank vials.

Control of starting materials

Certificates of analysis with predefined specifications have been established for the following points: the pre-harvested cell culture fluid (to demonstrate freedom from adventitious viral or mycoplasma contamination), the formulated bulk for shipment where the primary emphasis is on testing for identity, purity, potency, strength and bioburden. A certificate of analysis with appropriate specifications is also required upon receipt of the bulk drug substance by Genentech. At this time, the bulk may be frozen for storage for up to 18 months at -20°C. The frozen formulated bulk is thawed and sterile filtered prior to aseptic filling at Genentech. A certificate of analysis completed by Genentech includes testing for sterility (meets PhEur), identity, endotoxin and protein content. Following final formulation of the bulk product, analysis for pH, Polysorbate 80 concentration and sodium concentration are performed, pH and osmolality of the final dosage form is confirmed.

For both MCBs prepared, the host cells were tested by several biochemical, biological and immunological tests to assess cell line identity and freedom from adventitious agents.

Bioburden, Rodent Parvovirus PCR, and mycoplasma (PCR) is tested for at the end of the production run. Action limits are set (positive/detectable).

Details of the preparation of the culture media have been provided. Cells are cultured in serum free medium. The composition of the medium used for production and cryopreservation of the cell banks has been provided.

Two changes have been introduced in the culture medium: addition of Gentamycin and the replacement of human transferrin by an increased amount of ferrous sulphate already present in the cell culture medium. Full-scale production data have shown that replacement of transferrin by an increased amount of ferrous sulphate has not affected any of the known characteristics of the molecule as demonstrated by the determination of potency, SDS-page, tryptic mapping and glycan distribution. This replacement does not affect the characteristics of the molecule. Gentamycin is added to the culture as a final prophylactic measure against mycoplasma contamination. Small-scale studies demonstrated that Gentamycin does not adversely affect the product and can be effectively removed by the purification process. The use of Gentamycin in the culture medium is acceptable and was examined in connection with the GMP inspections.

Both the initial MCB and the WCB were frozen in medium containing 95% FBS. FBS was tested for the presence of bovine viruses BVD, PI-3 and IRB. It was confirmed that material derived from bovine sources complies with the NfG on BSE. Stability studies for the replacement MCB have been provided.

Characterisation

Rituximab is a highly purified 1328-amino acid chimeric mouse/human antibody that is produced in mammalian cell culture using Chinese Hamster Ovary (CHO) cells. This IgG₁ kappa antibody contains murine light and heavy chain variable regions, and human gamma 1 heavy chain and kappa light chain constant regions. The molecular weight of this antibody is 144,544 Daltons, calculated from the primary sequence of the reduced, non-glycosylated form. The light chain consists of 213 amino acids and heavy chain consists of 451 amino acids.

The characterisation of the molecule is extensive utilising a large battery of different techniques as amino acid analysis, amino-terminal sequence analysis, peptide mapping, and analysis of oligosaccharides, ion-exchange chromatography, cIDF, SDS-PAGE, and CD.

The oligosaccharide structure was investigated by capillary zone electrophoresis (CE) and three oligosaccharides G0, G1 and G2 are identified. The same three glycoforms were identified by MALDI-TOF after isolation from HPAEC-PAD and data report of this analysis was submitted. There is no evidence for a terminal sialic acid containing oligosaccharide.

Analytical Development

The techniques employed for control of cell banks, intermediates, active ingredient and final product are described in detail. All methods have been fully validated in accordance to the relevant guideline for all relevant parameters as linearity, accuracy, LOD/LOQ, precision, robustness, specificity, lot-to-lot comparison and stability indicating properties.

Process validation

The full-scale production process was validated through compilation of process results of all successful runs. During fermentation the bioreactor operating parameters, cell growth, % viable cells and run hours were submitted. In view of the number of runs (fermentation 15 runs and purification process 14 runs) and the results obtained, the in-process criteria are met. No deviations of processing instructions are reported. Appropriate in-process controls have been established for detection of Minute Virus of Mice (MVM) and bioburden at the pre-harvested cell culture fluid step. During the recovery process, limits for product titer, protein step yields, Bovine IgG, Protein A, bioburden, and endotoxin have been established to ensure that the process operates consistently.

Control tests on the finished product

The analytical methods are fully described and are properly validated.

Stability

The results of the ongoing stability studies of the 10 ml and 50 ml filled at Genentech to support the claimed shelf life were provided.

The company is committed to provide real time shelf-life stability studies for the bulk formulated product and the finished product on an on-going basis for production batches using the new media composition.

A shelf life of 2-8 °C for 2 years protected from direct sunlight can be accepted.

Virus validation

Virus validation is done in accordance with the appropriate ICH guidelines.

3. Toxicopharmacological aspects

Pharmacodynamics

Rituximab is a chimeric mouse/human monoclonal antibody, which targets an epitope CD20 on human B-lymphocytes. For primary pharmacodynamics only experiments in **non-human primates** are relevant. Neither rodent nor canine B-cells bind rituximab. In long-term administration studies the problem of immunogenicity of rituximab in Cynomolgus could make the results inconclusive. Antibodies against rituximab may appear after 2 weeks of treatment. Therefore, no xenograft experiments are feasible. No animal model is available for evaluating the antineoplastic effect. Pharmacodynamic studies consist of immunoanatomic distribution and immunopathologic analysis of rituximab. The initial in-vitro characterisation of rituximab was performed with an early-purified antibody from first CHO-cultures. During the development, rituximab was produced at different facilities with slight modifications of the manufacturing processes. The applicant has investigated rituximab's immunoanatomic distribution with *Suspension Culture Produced* antibody, *Hollow Fiber Produced* antibody, and *Stirred Tank Produced* antibody at the Torreyana Facility.

A number of in-vitro studies were performed to confirm the specificity and affinity for the CD20 epitope. The apparent binding affinity constant was 5.2×10^9 M. The binding of human complement C1q and complement dependent cytotoxicity and antibody dependent cytotoxicity was documented by fluorescein conjugation and 51-Cr release. The tissue specificity was demonstrated in several human

cross reactivity studies. Human hematopoietic progenitor cells depleted of B-cells by incubation of rituximab retained their colony formation and no effect was noted on CD34+ cell population. Doses of 0.1, 0.4 or 1.6 mg/kg/day x 4 were equally effective for a greater than 80% depletion of peripheral B-cells. The duration of the depletion was about 7 days after the last injection. A slow recovery of B-cells was observed thereafter. Full recovery was not seen with certainty at the end of the study period (day 90). Compared to saline treated animals a dose of 16.8 mg/kg depleted >79% of CD20+ bone marrow cells at the time when the animals were sacrificed and 69% depletion of lymph node CD20+ cells. Immuno-histochemical studies on human tissue cross-reactivity were presented. Rituximab was highly tissue restrictive.

Rituximab had no effect on human haematopoietic progenitor cells. The B-cell depleting effect was demonstrated in Cynomolgus monkeys both in peripheral blood and lymphatic tissues. The major concerns were the low level of exposure in Cynomolgus as compared to human level of exposure (1:1) and the lack of long-term animal studies, since B-cell recovery was not complete 90 days post dose. The only unexpected clinical sign in monkeys was nausea; otherwise rituximab appeared to be very safe. Only pharmacologic effects were observed in the laboratory parameters.

No studies were performed to compare the affinity of rituximab with B-cells of humans versus cynomolgus monkeys and to determine the density of CD20 expression on monkey B-cells. However, such studies are unnecessary because B-cells in cynomolgus monkeys are lysed by a single dose of rituximab, which is evidence of relevant activity even if affinity and CD20 expression may be different in humans and primates.

The monkey experiments do not provide any evidence that rituximab can fix complement and mediate ADCC in vivo other than a reduction in CD20 counts. Experimental proof that cell killing really occurs has not been provided. From a clinical point of view, further studies in healthy monkeys are not needed. The effects of rituximab in different B-cell populations are sufficiently documented. As pre B-cells and plasma cells do not express CD20 not all B-cell subpopulations are susceptible to the antibody.

Pharmacokinetics:

The preclinical pharmacokinetics of a monoclonal antibody is of lesser relevance as the results mainly depend of the isotype of the immunoglobulin, and specific metabolic and excretory studies are not required. Due to the binding to cellular CD20 and lysis of normal and malignant cells, plasma pharmacokinetics are influenced by the number of target cells and will depend on the size of the B lymphocyte pool at a given time point. It may be anticipated that PK values will be different after first and subsequent doses because of the B-cell depleting effect. In animal studies the development of antibodies to rituximab may influence the interpretation of multiple dose kinetics. Different compartments of B-lymphoid tissue may be targeted more or less easily. Finally the kinetics of B-cell in cynomolgous and man may be different.

Single dose pharmacokinetics was performed in rats and cynomolgous monkeys. In both species $t_{1/2}$ was 3-7 days. Serum concentrations increase dose-dependently in cynomolgous monkeys. Sex-difference was also observed and could not be explained. Multiple dose kinetics was assessed in the cynomolgous monkey toxicity studies. Only C_{max} data are available suggesting that the exposure levels in the toxicity studies were similar to those attained in humans.

Formal studies on absorption, metabolism and excretion are not needed. Biodistribution was not studied, however it is clear that the antibody penetrates the lymphoid tissues. It may also cross the placenta and deplete embryonic B-cells. It is not known whether rituximab is present in the milk.

Toxicity

Rituximab has been shown to be highly specific to the CD20 antigen on B-cells. No effect other than the expected pharmacological depletion of B-cells in peripheral blood as well as in lymphatic tissues was observed in toxicity studies. The B-cell population showed reconstitution after cessation of treatment. Significantly, adverse reactions unrelated to the targeted effect were seen, neither in single nor in multiple dose studies in the Cynomolgus monkey.

Single dose toxicity

Rituximab did not show any intrinsic toxicity when given as a single intraperitoneal injection to 5

mice (108 mg/kg) and 2 guinea pigs (66 mg/kg) as the pharmacologically non-responsive species. The results are not considered instructive for the safety characterisation of rituximab.

In Cynomolgus monkeys, B-cell depletion in the peripheral blood (along with gradual depletion in peripheral lymphatic tissues) could be induced with a single i.v. injection using a dose of 0.4 and 6.5 mg/kg, with only marginal recovery by day 35. No signs and symptoms of acute adverse reactions were observed. In a single high-dose experiment with doses of 10, 30 and 100 mg/kg (= 1345 mg/m²), rituximab was systemically and locally well tolerated, with only a mild transient decrease of platelets observed after dosing in the 30 and 100 mg/kg dose groups. The only adverse event involved one male monkey, which vomited one day after dosing in the 100-mg/kg-dose group. Thus, serious dose limiting toxicity was not observed, even though the doses used in this study are far above a therapeutically effective dose in monkeys as well as the anticipated clinical dose.

Repeated dose toxicity

A repeated pilot pharmacology/toxicology experiment in Cynomolgus monkeys (using 16.8 mg/kg doses) demonstrated the relationship between exposure of multiple injections of rituximab to the degree of B-cell depletion in the peripheral blood and bone marrow, as well as within the lymphatic tissues. This experiment formed the basis for the initial dose escalating study in humans. Weekly dose of rituximab up to 20 mg/kg (= 276 mg/m²) was generally well tolerated over up to 8 weeks of treatment in a further GLP toxicity study in Cynomolgus monkeys. Occasional emesis was also observed in these experiments.

In addition, high plasma levels of rituximab, ranging from 137 to 438 mcg/ml were achieved in all animals 24 h after the first and second dose and persisted at significant levels (91–97 mcg/ml) during the treatment intervals.

Local tolerance

Rituximab was given in all preclinical safety studies as an i.v. injection, and the formulation was well tolerated locally. The formulation used in preclinical experiments was identical to the formulation to be marketed.

Immunotoxicity

As described above, apart from the expected depletion of B-cells, there was no other finding in clinical pathology and histopathology. Particularly, there was no evidence of toxicity to the hematopoietic system. T-cells or other cells of the non-CD20+ lymphocyte lineage were not affected in any of the experiments. It does not affect the functionality of the pool of CD20 neg. antibody-producing plasma cells. However, specific experiments to demonstrate the difference between overall and B-cell specific immunosuppression have not been performed in preclinical studies. Rituximab's selectivity should result in a lower immunosuppressive potential (with lower risk and incidence of opportunistic infections). None of the rituximab-treated monkeys developed any signs of infections. No risk of neotransformation of B-cells to lymphoma cells due to acute Epstein-Barr virus reactivation should be expected for rituximab.

The risk for developing an immune or allergenic response under treatment of rituximab is very low. However, because rituximab does not deplete antibody-producing plasma cells, patients with an existing allergy to murine proteins should not be treated with rituximab.

The lack of reproductive, mutagenic, genotoxic and carcinogenic studies is justified, and SPC has been amended appropriately. Findings of testicular hypospermatogenesis or aspermatogenesis and thymic lymphoid atrophy were reported in study 204 and were analysed with respect to the negative results of the cross-reactivity studies with human tissues. Rituximab has no direct binding specificity or cytotoxicity to thymic or testicular tissue in cross-reactivity studies. The hypo- and aspermatogenesis was most likely due to sexual immaturity in the monkeys. Thymic atrophy was considered to be caused by experimental stress and is not a toxic effect of rituximab. In several studies the induction of antibodies (Monkey Anti-chimeric Antibodies) against the chimeric antibody MabThera in Cynomolgus monkeys is reported. This is explained, as there are sequence differences between the monkey IgG and both parts of the chimeric antibody. The antigenicity of rituximab in such preclinical studies has no predictive value to humans.

Overall conclusion

The mechanism underlying B-cell depletion and potential B-cell kill in monkeys has not been fully elucidated neither has the question whether rituximab has been internalised or not after binding to CD20 on human lymphocytes been answered with firm experimental data. Some of the shortcomings of animal safety data are now substituted by clinical data from patients with malignant lymphoma showing that plasma concentrations are irreversibly correlated with frequency of adverse events (i.e. more CD20 binding sites and lower plasma concentrations are more likely to induce the flue-like syndrome). The very short observation time (90 days) in animals is a clear-cut deficiency, but additional animal studies are not indicated.

4. Clinical aspects

Clinical aspects

4.1 Stage III-IV chemoresistant follicular lymphoma

The therapeutic indication, which initially was for “indolent B-cell lymphomas”, has been modified to the more accurate term “follicular lymphoma”. The assessment focused on this well-defined histologic subtype of NHL. The approved indication was restricted to the treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

Pharmacodynamics

Two phase I studies have been submitted. The first tested single dose escalating from 10 mg/m² to 500 mg/m² and the second study used the proposed weekly dosing schedule with a total of 4 courses with 3 doses 125, 250 or 375 mg/m². The optimal dose regimen has not been established. The applicant has justified the use of only a 4-week regimen. The recommended dosage is based on extrapolation from PK studies. Higher doses would have implied longer infusion times and hospitalisation for the patient. It appears that rituximab is well tolerated after an i.v. infusion of a dose of 375 mg/m². No relationship was observed between dose level and number of AEs.

Study 102-01 was conducted in 15 patients in groups of 3 with the following dose levels: 10, 50, 100, 250 or 500 mg/m². 14/15 patients had a rapid and selective depletion of circulating B-cells within the first day post infusion. The effect lasted from 1 to more than 3 months in nearly all patients receiving a dose > 50 mg/m².

Excisional biopsies performed 2 weeks post therapy revealed binding of rituximab to tumour specimens in 6/7 patients tested and a decrease in the percentage of B-cells and a corresponding increase in T-cells. In biopsies from two additional patients, tumour was either no longer present or tissue was necrotic. 63 AEs were observed in 14/15 patients and were graded as 1 or 2 except from 2 cases of grade 3 thrombocytopenia, which was the only laboratory abnormality. The most common were fever, chills, nausea and headache.

Study 102-02 was conducted in 18 patients, which were monitored for dose limiting and infusion-rate limiting adverse events. They were assessed for antitumour efficacy, development of HACA and HAMA, depletion of peripheral blood B-cells, serum immunoglobulin levels and pharmacokinetics. 33% of these patients had a partial response (PR). The median time for responses was 50 days. B-cell depletion assayed by CD20+ and CD19+ was effective. The most common AE was fever, followed by chills, asthenia, and nausea.

Pharmacokinetics

In patients treated with either 125, 250 or 375 mg/m² body surface of MabThera, given as an intravenous infusion once weekly for four weeks, serum antibody concentrations increased with increasing dose. In patients receiving the 375 mg/m² dose, the mean serum half-life of rituximab was 68.1 hr, the C_{max} was 238.7 µg/ml and the mean plasma clearance was 0.0459 L/hr after the first infusion; after the fourth infusion, the mean values for serum half-life, C_{max} and plasma clearance were 189.9 hr, 480.7 µg/ml and 0.0145l/hr, respectively.

Additionally, rituximab serum concentrations were statistically significantly higher for responding

patients after the third infusion. Typically, rituximab was detectable for 3 to 6 months.

Dose-finding studies are very limited and the actual choice of dosage/schedule is not based on the optimal antitumour activity. AE was not dose-related in the initial phase-I trials. This deficiency is not considered as a major objection for a medicinal product of this type where the dosing optimally should be based on the number of target CD20+ lymphoma cells.

This application concerns MabThera as monotherapy. For efficacy the applicant has submitted two clinical trials utilising rituximab 375 mg/m² as intravenous infusion weekly for 4 doses in outpatients with relapsed or chemoresistant malignant lymphoma with the histologic subtypes A, B, C, and D of the International Working Formulation of Non-Hodgkin's Lymphoma for Clinical Usage (IWF). The first trial **102-02** was a phase II trial using the dose which seemed to be the optimal based on antitumour activity and clinical safety in a small phase I trial. The second trial **102-05** was not a randomised comparative study, but as it used two *historical control* methods it was defined as a phase III study. Overall 203 patients (37 + 166 patients) were included in these two trials. The most pertinent results of these two trials are shown in Tables below:

Efficacy

The population to support the therapeutic indication and the recommended dose derives from two clinical trials (102-02-part II: 37 patients and 102-05: 166 patients). The primary efficacy parameter was the overall response rate (PR+CR). The secondary efficacy parameters considered only responding patients.

Tumor Response Rates in Efficacy Studies 102–05 and 102–02 Part II

Patient Group	Study	N	CR (%)	PR (%)	CR and PR (%)	95% CI (CR and PR)
Intent to Treat	102–02–II	37	3 (8%)	14 (38%)	17 (46 %)	30 – 62 %
	102–05	166	10 (6%)	70 (42%)	80 (48%)	41 – 56 %
	Total	203	13 (6%)	84 (41%)	97 (48%)	41 – 55 %
Evaluable*	102–02–II	34	3 (9%)	14 (41%)	17 (50%)	33 – 67 %
	102–05	151	9 (6%)	67 (44%)	76 (50%)	42 – 58 %
	Total	185	12 (6%)	81 (44%)	93 (50%)	43 – 57 %

The overall response rate covers a RR of 11% for IWF subtype A as compared to 57% for patients with follicular lymphomas.

PR = partial response, CR = complete response

Time to First Tumor Response in Efficacy Studies 102–05 and 102–02 Part II

	Number of Responders	Average Time (Days)	Median Time (Days)	Minimum Time (Days)	Maximum Time (Days)
102–02–II	17	58.2	50	7	112
102–05	80	65.3	50	21	288
Total	97	64	50	7	288

Duration of Response in Efficacy Studies 102–05 and 102–02 Part II

Study	Number of Responders	Average Duration (Months)	Median Duration (Months)	Minimum Duration (Months)	Maximum Duration (Months)
102–02–II	17	11.2+	8.6	2.6	26.2+
102–05	80	6.2+	6.5	0.9+	12.0+
Total	97	7.0+	6.5+	0.9	26.2+

The comparisons with reported series of patients treated with cladribine or fludarabine point to an at least similar efficacy for rituximab. The intra-patient control comparing the response and duration of response after rituximab with the same parameters achieved with the regimen immediately prior to rituximab is very interesting but this method is hardly validated. However, using this method of comparison the efficacy of rituximab in terms of response rate was not different from other regimens used for relapsed lymphoma.

Kaplan–Meier analyses of time to progression (TTP) for all patients enrolled in studies 102–05 and 102–02 part II, and for patients in these studies who had a CR or PR showed that median TTP for responders has not yet been reached after a median follow-up of 9.2 months.

The response rate was 57% in patients with relapsed or refractory follicular lymphoma whereas the response rate was only 11 % in patients with small B-lymphocytic lymphoma. The company provided additional data on 19 patients with bulky disease (>10 cm diameter) which show comparable response rates (63%) and possibly an increased incidence of grade 3-4 adverse events (17%).

The company provided an updated follow-up of response duration and time to progression for the patients included in the pivotal studies. The response rates remained unchanged. It is reassuring that rituximab appears to have the same efficacy in patients normally considered to be almost unresponsive to conventional chemotherapy.

Safety

For safety 282 patients receiving rituximab as monotherapy have been evaluated. Of these 164 had a cumulative dosage between 1001-1500 mg/m², and 81 had a cumulative dosage between 1501-3000 mg/m². Adverse events were predominantly seen during the first infusion and consisted of a *cytokine release* or *chemical mediator release syndrome* with fever, chills, flushing, angioedema etc. occurring in > 50% of the patients. These symptoms were accompanied by hypotension and bronchospasm in about 10% of the cases.

The incidence of infection was 17% during treatment and 12% in the follow-up period. None of these infections were considered by the CPMP as severe but included common viral and bacterial infections very different to those seen after chemotherapy. It should be remembered that rituximab does not deplete plasma cells or progenitor cells. As the B-cell depleting effect has not resolved completely during the follow-up period, the possibility of later infectious events cannot be completely ruled out.

Updated safety data with special emphasis on normal B-cell recovery did not show any detrimental consequences of B-cell depletion. The company has not provided any data on the functional behaviour and expression of phenotypic markers of B-cells in patients. However, all clinical evidence points to a low incidence of infections, as compared to infections due to neutropenia and T-cell suppression seen after conventional chemotherapy including newer cytostatics such as cladribine or pentostatin.

The results of a phase III combination study with CHOP + MabThera in 40 patients were provided. In this non-comparative study there was no evidence of additive or synergistic toxicity.

Serious and fatal infusion-related reactions reported post-authorisation.

Thirty-nine fatalities and 66 serious infusion related reactions, representing all world-wide spontaneous reported events and trial-related serious ADR reports from IDEC, Genentech and Roche were presented on 15 December 1998 at the request of the CPMP.

The reporting period was 1 November 1997 to 22 November 1998. According to the MAH 12,000 to 14,000 patients with various B-cell neoplasias have been exposed to rituximab up to that date. Most

fatal cases were observed in patients who were treated for other B-cell neoplasias than covered by the authorised therapeutic indication. These events were classified as in the following table.

1. Infusion related syndrome with fatal outcome	
a. within 24 hours	4 patients
b. within a few days	5 patients
2. Deaths from causes possibly induced by rituximab	6 patients
3. Deaths from causes probably unrelated to rituximab	
a. with infusion ADR	4 patients
b. without infusion ADR	13 patients
4. Deaths not classifiable due to lack of information	7 patients
Total	39 patients

The pathophysiological mechanisms behind this *rapid onset infusion-related syndrome* should be further elucidated in order to prevent or at least attenuate it. It seems reasonable to conclude that elevated WBC reflecting high number of circulating blood tumour cells constitute a serious risk factor for the development of the syndrome.

Other risk factors possibly include:

- a high tumour cell burden in other lymphomatous organ compartments (lymph nodes, spleen, bone marrow, extranodal sites)
- baseline LDH level, histologic subtype etc.

One feature of the syndrome appears to be fairly consistent, namely dyspnoea, bronchospasm, and hypoxaemia (in those patients who had oxygen saturation and/or oxygen tension assessed) combined with pulmonary infiltrates (in those patients who had chest X-ray performed) occurring almost exclusively during the first infusion. Consecutive WBC measurements point to a very rapid decline (over hours) in CD20-positive tumour cells. It could be hypothesised that the rapid cell lysis leads to sludging of cellular debris in the lung capillaries. Hypotension, another consistent feature might thus be a secondary symptom. The Summary of Product Characteristics was revised to address properly the infusion related events.

Severe skin disorders reported post-authorisation.

Six cases of severe skin disorders (paraneoplastic pemphigus, toxic epidermal necrolysis, lichenoid dermatitis and lichen planus) were reported post-authorisation. A causal relationship to rituximab has not been established. The summary of product characteristics was revised to include these disorders.

Risk/benefit assessment

The following considerations were taken into account for the assessment of the product:

- The identifiable medical needs for an effective agent in relapsed patients who are resistant or poorly responsive to conventional chemotherapy, or who are unable to tolerate its cumulative toxicity.
- The low toxicity of MabThera observed in monotherapy studies, clearly superior to the safety profile of conventional chemotherapy.
- The novel mechanism of action of the product.

In patients with relapsed or refractory follicular lymphoma the response rate was 57% whereas the response rate was only 11 % in patients with small B-lymphocytic lymphoma. The company provided additional data on 19 patients with bulky disease (>10 cm diameter), which show comparable response rates (63%) and possibly an increased incidence of grade 3-4 adverse events (17%). Kaplan–Meier

analyses of time to progression (TTP) for all patients enrolled in studies 102–05 and 102–02 part II, and for patients in these studies who had a CR or PR showed that median TTP for responders has not yet been reached after a median follow-up of 9.2 months.

The safety profile of rituximab appears to be favourable. First, treatment can be given on an outpatient basis. The total duration of treatment is 22 days and, except for a cytokine release syndrome with fever and chills, which may be combined with mild hypotension and bronchospasm during the first cycle of therapy, other adverse events are rare and mild. Grade 4 haematological toxicity is infrequent (2-3%) as compared to conventional chemotherapy.

On the basis of the current data it was concluded that the use of MabThera should be restricted to patients with stage III-IV follicular NHL who are chemoresistant or are in their second or subsequent relapse after chemotherapy. The product showed a good tolerability profile in that group of patients with a good response rate and a sufficiently prolonged duration of response. Moreover no satisfactory standard treatment in this particular population is available.

It was agreed that for the specific restricted group of patients, as outlined above, no prospective comparative randomised phase III study would be required as in the absence of an established chemotherapeutic regimen, such a study would not be feasible. The Company should provide additional information from ongoing phase II studies, undertaken in this population.

Any application for the extension of the indications for MabThera outside the restricted population indicated above would require controlled clinical trials. As there are standard chemotherapeutic regimens available for patients with first relapse and these patients have good prognosis, comparative studies are required to identify the place of MabThera in this situation.

Following the evaluation of the safety finding obtained from post-authorisation exposure to rituximab, the risk/benefit assessment seems not to be affected. Out of 12,000 to 14,000 patients with various B-cell neoplasias 9 fatal cases were classified as probably related and 6 fatal cases as possibly related to rituximab. The toxicity of rituximab still compares favourably with most cytostatic agents. Most of the treated patients have end-stage disease, have received several regimens of chemotherapy and are left with very few other therapeutic options.

4.2. Diffuse Large Cell Lymphoma in combination with CHOP

The application for the indication of DLCL is based on 3 clinical trials: a pivotal phase III randomized trial and two supportive phase II trials. All were conducted in accordance with the Helsinki declaration and complied with GCP requirements.

Study SO15165, an open-label, multicenter, randomized dose-finding phase II studies in 54 patients with DLCL or Roche conducted other CD20+ aggressive NHL's. It compared rituximab as single agent therapy at doses of 375 mg/m² (group A) versus 500 mg/m² (group B). Rituximab was given weekly for 8 weeks unless lack of response at 4 weeks, progressive disease or toxicity prevented further therapy.

Study U0715s, a single arm phase II study in 33 patients with newly diagnosed aggressive NHL, including DLCL, was conducted by Genentech with the purpose to establish the feasibility of the rituximab-CHOP combination

Study LNH98-5, a phase III randomized study in 399 elderly (> 60) patients from 86 European centers, with newly diagnosed DLCL was conducted by the GELA cooperative group and supported by Roche. It compared treatment with rituximab plus CHOP to CHOP. A total of 399 patients were enrolled, of whom 197 were randomised to CHOP alone and 202 were randomised to rituximab + CHOP. One patient in study LNH98-5 received no treatment.

The pharmacodynamics following the combination of rituximab and CHOP was not studied separately, but was in part included in the studies U0715s and LNH98-5.

In study U0715s the effect on lymphoid B-cells in peripheral blood was followed by flow cytometry by using CD19 as a marker. The CD19+ cells decreased from a median baseline count of 89/μl before rituximab + CHOP to undetectable levels in all patients during the treatment phase, and was undetectable in 27/29 patients at week 10 and 22/25 patients at week 20. Recovery to baseline was observed by month 12 in 4/12 patients and by month 24 in 15/21 patients.

The immediate infusion related effects were studied in a subset of 55 patients in study LNH98-5. Both CHOP and R-CHOP were found in the hours post-infusion to lead to increases in neutrophil counts and decrease in lymphocyte- and monocyte counts with no major difference between the regimens. However, R-CHOP also led to increase in LDH, C3a and TNF, probably associated with rapid lysis of normal and malignant B-lymphocytes. The findings were pronounced already at one hour.

A beneficial effect of rituximab in the combination seems related to the chemosensitization. This again seems related to the crosslinking of CD20 on the target B-cell surface leading to a downregulation of IL-10 transcription and protein expression. This causes downregulation of BCL-2 expression and thereby increased cellular sensitivity to chemotherapy –mediated cytotoxicity and apoptosis.

Clinical Pharmacokinetics

The pharmacokinetic pattern was reported in the original MAA and has not been extensively restudied in patients with DLCL. In the original studies weekly doses for 4 weeks of 125, 250 or 350 mg/m² led to dose dependent increases in serum concentration. At 375 mg/m² the mean serum half-life of rituximab was 68.1 hours, C_{max} was 238.7 µg/ml and the mean plasma clearance was 0.0459 L/h after the first infusion. Following the fourth infusion the corresponding values were 189.9 h, 480.7 µg/ml and 0.0145 L/h, respectively. The increase in half-life seems related to the reduction in CD20 positive tumor mass and serum values of rituximab were inversely related to tumor load. Measurable rituximab concentrations were present in serum as late as 3-6 months post treatment.

The applicant states that rituximab serum concentrations in the DLCL patients were comparable to those found in patients with follicular lymphomas following treatment with similar doses.

There is no reason to believe that rituximab has any influence on the kinetics of the CHOP components. It does not affect any of the cytochrome families responsible for metabolizing cyclophosphamide, doxorubicin, or vincristine or their excretion pathways. Furthermore the achievement of a similar dose intensity and toxicity of the CHOP component in the CHOP arm and the R-CHOP arm suggests that rituximab exerts no influence on the pharmacokinetics of the CHOP drugs.

Efficacy results from Phase II Study SO15165

The study was rather brief due to the aggressive nature of the disease and the relapse status of most of the patients, with last observation at day 106. The endpoints were safety measures and response, evaluated with standard criteria as CR, CRu and PR.

The response rate in the ITT group was 31% CR+PR in group A versus 32% in group B (NS). In the pooled data the response in 54 intent-to-treat patients was 9% CR and 22% PR. In the DLCL patients the overall response rate was 37 %. Median time to response was 56 days.

The response rate was higher in relapsed than in refractory patients, it was higher in DLCL and MCL than in patients with undefined histology and it was higher in patients with small tumor masses (< 5cm) than in those with larger lymphomas. Previous ABMT was not a negative prognostic factor.

Due to the short study the only statement given with respect to time dependant parameters was, that the median time to progression exceeded 105 days (for the 17 responders 246 days).

This first study of rituximab monotherapy in patients with intermediate or high grade lymphomas demonstrated a clear antineoplastic effect with only moderate toxicity. Compared to the standard dose of 375 mg/m² the higher dose 500 mg/m² did not lead to an increase in response rate, but was accompanied by higher frequencies of grade 3-4 AE and SAE, more infusion-related changes in dose and higher frequency of severe neutropenia and thrombocytopenia.

Since the efficacy was the same, but the safety profile less favorable with the high dose, it was decided to continue the studies in large cell lymphomas with the standard dose of 375 mg/m².

Efficacy results from Phase II Study U0715s

The purpose of this study was to evaluate the safety and efficacy of 6 cycles of rituximab 375mg/m² in combination with CHOP in 33 previously untreated patients with intermediate or high grade NHL. Standard criteria were used for response-evaluation, which was carried out at baseline, week 10, 20 and 24 and follow-up months 4, 8, 12, 18 and 24. Confirmatory evaluations of response were carried out within 4 weeks of its onset. Responses were sponsor assessed. Primary efficacy measure was rate of CR at week 24, secondary efficacy variables were overall response rate (ORR), time to response,

time to progression (TTP) / progression free survival (PFS), and survival at 2 years. By week 24, 20/33 patients (61%) had achieved a CR and 11 (33%) a PR for an ORR of 94%. Among the partial responders further tumor regression took place after week 24 and by month 4 in four patients (without further therapy) and by month 12 in one patient (following consolidation radiotherapy). All five patients had converted from a PR status to a CR status. Best response on study was therefore 25/33 or 76% CR and 6/33 or 18% PR. Two patients experienced progression during the study.

At follow-up month 24 only 4 patients had experienced disease progression (3 patients) or death without disease progression (one patient, died from a stroke while in remission). The median time to progression has not been reached. The 2-year PFS is 88%. Twenty-nine responders were in continued remission at the time of the database lock on 18 February 2000 after a median observation time of 26 months. The median duration of response has therefore not been reached, with a range of 6 to 35+ months.

Survival (from start of treatment to death from any cause) was 94 % at the 2-year point. Three patients had died (one from stroke, two from progressive disease). The median length of follow-up for the surviving patients was 871 days.

Efficacy results from Phase III Study LNH98-5 (GELA)

This is a randomised, open-label, parallel group, multicenter, phase III trial carried out by the Groupe d'Etude des Lymphomes de l'Adulte (GELA) in cooperation with the MAH. The objectives were to compare the efficacy and safety of CHOP chemotherapy versus CHOP plus rituximab with respect to event-free survival, response rate, progression rate, disease-free survival, overall survival and toxicity.

Patients were randomised to one of the two treatments

- Standard CHOP (cyclophosphamide 750 mg/m² IV on day 1, doxorubicin 50 mg/m² IV on day 1, vincristine 1.4 mg/m² IV on day 1, prednisolone 40 mg/m² IV day 1, PO days 2-5 of each cycle) given every 21 days for 8 cycles
- Rituximab 375 mg/m² plus standard CHOP (R-CHOP) given every 21 days for 8 cycles. Rituximab was administered on day one, following the corticosteroid part of CHOP, but before the cytotoxic agents. Pretreatment with paracetamol and dexchlorpheniramine was given to prevent infusion-related syndrome. Dose modification followed standard criteria; initially 50 mg/h and then escalated to a maximum of 400 mg/h. If severe infusion-related AE developed guidelines indicated stopping rules and attempts at reinfusion.

The randomization was stratified by center and age-adjusted IPI score (0-1 vs 2-3).

Clinical assessments were performed at the start of each treatment cycle and tumor response was assessed after cycle 4 and 8. After the treatment phase the patients were to be re-evaluated at follow-up visits every 3 months for 2 years, then every 6 months for the following 2 years and annually thereafter. An interim analysis was planned when 50% of the planned 400 patients had been randomized, 107 events had occurred, and 100 patients had been followed for a minimum of one year.

No comprehensive dose finding has been done for rituximab in combination with CHOP. In the study SO15165, where a dose of 375 mg/m² was compared 500 mg/m², the higher dose did not prove more effective and was associated with more pronounced toxicity. The 375-mg/m² doses, which previously was approved for follicular lymphomas, therefore also was chosen as the standard dose in combination with CHOP chemotherapy in the DLCL studies.

The primary efficacy parameter was event free survival, calculated from randomization date to relapse, progression, change to new therapy, or death from any cause.

Secondary efficacy parameters were: TTP calculated as above but not including change of therapy or death from causes unrelated to lymphoma, disease-free survival (DFS), overall survival (OS), response rate after cycle 4 and 8 measured as CR, CRu, PR, SD, PD, and duration of response.

Inclusion criteria included histologic diagnosis of B-cell DLCL (REAL/WHO), age 60 to 80 years, no previous treatment, Ann Arbor stage II-IV, performance 0-2 (ECOG scale). Organ and bone marrow function were to be adequate; CNS lymphoma, and a history of indolent lymphoma were among the exclusion criteria.

The study recruited 399 randomized patients from 86 European centers. All except one patient, who did not receive study treatment, are included in the 398-patient safety analysis population (SAP), but only those included in the study at the time of the interim-analysis (July 24, 2000) are included in the efficacy analysis. This interim-analysis population (IAP) consists of 328 patients, 159 randomized to CHOP and 169 to R-CHOP. As of June 1, 2000, the median duration of follow-up for the IAP was 378 days, for the SAP was 476 days. A third population for analysis, the per protocol analysis population (PPAP) was defined as the IAP minus the excluded patients. The PPAP numbers were 121 for CHOP and 139 for R-CHOP, respectively. The efficacy analyses were mainly carried out in the IAP, and the PPAP was only used for a few confirmatory analyses. An overview of the efficacy results, based on the IAP and based on investigator assessments, is presented in table 1.

Table 1 Overview of Efficacy Results in Study LNH98-5 (IAP)

Variable	CHOP (N=159)	R-CHOP (N=169)	p-value
12-Month Event-Free Survival	48%*	68%*	0.0002 (log-rank)
12-Month Overall Survival	68%*	83%*	0.0055 (log-rank)
12-Month Progression-Free Survival	54%*	74%*	0.0001 (log-rank)
12-Month Disease-Free Survival	64%*	80%*	0.0048 (log-rank)
CR/ CRu at 8 week assessment	93 (59%)	120 (71%)	0.018 (χ^2)

* Kaplan-Meier estimates

The primary efficacy parameter event-free survival was statistically significantly increased in the R-CHOP group ($p=0.0002$). The median time to event was approximately one year in the CHOP group, but has not been reached in the R-CHOP group. The risk of having an event was reduced by about 50% in the R-CHOP group, the unadjusted risk ratio by Cox analysis was 0.52 and following IPI score adjustment 0.53.

The total number of events was 77 in the CHOP group and 49 in the R-CHOP group. The most frequent events were progression during randomized treatment (34 vs 14), relapse for CR patients (25 vs 14), new treatment (5 vs 6) and death from any cause without progression (11 vs 12). The analysis was repeated in the smaller Per Protocol Population (PPAP) and gave the same result with a p-value of 0.0004. The CEC review changed details on responses for only 2 patients in the CHOP group (one was progression after PR instead of relapse after CR and the other was a data entry error). The results of the re-analysis following these 2 changes were the same.

The interim analysis shows that the addition of rituximab to CHOP compared to CHOP alone significantly increase the tumor response rate with significant prolongation of the event-free survival, progression-free survival, disease-free survival and overall survival.

At the request of the CPMP the MAH has supplied a number of further analyses based on a more recent update. The antineoplastic advantage of R-CHOP as compared to CHOP is retained in the new update (reduction of the risk of an event in event-free survival by 42% and reduction in the risk of death in overall survival by 37%) and these results are confirmed in the DLCL panel-confirmed histology group. A 24-month analysis of both the previously presented interim study population and the population of all 399 randomized patients is now presented. Thus as demonstrated in table 2 and figure 1 event-free survival of all randomized patients is significantly prolonged in the R-CHOP arm as compared to CHOP treatment ($p=0.0001$) and the risk of an event is reduced by 42%.

Table 2 Event-free Survival (All Randomized Patients, N = 399)

Parameter	18-month Update (cut-off: Feb. 1, 2000)		24-month Update (cut-off: July 1, 2001)	
	CHOP N = 197	R-CHOP N = 202	CHOP N = 197	R-CHOP N = 202
No. of patients with event at clinical cut-off	111	76	120	86
Event-free survival rate (Kaplan-Meier estimates)				
12-month	50.3%	67.5%	50.3%	67.8%
18-month	43.2%	61.8%	42.8%	62.0%
24-month ¹	–	–	37.3%	57.0%
p-value (log rank test)	0.0001		0.0001	
Risk ratio	0.57		0.58	
CI _{95%} (Cox regression)	0.42 – 0.76		0.44 – 0.77	

¹ Not reported for the 18-month update because of the low number of patients at risk at 24 months

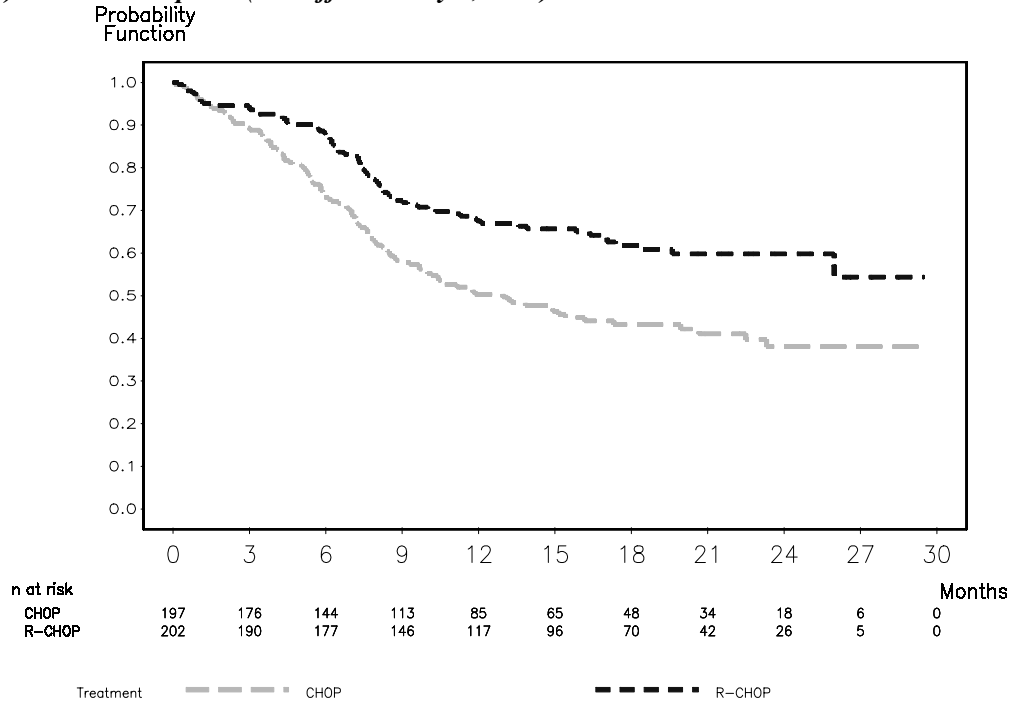
Table 3 Overall Survival (All Randomized Patients, N = 399)

Parameter	18-month Update (cut-off: Feb. 1, 2001)		24-month Update (cut-off: July 1, 2001)	
	CHOP N = 197	R-CHOP N = 202	CHOP N = 197	R-CHOP N = 202
No. of patients dead at clinical cut-off	73	51	81	59
Overall survival rate (Kaplan-Meier estimates)				
12-month	69.7%	82.2%	69.5%	82.7%
18-month	61.1%	73.5%	62.0%	74.6%
24-month ¹	–	–	57.3%	70.2%
p-value (log rank test)	0.0063		0.0072	
Risk ratio	0.61		0.63	
a) CI _{95%} (Cox regression)	0.43 – 0.87		0.45 – 0.89	

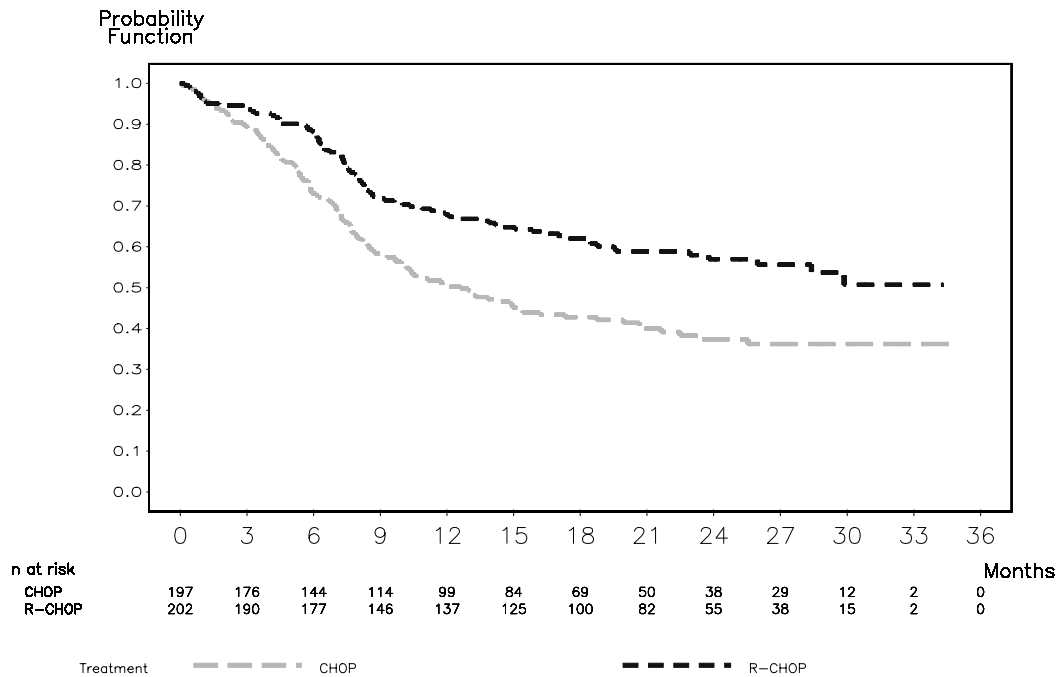
¹ Not reported for the 18-month update because of the low number of patients at risk at 24 months

Figure 1 Event-free Survival (All Randomized Patients, N = 399)

a) 18-Month Update (Cut-off February 1, 2001)



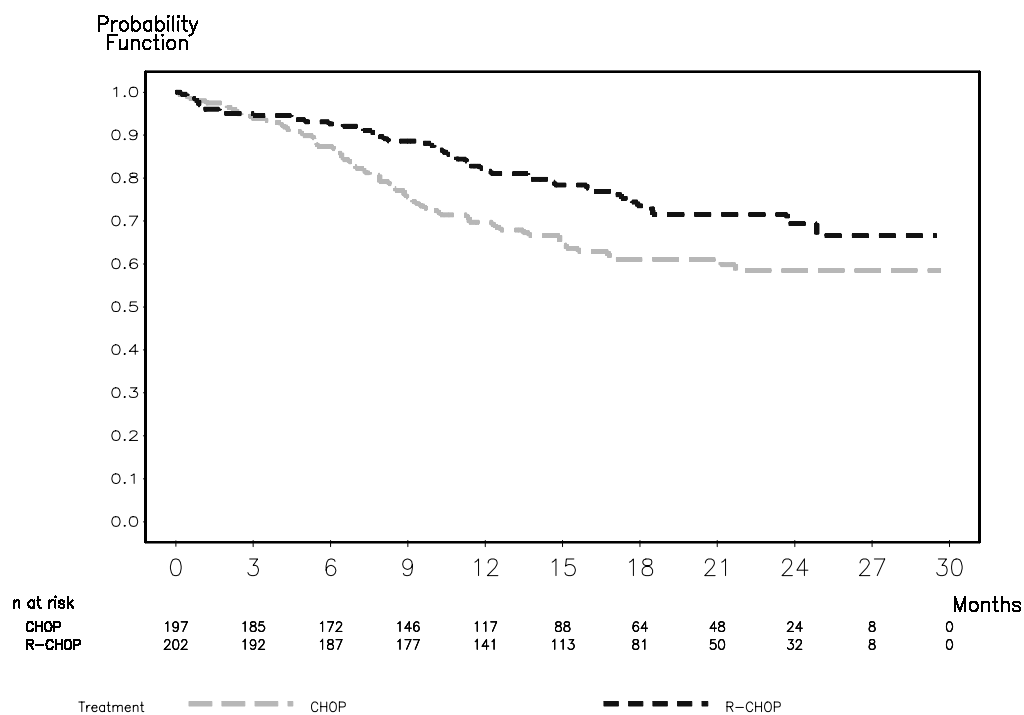
b) 24-month Update (Cut-off July 1, 2001)



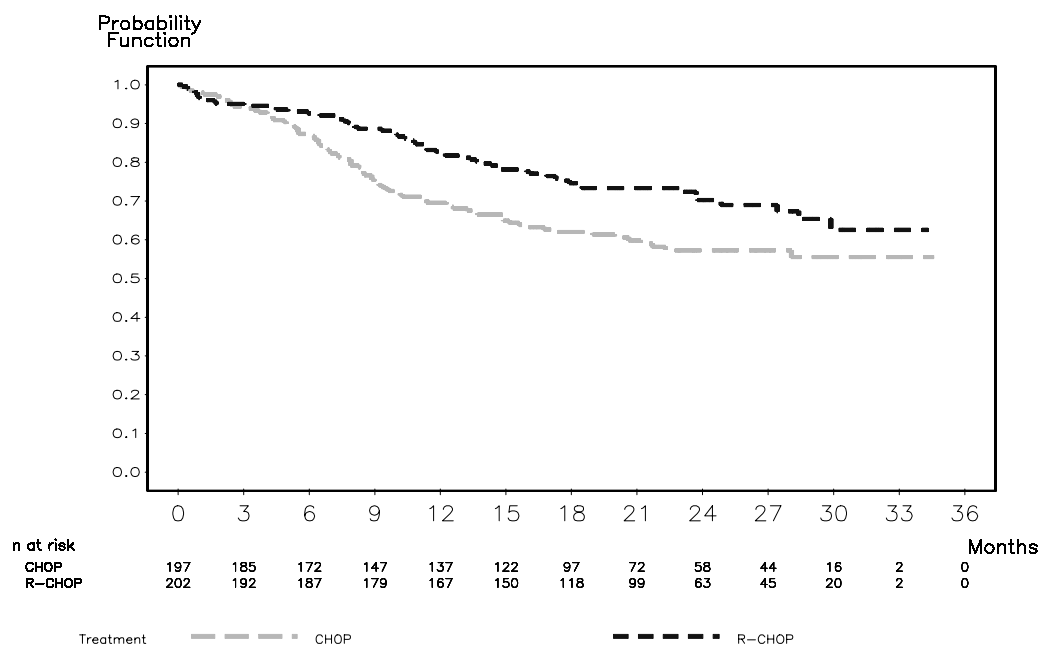
Overall survival is, as demonstrated in table 3 and figure 2 in the updated analysis, still significantly prolonged by R-CHOP ($p= 0.0072$) with a 37% reduction in the risk of death.

Figure 2 Overall survival (all randomized patients, n= 399)

a) 18-Month Update (Cut-off February 1, 2001)



b) 24-month Update (Cut-off July 1, 2001)



The analysis of the subgroup of patients with DLCL confirmed by the pathology review panel (n=334) versus unconfirmed (n=65) was based on the results from the 18-month follow-up. Event-free survival was significantly improved by R-CHOP in the DLCL group (p< 0.0001) and the risk of an event was reduced by 49 %. In the group with an unconfirmed DLCL diagnosis there was no difference in EFS between CHOP and R-CHOP. Overall survival was also significantly prolonged by R-CHOP (p=0.0066) in the DLCL-confirmed group with a reduction in risk of death by 41%. In the group with unconfirmed DLCL a risk reduction of 25% was not statistically significant.

Safety

The majority of the AE in study SO15165 were infusion-related events during or following the first infusion, which are well known from other rituximab studies. The higher dose of 500 mg/m² in study SO15165 did not prove more effective and was associated with more pronounced toxicity.

Two patients (4%) withdrew from the study, one with anaphylactic shock in group A and one with serum sickness in group B. Twenty-four (86%) patients experienced 63 drug-related events in group A and 21 patients (81%) experienced 84 drug related events in group B with the most frequent events being fever, rigors, hypothermia and hypotension. Grade 3 and 4 drug-related events occurred in 18% and 23% in group A and B, respectively. Drug related SAE's occurred in 11% in group A and 23% in group B. Severe neutropenia was seen in 4% and 12% in groups A and B, severe thrombocytopenia in 0% and 12% and severe lymphocytopenia in 61% and 81 %, respectively. CD20+ B cells were rapidly depleted from peripheral blood, but with considerable variation between patients, and depletion was usually complete following 3 infusions. Infectious episodes were noted in 39% and 31% in groups A and B, respectively and drug related infections in 18% and 19%. No grade 3 or 4 infections were noted.

In study U0715s the AE's in general were those expected from CHOP chemotherapy plus those expected from rituximab therapy, with no signs of interaction. All 33 patients experienced at least one AE; the most frequent events were alopecia, neutropenia, asthenia, nausea, and fever. Grade 3 or 4 AE's occurred in 31 patients (94%) with the most frequent being neutropenia and leukopenia. Serious AE's occurred in 14 patients (42%), the most frequent were neutropenia, sepsis, fever, leukopenia, and dehydration. The investigators assessed most AE's to be related to CHOP. The most frequent events assessed to be related to rituximab were grade 1 and 2 fever (11 patients) and chills (10 patients). Infusion-related AE's (fever, chills and allergic reaction in 36%, 30% and 12%, respectively, were mainly seen in cycle 1 and were not reported after cycle 1 except for grade 1 fever, which was reported in cycles 2 and 5 (1 patient, 3%).

There were 3 deaths during the study. One patient in CR died from a stroke and 2 died from progressive disease. Laboratory tests mainly revealed the hematologic changes. Twenty-nine patients were tested for HACA response, and no positive reactions were found. Subnormal values for IgG, IgA, and IgM were found throughout week 20 in 15%-30 % of the patients but were not considered clinically relevant.

The main safety data deriving from the randomised Phase III trial LNH 98-5 (GELA) can be summarised as follows:

Grade 3 and 4 infusion-related reactions occurred in approximately 9% of patients at the time of the first cycle of R-CHOP. The incidence of infusion-related reactions decreased to less than 1% by the eighth cycle of R-CHOP. The signs and symptoms were consistent with those observed during monotherapy, and included fever, chills, hypotension, hypertension, tachycardia, dyspnea, bronchospasm, nausea, vomiting, pain and features of tumor lysis syndrome.

The proportion of patients with grades 2 to 4 infections and/or febrile neutropenia was 54.5% in the R-CHOP group and 50.5% in the CHOP group. Febrile neutropenia (i.e. no report of concomitant documented infection) was reported only during the treatment period, in 20.3% in the R-CHOP group and 15.3% in the CHOP group, respectively. The overall incidence of grade 2 to 4 infections was 44.6% in the R-CHOP group and 41.3% in the CHOP group with no difference in the incidence of systemic bacterial and fungal infections.

After each treatment cycle, grade 3 and 4 leukopenia (88% vs 79%) and neutropenia (97% vs 87%) occurred more frequently in the R-CHOP group than in the CHOP group. No difference between the two treatment arms was observed with respect to grade 3 and 4 anaemia (19% in the CHOP group vs 14% in the R-CHOP group) and thrombocytopenia (15% in the CHOP group vs 16% in the R-CHOP

group). The time to recovery from all hematological abnormalities was comparable in the two treatment groups.

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 (5.9%) as compared to the CHOP group (1.0%). All of these arrhythmias either occurred in the context of the 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.

Laboratory data and the incidence of infections reported during the follow-up period indicate that the patients treated with R-CHOP were not at increased long-term risk of adverse events related to bone marrow failure (myelosuppression) or immunosuppression after the end of study treatment. The safety information collected during the follow-up phase comprised severe adverse events (all grade 3 or 4 events, and grade 2 to 4 infections), and hematology data (hemoglobin, and white cell, platelet and neutrophil counts). Follow-up visits were scheduled to take place every 3 months during the first 2 years after the end of the study treatment phase. In all adverse event summary tables, events are considered to have started in the follow-up phase if they had an onset date more than 33 days (28 + 5 days) after the first day of the last treatment cycle. Two deaths were reported, both due to progressive disease.

At the request of the CPMP, the MAH added the following sentence to Section 4.8 of the SmPC: “One case of serum sickness has been reported in a clinical trial using MabThera monotherapy for treatment of diffuse large B-cell lymphoma.”

GCP inspections

The CPMP, in view of the importance of the results of the Phase III studies, requested a GCP inspection. Three investigator sites were inspected in France. In summary it can be concluded that the efficacy data presented in the interim trial report are of an acceptable standard. Deficiencies identified were related to definition and follow-up of serious adverse events, use of oral instead of I.V. corticosteroid administration and inadequacy of documentation regarding treatment administration to the patients. The CPMP considered these deficiencies as minor. The overall monitoring of safety appears to be satisfactory in the context of an oncologic/haematologic clinical environment.

Benefit /risk assessment in the indication of DLCL

The therapeutic benefit of R-CHOP as compared to CHOP includes a risk reduction of events in the event-free survival by 42% and a reduction in the risk of death in overall survival by 37%. These results are confirmed in the DLCL panel-confirmed histology group.

The toxicity of CHOP and the toxicity of rituximab have been well described. The particular issue in this comparative trial was the question of whether there is an interaction between CHOP and rituximab with respect to quality and quantity of the adverse effects. The results proved that the safety profile for R-CHOP was consistent with the expected toxicity from each of the components and that the added toxicity in comparison with the CHOP group mainly consisted of the infusion-related side effects typical of the initiation of rituximab treatment.

Therefore, the benefit-risk assessment for the combination therapy with rituximab in the treatment of patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy is positive.

The MAH committed to present the final GELA study report when available, to providing an update of the overall survival of study LNH 98-5 regularly each year after marketing and to try to obtain and present to the CPMP data from the two independent ongoing trials as soon as it is possible.

4. 2. 1. Final report from study LNH98-5 – Efficacy and Safety Update

The study compared the safety and efficacy of 8 cycles of rituximab combined with CHOP chemotherapy (R-CHOP) with 8 cycles of CHOP alone in previously untreated elderly patients (> 60 years) with diffuse large B-cell lymphoma. Three hundred and ninety-nine patients were entered into

the study (197 CHOP, 202 R-CHOP). The study demonstrated a significant increase in event-free survival in the R-CHOP group compared with the CHOP group, as a result of lower rates of relapse and progression as well as a significant increase in overall survival with the R-CHOP regimen when compared to CHOP.

On the basis of the schedule of the pivotal trial, the recommendation for the number of cycles of therapy (8 cycles) was included in Section 4.2 “Posology and method of administration”.

The question as to whether 6 or 8 cycles should be recommended was an issue of discussion also during the first assessment of the indication. Patients in study LNH98-5/BO16368 were randomized to receive 8 cycles of CHOP or R-CHOP. As detailed in the study report, 72.4% of patients in the CHOP group and 79.7% of patients in the R-CHOP group received 8 cycles of study treatment. The complete response rate after cycle 8 was significantly higher with R-CHOP than with CHOP (76.2 vs. 62.4%) and it is now appropriate to recommend, in the MabThera SPC, the number of cycles of R-CHOP therapy that patients should receive.

Efficacy update

The final efficacy analysis included all 399 randomized patients (197 CHOP, 202 R-CHOP), compared to 328 patients at the time of the interim analysis. It also reflects a longer median follow-up period of 31 months compared to a median of 12 months at the time of the interim analysis. The final efficacy analysis supports the significant benefit for diffuse large B-cell non-Hodgkin’s lymphoma patients after 8 cycles of R-CHOP, compared to CHOP alone, seen at the time of the interim analysis.

The final analysis confirmed that R-CHOP treatment was associated with a clinically relevant and statistically significant improvement in the duration of event-free survival ($p = 0.0001$). Kaplan Meier estimates of the median 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) were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a relative risk reduction of 41%.

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

Data from the most recent analysis of overall survival (OS) with a median follow-up of approximately 60 months has been added to reflect the continuing benefit of R-CHOP over CHOP ($p=0.0071$, log rank test). The risk of death was reduced by 32% in the R-CHOP group compared to the CHOP group. The two year rates for overall survival were 68.8% in the R-CHOP arm compared to 57.9% in the CHOP arm.

Section 5.1 “Pharmacodynamic Properties” of the SPC was updated to reflect the final efficacy results of the study as detailed in the clinical report.

Safety update

The safety population in the study comprised 398 patients (196 CHOP, 202 R-CHOP); almost all of the R-CHOP patients received the full dose of rituximab at each treatment cycle.

The overall safety profile of R-CHOP was consistent with the expected toxicity profile of CHOP, with the added infusion-related reactions (IRRs) previously described with rituximab. There was no difference between the groups in the incidence of systemic or bacterial infections but R-CHOP was associated with an increased number of reports of herpes zoster infection. There were also more

reports of supraventricular arrhythmias and tachycardia in the R-CHOP group – these events were infusion-related or occurred in patients with other predisposing events or diseases.

Section 4.8 “Undesirable effects” was amended to reflect the safety data from the final study report and to bring the presentation of information into compliance with SPC guidelines, as requested in the assessment report for the MA renewal. The table in the SPC now shows those grade 3 and 4 adverse reactions occurring in a higher proportion of R-CHOP patients (2% or greater) than CHOP patients and which are therefore likely to be attributable to the R-CHOP regimen.

4.2.2 Clinical trial ECOG 4494

ECOG 4494 is a similar phase III trial of rituximab-CHOP (R-CHOP) vs. CHOP with a second randomisation to maintenance rituximab (MR) or observation in patients 60 years of age and older with diffuse large B-Cell lymphoma (DLBCL) conducted in the US. The MAH was requested to commit to submit an abstract and when the trial is completed the whole study report.

Data presented in the abstract cannot be directly compared to the data from the GELA study due to

- Differences in the induction dose of MabThera; 4-5 infusions in the ECOG trial versus 8 infusions in the GELA trial.
- Different dosing schedules; in the ECOG trial, 2 infusions of MabThera were given before chemotherapy and then given with every other cycle of chemotherapy. In the GELA trial, MabThera was given together with each of the chemotherapy cycles.

Differences in study design; the second randomisation in the ECOG trial to either maintenance or observation arm confounded the results of the first study part and made interpretation of data difficult. In the GELA trial, there was no second randomisation.

4.3. Rituximab in combination with CVP chemotherapy for previously untreated patients with stage III-IV follicular non-Hodgkin's lymphoma (NHL).

The MAH submitted a type II variation application for extending the therapeutic indication of MabThera (rituximab) to include the use of rituximab in combination with CVP (cyclophosphamide, vincristine, prednisolone) chemotherapy for the treatment of previously untreated patients with stage III-IV follicular non-Hodgkin's lymphoma (NHL).

4.3.1. Introduction

Follicular lymphoma comprises approximately 70% of the low grade lymphomas. Because of the indolent nature of the disease with a median survival of 8-10 years, management of stage III and IV patients ranges from an initial “watch and wait” policy, to combination chemotherapy and bone marrow transplantation depending on a variety of factors including stage of disease, age, and performance status.

According to current treatment guidelines for newly diagnosed follicular lymphoma in the EU, European Society of Medical Oncology (ESMO) and in the USA (National Cancer Institute), the CVP regimen represents one of several first line treatment options for stage III and IV follicular NHL. However, there is no universally accepted standard first line treatment, the choice is largely based on physician preference and in the majority of cases the goal of treatment is to achieve a complete and durable remission. Hence, many physicians believe that the most efficacious regimen should be used in first line treatment so as to maximize the number of patients achieving a complete response. Moreover, studies have indicated that achievement of molecular remission, by eradication of cells bearing the bcl-2 rearrangement (present in 50% to 70% of patients), may predict prolonged response in follicular NHL.

Monotherapy with alkylating agents such as chlorambucil or cyclophosphamide has been a commonly used first line treatment option for many years. The addition of vincristine and prednisolone to cyclophosphamide may be a more effective combination regimen in terms of overall response rate and the frequency of complete remission, but survival has not been improved and durable remissions are extremely rare. More intensive anthracycline containing regimens such as CHOP have not

demonstrated a survival benefit over non anthracycline containing regimens, and anthracycline-induced cardiotoxicity is a serious drawback.

The 86 Trial from the Groupe d'Etude des Lymphomes Folliculaires included patients with advanced stage and clinically aggressive follicular NHL¹ showed that the addition of INF- α to an anthracycline containing regimen CHVP (cyclophosphamide, doxorubicin, teniposide, prednisone) increased progression-free survival (PFS) and overall survival as compared to CHVP, but unfortunately, the results have never been reproduced by other centres or cooperative groups and moreover the treatment is toxic. Despite these findings, the use of INF- α has not been widely adopted in clinical practice.

The experience with newer cytostatics in newly diagnosed follicular NHL is limited, one recent European intergroup comparative trial (Hagenbeck et al.) of fludarabine vs. standard CVP (cyclophosphamide 750 mg/m² iv Day 1, vincristine 1,4 mg/m² iv Day 1 (max. 2 mg), and prednisolone 40 mg/m² po Days 1-5 every 4 weeks) indicate that fludarabine monotherapy has comparable efficacy and safety profile to CVP.

The optimal duration of treatment for follicular lymphoma is currently unknown. The results in terms of overall survival do not support that continuous treatment over several years has any advantage over intermittent treatment in follicular NHL. The continuous relapsing pattern supports the use of short course therapy since no first-line treatment has proven curative or more effective in long-term control. Therefore, both acute and chronic toxicity of the therapy carry great weight when the type of therapy is to be selected.

In the initial pivotal study (102-05, McLaughlin P *et al.*), in patients with relapsed or refractory follicular NHL, rituximab monotherapy demonstrated a 58% overall response rate (ORR), most of the responses being partial. The projected median time to disease progression in responding patients was 13.0 months. The standard regimen with rituximab 375 mg/m² once weekly for four doses was used in this study.

Data from five monotherapy studies with rituximab in previously untreated patients are available. In previously untreated patients, even higher ORR have been reported, and also molecular responses as measured by PCR for the bcl-2-J_H rearrangement have been observed². Time to progression (TTP) depends on the tumour burden at entry. Median TTP estimates are available from two studies in patients with relatively low tumour burden (M39006 Colombat et al. and the North Central Cancer Treatment Group, Witzig et al.), the estimates being comparable (18.4 and 20 months, respectively).

4.3.2 Clinical trial M39021

One single study (**M39021, Marcus R *et al.***) provided data on the efficacy of the R-CVP regimen versus standard CVP in previously untreated patients with follicular NHL. Study M39021 was conducted in accordance with current Good Clinical Practice (GCP) standards. Five study centres were audited during the randomisation phase of the study by the MAH.

This was an open-label study. Patients were randomised on a 1:1 basis to 8 cycles of CVP (cyclophosphamide 750 mg/m² i.v. on day 1; vincristine 1.4 mg/m² i.v. (max. 2 mg) on day 1; prednisolone 40 mg/m² p.o. on day 1 to 5) with or without rituximab 375 mg/m² on day 1 of each 21-day cycle. Dose modification for toxicity was conventional and in accordance with accepted criteria.

Randomisation was stratified by center and International Prognostic Index (IPI).

The IPI index uses 5 prognostic factors (age > 60 years, stage III-IV, LDH > normal, ECOG performance status > 2, > 1 extra-nodal site). After the start of the study, a follicular lymphoma specific system has been developed, the Follicular Lymphoma International Prognostic Index (FLIPI). The FLIPI includes 5 prognostic factors (Age > 60 years; Ann Arbor stage III-IV; number of nodal sites \geq 5; haemoglobin > 12g/dL; LDH:> normal). The resulting FLIPI ranges from 0 to 5 where 0-1 is categorised as good prognosis, FLIPI 2 is intermediate, and FLIPI 3-5 is poor prognosis. The FLIPI was used retrospectively to get a prognostic profile of the study population.

¹ J Clin Oncol 1998;16:2332-38

² Blood 2001;97:101-106

Eligibility criteria

Patients \geq 18 years of age with previously untreated with CD20 positive follicular NHL (Ann Arbor Stage III-IV) were included. The investigators' diagnosis of follicular lymphoma (grades 1-3 according to the Revised European American Lymphoma (REAL) classification), was confirmed centrally by a haematopathologist at the British National Lymphoma Investigation group (BNLI).

Patients had to have bi-dimensionally lesions in at least one site that had not been irradiated, an ECOG performance status 0-2, a life-expectancy $>$ 3 months with no need of immediate intervention to treat life-threatening complications. Patients with evidence of histologic transformation, $WBC > 25 \times 10^9/L$ or evidence of NHL involving the CNS were excluded from participation.

Objectives

The primary objective was to evaluate clinical efficacy (TTF) of repeated doses of rituximab in combination with CVP in patients with newly diagnosed CD20-positive follicular NHL as compared with CVP alone.

Secondary objectives included an evaluation of the following parameters: Overall response rate (CR and PR), overall survival at 3 and 5 years, time to new lymphoma treatment (NLT), duration of response, and disease-free survival.

Finally, time to disease progression (TTP), which was not defined in the study protocol but was defined in the statistical analysis plan prior to database closure, was included as an exploratory parameter.

Outcomes/endpoints

Primary efficacy endpoint was Time to treatment failure (TTF); treatment failure defined as any of the following five events, 1.disease progression, 2.relapse after response, 3.institution of new lymphoma treatment during or after the randomised treatment phase, 4.stable disease after cycle 4 (SD4) or 5. death from any cause.

TTF, as defined in study M39021, may be viewed as a non standard definition of TTF when compared with other clinical trials due to the inclusion of stable disease after cycle 4 (SD4). According to the original protocol, patients with SD4 were to discontinue trial treatment. This was not followed consistently for all patients and the Data Safety Monitoring Committee (DSMC) assumed that patients with SD4 were more likely to continue treatment in the R-CVP arm whereas those in the CVP arm were more likely to be withdrawn and start alternative treatment. Therefore, the DSMC recommended to declare SD4 a treatment failure event to avoid a bias in the analysis of the primary efficacy parameter (Amendment F to the protocol). To make the data from this study comparable to other trials, time to disease progression (TTP - defined in the statistical analysis plan for the second interim analysis and the study prior to data base closure) was analysed as an exploratory parameter based on the recommendation of the DSMC. Full data enabling the determination of TTP was collected for all patients in the study, regardless of whether a patient had SD4 or started new lymphoma treatment (NLT).

The definition of response criteria to assess relapse and disease progression was in accordance with the Cheson criteria³. The investigator's assessment of response was reassessed by an independent committee. Tumour assessment were done during the pre-entry screening phase, after treatment cycle 4 and 28 days after treatment cycle 8. Thereafter, tumour assessment was to be performed every 6 months during the first 3 years, and thereafter when clinically indicated.

The following response categories were utilised: Complete remission (CR), CR unconfirmed (CRu), partial response (PR), stable disease (SD), relapse from either CR or CRu, disease progression from PR or non-response.

Overall survival was determined from the date of randomisation to the date of death irrespective of cause. Duration of response was the time between first date of response and the date of relapse or death. Time to NLT or death was calculated from the date of randomisation. Disease-free survival was

³ J Clin Oncol 1999;17:1244-53

defined as the interval between the date of CR/CRu and the date of disease progression/relapse or death.

Sample size

Sample size calculation was based on the assumption of a median TTF of 18 months in patients with low grade NHL treated with CVP. Hence in order to detect a 50% increase in median TTP (i.e. from 18 to 27 months) with R-CVP, 318 patients, randomised 1:1 between the two treatment groups recruited over 2 years and followed for a minimum of 3 years, would provide 85% power at a significance level of 5% (two-sided) to detect the expected difference in median time to TTF (assuming 219 treatment failures by this time). The calculation also included an expected 20% exponential dropout rate throughout the recruitment period.

Statistical methods

Statistical analysis populations prospectively defined in the study protocol were: 1) All randomised patients that received at least one dose of study medication (Intent-to-Treat principle); 2) The per protocol data set included all patients that received at least 4 cycles of randomised treatment unless they had disease progression or had died, and who adhered to the study protocol (evaluable patients); 3) The safety analysis set included all patients that received at least one dose of trial medication and a safety follow-up, whether withdrawn prematurely or otherwise.

The final and primary analysis for the study report is based on the investigator response assessment with a data cut-off date of January 31, 2003. An analysis based on the independent Committee (CEC) dataset with the same cut-off date as well as a provisional (snapshot) analysis with a later data cut-off (September 24, 2003) are presented in support of the final analysis.

The results submitted in this dossier are based on the data of the 2nd pre-planned interim analysis. It was estimated that by January 31, 2003, 165 (75%) of the 219 events needed for the final analysis would have been observed. Assuming that the interim analysis would have been done at that time, the nominal p-value would be 0.019509 for the second interim analysis and 0.044121 for the final analysis. In fact the second interim analysis was performed when 188 patients reported treatment-failure events, resulting a nominal p-value of 0.030988 for the second interim analysis and 0.041156 for the final analysis.

After reviewing these data from the second formal interim analysis (median study observation time of 18 months), the DSMC recommended that the study be stopped and the data analysed in full. The DSMC considered that the results and conclusions would not change compared to an analysis when 219 patients had experienced a treatment-failure event.

The results are analysed with the log-rank test and Cox regression models.

4.3.3. Results

Patients participation and characteristics

Thirteen patients on CVP and 6 on R-CVP discontinued study medication before treatment cycle 4 (in most cases due to insufficient clinical response). Moreover, 38 patients on CVP and 19 patients on R-CVP discontinued between cycles 4 and 7, mainly due to having SD4.

Treatment groups were well balanced with respect to baseline characteristics (Table 1). Disease risk was considered low-intermediate to high-intermediate for 51% of patients according to the IPI (38 % IPI 2, 13% IPI 3) and intermediate to high risk according to FLIPI in 91% of patients (42% intermediate, 49% poor).

Table 1 Key Baseline Characteristics (Study M39021)

	CVP N=159	R-CVP N=162
Median age (range)	53 (29 – 80)	52 (27 – 79)
Stage III-IV	99%	99%
Histology – Follicular NHL		
Grade 1 and 2	89%	90%
Grade 3	8%	9%
Elevated LDH	26%	26%
B-symptoms	32%	40%
Bulky disease	46%	39%

Efficacy results

An overview of the efficacy results are presented in tables 2, 3 and in figure 1 below.

Table 2. Summary of Overall Efficacy: Investigators' Assessment - data cut-off 31.01. 2003

	Kaplan Meier Estimate of Median Time to Event (Months) ^a			Risk Reduction
	CVP	R-CVP	Log-Rank p value	
Primary Efficacy parameter				
Time to Treatment Failure	6.7	25.9	< 0.0001	67%
Secondary Efficacy parameter				
Overall Survival	NE	NE	0.1854	41%
Overall Tumor Response Rate (CR, CRu, PR) ^b	57%	81%	<0.0001**	3.2 ^c
CR, Cru Response ^b	10%	41%	< 0.0001**	5.4 ^c
Duration of Response	9.8	NE	< 0.0001	70%
Disease Free Survival	NE	NE	0.1807	58%
Time to New Lymphoma Treatment	12.3	NE	< 0.0001	66%
Exploratory parameter				
Time to disease Progressive or death	14.5	27.0	< 0.0001	59%
Robustness of Primary Analysis				
TTF ignoring SD4	9.2	27.0	<0.0001	67%
TTF in confirmed FL	7.4	27.0	<0.0001	73%
TTF in Per Protocol Population	7.5	25.9	<0.0001	67%

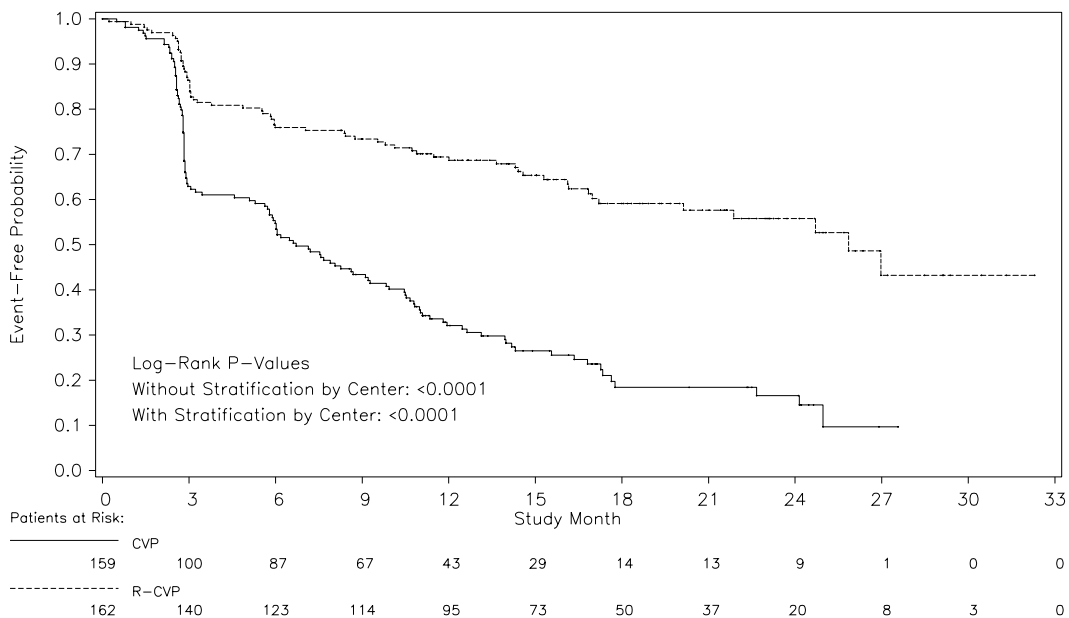
NE: not estimable.

^a Median observation time (from randomisation to either last contact or death) = 17.5 months for the CVP group and 17.8 months for the R-CVP group. ^b Overall response and complete response rates are calculated from the tumor response as assessed at the end of trial treatment. ^c odds ratio. ** chi-square test.

The most common reasons for treatment failure were relapse after initial response and SD4.

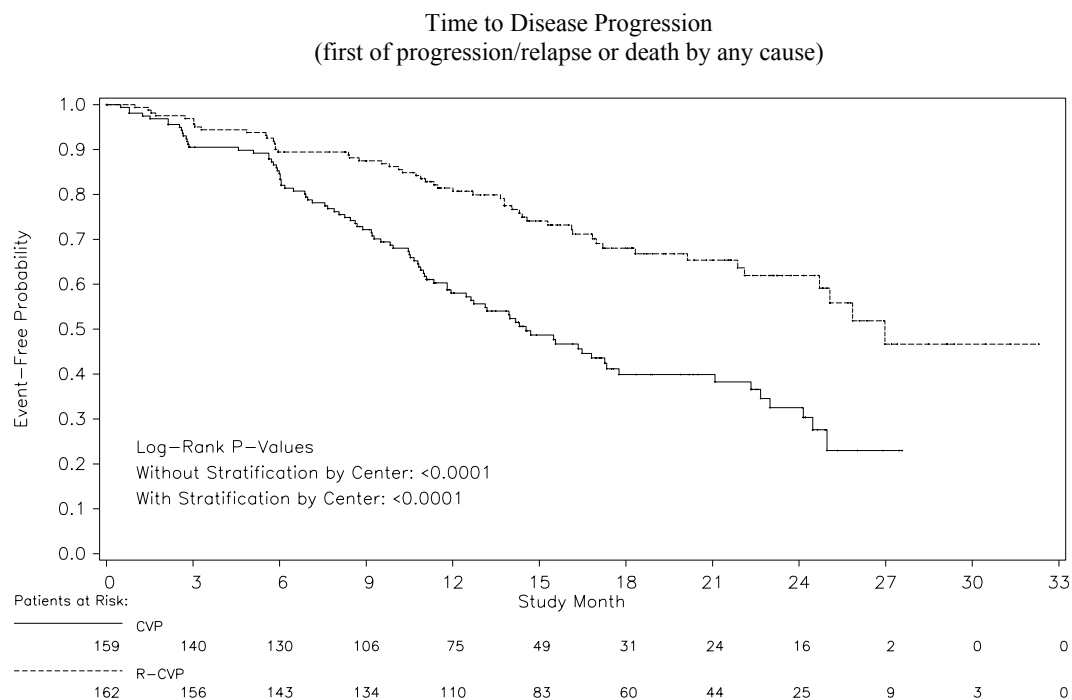
Figure 1 Kaplan-Meier Plot of Time to Treatment Failure: as Assessed by the Investigator (Study M39021)

Time to Treatment Failure (first of progressive disease, relapse after response, institution of new lymphoma treatment, SD4, or death by any cause)



The plot of Kaplan-Meier estimates of event free rates for disease progression (an exploratory analysis defined in the statistical analysis plan prior to the 2nd interim analysis) is shown in Figure 2.

Figure 2 Kaplan-Meier Plot of Time to Disease Progression: as Assessed by the investigator (Study M39021)



The independent review of tumor response carried out by a Critical Event Committee CEC generally confirmed the results of the final analysis (based on the investigators' assessment of response) and demonstrated a similar magnitude of effect of R-CVP over CVP in terms of TTF, TTP and ORR (the analysis based on the investigators' assessment was the main analysis for this study) (see Table 3).

Table 3. Comparison of Efficacy between the Investigators' and CEC's Analyses

Parameter	Investigator Analysis (n = 321)				CEC Analysis (n = 300)			
	Kaplan-Meier estimate of Median Time to Event (Months)		Log-rank p-value	Treatment Effect [†]	Kaplan-Meier estimate of Median Time to Event (Months)		Log-rank p-value	Treatment Effect [†]
	CVP	R-CVP			CVP	R-CVP		
ORR*	57%	81%	<0.0001**	3.2***	43%	77%	<0.0001**	4.5***
TTF	6.7	25.9	<0.0001	67%	3.0	14.7	<0.0001	65%
TTP	14.5	27.0	<0.0001	59%	11.9	19.2	<0.0001	56%

[†] Treatment effect: For event free parameters, estimates were calculated by risk reduction; for tumor response, odd ratio was used. TTF: time to treatment failure; *ORR: Overall response rate (CR, CRu, PR) was calculated from the tumour response as assessed at the end of trial treatment; ** chi-square test; *** odds ratio; TTP: Time to disease progression or death.

The results of the final analysis are supported by provisional data from the 'snapshot' analysis performed with a data cut-off date of September 24, 2003, which includes an additional 7 months of observation time (table 4). This confirms the interpretation made by the DSMC that the statistical and clinical relevance of the results would not change upon longer follow-up.

Table 4. Comparison of TTF and TTP (Investigator Assessment) between the Final Analysis and the Snapshot analysis (data cut-off September 24, 2003)

Parameter	Final Analysis (n = 321)				Snapshot Analysis (n = 321)			
	Kaplan-Meier estimate of Median Time to Event (Months)		Log-rank p-value	Treatment Effect [†]	Kaplan-Meier estimate of Median Time to Event (Months)		Log-rank p-value	Treatment Effect [†]
	CVP	R-CVP			CVP	R-CVP		
TTF	6.7	25.9	<0.0001	67%	6.7	27.0	<0.0001	67%
TTP	14.5	27.0	<0.0001	59%	14.5	30.1	<0.0001	58%

[†] Treatment effect: for event free parameters, estimates were calculated by risk reduction; TTF: time to treatment failure; TTP: Time to disease progression or death.

Clinical Safety

Patient exposure

A higher percentage of patients received 8 cycles of treatment in the R-CVP group (85%) compared with the CVP group (68%), mainly due to the insufficient therapeutic response with CVP. This resulted in a longer safety reporting period in the R-CVP group. Amongst the patients that received 8 cycles of trial treatment, the proportion that received more than 90% of the planned dose of all components was higher in the CVP group (71%) compared with the R-CVP group (57%); this was mainly due to more patients on R-CVP having cyclophosphamide dose reductions due to neutropenia. There was no evidence that the addition of rituximab to CVP caused a delay between cycles.

Adverse events

There were no unexpected toxicities with R-CVP treatment in study M39021. Adverse events with higher incidence in the R-CVP group were those already recognized as belonging to the safety profile of rituximab (rigors, pyrexia, influenza-like illness, pain, chest pain, chest tightness, rash, pruritus, urticaria, cough, dyspnoea, flushing, hypertension, hypotension, and neutropenia) as well as oral pain and muscle cramp. There was no evidence of an imbalance between the treatment groups for any adverse events of the cardiac or nervous systems, or for infections and infestations. Hematotoxicity was modest in both treatment arms, with a higher incidence of neutropenia in the R-CVP arm. However, this difference may in part be accounted for by the longer safety reporting period in the R-CVP group, due to patients completing more cycles of therapy.

4.3.4. Discussion of efficacy

The addition of rituximab to a well-established chemotherapy regimen CVP demonstrated a highly statistically significant improvement in TTF, TTP, and ORR when compared to CVP alone in previously untreated patients with stage III-IV follicular NHL.

The investigators' assessment of response was confirmed by an analysis of response assessment data according to an independent review committee (CEC). The results submitted in the dossier are based on the data of the 2nd pre-planned interim analysis. This interim analysis was conducted after all patients had completed randomised trial treatment. The difference in favour of the R-CVP arm was large and the predefined statistical criterion for stopping the study was met. The observed difference in the "final analysis" seems to be maintained in the "snapshot analysis" with an additional 7 months of observation time.

One area of controversy is the clinical significance of a prolonged TTF/TTP in a neoplastic disease with a long median survival and a pattern of multiple treatable relapses. Although the results are convincing and in complete agreement with the current CPMP guideline for anticancer medicinal products, the correlation between primary and secondary efficacy parameters and their potential

impact on survival for patients with follicular NHL was debated.

It is agreed that the achievement of CR is the single most important prognostic factor in follicular lymphoma regardless of the treatment regimen utilised. Evidence from clinical trials suggests there is a relationship between time-dependent efficacy endpoints and overall survival in follicular lymphoma. However, in a chronic disease characterised by multiple relapses and progressions it is difficult to assess the contribution of first-line therapy to overall survival especially due to the influence of multiple subsequent therapies.

The MAH submitted an updated analysis of study M39021 with a median follow-up of 30 months which has demonstrated a continued large and consistent benefit for the R-CVP regimen over CVP across all primary and secondary efficacy parameters. In this updated analysis, the median TTP for R-CVP is 31.9 months compared with 14.5 months for CVP. The median time to new anti-lymphoma treatment (TNLT) has not been reached in the R-CVP arm and is 12.3 months for the CVP arm and was 13.5 months versus 35.0 months for duration of response. This large and durable benefit in TTP and TNLT, as well as in overall response rate and duration of response, may translate into an improvement in overall survival with longer follow-up. The update of the efficacy results with a median observation time of 30 months provides reassuring information. The superiority of the CVP-R compared with CVP as regards the time-dependent endpoints TTF/TTP and DR is maintained. Longer follow-up will be required for a more definite evaluation of the CVP-R regimen.

The benefit of adding rituximab to CVP was seen consistently throughout the population recruited in study M39021 (randomized according to BNLI criteria (no versus yes), age (≤ 60 years, > 60 years), number of extra-nodal sites (0-1 versus >1), bone marrow involvement (no versus yes), LDH (elevated, not elevated), β_2 -microglobulin (elevated, not elevated), B symptoms (absent, present), bulky disease (absent, present), number of nodal sites (< 5 versus ≥ 5), hemoglobin (≤ 12 g/dL versus >12 g/dL), IPI (≤ 1 versus >1), and FLIP index (0-2 versus 3-5)).

The presence of constitutional so-called B-symptoms is not the only trigger for initiating therapy of patients with follicular lymphoma. Bulky disease/number of regions involved as well as the patient's acceptance of deferred treatment are other important factors in the decision process. Moreover, there is no universal agreement on when to use the wait and watch approach in asymptomatic patients.

Taking into account the accepted clinical practice that only symptomatic follicular lymphoma patients should be treated with therapeutic agents, and that currently the major goal of treatment is the alleviation of symptoms since there is no globally established treatment option that provides a consistent survival benefit, it would have been appropriate to also include the effects of treatment on the alleviation of symptoms. The effect of treatment was only analysed for ECOG performance status and B-symptoms. At the request of the CPMP, the MAH provided additional analyses on the basis of the following criteria with potential impact on patient symptomatology

- B-Symptoms: assessed during treatment phase and follow-up phase.
- Performance status (ECOG): assessed during treatment phase and follow up phase.
- Bulky disease: assessed during treatment phase but not follow-up phase.
- >3 Nodal sites diameter > 3 cm: assessed during treatment phase but not follow-up phase.

Based on these analyses, a numerical trend in favour of R-CVP is seen for all parameters analysed: B-symptoms (89% improved with R-CVP vs. 70% improved with CVP at last observation), ECOG performance status (71% improved with R-CVP vs. 49% with CVP at last observation), nodal disease (>3 sites >3 cm) (84% improved with R-CVP vs. 69% with CVP at end of treatment), and bulky disease (62% with R-CVP vs. 44% with CVP at end of treatment).

From the data presented by the MAH it is clear that the population entered in Study M39021 is representative for patients that most haematologists/oncologists would consider "requiring treatment". The data also support the fact that symptomatic patients also benefit from a tumour response.

The choice of regimen of 8 cycles of R-CVP was also discussed. Since 8 cycles of CVP as used in study M39021 is regarded as a standard treatment option in previously untreated follicular lymphoma patients, this seems it is an appropriate control regimen to evaluate the efficacy of a new regimen.

Furthermore, in vitro studies demonstrated synergistic activity between rituximab and various cytotoxic agents and in order to take advantage of this, rituximab was given on the same day as the chemotherapy agents in each cycle.

Apart from study M39021, another trial (investigator initiated) incorporating an R-CVP regimen (U2094n, Hainsworth et al. 2002- conference abstract) has provided data in previously untreated follicular NHL patients. Patients received four weekly doses of rituximab given as monotherapy followed by three cycles of R-CVP or R-CHOP. Results are not available for the individual treatment groups - R-CVP (25 patients) or R-CHOP (60 patients). The MAH commits to provide results from study U2094n to the CPMP once publicly available.

4. 3. 5. Discussion of safety

New safety issues have not emerged from the assessment of this variation dossier. Rituximab can safely be combined with CVP as well as CHOP.

Long-term safety data are not available. The observation for secondary neoplasias and cardiac events beyond 5 years is indicated for this group of patients with a median overall survival of up to 10 years. Follow-up data should be provided post-marketing.

4. 3. 6. Benefit – risk assessment

The overall benefit risk appears to be positive for the extension the indication.

The MAH committed to submit yearly updates with regard to time to treatment failure, overall survival, duration of response, time to new anti-lymphoma treatment, disease-free survival, and time to disease progression to the CPMP during a follow-up period of up to 7 years.

The MAH also committed to closely monitor the incidence of secondary neoplasias and cardiac events in the target group of patients as part of cumulative data review.

5. Conclusion

Based on the CPMP review of data on quality, safety and efficacy and taking into consideration the outcome of the ad-hoc experts meeting on clinical issues held on 7 January 1998 and the oral explanations provided by the company during the hearing held on 27 January 1998, the CPMP considered by consensus that the benefit/risk profile of MabThera was favourable in the indication of

- treatment of patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.

The CPMP also considered the Type II variations for the extensions of the indication to be acceptable and agreed on the proposed wordings to be introduced into the Summary of Product Characteristics, and reflected into the Package Leaflet.

The CPMP on 18 October 2001 adopted by consensus an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation of Mabthera for the indication.

- treatment of patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy.

The CHMP adopted on 23 June 2004 an Opinion on a Type II variation to be made to the terms of the Community Marketing Authorisation.

- treatment of previously untreated patients with stage III-IV follicular non-Hodgkin's lymphoma (NHL) in combination with CVP (cyclophosphamide, vincristine, prednisolone) chemotherapy.