Horizon Scanning in Oncology

Rituximab (Rituxan®/MabThera®) for the first- and second-line treatment of chronic lymphocytic leukaemia

1st Update 2011

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology Nr. 004/Update 2011
ISSN online 2076-5940

Horizon Scanning in Oncology

Rituximab (Rituxan®/MabThera®) for the first- and second-line treatment of chronic lymphocytic leukaemia

1st Update 2011

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, October 2011

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

Author(s): Dr. Anna Nachtnebel, MSc

Internal Review: Katharina Hintringer, BA

External Review: Prof. Dr. med. Wolf-Dieter Ludwig
Klinik für Hämatologie, Onkologie und Tumorimmunologie
HELIOS Klinikum Berlin-Buch
Schwanebecker Chaussee 50
13125 Berlin

DISCLAIMER

CONTACT INFORMATION

Publisher:
Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

Responsible for Contents:

Ludwig Boltzmann Institute of Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at "http://eprints.hta.lbg.ac.at":

DSD: Horizon Scanning in Oncology Nr. 004/Update 2011
ISSN online 2076-5940

http://eprints.hta.lbg.ac.at/view/types/dsd.html

1 Background

1.1 Drug description

Generic/Brand name/ATC code:

Rituximab/Rituxan® (United States, Japan, Canada), MabThera® (rest of the world)/ L01X C02

Developer/Company:

Genentech, Inc., and Biogen Idec. co-market MabThera® in the United States. Chugai Pharmaceutical and Zenyaku Kogyo Co. Ltd. co-market MabThera® in Japan. Hoffmann-La Roche Ltd. markets MabThera® in the rest of the world [1].

Description:

Rituximab belongs to the pharmacotherapeutic group of antineoplastic agents and monoclonal antibodies [2].

rituximab induces lysis and apoptosis of normal and malignant human B-cells by binding to the CD20 antigen

Rituximab is a chimeric murine/human anti-CD20 monoclonal antibody targeted against the cluster of differentiation (CD) 20 antigen expressed on the surface of human B-cells. By binding to the CD20 antigen it promotes antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity and induces lysis and apoptosis of normal and malignant human B- cells. Furthermore, it sensitises malignant B-cells to the cytotoxic effect of chemotherapy [2, 3].

Administration:

rituximab intravenously once at the beginning of each cycle

Six treatment cycles of rituximab are administered in combination with fludarabine and cyclophosphamide at intervals of 28 days (= 1 cycle). Rituximab is administered only once at the beginning of every cycle with an initial starting dose of 375mg/m^2 body surface area (BSA) intravenously (iv) (cycle 1), followed by 500mg/m^2 iv (cycle 2-6) [2].

1.2 Indication

Rituximab in combination with chemotherapy is indicated for the first and second-line treatment of patients with CD20+ chronic lymphocytic leukaemia (CLL) [2].

1.3 Burden of disease

CLL is the most common leukaemia in industrialised countries, and affects mainly patients aged ≥65 years

CLL belongs to the entity of indolent B-cell non-Hodgkin lymphomas (NHL) and is the most common adult leukaemia in the Western World, accounting for approximately 30% of all leukaemias. The vast majority of patients that is 70% are older than 65 years when diagnosed with CLL [4], corresponding to a median age of 72 years at diagnosis [4]. Men are affected twice as often as women [5, 6] and the median age of death is 79 years [4].

Risk factors for developing CLL include older age, male sex, white ethnicity, family history of CLL or other blood and bone marrow cancers and exposure to certain chemicals, such as herbicides and insecticides [7].

the majority of patients is asymptomatic at diagnosis; symptoms may be lymphadenopathy and "B" symptoms

In the majority of cases CLL is diagnosed incidentally by routine complete blood count examination. Most patients are asymptomatic at the time of diagnosis. The most common symptom is lymphadenopathy, followed by so called "B" symptoms, including fever, night sweats and weight loss. The life expectancy of patients with early stage disease at diagnosis is greater than ten years but decreases with advanced disease at diagnosis to a median survival of less than one year [8, 9].

diagnosis requires B lymphocytosis ≥5.0 x 10^9/L in the peripheral blood for ≥ 3 months

clinical staging depends on standard laboratory tests and physical examination

There are two classification systems for the clinical staging of CLL, depending on standard laboratory tests and physical examination, including the Rai classification and the Binet staging system. The Rai classification distinguishes low (formerly Rai stage 0), intermediate (formerly Rai stage I or II) and high (formerly Rai stage IV and V) risk disease, whereas the Binet staging is subdivided into stage A, B and C (see Table 1) [10, 11].

Table 1: Binet staging system for CLL (from [4])

Binet stage	Clinical features	Median survival (years)
A	Fewer than 3 areas of lymphadenopathy, no anaemia or thrombocytopenia	12
B	More than 3 involved node areas or thrombocytopenia	7
C	Haemoglobin >100g/L, platelets <100 x 10g/L	2-4

advanced disease stage, short lymphocyte doubling time, etc. worsen the prognosis

Besides clinical staging, several other markers can be used as predicting factors. For example, cytogenetic abnormalities detected by fluorescence-in situ hybridisation are found in about 80% of all CLL patients [12, 13]. The most common one, that is deletion (del) 13q (in about 55%), is associated with a favourable prognosis whereas del17p and del11q are high-risk features predictive of disease progression [12, 13]. Also, patients with unmutated immunoglobulin variable region heavy chains (IGHV) have a shorter survival and a higher risk of relapse after initial therapy [13, 14]. Further factors related to poor prognosis are high serum levels of beta-2-microglobulin and high levels of ZAP-70 (zeta-chain associated protein kinase 70) and CD38 expression [10, 12-14].

initiation of treatment depends on clinical staging; adenopathy, hepatosplenomegaly, autoimmune cytopenias, and marrow failure require treatment

The initiation of treatment is not recommended for asymptomatic early-stage disease (Rai 0, Binet A). In these patients a watch-and-wait strategy

with controls of blood cell counts and clinical examination every three to six months is recommended until disease progression. In patients with intermediate and high risk disease, according to the Rai classification as well as patients with Binet stage B or C disease, the initiation of treatment is recommended, whereas some patients with intermediate disease or Binet stage B might as well be monitored until disease progresses [10, 11]. Disease progression requiring treatment is based on certain criteria, such as increasing adenopathy, hepatosplenomegaly, development of auto-immune cytopenias, and marrow failure [5, 11].

incidence of CLL in Austria is increasing

In Austria, no data are available for specific types of leukaemia, but the overall incidence of all forms of leukaemia (C91-C95 according to the World Health Organization's International Classification of Diseases – 10) was 890 and 740 people died in 2008 [6]. The incidence of CLL in Austria is expected to rise in the future due to an increasing elderly stratum of the population.

1.4 Current treatment options

several treatment options for first- and second-line therapy

Patients diagnosed with CLL at an early stage should be observed only, whereas therapy should be initiated in patients with symptomatic disease, rapid disease progression, bulky lymphadenopathy and/or splenomegaly [4]. There are various treatment options for CLL depending on disease stage, patient's age, presence of cytogenetic lesions, concomitant diseases and – in second line therapy – duration of response [15].

1st-line: R-FC for younger and fit patients, chlorambucil for older patients with comorbidities

Just briefly, either participation in a clinical trial or fludarabine-based therapies, foremost fludarabine plus rituximab (FR), or fludarabine, cyclophosphamide and rituximab (R-FC) are increasingly recommended as 1st-line therapy for younger and fit patients [4, 12, 16], whereas chlorambucil is preferred for older patients with comorbidities [17]

relapsed patients: retreatment with initial therapy

refractory patients: chemotherapy

Several treatment options are available for patients with relapsed disease (=progressive disease after either complete or partial response for ≥6months); one recommendation is to re-treat them with the initial therapy. For patients with refractory disease (=either no response, or disease progression within <6 months), chemotherapy is indicated but it is unclear which regimen should be used [18].

1.5 Current regulatory status

EMA approval for untreated and previously treated CLL patients

Rituximab (MabThera®) is approved by the European Medicines Agency (EMA) [2] for

- Non-Hodgkin's lymphoma (NHL) (first approval was granted in 1998 with subsequent extensions of indication),
  - for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with chemotherapy.
  - as maintenance therapy for the treatment of follicular lymphoma patients responding to induction therapy.

- as mono-therapy for treatment of patients with stage III-IV follicular lymphoma who are chemo-resistant or are in their second or subsequent relapse after chemotherapy.
- for the treatment of patients with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy.

- CLL
  - in combination with chemotherapy for the treatment of patients with previously untreated (licensed January 2009) and relapsed/refractory CLL (July 2009).

- Rheumatoid arthritis (RA)

  in combination with methotrexate for the treatment of adult patients with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other disease-modifying antirheumatic drugs including one or more tumour necrosis factor inhibitor therapies (June 2006).

FDA approval for previously treated and untreated patients in combination with FC

Rituximab (Rituxan®) is approved by the United States Food and Drug Administration (FDA) for

- Non-Hodgkin's Lymphoma (NHL)
- RA in combination with methotrexate in adult patients with moderately to severely-active RA who have inadequate response to one or more tumour necrosis factor antagonist therapies
- Wegener's Granulomatosis and Microscopic Polyangiitis
- CLL in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL since January 2011 [19].

1.6 Treatment costs

total costs of € 15,700 in addition to chemotherapy

In Austria, rituximab is marketed by Roche Austria, Vienna. One package of 100mg rituximab (10mg/ml) concentrate for solution for infusion consisting of two single-use vials is € 616.15. In addition, one package of 500mg rituximab (10mg/ml) concentrate for solution for infusion containing one single-use vial is € 1,492.75 [20].

Assuming an average body surface area, based on height and weight, of 1.7 m^2 for both men and women, total treatment costs for the recommended rituximab regimen can be estimated. The first cycle of rituximab infusion would be € 2,109, followed by € 2,725 for cycle two to six (assuming that two packages containing two 100mg vials are used) which would add up to total treatment costs of € 15,734 in addition to chemotherapy, corresponding to monthly treatment costs of about € 2,600.-

2 Evidence

two phase III studies now fully published

A literature search was conducted on 2nd of August 2011 in four databases (EMBASE, Ovid, Cochrane Library and the CRD Database). After removal of duplicates, 340 references were found for 1st-line therapy and 180 for 2nd-line therapy.

Only results of randomized controlled trials (RCTs) were included, yielding three relevant references reporting results of two RCTs [21-23]. Three studies [24-26] were excluded, because one was not powered to detect clinically significant differences between treatment arms and did not present statistical comparisons [25], whereas the other one, only published as abstract, investigated treatment in a heterogeneous population of treatment- naïve and minimally treated patients [24]. The third study was excluded, because trial recruitment was stopped due to excess mortality in the comparator group [26].

CLL is biologically and in its clinical course heterogeneous

In comparison to our initial HSS report [27], no further RCTs were included, but both studies have been fully published in the meantime and long-term results have become available.

2.1 Efficacy and safety - RCTs

Table 2: Phase III studies of rituximab for the first- and second-line treatment of CLL

Reference	Hallek et al., CLL-8 [21, 22]	Robak et al. , REACH trial [23]
Sponsor	Hoffmann-La Roche	Hoffmann-La Roche
Country	central study office: Germany 190 study centres in 11 countries	central study office: Poland 88 study centres in 18 countries
Design	randomised, open-label, multicentre, phase 3 study	randomised, multicentre, open-label, phase III
Hypothesis	superiority	superiority
Number of patients	I 408 vs C 409	I 276 vs C 276
Treatment		
Intervention	375mg/m² (do in 1st cycle) - 500mg/m² (d1 in 2nd – 6th cycle) rituximab iv +25mg/m²/d fludarabine + 250mg/m² (d1-3) cyclophosphamide	375mg/m² - 500mg/m² (d1) rituximab + 25mg/m²/d fludarabine + 250mg/m²(d1-3) cyclophosphamide
Control	25mg/m²/d fludarabine + 250mg/m² (d1-3) cyclophosphamide	25mg/m²/d fludarabine + 250mg/m² (d1-3) cyclophosphamide
Inclusion criteria	untreated, active CLL and good physical fitness (Cumulative illness rating scale ≤6), Binet stage C or with confirmed active disease Binet stages A or B, ECOG PS 0-1	previously treated, CD20+ CLL, one prior line of therapy (single-agent chlorambucil (±prednisone/prednisolone), single-agent fludarabine (or other nucleoside analogue), or an alkylator containing combination regimen, but not an alkylator/nucleoside analog). Patients could be sensitive or refractory to prior alkylating agents but had to be sensitive to fludarabine (defined as achieving a response that lasted ≥6 months). Prior treatment with interferon, rituximab, other monoclonal antibodies, or stem-cell transplantation was not permitted. ECOG PS ≤1, life expectancy of more than 6 months

Participants characteristics		
Median age (years; (range))	I 61 (30-80) vs C 61 (36-81)	I 63 (35 -83) vs C 62 (35 -81)
≥65 years (%)	I 31 vs C 29	I 42 vs C 44
Men (%)	I 74 vs C 74	I 68 vs C 66
Binet stage A (%)	I 4 vs C 5	I 9 vs C 11
Binet stage B (%)	I 64 vs C 63	I 60 vs C 58
Binet stage C (%)	I 31 vs C 31	I 31 vs C 31
ECOG PS 0 (%)	I 56 vs C 58	I 61 vs C 59
Presence of B-symptoms (%)	I 41 vs C 49	I 26 vs C31
IGHV unmutated (%)	I 63 vs C 63	I 61 vs C 65
Del(13q) (%)	I 54 vs C 60	I 56 vs C 60
Del(11q) (%)	I 27 vs C 22	I21 vs C22
Del(17p) (%)	I 7 vs C 10	I 7 vs C 9
Trisomy 12 (%)	I 10 vs C 14	I 11 vs C 15
Follow-up	NA	25 months
OS		
Median (months)	NA	I NR vs C 52 (p=0.287)
HR	0.67 (95%CI 0.48 – 0.92; p=0.012)	0.83 (95%CI 0.59 – 1.17; p=0.287)
PFS	(primary endpoint)	(primary endpoint)
Median (months)	I 51.8 vs. C 32.8 (p<0.0001)	I 27.0 vs C 21.9 (p<0.0218)*
HR	0.56 (95%CI 0.46 – 0.69; p<0.0001)	0.76 (95%CI 0.60 – 0.96; p<0.22)

Tumour response						
ORR (%)	I 90 vs C 80 (p<0.0001)			I 61 vs C 49 (p=0.0048)*		
CR (%)	I 44 vs C 22 (p<0.0001)			I 9 vs C 3 (p=0.0046)		
QoL	EORTC C30 questionnaire at 3 and 6 months: no difference in global health status, functional scales and symptom scales, dyspnoea score: I 18 vs C 23, p=0.023; at 12, 24 and 36 months follow-up: no difference			FACT-G: no difference between treatment arms		
Adverse events according to NCI CTC v 2.0						
Any grade		I	C		I	C
Overall		NA	NA		99	96
Hematologic		NA	NA		NA	NA
Non-hematologic		NA	NA	Nausea Vomiting Pyrexia Fatigue Asthenia Chills Constipation Diarrhoea Cough Headache	40 21 25 16 10 15 15 12 12 9	35 19 15 17 11 2 11 12 9 11
Grade ≥3		I	C		I	C
Overall (%)		76	63		80	74
Hematologic (%)	Haematologic toxicity Neutropenia Leucocytopenia Thrombocytopenia Anaemia Autoimmune-haemolytic anaemia	56 34 24 7 5 <1	40 21 12 11 7 1	Neutropenia Febrile neutropenia Anaemia Thrombocytopenia Granulocytopenia Pancytopenia	42 12 12 9 7 3	40 12 13 11 4 5

on-hematologic (%)	Infections (overall) Bacterial infections Tumour lyses syndrome Cytokine release syndrome	25 3 <1 <1	21 1 <1 0	Pneumonia Hepatitis B	5 1.8	6 0
Deaths associated with AEs (%)		2	3		14	10
AEs leading to discontinuation		NA	NA		26	25
Notes	In January, 2008, the pre-planned interim analysis showed a significant difference in the primary efficacy analysis and the study was formally ended. At this point, all patients had been enrolled and completed treatment.			More patients started a subsequent treatment for CLL in the C arm (=69%) than in the I arm (=47%)		

I = intervention, C = control, NR= not reached, NA = not available, NCI CTC = National Cancer Institute Common Toxicity Criteria, CI = confidence interval, HR =hazard ratio, ORR = overall response rate, QoL = quality of life, AE= adverse event, ECOG PS = Eastern Cooperative Oncology Group Performance Status, EORTC C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, FACT-G= Functional Assessment of Cancer Therapy – General, OS =overall survival, PFS = progression-free survival, Cumulative illness rating scale = a scale classifying co-morbidities by organ systems, grading each condition from 0 (no problem) to 4 (severely incapacitating or life-threatening condition) [28].

**results from independent review committee assessments*

Published results of two randomised trials were found, one assessing rituximab as 1st- line therapy [21, 22] and the other evaluating rituximab in previously treated patients [23].

1st-line:

R-FC in comparison to FC as 1st-line therapy

Hallek et al. [21] compared R-FC to FC only in overall 817 patients. The study population consisted of mainly younger patients (29% of the patients were ≥65 years) with good performance status. Previous results of an interim analysis at a median follow-up of 20.7 months showed that progression-free survival (PFS), the primary outcome, was 39.8 months for the R-FC group and 32.2 months for the FC group ($p<0.001$) [29]. In the published article [21], no information about the median follow-up is provided, but the results at 3 years after randomisation showed also improved results for the chemo-immunotherapy group (median OS I 51.8 months vs C 32.8 months), yielding a hazard ratio of 0.56 ($p<0.0001$). A subgroup analysis produced similar findings for most prognostic subgroups, but results were not statistically significant for patients with Binet stage A or C and for individuals without genetic abnormalities. In contrast, however, several other documents (e.g. EMA's European Public Assessment Report) report improved outcomes in PFS also for other disease stages [29, 30]. OS showed also superior results overall, because the risk of death was reduced by 33% for patients treated with R-FC. Identical outcomes were observed for only some subgroups, that is patients with Binet stage B, del(13q), del(11q) and unmutated IGHV. It should be mentioned though that these findings might have been confounded since study treatment was stopped in patients with stable or progressive disease and a new therapy was started based on physicians' choice. Even though ORR, which is the sum of patients with partial and complete responses, was high, 10% of patients in the R-FC group and 20% of patients in the FC group received treatments other than the study therapy, a fact which could have influenced OS. Of note, however, of the 90% of patients in the R-FC group, a complete response was achieved in 44%, in comparison to 22% in the comparator group. Based on these findings the study was ended at the pre-planned interim analysis in January 2008.

PFS, OS and ORR significantly improved

but OS possibly influenced by subsequent therapy

PFS: hazard ratio =0.56

complete responses in 44% of patients treated with R-FC

In terms of AEs, any grade 3 or 4 side effects as well as haematological AEs overall and more specifically, neutropenia and leucocytopenia occurred significantly more frequent in the combination arm. The authors additionally analysed toxicities according to age groups and reported that older patients (i.e. ≥65years) experienced side-effects more frequently than younger ones, due to haematological AEs as well as due to bacterial infections. The overall rate of infections, in contrast, did not differ, possibly, because granulocyte-colony stimulating factor was given more frequently in the chemo-immunotherapy group. Some results for QoL are presented as abstract, where no differences were found between the two groups; only dyspnoea scores showed favourable results for the R-FC group at 3 and 6 months [22].

AEs, foremost haematological, more frequent in rituximab arm

more often in patients ≥65 years

no difference in QoL

2nd line:

The study by *Robak et al.* [23] investigated R-FC in comparison to FC in 552 previously treated CLL patients. One prior therapy was allowed but 1st-line therapy with an alkylator/nucleoside analogue combination (e.g. fludarabine + cyclophosphamide) as well as any previous monoclonal antibody was not allowed. Patients also had to be sensitive to fludarabine (defined as achieving a response that lasted ≥6 months) and about 55% of all patients were also sensitive to alkylating agents. Most patients had thus relapsed disease rather than refractory disease.

R-FC vs FC in previously treated patients

prior R-FC therapy not allowed

patients had to be fludarabine-sensitive

PFS and ORR were significantly improved for the R-FC group by both the investigator assessment and the independent review committee assessment. However, the findings of these two assessments rather deviate, as the difference in median PFS was 10 months according to the investigator assessment and only 5.1 months according to the independent review committee assessments. At least some of this difference can be explained, because the investigator assessment took place one year after the independent assessment [31]. The investigators furthermore observed a complete response in 24% of patients in the R-FC group in contrast to 9% by the IRCA. For OS no difference was found, but this has to be interpreted with caution due to immature data and ensuing therapies after study treatment discontinuation. QoL, similarly to the 1st-line study, did not differ between groups.

PFS + ORR significantly improved

differences between investigator assessment and independent review assessment

no difference for OS and QoL

AEs of any grade as well as higher grade AEs, and fatal side-effects were more frequent in the R-FC group than in the FC only group. Even though no detailed numbers are provided, the authors mention that AEs were also more frequent and more severe in older patients.

3 Commentary

Rituximab is licensed in combination with chemotherapy for untreated and previously treated CLL patients. In Europe there is no specific chemotherapy regimen to be combined with rituximab, whereas in the US it is defined. The FDA licensed it only in combination with FC and also several guidelines recommend rituximab in addition to FC [16, 28]. In this context it should be mentioned, that in both trials which had used R-FC regimens, the majority of patients were younger than 65 years and had a good performance status, thus reflecting the population which is eligible for fludarabine-based therapy in the first instance, but which is not representative for the average CLL patient. In addition, AEs were observed more frequently in older patients. Consequently, an assessment conducted by the National Institute for Health and Clinical Excellence (NICE) concluded that combination with other chemotherapeutic regimens cannot be recommended, especially not in addition to chlorambucil – a therapy which is used for patients with poor performance status and co-morbidities [29] (trials are currently on-going comparing chlorambucil to rituximab [32]). Several guidelines also take age, but foremost presence of comorbidities and performance status into account and tend to prefer R-FC for younger and fitter patients [12, 13, 16, 28].

EMA approved rituximab for 1st -line therapy in combination with chemotherapy without further defining which one

FDA: rituximab only in combination with FC

also some guidelines prefer this combination, for younger patients without comorbidities

PFS improved in both, 1st and 2nd-line therapy

but 2nd-line study excluded patients previously treated with R-FC

R-FC increasingly used as 1st-line therapy, potential to benefit for patients re-treated with R-FC unclear

PFS, the primary outcome in both phase III studies, demonstrated better results for R-FC, yielding a risk reduction of progression by 44% in the 1st-line setting. The trial assessing R-FC in previously treated, but fludarabine-sensitive patients, excluded individuals which had received prior treatment with, for example, R-FC. But, as already mentioned, R-FC is increasingly recommended as 1st-line therapy [12, 16, 28], especially for patients <70 years and with good performance status – all characteristics the study population showed. It therefore remains unclear if patients previously treated with R-FC will also benefit when re-treated with R-FC. Similar concerns were expressed by NICE, which, after appeals from several organisations (e.g the UK Chronic Lymphocytic Leukaemia Forum, British Society for Haematology), had to re-formulate its guidance [30]: Re-treatment with rituximab got only allowed either in the context of a clinical trial, at a dose lower than the dose currently licensed for CLL or in combination with chemotherapies other than FC [14]. In this context, it is also of interest, how ofatumumab, a monoclonal antibody also targeting CD20, which showed activity in fludarabine-refractory patients, will compare to R-FC treatment in fludarabine-sensitive patients [13].

biomarkers to guide treatment decisions?

optimal dosage?

Another topic of investigation is how to incorporate biomarkers (e.g. del(17p), unmutated IGVH) to guide treatment decisions [13]. *Hallek et al.* [21] for example suggest that patients with del(17p) might not benefit from R-FC treatment, but might profit from treatments such as stem cell transplantation. Another not completely resolved question concerns the optimal dosage of rituximab. Even though the labelled dose which was also used in all of the trials mentioned above, is 375mg/m^2 in cycle 1, followed by 500mg/m^2 for each subsequent cycle, some authors argue that differing schedules might be used [4] which might potentially decrease treatment costs. In the absence of trials which demonstrate efficacy of rituximab also at lower doses, changes are not yet indicated [4].

OS in 1st-line setting improved, but might be distorted due to subsequent lines of therapy

due to increases in PFS and ORR, prolongation of OS also likely

In terms of OS, data for previously treated patients were immature and did not show any difference between treatment arms. In the 1st –line setting, OS was significantly improved, but because patients, who either not-responded or progressed, received alternative therapies this result has to be interpreted with caution. However, the gain in PFS and the improved response rates, especially in the 1st-line setting suggest that a better OS in patients treated with rituximab is also likely. Nonetheless, these improvements did not translate into more favourable outcomes for QoL but, at least, QoL was not significantly compromised by the addition of rituximab - despite more frequent AEs in the R-FC arm than in the FC arm only. Other regimens, such as FR or pentostatin+cyclophosphamide+rituximab might be less toxic, but final study results comparing these therapies to R-FC are still missing [13].

4 References

1. UpToDate 19.3. *Initial treatment of chronic lymphocytic leukemia*. 2011 [cited 2011 08. August]; Available from: http://www.uptodate.com.
2. European Medicines Agency. *EPARs for authorised medicinal products for human use*. 2011 [cited 2011 8. September]; Available from: http://www.emea.europa.eu/humandocs/Humans/EPAR/mabthera/mabthera.htm.
3. Quintas-Cardama, A. and S. O'Brien, *Targeted therapy for chronic lymphocytic leukemia.* Target Oncol, 2009. **4**(1): p. 11-21.
4. Gribben, J.G., *How I treat CLL up front.* Blood, 2010. **115**(2): p. 187-197.
5. Carney, D.A. and S.P. Mulligan, *Chronic lymphocytic leukaemia: current first-line therapy.* Intern Med J, 2009. **39**(1): p. 44-8.
6. UpToDate 19.3. *Epidemiology and clinical manifestations of chronic lymphocytic leukemia*. 2011 [cited 2011 21. November]; Available from: http://www.uptodate.com.
7. Taylor, R.P. and M.A. Lindorfer, *Immunotherapeutic mechanisms of anti-CD20 monoclonal antibodies.* Curr Opin Immunol, 2008. **20**(4): p. 444-9.
8. Maddocks, K.J. and T.S. Lin, *Update in the management of chronic lymphocytic leukemia.* J Hematol Oncol, 2009. **2**: p. 29.
9. Migkou, M., et al., *Applications of monoclonal antibodies for the treatment of hematological malignancies.* Expert Opin Biol Ther, 2009. **9**(2): p. 207-20.
10. Eichhorst, B., et al., *Chronic lymphocytic leukemia: ESMO Minimum Clinical Recommendations for diagnosis, treatment and follow-up.* Ann Oncol, 2009. **20**(Suppl 4): p. iv102-iv104.
11. Hallek, M., et al., *Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updating the National Cancer Institute-Working Group (NCI-WG) 1996 guidelines.* Blood, 2008. **111**(12): p. 5446-56.
12. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas*. V.4.2011 [cited 2011 August 2]; Available from: http://www.nccn.org.
13. Gribben, J.G. and S. O'Brien, *Update on therapy of chronic lymphocytic leukemia.* Journal of Clinical Oncology, 2011. **29**(5): p. 544-550.
14. UpToDate 19.3. *Staging and prognosis of chronic lymphocytic leukemia*. 2011 [cited 2011 21. November]; Available from: http://www.uptodate.com.
15. U.S. National Institutes of Health. National Cancer Institute. *Chronic lymphocytic leukemia treatment* 2011 [cited 2011 September 22]; Available from: http://www.cancer.gov/cancertopics/pdq/treatment/CLL/HealthProfessional/page1.
16. Antonia, S.J., M. Extermann, and R.A. Flavell, *Immunologic nonresponsiveness to tumors.* Crit Rev Oncog, 1998. **9**(1): p. 35-41.
17. Eichhorst, B.F., et al., *First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients*

with advanced chronic lymphocytic leukemia. Blood, 2009. **114**(16): p. 3382-3391.

18. UpToDate 19.3. *Treatment of relapsed or refractory chronic lymphocytic leukemia.* 2011 [cited 2011 24. August]; Available from: http://www.uptodate.com.
19. FDA - U.S. Food and Drug Administration. *Rituxan - Label and Approval History.* 2011 [cited 2011 22. August]; Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory.
20. Arzneispezialitäten und Wirkstoffe. *ami-Arzneimittelinformation.* 2009 [cited 2011 September 10]; Available from: www.ami-info.at.
21. Hallek, M., et al., *Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial.* Lancet, 2010. **376**(9747): p. 1164-74.
22. Eichhorst, B.F., et al., *Health related quality of life (HRQOL) in patients receiving chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) or fludarabine and cyclophosphamide (FC) for first line therapy with advanced chronic lymphocytic leukemia (CLL).* Blood, 2009. **114**(22): p. Abstract No 3438.
23. Robak, T., et al., *Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2010. **28**(10): p. 1756-65.
24. Reynolds, C., et al., *Phase III Trial of Fludarabine, Cyclophosphamide, and Rituximab Vs. Pentostatin, Cyclophosphamide, and Rituximab in B-Cell Chronic Lymphocytic Leukemia.* Blood (ASH Annual Meeting Abstracts), 2008. **112**: p. Abstract No. 327.
25. Hillmen, P., et al., *A randomized phase II trial of fludarabine, cyclophosphamide and mitoxantrone (FCM) with or without rituximab in previously treated chronic lymphocytic leukaemia.* British Journal of Haematology, 2011. **152**(5): p. 570-8.
26. Remi, L., et al., *CLL2007FMP, a phase III randomized multicentric trial of the french cooperative group on CLL and WM (FCGCLL/MW) and the "groupe ouest-est d'etudes des leucemies aigues et autres maladies du sang" (GOELAMS): immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) yields a significantly better response than fludarabine (F), cyclophosphamide (C) and MabCampath (Cam) (FCCam) in previously untreated b-chronic lymphocytic leukemia patients as evaluated by a sensitive 6 color flow cytometry MRD* Blood (ASH Annual Meeting Abstracts), 2010. **116**: p. Abstract No. 698.
27. Warmuth, M., *Rituximab (Rituxan/MabThera) for the first- and second-line treatment of chronic lymphocytic leukaemia (Structured abstract)*, in *Vienna: Ludwig Boltzmann Institut fuer Health Technology Assessment (LBI-HTA).* 2009, Ludwig Boltzmann Institut fuer Health Technology Assessment (LBI-HTA).
28. Extermann, M., et al., *Comorbidity and functional status are independent in older cancer patients.* J Clin Oncol, 1998. **16**(4): p. 1582-7.

29. National Institute for Health and Clinical Excellence, *Rituximab for the first-line treatment of chronic lymphocytic leukaemia*. 2009, London: National Institute for Health and Clinical Excellence (NICE).
30. European Medicines Agency, *Annex I - Summary of Product Characteristics*. 2011.
31. National Institute for Health and Clinical Excellence, *Rituximab for the treatment of relapsed or refractory chronic lymphocytic leukaemia*. 2010, NICE.
32. ClinicalTrials.gov. 2011 [cited 2011 24. August]; Available from: http//www.clinicaltrials.gov.