ERASMUS UNIVERSITEIT ROTTERDAM

iMTA

Report ZonMw

Rituximab – Follicular lymphoma

H.M. Blommestein[1], D.E. Issa[2], P.C. Huijgens[2], C.A. Uyl-de Groot[1]

[1] Institute for Medical Technology Assessment, Erasmus University, Rotterdam
[2] VU medical center, Amsterdam

Samenvatting rituximab bij folliculair lymfoom

Folliculair lymfoom (FL) is een subtype van non-hodgkin lymfoom (NHL). De incidentie in 2008 van FL in Nederland werd geschat tussen de 668 en 1003 patiënten. Patiënten met FL worden frequent behandeld met chemotherapie. Rituximab is geregistreerd in combinatie met chemotherapiekuren voor FL. In dit rapport is de farmacotherapeutische waarde van rituximab in combinatie met chemotherapie beschreven. Systematische zoekopdrachten in Pubmed en Embase leverde 6 artikelen op over de effectiviteit. Uit deze artikelen kon geconcludeerd worden dat de toevoeging van rituximab de overleving en response significant verbeterde. Rituximab kan relatief veilig aan chemotherapie worden toegevoegd. Momenteel lopen er nog studies naar de effectiviteit van rituximab bij oudere FL patiënten, de combinatie met interferon en ideale toedieningwijze.

Indien iedere nieuw gediagnosticeerde FL patiënt behandeld zou worden met 6-8x rituximab zou dit tussen de € 7.224.180 en € 14.547.512 extra kosten (exclusief de kosten voor het toedienen). Onderzoek naar de kwaliteit van leven (6 publicaties) laat zien dat rituximab niet alleen de levensduur verlengt, maar dat de gewonnen levensjaren over het algemeen van hoge kwaliteit zijn. De kosten per QALY (gebaseerd op 7 publicaties) variëren van € 2.661 tot € 49.465 afhankelijk van het type chemotherapie en de assumpties over tijdshorizon, perspectief, leeftijd etc.

De informatie over het gebruik van rituximab in de dagelijkse praktijk is op dit niet beschikbaar. Een population based registry (PHAROS) zal in de toekomst duidelijkheid over de effecten en kosten in de dagelijkse praktijk moeten brengen.

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Abbreviations

ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
CCC	comprehensive cancer centres
CHOP	Cyclophosphamide, Doxorubicine, Vincristine and Prednisone
CHVP+I	Cyclophosphamide, Adriamycin, Etoposide and Prednisone + Interferon
CR	Complete response
Cru	Complete response unconfirmed
CVP	Cyclophosphamide, Vincristine and Prednisone
CVZ	College voor zorgverzekeringen, Dutch Health Care Insurance Board
DLBCL	Diffuse large B-cell lymphoma
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
FCM	Fludarabine, Cyclophosphamide and Mitoxantrone
FL	Follicular lymphoma
FLIPI	Follicular Lymphoma International Prognostic
HOVON	stichting Hemato-Oncologie voor Volwassenen Nederland
ICER	Incremental Cost-Effectiveness Ratio
LDH	Lactate dehydrogenase
LYG	Life Years Gained
MCP	Mitoxantrone, Chlorambucil and Prednisone
NCI-CTC scale	National Cancer Institute's Common Toxicity Criteria Scale
NHL	Non-Hodgkin’s lymphoma
NICE	National Institute for Health and Clinical Excellence
NKR	Nederlandse Kankerregistratie
NM	not mentioned
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
QALY	Quality-Adjusted Life Year
RCT	Randomised Clinical Trial
RIVM	Rijksinstituut voor Volksgezondheid en Milieu, National Institute for Public Health and the Environment
SFK	Stichting Farmaceutische Kengetallen, Foundation for Pharmaceutical Statistics
SPC Roche	Summary of Product Characteristics Roche

1. Type of disorder

Non-Hodgkin's lymphoma (NHL) is a heterogenic group of malignancies that occur in lymphatic tissue. Most NHL types, around 90%, originate in B-lymphocytes (Löwenberg et al. 2008). Follicular lymphoma (FL) is a NHL subtype and characterised as a slow-growing cancer where cells tend to grow in a circular pattern in the lymph nodes. FL patients are graded according to the following four Ann-Arbor stages.

Ann-Arbor stages:

Stage I	The cancer is concentrated in one region; usually one lymph node is involved (and the surrounding area).
Stage II	The cancer is located in two regions. Both regions are on one side of the diaphragm.
Stage III	The cancer has spread to both sides of the diaphragm.
Stage IV	Diffuse involvement of one or more extra lymphatic organs with or without nodular involvement.

In 90% of the FL cases the disease has already become an Ann-Arbor stage III or IV at the moment it is diagnosed and 55% of the patients has infiltrated bone marrow (Löwenberg et al. 2008). The main focus of this report is on grade III and IV FL patients.

Prognosis

FL patients are classified in three risk groups (low, intermediate and high) by the Follicular Lymphoma International Prognostic Index (FLIPI) (Löwenberg et al. 2008). This classification is based on five prognostic factors: age (≤60/>60), Ann-Arbor stage (I-II / III-IV), anaemia (no / yes), number of affected lymph glands (0-4 / >4) and serum-LDH level (normal/above normal).

Low risk: 36% of the FL patients can be categorised as low risk and their five year survival is 91%.

Intermediate risk: 37% of the FL patients are in the intermediate group and have a five-year survival of 78%.

High risk: 27% of the FL patients are in the high risk group and their five year survival is 53%.

(Löwenberg et al. 2008).

Epidemiological data

NHL is the largest group of malignancies (40-50%) within the haemato-oncological disorders (Löwenberg et al. 2008). The incidence of NHL in the Netherlands is based on the comprehensive cancer centers (CCC). Three sources were found (Hoeymans et al. 2010, CCC 2010a, CCC 2010b) that reported incidence numbers for 2007 and 2008. While all sources based their incidence numbers on the Dutch cancer registration, the published numbers varied. Of all NHL patients, 20-30% patients are FL patients. Assuming the incidence from the CCC (2010a), the incidence of FL in 2008 would range between 668 and 1,003.

Table 1 Incidence of NHL and FL for 2007 and 2008

		Incidence NHL		Incidence FL 20%		Incidence FL 30%	
Source	Year	2007	2008	2007	2008	2007	2008
Hoeymans et al. 2010		2,760		552		828	
CCC 2010a		3,272	3,342	654	668	982	1,003
CCC 2010b		3,526	3,581	705	716	1,058	1,074

According to the RIVM the NHL prevalence was approximately 17,748 and this would mean the FL prevalence ranged from 3560 to 5340 (Hoeymans et al. 2010, based on CCC).

Treatment of follicular lymphoma and rituximab
The treatment of Ann-Arbor stage III/IV FL patients usually starts with a 'wait-and-see' policy. When treatment is indicated different options are available (Löwenberg et al. 2008);

- Chemotherapy, mono or combination schemes, with different levels of aggression and toxicity levels.
- Autologous stem cell transplantation
- Allogenic stem cell transplantation
- Immunotherapy like interferon,
- Rituximab (frequently combined with chemotherapy) and radio-immunotherapy

Rituximab is a genetically engineered, chimeric murine / human monocloncal antibody that binds to the CD 20 antigen, thereby inducing lysis and apoptosis leading to dell death (CVZ 2006/26078647). The transmembrane antigen, CD20 is a non-glycosylated phosphoprotein that is located on B lymphocytes and expressed on > 95 % of all B cell NHL (SPC Roche 2010).

Rituximab is registered for the following indications in the Netherlands:

- For treatment of patients with stage III-IV follicular lymphoma who are chemo resistant or by whom a second or next relapse occurs after chemotherapy (since 1998).
- For the treatment of previously untreated patients with follicular lymphoma stage III-IV in combination with cyclophosphamide, vincristine and prednisone (CVP) (since 2004).
- Maintenance for patients with relapse of refractory follicular lymphoma who respond to induction therapy (since 2006).
- For the treatment of patients with CD-20 positive diffuse large B-cell lymphoma in combination with cyclophosphamide, doxorubicine, vincristine and prednisone (CHOP) (since 2003)

(CVZ 2006/26078647).

2. Pharmacotherapeutic value

This section describes the pharmacotherapeutic value of rituximab. This includes, in this report, the effectiveness, adverse effects and safety, applicability and the ease of use.

2.1 Effectiveness

Several trials have been conducted in the past years comparing the addition of rituximab to chemotherapy. In 2009 the Cochrane collaboration published a comprehensive systematic review and meta-analysis of indolent and mantle cell lymphoma by Schulz et al. Their study included randomised controlled trials in which patients were randomly assigned to receive R-chemo or chemotherapy alone. Electronic databases such as the Cochrane Controlled Trial Register, MEDLINE, EMBASE, Lilac and Internet databases of on-going trials were searched according to the strategy of Dickersin (1994) to identify relevant randomised controlled trials published between 1990 and 2005. In addition, hand searches were performed of conference proceedings of the American Society of Hematology, American Society of Clinical Oncology and European Society of Medical Oncology. Five randomised controlled trials among FL patients were included in the meta-analysis:

- Forstpointner 2004
- Herold 2004
- Hiddeman 2005
- Marcus 2005
- Van Oers 2006

The meta-analysis was based on a fixed effect model. Relative risk ratios were estimated for response rates and hazard ratios for disease control and overall survival.

Results:
Subgroup analysis focusing on 1480 FL patients indicated in the R-chemo group statistically significant better overall survival, disease control and response rates.
Overall Survival: Hazard ratio 0.63 [95% CI: 0.51 - 0.79]
Disease control: Hazard ratio 0.58 95% CI: 0.50 – 0.68]
Overall response rate: Risk ratio 1.19 [95% CI: 1.13 – 1.24]
Complete response rate: Risk ratio 2.16 [95% CI: 1.77 – 2.63]

Conclusions:
The review of Schulz et al. demonstrated improved overall response, complete response, disease control and overall survival for FL patients treated with R-chemo compared with chemotherapy alone.

Effectiveness - Method

The review of Schulz et al. (2009) was taken as a starting point. The literature research of the Cochrane review covered the period from 1990 to December 2005. These results were complemented with an additional systematic search from 2005 to 2010 (October). With a systematic literature search we tried to identify randomised controlled trials which investigated the effectiveness of adding rituximab to chemo schemes in the treatment of FL (Annex I). The electronic databases PubMed and Embase were searched. The in- and exclusion criteria were obtained from Schulz et al. (2009) (Annex II).

Effectiveness - results

The search resulted in 6 articles that met the criteria. The in- and exclusion process is described in Annex III. Five of these articles were already included in the review of Schulz et al. (2009). However, full text or longer follow-up of the studies were available. The article of Salles et al. (2008) was not included in the review of Schulz et al (2009).

The Cochrane and additional literature search resulted in six studies that compared the addition of rituximab to chemo schemes. This section describes first the characteristics of the included studies followed by the effectiveness results of rituximab.

Study characteristics

The characteristics of the six trials are described by Table 2. In the first two columns the total number of patients and the number of FL patients are described. Forstpointner et al. (2004) and Herold et al. (2007) studied a large group of NHL patients and performed separate analysis on FL patients. The other four studies were specifically designed for FL patients.
The following columns of Table 2 describe the chemo regimens and the number of patients in both arms. The chemo schemes include FCM (fludarabine, cyclophosphamide and mitoxantrone), MCP (mitoxantrone, chlorambucil and prednisone), CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), CVP (cyclophosphamide, vincristine and prednisone), and CHVP+I (cyclophosphamide, adriamycin, etoposide, prednisone and interferon). Since all

studies were randomised controlled trials, the distribution between both arms is equal. The following columns describe the Ann-Arbor stage of the included patients. The study of Salles et al. (2008) is the only study that also included patients with an Ann-Arbor stage II. Although the focus of this review is on stage III and IV, the study of Salles et al. (2008) is included because the percentage of High FLIPI risk patients is comparable to the other included studies. The percentage of patients in the High FLIPI risk was available for all studies except for the study of Forstpointer et al. (2004). Since this risk qualification was introduced in 2004 the score was often assigned retrospectively based on the recorded patient characteristics. Of the included studies, at least 37% of the patients belonged to the high risk category. The patients from the high risk group have a substantial lower 5 year overall survival. The last column of Table 2 shows the median observation which was at least eighteen months. Salles et al. (2008) report the outcome measures after 18 and 60 months. Both results are included in the tables of this paragraph.

Table 2 Characteristics of the included studies

Author	Total (N)	FL (N)	Therapy (R+chemo) Nr. of patients	Therapy (chemo) Nr. of patients	Ann-Arbor stage	High FLIPI risk	Median observation months
Forstpointner et al. 2004	128	65	4x R-FCM N=35	4x FCM N=30	III/IV	NA	18
Hiddemann et al. 2005	428	428	6-8x R-CHOP N=223	6-8x CHOP N=205	III/IV	45%	36
van Oers et al. 2006	465	465	8x R-CHOP N=234	8x CHOP N=231	III/IV	37%	39
Herold et al. 2007	358	201	8x R-MCP N=105	8x MCP N=96	III/IV	56%	36
Marcus et al. 2008	321	321	8x R-CVP N=162	8x VCP N=159	III/IV	45%	18
Salles et al. 2008*	358	358	6x R + 6x CHVP-I N=175	12x CHVP-I N=183	II/III/IV	46%	18/60

* Pathologic review of 344 cases, 4 diagnoses of FL could not be confirmed, 12 cases non FL

Effectiveness of rituximab

The overall response rate (ORR), complete response rate (CR) and overall survival (OS) between the chemo and R-chemo schemes from the included studies are described in Table 3.

Overall Response Rate

The ORR consists of the patients with a CR and partial response (PR). Five of the included studies (Forstpointner et al (2004), Hiddeman et al (2005), Van Oers et al. (2006), Herold et al. (2007), Marcus et al. (2008)) measured a statistical significant difference ($p<0.05$) between the ORR in the chemo and the R-chemo group. Forstpointner et al. (2004) showed an ORR of 70% among the patients who received regular chemo while 94% of the patients obtained a response in the group with rituximab. Hiddeman et al. (2005) show large ORR percentage in both groups; 90% and 96% in the chemo and R-chemo group respectively. Van Oers et al. (2006) demonstrated an ORR of 72.3% for patients who were treated with only chemotherapy compared to 85.1% for patients who received rituximab. Herold et al. (2007) presented quite a substantial difference between the ORR of the group without rituximab (75%) and the patients who received R-chemo (92%). The difference between both groups was even larger in the study of Marcus et al. (2008) where the chemo group reached an ORR of 57% compared to 81% of the R-chemo group. Together with the study of Forstpointner et al. (2004), they showed the largest difference between the two groups in absolute percentages. Salles et al. (2008) show

72% ORR among the patients who did not receive rituximab and 81% in the group of patients who were treated with rituximab.

Complete response
A CR is the best response patients can achieve (Annex IV). The studies of Marcus et al. (2008) and Salles et al. (2008) made a distinction between CR and unconfirmed CR (Cru). For comparability reasons these percentages were summed. Forstpointner et al. (2004) showed CR for 23% of the chemo patients and 40% of the R-chemo patients. Hiddeman et al. (2005) showed a very small difference in CR for the chemo group (17%) and the R-chemo group (20%). A significant difference ($p<0.05$) was observed by Van Oers et al. (2006); 15.6% and 29.5% in the chemo and R-chemo group respectively. Herold et al. (2007), Marcus et al. 2008 and Salles et al. (2008) showed much larger differences; 25% (Chemo) *vs.* 50% (R-chemo), 10% (Chemo) *vs.* 41% (Rchemo), 50% (Chemo) *vs.* 67% (R-chemo) correspondingly. The differences observed in these three studies were significant ($p<0.05$).

Overall Survival
Since the time frames of the OS and the chemo schemes used differed between the studies, we can not compare the percentages. However, the OS for R-chemo is superior in all studies. Forstpointner et al. (2004) described the 2 year OS. Within the Chemo group 70% survived two years compared to 90% in the R-chemo group. Hiddeman et al. (2005) also measured the 2 year OS which was higher in both groups. The OS was 90% in the Chemo group compared to 95% in the R-chemo group. The difference between both groups was significant ($p<0.05$). Van Oers et al (2006) measured the 3 year OS which was 71.9% *vs.* 82.5% in the Chemo and R-chemo group respectively. The study of Herold et al. (2007) measured a significant ($p<0.05$) different 4 year OS, 74% of the patients who did not receive rituximab survived 4 years compared to 87% of the patients who received rituximab. The 4 year OS is also described by Marcus et al. (2008). The 4 year OS was 77% among the chemo patients and 83% among the R-chemo patients. The difference in survival between the groups was significant ($p<0.05$). According to Salles et al. (2008) 79% of the group without rituximab and 84% of the patients who received rituximab survived 5 year.

Table 3 Differences in response (ORR, CR, OS) between the R-chemo and chemo schemes.

Author	ORR		CR		OS	
Therapy	Chemo	R-Chemo	Chemo	R-Chemo	Chemo	R-Chemo
Forstpointner et al. (2004) FCM VS R-FCM	70%	94%*	23%	40%	70% 2 years^	90% 2 years^
Hiddeman et al. (2005) CHOP VS R-CHOP	90%	96%*	17%	20%	90% 2 years^	95%* 2 years^
Van Oers et al. (2006) CHOP VS R-CHOP	72.30%	85.1%*	15.6%	29.5%*	71,9% 3 years	82,5% 3 years
Herold et al. (2007) MCP VS R-MCP	75%	92%*	25%	50%*	74% 4 years	87%* 4years
Marcus et al. (2008) CVP VS R-CVP	57%	81%*	10%	41%*	77% 4 years	83%* 4 years
Salles et al. (2008) (18 months) CHVP-I VS R-CHVP-I	72%	81%	50%	67%*		
Salles et al. (2008) (60 months) CHVP-I VS R-CHVP-I					79% 5 years	84% 5 years

^ Estimated (not reached)
* Difference significant $p<0.05$

Effectiveness – conclusion

All included studies demonstrate the superiority of adding rituximab to chemo schemes for FL patients. According to Table 3, adding rituximab to chemo (significantly) increased the ORR, CR and OS. The included studies were large randomised controlled trials and it can be assumed that the difference between the intervention and control group is caused by the addition of rituximab. Adding rituximab to chemotherapy is a more effective treatment strategy compared to chemotherapy alone.

2.2 Adverse events

The previous section described the higher response rates and better survival for patients who received rituximab. The addition of another pharmaceutical to the chemo scheme might be at the costs of (more) adverse events. The following section describes the adverse events.
First the adverse events and precautions for use reported by Roche (SPC Roche 2010) are described in the following section.

Safety and serious adverse drug reactions reported by Roche (SPC Roche 2010)
The pharmaceutical company that produces rituximab describes a safety profile and investigated the serious adverse drug reactions.
Hypersensitivity to the active substance or to any of the excipients or to murine proteins or active, severe infections are contraindications for prescribing rituximab (SPC Roche 2010).

Precautions for use
Patients with a high tumour burden or with a high number (≥25 x 10^9/l) of circulating malignant cells should be treated with extreme caution. Very close monitoring and reduced rates for the first infusion are advised (SPC Roche 2010).

A safety profile by Roche was described and the most frequent or observed serious adverse drug reactions were:

- Infections and infestations
- Infusion related reactions
- Cardiovascular events

Adverse events - Method
The six studies that were used to describe the response and survival also investigated differences in adverse events (AEs) between the two patient groups. From these studies, three AEs were selected based on the number of studies that reported them and the frequency at which they occur.

Adverse events – Results
First the scale on which toxicities were measured is described. This is followed by a summary of the most important AEs; infections, granulocytopenia and lymphocytopenia.

Adverse event scale
In most articles the *National Cancer Institute's* Common Toxicity Criteria Scale (NCI-CTC) scale was used to categorise the adverse events. Van Oers et al. (2006) did not mention the assessment scale of the adverse events. However, they did report the percentages for grade 3 and 4 AEs. It might be reasonable to assume they also used the NCI-CTC scale since this scale is most common and a similar grading system is used. Table 4 presents the scale of AEs in each study.

Table 4 Measuring adverse events

Author	Adverse Event scale
Forstpointner et al. (2004) FCM *vs.* R-FCM	NCI-CTC scale
Hiddeman et al. 2005 CHOP *vs.* R-CHOP	WHO Toxicity scale
Van Oers et al. 2006 CHOP *vs.* R-CHOP	Not Reported
Herold et al. 2007 MCP *vs.* R-MCP	NCI-CTC scale
Marcus et al. 2008 CVP *vs.* R-CVP	NCI-CTC scale
Salles et al. 2008 (6 months) CHVP-I *vs.* R-CHVP-I	NCI-CTC scale
Salles et al. 2008 (at 18 months) CHVP-I *vs.* R-CHVP-I	NCI-CTC scale

Forstpointner et al. (2004) have conducted a large randomised controlled trial in which they performed a separate analysis for the response of FL patients. However, the separate analysis was not performed for the AEs. The percentages of their study presented in the following graphs are based on a large group of NHL patients (128) of which the FL subtype is a subgroup (65). Hiddeman et al. (2005) and Herold et al. (2007) report the percentage of patients for each of the four grades separately. Forstpointner et al. (2004), Van Oers et al. (2006) and Salles et al. (2008) summed the grade 1 and 2 and the grade 3 and 4 infections. For comparability reasons two categories are made (grade 1+2 and grade 3+4).

Table 5 describes the infections among the patients who did and did not receive rituximab. The first two columns in Table 5 present the grade 1 and 2 infections for the chemo and R-chemo group. The next two columns present the grade 3 and 4 infections for the chemo and R-chemo group. Forstpointner et al. (2004) report almost similar grade 1 and 2 infections in both groups. The patients in the group without rituximab had a 0.3% higher infection rate. In the studies of Hiddeman et al. (2005) and Herold et al. (2007) the opposite was observed. A slightly higher percentage of grade 1 and 2 infections among the patients who received rituximab was observed (4% and 7% difference).

The difference in grade 3 and 4 infections is especially relevant since these infections are more serious. Small differences are observed between the chemo and R-chemo groups. Forstpointner et al. (2004), Hiddeman et al. (2005) and Herold et al. (2007) reported a higher infection rates among the patients who received Chemo (1.8% *vs.* 1.4, 7% *vs.* 5%, 8% *vs.* 7% respectively). Salles et al. (2008 at 6 months) report a higher percentage of infections among the patients who received rituximab after the first 6 months of their study (0% *vs.* 2%). During the additional 12 months that followed they report equal percentages of infections (1% *vs.* 1%).

Table 5 Adverse events: Infection

Author	Infection Grade 1+2		Infection Grade 3+4	
Therapy	Chemo	R-Chemo	Chemo	R-Chemo
Forstpointner et al. (2004) FCM *vs.* R-FCM	6.6%	6.3%	1.8%	1.4%
Hiddeman et al. 2005 CHOP *vs.* R-CHOP	29%	33%	7%	5%
Van Oers et al. 2006 CHOP *vs.* R-CHOP	NR	NR	NR	NR
Herold et al. 2007 MCP *vs.* R-MCP	35%	42%	8%	7%
Marcus et al. 2008 CVP *vs.* R-CVP	NR	NR	NR	NR
Salles et al. 2008 (6 months) CHVP-I *vs.* R-CHVP-I	NR	NR	0%	2%
Salles et al. 2008 (18 months) CHVP-I *vs.* R-CHVP-I	NR	NR	1%	1%

Another adverse event reported by the included studies was granulocytopenia and the percentages are presented by Table 6. Granulocytes are white blood cells that help to fight infections. The grade 1 and 2 granulocytopenia were only reported by Forstpointner et al. (2004) and Hiddeman et al. (2005) (14.3% *vs.*18.7% and 20% *vs.* 19% in the Chemo and R-chemo group). The grade 3 and 4 granulocytopenia were much more common in both the Chemo and R-chemo groups. Small differences between the groups were reported by Forstpointner et al. (2004) (40.6% vs*.* 39.6), and Salles et al. (2008 6 months) (62% *vs.* 59%). In both studies the percentage of

granulocytopenia was higher among the patients who did not receive rituximab. The same was shown by Salles et al. (2008 18 months). They described a statistical difference ($p<0.001$) between the Chemo group (38%) and R-chemo group (6%). Although the percentages between the groups were quite similar after 6 months, during the additional 12 months the grade 3 and 4 granulocytopenia among the rituximab patients seems to have decreased to a much larger extend compared to the Chemo group.

Less favourable results for the R-chemo patients are indicated by the three other studies. In the study of Hiddeman et al. (2005) 53% of the chemo patients had grade 3 or 4 granulocytopenia compared to 63% in the R-chemo group (difference significant $p<0.05$). Van Oers et al. (2006) report 48.2% and 54.7% for the chemo and R-chemo group. Differences between the chemo (14%) and R-chemo (24%) were reported by Marcus et al. (2008). However, this difference was clinically of minor relevance, because no increase in infectious complications was observed.

Table 6 Adverse events: Granulocytopenia

Author	Granulocytopenia Grade 1+2		Granulocytopenia Grade 3+4	
Therapy	Chemo	R-Chemo	Chemo	R-Chemo
Forstpointner et al. (2004) FCM VS R-FCM	14.3%	18.7%	40.6%	39.6%
Hiddeman et al. 2005 CHOP VS R-CHOP	20%	19%	53%	63%*
Van Oers et al. 2006 CHOP VS R-CHOP	NR	NR	48.2%	54.7%
Herold et al. 2007 MCP VS R-MCP	NR	NR	NR	NR
Marcus et al. 2008 CVP VS R-CVP	NR	NR	14%	24%
Salles et al. 2008 (6 months) CHVP-I VS R-CHVP-I	NR	NR	62%	59%
Salles et al. 2008 (18 months) CHVP-I VS R-CHVP-I	NR	NR	38%	6%*

* Difference significant $p<0.05$

The third frequently reported adverse event is lymphocytopenia. Lymphocytes are an important part of the immune system and lymphocytopenia means having an abnormal low level of lymphocytes. The percentages in the different groups were reported by three articles and are presented by Table 7. The grade 1 and 2 lymphocytopenia percentages for the chemo and R-chemo group were 3.9% *vs.* 10.3% (Forstpointner et al. 2004), 28% *vs.* 24% (Hiddeman et al. (2005) and 8% *vs.* 3% (Herold et al. 2007). All three articles reported higher grade 3 and 4 lymphocytopenia percentages in the R-chemo. Forstpointner et al. (2004) reported 39.4% *vs.* 51.2% for the chemo and R-chemo group. The differences between the groups was significant ($p=0.006$). However, the difference was according to the authors clinically irrelevant because the higher percentages were not associated with an increased risk of infectious complication. According to Hiddeman et al. (2005) 61% of the chemo patients had grade 3 or 4 lymphocytopenia compared to 69% in the R-chemo group. In the study of Herold et al. (2007) the percentages were 58% and 72% in the chemo and R-chemo group.

Table 7 Adverse event: Lymphocytopenia

Author	Lymphocytopenia Grade 1+2		Lymphocytopenia Grade 3+4	
Therapy	Chemo	R-Chemo	Chemo	R-Chemo
Forstpointner et al. (2004) FCM VS. R-FCM	3,9%	10,3%	39,4%	51,2%
Hiddeman et al. 2005 CHOP VS. R-CHOP	28%	24%	61%	69%
Van Oers et al. 2006 CHOP VS. R-CHOP	NR	NR	NR	NR
Herold et al. 2007 MCP VS. R-MCP	8%	3%	58%	72%
Marcus et al. 2008 CVP VS. R-CVP	NR	NR	NR	NR
Salles et al. 2008 (6 months) CHVP-I VS. R-CHVP-I	NR	NR	NR	NR
Salles et al. 2008 (18 months) CHVP-I VS. R-CHVP-I	NR	NR	NR	NR

Adverse events – Conclusion

This section first mentioned some contraindications of rituximab followed by three commonly reported adverse events. It can be concluded that treatment with rituximab does not necessarily lead to a higher percentage of serious infections or granulocytopenia. However, the chance of having severe lymphocytopenia increases when rituximab is added to the chemo scheme. Higher lymphocytopenia does not necessarily lead to higher infectious complications. Generally, rituximab can be added to chemo quite safely.

2.3 Applicability

The CVZ (CVZ 2006/26078647) concluded rituximab can be administered to eligible patients taking into account the occurrence of (sometimes very serious) infusion and hypersensitivity reactions and factors influencing the development of these reactions.

2.4 Ease of use

Rituximab is intravenous administrated.

3. Guidelines

Treatment guidelines from the HOVON or Dutch Institute for Healthcare Improvement (CBO) for the treatment of DLBCL patients not included in trials are unavailable. The obtained guidelines from the Haematology department of Erasmus MC (Vademecum Erasmus MC 2008) recommend rituximab in addition to CVP as first line treatment for FL patients with stage III/IV for which a wait and see policy is not recommend (f.e. B-symptoms, PD within 3 months, obstruction or bonemarrow failure, Bulky disease). For frail elderly or R-CVP ineligible patients the recommended treatment is rituximab combined with chlorambucil. Also in the second treatment line of FL patients rituximab is part of the recommended treatments. Rituximab is recommended in combination with fludarabine and cyclophosphamide, and CHOP. If the recidief is within three months after R-chemo, rituximab is no longer advised. In the third treatment line similar combinations are recommended if these provided the patient with a response longer than 6 months. R-CHOP is recommended if a transformation is expected or as a pre-treatment for stem cell transplantation (Vademecum Erasmus MC 2008).

4. Utilisation in daily practice

There is not much information available about the daily practice utilisation of rituximab. Administration usually does not cause many problems and dose reductions do not happen frequently.

5. Costs

In 2007 € 42.6 million was spent on rituximab in the Netherlands and it was one of the three expensive drugs that accounted for more than 50% of the total costs on expensive drugs (SFK 2009). Rituximab is not only prescribed for the treatment of B-cell NHL (FL, DLBCL etc.), it is also used in B-cell leukaemia and rheumatoid arthritis. Rituximab has been admitted to the expensive drug list for all three indications.

Assuming a dosage of 375 milligram per m^2 body surface, the costs of one treatment are on average € 1,813.- (SFK 2009). According to the Z-index of the pharmacotherapeutic compass one vial of 100 milligram is € 257.49 and a vial of 500 milligram €1,287.46. With an average body surface of 1.7 m^2 637.5 mg is required per treatment. According to these estimates, the average costs of one rituximab administration are € 1,802.44.

In the first paragraph of this report the estimated incidence of FL in the Netherlands ranged from 668 to 1003 per year. From the studies of Forstpointner et al (2004), Hiddeman et al (2005), Van Oers et al. (2006), Herold et al. (2007), Marcus et al. (2008) and Salles et al. (2008) it can be concluded that 6 to 8 treatments with rituximab are reasonable. The costs of treating all newly diagnosed FL patients in the Netherlands with 6x rituximab would range from € 7.224.180 to € 10.847.084 (based on the Z-index) and € 7.266.504 to € 10.910.634 (assuming the SFK estimates). Assuming 8x rituximab would lead to cost estimates of € 9.632.239 to € 14.462.779 (Z-index) and € € 9.688.672 to € 14.547.512 (SFK). The estimated costs of treating FL patients with rituximab for the different scenarios are presented by Table 8.

Table 8 Total costs in the Netherlands per year: estimated for different scenarios

	6x rituximab treatment		8x rituximab treatment	
	668 FL patients	1003 FL patients	668 FL patients	1003 FL patients
Z-index: average 1.7m^2, 637.5mg	€ 7.224.180	€ 10.847.084	€ 9.632.239	€ 14.462.779
SFK: € 1813,- per treatment	€ 7.266.504	€ 10.910.634	€ 9.688.672	€ 14.547.512

6. Quality of life

The previous sections described the increased ORR, CR and OS and the adverse events. However, response rates and survival do not necessarily mean a good quality of life. This paragraph will add information about the quality of life of the patients treated with rituximab. QALYs are frequently used to measure the quality of life and one QALY presents one additional life year in perfect health. This section describes the additional QALYs that can be obtained with rituximab treatment.

QALY – Method

We conducted a systematic literature search in PubMed and Embase. The search strategies are reported in Annex V. In addition, the ASCO and ASH conference abstracts were searched.

QALY - Results

The searches resulted in 79 publications. After reading titles and abstracts, five articles and three abstracts remained. The articles of Hornberger et al. (2008), Boland et al. (2009), Dundar et al. (2009) Marcus et al. (2010), Ray et al. 2010) and the abstracts of Lewis et al. (2006), Rubio-Terrés (2008) and Braga et al. (2009) were included.

Olin et al. (2010) did not describe absolute increases in QALYs. They designed a Markov model to evaluate the parameters affecting the choice of early therapy in FL

(previously untreated advanced stage 3/4). Three different treatment strategies were included; R-CHOP, R-Flu (Fludurabine) and R-CVP. From current available data Olin et al. (2010) conclude that R-CHOP followed by RFlu is the optimal treatment. Their results also suggest that regimens associated with a longer progression free survival (PFS) provide a larger number of total QALYs despite the short-term toxicities. PFS has not been reported in the effectiveness section of this review since only two studies reported this measure. Van Oers et al. (2006) (PFS CHOP: 20.2 months, R-CHOP 33.1 months) and Herold et al. (2007) (PFS MCP 28.8 months, R-MCP not reached) reported statistically different ($p<0.001$) PFS in favour of the rituximab groups. A longer PFS leads, according to Olin et al. (2010), to a larger number of QALYs.

Dundar et al. (2009) reported additional QALYs among patients that were treated wirh R-chemo. However, additional QALYs at the patient-level were not reported separately and are not reported in this paragraph.

The six remaining studies all confirm that the addition of rituximab to chemo regimens increases the number of QALYs. The highest incremental QALYs are realised by the MCP, CVP and CHOP schemes. It seems that rituximab is especially increasing the number of QALYs when it is added to these schemes.
The additional QALYs gained by adding rituximab to CHVP-I are relative lower. This is probably caused by the lower number of life years gained. Boland et al. (2009) made a comparison between the QALYs gained in R-CHOP with rituximab maintenance and CHOP with rituximab maintenance. The incremental QALYs were 0.3699 in favour of the R-CHOP>R treatment. The incremental QALYs for the R-CHOP and observation *vs.* CHOP and observation were 0.5368.

Table 9 Incremental QALYs

Incremental QALYs						
Therapy	Lewis 2006	Hornberger 2008	Rubio-Terrés 2008	Braga 2009	Boland 2009	Ray 2010
R-MCP *vs.* MCP			1.129			1.184
R-CVP *vs.* CVP	1.2	0.930	0.795	0.728		0.914
R-CHOP *vs.* CHOP			0.971			0.831
R-CHVP-I *vs.*CHVP-I						0.458
R-CHOP>O *vs.* CHOP>O					0.537	
R-CHOP>R *vs.*CHOP>R					0.370	

QALY – Conclusion
From the results presented in this paragraph it can be concluded that rituximab does not only increases the survival and response rates, these years are generally spent in good health. Adding rituximab to chemo regimens increases the number of QALYs.

7. Cost – effectiveness
Complementary to the effectiveness and QALY searches, literature of the cost-effectiveness was reviewed. This section describes the cost-effectiveness of adding rituximab to chemo regimens in the treatment of FL.

Cost-effectiveness – Method

The recently conducted review on the economics (including treatment costs) of FL patients by Foster et al. (2009) was taken as a starting point. Foster et al. (2009) conducted different searches to identify the primary pharmacoeconomic articles.

Foster et al. (2009) conducted systematic literature searches from October 1998 to October 2008 (Annex IV). Medlineand published abstracts from professional meetings like the American Society of Clinical Oncology (ASCO) and American Society of Hematology (ASH) meetings were searched. In addition, a 'grey' literature search was conducted on the websites of NICE, EORTC and other governmental and organisation-sponsored websites. The systematic literature search of Foster et al. (2009) was repeated and updated until 2010. Due to limited time available the 'grey' literature search was not updated. The websites from NICE and ROCHE, which provided the only two valuable sources for 1998-2008, were searched. This did not lead to any additional studies. The results obtained from Embase during the systematic search for quality of life (Annex V) were also included.

The study of Foster et al. (2009) included twelve studies describing the cost-effectiveness of FL treatment. Seven of the CE studies they found, will not be discussed further since they did not describe treatment with rituximab [1], described treatment with rituximab maintenance [5] or only described the mean costs per disease-free month [1]. Five studies remained:

- Lewis et al. (2006)
- NICE (2006)
- NICE (2007)
- Roche (2006)
- Hornberger et al. (2007)
-

Cost-effectiveness - Results

The updated search in Pubmed from October 2008 until October 2010 resulted in five studies namely, Boland et al. (2009), Dundar et al. (2009), Foster et al. (2009), Hagemeister et al (2010) and Ray et al. (2010). The review of Foster et al. is discussed in the previous paragraph. The articles of Dundar et al. (2009) and Boland et al. (2009) are updates of HTA assessments by NICE (2006,2007) and earlier versions were already included by Foster et al. (2009). From the study of Hagemeister et al. (2010) is only an abstract available and since this does not mention ICERs, their study is excluded from this report.
From the abstract archives of ASCO and ASH meetings seven abstracts were derived. However, none of these were suitable to include in this report because they did not discuss rituximab [6] or because it discussed rituximab maintenance [1]. From Embase, two abstracts were obtained that had not been identified by the other searches (Rubio-Terrés et al. 2008, Braga et al. 2009).

The search from Foster et al. (2009) and the update resulted in seven studies. These studies calculated cost per QALY or life year gained for the additional of rituximab to chemo. Since different chemo regimens and perspectives were used, a comparison between these studies is very difficult. None of the studies were conducted from a Dutch perspective. Lewis et al. (2006), Dundar et al. (2009) and Ray et al. (2010) used a UK perspective, Braga et al. (2009) used the Portugese NHS perspective, Rubio-Terrés et al. (2008) the Spanish NHS perspective and the study of Hornberger et al. (2008) was conducted in the US.

The included studies estimated the additional costs of adding rituximab to chemo and divided these costs by the additional effects. Effects could be life years gained or

QALYs. Table 10 presents the costs per QALY and the costs per life year gained (LYG) for the studies included in our cost-effectiveness review.

R-CVP *vs.* CVP

The costs per QALY in R-CVP compared to CVP were calculated by seven studies. The differences between the estimated ICERs is large and ranges from € 2,661 (Braga et al. 2009) to € 31,785 *undiscounted* (Dundar et al. 2009). The estimate of Braga et al. (2009) € 2,661 is remarkable low compared to the other estimates which is probably due to the fact that Braga et al. (2009) only included direct medical costs and a horizon of 10 years. Dundar et al. (2009) modelled several different scenarios in which the proportion of PFS leading to OS gain varied from 0% to 60% and age from 50 to 75 years. The best (age 50) and worst (0% of PFS leads to OS) case scenarios are included in Table 10.

The studies of Lewis et al. (2006), Hornberger et al. (2008), Braga et al. (2009), Dundar et al (2009) and Ray et al. (2010) were all based on the effectiveness results of Marcus et al. (2005/2008) and all except Dundar et al. (2009) assumed an average age of 53 years old for the FL patients.

Lewis et al. (2006) and Ray et al. (2010) report also relative low costs per QALY. However, Lewis et al. (2006) mention uncertainty around the progression of FL and treatment costs. By using a wide variation in each parameter their ICER did not exceed € 24,743 (£ 21,500). Although this seems to be a maximum, it is close to the estimate of Hornberger et al. (2008) and some of the scenarios of Dundar et al. (2009).

Differences between the ICERs

The large differences between the ICERs seems to be caused by different estimates for the (lifetime) health-service costs for CVP and R-CVP. This could be related to and time horizons of the studies. Different perspectives and horizons cause dissimilar cost estimates. The incremental costs per patient for R-CVP were € 2,661 (Braga et al. (2009), € 9,062 (Ray et al. 2010), € 11,934 (Lewist et al. 2006), compared to € 18,543 (Hornberger et al. (2008). The variation in absolute numbers is even more remarkable; lifetime health-service costs for R-CVP treatment is € 23,416 (Lewis et al. 2006), € 32,893 (Ray et al. 2010), € 74,065 (Hornberger et al. 2008) or € 87,774 (Braga et al 2009) (10 years). The result of Braga et al. (2009) is especially remarkable considering they estimated the costs for 10 years instead of a life time perspective. Since no detailed specification of the costs is provided by Lewis et al. (2006), Braga et al. (2009) and Ray et al. (2010) the differences can not be analysed in further detail.

R-CHOP(>R) *vs.* CHOP(>R)

Rubio-Terrés et al. (2008), Boland et al. (2009) and Ray et al. (2010) calculated the ICERs for CHOP regimens. In the study of Boland et al. (2009) the effect of adding rituximab to a CHOP regimen already including maintenance with rituximab was calculated. They describe discounted and undiscounted ICERs. However, the discounted ICERs should be interpreted carefully since also model modifications have been made[1]. These modifications are probably to a large extent responsible for the large difference between the discounted and undiscounted costs in Table 10.

According to Rubio-Terrés et al. (2008) the costs per QALY for R-CHOP were € 7,855. Ray et al. (2010) obtained effectiveness results from the study of Hiddeman et al. (2005) and present ICERs for CHOP regimens without rituximab maintenance.

[1] Amended discounting logic, increased cost of drug administration; revised calculation of relapsed treatment costs; inclusion of £5000 per patient terminal care costs; replace projected overall and progression-free survival estimated with K-M estimates at 1500 days.

The discounted ICER is € 12,286 and much lower compared to the discounted and modified ICER of Boland et al. (2009) € 49,465. Although the studies might not be comparable it seems that adding rituximab to CHOP leads to much higher costs per QALY when rituximab maintenance is already included.

R-MCP vs. MCP, R-CHVP-I vs. CHVP-I
Rubio-Terrés et al. (2008) estimated the costs per QALY for R-MCP were € 6,092. Ray et al. (2010) obtained effectiveness information from the earlier discussed study of Herold et al. (2007) and Salles et al. (2008) for the MCP and CHVP-I regimens. The ICERs of these schemes are € 8,580 (R-MCP) and € 9,780 (R-CHVP-I) and comparable to the ICERs of Ray et al. (2010) for R-CVP. Both are below the ICERs of CHOP

Cost-effectiveness - Conclusion
The costs per QALY or life year gained were discussed for the addition of rituximab to several chemo schemes. The differences between these ICERs are substantial which might be partly caused by different perspectives and assumptions used for modelling the effects or costs for a life-time period.
A final decision about the cost-effectiveness of adding rituximab to chemo regiments is depended on the threshold. When a threshold of € 25,000 per QALY is assumed, all except the studies of Boland et al. (2009) and the worst case scenario of Dundar et al. (2009), show that the addition of rituximab is acceptable.

Productivity loss
Foster et al. (2009) did not only investigate the CE ratio. They had a broader cost approach and also described productivity loss. Their results were based on a single Canadian study (Cheung et al. 2006). They conducted a survey of 84 patients with FL or other indolent NHL. According to their results, there were substantial productivity losses among patients with systematic therapy. Many patients missed days from work because of the illness (2.1 days in the previous 4 weeks). One third was not able to continue working full-time after their diagnosis. Besides, many patients rely heavily on caregivers (who also missed work).

Table 10 Costs per QALY and life year gained.

Author	Treatment	Discounted costs per QALY	Undiscounted Costs per QALY	Discounted Costs per QALY €	Undiscounted costs per QALY €	Year	LYG	LYG €	Discount rate	Horizon
Lewis et al. 2006	R-CVP *vs.* CVP	£8,290	£8,642	€ 9,540	€ 9,945	2006	£4,714	€ 5,425	3.5%	LT
Hornberger et al. 2008	R-CVP *vs.* CVP	$28,565		€ 20,034		2008	$17,504	€ 12,276	3%	30 (LT)
Rubio-Terrés et al. 2008	R-CVP *vs.* CVP	€ 10,190		€ 10,190		2008*	€ 10,168	€ 10,168	3.5%	10
Dundar et al. 2009	R-CVP *vs.* CVP		£8,577		€ 9,871	2007*			NM	?
Dundar et al. 2009	R-CVP *vs.* CVP		£27,619		€ 31,785	2007*			NM	?
Braga et al. 2009	R-CVP *vs.* CVP	€ 2,661	€ 2,661	€ 2,661		2008	€ 2,407	€ 2,407	5%	10
Ray et al. 2010	R-CVP *vs.* CVP	£8,613		€ 9,912		2008	£ 7473	€ 8,600	3.5%	LT
Rubio-Terrés et al. 2008	R-MCP *vs.* MCP	€ 6,092		€ 6,092		2008*	€ 6,348	€ 6,348	3.5%	10
Ray et al. 2010	R-MCP *vs.* MCP	£7,455		€ 8,580		2008	£ 6,503	€ 7,484	3.5%	LT
Rubio-Terrés et al. 2008	R-CHOP *vs.* CHOP	€ 7,855		€ 7,855		2008*	€ 8,190	€ 8,190	3.5%	10
Ray et al. 2010	R-CHOP *vs.* CHOP	£10,676		€ 12,286		2008	£ 9,294	€ 9,293	3.5%	LT
Boland et al. 2009	R-CHOP>R *vs.* CHOP>R	£42,982^	£16,749	€ 49,465^	€ 19,275	2008*			NM	30 (LT)
Ray et al. 2010	R-CHVP-I *vs.* CHVP-I	£8,498		€ 9,780		2008	£ 7,370	€ 8,482	3.5%	LT

* Year of cost estimates unknown, year of publication
^ Besides discounting also model modifications

Converting rate
£ 1 = € 1.15084
$ 1 = € 0.70135 euro

9. Future research

On the website of Roche three trials (Phase III) are mentioned that study rituximab in the treatment of FL patients. Results are expected in the (near) future.

- A Study of MabThera (rituximab) Alone and in Combination With Roferon-A (interferon) in Patients With Follicular or Other CD20+ Low-Grade (Indolent) Lymphoma (Protocol number ML16865).
- A Study of MabThera (rituximab) in Elderly Patients With Untreated Follicular Non-Hodgkin's's Lymphoma (NHL) (Protocol number ML17638).
- A Study of MabThera (rituximab) Subcutaneous *vs.* MabThera (rituximab) Intravenous in Patients With Follicular Non-Hodgkin's's Lymphoma (Protocol number BO22334).

These studies should provide more information about the combination of rituximab with interferon, the effect among elderly and the optimal route of administration.

10. Gap in current research

Information about the daily practice utilisation and effects of rituximab in the Netherlands is definitely lacking. Currently, only effectiveness results and costs from (international) trials can be obtained. Although randomised controlled trials provide valid information about the effects due to their strictly controlled circumstances. Substantial different results in daily practice may be observed. Daily practice cost-effectiveness information seems a requirement for making informed decisions about for example reimbursement.

11. Filling the gaps

The gap could be chased by having a population based registry which registers the daily practice effects and health care utilisation. For example, the Population HAematological Registry for Observational Studies (PHAROS). This is an observational population based registry for haematological diseases that was created to facilitate outcome research. The registry includes FL patients and aims to monitor dynamics in daily practice, treatment regimes and survival. The big advantage of maintaining a registry that includes all patients for certain malignancies is that treatment combinations can be studied simultaneously and compared to other treatments. Besides, separate research for expensive drugs is no longer necessary. Since all patients are included, sub-analysis can be performed on the effects and costs of patients in different age and risk categories. By applying the same method for the evaluation of different treatment options, the bias caused by different perspectives or time horizons will be eliminated.

References

Boland, A., A. Bagust, J. Hockenhull, H. Davis, P. Chu, and R. Dickson. 2009. Rituximab for the treatment of relapsed or refractory stage III or IV follicular non-hodgkin's lymphoma. *Health Technology Assessment (Winchester, England)* 13 Suppl 2 (Sep): 41-8.

Braga, P., S. Carvalho, M. Gomes, L. Guerra, P. Lucio, H. Marques, F. Negreiro, C. Pereira, C. Silva, and A. Teixeira. 2009. Health outcomes and costs of rituximab in combination with cyclophosphamide, vincristine and prednisolone in the treatment of patients with advanced follicular lymphoma in portugal. *Blood* 114 (22) (2009/11).

CCC 2010 a. NKR document aantal invasieve tumoren bij mannen en vrouwen naar lokalisatie en incidentiejaar. [2010]. Available from http://www.ikcnet.nl/page.php?id=2902&nav_id=114.

CCC 2010 b. NKR cijfers incidentie cijfers. in IKC [database online]. 2010b Available from http://www.ikcnet.nl/cijfers/index.php?taal=nl&frequentiemaat=1&regio=Landelijk&soort_kanker=49&soort_morfologie=&periode=2008%2C2007&inputRegioLandelijk=on&inputRegioMZ=&fInvasief=1&uitkomstmaat=1&periode_input=2008&periode_input=2007&leeftijdsklassen=1.

Cheung, Matthew C., Kevin R. Imrie, Jessica Friedlich, Rena Buckstein, Lisa K. Hicks, Yael Zaretsky, Brigette Hales, Eugenia Piliotis, and Nicole Mittmann. 2006. The potential for lost productivity and daily activity impairment in patients with follicular (FL) and other indolent non-hodgkin's lymphoma (NHL). *ASH Annual Meeting Abstracts* 108 (11) (November 16): 344.

CVZ. 2006. *Farmacotherapeutisch rapport rituximab (mabthera®) bij de indicatie onderhoudsbehandeling van folliculair lymfoom. 26078647 def. versie rituximab (mabthera®).* Diemen: CVZ (Dutch Health Care Insurance Board), .

Dickersin, K., R. Scherer, and C. Lefebvre. 1994. Systematic reviews: Identifying relevant studies for systematic reviews. *BMJ* 309 (6964) (November 12): 1286-91.

Dundar, Y., A. Bagust, J. Hounsome, C. McLeod, A. Boland, H. Davis, T. Walley, and R. Dickson. 2009. Rituximab for the first-line treatment of stage III/IV follicular non-hodgkin's lymphoma. *Health Technology Assessment (Winchester, England)* 13 Suppl 1 (Jun): 23-8.

Forstpointner, R., M. Dreyling, R. Repp, S. Hermann, A. Hanel, B. Metzner, C. Pott, et al. 2004. The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the german low-grade lymphoma study group. *Blood* 104 (10) (Nov 15): 3064-71.

Foster, T., J. D. Miller, M. E. Boye, and M. W. Russell. 2009. Economic burden of follicular non-hodgkin's lymphoma. *PharmacoEconomics* 27 (8): 657-79.

Herold, M., A. Haas, S. Srock, S. Neser, K. H. Al-Ali, A. Neubauer, G. Dolken, et al. 2007. Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone

chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular lymphoma: An east german study group hematology and oncology study. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 25 (15) (May 20): 1986-92.

Hiddemann, W., M. Kneba, M. Dreyling, N. Schmitz, E. Lengfelder, R. Schmits, M. Reiser, et al. 2005. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: Results of a prospective randomized study of the german low-grade lymphoma study group. *Blood* 106 (12) (Dec 1): 3725-32.

Hoeymans, N., J. M. Melse, and C. G. Schoemaker. 2010. *Gezondheid en determinanten. deelrapport van de VTV 2010 van gezond naar beter.* Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu, .

Hornberger, J., C. Reyes, D. Lubeck, and N. Valente. 2008. Economic evaluation of rituximab plus cyclophosphamide, vincristine and prednisolone for advanced follicular lymphoma. *Leukemia & Lymphoma* 49 (2) (Feb): 227-36.

Lewis, G., R. E. Marcus, S. J. Proctor, M. Gyldmark, J. Creeden, R. Aultman, and F. Jost. 2006. The cost-effectiveness of rituximab, cyclophosphamide, vincristine and prednisolone (RCVP) compared with CVP for the treatment of follicular non-hodgkin's lymphoma (NHL) in the UK. Abstract. *Blood (ASH Annual Meeting Abstracts)* 108, no. Abstract 345:.

Löwenberg, B., G. J. Ossenkoppele, T. de Witte, and M. Boogaerts. 2008. *Handboek hematologie*. Utrecht: De Tijdstroom.

Marcus, R., K. Imrie, A. Belch, D. Cunningham, E. Flores, J. Catalano, P. Solal-Celigny, et al. 2005. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. *Blood* 105 (4) (Feb 15): 1417-23.

Marcus, R., K. Imrie, P. Solal-Celigny, J. V. Catalano, A. Dmoszynska, J. C. Raposo, F. C. Offner, et al. 2008. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology* 26 (28) (Oct 1): 4579-86.

Ray, J. A., E. Carr, G. Lewis, and R. Marcus. 2010. An evaluation of the cost-effectiveness of rituximab in combination with chemotherapy for the first-line treatment of follicular non-hodgkin's lymphoma in the UK. *Value in Health* 13 (4) (/): 346-57.

Rubio-Terrés, C., J. Gómez-Codina, E. Ríos Herranz, A. J. Castro, C. Varela, and J. A. Ray. 2008. PHARMACOECONOMIC ANALYSIS OFTHE ADDITION OF RITUXIMAB TO FIRST-LINE CHEMOTHERAPY TREATMENT REGIMENS IN SPANISH PATIENTS WITH ADVANCED FOLLICULAR LYMPHOMA. Abstract. *Value in Health* 11, A362.

Salles, G., N. Mounier, S. De Guibert, F. Morschhauser, C. Doyen, J. -F Rossi, C. Haioun, et al. 2008. Rituximab combined with chemotherapy and interferon in follicular lymphoma patients: Results of the GELA-GOELAMS FL2000 study. *Blood* 112 (13) (2008/12): 4824-31.

Schulz, Holger, Julia Bohlius, Nicole Skoetz, Sven Trelle, Thilo Kober, Marcel Reiser, Martin Dreyling, et al. 2009. *Chemotherapy plus rituximab versus chemotherapy alone for B-cell non-hodgkin's lymphoma.* Ltd: Cochrane Database of Systematic Reviews John Wiley & Sons, CD003805.

SFK. 2009. *Monitor dure geneesmiddelen. kosten van dure- en weesgeneesmiddelen in het ziekenhuis.* Den Haag: Stichting Farmaceutische Kengetallen, mei 2009, .

Sonneveld, P., B. Löwenberg, J. J. Cornelissen, J. Doorduijn, I. De Greef, F. Leebeek, and et al. 2008. *Vademecum hematologie ErasmusMC*. Rotterdam: Erasmus MC.

SPC Roche. Summary of product characteristics. mabthera 100mg and 500mg concentrate for solution for infusion. in The electronic Medicines Compendium (eMC). Datapharm Communications [database online]. Ltd, 201011,2010]. Available from http://www.medicines.org.uk/emc/medicine/2570/SPC/Mabthera+100mg+and+500mg+concentrate+for+solution+for+infusion/.

van Oers, M. H., R. Klasa, R. E. Marcus, M. Wolf, E. Kimby, R. D. Gascoyne, A. Jack, et al. 2006. Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-hodgkin lymphoma in patients both with and without rituximab during induction: Results of a prospective randomized phase 3 intergroup trial. *Blood* 108 (10) (Nov 15): 3295-301.

Annex I Search strategy Pubmed and Embase

Pubmed search strategy:
("Lymphoma, Follicular"[Mesh] AND "rituximab "[Substance Name]) AND "Clinical Trial "[Publication Type] AND ("humans"[MeSH Terms] AND ("2006/01/01"[PDAT] : "2010/08/27"[PDAT]))

Full search
(Follicular Lymphomas OR Lymphomas, Follicular OR Follicular Lymphoma OR Lymphoma, Nodular OR Lymphomas, Nodular OR Nodular Lymphoma OR Nodular Lymphomas OR Giant Follicular Lymphoma OR Lymphoma, Giant Follicular OR Brill-Symmers Disease OR Brill Symmers Disease OR Disease, Brill-Symmers OR Follicular Lymphoma, Giant OR Follicular Lymphomas, Giant OR Giant Follicular Lymphomas OR Lymphomas, Giant Follicular OR Lymphoma, Small Cleaved-Cell, Follicular OR Lymphocytic Lymphoma, Nodular, PoORly-Differentiated OR Lymphoma, Lymphocytic, Nodular, PoORly Differentiated OR Small Follicular Center-Cell Lymphoma OR Small Follicular Center Cell Lymphoma OR Lymphoma, Small Cleaved Cell, Follicular OR Lymphoma, Small Follicular Center-Cell OR Lymphoma, Small Follicular Center Cell OR Lymphoma, Small Lymphoid, Follicular OR Small Cleaved-Cell Lymphoma, Follicular OR Small Cleaved Cell Lymphoma, Follicular OR Lymphocytic Lymphoma, Nodular, PoORly Differentiated OR Lymphoma, Lymphocytic, Nodular, PoORly-Differentiated OR Lymphoma, Large-Cell, Follicular OR Large-Cell Lymphoma, Follicular OR Large Cell Lymphoma, Follicular OR Lymphoma, Follicular Large-Cell OR Lymphoma, Follicular Large Cell OR Lymphoma, Histiocytic, Nodular OR Lymphoma, Large Cell, Follicular OR Histiocytic Lymphoma, Nodular OR Histiocytic Lymphomas, Nodular OR Lymphoma, Nodular Histiocytic OR Lymphomas, Nodular Histiocytic OR Nodular Histiocytic Lymphoma OR Nodular Histiocytic Lymphomas OR Lymphoma, Nodular, Large Follicular Center Cell OR Lymphoma, Nodular, Large Follicular Center-Cell OR Nodular Large Follicular Center-Cell Lymphoma OR Nodular Large Follicular Center Cell Lymphoma OR Follicular Large-Cell Lymphoma OR Follicular Large Cell Lymphoma OR Follicular Large-Cell Lymphomas OR Large-Cell Lymphomas, Follicular OR Lymphomas, Follicular Large-Cell OR Large Lymphoid Lymphoma, Nodular OR Lymphoma, Large Lymphoid, Nodular OR Lymphoma, Follicular, Grade 2 OR Follicular Lymphoma, Grade 2 OR Lymphoma, Follicular, Grade 3 OR Follicular Lymphoma, Grade 3 OR Lymphoma, Mixed-Cell, Follicular OR Lymphoma, Follicular, Mixed Cell OR Lymphoma, Follicular, Small and Large Cleaved-Cell OR Lymphoma, Follicular, Mixed Lymphocytic-Histiocytic OR Mixed-Cell Lymphoma, Follicular OR Mixed Cell Lymphoma, Follicular OR Lymphoma, Follicular, Small and Large Cleaved Cell OR Lymphoma, Nodular, Mixed Lymphocytic Histiocytic OR Lymphoma, Nodular, Mixed Lymphocytic-Histiocytic OR Lymphoma, Nodular, Mixed Small and Large Cell OR Follicular Mixed-Cell Lymphoma OR Follicular Mixed Cell Lymphoma OR Follicular Mixed-Cell Lymphomas OR Lymphoma, Follicular Mixed-Cell OR Lymphomas, Follicular Mixed-Cell OR Mixed-Cell Lymphomas, Follicular OR Lymphoma, Follicular, Mixed Small and Large Lymphoid OR Lymphoma, Follicular, Grade 1 OR Follicular Lymphoma, Grade 1) AND (CD20 antibody, rituximab OR Mabthera OR Roche brand of rituximab OR Rituxan OR Hoffmann-La Roche brand of rituximab OR IDEC brand of rituximab OR Genentech brand of rituximab OR IDEC-C2B8 antibody OR IDEC-C2B8) AND (Clinical Trial, Phase I [PT] OR Clinical Trial, Phase II [PT] OR Clinical Trial, Phase III [PT] OR Clinical Trial, Phase IV [PT] OR Controlled Clinical Trial [PT] OR Multicenter Study [PT] OR Randomized Controlled Trial [PT] AND (Man (Taxonomy) OR Man, Modern OR Modern Man OR Human OR Homo sapiens).

Embase search strategy:
'follicular lymphoma'/exp AND 'rituximab'/exp AND 'survival'/exp AND ([article]/lim OR [article in press]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [review]/lim) AND [humans]/lim AND [english]/lim AND [randomized controlled trial]/lim AND [2006-2011]/py

Annex II

Criteria of Cochrane review (Schulz et al. 2009):

Study requirements
- RCT
- Patients 18 year and older
- Histologically proven indolent lymphoma regardless of stage of disease or previous therapy
- R-chemo was compared with identical chemotherapy alone

Type of publications included
- Full-text
- Abstract publication
- Unpublished data

Type of publications excluded
- Ongoing studies
- Interim analysis
- Quasi-randomised studies
- Patients with 10 or fewer patients per study arm
- Studies on patients with human immunodeficiency (HIV) or primary central nervous system lymphoma

Subgroup analysis to compare treatment arms with a known COA (concealment of allocation) with those with an unreported one.

Type of participants

Inclusion
- All persons older than 18 years with histologically proven indolent lymphoma and mantle cell lymphoma

Exclusion (not about FL)
- Patients with Human Immunodeficiency Virus (HIV)
- Patients with Hepatitis B or C
- Patients with T-cell lymphoma
- Patients with primary central nervous system lymphoma (PCNSL)

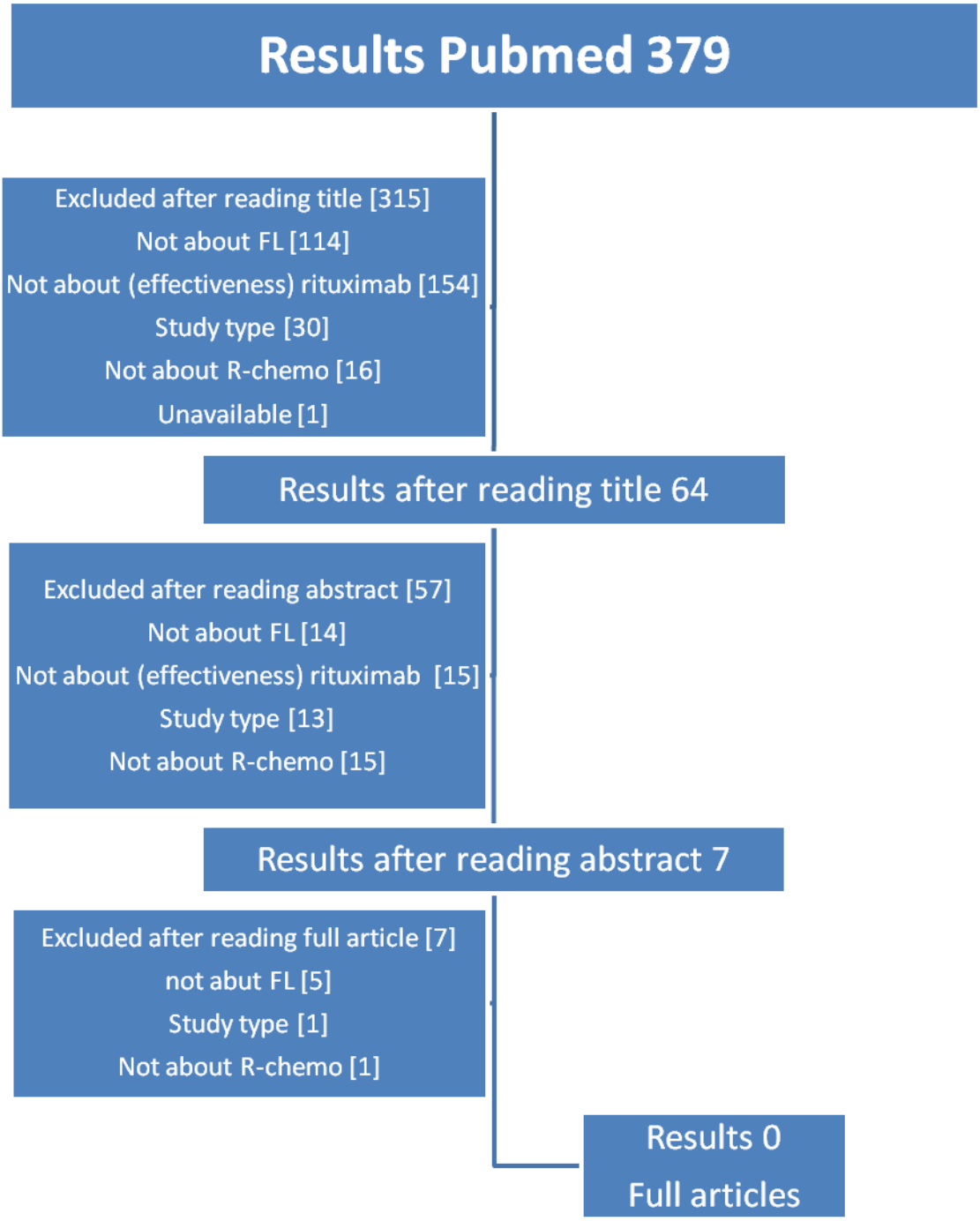
Type of interventions
Administration of combined chemotherapy with or without the monoclonal ant-CD20 antibody (rituximab/Mabthera) to determine whether rituximab improves disease control and overall survival (OS).

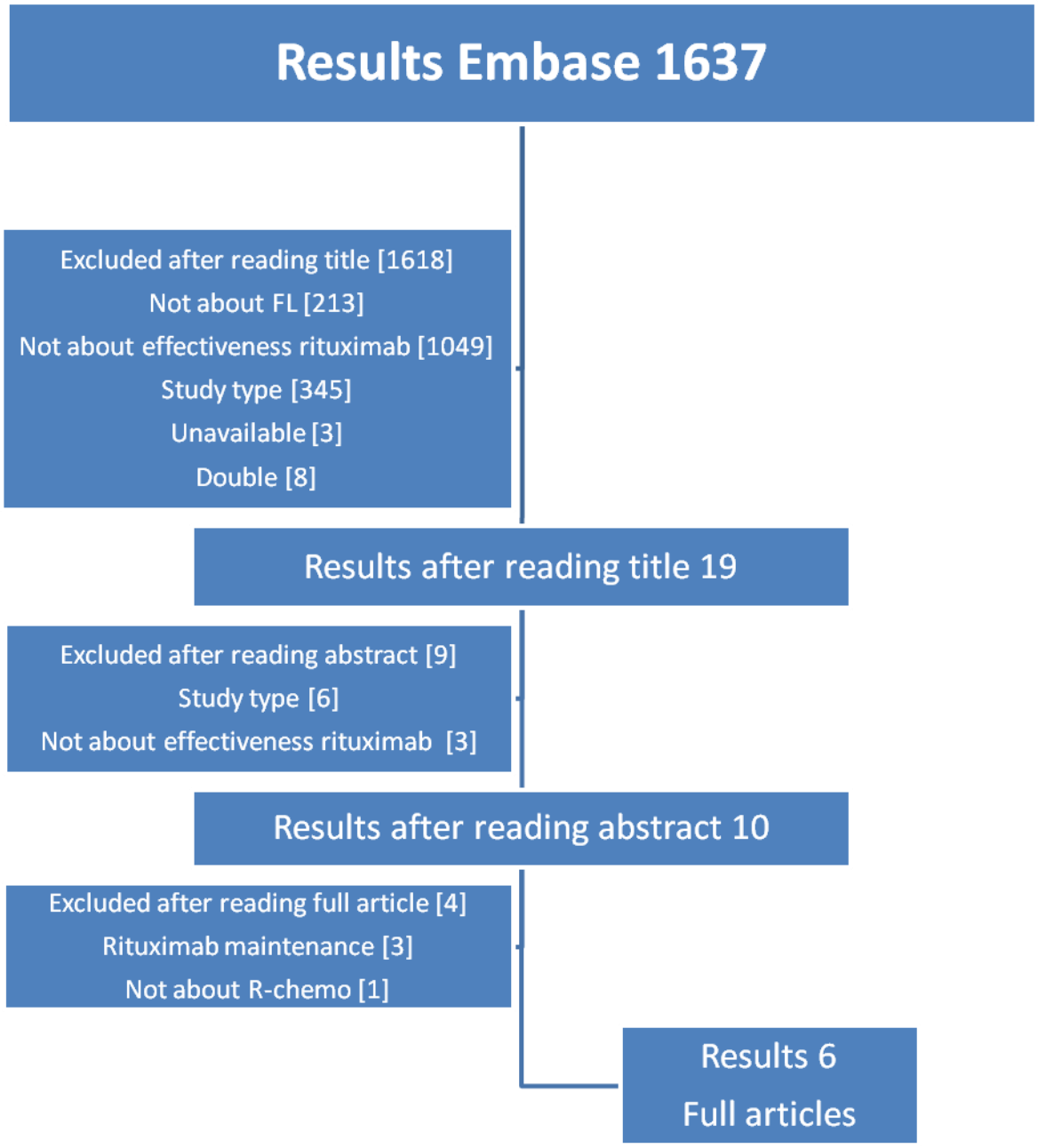
Type of outcome measures

Primary outcomes
- Overall survival (OS)
- Disease control as assessed by time to treatment failure, event free-survival, progression free-survival and time to progression

Secondary outcomes
- Overall response rate (ORR)
- Complete Response (CR) and Partial Response (PR)
- Toxicity

Annex III
In- and exclusion process




Results Embase 1637
Excluded after reading title [1618]
Not about FL [213]
Not about effectiveness rituximab [1049]
Study type [345]
Unavailable [3]
Double [8]
Results after reading title 19
Excluded after reading abstract [9]
Study type [6]
Not about effectiveness rituximab [3]
Results after reading abstract 10
Excluded after reading full article [4]
Rituximab maintenance [3]
Not about R-chemo [1]
Results 6
Full articles

Annex IV

Response criteria

Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to<10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note:the appearance of one or more new lesions is also considered progression).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of non-target lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalisation of tumour marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression (see comments below) of existing non-target lesions. (Note:the appearance of one or more new lesions is also considered progression).

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. 2009. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer (45):228-247.

Annex V

Search strategy Pubmed

("Quality-Adjusted Life Years"[Mesh] AND "rituximab "[Substance Name]) AND "Lymphoma, Follicular"[Mesh]

Search strategy Embase

("Quality-Adjusted Life Years"[Mesh] AND "rituximab "[Substance Name]) AND "Lymphoma, Follicular"[Mesh]

Results Pubmed + Embase 79

Reason	Number of publications	
maintenance	13	
not about QALY	20	
not about FL	7	
not costs	1	
publication type (comment/editorial)	3	
not available	2	
language	2	
not about rituximab	15	
review	9	
not measured at individual level	1	
	73	
Included		
Abstract	2	Rubio-Terrés Braga
Full article	4	Ray Olin Boland Hornberger

Annex VI

Search strategy Foster et al. (2009) Economic Burden of Follicular non-Hodgkin's lymphoma

Search strategy Foster et al. (2009) Pubmed

(follicular OR nodular) AND (non-Hodgkin's) AND (lymphoma [ti]) AND (cost OR cost OR economic* OR pharmacoeconomic* OR utilize* OR expenditure*) NOT PCR NOT 'case reports'[Publication Type].

Full search

(follicular[All Fields] OR nodular[All Fields]) AND non-Hodgkin's[All Fields] AND lymphoma[ti] AND (("economics"[Subheading] OR "economics"[All Fields] OR "cost"[All Fields] OR "costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields]) OR ("economics"[Subheading] OR "economics"[All Fields] OR "cost"[All Fields] OR "costs and cost analysis"[MeSH Terms] OR ("costs"[All Fields] AND "cost"[All Fields] AND "analysis"[All Fields]) OR "costs and cost analysis"[All Fields]) OR (economic[All Fields] OR economic/activity[All Fields] OR economic/administrative[All Fields] OR economic/biophysical[All Fields] OR economic/bureaucratic[All Fields] OR economic/business[All Fields] OR economic/career[All Fields] OR economic/cost[All Fields] OR economic/cultural[All Fields] OR economic/decision[All Fields] OR economic/demographic[All Fields] OR economic/development[All Fields] OR economic/ecological[All Fields] OR economic/educational[All Fields] OR economic/efficient[All Fields] OR economic/environmental[All Fields] OR economic/epidemiological[All Fields] OR economic/family[All Fields] OR economic/family/personal[All Fields] OR economic/financial[All Fields] OR economic/function[All Fields] OR economic/game[All Fields] OR economic/health[All Fields] OR economic/high[All Fields] OR economic/historical[All Fields] OR economic/household[All Fields] OR economic/industrial[All Fields] OR economic/job[All Fields] OR economic/legal[All Fields] OR economic/life[All Fields] OR economic/logistic[All Fields] OR economic/low[All Fields] OR economic/management[All Fields] OR economic/market[All Fields] OR economic/material[All Fields] OR economic/materialistic[All Fields] OR economic/mathematical[All Fields] OR economic/medical[All Fields] OR economic/nutritional[All Fields] OR economic/occupational[All Fields] OR economic/policy[All Fields] OR economic/political[All Fields] OR economic/production[All Fields] OR economic/productive/social[All Fields] OR economic/professional[All Fields] OR economic/psychosocial[All Fields] OR economic/public[All Fields] OR economic/quality[All Fields] OR economic/reimbursement[All Fields] OR economic/relative[All Fields] OR economic/resource[All Fields] OR economic/social[All Fields] OR economic/social/professional[All Fields] OR economic/societal[All Fields] OR economic/sociodemographic[All Fields] OR economic/structural[All Fields] OR economic/systems[All Fields] OR economic/technological[All Fields] OR economic'[All Fields] OR economic's[All Fields] OR economica[All Fields] OR economical[All Fields] OR economical/imaging[All Fields] OR economicall[All Fields] OR economically[All Fields] OR economically/socially[All Fields] OR economically'[All Fields] OR economicallyoriented[All Fields] OR economicalness[All Fields] OR economicaly[All Fields] OR economicamente[All Fields] OR economicas[All Fields] OR economicbranches[All Fields] OR economiccas[All Fields] OR economice[All Fields] OR economiche[All Fields] OR economicheskie[All Fields] OR economicheskii[All Fields] OR economicheskikh[All Fields] OR economici[All Fields] OR economicist[All Fields] OR economicist'[All Fields] OR economicistica[All Fields] OR economicita[All

Fields] OR economicitate[All Fields] OR economicite[All Fields] OR economicity[All Fields] OR economicmicro[All Fields] OR economico[All Fields] OR economicomathematical[All Fields] OR economicos[All Fields] OR economicosociais[All Fields] OR economicosocial[All Fields] OR economicosociales[All Fields] OR economics[All Fields] OR economics/030[All Fields] OR economics/business[All Fields] OR economics/centre[All Fields] OR economics/cost[All Fields] OR economics/department[All Fields] OR economics/economics[All Fields] OR economics/ecotoxicology[All Fields] OR economics/education[All Fields] OR economics/heb[All Fields] OR economics/hero[All Fields] OR economics/history[All Fields] OR economics/manpower[All Fields] OR economics/margaret[All Fields] OR economics/medical[All Fields] OR economics/methods[All Fields] OR economics/nutrition[All Fields] OR economics/outcomes[All Fields] OR economics/public[All Fields] OR economics/standards[All Fields] OR economics/technology[All Fields] OR economics/trends[All Fields] OR economics/utilization[All Fields] OR economics'[All Fields] OR economicsa[All Fields] OR economicscience[All Fields] OR economicum[All Fields] OR economicus[All Fields] OR economicus'rationalism[All Fields]) OR (pharmacoeconomic[All Fields] OR pharmacoeconomic/health[All Fields] OR pharmacoeconomic/pharmacotherapeutic[All Fields] OR pharmacoeconomical[All Fields] OR pharmacoeconomically[All Fields] OR pharmacoeconomics[All Fields]) OR (utilize[All Fields] OR utilize'[All Fields] OR utilized[All Fields] OR utilized/4[All Fields] OR utilized/hour/mg[All Fields] OR utilized/mg[All Fields] OR utilized/min[All Fields] OR utilized/min/mg[All Fields] OR utilized/mol[All Fields] OR utilized/nadh[All Fields] OR utilized/number[All Fields] OR utilizedfor[All Fields] OR utilizedin[All Fields] OR utilizees[All Fields] OR utilizeng[All Fields] OR utilizer[All Fields] OR utilizers[All Fields] OR utilizers'[All Fields] OR utilizes[All Fields] OR utilizesfluorescent[All Fields] OR utilizesuperimposed[All Fields] OR utilizeswave[All Fields]) OR (expenditure[All Fields] OR expenditure/1[All Fields] OR expenditure/1,000[All Fields] OR expenditure/1000[All Fields] OR expenditure/24[All Fields] OR expenditure/adult[All Fields] OR expenditure/balance[All Fields] OR expenditure/basal[All Fields] OR expenditure/bcm[All Fields] OR expenditure/bmr[All Fields] OR expenditure/body[All Fields] OR expenditure/burden[All Fields] OR expenditure/cost[All Fields] OR expenditure/day[All Fields] OR expenditure/ddd[All Fields] OR expenditure/ddds[All Fields] OR expenditure/defined[All Fields] OR expenditure/energy[All Fields] OR expenditure/estimated[All Fields] OR expenditure/fat[All Fields] OR expenditure/fuel[All Fields] OR expenditure/g[All Fields] OR expenditure/h[All Fields] OR expenditure/hour[All Fields] OR expenditure/inhabitant[All Fields] OR expenditure/intake[All Fields] OR expenditure/isoprostane[All Fields] OR expenditure/kg[All Fields] OR expenditure/lactate[All Fields] OR expenditure/m2[All Fields] OR expenditure/metabolic[All Fields] OR expenditure/predicted[All Fields] OR expenditure/prescription[All Fields] OR expenditure/requirement[All Fields] OR expenditure/resting[All Fields] OR expenditure/revenue[All Fields] OR expenditure/rmr[All Fields] OR expenditure/sleeping[All Fields] OR expenditure/thermogenesis[All Fields] OR expenditure/utilisation[All Fields] OR expenditure/week[All Fields] OR expenditure/wk[All Fields] OR expenditure/workout[All Fields] OR expenditure'[All Fields] OR expenditure's[All Fields] OR expenditureled[All Fields] OR expenditures[All Fields] OR expenditures/day[All Fields] OR expenditures/ddds[All Fields] OR expenditures/episode[All Fields] OR expenditures/woman[All Fields] OR expenditures'[All Fields])) NOT PCR[All Fields]

Results: 5 articles [4 included, 1 excluded did not mention ICERs]

Search strategy Foster et al. (2009) ASCO meetings

follicular AND (cost OR costs OR economic OR pharmacoeconomic OR expenditure OR expenditures OR resource utilization)

Results: 0 about rituximab