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Mabthera (rituximab): a cost-effective therapy in hematology

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Abstract

Current economic situation makes payers in most countries face dilemmas regarding decisions on financing of health care services, including medicines. The choice of what is essential, necessary and whether it is worth financing from public resources are the questions asked by decision makers. One of the tools that were designed and implemented to assist their choices was health technology assessment. However, designed as a supportive tool often becomes a trap impeding or delaying introduction of innovative technologies into daily clinical practice. The example of rituximab (Mabthera) shows that some innovative technologies can stand up to stringent requirements of technology assessment and threshold and in variety of indications proves to be cost-effective therapeutic option. Hereby presented results of cost-effectiveness analysis for rituximab in the treatment of follicular lymphoma, diffuse large B-cell lymphoma and chronic lymphocytic leukemia confirm that Mabthera brings clinical benefits to patients and is as well cost-effective option for the public payer in Poland.

Keywords: rituximab, lymphoma, DLBCL, CLL, FL, cost-effectiveness

Introduction

Nowadays, due to the worldwide economic crisis, the payer attaches special importance to money allocation in the health care sector. In many countries health technology assessment (HTA) plays an important role in the decision making process of drug reimbursement. In Poland the HTA agency, AHTAPol (Agency for Health Technology Assessment in Poland), was created to support the Minister of Health in the reimbursement decisions. The requirements for the HTA documentation to be fulfilled are described in the AHTAPol HTA guidelines, the latest version dated April 2009. Each new technology has to be proven to be an effective, safe and cost-effective treatment. Additionally the budget impact should be calculated. This applies to all newly introduced drugs and new indications for already used technologies. In 2011 Polish Parliament enacted a new legal act regarding reimbursement procedures, which has been in force since January 2012.

Among other regulations the new Reimbursement Act clearly defines the threshold for cost-effectiveness and cost-utility analysis, which has been set at 3xGDP (Gross Domestic Product) per capita level, taking the mean value for GDP per capita from the last 3 years. For 2012 it has been calculated at 99 543 PLN.

The important implication of such regulation is that there are no exceptions. The threshold remains the same for all technologies, including oncology, rare diseases and orphan drugs. Reviewing the AHTAPol President's Recommendations it seems very rare and unlikely for an innovative oncology/hematology treatment to meet those criteria.

Mabthera (rituximab) a genetically engineered monoclonal antibody has been registered and approved for use in different indications in hematology (non-Hodgkin's lymphoma, NHL; chronic lymphocytic lymphoma, CLL) and in rheumatoid arthritis. It has been used successfully in clinical practice for over a decade and is now a renowned and widely studied drug. The economic aspects and cost-effectiveness of Mabthera use have also been subjects of investigations in many countries. Likewise in other countries, in Poland the use of Mabthera in all registered indications and across wide population of patients was consistently proven to be safe and cost-effective.

Methods

We have reviewed the analyses prepared for Mabthera in the following indications and submitted for the assessment by AHTAPol:

Non-Hodgkin's lymphoma:

-previously untreated patients with stage III-IV follicular lymphoma (FL),

-maintenance treatment of follicular lymphoma patients responding to induction treatment (1st and subsequent lines),

-CD20 positive diffuse large B-cell non-Hodgkin's lymphoma,

Chronic lymphocytic leukemia:

-previously untreated and relapsed/refractory chronic lymphocytic leukemia (1st and 2nd line treatment).

The analyses were performed in line with the AHTAPol guidelines. The cost-effectiveness analyses were preceded by systematic reviews of the literature. Analyses considered Polish clinical treatment practice, standards of care, as well as the adverse events treatment patterns and costs. Data was identified and gathered using a questionnaire filled in by Polish clinical experts from different oncology centers. Corresponding incurred costs were calculated from the Polish public payer (National Health Fund, NHF) perspective. Markov models were used and cost-effectiveness and cost-utility techniques applied to calculate incremental cost-effectiveness and cost-utility ratios. Sensitivity analysis was performed to assess the impact of change in crucial assumptions on the overall results and conclusions.

Results

Follicular lymphoma

Previously untreated patients with stage III-IV follicular lymphoma

The treatment of patients with stage III-IV follicular lymphoma with rituximab in combination with chemotherapy is financed by the public payer in Poland through a therapeutic program. Immumochemotherapy is recommended by Polish and international organizations as an effective and safe treatment of FL patients. The analysis aimed at assessing the clinical efficacy, safety and cost-effectiveness of rituximab administered with chemotherapy CVP (cyclophosphamide, vincristine, prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in the treatment of previously untreated patients diagnosed with stage III-IV follicular lymphoma.

Systematic review of Medline, Cochrane and Embase databases allowed for identification of randomized clinical trials (RCT) directly comparing R-CVP vs. CVP (Marcus 2005, Markus 2008, Markus 2010) and R-CHOP vs. CHOP (Hidemann 2005, Buske 2006) regimens used in the treatment of previously untreated patients diagnosed with stage III-IV follicular lymphoma. Patients received rituximab at 375 mg/m2 day 1 of each 21 day chemotherapy cycle for maximum 6 cycles with CVP and 6-8 cycles with CHOP.

The analysis demonstrated that addition of rituximab to CVP treatment statistically significantly improves: overall survival (OS), time to treatment failure (TTF), median duration of response (RD), median disease free survival (DFS), median time to next lymphoma treatment (TNLT), overall and complete response rate (Tab 1.). The estimated 4-year survival was significantly higher in R-CVP group than in patients receiving CVP alone (83% vs. 77%, p=0.029).The safety profile of R-CVP treatment was favorable. No deaths related to R-CVP were reported. Two patients were withdrawn from the study due to rituximab infusion related reactions. There were no differences between analyzed groups in relation to frequency of infections and neutropenia related sepsis.

Patients receiving rituximab with CHOP regimen had significantly lower risk of experiencing treatment failure, disease progression and disease relapse in comparison to those treated with CHOP alone (Table 2). The overall survival and overall response rates and were also higher in R-CHOP group. The non-hematological adverse events were more frequent with CHOP treatment, however grade 3 and 4 granulocytopenia was observed more often in patients treated with R-CHOP regimen. The probability of disease progression related death was higher in CHOP treated patients.

Clinical analysis demonstrated that rituximab in combination with CVP or CHOP chemotherapy is an effective and safe treatment for previously untreated patients diagnosed with stage III-IV follicular lymphoma. Moreover, long term follow-up data indicate that treatment with rituximab renders positive and durable effects, with favorable safety profile maintained.

Table 1. Results of R-CVP vs. CVP treatment comparison in previously untreated patients diagnosed with stage III-IV follicular lymphoma

End point	R-CVP (N=162)	CVP (N=159)	RR*** (or HR) (95% CI)	NNT*** (or NNH) (95% CI)	P value^
Time to treatment failure (TTF; median, months)	27 (95% CI: 25-37)	7 (95% CI: 6-9)	-	-	<0.0001*
Time to progression (TTP; median, months)	34 (95% CI: 25-37)	15 (95% CI: 12-18)	-	-	<0.0001*
Duration of response (RD; median, months)	38 (95% CI: 28 – not reached)	14 (95% CI: 9-18)	HR: 0.48 (0.36-0.62)	-	<0.0001**
Disease free survival (DFS; median, months)	not reached (95% CI:35 – not reached)	21 (95% CI: 14-38)	-	-	<0.0001*
Time to next lymphoma treatment (TNLT) or death (median, months)	49 (95% CI: 32 – not reached)	12 (95% CI: 10-18)	-	-	<0.0001*
No overall survival- 4-years follow-up (% patients) #	17%***	23%***	0.74 (0.48-1.15)	-	0,029
No overall treatment response ((ORR): CR+CRu+PR; n (%) patients) #	31 (19%)***	69 (43%)***	0.44 (0.31-0.63)	5 (3-7)	<0.0001**
Stable disease- 30 month follow-up (SD; n (%) patients) #	150 (93%)***	126 (79%)***	1.17 (1.07-1.28)	NNH: 7 (5-17)	0.0008
Disease progression- 30 month follow-up (PD; n (%) patients)	17 (11%)	31 (20%)	0.54 (0.31-0.93)	11 (6-86)	0.03
Death (n (%) patients)	31 (19%)	46 (29%)	0.66 (0.44-0.99)	-	0.054***
Quality-adjusted time without symptoms of disease or toxicity (Q-TWiST; months)	50.31	41.97	-	-	<0.001

*** Log-rank test stratified by centre, ** Test X2, *** calculated based on available data, ^ p value from clinical trials (exc. death rate), # positive endpoints (OS, ORR, SD) were converted into negative endpoints in order to standardize conclusions regarding RR for all analysed endpoints.**

Table 2. Results of R-CHOP vs. CHOP treatment comparison in previously untreated patients diagnosed with stage III-IV follicular lymphoma

End point	R-CHOP N=223	CHOP N=205	RR* (95% CI)	NNT* (95% CI)	P value^
Treatment failure (TTF; % patients)	32%	65%	0.52 (0.42-0.63)	3 (2-4)	<0.0001
No disease response to the treatment (RD; % patients)#	34%	65%	0.54 (0.44-0.67)	3 (3-5)	<0.0001
No overall survival (OS; % patients)#	10%	16%	0.61 (0.37-1.02)	-	0.0493
No overall treatment response (ORR; % patients)#	3%	9%	0.36 (0.15-0.84)	18 (9-87)	0.005
No stable disease (SD; % patients)#	98%	95%	1.04 (1.00-1.08)	-	0.081*
Disease progression during therapy (% patients)	1%	3%	0.26 (0.06-1.25)	-	0.14*

*** calculated based on available data, # positive endpoints (OS, ORR, SD, RD) were converted into negative endpoints in order to standardize conclusions regarding RR for all analysed endpoints, ^ p value from clinical trials (exc. stable disease and disease progression during therapy).**

Following confirmation of positive results of treatment with rituximab, cost-effectiveness and cost-utility analysis were performed. Data on clinical practice regarding the therapy of previously untreated patients diagnosed with stage III-IV follicular lymphoma, the therapy of treatment related adverse events and costs were gathered in 5 oncology centers in Poland using a detailed questionnaire. The three state Markov model (disease progression free, disease progression and death) was used to extrapolate clinical efficacy data from clinical trials and to translate experimental efficacy into life years gained (LYG) and quality-adjusted life years (QALY). The public payer's perspective was assumed as most treatment and treatment related costs are covered from public resources. The analysis time horizon was set at 26 years for both efficacy and cost assessment. The utility data were extracted from the Cost-effectiveness Analysis Registry (CEAR). Following costs were calculated and included:

-1st line chemotherapy costs (treatment administration costs and drug costs),

-patients' monitoring and care in disease progression free state,

-patients' monitoring and care in disease progression state,

-treatment related adverse events therapy.

Costs of active substances were retrieved from NHF and Minister of Health (MoH) published price lists. In line with AHTAPol guidelines cost were discounted at 5% and effects at 3.5%. Deterministic and probabilistic sensitivity analyses were performed to test the results from base case analysis.

The analyses results for both R-CVP vs. CVP and R-CHOP vs. CHOP comparisons show that the incremental cost-effectiveness (ICER, 36 189.31 PLN, 35 392.05 PLN respectively) and incremental cost-utility (ICUR, 41 191.65 PLN, 39 949.48 PLN respectively) ratios are far below assumed in the

Poland's cost-effectiveness threshold. Therefore the use of rituximab in combination with CVP or CHOP regimens in the treatment of previously untreated patients diagnosed with stage III-IV follicular lymphoma is a highly cost effective therapeutic option. The sensitivity analysis indicated that results were sensitive to change in the assumed time horizon, however still the calculated ratios remained far below the threshold.

Rituximab as a treatment option for previously untreated patients diagnosed with stage III-IV follicular lymphoma should be considered as highly effective and highly cost-effective from the the public payer's perspective in Poland.

Table 3. Cost-effectiveness and cost-utility analysis results: R-CVP vs. CVP

Parameter		Value
R-CVP	Life year (LY)	9.20520
	Quality-adjusted life year (QALY)	6.536
	Total costs (PLN)	152 419.54
CVP	Life year (LY)	7.68763
	Quality-adjusted life year (QALY)	5.203
	Total costs (PLN)	97 499.66
ICER: cost per LYG		**36 189.31**
ICUR: cost per QALY		**41 191.65**

Table 4. Cost-effectiveness and cost-utility analysis results: R-CHOP vs. CHOP

Parameter		Value
R-CVP	Life year (LY)	10.27610
	Quality-adjusted life year (QALY)	7.502
	Total costs (PLN)	139 445.74
CVP	Life year (LY)	9.09245
	Quality-adjusted life year (QALY)	6.454
	Total costs (PLN)	97 554.12
ICER: cost per LYG		**35 392.05**
ICUR: cost per QALY		**39 949.48**

Maintenance treatment of follicular lymphoma

Maintenance treatment aims at maintaining as long as possible the response achieved with the induction therapy, allowing at the same time postponement of subsequent treatment lines. The ESMO (European Society for Medical Oncology) and NCCN (National Comprehensive Cancer Network) guidelines indicate rituximab maintenance as the most optimal and effective strategy to be implemented after induction in patients with follicular lymphoma. This therapeutic approach can be applied instead of watch and wait strategy and, as clinical trials results show, is regarded as highly effective and safe at the same time. The analysis prepared for rituximab assessed efficacy, safety and cost-effectiveness of maintenance monotherapy, both after 1st and subsequent lines of induction treatment, when administered in follicular lymphoma patients.

Maintenance treatment of follicular lymphoma patients responding to 1st line induction treatment

A systematic review was performed in Medline, Embase and Cochrane databases to identify available data on efficacy and safety of maintenance treatment in patients responding to 1st line induction treatment in comparison to watch and wait strategy. One relevant randomized clinical trial was identified. In PRIMA study (Salles 2010) patients received R-CHOP, R-CVP or R-FCM (rituximab, fludarabine, cyclophosphamide, mitoxantron) as an induction therapy and those who achieved response were randomized to either maintenance with rituximab monotherapy or watch and wait strategy. Rituximab in maintenance phase was administered at 375 mg/m2 every 8 weeks for maximum 12 cycles or until disease progression.

The results showed that administration of rituximab as the maintenance therapy reduces the disease progression risk by 45% in comparison to observation during 36 months of the follow-up. A 3-year progression free survival in the rituximab maintenance group was higher than in observation (74.9% vs. 57.6% respectively). Rituximab administered as maintenance treatment after 1st line induction also reduced risk of next anti-lymphoma treatment by 40% and risk of next chemotherapy by 38% in 36 months of the follow-up. It also statistically significantly improved the complete response and complete unconfirmed response rates at 2 years in patients who achieved partial response after induction treatment and at 36 months follow-up. The risk of death was reduced by 13% in rituximab maintenance group; however the results were not statistically significant.

The results of the PRIMA study indicated that maintenance treatment with rituximab has an acceptable profile with infections and neutropenia grade 3 and 4 more frequent in the rituximab group. The increased frequency of adverse events (infections and neutropenia) in the rituximab group did not translate into the increased risk of death due to adverse events. The overall results of the clinical efficacy and safety analysis indicate that rituximab should be considered as an option for patients who responded to 1st line induction therapy.

The economic evaluation of rituximab maintenance therapy after 1st line induction treatment was prepared from the public payer's perspective assuming 25 year (life-time) time horizon to capture all effects and costs that could appear throughout the whole patient's life. Direct medical costs were assessed based on the data regarding clinical practice of FL treatment and data related to medical resources use gathered in 5 oncology centers in Poland. The following cost categories were identified as important and included in the analysis: cost of drugs and drug administration, treatment-related adverse events costs, lymphoma relapse treatment costs and patient health monitoring costs. Costs were discounted at 5% and effects at 3.5% rate. The four health state Markov model (progression-free 1st line, progression-free subsequent line, progression and death) was used. Sensitivity analysis was performed testing the influence of critical parameters such as utilities values, different costs categories, length of time horizon and patient's body surface.

Mean number of cycles administered was 10.6 (the PRIMA study). Based on those data and assuming 1.81 m2 body surface area total dose of rituximab and drug administration costs were calculated.

Introduction of 1st line rituximab maintenance therapy resulted in gain of 1.4 life years and 1.3 quality adjusted life years compared to observation. The total incremental costs were 60 707 PLN which corresponded to an incremental cost-effectiveness ratio (ICER) of 43 348 PLN and an incremental cost-utility ratio (ICUR) of 47 357 PLN. Both values are below cost-effectiveness threshold assumed by the Polish public payer for cost-effective technologies.

Table 5. Results of clinical analysis: maintenance with rituximab vs. observation in follicular lymphoma patients responding to 1st line induction treatment; ns- not statistically significant

End point		Statistically significant advantage of rituximab maintenance	Statistically significant advantage of observation
		OR/HR (95% CI)	
Progression free survival (PFS)		HR=0.55 (0.44; 0.68)	-
3-year PFS		OR=2.20 (1.68; 2.87) RD=0.17 (0.12; 0.23) NNT=6 (5; 9)	-
Event free survival (EFS)		HR=0.59 (0.48; 0.72)	-
Overall survival (OS)		ns	
Next lymphoma treatment during 36 months follow-up		OR=0.52 (0.39; 0.70); RD=-0.12 (-0.18; -0.07) NNT=9 (6; 15) HR=0.60 (0.47; 0.76)	-
Next chemotherapy during 36 months follow-up		OR=0.56 (0.41; 0.76) RD=-0.09 (-0.14; -0.04) NNT=12 (8; 25) HR=0.62 (0.47; 0.81)	-
Complete response (CR/CRu) in patients who completed maintenance treatment or observation		OR=2.29 (1.77; 2.97) RD=0.19 (0.13; 0.25) NNT=6 (4; 8)	-
Complete response (CR/CRu) during 2 years in patients with partial response after induction		OR=2.56 (1.58; 4.14) RD=0.22 (0.11; 0.33) NNT=5 (4; 10)	-
Disease progression during 36 months follow-up in patients qualified to maintenance treatment or observation		OR=0.47 (0.36; 0.61) RD=-0.17 (-0.22; -0.11) NNT=6 (5; 10)	-
Disease progression risk during 36 months follow-up	**After R-CHOP induction**	HR=0.51 (0.39; 0.65)	-
	After R-CHOP induction	ns	
	After R-FCM induction	ns	
	Patients with CR/CRu after induction	HR=0.57 (0.44; 0.74)	-
	Patients with PR after induction	HR=0.48 (0.32; 0.72)	-
Quality of life	**FACT-G**	ns	
	EORTC QLQ-C30	ns	

Table 6. Cost-effectiveness and cost-utility analyses results: rituximab maintenance vs. observation

	Life years gained [LYG]	Incremental cost [PLN]	ICER [PLN/LYG]
Rituximab vs. observation	1.400	60 707	43 348
	Quality adjusted years gained [QALY]	Incremental cost [PLN]	ICUR [PLN/QALY]
	1.282	60 707	47 357

The results were sensitive to changes in discount rates, utilities values applied to the specific health states, length of time horizon. None of the tested scenarios resulted in values of ICUR and ICER exceeding the 99 543 PLN threshold, providing evidence that the rituximab treatment is cost-effective from the public payer's perspective. The probability of 1st line maintenance therapy with RTX being cost-effective was 100%.

Rituximab 1st line maintenance treatment of follicular lymphoma patients who responded to induction treatment is an effective, safe and highly cost-effective therapeutic option.

The maintenance therapy prolongs patient's life and at the same time improves their quality of life. Therefore, need for a structured financing from public resources of maintenance therapy with rituximab should be recognized, so that the option would be available for Polish lymphoma patients.

Maintenance treatment of follicular lymphoma patients responding to 2nd and subsequent lines induction treatment

Maintenance therapy with rituximab of follicular lymphoma patients responding to 2nd and subsequent lines of induction treatment has already been implemented into the daily clinical practice in Poland and is accepted as effective and safe option for patients who would otherwise be subjected to observation only. The therapy is financed from public resources through the therapeutic program. The analyses were prepared to confirm that the decision to finance this option for follicular lymphoma patients was justified and well-funded.

Systematic review of Medline, Embase and Cochrane databases revealed 2 publications of randomized clinical trials results: EORTC 20981-van Oers 2010 (induction with either R-CHOP or CHOP regimens) and Forstpointner 2006 (induction with R-FCM or FCM). Rituximab in maintenance phase was administered every 3 months for 2 years or until disease relapse at 375 mg/m2 dose in van Oers 2010 and in 2 courses, each consisting of 4 doses of 375 mg/m2/day given for 4 consecutive weeks, given 3 and 9 months after completion of salvage therapy in Forstpointner 2006 trial.

Rituximab administered as maintenance therapy reduced risk of disease progression by 45% in comparison to observation. The disease progression risk reduction was also noted in subgroup analysis in patients treated in induction phases with CHOP or R-CHOP regimen and those who achieved complete or partial response after induction treatment. In patients who received rituximab in maintenance therapy the response duration was significantly longer. There were no differences between compared options regarding 5-year survival, however the results were on the border line of statistical significance, therefore trend in improvement of this parameter could be observed as well.

The results of the clinical efficacy and safety analysis indicate that rituximab administration as the maintenance strategy in patients with follicular lymphoma, who responded to 2nd or subsequent lines of induction treatment is an effective and safe therapeutic option.

Economic analysis assessed the cost-effectiveness of rituximab maintenance therapy based on the results of clinical analysis. Life-time horizon was assumed as effects and costs of the maintenance strategy can be observed throughout whole patient's life. The four health state Markov model was used (progression free- induction, progression free- maintenance, progression, death). Discoun-

ting was performed at 3.5% for effects and 5% for costs (in the sensitivity analysis those were tested according to AHTAPol guidelines at 5% or 0% for both effects and costs and 0% for effects and 5% for costs). The data regarding utilities were derived from the CEAR. Data on clinical practice and resource utilization were gathered in the 5 oncology centers in Poland. Costs were calculated from the perspective of the public payer's and included costs of drugs, drug administration costs (induction and maintenance phase), costs of adverse events treatment, costs disease relapse therapy and patient's health monitoring costs. Sensitivity analysis (one- and multiway) tested changes in various parameters including: utility values, body surface area, administration costs changes, number of treatment cycles induction or maintenance, costs of adverse events therapy, time horizon.

The results showed that administering rituximab in maintenance therapy to patients with follicular lymphoma who responded to 2nd or subsequent line of treatment instead of subjecting them only to observation is not only clinically justified but cost-effective from the public payer's perspective as well. The ICER was 77 113 PLN/LYG and ICUR 92 612 PLN/QALY. Both results fall below the threshold of 99 543 PLN/QALY or LYG. The sensitivity analysis indicated that the base case results are robust and in all tested scenario cost-effectiveness ratios remained below the threshold.

Table 7. Clinical efficacy results: rituximab maintenance vs. observation in follicular lymphoma patients responding to 2nd or subsequent lines of induction treatment

End point		Statistically significant advantage of rituximab maintenance	Statistically significant advantage of observation
		OR/HR (95% CI or p value)	
PFS	Overall	HR=0.55 (p<0.0001)	ns
	After CHOP	HR=0.37 (p<0.001)	ns
	After R-CHOP	HR=0.69 (p=0.043)	ns
	Patients with PR after induction	HR=0.58 (p<0.001)	ns
	Patients with CR after induction	HR=0.48 (p=0.003)	ns
Duration of response (median)		p=0.035	ns

Table 8. Cost-effectiveness and cost-utility analysis results: rituximab maintenance vs. observation in follicular lymphoma patients responding to 2nd or subsequent lines of induction treatment

	Life years gained [LYG]	Incremental cost [PLN]	ICER [PLN/LYG]
Rituximab vs. observation	0.691	53 280	77 113
	Quality adjusted years gained [QALY]	Incremental cost [PLN]	ICUR [PLN/QALY]
	0.575	53 280	92 621

Chronic lymphocytic leukemia

Chronic lymphocytic leukemia 1st line treatment

In patients with low grade chronic lymphocytic leukemia and slow course of the disease administration of chemotherapy can be postponed for years and watch and wait strategy applied instead. However, in some patients (about 1/3 of all cases) CLL has a more aggressive form and patient's condition deteriorates very quickly. In such cases chemotherapy should be indicated as soon as possible. The choice of chemotherapy depends on patient's general health status, age, the disease stage according to Binet or Rai classification and presence of prognostic factors. The treatment aims at achieving complete remission to prolong disease free survival, overall survival and improve quality of life (this is especially important in the older patients). There are several treatment options available; however most clinical recommendations issued by ESMO, NCCN, PUO (Polska Unia Onkologii, Polish Oncology Union) indicate immunochemotherapy with rituximab in combination with fludarabine and cyclophosphamide (R-FC) or chlorambucil monotherapy as the most optimal 1st line treatment in CLL patients. In Poland the use of rituximab in the 1st line treatment of CLL patients is financed from public resources through the catalogue of chemotherapy. The analyses were performed to assess whether the decision to finance this treatment is beneficial for patients and cost-effective from the public payer's perspective.

The systematic review performed within clinical efficacy and safety analysis helped to identify one randomized clinical trial GCLLSG CLL8 (German Chronic Lymphocytic Lymphoma Study Group) comparing the 1st line R-FC treatment with FC alone. The attempts to identify trials directly comparing R-FC vs. chlorambucil failed. Therefore indirect comparison with Bucher method was performed based on the results of GCLLSG and LFR CLL4 trials results; however due to differences in the characteristics of FC regimens used as a common comparator in both trials the results are prone to be burdened with errors.

In the GCLLSG study rituximab was administered on day 1 of each cycle at 375 mg/m2 (cycle 1) and 500 mg/m2 cycles 2-6 with standard dosages of FC regimen. In the 3-year follow up R-FC therapy prolonged progression free survival (in the general population and in subgroups analyzed: Binet stage B, patients with unfavorable prognostic factors, all age groups). Probability of achieving treatment response and complete remission was statistically significantly higher in R-FC group than in patients treated with chemotherapy alone. The overall survival was also significantly longer in patients receiving R-FC than FC (62.5 months vs. 46.8 months). The positive results for R-FC treatment were also confirmed in the subgroup analysis.

Further analysis showed that the addition of rituximab to FC regimen significantly reduces minimal residual disease levels, which can have impact on the prolongation of progression free survival.

The safety analysis indicated that R-FC increases probability of hematologic grade 3 and 4 adverse events occurrence, including neutropenia and leukopenia, although those incidents do not result in the increased probability of death. Moreover, administration of rituximab as an addition to FC regimen does not negatively influence the patient's quality of life. The overall safety profile was assessed as favorable.

Table 9. Clinical efficacy results: R-FC vs. FC in the 1st line treatment of CLL patients

Parameter	Hazard ratio (95%CI)	P value
Progression free survival	HR=0.56 (95%CI: 0.46; 0.69)	p<0.0001
Treatment response	RB=1.13 (95%CI: 1.07; 1.20)	p<0.0001
Complete remission	RB=2.05 (95%CI: 1.66; 2.56)	p<0.0001
Overall survival	HR=0.67 (95%CI: 0.48; 0.92)	p=0.012
Death	RR=0.75 (95%CI: 0.57; 1.01)	p>0.05

Table 10. Cost-effectiveness and cost-utility analysis results: R-FC vs. FC and R-FC vs. chlorambucil monotherapy in previously untreated CLL patients

Parameter	RFC vs. FC	RFC vs. chlorambucyl
Incremental LYG	0.921	1.826
Incremental QALY	0.893	1.779
Incremental costs	51 894.24 PLN	67 782.92 PLN
ICER: cost per LYG (PLN)	56 321.18 PLN	37 121.16 PLN
ICUR: cost per QALY (PLN)	58 080.35 PLN	38 107.03 PLN

The economic analysis was performed from the public payer's perspective for the comparisons of R-FC vs. FC and of R-FC vs. chlorambucil. Data on clinical practice and resources utilization were gathered in 4 oncology and hematology centers in Poland. The Markov model (progression free, progression, death) was used and cost-effectiveness and cost-utility analysis performed. Utility data came from CEAR data base. Only direct medical costs were considered as no other cost categories were identified as important for the payer. The following cost categories were included:

-1st and 2nd line therapy costs (drugs, drug administration, treatment efficacy assessment costs),

-Monitoring patient's health in progression free and progression states,

-Grade 3 and 4 adverse events treatment,

-Allogeneic stem cell transplantation costs,

-Cost of transfusion of 1 unit of blood.

Costs of drugs and procedures valuation were derived from NHF and MoH price lists. The time horizon for the analysis of costs and effects was set at 15 years (median survival of CLL patients is 3 to 10 years depending on disease stage). Discounting was applied according to AHTAPol guideline- 5% for costs and 3.5% for effects. The deterministic analysis testing influence of changes in FC and R-FC treatment costs, adverse events treatment costs, utility values, body surface area, time horizon (5 and 10 years) and discounting rates (0% for effects and costs, 5% for effects and costs, 0% for effects and 5% for costs). A probabilistic analysis was also performed.

The results of the economic analysis once again confirmed the value of rituximab treatment. ICER and ICUR values were for both comparisons (vs. FC and vs. chlorambucil) far below the threshold (56 321.18 PLN/LYG, 58 080.35 PLN/QALY and 37 121.16 PLN/LYG and 38 107.03 PLN/QALY respectively).

Sensitivity analysis results confirmed the cost-effectiveness and cost-utility of R-FC regimen. ICER and ICUR values remained far below the threshold in almost all variants of the analysis (except for the scenario when the time horizon was shortened to 5 years). The cost-effectiveness of R-FC vs. FC and of R-FC vs. chlorambucil were close to 100%.

Both clinical efficacy and economic analysis results confirm that rituximab is a beneficial and cost-effective treatment option for previously untreated CLL patients.

Chronic lymphocytic leukemia 2nd line treatment

Similarly as in previously untreated CLL patients, the 2nd line therapy (for patients with relapsed or refractory CLL) is selected by a physician according to patient's age, health state, lymphoma course and prognostic factors. The treatment aims at this stage at achieving best possible response, progression free survival and prolongation of treatment response duration, without compromising the safety aspects. As the comparators for R-FC scheme FC and bendamustine in monotherapy were selected after reviewing clinical guidelines (ESMO, NCCN). The 2nd line treatment of CLL patients in financed in Poland from public resources through the catalog of chemotherapy. In the systematic

review of Medline, Embase, Cochrane data bases, as well as ASCO (American Society of Clinical Oncology), ESMO and ASH (American Society of Hematology) conference abstract databases, one randomized clinical trial (REACH) directly comparing R-FC to FC treatment in patients with relapse or refractory CLL was identified, supplemented with abstract on quality of life of patients from REACH study presented at ASH conference. No trials directly comparing efficacy or safety of R-FC vs. bendamustine treatment were found, therefor an attempt to find data allowing for indirect comparison was made. However also this search was unsuccessful and the analysis authors concluded that there was no possibility to compare R-FC vs. bendamustine.

In REACH trial patients received rituximab on day 1 of each cycle at 375 mg/m2 in cycle 1 and 500 mg/m2 cycles 2-6. Rituximab was combined with the standard doses of FC chemotherapy. Immunotherapy was more efficacious than the FC scheme regarding progression of free survival, treatment response rate, complete and partial treatment response duration of treatment response and time to next lymphoma treatment.

Table 11. Clinical efficacy: R-FC vs. FC in patients with relapsed or refractory CLL

Parameter	R-FC vs. FC
Progression free survival (months); investigator's assessment	30.6 vs. 20.6; HR=0.65; 95%CI: 0.51; 0.82; p<0.001
Progression free survival (months); Independent Reviewing Committee	27.0 vs. 21.9; HR=0.76; 95%CI: 0.60; 0.96; p=0.0218
Treatment response; complete or partial; investigator's assessment	69.9% vs. 58.0%; RB=1.21; 95%CI: 1.06; 1.37; p=0.0034; NNT=9 (6; 26)
Complete response rate	24.3% vs. 13.0%; RB=1.86; 95%CI: 1.29; 2.69; p<0.001; NNT=9 (6; 21)
Partial treatment response	45,7% vs 44,9%; RB=1,02; 95%CI: 0,84; 1,22; p>0,05
Treatment response; complete or partial; Independent Reviewing Committee	61% vs. 49%; RB=1.24; 95%CI: 1.07; 1.45; p=0.0048; NNT=9 (5; 28)
Complete response rate; Independent Reviewing Committee	9% vs. 3%; RB=3.125; 95%CI: 1.47; 6.70; p=0.0046; NNT=17 (10; 44)
Stable disease	17.0% vs. 22.1%; RR=0.77; 95%CI: 0.55; 1.08; p>0.05
Disease progression	2.5% vs 5.4%; RR=0.47; 95%CI: 0.20; 1.09; p>0.05
Duration of response; months	39.6 vs. 27.7; HR=0.69; 95%CI: 0.50; 0.96; p=0.0252
Median time to next lymphoma treatment; months	Not reached vs. 34.3; HR=0.65; 95%CI: 0.49; 0.86; p=0.0024
Overall survival; months	Not reached vs. 52; HR=0.83; 95%CI: 0.59; 1.17; p=0.2874
Absence of minimal residual disease	43% vs. 31%; RB=1.38; 95%CI: 0.75; 2.64; p>0.05

Regarding a safety profile, there are no statistically significant differences between R-FC and FC groups in relation to probability of adverse events occurrence, including grade 3 and 4 adverse events, hematologic adverse events (neutropenia, thrombocytopenia, granulocytopenia or anemia). Quality of life analysis indicated that R-FC therapy prolongs time without disease manifestation, without increasing the risk of treatment related adverse events.

The economic analysis was prepared to assess the cost-effectiveness of R-FC treatment of patients with relapsed or refractory CLL. The calculations were done from the public payer's perspective with the 15 year time horizon for effects and costs assessment. Only following direct medial costs were considered:

-2nd and 3rd line therapy costs (drugs, drug administration, treatment efficacy assessment costs),

-Monitoring a patient's health in progression free and progression states,

-Grade 3 and 4 adverse events treatment,

-Allogeneic stem cell transplantation costs,

-Cost of transfusion of 1 unit of blood.

The three state Markov model was used and cost-effectiveness and cost-utility techniques applied. Utilities were found in the CEAR data base. Deterministic and probabilistic sensitivity analyses were performed. Discounting was performed (5% for costs and 3.5% for effects).

The R-FC treatment of patients with relapsed or refractory CLL was proven to be cost-effective from the public payer's perspective and moreover highly beneficial for patients. The results of sensitivity analysis provided evidence that conclusions on cost-effectiveness of rituximab treatment were sound and well-based.

Diffuse large B-cell lymphoma treatment

Rituximab in combination with CHOP chemotherapy is regarded as the golden standard of treatment of patients with diffuse large B-cell lymphoma. The R-CHOP regimen is financed from public resources in Poland through therapeutic programme. Immunochemotherapy is deeply set in clinical practice and the analyses were performed to justify the wide use and public financing of rituximab in the treatment of DLBCL patients.

Clinical analysis aimed at assessing the efficacy and safety of immunochemotherapy with rituximab in combination with CHOP regimen vs. CHOP alone in patients with diffuse large B-cell lymphoma. The systematic review covered among other Medline, Embase, Cochrane and CDR data bases and rendered publications on 2 randomized clinical trials for general DLBCL population and DLBCL patients with HIV co-infection. Rituximab was administered at 375 mg/m2 7 and 3 days before cycle 1 and 2 days before cycles 3, 5 and 7 every 21 days with standard dosing of CHOP regimen. Patients who achieved complete remission after four cycles received six cycles in total and those with continued response completed 8 cycles. In the HIV patients rituximab was administered at 375 mg/m2 2 days prior to each CHOP chemotherapy cycle.

Table 12. Cost-effectiveness and cost-utility analysis results: R-FC vs. FC in patients with relapsed or refractory CLL

Parameter	RFC vs. FC
Incremental costs (PLN)	48 772.15
Incremental LYG	0.62
Incremental QALY	0.61
ICER: cost per LYG (PLN)	78 709.13
ICUR: cost per QALY (PLN)	79 920.61

Patients who achieved partial or complete response received 3 monthly maintenance doses of rituximab also at 375 mg/m2.

The results of the analysis demonstrated that treatment with R-CHOP is effective and safe in all patients, regardless of age or potential HIV co-infection. Immunochemotherapy with rituximab prolonged overall survival, progression free survival, time to event and failure free survival, increased probability of complete and complete unconfirmed response. At the same time R-CHOP in comparison to CHOP alone associated with decreased probability of disease relapse, disease progression and disease progression during treatment, death due to lymphoma or an adverse event. The safety profile in general population and in patients with HIV co-infection was favourable. Although R-CHOP therapy was associated with higher risk of cardio toxicity, infusion related complications and shingles, the overall efficacy outweighed potential negative effects of R-CHOP treatment.

The economic analysis was based on the results of clinical efficacy and safety analysis. The cost-effectiveness and cost-utility analyses were performed from the public payer's perspective. All costs and effects were estimated in 30 year horizon (lifetime). The Markov model was applied with progression, progression free and death health states. The utility data were derived from the CEAR base. Patients were split into two subgroups according to age: ≥60 years and ‹60 years. The following costs were identified as crucial from the public payer's perspective and included in the analysis:

-Cost of drugs (1st and 2nd line chemotherapy),

-Drug administration costs,

-Costs of treatment efficacy assessment,

-Patient's health monitoring costs,

-Grade 3 and 4 adverse events treatment costs,

-Cost of autologous stem cell transplantation.

Only direct medical costs were included. Prices of drugs and costs of procedures were drawn from NHF and MoH price lists. Data on resource utilization and clinical practice were determined based on a questionnaire study conducted in the 5 Polish oncology and haematology centres. In line with AHTAPol guidelines costs were discounted by 5% and effects by 3.5% in the base case analysis. Deterministic and probabilistic analyses were performed. Various assumptions were checked for their impact on overall analysis results and conclusions.

Both in the under and over 60-year-old population the administration of R-CHOP instead of CHOP regimen alone allowed for gain in LYGs and QALYs. The incremental costs related to R-CHOP vs. CHOP were counterbalanced with efficacy gain rendering ICERs and ICURs values far below the threshold assumed in Poland.

All tested in sensitivity analysis options resulted in ICERs and ICURs (in both under- and over-60-years groups) far below the threshold, thus confirming efficacy and cost-effectiveness of R-CHOP treatment of patients with DLBCL.

Analyses performed for rituximab in combination with CHOP chemotherapy used in the treatment of DLBCL patients indicate that the position of rituximab as the golden standard is justified and sound. Both clinical and economic data show that administration of immunochemotherapy is beneficial for patients and cost-effective for the Polish public payer.

Table 13. Cost-effectiveness and cost-utility analysis results: R-CHOP vs. CHOP in DLBCL over 60 patients

Parameter	R-CHOP vs. CHOP
Incremental costs (PLN)	50 905.10 PLN
LYG gain	1.696 LYG
QALY gain	1.462 QALY
ICER: cost per LYG (PLN)	30 009.60 PLN/LYG
ICUR: cost per QALY (PLN)	34 818.82 PLN/QALY

Table 14. Cost-effectiveness and cost-utility analysis results: R-CHOP vs. CHOP in DLBCL under 60 patients

Parameter	Porównanie R-CHOP vs CHOP
Incremental costs (PLN)	47 825.94 PLN
LYG gain	2.721 LYG
QALY gain	2.321 QALY
ICER: cost per LYG (PLN)	17 577.27 PLN/LYG
ICUR: cost per QALY (PLN)	20 602.97 PLN/QALY

Discussion

Rituximab has been introduced into the clinical practice several years ago and since then became a standard addition to chemotherapy of patients with FL, DLBCL and CLL. In clinical trials Mabthera has proven its value with significant overall survival, progression free survival, event free survival and overall response time and rates improvement. The treatment with rituximab also allowed for prolongation of time to next lymphoma therapy and had a positive effect on the patient's quality of life. In terms of economic impact, the analyses that were prepared from the public payer's perspective in Poland showed that the clinical benefits are linked with very favorable economic results. In all analyzed indications Mabthera was highly cost-effective and conclusions drawn from these analyses justify financing of this treatment option from public resources. The economic results from Polish analyses were consistent with those published worldwide, where treatment with Mabthera was also proven to be cost-effective from the public payers' perspectives. Independent of health care system in which Mabthera was administered the treatment remained an effective and cost-effective option for the payers and societies (where societal perspective was assumed).

In Portugal analysis conducted for R-CVP vs. CVP treatment in previously untreated FL patients demonstrated that addition of rituximab to CVP regimen is cost-effective from Portuguese National Health System perspective (Braga 2010). Similar findings were published for the UK, where rituximab was added to MCP (mitoxantrone, chlorambucil, prednisolone), CVP, CHOP, and CHVP (cyclophosphamide, etoposide, doxorubicin, prednisolone, interferon alpha) regimens. In all of the analyzed options ICERs far below the threshold assumed for cost-effectiveness in the UK (Ray 2010). In the US were societal perspective was assumed economic analysis results also confirmed that addition of rituximab to chemotherapy is cost-effective in treatment of FL patients (Hornberger 2008). The same conclusions were drawn for maintenance treatment with rituximab after 1st line induction therapy in the Finnish health care system (Soini 2011) and for the maintenance treatment in the management of relapsed or refractory FL patients in French health care setting, where calculated ICERs fell below those observed for other therapies in the oncology (Deconinck 2010). Findings were similar in Sweden (Kasteng 2009).

Published data on cost-effectiveness of 1st line R-FC therapy of CLL patients showed that administration of Mabthera in this indication is cost-effective from a third-party payer and societal perspective in the US (Hornberger 2012). The same conclusions were drawn earlier from analyses conducted in the UK and Spain both for 1st and subsequent lines of CLL patients treatment with R-FC (Main 2010, Dretzke 2010, Casado 2011).

The DLBCL patients' treatment with rituximab also showed very good economic results in many countries. The analysis prepared by Canadian Centre for Applied Research in Cancer Control (ARCC) and British Columbia Cancer Agency confirmed that R-CHOP treatment in DLBCL patients in a cost-effective option for the payer. Similar results were observed in France (Best 2005) and the US where analyses confirmed that R-CHOP regimen is cost-

effective in older patients' population (Hornberger 2005).

The coherent clinical efficacy and safety data with positive economic analyses results place rituximab in a unique position amongst innovative oncology treatments. Regardless of health care or financing systems rituximab proves its value, even when confronted with rigid HTA requirements. Clinicians and payers have at their disposal highly valuable therapeutic option for patients.

Conclusion

Based on available randomized clinical trials results, numerous conference reports and health technology assessment dossiers prepared for Mabthera in treatment of patients with FL (I line and maintenance, II line maintenance), DLBCL and CLL (I and II line) in Poland it has been proven that it is an clinically effective and beneficial for patients and cost-effective for the public payer treatment option.

References:

1. Marcus M., Imrie K., Belch A., Cunningham D., Flores E., et al. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. Blood 2005; 105: 1417-1423.

2. Marcus M., Imrie K., Solal-Celigny P., Catalano J.V., Dmoszyńska A., et al. 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 2008; 26: 4579-4586.

3. Marcus R., Aultman R., Jost F. A quality-adjusted survival analysis (Q-TWiST) of rituximab plus CVP v CVP alone in first-line treatment of advanced follicular non-Hodgkin's lymphoma. British Journal of Cancer 2010; 102: 19-22.

4. Imrie K., Belch A., Pettengell R., Rueda A., McKendrick J., et al. Rituximab plus CVP chemotherapy vs CVP alone as first-line treatment for advanced follicular lymphoma: treatment effect according to baseline prognostic factors. Journal of Clinical Oncology 2005; 23 (Suppl.): 16S. ASCO Annual Meeting Proceedings 2005, abstract: 6525.

5. Imrie K., Belch A., Pettengell R., Rueda A., McKendrick J., et al. CVP plus rituximab compared to CVP alone in previously untreated patients with follicular lymphoma: impact of baseline prognostic factors. http://annonc.oxfordjournals.org/content/16/suppl_5/v105.full.pdf łostatnia aktualizacja: 15. 09. 2010ł. Ann Oncol 2010; Abstract: 249.

6. Marcus R.E., Solal-Celigny P., Imrie K., Catalano J.V., Dmoszyńska A., et al. MabThera (rituximab) plus cyclophosphamide, vincristine and prednisone (CVP) improves survival in previously untreated patients with advanced follicular non-Hodgkin's lymphoma (NHL). Blood 2006; 108: Abstract 481. ASH Annual Meeting Abstracts.

7. Solal-Celigny P., Imrie K., Belch A., Robinson K.S., Cunningham D., et al. MabThera (rituximab) plus CVP chemotherapy for first-line treatment of stage III-IV follicular non-Hodgkin's lymphoma (NHL): confirmed efficacy with longer follow-up. Blood 2005; 106: Abstract 350. ASH Annual Meeting Abstracts.

8. Hidemann W., Kneba M., Dreyling M., Schmitz N., Lengfelder E., et al. 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 2005; 106: 3725-3732.

9. Buske C., Hoster E., Dreyling M., Hasford J., Unterhalt M., et al. The Follicular Lymphoma International Prognostic Index (FLIPI) separates high-risk from intermediate- or low-risk patients with advanced follicular lymphoma treated front-line with rituximab and the combination of cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) with respect to treatment outcome. Blood 2006; 108: 1504-1508.

10. Buske C., Hoster E., Dreyling M., Frostpointer R., Kneba M., et al. Rituximab in combination with CHOP in patients with follicular lymphoma: analysis of treatment outcome of 552 patients treated in a randomized trial of the German Low-Grade Lymphoma Study Group (GLSG) after a follow up of 58 months. Blood 2008; 112: Abstract 2599. ASH Annual Meeting Abstracts.

11. Buske C., Hoster E., Dreyling M., Hasford J., Unterhalt M., et al. The Follicular Lymphoma International Prognostic Index (FLIPI) predicts treatment outcome in patients with advanced stage follicular lymphoma treated front-line with rituximab and the combination of cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP). Blood 2005; 106: Abstract 925. ASH Annual Meeting Abstracts.

12. Buske C., Kneba M., Lengfelder E., Pfreundschuh M., Ludwig W.D., et al. Front-line combined immune-chemotherapy (R-CHOP) significantly improves the time to treatment failure and overall survival in elderly patients with advanced stage follicular lymphoma – results of a prospective randomized study of the German Low-Grade Lymphoma Study Group (GLSG). Blood 2006; 108: Abstract 482. ASH Annual Meeting Abstracts.

13. Buske C., Hoster E., Dreyling M., Frostpointer R., Kneba M., et al. Rituximab overcomes sex as a strong adverse prognostic factor for treatment outcome in patients with follicular lymphoma: analysis of patients treated with rituximab/CHOP or CHOP

in randomized trials of the German Low-Grade Lymphoma Study Group (GLSG). Blood 2009; 114: Abstract 3706. ASH Annual Meeting Abstracts.

14. Salles G.A., Seymour J.F., Feugier P., et al. Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy, Abstract No 8004, Journal of Clinical Oncology 2010, 28:15s (suppl).

15. Salles G.A., Seymour J.F., Offner F. Rituximab maintenance for 2 years in patients with high tumor burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA 2010): a phase 3, randomized controlled trial, opublikowano online 21.12.2010, www.thelancet.com.

16. Forstpointner R., Dreyling M., Rituximab maintenance therapy in follicular lymphoma. Current Hematologic Malignancy Reports 2007, 2(4): 213-218.

17. Forstpointner R., Unterhalt M., Dreyling M., i in., Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG). Blood 2006, Vol 108, No 13: 4003-8.

18. van Oers M.H., Klasa R., Marcus R.E., et al. 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 2006, Vol 108, No 10: 3295-301.

19. van Oers M.H., Van Glabbeke M., Giurgea L., et al. Rituximab maintenance treatment of relapsed/resistant follicular non-Hodgkin's lymphoma: long-term outcome of the EORTC 20981 phase III randomized intergroup study. Journal of Clinical Oncology 2010, Jun 10;28(17): 2853-8.

20. van Oers M.H.J., Hagenbeck A., Van Glabbeke M., et al. Chimeric anti-CD20 monoclonal antibody (Mabthera) in remission induction and maintenance treatment of relapsed follicular non-Hodgkin's lymphoma: A phase III randomized clinical trial - Intergroup Collaborative Study. Annals of Hematology 2002, 81(10): 553-557.

21. Habermann TM., Weller EA., Morrison VA., Rituximab- CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B - cell lymphoma. Journal of Clinical Oncology 2006 24: 19 (3121-3127).

22. Morrison VA., Hong F., Habermann TM., et al. R-CHOP versus (vs) CHOP followed by maintenance rituximab (MR) vs observation in older diffuse large b-cell lymphoma (DLBCL) patients (pts): long-term follow-up of intergroup E4494/C9793 łAbstract No. 589ł. Blood 2010. Volume 116. Issue 21.

23. Habermann T., Weller E., Morrison V., et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large b-cell lymphoma łAbstract No. 225ł. Annals of Oncolog 2005. Volume 16 Suppl. 5. Issue 12. Pages 103.

24. Morrison VA., Weller EA., Habermann TM., et al. Patterns of growth factor (GF) usage and febrile neutropenia (FN) among older patients with diffuse large B-cell lymphoma (DLBCL) treated with CHOP or R-CHOP: an Intergroup experience (CALGB 9793, ECOG-SWOG 4494). Blood 2004. Volume 104. Issue 11. Pages 904a.

25. Habermann TM., Weller E., Morrison VA., et al. Rituximab-CHOP Versus CHOP with or without Maintenance Rituximab in Patients 60 Years of Age or Older with Diffuse Large B-Cell Lymphoma (DLBCL): An Update łabstractł. Blood 2004. Volume 104. Issue 11 Part 1. Pages 40.

26. Habermann TM., Weller EA., Morrison VA., et al. Phase III trial of rituximab-CHOP (R-CHOP) vs CHOP with a second randomization to maintenance rituximab (MR) or observation in patients 60 years of age and older with diffuse large B-cell lymphoma (DLBCL). Blood. Location of Proceedings San Diego, California 2003. Volume 102. Issue 11 (Pt 1). Pages 6a.

27. Winter JN., Weller EA., Horning SJ., et al. Prognostic significance of Bcl-6 protein expression in DLBCL treated with CHOP or R - CHOP: A prospective correlative study. Blood 2006 107:11 (4207-4213).

28. Winter JN., Li S., Aurora V., et al. Expression of p21 protein predicts clinical outcome in DLBCL patients older than 60 years treated with R - CHOP but not CHOP: A prospective ECOG and Southwest Oncology Group correlative study on E4494. Clinical Cancer Research 2010 16: 8 (2435-2442).

29. Winter J., Weller E., Horning S., et al. Rituximab (R) added to chop improves outcome in bcl-6 negative but not in bcl-6 positive DLBCL patients >60 years łAbstract No. 209ł. Annals of Oncology. 2005. Volume 16 Suppl. 5. Issue 12. Pages 98.

30. Coiffier B., Lepage E., Brière J., et al. Chop chemotherapy plus rituximab compared with chop alone in elderly patients with diffuse large - B - cell lymphoma. New England Journal of Medicine 2002 346: 4 (235-242).

31. Feugier P., Van Hoof A., Sebban C., et al. Long-term results of the R - CHOP study in the treatment of elderly patients with diffuse large B - cell lymphoma: A study by the groupe d'etude des lymphomes de l'adulte. Journal of Clinical Oncology 2005 23: 18 (4117-4126).

32. Mounier N., Briere J., Gisselbrecht C., et al. Rituximab plus CHOP (R - CHOP) overcomes bcl-2-associated resistance to chemotherapy in elderly patients with diffuse large B - cell lymphoma (DLBCL). Blood 2003 101: 11 (4279-4284).

33. Maung K., D'Orazio Al. Rituximab plus CHOP is superior

to CHOP alone for aggressive diffuse large B - cell lymphoma: Updated results of a GELA phase III trial. Clinical Lymphoma 2001 2: 2 (74-79).

34. D'Orazio AI. Rituximab plus CHOP is superior to CHOP alone for aggressive diffuse large B - cell lymphoma: Interim results of a GELA phase III trial. Clinical Lymphoma 2001 1: 4 (257-258).

35. Coiffier B., Thieblemont C., Van Den Neste E., et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood. 2010 Sep 23; 116 (12): 2040-5.

36. Coiffier B., Feugier P., Bouabdallah R., et al. Long-term results of the Gela study comparing R-CHOP and CHOP chemotherapy in older patients with diffuse large B-Cell Lymphoma show a long term benefit for the adjunction of Rituximab to CHOP łAbstract No. 0407ł. Haematologica, the hematology journal: abstract book 2007. Volume 92. Issue Suppl 1. Pages 150.

37. Coiffier B., Feugier P., Mounier N., et al. Long-term results of the GELA study comparing R-CHOP and CHOP chemotherapy in older patients with diffuse large B-cell lymphoma show good survival in poor-risk patients łabstractł. Source Journal of Clinical Oncology: ASCO annual meeting proceedings. Date of Publication 2007; Volume 25. Issue 18S Part I. Pages 443.

38. Mounier N., Briere J., Gisselbrecht C., et al. Estimating the impact of rituximab on bcl-2-associated resistance to CHOP in elderly patients with diffuse large B-cell lymphoma. Haematologica. 2006 May; 91 (5): 715-6.

39. Bienvenu J, Chvetzoff R, Salles G, et al. Tumor necrosis factor alpha release is a major biological event associated with rituximab treatment. Hematol J. 2001; 2 (6): 378-84.

40. Mounier N., Gisselbrecht C., Gaulard P., et al. Rituximab plus CHOP (R-CHOP) in the treatment of elderly patients with diffuse large B-cell lymphoma (DLBCL) overcomes Bcl-2 associated chemotherapy resistance. Blood Location of Proceedings Philadelphia, Pennsylvania. Date of Publication 2002. Volume 100. Issue 11/2. Pages 161a.

41. Coiffier B., Lepage E., Gaulard P., et al. Prognostic Factors Affecting the Efficacy of Rituximab Plus CHOP (R-CHOP) Therapy in Elderly Patients with Diffuse Large B-Cell Lymphoma (DLCL): Results of a Randomized GELA Trial. Proc Am Soc Clin Oncol 20: 2001 (abstr 1131).

42. Coiffier B., Bienve-Chvetzoff J., Tilly H. Laboratory changes associated with rituximab treatment: a prospective study in diffuse large B-cell lymphoma (DLCL) patients randomized between CHOP and CHOP plus rituximab. A GELA study. Blood Location of Proceedings San Francisco, California. Date of Publication 2000. Volume 96. Issue 11. Pages 138a.

43. Coiffier B., Lepage E., Herbrecht R., et al. Mabthera (rituximab) plus CHOP is superior to CHOP alone in elderly patients with diffuse large B-cell lymphoma (DLCL): interim results of a randomized GELA trial. Blood. Location of Proceedings San Francisco, California 2000. Volume 96. Issue 11. Pages 223a.

44. Coffier B, Gisselbrecht C, Bosly A, et al. 10 years follow-up of the GELA LNH98.5 study, first randomized study comparing R CHOP to CHOP chemotherapy in patients with diffuse large B-cell lymphoma łabstract no. 3741ł. 51st Annual Meeting and Exposition of the American Society of Hematology; 2009 Dec 5-8; New Orleans (LA).

45. Coiffier B., Feugier P., Sebban C., et al. Long Term Results of the GELA Study, R-CHOP vs. CHOP in Elderly Patients with Diffuse Large B-Cell Lymphoma. Blood (ASH Annual Meeting Abstracts) 2004 104: Abstract 1383.

46. Feugier P, Virion JM, Tilly H, et al. Incidence and risk factors for central nervous system occurrence in elderly patients with diffuse large-B-cell lymphoma: influence of rituximab. Ann Oncol. 2004 Jan; 15 (1): 129-33.

47. Coiffier B. Rituximab in combination with CHOP improves survival in elderly patients with aggressive non-Hodgkin's lymphoma. Semin Oncol. 2002 Apr; 29 (2 Suppl 6): 18-22.

48. Kaplan DL., Lee JY., Ambinder RF., et al. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma: AIDS-Malignancies Consortium Trial 010. Blood September 1, 2005 vol. 106 no. 5 1538-1543.

49. Hallek M, Fischer K, Fingerle-Rowson G, Fink AM. et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia: a randomized, open-label, phase 3 trial. Lancet. 2010 Oct 2;376(9747):1164-74.

50. Eichhorst B.F., Fischer K., Fink A.M. 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: abstrakt 3438.

51. Boettcher S., et al. Quantitative assessments predict progression free survival in CLL patients with fludarabine and cyclophosphamide with or without rituximab – a prospective analysis in 471 patients from the randomized GCLLSG CLL8 trial. Blood, 2008; 112: abstract 326.

52. Catovsky D., et al. Assessment of fludarabine plus cyclophosphamide for patients with chronic lymphocytic leukemia (the LRF CLL4 Trial): a randomized controlled trial. Lancet 2007; 370: 230–239.

53. Robak T, Dmoszynska A, Solal-Céligny P. et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. J Clin Oncol. 2010 Apr 1; 28(10):1756-65.

54. Robak T, Aultman R, Oertel SHK. et al. Quality-adjusted survival (Q-TWiST) analysis of patients with relapsed or refractory chronic lymphocytic leukemia treated with rituximab plus fludarabine and cyclophosphamide (R-FC) versus FC alone łabstract no. 1368ł. 51st Annual Meeting and Exposition of the American Society of Hematology; 2009 Dec 5-8; New Orleans (LA).

55. Łopuch S, Skałka N, Ciurkot K, Kawalec P. Analiza kliniczna oparta o przegląd systematyczny, dla zastosowania produktu leczniczego MabThera® (rytuksymab) w skojarzeniu z chemioterapią (CHOP lub CVP) w terapii chorych na nieziarnicze chłoniaki grudkowe w III-IV stopniu klinicznego zaawansowania, wcześniej nieleczonych. Kraków, listopad 2010.

56. Mucha J, Podbiegły J, Rudź R, Kawalec P. Analiza ekonomiczna stosowania produktu leczniczego MabThera (rytuksymab) w skojarzeniu z chemioterapią (CHOP lub CVP) w leczeniu chorych na nieziarnicze chłoniaki grudkowe w III-IV stopniu klinicznego zaawansowania wcześniej nieleczonych, w odniesieniu do stosowania samej chemioterapii CHOP lub CVP. Kraków, marzec 2011.

57. Gadaj A, Jasińska E, Poręba A, Jachimowicz M, Pruszko C. Rytuksymab w leczeniu podtrzymującym po I linii terapii indukcyjnej u dorosłych chorych na chłoniaki grudkowe. Przegląd systematyczny. Warszawa, luty 2011.

58. Prokurat A, Broniarek M, Różycki J, Szerling P, Jachimowicz M, Pruszko C. Rytuksymab w leczeniu podtrzymującym po I linii terapii indukcyjnej u dorosłych chorych na chłoniaki grudkowe. Analiza ekonomiczna. Warszawa, marzec 2011.

59. Gadaj A, Polkowska M, Poręba A, Jachimowicz M, Pruszko C. Rytuksymab w leczeniu podtrzymującym chorych na chłoniaki grudkowe. Przegląd systematyczny. Warszawa, wrzesień 2010.

60. Prokurat A, Broniarek M, Różycki J, Jachimowicz M, Pruszko C. Rytuksymab w leczeniu podtrzymującym, po co najmniej II linii terapii indukcyjnej u dorosłych chorych na chłoniaki grudkowe. Analiza ekonomiczna. Warszawa, marzec 2011.

61. Kowalczyk M, Wiśniewska N, Banek A, Kawalec P. Analiza kliniczna produktu leczniczego Mabthera (rytuksymab) stosowanego w skojarzeniu z chemioterapią według schematu CHOP w leczeniu indukcyjnym (I linia terapii) chorych na chłoniaka nieziarniczego rozlanego z dużych komórek B (ang. Diffuse Large B-Cell Lymphoma; DLBCL) z dodatnim antygenem CD20 względem komparatora: chemioterapii według schematu CHOP. Kraków, grudzień 2011.

62. Mucha J, Chęć K, Kawalec P. Analiza ekonomiczna dotycząca stosowania w warunkach polskich produktu leczniczego Mabthera (rytuksymab) w skojarzeniu z chemioterapią CHOP (cyklofosfamid, doksorubicyna, winkrystyna, prednizon) w leczeniu pierwszej linii u chorych na chłoniaka nieziarniczego rozlanego z dużych komórek B z dodatnim antygenem CD20. Kraków, grudzień 2011.

63. Mikrut A, Zając G, Banek A, Kawalec P. Analiza efektywności klinicznej rytuksymabu (Mabthera) stosowanego w skojarzeniu z fludarabiną i cyklofosfamidem w porównaniu do chemioterapii fludarabiną z cyklofosfamidem lub monoterapii chlorambucylem w leczeniu pierwszej linii u chorych na przewlekłą białaczkę limfocytową. Kraków, wrzesień 2011.

64. Stawowczyk E, Mucha J, Chęć K, Kawalec P. Analiza ekonomiczna stosowania produktu leczniczego Mabthera (rytuksymab) w skojarzeniu z fludarabiną oraz cyklofosfamidem w leczeniu wcześniej nieleczonych chorych na przewlekłą białaczkę limfocytową w warunkach polskich w odniesieniu do wybranych komparatorów. Kraków, listopad 2011.

65. Mikrut A, Kryst J, Banek A, Kawalec P. Analiza efektywności klinicznej rytuksymabu (Mabthera) stosowanego w skojarzeniu z fludarabiną i cyklofosfamidem w porównaniu do chemioterapii fludarabiną z cyklofosfamidem lub terapii bendamustyną w leczeniu przewlekłej białaczki limfocytowej u chorych opornych na leczenie lub z nawrotem choroby. Kraków, wrzesień 2011.

66. Mucha J, Oleszko R, Chęć K, Kawalec P. Ocena ekonomiczna stosowania produktu leczniczego Mabthera (rytuksymab) w skojarzeniu z fludarabiną oraz cyklofosfamidem w leczeniu chorych na przewlekłą białaczkę limfocytową opornych na leczenie lub z nawrotem choroby, w warunkach polskich. Kraków, październik 2011.

67. Hornberger J, Reyes C, Shewade A, Lerner S, Friedmann M, Han L, Gutierrez H, Satram-Hoang S, Keating MJ. Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for the treatment of previously untreated chronic lymphocytic leukemia. Leuk Lymphoma 2012; 53(2): 225-234.

68. Main C, Pitt M, Moxham T, Sten K. The clinical efficacy and cost-effectiveness of rituximab for the fist-line treatment of chronic lymphocytic leukemia: an evidence review of the submission from Roche. Health Technol Assess 2010; 14(Suppl. 2): 27-32.

69. Dretzke J, Barton P, Kaambwa B, Connock M, Uthman O, Bayliss S, Meads C. Rituximab for the treatment of relapse/refractory chronic lymphocytic leukaemia. Health Technol. Assess. 2010; 14(Suppl. 2): 19-26.

70. Casado LF, Garcia Marco JA, Gilsanz F, Gonzalez M, Rios E, de la Serna J, Urbano A, Vincente V, Rubio-Terres C, Castro AJ. Economic evaluation of rituximab added to fludarabine plus cyclophosphamide versus fludarabine plus cyclophosphamide for the treatment of chronic lymphocytic leukemia. Gac Sanit 2011; 25(4):274-81.

71. Braga P, Carvalho S, Gomes M, Guerra L, Lucio P, Marques H, Negreiro F, Pereira C, Silva C, Teixeira A. Economic analysis of rituximab in combination with cyclophosphamide, vincristine and prednisolone in the treatment of patients with advanced follicular lymphoma in Portugal. Acta Med Port. 2010; 23(6): 1025-1034.

72. Soini EJ, Martikainen JA, Nousisiainen T. Treatment of follicular non-Hodgkin's lymphoma with or without rituximab: cost-effectiveness and value of information based on a 5-year follow-up. Ann Oncol 2011; 22(5): 1189-1197.

73. Johnston KM, Marra CA, Connors JM, Najafzadeh M, Sehn L, Peacock SJ. Cost-effectiveness of the addition of rituximab to CHOP chemotherapy in first-line treatment for diffuse large B-cell lymphoma in a population based observational cohort in British Columbia, Canada. Value Health 2010; 13(6): 703-711.

74. Ray JA, Carr E, Lewis G, Marcus R. 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 Health 2010; 13(4): 346-357.

75. Deconinck E, Miadi 0, Fargier H, Pen CL, Brice P. Cost-effectiveness of rituximab maintenance therapy in follicular lymphoma: long-term economic evaluation. Pharmacoeconomics 2010; 28(1): 35-46.

76. Kasteng F, Erlanson M, Hagberg H, Kimby E, Relander T, Lunkvist J. Cost-effectiveness of maintenance rituximab treatment after second line therapy in patients with follicular lymphoma in Sweden. Acta Oncol. 2008; 47(6): 1029-1036.

77. Hornberger J, Reyes C, Ludebeck D, Valente N. Economic evaluation of rituximab plus cyclophosphamide, vincristine and prednisolone for advanced follicular lymphoma. Leuk Lymphoma 2008; 49(2): 227-236.

78. Hornberger JC, Best JH. Cost-utility in the United States of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone for the treatment of elderly patients with diffuse large B-cell lymphoma. Cancer 2005; 103(8): 1644-1651.

79. Best J, Hornberger J, Proctor SJ, Omnes LF, Jost F. Cost-Effectiveness Analysis of Rituximab Combined with CHOP for Treatment of Diffuse Large B-Cell Lymphoma. Value Health 2005; 8(5): 462-470.