אוקטובר 2019

רופא/ה רוקח/ת נכבד/ה,

חברת פריגו ישראל סוכנויות בע"מ מבקשת להודיע על **תוספת התוויה של** (**Non-Hodgkin's lymphoma (NHL**) ועל העדכונים הבאים בעלון לצרכן ולרופא המפורטים בהמשך עבור התכשיר:

Truxima
טרוקסימה
Concentrate for solution for infusion
חומר פעיל: Rituximab

<u>התוויה כפי שאושרה בתעודת הרישום:</u>

Truxima is indicated in adults for the following indications:
*** Non-Hodgkin's lymphoma (NHL) Truxima is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, B-cell non-hodgkin's lymphoma. Truxima is indicated for the treatment of previously untreated patients with low-grade or follicular lymphoma in combination with chemotherapy. Truxima is indicated for the treatment of patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy. Truxima maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.**

* Chronic lymphocytic leukaemia (CLL)
Truxima in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory CLL. Only limited data are available on efficacy and safety for patients previously treated with monoclonal antibodies including rituximab or patients refractory to previous rituximab plus chemotherapy.

* Granulomatosis with polyangiitis and microscopic polyangiitis
Truxima, in combination with glucocorticoids, is indicated for the treatment of adult patients with granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis (WG)) and microscopic polyangiitis (MPA).

בהודעה זו מצוינים ומסומנים ברקע צהוב השינויים המתייחסים לתוספת ההתוויה. בעלונים בוצעו עדכונים נוספים אשר אינם קשורים לתוספת ההתוויה (בעיקר שינויי פורמט).

העלונים המעודכנים לצרכן ולרופא זמינים במאגר התרופות שבאתר האינטרנט של משרד הבריאות http://www.health.gov.il וניתן לקבלם מודפסים ע"י פניה לחברת פריגו ישראל, בטלפון: 03-5773700.

בברכה,
פריגו ישראל סוכנויות בע"מ

עלון לצרכן:

1. למה מיועדת התרופה?

טרוקסימה מיועדת לטיפול בחולים מבוגרים במקרים הבאים:

1. לימפומה שאינה הודג'קין (Non-Hodgkin lymphoma): טרוקסימה מיועדת לטיפול במטופלים עם לימפומה שאינה הודג'קין של תאי B, חוזרת או שאינה מגיבה, שהיא מדרגה נמוכה או זקיקית (פוליקולרית). טרוקסימה מיועדת לטיפול במטופלים עם לימפומה מדרגה נמוכה או לימפומה זקיקית, שלא טופלו בעבר, בשילוב עם כמותרפיה.
טרוקסימה מיועדת לטיפול במטופלים עם לימפומה שאינה הודג'קין מסוג לימפומה מפושטת של תאי B גדולים עם CD20 חיובי בשילוב עם כימותרפיה CHOP.
טיפול אחזקה (maintenance therapy) של טרוקסימה מיועד לטיפול במטופלים עם לימפומה זקיקית המגיבים לטיפול אינדוקציה (induction therapy).

[***]

3. כיצד טרוקסימה ניתנת?

[***]

מהי הכמות ובאיזה תדירות תקבל את הטיפול

אם אתה מקבל טיפול עבור לימפומה שאינה הודג'קין (NHL):
כאשר אתה מטופל בטרוקסימה בלבד, אתה תקבל טרוקסימה פעם בשבוע למשך 4 שבועות. טיפולים חוזרים בטרוקסימה אפשריים.
כאשר אתה מטופל בטרוקסימה בשילוב עם כימותרפיה, אתה תקבל טרוקסימה ביום בו תקבל את הכימותרפיה. לרוב הטיפול ניתן כל 3 שבועות, עד ל-8 פעמים.
במידה ואתה מגיב היטב לטיפול, ייתכן ותקבל טרוקסימה בכל חודשיים או 3 חודשים למשך שנתיים. ייתכן והרופא ישנה את המינון, בהתאם לתגובתך לטיפול.

[***]

4. תופעות לוואי

[***]

תופעות לוואי נוספות

אם אתה מקבל טיפול עבור לימפומה שאינה הודג'קין (NHL) או לוקמיה כרונית של תאי הלימפה (CLL):

תופעות לוואי שכיחות מאוד (יכולות להופיע אצל יותר מאחד מבין עשרה אנשים)

[***]

עלון לרופא:

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Truxima is indicated in adults for the following indications:

Non- Hodgkin's lymphoma (NHL)

Truxima is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, B-cell non-hodgkin's lymphoma. Truxima is indicated for the treatment of previously untreated patients with low-grade or follicular lymphoma in combination with chemotherapy. Truxima is indicated for the treatment of patients with CD20 positive diffuse large B-cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy. Truxima maintenance therapy is indicated for the treatment of follicular lymphoma patients responding to induction therapy.

[***]

4.2 Posology and method of administration

[***]

In patients with non-Hodgkin's lymphoma and CLL, premedication with glucocorticoids should be considered if Truxima is not given in combination with glucocorticoid-containing chemotherapy.

[***]

Posology

Non-Hodgkin's lymphoma

Follicular non-Hodgkin's lymphoma

Combination therapy
The recommended dose of Truxima in combination with chemotherapy for induction treatment of previously untreated or relapsed/ refractory patients with follicular lymphoma is: 375 mg/m2 body surface area per cycle, for up to 8 cycles.
Truxima should be administered on day 1 of each chemotherapy cycle, after intravenous administration of the glucocorticoid component of the chemotherapy if applicable.

Maintenance therapy

• Previously untreated follicular lymphoma
The recommended dose of Truxima used as a maintenance treatment for patients with previously untreated follicular lymphoma who have responded to induction treatment is: 375 mg/m2 body surface area once every 2 months (starting 2 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

• Relapsed/refractory follicular lymphoma
The recommended dose of Truxima used as a maintenance treatment for patients with relapsed/refractory follicular lymphoma who have responded to induction treatment is: 375 mg/m2 body surface area once every 3 months (starting 3 months after the last dose of induction therapy) until disease progression or for a maximum period of two years.

Monotherapy
• Relapsed/refractory follicular lymphoma
The recommended dose of Truxima monotherapy used as induction treatment for adult patients with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse

after chemotherapy is: 375 mg/m2 body surface area, administered as an intravenous infusion once weekly for four weeks.

For retreatment with Truxima monotherapy for patients who have responded to previous treatment with Truxima monotherapy for relapsed/refractory follicular lymphoma, the recommended dose is: 375 mg/m2 body surface area, administered as an intravenous infusion once weekly for four weeks (see section 5.1).

Diffuse large B cell non-Hodgkin's lymphoma

Truxima should be used in combination with CHOP chemotherapy. The recommended dosage is 375 mg/m2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles after intravenous infusion of the glucocorticoid component of CHOP. Safety and efficacy of Truxima have not been established in combination with other chemotherapies in diffuse large B cell non-Hodgkin's lymphoma.

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

[***]

Method of administration
[***]
Patients with non-Hodgkin's lymphoma should then be evaluated for evidence of tumour lysis syndrome including appropriate laboratory tests and, for pulmonary infiltration, with a chest X-ray.

[***]

4.3 Contraindications

Contraindications for use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia
[***]

4.4 Special warnings and precautions for use
[***]
Non-Hodgkin's lymphoma and Chronic lymphocytic leukaemia
[***]
Infections
[***]
Very rare cases of progressive multifocal leukoencephalopathy (PML) have been reported during post-marketing use of rituximab in NHL and CLL (see section 4.8).
[***]

Immunisations
The safety of immunisation with live viral vaccines, following Truxima therapy has not been studied for NHL and CLL patients and vaccination with live virus vaccines is not recommended. Patients treated with Truxima may receive non-live vaccinations. However, with non-live vaccines response rates may be reduced. In a non-randomised study, patients with relapsed low-grade NHL who received rituximab monotherapy when compared to healthy untreated controls had a lower rate of response to vaccination with tetanus recall antigen (16% vs. 81%) and Keyhole Limpet Haemocyanin (KLH) neoantigen (4% vs. 76% when assessed for >2-fold increase in antibody titer). For CLL patients similar results are assumable considering similarities between both diseases but that has not been investigated in clinical trials.
[***]

4.8 Undesirable effects
Summary of the safety profile (non-Hodgkin's lymphoma and chronic lymphocytic leukaemia)

The overall safety profile of rituximab in non-Hodgkin's lymphoma and CLL is based on data from patients from clinical trials and from post-marketing surveillance.
[***]
Infectious events (predominantly bacterial and viral) occurred in approximately 30-50% of patients during clinical trials in patients with NHL and in 30-50% of patients during clinical trials in patients with CLL
[***]
Table 1
ADRs reported in clinical trials or during post-marketing surveillance in patients with NHL and CLL disease treated with rituximab monotherapy/maintenance or in combination with chemotherapy
[***]

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
[***]

Clinical experience in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia

Follicular lymphoma

Monotherapy

Initial treatment, weekly for 4 doses
In the pivotal trial, 166 patients with relapsed or chemoresistant low-grade or follicular B cell NHL received 375 mg/m2 of rituximab as an intravenous infusion once weekly for four weeks. The overall response rate (ORR) in the intent-to-treat (ITT) population was 48 % (CI95% 41% - 56%) with a 6% complete response (CR) and a 42% partial response (PR) rate. The projected median time to progression (TTP) for responding patients was 13.0 months. In a subgroup analysis, the ORR was higher in patients with IWF B, C, and D histological subtypes as compared to IWF A subtype (58% vs. 12%), higher in patients whose largest lesion was < 5 cm vs. > 7 cm in greatest diameter (53% vs. 38%), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response < 3 months) relapse (50% vs. 22%). ORR in patients previously treated with autologous bone marrow transplant (ABMT) was 78% versus 43% in patients with no ABMT. Neither age, sex, lymphoma grade, initial diagnosis, presence or absence of bulky disease, normal or high LDH nor presence of extranodal disease had a statistically significant effect (Fisher's exact test) on response to rituximab. A statistically significant correlation was noted between response rates and bone marrow involvement. 40% of patients with bone marrow involvement responded compared to

59% of patients with no bone marrow involvement (p=0.0186). This finding was not supported by a stepwise logistic regression analysis in which the following factors were identified as prognostic factors: histological type, bcl-2 positivity at baseline, resistance to last chemotherapy and bulky disease.

Initial treatment, weekly for 8 doses
In a multicentre, single-arm trial, 37 patients with relapsed or chemoresistant, low grade or follicular B cell NHL received 375 mg/m2 of rituximab as intravenous infusion weekly for eight doses. The ORR was 57% (95% Confidence interval (CI); 41% – 73%; CR 14%, PR 43%) with a projected median TTP for responding patients of 19.4 months (range 5.3 to 38.9 months).

Initial treatment, bulky disease, weekly for 4 doses
In pooled data from three trials, 39 patients with relapsed or chemoresistant, bulky disease (single lesion ≥ 10 cm in diameter), low grade or follicular B cell NHL received 375 mg/m2 of rituximab as intravenous infusion weekly for four doses. The ORR was 36 % (CI95% 21% – 51%; CR 3%, PR 33%) with a median TTP for responding patients of 9.6 months (range 4.5 to 26.8 months).

Re-treatment, weekly for 4 doses
In a multicentre, single-arm trial, 58 patients with relapsed or chemoresistant low grade or follicular B cell NHL, who had achieved an objective clinical response to a prior course of rituximab, were re-treated with 375 mg/m2 of rituximab as intravenous infusion weekly for four doses. Three of the patients had received two courses of rituximab before enrolment and thus were given a third course in the study. Two patients were re-treated twice in the study. For the 60 re-treatments on study, the ORR was 38% (CI95 % 26% – 51%; 10% CR, 28% PR) with a projected median TTP for responding patients of 17.8 months (range 5.4 – 26.6). This compares favourably with the TTP achieved after the prior course of rituximab (12.4 months).

Initial treatment, in combination with chemotherapy

In an open-label randomised trial, a total of 322 previously untreated patients with follicular lymphoma were randomised to receive either CVP chemotherapy (cyclophosphamide 750 mg/m2, vincristine 1.4 mg/m2 up to a maximum of 2 mg on day 1, and prednisolone 40 mg/m2/day on days 1 -5) every 3 weeks for 8 cycles or rituximab 375 mg/m2 in combination with CVP (RCVP). Rituximab was administered on the first day of each treatment cycle. A total of 321 patients (162 R-CVP, 159 CVP) received therapy and were analysed for efficacy. The median follow up of patients was 53 months. R-CVP led to a significant benefit over CVP for the primary endpoint, time to treatment failure (27 months vs. 6.6 months, $p < 0.0001$, log-rank test). The proportion of patients with a tumour response (CR, CRu, PR) was significantly higher ($p< 0.0001$ Chi-Square test) in the R-CVP group (80.9%) than the CVP group (57.2%). Treatment with R-CVP significantly prolonged the time to disease progression or death compared to CVP, 33.6 months and 14.7 months, respectively ($p < 0.0001$, log-rank test). The median duration of response was 37.7 months in the R-CVP group and was 13.5 months in the CVP group ($p < 0.0001$, log-rank test).

The difference between the treatment groups with respect to overall survival showed a significant clinical difference (p=0.029, log-rank test stratified by centre): survival rates at 53 months were 80.9% for patients in the R-CVP group compared to 71.1 % for patients in the CVP group.

Results from three other randomised trials using rituximab in combination with chemotherapy regimen other than CVP (CHOP, MCP, CHVP/Interferon-α) have also demonstrated significant improvements in response rates, time-dependent parameters as well as in overall survival. Key results from all four studies are summarised in table 3

Table 3 :Summary of key results from four phase III randomised studies evaluating the benefit of rituximab with different chemotherapy regimens in follicular lymphoma

Study	Treatment, N	Median FU, months	ORR, %	CR,%	Median TTF/PFS/ EFS mo	OS rates, %
M39021	CVP, 159 R-CVP, 162	53	57 81	10 41	Median TTP: 14.7 33.6 P<0.0001	53-months 71.1 80.9 p=0.029
GLSG'00	CHOP, 205 R-CHOP, 223	18	90 96	17 20	Median TTF: 2.6 years Not reached p < 0.001	18-months 90 95 p = 0.016
OSHO-39	MCP, 96 R-MCP, 105	47	75 92	25 50	Median PFS: 28.8 Not reached p < 0.0001	48-months 74 87 p = 0.0096
FL2000	CHVP-IFN, 183 R-CHVP-IFN, 175	42	85 94	49 76	Median EFS: 36 Not reached p < 0.0001	42-months 84 91 p = 0.029

EFS – Event Free Survival
TTP – Time to progression or death
PFS – Progression-Free Survival
TTF – Time to Treatment Failure
OS rates – survival rates at the time of the analyses

Maintenance therapy

Previously untreated follicular lymphoma

In a prospective, open label, international, multicentre, phase III trial 1193 patients with previously untreated advanced follicular lymphoma received induction therapy with R-CHOP (n=881), R-CVP (n=268) or R-FCM (n=44), according to the investigators' choice. A total of 1078 patients responded to induction therapy, of which 1018 were randomised to rituximab maintenance therapy (n=505) or observation (n=513). The two treatment groups were well balanced with regards to baseline characteristics and disease status. Rituximab maintenance treatment consisted of a single infusion of rituximab at 375 mg/m2 body surface area given every 2 months until disease progression or for a maximum period of two years.

After a median observation time of 25 months from randomisation, maintenance therapy with rituximab resulted in a clinically relevant and statistically significant improvement in the primary endpoint of investigator assessed progression-free survival (PFS) as compared to observation in patients with previously untreated follicular lymphoma (Table 4).

Significant benefit from maintenance treatment with rituximab was also seen for the secondary endpoints event-free survival (EFS), time to next anti-lymphoma treatment (TNLT) time to next chemotherapy (TNCT) and overall response rate (ORR) (Table 5). The results of the primary analysis were confirmed with longer follow-up (median observation time: 48 months and 73 months), and have been added to Table 5 to show the comparison between the 25 and 48 and 73 month follow up periods.

Table 4
Maintenance phase: overview of efficacy results rituximab vs. observation after 73 months median observation time (compared with results of primary analysis based on 25 months median observation time, and updated analysis based on 48 months median observation time)

	Observation N=513	**Rituximab N=505**	**Log-rank p value**	**Risk reduction**
Primary efficacy				
PFS (median)	48.5 months [*48.4 months*] (NR)	NR [*NR*] (NR)	<0.0001 [*<0.0001*] (<0.0001)	42% [*45%*] (50%)
Secondary efficacy				
EFS (median)	48.4 months [*47.6 months*] (37.8 months)	NR [*NR*] (NR)	<0.0001 [*< 0.0001*] (< 0.0001)	39% [*42%*] (46%)
OS (median)	NR [*NR*] (NR)	NR [*NR*] (NR)	0.8959 [*0.9298*] (0.7246)	-2% [*-2%*] (11%)
TNLT (median)	71.0 months [*60.2 months*] (NR)	NR [*NR*] (NR)	<0.0001 [*<0.0001*] (0.0003)	37% [*39%*] (39%)
TNCT (median)	85.1 months [*NR*] (NR)	NR [*NR*] (NR)	0.0006 [*0.0006*] (0.0011)	30% [*34%*] (40%)
ORR*	60.7% [*60.7%*] (55.0%)	79.0% [*79.0%*] (74.0%)	<0.0001# [*<0.0001#*] (< 0.0001)	OR=2.43 [*OR=2.43*] (OR =2.33)
Complete response (CR/CRu) rate*	52.7% [*52.7%*] (47.7%)	66.8% [*72.2%*] (66.8%)	<0.0001 [*<0.0001*] (< 0.0001)	OR=2.34 [*OR=2.34*] [(OR = 2.21)

*At end of maintenance/observation; # p values from chi-squared test
Main values correspond to 73 months median observation time, italicised values in brackets correspond to 48 months median observation time, and values in parentheses correspond to 25 months median observation time (primary analysis). PFS: progression-free survival; EFS: event-free survival; OS: overall survival; TNLT: time to next anti-lymphoma treatment; TNCT: time to next chemotherapy treatment; ORR: overall response rate; NR: not reached at time of clinical cut-off, OR: odds ratio.

Rituximab maintenance treatment provided consistent benefit in all predefined subgroups tested: gender (male, female), age (< 60 years, >= 60 years), FLIPI score (≤1, 2 or ≥ 3), induction therapy (R-CHOP, R-CVP or R-FCM) and regardless of the quality of response to induction treatment (CR, CRu or PR). Exploratory analyses of the benefit of maintenance treatment showed a less pronounced effect in elderly patients (> 70 years of age), however sample sizes were small.

Relapsed/Refractory follicular lymphoma

In a prospective, open label, international, multicentre, phase III trial, 465 patients with relapsed/refractory follicular lymphoma were randomised in a first step to induction therapy with either CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone; n=231) or rituximab plus CHOP (R-CHOP, n=234). The two treatment groups were well balanced with regard to baseline characteristics and disease status. A total of 334 patients achieving a complete or partial remission following induction therapy were randomised in a second step to rituximab maintenance therapy (n=167) or observation (n=167). Rituximab maintenance treatment consisted of a single infusion of rituximab at 375 mg/m^2 body surface area given every 3 months until disease progression or for a maximum period of two years.

The final efficacy analysis included all patients randomised to both parts of the study. After a median observation time of 31 months for patients randomised to the induction phase, R-CHOP significantly improved the outcome of patients with relapsed/refractory follicular lymphoma when compared to CHOP (see Table 5).

Table 5 Induction phase: overview of efficacy results for CHOP vs. R-CHOP (31 months median observation time)

	CHOP	**R-CHOP**	**p-value**	**Risk reduction[1)]**
Primary efficacy				
ORR[2)]	74 %	87 %	0.0003	NA
CR[2)]	16 %	29 %	0.0005	NA
PR[2)]	58 %	58 %	0.9449	NA

1) Estimates were calculated by hazard ratios
2) Last tumour response as assessed by the investigator. The “primary” statistical test for “response” was the trend test of CR versus PR versus non-response ($p < 0.0001$)
Abbreviations: NA, not available; ORR: overall response rate; CR: complete response; PR: partial response

For patients randomised to the maintenance phase of the trial, the median observation time was 28 months from maintenance randomisation. Maintenance treatment with rituximab led to a clinically relevant and statistically significant improvement in the primary endpoint, PFS, (time from maintenance randomisation to relapse, disease progression or death) when compared to observation alone ($p< 0.0001$ log-rank test).The median PFS was 42.2 months in the rituximab maintenance arm compared to 14.3 months in the observation arm. Using a Cox regression analysis, the risk of experiencing progressive disease or death was reduced by 61 % with rituximab maintenance treatment when compared to observation (95 % CI; 45 %-72 %). Kaplan-Meier estimated progression-free rates at 12 months were 78 % in the rituximab maintenance group vs. 57 % in the observation group. An analysis of overall survival confirmed the significant benefit of rituximab maintenance over observation (p=0.0039 log-rank test). Rituximab maintenance treatment reduced the risk of death by 56 % (95 % CI; 22 %-75 %).

Table 6 Maintenance phase: overview of efficacy results rituximab vs. observation (28 months median observation time)

Efficacy parameter	Kaplan-Meier estimate of median time to event (months)			Risk reduction
	Observation (N = 167)	Rituximab (N=167)	Log-rank p value	
Progression-free survival (PFS)	14.3	42.2	< 0.0001	61 %
Overall survival	NR	NR	0.0039	56 %
Time to new lymphoma treatment	20.1	38.8	< 0.0001	50 %
Disease-free survival[a]	16.5	53.7	0.0003	67 %
Subgroup analysis PFS				
CHOP	11.6	37.5	< 0.0001	71 %
R-CHOP	22.1	51.9	0.0071	46 %
CR	14.3	52.8	0.0008	64 %
PR	14.3	37.8	< 0.0001	54 %
OS				
CHOP	NR	NR	0.0348	55 %
R-CHOP	NR	NR	0.0482	56 %

NR: not reached; a: only applicable to patients achieving a CR

The benefit of rituximab maintenance treatment was confirmed in all subgroups analysed, regardless of induction regimen (CHOP or R-CHOP) or quality of response to induction treatment (CR or PR) (table 6). Rituximab maintenance treatment significantly prolonged median PFS in patients responding to CHOP induction therapy (median PFS 37.5 months vs. 11.6 months, p< 0.0001) as well as in those responding to R-CHOP induction (median PFS 51.9 months vs. 22.1 months, p=0.0071). Although subgroups were small, rituximab maintenance treatment provided a significant benefit in terms of overall survival for both patients responding to CHOP and patients responding to R-CHOP, although longer follow-up is required to confirm this observation.

Diffuse large B cell non-Hodgkin's lymphoma

In a randomised, open-label trial, a total of 399 previously untreated elderly patients (age 60 to 80 years) with diffuse large B cell lymphoma received standard CHOP chemotherapy (cyclophosphamide 750 mg/m2, doxorubicin 50 mg/m2, vincristine 1.4 mg/m2 up to a maximum of 2mg on day 1, and prednisolone 40 mg/m2/day on days 1-5) every 3 weeks for eight cycles, or rituximab 375 mg/m2 plus CHOP (R-CHOP). Truxima was administered on the first day of the treatment cycle.

The final efficacy analysis included all randomised patients (197 CHOP, 202 R-CHOP), and had a median follow-up duration of approximately 31 months. The two treatment groups were well balanced in baseline disease characteristics and disease status. The final analysis confirmed that RCHOP treatment was associated with a clinically relevant and statistically significant improvement in the duration of event-free survival (the primary efficacy parameter; where events were death, relapse or progression of lymphoma, or institution of a new anti-lymphoma treatment) (p = 0.0001). Kaplan Meier estimates of the median duration of event-free survival were 35 months in the R-CHOP arm compared to 13 months in the CHOP arm, representing a risk reduction of 41 %. At 24 months, estimates for overall survival were 68.2 % in the R-CHOP arm compared to 57.4 % in the CHOP arm.

A subsequent analysis of the duration of overall survival, carried out with a median follow-up duration of 60 months, confirmed the benefit of R-CHOP over CHOP treatment (p=0.0071), representing a risk reduction of 32 %.

The analysis of all secondary parameters (response rates, progression-free survival, disease-free survival, duration of response) verified the treatment effect of R-CHOP compared to CHOP. The complete response rate after cycle 8 was 76.2 % in the R-CHOP group and 62.4 % in the CHOP group (p=0.0028). The risk of disease progression was reduced by 46 % and the risk of relapse by 51 %. In all patients subgroups (gender, age, age adjusted IPI, Ann Arbor stage, ECOG, β2 microglobulin, LDH, albumin, B symptoms, bulky disease, extranodal sites, bone marrow involvement), the risk ratios for event-free survival and overall survival (R-CHOP compared with CHOP) were less than 0.83 and 0.95 respectively. R-CHOP was associated with improvements in outcome for both high- and low-risk patients according to age adjusted IPI.

Clinical laboratory findings

Of 67 patients evaluated for human anti-mouse antibody (HAMA), no responses were noted. Of 356 patients evaluated for HACA, 1.1 % (4 patients) were positive.
[***]

5.2 Pharmacokinetic properties

Non-Hodgkin's lymphoma

Based on a population pharmacokinetic analysis in 298 NHL patients who received single or multiple infusions of rituximab as a single agent or in combination with CHOP therapy (applied rituximab doses ranged from 100 to 500 mg/m2), the typical population estimates of nonspecific clearance (CL1), specific clearance (CL2) likely contributed by B cells or tumour burden, and central compartment volume of distribution (V1) were 0.14 L/day, 0.59 L/day, and 2.7 L, respectively. The estimated median terminal elimination half-life of rituximab was 22 days (range, 6.1 to 52 days). Baseline CD19-positive cell counts and size of measurable tumour lesions contributed to some of the variability in CL2 of rituximab in data from 161 patients given 375 mg/m2 as an intravenous infusion for 4 weekly doses. Patients with higher CD19-positive cell counts or tumour lesions had a higher CL2. However, a large component of inter-individual variability remained for CL2 after correction for CD19-positive cell counts and tumour lesion size. V1 varied by body surface area (BSA) and CHOP therapy. This variability in V1 (27.1% and 19.0%) contributed by the range in BSA (1.53 to 2.32 m2) and concurrent CHOP therapy, respectively, were relatively small. Age, gender and WHO performance status had no effect on the pharmacokinetics of rituximab. This analysis suggests that dose adjustment of rituximab with any of the tested covariates is not expected to result in a meaningful reduction in its pharmacokinetic variability.

Rituximab, administered as an intravenous infusion at a dose of 375 mg/m2 at weekly intervals for 4 doses to 203 patients with NHL naive to rituximab, yielded a mean Cmax following the fourth infusion of 486 µg/mL (range, 77.5 to 996.6 µg/mL). Rituximab was detectable in the serum of patients 3 – 6 months after completion of last treatment.

Upon administration of rituximab at a dose of 375 mg/m2 as an intravenous infusion at weekly intervals for 8 doses to 37 patients with NHL, the mean Cmax increased with each successive infusion, spanning from a mean of 243 µg/mL (range, 16 – 582 µg/mL) after the first infusion to 550 µg/mL (range, 171 – 1177 µg/mL) after the eighth infusion.

The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.
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