Healthcare Management Director <Rocho/

13thJuly 2007

Meindert Boysen
Associate Director - STA Programme
National Institute for Health and Clinical Excellence

MidCity Place
71 High Holborn
LONDON
WC1V 6NA

BY E-MAIL

Dear Meindert,

SINGLE TECHNOLOGY APPRAISAL

Rituximab for follicular Non-Hodgkin's Lymphoma

Thank you for your letter of 29th June.

Please find below answers to the clarification questions raised regarding the use of rituximab in relapsed/refractory follicular lymphoma. Roche welcomes the opportunity to provide this further clarification around our submission.

It has not been possible to provide the IPD extracts or the disposition tables as originally requested in your clarification letter. Instead, we have tried to answer as fully as possible the additional questions which you raised during our teleconference as being the reasons why we were being asked to supply the IPD extracts and disposition tables. If we have not addressed all of these reasons / questions fully, then please contact us as soon as possible in order that we can provide further clarification and explanation.

If you have any other uncertainties or questions regarding our submission whatsoever then we would request that you also contact us at the earliest opportunity so that they can be addressed prior to the first meeting of the Appraisal Committee.

Yours sincerely,

Roche Products Limited 6 Falcon Way
Shire Park
Welwyn Garden City
Hertfordshire
AL7 1TW

Healthcare

Registered
100674 London

Number

Management Tel:
Fax:
Mobile:
E-mail:

.

Section A -Clarification on Effectiveness Data

A1.

A2.

A3.

A4.

A5.

Please provide full copies of any search strategies used in the review of
the clinical literature. On page 36 of the submission it is stated that a copy
of the search strategy is appended in Appendix 2. Appendix 2 does not
include a copy of the search strategy. Currently none of the searches is reproducible for checking by LRiG.

The search strategies referred to on page 36 of our submission were omitted from Appendix 2 in error and are now supplied in Appendix 1 below along with a complete list of references found using these strategies. We apologise for this omission.

The submission states that databases were searched from 01/01/2000 to present, please clarify the specific end date for the search period

Search dates (i.e. "present" date) were as follows:

ASH Abstracts using Biosys

Medline in process (last 8 weeks) - Medline and Embase

15.05.07
24.04.07
17.05.07

The scope for this appraisal requires a review of the evidence base for the current guidance on remission induction with rituximab monotherapy that was given in TA37. Very few details of the methods used to review this specific evidence base are presented. Please provide more detail on this particular aspect of the review of clinical literature.

The search strategy employed by Roche was designed to identify all clinical trials of rituximab in relapsed or refractory follicular lymphoma. This would have identified any relevant studies on rituximab monotherapy used for remission induction. No such studies were found. We therefore believe that there is no

new evidence to assess in this regard.

Please provide a copy of the Eugen (2002) abstract listed in Table4.

The requested abstract is included in Appendix 2 below. It was not provided originally as it gave no information relevant to this appraisal and was excluded from the final set of publications reviewed.

Why were the Hainsworth and Hochster papers (referred to on page 41) not included in table 4?

Table 4 appears in Section 5.2.1 of the STA pro-forma which requires Roche to submit a list of "all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group". Roche believes that the Hochster and Hainsworth studies referred to do not meet this description. The

2

A6.

Hochster study included only patients receiving their first chemotherapy
treatment, Le. they are not in a group directly relevant to an evaluation of
rituximab in relapsed follicular lymphoma. The Hainsworth study although a randomised study includes rituximab in both arms and so does not "compare the intervention with other therapies". However, as noted in our submission both
studies are highly supportive of the contention that rituximab maintenance is clinically valuable regardless of the method of remission induction or line of therapy.

Table 7 on page 49 of the submission appears to be incorrect. The assessment group were particularly interested in the numbers for bone marrow involvement that do not sum up across the row. In addition many of the totals in individual rows do not sum up to the number at the top of the column? Is there a reason for this? Please provide us with the correct figures.

In Table A7, data on all patients was not available for all characteristics described, therefore the numbers of patients in each cell do not necessarily add up to those in the trial arm as denoted in the header row of the table. To clarify matters, the numbers of patients included have been added in each row of the table. Additionally there was a "cut and paste" error in one of the cells of the line dealing with bone marrow involvement. This has now been corrected in the table below. We apologise for this error.

3

Section B. Clarification on Cost Effectiveness Data

81. Please provide the estimated means and standard errors for Kaplan-Meier analyses of OS and PFS for each treatment group in both models (full data
set, without truncation).

Please see the table below which outlines the estimated means and standard

errors for Kaplan-Meier analyses of OS and PFS for each treatment group in
both the 2 arm and 4 arm models.

For further details see the MS-Word documents attached containing the Kaplan-Meier output which includes the PFS and OS means and SE for each of the treatment arms using un-truncated data.

U:\MabThera RCVP\ U:\MabThera RCVP\ U:\MabThera RCVP\
MabMaintenanceAnd MabMaintenanceAndMabMaintenanceAnd

NOTE: There is a large amount of output in these tabulations and one will need
to search on the word "mean" and then move back one page looking to the title
to determine which treatment arm the observed mean applies and whether the
mean reflects OS or PFS.

82. Please provide details of the number of patients who were still in the trial beyond 1500 days by randomised treatments, and by response to initial
treatment.

Firstly, it should be noted that no patient was excluded from the truncated
efficacy analyses. Patients that had not died or progressed with respect to OS
and PFS respectively at 1,500 days or longer were censored at 1,500 days.
The number of patients who were censored due to the truncation was N=55, this

5

Treatment Mean OS se Mean PFS

I

se

arm (days) (days) (days) (days)
4arm
CHOP 1351.25 104.45 522.12 60.08

CHOP- 1610.84 107.62 649.42 63.82 Observation

CHOP- 1851.88 84.65 1262.68 89.90 Rituximab
RCHOP 1299.69 134.35 785.20 115.25

RCHOP- 1569.41 64.55 970.59 69.01 Observation
RCHOP- 1987.98 61.78 1293.43 76.45 Rituximab
2 arm
Observation 1683.28 70.03 830.74 49.81

-

Rituximab 1683.28 50.31 1284.75 59.80

included those patients that were followed up for OS despite having failed therapy during the induction period. Nineteen patients were censored for PFS.

Induction only patients (patients that progressed and were not included in the 2ndrandomisation) or patients that were randomised to either MabThera or Observation (Maintenance Phase) that were censored at 1,500 days are detailed below. The distribution of patients that were randomised to maintenance therapy and censored at 1,500 days is as follows:

. CHOP-OBS
. CHOP-R
. R-CHOP-OBS
. R-CHOP-R

8 patients
10 patients
9 patients
15 patients

The remaining 13 patients progressed during the induction period but were followed up for overall survival. Please see the attached MS-Word document
for patient listing and their respective treatment regimen.

U:\PBSE\Mabthera \
m39022\NICE\truncal

83. Please clarify the case for using Weibull survival models for all models (OS &PFS, all treatment groups) when the 'goodness of fit' statistics
appear to favour other options (exponential and log normal) in several
cases.

When selecting the most appropriate parametric function it is not solely the "goodness of fit" that is relied upon, what is also required is a function that is
realistic and externally valid in predicting PFS and OS. Therefore, there has to be a compromise between the function that statistically best fits the data and a function that makes externally valid survival predictions with realistic tails to the curves. The Log-logistic function is an accelerated failure model which produces optimistic OS and PFS predictions, as the graphs below illustrate.

6

Figure 3: CHOP Overall survival curves (Log logistic)

0.9
0.8

0.7

0.6

0.5 I-CHOP>R I - - CHOP>O

0.4

0.3
0.2

0.1
0
0 4 7 10 14 17 20 24 27 30
Year

Figure 4: CHOP Progression free survival curves (Log logistic)

0.6

0.9
0.8
0.7

0.5 I-CHOP>R - - CHOP>OI

0.4
0.3

0.2

\ 0.1 "--- 0

0 4 7 10 14 17 20 24 27 30
Year

The above PFS and OS curves show that at 30 years there are some patients still alive in both arms. This is not a realistic prediction and does not align with reported life expectancy for relapsed/refractory follicular non-Hodgkin's lymphoma patients of 8-10 years from the point of diagnosis (Sweetenham et ai, 1999). (Please see the 2 arm and 4 arm models which include the Log Logistic model.) The Log Normal model is very similar in fit to the Log Logistic and is, like the Log Logistic function, an accelerated failure model both of which are optimistic in the tails.

This is in contrast to the Weibull model which predicted much more realistic PFS and OS estimates.

8

Figure 4: CHOP Progression free survival curves

0.3

0.9

0.7
0.6

I-CHOP>R - - CHOP>OI 0.5

0.4

0.2

\ 0.1

0
0

"- -- 4 7 10 14 17 20 24 27 30

Vear

The 2-arm model predicts that 2ndline maintenance rituximab and observation patients have an average life expectancy of 6.6 and 5.4 years (undiscounted). The 4-arm model predicts that 2nd line R-CHOP induction followed by maintenance rituximab and CHOP induction followed by maintenance rituximab patients have an average life expectancy of 6.4 and 5.8 years respectively.As the model excludes the duration of first line treatment and remission, comparing these predictions to the Sweetenham paper helps illustrate that the model is

making survival predictions within a plausible range, as outlined in our original submission in section 6.2.13.

The Gompertz function, theoretically the 2ndbest option, failed to converge for PFS therefore it was selected out as an option. The Exponential, as seen by the AIC (see Word document below), was the poorest fit to the data. Using the Exponential would result in an overestimation of life years, generating implausible clinical and cost outcomes. Generally, it is not recommended to mix parametric functions, (e.g., Log Logistic for PFS and Weibull for OS) as the risk of introducing the impossible case (more patients in PFS than are in OS) increases.

To help answer any further uncertainties regarding the choice of goodness of fit models please see the table below which outlines the predicted PFS and OS for each of the arms for all extrapolations.

10

Table 1: MeanOverall and Progression FreeSurvival Timefor eachtreatment arm,for all extrapolations (30yeartime horizon)

Table 2: Incremental mean Overall and Progression Free Survival time for each treatment arm,for all extrapolations (30yeartime horizon)

Note: The numbers highlighted are those with the lowest increment across all the functions

With the exception of the RCHOP-R vs CHOP-O comparison, in all cases the predicted incremental mean overall and progression free survival is at its lowest when the Weibull model is utilised. Therefore in terms of parametric function selection and its impact upon the finallCER of rituximab, the Weibull function produces the smallest incremental benefit and a higher ICER compared to other functions. In the case of the RCHOP-R vs RCHOP-O scenario, use of the Weibullleads to an increase in approximately 35 days over the function with the lowest incremental survival again. However when reducing the baseline
incremental QALY for this scenario by the 35 days the ICER for RCHOP-R
increases to only £15,000. It is also important to note that the 2 alternative
parametric functions would lead to a lower ICER than the base case for this
scenario.

11

Treatment OS PFS

arm Weibull Log- Log- Exponential Weibull Log- Log- Exponential
Normal Logistic Normal Logistic
4 arm (days)
CHOP-

1,979.16 3,030.08 2,663.83 3,654.88 603.07 711.42 714.14 686.75 Observation
CHOP-

2,965.88 4,421.34 3,875.30 5,850.31 1,422.76 1,527.54 1,637.23 2,121.65 Rituximab
RCHOP-

2,115.02 3,734.37 2,929.74 4,712.88 1,036.59 1,366.84 1,373.84 1,316.62 Observation

RCHOP- 3,164.50 4,748.88 4,100.34 7,075.75 1,686.13 1,999.95 2,098.66 2,434.52 Rituximab
2 arm (days)
Observation 2,076.36 3,436.82 2,853.59 4,217.80 823.60 1,022.93 1,031.19 992.65
Rituximab 3,090.79 4,639.92 4,025.64 6,475.30 1,578.13 1,794.48 I 1,901.67 I 2,281.88

Treatment OS PFS

arm Weibull Log- Log- Exponential Weibull Log- Log- Exponential
Normal Loaistic Normal Loaistic

4 arm (days) (days)

RCHOP-R 198.62 327.54 225.04 1,225.44 263.37 472.41 461.43 312.87 v's CHOP-R
RCHOP-R '"" 'FM" '"
v's RCHOP- 1,049.48 1,014.51 1,170.60 2,362.87 649.54 633.11 724.82 1,117.90
0
RCHOP-R

1,185".,,34 1,718.80 1,436.51 3,420.87 1,083.06 1,288.53 1,384.52 1,747.77 v's CHOP-O
2 a"rm'" (daV$ +'" M'U'" +";'J _FUF "FbY' ""U'"';'/',,"c ""'Wf'
Rituximab

v's 1,014.43 1,203.10 1,172.05 2,257.50 754.53 771.55 870.48 1,289.23
Observation

B4.

B5.

B6.

Furthermore, the underlying assumption of the Kaplan-Meier is of proportional
hazard and the Weibull is consistent with this assumption. The Log Logistic and
Log Normal functions do not have this attribute of proportional hazards.

The sensitivity of the ICER to uncertainty in the extrapolation methods was also explored in probabilistic sensitivity analysis (PSA) which was presented in our original submission. The PSA of the 2 arm model included uncertainty in the shape and scale parameters of the Weibull function and showed that the cost per QALY of maintenance rituximab was below the £20,000 threshold in all 2,000 simulations. PSA of the 4-arm model, which also incorporated parameter uncertainty around the Weibull survival function, showed that there is greater than 82% probability of R-CHOP - R being cost effective at the £30,000 threshold. Please see, in our original submission, page 162-167 for the results of one way sensitivity and probabilistic sensitivity analysis and Appendix 9 for a description of the PSA in both models.

Please see Appendix 5 of our original submission for further discussion on goodness of fit.

Please explain why only 3 Weibull parameters were estimated instead of 4 in projections for pairs of treatment groups.

If the model assumption is of proportional hazard (Le. same shape) then the two curves for OS or PFS will differ only in the scale (location) parameter however their shape parameters will be the same. In this model the assumption of proportional hazard was maintained and thus only 3 parameters were estimated (1 shape, 2 scale) for PFS and 3 for OS.

Were 'event-free' initial periods used for projection models? If so, can you clarify if these were assumed or estimated jointly with other parameters?

'Event-free' initial periods were not used for projection models. The censoring was defined in the protocol and no further assessment of censoring in either the 2 or 4 -arm analyses was undertaken. The data was used as defined in the clinical study protocol with the only exception being that the data was truncated at 1,500 days (see 87) to reduce the influence of the flat tails on the parameter estimation.

Please confirm that survival analyses for 2-arm model use only data from time of second randomisation. Was the same truncation point (1500 days from first randomisation) used for these analyses as for the 4-arm model?

The starting point of the economic model was from 2ndrandomisation utilising data from the 334 patients randomised to maintenance or observation only. For the first two years of the economic model, the corresponding Kaplan Meier data direct from EORTC20981 was utilised. For the remaining time horizon of the model, hazard rates derived from a Weibull parametric survival function were utilised. When actually estimating the Weibull parametric function, Kaplan Meier data that included the induction phase for the 334 patients was used.

12

B7.

B8.

The induction phase survival outcomes (PFS and OS) are identical for those patients re-randomised (for the 334 patients of interest there were no deaths or cases of progressive disease). Furthermore, the 150 day induction phase represents only a very small proportion of the overall length of follow up.
Therefore the inclusion or exclusion of the induction phase when deriving the corresponding Weibull function is not anticipated to be a major driver of the estimated incremental benefit of rituximab.

The same truncation point of 1,500 days from first randomisation was used for the 2-arm analysis.

Was any consideration given to the differing proportions of patients

receiving rituximab initiation treatment, when modelling OS and PFS for the 2-arm model?

Patients were randomised in the induction period to CHOP (N=231) or R-CHOP (N=234). Patients not having progressed after 6 cycles of therapy were then randomized in the maintenance phase to receive rituximab or observation therapy. The expectation is that the randomisation will preclude the introduction of a treatment bias. The distribution of patients at 2ndrandomisation were as follows: 76 patients having received CHOP in the induction phase were randomized to receive rituximab in maintenance phase, 69 patients having received CHOP in the induction phase were randomized to receive observation in maintenance phase, 91 patients having received R-CHOP in the induction phase were randomized to receive rituximab in maintenance phase and 98 patients having received R-CHOP in the induction phase were randomized to receive observation in maintenance phase.

The distribution of patients appeared reasonably balanced and thus no further consideration to assess potential treatment bias was undertaken.

The following links shown in the 2ARM model appear not to be functional:
- 2ARM Weibull parameters.xls
- 2ARMLogLog parameters.xls

Please find attached copies of the Weibull and LogLog parameter documents.

U:\MabThera RCVP\ U:\MabThera RCVP\
MabMaintenanceAnd MabMaintenanceAnd

13

89. Please provide the protocol document for EORTC20981

Please find attached the trial protocol for EORTC20981.

Protocol-20981-versi
on_6.1. pelf

810. Please provide the CSR for EORTC20981 including results and
supplementary tables and appendices relating to analyses of outcome
variables.

As the current STA template does not request a copy of the CSR and as no
specific reason or need for the CSR is provided in question B10 further dialogue
was requested. Following a teleconference with the Liverpool ERG and NICE (05/07/07) it was confirmed that the request for the CSR was due to concerns regarding the methods of randomisation of patients in the EORTC20981 clinical trial. The CSR may then aid the ERG in further assessing and validating the design of the EORTC20981 study. Therefore, please find attached the required section of the CSR for EORTC20981 which describes in detail the

randomisation criteria. Sections 3, 4 and 12 of the attached protocol also
describe the randomisation criteria. It is important to consider that the EMEA
have already thoroughly reviewed and validated the structural integrity of the EORTC20981 clinical trial as part of the regulatory review process.

U:\MabThera RCVP\
MabMaintenanceAnd

811. Please provide an anonymised extract IPDfile of EORTC20981 data, as
specified in the attached specification file below

It was confirmed during the aforementioned teleconference that the purpose of
the IPO request was to perform additional analysis evaluating the sensitivity of
the ICER to alternative parametric survival functions. This supplementary
analysis has subsequently been performed by Roche and presented in detail in question B3 above. The analysis illustrates that the selection of the Weibull function produces the most conservative predictions of incremental benefit for rituximab and hence alternative survival functions will produce lower ICER estimates for rituximab. This can be assumed as rituximab drug cost if not a function of survival. The exception being the log-logistic function for one of the 4 arm model scenarios, however sensitivity analysis illustrates that the ICER does not rise above £30,000 if the function predicting the smallest survival benefit for rituximab is utilised.

14

812. Please provide the information required to complete the disposition table attached to this letter for EORTC20981in order to ensure that a
comprehensive summary of allrandomised trialpatients is available.All categories are mutually exclusive, and should sum to the correct totals in
each phase. Please complete the disposition table in Excel and not in
Word.

Following the teleconference with Liverpool ERG and NICE it was decided not to supply the disposition table, as the specific questions relating to this request for
this data (EORTC20981 trial randomisation methods) have been addressed by supplying the the relevant section of the CSR in question 810 and the trial
protocol.

813. The methods and results of the economic searches are unclear. Please

can you provide further details on the economic searches undertaken (e.g summary table of number of identified studies by database; summary of
the inclusion and exclusion terms used). Please can you confirm that all of
the papers identified (n=73) could have been identified by searching NHS
EED and HEED only.

The search terms used to identify the economic studies from NHS EED, HEED,

ASH, Medline and Embase were presented in section 9.3.4 or our original submission. Please see the table below which outlines the search terms used.

15

No. Search terms

1 Monoclonal antibodies

2 Rituxan

3 CHOP

4 Rituximab

5 Economics

6 Follicular

7 Indolent

8 Economic evaluation

9 Cost benefit analysis

10 Cost effectiveness analysis

11 Cost minimization analysis

12 Cost utility analysis

The number of studies identified by searching each database were:
- 24 studies identified by searching ASH
- 20 studies identified by searching Medline and Embase
- 32 studies identified by searching NHS EED and
- 4 studies identified by searching HEED.

Please find attached documents summarising the papers identified by searching each database, similar to those presented in Appendix 10 of our original submission.

Medline and Embase

CHOPF or indolent & MabThera F or
econonic evaluation!indolent & econonic E

ASH

U:\MabThera RCVP\
MabMaintenanceAnd

NHS EED

U:\MabThera RCVP\
MabMaintenanceAnd

HEED

U:\MabThera RCVP\
MabMaintenanceAnd

Not all economic studies could have been identified by searching NHS EED and HEED only.

Please find attached below a combined list of all the studies identified through the literature searchs of ASH, NHS EED, HEED, Medline and Embase. Beneath each study is a note on whether it was included or excluded. If it was included a summary is provided in Appendix 4 of the original submission, if it was excluded a justfication is provided beside the "not included" statement.

U:\MabThera RCVP\
MabMaintenanceAnd

16

13 Cost comparison

14 Non Hodgkins Lymphoma

15 Follicular lymphoma

16 Quality Adjusted Life Years/QAL Y

814. Themodel assumes that all rituximab infusions occur in the outpatient setting. Canyou confirm that this is what occurs in routine NHS care.

It is standard clinical practice for patients to receive rituximab infusions in the outpatient setting, however it cannot be guaranteed that this is always the case
in all Trusts. The sensitivity of the ICER to this assumption is tested in further sensitivity analysis below. Please see the table below which illustrates the impact on the cost per QALY when the cost of administration is varied to reflect other potential cost sources.

This analysis illustrates that when setting the administration cost, in the 4 arm model, of CHOP chemotherapy to £0 and varying the incremental cost of administration for R-CHOP induction and rituximab maintenance from £86 to £419, R-CHOP induction followed by maintenance rituximab continues to be cost effective and remains below the £30,000 threshold. The two arm model also shows as the cost of administration for maintenance rituximab is varied the ICER

does not exceed the £10,000 threshold.

17

2 arm model

Administration Administration costs maintenance
costs rituximab arm

ICER
Observation arm

£0 £133 (Medtap database uplifted to 2006-2007 £8,023 prices)

£0 £419 (NHS Reference costs 2005, Day Case £9,901 HRG Data, uplifted to 2006-2007 prices)

4arnlmodel
Induction Maintenance
Administration Administration Administration cost ICER
costs CHOP arm costs R- CHOP arm rituximab

£86 (NHS Reference £86 (NHS Reference R-CHOP-R V's CHOP-R £18,015
£0 costs, original costs, original R-CHOP-R V's R-CHOP-O £11,904
submission) submission R-CHOP-R V's CHOP-O £12,378
£133 (Medtap
database uplifted to
2006-2007 prices; £133 (Medtap R-CHOP-R V's CHOP-R £18,871
£0 Inpatient database uplifted to R-CHOP-R V's R-CHOP-O £12,381
Hospitalisation 2006-2007 prices) R-CHOP-R V's CHOP-O £12,866
Medical Oncology
Ward per dav)
£0 £419 (NHS £419 (NHS R-CHOP-R V's CHOP-R £24,082
Reference costs Reference costs R-CHOP-R V's R-CHOP-O £15,285
2005, Day Case 2005, Day Case R-CHOP-R V's CHOP-O £15,838
HRG Data (Code HRG Data, uplifted to
S98), uplifted to 2006-2007 prices)
2006-2007 prices;)

Appendix 2

Unexpected
Fludarabine

Lymphoma.
Dialog eLinks
Fulltext available at

Accession number & update PREV20030036822920030101.
Author(s)

Leo-Eugen, Scheuer-Lars, Kraemer-Alwin,Kerowgan-Mohammed, Leo- Albrecht,Ho-Anthony-D. Source
Blood,November 16, 2002, vol. 100, no. 11, p. Abstract No. 4745, ISSN: 0006-4971.
Abstract

Background: Fludarabin (F) in combination with cyclophosphamide (C) is an effective combination in thetreatment for newlydiagnosed as wellas relapsed follicular lymphoma (FL).The anti-CD20 antibody Rituximab (R) has been used for the same indicationssuccessfully as monotherapy or in combination withchemotherapeutic agents. No such data were available on a combined use of these agents. Therefore, we conducted a phase 11study to evaluate the safety and efficacy of a combination of R, F and C for the treatment of relapsed FL. With Flu being aT-cell and R a B-cell toxic agent R infusions were limited to two cycles to avoid potentially excessive infectious complications. Methods: Patients (pts) received R 375mg/m2 day 1 (cohort A: cycle 1+2, cohort B: cycle 5+6, to test optimum time point (bulkreductionvs. MRD- treatment) for the use of R), C 750mg/m2 day 2 and F 25mg/m2 IV days 2-5 for a maximum of 6 cycles. Dosages for R, F and C corresponded to dosages employed in previous studies. Cycle interval was 28 days. Support therapy consisted of trimethoprim/sufametho-xasole and acyclovir (day 1-14 of ea. cycle or longer if leukopenia persisted), and G-CSF if prolonged granulocytopenia occurred. In a pilot phase 10 patients were treated in cohort A, thereafter, 7 more patients were randomized between cohort A and B. One pt was later excluded from the study after diagnosis was revised by the reference pathologist. One pt. underwent high-dose chemotherapy with autologous stem cell transplantation 6 weeks after the study treatment as consolidation treatment.. Response is summarized in table 1. Toxicity was assessed according to WHO criteria. Regarding infectious toxicity 1 pt developed bronchitis and zoster during therapy, 1 pt developed PCP- pneumonia 6 moopost end of treatment and died. 2 pts died from progressive disease and infection 2 and 8 moopost treatment. Beyond that, a significant hematotoxicity (namely thrombocytopenia) occurred. 2/17 pts showed thrombocytopenia (tcp) WHO grade III and 5/17 pts grade IV. Therapy had to be terminated in 5 pts after 3,6 cycles (range 3-5)due to prolonged (> 1 mo.) tcp. Leukopenia occurred in 4/17 pts (grade Ill) and 7/17 (grade IV) and led to delays in therapy in 2 pts. 5/7 pts recovered from tcp after an average of 2,4 mo.(range 1-4 mo.), 2/7 pts showed persistent tcp, one pt received an autograft and recovered. Serologic investigations gave no evidence for an autoimmune process and bone marrow aspirations in pts with tcp pointed towards a direct toxic effect. The excessive hematotoxicity led to activation of a stopping rule and the study was terminated. Conclusions: R-FC is an effective regimen in pts with relapsed FL. Yet, combining Rand FC at dosages that have been applied safely before for Rand FC individually, led to an unexpected and significant increase in hematotoxicity.

Hematotoxicity Associated with a Combination of Rituximab,
and Cyclophosphamide in the Treatment of Relapsed Follicular

19