Rituximab improves the treatment results of DHAP-VIM-DHAP and ASCT in relapsed/progressive aggressive CD20+ NHL. A prospective randomized HOVON trial.


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**Abstract**

We evaluated the role of Rituximab during remission induction chemotherapy in relapsed aggressive CD20⁺ Non-Hodgkin Lymphoma (NHL). A total of 239 patients were included of which 225 were evaluable for analysis. Randomized to DHAP-VIM-DHAP chemotherapy with (R)Rituximab (R-DHAP arm) were 119 patients (113 evaluable) and to chemotherapy without Rituximab (DHAP arm) 120 patients (112 evaluable). Patients in complete remission (CR) and partial remission (PR) after 2-chemotherapy courses were eligible for ASCT.

After the 2nd chemotherapy cycle, 75% of the patients in the R-DHAP arm had responsive disease (CR or PR) vs 54% in the DHAP arm (p=.01). With a median follow-up of 24 months there was a significant difference in failure free survival (FFS24) (50% vs 24% vs, p<.001), and progression free survival (PFS24, 52% vs 31% p<.002) in favor of the R-DHAP arm. Cox-regression analysis demonstrated a significant effect of Rituximab treatment on FFS24 (HR 0.41) (95%CI 0.29-0.57) vs 0.51 (0.37-0.70) and overall-survival (OS24) (HR 0.60 (0.41-0.89) vs 0.76 (0.52-1.10) when adjusted for the variables: time since upfront treatment, age, WHO performance status and sAAIPI. These results demonstrate an improved FFS and PFS for relapsed aggressive B-NHL, if Rituximab is added to the re-induction chemotherapy regimen.
**Introduction**

High dose chemotherapy with autologous stem cell transplantation (ASCT) is curative in a proportion of patients with relapsed or refractory aggressive Non Hodgkin Lymphoma (NHL). In general the 5 yrs overall survival is 30%-50%. Different parameters have been identified that have important impact on the overall survival results. Chemosensitivity, i.e. the ability to induce a partial remission (PR) or complete remission (CR) on re-induction chemotherapy before ASCT is especially important. Different re-induction regimens have been applied in this setting, including DHAP (cisplatin- cytarabine-dexamethasone), VIM (etoposide-ifosfamide-methotrexate), ICE (ifosfamide-carboplatin-etoposide) or combinations. However, so far no distinct differences have been demonstrated in the efficacy of the different chemotherapy regimens although comparative studies have not been performed.

For patients with newly diagnosed aggressive CD20+ B-cell NHL it has recently been shown that the addition of Rituximab to an anthracyclin based regimen improves the CR rate and overall survival (OS) significantly, with up to 10% -15% improvement. In patients with relapsed or primary refractory aggressive CD20+ B-cell NHL, no prospective randomized studies have been performed. Kewalramani et al reported the results of 36 relapsed patients treated with Rituximab plus ICE (RICE) followed by ASCT and compared these results with a historical control group. They observed a significant improvement in the CR rate after 3 cycles of RICE without a difference in OS so far. Comparable results were described in patients with recurrent B-cell NHL treated with high-dose Rituximab in conjunction with ASCT. In the present prospective randomized phase III study conducted by the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) the efficacy of Rituximab added to the DHAP-VIM-DHAP regimen followed by ASCT in patients with relapsed or primary
refractory aggressive CD20+ B-cell NHL was tested. The results demonstrate that the addition of Rituximab to second line chemotherapy followed by ASCT results in a significant improvement in failure free survival (FFS) and progression free survival (PFS).

**Patients and methods**

**Patients**

Patients aged 18 to 65 years who had aggressive CD20+ B-cell NHL, including diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicle centre lymphoma grade III, who relapsed after, or were refractory/progressive on a standard anthracyclin-based (CHOP-like) regimen were eligible. Before enrolment, all patients were required to have a histological confirmation of a CD20+ aggressive B-cell NHL. All biopsies were reviewed by hematopathologists of the participating transplantation centers.

Eligible patients had a WHO performance status of 0-1. Exclusion criteria included CNS involvement, history of HIV infection, post-transplant lymphoproliferative disorder or inadequate organ function. Patients were fully staged, including computed tomography scanning of thorax and abdomen, and bone marrow biopsy. All patients gave informed consent for study participation according to the regulations of the Dutch health authorities. The study was performed and evaluated by HOVON according to the Helsinki agreement. The participating HOVON institutions and investigators are listed in the Appendix I. Enrolment took place between December 2000 and December 2005.
**Study design and treatment**

This was a multi-center randomized phase III trial. Patients were stratified according to type of response to first-line treatment: response duration more than 3 months versus progression or response duration less than 3 months. The planned treatment consisted of 3 cycles of re-induction chemotherapy\(^6\) (Figure 1). Patients received re-induction chemotherapy with DHAP-VIM-DHAP followed by ASCT (DHAP arm) or DHAP-VIM-DHAP in conjunction with Rituximab followed by ASCT (R-DHAP arm). The DHAP regimen consisted of cisplatin (100 mg/m\(^2\)) on day 1 via continuous infusion over 24 h, followed on day 2 by cytarabine at 2 g/m\(^2\) in a 3-h infusion dose, repeated after 12 h. Dexamethasone, 40 mg/d given orally or iv, was administered for four consecutive days. The VIM regimen consisted of etoposide (90 mg/m\(^2\)) iv on day 1, 3 and 5; ifosfamide (1200 mg/m\(^2\) iv) on day 1–5; and methotrexate (30 mg/m\(^2\) iv) on day 1 and 5. Rituximab (375 mg/m\(^2\)) was administered on day 5 of the DHAP course or on day 6 of the VIM course. Following the second DHAP course, beginning on day 10, granulocyte colony stimulating factor (Filgastrim; Amgen, Thousand Oaks, CA)) was administered subcutaneously at a dose of 5 µg/kg each day until the end of leukapheresis. Cycles were given every 4 weeks. In case patients were non-responsive to (R)-DHAP but responsive to (R)-VIM, it was allowed to repeat the (R)-VIM regimen as third cycle of re-induction chemotherapy.

**Peripheral blood stem cell collection**

After the third cycle of chemotherapy, once the white blood cell count recovered from nadir to more than 2 x 10\(^9\)/l, leukapheresis was performed until at least 2 x 10\(^6\) CD34\(^+\) cells/kg had been collected. In case of inadequate peripheral stem cell collection, a bone marrow harvest was allowed as previously described\(^6\).
Assessment of response

Response to (R)-DHAP-(R)-VIM was assessed by conventional diagnostic methods, including CT scanning approximately 14 to 21 days after the second chemotherapy course. Bone marrow biopsies were repeated only if samples were abnormal before treatment. Response evaluation was repeated post-transplantation or at an earlier time point if clinical indicated. Response was assessed using the International Working Group criteria.12

ASCT

Only those patients who achieved CR or PR after 2 cycles of chemotherapy were considered candidates for ASCT. These patients received after the 3rd chemotherapy cycle, high-dose chemotherapy according to the BEAM (carmustine, etoposide, cytarabine, melphalan) protocol. This included administration of carmustine (300 mg/m²) on day−6, etoposide (200 mg/m²) and cytarabine (200 mg/m²) on day−5 to day−2, and melphalan (140 mg/m²) on day−1. Peripheral blood stem cells were thawed and reinfused on day 0, at least 24 h after completion of BEAM. Radiotherapy post-transplantation of involved areas was allowed.

Supportive care and clinical monitoring

Antibiotic prophylaxis to decontaminate the gastrointestinal tract was applied at a neutrophil count < 0.5 x 10⁹/l according to local protocols in the various centers. No hematopoietic growth factors were applied after the infusion of stem cells. Therapeutic antibiotic, antiviral and antimycotic treatment was left to the discretion of the investigator, but was initiated at least at a body temperature > 38.5°C after two
readings taken 2 h apart, and the treatment was to be discontinued once the patient had remained afebrile for 72 h. Irradiated platelet transfusions were scheduled to be given if the platelet count was < 10 x 10^9/l or in cases of significant bleeding. Irradiated red blood cells were transfused according the policy of each institution. Complete blood counts and vital signs were monitored daily during hospitalization. Afebrile patients not requiring intravenous treatment were discharged from the hospital at a neutrophil count of > 0.5 x 10^9/l.

The sAAIPI

The secondary age adjusted IPI (sAAIPI) was assessed according to absence or presence of 3 risk factors at the time of start of re-induction treatment in this study: ECOG performance score greater than 1, LDH level greater than upper level of normal, and stage III or IV disease^13,14^. Patients with 0, 1, 2, or 3 risk factors are considered to have low, low-intermediate, high-intermediate, or high-risk disease, respectively. In the present study patients were categorized for risk of disease as low (0-risk factors), intermediate (1-risk factor), or high (2-3 risk factors).

Statistics

The data were analyzed as of April 2007. Patient characteristics were compared between the two treatment arms using the Pearson χ^2^ or the Fisher's exact test, whichever was appropriate for discrete variables, or the Wilcoxon rank sum test for continuous variables. Study end points were CR and PR rate, FFS, progression free survival (PFS), and OS. FFS was defined as the time from start of treatment to no response after cycle II, progression, relapse, or death as a result of any cause, whichever came first. Patients without progression or relapse who were still alive
were censored at the date of last contact. The intention to treat principle was applied. Only patients that turned out not to have been eligible for the study were excluded from analysis, while eligible patients that were not treated according to protocol were analyzed according to treatment arm. Patients that received alternative treatment not according to the protocol were only considered as failure if they did not respond to the treatment at that timepoint. PFS is defined as the time from study entry until disease progression or death as a result of any cause. OS was defined as the time from the start of treatment to death irrespective of cause; patients still alive were censored at the date of last contact.

The chi-square test was used to compare response rates between the two arms. The Kaplan-Meier method was used to estimate FFS, PFS, and OS, and 95% CIs were calculated. Cox regression analysis was used to calculate the hazard ratio (HR) between the two arms with the 95% confidence interval and the P-value based on the likelihood ratio test in unadjusted and adjusted analysis. Adjustment was done for a number of prognostic factors which were identified also by Cox regression analysis. The previous response and previous response duration turned out to be scored inconsistently. Therefore we used a simple factor that is strongly related to the duration of previous response, namely the time since upfront treatment, i.e. the interval in months between start of first line treatment and registration in this study. The logarithm of this variable was used in Cox regression analysis. A split of this variable in three classes with cut-off points at 6 and 12 months respectively was used to show the impact of this factor on FFS and OS with survival curves.

All reported $P$ values are two sided and a significance level $\alpha = .05$ was used.
**Results**

**Patient characteristics**

Two hundred thirty nine (n=239) patients were enrolled in the study of which 14 turned out to be not eligible on the basis of incorrect histology (n=5), second relapse (n=3), no previous treatment with an antracyclin containing regimen (n=2), no signs of progression or relapse (n=2) and incorrect or withdrawal of informed consent (n=2). Thus, 225 patients were analyzed on basis of intent to treat, 112 patients in the control arm (DHAP) and 113 patients in the Rituximab containing arm (R-DHAP).

Characteristics of the evaluable patients are listed in table 1. No significant differences between both arms were observed for WHO performance, LDH and B symptoms. According to the sAAIPI 25%, 35%, and 40% of the patients in the DHAP-arm belonged to the low, intermediate and high risk group and 15%, 43%, and 42% respectively in the R-DHAP arm (n.s). Both arms included mostly patients with diffuse large B-cell NHL (DLBCL), 88% in the DHAP arm and 91% in the R-DHAP arm (table 2). The majority of the patients (85%) had been treated with a CHOP-like regimen as first-line treatment and only few had been exposed to Rituximab previously (4%). In the DHAP arm 54% of the patients had received upfront treatment more than one year ago vs 43% in the R-DHAP arm (ns).

**Response to chemotherapy and ASCT**

Response (CR and PR) after (R)-DHAP and (R)-VIM was attained in 54% of the patients in the DHAP arm and 75% of the patients in the R-DHAP arm (p=.01). These patients were eligible to proceed to ASCT and were treated with a third re-induction course followed by peripheral stem cell collection. Inadequate stem cell collection
was observed in 1 patient of the DHAP-arm and in 3 patients in the R-DHAP arm. Six patients in the DHAP-arm and 9 patients in the R-DHAP arm received (R)-VIM instead of (R)-DHAP as third re-induction chemotherapy course. Between the second cycle of re-induction chemotherapy and planned ASCT, 6 patients in the DHAP-arm and 7 patients in the R-DHAP arm demonstrated progressive disease and went off protocol. One patient in PR after DHAP and VIM did not proceed and went off protocol. This patient received consolidation chemotherapy, Rituximab and ASCT. In the R-DHAP arm one patient went off protocol in PR after 2 cycles of chemotherapy and received an allogeneic SCT. An additional patient in PR went off protocol without further treatment. For this patient the response improved to CRu. Ultimately, ASCT was performed in 52 (46%) patients of the DHAP-arm and in 72 (63%) patients of the R-DHAP arm (p=0.01). Radiotherapy post-transplantation was given in 3 patients in the DHAP-arm and 9 patients in the R-DHAP arm. The overall response rate in the DHAP-arm was CR 35% and PR in 15% vs 46% and 27% in the R-DHAP arm respectively (p=.003). The majority of non-responding patients were offered third-line chemotherapy, which included Rituximab for 31 (28%) non-responding patients of the DHAP arm and 13 (11%) patients of the R-DHAP arm.

Treatment outcome

The median follow-up was 31 months (range 9 – 67). In the DHAP arm 60 patients died versus 50 patients in the R-DHAP arm. The main cause of death was progressive disease in 51 (45%) patients in the DHAP-arm and in 37 (33%) patients in the R-DHAP arm.

A significant difference was observed in FFS and PFS in favor of the R-DHAP arm at a median follow up of 24 months (figure 2). The FFS was 24% in the DHAP-arm
versus 50% in the R-DHAP arm (p < .001). For the PFS\textsubscript{24} these values are 31% vs 52% (p < .002) and for OS\textsubscript{24} 52% vs 59% (p=.15) respectively. The effect of Rituximab persisted post-ASCT. A significant improved FFS\textsubscript{24} was observed for the R-DHAP patients achieving CR/PR after the two chemotherapy courses (p=.01, figure 2). If the patients were stratified according to time since upfront treatment, i.e. less than 6 months (n=34) or 6-12 months (n=81) or more than 12 months (n=110), a significant difference was observed in FFS\textsubscript{24} and OS\textsubscript{24} between the different groups in favor of the patients with the longest time since upfront treatment (table 3, figure 3AB). A number of additional prognostic parameters were also tested that might have impact on FFS and OS. As depicted in table 3, time since upfront treatment, sAAIPI, age and WHO performance had a significant impact on FFS. The effects on FFS and OS of the different subgroups according the sAAIPI score are depicted in figure 3C and D. B-symptoms and LDH above normal were also relevant, but no longer when adjusted for time since upfront treatment, sAAIPI, age and WHO performance status. Most of these factors had the same impact on OS. A Cox regression analysis was then performed to demonstrate the effect of Rituximab on FFS and OS with and without adjustment for these additional prognostic parameters i.e. time since upfront treatment, sAAIPI, age and WHO performance. As depicted in table 4, Rituximab treatment had a significant effect on FFS\textsubscript{24} (HR 0.41) (95% CI 0.29-0.57) vs 0.51 (0.37-0.70) and OS\textsubscript{24} (HR 0.60 (0.41-0.89) vs 0.76 (0.52-1.10) when adjusted for the additional risk factors. The beneficial effect of Rituximab on FFS in the R-DHAP treatment arm was similar within subgroups split according to time since upfront treatment (with test of interaction p=0.73); i.e. less than 6 months (HR 0.45 95%CI 0.21-0.97), or 6-12 months (HR 0.29 95%CI 0.17-0.51), or more than 12 months (HR 0.45 95%CI 0.27-0.76). Also with endpoint OS there was no evidence of a difference
in treatment effect in the subgroups split by time since upfront treatment (test for interaction p=0.34).

**Discussion**

The present study demonstrates that Rituximab has a significant impact on the treatment results of second-line chemotherapy in Rituximab naïve relapsed CD20+ aggressive NHL. A significant improvement in FFS and PFS was observed in favor of the Rituximab treatment. Moreover the beneficial effects of Rituximab were observed both in patients with progression on first-line treatment as well in relapsed patients.

So far different chemotherapy regimens are applied in patients with relapsing aggressive NHL. ICE, DHAP, VIM or combinations are used as re-induction chemotherapy followed by ASCT\(^1\)\(^-\)\(^6\). In general no significant differences between the different regimens are observed although no direct comparison has been performed. Parameters having the most significant impact on outcome are: time since upfront treatment, sAAIPI score at relapse and response on second-line chemotherapy as determined by FDG-PET\(^13\)\(^-\)\(^16\). The prognosis of patients who do not respond on re-induction chemotherapy is poor, as also shown in the present study, where 76% of the non-responding patients died versus 33% of the responding patients.

The present study demonstrates that the group of responders on re-induction chemotherapy can be enlarged from 54% to 74% by the addition of Rituximab. However it appeared that the impact of the addition of Rituximab on OS was smaller than on FFS and PFS and not significant in unadjusted analysis (HR 0.76). When adjusted for important prognostic factors such as time since upfront treatment, sAAIPI, age and WHO performance status, the effect was stronger (HR 0.60) and statistically significant. This finding can likely be ascribed to the fact that a proportion
of the non-responding and relapsing patients could be treated successfully with a third line treatment, including Rituximab.

In the present study only three infusions with Rituximab were given. Compared to ongoing protocols for upfront treatment in DLBCL, the applied dose of Rituximab was relatively low. In most upfront studies 6-8 infusions are given in conjunction with an anthracyclin containing regimen\(^7\)-\(^{10}\). No convincing data are available demonstrating that infusion of six cycles might initiate a better apoptotic response compared to three cycles of Rituximab. However there is some clinical data suggesting that more frequent application of Rituximab at start of therapy, and higher circulating blood levels might induce a longer and perhaps improved cytotoxic response. Khouri et al investigated this issue by administrating high-dose Rituximab in patients with recurrent aggressive NHL who were eligible for ASCT\(^{11}\). However, the response rate in their study was not distinctly different from the response rate in the R-DHAP arm of our study. Neither was the PFS in responding patients. Future randomized studies will prove whether increasing Rituximab dose and or frequency is a feasible and effective approach to enlarge the number of responding patients eligible for ASCT.

At start of the present study only a small fraction of the relapsed/progressed patients had a prior exposure to Rituximab. This situation has changed significantly. At present Rituximab is part of the first-line treatment regimen applied to almost all patients with aggressive CD20\(^+\) NHL. Whether, these patients will respond differently at relapse compared to patients in the present study has until now not been studied but seems unlikely for the majority of them. A prerequisite for the effects of Rituximab is the presence of CD20 antigen on the cell surface of the malignant lymphoid cells. It is likely that the CD20 antigen will be re-expressed in the majority of patients when Rituximab has disappeared from the circulation. This occurs mostly some weeks
after cessation of therapy\textsuperscript{17}. However, whether patients who are progressive or non-responding on first-line treatment will have the same beneficial effects of Rituximab as observed in the present study is uncertain. On the one hand it is conceivable that the sensitizing effects of Rituximab become only significant when it is co-administered with an effective second-line chemotherapy regimen. On the other hand, it has to be considered that the tumor of relapsing patients after first-line treatment with an R-CHOP like regimen might have a more aggressive behavior. The recurrent lymphoid clone is resistant to five separate agents with their own cytotoxicity profile compared to four agents in the setting of the CHOP-like regimen. Preliminary results from the ongoing international CORAL intergroup study, suggest that the treatment results in this group of patients might be less impressive\textsuperscript{18}.

A significant in vivo B-cell depletion will have occurred in patients treated with Rituximab. This might have a beneficial effect on the final outcome of the R-DHAP arm. The stem cell transplant is purged in-vivo by Rituximab from residual malignant B-cells. On other hand, the humoral immunity might also be impaired before, during and after the ASCT thus increasing the risk for bacterial infections. However no increased infection rate was observed in the R-DHAP arm (data not shown). Moreover the recovery of granulocytes and platelets was not hampered in the Rituximab treated patients compared to the controls, indicating that this agent can safely be applied in this setting.

In conclusion this randomized prospective study demonstrates an improved FFS and PFS for patients treated for relapsing aggressive CD20\textsuperscript{+} NHL if Rituximab is added to the re-induction chemotherapy regimen.
Authorship

Contribution: E.V., W.E.F. and P.C.H. designed the research protocol;
P.J.L. and P.C.H. were involved in performing the clinical research;
E.V. and W.L.J.v.P. collected and analyzed the data;
P.J.L. and P.C.H. wrote the paper and critically contributed to the final preparation of
the article.

Conflict-of-interest disclosure: The authors declare no competing financial interest.
References


**Figure legends**

Figure 2:
FFS (failure free survival) and OS (overall survival) for patients treated according the DHAP (n=112) or R-DHAP (n=113) arm and FFS for patients attained CR/PR after 2 cycles of (R)-DHAP and (R)-VIM which was followed by a third chemotherapy cycle and ASCT.

Figure 3:
FFS (failure free survival) and OS (overall survival) of treated patients according to time since upfront (A/B) treatment (<6, 6-12, >12 months) or according the sAAIPI (C/D).
Table 1. Patients characteristics.

<table>
<thead>
<tr>
<th></th>
<th>DHAP-arm (n=112)</th>
<th>R-DHAP-arm (n=113)</th>
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<tbody>
<tr>
<td>Age (median, range)</td>
<td>53 (25-65)</td>
<td>56 (25-65)</td>
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<tr>
<td>Sex (m/f)</td>
<td>65/47</td>
<td>65/48</td>
</tr>
<tr>
<td>WHO performance</td>
<td>62%</td>
<td>65%</td>
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<tr>
<td></td>
<td>38%</td>
<td>35%</td>
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<tr>
<td>LDH above normal</td>
<td>50%</td>
<td>57%</td>
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<tr>
<td>B-symptoms</td>
<td>22%</td>
<td>25%</td>
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<tr>
<td>sAAIPI:</td>
<td></td>
<td></td>
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<tr>
<td>- low (0 risk factors)</td>
<td>25%</td>
<td>15%</td>
</tr>
<tr>
<td>- intermediate (1 risk factor)</td>
<td>35%</td>
<td>43%</td>
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<tr>
<td>- high (2-3 risk factors)</td>
<td>40%</td>
<td>42%</td>
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</table>

Legend:
sAAIPI: secondary age adjusted international prognostic index; m: male; f: female.
Table 2. Characteristics of patients treated according to HOVON 44 protocol

<table>
<thead>
<tr>
<th></th>
<th>DHAP-arm (n=112)</th>
<th>R-DHAP-arm (n=113)</th>
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<tbody>
<tr>
<td><strong>Histology</strong>*:</td>
<td></td>
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<tr>
<td>DLBCL</td>
<td>88%</td>
<td>91%</td>
</tr>
<tr>
<td>FL grade III</td>
<td>10%</td>
<td>6%</td>
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<tr>
<td>Other</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>Prior treatment:</strong></td>
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<td></td>
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<tr>
<td>- CHOP-21</td>
<td>63%</td>
<td>64%</td>
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<tr>
<td>- CHOP-14</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>- CHOP-intensified</td>
<td>15%</td>
<td>11%</td>
</tr>
<tr>
<td>- Other</td>
<td>17%</td>
<td>19%</td>
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<tr>
<td>- + Rituximab</td>
<td>4%</td>
<td>4%</td>
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<tr>
<td><strong>Time since upfront treatment</strong></td>
<td></td>
<td></td>
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<tr>
<td>≤ 6 months</td>
<td>13%</td>
<td>18%</td>
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<tr>
<td>6-12 months</td>
<td>33%</td>
<td>39%</td>
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<tr>
<td>&gt; 12 months</td>
<td>54%</td>
<td>43%</td>
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Legend:
* Histology according to WHO classification; DLBCL: Diffuse Large B-Cell Lymphoma; FL grade III: Follicular grade III NHL
Table 3. Prognostic value of several parameters on FFS and OS (univariate)

<table>
<thead>
<tr>
<th>Prognostic parameter</th>
<th>Impact on FFS (%)</th>
<th>P-value(^a)</th>
<th>P-value(^b)</th>
<th>Impact on OS (%)</th>
<th>P-value(^a)</th>
<th>P-value(^b)</th>
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<tr>
<td>Time since upfront treatment</td>
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<tr>
<td>&lt;6, 6-12, &gt; 12 months</td>
<td>17%-32%-47%</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>23%-50%-70%</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
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<td>sAAIPI</td>
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<td>Low-intermediate-high</td>
<td>46%-35%-23%</td>
<td>.0004</td>
<td>.04</td>
<td>81%-60%-39%</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
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<td>Age</td>
<td></td>
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<tr>
<td>&lt;50, 51-60, &gt; 60 yrs</td>
<td>29%-28%-12%</td>
<td>.04</td>
<td>.001</td>
<td>65%-52%-47%</td>
<td>.02</td>
<td>.04</td>
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<tr>
<td>B-symptoms</td>
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<tr>
<td>No vs yes</td>
<td>40%-28%</td>
<td>.04</td>
<td>.17</td>
<td>61%-39%</td>
<td>.001</td>
<td>.02</td>
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<td>WHO performance</td>
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<tr>
<td>0 vs 1-2</td>
<td>46%-20%</td>
<td>&lt;.0001</td>
<td>.03</td>
<td>66%-38%</td>
<td>.0002</td>
<td>.17</td>
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<tr>
<td>Normal vs above upper limit</td>
<td>45%-29%</td>
<td>.004</td>
<td>.15</td>
<td>69%-44%</td>
<td>&lt;.0001</td>
<td>.0005</td>
</tr>
</tbody>
</table>

Legend:
FFS\(_{24}\) (failure free survival) and OS\(_{24}\) (overall survival) at a follow of 24 months.
P-values based on likehood ratio test in Cox regression analysis; (a) stratified by arm, unadjusted for other factors; (b) stratified by arm, adjusted for other factors
- Time since upfront treatment adjusted for WHO, age and sAAIPI.
- sAAIPI adjusted for WHO, age and time since upfront treatment.
- Age adjusted for WHO, sAAIPI and time since upfront treatment.
- B-symptoms adjusted for WHO, age, sAAIPI and time since upfront treatment.
- WHO adjusted for age, sAAIPI and time since upfront treatment.
- LDH adjusted for WHO, age and time since upfront treatment and sAAIPI.
Table 4. The effect of Rituximab treatment on FFS and OS; results of Cox regression analysis

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted</th>
<th>Adjusted *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>R-DHAP v DHAP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFS</td>
<td>0.51</td>
<td>0.37-0.70</td>
</tr>
<tr>
<td>OS</td>
<td>0.76</td>
<td>0.52-1.10</td>
</tr>
</tbody>
</table>

Legend:
Cox-regression analysis was performed to demonstrate the effect of Rituximab treatment on failure free survival (FFS) and overall survival (OS) without (unadjusted) and with adjustment (adjusted) for time since upfront treatment, sAAPl, age and WHO performance status. HR: hazard ratio.
Figure 1. Treatment schedule of patients treated according HOVON-44 protocol

HOVON-44 study
Inclusion

“DHAP-arm”

R

“R-DHAP-arm”

DHAP

Rituximab + DHAP

VIM

Rituximab + VIM

Re-evaluation:

Progressive disease or less than PR

DHAP (VIM) + stem cell mobilization

Rituximab + DHAP (VIM) + stem cell mobilization

BEAM and reinfusion stem cells

BEAM and reinfusion stem cells

Radiotherapy (optional)

Radiotherapy (optional)

Off protocol treatment

Follow up

Legend:
Re-evaluation was performed after (R)-DHAP and (R)-VIM. In the case of partial or complete response patients continued the treatment with (R)-DHAP. In a limited number of patients non-response or toxicity was observed on (R)-DHAP. In this situation the third course consisted of (R)-VIM.
Figure 2

Failure free survival

Overall survival

Failure free survival
Patients with CR/PR and BEAM/SCT
Rituximab improves the treatment results of DHAP-VIM-DHAP and ASCT in relapsed/progressive aggressive CD20 + NHL. A prospective randomized HOVON trial