VOLUME 35 · NUMBER 5 · FEBRUARY 10, 2017

# JOURNAL OF CLINICAL ONCOLOGY

# ORIGINAL REPORT

Response to Rituximab Induction Is a Predictive Marker in B-Cell Post-Transplant Lymphoproliferative Disorder and Allows Successful Stratification Into Rituximab or R-CHOP Consolidation in an International, Prospective, Multicenter Phase II Trial

Ralf U. Trappe, Daan Dierickx, Heiner Zimmermann, Franck Morschhauser, Peter Mollee, Jan M. Zaucha, Martin H. Dreyling, Ulrich Dührsen, Petra Reinke, Gregor Verhoef, Marion Subklewe, Andreas Hüttmann, Thomas Tousseyn, Gilles Salles, Volker Kliem, Ingeborg A. Hauser, Corrado Tarella, Eric Van Den Neste, Olivier Gheysens, Ioannis Anagnostopoulos, Veronique Leblond, Hanno Riess, and Sylvain Choquet

Author affiliations and support information (if applicable) appear at the end of this article.

Published at ascopubs.org/journal/jco on December 19, 2016.

Clinical trial information: NCT00590447.

Corresponding author: Ralf U. Trappe, MD, Department of Internal Medicine II: Hematology and Oncology, DIAKO Hospital Bremen, Gröpelinger Heerstr 406-408, 28239 Bremen, Germany; e-mail: rtrappe@gwdg.de.

© 2016 by American Society of Clinical Oncology

0732-183X/17/3505w-536w/\$20.00

#### A B S T R A C 1

#### Purpose

The Sequential Treatment of CD20-Positive Posttransplant Lymphoproliferative Disorder (PTLD-1) trial (ClinicalTrials.gov identifier, NCT01458548) established sequential treatment with four cycles of rituximab followed by four cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy as a standard in the management of post-transplant lymphoproliferative disorder (PTLD) and identified response to rituximab induction as a prognostic factor for overall survival. We hypothesized that rituximab consolidation might be sufficient treatment for patients with a complete response after rituximab induction.

# **Patients and Methods**

In this prospective, international, multicenter phase II trial, 152 treatment-naive adult solid organ transplant recipients, with CD20<sup>+</sup> PTLD unresponsive to immunosuppression reduction, were treated with four weekly doses of rituximab induction. After restaging, complete responders continued with four courses of rituximab consolidation every 21 days; all others received four courses of rituximab plus CHOP chemotherapy every 21 days. The primary end point was treatment efficacy measured as the response rate in patients who completed therapy and the response duration in those who completed therapy and responded. Secondary end points were frequency of infections, treatment-related mortality, and overall survival in the intention-to-treat population.

#### Results

One hundred eleven of 126 patients had a complete or partial response (88%; 95% CI, 81% to 93%), of whom 88 had a complete response (70%; 95% CI, 61% to 77%). Median response duration was not reached. The 3-year estimate was 82% (95% CI, 74% to 90%). Median overall survival was 6.6 years (95% CI, 5.5 to 7.6 years). The frequency of grade 3 or 4 infections and of treatment-related mortality was 34% (95% CI, 27% to 42%) and 8% (95% CI, 5% to 14%), respectively. Response to rituximab induction remained a prognostic factor for overall survival despite treatment stratification.

#### Conclusion

In B-cell PTLD, treatment stratification into rituximab or rituximab plus CHOP consolidation on the basis of response to rituximab induction is feasible, safe, and effective.

J Clin Oncol 35:536-543. @ 2016 by American Society of Clinical Oncology

# INTRODUCTION

Post-transplant lymphoproliferative disorders (PTLDs) are a serious but rare consequence of immunosuppression after solid organ transplantation (SOT). Their rarity, variety of histologic manifestations, and the complex medical

history of patients with PTLD have slowed the development of evidence-based therapies. For all of the rarer subtypes and in the relapsed or refractory setting, case reports and small case series remain the only source of evidence.<sup>1,2</sup>

Although the histologic range stretches from polymorphic PTLD to monomorphic lymphomatype PTLD, the majority of cases are of CD20<sup>+</sup>

# ASSOCIATED CONTENT



B-cell lineage.<sup>3</sup> In pediatric CD20<sup>+</sup> PTLD, favorable results have been reported in a phase II trial of rituximab, cyclophosphamide, and corticosteroids.4 Through international cooperation, we have been able to assemble adult patient cohorts large enough for meaningful first-line therapy trials. The phase II Sequential Treatment of CD20-Positive Post-Transplant Lymphoproliferative Disorder (PTLD-1) trial recruited 70 patients from 2003 to 2007 and established sequential treatment (ST) with four cycles of weekly rituximab followed by four cycles of chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone every 21 days (CHOP-21) as a standard in CD20<sup>+</sup> PTLD after SOT.<sup>5</sup> Median overall survival (OS) was 6.6 years, a clear improvement over the preceding smaller rituximab monotherapy trials (1.2 to 3.5 years). 6-8 Toxicity, particularly treatment-related mortality (TRM), was 13%, thus lower than in the preceding retrospective case series of first-line chemotherapy in PTLD (up to 31%). 5,9-15

We observed that response to four cycles of rituximab induction was a prognostic factor for OS after completion of ST.<sup>5</sup> On this basis, we hypothesized that rituximab consolidation might be sufficient treatment for patients with a complete response (CR) after rituximab induction. The PTLD-1 protocol was therefore amended in 2006 to introduce risk-stratified sequential treatment (RSST) with rituximab consolidation for patients in CR after rituximab induction. Treatment of patients not in CR after four weekly cycles of rituximab was changed from CHOP-21 to rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone every 21 days (R-CHOP-21). The rationale for the latter had several components; large trials in immunocompetent patients with diffuse large B-cell lymphoma (DLBCL) demonstrated a higher efficacy of R-CHOP than CHOP. 16,17 Moreover, safety concerns with regard to the use of R-CHOP in immunosuppressed patients at the time the protocol for PTLD-1 was developed in 2002 started to be allayed by 2006. 18 The goal of this trial was to demonstrate the feasibility, safety, and efficacy of RSST on the basis of patient response to rituximab induction.

# **PATIENTS AND METHODS**

In 2006, after inclusion of 70 patients, the second planned interim analysis of the PTLD-1 trial (ClinicalTrials.gov identifier, NCT01458548) was performed, and response to four courses of rituximab was identified as a prognostic factor for OS. The protocol was amended to introduce RSST, the results of which are reported in this article. The trial design outside the treatment schedule remained unchanged. The trial was stopped after it had reached its target recruitment (225 patients in total, 150 treated with RSST).

#### Study Design and Patients

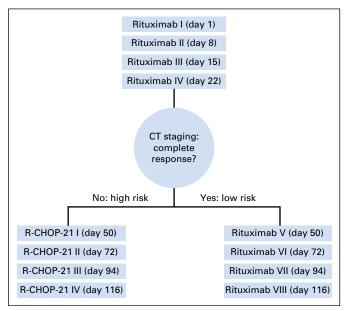
An international, prospective, multicenter, open-label, phase II trial was performed at 32 centers in Germany, Belgium, France, Australia, Poland, and Italy. Treatment-naive adult SOT recipients diagnosed with CD20 $^+$  PTLD were enrolled after activation of the amendment in their participating country from October 24, 2006, until October 3, 2014. Inclusion and exclusion criteria remained unchanged from the original PTLD-1 trial $^5$  and also included response failure to upfront immunosuppression reduction (with or without antiviral therapy), measurable disease > 2 cm in diameter (and/or bone marrow involvement), and an Eastern Cooperative Oncology Group performance status  $\le 2$ . The extent and duration of upfront immunosuppression reduction were at the

discretion of the treating physician, but usually calcineurin inhibitors were reduced by 30% to 50%, and azathioprine or mofetil mycophenolate were stopped. Response failure to immunosuppression reduction was defined as stable disease at 2 to 4 weeks after immunosuppression reduction or as progressive disease at any time. The main exclusion criteria were CNS involvement, a history of HIV infection, and the presence of severe organ dysfunction not related to PTLD.

Diagnostic tissue samples were reviewed by an expert hematopathologist and classified according to 2004 WHO criteria. Epstein-Barr virus (EBV) association was confirmed by in situ hybridization for EBV-encoded small RNA transcripts. Disease stage at enrollment was determined through a complete patient history; physical examination; laboratory investigations (including full blood count, lactate dehydrogenase [LDH] activity and renal and liver function tests); bone marrow biopsy findings; cerebrospinal fluid analysis; and computed tomography (CT) scans of the head, chest, and abdomen. The responsible local ethics committees approved the trial, and all patients gave written informed consent according to the Declaration of Helsinki.

# Treatment Plan

Treatment consisted of rituximab (375 mg/m² intravenously [IV]) on days 1, 8, 15, and 22 followed by interim staging by CT scan (days 40 to 50; Fig 1). Starting on day 50, patients with CR at interim staging (low-risk group) continued with four courses of rituximab monotherapy (375 mg/m² IV) every 21 days, whereas all others (high-risk group) received four cycles of R-CHOP-21 (rituximab 375 mg/m² IV on day 1, cyclophosphamide 750 mg/m² IV on day 1, doxorubicin 50 mg/m² IV on day 1, vincristine 1.4 mg/m² [maximum, 2 mg] IV on day 1, and prednisone 50 mg/m² orally on days 1 through 5, every 21 days). In case of clinical signs of disease progression at any time during rituximab monotherapy or before interim staging, restaging was performed prematurely, and R-CHOP-21 was commenced immediately if disease progression was confirmed. Supportive treatment with granulocyte colony-stimulating factor after R-CHOP-21 chemotherapy was obligatory. *Pneumocystis jirovecii* chemoprophylaxis was recommended. The final



**Fig 1.** Risk-stratified sequential treatment schedule. Rituximab signifies rituximab 375 mg/m² intravenously (IV), R-CHOP-21 signifies rituximab 375 mg/m² IV on day 1 plus cyclophosphamide 750 mg/m² IV on day 1, doxorubicin 50 mg/m² IV on day 1, vincristine 1.4 mg/m² (maximum, 2 mg) IV on day 1, and prednisone 50 mg/m² orally on days 1 through 5, every 21 days. In case of progressive disease from day 1 through day 50, patients proceeded to R-CHOP-21 immediately. CT, computed tomography.

response assessment was performed 1 month ( $\pm$  7 days) after the last cycle of therapy. Subsequently, patients underwent follow-up examinations every 3 months for 2 years, every 6 months for years 3 through 5, and annually thereafter. Interim, final response, and follow-up assessments included a complete patient history, physical examination, laboratory investigations, and CT scans of the chest and abdomen. Further investigations, such as bone marrow biopsy, CT scans of the head, or endoscopy, were performed if clinically indicated to determine remission status. Follow-up data were evaluated up to July 2015, with a median follow-up of 4.5 years.

# Statistical Analysis

The primary end point was treatment efficacy measured as response rate in patients who completed therapy and response duration (RD) in those who completed therapy and responded. Secondary end points were frequency of infections, TRM, OS, and time to progression (TTP) in the intention-to-treat (ITT) population. Response to treatment and disease progression were classified according to WHO criteria using CT imaging. RD was defined from the date of best response (CR or partial response) to disease progression, whereas TTP was defined from start of treatment to disease progression (all patients). OS was defined from start of treatment to death attributable to any cause. Adverse events and serious adverse events were documented according to the WHO toxicity grading scale. Analysis was by ITT.

CIs and best point estimates for observed response rates were calculated using the adjusted Wald method. Time-to-event outcomes were described using Kaplan-Meier statistics. Exploratory analyses were performed using two-sided stratified log-rank tests as well as  $\chi^2$  tests for categorical variables, and the independent samples Kruskal-Wallis test was used for continuous variables. Multivariable analyses were performed with Cox regression models (log-rank ratio test, backward elimination). The two-sided significance level was set at .05, and SPSS 22.0.0.0 statistical software (IBM Corporation, Chicago, IL) was used for all analyses. The results of the 70 patients treated with the original PTLD-1 trial protocol (the ST cohort)<sup>5</sup> and its subgroups (on the basis of rituximab response) were used for post hoc comparisons of efficacy, survival, and toxicity.

# **RESULTS**

# **Patients**

One hundred fifty-two patients were enrolled at centers in Germany (72 patients), Belgium (36 patients), France (24 patients), Australia (seven patients), Poland (seven patients), and Italy (six patients). Their baseline characteristics are listed in Table 1. Median age was 56.4 years (range, 18 to 82 years). Sixty-nine patients had undergone kidney transplantation, 40 patients had undergone liver transplantation, 18 patients had undergone lung transplantation, 15 patients had undergone heart transplantation, five patients had undergone heart and kidney transplantation, three patients had undergone kidney and pancreas transplantation, and two patients had undergone heart and lung transplantation. Median time from transplantation to PTLD was 9.0 years. Most patients (112 of 152 [74%]) were diagnosed with monomorphic DLBCL-type PTLD, 67 of 144 (47%) had EBV-associated tumors and 101 of 151 (67%) had Ann Arbor Conference classification of disease stage III or IV. Ninety-seven (65%) of 150 patients had an elevated serum LDH activity at diagnosis, and 55 (38%) of 143 had an international prognostic index (IPI) score of  $\geq 3$  (risk factors are age > 60 years, Ann Arbor stage ≥ III, Eastern Cooperative Oncology Group performance status ≥ 2, elevated LDH, and more than one extranodal disease manifestation). 19 Four patients were

**Table 1.** Baseline Characteristics of Patients Enrolled (intention-to-treat population [n = 152])

Characteristic	No. (%)
Median age (range), years	56.4 (18-82)
≥ 60 years of age	60 (40)
Male	115 (76)
Transplant type	60 (45)
Kidney Liver	69 (45) 40 (26)
Lung	18 (12)
Heart	15 (10)
Heart and kidney	5 (3)
Kidney and pancreas	3 (2)
Heart and lung	2 (1)
Median time from transplantation	9.0 (0.2-27.9
to PTLD (range), years	
< 1 year	32 (21)
≥ 1 year	120 (79)
Histology	0 (4)
Early lesion	2 (1)
Polymorphic	20 (15)
Monomorphic Burkitt	129 (85) 6 (4)
DLBCL	112 (74)
Other B-cell, CD20 <sup>+</sup>	8 (5)
Other B-cell, CD20 <sup>-</sup> *	3 (2)
Multicentric Castleman disease*	1 (1)
EBV association (n = 144)	. (.)
EBV associated	67 (47)
Non-EBV associated	77 (53)
Ann Arbor Conference classification	
of disease stage (n = 151)	
1	30 (20)†
II.	20 (13)
III IV	22 (15)
Lactate dehydrogenase (n = 150)	79 (52)
Within normal range	53 (35)
Elevated	97 (65)
Nodal disease (n = 151)	110 (73)
Extranodal disease (n = 151)	108 (72)
GI	43 (28)
Liver	34 (23)
Lung	26 (17)
Kidney	4 (3)
Bone marrow	12 (8)
Graft	13 (9)‡
International prognostic index (n = 143)	00 (00)
< 3 ≥3	88 (62) 55 (29)
	55 (38)
ECOG performance status (n = 144) 0	40 (28)
1	66 (46)
2	32 (22)
3	6 (4)

Abbreviations: DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; ECOG, Eastern Cooperative Oncology Group; PTLD, post-transplant lymphoproliferative disorder.

reclassified with a diagnosis other than CD20<sup>+</sup> PTLD on pathology review.

#### Treatment

Of the 152 patients enrolled, one died before the start of treatment. One hundred forty-eight patients could be evaluated for

<sup>\*</sup>Diagnosis changed upon pathology review.

<sup>†</sup>This includes 21 patients in stage IE.

<sup>‡</sup>Eight of 13 were patients who had undergone lung transplantation.

response to rituximab induction, 134 of whom had received all four scheduled applications (Fig 2). Thirty-seven (25%) of 148 patients achieved CR at interim staging and were allocated to rituximab monotherapy consolidation in the low-risk group. Three of these patients did not receive further treatment—one patient choose to withdraw from further treatment, one was withdrawn after GI perforation, and one died as a result of pulmonary hemorrhage. Thus, 34 patients received rituximab monotherapy consolidation. Of the 111 patients who were not in CR after rituximab induction (high-risk group), 100 went on to receive treatment with R-CHOP-21. Two patients died before treatment continuation (carotid perforation and liver abscesses). Nine patients were withdrawn from treatment because of: progressive disease that involved the CNS (two patients); renal failure (two patients); physician choice in favor of radiotherapy (two patients, both of whom in partial response); and GI perforation, hepatitis B viral infection, and hypokinetic cardiomyopathy (one patient each). Ninety-two patients could be evaluated for response to R-CHOP-21. Four patients died during therapy. Three patients were withdrawn from therapy as a result of infectious complications, and one patient was lost to follow-up.

Although early PTLD, EBV association, and low baseline IPI were significantly more common in the low-risk group than in the high-risk group (Data Supplement), 31 of 37 patients in the low-risk group had monomorphic PTLD, 21 of 37 had late PTLD, 13 of 36 had EBV-negative tumors, and eight of 34 had an IPI  $\geq$  3. Of note, six of 18 patients with PTLD who had undergone lung transplantation, a subgroup with historically poor OS,<sup>20</sup> were allocated to the low-risk group.

# Outcome

The overall response rate (ORR) of RSST was 88% (111 of 126 patients; 95% CI, 81% to 93%) and the CR rate was 70% (88 of 126; 95% CI, 61% to 77%). Median RD (Fig 3A) was not reached;

the 3-year Kaplan-Meier estimate was 82% (95% CI, 74% to 90%). In the ITT population (152 patients), median TTP (Fig 3B) was not reached. The 3-year Kaplan-Meier estimate was 75% (95% CI, 67% to 82%). Median OS (Fig 3C) was 6.6 years (95% CI, 5.5 to 7.6 years) with a 3-year estimate of 70% (95% CI, 62% to 77%). These results were confirmed by a per-protocol analysis (Data Supplement).

# **Toxicity**

Fifty-seven (63%) of 91 patients experienced grade 3 or 4 leukopenia (95% CI, 52% to 72%; no repeat blood counts in 60 patients), whereas 52 (34%) of 151 patients experienced grade 3 or 4 infections (95% CI, 27% to 42%). The most common infection experienced by patients was febrile neutropenia (24 patients), whereas Clostridium difficile colitis, P jirovecii pneumonia (PcP), and invasive aspergillosis were experienced by three patients each. At least two of the patients with PcP did not receive prophylaxis, and two of those who experienced PcP were low-risk patients. Twelve (8%) of 151 patients experienced treatment-related mortality (95% CI, 5% to 14%). Five patients died as a result of infections, two each from hemorrhage and the sequelae of GI perforation and one as a result of an unknown cause. During the follow-up period, one patient experienced fatal progressive multifocal leukencephalopathy and one patient experienced secondary acute myeloid leukemia. Only five of 52 patients who experienced grade 3 or 4 infections were in the low-risk group, and all but one treatment-related death occurred in the high-risk group.

# **Prognostic Factors**

Response to four applications of rituximab was a highly significant predictor of TTP and OS despite treatment stratification (n = 148; both P < .001; Data Supplement). We can confirm the significance of the baseline IPI (< 3 or  $\ge 3$ ) previously reported as

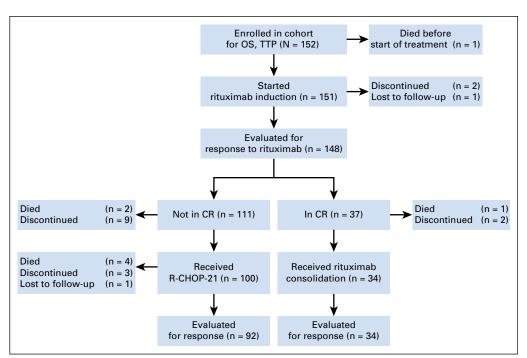


Fig 2. Diagram of number of patients enrolled, treated, and evaluated for response. CR, complete response; ITT, intention to treat; OS, overall survival; R-CHOP-21, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; TTP, time to progression.

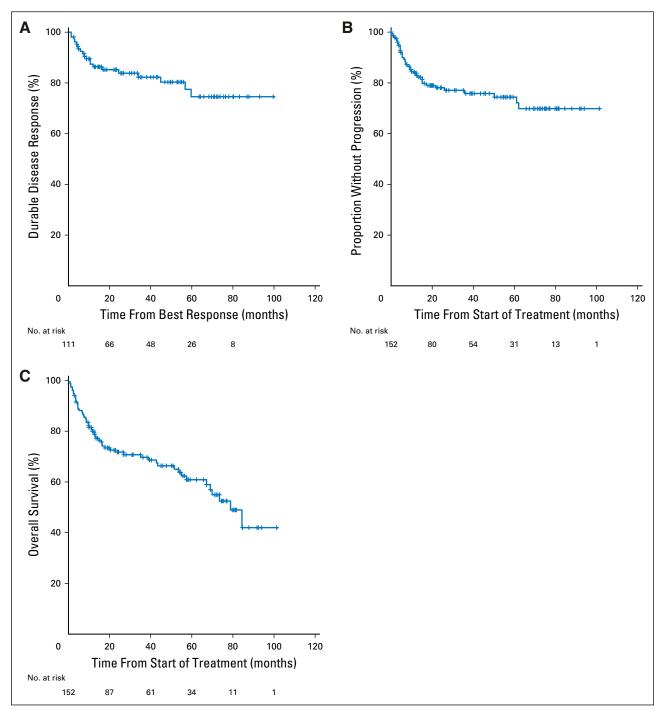


Fig 3. Response duration, time to progression, and overall survival. Median time of follow-up was 4.5 years. (A) Response duration (patients in complete response or partial response). (B) Time to progression (all patients). (C) Overall survival (all patients).

a significant prognostic factor for OS in PTLD-1 ST<sup>21</sup> in the RSST cohort for TTP and OS (complete IPI data available in 143 patients; P=.001; Data Supplement). On the other hand, there was no significant difference in ORR between EBV-positive and EBV-negative PTLD (48 [86%] of 56 patients and 59 [92%] of 64 patients; P=.255). No significant differences in TTP (P=.908) or OS (P=.793) were found (Data Supplement). In a multivariable analysis (Data Supplement), both response to four applications of

rituximab and the baseline IPI (< 3 or  $\ge 3$ ) were highly significant independent prognostic factors for TTP and OS.

# Comparison With PTLD-1 ST

Baseline characteristics of both trial cohorts were similar, and the only significant difference was time from transplant to PTLD (Data Supplement). The overall response rate of RSST was 111 (88%) of 126 patients compared with 53 (90%) of 59 patients in the PTLD-1 ST cohort. Median OS was identical (6.6 years), and 3-year Kaplan-Meier estimate was 70% (95% CI, 62% to 77%) compared with 61% (95% CI, 49% to 72%) in PTLD-1 ST. The comparisons for RD (3-year estimates, 82% [95% CI, 74% to 90%]  $\nu$  74% [95% CI, 62% to 86%]) and TTP (3-year estimates, 75% [95% CI, 67% to 82%]  $\nu$  69% [95% CI, 57% to 80%]) were favorable. The frequency of both grade 3 or 4 infections (34%  $\nu$  41%) and TRM (8%  $\nu$  13%) were lower in RSST.

# Low-Risk Group and Comparison With PTLD-1 ST

The TTP estimate in the low-risk rituximab consolidation group was 89% (95% CI, 76% to 100%) at 3 years compared with 69% (95% CI, 44% to 95%) in the 14 patients in PTLD-1 ST who had reached CR with rituximab induction and continued ST with CHOP chemotherapy (Fig 4A). OS in these two cohorts was similar, with 3-year Kaplan-Meier estimates of 91% (95% CI, 82% to 100%) and 86% (95% CI, 67% to 100%), respectively (Fig 4B). An analogous comparison of the high-risk R-CHOP consolidation group with patients in the PTLD-1 ST group who had not reached CR after rituximab induction can be found in the Data Supplement.

#### DISCUSSION

When published in 2012, the PTLD-1 ST trial with 70 patients had been the largest prospective trial in PTLD and demonstrated an unprecedented median OS of 6.6 years.<sup>5</sup> We present the results of a prospective trial with more than twice as many patients recruited in six countries from a wide range of clinical settings.

The results of the 70 patients treated with ST in the PTLD-1 trial from 2003 to 2007 provide a suitable benchmark. Despite the limiting of chemotherapy to the high-risk group, the ORR of 88% and median OS of 6.6 years of RSST closely match the results of ST, where all patients received CHOP chemotherapy. Furthermore, the Kaplan-Meier estimates of RD, TTP, and OS compare favorably, and the infection and mortality safety parameters were lower in the RSST cohort.

The 3-year TTP of 89% (95% CI, 76% to 100%) in the lowrisk rituximab consolidation group confirmed the key hypothesis of this protocol—A CR to rituximab induction identifies a group of patients with B-cell PTLD who do not need chemotherapy. This is further supported by our observation that response to rituximab monotherapy is a predictive marker for OS and TTP.

The safety profile of RSST was favorable. TRM was 8% and thus comparable to that reported in immunocompetent patients with DLBCL older than 60 years of age (7% with six cycles of R-CHOP every 14 days in RICOVER-60 [Six Versus Eight Cycles of Biweekly CHOP-14 With or Without Rituximab in Elderly Patients With Aggressive CD20<sup>+</sup> B-Cell Lymphomas] and 6% with eight cycles of CHOP-21 with or without rituximab in LNH98.5 [CHOP Chemotherapy Plus Rituximab Compared With CHOP Alone in Elderly Patients With DLBCL]). <sup>16,22</sup> R-CHOP immunochemotherapy in the high-risk patients did not result in excess toxicity or mortality. We conclude that R-CHOP, the proven standard in

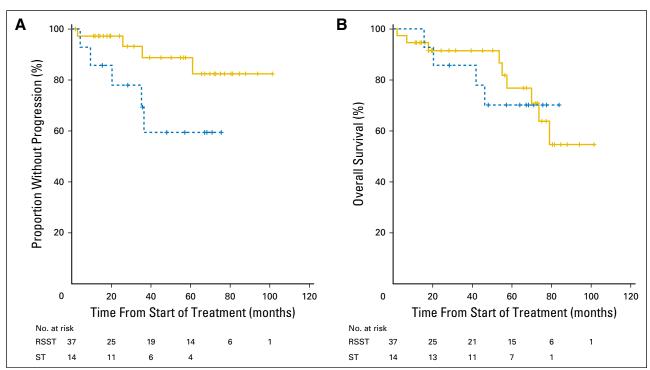


Fig 4. Patients in complete response after rituximab induction (low-risk group). Time to progression and overall survival in the risk-stratified sequential treatment (RSST) cohort (n = 37; solid line) and the sequential treatment (ST) cohort (n = 14; dashed line). (A) Time to progression. The 3-year Kaplan-Meier estimate was 89% (95% CI, 76% to 100%) compared with 69% (95% CI, 44% to 95%) in the 14 patients in the PTLD-1 (Sequential Treatment of CD20-Positive Post-Transplant Lymphoproliferative Disorder trial) ST cohort. (B) Overall survival. The 3-year Kaplan-Meier estimate was 70% (95% CI, 62% to 77%) compared with 61% (95% CI, 49% to 72%) in PTLD-1 ST cohort. Of the six late deaths that occurred in the RSST low-risk cohort, two were attributable to progressive PTLD (after first and second relapse) whereas four were not (one death as a result of unknown causes and three as a result of infections).

immunocompetent patients with CD20<sup>+</sup> DLBCL<sup>16,17,22</sup> can be safely used in PTLD as part of ST. However, the spectrum of infections observed included entities typically associated with longstanding immunosuppression (PcP, aspergillosis, progressive multifocal leukencephalopathy).<sup>23-25</sup>

The optimal treatment of PTLD has long been a source of controversy. <sup>26</sup> This study lend further support to the argument that B-cell PTLD should not be treated with upfront R-CHOP immunochemotherapy in analogy with immunocompetent patients with DLBCL. Upfront chemotherapy in PTLD, to our knowledge, has never been tested in a prospective setting. In retrospective case series of CHOP or CHOP-like protocols, TRM has been reported to be as high as 26% and 31%. <sup>12,15</sup> We observed a more acceptable rate of TRM (13%) in our previous prospective trial of ST, where CHOP was administered after rituximab induction, possibly as a result of reduced tumor burden and a delay of 50 days between reduction of immunosuppression and start of chemotherapy. <sup>5</sup> The current trial demonstrates that approximately 25% of patients with PTLD do not need chemotherapy.

Furthermore, the results with continued rituximab strongly suggest that rituximab consolidation is superior to no consolidation (ie, that eight, not four, courses of rituximab are the best available therapy for patients in CR after rituximab induction). Although we have not formally tested this hypothesis, the TTP with RSST in the low-risk group (97% at 24 months; Fig 4A) compares favorably with previous trials where only four cycles of rituximab were administered. In the German and French rituximab monotherapy trials, four of 25 patients in CR experienced a relapse within 12 months, and Blaes et al reported a median duration of CR of 8 months. <sup>27,28</sup>

In summary, this study establishes the feasibility, efficacy, and safety of RSST in CD20<sup>+</sup> PTLD. In the absence of any randomized trial data, the results define RSST as a new therapeutic standard in adult CD20<sup>+</sup> PTLD after SOT and demonstrate that PTLD is a successfully treatable lymphoma.

# AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

# **AUTHOR CONTRIBUTIONS**

Conception and design: Ralf U. Trappe, Daan Dierickx, Franck Morschhauser, Peter Mollee, Jan M. Zaucha, Martin H. Dreyling, Ulrich Dührsen, Petra Reinke, Gregor Verhoef, Marion Subklewe, Andreas Hüttmann, Thomas Tousseyn, Gilles Salles, Volker Kliem, Ingeborg A. Hauser, Corrado Tarella, Eric Van Den Neste, Olivier Gheysens, Veronique Leblond, Hanno Riess, Sylvain Choquet

Collection and assembly of data: Ralf U. Trappe, Daan Dierickx, Heiner Zimmermann, Franck Morschhauser, Peter Mollee, Jan M. Zaucha, Martin H. Dreyling, Ulrich Dührsen, Thomas Tousseyn, Gilles Salles, Corrado Tarella, Eric Van Den Neste, Ioannis Anagnostopoulos, Veronique Leblond, Sylvain Choquet

**Data analysis and interpretation:** Ralf U. Trappe, Daan Dierickx, Heiner Zimmermann, Sylvain Choquet

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

# **REFERENCES**

- 1. Zimmermann H, Trappe RU: EBV and post-transplantation lymphoproliferative disease: What to do? Hematology (Am Soc Hematol Educ Program) 2013:95-102, 2013
- **2.** Dierickx D, Tousseyn T, Gheysens O: How I treat posttransplant lymphoproliferative disorders. Blood 126:2274-2283, 2015
- 3. Swerdlow SH, Campo E, Harris NL, et al: Post-transplant lymphoproliferative disorders, in Swerdlow SH, Campo E, Harris NL, et al (eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues (ed 4). Lyon, France, International Agency for Research on Cancer, 2008, pp 343-349
- **4.** Gross TG, Orjuela MA, Perkins SL, et al: Low-dose chemotherapy and rituximab for posttransplant lymphoproliferative disease (PTLD): A Children's Oncology Group Report. Am J Transplant 12: 3069-3075, 2012
- 5. Trappe R, Oertel S, Leblond V, et al: Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): The prospective international multicentre phase 2 PTLD-1 trial. Lancet Oncol 13:196-206, 2012
- **6.** Oertel SH, Verschuuren E, Reinke P, et al: Effect of anti-CD 20 antibody rituximab in patients with post-transplant lymphoproliferative disorder (PTLD). Am J Transplant 5:2901-2906, 2005
- 7. Choquet S, Leblond V, Herbrecht R, et al: Efficacy and safety of rituximab in B-cell post-

- transplantation lymphoproliferative disorders: Results of a prospective multicenter phase 2 study. Blood 107:3053-3057, 2006
- **8.** González-Barca E, Domingo-Domenech E, Capote FJ, et al: Prospective phase II trial of extended treatment with rituximab in patients with B-cell post-transplant lymphoproliferative disease. Haematologica 92:1489-1494, 2007
- **9.** Garrett TJ, Chadburn A, Barr ML, et al: Post-transplantation lymphoproliferative disorders treated with cyclophosphamide-doxorubicin-vincristine-prednisone chemotherapy. Cancer 72:2782-2785, 1993
- **10.** Mamzer-Bruneel MF, Lomé C, Morelon E, et al: Durable remission after aggressive chemotherapy for very late post-kidney transplant lymphoproliferation: A report of 16 cases observed in a single center. J Clin Oncol 18:3622-3632, 2000
- **11.** Norin S, Kimby E, Ericzon BG, et al: Post-transplant lymphoma—A single-center experience of 500 liver transplantations. Med Oncol 21:273-284, 2004
- **12.** Elstrom RL, Andreadis C, Aqui NA, et al: Treatment of PTLD with rituximab or chemotherapy. Am J Transplant 6:569-576, 2006
- **13.** Fohrer C, Caillard S, Koumarianou A, et al: Long-term survival in post-transplant lymphoproliferative disorders with a dose-adjusted ACVBP regimen. Br J Haematol 134:602-612, 2006
- **14.** Taylor AL, Bowles KM, Callaghan CJ, et al: Anthracycline-based chemotherapy as first-line treatment in adults with malignant posttransplant lymphoproliferative disorder after solid organ transplantation. Transplantation 82:375-381, 2006

- **15.** Choquet S, Trappe R, Leblond V, et al: CHOP-21 for the treatment of post-transplant lymphoproliferative disorders (PTLD) following solid organ transplantation. Haematologica 92:273-274, 2007
- **16.** Coiffier B, Lepage E, Briere J, et al: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 346:235-242, 2002
- 17. Pfreundschuh M, Trümper L, Osterborg A, et al: CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: A randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol 7: 379-391, 2006
- **18.** Kaplan LD, 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 106:1538-1543, 2005
- 19. The International Non-Hodgkin's Lymphoma Prognostic Factors Project: A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 329:987-994. 1993
- **20.** Zimmermann H, Choquet S, Dierickx D, et al: Early and late posttransplant lymphoproliferative disorder after lung transplantation—34 cases from the European PTLD Network. Transplantation 96: e18-e19. 2013
- 21. Trappe RU, Choquet S, Dierickx D, et al: International prognostic index, type of transplant and response to rituximab are key parameters to tailor

treatment in adults with CD20-positive B cell PTLD: Clues from the PTLD-1 trial. Am J Transplant 15: 1091-1100, 2015

- 22. Pfreundschuh M, Schubert J, Ziepert M, et al: Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: A randomised controlled trial (RICOVER-60). Lancet Oncol 9: 105-116, 2008
- **23.** Martin SI, Fishman JA: Pneumocystis pneumonia in solid organ transplantation. Am J Transplant 13:272-279, 2013 (suppl 4)
- **24.** Pappas PG, Alexander BD, Andes DR, et al: Invasive fungal infections among organ transplant recipients: Results of the Transplant-Associated Infection Surveillance Network (TRANSNET). Clin Infect Dis 50:1101-1111, 2010
- 25. Schmedt N, Andersohn F, Garbe E: Signals of progressive multifocal leukoencephalopathy for immunosuppressants: A disproportionality analysis of spontaneous reports within the US Adverse Event Reporting System (AERS). Pharmacoepidemiol Drug Saf 21:1216-1220, 2012
- 26. Starzl TE, Nalesnik MA, Porter KA, et al: Reversibility of lymphomas and lymphoproliferative

lesions developing under cyclosporin-steroid therapy. Lancet 1:583-587, 1984

- 27. Choquet S, Oertel S, LeBlond V, et al: Rituximab in the management of post-transplantation lymphoproliferative disorder after solid organ transplantation: Proceed with caution. Ann Hematol 86: 599-607 2007
- **28.** Blaes AH, Peterson BA, Bartlett N, et al: Rituximab therapy is effective for posttransplant lymphoproliferative disorders after solid organ transplantation: Results of a phase II trial. Cancer 104:1661-1667, 2005

#### **Affiliations**

Ralf U. Trappe and Heiner Zimmermann, DIAKO Evangelisches Diakonie-Krankenhaus Bremen, Bremen; University Medical Centre Schleswig-Holstein, Kiel; Ralf U. Trappe, Petra Reinke, Ioannis Anagnostopoulos, and Hanno Riess, Charité-Universitätsmedizin Berlin, Berlin; Martin H. Dreyling and Marion Subklewe, University of Munich, Munich; Ulrich Dührsen and Andreas Hüttmann, University of Duisburg-Essen, Essen; Volker Kliem, Nephrological Centre Lower Saxony, Hann. Münden; Ingeborg A. Hauser, J.W. Goethe University Hospital, Frankfurt, Germany; Daan Dierickx, Gregor Verhoef, Thomas Tousseyn, and Olivier Gheysens, Catholic University Leuven, Leuven; Eric Van Den Neste, Cliniques Universitaires Saint-Luc, Brussels, Belgium; Franck Morschhauser, Hôpital Claude Huriez, Lille; Gilles Salles, Hospices Civils de Lyon and Université de Lyon, Pierre-Bénite; Veronique Leblond and Sylvain Choquet, Université Pierre et Marie Curie, Paris, France; Peter Mollee, University of Queensland, Brisbane, Queensland, Australia; Jan M. Zaucha, Medical University of Gdansk, Gdansk; Polish Lymphoma Research Group, Warsaw, Poland; and Corrado Tarella, European Institute of Oncology, Milan, Italy.

# Support

The Sequential Treatment of CD20-Positive Post-Transplant Lymphoproliferative Disorder (PTLD-1) trial was planned and initiated in 2003 and amended in 2006 as an investigator-initiated trial by the German and French PTLD Study Groups. In 2004, F. Hoffmann-La Roche, Amgen, and Chugai Pharmaceutical, France granted financial support. The companies were involved neither in the protocol design nor in the data collection, analysis, and interpretation. They played no role in writing the manuscript and were not involved in the decision to submit for publication. The principal investigator (R.U.T.) had full access to study data and final responsibility for the decision to submit for publication.

#### **Prior Presentation**

Presented in part at the 51st American Society of Hematology Annual Meeting and Exposition, New Orleans, LA, December 5-9, 2009; the 48th Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 1-5, 2012; and the 57th American Society of Hematology Annual Meeting and Exposition, Orlando, FL, December 5-8, 2015.

# **AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

Response to Rituximab Induction Is a Predictive Marker in B-Cell Post-Transplant Lymphoproliferative Disorder and Allows Successful Stratification Into Rituximab or R-CHOP Consolidation in an International, Prospective, Multicenter Phase II Trial

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Ralf U. Trappe

**Stock or Other Ownership:** Roche, Novartis, Bristol-Myers Squibb, AbbVie

Honoraria: Novo Nordisk, Roche

Research Funding: Roche (Inst), Novartis (Inst), CSL Behring (Inst) Travel, Accommodations, Expenses: Roche, Takeda Pharmaceuticals, LEO Pharma, Celgene, Janssen Pharmaceuticals, TEVA Pharmaceutical Industries, Gilead Sciences

Daan Dierickx

No relationship to disclose

Heiner Zimmermann

Honoraria: Roche

Research Funding: Roche (Inst)

Travel, Accommodations, Expenses: Celgene

Franck Morschhauser

**Honoraria:** Celgene, Roche, Genentech, Gilead Sciences, Janssen-Cilag **Consulting or Advisory Role:** Gilead Sciences, Institut de Recherches Internationales Servier

Travel, Accommodations, Expenses: Celgene, Roche Pharma AG,

Peter Mollee

Consulting or Advisory Role: Celgene, Amgen

Research Funding: Janssen Pharmaceuticals (Inst), Celgene (Inst)

Jan M. Zaucha

No relationship to disclose

Martin H. Dreyling

Honoraria: Roche

Consulting or Advisory Role: Roche Research Funding: Roche (Inst)

Ulrich Dührsen

Honoraria: Roche

Research Funding: Amgen, Roche

Travel, Accommodations, Expenses: Roche

Petra Reinke

Honoraria: TEVA Pharmaceutical Industries, Pfizer, Astellas Pharma Consulting or Advisory Role: MSD, Pluristem Therapeutics, Baxalta Travel, Accommodations, Expenses: TEVA Pharmaceutical Industries, Astellas Pharma, Thermo Fisher Scientific, Pluristem Therapeutics, Baxalta, Novartis

Gregor Verhoef

No relationship to disclose

Marion Subklewe

Consulting or Advisory Role: Amgen, Pfizer

Research Funding: Amgen

Andreas Hüttmann

No relationship to disclose

Thomas Tousseyn

No relationship to disclose

Gilles Salles

Honoraria: Roche, Genentech, Amgen, Mundipharma

Consulting or Advisory Role: Roche, Genentech, Gilead Sciences, Janssen

Pharmaceuticals, Mundipharma, Celgene, Novartis, Servier

Research Funding: Roche (Inst), Genentech (Inst)

Travel, Accommodations, Expenses: Roche, Genentech

Volker Kliem

Honoraria: Astellas Pharma, Roche, Pfizer, Novartis

Ingeborg A. Hauser

Honoraria: Novartis, Chiesi Farmaceutici, Sanofi, Hexal, Astellas Pharma Consulting or Advisory Role: Novartis, Chiesi Farmaceutici, Roche,

Sanofi, Teva Pharmaceutical Industries

Travel, Accommodations, Expenses: Hexal, Astellas Pharma

Corrado Tarella

Honoraria: Gilead Sciences

Travel, Accommodations, Expenses: Celgene, Amgen

Eric Van Den Neste

Travel, Accommodations, Expenses: Janssen Pharmaceuticals, Roche

Olivier Gheysens

Consulting or Advisory Role: Novartis (I)

Speakers' Bureau: FluoroPharma

Research Funding: FluoroPharma (Inst), GE Health Care (Inst)

Travel, Accommodations, Expenses: GE Health Care

Ioannis Anagnostopoulos

Travel, Accommodations, Expenses: Menarini

Veronique Leblond

Honoraria: Roche

Consulting or Advisory Role: Roche

Speakers' Bureau: Roche

Travel, Accommodations, Expenses: Roche

Hanno Riess

Honoraria: Aspen, Bayer AG, Boehringer Ingelheim, Celgene, Pfizer,

Roche

Consulting or Advisory Role: Boehringer Ingelheim, Aspen, Celgene,

Bayer AG

Sylvain Choquet

Consulting or Advisory Role: Roche

Research Funding: Roche (Inst), Chugai Pharmaceutical (Inst)

Travel, Accommodations, Expenses: Roche