Treatment of patients with MYC rearrangement positive large B-cell lymphoma with R-CHOP plus lenalidomide: results of a multicenter phase II HOVON trial

Martine E.D. Chamuleau,¹ Coreline N. Burggraaff,² Marcel Nijland,² Katerina Bakunina,³ Rogier Mous,⁴ Pietermella J. Luftenburg,⁵ Daan Dierickx,⁶ Gustaaf W. van Imhoff,⁷ Joost S.P. Vermaat,⁷ Eric A.F. Marij,⁷ Otto Visser,⁸ Caroline Mandigers,⁹ Yavuz M. Bilgin,¹⁰ Aart Beeker,¹¹ Mark F. Durian,¹² Bas P. van Rees,¹² Sara H. Bohmer,¹³ Lidwine W. Tick,¹⁵ Rinske S. Boersma,¹⁶ Tjeerd J.F. Snijders,¹⁷ Harry C. Schouten,¹⁷ Harry R. Koene,¹⁷ Eva de Jongh,¹⁷ Nathalie Hijmering,¹⁷ Arjan Diepstra,¹² Anke van de Berg,²² Anne I.J. Arens,²³ Julia Huibregts,²⁴ Otto Hoekstra,²⁵ Josee M. Zijlstra,¹ Daphne de Jong²⁶ and Marie José Kersten²⁶

¹Department of Hematology, Amsterdam UMC, VU University Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands; ²Department of Hematology, UMC Groningen, Groningen, the Netherlands; ³Department of Hematology, HOVON Data Centre, Erasmus MC Cancer Institute, Rotterdam, the Netherlands; ⁴Department of Hematology, UMC Utrecht Cancer Centre, University Medical Centre Utrecht, Utrecht, the Netherlands; ⁵Department of Hematology Erasmus MC Cancer Institute, Rotterdam, the Netherlands; ⁶Department of Hematology, University Hospitals Leuven, Leuven, Belgium; ⁷Department of Hematology, Leiden University Medical Centre, Leiden, the Netherlands; ⁸Department of Hematology, Oncology Centre Isala, Zwolle, the Netherlands; ⁹Department of Hematology, Canisius-Wilhelmina Hospital, Nijmegen, the Netherlands; ¹⁰Department of Internal Medicine, Admiraal de Ruijter Hospital Goes, the Netherlands; ¹¹Department of Internal Medicine, Spaarne Gasthuis, Hoofddorp, the Netherlands; ¹²Department of Internal Medicine, Tweesteden Hospital, Tilburg, the Netherlands; ¹³Department of Internal Medicine, Tjongerschans Hospital, Heerenveen, the Netherlands; ¹⁴Department of Internal Medicine, Haga Hospital, Den Haag, the Netherlands; ¹⁵Department of Internal Medicine, Máxima Medisch Centrum, Veldhoven, the Netherlands; ¹⁶Department of Internal Medicine, Amphia Hospital, Breda, the Netherlands; ¹⁷Department of Hematology, Medisch Spectrum Twente, Enschede, the Netherlands; ¹⁸Department of Hematology, Maastricht UMC, Maastricht, the Netherlands; ¹⁹Department of Internal Medicine, St Antonius Hospital, Nieuwegein, the Netherlands; ²⁰Department of Internal Medicine, Albert Schweitzer Hospital, Dordrecht, the Netherlands; ²¹Department of Pathology, Amsterdam UMC, location VU University Amsterdam, Amsterdam, the Netherlands; ²²Department of Pathology and Medical Biology, UMC Groningen, University of Groningen, Groningen, the Netherlands; ²³Department of Radiology and Nuclear Medicine, Radboud University Medical Centre, Nijmegen, the Netherlands; ²⁴Department of Radiology and Nuclear Medicine, Gelre Hospital, Apeldoorn, the Netherlands; ²⁵Department of Radiology and Nuclear Medicine, Amsterdam UMC, VU University Amsterdam, Amsterdam, the Netherlands and ²⁶Department of Hematology, Amsterdam UMC, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands

ABSTRACT

Patients with MYC-rearrangement positive large B-cell lymphoma (MYC+ LBCl) have an inferior prognosis following standard first-line therapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) compared to patients without MYC rearrangement. Although intensive chemotherapy regimens yield higher remission rates, toxicity remains a concern. Lenalidomide is an oral immunomodulatory drug which downregulates MYC and its target genes thereby providing support using lenalidomide as additional therapeutic option for MYC+ LBCl. A phase II trial was conducted evaluating the efficacy of lenalidomide (15 mg day 1-14) in combination with R-CHOP (R2CHOP) in newly diagnosed MYC+ LBCl patients identified through a nationwide MYC-FISH screening program. The primary endpoint was complete metabolic response (CMR) on centrally reviewed ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET)-computer tomography (CT)-scan at end-of-treatment. Secondary endpoints were overall survival (OS), disease-
free survival (DFS) and event-free survival (EFS). Eighty-two patients with stage II-IV MYC+ LBCL were treated with six cycles of R2CHOP. At end of treatment, 67% (95% Confidence interval [CI]: 58-75) of the patients reached CMR. With a median follow-up of 25.4 months, 2-year estimates for OS, DFS, EFS were 73% (95% CI: 62-82), 75% (95% CI: 63-84) and 63% change to: (95% CI: 52-73) respectively. In this prospective trial for newly diagnosed MYC+ LBCL patients, we found that administering R2CHOP was safe, and yields comparable CMR and survival rates as in studies applying more intensive chemotherapy regimens. Hence, these findings offer new prospects for MYC+ LBCL patients and warrant comparison in prospective randomized clinical trials. This trial was registered at www.clinicaltrialsregister.eu (#2014-002654-39).

**Methods**

**Screening program and patient eligibility**

To support timely diagnosis of MYC+ LBCL and optimal enrolment in the present clinical trial, a nationwide diagnostic support program for MYC rearrangement assessment by fluorescence in situ hybridization (FISH) was implemented. Patients ≥18 years with newly diagnosed DLBCL or with B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma (BLC-U) according to the WHO 2008 classification with a proven MYC rearrangement by FISH analysis including SH (not Burkitt lymphoma), DH or TH DLBCL were eligible.

During the screening period one cycle of R-CHOP, a short course of steroids, or irradiation to control local symptoms was allowed. Patients with Ann Arbor stage II-IV, a WHO performance status (PS) of 0-3, ≥ one lesion of ≥1.5 cm on a contrast-enhanced CT scan and zone positive lesion on PET-CT scan were eligible. Patients diagnosed with any other subtype of aggressive B-cell lymphoma, a history of follicular lymphoma, proven CNS localization or HIV positivity were excluded.

**Treatment**

Treatment consisted of six cycles of standard R-CHOP every 3 weeks plus lenalidomide 15 mg orally on day 1-14 (R2CHOP: Online Supplementary Table S1), followed by two additional rituximab administrations.

Prophylactic intrathecal methotrexate or cytarabine (≥4 administrations), pegfilgrastim, venous thromboembolism prophylaxis (with aspirin or low-molecular-weight-heparin), and *Pneumocystis* prophylaxis were mandatory.

**Safety assessments**

Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (AE), version 4.03. AE grade 1 were not reported.

**Study overview**

This multicenter, phase II study was designed by investigators of HOVON and was approved by the medical ethics committee of the Amsterdam UMC. All patients provided written informed consent. The trial was conducted in accordance with the
Declaration of Helsinki and Good Clinical Practice guidelines. An independent data and safety monitoring board conducted a review during the planned interim analysis.

Endpoints

The primary endpoint of the study was CMR on EOT PET-CT scan as determined by central review plus EOT bone marrow (BM) examination in case of BM localization at diagnosis. In case a BM examination was not repeated at EOT in patients with baseline BM localization and the EOT-PET scan showed no BM uptake localization, the response was classified as CMR (based on recent findings that CMR on PET-CT has a high negative predictive value for BM localization).22,24

Secondary endpoints were: OS defined as time from registration to death; DFS defined as time from achievement of first CMR on protocol until relapse or death whichever comes first; EFS defined as the time from registration to lack of CMR on EOT-PET-CT, relapse or death; and positive predictive value (PPV) and negative predictive value (NPV) of iPET-CT for EOT result.

Statistical analyses

An optimal Simon two-stage design was used with a response rate of 45% as the null hypothesis, and 60% as the alternative hypothesis. With a statistical significance level of 5% and a power of 80%, the required number of patients was 77, with an interim analysis for futility involving the first 26 included patients. In order to overcome dropouts due to ineligibility, 85 patients were enrolled. All efficacy analyses were restricted to eligible patients, while safety analyses included all enrolled patients. Data cut-off was June 28, 2019.

For the clinical protocol, central pathology review, central PET-CT review and additional statistical information, see the Online Supplementary Data.

Results

Clinical characteristics

From April 2015 to February 2018, 85 patients were included from 20 hospitals in the Netherlands and Belgium. Three patients were declared ineligible (two because the MYC+ status was based on immunohistochemistry and not on FISH and one because of a transformed lymphoma), leaving 82 patients for efficacy and 85 patients for safety analyses.

Baseline patient and disease characteristics are shown in Table 1. The median age was 63 years (range: 28-82 years). 49 of 81 patients (60%) had a WHO performance status (PS) of 0; 58 of 71 patients (71%) had stage IV disease, and 42 of 82 patients (51%) had ≥2 extranodal localizations. The IPI score was high-intermediate and high in 65% of patients.

During treatment 12 of 82 patients went off protocol before completion (progressive disease [n=7], toxicity [n=2]; pulmonary embolism and diarrhea, other reasons [n=3]; new diagnosis of colon cancer, patient refusal, and vertebral fracture), see Figure 1.

Pathology review

Diagnostic biopsy samples of all 85 patients were available for pathology review. Results of all 82 eligible patients are summarized in Table 1 and the Online Supplementary Table S2. A diagnosis of DLBCL according to the WHO 2008 classification was confirmed in 65 of 82 patients (79%) and BCL-U in 12 of 82 patients (15%) and morphology was indiscernible between DLBCL and BCL-U in 5 of 82 patients (6%). For classification according to the WHO classification 2017 see the Online Supplementary Table S2.

In 81 of 82 patients MYC rearrangement was confirmed at central review. Based on the intention to treat principle, the one patient in whom MYC rearrangement could not be confirmed was included in all analyses. In 9 of 82 cases, insufficient material was available to perform additional BCL2 and BCL6 rearrangement. In 73 of 82 cases, data on BCL2 and BCL6 rearrangement were available: 20 of 82 (26%) had a single MYC rearrangement (SH); 44 of 82 (54%) had DH lymphoma (31 patients had MYC/BCL2 rearrangements and 13 patients MYC/BCL6 rearrangements), and 9 of 82 (11%) had all three rearrangements (TH).

COO classification using a standard Hans algorithm showed GCB phenotype in 63 of 71 (89%) and non-GCB phenotype in 8 of 71 (11%). Lymph2Cx classification was performed in 38 cases showing GCB-subtype in 29 of 38 patients (76%), ABC-subtype in 7 of 38 patients (18%), and intermediate subtype in 2 of 38 patients (5%). Out of the 24 DH of TH patients, 21 showed GCB-subtype and 3 ABC-subtype. Out of the 12 SH patients, 8 showed GCB-subtype and 4 ABC-subtype.

Treatment

Most patients (n=68) started with lenalidomide in the second cycle and continued lenalidomide for 14 days after the sixth cycle of R-CHOP. When MYC FISH results were available at diagnosis, R2CHOP was started in the first cycle (n=14) (Figure 1).

Patients received a median (interquartile range [IQR]) dose of the planned drugs in the R-CHOP regimen as follows: cyclophosphamide 99.9% (99.0-101); vincristine 100% (72.5-100); doxorubicin 99.5% (97.7-101); prednisone 100% (100-100); rituximab 98.1% (95.1-100); pegfilgrastim 100% (100-100). Lenalidomide was given at a median dose intensity of 100% (range: 85.7-100). 57 of 82 patients (70%) received the planned 4 intrathecal prophylactic administrations.

Primary endpoint: CMR at EOT

At EOT PET-CT, 55 of 82 patients (67%) reached the primary endpoint of CMR (95% CI: 58-75, P<0.001), 5 of 82 patients (6%) reached a partial metabolic response (PR), and 21 of 82 patients (26%) had progressive metabolic disease (PMD) (Table 2).

One patient went off protocol due to toxicity after cycle 5 without EOT PET-CT (response unknown).

Univariate logistic regression analysis of baseline characteristics (BM localization, WHO performance status, stage, B symptoms, IPI, number of extranodal sites and age) did not reveal any significant predictors for reaching CMR.

Exploratory descriptive subgroup analyses revealed no differences between SH and DH/TH patients regarding achievement of the primary endpoint: CMR rate in both groups was 70% and 66% respectively (nine patients with unknown BCL2 and BCL6 rearrangement not included).

Secondary endpoints: survival analyses

With a median follow-up of 25.4 months (IQR 18.3-30.3), 1-year OS was 85% (95% CI: 76-91), DFS 77% (95% CI: 65-85) and EFS 66% (95% CI: 54-73). 2-year estimates for OS, DFS, EFS were and 73% (95% CI: 62-82),
75% (95% CI: 63-84) and 63% (95% CI: 52-73) respectively (Figure 2A-C).

Baseline patient characteristics (BM localization, WHO performance status, stage, B symptoms, IPI, number of extranodal sites and age) were not significantly predictive for prolonged OS in a univariate analysis at the 5% significance level.

Univariate regression analyses indicated that SH and DH/TH patients had comparable EFS and DFS, however DH/TH patients had a tendency for a higher risk of death compared to SH patients (Hazard ratio [HR] 1.84, P=0.055; 95% CI: 0.95-3.53, P=0.055). (Figure 3). EOT PET-CT predicted relapse within 12 months, with a positive predictive value (PPV) of 31% and a negative predictive value (NPV) of 93% (Online Supplementary Figure S1A-B).

In univariate analyses with response as time dependent covariate we found that patients who had achieved CMR at EOT PET experienced a reduced risk of death compared to patients who had not achieved CMR (HR 0.1, 95% CI: 0.08-0.53, P<0.001, (Figure 3). EOT PET-CT predicted relapse within 12 months, with a positive predictive value (PPV) of 31% and a negative predictive value (NPV) of 93% (Online Supplementary Table S3A).

In total, 29 patients showed progressive disease (11 without achieving CMR, 18 after achieving CMR [at interim or EOT PET-CT]) including one patient with a CNS relapse.

Safety
Grade 2, 3 and 4 AE were seen in 27 (32%), 33 (39%) and 14 (16%) of all 85 registered patients respectively (Table 3). The most common grade 3–4 AE were neutropenia (18%), infections (14%) and gastrointestinal disorders (14%). Four patients experienced deep venous thrombosis (grade 2), and two patients pulmonary embolism (grade 3). Two of these patients (one with deep venous thrombosis and one with pulmonary embolism) had not received the mandatory thrombosis prophylaxis (protocol violation). One patient went off protocol due to grade 3 diarrhea.

71 serious AE were reported in 36 patients; 66 were due to hospitalization (42% infections, 26% gastrointestinal disorders), four to other conditions [two second primary malignancies, two recurrence of previously diagnosed (>5 year) malignancies]. One patient died during treatment due to progression. There were no treatment related deaths.

Observational analysis: predictive value of iPET-CT
At iPET-CT after three cycles of R2CHOP, 57 of 82 patients (70%) were in CMR; of these 45 of 57 (79%) were still in CMR and 11 of 57 (19%) showed PMD at EOT PET-CT, and one missed EOT evaluation (Table 2). 23 of 82 patients (28%) were in PMR at iPET-CT; 10 of 23 (43%) of these converted to CMR, 4 of 23 (17%) remained in PMR, 9 of 23 (39%) showed PMD at EOT. The PPV of iPET-CT for predicting EOT PET-CT result was 60% (15 of 25), the NPV 79% (45 of 57) (Online Supplementary Table S3B).

Discussion
From retrospective series it is clear that first-line R-CHOP therapy is not sufficiently effective for patients with MYC+ LBCL with CR rates of 40-50% and 3-year OS rates of 85% only.31 Intensiﬁed chemotherapy regimens such as R-CODOX-M/R-IVAC or autologous stem cell transplantation have not improved OS, and result in increased toxicity.5,9,11

We designed a prospective clinical trial for MYC+ LBCL patients, in which a time window of one cycle of R-CHOP was allowed to perform molecular diagnostics. This approach permitted high risk patients to start treatment immediately and overcome the bias of inclusion of mainly
lower risk patients due to enrolment delays. In this trial we show that the addition of lenalidomide to R-CHOP resulted in EOT CMR rate of 67%, CMR and 2-year survival rates of 73%, 75%, and 63% for OS, DFS and EFS respectively. To our knowledge, this is the second prospective trial especially designed for MYC+ LBCL patients. Recently, Dunleavy and colleagues reported a single arm phase II study in which the efficacy of DAEPOCH-R for MYC+ LBCL patients was explored. Results for EOT CMR and survival rates are largely comparable between both approaches with EOT CMR rate of 74%, 4-year OS rates of 77% and EFS of 71% in the study.

**Figure 1. Disposition of the patients.** Eighty-two patients were included. In 14 patients, MYC fluorescence in situ hybridization (FISH) was performed immediately at diagnosis, these patients started with R2CHOP (lenalidomide in combination with rituximab cyclophosphamide, doxorubicin, vincristine, and prednisolone) in cycle 1. In 68 patients, MYC results became available during the first cycle of R-CHOP; these patients were registered after the first cycle of R-CHOP and started with R2CHOP in the second cycle and continued lenalidomide for 14 days after the sixth cycle of R-CHOP. During treatment 13 patients went off protocol (progressive disease [n=7], toxicity [n=2; pulmonary embolism and diarrhea], other reasons [n=3; new diagnosis of colon cancer, patient refusal, and vertebral fracture]). R: rituximab, R2: rituximab + lenalidomide
of Dunleavy. When compared to the trial of Dunleavy, our patient population was larger (82 vs. 53 patients), comparable in age (median 63 vs. 61 years) but included more patients with IPI ≥3 (65% vs. 49%) and more patients with DH/TH (65% vs. 45%). Regarding safety, grade 3/4 infections were seen in 24% of cycles with DA-EPOCH-R versus grade 3 (and no grade 4 infections) in only 2.8% of cycles (18 episodes) with R2CHOP. DA-EPOCH-R resulted in three treatment related deaths vs. none with R2CHOP.

Lenalidomide penetrates the CNS, and thereby may aid to prevent CNS relapses as has been suggested for non-germinal center B-cell (GCB) subtype lymphoma patients treated with R2CHOP. Indeed, in this study, which combined lenalidomide and intrathecal prophylaxis, a remarkably low rate of CNS relapse at a median follow-up of 25.4 months was seen (n=1).

Several remarks regarding our study can be made. First, although correlation of CMR at EOT PET-CT with survival in MYC+ LBCL has been described in a retrospective study, one might argue that it is not an ideal primary endpoint. Given the high FDG-avidity of MYC+ LBCL and the fact that CMR at EOT PET-CT in our study was highly predictive for DFS (NPV of 93%), we feel that using CMR at EOT PET-CT as a surrogate endpoint for highly aggressive B-cell lymphomas such as MYC+ LBCL is justified.

Second, clinical prognostic markers, including age, stage, IPI score, as well as COO were not significantly correlated to CMR on EOT PET-CT and survival, which might be explained by the inclusion of high risk patients; 65% of our patients have an IPI score of ≥3, versus only 27% in Ziepert’s meta-analysis of the value of IPI in the rituximab era.

### Table 2. Response rates on interim and EOT PET-CT scan.

|     | EOT | CMR | PMR | PMD | unknown | total |
|-----|-----|-----|-----|-----|---------|-------|
| Interim | n   | n   | n   | n   | n       | n     |
| CMR    | n   | 45  | 0   | 11  | 1       | 57    |
| PMR    | n   | 10  | 4   | 9   | 0       | 23    |
| PMD    | n   | 0   | 1   | 1   | 0       | 2     |
| total  | n   | 55  | 5   | 21  | 1       | 82    |

Response rates on interim and EOT PET-CT scan. Correlation of interim and end of treatment (EOT) response rates by centrally reviewed positron emission tomography (PET)-computer tomography (CT) scan. One patient was in complete metabolic response (CMR) at interim scan but went off protocol due to toxicity without an EOT scan. PMR: partial metabolic response; PMD: progressive metabolic disease.
Furthermore, our patient population included patients with SH lymphoma (24%) based on previous reports demonstrating poor prognosis of these patients following R-CHOP. However, in the revised WHO 2017 classification, SH is not recognized as a separate entity in contrast to DH/TH lymphoma. Recently, Rosenwald et al. demonstrated that the inferior prognosis of MYC rearranged patients is largely observed in patients with DH lymphoma. However, SH patients still have a worse prognosis compared to patients without a MYC rearrangement, although this is not statistically significant when regarding OS ($P=0.077$). Our trial was not powered to study the prognostic impact of SH versus DH/TH in the R2CHOP setting.

Finally, we explored the role of iPET-CT scanning as a tool for early identification of refractory MYC+ LBCL. In non-selected cases of DLBCL, CMR on iPET-CT after two to four R-CHOP cycles has a high NPV for 2-year PFS, but the PPV varies widely. In our study, the PPV of iPET-CT for achievement of CMR on EOT PET-CT was only 60% and therefore does not support the use of an interim PET-CT scan as interpreted with the current standard criteria to identify primary refractory cases treated with R2CHOP.

In this prospective trial for newly diagnosed MYC+ LBCL patients, we found that administering R2CHOP was safe, and yielded comparable CMR and survival rates as in studies applying intensive chemotherapy regimens. Moreover, R2CHOP can be delivered on an outpatient setting.

### Table 3. Adverse events.

|                         | grade 2 | grade 3 | grade 4 |
|-------------------------|---------|---------|---------|
|                         | n       | %       | n       | %       | n       | %       |
| **Hematologic**         |         |         |         |         |         |         |
| neutropenia             | 1       | 1       | 5       | 6       | 10      | 12      |
| febrile neutropenia     |         |         | 6       | 7       |         |         |
| thrombocytopenia        | 2       | 2       | 2       | 2       | 4       | 5       |
| anemia                  | 6       | 7       | 5       | 6       |         |         |
| **Infectious**          |         |         |         |         |         |         |
|                         | 15      | 18      | 12      | 14      |         |         |
| **Vascular disorders**  |         |         |         |         |         |         |
| pulmonary embolism      | 2       |         | 3       |         |         |         |
| deep venous thrombosis  | 4       | 5       |         |         |         |         |
| superficial thromboembolitis | 4 | 5 |         |         |         |         |
| **Nervous system disorders (PNP)** | 25 | 29 | 9 | 11 |         |         |
| **Gastrointestinal disorders** | 17 | 20 | 12 | 14 |         |         |
| **Hepatobiliary disorders (ALT, AST increased)** | 5 | 6 | 1 | 1 | 2 | 2 |
| **General disorder**    | 11      | 13      | 5       | 6       | 1       | 1       |
| **Any**                 | 27      | 32      | 33      | 39      | 14      | 16      |

Adverse events were graded per patient (maximum grade per cycle) according to National Cancer Institute Common Terminology Criteria for AE. AE events grade 1 were not reported. *In this row each patient is counted only once with the highest grade AE experienced. PNP: polyneuropathy; ALT: alanine transaminase; AST: aspartate transaminase.

![Figure 3. Survival according to end-of-treatment PET-CT scan result.](image-url)
basis in contrast to Burkitt schemes and is easier to deliver than DA-EPOCH-R, since it does not require placement of a central line. These findings offer new prospects for MYC+ LBCL patients and warrant comparison in prospective randomized trials.

Acknowledgments
The authors wish to acknowledge: the trial managers and central data managers of the study (N. Lamers and A. Elsinghorst, R. Sewarson and H. Hofwegen), HOVON data center in Rotterdam; Dr Staudt’s Laboratory at NCI/NIH Bethesda, MD, USA, for online analysis of Lymph2Cx raw data for COO characterization; and the DSMB members M. Jerkeman, K. Dunleavy and E. van Werkhoven for their advice following the interim analysis.

Funding
This work was supported by Celgene who funded the research, provided lenalidomide free of charge, approved the original protocol and all amendments as written, but had no role in either the design of the study, the collection, analysis, and interpretation of the data, or the preparation of the manuscript. The Dutch Cancer Society provided funding for the screening program and the clinical trial.

References
1. Suerdow SH, Campo E, Fillet SA, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2387-2390.
2. Ziepert M, Hasenclever D, Kuhnt E, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(14):2573-2580.
3. Lenz G, Wright GW, Emer NC, et al. Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. Proc Natl Acad Sci U S A. 2008;105(36):13520-13525.
4. Aukema SM, Kreuz M, Kohler CW, et al. Biologic characterization of adult MYC-translocation positive mature B-cell lymphomas other than molecular Burkitt lymphoma. Haematologica. 2014;99(4):726-735.
5. Oki Y, Nooani M, Lin P, et al. Double hit lymphoma: the MD Anderson Cancer Center clinical experience. Br J Haematol. 2014;166(6):891-901.
6. Savage KJ, Johnson NA, Ben-Neriah S, et al. MYC gene rearrangements are associated with a poor prognosis in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. Blood. 2009;114(17):3533-3537.
7. Rosenwald A, Bens S, Advani R, et al. Prognostic significance of MYC rearrangement and translocation partner in diffuse large B-cell lymphoma: a study by the Lunenburg Lymphoma Biomarker Consortium. J Clin Oncol. 2019;37(5):3559-3568.
8. Barrans S, Crouch S, Smith A, et al. Rearrangement of MYC is associated with poor prognosis in patients with diffuse large B-cell lymphoma treated in the era of rituximab. J Clin Oncol. 2010;28(20):3360-3365.
9. Howlett C, Sneedecor SJ, Landsburg DJ, et al. Front-line,dose-escalated immunotherapy is associated with a significant progression-free survival advantage in patients with double-hit lymphomas: a systematic review and meta-analysis. Br J Haematol. 2015;170(4):504-514.
10. Petrich AM, Gandhi M, Jovanovic B, et al. Impact of induction regimen and stem cell transplantation on outcomes in double-hit lymphoma: a multicenter retrospective analysis. Blood. 2014;124(15):2554-2561.
11. Landsburg DJ, Falkiewicz MK, Maly J, et al. Outcomes of patients with double-hit lymphoma who achieve complete remission. J Clin Oncol. 2017;35(20):2260-2267.
12. Dunlevy K, Fanale MA, Abramson JS, et al. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study. Lancet Haematol. 2018;5(12):e609-e617.
13. Witzig TE, Wiemik FH, Moore T, et al. Lenalidomide oral monotherapy produces durable responses in relapsed or refractory indolent non-Hodgkin’s lymphoma. J Clin Oncol. 2009;27(52):5404-09.
14. Lopez-Girona A, Heintel D, Zhang LH, et al. Lenalidomide downregulates the cell survival factor, interferon regulatory factor-4, providing a potential mechanistic link for predicting response. Br J Haematol. 2011;154(3):325-336.
15. Ayed AO, Chiappella A, Pederson L, et al. CNS relapse in patients with DLBCL treated with lenalidomide plus R-CHOP (R2CHOP): analysis from two phase 2 studies. Blood Cancer J. 2018;8(7):85.
16. Castellino A, Chiappella A, LaFlant RR, et al. Lenalidomide plus R-CHOP-F1 in newly diagnosed diffuse large B-cell lymphoma (DLBCL): long-term follow-up results from a combined analysis from two phase 2 trials. Blood Cancer J. 2018;8(11):108.
17. Vitolo U, Witzig TE, Gascoyne RD, et al. ROBUST: first report of phase III randomized study of lenalidomide-R-CHOP (R3- CHOP) vs placebo/R-CHOP in previously untreated ABC-type diffuse large B-cell lymphoma. Haematol Oncol. 2019;37(52):36-37.
18. Chamuleau M, Nijland M, Lamers N, et al. First Report on a successful screening program for MYC rearrangements and a prospective clinical trial based on MYC rearrangement in newly diagnosed DLBCL patients in the Netherlands. Blood. 2017;130(Supplement 1):1144.
19. Scott DW, Wright GW, Williams FM, et al. Determining cell-of-origin subtypes of diffuse large B-cell lymphoma using gene expression in formalin-fixed paraffin-embedded tissue. Blood. 2014;123(12):2117-2127.
20. Barrington SE, Mikhail NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2014;32(27):3048-3058.
21. Cheson BD, Fisher RI, Barrington SE, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068.
22. Boellard R, Delgado-Bolton R, Oven WJ, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015;42(2):528-354.
23. Teagle AR, Barton H, Charles-Edwards E, Dizdalevic S, Chevassut T. Use of FDG PET/CT in identification of bone marrow involvement in diffuse large B cell lymphoma and follicular lymphoma: comparison with iliac crest bone marrow biopsy. Acta Radiol. 2017;58(12):1476-1484.
24. Berthet L, Cochet A, Kanoun S, et al. In newly diagnosed diffuse large B-cell lymphoma, determination of bone marrow involvement with 18F-FDG PET/CT provides better diagnostic performance and prognostic stratification than does biopsy. J Nucl Med. 2015;56(8):1244-1250.
25. Maurer MJ, Ghesquieres H, Link BK, et al. Diagnosis-to-treatment interval is an important clinical factor in newly diagnosed diffuse large B-cell lymphoma and has implication for bias in clinical trials. J Clin Oncol. 2018;36(16):1600-1610.
26. Cohen JB, Geyer SM, Lozanski G, et al. Complete response to induction therapy in patients with Myc-positive and double-hit non-Hodgkin lymphoma is associated with prolonged progression-free survival. Cancer. 2014;120(11):1677-1685.
27. Landsburg DJ, Falkiewicz MK, Pettich AM, et al. Sole rearrangement but not amplification of MYC is associated with a poor prognosis in patients with diffuse large B-cell lymphoma and B cell lymphoma unclassifiable. Br J Haematol. 2016;175(4):651-640.
28. Burggraaff CN, de Jong A, Hoekstra OS, et al. Predictive value of interim positron emission tomography in diffuse large B-cell lymphoma: a systematic review and meta-analysis. Eur J Nucl Med Mol Imaging. 2019;46(1):65-79.