Molecular Characteristics of Diffuse Large B-Cell Lymphoma and Correlation with Baseline Metabolic Tumor Volume (MTV) and Interim Positron Emission Tomography (iPET) and Outcome in the PETAL Trial.

Julia Richter1, Andreas Hüttmann2,*, Jan Rekowskii3, Christine Schmitz2, Selina Gaertner2, Andreas Rosenwald4, Martin-Lee Hansmann5, Sylvia Hartmann6, Peter Möller1, Hans-Heinrich Wacker4, Alfred Keller7, Christoph Thron8, Stefan Müller9, Ulrich Dürrsen9, and Wolfram Klapper10

1Institut für Krebsforschung, Freiburg; 2Department of Hematology, University Hospital Schleswig-Holstein, Kiel, Germany; 3Department of Gastro-Intestinal Oncology, University Hospital Leipzig, Germany; 4Department of Pathology, University Hospital Essen, Germany; 5Department of Pathology, University Hospital of Schleswig-Holstein, Kiel, Germany; 6Department of Internal Medicine I, University Hospital of Schleswig-Holstein, Kiel, Germany; 7Department of Radiology, University Hospital of Schleswig-Holstein, Kiel, Germany; 8Department of Hematology and Medical Oncology, University Hospital of Schleswig-Holstein, Kiel, Germany; 9Clinic for Medical Oncology and Hematology, University Hospital of Schleswig-Holstein, Kiel, Germany; 10Department of Nuclear Medicine, University Hospital Essen, University of Duisburg-Essen, Essen, Germany. The authors declare no conflict of interest. The manuscript was written by all authors. All authors have seen and approved the final version of the manuscript.

Introduction: Treatment results in diffuse large B-cell lymphoma (DLBCL) are heterogeneous. Established risk models like the International Prognostic Index (IPI) and molecular lymphoma features such as MYC translocations and the cell origin (COO) subtype are prognostic of outcome. A positive iPET scan after 2 cycles of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) has recently been shown to predict poor outcome independently of the IPI (Positron Emission Tomography-Guided Therapy of Aggressive Non-Hodgkin Lymphomas trial (PETAL); Duhren et al., J Clin Oncol 36:2024, 2018). Another PET-derived parameter of potential prognostic significance is baseline MTV. This retrospective analysis of lymphoma biopsies from the PETAL trial investigated the relationship between molecular lymphoma features and PET parameters.

Methods: Available lymphoma specimens were analyzed for COO by immunohistochemistry employing the Hans classifier (HC) and by gene expression (GE) using the HTG EdgeSeq System (HTG Molecular Diagnostics). MYC and BCL2 and/or BCL6 translocations (“double-hit” [DH]) were assessed by fluorescence in situ hybridization (FISH). MTV was determined applying the 41% SUVmax segmentation method, and iPET was evaluated using the deltaSUVmax method. Association between iPET result and molecular lymphoma features was assessed by risk ratios (RR). Survival curves of time-to-event endpoints were compared using hazard ratios (HR) from Cox regression and the log-rank test.

Results: Figure 1: Overview of PETAL trial design. Distribution of DLBCL patients according to iPET stratification and randomization result in iPET positive cases.

Table 1: Distribution between treatment arms according to lymphoma classification by cell of origin analyses (HC, GE) and double-hit status. Abbreviations: ABC, activated B-like diffuse large B-cell lymphoma; Amp, amplification; GCB, germinal centre B-like diffuse large B-cell lymphoma; GE, gene expression; HC, Hans classifier; QC, quality control.

Table 2: Univariate analysis of factors determining iPET response and allocation to the high MTV group (≥30 ml).

Figure 2: Mosaic plot visualizing the relationship between the three variables Hans-classifier (HC; immunohistochemistry), gene expression (GE; next generation sequencing) and “double-hit” status (DH; FISH) in 170 patients for whom complete information was available.

Figure 3: Multivariable analysis of factors determining the event-free survival and overall survival in DLBCL patients. The left panel shows the results for event-free survival and the right panel shows the results for overall survival. Abbreviations: DH, double-hit; iPET, interim positron-emission tomography; GCB, germinal centre B-like diffuse large B-cell lymphoma; GE, gene expression; HC, Hans classifier; iPET, interim positron-emission tomography; IPI, International Prognostic Index; MTV, metabolic tumor volume.

Figure 4: Event-free (EFS, left) and overall survival (OS, right) according to GCB and non-GCB status by Hans classifier.

Figure 5: EFS (left) and OS (right) according to ABC and GCB gene expression signature.

Conclusion: HC and GE showed good concordance with respect to COO classification, but COO was not correlated with MTV, iPET, EFS or OS. By contrast, MYC-rearranged lymphomas with or without BCL2 or BCL6 breaks were statistically significantly associated with a positive iPET, and DH lymphomas were correlated with poor outcome. Yet, the unfavorable prognosis of iPET-positive DLBCL cannot solely be explained by MYC translocations because most iPET-positive lymphomas lacked this genetic anomaly. Our results strengthen the role of iPET as a prognostic tool, independent not only of IPI, but also of COO status and MYC translocation. Furthermore, pre-treatment MTV was associated with strong predictive power for event-free and overall survival.