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Letter to the Editor

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Identification of a Patient Cohort with Relapsing Diffuse Large B-Cell Lymphoma with a Low International Prognostic Index in PET/CT Using a 2-Gene (LMO2/TNFRSF9) Scoring System

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Treating patients with diffuse large B-cell lymphoma (DLBCL) remains a challenge, with a remission rate of 75% at 2 years from diagnosis. The International Prognostic Index (IPI) [1] and molecular characterization [2] are employed in the stratification and relapse prediction. Additionally, ^{18}F-fluorodeoxyglucose positron emission tomography (PET) and computed tomography (CT) have now become part of standard care in differentiating metabolic activity of the disease from fibrosis or necrosis [3]. Early optimism that the speed of response to treatment, as indicated by an interim-PET (iPET) scan after 2–3 cycles of chemotherapy, might reliably predict cure has not been fulfilled [4].

To investigate the role of both an interim and an end-treatment-PET (ePET) scan for the management of DLBCL in an international setting, at a time when PET centers were becoming established globally, the International Atomic Energy Agency (IAEA) sponsored a study across 7 countries in Europe, South Asia, Southeast Asia, and South America [5]. This study, the largest study to date, found that 34% of cases were iPET+ after 2 or 3 cycles of standard chemotherapy (R-CHOP), but 54% of the iPET+ cases became ePET–; and that these "slow responders" had relatively good outcomes at 2 years (event-free survival, EFS: 86%). Notably, the study found that by combining a negative iPET scan with 2 clinical components of the IPI (normal LDH and good performance status), it was possible to identify a population, 35% of all cases, 98% of whom were disease free 2 years after diagnosis. By contrast, iPET+ cases that remained PET+ at the end of treatment had dismal outcomes. These findings raise the important question of how to separate slow-responding iPET+ cases who are PET– at the end treatment, who are destined for good survival, from those who will fail to achieve a complete or stable remission by continuing standard therapy.

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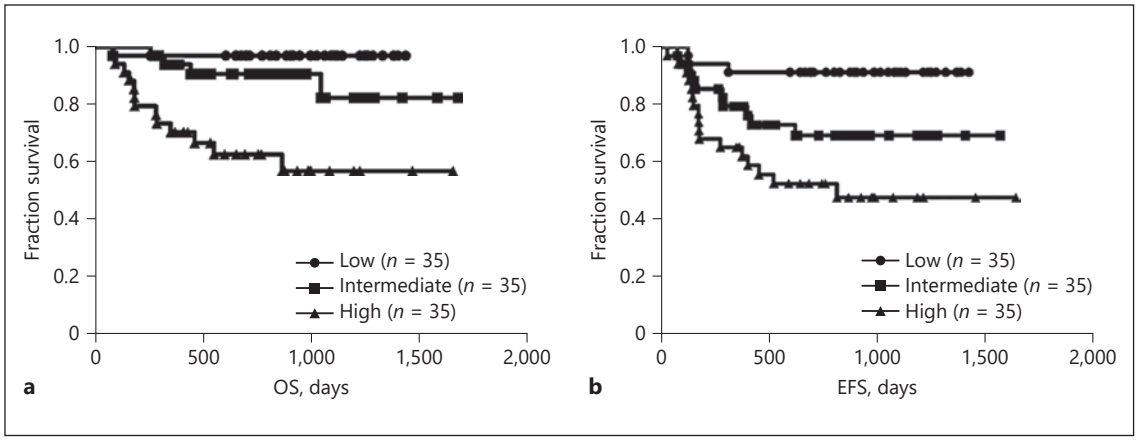

Fig. 1. a Overall survival (OS) of the TGS-IPI tertile groups: (2-gene score IPI = [0.93 × TGS] + [0.6 × IPI]). **b** Event-free survival (EFS) of TGS-IPI tertile groups.

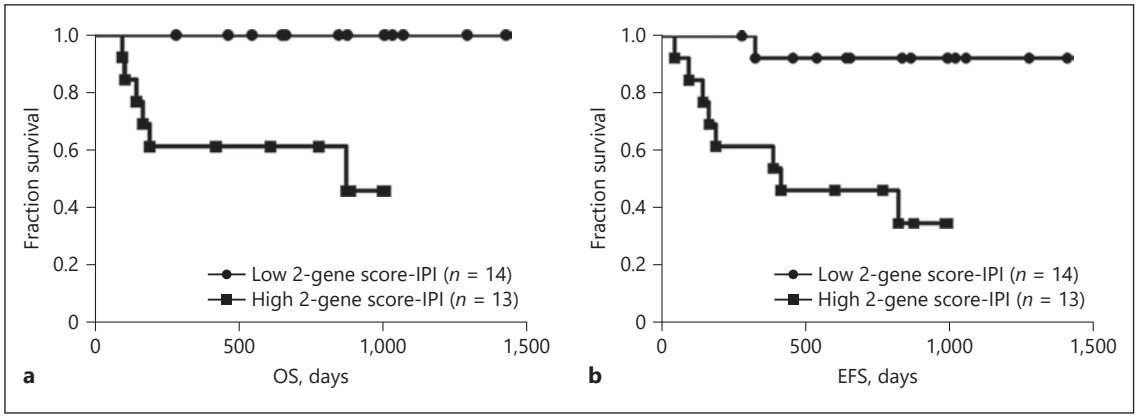

Fig. 2. Overall survival (OS; **a**) and event-free survival (EFS; **b**) of TGS-IPI within the iPET+/ePET– subgroup.

As part of this international study, available biopsy tissue from 105 subjects (online supplementary Table 1; see www.karger.com/doi/10.1159/000505605 for all online suppl. material) was transferred to a centralized laboratory to assess expression of recognized prognostic genes. Using the 6-gene model [6], initial studies demonstrated significant molecular heterogeneity of DLBCL cases between different countries, but within a country case cluster, clinical IPI score was more predictive of outcome than gene expression signature [7].

We report here the analysis of gene expression based on a published 2-gene score [8] and its interaction with IPI (TGS-IPI) and iPET to predict outcome.

As previously reported by us and others [2, 8], *LMO2* expression, a transcription regulator in normal hematopoiesis and endothelial cell remodeling, demonstrates the strongest independent prognostic value of a single gene. Consistent with previous data, high *LMO2* expression in this cohort was associated with a favorable risk in terms of overall survival (OS) (online suppl. Fig. 1A; $p < 0.01$; HR 3.7, 95% CI 1.5–9.5) and EFS (online suppl. Fig. 1B; $p < 0.05$; HR 2.2, 95% CI 1.1–4.4). Conversely, lower expression of *TNFRSF9*, which reflects the influence of the microenvironment, showed a marginal favorable risk in terms of OS but not reaching significance in this cohort (online suppl. Fig. 1C; $p = 0.27$; HR 1.7, 95% CI 0.7–4.2). The bivariate model [8], in which the weighted independent contributions from these 2 genes are analyzed, was applied to the cohort. The patients were ranked according to the 2-gene score and divided into high- and low-risk groups. A clear advantage in the low-2-gene score group in terms of OS (online suppl. Fig. 1D; $p < 0.05$; HR 0.39, 95% CI 0.15–0.97) but not EFS (online suppl. Fig. 1E; $p = 0.20$; HR 1.6, 95% CI 0.78–3.26) was observed.

By employing the recently described composite model integrating the 2-gene score with the IPI, patients could be separated into 3 evenly distributed groups ($n = 105$) with low, intermediate, and high 2-gene-IPI scores, with results consistent with those of a previously published work [8]. In terms of OS, a significant difference was observed between the intermediate and high 2-gene score IPI cohorts (Fig. 1a; $p < 0.01$, 95% CI 0.10–0.71), whilst in terms of EFS significance was observed between the low and intermediate 2-gene score IPI cohorts (Fig. 1b; $p < 0.05$; HR 0.30, 95% CI 0.10–0.88). However, omission of rituximab (as eligible patients might otherwise be excluded for

financial reasons) had no significant effect on these observations.

Next, the relationship between PET response at interim and/or end treatment and the 2-gene IPI score was explored. First, we tested whether iPET with ePET status (i.e., 4 combinations) and the 2-gene IPI score were independent variables. Using the χ^2 analysis, no relationship was observed ($p = 0.08$). Secondly, taking all iPET+ patients, irrespective of ePET status, the 2-gene IPI score did not identify a group with a significant survival advantage or disadvantage ($p = 0.18$), demonstrating that the 2-gene IPI score could not risk stratify at the point of mid-treatment response assessment.

The subcohort of patients ($n = 27$) who were iPET+/ePET– was proportionally similar to our previously published work (26%) [5]. This cohort was next divided into 2 distinct low and high 2-gene score IPI groups. Hence, when the TGS-IPI score was applied to the iPET+/ePET– subgroup, a group that in our previous analysis of stratification by PET response alone was found to have a generally good EFS and OS [5], it was found that the TGS-IPI score became a powerful predictor of longer-term outcomes, OS ($p < 0.005$; HR 0.09, 95% CI 0.02–0.48), EFS ($p < 0.005$; HR 0.13, 95% CI 0.04–0.51; Fig. 2a, b). Distinction between the subgroups revealed a clinically important degree of EFS advantage for patients with a low TGS-IPI, in contrast to early relapse and surprisingly poor outcomes for those with high TGS-IPI scores.

In conclusion, we have demonstrated that calculation of the 2-gene-IPI score for those iPET+ patients, who have achieved complete response by international criteria on completion of treatment, can be stratified into those with an excellent long-term outcome and those who are at risk of early disease progression. This novel combined modality approach, whilst requiring further assessment in a larger cohort, for the first time enables identification of a specific cohort who, though achieving complete response at the end of standard treatment, would benefit from close monitoring and perhaps additional intensive consolidation therapy.

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Statement of Ethics

Written informed consent in accordance with the Declaration of Helsinki was provided by all patients.

Disclosure Statement

The authors have no relevant conflicts of interest.

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Author Contributions

N.O., N.T., and R.B. performed the experiments, analyzed the data, and wrote the manuscript; P.C., F.B., B.T., E.G., N.S., and M.P.D. supervised and performed the experiments; C.A., T.G., F.R., R.N., and C.G. took care of patients, provided clinical information, and supervised the experiments; J.J.C. analyzed the experimental data; D.P., S.F., H.O., R.A.P., and R.C. conceived the study, directed the research, and wrote the manuscript.

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