Prognostic significance of immunohistochemical biomarkers in diffuse large B-cell lymphoma: a study from the Lunenburg Lymphoma Biomarker Consortium

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The Lunenburg Lymphoma Biomarker Consortium (LLBC) evaluated the prognostic value of IHC biomarkers in a large series of patients with diffuse large B-cell lymphoma (DLBCL). Clinical data and tumor samples were retrieved from 12 studies from Europe and North America, with patients treated before or after the rituximab era. Using tissue microarrays from 1514 patients, IHC for BCL2, BCL6, CD5, CD10, MUM1, Ki67, and HLA-DR was performed and scored according to previously validated protocols. Optimal cut points predicting overall survival of patients treated in the rituximab era could only be determined for CD5 (P = .003) and Ki67 (P = .02), whereas such cut points for BCL2, BCL6, HLA-DR, and MUM1 could only be defined in patients not receiving rituximab. A prognostic model for patients treated in the rituximab era identified 4 risk groups using BCL2, Ki67, and International Prognostic Index (IPI) with improved discrimination of low-risk patients. Newly recognized correlations between specific biomarkers and IPI highlight the importance of carefully controlling for clinical and biologic factors in prognostic models. These data demonstrate that the IPI remains the best available index in patients with DLBCL treated with rituximab and chemotherapy. (Blood. 2011;117(26):7070-7078)

Introduction

The prediction of outcome in patients with lymphoma is an important challenge facing clinicians. After the description of various clinical prognostic factors, decisive progress was made > 15 years ago with the establishment of the International Prognostic Index (IPI) for diffuse large B-cell lymphoma (DLBCL), the result of a large, international cooperative effort.1 However, it was clearly assumed that the variables used to build this index were surrogates of DLBCL biology. This heterogeneity was already appreciated through various morphologic, immunologic, and cytogenetic features, resulting in numerous studies attempting to assess the prognostic value of single biomarkers.2 More recently, gene-expression profiling data revealed a greater level of molecular complexity in DLBCL, with the identification of specific gene-expression signatures such as germinal-center B-cell (GCB) or activated B-cell (ABC) signatures, which are associated with distinct genetic alterations and significantly different survival rates.3,5 Given the difficulties in applying these molecular approaches in daily practice, an attempt was made to transfer this molecular classification into an IHC score.6 However, the prognostic value of this algorithm has provided very inconsistent results.7,13 These discrepant data may be related to patient selection criteria and the limited sample sizes of some series, but also to variability in technical aspects such as antibodies, different scoring methods, criteria, and cut points. A validation study assessing the reproducibility of IHC marker scoring conducted by our consortium established that the staining and scoring methodologies should be normalized to obtain a reasonable level of confidence in interpreting these markers.14,15 Furthermore, it has been shown that the predictive value of markers may be dependent on treatment, especially with the use of anti-CD20 antibodies.16,17 Given these challenges, the Lunenburg Lymphoma Biomarker Consortium (LLBC) decided to launch a study based on a large series of patients with DLBCL uniformly treated with rituximab plus cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone/prednisolone (R-CHOP) within clinical studies. In this effort, controlled marker assessment as developed in the previous “validation study”14,15 was applied to determining the prognostic value of individual IHC markers or to explore a possible combined clinicobiologic index. Two additional series of CHOP-treated patients were also studied to provide further...
Methods

Patients
Prospective clinical studies organized by European and American collaborative groups or population-based reference centers were selected for this study based on (1) inclusion of patients with DLBCL treated with standard anthracycline-based therapy, with at least 6 cycles of CHOP or CHOP-like chemotherapy with or without rituximab; (2) availability of complete clinical data at study registration and an updated follow-up of at least 3-years; and (3) the possibility of retrieving paraffin blocks from the diagnostic biopsy samples. Six of these studies—GELA 98-58 and 05-1 (NCT001355409), ECOG4494,18 BCaCa,20 MINT,21 and HOVON-46 (NCT00012871)—performed between February 1998 and August 2005, included patients treated with R-CHOP in 2-armed studies with a control group treated with CHOP only or patients from registry data selected within 18 months of when rituximab was introduced (BCCa only). These cohorts are designated as rituximab-CHOP (r-CHOP) and control-CHOP (c-CHOP), respectively. The other studies (EORTC-20901, HOVON-25/26,22 GLHSG-B1/B2,23,24 and UK-Bart’s & Manchester) included patients treated before the rituximab era, between August 1989 and February 2004; these patients are designated as earlier CHOP (e-CHOP) patients.

This study was approved by the ethical committees of all collaborating trial organizations and centers to comply with the Declaration of Helsinki. Data obtained from each corresponding group were electronically transferred to the LLBC statisticians and checked for data completeness and consistency with previous original publications of the clinical studies.

Sample collection, processing, IHC, and marker assessment
Tissue microarrays (TMAs) were constructed by each pathology reference center for all available samples using 0.6-mm core samples in triplicate, as described previously.14 Based on the results of the validation study, a policy of “one marker/one laboratory” was followed, implying that sections of all described previously.14

Results

Patient population and biomarker assessment
Clinical data were collected for 2451 patients with DLBCL from 12 studies (e-CHOP, 674 patients; c-CHOP, 620 patients; and e-CHOP, 1157 patients). Material for TMA was available for 12 studies (r-CHOP, 674 patients; c-CHOP, 620 patients; and e-CHOP, 1157 patients). Clinical data were collected for 2451 patients with DLBCL from 12 studies (r-CHOP, 674 patients; c-CHOP, 620 patients; and e-CHOP, 1157 patients). Material for TMA was available for 12 studies (r-CHOP, 674 patients; c-CHOP, 620 patients; and e-CHOP, 1157 patients).
Table 1. Distribution of IPI and survival estimates in the 3 groups among the 1514 of 2451 patients for which blocks were available for construction of a TMA

<table>
<thead>
<tr>
<th>Analysis group</th>
<th>All patients</th>
<th>Age &gt; 60 y</th>
<th>IPI category low</th>
<th>IPI category intermediate</th>
<th>IPI category high</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4-year OS</td>
<td>No. of patients (%)</td>
<td>4-year OS (95% CI)</td>
<td>No. of patients (%)</td>
<td>4-year OS (95% CI)</td>
</tr>
<tr>
<td>r-CHOP (n = 347)</td>
<td>69% (64.7%)</td>
<td>231 (67%)</td>
<td>94 (27%)</td>
<td>85% (75, 91%)</td>
<td>80 (23%)</td>
</tr>
<tr>
<td>c-CHOP (n = 289)</td>
<td>55% (49, 61%)</td>
<td>211 (73%)</td>
<td>79 (27%)</td>
<td>84% (73, 91%)</td>
<td>63 (22%)</td>
</tr>
<tr>
<td>e-CHOP (n = 878)*</td>
<td>59% (55, 62%)</td>
<td>411 (47%)</td>
<td>428 (50%)</td>
<td>76% (72, 80%)</td>
<td>208 (25%)</td>
</tr>
</tbody>
</table>

Median follow-up was 4.4, 5.2, and 5.8 years among the r-CHOP, c-CHOP, and e-CHOP patients, respectively.

*Thirty-three e-CHOP patients (4%) did not have IPI data.

Il II/IV), had fewer extranodal sites of involvement (20% vs 41% with >1 extranodal site), and were less likely to have elevated lactate dehydrogenase levels (47% vs 59% above normal value), resulting in a higher percentage of low-risk patients (41% vs 20%, P < .001). As expected, OS was significantly longer (P < .0001 for each cohort). In addition, highly significant differences in OS were detected by IPI risk groups (P < .0001 for all 3 cohorts; Table 1 and Figure 1).

Of the 1514 patients, 793 (52%) had all 8 immunohistochemical markers scored, 320 (21%) patients had 7 of the 8 markers scored, and 137 (9%) had 6 of 8 markers scored. Markers could not be scored in individual cases for various reasons; for example, not representative or missing cores in the immunostained TMA section, inadequate staining results, or absence of an internal control staining precluding scoring as absence of staining in tumor cells. The proportion of patients whose TMA could be scored by each marker was as follows: 1306 (86%) for BCL2, 985 (65%) for BCL6, 1344 (89%) for CD10, 1366 (90%) for CD5, 1377 (91%) for HLA-DR, 1138 (75%) for Ki67, and 1249 (82%) for MUM1 (supplemental Table 1, available on the Blood Web site; see the Supplemental Materials link at the top of the online article). A detailed distribution of biomarkers scores in the r-CHOP cohort is provided in Figure 2.

Assessing the optimal cut point that predicted patient outcome for each biomarker

In a univariate analysis, we selected optimal cut points for OS based on the maximum log-rank statistic (Table 2). Among the r-CHOP patients, only CD5 (≤ 75% vs > 75%) and Ki67 (≤ 75% vs > 75%) could discriminate patient outcome (P < .05). A marginal difference (P = .09) was detected for BCL2 (≤ 75% vs > 75%) but not for BCL6 (Figure 3). Among the e-CHOP patients, which represent a broader range of age groups, the optimal cut points could be determined for BCL2 (≤ 75% vs > 75%), BCL6 (no staining vs any staining), CD5 (no staining vs any staining), HLA-DR (positive vs negative), and MUM1 (≤ 75% vs > 75%; Table 2). Several markers identified in the e-CHOP cohort retained their significance in the c-CHOP cohort (BCL6, MUM1, and marginally for CD5). The optimal Ki67 cut point of 57% vs > 75% determined in the r-CHOP cohort was not found to be predictive in univariate analysis for the e-CHOP cohort (or for the c-CHOP cohort). No difference in OS was found for CD10 (positive vs negative; Table 2). Similar cut points were found using data obtained with imputation for missing scores (not shown).

The impact of combined markers that might define GCB versus non-GCB patients on OS was evaluated using an adjusted GCB/non-GCB algorithm (where BCL6 was dichotomized as no-staining/staining) and an optimized LLBC algorithm that uses optimal cut points determined from the univariate analysis (GCB/non-GCB LLBC with MUM1 dichotomized as ≤ 75% vs > 75% and BCL6 dichotomized as no-staining/staining). The adjusted GCB/non-GCB algorithm was not of prognostic value for c-CHOP or r-CHOP patients (hazard ratio [HR] = 1.3; 95% confidence interval [CI] 0.8-1.9 and HR = 1.1; CI 0.6-1.8, respectively, P > .25), but was of prognostic for the e-CHOP
The large number of cases with available IHC data allowed assessment of the associations between the expression of each dichotomized biomarker and IPI category distribution using all 3 patient cohorts. As shown in Table 3, the percentage of patients expressing certain biomarkers differed between IPI categories. Patients with tumor cells that overexpressed BCL2 had a significantly higher IPI at diagnosis (HR = 1.4; CI 1.1-1.7, P = .01; Figure 4). The GCB/non-GCB LLBC also lacked prognostic significance in the r-CHOP cohort (HR = 1.4; CI 0.8-2.6, P = .23 for r-CHOP), whereas it appeared to have a higher relative risk in the 2 CHOP patient cohorts (HR = 1.7; CI 1.3-2.2, P < .0001 for e-CHOP; HR = 1.8; CI 1.1-2.8, P = .01 for c-CHOP).}

### Pairwise correlation for prognostic biomarkers and the IPI categories

The large number of cases with available IHC data allowed assessment of the associations between the expression of each dichotomized biomarker and IPI category distribution using all 3 patient cohorts. As shown in Table 3, the percentage of patients expressing certain biomarkers differed between IPI categories. Patients with tumor cells that overexpressed BCL2 (75%) presented significantly more frequently with a higher IPI (P < .0001), whereas those that were either CD10 or HLA-DR positive had a significantly lower IPI at diagnosis (P = .008 and P = .04, respectively). Interestingly, pairs of markers also showed strong correlations. As expected, CD10 and BCL6 were correlated and CD10 and MUM1 inversely correlated. High BCL2 expression was also more frequently observed in patients who highly expressed MUM1. Expression of CD5 was also correlated with the high expression of BCL2 as well as lack of CD10. Finally, cases with high expression of MUM1 were found to be HLA-DR negative and had high expression of Ki67 (P < .002 for all; Table 4). These findings highlight the coordinated expression of biomarkers associated with the same impact on patient outcome and possibly a common biologic background.

### Developing a prognostic model using biomarkers

We developed a model using the biomarkers as originally scored on all r-CHOP patients with at least one marker scored (n = 342 of 347). The low-risk patients were separated by BCL2 and the low-intermediate/ high-intermediate patients were separated by Ki67 (Figure 5A). This model distinguished 4 groups (groups 1-4) of approximately equal size with improved model evaluation measures relative to the IPI (BIC = 1145 vs 1153; c-index = 0.69 vs 0.67; Table 5 and Figure 5B). The most favorable group comprised patients with a low IPI and BCL2 > 75% and had an expected 4-year OS of 94%. Group 2 (81%...
4-year OS) included low-IPI patients with BCL2 \(>75\%\) and low-intermediate/ high-intermediate IPI patients with Ki67 positivity in \(\leq 75\%\) of cells. Group 3 (62\% 4-year OS) comprised low-intermediate/ high-intermediate patients with Ki67 \(>75\%\), and group 4 comprised patients with a high IPI (4-year OS 45\%; Figure 5C). When this model was applied to c-CHOP patients, the prognosis for group 2 and 3 appeared similar (Table 5).

The impact of the biomarkers and IPI on OS was also evaluated among the e-CHOP series, which included a broader cross-section of ages and IPI groups. This analysis also resulted in the discrimination of low-IPI patients according to BCL2 and HLA-DR expression, with 4 separate risk groups identified (not shown). When evaluated in the r-CHOP cohort, this model, which was optimized for the e-CHOP series, did not result in substantial improvement of risk group definitions. Similar results were obtained by applying...
Table 3. Biomarker expression and IPI category distribution in all patients with DLBCL

<table>
<thead>
<tr>
<th>Biomarker expression</th>
<th>No. of patients with biomarker scored and IPI</th>
<th>No. of patients with biomarker expression (%)</th>
<th>Biomarker expression percentage by IPI categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low/intermediate</td>
<td>High/intermediate</td>
<td>High</td>
</tr>
<tr>
<td>BCL2 &gt; 75%</td>
<td>1279</td>
<td>630 (49%)</td>
<td>39</td>
</tr>
<tr>
<td>BCL6 staining</td>
<td>965</td>
<td>842 (87%)</td>
<td>91</td>
</tr>
<tr>
<td>CD10 staining</td>
<td>1316</td>
<td>558 (42%)</td>
<td>49</td>
</tr>
<tr>
<td>CD5 &gt; 75%</td>
<td>1339</td>
<td>115 (9%)</td>
<td>7</td>
</tr>
<tr>
<td>HLA-DR staining</td>
<td>1348</td>
<td>1180 (88%)</td>
<td>91</td>
</tr>
<tr>
<td>Ki67 &gt; 75%</td>
<td>1119</td>
<td>627 (56%)</td>
<td>61</td>
</tr>
<tr>
<td>MUM1 &gt; 75%</td>
<td>1252</td>
<td>264 (22%)</td>
<td>20</td>
</tr>
<tr>
<td>GCB/non-GCB§ (adjusted)</td>
<td>1046</td>
<td>709 (68%)</td>
<td>72</td>
</tr>
<tr>
<td>GCB/non-GCB§ (LLBC)</td>
<td>1046</td>
<td>828 (79%)</td>
<td>83</td>
</tr>
</tbody>
</table>

*The number of the 1514 patients scored for BCL2, BCL6, CD5, CD10, HLA-DR, Ki67, MUM1, GCB (adjusted), and GCB (LLBC) are 1306, 985, 1366, 1344, 1377, 1138, 1249, 1067, and 1067, respectively.
†The number of additional patients without IPI for BCL2, BCL6, CD5, CD10, HLA-DR, Ki67, MUM1, GCB (adjusted), and GCB (LLBC) are 27, 20, 18, 27, 29, 19, 24, 21, and 21, respectively.
$\chi^2$ P values are adjusted for 9 multiple comparisons
§Among the 1046 patients scored using the adjusted GCB algorithm and with complete IPI data, 558 were CD10 (GCB), 151 were CD10/BCL6/MUM1-(GCB), 242 were CD10/BCL6/MUM1-(non-GCB), and 95 were CD10/BCL6-(non-GCB). Among the 1046 patients scored using the LLBC GCB algorithm and with complete IPI data, 558 were CD10 (GCB), 270 were CD10/BCL6/MUM1-(GCB), 123 were CD10/BCL6/MUM1-(non-GCB), and 95 were CD10/BCL6-(non-GCB).
NS indicates nonsignificant.

The number of the 1514 patients scored for BCL2, BCL6, CD5, CD10, HLA-DR, Ki67, MUM1, GCB (adjusted), and GCB (LLBC) are 1306, 985, 1366, 1344, 1377, 1138, 1249, 1067, and 1067, respectively.

The number of additional patients without IPI for BCL2, BCL6, CD5, CD10, HLA-DR, Ki67, MUM1, GCB (adjusted), and GCB (LLBC) are 27, 20, 18, 27, 29, 19, 24, 21, and 21, respectively.

First, the optimal cut points for single markers that provided the best discrimination for patient outcome were identified on a rational basis and appeared to be different from those arbitrarily used in previous studies. Second, new correlations between individual biomarkers and IPI, as well as between biomarkers themselves, were identified. These were probably underestimated in previous studies and could likely account for some discordant results. The positive correlations between CD10 and BCL6 expression and the negative correlation between CD10 and MUM1 expression was expected, because they represent features consistent with the GCB subtype definition. Further, BCL2 overexpression has been reported in ABC-type DLBCL cases that overexpress MUM1. As described previously, a correlation among CD5, BCL2, and an inverse with CD10 was noted, which may represent a biologically separate, small subclass of CD5+ DLBCL. These interrelations between biomarkers themselves and IPI parameters highlight the importance of carefully controlling for clinical and biologic characteristics when multiple markers are tested in prognostic models.

Table 4. Pairwise frequency of biomarkers

<table>
<thead>
<tr>
<th>Score</th>
<th>BCL2</th>
<th>CD10</th>
<th>CD5</th>
<th>HLA-DR</th>
<th>Ki67</th>
<th>MUM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>No staining</td>
<td>56 (12%)</td>
<td>387 (59%)</td>
<td>529 (95%)</td>
<td>154 (13%)</td>
<td>15 (12%)</td>
<td>104 (95%)</td>
</tr>
<tr>
<td>Staining</td>
<td>433 (88%)</td>
<td>267 (41%)</td>
<td>56 (7%)</td>
<td>1057 (87%)</td>
<td>15 (8%)</td>
<td>89 (5%)</td>
</tr>
</tbody>
</table>

*Biomarkers that are significantly (P < .002) correlated. Adjusting for multiple comparisons using the Bonferroni method. $\chi^2$ P values < .05/21 are considered significant.
Among 347 patients treated with R-CHOP, this study demonstrates that only CD5 retained a prognostic significance. This is in contrast to the e-CHOP and c-CHOP cohorts in which BCL2, BCL6, and MUM1 and IHC algorithms related to gene expression in CHOP-treated patients were prognostic for OS. This difference clearly confirms that response to rituximab may differ in distinct biologic groups. It also emphasizes that the impact of prognostic factors may be strongly influenced by the nature of the therapy administered, and that immunotherapy may differ in that way from chemotherapy. The present r-CHOP (and c-CHOP) cohorts are, however, biased toward patients older than 60 years of age with adverse IPI scores, and such findings may need confirmation in larger r-CHOP cohorts. It should be noted that the GCB/non-GCB algorithms used in this study were not specifically designed as optimized surrogates for the biologic gold standard of GCB/ABC subtypes based on gene-expression analysis, but rather represent potential prognostic tools validated using IHC. However, the present data indicate that the GCB/non-GCB IHC-based algorithm based on CD10, BCL6, and MUM1 expression does not provide prognostic information in the rituximab era, in agreement with another large patient series reported recently. Overall, these results emphasize that prognostic indicators developed before the use of rituximab need to be thoroughly reassessed before any implementation in the current era of therapy may be considered.

Figure 5. Prognostic model using biomarkers and IPI. (A) Hierarchical tree model. Numbers indicate the number of deaths observed at each level in the population at risk. (B) Number of patients, 4-year OS, and HR for the risk of death (without and with imputation for samples with missing scores) in the r-CHOP cohort. (C) OS for r-CHOP patients according to the IPI and the biomarker and IPI model, respectively. Log-rank P values for both models were < .0001.
Most importantly, this study demonstrates that variations in biologic features are largely overshadowed by the IPI for prognostic impact, and that biomarkers only allow subtle refinements of the IPI. This is demonstrated by the modest HR for death (ranging from 1.3 up to 1.8) conferred for individual biomarkers in the r-CHOP cohort (as well as in larger e-CHOP cohorts). Attempts to build an index using biomarkers alone, the GCB LLBC classification, or the combination of biomarkers with IPI individual factors (instead of IPI categories) did not result in an improved model fit or discrimination (data not shown). Several biomarkers appear to be able to further discriminate subgroups with distinct outcome within IPI categories. BCL2 was found to discriminate the outcome of low- or intermediate-risk patients treated with (and without) rituximab. This may be clinically relevant, because BCL2 overexpression is well known to confer chemotherapy resistance, and therapeutic targeting of this protein is currently under development. The adverse outcome associated with CD5 expression, also reported by others, may reflect the distinct origin of DLBCL expressing this antigen. Finally, in contrast to findings in patients treated without rituximab, Ki67 overexpression appears to confer a poor prognosis in patients treated with R-CHOP, which may be of importance for patients with intermediate IPI scores. The inability of biomarkers to further stratify outcome of high-IPI patients may reflect the importance of patient characteristics over biologic characteristics of tumor cells in this patient subset. However, in addition to their impact on patient prognosis, biomarkers may also contribute to define more homogeneous biologic subsets of DLBCL for which targeted therapies are investigated.

Finally, this study indicates that attempts to validate IHC biomarkers for the prognostic stratification of patients clearly require large cohorts and reproducible methodology that allows for the control of cofactor interactions. In this regard, stratification based on biomarkers for guiding treatment options should be viewed cautiously. Various algorithms recently evaluated for their concordance with gene-expression classification of the cell of origin may also have to be evaluated in larger cohorts. The data in the present study demonstrate that the IPI remains the best available index in patients with DLBCL treated with rituximab and chemotherapy. Some progress may be possible with more reliable IHC markers, cytogenetic markers, or molecular markers, but their assessment as prognostic factors need to be carefully evaluated to implement their routine use in clinical practice.

Table 5. Patient distribution and estimated relative risk of death for the prognostic model using biomarkers compared with the IPI in the r-CHOP cohort

<table>
<thead>
<tr>
<th>IPI groups</th>
<th>Biomarkers and IPI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low-intermediate</td>
</tr>
<tr>
<td>r-CHOP 4-year OS</td>
<td>85%</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1</td>
</tr>
<tr>
<td>c-CHOP 4-year OS</td>
<td>84%</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1</td>
</tr>
</tbody>
</table>

*Biomarkers and IPI: Group 1 = low IPI and BCL2  75%; Group 2 = low IPI and BCL2  75% or high-intermediate IPI and Ki67  75%; Group 3 = low-intermediate IPI/high-intermediate IPI and Ki67  75%; Group 4 = high IPI.
†Two hundred eighty-four of 347 r-CHOP and 244 of 289 c-CHOP patients had data available to compute biomarker and IPI index.

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Authorship

Contribution: G.S., D.d.J., A.R., R.D.G., and E.W designed the study, contributed and analyzed data, and wrote the manuscript; M. Chhanabhai, P.G., W.K., B.S., E.C., M.P., S.H., A. Lister, A. Rosenwald, M. van Glabbeke, H. Kluin-Nelemans, J. Raemaekers (EORTC Lymphoma Group–DSHNHL); P. Sonneveld, J. Doorduin, P. Huijgens, L.F. Verdonck, G. van Imhoff, M. Steijiaert, I. Meulendiks, M. Testroote, W. van Putten, W. van der Holt, W. graveland, A. Mulder, D. de Jong, K. Lam, J. van den Tee (HOVON); B. Sander, E. Kimby (Nordic Lymphoma Study Group); J. Radford (Manchester, United Kingdom); M. Calaminici, A. Lee, A. Norton, A. Clear, A. Lister (St Bartholomew’s Hospital); E. Campo, Independent pathology advisor (Barcelona, Spain); E. Weller, W. Xie, Y. He, B. Giblin (Dana-Farber Cancer Institute); M.-J. Kersten (Amsterdam, The Netherlands).

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References

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