Revised Response Criteria for Malignant Lymphoma

Abstract

Purpose
Standardized response criteria are needed to interpret and compare clinical trials and for approval of new therapeutic agents by regulatory agencies.

Methods
The International Working Group response criteria (Cheson et al, J Clin Oncol 17:1244, 1999) were widely adopted, but required reassessment because of identified limitations and the increased use of [18F]fluorodeoxyglucose-positron emission tomography (PET), immunohistochemistry (IHC), and flow cytometry. The International Harmonization Project was convened to provide updated recommendations.

Results
New guidelines are presented incorporating PET, IHC, and flow cytometry for definitions of response in non-Hodgkin’s and Hodgkin’s lymphoma. Standardized definitions of end points are provided.

Conclusion
We hope that these guidelines will be adopted widely by study groups, pharmaceutical and biotechnology companies, and regulatory agencies to facilitate the development of new and more effective therapies to improve the outcome of patients with lymphoma.


Introduction

Standardized response criteria provide uniform end points for clinical trials, allowing for comparisons among studies, facilitating the identification of more effective therapies, and aiding the approval process for new agents by regulatory agencies. Before 1999, response criteria for malignant lymphomas varied widely among study groups and cancer centers with respect to the size of a normal lymph node, the frequency of assessment and the time point the response assessment was made, the methods used to assess response, whether response was assessed prospectively or retrospectively, the percentage increase required for disease progression, and many other factors.¹ Even relatively minor differences in the definition of normal size of a lymph node can have a major influence on response rates.²

In 1999, an international working group (IWG) of clinicians, radiologists, and pathologists with expertise in the evaluation and management of patients with non-Hodgkin’s lymphoma (NHL) published guidelines for response assessment and outcomes measurement.¹ These recommendations were adopted rapidly and widely by clinicians and regulatory agencies, and were used in the approval process for a number of new agents. However, they were subject to considerable inter- and intraobserver variation and recommended technologies, such as gallium scans, are no longer considered state-of-the-art. Several points were subject to misinterpretation, notably the application of the complete remission/unconfirmed (CRu), and the recommendations did not include assessment of extranodal disease. The widespread use of positron emission tomography (PET) scans and immunohistochemistry warranted a reassessment of the prior response criteria. Since the Hodgkin’s lymphoma study groups had adopted these IWG criteria, any new recommendations needed to account for those patients as well. As a result, an International Harmonization Project was initiated by the German Competence Network Malignant Lymphoma to develop recommendations that were consistent across study groups.³ Subcommittees were organized on Response criteria, End Points for Clinical Trials, Imaging, Clinical Features, and Pathology/Biology, and the recommendations are reflected in this report.
MODIFICATIONS OF THE IWG CRITERIA

PET

PET using $[^{18}F]F$luorodeoxyglucose (FDG), has emerged as a powerful functional imaging tool for staging, restaging, and response assessment of lymphomas.\(^2\)\(^-\)\(^4\)\(^,\)\(^2\)\(^3\)\(^-\)\(^2\)\(^4\)\(^,\)\(^2\)\(^5\) The advantage of PET over conventional imaging techniques such as computed tomography (CT) or magnetic resonance imaging is its ability to distinguish between viable tumor and necrosis or fibrosis in residual mass(es) often present after treatment.\(^9\)\(^,\)\(^1\)\(^1\)\(^,\)\(^2\)\(^6\)\(^-\)\(^2\)\(^8\) This information may have important clinical consequences. Juweid et al.\(^2\)\(^0\) evaluated the impact of integrating PET into the IWG criteria in a retrospective study of 54 patients with diffuse large B-cell NHL who had been treated with an anthracycline-based regimen. PET increased the number of complete remission (CR) patients, eliminated the CRu category, and enhanced the ability to discern the difference in progression-free survival (PFS) between patients experiencing CR and partial remission (PR). Such findings provided rationale for incorporating PET into revised criteria.

However, a number of issues with PET need to be considered. The technique for performing and interpreting PET has only recently been standardized.\(^2\)\(^9\) There is variability among readers and equipment. PET is also associated with false-positive findings due to rebound thymic hyperplasia, infection, inflammation, sarcoidosis, or brown fat. Diffusely increased bone marrow uptake is often observed after treatment or administration of hematopoietic growth factors.\(^1\)\(^9\)\(^,\)\(^2\)\(^8\)\(^,\)\(^3\)\(^3\)\(^,\)\(^3\)\(^4\) There are also false-negative results with PET relating to the resolution of the equipment, technique, and variability of FDG avidity among histologic subtypes.\(^1\)\(^0\)\(^,\)\(^2\)\(^9\)\(^-\)\(^3\)\(^2\) These and other considerations regarding interpretation of PET scans have recently been addressed.\(^2\)\(^9\)

Recommendations for the use of PET or PET/CT. Current recommendations for the use of PET scans reflect the FDG avidity of the lymphoma subtype, and the relevant end points of the clinical trial (Table 1).

1. PET is strongly recommended before treatment for patients with routinely FDG-avid, potentially curable lymphomas (eg, diffuse large B-cell lymphoma [DLBCL], Hodgkin’s lymphoma) to better delineate the extent of disease; however, currently it is not mandated because of limitations imposed by cost and availability. For incurable, routinely FDG-avid, indolent, and aggressive histologies (eg, follicular lymphoma and mantle-cell lymphoma), and for most variably FDG-avid lymphomas, the primary end points for clinical trials generally include PFS, event-free survival, and overall survival. PET is not recommended before treatment unless response rate is a major end point of the trial.

2. Numerous studies have demonstrated that PET performed after one to four cycles of multiagent chemotherapy predicts therapeutic outcome.\(^5\)\(^-\)\(^7\)\(^,\)\(^2\)\(^1\)\(^,\)\(^2\)\(^3\)\(^,\)\(^3\)\(^5\)\(^,\)\(^3\)\(^6\); however, no currently available data demonstrate improvement in results by altering treatment based on this information. Until such data exist, this practice should be restricted to clinical trials evaluating PET in this context.

3. PET is essential for the post-treatment assessment of DLBCL and Hodgkin’s lymphoma because a complete response is required for a curative outcome. However, PET is recommended in the other, incurable histologies only if they were PET positive before treatment and if response rate is a primary end point of a clinical study.

4. Current data are inadequate to recommend routine surveillance PET scans after the restaging study.

Timing of PET scans after therapy. Post-therapy inflammatory changes may persist for up to 2 weeks after chemotherapy alone in lymphoma patients and for up to 2 to 3 months or longer after radiation therapy or chemotherapy plus radiation. To minimize the frequency of these potentially confounding interpretation findings, PET scans should not be performed for at least 3 weeks, and preferably 6 to 8 weeks, after completion of therapy.\(^2\)\(^9\)

Definition of a positive PET scan. Visual assessment currently is considered adequate for determining whether a PET scan is positive, and use of the standardized uptake value is not necessary.\(^2\)\(^9\) A more extensive description of interpretation of PET scans is provided in the consensus guidelines of the Imaging Subcommittee.\(^2\)\(^9\) In brief, a positive scan is defined as focal or diffuse FDG uptake above background in a location incompatible with normal anatomy or physiology, without a specific standardized uptake value cutoff.\(^2\)\(^9\) Other causes of false-positive scans should be ruled out. Exceptions include mild and diffusely increased FDG uptake at the site of moderate- or large-sized masses with an intensity that is lower than or equal to the mediastinal blood pool, hepatic or splenic nodules 1.5 cm with FDG uptake lower than the surrounding liver/spleen.

### Table 1. Recommended Timing of PET (PET/CT) Scans in Lymphoma Clinical Trials

<table>
<thead>
<tr>
<th>Histology</th>
<th>Pretreatment</th>
<th>Mid-Treatment</th>
<th>Response Assessment</th>
<th>Post-Treatment Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routinely FDG avid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>Yes*</td>
<td>Clinical trial</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>HL</td>
<td>Yes*</td>
<td>Clinical trial</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Follicular NHL</td>
<td>Not†</td>
<td>Clinical trial</td>
<td>Not†</td>
<td>No</td>
</tr>
<tr>
<td>MCL</td>
<td>Not†</td>
<td>Clinical trial</td>
<td>Not†</td>
<td>No</td>
</tr>
<tr>
<td>Variably FDG avid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other aggressive NHLs</td>
<td>Not†</td>
<td>Clinical trial</td>
<td>Not†</td>
<td>No</td>
</tr>
<tr>
<td>Other indolent NHLs</td>
<td>Not†</td>
<td>Clinical trial</td>
<td>Not†</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: PET, positron emission tomography; CT, computed tomography; FDG, $[^{18}F]F$luorodeoxyglucose; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin’s lymphoma; NHL, non-Hodgkin’s lymphoma; MCL, mantle-cell lymphoma; ORR, overall response rate; CR, complete remission.

*Recommended only if ORR/CR is a primary study end point.
†Recommended only if not required pretreatment.
‡Recommended only if PET is positive pretreatment.
uptake, and diffusely increased bone marrow uptake within weeks after treatment. Specific criteria for lung nodules based on lesion size have been developed.29

**Bone Marrow Assessment**

Restaging bone marrow examinations are commonly used to assess response to therapy. The determination of involvement may be difficult, given that no universally accepted standards exist. The usual approach to response determination relies on morphologic assessment of the bone marrow biopsy, and clot section if adequate and available, whereas ancillary studies using immunohistochemistry, flow cytometry, and polymerase chain reaction methodology are largely ignored or underused. Moreover, a direct comparison of these studies and their respective sensitivity and specificity for the detection of occult but clinically meaningful involvement are lacking. Thus, recommendations regarding the use of these strategies and their interpretation are largely empiric at this time.

The recommendation for bone marrow response is that histologically normal bone marrows with a small (< 2%) clonal B-cell population detected by flow cytometry should be considered normal, given that definitive clinical studies that demonstrate an inferior outcome are lacking. Immunohistochemistry has a clear role in the assessment of the bone marrow at diagnosis and restaging after therapy. When antibodies are used to detect CD20 and CD3 expression, morphologically normal bone marrows can often be shown to harbor disease. Sensitivity can be increased with the use of subtype-specific antibody panels directed at CD5, cyclin D1, CD23, CD10, DBA44, and kappa and lambda light chains. Less common lymphoma subtypes with occult bone marrow disease are particularly well suited to this approach, including splenic marginal zone B-cell lymphomas and a number of subtypes of DLBCL (ie, intravascular large B-cell lymphoma and HIV-related DLBCL). Indolent B-cell lymphomas and chronic lymphocytic leukemia are more difficult to assess, given that the distinction from reactive lymphoid aggregates and nodular partial remissions in the bone marrow can be difficult to assess because of the frequent admixture of reactive T cells in these diseases. Immunohistochemistry using anti-CD5 and anti-CD23 can be helpful in this setting, as are stains for kappa and lambda light chains that can detect surface membrane immunoglobulin in paraffin sections. Similarly, antibodies to cyclin D1 and CD10 are useful for recognizing subtle bone marrow involvement in mantle-cell lymphoma and follicular lymphoma, respectively. In the future, antibodies to Bcl-6 may improve detection of occult follicular lymphoma in the bone marrow; however, technical problems preclude their general use at this time. In fact, many routinely used immunohistochemical reagents can be difficult to apply consistently to the evaluation of bone marrow samples, largely due to subtleties in fixation methods and decalcification techniques.

Caution is recommended when interpreting biopsies post-therapy for residual disease. The use of rituximab may lead to a false-negative interpretation of residual B-cell disease, despite the fact that the widely used commercial anti-CD20 (L26) recognizes a cytoplasmic epitope of CD20, in contrast to the surface epitope recognized by rituximab. The judicious use of another pan–B-cell antibody, CD79a, is strongly recommended when evaluating post-treatment samples. Similar caution is required when interpreting CD20 flow cytometric data for several months after therapy with rituximab, given that surface epitopes may be blocked. The availability of clot sections allows for immunohistochemical analysis without the influence of decalcification and may be useful for the post-treatment evaluation of bone marrow involvement.

Lastly, the role of molecular genetic analyses in the determination of response to therapy is difficult to resolve. Assay techniques and sensitivity vary enormously between laboratories, making systematic recommendations impossible. Residual clonal disease may exist without morphologic evidence of lymphoma (ie, gastric mucosa-associated lymphoid tissue [MALT] lymphoma after therapy). In aggregate, these data suggest that the disappearance of the molecular clone may lag behind the disappearance of morphologic evidence of disease. Alternatively, these findings may represent the persistence of residual disease or potentially repopulating lymphoma stem cells in biopsies lacking morphologic evidence of lymphoma. These distinctions need to be reconciled before molecular testing can be considered routine, particularly when the findings affect treatment decisions.

Sensitive and sophisticated diagnostic approaches such as flow cytometry and/or molecular genetic analyses should be incorporated into clinical trials to determine their relevance and potential utility for directing therapy. However, for routine practice we do not recommend that clinical decision making be based solely on flow cytometry and/or molecular genetic analyses that indicate a residual small (< 2% of gated or live events) B-cell clone in the absence of other supportive findings from morphology and immunohistochemistry. We strongly encourage investigators to collect these data together with clinical correlative data that might eventually support their routine use for the assessment of response criteria for lymphoid malignancies.

---

**REVISED RESPONSE CRITERIA**

The designation of CR requires the following (Table 2):

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2a. Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Variously FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤ 1.0 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

**CRu**

The use of the above definition for CR and that below for PR eliminates the category of CRu.

**PR**

The designation of PR requires all of the following:

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by ≥ 50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.

When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

6. No new sites of disease should be observed.

7. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

8. Variably FDG-avid lymphomas/FGD-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

### Stable Disease

Stable disease (SD) is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease after CR/Progressive Disease after PR, SD).

2. Typically FDG-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

3. Variably FDG-avid lymphomas/FGD-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

---

**Table 2. Response Definitions for Clinical Trials**

<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Nodal Masses</th>
<th>Spleen, Liver</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all evidence of disease</td>
<td>(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT</td>
<td>Not palpable, nodules disappeared</td>
<td>Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative</td>
</tr>
<tr>
<td>PR</td>
<td>Regression of measurable disease and no new sites</td>
<td>≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT</td>
<td>≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen</td>
<td>Irrelevant if positive prior to therapy; cell type should be specified</td>
</tr>
<tr>
<td>SD</td>
<td>Failure to attain CR/PR or PD</td>
<td>(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT</td>
<td>&gt; 50% increase from nadir in the SPD of any previous lesions</td>
<td>New or recurrent involvement</td>
</tr>
<tr>
<td>Relapsed disease or PD</td>
<td>Any new lesion or increase by ≥ 50% of previously involved sites from nadir</td>
<td>Appearance of a new lesion(s) &gt; 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node &gt; 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Abbreviations: CR, complete remission; FDG, [18F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.
Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes \( \geq 1.0 \times \geq 1.0 \) cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by \( \geq 50\% \) and to a size of 1.5 \( \times \) 1.5 cm or more than 1.5 cm in the long axis.

3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent, unless, while an abnormality is still noted by imaging studies or pleural effusions, bone lesions) will be recorded as present or absent. Disease that is only assessable (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by \( \geq 50\% \) and to a size of 1.5 \( \times \) 1.5 cm or more than 1.5 cm in the long axis.

Primary CNS Lymphomas

Recommendations of the International Workshop on Evaluation of Primary Central Nervous System Lymphomas were adopted in their entirety. 37

Primary Gastric Lymphoma

Evaluation of patients with primary gastric lymphomas, especially MALT lymphomas, is difficult and confounded by the observation that prolonged clinical remissions may be associated with transient histologic and molecular relapses, and persistence of monoclonal B cells after histologic regression. 38,39 Repeated biopsies remain a fundamental follow-up procedure, despite problems with reproducibility.

Interpretation of residual lymphoid infiltrates in post-treatment gastric biopsies can be difficult, with no uniform criteria for the definition of histologic remission. Older assessment systems have not been adopted uniformly. 40,41 A histologic grading system proposed by the Groupe d’Etude des Lymphomes de l’Adulte may be an improvement over prior schemes, but will require additional validation. 42,43

Follow-Up Evaluation

The manner in which patients are evaluated after completing treatment may vary according to whether treatment was administered in a clinical trial or clinical practice, or whether treatment was delivered with curative or palliative intent. Good clinical judgment and a careful history and physical examination are the most important components of monitoring patients after treatment. Additional testing at follow-up visits should include CBC and serum chemistries, including lactate dehydrogenase and other blood tests and imaging studies for relevant clinical indications. There is no evidence to support regular surveillance CT scans, given that the patient or physician identifies the relapse more than 80% of the time without the need for imaging studies. 44-47 Data with PET are also insufficient to recommend routine procedures at this time. 48

In a clinical trial, uniformity of reassessment is necessary to ensure comparability among studies with respect to the major end points of event-free survival, disease-free survival, and PFS. It is obvious, for example, that a protocol requiring re-evaluation every 2 months will produce different results compared with one requiring the same testing annually, even if the true times to events are the same. One recommendation has been to assess patients on clinical trials after completion of treatment at a minimum of every 3 months for 2 years, then every 6 months for 3 years, and then annually for at least 5 years. 4 Few recurrences occur beyond that point for patients with diffuse large-cell NHL or Hodgkin’s lymphoma. However, the risk of relapse for patients with follicular and other indolent histologies is continuous. These intervals may vary with specific treatments, duration of treatment, protocols, or unique drug characteristics. Recently, the National Comprehensive Cancer Network published recommendations for follow-up of patients with Hodgkin’s and NHL: 49,50 for patients with Hodgkin’s lymphoma in an initial CR, an interim history and physical examination every 2 to 4 months for 1 to 2 years, then every 3 to 6 months for the next 3 to 5 years, with annual monitoring for late effects after 5 years. For follicular or other indolent histology lymphoma patients in a CR, the recommendation for follow-up was every 3 months for a year then every 3 to 6 months. For diffuse large B-cell NHL, the guidelines proposed follow-up every 3 months for 24 months then every 6 months for 36 months. 49,50

Patients with a follicular or low-grade NHL who are being managed with a so-called watch and wait approach should be monitored for the development of disease-related symptoms or signs of organ involvement. No consensus regarding the frequency of follow-up of such patients exists and the interval should be specified in the protocol. Otherwise, imaging studies should be individualized based on the location of the disease and informed by the behavior of palpable disease.

END POINTS

The major end points of clinical trials should reflect the histology, clinical situation (eg, initial treatment v salvage), and objectives of the study (Table 3). It is important that consistent definitions of end points are used, and we hope that this document will harmonize the use of those definitions.

End points based on tumor measurements are greatly influenced by response criteria. Overall and complete response rates usually can be assessed accurately in single-arm as well as randomized trials.
However, response rates do not necessarily influence other measures of overall clinical benefit or outcome in patients with lymphoma, and are not considered as important as other end points. Exceptions are phase II trials of novel new agents, in which identification of biologic activity is of interest. Durable complete responses, if associated with measures of clinical benefit, may also be relevant.

**Overall Survival**

Overall survival is the least ambiguous end point, although it usually is not optimal to use for a lymphoma clinical trial. Overall survival is defined as the time from entry onto the clinical trial (random assignment in a phase III study) until death as a result of any cause. Survival, as well as other time-dependent variables (PFS, event-free survival) should be measured in a randomized trial because data derived from historical controls are unreliable and subject to bias. Survival should be measured in the intent-to-treat population, including all patients even if they did not fulfill the eligibility criteria. A per-protocol analysis includes all patients who received the treatment to which they were assigned. A treatment-given analysis includes all patients who received a particular treatment. Both of these types of analyses should be interpreted with caution because they are subject to considerable bias.

**PFS**

PFS is defined as the time from entry onto a study until lymphoma progression or death as a result of any cause. PFS is often considered the preferred end point in lymphoma clinical trials, especially those involving incurable histologic subtypes (eg, follicular, other low-grade lymphoma, or mantle cell lymphoma). PFS reflects tumor growth, and therefore is interpretable earlier than the end point of overall survival. In addition, PFS is not confounded by the administration of subsequent therapy. However, in studies in which failure to respond without progression is considered an indication for administration of subsequent therapy, censoring of the data may be defined as the last date at which response duration was assessed adequately or the first date of unscheduled new antilymphoma treatment.

**Event-Free Survival**

Event-free survival (time to treatment failure) is measured from the time of study entry to any treatment failure including disease progression, or discontinuation of treatment for any reason (eg, disease progression, toxicity, patient preference, initiation of new treatment without documented progression, or death). This composite end point is generally not encouraged by regulatory agencies because it takes into account efficacy, toxicity, and patient withdrawal. However, it may be useful in the evaluation of some therapies such as those that are highly toxic.

**Time to Progression**

Time to progression (TTP) is defined as the time from study entry until documented lymphoma progression or death as a result of lymphoma. In TTP, deaths from other causes are censored either at the time of death or at an earlier time of assessment, representing a random pattern of loss from the study. TTP is not as useful as PFS unless the majority of deaths on a study are unrelated to the lymphoma due to the toxicity of the treatment and/or prolonged follow-up.

**Disease-Free Survival**

Disease-free survival is measured from the time of occurrence of disease-free state or attainment of a CR to disease recurrence or death as a result of lymphoma or acute toxicity of treatment. This definition may be complicated by deaths that occur during the follow-up period that are unrelated to the lymphoma, and there is controversy about whether such deaths should be considered as events or censored at the time of occurrence. Although it is often possible to identify those deaths related to the lymphoma, there is the potential for bias in the attribution of deaths.

**Response Duration**

Response duration is from the time when criteria for response (ie, CR or PR) are met, for which the event is the first documentation of relapse or progression.

---

<table>
<thead>
<tr>
<th>Table 3. Efficacy End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>End Point</strong></td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Primary</strong></td>
</tr>
<tr>
<td>Overall survival</td>
</tr>
<tr>
<td>Progression-free survival</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
</tr>
<tr>
<td>Event-free survival</td>
</tr>
<tr>
<td>Time to progression</td>
</tr>
<tr>
<td>Disease-free survival</td>
</tr>
<tr>
<td>Response duration</td>
</tr>
<tr>
<td>Lymphoma-specific survival</td>
</tr>
<tr>
<td>Time to next treatment</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; PR, partial remission.
Lymphoma-Specific Survival

Lymphoma-specific survival (eg, disease-specific survival, cause-specific survival) is defined as time from study entry to death as a result of lymphoma. This end point is potentially subject to bias because the exact cause of death is not always easy to ascertain. To minimize the risk of bias, the event should be recorded as death as a result of lymphoma, or as a result of toxicity from the drug. Death as a result of unknown causes should be attributed to the therapy.

Time to Next Treatment

For certain trials, time to next lymphoma treatment may be of interest, and is defined as time from the end of primary treatment until the institution of the next therapy.

Clinical Benefit

One of the most important end points for patients as well as for drug approval by regulatory agencies has been evidence of clinical benefit. Clinical benefit may reflect improvement in quality of life, or reduction in patient symptoms, transfusion requirements, frequent infections, or other parameters. Time to reappearance or progression of lymphoma-related symptoms can also be used in this end point.

We hope that these revised guidelines will improve comparability among studies, and facilitate new agent development leading to improved therapies for patients with lymphoma.

References


Acknowledgment
We thank our other colleagues who provided input into these guidelines: Lauren Abrey, Ralph Meyer, Otto S. Hoekstra, Gregory Wiseman, Markus Dietlein, Sven Reske, Ali Guermazi, Markus Schwaiger, Mary Gospodarowicz, Michael Pfreundschuh and the German High-Grade Lymphoma Study Group, Myriam Mendila, David Schenkein, Nancy Valente, Daphne de Jong, the EORTC Lymphoma Group, and the Nordic Lymphoma Study Group, Josée Zijlstra, Michinori Ogura, and the JCOG Lymphoma Study Group, A.J. Ferrieri, and C. Copie-Bergmann.