LYMPHOMA

Definitions of Response According to Non-Hodgkin’s Lymphoma (NHL) Criteria

Listed below is the new NCI Lymphoma criteria for evaluation and endpoint definitions for Non-Hodgkin’s Lymphoma response assessment. The primary reference for these criteria is the revised response criteria for malignant lymphoma Cheson et al. criteria J Clin Oncol 25:579-86, 2007.

Please note that newer lymphoma studies (e.g. S1608) will be using Lugano Treatment Response Criteria (2014). (see page 7)

Each protocol will define response in Section 10.0 and provide criteria for assessing that response. A schedule of assessments is also provided in the study calendar of each protocol.

The outcome categories include:

1) Complete remission (CR)
2) Partial remission (PR)
3) Stable disease (SD)
4) Relapsed disease (RD)
5) Relapsed Disease (after CR)/Progressive disease (after PR, SD)

NHL Tumor Response Assessment

Generally, SWOG Lymphoma protocols activated October, 2000 and beyond are assessed using the NHL response criteria.

Criteria For Evaluation And Endpoint Definitions

Measurability of Lesions:
Measurable Disease: Lesions that can be accurately measured in two dimensions by CT, MRI, plain x-ray, or other conventional technique and have a greatest transverse diameter of 1 cm or greater; or palpable lesions with both diameters 2 cm or greater. Splenomegaly alone is not sufficient to qualify as measurable disease. Note: PET scans are insufficient for evaluation of measurable disease.

Non-Measurable Disease: All other lesions including unidimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusion, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed or followed by CT or disease documented only by PET imaging or indirect evidence (e.g., lab values).

Objective Disease Status
Objective status is to be recorded at each evaluation according to the 2007 revised Cheson et al. criteria. All measurable lesions up to a maximum of 6 lesions (largest) should be identified as
target lesions at baseline. If there are more than 6 measurable lesions the remaining will be identified as non-target lesions and included as non-measurable disease. The 6 lesions should be selected according to the following features: they should be from disparate regions of the body as possible and they should include mediastinal and retroperitoneal areas of disease if these sites have measurable lesions. Measurements must be provided for target lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

**Complete Response (CR):**
Complete disappearance of all measurable and non-measurable disease with the exception of the following. In patients with a positive PET scan before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative. If the PET scan was negative before therapy, all nodal masses > 1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to < 1.5 cm in GTD and all nodal masses > 1 cm and < 1.5 cm in GTD and > 1 cm in their short axis before treatment must have regressed to < 1 cm in their short axis. No new lymphoma lesions should be visible on PET scan or by any other imaging studies. The spleen and/or liver, if considered enlarged at baseline based on physical examination or imaging study (other than PET), must have regressed in size and must not be palpable. If bone marrow was positive at baseline, it must be negative based on biopsy and aspirate at same site. Normalization of markers (e.g., LDH) definitely assignable to NHL. Tumor measurements must be obtained by an imaging modality other than PET. All disease must be assessed using the same technique as baseline.

**Partial Response (PR):**
Applies to patients with at least one lesion that does not qualify for a CR. For patients with measurable disease, ≥ 50% decrease in the sum of the product of the diameters (SPD) of up to six dominant lesions identified at baseline. No new lesions and no increase in the size of the liver, spleen, or other nodes. Splenic and hepatic nodules must have regressed by ≥ 50% in SPD. In patients with a positive PET scan before therapy, PET should be positive in at least one previously involved site. Tumor measurements must be obtained by an imaging modality other than PET. All disease must be assessed using the same technique as baseline. Note: Patients who meet all other criteria, but have new lesions observed on PET scan only (i.e., not confirmed on CT or other imaging studies), are considered partial responders.

**Stable (SD):**
Does not qualify for CR, PR, or Relapsed/Progressive Disease. Tumor measurements must be obtained by an imaging modality other than PET. Persistent abnormalities seen on CT scans must be FDG-avid on PET scans. All disease must be assessed using the same technique as baseline.

**Relapsed Disease (after CR)/Progressive Disease (after PR, SD):**
At least 50% increase in the SPD of target measurable nodal lesions over the smallest sum observed (over baseline if no decrease during therapy), or ≥ 50% increase in the GTD of any node > 1 cm in shortest axis, or ≥ 50% increase in the SPD of other target measurable lesions (e.g., splenic or hepatic nodules) over the smallest sum observed. Appearance of any new bone marrow involvement. Appearance of any new lesion > 1.5 cm in longest axis, or ≥ 50% increase in GTD of any previously involved node with a diameter ≤ 1 cm in the short axis such that its longest axis is now > 1.5 cm. Lymph nodes should be considered abnormal for relapse or progressive disease only if the long axis is > 1.5 cm, or if both the long and short axes are > 1 cm. In patients with a positive PET scan before therapy, lesions should be PET positive. Tumor
measurements must be obtained by an imaging modality other than PET. All disease must be assessed using the same technique as baseline. Note: Appearance of any new lesion on PET alone (not confirmed by CT or other imaging modality) is NOT considered relapse/progression.

**Assessment inadequate, objective status unknown:**
Progression has not been documented and one or more target lesions or other sites of disease have not been assessed or inconsistent methods of assessment were used.

**Notes:** Bone marrow status is evaluated as follows: Positive: Unequivocal cytological or architectural evidence of malignancy. Negative: No aggregates or only a few well-circumscribed lymphoid aggregates. Indeterminate: Does not qualify for either Positive or Negative Status. Note this typically consists of increased number or size of aggregates without cytological or architectural atypia.

**Best Response:**
1. **CR:** One objective status of CR documented before relapse.
2. **PR:** One objective status of PR documented before progression but not qualifying as a CR.
3. **Stable:** At least one objective status of stable documented at least 6 weeks after registration, not qualifying as anything else above.
4. **Increasing Disease:** Objective status of progression within 12 weeks of registration not qualifying as anything else above.
5. **Inadequate assessment, response unknown:** Progression greater than 12 weeks after registration and no other response category applies.

**General Guidelines for Assessing Non-Hodgkin’s Lymphomas (NHL)**
1. Always use the response criteria and schedule given in the protocol.
2. Every disease assessment called for on the study calendar must be done and done on time.
3. Each site of disease must be assessed at every scheduled disease assessment.
4. The same method of measuring the disease must be used at each assessment.
Lymphoma Response Exercises

The following exercises distinguish between ‘response/endpoint’ and ‘best response’. Response/endpoint refers to the patient’s response at each scheduled assessment. Best response is the patient’s most favorable response over all assessments.

**Exercise 1**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Method</th>
<th>Prestudy</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>R axilla</td>
<td>CT</td>
<td>3.2 x 1.8cm</td>
<td>0.0 x 0.0cm</td>
</tr>
<tr>
<td>R Iliac</td>
<td>CT</td>
<td>1.2 x 1.2cm</td>
<td>0.8 x 0.8cm</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>biopsy</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>(Sum of Products of greatest Diameters -SPD)</td>
<td></td>
<td>(7.2)</td>
<td>(0.64)</td>
</tr>
<tr>
<td>RESPONSE per Sect. 10.0</td>
<td></td>
<td>10.0</td>
<td>CR</td>
</tr>
<tr>
<td>BEST RESPONSE per Sect. 10.0</td>
<td></td>
<td></td>
<td>CR</td>
</tr>
</tbody>
</table>

Prestudy: The right axilla lesion has greatest transverse diameter (GTD) > 1.5cm. The right iliac lesion has GTD of 1.2cm.

Week 4: The right axilla lesion disappears entirely. The right iliac lesion, which was between 1-1.5cm in GTD at baseline, reduces to <1.0cm in GTD at week 4. No new disease is evident. Response is CR.

Since only one objective response of CR constitutes a best response of CR, best response is also CR.

**Exercise 2**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Method</th>
<th>Prestudy</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>R axilla</td>
<td>CT</td>
<td>3.2 x 1.8cm</td>
<td>0.0 x 0.0cm</td>
</tr>
<tr>
<td>R Iliac</td>
<td>CT</td>
<td>1.2 x 1.2cm</td>
<td>0.8 x 0.8cm</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>biopsy</td>
<td>positive</td>
<td>indeterminate</td>
</tr>
<tr>
<td>(SPD)</td>
<td></td>
<td>(7.2)</td>
<td>(0.64)</td>
</tr>
<tr>
<td>RESPONSE per Sect. 10.0</td>
<td></td>
<td>10.0</td>
<td>PR</td>
</tr>
<tr>
<td>BEST RESPONSE per Sect. 10.0</td>
<td></td>
<td></td>
<td>PR</td>
</tr>
</tbody>
</table>

Prestudy: The right axilla lesion has greatest transverse diameter (GTD) > 1.5cm. The right iliac lesion has GTD of 1.2cm. Bone marrow is positive on biopsy.

Week 4: The right axilla lesion disappears entirely. The right iliac lesion, which was between 1-1.5cm in GTD at baseline, reduces to <1.0cm in GTD at week 4. No new disease is evident, but bone marrow is indeterminate. A CR would require negative bone marrow. Indeterminate bone marrow indicates a response of PR.
Exercise 3

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Method</th>
<th>Prestudy</th>
<th>Week 4</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>R hilar</td>
<td>CT</td>
<td>8.0 x 7.0cm</td>
<td>4.0 x 6.0cm</td>
<td>8.0 x 7.5cm</td>
</tr>
<tr>
<td>Bone Marrow (SPD) biopsy</td>
<td></td>
<td>positive (56)</td>
<td>positive (24)</td>
<td>positive (60)</td>
</tr>
</tbody>
</table>

RESPONSE per Sect. 10.0
BEST RESPONSE per Sect. 10.0

Prestudy: The right hilar lesion has SPD=56. Bone marrow is positive on biopsy.

Week 4: The right hilar lesion has SPD=24, which is a decrease of >50%. Bone marrow remains positive on biopsy. No new disease is evident. Response is PR.

Week 12: The right hilar lesion has SPD=60, a >50% increase in size over smallest sum observed. Patient has progressed.

Since only one objective response of PR constitutes a best response of PR, best response is PR.

Exercise 4

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Method</th>
<th>Prestudy</th>
<th>Week 6</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLQ liver</td>
<td>CT</td>
<td>10.0 x 12.0cm</td>
<td>10.0 x 10.0cm</td>
<td>12.0 x 16.0cm</td>
</tr>
<tr>
<td>ULQ liver</td>
<td>CT</td>
<td>5.0 x 5.0cm</td>
<td>5.0 x 5.0cm</td>
<td>7.0 x 5.0cm</td>
</tr>
<tr>
<td>Bone marrow (SPD) biopsy</td>
<td></td>
<td>negative (145)</td>
<td>negative (125)</td>
<td>negative (227)</td>
</tr>
</tbody>
</table>

RESPONSE per Sect. 10.0
BEST RESPONSE per Sect. 10.0

Prestudy: The SPD for the liver lesions is 145. Bone marrow is negative on biopsy.

Week 6: The SPD for the liver lesions is 125, a <50% decrease. No new disease is evident. Response is stable.

Week 12: The SPD for the liver lesions is 227, a >50% increase in size over smallest sum observed. Patient has progressed.

Since only one objective response of stable constitutes a best response of stable, best response is stable.
**Exercise 5**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Method</th>
<th>Prestudy</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLQ liver</td>
<td>CT</td>
<td>10.0 x 12.0cm</td>
<td>10.0 x 16.0cm</td>
</tr>
<tr>
<td>ULQ liver</td>
<td>CT</td>
<td>5.0 x 5.0cm</td>
<td>10.0 x 8.0cm</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>biopsy</td>
<td>positive</td>
<td>negative</td>
</tr>
<tr>
<td>(SPD)</td>
<td></td>
<td>(145)</td>
<td>(240)</td>
</tr>
</tbody>
</table>

**RESPONSE per Sect. 10.0**
Progression

**BEST RESPONSE per Sect. 10.0**
Progression

Prestudy: The SPD for the liver lesions is 145. Bone marrow is positive on biopsy.

Week 6: The SPD for the liver lesions is 240, a >50% increase in size over smallest sum observed. Patient has progressed, regardless of the fact that bone marrow is now negative on biopsy.

Best response is progression.

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**Exercise 6**

<table>
<thead>
<tr>
<th>Lesion</th>
<th>Method</th>
<th>Prestudy</th>
<th>Week 6</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>LLQ liver</td>
<td>CT</td>
<td>10.0 x 12.0cm</td>
<td>0 x 0cm</td>
<td>0 x 0cm</td>
</tr>
<tr>
<td>ULQ liver</td>
<td>CT</td>
<td>5.0 x 5.0cm</td>
<td>0 x 0cm</td>
<td>0 x 0cm</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>biopsy</td>
<td>positive</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>Lung</td>
<td>CT</td>
<td>clear</td>
<td>clear</td>
<td>2.0 x 5.0cm</td>
</tr>
<tr>
<td>(SPD)</td>
<td></td>
<td>(145)</td>
<td>(0)</td>
<td>(10)</td>
</tr>
</tbody>
</table>

**RESPONSE per Sect. 10.0**
CR

**BEST RESPONSE per Sect. 10.0**
CR

Prestudy: The SPD for the liver lesions is 145. Bone marrow is positive on biopsy.

Week 6: The liver lesions disappear. Bone marrow is negative on biopsy. No new disease is evident. Response is CR.

Week 12: The liver remains clear of disease and bone marrow is still negative, but new disease is evident in the lung on CT. The patient has relapsed.

Since one objective response of CR is required for best response of CR, best response is CR.
Lugano Treatment Response Criteria (2014)

The outcome categories include:

1. Complete Metabolic Response
2. Partial Metabolic Response
3. No Metabolic Response
4. Progressive Metabolic Disease

Schedule of Evaluations:

A whole body or limited whole body PET/CT scan will be performed at baseline and then after 6 cycles of therapy, after 12 cycles of therapy and at month 30 (± 2 weeks) from initiation of therapy for response assessments. Additional scans are to be performed at the discretion of the treating physician at the time of suspected disease progression or off treatment evaluation.

Measurement of Treatment/Intervention Effect:

Target Lesions and Target Lymph Nodes:

FDG avid lesions: Up to five of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly FDG avid. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.

PET 5-Point Scale / Deauville score:

• 1, no FDG uptake above background;
• 2, FDG uptake ≤ mediastinum;
• 3, FDG uptake > mediastinum but ≤ liver;
• 4, FDG uptake moderately > liver;
• 5, FDG uptake markedly higher than liver and/or new lesions;
• X, new areas of uptake unlikely to be related to lymphoma.

Metabolic Response at the end of Cycle 6, at the end of Cycle 12, and at 30 Months from Treatment Initiation Assessment:

Complete Metabolic Response (CR) (as defined by all the following):

a. Deauville Score of 1, 2, or 3 with or without a residual mass or nodal lesion:
   • 1, no FDG uptake above background;
   • 2, FDG uptake ≤ mediastinum;
   • 3, FDG uptake > mediastinum but ≤ liver;

b. In Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may
be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic
response may be inferred if uptake at sites of initial involvement is no greater than
surrounding normal tissue even if the tissue has high physiologic uptake.

c. No new lesions.

d. No evidence of FDG avid disease in marrow unless as noted in (b) above.

e. If a patient had evidence of marrow involvement by bone marrow biopsy at baseline, a repeat
marrow will be required to confirm CR. 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.

Partial Metabolic Response (PR) (as defined by all the following):

a. Deauville Score of 4 or 5 with reduced uptake compared to baseline and residual mass(es) of
any size.

b. No new lesions.

c. Residual marrow uptake higher than uptake in normal marrow but reduced compared with
baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If
there are persistent focal changes in the marrow in the context of a nodal response,
consideration should be given to further evaluation with a BM biopsy.

No Metabolic Response (SD) (as defined by all the following):

a. Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of
treatment.

b. No new lesions.

c. No change in marrow uptake from baseline.

Progressive Metabolic Disease (PD) (as defined by all the following):

a. Score 4 or 5 with an increase in intensity of uptake from baseline.

b. New FDG-avid foci consistent with lymphoma.

c. New or recurrent FDG-avid foci in the bone marrow.