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1. **Introduction**

This tip sheet is intended to provide guidance on the completion of the Tumor Assessment Case Report Forms (CRF) for the M34103-053 study. For a full description of the modified Cheson criteria being used in the study refer to protocol Amendment #1, section 3.8.

1.1 **Categories of tumor lesions**

There are three (3) categories of tumor lesions described in Amendment #1 to the M34103-053 protocol as follows:

- **Dominant lymph node (LN) masses** - include up to 6 nodal masses that are clearly measurable in 2 perpendicular dimensions and >1.5 cm in each dimension. The dominant nodal masses should be chosen such that they are representative of the subject’s disease. If there are lymph node masses in the mediastinum or pelvis >1.5 cm in 2 perpendicular dimensions, they should always be chosen as dominant masses. In addition, the dominant masses should be from as disparate regions of the body as possible.

- **Non-dominant/ measurable sites of disease** - lymph node masses, splenic nodules and hepatic nodules that are thought to contain lymphoma, and are >1 cm in the longest transverse dimension.

- **Assessable disease** - includes objective evidence of disease that is identified by radiological imaging, physical examination, or other procedure as necessary but is not measurable as defined above. Examples of assessable disease include sites of disease such as lung nodules, effusions, pleural, peritoneal or bowel wall thickening, and disease limited to bone marrow.

Note: Measurable sites of disease include dominant and non-dominant sites of disease as defined above.

1.2 **Measurement of tumor lesions**

When measuring response to study drug there are several different ways to calculate change in tumor lesion size, depending on the response being assessed, as follows:

- **CR, CRu and PD** – the product of diameters (long axis x longest transverse dimension) of each individual lesion should be used

- **PR** – the sum of the product of the longest perpendicular dimensions (SPD) which refers to the combined sum of the products of the diameters of all dominant nodes should be used

Example if 3 nodes are present 2 x 2 cm (LN mass #1), 3 x 2 cm (LN mass #2) and 3 x 1.2 cm (LN mass #3):

- For CR each individual mass is assessed separately, therefore, LN masses #1 and #2 must have resolved such that the longest transverse dimension is ≤1.5 cm and LN mass #3 must have resolved such that the longest transverse dimension is ≤1 cm, or the product of the diameters for #3 must have decreased by >75% (to <0.9 cm).
• For CRu each individual mass is assessed separately, therefore, for LN masses #1 and #2 the products of the diameters must each have decreased by >75% (to <1 cm for #1 and <1.5 cm for #2), LN mass #3 need not have shrunk, since its longest transverse dimension is already <1.5 cm.

• For PR the sum of the product of the longest perpendicular dimensions (SPD) of all dominant masses must have decreased by ≥50%, therefore, LN masses #1 and #2 must have resolved such that the SPD [(2x2) + (3x2)] = 10 cm, would be ≤5.0 cm. The product of the diameters of LN mass #3 must also have been decreased by ≥50% (to ≤1.8 cm).

• For PD each individual mass is assessed separately.

A more detailed example is provided in section 2.0 of this document.

If a single lymph node mass breaks apart into multiple discrete lymph nodes during the course of therapy, that group of nodes should continue to be considered as a single lesion on the CRF. The measurement of the group of nodes should be recorded as the SPD of all of the nodes in the group. Under the “Site of Lesion” section of the Tumor Assessment CRFs please use the word “multiple” to clearly note that the measurement reported is a sum of several lesions that have broken apart.

If several masses are separate at screening and in subsequent measurements appear to coalesce, this is usually an indication of PD or a technical issue with the CT scans. Please assess these lesions accordingly.

To follow is a drawing depicting the location of the longest transverse dimension and long axis on a lymph node:
1.3 Tips for following subject’s disease

1. If a subject has a positive bone marrow biopsy at screening, the bone marrow biopsy need only be repeated if the subject achieves a CR in all other respects. Additionally, if a patient has an indeterminate BM evaluation at screening it should be repeated if they achieve CR in other respects.

2. All sites of measurable and assessable disease that can be evaluated by non-invasive techniques, such as imaging or physical exam, must be evaluated at all time points when disease assessments are required. Examples include:
   a. subject with a soft tissue mass in an extremity that is measured by MRI, that site must be evaluated by MRI at each disease assessment.
   b. subject with mucosal bowel lesions that can only be evaluated by colonoscopy, repeat colonoscopy only need be repeated if the subject achieves a CR in all other respects. If the bowel lesions are the only site of disease, the subject is a poor candidate for 053, but may participate if a colonoscopy can be done at the each time point that a disease assessment is required.

3. If a subject does not have any measurable or assessable sites of disease other than the bone marrow, they are a poor candidate for 053. However, they may be enrolled, and will require a bone marrow biopsy at all time points when disease assessments are required per the protocol.

1.4 Cheson Response Assessment Criteria

To follow is a table summarizing the modified Cheson Response Assessment Criteria to be used in the M34103-053 study.
<table>
<thead>
<tr>
<th>Assessment</th>
<th>CR (requires all of the following):</th>
<th>CRu (requires all of the following):</th>
<th>PR (requires all of the following):</th>
<th>SD</th>
<th>PD or Relapse*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph Nodes and Nodal Masses</td>
<td>All lymph node masses must have regressed to normal size. Each lymph node mass that was &gt;1.5 cm in longest transverse dimension must have regressed to ≤1.5 cm. Each lymph node mass that was 1.1-1.5 cm in longest transverse dimension and thought to be involved with lymphoma must have regressed to ≤1 cm in longest transverse dimension, or by more than 75% of the product of the longest perpendicular dimensions compared to the pretreatment baseline. Complete disappearance of all radiographic evidence of disease. No new sites of lymphoma.</td>
<td>Each residual lymph node mass &gt;1.5 cm in longest transverse dimension must have regressed by more than 75% of the product of the longest perpendicular dimensions compared to the pretreatment baseline. Complete disappearance of all radiographic evidence of disease. No new sites of lymphoma.</td>
<td>50% or greater decrease in the sum of the products of the longest perpendicular dimensions (SPD) of the previously identified dominant lymph node masses No increase in the size of other lymph nodes, the liver or the spleen No new sites of lymphoma.</td>
<td>Neither sufficient shrinkage to qualify for PR, nor increase for PD. No new sites of lymphoma.</td>
<td>Appearance of any new sites of lymphoma OR 50% or greater increase in the product of the longest perpendicular dimensions of any previously identified lymph node mass OR 50% or greater increase in the size of any other previously involved site of lymphoma.</td>
</tr>
<tr>
<td>Spleen</td>
<td>All nodules resolved Not palpable on PE, and if previously enlarged on CT due to disease involvement must have decreased in size.</td>
<td>All nodules resolved Not palpable on PE, and if previously enlarged on CT due to disease involvement must have decreased in size.</td>
<td>≥50% decrease in SPD of any nodules No increase in size No new nodules.</td>
<td>No new nodules New nodules or ≥50% increase in SPD.</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>All nodules resolved</td>
<td>All nodules resolved</td>
<td>≥50% decrease in SPD of any nodules No increase in size No new nodules.</td>
<td>No new nodules New nodules or ≥50% increase in SPD.</td>
<td></td>
</tr>
<tr>
<td>Bone Marrow (Biopsy)</td>
<td>Biopsy Cleared, if involved at baseline</td>
<td>Indeterminate Bone Marrow (increased number or size of aggregates without cytological or architectural atypia) not applicable not applicable not applicable</td>
<td>not applicable not applicable not applicable</td>
<td>not applicable not applicable not applicable</td>
<td>not applicable not applicable not applicable</td>
</tr>
<tr>
<td>Disease-Symptoms:</td>
<td>Disappearance of all symptoms (from baseline)</td>
<td>Disappearance of all symptoms (from baseline)</td>
<td>not applicable not applicable not applicable</td>
<td>not applicable not applicable not applicable</td>
<td></td>
</tr>
<tr>
<td>NHL Biochemical abnormalities:</td>
<td>Normal LDH. No lab abnormalities due to lymphoma</td>
<td>Normal LDH. No lab abnormalities due to lymphoma</td>
<td>not applicable not applicable not applicable</td>
<td>not applicable not applicable not applicable</td>
<td></td>
</tr>
<tr>
<td>LDH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a) The smallest prior measurement should be used for comparison when evaluating for progressive or relapsed disease.*
2. Sample Disease Response Calculation

To follow is a description for sample subject 001-001/ABC of what criteria would have to be met in order to consider the subject to have one of the responses listed below. In all cases other indications of disease, such as physical exam, disease symptoms, bone marrow, and laboratory values, must also be assessed in order to make a disease response determination.

When calculating measurements round up if the 3rd digit of the product of measurements of longest perpendicular dimensions is \( \geq 5 \), e.g. if a product is 2.85 cm round to 2.9 cm, if the product is 2.84 cm round down to 2.8 cm.

**Complete Response (CR) – as compared to baseline**

**Dominant Nodes**
- D1 to D4 each should be reduced to \( \leq 1.5 \) cm in their longest transverse dimension. The long axis may still be >1.5 cm.

**Non-dominant/Measurable Nodes**
- M1 should be reduced to \( \leq 1.0 \) cm in longest transverse dimension, or the product of measurement should be reduced by \( >75\% \), i.e. should be <0.9 cm (3.6 x 25%)
- M2 should be reduced to \( \leq 1.0 \) in longest transverse dimension, or the product of measurement should be reduced by \( >75\% \), i.e. should be <0.4 cm (1.7 x 25%)
- Note: In a CR or CRu, only LN masses may be present as residual masses. Residual masses may be present because normal LN masses may remain after disease. Disease outside the LN must have resolved completely (this includes splenic and hepatic nodules).

**Assessable Nodes**
- E1 should not be palpable on PE
- E2 should not be visible on colonoscopy

**Complete Response unconfirmed (CRu) - as compared to baseline**

**Dominant Nodes**
- D1 the product of measurement should be reduced by \( >75\% \), i.e. should be <1.0 cm (3.8 x 25%)
- D2 the product of measurement should be reduced by \( >75\% \), i.e. should be <3.2 cm (12.8 x 25%)
- D3 the product of measurement should be reduced by \( >75\% \), i.e. should be <1.0 cm (4.0 x 25%)
- D4 the product of measurement should be reduced by \( >75\% \), i.e. should be <0.7 cm (2.9 x 25%)

**Non-dominant/Measurable Nodes**
- Same as CR

**Assessable Nodes**
- Same as CR
Partial Response (PR) - as compared to baseline

**Dominant Nodes**
- D1 to D4 sum of the product of measurement should be reduced by $\geq 50\%$, i.e. should be $\leq 11.8$ cm ($23.5 \times 50\%$)

**Non-dominant/Measurable Nodes**
- M1 and M2 sum of the product of measurement should be reduced by $\geq 50\%$, i.e. should be $\leq 2.7$ cm ($5.3 \times 50\%$)

**Assessable Nodes**
- E1 should not be larger than baseline
- E2 should not be larger than baseline

Stable Disease (SD) - as compared to baseline

Disease response is less than that required for PR, but the criteria for relapse or progressive disease are not met.

**Progressive Disease (PD) or Relapse - as compared to the smallest prior assessment**

Any new site of disease
OR

**Dominant Nodes**
- D1 should be increased to $\geq 5.7$ cm ($3.8 \times 150\%$)
- D2 should be increased to $\geq 19.2$ cm ($12.8 \times 150\%$)
- D3 should be increased to $\geq 6.0$ cm ($4.0 \times 150\%$)
- D4 should be increased to $\geq 4.4$ cm ($2.9 \times 150\%$)

**Note:** Dominant and measurable nodes are also considered to have progressed if there is a $\geq 50\%$ increase in the longest dimension. In this example it is only relevant to D4, where a 50% increase in the 1.8 cm dimension is 2.7 cm, and $2.7 \times 1.6 \approx 4.3$. In the case of D1, D2 and D3 a 50% increase in the long axis results in a $\geq 50\%$ increase in the product of the diameters.

**Non-dominant/Measurable Nodes**
- M1 should be increased to $\geq 5.4$ cm ($3.6 \times 150\%$)
- M2 should be increased to $\geq 2.6$ cm ($1.7 \times 150\%$)

**Assessable Nodes**
- E1 and E2 should be larger than baseline

**Note:** In the case of Progressive Disease or Relapse assessments, this example is valid ONLY for the first post-baseline assessment, because when evaluating for PD each measurement is compared to nadir (the smallest previous measurement). Therefore, each time you should review all previous measurements, not just baseline, to check for PD.
A Phase 2 Study of VELCADE™ in Subjects with Relapsed or Refractory Mantle Cell Lymphoma

Subject ID: M34103053
Site: 01
Subject Number: 01

Visit: Screening

TUMOR ASSESSMENT

Were there any dominant nodes?  Yes  No

Dominant lymph node masses include up to 6 nodal masses that are clearly measurable in 2 perpendicular dimensions and >1.5 cm in each dimension. Measurement may be determined by radiological imaging or physical examination. The dominant nodal masses should be chosen such that they are representative of the subject's disease. If there are lymph node masses in the mediastinum or pelvis larger than 1.5 in 2 perpendicular dimensions, they should always be chosen as dominant masses. In addition, the dominant masses should be from as disparate regions of the body as possible.

<table>
<thead>
<tr>
<th>Lesion Number</th>
<th>Site of Lesion</th>
<th>Tissue Site</th>
<th>Method</th>
<th>Date of evaluation (DD/MMM/YYYY)</th>
<th>Longest perpendicular dimensions</th>
<th>Product of measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>L. Axilla</td>
<td>12</td>
<td>1</td>
<td>9/4/93</td>
<td>2.4 x 1.6</td>
<td>9.03.8</td>
</tr>
<tr>
<td>D2</td>
<td>Subcarinal</td>
<td>14</td>
<td>1</td>
<td></td>
<td>0.4 x 0.9</td>
<td>9.12.8</td>
</tr>
<tr>
<td>D3</td>
<td>L. Para-aortic</td>
<td>11</td>
<td>1</td>
<td></td>
<td>0.3 x 0.2</td>
<td>9.04.0</td>
</tr>
<tr>
<td>D4</td>
<td>R. epitracheal</td>
<td>17</td>
<td>3</td>
<td>06/06/03</td>
<td>9.1 x 0.1</td>
<td>9.92.9</td>
</tr>
<tr>
<td>D5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sum of products of measurements: 923.5

1 Tissue Site Code Key:
1 = Ascites  5 = Effusion, pericardial  9 = Liver  13 = Node, inguinal  17 = Node, other  22 = Other
2 = Bone  6 = Effusion, other  10 = Lung  14 = Node, mediastinum  18 = Peritoneum  23 = Spleen nodule
3 = Brain  7 = Intestine  11 = Node, abdomen  15 = Node, neck  19 = Pleura  24 = Splenomegaly
4 = Effusion, pleural  8 = Leptomeninges  12 = Node, axilla  16 = Node, pelvis  20 = Soft Tissue

2 Method Key:
1 = CT Scan  2 = MRI  3 = Physical Exam  4 = Other, specify  5 = Not Evaluated
A Phase 2 Study of VELCADE™ in Subjects with Relapsed or Refractory Mantle Cell Lymphoma

Subject ID: M34103053 001 001

Visit: Screening

TUMOR ASSESSMENT

Were there any nondominant/measureable nodes? [ ] Yes [ ] No

Measureable sites of disease are defined as lymph node masses, splenic nodules, and hepatic nodules that are thought to contain lymphoma, and are greater than 1 cm in the longest transverse dimension. Other sites of disease are considered assessable, but not measurable. If additional lines are needed use the Supplemental Tumor Assessment CRF.

<table>
<thead>
<tr>
<th>Lesion Number</th>
<th>Site of Lesion</th>
<th>Tissue Site</th>
<th>Method</th>
<th>Date evaluation (DD/MMM/YYYY)</th>
<th>Longest perpendicular dimensions</th>
<th>Product of measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>Liver</td>
<td>9</td>
<td>1</td>
<td>01/01/2023</td>
<td>13.0 x 11.2</td>
<td>003.16</td>
</tr>
<tr>
<td>M2</td>
<td>Spleen</td>
<td>23</td>
<td>1</td>
<td></td>
<td>11.5 x 11.1</td>
<td>001.17</td>
</tr>
</tbody>
</table>

Sum of products of measurements on this and all any supplemental pages: 005.3

Were there any Assessable nodes? [ ] Yes [ ] No

Assessable disease includes objective evidence of disease that is identified by radiological imaging, physical examination, or other procedure as necessary but is not measurable as defined above. If additional lines are needed use the Supplemental Tumor Assessment CRF.

<table>
<thead>
<tr>
<th>Lesion Number</th>
<th>Site of Lesion</th>
<th>Tissue Site</th>
<th>Method</th>
<th>Date evaluation (DD/MMM/YYYY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1</td>
<td>Splenomegaly</td>
<td>24</td>
<td>3</td>
<td>06/05/2003</td>
</tr>
<tr>
<td>E2</td>
<td>Sigmoid colon</td>
<td>22</td>
<td>4 (colonoscopy)</td>
<td>01/12/2003</td>
</tr>
<tr>
<td>E3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Tissue Site Code Key
1 = Ascites
2 = Bone
3 = Brain
4 = Effusion, pleural
5 = Effusion, pericardial
6 = Effusion, other
7 = Intestine
8 = Leptomeninges
9 = Liver
10 = Lung
11 = Node, abdomen
12 = Node, axilla
13 = Node, inguinal
14 = Node, mediastinum
15 = Node, neck
16 = Node, pelvis
17 = Node, other
18 = Peritoneum
19 = Pleura
22 = Other
23 = Spleen nodule
24 = Splenomegaly

2 Method Key:
1 = CT Scan
2 = MRI
3 = Physical Exam
4 = Other, specify
5 = Not Evaluated