MILLENNIUM®

M34103-053

Tumor Assessments (CHESON)

Tip Sheet

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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).

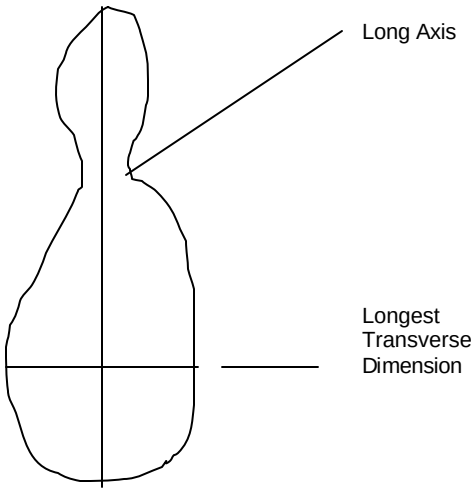
- For CRu each individual mass is assessed separately, therefore, for LN masses #1 and #2 the products of the diameters must each have decreased by >75% (to <1 cm for #1 and <1.5 cm for #2), LN mass #3 need not have shrunk, since its longest transverse dimension is already <1.5 cm.
- For PR the sum of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

Assessment	CR (requires all of the following):	CRu (requires all of the following):	PR (requires all of the following):	SD	PD or Relapse [a]
Lymph Nodes and Nodal Masses	All lymph node masses must have regressed to normal size. Each lymph node mass that was >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	Each residual lymph node mass >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	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	Neither sufficient shrinkage to qualify for PR, nor increase for PD. No new sites of lymphoma	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 longest dimension of any previously identified lymph node mass greater than 1 cm in longest transverse dimension OR 50% or greater increase in the size of any other previously involved site of lymphoma
Spleen	All nodules resolved Not palpable on PE, and If previously enlarged on CT due to disease involvement must have decreased in size	All nodules resolved Not palpable on PE, and If previously enlarged on CT due to disease involvement must have decreased in size	≥ 50% decrease in SPD of any nodules No increase in size	No new nodules	New nodules or ≥ 50% increase in SPD.
Hepatic	All nodules resolved	All nodules resolved	≥ 50% decrease in SPD of any nodules No increase in size	No new nodules	New nodules or ≥ 50% increase in SPD
Bone Marrow (Biopsy)	Biopsy Cleared, if involved at baseline	Indeterminate Bone Marrow (increased number or size of aggregates without cytological or architectural atypia)	not applicable	not applicable	not applicable
Disease-Symptoms:	Disappearance of all symptoms (from baseline)	Disappearance of all symptoms (from baseline)	not applicable	not applicable	not applicable
NHL Biochemical abnormalities: LDH	Normal LDH. No lab abnormalities due to lymphoma	Normal LDH. No lab abnormalities due to lymphoma	not applicable	not applicable	not applicable

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 ≥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 ≤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 ≤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 ≤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 ≥50%, i.e. should be ≤11.8 cm (23.5 x 50%)

Non-dominant/Measurable Nodes

- M1 and M2 sum of the product of measurement should be reduced by ≥50%, i.e. should be ≤2.7 cm (5.3 x 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 ≥5.7 cm (3.8 x 150%)
- D2 should be increased to ≥19.2 cm (12.8 x 150%)
- D3 should be increased to ≥6.0 cm (4.0 x 150%)
- D4 should be increased to ≥4.4 cm (2.9 x 150%)
- Note: Dominant and measurable nodes are also considered to have progressed if there is a ≥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 2.7x1.6=4.3. In the case of D1, D2 and D3 a 50% increase in the long axis results in a ≥50% increase in the product of the diameters.

Non-dominant/Measurable Nodes

- M1 should be should be increased to ≥5.4 cm (3.6 x 150%)
- M2 should be should be increased to ≥2.6 cm (1.7 x 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.

Subject ID M 3 4 1 0 3 0 5 3 (Protocol Number) | 9 0 1 (Site) | 0 0 1 (Subject Number)

Subject's Initials A B C (First Middle Last)

SDV

CRF

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.

Lesion Number	Site of Lesion	Tissue Site[1]	Method [2]	Date of evaluation (DD/MMM/YYYY)	Longest perpendicular dimensions	Product of measurements
D1	L. Axilla	12	1	09 DEC 2003	02.4 x 01.6	003.8
D2	subcarinal	14	1		04.9 x 03.2	012.8
D3	L. Para-aortic	11	1		02.0 x 02.0	004.0
D4	R. epitrochlear	17	3	06 DEC 2003	01.6 x 01.8	002.9
D5					. x .	.
D6					. x .	.

Sum of products of measurements 023.5

[1] Tissue Site Code Key

1 = Ascites	5 = Effusion, pericardial	9 = Liver	13 = Node, inquinal	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

Subject ID M 3 4 1 0 3 0 5 3 (Protocol Number) | 0 0 1 (Site) | 0 0 1 (Subject Number)

Subject's Initials A B C (First Middle Last)

SDV

CRF

Visit: Screening

TUMOR ASSESSMENT

Were there any nondominant/measureable nodes? ☒ Yes ☐ No

Measurable 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.

Lesion Number	Site of Lesion	Tissue Site [1]	Method [2]	Date evaluation (DD/MMM/YYYY)	Longest perpendicular dimensions	Product of measurements
M1	L lobe liver	9	1	01 DEC 2003	03.0 x 01.2	003.6
M2	Spleen	23	1	↓	01.5 x 01.1	001.7
M3					. x .	

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.

Lesion Number	Site of Lesion	Tissue Site [1]	Method [2]	Date evaluation (DD/MMM/YYYY)
E1	splenomegaly	24	3	06 DEC 2003
E2	Sigmoid colon	22	4, colonoscopy	01 DEC 2003
E3				
E4				

[1]Tissue Site Code Key

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