

Disease Response What Are We Looking For?

Navneet Majhail, MD, MS
Assistant Scientific Director



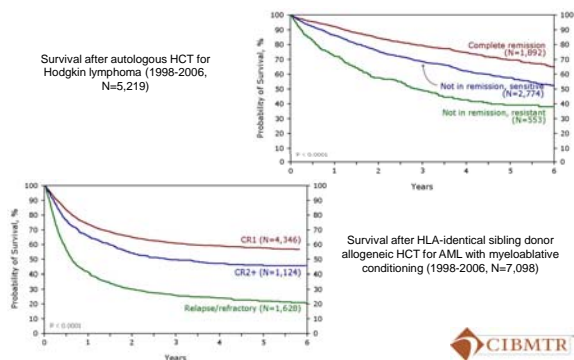
Objectives

- ◆ Review importance of disease response in CIBMTR research
- ◆ Review examples of disease response criteria for CML and lymphomas

Disease Response = Outcomes

- ◆ One of the most important endpoints for transplant research studies
- ◆ Correlates with overall HCT outcomes and survival
- ◆ Used to classify other outcomes (e.g. treatment related mortality)
- ◆ Accurate assessment of pre-HCT response is also very important

Pre-HCT Response and HCT Outcomes



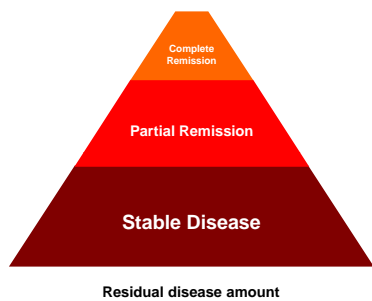
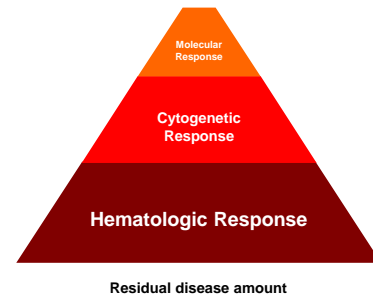
Accurate Assessment of Disease Response is Crucial to CIBMTR Studies

Response Reporting Is Not (Always) Easy

- ◆ Response criteria can be ambiguous
- ◆ Many acceptable response criteria may be available
- ◆ Response criteria can change with time



General Definitions



Hematologic Response/Remission

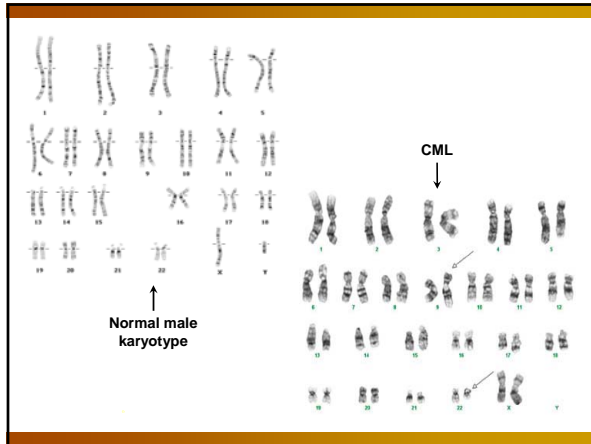
- ◆ Generally used for ALL, AML and CML
- ◆ Absence of disease in the peripheral blood
- ◆ Absence of disease in the bone marrow (on routine morphology and stains)

Cytogenetic Response/Remission

- ◆ Generally used for ALL, AML and CML
 - May also be used for other diseases (e.g. myeloma, CLL, lymphoma)
- ◆ Chromosomal abnormalities are evaluated
- ◆ Two common methods
 - Chromosomal banding
 - FISH

Chromosomal Banding

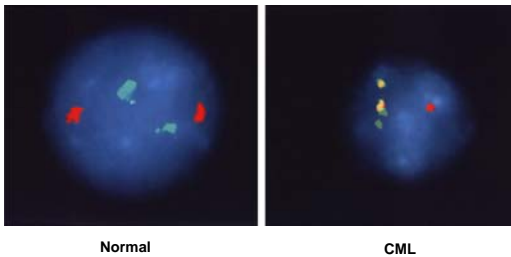
- ◆ Also called 'routine cytogenetics'
 - Cell division is arrested in metaphase stage
 - Chromosomes are stained using dyes
 - Advantage – entire genome is viewed
 - Disadvantage – labor intensive, only detects major abnormalities



FISH

- ◆ Fluorescent in-situ hybridization
 - Fluorochrome labeled DNA probe is applied to cells – visualized by fluorescence microscopy
- ◆ Advantage – better resolution, more sensitive and specific, straightforward test
- ◆ Disadvantage – identifies abnormality specific to the probe applied, cannot identify other abnormalities

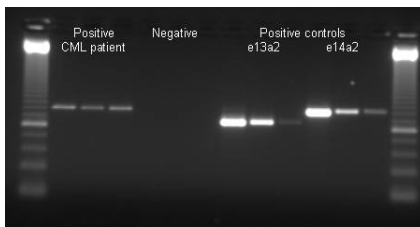
FISH for CML



Molecular Response/Remission

- ◆ Generally used for CML
 - May also be used for other diseases (e.g. ALL, AML, CLL, lymphoma)
- ◆ DNA is evaluated
- ◆ Polymerase chain reaction (PCR)
 - Most frequently used molecular test
 - DNA is amplified many fold
 - Amplified DNA can be analyzed further (e.g. gel electrophoresis)
 - Extremely sensitive

PCR for CML



Complete/Partial Response

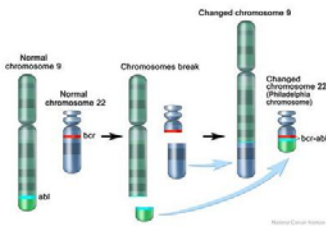
- ◆ Used for diseases that can be 'measured'
 - Myeloma, lymphoma, CLL
- ◆ Assessed by blood tests (e.g. M-protein) or imaging studies (e.g. CT or PET)

Examples

CML

CML

- ◆ Characteristic feature is Philadelphia chromosome t(9;22) → leads to formation of BCR-ABL



Diagnosis and Disease Assessment

- ◆ Peripheral blood and/or bone marrow counts and morphology
- ◆ Cytogenetics for t(9;22)
 - Chromosome banding from bone marrow
 - FISH for t(9;22) from blood or bone marrow
- ◆ Molecular testing for BCR-ABL
 - Qualitative or quantitative PCR
 - PCR's from different labs are not always comparable

CML Natural History

- ◆ Three disease phases
 - Chronic phase
 - Accelerated phase
 - Many criteria (MD Anderson, Sokal, WHO)
 - Blast phase (>20% blasts)
- ◆ Patients can go from accelerated or blast phase to chronic phase (2nd or greater chronic phase)

Response Criteria for CML

- ◆ Complete hematologic response or remission (all must be present)
 - Platelet count <450,000/uL
 - WBC count <10,000/UI
 - No immature neutrophils
 - <5% basophils
 - Spleen not palpable

Cytogenetic and Molecular Response

- ◆ Cytogenetic response/remission
 - No response - >95% Ph+ cells
 - Minor response - 36-95% Ph+ cells
 - Major response - <35% Ph+ cells
 - Complete response - no Ph+ cells
- ◆ Molecular response/remission
 - Major response - >3 log reduction
 - Complete response - no BCR-ABL transcript detectable

Form 2012 (Pre-HSCT, CML)

Pre-HSCT Treatment for Chronic Myelogenous Leukemia

22. Was therapy given between diagnosis and the start of the preparative regimen?

yes
 no
 unknown

Line of Therapy	1st Line of Therapy	2nd Line of Therapy
Systemic Therapy	23. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> not assessed	39. <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> not assessed
Date therapy started	24. [Month] [Day] [Year]	37. [Month] [Day] [Year]
Date therapy stopped	25. [Month] [Day] [Year]	38. [Month] [Day] [Year]

Therapy response:

* Molecular remission? 47. yes no not assessed

Date molecular remission established: 48. [Month] [Day] [Year]

Cytogenetic remission? 49. yes no not assessed

Specify remission: 50. minor (≥ 50% Ph+ megakaryocytes) major (≥ 100% Ph+ megakaryocytes)

Date cytogenetic status established: 51. [Month] [Day] [Year]

* Hematologic remission? 52. yes no

Date hematologic remission established: 53. [Month] [Day] [Year]

Did disease relapse/progress following this line of therapy? 54. yes no

Date of relapse/progression: 55. [Month] [Day] [Year]

56. [Month] [Day] [Year] 57. [Month] [Day] [Year] 58. [Month] [Day] [Year]

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200. [Month] [Day] [Year]

Copy this page to report more than 2 lines of therapy; check here if additional pages are attached.

* Complete hematologic remission or complete molecular remission

Form 2012 (Pre-HSCT, CML)

Disease Status at the Last Assessment Prior to the Preparative Regimen

96. What was the status of the primary disease immediately prior to the preparative regimen?

first chronic phase
 hematologic remission
 accelerated phase

Specify remission:
100. yes no unknown Cytogenetic complete remission (Ph-negative)
101. yes no unknown Molecular complete remission (BCR/ABL-negative)

102. Was this the first accelerated phase?
 yes
 no

Specify which of the following were present:
103. yes no 10-19% blasts in blood or marrow
104. yes no ≥ 20% blasts in peripheral blood
105. yes no Clonal marrow cytogenetic abnormalities in addition to the single Philadelphia chromosome
106. yes no Increasing spleen size
107. yes no Increasing WBC
108. yes no Thrombocytopenia (platelets < 100 × 10⁹/L) unresponsive to therapy
109. yes no Thrombocytosis (platelets > 1,000 × 10⁹/L) unresponsive to therapy

Continued...

Form 2012 (Pre-HSCT, CML)

blast crisis → 110. How many blast crises has the recipient ever experienced?
 one
 two or more

second or greater chronic phase → 111. Specify the type of blast cells:
 myeloid only
 myeloid and myeloid
 unknown - indeterminate results

current disease status follows a previous HSCT → 112. Has the recipient ever been in blast phase prior to the current chronic phase?
 yes
 no

113. Specify the number of blast phases prior to the current chronic phase:
 one
 two
 three or more

114. Specify current disease status immediately prior to the preparative regimen:
 cytogenetic relapse
 molecular relapse
 unknown

115. Specify the number of phases experienced:
 one
 two
 three or more

Form 2112 (Post-HSCT, CML)

Disease Assessment at the Time of Best Response to the HSCT

13. Was a complete remission (CR) ever achieved in response to the HSCT? (Include any therapy planned as of Day 0, but exclude any change in therapy in response to a disease assessment)
 disease was in remission at the time of the preparative regimen
 yes, post-HSCT CR was achieved → 14. Specify the date complete remission was achieved: [Month] [Day] [Year]

no, CR was never achieved post-HSCT

15. Was the date and disease assessment method for this CR previously reported?
 yes → Continue with question 23
 no

Laboratory Studies Supporting Best Response (Including Planned Therapy)

16. Did molecular testing confirm the presence of the complete remission?
 yes
 no
 not tested

17. Specify the date the molecular CR was determined: [Month] [Day] [Year]

Continued...

Form 2112 (Post-HSCT, CML)

13. Did cytogenetic testing confirm the presence of the complete remission?
 yes
 no
 not tested

19. Was FISH used to determine cytogenetic CR status?
 yes
 no

20. Specify the date the cytogenetic CR was determined via FISH: [Month] [Day] [Year]

21. Were conventional cytogenetics used to determine cytogenetic CR status?
 yes
 no

22. Specify the date the cytogenetic CR was determined via conventional cytogenetics: [Month] [Day] [Year]

Form 2112 (Post-HSCT, CML)

Disease Status at the Time of Assessment for This Reporting Period

62. Was the disease status assessed since the date of the last report?
 1 yes
 2 no

Specify the method(s) used to assess the disease status:
 63. Current molecular assessment
 1 yes
 2 no

64. Date of the molecular assessment:
 Month: [] Day: [] Year: [2][0][]

65. Was there evidence of disease?
 1 yes
 2 no

66. Was the status considered a disease relapse, progression, or persistent disease?
 1 yes
 2 no

67. Current cytogenetic assessment
 1 yes
 2 no

68. Was the disease status assessed via FISH?
 1 yes
 2 no

69. Date of FISH test:
 Month: [] Day: [] Year: [2][0][]

70. Was there evidence of disease?
 1 yes
 2 no

71. Was the status considered a disease relapse, progression, or persistent disease?
 1 yes
 2 no

Continued...

Form 2112 (Post-HSCT, CML)

72. Was the disease status assessed via conventional cytogenetics?
 1 yes
 2 no

73. Date of conventional cytogenetic test:
 Month: [] Day: [] Year: [2][0][]

74. Was there evidence of disease?
 1 yes
 2 no

75. Was the status considered a disease relapse, progression, or persistent disease?
 1 yes
 2 no

76. Current clinical / hematologic assessment
 1 yes
 2 no

77. Date of the clinical / hematologic assessment:
 Month: [] Day: [] Year: [2][0][]

78. Was the status considered a relapse, progression, or persistent disease?
 1 yes
 2 no

CBMTR Form 2112 (CML) v1.0 (9-8) July 2007
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Hodgkin and Non-Hodgkin Lymphoma

- ## Lymphomas
- ◆ Malignant hematologic disorders characterized by involvement of:
 - Lymph nodes
 - Bone marrow
 - Occasionally, peripheral blood and other sites
 - ◆ Response assessment can be challenging
 - Many lymphoma types with varying presentation and patterns of response

Large Number of Lymphoma Types

Classical Hodgkin Lymphoma Codes:		
01 nodular lymphocyte predominant Hodgkin lymphoma	12 follicular, mixed, small cleaved and large cell (Grade II follicle center lymphoma)	24 extranodal NK / T-cell lymphoma, nasal type
02 lymphocyte-rich	13 follicular, predominantly large cell (Grade III follicle center lymphoma)	25 enteropathy-type T-cell lymphoma
03 nodular sclerosis	14 follicular (grade unknown)	26 hepatosplenic gamma-delta T-cell lymphoma
04 mixed cellularity	15 mantle cell lymphoma	27 subcutaneous panniculitis-like T-cell lymphoma
05 lymphocyte depleted	16 diffuse, large B-cell lymphoma — intravascular large B-cell lymphoma subtype	28 mycosis fungoides
06 Hodgkin lymphoma, not otherwise specified	17 diffuse, large B-cell lymphoma — mediastinal large B-cell lymphoma subtype	29 Sezary syndrome
Non-Hodgkin Codes:		
07 lymphoplasmacytic lymphoma	18 diffuse, large B-cell lymphoma — primary effusion lymphoma subtype	30 anaplastic large-cell lymphoma, T / null cell, primary cutaneous type
08 splenic marginal zone B-cell lymphoma	19 diffuse, large B-cell lymphoma — subtype unknown	31 angioimmunoblastic T-cell lymphoma
09 extranodal marginal zone B-cell lymphoma of mucosal associated lymphoid tissue type (MALT)	20 Burkitt lymphoma / Burkitt cell leukemia (provisional entry)	32 anaplastic large-cell lymphoma, T / null cell, primary systemic type
10 nodal marginal zone B-cell lymphoma (± monocytoid B-cells)	21 high grade B-cell lymphoma, Burkitt-like	33 other T-cell / NK-cell lymphoma, specify above
11 follicular, predominantly small cleaved cell (Grade I follicle center lymphoma)	22 primary CNS lymphoma	34 large T-cell granular lymphocytic leukemia
	23 other B-cell lymphoma, specify above	35 aggressive NK-cell leukemia
		36 adult T-cell lymphoma / leukemia (HTLV1 associated)
		37 Waldenström macroglobulinemia

Form 2018

- ## Diagnosis and Disease Assessment
- ◆ Lymph node aspiration or biopsy
 - ◆ Peripheral blood counts and morphology
 - ◆ Bone marrow morphology
 - ◆ Flow cytometry
 - ◆ Cytogenetics
 - ◆ Molecular testing
 - ◆ Imaging

Cytogenetics and Molecular Testing

- ◆ Chromosome banding/FISH or PCR can be done for chromosomal abnormalities or gene fusion products
 - T-cell NHL: t(2;5) → ALK/NPM genes
 - Burkitt's NHL: t(8;14) → MYC/IGH
 - Follicular NHL: t(14;18) → IGH/BCL2
 - Mantle cell NHL: t(11;14) → IGH/CCND1

Flow Cytometry

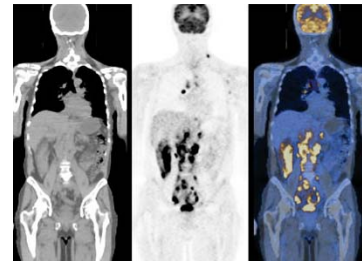
- ◆ Stream of cells can be manipulated (e.g. tagged with fluorescent dye) and passed through a laser beam
 - Cells can be separated for counting and analysis
- ◆ Positive result usually correlates with bone marrow morphology findings
 - Residual small (<2%) B-cell clone on flow cytometry only in absence of other findings → unclear significance

Imaging for Staging Lymphoma

- ◆ Computed tomography (CT)
- ◆ Positron emission tomography (PET)
 - ¹⁸F-glucose (FDG) radio isotope is used → avidly taken up by lymphoma
 - More sensitive than CT scan
 - Different types have varying PET avidity (diffuse large B-cell, Hodgkin's, follicular, mantle cell lymphoma are PET avid)
- ◆ MRI for assessment of specific sites (e.g. central nervous system)

PET-CT

- ◆ Combines PET scan and CT scan



Lymphoma Response Criteria

- ◆ Complete remission
 - No clinical evidence of disease
 - Typically PET avid lymphomas: post-therapy residual mass of any size should be PET negative
 - Variably PET avid lymphomas: all lymph nodes normal size by CT
 - No palpable liver or spleen
 - Bone marrow biopsy should be negative

Cheson et al, J Clin Oncol, 2007;25; 579

Lymphoma Response Criteria

- ◆ Partial remission
 - ≥50% decrease in lymph node size and/or hepatic/splenic nodules (sum of the product of diameters)
 - Typically PET avid lymphomas: PET positive in at least one previous site
 - No new sites of disease

Lymphoma Response Criteria

- ◆ Stable disease
 - Failure to attain CR/PR or progressive disease
 - Typically PET avid lymphomas: PET positive at prior sites of disease, no new sites of disease

Lymphoma Response Criteria

- ◆ Progressive disease or relapse
 - Appearance of new lesions (lymph node, bone marrow or other sites)
 - 50% increase in lymph node size
 - Increase in PET uptake

Form 2018 (Pre-HSCT, Lymphoma)

Pre-HSCT Treatment for Non-Hodgkin's Lymphoma / Hodgkin's Lymphoma

131. Was therapy given between diagnosis and the start of the preparative regimen?

1 yes
2 no

Line of Therapy:	1st Line of Therapy	2nd Line of Therapy
Chemotherapy:	1 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unk. with 64	80 <input type="checkbox"/> yes <input type="checkbox"/> no <input type="checkbox"/> unk. with 115
Date therapy started:	33	81
Date therapy stopped:	33	82

Best Response Definitions

- 1 Complete remission (CR) - complete disappearance of all lymph disease for ≥ 4 weeks
- 2 CR Undetermined (CRU) - as above with the exception of persistent scan abnormalities of unknown significance
- 3 Partial remission (PR) - $\geq 50\%$ reduction in greatest diameter of all sites of known disease and no new sites
- 4 No response / Stable disease (NR / SD) - $\geq 50\%$ reduction in greatest diameter of all sites of known disease
- 5 Progressive disease (Prog) - increase in size of known disease or new sites of disease
- 6 Not assessed - Unknown

CRU – With use of PET, no longer included in most recent criteria; okay to use if PET scan is not done as part of staging workup

Best Response to Line of Therapy:	76 <input type="checkbox"/> CR <input type="checkbox"/> CRU	83 <input type="checkbox"/> NR / SD	126 <input type="checkbox"/> CR <input type="checkbox"/> CRU	84 <input type="checkbox"/> NR / SD
(one version of 60)	4 <input type="checkbox"/> CR <input type="checkbox"/> CRU	3 <input type="checkbox"/> PR <input type="checkbox"/> Prog	4 <input type="checkbox"/> CRU <input type="checkbox"/> PR <input type="checkbox"/> Prog	4 <input type="checkbox"/> CR <input type="checkbox"/> CRU
Date response established:	77	78	127	85
But disease relapsed/progressed following this line of therapy?	79 <input type="checkbox"/> yes <input type="checkbox"/> no	80 <input type="checkbox"/> yes <input type="checkbox"/> no	127 <input type="checkbox"/> yes <input type="checkbox"/> no	86 <input type="checkbox"/> yes <input type="checkbox"/> no
Date of relapse/progression:	79	80	128	86

Form 2018 (Pre-HSCT, Lymphoma)

Most Recent Disease Assessment Prior to the Start of the Preparative Regimen

129. Was a PET scan performed at any time between diagnosis and the start of the preparative regimen?

1 yes
2 no

130. Was the PET scan positive for lymphoma involvement at any disease site?

1 yes
2 no

143. Was molecular testing performed at the time of the pre-HSCT disease status determination?

1 yes
2 no

140. Specify the date molecular testing was performed:

140. Was disease detected? yes no

151. What was the sensitivity of the lymphoma to chemotherapy prior to the preparative regimen? (Report the response to the last chemotherapy given prior to HSCT; treatment must be given ≤ 6 months prior to HSCT.) (see disease state definitions at question 60.)

- 1 sensitive - $\geq 50\%$ reduction in the bidimensional diameter of all disease sites with no new sites of disease (PR, CR, CRU, REL, res)
- 2 resistant - $< 50\%$ reduction in the diameter of all disease sites, or development of new disease sites (PR, res, REL, res)
- 3 unknown (PRF, unk, REL, unk)

* Primary induction failure (PIF): failure to achieve CR or PR with any pre-HSCT therapy; Sensitive/resistant: response to chemotherapy (if CR/PR \rightarrow sensitive disease)

Form 2018 (Pre-HSCT, Lymphoma)

150. What was the disease response state immediately prior to the preparative regimen?

- 1 Disease untreated
- 2 PIF unk - Primary induction failure - resistant; NEVER in COMPLETE remission but with partial remission on treatment
- 3 PIF sens - Primary induction failure - sensitive; NEVER in COMPLETE remission but with partial remission on treatment
- 4 PIF unk - Primary induction failure - sensitivity unknown
- 5 CR1 - 1st complete remission: no bone marrow or extramedullary relapse prior to transplant
- 6 CR2 - 2nd complete remission
- 7 CRU1 - 1st complete remission; undetermined; as above with the exception of persistent scan abnormalities of unknown significance
- 8 CRU2 - 2nd complete remission; undetermined
- 9 CRU3+ - 3rd or subsequent complete remission; undetermined
- 10 REL1 unk - 1st relapse-untreated; includes either bone marrow or extramedullary relapse
- 11 REL1 res - 1st relapse-resistant; stable or progressive disease with treatment
- 12 REL1 unk - 1st relapse-sensitive; partial remission (if complete remission achieved, classify as CR2, code 6)
- 13 REL1 unk - 1st relapse-sensitivity unknown
- 14 REL2 unk - 2nd relapse-untreated; includes either bone marrow or extramedullary relapse
- 15 REL2 res - 2nd relapse-resistant; stable or progressive disease with treatment
- 16 REL2 unk - 2nd relapse-sensitive; partial remission (if complete remission achieved, classify as CR3+, code 7)
- 17 REL2 unk - 2nd relapse-sensitivity unknown
- 18 REL3 unk - 3rd or subsequent relapse-untreated; includes either bone marrow or extramedullary relapse
- 19 REL3 res - 3rd or subsequent relapse-resistant; stable or progressive disease with treatment
- 20 REL3 unk - 3rd or subsequent relapse-sensitive; partial remission (if complete remission achieved, classify as CR3+, code 7)
- 21 REL3 unk - 3rd relapse or greater-sensitivity unknown

Form 2118 (Post-HSCT, Lymphoma)

1. Compared to the disease status prior to the preparative regimen, what was the best response to HSCT since the date of the last report? (Include response to any post-HSCT treatment planned as of Day 0.)

- 1 continued complete remission (CCR) (for patients transplanted in CR)
- 2 complete remission (CR); complete disappearance of all known disease for ≥ 4 weeks
- 3 complete remission undetermined (CRU); as above with the exception of persistent scan abnormalities of unknown significance
- 4 partial remission (PR); $\geq 50\%$ reduction in greatest diameter of all sites of known disease and no new sites
- 5 no response / stable disease (NR / SD); $< 50\%$ reduction in greatest diameter of all sites of known disease
- 6 relapse / progressive disease: increase in size of known disease, or new sites of disease
- 7 not assessed

2. Date the best response first began: date of the best response was previously reported

Form 2118 (Post-HSCT, Lymphoma)

46. Was a positron emission tomography (PET) scan performed since the date of the last report?

1 yes
 2 no

50. Date of most recent PET scan: Month Day 20 Year

51. Results of most recent PET scan:

1 positive
 2 negative
 3 indeterminate / equivocal

52. Was the positive result considered a disease recurrence or progression?

1 yes
 2 no

Disease Status at the Time of Assessment for This Reporting Period

53. Was the current disease status assessed by molecular testing?

1 yes
 2 no

54. Date of most recent molecular assessment: Month Day 20 Year

55. Was disease detected?

1 yes
 2 no

56. Was the current disease status assessed by conventional cytogenetics / FISH?

1 yes
 2 no

57. Date of most recent cytogenetic / FISH assessment: Month Day 20 Year

58. Was disease detected?

1 yes
 2 no

Troubleshooting

Not Sure How to Report Response?

- ◆ Ask your center director or physician taking care of patient
- ◆ Contact us!!
 - Provide us with documentation to determine appropriate response

Response in Long-term Survivors

- ◆ Staging studies (e.g. CT, PET, bone marrow) may not be repeated
- ◆ If no clinical evidence of disease (e.g. history and physical exam) → can classify as continuing complete remission

Remember...

- ◆ Accurate reporting of response (pre and post-HCT) is very important for CIBMTR research studies

QUESTIONS?