



Disease Response

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*CRA Committee: New CRA Session
2010 Summer Group Meeting*

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Objectives

- Review response criteria for solid tumor cancers, lymphomas, and leukemias
- Review how lesions are measured
- Distinguish between responding, stable, and progressive disease
- Demonstrate accurate and correct documentation of response

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Importance of Response

- Clinical response rates
- Response duration or progression-free survival (PFS)
- Not all protocols assess response
- For some protocols, response will be defined as the end point of the study

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Solid
Tumor
Response:
RECIST 1.0

Solid Tumor Response

- Examples of solid tumor diseases are:
 - Breast
 - Gastrointestinal (GI)
 - Genitourinary (GU) including prostate, renal, and bladder
 - Respiratory

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Key Points

- Defining RECIST 1.0 and RECIST 1.1
- Defining and applying appropriate measurement methods
- Understanding response criteria
- Determining the patient's best overall response

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RECIST 1.0

- **RECIST: Response Evaluation Criteria In Solid Tumors**
- Target/non-target lesions
- Involves uni-dimensional (1-dimensional) measurements.

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Target Lesions

- Measurable lesions
 - ≥ 2 cm by regular CT or ≥ 1 cm by spiral CT
- Lesion selection
 - Maximum of 5 lesions per organ
 - 10 lesions total
 - Size and suitability for *accurate repeated measurements*
 - Representative of all involved organs

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Non-Target Lesions

- All other sites of disease
- Evaluable lesions
- Lesions < 2 cm (< 1 cm by spiral CT)
- Record as "present" or "absent" on the measurement form
- Examples of non-target lesions
 - Bone, Leptomeningeal disease, (Brain/CNS), Ascites, Abdominal masses (not confirmed by imaging), Pleural/pericardial effusion, Cystic lesions, Tumors situated in previously irradiated areas

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Evaluating Lesions

- Complete Response (CR)
- Partial Response (PR)
- Stable Disease (SD)
- Progressive Disease (PD)

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Complete Response

- Disappearance of all target and non-target lesions
- Normalization of tumor marker level
 - Example: Prostate Specific Antigen (PSA)
- Requires confirmation at least 4 weeks later
- No new lesions

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Partial Response

- Recognized in target lesions only
- $\geq 30\%$ reduction in sum of longest diameters from baseline
- Requires confirmation at least 4 weeks later
- No new lesions

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Stable Disease

- Target Lesions
 - Insufficient decrease in sum of the longest diameters to qualify as a Partial Response
 - Insufficient increase in sum of the longest diameters to qualify as a Progression
- Non-Target Lesions
 - Persistence of non-target lesion(s)
 - Maintenance of tumor marker level
- No New Lesions

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Progression/Relapse

- At least a 20% increase in the sum of the longest diameters of all target lesions; compared to the *smallest* sum of the longest diameters since starting protocol
- Appearance of one or more new lesions (target and/or non-target)

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RECIST 1.0 Overall Response

Target Lesions	Non-target Lesions	New Lesion	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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RECIST 1.1 Implementation

- Solid tumor protocols activating after Nov 1, 2009 will use RECIST 1.1 (Currently 30801 and 80802)
- Currently active studies will not convert to the new criteria.
- Studies using RECIST 1.1 will require the submission of the C-2000 Solid Tumor Evaluation Form.

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Measuring Target Tumor Burden

- Measure in at least one dimension with a minimum size of:
 - 10 mm by CT scan (regardless of scanner type) and MRI
 - 10 mm caliper measurement by clinical exam (when superficial)
 - 20 mm by chest X-ray
- Include all target lesions:
 - Up to a maximum of *five* lesions
 - Maximum of two lesions per organ
 - Representative of all involved organs

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Assessment of Lymph Nodes

- Target nodes measured in the *short* axis
- Definitions:
 - Target lesion: short axis ≥ 15 mm
 - Non-target lesion: short axis 10mm to < 15 mm
 - Normal size: short axis < 10 mm
- *Short axes* of target nodes added to the sum of diameters

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Summary of Target Lesions

- Non lymph node lesions ≥ 10 mm by CT or MRI
- Lymph nodes with short axis ≥ 15 mm by CT or MRI
- Lytic bone lesions that meet definition of target lesion
- Cystic lesions that can be re-measured and meet definition of target lesion

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Complete Response

- Disappearance of all lesions
- All pathological lymph nodes (target or non-target) must have reduction in short axis to <10 mm
- *The sum may not be "0" if there are target lymph nodes*
- Normalization of tumor marker level

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Progressive Disease

- Target Lesions:
 - 20% increase in the sum of diameters taking as reference the smallest sum of diameters recorded since the treatment started (nadir)
- AND
- Minimum 5 mm increase over the nadir
 - Any new lesion

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Comprehensive
online training for
RECIST 1.1 is
available on the
CALGB web site
training tab

Lymphoma Disease Types

- Hodgkin's Lymphoma (HL) – 15%
 - Specific mutation in Reed-Sternberg cells
 - Classical & nodular lymphocyte-predominant
- Non-Hodgkin's Lymphoma (NHL) – 85%
 - Mutations in B-cells (80%) & T-cells (20%)
 - Diffuse large B-cell, follicular, mantle cell

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Lymphoma Response Criteria

- The Cheson Criteria
 - Cheson, et al: Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. *J Clin Oncol* 17: 1244-1253, **1999**
 - Cheson, et al: Revised Response Criteria for Malignant Lymphoma. *J Clin Oncol* 25: 579-586, **2007**

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Four Factors Impacting Disease Response

- Target lesions – measurable
 - Most CALGB studies require measurable disease
 - Tumor mass measuring >1cm in longest axis
- Non-target lesions – non-measurable
- Bone marrow
- Positron Emission Tomography (PET)

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Target Lesions

- Selecting target lesions (measurable)
 - Maximum of 6 target lesions with the following features:
 - Measurable in at least 2 perpendicular dimensions
 - Representative of all involved organs & from as disparate regions of body as possible
 - Suitable for accurate repeat measurements
 - Include mediastinal and retroperitoneal areas of disease when involved

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Target Lesions

- Reporting target lesions (measurable)
 - Name/describe and number each lesion
 - Should not change throughout treatment and follow-up
 - Calculate SPD
 - Multiply each lesion's two longest diameters
 - Sum the Products of the greatest transverse Diameters (SPD or total tumor size)
 - Use correct units (cm v. mm)

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Non-Target Lesions

- Selecting non-target lesions (assessable)
 - Masses that **cannot** be measured bi-dimensionally (i.e. too small)
 - Organ involvement (liver and spleen)
 - Ascites or pleural/pericardial effusion
 - Bone marrow
- Reporting non-target lesions (assessable)
 - “present” at baseline
 - “no change,” “increased,” “decreased,” or “absent” at follow-up

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Bone Marrow

- Bone marrow status
 - Considered assessable disease
 - Report as +/- and extent of involvement
 - Normal BM < 2% clonal B-cell population
 - Determination of involvement relies largely on morphologic (form & structure) findings
 - Immunohistochemistry (IHC) increases sensitivity using subtype-specific antibody panels to detect involvement (i.e. CD20)

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Positron Emission Tomography

- PET Scan
 - Distinguish viable tumor from necrosis/fibrosis
 - Strongly recommended for routinely FDG-avid and potentially curable lymphomas (i.e. DLBCL and HL)
 - PET shown to predict outcome to treatment
 - Visual assessment adequate to determine positivity; SUV not necessary

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Response Assessment Table

11.2 Response Assessment Table

Measurable Sites	Assessable Sites (e.g., liver, spleen)	Bone Marrow	Overall Response
CR	CR	Negative	CR
CRu	CR	Negative or Indeterminate	CRu (CR - uncertain)
CR	CR	Indeterminate	CRu (CR - uncertain)
PR	No Increase	Irrelevant	PR
CR	Decrease	Irrelevant	PR
CR	No Increase	Positive	PR
SD	No Increase	Irrelevant	SD
No PD	No Change	Irrelevant	SD
New or Increased	Irrelevant	Irrelevant	Relapse or PD
Irrelevant	Irrelevant	Positive (after a CR)	Relapse or PD
Irrelevant	New or Increased	Irrelevant	Relapse or PD

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Evaluation of Response

- Complete Response (CR)
- *Complete Response Unconfirmed (CRu)*
 - Studies prior to the 2007 Revised Cheson Criteria
- Partial Response (PR)
- Stable Disease (SD)
- Progression/Relapse (PD)

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Complete Response (CR)

- Complete disappearance of all detectable clinical evidence of disease and disease related symptoms
- ***If PET+ pretreatment, a residual mass of any size is permitted if PET-***
- ***If PET- pretreatment, all lymph nodes and masses must be normal size***
- Spleen and/or liver should not be palpable and should be considered normal by imaging study
- Bone marrow is clear of disease

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CR Unconfirmed (CRu)

- Studies opened prior to the 2007 Revised Cheson Criteria include CRu
 - Complete disappearance of all detectable clinical evidence of disease and disease related symptoms
 - Spleen and/or liver should not be palpable and should be considered normal by imaging study
 - **Residual node > 1.5 cm has regressed 75%**
 - Indeterminate bone marrow

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Partial Response (PR)

- $\geq 50\%$ decrease in total tumor size (SPD)
- No increase in size of other nodes, liver, or spleen
- Splenic and hepatic nodules regressed by $\geq 50\%$
- Bone marrow assessment irrelevant
- No new sites of disease
- ***If PET+ pretreatment, scan should be + in at least one previously involved site***
- ***If PET- pretreatment, standard CT criteria should be used***

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Stable Disease (SD)

- Failure to meet criteria needed for CR or PR, but does not fulfill criteria for PD
- ***If PET+ pretreatment, PET should be + at prior sites with no new areas of involvement***
- ***If PET- pretreatment, no change in size of previous lesions by CT***
- Refer to the smallest tumor size achieved since treatment started, which may not necessarily be the baseline measurement

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Progression / Relapse (PD)

- Any new lesions > 1.5 cm in any axis
- Increase \geq 50% from nadir in the SPD or in a single involved node
- Increase \geq 50% in the longest diameter of any node > 1 in the short axis
- ***If PET+ pretreatment, should be PET+ at PD***
- Positive bone marrow after achieving a complete response

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Leukemia Response

Factors Impacting Leukemia Response

- Hematologic features
 - ANC, platelet counts, hemoglobin
- Bone marrow features
 - Cellularity and blast cell percentage
- Clinical features
 - Lymphadenopathy/Splenomegaly/CNS involvement

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Standard Leukemia Response Types

- **Always** refer to the “Criteria for Response” section of the protocol for specifics.
- Response terminology and criteria in leukemia are disease specific.

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General Response Criteria for Leukemia

- Complete Response (CR)
 - Disappearance of signs and symptoms of disease
 - Peripheral blood counts within normal limits
- Partial Response (PR)
 - Decrease in white blood cell count or peripheral lymphocyte count
 - Reduction in size of enlarged organs

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General Response Criteria for Leukemia *(continued)*

- Progression/Relapse (PD)
 - Increased WBC or platelet count (CML)
 - Increase in size of liver or spleen (CML/CLL)
 - Appearance of new lymph node (CLL)
 - Finding circulating blasts cells in peripheral blood or > 5% myeloblasts in bone marrow (AML/ALL)

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Review

- Every protocol is unique
- Response status and criteria will vary
- Document all responses
- Submit source documentation as per protocol instructions

Resources

- Protocols on www.calgb.org
- www3.cancer.gov/dip/RECIST.htm
- www.cancer.gov (NCI)
- www.eortc.be/Recist/documents/RECISTGuidelines.pdf
- <https://training.calgb.org/recist1p1>
- Data Coordinator at the CALGB Statistical Center in Durham, NC