SUMMARY OF CHANGES
Update Date: April 12, 2012
(Broadcast: April 12, 2012)

RTOG 0524, "A Phase I/II Trial Of A Combination Of Paclitaxel And Trastuzumab With Daily Irradiation Or Paclitaxel Alone With Daily Irradiation Following Transurethral Surgery For Non-Cystectomy Candidates With Muscle-Invasive Bladder Cancer"

Study Chair: M. Dror Michaelson, MD, PhD; 617-726-1594; dmichaelson1@partners.org

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RTOG 0524 has been updated as follows:

Section 10.2.6: The street address for the RTOG Biospecimen Resource was updated.

SUMMARY OF CHANGES
Amendment 9, Version Date: January 30, 2012
(Broadcast: January 31, 2012)

RTOG 0524, "A Phase I/II Trial Of A Combination Of Paclitaxel And Trastuzumab With Daily Irradiation Or Paclitaxel Alone With Daily Irradiation Following Transurethral Surgery For Non-Cystectomy Candidates With Muscle-Invasive Bladder Cancer"

Study Chair: M. Dror Michaelson, MD, PhD; 617-726-1594; dmichaelson1@partners.org

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RTOG 0524 has been amended as follows:

Appendix I (sample consent):

- Will my medical information be kept private?
  Per NCI, the paragraph beginning "A description of this clinical trial will be available…" [new FDA language per 21 CFR 50.25(c)] and the "Note to Informed Consent Authors" were inserted to provide additional details to participants and the local institution.

- Where can I get more information?
  The NCI's TTY number is no longer in service and was deleted.

SUMMARY OF CHANGES
Amendment 8, Version Date: January 12, 2012
(Broadcast January 31, 2012)

RTOG 0524, "A Phase I/II Trial Of A Combination Of Paclitaxel And Trastuzumab With Daily Irradiation Or Paclitaxel Alone With Daily Irradiation Following Transurethral Surgery For Non-Cystectomy Candidates With Muscle-Invasive Bladder Cancer"

Study Chair: M. Dror Michaelson, MD, PhD; 617-726-1594; dmichaelson1@partners.org

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RTOG 0524 has been amended as follows:

*In response to a CTEP Request for Amendment (RA), **RTOG 0524** was revised to reflect modified risk information in the Comprehensive Adverse Events and Potential Risks List (CAEPR) for Trastuzumab. Changes were made to the following sections of the protocol*:

Title Page: Revised Protocol Version Date for the amendment and amendment number included.

Section 7.3.4: Trastuzumab CAEPR Version 2.1 (March 23, 2010) was replaced with CAEPR Version 2.2 (September 29, 2011). Specific changes to the CAEPR are as follows:

- The Agent Specific Adverse Event List (ASAEL) is now termed the Specific Protocol Exceptions to Expedited Reporting (SPEER) and includes grades for adverse events found on the SPEER that are used to determine if expedited reporting is required.

- Added New Risk:
  - Also Reported on Trastuzumab Trials But With the Relationship to Trastuzumab Still Undetermined: Acute coronary syndrome; Atrial fibrillation

- Decrease in Risk Attribution:
  - Changed to Rare but Serious from Less Likely: Adult respiratory distress syndrome; Bronchospasm; Pneumonitis
  - Changed to Reported But Undetermined from Less Likely: Cardiac arrest; Cardiac troponin I increased; Pleural effusion

- Provided Further Clarification:
  - The footnote has been deleted from Pleural effusion.
  - The footnote for Urticaria has been deleted.

- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
  - Added: Back pain; Bone pain; Flu like symptoms; Pain; Rash acneiform
  - Deleted: Allergic reaction; Bronchospasm

- Deleted Risk:
  - Less Likely: White blood cell decreased

Appendix I (sample consent), under "Risks and side effects associated with trastuzumab":

- Decrease in Risk Attribution:
  - Changed to Rare but Serious from Less Likely: Inflammation of the lungs that may cause difficulty breathing and can be life-threatening; Severe potentially life-threatening damage to the lungs which can lead to fluid in the lungs; Sudden constriction of the small airways of the lung that can cause wheezing and shortness of breath

    - Changed to Reported But Undetermined from Less Likely (i.e., Removed from the Risk Profile): Build up of a large amount of fluid between the layers of tissue that line the lungs and chest cavity; Increased blood level of a heart muscle protein (troponin I) indicating damage to the heart muscle; The heart stops pumping blood

- Deleted Risk:
    - Less Likely: Decrease in the total number of white blood cells (leukocytes)

Additional revisions within the protocol are as follows:

Section 6.0: The following subsections were modified to include additional details regarding treatment planning/target volumes and the bowel:

- 6.4.1
- 6.4.2
- 6.4.3
- 6.5

Sentence regarding use of anti-diarrheal agents added to the following sections:

- Section 6.7 (end of section)
- 7.2.5 (gastrointestinal section)
- 7.4.5

Section 13.1.1: "Acute treatment-related toxicity in patients with her2/neu overexpression or not treated with paclitaxel ± trastuzumab and concurrent radiation therapy as defined by…." was revised to *"Acute treatment-related toxicity (that does not resolve to Grade ≤1 within 7 days or a reasonable timeframe as determined by the study chairs and treating physicians) in patients with her2/neu overexpression or not treated with paclitaxel ± trastuzumab and concurrent radiation therapy as defined by….".*

SUMMARY OF CHANGES
Amendment 7, Version Date: April 11, 2011
(Broadcast Date: April 26, 2011)

RTOG 0524, "A Phase I/II Trial Of A Combination Of Paclitaxel And Trastuzumab With Daily Irradiation Or Paclitaxel Alone With Daily Irradiation Following Transurethral Surgery For Non-Cystectomy Candidates With Muscle-Invasive Bladder Cancer"

Study Chair: M. Dror Michaelson, MD, PhD; 617-726-1594; dmichaelson1@partners.org

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RTOG 0524 has been amended as follows:

Global: All web links and related descriptions to sub-pages of the RTOG web site were updated.

Title Page: Dr. Pham added in place of Dr. Pollack as Radiation Oncology Co-Chair (corresponding changes were made in **Sections 6.1 and 6.9**); Dr. Hunt's e-mail address was updated; protocol document history table added.

Section 5.2.1.1: This subsection regarding translation of regulatory documents was added, per RTOG standard.

Section 7.3.5: The last two sentences regarding the PMB's Policy and Guidelines for Investigational Agent Distribution were added for reference.

Section 10.3: The RTOG reimbursement text was updated. The updated text includes a web address for the Reimbursement and Case Credit Schedule located on the RTOG web site.

Appendix I (Sample Consent):

- Under "Reproductive Risks", the second sentence regarding RT plus trastuzumab use during pregnancy was added.
- Under "About Using Tissue for Research", in the last sentence of the second paragraph, the NCI web site address was updated to the current web link.

SUMMARY OF CHANGES
Amendment 6, Version Date: March 18, 2011
(Broadcast Date: April 26, 2011)

RTOG 0524, "A Phase I/II Trial Of A Combination Of Paclitaxel And Trastuzumab With Daily Irradiation Or Paclitaxel Alone With Daily Irradiation Following Transurethral Surgery For Non-Cystectomy Candidates With Muscle-Invasive Bladder Cancer"

Study Chair: M. Dror Michaelson, MD, PhD; 617-726-1594; dmichaelson1@partners.org

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RTOG 0524 has been amended as follows:

As mandated by NCI-CTEP, **Section 7.8** (first paragraph) has been amended to require the use of CTCAE version 4 for grading of all adverse events reported via AdEERS as of April 1, 2011.

Note: References to CTCAE, version 3.0 may remain in the protocol. These are appropriate, as treatment decisions for patients enrolled on this study were based on that version.

Other Changes
Section 7.8: The RTOG web address in the third paragraph was updated; the fifth paragraph regarding 24-hour telephone notification to CTEP was added.

Section 7.8.3: Amended as required per current NCI-CTEP reporting requirements for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) via AdEERS.

SUMMARY OF CHANGES
Amendment 5, Version Date: May 12, 2010
(Broadcast: June 8, 2010)

RTOG 0524, "A Phase I/II Trial Of A Combination Of Paclitaxel And Trastuzumab With Daily Irradiation Or Paclitaxel Alone With Daily Irradiation Following Transurethral Surgery For Non-Cystectomy Candidates With Muscle-Invasive Bladder Cancer"

Study Chair: M. Dror Michaelson, MD, PhD; 617-726-1594; dmichaelson1@partners.org

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*In response to a CTEP Request for Amendment (RA), **RTOG 0524** was revised to reflect changes to the Comprehensive Adverse Events and Potential Risks List (CAEPR) for Trastuzumab. Changes were made to the following sections*:

Section 7.3.4: Trastuzumab CAEPR Version 1.0 (February 25, 2005) was replaced with CAEPR Version 2.1 (March 23, 2010). Specific changes are as follows:

- This CAEPR version includes frequency data. The previous version did not have the categories for Likely, Less Likely, or Rare but Serious.
- This section utilizes CTCAE 4.0 language unless otherwise noted.
- Added New Risk:
  - Less Likely: Supraventricular tachycardia
  - Reported on Trastuzumab Trials but with the Relationship to Trastuzumab Still Undetermined: Myocardial infarction; Ventricular arrhythmia; Ventricular fibrillation; Ventricular tachycardia; Extraocular muscle paresis; Dyspepsia; Gastritis; Immune system disorders - Other (autoimmune thyroiditis); Alanine aminotransferase increased; Creatinine increased; Platelet count decreased; Proteinuria; Pharyngolaryngeal pain; Pulmonary hypertension; Nail loss; Pruritus
- Increase in Risk Attribution:
  - Changed to Less Likely from Reported but Undetermined: Peripheral sensory neuropathy
- Decrease in Risk Attribution:
  - Changed to Reported but Undetermined from Less Likely: Neuralgia; Voice alteration; Skin ulceration
- Provided further clarification:
  - Mucositis/stomatitis (functional/symptomatic) - Select *(CTCAE version 3.0 language)* is now only reported as the following individual event, Mucositis oral.
  - Cytokine release syndrome/acute infusion reaction *(CTCAE version 3.0 language)* is now reported as Infusion related reaction.

    - GU obstruction (verbatim from source documents) is now reported as the following individual events: Urinary tract obstruction, Fallopian tube obstruction, Prostatic obstruction, Spermatic cord obstruction, Uterine obstruction, and Vaginal obstruction.
    - Muscle weakness *(verbatim from source documents)* is now reported as the following individual events: Generalized muscle weakness, Muscle weakness left-sided, Muscle weakness lower limb, Muscle weakness right-sided, Muscle weakness trunk, and Muscle weakness upper limb.
    - Allergic reaction/hypersensitivity (including drug fever *(CTCAE version 3.0 language)* is now reported as Allergic reaction and Anaphylaxis.
    - The following footnote was added to Allergic reaction, Adult respiratory distress syndrome, Bronchospasm, Dyspnea, Hypoxia, Pleural effusion, and Pneumonitis: "Severe hypersensitivity reactions including, angioedema and pulmonary adverse events (e.g., hypoxia, dyspnea, pulmonary infiltrates, pleural effusion, and acute respiratory distress syndrome) have been reported."
    - Footnote #4 was added to clarify those adverse events that were previously on the version 1.0 CAEPR under Infection with unknown ANC - Select (*CTCAE 3.0 language*).
    - The following footnote was added to Urticaria: "Urticaria may be observed in conjunction with anaphylaxis."
    - The following footnote was added to Hypotension: "Associated with infusion reactions."
- Modified Agent Specific Adverse Events List (ASAEL) reporting requirements:
    - Added: Infusion related reaction; Urticaria
- Deleted Risk:
    - Possible *(CTCAE version 3 language)*: Allergy/Immunology - Other (Angioedema); Supraventricular arrhythmia - nodal/junctional; Infection - Other (Herpes simplex)
    - Reported on Trastuzumab Trials but with the Relationship to Trastuzumab Still Undetermined: *(verbatim from source documents)*: Sinus bradycardia; GI obstruction; Ileus; Reduced growth velocity; Hemorrhage; Hypercalcemia; Hypoglycemia; Nephrotic syndrome; Viral hepatitis; Meningitis

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.1, and associated risk information for the Informed Consent Document (ICD), to the most recent CAEPR Version 1.0. Please note version 2.0 was never released.

Appendix I (Sample Consent): A risk profile for trastuzumab is being provided for the first time. The risks for trastuzumab presented in the consent were updated with the risks included in the risk profile provided with the updated CAEPR. Specific risk changes are as follows:

- Added New Risk:

    - Less Likely: Fast heartbeat usually originating in an area located above the ventricles
- Increase in Risk Attribution:
    - Changed to Less Likely from Reported but Undetermined: Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning
- Under "Likely", "Less Likely", and "Rare But Serious": Some of the text that was included in these sections prior to the implementation of CAEPR version 2.0 were retained. For example, the following bulleted item, "Leukopenia (decrease in white blood cell counts, which can lead to a risk of infection) NOTE: This side effect is likely when trastuzumab is used in combination with paclitaxel, as it is in this study. When trastuzumab is given alone, the risk of leukopenia is less likely", is specific to RTOG 0524 and was not deleted or revised.
- Under "Likely" and "Less Likely":
    - Dizziness and pain at the site of the trastuzumab injection were deleted from the "Likely" section
    - Decrease in the total number of white blood cells (leukocytes) was deleted from the "Less Likely" section; it is included under "Likely".

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to trastuzumab is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Additional revisions are as follows:

Title Page: Dr. Hunt's e-mail address was updated. Dr. Swanson's phone and fax numbers and e-mail address were updated.

Section 6.4.1: A typo in the last sentence was corrected.

Appendix I (Sample Consent): Under "About Using Tissue for Research", the web address in the second paragraph was updated.

Appendix VI (CTSU Logistics): The office hours for CTSU patient registration were updated.

SUMMARY OF CHANGES
Amendment 4, Version Date: August 12, 2009
(Broadcast 8/20/09)

RTOG 0524, "A Phase I/II Trial Of A Combination Of Paclitaxel And Trastuzumab With Daily Irradiation Or Paclitaxel Alone With Daily Irradiation Following Transurethral Surgery For Non-Cystectomy Candidates With Muscle-Invasive Bladder Cancer"

Study Chair: M. Dror Michaelson, MD, PhD; 617-726-1594; dmichaelson1@partners.org

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RTOG 0524 has been amended as follows:

Due to a recent death of a patient on study possibly related to treatment, the toxicities/risks associated with radiation therapy to the pelvis were amended in **Section 6.10** and in **Appendix I** to include bowel perforation.

Other Changes:

Title page: Contact information for the study statistician, Dr. Hunt, was added to amend the title page to the current RTOG standard.

Section 3.1.1: The phrase, "OR patients with stage T1, grade 3/3 as described in Section 3.1.5", was added for clarity and to be consistent with Section 3.1.5. In addition, the timeframe of "within 12 weeks of registration" was deleted, since it is possible that the most recent TURB (within 12 weeks) had no residual malignancy (if the initial TURB, more than 12 weeks prior, removed all visible tumor). These changes also were made in question 1, page 1 of the **Eligibility Checklist**.

Section 3.1.15 was amended for clarity to read, "Protocol treatment should begin within 3 to 12 weeks of the most recent TURB". This change also was made in the following sections: **Eligibility Checklist**, page 2, question 20 and **Sections 5.1** (last sentence), **6.1, 7.1.2.1, and 7.1.2.2.**

Section 5.2, "Regulatory Pre-Registration Requirements", was added to amend the protocol to the current RTOG standard text. The subsequent section was appropriately renumbered.

Section 6.3: The word, "stimulation", in the title and in the 7th sentence was corrected to "simulation".

Section 6.11: The word, "therapy", was added to the title to amend it to the current RTOG standard text.

Sections 7.8, 7.8.1, and 7.8.2 were amended to the current RTOG standard text.

Section 8.2: The timeframe for the post-chemoradiation endoscopic response evaluation was amended to "6-8 weeks following the completion of chemoradiotherapy to be consistent with Section 12.1.

Section 10.1: The "Note" was added to amend the section to the current RTOG standard text.

Section 10.2.6: The phrase, "U.S. Postal Service" was added to "Mailing Address" for clarity. In the Courier Address, "DHL" was replaced by "UPS".

The following changes were made to **Appendix I** to make the sample consent consistent with Sections 11.1 and 12.1:

- Under "What will happen if I take part in this research study"; "Pre-Study":
    - In the 1st bulleted item, "evaluate your ability to carry out daily activities", "record your weight", and "your body surface area" were added.
    - The 4th bulleted item, "An x-ray or CT scan of the chest will be done", was added.
    - The 5th bulleted item was amended to read, "A CT scan of the abdomen and pelvis will be done".
    - In the 8th bulleted item, the 1st and 2nd sentences were amended to describe the bimanual examination of the bladder.
- Under "What will happen if I take part in this research study"; "During the Study": In the 1st bullet: the phrase, "and recording your weight", was added.
- Under "What will happen if I take part in this research study"; "End of Study":
    - The title of this subsection was amended for clarity to "End of Study Treatment".
    - The 3rd bullet was amended to be consistent with Section 11.1.
- Under "How long will I be in the study", the timeframe for follow-up visits was amended to be consistent with the timeframe in Section 12.1.

Appendix II: The Karnofsky Performance Scale was deleted, and in the Zubrod Performance Scale table, parenthetical REFERENCES to Karnofsky scores were deleted, as the Zubrod is the performance scale being used in the study.

SUMMARY OF CHANGES
Update Date: February 24, 2009
(Broadcast Date: February 24, 2009)

RTOG 0524, "A Phase I/II Trial Of A Combination Of Paclitaxel And Trastuzumab With Daily Irradiation Or Paclitaxel Alone With Daily Irradiation Following Transurethral Surgery For Non-Cystectomy Candidates With Muscle-Invasive Bladder Cancer"

Study Chair: M. Dror Michaelson, MD, PhD; 617-726-1594; dmichaelson1@partners.org

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RTOG 0524 has been updated as follows:

Title page: The contact information for Dr. Pollack, the Radiation Oncology Co-Chair, was updated. Dr. Pollack's telephone number was also updated in **Section 6.1**.

Sections 4.1, 5.1, 8.1, and 10.0: References to "LDS Hospital" were replaced with "RTOG Biospecimen Resource" throughout. In Sections 4.1 and 5.1, "LDS Hospital" was replaced with the "Intermountain Central Laboratory". In addition, as a result of the changes to these areas of the protocol, "LDS Hospital" was replaced with "RTOG Biospecimen Resource" in question 4 on page 1 of the Eligibility Checklist.

SUMMARY OF CHANGES
Amendment 3, Version Date: January 9, 2007

RTOG 0524, "A Phase I/II Trial Of A Combination Of Paclitaxel And Trastuzumab With Daily Irradiation Or Paclitaxel Alone With Daily Irradiation Following Transurethral Surgery For Non-Cystectomy Candidates With Muscle-Invasive Bladder Cancer"

Study Chair: M. Dror Michaelson, MD, PhD; 617-726-1594; dmichaelson1@partners.org

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At the request of the Cancer Trials Support Unit (CTSU), **RTOG 0524** has been amended as follows:

- **Title page**: The statement at the bottom of the page regarding patient enrollments from institutions not aligned with RTOG was deleted, and text was added to the subsequent page.

- **Appendix VI**: All prior CTSU logistics text was deleted and was replaced with new CTSU logistics.

SUMMARY OF CHANGES
Amendment 2, Version Date: November 7, 2006

RTOG 0524, "A Phase I/II Trial Of A Combination Of Paclitaxel And Trastuzumab With Daily Irradiation Or Paclitaxel Alone With Daily Irradiation Following Transurethral Surgery For Non-Cystectomy Candidates With Muscle-Invasive Bladder Cancer"

Study Chair: M. Dror Michaelson, MD, PhD; 617-726-1594;
dmichaelson1@partners.org

RTOG 0524 has been amended as follows:

RTOG 0524 includes a targeted therapy component, which is of great interest to bladder cancer researchers, and there is broad cooperative group interest in the study. In order to make this clinically relevant and valuable trial available to all U.S. cooperative groups, U.S. independent research sites, and the NCIC CTG in Canada, the Cancer Trials Support Unit (CTSU) has agreed to participate in this study and to include 0524 on the CTSU menu. In addition, ECOG and SWOG have endorsed this study through the CTSU. The following sections of the protocol were amended for these changes:

- **Title page**: The names and contact information for the ECOG and SWOG Co-Chairs was added. In addition, a paragraph was added directing sites not aligned with RTOG to enroll patients via CTSU.
- **Appendix I**, the sample consent: Under "Will my medical records be kept private?", CTSU was added as one of the organizations with access to patients' medical records.
  Appendix VI, "CTSU Participant Procedures", was added. This appendix also was added to the **Index page**.

  Other changes

  Section 6.4.1: In the third sentence, the phrase, "at least" was deleted, and "1.5 cm laterally" was amended to "1.5-2.0 cm laterally". In the fifth sentence, the phrase, "at least 1.5 cm" was amended to "at least 2.5 cm", and the phrase, "although care should be taken to avoid fall-off anteriorly and < 2.5 cm may be required in some patients", was added to the sentence. These changes were made to make Section 6.4.1 more consistent with the subsequent two sections.

  Section 11.1: In the table, the footnote, "f" was added to the pre-study bone scan, which only needs to be done if clinically indicated. **Appendix I** was amended to be consistent with this change; under "Pre-study" procedures, "bone scan" was deleted from the fourth bulleted item, and added as the next item: "A bone scan will be done, if recommended by your study doctor."

SUMMARY OF CHANGES

Amendment #1, Version Date: September 7, 2005

RTOG 0524, "A Phase I/II Trial of a Combination of Paclitaxel and Trastuzumab With Daily Irradiation or Paclitaxel Alone With Daily Irradiation Following Transurethral Surgery for Non-Cystectomy Candidates With Muscle-Invasive Bladder Cancer"

Study Chair: M. Dror Michaelson, MD, PhD; 617-726-1594; Fax: 617-724-3166; dmichaelson1@partners.org

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RTOG 0524 has been amended as follows:

Eligibility Checklist, page 2, **Question #18:** Cutoff for left ventricular ejection fraction added (See **Section 3.1.13** below).

Section 1.1

- Fifth paragraph, second sentence: "selected" added before lung cancer patients for increased accuracy.
- Last paragraph added to explain the rationale for the left ventricular ejection fraction cutoff (See **Section 3.1.13** below).

Section 1.2: References in this paragraph renumbered due to addition of text and references in **Section 1.1**.

Section 3.1.13: Added due to possibility of enhanced cardiotoxicity with trastuzumab in patients with compromised cardiac function at baseline; all subsequent portions of **Section 3.1** renumbered.

Section 7.2.1: Reference renumbered due to the addition of text and references in **Section 1.1**.

Section 12.1: "Color" added before DVH in T6 form to avoid receipt of black and white copies.

Section 13.1.1: Second-to-last sub-bullet revised to monitor grade 3 left ventricular failure.

Section 13.2.2: Reference renumbered due to the addition of text and references in **Section 1.1**.

Section 13.4.3: First sentence revised to monitor grade 3 left ventricular failure; last paragraph added as stopping rules specifically addressing cardiac serious adverse events.

Section 13.4.4: Reference renumbered due to the addition of text and references in **Section 1.1**.

References: References 31 and 32 added due to the addition of text in **Section 1.1**; all subsequent references renumbered.

Appendix I/Sample Consent

- **What Will Happen If I Take Part in This Research Study/Pre-Study**: "Echocardiogram" added to first bullet of last section for consistency with the protocol.
- **Risks and Side Effects Associated With Trastuzumab**: Heart damage and related information added as last bullet under "less likely"; heart damage deleted from "rare but serious." This information was revised due to the possibility of enhanced cardiotoxicity with trastuzumab in patients with compromised cardiac function at baseline.