For Protocol Amendment #6 of: RTOG 9601, “A Phase III Trial of Radiation Therapy with or without Casodex in Patients with PSA Elevation Following Radical Prostatectomy for pT3N0 Carcinoma of the Prostate”

NCI/Local Protocol #: RTOG-9601

NCI Protocol Version Date: December 19, 2014 (Broadcast Date: January 20, 2015)

Study Chair: William U. Shipley, MD; (617) 726-8146; wshipley@partners.org

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
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<tbody>
<tr>
<td>Title page</td>
<td>Due to the transition to the NCI National Clinical Trials Network (NCTN), “Radiation Therapy Oncology Group” and “RTOG Headquarters: were replaced with “NRG Oncology” .</td>
</tr>
<tr>
<td>Schema page</td>
<td>Version Date was updated</td>
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For Protocol Administrative Update of RTOG 96-01, “A Phase III Trial of Radiation Therapy With or Without Casodex in Patients With PSA Elevation Following Radical Prostatectomy for pT3N0 Carcinoma of the Prostate”

NCI/Local Protocol #: RTOG-96-01/RTOG 96-01

NCI Protocol Version Date: December 31, 2008   Update Broadcast Date: May 1, 2014

<table>
<thead>
<tr>
<th>Section</th>
<th>Change</th>
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<tbody>
<tr>
<td>7.3</td>
<td>As required by CTEP, references to the “Adverse Event Reporting System (AdEERS)” have been changed to “CTEP Adverse Event Reporting System (CTEP-AERS)” throughout these sections.</td>
</tr>
<tr>
<td>Title page</td>
<td>The “update date” was revised.</td>
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RTOG 96-01, A Phase III Trial of Radiation Therapy With or Without Casodex in Patients With PSA Elevation Following Radical Prostatectomy for pT3N0 Carcinoma of the Prostate

Study Chair: William U. Shipley, MD; 617-726-8146; wshipley@partners.org

RTOG 96-01 has been amended as follows:

Title Page: "Principal Investigator" was added next to Dr. Shipley's name for clarity. Dr. Grignon's contact information was updated.

Section 1.1: The last paragraph was revised to include "metastasis, further PSA progression, other-cause mortality and toxicity" in the description of the study's evaluation plan.

Section 2.0: The study's objectives were revised to include comparisons of the treatment with non-disease-specific survival, 5-year and 10-year freedom from progression rates, and unintended adverse effects of treatment.

Section 11.3:

- Section 11.3.2: In the phrase, "or less than 0.3 ng/ml", 0.3 was corrected to 0.2.
- Section 11.3.3, "Time to PSA Progression": This section was amended.
- Section 11.3.6.3, "Time to Second PSA Progression": The first sentence was amended to read, "This will be measured from the date of randomization to the date of a second failure."
- Section 11.3.7, "Time to Third PSA Progression": This section was amended.
- Section 11.3.9, Disease-Specific Survival": The second bulleted item was added, the third bulleted item was amended, and the last bulleted item ("Death from other causes...") was deleted. In addition, the last sentence, regarding death while in PSA remission, was added.
- Sections 11.3.10 and 11.3.11, "Non-Disease-Specific Survival" and "Freedom From Progression", were added.

Section 13.0:

- The numbering in Section 13.1 was revised.
• Section 13.1.2.2, "Time to Second PSA failure": (formerly Section 13.1.3) The reference to the definition was amended to Section 11.3.6.3.
• Section 13.1.2.5, "Time to Distant Failure": (formerly Section 13.1.6) A reference was added to the definition in Section 11.3.5, and the prior definition of failure was deleted.
• Section 13.1.2.7, "Non-disease specific survival" was added to correspond to the addition of Section 11.3.10.
• Section 13.2, "Overview": The second paragraph regarding the preliminary outcome analysis and the RTOG Data Monitoring Committee's approval of same was added.
• Section 13.3, "Sample Size": The first sentence, referring to the prior amendment of the sample size in Section 13.8, was added.
• Section 13.7.1, "Methods for Estimation and Testing": Non-disease specific survival was added to the first sentence.
• Section 13.7.3, "Significance Testing for Early Termination": The first sentence, referring to the amendment of the interim analysis plan in Section 13.9, was added.
• Section 13.9, "Significance Testing for Early Termination: The last two sentences of the section, regarding the first, second, and third interim analyses, were deleted.
• Section 13.11, regarding the preliminary outcome analysis, was added.
At the request of the Cancer Trials Support Unit (CTSU), RTOG 96-01 has been amended as follows:

Text regarding patient enrollments from institutions not aligned with RTOG was added to the page following the title page.

Prior CTSU logistics text in the following sections was replaced with new logistics text: Sections 5.2.1, 7.3, and 12.2.

New logistics concerning CTSU Regulatory and Monitoring were added as Section 7.4. (The subsequent section, "Code Breaks", was renumbered as Section 7.5, and reference to the Code Breaks section in Section 9.2.1 was renumbered from Section 7.4 to 7.5 as well.)
RTOG 96-01, “A Phase III Trial of Radiation Therapy With or Without Casodex in Patients With PSA Elevation Following Radical Prostatectomy for pT3N0 Carcinoma of the Prostate”

Study Chair: William U. Shipley, M.D., (617) 726-8146, wshipley@partners.org

RTOG 96-01 has been updated as follows:

Title Page: Dr. Himu Lukka has been added as the co-chair for Radiation Oncology.

Appendix IX: The contact information for McKesson BioServices was updated.

NOTE: This is an editorial/administrative change to the protocol. NCI now requires that these changes be documented on the protocol title page with the date of the update noted as “Update Date”.

An updated protocol is available (no password required) on the RTOG website: http://www.rtog.org/
SUMMARY OF CHANGES

RTOG 96-01 Prostatectomy                 September 5, 2000

CTSU

This protocol is on the Clinical Trials Support Unit’s (CTSU) menu; the following sections were added or corrected: Sections 5.2, 7.1.4.8, 7.3, 10.7, 12.2, 12.3, Appendix I (Confidentiality re: CTSU), VIII and X.

OTHER CHANGES

Based on review by the RTOG Data Monitoring Committee, the total required sample size was lowered to 810 men (Sections 13.8, 13.9, 13.10, and References 36-37 were added).

2. The lowest eligible entry PSA is 0.2 ng/ml. (Schema, Eligibility Checklist, Sections 3.1.2 and 13.6 were updated).
3. Section 3.1.8 – abdominal/pelvic CT was changed to pelvic CT (also in Sections 4.6 and 11.1).
4. Section 4.4.1 was added to include acceptable commercial PSA assays.
5. Section 5.1 was updated for patient entries.
SUMMARY OF CHANGES

RTOG 96-01 Prostatectomy

October 26, 1999

The following changes are in effect:

**Cover Page** Dr. Pierre Major replaced Dr. Derek Raghavan as Medical Oncology Study Chair.

**Section 3.1** Changed to

3.1.1 The patient on entry will have no clinical evidence of disease by physical exam or by imaging studies. A positive ProstaScint scan alone without a confirmatory biopsy must not be used to exclude a patient. Eligible patients will be those who have undergone a radical prostatectomy (*either retropubic or perineal*) and pelvic lymphadenectomy (*either open or laparoscopic*) for carcinoma of the prostate, pathologic stage T3N0, or pT2 pN0 with positive inked resection margin, at least 12 weeks prior to study entry.

3.1.1.1 Pathologic T2 patients without positive margins, who are also pathologic N0 with prostatic fossa/anastamosis biopsy at the time of rising PSA documenting recurrent cancer are eligible.

**Section 3.1.2** The lowest eligible PSA is 0.3 ng/ml.

**Section 3.1.7** a) labs must be done within 6 weeks prior to study entry.

b) minimum platelet count is 100,000.

**Section 3.1.10** Prior or concurrent basal or squamous cell skin cancer is eligible.

The changes to Section 3.0 also affect the Schema and the Eligibility Checklist.

**Section 4.4** Deleted “PSA should be measured by the same assay at followup” and added the PSA statement formerly in Section 4.7, changing it to “between 2 and 20 weeks post-surgery . . .”

**Section 11.3.1** Added after the first sentence

“A positive ProstaScint scan alone without a confirmatory biopsy must not be used to exclude a patient.

**Section 11.3.2** Changed to “ . . . as reaching a PSA nadir of less than detectable by
institutional assay, or less than 0.3 ng/ml for those laboratories specifying PSAs below that level.

**Section 13.6** Item 4 was updated to “. . . 0.3 ng/ml . . . ”
The following changes are in effect:

**Schema** - pT2 is eligible only if there is a positive inked resection margin. This change also affects the Eligibility Checklist (Q2), Section 3.1.1 and Section 3.2.1.

**Section 3.1.3** - Changed to “A post-prostatectomy radioisotopic bone scan . . .”

**Section 4.7** - Changed to “. . . between 4 and 16 weeks post-surgery . . .”

**Section 6.1** - Photon energies $\geq 6$ to $10$ MeV are allowed unless the patient is large, i.e., the anterior/posterior separation is $> 24$ cm.

**Section 7.1.4.4** - Added “MBS will include a reorder form with the initial shipment.”

**Section 13.7.3** - Was rewritten to clarify the early stopping rules.

**Section 13.7.4** - line 8 - The significance level was changed to 0.046 (from 0.047).

**Appendix I**, a) paragraph 3 - added “impotence or loss of libido”

b) paragraph 5 - added “from Zeneca” to the first sentence

**Appendix IX** Items 4, 6, 7, and 9 were updated.