A PHASE III RANDOMIZED STUDY OF PATIENTS WITH HIGH RISK, HORMONE-NAÏVE PROSTATE CANCER: ANDROGEN BLOCKADE WITH 4 CYCLES OF IMMEDIATE CHEMOTHERAPY VERSUS ANDROGEN BLOCKADE WITH DELAYED CHEMOTHERAPY

The following cooperative groups* have endorsed this trial:

**ECOG**
Naomi Balzer-Haas, M.D.
(215) 728-2974
FAX (215) 728-3639
nb_haas@fccc.edu

**SWOG** *(5/19/03)*
Gregory Swanson, M.D.
(509) 473-1600
FAX (509) 473-1661
Greg.swanson@usoncology.com

Primo N. Lara, Jr., M.D.
(916) 734-377
FAX (916) 734-7946
Primo.lara@ucdmc.ucdavis.edu

**CALGB** *(5/19/03)*
Arif Hussain, M.D.
(410) 328-3911
FAX (410) 328-6559
ahussain@som.umaryland.edu

**CTSU (RTOG P-0014)**
Westat
CTSU Data Operations Center
1441 W. Montgomery Avenue
Rockville, MD 20850-2062
888-462-3009
FAX# 888-691-8039

RTOG Headquarters/Statistical Unit
215-574-3189
1-800-227-5463, ext. 4189

*Cooperative Group members will enroll patients to this study and submit data via the Cancer Trials Support Unit (CTSU)
This protocol was designed and developed by the Radiation Therapy Oncology Group (RTOG) of the American College of Radiology (ACR). It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by RTOG nor does RTOG assume any responsibility for unauthorized use of this protocol.
INDEX

Schema

Eligibility Check

1.0 Introduction

2.0 Objectives

3.0 Patient Selection

4.0 Pretreatment Evaluations

5.0 Registration Procedures

6.0 Radiation Therapy

7.0 Drug Therapy

8.0 Surgery

9.0 Other Therapy

10.0 Pathology

11.0 Patient Assessments

12.0 Data Collection

13.0 Statistical Considerations

References

Appendix I - Sample Consent Form
Appendix II - Performance Status Scoring
Appendix III - Staging System
Appendix IV - Toxicity Criteria
Appendix V - Adverse Reaction Reporting Guidelines
Appendix VI - CTSU Participation Procedures
**AB** = Arm 1: Androgen blockade utilizing LHRH agonists continuously; nonsteroidal antiandrogen (*bicalutamide, flutamide*) for at least one month. Patients may receive complete androgen blockade or monotherapy. Regimen choice and choice of complete androgen blockade vs. one-month nonsteroidal antiandrogen blockade is at discretion of enrolling physician.

Arm 2: All patients will receive AB; patients may have complete androgen blockade as long as the patient goes through complete androgen withdrawal prior to chemotherapy at time of failure of hormonal therapy (6 weeks bicalutamide; 4 weeks flutamide). Regimen choice and choice of complete androgen blockade vs. one-month nonsteroidal antiandrogen blockade is at discretion of enrolling physician.

*Chemotherapy:*

Arm 1: Patients on Arm 1 will receive chemotherapy starting within 4 weeks of AB with LHRH agonists. Once a chemotherapy regimen is chosen for a patient on Arm 1, that regimen may be reduced/stopped for toxicity; however, patients may not be changed from regimen to regimen in Arm 1 during the initial chemotherapy. Each investigator or Oncology Group may choose the regimen from the list included within the protocol for each patient. A patient may receive further therapy with protocol or non-protocol chemotherapy at physician discretion when a patient progresses on Arm 1.

Arm 2: Patients on Arm 2 will receive chemotherapy at the time of failure of AB (as defined above): If imaging studies are positive, chemotherapy must be started; if PSADT is \( \leq 32 \) weeks and imaging studies are negative, initiation of chemotherapy is at physician discretion. There is no PSA value minimum for initiation of chemotherapy in Arm 2. Each investigator or Oncology Group may choose the regimen from the list included within the protocol for each patient. In Arm 2, patients may stay on a chemotherapy regimen longer than 4 cycles at physician discretion if patient is deemed to be responding. A patient may receive non-protocol chemotherapy regimens at physician discretion if a patient fails the first protocol chemotherapy regimen or the regimen is stopped secondary to toxicity in Arm 2. This choice of therapy is at physician discretion and is not limited to the regimens listed in this protocol.

1) *estramustine 280 mg t.i.d. x 5d + docetaxel 60 mg / m² on day 3 q 3 weeks + Coumadin®*
   
   Or

2) *estramustine 280 mg b.i.d. x 5d q 7 days + paclitaxel 90 mg/m² on day 3 weekly x 6 out of 8 weeks + Coumadin®*
   
   Or
3) ketoconazole 400 mg t.i.d. days 1-7, 15-21, 29-35 + doxorubicin 20 mg/m² days 1, 15, 29 + vinblastine 4 mg/m² days 8, 22, 36 + estramustine 140 mg t.i.d. days 8-14, 22-28, 36-42 + hydrocortisone 20 mg every a.m. and 10 mg every p.m.

Or

4) estramustine 140 mg t.i.d. x 4 days q 7 days x 3 weeks out of 4 weeks + docetaxel 30 mg/m² i.v. over 1 hour (on day 3 of each week) x 3 weeks out of 4 weeks + Coumadin®

Or

5) docetaxel 60-70 mg/m² i.v. q 3 weeks

Or

6) docetaxel 30mg/m² i.v. weekly x 3 weeks out of 4 weeks

Or

7) Future regimens may be added that have demonstrated activity in Phase II clinical trials and are approved by the GU committee of RTOG.

Eligibility: (See Section 3.0 for details)(3/30/04)

- Diagnosis of adenocarcinoma of the prostate
- Failure of local treatments (surgery and/or radiation and/or brachytherapy) as defined by a rising PSA of ≥ 2.0 and a doubling time of ≤ 32 weeks in patients with original Gleason ≥ 7 or Gleason 6 with capsular penetration or positive seminal vesicles or lymph nodes; PSA ≥ 2 must be confirmed by two measurements at least two weeks apart. To be eligible, the patient must have a PSA of ≥ 2 at the time of randomization. Values of less than 2 can be used to calculate the doubling time. The PSA doubling time is calculated in the following manner:

Doubling time in weeks = amount of time between PSA values in weeks / [change in PSA/1st value]. If this number is less than or equal to 32 weeks, the patient meets this criteria.

Example 1: on January 25, 2002, the PSA is 1.5. On December 6, 2002 the PSA is 3.2. On December 20, 2002, the PSA is 3.4.

DT = 47 weeks/(3.4-1.5/1.5) = 47/ (1.9/1.5) = 47/1.27 = 37 weeks. The patient is not eligible.

Example 2: on January 25, 2002, the PSA is 1.5. On December 6, 2002 the PSA is 2.8. On December 20, 2002, the PSA is 2.9.

DT = 47 weeks/(2.9-1.5/1.5) = 47/(1.4/1.5) = 47/.93 = 51 weeks. The patient is not eligible.

Example 3: on January 25, 2002, the PSA is 1.5. On June 15, 2002, the PSA is 3. This patient has a doubling time of 20 weeks and is eligible. No equation needed, however:

DT = 20 weeks/(3-1.5/1.5) = 20/(1.5/1.5) = 20/1 = 20 weeks. The patient is eligible.

Example 4: on January 25, 2002, the PSA is 1.5. On June 15, 2002, the PSA is 2.0. This patient has values 20 weeks apart.

DT = 20 weeks/(2.0-1.5/1.5)= 20/ (0.5/1.5) = 20/.33 = 61 weeks. The patient is not eligible

Example 5: on January 25, 2002, the PSA is 1.5. On June 15th, 2002, the PSA is 2.2. This patient has values 20 weeks apart.

DT = 20 weeks/(2.2-1.5/1.5)=20/(.7/1.5) = 20/.47 = 43 weeks. The patient is not eligible.
- No clinical or radiographic evidence of disease.
- Zubrod performance status 0-1
- No chemotherapy in last 5 years
- Prior vaccine therapy allowed if completed at least 6 weeks prior to randomization
- Prior hormonal therapy in the form of neoadjuvant or adjuvant therapy is allowed as long as neither lasted more than 32 weeks. Androgen therapy must have been completed at least one year prior to randomization. Patients could not have had a rising PSA at the time that neoadjuvant or adjuvant therapy was stopped.
- Adequate hematologic, hepatic and renal function: absolute granulocytes \( \geq 1500/\mu l \), platelets \( \geq 100,000/\mu l \), Hgb \( \geq 10 \) gm/100 ml, bilirubin \( \leq 1.5 \) mg/dl, liver enzymes \( \leq 1.5 \) ULN, BUN \( \leq 1.2 \) x institutional norm, creatinine \( \leq 1.5 \) mg/dl
- Patients treated with bisphosphonate therapy before or after randomization are eligible to continue in the study.
- No serious intercurrent medical illness, including symptomatic heart disease, within 6 months
- No prior history of thromboembolic events; no prior MI
- No contraindications to Coumadin\((warfarin)\) therapy; patients currently receiving Coumadin\((warfarin)\) are eligible.
- Negative bone scan
- Negative CT scan or MRI of the pelvis
- Negative chest x-ray
- No prior or concurrent malignancy other than superficial skin cancer, unless disease free for at least 5 years
- Patient must sign study-specific informed consent prior to study entry

**Required Sample Size:** 1050
1. Is there histologically confirmed adenocarcinoma of the prostate?

2. Is PSA > 2 and Gleason score \( \geq 7 \) (any T-stage) or Gleason 6 with capsular penetration or positive seminal vesicles or lymph nodes?

3. Does the patient have a PSA doubling time of \( \leq 32 \) weeks?

4. Does patient have a negative bone scan?

5. Does patient have a negative CT scan or negative MRI scan of the pelvis?

6. Does the patient have a negative CXR?

7. Is there clinical or radiographic evidence of disease?

8. Has the study entry PSA been done prior to randomization and prior to start of any protocol hormone therapy?

9. Is Zubrod performance status 0-1?

10. Are lab values as defined in 3.1.9, 3.1.10, and 3.1.11?

11. Has the patient received hormones for prostate cancer?

   If yes, were they delivered in the neoadjuvant or adjuvant setting for \( \leq 32 \) weeks?

12. Has the patient received hormones in the last 12 months?

13. Any prior or concurrent malignancy other than superficial skin cancer unless disease free for at least 5 years?

14. Has there been previous chemotherapy for malignancy within last 5 years?

15. Does patient have any major medical or psychiatric illness, including symptomatic heart disease within the last 6 months, which would prevent completion of treatment and would interfere with follow-up?

16. Does the patient have any history of thromboembolic events, MI, or contraindications to Coumadin® use as per Sections 3.2.6 and 3.2.7?

The following questions will be asked at Study Registration:

1. Name of institutional person registering this case?

2. Has the Eligibility Checklist \( \text{(above)} \) been completed?

3. Is the patient eligible for this study?

(continued on next page)
Institution #  ______________

RTOG P-0014  ELIGIBILITY CHECKLIST (10/02/02) (3/30/04)

Case #  ______________  (page 2 of 2)

4. Date the study-specific Consent Form was signed? (must be prior to study entry)
5. Patient’s Initials (First, Middle, Last)  If no middle, use hyphen.
6. Verifying Physician
7. Patient’s ID Number
8. Date of Birth
9. Race
10. Social Security Number
11. Patient’s Country of Residence
12. Zip Code
13. Patient’s Insurance Status
14. Will any component of the patient’s care be given at a military or VA facility?
15. Medical Oncologist’s Name
16. PSA Value
17. Specify prior treatment (surgery, radiation and/or brachytherapy, both)
18. Specify original Combined Gleason (6 vs. 7 vs. 8-10)
19. Prior Vaccine (no vs. yes)
20. Current bisphosphonate use (no vs. yes)
21. Date of Randomization
22. Treatment Assignment

The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

Completed by  _______________________________  Date  _______________________________
INTRODUCTION (3/30/04)

Currently, approximately 40,000 men die annually of metastatic, hormone refractory prostate cancer. Androgen blockade (AB) is palliative and is effective for an average of 2-3 years until a patient develops androgen independent disease. Newer chemotherapeutic regimens can induce remissions in approximately 50% of patients; however, these remissions are short lived, and median survival for patients with androgen independent disease is still 8-12 months.\(^1\)\(^2\) Overall survival for patients with stage D disease continues to be in the range of 4-5 years with a median survival for Do patients of approximately 5 years.\(^3\)\(^4\) The strategy of using chemotherapy regimens after AB has been proven to be non-curative. New approaches are needed to attempt to cure patients with advanced disease. It has been demonstrated in the preclinical setting that androgen withdrawal induces apoptosis in cancer cells (both the Shinogi breast cancer model and the LNCaP prostate cancer model).\(^5\)\(^6\) However, in both of these models, androgen withdrawal was not curative, and the tumors grew back in a hormone independent state. We hypothesize that the addition of chemotherapy at the time of initial androgen ablation will improve cell kill by potentiating apoptosis. Improving cell kill should also kill cells that might otherwise have mutated to androgen independent cells if allowed to continue to cycle and grow. We propose giving patients chemotherapy at the beginning of AB to see if this therapy improves patient survival. If this therapeutic approach is effective, it would change clinical practice significantly, allowing the administration of chemotherapy in patients with prostate cancer when they have a minimal disease burden. We believe that the use of chemotherapy in the early setting for a limited period of time will not significantly affect the patient’s quality of life in the long-term. We believe, therefore, that AB combined with chemotherapy at the initiation of treatment will provide a survival advantage to patients with advanced prostate cancer.

Several studies have been done to test whether early chemotherapy affects progression free survival as well as overall survival in patients with stage D prostate cancer. The results appear to be agent dependent. Three randomized trials compared the use of antiandrogens to antiandrogens plus mitomycin in newly diagnosed hormone-naïve patients with advanced disease. In a prospective trial conducted by the Gruppo Onco Urologico Piemontese, newly diagnosed prostate cancer patients with bone metastases were randomized to receive goserelin (3.6 mg subcutaneously every 4 weeks) or goserelin plus mitomycin at 14 mg/m\(^2\) i.v. every 6 weeks.\(^6\) Treatment was planned to be continued until progression; however, when 63 patients had been recruited, the study was interrupted because of inadequate accrual rate. At that time, there was no difference in time to progression and overall survival between the study treatments. However, 56.5% of assessable patients allocated to the chemotherapy arm presented a greater than or equal to 90% reduction of prostate-specific antigen levels compared with 36.3% in the goserelin group, and previously elevated levels normalized in 73.9% versus 45.4%. Non-progressing patients received 5-7 cycles of mitomycin C with acceptable toxicity, but the cytotoxic treatment was interrupted early in all cases within the first year due to cumulative myelotoxicity. The investigators concluded that there was no clear advantage in terms of cost/benefit of chemotherapy plus hormone therapy over hormone treatment alone in advanced prostate cancer with bone involvement.

The European Organization for Research in Cancer Therapy Genitourinary Group performed a randomized, multicenter phase III trial to test the outcome of orchiectomy alone versus orchiectomy followed in 1 week by intravenous 15 mg/m\(^2\) mitomycin C. Mitomycin C was administered every six weeks, and treatment was continued as long as tolerance and patient compliance allowed, and no progression was observed. A total of 189 patients with metastatic prostate cancer and poor prognostic factors were randomized in this trial by 42 institutions. No significant differences for time to overall (\(P = 0.17\)), subjective (\(P = 0.25\)), and objective (\(P = 0.08\)) progression were found between the two treatment groups.

A third study utilizing mitomycin C also did not show a survival benefit.\(^5\)\(^-\)\(^9\) One hundred seventy-eight patients with histologically proven and previously untreated metastatic prostate cancer were included in a prospective, randomized multicenter trial. Randomization was done centrally between orchiectomy alone and orchiectomy with Mitomycin C. One hundred forty-eight patients were evaluable. There was no statistically significant difference in the real time to progression or in the estimated cancer related and overall survival between both groups. Mean time to progression was 29 months in group one (orchiectomy alone), and 26 months in group two (orchiectomy and Mitomycin C) (\(p = 0.64\)). Mean time to cancer related death was 32 months.

A Japanese group investigated the use of cyclophosphamide in a multicentered randomized trial comparing hormonal therapy, using a luteinizing hormone-releasing hormone (LH-RH) agonist, with chemohormonal therapy (hormonal therapy plus cyclophosphamide [CPM], in patients with newly diagnosed clinical stage D prostatic cancer.\(^10\) Between January 1991 and March 1995, 41 evaluable patients with stage D prostatic cancer were randomized into two groups: group A (hormonal therapy alone), goserelin acetate depot 3.6 mg subcutaneously every 4 weeks and group B (chemohormonal therapy), goserelin acetate depot 3.6 mg...
subcutaneously and CPM 1000 mg/m² intravenously every 4 weeks. There was no advantage with chemohormonal therapy observed in the survival rate and progression-free survival rate, however, the survival rate and progression-free survival rate of responders were significantly higher than those of nonresponders in both groups. When the results were categorized by histologic grade, patients with poorly-differentiated adenocarcinoma had significantly higher response rates, survival rates, and disease-progression-free survival rates in Group B compared to similar patients in Group A. The authors concluded that chemohormonal therapy does not definitely improve the clinical response and prognosis of patients with stage D prostate cancer; however, for patients with poorly differentiated adenocarcinoma, chemohormonal therapy is a useful treatment.

Murphy and colleagues evaluated 265 patients with newly diagnosed metastatic prostate cancer. They were randomized to one of three treatment protocols: A. diethylstilbestrol (DES) or bilateral orchiectomy, B. the leutinizing hormone-releasing hormone (LHRH) analog buserelin, or C. methotrexate plus DES or orchiectomy. In 261 evaluable patients, there was no significant difference in survival between the three groups. However, progression-free survival (PFS) was significantly different (P less than 0.0005, log-rank test). Of the possible pairwise comparisons for PFS, two showed significance: buserelin was inferior to DES/orchiectomy (P less than 0.05), and buserelin was inferior to methotrexate plus DES/orchiectomy (P less than 0.0001).

The combination of hormones +/- adriamycin, cisplatin, and UFT has also been tested in hormone-naïve patients. Thirty-one patients received 1 mg ethynylestradiol daily with or without orchiectomy. In addition, they received three courses of chemotherapy consisting of 20 mg/m² cisplatin given on days one, three, and five and 20 mg/m² Adriamycin or 40 mg/m² epirubicin given on day five. Subsequently, for maintenance therapy, the patients received 1 mg ethynylestradiol and 150 mg 5-fluorouracil (or 300 mg tegafur plus uracil (UFT)) daily. Patients given the chemoendocrine therapy had a significantly better prognosis than did the controls treated with endocrine therapy alone (P = 0.05), although treatment was not randomized. The cause-specific survival rates at five years for the endocrine therapy patients and the control group were 65.4% and 37.4%, respectively. A multivariate analysis of possible prognostic factors, i.e., age, histological grade, prostatic acid phosphatase, tumor related pain, the extent of disease (EOD) on bone scan, and the type of initial treatment, confirmed that the initial treatment (P = 0.03) and the EOD grade (P = 0.05) had a significant effect on survival.

A prospective, randomized clinical trial was conducted to evaluate the efficacy of endocrine chemotherapy with uracil and tegafur (in a molar ratio of 4:1 [UFT]) in patients with prostate cancer. The study included two treatment arms: endocrine plus UFT and endocrine-only therapy. Of the 136 patients with prostate cancer enrolled in this study from April 1990 to December 1992, 69 received endocrine plus UFT therapy and the remaining 67 received endocrine-only therapy. Among those receiving UFT therapy, eight patients had stage A2 and B prostate cancer, eleven had stage C disease, and fifty had stage D disease. In the endocrine-only group, ten patients had stage A2 and B disease, seven had stage C disease, and fifty had stage D disease. Tumors were well differentiated in twenty patients, moderately differentiated in thirty-eight patients, and poorly differentiated in eleven patients receiving UFT. The endocrine-only group included twenty-nine patients with differentiated tumors, twenty-six with moderately differentiated tumors, and twelve with poorly differentiated carcinomas. After a mean follow-up period of 54.9 months for patients receiving endocrine plus UFT therapy and 47.8 months for patients receiving endocrine-only therapy, disease had not progressed in 53.0% of the UFT-treated patients and 43.8% of the endocrine-only-treated patients (P = .114). The five year cancer-specific survival rates were 67.4% for the UFT group and 49.5% for the endocrine-only group (P = .273). The five year survival rates were 47.4% for the UFT group and 35.4% for the endocrine-only group (P = .177). Adverse effects, such as bone marrow suppression, nausea, vomiting, and anorexia, occurred in thirty-six patients in the UFT group and forty-one patients in the endocrine-only group. However, adverse effects were not specifically related to UFT use. The authors concluded that endocrine chemotherapy plus UFT is a tolerable regimen that might be effective for patients with prostate cancer.

The Southwest Oncology Group (SWOG) performed a randomized trial between September 1982 and October 1986 comparing endocrine therapy (diethylstilbestrol [DES] or orchiectomy) alone followed by cyclophosphamide-Adriamycin (doxorubicin; Adria Laboratories, Columbus, OH) chemotherapy at progression versus initial combined chemo-endocrine therapy. One hundred forty-three patients were registered, and only six were declared ineligible. Patients on the combined chemo-endocrine therapy arm had a slightly higher response rate (63%) compared with endocrine therapy alone (48%). A log-linear model of tumor response and treatment arm adjusted for the stratification factors favored the combination arm (P = .059). Only three of twenty-seven patients on the endocrine therapy alone arm had an objective partial response when crossed over to chemotherapy, while two others had stable disease. Despite the difference in initial response...
rate, time to treatment failure and survival were identical in the two treatment arms. No significant effect of
treatment on survival was observed even after adjustment for the stratification variables in a Cox regression
model. Exploratory survival analyses with patients on both arms combined did show a marginally significant
time to treatment failure and survival advantage for patients treated with DES rather than orchiectomy as initial
endocrine therapy. The authors concluded that the data did not support the addition of cytotoxic chemotherapy
to initial endocrine therapy in patients with metastatic prostate cancer.

Wang and colleagues investigated the role of mitoxantrone as an adjunctive therapy to hormonal therapy in
patients with advanced prostate cancer. Ninety-six patients were randomized to receive either hormonal
therapy or hormonal therapy + 4 cycles of mitoxantrone therapy at the time of diagnosis of prostate cancer.
Patients had T3, T4, or metastatic disease at the time of diagnosis. Although there was no difference in survival
in patients with metastatic disease, there was a significant increase in survival in patients with locally advanced
disease in favor of patients treated with combination therapy 84 months versus 41 months; \(P=0.028\).

It should be noted that none of these chemoendocrine trials utilized regimens that oncologists would consider
active in the treatment of advanced prostate cancer. Multiple new regimens developed in the last five years
have demonstrated activity against hormone refractory prostate cancer in the phase II setting. These include
estramustine(etoposide, estramustine/docetaxel, estramustine/paclitaxel, estramustine/etoposide/paclitaxel, and
ketoconazole/adriamycin/vinblastine/estramustine. In the hormone refractory setting, these regimens have
demonstrated 50% response rates or greater as measured by PSA response or soft tissue disease regression. No trial of early chemoendocrine therapy in hormone naïve patients has been published utilizing these powerful
new regimens. Data from previous studies, both positive and negative, do not negate the fact that this type of
principle has not been tried in a large, definitive, proof-of-concept trial with regimens that have demonstrated
activity in the phase II setting. By allowing chemotherapy of choice in the new study design, we will take into
account the incorporation of better regimens as they are developed. Therefore, future regimens may be added
that have demonstrated activity in Phase II clinical trials and are approved by the GU committee of RTOG.

We have established objective criteria for the chemotherapy regimens that are included in the protocol. These
criteria include: A regimen which has been demonstrated in a published phase II or phase III clinical trial to
have a demonstrable response rate as measured by PSA decrease from baseline over two measurements 4
weeks apart or a decrease in measurable soft tissue disease by 50% in two dimensions. These criteria are based
on a NIH consensus conference on criteria for evaluating Phase II clinical trials in prostate cancer. Regimens
may be added only if they are approved by the GU committee of RTOG.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>MD(^a)N (RR(^b))</th>
<th>PSA(^a)N (RR(^b))</th>
<th>Toxicity(^d)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoposide + Emcyt(^a)</td>
<td>56</td>
<td>15/33 (45)</td>
<td>30/52 (58%)</td>
<td>13% neutropenia, 2% anemia, 7% thrombocytopenia, 4% N/V</td>
<td>22</td>
</tr>
<tr>
<td>Etoposide + Emcyt(^a)</td>
<td>62</td>
<td>15 (53)</td>
<td>24/62 (39%)</td>
<td>3% neutropenia, 3% anemia, 6% thrombocytopenia, 2% infection</td>
<td>23</td>
</tr>
<tr>
<td>Taxol + Emcyt(^a)</td>
<td>63</td>
<td>6/22 (27%)</td>
<td>36/63 (58%)</td>
<td>neutropenia 6%, fatigue 14%, TE 6% edema diarrhea, neuropathy, dyspnea 5%; cardiac ischemia 3%</td>
<td>24</td>
</tr>
<tr>
<td>Taxol + Emcyt(^b)</td>
<td>41</td>
<td>20/41 (49%)</td>
<td>23/41 (56%)</td>
<td>22% neutropenia, 5% anemia, 2.5% infection, 2.5% asthenia</td>
<td>25</td>
</tr>
<tr>
<td>TEE(^a)</td>
<td>40</td>
<td>10/16 (63%)</td>
<td>26/40 (65%)</td>
<td>11% neutropenia, 5% infection</td>
<td>26</td>
</tr>
<tr>
<td>KAVE(^a)</td>
<td>46</td>
<td>12/16 (75%)</td>
<td>31/46 (67%)</td>
<td>Peripheral edema (49%), neutropenia 23%,DVT (18%)</td>
<td>27</td>
</tr>
<tr>
<td>Taxotere + Emcyt(^b)</td>
<td>17</td>
<td>1/6 (17%)</td>
<td>14/17 (82%)</td>
<td>23% neutropenia</td>
<td>28</td>
</tr>
<tr>
<td>Taxotere + Emcyt(^a)</td>
<td>34</td>
<td>5/18 (28%)</td>
<td>21/33 (63%)</td>
<td>32% neutropenia, 3% constipation, 3% esophagitis, 3% infection</td>
<td>29</td>
</tr>
<tr>
<td>Taxotere(^b)</td>
<td>35</td>
<td>7/25 (28%)</td>
<td>16/35 (46%)</td>
<td>17% fatigue, 3% PE (death), 3% pneumonia (death)</td>
<td>38</td>
</tr>
<tr>
<td>Taxotere(^a)</td>
<td>30</td>
<td>0/7 (0%)</td>
<td>14/30 (48%)</td>
<td>7% neutropenia</td>
<td>39</td>
</tr>
</tbody>
</table>

a. MD = Measurable Disease
b. PSA = Prostate Specific Antigen used as marker of response
c. RR = response rate
d. Toxicity = Grade 3, 4, 5 only
e. Etoposide 50 mg/m2/day and Emcyt 140 mg TID X21 days
f. Etoposide 50 mg/m2/day and Emcyt 10/mg/kg/day X21 days
g. Taxol 90 mg/m2 on day 2, Emcyt 280 mg BID days 1-3, weekly for 6 of 8 weeks
h. Taxol 60-90 mg/m2 weekly X6, Emcyt 280 mg BID
i. Taxol 135 mg/m2 on day 2, Etoposide 100 mg po qD X14 days, Emcyt 280 mg po TID X14 days q21 days
j. Doxorubicin (20 mg/m2/week) plus oral ketoconazole (400 mg three times a day) given at weeks 1, 3, and 5 and vinblastine (5 mg/m2/week) plus oral estramustine (140 mg three times a day) given at weeks 2, 4, and 6. No therapy given at weeks 7 and 8.
k. Docetaxel 40-80mg/m2 q21days, Emcyt 12-14 mg/kg/day X5 days
l. Docetaxel 40-80mg/m2 q21days, Emcyt 280 mg TID X5 days
m. Docetaxel 75mg/m2 q21 days
n. Docetaxel 35 mg/m2 weekly x 6 q8 weeks

2.0 OBJECTIVES
2.1 Primary Objective:
2.1.1 Evaluate survival improvement: early chemotherapy done at the initiation of AB will improve survival by 10% at 5 years.
2.2 Secondary Objectives: (3/30/04)
2.2.1 Biochemical Control; PSA failure is defined as a PSA doubling time \( \leq 32 \) weeks.
2.2.2 Time to clinical failure as measured by progression on bone scan or CT scan (done as these scans are clinically indicated) or a PSA doubling time \( \leq 32 \) weeks
2.2.3 Evaluate toxicity: Frequency of non-hematologic (\( \geq \) grade 3); hematologic (\( \geq \) grade 4); and fatal (grade 5) toxicities.

3.0 PATIENT SELECTION
3.1 Conditions for Patient Eligibility (3/30/04)
3.1.1 Diagnosis of adenocarcinoma of the prostate
3.1.2 Original Gleason \( \geq 7 \) or Gleason 6 with capsular penetration or positive seminal vesicles or lymph nodes
3.1.3 Failure of local treatments (surgery and/or radiation and/or brachytherapy) as defined by a rising PSA of \( \geq 2.0 \) and a doubling time of \( \leq 32 \) weeks; PSA \( \geq 2 \) must be confirmed by two measurements at least two weeks apart. The PSA doubling time is calculated in the following manner:

Doubling time in weeks = amount of time between PSA values in weeks/[change in PSA/1st value]. If this number is less than or equal to 32 weeks, the patient meets this criteria,

Example 1: on January 25, 2002, the PSA is 1.5. On December 6, 2002 the PSA is 3.2. On December 20, 2002, the PSA is 3.4.

\[ DT = 47 \text{ weeks}/(3.4-1.5/1.5) = 47/(1.9/1.5) = 47/1.27 = 37 \text{ weeks}. \] The patient is not eligible.

Example 2: on January 25, 2002, the PSA is 1.5. On December 6, 2002 the PSA is 2.8. On December 20, 2002, the PSA is 2.9.

\[ DT = 47 \text{ weeks}/(2.9-1.5/1.5) = 47/(1.4/1.5) = 47/.93 = 51 \text{ weeks}. \] The patient is not eligible.

Example 3: on January 25, 2002, the PSA is 1.5. On June 15, 2002, the PSA is 3. This patient has a doubling time of 20 weeks and is eligible. No equation needed, however:

\[ DT = 20/(3-1.5/1.5) = 20/(1.5/1.5) = 20/1 = 20 \text{ weeks}. \] The patient is eligible.

Example 4: on January 25, 2002, the PSA is 1.5. On June 15, 2002 the PSA is 2.0. This patient has values 20 weeks apart

\[ DT = 20 \text{ weeks}/(2.0-1.5/1.5)=20/(0.5/1.5)= 20/.33 = 61 \text{ weeks}. \] The patient is not eligible.
Example 5: on January 25, 2002, the PSA is 1.5. On June 15, 2002 the PSA is 2.2. This patient has values 20 weeks apart.

\[
DT = 20 \text{ weeks}/(2.2 - 1.5) = 20/(.7/1.5) = 20/ .47 = 43 \text{ weeks.} \]

The patient is not eligible.

3.1.4 Zubrod performance status 0-1
3.1.5 Prior vaccine therapy allowed if completed at least 6 weeks prior to randomization
3.1.6 Prior hormonal therapy in the form of neoadjuvant or adjuvant therapy is allowed as long as neither lasted more than 32 weeks; androgen therapy must have been completed at least one year prior to randomization. Patients could not have had a rising PSA at the time that neoadjuvant or adjuvant therapy was stopped.
3.1.7 Prior brachytherapy for prostate cancer is allowed.
3.1.8 Patients currently receiving Coumadin® (warfarin) are eligible.
3.1.9 Adequate hematologic function within 4 weeks prior to randomization: absolute granulocytes ≥ 1500/µl, platelets ≥ 100,000/µl, Hgb ≥ 10 gm/100 ml
3.1.10 Adequate hepatic function within 4 weeks prior to randomization: bilirubin ≤ 1.5 mg/dl, liver enzymes ≤ 1.5 x ULN
3.1.11 Adequate renal function within 4 weeks prior to randomization: BUN ≤ 1.2 x institutional norm; creatinine ≤ 1.5 mg/dl
3.1.12 Patients treated with bisphosphonate therapy before or after randomization are eligible to continue in the study.
3.1.13 Negative bone scan within 8 weeks prior to randomization
3.1.14 Negative CT scan or MRI of the pelvis within 8 weeks prior to randomization
3.1.15 Negative CXR for metastatic disease within 8 weeks prior to randomization
3.1.16 Prior XRT for sites other than prostate cancer is eligible as long as > 5 years ago.
3.1.17 Patients must sign study-specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility (3/30/04)

3.2.1 PSA < 2.0
3.2.2 Chemotherapy in last 5 years
3.2.3 Serious intercurrent medical illness including symptomatic heart disease within 6 months
3.2.4 Previous or concurrent invasive cancers other than superficial skin cancers, unless disease-free for at least 5 years
3.2.5 Major medical or psychiatric illness, which, in the investigators opinion, would prevent completion of treatment and would interfere with follow-up
3.2.6 History of thromboembolic events (deep venous thrombosis, symptomatic cerebrovascular events, or pulmonary embolism); history of MI
3.2.7 History of bleeding disorders that would contraindicate Coumadin® (warfarin) including: esophageal varices and clotting factor defects
3.2.8 Clinical or radiographic evidence of disease.

4.0 PRETREATMENT EVALUATION (3/30/04)

Protocol treatment must begin within 4 weeks after registration.

4.1 History and physical examination; Zubrod performance status, height and weight
4.2 Documentation of histologic evaluation; Gleason Score is mandatory.
4.3 Mandatory laboratory studies (obtained within 4 weeks prior to randomization): CBC with platelets, PSA, bilirubin, ALT, alkaline phosphatase, BUN, creatinine, testosterone
4.4 Bone scan within 8 weeks prior to randomization
4.5 Pelvic lymph node assessment by one of the following procedures: pelvic CT, pelvic MRI within 8 weeks prior to randomization
4.6 Chest x-ray within 8 weeks prior to randomization

5.0 REGISTRATION PROCEDURES (3/30/04)

5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET or via the RTOG website 24 hours 7 days a week. The patient will be registered to a treatment arm and a case number will be assigned and
confirmed by mail. The Eligibility Checklist must be completed in its entirety prior to calling RTOG. The completed, signed, and dated Checklist used at study entry must be retained in the patient’s study file and will be evaluated during an institutional NCI/RTOG audit.

6.0 RADIATION THERAPY
Not applicable to this study.

7.0 DRUG THERAPY (3/30/04)

7.1 Hormonal Therapy (Agents)(3/30/04)

7.1.1 Treatment Plan
Hormonal therapy in the form of androgen ablation (AB) will be delivered identically to patients in both Arm 1 and Arm 2.

Arm 1: All patients will receive LHRH agonists continuously.

The enrolling physician may choose the regimen, and the hormone regimen may be changed at the physician’s discretion in cases of drug toxicity. Administration of drug will be suspended only if there is an apparent or suspected reaction to the drug.

All patients will receive a nonsteroidal antiandrogen (bicalutamide or flutamide) for at least one month. Choice of complete androgen blockade versus the use of a nonsteroidal antiandrogen for only one month is at discretion of the enrolling physician. Chemotherapy is initiated within 4 weeks of beginning androgen blockade with LHRH agonist. Patients may have their nonsteroidal antiandrogen stopped while on chemotherapy.

Arm 2: All patients will receive LHRH agonists continuously. The enrolling physician may choose the regimen, and the hormone regimen may be changed at the physician’s discretion in cases of drug toxicity. Administration of drug will be suspended only if there is an apparent or suspected reaction to the drug. All patients will receive a non-steroidal antiandrogen (bicalutamide or flutamide) for at least one month. Choice of complete androgen blockade versus the use of a non-steroidal antiandrogen for only one month is at discretion of the enrolling physician. Patients may have complete androgen blockade as long as the patient goes through bicalutamide/flutamide withdrawal prior to initiation of chemotherapy.

7.1.2 Note: Please see the package insert for full prescribing information for any commercially-available agents listed below.

7.2 LHRH Agonists (such as leuprolide, goserelin, buserelin, triptorelin)

7.2.1 Description
LHRH agonists are long-acting analogs of the native LHRH peptide and are effective at reducing serum testosterone.

7.2.2 Supply
LHRH analogs are commercially available. Currently four have been approved by the FDA in the U.S. and are considered similarly effective at reducing serum testosterone.

7.2.3 Storage
LHRH analogs should be stored as directed by the commercial supplier.

7.2.4 Administration
LHRH analogs are administered with a variety of techniques, including subcutaneous insertion of a solid plug in the abdominal wall (Zoladex), intramuscular injection (Lupron), subcutaneous injection (Eliargd), or insertion of a long-acting cylinder that slowly releases the agent (Viadur). The manufacturer’s instructions should be followed.

7.2.5 Toxicity
Class related toxicity is generally a manifestation of the mechanism of action and due to low testosterone levels. In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. The most common side effect of LHRH analogs is vasomotor hot flashes; edema, gynecomastia, bone pain, thrombosis, and GI disturbances have occurred. Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms.

7.2.6 Drug Interactions
See package insert for drug interactions.

7.3 Casodex (bicalutamide)

7.3.1 Description
Casodex is a nonsteroidal antiandrogen, which has no androgenic or progestational properties. The chemical name is propanamide, \( N\-[4\text{-cyano-3(trifluoromethyl)phenyl}\]-3-\[4\text{-fluorophenyl}sulphonyl\]-2-\hydroxy-2-\methyl\), \((\pm,\pm)\). Casodex is a racemic mixture with the antiandrogen activity residing exclusively in the \((\pm)\) or \((R)\) enantiomer. Casodex 50 mg has the status of an approved new drug. Casodex has a long half-life compatible with once-daily dosing. Casodex is well tolerated and has good response rates in phase II trials (Kennealey and Furr 1991, Tyrrell 1994).

7.3.2 Supply
Casodex is commercially available as a 50 mg tablet.

7.3.3 Storage
Casodex should be stored in a dry place at room temperature between 68\(^\circ\)F-77\(^\circ\)F.

7.3.4 Administration
Casodex is administered orally at a dose of one 50 mg tablet per day. Administration will be suspended only if there is an apparent or suspected reaction to the drug.

7.3.5 Toxicity
In animal experiments, birth defects (abnormal genitalia, hypospadias) were found in male offspring from female animals dosed with Casodex during pregnancy. Although offspring from male animals dosed with Casodex did not show any birth defects, patients enrolled in this trial are advised to neither cause pregnancy nor to donate sperm while receiving protocol therapy or during the first 3 months after cessation of therapy. The use of barrier contraceptives is advised.

The most frequent adverse events reported among subjects receiving bicalutamide therapy are breast tenderness, breast swelling, and hot flashes. When bicalutamide 50 mg was given in combination with an LHRH analogue, the LHRH analogue adverse event profile predominated with a high incidence of hot flashes (53%) and relatively low incidences of gynecomastia (4.7%) and breast pain (3.2%).

7.3.6 Dose Modification Schedule
Casodex should be discontinued in instances of chemical liver toxicity. ALT will be measured pretreatment and then monthly. If the ALT rises \(\geq 2\) x the institutional upper limit of normal, Casodex must be discontinued.

7.3.7 Drug Interactions
In vitro protein binding studies have shown that bicalutamide can displace coumarin anticoagulants from binding sites. Prothrombin times should be closely monitored in patients already receiving coumarin anticoagulants who are started on Casodex.

7.4 Eulexin (flutamide)

7.4.1 Description
Flutamide is a substituted anilide. It is a fine, light, yellow powder, insoluble in water but soluble in common organic solvents such as aromatic or halogenated hydrocarbons. Its concentration in plasma can be determined by gas chromatography. Flutamide is a nonsteroid antiandrogen that is metabolized into a hydroxylated derivative, which effectively competes with the hydrotestosterone for androgen receptor sites.

7.4.2 Supply
Flutamide is supplied as 125 mg capsules and is commercially available.

7.4.3 Storage
Flutamide should be stored at temperatures ranging from 20-30\(^\circ\)C (36\(^\circ\)F-86\(^\circ\)F) and protected from excessive moisture.

7.4.4 Administration
The drug is administered orally at a dose of two 125 mg capsules three times a day for a total daily dose of 750 mg (six capsules).

7.4.5 Toxicity
The reported side effects of treatment include diarrhea and anemia. A high percentage of patients treated with flutamide alone developed gynecomastia within 2-8 months. There have been post-marketing reports of hospitalization, and, rarely, death due to liver failure in patients taking flutamide. Evidence of hepatic injury included elevated serum transaminase levels, jaundice, hepatic encephalopathy, and death related to acute hepatic failure. The hepatic injury was reversible after prompt discontinuation of therapy in some patients. Approximately half of the reported cases occurred within the initial 3 months of treatment with flutamide.

7.4.6 Dose Modification Schedule (3/30/04)
If gastrointestinal disturbances (cramps, diarrhea) occur, flutamide will be withheld until the side effects subside and then reintroduced at a dose of 250 mg/day increasing the dose (at 3 day...
intervals) to 500 mg/day then to 750 mg/day as tolerated. However, if diarrhea continues to be severe, the drug will be permanently discontinued. ALT will be measured pretreatment, then once during the month of antiandrogen therapy. If ALT increases ≥ 2 × upper institutional limit of normal, flutamide must be discontinued.

### 7.4.7 Drug Interactions
Interactions between Eulexin capsules and LHRH-agonists have not occurred. Increases in prothrombin time have been noted in patients receiving warfarin therapy. Increases in prothrombin time have been noted in patients receiving long-term warfarin therapy after flutamide was initiated. Therefore, close monitoring of prothrombin time is recommended and adjustment of the anticoagulant dose may be necessary when Eulexin capsules are administered concomitantly with warfarin.

### 7.5 Chemotherapy (Agents)

#### 7.5.1 Treatment Plan (3/30/04)
All patients will receive androgen ablation (AB).

**Arm 1:**
Patients in Arm 1 will receive 4 cycles of chemotherapy starting within 4 weeks of the initiation of AB. Chemotherapy is initiated within 4 weeks of beginning androgen blockade with LHRH agonist. Patients may have their non-steroidal antiandrogen stopped while on chemotherapy. If a regimen is stopped due to secondary toxicity, a new regimen is not started in Arm 1 during the initial chemotherapy treatment period. In Arm 1, a patient may receive other protocol or non-protocol chemotherapy regimens when the patient progresses at physician discretion. This choice of therapy is at physician discretion and is not limited to the regimens listed in this protocol.

**Arm 2:**
Patients on Arm 2 will receive 4 cycles of chemotherapy at the time of failure of AB as defined by a positive bone scan, or a positive CT or MRI scan of the pelvis or a PSA doubling time (PSADT) of ≤ 32 weeks and a concurrent decision by the physician to initiate chemotherapy. There is no minimum PSA requirement to initiate chemotherapy in Arm 2. The initiation of chemotherapy is at physician discretion when the PSADT is ≤ 32 weeks and imaging studies are negative; the physician can choose to begin chemotherapy at any time after the PSADT is ≤ 32 weeks, but is not forced to initiate chemotherapy. If imaging studies are positive, chemotherapy must be started. The choice of chemotherapy regimen for patients on Arm 2 may be delayed until hormone failure.

Note: In Arm 2, patients may stay on a protocol chemotherapy regimen longer than 4 cycles at physician discretion if patient is deemed to be responding to therapy. A patient may receive other non-protocol chemotherapy regimens at physician discretion if a patient fails the first chemotherapy regimen or the regimen is stopped secondary to toxicity in Arm 2. This choice of therapy is at physician discretion and is not limited to the regimens listed in this protocol.

#### 7.6 Emcyt (estramustine)

#### 7.6.1 Description
Estramustine phosphate (EMCYT Estracyt), a nitrogen mustard derivative of estradiol-17-b-phosphate, has been studied in several randomized trials by the National Prostate Cancer Project (NPCP) and by the European Organization for Research on the Treatment of Cancer (EORTC), both as a single agent or in combination with other agents. As initial therapy for advanced disease, an objective response was observed in approximately 80% of patients, a response rate similar to treatment with orchiectomy or estrogens. Treatment of hormone refractory patients with Emcyt appears to have an objective response rate of 0 to 37%. Emcyt in combination with standard chemotherapeutic agents produced similar results. The mechanism of action is unknown. It appears to have antineoplastic activity independent of its alkylating moiety. The initial half-life is approximately 24 hours. The oral formulation has a bio-availability of about 75%. Excretion is split between urine and bile for both the estradiol and nitrogen mustard moieties. Estramustine appears to act as a relatively weak alkylating agent and imports a weak estrogenic activity. The estrogenic portion of the molecule acts as a carrier to facilitate selective uptake of the drug into estrogen receptor-positive cells. Due to the selective steroidal uptake, the alkylating effect of the nitrogen mustard is enhanced in these cells.

#### 7.6.2 Supply
Estramustine is available in 140 mg capsules.

#### 7.6.3 Storage
Capsules may be stored in the refrigerator at 2°-8°C and are stable for at least 12 months.

#### 7.6.4 Administration
Regimen dependent. To be described for each regimen in Section 7.14.

7.6.5 Toxicity
The principal dose-limiting toxicity is gastrointestinal, with nausea and vomiting reported in approximately 25% of patients. Peripheral edema was demonstrated in 15% of patients. Breast tenderness was described by 70% of patients but was not considered to be dose limiting. Hematologic side effects, as manifested by leukopenia or thrombocytopenia, were reported in only 4% of patients. The maximally tolerated dose is 15 mg/kg/day.

Deep venous thrombosis and other cardiovascular events have been noted with estramustine administration. Coumadin® (warfarin) administration has been incorporated into the protocol chemotherapy regimens involving estramustine. If the patient suffers a confirmed thromboembolic event (e.g., DVT, PE, stroke, MI), chemotherapy involving estramustine should be discontinued immediately. If the patient suffers a bleeding event that requires discontinuation of Coumadin® (warfarin), chemotherapy involving estramustine should be discontinued immediately.

7.6.6 Drug Interactions
Food/Drug Interaction: Milk, milk products, and calcium-rich foods or drugs may impair the absorption of Emcyt.

7.7 Taxol (paclitaxel)
7.7.1 Description
Paclitaxel is a poorly soluble plant product from the western yew, Taxus brevifolia. Improved solubility requires a mixed solvent system with further dilutions of either 0.9% sodium chloride or 5% dextrose in water. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described above, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours. Paclitaxel is available in 5, 16.7, and 50 ml vials (30, 100, and 300 mg vials). A sterile solution concentrate is available, 6 mg/ml in 5 ml vials (30 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. The contents of the vial must be diluted just prior to clinical use. Paclitaxel, at the appropriate dose, will be diluted in 1000 ml of D5W, USP, in 5% polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. NOTE: Formation of a small number of fibers in solution (NOTE: acceptable limits established by the USP Particular Matter Test for LVP’s) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: Millex-GV Millipore Products) into the i.v. fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used. There is documentation of a potential drug-drug interaction between paclitaxel and etoposide. Etoposide is an inhibitor of cytochrome P450 isoenzyme CYP2C8 that may increase paclitaxel levels.

7.7.2 Supply
Paclitaxel is commercially available.

7.7.3 Storage
Paclitaxel vials should be stored between 20°-25°C (68°-77°F).

7.7.4 Administration
Dosage per individual regimens described in Section 7.14. Do not give paclitaxel therapy to patients with baseline neutrophil counts of ≤ 1500 cells/mm³. Paclitaxel, at the appropriate dose and dilution (0.3-1.2 mg/ml), should be given over 3 or 24 hours. The paclitaxel is mixed in 500 or 1000 cc of D2W in non-PVC containers and infused via polyolefin-lined nitroglycerin tubing or low absorption AVI‰ with 0.22 m in-line filter. Paclitaxel will be administered via an infusion control device (pump) using non-PVC tubing and connectors, such as the i.v. administration sets (polyethylene or polyolefin) which are used to infuse parenteral Nitroglycerin. Nothing else is to be infused through the line through which paclitaxel is administered.

7.7.5 Toxicity
- Hematologic: Myelosuppression
- Gastrointestinal: Nausea and vomiting, diarrhea, stomatitis, mucositis, pharyngitis, typhlitis, ischemic colitis, neutropenic enterocolitis, increase in liver function tests (SGOT, SGPT, bilirubin, alkaline phosphatase) hepatic failure, hepatic necrosis
- Heart: Arrhythmias, heart block, ventricular tachycardia, myocardial infarction (MI), bradycardia, atrial arrhythmia, hypotension, hypertension, lightheadedness
- Neurological: Sensory (taste), peripheral neuropathy, seizures, mood swings, hepatic encephalopathy, encephalopathy, sensation of flashing lights, blurred vision, scintillating scotoma
- Allergy: Anaphylactoid and urticarial reactions (acute), flushing, rash, pruritis
- Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration), radiation recall reaction

7.7.6 Suggested Premedication Regimen
Dexamethasone 20 mg i.v. or p.o. 30 minutes prior to administration, Diphenhydramine 50 mg i.v. and Pepcid 20 mg (or Ranitidine 50 mg or Cimetidine 300 mg) i.v. 30 minutes prior to administration.

7.7.7 Drug Interactions
Two published studies report that initial administration of paclitaxel infused over 24 hours followed by doxorubicin administered over 48 hours resulted in a significant decrease in doxorubicin clearance with more profound neutropenic and stomatitis episodes than the reverse sequence of administration.

7.8 Taxotere (docetaxel)
7.8.1 Description
Docetaxel is a semi-synthetic taxane under investigation in multiple tumor types and is prepared with a precursor extracted from the yew plant. Docetaxel’s effect is due to disruption of the microtubular network in cells that is required for mitotic and interphase cellular functions. After i.v. injection, t1/2, 3 phases: 4 min, 36 min, and 11.1 hour. It is metabolized in the liver, and metabolites and small amounts of unchanged drug are excreted through both the feces (75%) and urine (6%).

7.8.2 Supply
Docetaxel is commercially available in the United States. Supplied for injection: 20 mg/0.5 mL, 80 mg/2 mL

7.8.3 Storage
Taxotere should be stored at a controlled temperature between 2°C-25°C (36°F-77°F).

7.8.4 Administration
Dosage per schedules in Section 7.14. See specific dilution instructions for docetaxel in the current package labeling. Docetaxel should be diluted to a concentration between 0.3 and 0.7 mg/ml and infused through a non-PVC containing infusion set within 4 hours of final dilution. Protocols involving the every three weeks or weekly administration of Taxotere are currently utilizing 30-minute or 15-minute infusion times in addition to a 1-hour infusion period. This is due to the fact that the infusion solution volume (100cc) for weekly.

7.8.5 Toxicity
- Hematologic: Neutropenia (virtually in 100% of clients given 100 mg/m²) leukopenia, thrombocytopenia, anemia, febrile neutropenia
- GI: nausea and vomiting, diarrhea, stomatitis, abdominal pain, constipation, ulcer, esophagitis, GI hemorrhage intestinal obstruction, ileus.
- Heart: Fluid retention (even with premedication), hypotension, atrial fibrillation, DVT ECG abnormalities, thrombophlebitis, pulmonary embolism, heart failure syncope, tachycardia, sinus tachycardia, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, hypertension (rare)
- Respiratory: Dyspnea, acute pulmonary edema, ARDS
- Dermatologic: Reversible cutaneous reactions characterized by a rash, including localized eruptions on the hands, feet, arms, face, or thorax, and usually associated with pruritus; nail changes, alopecia
- Hypersensitivity: Flushing, localized skin reactions. Severe hypersensitivity reactions characterized by hypotension, bronchospasm, or generalized rash/erythema
- Musculoskeletal: Myalgia, arthralgia
- Neurologic: Paresthesia, dysesthesia, pain in those with anthracycline-resistant breast cancer; distal extremity weakness
- Reactions at infusion site: Hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis, extravasation, mild swelling of the vein
- Miscellaneous: Septic death, nonseptic death infections, fever in absence of infections, asthenia, diffuse pain, chest pain, renal insufficiency, confusion. Weekly administration of Taxotere is well tolerated and produces substantially less myelosuppression than is observed with standard
Taxotere administration every 3 weeks. Acute toxicities are uncommon, as is peripheral neuropathy. Prolonged treatment with weekly Taxotere results in chronic toxicities, which include asthenia (fatigue), anemia, edema, excessive lacrimation (epiphora), and onycholysis. Chronic toxicities are most prominent when Taxotere is administered on a continuous weekly basis, i.e., without a break, and are delayed in onset by providing breaks in treatment (for example, treating 6 out of 8 weeks or 3 out of 4 weeks); these chronic toxicities occur at a lower cumulative dose when a continuous weekly schedule of Taxotere is utilized.

7.8.6 Suggested Premedication Regimen
Premedication with dexamethasone is recommended for all patients receiving weekly Taxotere therapy to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. A variety of dexamethasone schedules have been used in studies with weekly Taxotere. Dexamethasone 4 to 8 mg x 3 doses taken orally the night before, the morning of, and the evening after Taxotere administration appears to be an effective schedule.

7.8.7 Drug Interactions
There have been no formal clinical studies to evaluate the drug interactions of Taxotere with other medications. In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4, such as cyclosporine, terfenadine, ketoconazole, erythromycin and troleandomycin. Caution should be exercised with these drugs when treating patients receiving TAXOTERE as there is a potential for significant interaction.

7.9 Adriamycin (doxorubicin)

7.9.1 Description
Produced by Streptomyces peucetius. Cell-cycle specific for the S phase of cell division. Antineoplastic activity may be due to binding to DNA by intercalating between base pairs resulting in inhibition of synthesis of DNA and RNA by template disordering and steric obstruction. The liposomal product is produced with surface-bound methoxypolyethylene in order to protect liposomes from detection by mononuclear phagocytes and to increase blood circulation time. It is believed the liposomes are able to penetrate altered and often compromised vasculature of tumors. Conventional doxorubicin is significantly bound to tissue and plasma proteins whereas the liposomal product is confined mostly to the vascular fluid and does not bind to plasma proteins. Metabolized in the liver to the active doxorubicinol as well as inactive metabolites, which are excreted through the bile. t1/2, doxorubicin, conventional: triphasic: 12 min, 3.3 hr, and 29.6 hr. t1/2, liposomes: About 55 hr.

7.9.2 Supply
Doxorubicin is available in a 2 mg/ml solution or as a lyophilized preparation in various sizes from different manufacturers.

7.9.3 Storage
Powder for injection, lyophilized: 10 mg, 20 mg, 50mg, 100 mg, 150 mg; Store lyophilized doxorubicin product between 15°- 30° C and liquid doxorubicin product between 2°-8°C.

7.9.4 Administration
Dosage per schedules in Section 7.14: 20 mg/m² over 30 min, as long as the client responds satisfactorily and tolerates the drug. For clients with hepatic dysfunction, use the same dosing schedule as conventional doxorubicin.

7.9.5 Toxicity
- Myocardial toxicity: Potentially fatal CHF
- Infusion reactions liposomal product: Flushing, SOB, facial swelling, headache, chills, back pain, tightness in chest and throat, hypotension
- GI: Nausea and vomiting, mucositis (stomatitis, esophagitis), anorexia, diarrhea; ulceration and necrosis of the colon
- Dermatologic: Reversible complete alopecia, hyperpigmentation of nail beds and dermal creases (especially in children), onycholysis, recall of skin reaction to prior radiotherapy, palmar-plantar erythrodysesthesia (swelling, pain, erythema, and desquamation of the skin on the hands and feet)
- Local: Severe cellulitis, vesication, and tissue necrosis if the drug is extravasated; Erythematous streaking along the vein next to injection site
- Hypersensitivity: Fever, chills, urticaria, cross-sensitivity with lincomycin, anaphylaxis
- Hematologic: Myelosuppression, thrombocytopenia
- Ophthalmic: Conjunctivitis, lacrimation

7.9.6 Drug Interactions
Paclitaxel: Two published studies report that initial administration of paclitaxel infused over 24 hours followed by doxorubicin administered over 48 hours resulted in a significant decrease in doxorubicin clearance with more profound neutropenic and stomatitis episodes than the reverse sequence of administration. Progesterone: In a published study, progesterone was given intravenously to patients with advanced malignancies (ECOG PS<2) at high doses (up to 10 g over 24 hours) concomitantly with a fixed doxorubicin dose (60 mg/m2) via bolus. Enhanced doxorubicin-induced neutropenia and thrombocytopenia were observed. Verapamil: A study of the effects of verapamil on the acute toxicity of doxorubicin in mice revealed higher initial peak concentrations of doxorubicin in the heart with a higher incidence and severity of degenerative changes in cardiac tissue resulting in a shorter survival. Cyclosporine: The addition of cyclosporine to doxorubicin may result in increases in AUC for both doxorubicin and doxorubicinol possibly due to a decrease in clearance of parent drug and a decrease in metabolism of doxorubicinol. Literature reports suggest that adding cyclosporine to doxorubicin results in more profound and prolonged hematologic toxicity than doxorubicin alone. Coma and/or seizures have also been described. Literature reports have also described the following drug interactions: phenobarbital increases the elimination of doxorubicin, phenytoin levels may be decreased by doxorubicin, streptozocin (Zanosar®) may inhibit hepatic metabolism of doxorubicin, and administration of live vaccines to immunosuppressed patients, including those undergoing cytotoxic chemotherapy, may be hazardous.

7.10 Nizoral (ketoconazole)

7.10.1 Description
Broad-spectrum antifungal. Inhibits synthesis of sterols (e.g., ergosterol), damaging the cell membrane and resulting in loss of essential intracellular material. Also inhibits biosynthesis of triglycerides and phospholipids and inhibits oxidative and peroxidative enzyme activity. When used to treat Candida albicans it inhibits transformation of blastospores into the invasive mycelial form. Inhibits growth of Pityrosporum ovale when used to treat dandruff. Use in Cushing's syndrome is due to its ability to inhibit adrenal steroidogenesis. Peak plasma levels: 3.5 mcg/mL after 1-2 hr after a 200-mg dose. t1/2 [biphasic]: first, 2 hour; second, 8 hr. Requires acidity for dissolution. Metabolized in liver to inactive metabolites and most is excreted through feces. Also used experimentally in advanced prostate cancer.

7.10.2 Supply
Ketoconazole is commercially available in 200 mg tablets.

7.10.3 Storage
Ketoconazole should be stored at room temperature.

7.10.4 Administration
Dosage per schedules in Section 7.14.

7.10.5 Toxicity
- GI: Nausea and vomiting, abdominal pain, diarrhea
- CNS: Headache, dizziness, somnolence, fever, chills, suicidal tendencies, depression (rare)
- Hematologic: Thrombocytopenia, leukopenia, hemolytic anemia
- Miscellaneous: Hepatotoxicity, photophobia, pruritus, gynecomastia, impotence, bulging fontanelles, urticaria, decreased serum testosterone levels, anaphylaxis (rare).

7.10.6 Drug Interactions
Ketoconazole is a potent inhibitor of the cytochrome P450 3A4 enzyme system. Coadministration of Nizoral® tablets and drugs primarily metabolized by the cytochrome P450 3A4 enzyme system may result in increase plasma concentrations of the drugs that could increase or prolong both therapeutic and adverse effects. Therefore, unless otherwise specified, appropriate dosage adjustments may be necessary. The following drug interactions have been identified involving Nizoral® tablets and other drugs metabolized by the cytochrome P450 3A4 enzyme system: Ketoconazole tablets inhibit the metabolism of terfenadine, resulting in an increased plasma concentration of terfenadine and a delay in the elimination of its acid metabolite. The increased plasma concentration of terfenadine or its metabolite may result in prolonged QT intervals. Pharmacokinetic data indicate that oral ketoconazole inhibits the metabolism of astemizole, resulting in elevated plasma levels of astemizole and its active metabolite desmethylandemizole which may prolong QT interval. Co-administration of astemizole with ketoconazole tablets is therefore contraindicated. Human pharmacokinetics data indicate that oral ketoconazole potently inhibits the metabolism of cisapride resulting in a mean eight-fold increase in AUC of cisapride. Data suggest that co-administration of oral ketoconazole and cisapride can result in prolongation of the QT interval on the ECG. Therefore, concomitant administration of ketoconazole tablets with cisapride is contraindicated. Ketoconazole tablets may alter the metabolism of cyclosporine, tacrolimus, and
methylprednisolone, resulting in elevated plasma concentrations of the latter drugs. Dosage adjustment may be required if cyclosporine, tacrolimus, or methylprednisolone are given concomitantly with Nizoral® tablets. Coadministration of Nizoral® tablets with midazolam or triazolam has resulted in elevated plasma concentrations of the latter two drugs. This may potentiate and prolong hypnotic and sedative effects, especially with repeated dosing or chronic administration of these agents. These agents should not be used in patients treated with Nizoral® tablets. If midazolam is administered parenterally, special precaution is required since the sedative effect may be prolonged. Rare cases of elevated plasma concentrations of digoxin have been reported. It is not clear whether this was due to the combination of therapy. It is, therefore, advisable to monitor digoxin concentrations in patients receiving ketoconazole. When taken orally, imidazole compounds like ketoconazole may enhance the anticoagulant effect of coumarin-like drugs. In simultaneous treatment with imidazole drugs and coumarin drugs, the anticoagulant effect should be carefully titrated and monitored. Because severe hypoglycemia has been reported in patients concomitantly receiving oral miconazole (an imidazole) and oral hypoglycemic agents, such a potential interaction involving the latter agents when used concomitantly with ketoconazole tablets (an imidazole) cannot be ruled out. Concomitant administration of ketoconazole tablets with phenytoin may alter the metabolism of one or both of the drugs. It is suggested both ketoconazole and phenytoin be monitored. Concomitant administration of rifampin with ketoconazole tablets reduces the blood levels of the latter. INH (isoniazid) is also reported to affect ketoconazole concentrations adversely. These drugs should not be given concomitantly. After the coadministration of 200 mg oral ketoconazole twice daily and one 20 mg dose of loratadine to 11 subjects, the AUC and Cmax of loratadine averaged 302% (± 142 S.D.) and 251% (± 68 S.D.), respectively, of those obtained after co-treatment with placebo. The AUC of desacetoxyloratadine, an active metabolite, averaged 155% (± 27 S.D.). However, no related changes were noted in the QT on ECG taken at 2, 6 and 24 hours after the coadministration. Also, there were no clinically significant differences in adverse events when loratadine was administered with or without ketoconazole. Rare cases of disulfiram-like reaction to alcohol have been reported. These experiences have been characterized by flushing, rash, peripheral edema, nausea, and headache. Symptoms resolved within a few hours.

7.11 Velban (vinblastine)

7.11.1 Description
Believed to interfere with metabolic pathways of amino acids leading from glutamic acid to the citric acid cycle and urea. Also affects cell energy production needed for mitosis (affects growing cells in metaphase) and interferes with nucleic acid synthesis. Rapidly cleared from plasma but poor penetration to the brain. About 75% bound to serum proteins. Almost completely metabolized in the liver after i.v. administration. t1/2, triphasic: initial, 3.7 min; intermediate, 1.6 hr; final, 24.8 hour. Metabolites are excreted in the bile with smaller amounts in the urine. No cross-resistance with vincristine.

7.11.2 Supply
Vinblastine is commercially available as powder for injection, 10 mg or as a 1 mg/ml, 10 ml solution.

7.11.3 Storage
Store the powder form at 2°-25°C (36°-77°F); store the liquid form at 2°-8°C (36°-46°F).

7.11.4 Administration
Dosage per schedules in Section 7.14. Injection: 1 mg/mL

7.11.5 Toxicity
Toxicity is dose-related and more pronounced in clients over age 65 or in those suffering from cachexia (profound general ill health) or skin ulceration.
- GI: Ileus, rectal bleeding, hemorrhagic enterocolitis vesiculation of the mouth, bleeding from a former ulcer
- Dermatologic: Total epilation, skin vesiculation
- Respiratory: Acute SOB, severe bronchospasm
- Neurologic: Paresthesias, neuritis, mental depression, loss of deep tendon reflexes, seizures; Extravasation may result in phlebitis and cellulitis with sloughing.

7.11.6 Drug Interactions
Solutions should be made with normal saline (with or without preservative) and should not be combined in the same container with any other chemical. Unused portions of the remaining solutions that do not contain preservatives should be discarded immediately. The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combination that
included vinblastine sulfate has been reported to have reduced blood levels of the anticonvulsant and to have increased seizure activity. Dosage adjustment should be based on serial blood level monitoring. The contribution of vinblastine sulfate to this interaction is not certain. The interaction may result from either reduced absorption of phenytoin or an increase in the rate of its metabolism and elimination. Caution should be exercised in patients concurrently taking drugs known to inhibit drug metabolism by hepatic cytochrome P450 isoenzymes in the CYP 3A subfamily, or in patients with hepatic dysfunction. Concurrent administration of vinblastine sulfate with an inhibitor of this metabolic pathway may cause an earlier onset and/or an increased severity of side effects. Enhanced toxicity has been reported in patients receiving concomitant erythromycin.

7.12 Hydrocortisone/cortisol

7.12.1 Description
Corticosteroid, naturally occurring; glucocorticoid-type; short-acting; t1/2: 80-118 min

7.12.2 Supply
Hydrocortisone is commercially available in 10 mg tablets.

7.12.3 Storage
Store at room temperature.

7.12.4 Administration
Dosage per schedules in Section 7.14.

7.12.5 Toxicity
- Heart: Sodium retention, fluid retention, CHF in susceptible patients, hypertension, myocardial rupture following recent myocardial infarction
- Musculoskeletal: Muscle weakness, steroid myopathy, loss of muscle mass, osteoporosis, vertebral compression fractures, aseptic necrosis of femoral and humeral heads, pathologic fracture of long bones, tendon rupture
- GI: Fluid and electrolyte disturbance, potassium loss, hypokalemia alkalosis, negative nitrogen balance due to protein catabolism, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large bowel, particularly in pts with inflammatory bowel disease, pancreatitis, abdominal distention, ulcerative esophagitis
- Dermatologic: Impaired wound healing, thin fragile skin, petechiae and ecchymoses, erythema, increased sweating, may suppress reactions to skin tests, Other cutaneous reactions, such as allergic dermatitis, urticaria, angioneurotic edema
- Neurologic: Convulsions, increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment, vertigo, headache, psychic disturbances
- Hormonal: Development of cushingoid state; secondary adrenocortical and pituitary unresponsiveness particularly in times of stress, as in trauma, surgery or illness; decreased carbohydrate tolerance, manifestations of latent diabetes mellitus, increased requirements for insulin or oral hypoglycemic agents in diabetics, hirsutism
- Ophthalmic: Posterior subcapsular cataracts, increased intraocular pressure, glaucoma, exophthalmos
- Hypersensitivity: Thromboembolism, weight gain, increased appetite, nausea, malaise.

7.12.6 Drug Interactions
Phenytoin, phenobarbital, ephedrine and rifampin may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels and lessened physiologic activity, thus requiring adjustment in corticosteroid dosage. The prothrombin time should be checked frequently in patients who are receiving corticosteroids and coumarin anticoagulants at the same time because of reports that corticosteroids have altered the response to these anticoagulants. Studies have shown that the usual effect produced by adding corticosteroids is inhibition of response to coumarins, although there have been some conflicting reports of potentiation not substantiated by studies. When corticosteroids are administered concomitantly with potassium-depleting diuretics, patients should be observed closely for development of hypokalemia.

7.13 Coumadin® (warfarin)

7.13.1 Description
Coumadin® is an anticoagulant that acts by inhibiting Vitamin K-dependent coagulation factors. Chemically, it is 3-([d-acetonylbenzyl]-4-hydroxycoumarin and is a racemic mixture of the R and S enantiomers.

7.13.2 Supply
Coumadin® is commercially available. It is supplied as a sterile, lyophilized powder that is reconstituted with sterile water for injection: 5 mg; or as tablets for oral use in: 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg strengths.

7.13.3 Storage
Store at controlled room temperature (59 °F - 86 °F, 15 °C - 30 °C) and protect from light.

7.13.4 Administration
Schedules/doses of Coumadin® per each chemotherapy regimen in Section 7.14.

7.13.5 Toxicity
7.13.5.1 Special Concerns: Geriatric clients may be more sensitive to the effects of the drug. Anticoagulant use in patients with the following conditions leads to increased risk: trauma, infection, renal insufficiency, sprue, vitamin K deficiency, severe to moderate hypertension, polycythemia vera, severe allergic disorders, vasculitis, indwelling catheters, severe diabetes, anaphylactic disorders, surgery or trauma resulting in large exposed raw surfaces. Use with caution in patients with impaired hepatic and renal function. Safety and efficacy have not been determined in children less than 18 years of age. Careful monitoring and dosage regulation are required during dentistry and surgery.

7.13.5.2 Side Effects:
- CV: Hemorrhage is the main side effect and may occur from any tissue or organ. Symptoms of hemorrhage include headache, paralysis, pain in the joints, abdomen, or chest; difficulty in breathing or swallowing; SOB, unexplained swelling or shock
- GI: Nausea, vomiting, diarrhea, sore mouth, mouth ulcers, anorexia, abdominal cramping, paralytic ileus, intestinal obstruction (due to intramural or submucosal hemorrhage)
- Hepatic: Hepatotoxicity, cholestatic jaundice
- Dermatologic: Dermatitis, exfoliative dermatitis, urticaria, alopecia, necrosis or gangrene of the skin, and other tissues (due to protein C deficiency)
- Miscellaneous: Pyrexia, red-orange urine, priapism, leukopenia, systemic cholesterol microembolization (“purple toes” syndrome), hypersensitivity reactions, compressive neuropathy secondary to hemorrhage adjacent to a nerve (rare)

7.13.5.3 Laboratory Test Alterations: False levels of serum theophylline determined by Schack and Waxler UV method (warfarin and dicumarol). Metabolites of indanedione derivatives may color alkaline urine red; color disappears upon acidification.

7.13.5.4 Overdose Management:
- Symptoms: Early symptoms include melena, petechiae, microscopic hematuria, oozing from superficial injuries (e.g., nicks from shaving, excessive bruising, bleeding from gums after teeth brushing), excessive menstrual bleeding.
- Treatment: Discontinue therapy. Administer oral or parenteral phytonadione (e.g., 2.5-10 mg p.o. or 5-25 mg parenterally). In emergency situations, 200-250 ml fresh frozen plasma or commercial factor IX complex should be given. Fresh whole blood may be needed in clients unresponsive to phytonadione.

7.13.6 Drug Interactions
Warfarin is responsible for more adverse drug interactions than any other group. Patients using anticoagulant therapy must be monitored carefully each time a drug is added or withdrawn. Monitoring usually involves determination of PT or INR. In general, a lengthened PT or INR means potentiation of the anticoagulant. Since potentiation may mean hemorrhages, a lengthened PT or INR warrants reduction of the dosage of the anticoagulant. However, the anticoagulant dosage must again be increased when the second drug is discontinued. A shortened PT or INR means inhibition of the anticoagulant and may require an increase in dosage.

7.14 Regimens (3/30/04)
1. Estramustine plus docetaxel (ED)
2. Weekly estramustine, paclitaxel (WEP)
3. Ketoconazole, doxorubicin (Adriamycin), vinblastine, estramustine (KAVE)
4. Weekly estramustine, docetaxel (WED)
5. Docetaxel (D)
6. Weekly docetaxel (WD)
7. Future regimens may be added that have demonstrated activity in Phase II clinical trials and are approved by the GU committee of RTOG.

15
7.14.1 Estramustine plus docetaxel (ED)(3/30/04)

7.14.1.1 Schedule/Doses

Patients will receive four 3-week cycles.

Oral estramustine 280 mg three times per day x 5 days q 21 days.

(Emcyt product labeling suggests that the drug not be taken one hour prior to or two hours after a meal to assure proper absorption of the drug. Emcyt absorption can be decreased with the intake of high calcium-containing foods or supplements; therefore, it is recommended not to take the drug with food.) [Emcyt comes as 140 mg pills].

plus
docetaxel 60 mg/m² i.v. over 1 hour on day 3 q 3 wks**

In order to minimize hypersensitivity reactions to docetaxel, all patients should be premedicated with corticosteroids.

plus
Coumadin® 2 mg p.o. from the start of therapy until 4 weeks after therapy is completed

Coumadin® dose is for DVT prophylaxis. The dose of 2 mg of Coumadin® is not intended to alter the INR of the patient above 2.0.

**(Premeds:  Dexamethasone 8 mg orally bid days 2-4 starting 24 hours before intravenous infusion)

7.14.1.2 Parameters

INR will be checked monthly; if INR is greater than 2, Coumadin® dose should be adjusted accordingly by physician.

Patients will be treated and followed on an ambulatory basis during treatment. CBC and platelets should be done on day 13-15 (to monitor granulocytopenia) and day 1-3 of the next cycle (CBC to be done once in each time period). Use of granulocyte and hemoglobin support measures per physician discretion.

Liver function tests should be checked the first week of every cycle on days 1, 2, or 3 (docetaxel treatment on day 3).

7.14.1.3 Dose Modification (3/30/04)

There is no dose modification for estramustine. Dose modifications for docetaxel are done for blood counts and not for other potential toxicities such as fatigue, etc. Dosage modification for docetaxel is based on docetaxel treatment day granulocyte and platelet counts for that treatment and additional weekly treatments. Treatment day counts may be obtained on days 1, 2, 3 of the cycle (docetaxel treatment on day 3). Dose modification is for the next cycle and all subsequent cycles. Docetaxel must not be administered until granulocyte count is ≥ 1,500 cell/mm³ and platelet count ≥100,000. If counts are below these levels, recheck weekly and retreat using parameters outlined below.

<table>
<thead>
<tr>
<th>Weekly count</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes 1000-1499 and/or platelets 75,000-99,999</td>
<td>HOLD, then resume docetaxel at 45 mg/m² i.v. (dose is decreased by 25%)*</td>
</tr>
<tr>
<td>Granulocytes &lt;1000 and/or Platelets &lt; 75,000</td>
<td>HOLD, then resume docetaxel at 30 mg/m² i.v. (dose is decreased by 50%)*</td>
</tr>
</tbody>
</table>

* If a patient cannot be treated after holding therapy for 3 weeks, then therapy should be discontinued.

7.14.1.4 Docetaxel administration is also modified for elevated liver function tests.

Docetaxel Dose Modification for Elevated Liver Function on Day of Treatment

<table>
<thead>
<tr>
<th>Bilirubin Test Results</th>
<th>ALT/AST x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 2.5 x ULN</td>
</tr>
<tr>
<td>Total bilirubin ≤ 1.5 mg/dl</td>
<td>100%</td>
</tr>
<tr>
<td>Total bilirubin &gt; 1.5 mg/dl</td>
<td>0</td>
</tr>
</tbody>
</table>

7.14.1.5 There will be no dose modification for neuropathy.
If the patient suffers a confirmed thromboembolic event (e.g., DVT PE, stroke, MI), all chemotherapy will be immediately discontinued. If the patient suffers a bleeding event that requires discontinuation of Coumadin® (warfarin), all chemotherapy will be immediately discontinued.

**Weekly estramustine, paclitaxel (WEP) (3/30/04)**

**7.14.2 Schedule/Doses**
Patients will receive four cycles. One cycle equals 6 continuous weeks followed by 2 weeks rest.

*Oral Emcyt* 280 mg b.i.d. x 5 days q 7 days x 6 weeks out of 8 weeks

*(Emcyt product labeling suggests that the drug not be taken one hour prior to or two hours after a meal to assure proper absorption of the drug. Emcyt absorption can be decreased with the intake of high calcium-containing foods or supplements; therefore, it is recommended not to take the drug with food.) [Emcyt comes as 140 mg pills].

*plus*

Coumadin® 2 mg p.o. from the start of therapy until 4 weeks after therapy is completed

Coumadin® dose is for DVT prophylaxis. The dose of 2 mg of Coumadin® is not intended to alter the INR of the patient above 2.0.

*plus*

paclitaxel 90 mg/m² i.v. over 1 hour on day 3 of each treatment week x 6 out of 8 weeks

In order to minimize hypersensitivity reactions to paclitaxel, all patients should be premedicated with corticosteroids and H2 blockers.

*(Premeds: Dexamethasone 20 mg i.v. or p.o. 30 minutes prior to administration, Diphenhydramine 50 mg i.v. and Pepcid 20 mg or Ranitidine 50 mg or Cimetidine 300 mg i.v. 30 minutes prior to administration)*

**7.14.2.2 Parameters**

INR will be checked monthly; if INR is greater than 2, Coumadin® dose should be adjusted accordingly by physician.

Patients will be treated and followed on an ambulatory basis during treatment. CBC and platelets should be done weekly on day of paclitaxel infusion. Use of granulocyte and hemoglobin support measures per physician discretion.

Liver function tests should be checked the first week of every cycle on the day of paclitaxel treatment.

**7.14.2.3 Dose Modification (3/30/04)**

There is no dose modification for estramustine. Dose modifications for paclitaxel are only done for blood counts and not for other potential toxicities such as fatigue, etc. **Dosage modification for paclitaxel is based on treatment day granulocyte and platelet counts for that treatment and additional weekly treatments.** Paclitaxel must not be administered until granulocyte count is ≥ 1,500 cell/mm³ and platelet count ≥100,000. If counts are below these levels, recheck weekly and retreat using parameters outlined below.

<table>
<thead>
<tr>
<th>Weekly Count</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes 1000-1499 and/or platelets 75,000- 99,999</td>
<td>HOLD, then resume paclitaxel at 67.5 mg/m² i.v. (dose is decreased by 25%) *</td>
</tr>
<tr>
<td>Granulocytes &lt;1000 and/or platelets &lt; 75,000</td>
<td>HOLD, then resume paclitaxel at 45 mg/m² i.v. (dose is decreased by 50%)*</td>
</tr>
</tbody>
</table>

*If a patient cannot be treated after holding therapy for 3 weeks, then therapy should be discontinued.

**7.14.2.4 Paclitaxel administration is also modified for elevated liver function tests.**

**Paclitaxel Dose Modification for Elevated Liver Function on Day of Treatment**

<table>
<thead>
<tr>
<th>Bilirubin Test Results</th>
<th>ALT/AST x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2.5 x ULN</td>
<td>&gt; 2.5 and ≤ 5.0 x ULN</td>
</tr>
<tr>
<td>Total bilirubin ≤ 1.5 mg/dl</td>
<td>100%</td>
</tr>
</tbody>
</table>
7.14.2.5 There will be no dose modification for neuropathy.

7.14.2.6 If the patient suffers a confirmed thromboembolic event (e.g., DVT PE, stroke, MI), all chemotherapy will be immediately discontinued. If the patient suffers a bleeding event that requires discontinuation of Coumadin® (warfarin), all chemotherapy will be immediately discontinued.

7.14.3 Ketoconazole, doxorubicin (Adriamycin), vinblastine, estramustine (KAVE) (3/30/04)

7.14.3.1 Schedule/Doses
Patients will receive four cycles:
- Oral estramustine 140 mg three times per day x 7 days on days 8-14, 22-28, 36-42 q 56 days.
  (Emcyt product labeling suggests that the drug not be taken one hour prior to or two hours after a meal to assure proper absorption of the drug. Emcyt absorption can be decreased with the intake of high calcium-containing foods or supplements; therefore, it is recommended not to take the drug with food.) [Emcyt comes as 140 mg pills].
- plus vinylastine 4 mg/m² days 8, 22, 36 q 56 days
- plus oral ketoconazole 400 mg t.i.d. days 1-7, 15-21, 29-35 q 56 days
- plus doxorubicin 20 mg/m² days 1, 15, 29 q 56 days
- plus hydrocortisone 20 mg every a.m. and 10 mg every p.m. with ketoconazole

7.14.3.2 Parameters
Patients will be treated and followed on an ambulatory basis during treatment. CBC and platelets should be done weekly. Use of granulocyte and hemoglobin support measures per physician discretion.
Liver function tests should be checked the first week of every cycle on the day of adriamycin treatment.

7.14.3.3 Dose Modification
There is no dose modification for estramustine. There is no dosage modification for ketoconazole. Dose modifications for adriamycin and vinblastine are only done for blood counts and not for other potential toxicities such as fatigue, etc. Dosage modification for adriamycin is based on Days 1,15,29 granulocyte and platelet counts for that dose and subsequent cycles. Dose modification for vinblastine is based on Days 8, 22, 36 granulocyte and platelet counts for that dose and subsequent cycles. Adriamycin and vinblastine must not be administered until granulocyte count is ≥ 1,500 cell/mm³ and platelet count ≥ 100,000. If counts are below these levels, recheck weekly and retreat using parameters outlined below. Dose modification is for dose that week and all subsequent doses of that agent.

<table>
<thead>
<tr>
<th>Day of Treatment Nadir</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes 1000-1499 and/or platelets 75,000-99,999</td>
<td>HOLD, then resume Adriamycin at 15 mg/m² (dose is decreased by 25%) *</td>
</tr>
<tr>
<td>Granulocytes &lt;1000 and/or platelets &lt; 75,000</td>
<td>HOLD, then resume Vinblastine at 3 mg/m² (dose is decreased by 50%)*</td>
</tr>
</tbody>
</table>

* If a patient cannot be treated after holding therapy for 3 weeks, then therapy should be discontinued.

7.14.3.4 Adriamycin administration is also modified for elevated liver function tests.

<p>| Adriamycin Dose Modification for Elevated Liver Function on Day of Treatment |
|-----------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Bilirubin Test Results</th>
<th>ALT/AST x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2.5 x ULN</td>
<td>&gt; 2.5 x ULN and ≤ 5.0 x ULN</td>
</tr>
<tr>
<td>Total bilirubin ≤ 1.5 mg/dl</td>
<td>100%</td>
</tr>
<tr>
<td>Total bilirubin &gt; 1.5 mg/dl</td>
<td>0</td>
</tr>
</tbody>
</table>
If the patient suffers a confirmed thromboembolic event (e.g., DVT PE, stroke, MI), all chemotherapy will be immediately discontinued.

7.14.4 Weekly estramustine, docetaxel (WED) (3/30/04)

7.14.4.1 Schedule/Doses
Patients will receive four cycles. A cycle is 3 weeks followed by one week rest.

7.14.4.1.1 Oral estramustine 140 mg t.i.d x 4 days q 7 days x 3 weeks out of 4 weeks.

7.14.4.1.2 Estramustine absorption can be decreased with the intake of high calcium-containing foods or supplements; therefore, it is recommended not to take the drug with food. [Estramustine comes as 140 mg pills].

7.14.4.1.3 Docetaxel 30 mg/m² i.v. over 1 hour day 3 of each treatment week x 3 out of 4 weeks**

In order to minimize hypersensitivity reactions to docetaxel, all patients should be premedicated with corticosteroids.

7.14.4.1.4 All patients should be premedicated with corticosteroids.

Coumadin® 2 mg p.o. from the start of therapy until 4 weeks after therapy is completed. Coumadin® dose is for DVT prophylaxis. The dose of 2 mg of Coumadin® is not intended to alter the INR of the patient above 2.0.

***(Premeds: Dexamethasone 4 mg orally bid days 2-4 starting 24 hours before intravenous infusion)

7.14.4.2 Parameters
INR will be checked monthly; if INR is greater than 2, Coumadin® dose should be adjusted accordingly by physician.

7.14.4.3 Dose Modification
There is no dose modification for estramustine. Dose modifications for docetaxel are done for blood counts and not for other potential toxicities such as fatigue, etc. Dosage modification for docetaxel is based on docetaxel treatment day granulocyte and platelet counts for that treatment and additional weekly treatments. Docetaxel must not be administered until granulocyte count is ≥ 1,500 cell/mm³ and platelet count ≥ 100,000. If counts are below these levels, recheck weekly and retreat using parameters outlined below.

<table>
<thead>
<tr>
<th>Weekly Count</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes 1000-1499 and/or platelets 75,000-99,999</td>
<td>HOLD, then resume docetaxel at 22.5 mg/m² i.v. (dose is decreased by 25%)*</td>
</tr>
<tr>
<td>Granulocytes &lt;1000 and/or platelets &lt; 75,000</td>
<td>HOLD, then resume docetaxel at 15 mg/m² i.v. (dose is decreased by 50%)*</td>
</tr>
</tbody>
</table>

* If a patient cannot be treated after holding therapy for 3 weeks, then therapy should be discontinued.

7.14.4.4 Docetaxel administration is also modified for elevated liver function tests.

<table>
<thead>
<tr>
<th>Bilirubin Test Results</th>
<th>ALT/AST x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 2.5 x ULN</td>
</tr>
<tr>
<td>Total bilirubin ≤ 1.5 mg/ dl</td>
<td>100%</td>
</tr>
</tbody>
</table>
7.14.4.5 There will be no dose modification for neuropathy.

7.14.4.6 If the patient suffers a confirmed thromboembolic event (e.g., DVT PE, stroke, MI), all chemotherapy will be immediately discontinued. If the patient suffers a bleeding event that requires discontinuation of Coumadin® (warfarin), all chemotherapy will be immediately discontinued.

7.14.5 *Docetaxel (D) (3/30/04)*

7.14.5.1 **Schedule/Doses**

Patients will receive 4 cycles.

docetaxel 60-70 mg/m² i.v. over 1 hour on day 1 q 3 wks

In order to minimize hypersensitivity reactions to docetaxel, all patients should be premedicated with corticosteroids. (Dexamethasone 8 mg orally bid days -1, day of, and +1, starting 24 hours before intravenous infusion.)

7.14.5.2 **Parameters**

Patients will be treated and followed on an ambulatory basis during treatment. CBC and platelets should be done on day 13-15 (to monitor granulocytopenia) and day -1 to 1 of the next cycle (CBC to be done once in each time period). Use of granulocyte and hemoglobin support measures per physician discretion.

Liver function tests should be checked the first week of every cycle on days -1 or 1, (docetaxel treatment on day 1).

7.14.5.3 **Dose Modification**

Dose modifications are done for blood counts and not for other potential toxicities such as fatigue, etc. **Dosage modification for docetaxel is based on docetaxel treatment day granulocyte and platelet counts for that treatment and additional weekly treatments. Treatment day counts may be obtained on days -1 and 1 of the cycle (docetaxel treatment on day 1). Dose modification is for the next cycle and all subsequent cycles.** Docetaxel must not be administered until granulocyte count is ≥ 1,500 cell/mm³ and platelet count ≥100,000. If counts are below these levels, recheck weekly and retreat using parameters outlined below.

<table>
<thead>
<tr>
<th>Weekly count</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes 1000-1499 and/or platelets 75,000-99,999</td>
<td>HOLD, then resume docetaxel at 45 mg/m² i.v. (dose is decreased by 25%)*</td>
</tr>
<tr>
<td>Granulocytes &lt;1000 and/or Platelets &lt; 75,000</td>
<td>HOLD, then resume docetaxel at 30 mg/m² i.v. (dose is decreased by 50%)*</td>
</tr>
</tbody>
</table>

* If a patient cannot be treated after holding therapy for 3 weeks, then therapy should be discontinued.

7.14.5.4 Docetaxel administration is also modified for elevated liver function tests.

### Docetaxel Dose Modification for Elevated Liver Function on Day of Treatment

<table>
<thead>
<tr>
<th>Bilirubin Test Results</th>
<th>ALT/AST x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 2.5 x ULN</td>
</tr>
<tr>
<td>Total bilirubin ≤ 1.5 mg/dl</td>
<td>100%</td>
</tr>
<tr>
<td>Total bilirubin &gt; 1.5 mg/dl</td>
<td>0</td>
</tr>
</tbody>
</table>

7.14.5.5 There will be no dose modification for neuropathy.

7.14.6 *Weekly docetaxel (WD) (3/30/04)*

7.14.6.1 **Schedule/Doses**

Patients will receive 4 cycles.

docetaxel 30 mg/m² i.v. over 1 hour day 1 of each treatment week x 3 out of 4 weeks
In order to minimize hypersensitivity reactions to docetaxel, all patients should be premedicated with corticosteroids. *(Dexamethasone 4 mg orally bid days -1, day of, and +1 starting 24 hours before intravenous infusion)*

### 7.14.6.2 Parameters

Patients will be treated and followed on an ambulatory basis during treatment. CBC and platelets should be done weekly on day of taxotere infusion. Use of granulocyte and hemoglobin support measures per physician discretion. Liver function tests should be checked the first week of every cycle on the day of docetaxel treatment.

### 7.14.6.3 Dose Modification

Dose modifications are done for blood counts and not for other potential toxicities such as fatigue, etc. **Dosage modification for docetaxel is based on docetaxel treatment day granulocyte and platelet counts for that treatment and additional weekly treatments.**

Docetaxel must not be administered until granulocyte count is ≥ 1,500 cell/mm^3 and platelet count ≥ 100,000. If counts are below these levels, recheck weekly and retreat using parameters outlined below.

<table>
<thead>
<tr>
<th>Weekly Count</th>
<th>Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytes 1000-1499 and/or platelets 75,000-99,999</td>
<td>HOLD, then resume docetaxel at 22.5 mg/m² i.v. <em>(dose is decreased by 25%)</em></td>
</tr>
<tr>
<td>Granulocytes &lt;1000 and/or platelets ≤ 75,000</td>
<td>HOLD, then resume docetaxel at 15 mg/m² i.v. <em>(dose is decreased by 50%)</em></td>
</tr>
</tbody>
</table>

* If a patient cannot be treated after holding therapy for 3 weeks, then therapy should be discontinued.

### 7.14.6.4 Docetaxel administration is also modified for elevated liver function tests.

**Docetaxel Dose Modification for Elevated Liver Function on Day of Treatment**

<table>
<thead>
<tr>
<th>Bilirubin Test Results</th>
<th>AST/ALT x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤ 2.5 x ULN</td>
</tr>
<tr>
<td>Total bilirubin ≤ 1.5 mg/dl</td>
<td>100%</td>
</tr>
<tr>
<td>Total bilirubin &gt; 1.5 mg/dl</td>
<td>0</td>
</tr>
</tbody>
</table>

### 7.14.6.5 There will be no dose modification for neuropathy.

### 7.14.7 Future regimens may be added that have demonstrated activity in Phase II clinical trials and are approved by the GU committee of RTOG. *(3/30/04)*

### 7.15 Adverse Drug Reaction Reporting *(3/30/04)*

7.15.1 This study will utilize the Common Toxicity Criteria (CTC) version 2.0 for grading of chemotherapy toxicity. A copy of the CTC version 2.0 can be downloaded from the CTEP homepage *(http://ctep.info.nih.gov)*. All appropriate treatment areas should have access to a copy of the CTC version 2.0. See Appendix V for Adverse Event Reporting Guidelines. This study will be monitored by the Clinical Data Update System *(CDUS)* version 1.1. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

7.15.2 The following guidelines for reporting adverse drug reactions *(ADR’s)* apply to any research protocol that uses commercial anticancer agents. The following ADR’s experienced by patients accrued to this protocol and attributed to the commercial agent(s) should be reported by telephone to RTOG Headquarters within 24 hours of discovery and then a written report sent to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within ten working days:

7.15.2.1 Any ADR which is both serious *(life-threatening [grade 4] or fatal [grade 5])* and **unexpected;**

7.15.2.2 Any increased incidence of a known ADR which has been reported in the package insert or the literature;
7.15.2.3 Any death on study if clearly related to the commercial agent(s).
7.15.3 The ADR report should be documented on FDA Form 3500 (*Form 3500A is the mandatory reporting form*) and mailed or faxed to the address on the form, as well as to the IDB and RTOG Data Management Department:

<table>
<thead>
<tr>
<th>Investigational Drug Branch</th>
<th>RTOG Data Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.O. Box 30012</td>
<td>1101 Market Street, 14th floor</td>
</tr>
<tr>
<td>Bethesda, MD 20824</td>
<td>Philadelphia, PA 19107</td>
</tr>
<tr>
<td><em>(301)</em> 230-2330, available 24 hours</td>
<td>Phone <em>(215)</em> 574-3214</td>
</tr>
<tr>
<td>Fax <em>(301)</em> 402-1584</td>
<td>Fax <em>(215)</em> 717-0990</td>
</tr>
</tbody>
</table>

All MedWatch forms submitted to RTOG Headquarters must include the RTOG study and case numbers; the non-RTOG intergroup study and case numbers must be included, when applicable.

7.15.4 Death from any cause while the patient is receiving protocol treatment or up to 30 days after the last protocol treatment, must be telephoned to the RTOG Headquarters Data Management department within ten days of discovery.

7.15.5 Acute myeloid leukemia (*AML*) or myelodysplastic syndrome (*MDS*) that is diagnosed during or subsequent to treatment in patients on NCI/CTEP-sponsored clinical trials must be reported using the NCI/CTEP Secondary AML/MDS Report Form available at [http://ctep.info.nih.gov](http://ctep.info.nih.gov). The report must include the time from original diagnosis to development of AML/MDS, characterization such as FAB subtype, cytogenetics, etc., and protocol identification. This form will take the place of the FDA Form 3500 and must be mailed within 30 days of AML/MDS diagnosis to the address on the form and to the RTOG Data Management Department:

<table>
<thead>
<tr>
<th>Investigational Drug Branch</th>
<th>RTOG Headquarters</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>(NCI/CTEP)</em> P.O Box 30012</td>
<td>AML/MDS Report</td>
</tr>
<tr>
<td>Bethesda, MD 20824</td>
<td>1101 Market Street, 14th floor</td>
</tr>
<tr>
<td><em>(NCI/CTEP)</em></td>
<td>Philadelphia, PA 19107</td>
</tr>
</tbody>
</table>

All forms submitted to RTOG Headquarters must include the RTOG study and case numbers; the non-RTOG intergroup study and case numbers must be included, when applicable.

8.0 **SURGERY**

Not applicable to this study.

9.0 **OTHER THERAPY**

Not applicable to this study.

10.0 **PATHOLOGY**

Not applicable to this study.

11.0 **PATIENT ASSESSMENTS**

11.1 Study Parameters for patients on hormonal therapy prior to chemotherapy (3/30/04)

*(Arm 2 patients and Arm 1 patients after completion of chemotherapy while remaining on AB)*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-therapy</th>
<th>Every 3 months</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;P</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Height/Weight</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zubrod</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Histological evaluation and Gleason Score</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC, Platelets</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>PSA, Serum ALT&lt;sup&gt;d&lt;/sup&gt;, Alk Phos, Bilirubin, BUN, creatinine, and testosterone</td>
<td>X&lt;sup&gt;a&lt;/sup&gt;</td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
<td>X&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>X^b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Bone Scan</td>
<td>X^b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic CT or Pelvic MRI</td>
<td>X^b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>lymph node assessment</td>
<td></td>
<td>X^c</td>
<td></td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>X^b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity Assessment</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Note of bisphosphonate</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>use</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- a. Within 4 weeks prior to study entry
- b. Within 8 weeks prior to study entry
- c. As clinically indicated
- d. Serum ALT will be measured monthly during antiandrogen therapy
### Study Parameters for patients on chemotherapy (Arm 1 and Arm 2 patients) (3/30/04)

#### Parameters Pre-therapy Prior to each cycle of chemotherapy During Chemotherapy After Chemotherapy

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Pre-therapy</th>
<th>Prior to each cycle of chemotherapy</th>
<th>During Chemotherapy</th>
<th>After Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;P</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Height/Weight</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zubrod</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC, Platelets</td>
<td>X</td>
<td>X</td>
<td>X^e</td>
<td></td>
</tr>
<tr>
<td>PT/INR</td>
<td>X</td>
<td>X</td>
<td>X^d</td>
<td></td>
</tr>
<tr>
<td>Serum ALT, Alk Phos, Bilirubin, BUN, creatinine, and testosterone</td>
<td>X</td>
<td>X</td>
<td>X^{ab}</td>
<td>X</td>
</tr>
<tr>
<td>PSA</td>
<td>X</td>
<td>X</td>
<td>X^e</td>
<td></td>
</tr>
<tr>
<td>Bone Scan</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pelvic CT or Pelvic MRI lymph node assessment</td>
<td>X</td>
<td></td>
<td>X^c</td>
<td></td>
</tr>
<tr>
<td>Chest x-ray</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity Assessment</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Note of bisphosphonate use</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. According to specific chemotherapy administration regimen chosen from Section 7.0
b. At baseline and as clinically indicated afterward
c. As clinically indicated during follow up, i.e, if deemed necessary by the physician to evaluate the patient who has new symptoms.
d. For chemotherapy regimens involving estramustine except KAVE: PT/INR will be analyzed at least every 4 weeks. The objective is to keep the INR less than or equal to 2.0. More frequent analysis is at the treating physician’s discretion.
e. PSA is monitored every 3 months while patient is off chemotherapy, but on AB.

## Follow-up Schedule

### 11.3.1 Every 3, 6, 9, and 12 months in year 1; q 3 months in year 2; q 6 mos. x 3 years, then annually. Also at progression/relapse and at death.

### 11.3.2 Bone scan as clinically indicated; Discretionary plain films may be needed to evaluate lesions seen on bone scan to confirm the diagnosis of metastatic disease

### 11.3.3 Radiologic studies such as CT scans or MRI at investigator discretion.

## Measurement of Effect (3/30/04)

### 11.4.1 PSA failure is defined as a PSA doubling time \( \leq 32 \) weeks. All measurable disease in cm must be recorded on the data collection forms for initial and follow-up evaluations of the patient. All measurable disease must be measurable in two dimensions by palpation or on radiographs. All PSA levels done during a follow-up interval will be recorded on the data forms.

### 11.4.2 After study entry, disease activity evaluations will be made and recorded using the following criteria:

#### 11.4.2.1 PSA Complete Response (PSA-CR): A PSA-CR will be declared if the PSA becomes undetectable (< 0.3 ng/ml).

#### 11.4.2.2 Evaluable Disease: Bone scans, once positive, are considered evaluable for disease progression and disease response.

#### 11.4.2.3 Progressive Disease (PD): An increase in the number of lesions on bone scan. Or a PSA doubling time of \( \leq 32 \) weeks.

## Other Response Parameters

### 11.5.1 Biochemical Control (PSA Failure): For this study, the "PSA nadir" will be defined as the lowest PSA value reached immediately preceding a "PSA failure." PSA failure is defined as a PSA doubling time \( \leq 32 \) weeks.

### 11.5.2 Time to Clinical Failure: The time to clinical failure will be measured from the date of randomization to the date of documented clinical failure as measured by a positive bone scan, positive disease evaluation of the pelvis or chest, or a PSA doubling time \( \leq 32 \) weeks. Radiologic
studies to be done as clinically indicated.

11.5.3 Disease-Free Survival: The progression-free survival will be measured from the date of randomization to the date of documentation of progression or until the date of death. This endpoint includes all measures of disease including physical exam, PSA, bone scans and/or radiographic evidence.

11.5.4 Overall Survival: The survival time will be measured from the date of randomization to the date of death. All patients will be followed for survival. Every effort should be made to document the cause of death. Post-mortem examination will be carried out when feasible, and a copy of the final autopsy report should be sent to RTOG.

12.0 DATA COLLECTION

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX# 215/928-0153)

12.1 Summary of Data Submission

<table>
<thead>
<tr>
<th>Item</th>
<th>Due</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic Form (A5)</td>
<td>Within 2 weeks of study entry.</td>
</tr>
<tr>
<td>Initial Evaluation Form (I1)</td>
<td></td>
</tr>
<tr>
<td>Follow-up Form (F1)</td>
<td>Every 3, 6, 9, and 12 months in year 1; q 3 months in year 2; q 6 mos. x 3 years, then annually. Also at progression/relapse and at death.</td>
</tr>
<tr>
<td>Long-Term Follow-up Form (FF)</td>
<td>Yearly after 5 years in place of the F1 form, as applicable. See FF form instructions.</td>
</tr>
<tr>
<td>Autopsy Report (D3)</td>
<td>As applicable.</td>
</tr>
</tbody>
</table>
13.0 STATISTICAL CONSIDERATIONS

13.1 Study Endpoints

13.1.1 Primary Endpoint
- Overall survival (Failure – death from any cause)

13.1.2 Secondary Endpoints (3/30/04)
- Biochemical control (PSA failure is defined as a PSA doubling time ≤ 32 weeks);
- Time to clinical failure (Time from study entry to positive bone scan or positive disease evaluation of the pelvis or chest or a PSA doubling time ≤ 32 weeks. Radiologic studies to be done yearly or as clinically indicated);
- Frequency of non-hematologic (≥ grade 3), hematologic (≥ grade 4) and fatal (grade 5) toxicities.

13.2 Sample Size

13.2.1 Stratification: The treatment allocation scheme described by Zelen\textsuperscript{30} will be used at randomization. The stratifying variables are prior treatment (surgery, radiation and/or brachytherapy, both), the Gleason score at diagnosis (6, 7, 8-10), and prior vaccine (yes, no).

13.2.2 Sample Size Derivation: The primary hypothesis of this trial is whether the immediate chemotherapy will reduce the hazard rate by 25% at five years comparing with the control arm. An estimate of fifty percent five-year survival for the control arm was derived from four published reports in patients with M0 disease.\textsuperscript{2-5} These reports were based on patients treated with hormonal therapy between 1980 and the early 1990’s. Since then, there have been evolving changes in the timing of interventions of any type in the treatment of prostate cancer. Therefore, it is conceivable that the men to be entered on this trial may have a more favorable prognosis compared to those in the cited hormonal studies. Because of that distinct possibility, 60 and 65% five-year survival rates will also be evaluated. Instead of selecting a specific five-year survival rate for the control arm, the number of events (deaths) was first determined to test the trial’s hypothesis under the following conditions:

1. Survival times are exponentially distributed for both treatment arms;
2. Immediate chemotherapy will reduce the annual hazard rate by 25% (which is same increasing median by 33%);
3. One-sided test at \( \alpha = 0.025 \);
4. Statistical power of 85%;
5. Three interim significance tests and the final test using O’Brien-Fleming boundaries.\textsuperscript{31}

The total number of events required under these conditions would be 449 deaths. Under different scenarios, the total study duration (length of the accrual period and post follow-up) was then calculated so that 449 deaths could be observed. The five-year survival rates for the control arm (50% vs. 60% vs. 65%), the total patient accrued to trial (800 vs. 1000 vs. 1200 patients), and the length of the accrual period (4 vs. 5 vs. 6 years) were varied. The goal was to have the total study duration to be approximately 10.0 years or less. In tables 1-3, the total study durations are presented for accrual periods of 4, 5, and 6 years in length. After considering this information, 1000 men were selected as the initial accrual target. If the baseline control rate is less than 50% or the yearly accrual exceeds 250 cases, the total study duration will be less than what is indicated in the tables.

| Table 1: Total duration of study by total sample size (4-Year Accrual) |
|-----------------|----------------|----------------|----------------|
|                  | Total Duration (years) | N=800 | N=1000 | N=1200 |
| 5-Year Survival  |
| Baseline Control | 50%          | 8.9   | 7.0   | 6.0   |
|                  | 60%          | 11.4  | 8.8   | 7.3   |
|                  | 65%          | 13.1  | 10.0  | 8.3   |

<p>| Table 2: Total duration of study by total sample size (5-Year Accrual) |
|-----------------|----------------|----------------|----------------|
|                  | Total Duration (years) | N=800 | N=1000 | N=1200 |
| 5-Year Survival  |
| Baseline Control | 50%          | 9.5   | 7.6   | 6.5   |</p>
<table>
<thead>
<tr>
<th>Total Duration (years)</th>
<th>N=800</th>
<th>N=1000</th>
<th>N=1200</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% 10.0</td>
<td>8.1</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>60% 12.4</td>
<td>9.8</td>
<td>8.4</td>
<td></td>
</tr>
<tr>
<td>65% 14.1</td>
<td>11.1</td>
<td>9.4</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Total duration of study by total sample size (6-Year Accrual)

Guarding against a possible 5% rate of cases ineligible or lost to follow-up, the final targeted accrual for this study will be 1050 cases.

13.2.2.1 Inclusion of patients with a Gleason score 6 and capsular penetration or positive seminal vesicles or lymph nodes will not impact the statistical design as originally written. These patients have a similar prognostic experience as those eligible for the study (i.e., Gleason $\geq 7$). Therefore, the sample size will not need to be adjusted to meet the study objectives. (3/30/04)

13.2.3 Patient Accrual: Based on patient accrual in previous RTOG randomized prostate studies, there will be relatively few entries during the initial six months while institutions are obtaining IRB approval. The Data Monitoring Committee (DMC) will evaluate patient accrual after the first six months from the study opening to patient entries. During the second year interval, the patient accrual is expected to at least double as compared to the first year interval. After that the patient accrual tends to level off. The patient accrual is projected to be about 15-22 cases per month. We expect to complete the accrual in less than 6 ½ years. If the average monthly accrual rate during the first year beyond the first six months is below 10 cases per month, the study will be re-evaluated for its feasibility. The participation of non-RTOG institutions through CTSU is expected to follow a similar pattern as seen in RTOG.

13.2.4 Analysis Plans: Overall survival will be calculated by the Kaplan-Meier method. The treatment effect with respect to all endpoints will be analyzed by the log rank test statistics All eligible and evaluable patients will be included in the intent-to-treat analysis. The cumulative incidence method will be used to estimate the five-year rates of biochemical failure and the clinical failure because of the competing risk of dying without either or both failures.

Allowing multiple chemotherapy regimens may maximize accrual and provide a true proof of principal trial of early versus late chemotherapy in patients with advanced prostate cancer. However, there will be insufficient statistical power to detect which chemotherapy regimen is the best in terms of either overall survival or such secondary endpoints as biochemical failure. The study will only be able to assess whether early or late chemotherapy delivery is best. The study is not powered to detect the best chemotherapy regimen. A much larger sample size would be needed to do so.

13.2.5 Interim Reports: Interim reports will be prepared every six months until the closure of the study. In general, the interim reports will include:

- The patient accrual rate for the overall study and within each stratum and a projection date for the completion of patient accrual;
- Protocol compliance and quality of submitted data;
- The frequencies and severity of the toxicities; these will be reported separately for each “allowable” chemotherapy regimen.

13.2.6 Interim Treatment Analysis for Early Stopping: Three such interim treatment comparisons shall be performed when we observe 112, 224, and 336 of the 449 required maximum number of deaths. The first interim analysis is projected to take place when 70% total accrual is reached. The second interim analysis is projected to take place when 100% of total accrual is reached. The third interim analysis is projected to take place at the third year after the closure. The boundary for early stopping (or the nominal significance level for the test) will be computed based on the observed number of deaths according to the O’Brien-Fleming alpha spending function approach. If the difference is highly significant, i.e., p value less than the nominal level, the responsible statistician will recommend to Data Monitoring Committee that the study be written up for publication. The nominal
levels are 0.001, 0.0017, 0.0095, and 0.0217. The nominal level for the first analysis is truncated at 0.001. At each planned interim analysis for early stopping and/or reporting of results, the p-value from the log-rank test for treatment efficacy and the conditional power \(^3\) for the alternative hypothesis will be reported to the RTOG Data Monitoring Committee (DMC). The conditional power for the alternative hypothesis given the observed data will be calculated at each planned interim analysis. Low conditional power suggests a small probability of a significant treatment effect even if future follow-up are assumed to have the same distribution under the alternative hypothesis. The responsible statistician for the study will recommend early stopping and/or reporting of the results if the treatment effect with respect to overall survival is highly significant, i.e. the p-value is less than the nominal value specified in a sequential design, or the conditional power is less than 10%. In making that recommendation, the accrual rate, treatment compliance, safety of the treatments, and importance of the study are also taken into consideration. The DMC then makes a recommendation about the trial to the study chair. The study chair generally accepts the DMC recommendation.

### 13.3 Toxicity Monitoring
Grade 3 and higher non-hematologic, grade 4 and higher hematologic and grade 5 toxicities for each “allowable” chemotherapy regimen will be monitored for excessive toxicity. Since the toxicity profile for these regimens differ, no uniform stopping rules can be incorporated into the trial. At every semi-annual RTOG meeting, the non-hematologic (≥ grade 3), hematologic (≥ grade 4) and fatal (grade 5) toxicities for each chemotherapy regimen will be reported to the RTOG Data Monitoring Committee, study chairs, and the GU chair. It will be their responsibility to independently review these toxicities associated with each regimen in terms of acceptability. If they determine the toxicities for an “allowable” regimen in this treatment population are excessive, it will be communicated to the Group Chair and the Research Strategy Committee for their consideration and action. Actions can include dose modifications of the regimen or the closing of the regimen to further accrual. Whenever any fatal treatment morbidity is reported, the study chair immediately will be asked to review it, and the reported morbidity may be followed by a conference call with all study chairs and GU chair to determine if a dose modification or closure is warranted for that “allowable” regimen.

### 13.4 Inclusion of Minorities
In conformance with the National Institute of Health Revitalization Act of 1993 with regard to inclusion of women and minorities in clinical research, we have also considered the possible interaction between race and treatments. Based on the latest accrual statistics from RTOG 94-13, we project that 70% of men in the study are white, 25% are black (not of Hispanic origin), 3% are Hispanic, 0.5% are Asian or Pacific Islander, 0.5% are American Indian or Alaskan Native, and 1% are others and unknown. The following table lists the projected accrual for each racial group. Assuming no difference among races with respect to survival, the statistical power for detecting the hypothesized difference is 72.2% and 33.2% for white and black, respectively. With 106 deaths in the African American population, we are able to detect a 43% hazard reduction by radiation therapy for the subset with statistical power of 80%. The projected categories are as follows:

<table>
<thead>
<tr>
<th>Male</th>
<th>American Indian or Alaskan Native</th>
<th>Asian or Pacific Islander</th>
<th>Black, not of Hispanic Origin</th>
<th>Hispanic</th>
<th>White, not of Hispanic Origin</th>
<th>Other or Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaskan Native</td>
<td>5</td>
<td>5</td>
<td>263</td>
<td>32</td>
<td>735</td>
<td>10</td>
<td>1050</td>
</tr>
</tbody>
</table>
REFERENCES (3/30/04)


APPENDIX I (3/30/04)

RTOG P-0014

SAMPLE CONSENT FOR RESEARCH STUDY

*Note: CTSU investigators must include the following text in the consent form: You will be entered onto this study as part of the Cancer Trials Support Unit (CTSU), a pilot project sponsored by the National Cancer Institute (NCI) to provide physicians and patients with greater access to NCI-sponsored phase III clinical trials.

PHASE III RANDOMIZED STUDY OF PATIENTS WITH HIGH RISK, HORMONE-NAÏVE PROSTATE CANCER: ANDROGEN BLOCKADE WITH 4 CYCLES OF IMMEDIATE CHEMOTHERAPY VERSUS ANDROGEN BLOCKADE WITH DELAYED CHEMOTHERAPY

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends and family. The National Cancer Institute (NCI) booklet, “Taking Part in Clinical Trials: What Cancer Patients Need To Know,” is available from your doctor.

You are being asked to take part in this study because you have prostate cancer that has failed local treatment and has most likely spread outside of the prostate.

WHY IS THIS STUDY BEING DONE?

The standard treatment for this stage of prostate cancer is hormone therapy. In this study all patients will receive hormones plus chemotherapy. The purpose of this study is to find out if having chemotherapy at the same time as hormone therapy is better than having chemotherapy when hormone therapy is no longer working. In addition, the effects (good and bad) of the hormone plus chemotherapy on you and your prostate cancer will be studied.

This research is being done because it is not known whether the addition of chemotherapy is worthwhile, whether the timing of the chemotherapy makes a difference, or which chemotherapy plan described above is better. This research study is being conducted by the Radiation Therapy Oncology Group and by the Cancer Trials Support Unit.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY

About 1050 people will take part in this study.
WHAT IS INVOLVED IN THE STUDY?

You will be “randomized” into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. A computer will determine into which group you are placed. You will have an equal chance of being placed in one of the following groups:

**Treatment 1 (3/30/04)**

If you are randomized to this treatment, you will receive hormone therapy and at the start of hormone therapy, you also will receive chemotherapy drugs for about 3-4 months.

You will receive one of the commercial hormone treatments currently being used for your condition for the rest of your life. In addition, you will take another hormone, either Eulexin or Casodex capsules for at least one month. Your doctor will recommend which hormone is best for you and for how long you will receive it.

The form of the commercial hormone treatment you will receive depends upon which one your doctor chooses to give you. If you are given Eulexin, you will take six (6) pills by mouth every day. If you are given Casodex, you will take one (1) pill by mouth every day. It is important that you take Casodex at the same time each day.

In addition to this hormonal therapy, you will receive four cycles of chemotherapy. Your doctor will discuss specific chemotherapy regimens with you. There are many available (for example, paclitaxel, docetaxel, doxorubicin, and vinblastine) that have been tested in patients with prostate cancer. These regimens appear to be generally similar in their chance of benefiting you, but most doctors have a preference for one or two specific combinations. Your doctor can recommend one that he/she prefers and feels would be suitable for you. Typical chemotherapy regimens include repeated injections in the vein of chemotherapy drugs weekly or every several weeks. These injections are usually done over a period of hours in a doctor’s office or hospital outpatient area. Injections can be combined with chemotherapy pills taken at home by mouth several times a day for repeated periods of anywhere from 5 to 21 days. The length of time that chemotherapy will continue depends upon which treatment you are given.

**Treatment 2 (3/30/04)**

If you are randomized to this treatment, you will receive the same hormone treatment described above in Treatment 1. However, you will not receive chemotherapy drugs at the start of hormone therapy. You will receive chemotherapy when there is evidence that hormone therapy is no longer controlling the cancer. This will be determined by how you feel, a positive bone scan or other x-ray test that shows cancer, or if a blood test for prostate specific antigen (PSA) starts to rise quickly.

You will receive four cycles of chemotherapy. Your doctor will discuss specific chemotherapy regimens with you. There are many available (for example, paclitaxel,
docetaxel, doxorubicin, and vinblastine) that have been tested in patients with prostate cancer. These regimens appear to be generally similar in their chance of benefiting you, but most doctors have a preference for one or two specific combinations. Your doctor can recommend one that he/she prefers and feels would be suitable for you. Typical chemotherapy regimens include repeated injections in the vein of chemotherapy drugs weekly or every several weeks. These injections are usually done over a period of hours in a doctor’s office or hospital outpatient area. Injections may be combined with chemotherapy pills taken at home by mouth several times a day for repeated periods of anywhere from 5 to 21 days. The length of time that chemotherapy will continue depends upon which treatment you are given.

If you take part in either treatment described above, you also will have the following tests and procedures:

- A physical examination prior to treatment, every 3 months during hormone therapy, prior to each cycle of chemotherapy, after chemotherapy is completed, then as your doctor feels it is necessary
- Blood tests prior to treatment, every 2 to 3 months during hormone therapy, prior to each cycle of chemotherapy, every month during chemotherapy, and after chemotherapy is completed
- X-ray studies, including a bone scan and a pelvic CT or MRI, will be done prior to treatment, annually, then as your doctor determines

It will be up to you and your doctor to decide on additional therapy, if additional therapy becomes necessary. Your doctor will ask you at times during treatment for the names of any alternative therapies, such as herbal medicines, that you are using. Some of these alternative therapies can affect PSA levels.

**HOW LONG WILL I BE IN THE STUDY? (3/30/04)**

You will receive chemotherapy for three to four months and hormone therapy for the rest of your life. You will see your doctor in follow-up visits at least every three months for the two years, every 6 months for three years and then annually for the rest of your life.

The researcher may decide to take you off this study if your doctor decides it is in your best interest, if side effects become very severe or your condition worsens, or if new information becomes available that indicates it is in your best interest.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.
WHAT ARE THE RISKS OF THE STUDY? (3/30/04)

While on the study, you are at risk for these side effects. You should discuss these with the researcher and/or your regular doctor. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the hormone and chemotherapy are stopped, but in some cases side effects can be serious or long-lasting or permanent.

The treatments in this study may interact with other drugs or medicines. Before starting any new medications, including herbal medicines or alternative therapies, you should tell your doctor.

Risks and side effects related to the drugs we are studying include:

**Hormones: LHRH Agonists such as leuprolide, goserelin, buserelin, triptorelin (3/30/04)**

*Very Likely*
- Hot flashes and sweating
- Dizziness
- Breast swelling and/or tenderness
- Inability to achieve an erection
- Increased difficulty urinating (in the first few weeks of treatment)

*Less Likely, but Serious*
- Unusual taste in the mouth
- Nausea and vomiting
- Increased thirst
- Increased urination
- Blood in urine
- Diarrhea
- Skin redness and/or hives
- Swelling in extremities
- Headache
- Mood swings
- Decreased memory
- Bone pain
- Irregular heartbeat and/or changes in blood pressure
- Liver not functioning properly
- Allergic reaction including a skin rash
- Difficulty breathing
- Heart failure
- Blood clots
Hormones: Eulexin and Casodex

*Very Likely*
- Hot flashes and sweating
- Breast swelling and/or tenderness
- Sexual dysfunction
- Fatigue
- Fluid retention
- Back pain

*Less Likely*
- Constipation
- Diarrhea
- Nausea
- Increased sensitivity to sunlight/ultraviolet light (Eulexin)

*Less Likely, but Serious*
- Changes in liver function; Symptoms could include: intense itching, yellow skin or eyes, loss of appetite, nausea and vomiting, abdominal tenderness, dark urine, “flu-like” symptoms. Your liver function will be checked every two months while you are taking this drug.
- Birth defects

*Rare*
- Severe liver damage leading to death (Eulexin)

Chemotherapy Drugs: Emcyt

*Very Likely*
- Breast tenderness
- Nausea and vomiting
- Swelling in the legs and/or arms

*Less Likely, but Serious*
- Lowering of blood counts leading to increased risk of infection, weakness, or bleeding complications
- Blood clots in the legs

*Rare*
- Blood clot in the lungs leading to shortness of breath and possibly, death
- Blood clot in the heart leading to a heart attack and possibly, death
- Blood clot in the brain leading to a stroke and possibly, death

Other Chemotherapy Drugs
Very Likely
- Hair loss
- Skin rash
- Changes to the nail beds
- Loss of appetite
- Taste changes
- Mouth sores
- Nausea and vomiting
- Diarrhea
- Fatigue
- Muscle aches and/or joint pain
- Blood in the urine
- Lowering of blood counts leading to increased risk of infection, weakness, or bleeding, which could have fatal complications
- Decreased sensation

Less Likely
- Sweating
- Fever and chills
- Headache
- Weight gain
- Muscle cramps
- Hives

Less Likely, but Serious
- Decreased vision, vision changes, or eye irritation
- Glaucoma and/or cataracts
- Dizziness
- Depression
- Seizures
- Muscle weakness
- Swelling in arms and legs
- Bone loss
- Irritation of skin at sites of prior radiation
- Damage to skin at the site of injection in the vein
- Slow wound healing
- Blood in urine
- Allergic reaction including skin rash and difficulty breathing
- Low blood pressure
- High blood sugars and/or imbalances of blood chemicals such as sodium or potassium
- Risk of developing leukemia, requiring treatment
- Shortness of breath
- Chest pain
- Slowing or irregular heart rhythm
- Heart damage
- Liver and kidney damage
[Less Likely, but Serious—specific for Adriamycin, taxol, or taxotere]
- Heart damage including changes in rhythm and poor pumping of blood

Ketoconazole

Very Likely
- Breast

Less Likely, but Serious
- Increase in liver enzymes
- Blood clots in the legs

Rare
- Serious liver injury, and possibly, death

Also, a warning has been issued about a drug interaction between ketoconazole and cisapride, possibly causing rapid beating or irregular rhythm of a chamber of the heart and possibly, death. In addition, a warning has been issued about a drug interaction between ketoconazole and astemizole, possibly causing irregular rhythm of a chamber of the heart.

Coumadin® (warfarin)

This medication helps decrease the clotting ability of the blood so that harmful blood clots do not form. Your doctor will determine if you should take this medicine and how often you should take it. Coumadin® is taken by mouth in tablet form. Your doctor should know what medications you are taking because certain medications do not react well with Coumadin®. Do not take any new medications without first discussing them with your doctor. While taking Coumadin®, you should avoid unusually large amounts of green, leafy vegetables in your diet. These foods are high in vitamin K, which helps your blood to clot.
The following risks are associated with taking Coumadin®:

**Less Likely**
- Abdominal gas, pain, or cramping
- Nausea and/or vomiting
- Diarrhea
- Headache
- Dizziness
- Taste disturbances
- Skin problems, such as rash, itching, and/or swelling
- Inability to tolerate cold, tiredness, and weakness

**Less Likely, but Serious**
- Allergic reaction including skin rash and difficulty breathing
- Excessive bleeding in any tissue or organ
- Necrosis (death of tissue) and/or gangrene (death of tissue due to lack of blood supply)
- Liver damage

Reproductive risks: Because the drugs in this study can affect an unborn baby, you should not father a baby while on this study. You must use adequate birth control measures to prevent pregnancy while participating in this study.

**ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

If you agree to take part in this study, there may or may not be direct medical benefit to you. It is not known whether the hormones and chemotherapy you will receive in this study will help your condition more than hormone therapy alone. A possible benefit of this study may be a decrease in the size of your tumor and longer survival, but these benefits are not certain or guaranteed. We hope the information learned from this study will benefit other patients with prostate cancer in the future.

**WHAT OTHER OPTIONS ARE THERE?**

You may choose to not participate in this study. Other treatments that could be considered for your condition may include the following: (1) hormone therapy or (2) no treatment except medications to make you feel better. With the latter choice, your tumor would continue to grow and your disease would spread. If you decide not to participate in this study, you still could receive hormone therapy similar to the therapy described above or a combination of hormones and chemotherapy.
Your doctor can tell you more about your condition and the possible benefits of the different available treatments.

Please talk to your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as the Food and Drug Administration (FDA), the National Cancer Institute (NCI) or its authorized representatives, the Cancer Trials Support Unit (CTSU), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study.

WHAT ARE THE COSTS?

Taking part in this study may lead to added costs to you or your insurance company. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization. (Medicare is considered a health insurance provider.)

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. If you choose to stop participating in the study, you should first discuss this with your doctor. In order to provide
important information that may add to the analysis of the study, he/she may ask your permission to submit follow-up data as it relates to the study. You may accept or refuse this request. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

**WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?**
*(This section must be completed)*

For information about your disease and research-related injury, you may contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For information about this study, you may contact:

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For information about your rights as a research subject, you may contact:

*(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)*

<table>
<thead>
<tr>
<th>Name</th>
<th>Telephone Number</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

You also may call the Project Office of the NCI Central Institutional Review Board (CIRB) at 1-888-549-0715 (from the continental U.S. only) or 1-800-937-8281, ext. 4445 (from sites outside the continental U.S.)

**WHERE CAN I GET MORE INFORMATION? (3/30/04)**

You may call the NCI’s Cancer Information Service at 1–800–4–CANCER (1–800–422–6237) or TTY: 1–800–332–8615
Visit the NCI’s Web sites for comprehensive clinical trials information at
www.cancer.gov/clinicaltrials
or
for accurate cancer information including PDQ
www.cancer.gov/cancerinfo/pdq
CancerFAX: Includes information about cancer treatment, screening, prevention, and supportive care. To obtain a contents list, dial 301-402-5874 or 1-800-624-2511 from a fax machine handset and follow the recorded instructions.

SIGNATURE

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol (full study plan).

______________________________  _________________________
Patient Signature (or legal Representative)  Date
APPENDIX II

KARNOFSKY PERFORMANCE SCALE

| 100 | Normal; no complaints; no evidence of disease |
| 90  | Able to carry on normal activity; minor signs or symptoms of disease |
| 80  | Normal activity with effort; some sign or symptoms of disease |
| 70  | Cares for self; unable to carry on normal activity or do active work |
| 60  | Requires occasional assistance, but is able to care for most personal needs |
| 50  | Requires considerable assistance and frequent medical care |
| 40  | Disabled; requires special care and assistance |
| 30  | Severely disabled; hospitalization is indicated, although death not imminent |
| 20  | Very sick; hospitalization necessary; active support treatment is necessary |
| 10  | Moribund; fatal processes progressing rapidly |
| 0   | Dead |

ZUBROD PERFORMANCE SCALE

| 0   | Fully active, able to carry on all predisease activities without restriction *(Karnofsky 90-100).* |
| 1   | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work *(Karnofsky 70-80).* |
| 2   | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours *(Karnofsky 50-60).* |
| 3   | Capable of only limited self-care, confined to bed or chair 50% or more of waking hours *(Karnofsky 30-40).* |
| 4   | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair *(Karnofsky 10-20).* |
APPENDIX III

AJCC STAGING SYSTEM
PROSTATE, 5th Edition

DEFINITION OF TNM

**Primary Tumor, Clinical (T)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1</td>
<td>Clinically inapparent tumor not palpable or visible by imaging</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor incidental histologic finding in 5% or less of tissue resected</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor incidental histologic finding in more than 5% of tissue resected</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor identified by needle biopsy <em>(e.g., because of elevated PSA)</em></td>
</tr>
<tr>
<td>T2</td>
<td>Tumor confined with prostate*</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor involves one lobe</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor involves both lobes</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor extends through prostate capsule**</td>
</tr>
<tr>
<td>T3a</td>
<td>Extracapsular extension <em>(unilateral or bilateral)</em></td>
</tr>
<tr>
<td>T3b</td>
<td>Tumor involves the seminal vesicle(s)</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor is fixed or invades adjacent structures other than the seminal vesicles: bladder neck, external sphincter, rectum, levator muscles and/or pelvic wall</td>
</tr>
</tbody>
</table>

*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c

**Note: Invasion into the prostatic apex or into *(but not beyond)* the prostatic capsule is not classified as T3, but as T2.

**Regional Lymph Nodes (N)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in regional lymph node or nodes</td>
</tr>
</tbody>
</table>

**Primary Tumor, Pathologic (pT)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>pT2</td>
<td>Organ confined</td>
</tr>
<tr>
<td>pT2a</td>
<td>Unilateral</td>
</tr>
<tr>
<td>pT2b</td>
<td>Bilateral</td>
</tr>
<tr>
<td>pT3</td>
<td>Extraprostatic extension</td>
</tr>
<tr>
<td>pT3a</td>
<td>Extraprostatic extension</td>
</tr>
<tr>
<td>pT3b</td>
<td>Seminal vesicle invasion</td>
</tr>
<tr>
<td>pT4</td>
<td>Invasion of bladder, rectum</td>
</tr>
</tbody>
</table>

***Note: There is no pathologic T1 classification

**Distant Metastasis*** (M)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Presence of distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
</tbody>
</table>
### APPENDIX III (continued)

#### AJCC STAGING SYSTEM

**PROSTATE, 5th Edition**

<table>
<thead>
<tr>
<th>M1</th>
<th>Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1a</td>
<td>Non regional lymph node(s)</td>
</tr>
<tr>
<td>M1b</td>
<td>Bone(s)</td>
</tr>
<tr>
<td>M1c</td>
<td>Other site(s)</td>
</tr>
</tbody>
</table>

****Note: When more than one site of metastasis is present, the most advanced category is used. pM1c is most advanced****

**Histopathologic Grade (G)**

- **GX**: Grade cannot be assessed
- **G1**: Well-differentiated (*slight anaplasia*)
- **G2**: Moderately differentiated (*moderate anaplasia*)
- **G3-4**: Poorly undifferentiated or undifferentiated (*marked anaplasia*)

**Stage Grouping**

<table>
<thead>
<tr>
<th>Stage I</th>
<th>T1a</th>
<th>N0</th>
<th>M0</th>
<th>G1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage II</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
<td>G2, G3-4</td>
</tr>
<tr>
<td></td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td></td>
<td>T1c</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N0</td>
<td>N0</td>
<td>Any G</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td>Stage IV</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N1,</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>Any G</td>
</tr>
</tbody>
</table>

---

44
<table>
<thead>
<tr>
<th>ORGAN TISSUE</th>
<th>GRADE 1</th>
<th>GRADE 2</th>
<th>GRADE 3</th>
<th>GRADE 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SKIN</td>
<td>None</td>
<td>Slight atrophy; Pigmentation change; Some hair loss</td>
<td>Patch atrophy; Moderate telangiectasia; Total hair loss</td>
<td>Marked atrophy; Gross telangiectasia</td>
</tr>
<tr>
<td>SUBCUTANEOUS TISSUE</td>
<td>None</td>
<td>Slight induration (fibrosis) and loss of subcutaneous fat</td>
<td>Moderate fibrosis but asymptomatic; Slight field contracture; &lt;10% linear reduction</td>
<td>Severe induration and loss of subcutaneous tissue; Field contracture &gt; 10% linear measurement</td>
</tr>
<tr>
<td>MUCOUS MEMBRANE</td>
<td>None</td>
<td>Slight atrophy and dryness</td>
<td>Moderate atrophy and telangiectasia; Little mucous</td>
<td>Marked atrophy with complete dryness; Severe telangiectasia</td>
</tr>
<tr>
<td>SALIVARY GLANDS</td>
<td>None</td>
<td>Slight dryness of mouth; Good response on stimulation</td>
<td>Moderate dryness of mouth; Poor response on stimulation</td>
<td>Complete dryness of mouth; No response on stimulation</td>
</tr>
<tr>
<td>SPINAL CORD</td>
<td>None</td>
<td>Mild L’Hermitte’s syndrome</td>
<td>Severe L’Hermitte’s syndrome</td>
<td>Objective neurological findings at or below cord level treated</td>
</tr>
<tr>
<td>BRAIN</td>
<td>None</td>
<td>Mild headache; Slight lethargy</td>
<td>Moderate headache; Great lethargy</td>
<td>Severe headaches; Severe CNS dysfunction (partial loss of power or dyskinesia)</td>
</tr>
<tr>
<td>EYE</td>
<td>None</td>
<td>Asymptomatic cataract; Minor corneal ulceration or keratitis</td>
<td>Symptomatic cataract; Moderate corneal ulceration; Minor retinopathy or glaucoma</td>
<td>Severe keratitis; Severe retinopathy or detachment</td>
</tr>
<tr>
<td>LARYNX</td>
<td>None</td>
<td>Hoarseness; Slight arytenoid edema</td>
<td>Moderate arytenoid edema; Chondritis</td>
<td>Severe edema; Severe chondritis</td>
</tr>
<tr>
<td>LUNG</td>
<td>None</td>
<td>Asymptomatic or mild symptoms (dry cough); Slight radiographic appearances</td>
<td>Moderate symptomatic fibrosis or pneumonitis (severe cough); Low grade fever; Patchy radiographic appearances</td>
<td>Severe symptomatic fibrosis or pneumonitis; Dense radiographic changes</td>
</tr>
<tr>
<td>HEART</td>
<td>None</td>
<td>Asymptomatic or mild symptoms; Transient T wave inversion &amp; ST Changes; Sinus tachycardia &gt;110 (at rest)</td>
<td>Moderate angina on effort; Mild pericarditis; Normal heart size; Persistent abnormal T wave and ST changes ; Low ORS</td>
<td>Severe angina; Pericardial effusion; Constrictive pericarditis; Moderate heart failure; Cardiac enlargement; EKG abnormalities</td>
</tr>
<tr>
<td>ESOPHAGUS</td>
<td>None</td>
<td>Mild fibrosis; Slight difficulty in swallowing solids; No pain on swallowing</td>
<td>Unable to take solid food normally; Swallowing semi-solid food; Dilation may be indicated</td>
<td>Severe fibrosis; Able to swallow only liquids; May have pain on swallowing</td>
</tr>
<tr>
<td>SMALL/LARGE INTESTINE</td>
<td>None</td>
<td>Mild diarrhea; Mild cramping; Bowel movement 5 times daily Slight rectal discharge or bleeding</td>
<td>Moderate diarrhea and colic; Bowel movement &gt;5 times daily; Excessive rectal mucus or intermittent bleeding</td>
<td>Obstruction or bleeding, requiring surgery</td>
</tr>
<tr>
<td>LIVER</td>
<td>None</td>
<td>Mild lassitude; Nausea, dyspepsia; Slightly abnormal liver function</td>
<td>Moderate symptoms; Some abnormal liver; function tests; Serum albumin normal</td>
<td>Disabling hepatic insufficiency; Liver function tests grossly abnormal; Low albumin; Edema or ascites</td>
</tr>
<tr>
<td>KIDNEY</td>
<td>None</td>
<td>Transient albuminuria; No hypertension; Mild impairment of renal function; Urea 25-35 mg%;Creatinine 1.5-2.0 mg%; Creatinine clearance &gt; 75%</td>
<td>Persistent moderate albuminuria (2+); Mild hypertension; No related anemia; Moderate impairment of renal function; Urea &gt;36-60mg% Creatinine clearance (50-74%)</td>
<td>Severe albuminuria; Severe hypertension Persistent anemia (&lt; 10%); Severe renal failure; Urea &gt;60 mg% Creatinine &gt;4.0 mg% Creatinine clearance &lt; 50%</td>
</tr>
<tr>
<td>BLADDER</td>
<td>None</td>
<td>Slight epithelial atrophy; Minor telangiectasia (microscopic hematuria)</td>
<td>Moderate frequency; Generalized telangiectasia; Intermittent macroscopic hematuria</td>
<td>Severe frequency &amp; dysuria Severe generalized telangiectasia (often with petechiae); Frequent hematuria; Reduction in bladder capacity (&lt; 150 cc)</td>
</tr>
<tr>
<td>BONE</td>
<td>None</td>
<td>Asymptomatic; No growth retardation; Reduced bone Density</td>
<td>Moderate pain or tenderness; Growth retardation; Irregular bone sclerosis</td>
<td>Severe pain or tenderness; Complete arrest of bone growth; Dense bone sclerosis</td>
</tr>
<tr>
<td>JOINT</td>
<td>None</td>
<td>Mild joint stiffness; Slight limitation of movement</td>
<td>Moderate stiffness; Intermittent or moderate joint pain; Moderate limitation of movement</td>
<td>Severe joint stiffness; Pain with severe limitation of movement</td>
</tr>
</tbody>
</table>
APPENDIX V

ADVERSE EVENT REPORTING GUIDELINES

Federal Regulations require that investigators report adverse events and reactions in a timely manner. This reporting improves patient care and scientific communication by providing information to the National Cancer Institute (NCI) whereby new findings can be more widely disseminated to investigators and scientists.

A. Definitions and Terminology

An adverse event is defined as an undesirable, unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. This may be a new event that was not pre-existing at initiation of treatment, a pre-existing event that recurs with increased intensity or frequency subsequent to commencement of treatment or an event, though present at the commencement of treatment, becomes more severe following initiation of treatment. These undesirable effects may be classified as “known or expected” or “unknown or unexpected”.

Known/expected events are those that have been previously identified as having resulted from administration of the agent or treatment. They may be identified in the literature, the protocol, the consent form, or noted in the drug insert. Unknown/unexpected events are those thought to have resulted from the agent, e.g. temporal relationship but not previously identified as a known effect.

Assessment of Attribution

In evaluating whether an adverse event is related to a procedure or treatment, the following attribution categories are utilized:

- **Definite**: The adverse event is clearly related to the treatment/procedure.
- **Probable**: The adverse event is likely related to the treatment/procedure.
- **Possible**: The adverse event may be related to the treatment/procedure.
- **Unlikely**: The adverse event is doubtfully related to the treatment/procedure.
- **Unrelated**: The adverse event is clearly NOT related to the treatment/procedure.

B. Grading of Adverse Events

Unless specified otherwise, the NCI Common Toxicity Criteria (CTC) version 2.0 is used to grade severity of adverse events. Protocols approved prior to March 1998 will use one of several different morbidity grading systems. To grade severity of adverse events in studies prior to this date, consult the protocol document for the appropriate rating system.

C. General Guidelines

In order to assure prompt and complete reporting of adverse events and toxicity, the following general guidelines must be observed. The guidelines apply to all RTOG studies. When protocol-specific guidelines indicate more intense monitoring than the standard guidelines, the study-specific reporting procedures supersede the General Guidelines. A protocol may stipulate that specific grade 4 events attributable to treatment are expected and therefore may not require the standard reporting; however, exceptions to standard reporting must be specified in the text of the protocol.

1. The Principal Investigator will report to the RTOG Group Chair, to the Headquarters Data Management Staff (215/574-3214) and to the Study Chair within 24 hours of discovery, the details of all unexpected severe, life-threatening (grade 4) and fatal (grade 5) adverse events if there is reasonable suspicion that the event was definitely, probably, or possibly related to protocol treatment.

2. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of attribution require telephone notification within 24 hours of discovery.

3. A written report, including all relevant clinical information and all study forms due up to and including the date of the event, will be sent by mail or FAX (215/928-0153) to RTOG Headquarters within 10 working days of the telephone report (unless specified otherwise within the protocol). The material must be labeled: ATTENTION: Adverse Event Reporting.

a. The Group Chair in consultation with the Study Chair will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this is warranted.
b. For events that require telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB), the Food and Drug Administration (FDA), to another co-operative group or to the study sponsor, the investigator may first call RTOG (as outlined above) unless this will unduly delay the required notification process.

A copy of all correspondence sent to recipients of the call, e.g. NCI, IDB, another cooperative group office (non-RTOG coordinated studies) must be submitted to RTOG Headquarters. **Copies must include the RTOG study and case numbers.**

4. When participating in non-RTOG coordinated intergroup studies or in RTOG sponsored pharmaceutical studies, the investigator must comply with the reporting specification required in the protocol.

5. Institutions must comply with their individual Institutional Review Board policy regarding submission of documentation of adverse events. All “expedited” adverse event reports should be sent to the local Institutional Review Board (IRB).

6. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

7. When submitting reports and supporting documentation for reports to RTOG on an RTOG protocol patient, **the study number and the case number must be recorded** so that the case may be associated with the appropriate study file. This includes submission of copies of FDA Form 3500 (MedWatch).

8. All data collection forms through the date of the reported event and the applicable reporting form are submitted to RTOG Headquarters data management department (Attention: Adverse Event) **within 10 working days** of the telephone report or sooner if specified by the protocol. Documentation must include an assessment of attribution by the investigator as previously described in section A.

9. MedWatch Forms (FDA 3500) submitted on RTOG protocol patients must be signed by the Principal Investigator.

10. All neuro-toxicity (≥ grade 3) from radiosensitizer or radioprotector drugs are to be reported to RTOG Headquarters Data Management, to the Group Chair, and to the Study Chair within 10 days of discovery.

**D. Adverse Event Reporting Related to Radiation Therapy**

1. All fatal events resulting from protocol radiation therapy must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management department and to the radiation therapy protocol Study Chair within 24 hours of discovery.

2. All grade 4, (CTC v 2.0 and RTOG/EORTC Late Radiation Morbidity Scoring Scheme Criteria) and life-threatening events (an event, which in view of the investigator, places the patient at immediate risk of death from the reaction) and grade 4 toxicity that is related, possibly related or probably related to protocol treatment using non-standard fractionated radiation therapy, brachytherapy, radiopharmaceuticals, high LET radiation, and radiosurgery must be reported by telephone to the Group Chair, to RTOG Headquarters Data Management and to the radiation therapy Study Chair within 24 hours of discovery. Expected grade 4 adverse events may be excluded from telephone reporting if specifically stated in the protocol.

3. All applicable data forms and if requested, a written report, must be submitted to RTOG Headquarters within 10 working days of the telephone call.

**E. Adverse Event Reporting Related to Systemic Anticancer Agents**

Adverse drug reactions (ADRs) are adverse events that are related to an anticancer agent and meet certain criteria: are unexpected effects of the drug or agent, or are severe (grade 3), life-threatening (grade 4), or fatal (grade 5), even if the type of event has been previously noted to have occurred with the agent.

1. **Commercial Agents/Non-Investigational Agents**

<table>
<thead>
<tr>
<th>Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite</th>
<th>Increased Incidence of an Expected AE(^1)</th>
<th>Hospitalization During Treatment(^2)</th>
<th>Secondary AML/MDS(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Form 3500(^1,3)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. Any increased incidence of a known AE.
2. Inpatient hospitalizations or prolongation of existing hospitalization for medical events equivalent to CTC Grade 3-5 which precipitated hospitalization must be reported regardless of the requirements or phase of study, expected or unexpected and attribution.
3. Reporting required during or subsequent to protocol treatment.
4. Submitted to Investigational Drug Branch, PO Box 30012, Bethesda, MD 20924-0012.
6. All grade 5 known toxicity.
7. Call RTOG Data Management (215) 574-3214. To leave a voice mail message when the office is closed, announce that you’re reporting an “adverse event”, provide your name, institution number, and a telephone number where you may be contacted.

2. Investigational Agents
An investigational agent is one sponsored under an Investigational New Drug Application (IND). Reporting requirements and timing are dependent on the phase of the trial, grade, attribution and whether the event is expected or unexpected as determined by the NCI Agent Specific Expected Adverse Event List, protocol and/or Investigator’s Brochure. An expedited adverse event report requires submission to CTEP via AdEERS (Adverse Event Expedited Report). See the CTEP Home Page, http://ctep.info.nih.gov for complete details and copies of the report forms.

a. AdEERS (Adverse Event Expedited Reporting System)
Effective January 1, 2001, the NCI Adverse Event Expedited Reporting System (AdEERS) was implemented for all protocols for which NCI is the supplier of an investigational agent.

Attribution: An expedited report is required for all unexpected and expected Grade 4 and Grade 5 adverse events regardless of attribution for any phase of trial. An expedited report is required for unexpected Grade 2 and Grade 3 adverse events with an attribution of possible, probable or definite for any phase of trial. An expedited report is not required for unexpected or expected Grade 1 adverse events for any phase of the trial.

RTOG uses “decentralized” notification. This means that all reportable events will be directly reported to NCI, just as has been done with paper-based reporting. AdEERS is an electronic reporting system; therefore, all events that meet the criteria must be reported through the AdEERS web application. Once the report is filed with AdEERS, the institution need not send notification to RTOG, as the AdEERS system will notify the Group Office. Institutions that utilize this application are able to print the report for local distribution, i.e., IRB, etc.

For institutions without Internet access, if RTOG is the coordinating group for the study, contact RTOG Data Management (215-574-3214) to arrange for AdEERS reporting. In these instances, the appropriate Adverse Event Expedited Report template (Single or Multiple Agents) must be completed. The template must be fully completed and in compliance with the instruction manual; i.e., all mandatory sections must be completed including coding of relevant list of value (LOV) fields before sending to RTOG. Incomplete or improperly completed templates will be returned to the investigator. This will delay submission and will reflect on the timeliness of the investigators’ reporting. A copy of the form sent to RTOG must be kept at the site if local distribution is required. Do not send the template without first calling the number noted above.

Templates for Single or Multiple Agents may be printed from the CTEP web page or will be supplied from the RTOG Registrar upon faxed request (FAX) (215) 574-0300.

When reporting an event on a patient in an RTOG-coordinated study, you must record the RTOG case number in the Patient ID field.

AdEERS reporting does not replace or obviate any of the required telephone reporting procedures.
Investigational Agent(s) used in a Clinical Trial Involving a Commercial Agent(s) on separate arms: An expedited adverse event report should be submitted for an investigational agent(s) used in a clinical trial involving a commercial agent(s) on a separate arm only if the event is specifically associated with the investigational agent(s).
Investigational Agent(s) used in a Clinical Trial in Combination with a Commercial Agent(s): **When an investigational agent(s) supplied under an NCI-sponsored IND is used in combination with a commercial agent(s), the combination should be considered investigational and reporting should follow the guidelines for investigational agents.**

b. **Expedited Reporting for Phase 1 Studies**

<table>
<thead>
<tr>
<th>Unexpected Event</th>
<th>Expected Event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grades 2-3</strong></td>
<td><strong>Grades 4 &amp; 5</strong></td>
</tr>
<tr>
<td>Attribution: Possible, Probable or Definite</td>
<td>Regardless of Attribution</td>
</tr>
<tr>
<td>Report by phone to IDB(^{1,2}) within 24 hrs. Expedited report to follow within 10 working days.</td>
<td><strong>Grades 1 - 3</strong></td>
</tr>
<tr>
<td>This includes deaths within 30 days of the last dose of treatment with an investigational agent.</td>
<td><strong>Grades 4 &amp; 5</strong></td>
</tr>
<tr>
<td><strong>Grades 4 &amp; 5</strong> Regardless of Attribution</td>
<td><strong>Grades 4 &amp; 5</strong> Regardless of Attribution</td>
</tr>
<tr>
<td>Report by phone to IDB(^{1,2}) within 24 hrs. Expedited report to follow within 10 working days.</td>
<td>Adverse Event Expedited Reporting NOT required.</td>
</tr>
<tr>
<td></td>
<td>Expedited report to follow within 10 working days.</td>
</tr>
</tbody>
</table>

1. Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you’re reporting an “adverse event”, provide your name, institution number and a telephone number where you may be contacted.

2. Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).

c. **Expedited Reporting for Phase 2 and Phase 3 Studies**

<table>
<thead>
<tr>
<th>Unexpected Event</th>
<th>Expected Event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grades 2-3</strong></td>
<td><strong>Grades 4 &amp; 5</strong></td>
</tr>
<tr>
<td>Attribution: Possible, Probable or Definite</td>
<td>Regardless of Attribution</td>
</tr>
<tr>
<td>Expedited report within 10 working days.</td>
<td><strong>Grades 1 - 3</strong></td>
</tr>
<tr>
<td><strong>Grades 4 &amp; 5</strong></td>
<td><strong>Grades 4 &amp; 5</strong></td>
</tr>
<tr>
<td>Regardless of Attribution</td>
<td>Regardless of Attribution</td>
</tr>
<tr>
<td>Expedited including Grade 5 aplasia in leukemia patients within 10 working days. Grade 4 myelosuppression not to be reported, but should be submitted as part of study results. Other Grade 4 events that do not require expedited reporting would be specified in the protocol.</td>
<td><strong>Grades 4 &amp; 5</strong></td>
</tr>
<tr>
<td>Expedited report to follow within 10 working days.</td>
<td>Regardless of Attribution</td>
</tr>
<tr>
<td></td>
<td>Expedited report within 24 hrs.</td>
</tr>
</tbody>
</table>

1. Report by telephone to RTOG Data Management (215) 574-3214, to the Group Chair and to the Study Chair. To leave a voice mail message with RTOG when the office is closed, announce that you’re reporting an “adverse event”, provide your name, institution number and a telephone number where you may be contacted.

2. Telephone reports to IDB (301) 230-2330 available 24 hours a day (recorder after 5 PM to 9 AM ET).
APPENDIX VI

CTSU Logistics for P-0014

Cancer Trials Support Unit

<table>
<thead>
<tr>
<th>For patient enrollments or to report adverse events:</th>
<th>To mail forms or data:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phone – 1-888-462-3009</td>
<td>CTSU Data Processing Manager</td>
</tr>
<tr>
<td>Fax – 1-888-691-8039</td>
<td>Westat</td>
</tr>
</tbody>
</table>

| CTSU Data Operations Center |
| 1441 W. Montgomery Avenue |
| Rockville, MD 20850-2062 |

All other questions (including forms-specific questions) should be communicated by phone or e-mail to:

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

CTSU public website is located at: www.ctsu.org

CTSU member website is located at http://members.ctsu.org

Registration Guidelines

**CTSU Investigators:**

Prior to the recruitment of a patient for this study, investigators and their institutions must be registered with the CTSU. Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit all IRB/regulatory documents to the CTSU before they can enroll patients. All forms and documents associated with this study can be downloaded from the P-0014 webpage on the CTSU member website (http://members.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and all pertinent forms and documents are approved and on file with the CTSU.

**CTSU Procedures for Patient Enrollment:** Contact the CTSU Patient Registration Office by calling 1-888-462-3009 to alert the CTSU Patient Registrar that an enrollment is forthcoming. Complete the following forms:

- CTSU Patient Enrollment Transmittal Form
- RTOG P-0014 Eligibility Checklist

Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 am and 4:30 p.m., Eastern time. The CTSU registrar will verify that the investigator is CTSU credentialed, that the enrollment forms are complete, and that all regulatory and patient eligibility requirements have been met. The CTSU registrar will follow up with the CTSU investigative site to resolve any discrepancies.

Once investigator and patient eligibility are confirmed, the CTSU registrar will contact the RTOG to obtain a randomization assignment and assignment of a unique patient ID. The CTSU registrar will then contact the enrolling site and convey the patient ID number (to be used on all future forms and correspondence) and the patient’s treatment assignment. An RTOG generated confirmation of registration e-mail will be forwarded by the CTSU to the enrolling site.

**Drug Information**

All agents for this study are commercially available in the United States. CTSU investigators should refer to the RTOG drug information section of the protocol for further details.
This study will utilize the CTC version 2.0 for toxicity and Adverse Event (AE) reporting. A link to the CTC guidelines is available on the CTSU website. CTSU investigators should employ definitions of adverse events as described in Section 7.15 of the protocol. All reporting should be conducted within the timeframes specified in the protocol. Reports and supporting documents must be submitted as outlined below:

**Submitting routine reports**

CTSU investigators should submit forms and supporting documents to the CTSU. The CTSU will then forward the information to RTOG.

**Submitting expedited reports**

**Treatment Arms Containing Commercial Agents Only:** Expedited reports are to be submitted to the CTSU (fax: 1-888-691-8039) within 10 working days of the event using form FDA Form #3500 (Medwatch). The CTSU will immediately forward any faxed reports to RTOG. RTOG will then distribute these documents internally and to the Investigational Drug Branch, CTEP, NCI, and the FDA.

For those adverse events requiring 24 hour phone notification, the CTSU investigator is responsible for reporting the event within 24 hours to the following persons/agencies:

- CTSU Data Center at 1-888-462-3009
- RTOG Headquarters at 215-574-3214
- NCI Investigational Drug Branch at (301) 230-2330

**Secondary AML/MDS reporting**

CTSU investigators will submit the NCI Secondary AML/MDS Report Form and supporting documentation to the CTSU. Once received, the CTSU will send this information to RTOG, and RTOG will forward it on to the IDB.

Your local Investigational Review Board must be informed of all reportable serious adverse reactions.

All adverse event reports submitted to the CTSU should be accompanied by a completed CTSU Data Transmittal Form.

**Forms Submission**

All data forms for this study are available for download from the RTOG P-0014 webpage located on the CTSU member website. CTSU investigators should use the protocol specific RTOG forms and adhere to the RTOG schedule for data submission.

Patient registration forms should be faxed to the CTSU Data Center (1-888-691-8039) according to instructions in the registration procedures section of the protocol.

All other forms are to be mailed directly to the CTSU Data Center at the address below. A CTSU Data Transmittal Form should accompany all forms and reports submitted to the CTSU. The CTSU will forward all information to the RTOG.

CTSU Data Processing Manager
Westat
CTSU Data Operations Center
1441 W. Montgomery Avenue
Rockville, MD 20850-2062