ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

CALGB 90203

A RANDOMIZED PHASE III STUDY OF NEO-ADJUVANT DOCETAXEL AND ANDROGEN DEPRIVATION PRIOR TO RADICAL PROSTATECTOMY VERSUS IMMEDIATE RADICAL PROSTATECTOMY IN PATIENTS WITH HIGH-RISK, CLINICALLY LOCALIZED PROSTATE CANCER

Commercial agent docetaxel (NSC #628503) distributed by CTEP, DCTD, NCI.

ClinicalTrials.gov Identifier: NCT00430183

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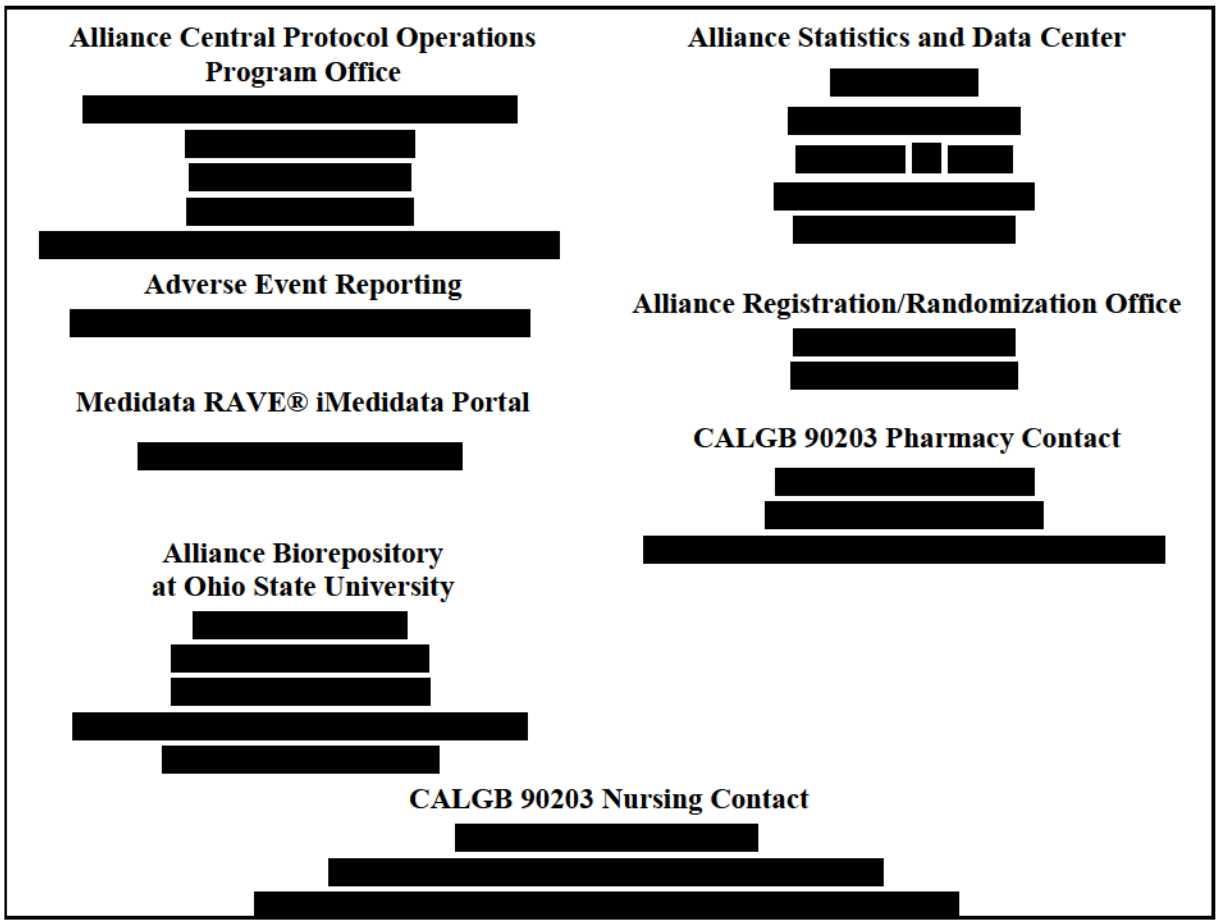
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CALGB 90203 Pharmacy Contact
[redacted]
Alliance Biorepository at Ohio State University
[redacted]
CALGB 90203 Nursing Contact
[redacted]

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] to receive further instruction and support. Contact the CTSU Regulatory Help Desk at [redacted] for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at [redacted].	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.		
For clinical questions (i.e. patient eligibility or treatment-related) see the Protocol Contacts, Page 2.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – [redacted]. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

A RANDOMIZED PHASE III STUDY OF NEO-ADJUVANT DOCETAXEL AND ANDROGEN DEPRIVATION PRIOR TO RADICAL PROSTATECTOMY VERSUS IMMEDIATE RADICAL PROSTATECTOMY IN PATIENTS WITH HIGH-RISK, CLINICALLY LOCALIZED PROSTATE CANCER

Patient Eligibility

Histologic documentation of prostatic adenocarcinoma

Patients with small cell, neuroendocrine, or transitional cell carcinomas are not eligible

No evidence of metastatic disease on cross sectional imaging and bone scan (see Sec. 4.2)

Patients must have EITHER:

1) a Kattan nomogram predicted probability of being disease free 5 years after surgery of < 60%
OR
2) Gleason sum ≥ 8 (see Sections 4.3 and 5.1)

Required Initial Laboratory Values	
ANC	≥ 1500/μL
Platelets	≥ 150,000/μL
Bilirubin	≤ ULN*
AST/ALT	≤ 1.5 x ULN
PSA	≤ 100 ng/mL
Creatinine	≤ 2.0 mg/dL

* See Section 4.9

No prior treatment for prostatic adenocarcinoma including prior surgery (excluding TURP), radiation therapy, or chemotherapy

Patients may have received up to 4 months of androgen deprivation prior to randomization.

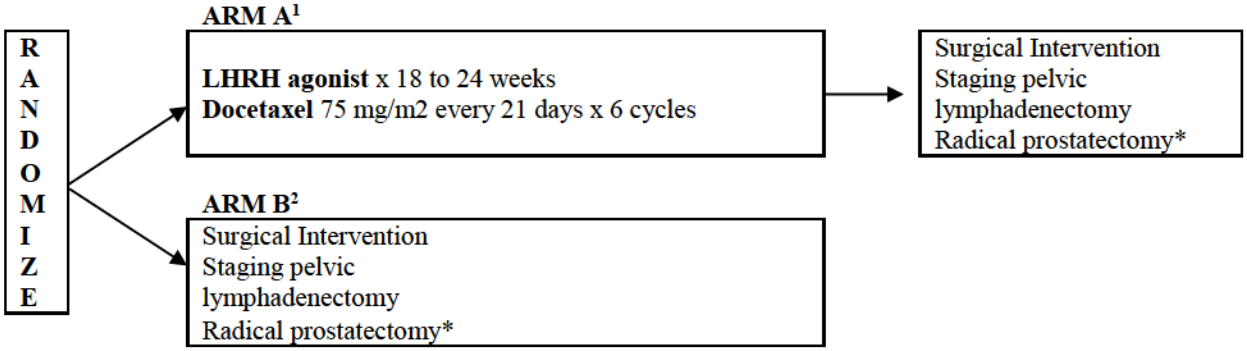
Patients must be appropriate candidates for radical prostatectomy (see Sec. 4.5)

Patients with a history of deep venous thrombosis, pulmonary embolism, and/or cerebrovascular accident or currently requiring systemic anticoagulation are eligible provided they are surgical candidates for radical prostatectomy.

ECOG performance status 0-2

≥ 18 years of age

Schema



1 Chemohormonal therapy is to begin within 14 days of randomization. Surgery will take place within 60 days following the completion of neoadjuvant therapy.

2 Surgery is to take place within 60 days of randomization.

* Patients with positive surgical margins, extraprostatic extension, and/or seminal vesicle invasion are allowed to receive adjuvant external beam radiation to the prostatic fossa at the discretion of the treating physician; adjuvant radiation must be initiated within 6 months of the date of surgery.

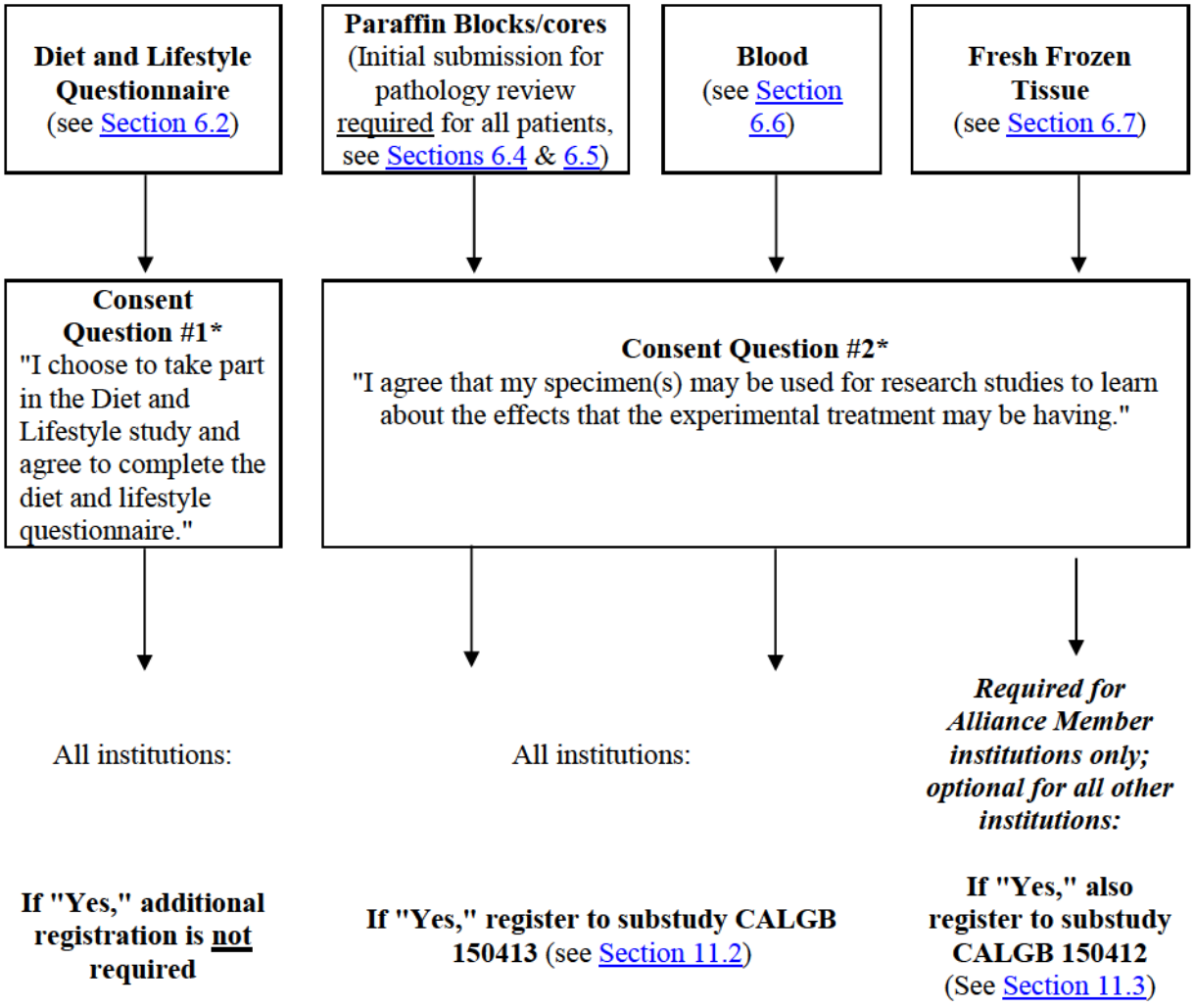
Patients in both arms who consent to participate will be asked to complete a diet and lifestyle questionnaire 3 months following surgery.

Nomogram probability: See Appendix III for information about calculating the nomogram predicted probability of 5-year progression-free survival.

Guide to Companion Study Registration

The following "roadmap" is meant to assist clinical research associates in companion study registration and sample procurement.

Type of Submission



* Please note that model informed consent questions are mapped to the OPEN registration system. As a result, it is highly recommended that the wording and order of the model informed consent questions be retained in order to facilitate patient registration.

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1.0 INTRODUCTION

1.1 Background and rationale

Prostate cancer is a heterogeneous disease. While disease progresses slowly with a prolonged natural history in some patients, others are destined for rapid progression and failure of definitive local therapy. (1) Some low risk patients may not be appropriate candidates for local therapy due to advanced age or co-morbid conditions. In contrast, patients with intermediate or high-risk disease characteristics may benefit from more extended local therapy or systemic treatments, respectively, to decrease risk of recurrence. Therefore, the goal of risk assessment in patients with localized prostate cancer is to distinguish between patients not requiring treatment, patients for whom local therapy alone produces long-term disease-free survival, and patients who require early initiation of systemic therapy due to a high likelihood of occult metastatic disease.

1.2 Identifying High-Risk Prostate Cancer Patients

There are a number of models or nomograms available to aid clinicians with pre-treatment risk assessment. For patients newly diagnosed with prostate cancer, there are three well-defined predictors of disease extent and outcome following treatment. These factors are clinical tumor stage, Gleason grades of the diagnostic biopsy specimen, and serum PSA level. However, each of these factors alone has not proven useful in predicting disease extent and outcome for an individual patient. Clinical staging by digital rectal examination may underestimate the presence of extracapsular disease extension in 30-50% of patients. (2) Although biopsy Gleason score may be helpful in predicting pathologic stage and outcome following treatment at either end of the spectrum (i.e. Gleason sum 2-4 or Gleason sum 7-10 tumors), it is not as helpful for the majority of patients who present with Gleason sum 5-8 tumors. In addition, the incidence of undergrading of the diagnostic biopsy specimen reaches 45% in some series. (2, 3) Finally, although serum PSA levels correlate with tumor volume and stage, the determination of serum PSA is also influenced by the volume of benign prostatic hyperplasia and the degree of tumor differentiation. In an effort to maximize the predictive value of each individual variable, several investigators have combined these variables into models that are designed to better predict pathologic tumor stage, the presence or absence of lymph node metastases and outcome following treatment. (4-6)

The nomogram developed by Kattan et al (4) predicts the probability that a man will remain free from disease recurrence for 5 years. It has been externally validated on over 6000 men treated at 7 different institutions spanning three continents (7) as well as in African-American men. (8) By computing a continuous probability of failure, the nomogram predicts outcome more accurately than by placing the patient into one of two or three risk groups (9, 10), a finding confirmed in other modalities (11, 12) and cancers (13-16). Work by Carroll and colleagues using the CapSURE database illustrates the heterogeneity of patients within a traditional risk group, which argues for the use of nomograms for more precise assessment of recurrence risk. In particular, this work illustrates that some patients in a traditional "high-risk" category are not of truly high risk when assessed by a more accurate approach (i.e., the nomogram), and that some patients in an "intermediate risk" group are actually high risk. Thus, using the nomogram to define eligibility should allow truly high risk patients to enroll on this trial while excluding those patients who are not of sufficient risk. Extensive details regarding the design of the nomogram are reported elsewhere. (17)

With use of the nomogram, a man's probability of recurrence can be calculated using clinical stage, primary and secondary Gleason grades, and serum PSA level immediately prior to prostate biopsy. High-risk patients will be defined as those having a less than 60% probability

of remaining free from recurrence 5 years after surgery as determined by the preoperative nomogram.

[Added with Update #3] When this study was conceptualized in 2002, approximately 15% of patients undergoing radical prostatectomy would have been eligible for this study using the Kattan Pre-Treatment Prostate Nomogram criteria (< 60% predicted probability of 5-year biochemical-free progression). Since that time, because of the earlier use of PSA high-risk prostate cancer patients are more likely to be identified because of biopsy Gleason score, rather than by PSA. However, risk definition in the Kattan nomogram is driven largely by PSA. Thus, in 2008, clinicians find that approximately 5% of patients undergoing radical prostatectomy meet the Kattan Nomogram-defined eligibility criteria for this study; a much smaller patient population than the 15% originally predicted. This reduced pool of potentially eligible patients led to a discussion of alternative characterizations of high-risk cancer by the CALGB GU Committee at the June 27th, 2008 Group Meeting. It was agreed to amend the eligibility criteria to add patients with Gleason score ≥ 8 on diagnostic prostate biopsy.

The rationale for this change is that patients with biopsy Gleason score ≥ 8 are certainly considered high-risk, having a reported biochemical recurrence rate 10 years after radical prostatectomy of 60-70%. The databases of two CALGB institutions have been examined to evaluate the 5 year bPFS rate after prostatectomy for Gleason score 8-10 patients (regardless of other features such as stage or PSA level.) These rates are 44% for Memorial Sloan-Kettering Cancer Center and 45% for the Roswell Park Cancer Institute. By including patients with biopsy Gleason score ≥ 8 in Update #3, eligibility will be expanded so that approximately 15% of patients undergoing surgery will be targeted for participation in this study. Since the Kattan nomogram definition of high risk will also remain an eligibility criterion, these patients will continue to be eligible for the study as well as those patients enrolled prior to the approval of Update #3.

1.3 Neoadjuvant Treatment Prior To Radical Prostatectomy [RP]

While it is apparent that local therapy alone is inadequate for many patients with high-risk, clinically localized prostate cancer, the optimal treatment strategy has not yet been defined. For high-risk patients choosing external beam radiation, the use of neoadjuvant and/or concomitant androgen deprivation appears to have had a beneficial impact on disease-free and overall survival in several published studies. (18) Unfortunately, this has not been the case for patients undergoing radical prostatectomy. The objectives of neoadjuvant androgen deprivation prior to radical prostatectomy include stage reduction ("downstaging"), decreasing the incidence of positive surgical margins, and effecting salutary changes in long-term local and distant cancer recurrence rates with the ultimate goal of improving cancer-specific survival. There have been more than 20 published studies evaluating neoadjuvant androgen deprivation in patients with clinical stage T3 prostate cancer undergoing radical prostatectomy. (19) While effective in decreasing serum PSA and prostate volume, there have been conflicting results with respect to downstaging and there has been no apparent benefit in disease-free survival. Neoadjuvant androgen deprivation has also been tested in a variety of phase II and III studies of patients with clinically localized (stage T1-2) prostate cancer in an attempt to decrease positive surgical margin rates and improve biochemical disease-free survival. (20-23) While all series to date have reported significantly lower positive surgical margin rates in those receiving neoadjuvant androgen deprivation, this reduction has not translated into better biochemical disease-free survival. There are several possible explanations for this discrepancy. First, these studies were designed to detect differences in positive margin rates and, therefore, may not have been powered to detect differences in biochemical disease-free survival. Second, too many low-risk patients may have been included in these studies. Third, the duration of neoadjuvant therapy, usually 3 months, may have been too short. Recent studies suggest that serum PSA continues to

decrease for as long as 8 months after the initiation of neoadjuvant androgen deprivation, (24) providing the impetus for a randomized, phase III study of 3 versus 8 months of neoadjuvant androgen deprivation prior to radical prostatectomy by the Canadian Urologic Oncology Group. However, preliminary results from this trial also suggest no significant impact of long-term androgen deprivation on long term outcomes. Fourth, most studies have suffered from short follow-up times. Finally, neoadjuvant androgen deprivation alone may provide no benefit over surgery alone for patients with clinically localized prostate cancer.

An alternative to neoadjuvant androgen deprivation would be the addition of early cytotoxic chemotherapy prior to local therapy for patients with high-risk prostate cancer. Systemic chemotherapy, long believed to be ineffective in men with prostate cancer, has more recently been shown to improve quality of life, cause measurable disease and PSA responses, and improve survival in men with hormone-refractory prostate cancer (HRPC). (25-27) Moreover, recent studies have demonstrated the feasibility of neoadjuvant chemotherapy prior to radical prostatectomy in high-risk prostate cancer patients (see below). If such a strategy was shown to be effective, future clinical practice could be altered significantly, as there is currently no accepted treatment strategy for patients with high-risk disease characteristics, and failure rates with local therapy alone remain high. The goal of such treatment is to prolong disease-specific and overall survival in patients at high risk for disease progression despite local therapy.

1.4 Taxane-based Chemotherapy in Advanced Prostate Cancer

Prior studies have demonstrated the effectiveness of chemotherapy in patients with advanced prostate cancer and the feasibility of administering chemotherapy in the neoadjuvant setting prior to radical prostatectomy. Randomized trials performed in both the United States and Canada using corticosteroids, with or without mitoxantrone, have shown that these regimens improve quality of life endpoints in patients with hormone-refractory prostate cancer (HRPC). (25, 27) More recently, taxane-based regimens have shown anti-tumor activity in men with advanced prostate cancer. Estramustine (EMP) dysregulates normal microtubule assembly, resulting in growth inhibition in human prostate cancer cell lines. (28-32) Moreover, estramustine has estrogenic effects that produces anorchid levels of testosterone similar to other forms of medical or surgical castration. (33) Although estramustine as a single agent appears to have limited anti-tumor activity in men with HRPC, prior studies suggest that estramustine may act synergistically with other microtubule agents including vinblastine, etoposide, paclitaxel and docetaxel. (34-38)

A multicenter Cancer and Leukemia Group B phase II trial reported by Savarese and colleagues examined docetaxel, estramustine and low-dose hydrocortisone in 47 men with HRPC. (26) In 44 patients with an elevated pre-treatment PSA, 68% experienced 50% or greater PSA decline. The measurable disease response rate was 50%, with 3 complete and 9 partial responses. Therapy was well tolerated. Neutropenia was the most common adverse effect with 30% of patients having grade 3 and 26% grade 4 granulocytopenia. There were no episodes of febrile neutropenia. Thromboembolic events occurred in 9% of patients, although patients were not routinely anticoagulated. Quality of life of these patients was assessed in tandem with this study, which demonstrated the feasibility of studying quality of life in clinical trials involving chemotherapy in men with prostate cancer. (39)

To confirm the clinical benefits of the microtubule agents, docetaxel-based regimens were compared to mitoxantrone plus prednisone in two multicenter phase III randomized trials (SWOG 9916 and TAX327). SWOG 9916 was an intergroup trial led by the Southwest Oncology Group that randomized 770 men to estramustine (280 mg po TID days 1-5) and docetaxel (60 mg/m2) every 3 weeks or mitoxantrone (12 mg/m2) every 3 weeks and prednisone 5 mg po BID. Patients treated with estramustine and docetaxel had a significant improvement

in median overall survival (17.5 vs. 15.6 months, p = 0.02) and progression free survival (6.3 vs.3.2 months, p = 0.02) compared to patients treated with mitoxantrone and prednisone. (40)

TAX 327 was an industry-sponsored trial that compared single agent docetaxel (75 mg/m2) every 3 weeks plus prednisone 5 mg b.i.d. to docetaxel (30 mg/m2) on a weekly schedule plus prednisone 5 mg b.i.d. to mitoxantrone (12 mg/m2) every 3 weeks and prednisone 5 mg p.o. b.i.d. When compared to the mitoxantrone-treated patients, men that received docetaxel every 3 weeks had a hazard ratio for death of 0.76 (p = 0.009) and those administered weekly docetaxel had a hazard ratio of 0.91 (p = 0.36). The median survival was 16.5 months for the mitoxantrone treated patients, 18.9 months for the patients that received docetaxel every 3 weeks and 17.4 months for patients that were given docetaxel weekly. (41) These results show that docetaxel-based therapy is superior to mitoxantrone and prednisone. While these trials did not address the relative contribution of EMP to docetaxel, the data suggests that EMP adds little to improve overall survival, increases morbidity and that docetaxel would be the most commonly used first line chemotherapeutic regimen in the community. Docetaxel and prednisone has become the first line standard therapy for patients with metastatic hormone refractory prostate cancer.

1.5 Neoadjuvant chemotherapy

The feasibility of taxane-based chemotherapy prior to radical prostatectomy has been demonstrated in several phase II trials. Konety and colleagues recently evaluated neoadjuvant paclitaxel, estramustine and carboplatin (TEC) in 36 patients with high-risk prostate cancer (99) who were treated for 16 to 24 weeks prior to radical prostatectomy. Patients were enrolled from 2 CALGB sites, Memorial Sloan-Kettering Cancer Center and the Dana Farber Cancer Institute. Thirty-four patients completed 4 cycles of chemotherapy, while 1 patient each completed 2 or 6 courses of chemotherapy. Neoadjuvant treatment resulted in lower clinical stage in 39% of patients while 36% of patients were assigned higher clinical stage following neoadjuvant chemotherapy. The most frequent significant chemotherapy-related toxicity was deep venous thrombosis in 22% of patients. Surgery was well tolerated with a median operative time of 270 minutes and a median estimated blood loss of 1250 cc. Immediate peri-operative complications occurred in 6 (17%) patients. The positive surgical margin rate was 22%, and at a median follow-up of 20 months, 50% of these high-risk patients remained free of biochemical recurrence, which was defined as a serum PSA >0.05 ng/ml on 3 separate occasions.

Clark and colleagues treated 18 patients with locally advanced, non-metastatic prostate cancer with three cycles of estramustine and etoposide before radical prostatectomy. (42) All 18 patients completed the three planned cycles of chemotherapy, with 16 patients choosing radical prostatectomy and two patients choosing external beam radiation. Pre-operative serum PSA was undetectable in 50% of patients and 94% demonstrated a local response to chemotherapy prior to surgery. Twenty eight percent of patients experienced grade 3 toxicity from the chemotherapy and one patient (6%) had grade 4 toxicity with a pulmonary embolus. Surgical outcomes including operative time, median blood loss, hospital stay and complications did not appear to be adversely affected by the neoadjuvant chemotherapy. Organ confined disease was found in 31% and specimen-confined disease in 56% of these high-risk patients. All patients achieved an undetectable serum PSA nadir after surgery.

Pettaway and colleagues demonstrated the feasibility of neoadjuvant chemotherapy in 33 patients with high-risk prostate cancer. (43) Patients were treated with 12 weeks of ketoconazole and doxorubicin alternating with vinblastine and estramustine (KAVE), then underwent radical prostatectomy. Ninety four percent of patients completed the two planned courses of KAVE prior to surgery. Most adverse effects were mild, with grades 3 or 4 hematologic toxicity in 12% of patients and three (9%) patients requiring hospitalization during systemic therapy. One patient refused surgery after systemic therapy. No major intraoperative complications were reported. Pathology demonstrated organ-confined disease or extracapsular disease extension in 33% and

66% of patients, respectively. Lymph node metastases were detected in 37% of these high-risk patients and 17% of patients had a positive surgical margin. All patients achieved undetectable serum PSA levels after surgery.

In preliminary results from Gleave and colleagues from the Canadian Urology group, 2 of 64 patients treated with docetaxel plus androgen deprivation therapy for 24 weeks had a complete pathological response and 14 patients had organ-confined disease. (44)

Oh and colleagues administered neo-adjuvant docetaxel for 6 months without estramustine or other forms of androgen deprivation therapy safely to 19 high risk localized prostate cancer patients. (45) Fifty-eight percent of these patients had a post-therapy decline in PSA greater than 50% from baseline with testosterone level remaining in the normal range. Sixteen of the 19 patients had a radical prostatectomy performed. While no complete pathologic responses were seen, 38% had organ-confined disease and none had lymph node involvement.

This trial illustrates the feasibility, safety and biologic effect of administering neo-adjuvant docetaxel without estramustine or androgen deprivation therapy. Whether the addition of androgen deprivation therapy to cytotoxic therapy will derive a greater clinical benefit is not known. Recently, preclinical data evaluating the optimal timing and combination of androgen deprivation therapy with cytotoxic chemotherapy in LNCaP and Shionogi prostate cancer xenografts showed that mice receiving simultaneous chemohormonal therapy had significant improvement in median time to progression versus best sequential therapy. (46) Lack of response to castration was observed after initial paclitaxel therapy and transcriptional profiling identified increased expression of several survival genes known to play a role in androgen independence after paclitaxel exposure. These findings support the use of simultaneous chemohormonal therapy in future neoadjuvant and adjuvant trials.

1.6 Trial design rationale

This randomized trial tests whether the addition of chemohormonal therapy improves PSA-progression free survival in patients with high risk, clinically-localized prostate cancer as defined by the Kattan nomogram. The neo-adjuvant approach is taken since there appears to be a higher acceptance rate in the prostate population for this type of therapy and several phase II trials have demonstrated its safety. While multiple chemotherapeutic therapies have shown efficacy in advanced prostate cancer, recent phase III data suggests that estramustine may not contribute to the overall improvement in survival but increases the morbidity of the treatment. Thus, docetaxel has become the community standard. Many high risk patients are initiated on LHRH agonists at or near the time of diagnosis of their prostate cancer. In order to allow the inclusion of these patients in the protocol, enhance enrollment and maintain compliance with therapy, up to 3 months of androgen deprivation therapy prior to enrollment will be permitted. This study will therefore be able to test the hypothesis that targeting both androgen-sensitive and chemotherapy-sensitive prostate cancer cells will improve outcomes in these high-risk patients.

1.7 PSA Doubling Time

A variety of clinical and pathological factors, including serum PSA level at diagnosis, biopsy Gleason score, clinical staging and pathological staging, have been associated with disease progression after treatment for clinically localized prostate cancer. More recently, PSA doubling time (PSADT) has been identified as a predictor of outcomes in men with prostate cancer. PSADT prior to treatment has been associated with biochemical failure after RP or radiation therapy as well as the time to development of distant disease and death from prostate cancer. (47-52) The association between a specific PSADT and time to metastatic disease and death from prostate cancer is as follows (D'Amico A, personal communication):

PSA Doubling Time (months)	Median Time to Metastases (months)	Median Survival Time (months)
3	24	72
6	48	96
9	72	120
12	96	144

Because PSADT appears to be associated with prostate cancer outcomes, especially in men with high-risk disease. In an effort to broaden our understanding about the behavior of prostate cancer, we propose to prospectively test the hypothesis that PSADT is a surrogate endpoint for time to clinical metastases and survival.

1.8 Inclusion of women and minorities

Minorities will be eligible for this study without alteration in eligibility criteria. We expect that the racial and ethnic composition of the patient group for the current trial will be similar to that seen in CALGB 9594.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	3	0	1	4
Asian	0	18	0	0	18
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	77	0	1	78
White	0	589	0	12	601
More Than One Race	0	0	0	0	0
Total	0	687	0	14	701

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	1	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	1	0	0	1
White	0	85	0	0	85
More Than One Race	0	0	0	0	0
Total	0	87	0	0	87

1.8.1 Final Accrual Total

CALGB 90203 met its original accrual goal of 750 patients on 06/24/15. To account for inevaluable patients, the study was left open to new patient accrual past the original goal of 750. The number of patient required for the statistical analysis, 788, was reached on 09/29/2015. Therefore, effective 10/02/15, CALGB 90203 was permanently close to new patient accrual.

2.0 OBJECTIVES

2.1 Primary Objective

To determine whether treatment with neoadjuvant docetaxel and androgen deprivation therapy prior to radical prostatectomy will increase the rate of 3-year biochemical progression-free survival (bPFS) compared to treatment with immediate radical prostatectomy alone for high-risk prostate cancer patients.

2.2 Secondary Objectives

2.2.1 To compare the 5-year bPFS rate, bPFS, disease progression, disease-free survival, and overall survival of patients randomized to the two arms of this trial.

2.2.2 To determine the safety and tolerability of neoadjuvant docetaxel and androgen deprivation therapy prior to surgery for high-risk patients undergoing radical prostatectomy.

2.2.3 To compare the impact of neoadjuvant docetaxel and androgen deprivation therapy on time to clinically apparent local disease recurrence and metastatic disease in high-risk patients undergoing radical prostatectomy for clinically localized prostate cancer.

2.2.4 To compare the impact of neoadjuvant docetaxel and androgen deprivation therapy relative to RP on pathologic tumor stage, frequency of lymph node metastases and positive margin rates for high-risk patients undergoing radical prostatectomy for clinically localized prostate cancer.

2.2.5 To determine if changes in serum testosterone levels will predict bPFS.

2.2.6 To determine prospectively whether PSA doubling time (PSADT) is a surrogate endpoint for time to clinical metastases and overall survival.

2.3 Diet and Lifestyle Objective

To evaluate associations between post-diagnosis diet and lifestyle, change in food group intake, and risk of prostate cancer recurrence, independent of treatment.

2.4 Correlative Science Objectives

[See Sections 11.2.2 and 11.3.2 for correlative science objectives.]

3.0 ON-STUDY GUIDELINES

The following guidelines are to assist physicians in selecting patients for whom protocol therapy is safe and appropriate. Physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent
- Medical conditions such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Unwillingness to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the chemotherapy utilized in this trial. Appropriate methods of birth control for participants and their female partners of child-bearing potential include, but are not limited to, oral contraceptives, implantable hormonal contraceptives (Norplant), or double barrier method (diaphragm plus condom).
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse.

4.0 ELIGIBILITY CRITERIA

All questions regarding eligibility should be directed to the Alliance Study Chair. Please note that the Study Chair cannot grant waivers to eligibility requirements.

4.1 Histologic documentation

Histologic documentation of prostatic adenocarcinoma. Patients with small cell, neuroendocrine, or transitional cell carcinomas are not eligible.

All eligible patients must have a known Gleason sum based on biopsy or TURP at the time of registration.

4.2 Clinically localized disease

Patients must have clinical stage T1-T3a and no radiographic evidence of metastatic disease as demonstrated by:

- • EITHER CT or MRI of the abdomen and pelvis, OR endorectal MRI of the pelvis that demonstrate no nodes > 1.5 cm.

If one or more pelvic lymph node(s) measures > 1.5 cm, a negative biopsy is required. If more than one lymph node is > 1.5 cm, the largest or most accessible node should be biopsied;

AND

- • Negative bone scan (with plain films and/or MRI and/or CT scan confirmation, if necessary).

Positive PET and Prostascint scans are not considered proof of metastatic disease.

4.3 Determination of high-risk status

Patients must have either:

- 1) A Kattan nomogram predicted probability of being free from biochemical progression at 5 years after surgery of < 60%. [6] See Appendix III for instructions for calculating this probability. Please note that for the purposes of the nomogram calculation, the pre-biopsy PSA value must be used.

OR

- 2) Prostate biopsy Gleason sum ≥ 8
- (NOTE: The Kattan nomogram probability must be calculated for all patients, including those eligible based on Gleason sum ≥ 8 only.)

4.4 Prior treatment

No prior treatment for prostate cancer including prior surgery (excluding TURP), pelvic lymph node dissection, radiation therapy, or chemotherapy. Patients may have received up to 4 months of androgen deprivation therapy (LHRH agonists, antiandrogens, or both) prior to being enrolled on the study.

4.5 Appropriate surgical candidates

Patients must be appropriate candidates for radical prostatectomy with an estimated life expectancy > 10 years as determined by a urologist. Evidence of underlying cardiac disease should be evaluated prior to enrollment to ensure that patients are not at high risk of cardiac complications.

4.6 Clotting history

Patients with a history of deep venous thrombosis, pulmonary embolism, and/or cerebrovascular accident or currently requiring systemic anticoagulation are eligible provided they are determined to be candidates for radical prostatectomy.

4.7 ECOG performance status: 0-2

4.8 Age: ≥ 18 years of age.

4.9 Required Initial Laboratory Values:

ANC	≥ 1500/μL
Platelet count	≥ 150,000/μL
Creatinine	≤ 2.0 mg/dL
Pre-registration serum PSA level	≤ 100 ng/mL
Bilirubin	≤ Upper limit of institutional normal (ULN)*
AST/ALT	≤ 1.5 X ULN

* For patients with Gilbert's Disease, ≤ 2.5 X ULN is allowed.

5.0 REGISTRATION/RANDOMIZATION AND STRATIFICATION

5.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at < [redacted] >. For questions, please contact the RCR ***Help Desk*** by email at < [redacted] >.

5.2 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRB Manager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

5.2.1 Downloading Site Registration Documents:

Site registration forms may be downloaded from the CALGB 90203 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree or click on the By Lead Organization folder to expand
- Click on the Alliance link to expand, then select trial protocol CALGB 90203.
- Click on LPO Documents, select the Site Registration Documents link, and download and complete the forms provided

5.2.2 Requirements for CALGB 90203 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

5.2.3 Submitting Regulatory Documents:

Submit completed forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:

[redacted]

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at [redacted] in order to receive further instruction and support.

5.2.4 Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

5.3 Randomization Requirements

- • **Informed Consent:** The patient must be aware of the neoplastic nature of his disease and willingly consent to participate after being informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Human protection committee approval of this protocol and a consent form are required.
- • **Kattan nomogram predicted probability:** The Kattan nomogram-predicted probability of being biochemical disease free 5 years after surgery must be calculated for all patients, including those eligible based on Gleason sum ≥ 8 only. [6] See Appendix III for instructions for calculating this probability. A printout of this calculation, with the CALGB study number and patient ID number noted, must be submitted with on-study data for all patients.
- • **Clinical staging, serum PSA level, and Gleason sum for the purpose of Kattan nomogram calculation:** The patient must have a clinical stage documented by the treating urologist within 90 days prior to randomization using the 2002 TNM staging system (53) (see Appendix IV). Clinical stage is based on digital rectal examination results and NOT on imaging studies, such as transrectal ultrasound, CT scan, and/or MRI. The clinical stage must be T1-T3a. For study purposes, the serum PSA prior to the prostate biopsy will be the PSA used for randomization. The serum PSA level must have been drawn within 3 months prior to the prostate biopsy and must be ≤ 100 ng/mL.

The highest Gleason sum from the prostate biopsy will be used to calculate the nomogram probability of being free from biochemical disease recurrence at five years. The clinical stage, serum PSA level, and biopsy Gleason sum will be used to calculate the nomogram probability.

5.4 Patient Registration/Randomization Procedures

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam >) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable)

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

To receive site reimbursement for specific tests and/or bio-specimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at [redacted].

5.5 Registration to companion studies

There are three substudies included within CALGB 90203:

- Diet and Lifestyle substudy (Section 10.0)
- Tumor and serum protein correlative substudy: CALGB 150413 (Section 11.2)
- Tumor RNA and DNA analysis substudy: CALGB 150412 (Section 11.3)

All English-speaking patients will be asked to complete the Diet and Lifestyle Survey. If a patient answers "yes" to "I choose to take part in the Diet and Lifestyle study and agree to complete the diet and lifestyle questionnaire," (Question #1) in the Model Consent, he has consented to participate in the Diet and Lifestyle study described in Section 10.0. There is no separate registration for this substudy.

For Alliance Members: If a patient answers "yes" to "I agree that my specimen(s) may be used for research studies to learn about the effects that the experimental treatment may be having," (Question #2) in the Model Consent, the patient should be enrolled to CALGB 150413 and 150412 at the same time that he is registered to the treatment trial (90203) and tissue blocks, frozen prostate samples, and blood samples submitted per Sections 6.4.2, and Sections 6.5—6.7. These companion studies are described in Sections 11.2 and 11.3.

- • NOTE: Materials required to prepare and ship the frozen OCT specimens are available at site request for submission of the fresh frozen samples required for sub-study 150412 and should be ordered from the Alliance Biorepository at OSU prior to radical prostatectomy. See Section 6.7.

For all other participating institutions: If a patient answers "yes" to "I agree that my specimen(s) may be used for research studies to learn about the effects that the experimental treatment may be having," (Question #2) in the Model Consent, the patient should be registered to CALGB 150413 at the same time that he is registered to the treatment trial (90203) and tissue blocks and blood samples submitted per Sections 6.4.2, 6.5, and 6.6. This companion study is described in Section 11.2.

Those institutions who wish to participate in the additional correlative science study, 150412, may also register to that study (described in Section 11.3) and submit additional prostate samples per Section 6.7.

See the "Guide to Companion Study Registration on page 4 of this protocol for a diagram outlining registration to the companion studies of this trial.

5.6 Stratification Factors:

5.6.1 Nomogram-predicted biochemical progression-free survival at 5 years:

- Group 1: 0%-20.9%
- Group 2: 21%-39.9%
- Group 3: 40%-59.9%
- Group 4: ≥ 60%

5.6.2 Androgen deprivation therapy prior to randomization (≤ 4 months):

- - no
- - yes

6.0 DATA AND SAMPLE SUBMISSION AND MODALITY REVIEW

6.1 Data submission

As of Update #10 to the protocol, this study will use Medidata Rave® for remote data capture (RDC) of all future data collection. All data originally received by the Alliance and Statistics and Data Center (SDC) (either electronically using the "Print and/or Submit to CALGB" button [i.e. Teleform form] or by mail) has been transferred to Medidata Rave ® and can be accessed via the Medidata Rave ® system. If necessary, data originally submitted to the SDC electronically (or by mail) can be amended via the Medidata Rave ® system.

The Rave system can be accessed through the iMedidata portal at https://login.imedidata.com. To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, CRA Lab Admin, SLA, or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

For additional information regarding account setup or training, please visit the training section of the Alliance website. Forms should be submitted in compliance with the table below, and a copy of the All Forms Packet can be downloaded from the Alliance and CTSU websites.

Site personnel with Rave roles assigned on the appropriate roster may receive a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. Personnel who did not receive an invitation should contact the Alliance Service Center.

Users who have not previously activated their iMedidata/Rave account at the time of an initial site registration approval for a study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website's Rave tab under the Rave Resource Materials heading (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at [redacted] or by e-mail at [redacted].

For the most up-to-date data forms, please visit the Alliance website at www.allianceforclinicaltrialsinoncology.org or the CTSU CALGB-90203 study page.

	Form	Submission Schedule
	Baseline	
C-1239 Report	Kattan prostate nomogram print-out[1] 90203 Registration Worksheet 90203 Eligibility Checklist 90203 On-Study Form *Pathology report from biopsy*	Within 1 week of registration
	During chemohormonal treatment (Arm A only)	
C-1240 C-1241	90203 Chemohormonal Treatment Form 90203 Adverse Event Form-Chemohormonal Therapy	After every cycle of chemohormonal therapy until chemohormonal therapy ends. If chemotherapy ends early, submit at the end of hormonal therapy.
	Pre- and Post-surgery	
C-1145	EPIC Short Form	At the last pre-surgery clinic visit and every 6 months after surgery for 3 years.
C-714 C-744	CALGB Prostate Specific Antigen Form CALGB Testosterone Form	Per Required Data for PSA and testosterone (Sec. 7.0).
C-1242 C-1243 C-2021 Report	90203 Surgical Complications and Morbidity Form[2] 90203 Surgery and Pathology Form 90203 Op Report Addendum Form *Operative and Pathology reports from surgery*	Within 1 month after surgery
C-1244	90203 Follow-up Form	Within 1 and 3 mos after surgery; then every 3 mos for first 3 yrs; then every 6 mos until 6 yrs after surgery; then annually until 15 yrs after registration or until progression (Sec. 14.1.1, 14.1.2). If patients experience treatment failure (Sec. 14.1.3, 14.1.4) within 3 yrs after surgery, submit every 6 mos. Also, at new primary; and at death.
	Diet and Lifestyle questionnaire[3]	At 3 months after surgery, see Sec. 6.2.
C-1275	90203 Late Postoperative Complications	3, 6, 9, and 12 months after surgery
	Pathology and scan reports	At the time of first local and first metastatic disease progression
	Other	
C-260	CALGB Remarks Addenda	When needed

1 See Appendix III.

2 To be completed twice, Day 3 and Day 30 after surgery.

3 For patients participating in Diet and Lifestyle Survey.

Common Toxicity Criteria: This study will use the NCI Common Terminology Criteria for Adverse Events version 3.0 for routine toxicity reporting on study forms. However, adverse events reported via CTEP-AERS must use CTCAE version 5.0 (See Section 14.0).

6.2 Diet and Lifestyle Questionnaire

Diet and lifestyle questionnaires will be given to all consenting patients enrolled on CALGB 90203 at 3 months following surgery. It is preferred that the questionnaire be completed during the 3-month clinic visit and given to institutional staff for submission to the Alliance Statistics and Data Center. However, patients may complete the questionnaire at home and either mail the completed questionnaire to institutional staff or bring it with them to the 6-month visit.

Completed original questionnaires must be mailed (not faxed) to:

[redacted]

6.3 Sample Submission

Questions regarding sample collection or submission should be directed to the Alliance Biorepository at the Ohio State University at [redacted].

All Patients registered to CALGB 90203: Retrospective histopathology review will be conducted using the paraffin prostate tissue from the diagnostic prostate biopsies and the radical prostatectomy specimens. **The submission of these samples for histopathology review is required for all patients registered to this study, including those who are found to be ineligible and those who do not receive protocol therapy. When available, these specimens will also be used for correlative analyses described in Section 11.3.**

Patients registered to sub-study 150413: All participating institutions must ask patients for their consent for the use of their specimens for the biomarker analysis study described in Section 11.2. For patients who consent, submit tissue and blood samples as described below.

Patients registered to sub-study 150412: In addition to the tissue and blood samples required for 150413, for patients who have consented to the use of their specimens at **Alliance Member Institutions**, frozen prostate tissue will also be submitted for the RNA and DNA studies described in Section 11.3.

Specimen Collection Time Points:

	Within 90 days of registration	**Prior to chemo-hormonal treatment (Arm A pts only)**	**Prior to surgery**	**At surgery**	**After surgery, every 3 months for 3 yrs, then every 6 months for the next 3 yrs, then yearly until treatment failure or progression*, and at treatment failure or progression†**
For patients all patients registered to 90203 submit:					
Paraffin block/slides for histopathology review	X			X	

For patients registered to 150413, also submit the following:					
Paraffin block/cores of prostate tissue from radical prostatectomy[1]				X[1]	
	Number and volume of tubes to draw				
Serum SST (marble top)[2]		2 x 5 mL**	2 x 5 mL**		2 x 5 mL**
Plasma (lavender top)[2]		1 x 10 mL	1 x 10 mL		1 x 10 mL

For patients registered to Substudy 150412, submit all of the specimens above, PLUS:					
Frozen prostate tissue from RP[3]				X	

* As defined in Sections 14.1.1 through 14.1.4.

† Treatment failure/progression samples may be collected and submitted up to 3 months after treatment failure or progression.

** Or, 1 x 10 mL.

1 Blocks/cores to be used for biomarker/TMA analysis (substudy 150413). Additional submission of RP blocks/cores is not necessary if blocks are submitted for histopathology review.

2 Serum and plasma to be used for biomarker analysis (substudy 150413)

3 To be used for RNA and DNA analyses (substudy 150412)

Specimen submission using the Alliance Biospecimen Management System

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BIOS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: [redacted]. For assistance in using the application or questions or problems related to specific specimen logging, please contact [redacted]

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (90203), Alliance patient number, patient's initials and date and type of specimen collected (e.g., serum, whole blood).

A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Shipment on Monday through Thursday by overnight service to assure receipt is encouraged.

All specimens should be sent to the following address:

[redacted]

Alliance Block Submission Policies: The goal of the Alliance Biorepository at OSU is to provide investigators with quality histology sections for their research while maintaining the integrity of the tissue. All paraffin blocks that are to be stored at the Alliance Biorepository at OSU will be vacuum packed to prevent oxidation and will be stored at 4ºC to minimize degradations of cellular antigens.

For these reasons it is preferred that the Alliance Biorepository at OSU bank the block until correlative studies have been initiated and the study investigator requests thin sections. Please contact the Alliance Biorepository at OSU if additional assurances with your hospital pathology department are required.

The Alliance has instituted special considerations for the small percentage (5%) of hospitals whose policy prohibits long-term storage of blocks, and the smaller percentage (4%) of hospitals whose policies prohibit release of any block. If, due to institutional policy, a block cannot be

sent, please call the Alliance Biorepository at OSU at [redacted] to obtain a protocol to cut the sections or to obtain the cores at your institution.

Pathology Reports: When shipping tissue samples to the Alliance Biorepository at OSU, a copy of the responsible pathologist's pathology report must be included.

This report should specify:

- The number of pelvic lymph nodes identified,
- presence or absence of cancer in each of the identified pelvic lymph nodes,
- presence or absence of extranodal tumor,
- prostate tumor histologic type and Gleason grade,
- presence and location of positive margins [defined as apical, anterior, bladder neck, and posterolateral],
- tumor size which can be quantitated as percentage of the gland involved by carcinoma, as determined by visual inspection, or as tumor volume, as measured by computer-assisted morphometry,
- presence or absence of capsular invasion [none, invasion into but not through the capsule, focal extracapsular extension, established extracapsular extension],
- presence or absence of tumor in the seminal vesicles,
- invasion of cancer into the bladder neck,
- specification of whether the tumor is unilateral or bilateral, and
- tumor pathologic stage, according to the 2002 TNM system, must also be specified.

6.4 Submission of paraffin blocks and/or slides for central pathology review;

Required for all patients registered to this study.

Consistent and accurate histologic grading using the Gleason grading system is important for this study. Submission of histologic slides from the diagnostic prostate biopsy and of paraffin blocks, cores, or slides (see below) from the radical prostatectomy is required for all patients enrolled to CALGB 90203.

While institutional Gleason scoring will be used to determine patient eligibility, a retrospective review of the histologic slides used for diagnosis of prostate cancer on these patients will be performed. Central pathology review is not required prior to registration.

Central histopathology review of radical prostatectomy blocks/slides should provide a more accurate picture of the comparative tumor Gleason grades as well as an assessment of treatment effects on tumor, including qualitative cytologic effects and quantitative amount of prostate cancer via image analysis.

6.4.1 Block/slide preparation

Label all blocks and/or slides with the following identification:

a) Procurement date
b) Institutional surgical pathology number
c) Patient study ID number
d) CALGB study number (i.e., 90203)
e) Specimen source (according to location within the prostate)

Pathology reports: When shipping samples to the Alliance Biorepository at OSU, include copies of the responsible pathologist's pathology report from the TREATING institution, and, if applicable, the REFERRING institution.

Follow shipping instructions outlined in Section 6.3.

6.4.2 Diagnostic biopsy sample submission

Within 90 days of patient registration/randomization, submit to the Alliance Biorepository at OSU the following materials:

- 1) One H&E slide from every prostate biopsy tissue block regardless of region or pathology,

AND:

- 2) One paraffin-embedded block with REPRESENTATIVE PRIMARY TUMOR
- OR
- Ten (10) unstained slides from a tumor-bearing block that will be suitable for immunohistochemical staining.

6.4.3 Radical prostatectomy sample submission for histopathology review

Within 90 days of radical prostatectomy, submit to the Alliance Biorepository at OSU the following materials:

- 1) One H&E slide from every prostate tissue block taken from the prostate regardless of region or final pathology,

AND

- 2) One paraffin-embedded block with REPRESENTATIVE PRIMARY TUMOR from each of the following regions:
- - Prostate
- - Seminal vesicle, if tumor present
- - Lymph node, if tumor present

OR

- Ten (10) unstained slides from a tumor-bearing block that will be suitable for immunohistochemical staining from each of the following regions:
- - Prostate
- - Seminal vesicle, if metastatic
- - Lymph node, if metastatic

6.5 Tissue submission requirements for patients enrolled to sub-study 150413

Formalin-fixed paraffin-embedded blocks or cores of prostate tissue are required for tissue microarray analysis for all patients enrolled to sub-study 150413. **If a block(s) from the surgical sample were submitted for histopathology review per Section 6.4.3, it is not necessary to submit additional tissue.**

For blood sample requirements for patients enrolled to 150413, see Section 6.6.

Please contact the Alliance Biorepository at OSU at [redacted] with additional questions PRIOR to submitting materials.

6.5.1 Radical prostatectomy tissue sample requirements: Within 90 days of radical prostatectomy, submit to the Alliance Biorepository at OSU the following materials:

- 1) **Blocks:** One paraffin-embedded block with REPRESENTATIVE PRIMARY TUMOR from each of the following tumor-bearing regions:
- - Prostate
- - Seminal vesicle, if tumor present
- - Lymph node, if tumor present

OR

- 2) **Cores:** If blocks cannot be provided, tissue core extraction (punches) are required. Punches (at least two) will be taken from tumor-rich areas as well as from benign areas (at least two). For each block with REPRESENTATIVE PRIMARY TUMOR, submit two cores from each of the following tumor-bearing regions:
- - Prostate
- - Seminal vesicle, if tumor present
- - Lymph node, if tumor present

Please contact the Alliance Biorepository at OSU at [redacted], to obtain instructions for tissue core extraction (punches). The punches will be used by the submitting institution's pathologist to extract tissue cores suitable for protocol requirements.

6.5.2 Radical prostatectomy tissue sample submission: Label each section or core with the following:

a) Procurement date
b) Institutional surgical pathology number
c) Patient study ID number
d) CALGB study number (i.e., 90203)
e) Specimen source (according to location within the prostate)

Within 90 days of the radical prostatectomy, submit samples to the Alliance Biorepository at OSU. Include the responsible pathologist's pathology report and follow shipping instructions outlined in Section 6.3.

6.6 Blood sample submission requirements for patients enrolled to sub-study 150413

For patients who consent to participate, in addition to the tissue samples collected and submitted as described above, serum and plasma samples will be used for the correlative science substudy described in Section 11.2 (150413). Blood samples should be collected prior to the initiation of chemohormonal therapy (for patients randomized to Arm A), prior to radical prostatectomy (or pelvic lymph node dissection for patients undergoing perineal prostatectomy), and every 3 months during the first three years after surgery, every 6 months for the next three years, and annually thereafter until treatment failure or progression as defined in Sections 14.1.1—14.1.4, and at treatment failure or progression.

For serum, a total of 10 mL of venous blood will be drawn in two red/black top serum separator tubes. Gently invert 5 times to mix clot activator with blood. Let blood clot for up to one hour. Observe a dense clot. Centrifuge at 1300g for 10 minutes. The sample should be refrigerated until shipped on cool pack by overnight mail to the Alliance Biorepository at OSU. The sample should be shipped the same day that the blood is drawn.

For plasma, 10 mL of venous blood will be drawn in purple top EDTA containing tubes. Invert tube 8-10 times, and refrigerate until shipped on cool pack by overnight carrier to the Alliance Biorepository at the Ohio State University. The sample should be shipped the same day that the blood is drawn.

Label samples with the following identification:

- 1) Procurement date
- 2) Patient study ID number
- 3) CALGB study number (i.e., 90203)
- 4) Serum or Plasma

6.7 Fresh frozen tissue sample submission requirements for patients enrolled to sub-study 150412

In addition to the tissue samples described in Sections 6.4.2 and 6.5, and blood samples described in Section 6.6, submission of FRESH prostate tissue is required for all patients from Alliance Member Institutions who have consented to the use of their specimen(s). All other institutions are encouraged, but not required, to submit fresh prostate tissue.

Materials required to prepare and ship the frozen OCT specimens are available for this sub-study upon site request. The materials may be requested by contacting the Alliance Biorepository at Ohio State University at [redacted].

6.7.1 Specimen submission requirements

The following samples should be submitted for patients registered to sub-study 150412 at Alliance Member Institutions:

- 1) Two OCT specimens collected from the site of cancer within the prostate. If present, the dominant tumor should be sampled; if no cancer is obvious on visible inspection of the prostate, then the area of the prostate positive on biopsy should be sampled.
- 2) One OCT specimen collected from 1 area of normal/benign prostate.
- 3) One OCT specimen collected from a lymph node positive for tumor, if available. (If lymph nodes are negative for tumor, no specimen should be submitted.

6.7.2 Specimen collection, preparation, and submission procedures

In the case of grossly positive pelvic lymph nodes, a portion of the involved node(s) should be frozen. Fresh prostate tissue may be harvested using a protocol in place at one's hospital, one of the published protocols (74-78), or, as follows:

- 1) After inking of the entire outer surface of the prostate gland, incision or sectioning of the whole prostate gland may be performed using the local standard of care.

  Care must be taken not to disrupt or harvest the outer surface of the gland as this may compromise histopathologic evaluation of extraprostatic extension of carcinoma and/or surgical margin status. Fresh tissue may be procured by taking tissue sections from underneath the prostatic "capsule" or by taking punch biopsies (74-78).

- 2) Sampling of several sites, including sites of any palpable or gross abnormalities, is desirable. For example, if large tissue sections are taken, sampling of both right and left sides of the prostate is recommended. For needle core sampling, 10 cores should be taken (75). Suspicious sites can be identified by induration on palpation, hyperemia, or other color irregularities from normal-appearing prostate gland.

  Sample one normal and two suspicious sites within the prostate by <u>either</u>:

  a) (Preferred) Incise prostate sections and remove samples approximately 20 to 30 mg (size of an eraser head on a pencil). DO NOT DISRUPT OR HARVEST THE OUTER SURVACE OF THE GLAND.

  <u>Or</u>

  b) (Alternate) Perform needle core sampling using an 18 gauge needle. 10 cores should be taken.

- 3) Label frozen samples sequentially with the following codes:
- FT1: Tumor sample one;
- FT2: Tumor sample two;
- FB1: Benign sample one;
- FB2: Benign sample two (optional)
- Label with the respective region using the following codes:
- <u>From the prostate:</u> FT1 and FT2, (targeting tumor); FB1 and FB2 (targeting benign tissues), RB (right prostate), RM (right mid), RA (right apex), LB (left base), LM (left mid), LA (left apex)
- <u>From the lymph node(s):</u> RO (right obturator), RII (right internal ileac), REI (right external ileac), LO (left obturator), LII (left internal ileac), LEI (left external ileac)
- 4) Place collected material, incised specimens or cores, onto a pre-frozen pallet of Optimal Cutting Temperature (OCT) compound.
- Pre-frozen pallets of OCT can be created by placing sufficient OCT to cover the bottom of a pre-labeled, plastic cryomold. The importance of having pre-frozen OCT is that the fresh tissue rapidly freezes when it contacts the frozen OCT. Cover sample with additional OCT and freeze rapidly in cryostat (at -20˚ C) or on dry ice.
- If an alternative method of freezing (i.e. liquid nitrogen submersion) is used, after the specimen is frozen, place sample in pre-labeled cryomolds, cover with OCT, and freeze OCT in dry ice or in a cryostat.

- 5) Label cassettes with the following identification:
  a) Institutional surgical pathology number
  b) Procurement date
  c) Sample type (e.g., FT1, FT2, or FB1)
  d) Respective region (e.g., RB, RM, RA, LB, LM, RO, RII, LO, LII, or LEI)
  e) Patient study ID number
  f) CALGB study number (i.e., 90203)
- 7) Temporarily place on dry ice (to move to storage).
- 8) Store in liquid nitrogen-vapor phase (ideal) or at -80˚ C (if necessary).
- 9) Ship on dry ice by overnight mail to the Alliance Biorepository at OSU at the address listed in Section 6.3. Please notify the Alliance Biorepository at OSU by fax [redacted] or email [redacted] of intended shipments. Shipments to the Alliance Biorepository at OSU can be made on a monthly basis by overnight carrier.
- Remember to include the responsible pathologist's pathology report as described in Section 6.3 when submitting samples to the Alliance Biorepository at OSU.

6.8 Surgical Quality Assurance Requirements

6.8.1 General Guidelines

All patients will undergo standard surgical intervention that will consist of: (1) staging pelvic lymphadenectomy and (2) radical perineal or retropubic prostatectomy. If the retropubic approach is chosen, lymphadenectomy will be performed concurrently with prostatectomy. In the case of perineal prostatectomy, lymphadenectomy should be performed no more than 2 weeks before prostatectomy.

Resection of the prostate gland will not be performed in the case of gross, macroscopic, histologically confirmed lymph node metastases. If nodal involvement is microscopic, surgery may proceed at the discretion of the surgeon. Following radical prostatectomy, pathology will be reviewed centrally to evaluate the pathologic endpoints. Radical prostatectomy specimens will be handled and sampled in a uniform fashion, with complete embedding of the entire prostate gland.

6.8.2 Surgical Quality Assurance

The surgical goals of the study are:

- • To perform a standard bilateral pelvic lymph node dissection including the external iliac, obturator and hypogastric lymph nodes
- • To perform a radical prostatectomy with complete removal of all gross tumor. The dissection should include complete removal of both seminal vesicles
- • To determine if neoadjuvant chemotherapy results in a more difficult surgical dissection

To ensure that these goals are met, and facilitate compliance with Surgical Quality Assurance Committee requirements, the following seven (7) items should be specifically commented on in the operative procedure:

- 1. A description of the extent of the lymph node dissection including specific mention of whether or not the external iliac, obturator, and/or hypogastric nodes were removed.
- 2. Were the nodes grossly positive or negative?

- 3. Was a frozen section of the lymph nodes and/or prostate sent at the time of surgery? If yes, what was the result?
- 4. An intraoperative assessment of the extent of disease within the prostate given using the "T" part of the TNM system (classified as T1c through T4).
- 5. A description of whether or not all gross disease was resected.
- 6. A statement regarding the difficulty of the procedure.
- 7. A statement of whether or not there were intraoperative complications.

Submission of the operative report is required (see Section 6.1) A sample dictation is as follows (the note would be adjusted based on the actual case):

"Findings: The patient is enrolled in CALGB 90203 and was randomized to receive neoadjuvant chemo-hormonal therapy. He is brought to the operating room within 60 days of his last treatment cycle. A bilateral pelvic lymph node dissection including the external iliac, obturator and hypogastric areas was performed. The nodes were grossly negative for metastatic disease. The prostate was indurated bilaterally without evidence of extraprostatic disease (intraoperative stage T2c). Both seminal vesicles were removed and all visual evidence of disease was resected. There were no intraoperative complications."

6.8.3 Monitoring of Surgical Quality

The Alliance study chair will assign relative weights (points) to the various surgical aspects of the procedure. If these elements are not performed, points are deducted during case review from a perfect score of 100% of all available points. Key events of the procedure are rated so that major protocol deviations require point deductions > 20%. Less important deviations have a smaller deduction. A passing score of 75% of total points is required for each patient and if not achieved initiates an interactive quality improvement process for the institution or investigator as appropriate.

Major Deviations

- • Failure to perform a pelvic lymphadenectomy
- • Performing a radical prostatectomy in the setting of grossly positive lymph nodes
- • Performing surgery outside the 60 day guideline after randomization (surgery only arm) or the completion of chemohormonal therapy (neoadjuvant chemohormonal therapy arm)

Minor Deviations

- • Performing a limited pelvic lymphadenectomy (not sampling the external iliac, obturator, AND hypogastric lymph nodes)
- • Failure to report extent of tumor based on intraoperative findings using 2002 TNM staging system in the operative report
- • Failure to report intraoperative complications in the operative report
- • Failure to remove the entire seminal vesicles
- • Failure to report completeness of resection

7.0 REQUIRED DATA

Guidelines for Pre-Study Testing

To be completed within 90 DAYS before registration:

- Diagnostic prostate biopsy confirming prostatic adenocarcinoma

To be completed within 42 DAYS before registration:

- Computed tomography or MRI scan of the abdomen and pelvis or endorectal MRI, and bone scan (with plain film or MRI confirmation, if necessary).

To be completed within 14 DAYS before registration:

- All blood work, physical examination, history

	Prior to registration	ARM A Day 1 of each cycle†	Pre-surgery‡	At surgery	Post-surgery follow-up*
Tests & Observations					
History and Progress Notes	X	X	X		X
Physical Examination	X	X	X		X
Pulse, Blood Pressure	X	X	X		X
Weight/BSA∞	X	X	X		
Height	X				
Performance Status	X		X		
Drug Toxicity Assessment		X	X#		
EPIC Short Form (C-1145)			D		D
Pathology review	A			B	
Laboratory Studies					
CBC, Differential, Platelets	X	X	X		
Serum Creatinine	X	X	X		
ALT, AST, Bilirubin	X	X	X		
LDH, Alk. Phos.	X				
Serum PSA	X	X	X		E
Serum Testosterone	X		X		X
EKG			X		
Staging					
Bone Scan	X				C
CT Scan or MRI of abd./pelvis OR erMRI of pelvis	X				
Companion Studies**					
Diet/Lifestyle Assessment	*At 3 months following surgery*				
Prostatectomy tissue samples	*To be collected at surgery, see Sections 6.4, 6.5 and 6.7.*				
Blood samples	*See Section 6.6*				

**** For patients who consent to participate. See also, Sections 6.2—6.7.**

† Labs may be obtained within 48 hours prior to each cycle of chemohormonal therapy. For cycle 1, baseline history and physical and labs may be used in place of Day 1 H & P and labs provided they are obtained within 14 days prior to treatment.

‡ Labs obtained within 30 days prior to surgery need not be repeated. Pre-registration physical exam may be used for pre-surgery PE if obtained within 14 days prior to surgery.

* Patients will be evaluated within 1 month and within 3 months after surgery, then every 3 months for the first 3 years following surgery, every 6 months for the next 3 years, and annually thereafter until 15 years after randomization. If patients experience treatment failure per Sections 14.1.3 or 14.1.4 during the first 3 years following surgery, evaluations may be done every 6 months. Follow all patients until biochemical or metastatic disease progression per Sections 14.1.1 or 14.1.2, then follow patients for survival until 15 years after registration.

∞ The dose of chemotherapy need not be changed unless the calculated dose changes by ≥ 10%.

\# For patients randomized to Arm A only.

A Diagnostic prostate blocks or slides, see Sections 6.4.

B Prostatectomy and pelvic lymph node blocks or slides, see Sections 6.4 and 6.5.

C Bone scans are to be performed on any patient with complaints of bone pain that cannot be attributed to intercurrent disease. Also, after PSA progression, scans are to be performed every 6 months until distant progression.

D The EPIC short form is required at the last pre-surgery clinic visit and every 6 months after surgery for 3 years regardless of disease or treatment status.

E Every 3 months until protocol progression of any type (per Section 14.1): confirmed biochemical disease progression (Section 14.1.1); radiographic disease (Section 14.1.2); post-operative radiotherapy started later than 6 months post-surgery (Section 14.1.3); or post-surgery systemic therapy (ADT) (Section 14.1.4). After any of these qualifying events, PSA

measurements are optional and may be taken at the discretion of the treating physician. Please continue to report all PSA measurements on the C-714 PSA form via Medidata Rave® and non-protocol therapies on the C-1244 Follow-up form via Medidata Rave® even after progression.

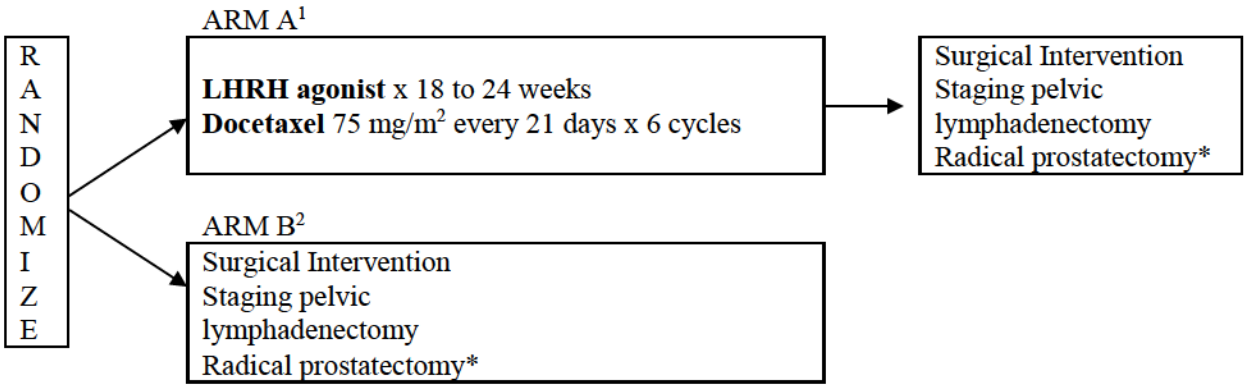
8.0 TREATMENT PLAN

Questions regarding treatment should be directed to the Alliance Study Chair or Co-chair.

Patients will be randomized to receive either 18 to 24 weeks of androgen deprivation therapy plus chemotherapy followed by radical prostatectomy OR immediate radical prostatectomy.

For patients randomized to Arm A, neoadjuvant treatment is to begin within 14 days of randomization. One cycle will be defined as 3 weeks of treatment. Surgery will then take place within 60 days following the completion of neoadjuvant therapy (i.e., sixty days plus 3 weeks after the last docetaxel dose was given).

For patients randomized to Arm B, surgery is to occur within 60 days of randomization.



* Patients with positive surgical margins extraprostatic extension, and/or seminal vesicle invasion are allowed to receive adjuvant external beam radiation to the prostatic fossa at the discretion of the treating physician. Adjuvant radiation must be initiated within 6 months of the date of surgery.

8.1 Neoadjuvant chemohormonal therapy (Arm A only)

Patients who have been randomized to Arm A will receive 6 cycles of docetaxel administered every 3 weeks combined with 18 to 24 weeks of androgen deprivation therapy.

8.1.1 Docetaxel: Docetaxel 75 mg/m^2 will be administered intravenously over 1 hour on Day 1 of each cycle, every 21 days.

Dexamethasone: During each cycle of chemotherapy, all patients should undergo premedication with dexamethasone 8 mg orally approximately 12 hours, 3 hours, and 1 hour prior to docetaxel (i.e., 8 mg of dexamethasone the night before, the morning of, and just prior to the infusion of docetaxel).

Alternatively, dexamethasone may be given twice daily the day before, the day of, and the day after docetaxel (i.e., 6 doses of 8 mg of dexamethasone during each cycle of therapy).

Lastly, dexamethasone may also be given intravenously according to institutional guidelines.

8.1.2 Androgen deprivation: Androgen deprivation will include 18 to 24 weeks (measured from the date of starting docetaxel) of an LHRH agonist (e.g., leuprolide acetate, goserelin acetate).

Oral antiandrogens may not be used, and must be discontinued prior to the initiation of protocol treatment.

8.1.3 Additional pre-medication and antiemetics may be given at the physician's discretion. However, the use of aprepitant as an antiemetic is not allowed. Use of additional medications should be recorded on the CALGB C-260 Remarks Addenda.

8.2 Radical Prostatectomy (Arms A and B)

All patients will undergo standard surgical intervention that will consist of:

(1) staging pelvic lymphadenectomy and

(2) radical perineal, retropubic, laparoscopic, or robotic-assisted prostatectomy.

In the case of perineal prostatectomy, lymphadenectomy should be performed no more than two weeks prior to prostatectomy. If the retropubic, laparoscopic, or robotic-assisted approach is chosen, lymphadenectomy will be performed concurrently with prostatectomy.

The surgical procedures will be performed within 60 days of the completion of neoadjuvant therapy for patients on Arm A. For patients randomized to Arm B, surgery is to be performed within 60 days of randomization. The procedure may be performed under general, regional, or general and regional anesthesia.

See Section 6.8 for surgical quality assurance requirements.

8.2.1 Staging Lymphadenectomy

Bilateral pelvic lymphadenectomy should include complete removal of all fibroadipose tissue dorsal to the external iliac vein, caudal to the hypogastric artery and vein, cephalad to Cooper's ligament and the pelvic floor, medial to the obturator muscular sidewall of the pelvis, lateral to the bladder, and ventral to the sciatic nerve. (54, 55)

Resection of the prostate gland will not be performed in the case of gross, macroscopic, histologically confirmed lymph node metastases. Because patients in the chemohormonal therapy arm may have a decreased chance of having/detecting positive lymph nodes, no frozen sections will be performed on the lymph nodes intraoperatively. This is required to keep the study arms balanced and to avoid selection bias. No frozen sections of visually and palpably negative nodes will be performed.

Androgen Deprivation: Patients with lymph node metastases at staging pelvic lymphadenectomy or radical prostatectomy will be followed. Although a matter of debate, recent data from Messing and colleagues suggests a significantly better outcome with respect to overall and progression-free survival for radical prostatectomy patients with pathologically proven lymph node metastases who receive immediate androgen deprivation therapy compared to those undergoing delayed treatment. (56) Therefore, these patients will be allowed to have immediate androgen deprivation therapy, if desired. Since androgen deprivation therapy will affect time to biochemical and metastatic disease progression, and possibly survival, these patients will be considered treatment failures at the time of initiation of androgen deprivation therapy. Investigators are encouraged to delay postoperative systemic therapy, including androgen deprivation therapy, until the patient has documented evidence of biochemical failure (defined as a serum PSA level > 0.2 ng/mL and rising on 2 separate occasions at least 3 months apart following radical prostatectomy).

8.2.2 Radical perineal prostatectomy

The patient is placed in an exaggerated lithotomy position, taking care to pad any pressure points. The incision is made from one ischial tuberosity to the other, with the apex of the incision approximately 1.5 cm above the anus. The incision is deepened through the adipose tissue, and the central tendon is divided. The rectal wall is retracted inferiorly and the pedicles to the prostate are identified lateral to the seminal vesicles and divided.

The urethra is identified and divided just distal to the apex of the prostate. The plane between the anterior aspect of the prostate and the dorsal venous complex is developed to the level of the bladder neck. The bladder neck is divided distal to the ureteral orifices. The dissection of the seminal vesicles is completed. The seminal vesicles should be removed in toto.

The bladder neck is reconstructed as needed and anastomosed to the urethra over a catheter. A drain is placed deep to the reconstructed central tendon following which the subcutaneous tissue and skin are closed.

8.2.3 Radical retropubic prostatectomy

A lower midline abdominal incision is made and a pelvic lymphadenectomy [see above description for limits of dissection] is performed. The endopelvic fascia is incised and the levator muscles are dissected off the lateral aspect and apex. The dorsal venous complex is divided with appropriate hemostatic control. The decision whether or not neurovascular bundle (NVB) preservation should be performed is at the discretion of the operating surgeon. At centers where nerve grafting is performed, this is permitted as part of routine surgical care. After either NVB mobilization or division at the apex, the urethra distal to the apex of the prostate is transected. Denonvilliers' fascia should be kept intact over base and posterolateral aspect of the prostate. The dissection, whether nerve sparing or not, proceeds in a retrograde fashion from the apex to the base of the prostate. The lateral vascular pedicles are divided. The seminal vesicles are dissected free in their entirety and resected intact with the prostate. The vasa are divided. The bladder neck should be circumferentially incised and the specimen removed.

The bladder neck is reconstructed as needed and anastomosed to the urethra over a catheter. The fascia and skin are closed in routine fashion.

A laparoscopic or robotic-assisted approach is permitted and should follow a similar anatomical approach as outlined with intact specimen delivery.

8.2.4 Positive surgical margins

Patients with positive surgical margins, extraprostatic extension, and/or seminal vesicle invasion will be allowed to receive adjuvant external beam radiation to the prostatic fossa based on the judgment of the treating physician. Although the efficacy and timing of such treatment is a matter of debate, physicians and patients may desire this treatment based on the available data. Such patients will not be considered treatment failures, but will continue on standard follow-up and will be included in the analysis. The decision for adjuvant radiation therapy must be made and started within 6 months of the date of surgery. See Section 14.1.3 for post-operative radiotherapy.

8.2.5 Handling of the pathologic material

Specimen submission of formalin-fixed, paraffin-embedded tissue (blocks or slides) from the radical prostatectomy (RP) specimen and metastatic pelvic lymph nodes for centralized pathology review is required for all patients.

Submission of frozen tissue is required for all patients enrolled at Alliance Main Member and At-Large institutions except for those who indicate on the consent form that they decline to participate in this companion study (150412). All other institutions are strongly encouraged, but not required, to submit this tissue. See Sections 6.5 and 6.7 for details regarding preparation of these samples for submission.

8.3 Potential Minor and Major Complications of Surgery

8.3.1 Potential minor complications include: wound infection, urinary tract infection, pelvic/scrotal/lower extremity edema, ileus, urinary frequency/urgency/nocturia, urinary retention, incisional or pelvic pain.

8.3.2 Potential major complications include: Rectal injury, ureteral injury, major vascular or nerve injury, hemorrhage requiring transfusion of non-autologous blood products, urinary incontinence, erectile dysfunction, bladder neck contracture, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, life threatening complications, and death.

9.0 CHEMOTHERAPY DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

No dose modifications will be made for LHRH agonists.

There will be no dose re-escalation once docetaxel dose is reduced. If dose reduction beyond level -2 is required (for any reason) or if docetaxel is held for greater than 3 weeks unless otherwise specified below, no further docetaxel will be administered; the patient will complete at least 18 weeks of androgen deprivation therapy and proceed to surgery

Dose Levels for Docetaxel

Dose Level	Docetaxel
Level 0 (Starting dose)	75 mg/m^2
Level -1	60 mg/m^2
Level -2	50 mg/m^2

9.1 Dose modifications for hematologic toxicity

For ANC < 1500 or platelets < 100,000, hold docetaxel, and repeat CBC weekly. Resume docetaxel when ANC ≥ 1500 and platelets ≥ 100,000. If docetaxel is held for hematologic toxicity for more than one week, resume docetaxel when toxicity resolves with one dose level reduction for all subsequent cycles.

For febrile neutropenia defined as ANC < 500 and T ≥ 38.2°C (100.8°F), decrease docetaxel by one dose level for all subsequent cycles.

9.2 Hepatic Dysfunction

For bilirubin ≤ 1.5 x ULN and AST 1.5 - 5 x ULN, decrease docetaxel by 1 dose level for all subsequent doses.

For bilirubin > 1.5 x ULN or AST > 5 x ULN, hold docetaxel and repeat LFT's weekly. Resume docetaxel when bilirubin ≤ 1.5 x ULN and AST ≤ 1.5 x ULN, with one dose level reduction.

9.3 Neurotoxicity

For grade 3 or 4 neurotoxicity, hold docetaxel until the toxicity resolves to grade 2 or less and then resume therapy with docetaxel at one lower dose level. If the neurotoxicity persists or worsens despite dose reduction, hold docetaxel until toxicity clears to grade 2 or less then resume with docetaxel at one more lower dose level. If therapy is held for more than six weeks or ≥ grade 3 neurotoxicity persists after 2 dose reductions, discontinue docetaxel and complete 18 weeks of androgen deprivation therapy as planned.

9.4 Gastrointestinal Toxicity

In this protocol, the routine use of an antiemetic is clinically appropriate.

For ≥ grade 3 mucositis, hold docetaxel until symptoms resolve to ≥ grade 2. Then resume docetaxel with one dose level reduction.

9.5 Fluid retention

If symptomatic, treat the patient early with diuretics of the physician's choice. If severe and refractory to symptomatic treatment, discontinue docetaxel.

9.6 Skin Toxicity

9.6.1 Extravasation of docetaxel may cause skin necrosis; stop the infusion immediately if extravasation is suspected, and administer the drug at another site.

9.6.2 Erythema, desquamation

Grade 0-2: No change.

Grade 3-4: Hold docetaxel until skin toxicity improves to ≤ grade 2, then decrease one dose level for all subsequent cycles of therapy. If grade 3-4 toxicity recurs, discontinue docetaxel.

9.7 Hypersensitivity Reactions

9.7.1 Grade 1: Interrupt infusion until resolution of symptoms, then complete infusion a the initial planned rate.

9.7.2 Grade 2: Stop infusion. Give diphenhydramine 50 mg IV with dexamethasone 10 mg IV plus an H2 blocker, all at the physician's discretion. Resume docetaxel infusion after recovery. Pretreat with diphenhydramine and H2 blocker for future cycles.

9.7.3 Grade 3 or 4: Stop infusion and discontinue docetaxel.

9.8 Corticosteroid Toxicity

High doses of dexamethasone may cause hyperglycemia, insomnia, and mental status changes. Treating physicians may modify the dose of dexamethasone as clinically indicated.

9.9 Other Toxicities

For grade 3 or grade 4 toxicities not listed above including fatigue (and excepting nausea and vomiting), all treatment should be withheld until the toxicity resolves to grade 1 or less. Docetaxel should be re-instituted (if medically appropriate) at one lower dose level. If treatment is withheld for longer than three weeks, no further chemotherapy will be administered, 18 weeks of androgen deprivation therapy will be completed, and the patient will proceed to surgery if clinically indicated.

9.10 Dose Modification for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, **all dosing is to be determined solely by (1) the patient's BSA as calculated from actual weight or (2) actual weight without any modification unless explicitly described in the protocol.** This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. **Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation.** Physicians who are uncomfortable with administering chemotherapy dose based on actual body weight should not enroll obese patients on Alliance protocols.

10.0 DIET AND LIFESTYLE SUBSTUDY

10.1 Background

Overall, red meat, total and specific fats, (50, 57-71) dairy and calcium intake (72) have been associated with an elevated risk of prostate cancer. For each of these, stronger associations were observed for the development of metastatic and fatal disease, suggesting that these dietary factors play a role late in carcinogenesis. In contrast, total and specific vegetables, lycopene/carotenoids/tomato products, fruits, vitamin E supplements, and selenium supplements have all been inversely linked to risk of prostate cancer. In particular, while not the primary endpoint of the studies, vitamin E was linked to an approximate 40% reduction in prostate cancer incidence and mortality in a randomized clinical trial. Similarly, selenium supplementation was associated with an approximate 1/3 reduction in prostate cancer incidence in a randomized clinical trial. (73)

In addition to the large body of evidence for incident prostate cancer, there is emerging evidence that post-diagnostic diet is also important for prostate cancer death. Chan and colleagues examined post-diagnostic diet relevant to pre-diagnostic diet and risk of prostate cancer recurrence in an observational, non-intervention study among 1202 incident prostate cancer cases, using prospectively collected dietary questionnaire data (Health Professionals Follow-up Study). In an analysis with 392 cases of recurrence, progression, and mortality, a positive change in intake of fish or tomato sauce after diagnosis (e.g. consuming more fish or tomato sauce after diagnosis relative to before diagnosis) appeared to be strongly protective against risk of prostate cancer recurrence/progression (HR = 0.73, 95% CI 0.32 - 1.02 for fish; HR = 0.56, 95% CI 0.38 - 0.82 for tomato sauce), independent of other food groups and total energy, and age at diagnosis. Adjusting for tumor stage at diagnosis and primary treatment did not affect these results (Chan, et al., CCC in press). In a separate analysis of 1511 incident prostate cancer cases from this cohort study, there were also provocative inverse associations for post-diagnostic physical activity and grain intake and the risk of prostate cancer-specific death (personal communication, JM Chan). While provocative, this sub-study was not designed to examine post-diagnostic clinical follow-up, and there was potentially incomplete data on clinical progression and treatment. Thus, food intake, exercise, and change in these behaviors pre- and post-diagnosis will be examined in this trial; more rigorous clinical data will be collected to confirm these preliminary results from the Health Professionals Follow-up Study. It is recognized that collection of change in diet and exercise patterns will require the retrospective assessment of these habits before diagnosis, and may be vulnerable to some recall bias and measurement error. However, the questions have purposely been phrased to inquire about a relative change in intake (rather than attempt an absolute assessment of previous diet), which will minimize possible measurement error.

Further evidence for a post-diagnosis role of diet in prostate cancer progression comes from intervention studies conducted among prostate cancer survivors. While these studies have been small and often lacked a control group, they have reported suggestive potential benefits of various low-fat plant-based diets on intermediate indicators of prostate cancer progression (PSA levels). (74-77)

10.2 Methods

Participants in this sub-study will be asked to complete a diet and lifestyle questionnaire at three months following surgery. The dietary survey (the Willet semi-quantitative food frequency questionnaire) is a validated food frequency survey that has been used in several large cohort studies for determining associations between nutrition and chronic disease. For each food, a commonly used unit or portion size (e.g., one egg or slice of bread) is specified, and participants are asked how often, on average over the past year, they consumed that amount of each food. There are nine possible responses that range from never to six or more times per day. The

lifestyle portion of the survey includes questions regarding the patient's physical activities and smoking history. (See Section 6.2 for submission instructions.)

11.0 CORRELATIVE SCIENCES COMPANION STUDIES

11.1 Background to Correlative Sciences Companion Studies – CALGB 150413 and 150412

In 2015 multiple analyses described somatic mutations, copy number alterations and structural DNA rearrangements in primary prostate cancer (78-81). While many studies are not able to assess the clinical relevance of tumor genetic alterations, several reports have suggested alterations of prognostic significance (82-84). Several groups have reported that copy number alteration burden across the genome was associated with PSA recurrence and metastasis after prostatectomy (82-85). The association was independent of PSA level and Gleason grade (82). Similarly Lalonde et al and Levin et al. found an association of DNA based genomic instability (copy number profiles) and PSA recurrence after local therapy (83-84)

Advanced technologies for genomic assessments are now available that are able to use smaller DNA/RNA inputs and available FFPE tissue and are suited to sampling obtained real time from clinical specimens. These technologies include whole exome and whole genome DNA sequencing and nanostring-RNA analyses (86-88) and RNA expression platforms (89).

Alliance 90203 specimens include prostatectomy tissues from untreated and treated (androgen deprivation and docetaxel) patients with high risk prostate cancer. Additionally pretreatment prostate biopsy specimens will be available in some participants. These tissues will provide opportunities to for DNA and RNA based discovery with correlation to clinical endpoints such as PSA failure rate.

11.2 Objectives

11.2.1 To identify genomic aberrations in matched diagnostic needle biopsy cores and radical prostatectomy specimens from men enrolled in the trial using deep targeted DNA-sequencing.

11.2.2 To identify mRNA expression changes of androgen receptor signaling genes, AR and the AR V7 splice variant, neuroendocrine prostate cancer, epithelial mesenchymal transition, and cell cycle-associated genes, TMPRSS2-ERG fusion transcript, and control/housekeeper genes in matched diagnostic needle biopsy cores and radical prostatectomy specimens.

11.2.3 To correlate the presence of baseline and post-treatment expression changes and genomic aberration and clonality states with pathologic response and clinical outcomes.

11.2.4 To correlate genomic and gene expression differences in prostatectomy specimens from treated vs. untreated cases with clinical outcomes.

11.2.5 Validation of the Decipher metastasis signature as predictive of response to neo-adjuvant docetaxel and androgen deprivation prior to radical prostatectomy versus immediate radical prostatectomy in patients with high-risk, clinically localized prostate cancer.

11.2.6 To test whether AR target gene signatures from clinical prostate cancer specimens obtained prior to administration of ADT will inform on response to ADT. This requires AR target gene

signatures to be summarized into AR activity scores and a quantization method to summarize AR target gene signatures into AR activity level.

11.2.7 To validate GEMCaP biomarkers in predicting recurrence using the 90203 control arm patient set and evaluate GEMCaP as a predictive biomarker of response to neoadjuvant chemotherapy/ADT using the 90203 test arm patient set.

11.2.8 To characterize expression of microRNAs in 90203 specimens.

11.2.9 To develop and validate a comprehensive prognostic models of clinical outcomes (3-year bPFS rate, bPFS metastases-free survival and overall survival) that can be used for risk stratification of patients with prostate cancer, using clinical and molecular markers.

11.3 Methods

DNA and RNA extractions from baseline biopsies and RP samples will be performed by Dr Gleave/Beltran's team from FFPE specimens and distributed to other groups for analysis.

We will review H&E slides from each diagnostic biopsy core. We will select from each patient two positive cores (with >50% tumor content). Each core will be assessed for Gleason score and other morphologic features. We will extract DNA and RNA from each FFPE biopsy core. DNA will be extracted using the Covaris truXTRAC FFPE DNA Kit. DNA concentration will be assayed using the Qubit and the Qubit dsDNA HS assay kit. RNA will be extracted using the Ambion RecoverAll™ Total Nucleic Acid Isolation Kit. RNA quality control will be performed on the Agilent 2100 Bioanalyzer system by annotating total RNA concentration and percentage of RNA greater than 300 nucleotides (nt) in length. For samples with more than 50% of total RNA greater than 300 nt, 100ng input RNA will be used; for samples with less than 50% of total RNA greater than 300 nt, the input RNA will be proportionally increased according to the level of degradation. Pathology review will be carried out simultaneously on matched radical prostatectomy specimens, where tumor size, grade (if possible) and evidence of any unusual features (e.g. neuroendocrine differentiation) will be documented. Macrodissection of tumor and benign tissue, and DNA and RNA extraction, will be performed as described above.

We will employ a deep targeted sequencing strategy for the identification of mutations and copy number changes using a custom NimbleGen SeqCap EZ Choice Library (specifically designed for aggressive prostate cancer by Dr. Wyatt) and our in-house Illumina sequencing machines. Our custom design includes 75 prostate-cancer relevant genes, including for example AR pathway genes, prostate cancer drivers (e.g. TP53, SPOP), cell cycle drivers (e.g. CCND1, RB1, CDK4/6), DNA repair genes (e.g. BRCA1/2, FANC family genes, ATM, MSH2/6), PI3K pathway genes (e.g. PIK3CA, PTEN). From each clinical specimen 10ng of DNA will be used for library construction using the KAPA Library Prep Kit, SeqCap EZ Reagent Kit and the SeqCap Adapter Kit (Roche). Target enrichment will be performed using the EZ Choice Library according to the manufacturer's protocol (Roche NimbleGen). Libraries will be sequenced in batches of 8-48, using our Illumina MiSeq with 25M read kits. DNA sequence reads will be trimmed and aligned with Bowtie-2.2.6 against GRCh37. Somatic mutations will be called by comparing allele read counts between tumor and benign samples, requiring a somatic mutation to have an allele fraction >1.0%, 20x higher allele fraction than paired benign and median of all benign samples, and to have a statistically significant difference in the mutant allele read count relative to paired benign ($p<1e-20$, chi-square test). All variants will be annotated for biological significance using ANNOVAR. Mutation candidates will be inspected visually for strand bias, amplicon bias, and positional bias within reads. To call copy number changes, aligned reads will be counted at each amplicon using bedtools-2.25.0. Sample-specific differences in overall read coverage will be multiplicatively corrected using medians-of-ratios calculated across regions

with low rates of copy number alterations in prostate cancer. After normalization, amplicon coverage log ratios will be calculated between tumor and paired benign samples.

For gene expression changes, we utilize NanoString nCounter® Analysis System using 100-300 ng RNA from FFPE tissue to quantify expression levels of a panel of 149 genes, including the AR signaling signature genes (n=30), AR and the AR V7 splice variant, neuroendocrine prostate cancer, epithelial mesenchymal transition, and cell cycle-associated genes, TMPRSS2-ERG fusion transcript, and control /housekeeper genes. Samples will be run according to the manufacturer's directions. Briefly, total RNA will be hybridized overnight at 65°, then run on the Prep Station at max sensitivity. Cartridges will then be scanned on the Digital Analyzer at 555 fields of view. Raw count data will be normalized using the nSolver™ analysis software version 2.0, which normalizes samples according to positive and negative control probes and the geometric mean of the 6 housekeeping primers.

Davicioni

Decipher has been identified (90) and independently validated for prediction of post-RP biochemical failure (91), metastasis (92-95), prostate cancer specific mortality (96) and benefit from adjuvant radiation therapy (97). However, since GC was originally developed as a prognostic model to predict metastasis after RP, there is no guarantee that this marker will validate as a predictive biomarker (i.e., a significant interaction term between the biomarker and treatment). Therefore, we will use the Decipher platform (i.e., a high density oligonucleotide microarray optimized to generate expression data from FFPE derived RNA) to enable discovery, evaluation and validation of published genes, signatures or key pathways in addition to validating the primary objective of the study. The Decipher platform is a clinical grade assay that interrogates over 1.4 million expressed markers from over 46,000 annotated genes and non-coding RNAs. We will also leverage the Decipher GRID (Genomic Resource Information Database), consisting of RNA expression profiles of over 5,000 prostate cancer patients from both retrospective and prospective cohorts to augment our analyses. Leveraging the Decipher GRID we can determine the expression levels of key genes involved in DNA repair and AR signaling pathways as described previously (99-100) in order to evaluate their ability to predict response/sensitivity or treatment failure/resistance. In addition, we will evaluate these pathways in a context specific manner using prostate cancer subtypes available on the GRID as described previously (101-102). The GRID analyses will help us understand the relationship be prevalence of alterations in these key pathways with clinical outcomes of patients in both arms of the trial in comparison to contemporary high risk prostate cancer patients. In addition, it is anticipated that by the time we obtain trial patient expression data for analysis additional signatures (e.g., Schaeffer and Karnes et al., "A novel ADT resistance signature predicts rapid metastasis after postoperative adjuvant hormonal therapy"; manuscript in preparation, You S et al., "Three intrinsic subtypes of prostate cancer with distinct pathway activation profiles differ in prognosis and treatment response"; manuscript in review) currently in development using the GRID will have been published and available for evaluation.

Heemers

RNA Data from Decipher array will be obtained from Dr Davicioni's team and analyzed as follows.

1. **AR target gene signatures to be summarized in AR activity scores**
    a. an AR target gene profile from ADT-naïve CaP cells serves to measure response to first-line ADT
    b. an AR target gene profile from ADT-recurrent CaP is included as it may mediate non-response to primary ADT
    c. similarly-sized random gene signatures are included as additional controls
2. **Quantitation method to summarize AR target gene signatures in AR activity level**

The expression profile of AR target gene signature(s) obtained from an individual patient's CaP specimen is summarized to measure quantitatively AR activity. Specifically, singular value decomposition is applied to the expression profile of the AR target gene signature, and the resulting top principle component is fitted to the Bayesian probit regression mode. Leave-one-out-cross validation is used to test the accuracy of the predictive signature.

3. Determining response to ADT

a. a. The decline in serum PSA levels serves as an indicator of treatment response. A fall in serum PSA by <90% is considered no response; fall by >/= 90% good response; fall by >/= 90% and to< 4 ng/ml excellent response; and a fall by >/= 90% and to undetectable [< 0.2 ng/ml] outstanding response, and

b. b. PCWG2 response criteria.

Statistical considerations

Association between AR activity score and response to ADT is assessed using Student's t-test. For populations with unequal variances, Welch's t-test is used. If normality is not satisfied (Kolmogorov-Smirnov test) even after log-transformation, wilcoxon rank sum test is used. Spearman rank correlation is used also to assess the association between continuous variables. Multiple testing correlations are performed when appropriate.

4. Defining the clinical utility of an AR activity assay to predict response to ADT

The predictive potential of AR activity scores is compared to that of clinical parameters claimed to predict response to ADT before (performance status, age, Gleason grade, serum levels of PSA, alkaline phosphatase or testosterone). The clinical utility of AR activity score to predict response to ADT will be determined in comparison with these parameters, individually or in combination (combination of 2 up to 5 parameters).

Statistical considerations

The diagnostic utility of AR target gene expression in discriminating patients in terms of dichotomized measures of clinical response will be examined through the generation of the receiver operating characteristic (ROC) curve. The area under the ROC curve (AUC) also will be computed. The area under the curve is a measure of the predictive power of a diagnostic model and thus may be taken as a measure of the overall diagnostic accuracy of expression in terms of predictability of outcome. A 95% confidence interval for the AUC will be calculated based on bootstrap re-sampling methods. In a similar fashion, the AUC for other predictors (pre-treatment PSA, Gleason score, etc.) will be calculated and compared using a hypothesis test for correlation with AR expression. The fact that the areas under the curve will be derived from the same set of patient data implies that the measures themselves will be correlated and so testing will be based on use of bootstrap methodology that incorporates this information. The bootstrapping algorithm will involve re-sampling of the within-patient values. A nominal significance level of 0.05 will be used.

Paris

Using existing genomic data (TBD: NGS, aCGH or SNP microarray), we will derive copy number for the GEMCaP loci. We have existing, published methods to derive GEMCaP copy number depending on the genomics platform used in 90203. The GEMCaP predictions will be compared to those from both CAPRA-S and the Kattan postoperative nomogram, which both only use clinical variables. (84, 98)

Tewari

MicroRNAs are short (~22 nt) noncoding RNAs that play important roles in regulating multiple mechanisms underlying carcinogenesis and cancer progression. Here we will

characterize expression of a panel of 10 candidate microRNA markers of prostate cancer aggressiveness, as well as perform global profiling of miRNAs to discover additional markers to be integrated into a multi-parameter outcome classifier. Technology development for miRNA analysis on RNA prepared by Gleave/Beltran team will be carried out. If this material is not suitable for miRNA work then RNA will be extracted from tissue specimens using standard methods (Ambion, Inc.), followed by microRNA analysis using qRT-PCR assays based on locked nucleic acid-based primers for enhanced sensitivity and specificity (Exiqon, Inc.). After nonspecific filtering (e.g., miRNAs not expressed in the vast majority of specimens), data will be normalized using global quantile normalization as well as plate calibrator assays. Differential expression analysis will be done using parametric and non-parametric methods with groups stratified by outcome and corrections for multiple comparisons.

12.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

12.1 Qualified personnel

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

12.2 Unused drug

Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

12.3 Calculation of dose

The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

12.4 Docetaxel (NSC #628503)

Please refer to the FDA-approved package insert for docetaxel for product information, extensive preparation instructions, and a comprehensive list of adverse events.

Availability

In the U.S., docetaxel will be provided by Sanofi-Aventis and distributed by the Pharmaceutical Management Branch (PMB). The one vial preparation (injection concentrate) is replacing the previous preparation (docetaxel plus diluent). It is supplied in a solution as 80 mg/4 mL (or 20 mg/mL). Each mL contains 20 mg docetaxel in 50/50 (v/v) ratio polysorbate 80/dehydrated alcohol.

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

ECOG-ACRIN institutions in Peru receive the drug directly from Sanofi-Aventis.

In Canada, docetaxel is provided and distributed by Sanofi-Aventis. Docetaxel may be requested by completing the Clinical Drug Request Form, found on the NCIC PRC.3 trial Web site.

Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, and a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: [redacted]
- NCI CTEP Investigator Registration: [redacted]
- PMB Online Agent Order Processing (OAOP) application: [redacted]
- CTEP Identity and Access Management (IAM) account: [redacted]
- CTEP Associate Registration and IAM account help: [redacted]

- IB Coordinator: [redacted]
- PMB email: [redacted]
- PMB phone and hours of service: [redacted] Monday through Friday between 8:30 am and 4:30 pm (ET)

Storage and Stability

Unopened packages of docetaxel may be stored at room temperature or under refrigeration (36-77°F). Freezing will not adversely affect the product. If stored under refrigeration, vials should be allowed to stand at room temperature prior to dilution.

Infusion solutions prepared in PVC containers are reported to be stable for four days. Solutions for infusion prepared in polyolefin containers are reported to be stable for four weeks refrigerated or at room temperature. (123)

Preparation

The desired dose of docetaxel concentrate should be withdrawn and added to 250 mL of 0.9% sodium chloride or 5% dextrose for IV infusion. Doses of docetaxel of greater than 200 mg should be diluted in a larger volume of infusion solution in order to maintain a final concentration of 0.3 to 0.74 mg/mL.

Administration

The docetaxel infusion solution should be administered intravenously as a 1-hour infusion.

Toxicities

The most common adverse events expected with docetaxel include neutropenia, fluid retention, alopecia, myalgias and arthralgias, and asthenia.

The usual dose limiting toxicity is neutropenia, which is dose and schedule dependent and rapidly reversible. Neutropenia is greater in patients with hepatic dysfunction (see Section 9.2).

Fluid retention: Fluid retention commonly begins in the lower extremities and may become generalized. Severe fluid retention may be characterized by peripheral edema, generalized edema, pleural effusion, dyspnea, cardiac tamponade, or ascites. The likelihood of fluid retention may increase with increasing cumulative dose of docetaxel. The pathophysiology of docetaxel induced fluid retention appears to be extensive transcapillary filtration proteins induced by docetaxel followed by later saturation of lymphatic drainage. Recommended pretreatment to prevent fluid retention consists of dexamethasone 8 mg b.i.d. for three days beginning the day before each docetaxel dose. Moderate fluid retention has been reported in 27% and severe in 6.5% of patients despite dexamethasone pretreatment.

Alopecia is seen in the majority of patients treated with docetaxel.

Myalgias and arthralgias have been reported in 10-20% of patients. Myalgias are severe in less than 2%. Severe asthenia has been reported in 11% of patients but has led to treatment discontinuation in only 2.6% of patients. Symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration of performance status in patients with progressive disease.

The following adverse events are less likely or less likely to be severe: thrombocytopenia, hypersensitivity reactions, neurologic toxicities, cutaneous reactions, gastrointestinal reactions, cardiovascular reactions, and increased lacrimation.

Thrombocytopenia is uncommon and rarely severe.

Hypersensitivity reactions: Severe hypersensitivity reactions (hypotension and/or bronchospasm, or generalized rash/erythema) have been reported in approximately 2% of patients receiving dexamethasone pretreatment. Hypersensitivity reactions may be seen within a few minutes of starting docetaxel infusions. Minor reactions do not require interruption of therapy. Patients should not be re-challenged with docetaxel if they develop a grade 3 or 4 hypersensitivity reaction.

Neurologic: Severe neurosensory symptoms (paresthesia, dysesthesia, pain) have been reported in 6% of patients. The dose of docetaxel should be modified for moderate or severe symptoms (see Section 9.3). Symptoms tend to be slowly reversible.

Cutaneous: Localized erythema of the extremities with edema followed by desquamation has been observed. In the case of severe skin toxicity, an adjustment in dosage is recommended (see Section 9.6.2). Nail changes which predominantly include hypo- or hyper-pigmentation and occasionally onycholysis have occurred in 1-2% of patients.

Gastrointestinal: Gastrointestinal reactions are generally mild to moderate. Severe reactions (nausea, vomiting, diarrhea, stomatitis) have been reported in approximately 5% of patients.

Cardiovascular: Hypotension has been reported in less than 5% of patients, Heart failure, sinus tachycardia, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, and hypertension have been reported rarely.

Docetaxel has been associated with increased lacrimation that is thought to result from canalicular stenosis. Docetaxel concentrations were measured in tears in six patients; lacrimal concentration ranged from 14 to 70% of plasma concentration. This side effect may be more common with weekly versus three-weekly docetaxel. Artificial tears and/or ophthalmic steroids have been used with variable success. Although increased lacrimation has reportedly improved following discontinuation of docetaxel, dacryocystorhinostomy with placement of permanent tubes has been required in some patients.

Potential Drug Interactions:

The metabolism of docetaxel may be modified by the concomitant administration of compounds that induce (e.g., phenobarbital) or inhibit (e.g., itraconazole, ketoconazole, erythromycin) cytochrome P-450 3A4. Docetaxel has also been shown to inhibit CYP 3A4 in studies with human liver microsomes. Thus, docetaxel might increase the concentration of other drugs metabolized by this isoenzyme. To date, there is little documentation of such interactions in patients.

12.5 LHRH agonists

At the physician's discretion, equivalent LHRH agonists other than those listed below may be used.

12.5.1 Leuprolide Acetate

Please refer to the FDA-approved package insert for leuprolide for product information, extensive preparation instructions, and a comprehensive list of adverse events.

Availability

Leuprolide acetate is commercially available as a kit or prefilled dual-chamber syringe containing 7.5 mg or 22.5 mg and intended for administration every four weeks or every

12 weeks. (Lupron Depot®). The leuprolide in these single dose preparations is present as lyophilized microspheres.

Sanofi-Aventis is providing the Eligard® brand of leuprolide for (some) Canadian institutions, based on local regulations regarding reimbursement. Refer to the PRC.3 appendix found on the NCIC PRC.3 Web site for details.

Storage and Stability

Intact kits and syringes should be stored at room temperature. Once reconstituted using the diluent provided in the kit or syringe, leuprolide suspension is stable for 24 hours.

Preparation

Reconstitute the microspheres with the diluent provided in the kit or release the diluent in the syringe into the microspheres. Gently shake the reconstituted product to yield a uniform suspension.

Administration

Leuprolide 7.5 mg or 22.5 mg is administered via intramuscular injection every 4 weeks or every 12 weeks, respectively.

Toxicities

Common toxicities are mostly related to the effects of decreased serum testosterone. Hot flashes are seen in more than 50% of patients. Gynecomastia, impotence, and decreased libido are also related to decreased testosterone, although they do not occur as often as hot flashes. Decreases in bone mineral density are seen with chronic administration (e.g., > 6 months). Nausea/vomiting or anorexia have been reported in approximately 5% of patients, and cardiovascular adverse events (e.g., arrhythmias, peripheral edema) are also described. Injection site reactions occur infrequently.

The FDA issued a safety communication in October, 2010 based on their ongoing safety review of LHRH agonists. The safety communication discusses the potential for an increased risk of diabetes and cardiovascular disease (myocardial infarction, sudden cardiac death, stroke) associated with these agents. The risk is thought to be low in men receiving LHRH agonists for prostate cancer. In this trial, LHRH agonists are being administered for a short period of time. FDA recommendations include management of cardiovascular risk factors according to current standards of practice.

12.5.2 Goserelin acetate

Please refer to the FDA-approved package insert for goserelin acetate for product information, extensive preparation instructions, and a comprehensive list of adverse events.

Availability

Goserelin acetate is commercially available as a prefilled syringe containing 3.6 mg or 10.8 mg and intended for administration every 4 weeks or every 12 weeks, respectively.

Storage and Stability

Intact syringes should be stored at room temperature.

Administration

Goserelin 3.6 mg or 10.8 mg is administered by subcutaneous injection into the upper abdominal wall, every 4 weeks or every 12 weeks, respectively.

Toxicities

Common toxicities are mostly related to the effects of decreased serum testosterone. Hot flashes are seen in more than 50% of patients. Gynecomastia, impotence, and decreased libido are also related to decreased testosterone, although they do not occur as often as hot flashes. Decreases in bone mineral density are seen with chronic administration (e.g., > 6 months). Nausea/vomiting or anorexia have been reported in approximately 5% of patients, and cardiovascular adverse events (e.g., arrhythmias, peripheral edema) are also described. Injection site reactions occur infrequently.

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13.0 ANCILLARY THERAPY

13.1 Supportive care

Patients should receive *full supportive care*, including transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. However, the use of aprepitant is prohibited in this study The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the CALGB C-260 Remarks Addenda.

13.2 Other chemotherapeutics agents

Treatment with *other chemotherapeutic agents* may not be administered except for steroids given for adrenal failure; hormones administered for non-disease-related conditions (e.g., insulin for diabetes); and intermittent use of dexamethasone as an antiemetic or as pretreatment for patients receiving docetaxel.

13.3 CALGB 90203 Policy Concerning the Use of Growth Factors

The following guidelines are applicable unless otherwise specified in the protocol:

13.3.1 Epoetin

The use of epoetin or darbopoetin is permitted at the discretion of the treating physician.

13.3.2 Filgrastim (G-CSF), sargramostim (GM-CSF), and pegfilgrastim

- 1. Filgrastim (G-CSF), sargramostim (GM-CSF), and pegfilgrastim treatment for patients on protocols that do not specify their use is discouraged.
- 2. Filgrastim, and sargramostim, and pegfilgrastim may not be used to avoid dose reductions or delays as specified in the protocol.
- 3. For the treatment of febrile neutropenia the use of CSF's should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSF's may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSF's in this setting. The use of CSF must be documented and reported on data forms.
- 4. If CSFs are used, they must be obtained from commercial sources.

14.0 CRITERIA FOR DISEASE PROGRESSION AND RELAPSE

14.1 Progression Free Survival (PFS)

The primary endpoint is the rate of 3-year biochemical progression-free survival (bPFS). Secondary endpoints include 5-year bPFS rate and bPFS. Patients will be followed with history, physical examination and serum PSA and testosterone levels every 3 months for the first 3 years following surgery, every 6 months for the next 3 years and annually thereafter until 15 years following registration.

If patients experience treatment failure per Sections 14.1.3 or 14.1.4 during the first 3 years following surgery, evaluations will be done every 6 months. These patients will be followed until biochemical or metastatic disease progression per Sections 14.1.1 or 14.1.2, then followed for survival until 15 years after registration.

It is expected that the majority of patients will relapse biochemically with a rising PSA.

Time to progression will be defined as the time from the date of randomization to the date of distant or local recurrence as defined below:

- • Biochemical failure (see Sec. 14.1.1)
- • Any new evidence of metastatic disease based on bone or CT/MRI scan. If based solely on PET or ProstaScint scan, it must be confirmed with a biopsy (see Sec. 14.1.2).
- • Local recurrence in prostate bed, which must be accompanied by pathologic confirmation (by biopsy) in addition to CT/MRI scan evidence (see Sec. 14.1.2).
- • Treatment with post-operative radiotherapy for a rising PSA or adjuvant radiation initiated more than 6 months following surgery (see Sec. 14.1.3).
- **Time to treatment failure** will be defined as the time from the date of randomization to the date of the following:
- • Initiation of androgen deprivation therapy (see Sec. 14.1.4).
- • Initiation of any other investigational therapy for the treatment of the prostate cancer (see Sec. 14.1.4).

Time to metastatic disease progression will be defined as time from date of randomization to date of evidence of systemic disease on bone scan or CT/MRI.

14.1.1 Biochemical Failure: Biochemical failure will be defined as a serum PSA level > 0.2 ng/mL that increases on 2 consecutive occasions each of which is at least 3 months apart. The time of biochemical failure is measured from the date of randomization to the date of the first PSA level > 0.2 ng/mL.

14.1.2 Development of radiographic disease: Any new evidence of metastatic disease on bone or CT\MRI scan will constitute disease progression. Evidence of disease progression based solely on PET or ProstaScint scan will only be accepted if a biopsy confirms the metastatic disease. Patients with local recurrence in the prostate bed will also be considered as disease progression if pathologic confirmation by biopsy is obtained.

14.1.3 Post-operative radiotherapy: Patients with positive surgical margins, extraprostatic extension, and/or seminal vesicle invasion will be allowed to receive adjuvant external beam radiation to the prostatic fossa based on the judgment of the treating physician; such therapy must be initiated within 6 months after surgery. Although the efficacy and timing of such treatment is a matter of debate, physicians and patients may choose this treatment based on the available data. These patients will not be considered treatment failures, but will continue on standard follow-up according to the protocol and will be included in the final analysis.

Post-operative radiotherapy for a rising PSA or adjuvant radiation initiated more than 6 months following surgery will be considered disease progression. The field of radiation will be according to the standard of the treating institution and may include whole pelvis irradiation or limit the field to the prostatic fossa. Adjuvant radiation including up to four months of neoadjuvant/concurrent androgen deprivation therapy will be allowed. For the radiation to be considered adjuvant, the patient also must not have met the definition of biochemical failure.

14.1.4 Systemic Therapy: Patients with lymph node metastases at staging pelvic lymphadenectomy or radical prostatectomy will be allowed to have immediate androgen deprivation therapy, if desired. Since androgen deprivation therapy will affect time to biochemical and metastatic disease progression, and possibly survival, these patients will be considered treatment failures at the time of initiation of androgen deprivation therapy. Investigators are encouraged to delay post-operative

systemic therapy, including androgen deprivation therapy, until the patient has documented evidence of biochemical failure.

Any other systemic therapy, including androgen deprivation therapy that is initiated for the treatment of the prostate cancer, will also be considered treatment failure.

14.2 Criteria for metastatic disease-free survival and overall survival

14.2.1 Time to metastatic disease progression will be defined as the date of randomization to date of evidence of systemic disease on bone scan or cross sectional imaging or death from any cause, whichever occurs first.

14.2.2 Overall survival will be defined as date of randomization to date of death due to any cause.

14.3 Criteria for biochemical response to chemo-hormonal therapy

Response to docetaxel and androgen deprivation therapy in the neoadjuvant arm is defined as those patients having a biochemical complete response (PSA < 0.1) prior to prostatectomy.

15.0 Removal of Patients from Protocol Therapy

15.1 Duration of Treatment

Disease Progression: Patients who experience disease progression per Sections 14.1.1, 14.1.2, or 14.1.3 will be treated at the treating physician's discretion. At that time, follow the patient for survival, new primary and secondary malignancy according to the data submission schedule.

Treatment Failure: For patients who experience treatment failure per Section 14.1.4, submit full follow-up data for this study until the patient has reached an endpoint (progression) for the study.

15.2 Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the Study Chair.
- Document the reason(s) for discontinuation of therapy on forms.
- Follow the patient for survival, new primary, and secondary malignancy until 15 years after randomization.

15.3 Study Endpoints

The endpoints for this study are:

- Biochemical progression-free survival and progression-free survival
- Death

16.0 Statistical Considerations

This is a randomized, phase III trial where a total of 750 men will be randomized with equal probability to one of two arms: the standard arm being immediate radical prostatectomy and bilateral pelvic node dissection and experimental arm being neoadjuvant androgen deprivation therapy and docetaxel chemotherapy followed by radical prostatectomy and bilateral pelvic node dissection. The randomization will be stratified by the Kattan nomogram-predicted 5-year biochemical progression-free survival (bPFS) of < 21%, 21-39.9%, 40-59.9%, and ≥ 60%; and prior androgen deprivation therapy (no, yes).

16.1 Statistical Considerations for the Clinical Study

16.1.1 Endpoints

The primary endpoint is the 3-year biochemical progression-free survival rate (3-year bPFS). Secondary endpoints are 5-year bPFS rate and bPFS. Other endpoints are time to clinical local recurrence, time to metastatic disease progression, unacceptable toxicity, prostate cancer-specific free survival, disease progression, and overall survival (OS). Biochemical disease failure will be defined as the time from randomization to the date of biochemical disease failure as defined in Section 14.1.1. Time to clinical local recurrence will be defined as the time from randomization to the first biopsy-proven recurrence in the prostatic bed (new mass). Time to metastatic disease progression will be defined as the date of randomization to date of evidence of systemic disease on bone scan or cross sectional imaging. Unacceptable toxicity will be defined as any grade 3 or higher toxicity.

Prostate cancer-specific free survival will be defined as the time from randomization to the time of death due to prostate cancer. OS will be defined as date of randomization to date of death due to any cause.

16.1.2 Sample Size Determination

The following calculations assume a monthly accrual rate of about 13 patients per month accrued over a 60-month period, and followed for 36 months after study closure. Based on the experience of patients treated at MSKCC, 5-year freedom from recurrence in the standard arm (i.e., those patients with a nomogram prediction < 60%) is expected to be approximately 40%. The 3-year bPFS rate in the standard arm is expected to be 57.7%. This study is designed so that the two sample binomial test has 89% power assuming a one-sided type I error rate = 0.025 to detect almost 12% difference between the two groups, when the true rates of 3-year bPFS are 57.7% (standard arm) and 69.1% (experimental arm).

16.1.3 Interim Analysis

The Alliance DSMB on a semi-annual basis will review the study for safety, progress toward completion, and, when appropriate, interim analyses of outcome data to coincide with the meetings of the DSMB. In this patient population, it is anticipated that biochemical progression may occur within 1-2 years after the patient is treated with RP. Furthermore, because the primary endpoint is 3-year bPFS rate, it is expected that data will not be available for formal analyses before 54 months after study activation. However, toxicity (grade 3 or higher) and survival data (proportion of patients dead) will be presented in the report to the DSMB. The first interim analysis will be performed when 30% of the patients have been followed for at least 3 years (at about 54 months after study activation, Table 1). In addition, there will be seven interim analyses besides the final analysis. The remaining analyses will be performed when 40% of the patients have completed at least 3 years of follow-up (about 60 months), and when 50% (about 66 months), 60% (about 72 months), 70% (about 78 months), 80% (about 84 months), 90% (about 90 months), and 100% of the patients have completed 3 years of follow up (about 96 months after study activation). It is not planned that accrual will be halted while the interim analyses are undertaken. **To help insure complete data on which to base the interim analyses, progression events (follow-up forms) should be faxed to the Alliance Statistics and Data Center within one week of being reported to the institution.**

A group sequential test design by O'Brien and Fleming (124) will be used to stop the trial early both to accept and to reject the null hypothesis. The z-score boundaries for stopping for superiority for bPFS are: 3.809, 3.299, 2.951, 2.694, 2.494, 2.333, 2.199, and 2.087. The z-score boundaries for stopping for futility for bPFS at a fixed alpha level = 0.005 are: -0.788, -0.512, -0.268, -0.048, 0.155, 0.343, 0.520, and 2.087. Should any boundary be crossed, accrual to the study will be recommended to be stopped.

Table 1
Boundaries for Interim Efficacy Analyses

Time (months)	Percent of patients with at least 3 years of follow-up (number)	z-scores For Superiority	z-scores For Futility
54	30% (225)	3.809	-0.788
60	40% (300)	3.299	-0.512
66	50% (375)	2.951	-0.268
72	60% (450)	2.694	-0.048
78	70% (525)	2.494	0.155
84	80% (600)	2.333	0.343
90	90% (675)	2.199	0.520
96	100% (750)	2.087	2.087

16.1.4 Data Analysis

A modified intent-to-treat approach will be used in this phase III study. The primary analysis will be based on the comparisons of the Kaplan-Meier bPFS rate at 3 years. Patients who had lymph node metastases at the time of radical prostatectomy (RP) will be censored at the first date of initiation of androgen deprivation therapy. The Kaplan-Meier product-limit estimator (125) will be used to estimate the 3-year and 5-year bPFS rates, bPFS, time to local recurrence, time to clinical metastases and OS. In addition, the stratified log-rank test (126) to compare the two treatment arms on bPFS, time to clinical metastases and OS.

Furthermore, the Chi-square test will be used to compare the two arms on pathologic tumor stage, the proportion of patients with lymph node metastases, positive margins, and grade 3 or higher toxicity. The proportional hazards model (127) will be used to assess the effect of the treatment arm on bPFS, time to metastases and OS adjusting on baseline patient characteristics, pathologic variables and stratification factors. All secondary analyses will use a two-sided type I error rate of 0.05. For objective 2.4, because of competing risks, we will use analyses based on cumulative incidence and cumulative conditional probability (128). For objective 2.6, the proportional hazard model will be used to test if the change (increase) in serum testosterone levels will predict bPFS outcome in men treated with neoadjuvant androgen deprivation therapy and docetaxel chemotherapy followed by radical prostatectomy and bilateral pelvic node dissection. This analysis will be exploratory in nature and will try to generate hypotheses among this group of high risk undergoing RP plus/minus neoadjuvant chemohormonal therapy.

16.1.5 Accrual and Follow-up

The target sample size is 750 and assuming that Alliance institutions will enroll about 13 patients per month, accrual will be completed in about 5 years after IRB approval. Accrual will be completed significantly sooner if, as anticipated, there is accrual from SWOG and ECOG-ACRIN institutions via the CTSU. All patients will be followed for PFS and OS for 15 years following registration.

16.1.6 Accrual Expansion with Update #08

The original target sample size was 750 evaluable patients. The target of 750 patients was reached on 06/24/2015. Due to the fact that over 4% of the patients did not have surgery or withdrew consent prior to observing the biochemical failure endpoint, the total sample size has been increased by 5% to 788 patients to account for these events.

16.1.7 Statistical Considerations for the PSADT as a surrogate Marker of Outcome

Prentice's criteria require that for an endpoint to be surrogate for the "true" endpoint, three conditions should be satisfied. First, there is a treatment effect with respect to the surrogate endpoint. Second, the surrogate endpoint is a prognostic factor of the true endpoint, and finally that the surrogate endpoint should capture all treatment effect on the true endpoint.

Prentice's criteria will be applied to determine if PSADT is a potential surrogate endpoint for time to metastatic disease progression and overall survival. PSADT will calculated as the ratio of natural log 2/slope of log PSA by time. The proportional hazards model will be used to test if the treatment is prognostic of overall survival and of the surrogate endpoint. Next, the proportional hazards model will be used to test if the surrogate endpoint is prognostic of overall survival. Finally, the proportional hazards model will be used to test if the treatment effect on overall survival is explained by the surrogate endpoint.

16.2 Statistical Considerations for the Diet and Lifestyle Study

16.2.1 Power Computation

The primary objective of the dietary component of this study is to test whether fish intake decreases the risk of biochemical progression at 3 years. Assuming that the 80% of the patients (n = 600) will complete the diet and food questionnaires, power computations are based on the proportions of patients who are progression-free at 3 years and univariate tests of hypothesis testing assuming two-sided significance levels of 0.01. The power was based on testing the null hypothesis of independence versus the alternative of a linear trend in the 3-year progression rate over quintiles. With 600 patients, the power is 80% to detect a relative risk of 2.1 (5th quintile versus 1st in fish consumption) assuming a two-sided alpha = 0.01.

16.2.2 Data Analysis

Because of the multiplicity of hypotheses and endpoints (3-year and 5-year bPFS rates and bPFS) being tested, we will use a type I error rate of 0.01 for all exploratory dietary hypotheses being tested. Physical activity will be computed into metabolic units per week (METs, continuous variable), and then examined as quintiles or categorical variables. Unconditional logistic regression will be used for the outcomes 3-year and 5-year bPFS rates. In addition, the proportional hazards model will be used to compare the bPFS among the low and high intakes groups (based on the median) and extreme quartiles of food consumption and change in food consumption. For example, the hazard associated with being in the upper 25th percentile of fish consumption vs. the lowest 25th percentile will be examined. Individual food groups (e.g. red meat, dairy, grains, vegetables, fruits) and

relative changes in intake of these food groups will be examined. The following variables will be adjusted on in the multivariable models: total caloric intake, physical activity, body mass index, smoking, age, race, family history, treatment arm, and clinical and pathologic variables (e.g. tumor stage, grade, Gleason score).

16.3 Statistical Considerations for the Correlative Sciences Studies

The target sample size for this study is 750 patients. However, we do not expect that frozen prostate tissue will be submitted for all patients enrolled through the CTSU. We do not have historical data on CTSU accrual among patients with hormone refractory prostate cancer, but based on a renal study (CALGB 90206) we expect that 40% of the total accrual will be through the CTSU. Thus, we assume that frozen tissue will be submitted for 60% of all patients enrolled to the study and from our experience, we expect that 65% of those samples will have enough tissue to make RNA. Based on other Alliance studies, we expect that tissue and blood samples will be submitted for 80% of patients enrolled to the study. We therefore estimate that the number of samples assumed to be available will be 294 for the RNA-expression analyses of tumor tissue, 600 samples for the DNA (SNP) analyses of tumor tissue, 600 samples for serum proteomic analyses, and 600 samples for tissue (TMA) protein analyses.

16.3.1 Power Computation

The primary endpoint in CALGB 90203 is 3-year biochemical progression-free survival rates. Other endpoint of interest is pathologic response and biochemical progression-free survival.

Power computation is based on testing whether genes will predict pathologic response.

We anticipate having access to 200 specimens from CALGB 90203. We assume that the specimens will yield enough RNA, DNA & microRNA data. We used the method by Yang et al to derive the power based on non-central F-distribution. The non-centrality parameter is defined as a function of the effect size $|\mu_2 - \mu_1|/\sigma_s$, and the type-I error rate adjusted for false discovery (α^*) where $\alpha^* = \alpha\ (\max[1, n_0])/n_g$ and α=0.05. By setting the type-I error = α^* ensures a false discovery rate = α, and note that when $n_0 = 1$, α^* is the Bonferroni-adjusted type-I error rate. Estimates for many of these parameters are usually unknown prior to the study but we use reasonable estimates from prior studies. For example, an effect size=2 corresponds to a two-fold difference between groups in mean expression ratios on a log(base 2) scale when variance between the subjects $\sigma_s^2 = 0.5$. This is a typical median value observed in tumor samples. Table 1 provides the power estimates assuming an adjusted type I error rate of 0.000005682, effect size of 2, five truly differentiated genes, and a total sample size of 200.

We estimated the power for comparing expression in 200 men with and without pathological response. Thus, the proposed sample size will give excellent power to detect at least 1.5-2-fold increases in expression ratios.

Table 1. Power computation for pathological response

Prevalence of Pathologic response	Variance Ratio (σ_e^2/σ_s^2)	Effect Size	Power
0.1	0.25	1.5	0.843
0.2	0.25	1.5	0.998
0.3	0.25	1.5	0.999

0.4	0.25	1.5	1.000
0.5	0.25	1.5	1.000
0.1	0.5	1.5	0.700
0.2	0.5	1.5	0.986
0.3	0.5	1.5	0.999
0.4	0.5	1.5	~1.000
0.5	0.5	1.5	1.000
0.1	1.0	1.5	0.439
0.2	1.0	1.5	0.904
0.3	1.0	1.5	0.984
0.4	1.0	1.5	0.996
0.5	1.0	1.5	0.997
0.1	0.25	2	0.997
0.2	0.25	2	1.000
0.3	0.25	2	1.000
0.4	0.25	2	1.000
0.5	0.25	2	1.000
0.1	0.5	2	0.986
0.2	0.5	2	1.000
0.3	0.5	2	1.000
0.4	0.5	2	1.000
0.5	0.5	2	1.000
0.1	1.0	2	0.904
0.2	1.0	2	0.999
0.3	1.0	2	0.999
0.4	1.0	2	1.000
0.5	1.0	2	1.000

In addition, we present the power computations based on the binary endpoint 3-year bPFS rate. Let θ =probability of $X_n<X_l$, where X_n is risk prediction scores is normally distributed in men who have not progressed with mean 0 and variance 1, and X_l will be normally distributed with mean 0.50 and variance=1 in men with progression prostate cancer. The null hypothesis to be tested is that the area under the ROC curve θ =0.50 versus the alternative hypothesis is different than 0.5. Table 2 presents the power for the Wilcoxon test to detect an area under the ROC curve (θ) =0.65 based on a 10,000 simulations assuming a total of 200 patients, unequal allocation between the two groups, and a two-sided type I error rate 0.05. Thus, the proposed sample size will give excellent power to detect θ =0.65. We assumed also assumed different distribution for the prediction scores (such as beta distribution) and they yielded similar empirical power.

Table 2. Power associated with ROC

Number of patients with lethal prostate cancer	Number of patients without lethal prostate cancer	Simulated type I error rate	Power
20	180	0.0485	0.5339
40	160	0.0508	0.7857
60	140	0.0501	0.8759
80	120	0.0522	0.9356
100	100	0.0483	0.9314

In addition, we provide power computation for validating the final model based on the a time-to-event endpoint, bPFS . Although the risk predictions follow a normal distribution, for simplicity in computing the power we dichotomize the risk scores: as less than the median and greater than the median. We do not know the number of events among the 200 patients, but we assume that there will be between 50-100 events. Table 3 provides the minimum hazard ratio detectable, assuming a two-sided type I error rate of 0.05, sample size of 200, power=0.80, event rate of 25%-50%, and prevalence of 0.10-0.50. The power computations are based on the assumption that the bPFS follows an exponential distribution. The log-rank test has sufficient power to detect moderate effect sizes.

Table 3. Minimum detectable HR under a range of conditions and assuming a two-sided type I error rate =0.05 and 200 patients.

Prevalence of risk prediction score	Number of events	Hazard ratio
0.10	50	3.75
0.10	100	2.54
0.20	50	2.69
0.20	100	2.01
0.30	50	2.37
0.30	100	1.84
0.40	50	2.24
0.40	100	1.77
0.50	50	2.21
0.50	100	1.75

16.3.2 Data Analysis

It is expected that once the designated laboratory data are generated, normalized data will be sent to the Alliance Statistics and Data Management Center for statistical analysis. There are several objectives in this CS study.

1. To identify genomic aberrations in matched diagnostic needle biopsy cores and radical prostatectomy specimens from men enrolled in the trial using deep targeted DNA-sequencing

   The genomic identification of significant targets in cancer (GISTIC) method will be used to identify genomic aberrations in matched diagnostic needle biopsy cores and radical prostatectomy specimens. GISTIC is a statistical method for analysis of genomic aberrations and was developed by Beroukhim et al.[1]. It identifies regions of the genome that are aberrant more often than would be expected by chance with greater weight given to high amplitude events (for example, high level copy number gains or homozygous deletions) that are less likely to be random. Each genomic aberration in GISTIC will be assigned a G-score that considers the amplitude of the aberration and the frequency of occurrence across samples [1,2] and then false discovery rate (FDR)

q-values are calculated for the aberrant regions. Regions with q-values below a user defined threshold are considered significant. GISTIC outputs the genomic location and calculated q-value for the aberrant regions and identifies the samples that exhibit each significant gains or deletions. After obtaining the genomic aberrations, we will compare aberrations from biopsy cores with that from radical prostatectomy specimens to identify matched and unmatched regions of aberrations. The employment of FDR may be problematic in this framework given the potentially strong spatial dependence among the genomic regions. Therefore, permutation resampling will also be employed, to adjust for the family-wise error rate (FWER) at the 0.05 level.

2. To identify mRNA expression changes of androgen receptor signaling genes, AR and the AR V7 splice variant, neuroendocrine prostate cancer, epithelialmesenchymal transition, and cell cycle-associated genes, TMPR-SS2-ERG fusion transcript, and control/housekeeper genes in matched diagnostic needle biopsy core and radical prostatectomy specimens.

   First, the raw data will be pre-processed and normalized using the DEseq algorithm. Briefly, the DEseq algorithm [3] takes the geometric mean of log values of each gene across samples and uses that as the reference expression data set. For each sample, a list of differences between log values of each gene expression and reference expression data set will be performed and then find median of a list. Then it takes exponential of the medians of each sample respectively and it divides gene expression values for each sample by each normalization factor. For the data analysis, we will use a parametric model based on the negative binomial distribution which explains better the technical and biological variance for count data and then takes permutation based multiple testing to detect significant expression changes.

3. To correlate the presence of baseline and post-treatment expression changes and genomic aberration and clonality states with pathologic response and clinical outcome (bPFS).

   We will utilize the univariate negative binomial regression model of two expressions for each marker. To identify significantly differentially expressed markers between the baseline and post-treatment changes, we will utilize multiple correction methods, such as FDR to control for the false-positive rate:

   We will also use the GISTIC method as outline in objective #1 to identify significant genomic aberrations between baseline and post-treatment.

4. To correlate genomic and gene expression differences in prostatectomy specimens from treated vs. untreated cases with clinical outcomes.

   We will also use simple negative binomial regression model for treated and untreated cases of each of expression markers. To identify significantly expressed marker between treated and untreated cases we will employ multiple correction methods. Similar to the above aims, we will use the GISTIC method to identify significant genomic aberrations between treated and untreated cases. In addition, the Spearman rank-correlation will be computed and these relationships between genes and clinical outcomes (pathologic response, 3-year bPFS) would be visualized with symmetric heatmaps.

5. Validation of the Decipher metastasis signature as predictive of response to neo-adjuvant docetaxel and androgen deprivation prior to radical prostatectomy versus immediate radical prostatectomy in patients with high-risk, clinically localized prostate cancer.

The Decipher score will be computed on all patients. A treatment arm by decipher score interaction will be used to detect possible predictive effect on bPFS. The Cox's proportional hazard model will be used with treatment arm, Decipher score and treatment arm-decipher score interaction term in predicting bPFS.

6. To test whether AR target gene signatures from clinical CaP specimens obtained prior to administration of ADT will inform on response to ADT. This requires AR target gene signatures to be summarized into AR activity scores and a quantitation method to summarize AR target gene signatures into AR activity level.

   Similar analyses as mentioned above will be performed.

7. Validate GEMCaP biomarkers in predicting recurrence using the 90203 control arm patient set and evaluate GEMCaP as a predictive biomarker of response to neoadjuvant chemotherapy/ADT using the 90203 test arm patient set.

   It is assumed that among the 200 patients, 100 patients will be from the control arm radical prostatectomy (RP). The GEMCAP score will be computed in the 100 patients randomized to RP. The Cox's proportional hazard model will be used with GEMCAP score as a covariate stratified on arm. The c-index will be computed as a measure of the predictive accuracy in predicting bPFS. In addition, the treatment arm-GEMCaP score interaction term will be tested using the Cox's proportional hazards model.

8. To characterize expression of microRNAs in 90203 specimens.

   Using the microRNA based on 376 gene expression levels. The comparative CT method algorithm will be used for normalization. The paired Wilcoxon test will be used to test for microRNA difference in matched benign and cancer tumors.

9. To develop and validate a comprehensive prognostic models of clinical outcomes (3-year bPFS rate, bPFS, metastases-free survival and overall survival) that can be used for risk stratification of patients with prostate cancer, using clinical and molecular markers.

   We will first perform univariate logistic regression (for the bPFS rate at 3 years) or Cox's regression (for the time-to-event endpoints) to identify genomic predictors of clinical outcomes. We will use Sure Independent Screening (SIS) and iterative SIS as a pre-screening step which will reduce the dimensionality of the data and then use variable selection methods (ALASSO). Both unadjusted (for multiplicity) and family-wise error rate (FWER) adjusted exact p-values, approximated by B=10,000 permutation replicates will be generated. Under the control of FWER, a list of significant biomarkers will be identified. Based on selected markers (expressions, RNA, microRNA, decipher score and GEMCap score etc.), we will build the best models which predict the clinical outcomes using variable selection models such as adaptive LASSO [4] and ELASTIC NET [5]. Because of the absence of external dataset, 5-fold cross-validation and bootstrapped approaches will be used to validate the final prognostic models of clinical outcomes. The c-index and time-dependent AUC will be computed as measures of predictive accuracy for the clinical outcomes.

   In addition, we plan to perform other analyses. We will employ the Kaplan-Meier product-limit method to estimate bPFS, MFS and OS distributions. We will also use the log-rank statistic to compare the bPFS, PFS, MFS and OS distribution by prediction levels (based on the model) categorized by quartiles. Moreover, the proportional hazards model will be used to assess the prognostic importance of the risk scores adjusting on

baseline clinical characteristics, such as stage, PSA and Gleason score in predicting the clinical outcomes.

17.0 ADVERSE EVENT REPORTING (AER)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Investigators are required to notify the Study Chair and their Institutional Review Board if a patient has a reportable adverse event. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for serious AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). All reactions determined to be "reportable" in an expedited manner must be reported using the CTEP Adverse Event Reporting System (CTEP-AERS), accessed via the CTEP website, https://eapps-ctep.nci.nih.gov/ctepaers.

CALGB 90203 Reporting Requirements:

CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of Treatment

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5	Grades 4 & 5
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment require reporting as follows:**
CTEP-AERS 10 calendar day report:
- Grade 4 unexpected events
- Grade 5 expected or unexpected events

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
  - ➢ "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exclusions from CTEP-AERS Expedited Reporting Requirements:

- Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor

growth or progression: clinical deterioration associated with a disease process) should be submitted.

- All grade 4 events that are unexpected and that are at least possibly related to treatment must be reported via CTEP-AERS within 10 calendar days.
- Any unexpected grade 4 event that precipitates hospitalization (or prolongation of existing hospitalization) must be reported via CTEP-AERS within 10 calendar days.
- Grade 4 events that are expected do not require CTEP-AERS expedited reporting, even if they result in hospitalization.
- Adverse events include those listed in Section 12.0 and in the package inserts.
- All adverse events reported via CTEP-AERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g., study summary forms or cooperative group data reporting forms (see Section 6.1 for required forms).
- Secondary malignancy: A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
    - CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. In CTCAE version 5.0, three options are available to describe the event:
    - -Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
    - -Myelodysplastic syndrome (MDS)
    - -Treatment-related secondary malignancy
    - Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.
- Second malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting unless otherwise specified.
- New primary malignancies should be reported using study form C-1244 via Medidata Rave®.
- Pregnancy loss is defined in CTCAE as "Death in utero." Any pregnancy loss should be reported expeditiously as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. A pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.
- A neonatal death should be reported expeditiously as Grade 4, "Death neonatal" under the General disorders and administration SOC.

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APPENDIX I

Collaborative Agreement Provisions

The docetaxel used in this protocol is provided to the NCI and Alliance under agreements between the **Sanofi-Aventis** (hereinafter referred to as Collaborator), the NCI Division of Cancer Treatment and Diagnosis and the Alliance for Clinical Trials in Oncology. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industry) contained within the terms of award, apply to the use of docetaxel in this study:

- 1. Docetaxel may not be used for any purpose outside the scope of this protocol, nor can docetaxel be transferred or licensed to any party not participating in the clinical study. Collaborator data for docetaxel are confidential and proprietary to Collaborator and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
-
- 2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):
- a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
- b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
- c. Any Collaborator having the right to use Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
-

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator, the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

- 4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
- 5. Any data provided to Collaborator for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
- 6. Any manuscripts reporting the results of this clinical trial should be provided to CTEP by the Group Office for Cooperative Group studies for immediate delivery to Collaborator for advisory review and comment prior to submission for publication. Collaborator will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator's intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator for courtesy review as soon as possible and preferably at three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract, and/or press release/media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

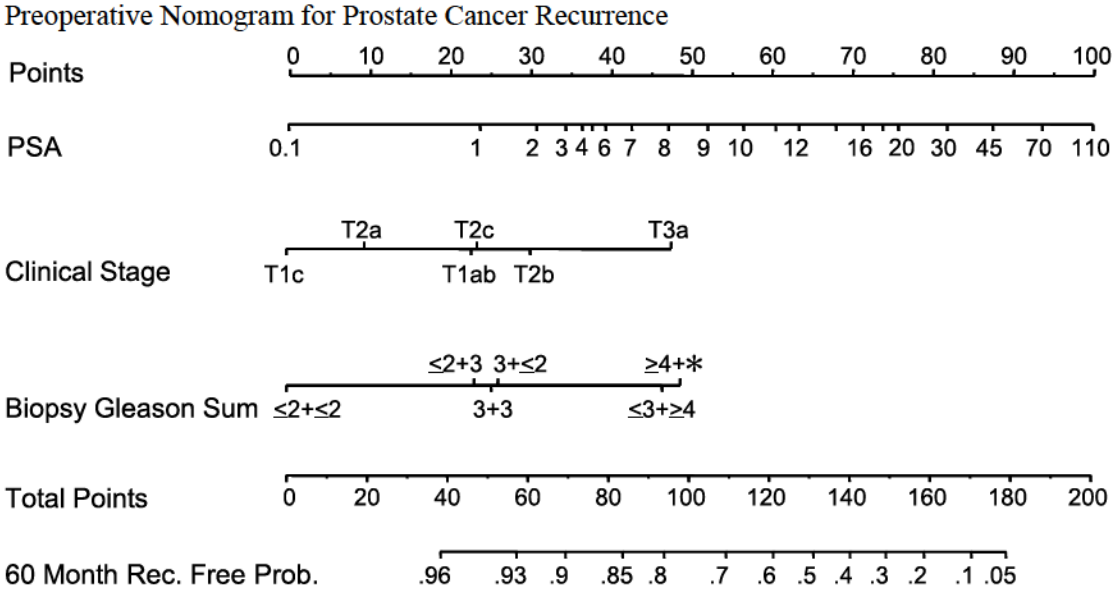
APPENDIX II

Kattan Nomogram Information

The Kattan preoperative nomogram for prostate cancer recurrence will be used to determine eligibility for this study.

An on-line calculator can be accessed at http://www.nomograms.org. A guide to the electronic calculator can be found on the following page.

The pre-biopsy PSA should be used for the Kattan nomogram calculator.



Instructions for Physician: Locate the patient's PSA on the **PSA** axis. Draw a line straight upward to the **Points** axis to determine how many points towards recurrence the patient receives for his PSA. Repeat this process for the **Clinical Stage** and **Biopsy Gleason Sum** axes, each time drawing straight upward to the **Points** axis. Sum the points achieved for each predictor and locate this sum on the **Total Points** axis. Draw a line straight down to find the patient's probability of remaining recurrence free for 60 months assuming he does not die of another cause first.

Note: This nomogram is not applicable to a man who is not otherwise a candidate for radical prostatectomy. You can use this only on a man who has already selected radical prostatectomy as treatment for his prostate cancer.

Instruction to Patient: "Mr. X, if we had 100 men exactly like you, we would expect between <predicted percentage from nomogram - 10%> and <predicted percentage + 10%> to remain free of their disease at 5 years following radical prostatectomy, and recurrence after 5 years is very rare."

Guide to Kattan nomogram on-line calculator

1. Use the link www.nomograms.org to access the Memorial Sloan-Kettering Cancer Center nomograms web site.
2. Click on the bullet, "Prostate Cancer," which will direct you to the "Prediction Tools" page.
3. Click on "Pre-Treatment" or scroll down to "pre-treatment nomogram" and click on this link.
4. A disclaimer will be shown; click "accept" at the bottom of the page.
5. Complete the "Enter Your Information" section, including clicking on the "Progression Free Probability after Radical Prostatectomy" button.
6. You do not need to fill in the "Planned or Non-Primary Treatment Information."
7. Scroll to "Enter Advanced Details (for Medical Professionals);" "Would you like to enter additional details" and click "no."
8. Click the "calculate" button.
9. Scroll back to the top of the page and on the right-hand side, click "Historical Model," which will be highlighted in blue.
10. The nomogram-predicted result is listed as: "Progression Free Probability after Radical Prostatectomy, 5-year."

APPENDIX III

2002 TNM Classification System [47]
Prostate

T-primary tumor

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 Clinically inapparent tumor not palpable
  - T1a Tumor incidental histologic finding in 5% or less of tissue resected
  - T1b Tumor incidental histologic finding in more than 5% of tissue resected
  - T1c Tumor identified by needle biopsy (e.g., because of an elevated serum PSA)
- T2 Tumor confined within the prostate
  - T2a Tumor involves one half of one lobe or less
  - T2b Tumor involves more then half of one lobe, but not both lobes
  - T2c Tumor involves both lobes
- T3 Tumor extends through the prostatic capsule
  - T3a Extracapsular extension (unilateral or bilateral)
  - T3b Tumor invades seminal vesicle(s)
- T4 Tumor is fixed or invades adjacent structures other than the seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall

N-Regional Lymph Nodes

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis

M-Distant Metastasis

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis
  - M1a Non-regional lymph node(s)
  - M1b Bone(s)
  - M1c Other site(s)

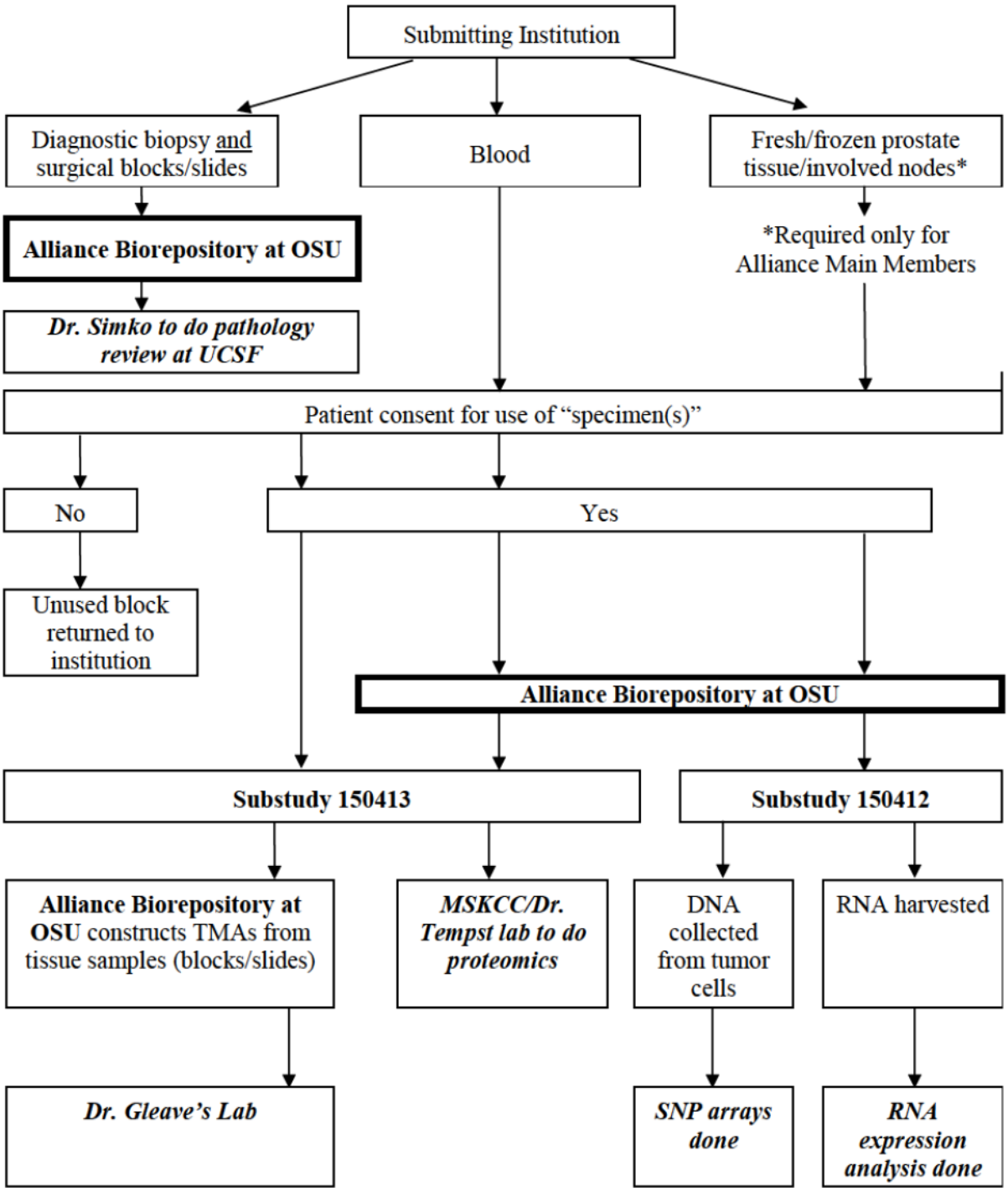
pTNM Pathological Classification

The pT, pN, and pM categories correspond to the T, N, and M categories. However, there is no pT1 category because there is insufficient tissue to assess the highest pT category.

APPENDIX IV

DISTRIBUTION SCHEMA, AND SAMPLE COLLECTION AND TMA CONSTRUCTION PROCEDURES FOR CORRELATIVE SCIENCE SUBSTUDIES

DISTRIBUTION SCHEMA



TMA CONSTRUCTION PROCEDURES FOR SUBSTUDIES 150412 AND 150413

1. Each participating institution will submit to the Alliance Biorepository at Ohio State University radical prostatectomy tissue blocks and the diagnosing pathologist's report.
2. The PCO will face each block and minimally cut (to preserve the tissue) a 4 micrometer section for H&E staining. Each section will be placed on slides, stained with H&E, dried overnight and checked for quality. Slides will be labeled with 90203 study number followed by a dash and a suffix indicating the specific block from which the section was collected (the same suffix written in the original tissue block). This will facilitate the identification of the specific block selected for TMA construction. If the quality of the H&E section causes the block to be excluded by the pathologist or the technician, the corresponding block will be returned.
3. The Alliance GU Pathologist will Gleason grade each region of each prostatectomy that contains CaP (outlining the area of cancer). The pathologist will determine those research subjects for whom the blocks should not be used because such research use would exhaust the specimen. S/he will also record Gleason primary and secondary grades directly on each H&E section/slides.
4. H&E slides will be digitized and the H&E images will be used for quality assurance review and for annotation of core locations for TMA construction. Three 3-micrometer sections will be cut and labeled with the original number and 90203 study number. These sections will be stored in case TMA construction proves inadequate.
5. In a pilot study (101), radical prostatectomy specimens yielded an average of 25 (range 2-66) blocks per subject. An average of 9 blocks (range 2-17) revealed cancer. Radical prostatectomy specimens contained an average of 2 (range 1-8) individual cancers.
6. A template of the radical prostatectomy will be made using Microsoft Excel as a guide to determine core coordinates. Each core location is described by x,y co-ordinates, research subject study number and 90203 study number. The annotated digital image will be used to determine the coring locations of the tissue blocks.
7. The location and number of punches to be made from each patient will be determined by consultation with Table 3 of Singh, et al. (101). TMAs will be constructed using the 2-quadrant technique. Each quadrant of 150 0.6 mm cores on the array will hold approximately 25 research subjects since each research subject has on average 5 CaP cores included on TMA (based on sampling strategy) and 1 "normal" tissue core. There are 300 total cores on each block that will include 12 "markers" (mouse lung) to determine proper orientation and 12 internal controls (rat liver).
8. Data accumulated by the Alliance Biorepository at OSU will contain the following information as either an Excel or Word file as needed:
    - 1) Research subject study number
    - 2) Research Block number
    - 3) Punch identifier
    - 4) Benign or cancer (Gleason primary and secondary grades)
    - 5) Percent prostatectomy specimen involved by tumor
    - 6) TMA block number
    - 7) TMA location (x,y-coordinates)

9. All H&E slides from study tumor blocks and all TMA blocks will be archived and stored at the PCO. After each TMA construction, all prostatectomy blocks used for that TMA will be returned to the submitting institution. Upon completion of TMA construction, the Alliance Biorepository at OSU will be responsible for cutting the TMA and staining for the biomarkers of interest. The Alliance Biorepository at OSU will also cut sections as requested by other qualified laboratories.

Detailed TMA construction protocol:

10. A recipient block made with paraffin-containing plasticizers be faced on a microtome and screwed firmly into place in the Beecher Instruments Microarrayer. 0.6 mm needles (one for recipient punch and one for donor block punch) are placed in the turret of the instrument and placed in the proper x, y-coordinates. The usable area of a TMA block is about 3 cm x 2 cm. Within this area, x, y-coordinates will be assigned to each punch for each research subject and recorded as described above.
11. A small core is removed from the recipient block and the turret is moved so that a punch can be taken from the donor block. The punch from the donor block is placed into a hole previously created. This process can only be done properly using the human eye and requires acquired technical skill.
12. After all research subjects and controls have been placed into the recipient block, the TMA is warmed briefly at 37˚C for 15 minutes with a smooth weight placed on top. This allows bonding between the recipient block and the donor cores and flattens the surface.
13. The newly created TMA is faced on a microtome and a slide cut for H&E evaluation. Any cores missing will be logged as "lost" and recorded in the database for future reference (up to 20% of cores may be lost).
14. The Instrumedics Adhesive Tape Transfer system works best for cutting 0.6 mm TMAs. This system requires that adhesive tape is placed on the microarray block prior to cutting each section. The tape is aligned on an Instrumedic slide that contains a PSA polymer for adhesion. The slides are incubated under UV light to polymerize the paraffin to the slide. After UV incubation, the slides are placed in a TPC solvent to remove the tape. The slides are placed in xylene for 60 seconds and air dried. Finally, the slides are dipped in melted paraffin once and allowed to cool. The TMA sections can be shipped or stored (failure to redip the TMA sections resulted in loss of antigenicity).