A phase II study of definitive therapy for newly diagnosed men with oligometastatic prostate cancer after prostatectomy

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Study Synopsis

Title: A phase II study of definitive therapy for newly diagnosed men with oligometastatic prostate cancer after prostatectomy

Objective: To assess the efficacy of treating men with oligometastatic prostate cancer with the following therapy: (1st) Systemic chemo-hormonal therapy with up to 6-months (~24 weeks) of adjuvant androgen deprivation and up to 6 cycles of chemotherapy, (2nd) definitive local tumor control with adjuvant radiation therapy, and (3rd) consolidative stereotactic radiation to oligometastatic lesions. The men will receive a total of 2 years of androgen deprivation. Androgen blockade will be the same throughout the course of treatment.

This is a companion study to J1618, "A phase II study of definitive therapy for newly diagnosed men with oligometastatic prostate cancer" in which men are diagnosed with oligometastatic (OM) disease prior to prostatectomy. This is a study to address those men with OM disease that have already undergone surgery, e.g., a man found to have positive lymph nodes at the time of surgery.

Study Design: Open label phase II study designed to assess the efficacy and therapeutic benefit of multimodality therapy in men presenting with newly diagnosed oligometastatic prostate cancer (≤5 sites of metastases). A total of sixty patients will be enrolled with the primary endpoint of the 3 year PSA progression-free (PSA<0.2 ng/ml) survival rate.

Adjuvant treatment (month 1 through ~6): All patients will be treated with up to 6 months of androgen deprivation, plus up to 6 cycles of docetaxel chemotherapy. Following docetaxel therapy, patients with a PSA response of at least a 50% decrease from baseline, will proceed to maximum consolidative therapy.

Radiation (month 7 though ~11): After completion of adjuvant chemotherapy, the men will be treated with definitive local therapy with adjuvant radiation therapy (RT). After definitive local therapy, patients will be treated with consolidative stereotactic body radiation therapy (SBRT) to the metastatic sites (if present).

Follow up: Patients will continue on androgen deprivation for a total of 2 years. They will be followed clinically and monitored with serum testosterone and PSA until 2-years after completion of systemic consolidation. Androgen blockade will be the same throughout the course of treatment.

Primary Center: Johns Hopkins Hospital. Patients not within commuting distance to JHH or its affiliate hospitals may undergo adjuvant radiation at radiation centers close to their home. Will include Sibley Hospital as a second site.

Support: Investigator initiated

Timeline: This study is planned to complete enrollment in four years, with 1-years of additional follow-up after completion of ADT treatment of the last subject, for a total of approximately 5 years.

Concept Rationale:
As more patients undergo surgery for high-risk prostate cancer, more patients are found to have disease detected in their lymph nodes at the time of surgery. The standard of care for these patients is adjuvant radiation therapy with hormonal therapy. In the setting of pathologic node-positive disease, the Eastern Cooperative Oncology Group (ECOG) 3886 trial established ADT as a standard of care. Institutional retrospective studies showed that ADT plus radiotherapy was associated with improved overall survival compared with ADT alone, but an analysis of the population-based Surveillance, Epidemiology and End Results-Medicare linked data did not show a benefit from radiotherapy [1]. Because current management is informed by mostly retrospective studies, clinical trials are needed to more definitively guide treatment decisions for patients with node-positive disease. In addition, patients are increasingly being diagnosed with oligometastatic disease due to the advent of sensitive imaging technologies as well as effective therapies that are allowing patients to live longer with the diagnosis of cancer. In addition, the fact that novel treatment options with acceptable safety profiles, such as stereotactic radiation, cryoablation, and minimally invasive surgery, are available to treat limited metastases, has led to a renewed interest in treating oligometastatic disease. Treatment of oligometastatic disease not only has the potential to prevent further evolution of genetically unstable clones and metastatic spread, it may improve overall disease control and delay more toxic systemic treatment. Therefore, the clinical implication of the oligometastatic state is that locally ablative therapies, given with the intent of targeting sites of clinically evident metastatic disease could result in long-term survival or cure. Treatment of oligometastatic disease may also result in decreased overall tumor burden, decreasing morbidity and increasing survival.

In addition to preventing further evolution of genetically unstable clones and additional metastatic spread, the combination therapies may be more effective in treating hormone-sensitive oligometastatic prostate cancer, before it becomes castrate resistant and more aggressive.

<u>Adjuvant therapy in men with oligometastatic prostate cancer</u>

The standard of care treatment for metastatic prostate cancer is androgen deprivation therapy (ADT). [NCCN Clinical Practice Guidelines, Version 1.2015] Although taxanes are the standard treatment approach in metastatic castrate-resistant prostate cancer, two recent randomized trials [1,2] investigated the combination of docetaxel + ADT in treatment naïve metastatic prostate cancer. In the CHAARTED trial (Phase III, E3805) 790 men with metastatic hormone sensitive prostate cancer, treatment naïve, were randomized to either ADT + up to 6 cycles of docetaxel *versus* ADT alone. The primary endpoint was overall survival. Patients were stratified according to high volume disease (visceral metastases and/or ≥4 bone metastases) versus low-volume disease, prior anti-androgen use > 30 days, age ≥ or < 70 years, ECOG 01- versus 2 and prior adjuvant ADT > or ≤ 12 months. After a median follow-up of 28.9 months, the docetaxel + ADT arm had an OS of 57.6 months, as compared to ADT alone OS of 44.0 months. Patients with high-volume metastatic disease (defined as visceral metastasis or ≥4 bone metastases), treated on the docetaxel + ADT arm had an increased OS (49.2 *versus* 32.2 months in the ADT alone arm,

HR 0.60, p<0.001). The median OS was not yet reached in either arm for those with low-volume disease. Other sub-group analyses (PSA < 0.2 at 6 mths/12mths, median time to CRPC, and median time to clinical progression) also showed that the combination of ADT + docetaxel was superior. In the docetaxel + ADT arm, grade 3/4 febrile neutropenia was 2.3%. [1,3-5]

In the GETUG 15 trial 385 men with metastatic hormone sensitive prostate cancer, were randomized to ADT + docetaxel *versus* ADT alone. The protocol allowed for up to 9 cycles of docetaxel. The primary endpoint was OS. Secondary endpoints included time to clinical progression and time to PSA progression. 81% of those enrolled had bone metastasis and 14.5% had visceral organ metastasis. Median number of cycles of docetaxel was 8. At 50 months median follow-up, OS was not different between the two arms, ADT + docetaxel versus ADT alone (58.9 versus 54.2 months, HR 1.01, p=0.955), despite that the combination therapy did yield a significant improvement in biochemical PFS and clinical PFS (22.9 versus 12.9 months, HR 0.72, p=0.005, and 23.5 versus 15.4 months, HR 0.75, p=0.015, respectively). [2,4,5] More recently, the authors reported on the comparison between patients' self assessment of treatment related toxicities versus investigators' evaluation of their patients' toxicities. [REF] The men were invited to complete a 26-symptom questionnaire at 3- and 6- months, while physicians assessed 18 symptoms. 220 and 165 patients completed questionnaires at 3- and 6-months. At the two assessment points (3 months and 6 months) all symptoms were reported more frequently by patients than by physicians. Positive agreement rates between patients and physicians, for the most commonly reported symptoms, included hot flushes (61 and 64%), fatigue (50 and 44%), sexual dysfunction (29 and 31%), and weight change (24 and 14%). However, ~50% of the time physicians did not report patients' hot flushes and ~90% of the time they did not report patients' joint/muscle pain. In comparison between the two arms, patients randomized to the ADT + docetaxel arm had more toxicities that those in the ADT alone arm. [6]

Alternatively, an arm of the STAMPEDE trial provides data on men with newly diagnosed metastatic prostate cancer who were randomized to standard-of-care therapy with androgen deprivation therapy. Cross-over was allowed at progression. The cohort of 917 men had a median follow-up of 20 months. Median failure free survival (FFS-time from randomization until biochemical failure, local or distant progression, or death from prostate cancer) was 11 months, and median OS was 42 months. 2 year FFS and OS were 29% and 72% respectively. This study demonstrated poor survival in men starting therapy with androgen deprivation only, despite the ability to initiate other treatments at failure of ADT. The median OS in this group was shorter than that of the control arm in GETUG-15, and was similar to the control arm in CHAARTED. [7]

<u>Local consolidation therapy with prostatectomy in men with oligometastatic prostate cancer</u>

There is a body of evidence, contrary to historical clinical practice, that treating men with metastatic prostate cancer to the lymph nodes at the time of diagnosis with surgery or radiation therapy results in increased long-term survival. Historically, the ideal patient to be cured by radical prostatectomy (RP) was one with organ-confined cancer. At that time, the morbidity of RP was substantial; therefore the surgery was generally only offered to those where the probability of cure was high. More recent data, however, show that RP may provide a survival benefit- albeit not a cure - to men with metastatic prostate cancer. Engel et al. [8] conducted a

retrospective study (n=938) and found that in men with prostate cancer and positive lymph nodes, treated with +/- RP, that the 5- and 10-yr survival rates and the prostate cancer specific survival rates, were better in men who had undergone RP. Cadeddu et al [9] conducted a retrospective study (n=38) and found that in men with prostate cancer and positive lymph nodes, treated with LND +/- RP, that the 5- and 10-yr prostate cancer specific survival was better in men who had undergone LND + RP.

In men with prostate cancer with limited metastases, radical prostatectomy may be advantageous in that the primary tumor and its ability to continuously metastasize, to secrete tumor promoting growth factors and immunosuppressive cytokines, and to generate bulk-related morbidity, is removed. Heidenreich et al. recently evaluated survival outcomes following radical prostatectomy (RP) in men with low volume metastatic prostate cancer. RP led to improved progression-free survival, time to castrate resistance and overall survival, as compared to a cohort treated with androgen deprivation therapy alone. [10] Moreover, Abdollah et al. found that in men with pN1 prostate cancer, treated with RP and extended lymph node dissection, adding adjuvant radiotherapy improved cancer-specific mortality [11].

Local consolidation therapy with radiation in men with oligometastatic prostate cancer

Ost et al (2014) conducted a systemic review of the literature of metastasis-directed therapy of regional and distant recurrences after curative treatment for PCa (prostate cancer). They found that salvage LND and RT appear to be safe in treatments for OM PCa recurrence.[12] Culp et al. [13] studied the impact of survival of definitive treatment of the prostate in men diagnosed with metastatic PCa. Using the SEER database, he reviewed 8185 men treated with NSR (no surgery no radiation), brachytherapy, or RT. The 5-year OS and disease specific survival (DSS) was significantly higher in men with metastases having undergone RT. [14]

Zapatero et al., reported on a study of men with intermediate and high risk localized prostate cancer (n=362), treated with RT + long term ADT *versus* short term ADT, and found that long term ADT was superior in 5-year biochemical disease free survival, metastasis free survival, and OS [15]. [14]

SBRT for oligometastatic sites in men with prostate cancer

While much of the literature supporting the oligometastatic states is within the surgical literature, there is an increasing body of literature describing the use of stereotactic body radiotherapy (SBRT) and stereotactic radiosurgery (SRS), in addition to conventional fractionated radiotherapy techniques. SBRT is a noninvasive method of delivering high doses of radiation to ablate a target lesion while sparing the neighboring normal tissue, thus reducing long-term effects of radiation on the non-malignant tissues. [14]

Although traditionally radiation therapy was thought to be immunosuppressive, there is increasing pre-clinical and clinical evidence that high dose, hypofractionated radiation –SBRT- may reverse antitumor immunity via CD8+ T-cells and cellular stress signals. Although uncommon, the abscopal effect (regression in tumors distant to the targeted field of radiation) is an example of recovery of anti-tumor immunity following RT. Thus, an emerging advantage of SBRT is the possibility that it may be exploited to benefit the immune system. [14]

Major advancements in radiation treatment planning and delivery have resulted in resurgence in the use of radiation therapy (RT) as a treatment for bone metastases. In selected patients, very high local control rates have been observed, with minimal toxicity. Bone metastases represent the major metastatic site (>90%) in men with rising PSA following primary treatment for their prostate cancer. [adapted from Johns Hopkins Oncology Clinical protocol J12137, NA_00069585]

The primary management of metastatic prostate cancer is systemic therapy in the form of androgen deprivation therapy (ADT), which rarely eradicates metastatic disease and adversely effects patient quality of life. Thus, even the ability to defer long-term ADT in men with oligometastatic prostate cancer represents a considerable clinical advance. [adapted from Johns Hopkins Oncology Clinical protocol J12137, NA_00069585]
The hypothesis of this study is that the combination of systemic therapy with complete androgen blockade plus chemotherapy in the adjuvant setting after definitive local therapy with prostatectomy, in combination with adjunctive radiation therapy, and definitive radiation to clinically evident metastatic sites with stereotactic ablative radiation therapy, is efficacious in patients with oligometastatic disease. The primary endpoint is the 3 year PSA progression-free (PSA<0.2 ng/ml) survival rate of multimodality therapy in men presenting with newly diagnosed oligometastatic prostate cancer post prostatectomy.

Treatment Plan:
This is an open label, multi-center, phase II study of adjuvant chemohormonal and definitive therapy in men with oligometastatic prostate cancer, beginning with up to 6 months of adjuvant androgen deprivation plus up to 6 cycles of docetaxel chemotherapy.

Androgen deprivation
Options for androgen deprivation therapy include the following: LHRH agonist or antagonist therapy, or surgical castration. Each drug will be dosed at its respective FDA approved dose. These dosages are as follows: leuprolide (Lupron Depot-3 Month) 22.5mg by intramuscular (IM) injection, or leuprolide (Eligard-3 Month) 22.5mg subcutaneous (SC) injection, or triptorelin (Trelstar) 11.25 mg intramuscular (IM injection, or other LHRH agonist including goserelin (Zoladex) 10.8 mg, or degarelix (Firmagon) 80mg (SC every 4 weeks) on day 1.

Use of combined androgen blockade (medical or surgical castration combined with anti-androgen treatment (e.g., bicalutamide (Casodex) 50mg by mouth daily and/or abiraterone acetate 1000 mg / day + prednisone 5mg / day) may be given at the investigator's discretion.
Docetaxel
Docetaxel (Taxotere) will be given at any of the following doses (75 mg/m^2, 65 mg/m^2, 55 mg/m^2 or 35 mg/m^2 IV) on day 1 every 3 weeks, up to 6 cycles at physician discretion.

The combination of the LHRH agonist, leuprolide (Lupron), + bicalutamide (Casodex) + docetaxel (taxotere) at these doses has been shown to have an acceptable safety profile [2,3].

All patients will have discontinued their adjuvant chemotherapy prior to adjuvant radiation therapy. After receiving local therapy, all patients will be treated with definitive stereotactic body radiation therapy (SBRT) to radiologically evident metastatic sites. Patients will continue

with adjuvant androgen deprivation for a total of 2 years, and will be monitored clinically and with serum PSAs and testosterone until the 4-year endpoint.

Definitions:

Oligometastases: Oligometastatic prostate cancer will be defined as prostate cancer with up to 5 sites of metastases, including bone lesions, regional and non-regional lymph nodes; men with visceral metastases will not be included.

Undetectable PSA:
PSA ≤ 0.2 ng/mL

PSA increase/PSA recurrence:
PSA >0.2, over two time-points

2-year undetectable PSA (time interval)**:**
2 years after completion of systemic consolidative therapy

3-year PSA progression-free survival:
(PSA<0.2 ng/ml) among men who have non-castrate testosterone levels 2 years after enrollment
*for men with a baseline testosterone ≤200ng/dL, 3-year PSA PFS is defined as a PSA <0.2 at baseline level of testosterone, 3 years after enrollment

Noncastrate testosterone level:
>200 ng/dL

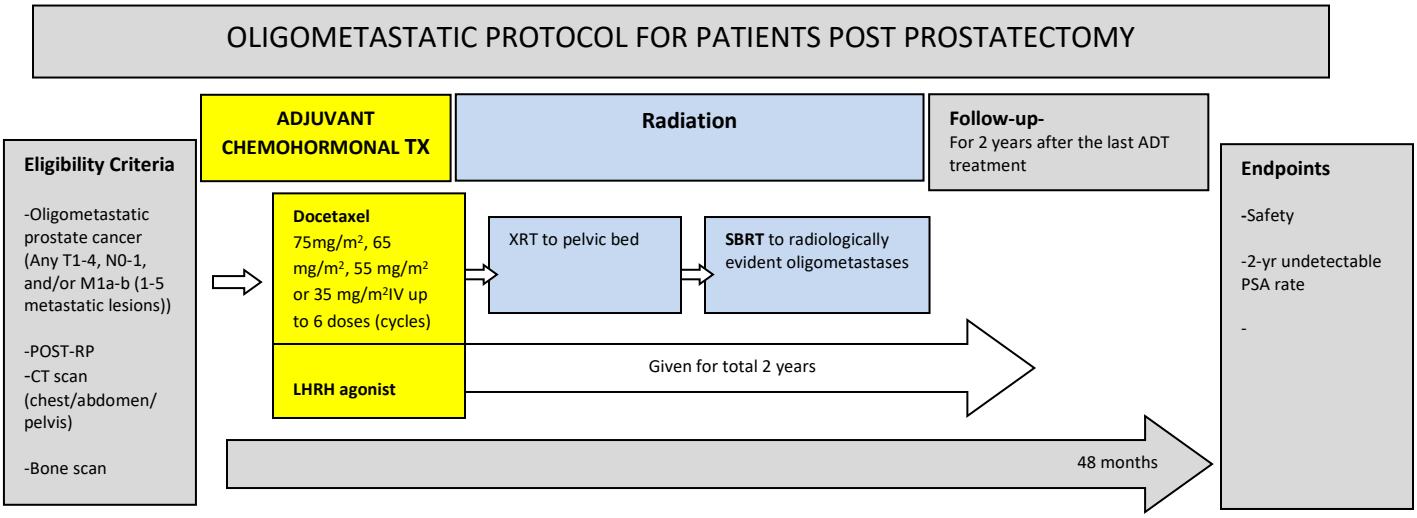
Replacement drugs:

Leuprolide: may be replaced with any LHRH agonist, or the LHRH antagonist degarelix
Biclutamide: no replacements allowed
Abiraterone: no replacements allowed
Docetaxel: no replacements allowed

Drug dose adjustments:

Leuprolide (or replacement): no adjustments allowed.
Biclutamide: no adjustments allowed
Abiraterone: dose may be interrupted or adjusted downward, at physician discretion, in response to, or to mitigate, toxicity. Dose may decreased to 750mg or 500 mg.
Docetaxel: dose may be adjusted downward, at physician discretion, in response to, or to mitigate, toxicity. Dose may decreased in the following intervals: 65 mg/M2, 55 mg/M2, 35 mg/M2.

Study schema



The primary endpoint is the 3 year PSA progression-free (PSA<0.2 ng/ml) survival.

Secondary endpoints will include safety, time to PSA recurrence following completion of therapy.

Study Population: Men with newly diagnosed synchronous oligometastatic prostate cancer (T_{1-4}, N_{0-1}, M1a-b) consisting of 1-5 metastatic lesions who are willing to undergo (1^{st}) Systemic chemo-hormonal therapy with up to 6-months (~24 weeks) of adjuvant androgen deprivation and up to 6 cycles of chemotherapy, (2^{nd}) definitive local tumor control with adjuvant radiation therapy, and (3^{rd}) consolidative stereotactic radiation to radiologically evident oligometastatic lesions.

Number of Patients: We plan to enroll 60 evaluable patients who complete C-ADT. Up to 66 patients will be enrolled if necessary in order to account for a potential 10% dropout rate.

Inclusion Criteria:

1. Willing and able to provide written informed consent.

2. Age ≥ 18 years

3. Eastern cooperative group (ECOG) performance status ≤2

4. Documented histologically confirmed adenocarcinoma of the prostate

5. Willing to undergo the following therapy: (1^{st}) Systemic chemo-hormonal therapy with up to 6-months (~24 weeks) of neoadjuvant androgen deprivation and up to 6 cycles of chemotherapy, (2^{nd}) definitive local tumor control with adjuvant radiation therapy, and (3^{rd}) consolidative stereotactic radiation to oligometastatic lesions. Additionally, must be willing to be treated with a full two years of androgen deprivation.

6. Oligometastatic prostate cancer: Stage T_{1-4}, N_{0-1} and/or M_{1a-b} (up to 5 metastatic lesions-including bone lesions and non-regional lymph nodes seen on bone scan, contrast enhanced CT scan, or PET scan)

Exclusion Criteria:

1. Prior local non-surgical therapy to treat prostate cancer (e.g. radiation therapy, brachytherapy)

2. Prior therapy to a metastatic site.

3. Prior systemic therapy for prostate cancer including, but not limited to:
    a. Hormonal therapy (e.g. leuprolide, goserelin, triptorelin, degarelix)
    b. CYP-17 inhibitors (e.g. ketoconazole)
    c. Antiandrogens (e.g. bicalutamide, nilutamide)
    d. Second generation antiandrogens (e.g. enzalutamide, abiraterone)
    e. Immunotherapy (e.g. sipuleucel-T, ipilimumab)
    f. Chemotherapy (e.g. docetaxel, cabazitaxel)

*Note: may be enrolled if hormone therapy of any kind was recently initiated (<90 days duration)). In the event that hormone therapy was initiated prior to study enrollment, the clock for 2 years of androgen deprivation would begin at the time of therapy initiation, rather than at study enrollment.

4. Ongoing systemic therapy for prostate cancer including, but not limited to:
    a. Immunotherapy (e.g. sipuleucel-T, ipilimumab)
    b. Non-protocol prescribed chemotherapy (e.g. cabazitaxel)

5. Evidence of serious and/or unstable pre-existing medical, psychiatric or other condition (including laboratory abnormalities) that could interfere with patient safety or provision of informed consent to participate in this study.

6. Any psychological, familial, sociological, or geographical condition that could potentially interfere with compliance with the study protocol and follow-up schedule.

7. Abnormal bone marrow function [absolute neutrophil count (ANC)<1500/mm^3, platelet count <100,000/mm^3, hemoglobin <9 g/dL]

8. Abnormal liver function (bilirubin >ULN; AST, ALT > 2.5 x upper limit of normal)

9. Active cardiac disease defined as active angina, symptomatic congestive heart failure, or myocardial infarction within previous six months.

10. Prior history of malignancy in the past 3 years with the exception of basal cell and squamous cell carcinoma of the skin. Other malignancies that are considered to have a low potential to progress may be enrolled at discretion of PI.

Primary Endpoint: To assess efficacy of the following therapy: (1st) Systemic chemo-hormonal therapy with up to 6-weeks (~24 weeks) of adjuvant androgen deprivation and up to 6 cycles of chemotherapy, (2nd) definitive local tumor control with adjuvant radiation therapy, and (3rd) consolidative stereotactic radiation to oligometastatic lesions. The men will receive a total of 2 years of androgen deprivation.

Efficacy is defined as the 3 year PSA progression-free (PSA<0.2 ng/ml) survival rate.

Secondary Endpoints:

1. Safety.
   Defined as the incidence of Grades 3 and 4 neutropenia and surgical- or radiation-induced toxicities.

2. Time to PSA recurrence.
   Defined as the time from an undetectable PSA (≤0.2 ng/mL) until the PSA is >0.2 over two time-points up to 3 years.

Statistical Considerations:

This open label single arm phase II study of treatment for oligometastatic disease will evaluate consolidation with adjuvant radiation therapy after systemic adjuvant chemo-hormonal therapy (C-ADT) and stereotactic body radiation to metastatic sites. The primary endpoint is efficacy, defined as the 3-year PSA progression-free (PSA<0.2 ng/ml) survival rate.

Early Stopping Boundaries for Toxicity

Expected non-neutropenic toxicities post prostatectomy or radiotherapy [17]: urinary incontinence, erectile dysfunction, minimally invasive urological procedures, admission to hospital, rectal or anal procedure, secondary malignancy, open surgical procedure.

Expected neutropenic toxicities post chemotherapy: neutropenia, febrile neutropenia.

We are concerned with 2 very different types of adverse event (AE): (1) Grade 3-4 neutropenia, and (2) Grade 3-4 acute toxicities from surgery or radiation. Because the management and

sequelae of these AEs differ we have defined separate stopping boundaries for neutropenic AEs and for acute surgical -or radiation -induced AEs. The study design incorporates safety monitoring after each patient, starting with the third patient.

Neutropenic AEs. We will say that the treatment is feasible and safe if risk of G3/4 neutropenia <50%. Before the study starts, we assume that the average risk of G3/4 neutropenia is around 30-40%, so we take 35% as our prior probability (95% CI: 22-78%), corresponding to a Beta(3.5,6.5) prior distribution for the risk. Using Bayes rule, we apply the accumulating data after each patient to generate posterior probability as a Beta(3.5+a, 6.5+b) distribution, where a=number of neutropenic AE, b=number of non-SAEs (Rosner 2016)(30). As we become more certain that the risk exceeds 50%, we want to consider stopping the study. If the data suggest that there are at least 2:1 odds that the risk of neutropenic AEs exceeds 50%, the stopping boundary will be crossed, and we will consider that as enough certainty that the true rate exceeds 50% to stop the trial.

The following table indicates the number of events that will cross the stopping boundary for each sample size up to 54 patients.

Number of patients (inclusive)	Trial stops if neutropenic AEs reach this value
5	5
6-7	6
8-9	7
10-11	8
12	9
13-14	10
15-16	11
17-18	12
19-20	13
21-22	14
23-24	15
25-26	16
27-28	17
29-30	18
31-32	19
33-34	20
35-36	21
37-38	22
39	23
40-41	24
42-43	25
44-45	26
46-47	27
48-49	28
50-51	29

52-53	30
54	31

Non-neutropenic acute surgical –or radiation-induced AEs. We will say that the treatment is feasible and safe if risk of G3/4 acute non-neutropenic AEs<20%. Before the study starts, we assume that the average risk of such AEs is around 10% (95% CI: 2-38%), corresponding to a Beta(1,9) prior distribution for the risk. Again, we apply the accumulating data after each patient to generate posterior probability as a Beta (1+a, 9+b) distribution, where a=number of non-neutropenic AE, b=number of non-AEs. As we become more certain that the risk exceeds 20%, we want to consider stopping the study. If the data suggest that there are at least 2:1 odds that the risk of non-neutropenic AEs exceeds 20%, the stopping boundary will be crossed, and we will consider that as enough certainty that the true rate exceeds 20% to stop the trial.

The following table indicates the number of events that will cross the stopping boundary for each sample size.

Number of patients (inclusive)	Trial stops if non-neutropenic AEs reach this value
3-5	3
6-10	4
11-14	5
15-19	6
20-23	7
24-28	8
29-33	9
34-38	10
39-42	11
43	12

Operating characteristics of both rules are given below in Section 13. Statistical Methods.

Data Analysis

The primary study endpoint is efficacy, defined as the 3 year PSA progression-free (PSA<0.2 ng/ml) survival rate among men who have non-castrate testosterone levels 3 years after enrollment. Since there is no direct comparator trial in this population, this will be compared to the historical rate from a randomized trial of men with biochemically-recurrent (non-metastatic) prostate cancer after prostatectomy and (for most men) after salvage radiotherapy, with PSADT <9 months. In that trial, at month 18, men who achieved a return to non-castrate testosterone blood levels who received abiraterone and degarelix had an undetectable PSA rate of 16% [18].. Based on these data we will set the null hypothesis at 15% PSA progression-free survival at 3 years in men with non-castrate testosterone.

Power is based on a 1-sample logrank test for comparing an observed survival to a historical control rate[19]. The table below shows PSA progression-free survival, $\mathbf{P_1}$, ranging from 30-50%

compared to a historical rate of 15% (**P_0**). We assume that 60 men will be enrolled in the trial, at least 90% will have ≥50% PSA decrease following C-ADT and go on to aRT and SBRT, and that 80% of those patients (n=43) will have non-castrate testosterone at 3 years. For all comparisons α=0.05 and a 2-sided test is used. Power is calculated using PASS v15 (NCSS Software, Kaysville, UT).

The table shows that with N=43, PSA progression-free survival of ≥0.32 can be detected with power ≥82%. These estimates may be conservative since the historical control rate is based on men without detectable metastases, whereas the current trial includes only men with oligometastatic disease.

Power (%)	N	P_0	P_1
74	48	.15	.30
82	48	.15	.32
91	48	.15	.35
97	48	.15	.40
>99	48	.15	.50

To conduct the safety analysis, rates of AEs will be calculated with 95% confidence intervals. Secondary time-to-event endpoints will be estimated with Kaplan-Meier methods, mean and median quality of life scores will be calculated with 95% confidence intervals, and chi-square test will be used for comparison of first metastatic sites. We will also compare secondary endpoints such as 2 year PSA failure-free survival to expected rates of 10-20% (based on data reported by CHAARTED (ASCO 2014) of 23% at 1 year for combined chemo-hormonal therapy) using a one-sample chi-square test. Although power is likely to be suboptimal we will also perform exploratory analyses to compare the above endpoints among subgroups such as by age, number of initial metastatic sites, and between radiation and surgery.

Table of Contents

1. Introduction

1.1. Oligometastasis

Hellman first proposed the theory of oligometastases in 1995 as a sequel to the spectrum theory of cancer metastasis. Hellman hypothesized that the process of cancer metastases occurred along a continuum, from locally confined cancer to widely metastatic disease. Although the phenomenon of limited and treatable cancer metastases had been noted historically, Hellman and Weichselbaum proposed the term oligometastases, suggesting that in some patients with a limited number of clinically detectable metastatic tumors, the extent of disease exists in a transitional state between localized and widespread systemic disease. In this model local control (LC) of oligometastases would have the potential to yield improved systemic control, going against the dogma that control of oligometastatic disease would not have a therapeutic benefit since it represents a clinical manifestation of a few detectable lesions in the setting of widespread occult disease. Oligometastasis continues to be defined as a state of metastatic disease that is limited in total disease burden, usually by number of clinically evident or radiographic sites (either 1-3 or 1-5), and that is not rapidly spreading to more sites. The clinical implication of oligometastasis suggests that if the primary site (if still present) is controlled, or resected, and the metastatic sites are ablated (surgically or with radiation), there will be a prolonged disease-free interval, and perhaps even cure. As the understanding of the mechanisms underlying cancer metastasis have evolved, possible mechanisms for the oligometastatic state must be explained and examined within that context. [14]

2. Overview and Rationale

We have initiated a trial at Johns Hopkins to treat men identified with OM PCa prior to any treatment: "A phase II study of definitive therapy for newly diagnosed men with oligometastatic prostate cancer ", IRB #: 00070003, SKCCC Protocol #: J1618. J1618 treats men with chemohormonal therapy in the neoadjuvant setting, followed by RP +/- adjuvant radiation, followed by SBRT to sites of OM disease. Hormonal therapy is given for a total of 1 year. Many men are now presenting with node positive disease at the time of surgery. This is a complimentary study to J1618 to allow us to treat these men in a multidisciplinary fashion.

2.1. Biological basis for oligometastasis

2.1.1. Theories of metastasis

Metastasis is the cause of most cancer-related deaths. In 1889, Stephen Paget theorized that circulating tumor cells would "seed" to an amenable "soil", suggesting that metastasis was not a matter of chance. Five years later, in 1894, Halstead theorized that cancer was an orderly disease that progressed in a contiguous manner, by direct extension from the primary tumor through the lymphatics, to the lymph nodes, and then to distant sites. Halstead proposed that breast cancer metastasis was a progressive, anatomical process of contiguous seeding; his hypothesis supported the use of radical surgery and radiotherapy. Radical en bloc surgery, radical hysterectomy, and primary and regional irradiation for several tumor sites were all based on Halstead's theory of tumor spread. James Ewing, in 1928, complemented the Paget and Halstead

theories to propose that cancer cells grow at a particular site because they are directed by the direction of blood flow and lymphatics. [14]

The 'systemic' theory of metastasis, first suggested by Keynes [15] and further developed by Fisher [20], held that clinically apparent cancer was a systemic disease, and that small tumors were an early manifestation of systemic disease. In this theory, nodal involvement was not part of an orderly contiguous extension but rather a marker of distant metastases. According to this theory, local control would not impact survival. [16]

In contrast to the 'Halsted' theory and the 'systemic' theory, the 'spectrum' theory of cancer metastases, first described for breast cancer metastases in 1994, held that disease stage at the time of initial disease presentation fell into a spectrum ranging from indolent disease to widely metastatic, with the degree of clonal evolution determining the ability of the tumor to metastasize. The spectrum theory was refined just one year later to describe the limited metastasis of any solid tumor and the term 'oligometastasis' was coined. [14]

The spectrum theory conceptualized the entire range of metastatic competence, analogous to a diapason, which is the entire range of an instrument. To that end, the social sciences concept of a diaspora has recently been utilized to inform biologic understanding and therapeutic paradigms of cancer metastasis. A diaspora refers to the scattering or movement of a population from its original homeland. In the case of systemic metastases, the diaspora resembles an imperial colonization in which the populations spread widely and eventually conquer the new host lands (aggressive cancer clones to multiple organs). Oligometastases resemble trading post diasporas, representing a limited number of outposts with limited growth potential (less aggressive cancer clones to few organs). Systemic versus oligometastatic diasporas may be dependent on the types of mutations present in the cancer cells (quality of the diaspora migrants), the quality of the original tumor site (factors in the homeland that cause the population to migrate), and the quality of the new hostland (factors that allow immigrants to establish and flourish). [14]

2.1.2. Biology of systemic and oligometastases

It is now widely accepted that there are discrete steps in tumor metastasis. Initially there is a loss in cellular adhesion, followed by increased motility > invasiveness of the primary tumor > entry into and survival in the circulation > entry into new organs > eventual colonization of these organs. Shortfalls at any stage of this metastatic progression could result in phenotypes of limited metastatic potential. Gupta et al. described specific tumorigenic genes - initiation, progression, and virulence genes - that fulfilled specific roles in the metastatic cascade. Initiation genes afford a selective advantage to primary tumor cells to enter circulation. Progression genes fulfill rate-limiting steps for colonization. Virulence genes provide a selective advantage in cells to colonize a secondary site(s). As Weichselbaum and Hellman noted, this paradigm suggests "*that there may be primary tumor cells with a limited capability in one or more of the necessary biological requirements for metastasis; thus proposing a possible biologic explanation of the origin of oligometastases"* [21]. [14]

In 2000, and updated in 2011, Hanahan and Weinberg proposed the, widely accepted, 'hallmarks of cancer'. The original cancer hallmarks consisted of six transformations in cellular physiology that allow cells to survive, proliferate and disseminate, and together support carcinogenesis. The update posited that underlying the original hallmarks were two 'enabling hallmarks': 'genome

instability and mutation' and 'tumor-promoting inflammation'. Additionally, the update proposed two new 'emerging hallmarks': 'deregulation of cellular energetics' and 'avoidance of immune destruction'. The exact sequence in which the transformations occur, and thus the appearance of the 'hallmarks' (self-sufficiency in growth signals ↔ insensitivity to anti-growth signals ↔ tissue evasion and metastasis ↔ limitless replicative potential ↔ sustained angiogenesis ↔ evading apoptosis) can vary throughout the course of progression. Despite the ordering, collectively, the hallmarks can terminate into a cancer. However, the ordering and the degree of specific hallmarks, may potentially allow for a subsequent oligometastatic state. For example, cancer cells that lack the hallmarks to actively metastasize still may be able to slough into the circulation and inefficiently establish metastases. Other cells may be less efficient at proliferation, establishing slow growing metastases. Warburg (1956) suggested that "We may have cells which indeed look like cancer cells but are still energetically insufficient… such cells which are clinically not cancer cells, have lately been found not only in the prostate, but also in the lungs, kidney, and stomach of elderly persons such cells have been referred to as "sleeping cancer cells" [22]. [14]

2.1.3. Preclinical models of oligometastasis

Traditional clinicopathologic factors are inadequate when attempting to define the potential underlying biology of oligometastases. Several investigations have demonstrated the marked genetic and epigenetic heterogeneity present in metastatic cancer sites within the same patient. These studies demonstrate that cancer cells at different sites within a patient can have varied malignant potential. Preclinical models of tumors with varying degrees of metastatic potential, including low metastatic potential exist. Using a cell line derived from B16F1 melanoma, Fidler et al. [23]found that variant metastatic cells pre-exist in a heterogeneous primary tumor as opposed to originating through adaption during metastasis from an otherwise homogenous primary tumor. This finding was advanced in later work that showed the KHT sarcoma line demonstrated similar heterogeneity whether grown in vitro or in vivo, which suggested that clonal variation seen in vitro derived from heterogeneity present in the primary tumor. As an extension of this work in the KHT sarcoma line, it was demonstrated that effective metastatic variants developed at a high rate with low frequency, as opposed to the more frequent and stable subpopulations of metastatic variants. In comparing B16 cell lines, Cillo et al. showed that the more highly metastatic, and less genetically stable cell line, generated increased metastatic variants corresponding to increased chemotherapy resistance [24]. Numerous in vitro studies and analyses of animal models have indicated that cells isolated from metastases differ greatly—both genetically and phenotypically—from cells isolated from their parental primary tumors. The preclinical models point toward variation in individual tumor cells' metastatic potential, which supports the concept of oligometastases. [14]

Given that stochastic models have been used to predict biologic phenomena, a Bayesian model has been proposed to predict the chance of occult metastases in the presence of detectable oligometastases. Using the size and number of metastases, the proposed model inferred, 1) that the probability of occult metastases may increase substantially with minor increases in metastatic potential and 2) that extended disease-free periods were predictive of a substantial decrease in additional occult disease. Although compelling, such models are in their infancy and as yet remain in pre-clinical testing where the host, tumor and experimental factors are controlled. [14]

2.1.4. Clinical evidence of oligometastasis

Evidence for the evolution of the oligometastatic phenotype comes from various clinical and pre-clinical sources. Recent studies of the molecular biology of renal cell cancer metastasis have implied biologic differences between less and more aggressive metastases, as well as between fewer and multiple metastases. In order to better determine which patients presenting with localized RCC harbor an aggressive tumor and may not benefit from surgery, Kosari et al. using gene expression profiling, found gene expression alterations associated with an aggressive tumor and metastatic potential in the primary tumor [25]. From a cohort of 20 resected pulmonary metastases taken from 18 patients, Wuttig et al demonstrated the predictive potential of identified gene signatures, when comparing disease-free intervals (DFI) and number of metastases, both of which are predictive of prognosis in metastatic RCC (mRCC). There were 306 differentially expressed genes in comparing DFI ≥5 years and DFI ≤9 months, and 135 differentially expressed genes in comparing multiple metastases (≥16) and few metastases (≤8). [26] [14]

In colorectal cancer, there is growing evidence that liver-limited disease is a distinct biological cohort that may benefit from aggressive management. While only a minority of patients are technically resectable, approximately 40% of patients with resected liver limited disease are alive 5 years after diagnosis compared with less than 1% for those with disseminated disease. There is genetic evidence that patients undergoing hepatic resection for metastatic cancer had a different disease than those who did not. For example, it was noted that BRAF V600E mutant tumors, which were typically associated with aggressive biology, rarely came to liver resection. In addition, novel chromosomal aberrations have been identified that are associated with intra- and extra-hepatic recurrence after liver resection. [14]

MicroRNAs, small non-coding RNA known to regulate tumor proliferation and apoptosis, are frequently dysregulated in cancer and metastasis. MicroRNA profiling has shown a possible method to distinguish patients with oligometastases from those with polymetastatic disease. Examples of pro-metastatic microRNAs include microRNA-10b (upregulated in primary breast tumors that had metastasized), microRNA-21 (correlated with advanced stage, incidence of metastases, and poor outcomes in breast and pancreatic tumors), and microRNA-373/520c (increased expression in breast metastases). MicroRNA-210, a known transcriptional target of the HIF-1a signaling pathway, was elevated in sera from patients with metastatic castrate-resistant prostate cancer, as compared to controls, and was correlated with treatment response as assessed by change in PSA. Lussiter et al. found microRNA-200c was associated with polymetastatic progression in a oligometastatic cell line, derived from patients treated with high-dose radiotherapy, tested in a xenograft model [27]. The investigators then stratified patients with resected pulmonary oligometastases into subgroups, based on high-risk versus low-risk of further metastatic progression. Differential microRNA expression patterns were identified between these two groups (high rate of progression (n=16 prioritized microRNAs) and low rate of progression (n=32 prioritized microRNAs) and, in an independent dataset, the expression patterns were associated with risk of progression and decreased overall survival. [28] Most recently, Uppal et al. identified three microRNAs overexpressed in clinical metastasis samples from patients with limited metastatic disease. MicroRNA-127-5p, microRNA-544a, and microRNA-655-3p were shown to limit, but not fully inhibit, metastasis in a model of breast cancer lung colonization. [14]

2.1.5. Controversies surrounding the treatment of oligometastatic disease

Hellman theorized that, 1) whereas some tumors were destined to remain localized, 2) other tumors, as they increased in size, acquired an increasingly greater metastatic phenotype, suggesting at an early stage these tumors seeded distant sites with clones that had not reached full metastatic potential, and finally, 3) that some tumors already had occult distant dissemination at the time they are diagnosed. He also proposed that metastatic potential was not only directed by the tumor phenotype, but that it was also influenced by the tumor's location, venous drainage, and host factors. Based on Hellman's theory, later scientists further theorized that tumors in the oligometastatic disease state were tumors early in their evolution of metastatic progression; therefore they produced metastases that were limited in number and location. These data support the presumption of a temporal evolution with an intermediate stage of limited metastatic capacity, where oligometastatic tumors may not have acquired the broad array of genetic changes required to develop widespread metastases. [14]

The clinical implication of the oligometastatic state is that locally ablative therapies, given with the intent of targeting sites of clinically evident metastatic disease could result in long-term survival or cure. Treatment of oligometastatic disease may also result in decreased overall tumor burden, decreasing morbidity and increasing survival. These arguments are opposed by the concept that clinical metastases are evidence of systemic disease and locally directed treatment will not alter the natural history of the disease course within a patient. In this scenario, only systemic therapy may be beneficial. Indeed, oligometastatic treatment paradigms are controversial (due to the limited data available). Without randomized studies, it is impossible to know if treatment of oligometastatic disease helps the patient. In addition, oligometastatic disease may represent indolent disease that does not require potentially toxic treatments. [14]

2.1.6. Rationale for the treatment of oligometastatic disease

Patients are increasingly being diagnosed with oligometastatic disease due to the advent of sensitive imaging technologies as well as effective therapies that are allowing patients to live longer with the diagnosis of cancer. In addition, the fact that novel treatment options with acceptable safety profiles, such as stereotactic radiation, cryoablation, and minimally invasive surgery, are available to treat limited metastases, has led to a renewed interest in treating oligometastatic disease. Treatment of oligometastatic disease not only has the potential to prevent further evolution of genetically unstable clones and metastatic spread, it may improve overall disease control and delay more toxic systemic treatment. Finally, the definition of oligometastases had gradually evolved, which further inflates the increasing population of patients diagnosed with oligometastasis. In the absence of data to guide decisions, treatment of oligometastatic disease may be seen as a quality-of-life oriented approach, choosing personalized treatments with a reasonable risk to benefit ratio and taking into account the patient's own attitude in guiding them toward more or less, intensive therapy. [14]

2.1.7. Further rationale for the treatment of oligometastatic prostate cancer

In addition to preventing further evolution of genetically unstable clones and additional metastatic spread, the combination therapies may be more effective in treating hormone-sensitive disease, before it becomes hormone refractory and more aggressive. While testing in the hormone sensitive population will require much longer follow-up to assess efficacy, as compared

to testing interventions in the castrate-resistant population, we have elected to assess safety as the primary endpoint and efficacy as a secondary endpoint.

2.2. Hormone therapy / complete androgen blockade

2.2.1. Hormone therapy in oligometastases

We reviewed the literature in search of clinical studies of hormone sensitive oligometastatic disease with hormone therapy included as an intervention. We searched PubMed using the terms breast, ovarian, and endometrial 'oligometastases', 'oligometastases', and 'breast, ovarian, and endometrial' oligometastatic cancer. There were no clinical studies focused solely on ovarian or endometrial oligometastatic cancer. Using the terms 'breast oligometastases', 'breast oligometastasis', and 'oligometastatic breast cancer'; results were as follows, n=20, n=5, and n=51, respectively. We omitted reviews (including special features), studies including mixed primary tumors, case reports, studies not in the English language, studies not focused on oligometastatic breast cancer, and a survey. There were seven clinical studies remaining; each study used a different therapy, none of which included a hormone therapy. [14]

We also searched for ongoing studies with hormone therapy included as an intervention. In clinicaltrials.gov multiple trials are underway to determine if the treatment of oligometastatic disease is beneficial in cancer. There were no trials for women with oligometastatic ovarian or endometrial cancer. For women with oligometastatic breast cancer, six studies are currently open investigating several therapies including various chemotherapy regimens, SABR + antibodies, SBRT, chemotherapy + antibodies + RT, targeted therapies and RT- however, none of the studies included hormone therapy. [14]

2.2.2. Hormone therapy / complete androgen blockade in metastatic prostate cancer

The standard of care treatment for metastatic prostate cancer is androgen deprivation therapy (ADT). Men with newly diagnosed metastatic prostate cancer, entered into the control arm of the Systemic Therapy Multi-Arm Randomized Controlled Trial (STAMPEDE) and treated with ≥2 years of ADT alone, had a 2-year OS of 72%. The response rate for primary hormonal therapy for men with metastatic prostate cancer exceeds 80% and the median duration of response is approximately 18-24 months. [14]

In 1941 the relationship was established between prostate adenocarcinoma and androgenic hormones [4]. These findings were the basis of androgen deprivation therapy (either pharmacologic or surgical) becoming first line therapy for men with metastatic prostate cancer. ADT continues to the mainstay, gold standard, initial therapy of metastatic prostate cancer, however it is not curative. The median time to development of resistance to primary ADT is 18-36 months. Currently medical castration is achieved with LHRH agonists (leuprolide or other LHRH agonists (i.e. goserelin, etc)) all of which are accepted as comparable. [4,5]

Combined androgen blockade (CAB) augments androgen ablation by using concurrent LHRH agonist and an antiandrogen. CAB may have a modest survival advantage over monotherapy, nonetheless it comes with increased risk of adverse effects. [4]

2.2.3. Hormone therapy / complete androgen blockade in oligometastatic prostate cancer

Currently we are awaiting the results of the STAMPEDE study arm for men with newly diagnosed M1 disease who are enrolled in a new treatment arm (enzalutamide, abiraterone and prednisone with ADT). [14]

We reviewed the literature in search of clinical studies of hormone sensitive oligometastatic prostate cancer with hormone therapy included as an intervention. We searched PubMed using the terms 'prostate cancer oligometastasis', 'prostate cancer oligometastases', and 'oligometastatic prostate cancer'; results were as follows, n=3, n=19, and n=22, respectively. We omitted reviews, studies including mixed primary tumors, studies not focused on oligometastatic prostate cancer, case reports, editorials/commentaries, studies that we were not able retrieve, and studies with no results reported. There were ten clinical studies remaining with 7 different treatment paradigms, of which 5 studies included hormone therapy. [14]

We also searched for ongoing studies with hormone therapy included as an intervention for oligometastic prostate cancer. In clinicaltrials.gov, nine trials are underway investigating a variety of therapies including single agent RT, RT in combination with HT, salvage treatment (surgical or RT) of metastases, and combination of HT + immunotherapy, of these nine trials, 3 include hormone therapy. [14]

2.3. Chemotherapy

2.3.1. Chemotherapy in oligometastases

We searched PubMed using the above described 'oligometastasis' terms for breast, lung, melanoma, colorectal cancer, sarcoma, and prostate cancer. Of those solid tumors, chemotherapy was used in breast, lung, colorectal, and sarcoma oligometastases. [14] In clinicaltrials.gov, of the multiple trials underway to determine if the treatment of oligometastatic disease is beneficial, 11/41 trials were using chemotherapy (including immunotherapy, monoclonal antibodies, tyrosine kinase inhibitors, anti-programmed death antibodies, anti-angiogenics) in their therapeutic regimen. [14]

We have initiated a trial at Johns Hopkins to treat men identified with OM PCa prior to any treatment: "A phase II study of definitive therapy for newly diagnosed men with oligometastatic prostate cancer ", IRB #: 00070003, SKCCC Protocol #: J1618. J1618 treats men with chemohormonal therapy in the neoadjuvant setting, followed by RP +/- adjuvant radiation, followed by SBRT to sites of OM disease. Hormonal therapy is given for a total of 1 year.

2.3.2. Chemotherapy in metastatic prostate cancer

Although taxanes are the standard treatment approach in metastatic castrate-resistant prostate cancer, two recent randomized trials investigated the combination of docetaxel + ADT in treatment naïve metastatic prostate cancer.

In the CHAARTED trial (Phase III, E3805) 790 men with metastatic hormone sensitive prostate cancer, treatment naïve, were randomized to either ADT + up to 6 cycles of docetaxel *versus* ADT alone. The primary endpoint was overall survival. Patients were stratified according to high volume disease (visceral metastases and/or ≥4 bone metastases) versus low-volume disease, prior anti-androgen use > 30 days, age ≥ or < 70 years, ECOG 01- versus 2 and prior adjuvant ADT > or ≤ 12 months. After a median follow-up of 28.9 months, the docetaxel + ADT arm had an OS of 57.6 months, as compared to ADT alone OS of 44.0 months. Patients with high-volume metastatic disease (defined as visceral metastasis or ≥4 bone metastases), treated on the docetaxel + ADT arm had an increased OS (49.2 *versus* 32.2 months in the ADT alone arm, HR 0.60, p<0.001). The median OS was not yet reached in either arm for those with low-volume disease. Other sub-group analyses (PSA < 0.2 at 6 mths/12mths, median time to CRPC, and median time to clinical progression) also showed that the combination of ADT + docetaxel was superior. In the docetaxel + ADT arm, grade 3/4 febrile neutropenia was 2.3%. [1,3-5]

In the GETUG 15 trial 385 men with metastatic hormone sensitive prostate cancer, were randomized to ADT + docetaxel *versus* ADT alone. The protocol allowed for up to 9 cycles of docetaxel. The primary endpoint was OS. Secondary endpoints included time to clinical progression and time to PSA progression. 81% of those enrolled had bone metastasis and 14.5% had visceral organ metastasis. Median number of cycles of docetaxel was 8. At 50 months median follow-up, OS was not different between the two arms, ADT + docetaxel versus ADT alone (58.9 versus 54.2 months, HR 1.01, p=0.955), despite that the combination therapy did yield a significant improvement in biochemical PFS and clinical PFS (22.9 versus 12.9 months, HR 0.72, p=0.005, and 23.5 versus 15.4 months, HR 0.75, p=0.015, respectively). [2,4,5] More recently, the authors reported on the comparison between patients' self assessment of treatment related toxicities versus investigators' evaluation of their patients' toxicities. [REF] The men were invited to complete a 26-symptom questionnaire at 3- and 6- months, while physicians assessed 18 symptoms. 220 and 165 patients completed questionnaires at 3- and 6-months. At the two assessment points (3 months and 6 months) all symptoms were reported more frequently by patients than by physicians. Positive agreement rates between patients and physicians, for the most commonly reported symptoms, included hot flushes (61 and 64%), fatigue (50 and 44%), sexual dysfunction (29 and 31%), and weight change (24 and 14%). However, ~50% of the time physicians did not report patients' hot flushes and ~90% of the time they did not report patients' joint/muscle pain. In comparison between the two arms, patients randomized to the ADT + docetaxel arm had more toxicities that those in the ADT alone arm. [6]

Alternatively, an arm of the STAMPEDE trial provides data on men with newly diagnosed metastatic prostate cancer who were randomized to standard-of-care therapy with androgen deprivation therapy. Cross-over was allowed at progression. The cohort of 917 men had a median follow-up of 20 months. Median failure free survival (FFS-time from randomization until biochemical failure, local or distant progression, or death from prostate cancer) was 11

months, and median OS was 42 months. 2 year FFS and OS were 29% and 72% respectively. This study demonstrated poor survival in men starting therapy with androgen deprivation only, despite the ability to initiate other treatments at failure of ADT. The median OS in this group was shorter than that of the control arm in GETUG-15, and was similar to the control arm in CHAARTED. [7]

2.3.3. Chemotherapy in oligometastatic prostate cancer

Several trials are currently underway for men with oligometastatic prostate cancer. In clinicaltrials.gov, there are nine trials investigating a variety of therapies including single agent RT, RT in combination with HT, salvage treatment (surgical or RT) of metastases, and combination of HT + immunotherapy. Of these nine trials, none included chemotherapy. [14]

2.4. Surgery

2.4.1. Surgery of oligometastastatic sites/metastasectomy

Historically, most of the surgical data in regards to oligometastatic disease is centered on hepatic resection. Perioperative mortality related to hepatic resection has decreased from 20% (before 1980) to 1%. Recent improvement in overall survival, following hepatectomy, are likely from improvements in patient selection (shift in definition of resectability to new criteria based on whether a macroscopic and microscopic complete resection of the liver lesion as well as complete resection of any extrahepatic disease), surgical technique, and more effective adjuvant therapy. The use of portal vein embolization and neoadjuvant chemotherapy has also expanded the population of patients who are eligible for resection. In a recent series of patients having undergone hepatic resection, despite progression on chemotherapy, the 5-yr survival was 53%. [14]

Secondary resection remains a worthwhile therapeutic goal; patients brought to resection by systemic therapy enjoy comparable long-term survival to patients who had resectable disease at the time of presentation, and far superior to those receiving palliative systemic chemotherapy. 10-20% of patients that develop colorectal liver metastases present with, or are converted by systemic treatment to, an oligometastatic state defined as metastatic lesions that are limited in number and involving only a single organ. This type of disease is potentially amenable to local therapeutic modalities, of which hepatic resection is the most effective. [14]

Surgery, when used to manage oligometastatic disease, tends to be seen as the gold standard as it allows for pathologic evaluation and assessment of the surgical margins. In addition, lesions greater than 7-8 cm and those difficult to target with SBRT, are better left for surgical management. [14]

2.4.2. Surgery in oligometastatic prostate cancer

There is a body of evidence, contrary to historical clinical practice, that treating men with metastatic prostate cancer to the lymph nodes at the time of diagnosis with surgery or radiation therapy results in increased long-term survival. Historically, the ideal patient to be cured by radical prostatectomy (RP) was one with organ-confined cancer. At that time, the morbidity of RP was substantial; therefore the surgery was generally only offered to those where the probability of cure was high. More recent data, however, show that RP may provide a survival benefit- albeit not a cure - to men with metastatic prostate cancer. Engel et al. [8] conducted a retrospective study (n=938) and found that in men with prostate cancer and positive lymph nodes, treated with +/- RP, that the 5- and 10-yr survival rates and the prostate cancer specific survival rates, were better in men who had undergone RP. Cadeddu et al [9] conducted a retrospective study (n=38) and found that in men with prostate cancer and positive lymph nodes, treated with LND +/- RP, that the 5- and 10-yr prostate cancer specific survival was better in men who had undergone LND + RP. [14]

In men with prostate cancer with limited metastases, radical prostatectomy may be advantageous in that the primary tumor and its ability to continuously metastasize, to secrete tumor promoting growth factors and immunosuppressive cytokines, and to generate bulk-related morbidity, is removed. Heidenreich et al. recently evaluated survival outcomes following radical prostatectomy (RP) in men with low volume metastatic prostate cancer. RP led to improved progression-free survival, time to castrate resistance and overall survival, as compared to a cohort treated with androgen deprivation therapy alone. [10] Moreover, Abdollah et al. found that in men with pN1 prostate cancer, treated with RP and extended lymph node dissection, adding adjuvant radiotherapy improved cancer-specific mortality [11]. [14]

2.5. Radiation Therapy / Stereotactic Radiation Therapy (SBRT)

2.5.1. Radiation therapy to the prostate in metastatic prostate cancer

Ost et al (2014) conducted a systemic review of the literature of metastasis-directed therapy of regional and distant recurrences after curative treatment for PCa (prostate cancer). They found that salvage LND and RT appear to be safe in treatments for OM PCa recurrence.[12] Culp et al. [13] studied the impact of survival of definitive treatment of the prostate in men diagnosed with metastatic PCa. Using the SEER database, he reviewed 8185 men treated with NSR (no surgery no radiation), brachytherapy, or RT. The 5-year OS and disease specific survival (DSS) was significantly higher in men with metastases having undergone RT. [14]

Zapatero et al., reported on a study of men with intermediate and high risk localized prostate cancer (n=362), treated with RT + long term ADT *versus* short term ADT, and found that long term ADT was superior in 5-year biochemical disease free survival, metastasis free survival, and OS [15]. [14]

2.5.2. SBRT for oligometastases

While much of the literature supporting the oligometastatic states is within the surgical literature, there is an increasing body of literature describing the use of stereotactic body radiotherapy (SBRT) and stereotactic radiosurgery (SRS), in addition to conventional fractionated radiotherapy techniques. SBRT is a noninvasive method of delivering high doses of radiation to ablate a target lesion while sparing the neighboring normal tissue, thus reducing long-term effects of radiation on the non-malignant tissues. The radiation is delivered from many beams originating from multiple directions that converge on the target site. Through improved targeting and management of tumor motion, SBRT may improve tumor control and reduce treatment-related toxicity, as compared to conventional fractionated RT. Improved radiation targeting allows for higher-dose, hypofractionated, more efficient treatment regimens that can be delivered within narrow margins sparring adjacent organs. 'Hypofractionation' is the delivery of large doses of radiation over a shorter time period as compared to conventional radiation fraction sizes. Therapy can generally be completed in 1-5 sessions, as compared to conventional radiation therapy that is delivered in smaller doses 5 days/week over ≥6 weeks. [14]

Intracranial stereotactic body radiation therapy (SBRT) has been shown to be a highly effective treatment for brain metastases. [29] This suggests that selective small extracranial tumors (either primary or metastatic tumors) may be effectively controlled by similar focal high-dose SBRT. There is an increasing experience with extracranial SBRT as effective local therapy for metastatic lesions. Local control in excess of 75% has been reported for metastatic tumors of the spine, lung and liver, which is significantly higher than standard conventional moderate dose radiation. [29-33] Toxicity has been minimal in multiple U.S., European and Japanese trials of extracranial stereotactic radiotherapy to the lung, liver, spine, pelvis and abdomen despite the use of very high biological equivalent doses for patients with both organ confined and metastatic cancer. [adapted from Johns Hopkins Oncology Clinical protocol J12137, NA_00069585]

SBRT can be used to manage oligometastatic disease presentations that would be associated with added morbidity if managed by surgery, such as deep-seated or osseous lesions. Patients who are poor surgical candidates may often be treated with SBRT, given that it is noninvasive and has a modest morbidity profile. [14]

Although traditionally radiation therapy was thought to be immunosuppressive, there is increasing pre-clinical and clinical evidence that high dose, hypofractionated radiation –SBRT- may reverse antitumor immunity via CD8+ T-cells and cellular stress signals. Although uncommon, the abscopal effect (regression in tumors distant to the targeted field of radiation) is an example of recovery of anti-tumor immunity following RT. Thus, an emerging advantage of SBRT is the possibility that it may be exploited to benefit the immune system. [14]

2.5.3. SBRT in oligometastatic prostate cancer

Major advancements in radiation treatment planning and delivery have resulted in resurgence in the use of radiation therapy (RT) as a treatment for bone metastases. In selected patients, very high local control rates have been observed, with minimal toxicity. Bone metastases represent the major

metastatic site (>90%) in men with rising PSA following primary treatment for their prostate cancer. [adapted from Johns Hopkins Oncology Clinical protocol J12137, NA_00069585]

The primary management of metastatic prostate cancer is systemic therapy in the form of androgen deprivation therapy (ADT), which rarely eradicates metastatic disease and adversely effects patient quality of life. Thus, even the ability to defer long-term ADT in men with oligometastatic prostate cancer represents a considerable clinical advance. [adapted from Johns Hopkins Oncology Clinical protocol J12137, NA_00069585]

3. Study Objectives

3.1. Primary Objective

To assess the efficacy of treating men with oligometastatic prostate cancer with the following therapy: (1st) Systemic chemo-hormonal therapy with up to 6-months (~24 weeks) of adjuvant androgen deprivation and up to 6 cycles of chemotherapy, (2nd) definitive local tumor control with adjuvant radiation therapy, and (3rd) consolidative stereotactic radiation to oligometastatic lesions. The men will receive a total of 2 years of androgen deprivation. Androgen blockade will be the same throughout the course of treatment.

Efficacy will be defined as the 3-year PSA progression-free (PSA<0.2 ng/ml) survival rate.

3.2. Secondary Objectives

1. Safety

Defined as the incidence of Grades 3/4 neutropenia and surgical- or radiation- induced toxicities.

2. Time to PSA recurrence.
   Defined as the time from an undetectable PSA (≤0.2 ng/mL) until the PSA is >0.2 over two time-points up to 3 years.

4. Patient Population

Men with newly diagnosed synchronous oligometastatic prostate cancer (T_{1-4}, N_{0-1}, M1a-b) consisting of 1-5 metastatic lesions who are willing to undergo (1st) Systemic chemo-hormonal therapy with up to 6-months (~24 weeks) of adjuvant androgen deprivation and up to 6 cycles of chemotherapy, (2nd) definitive local tumor control with adjuvant radiation therapy, and (3rd) consolidative stereotactic radiation to radiologically evident oligometastatic lesions.

4.1. Inclusion Criteria

1. Willing and able to provide written informed consent

2. Age ≥ 18 years

3. Eastern cooperative group (ECOG) performance status ≤2

4. Documented histologically confirmed adenocarcinoma of the prostate

5. Willing to undergo the following therapy: (1st) Systemic chemo-hormonal therapy with up to 6-months (~24 weeks) of neoadjuvant androgen deprivation and up to 6 cycles of chemotherapy, (2nd) definitive local tumor control with adjuvant radiation therapy, and (3rd) consolidative stereotactic radiation to oligometastatic lesions. Additionally, must be willing to be treated with a full two years of androgen deprivation.

6. Oligometastatic prostate cancer: Stage T_{1-4}, N_{0-1} and/or M_{1a-b} (up to 5 metastatic lesions- including bone lesions and non-regional lymph nodes)

4.2. Exclusion Criteria

1. Prior local non-surgical therapy to treat prostate cancer (e.g. radiation therapy, brachytherapy)

2. Prior therapy to a metastatic site.

3. Prior systemic therapy for prostate cancer including, but not limited to:
    a. Hormonal therapy (e.g. leuprolide, goserelin, triptorelin, degarelix)
    b. CYP-17 inhibitors (e.g. ketoconazole)
    c. Antiandrogens (e.g. bicalutamide, nilutamide)
    d. Second generation antiandrogens (e.g. abiraterone, enzalutamide)
    e. Immunotherapy (e.g. sipuleucel-T, ipilimumab)
    f. Chemotherapy (e.g. docetaxel, cabazitaxel)

*Note: may be enrolled if has recently initiated hormone therapy of any kind (<90 days duration). In the event that hormone therapy was initiated prior to study enrollment, the clock for 1 year of androgen deprivation would begin at the time of therapy initiation, rather than at study enrollment.

4. Ongoing systemic therapy for prostate cancer including, but not limited to:
    a. Immunotherapy (e.g. sipuleucel-T, ipilimumab)
    b. Non-protocol prescribed chemotherapy (e.g. cabazitaxel)

5. Evidence of serious and/or unstable pre-existing medical, psychiatric or other condition (including laboratory abnormalities) that could interfere with patient safety or provision of informed consent to participate in this study.

6. Any psychological, familial, sociological, or geographical condition that could potentially interfere with compliance with the study protocol and follow-up schedule.

7. Abnormal bone marrow function [absolute neutrophil count (ANC)<1500/mm^3, platelet count <100,000/mm^3, hemoglobin <9 g/dL]

8. Abnormal liver function (bilirubin >ULN; AST, ALT ≥ 2.5 x upper limit of normal)

9. Active cardiac disease defined as active angina, symptomatic congestive heart failure, or myocardial infarction within previous six months.

10. Prior history of malignancy in the past 3 years with the exception of basal cell and squamous cell carcinoma of the skin. Other malignancies that are considered to have a low potential to progress may be enrolled at discretion of PI.

4.3. Inclusion of Women and minorities

This study is focused on prostate cancer and therefore includes men only.

Men from all ethnic and race groups are eligible for this study.

5. Treatment Plan

5.1. Study Design

To assess the efficacy of treating men with oligometastatic prostate cancer with the following therapy: (1st) Systemic chemo-hormonal therapy with up to 6-months (~24 weeks) of adjuvant androgen deprivation and up to 6 cycles of chemotherapy, (2nd) definitive local tumor control with adjuvant radiation therapy, and (3rd) consolidative stereotactic radiation to oligometastatic lesions. The men will receive a total of 2 years of androgen deprivation. Androgen blockade will be the same throughout the course of treatment.

Open label phase II study designed to assess the efficacy and therapeutic benefit of multimodality therapy in men presenting with newly diagnosed oligometastatic prostate cancer (≤5 sites of metastases). A total of sixty patients will be enrolled with the primary endpoint of the 3 year PSA progression-free (PSA<0.2 ng/ml) survival rate.

Adjuvant treatment (month 1 through ~6): All patients will be treated with up to 6 months of androgen deprivation, plus up to 6 cycles of docetaxel chemotherapy. Following docetaxel therapy, patients with a PSA response of at least a 50% decrease from baseline, will proceed to maximum consolidative therapy.

Radiation (month 7 though ~11): After completion of adjuvant chemotherapy, the men will be treated with definitive local therapy with adjuvant radiation therapy (RT). After definitive local therapy, patients will be treated with consolidative stereotactic body radiation therapy (SBRT) to the metastatic sites (if present).

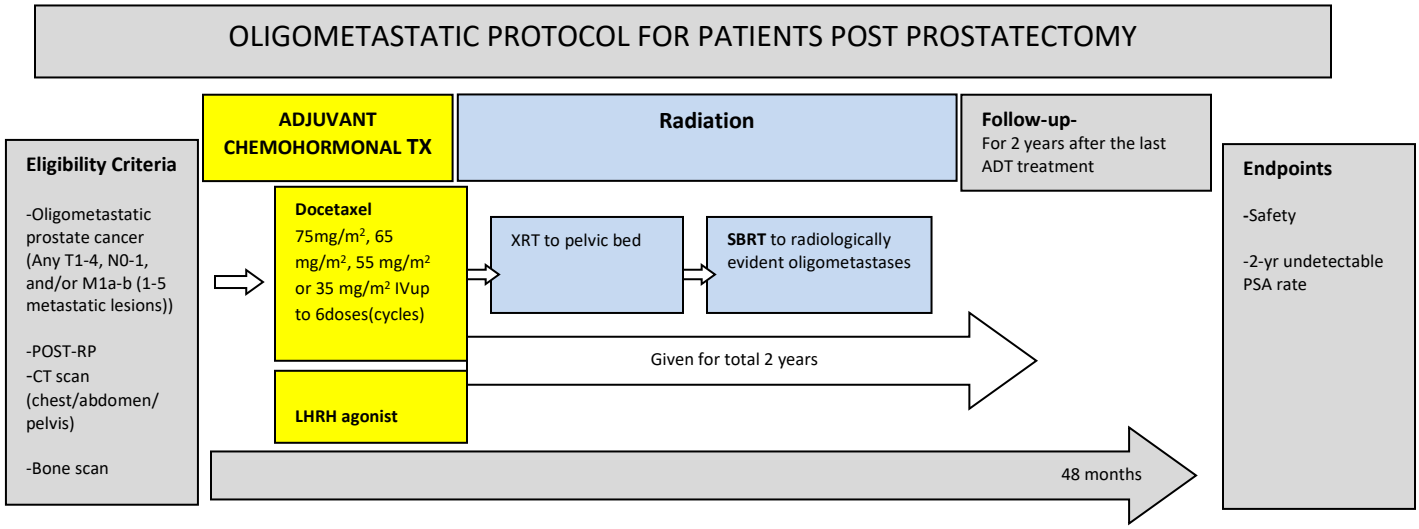
Follow up: Patients will continue on androgen deprivation for a total of 2 years. They will be followed clinically and monitored with serum testosterone and PSA until 2-years after completion of systemic consolidation. Androgen blockade will be the same throughout the course of treatment.

Primary Center: Johns Hopkins Hospital. Will include Sibley Hospital as a second site.

Adjuvant chemohormonal therapy is expected to be safe. Two recent randomized trials (CHAARTED and GETUG-AUF15) investigated the combination of docetaxel + ADT in treatment naïve metastatic prostate cancer. In the CHAARTED trial (Phase III, E3805) 790 men with metastatic hormone sensitive prostate cancer, treatment naïve, were randomized to either ADT + docetaxel *versus* ADT alone. The primary endpoint was overall survival. Data from 1/16/14 with a median follow-up of 29 months included 137 deaths on ADT alone arm *versus* 104 deaths on the ADT + docetaxel arm. In the ADT + docetaxel arm, grade 3-4 neutropenia was 4%-2%; grade 3 neuropathy was 1% sensory and 1% motor; one patient died while on treatment, however there were no deaths attributed to treatment on ADT. [3-5]

In the GETUG-AUF 15 trial 385 men with metastatic hormone sensitive prostate cancer, were randomized to ADT + docetaxel *versus* ADT alone. The protocol allowed for up to 9 cycles of docetaxel. The primary endpoint was OS. Secondary endpoints included time to clinical progression and time to PSA progression. 81% of those enrolled had bone metastasis and 14.5% had visceral organ metastasis. Median number of cycles of docetaxel was 8. Grade 3-4 adverse events were higher in the docetaxel + ADT arm. The most common grade 3-4 adverse events in the docetaxel + ADST arm were neutropenia (32%), febrile neutropenia (7%), and fatigue (7%). Docetaxel was dose reduced in 11% of the patients. [2,4,5]

Study schema



The primary endpoint is the 3 year PSA progression-free (PSA<0.2 ng/ml) survival.

Secondary endpoints will include 2-year undetectable PSA rate, time to PSA recurrence following completion of therapy.

5.3. Removal of Patients from Study

A patient may be removed from the study for a variety of reasons, including:

1. An increase in PSA, defined as PSA increased consistently over 3 time-points

2. Disease progression of metastatic sites, or new metastatic lesions, demonstrated on imaging at completion of chemotherapy.

3. Diagnosis of >5 metastases on entry imaging studies before SBRT.

4. Worsening symptoms that can be attributed to prostate cancer

5. Unacceptable adverse event(s)
   - Patients who develop grade 3 or higher liver function abnormalities:
     - o Bilirubin ≥ 3 times institutional upper limit of normal (ULN)
     - o AST (SGOT) or ALT (SGPT) ≥ 5 times ULN
   - Patients develop decreased renal function with serum creatinine ≥ 2.5 times baseline level

6. Patients develop hypersensitivity or anaphylactoid reactions to leuprolide (Lupron) (LHRH analogs), or its replacement drugs, or docetaxel (taxotere). Intercurrent illness that prevents further participation

7. Experiencing a treatment delay of longer than 4 weeks due to drug, surgical or radiation toxicity; however, if the patient is receiving clinical benefit, treatment may be delayed for longer than 4 weeks and then resumed at the discretion of the Investigator.

8. Patient refuses further treatment through the study and/or withdraws consent to participate

9. Patient is noncompliant with respect to taking drugs, keeping appointments, or having tests required for the evaluation of safety and efficacy

10. General or specific changes in the patient's condition that render the patient unacceptable for further treatment in this study in the judgment of the investigator.

11. Under no circumstance will care of a withdrawn patient be adversely affected by a decision to withdraw or be withdrawn from the study.

6. Treatment Screening

*All required screening study procedures and assessments must be done within 30 days prior to enrollment unless otherwise noted. Prior to enrollment, patients will be seen by a Medical Oncologist, Urologist, and Radiation Oncologist to ensure the patient is aware of risks and potential benefits of each type of treatment.

6.1. Screening (performed within prior to Cycle 1 Day 1)

1. Informed consent
2. Medical History
3. Physical Examination and ECOG Performance Status: A complete physical examination will be completed at screening and the End of Study visit; symptom-directed physical examinations will be completed at the times specified in the study calendar
4. Patient Height and Weight
5. Vital Signs: Vital sign measurements include measurements of diastolic and systolic BP, heart rate, and temperature.
6. Concomitant Medications and Procedures
7. CBC (Complete blood count) with differential and platelet count.
8. CMP (Comprehensive Metabolic Panel - Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, CO2).
9. Serum PSA
10. Serum Testosterone
11. CT scan (chest-abdomen-pelvis) with contrast
12. Bone scan- whole body (within 90 days of study enrollment)
13. MRI (optional)
14. PET scan (optional)
15. Quality of Life (FACT-P and FACT-Taxane)

7. Treatment and Assessments on Study

*All required treatment and end of study procedures and assessments must be done within 7 days (+/-) of the specified study visit date unless otherwise noted. Long-term follow-up procedures and assessments should occur within 21 days (+/-) from the specified study visit date.

7.1. Adjuvant Treatment and assessments

Hormone therapy-

LHRH analog (3 month injection)- given twice, at beginning of Cycle 1 chemotherapy, and repeat every 3 months for a total of 2 years.

* At Investigator discretion- Complete androgen blockade may be administered by adding the anti-androgen, bicalutamide (50 mg daily, oral) and/or abiraterone acetate (1000 mg / day + prednisone 5mg / day), to the LHRH analog

Chemotherapy- administered every 3 weeks, in 6 cycles. The cycles may be adjusted to up to every 5 weeks for toxicity and scheduling convenience

Cycle 1-Cycle 6 Docetaxel Administration (intravenous) (± 7 days)

- Clinical assessment and ECOG Performance Status same day, prior to Docetaxel Administration
- Vital Signs and weight
- CMP, CBC, PSA
- CBC- 1-week post
- Adverse events
- Concomitant Medications and Procedures

Re-staging, 4 weeks after final cycle of chemotherapy is given (up to month 7)

- Physical Examination and ECOG Performance Status
- Vital Signs: Vital sign measurements include measurements of diastolic and systolic BP, heart rate, and temperature.
- Weight
- Adverse events
- CBC (Complete blood count) with differential and platelet count.
- CMP (Comprehensive Metabolic Panel - Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, CO2).
- Serum PSA
- Serum Testosterone
- CT scan (chest-abdomen-pelvis) with contrast
- Whole body bone scan
- MRI (Optional)
- Quality of Life (FACT-P and FACT-Taxane)

7.2. Radiation

Adjuvant radiation to pelvic bed (given 1-2 months after completion of chemotherapy); given over 6-8 weeks.

SBRT to OM sites (If indicated secondary to radiologically evident OM disease); depending on number of OM sites, SBRT delivered over 1-5 weeks, timing (during or right after EBRT) secondary to Radiation Oncologist discretion.

7.3. Follow-up

7.1. Follow Up, 24 months after the last ADT treatment

1. Serum PSA every 3 months
2. Serum Testosterone every 3 months
3. Bone scan (whole body), only clinically indicated
4. CT scan (chest, abdomen, pelvis), only clinically indicated

End of Study Visit at 48 months:

- Physical Examination and ECOG Performance Status
- Vital sign measurements
- Weight
- CBC (Complete blood count) with differential and platelet count.
- CMP (Comprehensive Metabolic Panel - Sodium, Potassium, Chloride, BUN, Serum Creatinine, Calcium, Total Protein, Albumin, Total Bilirubin, AST, ALT, Alkaline Phosphatase, CO2).
- Serum PSA
- Serum Testosterone
- CT scan (chest-abdomen-pelvis) with contrast (only clinically indicated)
- Whole body bone scan (only clinically indicated)

8. Study Calendar

		Adjuvant treatment [a]		**Radiation [b]**			**Follow-Up [c,d,y]**	**End of Study Visit [e,f,y]**
	Screening [g, x]	**6 Cycles (Q3 weeks ±7 days)**	**Re-Staging Visit [h] ±7 days**		**Adjuvant RT to pelvic bed [i]**	**SBRT to Oligomet. Sites [j]**	**±28 days**	**±28 days**
Informed consent	X							
Inclusion/Exclusion Criteria	X							
Medical history	X							
Physical assessment	X	X	X					X
Vital signs [k]	X	X	X					X
Weight	X	X	X					X
Height	X							
ECOG Performance status	X	X	X					X
Adverse Events Assessment	X	X	X					X
Concomitant Medications	X	X	X					X
Quality of life [l]	X		X					
Hematology [u]	X	X [w]	X					X
Serum Chemistry [v]	X	X	X					X
PSA	X	X	X		X		Q3mo	X
Testosterone	X		X		X		Q3mo	X

		Adjuvant treatment [a]		**Radiation [b]**			**Follow-Up [c,d,y]**	**End of Study Visit [e,f,y]**
	Screening [g, x]	**6 Cycles (Q3 weeks ±7 days)**	**Re-Staging Visit [h] ±7 days**		**Adjuvant RT to pelvic bed [i]**	**SBRT to Oligomet. Sites [j]**	**±28 days**	**±28 days**
CT/MRI [m]	X [m]		X [m]				X [m]	X [m]
Bone Scan [n]	X [n]		X [n]				X [n]	X [n]
Chemotherapy [o]		X						
Hormone therapy [P]		X						
Bicalutamide and/or abiraterone [q]		X						
Adjuvant radiation therapy (RT) [s]					X			
SBRT						X		
MRI [t]			X					
Survival Follow-Up [f,y]								X [f]

a. Adjuvant treatment (month 1 through ~6*)*: All patients will be treated with up to 6 months of androgen deprivation, plus up to 6 cycles of docetaxel chemotherapy (Docetaxel 75 mg/m^2, 65mg/m^2, 55mg/m^2, or 35mg/m^2 at physician discretion every 3 weeks as a 1hour intravenous infusion).
b. Radiation (month 7 though ~11): After completion of neoadjuvant therapy, men will be treated with definitive local therapy with +/- adjuvant radiation therapy (RT). After definitive local therapy, patients will be treated with consolidative stereotactic body radiation therapy (SBRT) to the metastatic sites
c. Follow up: Patients will be followed for 2 years after the last ADT treatment.
d. PSA and Testosterone should be obtained at every 3 months and can be done at an outside facility.
e. End of Study Visit will be at 48 months.
f. Study Subjects may be contacted every 3 months for survival data. Other potential data such as the subjects' follow-up treatment or care may be requested during these contacts. The contacts can be via telephone or correspond with disease assessment visits or other scheduled visits.

g. Screening will be performed within 30 days of Cycle 1 Day 1.
h. Re-staging, 4 weeks after final cycle of chemotherapy is given.
i. Adjuvant radiation to pelvic bed (if indicated, given 1-2 months after completion of chemotherapy); given over 3 weeks.
j. SBRT to oligometastatic sites, (If indicated secondary to radiologically evident OM disease) Depending on number of OM sites, SBRT delivered over 1-5 weeks, timing (during or right after EBRT) secondary to Radiation Oncologist discretion
k. Vital sign measurements include diastolic and systolic BP, heart rate, and temperature.
l. Quality of life scoring using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) [REF] supplemented with the FACT-Taxane [REF]. QOL instruments will be administered at Screening and Re-Staging.
m. Radiographic evaluation will be performed at screening (up to 30 days before Cycle 1 Day1) and restaging visit; however subsequent radiographic assessments may be performed as clinically indicated. Testing will include CT with intravenous contrast or MRI of the chest, abdomen, and pelvis. The scans can be done at an outside facility.
n. Bone scanning will be performed at screening (screening Bone scan may be done up to 90 days before Cycle 1 Day 1) and restaging visit. Requirements for additional Bone scans will be performed as clinically indicated. The scans can be done at an outside facility.
o. Docetaxel will be given at any of the following doses (75 mg/m^2, 65 mg/m^2, 55 mg/m^2 or 35 mg/m^2 IV) on day 1 every 3 weeks, up to 6 cycles at physician discretion.
p. LHRH analog (Q3 month injection). Androgen deprivation therapy may have started up to 90 days before Day 1. It is given for a total of 1 year; the clock for 1 year of androgen deprivation would begin at the time of therapy initiation, rather than at study enrollment.
q. Bicalutamide (Casodex) (50mg daily) and/or or abiraterone acetate 1000 mg / day + prednisone 5mg / day) may be added to the leuprolide in the event that the Investigator elects to administer complete androgen blockade. No replacements are allowed for bicalutamide or abiraterone. No dose adjustments are allowed for bicalutamide .
r. Following docetaxel therapy, patients with a PSA response of at least a 50% decrease from baseline, will proceed to maximum consolidative therapy.
s. Adjuvant radiation to pelvic bed (if indicated, given 3 months after prostatectomy). Radiation therapy to pelvic bed indicated if positive margins at prostatectomy and/or Radiation therapy to pelvic bed indicated if pT3 and/or R1 (per AUA-ASTRO guidelines)
t. Optional MRI, standard of care
u. Hematology: hemoglobin, hematocrit, RBC count, WBC count with differential, ANC and platelet count. Labs must be done within 7 days (+/-) of the specified study visit date unless otherwise noted.
v. Serum Chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, ALT, AST, alkaline phosphatase, total bilirubin, total protein, albumin, calcium. Labs must be done within 7 days (+/-) of the specified study visit date unless otherwise noted.
w. Hematology: CBC- 1-week post Docetaxel administration.
x. Prior to enrollment, patients will be seen by a Medical Oncologist, Urologist, and Radiation Oncologist to ensure the patient is aware of risks and potential benefits of each type of treatment.
y. In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.

9. Study Assessments

Response and progression of targeted metastatic prostate cancer lesions will be evaluated as follows:

1) CT scans (to assess lymph nodes)- Using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Committee [34]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

2) Bone scans- Lesions by bone scan will be evaluated as positive, negative or no change.

3) Serial PSA changes.
4) Adverse events (AEs) will be monitored every 3 weeks during neoadjuvant therapy and at two-months post surgery. Patients requiring adjuvant EBRT will be assessed as per standard of care during treatment and at two-months days post therapy. AEs will be monitored as per standard of care during treatment and at two-months post therapy.. AEs will then be monitored 3 months (per study calendar).

9.1. Definitions

Oligometastases:
Oligometastatic prostate cancer will be defined as prostate cancer with up to 5 sites of metastases, including bone lesions, regional and non-regional lymph nodes; men with visceral metastases will not be included.

Undetectable PSA:
PSA ≤ 0.2 ng/mL

PSA increase/PSA recurrence:
Surgery arm: PSA >0.2, over two time-points
Radiation therapy arm: PSA increased 2ng/mL over nadir (nadir is determined after therapy)

2-year undetectable PSA (time interval)**:**
2 years after completion of systemic consolidative therapy

3-year PSA progression-free survival:
(PSA<0.2 ng/ml) among men who have non-castrate testosterone levels 3 years after enrollment
*for men with a baseline testosterone ≤200ng/dL, 3-year PSA PFS is defined as a PSA <0.2 at baseline level of testosterone, 3 years after enrollment

Noncastrate testosterone level:
>200 ng/dL

9.2. Imaging

Patients should be re-evaluated for 6 months, and as clinically indicated.

CT SCAN
Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis.
Radiographic response assessed using RECIST 1.1 criteria [34].

Bone SCAN
To be performed as per standard of care to assess response of osseous lesions to therapy.
Radiographic response assessed using the following criteria: progression, no change, and response.

9.3. Safety

Safety will evaluated based on the incidence, severity, duration, causality, seriousness, and type of adverse events (AEs), and changes in the patient's physical examination, vital signs, and clinical laboratory results. Investigators will use the NCI CTC version 4.0 (published 14 June 2010) to assess the severity of AEs and toxicities (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). For safety considerations specific to the study drugs, see section 10 of the protocol.

Adverse events (AEs) will be monitored every 3 weeks during neoadjuvant therapy and at two-months post surgery. Patients requiring adjuvant EBRT will be assessed as per standard of care during treatment and at two-months days post therapy. AEs will be monitored as per standard of care and at two-months post SBRT. AEs will then be monitored 3 months (per study calendar).

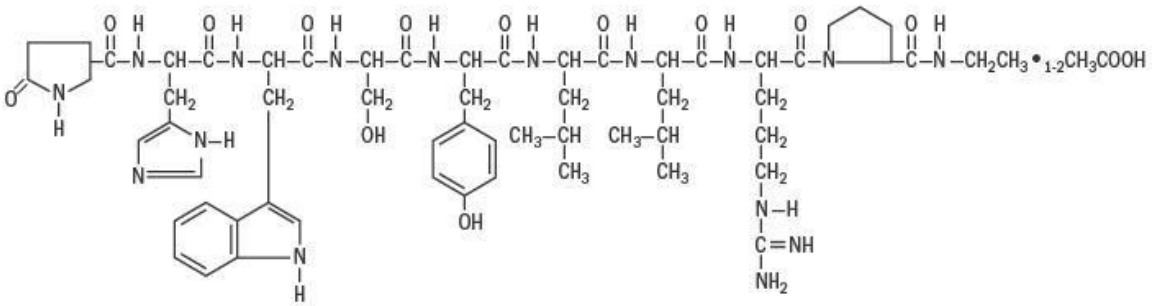
Please see Section 13.1, Early Stopping Boundaries for Toxicity

10. Pharmaceutical Information

10.1. Drug Name: leuprolide acetate

[Adapted from FDA prescribing information]

[Note: for leuprolide replacements, following FDA prescribing information]



- **Chemical Name:** 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt)
- **Molecular Formula:** $C_{59}H_{84}N_{16}O_{12}\cdot C_2H_4O_2$
- **Molecular Weight:** 1269.45

Description

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone.

Leuprolide acetate injection is a sterile, aqueous solution intended for subcutaneous injection. It is available in a 2.8 mL multiple-dose vial containing 5 mg/mL of Leuprolide acetate, 6.3 mg/mL sodium chloride, USP for tonicity adjustment, 9 mg/mL of benzyl alcohol as a preservative and water for injection, USP. The pH may have been adjusted with sodium hydroxide, NF and/or acetic acid, NF.

Clinical Pharmacology

Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation of gonadotropins, chronic administration of Leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of Leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs.

In humans, subcutaneous administration of single daily doses of Leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in pre-menopausal females). However, continuous daily administration of Leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In pre-menopausal females, estrogens are reduced to post-menopausal levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for periods of up to five years.

Leuprolide acetate is not active when given orally.

Safety/Precautions

- **Tumor Flare**
  Initially, Lupron Depot, like other GnRH agonists, causes increases in serum levels of testosterone to approximately 50% above baseline during the first weeks of treatment. Isolated cases of ureteral obstruction and spinal cord compression have been observed, which may contribute to paralysis with or without fatal complications. Transient worsening of symptoms may develop. A small number of patients may experience a temporary increase in bone pain, which can be managed symptomatically.

  Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy.

- **Hyperglycemia and Diabetes**
  Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycemia may represent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycemia or diabetes.

- **Cardiovascular Diseases**
  Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.

- **Effect on QT/QTc Interval**
  Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

- **Convulsions**
  Postmarketing reports of convulsions have been observed in patients on leuprolide acetate therapy. These included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and in patients on concomitant medications that have been associated with convulsions such

as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above. Patients receiving a GnRH agonist who experience convulsion should be managed according to current clinical practice.

Information for Patients

Patients should be informed that:

- The most common side effects associated with Lupron Depot are hot flashes, pain (especially joint pain and back pain), injection site pain and fatigue.
- If they have had an allergic reaction to other drugs like Lupron Depot, they should not use this drug.
- Lupron Depot may cause impotence.
- The increase in testosterone that occurs during the first weeks of therapy can cause an increase in urinary symptoms or pain.
- If they have metastatic cancer to the spine or urinary tract, they need close medical attention during the first weeks of therapy.

Laboratory tests

Response to Leuprolide acetate should be monitored by measuring serum levels of testosterone and prostate-specific antigen (PSA). In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. Castrate levels were reached within two to four weeks and once attained were maintained for as long as drug administration continued.

Drug Interactions

No pharmacokinetic-based drug-drug interaction studies have been conducted with Leuprolide acetate. However, because Leuprolide acetate is a peptide that is primarily degraded by peptidase and the drug is only about 46% bound to plasma proteins, drug interactions would not be expected to occur.

Adverse Reactions

In the majority of patients testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. This transient increase was occasionally associated with a temporary worsening of signs and symptoms, usually manifested by **an increase in bone pain**. In a few cases a **temporary worsening of existing hematuria and urinary tract obstruction** occurred during the first week. Temporary **weakness and paresthesia of the lower limbs** have been reported in a few cases.

Potential exacerbations of signs and symptoms during **the first few weeks of treatment** is a concern in patients with **vertebral metastases and/or urinary obstruction** which, if aggravated, may lead to neurological problems or increase the obstruction.

Administration, Supply and Storage

Administration

The recommended dose is 1 mg (0.2 mL or 20 unit mark) administered as a single daily subcutaneous injection. As with other drugs administered chronically by subcutaneous injection, the injection site should be varied periodically. Each 0.2 mL contains 1 mg of Leuprolide acetate, sodium chloride for tonicity adjustment, 1.8 mg of benzyl alcohol as preservative and water for injection. The pH may have been adjusted with sodium hydroxide and/or acetic acid.

Supply

Leuprolide Acetate Injection is a sterile solution, supplied as follows:

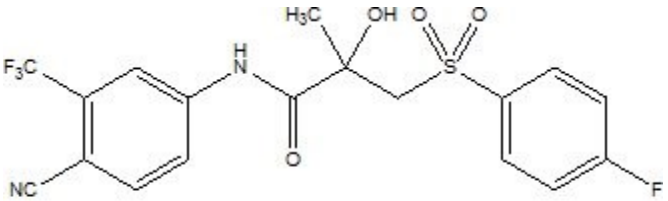
- 2.8mL multiple dose vial
- one multiple-dose vial per one 14-day patient
- 1 mg/0.2 mL
- administration kit with 14 disposable syringes and 28 alcohol swabs
- NDC number: 0703-4014-18

Storage

Store below 25°C (77° F). DO NOT FREEZE. Protect from light. Store vial in carton until contents are used.

10.2. Drug Name: <u>bicalutamide</u>

[Adapted from FDA prescribing information]



$C_{18}H_{14}F_4N_2O_4S$

- **Chemical Name:** ropanamide, (+-)-N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide.
- **Molecular Formula:** $C_{18}H_{14}F_4N_2O_4S$
- **Molecular Weight:** 430.37

Description

Bicalutamide tablets, USP contain 50 mg of Bicalutamide, a non-steroidal androgen receptor inhibitor with no other known endocrine activity.

Clinical Pharmacology

Bicalutamide tablets are a non-steroidal androgen receptor inhibitor. It competitively inhibits the action of androgens by binding to cytosol androgen receptors in the target

tissue. Prostatic carcinoma is known to be androgen sensitive and responds to treatment that counteracts the effect of androgen and/or removes the source of androgen.

When Bicalutamide tablets are combined with luteinizing hormone releasing hormone (LHRH) analog therapy, the suppression of serum testosterone induced by the LHRH analog is not affected. However, in clinical trials with Bicalutamide tablets as a single agent for prostate cancer, rises in serum testosterone and estradiol have been noted.

In a subset of patients who have been treated with Bicalutamide tablets and an LHRH cv agonist, and who discontinue Bicalutamide tablets therapy due to progressive advanced prostate cancer, a reduction in Prostate Specific Antigen (PSA) and/or clinical improvement (antiandrogen withdrawal phenomenon) may be observed.

Safety/Precautions

- **Hepatitis** Cases of death or hospitalization due to severe liver injury (hepatic failure) have been reported post-marketing in association with the use of Bicalutamide tablets. Hepatotoxicity in these reports generally occurred within the first 3 to 4 months of treatment. Hepatitis or marked increases in liver enzymes leading to drug discontinuation occurred in approximately 1% of Bicalutamide tablets patients in controlled clinical trials.
  Serum transaminase levels should be measured prior to starting treatment with Bicalutamide tablets, at regular intervals for the first 4 months of treatment, and periodically thereafter. If clinical symptoms or signs suggestive of liver dysfunction occur (e.g., nausea, vomiting, abdominal pain, fatigue, anorexia, "flu-like" symptoms, dark urine, jaundice, or right upper quadrant tenderness), the serum transaminases, in particular the serum ALT, should be measured immediately. If at any time a patient has jaundice, or their ALT rises above two times the upper limit of normal, Bicalutamide tablets should be immediately discontinued with close follow-up of liver function.

- **Gynecomastia and Breast Pain** In clinical trials with Bicalutamide tablets 150 mg as a single agent for prostate cancer, gynecomastia and breast pain have been reported in up to 38% and 39% of patients, respectively.

- **Glucose Tolerance** A reduction in glucose tolerance has been observed in males receiving LHRH agonists. This may manifest as diabetes or loss of glycemic control in those with preexisting diabetes. Consideration should therefore be given to monitoring blood glucose in patients receiving Bicalutamide tablets in combination with LHRH agonists.

Information for Patients

- Patients should be informed that therapy with Bicalutamide tablets and the LHRH analog should be started at the same time and that they should not interrupt or stop taking these medications without consulting their physician.

- During treatment with Bicalutamide tablets, somnolence has been reported, and those

patients who experience this symptom should observe caution when driving or operating machines.

- Patients should be informed that diabetes, or loss of glycemic control in patients with preexisting diabetes has been reported during treatment with LHRH agonists. Consideration should therefore be given to monitoring blood glucose in patients receiving Bicalutamide tablets in combination with LHRH agonists.

Laboratory tests

- Regular assessments of serum Prostate Specific Antigen (PSA) may be helpful in monitoring the patient's response.

- If PSA levels rise during Bicalutamide tablets therapy, the patient should be evaluated for clinical progression. For patients who have objective progression of disease together with an elevated PSA, a treatment-free period of antiandrogen, while continuing the LHRH analog, may be considered.

Drug Interactions

Clinical studies have not shown any drug interactions between Bicalutamide and LHRH analogs (goserelin or leuprolide). There is no evidence that Bicalutamide induces hepatic enzymes.

In vitro studies have shown that R-Bicalutamide is an inhibitor of CYP 3A4 with lesser inhibitory effects on CYP 2C9, 2C19 and 2D6 activity. Clinical studies have shown that with coadministration of Bicalutamide tablets, mean midazolam (a CYP 3A4 substrate) levels may be increased 1.5 fold (for Cmax) and 1.9 fold (for AUC). Hence, caution should be exercised when Bicalutamide tablets are coadministered with CYP 3A4 substrates.

In vitro protein-binding studies have shown that Bicalutamide can displace coumarin anticoagulants from binding sites. Prothrombin times should be closely monitored in patients already receiving coumarin anticoagulants who are started on Bicalutamide tablets and adjustment of the anticoagulant dose may be necessary.

Adverse Reactions

In patients with advanced prostate cancer treated with Bicalutamide tablets in combination with an LHRH analog, the most frequent adverse reaction was hot flashes (53%).

In the multicenter, double-blind, controlled clinical trial comparing Casodex 50 mg once daily with flutamide 250 mg three times a day, each in combination with an LHRH analog, the following adverse reactions with an incidence of 5% or greater, regardless of causality, have been reported: pain (general), back pain, asthenia, pelvic pain, infection, abdominal pain, chest pain, headache, fly syndrome, hot flashes, hypertension, constipation, nausea, diarrhea, increased liver enzyme, dyspepsia, flatulence, anorexia,

vomiting, anemia, peripheral edema, weight loss, hyperglycemia, AP increased, weight gain, bone pain, myasthenia, arthritis, pathological fracture, dizziness, paresthesia, insomnia, anxiety, depression, dyspnea, increased cough, pharyngitis, bronchitis, pneumonia, rhinitis, rash, sweating, nocturia, hematuria, urinary tract infection, gynecomastia, breast pain, urinary frequency, urinary retention, urinary impaired, and urinary incontinence.

Administration, Supply and Storage

Administration

The recommended dose for Bicalutamide tablets therapy in combination with an LHRH analog is one 50 mg tablet once daily (morning or evening), with or without food. It is recommended that Bicalutamide tablets be taken at the same time each day. Treatment with Bicalutamide tablets should be started at the same time as treatment with an LHRH analog.

Supply

Bicalutamide Tablets, USP are available containing 50 mg of Bicalutamide, USP.

The 50 mg tablets are white film-coated, round, unscored tablets debossed with **M** on one side of the tablet and **C17** on the other side. They are available as follows:

NDC 0378-7017-93
bottles of 30 tablets

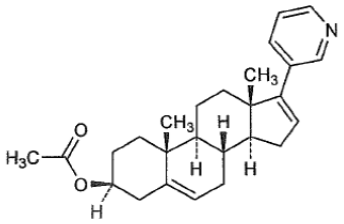
NDC 0378-7017-05
bottles of 500 tablets

Storage

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

10.3. Drug name: abiraterone

[Adapted from FDA prescribing information]



- **Chemical Name:** Abiraterone acetate; 154229-18-2; Zytiga; CB7630; CB-7630

- **Molecular Formula:** $C_{26}H_{33}NO_2$
- **Molecular Weight:** 391.555 g/mol

Description

Abiraterone acetate, the active ingredient of ZYTIGA is the acetyl ester of abiraterone. Abiraterone is an inhibitor of CYP17 (17α-hydroxylase/C17,20-lyase). Each ZYTIGA tablet contains 250 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3β)-17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate.

Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is C26H33NO2 and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19.

Inactive ingredients in the tablets are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate, and colloidal silicon dioxide.

Clinical Pharmacology

Abiraterone acetate (ZYTIGA) is converted in vivo to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals (see Warnings and Precautions [5.1]).

Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with GnRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor.

ZYTIGA decreased serum testosterone and other androgens in patients in the placebocontrolled phase 3 clinical trial. It is not necessary to monitor the effect of ZYTIGA on serum testosterone levels.

Changes in serum prostate specific antigen (PSA) levels may be observed but have not been shown to correlate with clinical benefit in individual patients.

Safety/Precautions

Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess. Use ZYTIGA with caution in patients with a history of cardiovascular disease. ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition [see Adverse Reactions (6) and

Clinical Pharmacology (12.1)]. Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions.

Adrenocortical Insufficiency. Adrenocortical insufficiency has been reported in clinical trials in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress.

Hepatotoxicity. Marked increases in liver enzymes leading to drug discontinuation or dosage modification have occurred. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter.

Food effect. ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of Reference ID: 2939553 4 ZYTIGA is taken. Abiraterone Cmax and AUC0-∞ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state.

Information for Patients

•Patients should be informed that ZYTIGA and prednisone are used together and that they should not interrupt or stop either of these medications without consulting their physician.

•Patients receiving GnRH agonists should be informed that they need to maintain this treatment during the course of treatment with ZYTIGA and prednisone.

•Patients should be informed that ZYTIGA must not be taken with food and that no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. They should be informed that the tablets should be swallowed whole with water. Patients should be informed that taking ZYTIGA with food causes increased exposure and this may result in adverse reactions.

•Patients should be informed that ZYTIGA is taken once daily and prednisone is taken twice daily according to their physician's instructions.

•Patients should be informed that in the event of a missed daily dose of ZYTIGA or prednisone, they should take their normal dose the following day. If more than one daily dose is skipped, patients should be told to inform their physician.

•Patients should be apprised of the common side effects associated with ZYTIGA, including peripheral edema, hypokalemia, hypertension and urinary tract infection.

• Patients should be advised that their liver function will be monitored using blood tests.

•Patients should be informed that ZYTIGA may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves. Patients should also be informed that it is not known whether abiraterone or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The patient should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with ZYTIGA.

Laboratory tests

Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA®.
Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress.

Permanently discontinue ZYTIGA® for patients who develop a concurrent elevation of ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA® treatment and closely monitor liver function.

Assess for hypertension, hypokalemia, and fluid retention: Baseline and at least once per month

Assess liver function tests (AST, ALT, bilirubin): baseline, every 2 weeks for first 3 months of treatment and monthly thereafter

Drug Interactions

Effects of Abiraterone on Drug Metabolizing Enzymes

ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid coadministration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug.

Drugs that Inhibit or Induce CYP3A4 Enzymes
Based on in vitro data, ZYTIGA is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, in vivo. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during ZYTIGA treatment.

Adverse Reactions

In a placebo-controlled, multicenter phase 3 clinical trial of patients with metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy, ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arm (N = 791). Placebo plus prednisone 5 mg twice daily was given to control patients (N = 394). The median duration of treatment with ZYTIGA was 8 months. The most common adverse drug reactions (≥5%) reported in clinical studies were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection. The most common adverse drug reactions that resulted in drug discontinuation were aspartate aminotransferase increased, alanine aminotransferase increased, urosepsis and cardiac failure (each in <1% of patient taking zytiga.

Adverse reactions and laboratory abnormalities related to mineralocorticoid effects were reported more commonly in patients treated with ZYTIGA than in patients treated with placebo: hypokalemia 28% versus 20%, hypertension 9% versus 7% and fluid retention (edema) 27% versus 18%, respectively. In patients treated with ZYTIGA, grades 3 to 4 hypokalemia occurred in 5% of patients and grades 3 to 4 hypertension was reported in 1% of patients.

Cardiovascular Adverse Reactions:
Cardiovascular adverse reactions in the phase 3 trial are shown in Table 1. The majority of arrhythmias were grade 1 or 2. Grade 3-4 arrhythmias occurred at similar rates in the two arms. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arm. No patients had sudden death or arrhythmia associated with death in the placebo arm. Cardiac ischemia or myocardial infarction led to death in 2 patients in the placebo arm and 1 death in the ZYTIGA arm. Cardiac failure resulting in death occurred in 1 patient on both arms.

Hepatotoxicity:
Drug-associated hepatotoxicity with elevated ALT, AST, and total bilirubin has been

reported in patients treated with ZYTIGA. Across all clinical trials, liver function test elevations (ALT or AST increases of > 5X ULN) were reported in 2.3% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. In the phase 3 trial, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5X ULN, or elevations in bilirubin > 3X ULN were observed, ZYTIGA was withheld or discontinued. In two instances marked increases in liver function tests occurred. These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40X ULN and bilirubin elevations 2 to 6 X ULN. Upon discontinuation of ZYTIGA, both patients had normalization of their liver function tests and one patient was re-treated with ZYTIGA without recurrence of the elevations.

Other Adverse Reactions:
Adrenal insufficiency occurred in two patients on the abiraterone arm of the phase 3 clinical trial (< 1%).

Administration, Supply and Storage

Administration

The recommended dose of ZYTIGA is 1,000 mg administered orally once daily in combination with prednisone 5 mg administered orally twice daily. ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. The tablets should be swallowed whole with water.

Supply

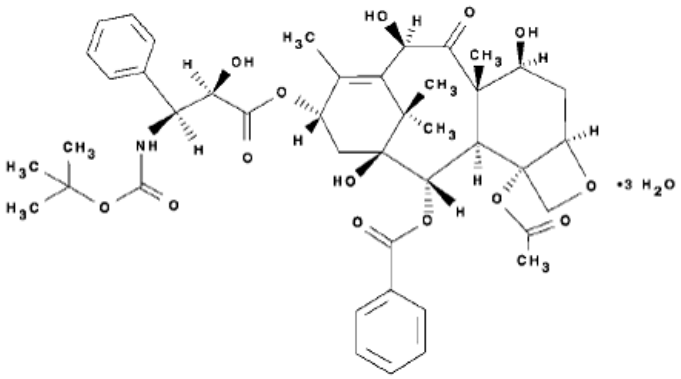
ZYTIGA (abiraterone acetate) 250 mg tablets are white to off-white, oval-shaped tablets debossed with AA250 on one side. ZYTIGA 250 mg tablets are available in high-density polyethylene bottles of 120 tablets. NDC Number 57894-150-12

Storage

ZYTIGA 250 mg tablets are available in high-density polyethylene bottles of 120 tablets. NDC Number 57894-150-12

10.4. Drug Name: <u>docetaxel</u>

[Adapted from FDA prescribing information]



- **Chemical Name:** (2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β-20epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate
- **Molecular Formula:** C43H53NO14• 3H2O
- **Molecular Weight:** 861.9

Description

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. Docetaxel is a white to almost-white powder with an empirical formula of C43H53NO14• 3H2O, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water.

Clinical Pharmacology

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

Safety/Precautions

Acute myeloid leukemia: In patients who received TAXOTERE, doxorubicin and cyclophosphamide, monitor for delayed myelodysplasia or myeloid leukemia

Cutaneous reactions: Reactions including erythema of the extremities with edema followed by desquamation may occur. Severe skin toxicity may require dose adjustment

Neurologic reactions: Reactions including. paresthesia, dysesthesia, and pain may occur. Severe neurosensory symptoms require dose adjustment or discontinuation if persistent.

Asthenia: Severe asthenia may occur and may require treatment discontinuation.

Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women of childbearing potential should be advised not to become pregnant when receiving TAXOTERE

Information for Patients

The patient should be informed that:

- TAXOTERE may cause fetal harm. Patients to avoid becoming pregnant while receiving this drug.
- It is important that they provide a detailed allergy and concomitant drug information history prior to TAXOTERE administration.
- It is important that they report if they were not compliant in taking the oral corticosteroids prior to taxotere
- Instruct patients to immediately report signs of a hypersensitivity reaction.
- Tell patients to watch for signs of fluid retention such as peripheral edema in the lower extremities, weight gain and dyspnea.
- Explain the significance of routine blood cell counts. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever.
- Instruct patients to report myalgia, cutaneous, or neurologic reactions.
- Explain to patients that side effects such as nausea, vomiting, diarrhea, constipation, fatigue, excessive tearing, infusion site reactions, and hair loss are associated with docetaxel administration.

Laboratory tests

Perform frequent peripheral blood cell counts on all patients receiving TAXOTERE. Patients should not be retreated with subsequent cycles of TAXOTERE until neutrophils recover to a level >1500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3. A 25% reduction in the dose of TAXOTERE is recommended during subsequent cycles following severe neutropenia (<500 cells/mm^3) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a TAXOTERE cycle.

Neutropenia (<2000 neutrophils/mm^3) occurs in virtually all patients given 60 mg/m^2 to 100 mg/m^2 of TAXOTERE and grade 4 neutropenia (<500 cells/mm^3) occurs in 85% of patients given 100 mg/m^2 and 75% of patients given 60 mg/m^2. Frequent monitoring of blood counts is, therefore, essential so that dose can be adjusted. TAXOTERE should not be administered to patients with neutrophils <1500 cells/mm^3.

Febrile neutropenia occurred in about 12% of patients given 100 mg/m^2 but was very uncommon in patients given 60 mg/m^2. Hematologic responses, febrile reactions and infections, and rates of septic death for different regimens are dose related

Drug Interactions

Docetaxel is a CYP3A4 substrate. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4.

In vivo studies showed that the exposure of docetaxel increased 2.2-fold when it was coadministered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors,

particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of TAXOTERE and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided. In patients receiving treatment with TAXOTERE, close monitoring for toxicity and a TAXOTERE dose reduction could be considered if systemic administration of a potent CYP3A4 inhibitor cannot be avoided

Adverse Reactions

The most serious adverse reactions from TAXOTERE are:

Toxic Deaths-

Breast Cancer

TAXOTERE administered at 100 mg/m^2 was associated with deaths considered possibly or probably related to treatment in 2.0% (19/965) of metastatic breast cancer patients, both previously treated and untreated, with normal baseline liver function and in 11.5% (7/61) of patients with various tumor types who had abnormal baseline liver function (AST and/or ALT >1.5 times ULN together with AP >2.5 times ULN). Among patients dosed at 60 mg/m^2, mortality related to treatment occurred in 0.6% (3/481) of patients with normal liver function, and in 3 of 7 patients with abnormal liver function. Approximately half of these deaths occurred during the first cycle. Sepsis accounted for the majority of the deaths.

Non-Small Cell Lung Cancer

TAXOTERE administered at a dose of 100 mg/m^2 in patients with locally advanced or metastatic non-small cell lung cancer who had a history of prior platinum-based chemotherapy was associated with increased treatment-related mortality (14% and 5% in two randomized, controlled studies). There were 2.8% treatment-related deaths among the 176 patients treated at the 75 mg/m^2 dose in the randomized trials. Among patients who experienced treatment-related mortality at the 75 mg/m^2 dose level, 3 of 5 patients had an ECOG PS of 2 at study entry.

Hepatotoxicity- Patients with combined abnormalities of transaminases and alkaline phosphatase should not be treated with TAXOTERE.

Neutropenia- Perform frequent peripheral blood cell counts on all patients receiving TAXOTERE. Patients should not be retreated with subsequent cycles of TAXOTERE until neutrophils recover to a level >1500 cells/mm^3 and platelets recover to a level > 100,000 cells/mm^3.

A 25% reduction in the dose of TAXOTERE is recommended during subsequent cycles following severe neutropenia (<500 cells/mm^3) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a TAXOTERE cycle.

Hypersensitivity- Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions

characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Severe hypersensitivity reactions require immediate discontinuation of the TAXOTERE infusion and aggressive therapy. Patients with a history of severe hypersensitivity reactions should not be rechallenged with TAXOTERE.

Fluid Retention - Severe fluid retention has been reported following TAXOTERE therapy. Patients should be premedicated with oral corticosteroids prior to each TAXOTERE administration to reduce the incidence and severity of fluid retention**.** Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.
When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.

Most common adverse reactions across all TAXOTERE indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, myalgia.

Administration, Supply and Storage

Administration

For hormone-refractory metastatic prostate cancer, the recommended dose of TAXOTERE is 75 mg/m^2 every 3 weeks as a 1hour intravenous infusion.
All patients should be premedicated with oral corticosteroids (see below for prostate cancer) such as dexamethasone 16 mg per day (e.g., 8 mg BID) for 3 days starting 1 day prior to TAXOTERE administration in order to reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions

Supply

TAXOTERE (docetaxel) Injection Concentrate is a sterile, non-pyrogenic, pale yellow to brownish-yellow solution at 20 mg/mL concentration.
Each mL contains 20 mg docetaxel (anhydrous) in 0.54 grams polysorbate 80 and 0.395 grams dehydrated alcohol solution.
TAXOTERE is available in single use vials containing 20 mg (1 mL) or 80 mg (4 mL) docetaxel (anhydrous).
TAXOTERE Injection Concentrate requires NO prior dilution with a diluent and is ready to add to the infusion solution.

Storage

TAXOTERE final dilution for infusion, if stored between 2°C and 25°C (36°F and 77°F) is stable for 4 hours. TAXOTERE final dilution for infusion (in either 0.9% Sodium Chloride solution or 5% Dextrose solution) should be used within 4 hours (including the 1 hour intravenous administration).

11. Study Treatments

11.1. Hormone Therapy

Each drug will be dosed at its respective FDA approved dose. The dosages are as follows: leuprolide (Lupron Depot-3 Month) 22.5mg by intramuscular (IM) injection on day 1 and then every three months thereafter.

Patients will receive androgen deprivation for a total of 1 year, and will be monitored clinically and with serum PSAs and testosterone until the 3-year endpoint.

Leuprolide may be replaced with any LHRH analog. No dose adjustments are allowed for the LHRH analog.

*In the event that the Investigator elects to administer complete androgen blockade, bicalutamide (Casodex) (50mg daily) and/or abiraterone acetate 1000 mg / day) may be added to the leuprolide. No replacements are allowed for bicalutamide or abiraterone. No dose adjustments are allowed for bicalutamide.
Pharmaceutical information is located in Section 10.1 (leuprolide) and Section 10.2 (bicalutamide).

11.2 Chemotherapy

Docetaxel (Taxotere) will be given at any of the following doses (75 mg/m^2, 65 mg/m^2, 55 mg/m^2 or 35 mg/m^2 IV) on day 1 every 3 weeks, up to 6 cycles at physician discretion.

Docetaxel will be given as neoadjuvant therapy for up to 6 months, along with androgen deprivation. Following up to 6 cycles of docetaxel therapy, patients with a PSA response of at least a 50% decrease from baseline, will proceed to maximum consolidative therapy.

Docetaxel may not be replaced with another drug. Docetaxel may be dose adjusted downward, at physician discretion, in response to, or to mitigate, toxicity. The dose may decreased in the following intervals: 65mg/M2, 55mg/M2, 35mg/M2.

Pharmaceutical information is located in Section 10.3 (docetaxel).

11.3 SBRT

SBRT treatment planning

A CT scan or MRI will be performed for tumor localization using rigid immobilization appropriate for stereotactic treatment. A separate PET-CT may be performed (all are optional) for diagnostic purposes and can be used for treatment planning with fusion -- this study would be done identically if the patient were having standard moderate dose radiation.

CT simulation will then be performed with fabrication of a radiation therapy immobilization device (such as the Alpha Cradle) which will be custom made for each patient. The treating radiation oncologist will identify the location of the tumor. Gross tumor volume (GTV) delineation will be performed with a diagnostic radiologist on sequential axial computed tomography images. A radiosurgical treatment plan will be developed based on tumor geometry and location. The dose will be prescribed to the minimal isodose line that completely covers the GTV plus a 5 mm margin. Adjacent normal structures including but not limited to the heart, esophagus, aorta, spinal cord, kidneys, rectum, bowel, liver, and stomach within 5 cm of the GTV will be identified for the purpose of limiting incidental radiation to these structures. [adapted from Johns Hopkins Oncology Clinical protocol J12137, NA_00069585]

In addition, prior to treatment delivery, a four-dimensional cone beam CT study will be performed on individual patients to assess respiration in these patients and to determine tumor targeting accuracy for those tumors that may be subject to respiratory motion such as those in the bones of the thorax. If tumor motion is greater than 5 mm, the planning target volume (PTV) will be expanded to account for respiration. [adapted from Johns Hopkins Oncology Clinical protocol J12137, NA_00069585]

SBRT procedure

Within three weeks of the initial treatment planning imaging study, SBRT will be administered using image-guidance. An Alpha Cradle (or equivalent immobilization device) will be used to minimize movement of the chest, spine, and abdomen during treatment. During treatment, real time cone beam CT images of the patient's body site of interest will be obtained. Cone beam CT scan will be obtained immediately prior to treatment and will be repeated until the treatment shift, required to align the CT planning scan and the cone beam CT scan performed on the day of treatment cone beam CT, is within tolerance for the body site. [adapted from Johns Hopkins Oncology Clinical protocol J12137, NA_00069585]

Within three weeks of the initial treatment planning imaging study, SBRT will be administered in a single dose to each treated lesion.
If scheduling or safety prevents all lesions from being irradiated within one day, participants may return within 30 days to complete SBRT to all metastatic sites. [adapted from Johns Hopkins Oncology Clinical protocol J12137, NA_00069585]

SBRT will be delivered in 1 to 5 fractions, and the dose and fractionation schedule will depend on the size and location of the lesion and the surrounding normal tissue constraints in accordance with AAPM Task Group 101 recommendations. Typical doses include 16 – 24 Gy in 1 fraction, 48 – 50 Gy in 4 fractions, and 50 – 60 Gy in 5 fractions. For example, isolated osseous lesions will be treated in a single fraction, lesions close to the lung and liver lesions will be treated in 3 to 5 fractions depending on their size (5 fractions for ≥ 3 cm or central tumors in close proximity to the mediastinum), and bone lesions will be treated in 5 fractions if small-bowel constrains fewer doses. [adapted from Johns Hopkins Oncology Clinical protocol J12137, NA_00069585]

The dose limits for surrounding critical structures are as follows:
Spinal Cord: maximal allowable dose should be = 1000 cGy in 1 fraction
Lung: 2/3 of the lung volume should be kept under 500 cGy.
Heart: 50 % of the heart volume should be kept under 1000 cGy.
Esophagus: 50 % of the esophagus volume should be kept under 1000 cGy and no single point dose in the esophagus should exceed 2000 cGy.
Brachial Plexus: maximal allowable point dose = 1000 cGy
Liver: One third of the uninvolved liver or approximately 700 cc <15 Gy.
Kidneys: 75% of volume of each kidney <5 Gy.
Small Bowel: <5% of bowel limited to <20 Gy.
[adapted from Johns Hopkins Oncology Clinical protocol J12137, NA_00069585]

SBRT potential toxicities

It is difficult at this time to predict with confidence the complication rate from the proposed SBRT; however, it is reasonable to extrapolate from the current experience with SBRT to the lung and pancreas. One significant toxicity is radiation pneumonitis, which can be manifested as fever, increased excertional dypsnea, pleuritic chest pain, and peritumoral infiltrate on chest imaging. It generally occurs between 1 to 3 months of completion of radiotherapy. The risk of grade 2-4 radiation pneumonitis is aproximately 10-15% in patients treated with standard fractionated large field radiotherapy and higher in patients treated with combined chemoradiotherapy. It is highly dependent on the volume of the lung treated to high dose and the mean lung dose. At this point, the incidence of RT pneumonitis from stereotactic radiosurgery for small pulmonary tumors is unknown. However, if the treated tumor volume is kept ≤ 65 cc, the risk should be < 10-15% with the proposed dose level. [adapted from Johns Hopkins Oncology Clinical protocol J12137, NA_00069585]

Other toxicities commonly associated with such treatment includes dysphagia, odynophagia, nausea, vomiting, anorexia, and weight loss. Some of these symptoms can also be due to tumor progression. Clinical and radiographic assessments will be performed as indicated to identify all adverse effects, ascertain their etiology, and provide the most appropriate palliative measures. Complications orther than radiation pneumonitis, if any, will be graded according to the Common Toxicity Criteria, National Cancer Institute, version 4.0. [adapted from Johns Hopkins Oncology Clinical protocol J12137, NA_00069585]

11.4. Adjuvant Radiation Therapy to Pelvic Bed

Adjuvant radiation therapy treatment planning

A CT scan or MRI will be performed for tumor localization using rigid immobilization appropriate for stereotactic treatment. A separate PET-CT may be performed (all are optional) for diagnostic purposes and can be used for treatment planning with fusion.

Adjuvant radiation therapy procedure
(As per standard of care)

12. Data Monitoring and Reporting Requirements

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring. Additionally, scheduled meetings will take place monthly and will include the protocol principal investigator, research nurse, data manager, and, when appropriate, the collaborators, sub-investigators, and biostatistician involved with the conduct of the protocol.

During these meetings the investigators will discuss matters related to: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for secondary objectives.

12.1. Principal Investigator

The Principal Investigator, Kenneth Pienta, MD, is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments
- Assuring that all participating institutions are using the correct version of the protocol
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study
- Reviewing and ensuring reporting of Serious Adverse Events (SAEs)
- Reviewing data from all sites

12.2. Adverse Event Monitoring and Reporting

An Adverse Event is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). The PI and/or the research nurse will monitor each patient closely for the development of adverse events and toxicities and record all such events. Patients will be evaluated for toxicity if they have received one dose of leuprolide or bicalutamide, on study, or one dose of docetaxel. The

timely reporting of adverse events (including toxic deaths) is required by the Food and Drug Administration (FDA).

12.3. Evaluating Adverse Events

The grade and severity of the event will be determined using the DCT/NCI Common Terminology Criteria, CTCAE v.4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. Study staff must use one of the CTCAE criteria to define the event. Adverse events not included in the CTCAE v.4.0 should be reported and graded under the "Other" adverse event within the appropriate category and grade 1 to 5 according to the general grade definitions, mild, moderate, severe, life-threatening, fatal or disabling, as provided in the CTCAE.

The event will be determined to be expected or unexpected.
The determination of whether an AE is expected is based on agent-specific adverse event information provided in Section 8: Pharmaceutical Information.
Unexpected AEs are those not listed in the agent-specific adverse event information provided in Section 8: Pharmaceutical Information.
The event will be evaluated for relationship to the medical treatment or procedure.
The investigator should document his/her opinion of the relationship of the event to study medication as follows:

- *Unrelated*- The adverse event is clearly not related to the investigational agent(s).
- *Unlikely*- The adverse event is doubtfully related to the investigational agent(s).
- *Possible*- The adverse event may be related to the investigational agent(s).
- *Probable*- The adverse event is most likely related to the investigational agent(s).
- *Definite*- The adverse event is clearly related to the investigational agent(s).

Based on this information, a decision will be made whether an adverse event should be reported as an expedited report (Serious Adverse Event, section 3.0) in addition to the routinely reported clinical data. All expedited adverse event reports should be submitted to the JHM Institutional Review Board (IRB) and to the FDA.

Documenting Adverse Events

Each individual sign or symptom must be documented separately. Worksheets must be signed and dated by person conducting evaluation to be used as source documentation. The attribution of all adverse events must be verified by an investigator. Evaluation of laboratory toxicities may be documented directly on a printed laboratory report or CRF

provided it is signed by the investigator. However, if an action was conducted due to this abnormality (e.g., RBC transfusion due to low Hgb) this would be recorded on the AE form also.

12.4. Serious Adverse Events

A SAE is any sign, symptom or medical condition that emerges during treatment or during a post-treatment follow-up period that (1) was not present at the start of treatment and is not a chronic condition that was part of the patient's medical history OR (2) was present at the start of treatment or as part of the patient's medical history but worsened in severity and/or frequency during therapy, AND that meets any of the following regulatory criteria:

- is fatal (i.e., results in death from any cause at any time) or life-threatening (i.e., the patient was, in the view of the investigator, at immediate risk of death from the reaction as it occurred)
- required or prolonged hospitalization (see exclusions below)
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly or a birth defect
- is medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious adverse event are hospitalizations for the:

- *Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition*
- *Treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen*

Any serious adverse event occurring in a patient from the first day of treatment and until 4 weeks after the last dose of treatment must be reported. The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated.
All serious adverse events must be followed to resolution (≤ 1 or baseline) or until considered stable or irreversible.

12.5. Expedited Reporting

JHM IRB reporting:
Serious adverse events and protocol problems will be reported in compliance with JHM IRB guideline, **"Organization Policy on Reports of Unanticipated Problems Involving Risks to Participants or Others" [Policy No. 103.6(b)]** (most current version). A copy of this document is located at http://www.hopkinsmedicine.org/institutional_review_board/guidelines_policies/

guidelines/unanticipatedflowchart.pdf All deaths on study regardless of attribution must be reported to the JHM IRB.

12.6. Data Entry

Data collected during this study will be entered into a secure database. Staff at SKCCC will be responsible for the initial study configuration and setup in the database and for any future changes.

12.7. Case Report Forms

Case report forms (e-crf) will be generated by Staff at SKCCC for the collection of all study data. Investigators will be responsible for ensuring that the CRFs are kept up-to-date.

12.8. Source documents

Study personnel will record clinical data in each patient's source documents (ie, the patient's medical record). Source documentation will be made available to support the patient research record.

12.9. Record Retention

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure, the investigator will maintain all source documents, study-related documents, and the CRFs. Because the length of time required for retaining records depends upon a number of regulatory and legal factors, documents should be stored until the investigator is notified that the documents may be destroyed. In this study, records are to be retained and securely stored for a minimum of 7 years after the completion of all study activities.

12.10. Protocol Amendments

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB before implementation.

12.11. Informed consent

Written informed consent will be obtained by a study investigator or study research nurse working on this study. An explanation of the nature of study, its purpose, procedures involved, expected duration, potential risks, and benefits will be provided to each participant by the investigator or the research nurse. Each participant will be informed that participation in the study is voluntary and that he

may withdraw from the study at any time, and that withdrawal of consent will not affect his subsequent medical treatment. Participants will be allowed time needed to make an informed decision. Participants will be encouraged to ask questions about the study and the consent before signing the consent form. Original signed consent forms will be filed in each patient's research chart, while each patient will receive a copy of the consent document. No patient will enter the study before his informed consent has been obtained.

13. Statistical Methods

This open label single arm phase II study of treatment for oligometastatic disease will evaluate consolidation with adjuvant radiotherapy (aRT) with systemic adjuvant chemo-hormonal therapy (C-ADT), followed by stereotactic body radiation to metastatic sites, 60 patients will be enrolled. If neutropenic toxicity is acceptable, RT will be offered to patients who achieve at least a 50% decrease in PSA following C-ADT. The primary endpoint is efficacy, defined as the 3-year PSA progression-free (PSA<0.2 ng/ml) survival rate. However, we will also evaluate safety, and the trial can be stopped early if toxicity exceeds acceptable limits, as described below.

13.1. Early Stopping Boundaries for Toxicity

We are concerned with 2 very different types of adverse event (AE): (1) Grade 3-4 neutropenia, and (2) Grade 3-4 acute toxicities from surgery or radiation. Because the management and sequelae of these AEs differ we have defined separate stopping boundaries for neutropenic AEs and for acute surgical -or radiation -induced AEs. The study design incorporates safety monitoring after each patient, starting with the third patient.

Neutropenic AEs. We will say that the treatment is feasible and safe if risk of G3/4 neutropenia <50%. Before the study starts, we assume that the average risk of G3/4 neutropenia is around 30-40%, so we take 35% as our prior probability (95% CI: 22-78%), corresponding to a Beta(3.5,6.5) prior distribution for the risk. Using Bayes rule, we apply the accumulating data after each patient to generate posterior probability as a Beta(3.5+a, 6.5+b) distribution, where a=number of neutropenic AE, b=number of non-SAEs ()(30). As we become more certain that the underlying risk exceeds 50%, we want to consider stopping the study. If the data suggest that there are at least 2:1 odds that the risk of neutropenic AEs exceeds 50%, the stopping boundary will be crossed, and we will consider that as enough certainty that the true rate exceeds 50% to stop the trial.

The following table indicates the number of events that will cross the stopping boundary for each sample size up to 54 patients:

Number of patients (inclusive)	Trial stops if neutropenic AEs reach this value

5	5
6-7	6
8-9	7
10-11	8
12	9
13-14	10
15-16	11
17-18	12
19-20	13
21-22	14
23-24	15
25-26	16
27-28	17
29-30	18
31-32	19
33-34	20
35-36	21
37-38	22
39	23
40-41	24
42-43	25
44-45	26
46-47	27
48-49	28
50-51	29
52-53	30
54	31

Non-neutropenic acute surgical –or radiation-induced AEs. We will say that the treatment is feasible and safe if risk of G3/4 acute non-neutropenic AEs<20%. Before the study starts, we assume that the average risk of such AEs is around 10% (95% CI: 2-38%), corresponding to a Beta(1,9) prior distribution for the risk. Again, we apply the accumulating data after each patient to generate posterior probability as a Beta(1+a, 9+b) distribution, where a=number of non-neutropenic AE, b=number of non-AEs. As we become more certain that the risk exceeds 20%, we want to consider stopping the study. If the data suggest that there are at least 2:1 odds that the underlying risk of non-neutropenic AEs exceeds 20%, the stopping boundary will be crossed, and we will consider that as enough certainty that the true rate exceeds 20% to stop the trial.

The following table indicates the number of events that will cross the stopping boundary for each sample sizeb up to 43 patients:

Number of patients (inclusive)	Trial stops if non-neutropenic AEs reach this value
3-5	3
6-10	4
11-14	5
15-19	6
20-23	7
24-28	8
29-33	9
34-38	10
39-42	11
43	12

The table below provides operating characteristics for both the neutropenic AE and non-neutropenic AE stopping rules based on 5000 simulations with the above sample sizes, assuming varying underlying toxicity risks. For neutropenic AE the the probability of early stopping exceeds 50% if the true risk is >50% and is relatively unlikely for true risk ≤45%, while for non-neutropenic AE the probability of early stopping exceeds 50% for true risk >20%, but is relatively unlikely for true risk ≤15%.

Neutropenic AE stopping rule			**Non-neutropenic AE stopping rule**		
Toxicity risk	Probability of early stopping (%)	Average sample size	Toxicity Risk	Probability of early stopping (%)	Average sample size
0.30	1.2	53.5	0.10	2.5	42.2
0.35	3.6	52.5	0.15	14.1	39.3
0.40	8.3	50.9	0.20	35.8	34.1
0.45	20.1	47.2	0.25	62.8	27.0
0.50	40.0	40.8	0.30	83.5	20.4
0.55	65.8	32.7	0.35	94.8	15.1
0.60	85.1	25.2	n/a	n/a	n/a

13.2. Data Analysis

Neutropenic and non-neutropenic toxicity rates will be calculated with 95% confidence intervals. If the trial enrolls the full sample size of 60 patients with acceptable neutropenic toxicity, we expect ≥ 90% of patients to achieve at least a 50% decrease in PSA following C-ADT and go on to RP±adjuvant RT, followed by SBRT. If the trial is not halted for non-neutropenic toxicity, the primary study endpoint of efficacy will be evaluated, defined as the 2 year PSA progression-free (PSA<0.2 ng/ml) survival rate among men who have non-castrate testosterone levels 2 years after enrollment. Since there is no direct comparator trial in this population, this will be compared to the historical rate from a randomized trial of men with biochemically-recurrent (non-metastatic) prostate cancer after prostatectomy and (for most men) after salvage radiotherapy, with PSADT <9 months. In that trial, at month 18, men with non-castrate testosterone blood levels who received abiraterone and degarelix had an undetectable PSA rate of 16% [18]. Based on these data we will set the null hypothesis at 15% PSA progression-free survival at 2 years in men with non-castrate testosterone.

Power for the efficacy endpoint is based on a 1-sample logrank test for comparing an observed survival to a historical control rate [19]. The table below shows PSA progression-free survival, $\mathbf{P_1}$, ranging from 30-50% compared to a historical rate of 15% ($\mathbf{P_0}$). We assume that 60 men will be enrolled in the trial, at least 54 will achieve PSA decrease ≥50% and go on to RP and consolidative therapy, and that 80% (n=43) will have non-castrate testosterone at 2 years. For all comparisons α=0.05 and a 2-sided test is used. Power is calculated using PASS v15 (NCSS Software, Kaysville, UT).

The table shows that with N=43, PSA progression-free survival of ≥0.32 can be detected with power ≥82%. These estimates may be conservative since the historical control progression-free rate is based on men without detectable metastases, whereas the current trial includes only men with oligometastatic disease, who may have lower progression-free survival under standard of care, i.e. ADT alone.

Power (%)	N	P_0	P_1
74	43	.15	.30
82	43	.15	.32
91	43	.15	.35
97	43	.15	.40
>99	43	.15	.50

To conduct the safety analysis, the rates of AEs will be calculated with 95% confidence intervals. Secondary time-to-event endpoints will be estimated with Kaplan-Meier methods, mean and median quality of life scores will be calculated with 95% confidence intervals, and chi-square test will be used for comparison of first metastatic sitesx, We will also compare secondary endpoints such as 2 year PSA failure-free survival to expected rates of 10-20% (based on data reported by CHAARTED (ASCO 2014) of 23% at 1 year for combined chemo-hormonal therapy) using a one-sample chi-square test. Although power is likely to be suboptimal we will also perform exploratory analyses to compare the above endpoints among subgroups such as by age, number of initial metastatic sites, and between radiation and surgery.

13.3. Multicenter Guidelines

The Protocol Chair

The Protocol Chair, Samuel Denmeade, MD, is responsible for performing the following Tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments
- Assuring that all participating institutions are using the current IRB approved version of the protocol
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study
- Reviewing and ensuring reporting of Serious Adverse Events (SAEs) from all sites
- Reviewing all study data from all sites

Coordinating Center Responsibilities (SKCCC)

Coordinating Centers must:

- Verify that each participating institution has a Federal Wide Assurance (FWA) number.
- Confirm that IRB approval has been obtained at each participating site prior to their first patient registration
- Maintain copies of IRB approvals from each site
- Implement central patient registration
- Prepare all submitted data for review by the Protocol Chair (Samuel Denmeade, MD)
- Establish procedures for documentation, reporting, and submitting of adverse events to the Protocol Chair (Samuel Denmeade, MD) and all applicable parties
- Facilitate audits by securing selected source documents and research records from participating sites for audit, or by conducting audits at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Follow the protocol as written and conduct the study within the guidelines of Good Clinical Practice.
- Collect and submit data, and report adverse events according to the schedule specified by the protocol.
- Register all patients with the Lead Center (SKCCC) by submitting patient registration forms, and signed informed consents promptly.
- Provide sufficient experienced clinical and administrative staff; as well as adequate

facilities and equipment to conduct a collaborative trial according to the protocol.

- Maintain regulatory binders on site, and provide copies of all required documents to the Lead Center (SKCCC)

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Appendix A:

APPENDIX A. Classification of Surgical Complications

Grades	Definition
Grade I:	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.
	Acceptable therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II:	Requiring pharmacological treatment with drugs other than such allowed for grade I complications.
	Blood transfusions and total parenteral nutrition are also included.
Grade III:	Requiring surgical, endoscopic or radiological intervention
Grade III-a:	intervention not under general anesthesia
Grade III-b:	intervention under general anesthesia
Grade IV:	Life-threatening complication (including CNS complications)‡ requiring IC/ICU-management
Grade IV-a:	single organ dysfunction (including dialysis)
Grade IV-b:	multi organ dysfunction
Grade V:	Death of a patient
Suffix 'd':	If the patient suffers from a complication at the time of discharge (see examples in Appendix B, http://Links.Lww-.com/SLA/A3), the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

‡ brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks (TIA); IC: Intermediate care; ICU: Intensive care unit
www.surgicalcomplication.info