



# Phase I/II study of pre-operative intensity-modulated radiation therapy (IMRT) and docetaxel for high-risk prostate cancer: a platform for radiosensitizer development

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## Abstract

**Background:** Treatment results from both adjuvant and salvage radiation trials show that local recurrence after prostatectomy for high-risk cancer is common. Pre-operative chemoradiation has the potential to reduce local recurrences and improve survival, but has not been studied in prostate cancer. The establishment of a pre-prostatectomy model that includes radiation would facilitate and promote the discovery of novel radiosensitizers.

**Methods:** The primary objectives of this trial are to define the maximal tolerated dose (MTD) of the combination of IMRT and docetaxel and to determine the pathologic response rate at the Phase II dose. Secondary objectives include PSA responses, relapse-free survival, surgical margin status, HRQOL and tissue and serum biomarker effects. Eligible patients have: 1) cT2b or resectable cT3a tumors, 2) a serum PSA  $\geq 15$  ng/ml, or 3) a primary Gleason grade  $\geq 4$ . All patients undergo pre-treatment placement of prostatic fiducial seed markers along with cryopreservation of study-designated tumor tissue. Patients receive 45 Gy IMRT over 25 fractions to the prostate and seminal vesicles. Prostatectomy is performed within 4 to 6 weeks after completion of chemoradiation during which time additional tumor tissues are cryopreserved for biomarker analyses. Escalating doses of weekly docetaxel are given for 5 consecutive weeks during IMRT. A minimum of 3 patients are accrued at each dose levels of 0 mg/m<sup>2</sup>, 10 mg/m<sup>2</sup>, 20 mg/m<sup>2</sup> and 30 mg/m<sup>2</sup>. The dose escalation continues to a planned dose of 30 mg/m<sup>2</sup> or until one or more patients per cohort experienced a dose-limiting toxicity (DLT), defined as greater than grade 3 non-hematological (excluding hyperglycemia) or grade 4 hematological toxicity. After definition of the MTD, a minimum of 15 additional patients are accrued at the Phase II dose. Minimum accrual target is 27 patients assuming no DLTs.

## Primary Study Objectives

1. To define the maximal tolerated dose (MTD) of the combination radiation (45 Gy) and docetaxel (with a pre-planned ceiling of docetaxel 30 mg/m<sup>2</sup>)
2. To determine the pathologic response rate (complete response defined as absence of detectable cancer in prostatectomy specimen) at the phase II dose.

## Secondary Study Objectives

PSA response, relapse-free survival, surgical margin status, HRQOL and biomarker changes

## Background:

1. PSA failure rates exceed 50% at 5 years after radiation or surgery.<sup>1</sup>
2. 15 yr-PCSM is 34% with surgery alone for high-risk disease.<sup>2</sup>
3. Data from adjuvant therapy trials now show that local disease is a major source of cancer recurrence after surgery.<sup>3-4</sup>

1. D'Amico et al., JAMA 1998, 2. Stephenson et al. JCO, 2009, 3. Swanson et al. JCO, 2007, 4. Bolla et al. NEJM 2009

## Unmet Needs:

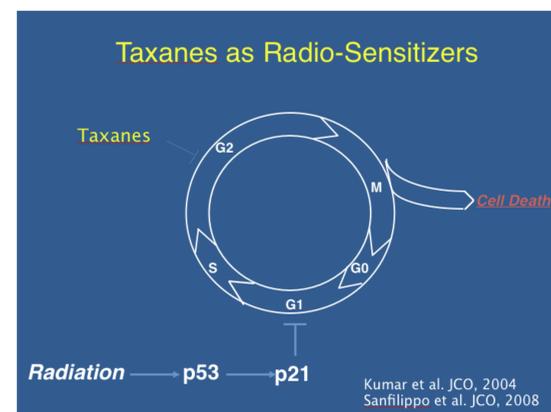
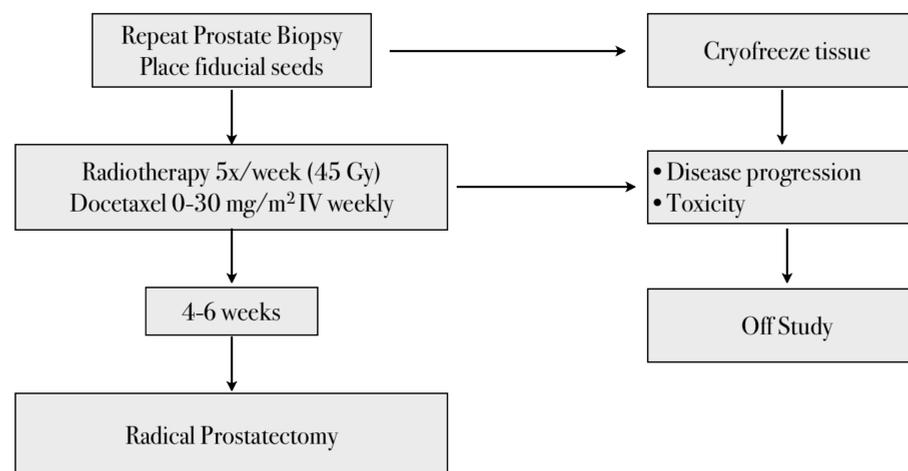
1. Strategies to improve local control after surgery
2. Lack of a platform to test novel radiosensitizers

## Materials and Methods

### Inclusion Criteria

1. Histologically confirmed adenocarcinoma of the prostate
2. Prostatectomy planned as primary therapy
3. 10 year or longer life expectancy
4. ECOG Performance status < 2
5. Any of the following high risk features:
  - Clinical stage T2b (palpable bilateral involvement) or T3 OR
  - PSA > 15 ng/ml OR
  - Gleason grade > 4+3 (4+3, 4+4)
6. No evidence of bone metastases on bone scan
7. No evidence of lymph nodes 2 cm in diameter on pelvic CT scan (scan only required in patients with a PSA > 40 ng/ml)

### Treatment Schema: Pre-operative Chemoradiation



## Schedule of Events

	Pre-Treatment	Weekly	Pre-Op	Post-Op
Screening and informed consent	X			
Physical Exam	X			
Bone Scan	X			
Pelvis CT scan (if PSA $\geq 40$ ng/ml)	X			
Prostate biopsy specimens (10)	X			
Testosterone	X		X	
PSA	X	X	X	X
CBC/differential	X	X	X	
Chemistry Panel	X	X	X	
HRQOL/AUA Questionnaires	X	X		X
Research only serum	X	X		X
Flash frozen prostatectomy specimens				X

## Summary of Planned Dose Levels

Dose Cohort	Docetaxel dose	Radiation dose
1	0 mg/ m <sup>2</sup>	45 Gy
2	10 mg/ m <sup>2</sup>	45 Gy
3	20 mg/ m <sup>2</sup>	45 Gy
4	30 mg/ m <sup>2</sup>	45 Gy

## Trial Significance:

1. This study aims to determine the safety and effectiveness of pre-operative chemo-radiation for high risk prostate cancer.
2. This study design may serve as a platform for the screening and identification of novel radio-sensitizers.

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