EORTC radiation Oncology Group

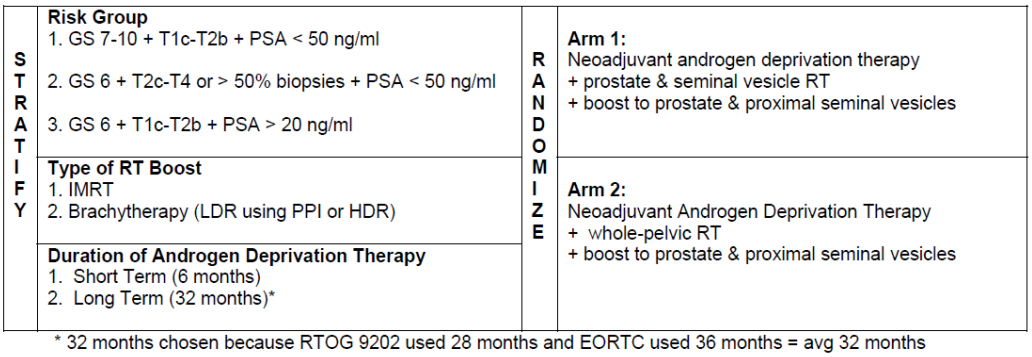
Intergroup collaboration with RTOG

EORTC 1331-ROG; RTOG 0924

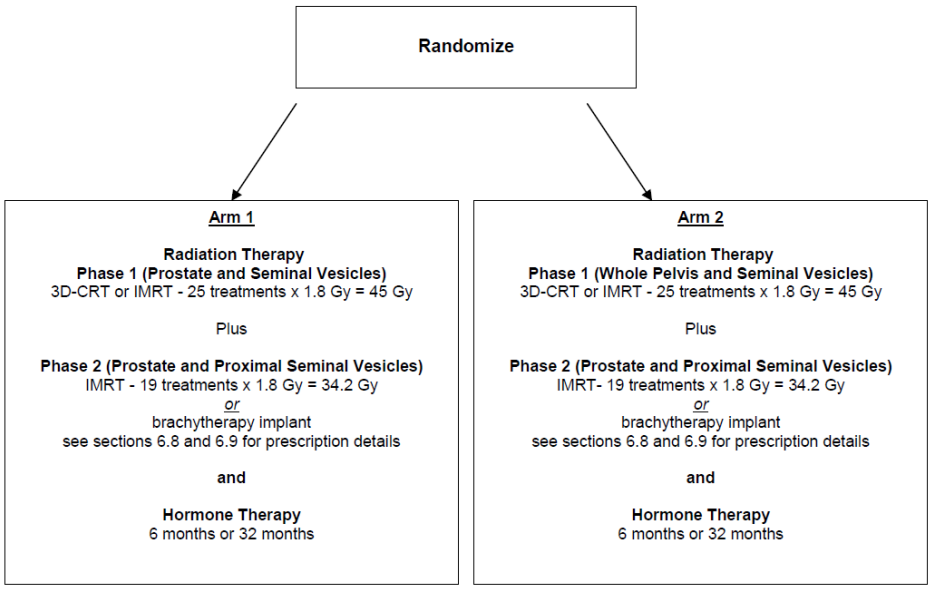
Title of the Study	**Androgen deprivation therapy and high dose radiotherapy with or without whole-pelvic radiotherapy in unfavorable intermediate or favorable high-risk prostate cancer: a phase III randomized trial.**
Medical Condition	Patients who are most likely to benefit from androgen deprivation therapy and whole-pelvic radiotherapy, defined as: a) Having a significant risk of lymph node involvement (e.g. >15%, based on the Roach formula); b) Being in one of the following risk groups: • GS 7-10 + T1c-T2b (palpation) + PSA < 50 ng/ml (includes intermediate and high risk patients); • GS 6 + T2c-T4 (palpation) or > 50% biopsies + PSA < 50 ng/ml; • GS 6 + T1c-T2b (palpation) + PSA > 20 ng/ml.
Methodology	This is a randomized comparative open-label phase III trial testing for superiority of prophylactic neoadjuvant androgen deprivation therapy (NADT) and wholepelvic radiation therapy (WPRT) over prophylactic neoadjuvant androgen deprivation therapy (NADT) and radiation therapy to the prostate and seminal vesicles.
Primary objective(s)	To demonstrate that prophylactic neoadjuvant androgen deprivation therapy (NADT) and wholepelvic radiation therapy (WPRT) improves overall survival (OS) in patients with "unfavorable" intermediate risk or "favorable" high risk prostate cancer compared to NADT and high dose prostate and seminal vesicle (SV) radiation therapy (P + SV RT) using intensity modulated radiotherapy (IMRT) or EBRT with a high dose rate (HDR) or a permanent prostate (radioactive seed) implant (PPI) boost
Secondary Objectives	To assess if prophylactic WPRT improves • biochemical control ("Phoenix definition"). **Patients not meeting these PSA criteria (Phoenix Definition) for failure who undergo salvage therapies (such as ADT, radical prostatectomy or brachytherapy, or Cryosurgery) should also be declared as failures at the time a positive biopsy is obtained or salvage therapy is administered, whichever comes first.** • distant metastasis (DM) free-survival, defined as imaging documented evidence of distant spread of disease; • cause specific survival (CSS) To compare acute and late treatment adverse events between patients receiving

	NADT + WPRT versus NADT + P & SV RT; Based on assessments of health related quality of life (HRQOL) as measured by the Expanded Prostate Cancer Index Composite (EPIC) and of fatigue assessed by PROMIS Fatigue Short Form in US patients, to determine if • HRQOL significantly worsens with increasing aggressiveness of treatment (Not applicable for EORTC centers) • whether more aggressive treatment (Arm 2, NADT + WPRT) is associated with a greater increase in fatigue (PROMIS Fatigue Short Form) from baseline to last week of treatment and to a greater increase in circulating inflammatory markers (IL-1, IL-1ra, IL-6, TNFalpha, and C-reactive Protein); • To determine whether changes in fatigue from baseline to the next three time points (week prior to radiation therapy, last week of treatment, and 3 months after treatment) are associated with changes in circulating cytokines, mood, sleep, and daily activities across the same time points.
Principal Inclusion criteria	**1** Pathologically (histologically or cytologically) proven diagnosis of prostatic adenocarcinoma at moderate to high risk for recurrence as determined by one of the following combinations: • Gleason score 7-10 + T1c-T2b (palpation) + PSA < 50 ng/ml (includes intermediate and high risk patients); • Gleason score 6 + T2c-T4 (palpation) or > 50% (positive) biopsies + PSA < 50 ng/ml; • Gleason score 6 + T1c-T2b (palpation) + PSA > 20 ng/ml. **2 2 Clinically** negative lymph nodes as established by imaging (pelvic ± abdominal CT or MR), but NOT by nodal sampling, or dissection. Patients post a negative lymph node dissection are not eligible. However patients with lymph nodes equivocal or questionable by imaging are eligible if the nodes are ≤ 1.5 cm. **3** No evidence of bone metastases (M0) on bone scan. Equivocal bone scan findings are allowed if plain films (or CT or MRI) are negative for metastasis. Baseline serum PSA value performed with a standardized assay (e.g., Abbott, Hybritech) within 12 weeks (90 days) prior to registration. **4** Zubrod/ECOG Performance Status 0-1(unless otherwise specified); **5** Age ≥ 18; **6** CBC/differential obtained within 2 weeks (14 days) prior to registration on study, with adequate bone marrow function defined as follows: **6.1** Absolute neutrophil count (ANC) ≥ 1,500 cells/mm3; **6.2** Platelets ≥ 100,000 cells/mm3; **6.3** Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.); **7 Patient must be able to provide study specific informed consent prior to study entry.**
Principal exclusion criteria	**1** Prior invasive (except non-melanoma skin cancer) malignancy unless disease-free for a minimum of 3 years (1095 days) not in the pelvis **2** Previous radical surgery (prostatectomy) or cryosurgery for prostate cancer

	3 Previous pelvic irradiation, prostate brachytherapy, or bilateral orchiectomy **4** Previous hormonal therapy, such as LHRH agonists (e.g., leuprolide, goserelin, buserelin, triptorelin) or LHRH antagonist (e.g. degarelix), anti-androgens (e.g., flutamide, bicalutamide, cyproterone acetate), estrogens (e.g., DES), or surgical castration (orchiectomy). Prior pharmacologic androgen ablation for prostate cancer is allowed only if the onset of androgen ablation is ≤ 45 days prior to the date of registration. **5** Use of finasteride within 30 days prior to registration **6** Use of dutasteride or dutasteride/tamsulosin (Jalyn) within 90 days prior to registration **7** Previous or concurrent cytotoxic chemotherapy for prostate cancer; note that prior chemotherapy for a different cancer is allowable. **8** Prior radiotherapy, including brachytherapy, to the region of the study cancer that would result in overlap of radiation therapy fields **9** Severe, active co-morbidity, defined as follows: **9.1** Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months **9.2** Transmural myocardial infarction within the last 6 months **9.3** Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration **9.4** Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration **9.5** Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects or severe liver dysfunction **9.6** Acquired immune deficiency syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. **10** Patients who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic. **11** Prior allergic reaction to the hormones involved in this protocol
Primary endpoint	Overall survival (OS): death due to any cause

Secondary endpoints	**1** Prostate cancer-specific survival (CSS) **2** Distant metastasis (DM); **3** Biochemical failure by the Phoenix definition (PSA ≥ 2 ng/ml over the nadir PSA) [Roach 2006]; **4** Incidence of "acute" adverse events (based on the current version of CTCAE) **5** Time to "late" grade 3+ adverse events (based on the current version of CTCAE): The time of a first late grade 3+ adverse event, defined as > 30 days from the completion of RT; For the side studies conducted in the US: **6** Comparison of prostate cancer-specific health related quality of life (HRQOL) change as measured by the EPIC-26 (bowel or urinary domain) (Not applicable for EORTC centers) **7** Comparison of fatigue status as measured by the Patient-Reported Outcome Measurement Information System (PROMIS) fatigue domain change score (from baseline to the last week of treatment); **8** Assessment and comparison of Quality Adjusted Life Years (QALYs) (Not applicable for EORTC centers)
Study scheme	**SCHEMA**  * 32 months chosen because RTOG 9202 used 28 months and EORTC used 36 months = avg 32 months

Therapeutic Scheme



Treatments :

Drug

All eligible patients receive NADT (neoadjuvant androgen deprivation therapy) consisting of an anti-androgen combined with an LHRH (luteinizing hormone releasing hormone) agent. Use of both drugs is considered combined androgen blockade (CAB). **Protocol treatment must begin within 6 weeks after randomization.**

Radiotherapy

Radiotherapy should begin at least 8 weeks (+/- 1 week) after starting LHRH agonist/antagonist injection.
This protocol allows for treatment with EBRT exclusively or EBRT + brachytherapy (at the discretion of the treating physician) this must be specified at the time of study enrollment.

Arm 1 (Sequential Boost Technique – Phases 1 and 2):
Phase 1: Treat prostate and seminal vesicles:

Acceptable Treatment Modalities: 3D-CRT or IMRT

Prescribed Dose :

- 45 Gy to cover 98% of PTV
- Minimum dose within PTV – 95% of prescribed dose and for a volume that is 0.03 cc
- Maximum dose within the PTV – 107% of prescribed dose and for a volume that is 0.03 cc

Phase 2*:* Reduce volume to boost prostate and proximal seminal vesicles

Acceptable Treatment Modalities: IMRT or permanent prostate implant (PPI) brachytherapy or HDR brachytherapy

Prescribed Dose:

- 34.2 Gy for IMRT to cover 98% of the PTV

- Minimum dose within PTV – 95% of prescribed dose and for a volume that is 0.03 cc
- Maximum dose within the PTV – 107% of prescribed dose and for a volume that is 0.03 cc
    - 110 Gy for low dose rate PPI with I–125
    - 100 Gy for low dose rate PPI with Pd-103
    - 15 Gy in one fraction for HDR

Arm 2 (Sequential Boost Technique)
Phase 1: Whole pelvis including prostate and seminal vesicles
Acceptable Treatment Modalities: 3D-CRT or IMRT
Prescription Dose:

- 45 Gy to cover 98% of PTV
- Minimum dose within PTV – 95% of prescribed dose and for a volume that is 0.03 cc
- Maximum dose within the PTV – 107% of prescribed dose and for a volume that is 0.03 cc

Phase 2: Reduce volume to boost prostate and proximal seminal vesicles
Acceptable Treatment Modalities; IMRT or permanent prostate implant (PPI) brachytherapy or HDR brachytherapy
Prescription Dose:

- 34.2 Gy for IMRT
- 110 Gy for low dose rate PPI with Pd-103
- 100 Gy for low dose rate PPI with I–125
- 15 Gy in one fraction for HDR

Technical factors:

- Either 3DCRT or IMRT may be used for phase 1 of either Arm 1 or 2. For 3DCRT treating the whole pelvis (WPRT), a minimum of 4-fields should be used and a 4 field plan is recommended. More than 4 conformal fields can be used for the Arm 1 prostate plus seminal vesicle treatments. For IMRT, no specific field arrangement is required. **For the prostate conedown boost in phase 2, IMRT must be used for patients designated for EBRT boost.**

- RT will be delivered with megavoltage equipment at energies ≥ 6 MV. Typically, except for tomotherapy and VMAT techniques, 5 to 9 gantry angles are employed for the boost EBRT treatment.

- Patients who receive brachytherapy as a boost component of their RT will

	undergo EBRT for Phase 1 implementing either 3DCRT or IMRT as described. The prostate and seminal vesicles will be treated to a dose of 45 Gy in 1.8 Gy fractions prescribed to a PTV dose as above. • Radiotherapy QA will be implemented as per EORTC ROG procedures
Duration of treatment	6 month or 32 months, depending on chosen duration of LHRH therapy
Statistical considerations	**Sample size: 2,580 patients** It is expected that the 10-year OS with the standard arm will be 53%. It is hypothesized for there to be a 6.5% increase in absolute OS in the NADT+WPRT arm (Arm 2), i.e., 10-year OS of 59.5%. This corresponds to **HR of 0.817**. With four interim analyses (for both superiority and futility) and one final analysis, 1,044 deaths are required to detect this magnitude of effect with overall 90% power employing a one-sided log-rank test at the 0.025 level of significance. With 2,400 patients accrued over 8 years, definitive analysis would occur at approximately 14.5 years from commencement of accrual. Guarding against an ineligibility or lack-of-data rate of up to 7.5% among patients enrolled, the final targeted accrual for this study will be **2,580 patients**.
Translational research	Not applicable for EORTC centers
Expected duration of the trial	Period of accrual: 8 years
	Period of treatment: 8 years + 32 months (treatment of last entered patient, if that patient opts for long LHRH therapy)
	Expected length of time until analysis of the primary Endpoint: years after the 1st inclusion: 14.5 years
	Estimated overall duration of the trial (including period of observation): 14.5 years