

**TRANS-TASMAN RADIATION ONCOLOGY GROUP
INCORPORATED**

**A RANDOMISED TRIAL INVESTIGATING THE EFFECT ON BIOCHEMICAL (PSA) CONTROL
AND SURVIVAL OF DIFFERENT DURATIONS OF ADJUVANT ANDROGEN
DEPRIVATION IN ASSOCIATION WITH DEFINITIVE RADIATION TREATMENT
FOR LOCALISED CARCINOMA OF THE PROSTATE**

**Version 1 – 17 April 2003
Version 2 – 13 October 2003
Version 3 – 20 November 2003
Version 4 – 16 July 2004
Version 5 – 14 October 2004**



Trial Management Committee:

Trial Executive:	Dr David Lamb (Wellington Hospital, New Zealand) Co-Chair Clinical Professor David Joseph (SCGH, Perth, WA) Co-Chair Professor Jim Denham (Newcastle Mater Misericordiae Hospital, NSW) Trial Coordinator Professor Gillian Duchesne (Peter Mac, Melbourne, VIC)
Other Members:	Associate Professor Chris Atkinson (Christchurch Hospital, NZ) Dr Lizbeth Kenny (QRI Royal Brisbane Hospital, QLD) Dr Kumar Gogna (QRI Mater Hospital, QLD) Dr Andrew Kneebone (Liverpool Hospital, NSW) Dr John Matthews (Auckland Hospital, NZ) Dr Nigel Spry (SCGH, Perth, WA) Dr Keen-Hun Tai (Peter Mac, Melbourne, VIC) Dr Sandra Turner (Westmead Hospital, NSW) Dr Terry Diamond (St George Hospital, NSW)
Project Manager:	Ms Marise Cheney (Newcastle Mater Misericordiae Hospital, NSW)
Safety & Data Monitoring Officer:	Ms Sally McIlvenie (Newcastle Mater Misericordiae Hospital, NSW)
Trial Statistician:	To be advised
Trial Pathologist:	Professor Brett Delahunt (Wellington Hospital, NZ)
Trial Physicist:	Ms Annette Haworth (SCGH, Perth)

Foreword

This document is intended to describe a Trans-Tasman Radiation Oncology Group (TROG) study and to provide information about procedures for entering patients. It is not intended that the protocol be used as a guide for the treatment of other patients. TROG will not accept any data for analysis unless the local ethics committee has approved this study for patient entry.

Amendments to the document may be necessary; these will be circulated to known participants in the study, but centres entering patients for the first time are advised to contact the TROG Central Operations Office, Newcastle, to confirm the details of the protocol in their possession.

GLOSSARY OF TERMS

3DCRT	Three dimensional conformal radiotherapy
AD	Androgen deprivation
AE	Adverse event
ASTRO	American Society for Therapeutic Radiation Oncology
BMD	Bone mineral density
BM-FS	Bony metastases
BP	Bisphosphonate therapy
CEBT (EBT)	Conventional external beam therapy
CR	Complete response
CRFs	Case report forms
CRT	Conformal radiotherapy
DEXA	Dual energy x-ray absorption
DRE	Digital rectal examination
EBRT	External beam radiation treatment
EORTC	European Organisation for Research and Treatment of Cancer
FA	False assessment
HDR	High dose rate
HDRB	High dose rate brachytherapy
ICRU	International Congress of Radiological Units
IMRT	Intensity modulated radiotherapy
ITAD	Intermediate term androgen deprivation
LF-FS	Reduce local failure
LH-RHa	Luteinising hormone – Releasing hormone analogue
LTAD	Long term androgen deprivation
MAB	Maximal androgen blockade
MAD	Maximal androgen deprivation
Month	One calendar month
OPF	Osteopenic fractures
OS	Overall Survival
PD	Progressive disease
PSA	Prostate Specific Antigen
PSA-Rel	PSA relapse
PSA-RFS	PSA Relapse free survival
QOL	Quality of life
RADAR	Randomised androgen deprivation and radiotherapy
RCT	Randomised control trial
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event
SDIC	Safety and Data Integrity Committee
STAD	Short term androgen deprivation
TACT	Technical Advisory Committee of the Trial
TMC	Trial management committee
Trial Centre	Treatment Centre/Hospital where local data management resources are located
TROG	Trans-Tasman Radiation Oncology Group

1. OVERVIEW

Objectives of the trial

The principal objective of the trial is to test the hypothesis that 12 months adjuvant androgen deprivation using Leuprorelin acetate starting immediately after standard therapy (ie 6 months of Leuprorelin acetate before and during radiotherapy) will improve biochemical (PSA) relapse free survival (PSA-RFS) when compared with standard therapy alone.

There are three secondary objectives:

- (a) to test the hypotheses that 12 months adjuvant androgen deprivation (specified above) will improve overall survival (OS), reduce local failure (LF-FS) and improve quality of life (QOL);
- (b) to test the hypotheses that 18 months of bisphosphonate therapy using zoledronic acid will reduce osteopenic fractures (OPF), improve bone mineral density (BMD), delay the onset of bony metastases (BM-FS) and improve QOL when compared to patients in this trial who are not treated with bisphosphonate therapy;
- (c) to determine the nature of interactions between the total duration of androgen deprivation and:
 - i the addition of bisphosphonate therapy with respect to BM-FS and PSA-RFS;
 - ii increasing radiation dose, within the structured radiation dose escalation program built into the design of the trial, with respect to LF-FS and PSA-RFS;
 - iii increasing Gleason score with respect to overall survival.

A tertiary objective of the trial is to determine whether intercurrent medical conditions, affecting the microvasculature, will impact independently on delayed radiotherapy morbidity ('late radiation toxicity').

Study Schema

Eligibility

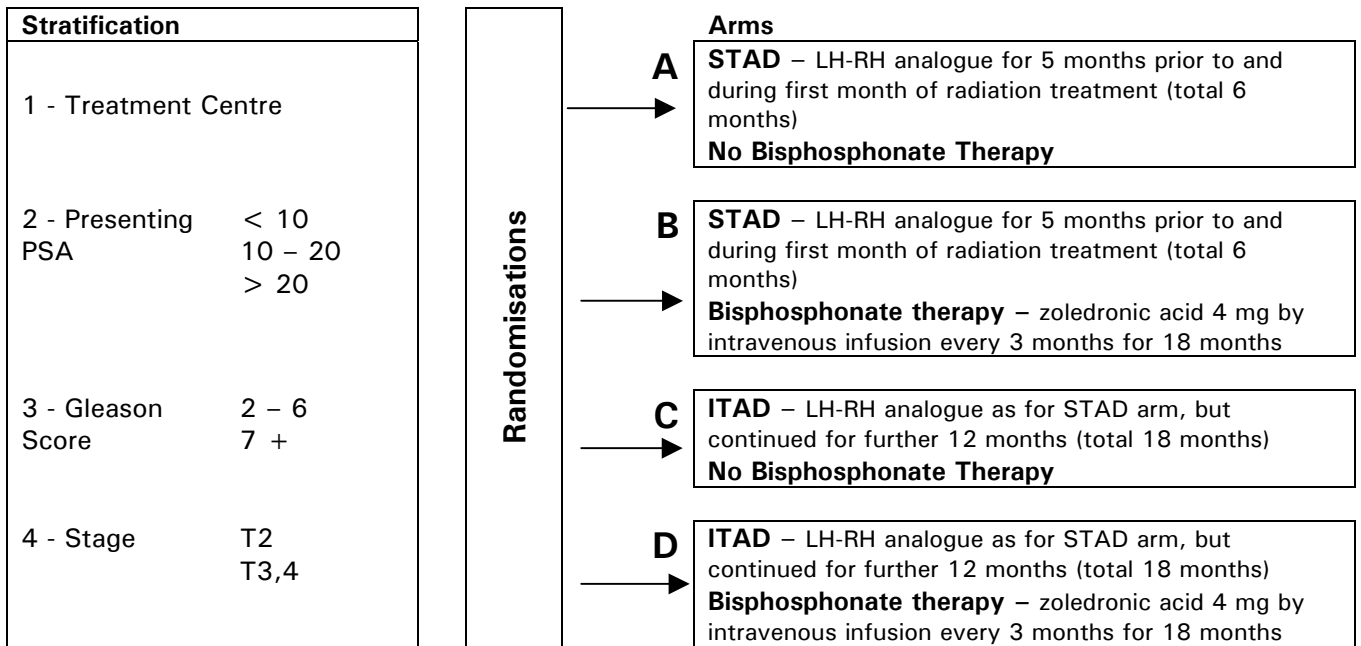
Patients with stage T2a (providing Gleason score 7 or more, **and** PSA 10 or more) and stage T2b-4 adenocarcinoma prostate without evidence of lymph node or distant metastases.

Ineligibility

Patients who have had radical prostatectomy, any prior hormone or bisphosphonate treatment, or pelvic radiotherapy. Evidence of lymph node and/or distant metastases; other major cancer; other medical conditions seriously limiting life expectancy; poor performance status, and osteoporosis resulting in >30% loss in vertebrae height in one or more thoraco-lumbar vertebrae.

Randomisation

Eligible patients will be randomised by the minimisation procedure at the Newcastle Central Trials Office (Tel: +61 2 4921 1462; Fax: +61 2 4921 1153; after the treatment centre has nominated the patient's radiotherapy technique and dose (see below).



Radiation Treatment

Treatment will be delivered using a conventional technique, unless the treatment centre of the participating clinician demonstrates an ability to deliver the treatment using a CRT, IMRT, or HDRB technique verified by the trial TACT.

- (a) **Conventional EBT**– 66 Gy in 33 daily fractions over 6.5 – 7 weeks prescribed to a volume that encompasses the prostate and potential local extensions only.
- (b) **3DCRT and/or IMRT** – an escalating total dose of radiation delivered in daily fractions of 2 Gy when at least part of the treatment is delivered using an approved CRT or IMRT technique to a volume that tightly encompasses the prostate and potential local extensions only. Dose escalation will only occur when criteria agreed by the TACT have been satisfied.
- (c) **HDR brachytherapy** – the trial allows a combination of initial external beam therapy (EBT) delivered using conventional or conformal EBT with a boost delivered using HDR brachytherapy.

At any time during the course of the study, the participating centre can elect to change from one method of delivery to another and one dose level to another, however verification from the TACT must be obtained before any change is initiated.

Drug Treatment

LH-RH analogue (LH-RHa) (Leuprorelin acetate 22.5 mg) will be delivered as a depot injection every 3 months. This will be administered as an Intramuscular injection (IMI).

Zoledronic acid 4 mg will be delivered as an intravenous infusion over 15 minutes once every 3 months for 18 months, in patients randomised to this therapy. No placebo therapy will be given to patients randomised to ‘no bisphosphonate therapy’ treatment arm.

2 OBJECTIVES

The principal objective of the trial is to test the hypothesis that 12 months adjuvant androgen deprivation using Leuprorelin acetate starting immediately after standard therapy (ie 6 months of Leuprorelin acetate before and during radiotherapy) will improve biochemical (PSA) relapse free survival (PSA-RFS) when compared with standard therapy alone.

There are three secondary objectives:

- (a) to test the hypotheses that 12 months adjuvant androgen deprivation (specified above) will improve overall survival (OS), reduce local failure (LF-FS) and improve quality of life (QOL);
- (b) to test the hypotheses that 18 months of bisphosphonate therapy using zoledronic acid will reduce osteopenic fractures (OPF), improve bone mineral density (BMD), delay the onset of bony metastases (BM-FS) and improve quality of life (QOL) when compared to patients in this trial who are not treated with bisphosphonate therapy;
- (c) to determine the nature of interactions between the total duration of androgen deprivation and:
 - i the addition of bisphosphonate therapy with respect to BM-FS and PSA-RFS;
 - ii increasing radiation dose, within the structured radiation dose escalation program built into the design of the trial, with respect to LF-FS and PSA-RFS;
 - iii increasing Gleason score with respect to overall survival.

A tertiary objective of the trial is to determine whether intercurrent medical conditions, affecting the microvasculature, will impact independently on delayed radiotherapy morbidity ('late radiation toxicity').

2.2 Endpoints

Primary: PSA relapse-free survival

Secondary:

- (a) Overall survival
- (b) Clinical, local and bony relapse-free survival and associated patterns of clinical failure
- (c) Changes in BMD and OPF
- (d) Quality of life self-assessment

Tertiary: Late radiation toxicity

3 TRIAL DESIGN

3.1 This is a randomised phase III multicentre clinical trial.

3.2 After informed consent is given and eligibility is double checked patients will be randomised to one of four trial arms. In the first, (a) 6 months of androgen blockade with an LH-RH analogue (5 months before start of radiotherapy) (STAD), (b) 18 months of androgen blockade with an LH-RH analogue (starting 5 months before start of radiotherapy) (ITAD), (c) 18 months of therapy with zoledronic acid 4 mg by intravenous infusion every 3 months for 18 months beginning concurrently with STAD (d) 18 months of therapy with zoledronic acid beginning concurrently with ITAD.

Stratification will be according to the following criteria:

T2 / T3, 4

Gleason score 2 – 6 / 7 +

Presenting PSA < 10 / 10 – 20 / > 20

Treatment centre*

** Note that centres opting to use both brachytherapy boost techniques and high dose conformal, or IMRT external beam techniques in different patient subgroups will be classed as two different centres for the purposes of stratification.*

4 PATIENT ELIGIBILITY

4.1 Inclusion criteria

- 4.1.1 Histological confirmation of adenocarcinoma of the prostate in the three months prior to randomisation
- 4.1.2 Gleason primary and secondary pattern reported. If the volume of tumour in biopsies is too small for the pathologist to allocate a secondary pattern, the primary pattern alone is sufficient.
- 4.1.3 Primary tumour stage T2b - 4 (UICC 2002), or T2a providing biopsies demonstrate Gleason score 7 or more, **and** presenting PSA 10 or more
- 4.1.4 PSA value obtained within one month of randomisation
- 4.1.5 No evidence of lymphatic or haematogenous metastases, as determined by negative chest x-ray, CT scan of abdomen and pelvis, and bone scan in the 3 months prior to randomisation
- 4.1.6 ECOG performance status 0 - 1
- 4.1.7 No concurrent medical conditions likely to significantly reduce prospects of 5 year survival
- 4.1.8 Patient accessible to follow up at intervals specified in protocol
- 4.1.9 Written informed consent given (signed by both patient and investigator prior to randomisation)

4.2 Exclusion criteria

- 4.2.1 Previous or concurrent malignancy within previous 5 years except for non-melanomatous skin cancer
- 4.2.2 Prostatectomy
- 4.2.3 Prior pelvic radiotherapy
- 4.2.4 Prior hormone treatment for prostate cancer
- 4.2.5 Inability to complete self administered QOL questionnaire
- 4.2.6 Prior bisphosphonate therapy
- 4.2.7 Serum creatinine > 2 x ULN
- 4.2.8 Osteoporosis resulting in >30% loss in vertebral height in one or more thoracolumbar vertebrae
- 4.2.9 Liver disease resulting in ALT or AST levels > 3 x ULN
- 4.2.10 Prolonged continuous glucocorticoid therapy > 10 mg/day of prednisone equivalent (>6 months)
- 4.2.11 Current treatment with bisphosphonate

5 REGISTRATION AND RANDOMISATION

- 5.1 Registration and randomisation will take place at the Central Trials Office, Department of Radiation Oncology, Newcastle Mater Hospital, Waratah NSW 2298, Australia
Tel: +61 (0)2 4921 1462, Fax: +61 (0)2 4921 1153.

5.2 Registration should be performed by faxing completed Patient Registration Forms (BPT-Pre-Random, CAO, R0) to the Central Trials Office, together with a copy of the local pathology report. The Registration Form includes a checklist of eligibility / ineligibility criteria. Randomisation will normally be performed, and the confirmed by fax, within one hour (Office hours: 8.30am to 5.00 pm AEST).

6 TREATMENT PLAN

RADAR PROSTATE TRIAL TREATMENT GROUPS

ARM [Redacted] Androgen Deprivation (LH-RH analogue) (6mths)
A [Redacted] Radiation treatment begins after 5 months AD

ARM [Redacted] Androgen Deprivation (LH-RH analogue) (6mths)
B [Redacted] Radiation treatment begins after 5 months AD
[Redacted] Bisphosphonate therapy every 3 months for 18 months

ARM [Redacted] Androgen Deprivation (LH-RH analogue) (18mths)
C [Redacted] Radiation treatment begins after 5 months AD

ARM [Redacted] Androgen Deprivation (LH-RH analogue) (18mths)
D [Redacted] Radiation treatment begins after 5 months AD
[Redacted] Bisphosphonate therapy every 3 months for 18 months

