A placebo-controlled double-blinded randomized pilot study of combination phytotherapy in biochemically recurrent prostate cancer

M. Diana van Die[1], Scott G. Williams[1,2], Jon Emery [1], Kerry M. Bone[3,4,] , Jeremy M. G. Taylor[5], Elizabeth Lusk[5], Marie V.Pirotta[1]

1. University of Melbourne Department of General Practice, Parkville, Victoria, Australia;

2. Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia;

3. Integria (MediHerb), Warwick, Queensland, Australia;

4. New York Chiropractic College; Seneca Falls, New York, USA;

5. University of Michigan Department of Biostatistics, Ann Arbor, Michigan, USA.

Email addresses:

diana.vandie@rmit.edu.au

Scott.Williams@petermac.org

jon.emery@unimelb.edu.au

kerry.bone@integria.com

jmgt@umich.edu

eilusk@umich.edu

m.pirotta@unimelb.edu.au

Correspondence: Dr Diana van Die, Department of General Practice, The University of Melbourne, 200 Berkeley St, Carlton, Victoria 3053, Australia. Email: diana.vandie@rmit.edu.au

Running title: A pilot study of herbal therapy in prostate cancer**ABSTRACT**

Background Men with biochemical recurrence of prostate cancer following local therapies often use natural supplements in an attempt to delay metastases and/or avoid the need for more aggressive treatments with undesirable side-effects. While there is a growing body of research into phytotherapeutic agents in this cohort, with some promising results, as yet no definitive recommendations can be made.

This pilot study was undertaken to assess the feasibility of a fully-powered study to examine the effects of this phytotherapeutic intervention (containing turmeric, resveratrol, green tea and broccoli sprouts) on PSA doubling time in men with biochemical recurrence with a moderate PSA rise rate.

Method A double blind, randomized, placebo controlled parallel trial was conducted with twenty-two men with biochemically recurrent prostate cancer and a moderate rise rate (PSA doubling time of 4–15 months and no evidence of metastases from conventional imaging methods). Patients were randomized to either the active treatment arm or placebo for 12 weeks. The primary endpoints were feasibility of study recruitment and procedures, and measurement of proposed secondary endpoints (prostate symptoms, quality of life, anxiety and depression as measured on the EORTC QLQ-C30 and PR-25, the IPSS and HADS). Data was collected to estimate PSA-log slopes and PSA-doubling times, using a mixed model, for both the pre-intervention and post intervention periods.

Results Adherence to study protocol was excellent, and the phytotherapeutic intervention was well-tolerated, with similar numbers of mild-to-moderate adverse events in the active and placebo arms. Both the intervention and data collection methods were acceptable to participants.

No statistical difference between groups on clinical outcomes was expected in this pilot study. There was between-subject variation in the PSA post treatment, but on average the active treatment group experienced a non-significant increase in the log-slope of PSA (pre-treatment doubling time = 10.2 months, post-treatment doubling time = 5.5 months), and the

placebo group experienced no change in the log-slope of PSA (pre-treatment doubling time= 10.8 months, post-treatment doubling time = 10.9 months).

Conclusion The findings suggest that a fully-powered study of this combination is feasible in men with biochemically recurrent prostate cancer and a moderate PSA rise rate.

Key words

Herbal medicine, phytotherapy, botanical medicine, randomized controlled trial, early prostate cancer

INTRODUCTION

Approximately 30-40% of men treated for localised prostate cancer (PC) with definitive local therapies such as radical prostatectomy or radiation therapy will develop biochemical biochemical recurrence (BCR) of disease, detected by a rising serum prostate-specific antigen (PSA) (1,2). BCR signifies the presence of incurable disease in most cases, however, there will typically be a period of several years of observation before further therapy is justified due to the indolent nature of many BCR cases (3). Salvage therapy for BCR is mostly based around androgen deprivation therapy (ADT) (4,5) that is associated with significant toxicities such as hot flushes, loss of libido, sarcopenia, metabolic syndrome, and bone loss (6-8). Understandably, many men with BCR attempt to delay the initiation of salvage therapies with the use of natural supplements (6,9).

Epidemiological and dietary studies support the PC chemopreventative effects of diets rich in plant-derived polyphenols, such as curcumin in turmeric; resveratrol found in grape skins and red wine, catechins in green tea; and glucosinolates (notably the isothiocyanate sulforaphane in broccoli sprouts)(10-15). Data from in vitro, in vivo and clinical trials also lend support to their anticancer activities(16-27). Randomized controlled trials (RCTs) of catechins from the leaves of green tea (*Camellia sinensis,* Theaceae family), notably epigallocatechin-3-gallate (EGCG), support its chemopreventive activity (28,29) and benefits on PSA dynamics in men with prostate cancer (30-32). In a RCT with 78 men with BCR, sulforap-

hane (an enzymatic degradation product from glucoraphanin in broccoli sprouts), 60 mg daily (Nutrinov^{TM}) for six months resulted in a 78% (21.7 month) increase in PSA-doubling time (PSA-DT) compared to placebo (12.2 months), with no effect on testosterone, and good tolerability (33). In a recent RCT of 203 men with BCR, the combination of green tea leaf, turmeric root, broccoli, pomegranate seed and whole fruit (Pomi-T$^{®}$) for six months showed a significant suppression of PSA progression (34,35).

While these phytotherapeutic agents are readily available, further human clinical trial data are required to fully support the use of these interventions, and particularly for the commonly-used multi-component formulations.

In the present study, we hypothesised that a combination therapy containing turmeric (*Curcuma longa,* L.*,* Zingiberaceae family), resveratrol from Japanese knotweed (*Polygonum cuspidatum* Sieb. & Zucc (Polygonaceae family)),, green tea (*Camellia sinensis,* Theaceae family), and broccoli sprouts (*Brassica oleracea* L. *var. italic,* Cruciferae/Brassicaceae family) would be well tolerated and safe to administer to a cohort of men with BCR and a moderate rate of PSA rise. We designed the study to evaluate both these hypotheses, along with the feasibility of a placebo-controlled double-blinded design.

MATERIALS AND METHODS

Study participants

Participants were recruited from Peter MacCallum Cancer Centre in East Melbourne, Australia, into this placebo-controlled double-blinded parallel randomized controlled trial. Men were allocated 1:1 between the control (placebo) and experimental arms. The trial was approved by the Human Research Ethics Committee of the Peter MacCallum Cancer Centre and the University of Melbourne Human Ethics Sub-Committee, and the trial registered on the Australian New Zealand Clinical Trials Registry (ANZCTR number: 366895). All participants were required to provide informed consent prior to enrolment.

To be eligible, men were required to be aged 18 years and over, and had developed BCR following treatment for histologically confirmed prostate adenocarcinoma with localised therapy. At enrolment, men required a minimum PSA value at of either (i) 0.4 ng/mL if the primary treatment was radical prostatectomy, or (ii) PSA nadir + 2 ng/mL if the primary treatment was radical radiotherapy, and a moderate PSA rise (PSA doubling time [PSA-DT]) of 4 - 15 months, as demonstrated by at least three PSA measurements obtained at least three months apart over a minimum of 12 months prior (6). Testosterone at baseline was required to be at least 6.9 nmol/L along with adequate hepatic function denoted by GGT less than double the upper limit normal (ULN), bilirubin less than 1.5 x ULN, and adequate renal function (eGFR by Cockcroft-Gault or comparable calculation >50 ml/min) and creatinine 70-120 µmol/L.

Men were excluded if there was evidence of metastastic disease on conventional imaging methods (computed tomography and nuclear bone scan). Other exclusion criteria included any of the following: significant uncontrolled comorbid condition, receiving concurrent chemotherapy or had previously received cytotoxic chemotherapy or androgen ablative therapy for recurrent disease; currently receiving biological response modifiers or high dose prednisolone (≥ 50 mg/day); history of intolerance to caffeine or any of the trial interventions.

Study intervention

The intervention consisted of two tablets twice daily of:

- turmeric (Curcuma longa) rhizome extract [TUMEP25] 25:1, standardised for curcumin 95%, assay 95-105% total curcuminoids; curcumin 100 mg (400 mg/day);
- resveratrol from *Polygonum cuspidatum* extract dry concentrate [POLEP100], standardised, 100:1, containing not less than 50% resveratrol, 30 mg (120 mg/day);
- green tea (*Camellia sinensis*) leaf dry concentrate [GRTEPE 50%], standardised, 25:1, containing not less than 50% polyphenols; catechins 100 mg (400 mg/day; [Details of the analytic methods for standardization are available on request.]

and two capsules twice daily of

- broccoli (*Brassica oleracea* var*. italica*) sprout concentrate [BROEPE] 20:1, equivalent to fresh sprouts 2,000 mg (8 g/day).

Matching placebo tablets contained the excipients: microcrystalline cellulose, calcium hydrogen phosphate, magnesium stearate, hypromellose. Active and placebo tablets were color-coated with iron oxide to give an identical appearance in terms of size, color, coating and weight. The placebo capsules contained powdered green oats, aerial parts (*Avena sativa,* L., Graminaceae family), 100 mg to color-match the active intervention. *Avena sativa* has no demonstrated activity in prostate cancer (36,37).

Tablets and broccoli sprout powder for capsules were manufactured according to the Code of Good Manufacturing Practice; the powdered green oats herb (the placebo for the broccoli sprout powder) was manufactured as a food. All were supplied by MediHerb/Integria Healthcare Australia Pty Ltd, who provided quality assurance data. Batch numbers for the active and placebo tablets were 160749 and 160750 respectively.

Retention samples of raw materials and finished tablets are securely stored at MediHerb; these were validated by chemical fingerprinting against verified botanical samples maintained at the Southern Cross University Herbarium. These underwent full internal identity and microbiological (BP) testing. Thin layer chromatography was used for identification and qualitative testing; quantitative analysis to determine total curcuminoids, resveratrol and total catechins was by high performance liquid chromatography). Details of the method for performing this analysis are available on request. Powders were encapsulated by Dartnell's compounding chemist, Surrey Hills, Melbourne, Australia. The batch numbers for the broccoli capsules was RD237, and for the green oat (placebo) capsules was 014E133. All products are included on the Australia Register of Therapeutic goods in as Listed Medicines and were administered within standard dosage levels.

The active and placebo supplements were supplied directly to Peter MacCallum Cancer Centre pharmacy from MediHerb/Integria and Dartnell's pharmacy, and were dispensed to trial participants in sealed containers. At the end of the study, any remaining tablets were returned to the study centre, and manually counted.

Outcome measures

PSA measurements (three to six for each patient) were obtained from hospital records for at least 12 months prior to enrolment to estimate PSA-DT. Baseline PSA was measured at usual care visits which ranged from 9 days to 1.8 months prior to randomization. However, one baseline PSA was not performed in an timely fashion due to an administrative error. The post-randomization PSA measurement was obtained within a week of end-of-treatment in most cases. Clinical process measures collected at baseline were PSA, blood pressure, urea and electrolytes, liver function tests and oestradiol (E2). Body mass index was calculated, and Karnofsky performance scale was rated at baseline. Health-related quality of life measures were the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) version 3, and Prostate 25 administered at baseline and week 12, and the International Prostate Symptom Score (IPSS) and Hospital Anxiety and Depression Scale (HADS). Dietary intake of trial substances were recorded in men's weekly diaries, along with adverse events, and collected at monthly telephone follow-ups. Adverse events were recorded on the Case Report Form, and graded according to the National Cancer Institute (NCI) common toxicity scale.

Sample size

This pilot study was not powered to detect a statistical difference between groups on clinical outcomes. A pragmatic sample size of up to 40 men was chosen to test recruitment procedures and acceptability of all aspects of running the study, including measuring proposed study endpoints at baseline and throughout the observation period.

Randomization

Eligible patients were allocated to active treatment or placebo by the unblinded pharmacist according to the next available sequence in a randomization schedule, produced by a clinical trials statistician using a reproducible permuted block method. To evaluate the success of blinding, participants' assessment of their group assignations were elicited at the end of the treatment phase prior to code breaking, and subsequently compared with actual group allocation.

Statistical methods

Data were analyzed for all eligible randomized participants. Compliance was considered as greater than 70% of tablets taken. Results are expressed as means $\pm$ SD; alpha level was set at 0.05.

A linear mixed model was used to assess the impact of the intervention on the doubling time of PSA. Log(PSA+0.1) was the response variable. The fixed effects were an intercept, an effect for intervention group, and 4 slopes corresponding to pre and post randomization time for both treatment groups. The model included a participant-specific intercept, participant-specific pre and post randomization slopes plus measurement error. The addition of 0.1 to PSA is to avoid taking the logarithm of zero and to better agree with the assumptions of the model. The addition of 0.1 is ignored in the calculation of the doubling time. The estimated slope for each time period and group can be converted into a doubling time using the equation:

doubling time=natural-logarithm(2)/slope.

95% confidence intervals for the doubling time are presented. The effect of the treatment is evaluated by (a) comparing the post randomization slopes between the two groups, (b) by comparing the change in slope at randomization between the two groups and (c) by comparing the pre and post randomization log PSA slopes separately for each treatment group.

Independent samples *t*- tests were used to compare groups at baseline on continuous variables. A Pearson's chi-square exact test was used to compare differences in categorical var-

variables. For secondary endpoints of EORTC QLQ-C30 and Prostate 25, the HADS and the IPSS, data are presented descriptively as means and standard deviations. Statistical analysis was conducted at the University of Melbourne and University of Michigan using R, STATA-IC12, and SAS 9.4.

Safety monitoring

Two general practitioners with experience of phytotherapy were recruited as safety monitors, and were available for rapid consultation in the event of suspected serious adverse events.

RESULTS

Twenty-two of 31 eligible patients were randomized between December 2014 and June 2015. All recruited men completed the study. Before unblinding, two men were excluded from the efficacy analysis for violation of the PSA inclusion criteria, but were retained for the safety analysis.

In this small sample, group characteristics were not equal at baseline on demographic variables. Age was significantly lower in the active arm (69 years in active group; 75 in placebo), while education was higher for the active group. Significantly more men in the placebo arm had been treated with radiotherapy-only (Table 1).

Mean PSA at baseline was 5.95 (range 0.43-28) for the active treatment arm and 8.39 (range 2.4-22) for the placebo group. The mean Gleason score was 7.1 in the active arm, and 7.5 in the placebo group (range 6-9 for both groups).

TABLE 1 Baseline characteristics of participants

Compliance

Adherence to protocol was excellent, ranging from 92% to 100%, except for one patient on placebo (78%). Mean compliance in the active arm was 98.6% (SD 2.35, range 93 -100),

and in the placebo arm was 96.1 (SD 7.1, range 78-100). Throughout the treatment phase Men maintained baseline dietary intakes of trial foods, according to diet diaries.

Blinding

Evidence of blinding was obtained by eliciting participants' assessment of their group allocation at the end of treatment prior to code breaking. Of those in the active group who made an assessment, 50% were correct, while 60% of those on placebo guessed correctly.

Adverse events

Overall, the intervention and control tablets were well tolerated. There were 12 reported adverse events (AEs) in the active treatment arm, three of which were probably study-related (table 2), and one possibly related (headache). Of these three, one case of heartburn and one of restlessness (probably caffeine-related) persisted throughout the treatment phase. Two men experienced increased nocturia initially, but this symptom resolved after one and two weeks respectively. All were mild, except for the heartburn, which was rated as moderate. There were 13 AEs in the placebo arm, three of which were possibly related to the green oats in the capsules, namely bloating (1 case), flatulence (1) and constipation (2).

Monitoring of dietary caffeine through a dairy revealed no increase in participants' dietary caffeine intake across the treatment phase that could have exacerbated any of these adverse events.

TABLE 2 Treatment-related adverse events

Effect on PSA doubling time

The results of the PSA kinetics are shown in Tables 3 and 4 and Figure 1. The doubling times from randomization to 12 weeks are not statistically significantly different between the two groups (p=0.22).The change in slope at the time of randomization is not statistically significantly different between the two groups (p=0.21). The change in slope of log PSA at the time of randomization was not significant for either group (p=0.98 for the placebo group and p=0.09 for the herbal treatment group).

TABLE 3 PSA doubling times by group and time of assessment

TABLE 4 PSA doubling times and slopes: individual data

FIGURE 1 PSA changes of individuals

Effect on secondary outcome measures

The results of effects on prostate symptoms as measured on the IPSS, and anxiety and depression measured on the HADS are shown in Table 5.

A non-significant reduction in anxiety was observed in the placebo group, consistent with known activity of green oats, the placebo ingredient for the broccoli powder capsules.

There was a non-significant reduction in depression scores in the active treatment arm, and a non-significant reduction in IPSS scores in placebo group.

TABLE 5 Effect of Intervention on prostate symptoms and anxiety and depression *

Results regarding the impact on health-related quality of life and prostate-related symptoms measured on the EORTC QLQ-C30 v3 and EORTC PR-25 respectively are presented in tables 6 and 7. Data for the individual symptom clusters (fatigue, nausea and vomiting, dyspnea, pain, insomnia, appetite loss, constipation, diarrhea, financial difficulties) are not included, but there were no significant changes across time for either group on any of these variables.

TABLES 6 Effect of Intervention on general quality of life

and 7 Effect of Intervention on prostate-related quality of life EORTC PR-25 scores

DISCUSSION

The goal of the current study was to assess, in a small number of participants, the feasibility of a randomized study on the phytotherapeutic combination of turmeric, resveratrol, green tea and broccoli sprouts in men with BCR. Feasibility was demonstrated in that processes to package and deliver the experimental compounds along with matching placebo tablets were logistically manageable, the phytotherapeutic combination well-tolerated, and adherence to

protocol was high despite the number of tablets and capsules administered (four of each daily), with mild side effects reported. The burden of completing outcome measurements was also accepted with high compliance.

Limitations

The main limitation was the slow rate of recruitment and the resultant smaller numbers of participants. This was partly due to the introduction of PSMA (Prostate-Specific Membrane Antigen) Positron-Emission Tomography scans at the recruitment hospital, which meant that micro-metastases were detected in many otherwise eligible men with BCR, who were then directed to salvage treatments.

The study was not powered to detect effects on any outcome measures including PSA kinetics. However, randomization failed to allocate patients treated with surgical and radiation therapy evenly to active and placebo in this small sample. PSA tests were not always undertaken at the same laboratory and hence, some variation is to be expected as there can be over 20% difference in results with laboratories using different assays (38). Baseline PSA measurements were collected at screening, and not repeated on the date of randomization. The period between these two points ranged from 9 days to 3 months in one case, due to the time taken to collect blood assays and dispense tablets. Most end-of-treatment PSA measurements were obtained within a week of trial completion, but a delay of 37 days (1.2 months) was experienced in one participant. PSA kinetics also improved in several men in the placebo arm during the treatment phase. This is unlikely to be related to the activity of green oats (*Avena sativa*), chosen as the placebo for the broccoli capsules, which has no demonstrated activity in prostate cancer (35,36).

This feasibility study was undertaken with no specific funding so additional end-of-treatment blood assays were not performed. However, all four components of the study intervention have previously been widely used and tested in humans and hence, pharmacokinetic data was not sought in this study (39).

Recommendations

This pilot study of a phytotherapeutic intervention, composed of turmeric, resveratrol, green tea and broccoli sprouts, was of interest to men with BCR prostate cancer and their treating oncologists. The tablet formulation and dosages were acceptable to the men and adverse events were few and mild. While the data on PSA trends did suggest worse outcomes for PSA in the herbal group, the differences were not significant, and the width of the confidence intervals in Table 3 allows the possibility that in a future study, those on the herbal group would have a better PSA outcome, consistent with other recent promising trials of similar herbal interventions (33,34).

The introduction of PSMA scans has resulted in earlier detection of micrometastases. Issues of trial eligibility will need to be carefully considered in future studies. Recruitment of sufficient numbers for a fully powered study would necessitate a larger number of trial sites. Stratification for initial therapy method could be considered to ensure similar numbers of post-surgical and post-radiotherapy patients are assigned to each arm, while PSA data should be collected on the date of randomization in future studies. It would also be useful collect end-of-treatment testosterone in addition to the baseline assays in future studies.

CONCLUSION

The findings of this pilot study suggest that a fully-powered study of this combination is feasible in men with biochemically recurrent prostate cancer and a moderate PSA rise rate.

The formulation was of high quality, manufactured under pharmaceutical Good Manufacturing Practices (GMP) in Australia, and contained therapeutically active levels of constituents. The dose and percentage active constituents were determined in conjunction with a phytochemist with over 30 years' experience (KB) to ensure therapeutic doses were achieved.

The success of blinding was demonstrated by comparing patients' group allocation with their assessment of group assignation elicited prior to code-breaking.

The inclusion of a placebo arm overcame any false positive results due to the natural variability of PSA-DT (40).

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CONFLICT OF INTEREST

Professor Kerry Bone is a consultant for Integria Healthcare/MediHerb which provided the herbal materials for use in the trial. Integria manufactures herbal products, including those containing the ingredients selected for use in the trial.

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TABLE 1 BASELINE CHARACTERISTICS OF PARTICIPANTS (N = 20)

MEAN (SD) UNLESS OTHERWISE STATED

	PLACEBO ***n* = 11**	**ACTIVE** ***n* = 9**
Age at trial start (years)		
Mean (SD)	75 (8.3)	69 (6.4)*
Median (range)	77 (58–84)	69 (56–77)
Weight in kg	83 (11.7)	78 (12·0)
Height in cm	175 (7.0)	171 (6·6)
BMI	27 (2.7)	26 (3.5)
Ethnicity, *n* (%)		
Caucasian	11 (100%)	7 (78%)
Asian	0 (0%)	2 (22%)
Education, *n* (%)		
Year 11 or under	7 (64%)	1 (11%)
Year 12	2 (18%)	3 (33%)
TAFE or University	1 (9%)	5 (56%)†
Postgraduate	1 (9%)	0 (0%)
Smokers, *n* (cigarettes per day, *n*)	0	1 (<10)
Standard alcoholic drinks per week	2.5 (1.2)	2.1 (1.1)
Dietary caffeine: cups of tea/coffee/cola drinks/day	4.8 (5.4)	3.7 (1.5)
Dietary intake of trial foods		
green tea/cups per day	0.3 (0.7)	0.2 (0.4)
turmeric/curries per week	0.1 (0.3)	0.3 (0.7)
broccoli, serves per week	1.6 (2.1)	2.0 (2.5)

red wine, standard glasses per week	4.8 (8.0)	2.7 (3.5)
Prior herbal medicine use, *n* (found it effective, *n*)	1 (1)	1 (1)
Prior use of trial supplements, *n* (found it effective, *n*)	(0)	(0)
Karnofsky, *n* (%)		
100	8 (73%)	9 (100%)
90	2 (18%)	0 (0%)
PSA values at screening (ng/mL)		
Mean (SD)	8.39 (6.03)	5.95 (8.74)
Median (range)	7.5 (2.4-22)	4.2 (0.43-28)
PSA-DT at screening (months)#	10.8	10.2
Pre-operative Gleason score, *n* (%)		
6	1 (9%)	2 (22%)
7	6 (55%)	4 (45%)
8	1 (9%)	2 (22%)
9	3 (27%)	1 (11%)
Prior treatment, *n* (%)		
surgery only	1 (9%)	2 (22%)
radiotherapy only	9 (82%)†	2 (22%)
both	1 (9%)	5 (56%)†
Months since first treatment, mean (SD)	107.4 (61.6)	94.2 (45.3)

* significant difference $p < .05$

† significant difference $p < .05$ using chi-square χ^2

calculated using linear mixed model

TABLE 2 TREATMENT-RELATED ADVERSE EVENTS

ADVERSE EVENT	GRADE*	NUMBER OF MEN	GROUP	WEEK RE-PORTED	LIKELIHOOD RELATED
nocturia	*1*	*2*	*active*	*1-2*	*probably*
heartburn	*2*	*1*	*active*	*8-12*	*probably*
headache	*1*	*1*	*active*	*4*	*possibly*
restlessness	*1*	*1*	*active*	*9-12*	*probably*

*Grade 1 = mild; grade 2 = moderate

TABLE 3 PSA DOUBLING TIMES BY GROUP AND PERIOD OF ASSESSMENT

	PRE-BASELINE PSA –DT (95% CI)*	BASELINE TO 12 WEEKS PSA –DT (95% CI)*
Active group (n=9)	10.2 months, 95% CI=(8.1,13.9)	5.5 months, 95% CI=(3.4,13.6)
Placebo group (n=11)	10.8 months, 95% CI=(8.5,14.4)	10.9 months, 95% CI=(5.2, infinity)

* 95 % confidence intervals

TABLE 4 PSA DOUBLING TIMES AND SLOPES[1]: INDIVIDUAL DATA

Id No.	Age	Gleason Score, pre-op	Tumour stage	PSMA result	Testost-erone baseline	PSA baseline	PSA end	PSA-DT baseline	PSA-DT end	PSA log slope baseline	PSA log slope end
Active treatment group											
3	56	8 (4+4)	2c	neg-ative	9.10	0.85	1.43	9.16	3.13	0.076	0.222
4	69	7 (4+3)	3b	n/a[2]	17.00	5.20	6.60	9.84	6.49	0.070	0.107
7	70	8 (3+5)	3a	n/a	19.40	0.60	1.20	10.16	3.86	0.068	0.179
8	77	6 (4+3)	3a	mets[3]	7.20	5.40	14.90	5.41	2.00	0.128	0.347
11	65	9 (4+5)	3a	n/a	8.50	0.43	0.49	21.20	12.69	0.033	0.055
13	66	7 (3+4)	3b	n/a	22.00	0.46	0.49	21.67	13.89	0.032	0.050
15	65	6 (3+3)	1c	n/a	26.60	4.20	5.60	13.20	34.66	0.053	0.020
19	74	7 (3+4)	1c	n/a	15.10	28.00	38.00	7.77	6.52	0.089	0.106
22	71	6 (3+3)	3a	n/a	15.40	8.40	9.00	11.06	12.90	0.063	0.054
Mean	***69***	***7.1***			***15.59***	***5.95***	***8.63***	***10.20***	***5.48***	***0.068***	***0.127***

(SD)	***(6.4)***				***(6.54)***	***(8.74)***	***(12.02)***			***(0.009)***	***(0.038)***
Placebo group											
1	84	7 (4+3)	1c	neg-ative	10.50	12.42	12.18	12.38	402.99	0.056	0.002
2	**77**	**6 (4+3)**	**3a**	**n/a**	**14.60**	**3.10**	**2.76**	13.69	11.19	0.051	0.062
5	58	9 (4+5)	3b	n/a	23.60	14.50	23.50	8.69	8.75	0.080	0.079
9	63	9 (4+5)	2c	mets	9.10	2.40	3.90	10.93	7.22	0.063	0.096
10	69	9 (4+5)	2c	mets	9.40	3.50	4.40	15.11	310.83	0.046	0.002
12	81	7 (4+3)	2a	n/a	13.70	7.50	9.10	13.24	infinite	0.052	-0.006
14	79	7 (3+4)	3a	neg-ative	29.80	9.30	10.60	12.57	1612.0	0.055	0.000
16	78	7 (4+3)	2c	n/a	10.50	9.12	14.65	7.25	3.63	0.096	0.191
17	76	8 (4+4)	3a	n/a	13.10	4.60	6.40	8.23	3.81	0.084	0.182
20	83	7 (4+3)	2c	n/a	13.20	22.00	21.70	10.49	34.12	0.066	0.020
21	76	6 (3+3)	1c	n/a	14.70	3.90	5.10	11.53	9.82	0.060	0.071
Mean	***75***	***7.5***			***14.75***	***8.39***	***10.39***	***10.75***	***10.90***	***0.064***	***0.064***
(SD)	***(8.3)***				***(6.39)***	***(6.02)***	***(7.09)***			***(0.008)***	***(0.035)***

[1]Calculated using linear mixed model

[23]mets – metastases detected on PSMA

n/a – PSMA not performed

TABLE 5 EFFECT OF INTERVENTION ON PROSTATE SYMPTOMS (IPSS) AND ANXIETY AND DEPRESSION (HADS) *

	IPSS		HADS DEPRESSION		HADS ANXIETY	
	Baseline	**End of treatment**	**Baseline**	**End of treatment**	**Baseline**	**End of treatment**
Placebo, n = 11	11 (10.48)	8.55 (5.65)	2.82 (3.63)	2.91 (3.08)	3.91 (4.60)	2.91 (3.21)
Active, n = 9	7.67 (6.96)	8.55 (8.13)	3.0 (2.55)	2.22 (2.59)	2.33 (2.18)	3.0 (3.5)

*Scores expressed as mean and standard deviation where higher scores reflect higher level of dysfunction.

IPSS International Prostate Symptom Score

HADS Hospital Anxiety and Depression Score

TABLE 6 EFFECT OF INTERVENTION ON GENERAL QUALITY OF LIFE* (MEAN AND STANDARD DEVIATION)

	Global Health status/QOL		Physical functioning		Role functioning		Emotional functioning		Cognitive functioning		Social functioning	
	Baseline	**Week 12**	***Baseline***	**Week 12**	***Baseline***	**Week 12**	***Baseline***	**Week 12**	***Baseline***	**Week 12**	***Baseline***	**Week 12**
Placebo (n = 11)	78.79 (23.97)	71.21 (17.62)	85.45 (15.44)	83.64 (13.12)	93.94 (13.48)	92.42 (11.46)	89.39 (24.75)	90.91 (17.66)	89.17 (15.56)	86.67 (15.86)	89.39 (25.03)	96.97 (10.05)
Active (n = 9)	83.33 (16.14)	82.41 (14.10)	97.04 (6.76)	94.81 (13.24)	96.30 (7.35)	92.69 (14.7)	95.37 (8.45)	91.67 (13.82)	89.17 (15.56)	86.67 (15.86)	87.04 (28.6)	96.30 (7.35)

*Measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) version 3; higher scores reflect higher level of functioning

TABLE 7 EFFECT OF INTERVENTION ON PROSTATE-RELATED QUALITY OF LIFE EORTC PR-25 SCORES* (MEAN AND STANDARD DEVIATION)

	Urinary symptoms		Bowel symptoms		Treatment-related symptoms		Sexual activity		Sexual functioning		Incontinence aid use	
	Baseline	**Week 12**	***Baseline***	**Week 12**	***Baseline***	**Week 12**	***Baseline***	**Week 12**	***Baseline***	**Week 12**	***Baseline***	**Week 12**

Placebo, n = 11	23.86 (18.55)	25.38 (14.49)	6.06 (6.55)	8.33 (9.13)	8.59 (14.35)	6.57 (9.88)	77.27 (28.16)	86.36 (16.36)	37.5 (17.68)	70.83 (5.89)	8.33 (16.67)	0 (0)
Active, n = 9	14.81 (17.32)	19.27 (21.12)	2.78 (5.89)	6.25 (8.63)	6.17 (7.05)	6.94 (7.12)	64.81 (24.22)	70.37 (27.36)	35.0 (20.75)	45.83 (29.27)	33.33 (47.14)	16.67 (19.25)

*Measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) version 3, and Prostate 25; higher scores reflect higher level of symptomatology or higher level of functioning

Figure 1 PSA changes of individuals .