



Evolution of Chemotherapy for Hormone Refractory Prostate Cancer

Ian F Tannock MD, PhD

Daniel E Bergsagel Professor of Medical Oncology
Princess Margaret Hospital and University of
Toronto



In 1985, two articles were published in JCO suggesting that there was no role for chemotherapy for men with prostate cancer, outside of a well designed clinical trial

A Reevaluation of Nonhormonal Cytotoxic Chemotherapy in the Treatment of Prostatic Carcinoma

By Mario A. Eisenberger, Richard Simon, Peter J. O'Dwyer, Robert F. Wittes, and Michael A. Friedman

Is There Evidence That Chemotherapy Is of Benefit to Patients With Carcinoma of the Prostate?

By Ian F. Tannock



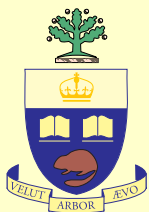


With that background, we and others began trials of non-hormonal systemic therapy for men with prostate cancer

Principles of treatment:

- Patients are often old and frail - use gentle drugs
- The aim is to palliate patients - i.e. to improve their duration and quality of survival
- Improvement in symptoms and quality of life should be measured directly
- Doctors are poor judges of patients' quality of life - **This must be assessed by the patients themselves**



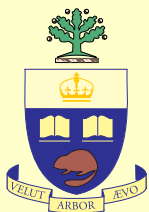


Using those principles the Canadian group undertook a RCT comparing mitoxantrone and prednisone to prednisone alone for men with HRPC and pain (Tannock et al JCO 1996;14:1756-64)

The trial showed improved pain control with chemotherapy - but no difference in survival (it was not powered to show a survival difference)

The FDA approved mitoxantrone and prednisone as palliative treatment for men with symptomatic HRPC - the first time a chemo drug had been approved based on a symptom control endpoint





Phase 3 Trials of Mitoxantrone + Corticosteroid

Study	N	Patients	Pain response	PSA Response	Diff in arms
M+ P vs P (Canadian)	161	Symptomatic	38%	34%	M+P > P
M+H vs H (CALGB)	242	Mixed	Better than H	37.5%	M+H > H
M+P vs P (Berry et al, 2002)	120	Asymptomatic	N/A	48%	M+P > P
M+P+clodronate vs M+P+placebo (Canadian)	209	Symptomatic	39%	29%	No diff

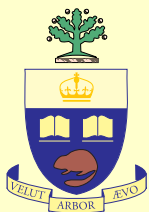




These trials showed that elderly men could tolerate chemotherapy and derive palliative benefit from it

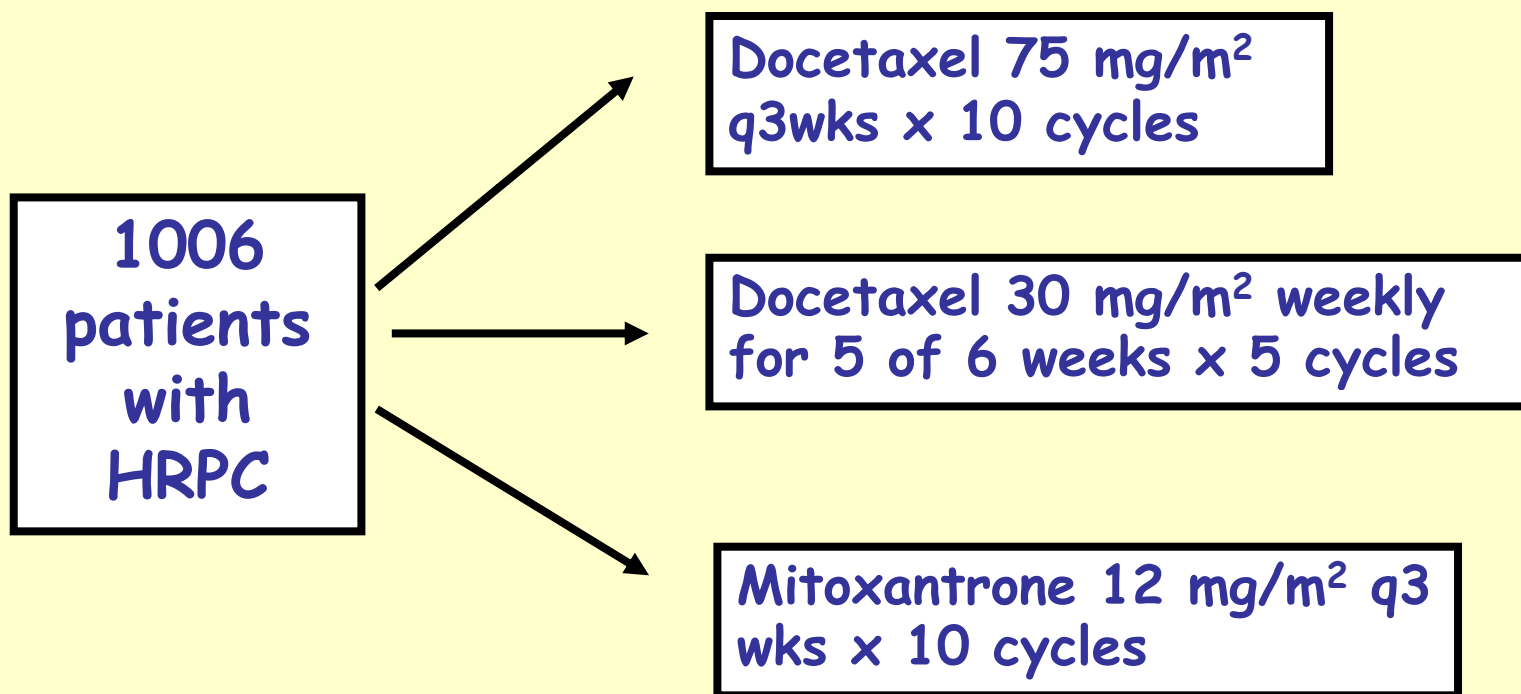
The next generation of chemotherapy trials sought to improve survival





TAX 327 Study

(Tannock et al, NEJM, 2004;351:1502-12)



All patients received prednisone 10mg/day





TAX 327: Endpoints

- **Primary endpoint:**

Overall survival (OS)

- **Secondary endpoints:**

Pain response (if Pain Intensity ≥ 2 or
Analgesic Score ≥ 10)

PSA response (if PSA ≥ 20)

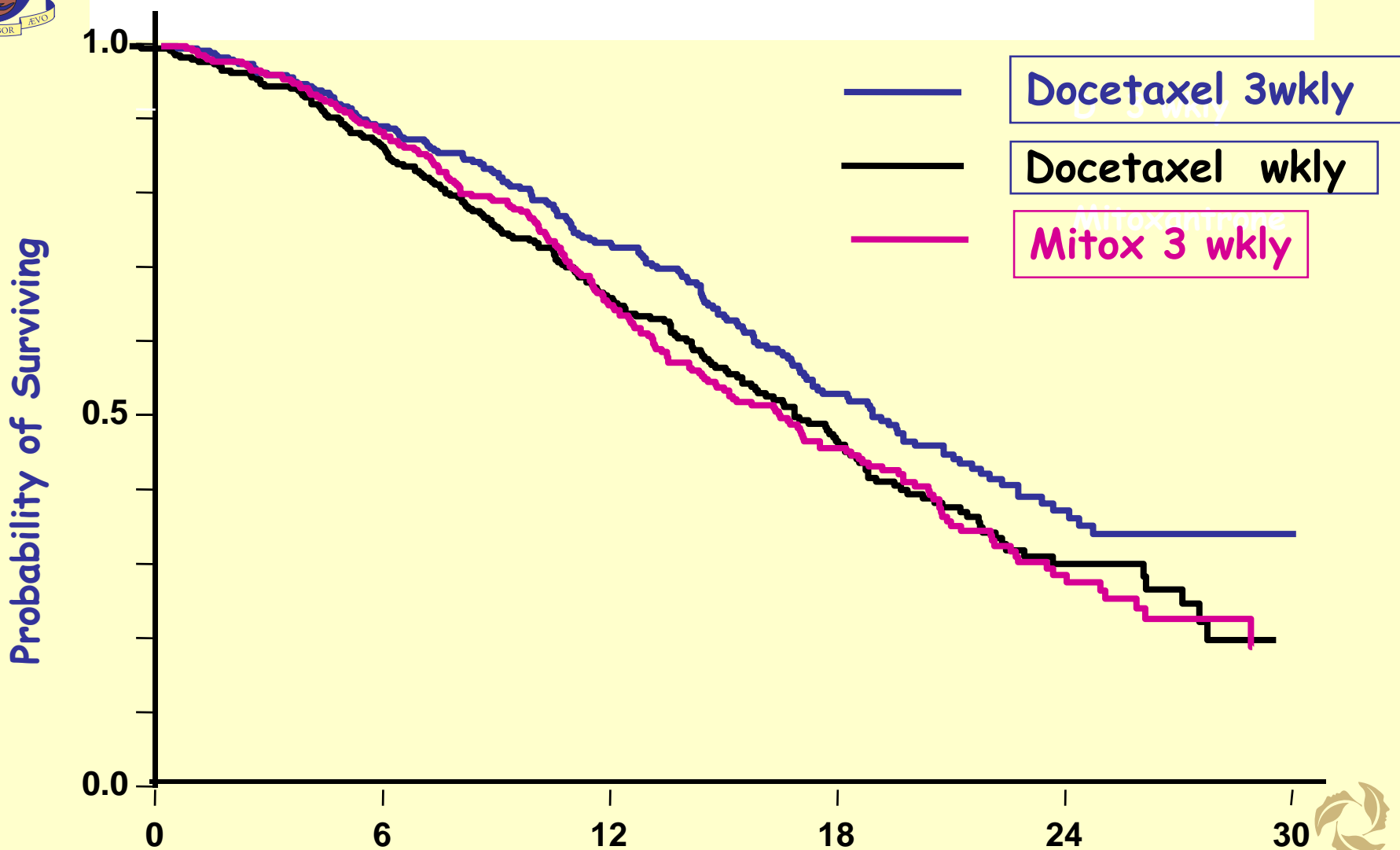
Measurable tumour response

QOL (10% improvement in FACT-P)

Safety



Overall Survival

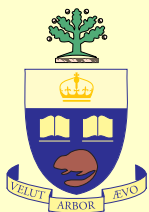


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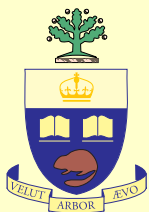


TAX 327: Updated survival

(Berthold et al, JCO 2008;26:242-5)

	Docetaxel q 3wks	Docetaxel weekly	Mitoxantrone
% dead	85.1%	85.3%	88.1%
Median survival	19.2 mos	17.8 mos	16.3 mos
Hazard Ratio	0.79 P=0.004	0.87 P=0.09	
3-year survivors	18.6%	16.8%	13.5%





TAX 327: Secondary Endpoints

	DOC q 3wk	DOC q wk	MTZ q 3wk
Pain Response Rate	34.6% p=0.01	31.2% p=0.08	21.7%
PSA Response Rate	45.4% p=0.0005	47.9% p<0.0001	31.7%
QOL Response rate	21.9% p=0.009	22.6% p=0.005	13.1%

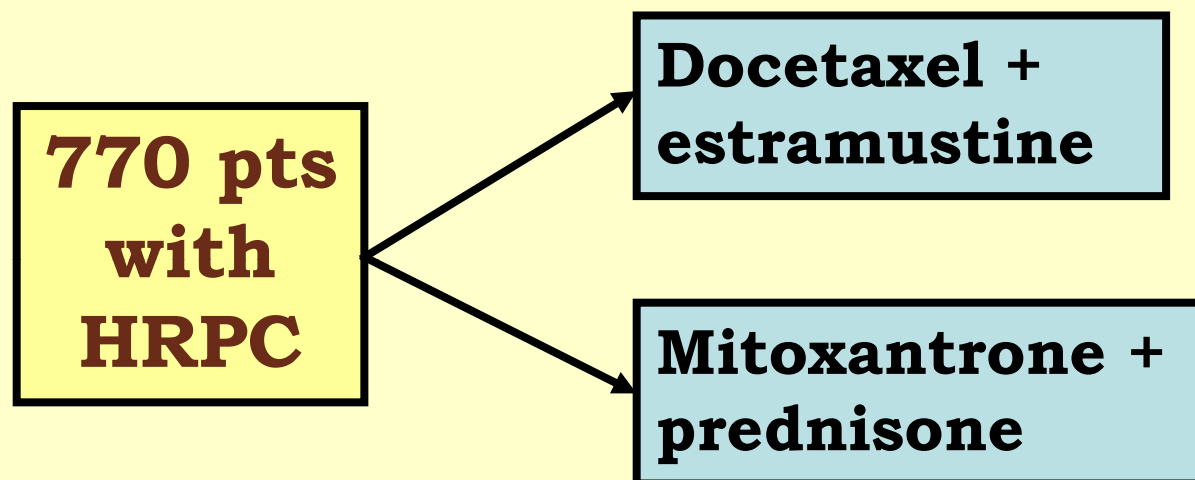
Rates are underestimates because they exclude patients who had worsening before improvement





SWOG 99-16 Study

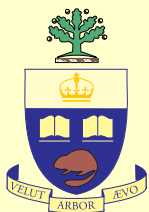
(Petrylak et al: NEJM 2004;351:1513-20)



Study shows:

1. Small difference in survival in favour of docetaxel arm
2. Greater toxicity with estramustine





TAX-327 and SWOG 9916

- The studies confirm the palliative benefit of Mitoxantrone + Prednisone, and this remains appropriate treatment for patients who are averse to side effects of Docetaxel
- **Estramustine adds only toxicity and should not be used**
- On the basis of its survival advantage, Docetaxel + Prednisone is appropriate treatment for many patients with HRPC



Principles of Management for castrate-resistant prostate cancer

- For those with slowly rising PSA and minimal symptoms:
 - Consider further hormonal manipulations (e.g. DES, ketoconazole) or clinical trials of targeted agents
- For those with symptoms or rapidly-rising PSA
 - Optimize pain control with regular dosing of narcotic medication, such as morphine
 - Give regular laxatives to control the constipation that will be caused by morphine
 - Consider local radiotherapy if there is a dominant site of pain
 - Consider chemotherapy or bone-seeking radioisotopes





New agents, new targets, new trials

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Design and End Points of Clinical Trials for Patients With Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group

Howard I. Scher, Susan Halabi, Ian Tannock, Michael Morris, Cora N. Sternberg, Michael A. Carducci, Mario A. Eisenberger, Celestia Higano, Glenn J. Bubley, Robert Driecer, Daniel Petrylak, Philip Kantoff, Ethan Basch, Wm. Kevin Kelly, William D. Figg, Eric J. Small, Tomasz M. Beer, George Wilding, Alison Martin, and Maha Hussain

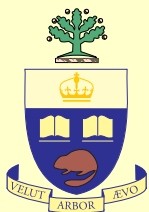
From the Sidney Kimmel Center for Prostate and Urologic Cancers, Memorial Sloan-Kettering Cancer Center, New York, NY.

Submitted May 4, 2007; accepted November 19, 2007.

A B S T R A C T

Purpose

To update eligibility and outcome measures in trials that evaluate systemic treatment for patients with progressive prostate cancer and castrate levels of testosterone.



Selected new criteria for prostate cancer trials

- Increased emphasis on “time to event” endpoints as compared to “response” endpoints
- Early changes in PSA or pain to be ignored (unless overwhelming evidence of clinical progression) and treatment to be continued for at least 12 weeks
- No need to wait for anti-androgen withdrawal if there was no response to adding the anti-androgen
- Decreased emphasis on bone scans and rigorous requirements for defining progression by bone scan





Several phase 3 trials are comparing docetaxel + prednisone +/- a biological agent, including

- Antiangiogenic agents (bevacizumab, VEGF-TRAP)
- OGX-011 (anti-clusterin - to stimulate apoptosis)
- Atrasentan and ZD4054 (endothelin receptor antagonists)
- Vaccines (GVAX: GM-CSF transduced irradiated prostate cancer cells)

Many additional agents are being evaluated in phase 2 trials





Cautionary tales: docetaxel is not an easy partner

- In a large phase 2 study (N=250) weekly docetaxel + DN-101 appeared to give better survival (not the primary endpoint) than weekly docetaxel alone (Beer et al, JCO 2007;25:669-74)
- A phase 3 trial with projected sample of >1000pts was initiated to compare weekly docetaxel + DN-101 vs 3-weekly docetaxel (with prednisone)
- Small Pharma (Novacea) sold rights to DN-101 to Big Pharma (Schering-Plough) for \$\$\$\$\$\$\$\$\$
- Phase 3 trial halted by DSMC because of excess deaths in DN-101 arm after recruitment of >900 pts
- Recently a large trial of docetaxel +/- GVAX also stopped because of increased toxicity in combination arm





Second-Line Therapy

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Mitoxantrone after docetaxel and vice versa (Berthold et al. *Annals Oncol* 2008;19:1749-53)

Investigator	M → D	D → M	Comments
Michels et al	N=33 RR=44%	N=35 RR=15%	Results favour initial docetaxel.
Saad et al	N=20 eval RR=85%		
Oh et al	N=33 RR=60% PFS 16.3 wks	N=35 RR=6% PFS 6.1 wks	Docetaxel active independent of sequence.
Joshua et al	N=20 RR=45%		Weekly docetaxel.
Rosenberg et al		N=41 RR=20%	Part of rand. Phase 2 study
Berthold et al (TAX 327)	N=25 RR=28%	N=71 RR=15%	D weekly and 3-weekly combined



Sipuleucel-T (Provenge)

Dendritic cells are leukapheresed from patients with prostate cancer, exposed to PAP (prostatic acid phosphatase) linked to GM-CSF and re-infused x3

- A small RCT (N=127) did not show significantly improved TTP (primary endpoint) but suggested improved survival

The FDA denied approval on the basis of this trial. Prostate cancer experts on the FDA advisory committee were offered police protection after receiving death threats following this decision.

- A Phase 3 double-blind RCT (N=500) of has completed accrual



Satraplatin and Prednisone Against Refractory Cancer (Sternberg et al, ASCO 2007; N=950)

Metastatic
HRPC after 1
prior chemo
(~50% prior
docetaxel)

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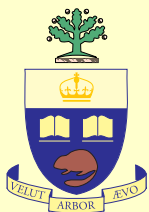
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Satraplatin 80mg/m² po daily 1-5
q35d + Prednisone 5mg po BID

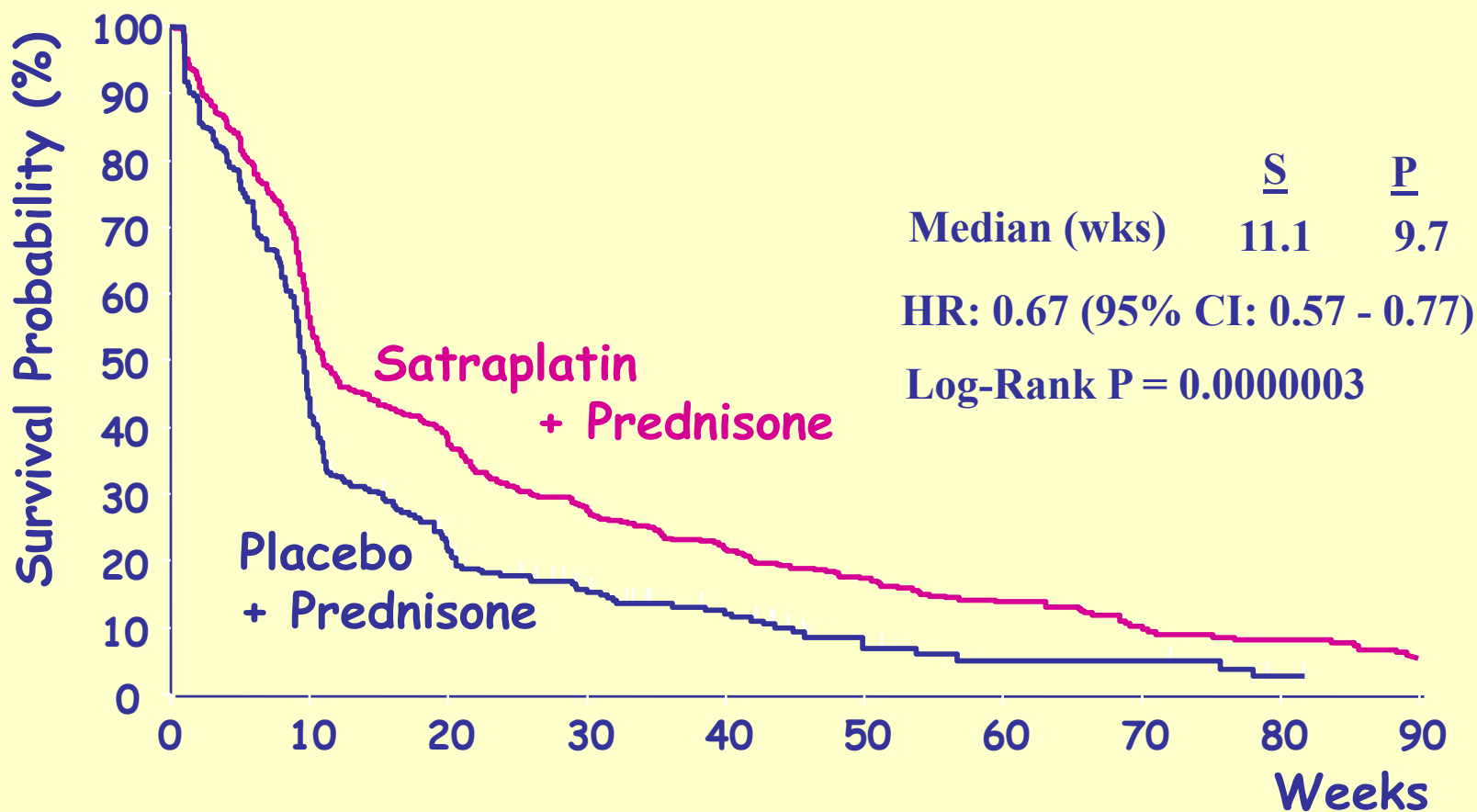
Placebo po daily 1-5 q35d +
Prednisone 5mg po BID

Primary endpoints were progression-free and
overall survival





Progression Free Survival



There was no difference in overall survival



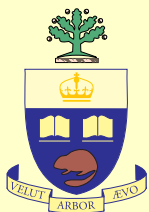


A question for future trials of second line chemotherapy

The basic tenet of a phase 3 trial is that it should compare experimental therapy with the current standard of care

Should the control arm be:

- A. Therapy that has been approved by regulatory bodies such as the FDA? (or minimal treatment if there are no approved therapies)? **or**
- B. Therapy that is most commonly applied in the oncologic community?



Androgen-dependent pathway remains an important target

- Several studies have shown substantial androgen levels within prostatic tissue (including cancer) which can stimulate androgen pathways in the face of very low levels of circulating androgens

Intraprostatic Androgens and Androgen-Regulated Gene Expression Persist after Testosterone Suppression: Therapeutic Implications for Castration-Resistant Prostate Cancer

Elahe A. Mostaghel,^{1,2} Stephanie T. Page,^{2,5} Daniel W. Lin,^{3,5} Ladan Fazli,⁶ Ilsa M. Coleman,¹ Lawrence D. True,⁴ Beatrice Knudsen,¹ David L. Hess,⁷ Colleen C. Nelson,⁶ Alvin M. Matsumoto,^{2,5} William J. Bremner,² Martin E. Gleave,⁶ and Peter S. Nelson¹

¹Fred Hutchinson Cancer Research Center; Departments of ²Medicine, ³Urology, and ⁴Pathology, University of Washington School of Medicine; ⁵Veterans Affairs Puget Sound Health Care System, Seattle, Washington; ⁶Vancouver General Hospital, Vancouver, British Columbia, Canada; and ⁷Oregon National Primate Research Center, Beaverton, Oregon

Abstract

Androgen deprivation therapy (ADT) remains the primary treatment for advanced prostate cancer. The efficacy of ADT has not been rigorously evaluated by demonstrating suppres-

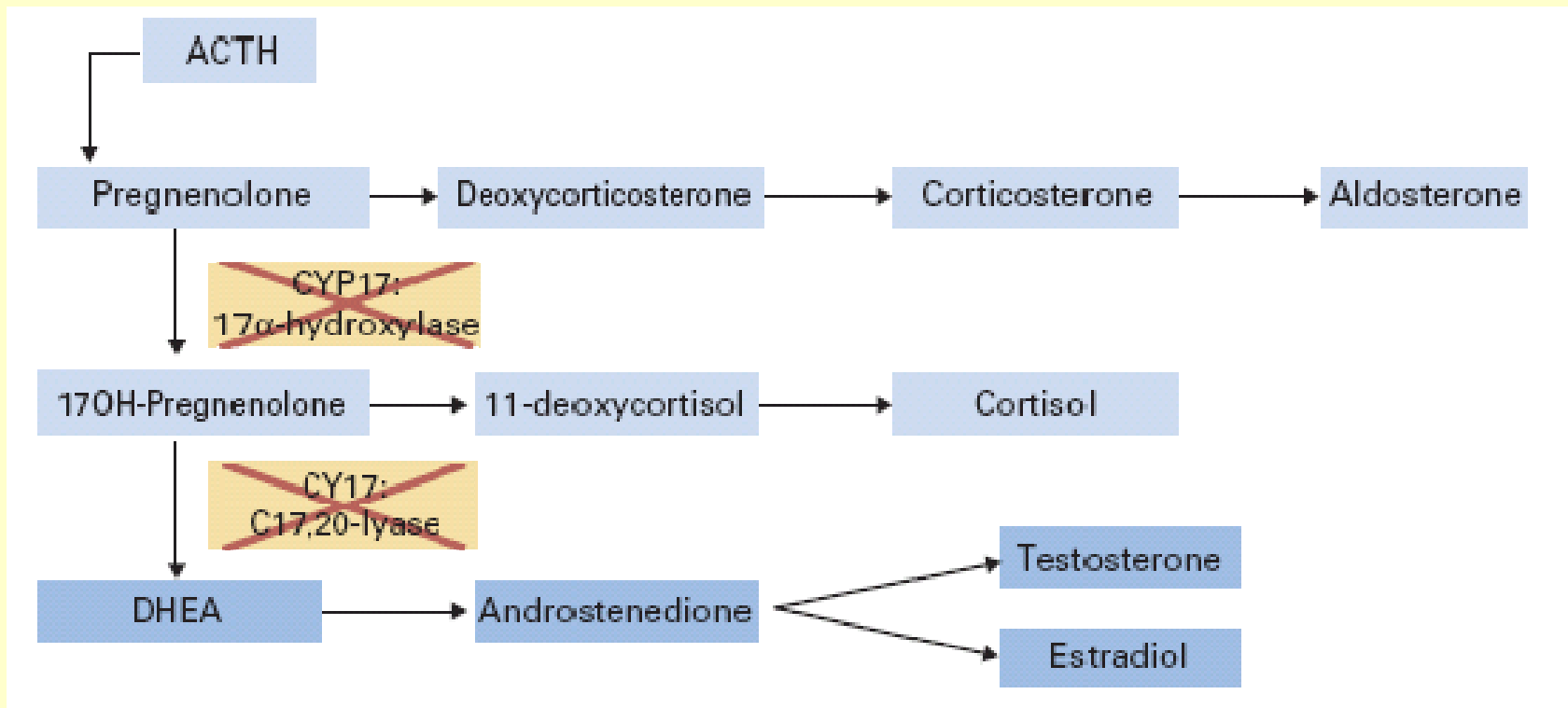
efficacy will require testing of novel approaches targeting complete suppression of systemic and intracrine contributions to the prostatic androgen microenvironment. [Cancer Res 2007;67(10):5033-41]

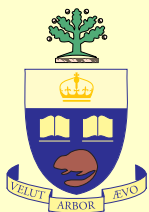




Abiraterone

(e.g. Attard et al, JCO [Oct 1] 2008)





Recent results for abiraterone acetate

De Bono (#5005. ASCO 2008): 72 evaluable pts with castration-resistant prostate cancer

>60% PSA response in chemo-naive pts

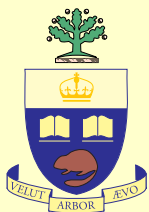
>40% PSA response in taxane-treated pts

Similar results in other trials from:

UCSF, MD Anderson and Memorial (#5017-5019)

A Phase III (2:1) double-blind, placebo-controlled trial (N=1160) of abiraterone plus prednisone has been initiated in patients with metastatic HRPC who have failed docetaxel-based chemotherapy



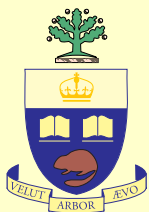


Targeting of receptor tyrosine kinases

- Prostate cancer cells express a variety of growth factor receptors
- Phase 2 trials of gefitinib (targeting erbB1) and of trastuzumab (targeting erbB2) had disappointing results
- Trial of sunitinib underway

As yet, no agent targeting receptor tyrosine kinases has shown promising activity in prostate cancer





Some hot-spots of translational research in prostate cancer

- Circulating Tumour Cells (CTC) as a strong predictor of survival in men with castration-resistant prostate cancer
- Gene expression patterns (e.g. ETS fusion genes) that are associated with disease progression and are potential targets for therapy
- Strategies to restore androgen sensitivity after castration-resistance
- Markers for putative prostate cancer stem cells (CD133+/ α 2 β 1 integrin/CD44+ phenotype)





Acknowledgements

- The many investigators who collaborated in the trials that I have described.
- The patients who participated in the trials and thereby contributed to knowledge about how to best treat this disease.
- The international fellows who stimulate my ideas (but are not responsible for them)





ASCO 2007

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