

Medical Treatments for Prostate Cancer

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A hypothetical patient

- **Mr Scott is a 68 year old man who has a 3-month history of pain in several bones.**
- **On rectal examination his prostate is enlarged and hard**
- **A needle biopsy shows prostate cancer, Gleason grade 8/10.**
- **His bone scan is “positive” and his serum level of PSA is 245.**

Mr Scott's bone scan



**The black spots
are secondary
tumours
(metastases)
from prostate
cancer**

How should Mr Scott be treated?

- **Prostate cancer is stimulated by male hormones (“androgens”), such as testosterone.**
- **Initial treatment therefore aims to remove stimulation by male hormones**
- **About 80% of men will respond to this type of treatment with a reduction of pain and a decrease in serum PSA**

What are the choices of hormonal treatment for Mr Scott?

Options for Hormonal Treatment

- **Orchiectomy**: surgical removal of the testicles – the main source of testosterone
- **Estrogen**: female hormone that suppresses production of male hormones (e.g. DES)
- **LHRH agonist**: cuts off stimulation of testicles to produce testosterone (e.g. goserelin = Zoladex; leuprolide = Lupron)
- **Antiandrogen**: blocks action of male hormones in cells (e.g. bicalutamide = Casodex; cyproterone acetate = Androcur)

Mr Scott's Treatment

- **Mr Scott decides to accept treatment with goserelin (Zoladex), given by 3-monthly depot injection**
- **He is given bicalutamide (Casodex) for the first 10 days to prevent a flare of his disease**
- **He becomes pain free within 2 weeks, and one year later he feels well and his PSA is 0.1**
- **However, he does have one or two side effects of treatment.....**

Side effects of hormonal therapy

- **Impotence**
- **Gynecomastia (increased breast tissue, sometimes with tenderness)**
- **Hot flashes (“male menopause”)**
- **Loss of muscle and bone**
- **Anemia**

Bone loss from hormonal therapy

Several studies provide evidence for loss of Bone Density for patients on hormone therapy

There is also evidence for reduced bone density in men with prostate cancer prior to starting hormonal (anti-androgen) treatment

Baseline bone density in men with prostate cancer

(Hussain et al: BJU Int 2003;92:690-4)

- **174 men with advanced prostate Ca about to start on hormonal treatment. Mean age 75 yrs**
 - 42% were osteoporotic**
- **106 men of similar age without prostate cancer**
 - 27% were osteoporotic**

Role of Bisphosphonate Drugs in Preventing Bone Loss

Several randomised controlled trials have shown that both pamidronate (Aredia) and zoledronate (Zometa) can prevent bone loss associated with hormone treatment for prostate cancer

Bone loss can also be prevented by regular physical activity

Smith et al: J Urol 2003;169:2008-12

**1-year
assessment**



A reasonable treatment for men who cannot exercise and/or with evidence of bone loss

Hormone Resistance

- **15 months after starting hormone therapy, Mr Scott's PSA has increased to 5**
- **At 18 months the PSA is 20**
- **At 21 months the PSA is 50 and he is beginning to have some aching pain.**

What to do?

Secondary hormonal therapy

- **Mr Scott is prescribed the anti-androgen bicalutamide (Casodex) in addition to his goserelin (Zoladex) injections.**
- **His PSA decreases and his pain improves, but about 6 months later he again has a rising PSA and pain.**
- **The bicalutamide is stopped and he again has a transient response for about 3 months**

Secondary hormonal therapy

- **About 80% of men respond to primary hormonal therapy (orchiectomy or LHRH agonist) for a median duration of 1-2 years.**
- **About 20-30% respond to the subsequent addition of an anti-androgen for a few months (Blocks androgens from the adrenal gland).**
- **About 20-30% of those who responded to addition of an anti-androgen will respond to its withdrawal**

(Drugs like Casodex can start to stimulate prostate cancer cells instead of killing them!)

Causes of Hormone Resistance

- **Hormone resistance occurs eventually in all patients**
- **During hormonal therapy there appears to be selection of a prostate cancer cells that are no longer dependent on stimulation by androgens (male hormones) for their growth**

Approaches to avoiding or delaying hormone resistance that have been investigated

- ***Combined androgen blockade***
- ***Intermittent hormone therapy***

Combined Androgen Blockade

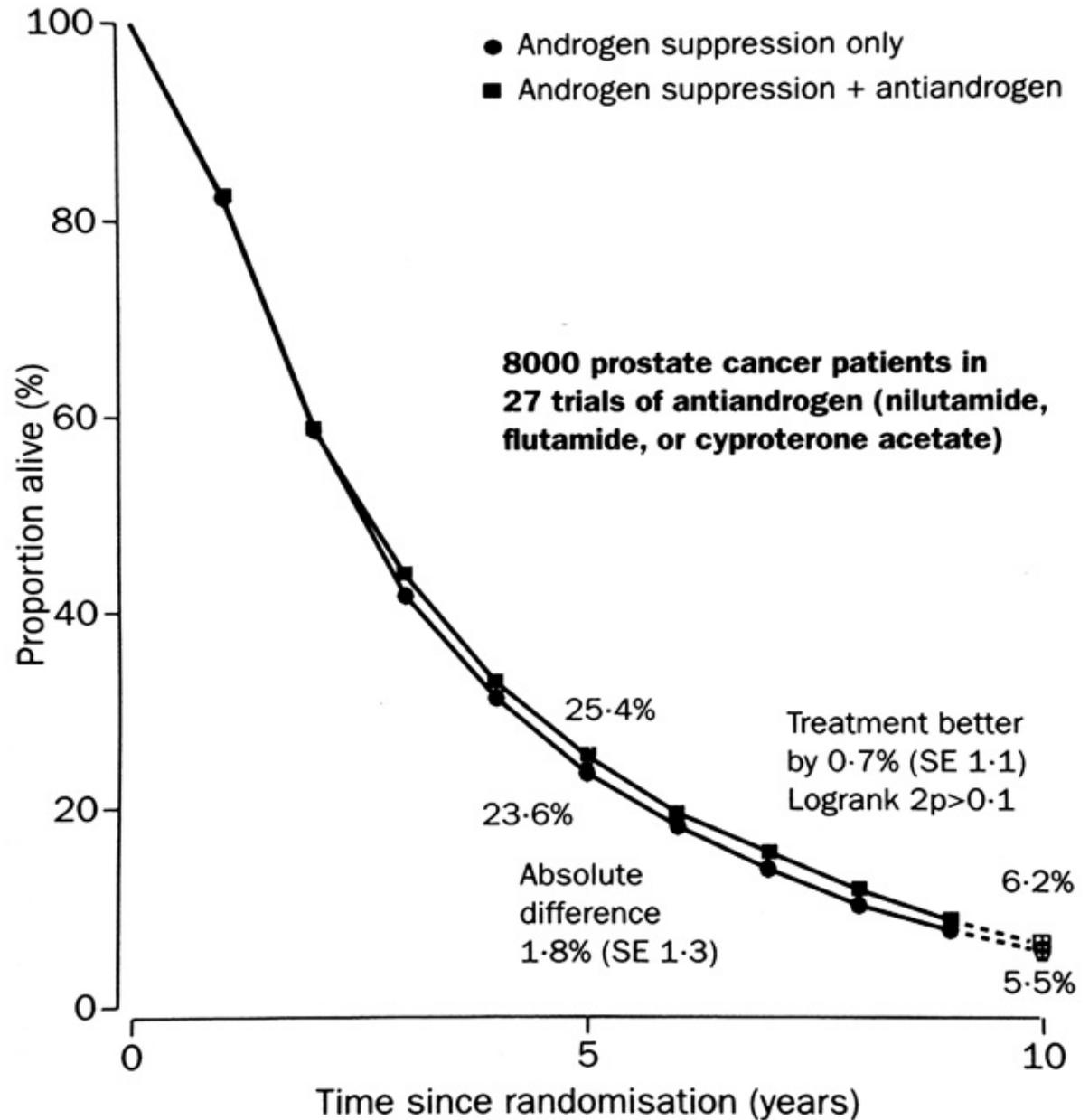
- **Patients are treated with orchiectomy or an LHRH agonist *and* an anti-androgen such as bicalutamide (Casodex).**
- **Almost 30 randomised clinical trials have tested this strategy against use of orchiectomy or an LHRH agonist alone**

An overview of these trials shows little or no benefit from combined androgen blockade.

It is expensive, adds toxicity, and should not be used as initial treatment.

Prostate Cancer Trialists' Collaborative Group

(Lancet 2000;
355:1491-8)



Intermittent hormonal therapy

- **Studies with animal models (conducted in Vancouver) showed delay to hormonal resistance**
- **Intermittent therapy is now being compared to standard therapy in large clinical trials**
- **One small trial is complete (de Leval et al: Clin Prostate Cancer 2002;1:163-71):**
 - N=68pts: 3yr PSA progression:**
 - Intermittent: 7+/-5%**
 - Continuous: 39+/-11%**
- **If effective, this strategy would also have the advantage of lower cost and less side effects**

When are men with prostate cancer truly hormone-resistant?

Even after orchiectomy or treatment with agents like Zoladex and Casodex, and withdrawal of Casodex, some pts may respond to:

- **Steroids like dexamethasone (Decadron) or prednisone**
- **Estrogens (e.g. DES)**
- **Ketoconazole (inhibits synthesis of all steroids, including male hormones, given with hydrocortisone)**

Most responses are transient

Antiandrogen withdrawal alone or with ketoconazole for HRPC

(Small et al: JCO 2004;22: 1025-33)

260 pts:

AAWD alone:

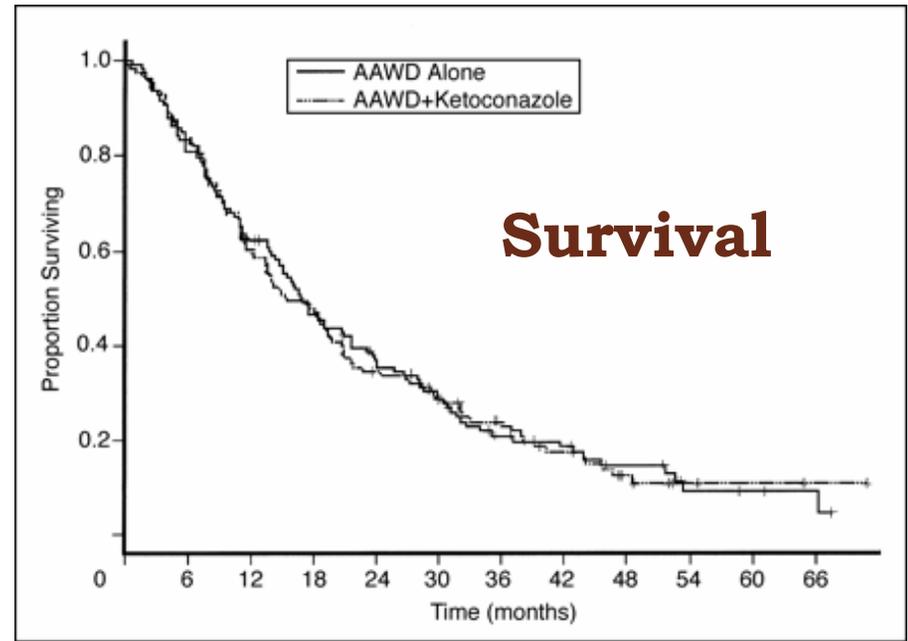
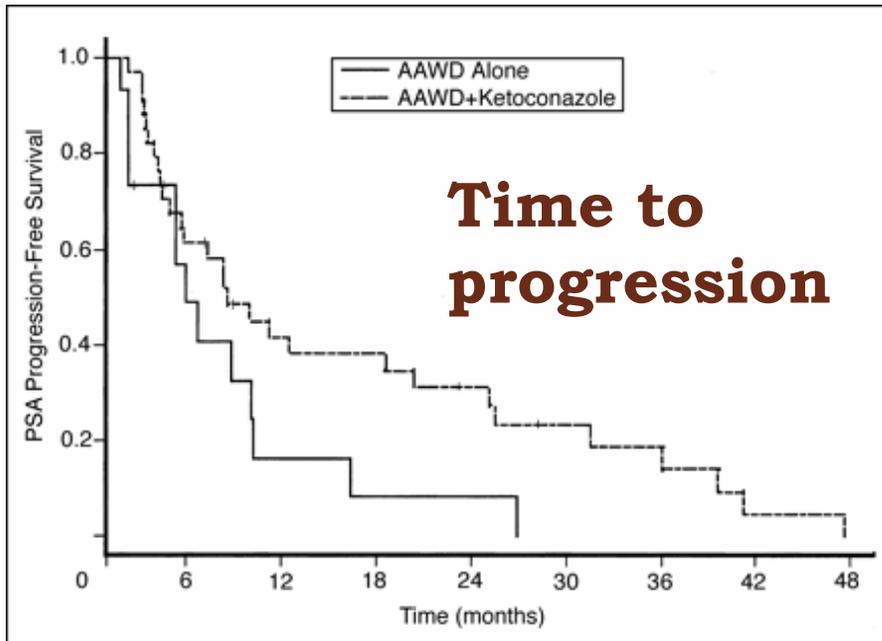
**AAWD + ketconazole
(400MG 3x/day + HC)**

PSA response

11%

27%

p=0.0002



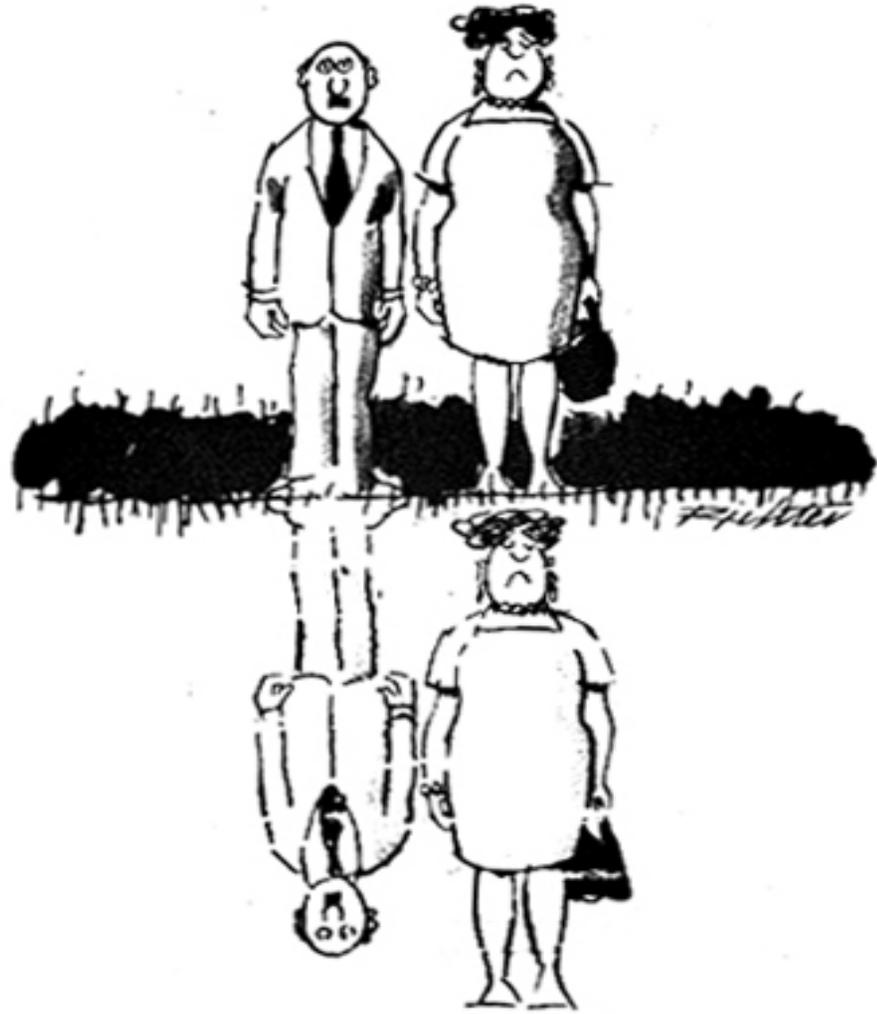
Mr Scott tries ketoconazole and hydrocortisone for 3 months, but his pain gets worse and his PSA level continues to rise

He now has hormone resistant prostate cancer

Mr Scott has severe pain in his right hip. He is fatigued and has several other painful areas.

What treatment should be given?

A pause for reflection...



Principles of Management

- **Optimise Mr Scott's pain control with regular dosing of narcotic medication, such as morphine.**
- **Give regular laxatives to control the constipation that will be caused by morphine**
- **Give local radiotherapy to the right hip, his dominant site of pain**

I feel a bit better, says Mr Scott 4 weeks later, but I still have aching bones, I'm very tired, and my PSA has gone up again (to 150).

Isn't there anything that you can do that would treat my disease?

Treatment of Hormone-resistant Prostate Cancer

Two treatments have been shown (in randomised trials) to relieve pain and improve quality of life:

Strontium-89

Chemotherapy

Strontium-89

- **Strontium-89 is a radioactive isotope that chemically is similar to Calcium.**
- **When strontium is injected, the body is “fooled” into thinking it is calcium. It is concentrated in bone and into the sclerotic (calcified) metastases from prostate cancer.**
- **In bone strontium gives local irradiation to the metastases, leading to cell killing and to improvement in pain.**

Chemotherapy for Prostate Cancer

Principles:

- Patients are often elderly and have other medical problems - **use gentle drugs**
- The aim is to palliate patients - i.e. to relieve their symptoms and improve quality of life.

This should be measured directly

- Doctors are poor judges of patients' quality of life.

This must be assessed by the patients themselves

**Which types of chemotherapy
are appropriate for Mr Scott?**

Misleading information from small clinical trials

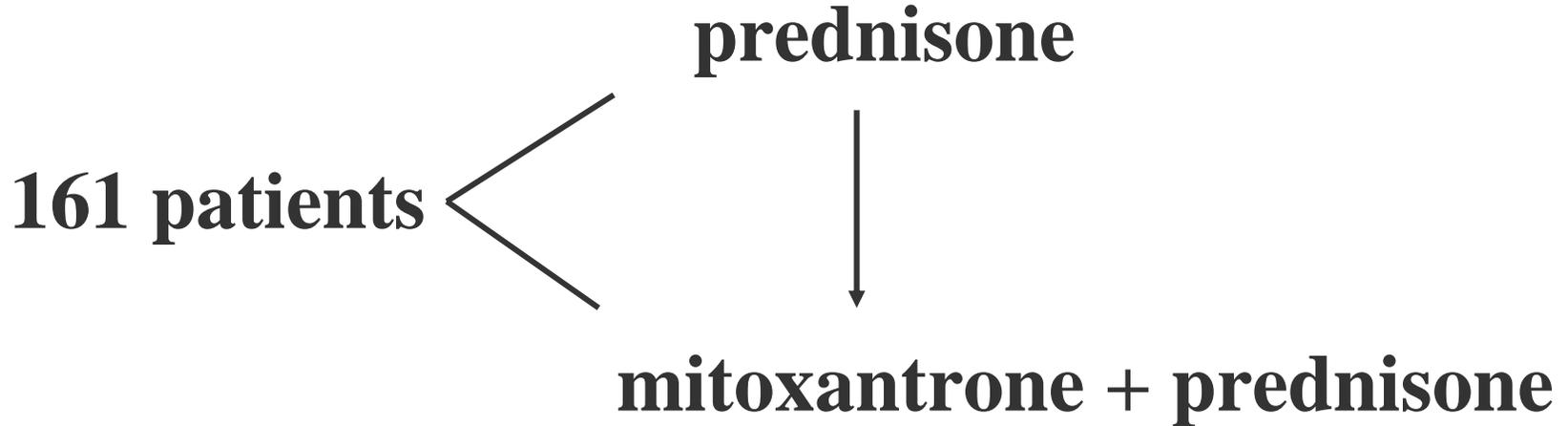
There are many trials where a small number of men are treated with chemotherapy, and which report:

- **A high rate of PSA response**
- **Improvement in pain as judged by doctors.**

These results are not reliable –

Participants are highly selected, and results do not necessarily imply benefit

The First Canadian Randomised Trial



Hypothesis: Chemotherapy will give a higher probability of **palliative response**

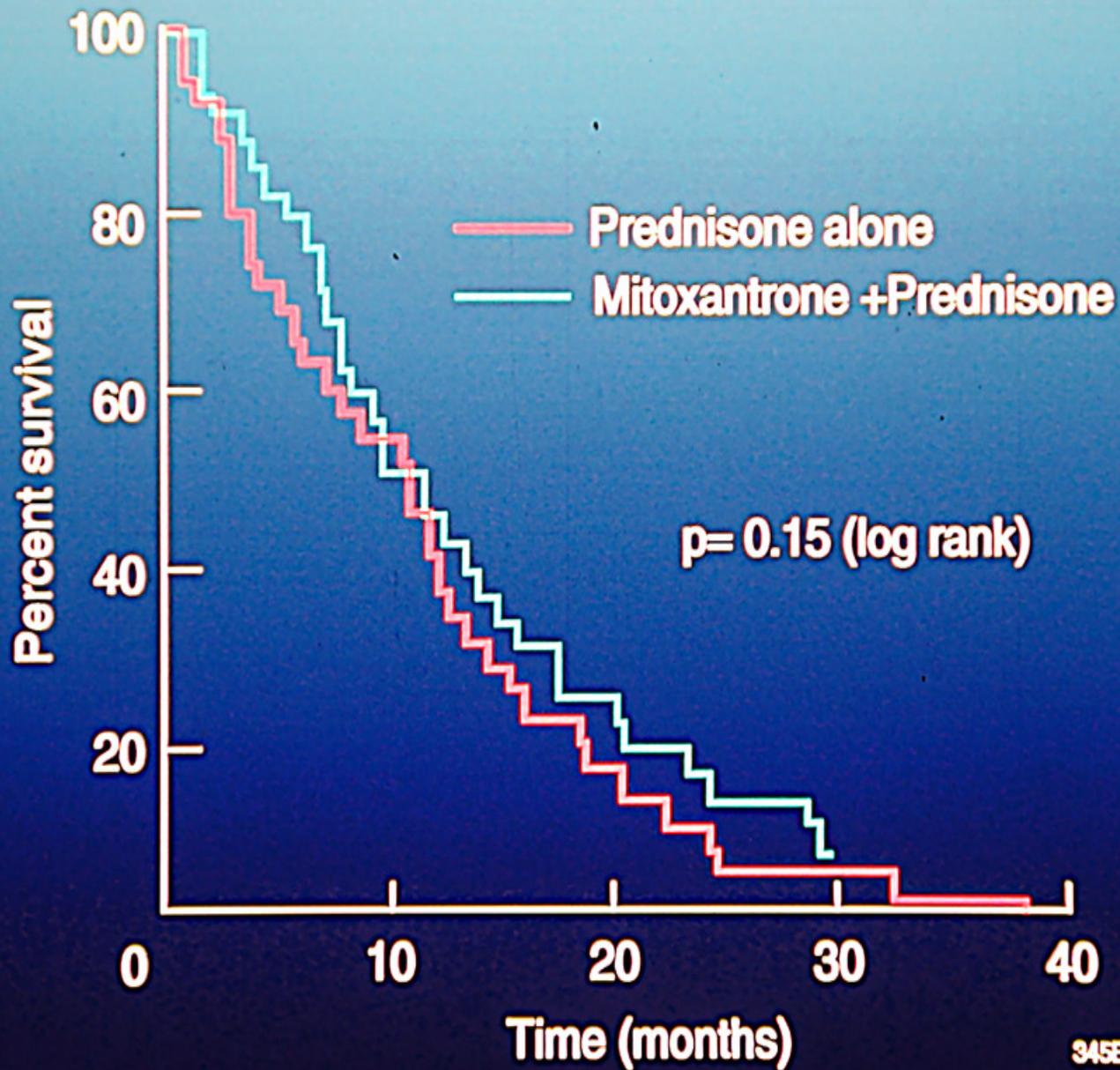
Criteria of Response

Primary:

- **2-point reduction in a 6-point pain scale (completed by the patient) without increase in pain medication**

Secondary:

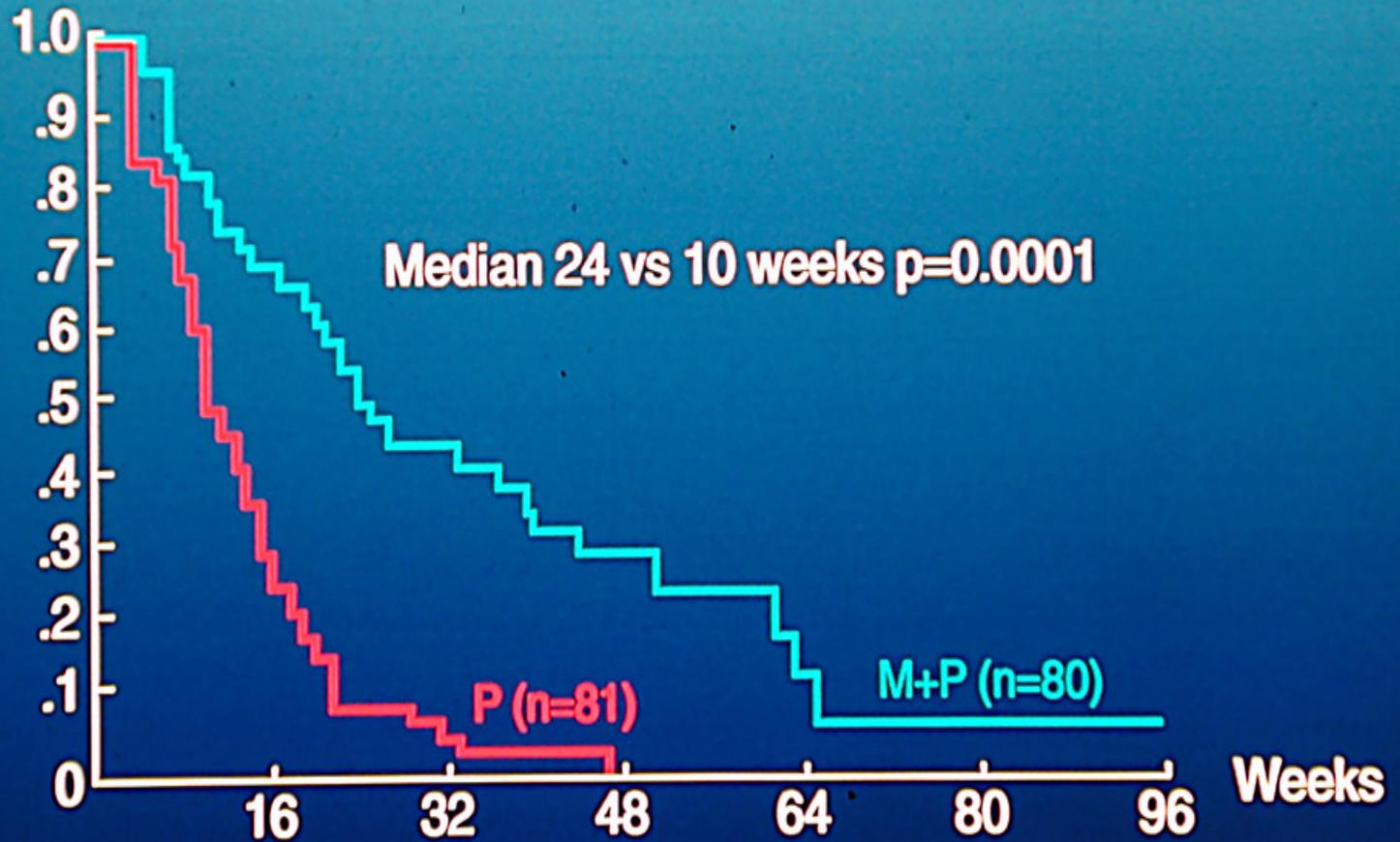
- **50% reduction in need for pain medication without increase in pain**
- **Duration of survival**
- **Quality of life**



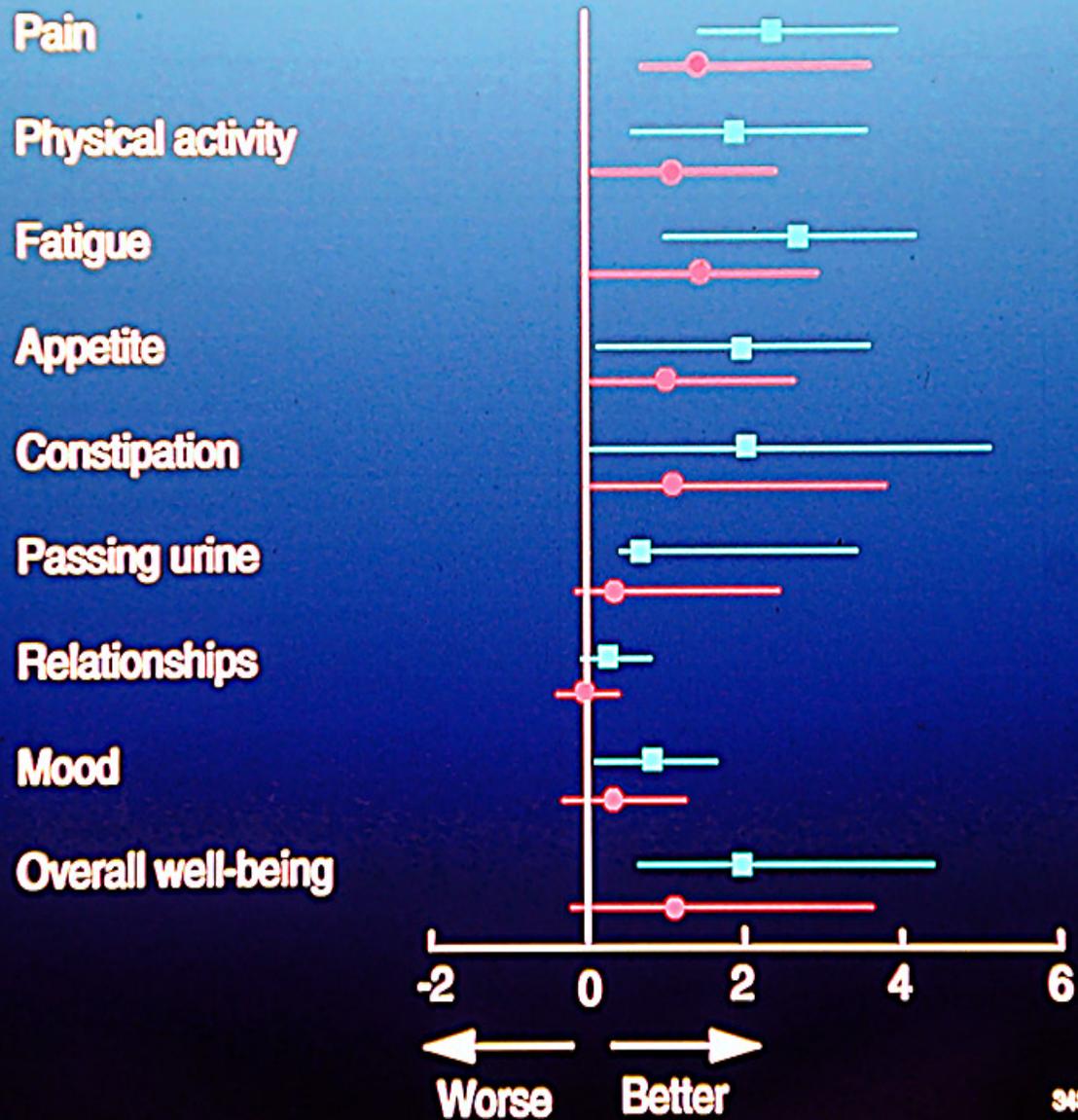
Palliative Response

	Prednisone	Mitoxantrone + prednisone	p
Primary endpoint (↓ pain)	10/81 (12%)	23/80 (29%)	0.01
Total response (↓pain or ↓pain medication)	17/81 (21%)	30/80 (38%)	0.025

Time to Progression (All Patients)



Best and Median Change in LASAs for Respondants



PSA Response

(Reduction \geq 50% lasting for 2 consecutive visits)

	prednisone	mitoxantrone + prednisone	p
Patients with repeated PSA measures	9/58 (16%)	27/68 (40%)	0.006
All patients	9/81 (11%)	27/80 (34%)	0.001

The Canadian Trial established mitoxantrone and prednisone as the standard chemotherapy for men with symptoms from hormone-resistant prostate cancer from 1996 -2004

- **It improves pain dramatically in ~40% and lowers PSA to at least half in about one third of patients.**
- **It is very easy treatment and improves Quality of Life**

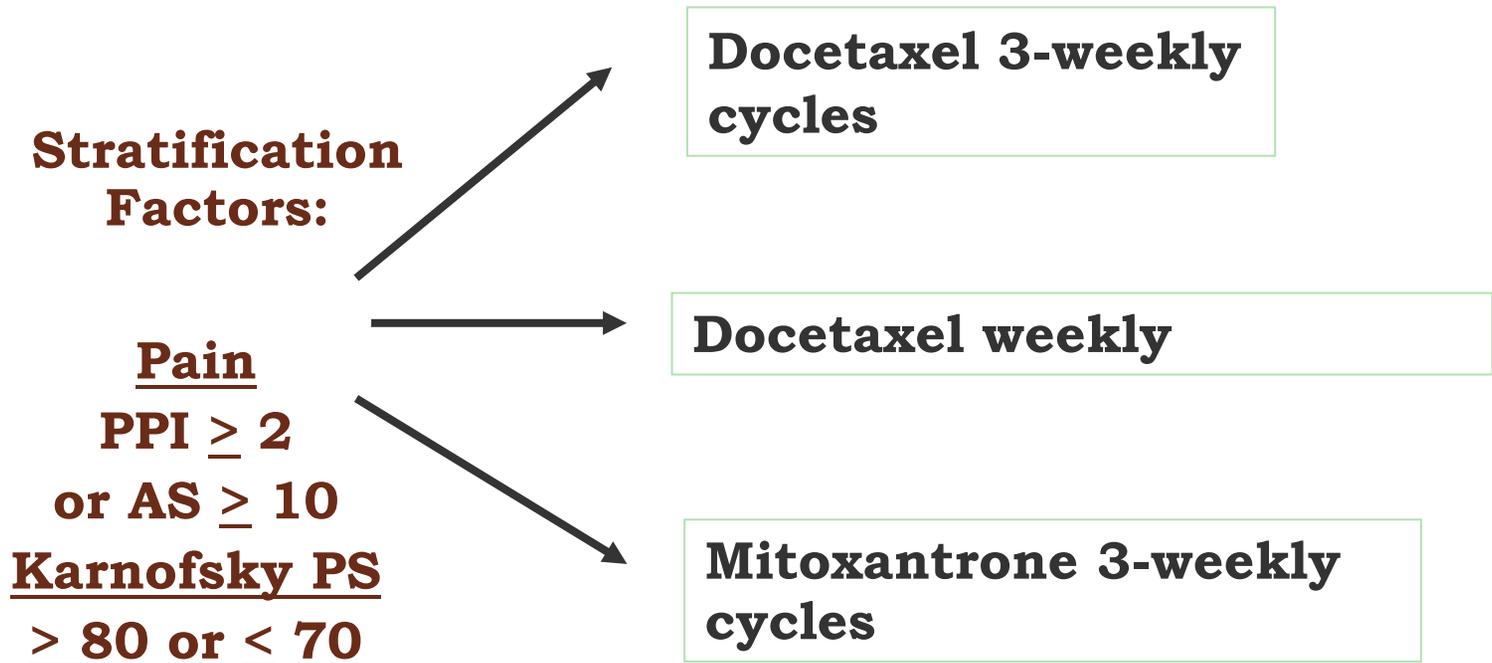
However:

- **It does not appear to prolong life expectancy**

Recent trials using docetaxel (Taxotere) have shown a small improvement in life expectancy

TAX 327 Study

N = 1,006 subjects with androgen-independent HRPC (105 sites, 24 countries) (Tannock et al, NEJM, Oct 2004)



All patients received prednisone 10m/day

TAX 327: Outcomes

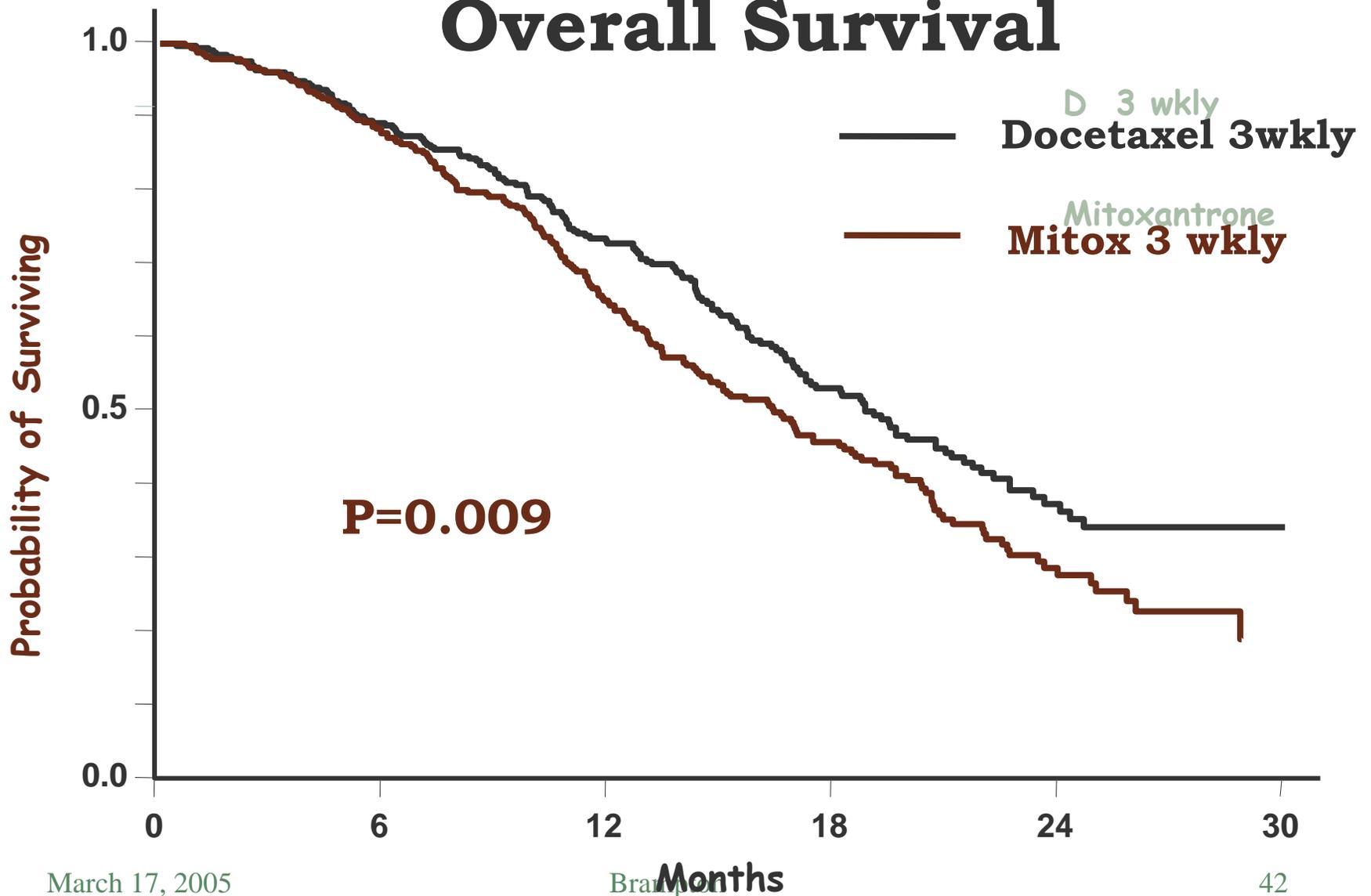
Primary measure:

- **Overall survival (OS)**

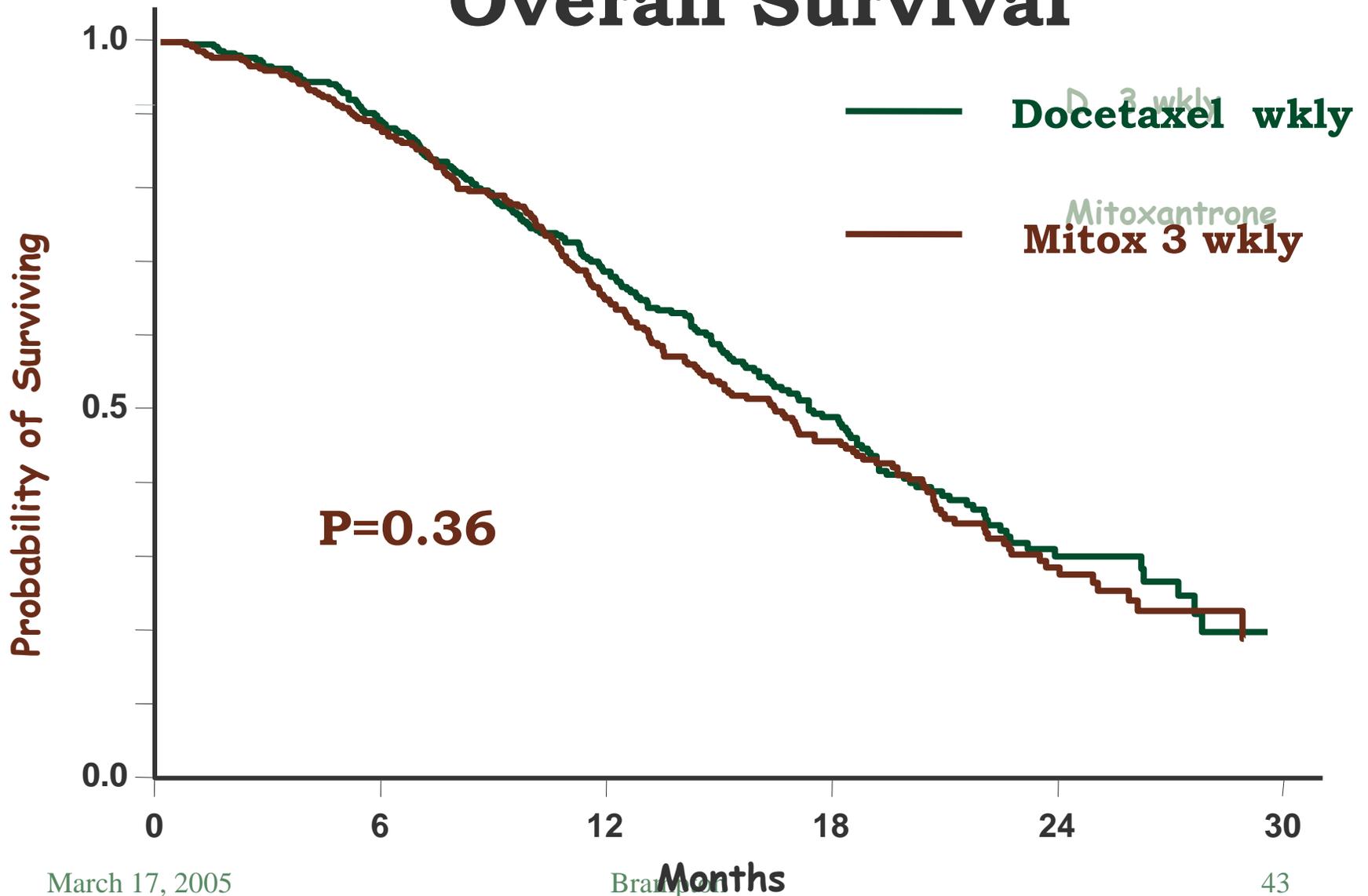
Secondary measures:

- **Pain, PSA and measurable tumour response rate & duration**
- **PSA-, pain-, tumour- and disease-progression free survival**
- **Quality of Life**
- **Safety**

Overall Survival



Overall Survival



TAX 327: Secondary Measures

	Docetaxel 3-weekly	Docetaxel weekly	Mitoxantrone 3- weekly
Pain Response	35% P=0.01	31% NS	22%
PSA Response	45% P=0.0005	48% p<0.0001	32%
Tumour Response	12% NS	8% NS	7%

NS =Not Significantly different from mitoxantrone

Toxicity in TAX 327

- **Toxicity is annoying rather than life-threatening – 3 probable drug-related deaths in 1004 pts**
- **More toxicity with docetaxel:**
Fatigue, numbness and tingling, diarrhea, hair loss, nail changes, swelling, taste changes, tearing, inflammation in the mouth
- **Infections were rare, mild and easily managed**
- **More heart toxicity with mitoxantrone, but rare**

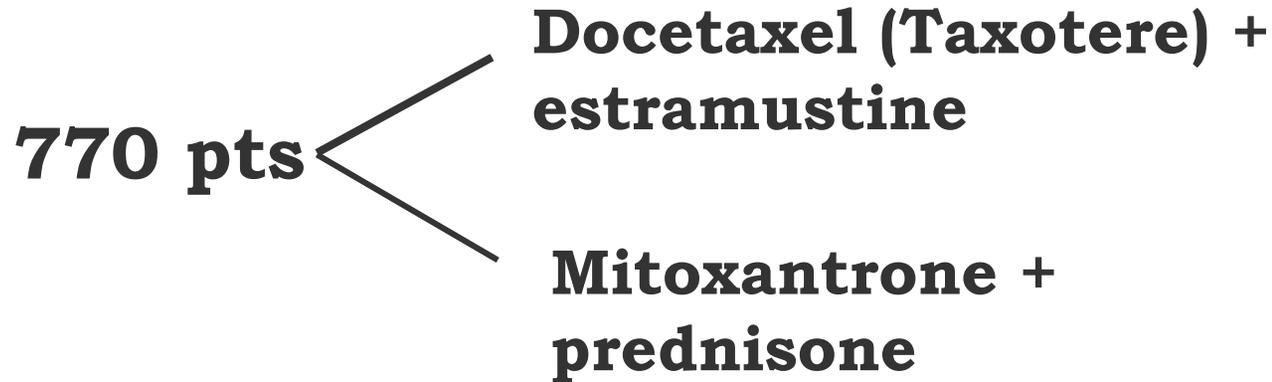
TAX-327: Quality of Life

	Docetaxel 3-weekly	Docetaxel weekly	Mitoxantrone 3- weekly
Number evaluable	278	270	267
Response Rate	22%	23%	13%
P-value	0.009	0.005	

Most improvement in prostate cancer items

SWOG 9916 Study

(Petrylak et al: NEJM, Oct 2004)

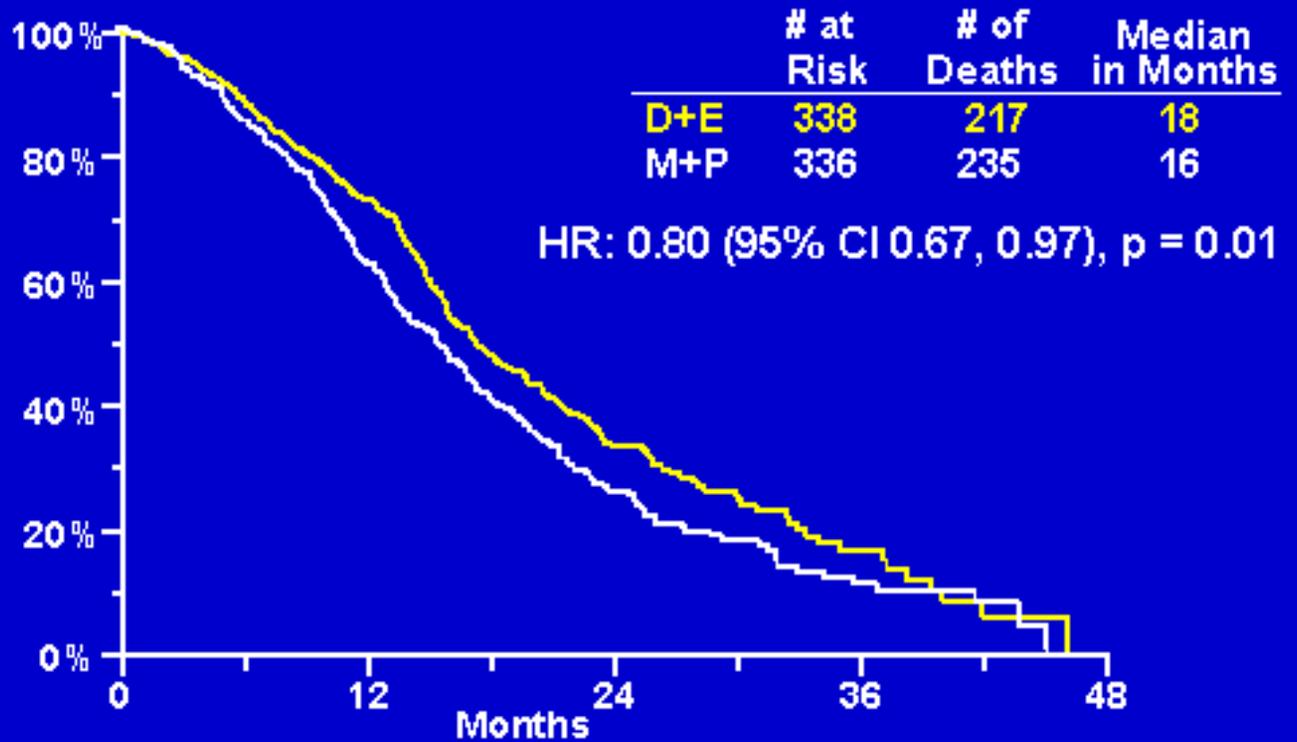


Study shows:

- 1. Small difference in survival in favour of docetaxel arm**
- 2. Greater toxicity with estramustine – this drug appears to add only toxicity as compared to prednisone**

SWOG 9916

Overall Survival



TAX-327 and SWOG 9916 Conclusions

- **The studies confirm the palliative benefit of Mitoxantrone + Prednisone - this remains appropriate initial treatment for men at risk of side effects of Docetaxel or who have slowly-progressive disease**
- **Estramustine adds only toxicity and should not be used**
- **On the basis of its survival advantage, Docetaxel + Prednisone is appropriate treatment for many men – especially if disease is progressing rapidly**

Mr Scott is treated with mitoxantrone every three weeks and low-dose prednisone.

He has relief of his pain and by the third course of treatment he is able to stop taking morphine, and his energy is better.

His PSA declines steadily from 150 to 25 with the first 6 courses of treatment, but then begins to rise again to 70 after 8 courses. He remains well.

His mitoxantrone is stopped because of this progression and to avoid side effects on the heart.

Three months after stopping chemotherapy with mitoxantrone, Mr Scott is beginning to experience new pain in several areas and is back on morphine.

His PSA is fairly stable in the range of 60-80.

Does this mean that his pain is due to causes other than progression of his disease?

Tumour Progression

No.

Just as hormone resistance may develop through selection of prostate cancer cells that are no longer dependent on male hormones -

Less commonly, there can be selection of prostate cancer cells that stop producing PSA, so that it is no longer a good marker of tumour volume

Mr Scott has treatment with docetaxel (Taxotere).

He improves for about 4 months but then experiences numbness and tingling in his hands and feet.

He starts to have pain again and is tired.

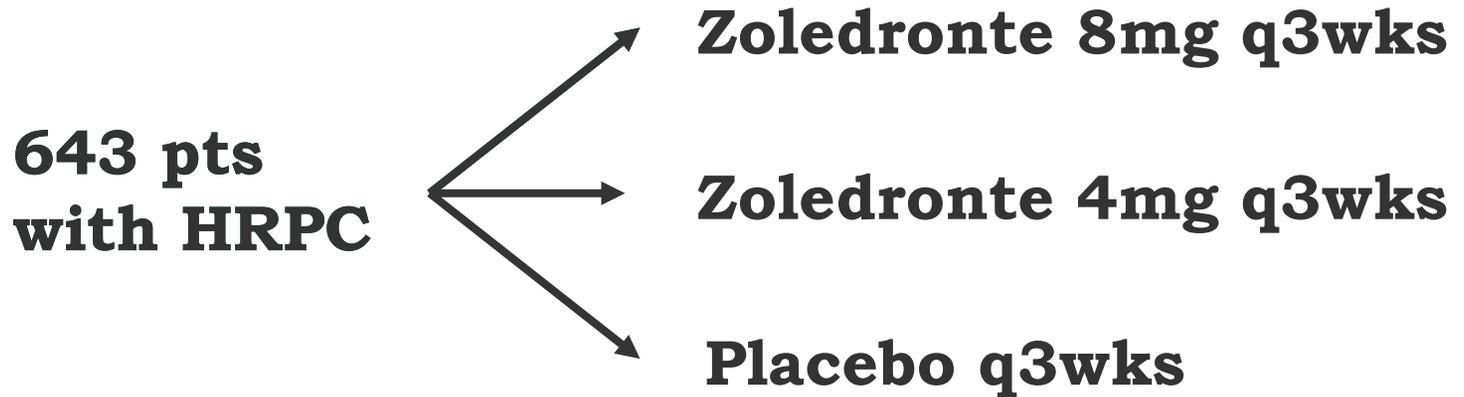
His treatment is stopped, and he accepts that treatment will now be designed to minimise his symptoms.

Should Mr Scott have also received a bisphosphonate drug like clodronate or zaledronate (Zometa)?

- These drugs decrease bone turnover and improve bone pain **in women with breast cancer.**
- In a Canadian randomised trial 204 men with prostate cancer received mitoxantrone and prednisone with or without clodronate - there was no difference in pain control
- In another large trial men received Zometa or placebo **every 3 weeks**

Zoledronate Study

(Saad et al, JNCI 2002;94:1458-68 and 2004;96:879-82)



1. 8mg dose caused kidney problems and dropped
2. Less bone events with 4mg dose (44%) compared to placebo (33%) but no difference in pain or Quality of Life
3. More low-grade toxicity with zoledronate

Why was this expensive drug used every 3 weeks when 3 months is enough to prevent bone loss?

On his next visit to clinic, Mr Scott is clearly failing, but his wife brings a newspaper clipping about new biological treatments for prostate cancer.

Couldn't these treatments be used to save my husband's life, she asks?

New therapies under investigation

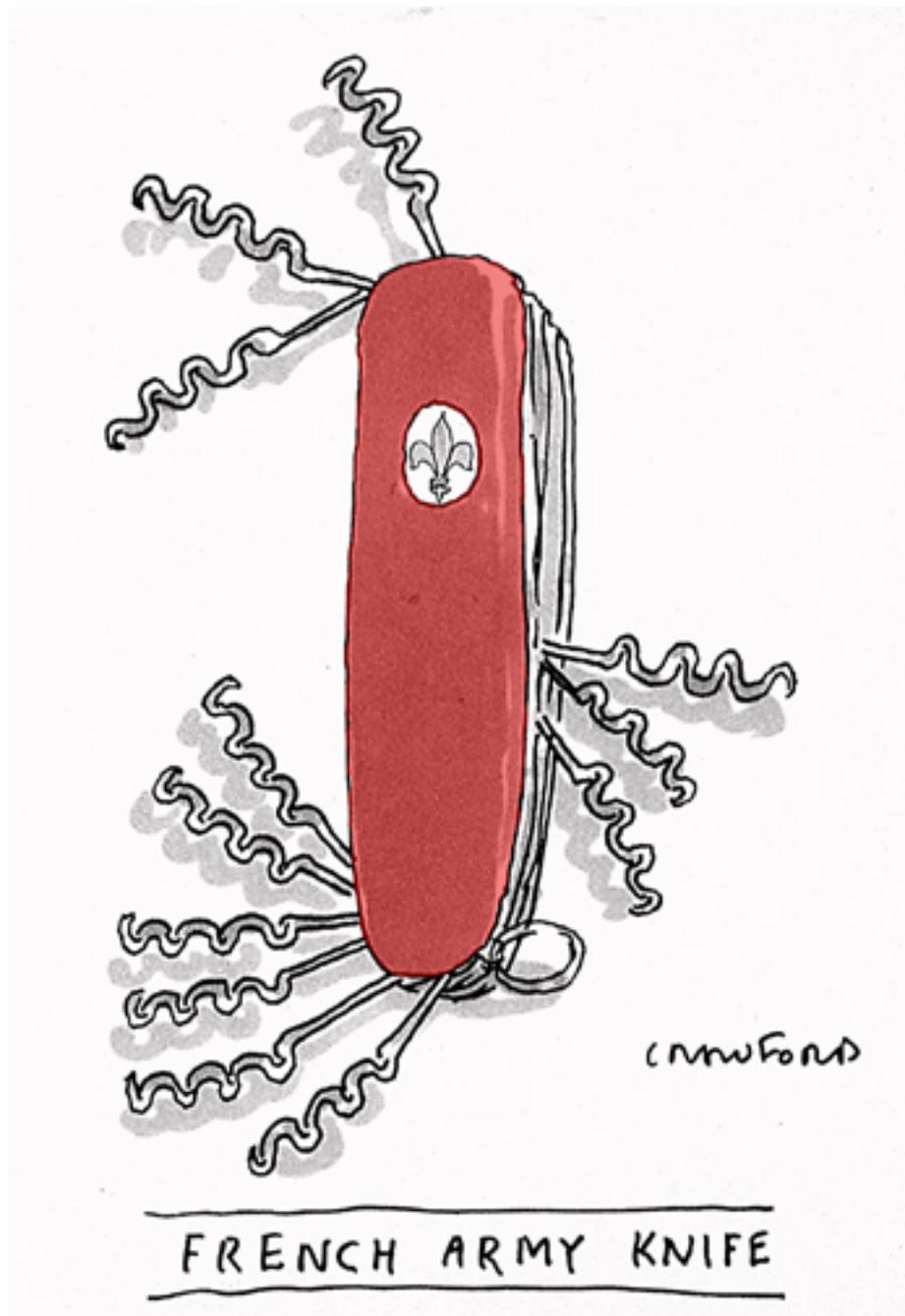
- **Inhibition of growth factors (or signalling pathways inside cells)that stimulate growth of cancer cells**
 - **Stimulation of processes that can make cancer cells more likely to die**
 - **Inhibition of formation of blood vessels (anti-angiogenesis) needed for the cancer to grow**
 - **Immunological approaches**
- etc**

A word of caution

- **Although they provide hope for more specific cancer treatment, thus far biological agents have not caused dramatic improvements in men with prostate cancer.**
- **These new treatments often have toxicity.**
- **There is little evidence to support lack of immunity as a reason for cancers to occur or to grow.**

**A reminder of
my Sabbatical
in France...**

**...that
improved my
Quality of Life**



March 17, 2005