Advances in systemic therapy for prostate cancer

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Princess Margaret Hospital and University of Toronto

5th Turkish Oncology Congress,
Antalya

Potential conflicts of interest

I have advised multiple companies about design of trials for prostate cancer for which I have received contributions to my research fund.

I have chaired international company-sponsored trials for hormone-refractory prostate cancer (TAX-327, VENICE)

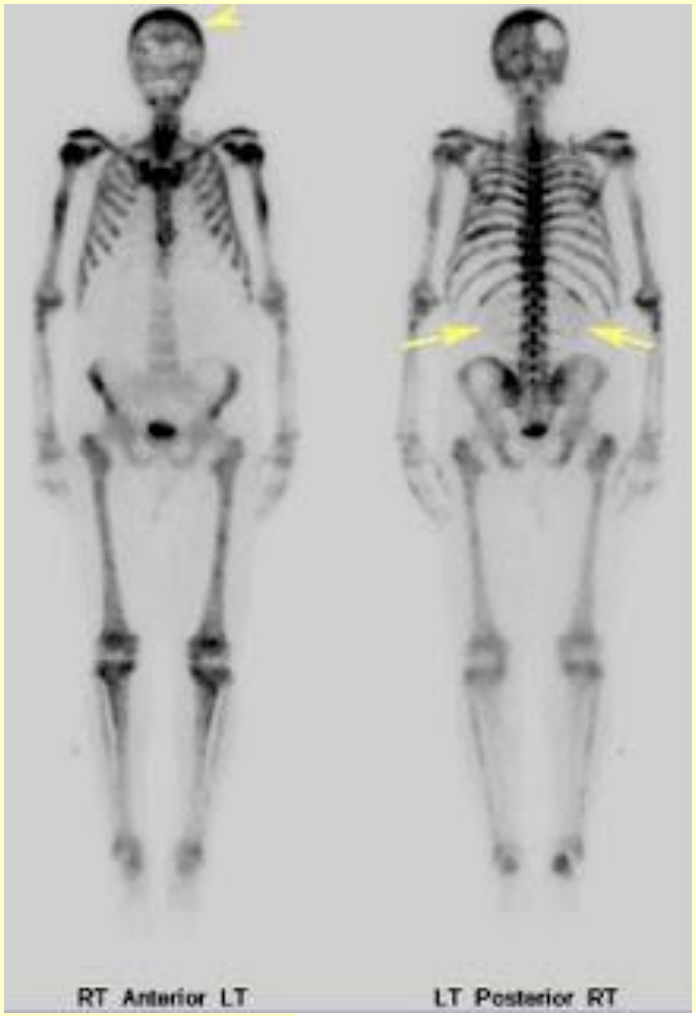
I do not accept personal remuneration from companies

Outline of Presentation

1. Advances in hormonal (androgen-deprivation) therapy (ADT)
   - Intermittent therapy
   - Toxicity of ADT
   - New hormonal agents
2. Advances in chemotherapy
   - Trials of docetaxel + other agents
   - Post-docetaxel
3. Bone-directed therapy
4. Immunotherapy
5. Personalized medicine?

A hypothetical patient

- **Mr Kemal:** 67 y.o. man with 3-month history of pain in several bones
- On rectal exam prostate is enlarged and hard
- Needle biopsy → prostate cancer, Gleason 8
- Bone scan is “positive” and serum PSA = 245ng/ml



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How should Mr Kemal be treated?

Which option for initial hormonal therapy would you recommend?

A. **Orchiectomy**

B. **LHRH agonist (e.g. goserelin; leuprolide)**

C. **LHRH antagonist (e.g.degarelix)**

D. **Anti-androgen alone (e.g. bicalutamide)**

E. **Maximum androgen blockade (LHRH agonist + anti-androgen)**

F. **Intermittent hormonal therapy**

Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials

*Prostate Cancer Trialists' Collaborative Group**

Lancet 2000; **355:** 1491–98

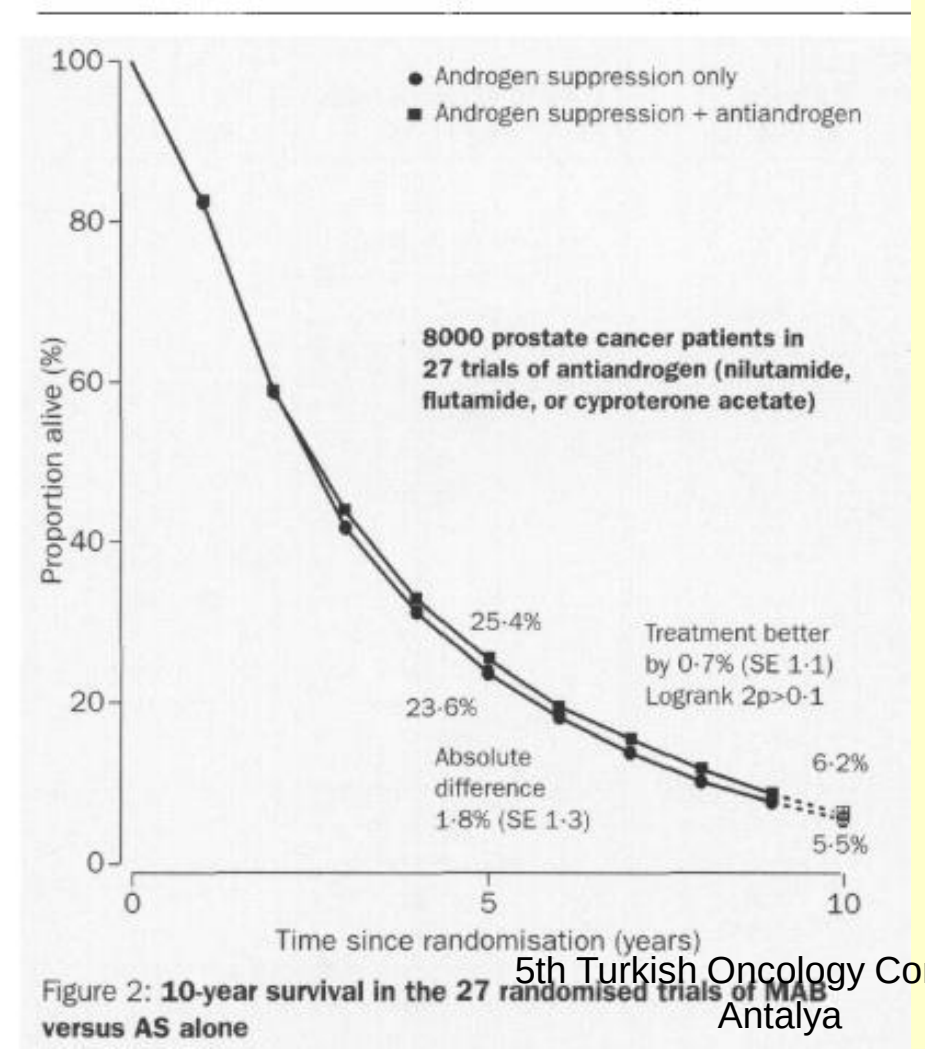


Figure 2: **10-year survival in the 27 randomised trials of MAB versus AS alone**

The patient-based meta-analysis showed no significant benefit of MAB after 8000+ patients and 27 trials

MAB is expensive, has increased toxicity and should not be used

Studies in animals show that intermittent ADT delays time to castrate-resistance

Is this a good treatment for Mr Kemal?

Intermittent versus Continuous Androgen Deprivation in Prostate Cancer

Maha Hussain, M.D., Catherine M. Tangen, Dr.P.H., Donna L. Berry, Ph.D., R.N.,

N Engl J Med 2013;368:1314-25.

This study failed to prove non-inferiority of intermittent ADT - but was initially misreported at ASCO to show that Intermittent ADT was inferior to continuous therapy

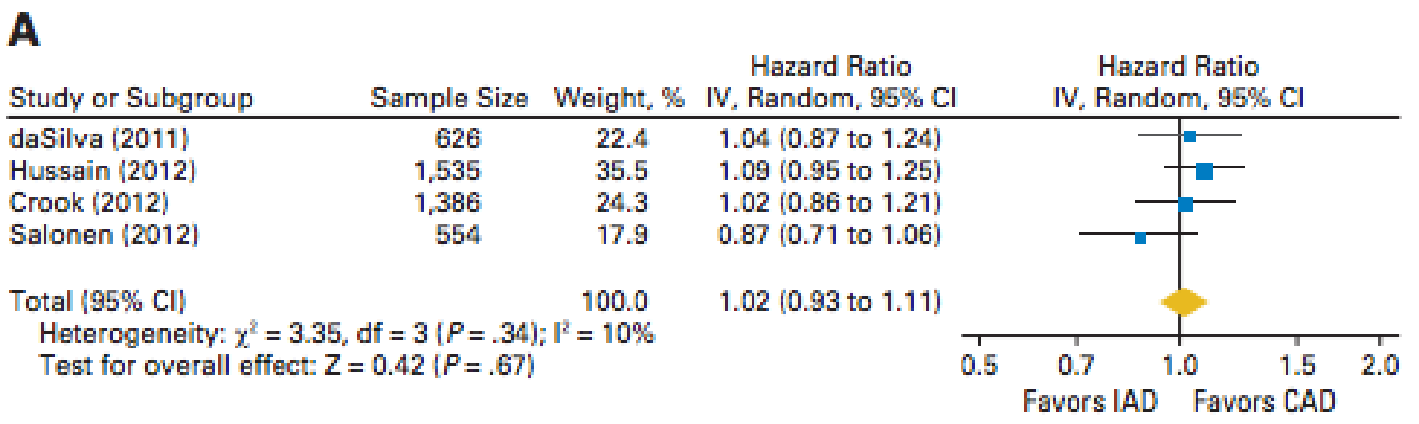
So, we performed a meta-analysis of all the randomized trials

Treatment of Prostate Cancer With Intermittent Versus Continuous Androgen Deprivation: A Systematic Review of Randomized Trials

J Clin Oncol 31:2029-2036. © 2013

Saroj Niraula, Lisa W. Le, and Ian F. Tannock

- **9 RCTs of intermittent (IAD) vs continuous androgen deprivation (CAD) (N=5508)**
- **Pooled HR for OS=1.02 (95% CI=0.94-1.11) for IAD compared to CAD**



- **Pooled HR for PFS=0.96 (95% CI=0.76-1.20)**
- **Better sexual function, hot flushes and general well-being was observed in some trials with IAD**
- **Median cost savings for eligible patients ≈ 48%.**

Should Mr Kemal have received an LHRH antagonist instead of an agonist?

Tombal et al: Degarelix versus luteinising hormone-releasing hormone (LHRH) agonists: Safety outcomes from six comparative randomised clinical trials. ECCO, Amsterdam, 2013

Conclusions (N= 2328 men)

During 1st year of treatment, those treated with degarelix had:

↓urinary tract symptoms

↓fractures

↓CV events

Disadvantage: Requirement for monthly injections

Summary-1 Primary ADT for men with advanced prostate cancer

- Orchiectomy or continuous LHRH agonist has been standard (Short course anti-androgen used to prevent flare)
- Combined androgen blockade should not be used
- Evidence to support intermittent ADT if good initial PSA response
- LHRH antagonists might provide treatment with less toxicity, and avoid need for prevention of flare
- At progression ~30% will have brief response to an anti-androgen (e.g. bicalutamide)
- ~20% of those who respond may respond to anti-androgen withdrawal

Mr Kemal's Treatment

He receives an LHRH agonist with short term bicalutamide to prevent flare

He becomes pain free within 2 weeks, and PSA declines

But he has some side effects.....

Which of these → is NOT a known side effect of hormonal therapy?

A. Impotence
B. Gynecomastia
C. Hot flashes
D. Loss of muscle and bone
E. Anemia
F. Thrombocytopenia
G. Increased risk of cardiovascular events

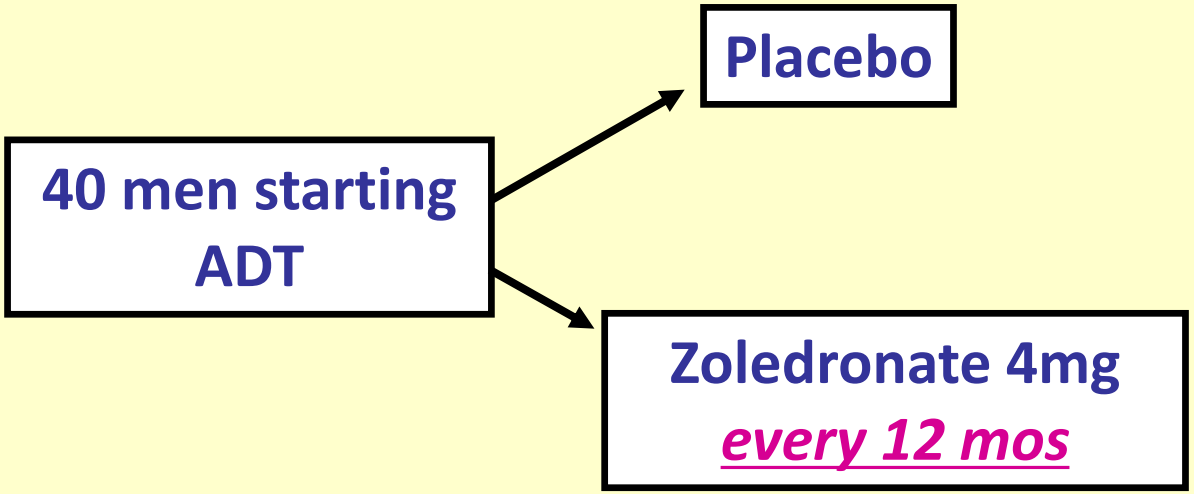
Prevention of Bone Loss

Exercise is probably best protection against loss of bone and muscle

All men receiving ADT should take vitamin D

RCTs have shown that bisphosphonates can prevent bone loss

e.g. **Michaelson et al: JCO 2007;25:1038-42**



3.1% decrease in bone density

4.0% increase

ADT raises insulin levels and may increase diabetes and cardiovascular disease

>73,000 men age>65 treated for localized Ca prostate 1992-1999, observed through 2001 >1 in 3 received ADT

(Keating et al, J Clin Oncol 2006;24:4448-56)

Events per 1000 person-years	Diabetes	CHF	MI	Sudden death
No treatment	20.9	61.3	10.9	9.0
LHRH agonist	29.0	72.3	13.6	12.9
Orchiectomy	24.5	63.3	13.2	12.5

Other health outcome studies have confirmed these effects

Summary-2: ADT can cause:

- Impotence, gynecomastia and hot flushes:
  Progestins can relieve hot flushes
- Anemia & loss of muscle → fatigue and ↓QoL: Encourage exercise
- Bone loss & ↑fractures. Men should have baseline bone density & take Ca^{++} and vit D: Bisphosphonates for those with bone loss
- Metabolic syndrome and ↑cardiac events.
  Use cautiously in men with pre-existing risk factors

Less is better! Avoid ADT in men with slowly rising PSA before or after local treatment.
Use intermittent ADT where feasible

Castration-resistance

Mr Kemal responds to leuprolide for 18 months, but then has ↑pain and ↑PSA. He has a further response to bicalutamide for 6 months, but then again has ↑pain and ↑PSA.

He might still respond to:

Other anti-androgens (e.g. nilutamide, flutamide)

Inhibitors of steroid synthesis (e.g. ketoconazole)

Estrogens (e.g. DES) or Glucocorticoids (e.g. Dexamethasone)

New agents: Abiraterone Acetate and Enzalutamide

"Castration-resistance" is more appropriate than "Hormone-refractory"

↑androgen levels *within* prostatic tissue can stimulate androgen pathways despite low circulating androgens

Abiraterone Acetate is a CYP 17 inhibitor and inhibits androgen synthesis at 2 steps.

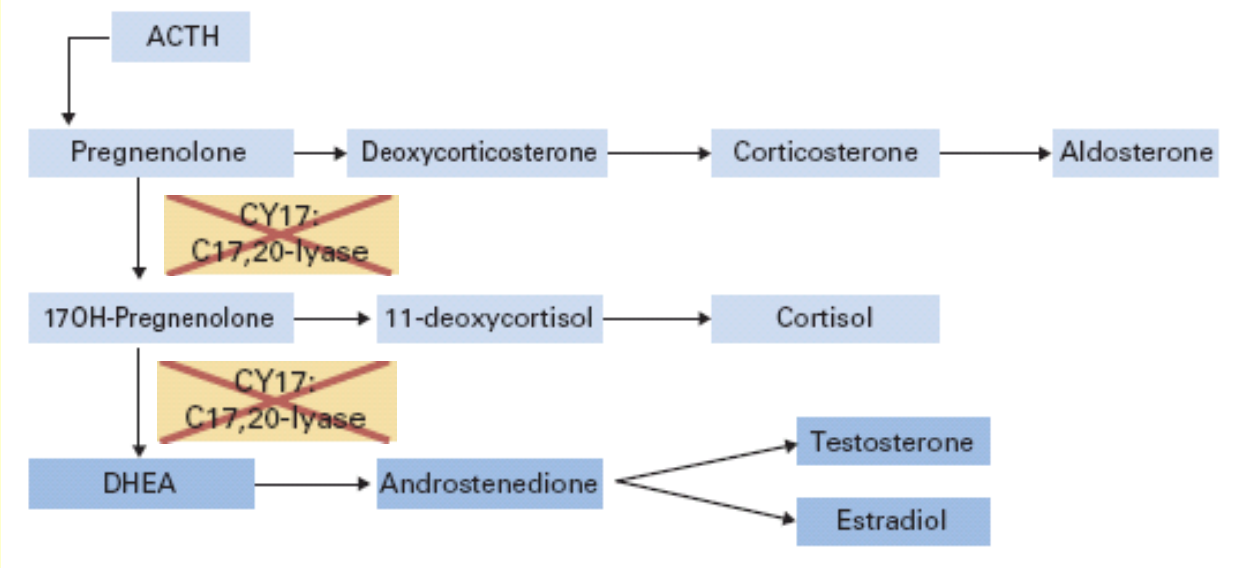
Enzalutamide (MDV 3100) is a potent and irreversible inhibitor of the androgen receptor.

These agents are active against CRPC because it remains (often) dependent on androgen stimulation. Androgens can be produced in prostatic tissue even when serum levels are undetectable

Both abiraterone and enzalutamide were registered based on RCTs showing improved survival in men who had progressed after chemotherapy, but recent RCTs show a marked effect to delay progression (and probably to improve survival) when given pre-chemotherapy

Abiraterone acetate:

Attard et al, JCO 2008 ;26: 4563;
de Bono et al, ESMO 2010



ESMO congress Milan 2010

COU-AA-301 Study Design

Patients
- 1195 patients with progressive, mCRPC
- Failed 1 or 2 chemotherapy regimens, one of which contained docetaxel

→ RANDOMIZED 2:1 →

Abiraterone 1000 mg daily
Prednisone 5 mg BID
N=797

Placebo daily
Prednisone 5 mg BID
n=398

→ **Efficacy endpoints (ITT)**

Primary end point:
- OS (25% improvement; HR 0.8)

Secondary end points (ITT):
- TTPP
- rPFS
- PSA response

Enzalutamide (MDV3100)

(Tran et al: Science 2010;324:787-90)

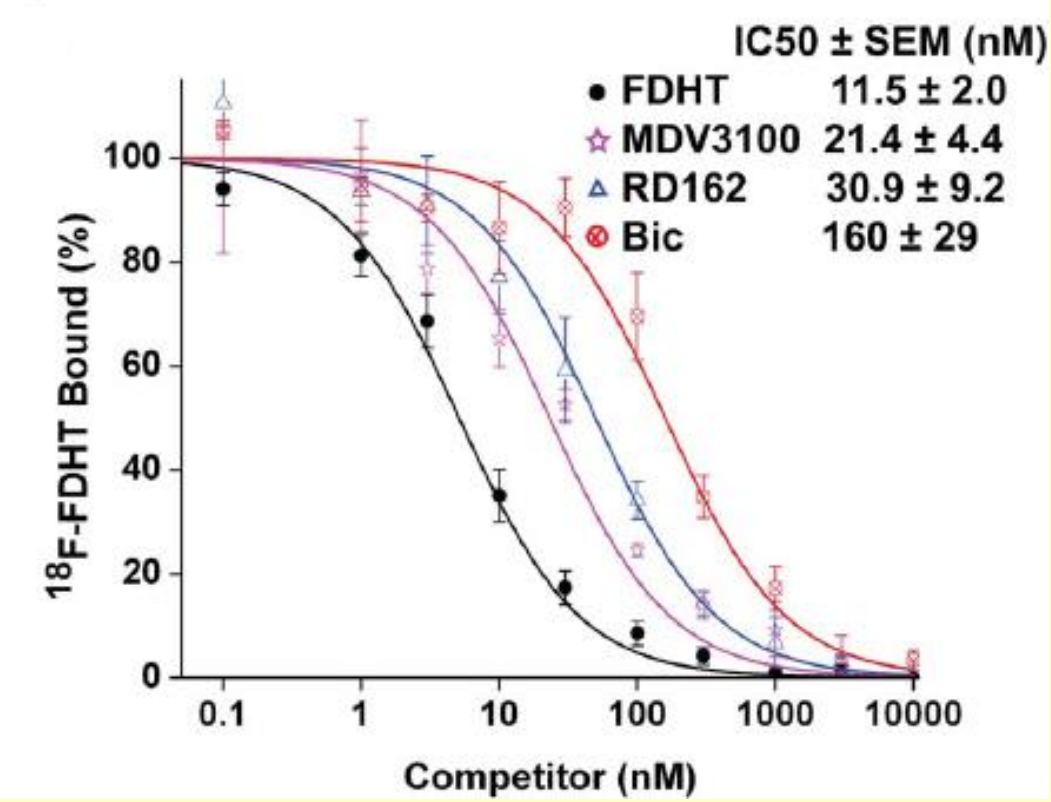
Derived from screen of anti-androgens that retain activity with ↑expression of the AR

↑ binding affinity to AR

↓ nuclear translocation of AR

↓ binding of DNA to androgen response elements

↓ recruitment of co-activators



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Abiraterone and Increased Survival in Metastatic Prostate Cancer

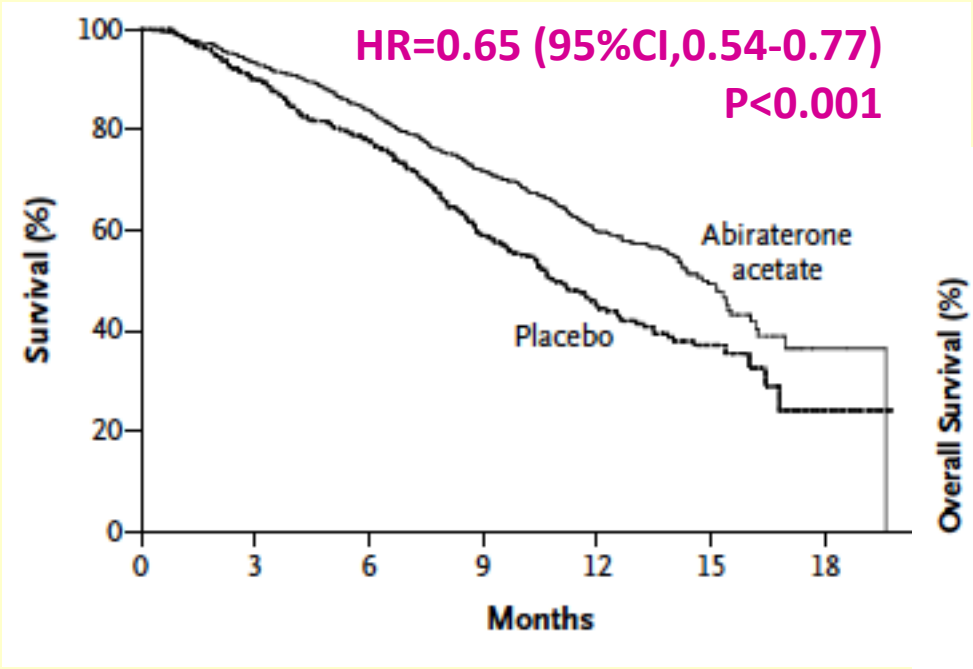
Johann S. de Bono, M.B., Ch.B., Ph.D., Christopher J. Logothetis, M.D., Arturo Molina, M.D., Karim Fizazi, M.D., Ph.D.,

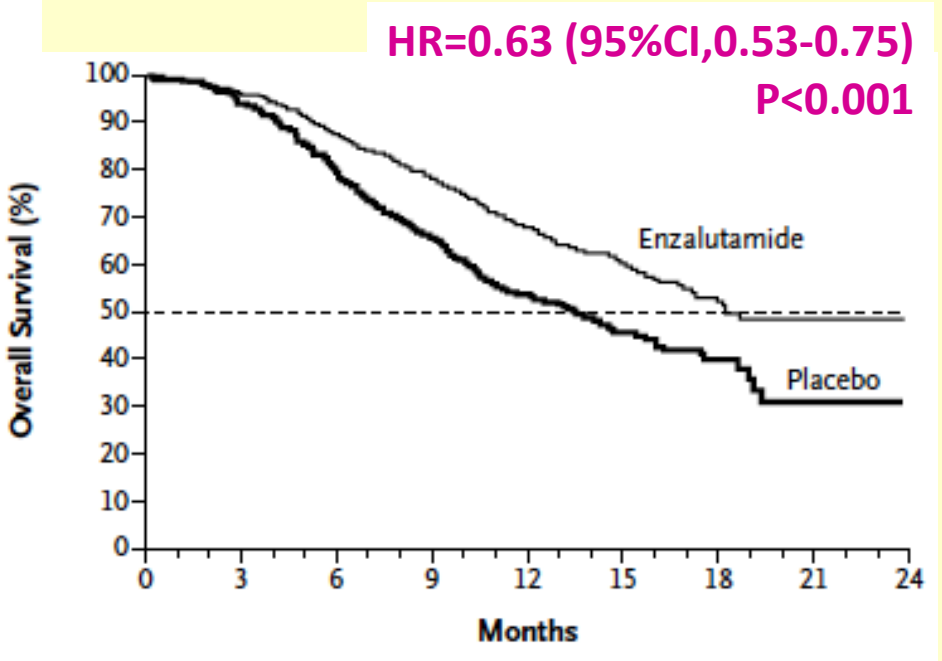
N Engl J Med 2011;364:1995-2005.

Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy

N Engl J Med 2012;367:1187-97.

Howard I. Scher, M.D., Karim Fizazi, M.D., Ph.D., Fred Saad, M.D., Mary-Ellen Taplin, M.D., Cora N. Sternberg, M.D.,



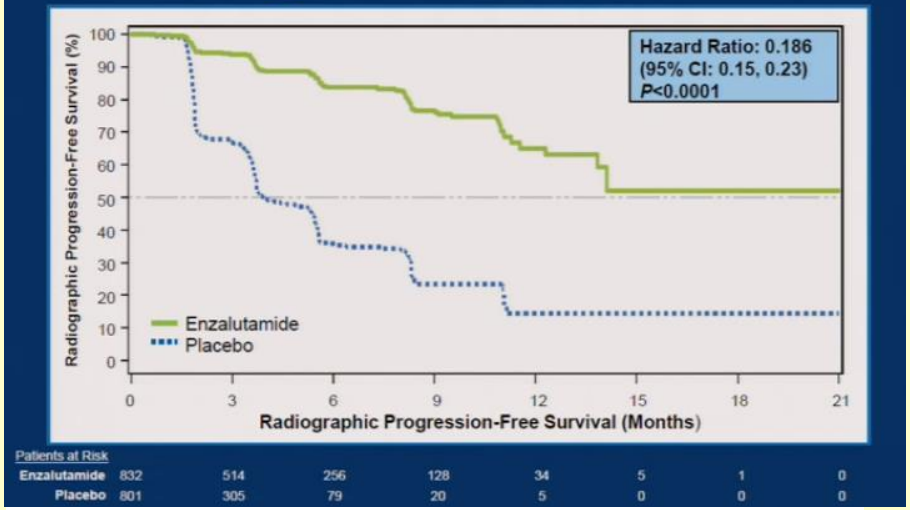


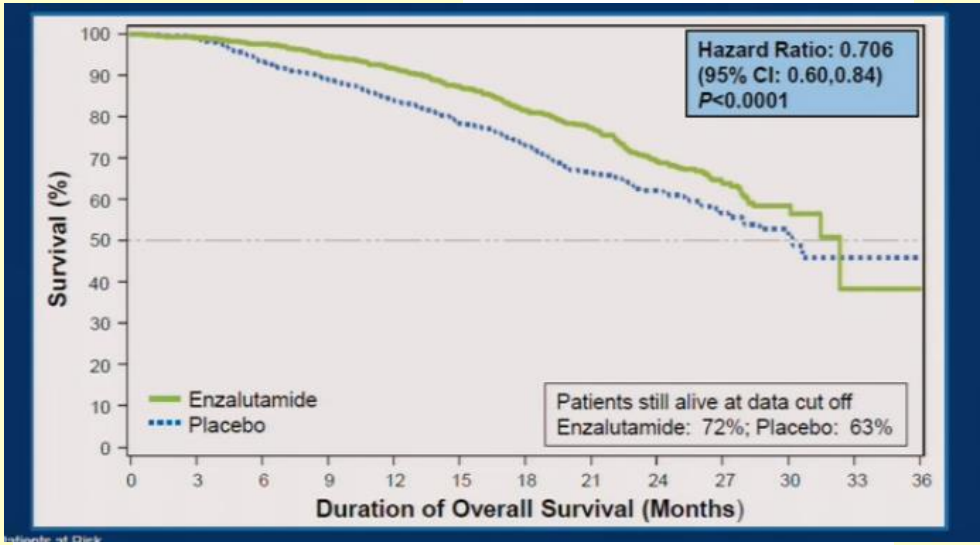
Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy

N Engl J Med 2013;368:138-48.

Charles J. Ryan, M.D., Matthew R. Smith, M.D., Ph.D.,

Enzalutamide Prolonged Radiographic Progression-Free Survival





Pre-Chemo Trial of Enzalutamide Halted After Meeting Endpoints

October 22, 2013

For OS: HR=0.70 (0.59-0.83), P=0.0001

For rPFS: HR=0.19 (0.15-0.23), P<0.0001

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Summary-3: New hormonal agents

- Androgen-dependent pathways active in CRPC. ↑testosterone in tumours despite castrate levels in blood
- New agents active in CRPC pre- and post-chemo
- Abiraterone → ↓androgen synthesis and ↑OS (~4 mos) after chemo, and ↑PFS pre-chemo
- Enzalutamide (MDV-3100) is irreversible anti-androgen with similar activity
- Major challenge is cost – but 500mg/day abiraterone on full stomach → similar PK to 1000mg/day fasting

Mr Kemal is treated with abiraterone. He responds with a decrease in PSA and improved pain for 9 months but then starts to progress again

How should Mr Kemal be managed ?

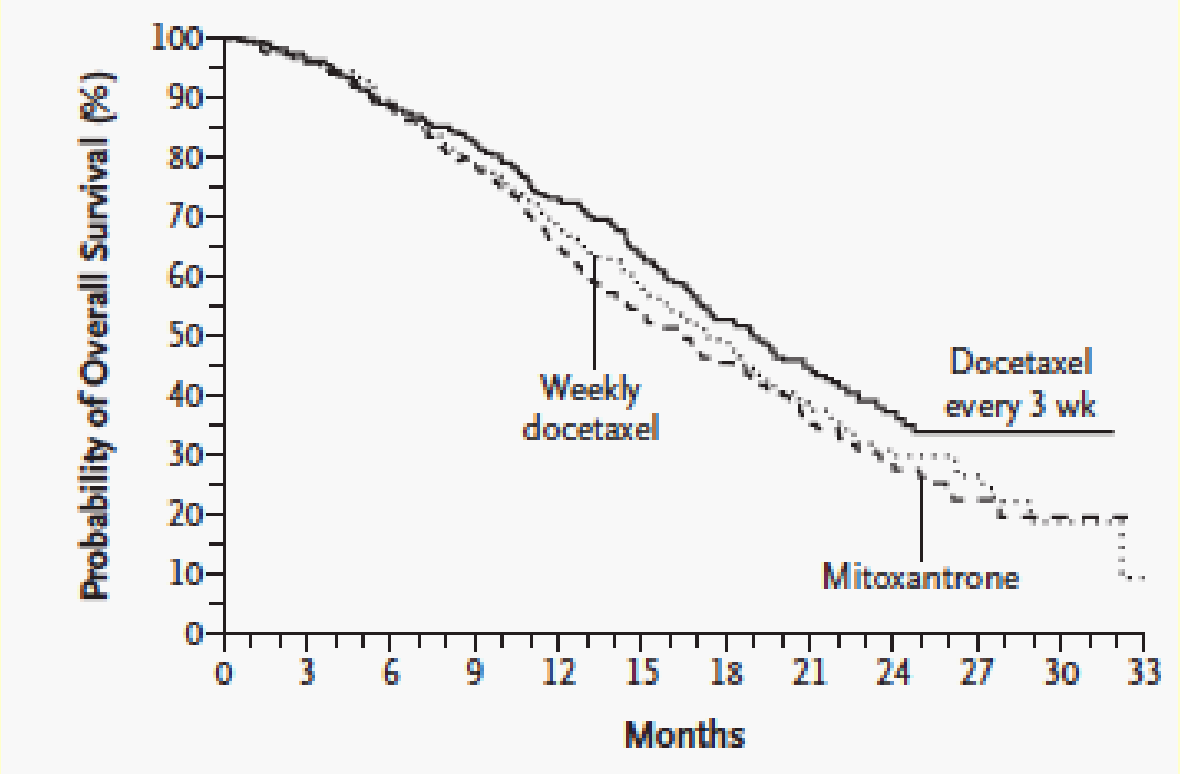
- He has incurable cancer: QoL is important
- Optimise Mr Kemal's pain control with regular narcotics
- Give regular laxatives to control constipation
- Give local radiotherapy to dominant site of pain
- Consider chemotherapy for diffuse symptoms or rapid PSA progression

Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer

N Engl J Med 2004;351:1502-12

Ian F. Tannock, M.D., Ph.D., Ronald de Wit, M.D., William R. Berry, M.D.,

Docetaxel and prednisone has been standard 1st-line chemotherapy since the TAX-327 RCT showed improved survival and symptom control compared to previous standard



TAX-327: Secondary endpoints

TAX-327 2° endpoints	Docetaxel q 3wk	Docetaxel wkly	Mitox 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%

Some important questions….

Which is more important?

3-month improvement in survival?

Improved pain and quality of life?

When to start chemotherapy?

You cannot make a well patient better – but you can cause symptoms from treatment - No evidence that starting chemo in asymptomatic men is better than waiting for symptoms.

Does prior abiraterone decrease response to docetaxel?

Antitumour activity of docetaxel following treatment with the CYP17A1 inhibitor abiraterone: clinical evidence for cross-resistance? *Annals of Oncology* 23: 2943–2947, 2012

J. Mezynski, C. Pezaro, D. Bianchini, A. Zivi, S. Sandhu, E. Thompson, J. Hunt, E. Sheridan, B. Baikady, A. Sarvadikar, G. Maier, A. H. M. Reid, A. Mulick Cassidy, D. Olmos, G. Attard*,‡ & J. deBono‡

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Is there a role for earlier docetaxel with ADT?

- CHAARTED clinical trial randomized 790 men with extensive metastatic hormone-sensitive PC to ADT alone or ADT + docetaxel (6 cycles over 18 weeks)
- NIH report indicates 3yr OS of 69.0% vs 52.5%

N.B. This is a press/NIH report released at request of the DSMB. No details are available.

Mr Kemal is treated with docetaxel and prednisone

- He has relief of pain and by the 3rd course of treatment he is able to stop taking morphine
- His PSA declines steadily after an initial increase but begins to rise again after 8 courses
- He has minimal acute toxicity but is tired and develops numbness in his hands and feet

Might Mr Kemal have increased benefit if treated with docetaxel + a targeted agent?

Nine large RCTs of docetaxel/prednisone +/- targeted agent have been completed with ~10,000 patients included at a cost of ~$1 billion

Trial	Partner	Result
ASCENT II	DN101 (calcitriol)	Poorer survival in experimental arm
VITAL II	GVAX vaccine	Poorer survival in experimental arm
SWOG S0421	Atrasentan	No difference in PFS or survival
ENTHUSE	Zibotentan	No significant difference in survival
MAINSAIL	Lenalidomide	No difference in survival (more toxicity)
CALGB 90401	Bevacizumab	No difference in survival (better PFS)
READY	Dasatinib	No difference in survival
VENICE	Aflibercept	No difference in survival (more toxicity)
SYNERGY	Custirsen (OGX-011)	Pending

VENICE (docetaxel/prednisone +/- aflibercept)

	Aflibercept/Docetaxel (N=611)	Placebo/Docetaxel (N=598)
Patients with ≥ 1 cycle delayed	49.4%	35.8%
Patients with ≥ 1 dose modification: aflibercept/placebo	10.6%	2.3%
docetaxel	30.9%	16.2%
Median dose intensity: aflibercept/placebo	0.97	0.99
docetaxel	0.93	0.97
Reason for treatment discontinuation		
Adverse event	43.5%	21.2%
Disease progression	30.4%	55.9%
Other reason	24.7 %	22.9%

What can we learn from this dismal experience?

Many of these trials (including VENICE) were undertaken with:

1. **Minimal evidence of benefit of the added targeted agent either alone or in combination in preclinical models**
2. **Lack of clinical data in phase I and phase II trials**
3. **Some randomised phase II trials (e.g. DN101) were misleading**

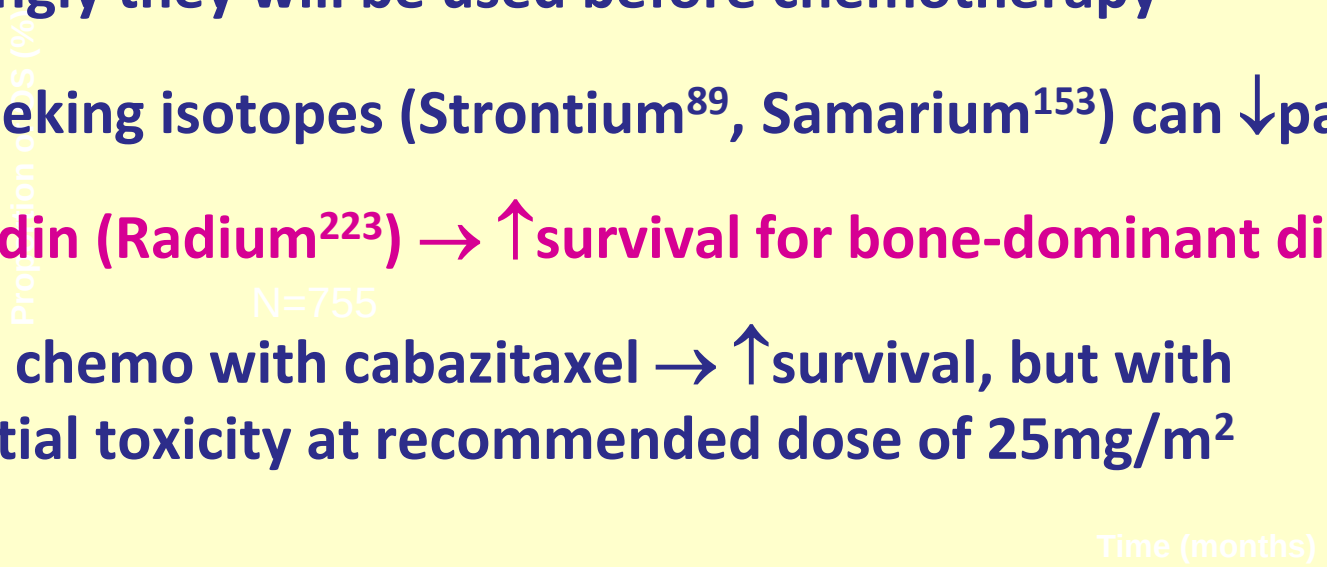
VENICE was initiated rapidly because it was expected that docetaxel + bevacizumab would become the new standard treatment

Summary-4: 1st-line chemo for CRPC

- Before chemo, optimise pain control, and consider local radiotherapy for pain
- Mitoxantrone and prednisone → ↓pain in some men. Drug is well tolerated
- Docetaxel (q 3 wks) with prednisone → ↑OS (~3 mos cf.mitoxantrone), with ↓pain and ↑QoL
- Targeted agents with docetaxel have not improved survival
- Randomised phase II studies can be misleading

How should men be treated after progressing on docetaxel?

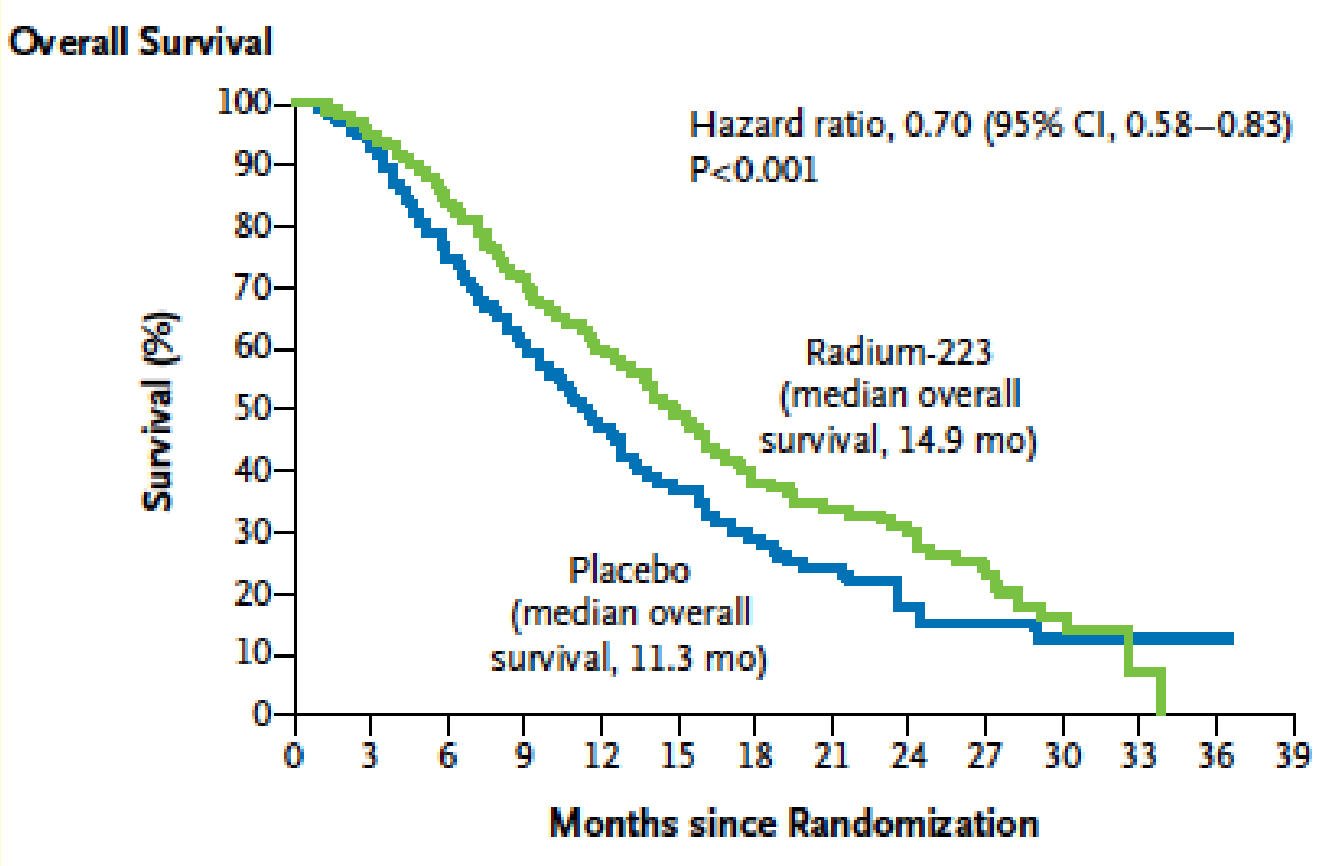
- Because of lower toxicity, abiraterone or enzalutamide are preferred (unless very short response to previous ADT) – but increasingly they will be used before chemotherapy
- Bone-seeking isotopes (Strontium^{89}, Samarium^{153}) can ↓pain.
- Alpharadin (Radium^{223}) → ↑survival for bone-dominant disease
- 2nd line chemo with cabazitaxel → ↑survival, but with substantial toxicity at recommended dose of 25mg/m^2



Alpha Emitter Radium-223 and Survival in Metastatic Prostate Cancer

N Engl J Med 2013;369:213-23.

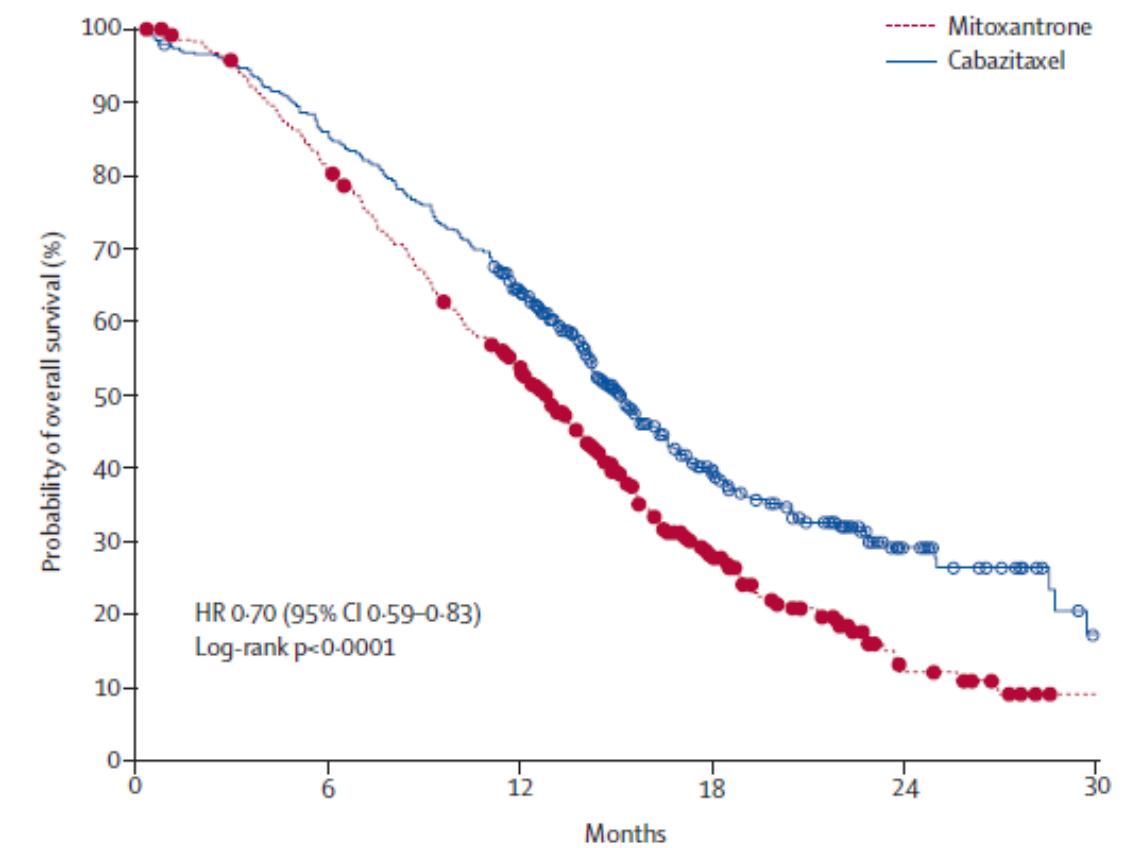
C. Parker, S. Nilsson, D. Heinrich, S.I. Helle, J.M. O'Sullivan, S.D. Fossâ, A. Chodacki, P. Wiechno, J. Logue, M. Seke,



Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial

Lancet 2010; 376: 1147–54

*Johann Sebastian de Bono, Stephane Oudard, Mustafa Ozguroglu, Steinbjørn Hansen, Jean-Pascal Machiels, Ivo Kocak, Gwenaelle Gravis, Istvan Bodrogi, Mary J Mackenzie, Liji Shen, Martin Roessner, Sunil Gupta, A Oliver Sartor, for the TROPIC Investigators**



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2° results of cabazitaxel trial

Efficacy	MP	CBZP	p-value	Comment
Tumor response (%)	4.4	14.4	0.0005	
PSA response (%)	17.8	39.2	0.0002	Mitoxantrone/prednisone consistent with other studies
Pain response (%)	7.7	9.2	0.63	Disappointing !

Toxicity	MP	CBZP	Comment
Toxic death	3 (0.8%)	18 (4.9%)	Concerning!
Neutropenic sepsis	1.3%	7.5%	
Diarrhea (≥ grade III)	0.3%	6.2%	

Summary-5: 2nd-line therapy after docetaxel for CRPC

- Some patients respond to retreatment with docetaxel
- Abiraterone or Enzalutamide = 1st choice after docetaxel for most patients, but many patients now receive either of these drugs prior to chemotherapy. Low response rate to second agent when used in sequence
- Alpharadin is useful in bone-dominant disease and has low toxicity
- Cabazitaxel → ↑OS cf.mitoxantrone, but ↑toxicity
- Mitoxantrone may be used 2nd line, associated with ~15-20% PSA RR after docetaxel

Should Mr Kemal receive treatment to ↓ bone events

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

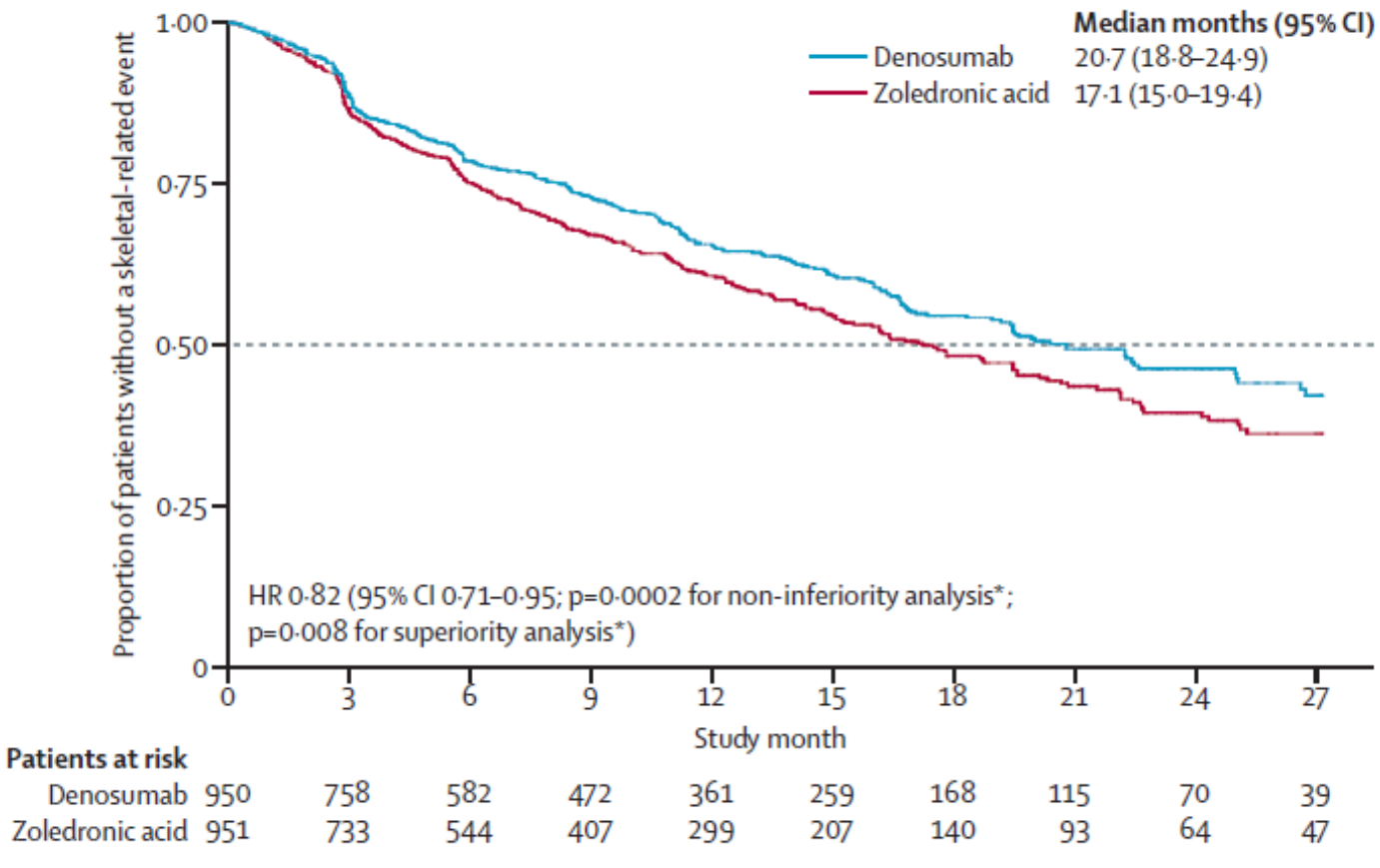
643 pts with HRPC

- Zoledronate 8mg q3wks
- Zoledronate 4mg q3wks
- Placebo q3wks

1. 8mg dose → renal insufficiency and ↓ to 4mg – but no sig difference to placebo for this arm
2. ↓bone events with 4mg dose (44%) cf. placebo (33%), (p=0.02) but no difference in Quality of Life. Most are asymptomatic.
3. ↑low-grade toxicity with zoledronate and risk of osteonecrosis of the jaw

Is denosumab superior to zoledronate?

Denosumab is a monoclonal Ab against RANK-ligand



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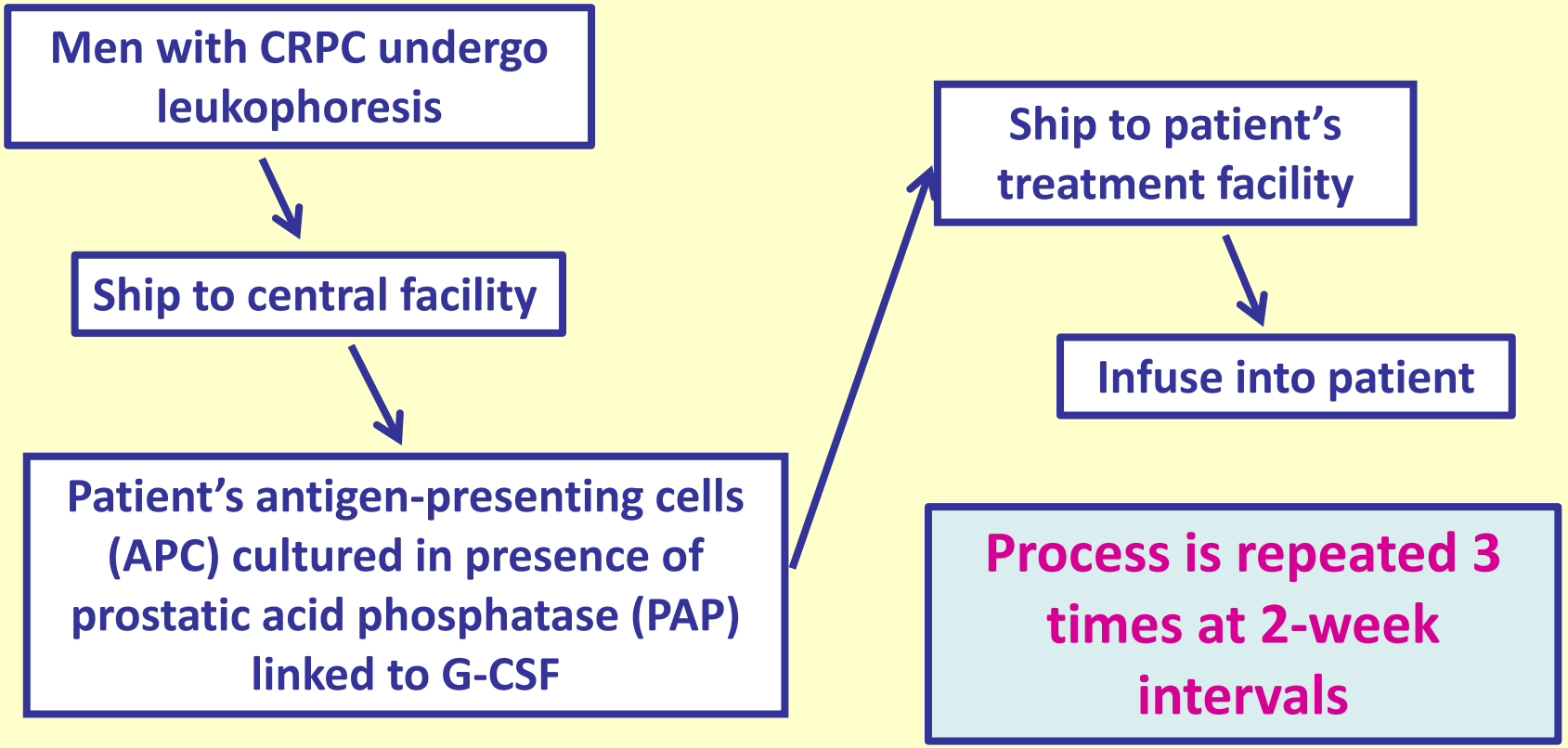
Summary 6- Use of zoledronate or denosomab in men with CRPC

- ↓bone events in selected patients
- Some osteonecrosis of the jaw
- Annual zoledronate is sufficient to ↓osteopenia in men on ADT - no evidence to support 3-weekly intervals
- Optimal dosing interval for denosomab unknown
- Neither drug is cost-effective

On next visit, Mr Kemal is failing, but his wife brings an article about Sipuleucil-T
"What is treatment" she asks, "could it save my husband's life?"

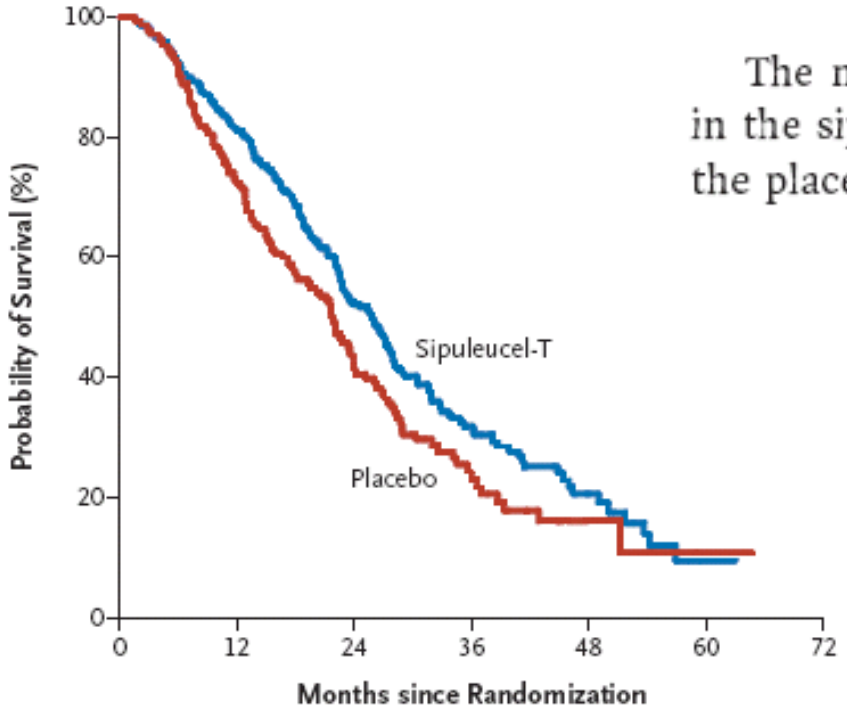


Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer

Philip W. Kantoff, M.D., Celestia S. Higano, M.D., Neal D. Shore, M.D., E. Roy Berger, M.D., Eric J. Small, M.D., David F. Penson, M.D., Charles H. Redfern, M.D., Anna C. Ferrari, M.D., Robert Dreicer, M.D., Robert B. Sims, M.D., Yi Xu, Ph.D., Mark W. Frohlich, M.D., and Paul F. Schellhammer, M.D., for the IMPACT Study Investigators*

N Engl J Med 2010;363:411-22.

A Primary Efficacy



No. at Risk						
Sipuleucel-T	341	274	129	49	14	1
Placebo	171	123	55	19	4	1

The median survival was 4.1 months longer in the sipuleucel-T group (25.8 months) than in the placebo group (21.7 months) (Fig. 2A). The

Estimated cost = $93,000

Interdisciplinary Critique of Sipuleucel-T as Immunotherapy in Castration-Resistant Prostate Cancer

Marie L. Huber, Laura Haynes, Chris Parker, Peter Iversen

J Natl Cancer Inst 2012;104:1–7

Table 2. Subgroup analysis by age of overall survival of patients in the phase III trials of sipuleucel-T for castration-resistant prostate cancer (6)*

	Sipuleucel-T		Placebo	
Patient age, y	No. of patients	Median survival (95% CI), mo	No. of patients	Median survival (95% CI), mo
<65	106	29.0 (22.8 to 34.2)	66	28.2 (23.4 to 32.5)
≥65	382	23.4 (22.0 to 27.1)	106	17.3 (13.5 to 21.4)

Overall, we believe that a detrimental effect of the placebo intervention is at least as plausible as a beneficial effect of sipuleucel-T as an explanation of the survival difference observed in the IMPACT trial.

Summary 7- Immunotherapy for prostate cancer

- Sipuleucil-T = first immunotherapy → ↑OS. Consistent results in 3 RCTs, but results "strange" because no effect on RR or TTP
- Logistically difficult and very expensive
- Controls undergo leukopharesis and infused with cells not exposed to PAP antigen – Recent analysis suggests this might be harmful to older men

Other strategies:

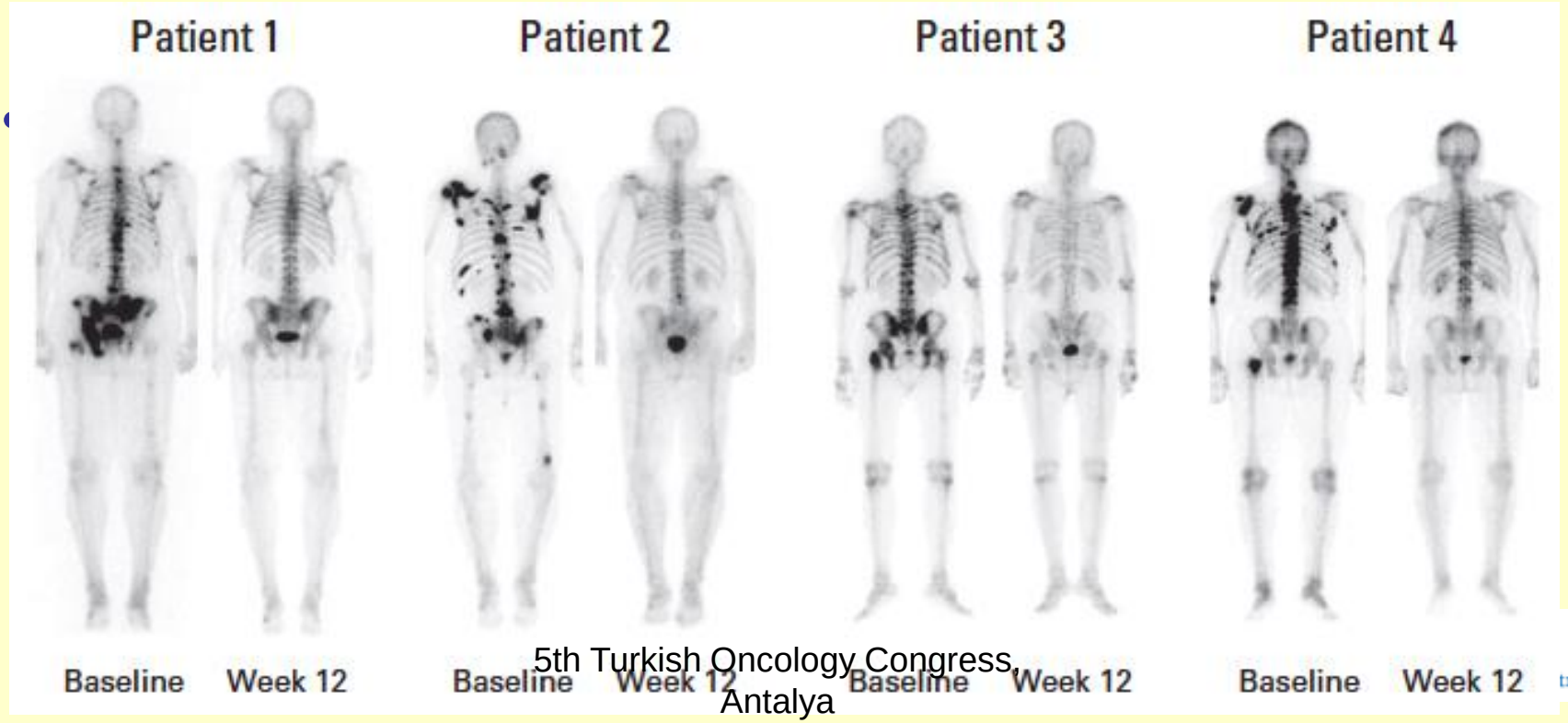
- Ipilumumab (after docetaxel) failed to improve survival significantly (ECCO, 2013)
- PROSTVAC trials in progress (encouraging results in phaseII)

Other agents in trials

- **Cabozantinib (XL-184) – MET inhibitor**

Phase II study shows interesting results with improvement in bone pain and bone scans with minimal effects on PSA

(Smith et al, JCO 2013;31:412-9)



Gene Sequencing and Personalised Medicine – Will this be the norm in 10 years?

The genomic complexity of primary human prostate cancer

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Exome sequencing identifies recurrent *SPOP*, *FOXA1* and *MED12* mutations in prostate cancer

Nature Genetics 2012

Christopher E Barbieri[1,2,16], Sylvan C Baca[3–5,16], Michael S Lawrence[3,16], Francesca Demichelis[6,7], Mirjam Blattner[1], Jean-Philippe Theurillat[3], Thomas A White[8], Petar Stojanov[3], Eliezer Van Allen[3,5], Ni... Ky... Kr... Al... Jua... Ph... Ga...

Punctuated Evolution of Prostate Cancer Genomes

Cell *153*, 666–677, April 25, 2013

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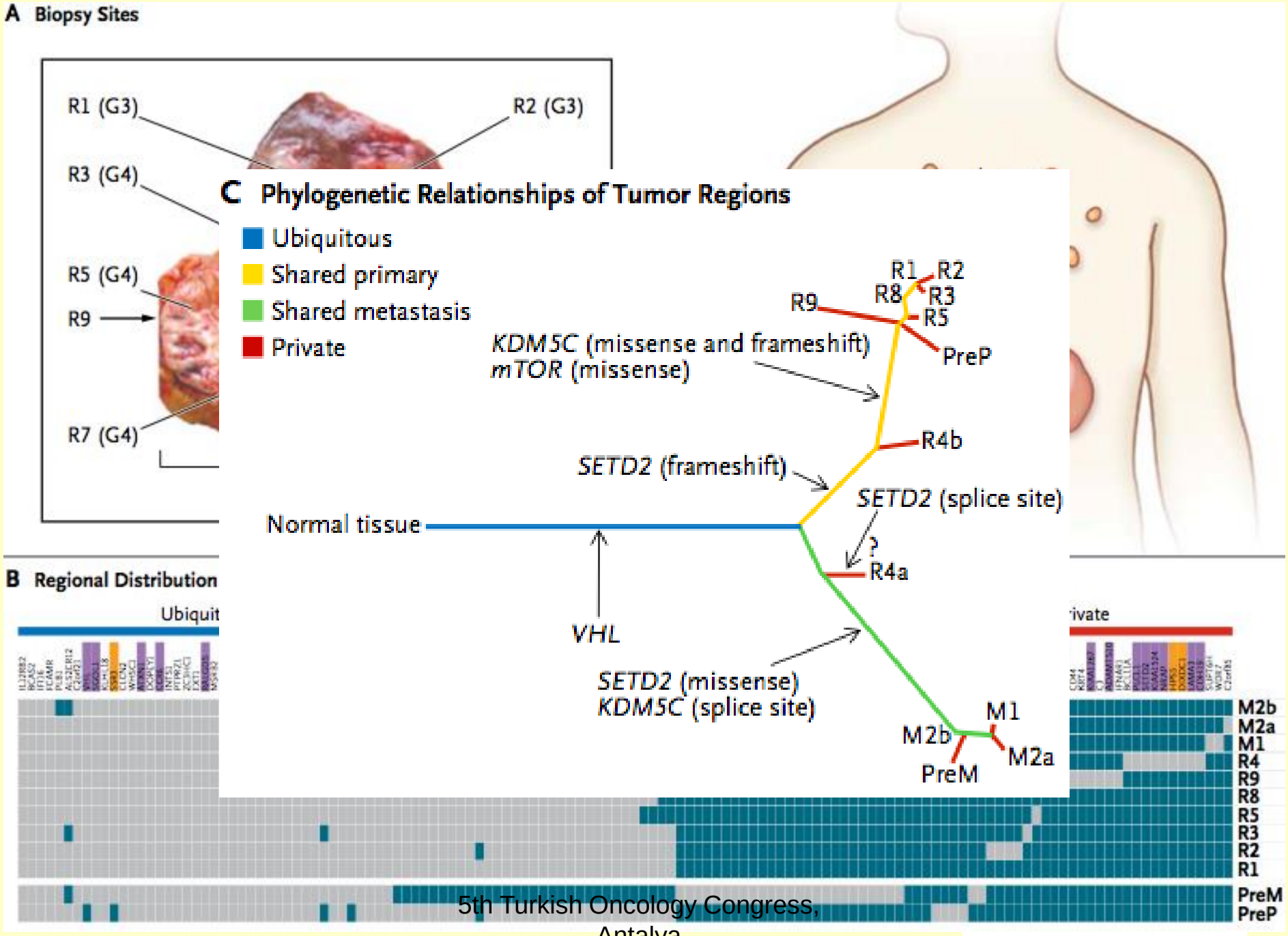
5th Turkish Oncology Congress,
Antalya

UHN Princess Margaret Cancer Centre


A Biopsy Sites
R1 (G3)
R2 (G3)
R3 (G4)
R5 (G4)
R9
R7 (G4)
C Phylogenetic Relationships of Tumor Regions
Ubiquitous
Shared primary
Shared metastasis
Private
R1
R2
R8
R3
R9
R5
PreP
KDM5C (missense and frameshift)
mTOR (missense)
R4b
SETD2 (frameshift)
SETD2 (splice site)
Normal tissue
?
R4a
VHL
SETD2 (missense)
KDM5C (splice site)
M1
M2b
M2a
PreM
B Regional Distribution
M2b
M2a
M1
R4
R9
R8
R5
R3
R2
R1
PreM
PreP

Gene Sequencing and Personalised Medicine – Will this be the norm in 10 years?

Why I do not think so:

1. Apart from the androgen receptor, no targeted agents have shown much activity against CRPC (including those targeting EGFR, HER2, mTOR, etc.)
2. Mutations in prostate cancer are complex and inter-related – so targeting a single mutation is unlikely to be beneficial – and combining targeted agents has been too toxic
3. Human tumors are very heterogeneous – not only between but within tumors

Thanks to our international fellows who stimulate my ideas (but are not responsible for them).....and have done much of the work. Thanks also to Mr Tabor and our patients

Especially: Dominik Berthold, Eitan Amir, Anthony Joshua, Saroj Niraula & Bostjan Seruga,