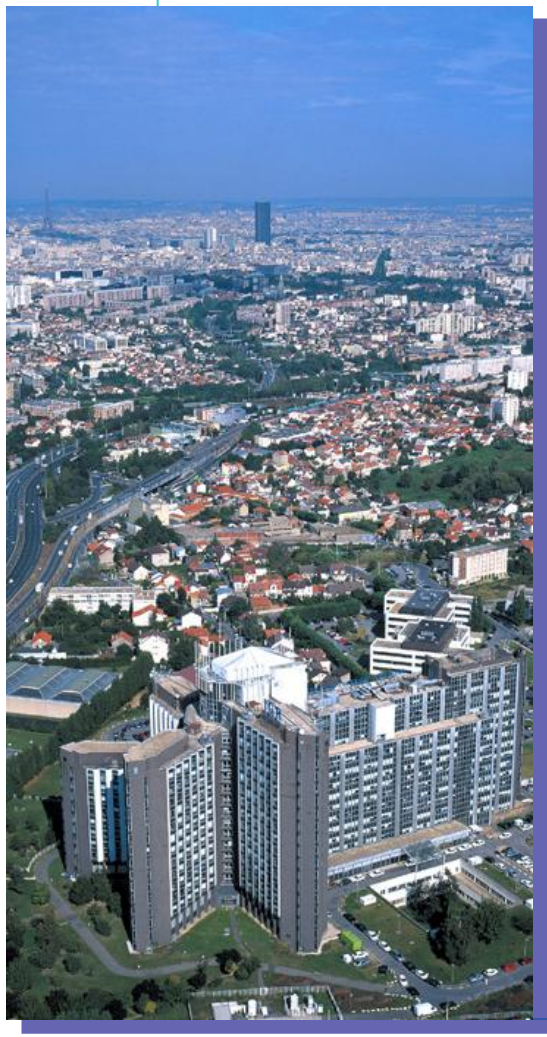
Tubulin-binding drug In prostate cancer



Early clinical trial unit

SITEP

www.igr.fr

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TAT Meeting, Paris, 2011

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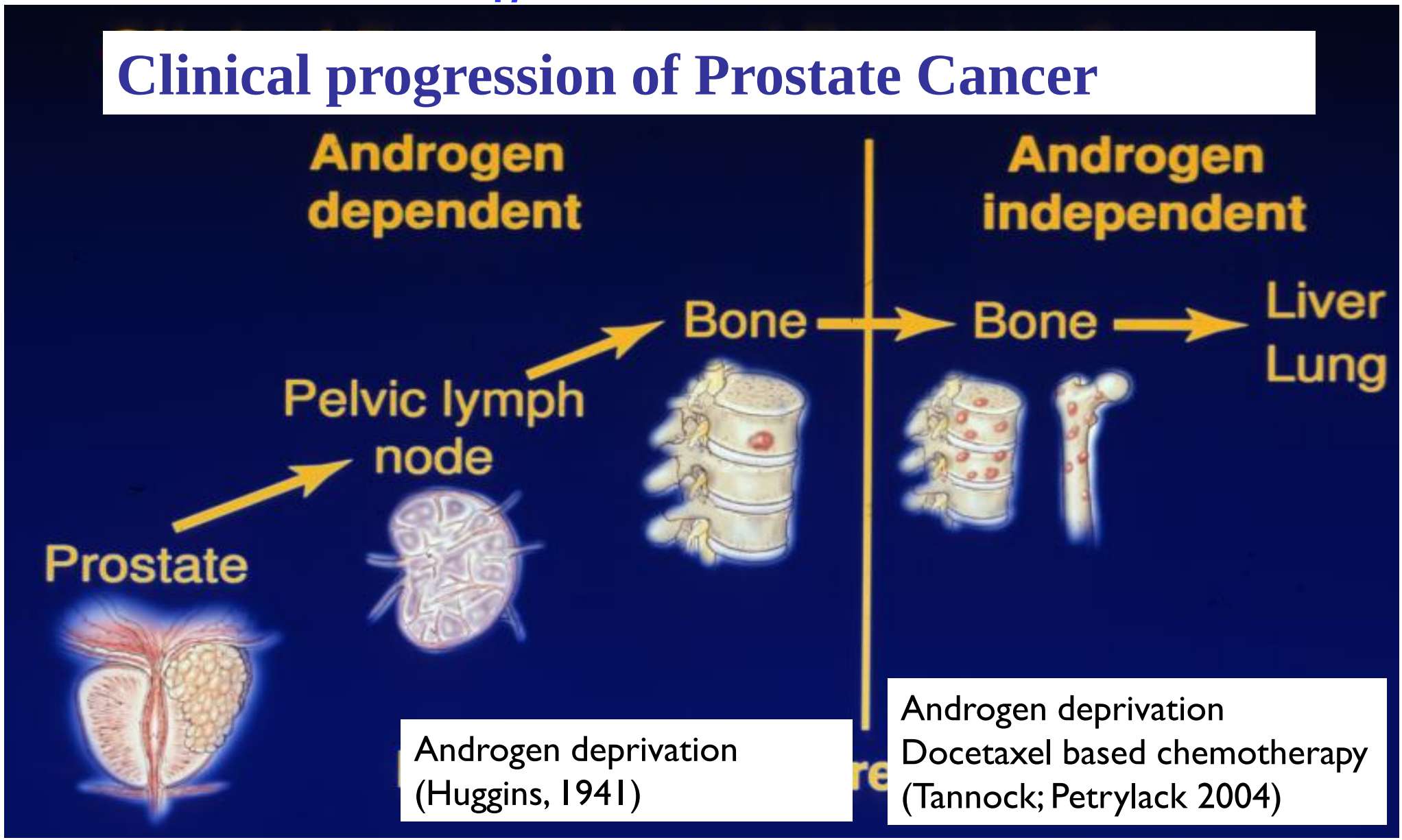
Chemotherapy in Prostate Cancer before 2010…



- Docetaxel based chemotherapy in CRPC
- New tubulin agent in CRPC: Cabazitaxel
- Other drugs and Combination therapy
- Strategy in prostate cancer (early stage)
- Perspectives

Docetaxel based chemotherapy in CRPC: TAX 327 and SWOG 9916

TAX 327

R

N=1006

- Mitoxantrone 12 mg/m^2 q 21 days
  Prednisone 5 mg po bid
- Docetaxel 75 mg/m^2 q 21 days
  Prednisone 5 mg po bid
  Dexamethasone 8 mg 12, 3 and 1 hour prior to D
- Docetaxel 30 mg/m^2 /wk 5 of 6 wks
  Prednisone 5 mg po bid
  Dexamethasone 8 mg 1 hour prior to D

Tannock IF, et al: NEJM 351:1502-12, 2004

SWOG 9916

R

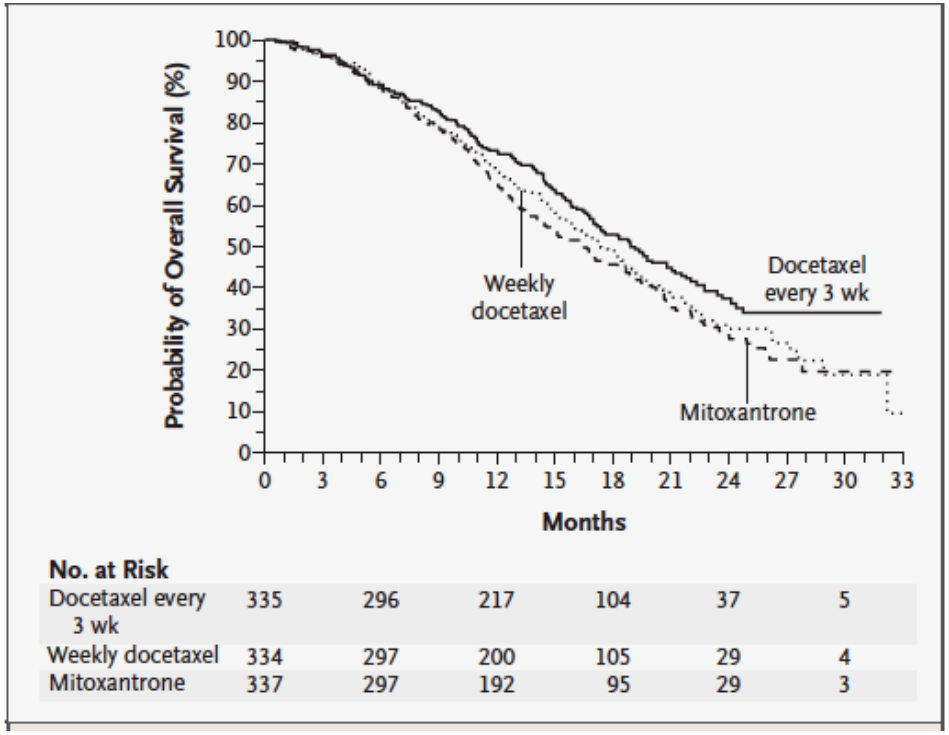
N=770

- Mitoxantrone 12 mg/m^2 q 21 days
  Prednisone 5 mg po bid
- Docetaxel 60 mg/m^2 IV J2/3 weeks
  Dexamethasone 20 mg x3/d

Petrylak DP, et al: NEJM 351:1513-20, 2004

Docetaxel based chemotherapy in CRPC: Overall Survival

TAX 327

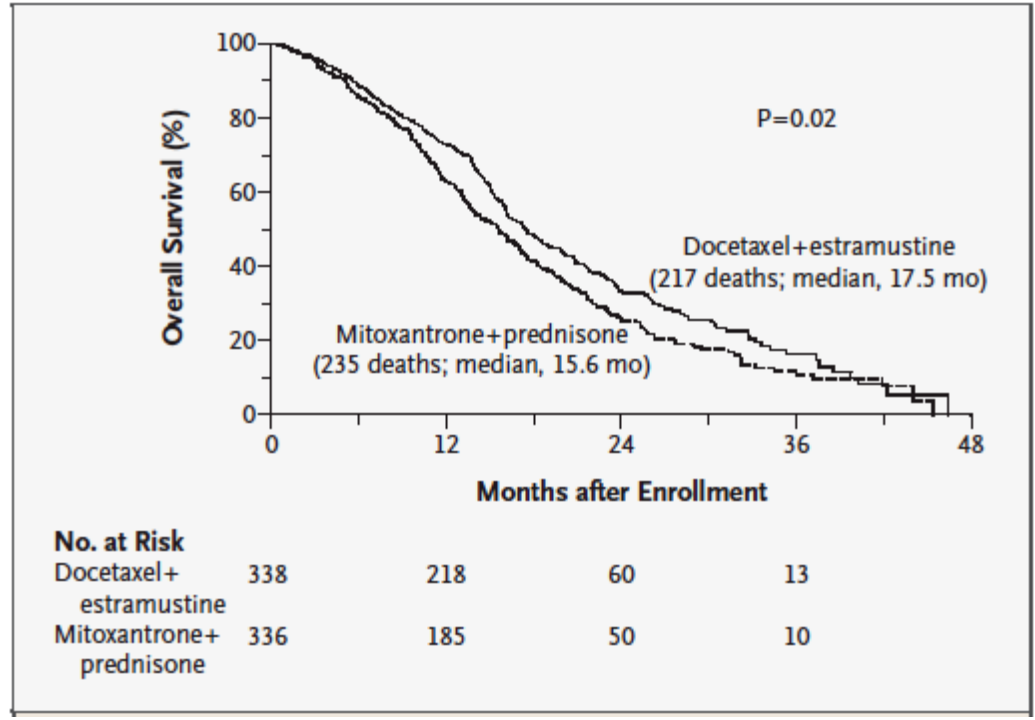


No. at Risk						
Docetaxel every 3 wk	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

Median OS: 18.9 months vs. 16.5 months
HR: 0.76 (0.62-0.94)

Tannock IF, et al: NEJM 351:1502-12, 2004

SWOG 9916



No. at Risk				
Docetaxel+ estramustine	338	218	60	13
Mitoxantrone+ prednisone	336	185	50	10

Median OS: 17.5 months vs. 15.6 months
HR: 0.80 (0.67-0.97)

Petrylak DP, et al: NEJM 351:1513-20, 2004

Chemotherapy works!
Arising questions

- What to do when docetaxel eventually fails?
- Docetaxel alone or in combination (estramustine)?
- Early (asymptomatic) or late (symptomatic) chemotherapy?

- Docetaxel based chemotherapy in CRPC
- New tubulin agent in CRPC: Cabazitaxel
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Mitoxantrone after first line Docetaxel

Author	Response rate
Michels (n=35)	15%
Oh (n=35)	6% (PFS: 6 weeks)

Cabazitaxel: A Next-Generation Taxane

- New semi-synthetic taxane
  - → Selected to overcome the emergence of taxane resistance

  (poor affinity for drug efflux pomp)
  - → Microtubule stabilizer

Phase I and Pharmacokinetic Study of XRP6258 (RPR 116258A), a Novel Taxane, Administered as a 1-Hour Infusion Every 3 Weeks in Patients with Advanced Solid Tumors

Alain C. Mita,[1] Louis J. Denis,[1] Eric K. Rowinsky,[1] Johann S. DeBono,[1] Andrew D. Goetz,[1] Leonel Ochoa,[1] Bahram Forouzesh,[1] Muralidhar Beeram,[1] Amita Patnaik,[1] Kathleen Molpus,[1] Dorothée Semiond,[2] Michèle Besenval,[2] and Anthony W. Tolcher[1]

- Preclinical data
  - → As potent as docetaxel against sensitive cell lines and tumor models
  - → Activity against tumor cells and tumor models that are resistant to taxanes

- Clinical data
  - → DLT was neutropenia
  - → Antitumor activity in taxane resistant CRPC
  - → No phase II data in CRPC

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Cabazitaxel + prednisone (CBZP) versus mitoxantrone + prednisone (MP) in the treatment of metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel-based regimen

Final Results of the Phase III TROPIC Trial

Oliver Sartor, MD

Piltz Professor of Cancer Research
Tulane University School of Medicine
New Orleans, USA

Johann de Bono, MD, PhD

Reader in Experimental Cancer Medicine
The Institute of Cancer Research
The Royal Marsden Hospital
Surrey, UK

On behalf of the TROPIC Investigators

TROPIC: Phase III Registration Study
146 Sites in 26 Countries

mCRPC patients who progressed during and after treatment with a docetaxel-based regimen (N=755)

Stratification factors

ECOG PS (0, 1 vs. 2) • Measurable vs. non-measurable disease

cabazitaxel 25 mg/m² q 3 wk + prednisone* for 10 cycles (n=378)	mitoxantrone 12 mg/m² q 3 wk + prednisone* for 10 cycles (n=377)

*Oral prednisone/prednisolone: 10 mg daily.

Primary endpoint: OS

Secondary endpoints: Progression-free survival (PFS), response rate, and safety

Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression

Patients characteristics

	Mitoxantrone (n=377)	Cabazitaxel (n=378)
Age		
Median (years)	67 (61–72)	68 (62–73)
≥75 years	70 (19%)	69 (18%)
Ethnic origin		
White	314 (83%)	317 (84%)
Asian	32 (8%)	26 (7%)
Black	20 (5%)	20 (5%)
Other	11 (3%)	15 (4%)
ECOG performance status 0 or 1	344 (91%)	350 (93%)
Extent of disease		
Metastatic	356 (94%)	364 (96%)
Bone metastases	328 (87%)	303 (80%)
Visceral metastases	94 (25%)	94 (25%)
Locoregional recurrence	20 (5%)	14 (4%)
Unknown	1 (<1%)	0
Median serum PSA concentration (µg/L)*	127·5 (44·0–419·0)	143·9 (51·1–416·0)
Serum PSA concentration ≥20 µg/L	325 (86%)	329 (87%)
Measurable disease	204 (54%)	201 (53%)
Pain at baseline†	168 (45%)	174 (46%)
Previous therapy		
Hormonal‡	375 (99%)	375 (99%)
Number of chemotherapy regimens		
1	268 (71%)	260 (69%)
2	79 (21%)	94 (25%)
>2	30 (8%)	24 (6%)
Radiation	222 (59%)	232 (61%)
Surgery	205 (54%)	198 (52%)
Biological agent	36 (10%)	26 (7%)
Number of previous docetaxel regimens		
1	327 (87%)	316 (84%)
2	43 (11%)	53 (14%)
>2	7 (2%)	9 (2%)
Total previous docetaxel dose (mg/m²)	529·2 (380·9–787·2)	576·6 (408·4–761·2)
Disease progression relative to docetaxel administration		
During treatment	104 (28%)	115 (30%)
<3 months from last dose	181 (48%)	158 (42%)
≥3 months from last dose	90 (24%)	102 (27%)
Unknown	2 (1%)	3 (1%)
Median time from last docetaxel dose to disease progression (months)	0·7 (0·0–2·9)	0·8 (0·0–3·1)

Most Frequent Grade ≥3 Treatment-Emergent AEs*
Safety Population

	Mitoxantrone (n=371)		Cabazitaxel (n=371)	
	All grades	Grade ≥3	All grades	Grade ≥3
Haematological†				
Neutropenia	325 (88%)	215 (58%)	347 (94%)	303 (82%)
Febrile neutropenia	--	5 (1%)	--	28 (8%)
Leukopenia	343 (92%)	157 (42%)	355 (96%)	253 (68%)
Anaemia	302 (81%)	18 (5%)	361 (97%)	39 (11%)
Thrombocytopenia	160 (43%)	6 (2%)	176 (47%)	15 (4%)
Non-haematological				
Diarrhoea	39 (11%)	1 (<1%)	173 (47%)	23 (6%)
Fatigue	102 (27%)	11 (3%)	136 (37%)	18 (5%)
Asthenia	46 (12%)	9 (2%)	76 (20%)	17 (5%)
Back pain	45 (12%)	11 (3%)	60 (16%)	14 (4%)
Nausea	85 (23%)	1 (<1%)	127 (34%)	7 (2%)
Vomiting	38 (10%)	0	84 (23%)	7 (2%)
Haematuria	14 (4%)	2 (1%)	62 (17%)	7 (2%)
Abdominal pain	13 (4%)	0	43 (12%)	7 (2%)
Pain in extremity	27 (7%)	4 (1%)	30 (8%)	6 (2%)
Dyspnoea	17 (5%)	3 (1%)	44 (12%)	5 (1%)
Constipation	57 (15%)	2 (1%)	76 (20%)	4 (1%)
Pyrexia	23 (6%)	1 (<1%)	45 (12%)	4 (1%)
Arthralgia	31 (8%)	4 (1%)	39 (11%)	4 (1%)
Urinary-tract infection	11 (3%)	3 (1%)	27 (7%)	4 (1%)
Pain	18 (5%)	7 (2%)	20 (5%)	4 (1%)
Bone pain	19 (5%)	9 (2%)	19 (5%)	3 (1%)

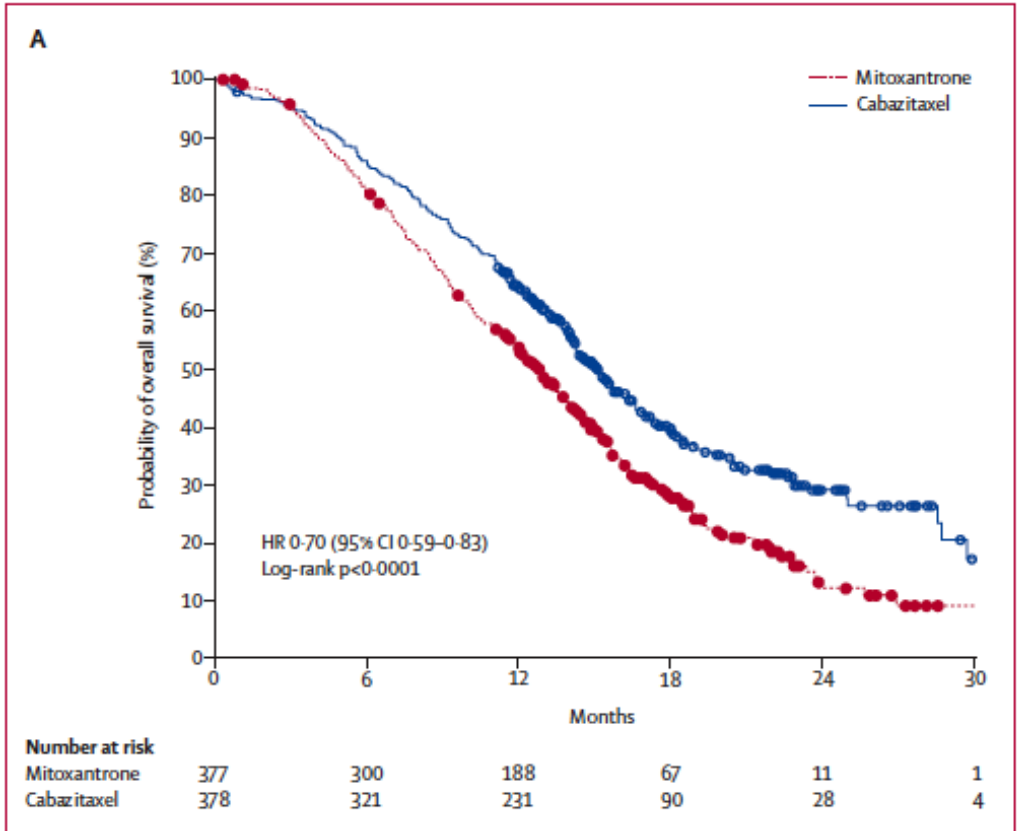
Deaths in patients who received at least one dose of study treatment

	Mitoxantrone (n=371)	Cabazitaxel (n=371)
Total deaths during the study	275 (74%)	227 (61%)
Deaths ≤30 days after last dose of study drug	9 (2%)	18 (5%)
Causes of death ≤30 days after last dose of study drug		
Disease progression	6 (2%)*	0
Adverse events		
Neutropenia and clinical consequences/sepsis	1 (<1%)	7 (2%)
Cardiac	0	5 (1%)
Dyspnoea†	1 (<1%)	0
Dehydration/electrolyte imbalance	0	1 (<1%)
Renal failure	0	3 (1%)
Cerebral haemorrhage	0	1 (<1%)
Unknown cause	0	1 (<1%)
Motor vehicle accident	1 (<1%)	0
Deaths >30 days after last dose of study drug	266 (72%)	209 (56%)

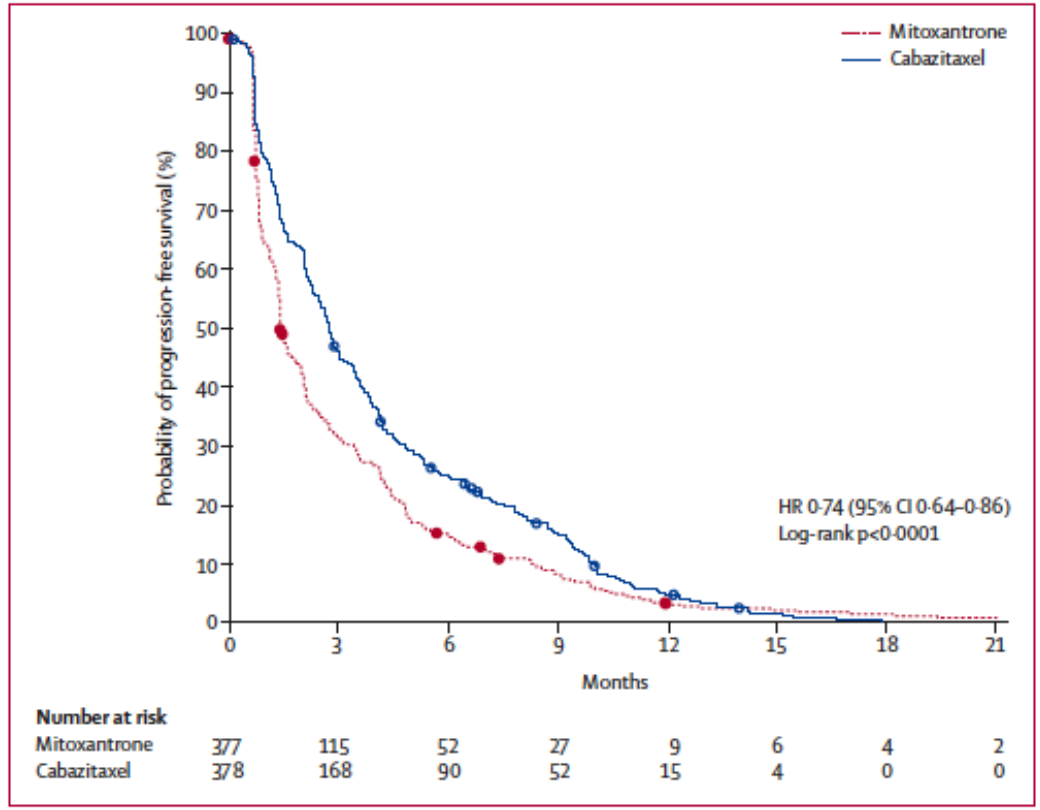
Data are number of patients (%). *Includes three patients whose death was reported as an adverse event coded as disease progression. †Dyspnoea was reported as the adverse event leading to death, but the investigator regarded the death as related to disease progression.

Table 5: **Deaths in patients who received at least one dose of study treatment**

Overall Survival and Progression Free Survival (TROPIC trial)



Median OS: 15.1 months (CBZ) vs. 12.7 monthsb (M)
HR: 0.70 (0.59-0.83)

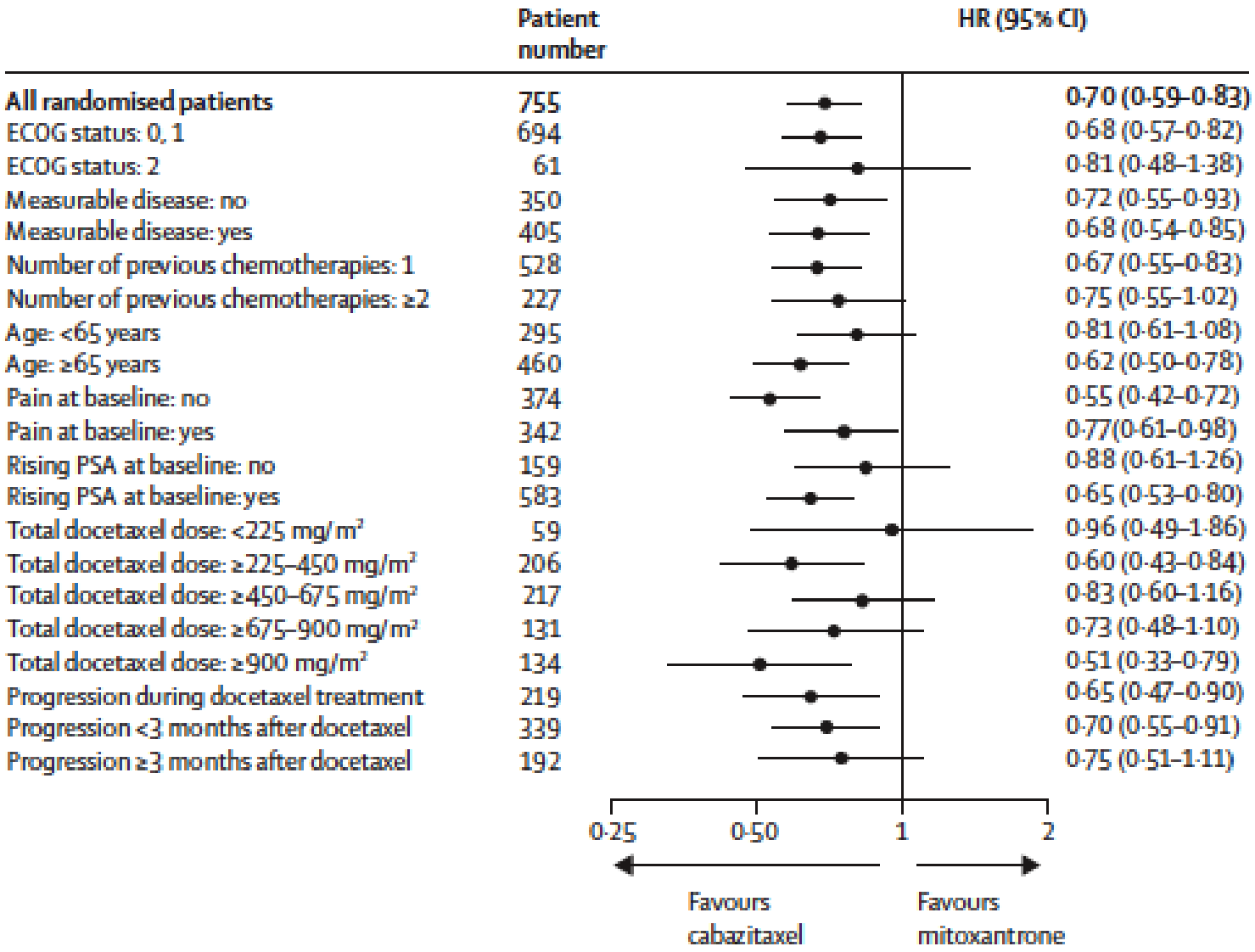


Median PFS: 2.8months (CBZ) vs. 1.4 monthsb (M)
HR: 0.74 (0.64-0.86)

De Bono et al, Lancet 2010

Overall Survival in subgroups of patients (TROPIC trial)

B



Chemotherapy works in second line!

- What to do when docetaxel eventually fails?
  - → Cabazitaxel or Abiraterone or …clinical trials
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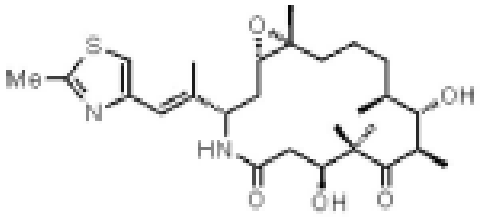
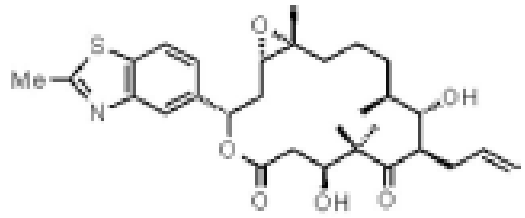
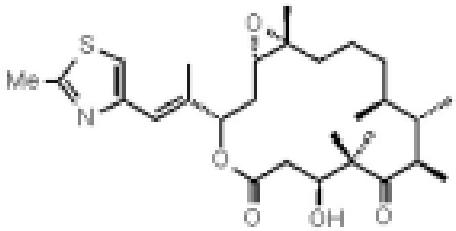
Epothilones and prostate cancer



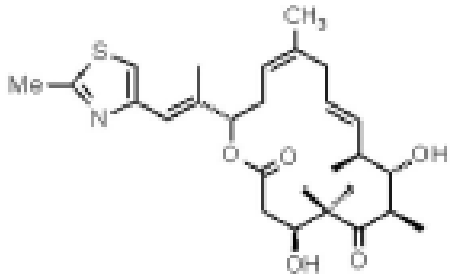
Epothilone B-Lactam (Ixabepilone)



Sagopilone (ZK-EPO)



Patupilone (Epothilone B)



Dehydelone (KOS-1584)

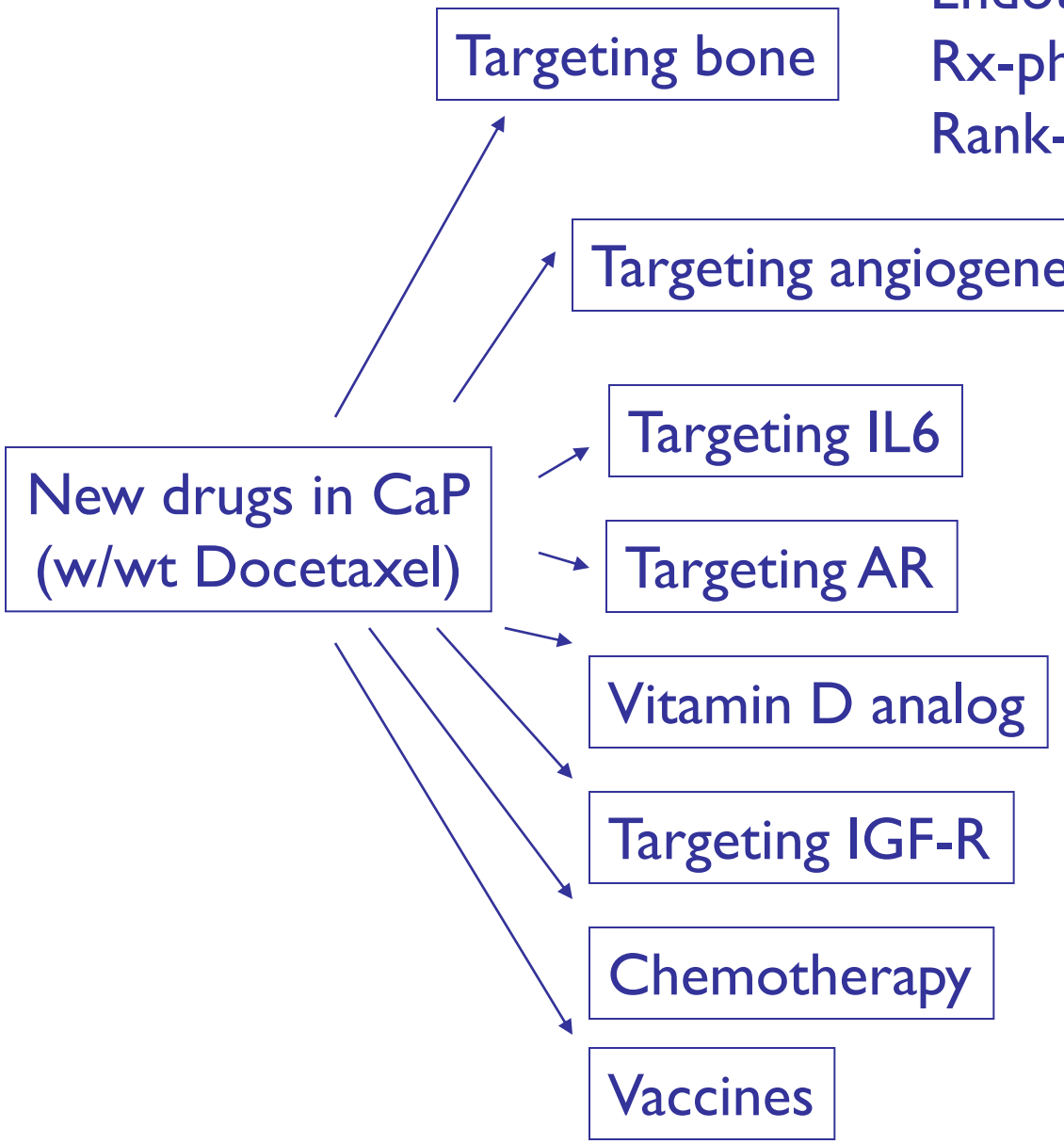
New class of cytotoxic tubulin agents (Sorangium cellulosum)

Large antineoplastic activity

In particular in taxane-resistant models (breast, prostate cancer)

	Pts (n)	Decline PSA	RR	mOS (months)
Ixabepilone+/- EMP	92	48-69%	32-48%	NA
Patupilone	45	13% (3/6 previous taxane)	0%	13.4

Galsky et al, 2005
Hussain et al, 2009



Endothelin-1 - ZD 4054, Atrasentan
Rx-pharms - Samarium
Rank-L axis - Denosumab

- Bevacizumab
- VEGF-Trap
- ZD 64 74

Centocor

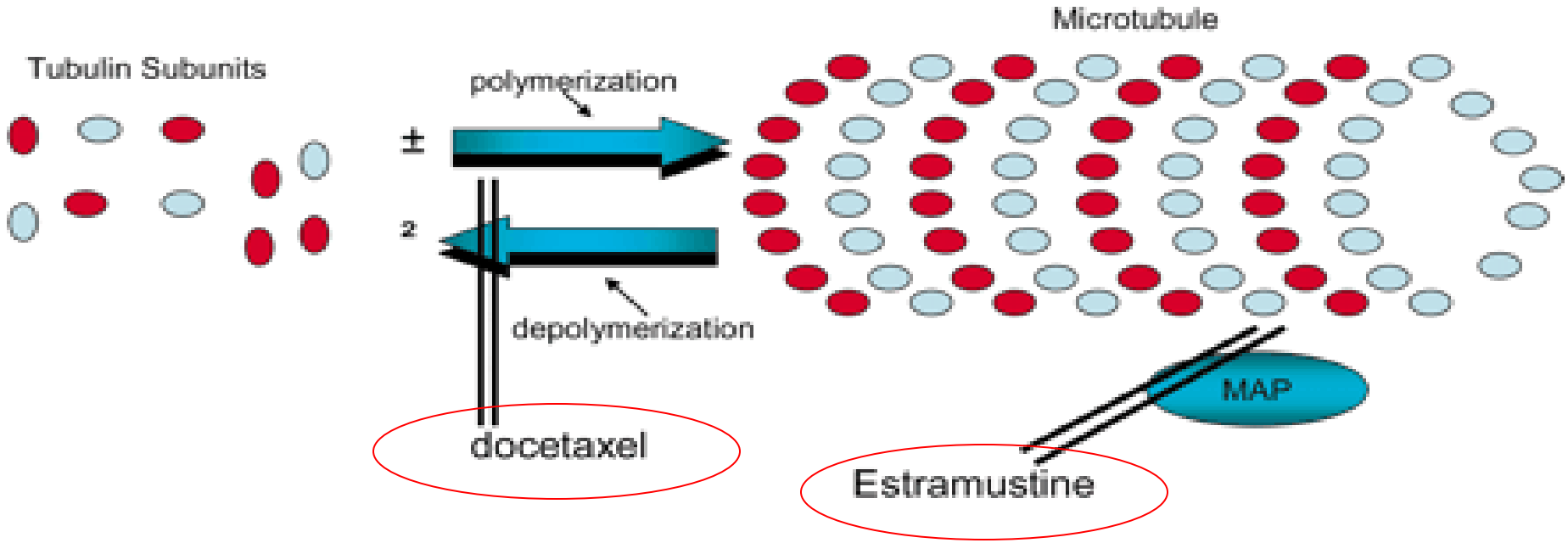
Abiraterone, MDV3100, TAK700…

DN-101 (calcitriol)

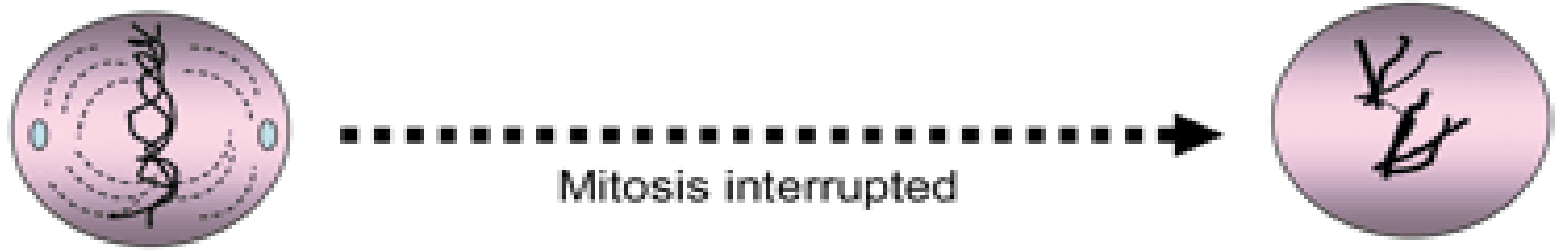
Anti-IGF-R

Estramustine, Satraplatin

APC 8015 (Provenge)
GVAX



Estramustine: Nornitrogen mustard-estradiol conjugate

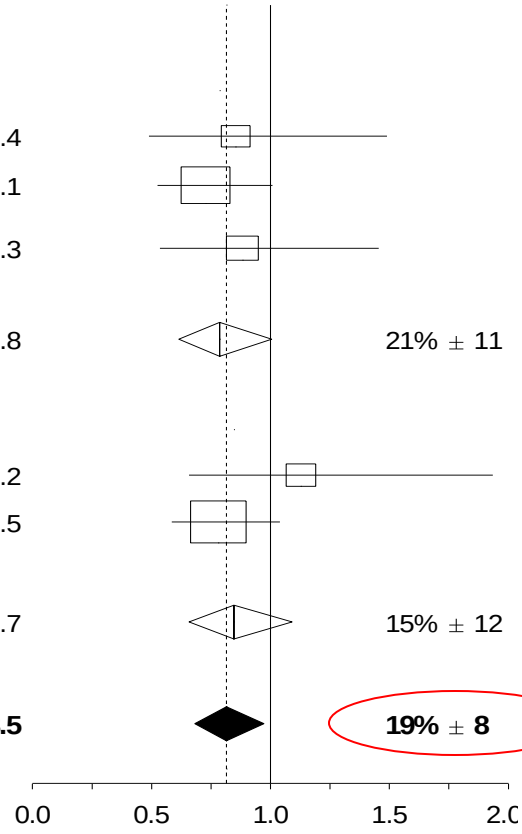


Metaphase microtubles forming spindles

Mitotic spindles broken down

Overall survival: chemotherapy + estramustine versus chemotherapy alone

Study	No. Events / No. Entered Estramustine	Control	O-E	Variance	Hazard ratio (Estramustine / Control)	Risk Redn (± SD)
(a) Taxanes and epothilone						
MSKCC	24/47	26/48	-2.0	12.4		
USON	70/81	80/85	-11.5	36.1		
Aventis	31/48	31/44	-1.9	15.3		
Subtotal (a)	125/176	137/177	-15.4	63.8		21% ± 11
(b) Vinblastine						
MDA	28/29	30/30	1.6	13.2		
Hoosier	94/94	98/98	-11.5	46.5		
Subtotal (b)	122/123	128/128	-9.9	59.7		15% ± 12
Total (a ... b)	**247/299**	**265/305**	**-25.3**	**123.5**		**19% ± 8**



Test for heterogeneity: $\chi^2_4 = 2.07$ p = 0.72

Test for interaction: $\chi^2_1 = 0.17$ p = 0.68

Estramustine effect with p = 0.02

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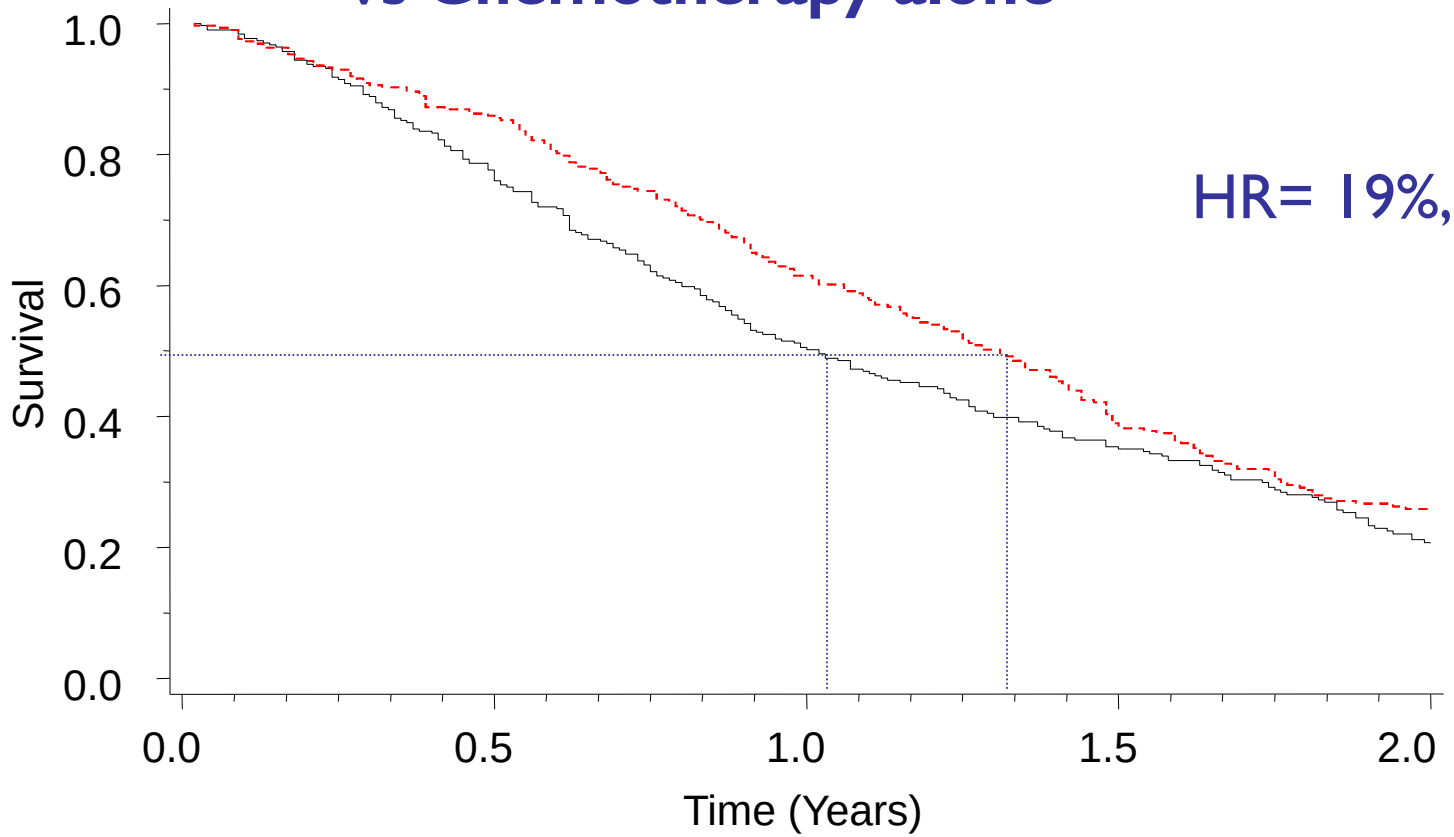
MECaP Meta-analysis of Estramustine in Prostate Cancer

Chemotherapy + Estramustine vs Chemotherapy alone

OS



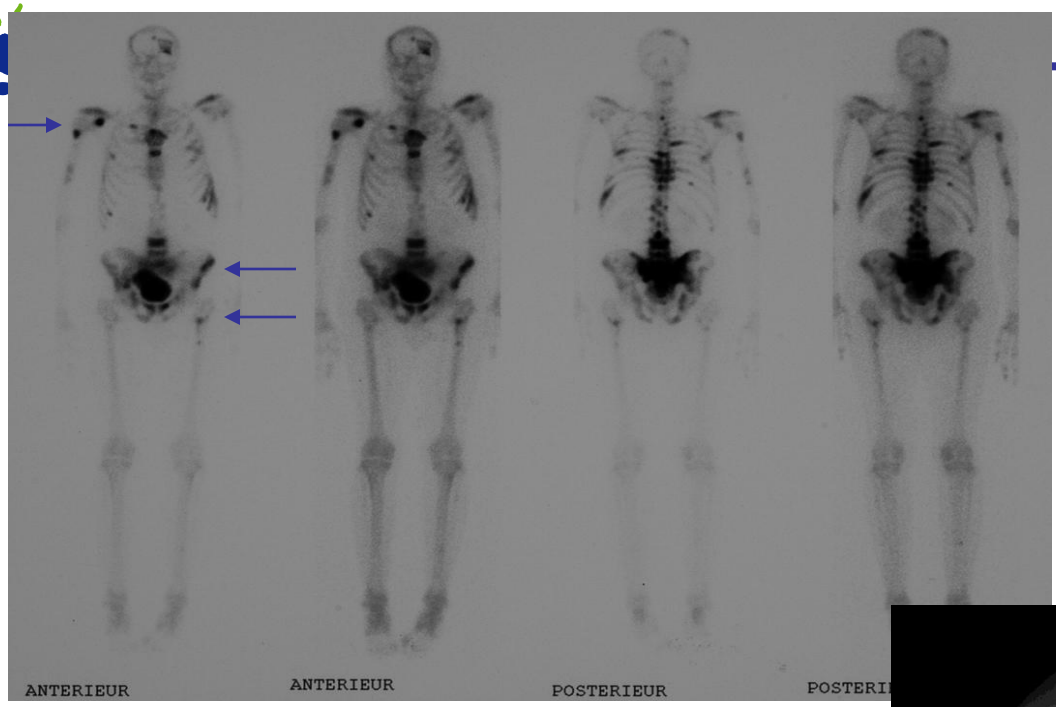
HR= 19%, p= 0.02

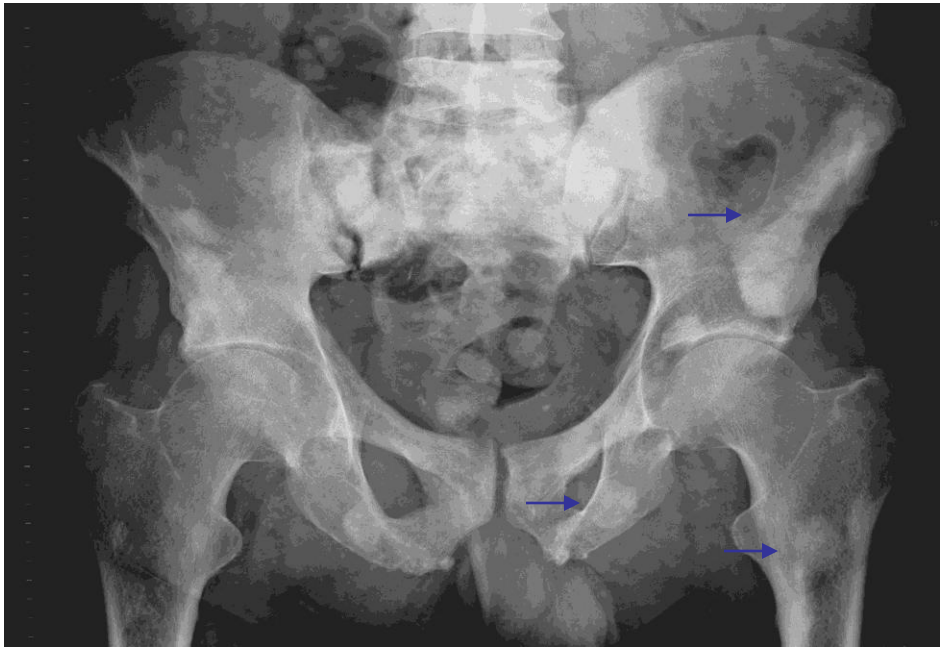
Patients at risk

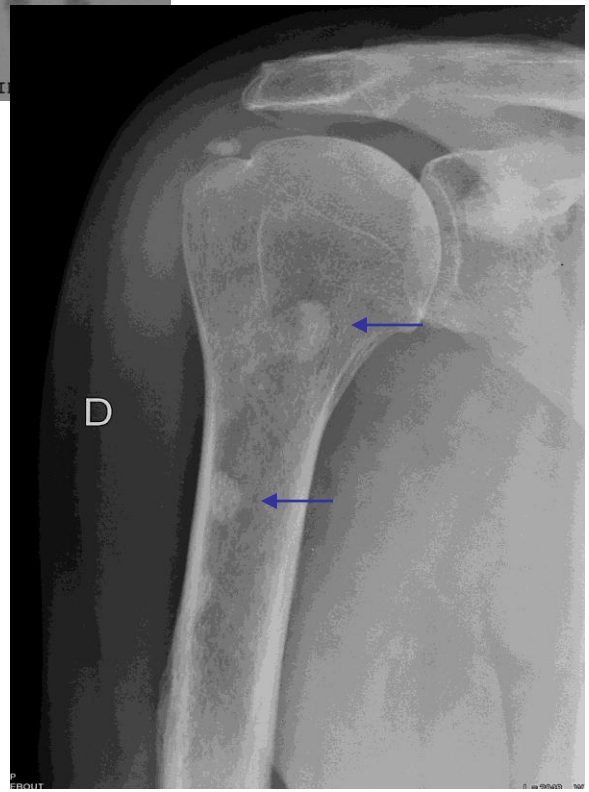
Control	304	235	153	101	46
Estramustine	299	255	180	107	62

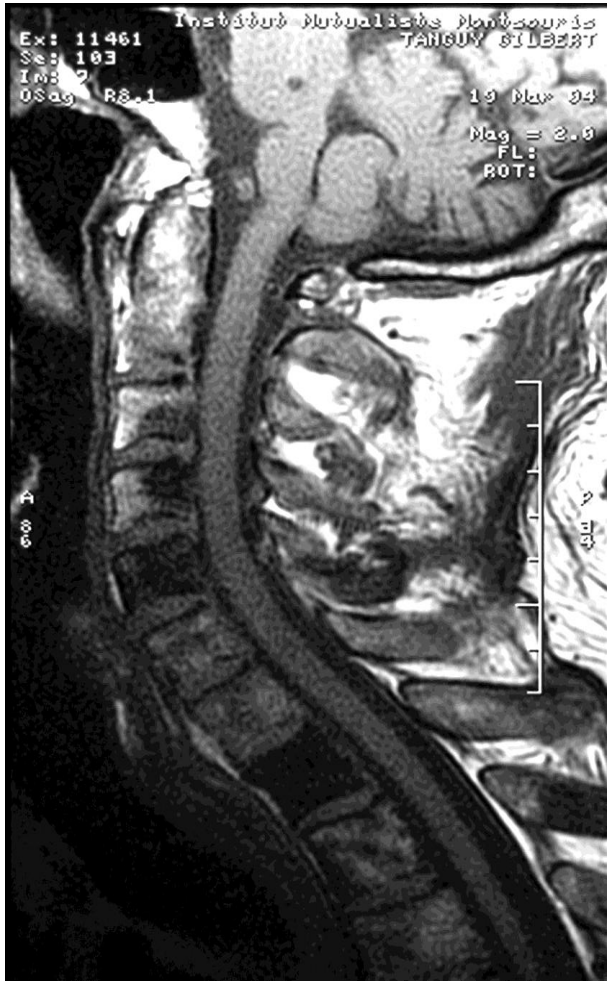
Fizazi et al., Lancet Oncol 2007

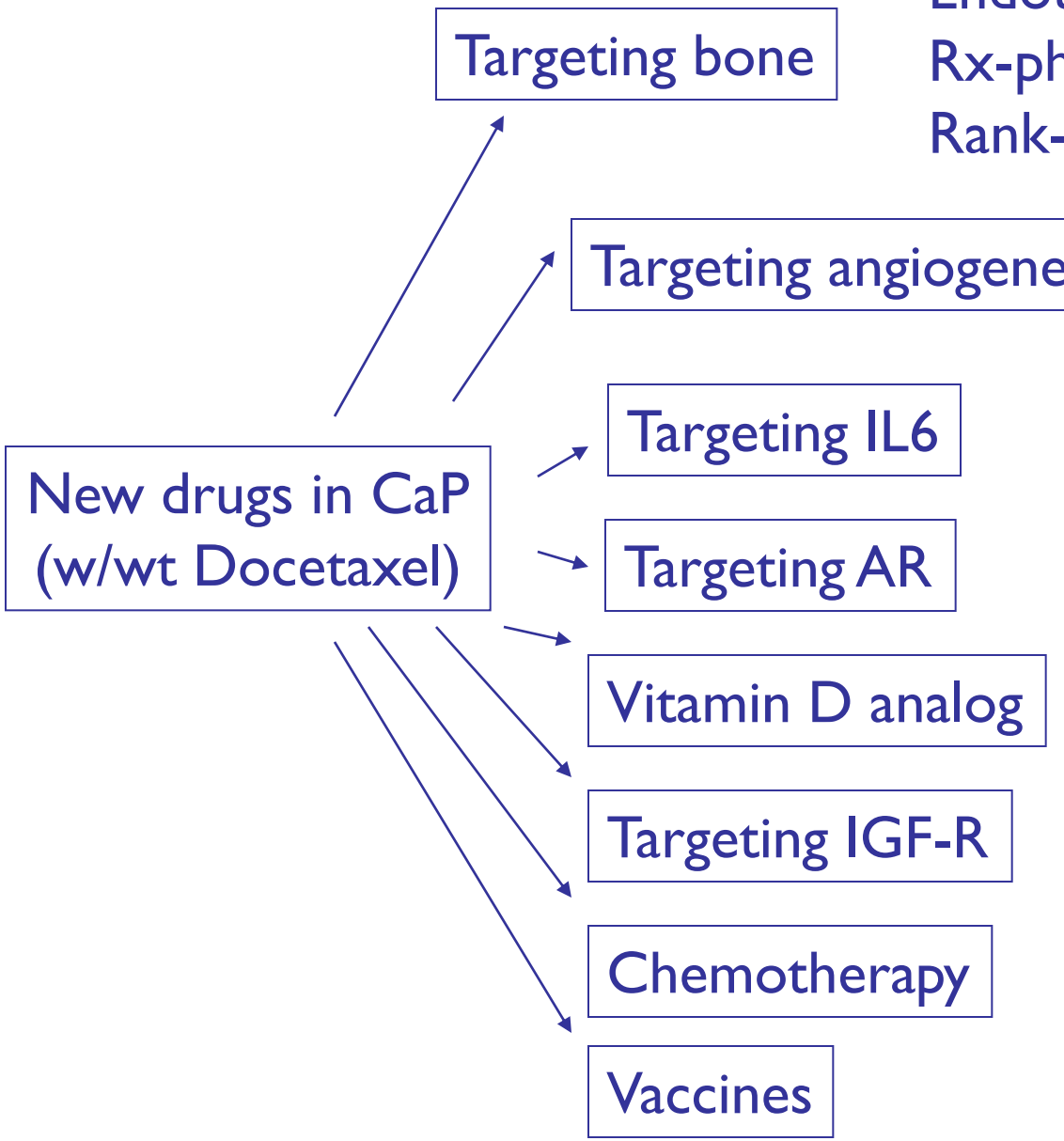
Bone metastases from prostate cancer











Endothelin-1 - ZD 4054, Atrasentan
Rx-pharms - Samarium, Strontium…
Rank-L axis - Denosumab

- Bevacizumab
- VEGF-Trap
- ZD 64 74

Centocor

Abiraterone, MDV3100, TAK700…

DN-101 (calcitriol)

Anti-IGF-R

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VOLUME 27 · NUMBER 15 · MAY 20 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

CRPC and bone metastases

↓

Induction regimen: n=43
- docetaxel 70 mg/m^2 day 2
- estramustine 10 mg/Kg/day, day 1-5

(1 cycle every 3 weeks)

↙ ↘

Response (n=31) or stabilization (n=11)

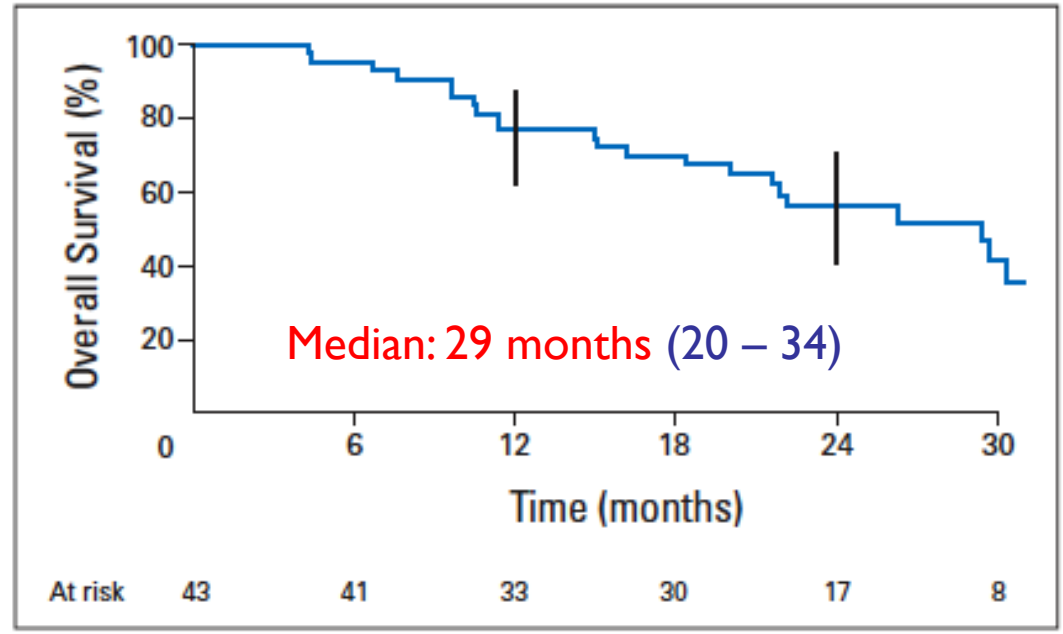
Progression n=1

↓

Consolidation regimen: n=42
- docetaxel 20 mg/m^2/w x 6 w
- samarium 1 injection week 1 (37 MBq/Kg)

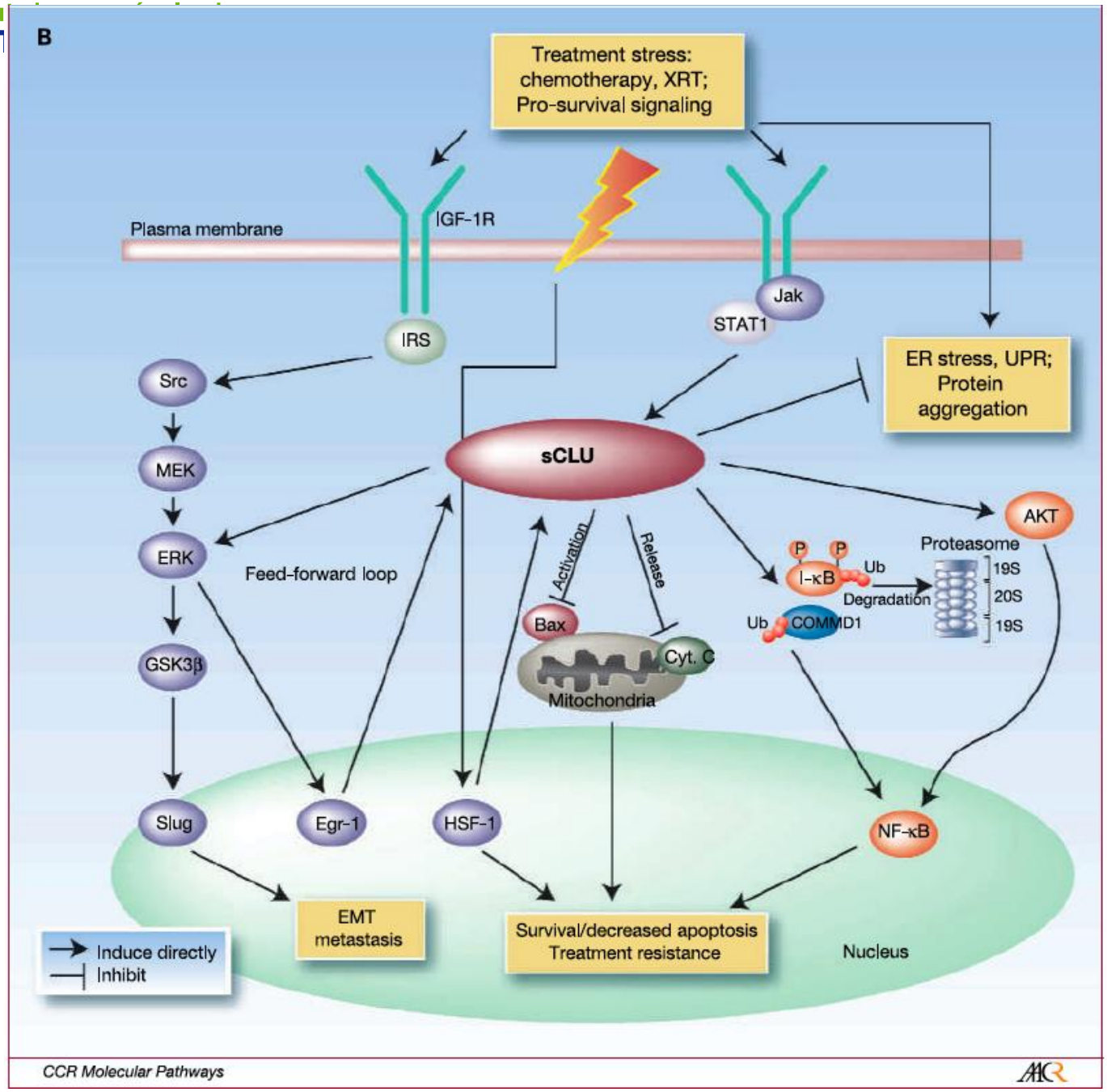
Phase II Trial of Consolidation Docetaxel and Samarium-153 in Patients With Bone Metastases From Castration-Resistant Prostate Cancer

Karim Fizazi, Philippe Beuzeboc, Jean Lumbroso, Vincent Haddad, Christophe Massard, Marine Gross-Goupil, Mario Di Palma, Bernard Escudier, Christine Theodore, Yohann Loriot, Elodie Tournay, Jeannine Bouzy, and Agnes Laplanche



1-year survival rate: 76% (62%-87%)

2-year survival rate: 63% (47%-77%)



Secretory clusterin
is a stress activated
cytoprotective chaperone

A Phase I Study of OGX-011, a 2′-Methoxyethyl Phosphorothioate Antisense to Clusterin, in Combination with Docetaxel in Patients with Advanced Cancer

Kim N. Chi, Lillian L. Siu, Hal Hirte, Sebastien J. Hotte, Jennifer Knox, Christian Kollmansberger, Martin Gleave, Emma Guns, Jean Powers, Wendy Walsh, Dongsheng Tu, and Elizabeth Eisenhauer

- 40 pts enrolled with

  Combination with docetaxel

  640 mg of OGX-011

  No major side effects

- Randomized phase II in CRPC 5 (Chi et al, 2010)
  - → 82 pts enrolled with CRPC
  - → No major side effect
  - → mOS: 23.8 months vs 16.9 months (with OGX-011 versus without)

- Large phase III ongoing

Chemotherapy works in first and second line!

- What to do when docetaxel eventually fails?
  - → Cabazitaxel or Abiraterone or …clinical trials
- Docetaxel alone or in combination (estramustine)?
  - → Other drugs in development
  - → Combination treatment in development
- Early (asymptomatic) or late (symptomatic) chemotherapy?

- Docetaxel based chemotherapy in CRPC
- New tubulin agent in CRPC: Cabazitaxel
- Other drugs and Combination therapy
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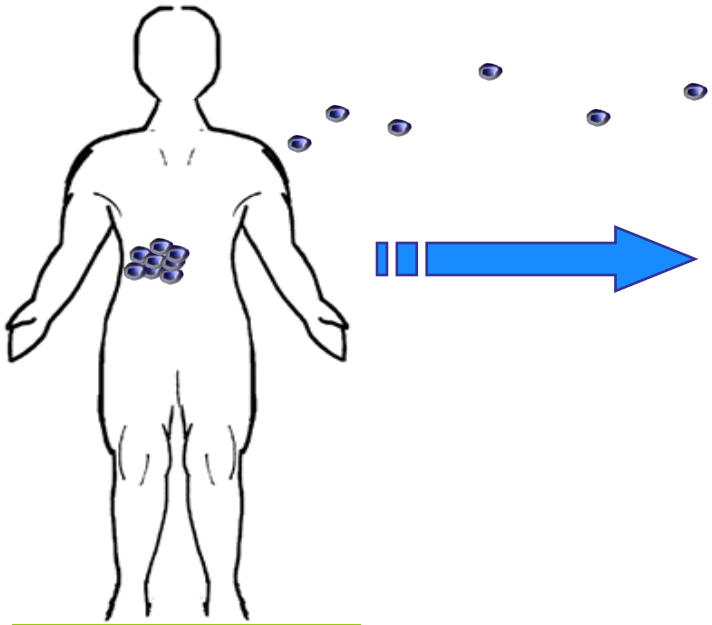
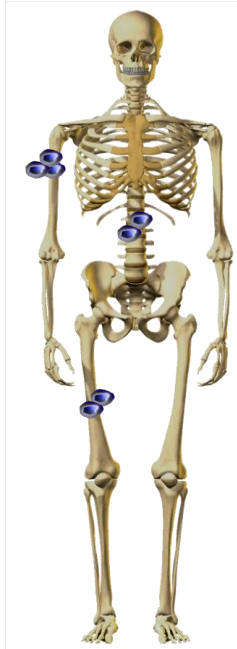
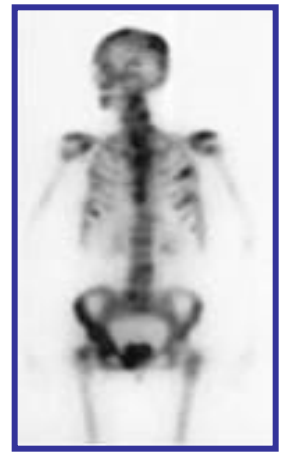
Early vs. Late chemotherapy in Prostate cancer: A French perspective

Early cancer → **Advanced cancer**







GETUG 12 trial
N=413

High risk localized PCa

R-PSA CP03 trial
GETUG 15 trial

Rising PSA

Metastatic hormone- senstive

No randomised trial

Pro's: Better clinical conditions, lower cancer burden
Con's: Impaired QoL related to chemotherapy in asymptomatic pts

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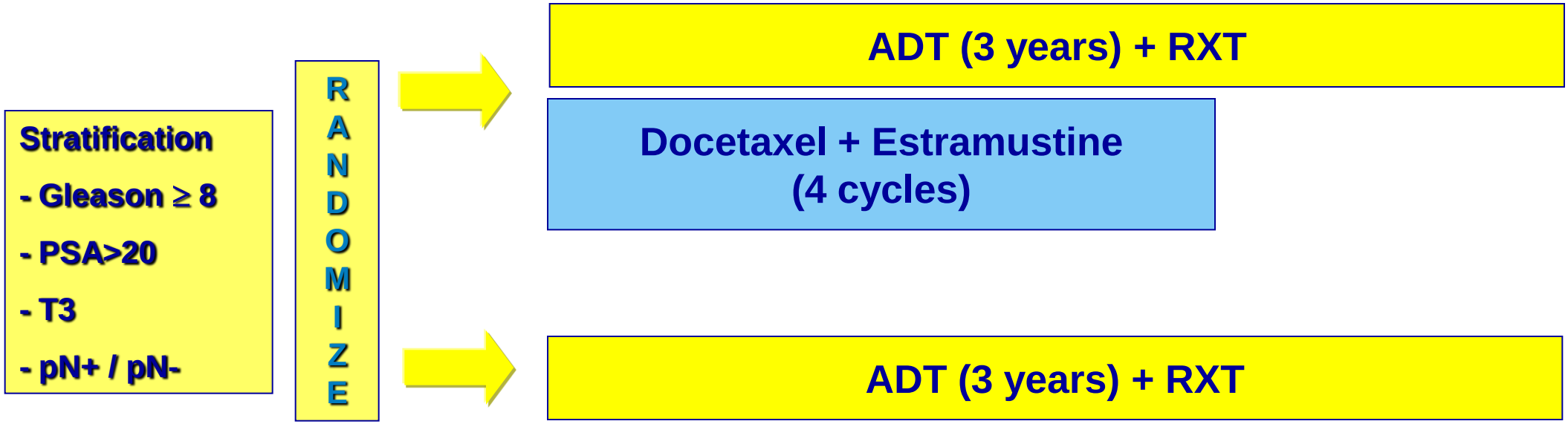
High risk prostate cancer
GETUG 12 trial



Primary endpoint: Progression-free survival

n = 413/400 pts

PI: K. Fizazi

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Early vs. Late chemotherapy in Prostate cancer: A French perspective

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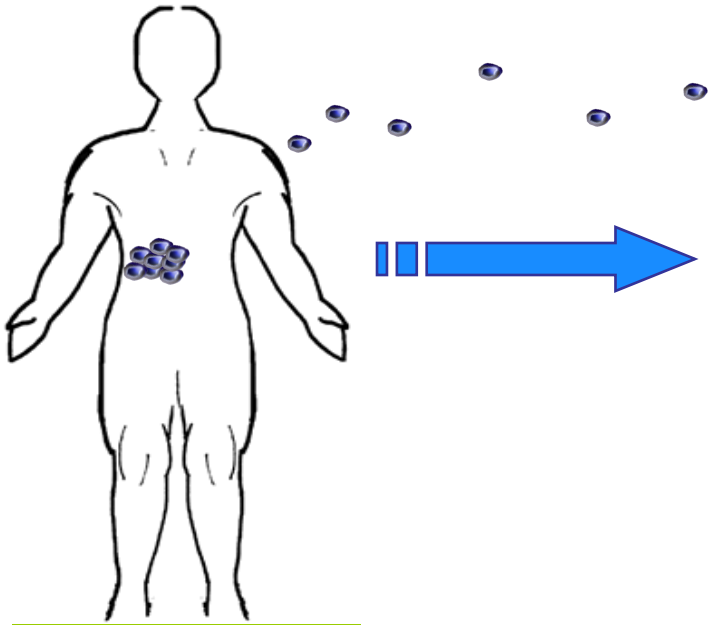

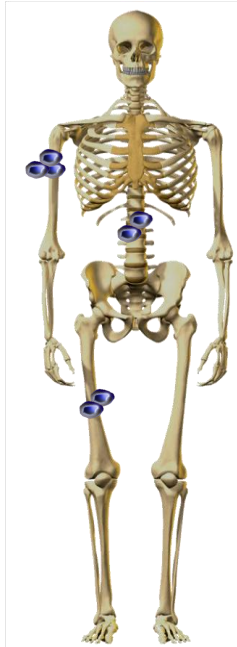

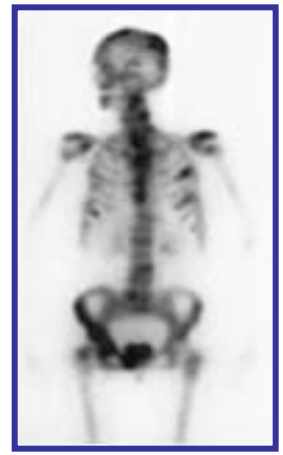

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Docetaxel rechallenge in CRPC…

- Common practive in medical oncology
  - → Platinum based chemotherapy: ovarian, SCLC, NSCLC…
  - → Oxaliplatine in colon cancer

- Only small retrospective trials in CRPC
  - → No randomized trial
  - → No clear definition of « taxane sensitive » disease

Authors	Pts (N)	PSA response	mPFS
Loriot et al, 2010	39	38-64%	4.3 months
Ross et al, 2008	34	18%	3 months

- Phase III trial docetaxel versus docetaxel+OGX011

When to start chemotherapy?

- What to do when docetaxel eventually fails?
  - → Cabazitaxel or Abiraterone or …clinical trials
- Docetaxel alone or in combination (estramustine)?
  - → Other drugs in development
  - → Combination treatment in development
- Early (asymptomatic) or late (symptomatic) chemotherapy?
  - → Clinical trials ongoing

- Docetaxel based chemotherapy in CRPC
- New tubulin agent in CRPC: Cabazitaxel
- Other drugs and Combination therapy
- Strategy in prostate cancer (early stage)
- Perspectives

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New drugs in CaP (w/wt Do

How to accelerate drug developement?

- Targeting bone
  - Endothelin-1 - ZD 4054, Atrasentan
  - Rx-pharms - Samarium
  - Rank-L axis - Denosumab
- Targeting angiogenesis
  - Bevacizumab
  - VEGF-Trap
  - ZD 64 74
- Targeting IL6
  - Centocor
- Vitamin D analog
  - DN-101 (calcitriol)
- Targeting IGF-R
  - Anti-IGF-R
- Alkylating agent
  - Satraplatin
- Vaccines
  - APC 8015 (Provenge)
  - GVAX

Courtesy K Fizazi

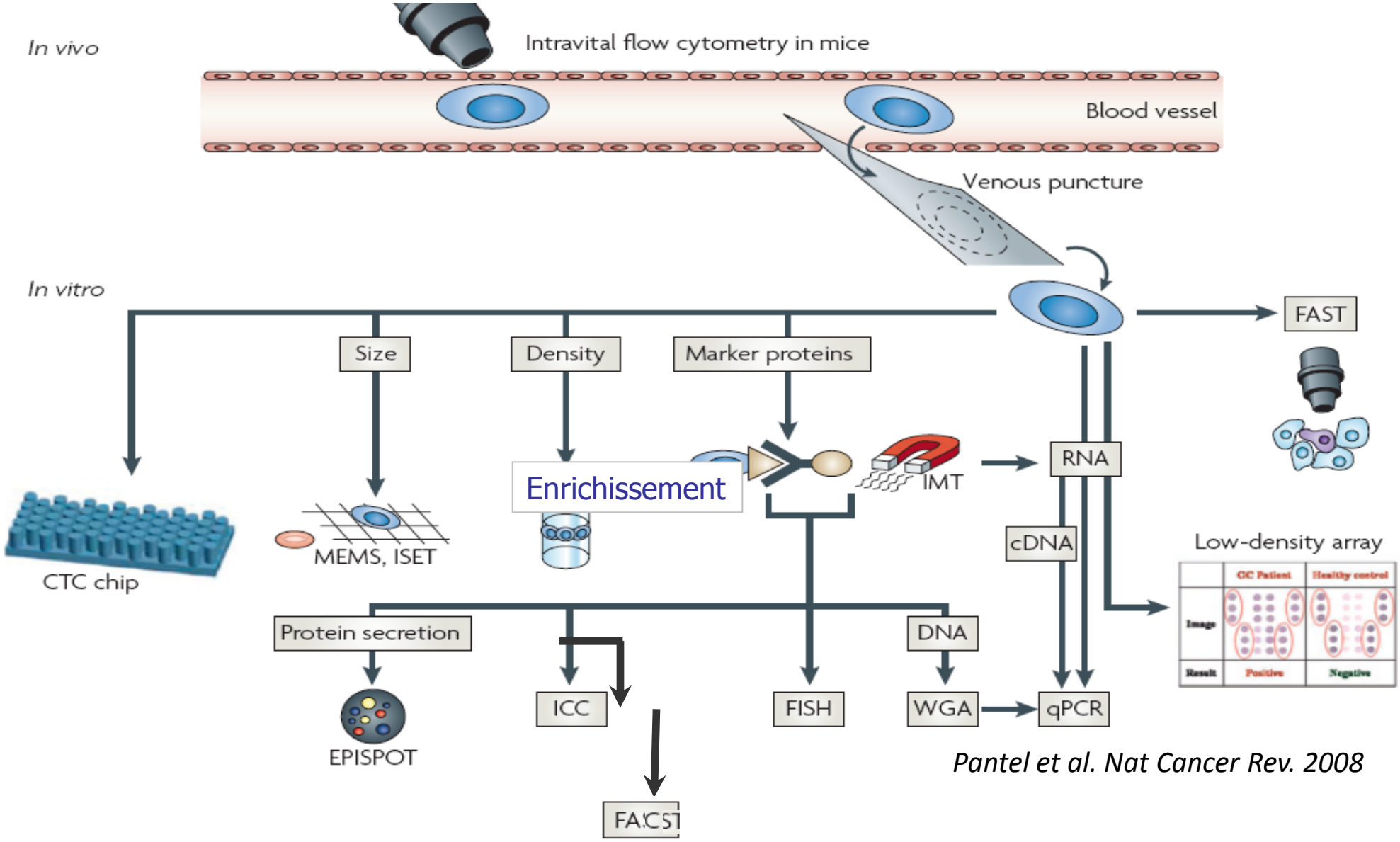
Learning too little, too late?

- We need to design clinical trials that can test and answer critical biological questions about disease drivers utilizing targeted drugs and biomarkers (DeBono, ASCO 2008)

- Molecular biology
  - → Personnalized Medicine
- CTC evaluation is one of the most promising biomarker in cancer
  - → Previous studies in breast, colon and prostate cancer have shown that CTC corrlete with survival

Moreno et al, Urology 2001; Moreno et al, Urology 2006;
Cristofanilli et al, NEJM 2004
Meropol et al, ASCO 2007

Isolation/Detection of CTC in peripheral blood



Pantel et al. Nat Cancer Rev. 2008

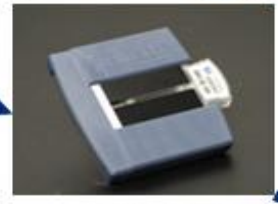
VERIDEX: CellSearch™ System

1. Selection positive EPCAM
2. Staining : CK 8/18/19, CD45, DAPI
3. others: HER2/Neu, MUC1, EGF-R)

Sample Collection

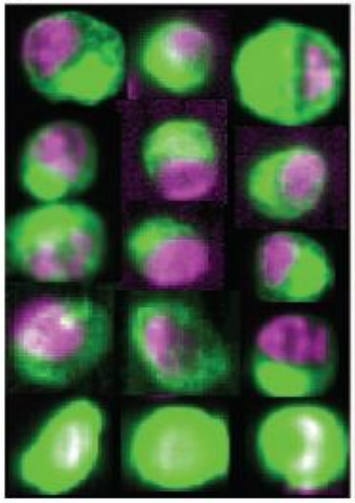
Reagents:
CTC capture
& staining

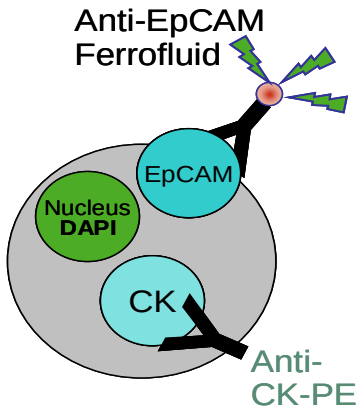
Sample
Processing



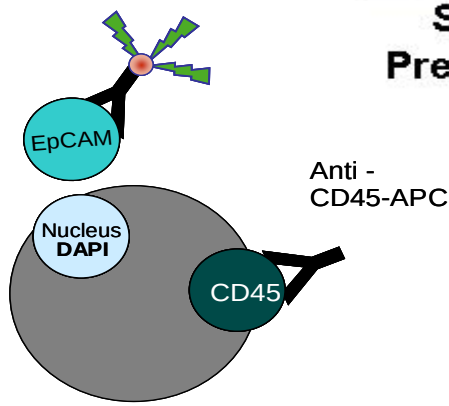
Sample
Presentation

Sample
Analysis





Epithelial
Cell

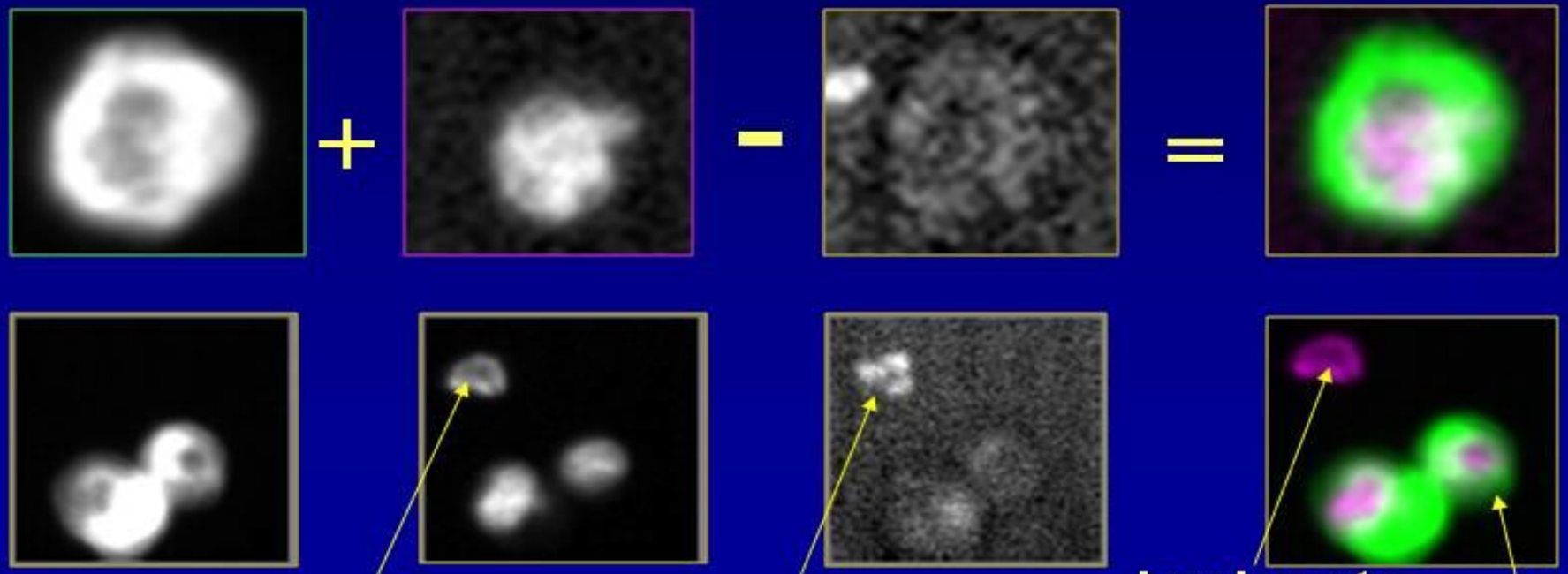


Leukocyte

CellSearch™ System: Images of Tumor Cells

Cytoplasm Nucleus Cell Membrane Composite

CK-PE pos		DAPI pos		CD45-APC neg		Tumor Cell



Leukocyte nucleus

CD45+ Membrane

Leukocyte

Tumor Cell

Potential Applications for detection of Micrometastatic Tumor Cells (CTCs)

Prediction of prognosis and real-time monitoring of the efficacy of systemic therapies

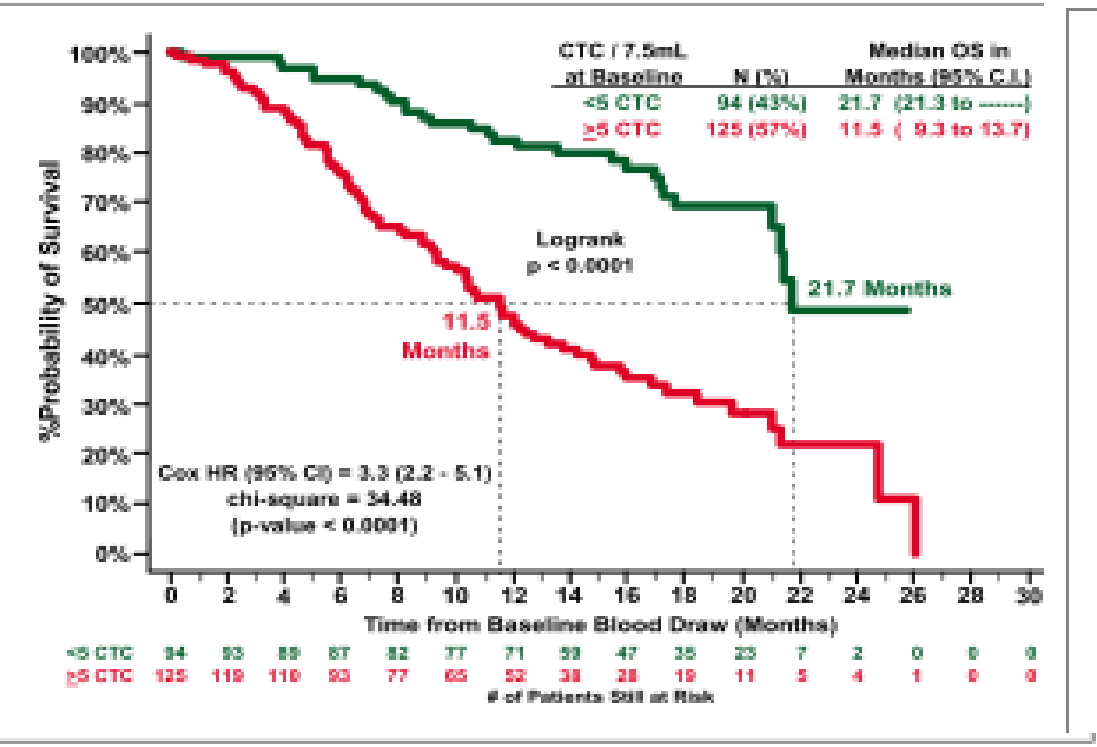
- Marker of recurrence (prognosis and stratification)
- Marker of response to therapy (surrogate marker)
- More readily available source of tumor to mesure target modulation (biological therapies)
- Source of material to study biology of metastasis

Circulating tumor cells (CTCs) and epithelial cancers

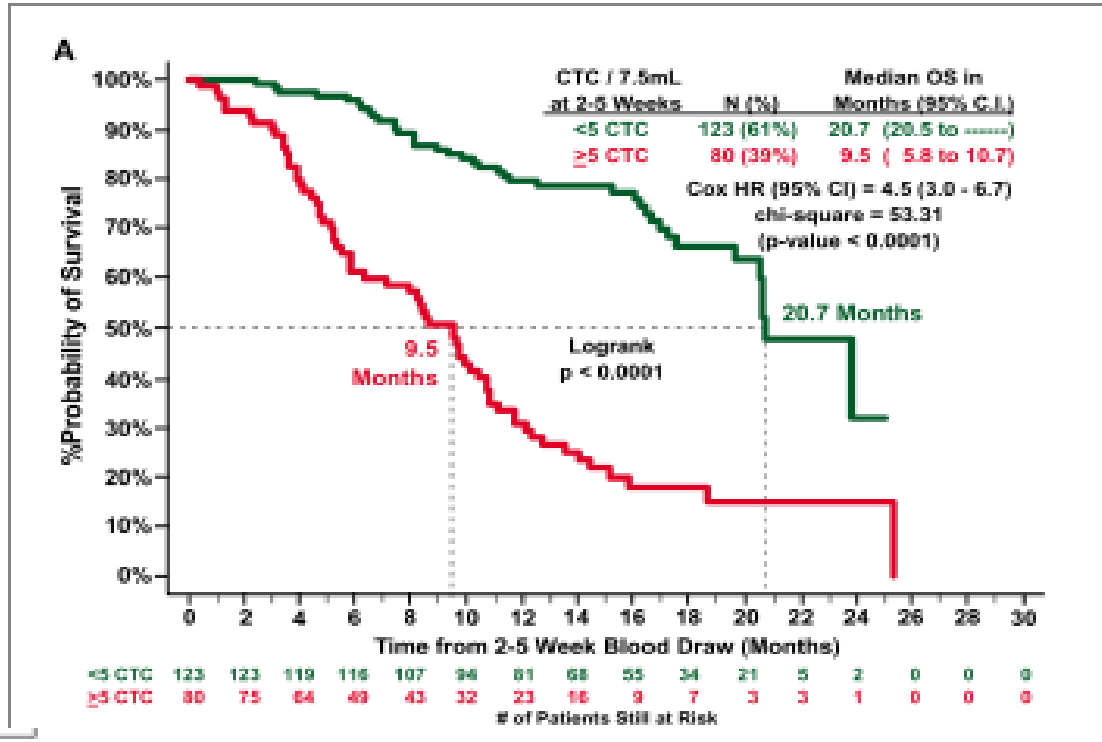
Prognostic and predictive information in advanced solid tumors

Breast cancer, colon cancer, prostate cancer…

Before



After



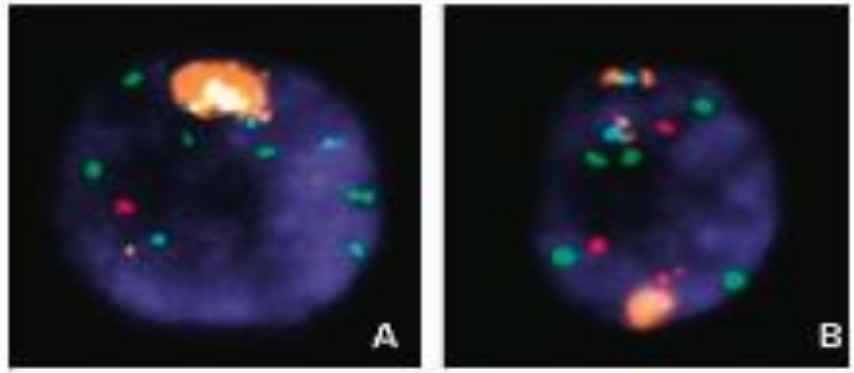
CTC at baseline and 2-5 weel after start of therapy predict survival in men undergoing treatment for CRPC

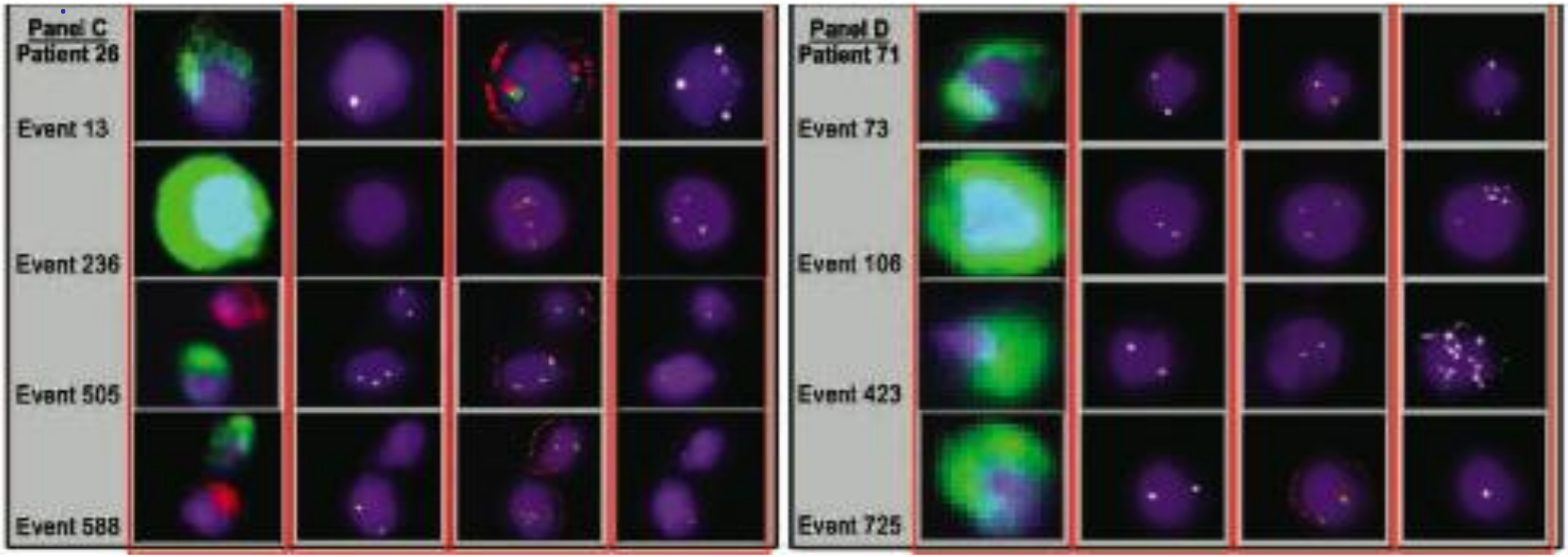
DeBono et al, CCR 2008

CTC as a « Surrogate » marker of tumor? Molecular characterization

The CellTracks® technology also supports the molecular evaluation of isolated CTC by:

- Immunofluorescence (IF) for protein expression
-Fluorescent in-situ hybridization (FISH)
for DNA amplification;
-Androgen receptor sequencing
- Detection of TMPRSS2/ETS gene translocations





Attard et al, Cancer Res 2009; Leversha et al, Clin Cancer Res 2009

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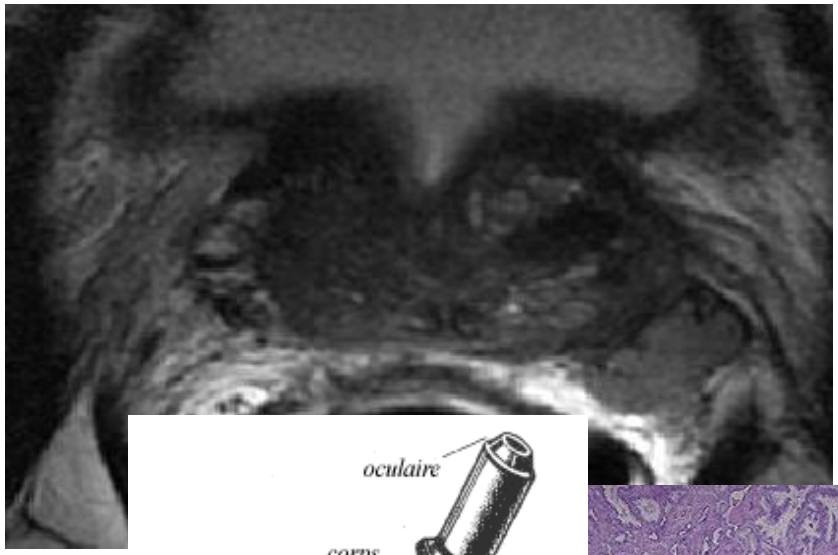
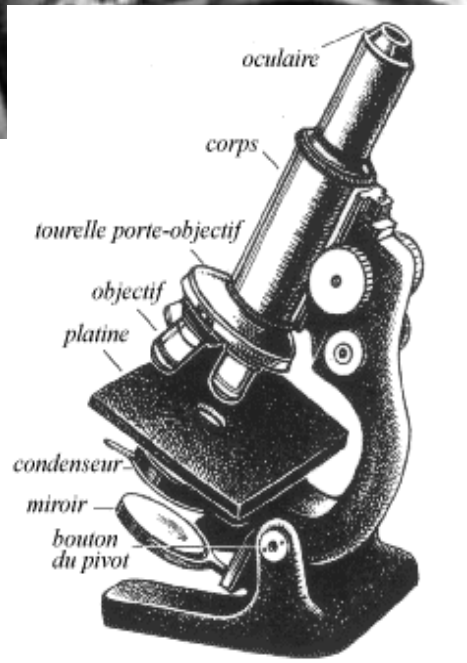
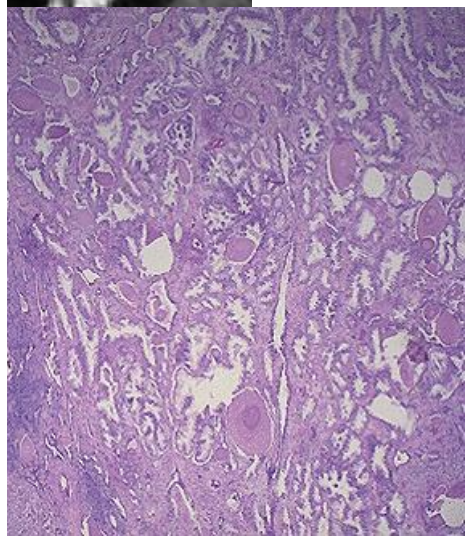
What is Prostate Cancer ? An Old view







The same treatment for everybody?
For different disease?

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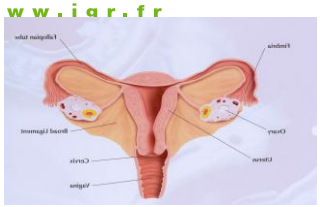
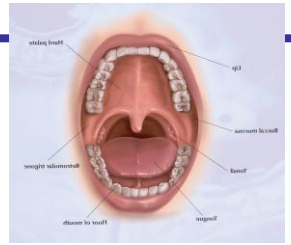
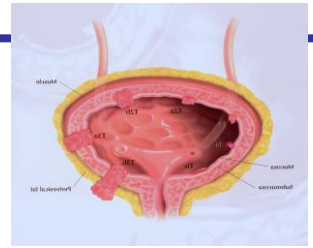
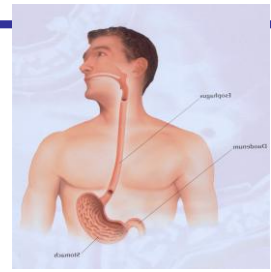
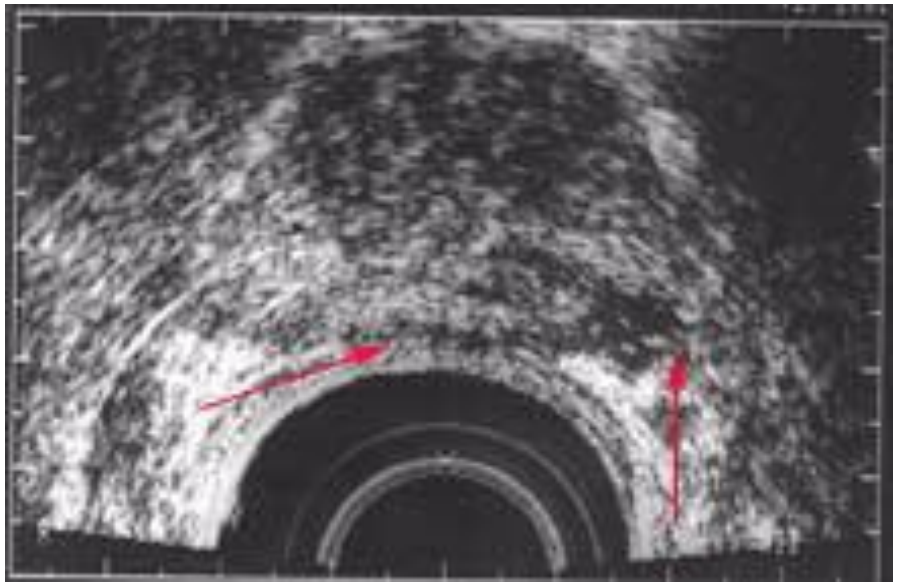
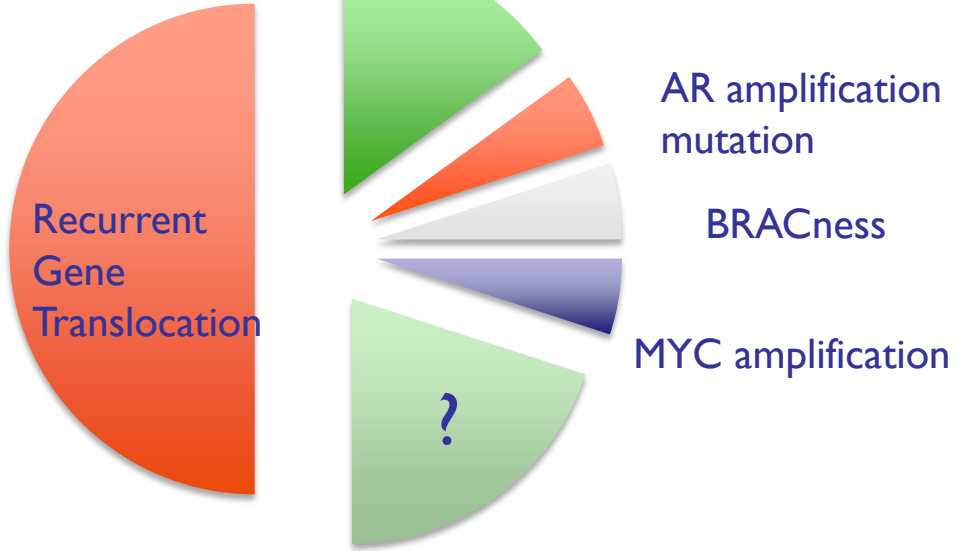





Pathology-based therapy

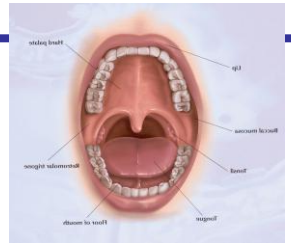
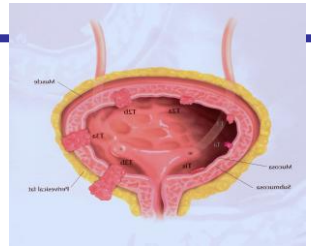
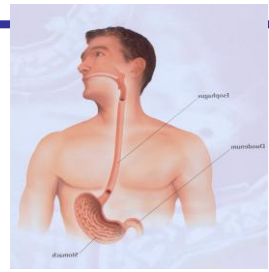
cytotoxic





IGF-1R activation
Bcl2 expression
P53
Pim Kinase

Molecular classification and Target-oriented therapy

Pathology-based therapy

cytotoxic

Courtesy to Dr Besse

PTEN loss

AR amplification
mutation

BRACness

MYC amplification

IGF-1R activation
Bcl2 expression
P53
Pim Kinase

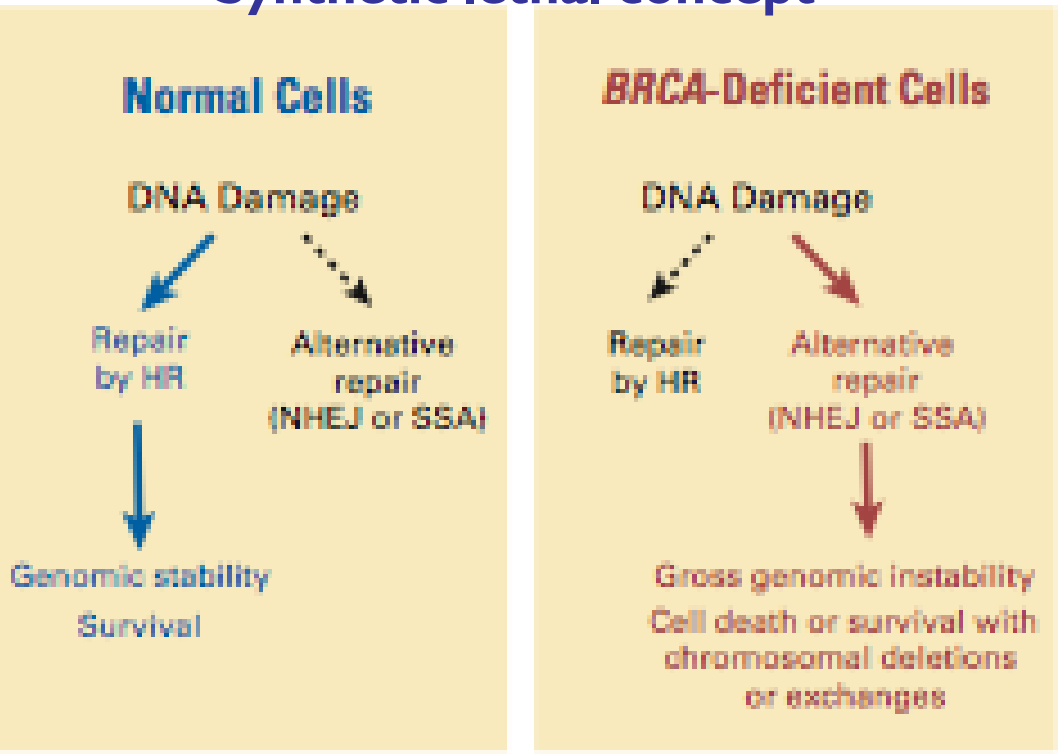
Molecular classification and Target-oriented therapy

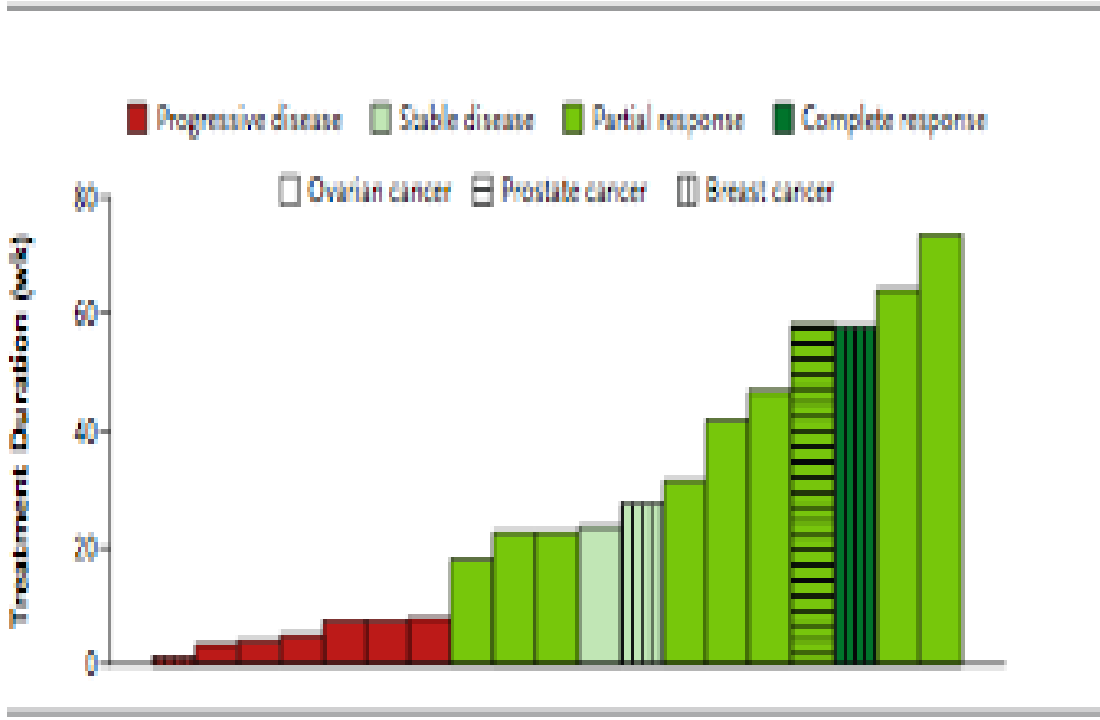
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 9, 2009 VOL. 361 NO. 2

Inhibition of Poly(ADP-Ribose) Polymerase in Tumors from *BRCA* Mutation Carriers

Synthetic lethal concept





Ashworth A, JCO 2008; Fong et al, NEJM 2009

Conclusion

- Docetaxel based chemotherpy is the standard of care in metastatic CRPC patients
- Cabazitaxel is a potential new therapeutic option for the treatment of patients with mCRPC after failure of docetaxel-based therapy
- Other agents are in development, alone or in combination with docetaxel/cabazitaxel based chemotherapy
- We need to incorporate molecular biology in our clinical daily practive in the next decade…

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