Le cancer de la prostate

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Service de pharmacie clinique

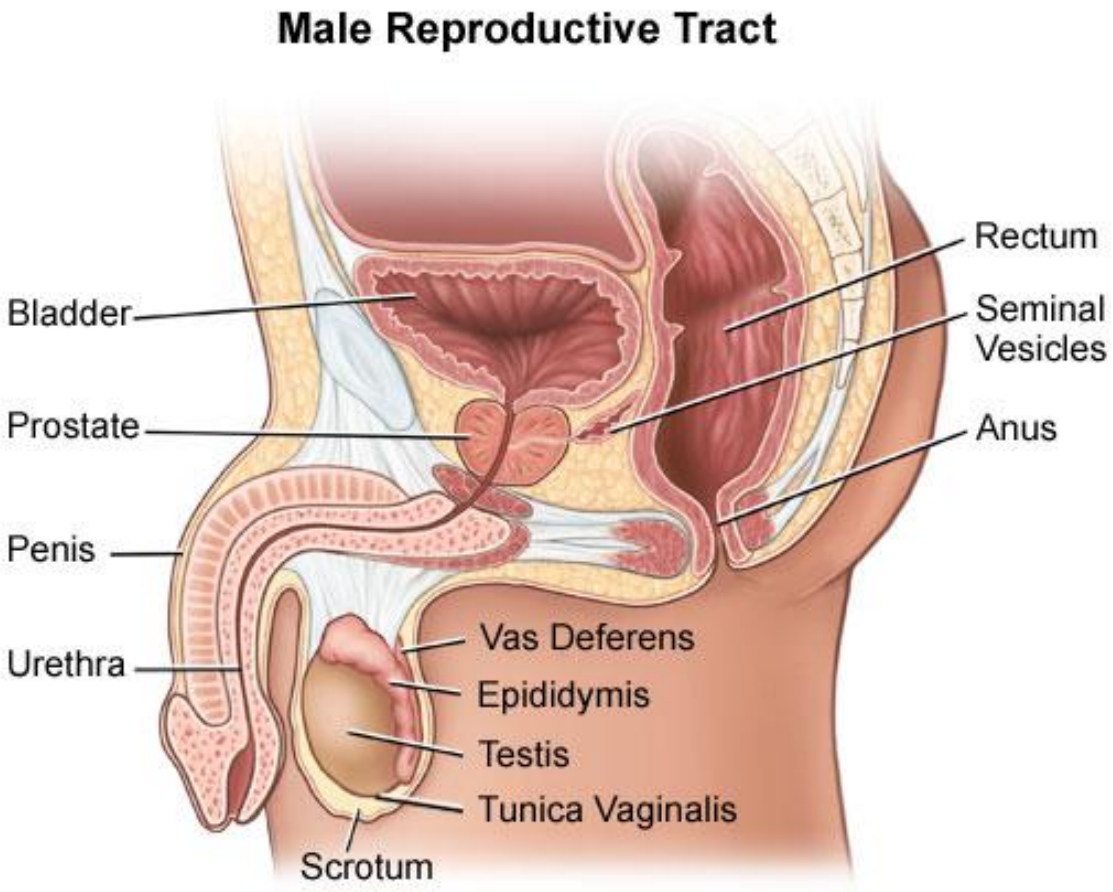
CHU de Liège

Structure de l'exposé

- Rappel anatomique
- Eléments d'épidémiologie
- Approche prophylactique
- Clinique
- Classification
- Thérapeutiques
- Perspectives

Adolph Gottlieb (1903-1974), Penumbra

Rappel anatomique



Epidémiologie

- 3ème cause de mortalité (Poumon>C-R>prostate)
- Mortalité en recul ~20% (1983-87 2003-07-
- 1er cancer urologique : Adénocarcinome>>
- Incidence en augmentation (PSA)

Incidence selon l'âge

Sur 100 000

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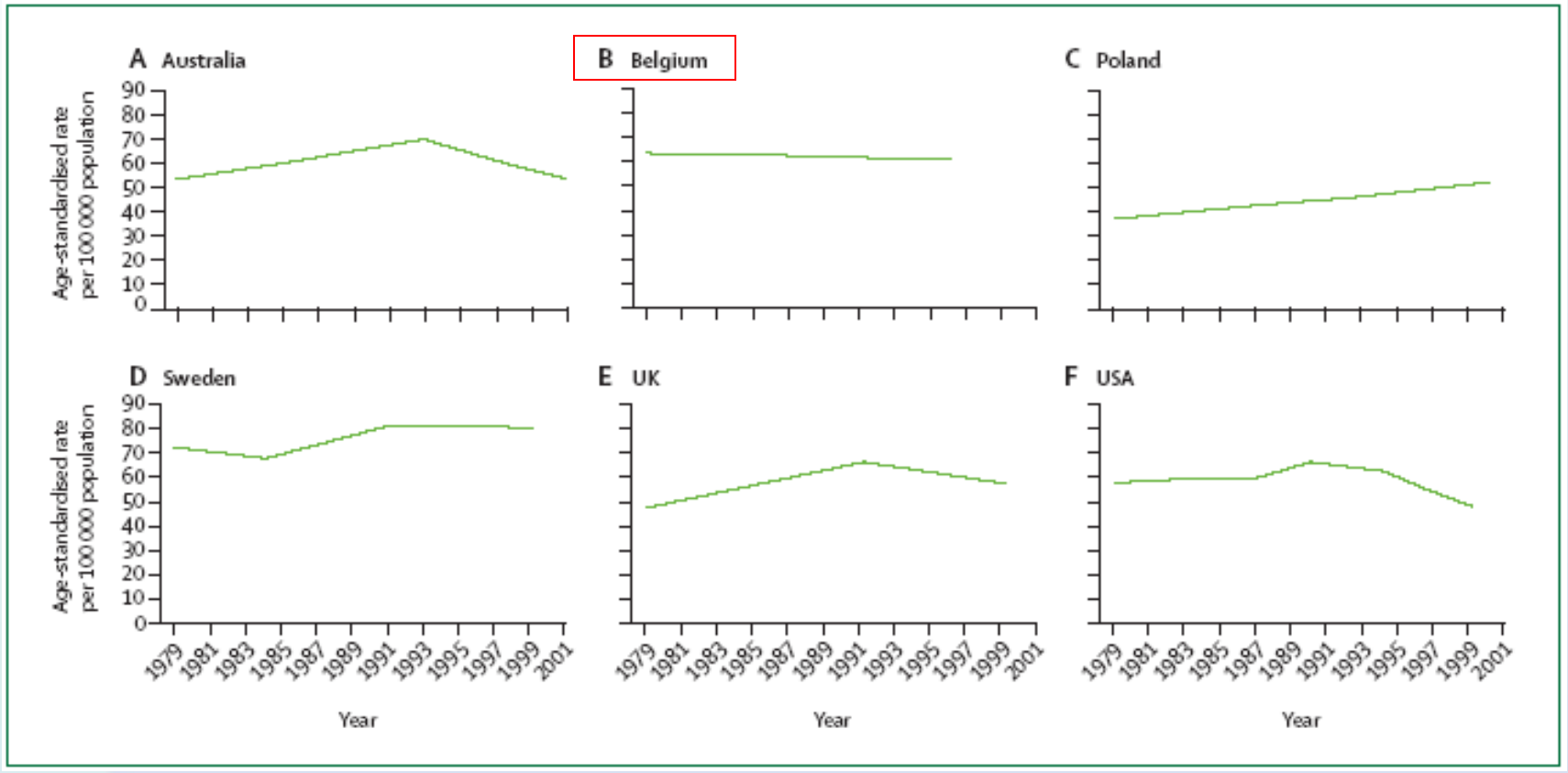
Mortalité



Lancet 2008; 371: 1710–21

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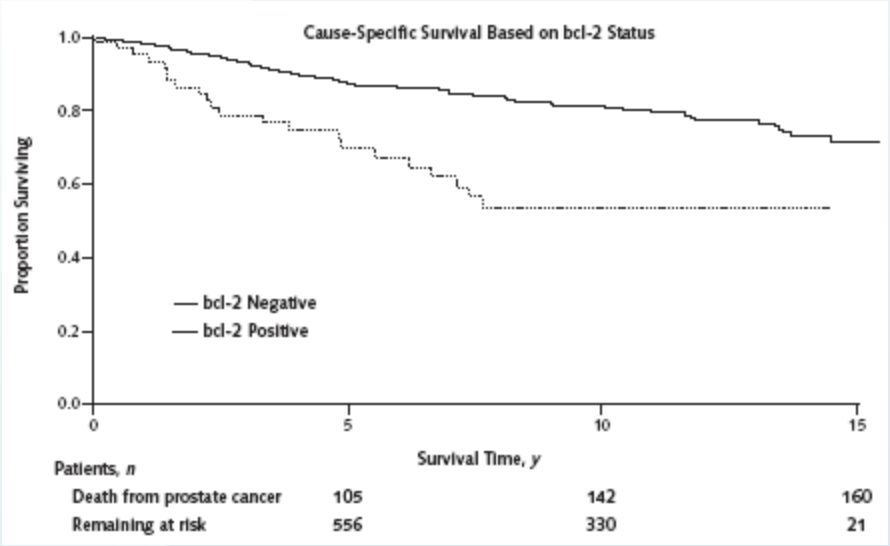
Facteurs prédictifs de mortalité ?

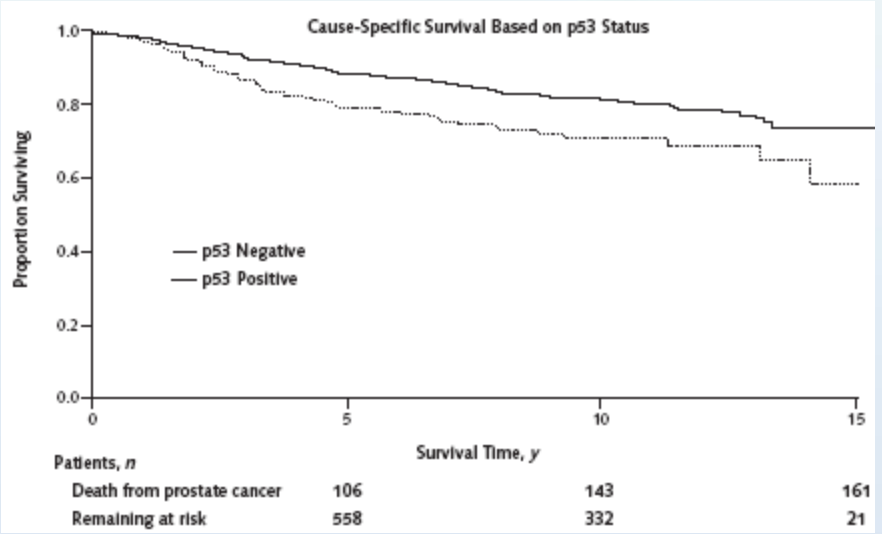
- Cycle cellulaire : **bcl-2** and **p53**
- Angiogenèse :β-3 integrin, VEGF, **densité de microvaisseaux**

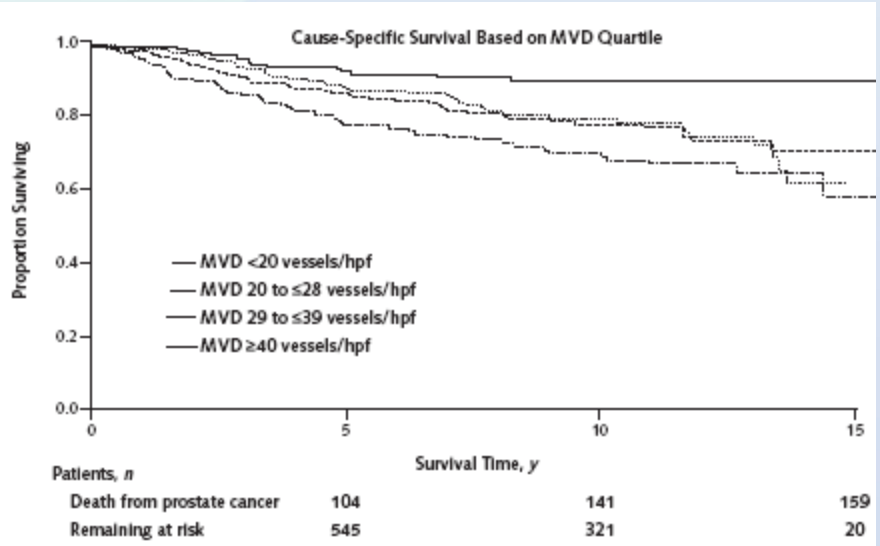
Annals of Internal Medicine | ARTICLE

Molecular Markers and Death From Prostate Cancer

John Concato, MD, MPH; Dhanpat Jain, MD; Edward Uchio, MD; Harvey Risch, MD, PhD; William W. Li, MD; and Carolyn K. Wells, MPH







Conclusion: Immunohistochemical evidence of bcl-2, p53, or high microvessel density in prostate cancer biopsy specimens at diagnosis is associated with an increased long-term risk for death from prostate cancer.

Ann Intern Med. 2009;150:595-603.

Facteurs de risque

- Sexe
- Age (! sarcome sujet jeune !)
- Obésité
- Ethnie : Africain > Blanc > Asiatique

  Rem : Agressivité Afro-blanc >>
- ATCD irradiation pelvienne
- Exposition à la testostérone *in utero*

Récemment…La chiromancie

- Testostérone *in utero* basse : index plus long

- Testostérone *in utero* élevée : index plus court

15 ans (1994-2009)

1524 patients cancéreux

3044 patients sains

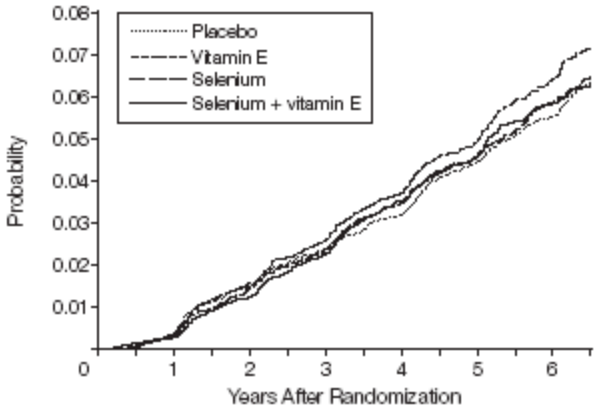
Br J Cancer. 2011 Jan 4;104(1):175-7..

Vers une « prophylaxie » ?

Effect of Selenium and Vitamin E on Risk of Prostate Cancer and Other Cancers

The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

Figure 2. Cumulative Incidence of Prostate Cancer Detected Each Year by Intervention Group

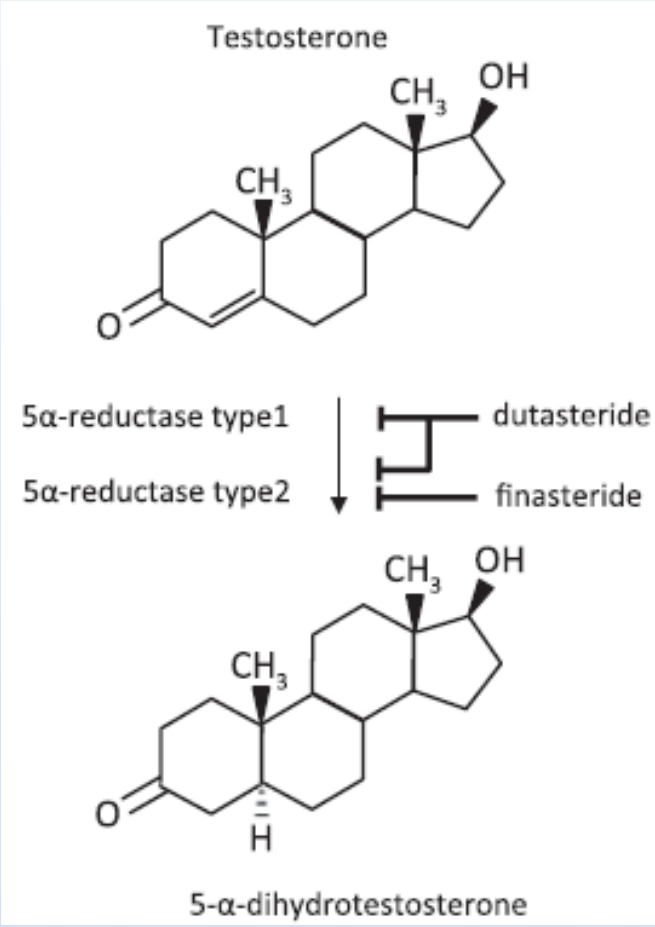


No. at risk							
Placebo	8689	8553	8328	8039	7389	4892	2516
Vitamin E	8732	8610	8373	8098	7401	4867	2537
Selenium	8750	8597	8341	8063	7393	4848	2558
Selenium + vitamin E	8700	8585	8371	8097	7428	4894	2580

Conclusion Selenium or vitamin E, alone or in combination at the doses and formulations used, did not prevent prostate cancer in this population of relatively healthy men.

JAMA, January 7, 2009—Vol 301, No. 1

Inhibition de la 5-α reductase ?



Best Practice & Research Clinical Endocrinology & Metabolism 25 (2011) 355–367

Vers une « prophylaxie » ?

PCPT study

« The Prostate Cancer Prevention Trial »

Rates of cancer diagnosis in the Prostate Cancer Prevention Trial

5 mg/j

	All Prostate Ca	
	Finasteride	Placebo
No. tumors	757	1,068
No. Gleason score (%):		
2–6	477 (63.0)	831 (77.8)
7	190 (25.1)	184 (17.2)
7–10	280 (37.0)	237 (22.2)
8–10	90 (11.9)	53 (5.0)

The Journal of Urology, Vol 182, Issue 2,2009, 499-508

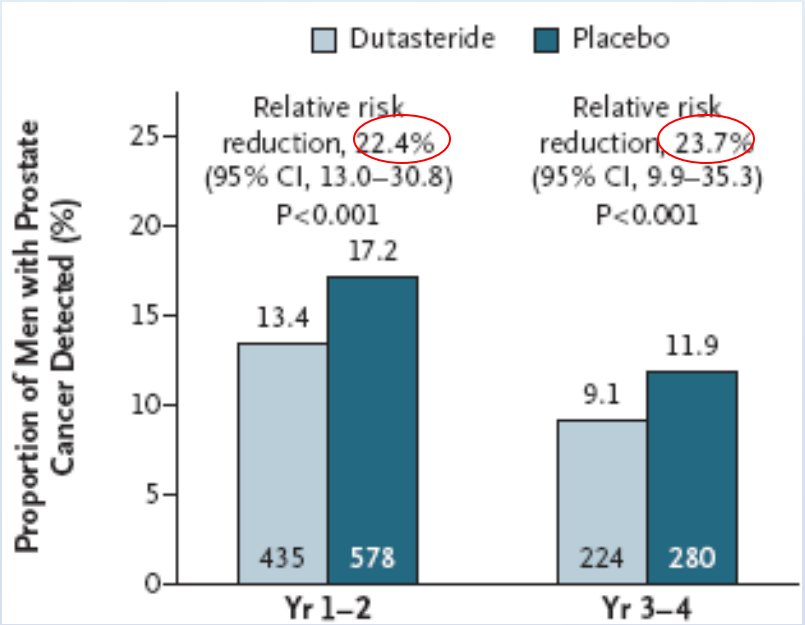
Vers une « prophylaxie » ?

ORIGINAL ARTICLE

Effect of Dutasteride on the Risk of Prostate Cancer

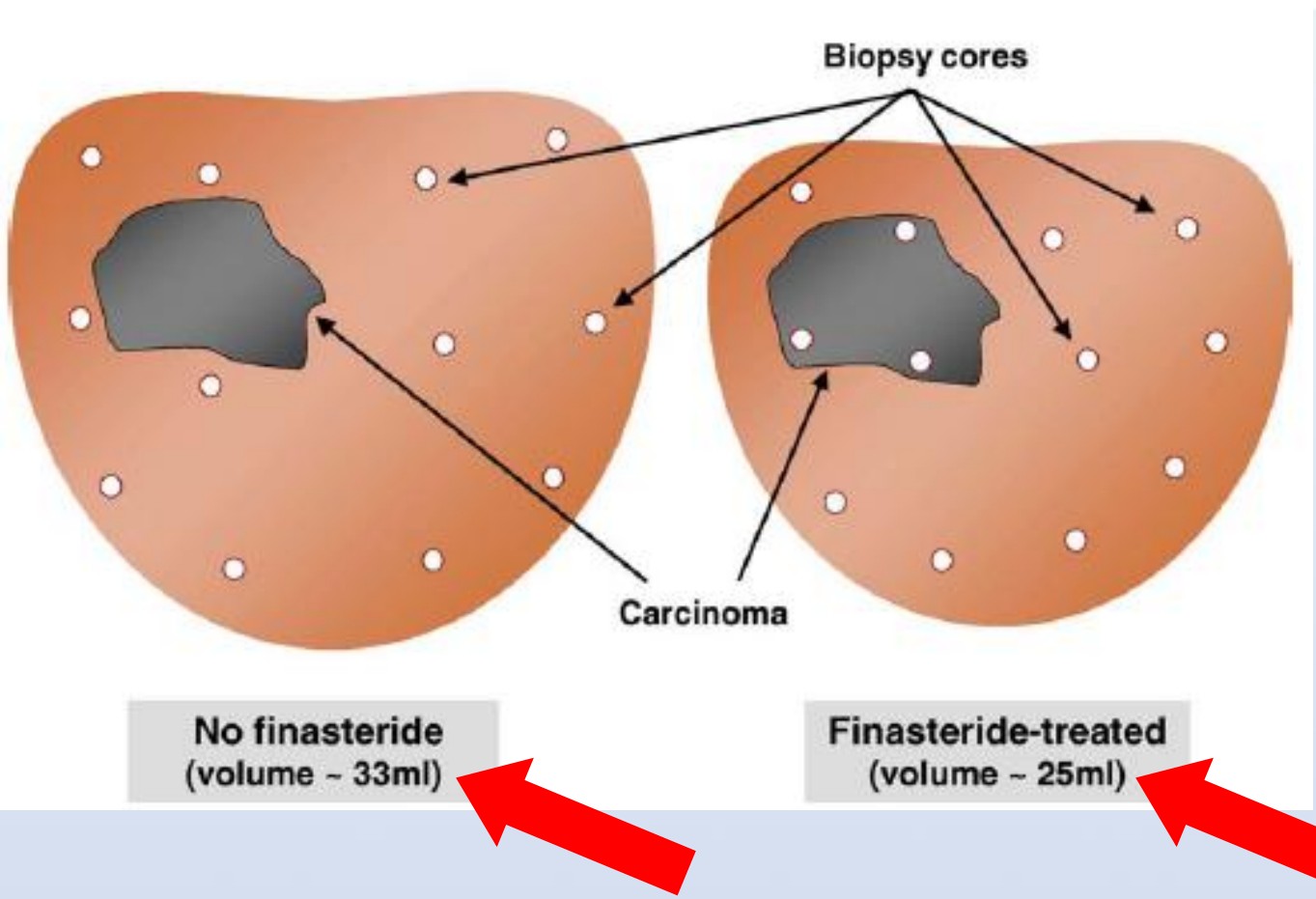
0,5 mg/j

Event	Dutasteride (N=4105)	Placebo (N=4126)	P Value†
	no. (%)		
Any adverse event	3017 (73.5)	2966 (71.9)	0.10
Any serious adverse event	748 (18.2)	837 (20.3)	0.02
Drug-related adverse event			
Any	904 (22.0)	604 (14.6)	<0.001
Leading to permanent discontinuation of treatment	176 (4.3)	83 (2.0)	<0.001
Occurring in ≥1% of subjects in either study group			
Decreased libido	137 (3.3)	65 (1.6)	<0.001
Loss of libido	79 (1.9)	54 (1.3)	0.03
Erectile dysfunction	369 (9.0)	237 (5.7)	<0.001
Decreased semen volume‡	56 (1.4)	9 (0.2)	<0.001
Gynecomastia	76 (1.9)	43 (1.0)	0.002
Death§	70 (1.7)	77 (1.9)	0.65



N Engl J Med 2010;362:1192-202.

Plus de tumeurs de haut grade ?



european urology supplements 5 (2 0 0 6) 634–639

Une question non élucidée…

Conclusion de Minerva

Chez des patients à risque élevé de cancer prostatique, un traitement par dutastéride pendant 4 ans réduit l'incidence de cancer prostatique détecté lors de biopsies systématiques mais avec augmentation des cancers prostatiques de haut grade. Des constatations semblables avaient été faites avec le finastéride.

Pour la pratique

Un guide de pratique récent[4] n'aborde pas l'intérêt des inhibiteurs des 5 alpha-réductases dans la prévention du cancer de la prostate. Une synthèse méthodique de la Cochrane Collaboration[3] souligne à ce propos un moindre risque de diagnostic de cancer chez des hommes à risque, avec des effets indésirables et sans connaissance de l'effet sur la mortalité. Sur base de ces données, des experts[5] n'en recommandent pas l'utilisation sauf chez des patients à haut risque et bien informés. La FDA vient de refuser cette extension d'indication pour le dutastéride (comme pour le finastéride)[6].

minerva juin 2011 volume 10 numéro 5

Clinique

- PROSTATISME (gène à la vidange)

  Dysurie
  Faible jet
  Pollakiurie (nocturne svt)
  Impériosité

- Hématurie
- Hémospermie,…

!NON SPECIFIQUE!

Le PSA

- = Glycoprotéine fabriquée par la cellule prostatique et éliminée essentiellement dans le sperme

- Petite fraction dans le sérum (norme 0 à 4 ng/ml) libre ou lié à des protéines

- [PSA]sg libre / [PSA]sg total < 18%

  ➔ SUSPICION NEOPLASIE

Le PSA

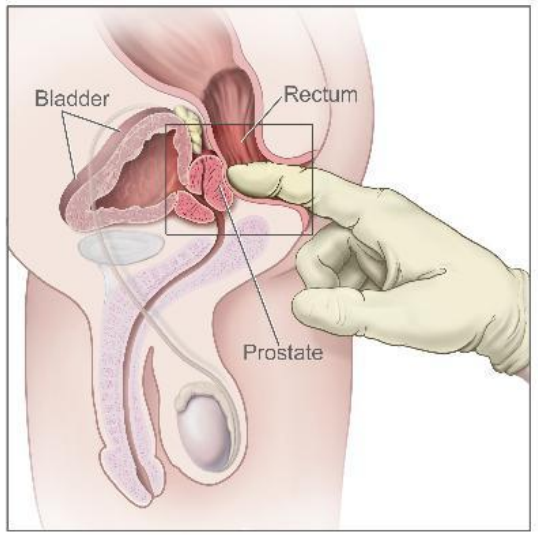
- Augmente en cas de prostatite, HTBP, cancer,etc. Bref, NON SPECIFIQUE
- Valeur pronostic de sa **vélocité**
- Augmentation avec l'âge physiologique

Tableau 1 Niveau de l'antigène spécifique de la prostate (PSA) selon l'âge.

Âge	PSA en ng ml^{-1}
40-49	0-2,5
50-59	0-3,5
60-69	0-4,5
70-79	0-6,5

Annales d'urologie 38 (2004) 137–147

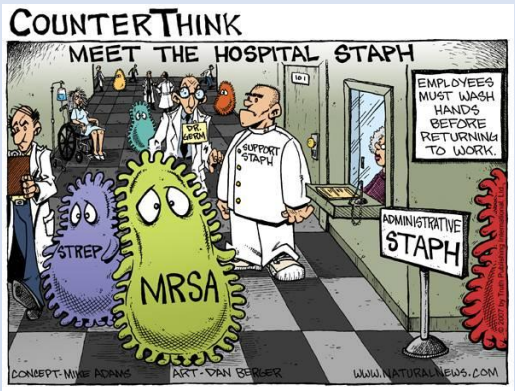
Examens



« Infos locales »

- Toucher rectal (nodule)
- Echographie endo-rectale +- Doppler (vascularisation)
- Biopsie (affirme ou infirme le diagnostic)

  Lavement rectal + AB



Gradification

- Grade de Gleason : I ➔ IV

- Score de Gleason = Somme des 2 grades les plus représentés (2 à 10)

Tableau 2 Comparaison de l'espérance de vie des patients non traités par rapport à une population de référence du même âge, en fonction du grade.[2]

	Espérance de vie à 65 ans	Espérance de vie à 70 ans	Espérance de vie à 75 ans
Population générale	15,8 ans	12,7 ans	10 ans
CaP T1-T2	10,6 ans	8,2 ans	6,2 ans
Score de Gleason 2-4	16,1 ans	13 ans	10,2 ans
Score de Gleason 5-7	11,3 ans	8,8 ans	6,7 ans
Score de Gleason 8-10	7,9 ans	5,9 ans	4,4 ans

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Annales d'urologie 38 (2004) 225–258

Examens

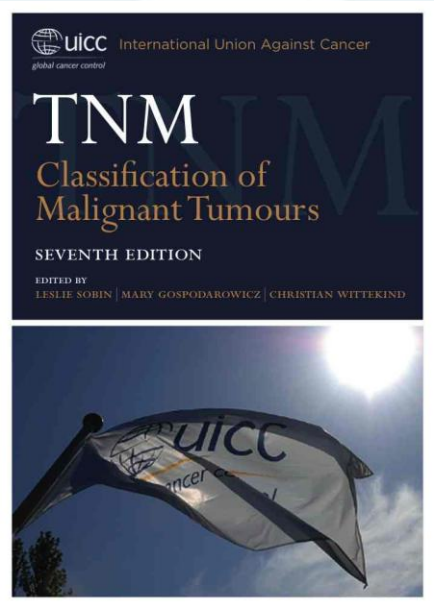
« Infos systémiques »

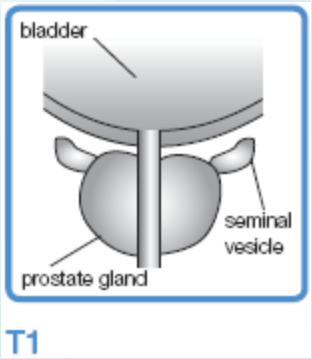
- Scintigraphie osseuse (M_0-M_1)
- PET scan $F^{18}DG$ (sauf cerveau, vessie)

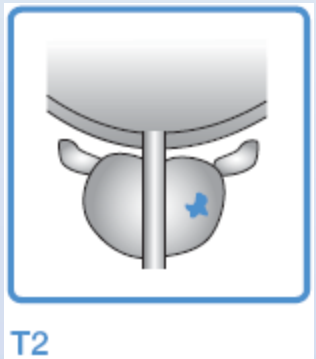
➔ Classification TNM

Classification TNM

- T : Taille (X, I→IV)
- N : Nodes (X, 0,1)
- M : Metastase (X, 0,1, 1a,1b)







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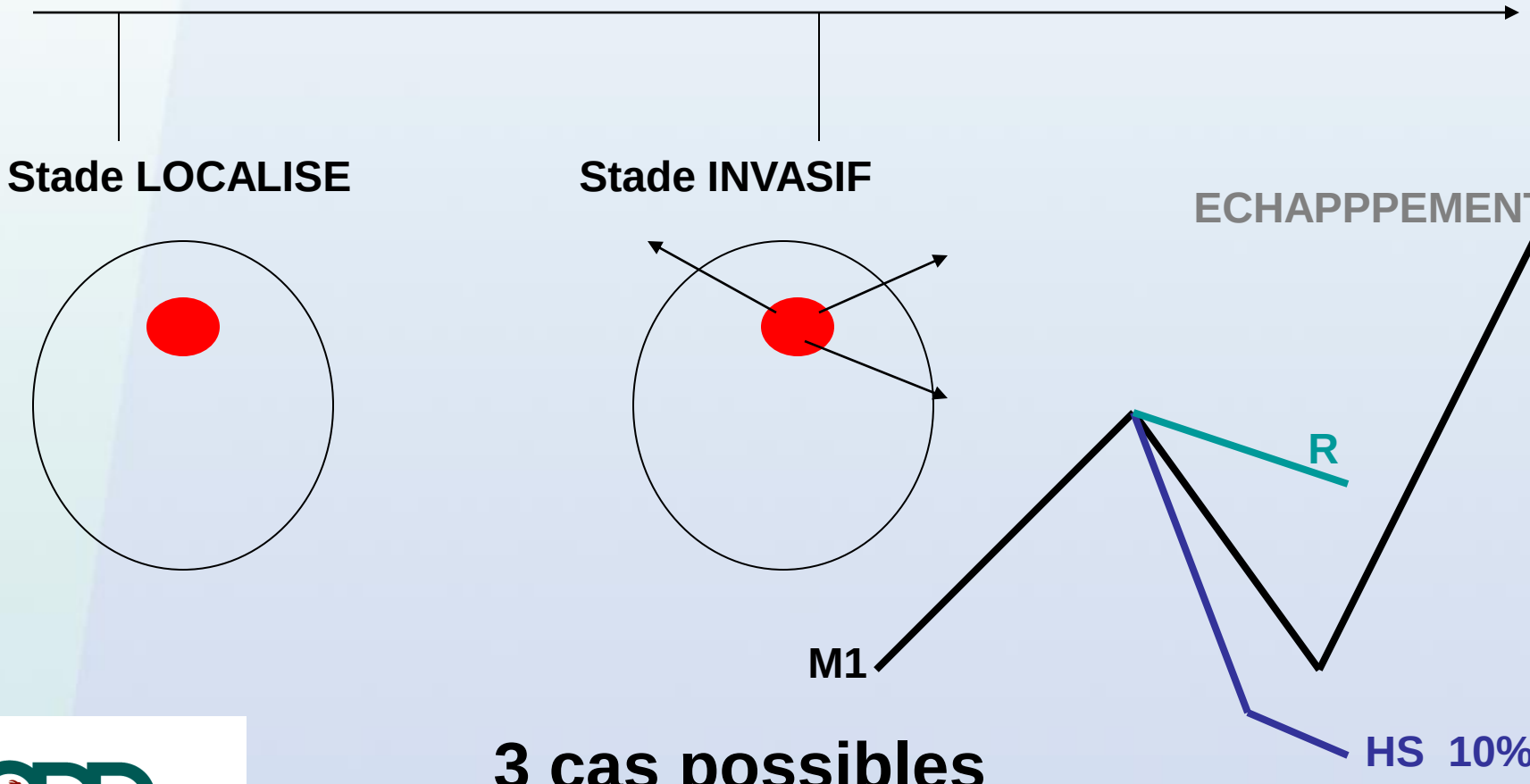
Histoire naturelle



3 cas possibles

« Combien de temps ? »

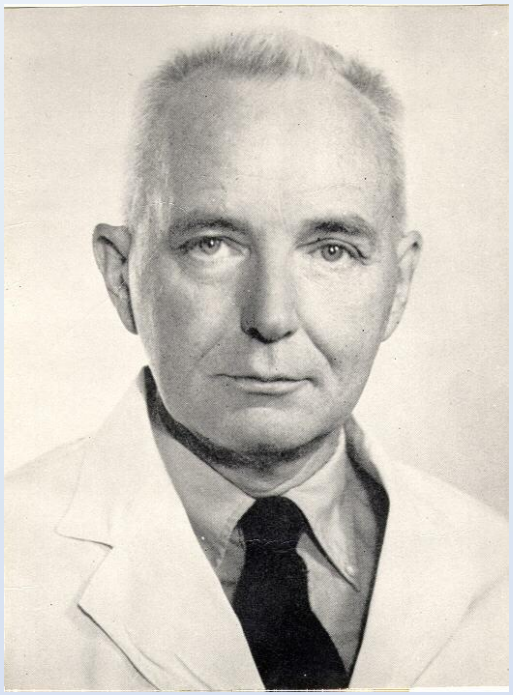
Stade	Survie Médiane
Rising PSA seult	**≈ 4 ans ?**
Métastases asymptomatiques (limitées)	**≈ 18–24 mois**
Métastases asymptomatiques (étendues)	**≈ 18 mois**
Métastases Symptomatiques	**≈ 9–16 mois**

Les traitements

- Hormonothérapie
- Chimiothérapie

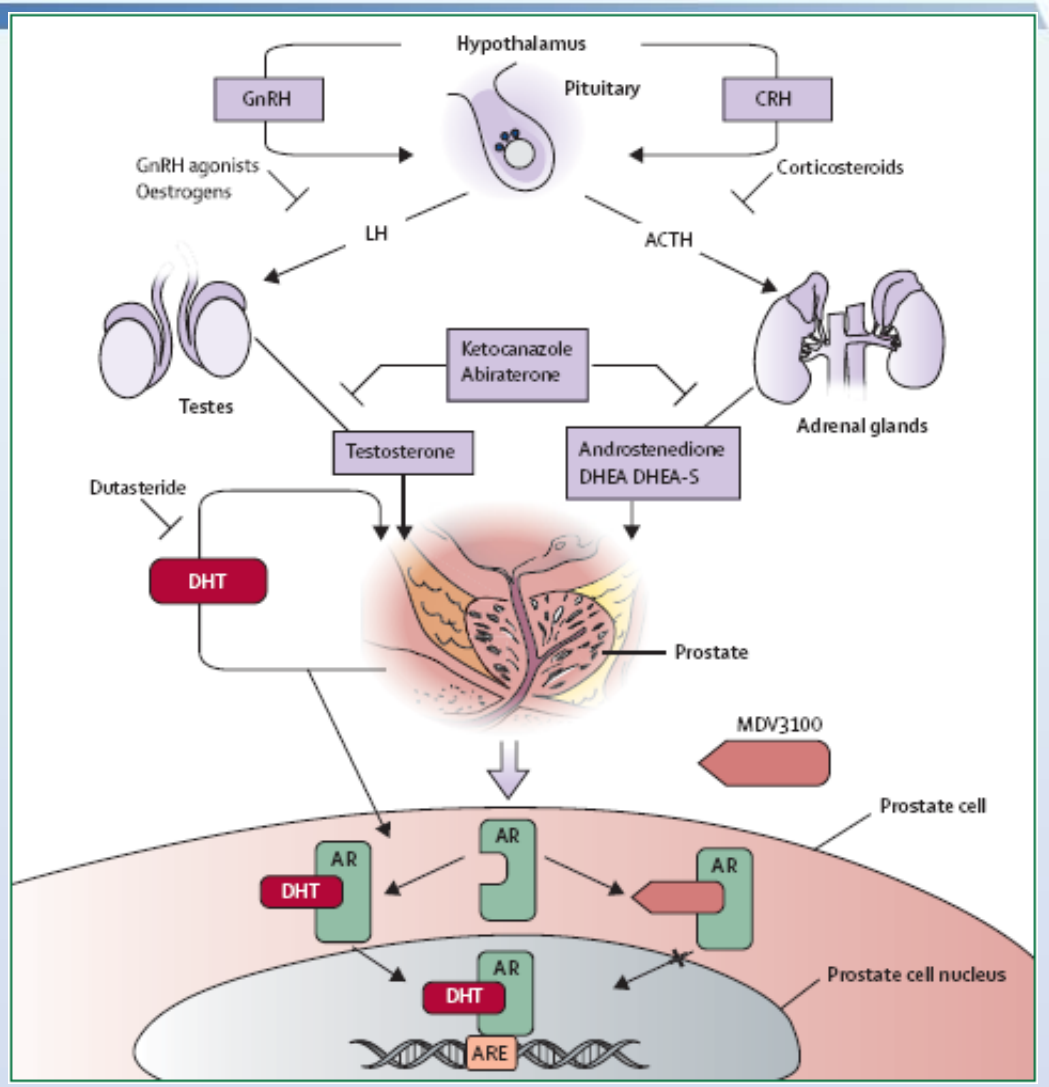
L'hormonothérapie

Cancer HORMONODEPENDANT



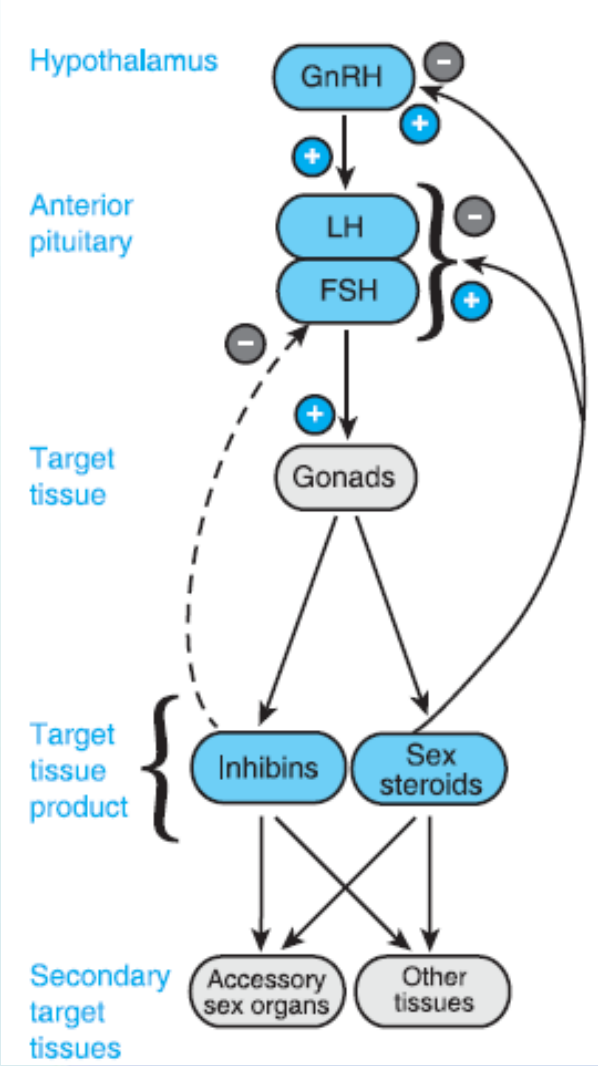
Huggins C., Hodges C.: Studies on prostatic cancer. Effects of castration, of oestrogen and of androgen injections on serum phosphatases in metastatic carcinoma of the prostate. Cancer Research (1941) 1: 293-297

Thérapeutique



Lancet Oncol 2009; 10: 981–91

Agonistes/Antagonistes LHRH



GnRH and GnRH Analogs

Analog (TRADE NAME)	Dosage Form
Agonists	
GnRH (FACTREL)	IV, SC
Leuprolide (LUPRON, ELIGARD, VIADUR)	IM, SC depot
Buserelin (SUPREFACT)	SC, IN
Nafarelin (SYNAREL)	IN
Deslorelin (SOMAGARD)	SC, IM, depot
Histrelin (SUPPRELIN)	SC
Triptorelin (TRELSTAR DEPOT, LA)	IM
Goserelin (ZOLADEX)	SC implant
Antagonists	
Cetrorelix (CETROTIDE)	SC
Ganirelix (ANTAGON)	SC
Abarelix (PLENAXIS)	SC depot

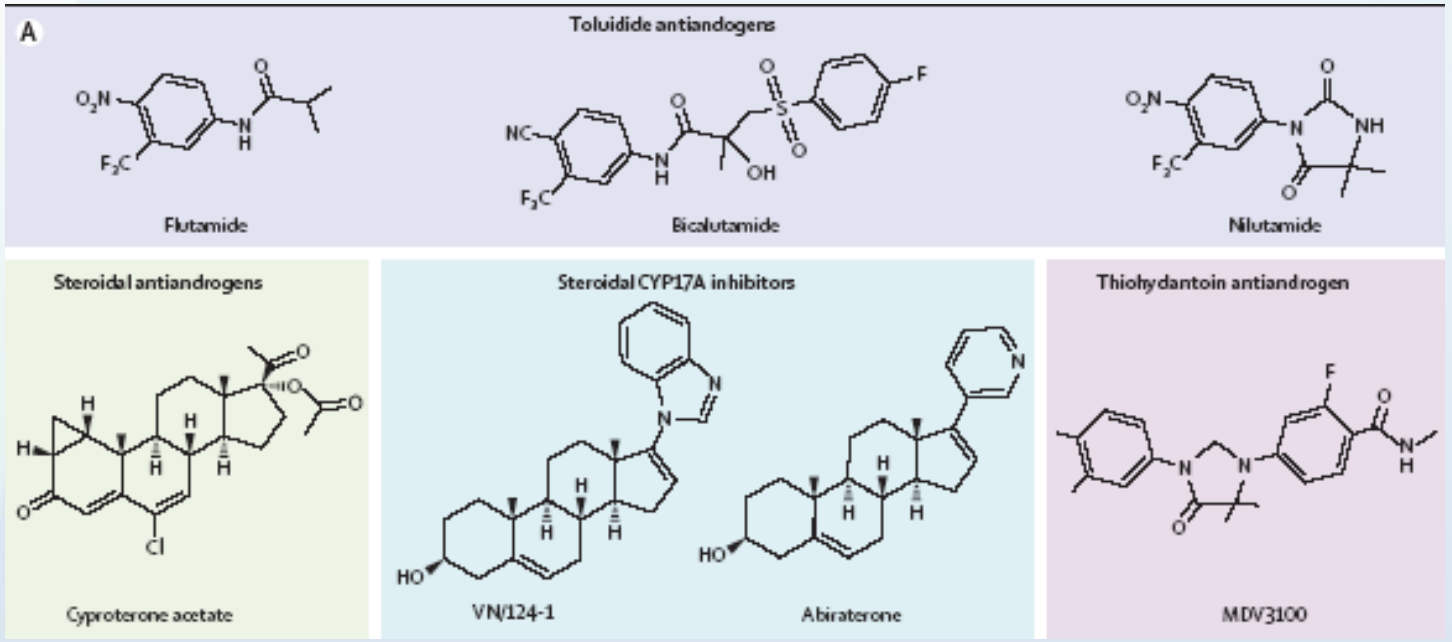
Agonistes/**Antagoniste LHRH**

LHRH = GnRH ➔ LH, FSH 

- *Buséréline* (SUPREFACT®)
- *Goséréline* (ZOLADEX®)
- *Histréline* (VANTASSE®)
- *Leuproréline* (DEPO-ELIGARD®) :7,5 mg/30j ; 22,5 mg/3 mois ; 44,5 mg/6mois
- *Triptoréline* (DECAPEPTYL®) : 0,1 mg (stérilité) ; 3,75 mg/ 4sem (CP + stérilité) ; 11,25 mg / 3mois ; 22,5 mg/6mois

- *Dégarélix* (FIRMAGON®): S.C. 2x120mg
- Abarélix

Médicaments



Lancet Oncol 2009; 10: 981–91

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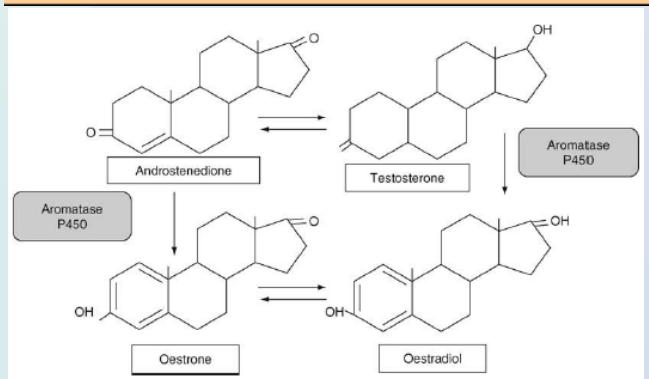
Anti-androgèniques

CASODEX ® **EULEXIN®** **ANDROCUR ®**

	Bicalutamide	Flutamide	Nilutamide	Cyproterone acetate
Half-life:	7 days	5–6 hours	2 days	30–40 hours
Dosage:	150 mg daily*	3 × 250 mg daily	3 × 100 mg daily†	3 × 100 mg daily
Side effects:	• hepatotoxicity (rarely) • hot flushes • breast tenderness • gynaecomastia (70%) • nausea • diarrhoea • impotence (20%)	• diarrhoea • hepatotoxicity (more frequent than other antiandrogens, may be fatal) • impotence (20%) • gynaecomastia	• visual disturbances (delayed adaptation to darkness 3%)‡ • alcohol intolerance (20%)‡ • nausea • hepatotoxicity (rarely, may be fatal) • interstitial pneumonitis° • impotence (50%),	• lower testosterone levels • loss of libido • impotence (80%) • rarely gynaecomastia • cardiovascular toxicity (4–40%§) • hepatotoxicity (may be fatal)

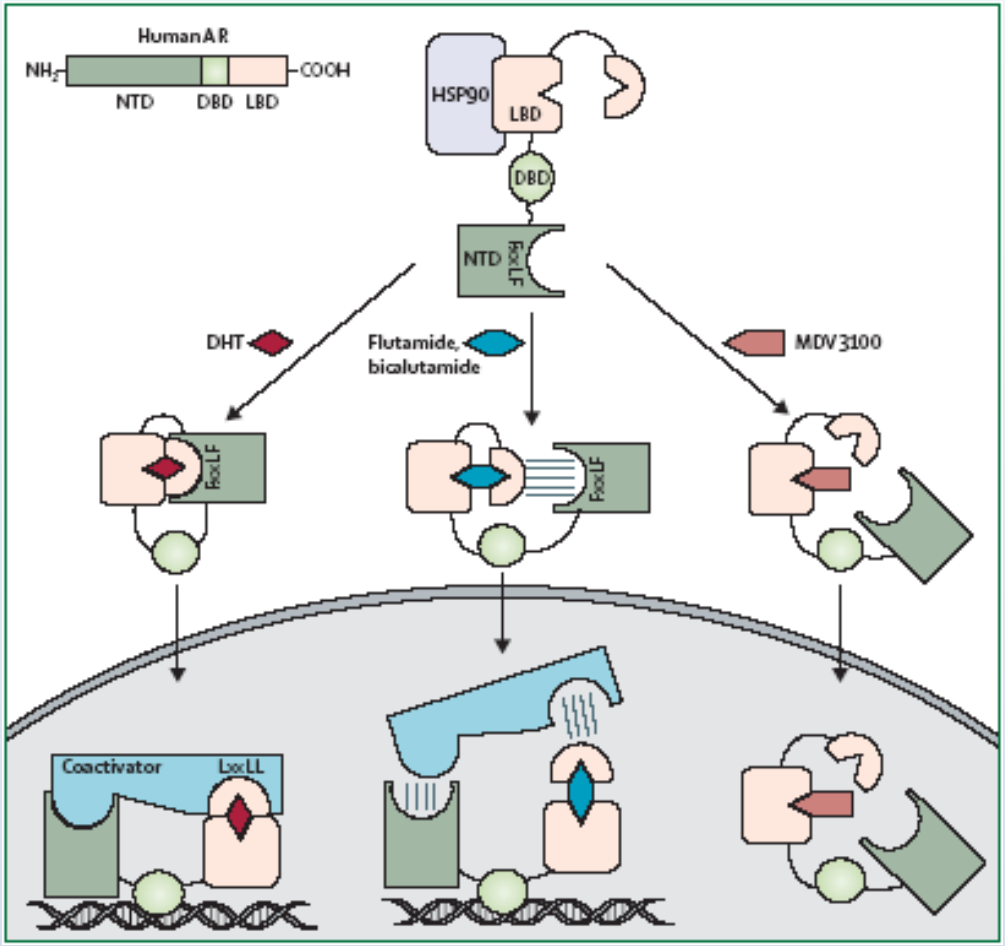
Pas sur le marché belge

* Monotherapy, 50 mg daily when combined with LHRH agonists.
† Not licenced for monotherapy.
‡ Not seen with other non-steroidal antiandrogens.
§ Hypotension, tachycardia, heart failure, syncope, myocardial infarct, haemorrhage, cerebrovascular accident, cardiovascular disorder, retinal vascular disorder, embolus, pulmonary embolism, superficial and deep thrombophlebitis, thrombosis, retinal vein thrombosis, phlebitis, vascular headache, shock.



European urology 51 (2 0 0 7) 306–314

Pharmacologie



Lancet Oncol 2009; 10: 981–91

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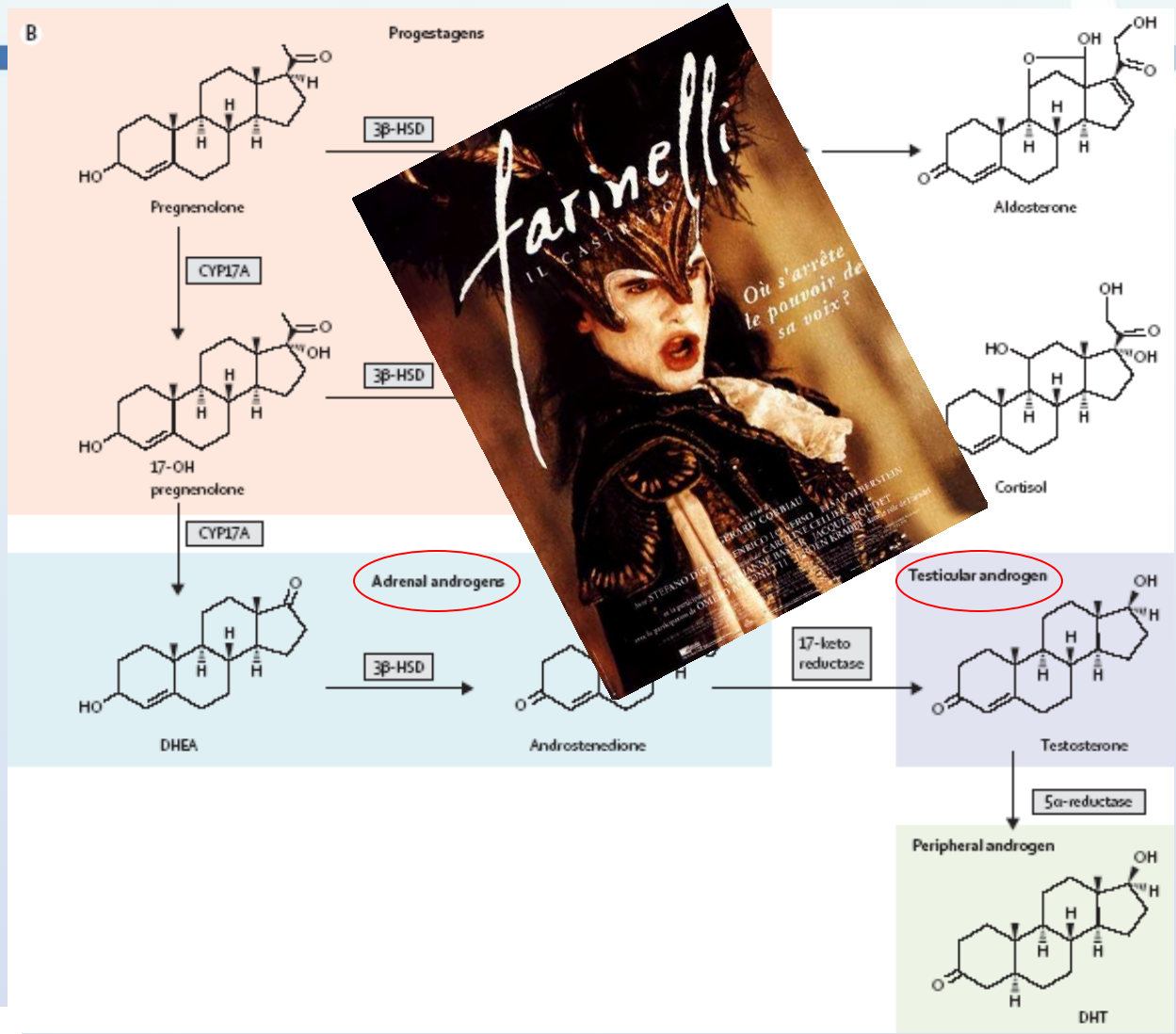
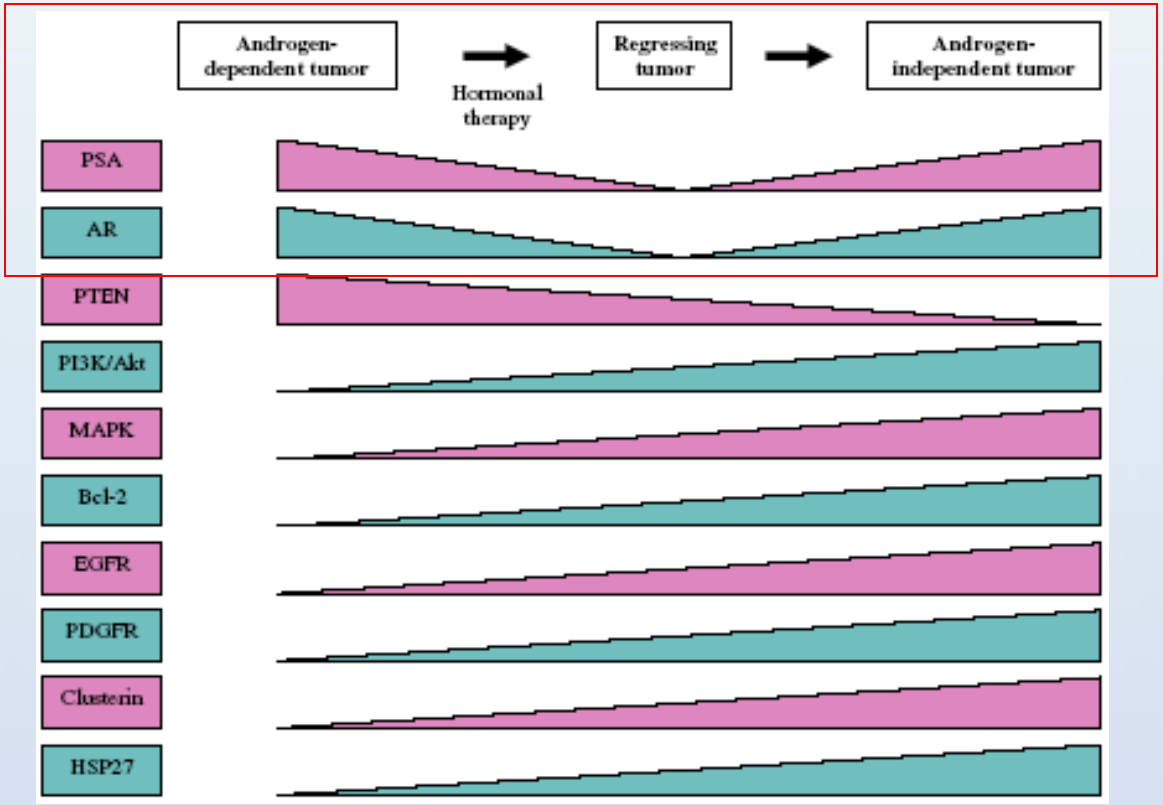


Lancet Oncol 2009; 10: 981–91

« Résistance »



Cancer Treatment Reviews 36 (2010) 122–130

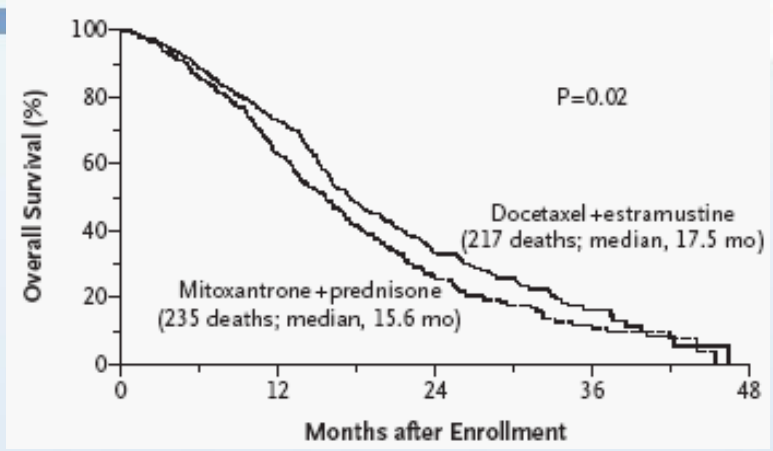
En 2004, la révolution…

- SWOG 99-16

- 770 patient avec CPMRC
- Docetaxel + estramustine vs mitoxantrone (/3sem)
- + prednisone 2 groupes
- Follow-up à 32 mois :

Survie sans progression :6.3 vs. 3.2 mois (p < .001)

Survie: 17.5 mois vs. 15.6 months (p = .02)



N Engl J Med 2004;351:1513-20.

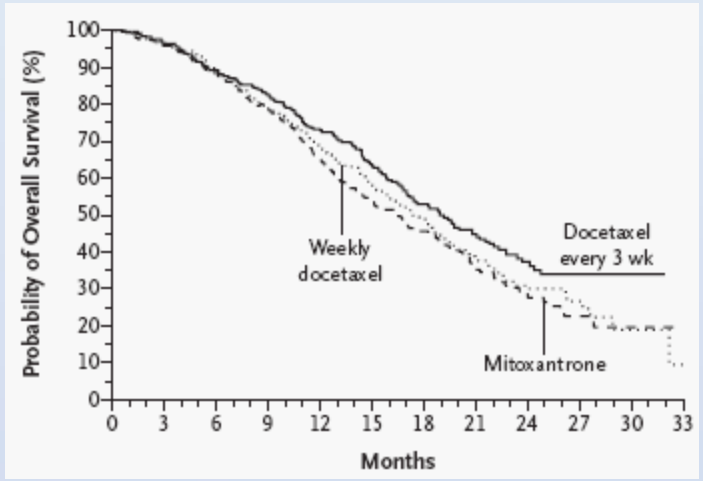
- TAX 327

- 1006 patient avec CPMRC
- 5 mg prednisone 2/j
+ 12 mg/m^2 mitox./3sem

ou

75 mg/m^2 docetaxel/3sem

Survie: 18.9 mois vs. 16.5 months



N Engl J Med 2004;351:1502-12.

Chimiothérapie

- Mono-chimiothérapie :

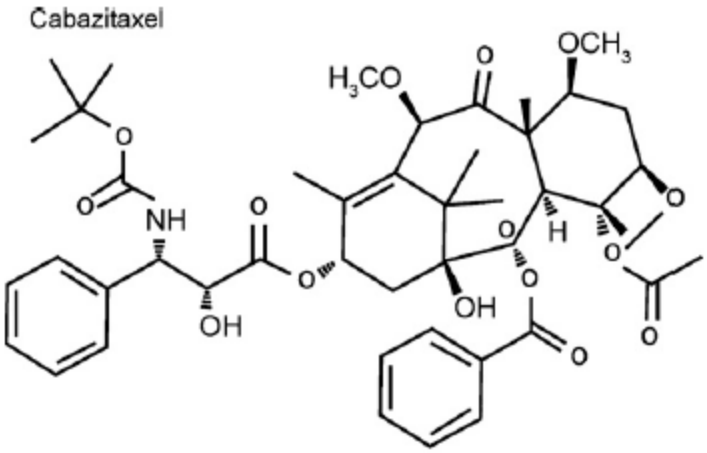
  Docetaxel (Taxotère®) 75 mg/m²/21 jours associé à 10 mg/j de predisone.

  10 cycles sont recommandés

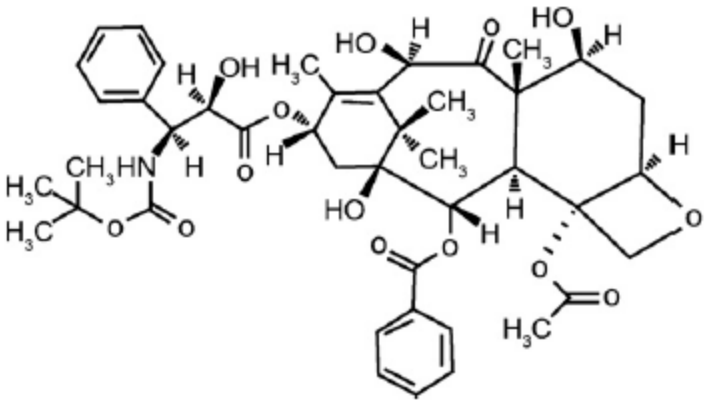
- Précocité
- PSA bas en cas de tumeur sécrétante.

Cabazitaxel (JEVTANA®)

Cabazitaxel

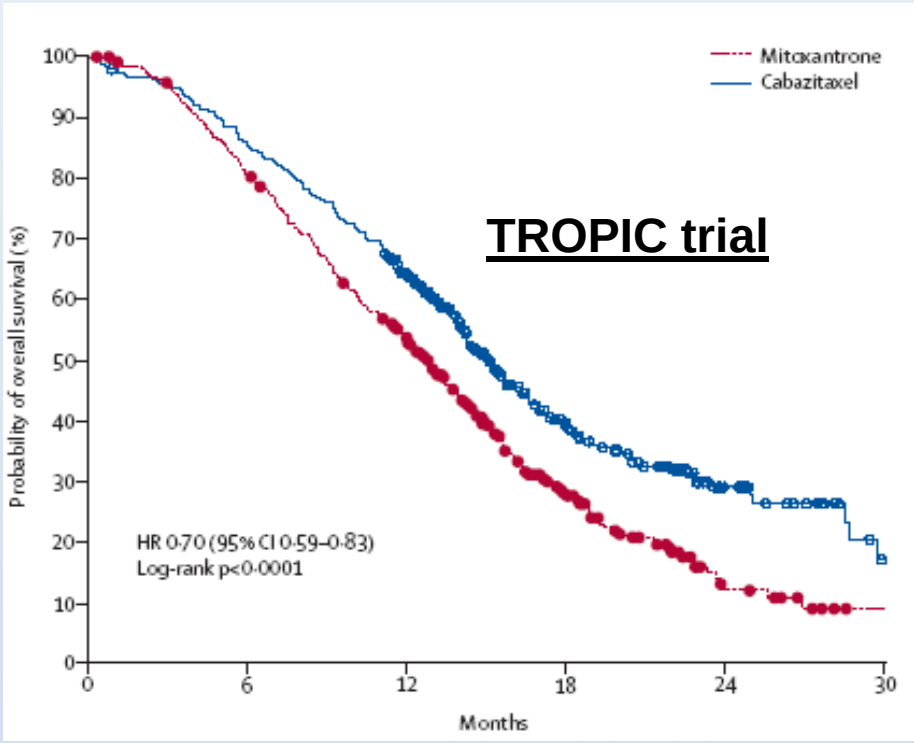


Docetaxel



Discussion

Cabazitaxel is the first drug to improve survival in patients with metastatic castration-resistant prostate cancer with progressive disease after docetaxel-based treatment,



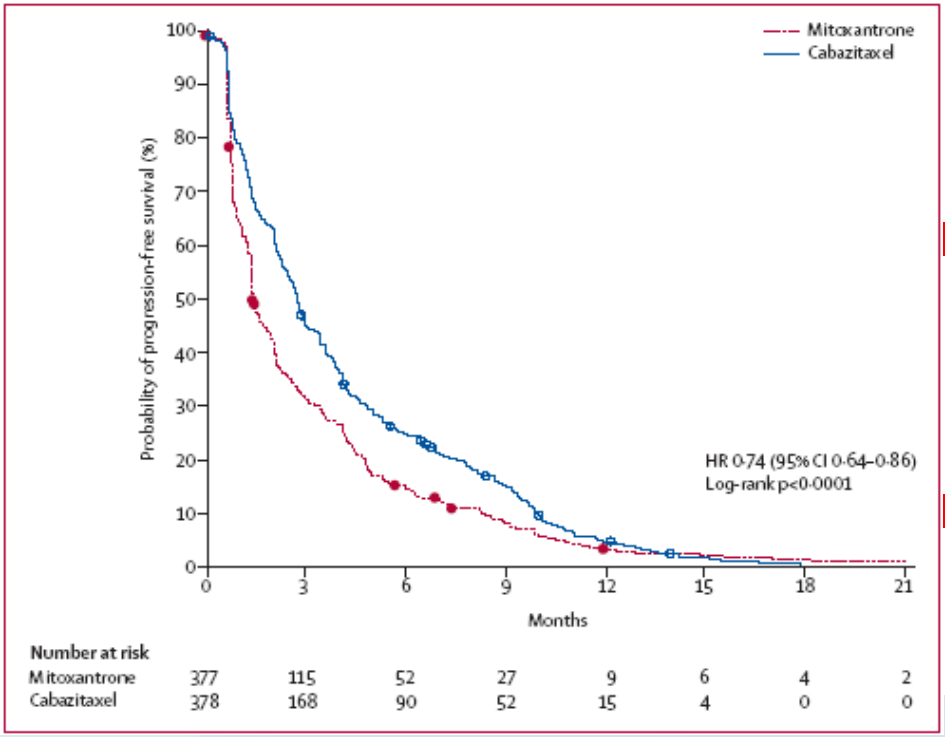
TROPIC trial

Lancet 2010; 376: 1147–54

Belgian Oncology Pharmacy Practitioners

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

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



	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

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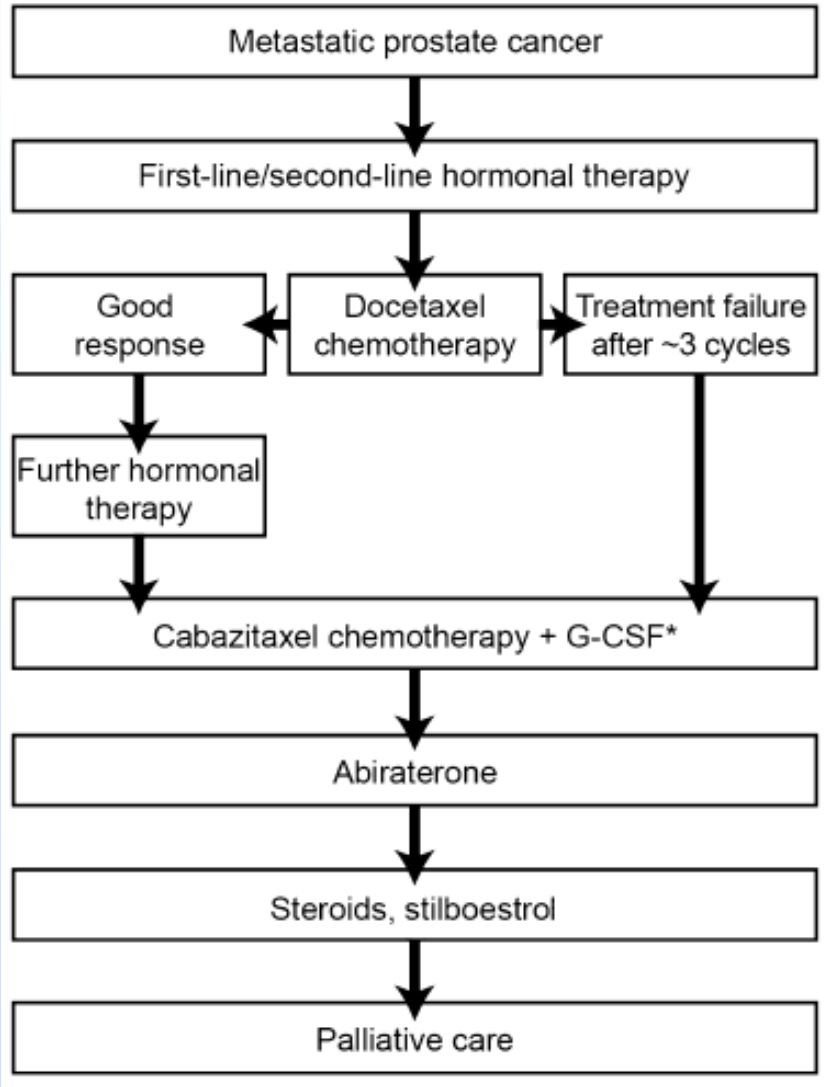
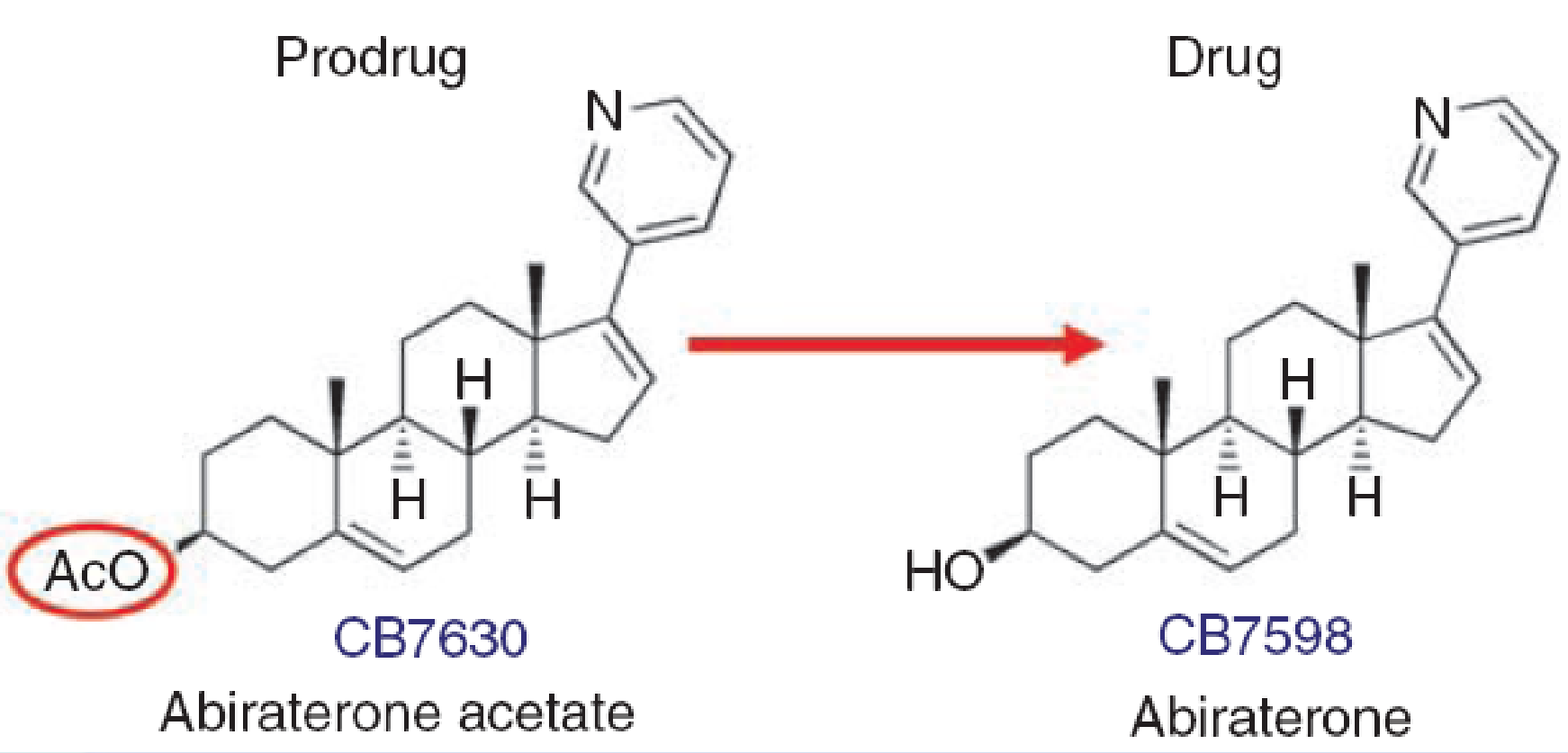
Lancet 2010; 376: 1147–54

Prise en charge thérapeutique

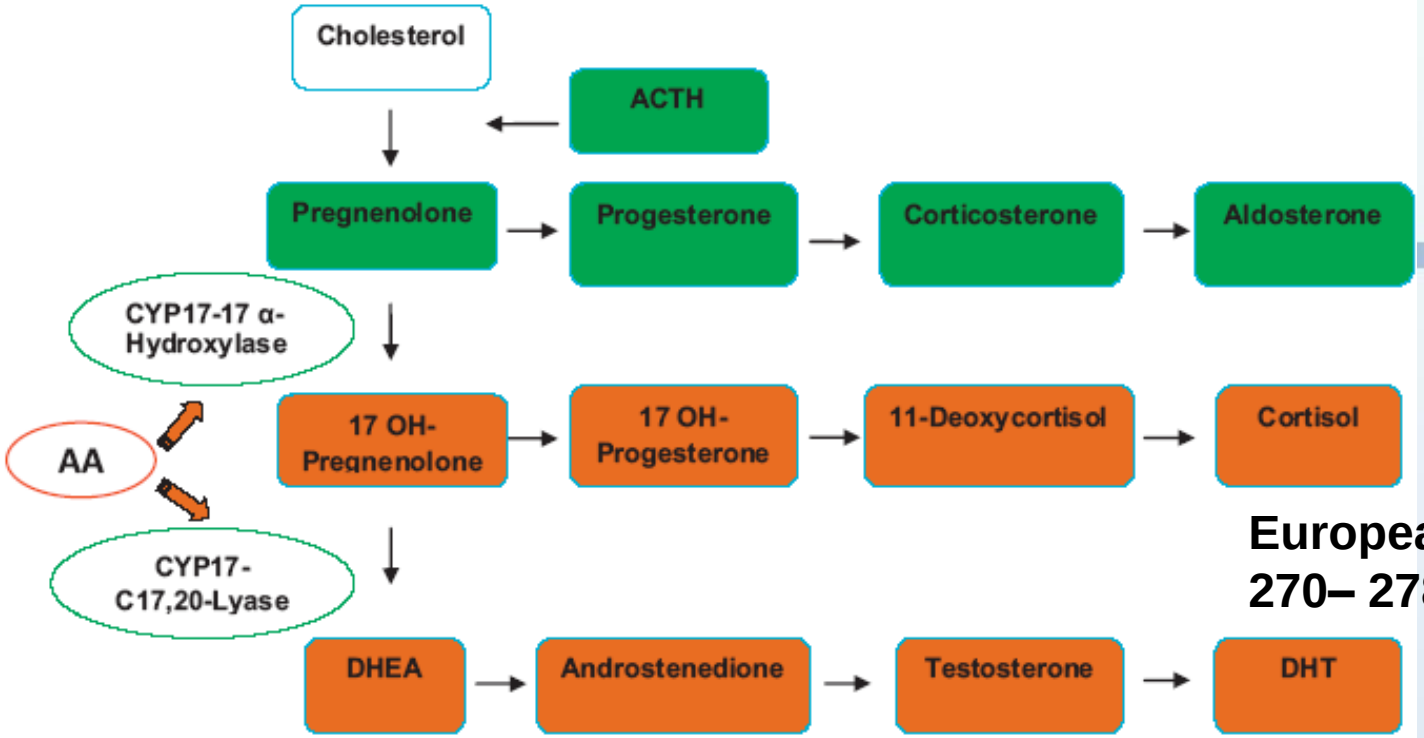


British Journal of Medical and Surgical Urology (2011) 4S, S14—S20

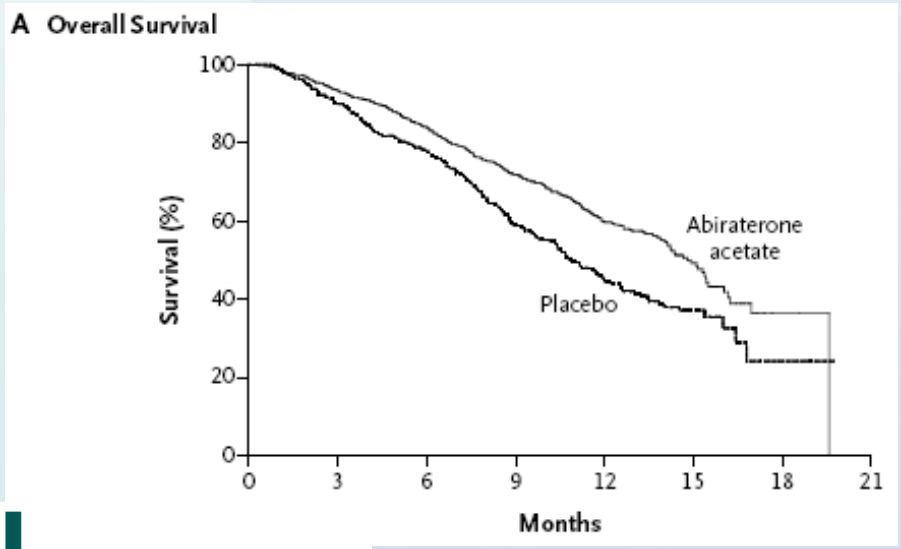
Abiraterone acétate

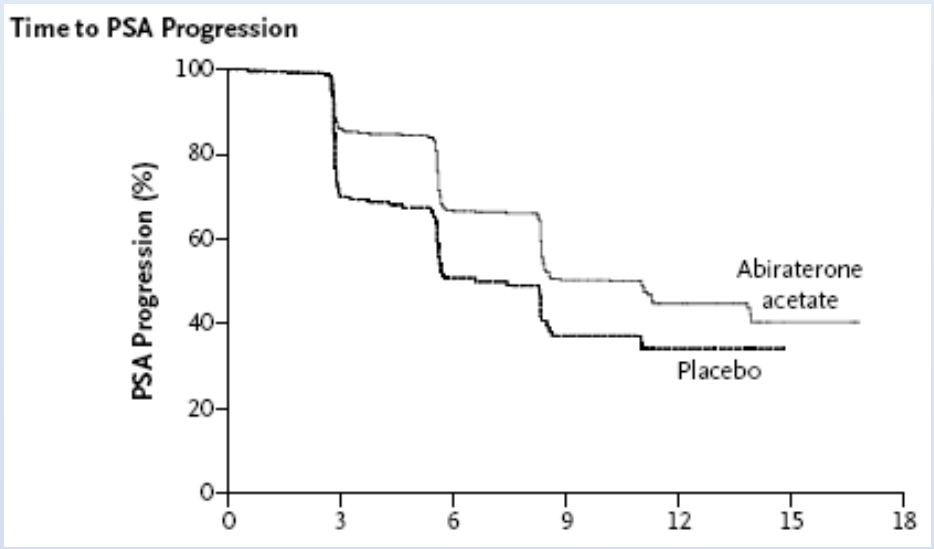


British Journal of Cancer (2009) 100, 671 – 675



European urology 60 (2011) 270– 278





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

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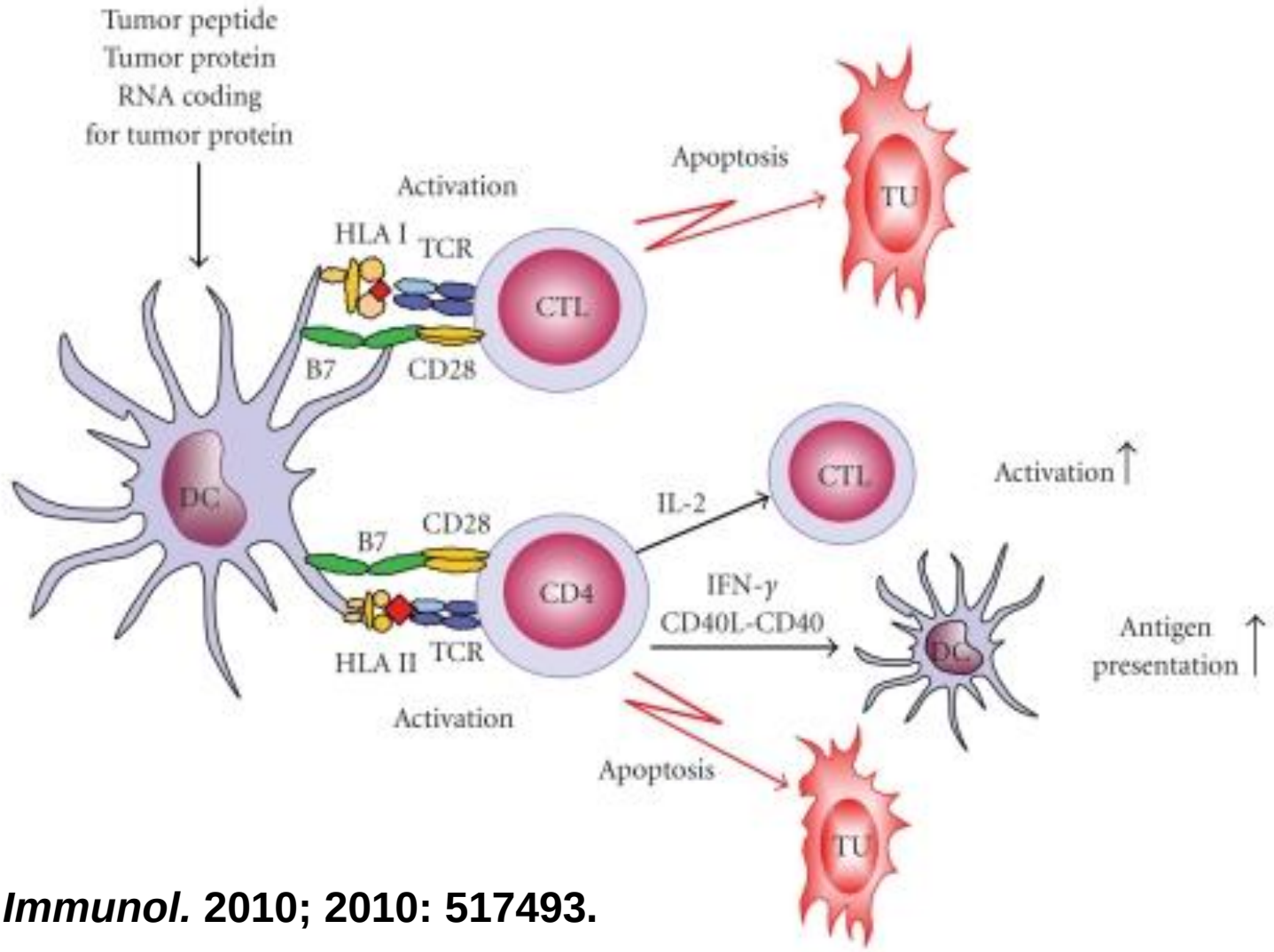
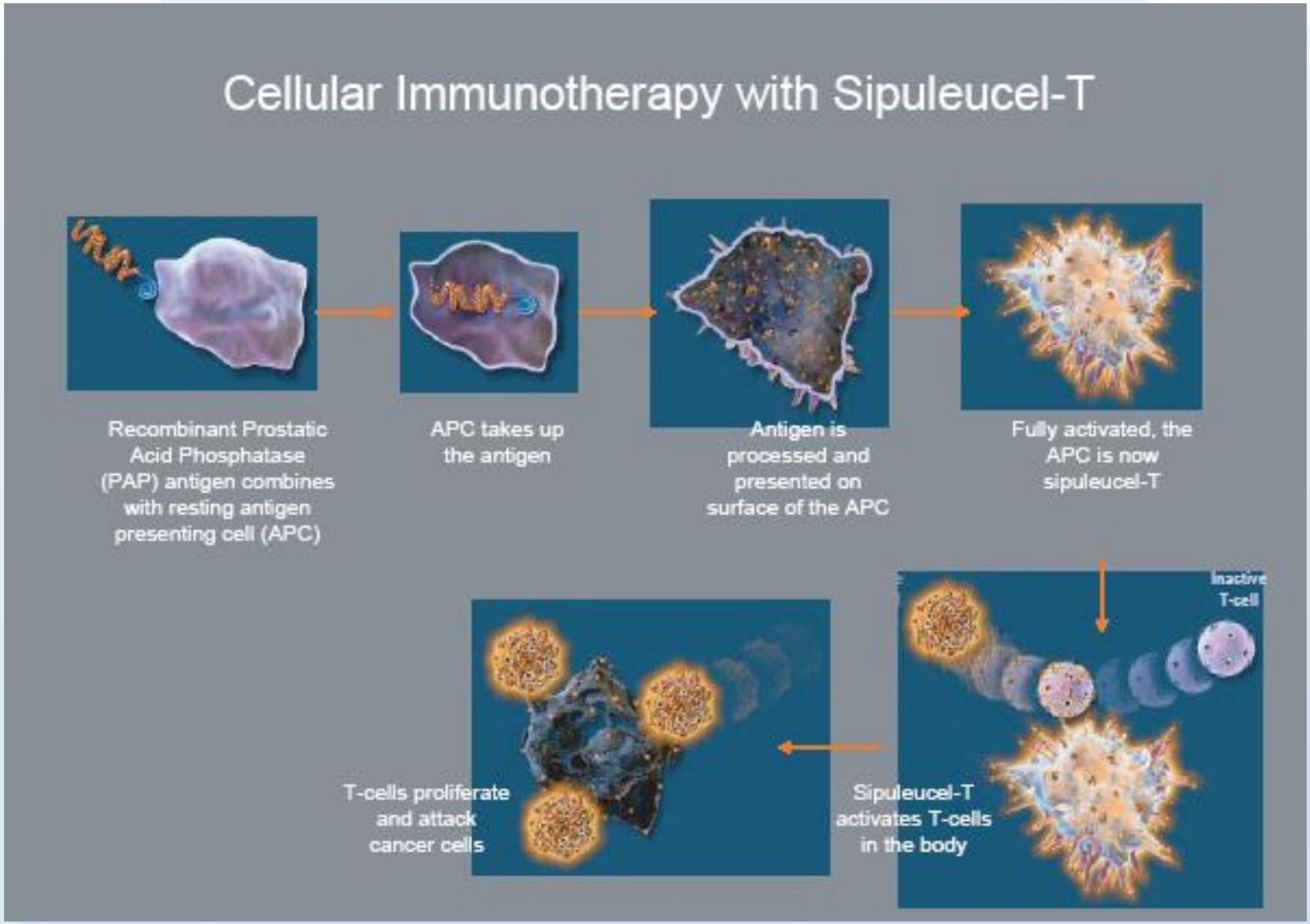
Sipuleucel-T (PROVENGE®)

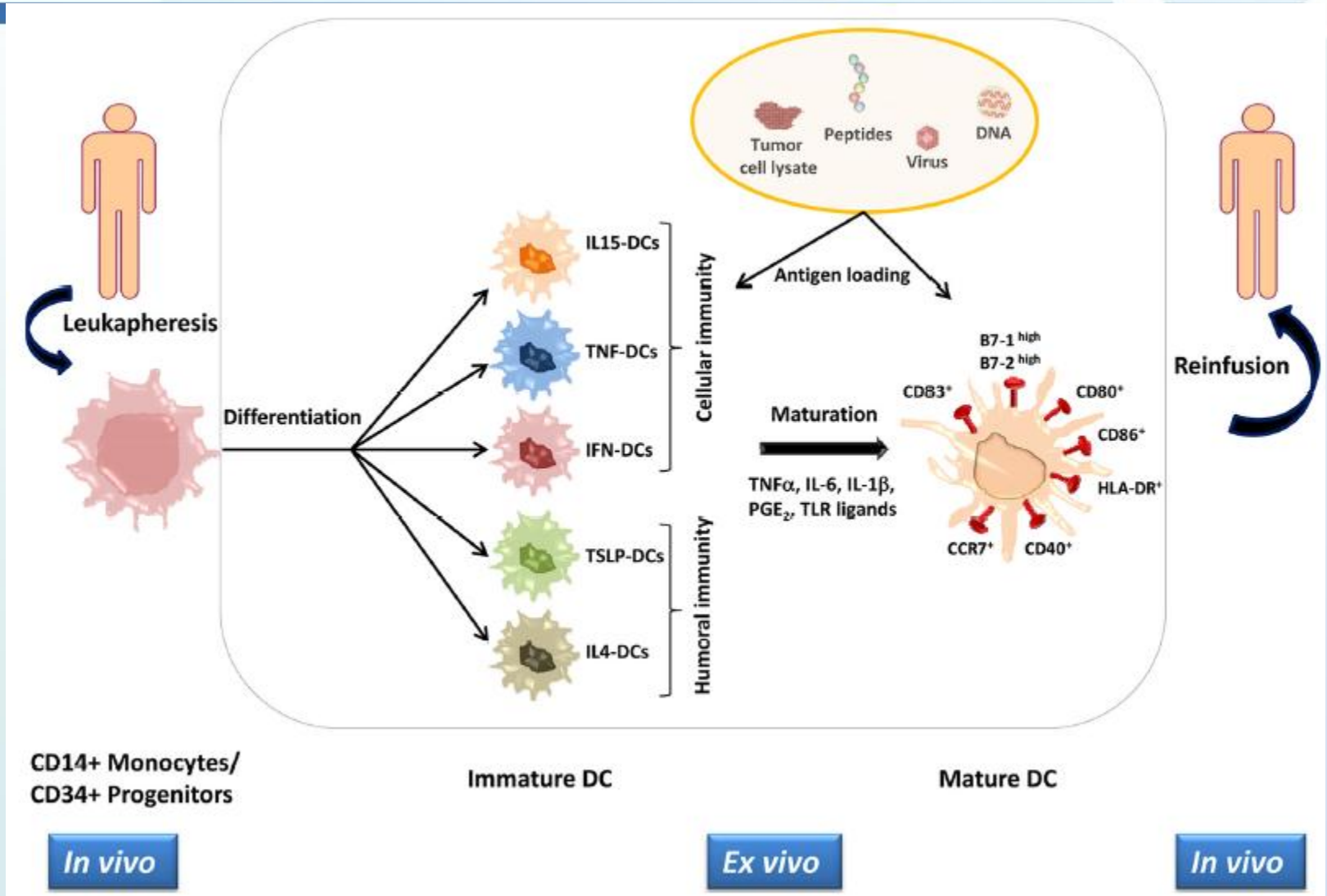


Clin Dev Immunol. **2010; 2010: 517493.**

Sipuleucel-T

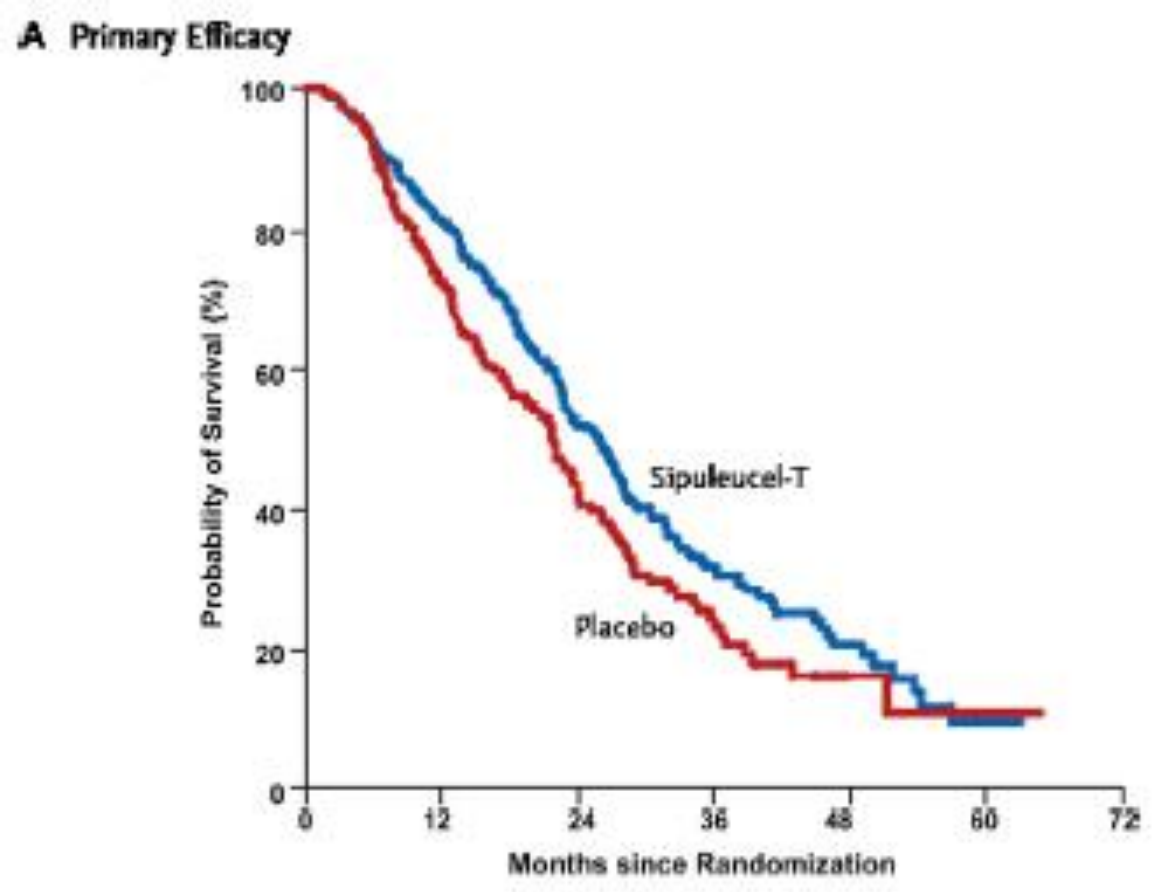


Sipuleucel-T : Mode opératoire



Clin Vaccine Immunol. 2011 January; 18(1): 23–34.

Sipuleucel-T



C'est quoi exactement?

produit cellulaire composé de cellules autologues présentatrices d'antigènes chargées avec une protéine de fusion PA2024 correspondant à la protéine phosphatase acide prostatique avec le *Granulocyte-macrophage colony-stimulating factor* (GM-CSF).

Maturitas 69 (2011) 296– 303

CONCLUSIONS

The use of sipuleucel-T prolonged overall survival among men with metastatic castration-resistant prostate cancer. No effect on the time to disease progression was observed. (Funded by Dendreon; ClinicalTrials.gov number, NCT00065442.)

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

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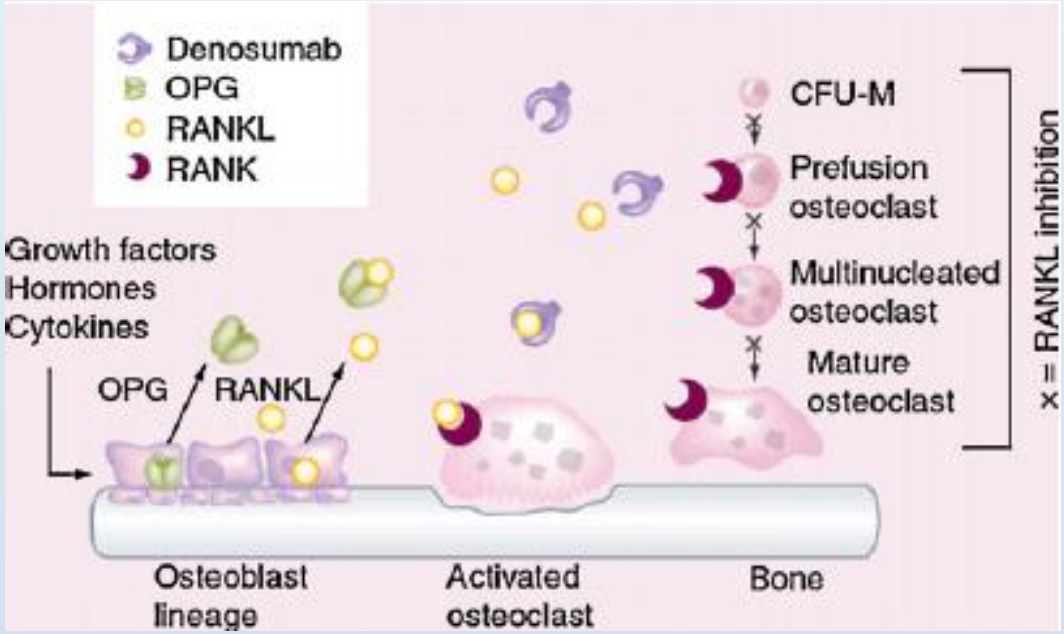
Evénements osseux

Acide zolédronique	Denosumab
Aminobisphosphonate	Mab humanisé IgG2 (receptor activator of nuclear factor-B ligand ou RANKL)
IV 4mg	SC 60mg
Adaptation selon GFR	
CI si GFR<30 ml/min	Pas de CI si IR
	E.I. Hypocalcémie, phosphatémie
Ostéonécrose de la machoire	

Denosumab (PROLIA®)

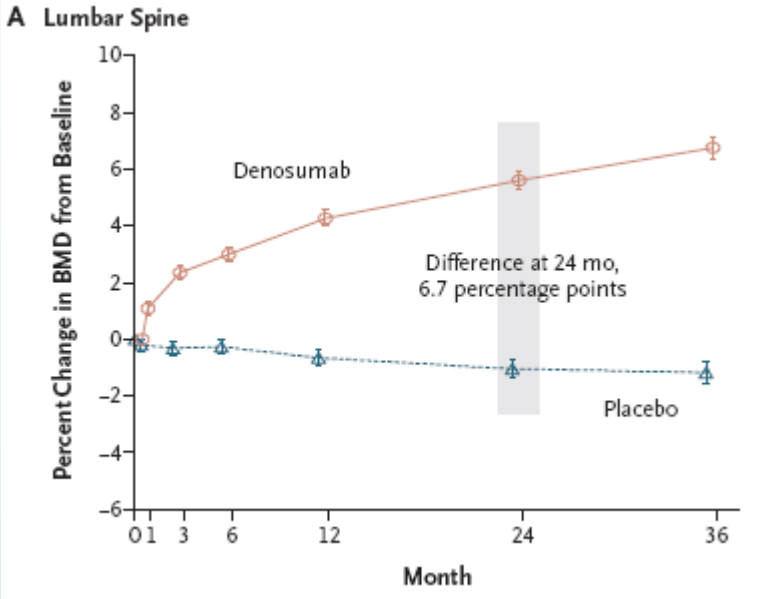
- Femme : ostéoporose
- Homme : Métastases osseuses cancer prostatique

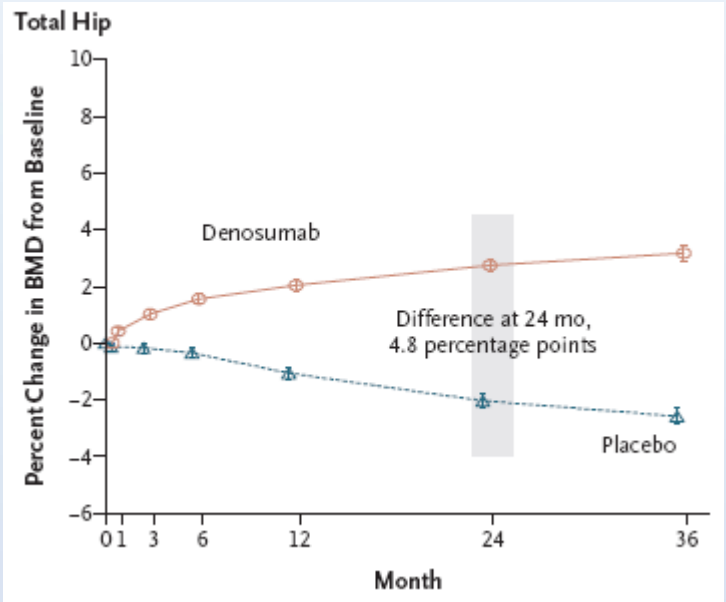


E.M. Lewiecki / Maturitas *66 (2010) 182–186*

Denosumab in Men Receiving Androgen-Deprivation Therapy for Prostate Cancer

Matthew R. Smith, M.D., Ph.D., Blair Egerdie, M.D., Narciso Hernández Toriz, M.D., Robert Feldman, M.D., Teuvo L.J. Tammela, M.D., Fred Saad, M.D., Jiri Heracek, M.D., Ph.D., Maciej Szwedowski, M.D., Chunlei Ke, Ph.D., Amy Kupic, M.A., Benjamin Z. Leder, M.D., and Carsten Goessl, M.D., for the Denosumab HALT Prostate Cancer Study Group*





CONCLUSIONS

Denosumab was associated with increased bone mineral density at all sites and a reduction in the incidence of new vertebral fractures among men receiving androgen-deprivation therapy for nonmetastatic prostate cancer. (ClinicalTrials.gov number, NCT00089674.)

N Engl J Med 2009;361:74555.

Métastases osseuses

Strontium 89 (Sr^{89}) IV	**Samarium-153 éthylène diamine-tétraméthylène (EDTMP-Sm^{153}) IV**
METASTRON® (Fr)	**QUADRAMET ® (Fr)**
émetteur bêta pur	**émetteur bêta/gamma**
$T_{1/2}$: 50 jours	**$T_{1/2}$: 2 jours**
Elimination urinaire : 48 1ère H	**Elimination urinaire : 6 1ère H**
Effet antalgique (après 1-3 sem)	

Une évolution surprenante

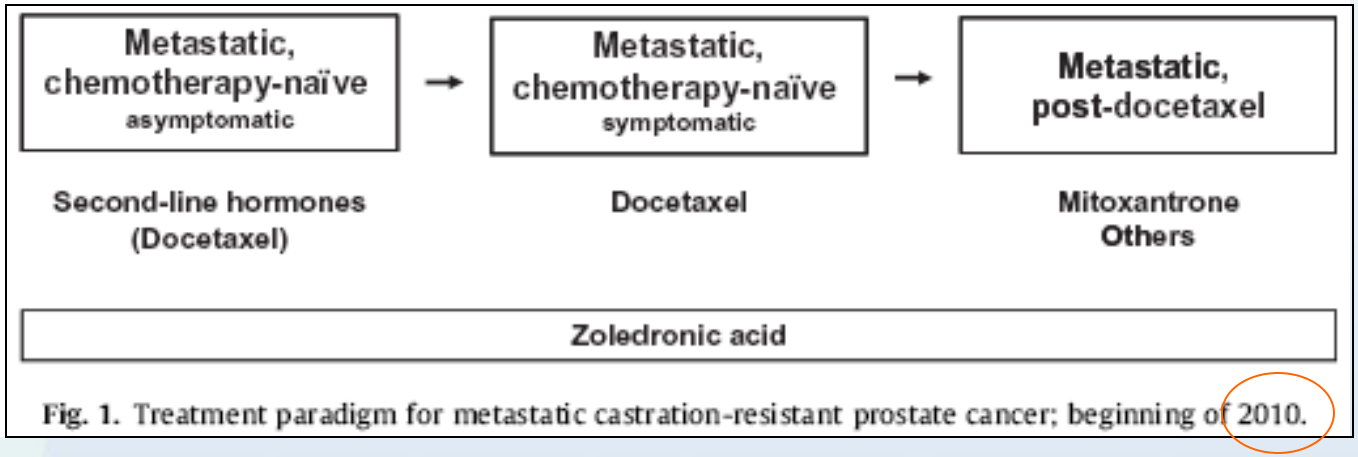


Fig. 1. Treatment paradigm for metastatic castration-resistant prostate cancer; beginning of 2010.

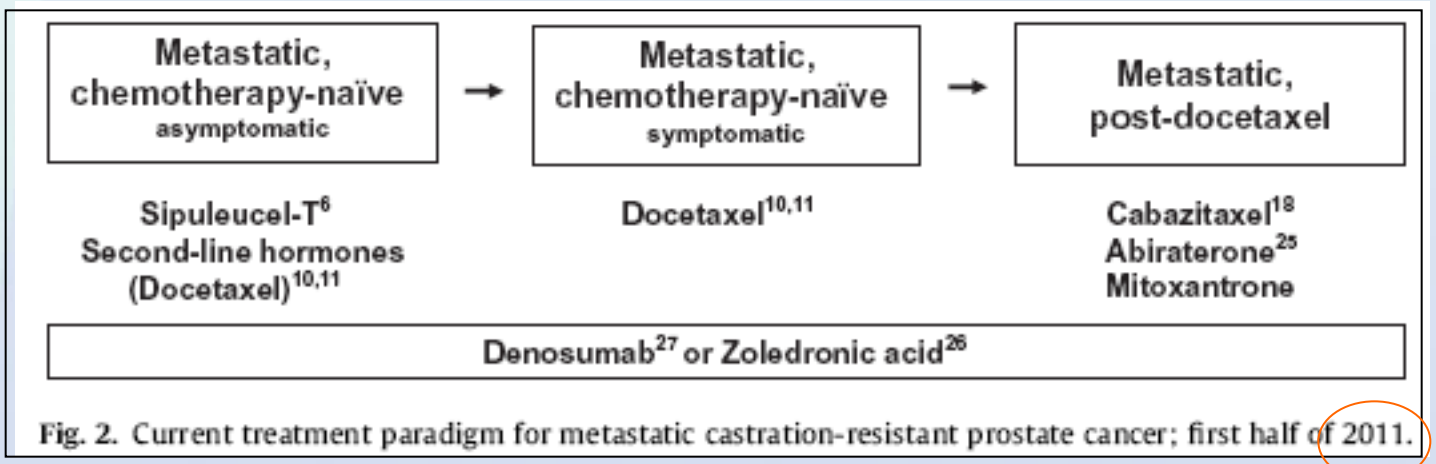
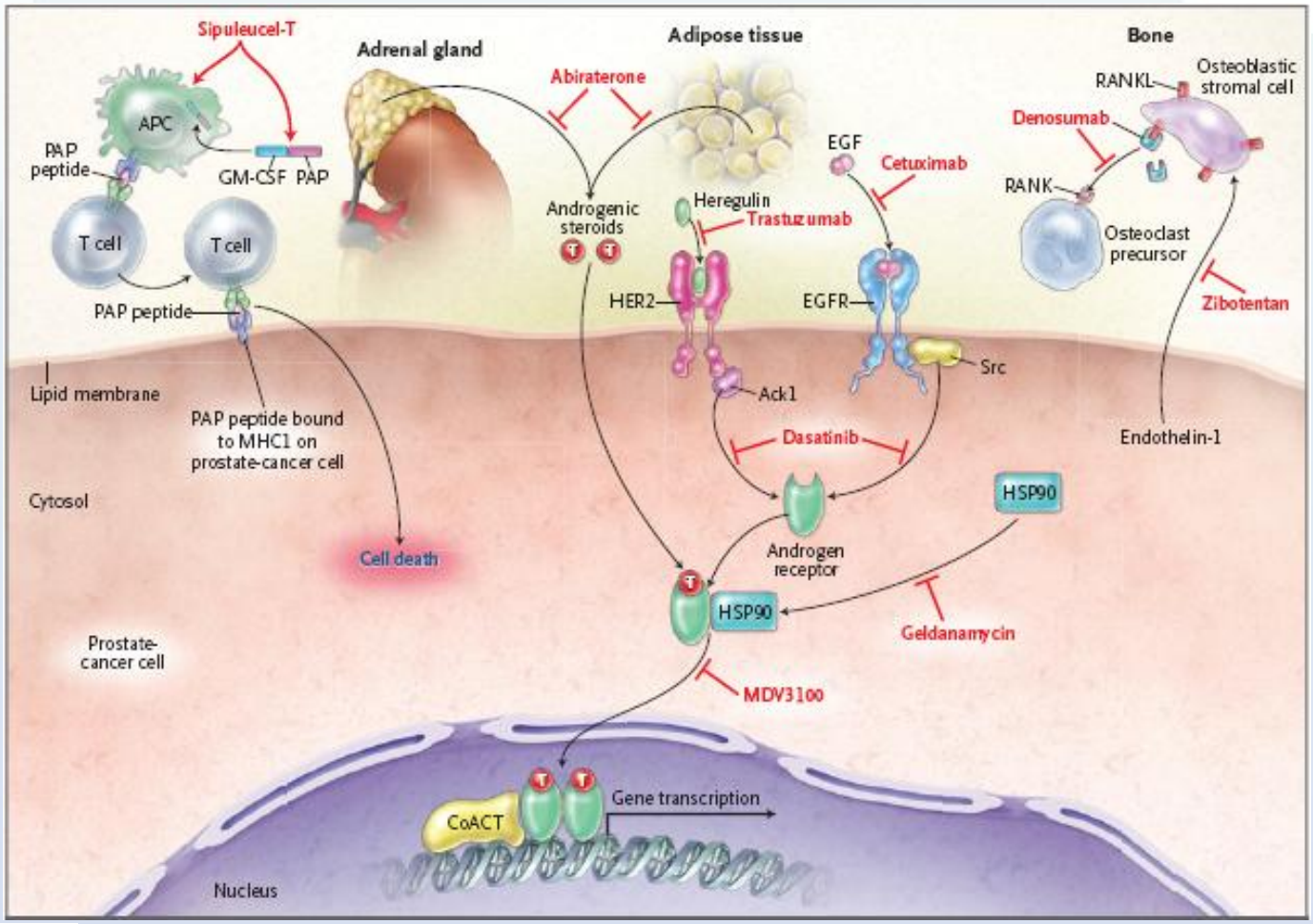


Fig. 2. Current treatment paradigm for metastatic castration-resistant prostate cancer; first half of 2011.

Higano CS. Cancer Treat Rev (2011)

Perspectives



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En cours d'évaluation

Table 1 – Ongoing trials of second line therapy for mCRPC.

Target	Agent	Phase	Design	Primary endpoint	Estimated number of patients	Clinical trials reference number
Androgen synthesis (CYP17)	Abiraterone plus prednisolone	III	Randomised, placebo controlled	OS	1,158	NCT00638690
Androgen synthesis	TAK700	I/II	Dose ranging	Safety	123	NCT00569153
Androgen analogue	HE3235	I/II	Dose ranging	Safety, PK, activity	64	NCT00716794
Androgen receptor	MDV3100	III	Randomised, placebo controlled	OS	1,200	NCT00974311
Clusterin	Custirsen plus docetaxel and prednisolone	III	Randomised, placebo controlled	Pain, palliation	292	NCT01083615
CTLA-4	Ipilimumab	III	Randomised, placebo controlled	OS	800	NCT00861614
IGF-1 receptor	Cixutumumab or ramucirumab plus mitoxantrone and prednisolone	II	Randomised, open label	PFS	132	NCT00683475
IGF-1 receptor	Figitumumab plus docetaxel and prednisolone	II	Randomised, open label	PSA and tumour response	120	NCT00313781
mTOR and VEGF	Temsirolimus and bevacuximab	I/II	Dose ranging	MTD	34	NCT01083368
VEGF receptor	Cediranib	II	Interventional, open label	PFS	59	NCT00436956
VEGF receptor	Cediranib with/without dasatinib	II	Randomised, open label	PFS	50	NCT01260688
TK	Sunitinib	II	Interventional, open label	PFS	50	NCT00748358
Androgen receptor	AZD3514	I	Interventional, open label	Safety and tolerability	50	NCT01162395
DNA and mTOR	Carboplatin, everolimus, and prednisone	II	Interventional, open label	TTP	56	
DNA and tubulin formation	Azacitidine, docetaxel and prednisone	I/II	Interventional, open label	MTD and PSA response	42	NCT00503984
Tubule formation	Cabazitaxel	III	Single arm, open label	Early access to cabazitaxel	808	NCT01254279
MAO and tubulin formation	Phenelzine sulphate and docetaxel	II	Interventional, open label	PSA response	20	NCT01253642
EGFR	Mitoxantrone with or without cetuximab	II	Randomised, open label	TTP	130	NCT00661492
Clusterin	OGX-011 and docetaxel	I/II	Interventional, open label	Safety	60	NCT00327340
DNA synthesis	Pemetrexed	II	Interventional, open label	PSA response	43	NCT00216099
VEGF	Enzastaurin	II	Interventional, open label	Objective response rate and PFS	72	NCT00428714
Hsp90	STA-9090	II	Interventional, open label	PFS	51	NCT01270880
Endoglin	TRC105	I/II	Interventional, open label	MTD	90	NCT01090765
Microtubule growth	Eribulin	II	Interventional, open label	PSA response	110	NCT00278993
Microtubule growth	Retaspimycin	II	Interventional, open label	Treatment response	19	NCT00564928
PSA production	PSA/TRICOM vaccine and 153Sm-EDTMP radiation	II	Randomised, open label	PFS	68	NCT00450619

OS, overall survival; PK, pharmacokinetics; PFS, progression-free survival; IGF, insulin-like growth factor; PSA, prostate-specific antigen; VEGF, vascular endothelial growth factor; MTD, maximum tolerated dose; TK, tyrosine kinase; TTP, time to progression; MAO, monoamine oxidase.

CANCER DE LA PROSTATE... NE PASSEZ PAS À UN DOIGT DU DIAGNOSTIC !

Tous les cancers de la prostate ne doivent pas être traités mais tous doivent être dépistés par un toucher rectal et une prise de sang.

À PARTIR DE 50 ANS, PARLEZ-EN À VOTRE MÉDECIN

bopp
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