

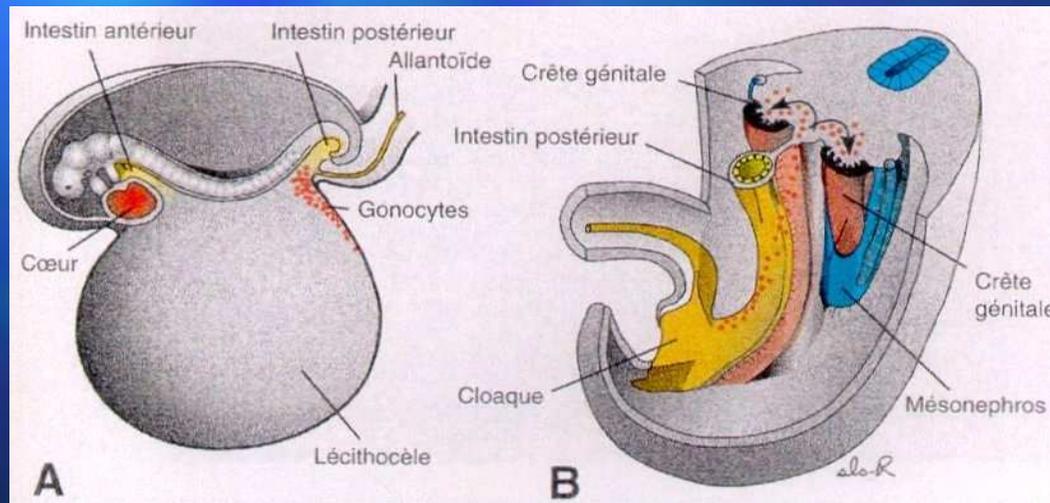
# **VERS L'INDIVIDUALISATION DES PRESCRIPTIONS ?**

**Cancers génito-urinaires**

**S. Culine**

# Chapitre I

## Les tumeurs germinales



# Formes métastatiques

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Un modèle en cancérologie

Taux de guérison = 90%

Un protocole

|            |   |
|------------|---|
| Bléomycine | <u>30</u> mg J1, J8, J15                |
| Etoposide  | <u>100</u> mg/m <sup>2</sup> /j J1 à J5 |
| Cisplatine | <u>20</u> mg/m <sup>2</sup> /j J1 à J5  |

# Classification IGCCCG

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## Facteurs pronostiques

**Site du primitif**

**Sites des métastases**

**Niveau d'élévation des  
marqueurs tumoraux sériques**

# Stratégie thérapeutique

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## Groupes pronostiques

### Bon pronostic

56% des patients

3 cycles de BEP

Survie à 5 ans = 92%

# Stratégie thérapeutique

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## Groupes pronostiques

### Pronostic intermédiaire ou mauvais

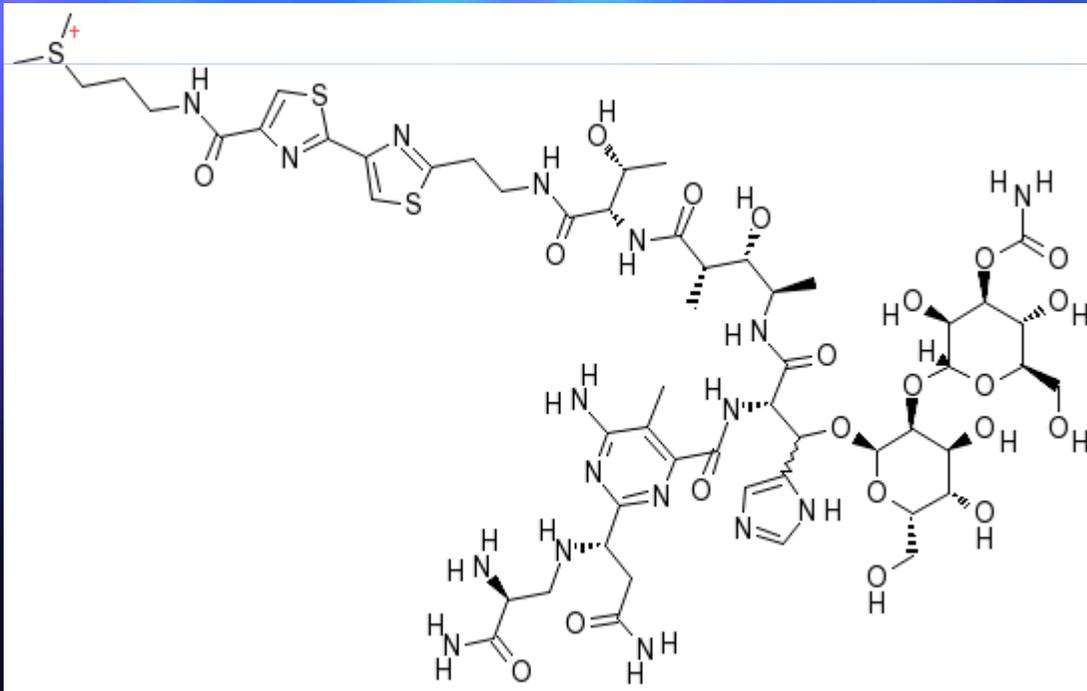
**4 cycles de BEP**

**Survie à 5 ans**

**De 80% à 50%**

# Mieux individualiser ?

## Bléomycine



Antibiotique polypeptidique  
*Streptomyces verticillus*

Liaison Fe  
Production de radicaux libres

Lésions de l'ADN

# Bléomycine

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## Bléomycine hydrolase

### Inactivation

#### Cystéine protéase

Coupe les sites de liaisons  
avec les atomes de fer

# Bléomycine

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## Bléomycine hydrolase

**Polymorphisme dans l'exon 11**

**Codon 443 Val>Ile**

**Le domaine C-terminal est important  
pour l'activité enzymatique**

# Bléomycine hydrolase

## Toxicité pulmonaire

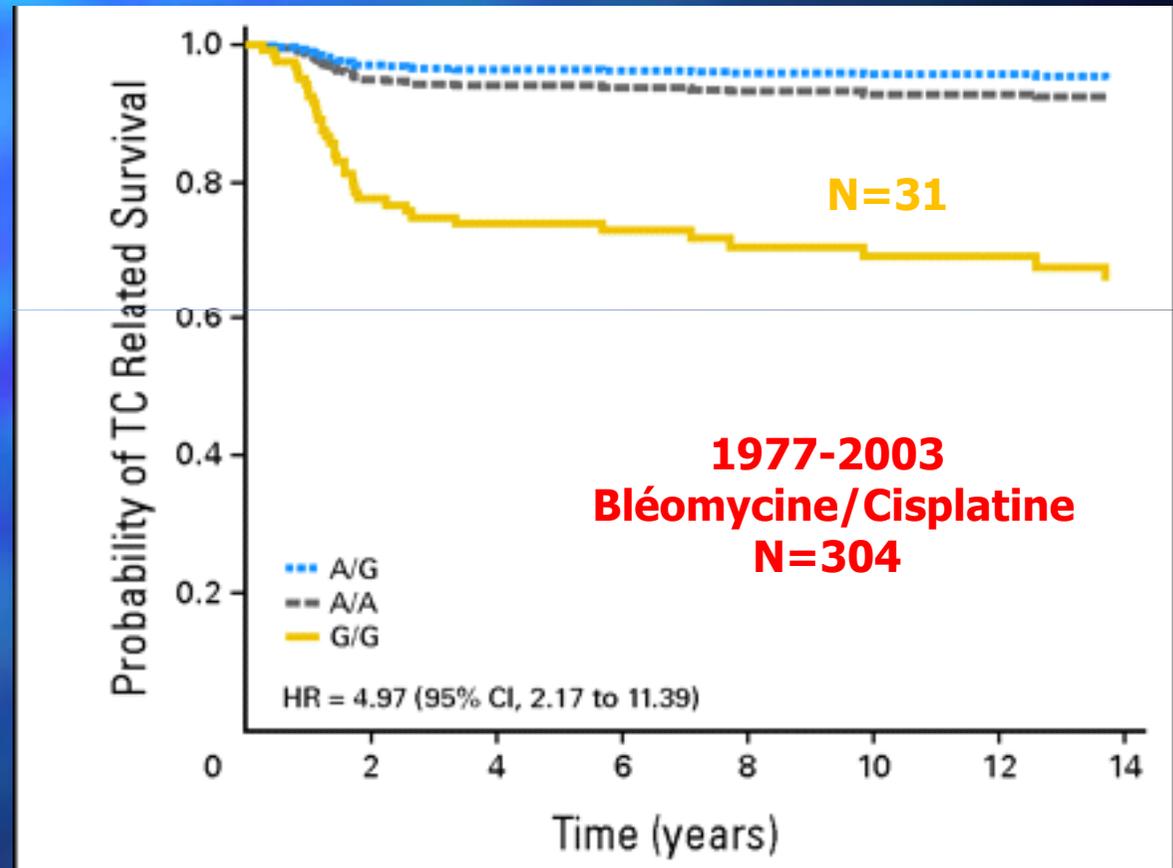
| <b>1977-2003</b><br><b>Bléomycine/Cisplatine</b><br><b>N=418</b> |       | Genotype frequency* |           |          |
|--|-------|---------------------|-----------|----------|
|  |       | A/A                 | A/G       | G/G      |
| Bleomycin-induced<br>pneumonitis                                 | N=38  | 21 (55%)            | 12 (32%)  | 5 (13%)  |
| No pulmonary toxicity  | N=302 | 135 (45%)           | 136 (45%) | 31 (10%) |

\*Pearson Chi-square,  $P=0.288$ .

# Bléomycine hydrolase

## Survie

Après ajustement  
sur les facteurs  
pronostiques  
classiques



# Bléomycine hydrolase

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**Avenir ?**

**A confirmer**

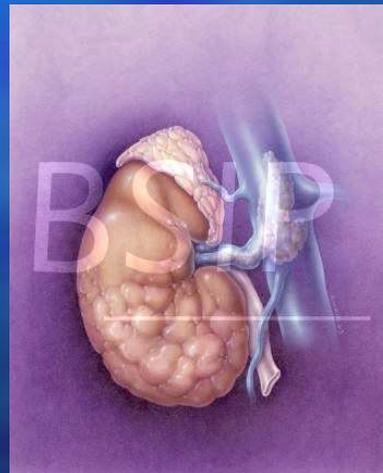
**Essai clinique**

**BEP pour patients AA et AG**

**BEP ou VIP pour patients GG**

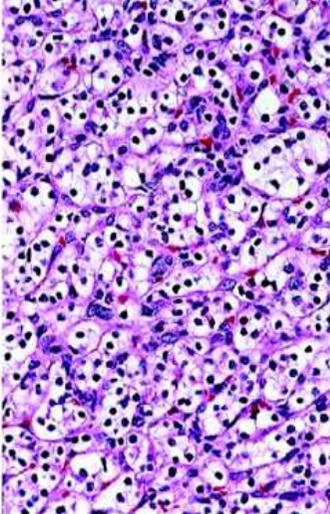
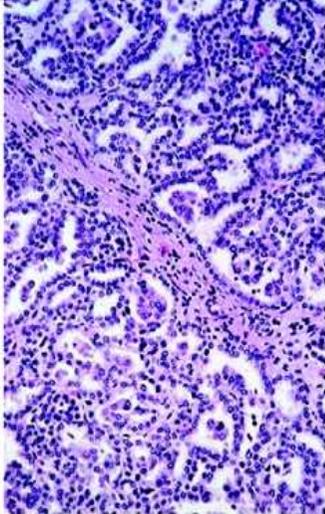
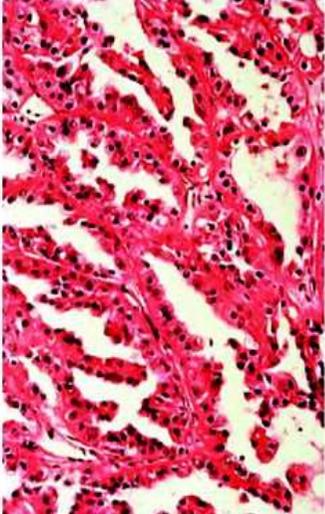
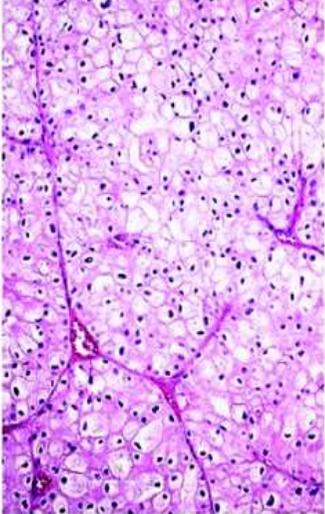
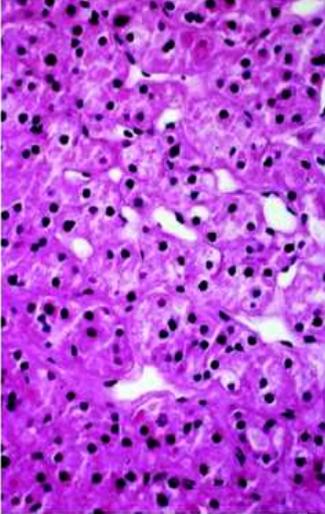
# Chapitre II

## Les cancers du rein



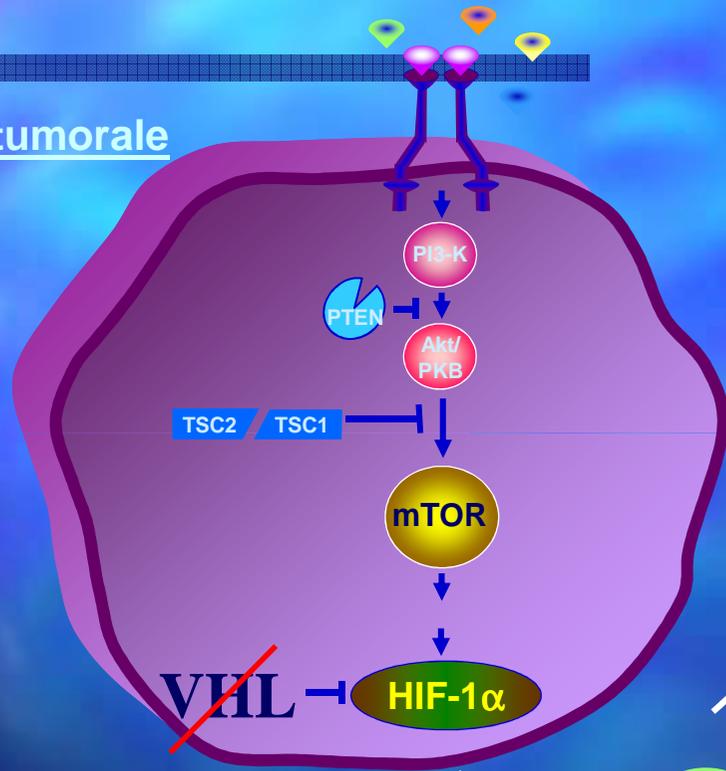
# Les bases biologiques

## Les cibles d'intérêt

|  |   |  |  |  |                  |
|--|---|--|--|--|------------------|
|  |  |  |  |  |                  |
| Type   | Clear Cell<br>75%   | Papillary Type 1<br>5%   | Papillary Type 2<br>10%  | Chromophobe<br>5%  | Oncocytoma<br>5% |
| Gene   | VHL   | Met  | FH   | BHD  |                  |

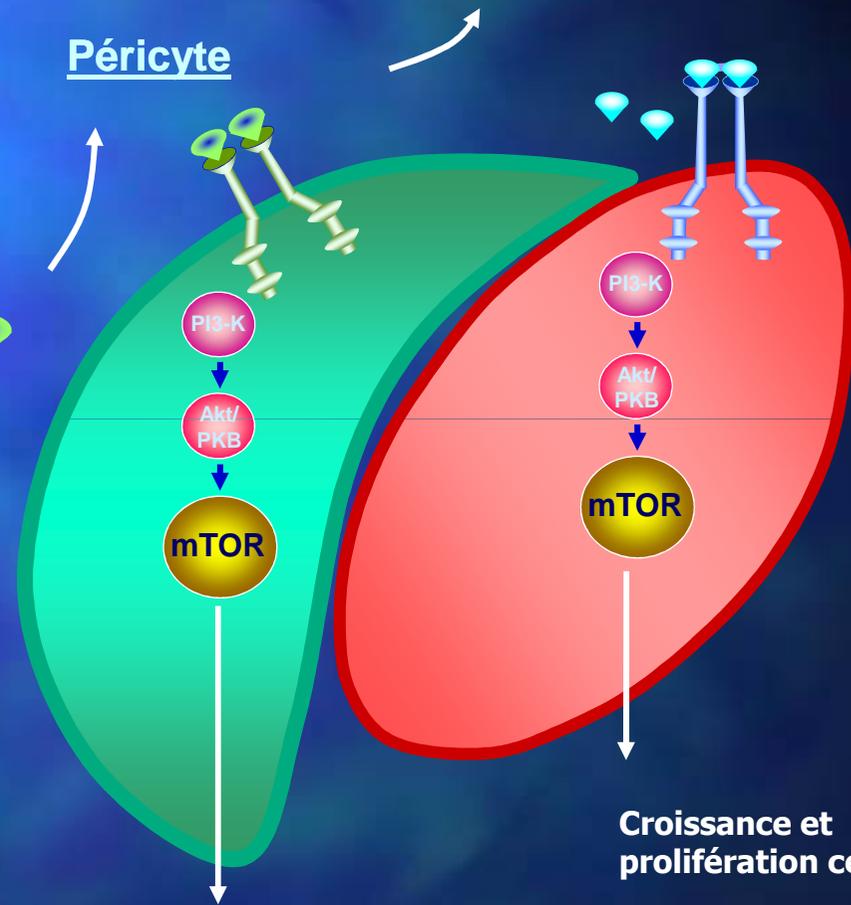
# Un modèle biologique

Cellule tumorale



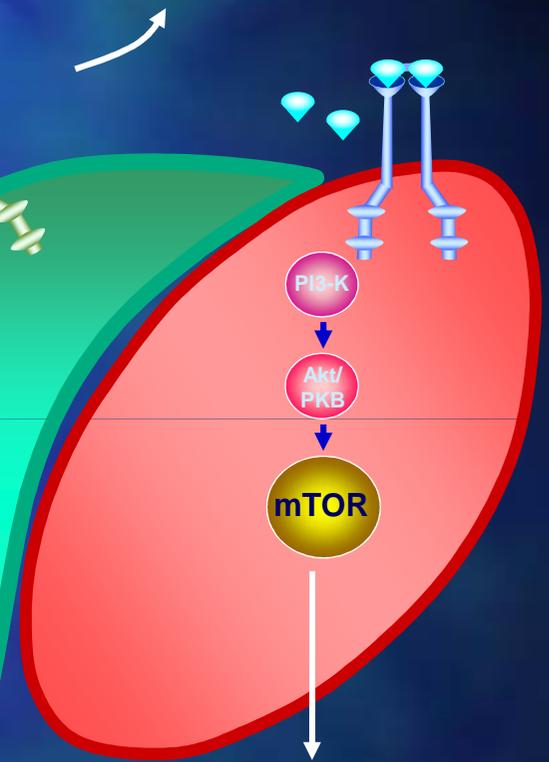
VEGF

Péricyte



Croissance et prolifération cellulaire

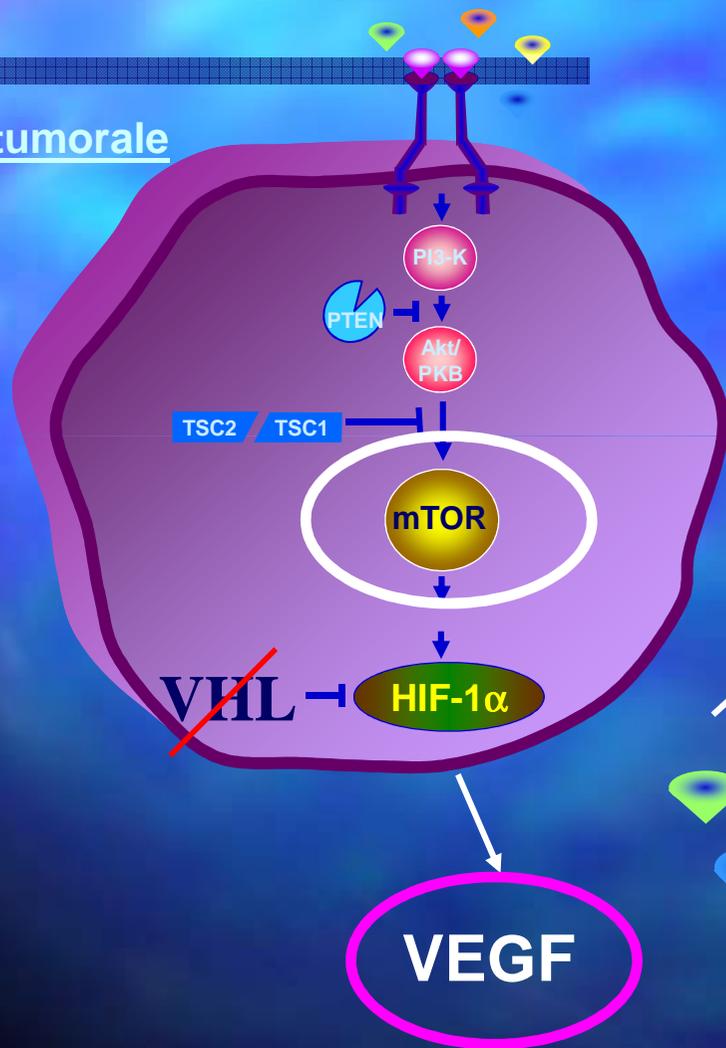
Cellule endothéliale



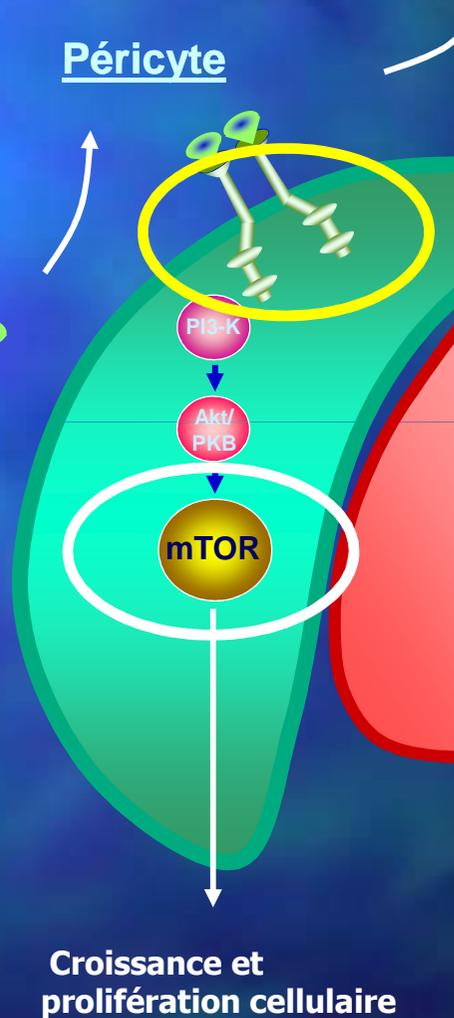
Croissance et prolifération cellulaire

# 3 cibles d'intérêt

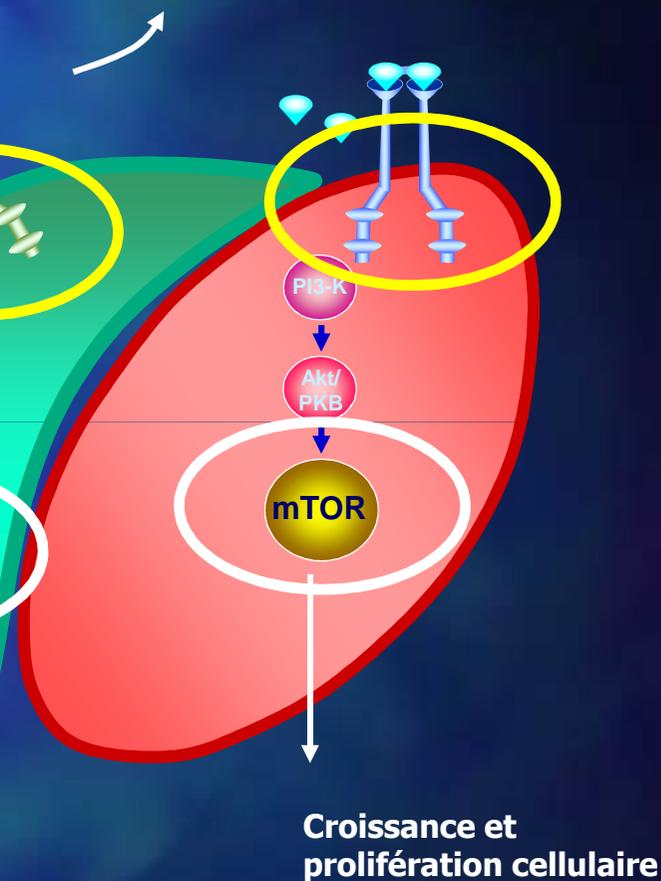
Cellule tumorale



Péricyte



Cellule endothéliale



# 6 thérapies ciblées



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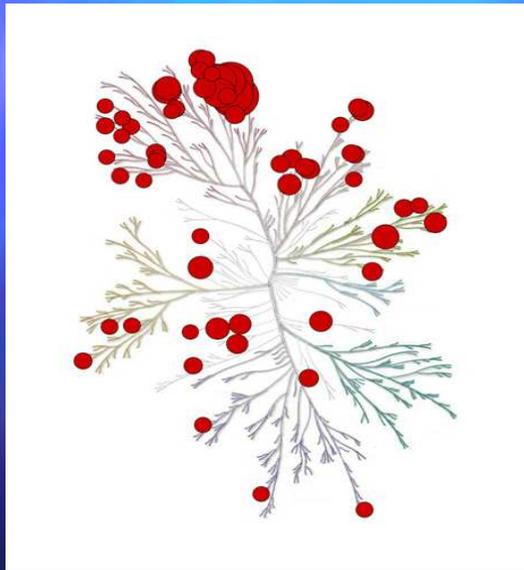
Bévacizumab (Avastin®)



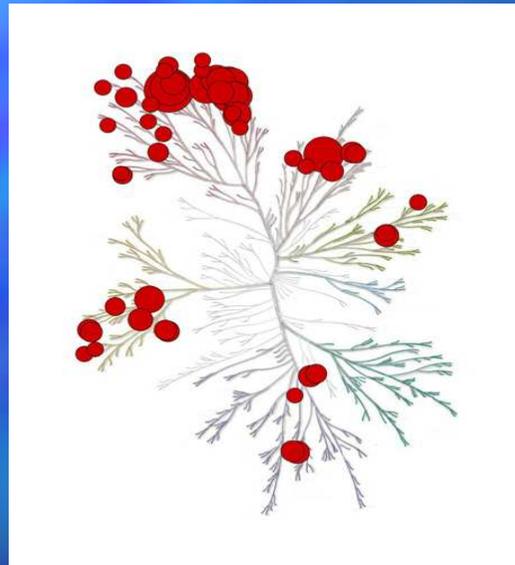
Temsirolimus (Torisel®)  
Everolimus (Afinitor®)

Sunitinib (Sutent®)  
Sorafénib (Nexavar®)  
Pazopanib (Votrient®)

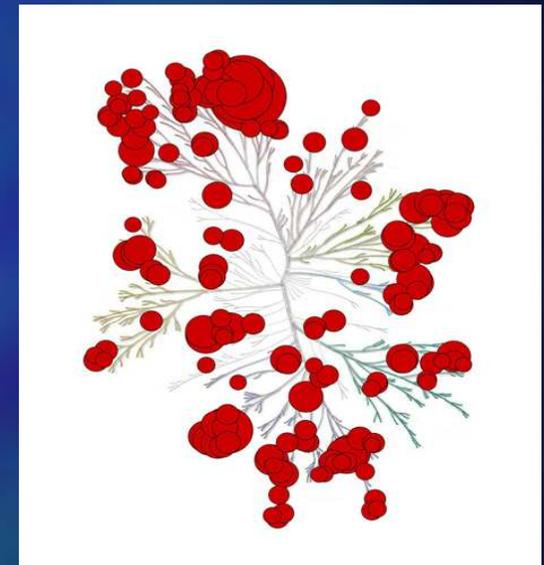
# Sélectivité comparée



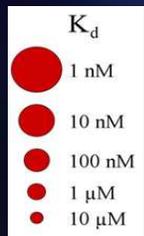
pazopanib



sorafénib



sunitinib



# Individualisation

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## VEGF et sorafénib

**Pas de valeur prédictive  
des taux circulants de VEGF**

**Bénéfice similaire du traitement  
quel que soit le niveau initial**

*Escudier et al, J Clin Oncol, 2009, 27:3312*

# Individualisation

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## Inactivation de VHL

**N = 43 patients**

**Sorafénib ou axitinib**

**60% inactivation VHL**

**Mutation ou  
méthylation du promoteur**

# Individualisation

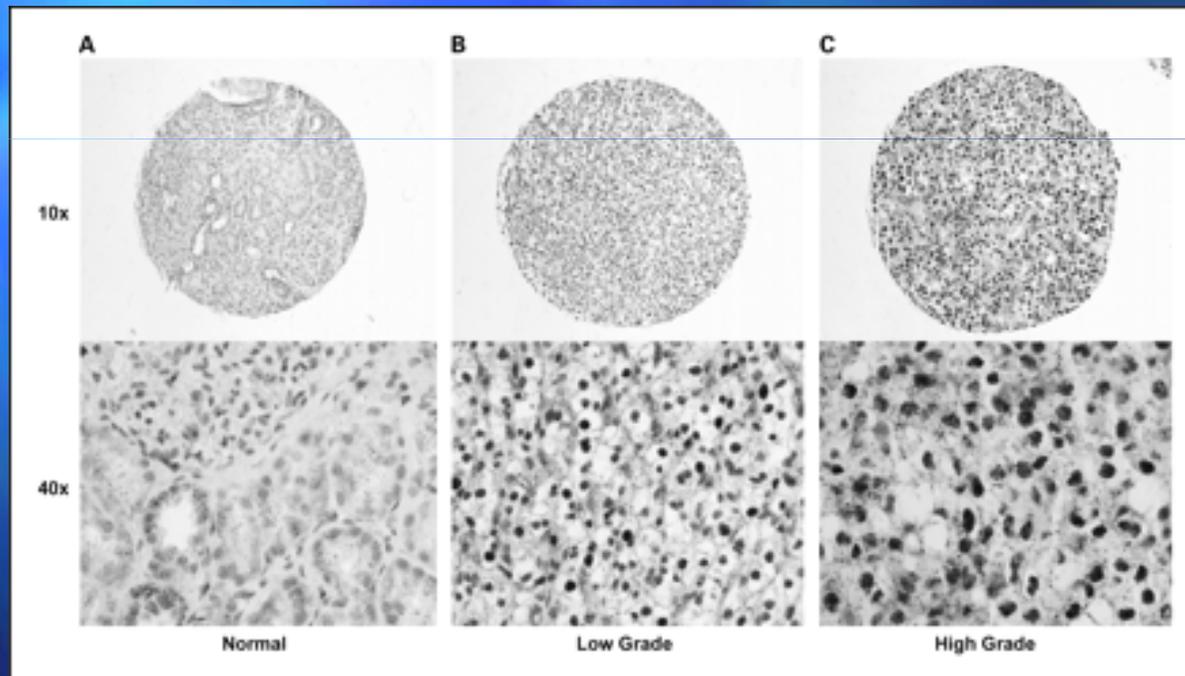
## Résultats

|                     | <b>VHLin</b>  | <b>VHLs</b> |
|---------------------|---------------|-------------|
| Réponses objectives | <b>48%</b>    | <b>35%</b>  |
| SSP médiane         | <b>13 m</b>   | <b>7 m</b>  |
|                     | <b>p=0,06</b> |             |

*Rini et al, BJU Int 2006,98:756*

# Individualisation

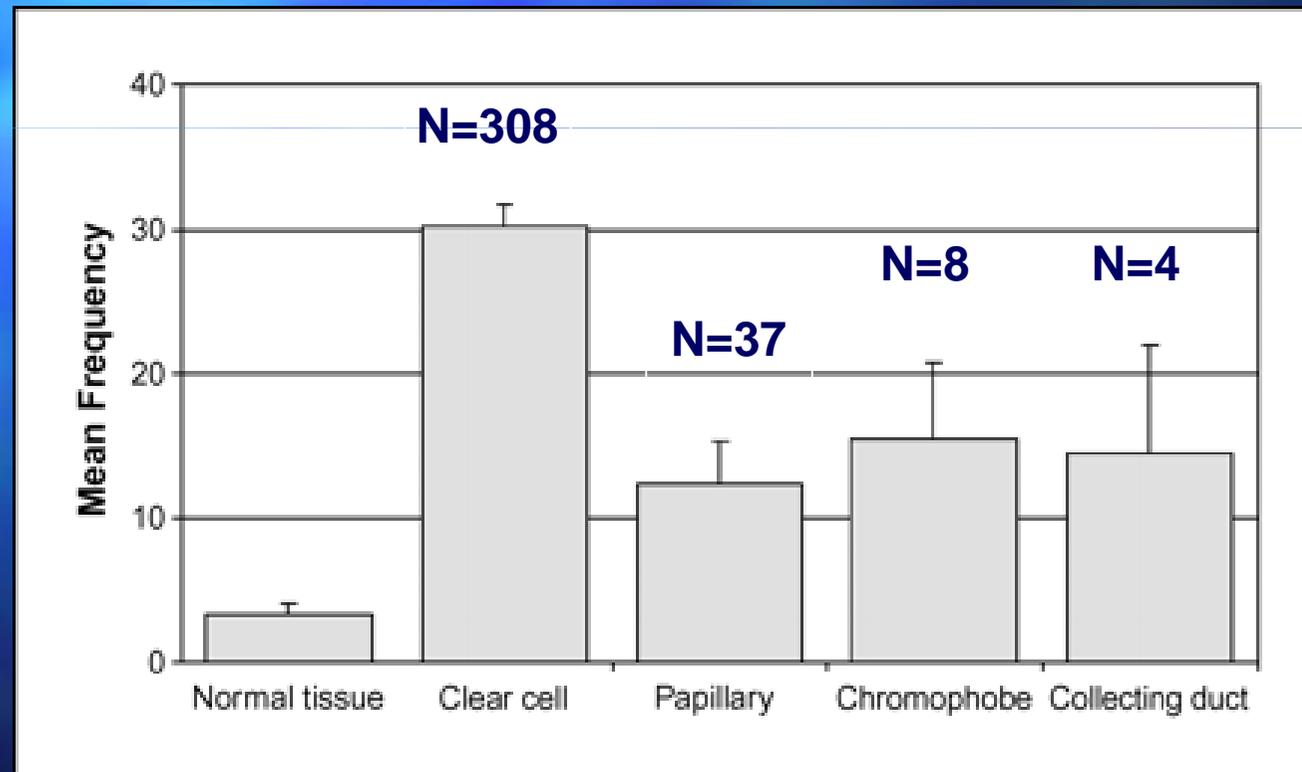
## HIF-1 $\alpha$



*Klatte et al., Clin Cancer Res, 2007, 13:7388*

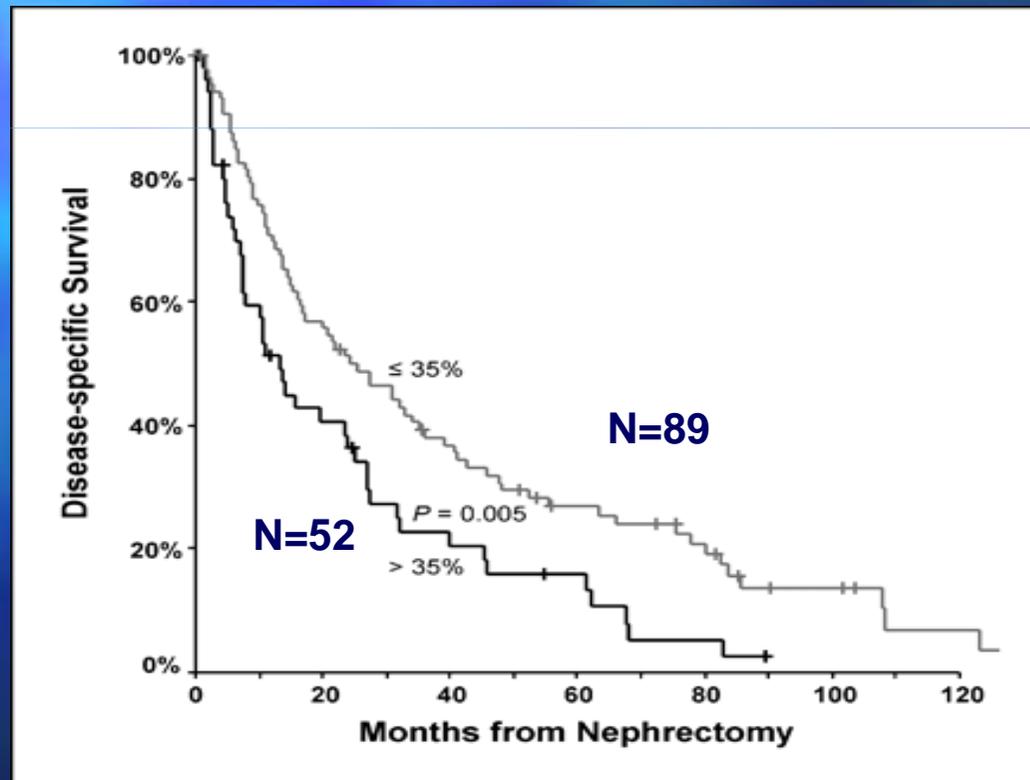
# Individualisation

## HIF-1 $\alpha$



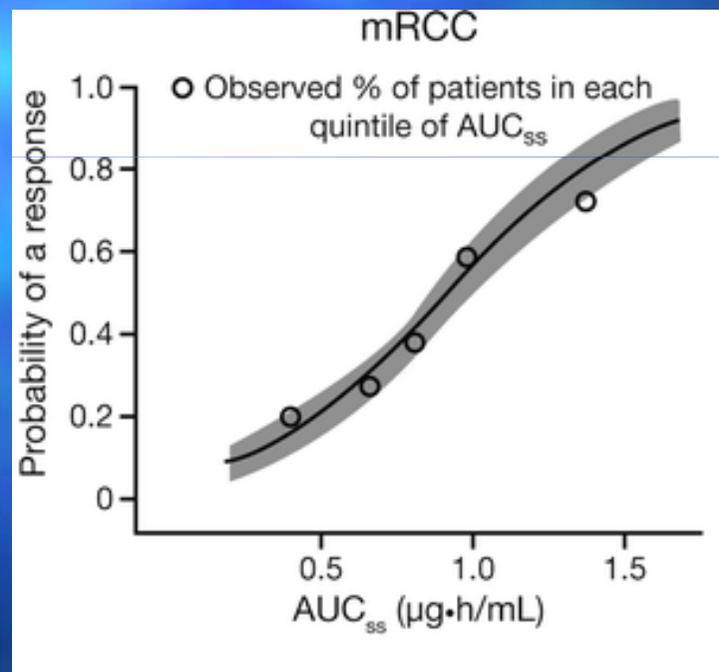
# Individualisation

## HIF-1 $\alpha$



# Individualisation

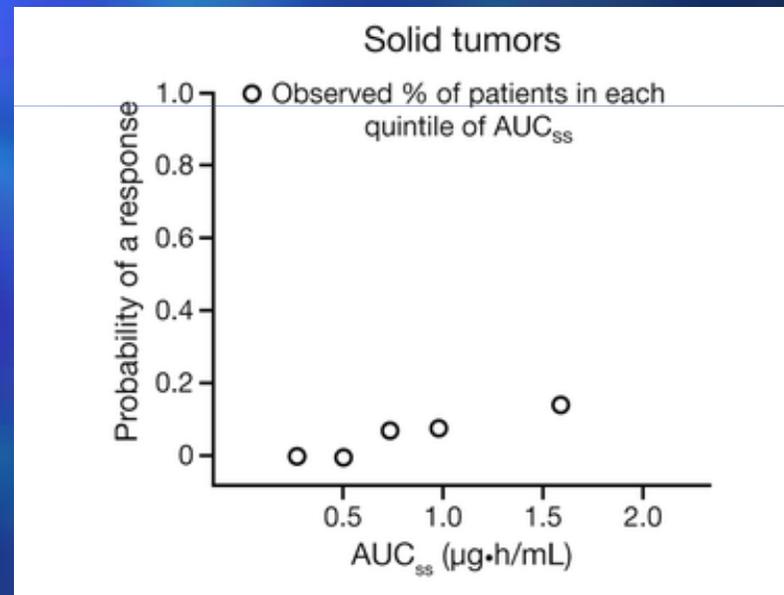
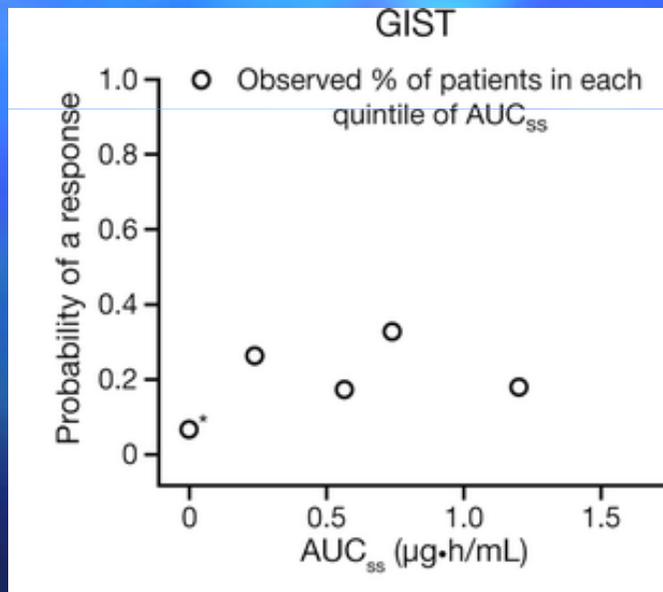
## Sunitinib



*Houk, Cancer Chemother Pharmacol, 2010, 66:357*

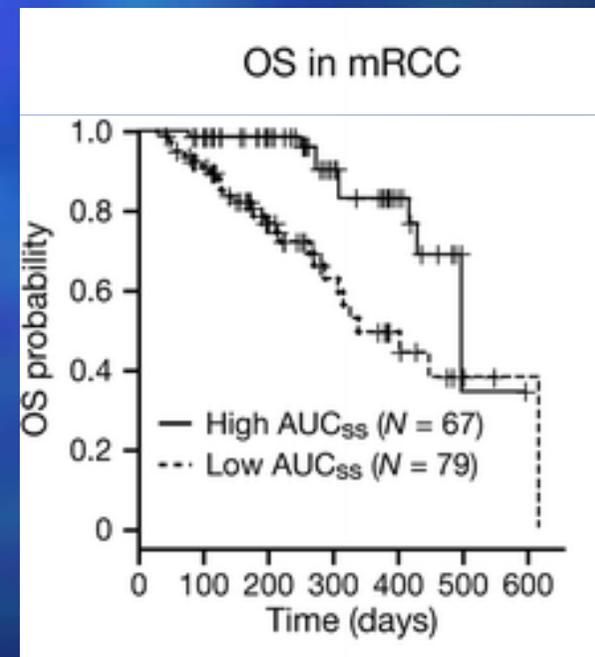
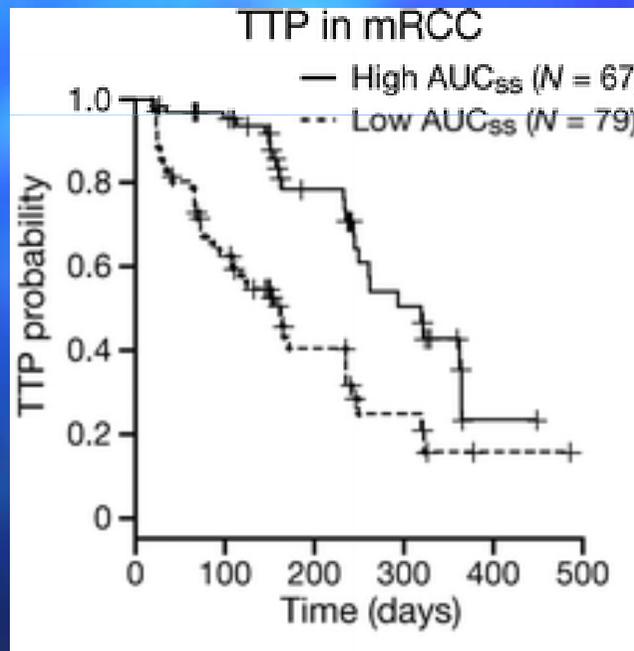
# Individualisation

## Sunitinib

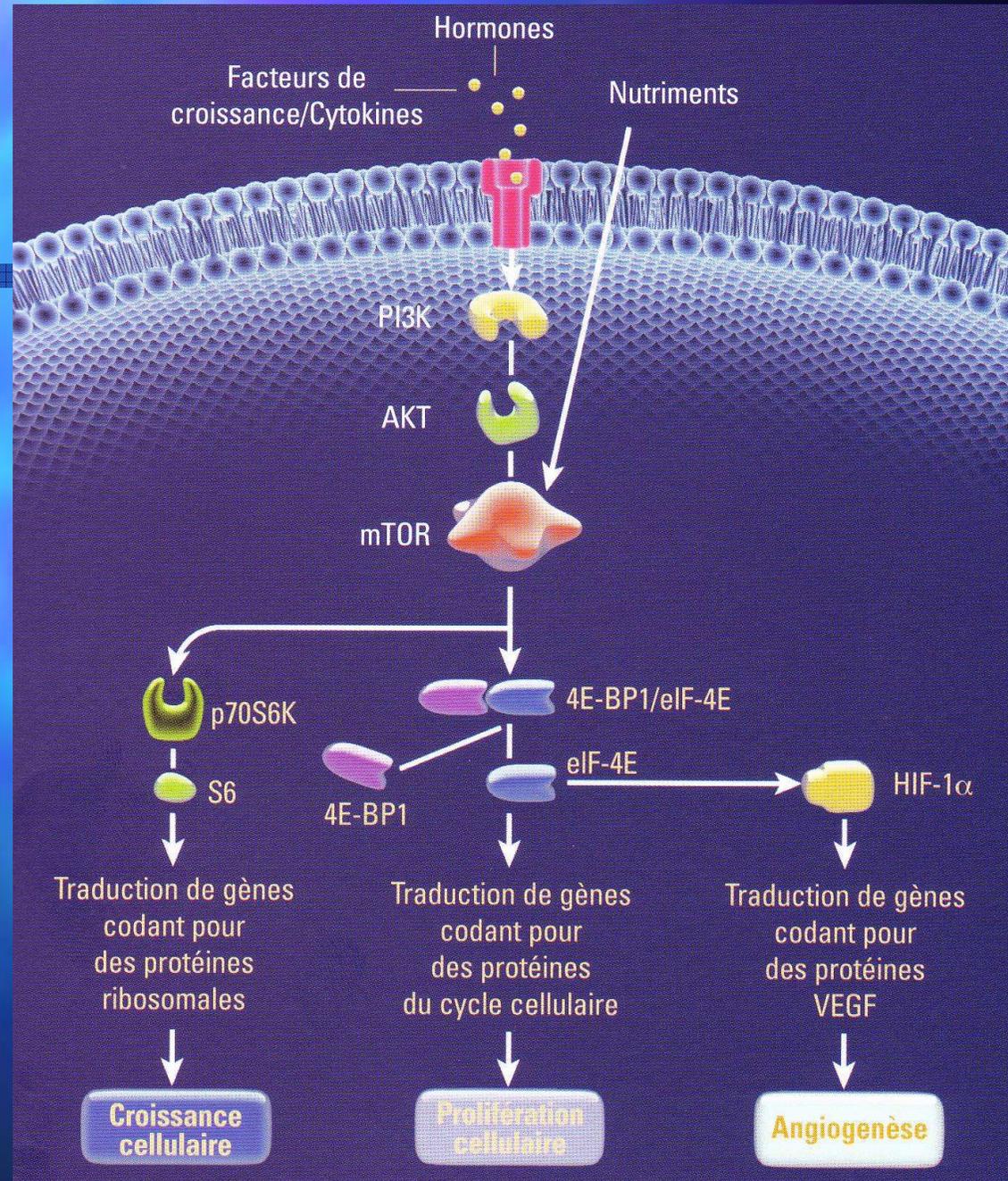


# Individualisation

## Sunitinib



# mTOR



# La voie mTOR

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**Etude TMA – 375 tumeurs**

**En amont**

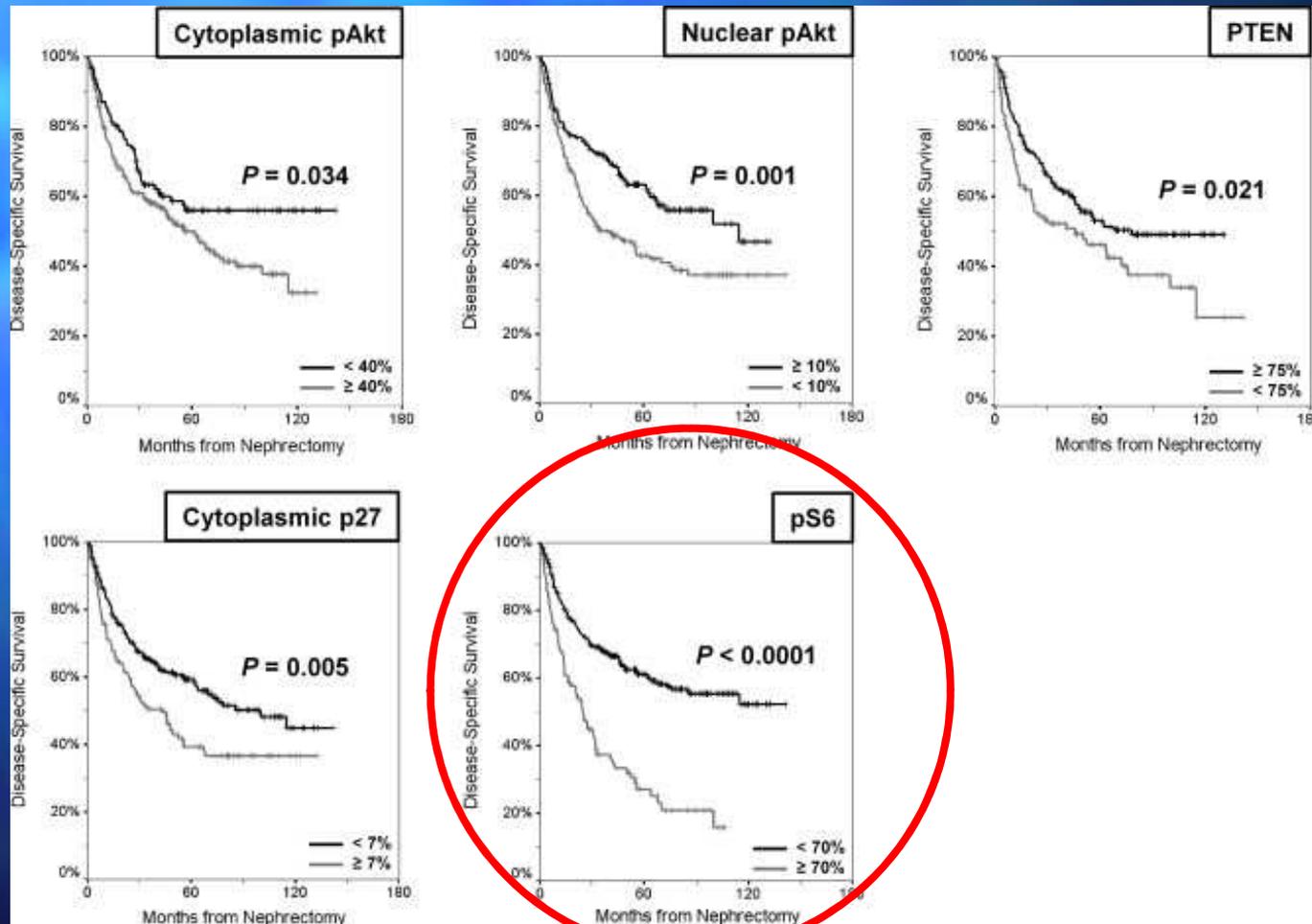
**pTEN et pAkt**

**En aval**

**pS6 et p27**

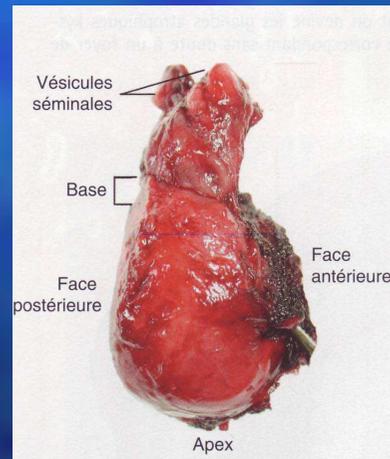
*Pantuck et al, Cancer, 2007, 109:2257*

# La voie mTOR



# Chapitre III

## Les cancers de prostate



# Stades métastatiques

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**Pas d'individualisation**

**Hormonothérapie  
(18-24 mois)**

**Chimiothérapie  
(18-24 mois)**

# Hormonothérapie

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## Pharmacogénétique

**529 patients (1988-2006)**

**Agoniste LH-RH ou pulpectomie**

**129 polymorphismes dans 20 gènes**

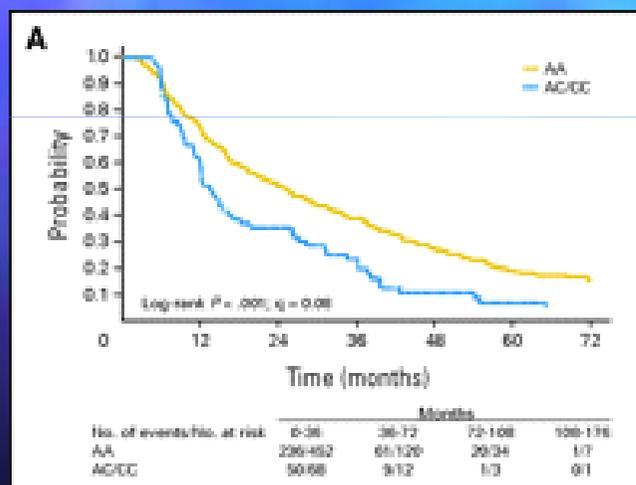
**impliqués dans la synthèse et le  
métabolisme des androgènes**

# Hormonothérapie

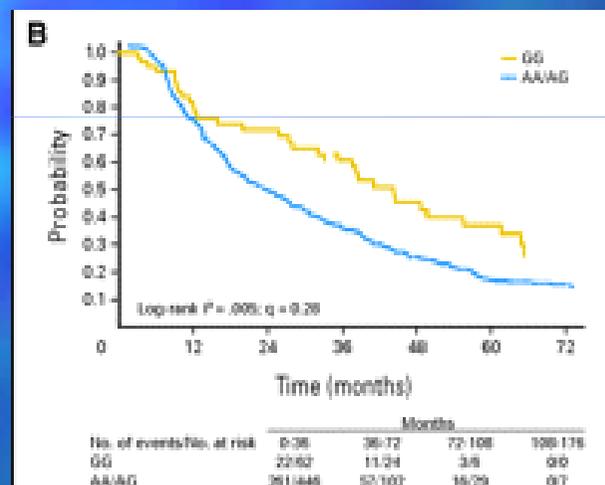
**SNP rs1870050  
CYP19A1**

**SNP rs1856888  
HSD3B1**

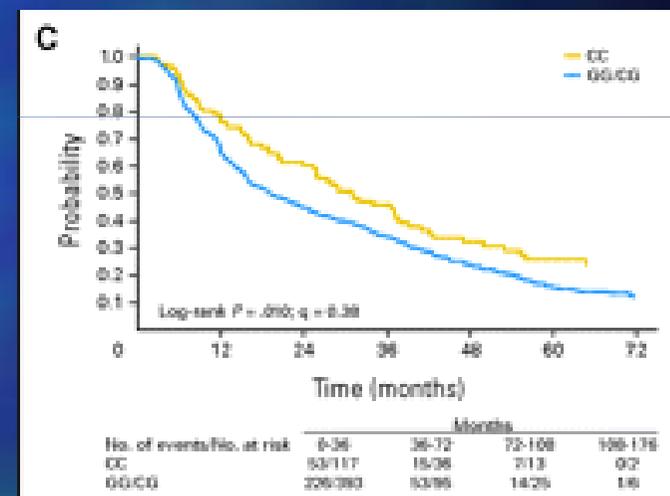
**SNP rs7737181  
HSD17B4**



**Aromatase**

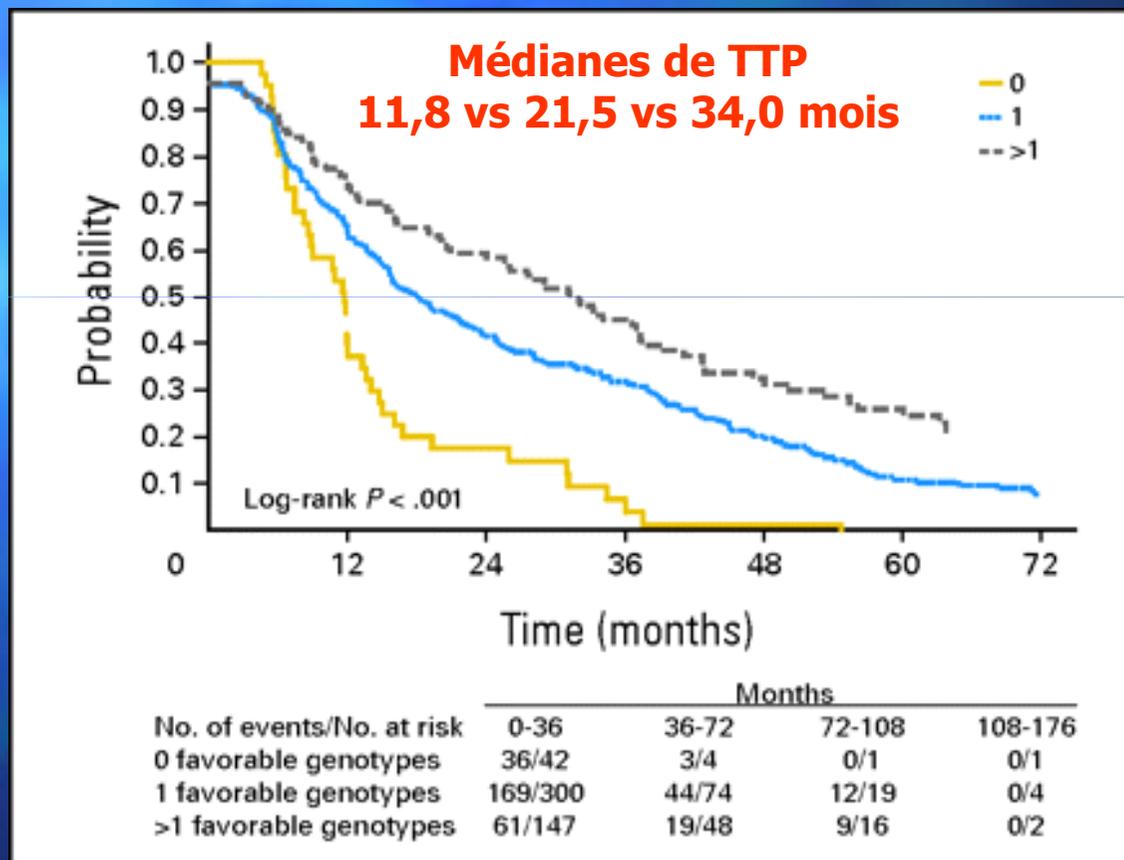


**Androstènedione**



**DHEA**

# Hormonothérapie



*Ross et al, J Clin Oncol, 2008, 26:842*

# Docétaxel

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**CYP1B1**

**Mono-oxygénase**

**Plusieurs SNPs**

**4326C>G (L432V)**

**Résistance au docétaxel**

# Docétaxel

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**CYP1B1**

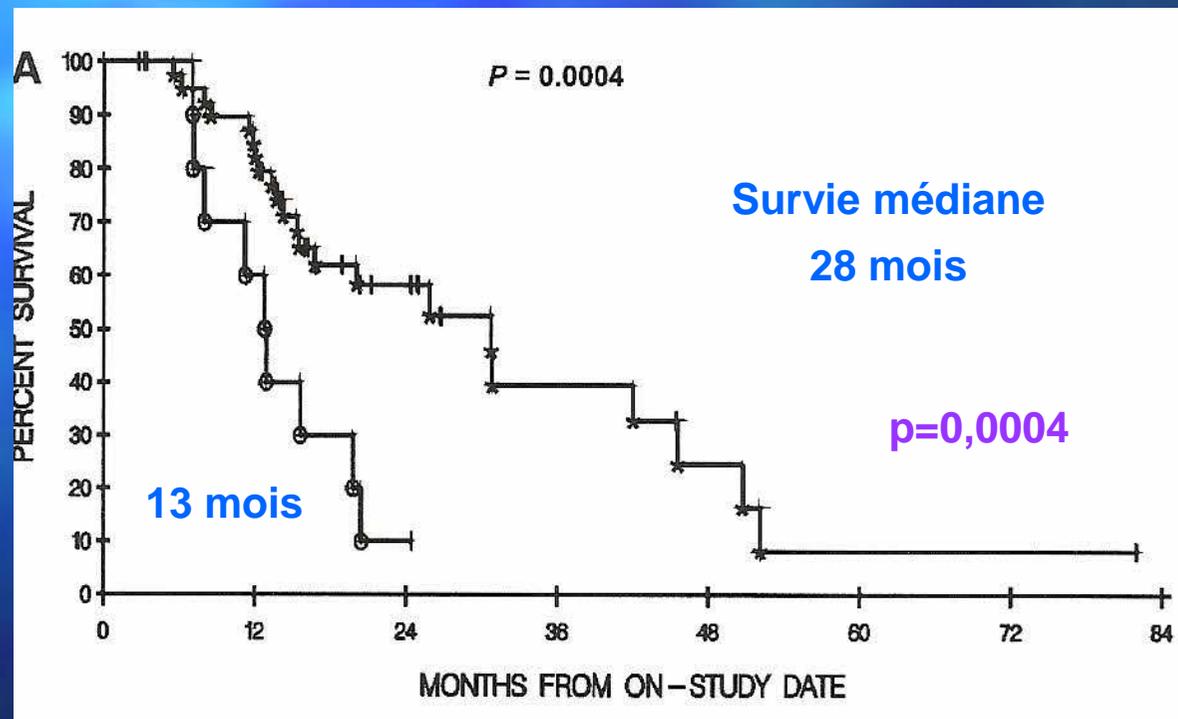
**52 patients**

**10 patients GG**

**Pas de différence dans la PK  
Devenir ?**

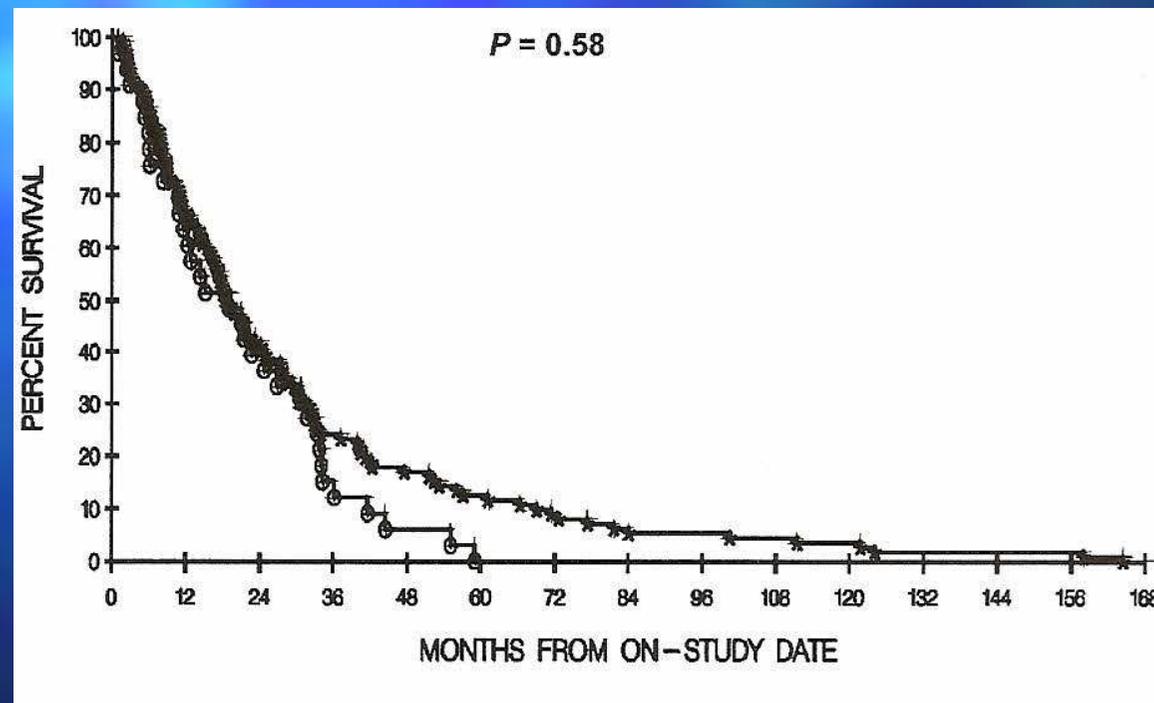
# Docétaxel

## Survie



# Suramine/Thalidomide

## Survival



# Docétaxel

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## CYP1B1

**60 patients**

**Etude des SNPs**

**4326C>G**

**4390A>G**

**142C>G**

# Docétaxel

## SNPs et réponses

| Genotype             | CR+PR (N=29) | SD+PD (N=31) | <i>P</i> |
|----------------------|--------------|--------------|----------|
|                      | N (%)        | N (%)        |          |
| <b>CYP1B1 4326CG</b> |              |              |          |
| CC + GC              | 23 (62.2)    | 14 (37.8)    | 0.014    |
| GG                   | 6 (26.1)     | 17 (73.9)    |          |
| <b>CYP1B1 4390GA</b> |              |              |          |
| AA                   | 21 (56.8)    | 16 (43.2)    | 0.164    |
| AG+ GG               | 8 (34.8)     | 15 (65.2)    |          |
| <b>CYP1B1 412CG</b>  |              |              |          |
| CC + CG              | 14 (48.3)    | 15 (51.7)    | 0.993    |
| GG                   | 15 (48.4)    | 16 (51.6)    |          |

Abbreviations: CR complete response; PD, progressive disease; PR, partial response; SD, stable disease. *P* was calculated with *Pearson- $\chi^2$  two-sided* test with continuity correction

# Docétaxel

## Analyse multifactorielle

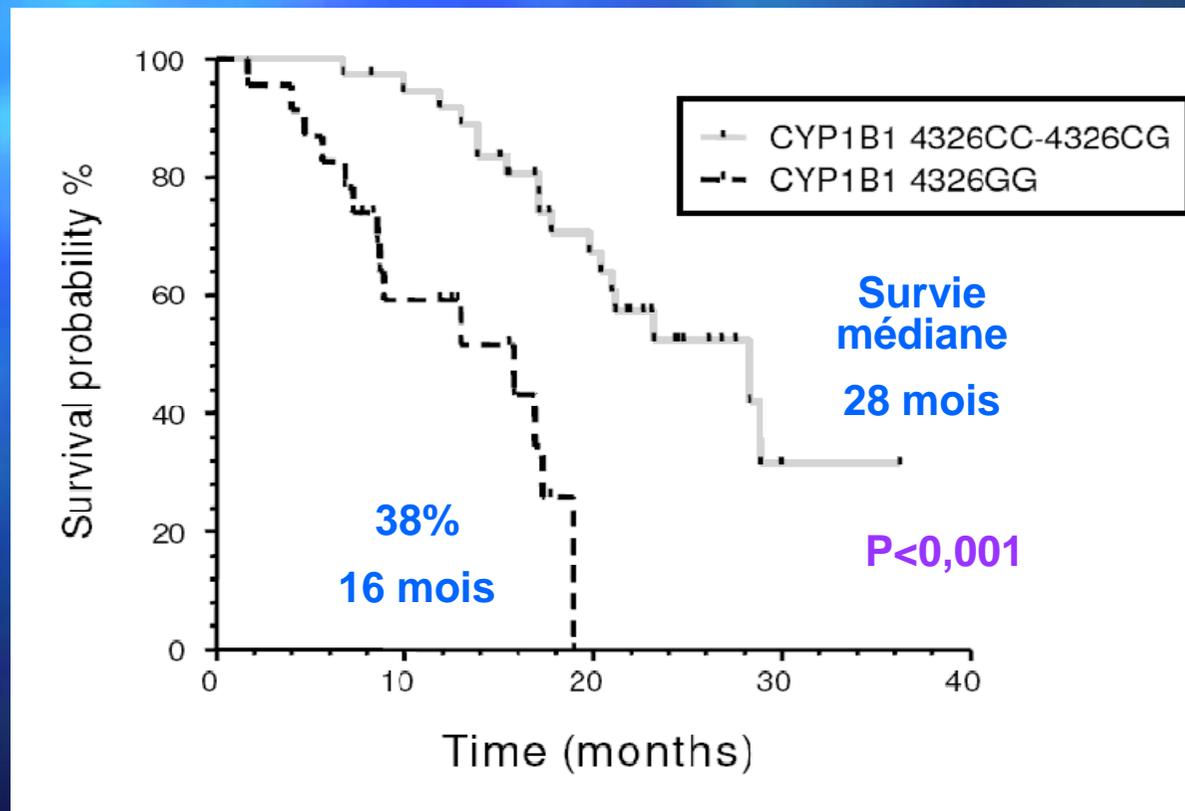
Table 4. Multivariate analysis of clinical and biological parameters for OS

| Covariates           |                      | HR (95% CI)    | df | P            |
|----------------------|----------------------|----------------|----|--------------|
| Visceral metastasis  | yes                  | 3.8 (1.4-10.0) | 1  | 0.008        |
|                      | no                   | 1 (Ref.)       |    |              |
| Anaemia              | yes                  | 1.0 (0.2-2.5)  | 1  | 0.935        |
|                      | no                   | 1 (Ref.)       |    |              |
| Pre-treatment PSA    | ≤median              | 1 (Ref.)       | 1  | 0.242        |
|                      | >median              | 0.64 (0.3-1.4) |    |              |
| <b>CYP1B1 G4326C</b> | <b>4326CG+4326CC</b> | 1 (Ref.)       | 1  | <b>0.003</b> |
|                      | <b>4326GG</b>        | 1.7-12.8       |    |              |

Abbreviations: Ref., Reference.

# Docétaxel

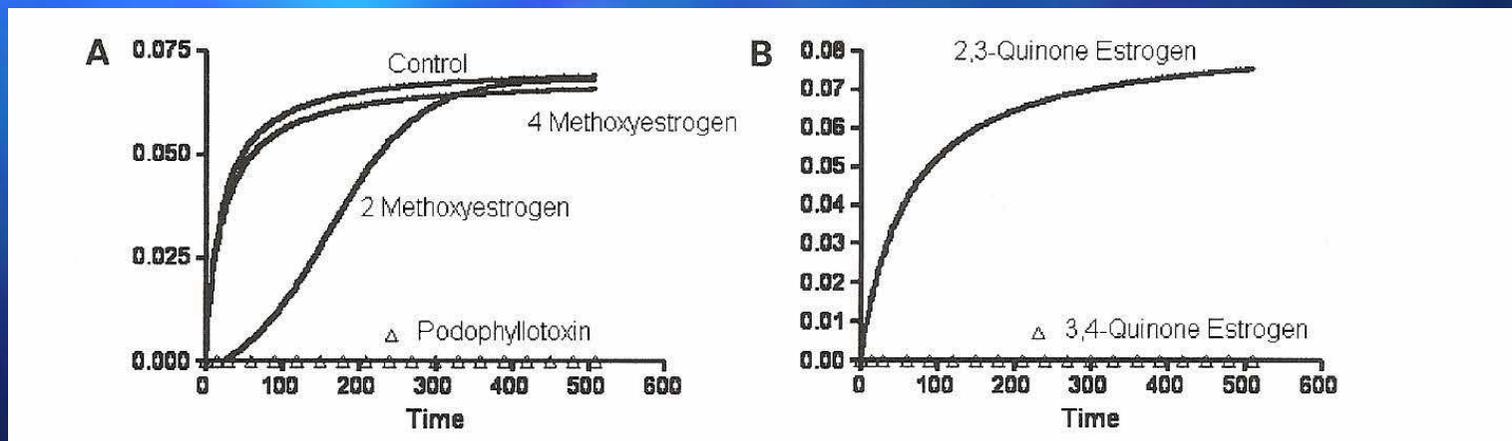
## Survie



# Docétaxel

## Mécanisme ?

4-OHE2  $\longrightarrow$  Estradiol-3,4 quinone



# Onco-urologie

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## Prédiction de l'efficacité

**Pas aujourd'hui**

**Demain**

**Pharmacogénétique ?**

**Limites : alternatives thérapeutiques**