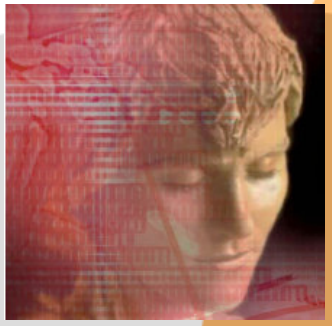


Thérapies ciblées dans le cancer de l'ovaire

Dr Paul COTTU
Département d'Oncologie Médicale
Institut Curie
Paris

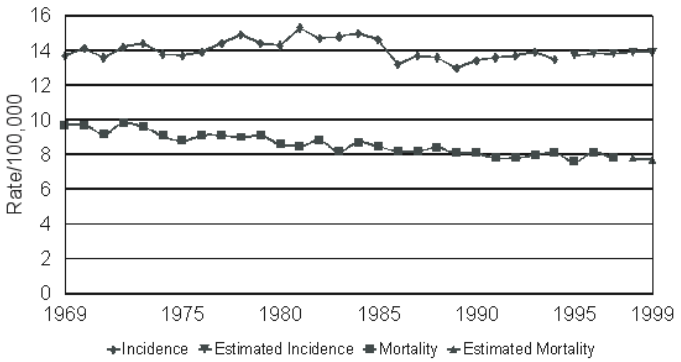
Le cancer de l'ovaire : un état stable

- **France 2008 : 4430 nouveaux cas**
  - **7ème cause de cancer féminin**
  - **Âge médian 65 ans**

- **Evolution de la chimiothérapie**
  - **Années 1970-1980 : alkylants et sels de platine**
  - **Années 1990 : taxanes**
  - **Survie globale environ 30 mois**

Age-standardized incidence and mortality rates for ovarian cancer, Canada, 1969-1999

(Source : Public Health Agency of Canada)



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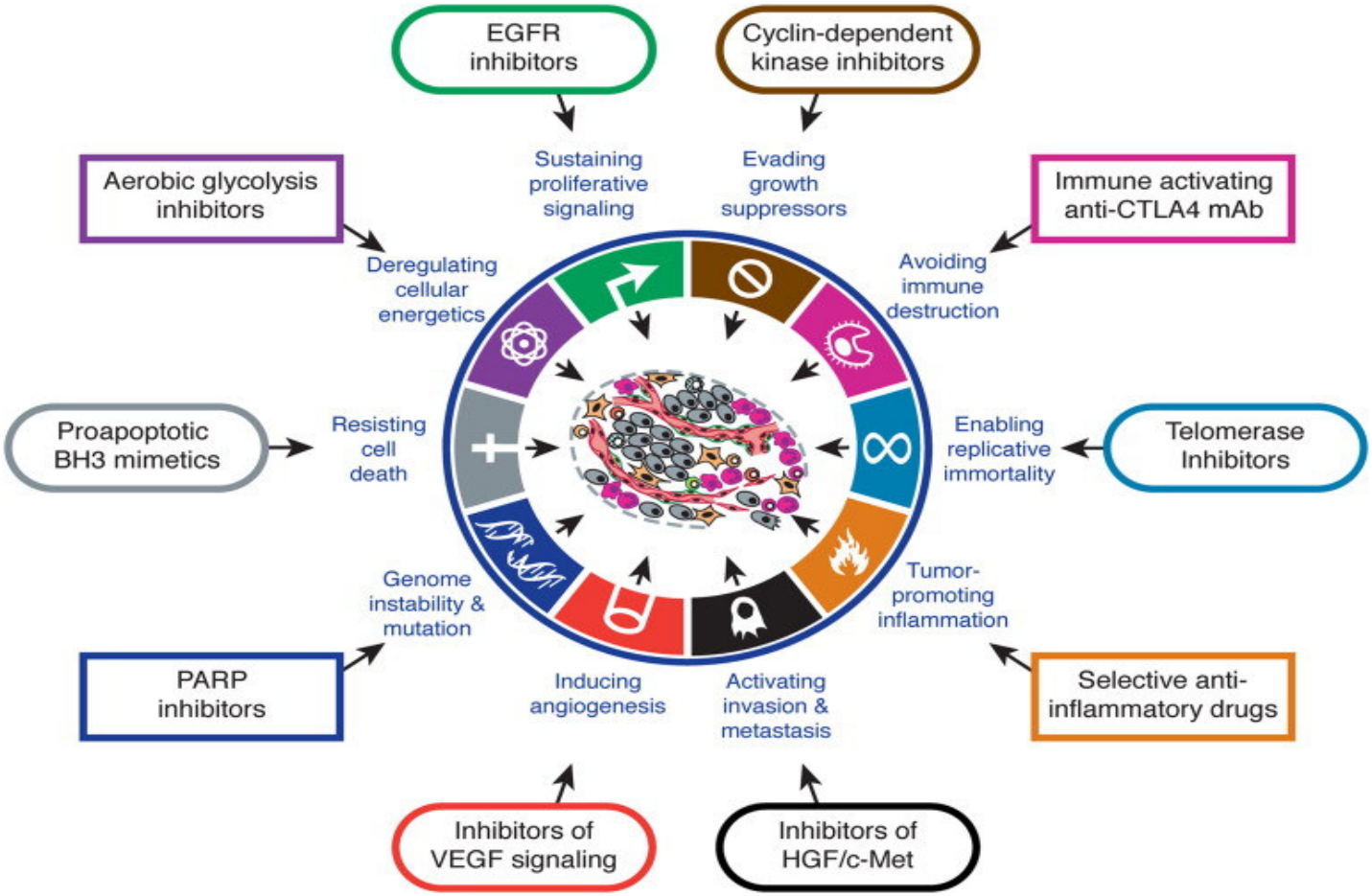
La révolution biologique
Hanahan et Weinberg, 2011



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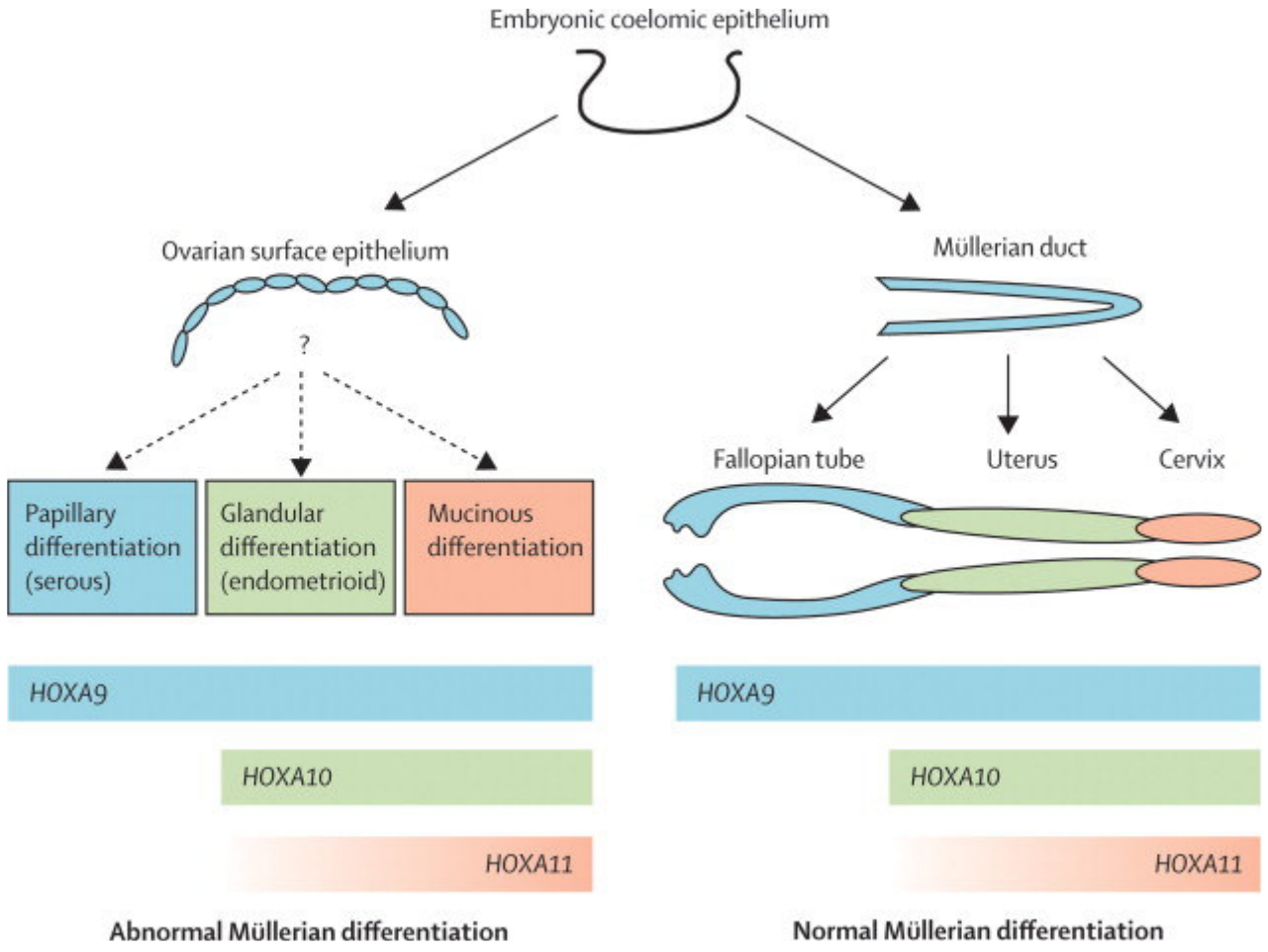
Approches biologiques



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Oncogenèse

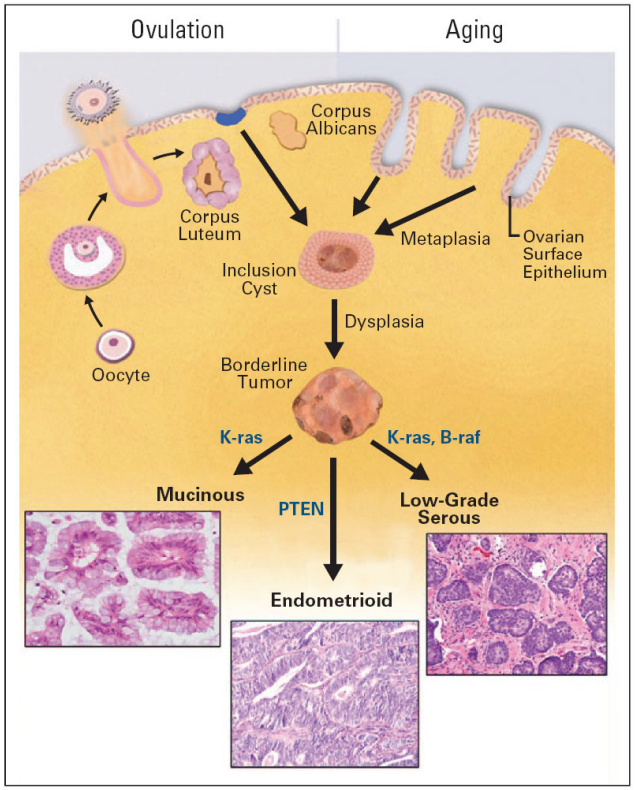

Fig 1. Transformation of ovarian surface epithelium (OSE). The OSE undergoes cyclic ovulation-induced rupture, leading to formation of cortical inclusion cysts (CICs). Entrapped within the ovarian cortex, the OSE undergoes Müllerian metaplasia, and is exposed to hormone and inflammatory stimuli that induce replicative stress and DNA damage which can lead to defined mutations and transformation into mucinous, endometrioid, and low-grade serous carcinomas.

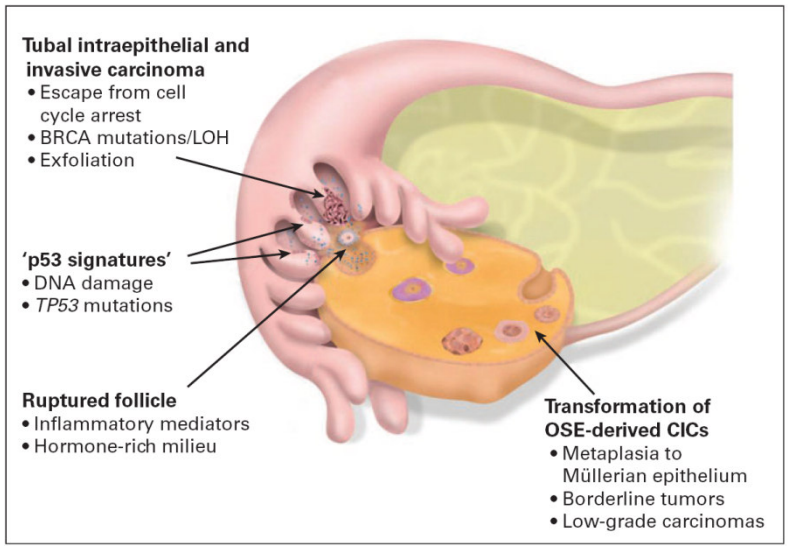

Fig 4. An integrated model of high-grade serous carcinogenesis. This model integrates the data about the stepwise development of serous carcinoma in the fimbria of the fallopian tube (FT) and in the ovarian surface epithelium (OSE) –derived cortical inclusion cysts (CICs). The hormone stimulation and the inflammatory mediators involved in ovulation are believed to have similar carcinogenic effect in both pathways.

Levanon, Journal of Clinical Oncology 2008; 26(32): 5284-5293.

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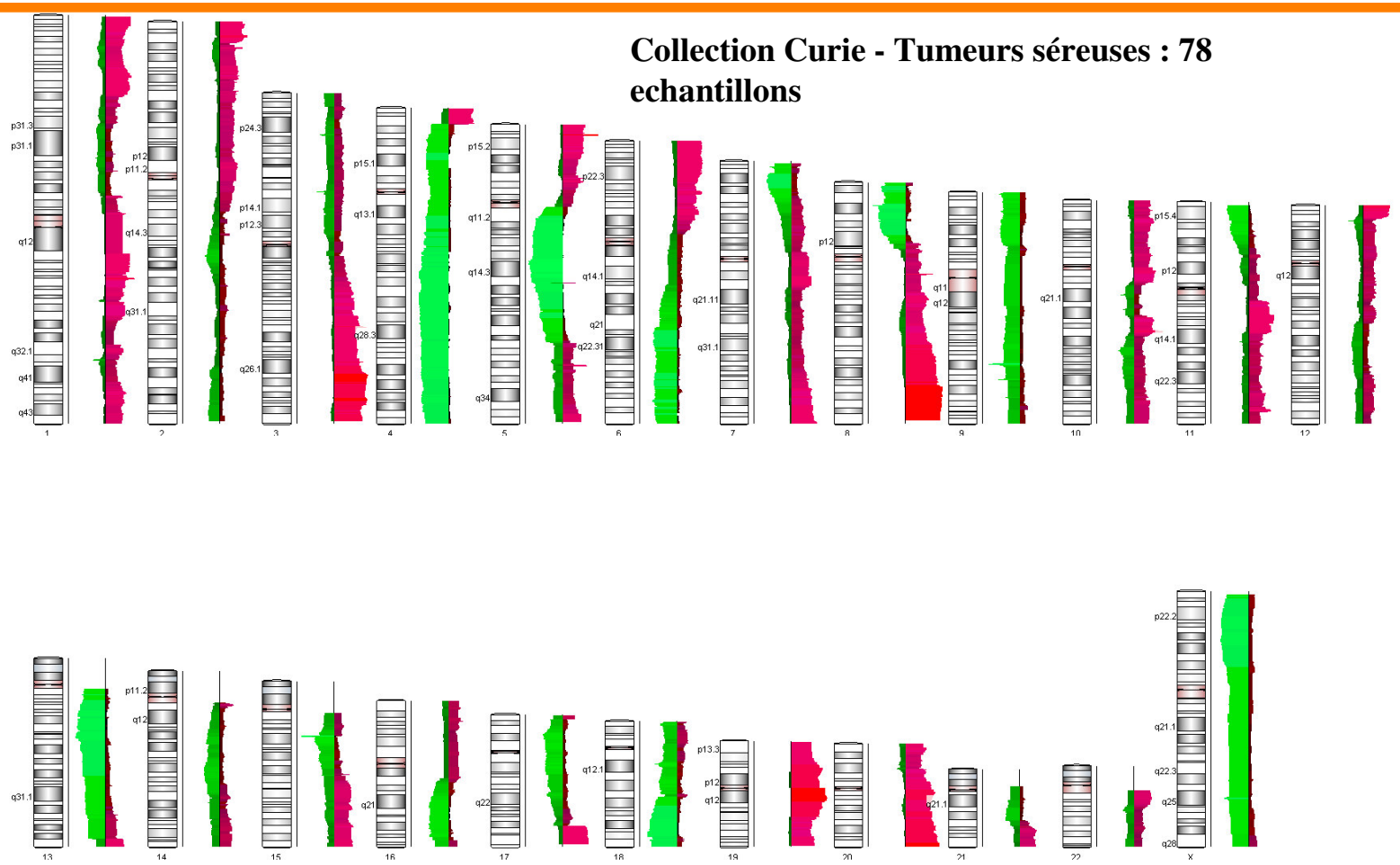
Génomique



© J-Ph Meyniel

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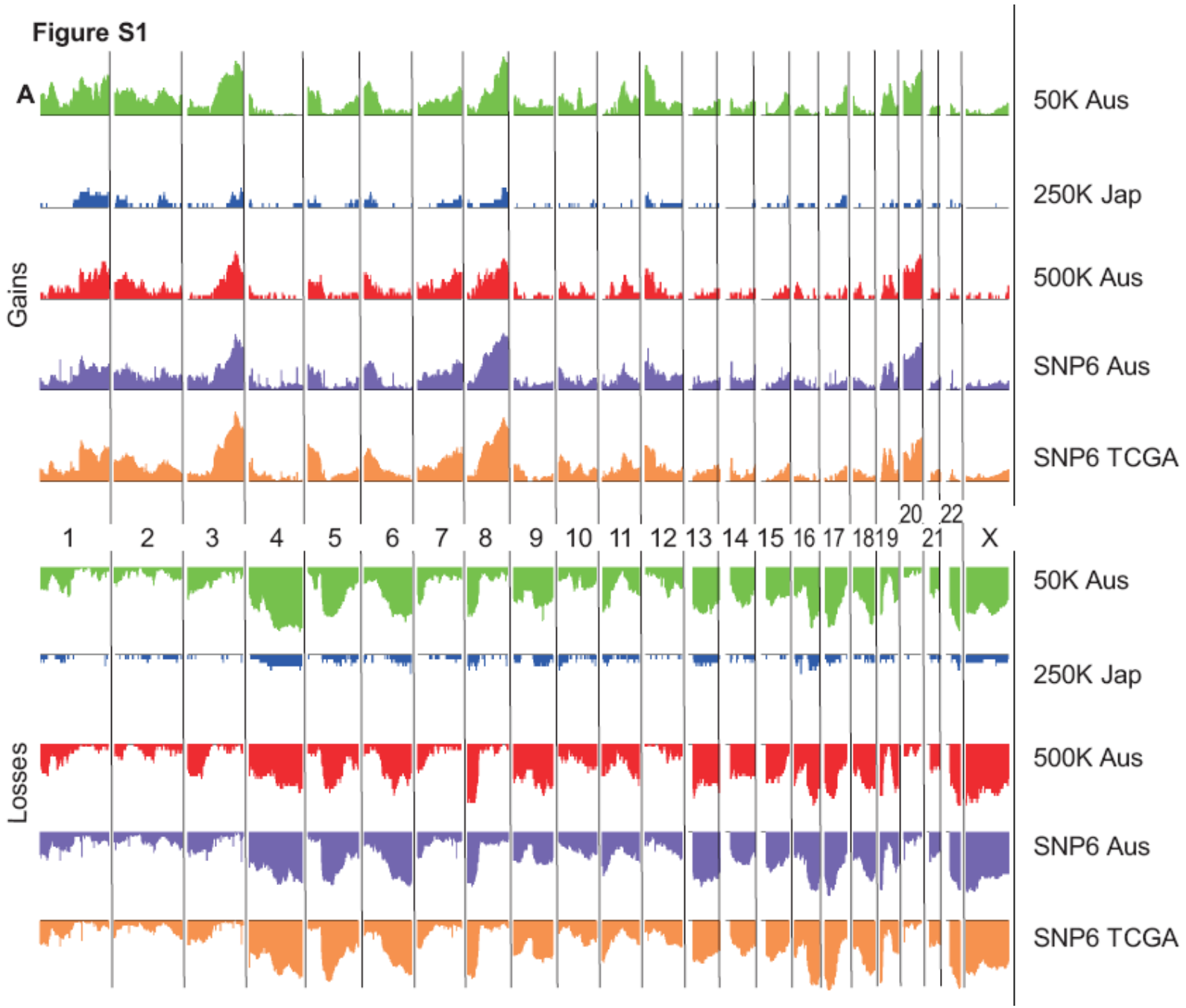
Gorringe, 2010



Caractérisation moléculaire

Table 1 | **Genetic abnormalities in epithelial ovarian cancer***

Event	Effect	Chromosome	Gene
Gene amplification‡	Activation	1q22 3q26 5q31 8q24 19q 20p 20q13.2	*RAB25* *PRKCI*, *EVI1* and *PIK3CA* *FGF1* *MYC* *PIK3R1* and *AKT2* ND *AURKA*
Gene deletion‡	Inactivation	4q, 5q, 16q, 17p, 17q, Xp and Xq	ND
Mutation§	Activation	NA	*KRAS* (15%), *BRAF* (12%), *CTNNB1* (12%), *CDKN2A* (10%), *APC* (9%), *PIK3CA* (8%), *KIT* (7%) and *SMAD4* (7%)
Hypomethylation	Activation	NA	*IGF2* and *SAT2*
Loss of heterozygosity	Inactivation	17p13 and 17q21 (in 50% of cases or more) 1p, 3p, 5q, 5q, 6q, 7q and 8q (in fewer than 30% of cases)	*ARHI*, *PEG3*, *PLAGL1*, *RPS6KA2*, *TP53*, *BRCA1*, *BRCA2*, *PTEN*, *OPCML* and *WWOX*
Mutation	Inactivation	NA	*TP53* (62%), *BRCA1* (5%), *BRCA2* (<5%) and *PTEN* (3–8%)
Promoter methylation‖	Inactivation	NA	*ARHI*, *DAPK1*, *CDH13*, *MLH1*, *ICAM1*,*PLAGL1*, *DNAJC15*, *MUC2*, *OPCML*, *PCSK6*, *PEG3*, *CDKN2A*, *CDKN1A*, *RASSF1*, *SOCS1*, *SOCS2*, *PYCARD* and *SFN*

The growth of ovarian cancer cells can also be induced by transfer of chromosomes 2, 3, 7 and 22. *Table adapted from REF. 11 ‡Determined by array comparative genomic hybridization. §Data obtained from http://www.sanger.ac.uk. ‖Expanded from REF. 29. *APC*, adenomatous polyposis coli; *AURKA*, aurora kinase A; *CDH13*, cadherin 13; CDKN, cyclin-dependent kinase inhibitor; *CTNNB1*; β-catenin 1; *DAPK1*, death-associated protein kinase 1; *EVI1*, ecotropic viral integration site 1; *FGF1*, fibroblast growth factor 1; *ICAM1*, intracellular adhesion molecule 1; *IGF2*, insulin-like growth factor 2; *MUC2*, mucin 2; NA, not applicable; ND, not determined; *OPCML*, opioid-binding protein/cell adhesion molecule-like; *PCSK6*, proprotein convertase subtilisin/kexin type 6; *PEG3*, paternally expressed 3; *PIK3CA*, PI3K catalytic subunit-α; *PIK3R1*, PI3K regulatory subunit 1; *PRKCI*, protein kinase Cι; *PLAGL1*, pleiomorphic adenoma gene-like 1; *RPS6KA2*, ribosomal protein S6 kinase 2; *SAT2*, spermidine/spermine N1-acetyltransferase family member 2; *SFN*, stratifin; SOCS, suppressor of cytokine signalling.

Bast, Nature Reviews Cancer 2009; 9: 415-428.

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Révision nosologique

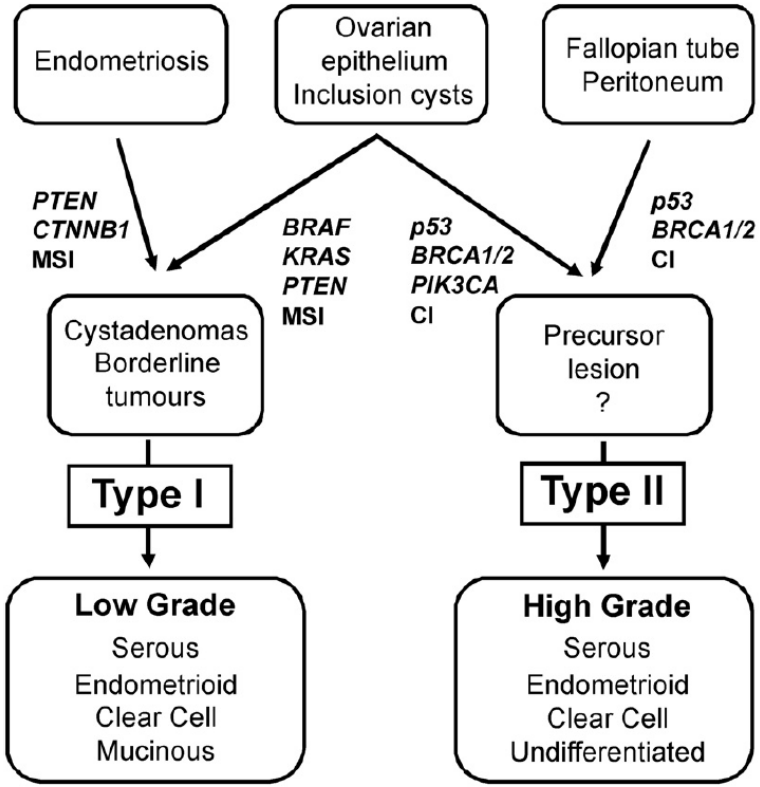

Fig. 1. Two-pathway concept of ovarian cancer development.

Table 2
New classification of ovarian tumours.

Tumour characteristics	Type I	Type II
Tumour type	Low-grade serous Low-grade endometroid Mucinous Clear cell	High-grade serous High-grade endometrioid Undifferentiated Clear cell
Frequency	~25%	~75%
Common mutations and genetic modifications	*KRAS*	*p53*
	BRAF	*BRCA1*
	PTEN	*BRCA2*
	CTNNB1	*PIK3CA*
	MSI	*CI*

MSI—microsatellite instability; CI—chromosome instability.

Ricciardelli, Maturitas 2009; 62: 270-275.

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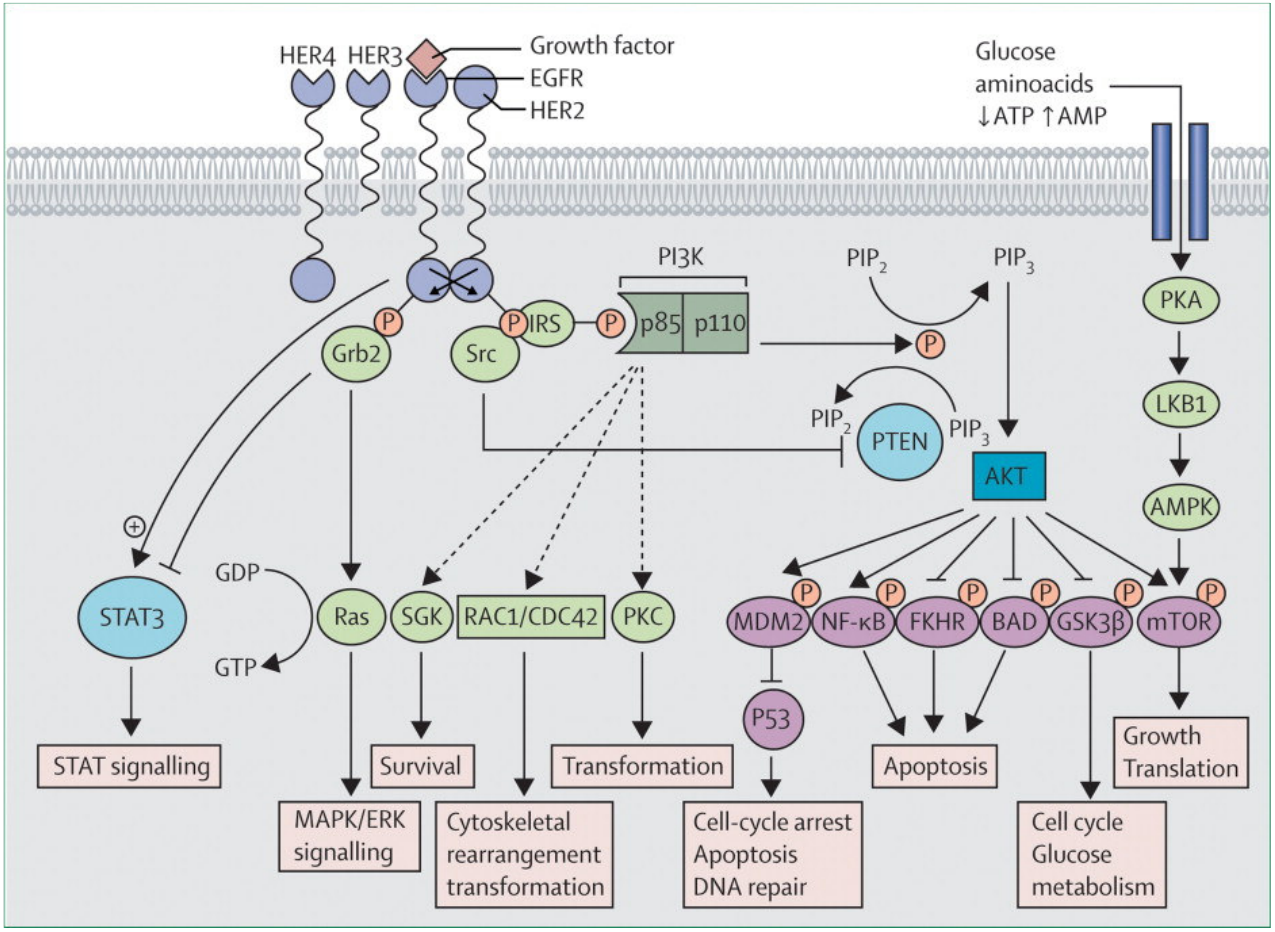
« Druggable targets »



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Thérapies ciblées

Target	Agent	Chemotherapy	RCT	Placebo	C M	Size	End-point	Trial number
First line								
VEGF	Bevacizumab	Platinum–taxane	III	N	C+M	1500	PFS	NCT00483782 (ICON7)
VEGF	Bevacizumab	Platinum–taxane	III	Y	C+M	2000	PFS	NCT00262847 (GOG 218)
EGFR TKI	Erlotinib	Platinum-based	III	Y	M	800	PFS	NCT00263822 (EORTC 55041/MRC OVO7)
VEGFR	Pazopanib	Platinum-based	III	Y	M	900	PFS	NCT00866697 (OVAR16)
VEGFR PDGFR FGFR	BIBF	Platinum–taxane	III	Y	C	1300	PFS	NCT01015118
EGFR TKI VEGF	Erlotinib Bevacizumab	Platinum–taxane	II	N	C+M	60	PFS Toxicity	NCT00520013
VEGFR, PDGFR C-Kit	Sorafenib	Platinum–taxane	II	N	C+M	60	PFS	NCT00390611
VEGFR, PDGFR C-Kit	Sorafenib	After platinum–taxane	II	Y	M	250	PFS	NCT00791778
IGF R1	AMG 479	Platinum–taxane	II	Y	M	160	PFS	NCT00718523
Platinum-sensitive relapse								
VEGF	Bevacizumab	Platinum–taxane	III	N	C+M	660	OS	NCT00565851 (GOG 213)
VEGF	Bevacizumab	Platinum-gemcitabine	III	Y	C	450	PFS	NCT00434642 (OCEANS)
VEGFR	Cediranib	Platinum-based	III	Y	C+M	2000	OS	NCT00532194 (ICON6)
Folate receptor	Farletuzumab	Platinum–taxane	III	Y	M	900	PFS	NCT00849667
PARP	Olaparib	Platinum–based	II	Y	M	250	PFS	NCT00753545 (Study19)
Src	AZD0530	Platinum–taxane	II	Y	M	241	RR	NCT00610714 (OVERT1)
Endothelin A	Zibotentan	Platinum–taxane	II	Y	C	122	PFS	NCT00929162
Platinum resistant relapse								
VEGF	Bevacizumab	Paclitaxel, topotecan, liposomal doxorubicin	III	N	C+M	300	PFS	NCT00976911 (AURELIA)
PARP	Olaparib	Liposomal doxorubicin	II	N	_	90	PFS	NCT00628251 (ICEBERG3)
VEGFR PDGFR C-Kit	Sorafenib	Topotecan	II	Y	C	184	PFS	NCT01047891 (TRIAS 2009)
VEGFR EGFR	Vandetanib	docetaxel	II	N	C+M	120	PFS	NCT00872989

Ledermann, Gyn Oncol 2010

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EGFR

Gefitinib	**Phase II Pautier** **Taxol-carboplatine**	**Contrôle tumoral** **69-81%**
Erlotinib	**Phase Ib Vasey** **Docetaxel** **carboplatine**	**Réponse 52%**
	Phase II Gordon **Maintenance**	**Survie 1 an** **35%**
	Phase III EORTC **Maintenance**	**En attente**
Cetuximab	**Phases II GOG** **Carboplatine**	**Réponses 9/26**

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HER 2

Trastuzumab	**Phase II GOG**	**Réponse 7%**
Pertuzumab	**Phase II Gordon** **Phase II Ambler** **Pertuzumab** **Gemcitabine**	**Réponse 4,3%** **SSP : +0,3 mois**

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Voie PI3K / mTOR

- **Etudes en cours**

- **Phase I/II**
  - **Temsirolimus**
  - **Temsirolimus + topotecan**

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Voie Src

- **Phase II OVERT 1**

–AZD0530/Placebo + taxol-carboplatine

–Maintenance AZD0530

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Voie IGF1

- **Etudes TRIO 14 et 15 en cours**

–AMG 386

- **TRIO 14 : adjuvant + maintenance**
- **TRIO 15 : première ligne sensible monothérapie**

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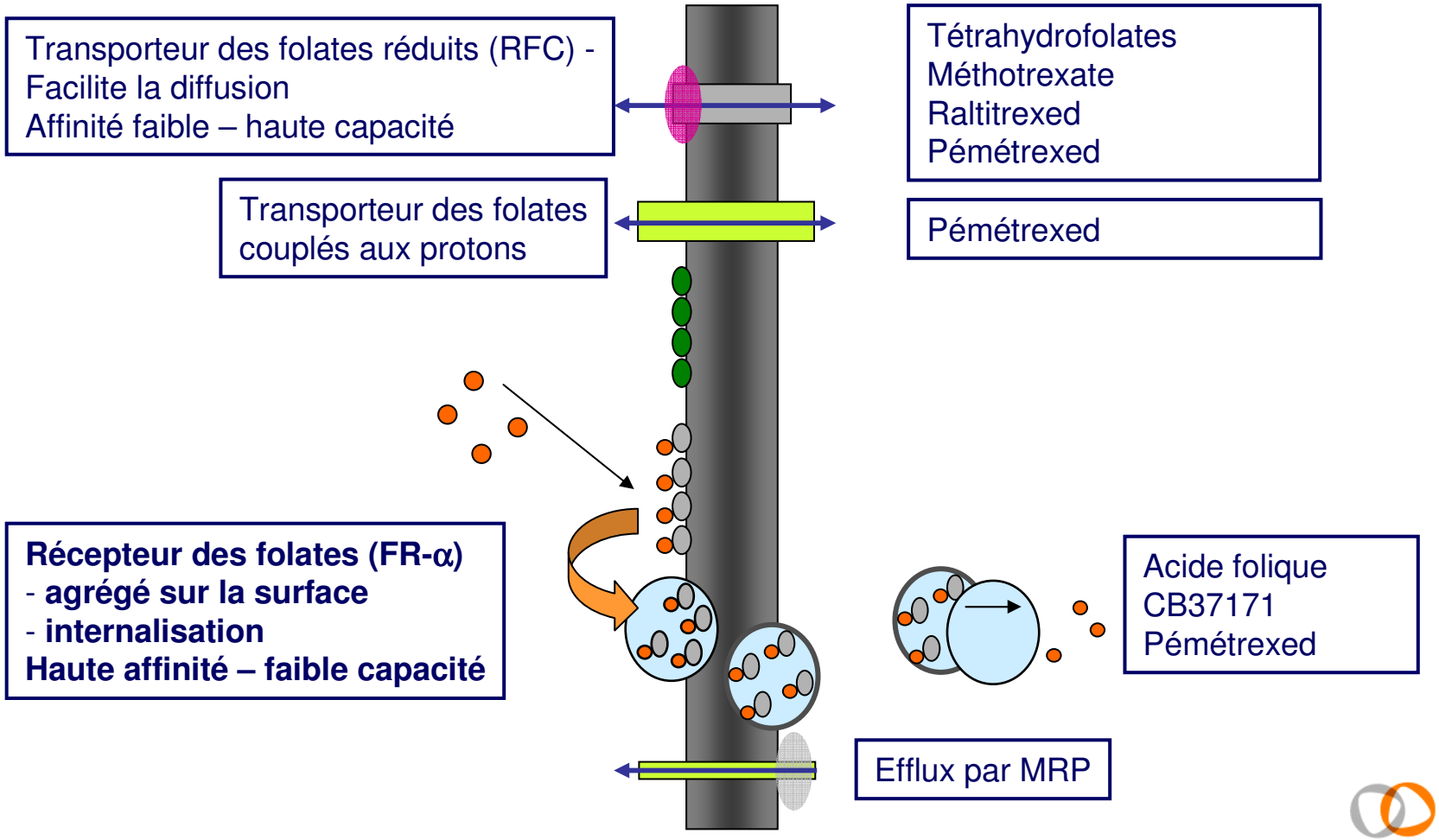
Transport membranaire des folates



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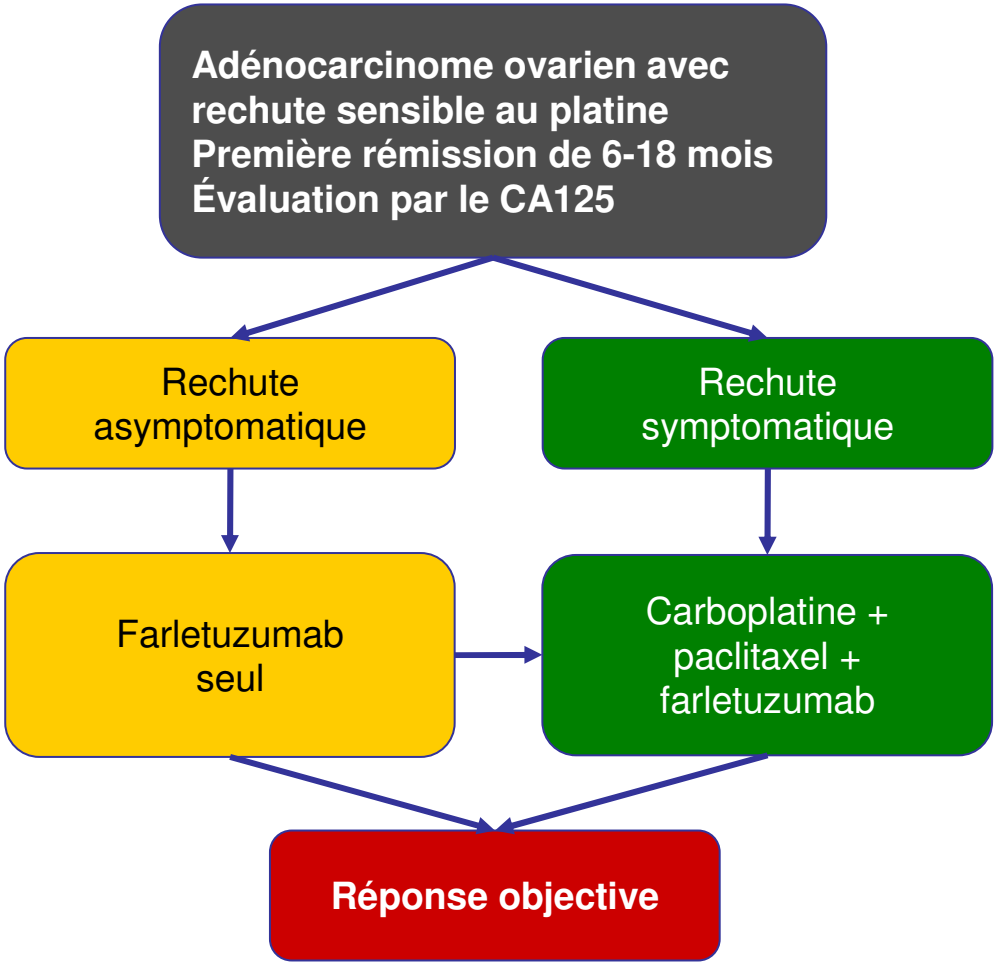
Farletuzumab : essai de phase II



- **43 patientes évaluables sur 44**
- **Revue centralisée**
- **Réponse complète : 7 %**
- **Réponse partielle : 63 %**
- **Stabilité : 23 %**
- **Progression : 7 %**

- **Réponses jusqu'à 44+ mois sous farletuzumab**

ASCO 2010 - D'après Karlan B et al., abstr. 5000 actualisé

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BRCAness

Gourley et al
JCO 2010

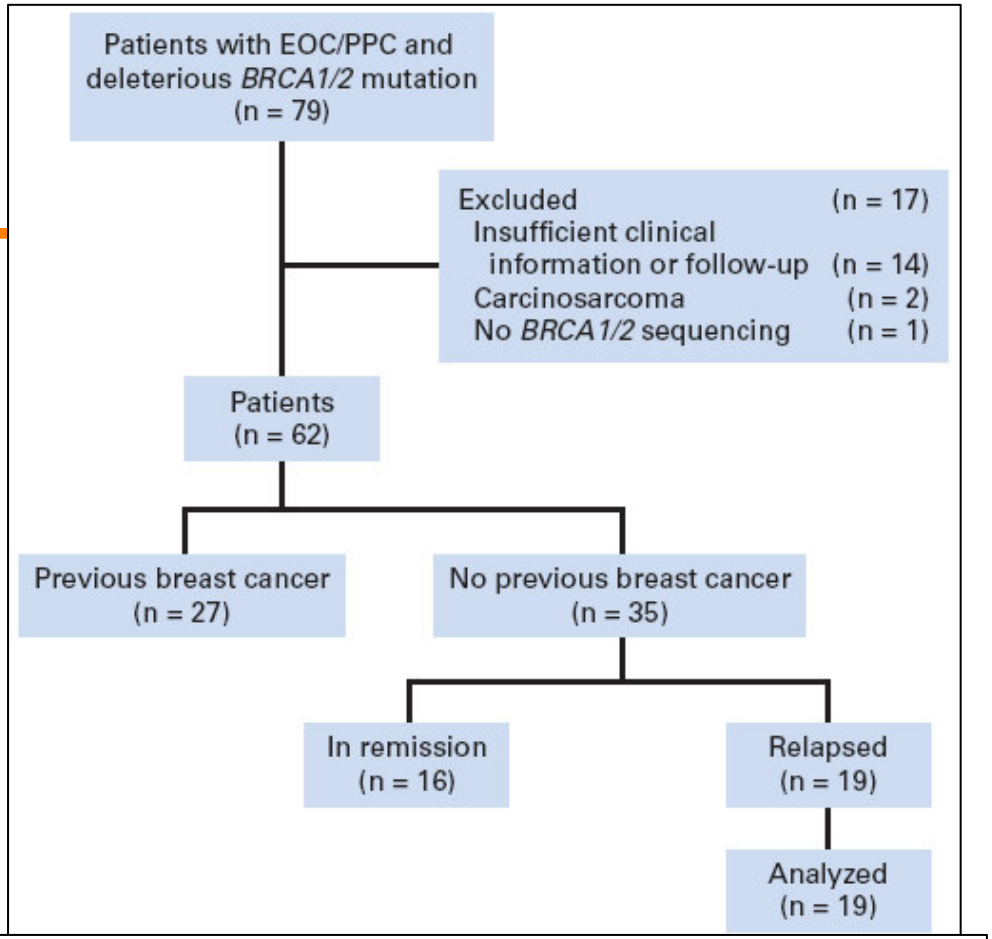

Table 5. Incidence of Visceral Metastases During Matched Follow-Up Period After First Progression in the Validation Data Set

Location of Metastases	BRCA1/2-Deficient (n = 24)		Nonhereditary Controls (n = 45)		*P* (Mantel-Haenszel)	Estimated Odds Ratio	95% CI for Estimated Odds Ratio
	No.	%	No.	%			
Liver	11	45.8	2	4.4	< .001	20.50	2.57 to 163.26
Lung	3	12.5	1	2.2	.153		
Splenic	4	16.7	1	2.2	.052		
Other visceral	2	8.3	2	4.4	1.000	2.50	0.165 to 37.79
Total visceral	15	62.5	5	11.1	< .001	25.00	3.04 to 205.80

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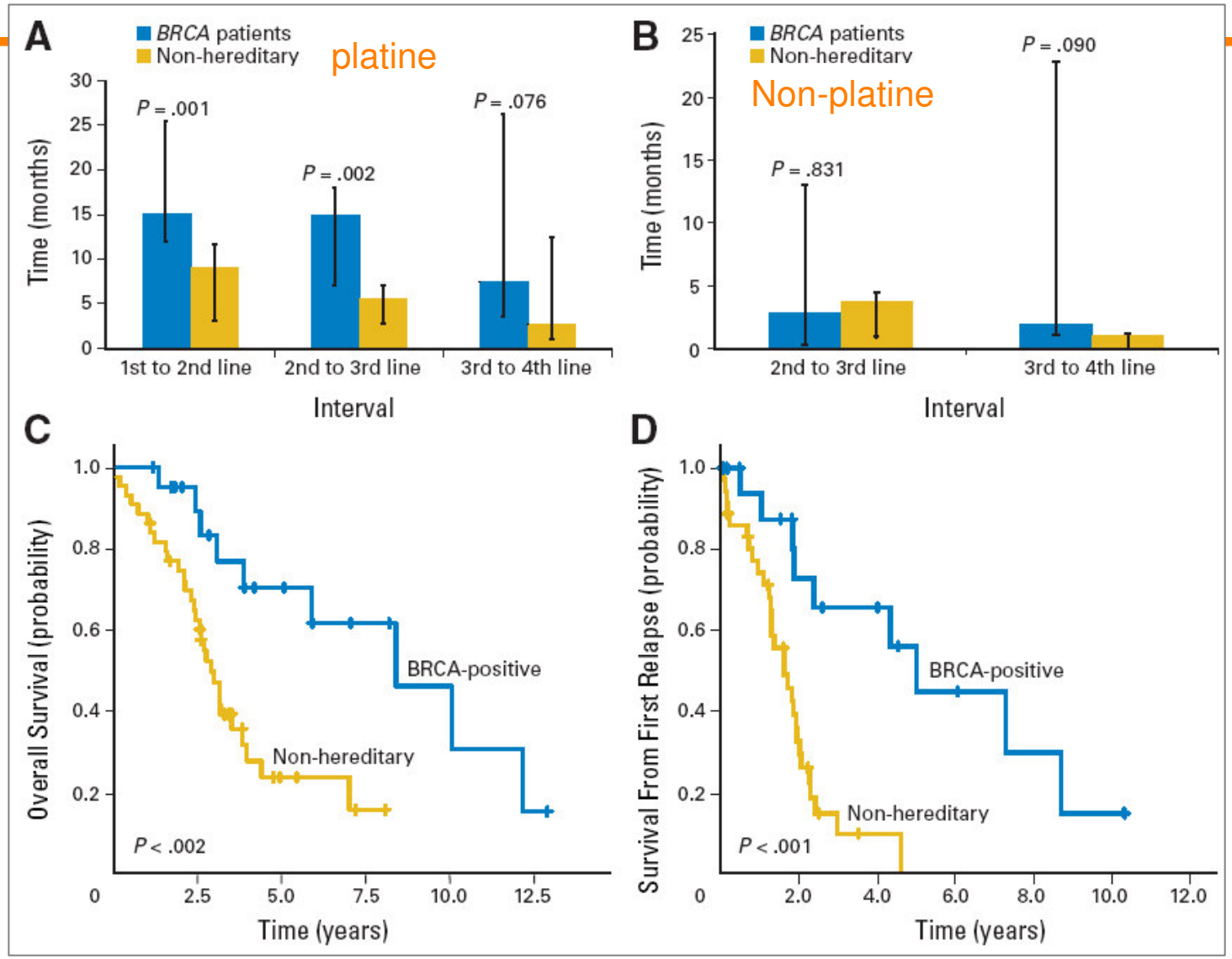
BRCAness (Tan et al, JCO, 2008)



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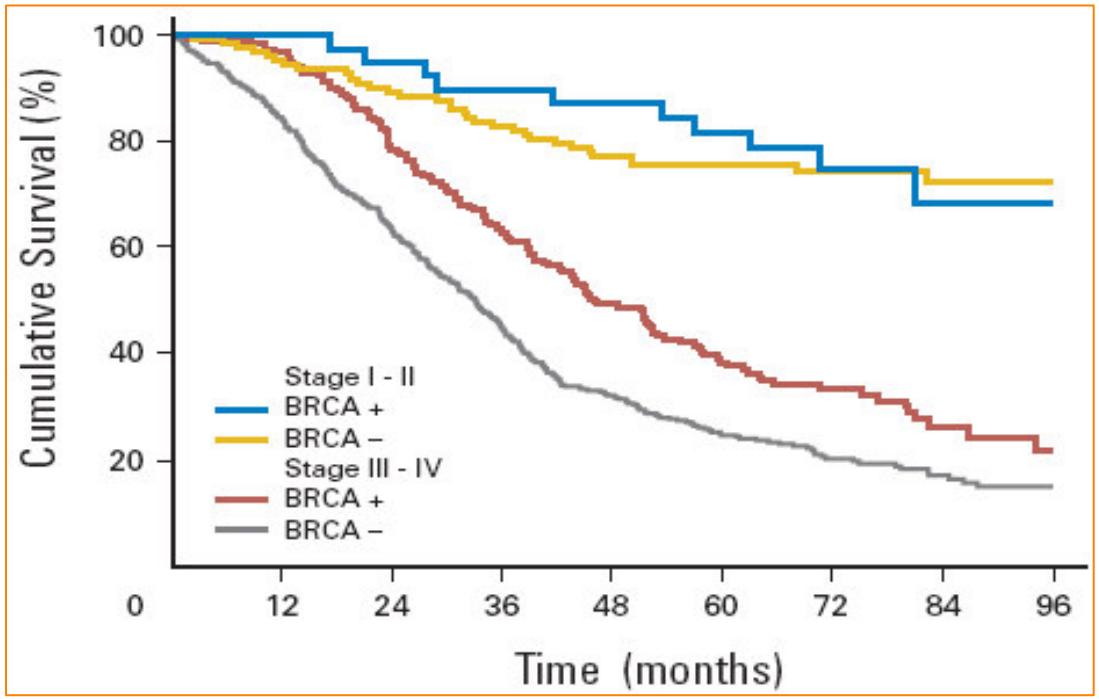
BRCAness



Chetrit, JCO, 2008

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Expression BRCA tumeurs sporadiques

Study	Year of Publication	Type of Analysis	No. of Tumors	% With Reduced Expression
Bozetti et al[66]	2004	LOH	23	35
Tong et al[67]	2000	LOH	51	53
Russell et al[73]	2000	LOH	57	44
		IHC	57	90
Wang et al[74]	2004	LOH	76	31
		IHC	76	72
Zheng et al[72]	2000	IHC	38	34
Thrall et al[69]	2006	IHC	230	65
		Hypermethylation	50	16
Wilcox et al[75]	2005	Hypermethylation	50	16
Baldwin et al[68]	2000	Hypermethylation	81	15
Esteller et al[76]	2000	Hypermethylation	31	13
		LOH	31	13
Chan et al[70]	2002	LOH	30	40
		Hypermethylation	30	50
		RNA	30	67
Hilton et al[71]	2002	Mutation, mRNA, LOH	92	82
Kato et al[77]	2004	FISH	47	53

Weberpals, JCO 2008

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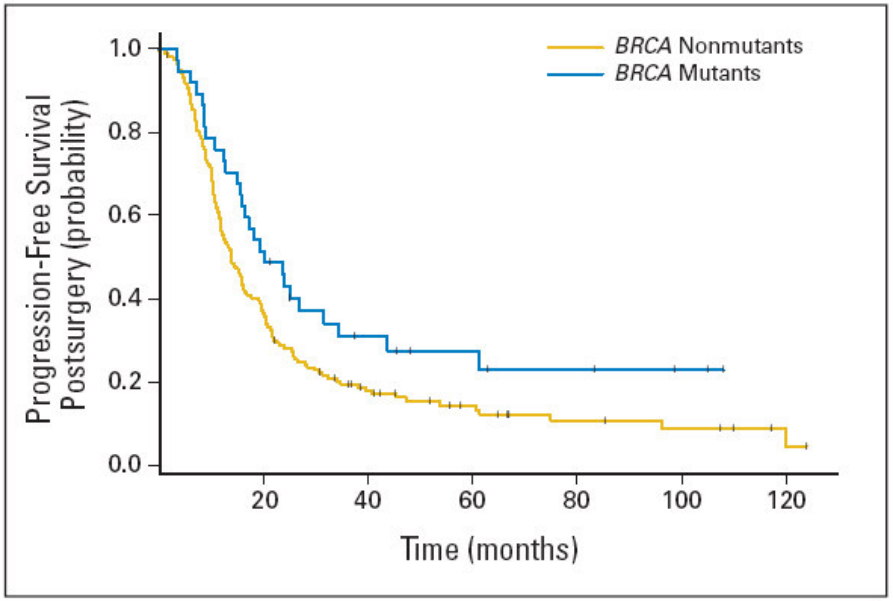
BRCAness (Hennessy, MDACC, JCO 2010)



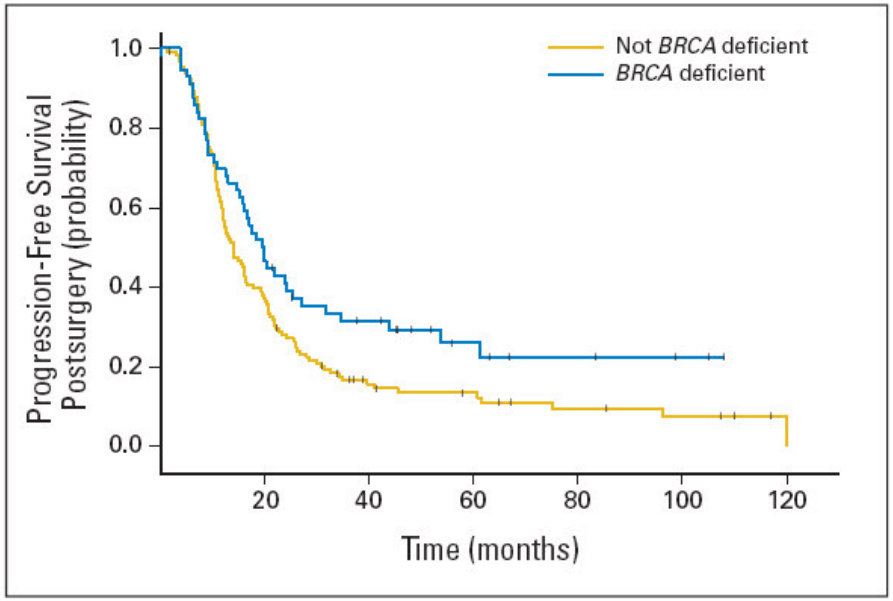


Table 3. Multivariable Cox Model of Progression-Free Survival in Women With Ovarian Cancer

Variable	*P*	Hazard Ratio	95% CI
Residual disease	.003	1.80	1.24 to 2.59
Stage	.002	2.43	1.30 to 4.54
Grade	.027	1.76	1.03 to 2.99
BRCA1/2 mutation status	.019	0.61	0.39 to 0.94

Table 4. Multivariable Cox Models of Progression-Free Survival in Women With Ovarian Cancer

Variable	*P*	Hazard Ratio	95% CI
Residual disease	.002	1.86	1.27 to 2.72
Stage	.002	2.40	1.28 to 4.48
Grade	.029	1.74	1.02 to 2.96
BRCA1/2 deficiency	.008	0.60	0.41 to 0.89

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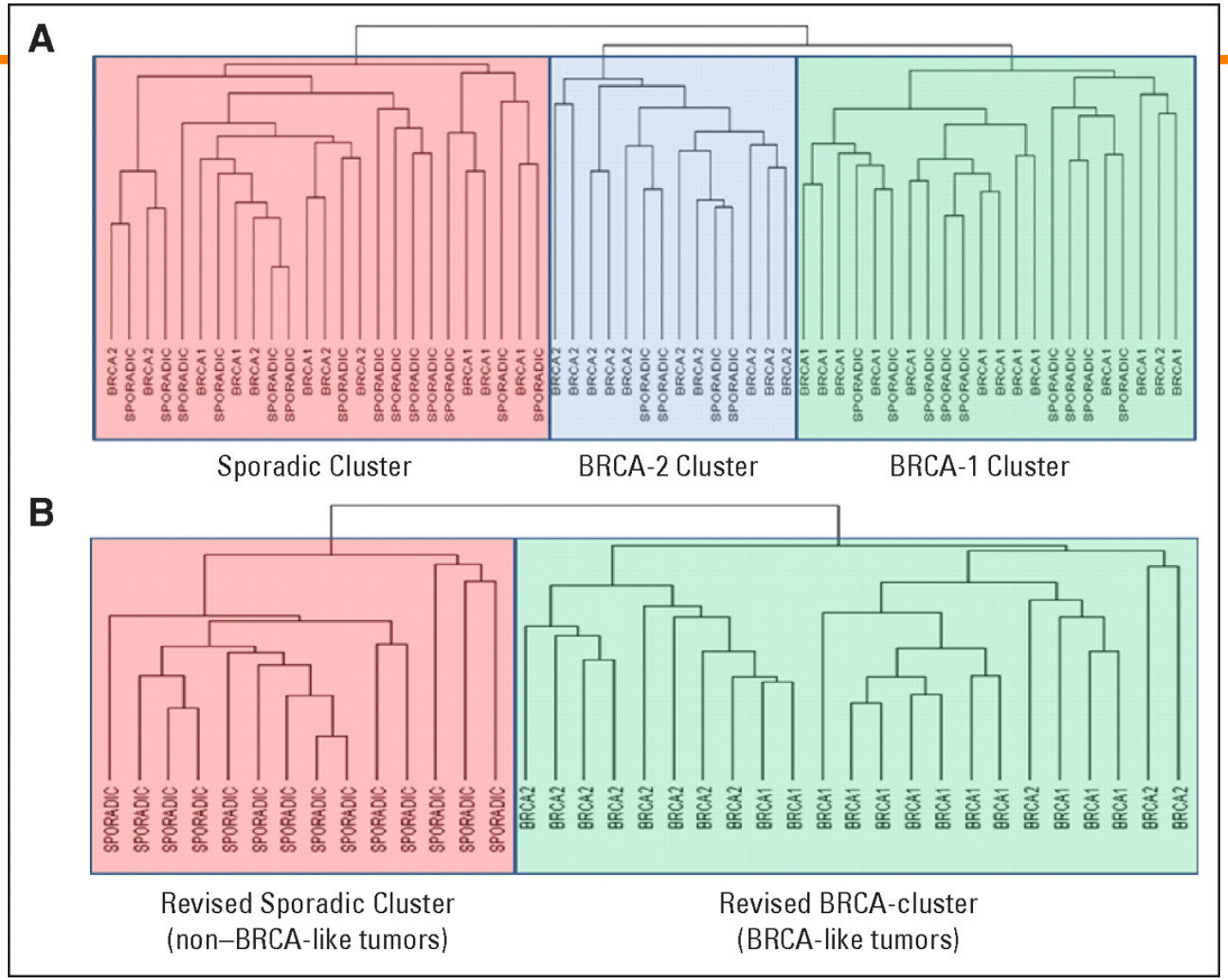
Development of the BRCAness gene expression profile.



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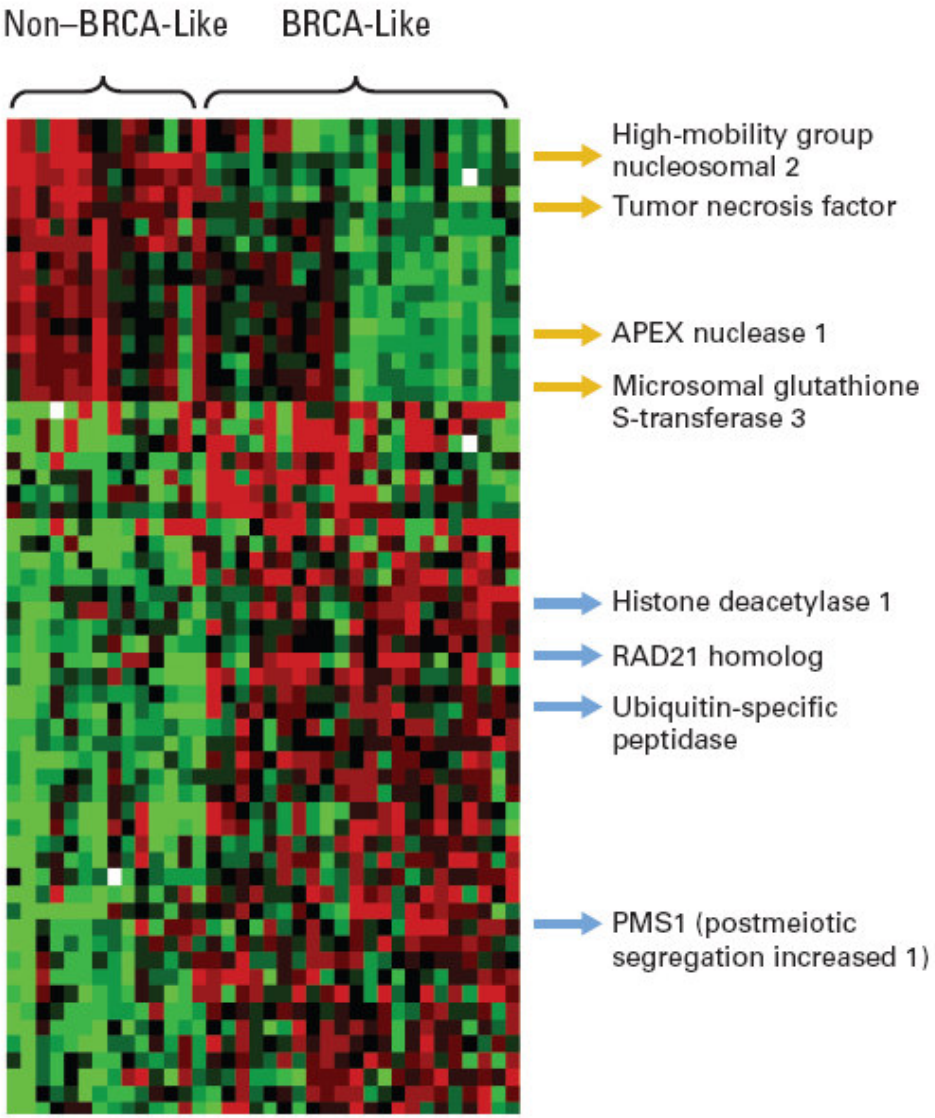
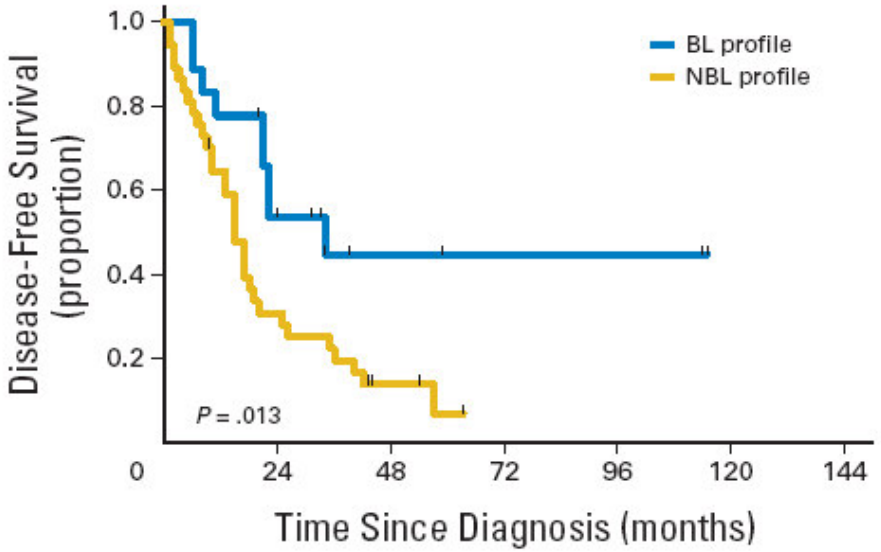
Konstantinopoulos P A et al. JCO 2010;28:3555-3561

Signature et prédiction (Konstantinopoulos, JCO 2010)





Cohorte combinée

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BRCAness

Définition Phénotypique	Définition Moléculaire
–sensibilité accrue aux sels de platine, initiale et à la rechute –intervalles libres longs –meilleure survie globale –type séreux prédominant –défaut de recombinaison homologue	–mutation germinale ou somatique de BRCA1/2 –extinction épigénétique de BRCA1/2 (5-31 %) –méthylation de FANCF (~20 %) perte de fonction d'autres gènes de la recombinaison homologue –amplification EMSY –mutation p53 –amplification de c-myc –instabilité génomique

Konstantinopoulos, JCO 2010

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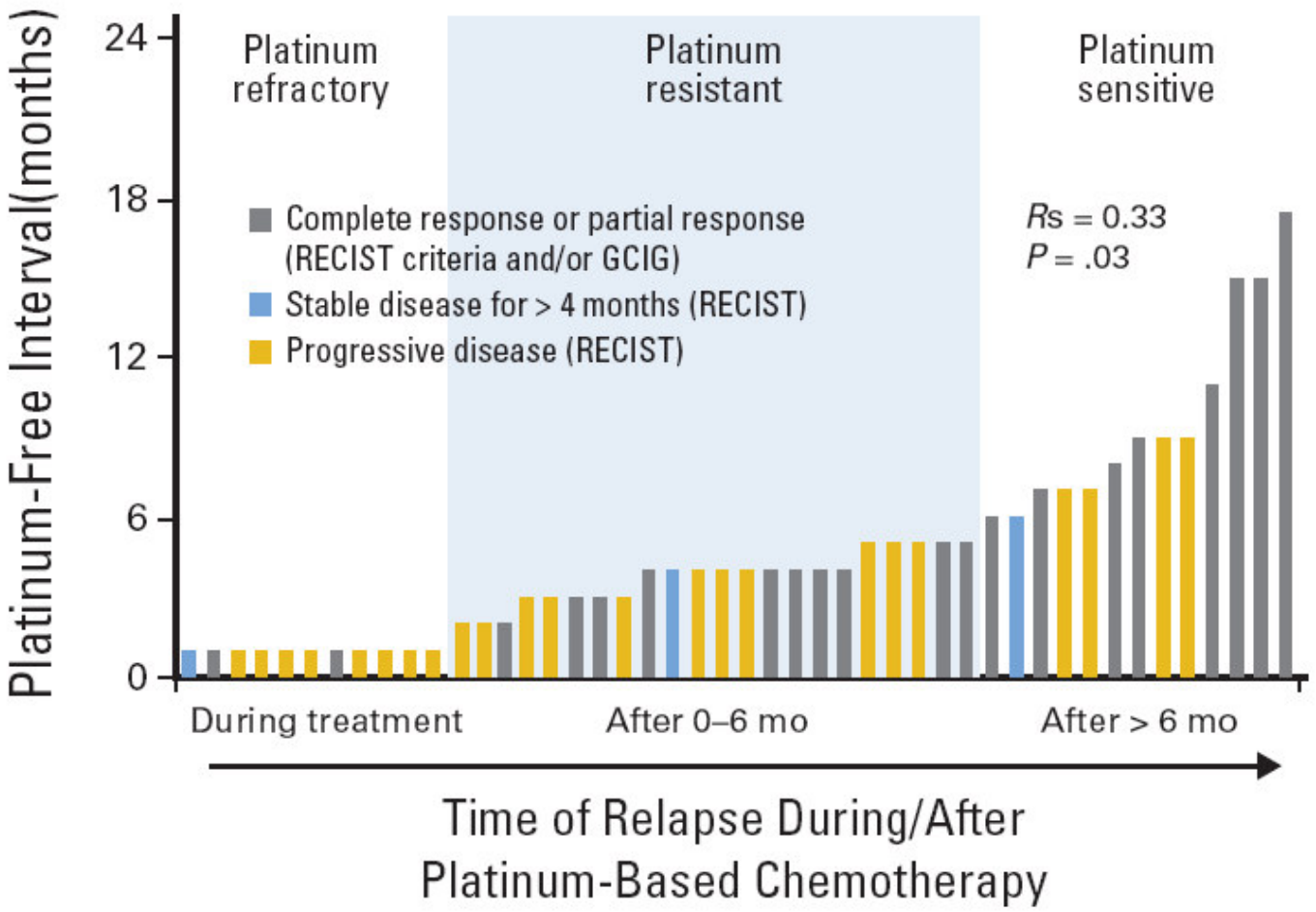
Sensibilité PARPi (Fong, JCO, 2010)



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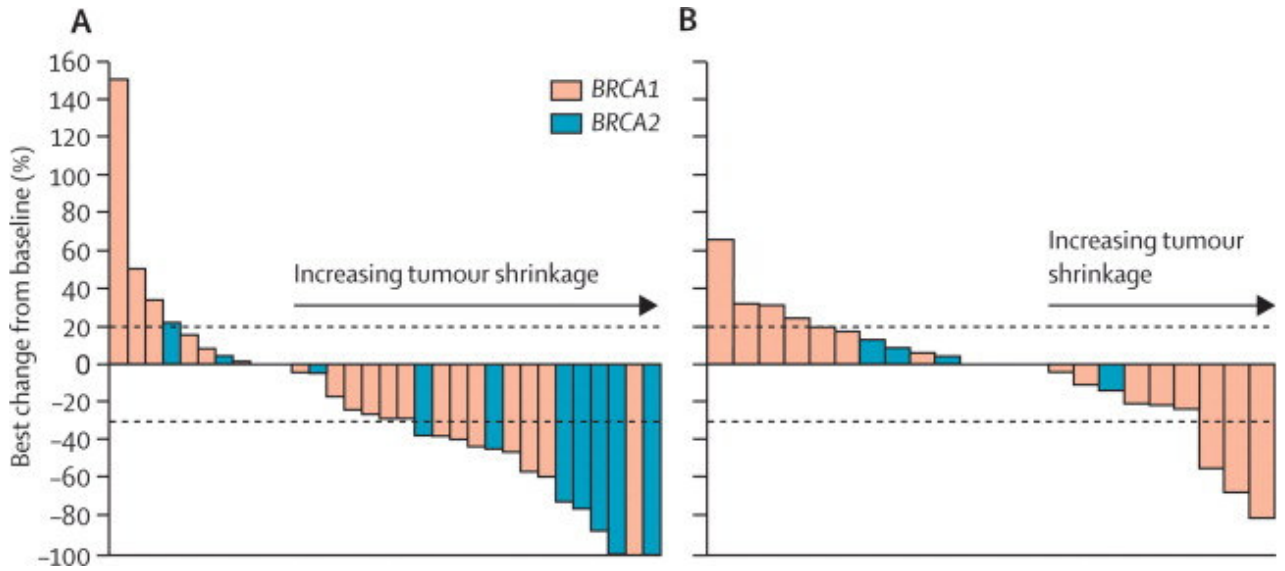
Audeh, Lancet 2010



Olaparib 400 100

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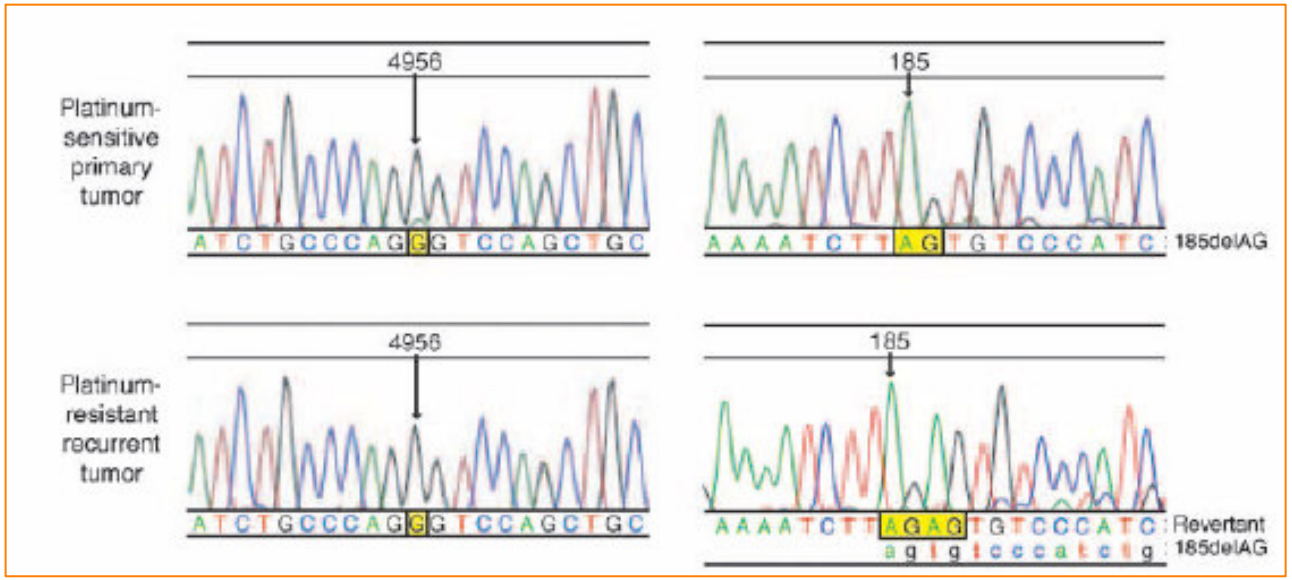
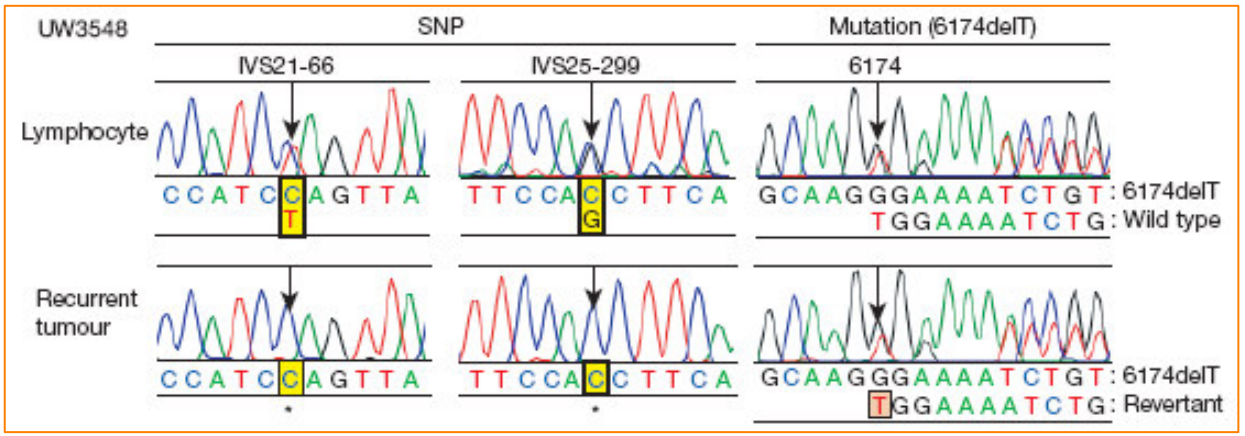
Réversion génétique de BRCA1 et 2 : résistance au platine et PARPi



Swisher
Canc Res 2008



Sakai
Nature, 2008

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Chimiothérapie intra-péritonéale

Un rationnel clinique

Primo-diagnostic : **75 %** stade FIGO III-IV

Rechute :

Plèvre	28 %
Poumon	34 %
Péritoine	**83 %**
Intestin grêle	44 %
Colon - Sigmoïde	50 %
Ganglions abdominaux	58 %
Ganglions pelviens	48 %
Os	1,2 %

Rose, Cancer 1989

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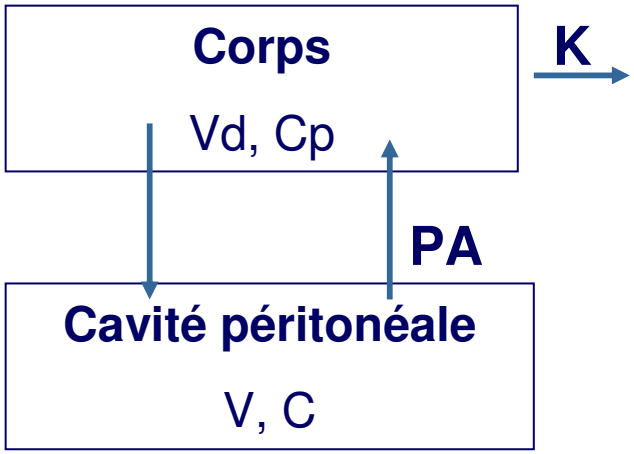
Chimiothérapie intra-péritonéale

Les bases pharmacologiques



$$\frac{K}{PA} = \frac{AUC\text{péritonéale}}{AUC\text{plasmatique}}$$

Modèle bi-compartimental de *Dedrick*

Cancer Treat Rep 1978

Drogues	Rapport des pics de concentration cavité péritonéale/plasma
Carboplatine	18
Cisplatine	**20**
Mitomycine	71
Méthotrexate	92
Melphalan	93
5-FU	298
Doxorubicine	474
Mitoxantrone	620
Paclitaxel	**1000**

Synthèse des résultats

- Bénéfice en **survie sans rechute** :

  HR : **0,79** (95% IC : 0,70 - 0,90)

- Bénéfice en **survie globale** :

  HR : **0,79** (95% IC : 0,70 - 0,89)

Jaaback K, Johnson N. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer (Cochran e Review). In: The Cochrane Library, Issue 1, 2006

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GOG 0252

	Carboplatine	**IV**	*J1*	*C1 - C6*
I	Paclitaxel	**IV**	*J1 J8 J15*	
	Bévacizumab	**IV**	*J1*	*C2 - C22*
	Carboplatine	**IP**	*J1*	*C1 - C6*
II	Paclitaxel	**IV**	*J1 J8 J15*	
	Bévacizumab	IV	*J1*	*C2 - C22*
	Cisplatine	**IP**	*J2*	
III	Paclitaxel	**IV**	*J1* **IP** *J8*	*C1 - C6*
	Bévacizumab	**IV**	*J1*	*C2 - C22*

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Conclusions

- La révision nosologique des cancers de l'ovaire est en route
- l'identification de cibles raisonnables se poursuit
- pistes principales
  - angiogenèse
  - BRCAness et PARP
  - FAR ?
  - IP et CHIP ?

- Aspects non abordés
  - Immunothérapie
  - Ciblage épidémiologique et dépistage

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