Cancer de l'ovaire
De la biologie au traitement

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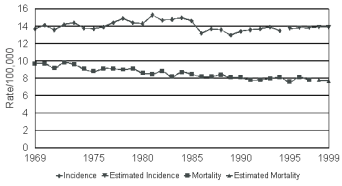
Le cancer de l'ovaire : un état stable

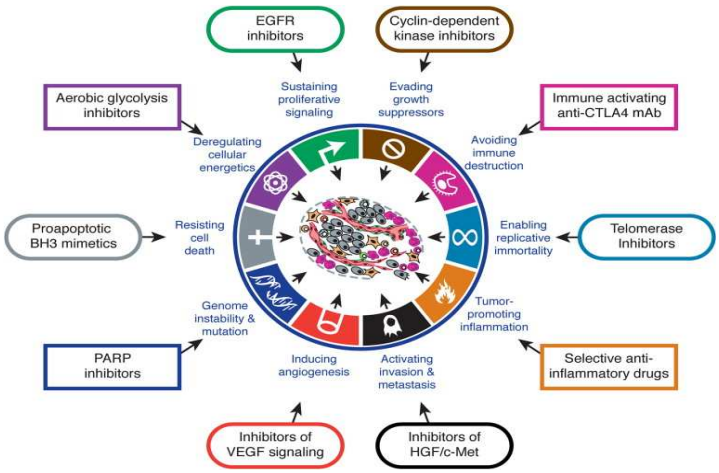
- **France 2008 : 4430 nouveaux cas**
  - **7ème cause de cancer féminin**
  - **Âge médian 65 ans**

- **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)



La révolution biologique
Hanahan et Weinberg, 2011



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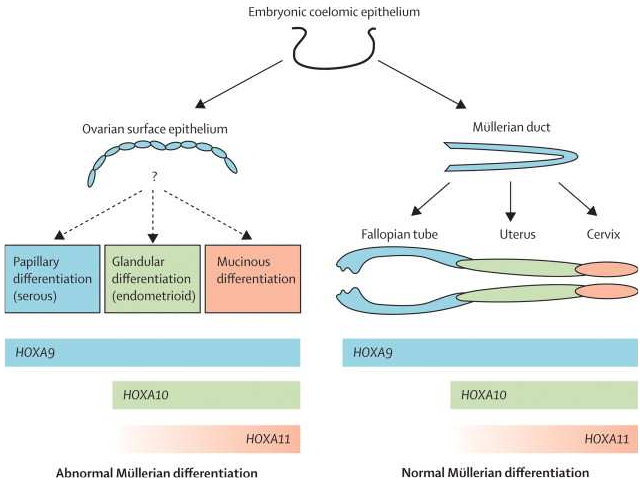
Approches biologiques



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Oncogenèse

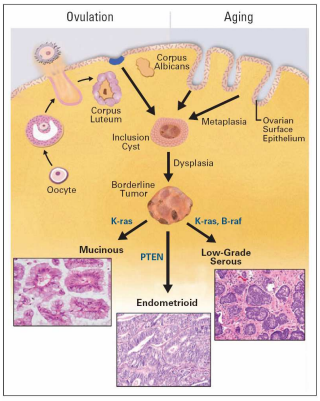

Fig 1. Transformation of ovarian surface epithelium (OSE). The OSE undergoes cyclic ovulation-induced rupture, leading to formation of cortical inclusion cysts (CICs). Entrapped within the ovarian cortex, the OSE undergoes Müllerian metaplasia, and is exposed to hormone and inflammatory stimuli that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

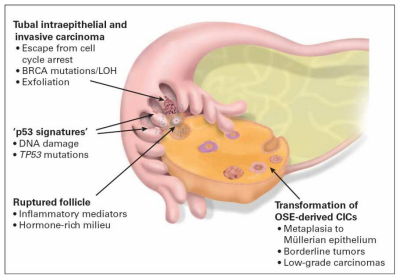

Fig 4. An integrated model of high-grade serous carcinogenesis. This model integrates the data about the stepwise development of serous carcinoma in the fimbria of the fallopian tube (FT) and in the ovarian surface epithelium (OSE) –derived cortical inclusion cysts (CICs). The hormone stimulation and 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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Révision nosologique

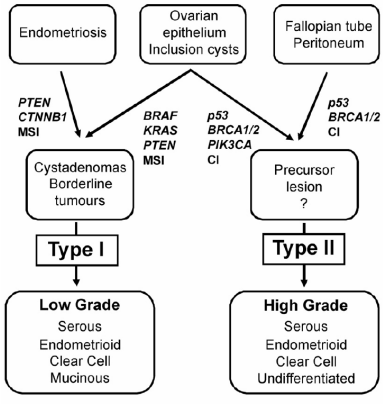

Fig. 1. Two-pathway concept of ovarian cancer development.

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* *BRAF* *PTEN* *CTNNB1* *MSI*	*p53* *BRCA1* *BRCA2* *PIK3CA* *CI*

MSI—microsatellite instability; CI—chromosome instability.

Ricciardelli, Maturitas 2009; 62: 270-275.

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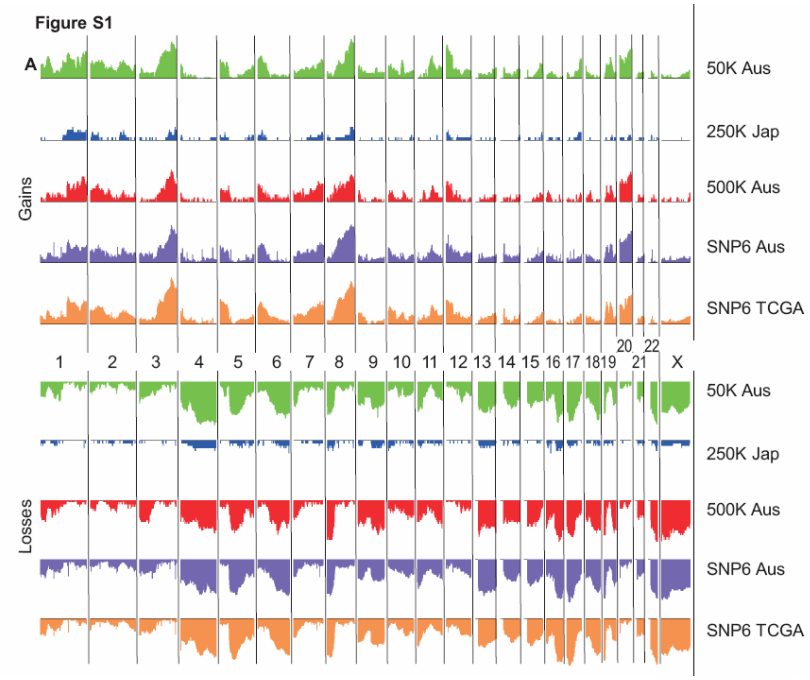
Gorringe, 2010



Integrated genomic analyses of ovarian carcinoma

Nature 2011

The Cancer Genome Atlas Research Network*

Data type	Platforms	Cases	Data access
DNA sequence of exome	Illumina GAIIx*†	236	Controlled
	ABI SOLiD‡	80	Controlled
Mutations present in exome		316	Open
DNA copy number/genotype	Agilent 244K§‖	97	Open
	Agilent 415K§	304	Open
	Agilent 1M‖	539	Open
	Illumina 1MDUO¶	535	Controlled
	Affymetrix SNP6*	514	Controlled
mRNA expression profiling	Affymetrix U133A*	516	Open
	Affymetrix Exon#	517	Controlled
	Agilent 244K**	540	Open
Integrated mRNA expression		489	Open
miRNA expression profiling	Agilent**	541	Open
CpG DNA methylation	Illumina 27K††	519	Open
Integrative analysis		489	Open
Integrative analysis with mutations		309	Open

Gene	No. of mutations	No. validated	No. unvalidated
TP53	302	294	8
BRCA1	11	10	1
CSMD3	19	19	0
NF1	13	13	0
CDK12	9	9	0
FAT3	19	18	1
GABRA6	6	6	0
BRCA2	10	10	0
RB1	6	6	0

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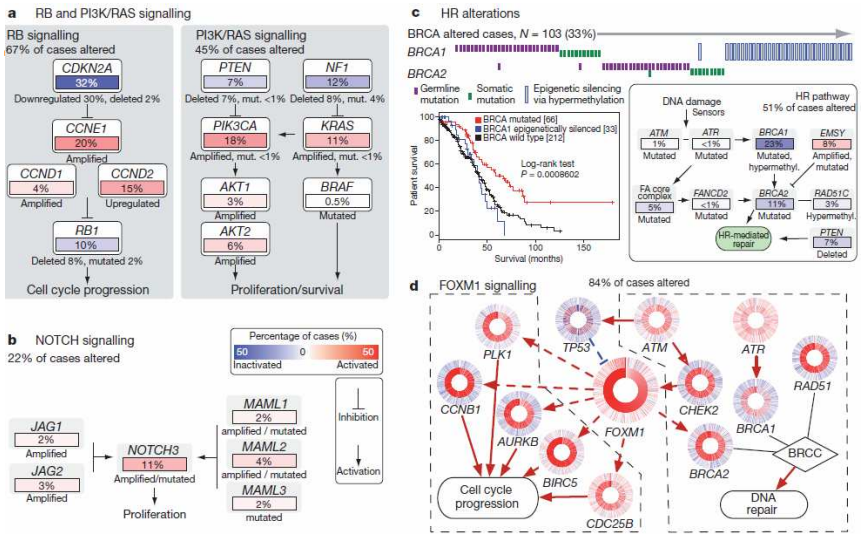

TCGA, Nature 2011

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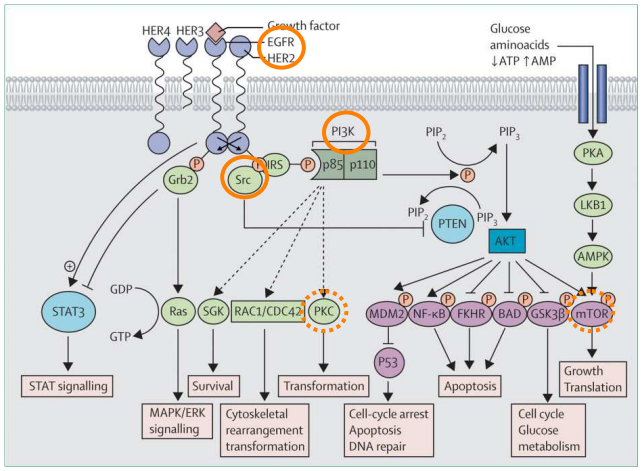
« Druggable targets »



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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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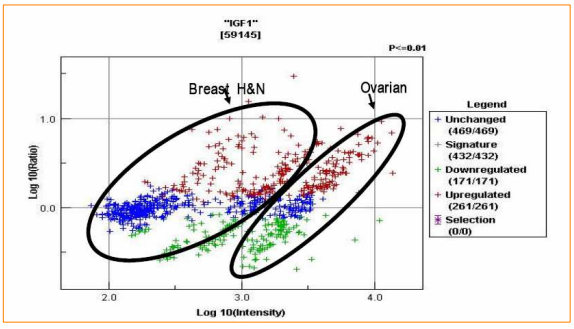
Voie IGF1

- **Etudes TRIO 14 et 15 en cours**
  - –AMG 386



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

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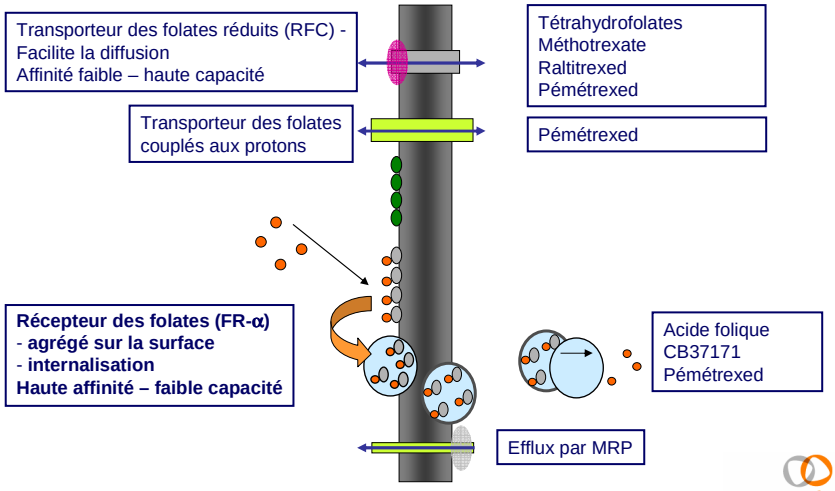
Transport membranaire des folates



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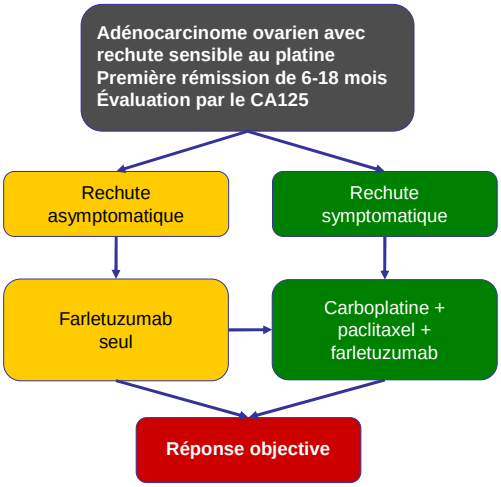
Farletuzumab : essai de phase II



- **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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BRCA

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ASCO 2011

5026 **Poster Discussion Session (Board #15), Fri, 2:00 PM-6:00 PM and 5:00 PM-6:00 PM**

Germ-line BRCA mutations in high-grade ovarian cancer: A case for routine BRCA mutation screening after a diagnosis of invasive ovarian cancer.

•Results

–134 pathogenic germline mutations were identified within the cohort, for an overall mutation frequency of **13.3%** in the Australian ovarian cancer population

–113 (84.3%) mutations were associated with serous histology. 57% of mutation carriers had no evidence of familiality

–Mutation carriers were more responsive to primary platinum treatment than non-carriers (87.4% had ≥6 months progression free survival, versus 68.4%), and were more likely to respond to platinum upon relapse (86% of mutation positive women responded to secondary platinum after relapsing ≥6 months after primary platinum treatment versus 60% of mutation negative women).

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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

47%

Weberpals, JCO 2008

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BRCAness

Gourley et al
JCO 2010

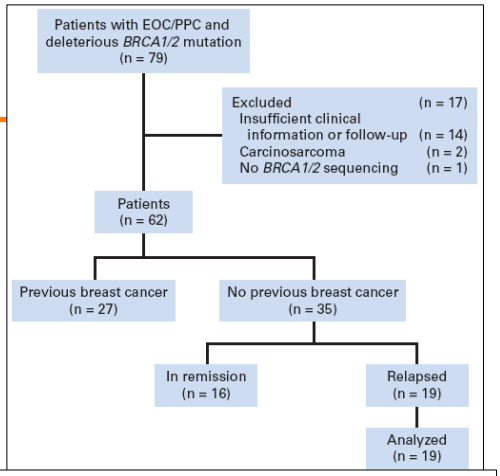

Table 5. Incidence of Visceral Metastases During Matched Follow-Up Period After First Progression in the Validation Data Set

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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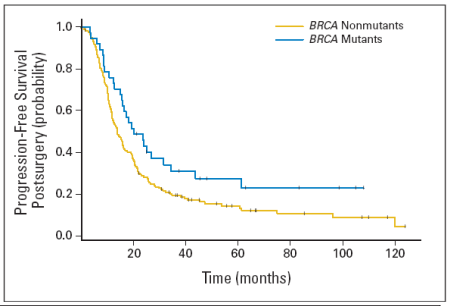
BRCAness (Hennessy, MDACC, JCO 2010)



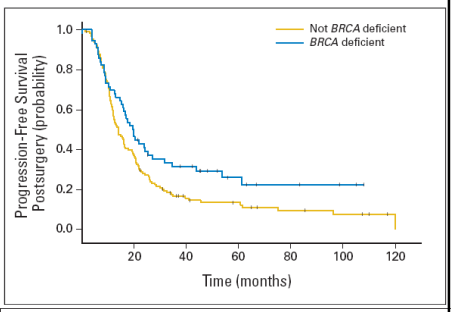


Table 3. Multivariable Cox Model of Progression-Free Survival in Women With Ovarian Cancer

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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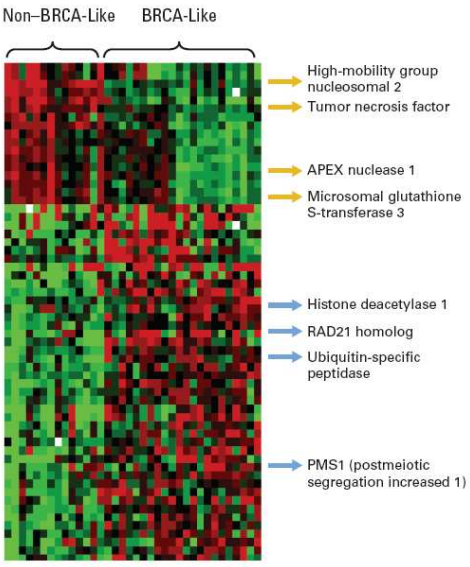
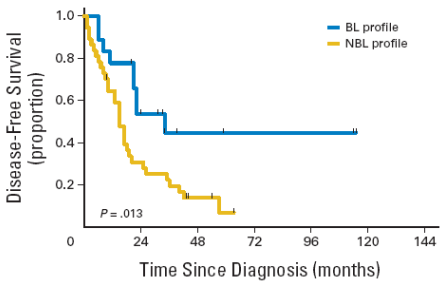
Signature et prédiction (Konstantinopoulos, JCO 2010)





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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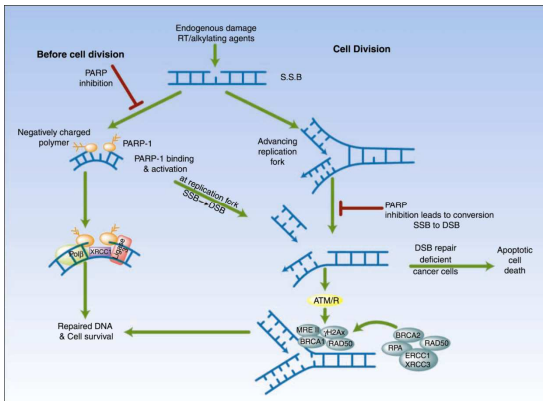
Homologous Recombination Deficient Cells More Susceptible to PARP Inhibition

- **BRCA-1, -2 are critical for DNA repair via HR**
- **Cells defective in BRCA-1, -2 are more sensitive to DNA-damaging therapy**
- **Cells defective in BRCA-1, -2 are more sensitive to PARP inhibition**
  - –PARP required for BER-directed single-stranded DNA repair
  - –Unrepaired SSBs become double-stranded breaks with DNA replication
  - –Cancer cells unable to repair double-stranded breaks die through apoptosis



Reprinted with permission from Figure 2 in Plummer ER, et al. Clin Cancer Res. 2007;13:6252-6256.

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Olaparib et cancer de l'ovaire

Auteur	BRCA muté
Fong, NEJM 2009	16/21
Fong, JCO 2010	48/50
Audeh, Lancet 2010	57/57
Gelmon, L Oncol 2011	17/63 (haut grade)
Kaye, JCO 2012	97/97

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Doses of Olaparib at Baseline in the Study Patients

Subgroup	< 100 mg Daily or BID 2 of Every 3 Wks	100 mg BID 2 of Every 3 Wks	100 mg BID Continuously	200 mg BID Continuously	400 mg BID Continuously	600 mg BID Continuously	All
All patients							
▪ Patients, N	18	4	5	20	8	5	60
▪ *BRCA-1*, n	1	1	1	7	6	1	17
▪ *BRCA-2*, n	0	0	0	5	0	0	5
▪ Wild-type *BRCA* or *BRCA* status unknown, n	17	3	4	8	2	4	38
Ovarian-cancer subgroup							
▪ Patients, N	4	2	1	7	6	1	21
▪ *BRCA-1*, n	1	1	1	5	6	1	15
▪ *BRCA-2*, n	0	0	0	1	0	0	1
▪ Wild-type *BRCA* or *BRCA* status unknown, n	3	1*	0	1	0	0	5

*Although 1 patient with ovarian cancer who was receiving olaparib at a dose of 100 mg BID every 2 of 3 wks was classified as having wild-type BRCA or unknown BRCA status, she was included in the BRCA-1 or BRCA-2 subgroup because she had a strong family history of BRCA-associated cancer but declined to undergo BRCA-mutation testing. Olaparib treatment was continued in all patients as long as they derived clinical benefit.

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Clinical Responses in Study Patients

Subgroup and Dose	Patients, N	Partial or Complete Radiologic Response	Radiologically SD	Tumor-Marker Response	Radiologic or Tumor-Marker Response	Radiologic or Tumor-Marker Response or Stable Disease
All patients, N	60	9	7	7	10	17
Patients with *BRCA1* or *BRCA2* ovarian, breast, or prostate cancer, n	19	9 (8 with ovarian cancer, 1 with breast cancer)	2 (1 with ovarian cancer, 1 with breast cancer)	7 (6 with ovarian cancer, 1 with prostate cancer)	10 (8 with ovarian cancer, 1 with breast cancer, 1 with prostate cancer)	12 (9 with ovarian cancer, 2 with breast cancer, 1 with prostate cancer)
▪ < 100 mg BID continuously, n	1	0	0	0	0	0
▪ 100 mg BID 2 of every 3 wks, n	2	1	0	1	1	1
▪ 100 mg BID continuously, n	1	0	0	0	0	0
▪ 200 mg BID continuously, n	10	4	2 (actual duration: 6 and 7 mos)	3	5	7
▪ 400 mg BID continuously, n	4	4	0	3	4	4
▪ 600 mg BID continuously	1	0	0	0	0	0

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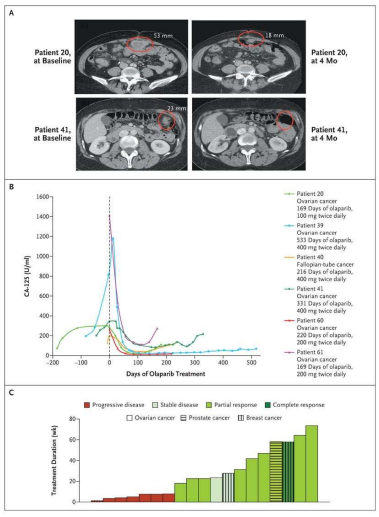
Radiologic Evidence of Tumor Response to Olaparib



Message 1:
Signal d'efficacité

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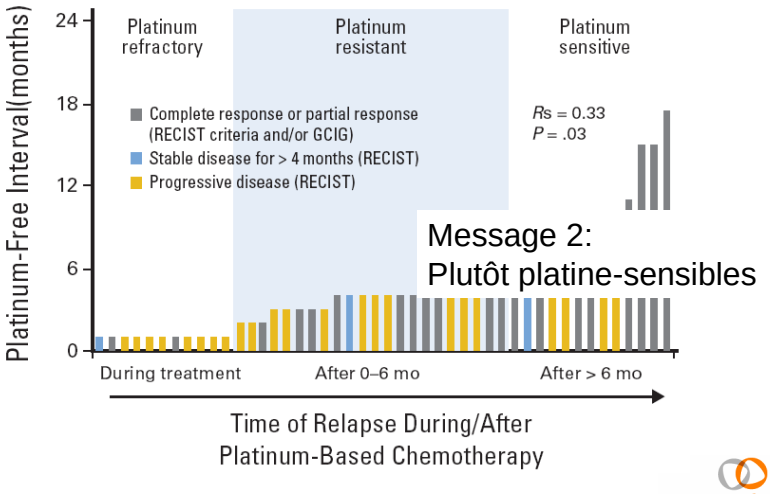
Sensibilité PARPi (Fong, JCO, 2010)



Message 2:
Plutôt platine-sensibles

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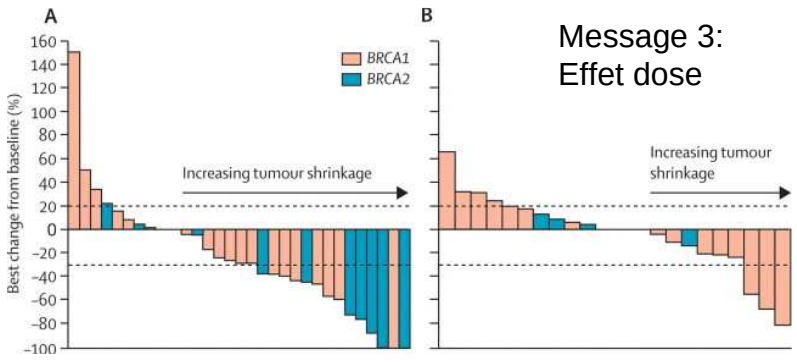
Audeh, Lancet 2010



Message 3:
Effet dose

Olaparib 400 100

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Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study

Karen A Gelmon, Marc Tischkowitz, Helen Mackay, Kenneth Swenerton, André Robidoux, Katia Tonkin, Hal Hirte, David Huntsman, Mark Clemons, Blake Gilks, Rinat Yerushalmi, Euan Macpherson, James Carmichael, Amit Oza

	Ovarian cancer					
	BRCA (n=17)				Non-*BRCA* (n=46)	Total (n=63)
	BRCA1	*BRCA2*	Both	Total		
Confirmed objective response	4 (24%)	3 (18%)	0	7 (41%)	11 (24%)	18 (29%)
Complete response	0	0	0	0	0	0
Partial response	4 (24%)	3 (18%)	0	7 (41%)	11 (24%)	18 (29%)
Stable disease ≥8 weeks	5 (29%)	1 (6%)	0	6 (35%)	18 (39%)	24 (38%)
Progressive disease	1 (6%)	1 (6%)	1 (6%)	3 (18%)	13 (28%)	16 (25%)
Not evaluable	1 (6%)	0	0	1 (6%)	4 (9%)	5 (8%)

Gelmon, L Oncol 2011

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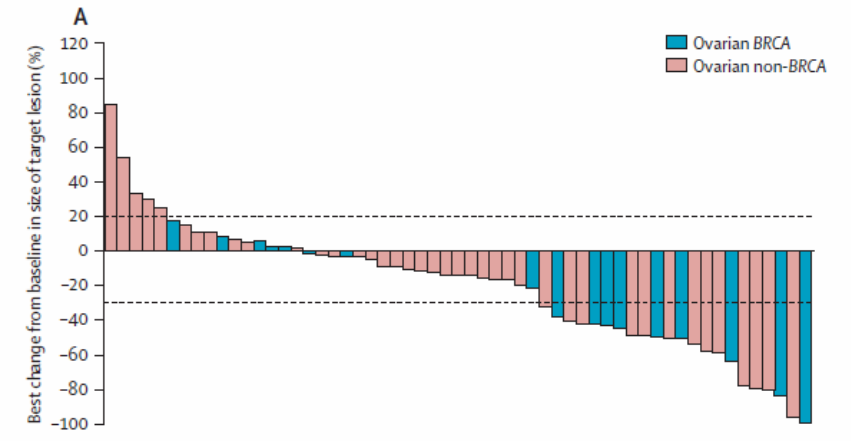

Message 4:
BRCA ! (mais pas seulement)

Gelmon, L Oncol 2011

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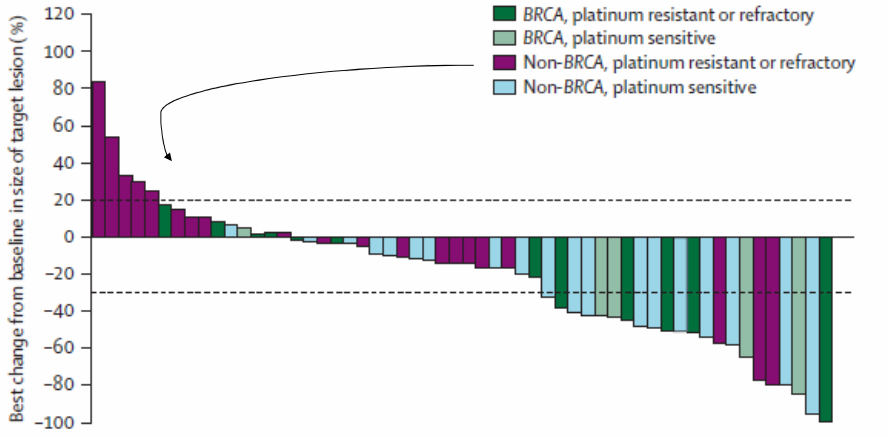

Confirmation
BRCA **ET** platine-sensible

Gelmon, L Oncol 2011

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Phase II, Open-Label, Randomized, Multicenter Study Comparing the Efficacy and Safety of Olaparib, a Poly (ADP-Ribose) Polymerase Inhibitor, and Pegylated Liposomal Doxorubicin in Patients With *BRCA1* or *BRCA2* Mutations and Recurrent Ovarian Cancer **<12 months**

Table 2. Summary of the Most Commonly Reported AEs by Grade in Each Treatment Arm

	Olaparib 200 mg Twice per Day (n = 32)				Olaparib 400 mg Twice per Day (n = 32)				PLD (n = 32)*			
	Grade 1 or 2		Grade 3 or 4		Grade 1 or 2		Grade 3 or 4		Grade 1 or 2		Grade 3 or 4	
AE	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Nausea	18	56	1	3	23	72	2	6	16	50	2	6
Fatigue	12	38	1	3	18	56	3	9	12	38	3	9
Abdominal pain	10	31	2	6	8	25	0	0	10	31	2	6
Vomiting	11	34	0	0	15	47	1	3	9	28	1	3
Constipation	7	22	2	6	5	16	0	0	12	38	0	0
Diarrhea	6	19	0	0	12	38	0	0	8	25	2	6
Asthenia	5	16	1	3	11	34	0	0	3	9	1	3
Urinary tract infection	5	16	0	0	11	34	0	0	3	9	1	3
Anemia	2	6	2	6	6	19	4	13	1	3	0	0
Rash	3	9	0	0	3	9	0	0	11	34	3	9
Palmar-plantar erythrodysesthesia syndrome	0	0	0	0	0	0	0	0	8	25	12	38
Stomatitis	0	0	0	0	0	0	0	0	17	53	2	6

Kaye, JCO 2012

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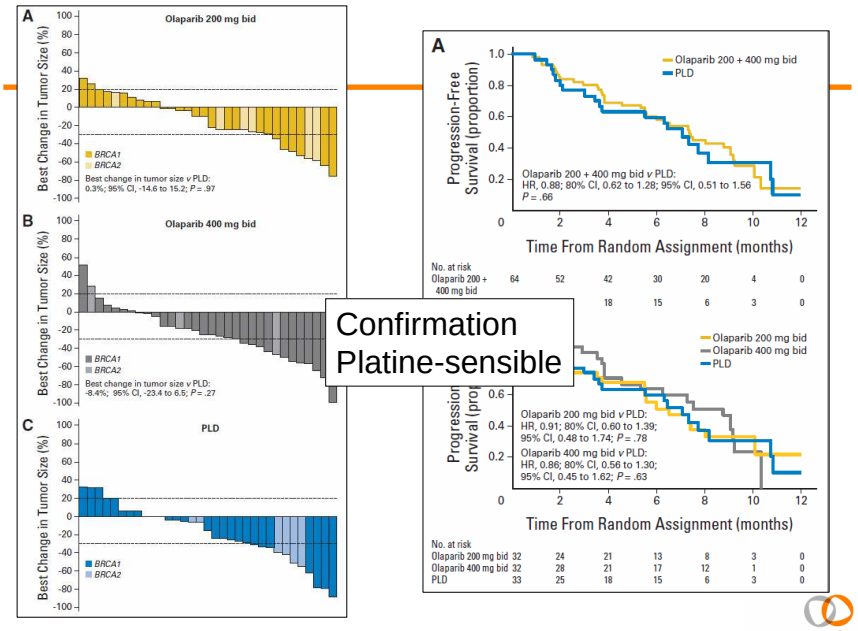

Confirmation
Platine-sensible

Kaye, JCO 2012

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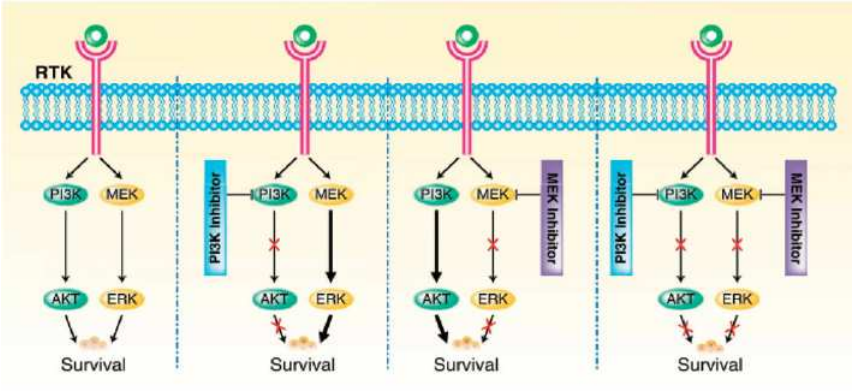
Synthetic lethality, V2



Murphy, AACR 2012
BEZ235 + olaparib !

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Autres formes

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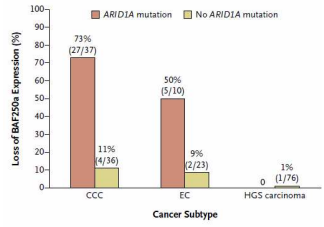
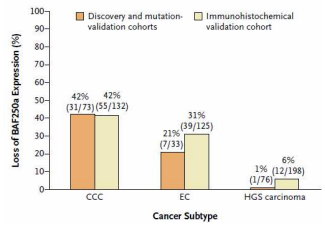
Cellules claires ARID1A





Wiegand NEJM 2010

	Number of cases (%)	
	ARID1A	*ARID1A*
Type of precursor lesion	Deficient	Intact
In the endometriosis-associated carcinomas		
In the ARID1A-deficient carcinomas		
Non-atypical endometriosis (distant; $n=10$)	0	10 (100)
Non-atypical endometriosis (adjacent; $n=14$)	12 (86)[a]	2 (14)
Atypical endometriosis (adjacent; $n=14$)	14 (100)	0
In the ARID1A-intact carcinomas		
Non-atypical endometriosis (adjacent; $n=7$)	0	7 (100)
Atypical endometriosis ($n=8$)	0	8 (100)
In the adenofibroma-associated carcinomas		
In the ARID1A-deficient carcinomas		
Benign clear-cell adenofibroma (adjacent; $n=3$)	3 (100)	0
Borderline clear-cell adenofibroma (adjacent; $n=6$)	6 (100)	0
In the ARID1A-intact carcinomas		
Benign clear-cell adenofibroma (adjacent; $n=10$)	0	7 (100)
Borderline clear-cell adenofibroma (adjacent; $n=14$)	0	7 (100)

Yamamoto Mod Pathol 2012

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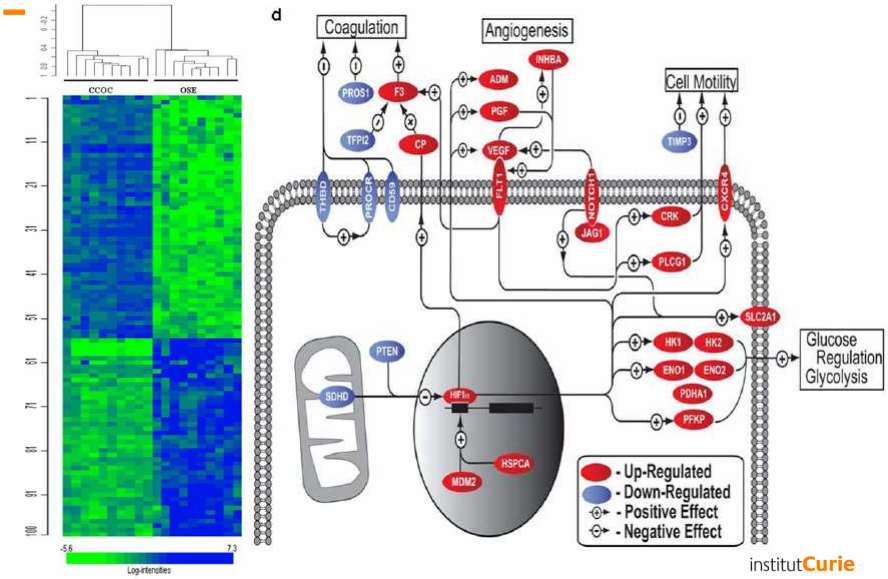
Cellules claires Stany PlosOne 2011



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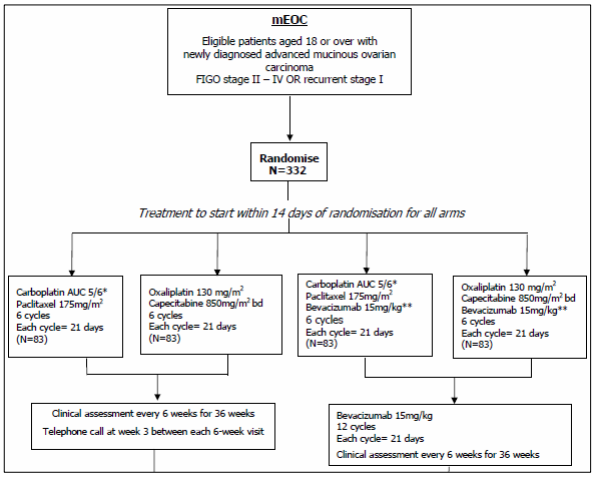
Mucineux : essai OMBELINE



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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**
  - **BRCAness et PARP**
  - **FAR ?**

- **Aspects non abordés**
  - **Immunothérapie**
  - **Ciblage épidémiologique et dépistage**

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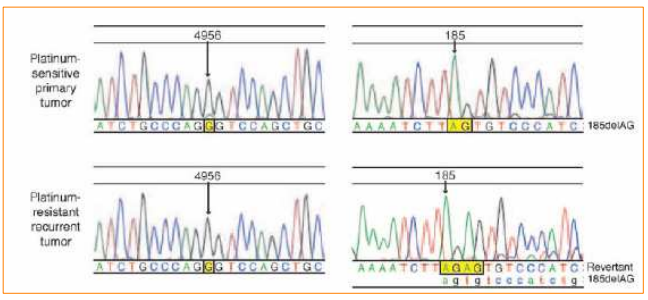
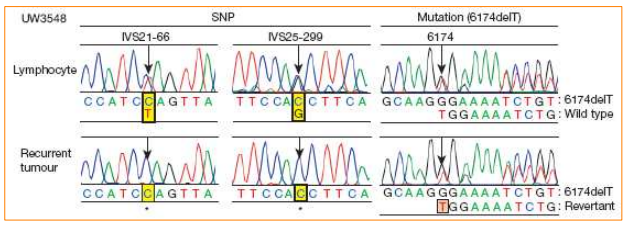
Réversion génétique de BRCA1 et 2 : résistance au platine et PARPi



Swisher
Canc Res 2008



Sakai
Nature, 2008

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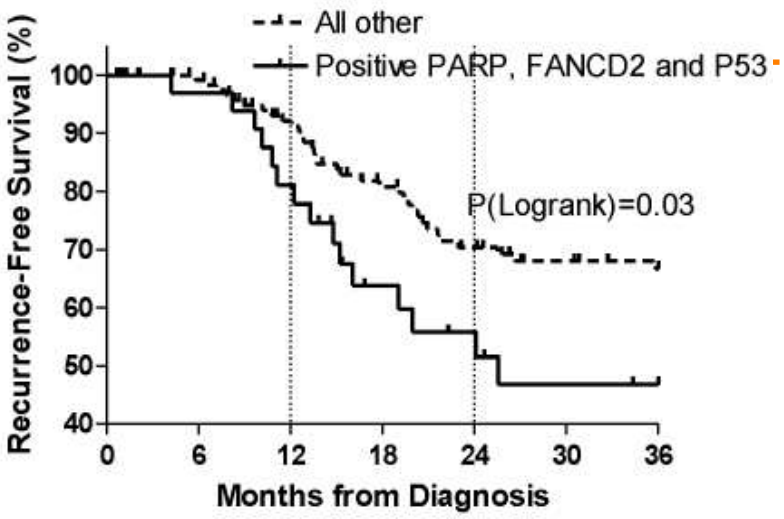

Wysham, PlosOne 2102

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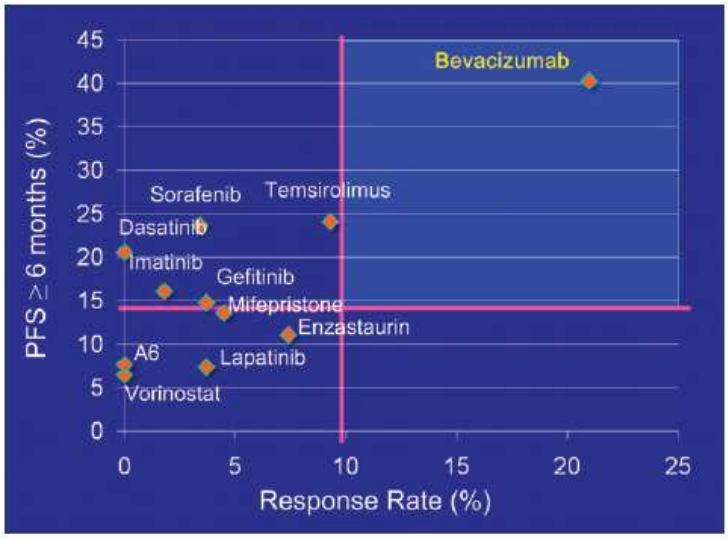

Figure 3. Impact of targeted therapy in the Gynecologic Oncology Group (GOG) 170 trials. When the fraction of responses and the fraction of patients with stable disease for 6 months are considered, treatment with bevacizumab has the best outcome (courtesy of Dr Robert Coleman).

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