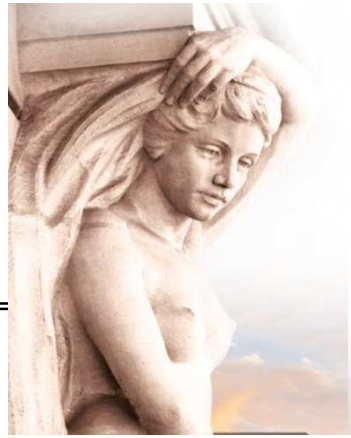


SOCIÉTÉ FRANÇAISE DE SÉNOLOGIE ET DE PATHOLOGIE MAMMAIRE

37ES JOURNÉES DE LA SOCIÉTÉ FRANÇAISE DE SÉNOLOGIE ET DE PATHOLOGIE MAMMAIRE

GUSTAVE ROUSSY
CANCER CAMPUS GRAND PARIS

Inhibiteurs de parp [et cancer du sein], où en sommes nous?

Suzette Delaloge
Institut Gustave Roussy

Conflits d'intérêts, S Delaloge, Nov 2015

	Consulting / expert	Conferences/ formations	Research grants /clinical trials	Stock options/patents
Amgen		x	x	
Astra Zeneca		x	x	
Eisei		x		
Novartis	x	x	x	
Pfizer	x	x	x	
Puma			x	
Roche	x	x	x	

Les inhibiteurs de parp en développement

Inhibiteur	Laboratoire	Cible	Etudes en cours (cancer du sein, mutation germinale BRCA1/2)
Olaparib	AstraZeneca	PARP 1/2/3	Phase III enregistrement en situation avancée (OLYMPIADE) et ligne 1/2, phase III adjuvant, phases II neoadjuvant et métastatique, etc
Veliparib	Abbott	PARP 1/2	Phase III enregistrement ligne1/2, Phase III en situation néo-adjuvante dans les cancers triple négatifs, autres phase II
Rucaparib	Clovis	PARP 1/2	Divers essais de phase II dont adjuvant TNBC + études dans des situations de « BRCAness » sans mutation BRCA1/2
Talazoparib	Biomarin	PARP 1/2	Phase III en situation avancée (EMBRACA), phases II en situation avancée et néo-adjuvante
CEP9722	Teva	PARP 1/2	Phases I/II
Niraparib	Merck	PARP 1/2	Phase III en situation avancée (BRAVO)

Plan

- Mécanismes/léthalité synthétique
- Données cliniques
- Résistances, synergies, perspectives

Plan

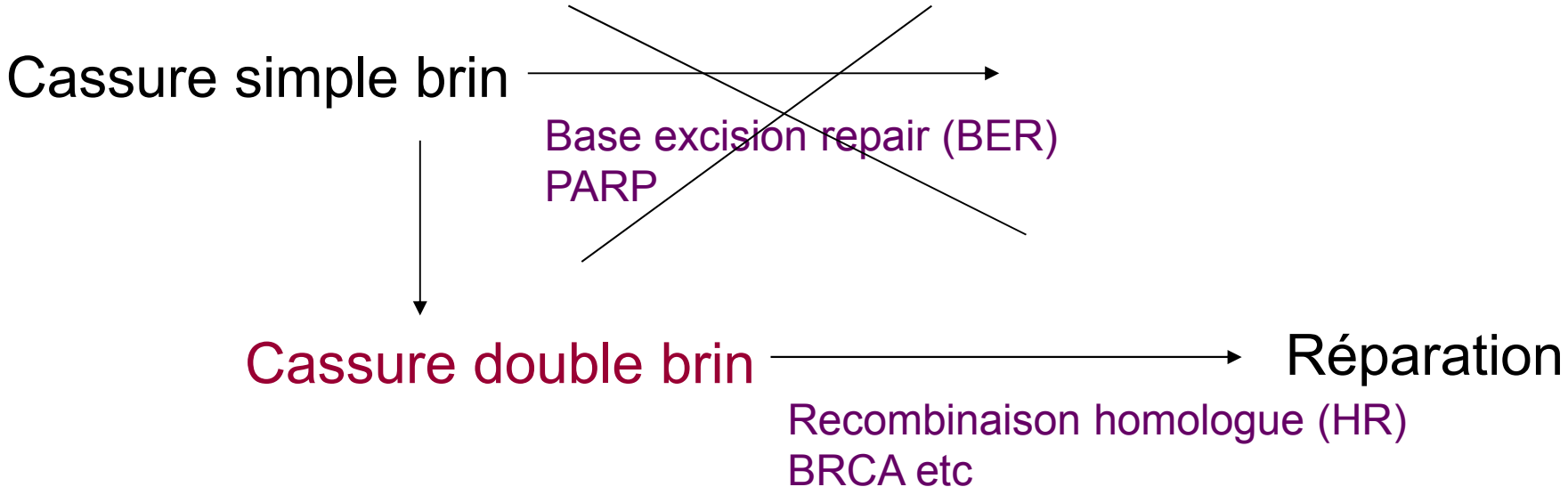
- Mécanismes/léthalité synthétique
- Données cliniques
- Résistances, synergies, perspectives

Réparation, parp et BRCA?

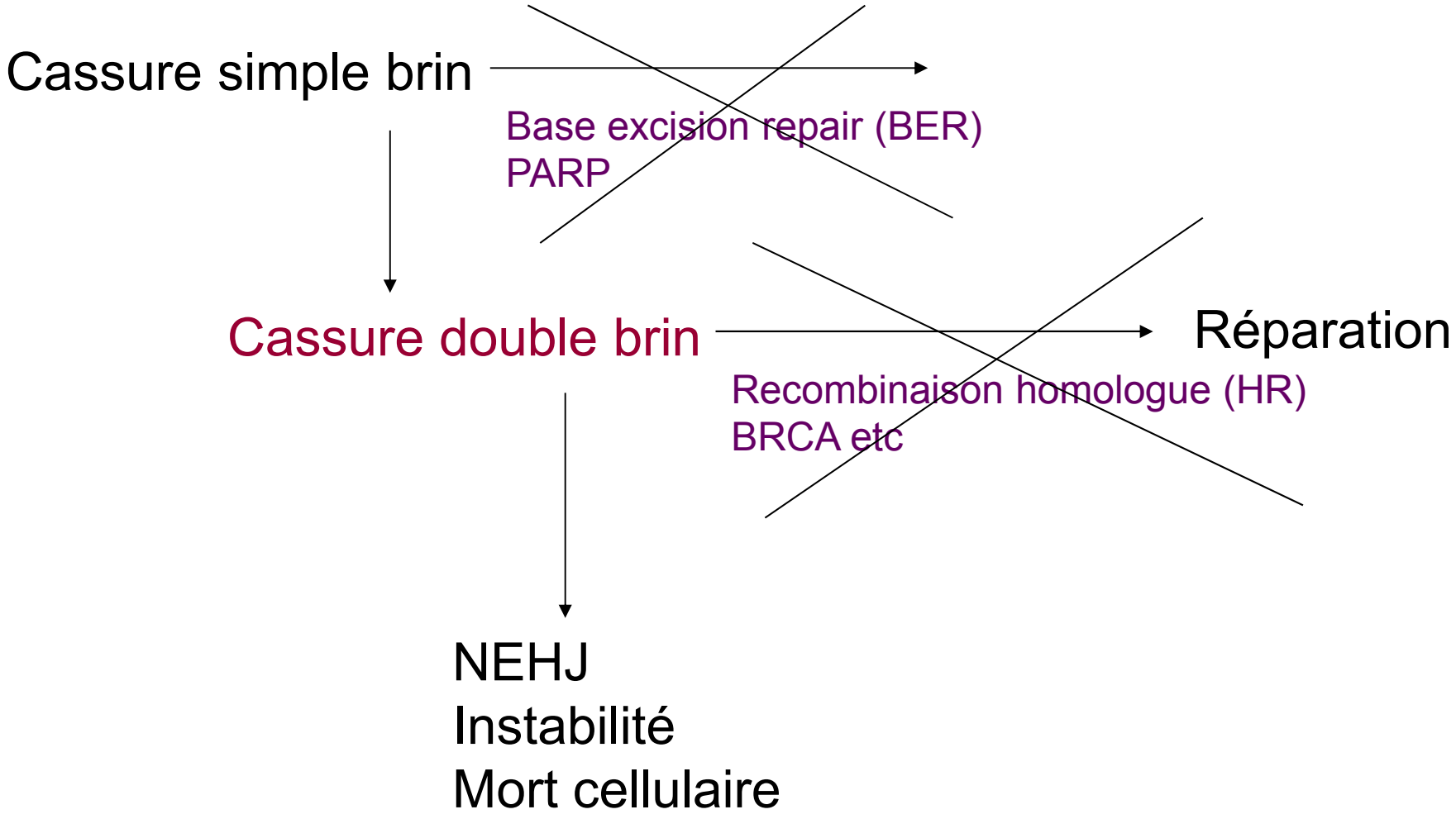
Cassure simple brin → Réparation

Base excision repair (BER)
PARP

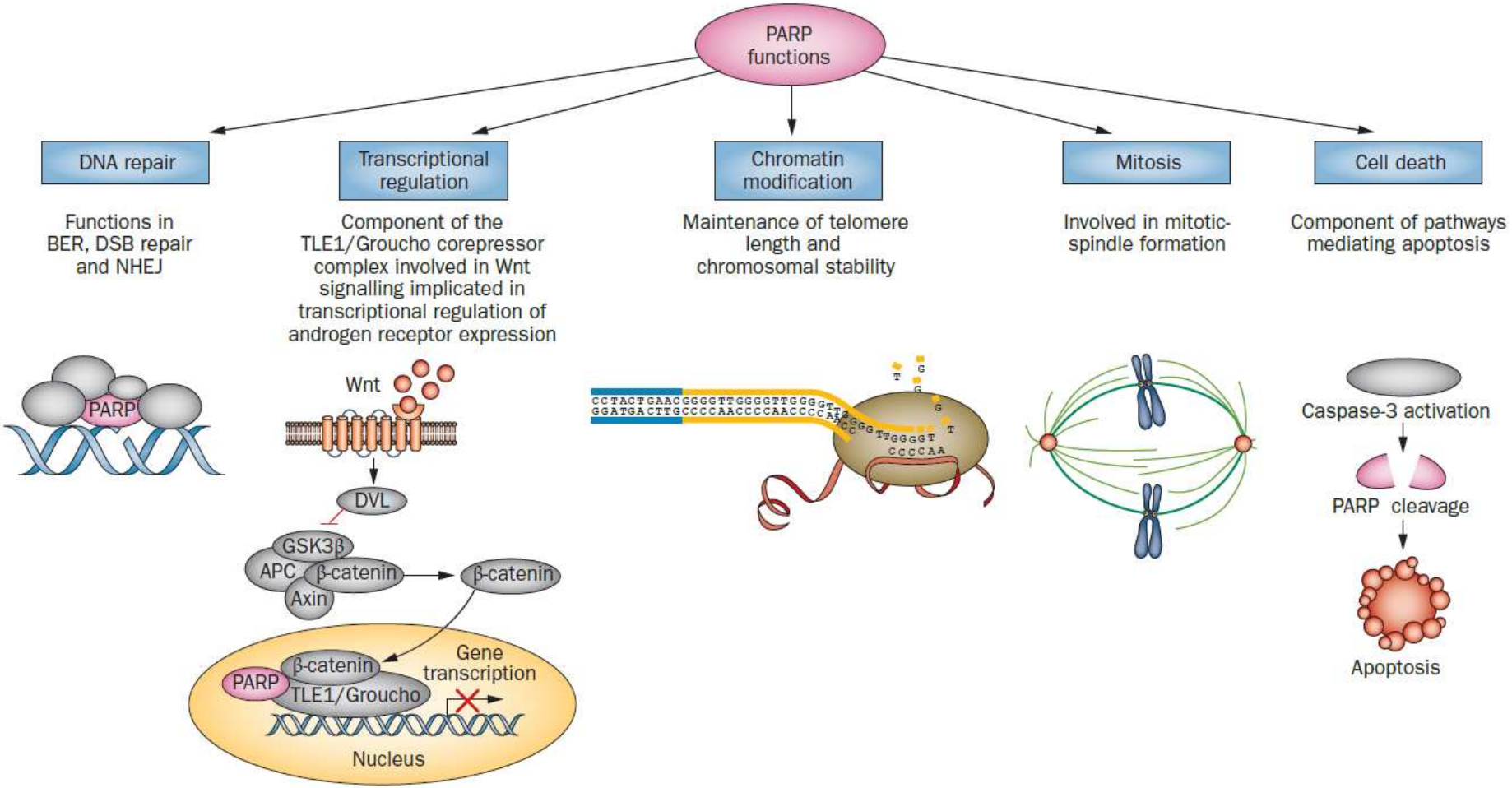
Réparation, parp et BRCA?



Réparation, parp et BRCA?

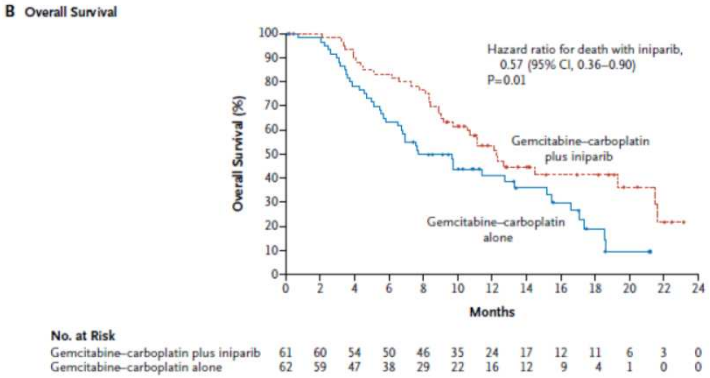


Les fonctions des PARP

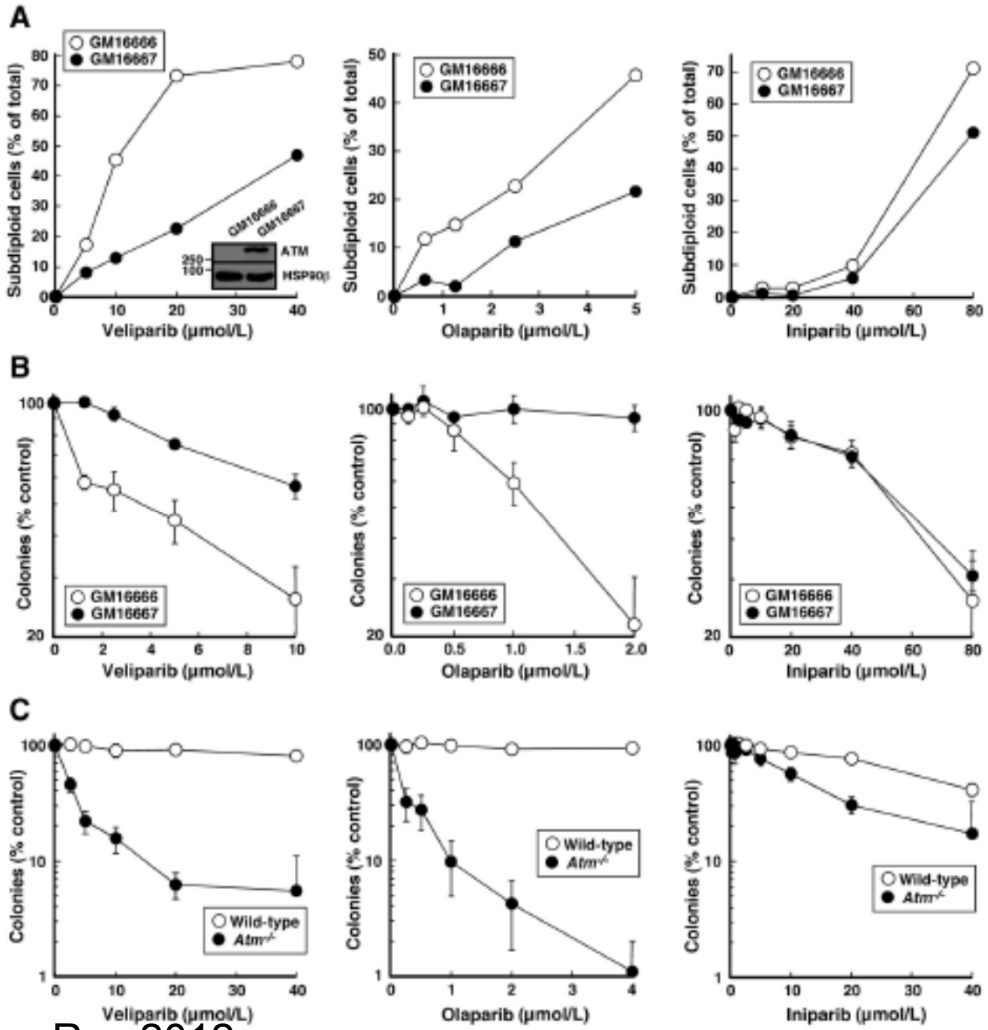


Sonnenblick et al, Nat Rev Clin Oncol 2015

Iniparib: pas un inhibiteur de parp



O'Shaugnessy et al NEJM 2011



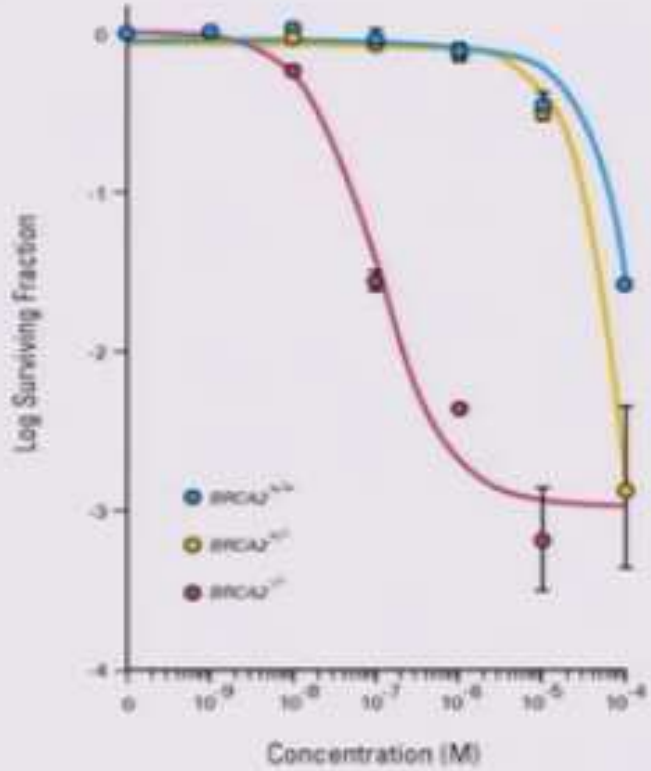
Phase II prometteuse
(cancers triple négatifs)

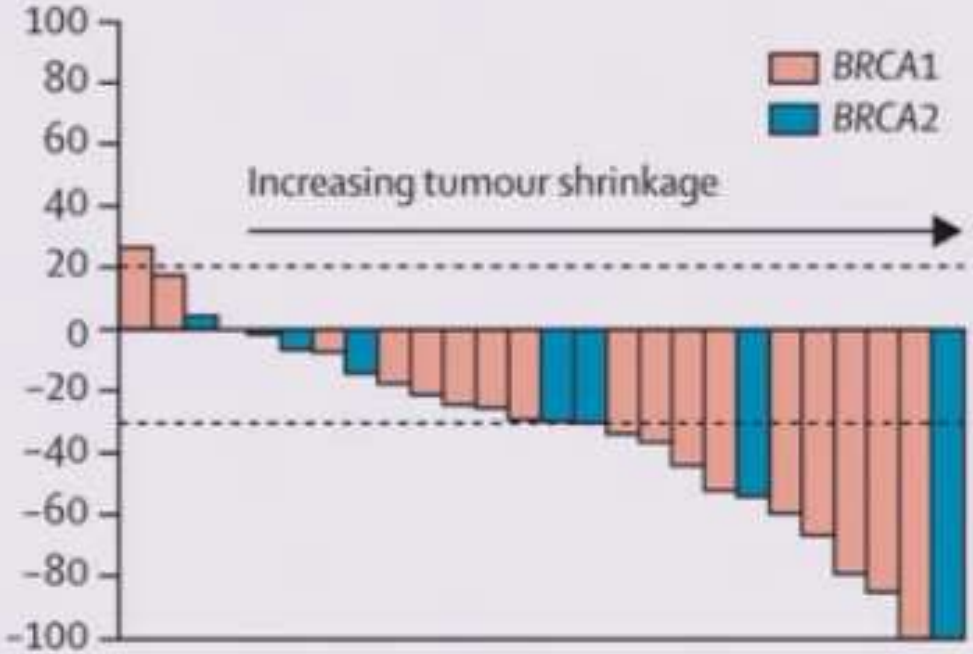
↓

Echec en phase III

O'Shaughnessy 2010-2011, Patel Clin Cancer Res 2012

Fin 2000: les cancers BRCA-/- sont extrêmement sensibles aux Inh parp





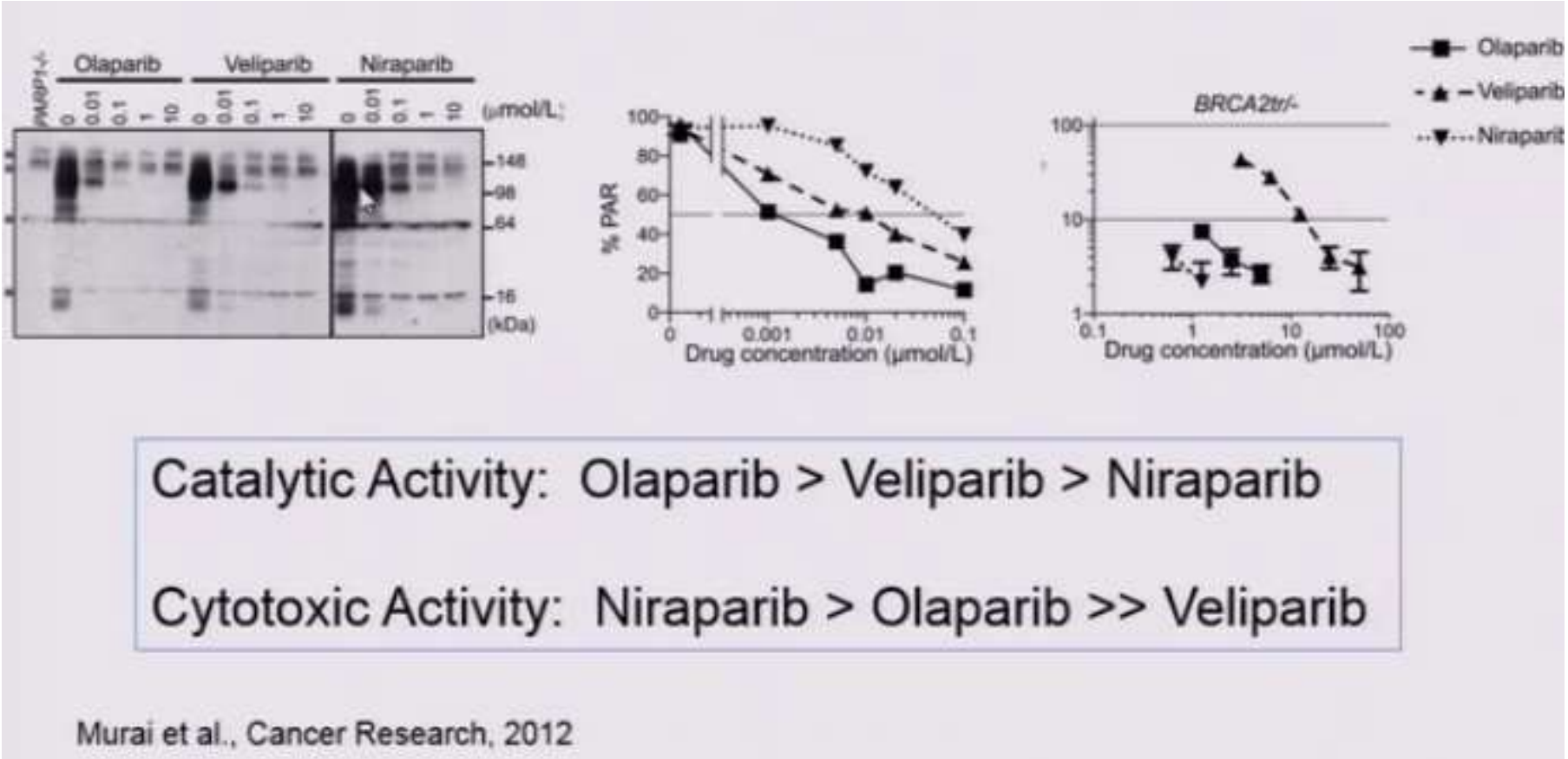
Ashworth, J Clin Oncol 2008;26:3785-3790

Tutt et al., Lancet 2010; 376: 235-244

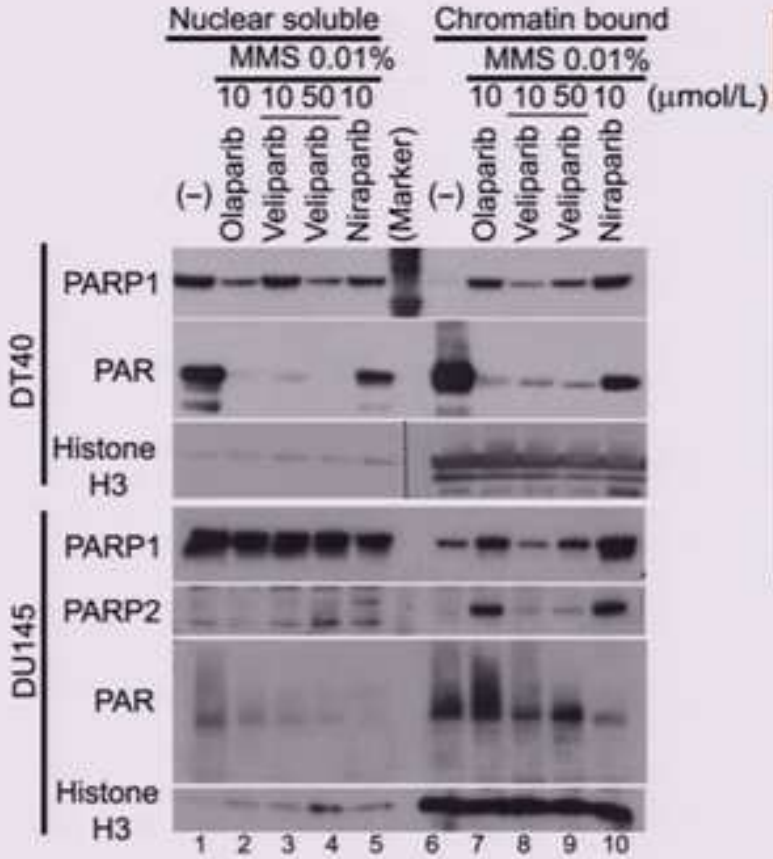
Murai et al., Cancer Research, 2012

Shapiro SABCS 2013

Activité catalytique versus trapping des inh parp



Trapping



Niraparib > Olaparib >> Veliparib

Phase 0 Trial : 25 mg veliparib inhibited catalytic activity in tumor biopsies
Phase 1 Trial in patients with BRCA-deficient tumors:
no RECIST responses until a dose of 300 mg BID

Murai et al., Cancer Research, 2012

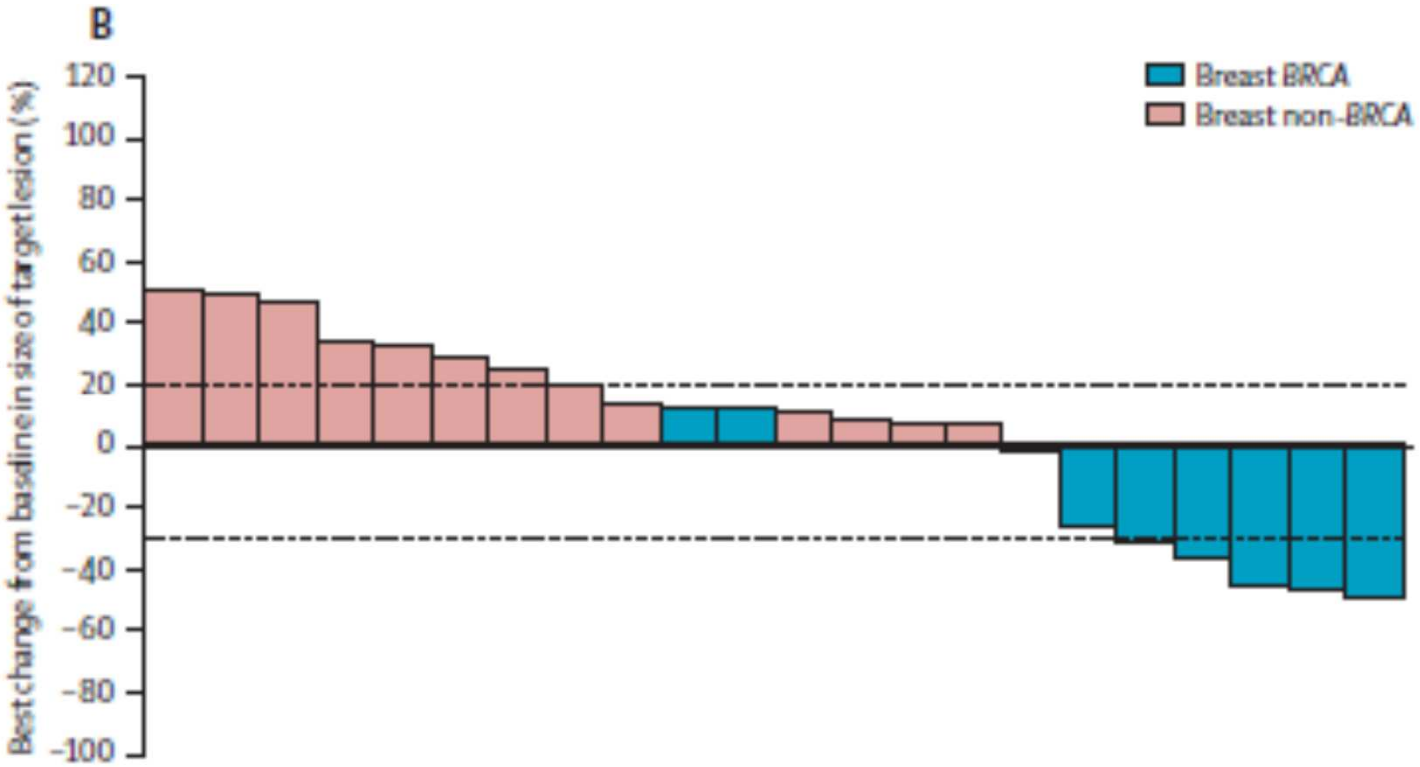
Plan

- Mécanismes/léthalité synthétique
- Données cliniques
- Résistances, synergies, perspectives

Les inh de parp ne sont pas un traitement des cancers triple négatifs

Olaparib

… dans leur globalité

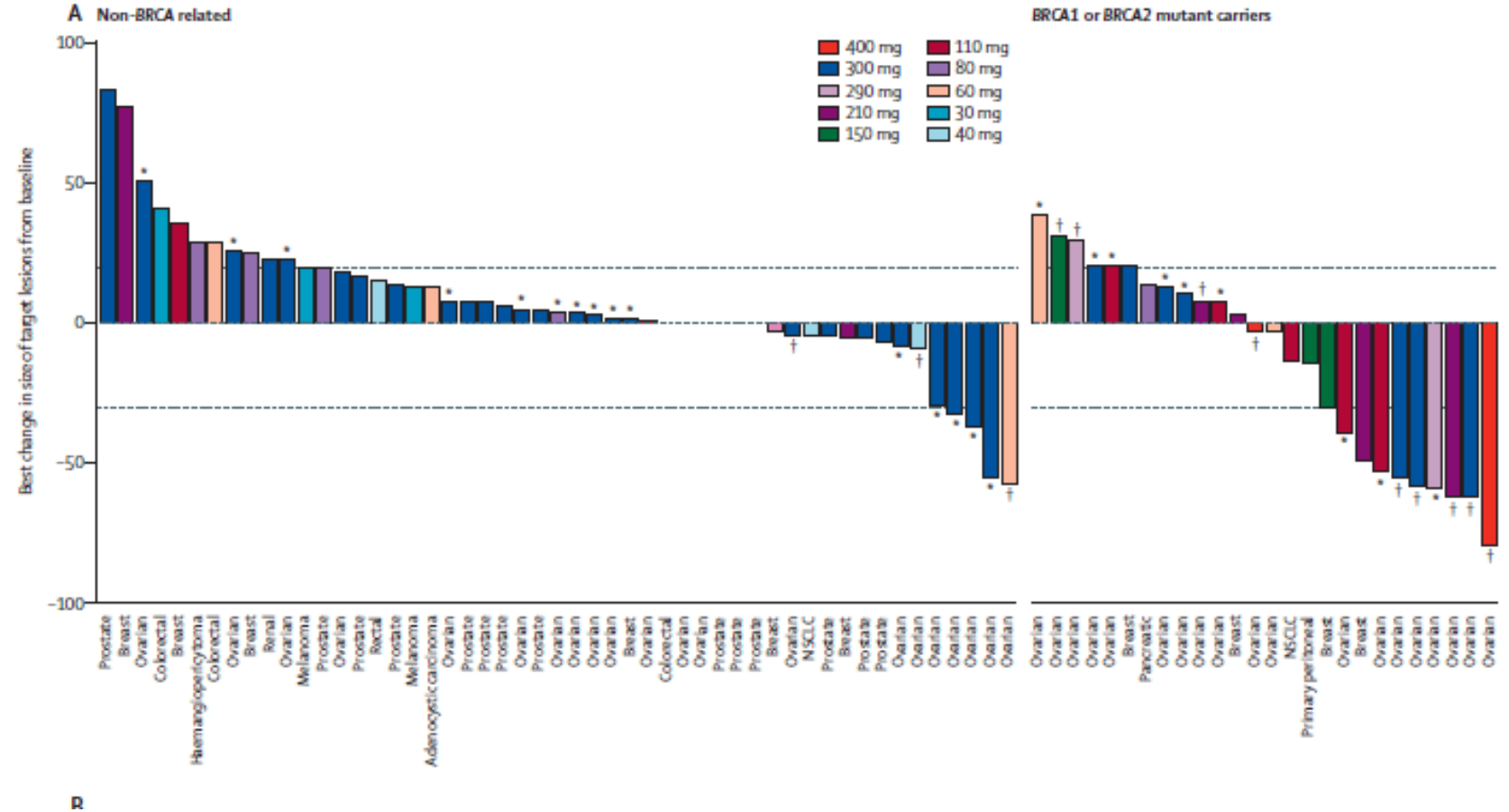


Gelmon, Lancet Oncol 2011

Les inh de parp ne sont pas un traitement des cancers triple négatifs

Niraparib

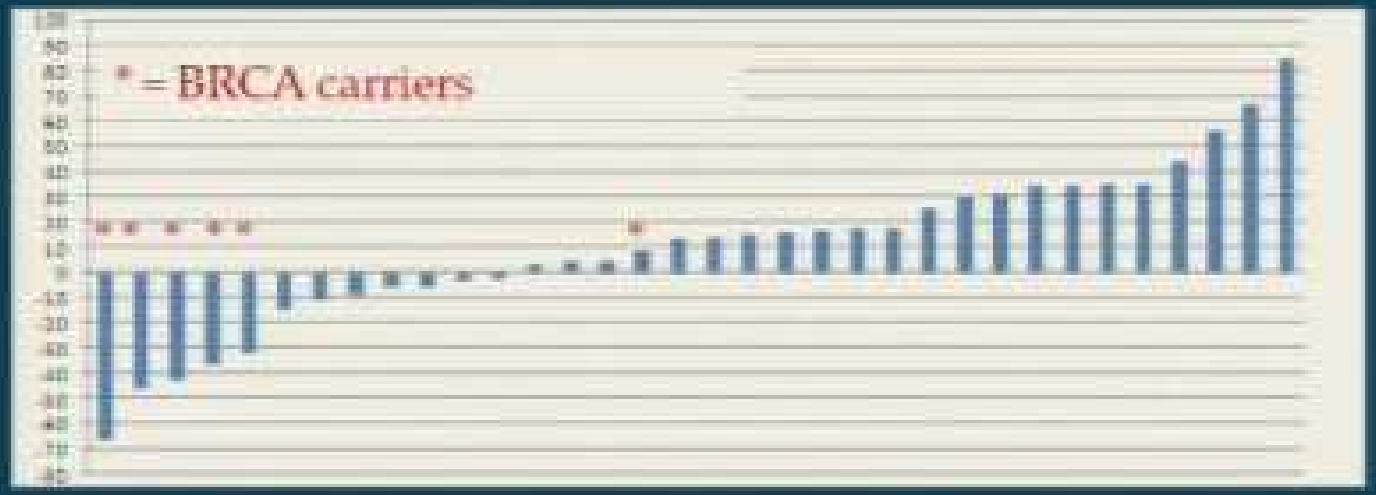
… dans leur globalité



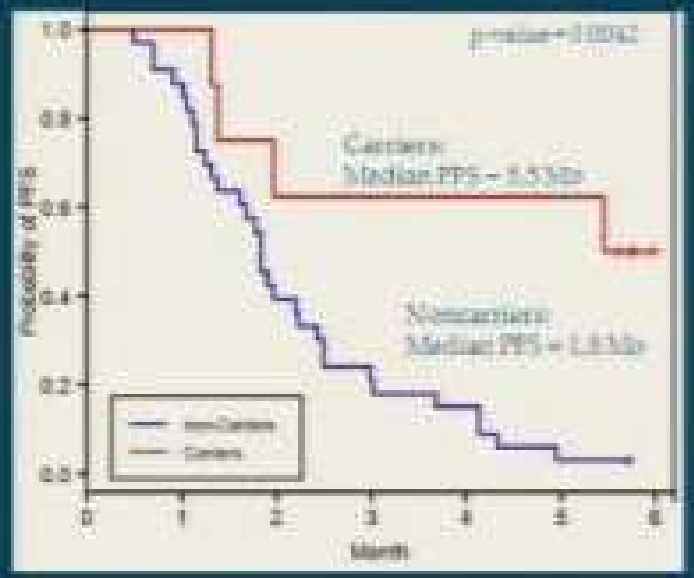
Sandhu, Lancet Oncol 2013

Veliparib

Isakoff 2010



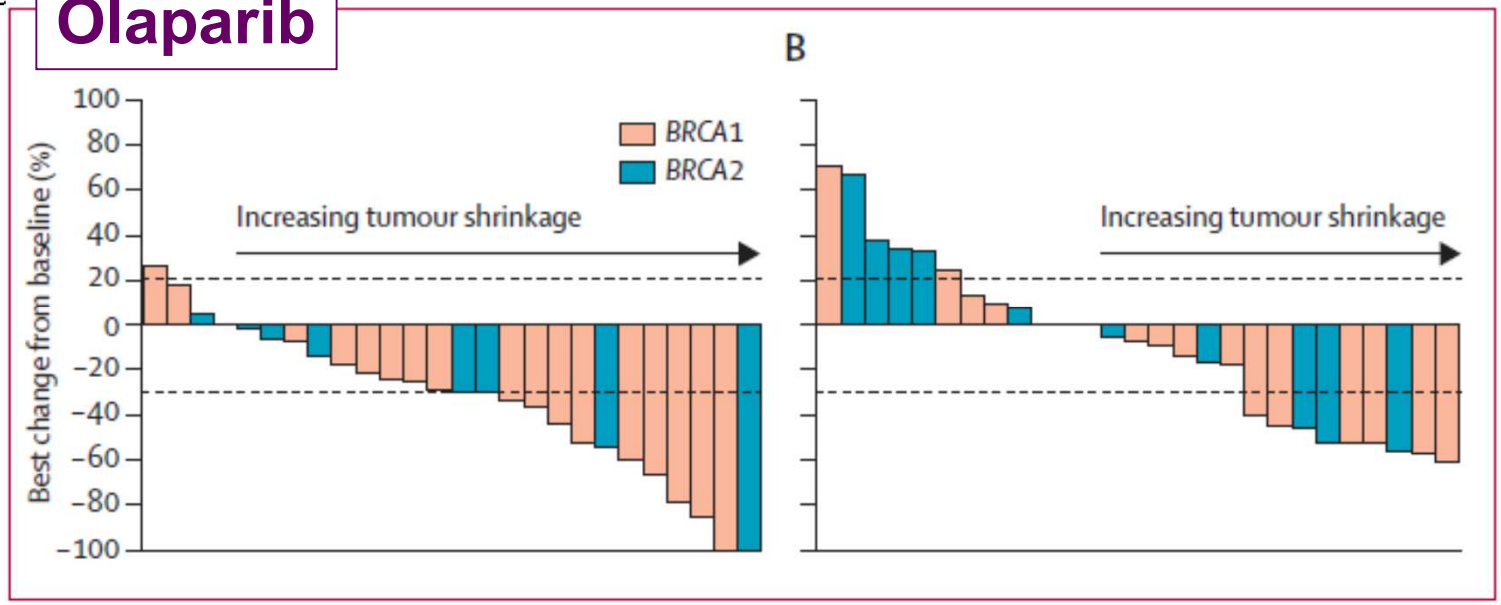
- ORR: 7%
  - All BRCA1/2+ (RR 38%)
- Toxicity:
  - marrow, nausea, electolyte, fatigue
  - no gr3-4 after dose change ABT888



ASCO Annual '10 Meeting

« Preuve de concept » cancers BRCA -/-

Olaparib



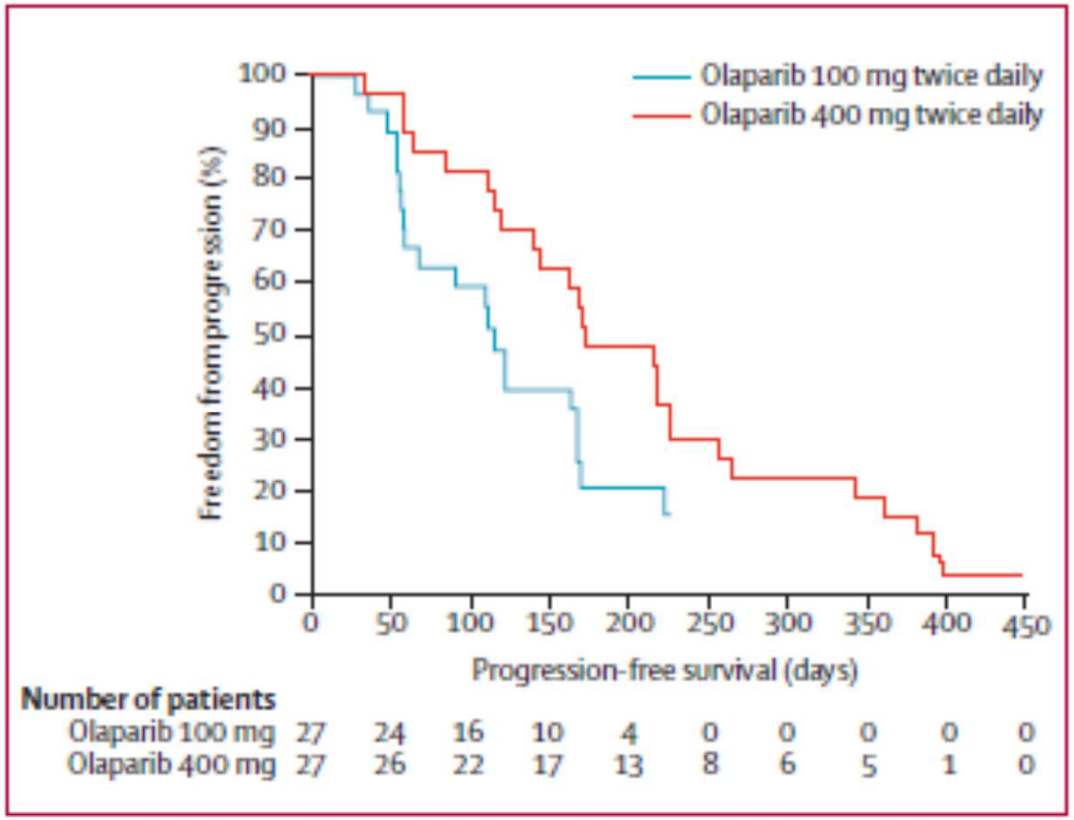
Olaparib monothérapie
Phase avancée

	Olaparib 400 mg twice daily (n=27)	Olaparib 100 mg twice daily (n=27)
Objective response	11 (41%; 25–59)	6 (22%; 11–41)
Complete response	1 (4%; 1–18)	0
Partial response	10 (37%; 22–56)	6 (22%; 11–41)
Stable disease	12 (44%; 28–63)	12 (44%; 28–63)
Progressive disease	4 (15%; 6–32)	9 (33%; 19–53)

Data are number (%; 95% CI).

Table 2: Best overall confirmed tumour response status (intention-to-treat population)

Tutt et al Lancet 2011



	Olaparib 400 mg twice daily (n=27)	Olaparib 100 mg twice daily (n=27)
Nausea		
1 or 2	11 (41%)	11 (41%)
3 or 4	4 (15%)	0
Fatigue		
1 or 2	11 (41%)	7 (26%)
3 or 4	4 (15%)	1 (4%)
Vomiting		
1 or 2	3 (11%)	4 (15%)
3 or 4	3 (11%)	0
Anaemia*		
1 or 2	1 (4%)	2 (7%)
3 or 4	3 (11%)	2 (7%)
Anorexia		
1 or 2	3 (11%)	3 (11%)
3 or 4	0	1 (4%)
Diarrhoea		
1 or 2	3 (11%)	2 (7%)
3 or 4	0	0
Constipation		
1 or 2	2 (7%)	4 (15%)
3 or 4	0	0
Headache		
1 or 2	2 (7%)	3 (11%)
3 or 4	0	0
Abdominal pain†		
1 or 2	2 (7%)	3 (11%)
3 or 4	0	0
Dyspepsia		
1 or 2	2 (7%)	1 (4%)
3 or 4	0	0
Gastro-oesophageal reflux disease		
1 or 2	2 (7%)	1 (4%)
3 or 4	0	0
Flatulence		
1 or 2	2 (7%)	0
3 or 4	0	0
Arthralgia		
1 or 2	0	3 (11%)
3 or 4	0	0

Olaparib monothérapie
Phase avancée

Tutt et al Lancet 2011

Olaparib monothérapie en phase avancée

Table 1. Baseline Patient Demographic and Clinical Characteristics by Tumor Type

Characteristic	Ovarian (n = 193)*		Breast (n = 62)		Pancreas (n = 23)		Prostate (n = 8)		Other (n = 12)†		Total (N = 298)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years												
Median	57		48		58		71		56		56	
Range	29-79		29-73		43-73		51-77		36-74		29-79	
Sex												
Female	193	100.0	61	98.4	10	43.5	0	0.0	8	66.7	272	91.3
ECOG PS												
0	113	58.5	32	51.6	11	47.8	1	12.5	6	50.0	163	54.7
1	69	35.8	27	43.5	9	39.1	4	50.0	6	50.0	115	38.6
2	10	5.2	3	4.8	3	13.0	3	37.5	0	0.0	19	6.4
BRCA status												
BRCA1 mutation	148	76.7	37	59.7	5	21.7	1	12.5	7	58.3	198	66.4
BRCA2 mutation	44	22.8	25	40.3	17	73.9	7	87.5	5	41.7	98	32.9
BRCA1 and *BRCA2* mutation	1	0.5	0	0.0	1	4.3	0	0.0	0	0.0	2	0.7
No. of prior regimens for advanced disease												
Mean	4.3		4.6		2.0		2.0		2.2		4.0	
SD	2.2		2.0		1.6		1.0		1.3		2.2	
Measurable disease at baseline	167	86.5	58	93.5	23	100.0	7	87.5	11	91.7	266	89.3

Kaufman B J Clin Oncol Nov 2014

Olaparib monothérapie en phase avancée

Table 2. Tumor Response Rates (full analysis set)

Response	Ovarian (n = 193)		Breast (n = 62)		Pancreas (n = 23)		Prostate (n = 8)		Other (n = 12)		Total (N = 298)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Tumor response rate	60	31.1	8	12.9	5	21.7	4	50.0	1	8.3	78	26.2
95% CI	24.6 to 38.1		5.7 to 23.9		7.5 to 43.7		15.7 to 84.3		0.02 to 38.5		21.3 to 31.6	
CR*	6	3	0	0	1	4	0	0	0	0	7	2
PR*	54	28	8	13	4	17	4	50	1	8	71	24
Stable disease ≥ 8 weeks	78	40	29	47	8	35	2	25	7	58	124	42
95% CI	33.4 to 47.7		34.0 to 59.9		16.4 to 57.3		3.2 to 65.1		27.7 to 84.8		36.0 to 47.4	
Stable disease	64	33	22	36	5	22	2	25	6	50	99	33
Unconfirmed PR	12	6	7	11	3	13	0	0	1	8	23	8
PD†	41	21	23	37	9	39	2	25	3	25	78	26
95% CI	15.7 to 27.7		25.2 to 50.3		19.7 to 61.5		3.2 to 65.1		5.5 to 57.2		21.3 to 31.6	
RECIST progression	33	17	16	26	6	26	1	13	3	25	59	20
Early death‡	8	4	7	11	3	13	1	13	0	0	19	6
Not evaluable	14	7	2	3	1	4	0	0	1	8	18	6
No follow-up assessments	12	6	2	3	1	4	0	0	0	0	15	5
Stable disease < 8 weeks	2	1	0	0	0	0	0	0	1	8	3	1

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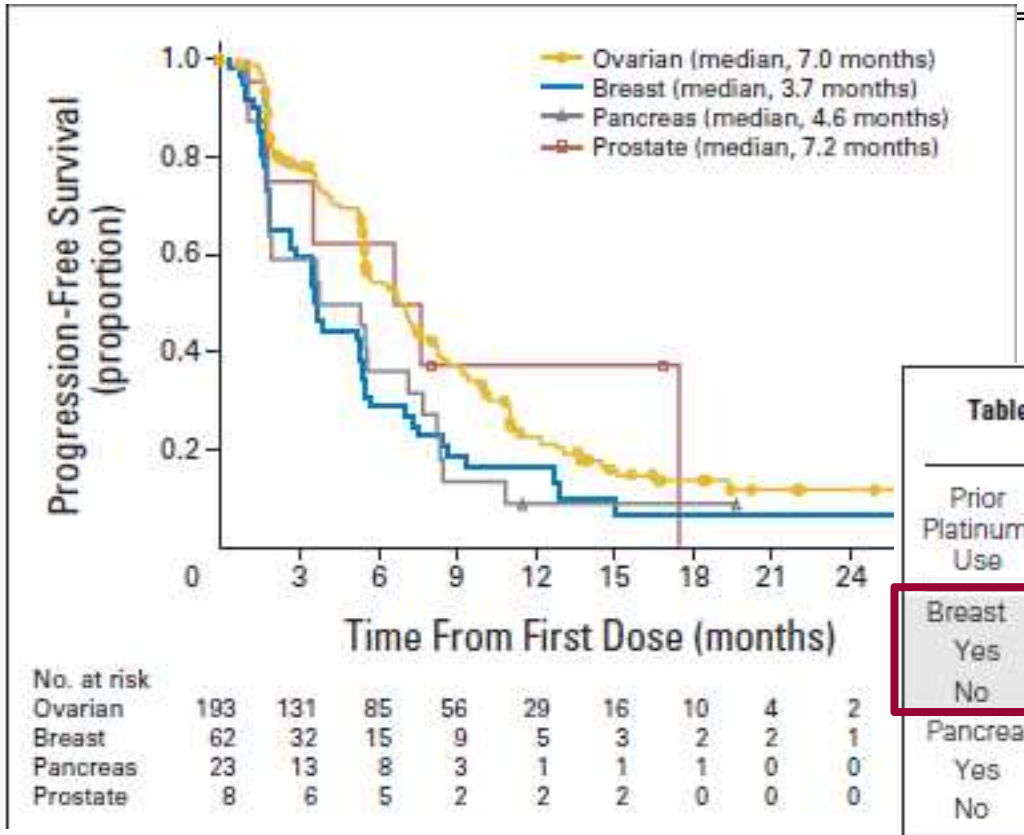
Olaparib monothérapie en phase avancée



PFS

Table 3. Tumor Response Rates by Prior Platinum Chemotherapy and Tumor Type

Prior Platinum Use	No. of Patients	No. of Responses	Response Rate (%)	95% CI (%)
Breast				
Yes	42	4	9.5	2.7 to 22.6
No	20	4	20.0	5.7 to 43.7
Pancreas				
Yes	15	3	20.0	4.3 to 48.1
No	8	2	25.0	3.2 to 65.1
Prostate				
Yes	4	1	25.0	0.6 to 80.6
No	4	3	75.0	19.4 to 99.4
Other				
Yes	9	1	11.1	0.3 to 48.3
No	3	0	0.0	0.0 to 70.8

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Olaparib monothérapie en phase avancée

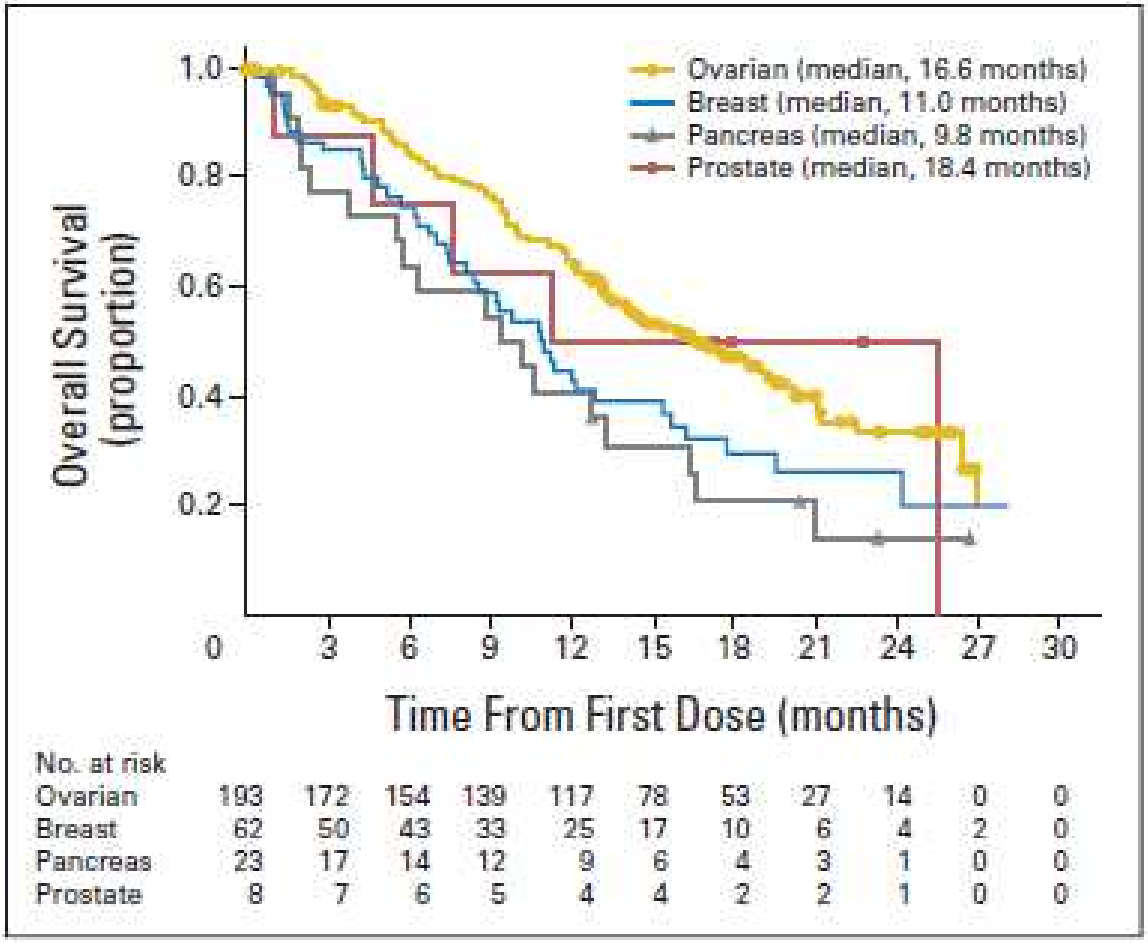

Fig 2. Overall survival.

OS

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Olaparib monothérapie en phase avancée

Tolérance

Table 4. Any-Grade AEs Reported in > 15% of Patients Overall or Grade ≥ 3 AEs Reported in > 5% of Patients Overall

	Ovarian (n = 193)				Breast (n = 62)				Pancreas (n = 23)				Prostate (n = 8)				Other (n = 12)				Total (N = 298)			
	Any Grade		Grade ≥ 3		Any Grade		Grade ≥ 3		Any Grade		Grade ≥ 3		Any Grade		Grade ≥ 3		Any Grade		Grade ≥ 3		Any Grade		Grade ≥ 3	
AE	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Fatigue	116	60.1	12	6.2	30	48.4	3	4.8	17	73.9	3	13.0	1	12.5	0	0.0	12	100.0	1	8.3	176	59.1	19	6.4
Nausea	119	61.7	1	0.5	33	53.2	0	0.0	11	47.8	0	0.0	3	37.5	0	0.0	10	83.3	0	0.0	176	59.1	1	0.3
Vomiting	75	38.9	5	2.6	21	33.9	1	1.6	9	39.1	1	4.3	0	0.0	0	0.0	6	50.0	0	0.0	111	37.2	7	2.3
Anemia	62	32.1	36	18.7	16	25.8	9	14.5	9	39.1	4	17.4	5	62.5	1	12.5	6	50.0	2	16.7	98	32.9	52	17.4
Diarrhea	56	29.0	3	1.6	11	17.7	1	1.6	7	30.4	0	0.0	3	37.5	0	0.0	4	33.3	0	0.0	81	27.2	4	1.3
Abdominal pain	58	30.1	14	7.3	5	8.1	1	1.6	7	30.4	1	4.3	0	0.0	0	0.0	7	58.3	1	8.3	77	25.8	17	5.7
Decreased appetite	36	18.7	1	0.5	17	27.4	0	0.0	4	17.4	0	0.0	2	25.0	0	0.0	3	25.0	0	0.0	62	20.8	1	0.3
Dyspepsia	38	19.7	0	0.0	9	14.5	0	0.0	2	8.7	0	0.0	0	0.0	0	0.0	3	25.0	0	0.0	52	17.4	0	0.0
Headache	32	16.6	0	0.0	14	22.6	1	1.6	1	4.3	0	0.0	0	0.0	0	0.0	1	8.3	0	0.0	48	16.1	1	0.3
Dysgeusia	39	20.2	0	0.0	4	6.5	0	0.0	1	4.3	0	0.0	0	0.0	0	0.0	3	25.0	0	0.0	47	15.8	0	0.0

Abbreviation: AE, adverse event.

Kaufman B J Clin Oncol Nov 2014

Plan

- Mécanismes/léthalité synthétique
- Données cliniques
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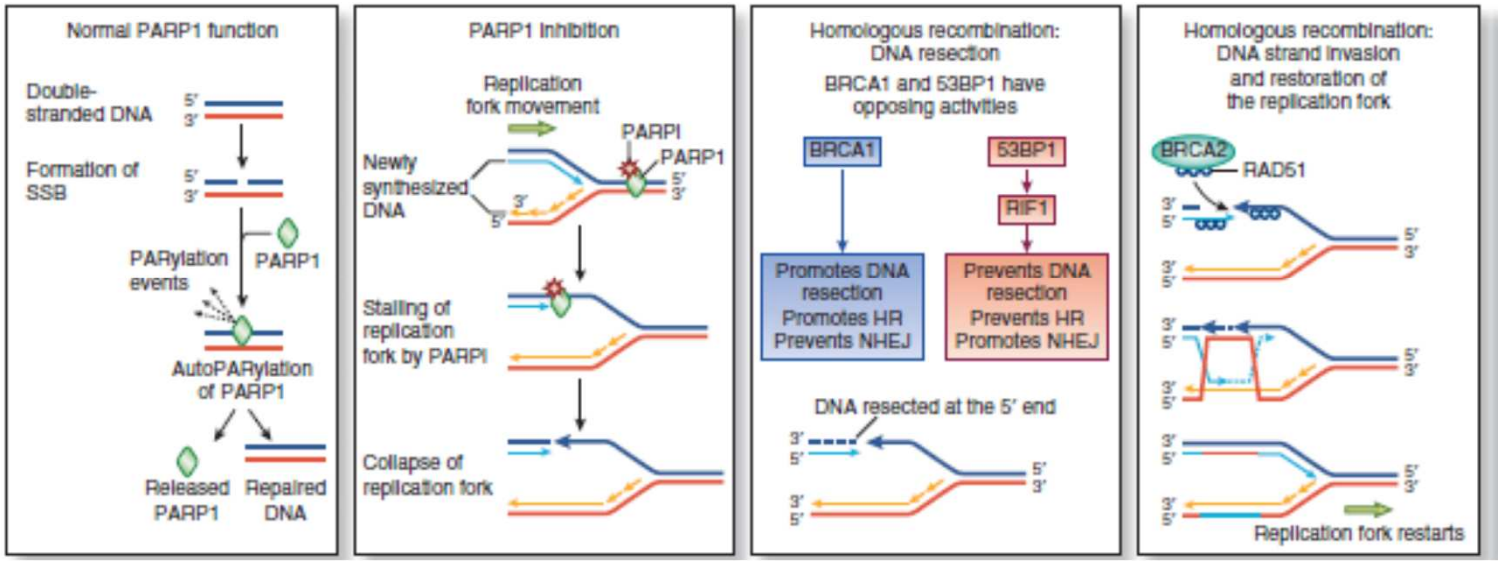
Résistance aux anti-parp…



Uprégulation PgP

Restauration de BRCA1/2

Perte d'expression de parp

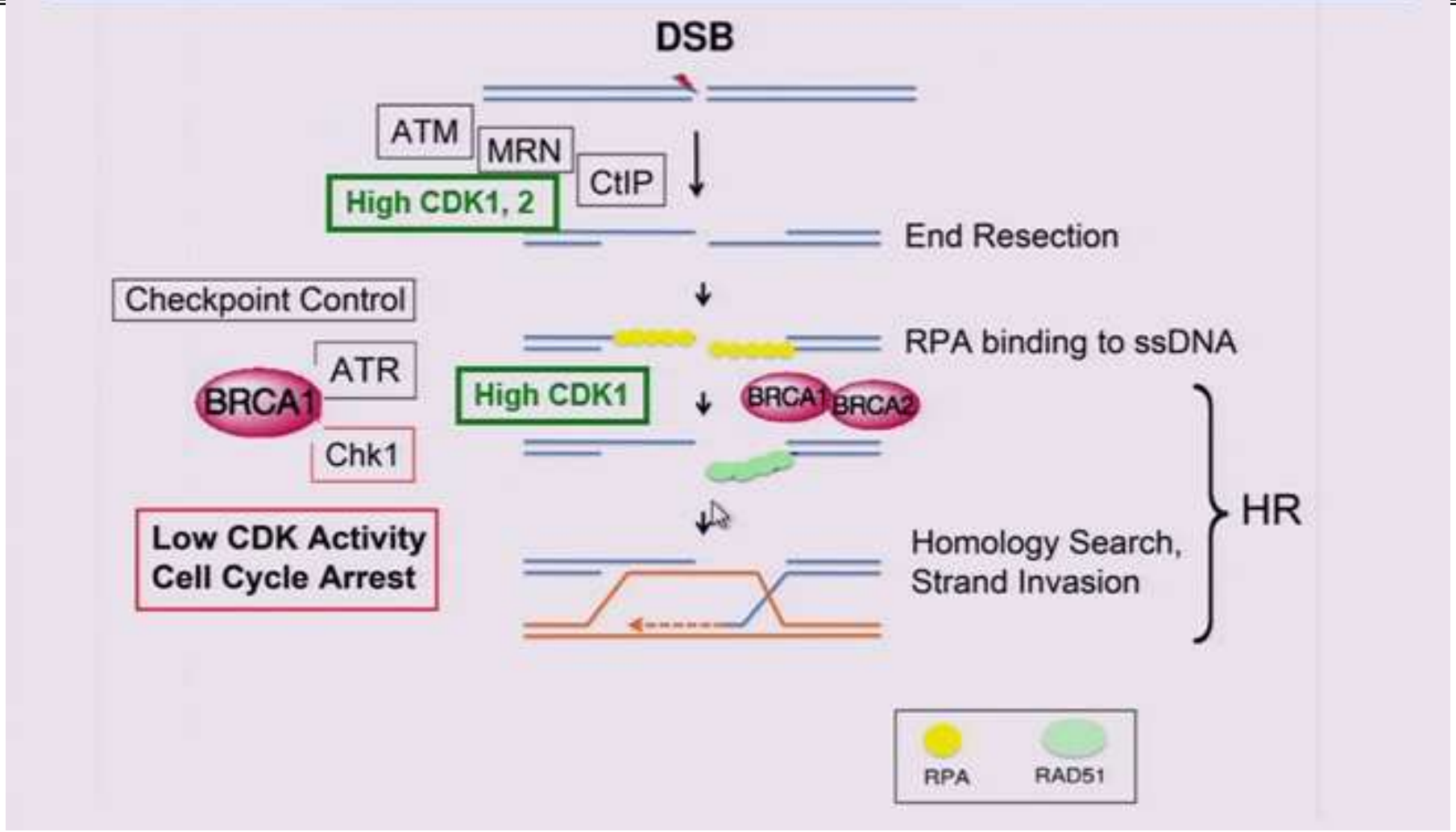
Perte de 53BP1 (si BRCA1 muté)

Lord and Ashworth Nat Genet 2014

Comment augmenter l'efficacité des Inh Parp si BRCA-

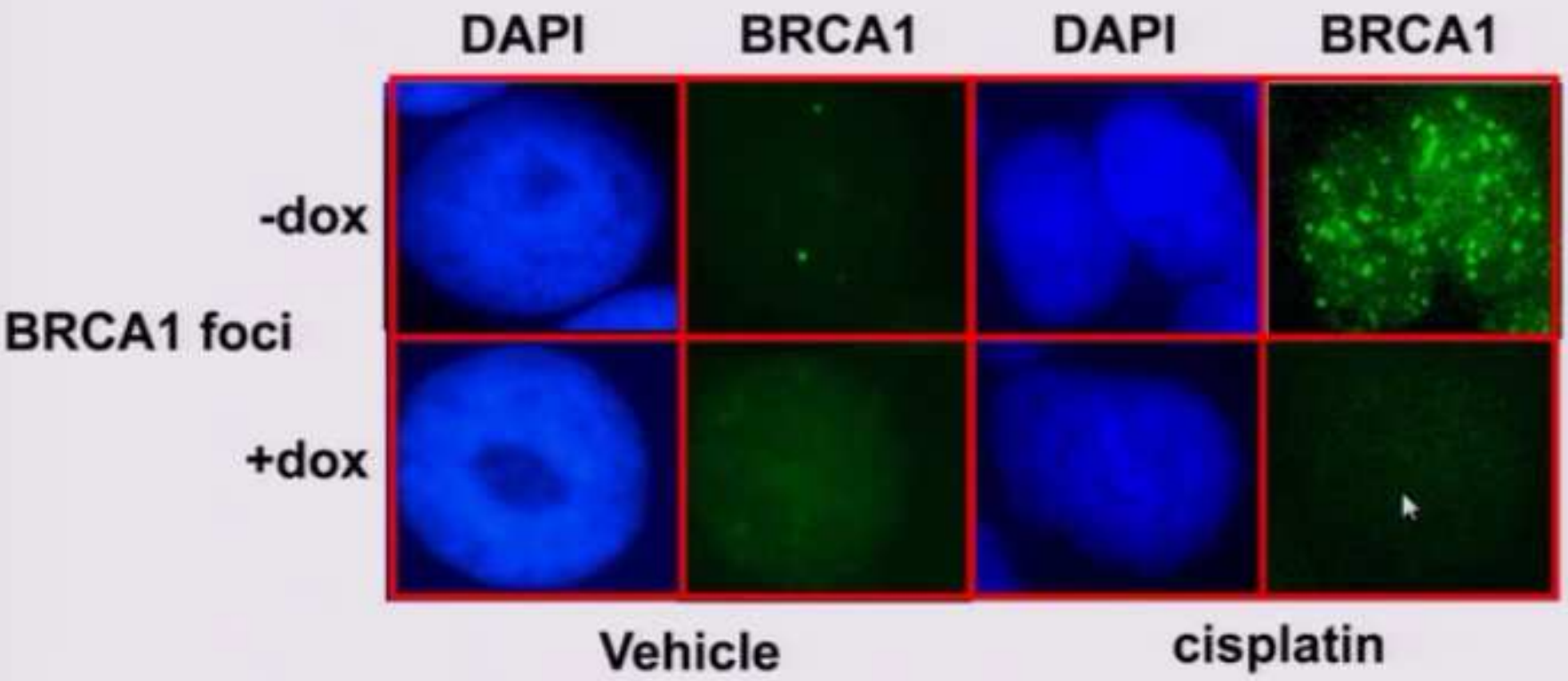
- Association avec chimiothérapie ou autres molécules stoppant le cycle
  - Alkylants, Topo I inh, platines
  - CDK inh
- Association avec d'autres médicaments ciblant/modulant la recombinaison homologue:
  - Checkpoint kinases Chek1/2; Rad51
  - PI3K (expression de BRCA1)
  - Proteasome, HSP
- Association aux checkpoint inhibiteurs

CDK Activity is Required Upstream in the DNA Damage Response

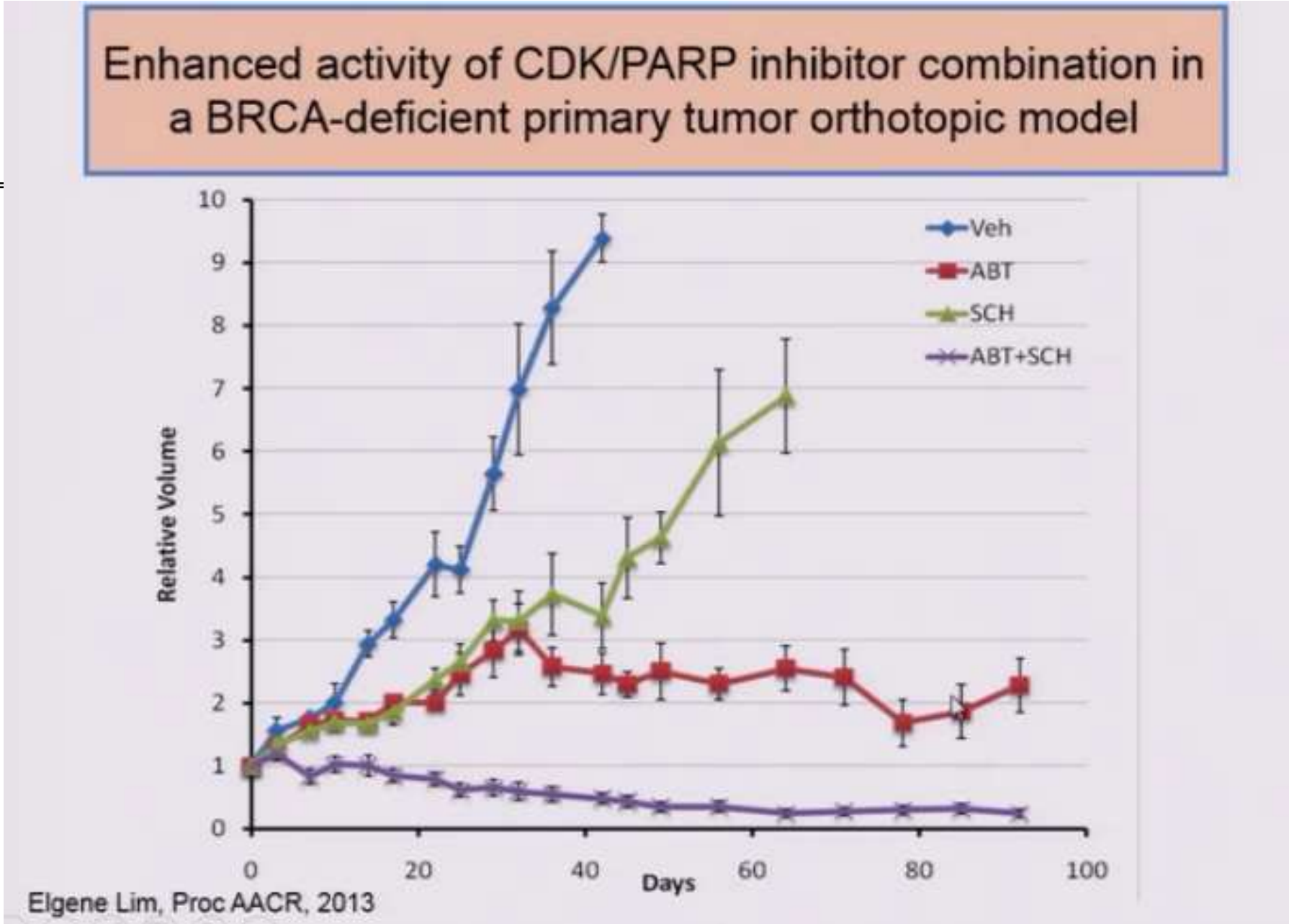


Shapiro SABCS 2013

Formation of BRCA1 Foci is Markedly Compromised in CDK1-Depleted Cells



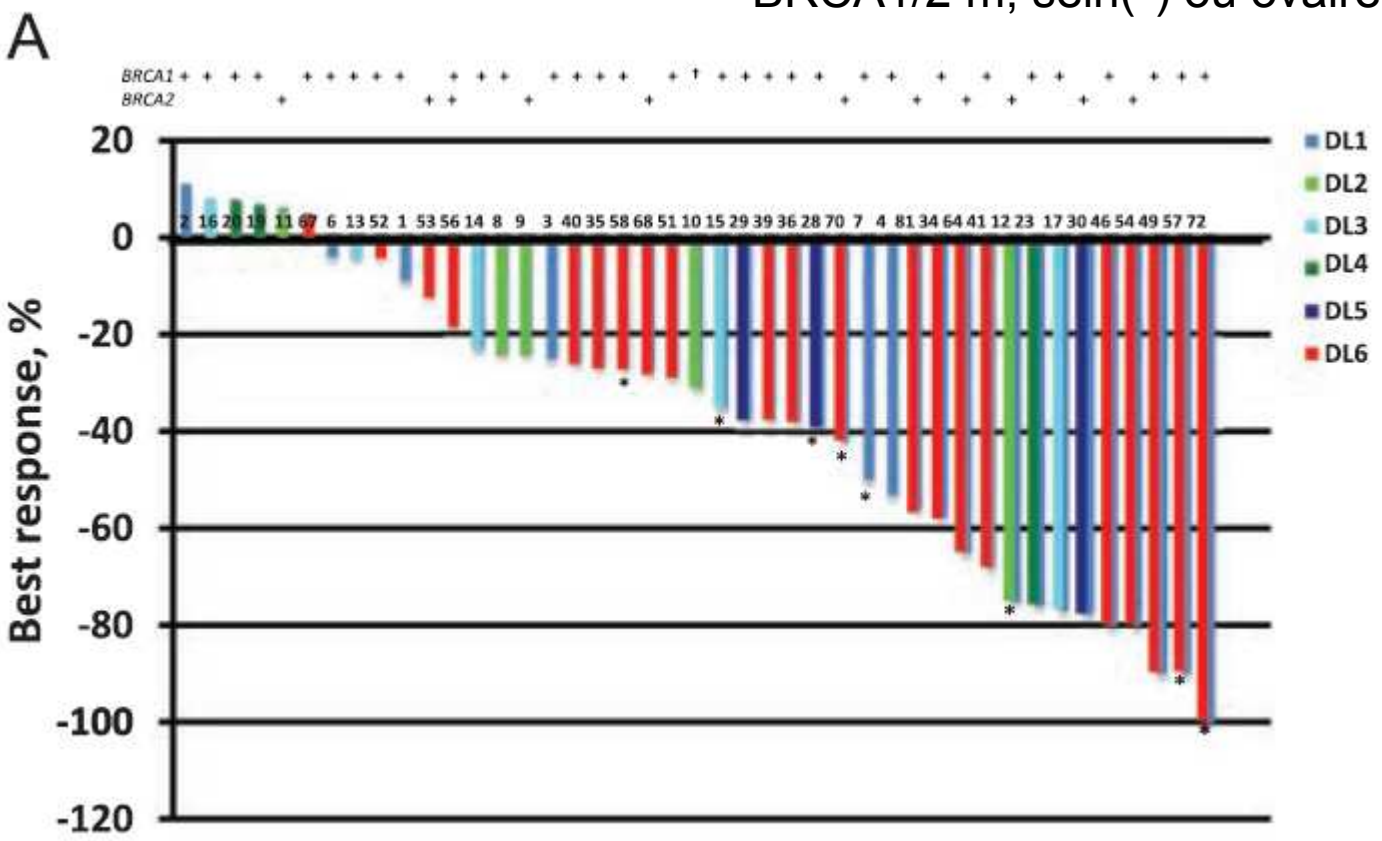
Johnson et al. Mol Cell, 2009



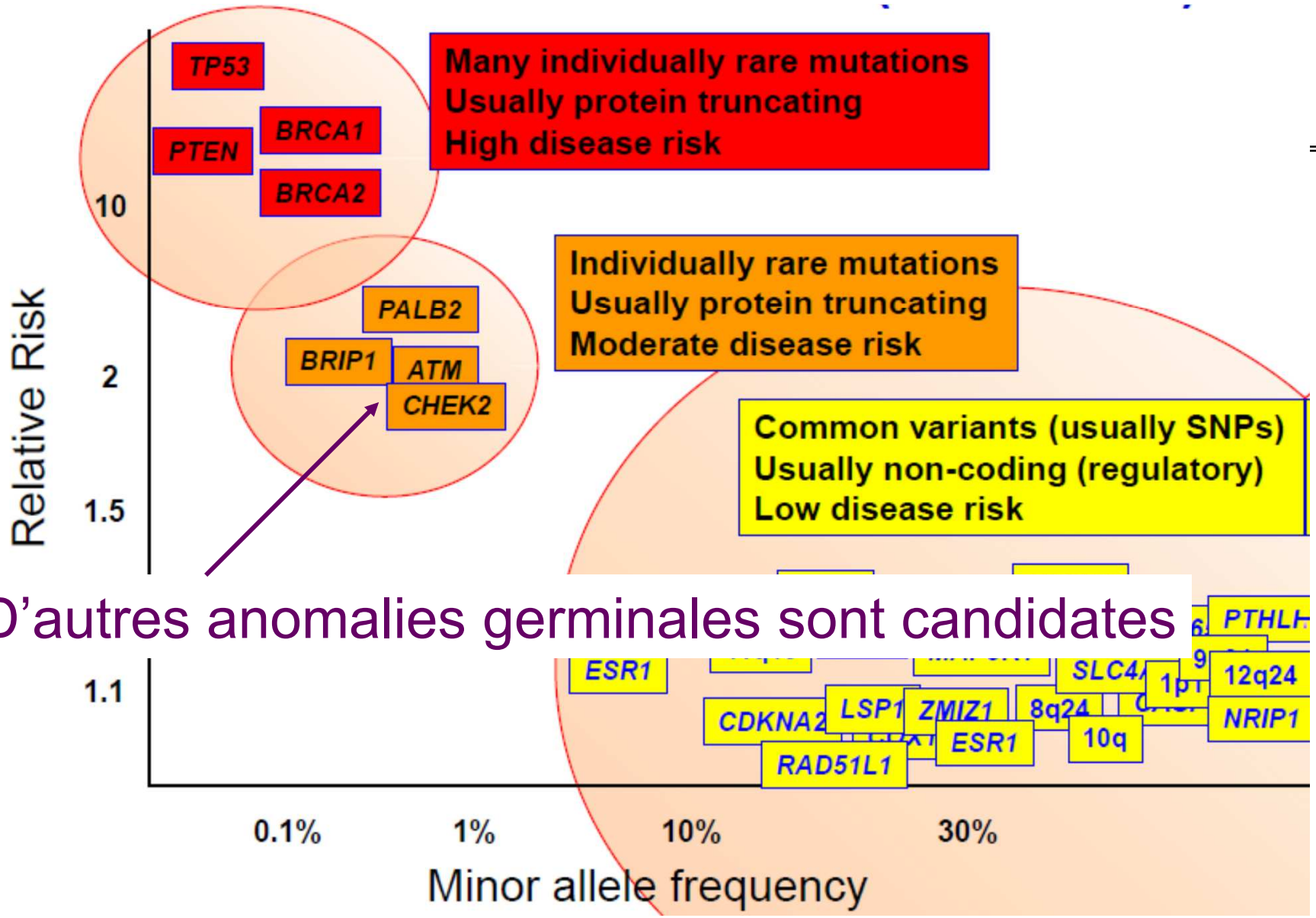
Shapiro SABCS 2013

Olaparib + carboplatine phase I

BRCA1/2 m, sein(*) ou ovaire



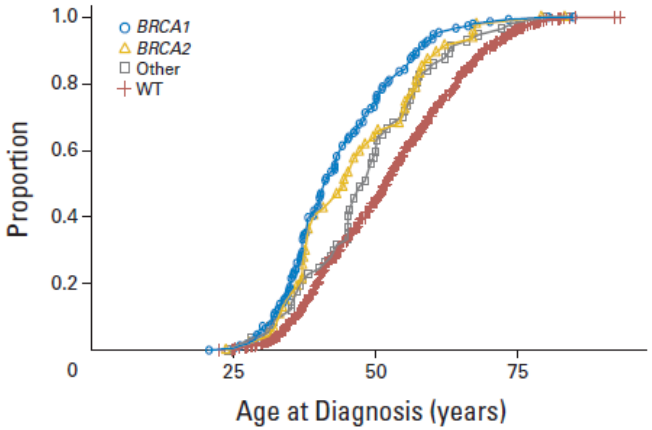
Lee et al, JNCI 2014



D'autres anomalies germinales sont candidates

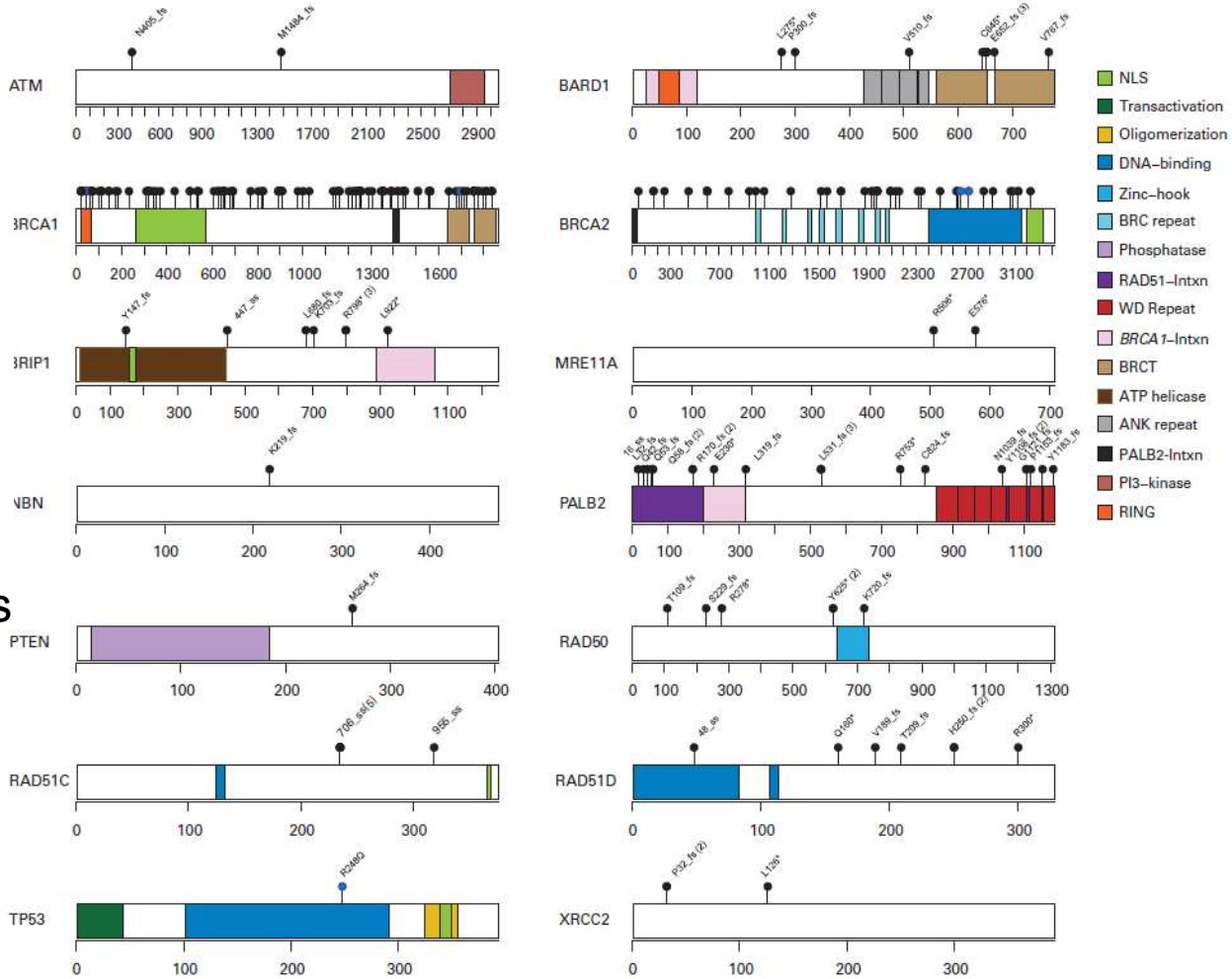
Prévalence de mutations germinales du HR si cancers du sein TN

N = 1824 femmes avec TNBC



14.6% mutations germinales

- 8.5% BRCA1
- 2.7% BRCA2
- 3.7% autres (PALB2, BARD1, Rad51, BRIP1…)

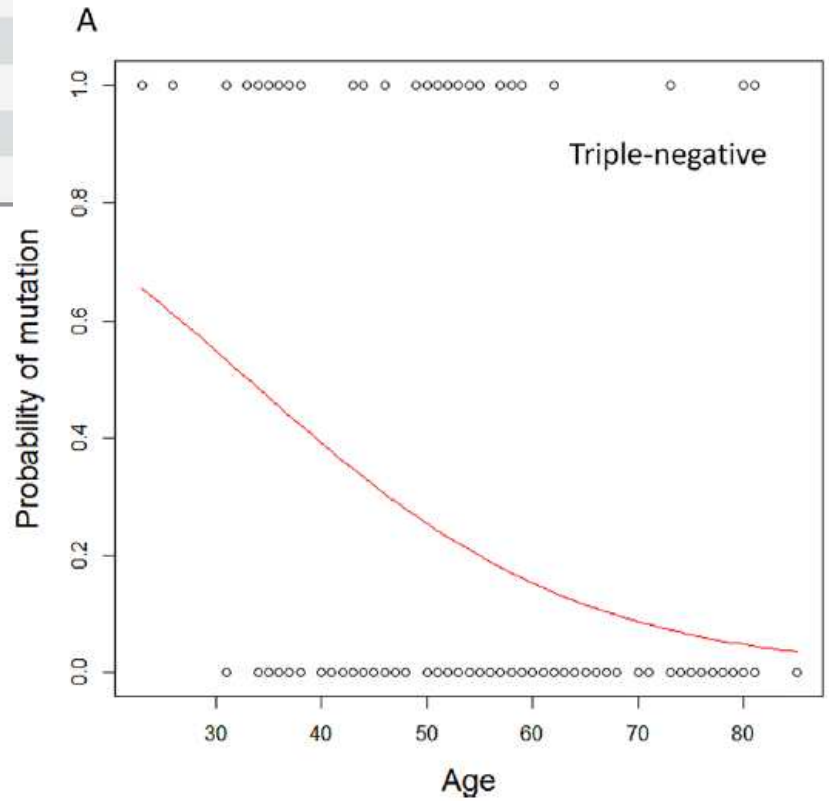


Couch et al, JCO 2015

Prévalence de mutations germinales du HR si cancers du sein TN

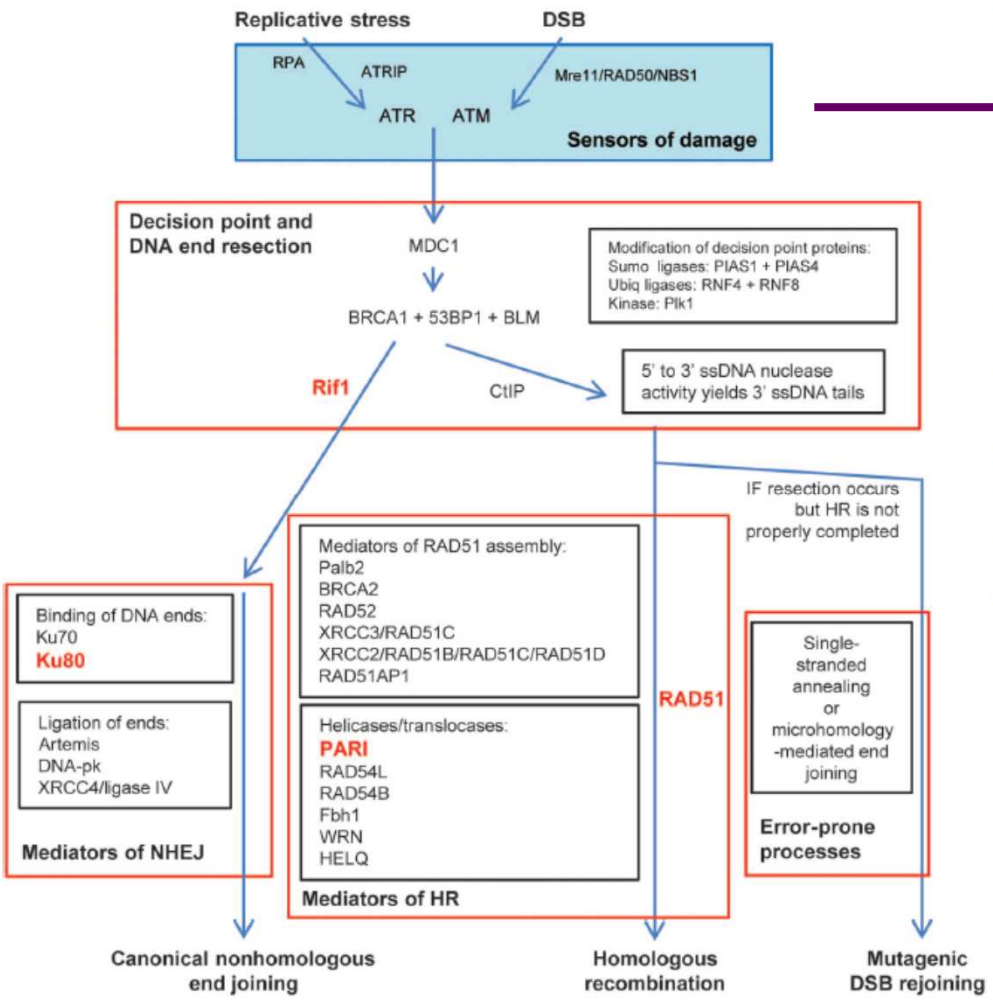
Gene	Triple-negative n = 158	%
BRCA1	27	17.2
CHEK2	2	1.3
NBN	3	1.9
PALB2	0	0
ATM	1	0.6
BRCA1/CHEK2[1]	1	0.6
BRCA1/NBN[2]	1	0.6
CHEK2/NBN[3]	0	0
All	35	22.2

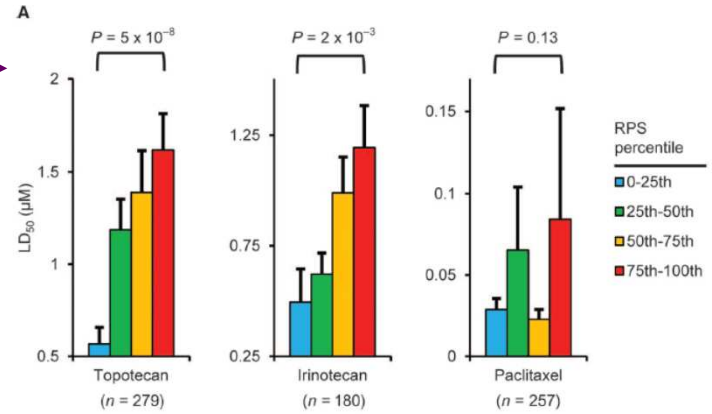
N= 158 TNBC
22.2% mutations germinales
- 17.2% BRCA1
- 5% autres

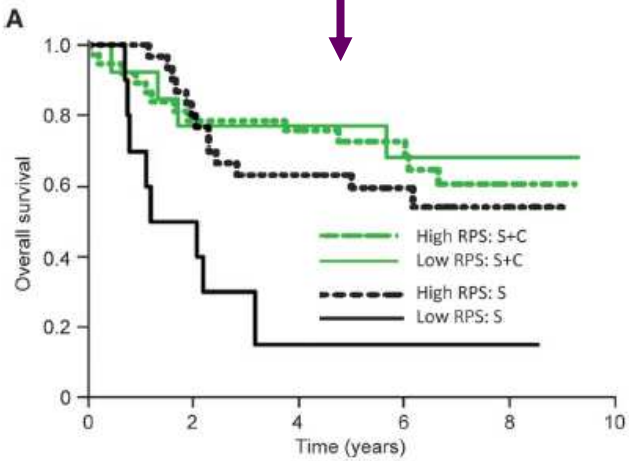


Domagala et al, PLOS One 2015

Recherche de « BRCAness »: score de recombinaison?







Pitroda, Science Translat oncol 2014

Germinal vs somatique + autres gènes DNA repair: exemple de la Prostate

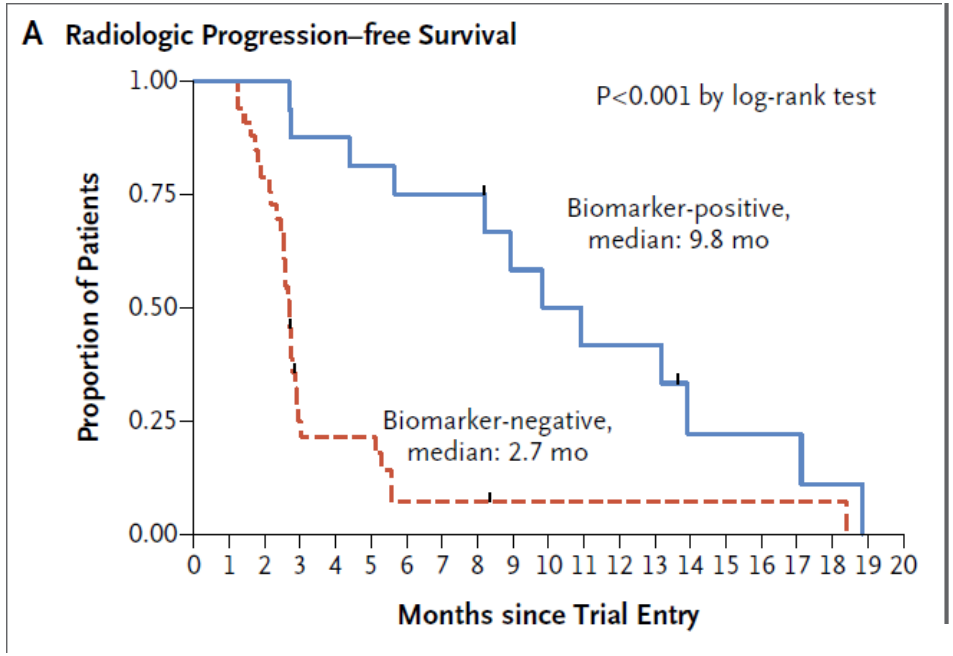
The NEW ENGLAND JOURNAL of MEDICINE

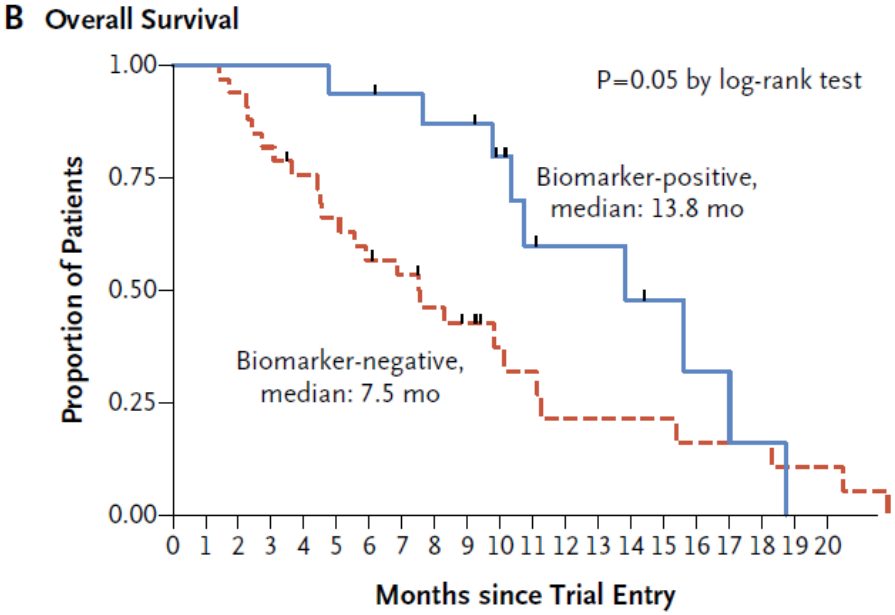
ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

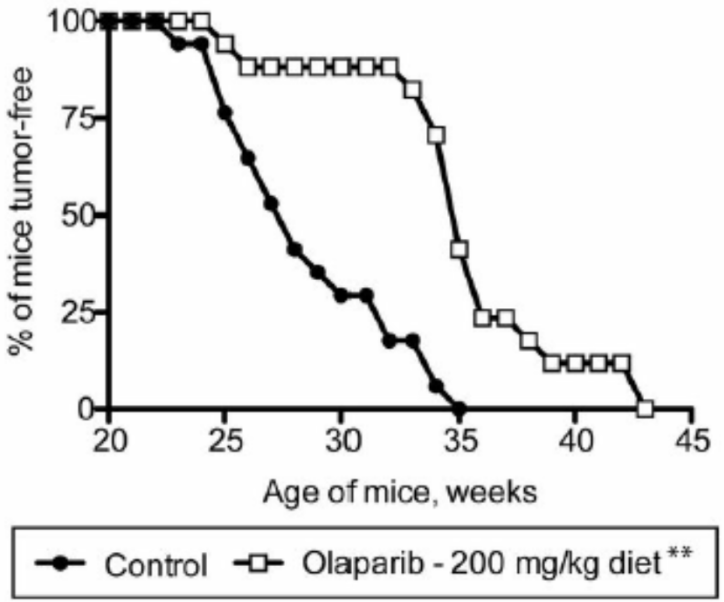
J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, J. Goodall, Z. Zafeiriou, C.T. Williamson, R. Ferraldeschi, R. Riisnaes, B. Ebbs, G. Fowler, D. Roda, W. Yuan, Y.-M. Wu, X. Cao, R. Brough, H. Pemberton, R. A'Hern, A. Swain, L.P. Kunju, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K.E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, and J.S. de Bono

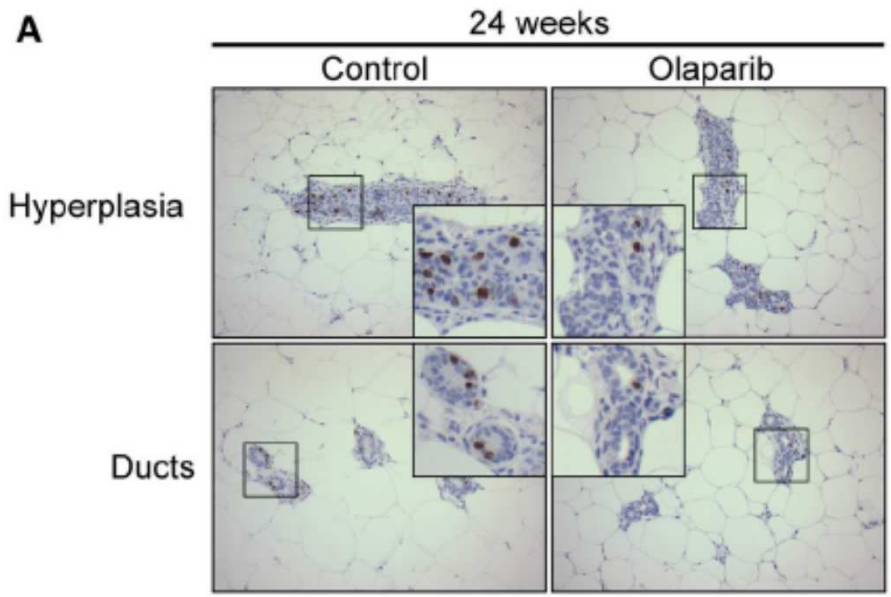
olaparib monothérapie

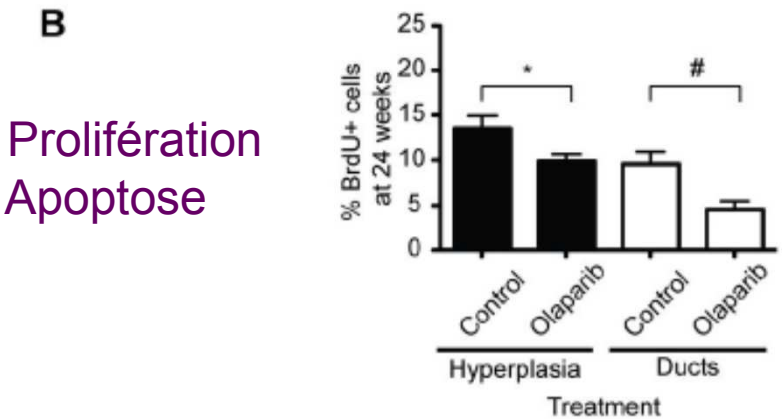




Modèles précliniques de prévention





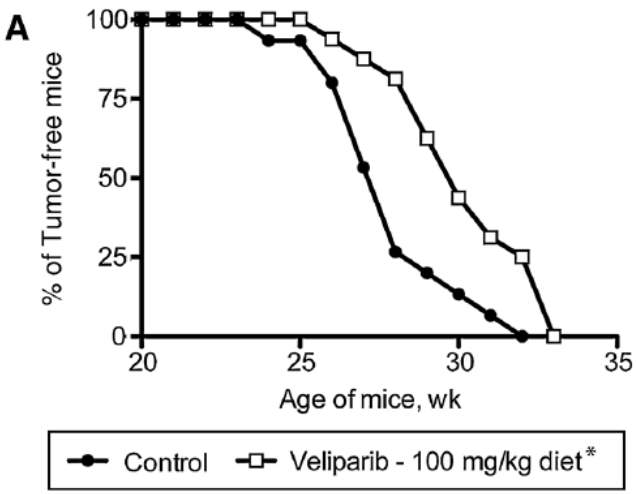


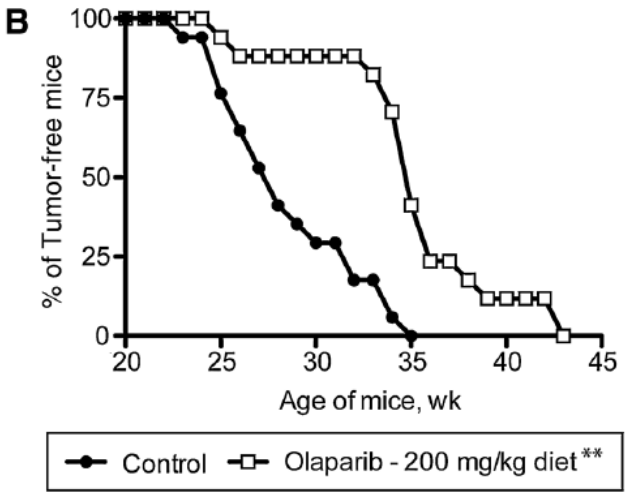
Modèle KO BRCA1 -/- TP53 +/-
↓ incidence de tumeurs

↓ Prolifération
↑ Apoptose

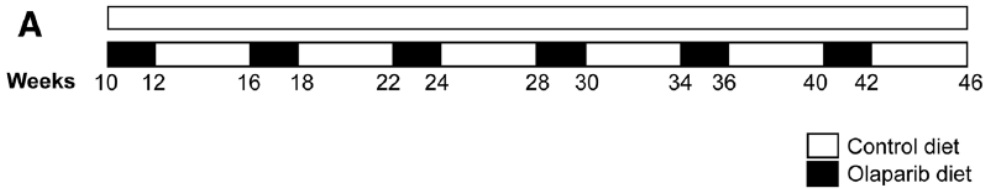
To C et al, Cancer Prev Res 2014

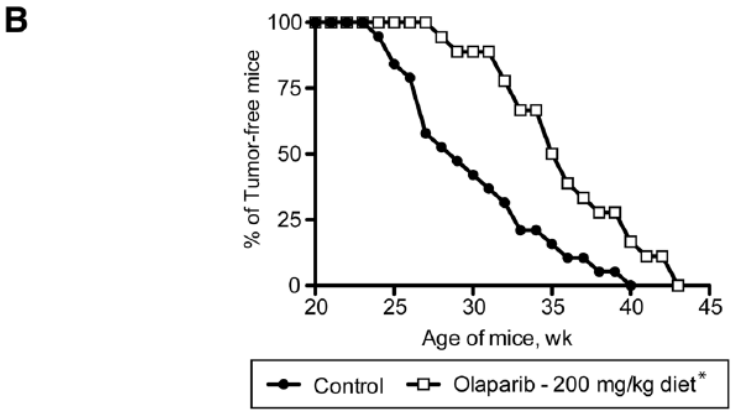
Modèles précliniques de prévention





- Retarde l'apparition de tumeurs, modèles KO
- Effet présent pour trt intermittent





To et al, Cancer Prev Res 2014

Etudes d'enregistrement en cours parp-inh, BRCA mutation carriers

Diagnosis

Neoadjuvant
olaparib,
veliparib

Surgery

Adjuvant
olaparib

Metastatic relapse

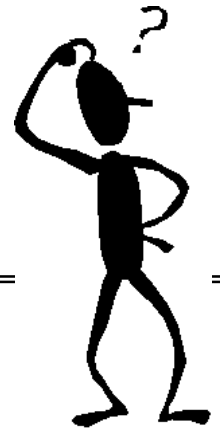
Advanced
niraparib,
olaparib,
veliparib,
talazoparib,
etc…

Conclusions: inhibiteurs de parp

- Promesses importantes dans des situations limitées mais à grand besoin médical+++

- Preuve de l'utilité clinique en cours dans le cancer du sein avancé et localisé (Phases III)
- Biomarqueurs prédictifs identifiés = mutations germinales de BRCA1 ou BRCA2
- Biomarqueurs additionnels en évaluation (BRCAness, autres gènes du HRD, etc)

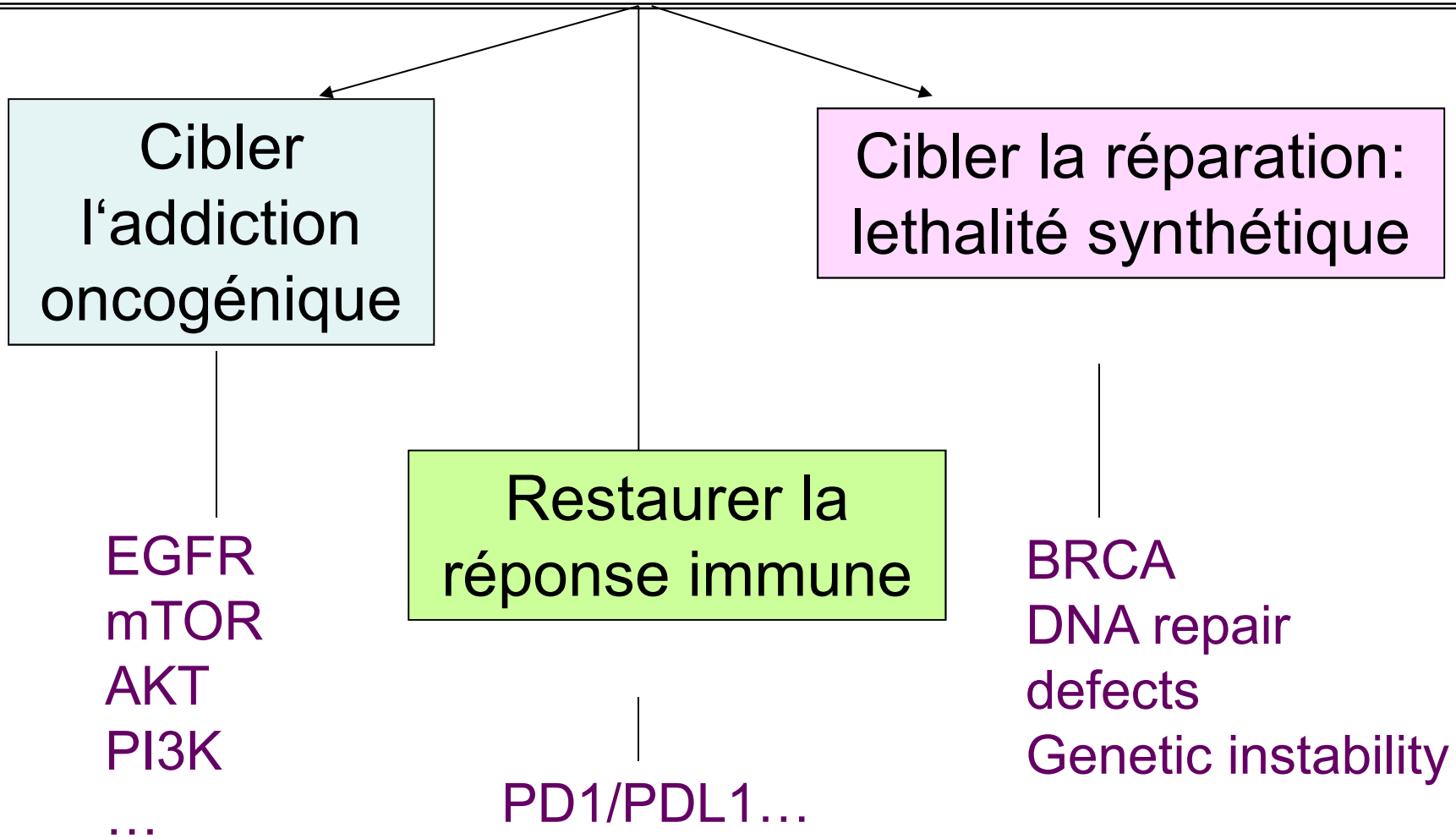
Questions!



- Toxicités à long terme de ces composés???
- Modalités et accès aux tests BRCA génétiques dans le futur (travail Inca…)
- Stratégie de choix de ces molécules dans le futur par rapport à d'autres médicaments disponibles dans la même situation, potentiellement (immunothérapies, thérapies ciblées en cas de cancer luminal ?...)
- Aller vers la prévention?....

Merci!!!

Perspectives: triple négatifs



Perspectives: triple négatifs

Cibler la réparation:
lethalité synthétique

BRCA
DNA repair
defects
Genetic instability