Actualités 2012-2013 sur les cancers gynécologiques

Actualités et controverses
Mont Saint-Michel, 17 mai 2013

Dr Hardy-Bessard
Clinique Armoricaine, Saint-Brieuc

COL UTERIN

Paclitaxel et carboplatine dans le cancer du col utérin

Schéma de l'étude

- Étude de phase III, randomisée, multicentrique (30 centres)
  - Cancer du col de stade IVB ou récidivant, non éligible à un traitement curatif par chirurgie/radiothérapie

Traitement standard : PCisP
Paclitaxel 135 mg/m² 24h J1
+ cisplatine 50 mg/m² 2h J2
(n = 127)

R

Tous les 21 jours pendant 6 cycles

Traitement expérimental : PCa
Paclitaxel 175 mg/m² 3h J1
+ carboplatine ASC5 1h J1
(n = 126)

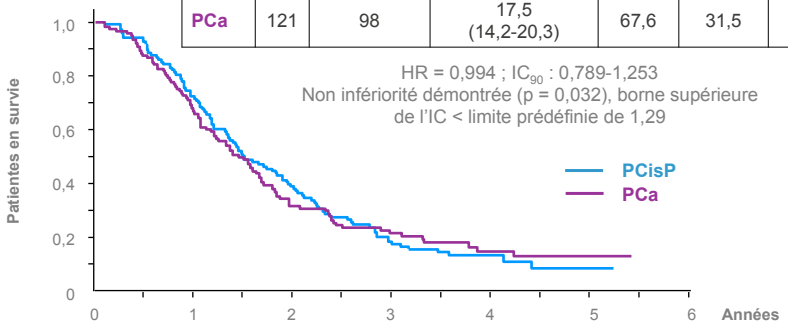
Stratification
- Tumeur en dehors du site d'irradiation antérieur (oui versus non)
- Statut OMS 0-1 versus 2
- Carcinome épidermoïde ou non
- Centre

ASCO® 2012 - D'après Kitagawa R et al., abstr. 5006 actualisé

Survie globale

Bras	n	Événements	Médiane (mois) - IC_{95}	SG à 1 an (%)	SG à 2 ans (%)	SG à 3 ans (%)
PCisP	123	106	18,3 (16,1-22,9)	72,4	38,8	18,3
PCa	121	98	17,5 (14,2-20,3)	67,6	31,5	21,3

HR = 0,994 ; IC_{90} : 0,789-1,253
Non infériorité démontrée (p = 0,032), borne supérieure de l'IC < limite prédéfinie de 1,29



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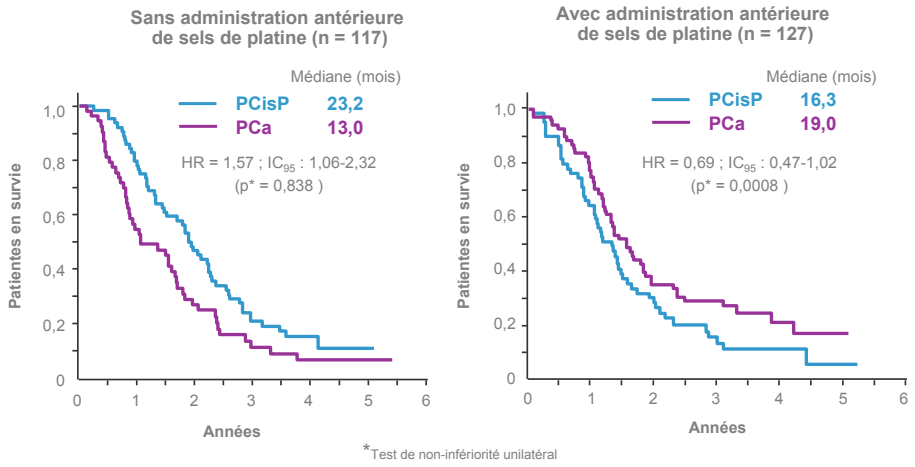
Effets sur la SG de l'administration antérieure de sels de platine



*Test de non-infériorité unilatéral

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OVAIRE
1° ligne

European Journal of Cancer (2013) 49, 142–149

Available at www.sciencedirect.com

SciVerse ScienceDirect

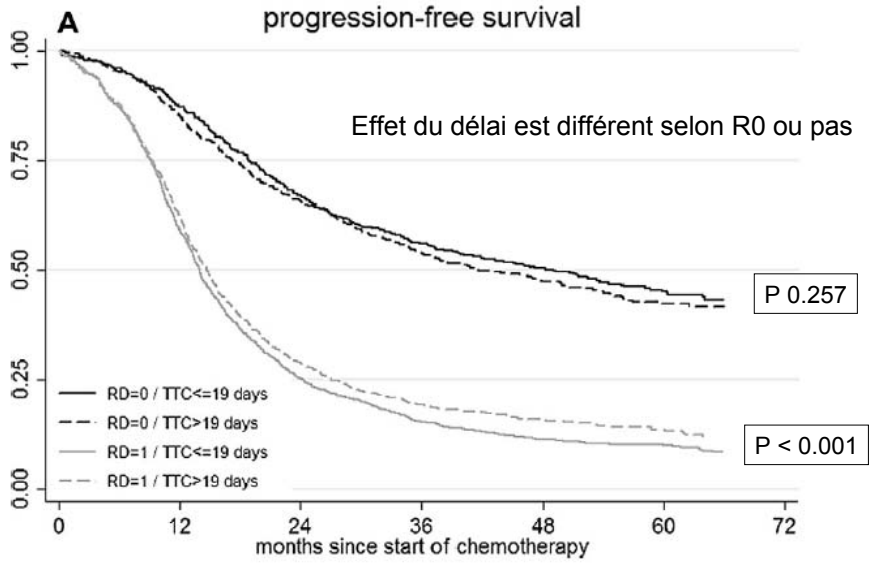
journal homepage: www.ejcancer.info

Prognostic impact of the time interval between surgery and chemotherapy in advanced ovarian cancer: Analysis of prospective randomised phase III trials

S. Mahner [a,*,1,2], C. Eulenburg [b,1,2], A. Staehle [c,1], K. Wegscheider [b,1], A. Reuss [d,1], E. Pujade-Lauraine [e,3], P. Harter [f,1], I. Ray-Coquard [g,3], J. Pfisterer [h,1], A. du Bois [f,1]

- 3 phases III randomisées de 95 à 2002,
- 1° ligne, platine taxanes
- 3326 patientes

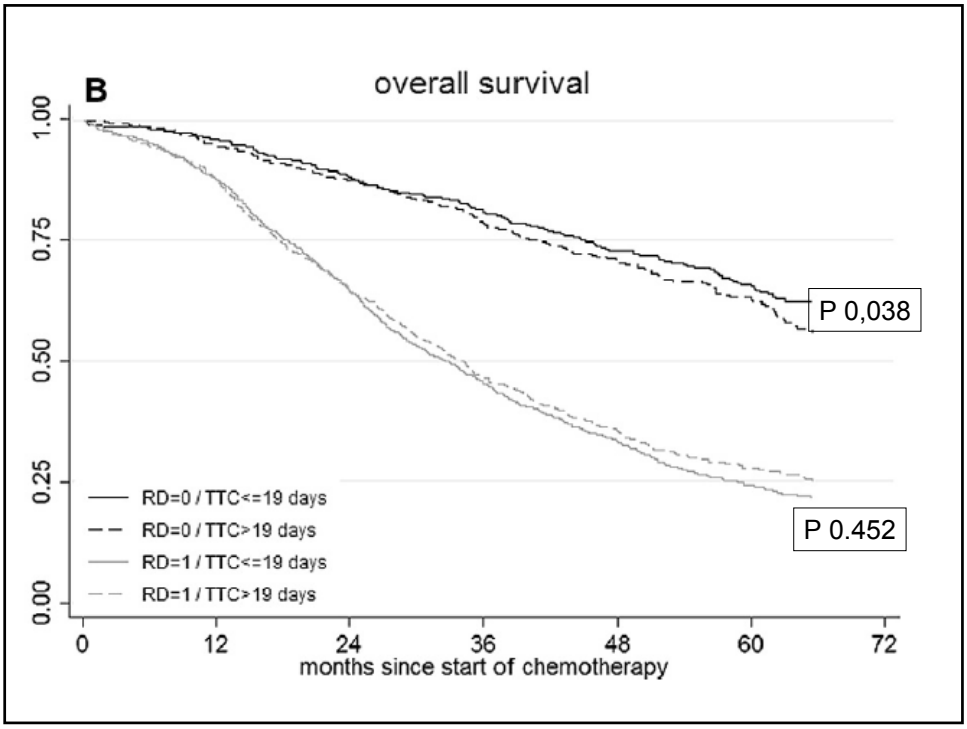
- Intervalle médian : 19 jours



Effet du délai est différent selon R0 ou pas

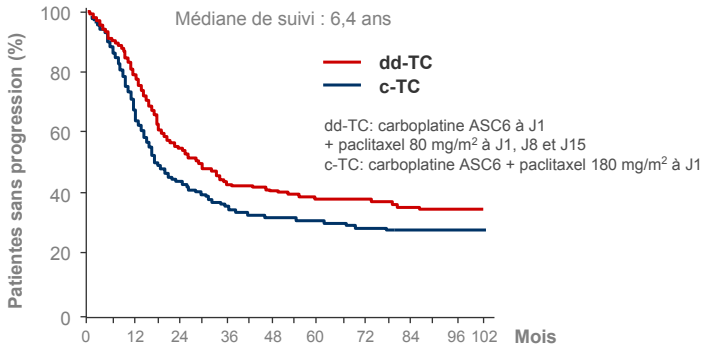
P 0.257

P < 0.001



Étude JGOG3016

Données actualisées de survie sans progression

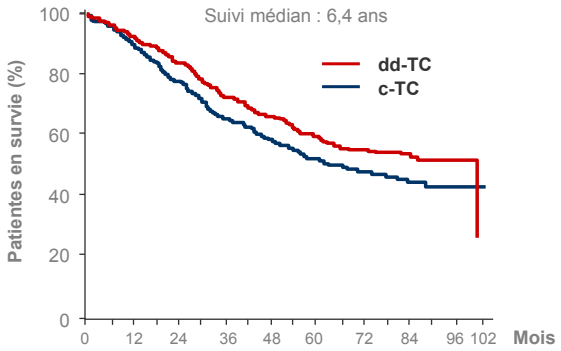


Traitement	n	Evénements, n (%)	SSP médiane (mois)	p	HR	IC_{95}
dd-TC	312	197 (63)	28,2	0,0037	0,76	0,62-0,91
c-TC	319	229 (72)	17,5			

ASCO® 2012 - D'après Katsumata N et al., abstr. 5003 actualisé

Étude JGOG3016 *(2)*

Données actualisées de survie globale

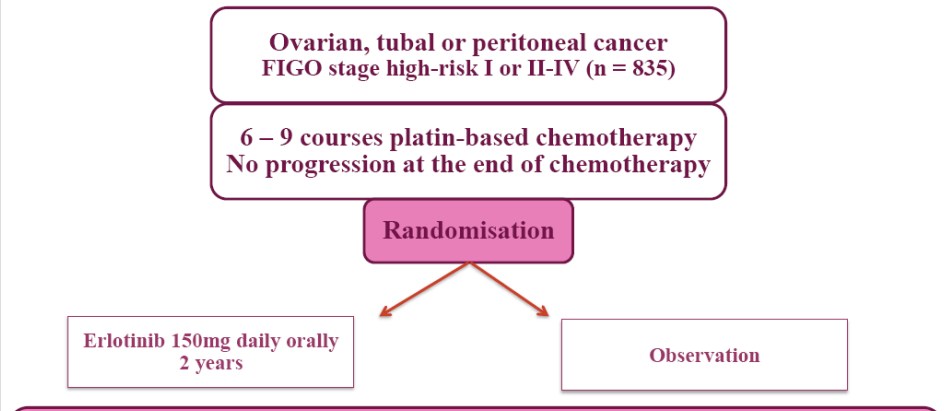


Traitement	n	Décès, n (%)	SG médiane	Survie à 5 ans (%)	p	HR	IC_{95}
dd-TC	312	139 (45)	Non atteinte	58,7	0,039	0,79	0,63-0,99
c-TC	319	168 (53)	62,2	51,1			

ASCO® 2012 - D'après Katsumata N et al., abstr. 5003 actualisé

OVAIRE
Maintenance

Randomised trial on Erlotinib vs observation in first-line ovarian cancer



Primary Endpoint: Progession-free survival

Secondary endpoints: Overall Survival, Quality of Life, Complications

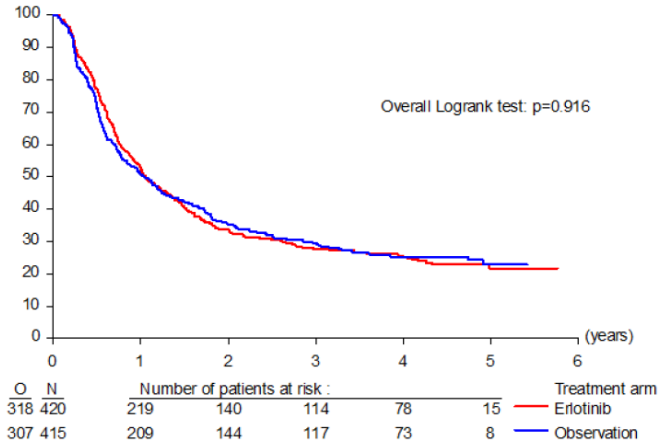
PRESENTED BY: Ignace Vergote PRESENTED AT: ASCO Annual '12 Meeting

Randomised trial on Erlotinib vs observation in first-line ovarian cancer: Eligibility

- Histologically confirmed ovarian epithelial, primary peritoneal, and fallopian tube cancer:
  - High-risk FIGO stage I (grade 3, or aneuploid grade 1 or 2, or clear cell), or
  - Stages II-IV.
- CR, PR or SD at end of first-line therapy.
- No more than 6 weeks since the end of first line chemotherapy.
- 6-9 cycles of Carboplatin AUC 5-6/3weeks or Cisplatin dose > 60 mg/m²/3 weeks alone or in combination with other agents.

PRESENTED BY: Ignace Vergote PRESENTED AT: ASCO Annual '12 Meeting

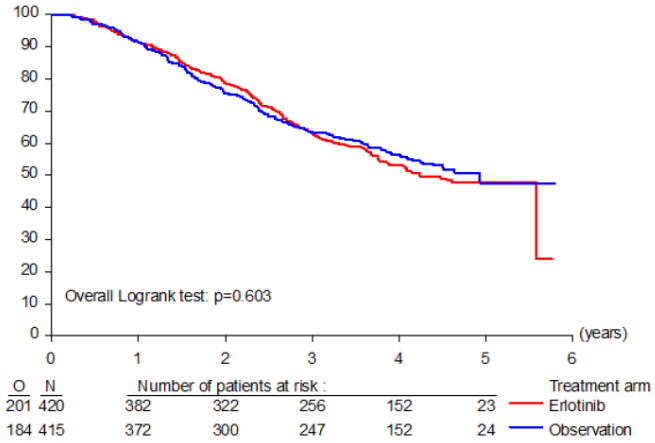
Randomised trial on Erlotinib vs observation in first-line ovarian cancer: Progression-free survival



PRESENTED BY: Ignace Vergote

PRESENTED AT: ASCO Annual '12 Meeting

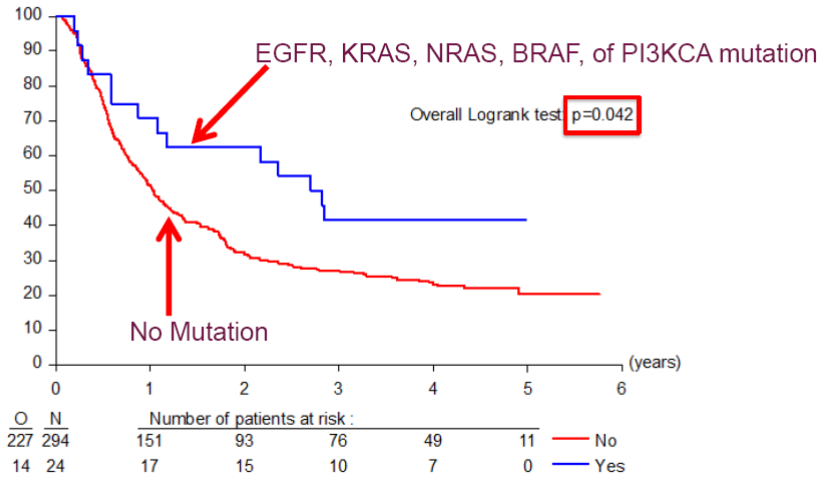
Randomised trial on Erlotinib vs observation in first-line ovarian cancer: Overall Survival



PRESENTED BY: Ignace Vergote

PRESENTED AT: ASCO Annual '12 Meeting

EGFR related Mutation analysis (n = 318) and Progression-free survival



CONCLUSION

- Mieux vaut réfléchir avant d'agir !!!!

MIMOSA : Abagovomab en maintenance

- Anticorps monoclonal murin anti-idiotype dont l'épitope est miroir du CA125
- 888 patientes stade III ou IV, en RC
- Versus placebo
- Maintenance 21 mois ou jusqu'à récidive

- **Résultats** :
  - Induction d'une réponse immunitaire mesurable
  - Pas d'amélioration de la RFS ni OS

JCO, Avril 2013

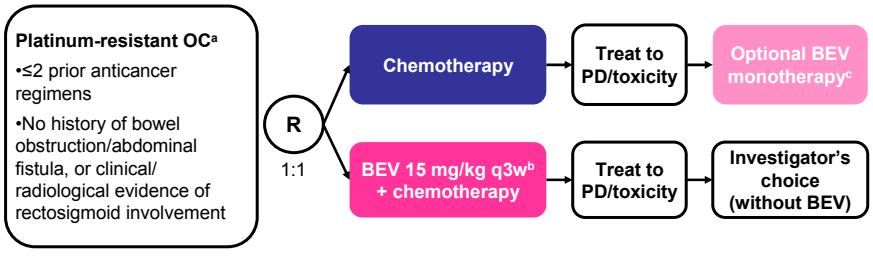
OVAR 16

- Pazopanib en maintenance

- Résultats ASCO 2013

OVAIRE
Récidive platine résistante

AURELIA trial design



Stratification factors:

- Chemotherapy selected
- Prior anti-angiogenic therapy
- Treatment-free interval (<3 vs 3–6 months from previous platinum to subsequent PD)

Chemotherapy options (investigator's choice):

- Paclitaxel 80 mg/m^2 days 1, 8, 15, & 22 q4w
- Topotecan 4 mg/m^2 days 1, 8, & 15 q4w (or 1.25 mg/m^2, days 1–5 q3w)
- PLD 40 mg/m^2 day 1 q4w

PD = progressive disease

[a]Epithelial ovarian, primary peritoneal, or fallopian tube cancer; [b]Or 10 mg/kg q2w; [c]15 mg/kg q3w, permitted on clear evidence of progression

Statistical design

Primary objective: To compare PFS with chemotherapy (CT) alone vs BEV + CT according to RECIST v1.0

Secondary objectives: To compare

- Objective response rate (ORR) according to RECIST v1.0 and/or GCIG CA-125 criteria
- Overall survival
- Quality of life
- Safety and tolerability

Statistical assumptions

- HR of 0.7 (median PFS 4.0 → 5.7 months with BEV)
- 80% power for 2-sided log-rank test at α=0.05

Primary analysis: PFS events in 301 of 361 patients

- Data cut-off: November 14, 2011

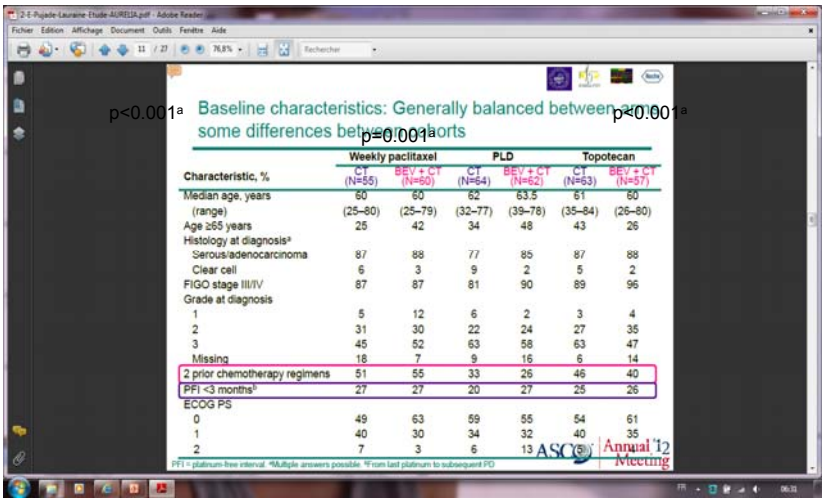
Baseline characteristics

Characteristic	CT (n=182) n (%)	BEV + CT (n=179) n (%)
Median age, years	61	62
(range)	(25–84)	(25–80)
Origin of cancer: Ovary	157 (86)	167 (93)
Serous/adenocarcinoma at diagnosis	152 (84)	156 (87)
Histologic grade at diagnosis		
1	9 (5)	10 (6)
2/3	153 (84)	147 (82)
Prior anti-angiogenic therapy[a]	14 (8)	12 (7)
Two prior chemotherapy regimens	78 (43)	72 (40)
PFI <3 months[a,b]	46 (25)	50 (28)
ECOG PS		
0	99 (54)	107 (60)
1/2	80 (44)	70 (39)
Measurable disease	144 (79)	143 (80)
Ascites	54 (30)	59 (34)

PFI = platinum-free interval

[a]Stratification factor. [b]From last platinum to subsequent PD

Summary of best overall response rates



Patients (%)

[a]*Two-sided chi-square test with Schouten correction*

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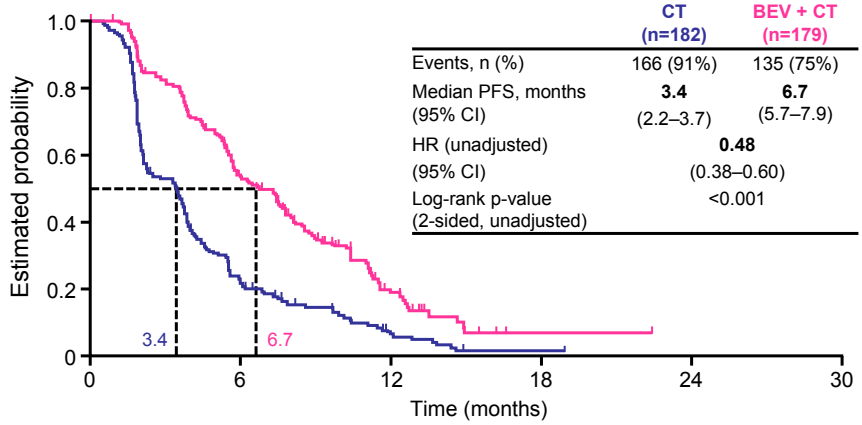
Progression-free survival



	CT (n=182)	BEV + CT (n=179)
Events, n (%)	166 (91%)	135 (75%)
Median PFS, months (95% CI)	**3.4** (2.2–3.7)	**6.7** (5.7–7.9)
HR (unadjusted) (95% CI)	**0.48** (0.38–0.60)	
Log-rank p-value (2-sided, unadjusted)	<0.001	

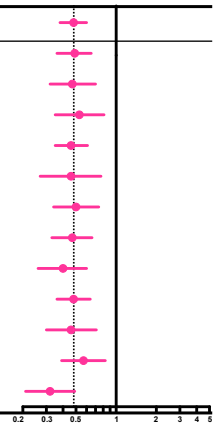
No. at risk:

CT	182	93	37	20	8	1	1	0	0
BEV + CT	179	140	88	49	18	4	1	1	0

Median duration of follow-up: 13.9 months (CT arm) vs 13.0 months (BEV + CT arm)

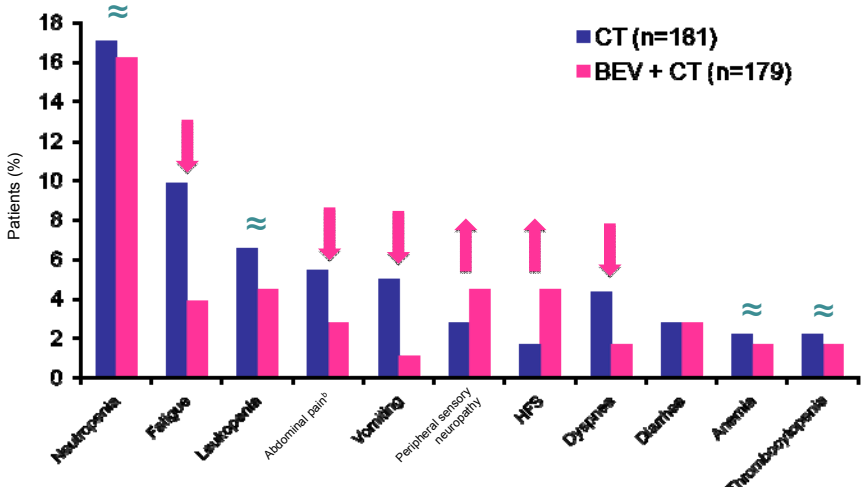
Subgroup analysis of PFS

Subgroup		No. of patients	Median PFS, months CT	Median PFS, months BEV + CT	HR[a]
All patients		361	3.4	6.7	0.48
Age, years	<65	228	3.4	6.0	0.49
	≥65	133	3.5	7.8	0.47
PFI, months[b]	<3	96	2.1	5.4	0.53
	3-6	257	3.6	7.8	0.46
Measurable disease, cm	No (<1)	74	3.7	7.5	0.46
	Yes (1-<5)	126	3.3	7.5	0.50
	Yes (≥5)	161	3.3	6.0	0.47
Ascites	Yes	113	2.5	5.6	0.40
	No	248	3.5	7.6	0.48
Chemotherapy	Paclitaxel	115	3.9	10.4	0.46
	PLD	126	3.5	5.4	0.57
	Topotecan	120	2.1	5.8	0.32



[a]Unadjusted. [b]Missing n=8

Additional grade ≥3 adverse events[a] in ≥2% of patients in either arm



HFS = hand-foot syndrome

[a]Preferred terms. [b]Includes abdominal pain upper

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Adverse events of special interest

Grade ≥3 adverse events of special interest, n (%)	CT (n=181)	BEV + CT (n=179)
Hypertension	2 (1.1)	13 (7.3)
Grade ≥2	12 (6.6)	36 (20.1)
Proteinuria	0	3 (1.7)
Grade ≥2	1 (0.6)	19 (10.6)
GI perforation	0	3 (1.7)
Grade ≥2	0	4 (2.2)
Fistula/abscess	0	2 (1.1)
Grade ≥2	0	4 (2.2)
Bleeding	2 (1.1)	2 (1.1)
Thromboembolic event	8 (4.4)	9 (5.0)
Arterial	0	4 (2.2)
Venous	8 (4.4)	5 (2.8)
Wound-healing complication	0	0
RPLS	0	1 (0.6)
CHF	1 (0.6)	1 (0.6)
Cardiac disorders (excluding CHF)	0	0

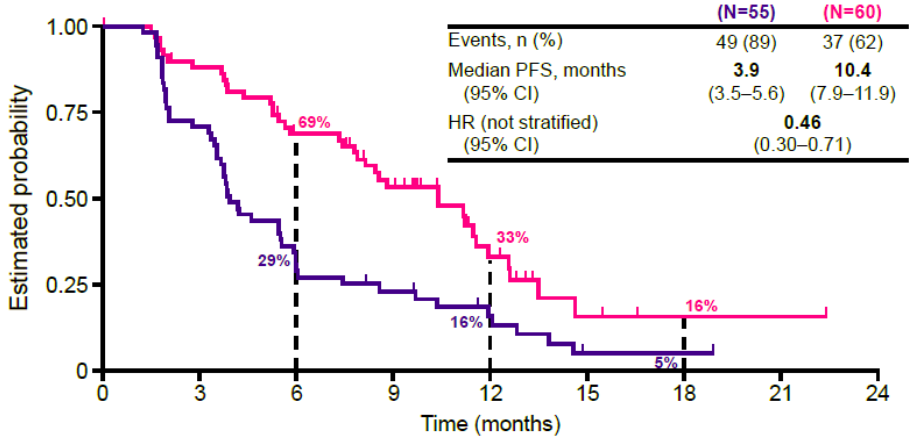
RPLS = reversible posterior leukoencephalopathy syndrome; CHF = congestive heart failure

Baseline characteristics: Generally balanced between arms, some differences between cohorts

Characteristic, %	Weekly paclitaxel		PLD		Topotecan	
	CT (N=55)	BEV + CT (N=60)	CT (N=64)	BEV + CT (N=62)	CT (N=63)	BEV + CT (N=57)
Median age, years	60	60	62	63.5	61	60
(range)	(25–80)	(25–79)	(32–77)	(39–78)	(35–84)	(26–80)
Age ≥65 years	25	42	34	48	43	26
Histology at diagnosis[a]						
Serous/adenocarcinoma	87	88	77	85	87	88
Clear cell	6	3	9	2	5	2
FIGO stage III/IV	87	87	81	90	89	96
Grade at diagnosis						
1	5	12	6	2	3	4
2	31	30	22	24	27	35
3	45	52	63	58	63	47
Missing	18	7	9	16	6	14
2 prior chemotherapy regimens	51	55	33	26	46	40
PFI <3 months[b]	27	27	20	27	25	26
ECOG PS						
0	49	63	59	55	54	61
1	40	30	34	32	40	35
2	7	3	6	13	5	4

PFI = platinum-free interval. [a]Multiple answers possible. [b]From last platinum to subsequent PD

PFS: Cohort treated with paclitaxel



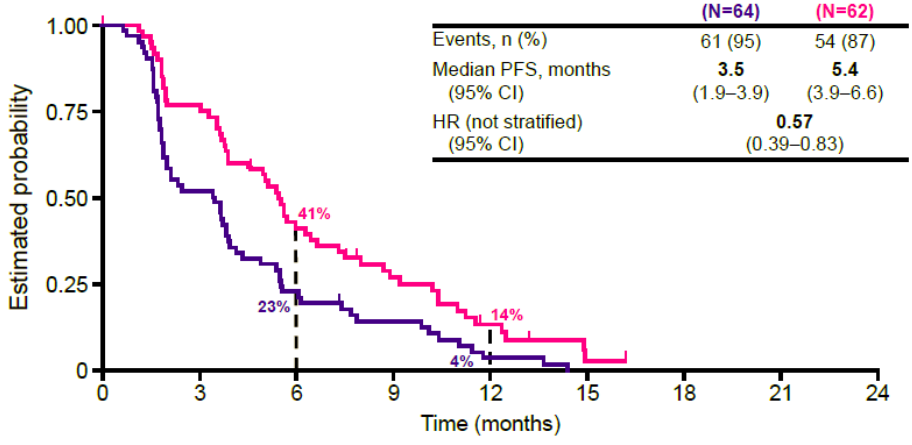
	CT (N=55)	BEV + CT (N=60)
Events, n (%)	49 (89)	37 (62)
Median PFS, months (95% CI)	**3.9** (3.5–5.6)	**10.4** (7.9–11.9)
HR (not stratified) (95% CI)	**0.46** (0.30–0.71)	

No. at risk:

CT	55	39	16	11	6	1	1	0	0
BEV + CT	60	51	38	27	11	3	1	1	0

Median duration of follow-up: 12.7 months (CT arm) vs 12.8 months (BEV + CT arm)

PFS: Cohort treated with PLD



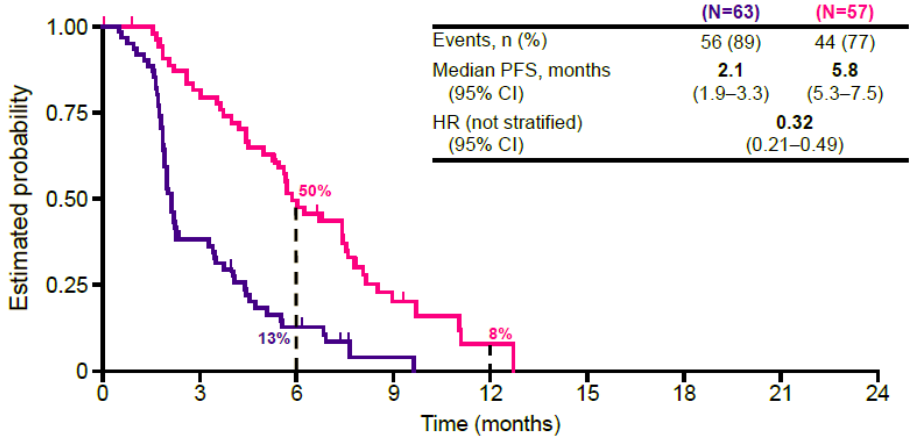
	CT (N=64)	BEV + CT (N=62)
Events, n (%)	61 (95)	54 (87)
Median PFS, months (95% CI)	**3.5** (1.9–3.9)	**5.4** (3.9–6.6)
HR (not stratified) (95% CI)	**0.57** (0.39–0.83)	

No. at risk:

CT	64	32	14	8	2	0	0	0	0
BEV + CT	62	46	24	14	6	1	0	0	0

Median duration of follow-up: 15.8 months (CT arm) vs 16.7 months (BEV + CT arm)

PFS: Cohort treated with topotecan



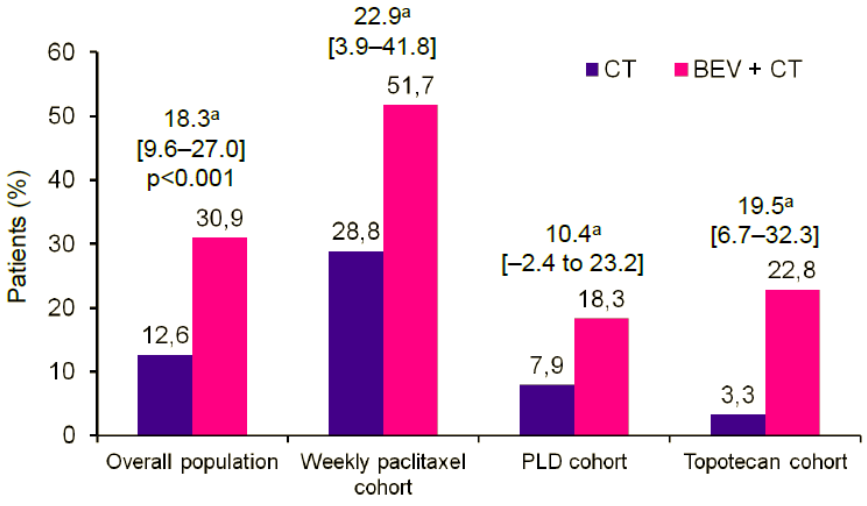
	CT (N=63)	BEV + CT (N=57)
Events, n (%)	56 (89)	44 (77)
Median PFS, months (95% CI)	**2.1** (1.9–3.3)	**5.8** (5.3–7.5)
HR (not stratified) (95% CI)	**0.32** (0.21–0.49)	

No. at risk:

CT	63	22	7	1	0	0	0	0	0
BEV + CT	57	43	26	8	1	0	0	0	0

Median duration of follow-up: 9.0 months (CT arm) vs 10.5 months (BEV + CT arm)

Summary of best overall response rates (RECIST, CA-125 criteria or both)



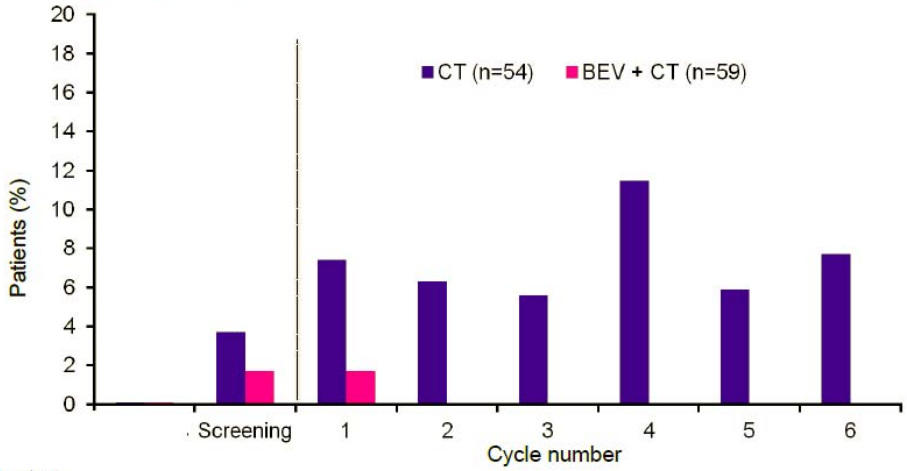
[a]*Difference in overall response rate; 95% CI with Hauck–Anderson continuity correction*

Analysis of subgroup of patients with ascites at baseline

- Of the total study ITT population of 361 patients, 113 (31%) had ascites at baseline according to the eCRF
  - 54 (30%) in the CT arm
  - 59 (33%) in the BEV + CT arm
- Exploratory analyses of efficacy and safety in this subgroup were prespecified
- Data cut-off for these analyses was 14 November 2011

CT = chemotherapy; eCRF = electronic case report form; ITT = intent to treat

Incidence of paracentesis during study therapy: Subgroup of patients with ascites at baseline



No. at risk:								
CT	54	54	54	48	36	26	17	13
BEV + CT	59	59	59	57	52	44	37	32

Data not shown for cycles with <10 patients in one or both arms

Summary

- The primary objective was met
  - PFS HR 0.48 (p<0.001) in favor of BEV combination therapy vs single-agent CT
  - Median PFS: 6.7 vs 3.4 months, respectively
- Significant improvement in ORR
  - 30.9% vs 12.6%, respectively (p=0.001) by RECIST and/or CA-125
- BEV safety profile consistent with previous experience
  - Patients at high risk of GI perforation were excluded from the study
- Overall survival data expected in 2013

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Conclusions

- AURELIA is the first randomized phase III trial in platinum-resistant OC to demonstrate:
  - Benefit with biologic therapy
  - Benefit with a combination regimen versus monotherapy

Bevacizumab combined with chemotherapy should be considered a new standard option in platinum-resistant ovarian cancer

OVAIRE
Récidive platine sensible

VOLUME 30 · NUMBER 17 · JUNE 10 2012

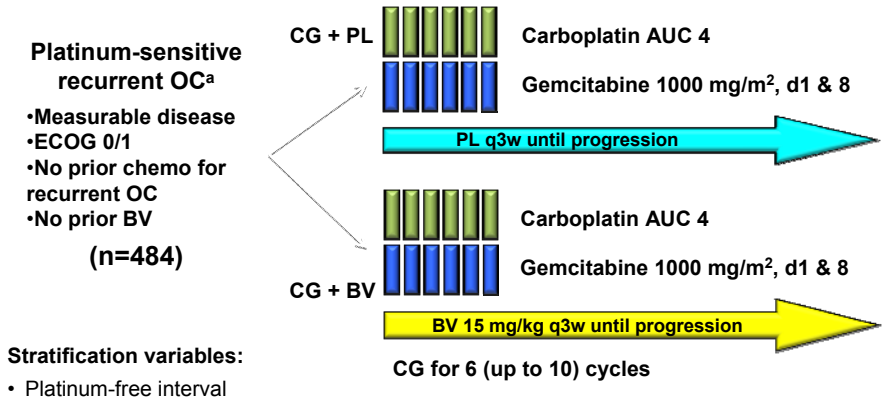
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

OCEANS: A Randomized, Double-Blind, Placebo-Controlled Phase III Trial of Chemotherapy With or Without Bevacizumab in Patients With Platinum-Sensitive Recurrent Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

Carol Aghajanian, Stephanie V. Blank, Barbara A. Goff, Patricia L. Judson, Michael G. Teneriello, Amreen Husain, Mika A. Sovak, Jing Yi, and Lawrence R. Nycum

OCEANS: Study schema



Stratification variables:

- Platinum-free interval (6–12 vs >12 months)
- Cytoreductive surgery for recurrent disease (yes vs no)

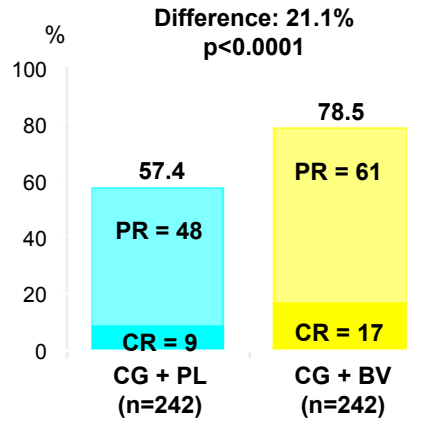
Primary end-point : PFS

BV = bevacizumab; PL = placebo
[a]Epithelial ovarian, primary peritoneal, or fallopian tube cancer

Patient characteristics

Characteristic	CG + PL (n=242)	CG + BV (n=242)
Median age, years (range)	61 (28–86)	60 (38–87)
Age ≥65 years, %	38	35
Race, %		
White	92	90
Other	8	10
ECOG PS 0, %	76	75
Histologic subtype, %		
Serous	84	78
Mucinous/clear cell	3	5
Other	14	17
Platinum-free interval, %		
6–12 months	42	41
>12 months	58	59
Cytoreductive surgery for recurrent disease, %	10	12

Objective response



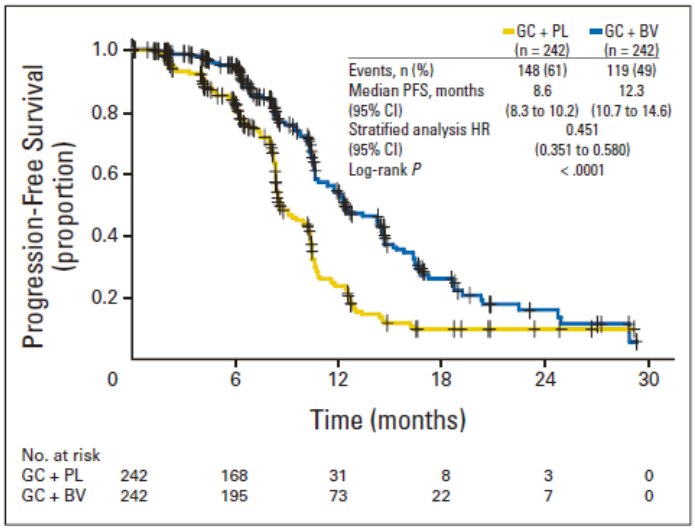


Fig 4. Kaplan-Meier estimates of progression-free survival (PFS) assessed by independent review committee, censoring for non–protocol-specified cancer therapy (randomly assigned patients). BV, bevacizumab; GC, gemcitabine plus carboplatin; HR, hazard ratio; PL, placebo.

Table 2. OS Results to Date

Result	First Interim OS Analysis*		Second Interim OS Analysis†	
	GC + PL (n = 242)	GC + BV (n = 242)	GC + PL (n = 242)	GC + BV (n = 242)
Median OS, months	29.9	35.5	35.2	33.3
95% CI	26.4 to NE	30.0 to NE	29.9 to 40.3	29.8 to 35.5
HR	0.751		1.027	
95% CI	0.537 to 1.052		0.792 to 1.331	

Abbreviations: BV, bevacizumab; GC, gemcitabine plus carboplatin; NE, not estimable; OS, overall survival; PL, placebo.
*Data cutoff date: September 17, 2010.
†Data cutoff date: August 29, 2011.

AEs of special interest

Patients, %	CG + PL (n=233)	CG + BV (n=247)
ATE, all grades	1	3
VTE, grade ≥3	3	4
CNS bleeding, all grades	<1	1
Non-CNS bleeding, grades ≥3	1	6
CHF, grades ≥3	1	1
Neutropenia, grade ≥3	56	58
Febrile neutropenia, grade ≥3	2	2
Hypertension, grade ≥3	<1	17
Fistula/abscess, all grades	<1	2
GI perforation, all grades	0	0[a]
Proteinuria, grade ≥3	1	9
RPLS, all grade	0	1
Wound-healing complication, grades ≥3	0	1

ATE = arterial thromboembolic event; CHF = congestive heart failure; GI = gastrointestinal; RPLS = reversible posterior leukoencephalopathy syndrome; VTE = venous thromboembolic event
[a]Two GI perforations occurred 69 days after last BV dose

OVAIRE
Les anti-parp ??

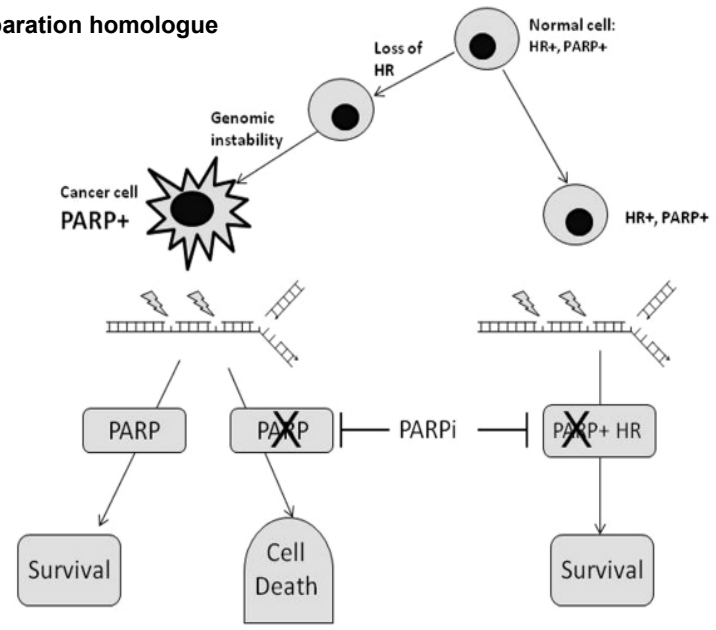
Mécanismes de réparation de l'ADN

- Réparation de l'excision des bases (Coupures simple brin) (BER)
- Réparation de l'excision des nucléotides (NER)
- Recombinaison homologue (coupures double brin)
- Miss Match Repair (Mésappariement)

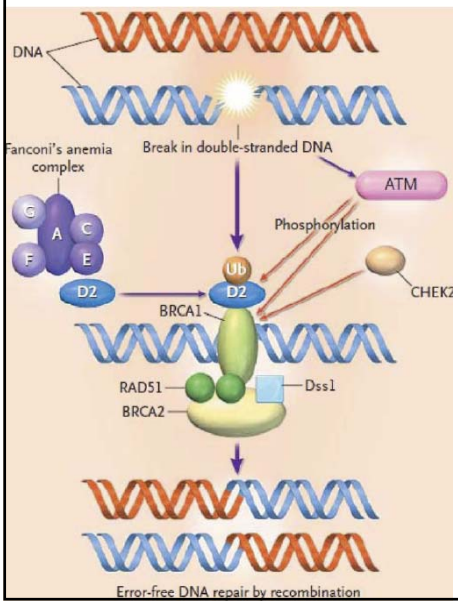
- PARP : 5-2 poly ADP ribose polymérase
- Enzyme impliquée dans la réparation des coupures simple brin d'ADN
- Cellule normale, en cas de protéine PARP non fonctionnelle,

réparation des cassures simples brins par recombinaison homologue

HR= réparation homologue



Protéines impliquées dans la recombinaison homologue



BRCA1/2

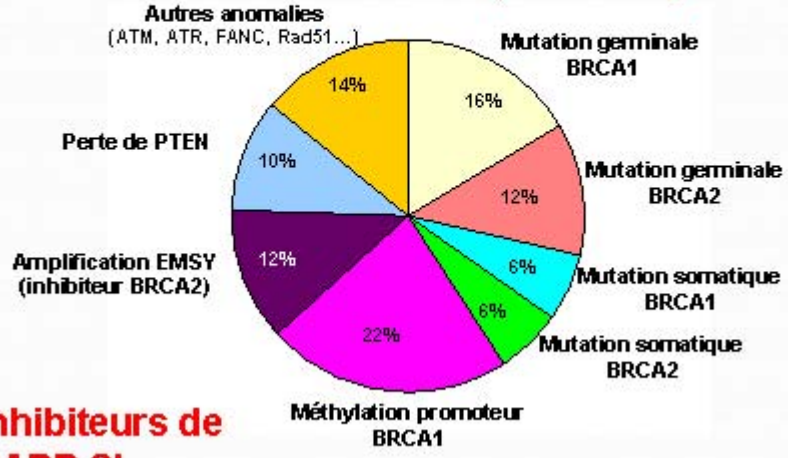
Autres gènes ou protéines impliqués

- PTen
- RAD51
- Gene de l'anémie de Fanconi (FA)
- Gene de l'ATM

Nature, 2011

Déficience de la recombinaison homologue dans les types II

Elle serait **retrouvée dans environ 50% des cas (« BRCAness »)**



➢ **Inhibiteurs de PARP ?!**

Cancer Genome Atlas Research Network, Nature 2011

VOLUME 30 · NUMBER 4 · FEBRUARY 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

Stan B. Kaye, Jan Lubinski, Ursula Matulonis, Joo Ern Ang, Charlie Gourley, Beth Y. Karlan, Amit Amnon, Katherine M. Bell-McGuinn, Lee-May Chen, Michael Friedlander, Tamar Safra, Ignace Vergote, Mark Wickens, Elizabeth S. Lowe, James Carmichael, and Bella Kaufman

See accompanying editorial on page 247

Olaparib monothérapie vs doxorubicine liposomale pégylée

97 patients
BRCA1/BRCA2

Rechute dans les 12 mois suivant le dernier traitement avec platine

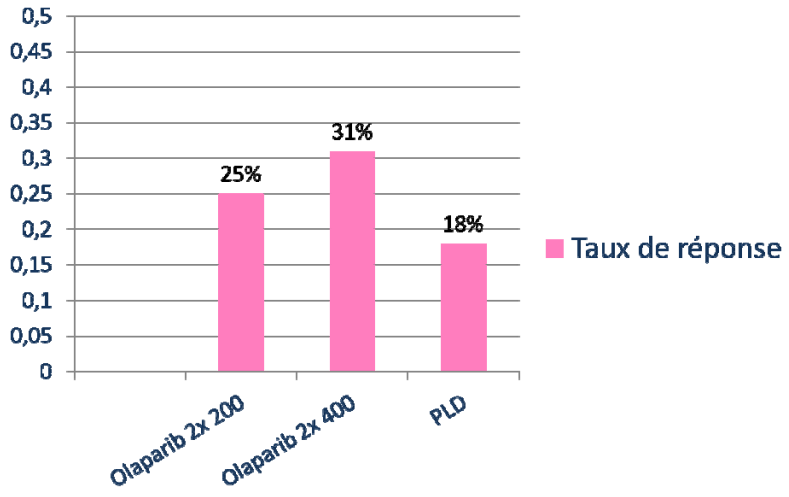
50% résistant aux platines

R

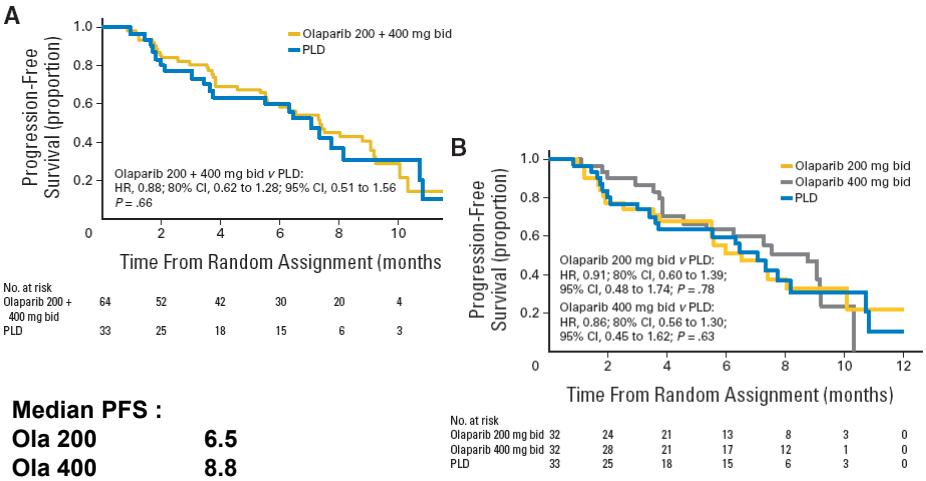
- Olaparib 2x 200 mg
- Olaparib 2x 400 mg
- DLP 50 mg/m²

- Objectif principal = SSP
- Objectifs secondaires = TR, SG, tolérance

Olaparib monothérapie vs doxorubicine liposomale pégylée



SSP



Median PFS :

Ola 200	**6.5**
Ola 400	**8.8**
PLD	**7.1**

Toxicités

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

AE	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	
	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

Abbreviations: AE, adverse event; PLD, pegylated liposomal doxorubicin.
*One patient was randomly assigned to PLD but did not receive it.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer

Jonathan Ledermann, M.D., Philipp Harter, M.D., Charlie Gourley, M.B., Ph.D., Michael Friedlander, M.B., Ph.D., Ignace Vergote, M.D., Ph.D., Gordon Rustin, M.D., Clare Scott, M.B., Ph.D., Werner Meier, M.D., Ph.D., Ronnie Shapira-Frommer, M.D., Tamar Safra, M.D., Daniela Matei, M.D., Euan Macpherson, M.Sc., Claire Watkins, M.A., M.Sc., James Carmichael, M.D., and Ursula Matulonis, M.D.

Avril 2012

Phase 2 maintenance

265 patientes

Tumeur séreuse
Sensible aux sels de platine
≤ 2 lignes préalables

21% BRCA+
15% BRCA-
64% BRCA?

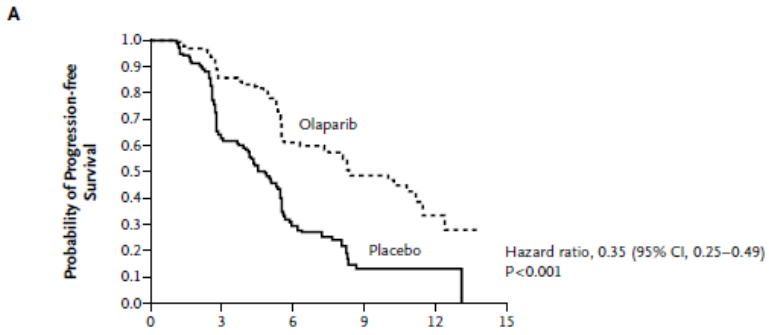
R

Olaparib 2x 400 mg

Placebo

- **Objectif principal = SSP**
- **Objectifs secondaires = SG, TR, tolérance**

PFS


A
Probability of Progression-free Survival
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Olaparib
Placebo
Hazard ratio, 0.35 (95% CI, 0.25–0.49)
P<0.001
0
3
6
9
12
15
Months since Randomization
No. at Risk
Olaparib 136 104 51 23 6 0
Placebo 129 72 23 7 1 0
No. of Patients/ Total No. (%)
60/136 (44.1)
93/129 (72.1)
Median Progression-free Survival (mo)
8.4
4.8