Actualités médicales et cancers de l'ovaire

Pr Florence JOLY, CFB, Caen

Centre de Lutte contre le Cancer François Baclesse

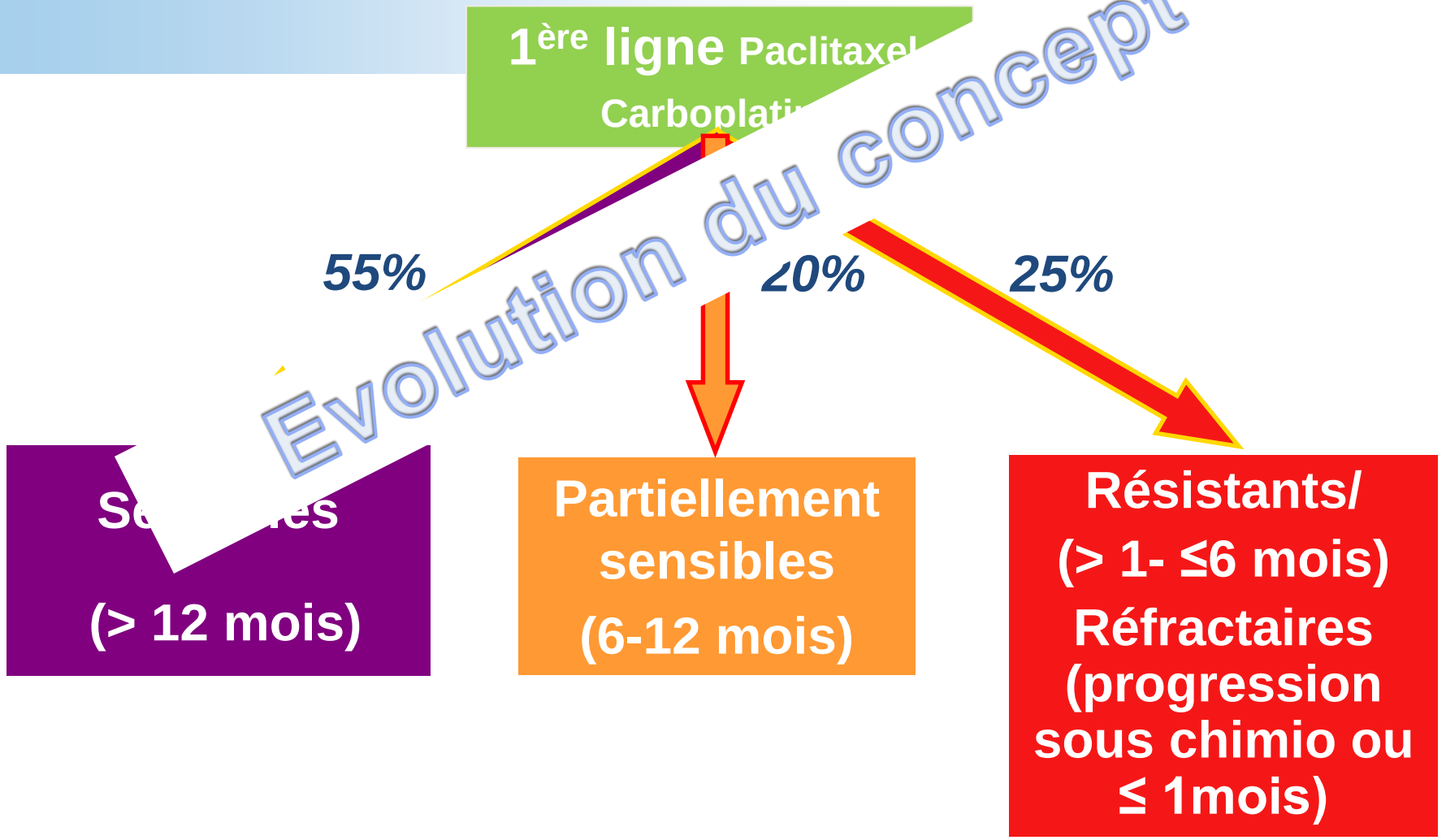
Journée inter-régionale Laurence Leroyer , 11ème édition, *Rennes, 18 Mai 2018*

La rechute

- **Des nouveautés**

- **Changement de paradigme**
- **L'intégration de la QDV**
- **Les inhibiteurs de Parp**

Intervalle libre sans platine débattu



Friedlander 2011; (4ème conférence de consensus sur les cancers de l'ovaire (Vancouver 2010)

The challenge of defining platinum-resistance

Based exclusively on TFIp (4th OCCC)

Platinum-

- Refractory: < 4 weeks
- Resistant: < 6 months
- Partially sensitive: 6-12 months
- Fully sensitive: > 12 months

Based on the possibility of platinum re-challenge (5th OCCC)

- Platinum is an option
- Platinum is not an option
  - Short platinum free interval (at least 6 months) based on RECIST or symptoms
  - Progression during platinum
  - Allergy to platinum
- Notion d'une variable continue (reci tardive> 1 an)

Wilson MK, et al. Ann. Oncol 2017; 28(4): 727–732

GUIDELINES ESMO 2018

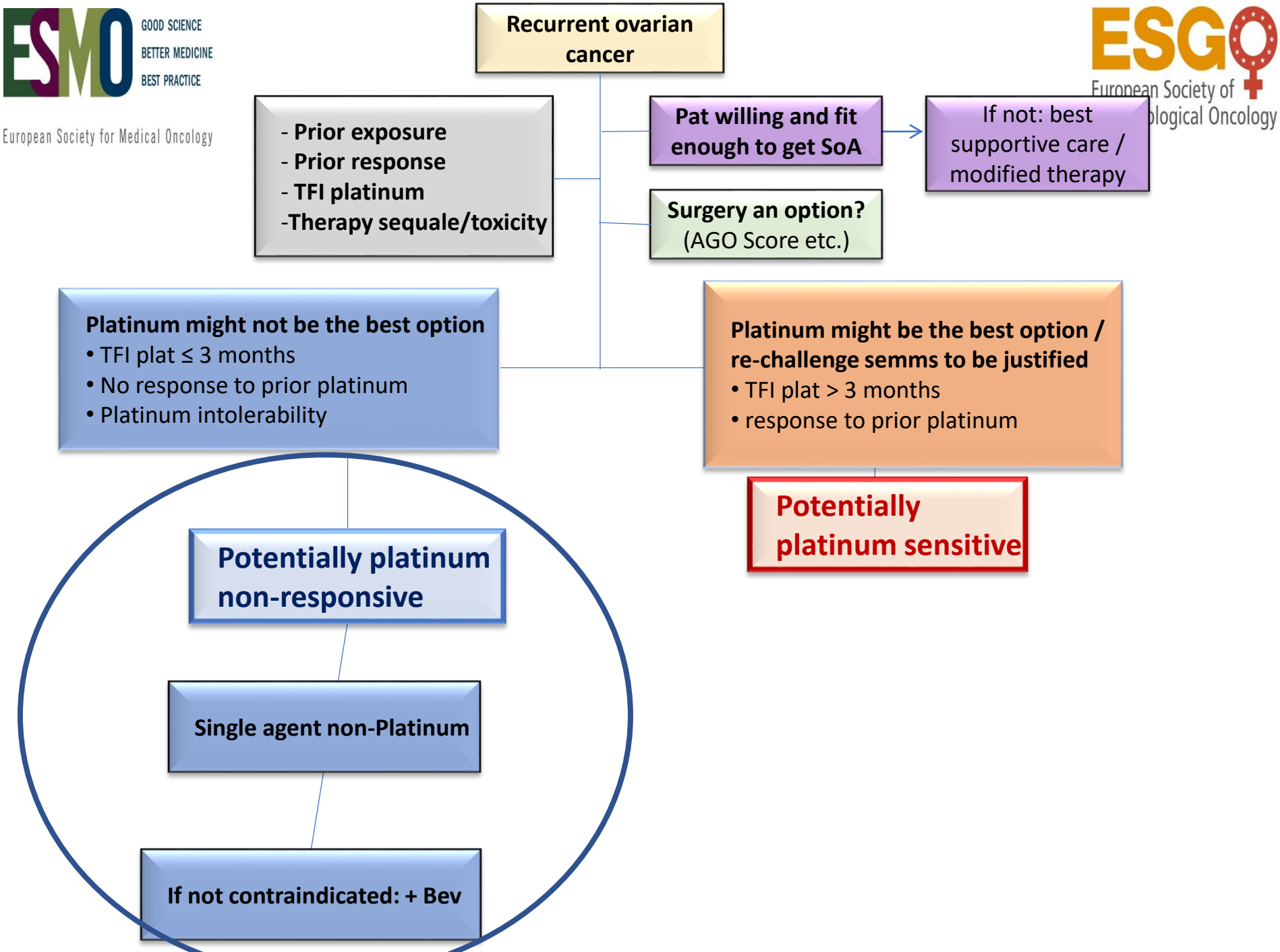
Classificaction of platinum-resistance AFTER platinum therapy

PLATINUM-RESPONDER:

Patient achieved OR as best response

PLATINUM NON-RESPONDER:

Patient not achieved OR as best response or relapse < 3 months


GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE
European Society for Medical Oncology
Recurrent ovarian cancer
- Prior exposure
- Prior response
- TFI platinum
-Therapy sequale/toxicity
Pat willing and fit enough to get SoA
If not: best supportive care / modified therapy
Surgery an option? (AGO Score etc.)
Platinum might not be the best option
• TFI plat ≤ 3 months
• No response to prior platinum
• Platinum intolerability
Platinum might be the best option / re-challenge semms to be justified
• TFI plat > 3 months
• response to prior platinum
Potentially platinum sensitive
Potentially platinum non-responsive
Single agent non-Platinum
If not contraindicated: + Bev
European Society of Gynaecological Oncology

Essais randomisés : rechute « précoce » : « platine non répondeuse »

- **Mono-chimiothérapie = drogues d'efficacité équivalente avec des profils de toxicités différents**
  - Topotecan *vs*. Treosulfan
  - Topotecan *vs*. Paclitaxel
  - Topotecan *vs*. Doxorubicine liposomale pégylée (DLP)
  - Gemcitabine *vs*. DLP
  - Paclitaxel *vs DLP*
- **Polychimiothérapie = efficacité identique à la monochimiothérapie mais plus toxiques**
- **Intégration précoce de la QDV dans le choix thérapeutique**

Recos St Paul , Pautier et al, Bull cancer 2017

PREDICTION D'ARRÊT PRÉCOCE DE LA CT ET DE SURVIE COURTE CANCER DE L'OVAIRE RESISTANTS /REFRACTAIRES
The GCIG Symptom Benefit Study

545 PRROC

19% stopped within 8 weeks

- disease progression (46%)
- patient preference (12%)
- adverse events (7%)
- clinician preference (6%)
- other (11%)
- Death (18%)

Median PFS 1.2 months

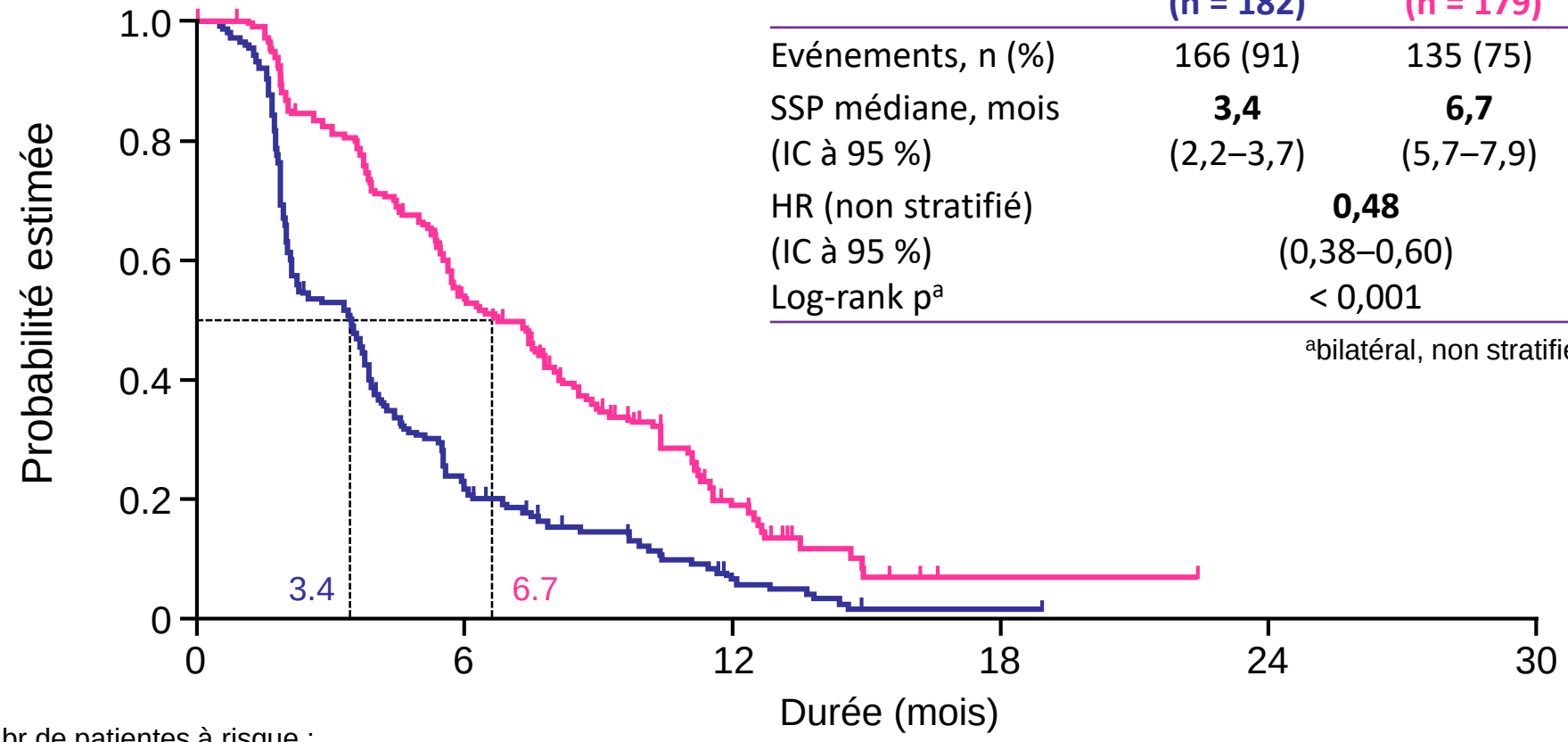
Median OS 2.9 months

Role Funtion and Physical Function were independent predictors in multivariate analysis

Roncolato et al. Oncologist 2017

Essai AURELIA: Ajour du beva à une mono-chimio en cas de rechute précoce (< 6 mois)

Survie sans progression



	CT (n = 182)	BEV + CT (n = 179)
Evénements, n (%)	166 (91)	135 (75)
SSP médiane, mois (IC à 95 %)	**3,4** (2,2–3,7)	**6,7** (5,7–7,9)
HR (non stratifié) (IC à 95 %)	**0,48** (0,38–0,60)	
Log-rank p[a]	< 0,001	

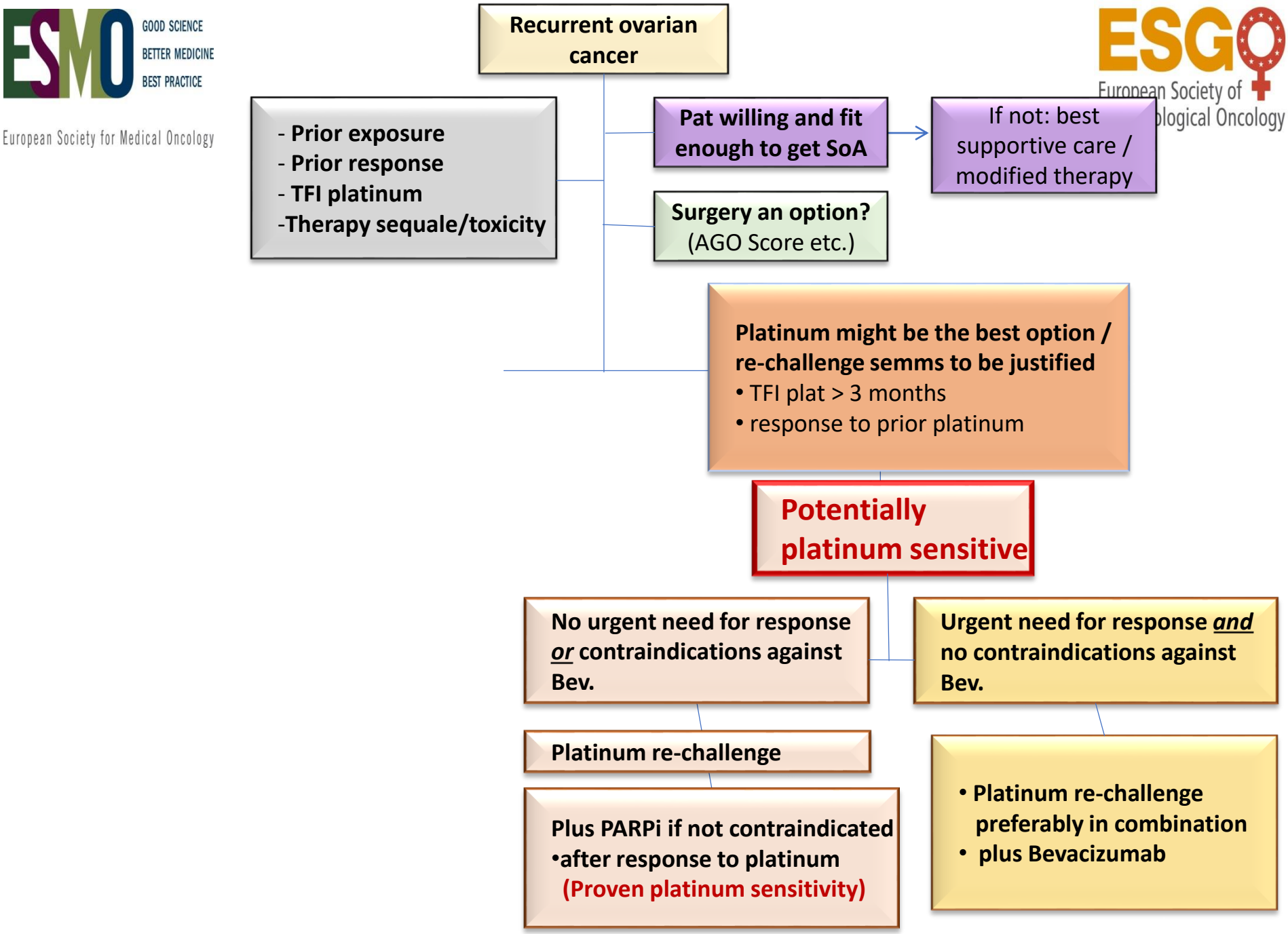
[a]bilatéral, non stratifié

Nbr de patientes à risque :

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

Durée médiane du suivi : 13.9 mois (bras CT) vs 13.0 mois (BEV + bras CT)

Pujade-lauraine, JCO 2014


Recurrent ovarian cancer
- Prior exposure
- Prior response
- TFI platinum
-Therapy sequale/toxicity
Pat willing and fit enough to get SoA
If not: best supportive care / modified therapy
Surgery an option? (AGO Score etc.)
Platinum might be the best option / re-challenge semms to be justified
• TFI plat > 3 months
• response to prior platinum
Potentially platinum sensitive
No urgent need for response or contraindications against Bev.
Urgent need for response and no contraindications against Bev.
Platinum re-challenge
Plus PARPi if not contraindicated
•after response to platinum
(Proven platinum sensitivity)
• Platinum re-challenge preferably in combination
• plus Bevacizumab

Essais randomisés: rechute « platine sensible »

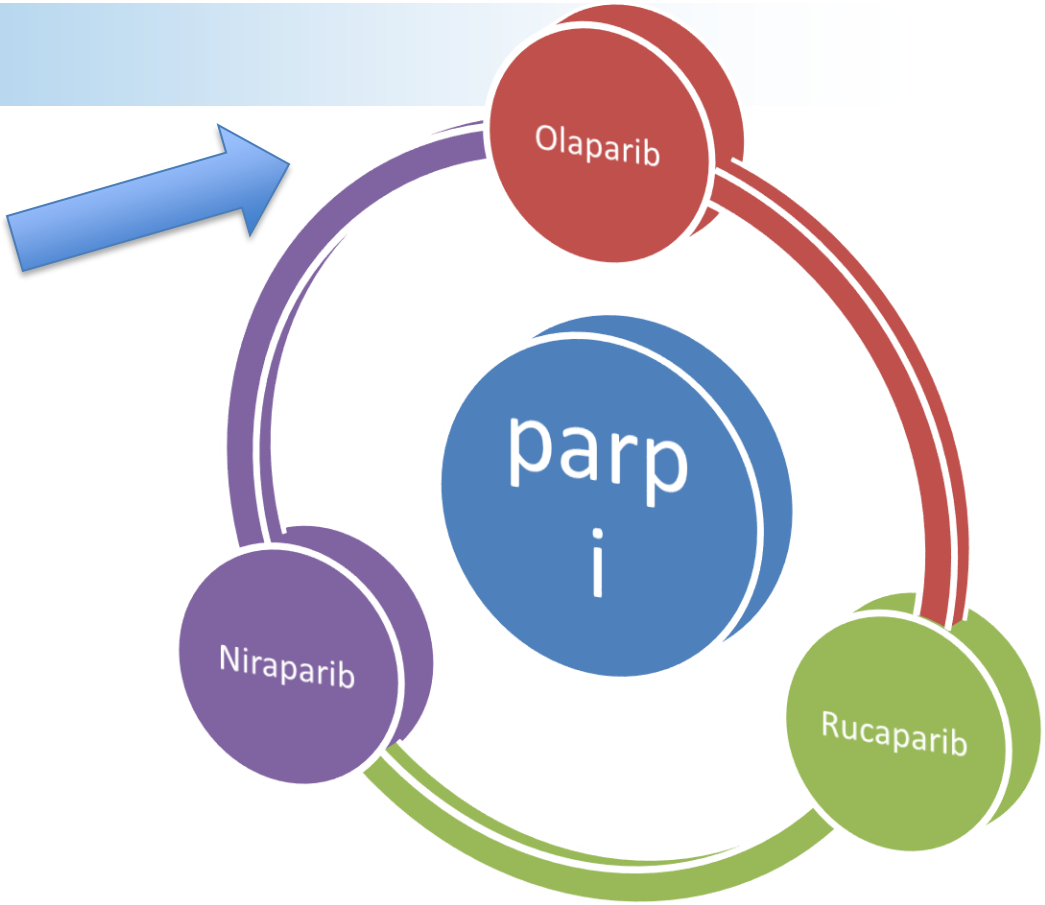
Etudes Randomisées	ICON4 [1] Pacli-Platine Vs Platine	AGO OVAR2.5 [2] Gem Carbo Vs carbo	GEICO [3] Pacli-Carbo Vs Carbo	OVA 301 [4] Trabectedine -DLP vs DLP	CALYPSO [5] DLP-carbo vs pacli-carbo	OCEANS [6] Gem-carbo vs Gem-carbo-beva	GOG213 Pacli-carbo vs pacli-carbo-beva
Nbres ptes ILSP > 12 ILSP 6-12 ILSP < 6	802 77% 33 0	356 60 40 0	81 57	2 35	974 65 35 0	484 58 42 0	
TR (%)	66 vs 54 NS		75 vs 50 **S**	30 vs 19 **S**	ND	57.4vs 78.5 **S**	
Médiane SSP (mois)	12 v **S**	8.6 vs 5.8 **S**	12.2 vs 8.4 **S**	9.7 vs 7.5 **S**	11.3 vs 9.4 **S** Non infériorité	8.4 vs 12.4 **S**	
Médiane SG (mois)	29 vs 24 **S**	18 vs 17.3 NS	ND	20.5 vs 19.4 (Platine S et R) NS	31,5 mo li	NS	**42.2 vs 37.3** NS
Médiane SSP 6-12 (mois)	**ND**	**7.9 vs 5.2** **S**		**S**	**9.4 vs 8.8** **S**	**11.9 vs 8** **S**	**10.4 vs 13.8** **S**
Médiane SG (mois) **6-12 mois** **> 12 mois**				**22.4 vs 16.4 (S)** **36.5 vs 31.7 (NS)**			

Combo avec platine

Combo carbo-gemsar (ou Paclitaxel) -beva

S : significatif, NA : Non atteinte, NS : Non significatif, ND : Non déterminé

La confirmation des inhibiteurs de Parp



Olaparib - maintenance
BRCA muté et BRCAness Olaparib *vs* placebo

- **Etude 19 - Phase II**

265 patientes

Tumeur séreuse
Sensible aux sels de platine
≤ 2 lignes préalables

23% BRCA+
13% BRCA-
64% BRCA?

R

Olaparib 2 x 400 mg

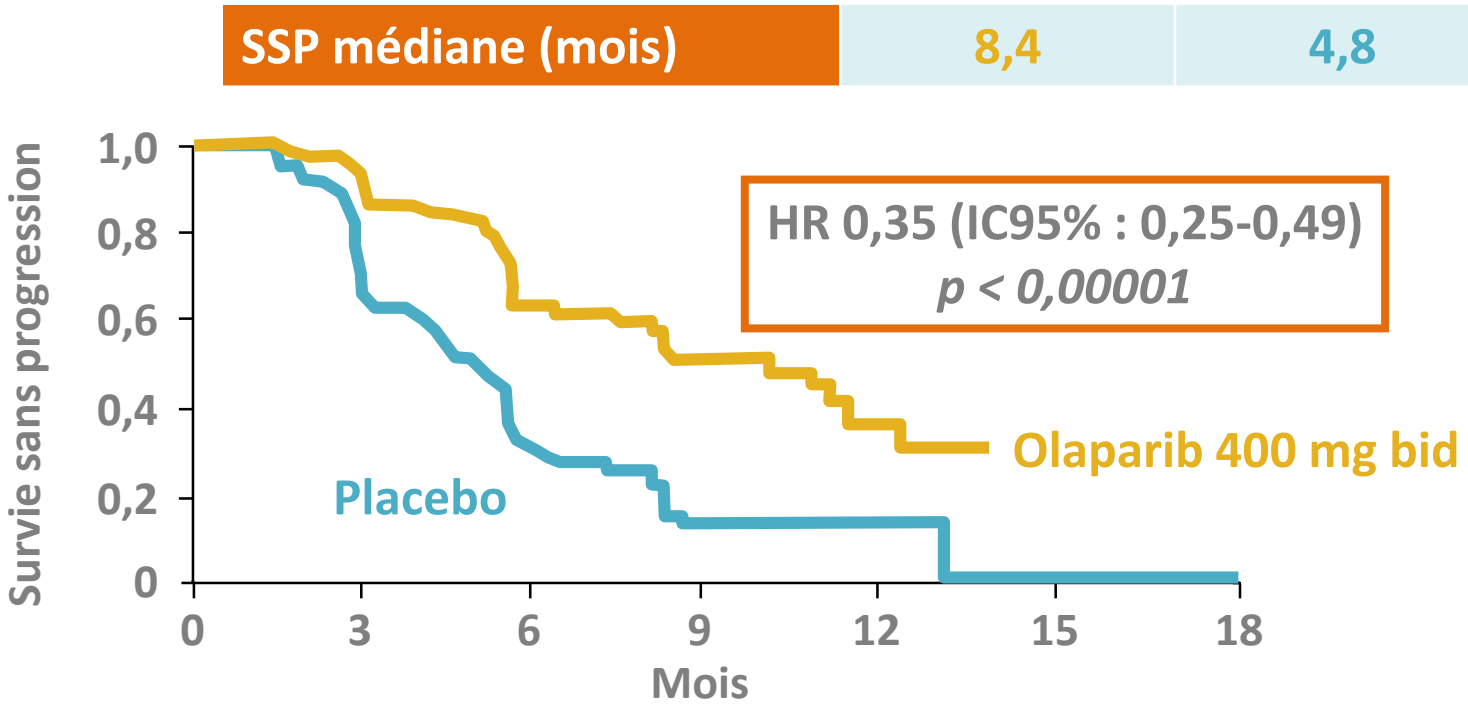
Placebo

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

Lederman JA et al. NEJM 2012

PARPi : olaparib maintenance, monothérapie

- **Survie sans progression**

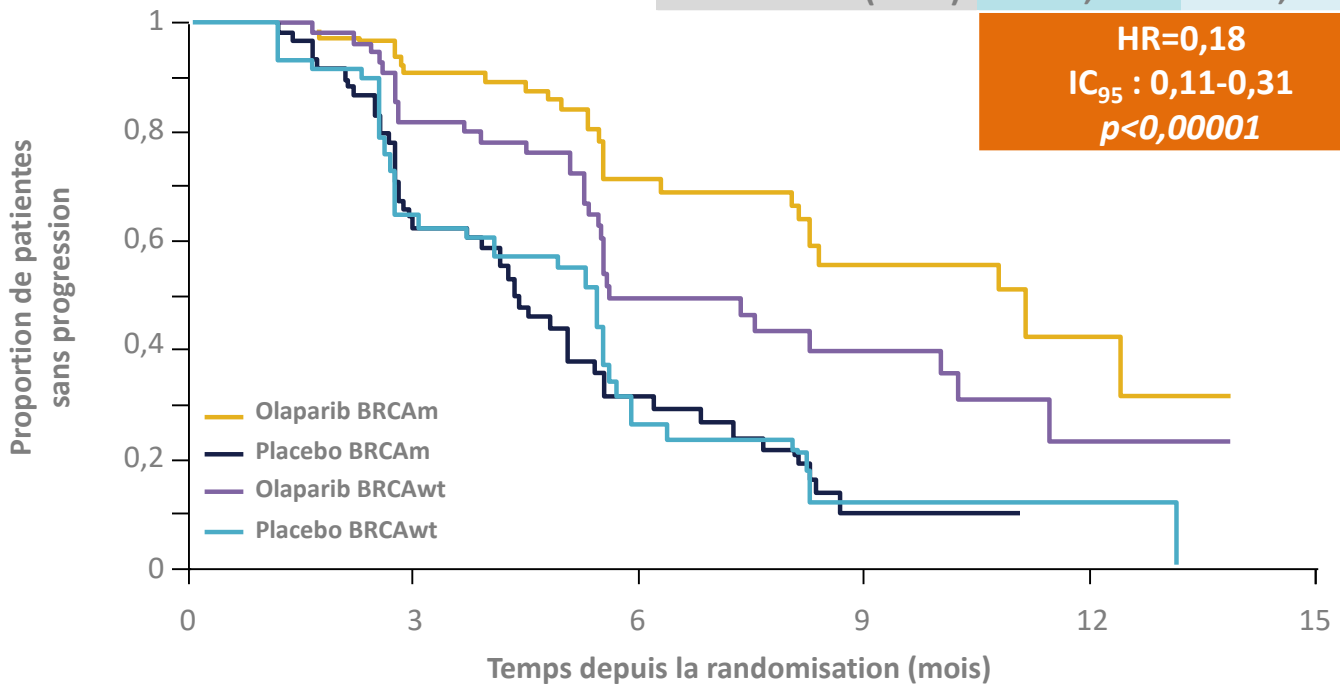


Lederman JA et al. NEJM 2012

Olaparib : Etude 19

- **Survie sans progression par statut BRCAm**

	BRCAm (n=136)		BRCAwt (n=118	
	Olaparib	Placebo	Olaparib	Placebo
Evt total, n (%)	26:74 (35,1)	46:62 (74,2)	32:57 (56,1)	44:61 (72,1)
SSP médiane (mois)	11,2	4,3	5,6	5,5
	HR=0,18 IC_{95} : 0,11-0,31 *p<0,00001*		HR=0,53 $IC9_5$: 0,33-0,84 *p=0,007*	

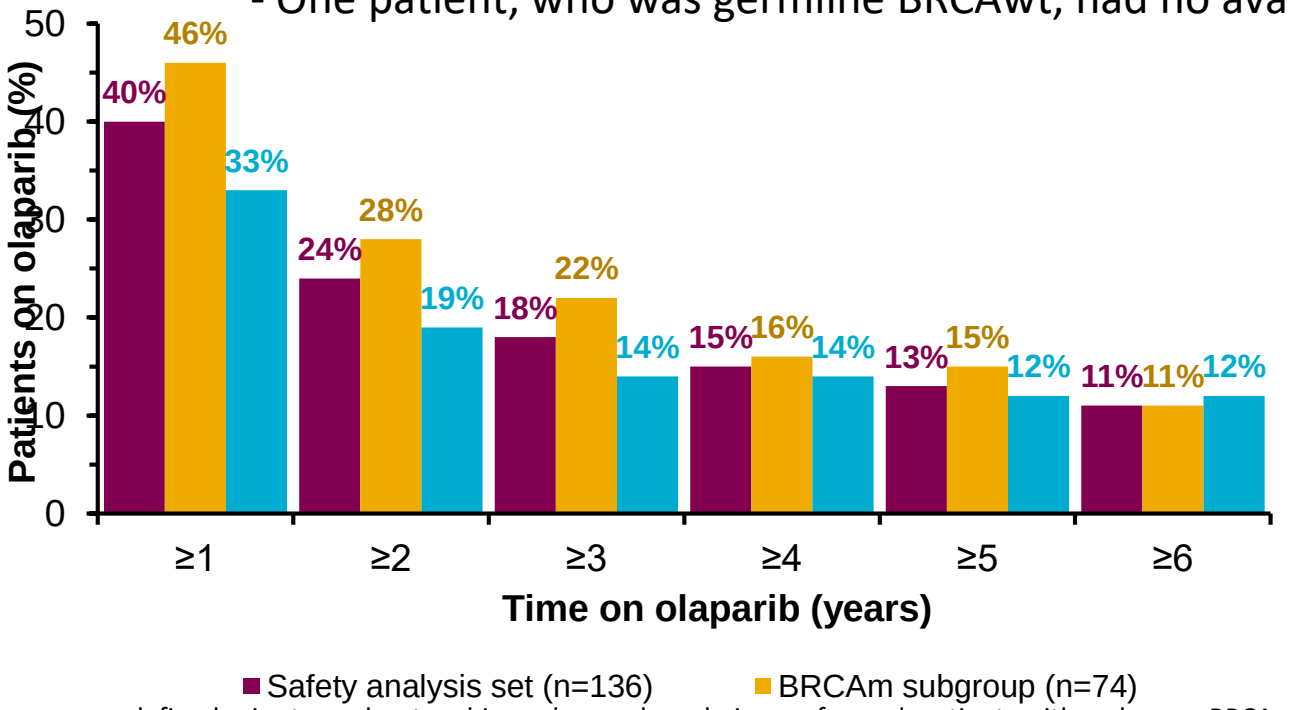


Ledermann et al . NEJM 2012

Bénéfice à long terme : 11% de patientes (15pts) sous TT ≥6 years[1]

Of these 15 patients

- Nine patients had a BRCAm, three of whom had a sBRCAm and slight preponderance of BRCA2 mutations was observed
- Five patients were BRCAwt (1-RAD51B, some without HRR, and 1-HRD negative)
- One patient, who was germline BRCAwt, had no available tumor test results



Subgroups were defined prior to exploratory biomarker analyses being performed; patients with no known *BRCA*m or a variant of unknown significance were classified as *BRCA*wt, and one patient with no known *BRCA*m who received olaparib treatment for ≥6 years was found to have a s*BRCA*m in subsequent Myriad tumor testing

DCO: May 2016

1. Gourley C et al. J Clin Oncol 35, 2017 (suppl; poster related to abstr 5533)

Etude SOLO2 : Etude de phase 3 : Maintenance par Olaparib (nvelle formulation) , platine sensible, mutation BRCA

Patients

- *BRCA1/2* mutation
- Platinum-sensitive relapsed ovarian cancer
- At least 2 prior lines of platinum therapy
- CR or PR to most recent platinum therapy

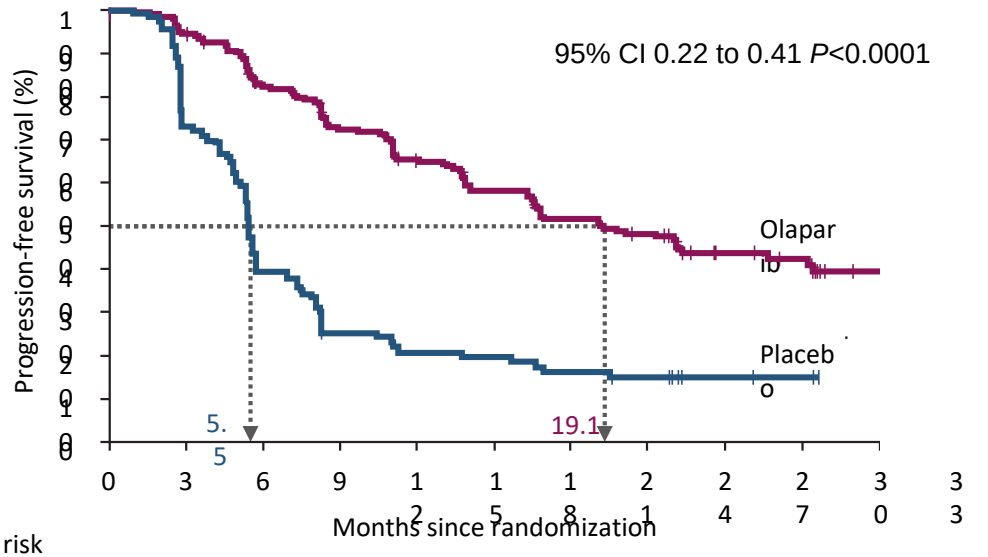
Randomized 2:1

- Olaparib 300 mg bid n=196
- Placebo n=99

→ **Primary endpoint**: Investigator-assessed PFS

	Olaparib (n=196)	Placebo (n=99)
Events (%)	107 (54.6)	80 (80.8)
Median PFS, months	19.1	5.5
HR 0.30		

95% CI 0.22 to 0.41 *P*<0.0001



No. at risk

Olaparib	1	1	1	1	1	1	8	8	3	2	3	2
	9	9	5	3	1	0	9	2	2	9	0	0
	6	2	6	4	8	4	1	1	7	6		
	9	7	3	2	1	1	4	2				
Placebo	9	0	7	2	8	7						

- Key secondary endpoints:
  - Time to first subsequent therapy or death (TFST),
  - Time to second progression (PFS2),
  - Time to second subsequent therapy or death (TSST),
  - Overall survival (OS)
  - Safety, health-related quality of life (HRQoL*)

Pujade-Lauraine et al. Lancet Oncology 2017 Sep;18(9):1274-1284

Circuit de prescription et de rendu des résultats des tests BRCA dans le cadre de l'AMM Olaparib (Gladieff et al Bull Cancer 2017)

Accord d'experts avec le Groupe Génétique et Cancer

Cancer de l'ovaire (haut grade)

Rechute sensible

Circuit rapide
coordination consultations et laboratoires correspondants

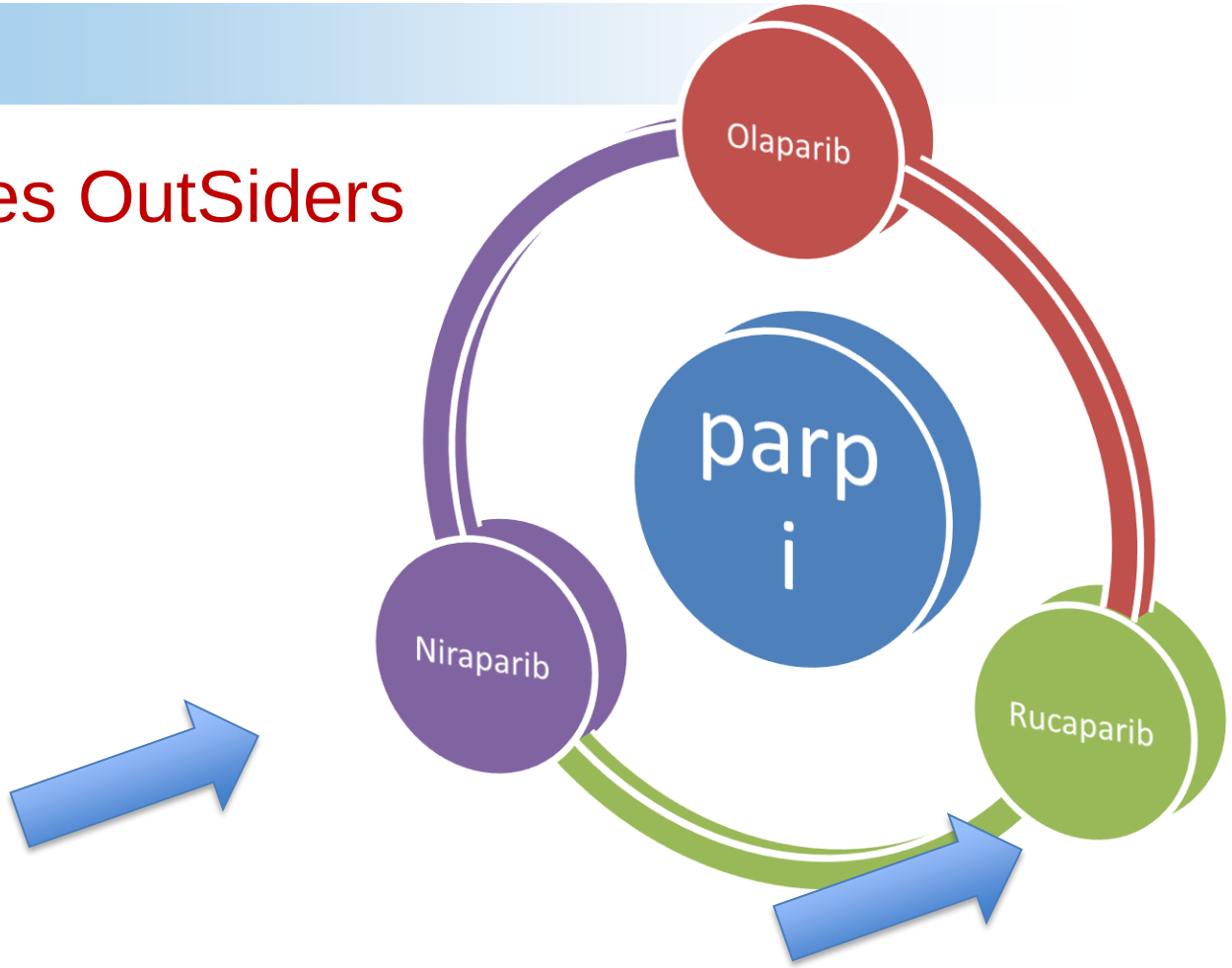
1-2 mois

***Statut BRCA* constitutionnel inconnu**	***Pas de mutation BRCA constitutionnelle identifiée****
Consultation d'oncogénétique **rapide** (< 15j) et étude constitutionnelle **rapide**	**Initier l'analyse tumorale via l'oncologue**
En parallèle, initier l'analyse **tumorale via l'oncologue ou l'oncogénéticien**	Les résultats de la recherche tumorale sont rendus par l'oncologue; Le résultat est transmis à l'oncogénéticien et au laboratoire génétique constitutionnelle
Les résultats de la recherche tumorale peuvent être rendus par l'oncologue qui doit s'assurer qu'une consultation d'oncogénétique est prévue	

*pas d'indication à réaliser une recherche tumorale en cas de mutation constitutionnelle connue de *BRCA* . *Si analyse ancienne, reconsidérer en parallèle une nouvelle analyse constitutionnelle*

La confirmation des inhibiteurs de Parp

Les OutSiders

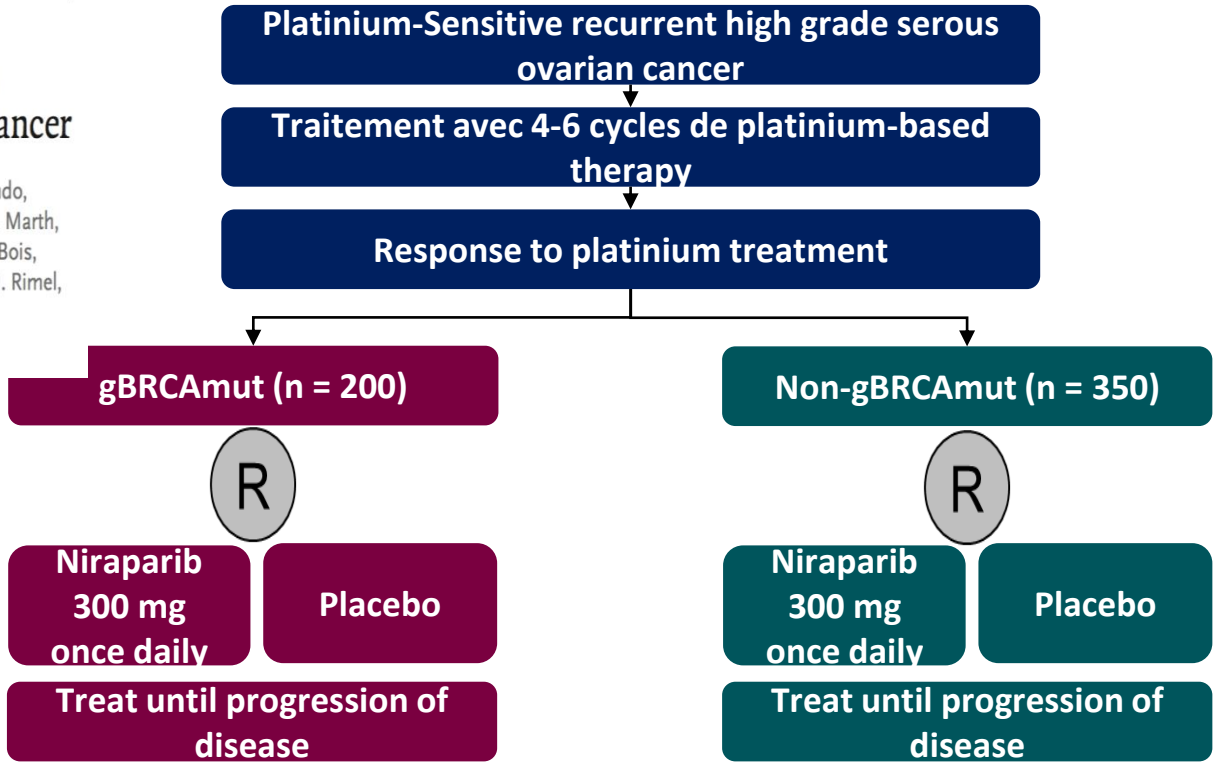


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer

M.R. Mirza, B.J. Monk, J. Herrstedt, A.M. Oza, S. Mahner, A. Redondo, M. Fabbro, J.A. Ledermann, D. Lorusso, I. Vergote, N.E. Ben-Baruch, C. Marth, R. Mądry, R.D. Christensen, J.S. Berek, A. Dørum, A.V. Tinker, A. du Bois, A. González-Martín, P. Follana, B. Benigno, P. Rosenberg, L. Gilbert, B.J. Rimel, J. Buscema, J.P. Balser, S. Agarwal, and U.A. Matulonis, for the ENGOT-OV16/NOVA Investigators*



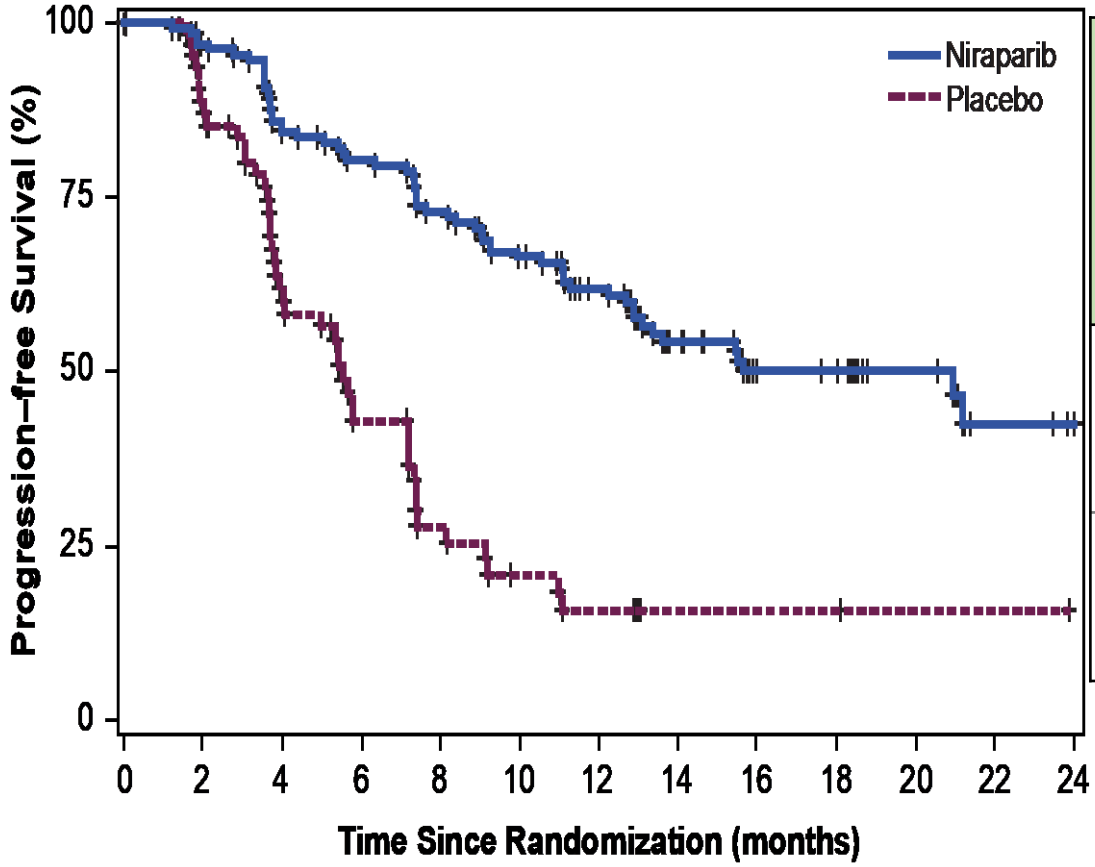
Primary Endpoint : PFS by central, blinded review

Tested at 100 events to achieve p < 0,05

HRDpos population
Tested at 100 events to achieve p<0.05;
If test was positive then:
Test overall non-gBRCAmut cohort (p<0.05)

ENGOT-OV16 / NOVA

Progression-free Survival: gBRCAmut



Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=138)	**21.0** (12.9, NR)	**0.27** (0.173, 0.410) p<0.0001	62 %	**50%**
Placebo (N=65)	**5.5** (3.8, 7.2)		16 %	16%

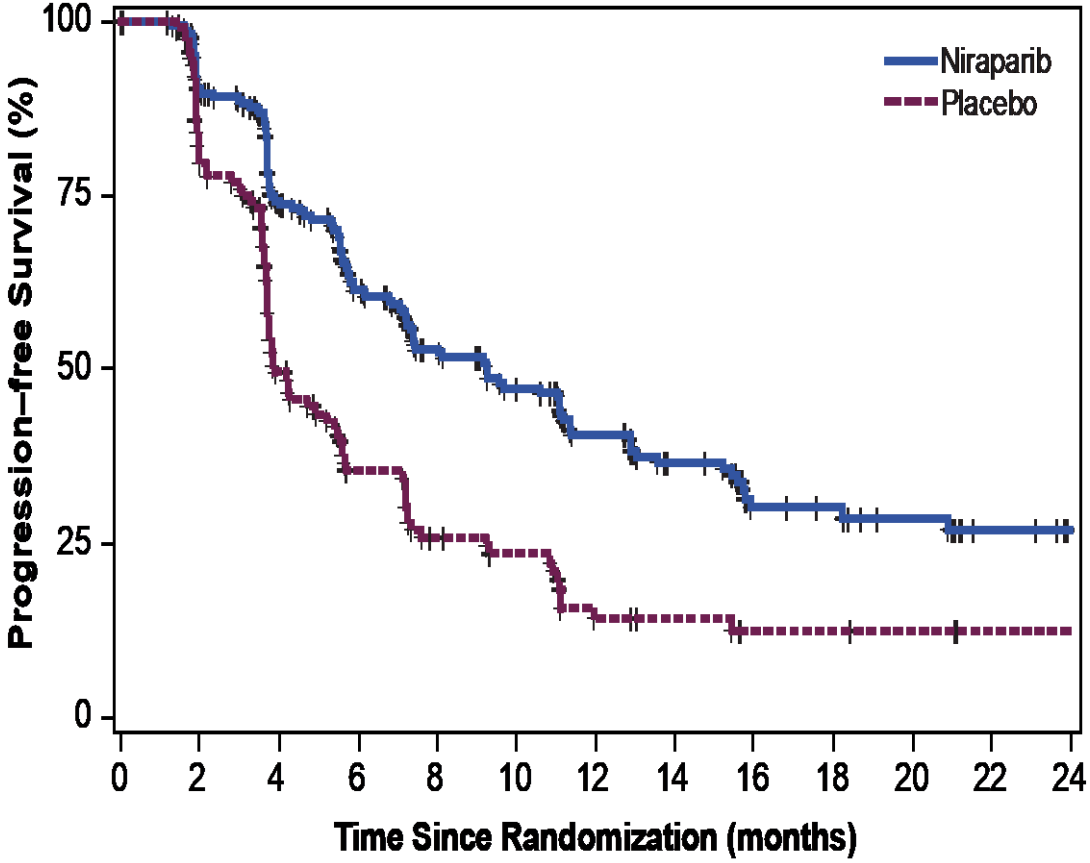
PFS was analyzed using a 2-sided log-rank test using randomization stratification factors, and summarized using the Kaplan-Meier methodology. Hazard ratios with 2-sided 95% confidence intervals were estimated using a stratified Cox proportional hazards model, with the stratification factors used in randomization.

NR=not reached

Mirza *et al*. N Engl J Med 2016;375:2154-64

ENGOT-OV16 / NOVA

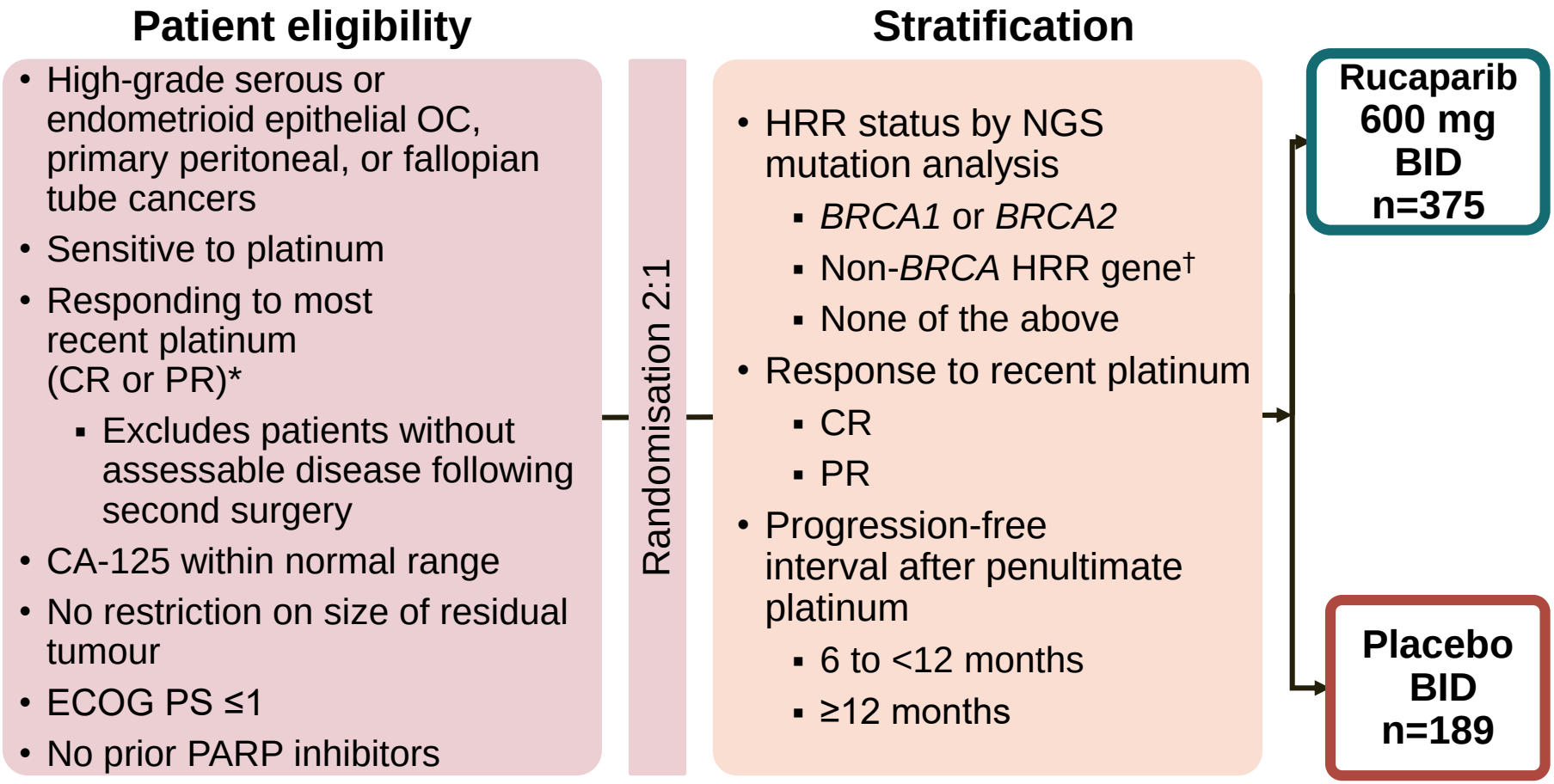
Progression-free Survival: Non-gBRCAmut



Treatment	PFS Median (95% CI) (Months)	Hazard Ratio (95% CI) p-value	% of Patients without Progression or Death	
			12 mo	18 mo
Niraparib (N=234)	**9.3** (7.2, 11.2)	**0.45** (0.338, 0.607) p<0.0001	41 %	**30%**
Placebo (N=116)	**3.9** (3.7, 5.5)		14 %	12%

PFS was analyzed using a 2-sided log-rank test using randomization stratification factors, and summarized using the Kaplan-Meier methodology. Hazard ratios with 2-sided 95% confidence intervals were estimated using a stratified Cox proportional hazards model, with the stratification factors used in randomization.

ARIEL3: Study Design

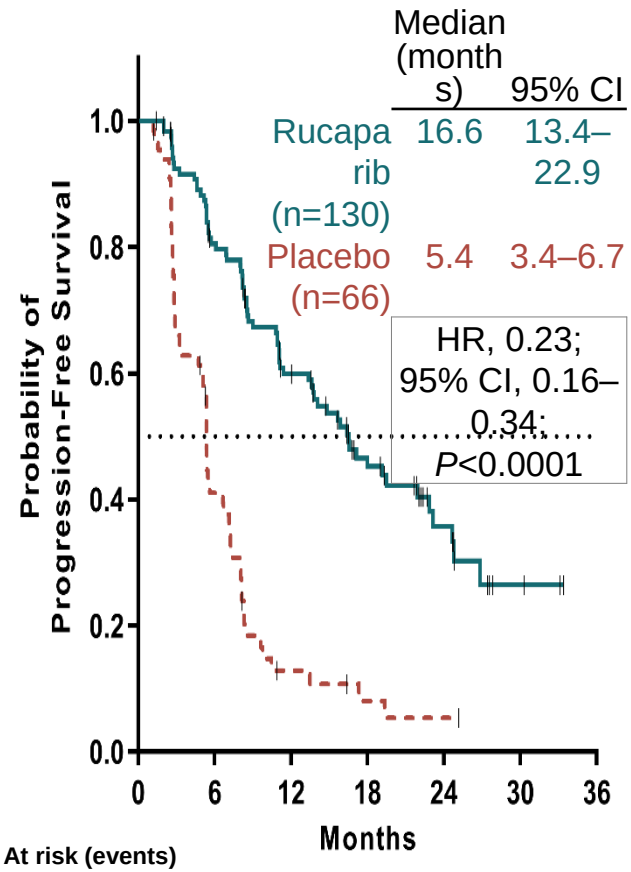


*CR (defined by RECIST v1.1) or PR (defined by RECIST v1.1 and/or a GCIG CA-125 response [CA-125 within normal range]) maintained until entry to ARIEL3 (≤8 weeks of last dose of chemotherapy). †*ATM, ATR, ATRX, BARD1, BLM, BRIP1, CHEK1, CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, MRE11A, NBN, PALB2, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD52, RAD54L, RPA1.*
HRR, homologous recombination repair; NGS, next-generation sequencing.

Coleman *et at.,* Lancet. 2017 Oct 28;390(10106):1949-1961

ARIEL3: PFS

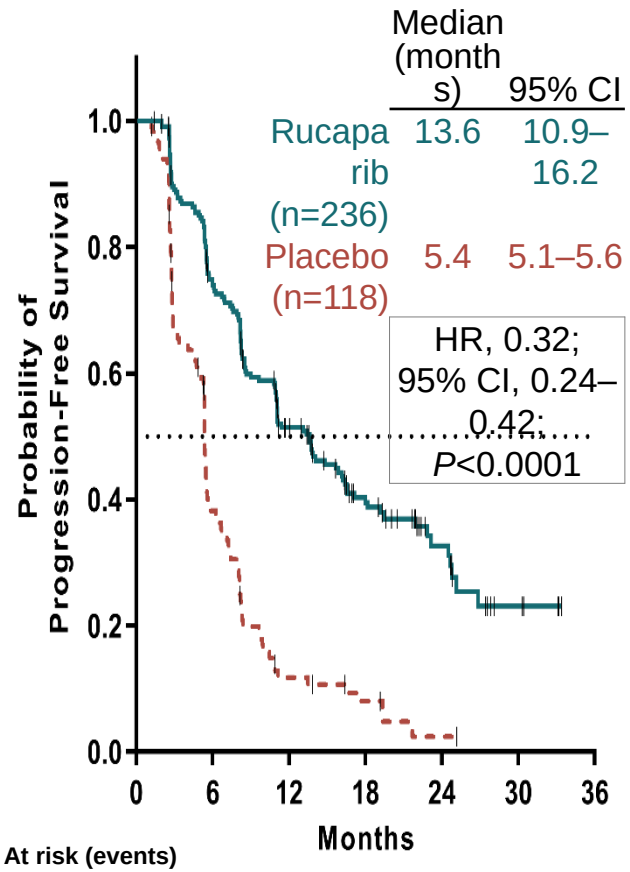
BRCA mutant



At risk (events)							
Rucaparib	130 (0)	93 (23)	63 (46)	35 (58)	15 (64)	3 (67)	0 (67)
Placebo	66 (0)	24 (37)	6 (53)	3 (55)	1 (56)	0 (56)	

Rucaparib, 48% censored Placebo, 15% censored

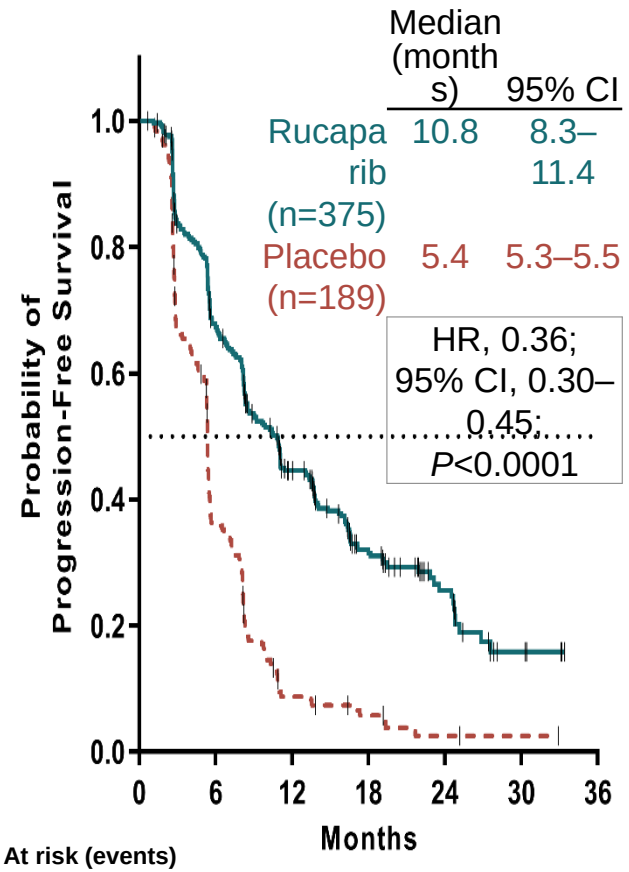
HRD



At risk (events)							
Rucaparib	236 (0)	161 (55)	96 (104)	54 (122)	21 (129)	5 (134)	0 (134)
Placebo	118 (0)	40 (68)	11 (95)	6 (98)	1 (101)	0 (101)	

Rucaparib, 43% censored Placebo, 14% censored

ITT



At risk (events)							
Rucaparib	375 (0)	228 (111)	128 (186)	65 (217)	26 (226)	5 (234)	0 (234)
Placebo	189 (0)	63 (114)	13 (160)	7 (164)	2 (167)	1 (167)	0 (167)

Rucaparib, 38% censored Placebo, 12% censored

Visit cutoff date: 15 April 2017.

PARPI IN MAINTENANCE SETTINGS

	SOLO2 (olaparib tablets)	NOVA (niraparib)	ARIEL3 (rucaparib)
Patients population	Germline BRCAmut Platinum sensitive and responsive	Germline BRCA^{mut} Platinum sensitive Responsive HRD + (My Choice Myriad)	Germline BRCA^{mut} Platinum sensitive Responsive LOH high (FMI)
		(Primary Endpoint)	Endpoint)
PFS non gBRCA	NA	Non gBRCA: 3.9 vs 9.3 mths HR 0.27 HRD +: 3.8 vs 12.9 HR 0.38 HRD - : 3.8 vs 6.9 HR 0.58	LOH high: 5.4 vs 9.7 HR 0.44 LOH low : 5.4 vs 6.7 months HR 0.58

Olaparib:

- **EMA label (capsules): maintenance in recurrent PS, g+s mBRCA OC**
- **FDA label (capsules): maintenance in recurrent mutated OC & gmBRCA ovarian cancer, 3+ previous lines, regardless of platinum sensitivity**
- **FDA label (tablets): maintenance in recurrent PS patients regardless of BRCA mutation**

Niraparib

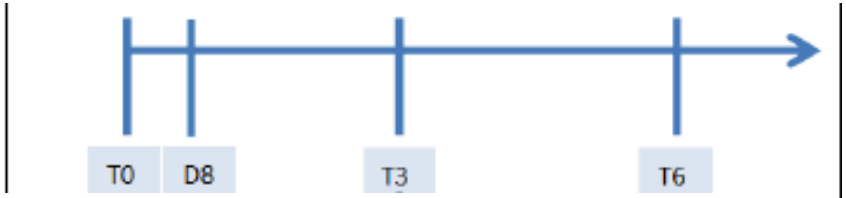
- **FDA label: maintenance in recurrent PS patients regardless of BRCA mutation**
- **EMA label : maintenance in recurrent PS patients regardless of BRCA mutation**

Rucaparib

- **FDA label: maintenance in recurrent PS regardless platinum sensitivity; BRCA (g +s) mutated ovarian cancer, 2+ previous lines**

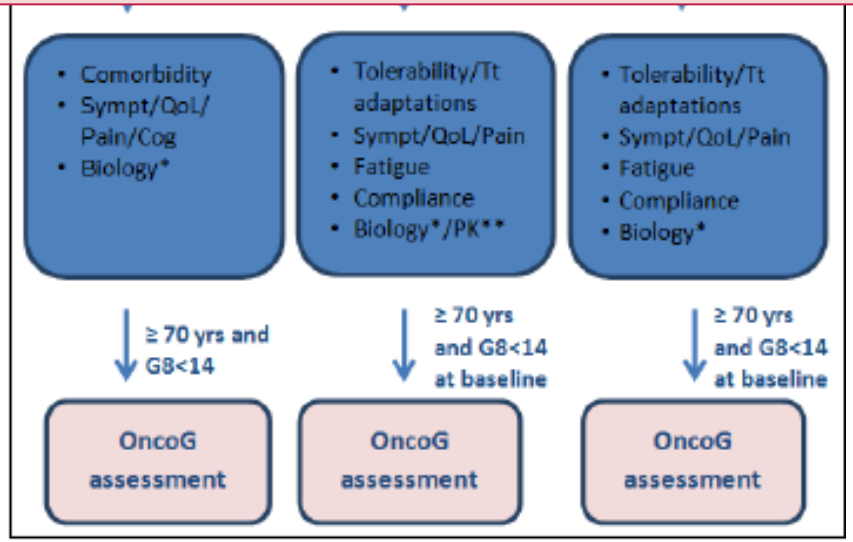
BIEN GÉRER LES EFFETS SECONDAIRES EN MAINTENANCE

Niraparib



- Follow-up of QoL and symptoms is encouraged to be integraded in routine practice (according to the different organisations of the institutions)

- Etude en vraie vie
- Suivi des effets secondaires par tablette
- Transmission aux médecins (lors de la cs)



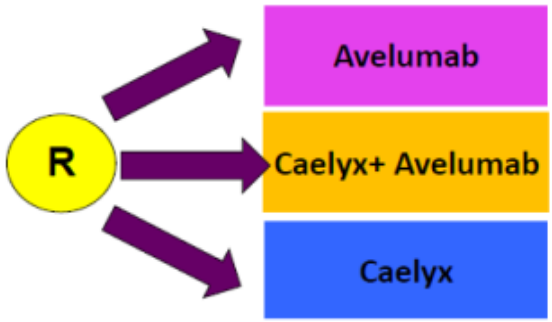
Le future?

- **Immunothérapie : seule ou avec CT**

En rechute sans platine

JAVELIN : SCHEMA DE L'ETUDE

- ≤ 6 mois post platine
- Pas plus de 3 lignes pour platine sensible
- Pas de ligne antérieure en resistant
- Mesurable
- Pas de ttt inhibiteur de checkpoint immunologique
- Tissu disponible



n = ~550 (282 events)
(200 events for each comparison)

Etude internationale, lead GINECO
PI Monde E Pujade Lauraine
Coordonnatrice France : AC HB

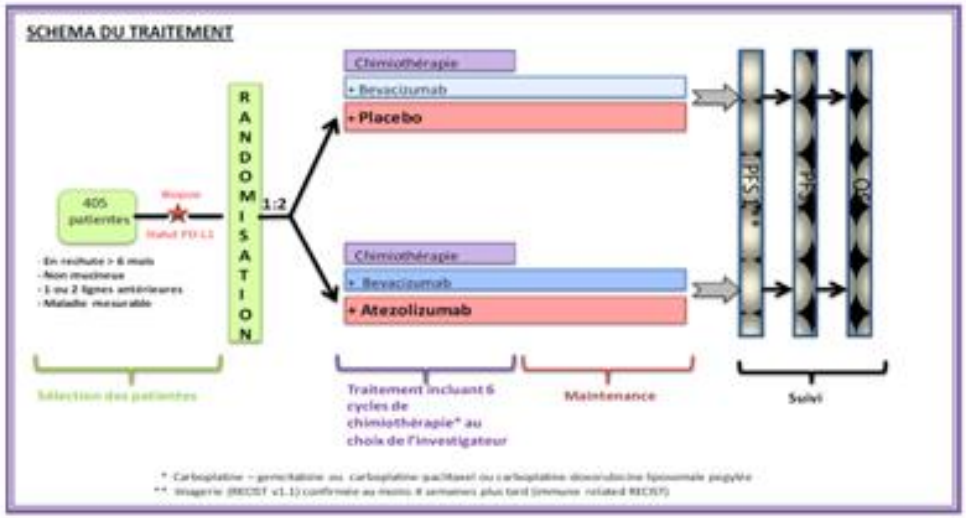
Le future?

- **Immunothérapie : en combo avec Antiangiogénique**

En rechute platine sensible

ENGOT GINECO **ATALANTE** GYNECOLOGIC CANCER INTERGROUP

Cancer de l'ovaire - Rechute > 6 mois



Centre François Baclesse

TRIALS COMBINING PARP INHIBITORS WITH ANTI-ANGIOGENIC DRUGS

Maintenance combinations	**ICON9** cediranib/olaparib vs olaparib, platinum-sensitive
olaparib combinations	**NGR-GYN 004** olaparib+ cediranib vs platinum based chemotherapy
	NGR-GYN 005 olaparib+ cediranib vs chemotherapy
	BAROCCO (ManGO) olaparib + cediranib vs chemotherapy
	CONCERTO (NCT 02889900) Olaparib +cediranib in DDP-resistant, gBRCAwt >
Niraparib+bevacizumab	**AVANOVA** niraparib+ bevacizumab in platinum sensitive ovarian cancer

La première ligne

- **Peu de modification de la prise en charge médicale**

- **Intérêt du Béva en néo-adjuvant**
- **Place des protocoles de chimiothérapie hebdomadaires**
- **Le future?**

Circuit de prescription et de rendu des résultats des tests BRCA dans le cadre de l'AMM Olaparib (Gladieff et al Bull Cancer 2017)

Accord d'experts avec le Groupe Génétique et Cancer

Cancer de l'ovaire (haut grade)

Diagnostic initial

Circuit standard

Consultation d'oncogénétique **habituelle** (information dans le cadre de la recherche d'une mutation constitutionnelle)

Circuit labo habituel (mutation constitutionnelle)

Résultats rendus à, et par l'oncogénéticien

5-6 mois

*pas d'indication à réaliser une recherche tumorale en cas de mutation constitutionnelle connue de *BRCA* . *Si analyse ancienne, reconsidérer en parallèle une nouvelle analyse constitutionnelle*

Critères de choix du traitement initial

Extension tumorale

Caractéristiques patient
(co-morbidités, âge)

Choix du traitement

Type histologique

Expérience équipe

Critères de choix de la chimio

Choix de la Stratégie thérapeutique

Résection chirurgicale

Caractéristiques patiente
(co-morbidités, âge)

Type de CT
(néo-adjuvante, adjuvante, post Chir d'intervalle)

Suites opératoires

Primo-traitement : Chimiothérapie adjuvante (post chirurgie)

- **Chimiothérapie (CT) standard**
  - Paraplatine AUC 5-7, Paclitaxel 175 mg/m^2 en IV
  - 3 semaines
- **Place du Bevacizumab**
  - En association avec la CT, toutes les 3 semaines
  - Et en maintenance après la CT
  - Posologie AMM : 15 mg/kg tous les 3sm, 15 mois
- **Intérêt d'un traitement par Paclitaxel hebdo ?**
  - Paclitaxel +/- carbo
  - Dose dense ou dose hebdo stricte (Réputé « mieux toléré »)

Phase III antiangiogéniques en maintenance dans le cancer de l'ovaire en première ligne

	Première ligne		
	ICON7[1] n = 759	GOG 218[2] n = 1873	OVAR-16[3] n = 940
	Carbo/Taxol +/- **bevacizumab**	Carbo/taxol +/- **bevacizumab**	Carbo/taxol +/- **pazopanib**
PFS median mois	17,3 vs 19	10.3 vs 14,1	12,3 vs 19,9
	0.81 P=0,0041	**0.717** p<0,0001	**0.766** p=0,0021
OS median mois	58,6 vs 58 (sous groupe ht risque : 28,8 vs 36,6)	39,3 vs 39,7	NR

1: *Burger R. et al. NEJM 2011; 2: PerrenT. et al. NEJM 2011; 3 : Du Bois JCO 2014*

Primo-traitement
Place du paclitaxel hebdomadaire sans beva

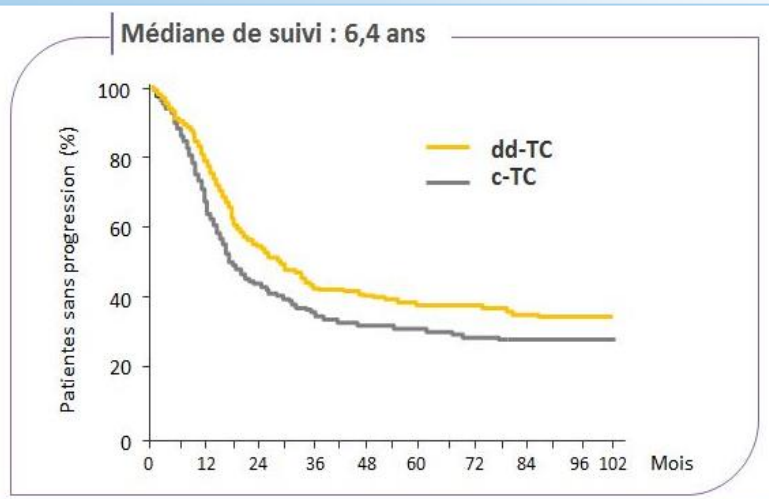
Essai Mito 7 (Carbo-taxol hebdo)	Carbo AUC2-Paclitaxel 60 mg/m2, les 2 hebdos Bras hebdo. : plus de reports, moins de réductions de doses
Essai JGOG (Taxol dose/dense)	Carbo AUC-5/6 (3sm) -Paclitaxel 80 mg/m2 hebdo Bras DD : plus d'anémie et de neuropathie Bevacizumab en option : impact ?

	Mito 7 (3S/DD)		JGOG (3S/DD)
PFS (mois)	17,3 m	18,3 m	**17,5 m/28,2 m**
	Ns		S
*sous-groupe sans Bev (n=112) HR = 0,60			

Pignata, lancet Oncol 2014, *Katsumata N et al. Lancet 2009*

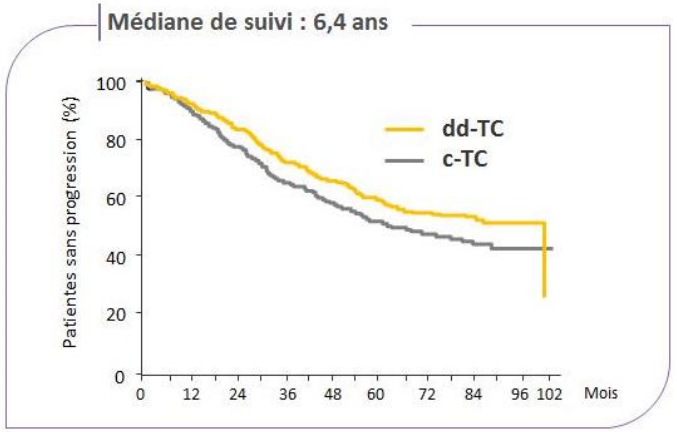
Primo-traitement
Place du paclitaxel hebdo dose dense

Etude Japonnaise



Traitement	n	Événements, 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



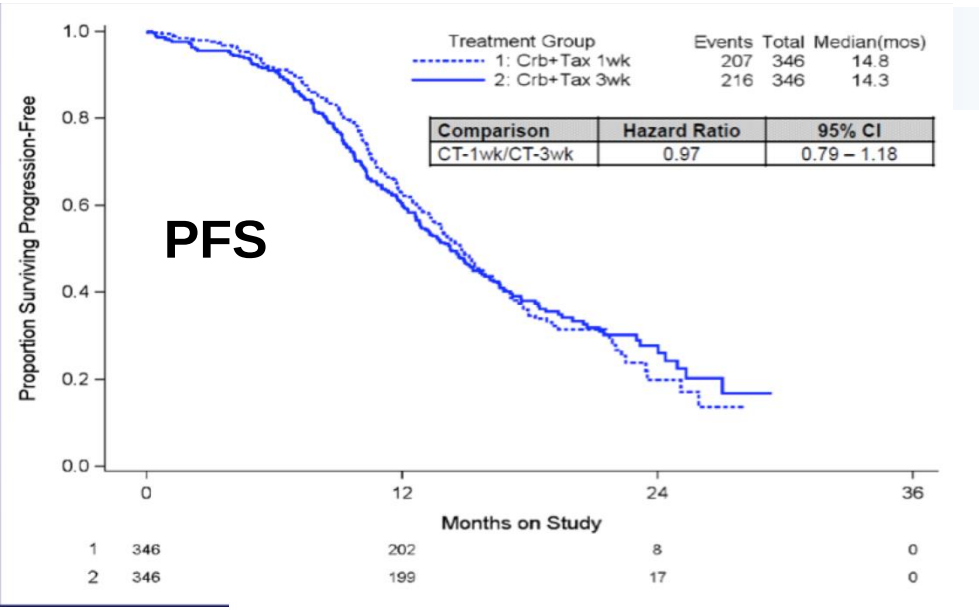
Traitement	n	Décès, n (%)	SG médiane	Survie à 5 ans (%)	*p*	HR	IC_{95}
dd-TC	312	139 (45)	Non atteinte	58,7	*0,039*	0,79	0,63-0,99
c-TC	319	168 (53)	62,2	51,1			

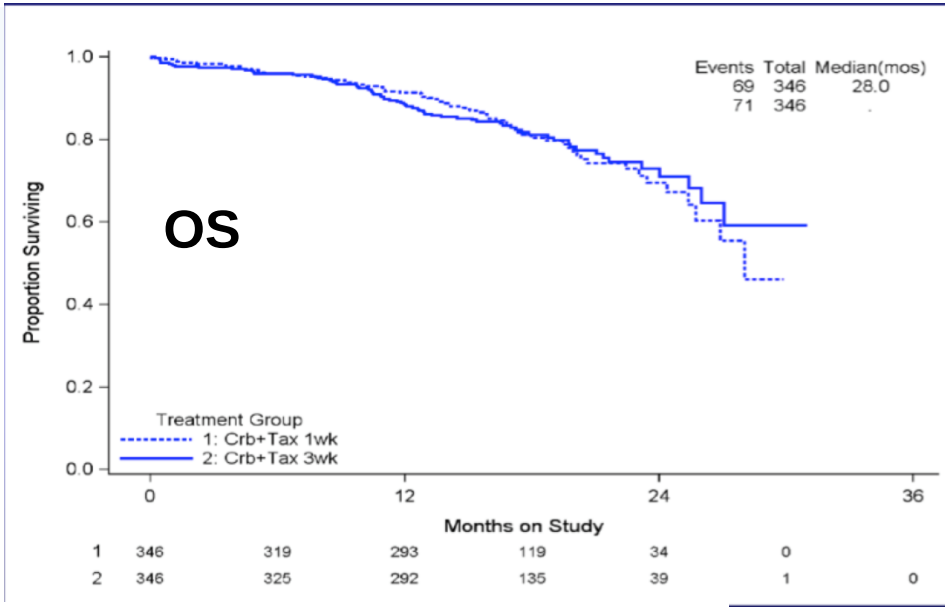
ASCO 2012 - D'après Katsumata N *et al.*, abstr. 5003 actualisé

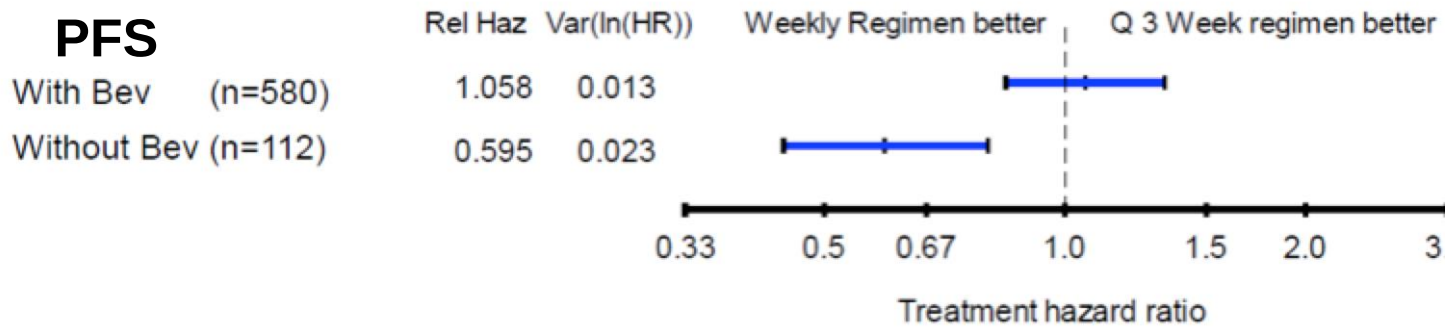
- **Données actualisées de l'essai JGOG 3016**
- **Dans cette étude japonaise :**
  - Schéma DD plus toxique (reports, réductions de doses, moins de poursuites au-delà de 6 cures)
  - Persistance du bénéfice du schéma DD Paclitaxel-Carboplatine avec plus de recul

Katsumata n et al. Lancet Oncol 2013;14(10):1020-1026

GOG 262 = +/- bevacizumab (etude américaine)





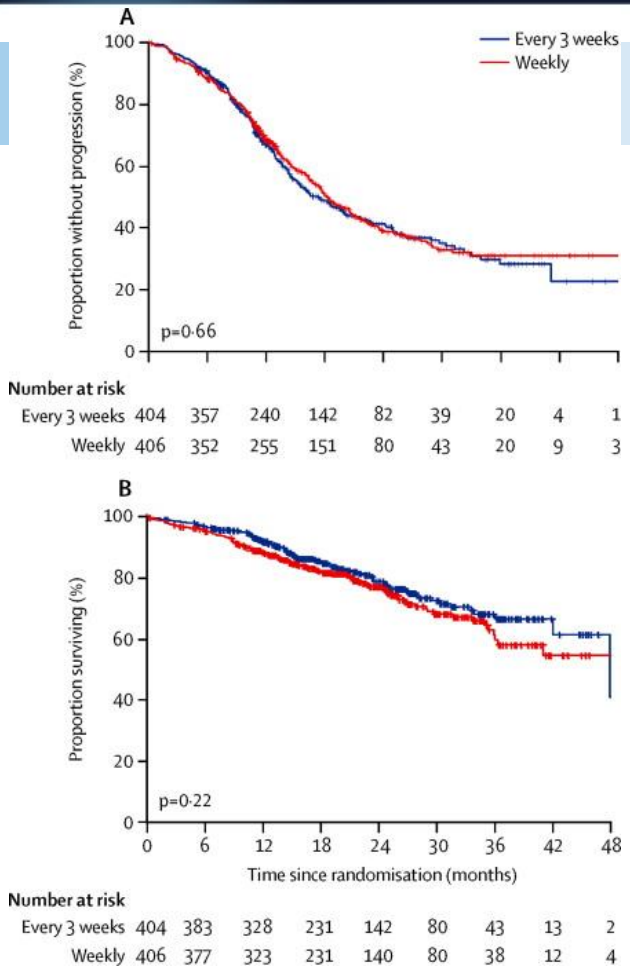


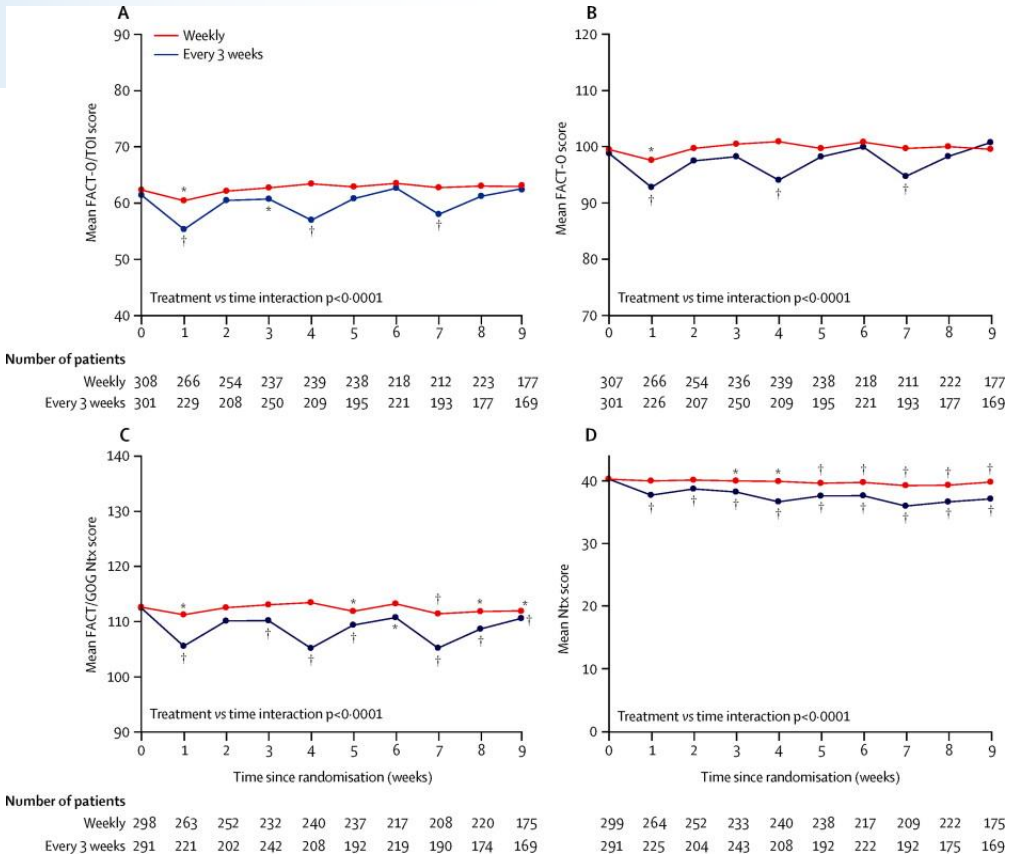
CARIO CENTRE ARMORICAIN RADIOTHÉRAPIE IMAGERIE MÉDICALE ONCOLOGIE

Chan, NEJM 2016

HGO HÔPITAL PRIVÉ DES CÔTES D'ARMOR GROUPE MUTUALISTE

Carbo et taxol dose hebdo : Etude Mito 7





- No difference in PFS and OS

- QoL, Coprimary endpoint, evaluated every week for the first 9 weeks
- PRO's in favor for the weekly schedule

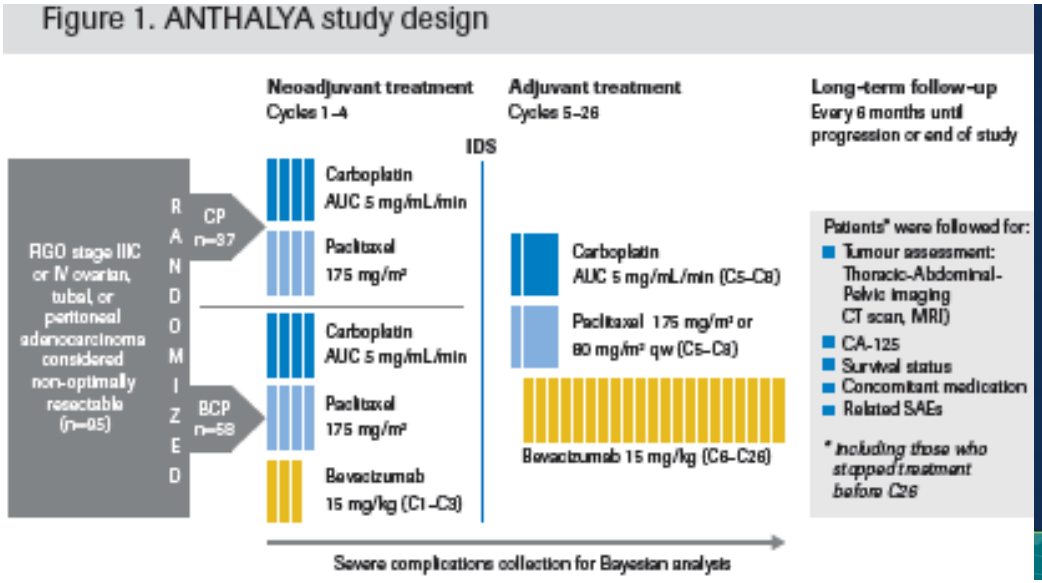
Pignata et al, Lancet Oncol 2014

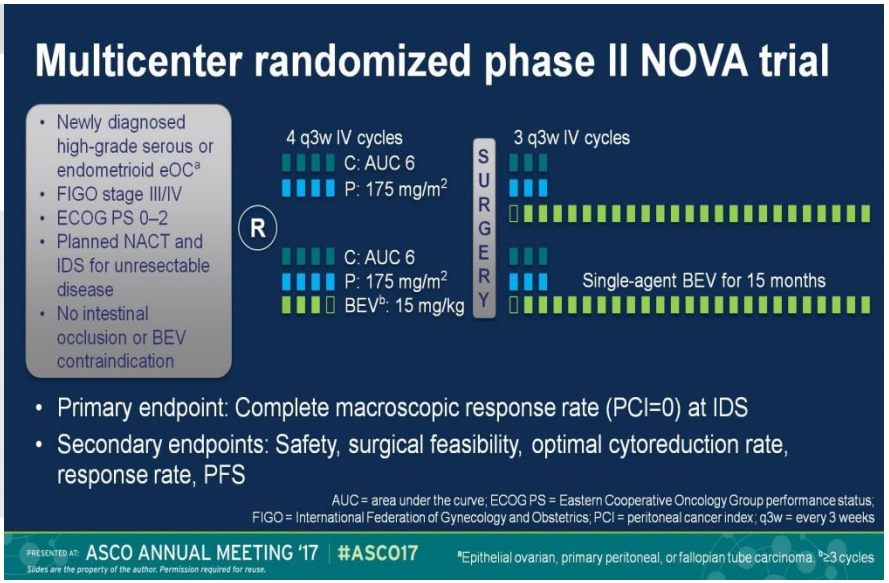
Que retenir du paclitaxel hebdomadaire?

- **Paclitaxel Dose-dense hebdo (80 mg/m²):**
  - Bénéfice que chez les asiatiques
  - Pas de bénéfice chez les non asiatiques
  - Plus toxique

- **Paclitaxel Hebdo 60 mg/m² carbo hebdo:**
  - pas de bénéfice en PFS ou OS
  - meilleure qualité de vie, et moins de toxicités

Interet du Beva en Néoadjuvante





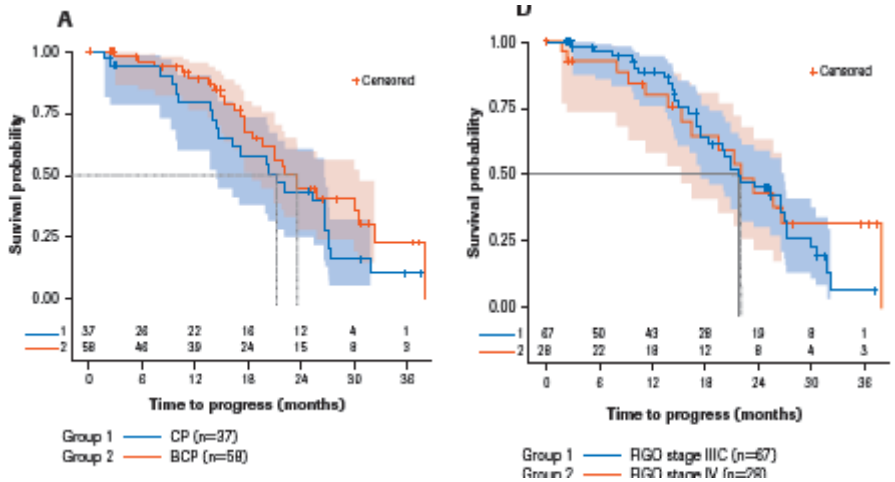
French study, joly et al

Spanish study, Garcia et al

Ovaire et Bev en Néoadjuvant

ANTHALYA showed that neoadjuvant bevacizumab (B) added to carboplatin and paclitaxel (CP) was well tolerated and achieved **high complete resection rates at IDS (58.6%).**[1]

Spain Nova study



- Disease progression occurred in 26 (44.8%) BCP patients and 24 (64.9%) CP patients during the overall study period. Median (95% CI) PFS was **23.5 (18.5, 30.6)** months and **21.2 (14.5, 26.7)** months, respectively (Figure 2A).
- Median PFS in subgroup analyses were:
  - **25.8 (21.0, 30.0)** months for patients with complete resection at IDS (n=53); **22.2 (9.8, 27.2)** months for patients who did not have IDS (n=33); and **14.5 (10.6, 17.1)** months for patients who had IDS but no complete resection (n=9; Figure 2B)
  - **25.8 (18.5, 27.2)** months and **21.0 (15.0, 25.4)** months for patients without (n=59) or with (n=29) baseline CTCs, respectively (Figure 2C)
  - **21.8 (17.5, 27.1)** months and **22.2 (15.3, 38.0)** months with FIGO IIIC (n=67) and IV (n=28) tumors, respectively (Figure 2D).

Secondary endpoints (ITT population)

No. of patients (%)		CP alone (n=33)	CP + BEV (n=35)	p-value
IDS surgical feasibility		22 (67)	31 (89)	0.029[a]
Surgical outcome	Complete resection/optimal surgery	21 (64)	23 (66)	0.858[a]
	Suboptimal	1 (3)	8 (23)	0.028[b]
	Unresectable	2 (6)	0	0.232[b]
	No surgery[c]	9 (27)	4 (11)	0.097[a]
Best response (RECIST)		(n=32) 22 (69)	(n=32) 28 (88)	0.175[a]

[a]Chi-squared test. [b]Fisher's exact test
[c]Surgery was planned in 2 patients but they were subsequently considered unresectable. Surgery was not attempted in the remaining patients
RECIST = Response Evaluation Criteria in Solid Tumors

- Consistent results in the PP population (n=64)

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17 Presented by: Y Garcia Garcia
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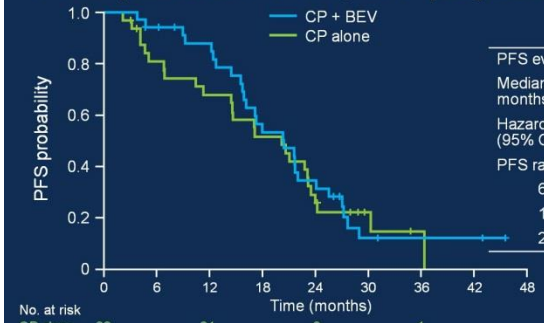
PFS (RECIST v1.1, ITT population)



	CP alone (n=33)	CP + BEV (n=35)
PFS events, n (%)	26 (79)	27 (77)
Median PFS, months (95% CI)	20.1 (14.7–25.6)	20.4 (14.4–26.3)
Hazard ratio (95% CI)	1.13 (0.66–1.93) Log-rank p=0.664	
PFS rate, %		
6-month	81	94
1-year	68	88
2-year	26	35

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Take Home Message

Béva en néo-adjuvant

- **Faisable**
- **Mais ne permet pas plus de résection complète ni d'augmentation de la PFS**
- **Peut-être un sous groupe qui pourrait en bénéficier**
  - Stades IV jugés comme inopérables

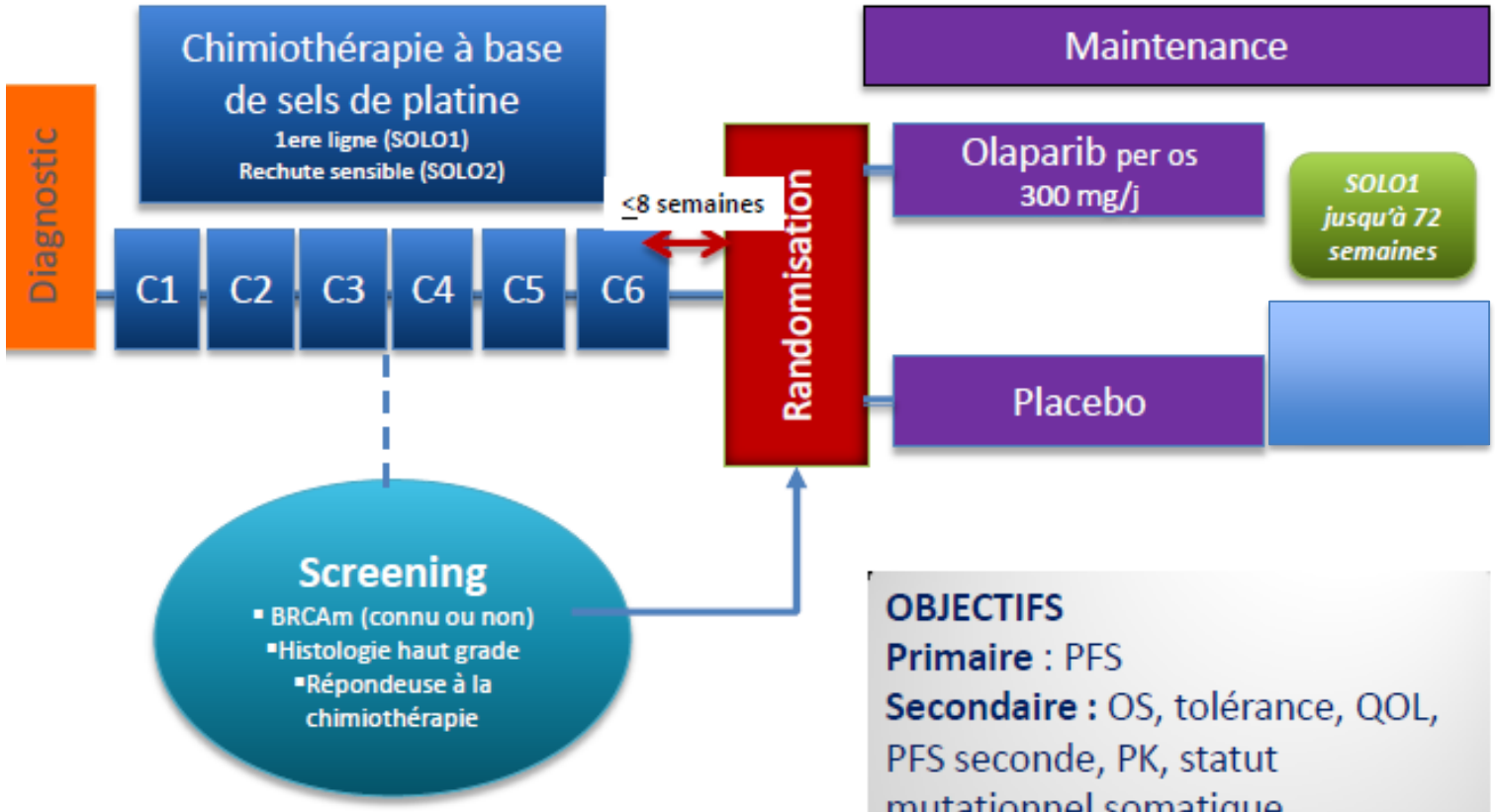
Take Home Message

ARCAGY - GINECO

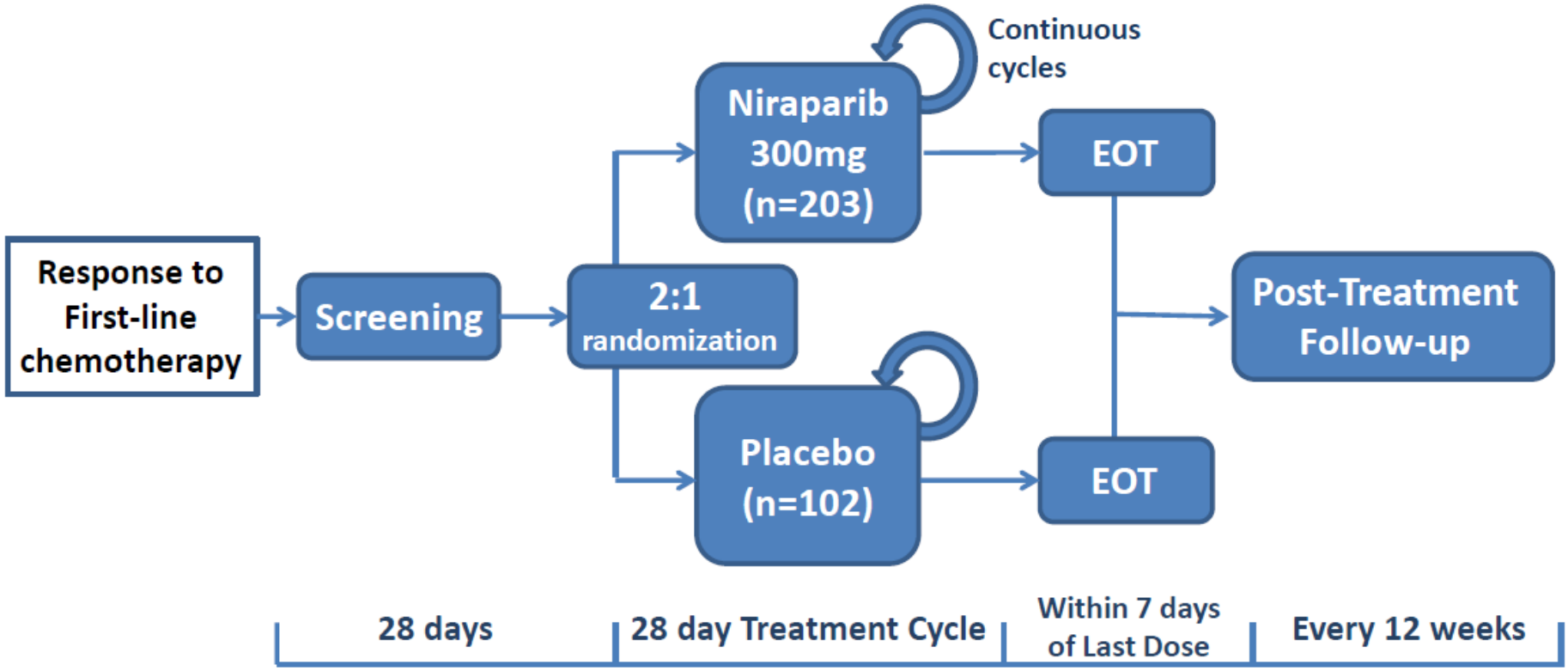
- **Standard = chirurgie complète initiale**
- **Alternative = chimiothérapie néo-adjuvante**
  - Chirurgie complète non envisageable
  - État général
- **Chimiothérapie standard : taxol carboplatine J21**
- **Bevacizumab formes avancées ou inopérables**
- **Oncogénétique**

Inh de parp en première ligne

- **Olaparib : etude Solo 1 - Schéma, résultats en attente**



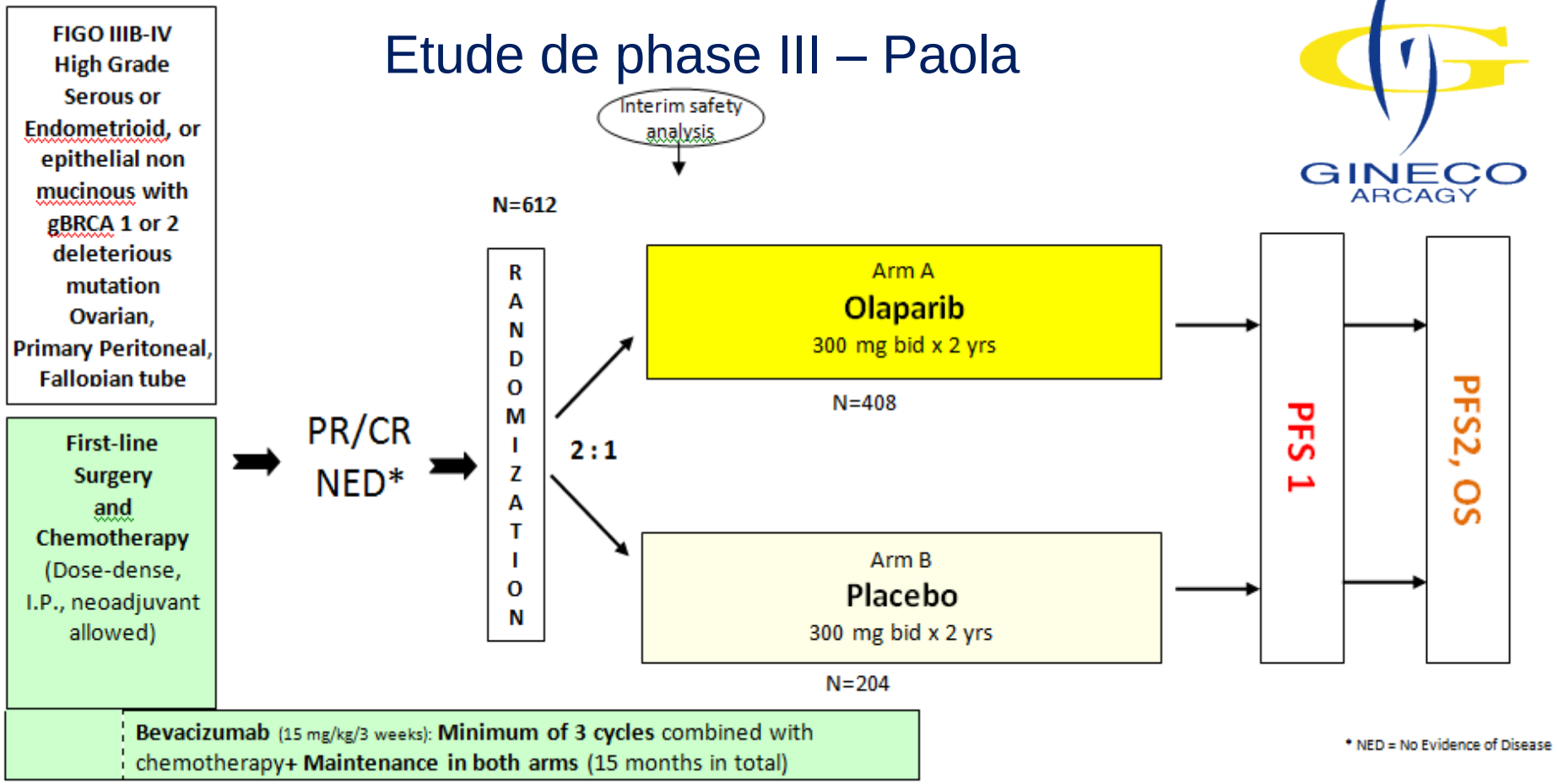
PRIMA: Ovarian Cancer Phase 3 Trial Design



Primary Endpoint	PFS (Interim analysis to be performed when 50% events (N=129) are observed)
Key Secondary Endpoints	• Overall survival (OS) • Patient-reported outcomes (PRO) • Time to CA-125 progression • PFS2 • Safety and tolerability

Le future
Combo AA et Inhibiteurs de Parp?

Etude de phase III – Paola

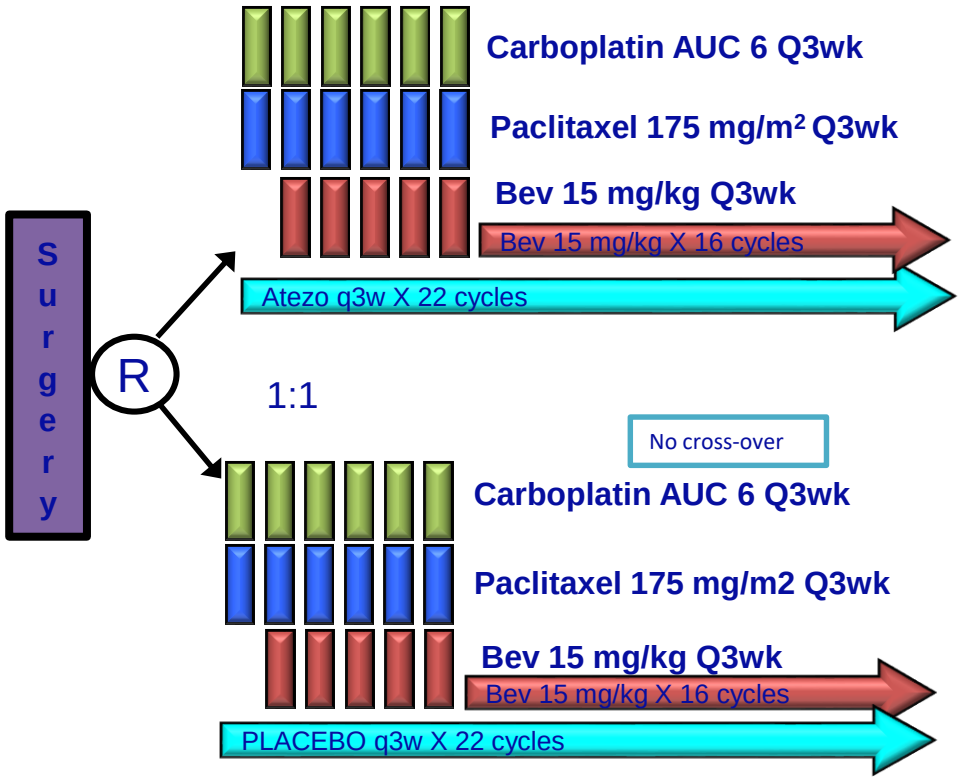


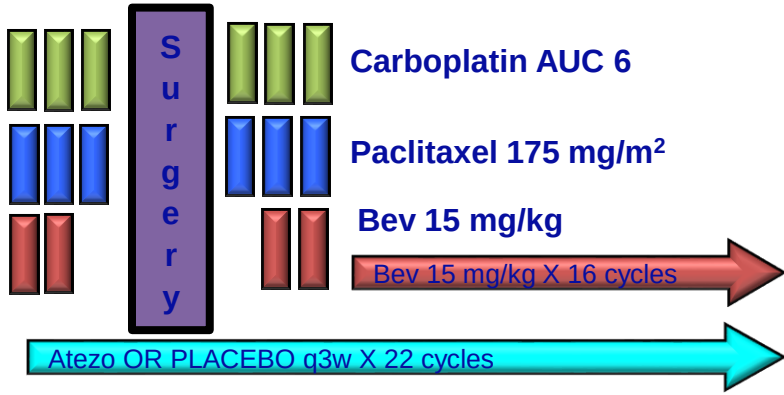
- *Evaluer entretien Olaparib à la CT par Carboplatine-Paclitaxel-Bevacizumab*
- *Objectif principal : PFS*

307/612 patientes randomisées au 01/09/2016

Le future
Combo AA et Immuno?

Double blinded, 1:1 randomized, placebo-controlled multi-center study



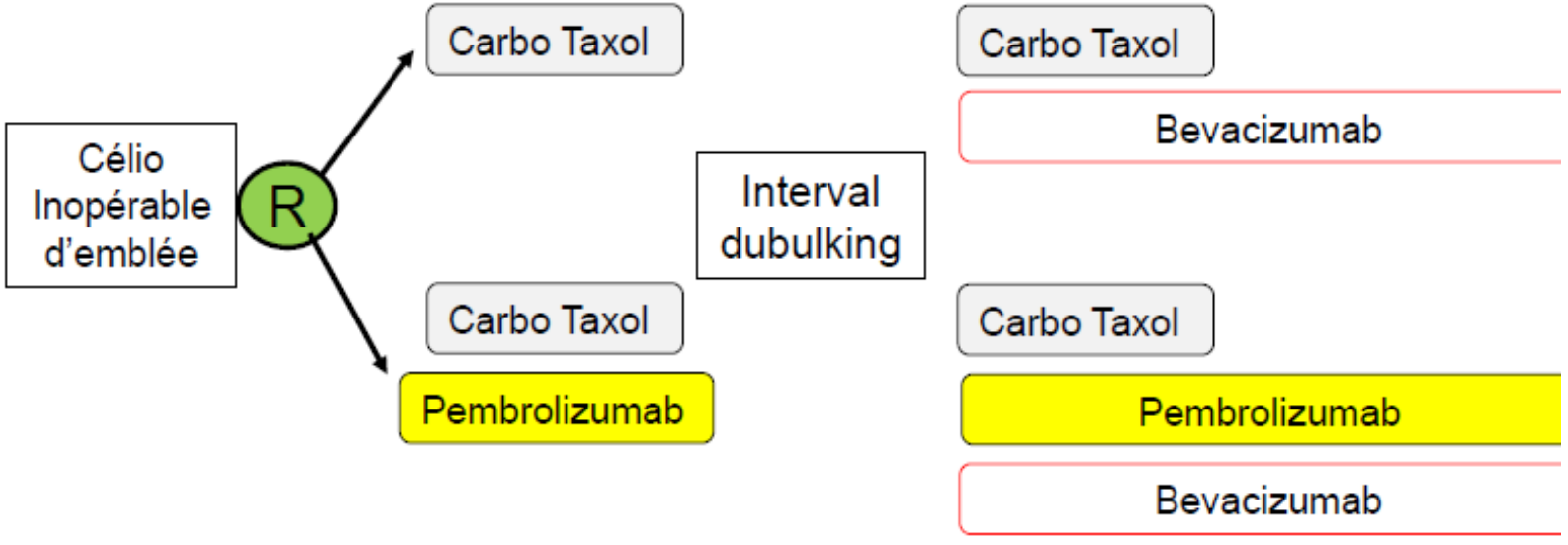


*Decision for NACT per investigator then 1:1 randomization prior to start of chemotherapy treatment

Etude IMaGyn050

N=1300 pts *globally*
En cours de recrutement

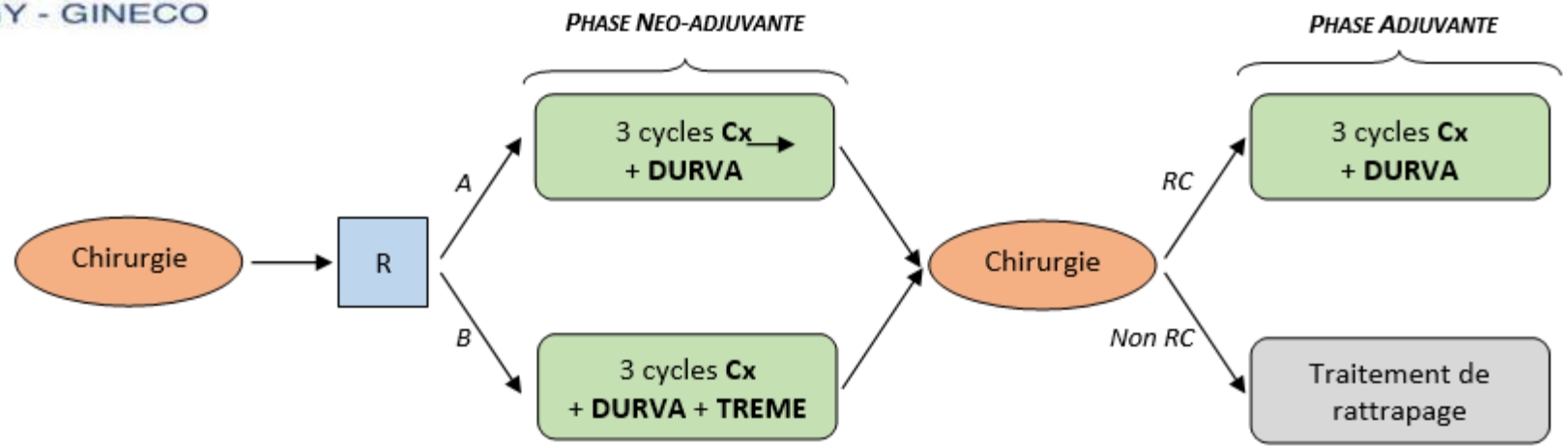
NeoPembOv: Neoadjuvant chemotherapy alone or in combination with Pembrolizumab



1er essai évaluant le bénéfice d'une chimiothérapie néoadjuvante avec un anti-PD1
Puis entretien par bevacizumab seul ou en association avec anti-PD1

INEOV : tester la combo immuno, modulée en fonction de la réponse

ARCAGY - GINECO



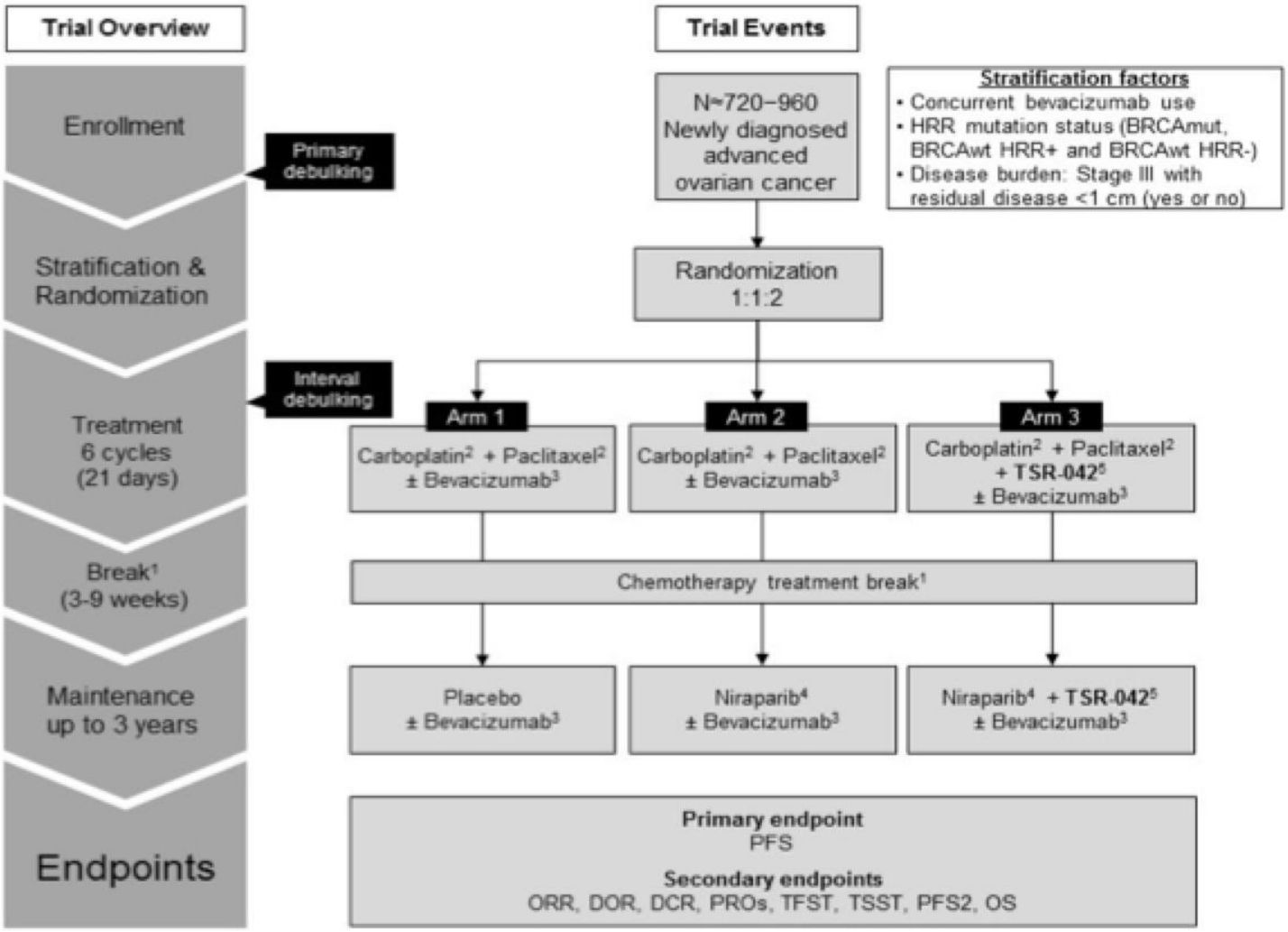
***Safety Run-in** = 6 patientes recevant 3 cycles Cx-DURVA puis 6 patientes recevant 3 cycles Cx-DURVA + TREME.*

***1 cycle = 21 jours ; Cx** = carboplatine + paclitaxel ; **DURVA** = Durvalumab ; **TREME** = Tremelimumab.*

***Traitement de rattrapage** :*
- *Dans le bras A, addition de Tremelimumab, chirurgie après 3 nouveaux cycles et entretien avec Durvalumab + Tremelimumab.*
- *Dans le bras B, traitement selon l'investigateur, y compris avec du bevacizumab.*

Combiner AA-Immuno- Inh de Parp

Etude First



Conclusions

- **Les traitements médicaux s'intensifient**
- **Les traitements médicaux se diversifient**
- **Marche arrière sur la personnalisation des traitements médicaux sur la biologie**

- **Toujours à la recherche de traitements à la carte**