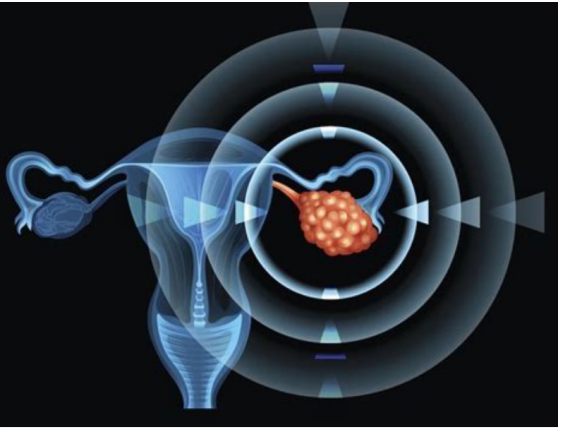
Place des iPARPs dans le cancer de l'ovaire avancé: point de vue de l'oncologue médical

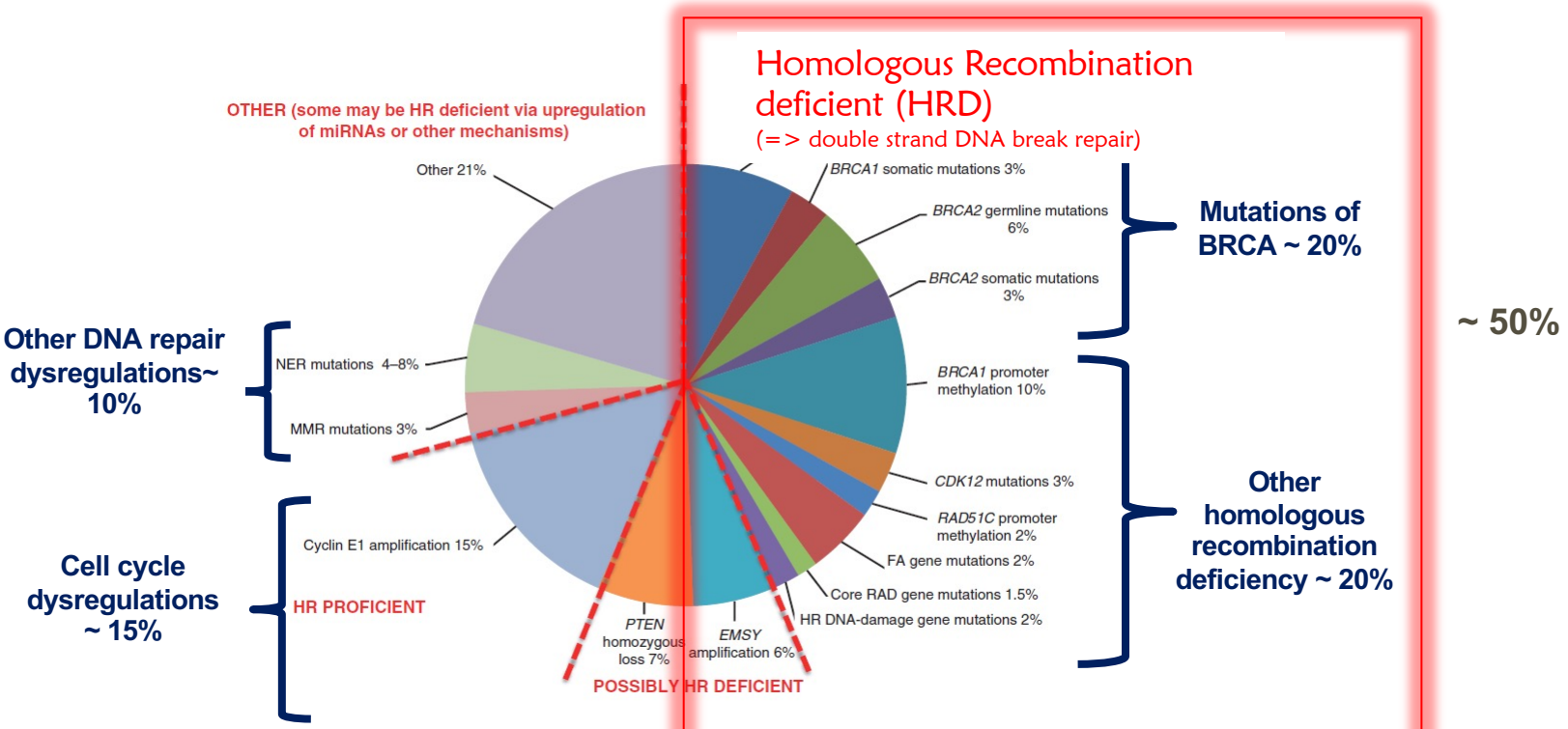


Dr David COEFFIC
Hôpital Privé de Provence

LIENS D'INTERET

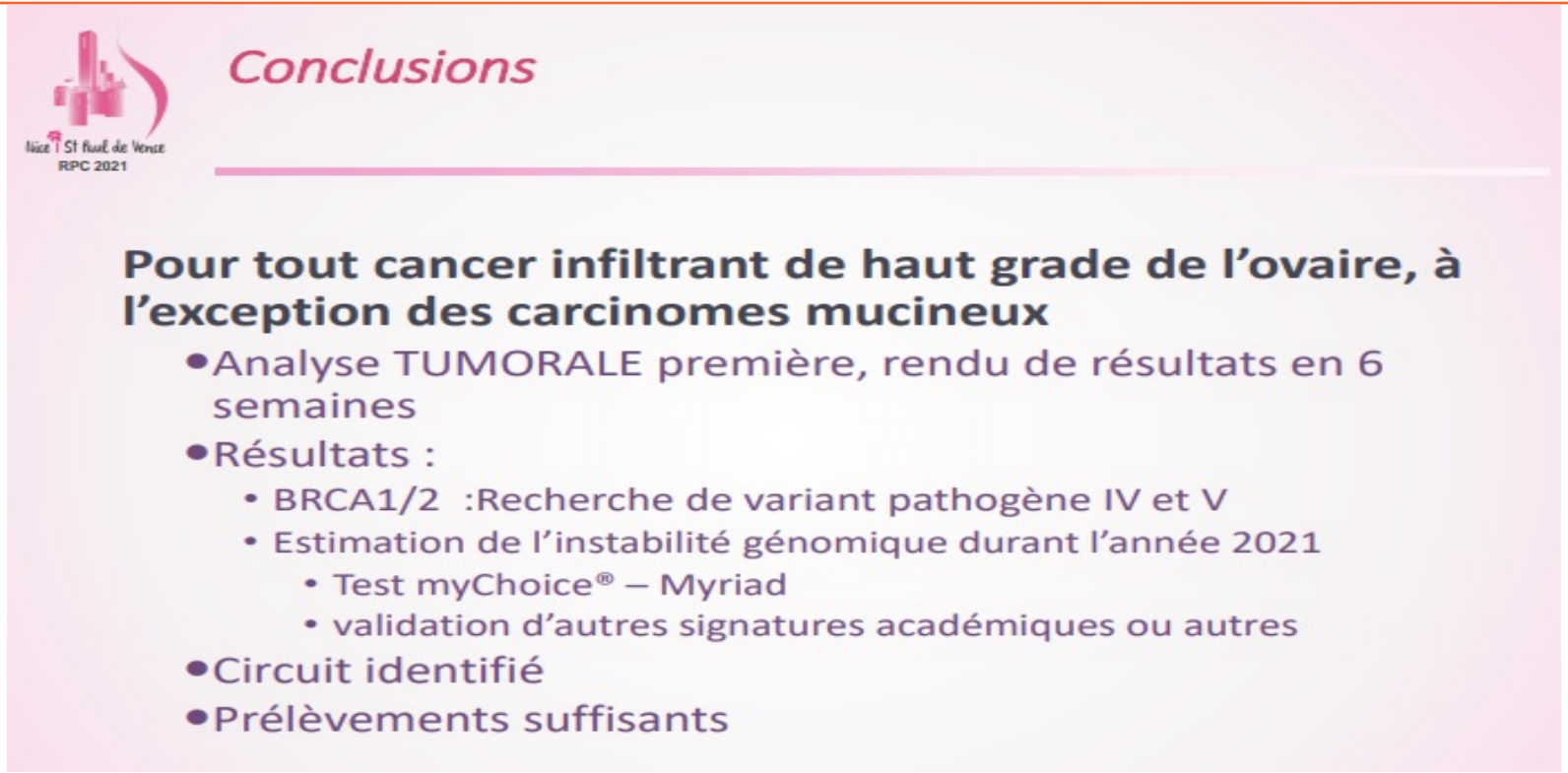
- AstraZeneca
- Pfizer
- Roche
- BMS
- GSK
- MSD
- Astellas

Anomalies moléculaires : mutations BRCA , HRD



konstantinopoulos PA, et al. Cancer Discov 2015;5:1137–54

Testing et Biologie



Recommandations Saint Paul de Vence 2021

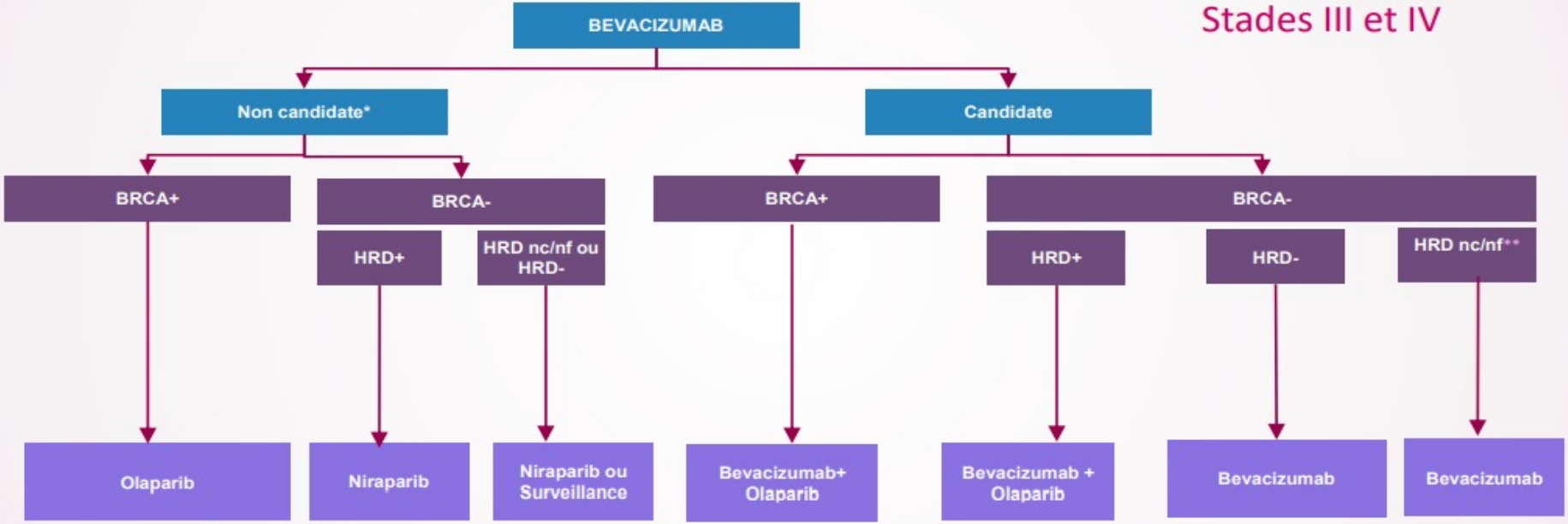
Abbreviations: BRCA, breast cancer gene;.

Quels changements en 1L en 2021 ?

Nice St Paul de Vence
RPC 2021

Algorithme de choix thérapeutiques avec les nouvelles ATU et post-ATU disponibles en 2021

Cancer ovaire – haut grade – Stades III et IV



*Non candidate: contre-indication ou option du bévacizumab non retenue par le médecin

HRD + : Test HRD positif (le test a identifié une défaillance de la recombinaison homologue)
HRD- : Test HRD négatif (le test n'a pas identifié de défaillance de la recombinaison homologue)
HRDnf : test non fait (à faire)
HRDnc : test non contributif (à refaire)

Nouvelles thérapeutiques en 1L de maintenance

Jusqu'à 2020, 2 traitements disponibles:

Bevacizumab en maintenance avec la CT puis pendant 15 mois

- AMM pour cancer épithélial ≥ stade IIIB
- Toutes patientes éligibles

Olaparib en maintenance pendant 2 ans

- AMM dans cancer avancé épithélial de haut grade , Stade III-IV
- Réponse complète ou partielle à base de sels de platine
- Patientes avec mutation BRCA1/2

Résumé des caractéristiques du produit Bevacizumab
Résumé des caractéristiques du produit Olaparib

Nouvelles thérapeutiques en 1L de maintenance

En 2021 , 2 nouvelles options thérapeutiques:

Niraparib en maintenance pendant 3 ans

- AMM dans le cancer avancé épithélial haut grade, Stade III-IV
- En réponse à chimiothérapie à base de sels de platine
- Toutes patientes

Olaparib + bevacizumab en maintenance pendant 2 ans

- AMM dans le cancer avancé épithélial haut grade, Stade III-IV
- En réponse à chimiothérapie à base de sels de platine
- Statut HRD ou mutation BRCA ou instabilité génomique
- en post ATU

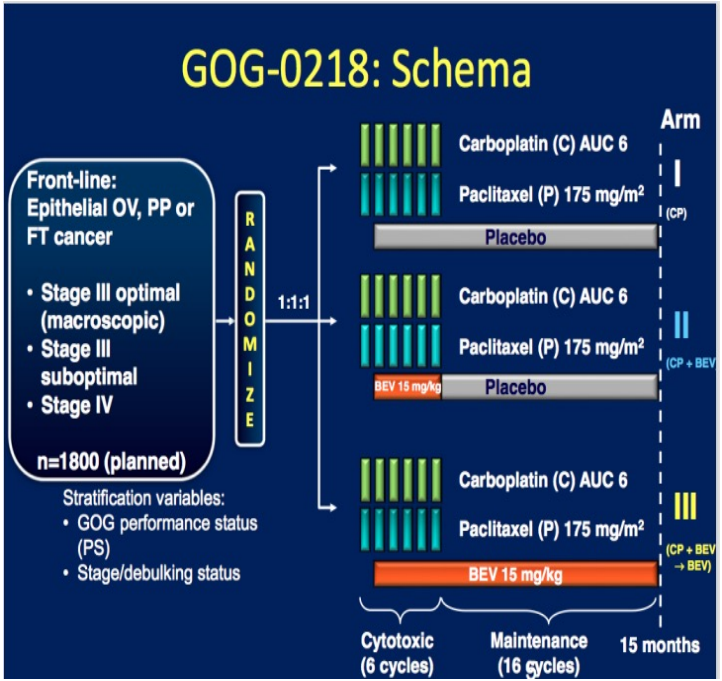
RCP NIraparib
HAS: Lynparza

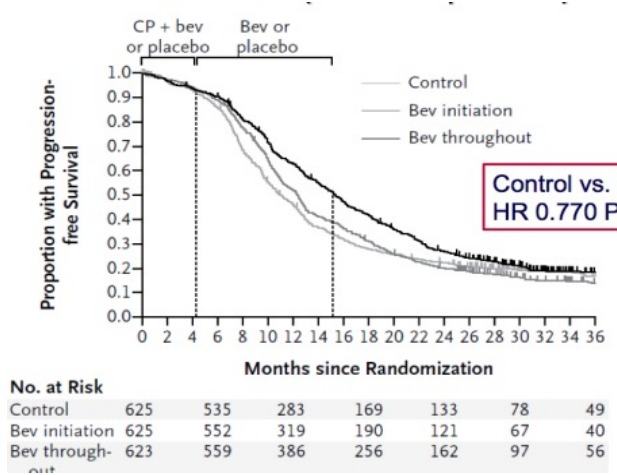
Quelles études en 1ère ligne ?

- Bevacizumab; GOG 218; ICON 7

- iPARP:
- Statut BRCAm: SOLO1
- Toutes patientes : PRIMA, PAOLA

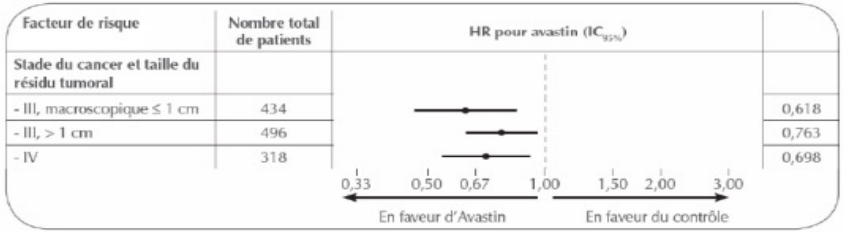
Bevacizumab en maintenance 1L : GOG-218





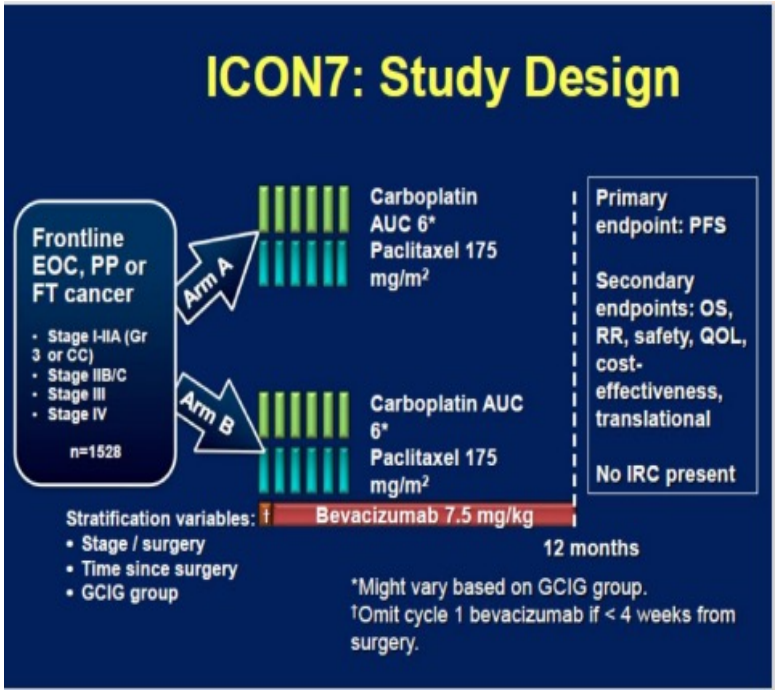
CT n=625	CT+bev n=623
10,3	14,1
HR : 0,770 95% CI, 0.625–0.824 P<0,001	

Pas de différence d'efficacité selon le résidu tumoral post opératoire

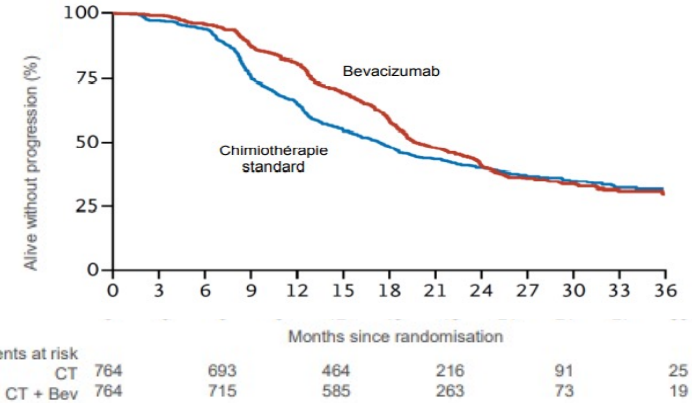


ASCO 2011 d'après Burger RA et al. N Engl J Med. 2011;365:2473-83.

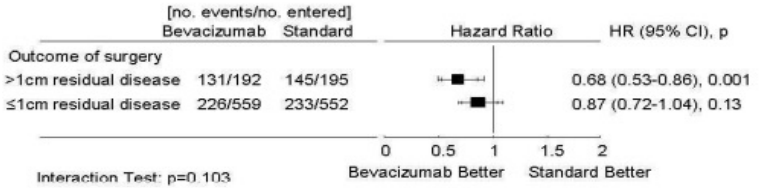
Bevacizumab en maintenance 1L : ICON7



PFS

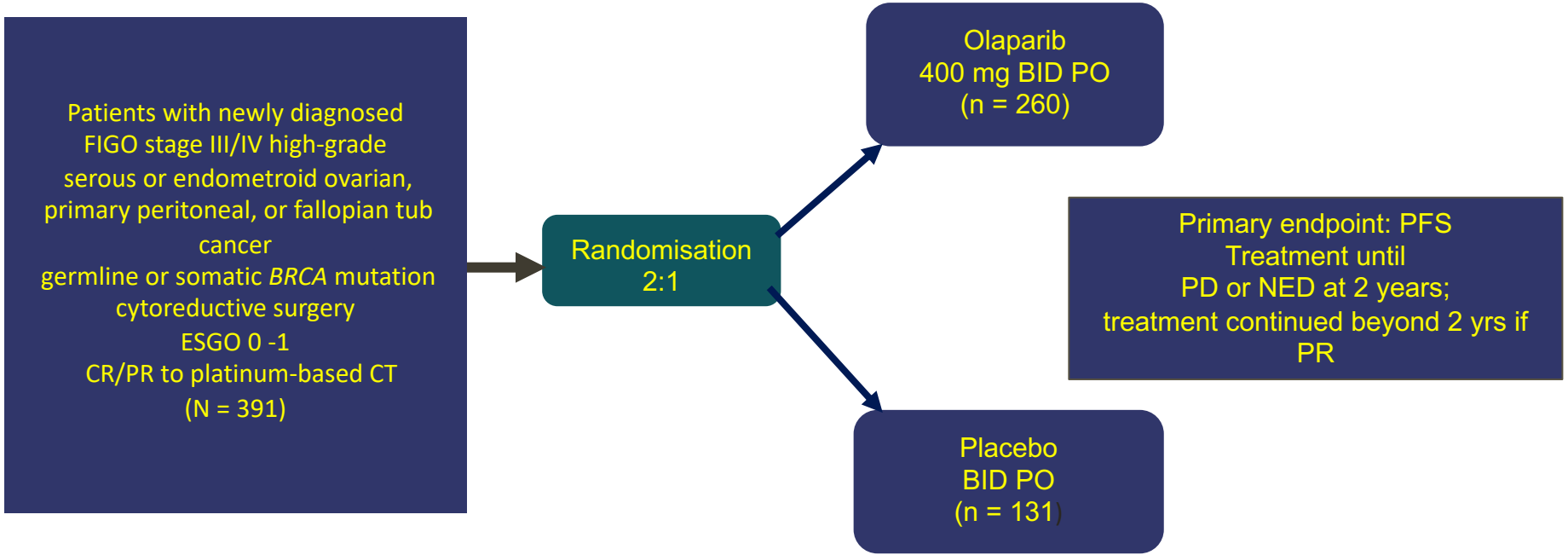


Outcome of surgery



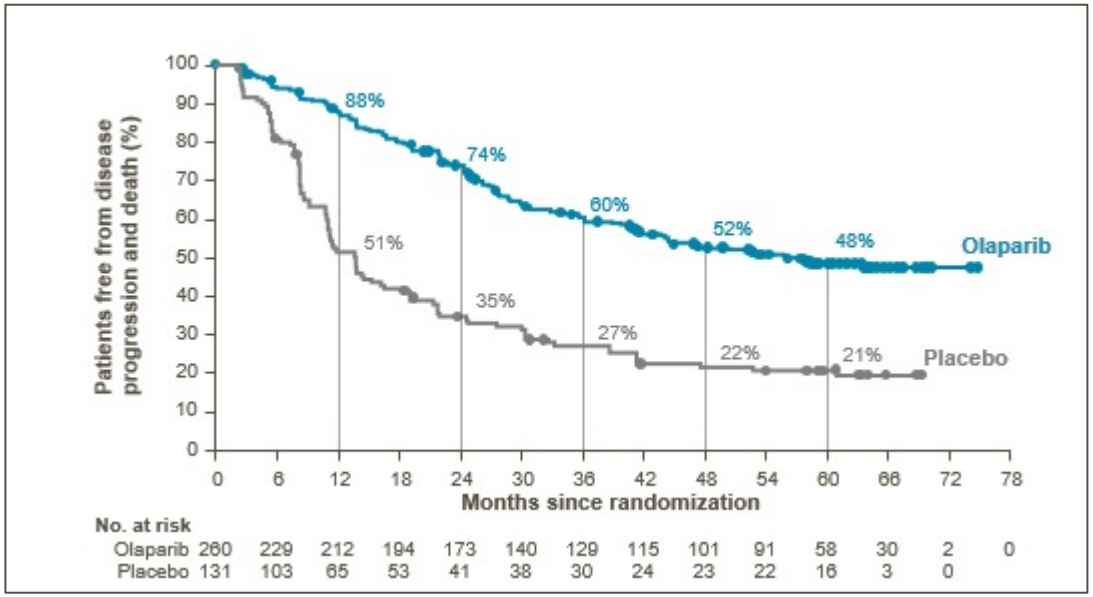
Perren TJ, et al. N Engl J Med 2011;365:2484-96; supplement to Perren TJ, NEJ 2011.

SOLO-1: Olaparib phase III



ESMO 2018 d'après Moore K, et al. N Engl J Med 2018;

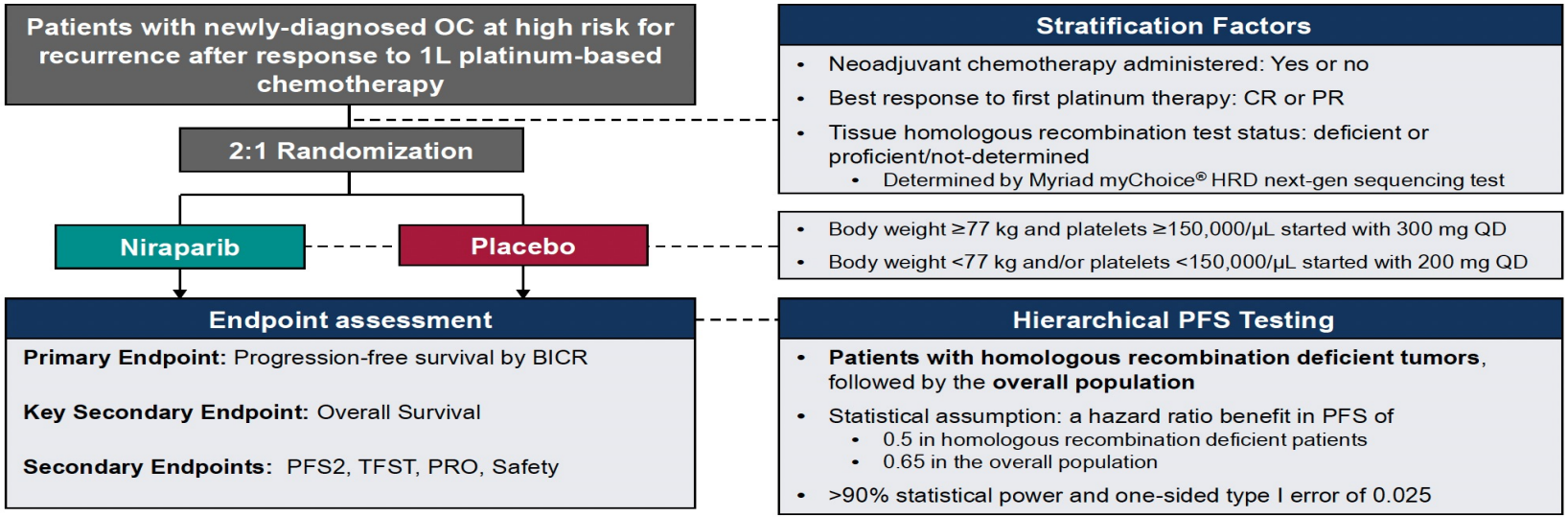
SOLO 1 – patientes BRCAm PFS à 5 ans



	Olaparib (n=260)	Placebo (n=131)
Events, n (%)	118 (45)	100 (76)
Median PFS, months	56.0	13.8
Difference, months	42.2	
	HR 0.33	
	95% CI 0.25–0.43	

Moore K, et al. N Engl J Med 2018;379:2495–505 Banerjee S, et al. presented at ESMO Congress, 19–21 Sep 2020

PRIMA : Niraparib Phase III



Population à haut risque de rechute:

- Stade III: PDS avec maladie résiduelle visible, IDS quelque soit le résidu, ou inopérable
- Stade IV: PDS quelque soit le résidu, NACT, ou inopérable

A.Gonzalez-Martin et al,N Engl J Med 2019;381:2391-402. Presented at ESMO 2019

PRIMA: individualized starting dose

- **The study protocol of PRIMA/ENGOT-OV26/GOG-3012 was amended to introduce the ISD regimen on November 16, 2017 (after ~65% of patients were dosed)**
  - After this amendment, randomized patients were assigned to receive either 200 mg or 300 mg based on their baseline body weight and platelet count

200 mg STARTING DOSE
for patients with

Baseline body weight

<77 kg

OR

Baseline platelets

<150,000/µL

300 mg STARTING DOSE
for patients with

Baseline body weight

≥77 kg

AND

Baseline platelets

≥150,000/µL

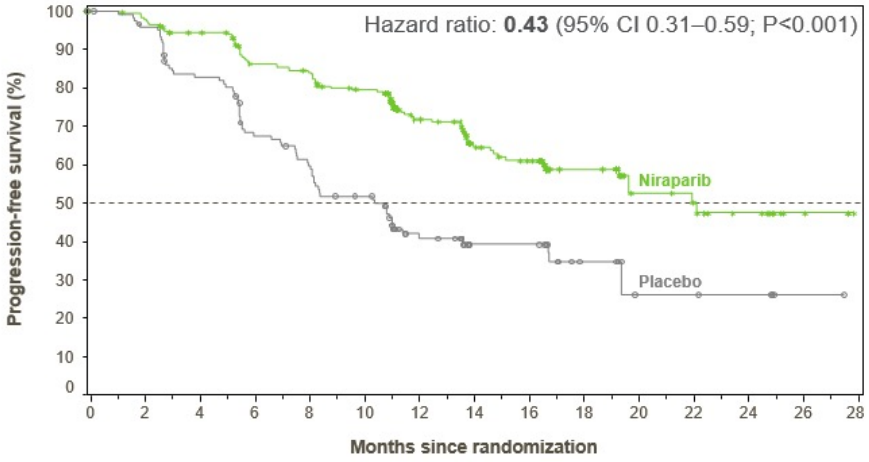
- Analysis of the ISD regimen was conducted on the safety population (all patients who received ≥1 dose of niraparib or placebo)

ISD, individualized starting dose; QD, once daily.

Mirza MR, et al. presented at ASCO 2020, 29–31 May (virtual); Korach J, et al. presented at ESGO SoA 2020, 14–16 Dec (virtual).

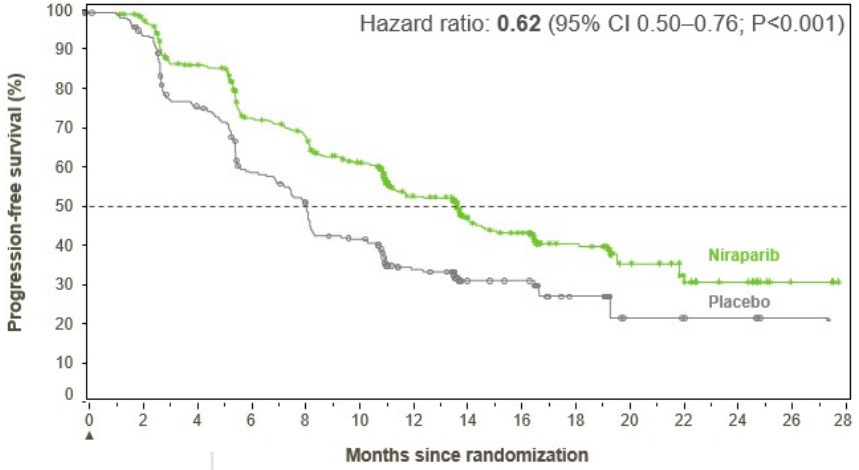
PRIMA – critère principal

PFS dans la population HRD



	Niraparib (n=247)	Placebo (n=126)
Median PFS		
Months	21.9	10.4
(95% CI)	(19.3–NE)	(8.1–12.1)

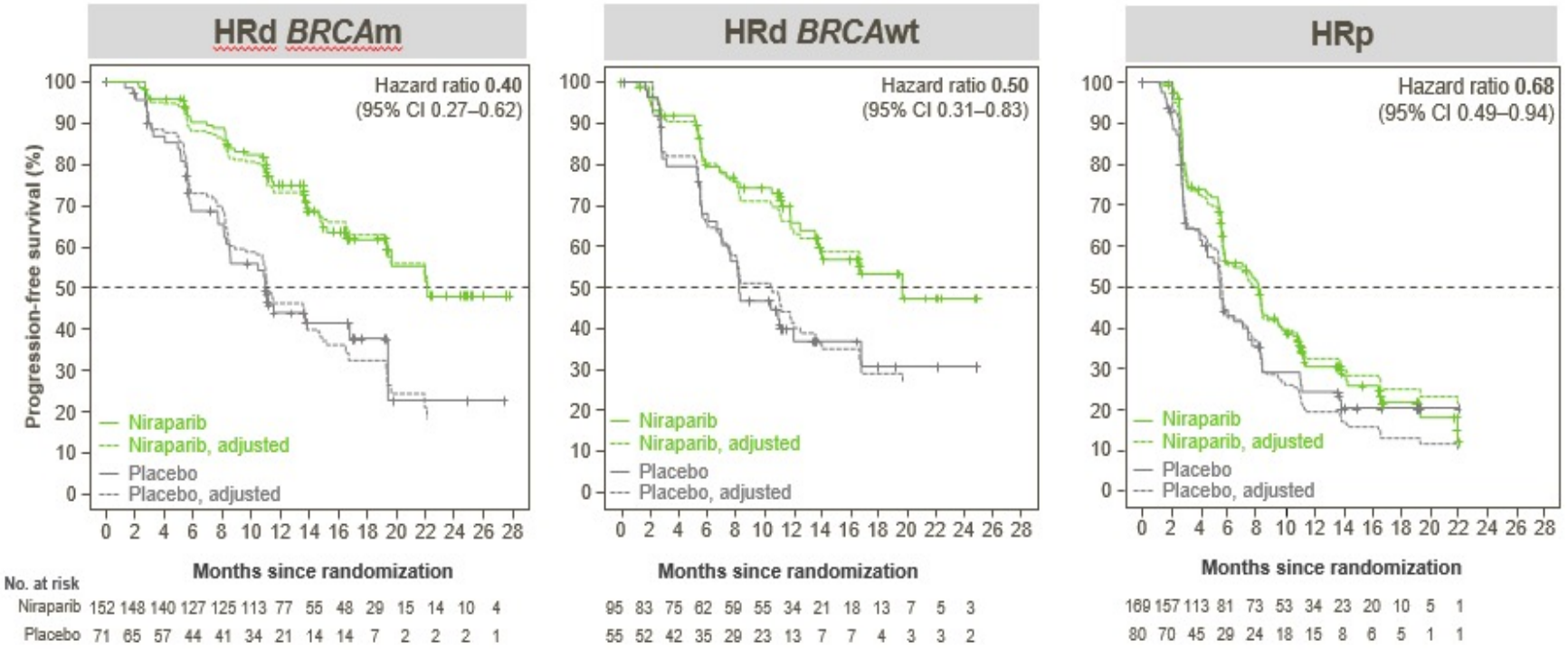
PFS dans la population totale



	Niraparib (n=487)	Placebo (n=246)
Median PFS		
Months	13.8	8.2
(95% CI)	(11.5–14.9)	(7.3–8.5)

González Martín A, et al. N Engl J Med. 2019,381:2391–402

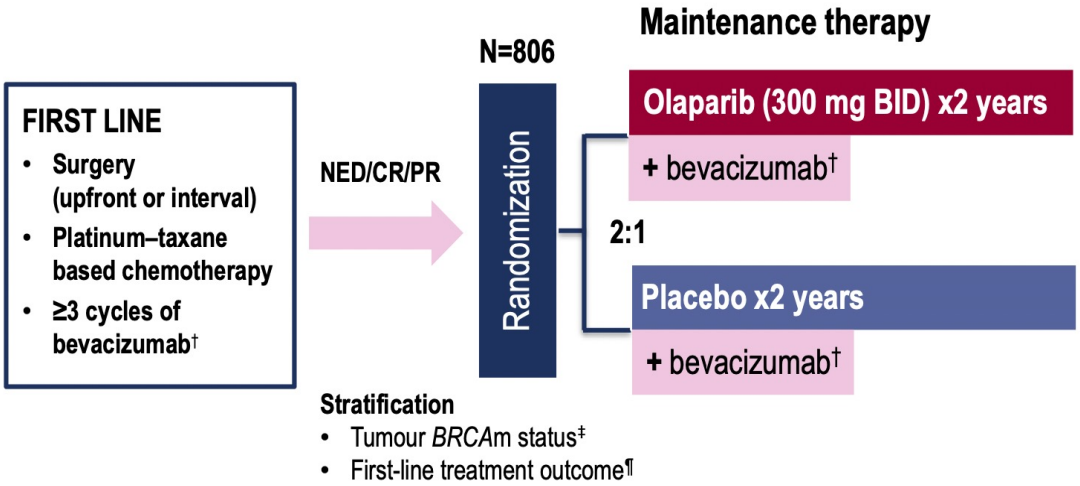
PRIMA analyses exploratoires



González Martín A, et al. N Engl J Med. 2019,381:2391–402; Monk B, et al. presented at SGO 2020

PAOLA : Olaparib + bev phase III : design

Primary endpoint: PFS

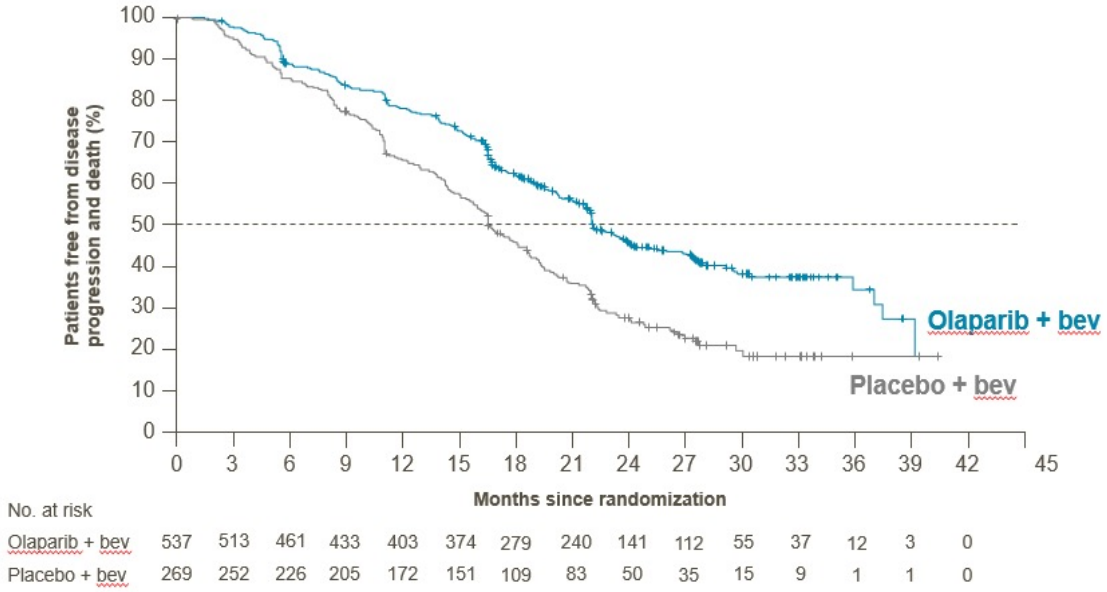


BARCELONA 2019 ESMO congress

*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline *BRCA1* and/or *BRCA2* mutation
†Bevacizumab: 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy; ‡By central labs; ¶According to timing of surgery and NED/CR/PR
BID, twice daily; *BRCA*m, *BRCA1* and/or *BRCA2* mutation; CR, complete response; NED, no evidence of disease; PR, partial response

Ray-Coquard I, et al. N Engl J Med 2019, ESMO 2019

PAOLA critère principal: ITT



	Olaparib + bevacizumab (n=537)	Placebo + bevacizumab (n=269)
Events, n (%) [59% maturity]	280 (52)	194 (72)
Median PFS, months	22.1	16.6

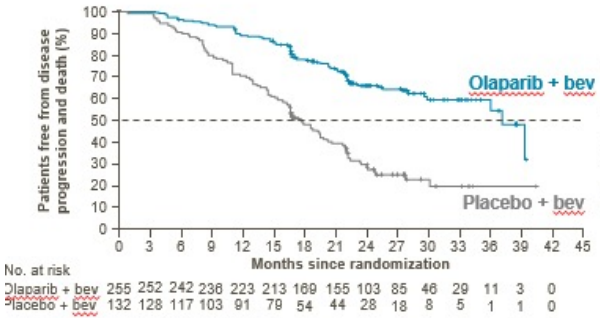
HR 0.59

95% CI 0.49–0.72
P<0.001

Ray-Coquard I, et al. N Engl J Med 2019

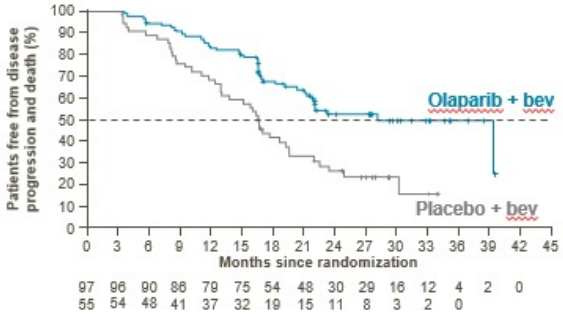
PAOLA analyses exploratoires

HRd, including tBRCAm



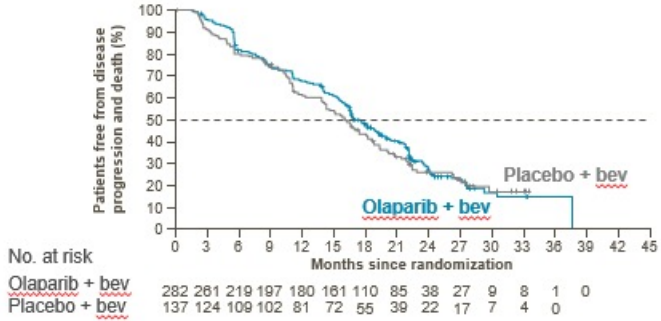
	Olaparib + bevacizumab (n=255)	Placebo + bevacizumab (n=132)
Events, n (%)	87 (34)	92 (70)
Median PFS, months	37.2[†]	17.7
HR 0.33		
95% CI 0.25–0.45		

HRd, excluding tBRCAm



	Olaparib + bevacizumab (n=97)	Placebo + bevacizumab (n=55)
Events, n (%)	43 (44)	40 (73)
Median PFS, months	28.1[†]	16.6
HR 0.43		
95% CI 0.28–0.66		

HRp/HRunknown



	Olaparib + bevacizumab (n=282)	Placebo + bevacizumab (n=137)
Events, n (%)	193 (68)	102 (74)
HR 0.92		
95% CI 0.72–1.17		

Ray-Coquard I, et al. N Engl J Med 2019

Conclusion Maintenance en 1L

Toute patiente présentant un cancer de l'ovaire avancé de haut grade doit avoir une recherche de mutation BRCA et/ou un test HR

→ Si mutation BRCA1/2 ou HRD positif : iPARP seul ou combo iPARP + bevacizumab

→ Si HRD négatif : Bevacizumab ou iPARP

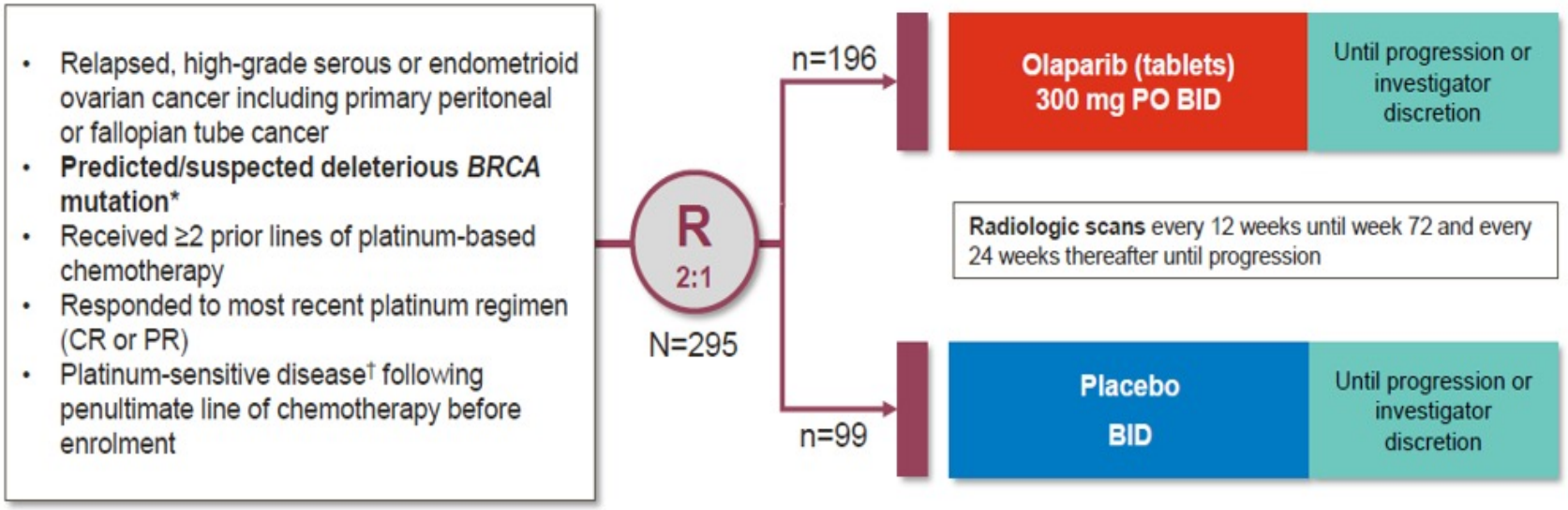
Un gain de PFS avec tous les traitements

Et en rechute quelle est la place des iPARP en 2021?

Principales études en rechute

- Patientes BRCAm → **Olaparib: SOLO2** – AMM
- Toutes patientes → **Niraparib** : **NOVA** - AMM
  → **Rucaparib** : **ARIEL3** – AMM
- En rechallenge → **Olaparib : OREO**

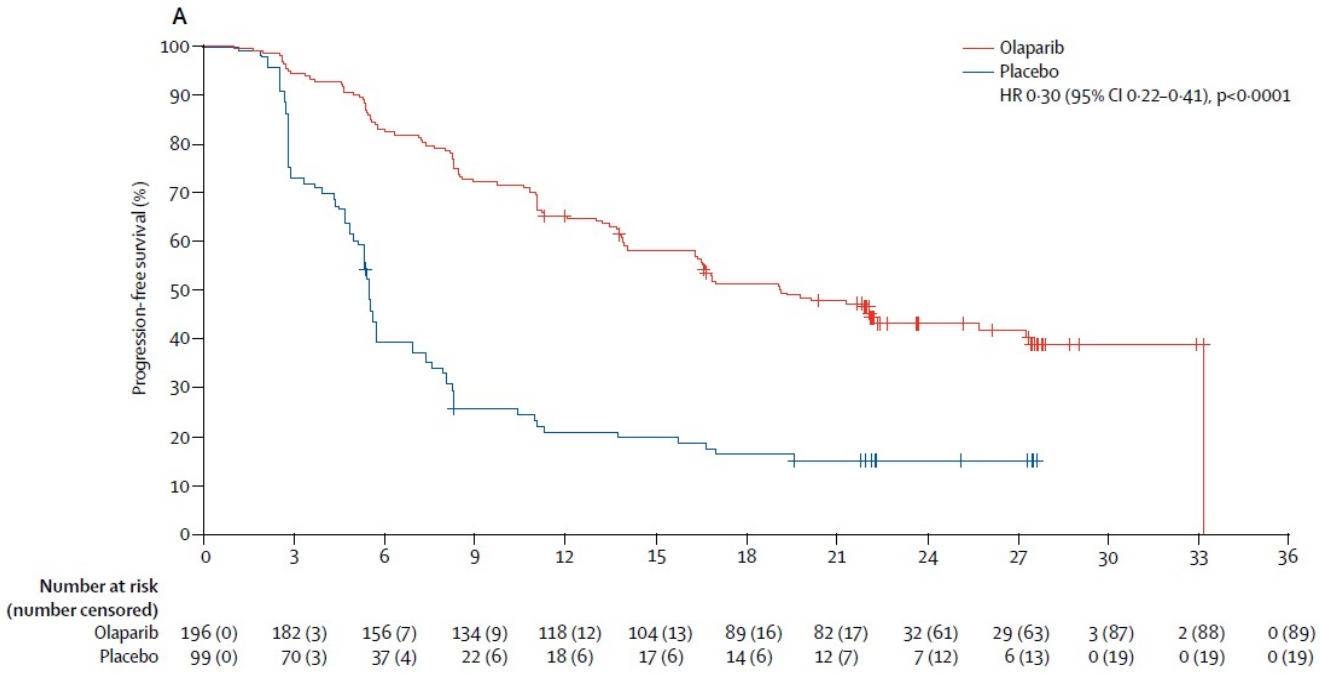
SOLO 2 : Olaparib phase III, BRCAm en rechute platine -S- Design



Critère Principal: mPFS

Pujade-Lauraine E, Lancet Oncol 2017

SOLO 2 : Olaparib phase III, BRCAm en rechute platine -S



	Olaparib (n=196)	Placebo (n=99)
Events, n (%)	107 (55)	80 (81)
Median PFS, months	19.1	5.5

HR 0.30

95% CI 0.22–0.41;
P<0.0001

Pujade-Lauraine et al, Lancet Oncol 2017

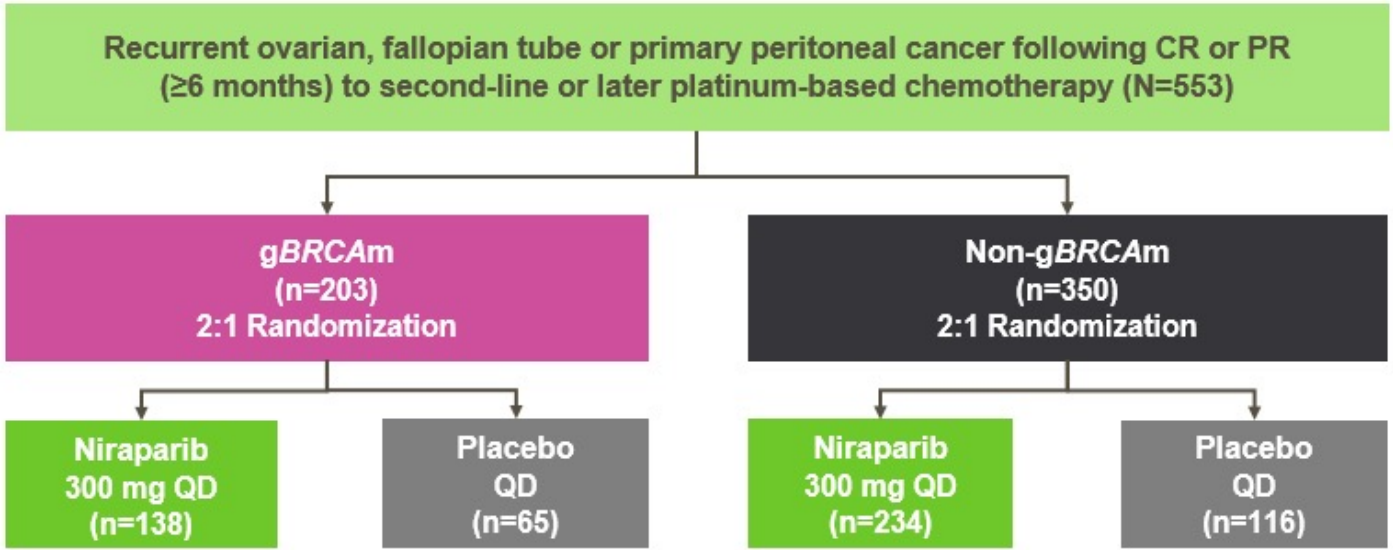
SOLO 2 : Données de Tolérance

	Olaparib (n=195)			Placebo (n=99)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any adverse event	120 (62%)	63 (32%)	8 (4%)	76 (77%)	15 (15%)	3 (3%)
Non-haematological						
Nausea	143 (73%)	5 (3%)	0	33 (33%)	0	0
Fatigue or asthenia*	120 (62%)	8 (4%)	0	37 (37%)	2 (2%)	0
Vomiting	68 (35%)	5 (3%)	0	18 (18%)	1 (1%)	0
Diarrhoea	62 (32%)	2 (1%)	0	20 (20%)	0	0
Dysgeusia	52 (27%)	0	0	7 (7%)	0	0
Headache	48 (25%)	1 (1%)	0	13 (13%)	0	0
Abdominal pain	42 (22%)	5 (3%)	0	28 (28%)	3 (3%)	0
Decreased appetite	43 (22%)	0	0	11 (11%)	0	0
Constipation	40 (21%)	0	0	20 (20%)	3 (3%)	0
Cough	32 (16%)	1 (1%)	0	5 (5%)	0	0
Arthralgia	29 (15%)	0	0	15 (15%)	0	0
Pyrexia	26 (13%)	0	0	6 (6%)	0	0
Dizziness	25 (13%)	1 (1%)	0	5 (5%)	0	0
Dyspnoea	21 (11%)	2 (1%)	0	1 (1%)	0	0
Back pain	22 (11%)	0	0	11 (11%)	2 (2%)	0
Dyspepsia	22 (11%)	0	0	8 (8%)	0	0
Abdominal pain upper	21 (11%)	0	0	12 (12%)	0	0
Nasopharyngitis	21 (11%)	0	0	11 (11%)	0	0
Urinary tract infection	17 (9%)	1 (1%)	0	10 (10%)	0	0
Haematological						
Anaemia†	47 (24%)	36 (18%)	2 (1%)	6 (6%)	2 (2%)	0
Neutropenia‡	28 (14%)	8 (4%)	2 (1%)	2 (2%)	3 (3%)	1 (1%)
Thrombocytopenia§	25 (13%)	2 (1%)	0	2 (2%)	1 (1%)	0
Hypomagnesaemia	28 (14%)	0	0	10 (10%)	0	0
Blood creatinine increased	21 (11%)	0	0	1 (1%)	0	0
Leucopenia	17 (9%)	2 (1%)	1 (1%)	1 (1%)	0	0

Pujade-Lauraine et al, Lancet Oncol 2017

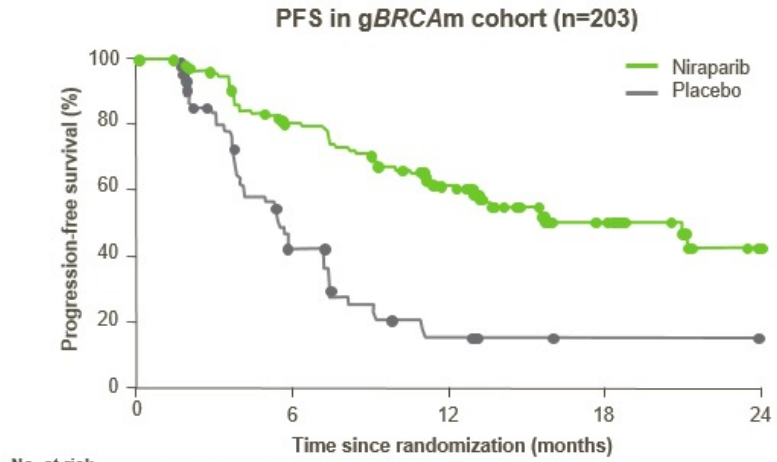
NOVA : Niraparib phase III en rechute platine-S
Design

Deux cohortes indépendantes : gBRCAm / non-gBRCAm
Critère principal: PFS

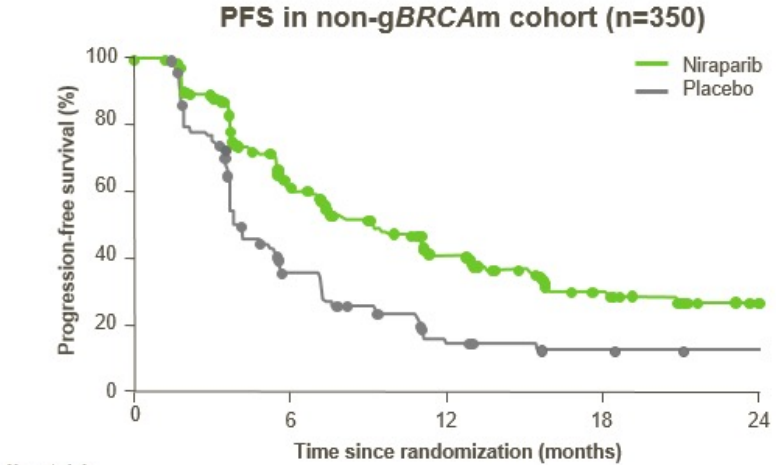


Mirza MR, et al. N Engl J Med 2016;375:2154–64

NOVA critère principal : PFS



	Niraparib (n=138)	Placebo (n=65)
mPFS (95% CI), months	21.0 (12.9–NR)	5.5 (3.8–7.2)
HR (95% CI)	0.27 (0.17–0.41)	
P value	<0.0001	

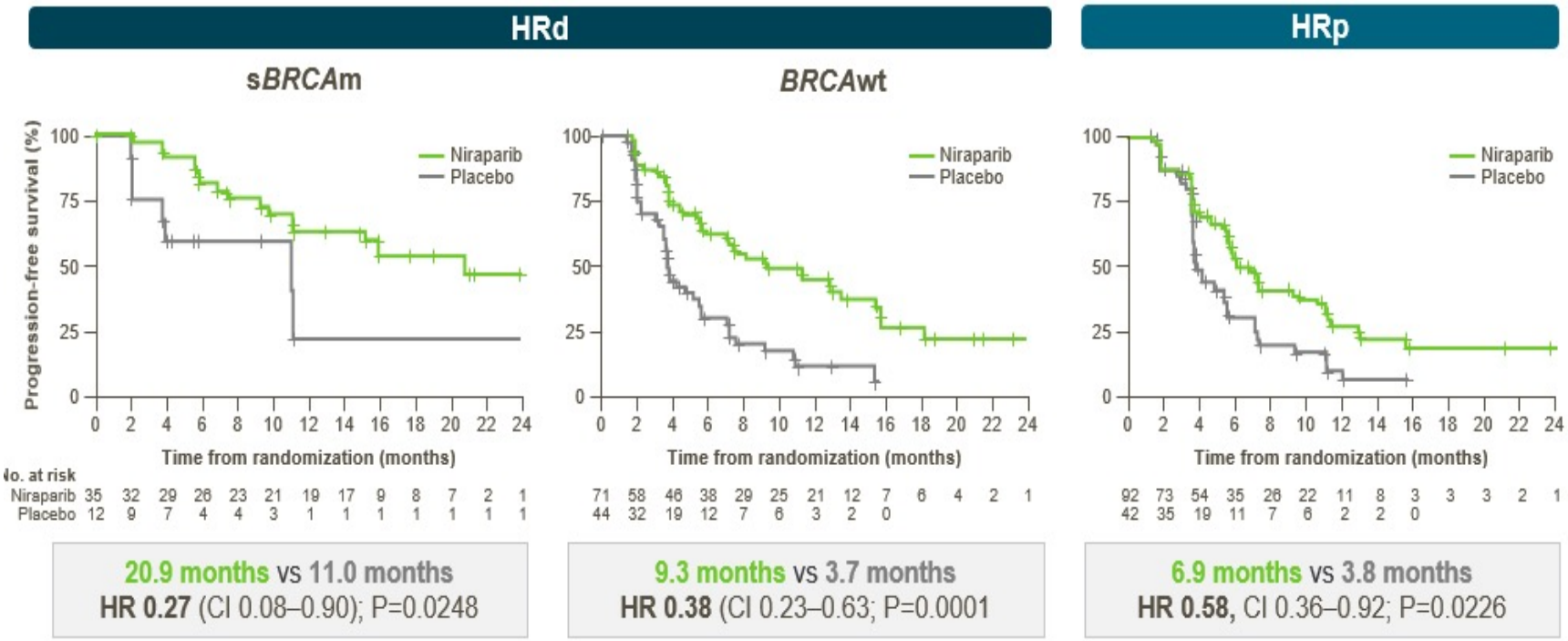


	Niraparib (n=234)	Placebo (n=116)
mPFS (95% CI), months	9.3 (7.2–11.2)	3.9 (3.7–5.5)
HR (95% CI)	0.45 (0.34–0.61)	
P value	*P*<0.0001	

Mirza MR, et al. N Engl J Med 2016;375:2154–64

Abbréviations: CI, confidence interval; g*BRCA*m, germline *BRCA* mutant; HR, hazard ratio; mPFS, median PFS; PFS, progression-free survival.

NOVA, analyses exploratoires : PFS sous-groupes dans la cohorte non-gBRCAm



Mirza MR, et al. N Engl J Med 2016

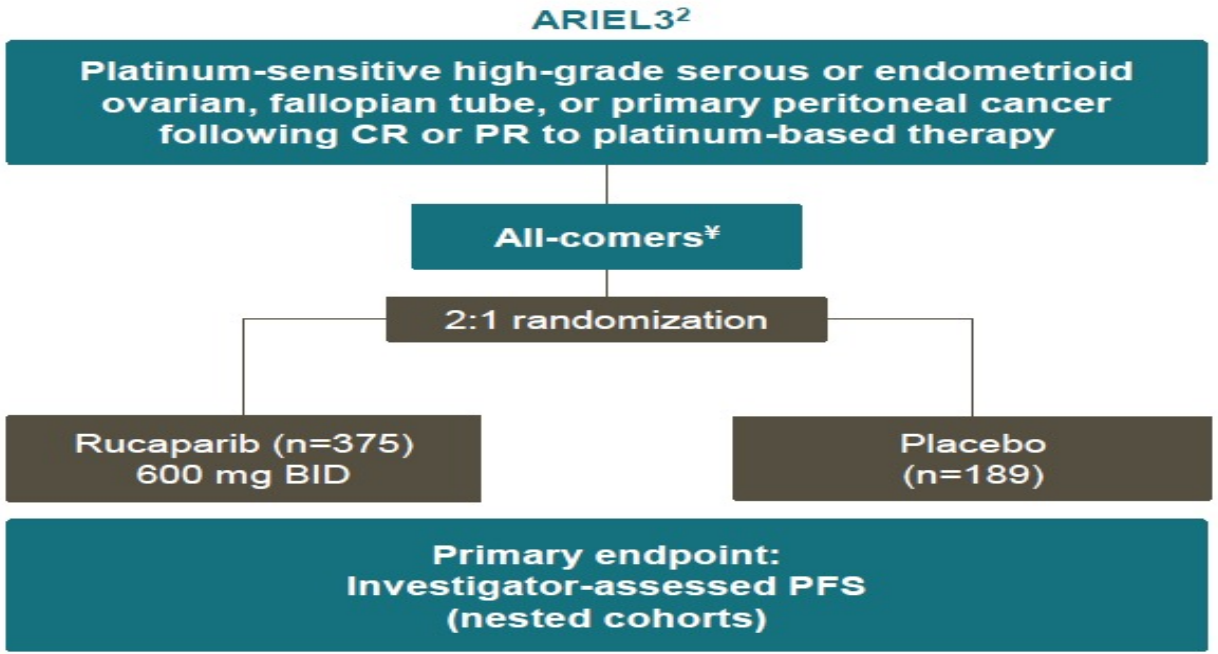
NOVA : données de tolérance

Table 2. Adverse Events.*

Event	Niraparib (N=367)		Placebo (N=179)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Nausea	270 (73.6)	11 (3.0)	63 (35.2)	2 (1.1)
Thrombocytopenia†	225 (61.3)	124 (33.8)	10 (5.6)	1 (0.6)
Fatigue‡	218 (59.4)	30 (8.2)	74 (41.3)	1 (0.6)
Anemia§	184 (50.1)	93 (25.3)	12 (6.7)	0
Constipation	146 (39.8)	2 (0.5)	36 (20.1)	1 (0.6)
Vomiting	126 (34.3)	7 (1.9)	29 (16.2)	1 (0.6)
Neutropenia¶	111 (30.2)	72 (19.6)	11 (6.1)	3 (1.7)
Headache	95 (25.9)	1 (0.3)	17 (9.5)	0
Decreased appetite	93 (25.3)	1 (0.3)	26 (14.5)	1 (0.6)
Insomnia	89 (24.3)	1 (0.3)	13 (7.3)	0
Abdominal pain	83 (22.6)	4 (1.1)	53 (29.6)	3 (1.7)
Dyspnea	71 (19.3)	4 (1.1)	15 (8.4)	2 (1.1)
Hypertension	71 (19.3)	30 (8.2)	8 (4.5)	4 (2.2)
Diarrhea	70 (19.1)	1 (0.3)	37 (20.7)	2 (1.1)
Dizziness	61 (16.6)	0	13 (7.3)	0
Cough	55 (15.0)	0	8 (4.5)	0
Back pain	49 (13.4)	2 (0.5)	21 (11.7)	0
Arthralgia	43 (11.7)	1 (0.3)	22 (12.3)	0
Dyspepsia	42 (11.4)	0	17 (9.5)	0
Nasopharyngitis	41 (11.2)	0	13 (7.3)	0
Urinary tract infection	38 (10.4)	3 (0.8)	11 (6.1)	2 (1.1)
Palpitations	38 (10.4)	0	3 (1.7)	0
Dysgeusia	37 (10.1)	0	7 (3.9)	0
Myalgia	30 (8.2)	1 (0.3)	18 (10.1)	0
Abdominal distention	28 (7.6)	0	22 (12.3)	1 (0.6)

Mirza MR et al, NEJM, 2016

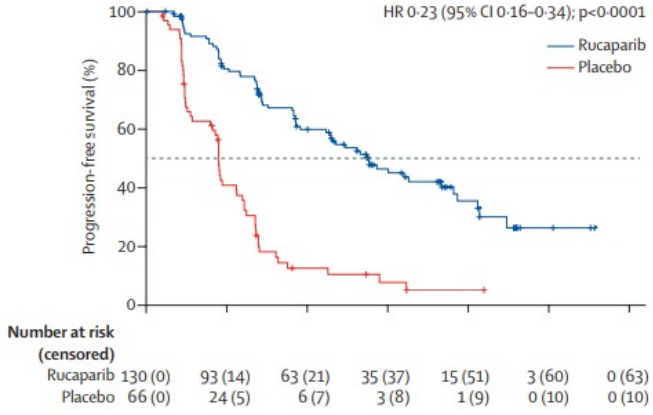
ARIEL 3 : Rucaparib, phase III en rechute platine-S
Design



Coleman RL, et al. Lancet. 2017;390:1949–61.

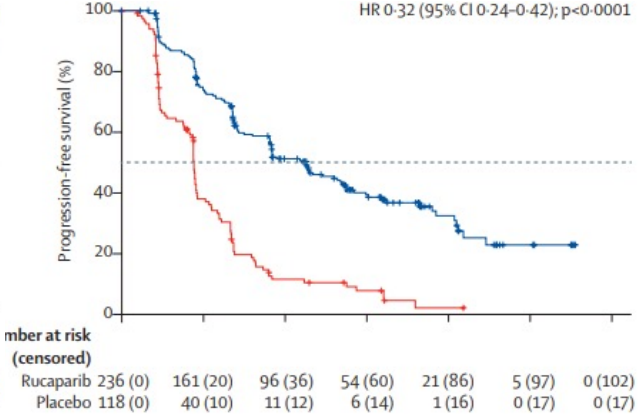
ARIEL 3, critère principal : PFS

mPFS BRCAm



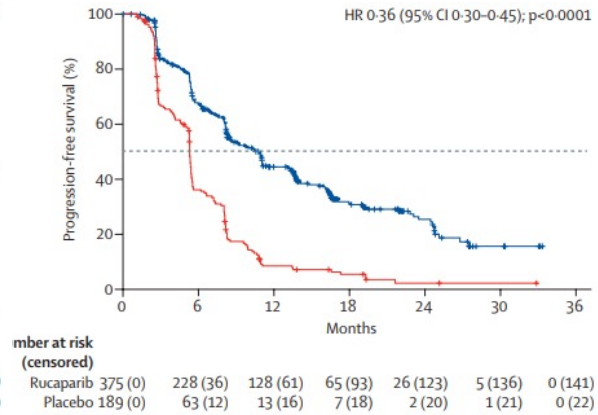
mPFS: 16,6 mois vs 5,4 mois

mPFS HRd



mPFS: 13,6 mois vs 5,4 mois

mPFS en ITT

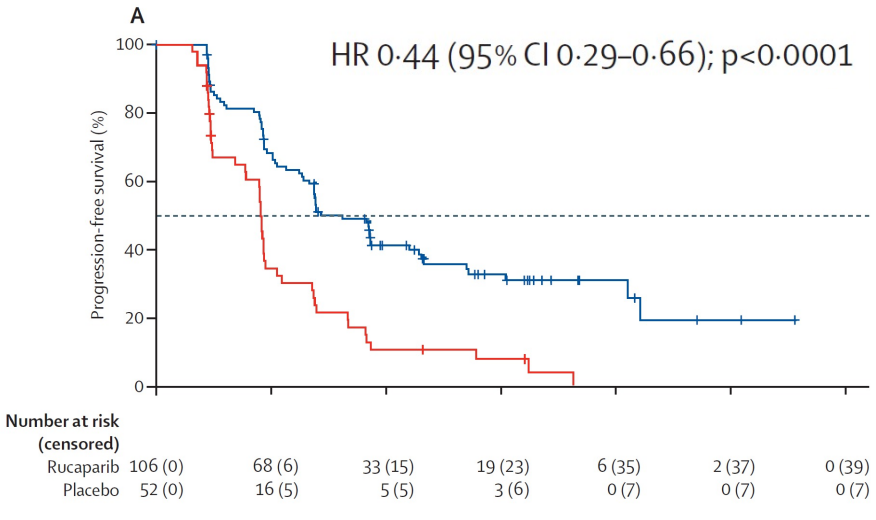


mPFS: 10,8 mois vs 5,4 mois

Coleman RL, et al. Lancet. 2017;390:1949–61

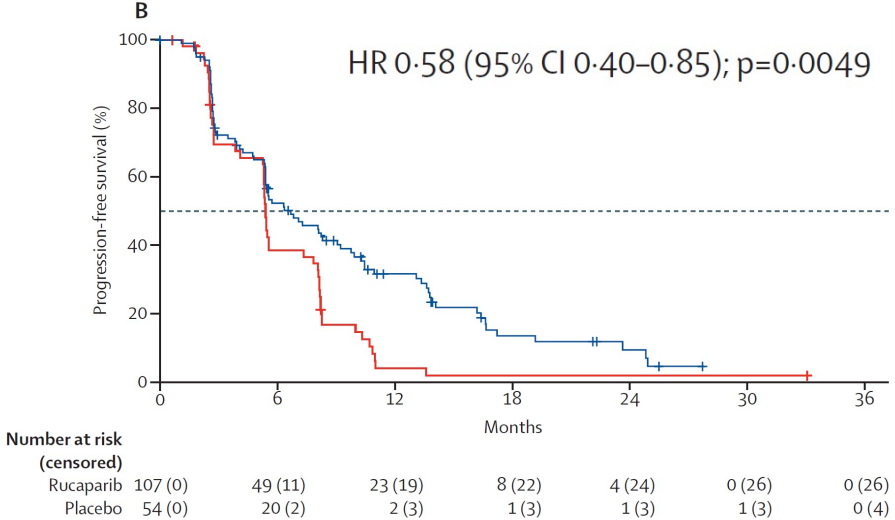
ARIEL 3, Analyses exploratoires BRCAwt

BRCAwt / HRd



mPFS: 9,7 mois vs 5,4 mois

HRp



mPFS: 6,7 vs 5,4 mois

Coleman RL, et al. Lancet. 2017;390:1949–61

ARIEL 3 : données de tolérance

	Rucaparib (n=372)				Placebo (n=189)			
	Any grade	Grade 1–2	Grade 3	Grade 4	Any grade	Grade 1–2	Grade 3	Grade 4
At least one AE	372 (100%)*	163 (44%)	179 (48%)	24 (6%)	182 (96%)†	154 (81%)	24 (13%)	2 (1%)
Blood and lymphatic system disorders								
Decreased haemoglobin concentration (anaemia)	139 (37%)	69 (19%)	67 (18%)	3 (1%)	11 (6%)	10 (5%)	0	1 (1%)
Decreased neutrophil count (neutropenia)	67 (18%)	42 (11%)	19 (5%)	6 (2%)	9 (5%)	7 (4%)	1 (1%)	1 (1%)
Decreased platelet count (thrombocytopenia)	104 (28%)	85 (23%)	13 (3%)	6 (2%)	5 (3%)	5 (3%)	0	0
Gastrointestinal disorders								
Abdominal distension	41 (11%)	41 (11%)	0	0	22 (12%)	22 (12%)	0	0
Abdominal pain	111 (30%)	102 (27%)	9 (2%)	0	49 (26%)	48 (25%)	1 (1%)	0
Upper abdominal pain	52 (14%)	50 (13%)	2 (1%)	0	10 (5%)	10 (5%)	0	0
Constipation	136 (37%)	129 (35%)	7 (2%)	0	45 (24%)	43 (23%)	2 (1%)	0
Diarrhoea	118 (32%)	116 (31%)	2 (1%)	0	41 (22%)	39 (21%)	2 (1%)	0
Dyspepsia	54 (15%)	53 (14%)	1 (<1%)	0	9 (5%)	9 (5%)	0	0
Nausea	280 (75%)	266 (72%)	14 (4%)	0	69 (37%)	68 (36%)	1 (1%)	0
Vomiting	136 (37%)	121 (33%)	15 (4%)	0	28 (15%)	26 (14%)	2 (1%)	0
General disorders and administration site conditions								
Fatigue (asthenia)	258 (69%)	233 (63%)	25 (7%)	0	83 (44%)	78 (41%)	5 (3%)	0
Peripheral oedema	39 (10%)	38 (10%)	1 (<1%)	0	14 (7%)	14 (7%)	0	0
Pyrexia	44 (12%)	44 (12%)	0	0	8 (4%)	8 (4%)	0	0
Infections and infestations								
Upper respiratory tract infection	41 (11%)	41 (11%)	0	0	6 (3%)	4 (2%)	2 (1%)	0
Investigations								
Increase in alanine aminotransferase or aspartate aminotransferase concentration‡	126 (34%)	87 (23%)	39 (10%)	0	7 (4%)	7 (4%)	0	0
Increase in blood creatinine concentration	57 (15%)	56 (15%)	1 (<1%)	0	3 (2%)	3 (2%)	0	0
Metabolism and nutrition disorders								
Decreased appetite	87 (23%)	85 (23%)	2 (1%)	0	26 (14%)	26 (14%)	0	0
Hypomagnesaemia	40 (11%)	39 (10%)	1 (<1%)	0	11 (6%)	11 (6%)	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	57 (15%)	55 (15%)	2 (1%)	0	24 (13%)	24 (13%)	0	0
Back pain	45 (12%)	45 (12%)	0	0	28 (15%)	28 (15%)	0	0
Nervous system disorders								
Dizziness	54 (15%)	54 (15%)	0	0	15 (8%)	14 (7%)	1 (1%)	0
Dysgeusia	146 (39%)	146 (39%)	0	0	13 (7%)	13 (7%)	0	0
Headache	67 (18%)	66 (18%)	1 (<1%)	0	30 (16%)	29 (15%)	1 (1%)	0
Psychiatric disorders								
Insomnia	53 (14%)	53 (14%)	0	0	15 (8%)	15 (8%)	0	0
Respiratory, thoracic, and mediastinal disorders								
Cough	54 (15%)	54 (15%)	0	0	25 (13%)	25 (13%)	0	0
Dyspnoea	50 (13%)	50 (13%)	0	0	14 (7%)	14 (7%)	0	0
Skin and subcutaneous tissue disorders								
Photosensitivity reaction	64 (17%)	62 (17%)	2 (1%)	0	1 (1%)	1 (1%)	0	0
Pruritus	47 (13%)	47 (13%)	0	0	19 (10%)	19 (10%)	0	0
Rash	46 (12%)	45 (12%)	1 (<1%)	0	17 (9%)	17 (9%)	0	0

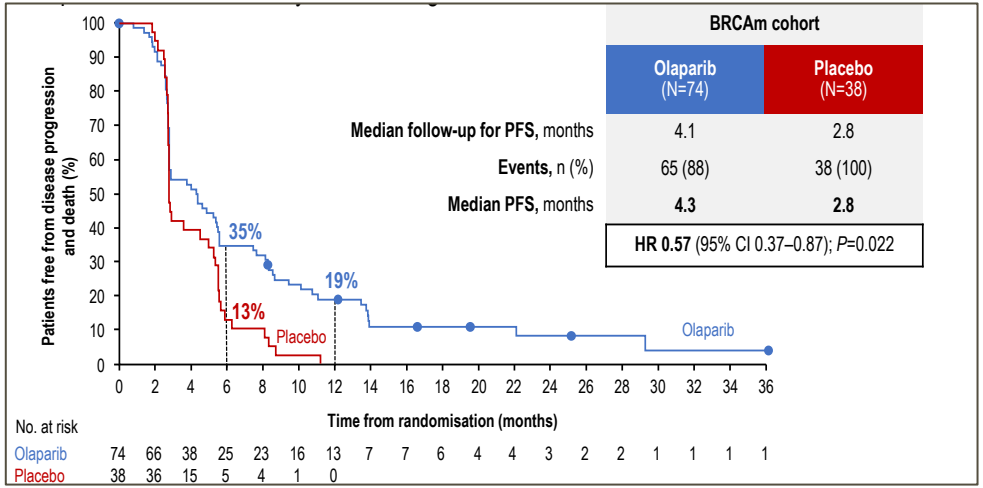
Data are n (%). AE=adverse event. *Includes six patients who died from a treatment-emergent adverse event. †Includes two patients who died from a treatment-emergent adverse event. ‡Elevations were generally transient, self-limiting, and not associated with other signs of liver toxicity.

Table 2: Treatment-emergent adverse events of any grade reported in at least 10% of patients in either group in the safety population

Coleman RL et al, the lancet, 2017

Place du Re-challenge iPARP : Essai OREO

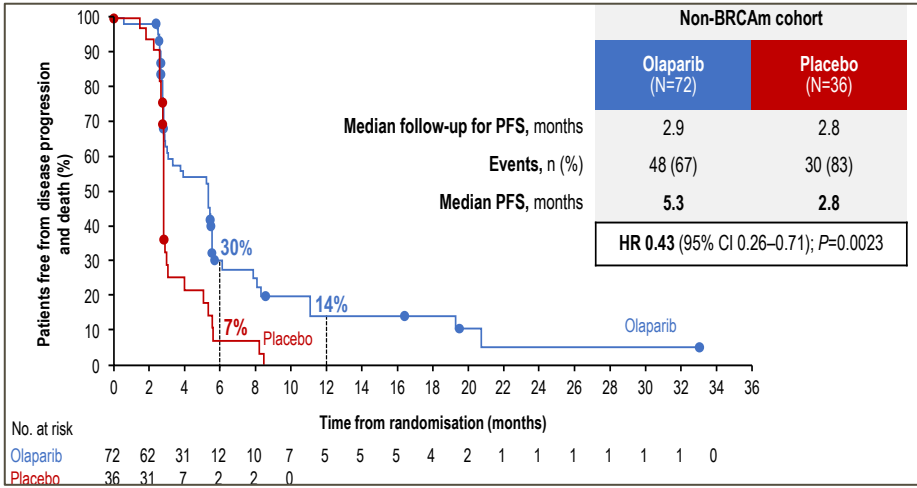
Cohorte BRCAm



BRCAm cohort	Olaparib (N=74)	Placebo (N=38)
Median follow-up for PFS, months	4.1	2.8
Events, n (%)	65 (88)	38 (100)
Median PFS, months	**4.3**	**2.8**

HR 0.57 (95% CI 0.37–0.87); *P*=0.022

Cohorte non-BRCAm



Non-BRCAm cohort	Olaparib (N=72)	Placebo (N=36)
Median follow-up for PFS, months	2.9	2.8
Events, n (%)	48 (67)	30 (83)
Median PFS, months	**5.3**	**2.8**

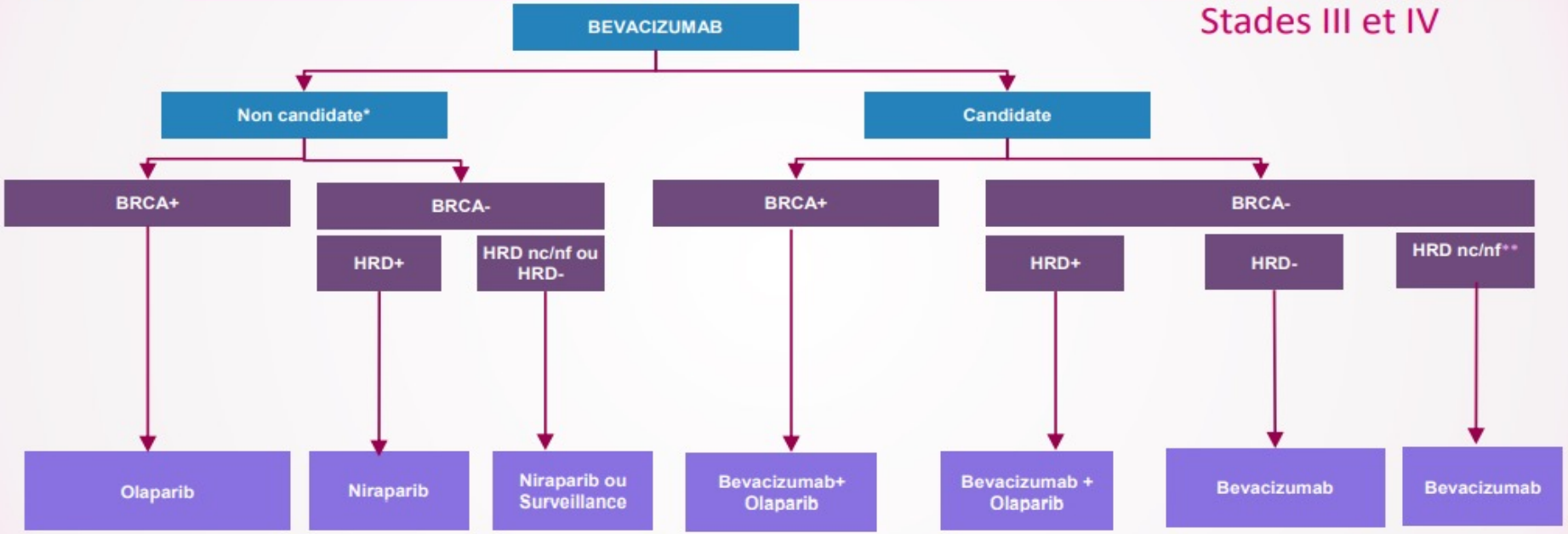
HR 0.43 (95% CI 0.26–0.71); *P*=0.0023

Pujade-Lauraine et al, ESMO 2021

Algorithme de choix thérapeutiques avec les nouvelles ATU et post-ATU disponibles en 2021

Nice St Paul de Vence
RPC 2021

Cancer ovaire – haut grade – Stades III et IV



*Non candidate: contre-indication ou option du bévacizumab non retenue par le médecin

HRD + : Test HRD positif (le test a identifié une défaillance de la recombinaison homologue)
HRD- : Test HRD négatif (le test n'a pas identifié de défaillance de la recombinaison homologue)
HRDnf : test non fait (à faire)
HRDnc : test non contributif (à refaire)

Conclusion

une avancée majeure en 1L et en rechute

Importance recherche mutation BRCA et statut HRD systématiquement

Un plus grand choix de traitements en 1L et en rechute pour les patientes

MERCI