Actualités Post ESMO en onco-gynécologie

Mardi 18 Octobre 2022

Dr Coriolan Lebreton

Institut Bergonié

Rétrospective Post Congrès 2022

Liens d'intérêts

- Orateur pour un laboratoire pharmaceutique :
  - Clovis, Eisai, MSD
- Prise en charge par un laboratoire pharmaceutique de la participation à un congrès national ou international :
  - Amgen, Chugai, Eisai, Pfizer, GSK
- Consultant : Non
- Investigateur principal d'un essai de l'industrie pharmaceutique : Non
- Parts sociales ou action dans un laboratoire pharmaceutique : Non

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ATALANTE
Atezolizumab and Avastin
in late recurrent disease

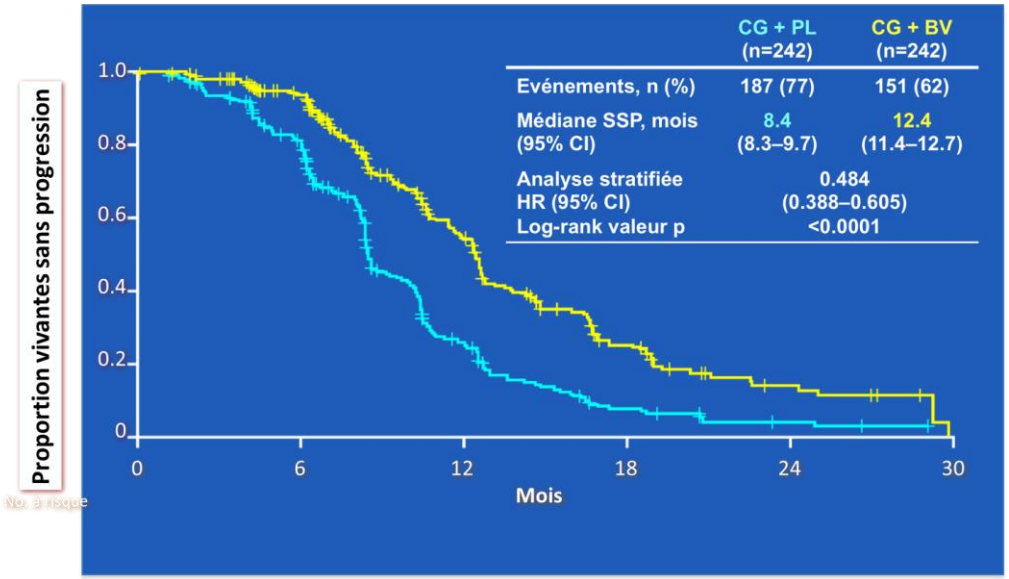
A randomized, double-blinded, phase III study of atezolizumab versus placebo in patients with late relapse of epithelial ovarian, fallopian tube, or peritoneal cancer treated by platinum-based chemotherapy and bevacizumab. GINECO-OV236b/ENGOT-ov29

J.E. Kurtz, E. Pujade-Lauraine, A. Oaknin, L. Belin, I. Tsibulak, D. Cibula, I. Vergote, O. Rosengarten, M. Rodrigues, N. de Gregorio, J. Martinez-Garcia, P. Pautier, M.A. Mouret Reynier, F. Selle, V. D'Hondt, F. Joly Lobbedez, E. Bultot Boissier, A. Floquet, P.-E. Heudel, F. Heitz

Rationnel :
Doublet à base de sel de platine et bevacizumab en rechute tardive

OCEAN

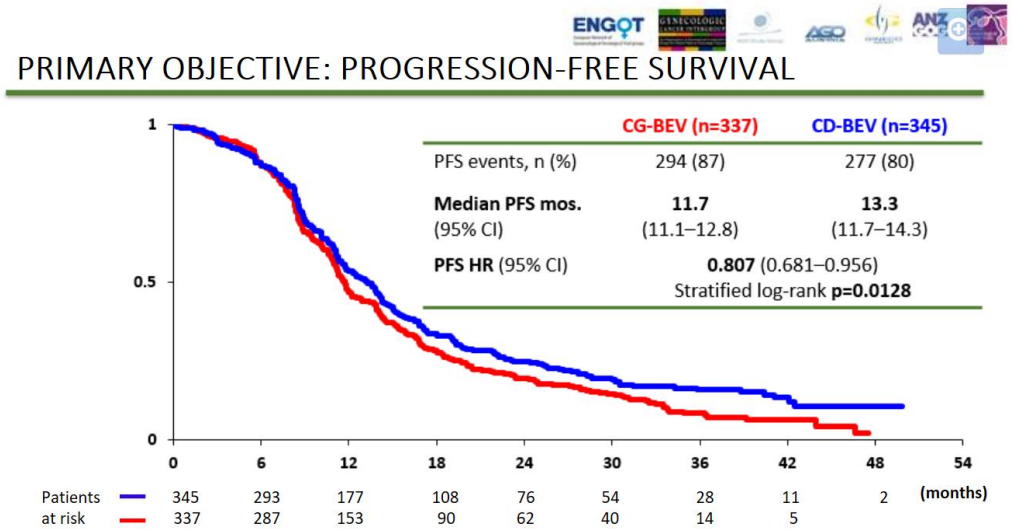
Carbo/gem/bev vs carbo/gem



+4mois *Aghajanian et al. J Clin Oncol 2012*

AGO 2.21

Carbo/PLD/bev vs Carbo/gem/bev



+1,6mois *Pfisterer et al. Lancet Oncol 2020*

addition d'inhibiteur de point de contrôle de l'immunité augmente l'activité antitumorale

du bevacizumab

de la chimiothérapie

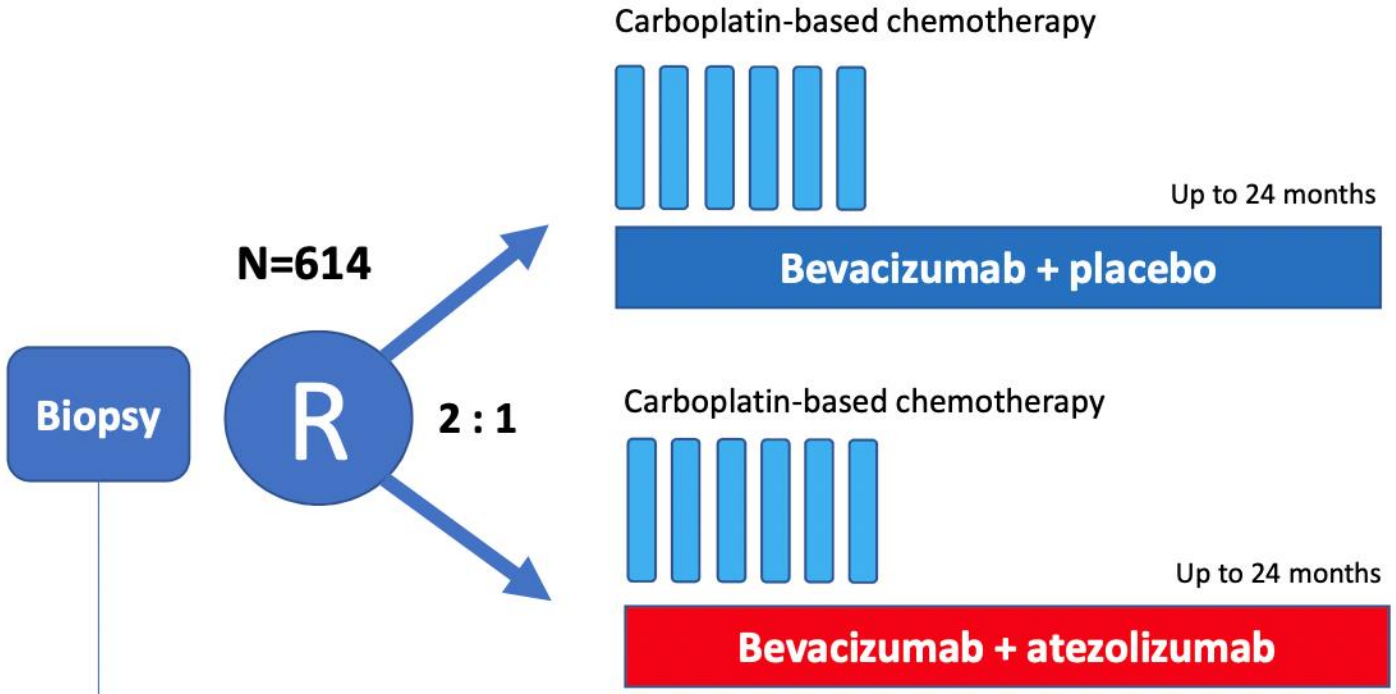
Bini et al. Lancet 2019
Socinski et al. N Engl J Med 2018

Design de l'étude

- Relapsed non-mucinous epithelial OC
- Platinum-free interval >6 mos
- 1 or 2 prior chemotherapy lines
- ECOG PS ≤1

Stratification factors

- PD-L1 ≥ 1% on immune cells vs <1% vs unknown (Ventana clone SP142)
- Chemotherapy: Cb-PLD or gemcitabine or paclitaxel
- Platinum-free interval: 6-12 vs >12 months



- **Co-primary endpoints** are progression-free survival (PFS1) according to investigator in the ITT and PD-L1-positive populations
- **Secondary endpoints:** TSST, TFST, OS, safety (NCI CTCAE V 4.03) and HrQoL (EORTC QLQ-C30, QOLQ OV-28, EQ5D-5L)

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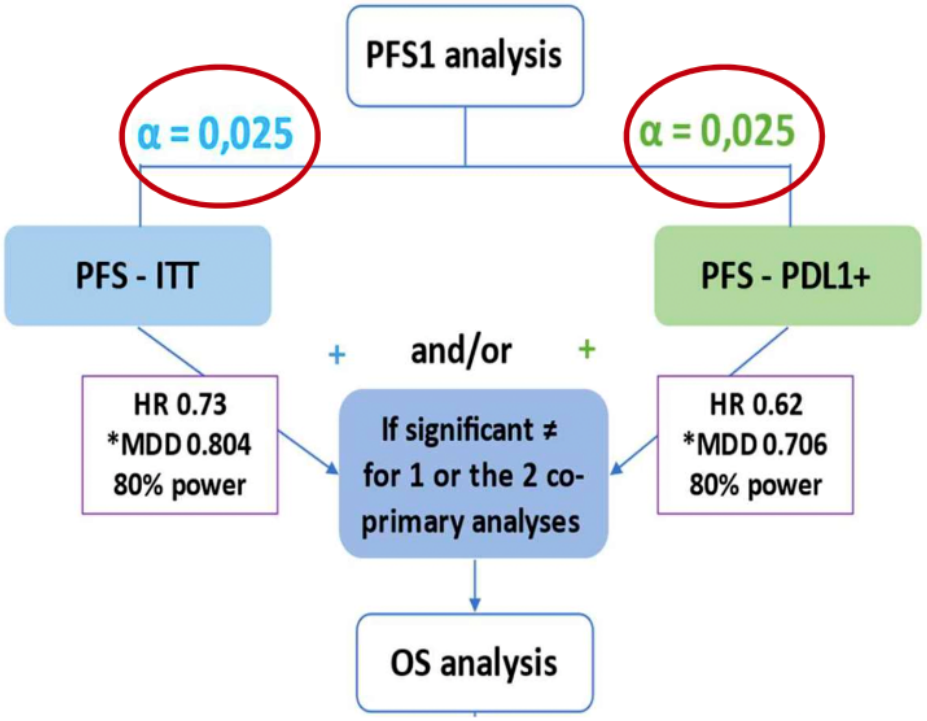
Kurtz et al. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089

Analyses statistiques

- PFS1 was analyzed using a Cox model adjusted by stratification factors with a two-sided α level at 0.025 and 80% power for each PFS co-primary in the ITT and PD-L1-positive populations
- 491 events in the ITT and 186 in the PD-L1-positive populations were expected to show a reduction in the risk of progression of 27% (difference of median PFS1 of 4.8 months) and of 38% (difference of median PFS1 of 9.0 months), respectively
- Following a hierarchical approach, if either of the co-primary PFS1 comparisons was significant, overall survival could then be analyzed in both the ITT and PD-L1-positive populations



Kurtz et al. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089

Caractéristiques des patientes

	Atezo (N=410)	Placebo (N=204)
Median (IQR) patient age, years	63 [55-70]	64 [55-71]
Histology, n (%)		
Serous high grade	346 (84)	169 (83)
Serous low grade	32 (8)	8 (4)
Endometrioid high grade	12 (3)	11 (5)
Clear cell	8 (2)	9 (4)
Others	12 (3)	7 (3)
ECOG, n (%)		
0	277 (68)	131 (64)
1	131 (32)	72 (35)
2	2 (<1)	0 (0)
Number of prior lines, n (%)		
1	307 (75)	147 (72)
2	103 (25)	57 (28)
Last line of therapy, n (%)		
Platinum	410 (100)	204 (100)
Bevacizumab	203 (50)	107 (52)
PARPi	74 (18)	40 (20)
Debulking surgery (within 6 months of inclusion), n (%)	62 (15)	30 (15)
Complete macroscopic resection	34 (8)	20 (10)

Kurtz et al. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089

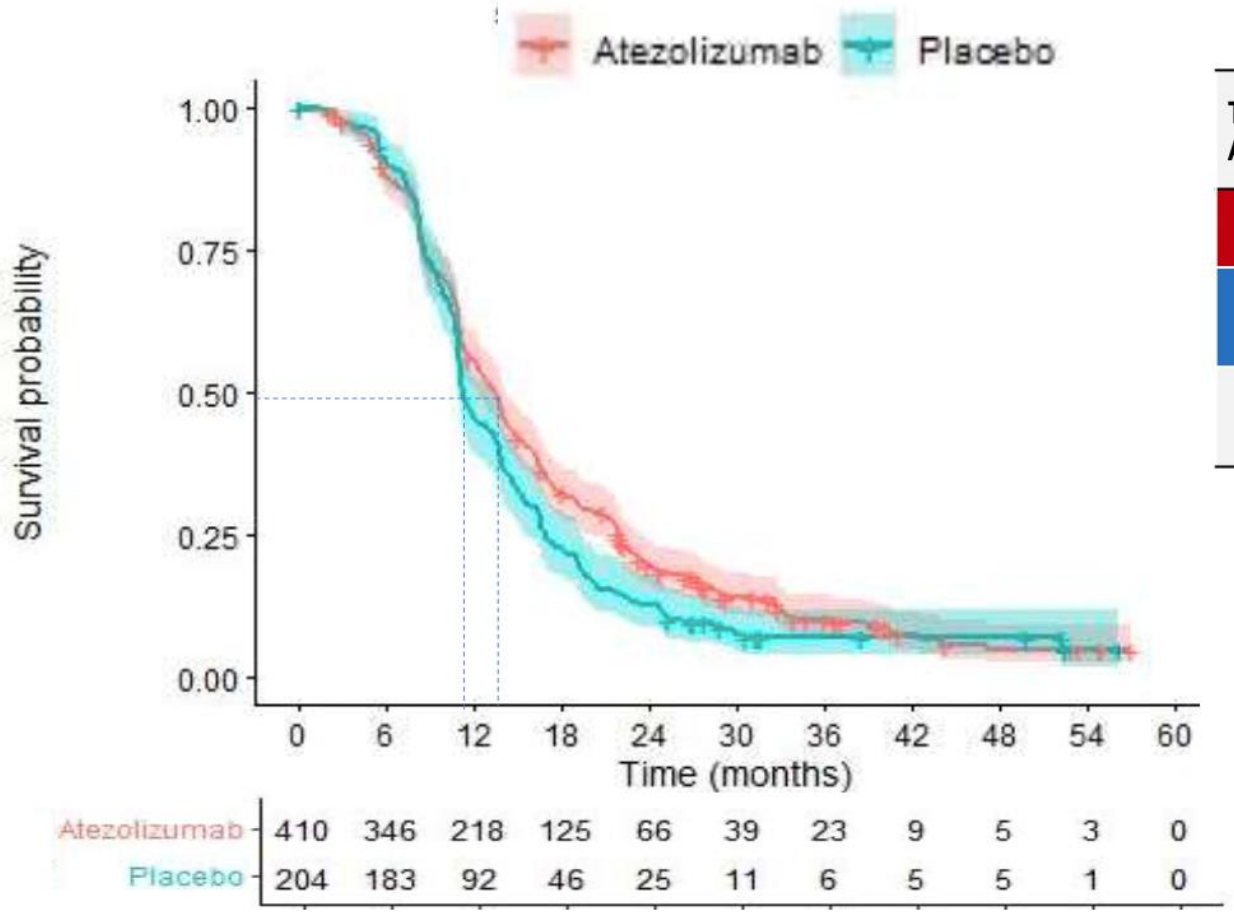
Caractéristiques des patientes

	Atezo (N=410)	Placebo (N=204)
PD-L1 status, n (%)		
≥1%	156 (38)	77 (38)
<1%	196 (48)	102 (50)
Inconclusive/missing	58 (14)	25 (12)
***BRCA* status, n (%)**		
Mutant	40 (10)	32 (16)
Non-mutant	241 (59)	118 (58)
Inconclusive/missing	129 (31)	54 (26)
Chemotherapy chosen by the investigator, n (%)		
Carboplatin-PLD	259 (63)	128 (63)
Carboplatin-gemcitabine	118 (29)	58 (28)
Carboplatin-paclitaxel	33 (8)	18 (9)

Kurtz et al. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089

Survie sans progression

En ITT



Treatment Arm	N	Event N (%)	PFS at 6m % (95% CI)	PFS at 12m % (95% CI)	PFS at 18m % (95% CI)	Median PFS (95% CI)
Atezo	410	348 (85)	88 (85-91)	56 (51- 61)	32 (28-37)	**13.5 mos** (12.2-14.2)
Placebo	204	187 (92)	91 (87- 95)	46 (39- 53)	23 (18-30)	**11.3 mos** (11.0-13.5)
		Hazard ratio= 0.83 [0.69-0.99]				**P=.041**

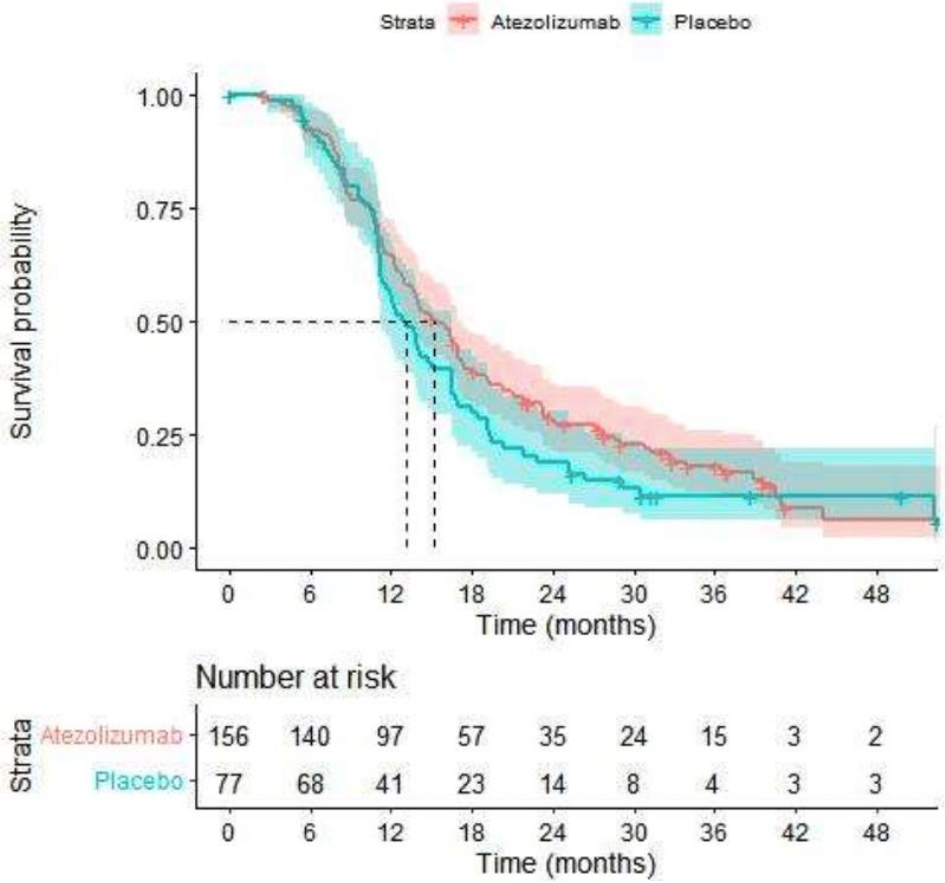
median follow-up : 36.6 months

The ATALANTE trial did not meet its first co-primary objective:
PFS1 in the ITT population

Kurtz et al. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089

Survie sans progression

Population PD-L1 positive



Treatment Arm	N	Events N (%)	PFS at 6m % (95% CI)	PFS at 12m % (95% CI)	PFS at 18m % (95% CI)	Median PFS (95% CI)
Atezo	156	124 (79)	93 (89-97)	64 (57- 72)	39 (32-47)	**15.2 mos** (13.6-17.3)
Placebo	77	66 (86)	92 (86- 98)	55 (45- 68)	31 (22-44)	**13.1 mos** (11.3-16.5)
		Hazard ratio= 0.86 [0.63-1.16]				***P*=.30**

The ATALANTE trial did not meet its co-primary objective:

PFS1 in the PD-L1 positive population

Kurtz et al. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089

Immune-related infusion reactions & auto-immune disorders (AESI)

AESI, n§ (%)	Atezo (N=410)	Placebo (N=204)
All grade AESI for atezolizumab	109 (27)	30 (15)
Grade 3/4 AESI	52 (13)	16 (8)
treatment-related	25 (6)	5 (2)
Immune related infusion reaction (all grades)	34 (8)	9 (4)
Autoimmune disorders (all grades)	91 (22)	23 (11)
Hypothyroidism	45 (11)	10 (5)
Hyperthyroidism	8 (2)	5 (2)
Hepatitis or transaminitis	9 (2)	1 (<1)
Colitis or severe diarrhea	4 (1)	4 (2)
Pancreatitis	4 (1)	0 (0)
Pneumonitis	3 (1)	0 (0)
Diabetes mellitus	2 (<1)	0 (0)
Adrenal insufficiency	2 (<1)	0 (0)
Ocular	1 (<1)	0 (0)
Nephritis	1 (<1)	0 (0)
Other	27 (7)	5 (2)

§Number of patients with at least one event

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Synthèse – discussion

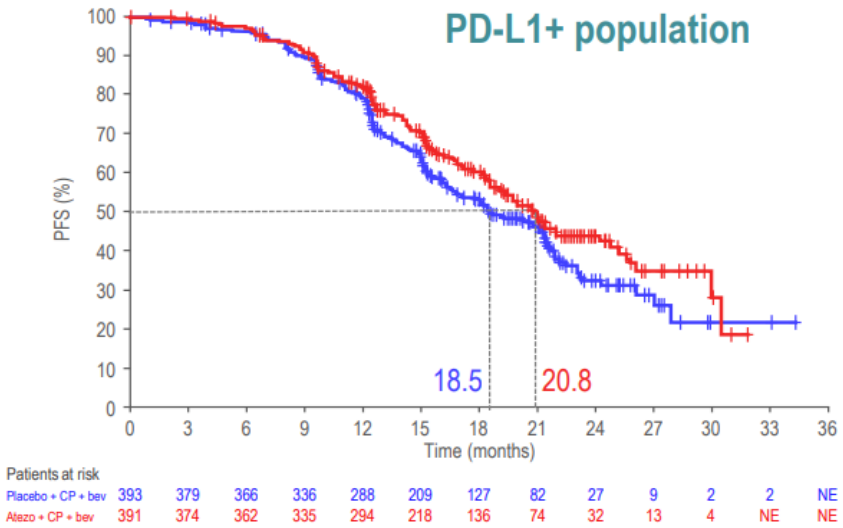
PD-L1 >/= 1

- Bon cut-off?

Quid du statut BRCA

- manquant chez 30% des patientes de l'étude
  - habituellement moins de réponse au bevacizumab en cas de mutation BRCA (1-2)

Intérêt du triple combo IO-beva-PARPinhibiteur?



PD-L1+ population	
Placebo + CP + bev (n=393)	Atezo + CP + bev (n=391)
199 (50.6)	167 (42.7)
18.5 (16.6–21.4)	20.8 (19.1–24.2)
0.80 (0.65–0.99)	
0.0376	
32.2 (25.4–39.0)	43.9 (37.2–50.5)

IMAGYN-050 en première ligne
Pas de bénéfice à l'adjonction de l'atezolizumab

(1) Burger NEJM 2011
(2) Harter GynOncol 2016
(3) Moore et al. ESMO 2020

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GINECO | ENGOT European Network of Gynaecological Oncological Trial groups | GCIG GYNECOLOGIC CANCER INTERGROUP

Final overall survival results from the Phase III PAOLA-1/ENGOT-ov25 trial evaluating maintenance olaparib plus bevacizumab in patients with newly diagnosed advanced ovarian cancer

Isabelle Ray-Coquard,[1] Alexandra Leary,[2] Sandro Pignata,[3] Claire Cropet,[4] Antonio González-Martín,[5] Gerhard Bogner,[6] Hiroyuki Yoshida,[7] Ignace Vergote,[8] Nicoletta Colombo,[9] Johanna Mäenpää,[10] Frédéric Selle,[11] Barbara Schmalfeldt,[12] Giovanni Scambia,[13] Eva Maria Guerra Alia,[14] Claudia Lefeuvre-Plesse,[15] Antje Belau,[16] Alain Lortholary,[17] Martina Gropp-Meier,[18] Eric Pujade-Lauraine,[19] Philipp Harter[20]

[1]Centre Léon BERARD, Lyon, and GINECO, France; [2]Institut Gustave Roussy, Villejuif, and GINECO, France; [3]Istituto Nazionale Tumori 'Fondazione G Pascale', IRCCS, Napoli, and MITO, Italy; [4]Centre Léon BERARD, Lyon,, France; [5]Clínica Universidad de Navarra, Madrid, and GEICO, Spain; [6]Paracelsus Medical University Salzburg, Salzburg, and AGO Au, Austria; [7]Saitama Medical University International Medical Center, Saitama, and GOTIC, Japan; [8]Leuven Cancer Institute, Leuven, and BGOG, Belgium; [9]European Institute of Oncology, Milan, and MANGO, Italy; [10]Tampere University and University Hospital, Tampere, and NSGO, Finland; [11]Groupe Hospitalier Diaconesses Croix Saint-Simon, Paris, and GINECO, France; [12]Universitätsklinikum Hamburg-Eppendorf, Hamburg, and AGO, Germany; [13]Università Cattolica del Sacro Cuore di Roma, Rome, and MITO, Italy; [14]Hospital Universitario Ramón y Cajal, Madrid, and GEICO, Spain; [15]Centre Eugène Marquis, Rennes, and GINECO, France; [16]Universitätsmedizin Greifswald, Frauenklinik & Frauenarztpraxis, Greifswald, and AGO, Germany; [17]Hopital privé du Confluent, Nantes, and GINECO, France; [18]Onkologie Ravensburg, Ravensburg, and AGO, Germany; [19]ARCAGY Research, Paris, France; [20]Kliniken Essen-Mitte, Essen, and AGO, Germany

ClinicalTrials.gov identifier: NCT02477644 | This study was sponsored by ARCAGY Research.

Design de l'étude

Patients
- Newly diagnosed, FIGO stage III–IV high-grade serous or endometrioid ovarian, fallopian tube and/or primary peritoneal cancer*

First-line treatment
- Upfront or interval surgery
- Platinum-taxane based chemotherapy plus ≥2 cycles of bevacizumab†,‡

≤9 weeks → NED/CR/PR

Maintenance therapy

Olaparib tablets 300 mg bid x 2 years
+ bevacizumab§

2:1 randomization stratified by:
- Tumour BRCAm status
- First-line treatment outcome¶

Placebo x 2 years
+ bevacizumab§

Primary endpoint
- Investigator-assessed PFS (RECIST v1.1)

Key secondary endpoints
- PFS2
- OS (planned for 3 years after the primary PFS analysis or 60% data maturity)

*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a gBRCAm; †Patients must have received ≥4 and ≤9 cycles of platinum-based chemotherapy; ‡Patients must have received ≥3 cycles of bevacizumab with the last 3 cycles of chemotherapy, apart from patients undergoing interval surgery who were permitted to receive only 2 cycles of bevacizumab with the last 3 cycles of chemotherapy; §Bevacizumab 15 mg/kg every 3 weeks for a total of 15 months, including when administered with chemotherapy; ¶According to timing of surgery and NED/CR/PR. bid, twice daily; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; gBRCAm, germline BRCA mutation; NED, no evidence of disease; PBC, platinum-based chemotherapy; PFS2, time from randomization to second progression or death; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours.

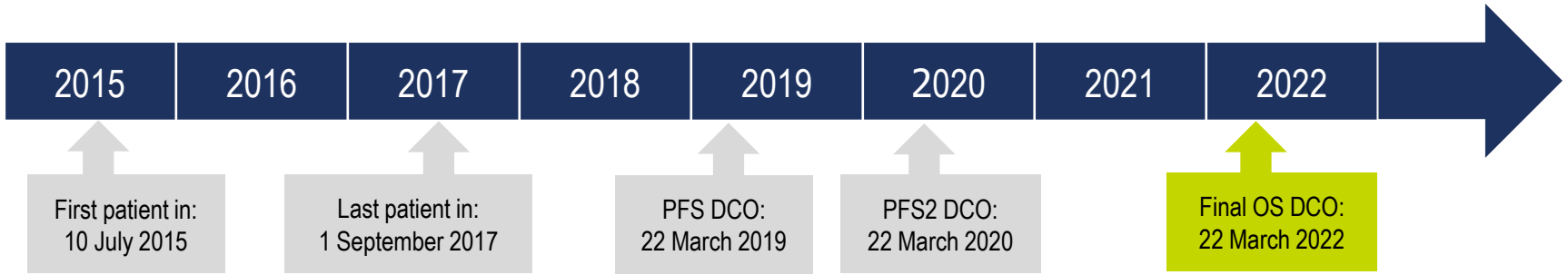
Ray-Coquard et al. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089

Analyse statistique

- A hierarchical testing strategy was applied for key endpoints

PFS	Statistically significant **PFS achieved**
PFS2	Statistically significant **PFS2 achieved**
OS	**OS** will be tested at full 5% alpha at final OS DCO

- Predefined OS subgroup analyses by tumour BRCAm status* and HRD score† will be performed



*By central labs; †By Myriad myChoice HRD Plus; defined as genomic instability score ≥42.
DCO, data cutoff.

Ray-Coquard et al. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089

Caractéristiques patientes

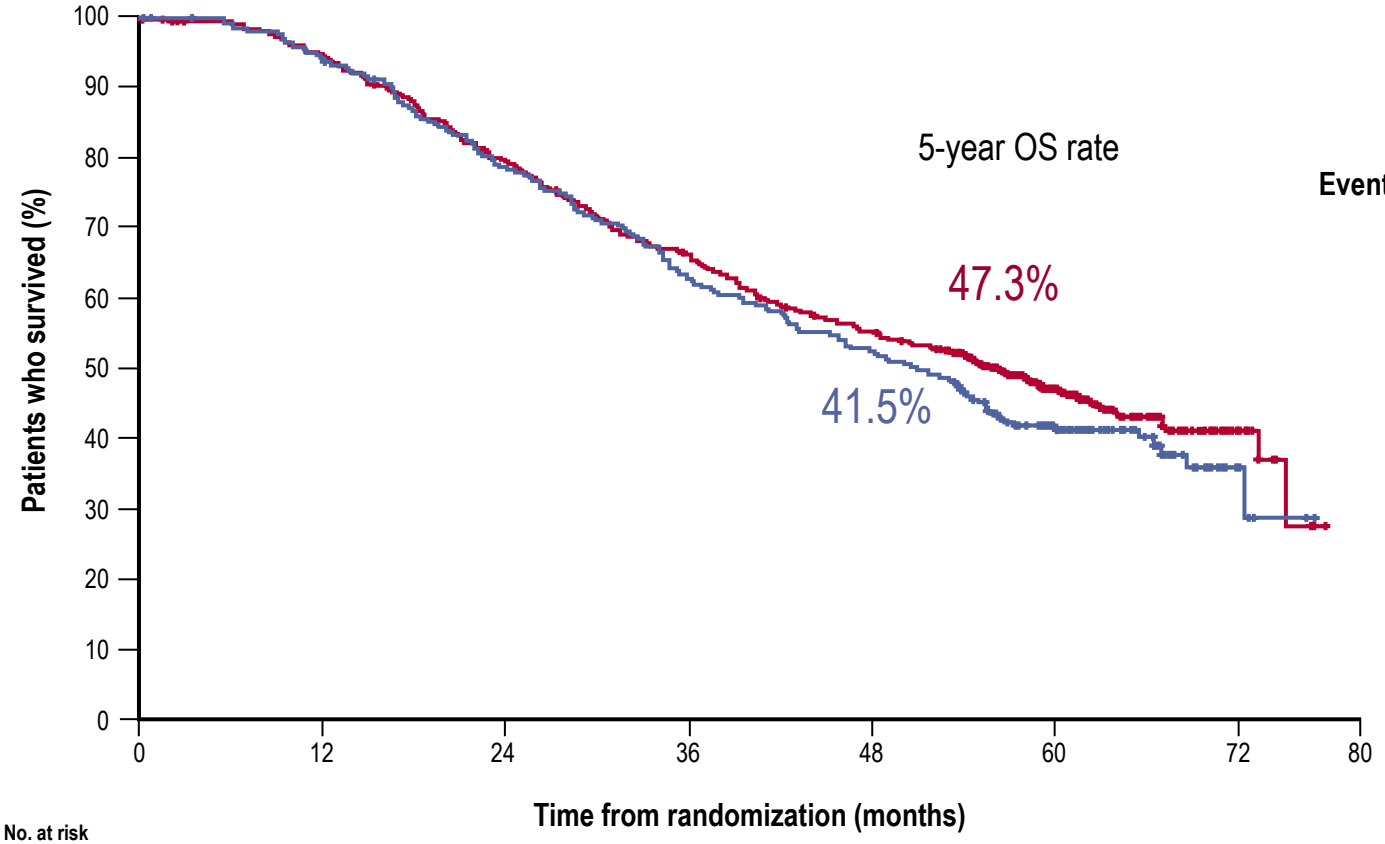
		Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Age, median, years (range)		61 (32–87)	60 (26–85)
FIGO stage, n (%)	III	378 (70)	186 (69)
	IV	159 (30)	83 (31)
HRD status,* n (%)	HRD positive	255 (47)	132 (49)
	tBRCAm	157 (29)	80 (30)
	HRD positive excluding tBRCAm	97 (18)	55 (20)
	HRD negative/HRD unknown	282 (53)	137 (51)
	HRD negative	192 (36)	85 (32)
History of cytoreductive surgery, n (%)	Upfront surgery	271 (50)	138 (51)
	• No residual macroscopic disease	160 (59)	85 (62)
	• Residual macroscopic disease	111 (41)	53 (38)
	Interval cytoreductive surgery	228 (42)	110 (41)
	• No residual macroscopic disease	163 (71)	75 (68)
	• Residual macroscopic disease	65 (29)	35 (32)
	No surgery	38 (7)	21 (8)
Response after surgery/PBC, n (%)	NED	290 (54)	141 (52)
	CR	106 (20)	53 (20)
	PR	141 (26)	75 (28)

*BRCAm status by central labs and HRD status by Myriad myChoice HRD Plus; patients in tBRCAm and HRD positive excluding tBRCAm subgroups do not equal the total number of patients in the HRD-positive subgroup because of different testing methods.
tBRCAm, tumour BRCAm.

Ray-Coquard et al. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089

Survie globale

ITT



No. at risk																										
Olaparib + bevacizumab	537	530	528	517	503	480	463	440	420	398	376	357	347	329	308	295	286	276	262	217	169	113	82	40	19	4	0
Placebo + bevacizumab	269	267	264	261	250	242	229	220	208	199	188	179	166	160	154	146	139	132	121	96	76	51	37	20	5	2	0

	Olaparib + bevacizumab (N=537)	Placebo + bevacizumab (N=269)
Events, n (%) [55% maturity]	288 (53.6)	158 (58.7)
Median OS, months	**56.5**	**51.6**
5-year OS rate, %	**47.3**	**41.5**
HR 0.92 (95% CI 0.76–1.12); ***P*=0.4118**		

Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: **19.6%** (105/537)
Placebo + bevacizumab: **45.7%** (123/269)

Median time from first cycle of chemotherapy to randomization = 6 months

PARP, poly(ADP-ribose) polymerase.

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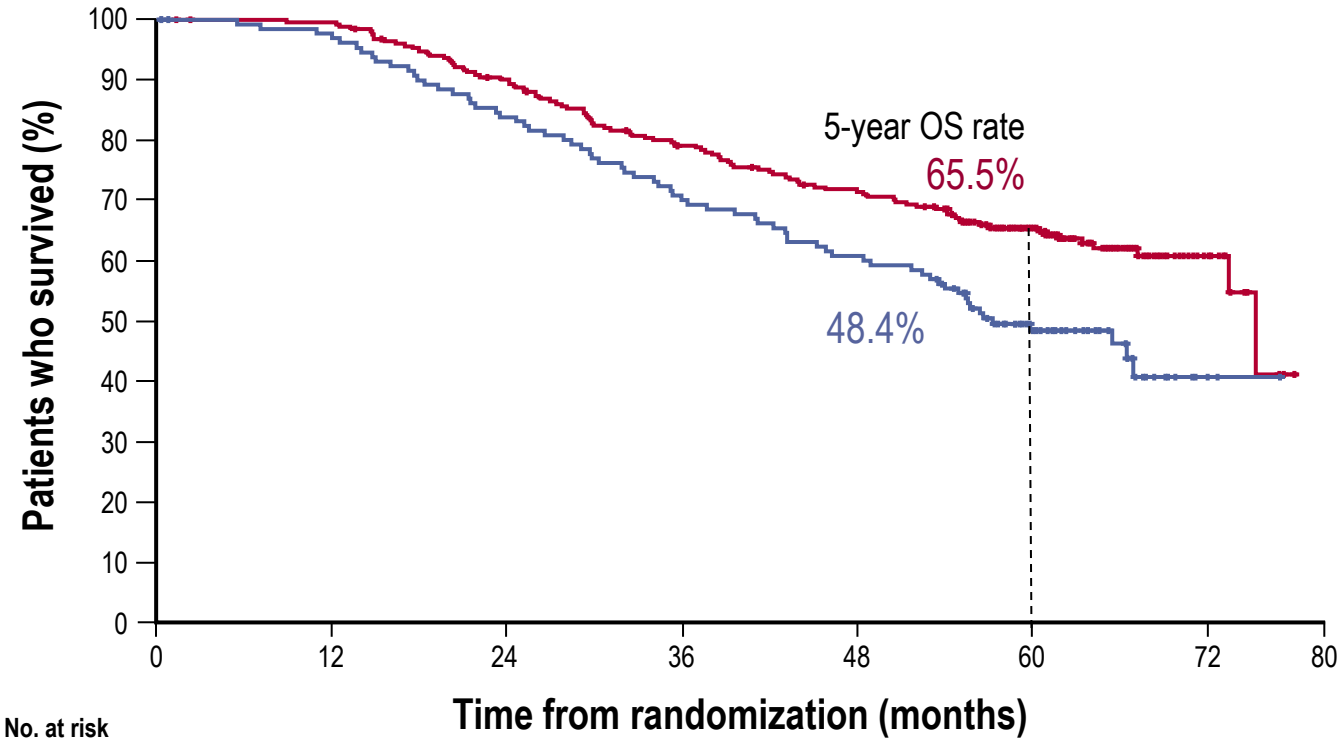
Survie globale

Population HRD



No. at risk																									
Olaparib + bevacizumab	255	253	253	252	252	244	238	231	225	215	205	200	195	189	183	176	174	170	164	142	116	83	62	32	17	4	0
Placebo + bevacizumab	132	130	129	128	126	121	117	114	109	105	100	96	91	89	86	82	79	77	70	59	44	29	21	9	2	1	0

	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	93 (36.5)	69 (52.3)
Median OS, months	**75.2** (unstable)*	**57.3**
5-year OS rate, %	**65.5**	**48.4**
HR 0.62 (95% CI 0.45–0.85)		

38% reduction in risk of death for olaparib + bevacizumab vs bevacizumab alone

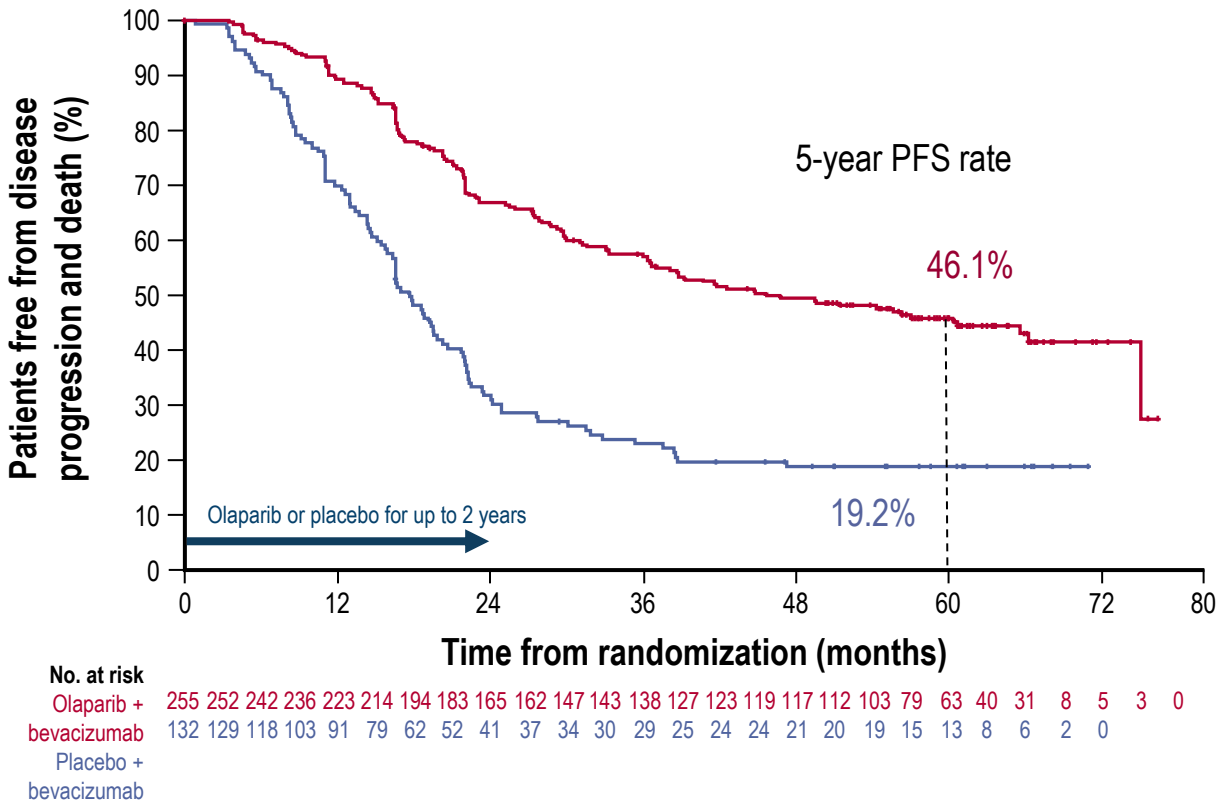
Patients receiving a PARP inhibitor during any subsequent treatment
Olaparib + bevacizumab: **17.3%** (44/255)
Placebo + bevacizumab: **50.8%** (67/132)

*Median unstable; <50% data maturity.
HRD positive defined as a tBRCAm and/or genomic instability score of ≥42 on the Myriad myChoice HRD Plus assay.

Ray-Coquard et al. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089

Survie sans progression mise à jour

Population HRD



	Olaparib + bevacizumab (N=255)	Placebo + bevacizumab (N=132)
Events, n (%)	136 (53.3)	104 (78.8)
Median PFS, months	**46.8**	**17.6**
5-year PFS rate, %	**46.1**	**19.2**
HR 0.41 (95% CI 0.32–0.54)		

59% reduction in risk of disease progression or death for olaparib + bevacizumab vs bevacizumab alone

*Descriptive analysis; PFS by investigator-assessment (modified RECIST v1.1).

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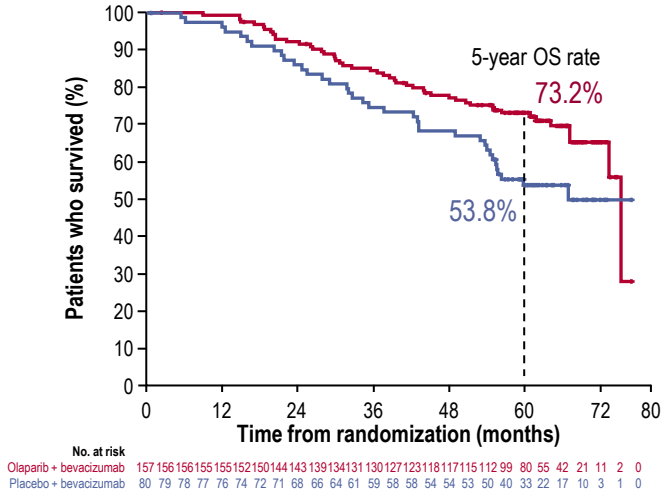
Survie globale

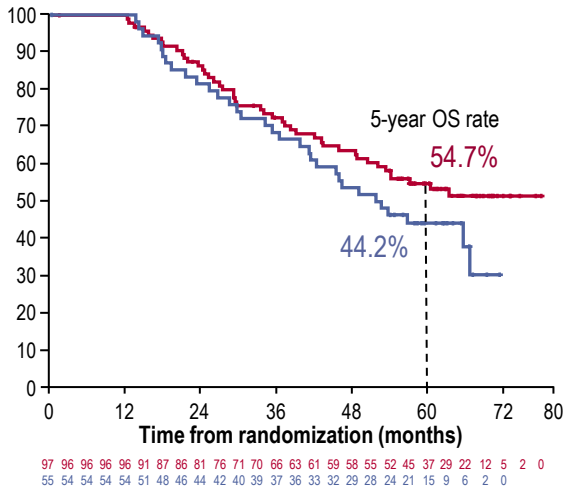
Population BRCAm, HRD et HRP

BRCAm*



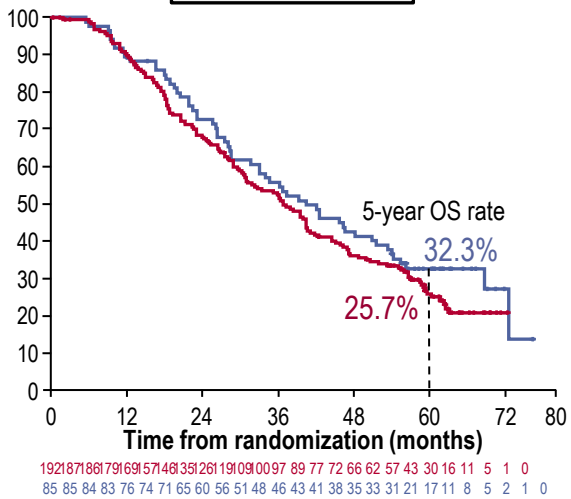
	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, months	75.2 (unstable)†	66.9
5-year OS rate, %	**73.2**	**53.8**
PARPi as subsequent treatment, n (%)	38 (24.2)	44 (55.0)
	HR 0.60 (95% CI 0.39–0.93)	

HRD positive‡ excluding BRCAm



Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
44 (45.4)	32 (58.2)
NR	52.0
54.7	**44.2**
9 (9.3)	23 (41.8)
HR 0.71 (95% CI 0.45–1.13)	

HRD negative†



Olaparib + bevacizumab (N=192)	Placebo + bevacizumab (N=85)
140 (72.9)	58 (68.2)
36.8	40.4
25.7	**32.3**
46 (24.0)	34 (40.0)
HR 1.19 (95% CI 0.88–1.63)	

*By central labs; †Unstable median; <50% data maturity; ‡By Myriad myChoice HRD Plus. NR, not reported.

Ray-Coquard et al. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089

Effets indésirables d'intérêt particulier

	Primary PFS analysis (DCO: 22 March 2019)		Final PFS2 analysis (DCO: 22 March 2020)		Final OS analysis (DCO: 22 March 2022)	
	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)	Olaparib + bevacizumab (N=535)	Placebo + bevacizumab (N=267)
MDS/AML/AA, n (%)	6 (1.1)	1 (0.4)	7 (1.3)	4 (1.5)	9 (1.7)	6 (2.2)
New primary malignancies, n (%)*	7 (1.3)	3 (1.1)	13 (2.4)	5 (1.9)	22 (4.1)	8 (3.0)
Pneumonitis/ILD/bronchiolitis, n (%)†	6 (1.1)	0 (0.0)	6 (1.1)	0 (0.0)	7 (1.3)	2 (0.7)

- All patients had discontinued treatment at PFS2 DCO
- TEAEs have been reported previously[1,2] and the olaparib safety profile has been well characterized

*New primary malignancies were: 1 plasma cell myeloma, 2 basal cell carcinoma, 11 breast cancer, 1 bronchial carcinoma, 1 colon cancer, 1 glioblastoma, 1 malignant neoplasm, 1 pancreatic carcinoma, 2 squamous cell carcinoma, and 1 ureteric cancer in the olaparib arm; and 1 papillary thyroid cancer, 4 breast cancer, 1 diffuse large B-cell lymphoma, 1 malignant lung neoplasm, and 1 malignant neoplasm in the placebo arm;
†Pneumonitis/ILD/bronchiolitis events were: 1 bronchiolitis, 1 pneumonia, 1 acute respiratory distress syndrome, 2 interstitial lung disease, and 2 pneumonitis in the olaparib arm; and 1 corona virus infection and 1 pneumonitis case in the placebo arm.

AA, aplastic anaemia; AE, adverse event; AML, acute myeloid leukaemia; ILD, interstitial lung disease; MDS, myelodysplastic syndrome.

1. Ray-Coquard I *et al. N Engl J Med* 2019;381:2416–28; 2. González-Martín A *et al. Eur J Cancer* 2022;174:221–31.

Ray-Coquard et al. Annals of Oncology (2022) 33 (suppl_7): S808-S869. 10.1016/annonc/annonc1089

Synthèse - Discussion

Confirmation en survie globale de l'association bevacizumab / olaparib

- Dans une population ciblée HRD+

Quel test compagnon à venir pour diagnostiquer cette population cible?

Données **descriptives** de survie globale de l'étude SOLO-1 à 7 ans de suivi

- population BRCAm

Intérêt du Bevacizumab pour toutes?

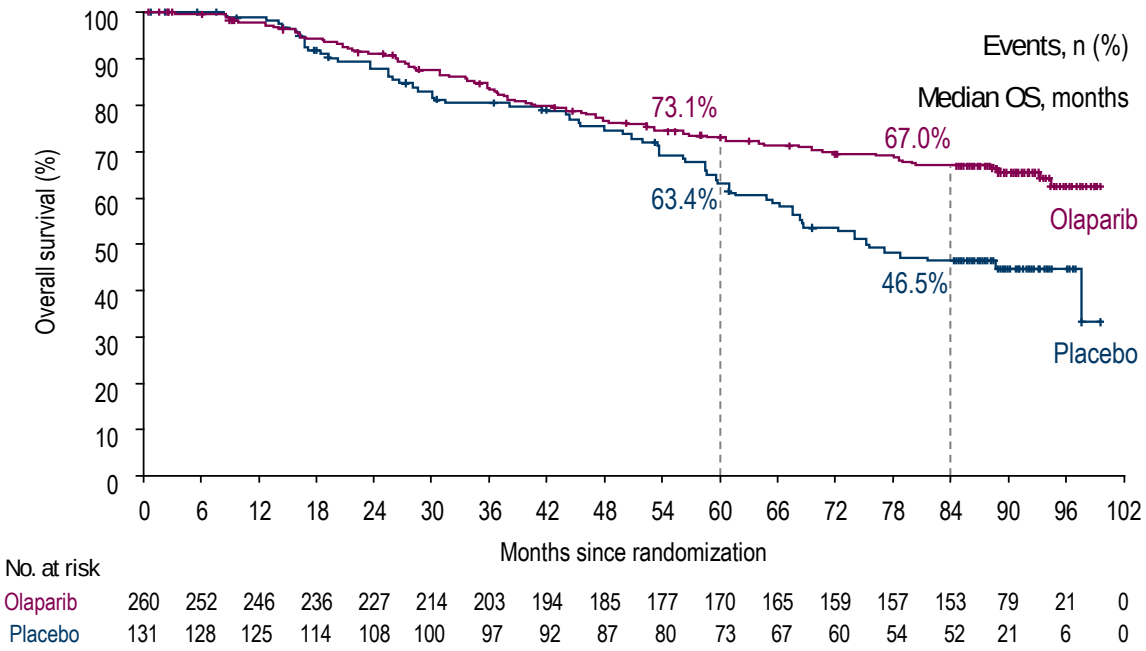
- essai NIRVANA-1 en cours de recrutement

Quid de l'association avec les anti-PD-(L)1?

- notamment dans la population HRp?

SOLO-1

Données descriptives de survie globale à 7 ans de suivi



	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	NR	75.2
HR 0.55 (95% CI 0.40–0.76); *P*=0.0004*		

44.3% of patients in the placebo group received subsequent PARP inhibitor therapy, compared with 14.6% of patients in the olaparib group

*$P<0.0001$ required to declare statistical significance

DiSilvestro et al. Annals of Oncology (2022) 33 (suppl_7): S235-S282. 10.1016/annonc/annonc1054

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Accès précoce Pembrolizumab L1 cancer du col

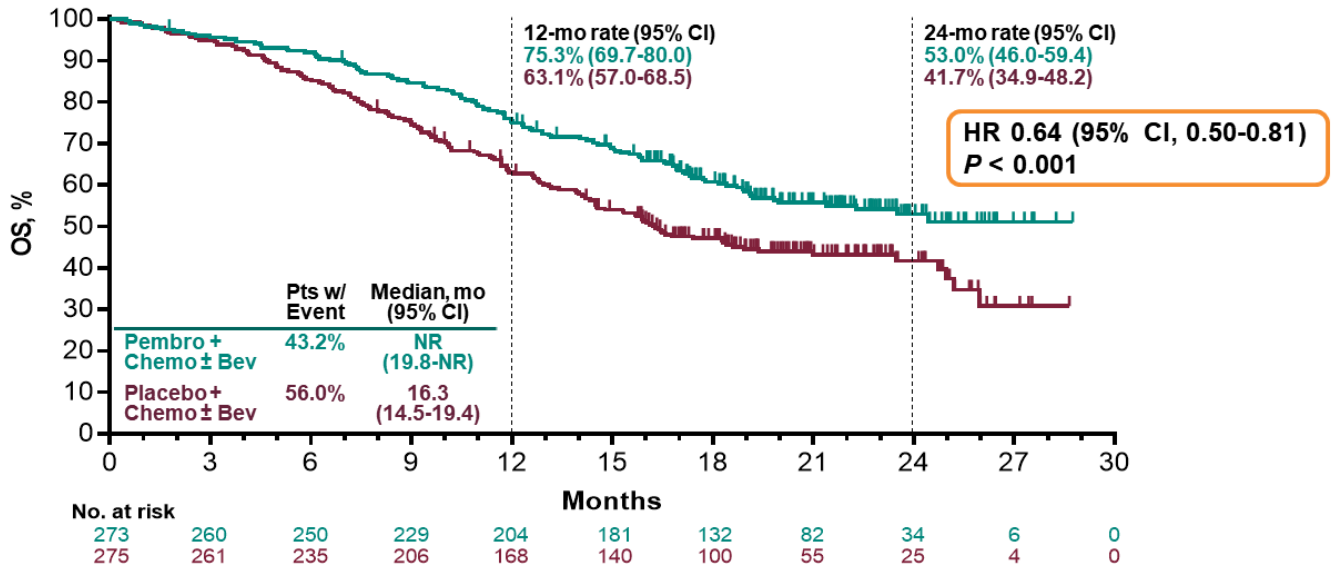
KEYTRUDA,

en association à une chimiothérapie avec ou sans bevacizumab,

est indiqué dans le traitement des patientes adultes atteintes d'un cancer du col de l'utérus persistant, récidivant ou métastatique

dont les tumeurs expriment PD-L1 avec un CPS ≥ 1

OS: PD-L1 CPS ≥1 Population



Data cutoff date: May 3, 2021.

Sur les données de l'étude KN826

Colombo et al. N Engl J Med 2021