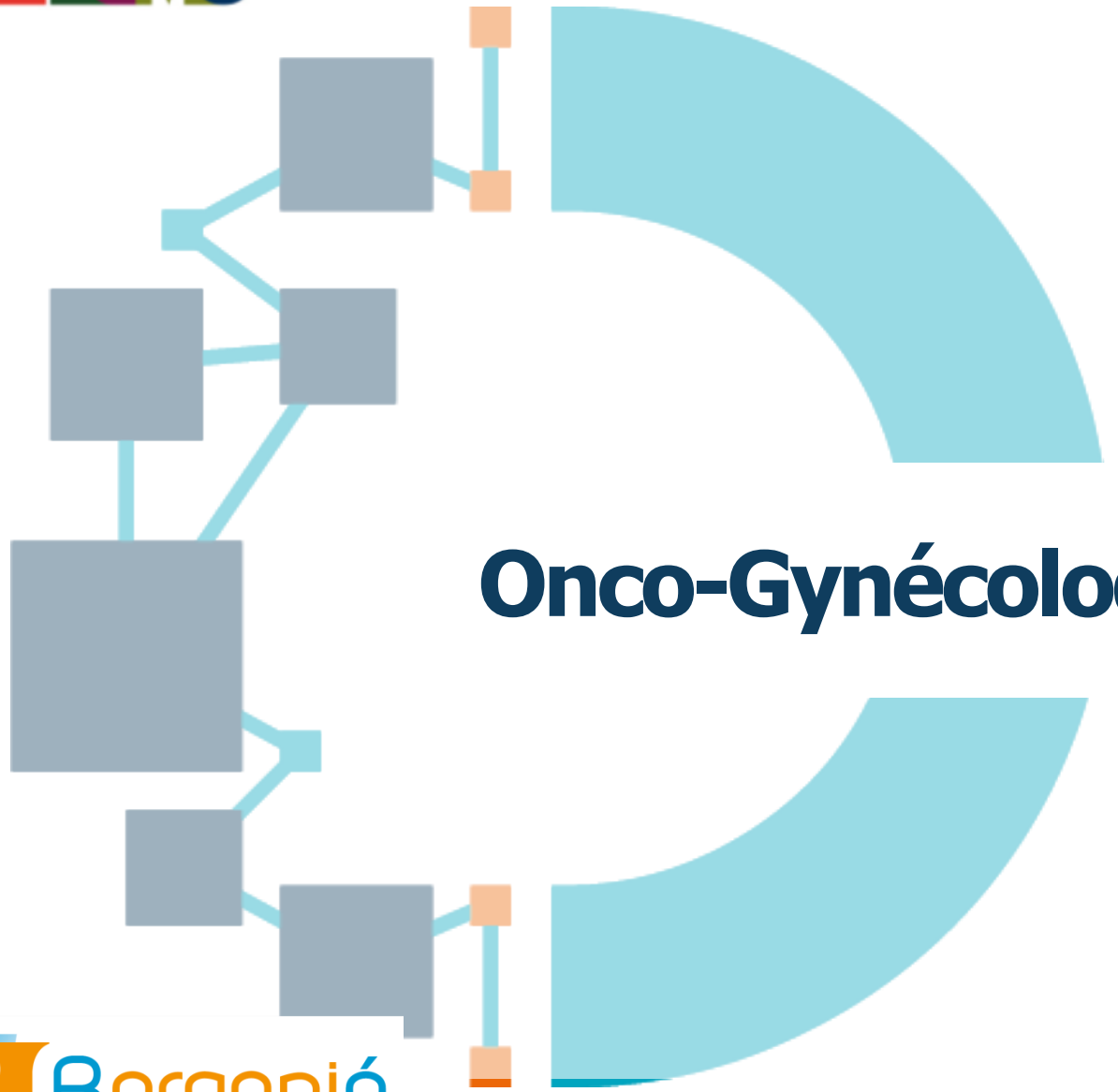
2021 ESMO congress

ONCO NOUVELLE-AQUITAINE
Réseau Régional de Cancérologie

BRIO BORDEAUX | Recherche Intégrée Oncologie



Onco-Gynécologie

5 Octobre 2021

Bordeaux

Dr Coriolan Lebreton

Bergonié
UNICANCER
NOUVELLE-AQUITAINE

université de BORDEAUX

Liens d'intérêts

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

Pembrolizumab plus Chemotherapy versus Placebo plus Chemotherapy for Persistent, Recurrent, or Metastatic Cervical Cancer: Randomized, Double-Blind, Phase 3 KEYNOTE-826 Study

Nicoletta Colombo,[1] Coraline Dubot,[2] Domenica Lorusso,[3] Valeria Caceres,[4] Kosei Hasegawa,[5] Ronnie Shapira-Frommer,[6] Krishnansu S. Tewari,[7] Pamela Salman,[8] Edwin Hoyos Usta,[9] Eduardo Yañez,[10] Mahmut Gümüş,[11] Mivael Olivera Hurtado de Mendoza,[12] Vanessa Samouëlian,[13] Vincent Castonguay,[14] Alexander Arkhipov,[15] Sarper Toker,[16] Kan Li,[16] Stephen M. Keefe,[16] Bradley J. Monk,[17] on behalf of the KEYNOTE-826 Investigators

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer

Rationnel

Platine Paclitaxel +/- Bevacizumab

- Standard de première ligne avancée métastatique
- Survie globale de 17,5 mois (1)

Données d'efficacité des anti-PD(L)-1 en monothérapie en situation après 1ère ligne

- Pembrolizumab/étude KEYNOTE 158 : taux de réponse de 14.3% chez PDL1+ (2)
- Cemiplimab/étude EMPOWER-Cervical 1 : augmentation de la SG de 8,5 à 12 mois vs chimiothérapie (HR 0.69 [IC95 0,56-0,84]) (3)

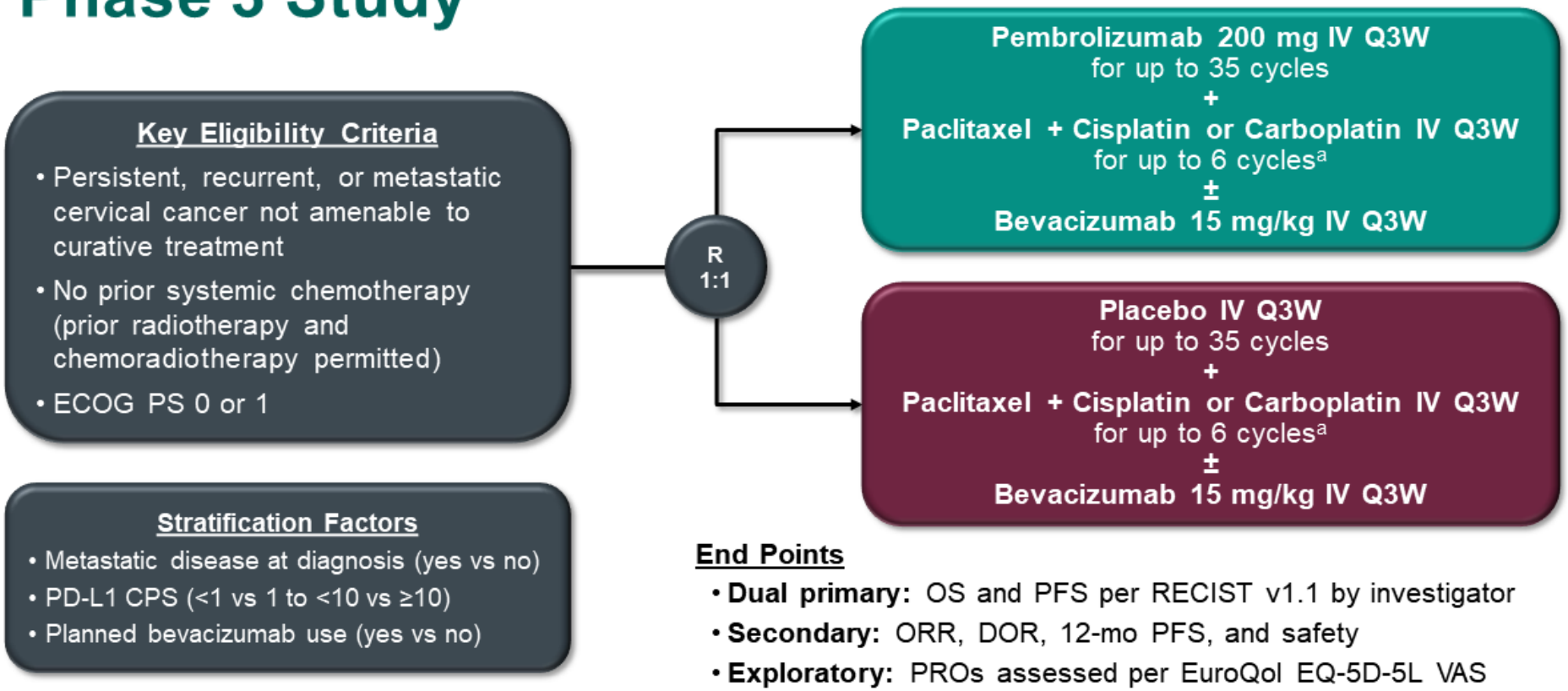
Rationnel à tester anti-PD(L)-1 en association avec chimiothérapie +/- Bevacizumab

(1)Tewari et al. N Engl J Med 2014
(2) Chang et al. J Clin Oncol 2019
(3) Tewari et al. AnnOncol 2021

Design

Colombo KN826 ESMO 2021

KEYNOTE-826: Randomized, Double-Blind, Phase 3 Study



End Points

- **Dual primary:** OS and PFS per RECIST v1.1 by investigator
- **Secondary:** ORR, DOR, 12-mo PFS, and safety
- **Exploratory:** PROs assessed per EuroQol EQ-5D-5L VAS

[a]Paclitaxel: 175 mg/m². Cisplatin: cisplatin 50 mg/m². Carboplatin: AUC 5 mg/mL/min. The 6-cycle limit was introduced with protocol amendment 2, although participants with ongoing clinical benefit who were tolerating chemotherapy could continue beyond 6 cycles after sponsor consultation.
CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100); PROs, patient-reported outcomes; VAS, visual analog scale. KEYNOTE-826 ClinicalTrials.gov identifier, NCT03635567.

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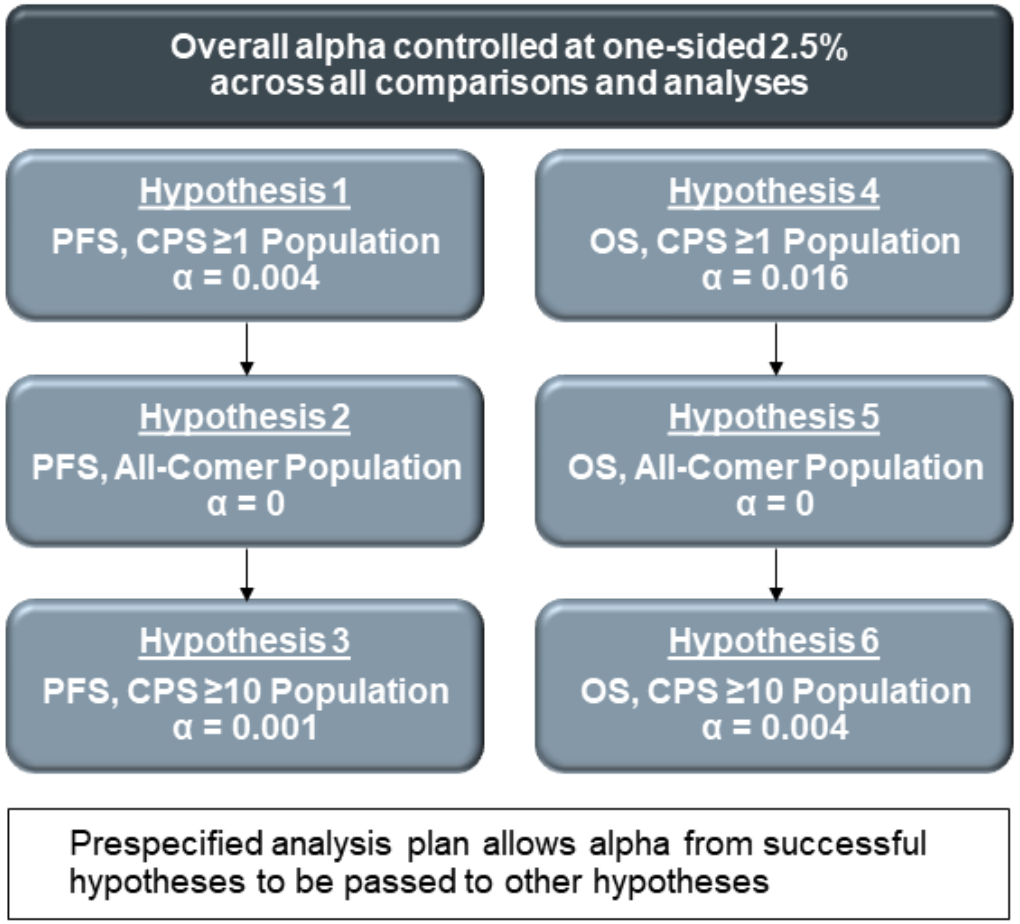
Statistiques



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Caractéristiques à baseline

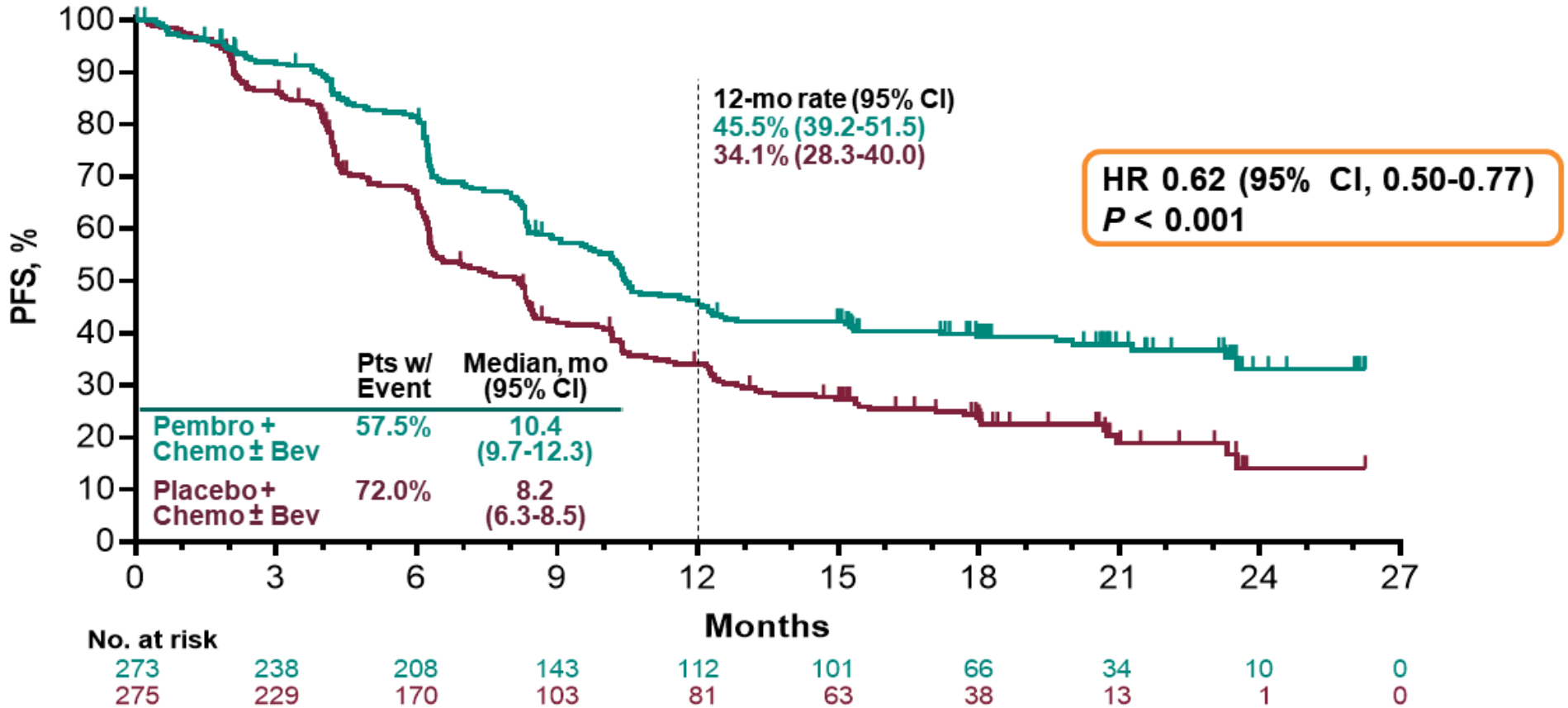
	Pembro Arm[a] (N = 308)	Placebo Arm[a] (N = 309)
Age, median (range)	51 y (25-82)	50 y (22-79)
ECOG PS 1	128 (41.6%)	139 (45.0%)
Squamous cell carcinoma	235 (76.3%)	211 (68.3%)
PD-L1 CPS		
<1	35 (11.4%)	34 (11.0%)
1 to <10	115 (37.3%)	116 (37.5%)
≥10	158 (51.3%)	159 (51.5%)
Prior therapy		
Chemoradiation or radiation with surgery	71 (23.1%)	79 (25.6%)
Chemoradiation or radiation only	156 (50.6%)	142 (46.0%)
Surgery only	23 (7.5%)	24 (7.8%)
None	58 (18.8%)	64 (20.7%)

	Pembro Arm[a] (N = 308)	Placebo Arm[a] (N = 309)
Stage at initial diagnosis (FIGO 2009/NCCN 2017 criteria)		
I	67 (21.8%)	58 (18.8%)
II	85 (27.6%)	93 (30.1%)
III	5 (1.6%)	8 (2.6%)
IIIA	4 (1.3%)	8 (2.6%)
IIIB	46 (14.9%)	42 (13.6%)
IVA	7 (2.3%)	4 (1.3%)
IVB	94 (30.5%)	96 (31.1%)
Disease status at study entry		
Metastatic[b]	58 (18.8%)	64 (20.7%)
Persistent or recurrent with distant metastases	199 (64.6%)	179 (57.9%)
Persistent or recurrent without distant metastases	51 (16.6%)	66 (21.4%)
Bevacizumab use during the study	196 (63.6%)	193 (62.5%)

[a]The treatment regimen in both arms included chemo ± bev.
[b]Includes participants with para-aortic lymph node involvement. These participants were diagnosed with stage IVB disease and entered the study with no prior treatment for cervical cancer.
Data cutoff date: May 3, 2021.

Colombo et al. Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741 ; N Engl J Med 2021

PFS: PD-L1 CPS ≥1 Population



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.

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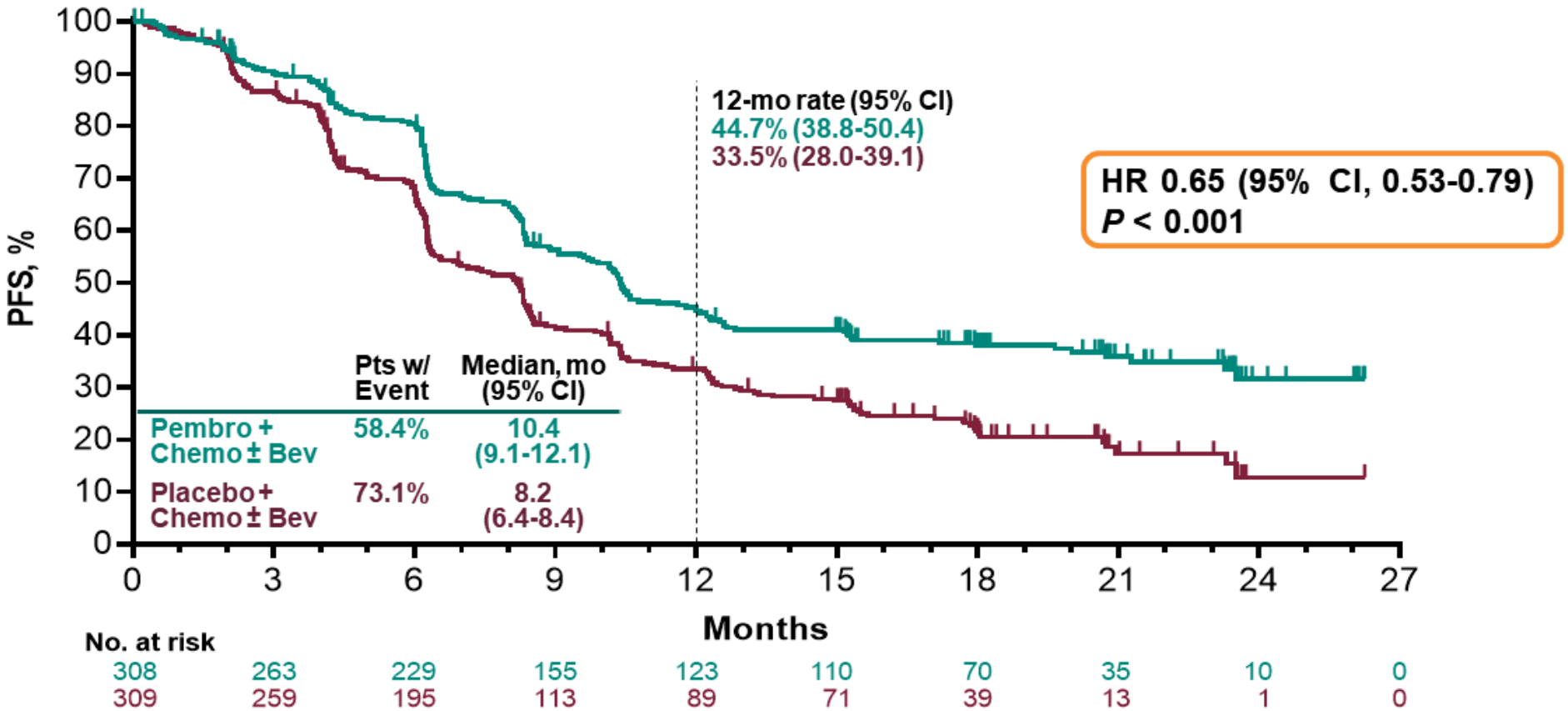
PFS: All-Comer Population



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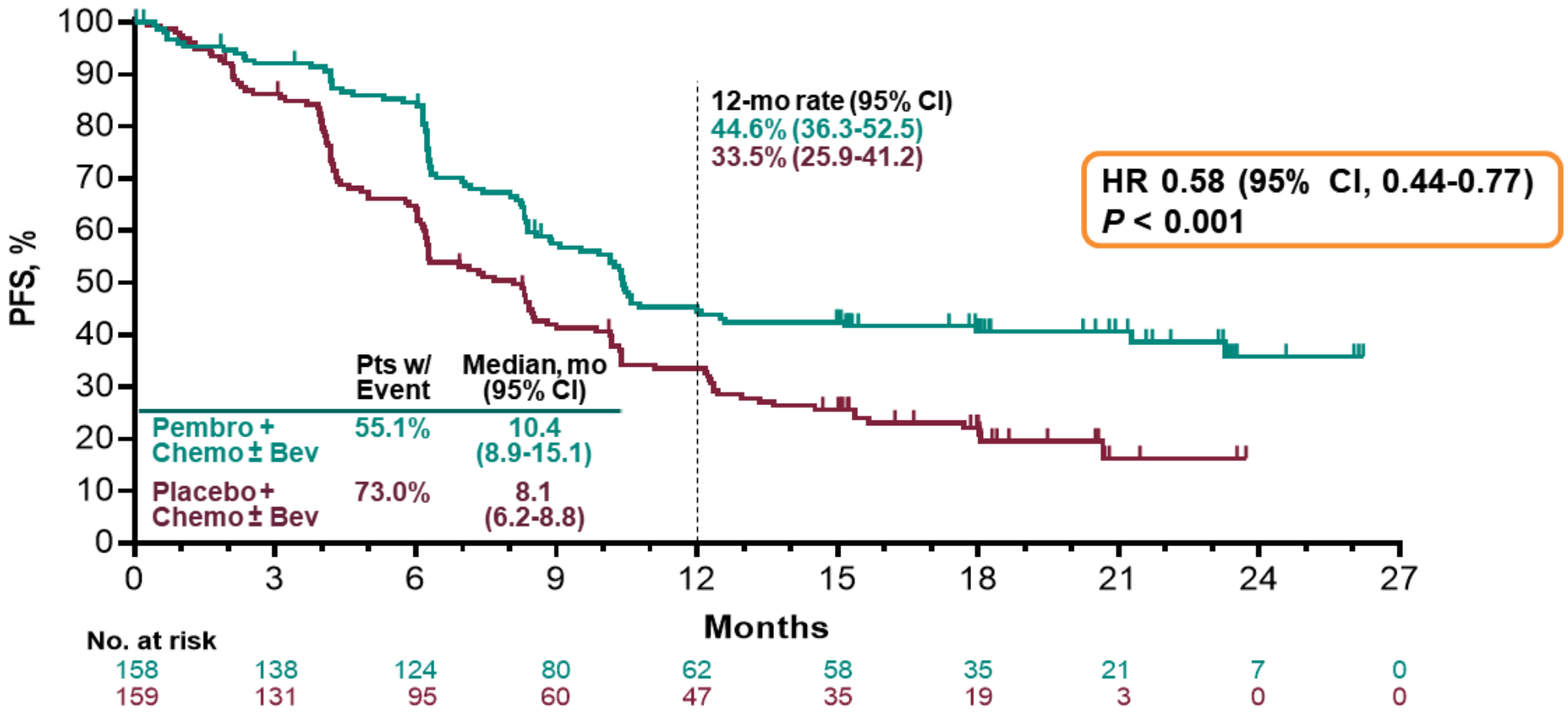
PFS: PD-L1 CPS ≥10 Population



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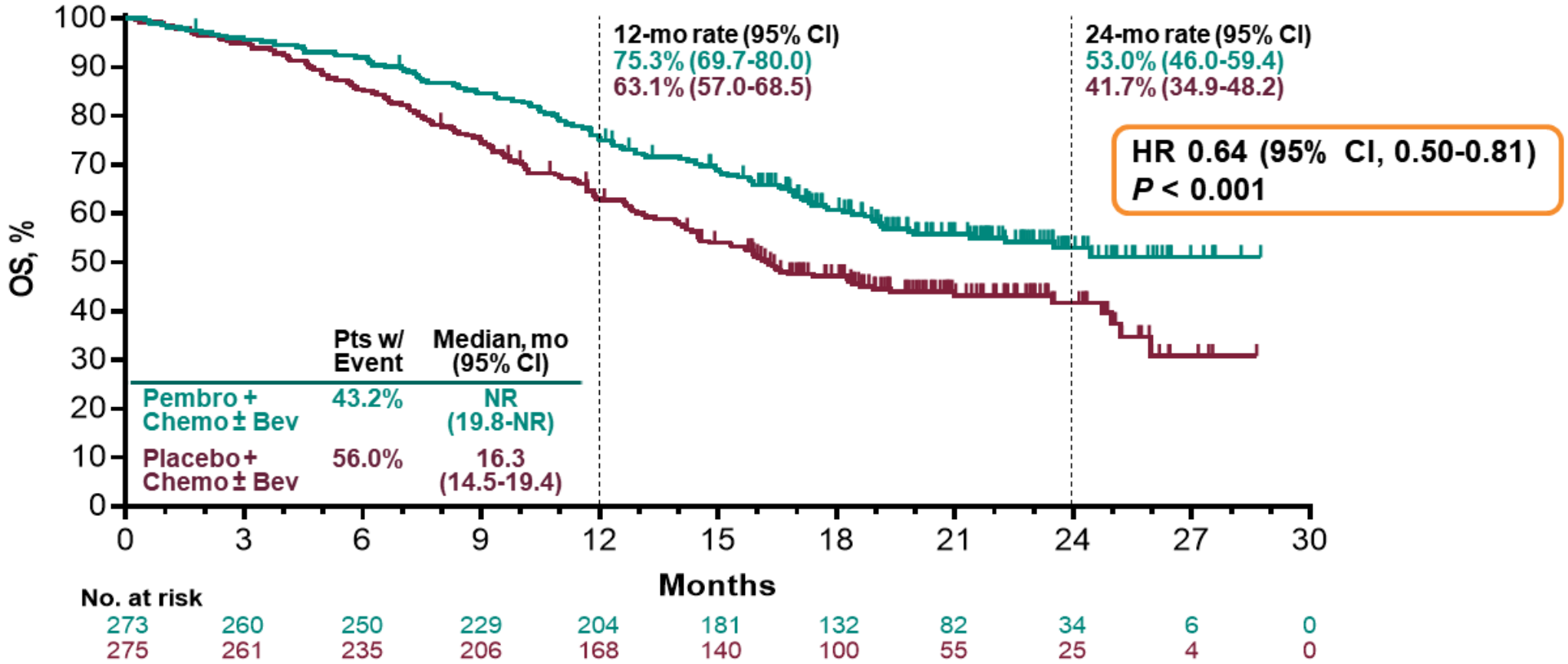
OS: PD-L1 CPS ≥1 Population



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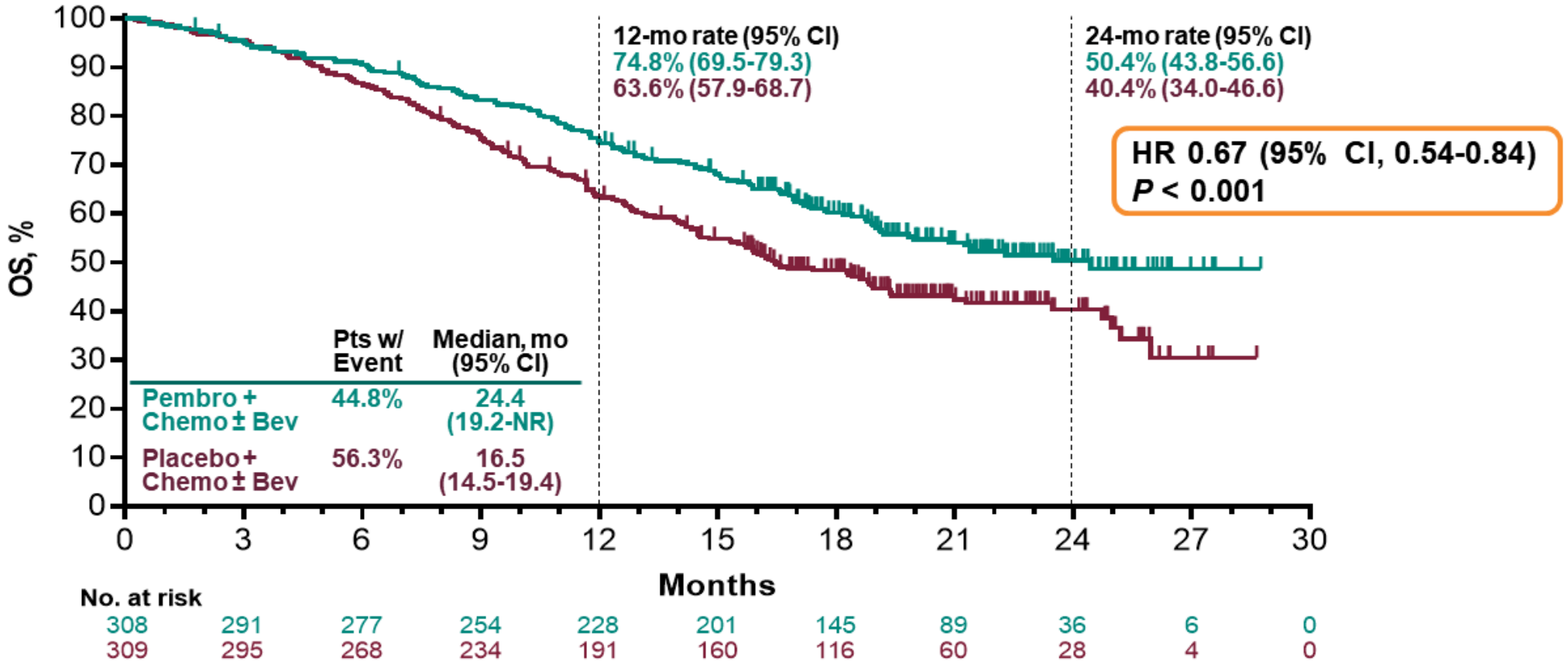
Colombo et al. Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741 ; N Engl J Med 2021

OS: All-Comer Population



Data cutoff date: May 3, 2021.

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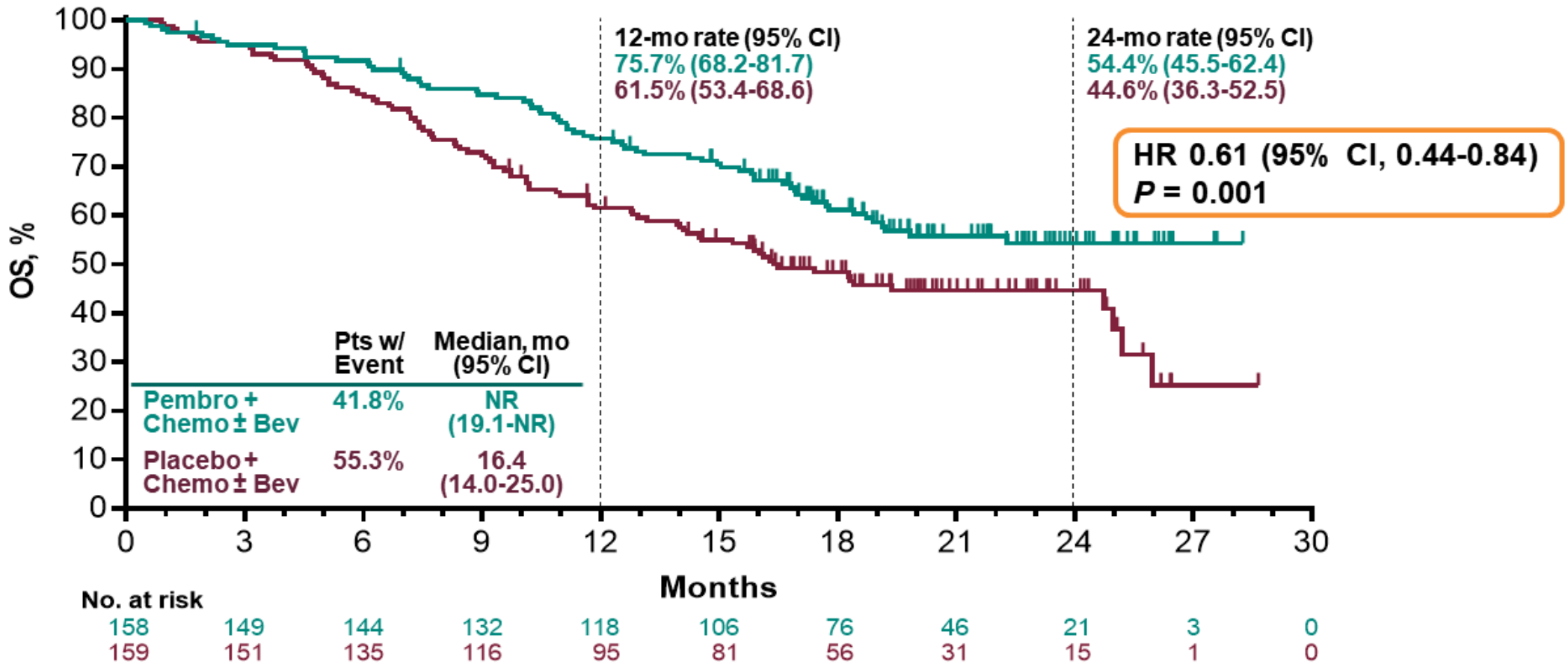
OS: PD-L1 CPS ≥10 Population



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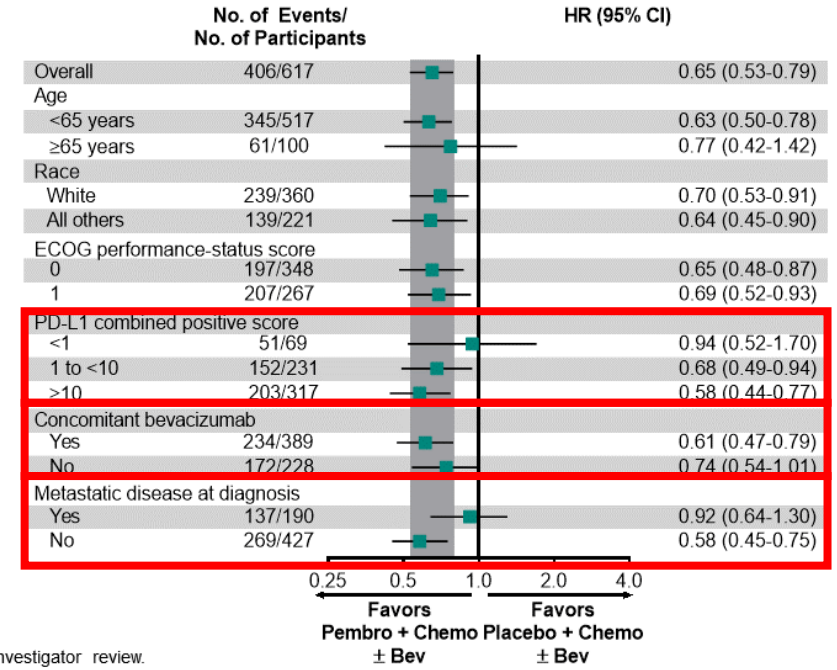
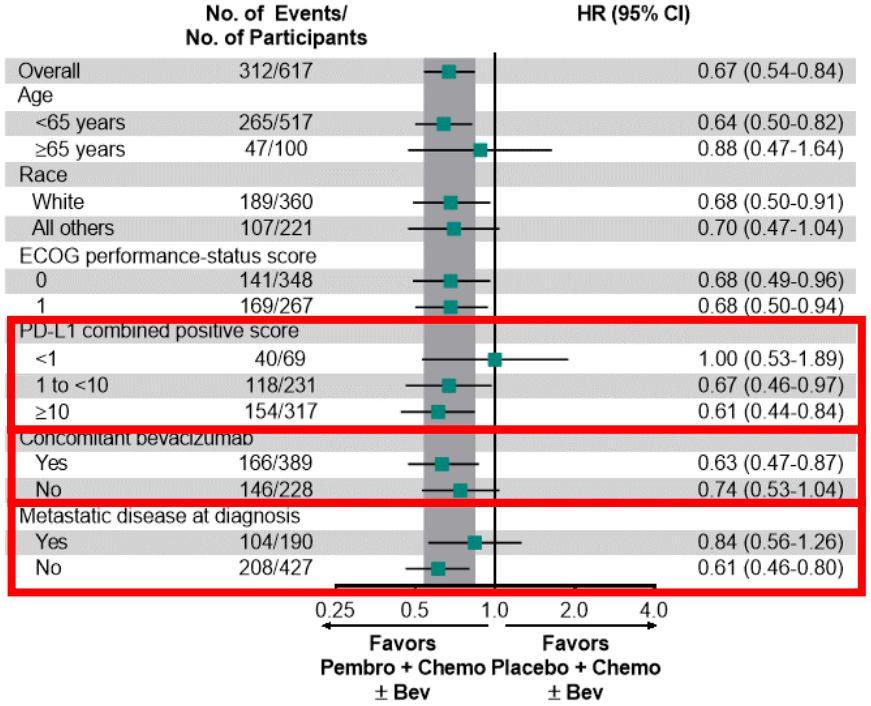
Colombo et al. Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741 ; N Engl J Med 2021

PFS: Protocol-Specified Subgroups, All-Comer Population



Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: May 3, 2021.

OS: Protocol-Specified Subgroups, All-Comer Population



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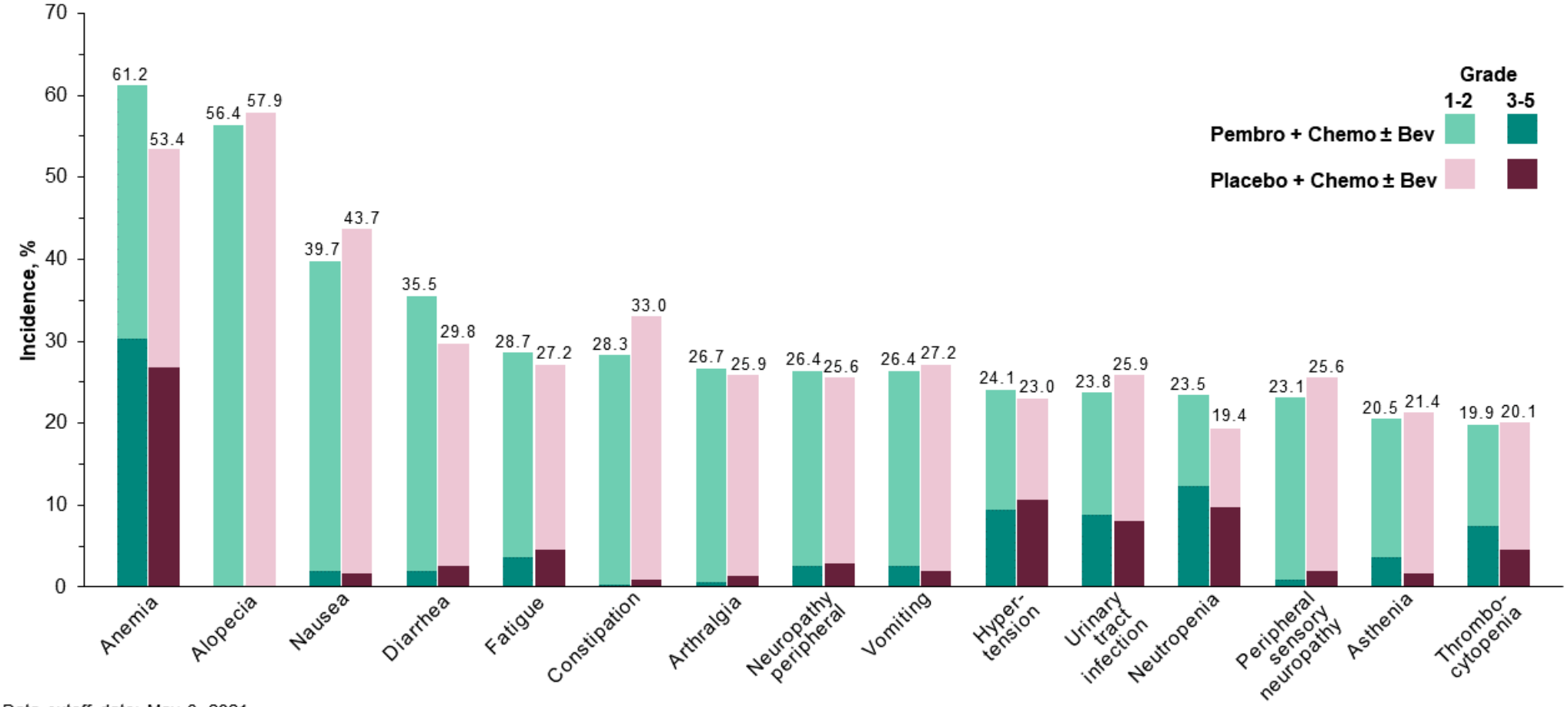
All-Cause AEs, Incidence ≥20% in Either Arm



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Conclusion

Bénéfice de l'adjonction du Pembrolizumab en SSP et SG

- Dans l'ensemble de la population analysée
- Indépendamment de l'administration ou non de bevacizumab

Avec toxicité manageable

Efficace?

- sur métastases de novo?
- sur adénocarcinomes?
- sur tumeur PD-L1 négative?

Probable nouveau standard de première ligne

- Attente résultats BEAT-CC

Maintenance olaparib rechallenge in patients with ovarian carcinoma previously treated with a PARP inhibitor: Phase IIIb OReO/ENGOT Ov-38 trial

Eric Pujade-Lauraine,[1] Frédéric Selle,[2] Giovanni Scambia,[3] Bernard Asselain,[4] Frederik Marmé,[5] Kristina Lindemann,[6] Nicoletta Colombo,[7] Radoslaw Madry,[8] Rosalind Glasspool,[9] Coraline Dubot,[10] Ana Oaknin,[11] Claudio Zamagni,[12] Florian Heitz,[13] Laurence Gladieff,[14] Maria Jesús Rubio-Pérez,[15] Paolo Scollo,[16] Christopher Blakeley,[17] Bob Shaw,[17] Isabelle Ray-Coquard,[18] Andrés Redondo[19]

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ClinicalTrials.gov identifier: NCT03106987 | This study was sponsored by AstraZeneca and is part of an alliance between AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Rationnel

Maintenance d'inhibiteurs de PARP après réponse à un doublet à base de sels platine : un standard

- En primo traitement d'un carcinome ovarien épithélial de haut grade
- En rechute platine sensible

Mais rechute dans la majorité des cas

Peut-on envisager une reprise des inhibiteurs de PARP après nouvelle réponse à la chimiothérapie à base de sels de platine?

Design de l'étude

Patients

- Relapsed non-mucinous epithelial ovarian cancer
- One prior course of PARPi maintenance therapy
- **CR/PR to most recent platinum regimen or NED** after surgery* with no rising CA-125
- Documented BRCAm status by local testing
- No limit to number of prior lines of therapy

BRCAm cohort

- gBRCAm or sBRCAm by local testing
- Prior PARPi exposure for **≥18 months after first-line chemotherapy** or **≥12 months after second-line or later chemotherapy**

Non-BRCAm cohort

- gBRCAm negative by local testing; may include patients with undetected sBRCAm
- Prior PARPi exposure for **≥12 months after first-line chemotherapy** or **≥6 months after second-line or later chemotherapy**

Maintenance therapy

Olaparib 300 mg bid or 250 mg bid if 300 mg not previously tolerated (N=74)

Placebo (N=38)

2:1 randomisation stratified by:

- Prior bevacizumab
- ≤3 vs ≥4 prior lines of platinum-based chemotherapy

Olaparib 300 mg bid or 250 mg bid if 300 mg not previously tolerated (N=72)

Placebo (N=36)

Until disease progression

Primary endpoint

- Investigator-assessed PFS (modified RECIST 1.1)

*NED was permitted if optimal cytoreductive surgery conducted prior to chemotherapy.

bid, twice daily; CA-125, cancer antigen 125; CR, complete response; gBRCAm, germline BRCA mutation; HRQoL, health-related quality of life; NED, no evidence of disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; sBRCAm, somatic BRCA mutation.

Pujade-Lauraine et al. Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741

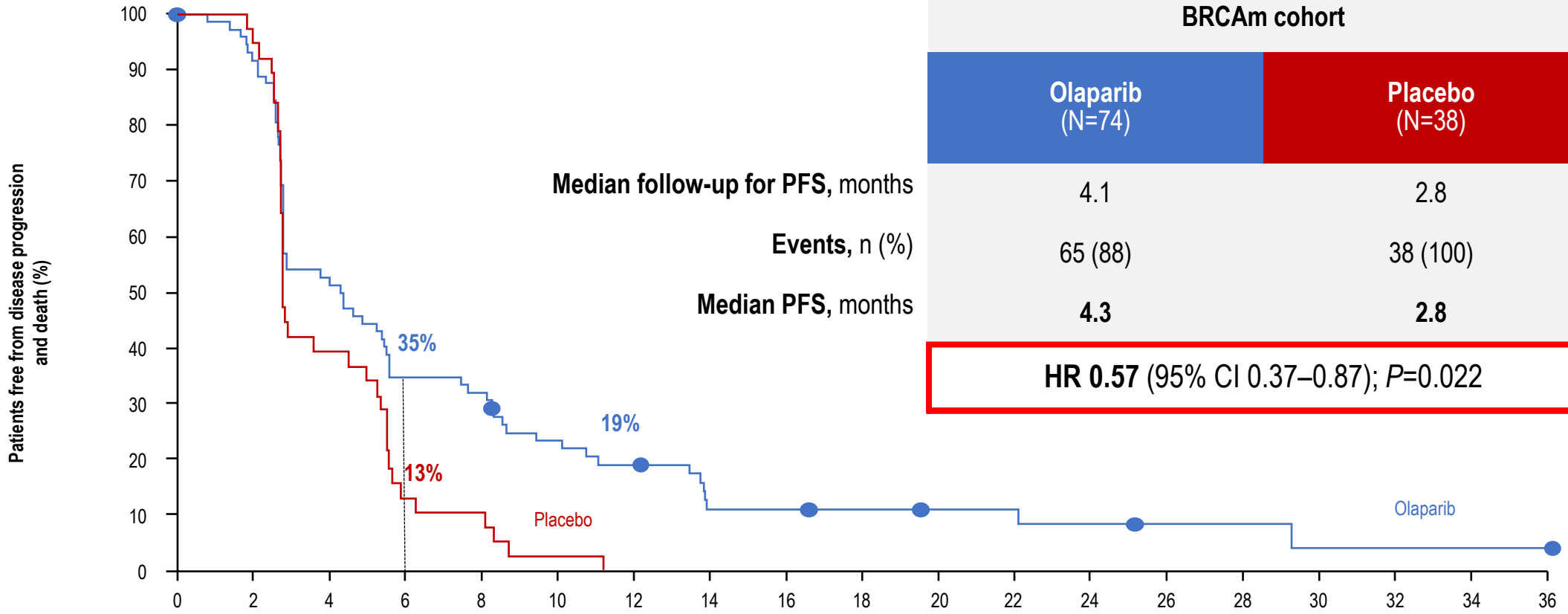
Caractéristiques patients

	BRCAm cohort (N=112)		Non-BRCAm cohort (N=108)	
	Olaparib (N=74)	**Placebo** (N=38)	**Olaparib** (N=72)	**Placebo** (N=36)
Median (range) patient age, years	58.5 (37–80)	61.5 (44–87)	66.5 (29–81)	62.5 (43–77)
No. of prior lines of any chemotherapy, n (%)				
2	5 (7)	3 (8)	10 (14)	5 (14)
3	31 (42)	16 (42)	31 (43)	17 (47)
4	21 (28)	11 (29)	11 (15)	6 (17)
>4	17 (23)	8 (21)	20 (28)	8 (22)
No. of prior lines of PBC, n (%)				
2	12 (16)	3 (8)	17 (24)	5 (14)
3	36 (49)	19 (50)	32 (44)	20 (56)
≥4	26 (35)	16 (42)	23 (32)	11 (31)
Response to PBC prior to study entry, n (%)				
Complete	15 (20)	13 (34)	19 (26)	11 (31)
Partial	58 (78)	25 (66)	53 (74)	25 (69)
Missing	1 (1)	0	0	0

Pujade-Lauraine et al. Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741

Augmentation statistiquement significative de la SSP avec olaparib dans la cohorte ***BRCAm***

Avec bénéfice clinique prolongé



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

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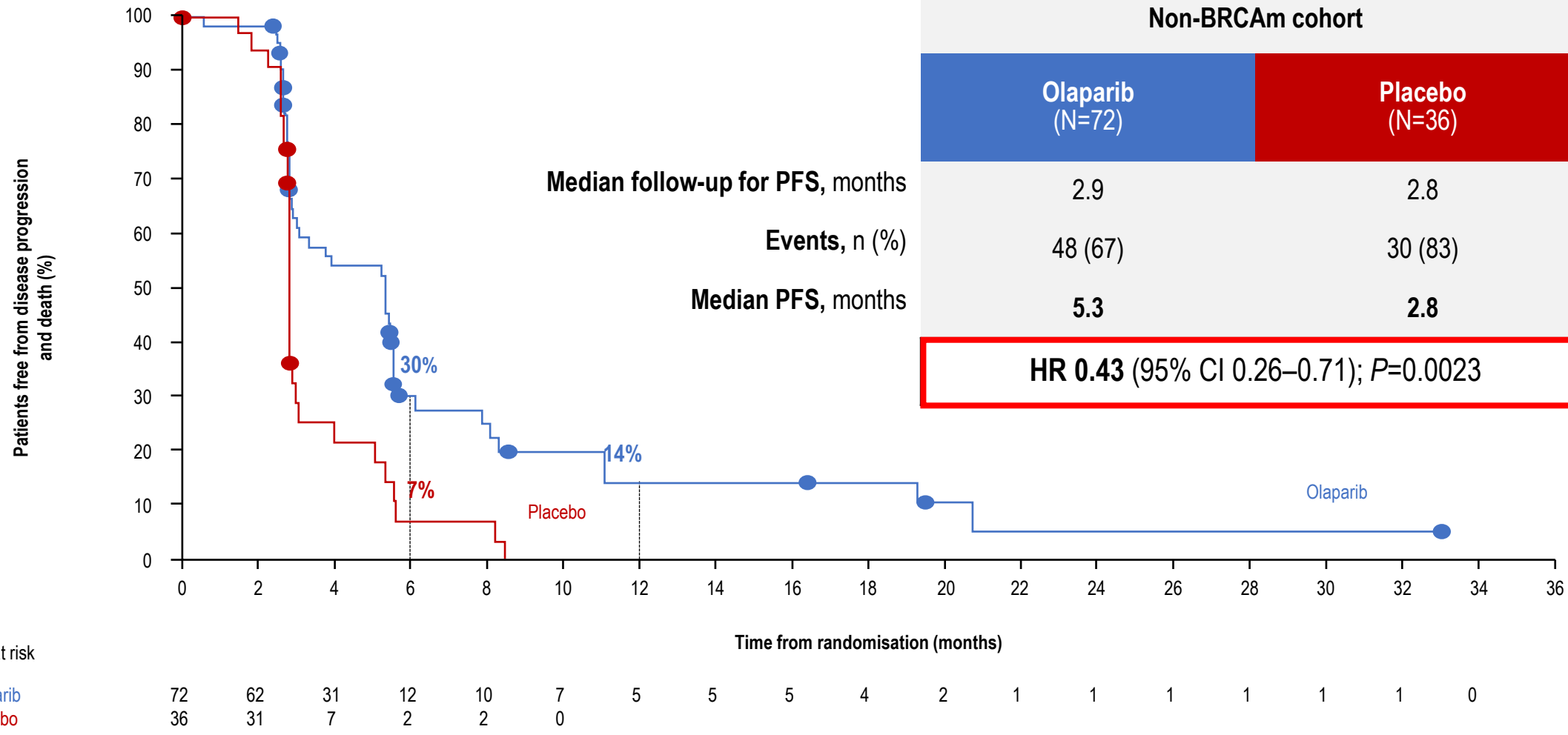
Augmentation statistiquement significative de la SSP avec olaparib dans la cohorte *non-BRCAm*

Avec bénéfice clinique prolongé



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

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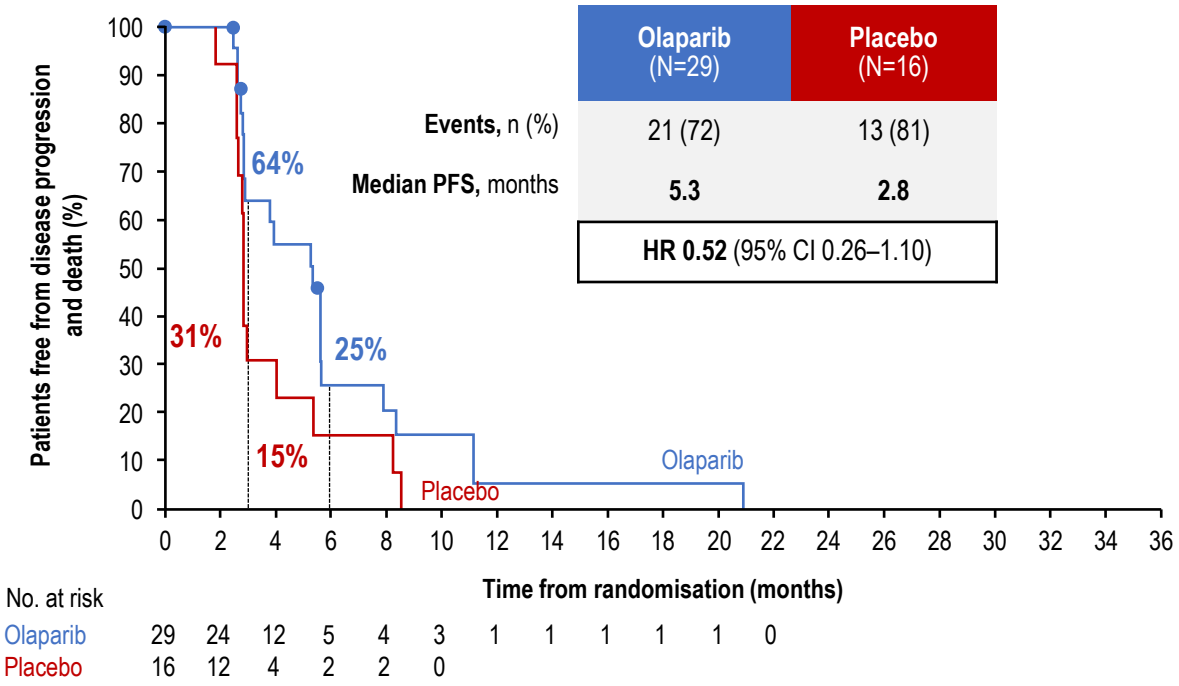
Dans la cohorte non-BRCAm, bénéfice quel que soit le statut HRD

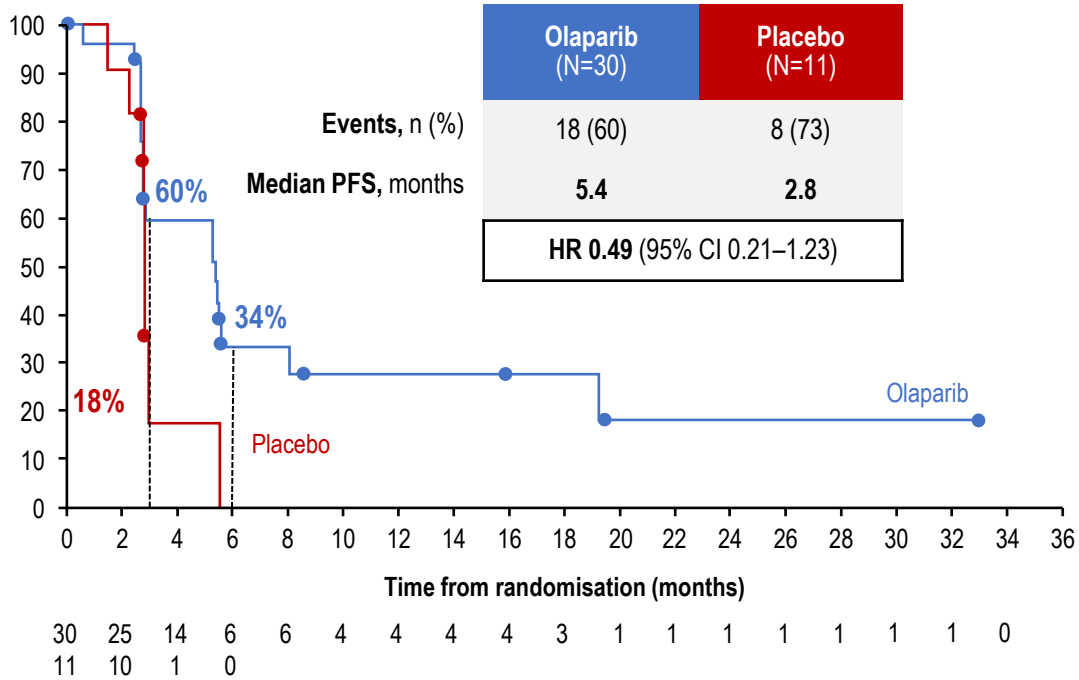
Analyses exploratoires

Non-BRCAm cohort: HRD-positive



	Olaparib (N=29)	Placebo (N=16)
Events, n (%)	21 (72)	13 (81)
Median PFS, months	**5.3**	**2.8**
HR 0.52 (95% CI 0.26–1.10)		

Non-BRCAm cohort: HRD-negative



	Olaparib (N=30)	Placebo (N=11)
Events, n (%)	18 (60)	8 (73)
Median PFS, months	**5.4**	**2.8**
HR 0.49 (95% CI 0.21–1.23)		

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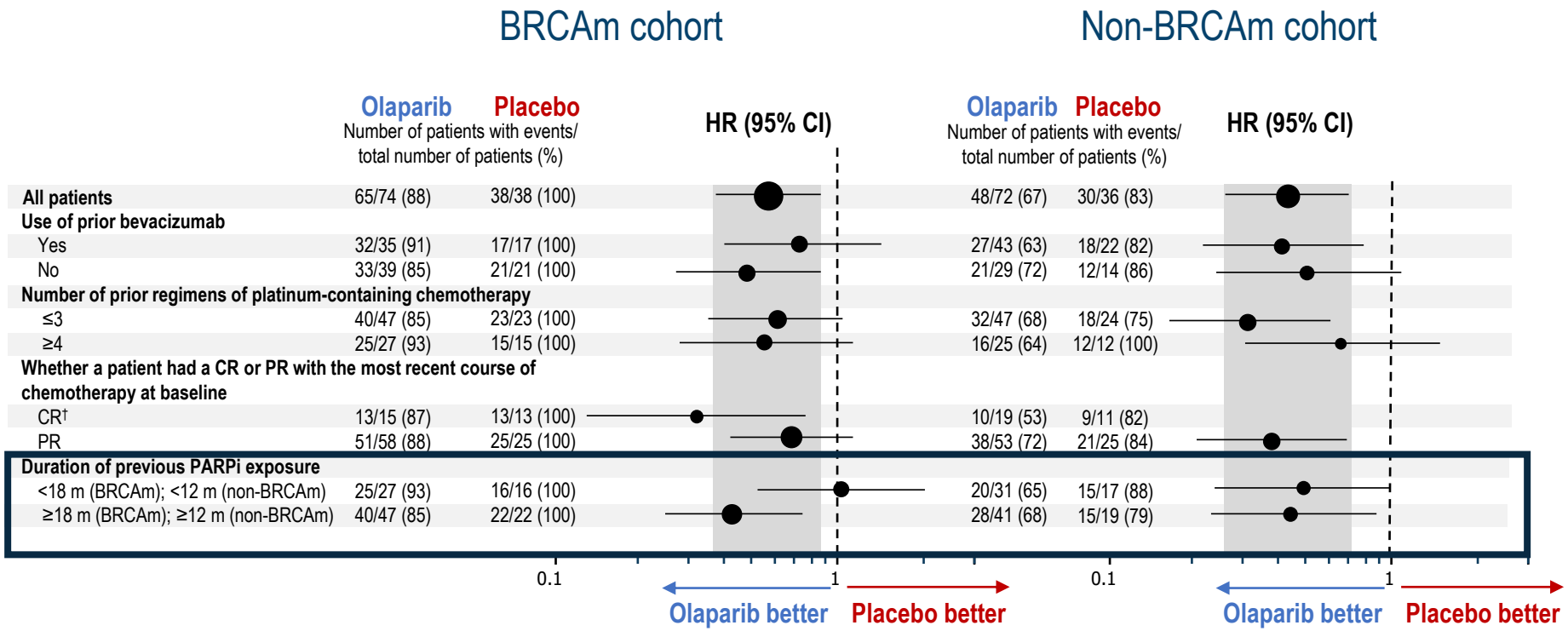
Bénéfice en SSP quel que soit le sous groupe*



Not all predefined subgroups are shown. *No statistical evidence of interaction;
†In the non-BRCAm cohort, subgroup not analyzed due to <20 PFS events, as prespecified in the statistical analysis plan. m, month.

Pujade-Lauraine et al. Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741

Pas de nouveaux effets indésirables décrits

	BRCAm cohort		Non-BRCAm cohort	
	Olaparib (N=74)	**Placebo** (N=38)	**Olaparib** (N=72)	**Placebo** (N=36)
Median (range) duration of treatment, months	4.73 (1.0–36.9)	3.35 (1.9–16.6)	3.98 (0.1–34.2)	2.86 (1.8–9.2)
Any TEAE, n (%)	64 (86)	33 (87)	66 (92)	31 (86)
Grade ≥3 TEAEs, n (%)	11 (15)	2 (5)	15 (21)	3 (8)
Serious TEAEs, n (%)	5 (7)	0	11 (15)	2 (6)
TEAE leading to dose interruption/reduction, n (%)	18 (24)	6 (16)	28 (39)	2 (6)
TEAE leading to treatment discontinuation, n (%)	2 (3)	0	1 (1)	0
AEs of special interest, n (%)				
New primary malignancies*	1 (1)	1 (3)	1 (1)	0
MDS/AML	0	0	0	0
Pneumonitis/ILD	0	0	0	0

AE data includes events that started or worsened in severity between first dose and 30 days after last dose of study treatment. AEs were graded using CTCAE version 4.03

*New primary malignancies were oesophageal squamous cell carcinoma in one olaparib patient and breast cancer in one placebo patient in the BRCAm cohort, and basal cell carcinoma in one olaparib patient in the non-BRCAm cohort.

AML, acute myeloid leukaemia; ILD, interstitial lung disease; MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event.

Pujade-Lauraine et al. Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. 10.1016/annonc/annonc741

Conclusion essai OReO

Efficacité de la reprise de maintenance de l'olaparib

- Dans une population prétraitée
- En terme de PFS
- Quelque soit le statut BRCA ou HRD

Sans nouveaux signaux de toxicité accrue

Survies sans progression moindres qu'en première maintenance

- Exploration des mécanismes de résistance

Vers un changement de pratique?

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

REVIEW

The systemic treatment of recurrent ovarian cancer revisited

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Reconsidérer la résistance aux sels de platine et reprendre des doublets à base de sels de platine

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