2021 ASCO ANNUAL MEETING

ONCO NOUVELLE-AQUITAINE Réseau Régional de Cancérologie

BRIO BORDEAUX | Recherche Intégrée Oncologie

Cancers gynécologiques

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2021 ASCO ANNUAL MEETING

Déclaration publique de liens d'intérêts

- Advisory Boards : Novartis, Pfizer, GSK, Lilly
- Congrès : Pfizer, Amgen, Roche, Novartis, GSK
- Honoraires: Astrazeneca, Daiichi, Lilly, Novartis, Pfizer, Fresubin, GSK

Chimiothérapie adjuvante après RT-CT dans le cancer du col de l'utérus localement avancé vs RT-CT seule : essai randomisé de phase III OUTBACK (ANZGOG 0902, RTOG 1174, NRG 0274)

Linda R. Mileshkin et al.

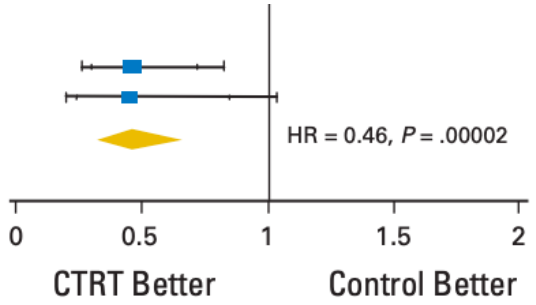
LBA3

Contexte : RT-CT = gold standard dans le traitement des cancers du col localement avancé (à partir de Ib3)

1/Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration – Méta-analyse 2008

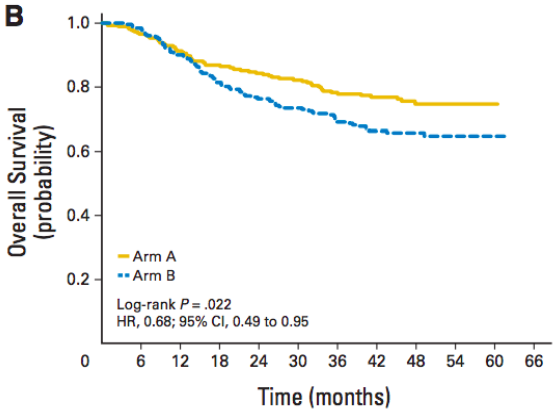
Trials of CTRT + adjuvant chemotherapy *v* radiotherapy						
SWOG8797[8,46] (CDDP FU)	28	135	54	133	-15.61	20.36
Kantardzic[45] (CDDP BLM)	15	40	25	40	-7.74	9.74
Sub-total	43	175	79	173	-23.35	30.10

BLM : Bléomycine



Pas de preuves suffisantes

2/RT-CT puis CT par CDDP + GEMZAR (2 cycles)

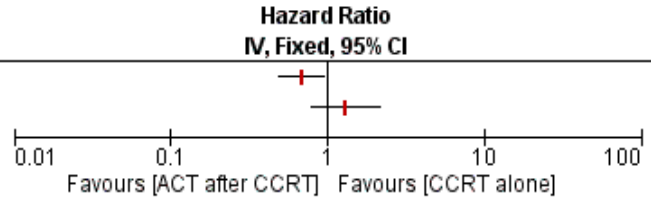


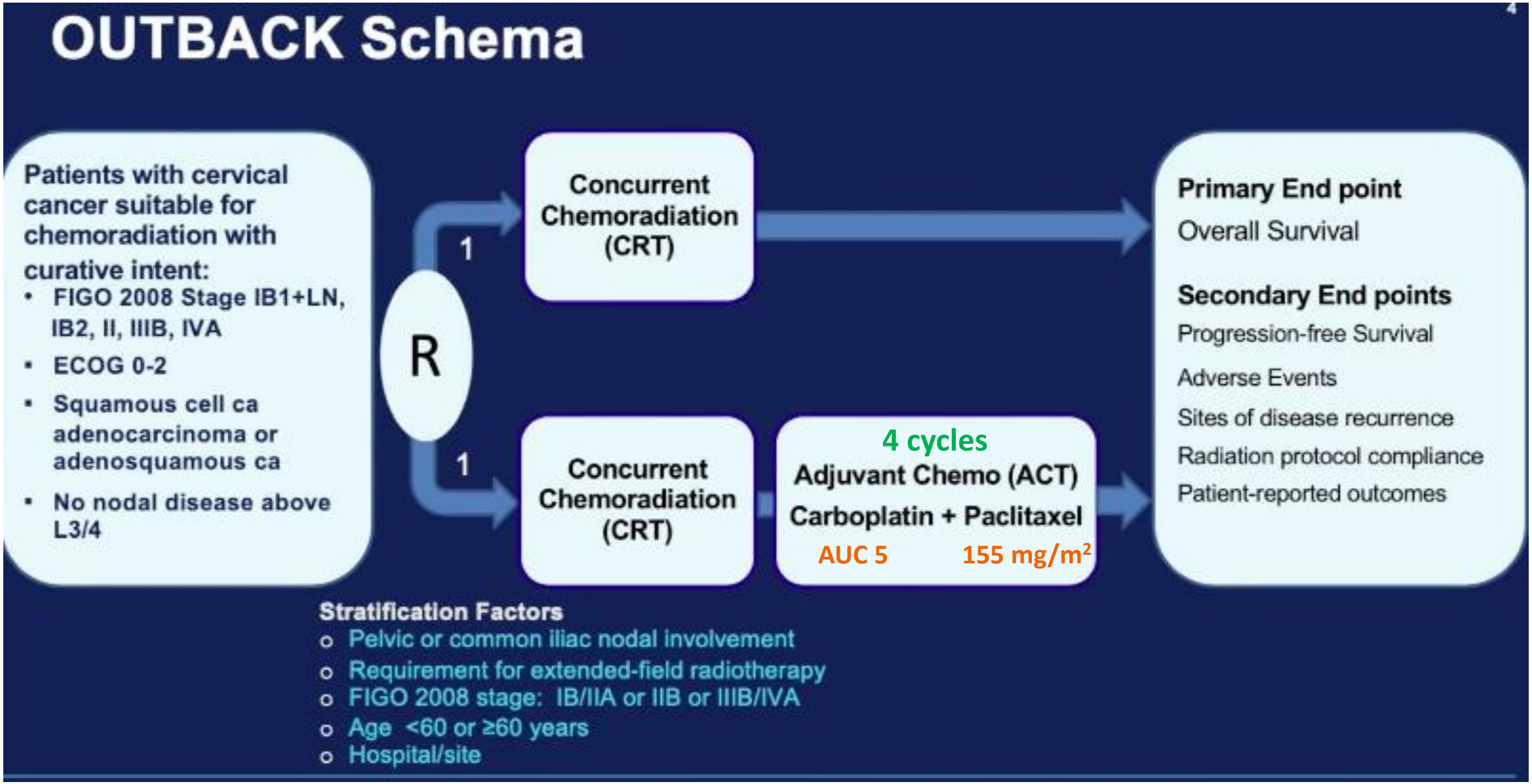
Alfonso Dueñas-González et al. JCO 2011

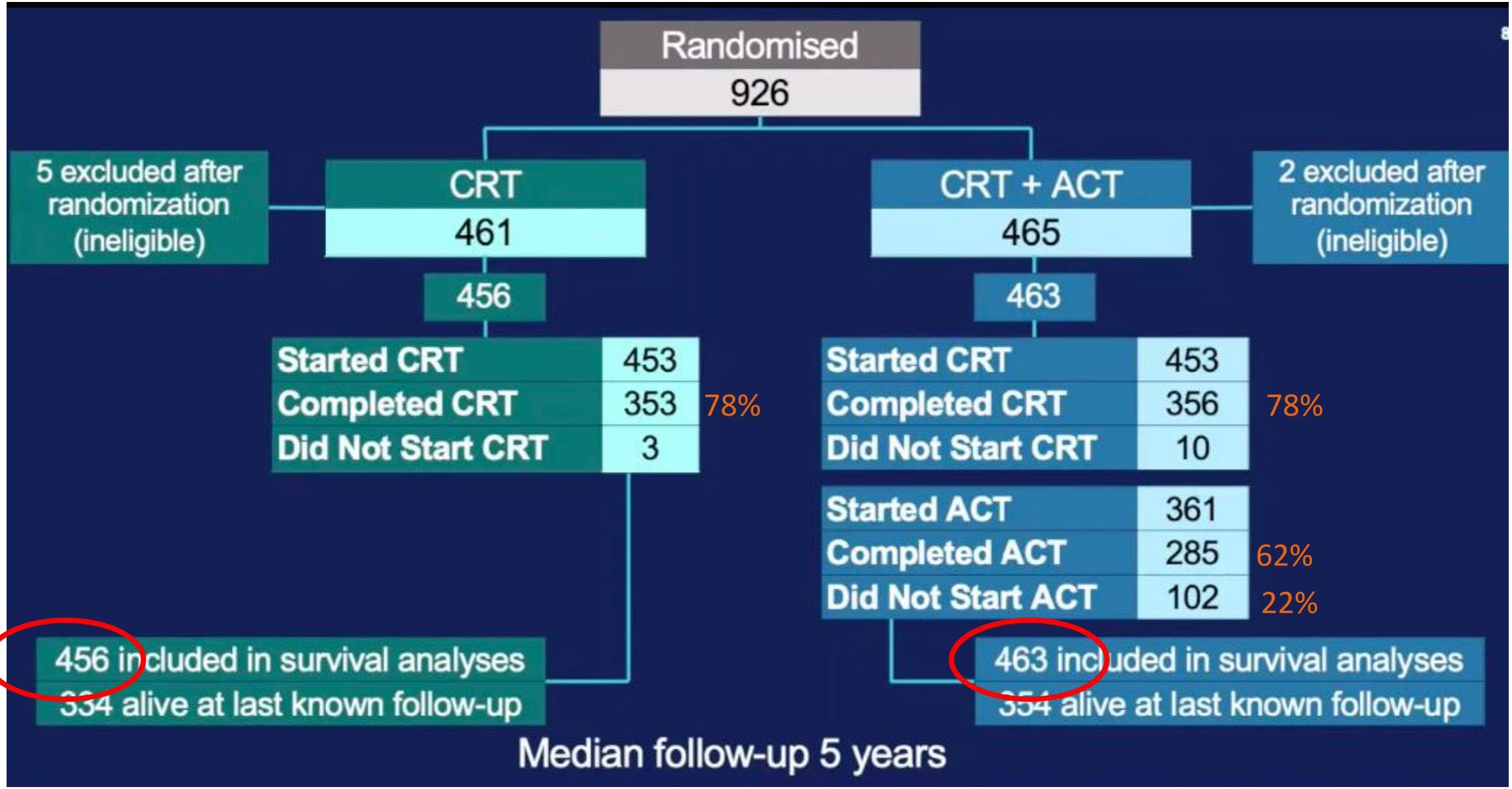
Protocole non standard
Toxicités importantes
2 décès toxiques

3/ Meta-analyse de Cochrane 2014

Study or Subgroup	log[Hazard Ratio]	SE	ACT after CCRT Total	CCRT alone Total	Hazard Ratio IV, Fixed, 95% CI
Dueñas-González 2011	-0.3857	0.1672	259	256	0.68 [0.49, 0.94]
Lorvidhaya 2003	0.26962158	0.25462099	230	242	1.31 [0.79, 2.16]




OUTBACK Schema
Patients with cervical cancer suitable for chemoradiation with curative intent:
• FIGO 2008 Stage IB1+LN, IB2, II, IIIB, IVA
• ECOG 0-2
• Squamous cell ca adenocarcinoma or adenosquamous ca
• No nodal disease above L3/4
R
1
1
Concurrent Chemoradiation (CRT)
Concurrent Chemoradiation (CRT)
4 cycles
Adjuvant Chemo (ACT)
Carboplatin + Paclitaxel
AUC 5
155 mg/m2
Primary End point
Overall Survival
Secondary End points
Progression-free Survival
Adverse Events
Sites of disease recurrence
Radiation protocol compliance
Patient-reported outcomes
Stratification Factors
Pelvic or common iliac nodal involvement
Requirement for extended-field radiotherapy
FIGO 2008 stage: IB/IIA or IIB or IIIB/IVA
Age <60 or ≥60 years
Hospital/site


Randomised
926
5 excluded after randomization (ineligible)
CRT
461
CRT + ACT
465
2 excluded after randomization (ineligible)
456
463
Started CRT 453
Completed CRT 353
Did Not Start CRT 3
78%
Started CRT 453
Completed CRT 356
Did Not Start CRT 10
78%
Started ACT 361
Completed ACT 285
62%
Did Not Start ACT 102
22%
456 included in survival analyses
334 alive at last known follow-up
463 included in survival analyses
354 alive at last known follow-up
Median follow-up 5 years

Baseline characteristics: disease

Characteristic	Value	CRT N=456		CRT+ACT N=463	
		n	%	n	%
Nodal involvement	None	225	49%	231	50%
	Pelvic alone	144	32%	149	32%
	Common iliac alone	33	7%	31	7%
	Pelvic and common iliac	44	10%	44	10%
	Unknown	10	2%	8	2%
Extended field planned	No	397	87%	404	87%
	Yes	59	13%	59	13%
FIGO stage (2008)	1B1 (all node positive), 1B2, IIA	152	33%	154	33%
	IIB	196	43%	197	43%
	IIIB or IVA	108	24%	112	24%
Histological type	Squamous cell carcinoma	358	79%	383	83%
	Adenocarcinoma	79	17%	68	15%
	Adenosquamous	19	4%	12	3%
Maximum tumour diameter	Median (range)		5.0 cm (0-11)		5.0cm (0-12)

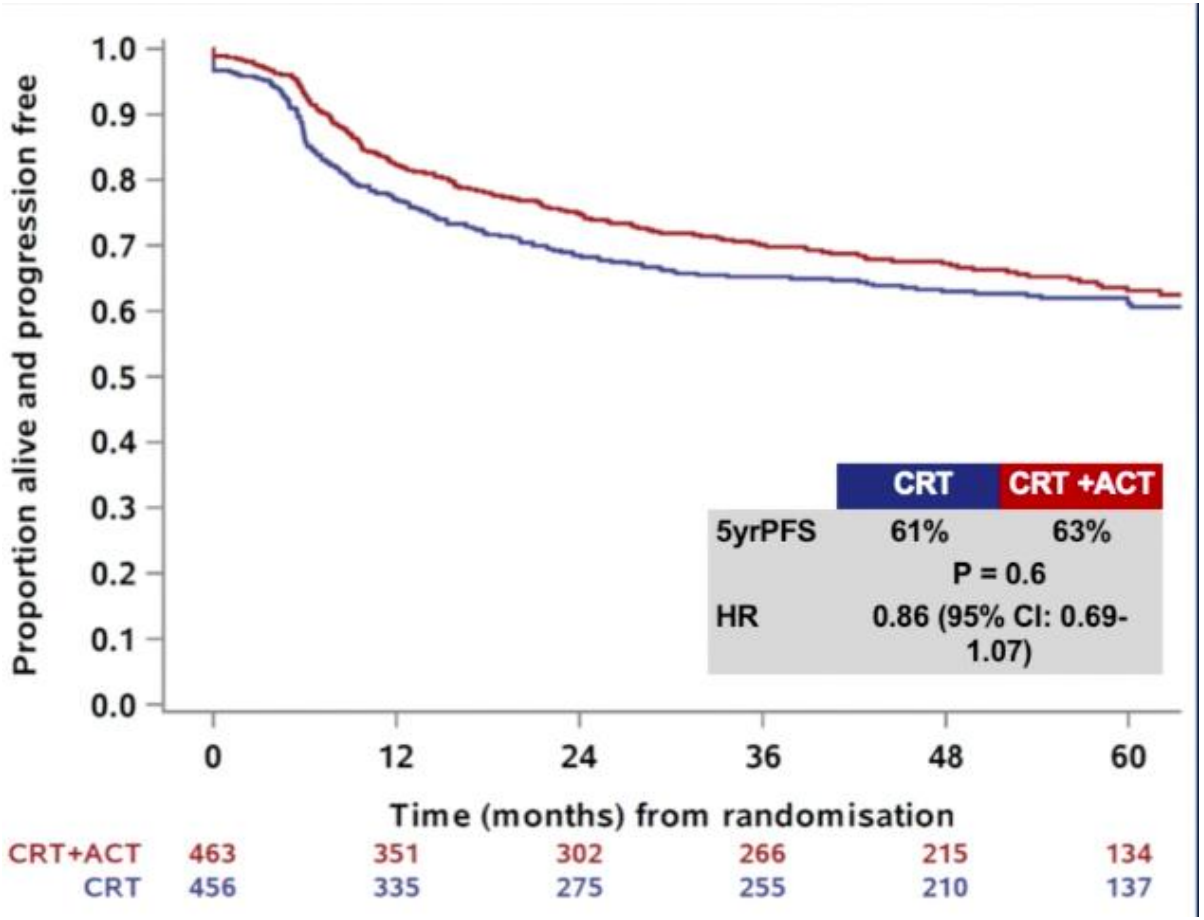
Adherence with adjuvant chemotherapy (CRT+ACT group)

Characteristic	Cycles given	N	%
Cycles of ACT	0	102	22%
	1	23	5%
	2	29	6%
	3	24	5%
	4	285	62%
4 full doses with no delay: Carboplatin	4	200	70%
4 full doses with no delay: Paclitaxel	4	197	69%

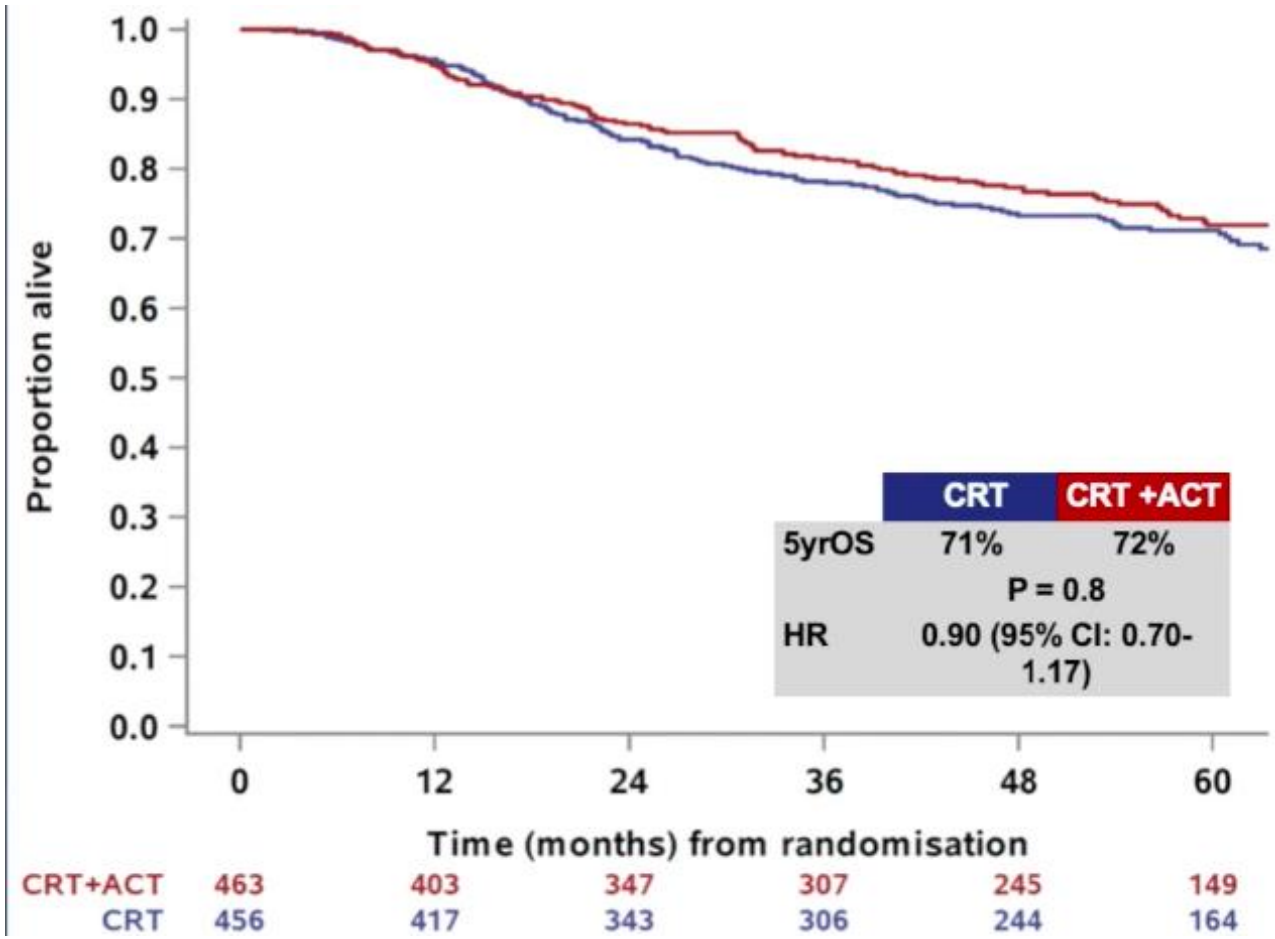
Odds of not starting adjuvant chemotherapy in the CRT+ACT group were:
- doubled in women aged >60
- doubled in non-Caucasian women
- tripled in those who did not complete CRT

Milleshkin et al, ESMO Congress, Barcelona 2019

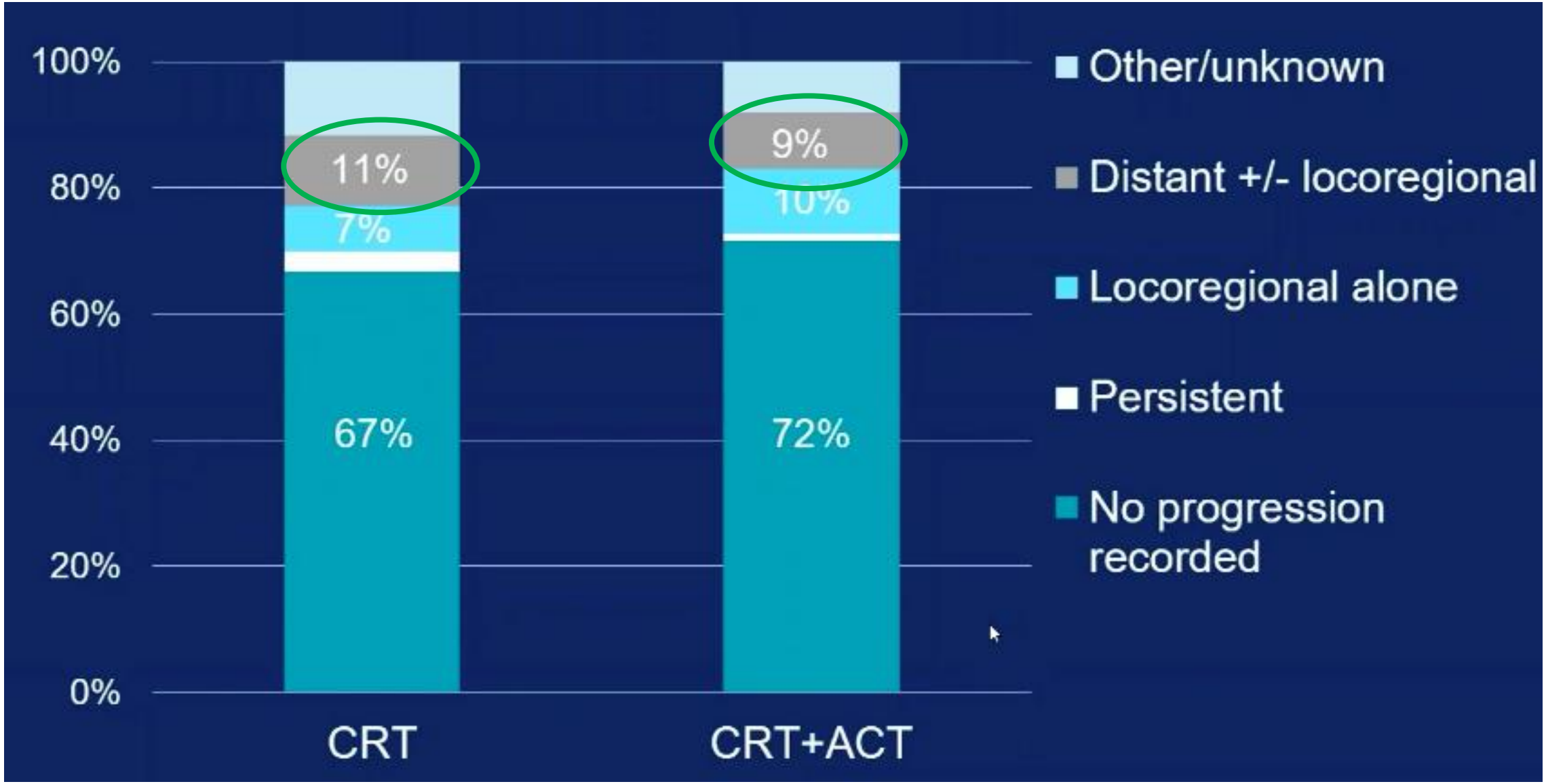
Survie sans progression



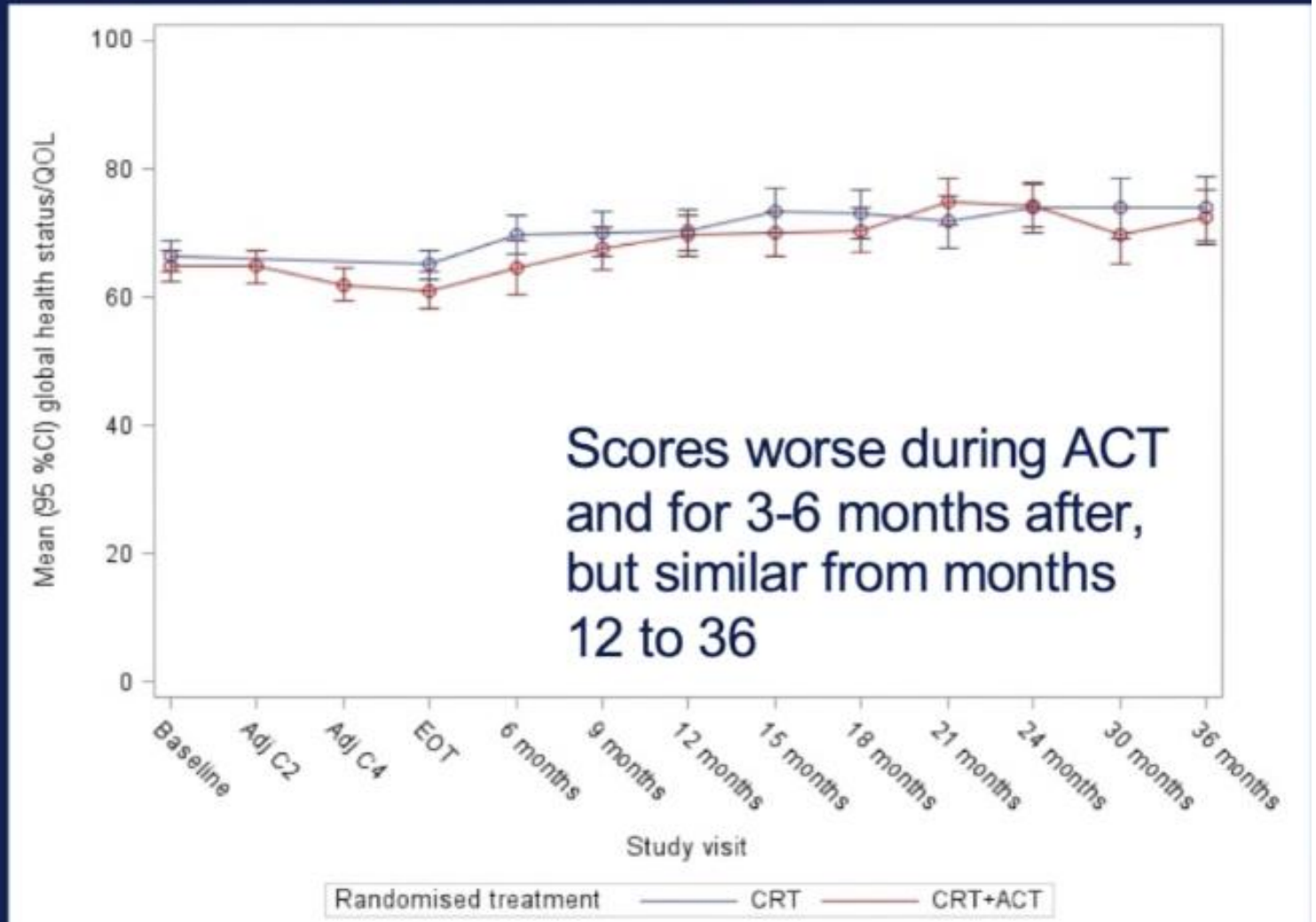
Survie globale



Patterns of disease recurrence



Global quality of life (QLQ-C30)



Autres éléments

- Pas de différences en terme d'effets secondaires excepté le taux de neuropathie (7% vs 2%)
- Pas de différence d'efficacité en fonction de la réalisation complète ou non de la CT

Strengths

- Large sample size
- Randomized treatment allocation
- Excellent adherence to CRT
- Multinational, intergroup collaboration

Limitations

- Randomization before CRT
- ACT not started in 22%
- Outcomes better than expected
- Confined to high income countries
- Sensitivity analyses for non-compliance are subject to bias

Additional strengths

- Completing the trial successfully
- Study modification based on reality.
- Success in completing external-beam radiation in both arms of the study without significant protraction of overall radiation time.
- Support for patients experiencing AEs especially in the adjuvant chemo study arm.

QUE RETENIR ?

Pas de changement de pratique

- Pas d'intérêt à faire une chimiothérapie adjuvante

- Futur : immunothérapie ?
  - ATEZOLACC (atézolizumab)
  - CALLA (durvalumab)
  - ENGOT-cx11/KEYNOTE-A18 (pembrolizumab)

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ARCAGY - GINECO

Résultats d'efficacité et de sécurité de l'étude neopembrov, Essai randomisé de phase II portant sur la chimiothérapie néoadjuvante (CT) avec ou sans pembrolizumab (P), suivie d'une chirurgie + chimiothérapie standarde ± P pour le carcinome séreux de haut grade (CSHG) avancé

Etude du groupe GINECO.

Isabelle Laure Ray-Coquard et al.

Abstract # 5500

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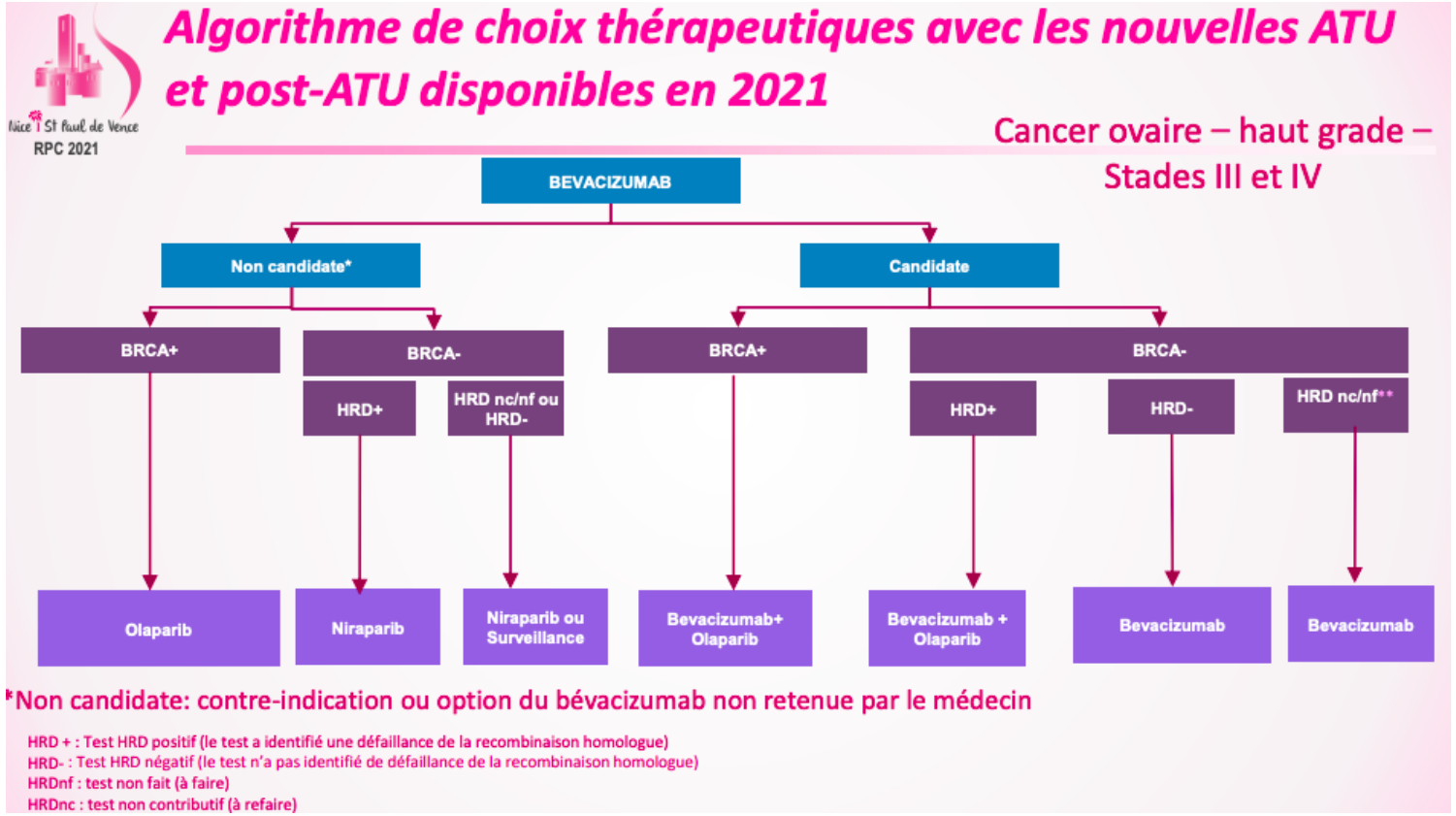
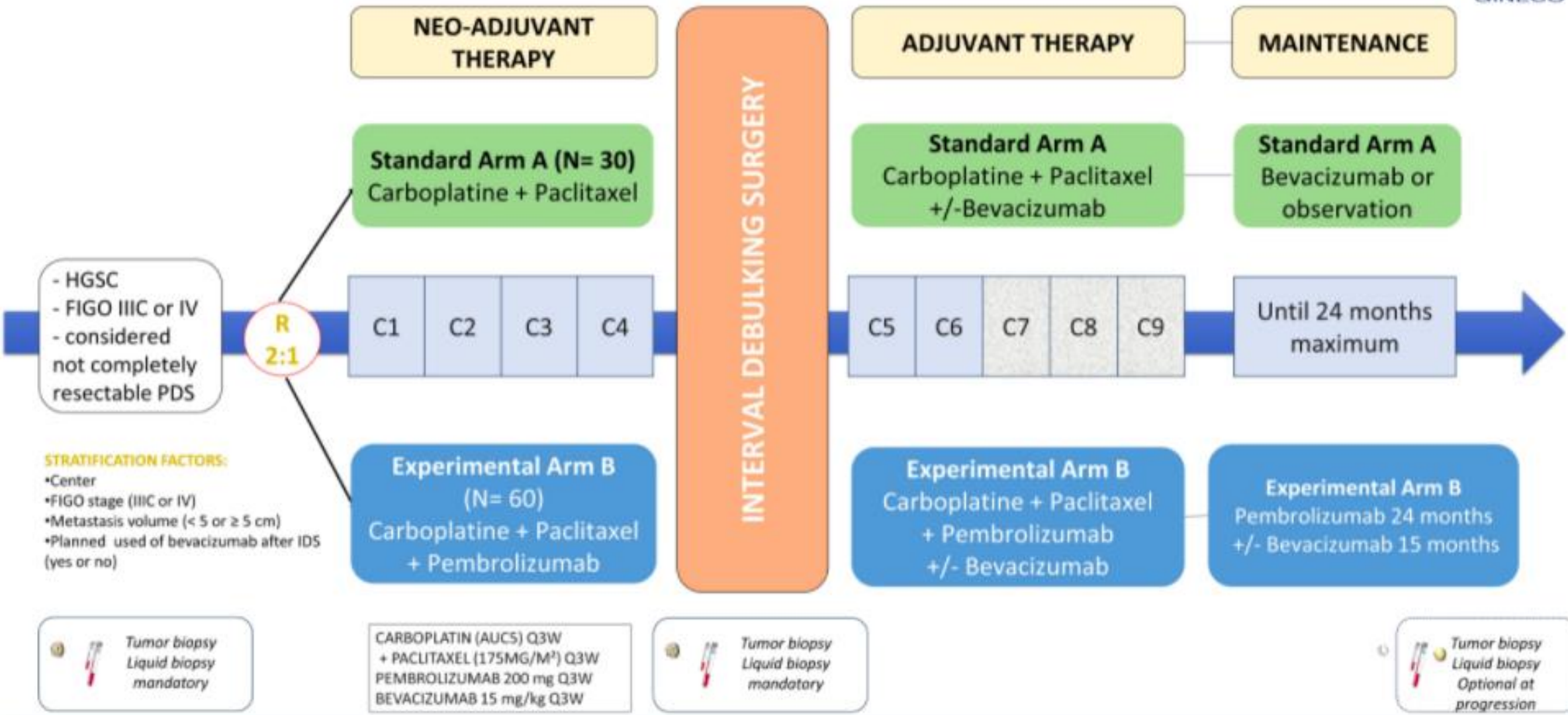
CONTEXTE

- Gold standard = chirurgie
- Si non résécable en CC0: indication à une CT néo-adj dans les stade III-IV
- Traitement standard : carboplatine + paclitaxel +/- bevacizumab et/ou inh de PARP



Study design



Study endpoints

1. **Primary endpoint: Complete resection rate (CC0) at IDS with blinded independent centralized review by 2 surgical experts.**
2. **Secondary endpoints :**

- **Efficacy:**
  - Response rate (using RECIST 1.1) to neoadjuvant treatment;
  - Best response to the global strategy
  - The rate of pCR
  - Progression-Free Survival (PFS)
  - Overall Survival
- **Safety during NACT. and adjuvant setting** including operative complications rate.
- **Translational:**
  - biomarkers predicting clinical responses to pembrolizumab
  - Mechanisms contributing to anti-PD1 resistance
  - anti tumoral immunity (B/plasma cell infiltration and TLS)

Patients characteristics

	Arm A (PC) n = 30 (%)	Arm B (PC + P) n = 61 (%)	Total n = 91(%)
Age (median/ y)	61.5 (40-79)	63 (42-76)	63 (40-79)
Histological type (%)			
High Grade Serous	28 (93.3)	60 (98.4)	88 (96.7)
$Other	2 (6.7)	1 (1.6)	3 (3.3)
ECOG (%)			
0	14 (46.7)	29 (47.5)	43 (47.3)
1-2	16 (53.3)	32 (52.5)	48 (52.7)
FIGO staging (%)			
IIIC	25 (83.3)	50 (82.0)	75 (82.4)
IV	5 (16.7)	11 (18.0)	16 (17.6)
Ca125			
Mean (std)	880.4 (936.4)	1385.1 (1935.1)	1222.5 (1690.1)
Diagnostic surgery by lapararoscopy (%)	29 (96.7)	53 (88.3)	82 (91.1)
Peritoneal cancer index (PCI) at baseline			
Median (range)	22 (7-39)	18 (3-39)	19 (3-39)
m*BRCA***			
Yes	3 (10.0)	13 (21.3)	16 (17.6)
No	24 (80.0)	41 (67.2)	65 (71.4)
Unknown	3 (10.0)	7 (11.5)	10 (11.0)
Bevacizumab used/anticipated (%)	28/29 (96.6)	52/59 (88.1)	80/88 (91)

Response to CT ± Bev +/- Pembrolizumab

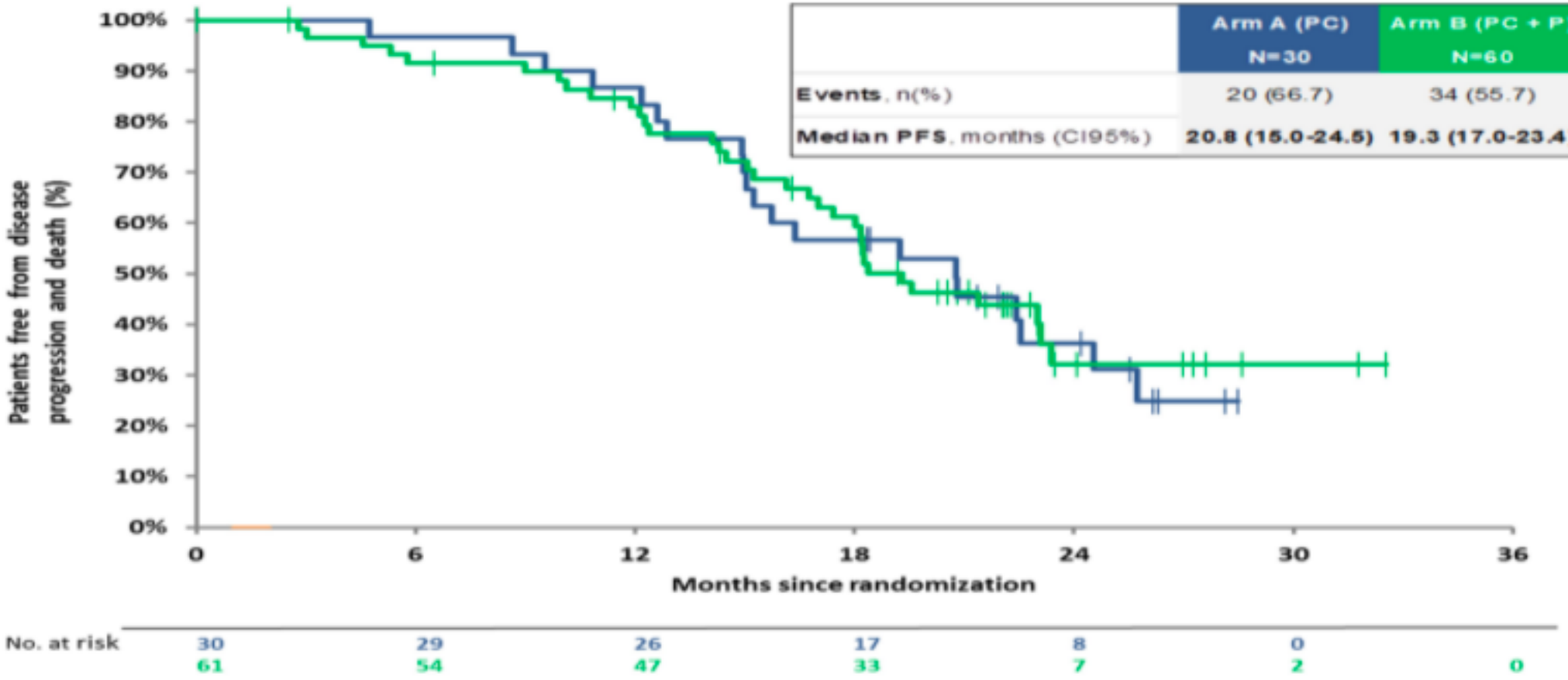
	Arm A (CP ± Bev) N = 30	Arm B (CP+ P ± Bev) N = 61
Interval debulking surgery performed (%)		
Yes	29 (96.7)	58 (95.1)
No	1 (3.3)	3 (4.9)
Response at IDS (PCI Decrease)		
mean [std]	- 9.58 [8.58]	- 10.19 [9.27]
Not evaluable	3	6
Primary Endpoint (ITT) Rate of complete debulking % [95% CI]	***70% [53.5% -]***	***73.8% [62.9% -]***
Complete cytoreductive surgery (CC0)	21 (72.4)	45 (77.5)
CC1	0	2 (3.4)
CC ≥ 3 or biopsies only	8 (27.6)	11 (18.9)
	N = 29	N = 58
Response Rate after 4 cy NACT (RECIST) (%)		
Complete response	2 (6.9)	2 (3.3)
Partial response	16 (55.2)	42 (70.0)
Stable	11 (37.9)	14 (23.3)
Progression	0 (0.0)	2 (3.3)
Not evaluable	1	1
ORR (95% CI)	***62.1% [42.3-79.3]***	***73.3% [60.3-83.9]***
Best Overall Response (%)		
Complete response	22 (75.9)	45 (75.0)
Partial response	3 (10.3)	10 (16.7)
Stable	4 (13.8)	5 (8.3)
Not evaluable	1	1
CR+PR	*25 (83.3)*	*55 (90.1)*
Ca125 normalization	22 (73.3)	46 (75.4)

Taux élevé de CC0

Taux élevé de normalisation

Progression Free survival

GINECO



	Arm A (PC) N=30	Arm B (PC + P) N=60
Events, n(%)	20 (66.7)	34 (55.7)
Median PFS, months (CI95%)	**20.8 (15.0-24.5)**	**19.3 (17.0-23.4)**

Median Follow-up of 22 months (min=6.8, max = 32.5)

Toxicities

During Neo-Adjuvant Therapy

	Arm A PC N = 30 (%)		Arm B PC + P N = 61 (%)	
Grade (NCI-CTCAE v4)	1 or 2	3 or 4	1 or 2	3 or 4
Hematological (%)				
Neutropenia	0 (0.0)	4 (13.3)	5 (8.2)	8 (13.1)
Anemia	9 (30.0)	2 (6.7)	17 (27.9)	3 (4.9)
Thrombopenia	5 (16.7)	0 (0.0)	5 (8.2)	2 (3.3)
Non-hematological (%)				
Nausea	9 (30.0)	0 (0.0)	25 (41.0)	0 (0.0)
Vomiting	2 (6.7)	1 (3.3)	3 (4.9)	0 (0.0)
Diarrhea	5 (16.7)	0 (0.0)	9 (14.8)	0 (0.0)
Constipation	5 (16.7)	0 (0.0)	14 (23.0)	0 (0.0)
Fatigue	3 (10.0)	0 (0.0)	3 (4.9)	0 (0.0)
High Blood Pressure	1 (3.3)	0	4 (6.6)	2 (3.3)
Venous Thrombosis	2 (6.6)	0 (0.0)	1 (1.6)	1 (1.6)
Pulmonary Embolism	0 (0)	1 (3.3)	3 (4.9)	2 (3.3)
Peripheral neuropathy	5 (16.7)	2 (6.7)	14 (23)	0 (0.0)
Dysthyroidism	0	0	8 (13.1)	0 (0)
Other iRRs	1 (3.3)	0	2 (3.2)	0

Operative and post operative

	Arm A PC	Arm B PC + P
Interval Debulking Surgery* N/Total (%)	29/30 (97)	59/61 (97)
Time from randomization to IDS (mths) Median (min-max)	3.3 (2.6-7.4)	3.2 (2.4-7.3)
Post-operative complication (%)**	4 (13.3%)	13 (21.3%)[$]

*No surgery due to infection (n =2), pulmonary embolism (n=1)
**more frequently infection, fistula, pleural effusion & hemorrhage
[$]one death due to post op peritonitis

During whole treatment

	Arm A PC ± Bev	Arm B PC + P ± Bev
Grade (NCI-CTCAE v4)		
AE	30 (100%)	61 (100%)
AE grade ≥ 3	20 (66.7%)	46 (75.4%)
AE related to P	-	42 (68.9%)
AE related to P G≥3	-	11 (18%)

Treatment compliance (NACT & post IDS)

GINECO

NACT	Arm A (CP) N = 30	Arm B (CP + P) N = 61
Dose reduction for AE (%)		
Carboplatin	2 (6.7)	2 (3.3)
Paclitaxel	6 (20)	3 (4.9)
Dose interruption (%)		
Pembrolizumab	-	0 (0)
Early stopping* (< 4 cy) (%)		
Carboplatin	1 (3.3)	1 (1.6)
Paclitaxel	2 (6.7)	1 (1.6)
Pembrolizumab	-	2 (3.3)

* For toxicity or progression or death

Post IDS	Arm A (CP) N = 30	Arm B (CP + P) N = 61
Dose reduction for AE (%)		
Carboplatin	4 (13.8)	4 (7.3)
Paclitaxel	8 (27.6)	11 (20.0)
Dose interruption for AE (%)		
Pembrolizumab	-	9 (17.0)
Early stopping (%)		
Carboplatin	3 (10.0)	8 (13.1)
Paclitaxel	6 (20.0)	11 (18.0)
Pembrolizumab	**-**	**40 (65.6)**
progression	-	23 (37.7)
toxicity	-	14 (23.0)
other	-	3 (4.9)
Bevacizumab	**21 (70.0)**	**41 (67.2)**
progression	15 (50.0)	23 (37.7)
toxicity	4 (13.3)	10 (16.4)
other	2 (6.7)	8 (13.1)

Pas de changement de pratique

QUE RETENIR ?

- Echec du traitement par pembrolizumab dans le cancer de l'ovaire

- Autres études négatives
  - SCO 2020 : JAVELIN (phase III) avec avélumab
  - ESMO 2020: IMagyn050 (phase III) avec atézolizumab

- Etudes en cours
  - DUO-O : durvalumab +/- olaparib
  - FIRST: dostarlimab +/- niraparib