Actualités en oncologie médicale

Mardi 28 novembre 2023

Limoges

Pr Elise DELUCHE

CHU de Limoges

Quelle prise en charge du cancer du col de l'utérus en 2023 ?

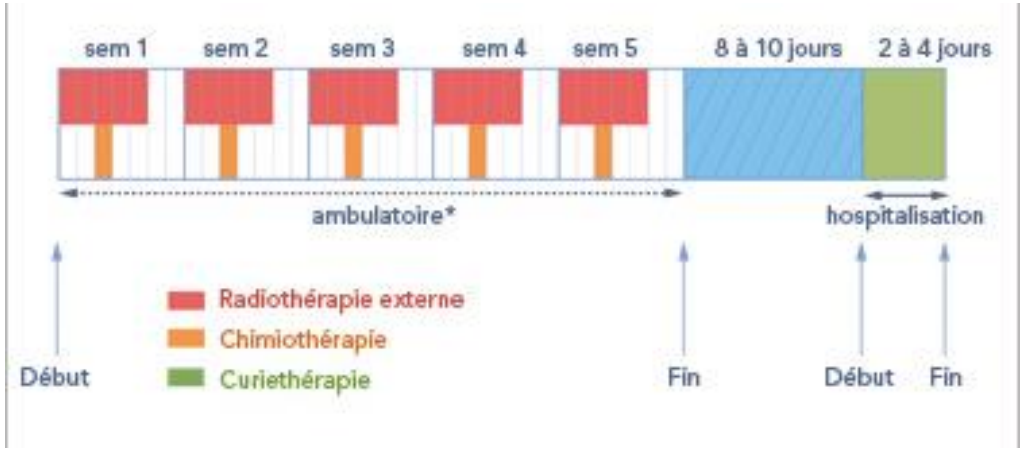
Liens d’intérêts

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

Prise en charge des cancers du col localement avancés

FIGO IA | IB1 | IB2 | IB3 | II | III | IVA | IVB

STANDARD : Radiochimiothérapie concomitante (45 Gy) + curiethérapie + CDDP 40 mg/m² par pendant 5-6 semaines



TRAITEMENT D'INDUCTION

Essai INTERLACE

Essai Colibri

TRAITEMENT DE MAITENANCE

Etude ENGOT-cx11/GOG-3047/KEYNOTE-A18=

Etude OUTBACK

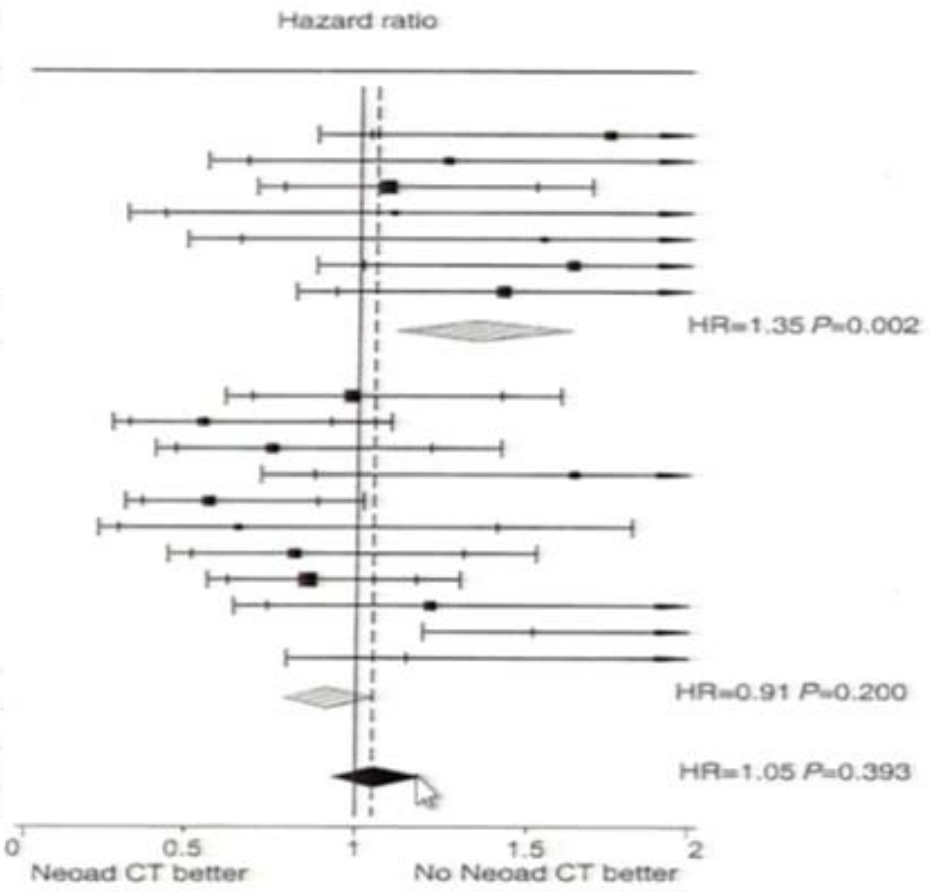
Etude CALLA

Essai randomisé de phase III comparant la chimiothérapie d'induction suivie d'une radio-chimiothérapie à la radio-chimiothérapie seule dans le cas d'un cancer du col de l'utérus localement avancé

The GCIG INTERLACE trial

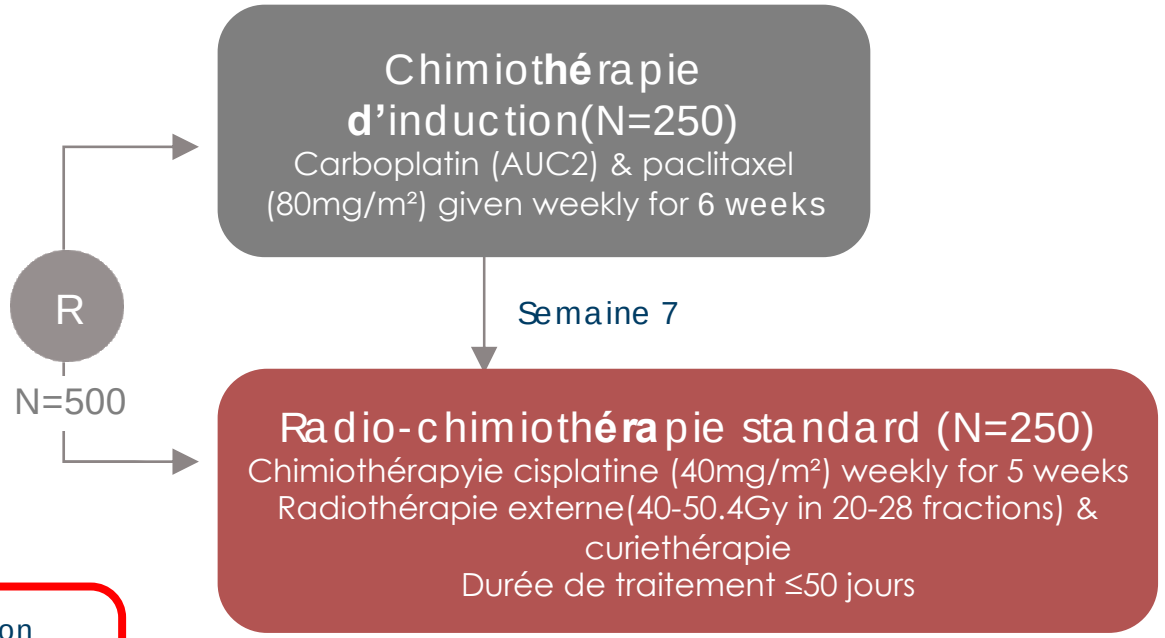
CT avant RT-CT

Trial	Neoad CT (no. events/no. entered)	No Neoad CT	O-E	Variance
<25 mg/m²/wk				
Souhami, 1991	29/48	31/55	7.64	13.64
Tattersall, 1992	20/34	18/37	2.17	9.41
Herod, 2000	68/89	62/88	2.60	32.39
Cardenas, 1991	7/13	9/18	0.37	3.84
Cardenas, 1993	12/14	8/16	2.16	4.91
CCSG AOCOA	38/129	28/131	8.08	16.31
Kumar, 1998	49/88	34/85	7.43	20.73
Sub-total	223/415	190/430	30.45	101.24
>25 mg/m²/wk				
Chauvergne, 1993	57/92	54/90	−0.47	27.66
Sardi, 1997	19/104	32/106	−7.97	12.69
Sardi, 1998	30/73	33/74	−4.61	15.56
Chiara, 1994	22/32	16/32	4.68	9.33
Sardi, 1996	34/54	41/54	−10.61	17.89
PMB	9/16	15/19	−2.68	5.94
Sundfor, 1996	31/48	35/48	−3.41	16.40
Symonds, 2000	68/105	76/110	−5.86	35.84
Leborgne, 1997	32/48	28/49	2.98	14.94
MRC CeCa	19/24	9/24	7.86	6.64
LGOG	9/15	2/12	3.61	2.73
Sub-total	330/611	341/618	−16.49	165.61
Total	553/1026	531/1048	13.96	266.85



Critères d'inclusion

- Cancer du col de l'utérus stades IB1 N+, IB2, II, IIIB, IVA
- N0 lombo aortique sur imagerie
- Indication de radio-chimiothérapie



Objectifs principaux

- SSP
- SG

Objectifs secondaires

- EIs
- Type de récidive
- QOL
- Temps jusqu'au traitement ultérieur

Facteurs de stratification

- Site
- Stade
- Satut ganglionnaire
- IMRT vs conformationel
- 2D v 3D curiethérapie
- Taille tumorale
- SCC v autre

Essai qui a mis 10 ans à recruter….

McCormack et al., ESMO® 2023, Abs # LBA8

Caractéristiques des patientes

	Radio-chimiothérapie N=250	Induction chimio + CTRT N=250
stade FIGO (2008)		
IB1	2 (<1)	2 (<1)
IB2	23 (9)	19 (8)
IIA	14 (6)	17 (7)
IIB	176 (70)	178 (71)
IIIB	30 (12)	26 (10)
IVA	5 (2)	8 (3)
Cell type		
Non épidermoïdes	45 (18)	44 (18)
Epidermoïdes	205 (82)	206 (82)
Statut ganglionnaire		
Négatif	142 (57)	146 (58)
Positif	108 (43)	104 (42)
Taille tumorale, cm médian (range)	4.9 (1.8-12.8)	4.8 (1.3-13.5)

McCormack et al., ESMO® 2023, Abs # LBA8

Cisplatine

	CRT alone N=250	IC + CRT N=250
Completed 5 weekly cycles	197 (79)	169 (68)
Main reasons for <5 cycles :		
Adverse events leading to discontinuation :	33 (13)	68 (27)
Haemotological	4	34
Non-haemotological	25	20
Both	4	14
Other	20 (8)	13 (5)

Radiothérapie

	CRT alone N=250	IC + CRT N=250
Received external beam radiotherapy	231 (92)	242 (97)
IMRT	93 (40)	102 (42)
3D conformal	138 (60)	140 (58)
Received brachytherapy	223 (97)	238 (98)
2D point A	49 (22)	46 (19)
3D point A	106 (48)	120 (51)
3D HRCTV D90	68 (30)	72 (30)
Median overall treatment time days (range)	45 (37-88)	45 (36-70)

McCormack et al., ESMO® 2023, Abs # LBA8

Suivi médian 64 mois

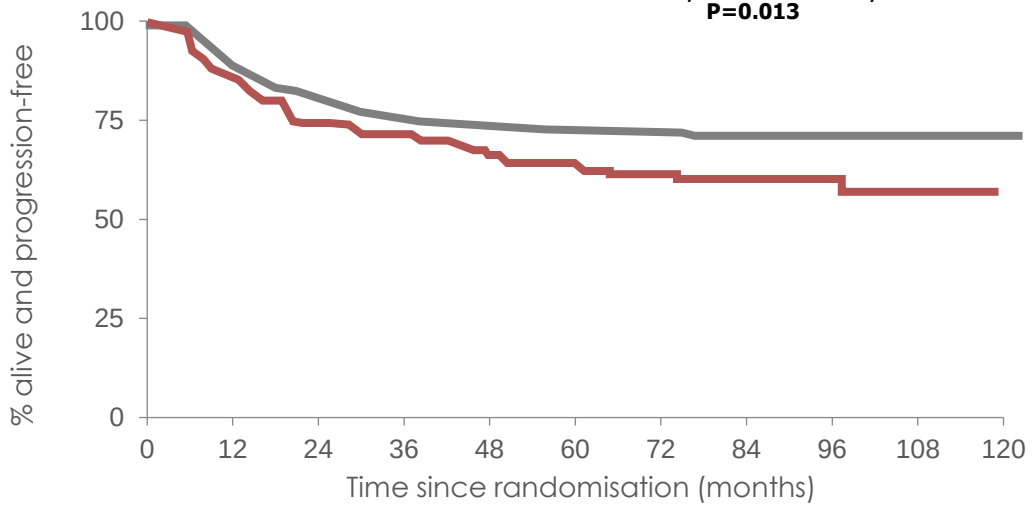
Etude positive en SSP et en SG

	CRT	CT + CRT
Total local/pelvic relapses	**41 (16)**	**40 (16)**
Total distant relapses	**50 (20)**	**30 (12)**

SSP

	Induction Chemo + CRT (N=250)	CRT alone (N=250)
3yr SSP	**75%**	**72%**
5yr SSP	**73%**	**64%**

146 SSP events
HR 0.65; 95% CI: 0.46-0;91
P=0.013

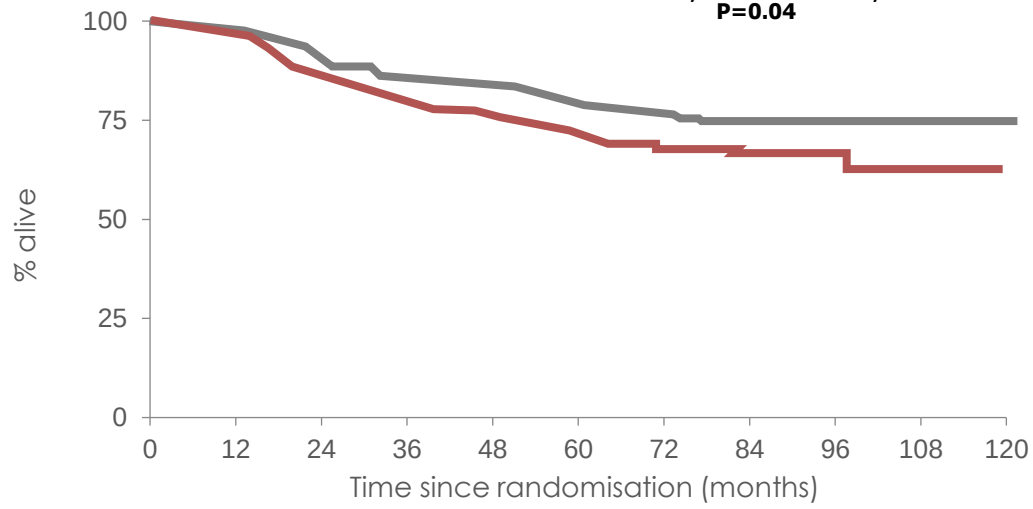


CRT alone	250	204	157	140	110	88	63	36	16	5	1
IC + CRT	250	220	178	152	132	105	72	40	19	8	1

SG

	Induction Chemo + CRT (N=250)	CRT alone (N=250)
3yr SG	**86%**	**80%**
5yr SG	**80%**	**72%**

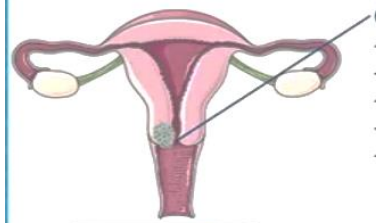
109 deaths
HR 0.61; 95% CI: 0.40-0;91
P=0.04



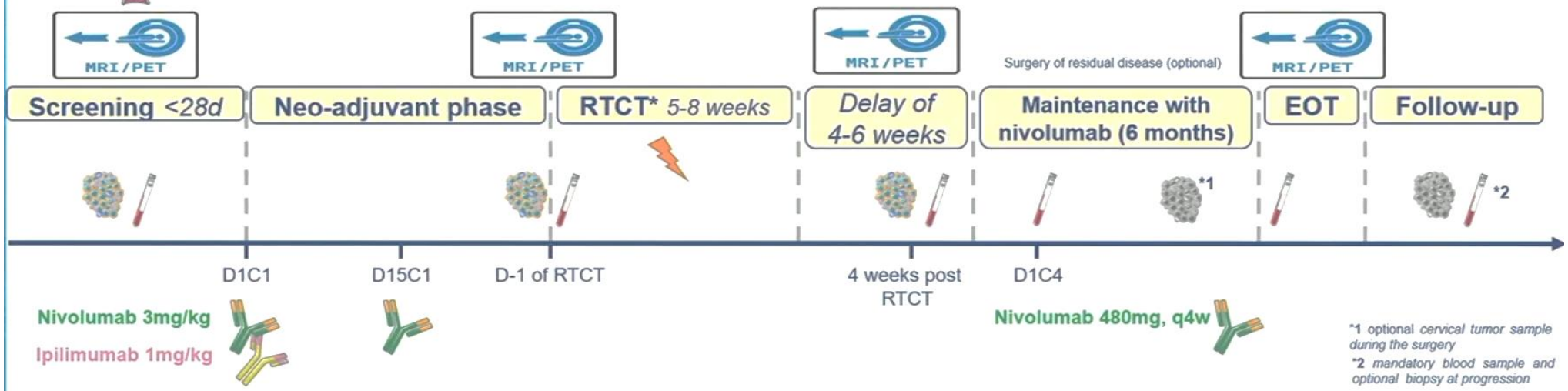
CRT alone	250	228	181	154	124	99	67	39	16	5	1
IC + CRT	250	236	195	168	146	111	75	42	19	8	1

McCormack et al., ESMO® 2023, Abs # LBA8

COLIBRI inclusion criteria & Study design



Cervical cancer
- Women aged ≥18 years
- Histologically confirmed cervical (adeno)squamous carcinoma
- LACC (FIGO 2018) stage IB3-IVA
- ECOG performance status of 0 or 1
- Multicentric single arm pilot study



***Chemoradiotherapy Regimen**

Platinum agent	Cisplatin 40 mg/m² or carboplatin AUC2 q1w × 5 weeks
EBRT	45 Gy in 25 fractions at 1.8 Gy/fraction, 5 fractions per week
Brachytherapy	High-dose rate: 27.5–30 Gy; Low/pulsed-dose rate: 35–40 Gy

2023 ASCO ANNUAL MEETING #ASCO23

PRESENTED BY: Isabelle RAY-COQUARD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

Safety- adverse events

	Neo-adjuvant ICB N = 40 (%)	RTCT N = 40 (%)	Maintenance N = 39 (%)
Any AE	**33 (82.5)**	**38 (95)**	**35 (87.5)**
Any AE of CTCAE grade ≥ 2	**14 (35)**	**33 (82.5)**	**17 (42.5)**
Any TRAE of CTCAE grade 3 or 4 *	**1 (2.5)**	**11 (27.5)**	**8 (20)**
Possibly related to Nivolumab Possibly related to Ipilimumab Possibly related to RTCT	1 (2.5) 1 (2.5) NA	3 (7.5) 3 (7.5) 10 (25)	6 (15) 1 (2.5) 5 (12.5)
Any AE with outcome of death	**0 (0)**	**0 (0)**	**0 (0)**
Any AE leading to discontinuation of ICB	**0 (0)**	**NA**	**2 (5)**
Possibly related to ICB			**1 (2.5)**
Any AE leading to discontinuation of RTCT	**NA**	0 (0)	NA
Possibly related to ICB	NA	0 (0)	NA

*Grade 3 or 4 related to ICB are lymphopenia, neutropenia, asthenia, muscular squeletal pain, cutaneous rash, proctitis, liver enzymatic abnormalities

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY: Isabelle RAY-COQUARD

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

L'association nivolumab plus ipilimumab en situation néoadjuvante avant radiochimiothérapie

- **est possible**
- **permettrait de recréer une réaction immunitaire in situ à même d'augmenter l'efficacité de la radiochimiothérapie ultérieure**

Pembrolizumab plus radio-chimiothérapie pour le cancer du col de l'utérus localement avancé à haut risque

Étude de phase 3 randomisée, en double aveugle, ENGOT-cx11/GOG-3047/KEYNOTE-A18

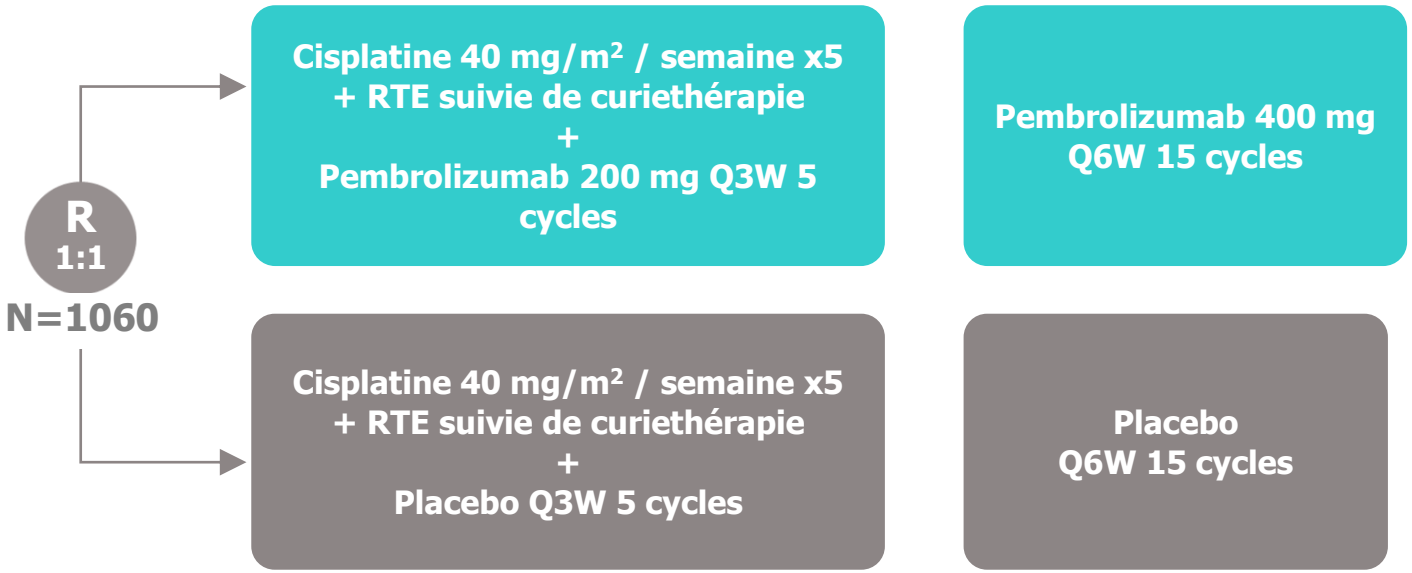
Critères d'inclusion

- stades IB2-IIB N+
- stades III-IVA (N0 ou N+)
- Non pré traités

(FIGO 2014)

Facteurs de stratification

- Type de radiothérapie externe (IMRT ou VMAT vs non)
- Stade au screening (stage IB2-IIB vs III-IVA)
- Dose totale de radiothérapie planifiée (<70 Gy vs >70 Gy [EQ2D]



Objectifs

- Primaires : SSP (RECIST v1.1) par investigateur ou confirmation histologique et SG
- Secondaires clés : SSP à 24 mois, taux de réponse, PRO, et tolérance

Lorusso D et al., ESMO® 2023, Abs #LBA38

Caractéristiques des patientes

	Pembro (N = 529)	Placebo (N = 531)
Age, médiane	49 ans (22-87)	50 ans (22-78)
PD-L1 CPS		
<1	22 (4.2%)	28 (5.3%)
≥1	502 (94.9%)	498 (93.8%)
ECOG PS 1	149 (28.2%)	134 (25.2%)
Carcinome épidermoide	433 (81.9%)	451 (84.9%)
Stade au screening (FIGO 2014)		
IB2-IIB	235 (44.4%)	227 (42.7%)
III-IVA	294 (55.6%)	304 (57.3%)
Atteinte ganglionnaire		
Seulement pelvienne	326 (61.6%)	324 (61.0%)
Lombo aortique	14 (2.6%)	10 (1.9%)
Pelvienne et lombo aortique	105 (19.8%)	104 (19.6%)
N0	84 (15.9%)	93 (17.5%)

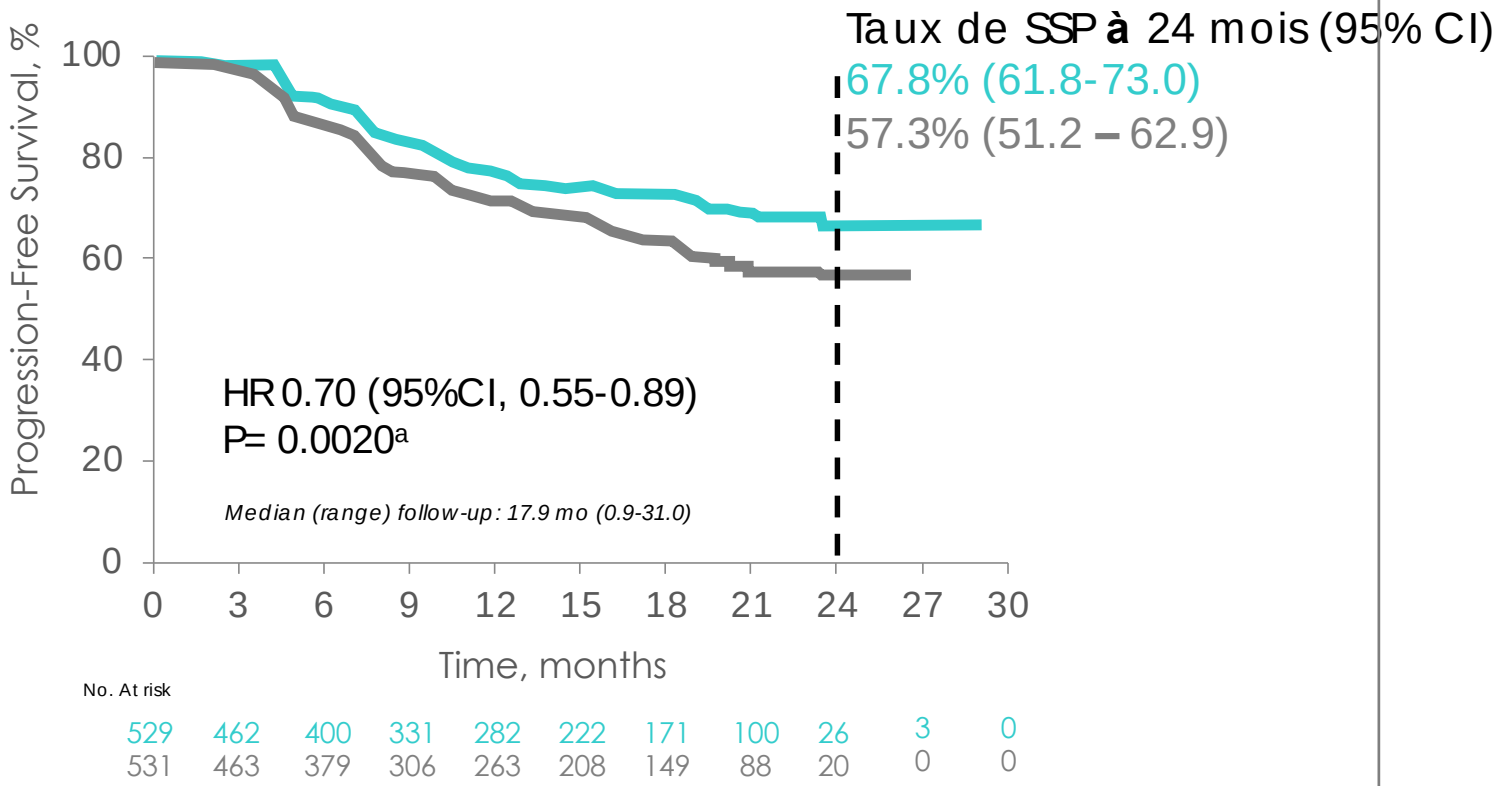
	Pembro (N = 529)	Placebo (N = 531)
Type de radiothérapie externe planifiée		
IMRT ou VMAT	469 (88.7%)	470 (88.5%)
Ni IMRT ni VMAT	60 (11.3%)	61 (11.5%)
Dose planifiée de radiothérapie totale (EQD2)		
< 70 Gy	47 (8,9)	46 (8,7)
≥ 70 Gy	482 (91,1)	485 (91,3)

15% de N-

Lorusso D et al., ESMO® 2023, Abs #LBA38

SSP Suivi 17.9 mois

Objectif principal : Progression-Free Survival

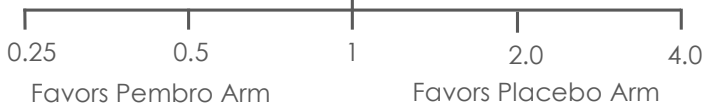


	Pts w/Event	Median, mo (95% CI)
Pembro	21.7%	NR (NR-NR)
Placebo	29.0%	NR (NR-NR)

- **Amélioration significative de la SSP**
- **Pas de différence significative en survie globale (pas mature)**

Bénéfice surtout sur les III et IVA

	No.of Events/ No. of Patients	HR (95% IC)
Overall	269/1060	0.70 (0.55-0.89)
Age		
< 65 years	236/927	0.72 (0.56-0.94)
> 65 years	33/133	0.57 (0.27-1.17)
Race		
White	143/518	0.83 (0.59-1.15)
All others	125/538	0.60 (0.42-0.86)
ECOG performance-status score		
0	197/777	0.79 (0.59-1.04)
1	72/283	0.53 (0.33-0.85)
Planned type ERBT		
IMRT/VMAT	237/939	0.68 (0.52-0.87)
Non-IMRT/-VMAT	32/121	0.92 (0.46-1.85)
FIGO 2014 stage at screening		
IB2 to IIB	113/462	0.91 (0.63-1.31)
III to IVA	156/598	0.58 (0.42-0.80)
Planned total radiotherapy dose		
< 70 Gy	25/93	0.62 (0.28-1.38)
> 70 Gy	244/967	0.71 (0.55-0.91)



TRAITEMENT D'INDUCTION

Essai INTERLACE : CT néo-adj

Essai Colibri : intérêt IO

TRAITEMENT DE MAITENANCE

Etude ENGOT-cx11/GOG-3047/KEYNOTE-A18 = pembrolizumab

Etude OUTBACK : échec CT adjuvante

Etude CALLA : échec Durvalumab

Chimiothérapie en 1ère ligne

A la récidive ou métastatique

Essai de phase III KEYNOTE-826

Colombo et al. LBA 2, NEJM 2021.

- Cancers du col en rechute/métastatique non éligibles à un traitement curatif
- ECOG 0-1
- Pas de traitement antérieur (RCT autorisée)

1

1

Pembrolizumab 200mg/3sem (35 cycles)
+ Paclitaxel 175mg/m² + Cisplatine 50mg/m² ou Carboplatine AUC5 /3sem
+/- Bevacizumab 15mg/kg/3sem

Placebo/3sem (35 cycles)
+ Paclitaxel 175mg/m² + Cisplatine 50mg/m² ou Carboplatine AUC5 /3sem
+/- Bevacizumab 15mg/kg/3sem

- **Critère primaire: OS + PFS (investigateur, RECIST 1.1)**
- **Critères secondaires :** PFS 12 mois, toxicité, taux de réponse, durée de réponse.
- **Critère exploratoire :** PRO

Stratification:
- Statut métastatique ou non au diagnostic
- PDL1/CPS : <1, 1 -10, ≥ 10
- Bevacizumab : oui/non

The NEW ENGLAND JOURNAL of MEDICINE

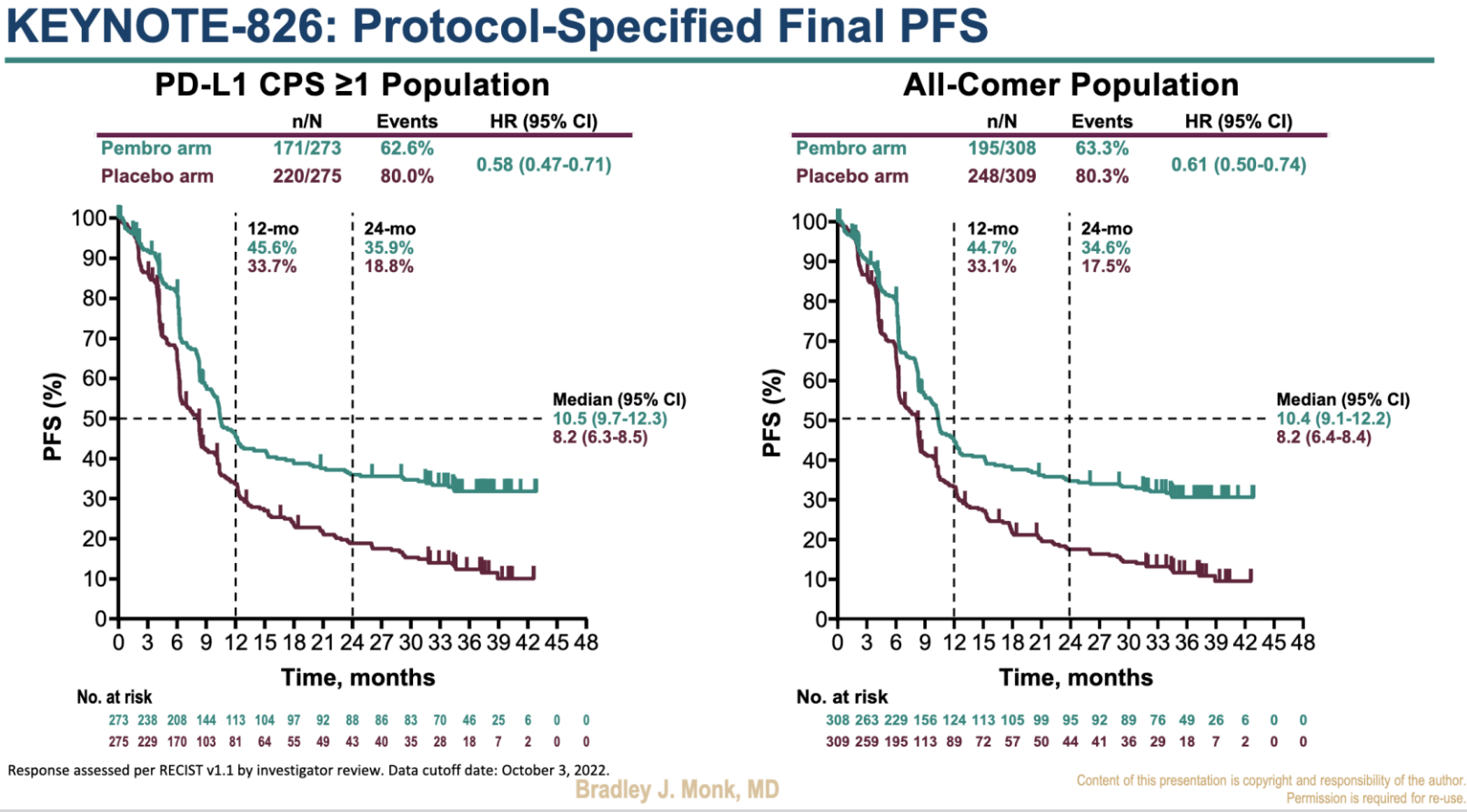
[1] Marth et al. Ann Oncol 2017, [2] Tewari et al. NEJM 2014, [3] Chung et al. JCO 2019.

2021 ESMO congress

Session plénière

Essai de phase III KEYNOTE-826

- 617 patientes
- 75 % C. épidermoïdes
- 30% stades IVB
- 20 % métastatiques d'emblée
- 89 % PDL1 + dont 50% ≥ 10
- 63% ont reçu le bévacizumab durant l'étude



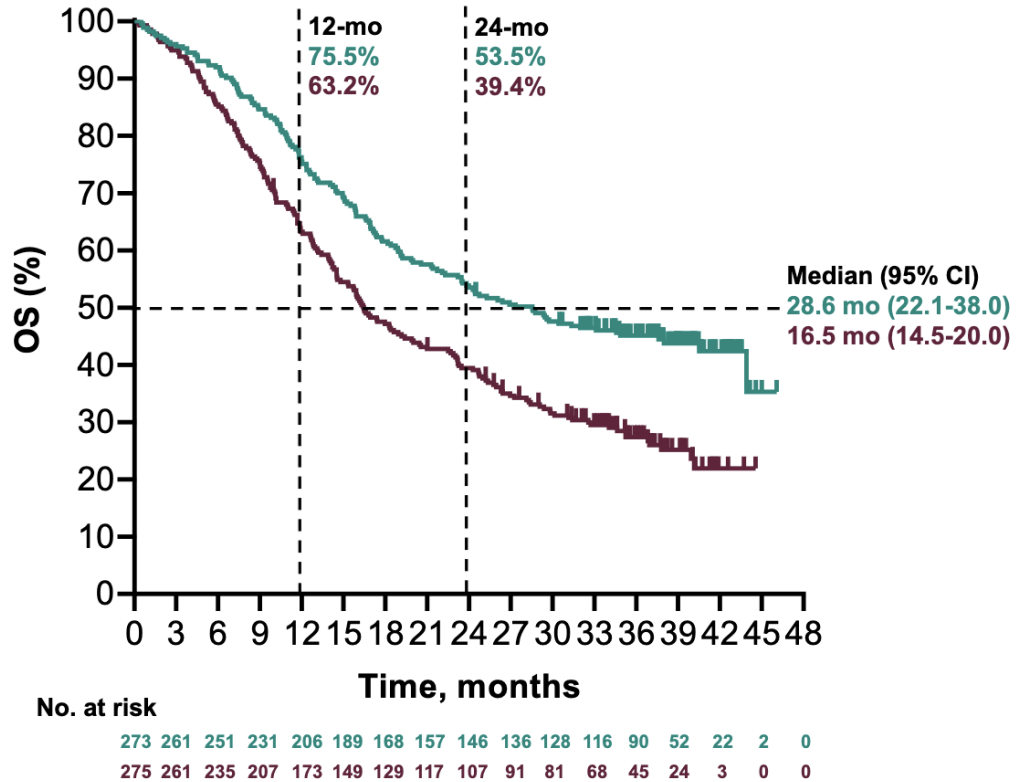
Suivi médian 22 mois

→ Avantage significatif en PFS au bras Pembrolizumab, quel que soit le score PD-1/CPS, sans différence selon les sous-groupes

KEYNOTE-826: Protocol-Specified Final OS

PD-L1 CPS ≥1 Population

	n/N	Events	HR (95% CI)
Pembro arm	153/273	56.0%	0.60 (0.49-0.74)
Placebo arm	201/275	73.1%	

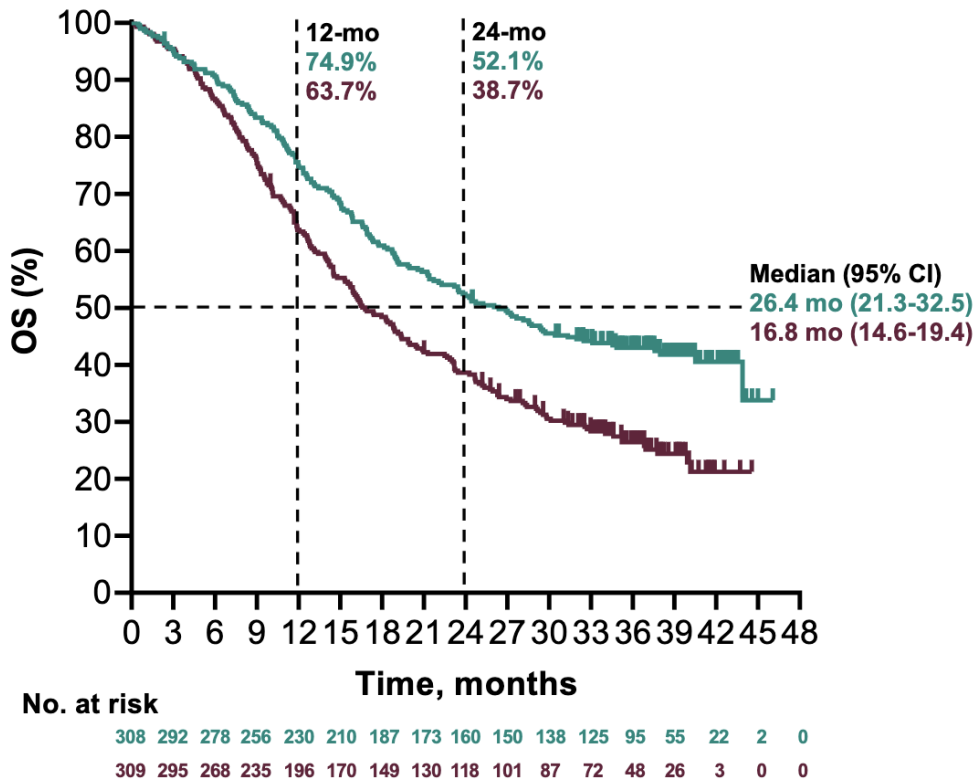


No. at risk

273	261	251	231	206	189	168	157	146	136	128	116	90	52	22	2	0
275	261	235	207	173	149	129	117	107	91	81	68	45	24	3	0	0

All-Comer Population

	n/N	Events	HR (95% CI)
Pembro arm	178/308	57.8%	0.63 (0.52-0.77)
Placebo arm	228/309	73.8%	



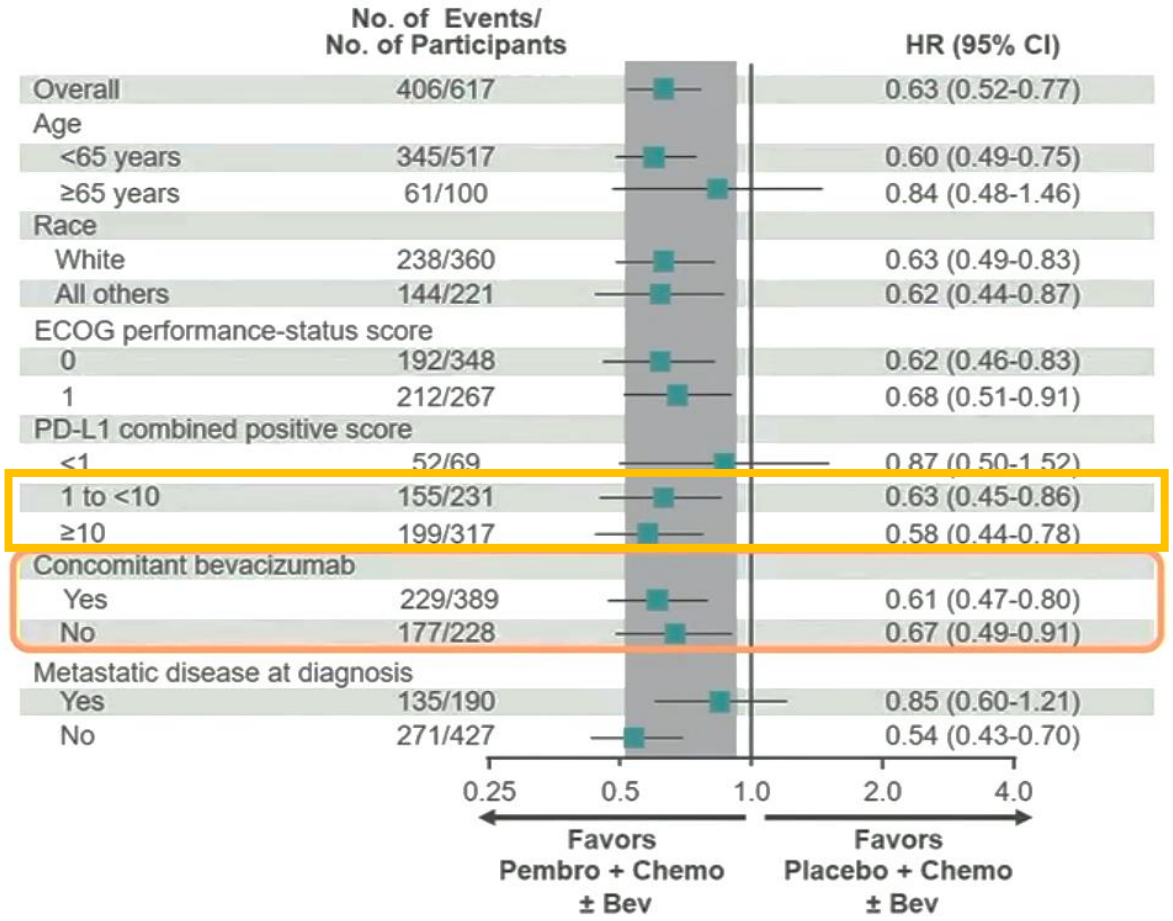
No. at risk

308	292	278	256	230	210	187	173	160	150	138	125	95	55	22	2	0
309	295	268	235	196	170	149	130	118	101	87	72	48	26	3	0	0

Data cutoff date: October 3, 2022.

Bradley J. Monk, MD

Protocol-Specified Final OS in Subgroups, All-Comer Population



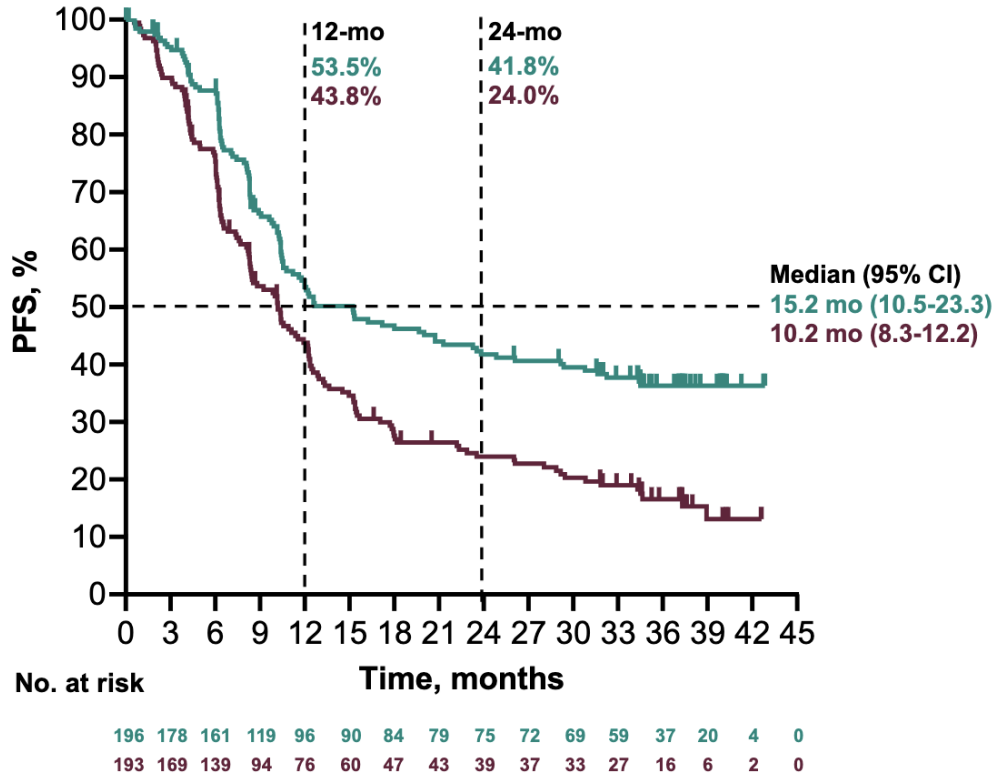
Petit avantage si ajout du BEVA ?

Data cutoff date: October 3, 2022.

KEYNOTE-826: PFS by Bevacizumab Use, All-Comer Population

With Bevacizumab (N=389)

	n/N	Events	HR (95% CI)
Pembro arm	115/196	58.7%	0.57 (0.45-0.73)
Placebo arm	149/193	77.2%	

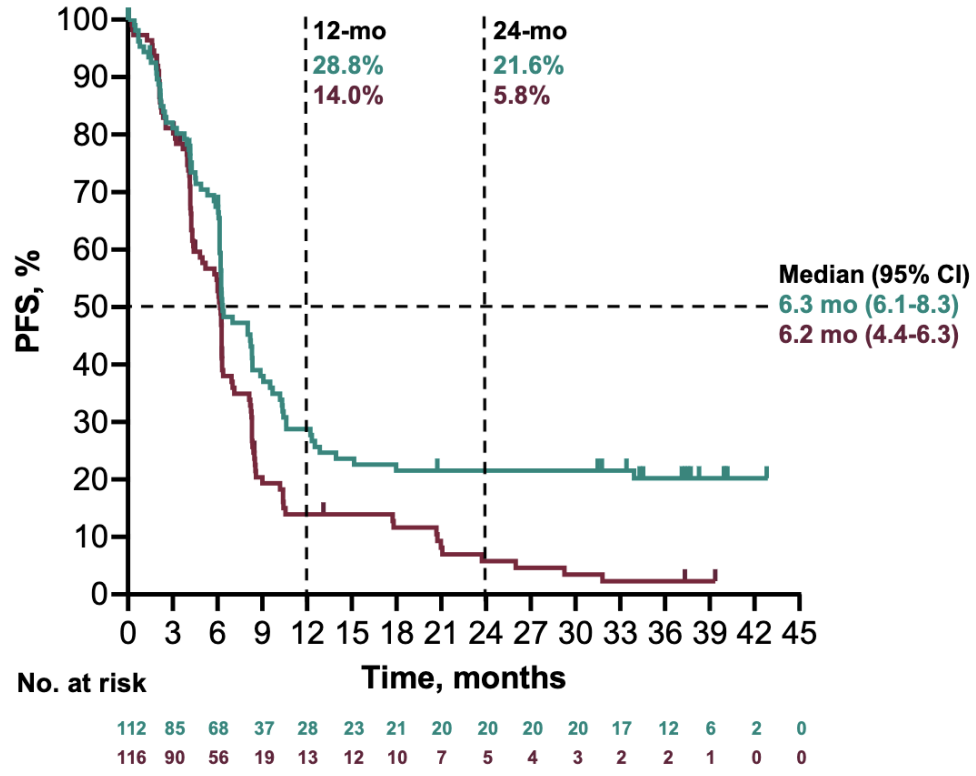


No. at risk

196	178	161	119	96	90	84	79	75	72	69	59	37	20	4	0
193	169	139	94	76	60	47	43	39	37	33	27	16	6	2	0

Without Bevacizumab (N=228)

	n/N	Events	HR (95% CI)
Pembro arm	80/112	71.4%	0.69 (0.50-0.94)
Placebo arm	99/116	85.3%	



No. at risk

112	85	68	37	28	23	21	20	20	20	20	17	12	6	2	0
116	90	56	19	13	12	10	7	5	4	3	2	2	1	0	0

Response assessed per RECIST v1.1 by investigator review. Data cutoff date: October 3, 2022.

- Toxicités : augmentation des AE ≥ grade 3 bras pembrolizumab (81,8% vs 75,1%), AE immuno-médiés de grade 1-2 essentiellement
- Augmentation du temps jusqu'à la détérioration de la qualité de vie dans le bras Pembrolizumab (médiane non atteinte vs 7,7 mois, HR 0,75)

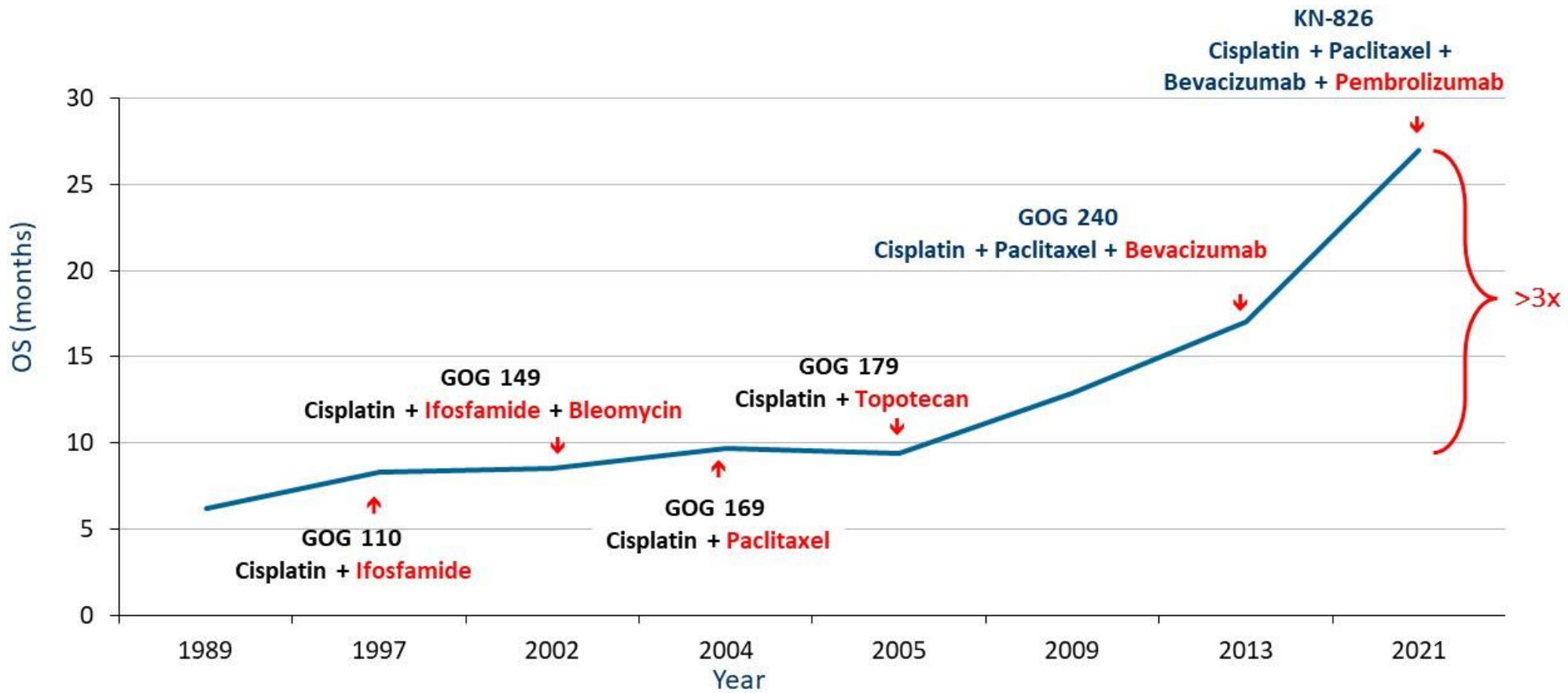
→ Augmentation significative de PFS et OS avec l'ajout du pembrolizumab

- **Quel que soit le soit le score PDL-1/CPS**
- **Indépendamment de l'utilisation du bévacizumab**

→ Profil de toxicité acceptable et attendu

→ Nouveau standard de traitement en 1ère ligne

Improving OS in Recurrent or Metastatic Cervical Cancer



BEATcc (ENGOT-Cx10/GEICO 68-C/JGOG1084/GOG-3030

BEATcc trial design (NCT03556839)

Open-label, multicentre, randomised, phase 3 trial in an all-comer population

- Metastatic, persistent or recurrent cervical cancer not amenable to curative therapy
- GOG/ECOG PS ≤1
- No prior systemic anti-cancer therapy for R/M CC
- In patients with pelvic disease, no bladder or rectal mucosa involvement
- Available archival or fresh tumour sample for PD-L1 expression

R 1:1

N=410

Atezolizumab 1200 mg + bevacizumab 15 mg/kg + paclitaxel + cis/carboplatin[a] all IV q3w

- Continued until disease progression/unacceptable toxicity
- Patients with CR after ≥6 cycles could stop chemotherapy and continue biological therapy alone
- Crossover from standard arm at progression not permitted

Bevacizumab 15 mg/kg + paclitaxel + cis/carboplatin[a] all IV q3w

Dual primary endpoints

- Investigator-assessed PFS (RECIST 1.1)
- OS

Key secondary endpoints

- ORR (RECIST v1.1)
- DoR (RECIST v1.1)
- TFST
- PFS2
- Safety

Stratification factors:

- Prior concurrent chemoradiation (yes vs no)
- Histology (squamous cell carcinoma vs adenocarcinoma[b] including adenosquamous carcinoma)
- Chemotherapy backbone (cisplatin vs carboplatin)

[a]Paclitaxel 175 mg/m^2 day 1 + platinum (cisplatin 50 mg/m^2 or carboplatin AUC5) day 1; [b]Capped at 20% of the overall population
CR = complete response; DoR = duration of response; ECOG = Eastern Cooperative Oncology Group; ORR = objective response rate; PFS2 = time from randomisation to second progression or death; PS = performance status; q3w = every 3 weeks; TFST = time from randomisation to first subsequent therapy or death

Baseline characteristics

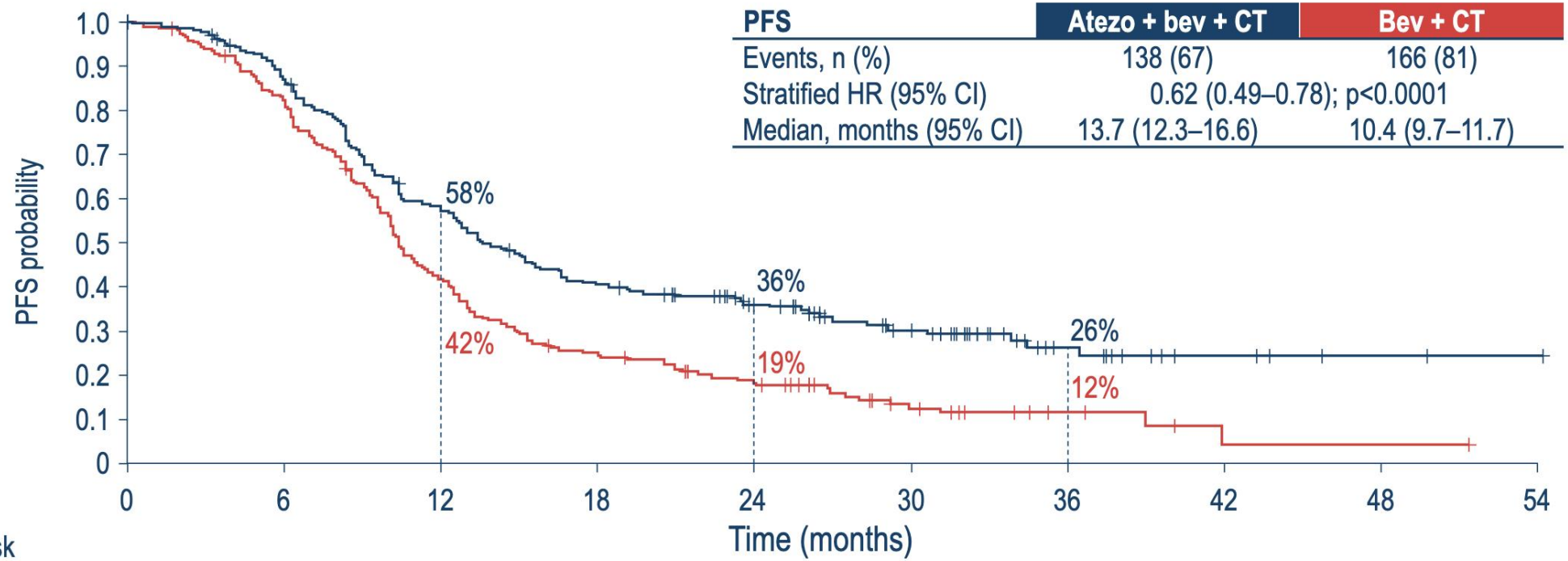
Characteristic, n (%)		Atezo + bev + CT (n=206)	Bev + CT (n=204)
Median (range) age, years		51.0 (24–90)	52.5 (21–79)
Age, n (%)	<65 years	171 (83)	168 (82)
GOG/ECOG PS, n (%)[a]	0	138 (67)	128 (63)
	1	68 (33)	73 (36)
Race, n (%)	White	111 (54)	113 (55)
	Other[b]	45 (22)	42 (21)
	Not available[c]	50 (24)	49 (24)
Histology, n (%)	Squamous cell carcinoma	164 (80)	157 (77)
	Adenocarcinoma/adenosquamous carcinoma	42 (20)	47 (23)
Disease status at screening, n (%)	Metastatic (stage IVB)	43 (21)	47 (23)
	Recurrent	150 (73)	151 (74)
	Persistent	13 (6)	6 (3)
Disease location at screening, n (%)	Pelvic and distant	102 (50)	90 (44)
	Distant only	71 (34)	74 (36)
	Pelvic only	33 (16)	40 (20)
Primary therapy	Concurrent chemoradiotherapy	70 (34)	85 (42)
	Surgery followed by chemoradiotherapy	64 (31)	44 (22)
	Surgery and/or radiotherapy	16 (8)	28 (14)
	None	56 (27)	47 (23)

[a]Missing in three patients. [b]Asian (n=58), Latin (n=18), Arab (n=5), Black (n=5), Gypsy (n=1). [c]Per local legislation

Dual primary endpoint: PFS

Statistically significant 38% reduction in risk of progression or death

PFS	Atezo + bev + CT	Bev + CT
Events, n (%)	138 (67)	166 (81)
Stratified HR (95% CI)	0.62 (0.49–0.78); p<0.0001	
Median, months (95% CI)	13.7 (12.3–16.6)	10.4 (9.7–11.7)

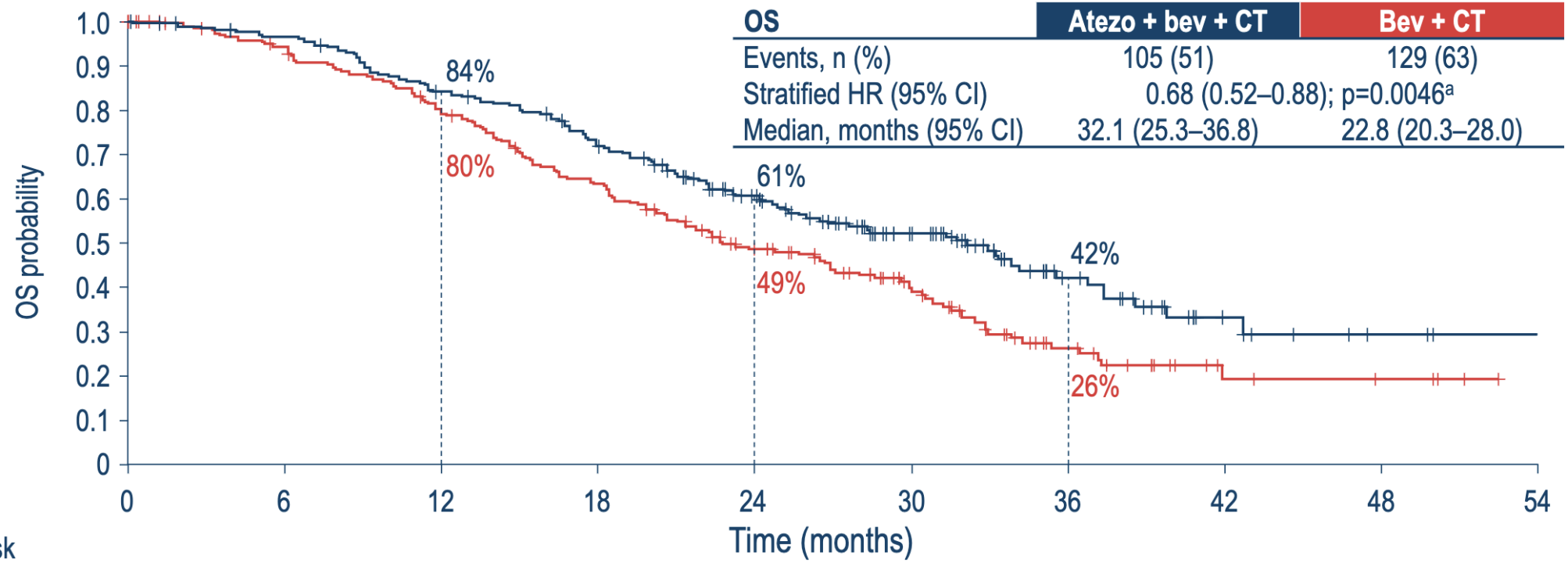


No. at risk										
Atezo + bev + CT	206	174	114	79	58	37	13	5	2	1
Bev + CT	204	159	80	47	31	13	5	1	1	0

Data cut-off: 17 Jul 2023 (median follow-up: 32.9 months; 95% CI, 31.2–34.6 months)

Dual primary endpoint: OS (interim analysis)

Statistically significant 32% reduction in risk of death

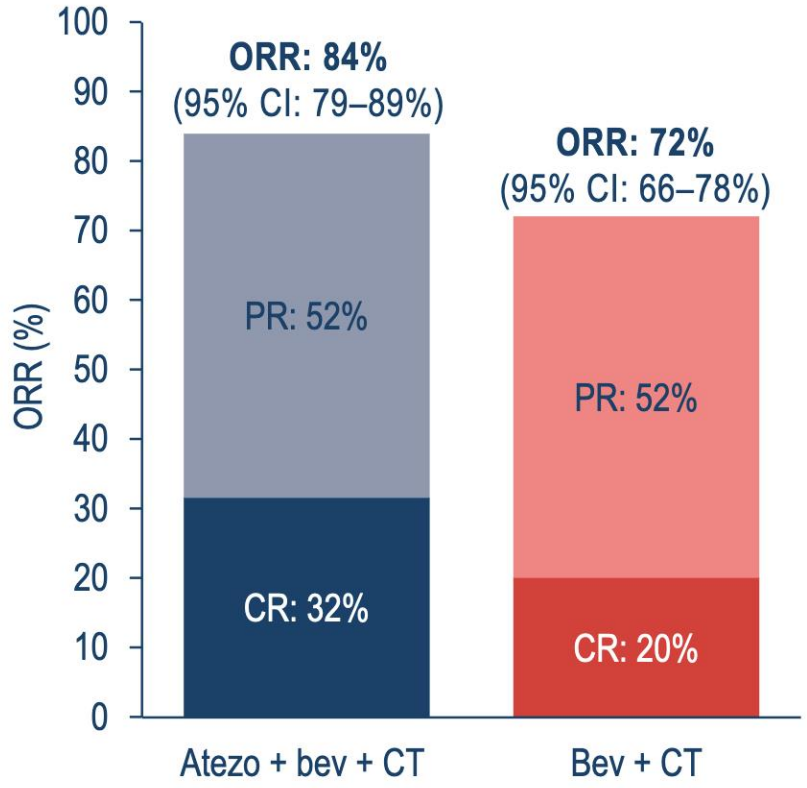


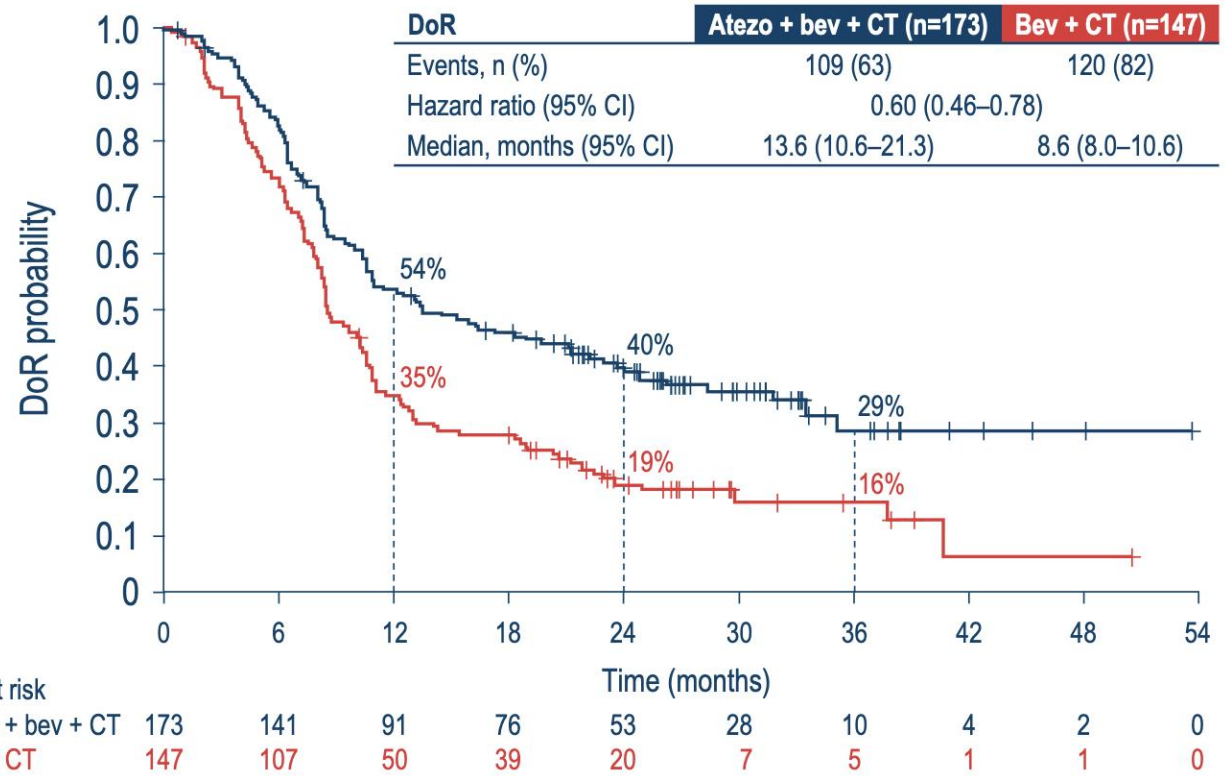
OS	Atezo + bev + CT	Bev + CT
Events, n (%)	105 (51)	129 (63)
Stratified HR (95% CI)	0.68 (0.52–0.88); p=0.0046[a]	
Median, months (95% CI)	32.1 (25.3–36.8)	22.8 (20.3–28.0)

No. at risk										
Atezo + bev + CT	206	194	167	140	103	64	27	9	3	1
Bev + CT	204	182	152	119	83	50	22	6	4	0

Data cut-off: 17 Jul 2023 (median follow-up: 32.9 months; 95% CI, 31.2–34.6 months). [a]Interim OS was statistically significant, crossing the boundary of p=0.0238

Secondary endpoints: ORR and DoR





DoR	Atezo + bev + CT (n=173)	Bev + CT (n=147)
Events, n (%)	109 (63)	120 (82)
Hazard ratio (95% CI)	0.60 (0.46–0.78)	
Median, months (95% CI)	13.6 (10.6–21.3)	8.6 (8.0–10.6)

No. at risk										
Atezo + bev + CT	173	141	91	76	53	28	10	4	2	0
Bev + CT	147	107	50	39	20	7	5	1	1	0

Data cut-off: 17 Jul 2023 (median follow-up: 32.9 months; 95% CI, 31.2–34.6 months)
PR = partial response

Différence entre KEYNOTE 826 et BEAT CC

KEYNOTE 826

BEAT CC

Population similaire entre les 2 études

Bras avec un placebo

Données sur le PDL1

BEVACIZUMAB obligatoire

→ Confirme intérêt du BEVA et les résultats de KEYNOTE 826

Hazard Ratios		
- Survival (median months and HR; 95%CI)	37.6 vs. 22.5; 0.61 (0.47-0.80)	32.1 vs. 22.8; 0.68 (0.52–0.88)
- Progression or Death (median months and HR; 95%CI)	15.2 vs.10.2; 0.57 (0.45-0.73)	13.7 vs 10.4; 0.62 (0.49–0.78)

Chimiothérapie 2ème ligne

Essai de phase III EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9

Tewari et al. VP-4.

Rationnel

- Traitement standard des cancers du col en rechute/métastatiques: chimiothérapie avec platine +/- bevacizumab.[1,2]
- Pas de bénéfice en survie d'une 2ème ligne de chimiothérapie → rationnel clinique et biologique pour développer l'immunothérapie.[3,4,5.]

- Cancers du col en rechute/métastatique résistant au platine, ≥ 2 lignes
- ECOG 0-1

Stratification:
- Type histologique
- Géographie
- ECOG 0 *vs* 1.
- Bevacizumab: oui/non

1

Cemiplimab (anti-PD-1) 350mg/sem

1

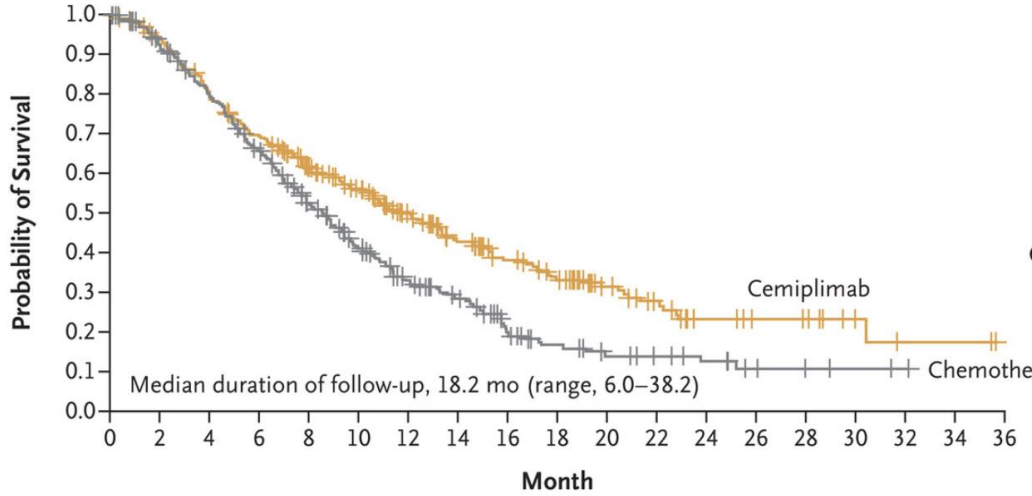
Chimiothérapie au choix de l'investigateur:
- Pemetrexed 500mg/m²/3sem
- Gemcitabine 1000mg/m², J1,J8 (J1=J21)
- Topotecan 1mg/m² 5j (J1=J21)
- Irinotecan 100mg/m²/sem x 4
- Vinorelbine 30mg/m², J1,J8 (J1=J21)

- **Critère primaire: OS**
- **Critères secondaires:** PFS 12 mois, toxicité, taux de réponse, durée de réponse, PRO
- **Critères exploratoires:** PK,PD,immunogénicité

2021 ESMO congress

[1] *Kitagawa et al. JCO 2015,* [2] *Tewari et al. NEJM 2014,* [3] *Chung et al. JCO 2019,* [4] *Heeren et al. Mod Pathol 2016,* [5] *Rischin et al. Gynecol Oncol 2020.*

A Overall Survival, All Patients

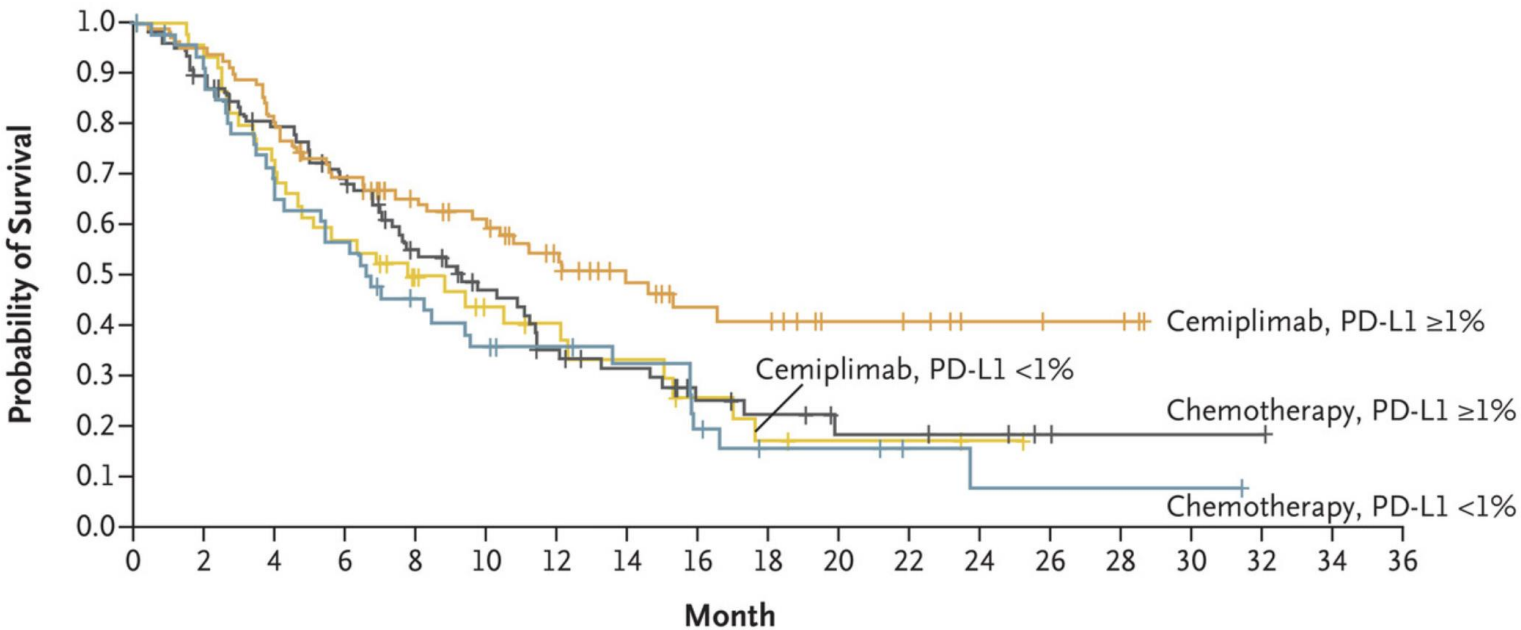


	No. of Patients	Median Overall Survival (95% CI)
		mo
Cemiplimab	304	12.0 (10.3–13.5)
Chemotherapy	304	8.5 (7.5–9.6)

Hazard ratio for death, 0.69 (95% CI, 0.56–0.84)
Two-sided P<0.001

No. at Risk

Cemiplimab	304	281	236	206	167	139	110	83	65	52	35	26	13	10	9	4	2	2	0
Chemotherapy	304	264	224	183	132	99	70	54	32	22	15	12	9	5	3	2	1	0	0



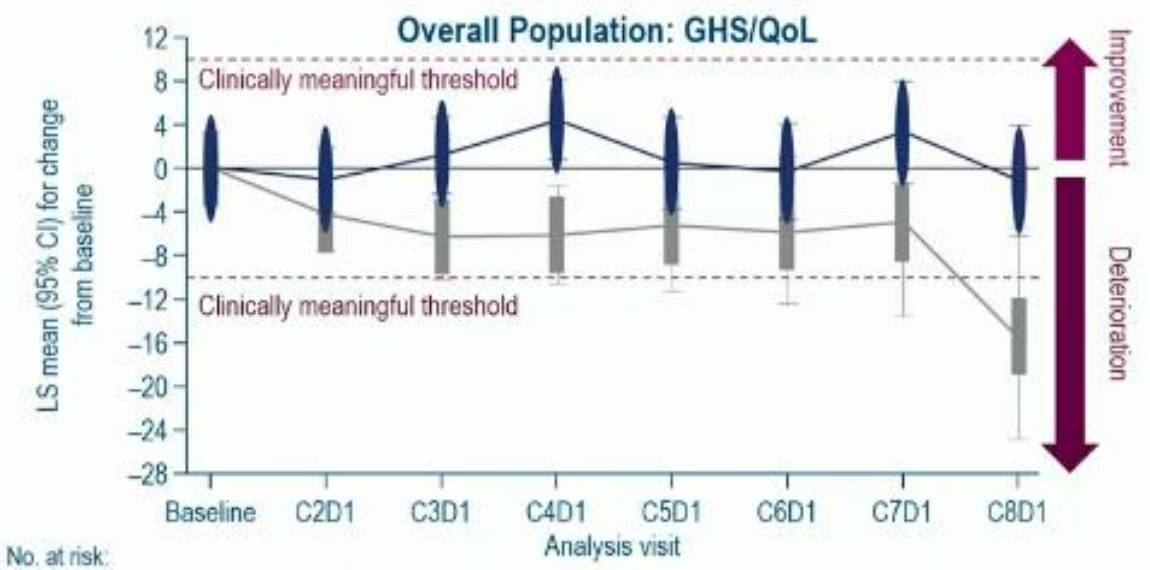
- 608 patientes
- 477 C. épidermoides, 131 adénocarcinomes

→ **Avantage en OS quel que soit le sous-type histologique**

→ **Avantage en OS si PDL-1 < 1%, mais bénéfice plus important si PDL-1 > 1%**

→ **Pas de nouveaux signaux de toxicité**

→ **Meilleure qualité de vie dans le bras immunothérapie**



Cemiplimab
Chimiothérapie

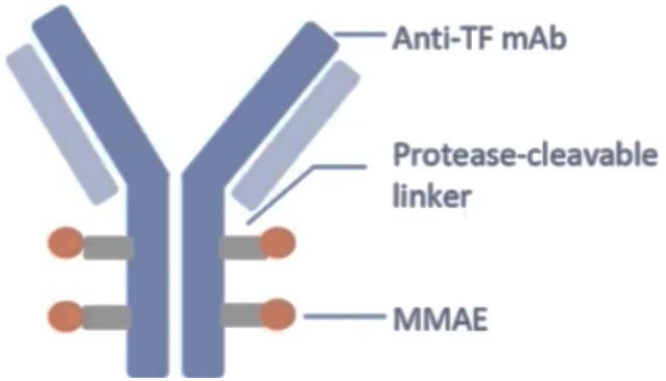
Table 2. **Adverse Events Regardless of Attribution.***

Adverse Event	Cemiplimab (N=300)		Chemotherapy (N=290)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Occurred in ≥10% in either group†				
Anemia	75 (25.0)	36 (12.0)	129 (44.5)	78 (26.9)
Nausea	55 (18.3)	1 (0.3)	97 (33.4)	6 (2.1)
Fatigue	50 (16.7)	4 (1.3)	45 (15.5)	4 (1.4)
Vomiting	48 (16.0)	2 (0.7)	68 (23.4)	7 (2.4)
Decreased appetite	45 (15.0)	1 (0.3)	46 (15.9)	2 (0.7)
Constipation	45 (15.0)	0	59 (20.3)	1 (0.3)
Pyrexia	35 (11.7)	1 (0.3)	61 (21.0)	0
Urinary tract infection	35 (11.7)	15 (5.0)	25 (8.6)	8 (2.8)
Asthenia	33 (11.0)	7 (2.3)	44 (15.2)	3 (1.0)
Back pain	33 (11.0)	4 (1.3)	25 (8.6)	2 (0.7)
Diarrhea	32 (10.7)	3 (1.0)	39 (13.4)	4 (1.4)
Arthralgia	31 (10.3)	1 (0.3)	8 (2.8)	0
Abdominal pain	29 (9.7)	3 (1.0)	33 (11.4)	3 (1.0)
Neutropenia	6 (2.0)	3 (1.0)	44 (15.2)	26 (9.0)

Étude internationale de phase 3, randomisée, ouverte, comparant le tisotumab védotin à la chimiothérapie choisie par l'investigateur dans les cas de cancer du col de l'utérus récurrent ou métastatique de type 2L ou 3L

InnovaTV 301/ENGOT-cx12/GOG-3057

- **Tisotumab vedotin is an ADC directed at TF[1]**



InnovaTV 204/GOG 3023/ENGOT cx6 Study Design

innovaTV 204 (NCT03438396) is a pivotal phase 2 single-arm, multicenter (United States and Europe) study evaluating tisotumab vedotin in patients with previously treated recurrent and/or metastatic cervical cancer

Key Eligibility Criteria
- Recurrent or extrapelvic metastatic cervical cancer
- Progressed during or after doublet chemotherapy with bevacizumab (if eligible)
- Received ≤2 prior systemic regimens
- ECOG PS 0-1

Enrolled: 102
Treated: 101

Tisotumab vedotin
2.0 mg/kg IV Q3W

Until PD or unacceptable toxicity

Tumor responses assessed using CT or MRI at baseline, every 6 weeks for the first 30 weeks, and every 12 weeks thereafter

*Study sample size calculated assuming a confirmed ORR of 21% to 25% with tisotumab vedotin and to provide ≥80% power to exclude an ORR of ≤11%

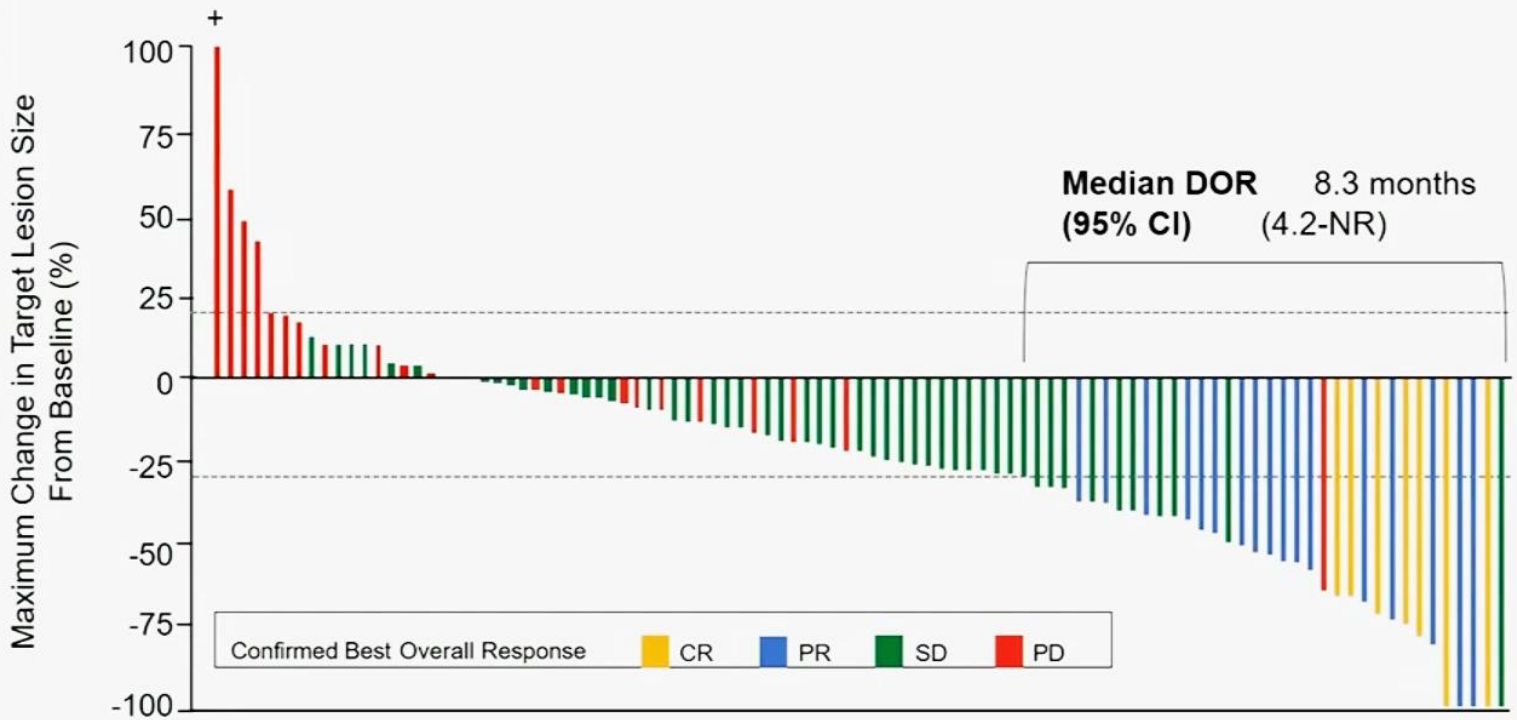
Primary Endpoint
- ORR per RECIST v1.1, by independent imaging review committee (IRC)

Secondary Endpoints
- ORR per RECIST v1.1, by investigator
- DOR, TTR, and PFS by IRC and investigator
- OS
- Safety

Exploratory Endpoints
- Biomarkers
- HRQoL

CT, computed tomography; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR QoL, health-related quality of life; MRI, magnetic resonance imaging; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours, TTR; time to relapse; Q3W, every 3 weeks

Coleman RL et al. ESMO 2020. Abstract LBA32.



	N=101
Confirmed ORR (95% CI), %	**24 (15.9–33.3)**
CR, n (%)	7 (7)
PR, n (%)	17 (17)
SD, n (%)	49 (49)
PD, n (%)	24 (24)
Not evaluable, n (%)	4 (4)

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months. + indicates a change greater than 100%. Horizontal dashed lines indicate 20% increase and 30% decrease in target lesion diameters from baseline for RECIST v1.1 assessment. Colored bars represent the best overall confirmed response. CR, PR, SD, and PD were based on RECIST v1.1 as evaluated by IRC.
CR, complete response; IRC, independent review committee; PD, disease progression; PR, partial response; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1; SD, stable disease.

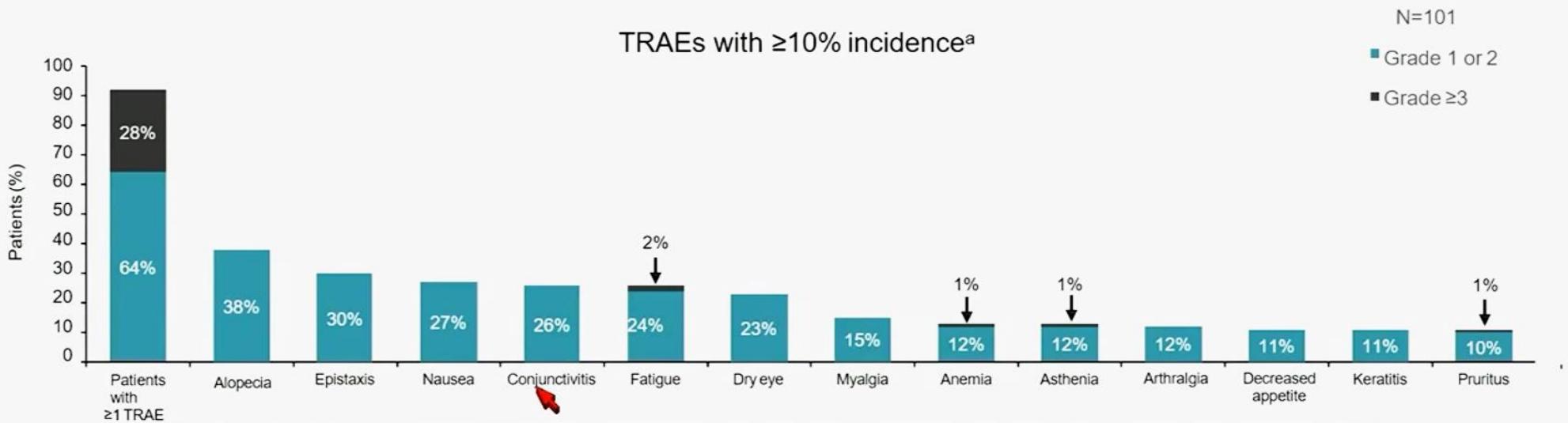
9

2023 ASCO ANNUAL MEETING #ASCO23 PRESENTED BY:

Coleman RL et al. ESMO 2020. Abstract LBA32.
Coleman RL. *Lancet Oncol.* 2021:S1470-2045(21)00056-5.

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Phase 2: Innova TV/GOG 3023/ENGOT cx6: Most Common TRAEs with Tisotumab Vedotin

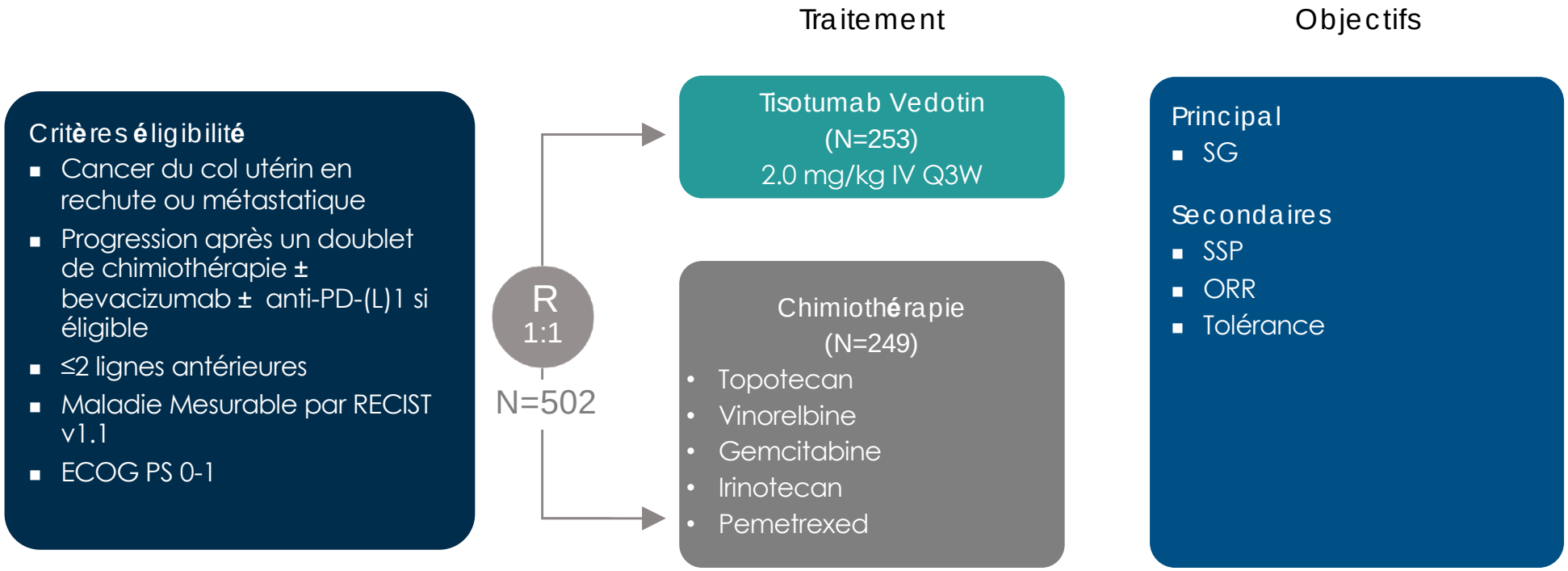


- Most TRAEs were grade 1 or 2 and no new safety signals were reported
- One death due to septic shock was considered by the investigator to be related to therapy[b]

Data cutoff: February 06, 2020. Median duration of follow-up: 10.0 months. Median duration of treatment: 4.2 months (range, 1–16).
[a]Any-grade AEs included if ≥10%. [b]Three treatment-emergent deaths unrelated to therapy included one case of ileus and two with unknown causes. TRAE, treatment-related adverse event.

Coleman RL et al. ESMO 2020. Abstract LBA32.
Coleman RL. *Lancet Oncol.* 2021:S1470-2045(21)00056-5.

PHASE III



Stratification:

- ECOG PS (0 vs 1)
- Bevacizumab (oui vs non)
- anti-PD-(L)1t antérieur(oui vs non)
- Région Géographiques (US, Europe, Autresr)

Ignace B. Vergote et al., ESMO® 2023, Abs #LBA9

Caractéristiques des patientes

	Tisotumab Vedotin (N=253)	IC Chimiothérapie (N=249)
Age, médian (range)	51 (26-80)	50 (27-78)
Baseline ECOG PS, n (%)		
0	137 (54.2)	136 (54.6)
1	116 (45.8)	113 (45.4)
Région, n (%)		
USA	16 (6.3)	14 (5.6)
Europe	106 (41.9)	104 (41.8)
Asie	85 (33.6)	88 (35.3)
Autre	46 (18.2)	43 (17.3)
Histologie, n (%)		
Epidermoide	160 (63.2)	157 (63.1)
Adenocarcinome	85 (33.6)	75 (30.1)
Adénosquameux	8 (3.2)	17 (6.8)
Type de rechute, n (%)		
Rechute pelvienne	27 (10.7)	24 (9.6)
Extra pelvienne	226 (89.3)	225 (90.4)

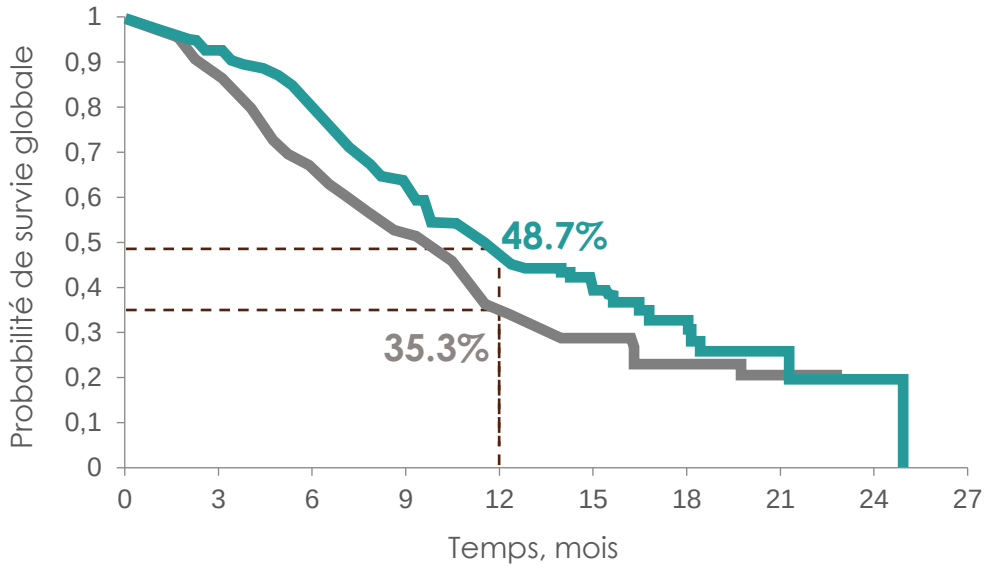
	Tisotumab Vedotin (N=253)	IC Chimiothérapie (N=249)
Nombre de lignes antérieures, n (%)		
1	159 (62.8)	149 (59.8)
2	93 (36.8)	100 (40.2)
Unknown	1 (0.4)	0
Bevacizumab, n (%)	164 (64.8)	157 (63.1)
anti-PD(L)1, n (%)	71 (28.1)	67 (26.9)
Atcd de radiothérapie, n (%)	205 (81.0)	203 (81.5)
Biopsie évaluable, n (%)	210 (83.0)	194 (77.9)
Positive membrane TF expression	194 (92.4)	183 (94.3)

SG (objectif principal) et SSP

SG (objectif principal

Traitement	Events/Total	Médiane (95% CI)
Tisotumab Vedotin	123/253	11.5 (9.8-14.9)
Chimiothérapie	140/249	9.5 (7.9-10.7)

Stratified log-rank P value: 0.0038
HR (95% CI): 0.70 (0.54-0.89)



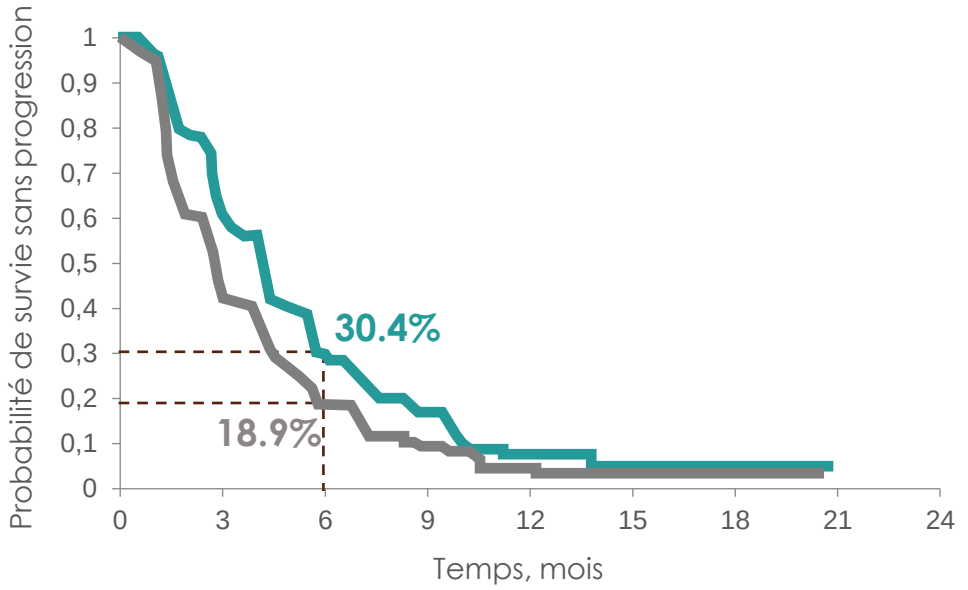
Patients à risque

Tisotumab vedotin	253	234	191	109	52	29	14	4	1	0
IC Chimiothérapie	249	212	150	87	37	19	11	1	0	0

SSP

Traitement	Events/Total	Médiane (95% CI)
Tisotumab Vedotin	198/253	4.2 (4.0-4.4)
Chimiothérapie	194/249	2.9 (2.6-3.1)

Stratified log-rank P value: <0.0001
HR (95% CI): 0.67 (0.54-0.82)

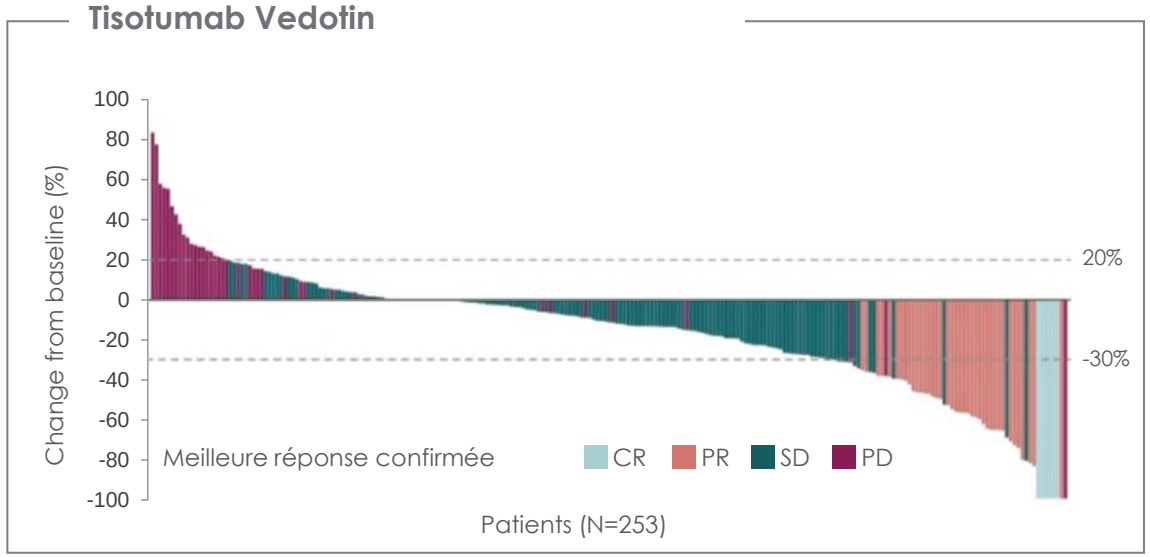


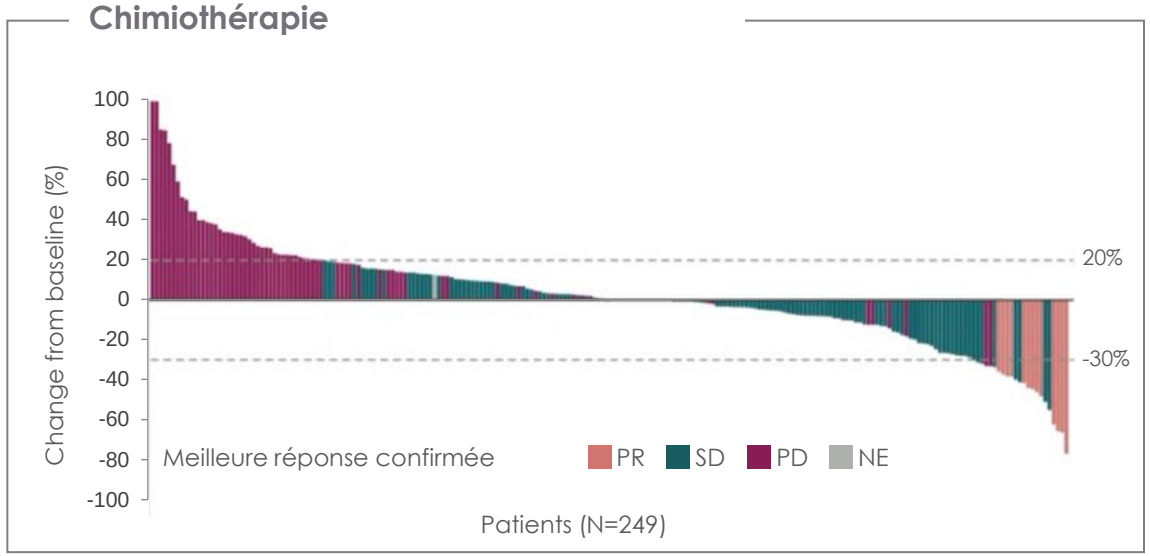
Patients à risque

Tisotumab vedotin	253	148	62	25	5	2	1	0	0
IC Chimiothérapie	249	96	34	11	4	1	1	0	0

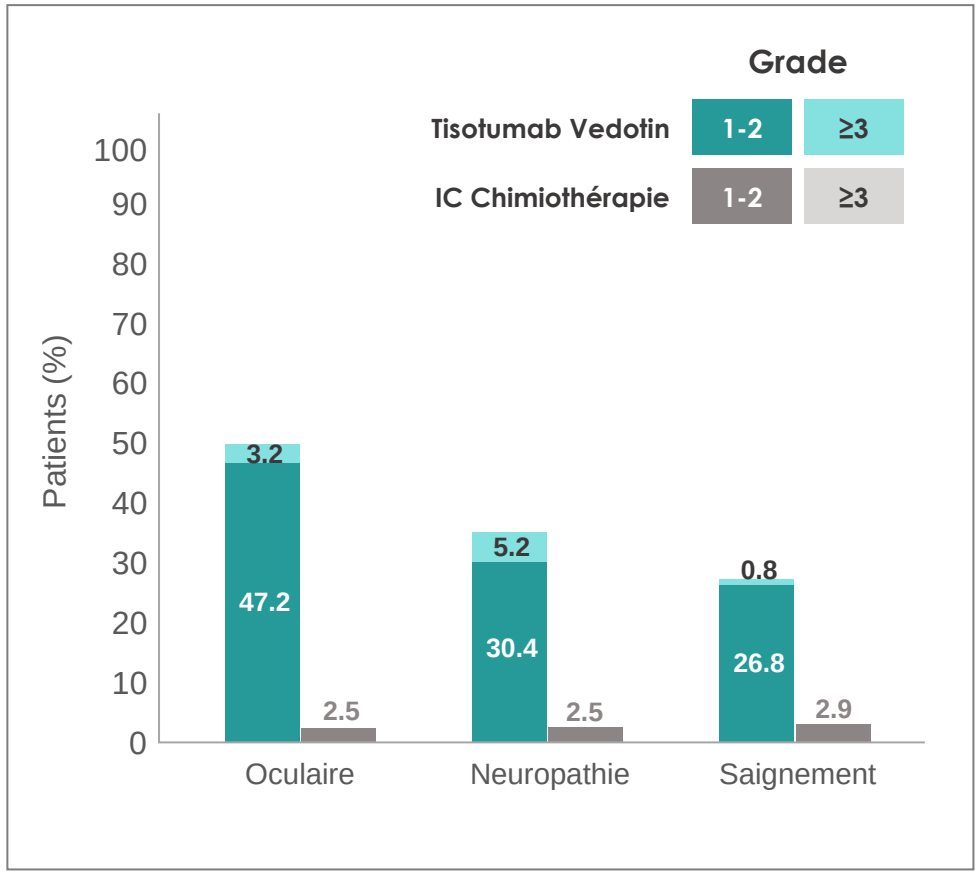
Taux de réponse

	Tisotumab Vedotin (N=253)	IC Chimiothérapie (N=249)
ORR, % (95% CI)	17.8 (13.3-23.1)	5.2 (2.8-8.8)
Odds ratio (95% CI)	4.0 (2.1-7.6)	
P value	P<0.0001	
Meilleure réponse, n (%)		
CR	6 (2.4)	0
PR	39 (15.4)	13 (5.2)
SD	147 (58.1)	132 (53.0)
PD	46 (18.2)	74 (29.7)
Non évaluable/non disponible	15 (5.9)	30 (12.0)
Taux de contrôle de la maladie, % (IC 95 %)	75.9 (70.1-81.0)	58.2 (51.8-64.4)
Durée médiane de réponse(95% CI)	5.3 (4.2-8.3)	5.7 (2.8-NR)





Tolérance



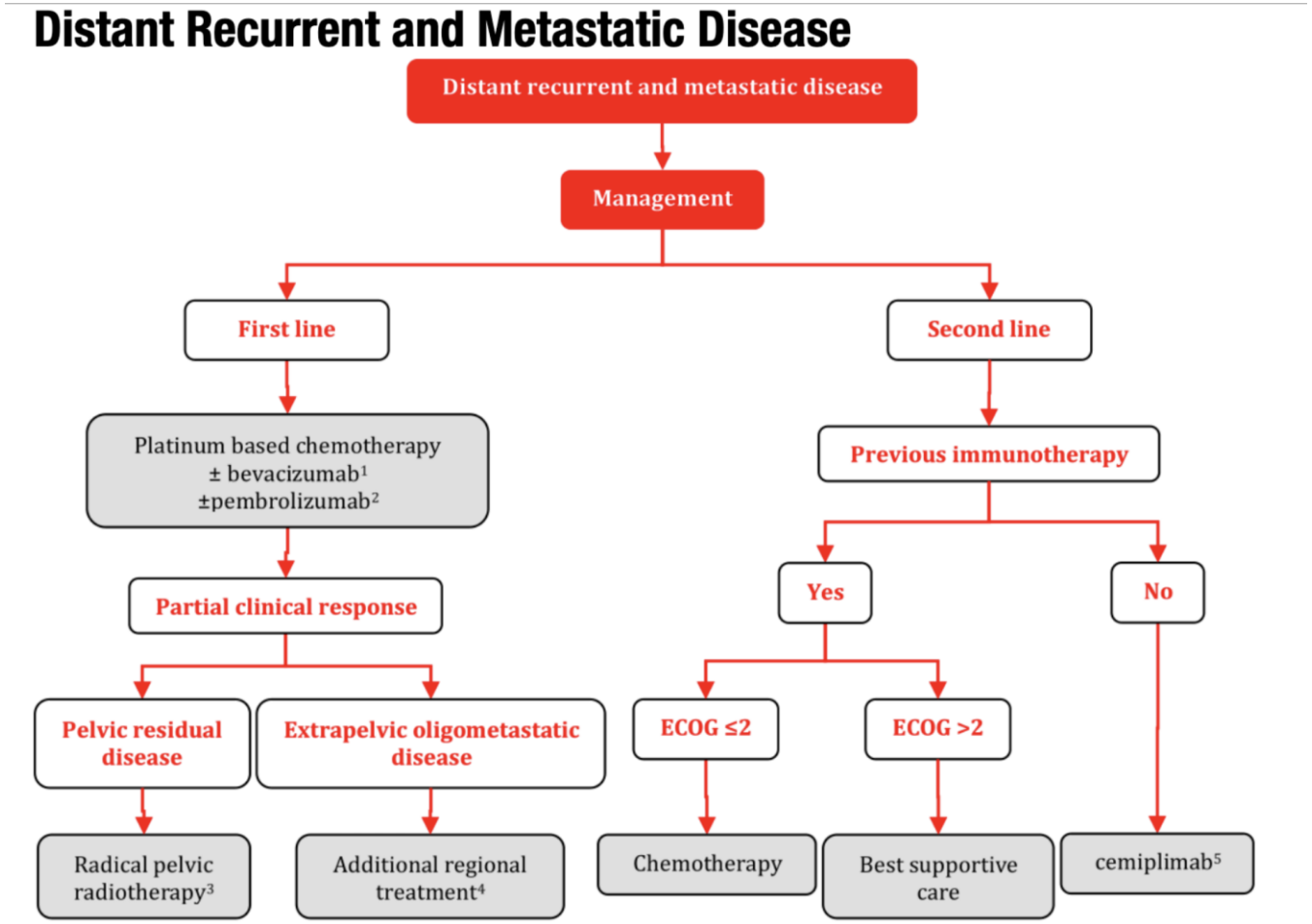
- **Pas de grade 4 or 5 AESIs**
- **5.6% d'arrêt pour toxicité oculaire ou neuropathie péripherique**

AE les plus fréquents	
Oculaire	Conjonctivite (30.4%), keratite (15.6%), Sécheresse oculaire(13.2%)
Neuropathie périphérique	Neuropathie périphérique sensitive(26.8%), paresthésies (2.8%), faiblesse musculaire(2.4%), neuropathie périphérique sensitivo motrice(2.4%)
Saignement	Epistaxis (22.8%), hématurie (3.2%), hémorragie vaginale(3.2%)

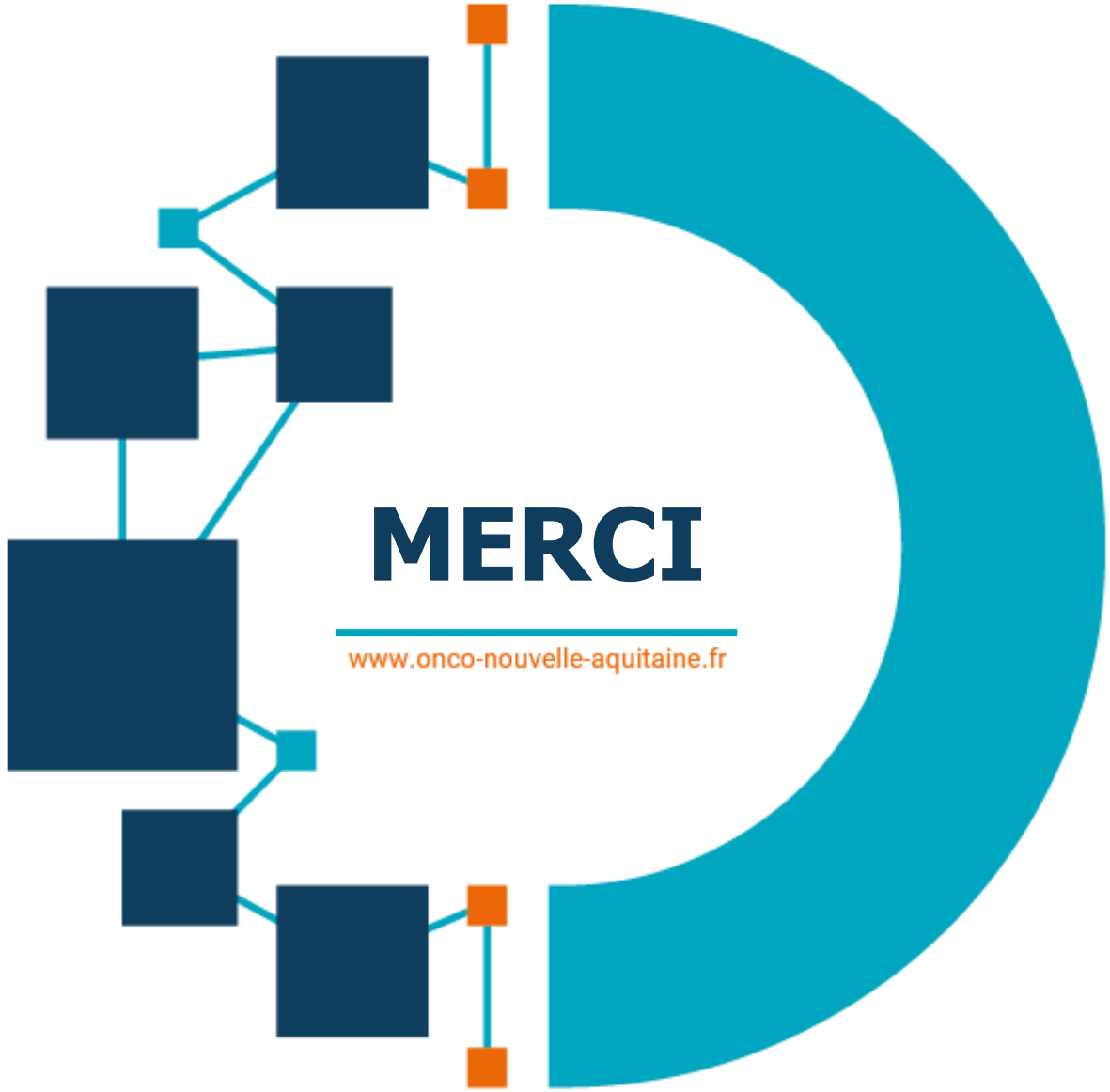
Recommandations

	ESMO	NCCN
1ère ligne	Carboplatine ou cisplatine + palitaxel +/- bevacizumab +/- Pembrolizumab si CPS > 1	- Carboplatine ou cisplatine + palitaxel +/- bevacizumab +/- Pembrolizumab si CPS > 1
2ème ligne	Cemiplimab (non disponible en France) - pas d'IO avant	Cemiplimab (non disponible en France) tisotumab védotin (non disponible en France) Pembrolizumab si CPS > 1 ou MSI (*Keynote 158*)

Recommandations



Cibula d, et al. Int J Gynecol Cancer 2023;33:649–666. doi:10.1136/ijgc-2023-00442


MERCI
www.onco-nouvelle-aquitaine.fr