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unicancer NICE

GYNAZUR
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Prise en charge oncologique du Cancer du col utérin

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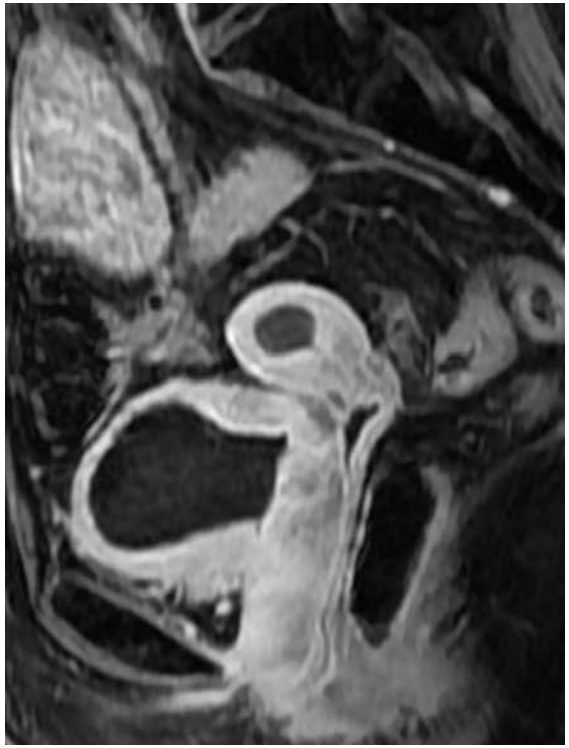
CENTRE DE LUTTE CONTRE LE CANCER DE NICE

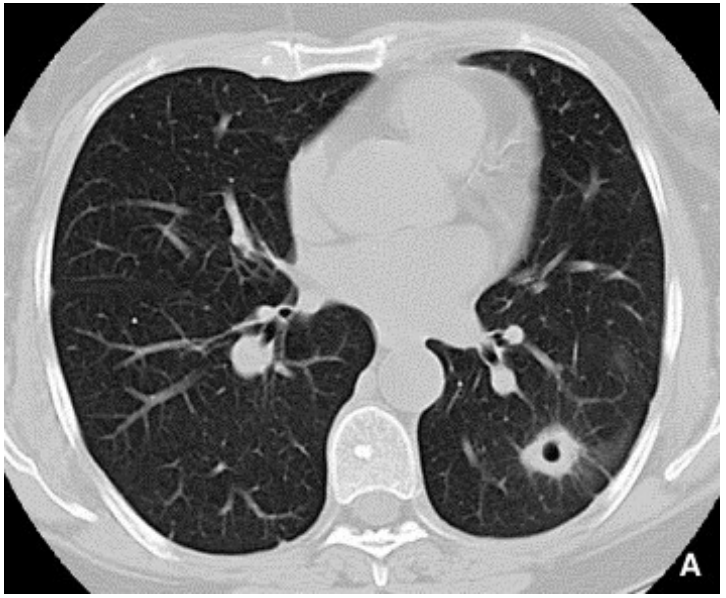
Liens d'intérêt

- **congrès**: Novartis, GSK, Daichii Sankio, Gilead
- **boards**: Astra zeneca, Novartis, GSK, Daichii Sankio
- **honoraires**: GSK, MSD, Novartis, Lilly

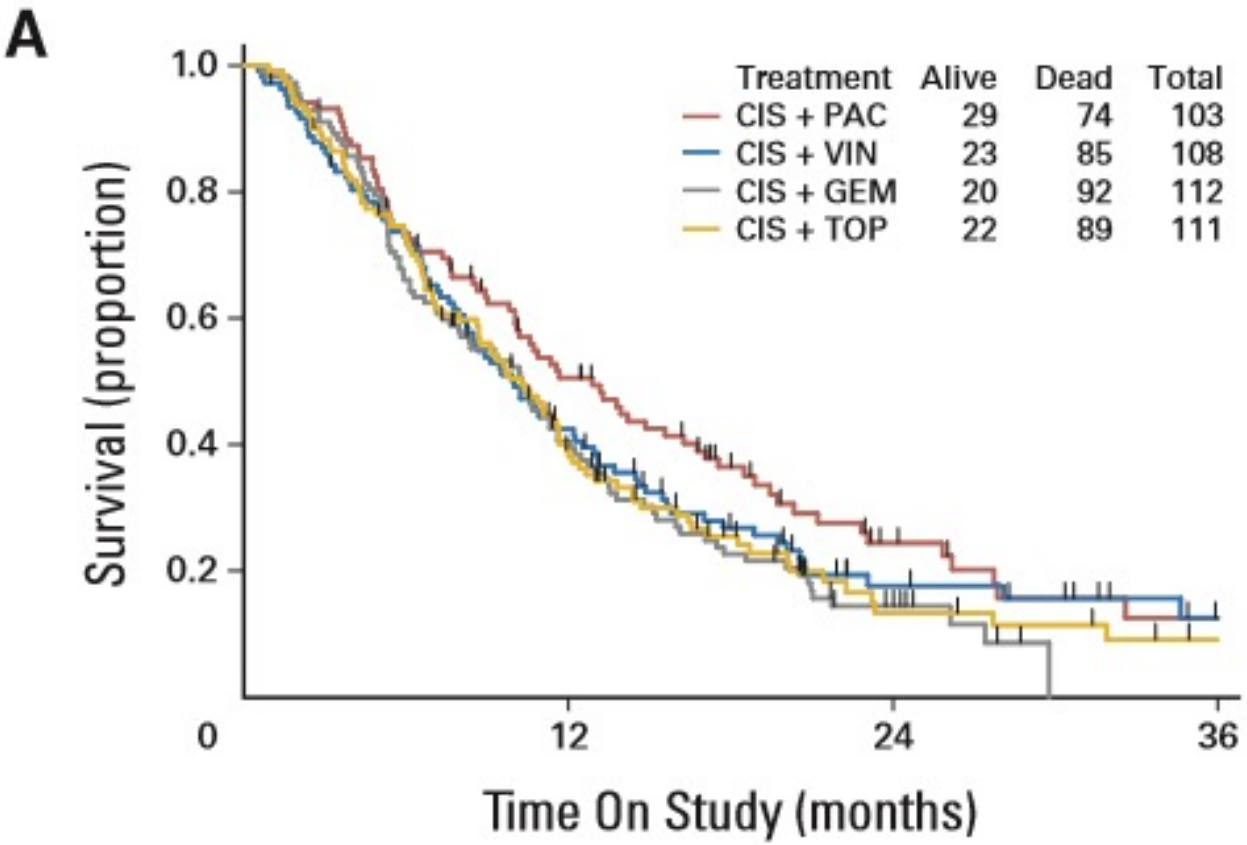
« Les présentations des orateurs au cours de cette réunion d'information à caractère exclusivement médical et scientifique organisée en France sont destinées à clarifier la prise en charge sur les pathologies, dans un domaine thérapeutique, ou un sujet donné en lien avec les besoins des professionnels de santé et des patients en conformité avec les recommandations thérapeutiques en vigueur. MSD rappelle que les informations partagées au cours de cette réunion n'ont pas de vocation promotionnelle. ***Le Bon usage des classes thérapeutiques éventuellement citées et leur place dans la stratégie thérapeutique doivent toujours être respectés****. Les informations présentées sont fournies à titre d'accompagnement aux professionnels de santé ; elles reflètent l'opinion des orateurs et pas nécessairement celle de MSD en France ni de sa maison mère Merck & Co., Inc., Kenilworth, NJ, USA, et de ses filiales. »*

Col utérin en rechute et/ou métastatique





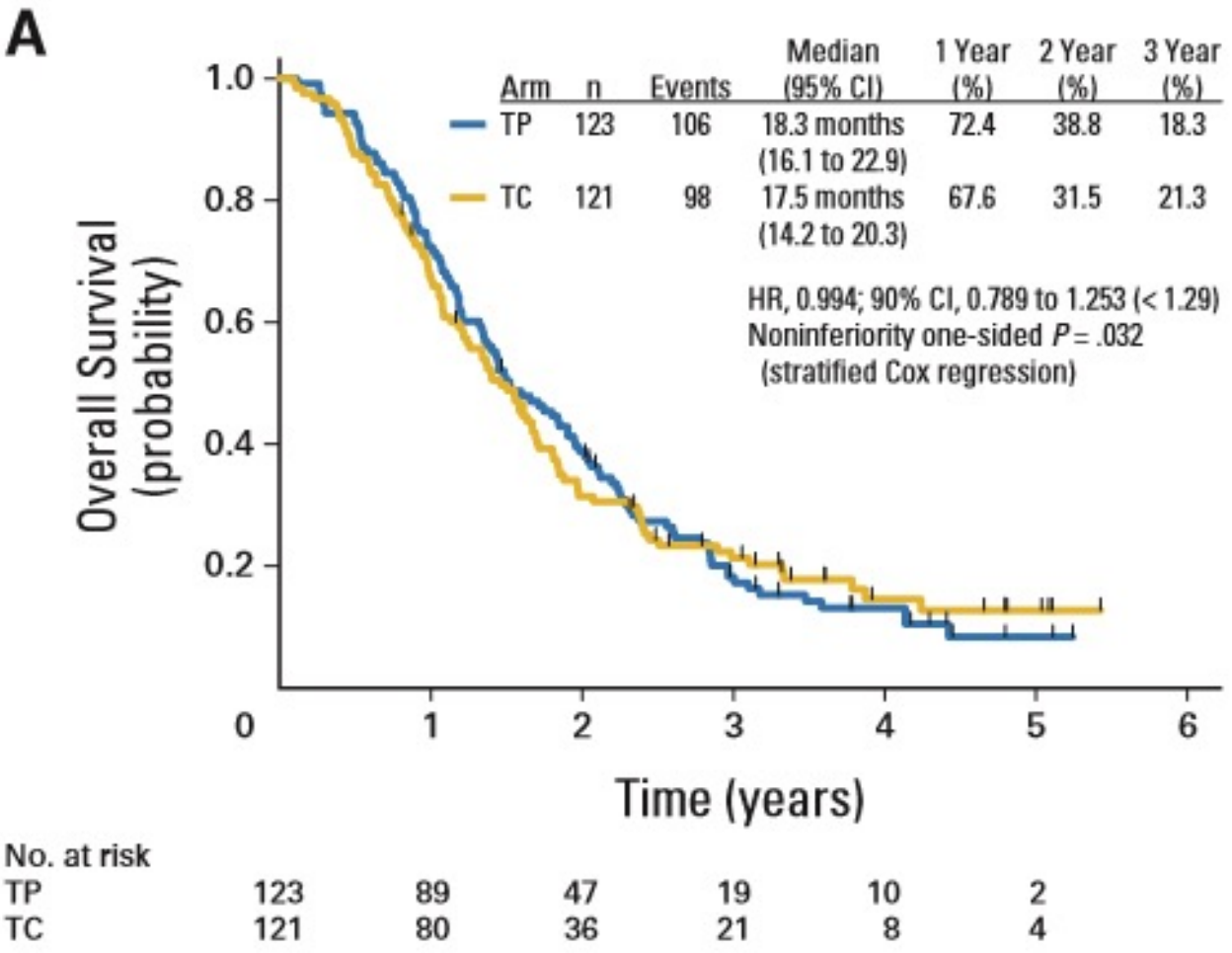
Le traitement historique de première ligne



Cisplatine + Paclitaxel
RR: 29,1%
SG: 12,87 mois

Monk BJ et al. J Clin Oncol 2009

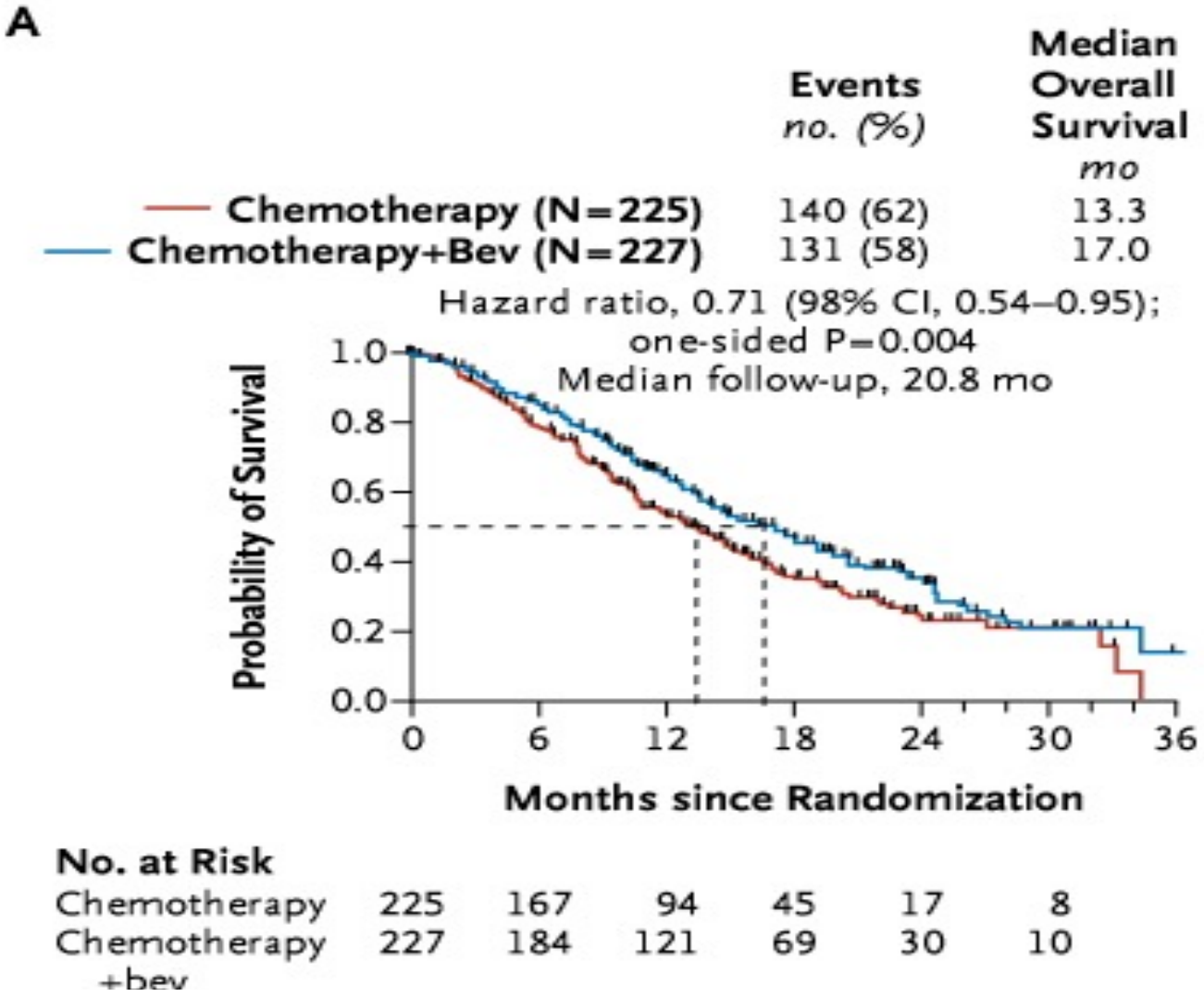
Remplacer CisP par CarboP chez prétraités



Pas d'hyperhydratation
Moins de neutropénie fébrile, nausées vomissements et d'élévation creat

Kitagawa R J Clin Oncol 2015

Ajout du Bevacizumab à la chimiothérapie



+ 3,7 mois de survie globale

Tewari KS et al NEJM 2014

Enfin un remboursement en 2022 …

Table 1. Selected Adverse Events among the Study Patients, According to Treatment Group.*

Event	Chemotherapy Alone (N=219)	Chemotherapy plus Bevacizumab (N=220)	Odds Ratio (95% CI)	P Value
	no. of patients (%)			
Gastrointestinal events, excluding fistulas (grade ≥2)	96 (44)	114 (52)	1.38 (0.93–2.04)	0.10
Fistula (grade ≥3)				
Gastrointestinal	0	7 (3)	NA (1.90–∞)	0.02
Genitourinary	1 (<1)	6 (3)	6.11 (0.73–282.00)	0.12
Total†	1 (<1)	13 (6)	13.69 (2.01–584.00)	0.002
Hypertension (grade ≥2)‡	4 (2)	54 (25)	17.50 (6.23–67.50)	<0.001
Proteinuria (grade ≥3)	0	4 (2)	NA (0.90–∞)	0.12
Pain (grade ≥2)	62 (28)	71 (32)	1.21 (0.79–1.85)	0.41
Neutropenia (grade ≥4)	57 (26)	78 (35)	1.56 (1.02–2.40)	0.04
Febrile neutropenia (grade ≥3)	12 (5)	12 (5)	1.00 (0.40–2.48)	1.00
Thromboembolism (grade ≥3)	3 (1)	18 (8)	6.42 (1.83–34.4)	0.001
CNS bleeding (grade ≥3)	0	0	NA	
Gastrointestinal bleeding (grade ≥3)§	1 (<1)	4 (2)	4.04 (0.39–200.00)	0.37
Genitourinary bleeding (grade ≥3)§	1 (<1)	6 (3)	6.11 (0.73–282.00)	0.12

Eviter en cas de récidive centro-pelvienne préalablement irradiée et les tumeurs en place

Tewari KS NEJM 2014

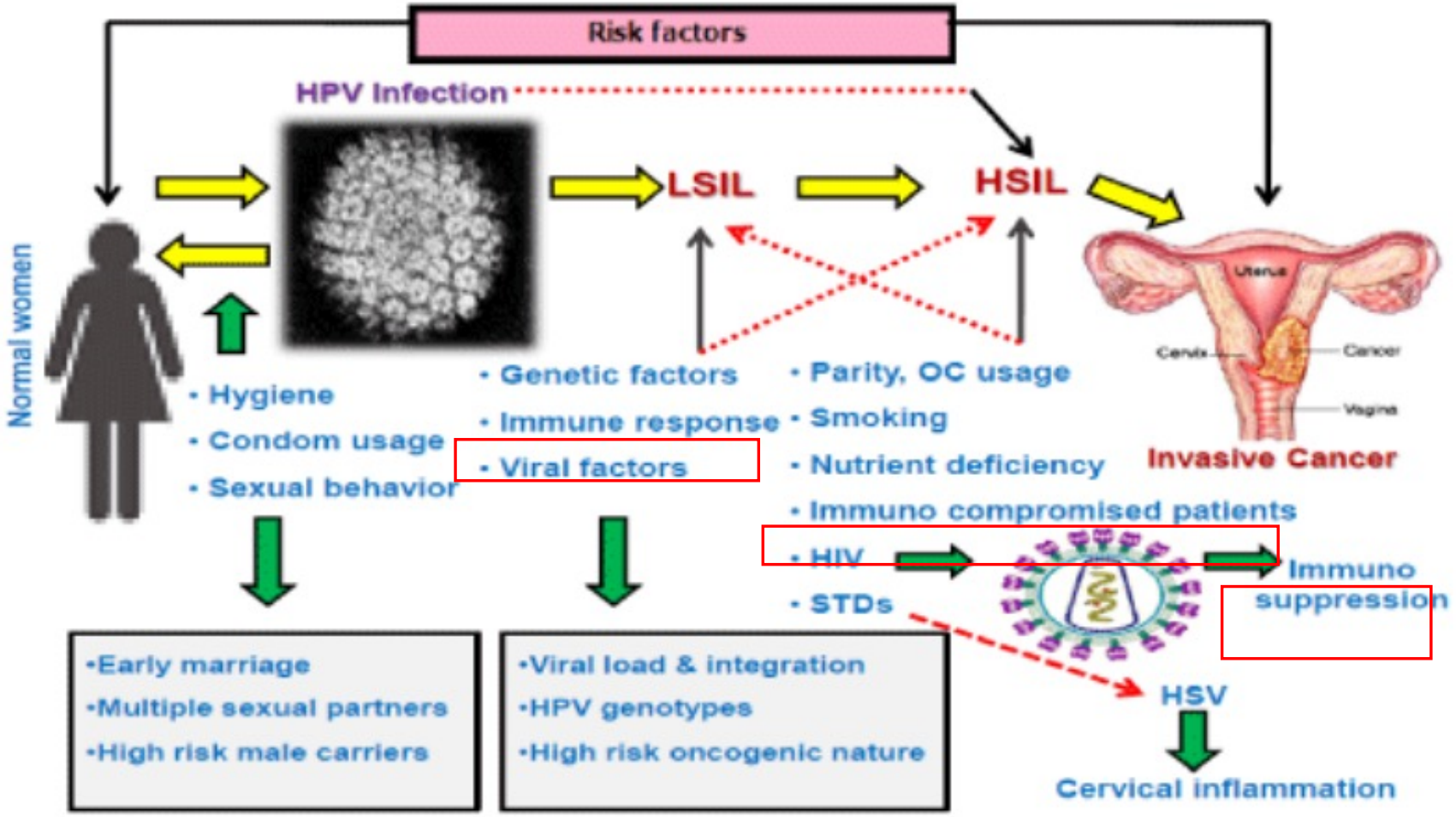
COURS ST-PAUL
RPC 2023

Cancer du col : efficacité des chimio en 2ème ligne

	N	Taux de Réponse (%)	Survie Sans Rechute (mois)	Survie Globale (mois)
Topotecan*	45	12,5	2,1	6,6
Vinorelbine*	44	13,7	-	-
Pemetrexed*	43	13,9	2,3	8
Docetaxel*	27	8,7	3,8	7
Gemcitabine*	22	4,5	2,1	6,5
Capecitabine***	23	0	-	5,7
Irinotecan**	42	21	-	6,4

* Yu et al Am J Hematol Oncol 2015
** Verschraegen et al J Clin Oncol 1997
*** Jenkins AD Gynecol Oncol 2005

Pourquoi l'immunothérapie dans le cancer du col



1. *Opzoomer JW et al. Front Immunol. 2019;10:1654.* ***2.*** *Kersten K et al. Front Immunol. 2015;6:516.* ***3.*** *Emens LA, Middleton G. Cancer Immunol Res. 2015; 3(5):436–443.*
4. *Galluzzi L et al. Cancer Immunol Res. 2016;4(11):895–902.*

Un cancer c’est quoi ?

La vision habituelle

- Une boule qui grossit dans le corps

L’immunologue

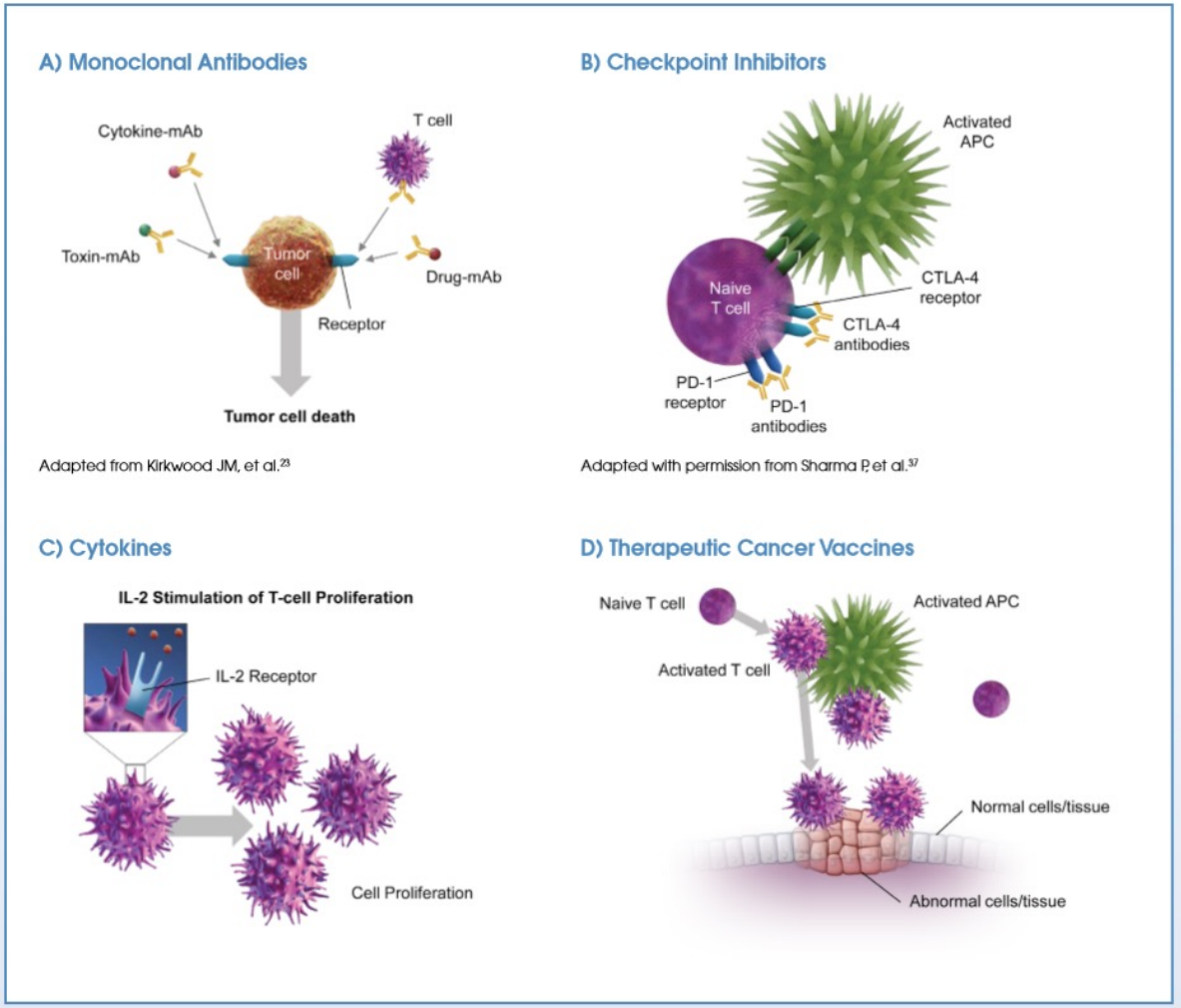
- Un corps qui laisse une boule grossir

1. *Opzoomer JW et al. Front Immunol. 2019;10:1654.* ***2.*** *Kersten K et al. Front Immunol. 2015;6:516.* ***3.*** *Emens LA, Middleton G. Cancer Immunol Res. 2015; 3(5):436–443.*
4. *Galluzzi L et al. Cancer Immunol Res. 2016;4(11):895–902.*

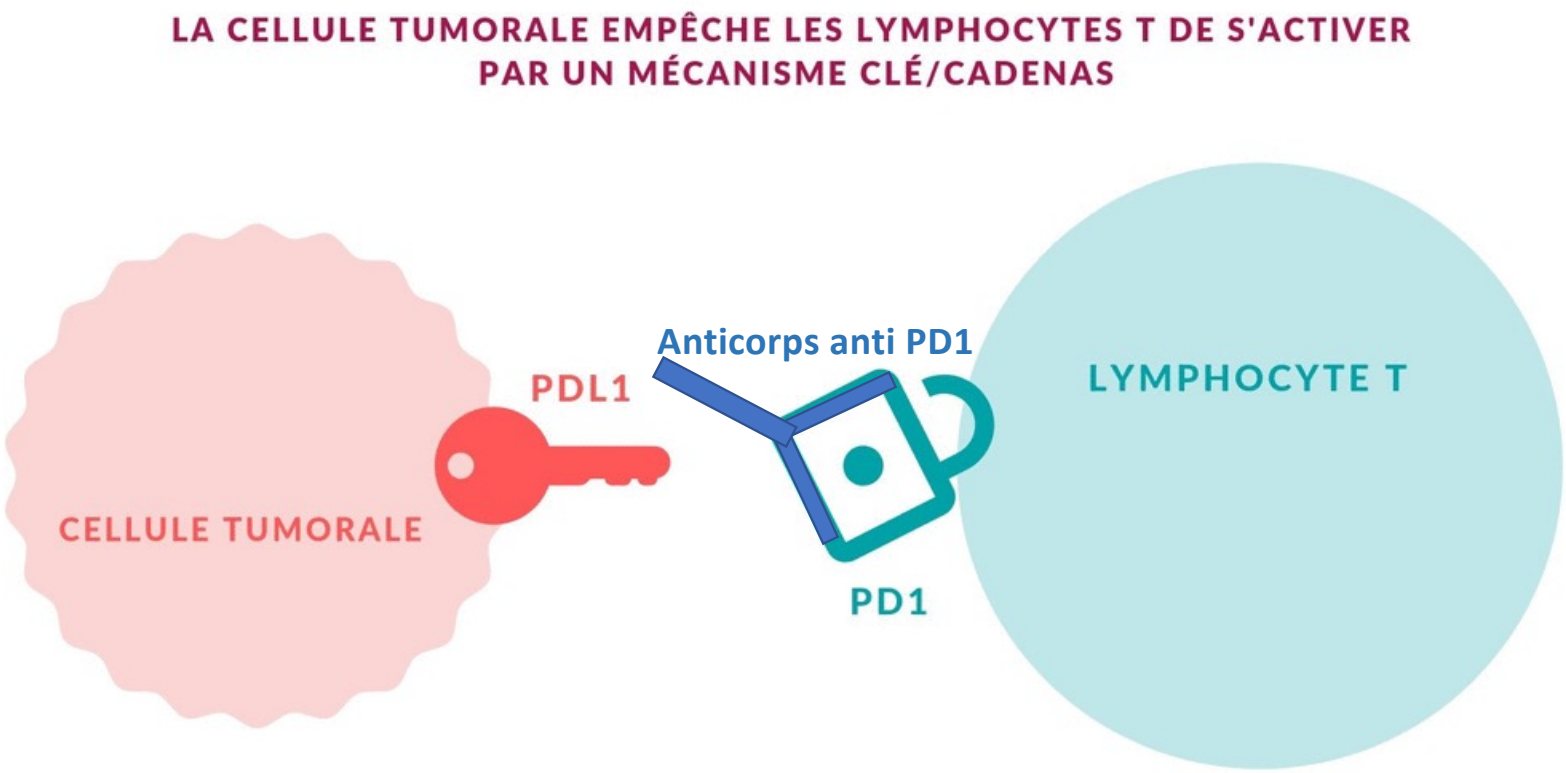
Mécanismes d'action de l'immunothérapie

PASSIVES

ACTIVES



Anticorps anti PD1



1. *Opzoomer JW et al. Front Immunol. 2019;10:1654.* ***2.*** *Kersten K et al. Front Immunol. 2015;6:516.* ***3.*** *Emens LA, Middleton G. Cancer Immunol Res. 2015; 3(5):436–443.*
4. *Galluzzi L et al. Cancer Immunol Res. 2016;4(11):895–902.*

KN826: Ajout du Pembrolizumab à la chimiothérapie

Colombo N et al. *N Engl J Med*. 2021;385(20):1856–1867

Colombo KN826 ESMO 2021

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

Key Eligibility Criteria

- Persistent, recurrent, or metastatic cervical cancer not amenable to curative treatment
- No prior systemic chemotherapy (prior radiotherapy and chemoradiotherapy permitted)
- ECOG PS 0 or 1

R 1:1

Pembrolizumab 200 mg IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

Placebo IV Q3W
for up to 35 cycles
+
Paclitaxel + Cisplatin or Carboplatin IV Q3W
for up to 6 cycles[a]
±
Bevacizumab 15 mg/kg IV Q3W

Stratification Factors

- Metastatic disease at diagnosis (yes vs no)
- PD-L1 CPS (<1 vs 1 to <10 vs ≥10)
- Planned bevacizumab use (yes vs no)

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.

Caractéristiques de la population

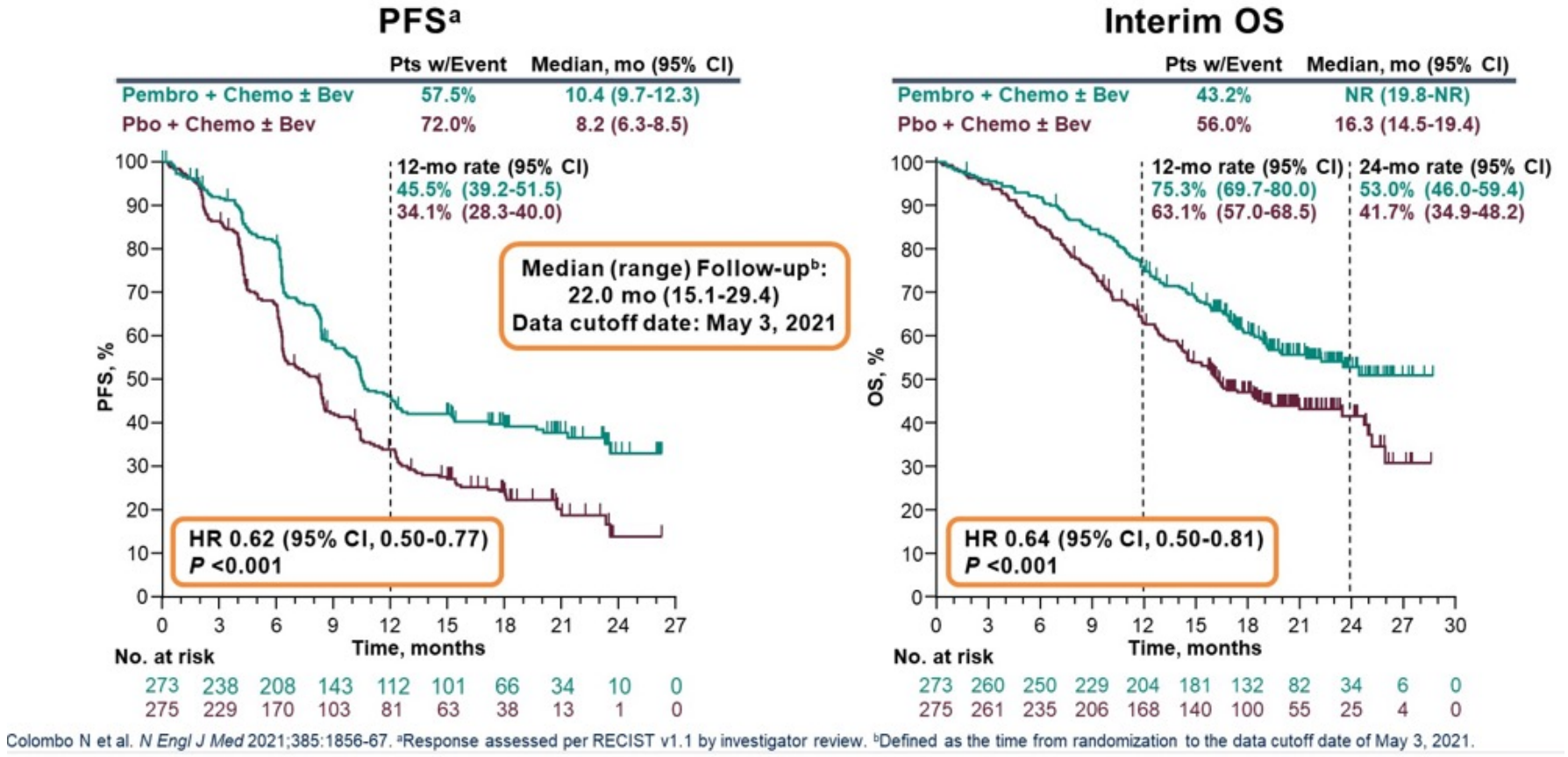
Colombo N et al. *N Engl J Med*. 2021;385(20):1856–1867

	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: October 3, 2022.

Objectifs principaux dans la population PDL1 CPS ≥1



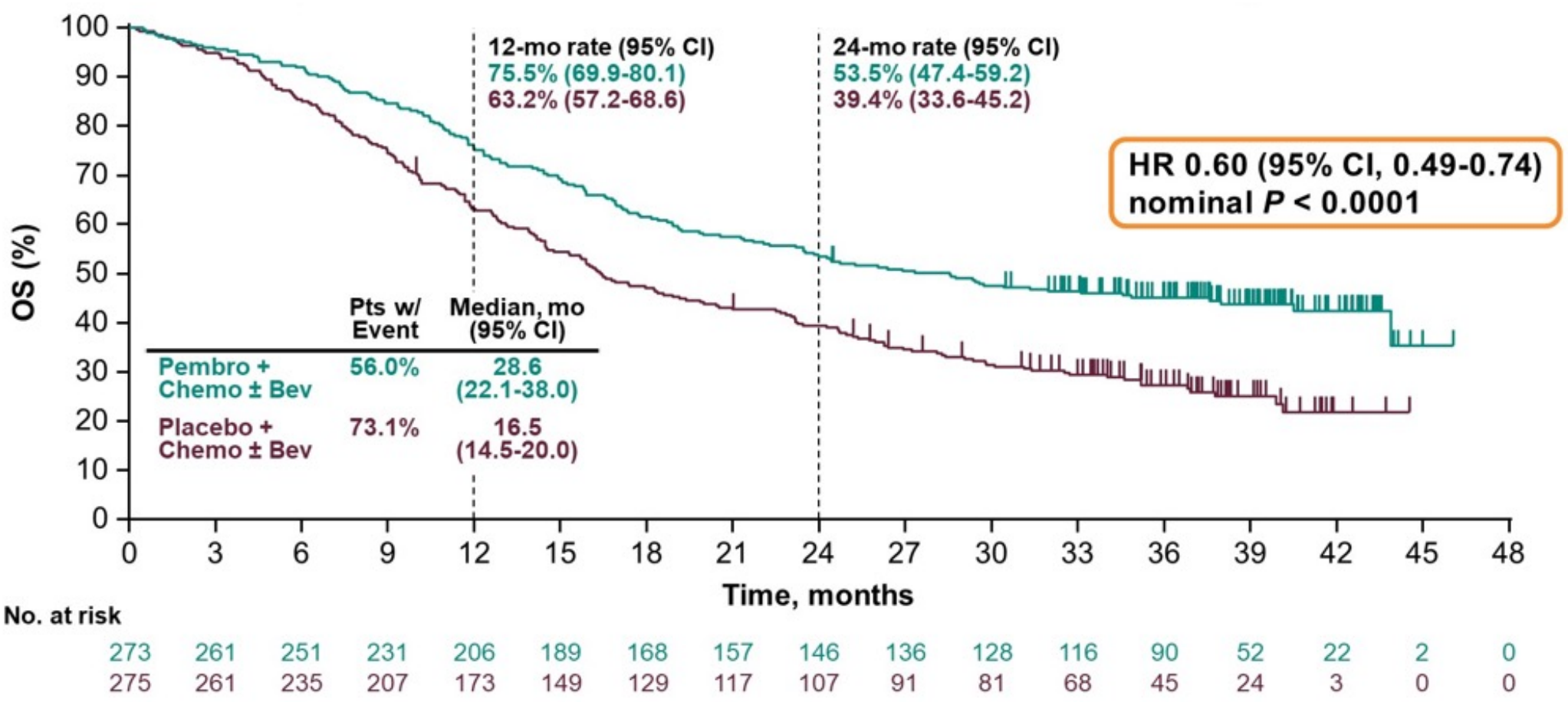
Colombo N et al. *N Engl J Med* 2021;385:1856-67. [a]Response assessed per RECIST v1.1 by investigator review. [b]Defined as the time from randomization to the data cutoff date of May 3, 2021.

Avis favorable HAS sept 2022

« en association à une chimiothérapie avec ou sans bevacizumab, 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 »

Colombo N et al. *N Engl J Med*. 2021;385(20):1856–1867

Survie globale finale population PDL1 CPS >1

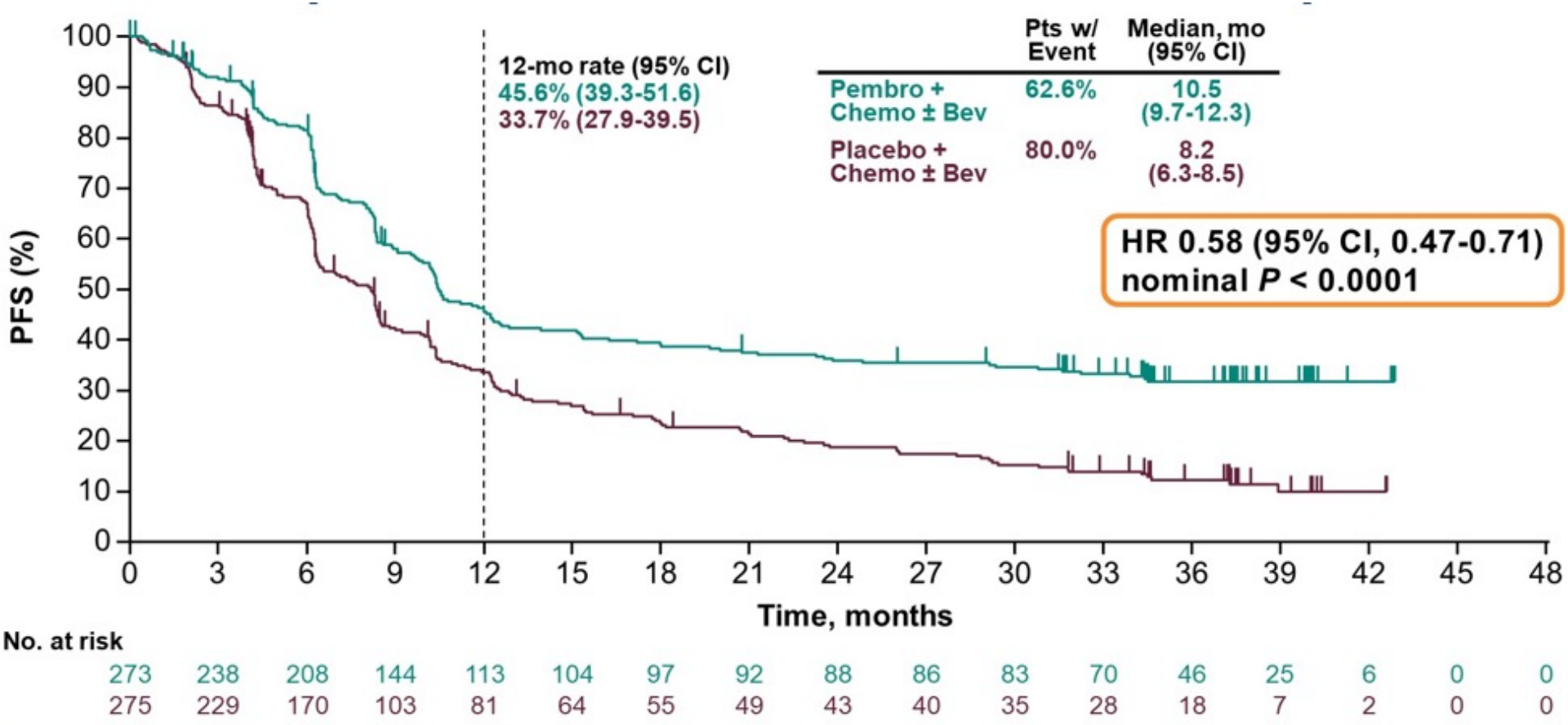


Data cutoff date: October 3, 2022.

PRESENTED BY: Bradley J. Monk, MD, FACS, FACOG – abstract #5500

Colombo N et al. *N Engl J Med*. 2021;385(20):1856–1867

Survie sans progression finale population PDL1 CPS >1

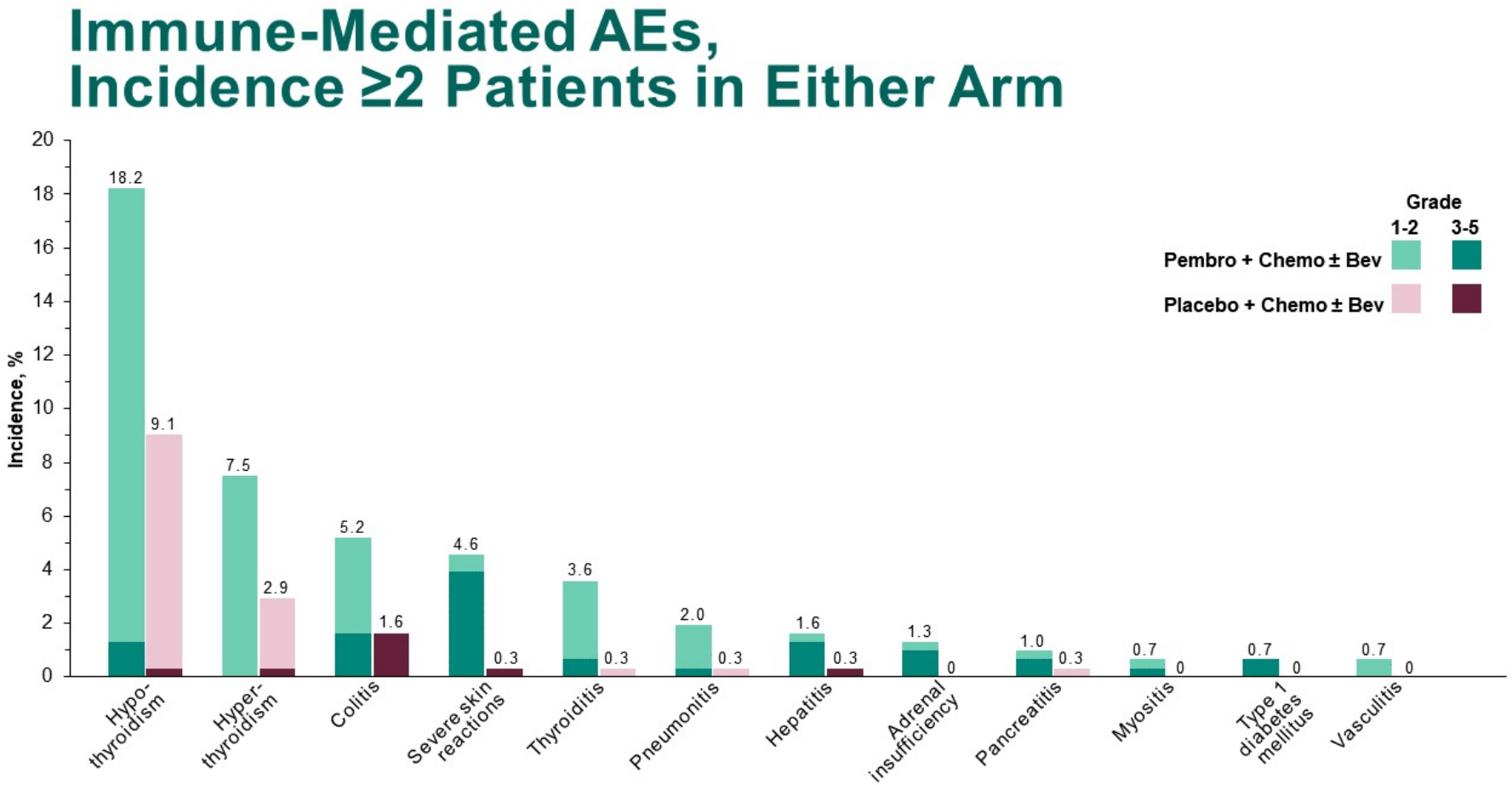


Response assessed per RECIST v1.1 by investigator review. Data cutoff date: October 3, 2022.

Colombo N et al. *N Engl J Med*. 2021;385(20):1856–1867

KN826: Toxicité spécifique à l'immunothérapie

Colombo KN826 ESMO 2021



[a]Events were considered regardless of attribution to treatment by the investigator. Related terms were included in addition to the specific terms listed.
Data cutoff date: May 3, 2021.

Colombo N et al. *N Engl J Med*. 2021;385(20):1856–1867

EMPOWER: Cemiplimab vs Chimio en 2eme ligne

Vergote I et al. Int J Gynecol Cancer 2019; 0: 1-4

Recurrent and metastatic cervical cancer resistant to platinum-based chemotherapy ≥2nd line
ECOG PS ≤1

N=608: 477 SCC, 131 AC
Randomised 1:1
Stratified by:
- Histology (SCC/AC)
- Geographic region
- Prior bevacizumab (Y/N)
- ECOG PS (0 vs 1)

Patients were enrolled regardless of PD-L1 expression

Cemiplimab 350 mg Q3W IV

IC chemotherapy

Options:
- Pemetrexed 500 mg/m² Q3W IV
- Gemcitabine 1,000 mg/m² IV on Days 1 and 8 and every 21 days
- Topotecan 1 mg/m² daily IV for 5 days, every 21 days
- Irinotecan 100 mg/m² IV weekly x 4, followed by 10–14 days rest
- Vinorelbine 30 mg/m² IV on Days 1 and 8 and every 21 days

Treat up to 96 weeks with option for re-treatment

Tumour imaging conducted on Day 42 (±7 days) of cycles† 1–4, 6, 8, 10, 12, 14, and 16

Primary endpoint: OS

Secondary endpoints:
PFS, ORR, DOR, safety, QoL

Exploratory endpoints:
PK, immunogenicity, biomarkers, PD

- Two interim analyses were prespecified per protocol
- At first interim analysis, IDMC recommended trial to continue
- At second interim analysis (85% of total OS events), IDMC recommended trial be stopped early for efficacy; presented here

*Performed according to ENGOT Model C.[1] †To account for differences in drug administration schedules, one cycle is defined as 6 weeks.
AC, adenocarcinoma or adenosquamous carcinoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IC, investigator's choice; IDMC, Independent Data Monitoring Committee; IV, intravenously; ORR, objective response rate; OS, overall survival; PD, pharmacodynamics; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; QoL, quality of life; SCC, squamous cell carcinoma.

1. Vergote I et al. *Int J Gynecol Cancer.* 2019;0:1–4.

EMPOWER: Caractéristiques patientes

	Cemiplimab (n=304)	Chemotherapy (n=304)	Total (N=608)
Age (years)			
n	304	304	608
Mean (SD)	51.1 (11.6)	51.2 (11.8)	51.1 (11.7)
Median	51.0	50.0	51.0
Q1 : Q3	42.0 : 60.0	43.0 : 59.0	43.0 : 59.0
Min : Max	22 : 81	24 : 87	22 : 87
Age groups (years), n (%)			
<65	269 (88.5)	264 (86.8)	533 (87.7)
≥65 and <75	30 (9.9)	29 (9.5)	59 (9.7)
≥75	5 (1.6)	11 (3.6)	16 (2.6)
Geographic region, n (%)			
North America	32 (10.5)	34 (11.2)	66 (10.9)
Asia	83 (27.3)	83 (27.3)	166 (27.3)
Rest of World	189 (62.2)	187 (61.5)	376 (61.8)
ECOG performance status, n (%)			
0	142 (46.7)	141 (46.4)	283 (46.5)
1	162 (53.3)	163 (53.6)	325 (53.5)

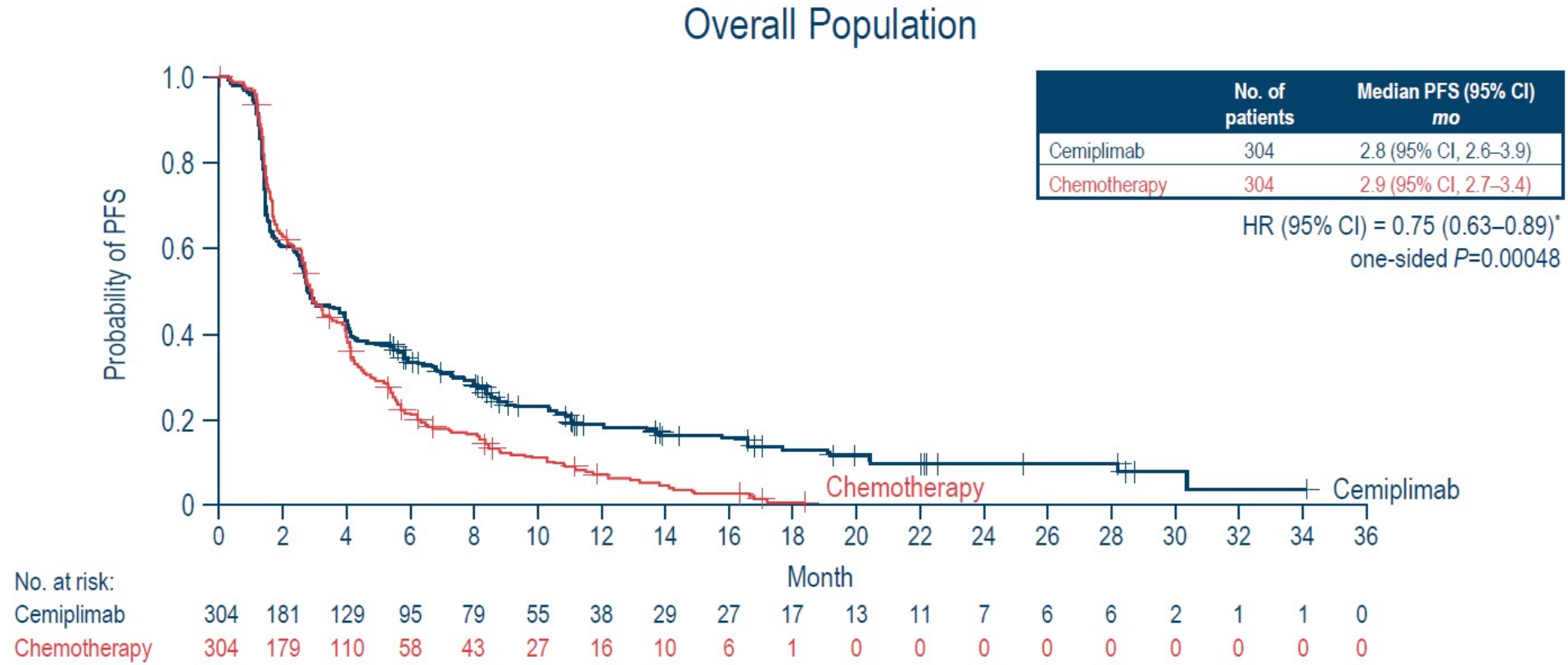
	Cemiplimab (n=304)	Chemotherapy (n=304)	Total (N=608)
Histology/cytology, n (%)			
SCC	240 (78.9)	233 (76.6)	473 (77.8)
Adenocarcinoma	54 (17.8)	62 (20.4)	116 (19.1)
Adenosquamous carcinoma	10 (3.3)	9 (3.0)	19 (3.1)
Extent of disease, n (%)			
Metastatic	284 (93.4)	290 (95.4)	574 (94.4)
Recurrent/persistent	20 (6.6)	14 (4.6)	34 (5.6)
Prior lines of therapy for R/M disease			
1	177 (58.2)	169 (55.6)	346 (56.9)
>1	124 (40.8)	135 (44.4)	259 (42.6)
Prior bevacizumab use, n (%)*			
Yes	149 (49.0)	147 (48.4)	296 (48.7)
No	155 (51.0)	157 (51.6)	312 (51.3)

- 608 patients were randomised
  - 477 with SCC*
  - 131 with AC*

*Based on interactive web response system data. AC, adenocarcinoma or adenosquamous carcinoma; ECOG, Eastern Cooperative Oncology Group; Q, quarter; R/M, recurrent or metastatic; SCC, squamous cell carcinoma; SD, standard deviation.

Vergote I et al. Int J Gynecol Cancer 2019; 0: 1-4

EMPOWER: Survie sans progression



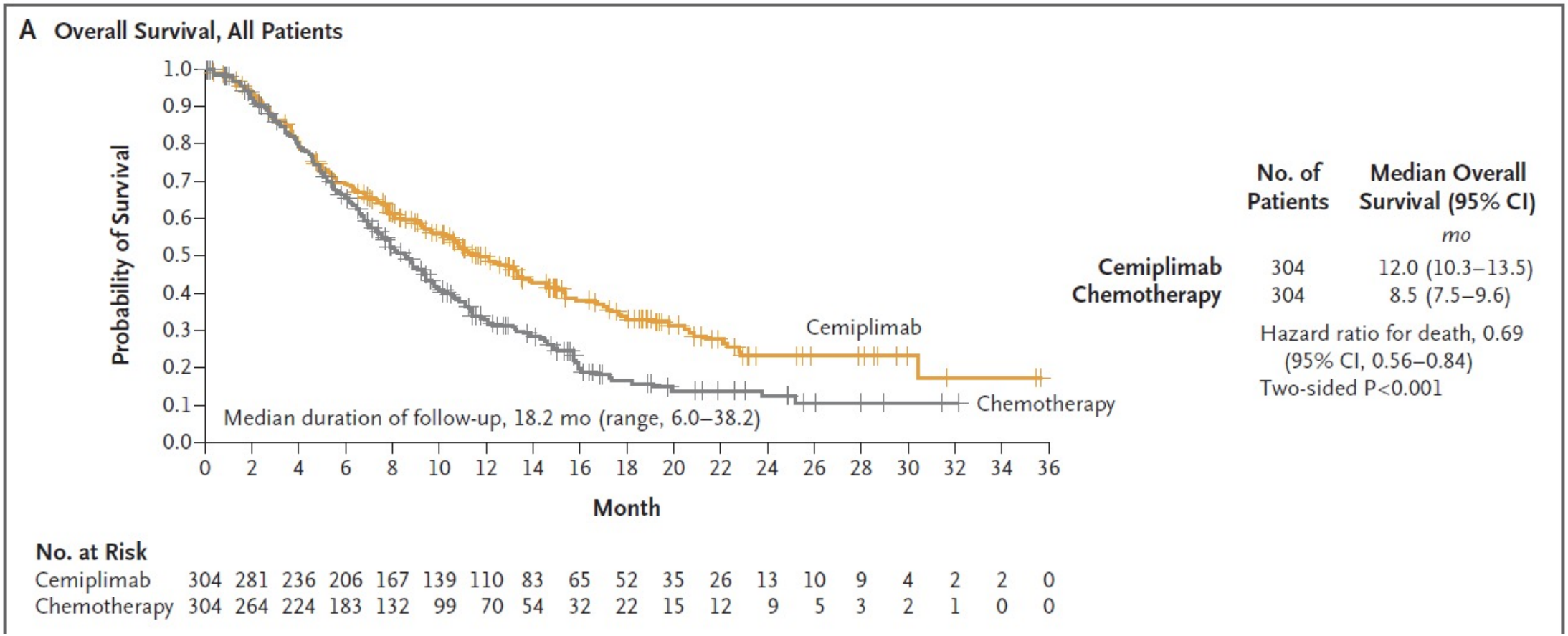
	No. of patients	Median PFS (95% CI) *mo*
Cemiplimab	304	2.8 (95% CI, 2.6–3.9)
Chemotherapy	304	2.9 (95% CI, 2.7–3.4)

HR (95% CI) = 0.75 (0.63–0.89)*
one-sided *P*=0.00048

Vergote I et al. Int J Gynecol Cancer 2019; 0: 1-4

*Stratified by geographic region (North America vs Asia vs ROW) and Histology (SCC vs AC) according to interactive web response system.
AC, adenocarcinoma or adenosquamous carcinoma; CI, confidence interval; HR, hazard ratio; mo, month; PFS, progression-free survival; ROW; rest of world; SCC, squamous cell carcinoma.

EMPOWER: Survie globale



AMM européenne, pas de remboursement en France

Tewari et al. N Engl J Med. 2022; 386:544-555

Tewari KS NEJM 2022

EMPOWER: Effets indésirables

n (%), unless stated	Cemiplimab (n=300)		Chemotherapy (n=290)	
Median duration of exposure (range), weeks	15.2 (1.4–100.7)		10.1 (1.0–81.9)	
Treatment-emergent AEs, regardless of attribution	**Any grade**	**Grade 3–5**	**Any grade**	**Grade 3–5**
Overall	265 (88.3)	135 (45.0)	265 (91.4)	155 (53.4)
Led to discontinuation	26 (8.7)	20 (6.7)	15 (5.2)	11 (3.8)
Led to death	5 (1.7)	5 (1.7)	2 (0.7)	2 (0.7)
Treatment-related AEs				
Overall	170 (56.7)	44 (14.7)	236 (81.4)	117 (40.3)
Led to discontinuation	17 (5.7)	12 (4.0)	10 (3.4)	8 (2.8)
Led to death	0	0	2 (0.7)	2 (0.7)
Sponsor-identified immune-related AEs				
Overall	48 (16.0)	18 (6.0)	2 (0.7)	2 (0.7)
Led to discontinuation	15 (5.0)	11 (3.7)	2 (0.7)	2 (0.7)
Led to death	0	0	0	0

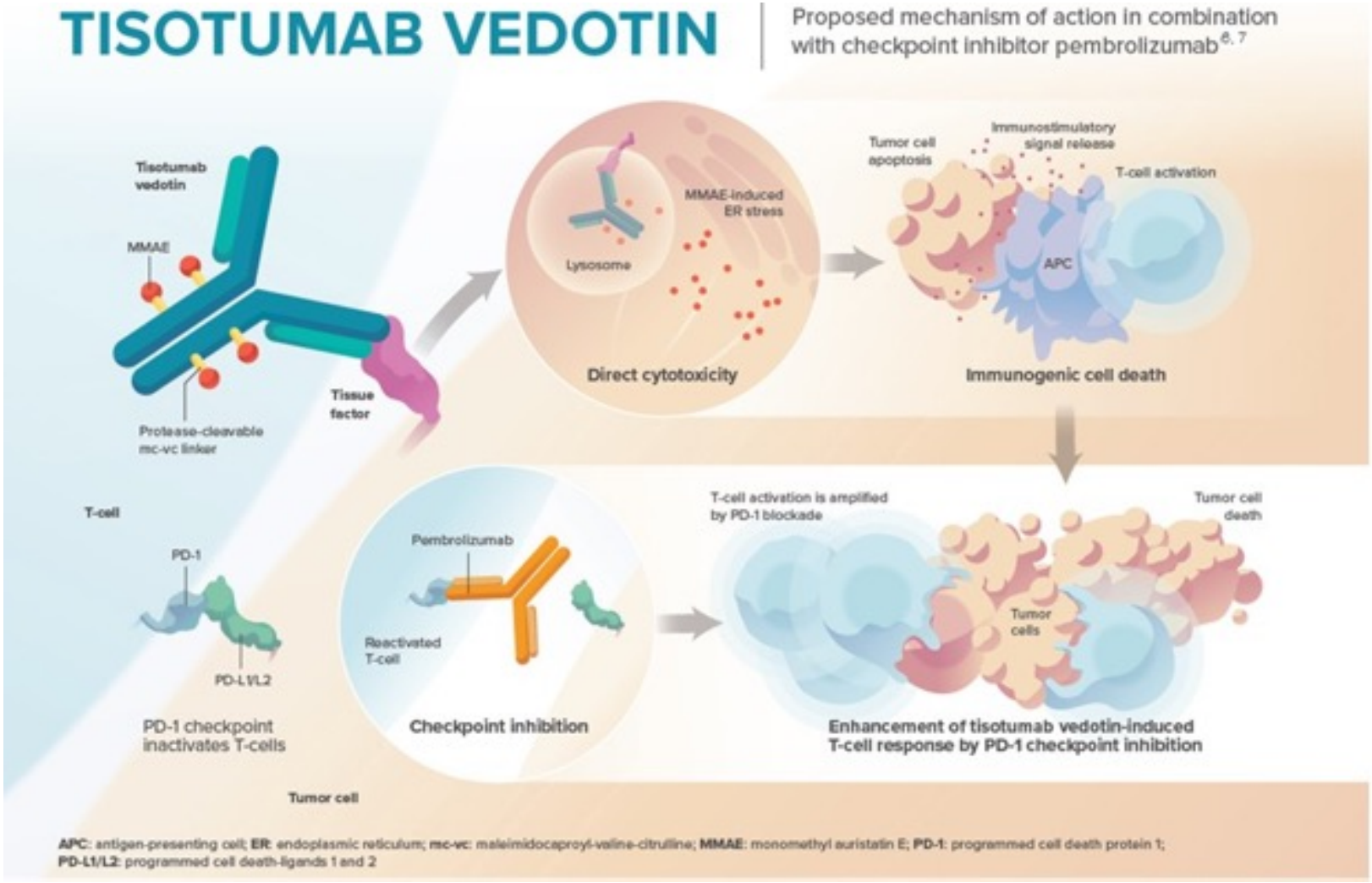
Treatment-emergent AEs in ≥15% of patients in either arm, n (%)	Cemiplimab (n=300)		Chemotherapy (n=290)	
	Any grade	**Grade 3–5**	**Any grade**	**Grade 3–5**
Overall	265 (88.3)	135 (45.0)	265 (91.4)	155 (53.4)
Anaemia	75 (25.0)	36 (12.0)	129 (44.5)	78 (26.9)
Nausea	55 (18.3)	1 (0.3)	97 (33.4)	6 (2.1)
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
Asthenia	33 (11.0)	7 (2.3)	44 (15.2)	3 (1.0)
Neutropenia	6 (2.0)	3 (1.0)	44 (15.2)	26 (9.0)

- There were no new immune-related AEs that are not well described for the PD-1/PD-L1 inhibitor class

Safety was analysed in all randomised patients who received any study treatment.
AE, adverse events; PD-1, programmed cell death-1; PD-L1, PD-ligand 1.

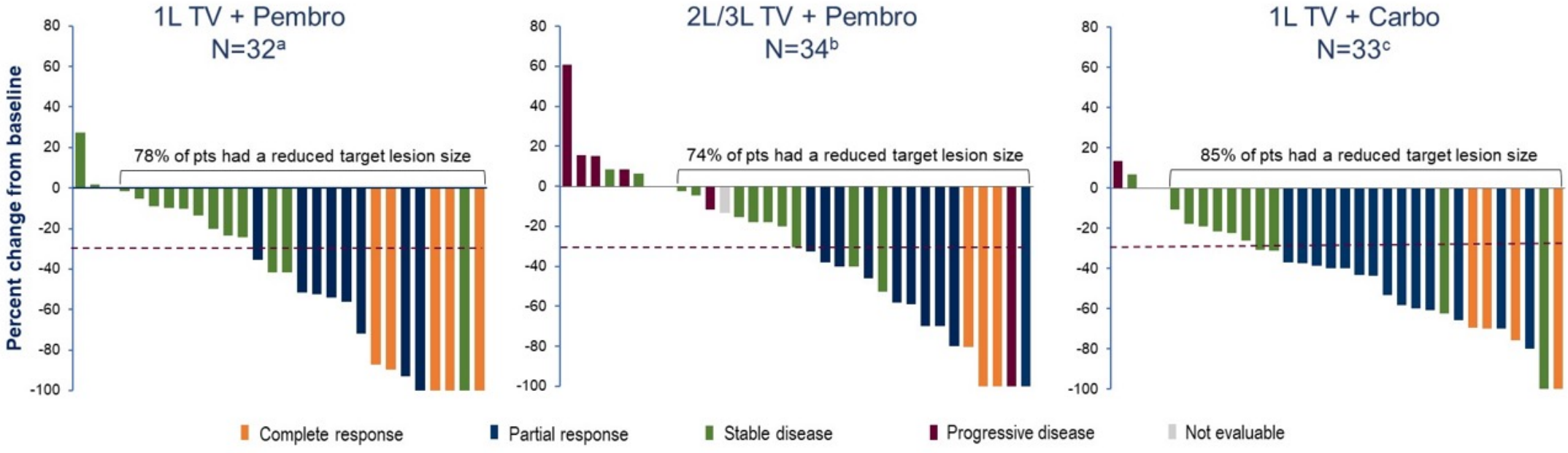
Vergote I et al. Int J Gynecol Cancer 2019; 0: 1-4 Tewari et al. N Engl J Med. 2022; 386:544-555

ADC: Ac conjugués à une chimiothérapie



Lorusso D ASCO 2022

Des résultats encourageants en phase II



Consistent and compelling reduction in target lesions across treatment arms

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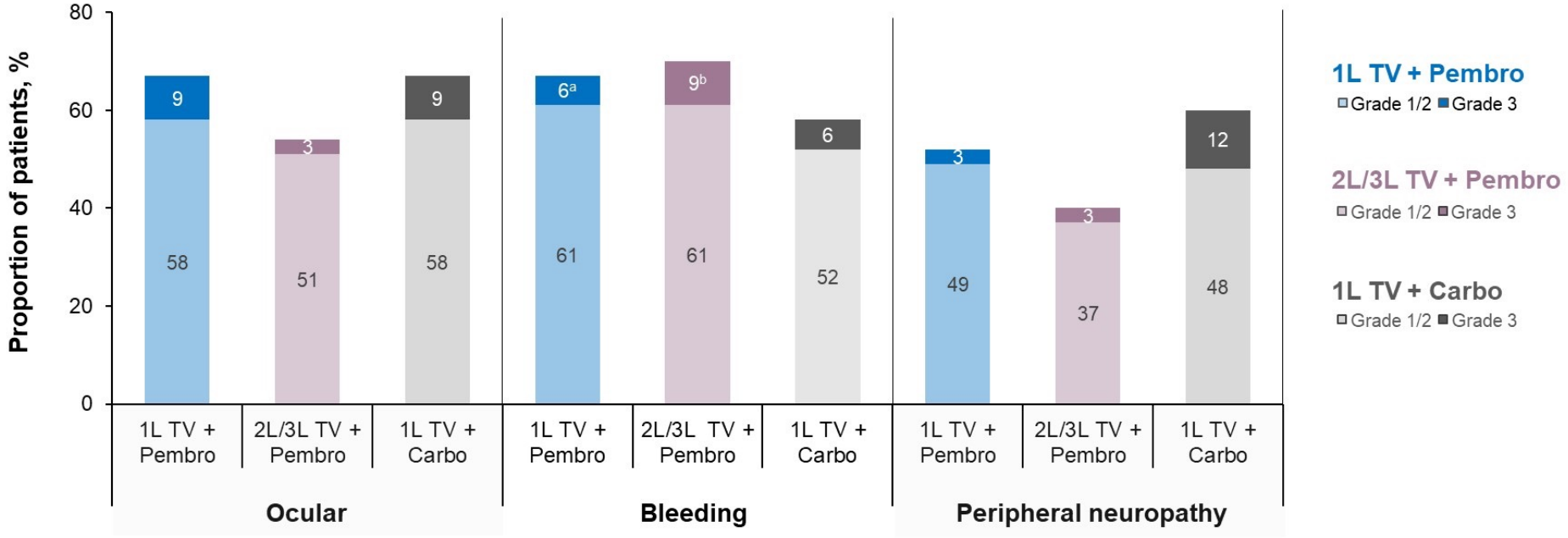
Adverse events of special interest with TV



[a]Includes one patient with grade 5 disseminated intravascular coagulation; [b]Includes one patient with grade 4 hematuria

AEs of special interest with TV were generally consistent across cohorts and were mostly grade 1-2

TV, tisotumab vedotin.

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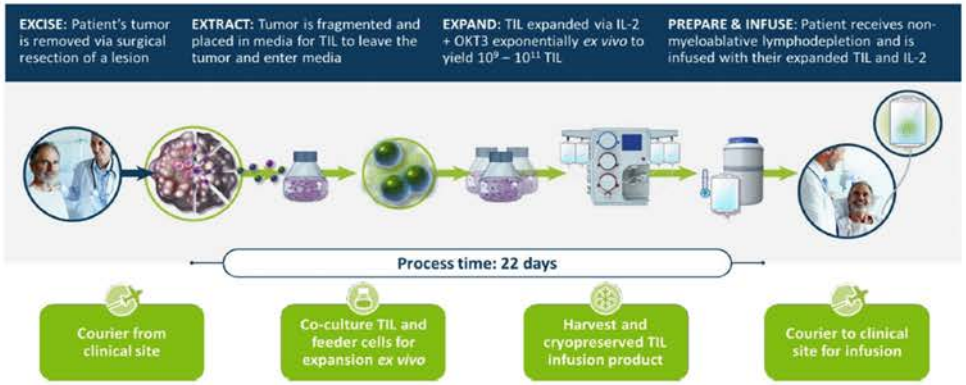
Adoptive T cell therapies: TIL therapy

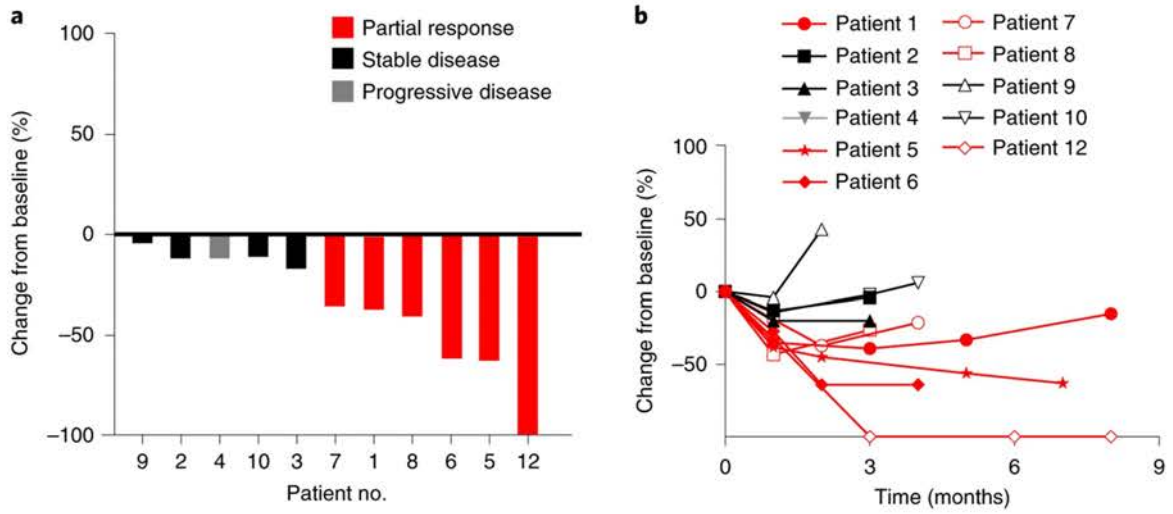


At median follow up of 7.4 months the median DOR has not been reached:

– range 2.6+ to 9.2+ months

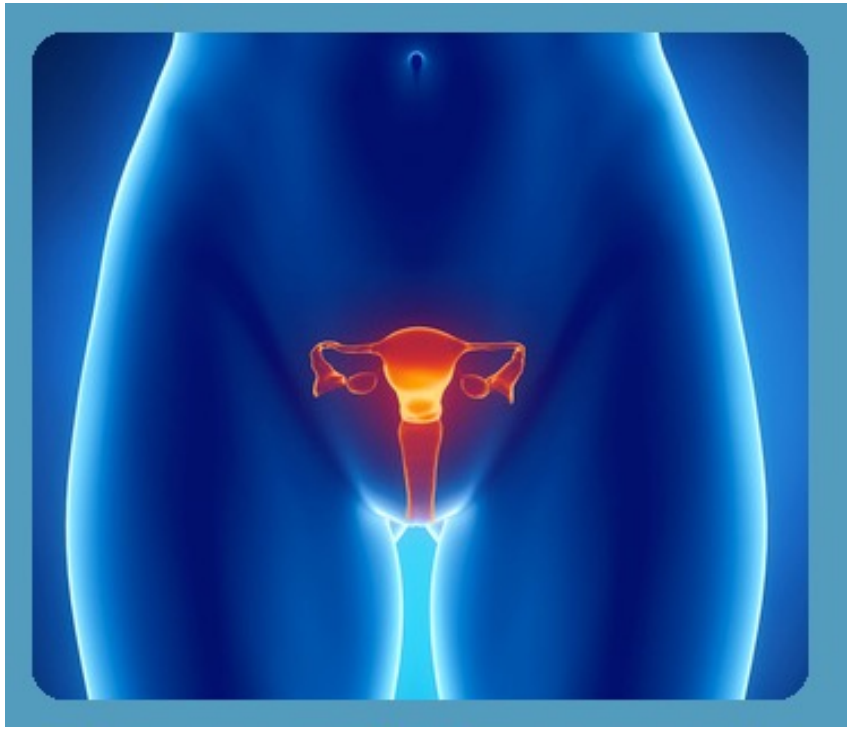
Jazaeri et al., ASCO 2019

Adoptive T cell therapies: engineered T cells targeting HPV 16 E7

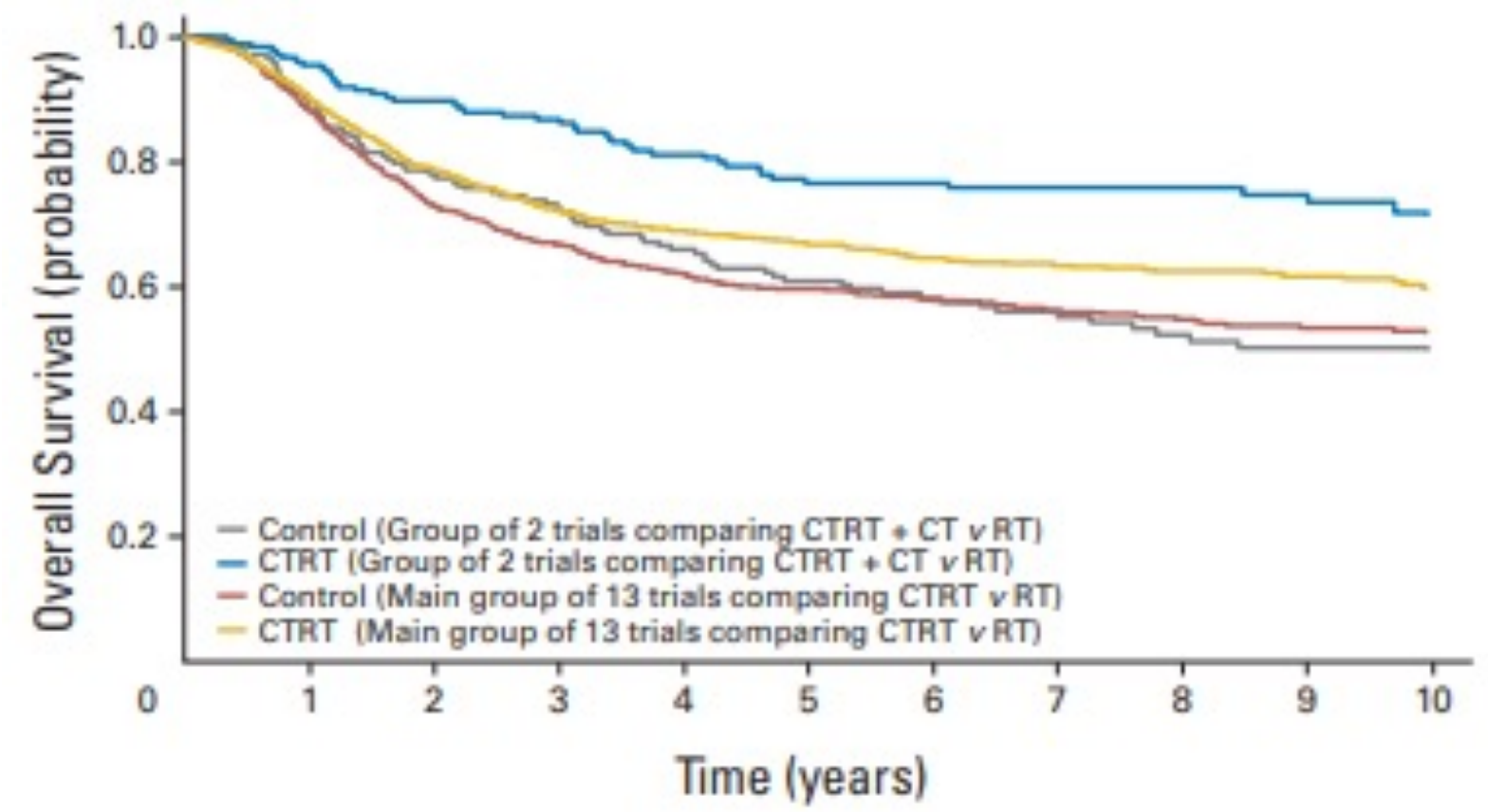


Nagarsheth, … Hinrichs CS, Nat Med. 2021.

Col utérin localement avancé



La RCT concomitante: un standard depuis 1999…

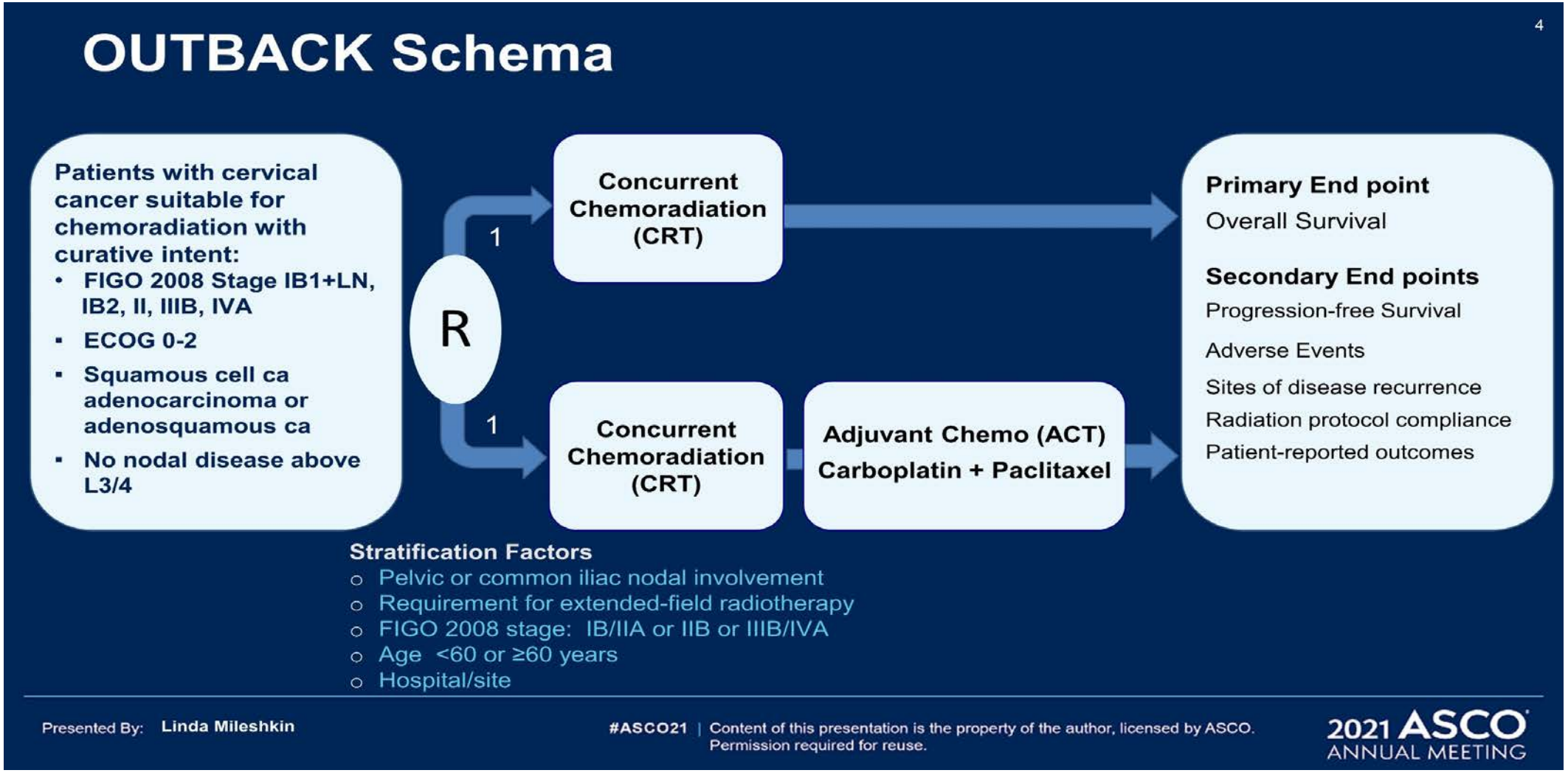


Amélioration de l'OS à 5 ans de 60 à 66% avec l'addition de CDDP à la radiothérapie

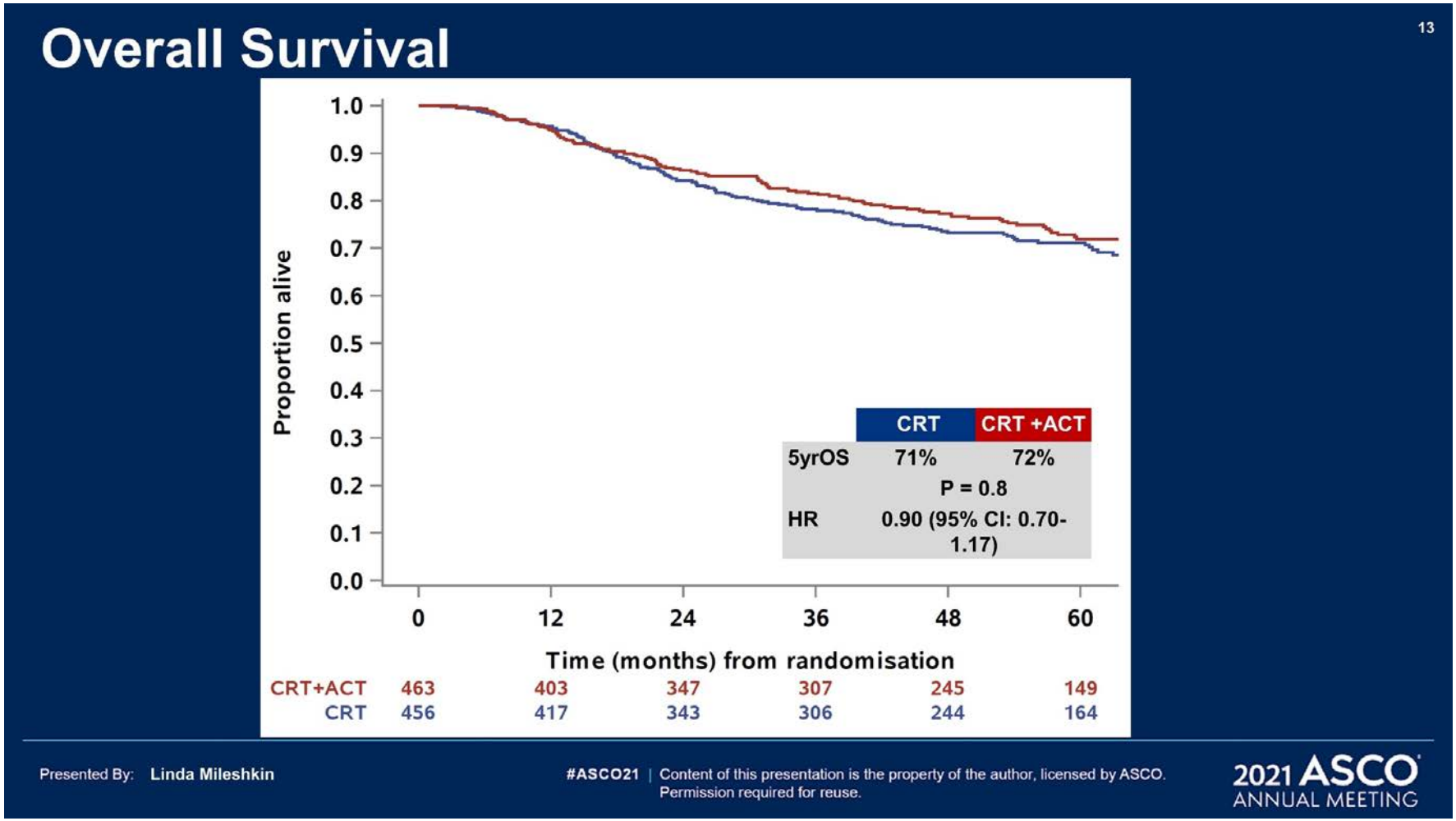
Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration J Clin Oncol 26:5802-5812. 2008

Lancet Oncology 2023 May;24(5):468-482

Ajout de chimiothérapie adjuvante



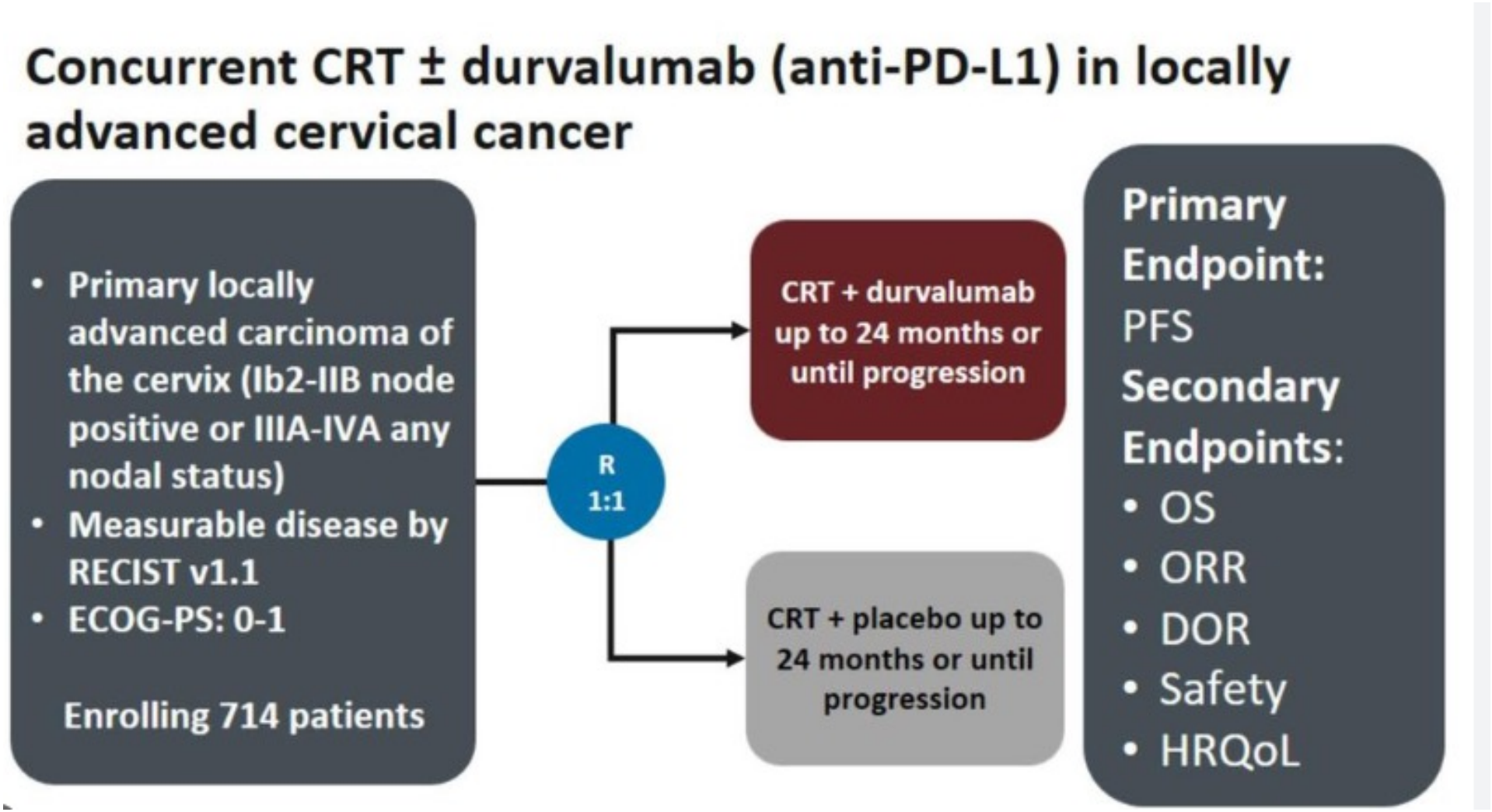
OUTBACK: pas d'amélioration de la PFS et de l'OS



Lancet Oncology 2023 May;24(5):468-482

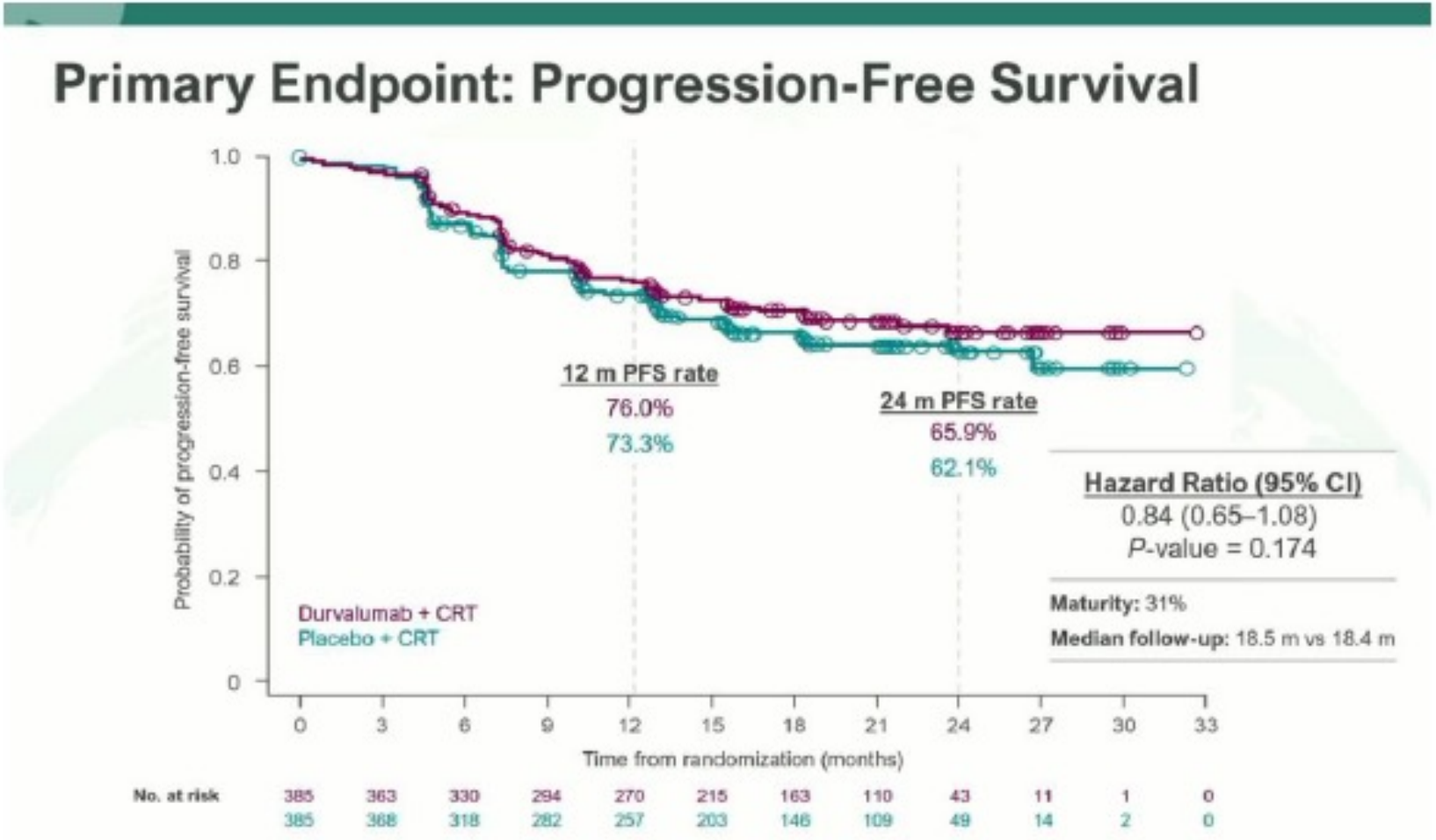
CALLA: addition de l'immunothérapie

Mayadev J, Nunes AT, Li M, *et al*. *Int J Gynecol Cancer* 2020;30:1065–1070.



CALLA: Pas d'amélioration de la PFS

Mayadev J, Nunes AT, Li M, *et al*. *Int J Gynecol Cancer* 2020;30:1065–1070.



Pour conclure

- L'immunothérapie est un nouveau standard thérapeutique dans les K col utérin en rechute et/ou métastatiques
- Mais pas de guérison supplémentaire aujourd'hui dans les stades localement avancé
- Attendre les résultats imminents des autres études +++
- La meilleure immunothérapie reste et restera la vaccination…

MISES EN GARDES SPECIALES / PRECAUTIONS D'EMPLOI

✓ **Effets indésirables potentiels d'origine immunologique (EII), y compris cas sévères et d'issue fatale, plusieurs systèmes d'organes possibles.**

- Avant le traitement et régulièrement pendant le traitement : vérification de l'état général + **bilan sanguin** notamment thyroïdien, hépatique, rénal…
- **Surveillance active** de l'apparition des EII par les professionnels de santé et les patients pour prise en charge précoce et réduction de leur intensité/sévérité.
- La plupart des effets indésirables d'origine immunologique ont été réversibles et pris en charge par une **suspension ou un arrêt définitif du traitement** (selon type/sévérité), l'administration de **corticostéroïdes** et/ou des soins de support.
- Principaux EII *(non exhaustif)* :
  - Toxicité cutanée
  - Endocrinopathies : insuffisance surrénalienne, hypophysite, dysthyroïdies, diabète de type 1 y compris acidocétose…
  - Pulmonaires : pneumopathie inflammatoire…
  - Digestifs : colite, hépatite, pancréatite…
  - Néphrologiques : néphrites
  - Oculaires : uvéite
  - Cardiaques : myocardite
  - Neurologiques : syndrome de Guillain-Barré, encéphalite, syndrome myasthénique, myélite…
  - Rhumatologiques : arthrite, myosite…
  - Complications d'une greffe de cellules souches hématopoïétiques allogénique
  - Autres : anémie hémolytique, sarcoïdose, vascularite, myélite, encéphalite etc.
  - …

✓ **Réactions potentielles liées à la perfusion**

MSD

GROSSESSE ET ALLAITEMENT

- ✓ Ne doivent pas être utilisés.
- ✓ **Méthode efficace de contraception** pendant toute la durée du traitement et pendant au moins 4 mois après la dernière administration.

EFFETS INDESIRABLES LES PLUS FREQUENTS (non exhaustif) (monothérapie et/ou en association)

- ✓ Fatigue,
- ✓ Eruption cutanée, prurit,
- ✓ Troubles digestifs (diarrhées, nausées, vomissements, constipation, diminution de l'appétit), colite, douleurs abdominales…
- ✓ Dysthyroïdies
- ✓ . . .
- ✓ Douleurs musculo-squelettiques, arthralgies/dorsalgies,
- ✓ Fièvre, céphalées,
- ✓ Toux, dyspnée,
- ✓ Infections urinaires,
- ✓ Anémie, neutropénie, thrombopénie…

Déclaration au CRPV ou sur https://signalement.social-sante.gouv.fr

MSD