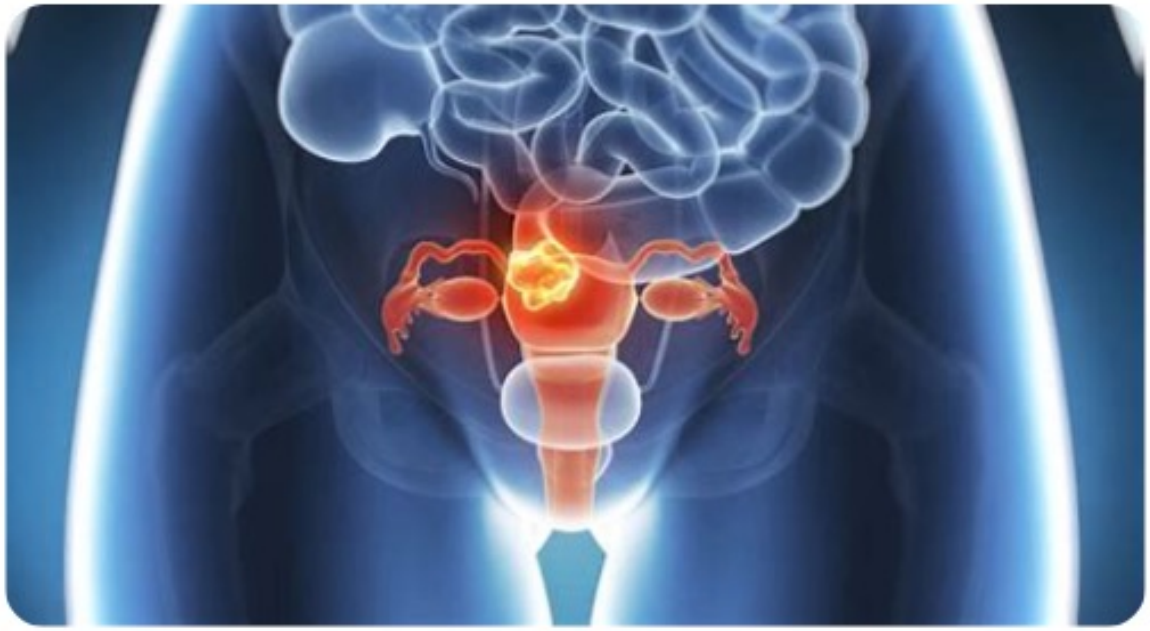
Antoine Lacassagne
CENTRE DE LUTTE CONTRE LE CANCER DE NICE

28 juin 2024
GYNAZUR

Nouvelles approches thérapeutiques dans les cancers gynécologiques

Philippe follana

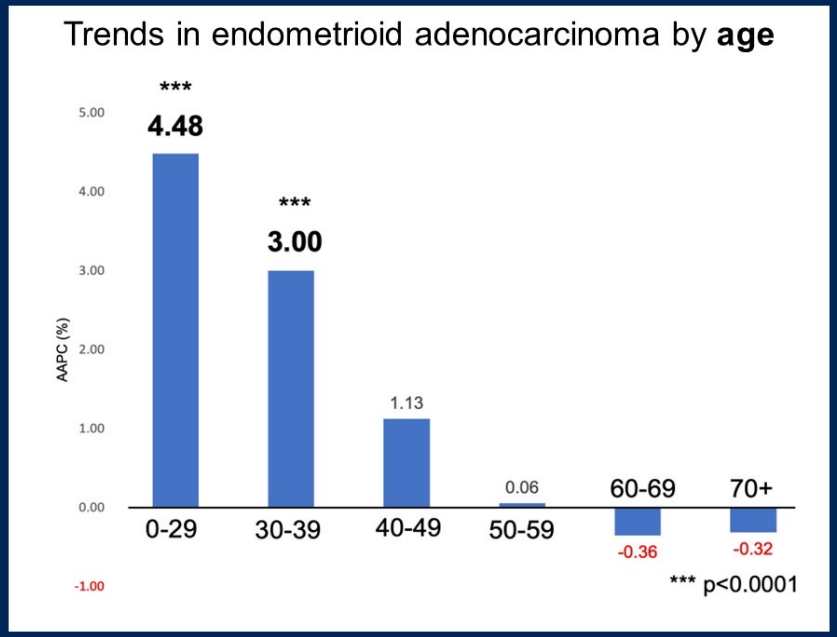
Cancer de l’endomètre



Evolution incidence US

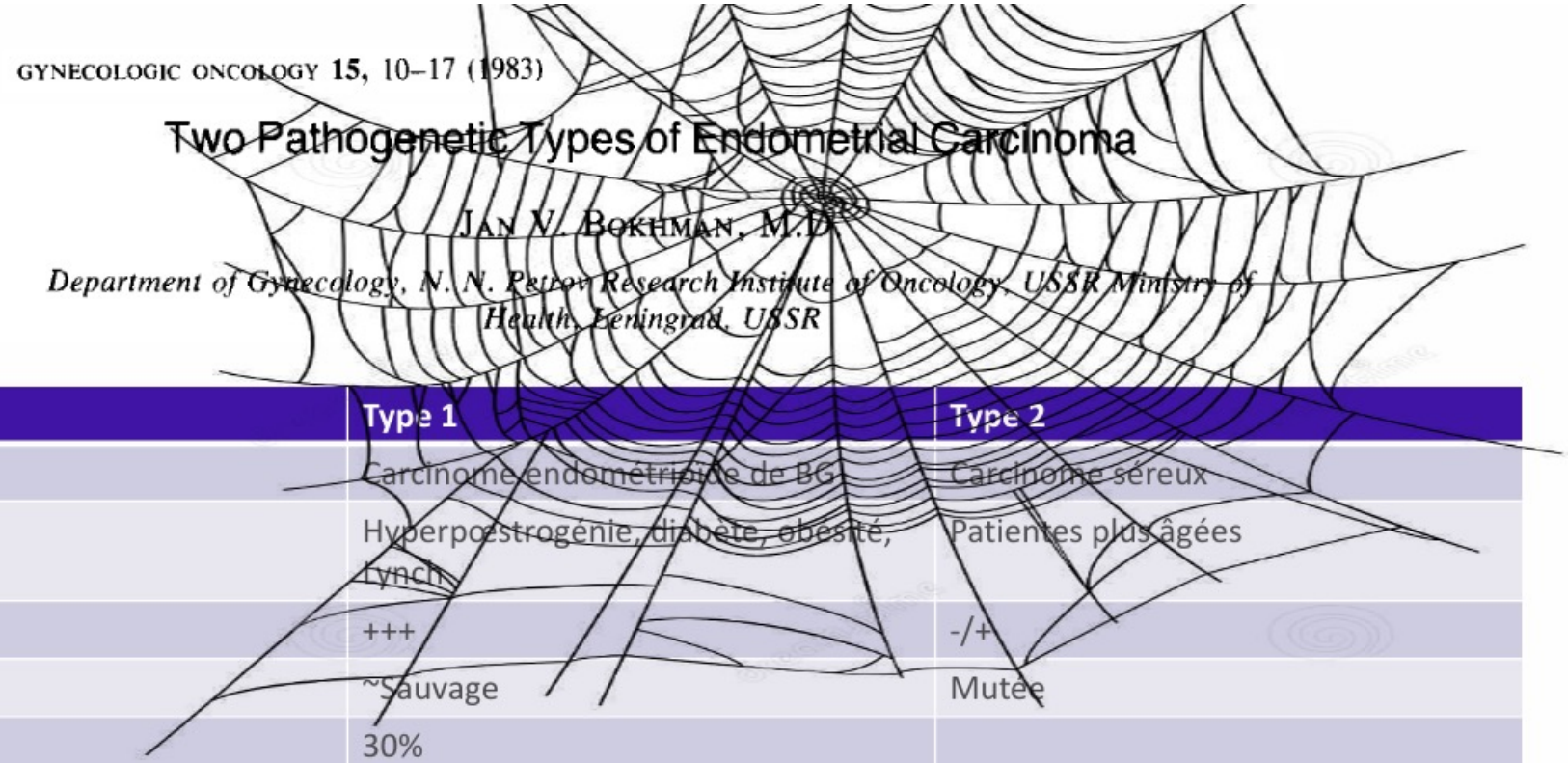
Results- Trends

- Rates are increasing in younger, reproductive age women
- **137.5%** increase in endometrioid adenocarcinoma in **0–29-year-old women** since 2001
- **71.8%** increase in **30–39-year-old women** since 2001



PRESENTED BY: Alex A. Francoeur MD

Type 1,type 2 le passé…



GYNECOLOGIC ONCOLOGY **15**, 10–17 (1983)

Two Pathogenetic Types of Endometrial Carcinoma

JAN V. BOKHMAN, M.D.

Department of Gynecology, N. N. Petrov Research Institute of Oncology, USSR Ministry of Health, Leningrad, USSR

	Type 1	Type 2
Modèle	Carcinome endométrioïde de BG	Carcinome séreux
Terrain	Hyperoestrogénie, diabète, obésité, Lynch	Patientes plus âgées
RO/RP	+++	-/+
P53	~Sauvage	Mutée
MSI	30%	
Pronostic	Bon	Mauvais

Bokhman JV et al., Gynecologic oncology 15, 10-17 (1983)

Nombreux types histologiques

- 75 % : Carcinome endométrioïde

→à grader !

- 10-15% : Carcinome séreux
- 5-10% : Carcinosarcome
- 10% : Types plus rares
  - Carcinome dédifférencié / indifférencié
  - Carcinome à cellules claires
  - Carcinome mésonéphrique-like
  - Carcinomes mixtes
  - Carcinome mucineux de type intestinal/gastrique

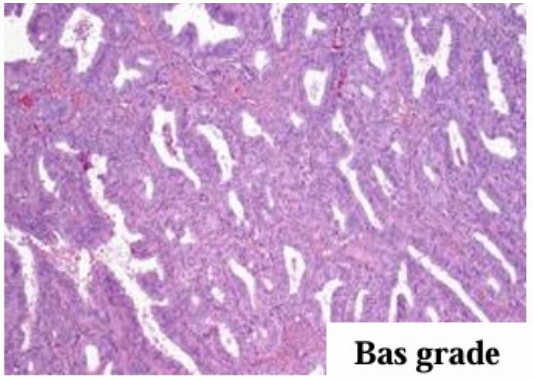
De haut grade par définition

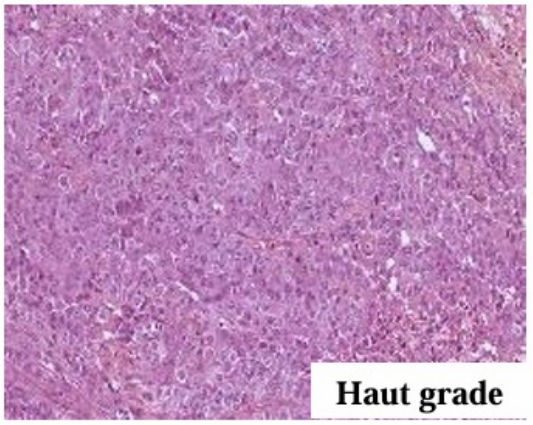
Grade

- Que pour les carcinomes endométrioïdes !
- Se base sur l'architecture solide
  - G1 : <5%
  - G2 : 5-50%
  - G3 : >50%
- Si atypies marquées et diffuses (>50% des cellules)
  - →augmenter le grade de 1 point

Bas grade
Grade 1
Grade 2

Haut grade
Grade 3

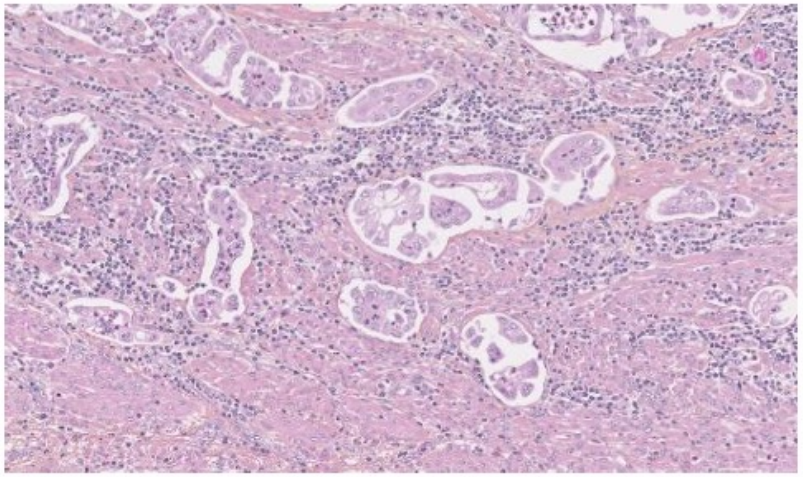


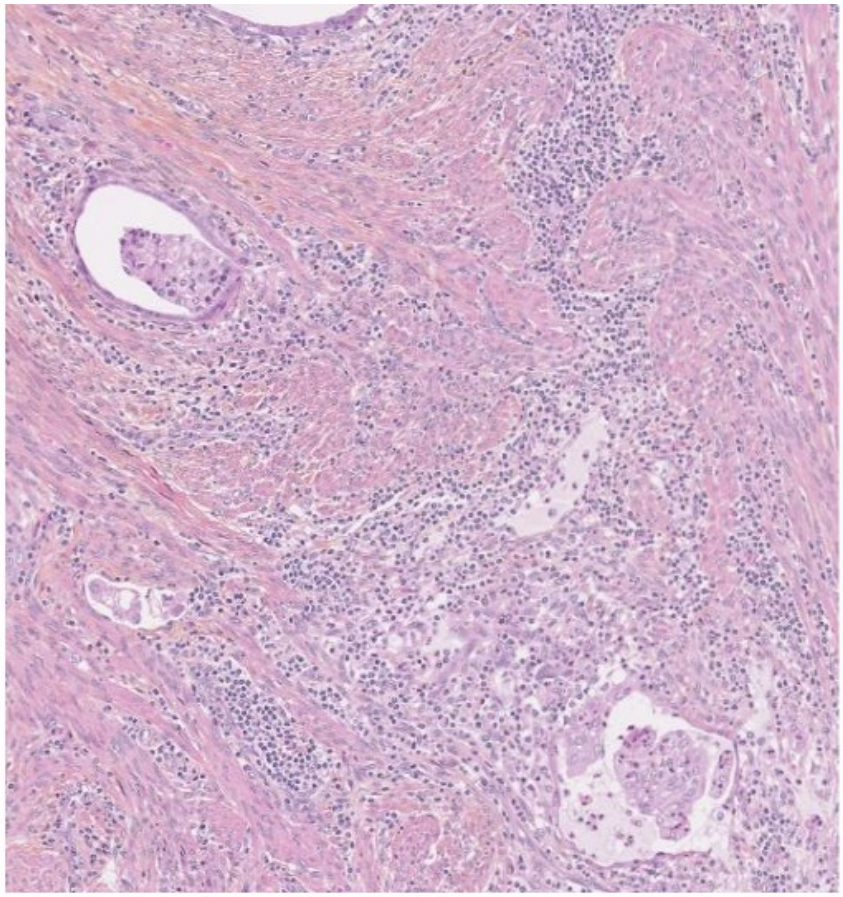


WHO classification of female genital tumours. IARC Press, 2020
Images : G. Bataillon

Embols

- **Variable pronostique indépendante**
- **Valeur pronostique <u>à partir de 5 emboles</u>**
  - **= emboles substantiels / significatifs**
- **Plus fréquents si :**
  - **Infiltration MELF**
  - **Statut dMMR / MSI**

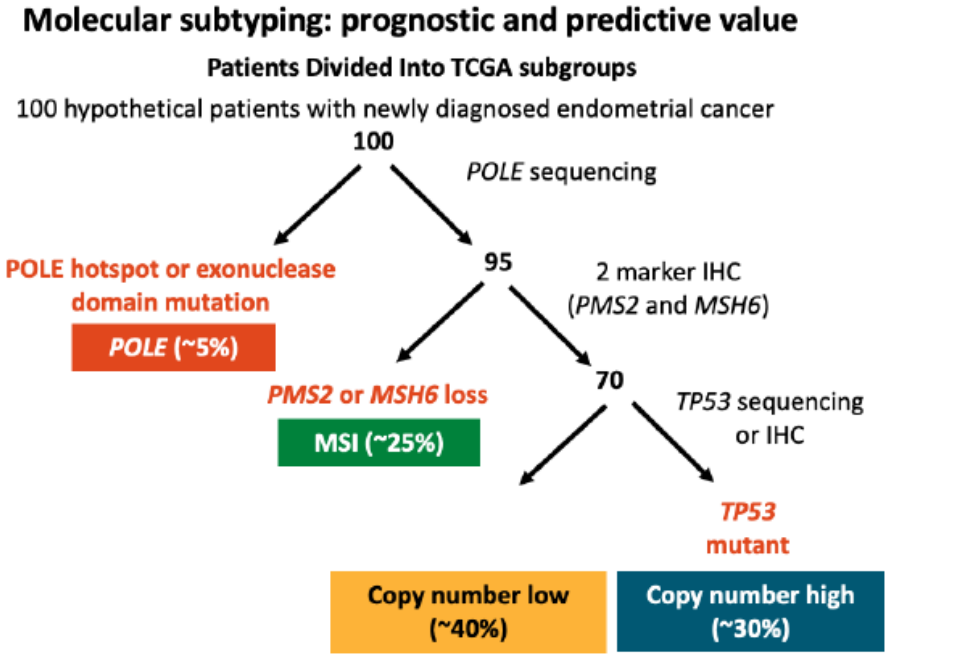




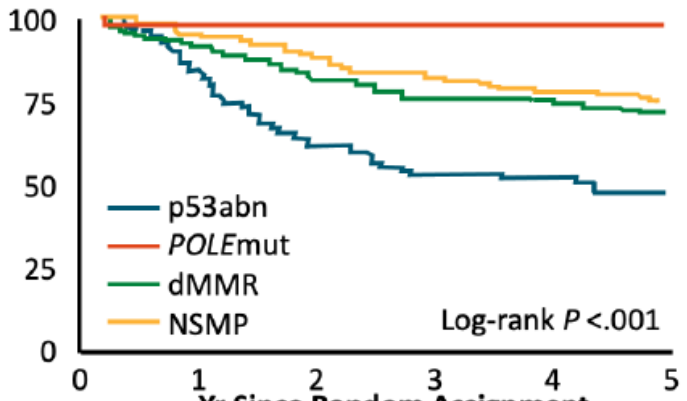
Stelloo, Clin Cancer Res, 2016 ; van den Heerik, Gynecol Oncol, 2022 ; Raffone, Gynecol Oncol 2022
WHO classification of female genital tumours. IARC Press, 2020,

Images : PA Just

2013: publication d'une classification moléculaire



- Prognostic value of molecular classification of high-risk endometrial cancer for benefit from chemotherapy
- 83% and 17% of endometrial cancer can be classified as endometrioid and non endometrioid, respectively



Patients at Risk, n						
p53abn	93	72	57	49	44	32
*POLE*mut	51	50	50	49	48	37
dMMR	137	124	112	102	96	74
NSMP	129	122	113	105	94	69

- 410 patients with successful molecular testing
  - 23% *p53*abn: *p53* abnormal
  - 12% *POLE*mut: *POLE* ultramutated
  - 33% dMMR: mismatch repair deficient
  - 32% NSMP: no specific molecular profile

TCGA network, Nature 497, 67–73 (2013); MacKay. Oncotarget. 2017;8:84579. León-Castillo. JCO. 2020;38:3388.

Nouvelle classification du risque

Groupes de risque ESGO/ESTRO/ESP

Table 2 Definition of prognostic risk groups

Risk group	Molecular classification unknown	Molecular classification known*†
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal	► Stage I–II ***POLEmut*** endometrial carcinoma, no residual disease ► Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	► Stage IB endometrioid + low-grade‡ + LVSI negative or focal ► Stage IA endometrioid + high-grade‡ + LVSI negative or focal ► Stage IA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion	► Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal ► Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade‡ + LVSI negative or focal ► Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High–intermediate	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II	► Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ► Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ► Stage II **MMRd/NSMP** endometrioid carcinoma
High	► Stage III–IVA with no residual disease ► Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	► Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ► Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ► Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	► Stage III–IVA with residual disease ► Stage IVB	► Stage III–IVA with residual disease of any molecular type ► Stage IVB of any molecular type

Concin et al, Int J Gynecol Cancer 2020

Nouvelle classification FIGO 2023

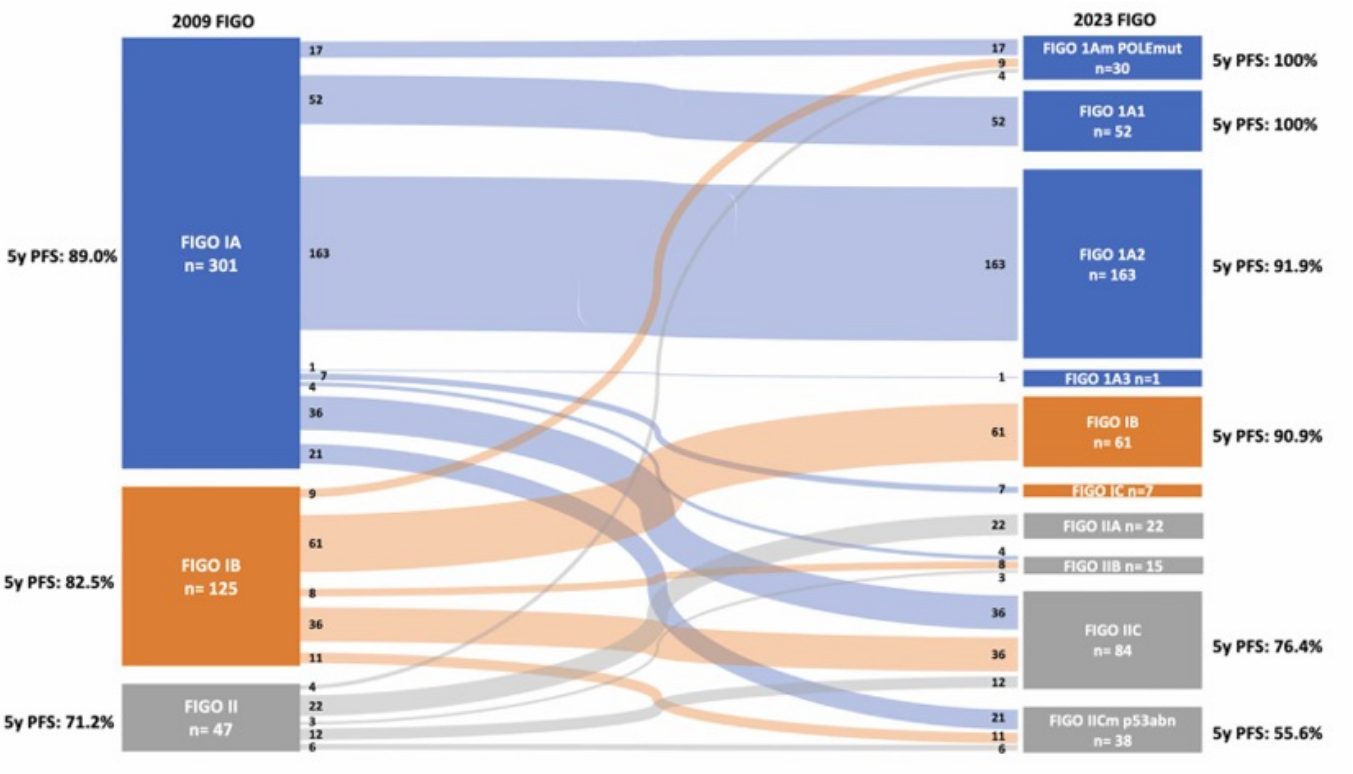
- **Groupes de risque ESGO/ESTRO/ESP**
- **Nouvelle classification FIGO 2023**
  - **Prend en compte :**
    - **Type histologique**
    - **Grade**
    - **Stade**
    - **Emboles**
    - **Et BM**

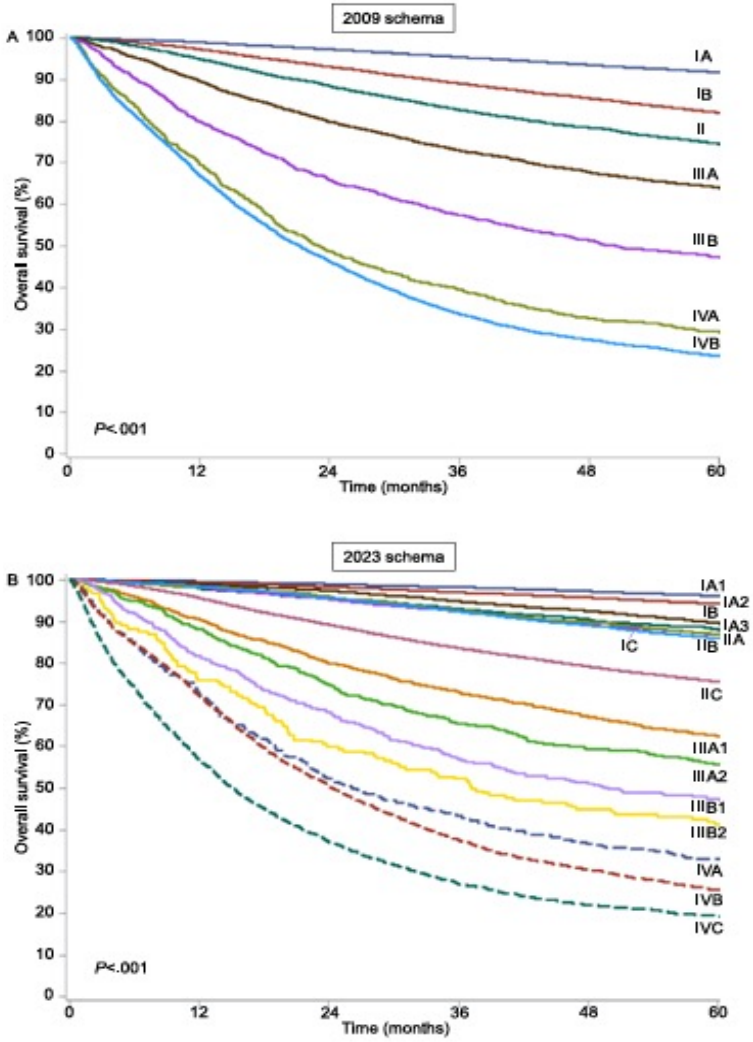
Stage	Description
Stage I	Confined to the uterine corpus and ovary[c]
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
	IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[c]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[d]
IC	Aggressive histological types[e] limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma with extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[d] of non-aggressive histological types
IIC	Aggressive histological types[e] with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c] IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[f]
	IIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIICii Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver,

Stage designation	Molecular findings in patients with early endometrial cancer (Stages I and II after surgical staging)
Stage $IAm_{POLEmut}$	*POLEmut* endometrial carcinoma, confined to the uterine corpus or with cervical extension, regardless of the degree of LVSI or histological type
Stage $IICm_{p53abn}$	p53abn endometrial carcinoma confined to the uterine corpus with any myometrial invasion, with or without cervical invasion, and regardless of the degree of LVSI or histological type

Berek, Int J Gynecol Obstet 2023

Pronostic nouvelle classification FIGO 2023



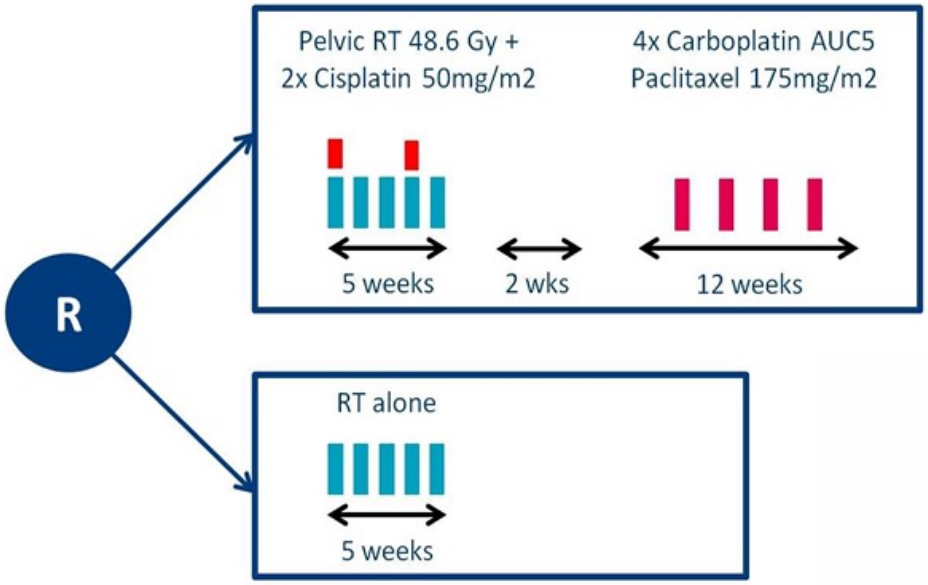


R. Schwameis et al. / European Journal of Cancer; K. Matsuo, L. Chen, M. Klar et al. Gynecologic Oncology

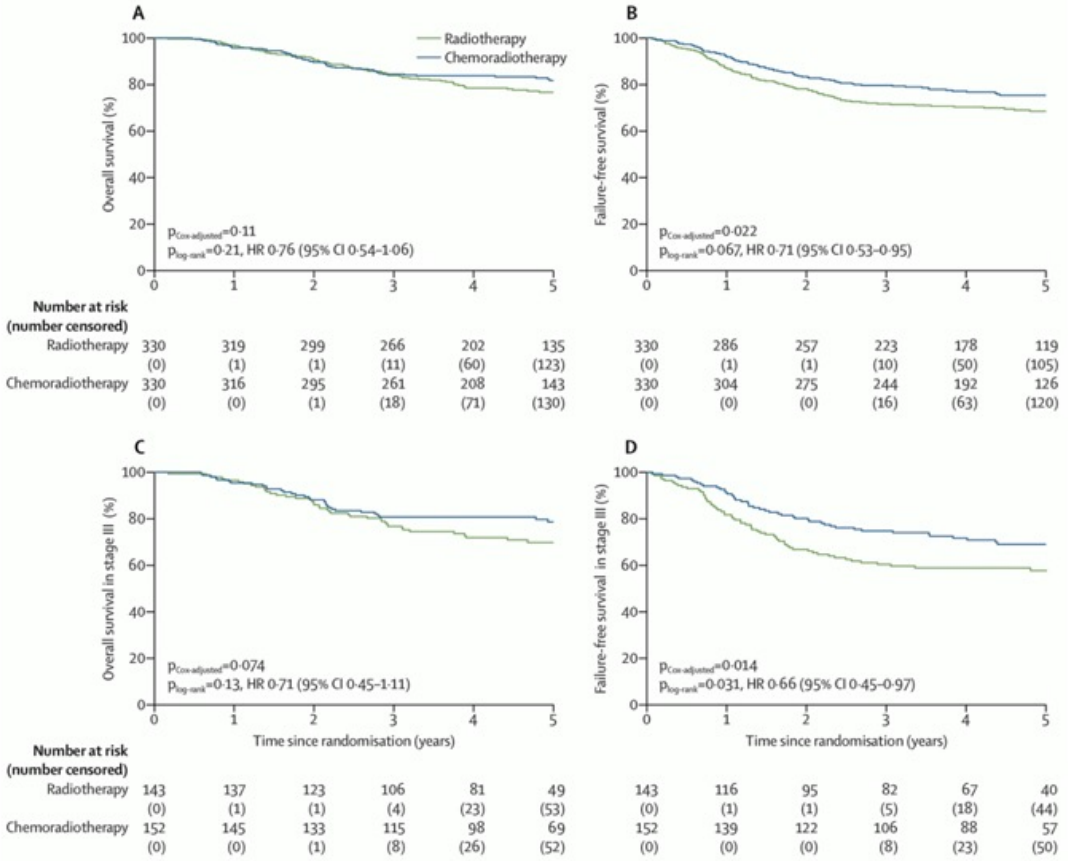
PORTEC-3 Trial Design and Results

High Risk:

- Stage I G3, Stage II-III
- Serous and clear cell



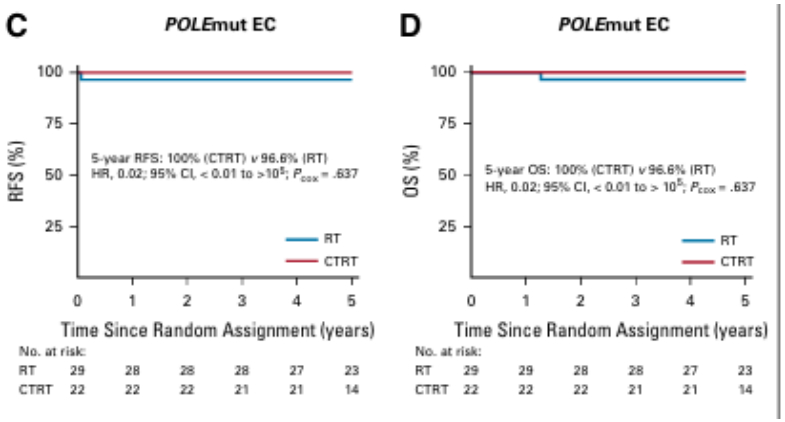
de Boer ASCO 2017



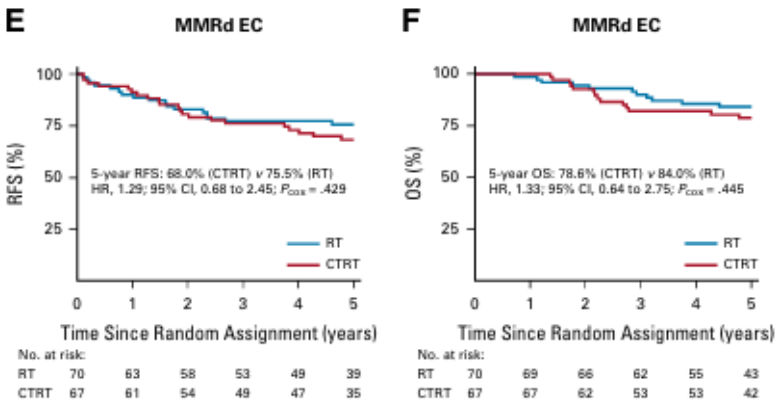
de Boer Lancet Oncol 2018

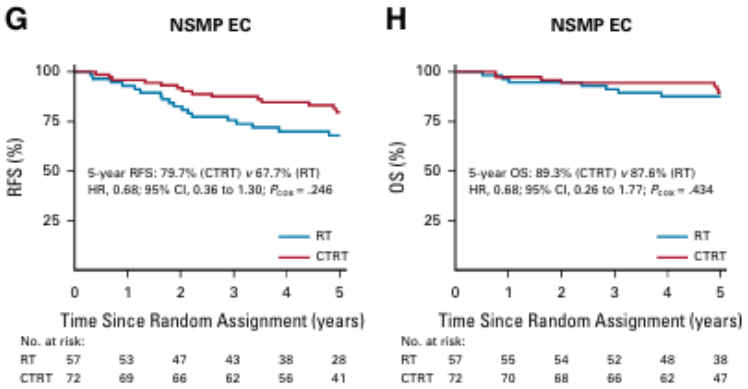
BARCELONA 2019 ESMO congress

PORTEC 3 Bénéfice Chimio selon classification moléculaire



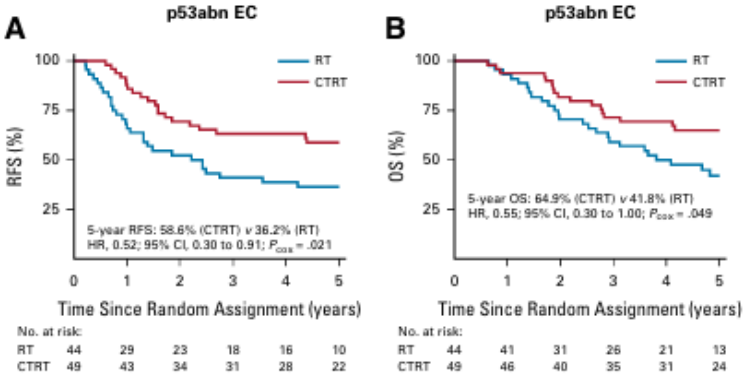
POLE m et MMRd: NON





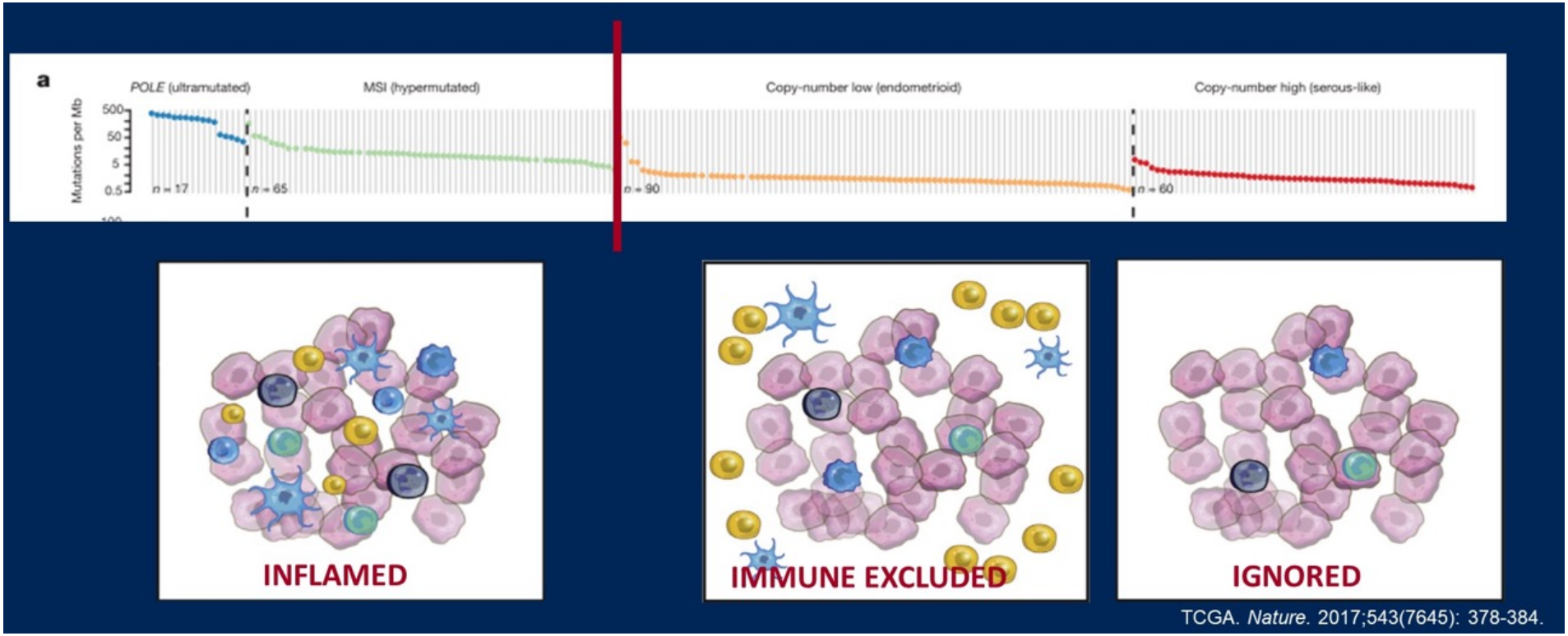
-NMSP: PEUT-ËTRE
(ht grade,RH - ?)

-p53abn: OUI

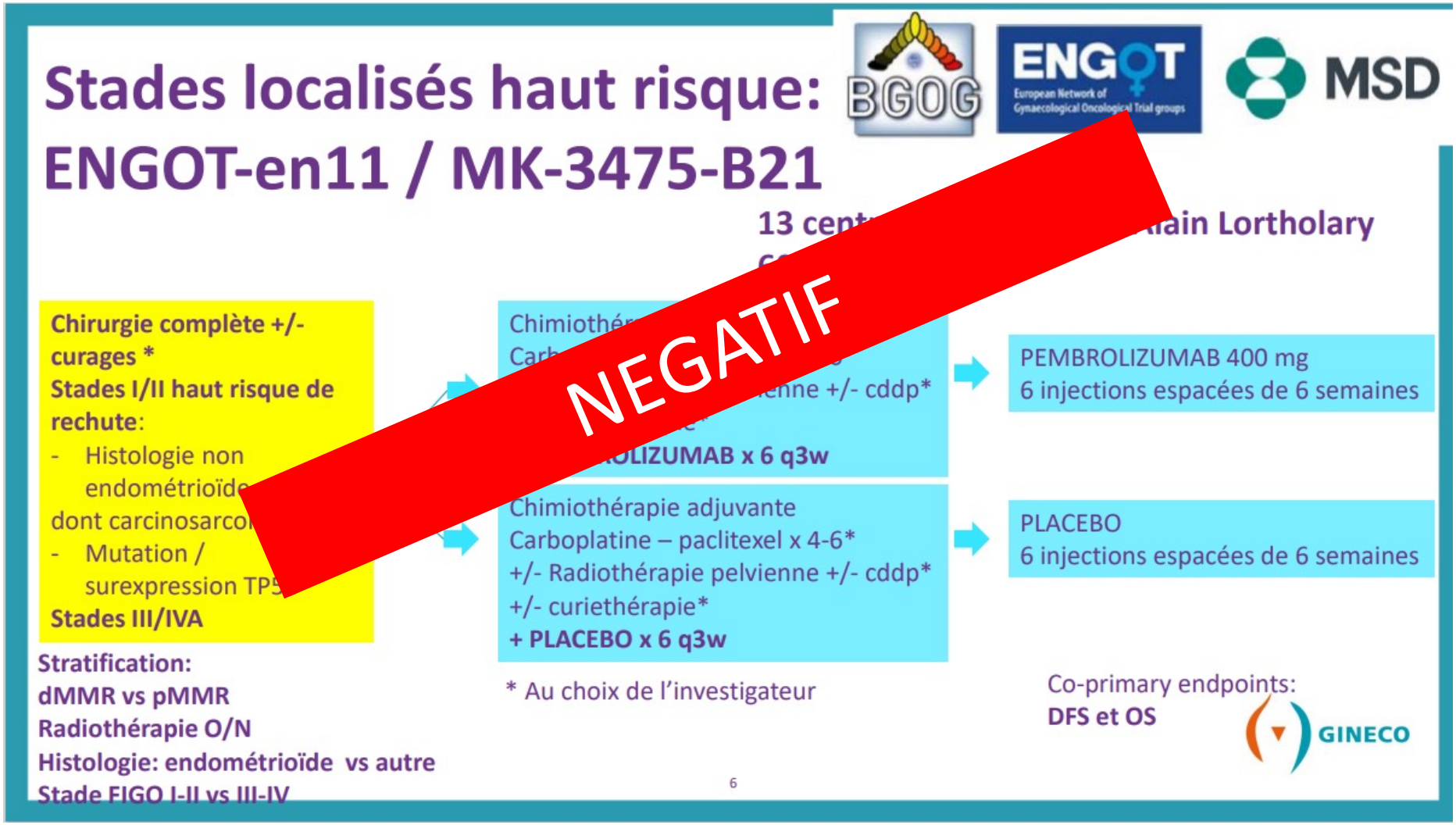


Leon-Castilloeta J Clin Oncol 38:3388-3397. 2020

Immunothérapie et classification moléculaire



K endomètre adjuvant: rajouter l'IO pour toutes



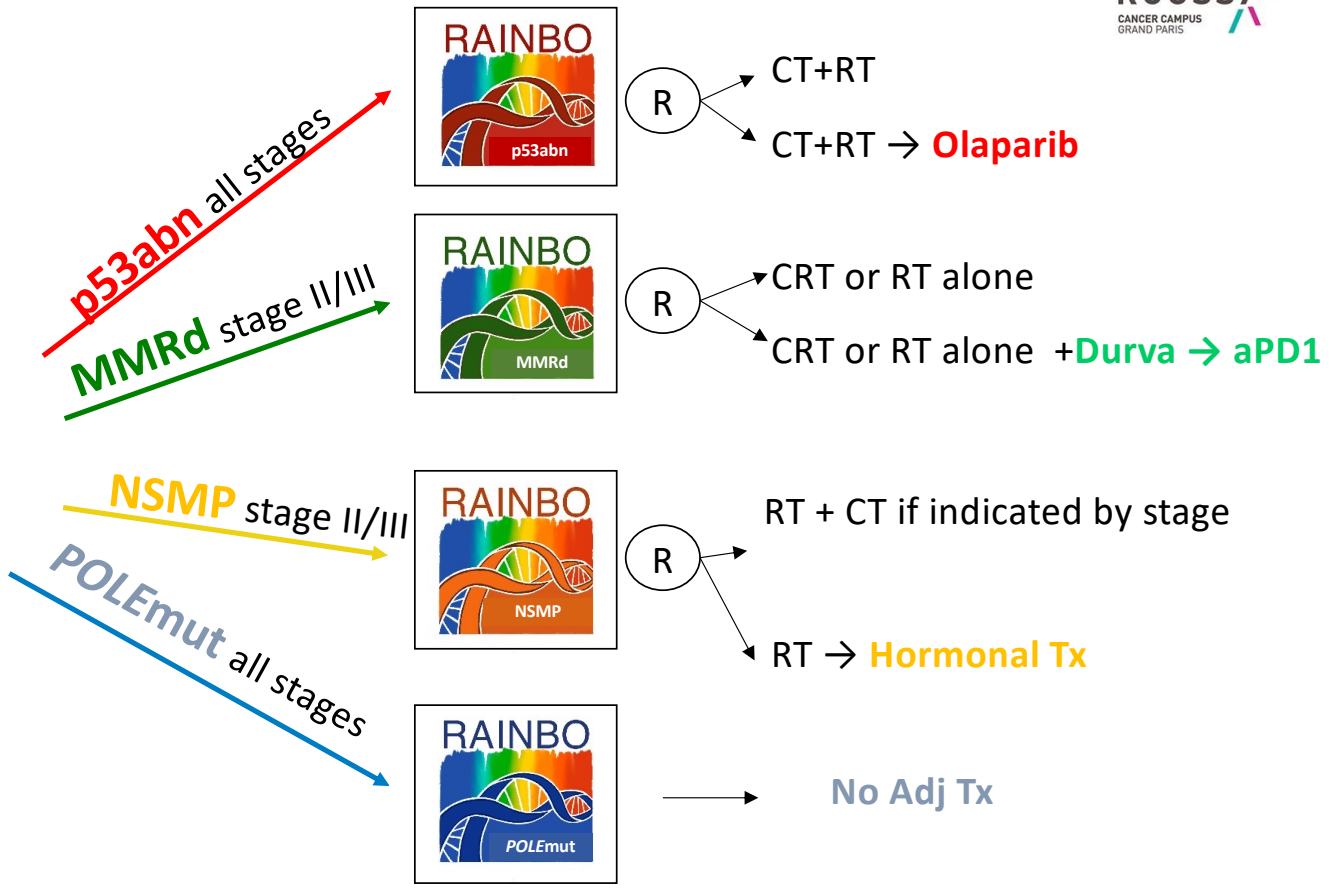
RAINBO: Refining Adjuvant treatment IN endometrial cancer Based On molecular profile

French sponsorship

Resected Endometrial Cancer
All histologic subtypes

Molecular Classification

(POLE mutation, MMR IHR, P53 IHC)
Molecular profile can be done locally or sent to French academic plateform

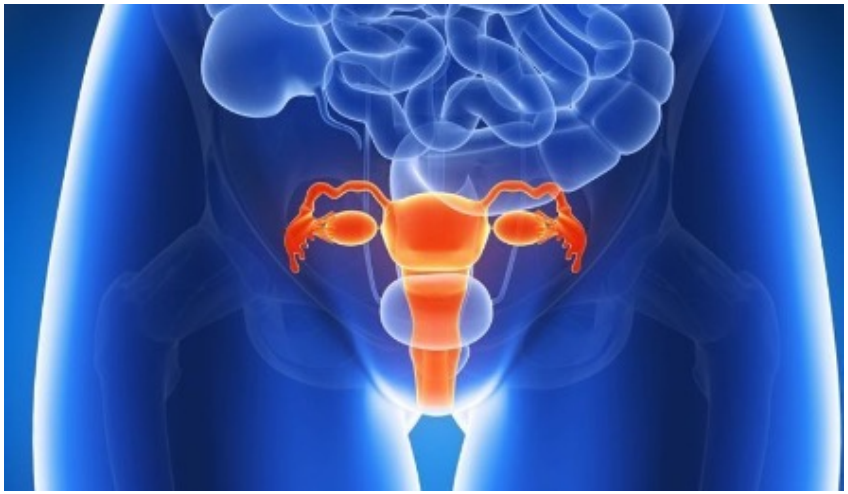


RAINBO umbrella program coordinated by *Trans*PORTEC consortium will allocate EC pts to 4 academic sub-trials each sponsored by one institute

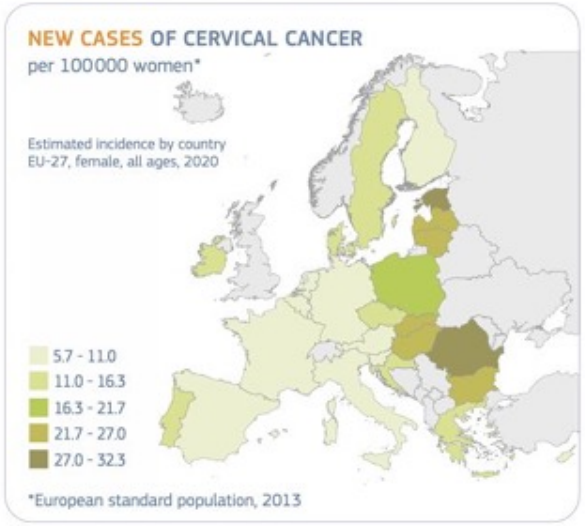
La prise en charge du K de l'endomètre se complexifie

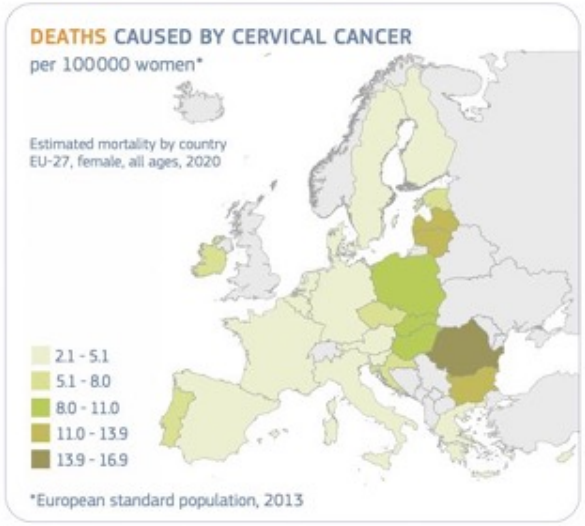
- Identique à la situation du K du sein au début des années 2000
- 4 grandes catégories de pronostic et de traitement potentiellement différent
- Les nouvelles classifications peuvent être appliquées dès maintenant
- Les essais modernes devront s'adresser à une population ciblée
- L'essai RAINBO recrute et permet dès maintenant une désescalade et/ou un traitement adapté

Cancer du col utérin



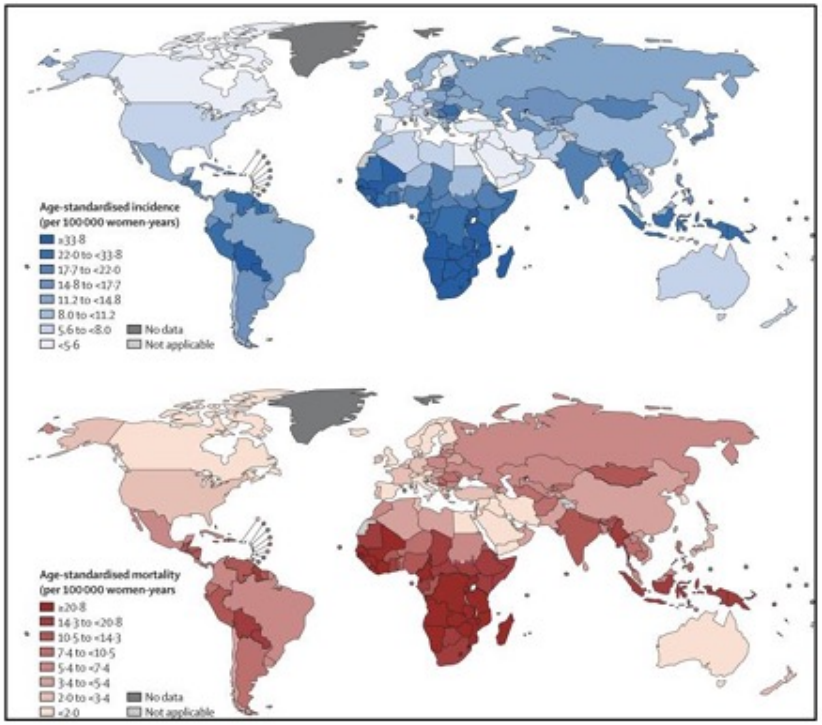
The Cervical Cancer Burden in EU-27





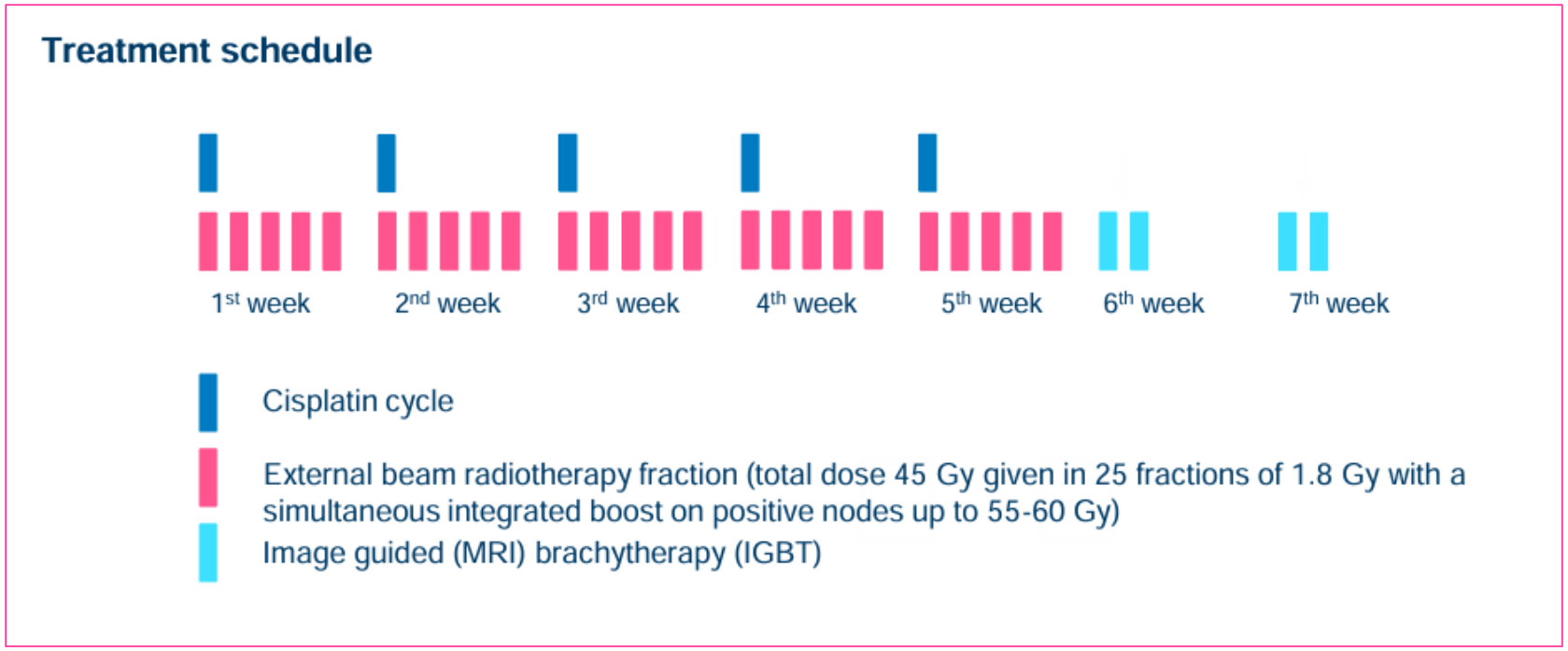
EU-27 2020
30,447 new cases
13,437 deaths

2020 Global Statistics
600,000 new cases
>300,000 deaths



Sung H, et al. CA Cancer J Clin 2021;71:209-49.

Traitement standard K col loc. avancé (IB3-IVa)



Survie sans maladie à 5 ans: 58-68%

-Beaucoup de patientes non guéries !

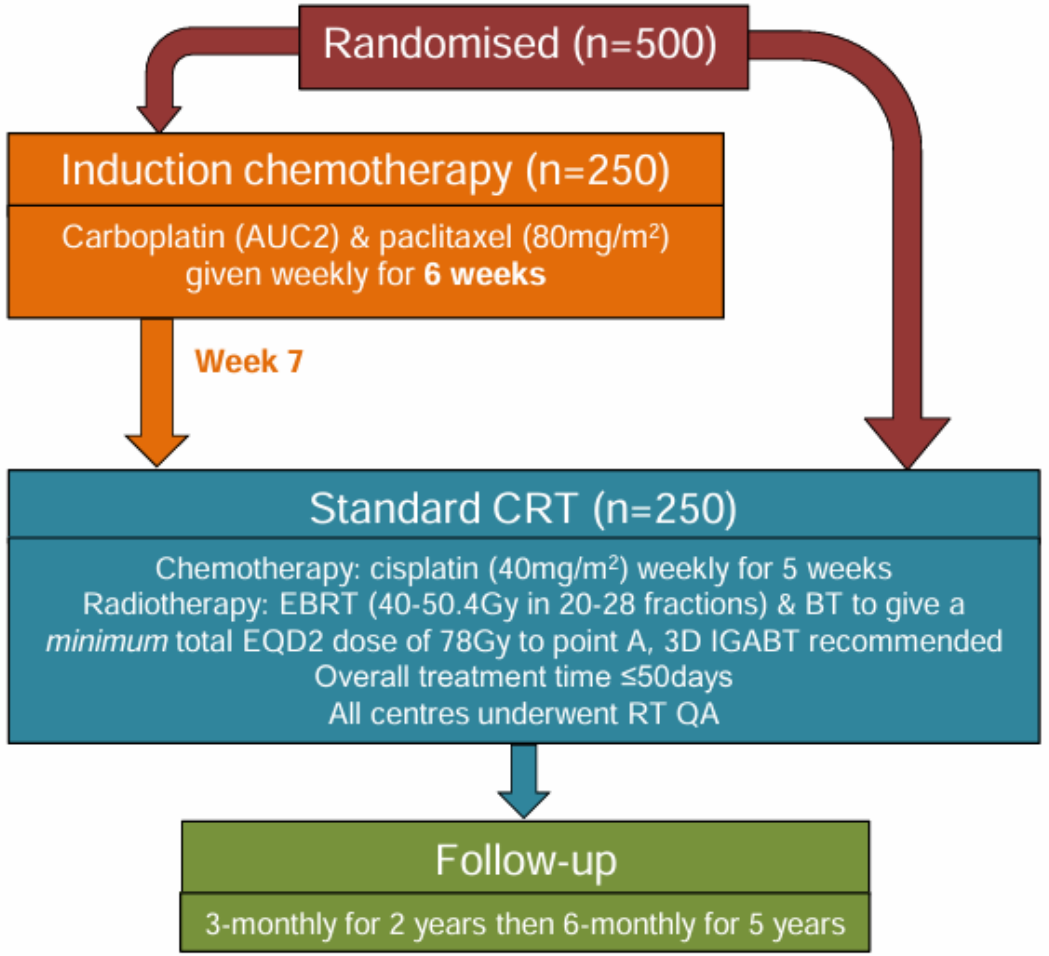
-Survenue de métastases à distance

INTERLACE Trial Design

Key eligibility criteria

- Newly diagnosed histologically confirmed FIGO (2008) stages IB1 node+,IB2, II, IIIB, IVA squamous, adeno, adenosquamous cervical cancer
- No nodes above aortic bifurcation on imaging
- Adequate renal, liver & bone marrow function
- Fit for chemotherapy & radical RT
- No prior pelvic RT

RT = Radiotherapy
3D-Conformal = 3D conformal radiotherapy
IMRT = Intensity modulated radiotherapy
EBRT = External beam radiotherapy
BT = Brachytherapy
IGABT = Image-guided adaptive brachytherapy
RT QA = Radiotherapy quality assurance



Stratified by

- Site
- Stage
- Nodal status
- 3D-Conformal v IMRT EBRT
- 2D v 3D BT
- Tumour size
- SCC v other

Primary endpoints

- PFS
- OS

Secondary endpoints

- Adverse events
- Pattern of relapse
- QOL
- Time to subsequent treatment

Mary McCormack

Demographics at Baseline

	CRT alone (n=250)	Induction Chemo + CRT (n=250)
Age, years median (range)	46 (24-78)	46 (26-78)
ECOG status	No. of patients (%)	
0	221 (88)	214 (86)
1	29 (12)	36 (14)
Country		
UK	190 (76)	190 (76)
Mexico	51 (20)	49 (20)
Italy	3 (1)	5 (2)
India	5 (2)	5 (2)
Brazil	1 (<1)	1 (<1)

Disease Characteristics at Baseline

	CRT alone (N=250)	Induction Chemo + CRT (N=250)
FIGO stage (2008)	**No. of patients (%)**	
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-squamous	45 (18)	44 (18)
Squamous	205 (82)	206 (82)
Nodal status		
Negative	142 (57)	146 (58)
Positive	108 (43)	104 (42)
Longest tumour diameter, cm median (range)	4.9 (1.8-12.8)	4.8 (1.3-13.5)

Adherence to Induction Chemotherapy

	Paclitaxel/Carboplatin (n=250) No. of patients (%)
Completed 6 weekly cycles	211 (84)
Completed at least 5 cycles	230 (92)
Main reasons for <6 cycles:	
Adverse events:	29 (11)
Haematological	9
Non-haematological	17
Both	3
Withdrawal/other	10 (4)
Median Interval from IC to RT days (range)	7 (5-53)

Adherence to Cisplatin

	CRT alone (n=250) No. of patients (%)	IC+ CRT (n=250) No. of patients (%)
Completed 5 weekly cycles	197 (79)	169 (68)
Completed at least 4 cycles	224 (90)	212 (85)
Main reasons for <5 cycles:		
Adverse events leading to discontinuation:	33 (13)	68 (27)
Haematological	4	34
Non-haematological	25	20
Both	4	14
Other	20 (8)	13 (5)

Adherence to Radiation

	CRT alone (n=250)	Induction Chemo + CRT (n=250)
	No. of patients (%)	
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)**

Adherence to Radiation

	CRT alone (n=250)	Induction Chemo + CRT (n=250)
	No. of patients (%)	
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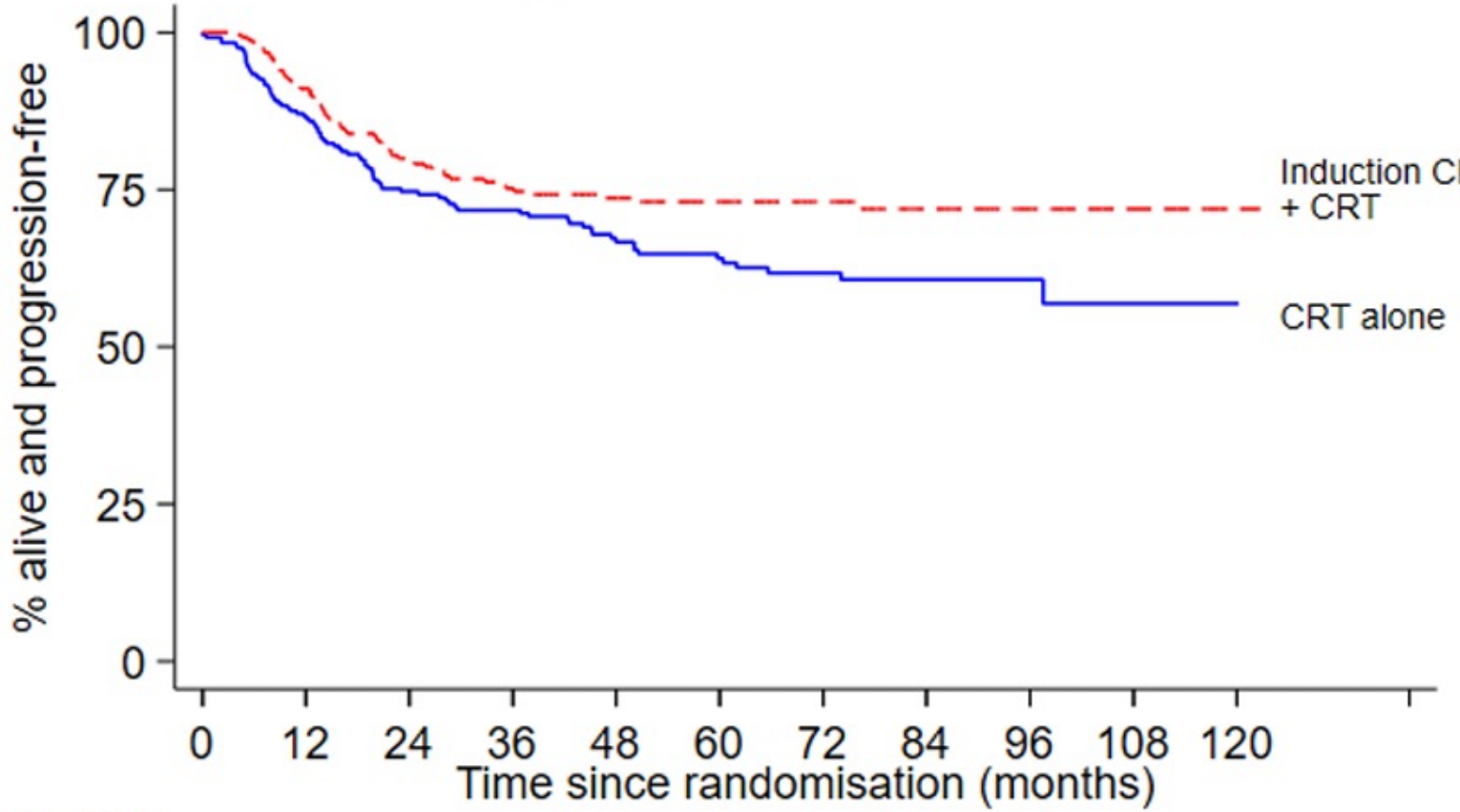
Median overall treatment time days(range)	**45 (37-88)**	**45 (36-70)**

INTERLACE Progression-Free Survival (median FU 64m)



146 PFS events
HR 0.65;95% CI:0.46 -0.91
P=0.013

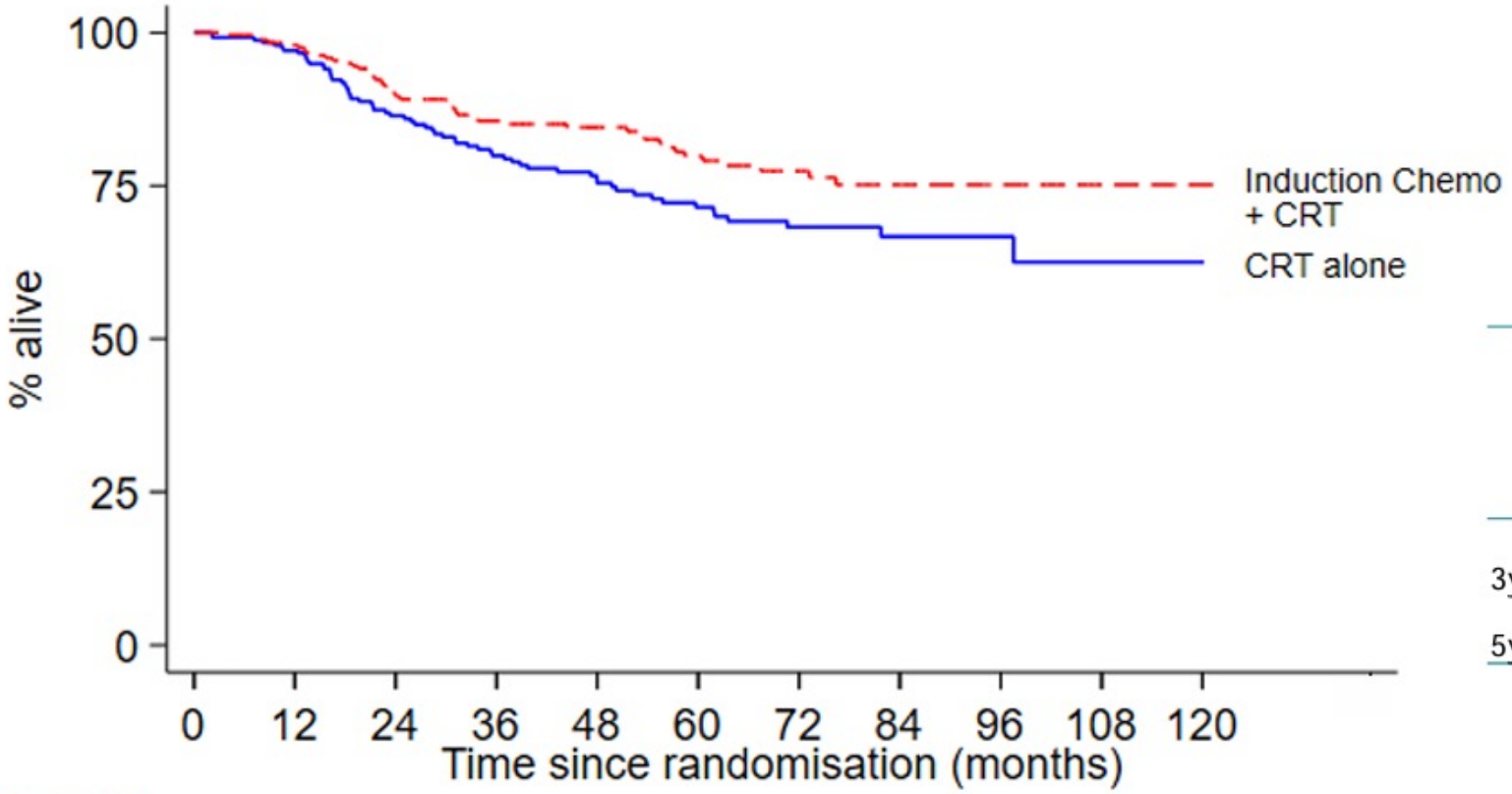
	Induction Chemo+ CRT (n=250)	CRT alone (n=250)
3yr PFS	75%	72%
5yr PFS	73%	64%

Number at risk											
CRT alone	250	204	157	140	110	88	63	36	16	5	1
Induction Chemo + CRT	250	220	178	152	132	105	72	40	19	8	1

MADRID 2023 ESMO congress

Mary McCormack

INTERLACE Overall Survival (median FU 64m)



109 deaths
HR 0.61;95% CI: 0.40-0.91
P=0.04

	Induction Chemo + CRT (n=250)	CRT alone (n=250)
3yr OS	86%	80%
5yr OS	80%	72%

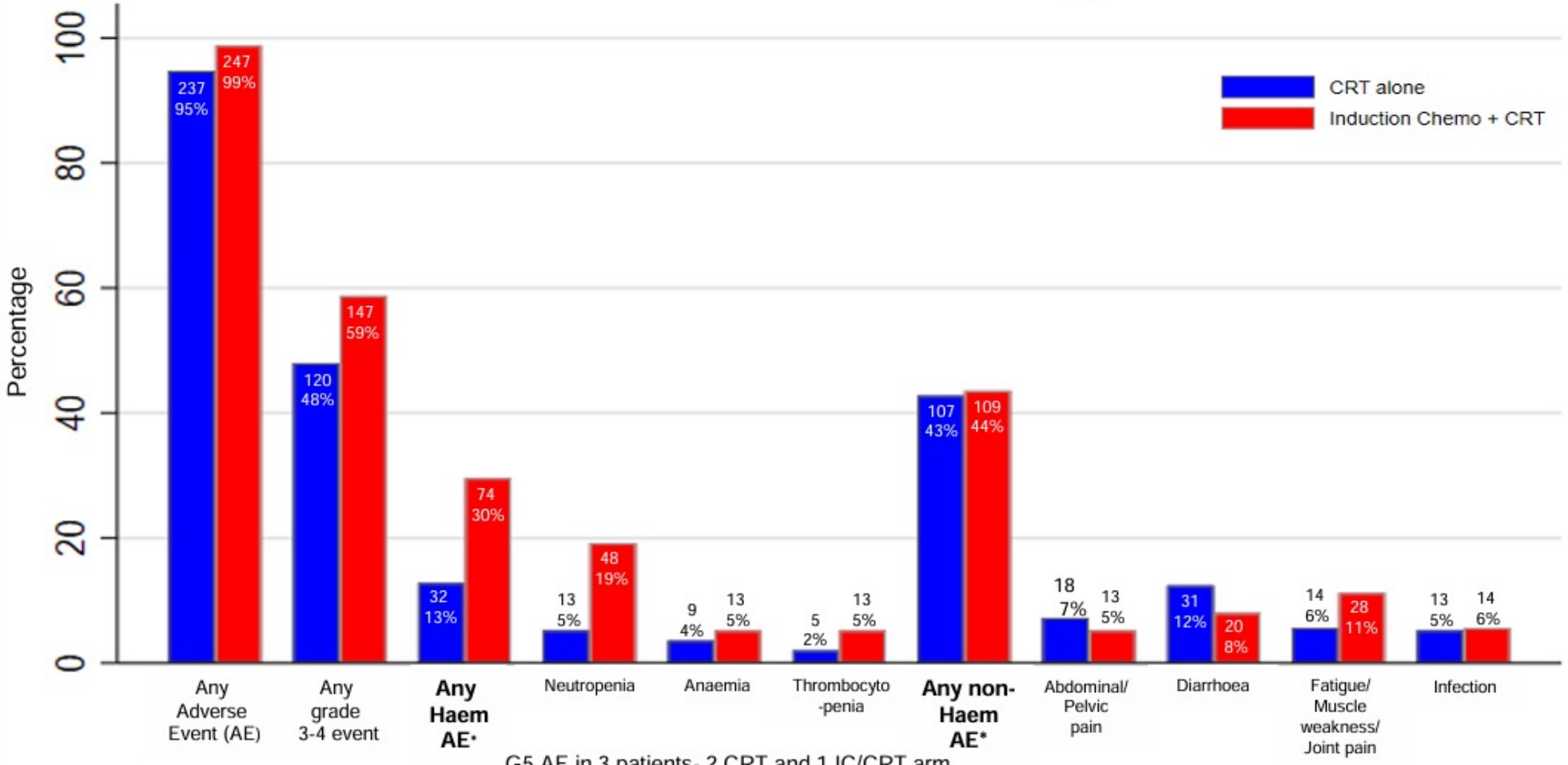
Number at risk

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

Patterns of Relapse

	CRT alone (n=250)	Induction Chemo + CRT (n=250)
	No. of patients (%)	
Local/pelvic	21 (8)	26 (10)
Local/pelvic & distant	20 (8)	14 (6)
Distant	30 (12)	16 (6)
Total local/pelvic relapses	41 (16)	40 (16)
Total distant relapses	50 (20)	30 (12)

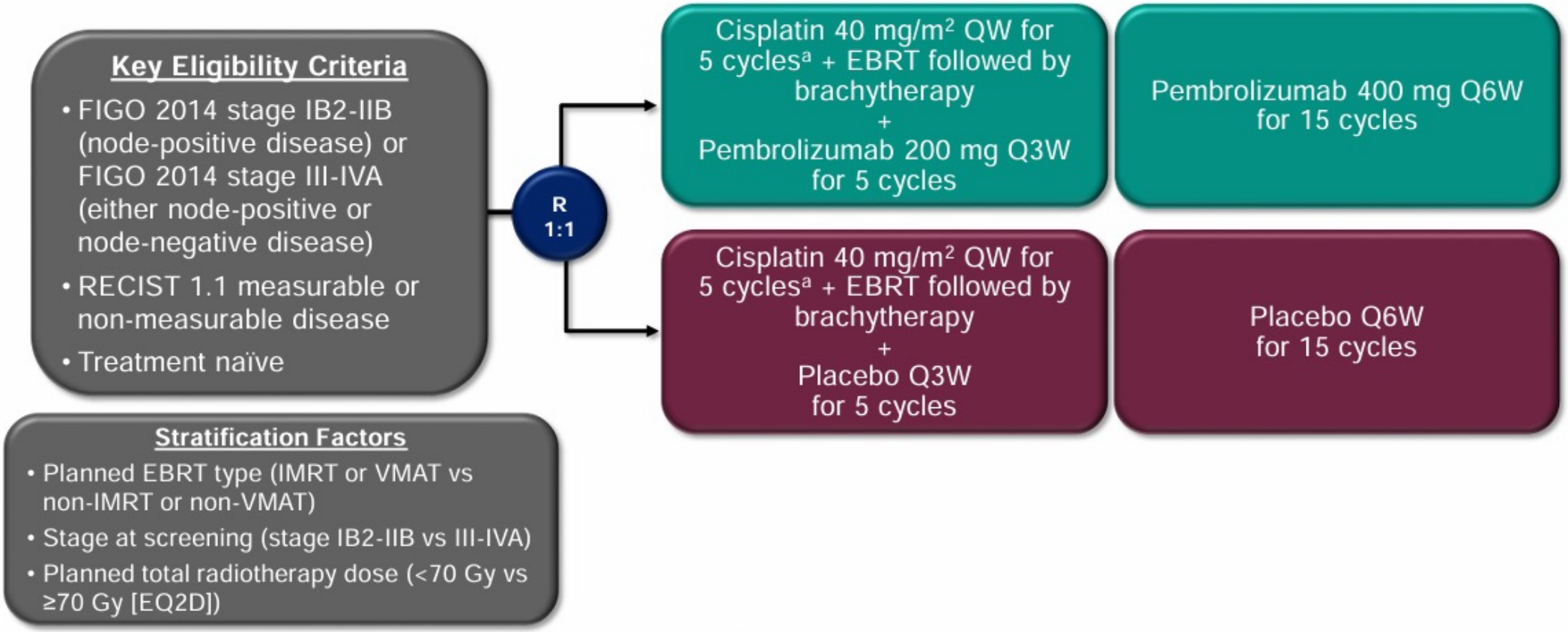
Adverse Events at any time



G5 AE in 3 patients- 2 CRT and 1 IC/CRT arm

*Grade 3-4 only . *106 people (42%) reported grade 2 alopecia in the IC/CRT*

ENGOT-cx11/GOG-3047/KEYNOTE-A18: Randomized, Double-Blind, Phase 3 Study



[a]A 6th cycle was allowed per investigator discretion. EBRT, external beam radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; Gy, grays; IMRT, intensity-modulated radiotherapy; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; VMAT, volumetric-modulated arc therapy. ENGOT-cx11/GOG-3047/KEYNOTE-A18 ClinicalTrials.gov identifier, NCT04221945.

Baseline Characteristics

	Pembro Arm (N = 529)	Placebo Arm (N = 531)
Age, median (range)	49 y (22-87)	50 y (22-78)
Race[a]		
White	254 (48.0%)	264 (49.7%)
Asian	155 (29.3%)	148 (27.9%)
Multiple	78 (14.7%)	86 (16.2%)
American Indian or Alaska Native	24 (4.5%)	22 (4.1%)
Black or African American	14 (2.6%)	8 (1.5%)
Native Hawaiian or Other Pacific Islander	2 (0.4%)	1 (0.2%)
PD-L1 CPS		
<1	22 (4.2%)	28 (5.3%)
≥1	502 (94.9%)	498 (93.8%)
Missing	5 (0.9%)	5 (0.9%)
ECOG PS 1	149 (28.2%)	134 (25.2%)
Squamous cell carcinoma	433 (81.9%)	451 (84.9%)

	Pembro Arm (N = 529)	Placebo Arm (N = 531)
Stage at screening (FIGO 2014 criteria)		
IB2-IIB	235 (44.4%)	227 (42.7%)
III-IVA	294 (55.6%)	304 (57.3%)
Lymph node involvement[b]		
Positive pelvic only	326 (61.6%)	324 (61.0%)
Positive para-aortic only	14 (2.6%)	10 (1.9%)
Positive pelvic and para-aortic	105 (19.8%)	104 (19.6%)
No positive pelvic or para-aortic	84 (15.9%)	93 (17.5%)
Planned type of EBRT		
IMRT or VMAT	469 (88.7%)	470 (88.5%)
Non-IMRT and non-VMAT	60 (11.3%)	61 (11.5%)
Planned total radiotherapy dose (EQD2)		
<70 Gy	47 (8.9)	46 (8.7)
≥70 Gy	482 (91.1)	485 (91.3)

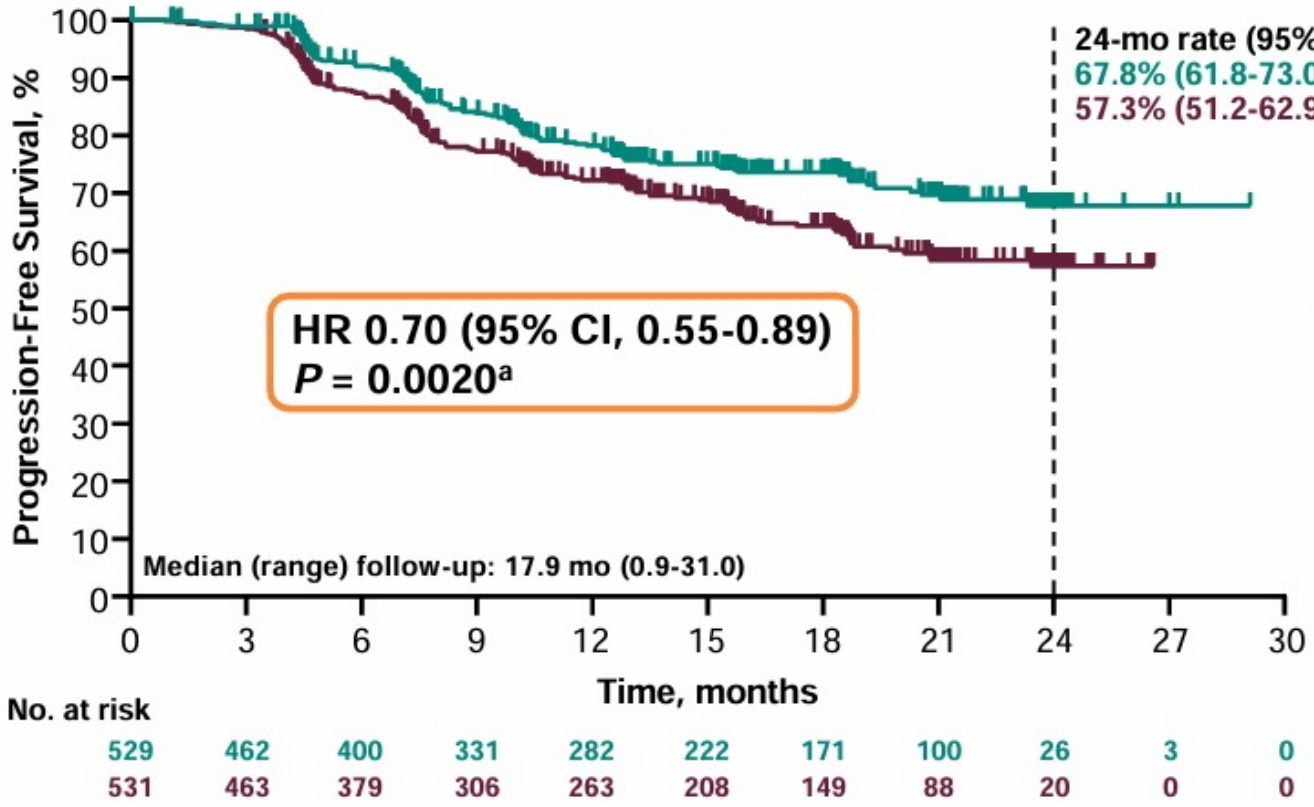
[a]In each treatment arm, 2 patients (0.4%) had missing information for race. [b]Per protocol, a positive lymph node is defined as ≥1.5 cm shortest dimension by MRI or CT. Data cutoff date: January 9, 2023.

Summary of Treatment Exposure

	Pembro Arm (N=528)	Placebo Arm (N=530)
Total number of cycles, median (range)		
Pembro or placebo	11 (1-20)	11 (1-20)
Cisplatin[a]	5 (1-7)	5 (1-7)
Radiation therapy, median (range)[a]		
Overall treatment time (days)	52 (12-139)	52 (2-166)
Within 50 days[b], n (%)	184 (35.5%)	194 (37.2%)
Within 56 days, n (%)	386 (74.5%)	390 (74.7%)
Cervix total dose (Gy), median (range)[a]		
Total cervix physical dose	76 (14-94)	76 (3-125)
Total cervix EQD2 dose	87 (14-118)	87 (3-207)

[a]Includes participants who completed concurrent chemoradiotherapy at this interim analysis and had final data review by the vendor (pembro arm N=518; placebo arm N=522). [b]Total radiation therapy (EBRT and brachytherapy) should not exceed 50 days, with extension to a maximum of 56 days for unforeseen delays, as per the study protocol. Data cutoff date: January 9, 2023.

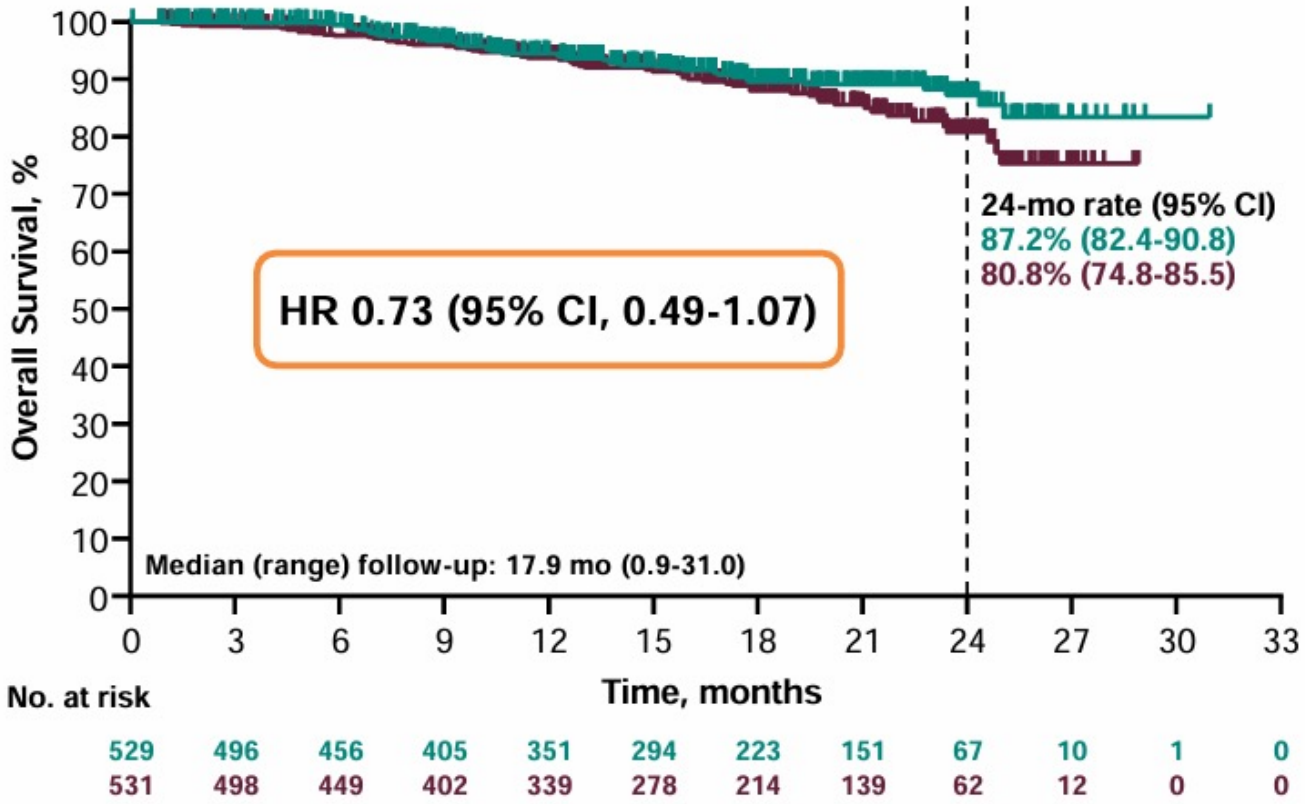
Primary Endpoint: Progression-Free Survival



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

Response assessed per RECIST v1.1 by investigator review or histopathologic confirmation. [a]With 269 events (88.5% information fraction), the observed *P* = 0.0020 (1-sided) crossed the prespecified nominal boundary of 0.0172 (1-sided) at this planned first interim analysis. The success criterion of the PFS hypothesis was met, and thus no formal testing of PFS will be performed at a later analysis. Data cutoff date: January 9, 2023.

Primary Endpoint: Overall Survival



	Pts w/ Event*	Median, mo (95% CI)
Pembro Arm	8.3%	NR (NR-NR)
Placebo Arm	11.1%	NR (NR-NR)

*42.9% information fraction[a]

[a]At this analysis, 103 of the 240 deaths expected at the final analysis had occurred.
Data cutoff date: January 9, 2023.

Adverse Events

	All-Cause AEs		Treatment-Related AEs[a]		Immune-Mediated AEs[b]	
	Pembro Arm (N = 528)	Placebo Arm (N = 530)	Pembro Arm (N = 528)	Placebo Arm (N = 530)	Pembro Arm (N = 528)	Placebo Arm (N = 530)
Any grade	525 (99.4%)	526 (99.2%)	507 (96.0%)	509 (96.0%)	172 (32.6%)	62 (11.7%)
Grade ≥3	394 (74.6%)	364 (68.7%)	354 (67.0%)	321 (60.6%)	22 (4.2%)	6 (1.1%)
Serious	150 (28.4%)	131 (24.7%)	91 (17.2%)	65 (12.3%)	15 (2.8%)	6 (1.1%)
Led to death	5 (0.9%)	6 (1.1%)	2 (0.4%)[c]	2 (0.4%)[d]	0	0
Led to discontinuation						
Any treatment	92 (17.4%)	75 (14.2%)	81 (15.3%)	67 (12.6%)	12 (2.3%)	2 (0.4%)
All treatment	1 (0.2%)	2 (0.4%)	0	1 (0.2%)	0	0

[a]Per investigator assessment. [b]Events were considered regardless of attribution to treatment by the investigator. [c]Immune-mediated gastritis and large intestine perforation. [d]Bone marrow failure and neutropenic colitis.
Data cutoff date: January 9, 2023.

En 2025 comment allons-nous choisir ?

- Selon le stade ?

Stades I/II: Chimiothérapie néoadjuvante

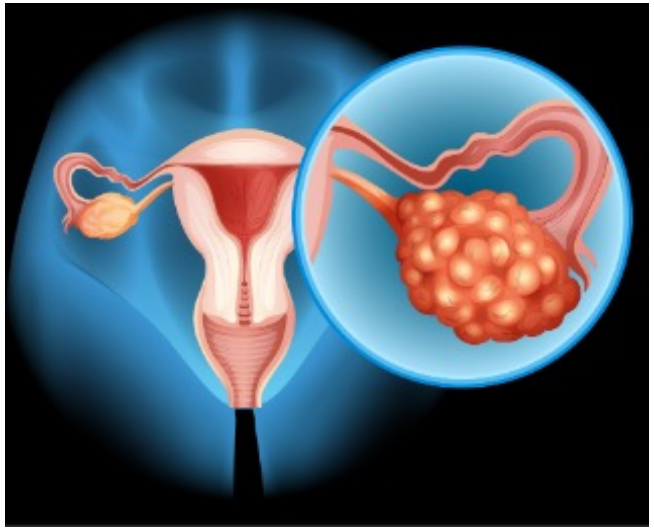
Stades III/IV: Immunothérapie

- Selon le coût ?

- Selon le type histologique ?

- Combiner les 2 attitudes ?

Cancer de l’ovaire



Place des curages cancer de l'ovaire stades III/IV

Avant 2018: curage systématique pelvien et lombo- aortique

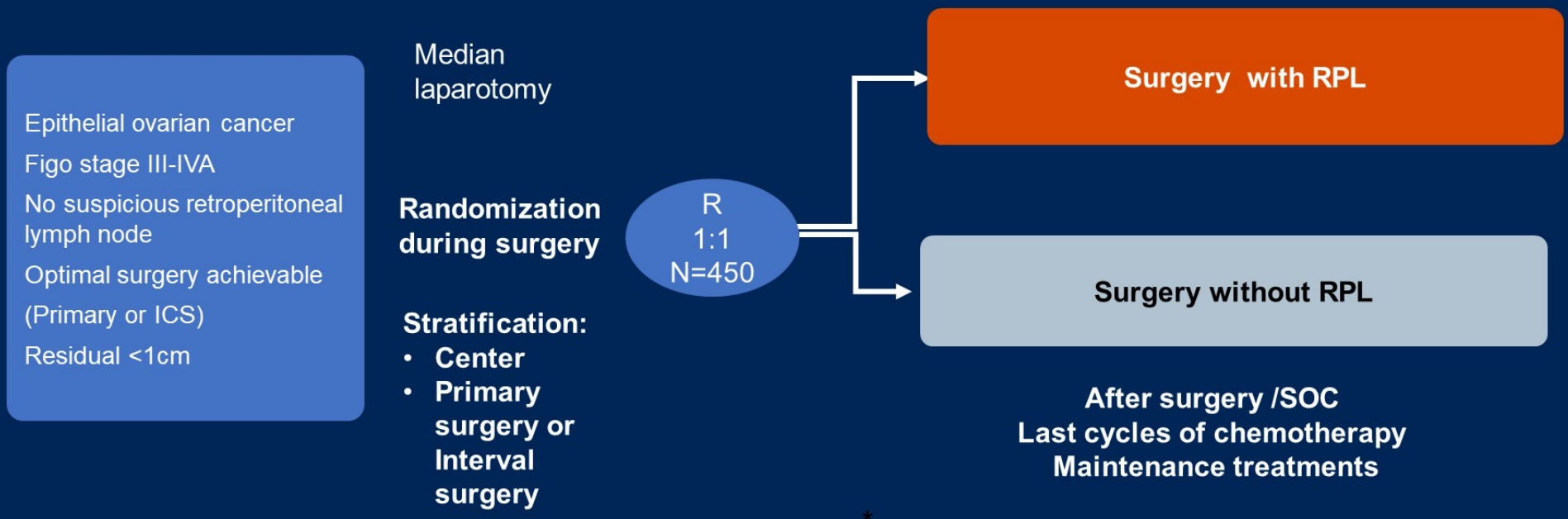
Recommandation

En Chirurgie première, s'il n'y a pas d'adénopathie suspecte à l'imagerie pré opératoire ou à la palpation per opératoire des aires ganglionnaires, il n'est pas recommandé de réaliser les curages ganglionnaires en routine

Nice St Paul de Vence

Harter et al, NEJM 2018

CARACO trial (NCT01218490): Multicenter randomized phase III trial



Keys: R: randomization, RPL: Retroperitoneal Lymphadenectomy, ICS: Interval Cytoreductive Surgery, SOC: Standard Of Care

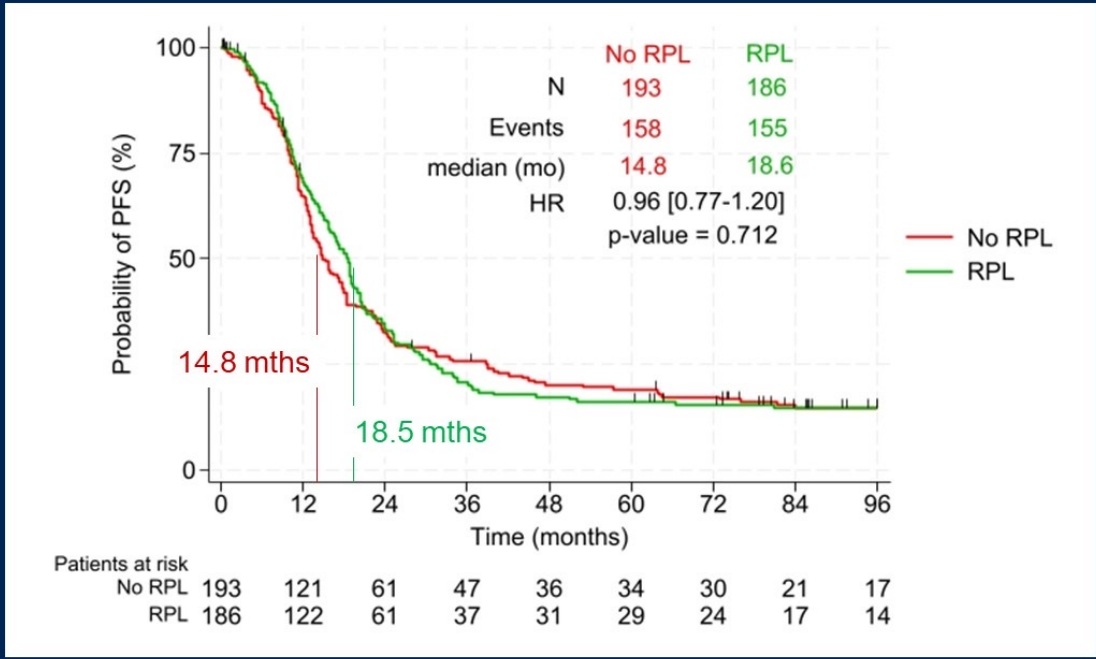
CARACO: Severe morbidity and mortality (within 30 days after surgery)*

No. of patients (%)	No RPL (n=193)	RPL (n=186)	p
Transfusion or blood loss	57 (29.7)	72 (39.3)	**P=0.049**
Re intervention	6 (3.1)	15 (8.3)	**P=0.031**
Urinary injury	0 (0.0)	7 (3.8)	**P=0.006**
Digestive fistula	2 (1.1)	4 (2.2)	NS
Phlebitis – Pulmonary embolism	7 (3.7)	3 (1.6)	NS
Mortality	1 (0.5)	2 (1.1)	NS

Key: RPL: Retroperitoneal Lymphadenectomy

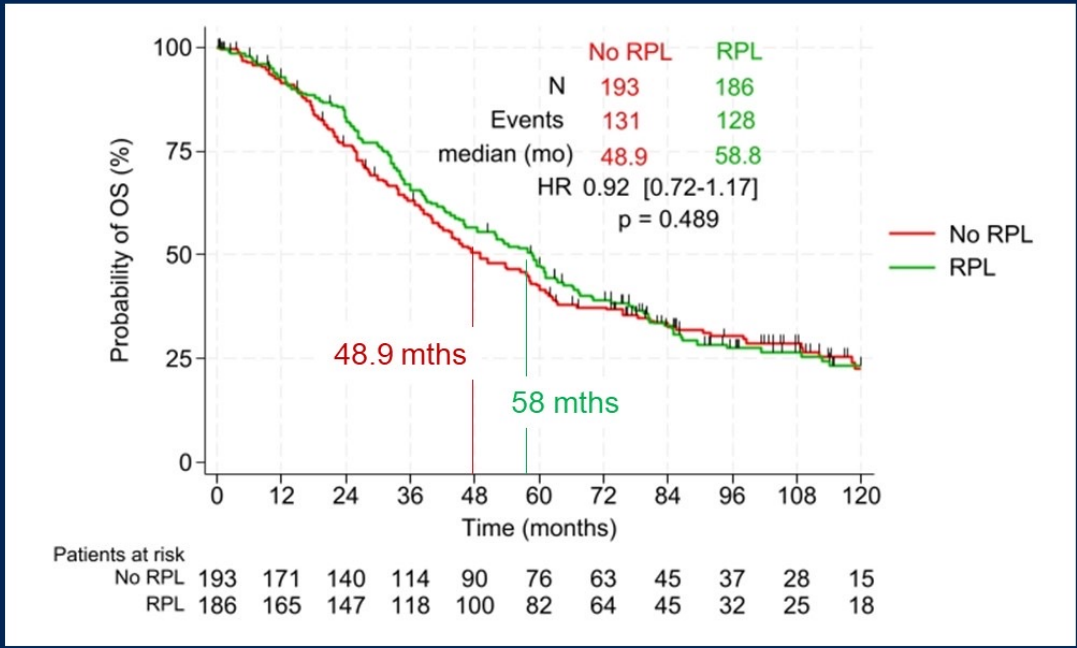
*** CTC-NCI version 3.0***

CARACO trial: Primary endpoint (PFS, ITT population)



Key: RPL: Retroperitoneal Lymphadenectomy

CARACO trial: OS (secondary endpoint, ITT population)



Key: RPL: Retroperitoneal Lymphadenectomy

Nice St Paul de Vence
RPC 2021

Place de la chirurgie à la rechute tardive

Pas de place hors essai au moment de la première récidive pour

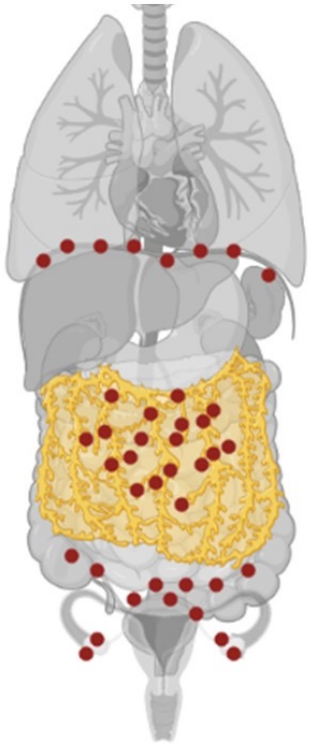
- La CHIP
- La PIPAC
- La Chimiothérapie Intra Péritonéale

Privilégier l'inclusion dans les essais

ARCAGY - GINECO

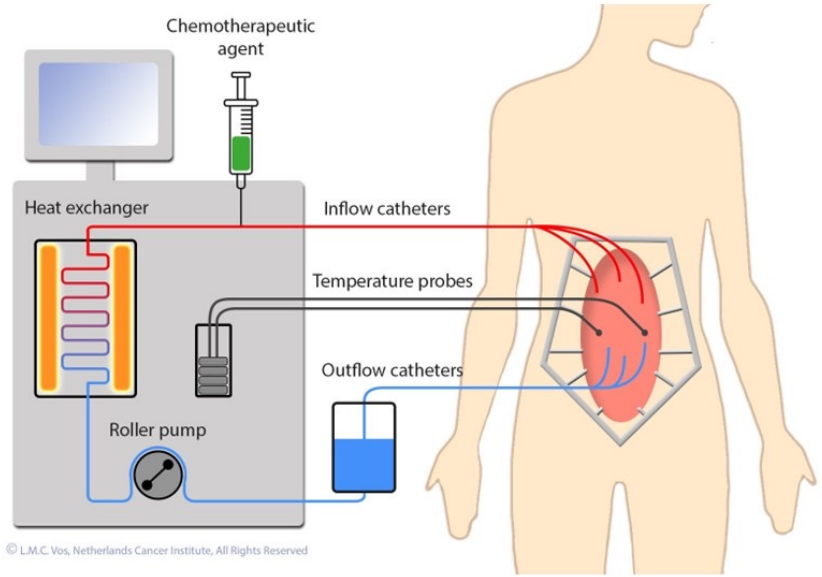
Rationale HIPEC

- High rate of peritoneal recurrence despite maximal cytoreductive surgery (CRS) and systemic therapy
- HIPEC targets microscopic residual disease on the peritoneal surface
- Hyperthermia is cytotoxic and synergizes with chemotherapy
- Single intra-operative perfusion with heated chemotherapy
- Increased local exposure with minimal systemic uptake

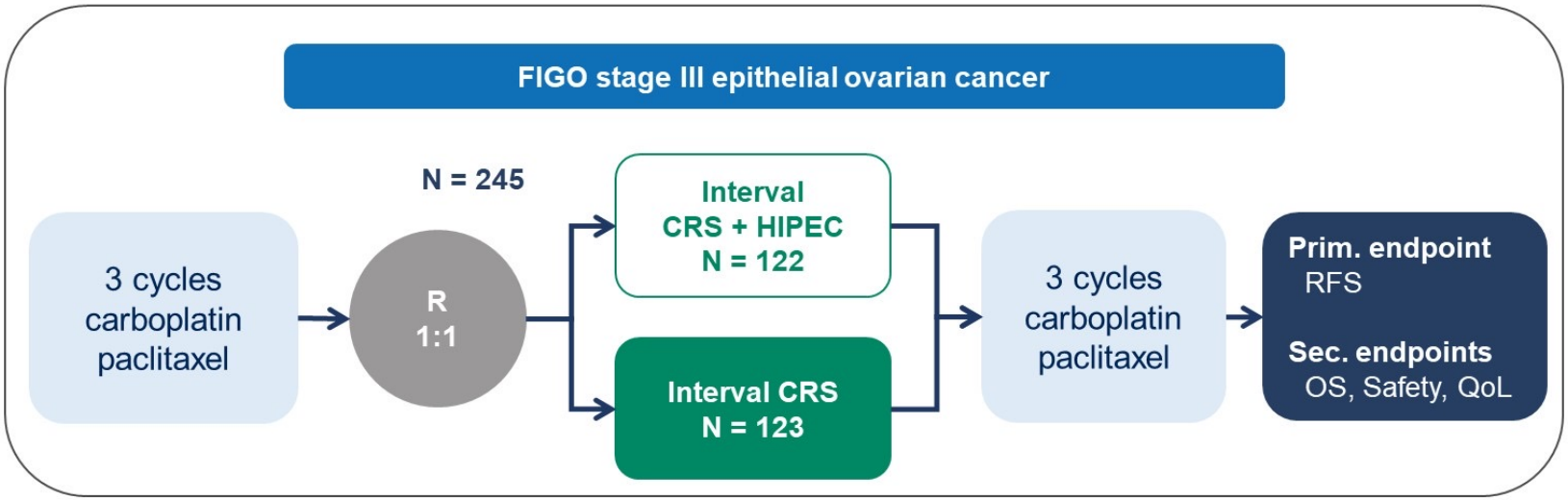


HIPEC procedure

- Open ‘colosseum’ technique
- Cisplatin 100 mg/m^2
  - 50% at the start
  - 25% after 30 min
  - 25% after 60 min
- Heated to 42°C, min flow of 1L/min
- Sodium thiosulfate for renal protection

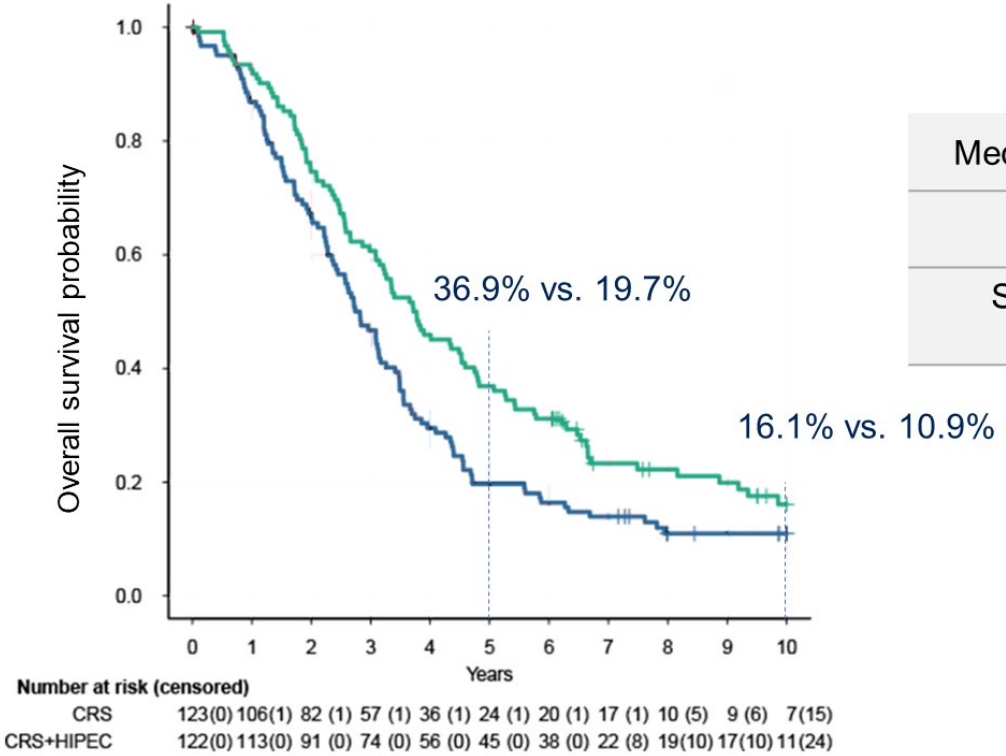


Study design



- Accrual between 2007-2016 in 8 centers in the Netherlands and Belgium
- Patients required neo-adjuvant chemotherapy due to extensive disease
- Follow-up visits every 3 months in year 1-2, every 6 months thereafter

OS after ten years of follow-up



	CRS-HIPEC	CRS
Median OS, mo	44.9	33.3
HR (95%CI)	**0.70 (0.53 – 0.92)**	
Stratified log-rank p	0.0113	

HIPEC improves long-term overall survival

CHIPOR trial (NCT01376752): Multicenter randomized phase III trial

unicancer

- First relapse of epithelial ovarian cancer
- PFI ≥6 months
- Response to 6 cycles of platinum-based chemotherapy
- Complete surgery achievable

N=415

Median laparotomy
Complete resection

SURGERY

CC0/1

Randomization during surgery

R 1:1

HIPEC
(cisplatin 75 mg/m^2 41°C for 60 min)
n=207

No HIPEC
n=208

SOC maintenance therapy

Stratification:
- **Center**
- **Residual disease (none vs <0.25 cm)**
- **PFI (6–12 vs >12–18 vs >18 months)**
- **Planned PARP inhibitor (yes vs no)[a]**

[a]Added Oct 8, 2020

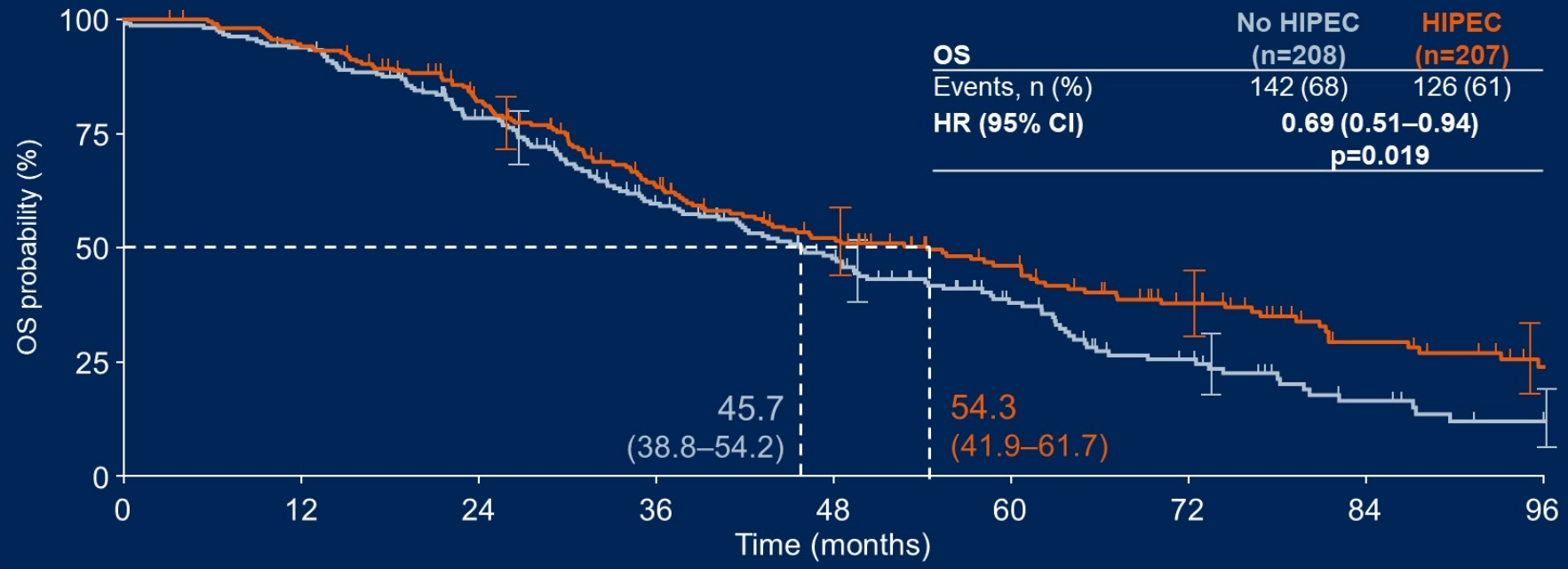
CC0 = no macroscopic residual; CC1 = residual <0.25 cm; PFI = platinum-free interval; SOC = standard of care

CHIPOR trial: Kidney failure

No. of patients (%)	No HIPEC (n=208)	HIPEC (n=207)
Severe kidney failure	3 (1.4%)	21 (10%)
Before thiosulfate amendment[a]	1/154 (0.7%)	19/156 (12%)
After thiosulfate amendment[a]	2/54 (3.7%)	2/51 (3.9%)

[a]Thiosulfate amendment, June 2018

CHIPOR trial: Primary endpoint (OS, ITT population)



OS	No HIPEC (n=208)	HIPEC (n=207)
Events, n (%)	142 (68)	126 (61)
HR (95% CI)	**0.69 (0.51–0.94)**	
	p=0.019	

No. at risk									
HIPEC	207	193	158	113	87	65	44	25	15
No HIPEC	208	194	150	106	75	48	27	13	7

Chirurgie du cancer de l'ovaire

- En chirurgie première ou d'intervalle en l'absence d'adénopathie suspecte au bilan pré-opératoire et à l'exploration per-opératoire il n'est pas recommandé de réaliser des curages.

- La CHIP est une option en chirurgie d'intervalle ou de la rechute en améliorant la survie et réduisant le risque de rechute péritonéale.

- Des essais de confirmation avec les traitements d'entretien modernes et en chirurgie première sont en cours.