Cancer gynécologique post ASCO 2024

Date de la réunion

Lieu de la réunion

Pr ELISE DELUCHE

Oncologie médicale CHU LIMOGES

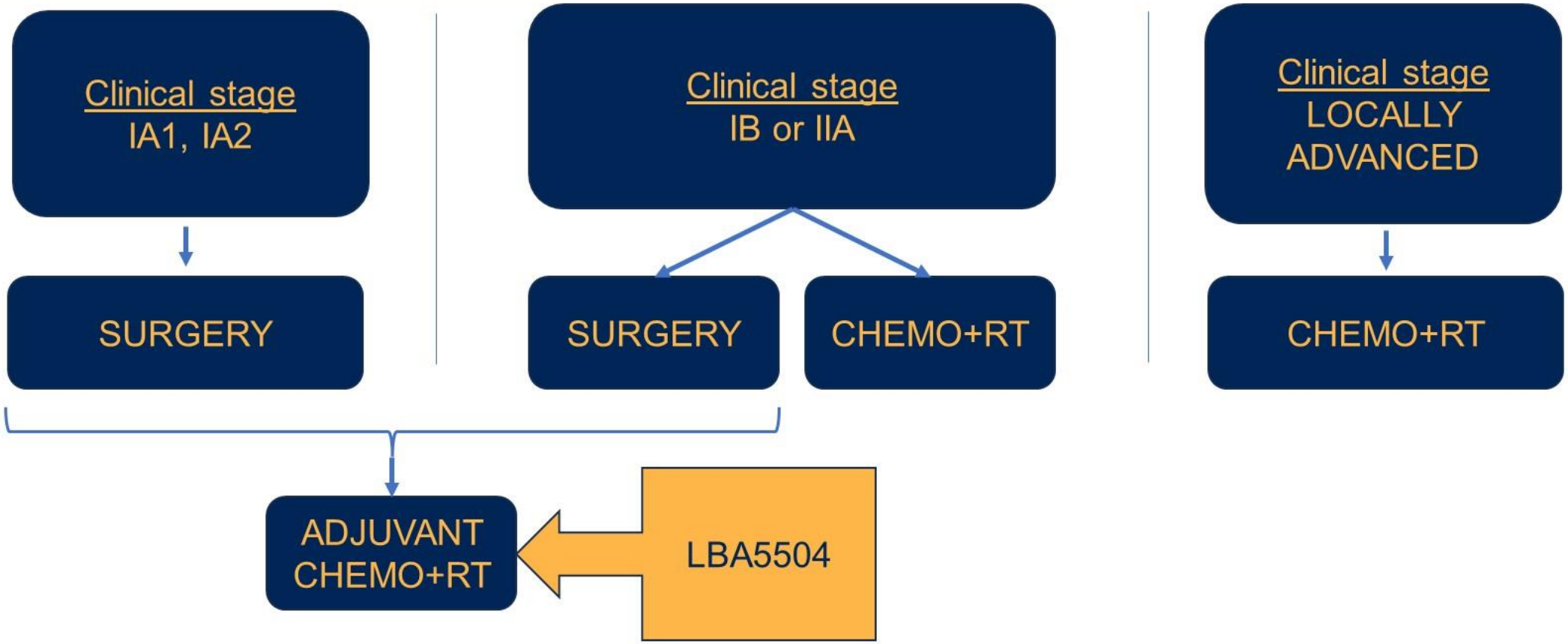
Titre de la réunion

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

LBA5504: Adjuvant chemotherapy following concurrent chemoradiation (CRT)

CURRENT LANDSCAPE OF CERVICAL CANCER



RT-CT post-opératoire ? Cancer du col initialement localisé → cancer du col avancé sur la pièce définitive

Analysis 1.1. Comparison 1 Radiotherapy plus chemotherapy versus radiotherapy, Outcome 1 Death from all causes.

Review: Adjuvant platinum-based chemotherapy for early stage cervical cancer

Comparison: 1 Radiotherapy plus chemotherapy versus radiotherapy

Outcome: 1 Death from all causes

Study or subgroup	RT+CT N	RT N	log [HR] (SE)	HR IV,Random,95% CI	Weight	HR IV,Random,95% CI
Peters 2000	127	116	-0.5677 (0.2692)		68.9 %	0.57 [0.33, 0.96]
Protocol CE3005	26	28	-0.6016 (0.4005)		31.1 %	0.55 [0.25, 1.20]
Total (95% CI)	**153**	**144**			**100.0 %**	**0.56 [0.36, 0.87]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.00$, df = 1 (P = 0.94); $I^2 = 0.0\%$

Test for overall effect: Z = 2.59 (P = 0.0096)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Radiotherapy plus chemotherapy versus radiotherapy, Outcome 3 Grade 4 toxicity.

Review: Adjuvant platinum-based chemotherapy for early stage cervical cancer

Comparison: 1 Radiotherapy plus chemotherapy versus radiotherapy

Outcome: 3 Grade 4 toxicity

Study or subgroup	RT+CT n/N	RT alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Peters 2000	21/122	4/112		87.9 %	4.82 [1.71, 13.61]
Protocol CE3005	8/26	0/28		12.1 %	18.26 [1.11, 301.35]
Total (95% CI)	**148**	**140**		**100.0 %**	**5.66 [2.14, 14.98]**

Total events: 29 (RT+CT), 4 (RT alone)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.80$, df = 1 (P = 0.37); $I^2 = 0.0\%$

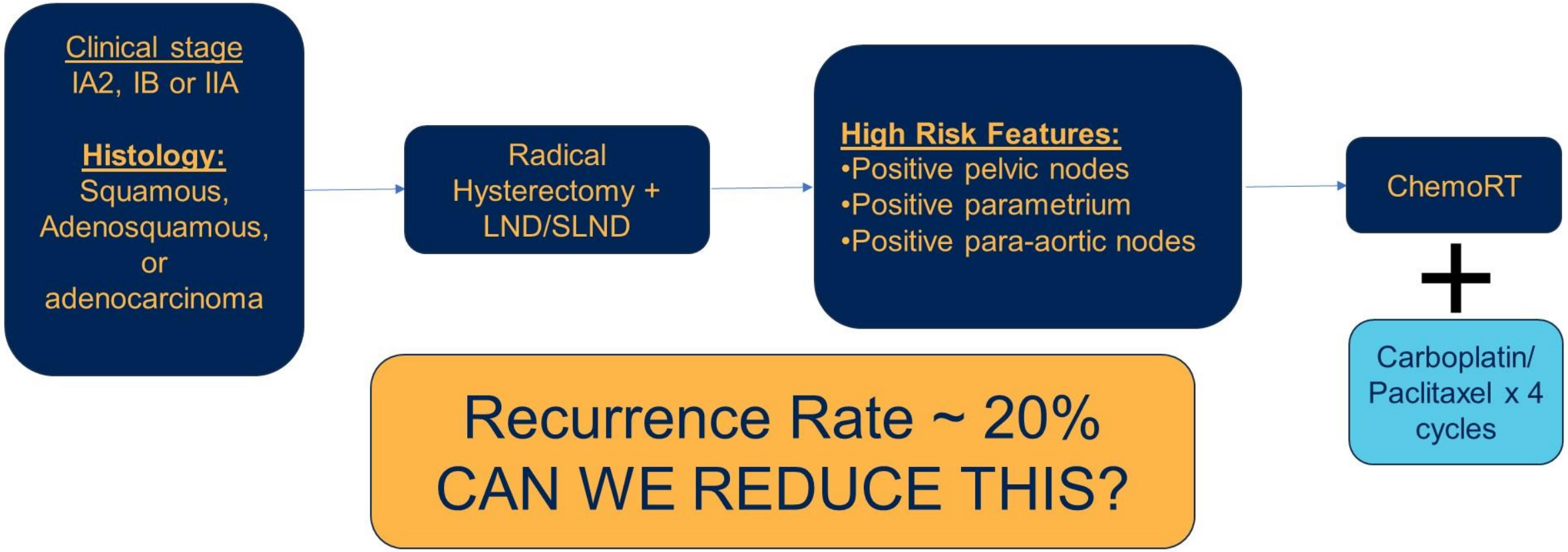
Test for overall effect: Z = 3.49 (P = 0.00048)

Test for subgroup differences: Not applicable

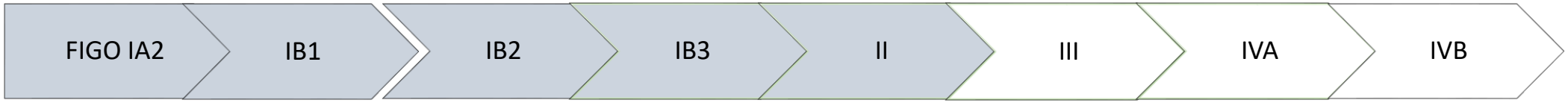
PETIT BENEFICE MAIS faible effectif, toxicités +++

LBA5504: Adjuvant chemotherapy following concurrent chemoradiation (CRT)

What PROBLEM is this research trying to solve?



PRESENTED BY: Shitanshu Uppal, MD MBA



RT-CT post-opératoire ? Cancer du col initialement localisé mais facteurs de risque → cancer du col avancé sur la pièce définitive

Schema

- Clinical stage IA2, IB, or IIA with high risk factors after surgery
- Radical hysterectomy – positive nodes and/or positive parametrium

STRATIFY		RANDOMIZE	
	Intention To Use Brachytherapy 1. No 2. Yes RT Modality 1. Standard RT 2. IMRT Radiation Therapy Dose 1. 45 Gy 2. 50.4 Gy		<u>Arm 1</u> Concurrent weekly cisplatin and RT ± brachytherapy Versus <u>Arm 2</u> Concurrent weekly cisplatin and RT ± brachytherapy FOLLOWED BY Carboplatin and paclitaxel

NRG ONCOLOGY

NRG/RTOG 0724/GOG-0724

Endpoints

- Primary endpoint – disease-free survival (DFS)
- Secondary endpoints - OS and AEs (CTCAE v4)
- Methods:
  - OS and DFS estimated by Kaplan-Meier and arms compared using log-rank test
  - Multivariable analyses (MVA) used Cox proportional hazards models

Results: Enrollment

- Enrollment: 9/16/2009 - 3/2/2022
- 236 patients randomized - 212 eligible
  - 109 Cisplatin-RT (Arm 1)
  - 103 Cisplatin-RT + Chemo (Arm 2)
- Median age 46 years (min-max: 25 -77)
- Median follow-up for all patients – 4.5 years (min-max: 0.02-12.8)

Results: Patient and Tumor Characteristics

	Cis + RT (n=109)	Cis + RT + chemo (n=103)	Total (n=212)
Race			
White	60 (55%)	49 (48%)	109 (51%)
Asian	42 (39%)	40 (39%)	82 (39%)
Other	7 (6%)	14 (14%)	21 (10%)
Hysterectomy			
Open	64 (59%)	54 (52%)	118 (56%)
Laparoscopic/Robotic	45 (41%)	49 (48%)	94 (44%)
Histological type			
Squamous cell	88 (81%)	74 (72%)	162 (76%)
Adenosqumous	6 (6%)	5 (5%)	11 (5%)
Adenocarcinoma	15 (14%)	24 (23%)	39 (18%)

NRG ONCOLOGY

NRG/RTOG 0724/GOG-0724

Results: Patient and Tumor Characteristics

	Cis + RT (n=109)	Cis + RT + chemo (n=103)	Total (n=212)
Stage			
IA2	3 (3%)	6 (6%)	9 (4%)
IB	97 (89%)	88 (85%)	185 (87%)
IIA	9 (8%)	9 (9%)	18 (8%)
Positive pelvic nodes			
No	33 (30%)	23 (22%)	56 (26%)
Yes	76 (70%)	80 (78%)	156 (74%)
Positive para-aortic nodes			
No	54 (50%)	43 (42%)	97 (46%)
Yes	3 (3%)	5 (5%)	8 (4%)
Not dissected	52 (48%)	55 (53%)	107 (50%)

Results: Radiation Therapy Plan at Study Entry

	Cis + RT (n=109)	Cis + RT + chemo (n=103)	Total (n=212)
Intention to use Brachytherapy			
No	61 (56%)	58 (56%)	119 (56%)
Yes	48 (44%)	45 (44%)	93 (44%)
RT modality			
Standard RT	46 (42%)	41 (40%)	87 (41%)
IMRT	63 (58%)	62 (60%)	125 (59%)
RT dose			
45 Gy	35 (32%)	30 (29%)	65 (31%)
50.4 Gy	74 (68%)	73 (71%)	147 (69%)

Results: Treatment

- 5 patients did not receive RT (4-Arm 1, 1-Arm 2)
- 4 patients did not receive concurrent cisplatin (2 in each arm)
- 27 (26%) Arm 2 patients did not receive adjuvant chemotherapy

Reasons adjuvant chemo not received	n=27
Disease progression	1 (4%)
Adverse events	6 (22%)
Patient withdrawal/refusal	16 (59%)
Other	3 (11%)
Unknown	1 (4%)

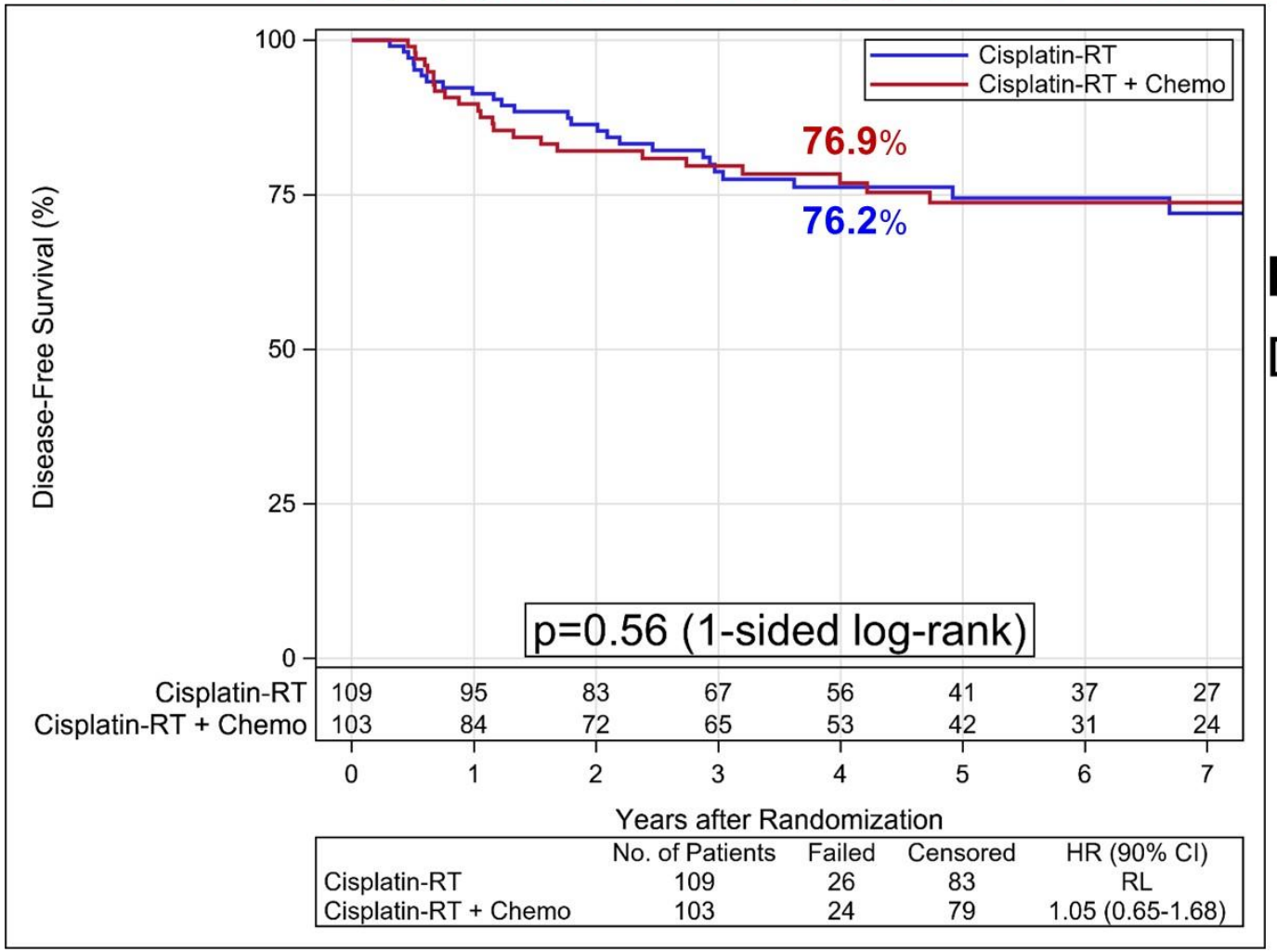
Results: Treatment-Related Adverse Events

System Organ Class	Cis + RT (n=107) n and (%) of Patients by Grade				Cis + RT + chemo (n=101) n and (%) of Patients by Grade			
	1	2	3	4	1	2	3	4
Overall Highest Grade	21 (20)	42 (39)	34 (32)	6 (6)	8 (8)	30 (30)	42 (42)	18 (18)
Blood and lymphatic system disorders	19 (18)	21 (20)	8 (7)	0 (0)	20 (20)	30 (30)	10 (10)	0 (0)
Gastrointestinal disorders	57 (53)	31 (29)	7 (7)	1 (1)	42 (42)	35 (35)	12 (12)	0 (0)
Infections and infestations	1 (1)	8 (7)	2 (2)	0 (0)	1 (1)	12 (12)	6 (6)	1 (1)
Investigations	12 (11)	25 (23)	24 (22)	4 (4)	4 (4)	27 (27)	25 (25)	16 (16)
Nervous system disorders	25 (23)	1 (1)	5 (5)	0 (0)	47 (47)	14 (14)	7 (7)	0 (0)
Renal and urinary disorders	21 (20)	8 (7)	4 (4)	0 (0)	31 (31)	14 (14)	1 (1)	1 (1)

Grade ≥ 3 (Cis+RT: 37% vs. Cis+RT+chemo: 59%, p=0.0015)

NRG ONCOLOGY CTCAE version 4 NRG/RTOG 0724/GOG-0724

Results: Disease-Free Survival



Most common 1st failure:

Distant Mets

- 37/50 (74%) All patients
- 20/26 (77%) CRT
- 17/24 (71%) CRT+chemo

NRG ONCOLOGY RL: reference level NRG/RTOG 0724/GOG-0724

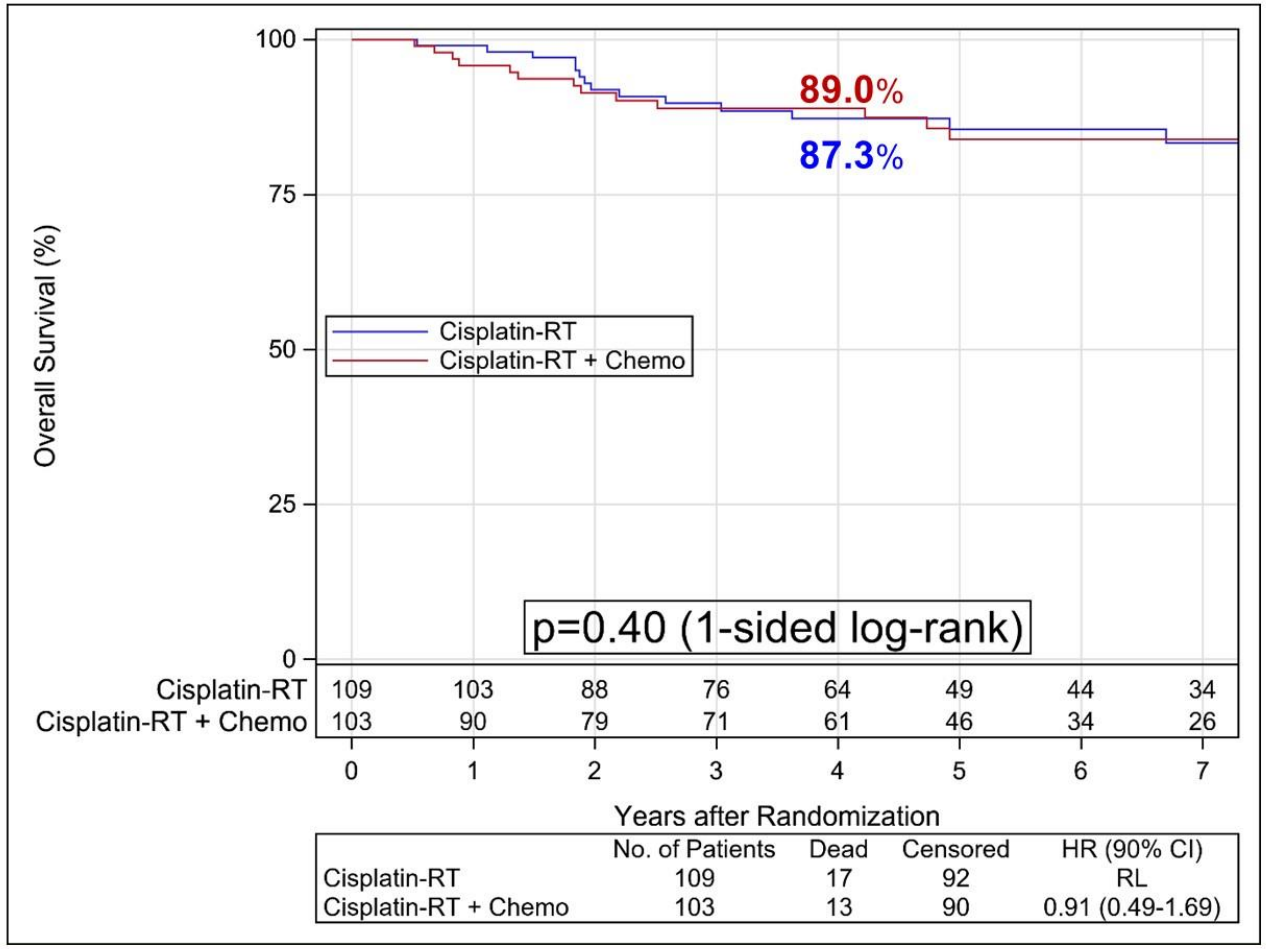
Results: Disease-Free Survival

Adjustment Variables	Comparison	Events/ Total	HR (95% CI)	p-value
Treatment arm	Cis + RT (RL) vs. Cis + RT + chemo	26/109 24/103	0.92 (0.52, 1.63)	0.78
Brachytherapy	No (RL) vs. Yes	20/128 30/84	3.32 (1.83, 6.04)	<0.0001
RT dose	< 50 Gy (RL) vs. ≥ 50 Gy	11/68 39/144	3.29 (1.59, 6.81)	0.0014
Histologic type	Adenocarcinoma, NOS (RL) vs. Squamous cell carcinoma/ Adenosquamous carcinoma	14/39 36/173	0.47 (0.25, 0.89)	0.02

Factors for worse DFS:

- Receiving vaginal brachytherapy
- RT dose > 50 Gy
- Adenocarcinoma histology

Results: Overall Survival



NRG ONCOLOGY

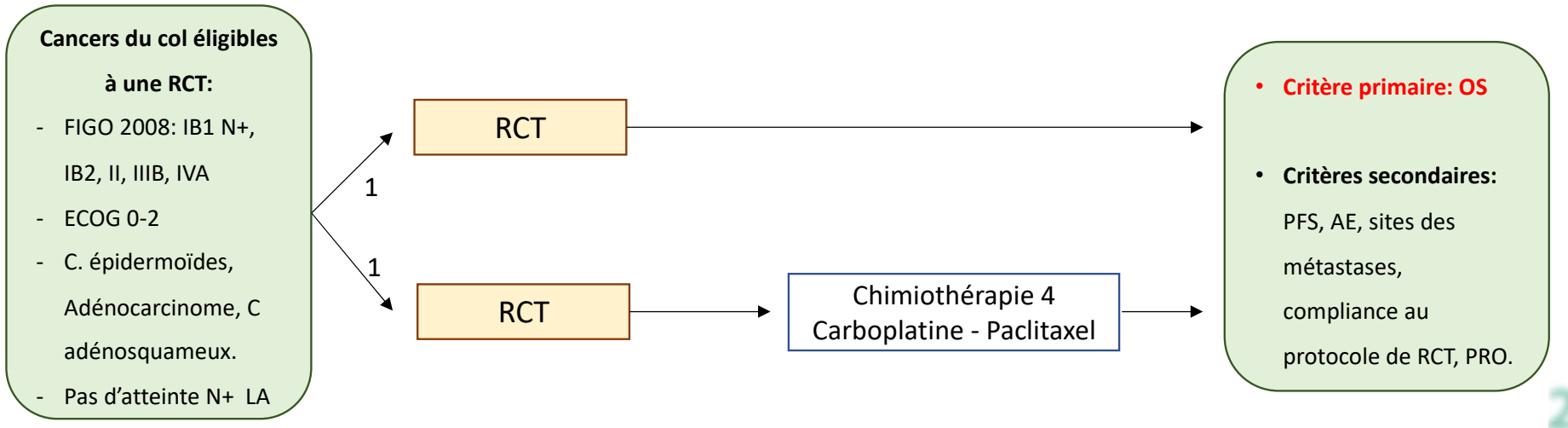
NRG/RTOG 0724/GOG-0724

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

Situation : cancer du col localement avancé → RT-CT → CT post-op

Essai de phase III OUTBACK (ANZGOG 0902, RTOG 1174, NRG 0274) *Mileshkin et al. Abstract LBA 3*

- Traitement standard des cancers du col localement avancés = radio-chimiothérapie (RCT).
- Rationnel: rechutes et métastases à distances après traitement standard → place de la chimiothérapie adjuvante?[1,2]



2021 ASCO ANNUAL MEETING

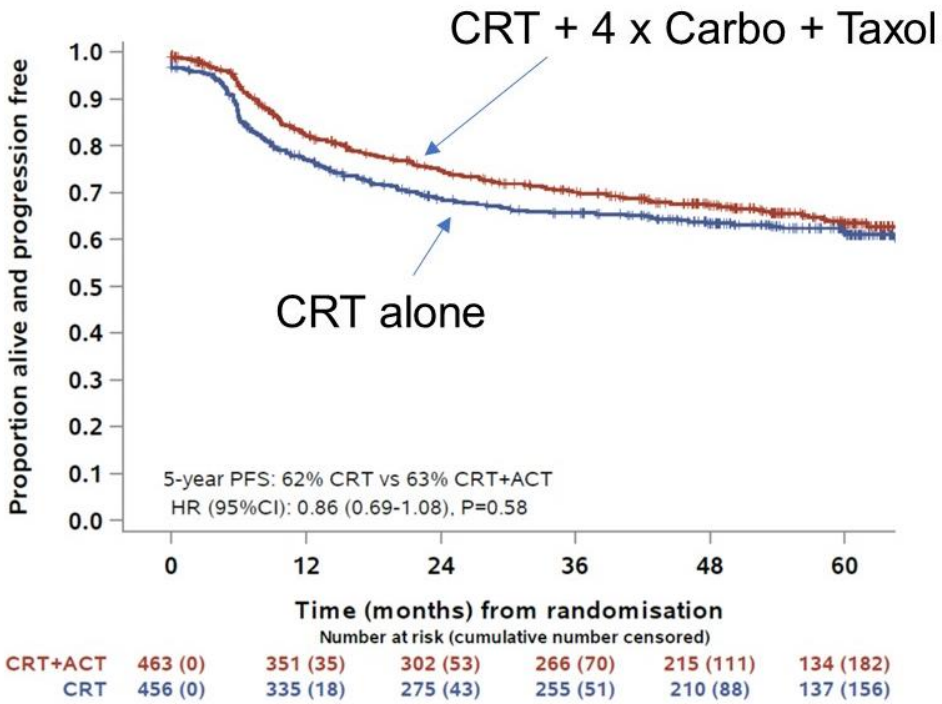
[1] *Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. JCO. 2008.*
[2] *Dueñas-González. JCO. 2011.*

Idem ACTLACC Trial Chokaew Tovanabutra et al. Asian Pac J Cancer Prev. 2021

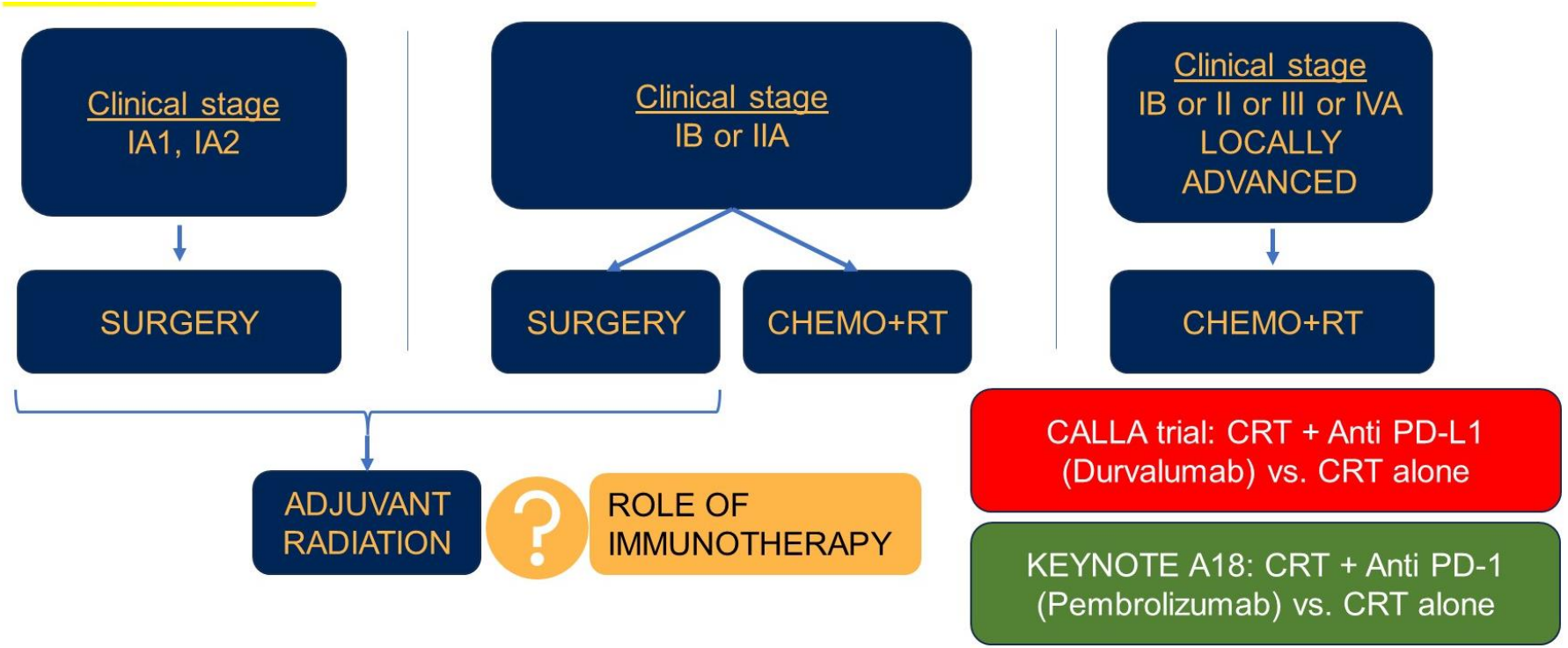
Adjuvant chemotherapy following chemoradiotherapy as primary treatment for locally advanced cervical cancer versus chemoradiotherapy alone (OUTBACK): an international, open-label, randomised, phase 3 trial

Linda R Mileshkin, Kathleen N Moore*, Elizabeth H Barnes, Val Gebski, Kailash Narayan, Madeleine T King, Nathan Bradshaw, Yeh Chen Lee, Katrina Diamante, Anthony W Fyles, William Small Jr, David K Gaffney, Pearly Khaw, Susan Brooks, J Spencer Thompson, Warner K Huh, Cara A Mathews, Martin Buck, Aneta Suder, Thomas E Lad, Igor J Barani, Christine H Holschneider, Sylvia Van Dyk, Michael Quinn, Danny Rischin, Bradley J Monk†, Martin R Stockler†*

- Overall Survival (OS):
  - Adjuvant Chemotherapy Group: 72%
  - Chemoradiotherapy Only Group: 71%
  - **Difference: 1%** (95% CI –6 to 7); Hazard Ratio: 0.90 (95% CI 0.70 to 1.17); **p=0.81.**



TAKE HOME MESSAGE



Pas d'indication de chimiothérapie adjuvante

2024 ASCO ANNUAL MEETING

Omission of lymphadenectomy in advanced epithelial ovarian cancer patients treated with primary or interval cytoreductive surgery after neoadjuvant chemotherapy: the CARACO phase III Randomized Trial

Jean-Marc Classe, Campion L, Lecuru F, Vergote I, Jankowski C, Werner R, Pomel C, Houvenaeghel G, Dupré PF, Mathevet P, Villet R, Joly F, Berton D, Debeaupuis E, Frenel JS, Loaec C

CARACO trial (NCT01218490): Multicenter randomized phase III trial

CARAC

Epithelial ovarian cancer
Figo stage III-IVA
No suspicious retroperitoneal lymph node
Optimal surgery achievable (Primary or ICS)
Residual <1cm

Median laparotomy

Randomization during surgery

R
1:1
N=450

Stratification:
- **Center**
- **Primary surgery or Interval surgery**

Surgery with RPL

Surgery without RPL

After surgery /SOC
Last cycles of chemotherapy
Maintenance treatments

*

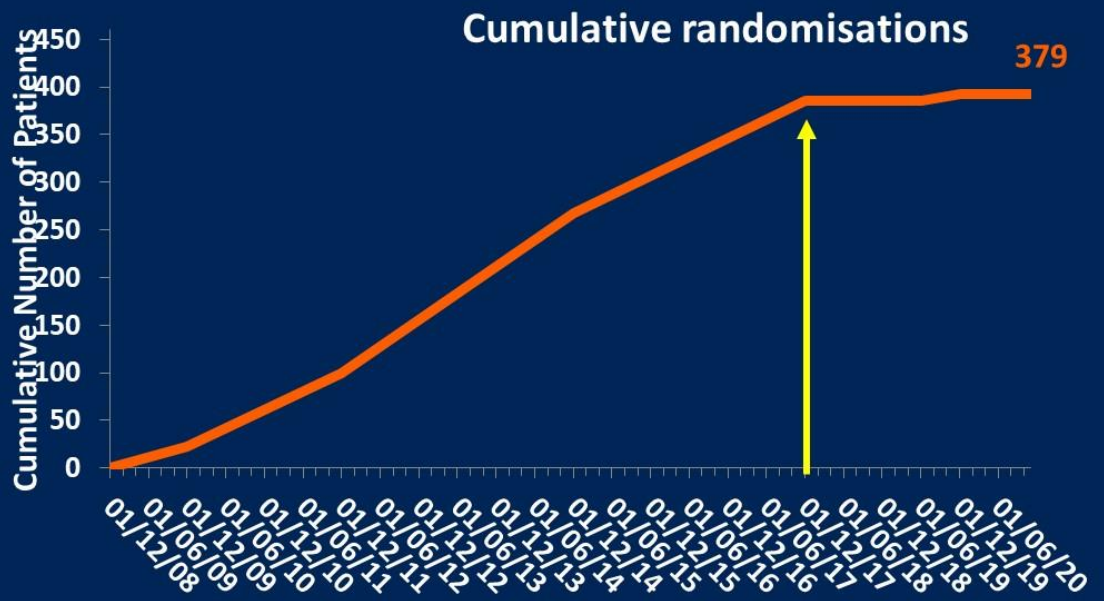
Keys: R: randomization, RPL: Retroperitoneal Lymphadenectomy, ICS: Interval Cytoreductive Surgery, SOC: Standard Of Care

Less inclusions and less events than required

- After presentation of the LION trial at ASCO meeting 2017, the inclusion rate stagnated, leading to the **premature closing of the trial**

- At the data cutoff: 01/31/2023, **379** patients were randomized (/ 450) from 14 Centers in France, 3 in Germany,1in Belgium and 1 in Canada

314 events were observed (/335) leading to a power analysis of 78% with a median follow-up of 9 years



CARACO trial: Inclusion / exclusion criteria

Inclusion criteria
> 18 years old
Epithelial ovarian cancer
Good performans status (Karnofsky >80) or ASA<2
Thoraco Abdomino Pelvic CT or MRI: no node >2cm, no nodes palpated during surgery
FIGO stage III-IVA (pleural effusion)
Feasible optimal Primary surgery or if not feasible interval surgery after NAC (residual tumour <1cm)

Exclusion criteria
Non epithelial carcinoma
Borderline carcinoma
FIGO stage I-II or IVB
Previous retroperitoneal lymph node resection
Thoraco Abdomino Pelvic CT or MRI: node >2cm before any treatment. A patient with lymph node >2cm before treatment and downstaged after NAC remains contra indicated
A residual tumour ≥1cm
Complete surgery still not feasible after 3/4 cycles of NAC

Keys: ASA: American Society of Anesthesiologist, CT: Computed Tomography, MRI: Magnetic Resonance Imaging, NAC: neoadjuvant chemotherapy

CARACO trial: Baseline characteristics

Characteristics	No RPL (n=193)	RPL (n=186)
Median age (IQR), years	65 (57-71)	64 (56-70)
Serous or endometrioid carcinoma, n (%)	166 (86.0)	163 (87.6)
Other pathological subtype MD	27 (14.0) 0	20 (10.8) 3 (1.6)
CA 125 before treatment (median - IQR)	498 (139-1469)	466 (105-1245)
PCI (median - IQR) (MD)	8 (4-14) (20)	9 (3-14) (23)

Keys: RPL: Retroperitoneal Lymphadenectomy MD: Missing Data, PCI: Peritoneal Cancer Index, IQR: Inter Quartile Range

CARACO trial: characteristics of surgery, and bevacizumab

Characteristics	No RPL (n=193)	RPL (n=186)
Surgery to not any residual, n (%)	161 (85.6)	158 (88.3)
Resected lymph nodes total (median IQR) Para aortic LN (median IQR) Pelvic LN (median IQR)		28 (19-36) 12 (7-18) 13 (9-19)
Patients with ≥1 involved LN		81 (43%)
Median duration of surgery (minutes)	240 (180-290)	300 (240-360)
Maintenance with Bevacizumab after surgery	46 (23.8)	44 (23.7)
Surgical strategy	PS: 50/ ICS: 143	PS: 40/ICS:146

Keys:RPL: Retroperitoneal Lymphadenectomy, IQR: Inter Quartile Range, LN: Lymph Node, PS: Primary Surgery, ICS: Interval Cyrtoreductive Surgery

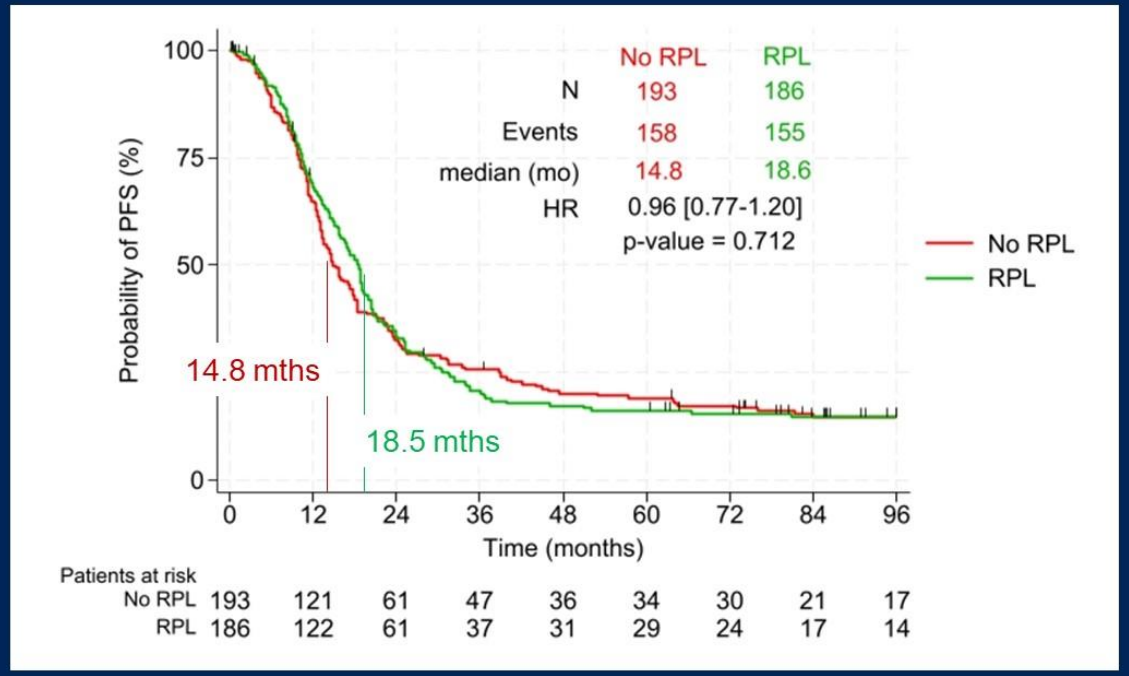
CARACO: Severe morbidity and mortality (within 30 days after surgery)*

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

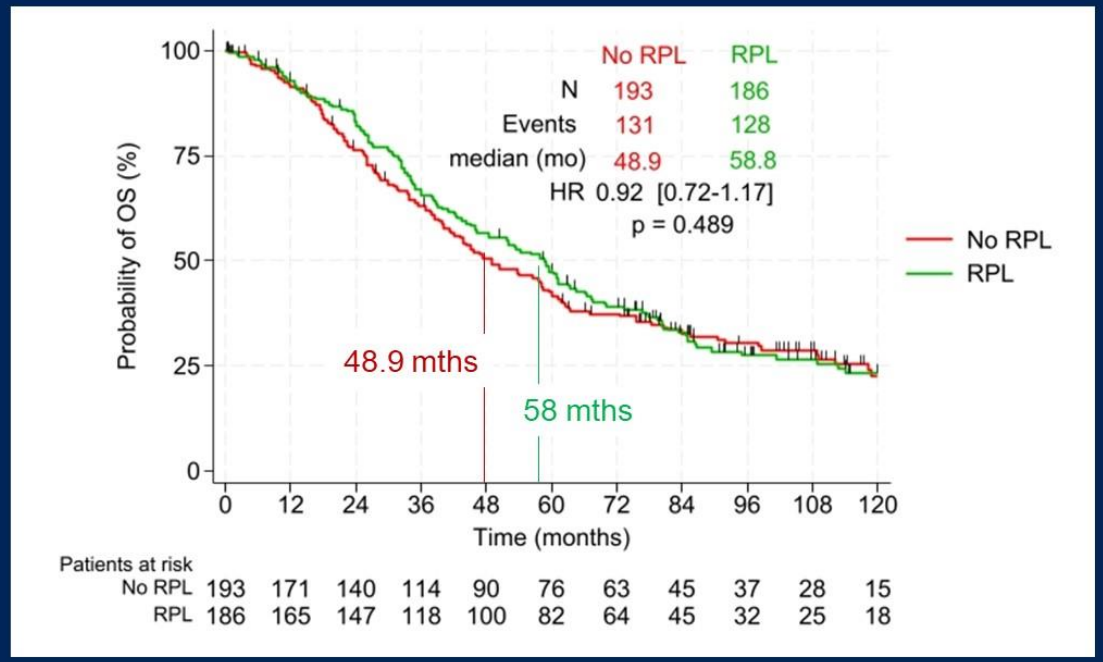
** CTC-NCI version 3.0*

CARACO trial: Primary endpoint (PFS, ITT population)



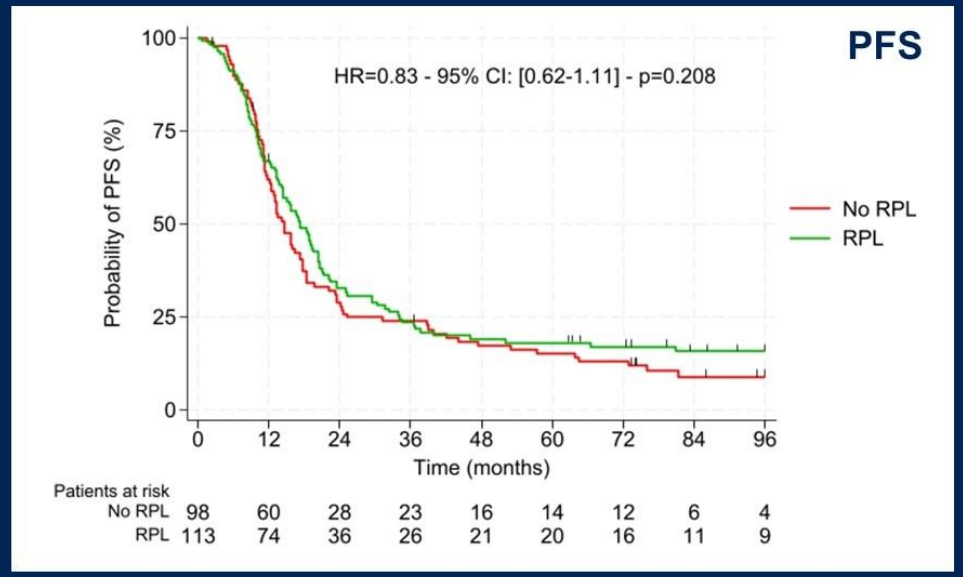
Key: RPL: Retroperitoneal Lymphadenectomy

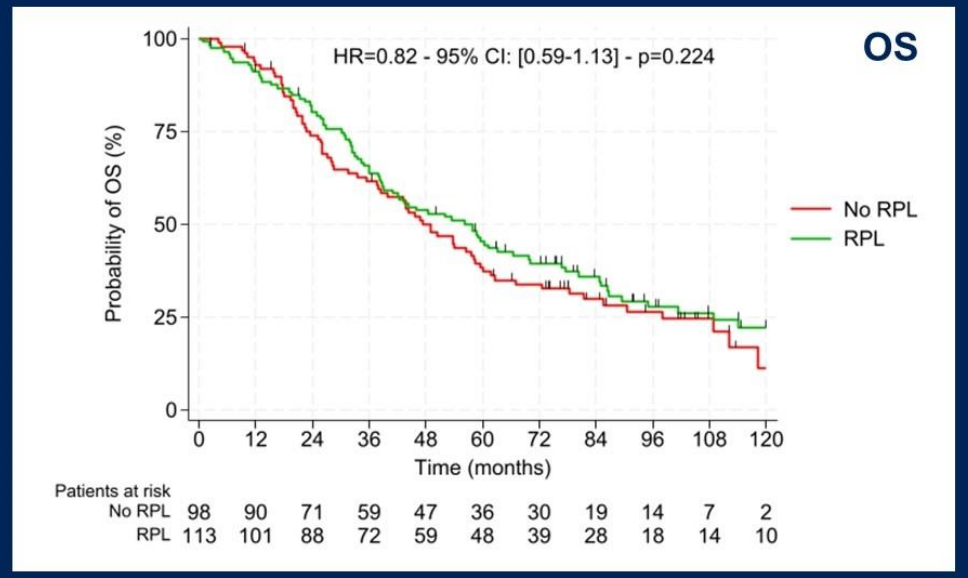
CARACO trial: OS (secondary endpoint, ITT population)



Key: RPL: Retroperitoneal Lymphadenectomy

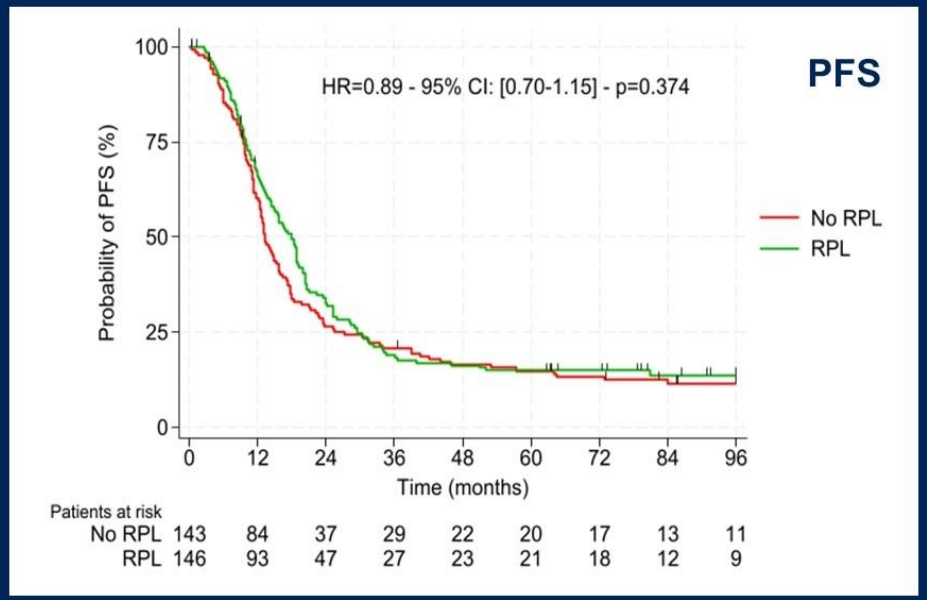
Subgroup analysis: High grade serous or endometrioid

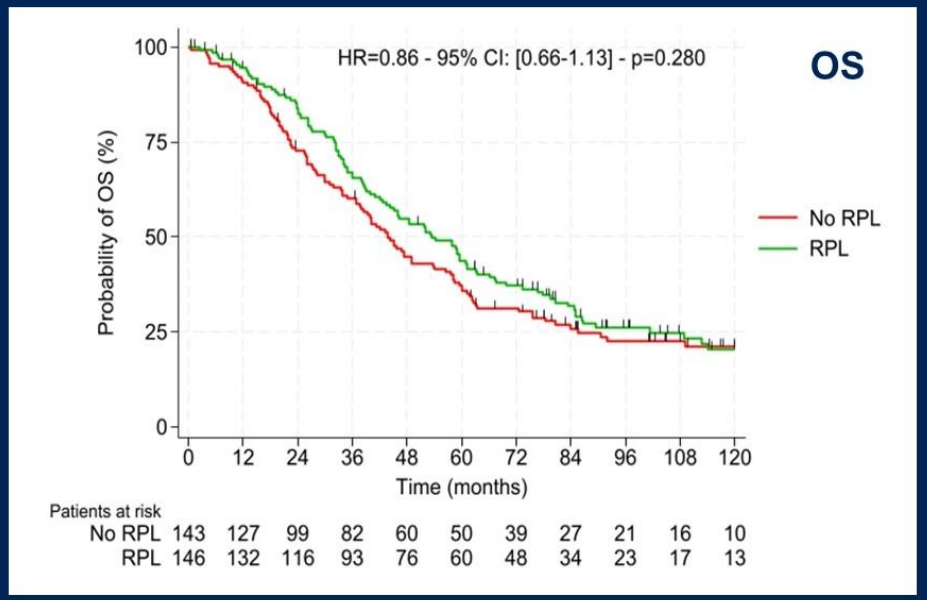




Key: RPL: Retroperitoneal Lymphadenectomy

Subgroup analysis: Interval surgery





Key: RPL: Retroperitoneal Lymphadenectomy

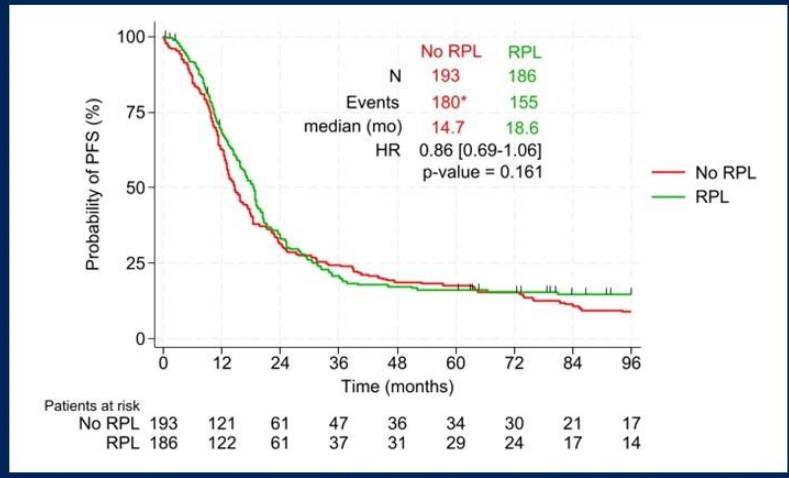
CARACO trial: Limits of the study

- ❑ **A lower number of events than expected (22 events /335 – 6% - missing)**

Considering « the worst case scenario* »:

- 22 missing events are added to the worst group, in order to virtually increase the difference with the best group.

No difference in PFS (p=0.161)



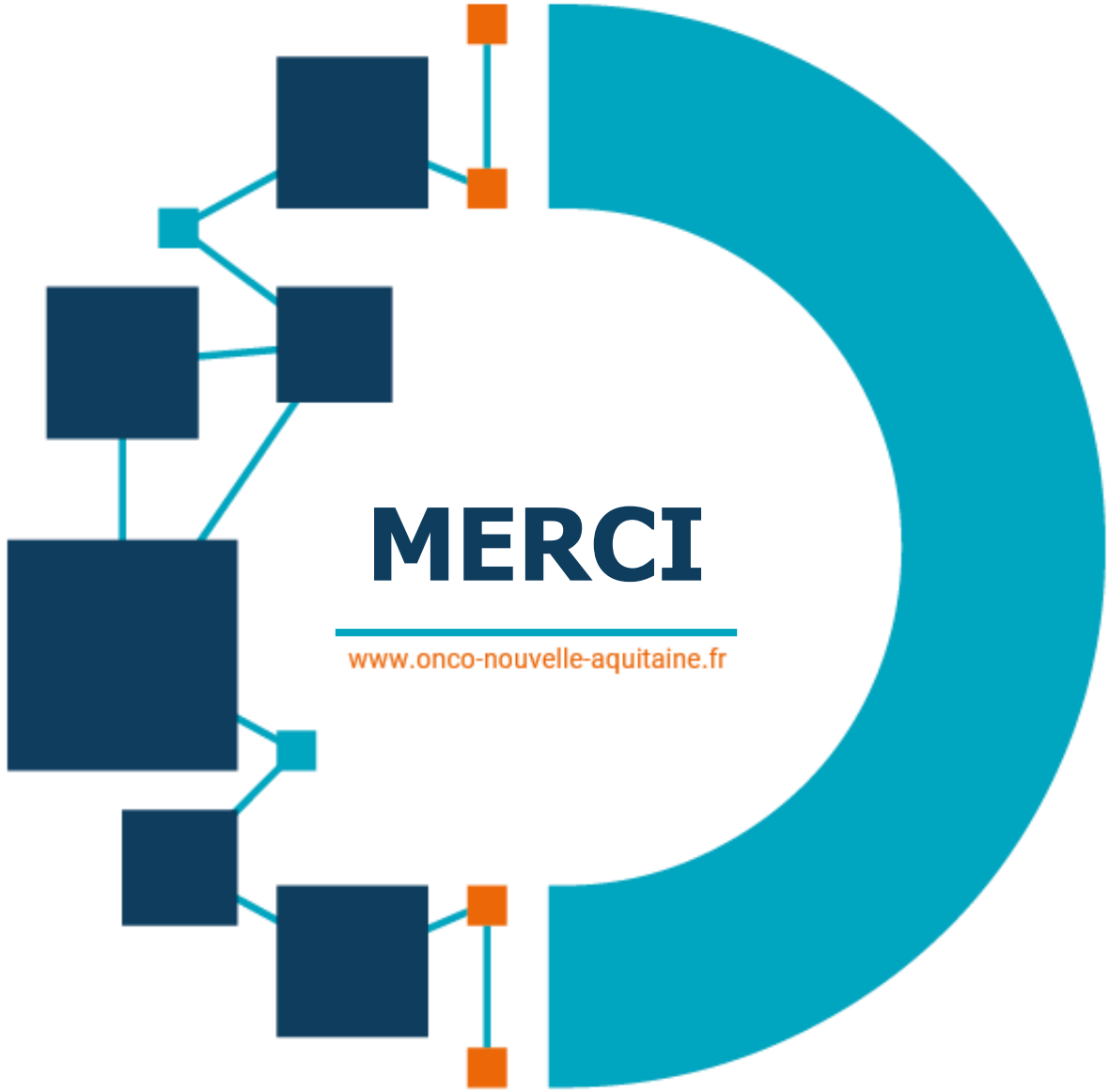
Key: RPL: Retroperitoneal Lymphadenectomy

- ❑ **No information about the mutational status collected**
- ❑ **Two different populations:** primary on interval surgery: it reflects real life of surgical management of these patients, with no proven survival difference

**Gamble C, et al, J Clin Epidemiol. 1995.*

TAKE HOME MESSAGE

- En cas de chirurgie d'intervalle et en l'absence de GG cliniquement visualisable : pas d'indication à faire un curage ganglionnaire
- On peut laisser les GG sans que cela impacte sur la survie sauf si visuellement détectables


MERCI
www.onco-nouvelle-aquitaine.fr