



# Role of HIPEC and PIPAC in Ovarian Cancer

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# Disclosures

- I do not have any relevant financial relationships.

*This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.*

**The off-label/investigational use of Cisplatin and Doxorubicin will be addressed.**

# Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

## STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

*The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.*

## **EXEMPTION:**

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

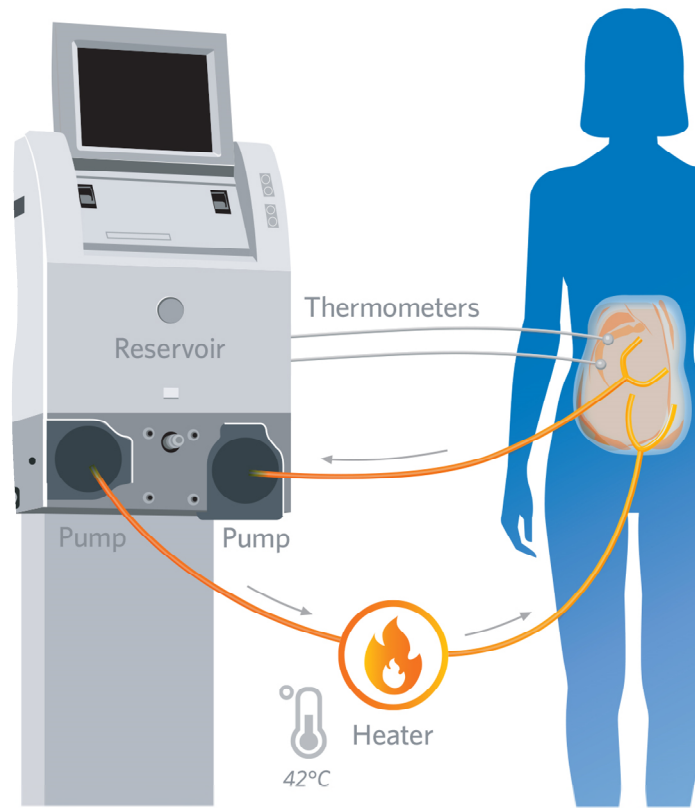
***This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.***

# Objectives

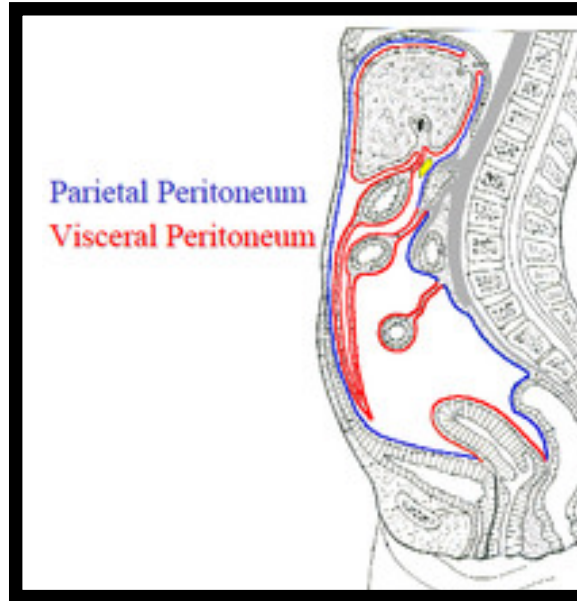
- To review role of Hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer
- To review evidence to date of Pressurized Intraperitoneal Aerosolized Chemotherapy (PIPAC) in ovarian cancer



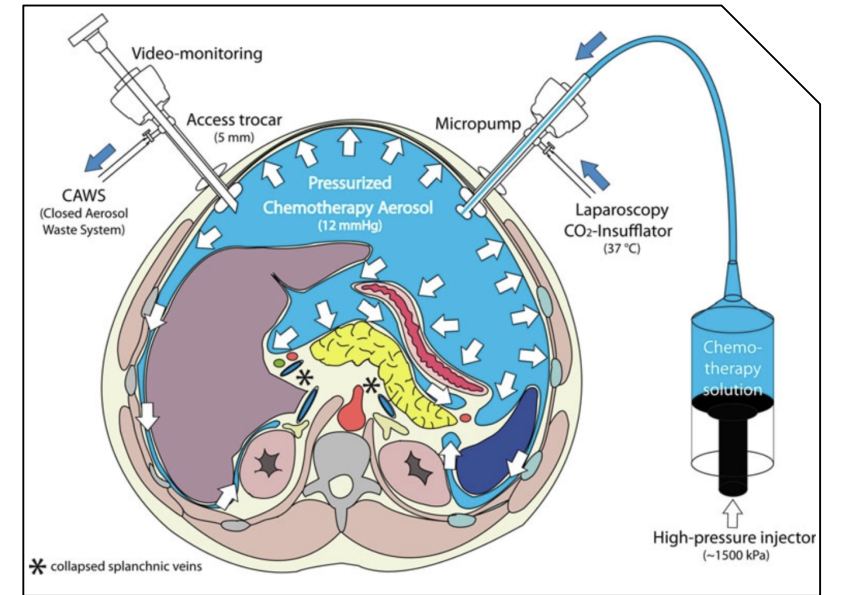
# HIPEC -- Hyperthermic IntraPeritoneal Chemotherapy



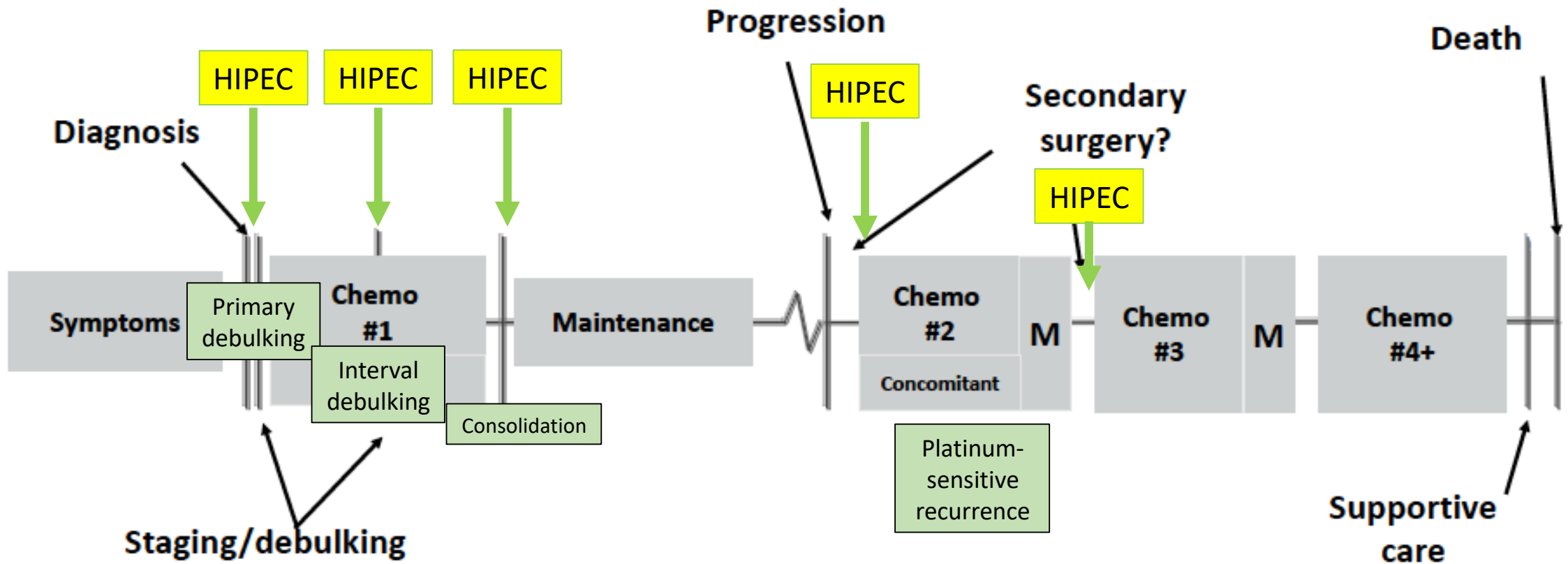
Hyperthermic Intraperitoneal Chemotherapy (HIPEC)



# PIPAC = Pressurized IntraPeritoneal Aerosolized Chemotherapy



# Potential indications for HIPEC in Ovarian Cancer



# HIPEC at different time points of ovarian cancer

## ▪ First-line

- **Upfront** at primary debulking
  - OVHIPEC-2 clinical trial in progress
  - Korean trial negative
- **Interval debulking**
  - recommended by NCCN guidelines for Stage III, after neoadjuvant chemo (NACT)
  - OVHIPEC-1
- **Consolidation**
  - may be considered after NACT

## ▪ Second-line

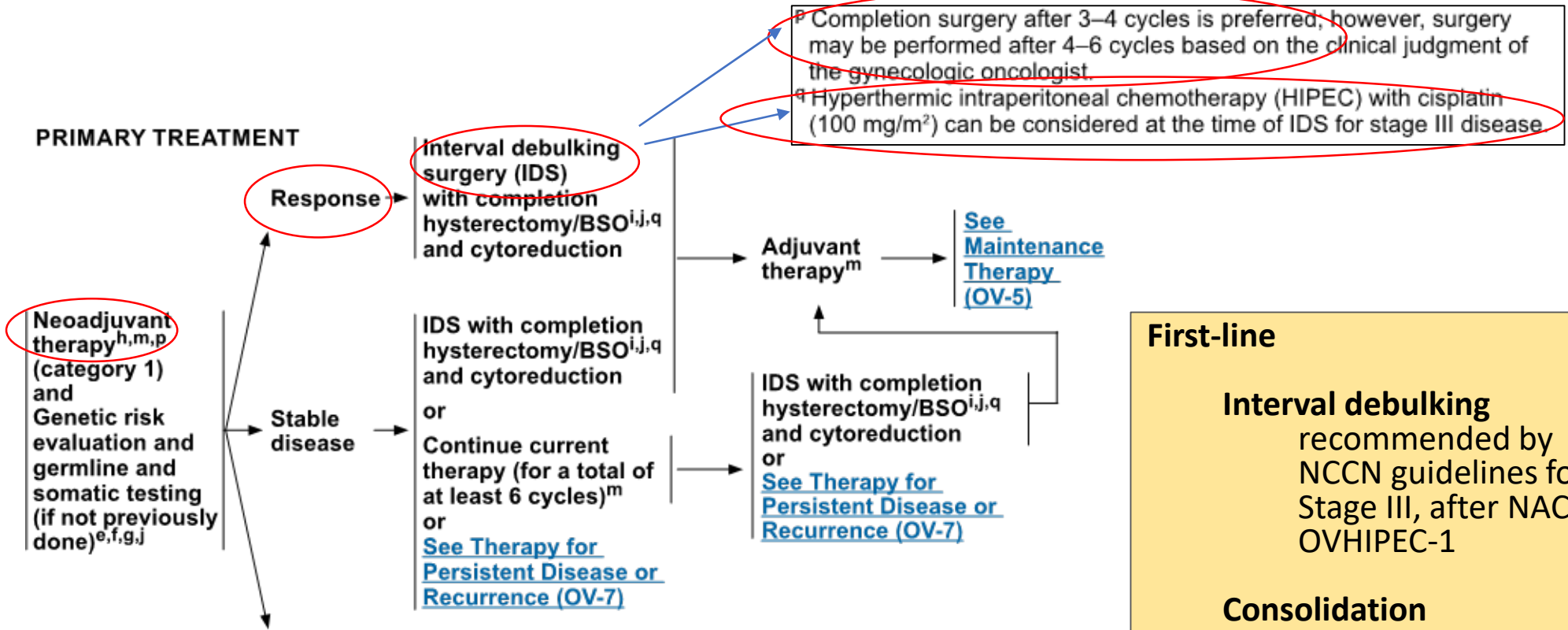
- **Upfront** HIPEC followed by adjuvant chemotherapy
  - not supported by MSK study (carboplatin)
- **Consolidation after NACT**
  - supported by CHIPOR trial (presented at ASCO 2023)

## ▪ Palliative

- Not indicated



# NCCN Guidelines Version 1.2023 Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer



**First-line**

**Interval debulking** recommended by NCCN guidelines for Stage III, after NACT OVHIPEC-1

**Consolidation** may be considered after NACT

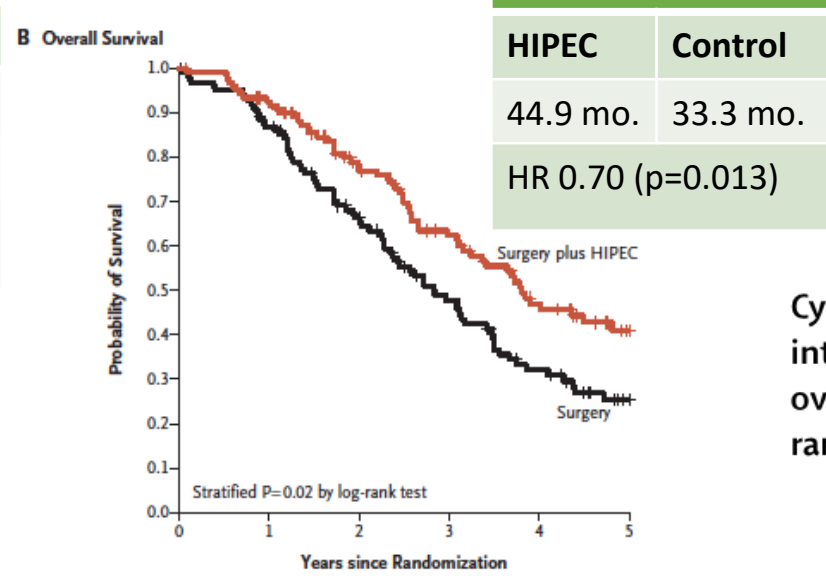
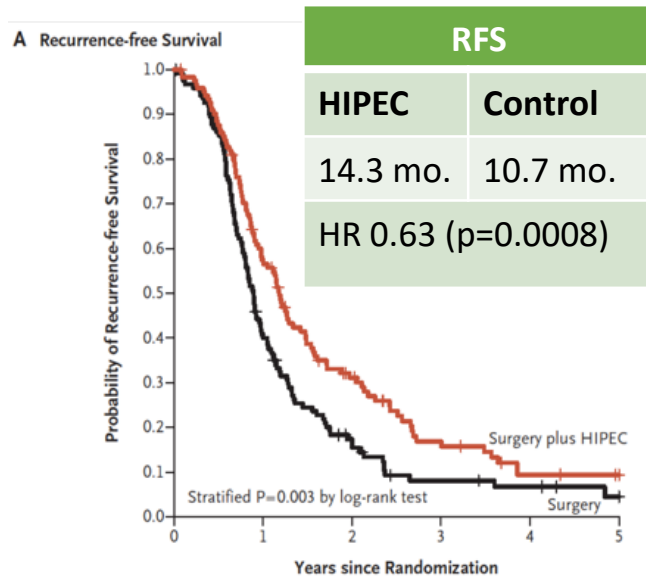
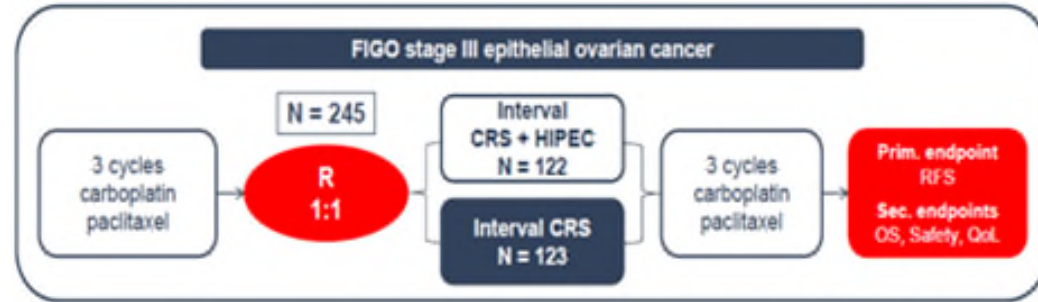
# Randomized ovarian cancer HIPEC trial in ovarian cancer demonstrates survival benefit

## OVHIPEC-01

ORIGINAL ARTICLE

### Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

W.J. van Driel, S.N. Koole, K. Sikorska, J.H. Schagen van Leeuwen,



10-year follow up

Cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy in patients with advanced ovarian cancer (OVHIPEC-1): final survival analysis of a randomised, controlled, phase 3 trial

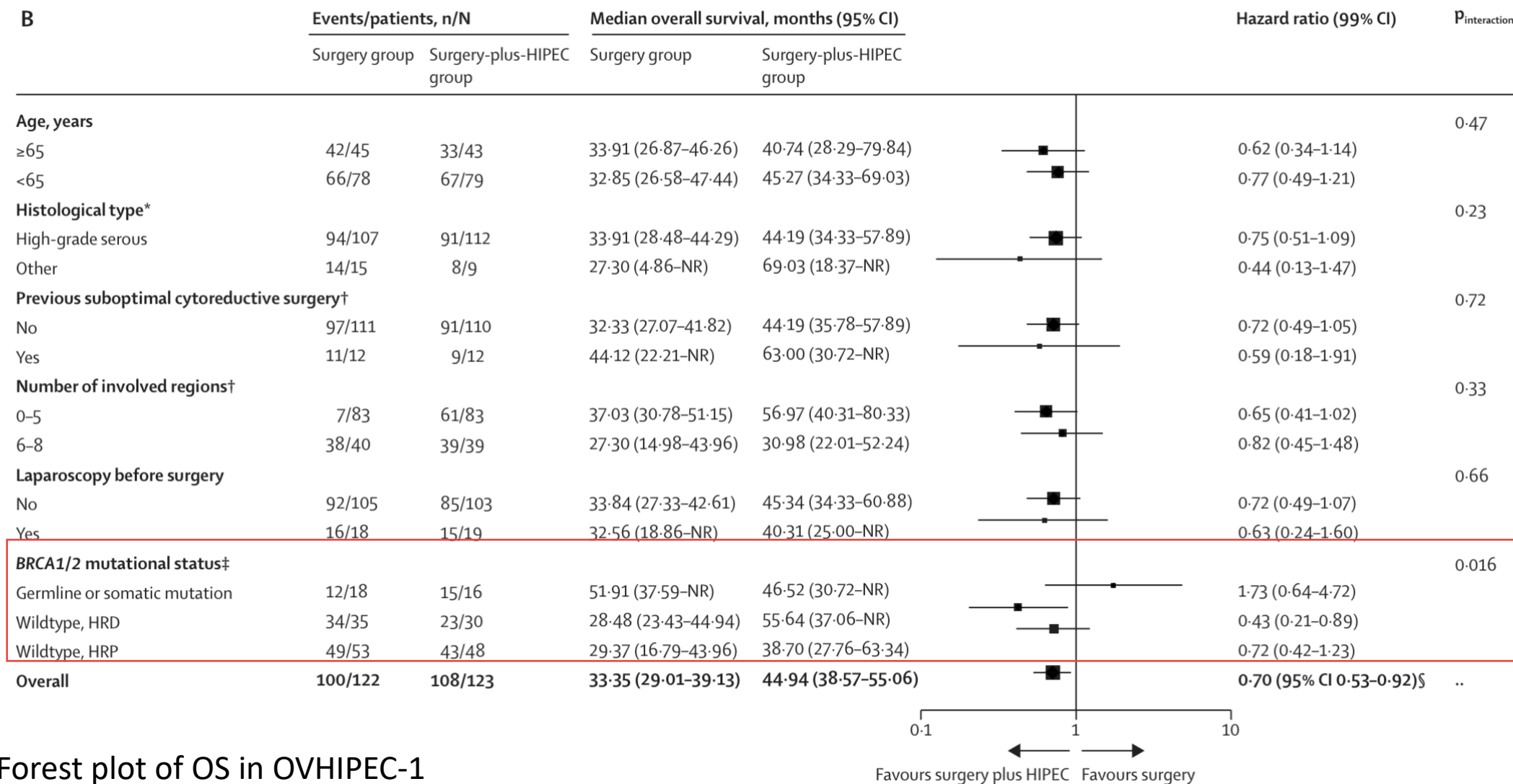
No. at Risk

	0	1	2	3	4	5
Surgery	123	48	18	7	5	2
Surgery plus HIPEC	122	67	31	15	7	5

No. at Risk

	0	1	2	3	4	5
Surgery	123	103	70	44	27	12
Surgery plus HIPEC	122	108	79	56	37	20

# BRCAs mutation and HIPEC



Forest plot of OS in OVHIPEC-1  
Aronson, Lancet Oncology, 2023



# Future trial: HIPEC + IDS with PARPi maintenance

N= 230

GOG Accrual: 0

GOG Activated Sites: 0

Primary Endpoint = PFS

Co-PIs: Zivanovic O; Crispens, M; Randall, L

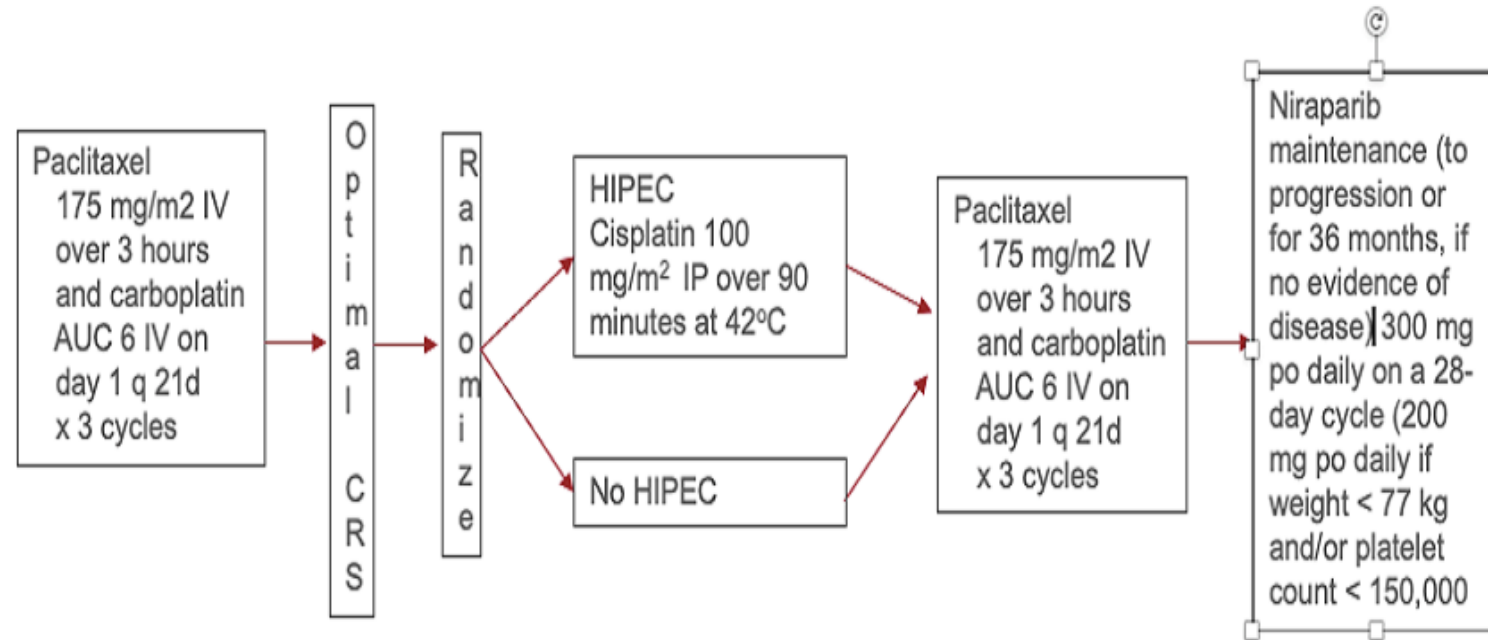
Site Selection Upcoming

## GOG-3068/HIPEC

A Phase III Randomized Trial of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) with Cisplatin versus no HIPEC at the Time of Optimal Interval Cytoreductive Surgery followed by Niraparib Maintenance in Patients with Newly Diagnosed Stage III and IV Ovarian, Primary Peritoneal, and Fallopian Tube Cancer

### Stratification:

- HRD status
- Residual disease (no gross residual or gross residual <1 cm)
- Stage (III vs IV)



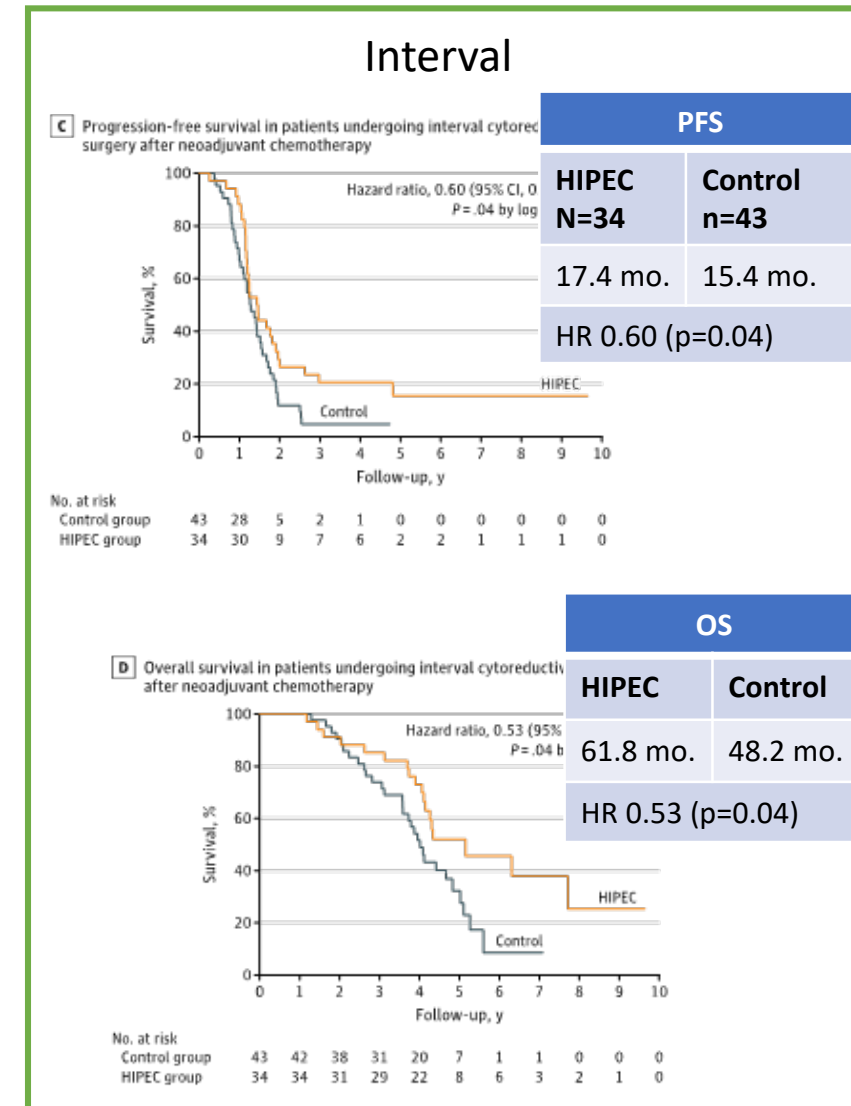
# Korean RCT – no difference for survival – heterogeneous study

JAMA Surgery | Original Investigation

## Survival After Hyperthermic Intraperitoneal Chemotherapy and Primary or Interval Cytoreductive Surgery in Ovarian Cancer A Randomized Clinical Trial

Myong Cheol Lim, MD, PhD; Suk-Joon Chang, MD, PhD; Boram Park, PhD; Heon Jong Yoo, MD, PhD; Chong Woo Yoo, MD, PhD;

Variable	Cytoreductive surgery			
	Primary		Interval	
	Control (n = 49)	HIPEC (n = 58)	Control (n = 43)	HIPEC (n = 34)
Age, median (IQR), y	53.0 (47.0-61.0)	51.0 (45.0-58.0)	54.0 (48.0-61.0)	55.0 (47.0-64.0)
Serum albumin, median (IQR), g/dL	4.1 (3.9-4.4)	4.1 (3.8-4.6)	4.4 (4.1-4.6)	4.4 (4.1-4.7)
FIGO stage <sup>b</sup>				
III	34 (69.4)	45 (77.6)	17 (39.5)	15 (44.1)
IV	15 (30.6)	13 (22.4)	26 (60.5)	19 (55.9)



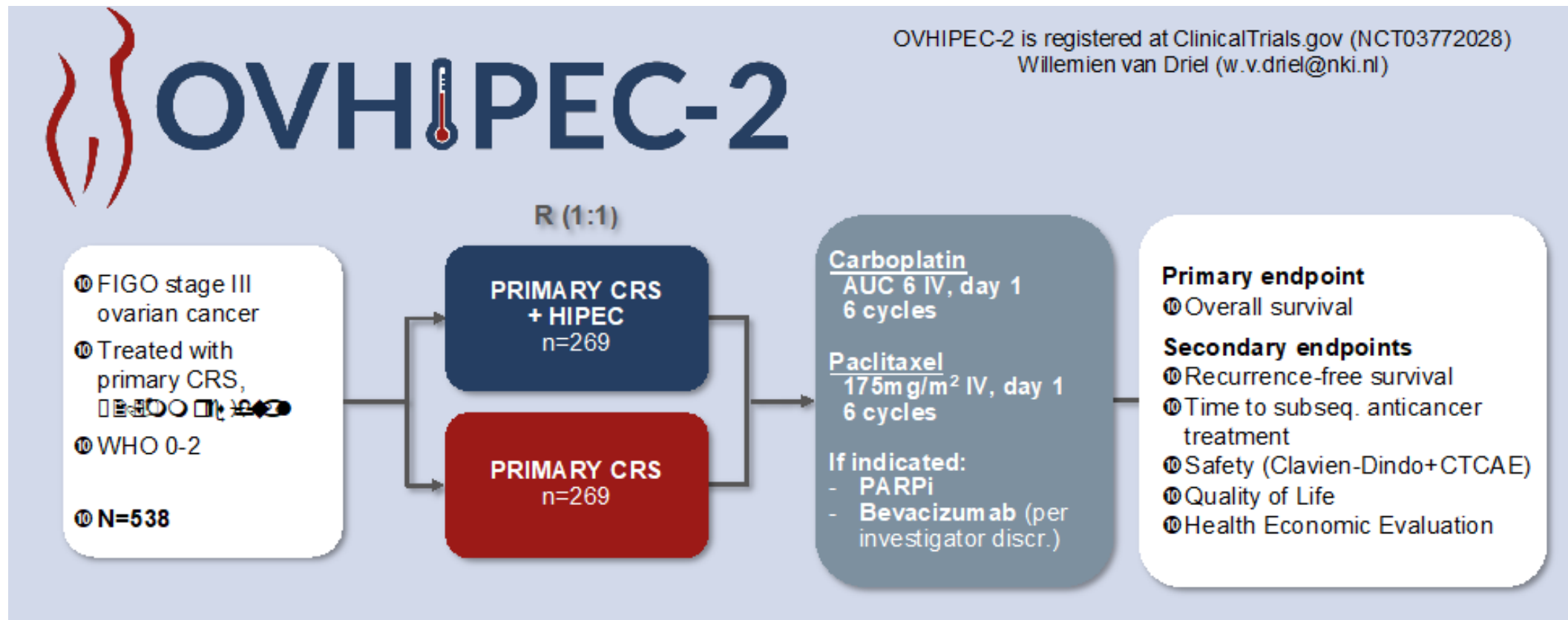


# HIPEC in primary upfront setting

## First-line

### Upfront at primary debulking

- OVHIPEC-2 clinical trial in progress
- Korean trial negative



52% accrued

# Platinum-sensitive recurrence

## Second-line

### Consolidation after NACT

- supported by CHIPOR trial (presented at ASCO 2023)

## CHIPOR trial (NCT01376752): Multicenter randomized phase III trial

Median Platinum free interval = 17 mo

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

N=415

SURGERY

CC0/1

R  
1:1

Randomization  
during surgery

HIPEC  
(cisplatin 75 mg/m<sup>2</sup>  
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)<sup>a</sup>

<sup>a</sup>Added Oct 8, 2020

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

Platinum/taxane

CC0 = 87%

Maintenance	No HIPEC	HIPEC
Bevacizumab	8%	3%
PARPi	22%	17%

### Patient characteristics

- HIPEC (n=207) vs no HIPEC (n=208)
- HGS or HG endometrioid ~80%
- ~30% BRCA mutated
- ~1/3 of patients were exposed to Bevacizumab in 1L

Safety	No HIPEC	HIPEC
G≥3 AE	17%	35%
Mortality	1.4%	0%

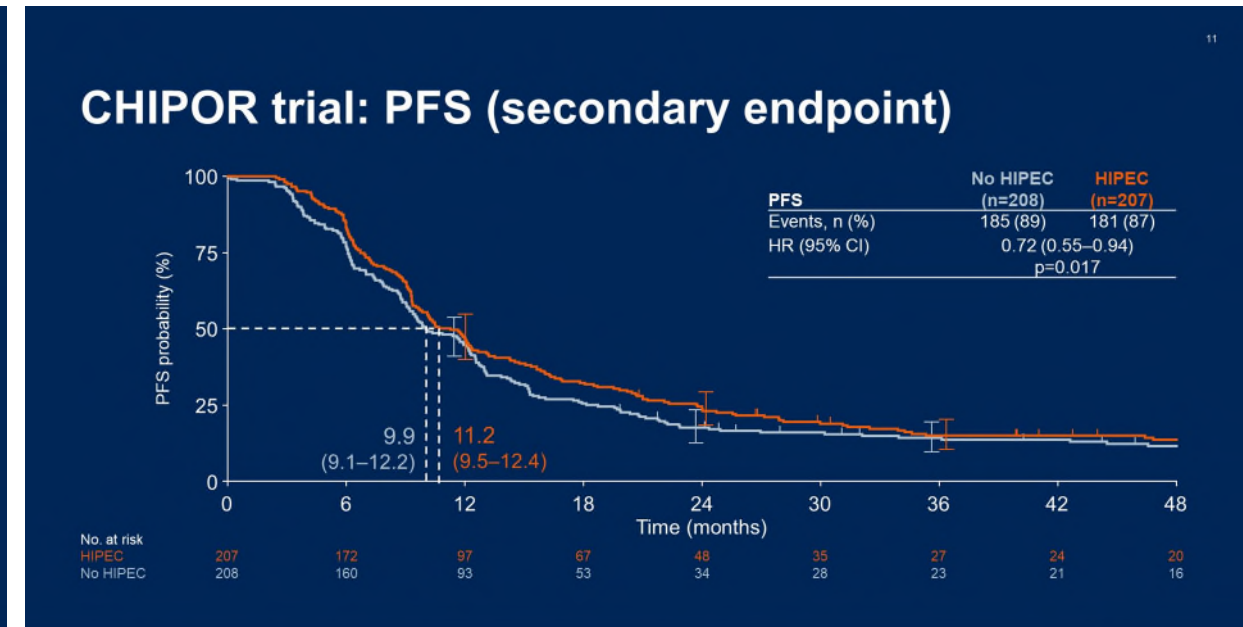
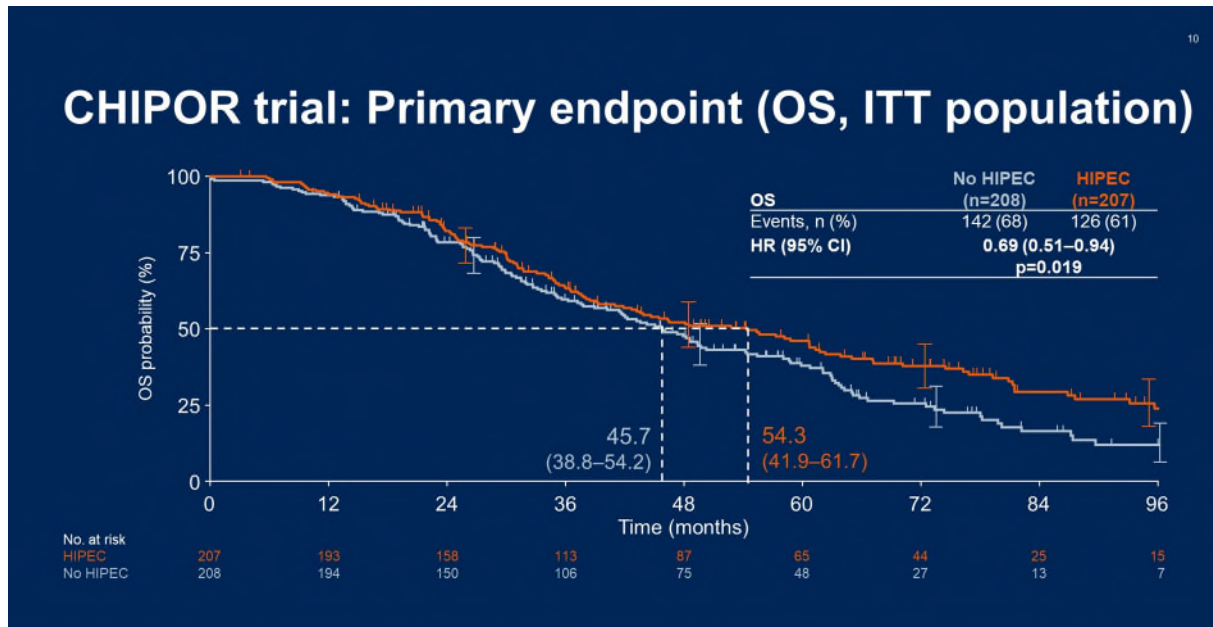
Primary endpoint: OS

Secondary endpoint: PFS

# CHIPOR – HIPEC in platinum sensitive recurrence

OS	
HIPEC	No HIPEC
54.3 mo.	45.7 mo.
HR 0.69 (p=0.019)	

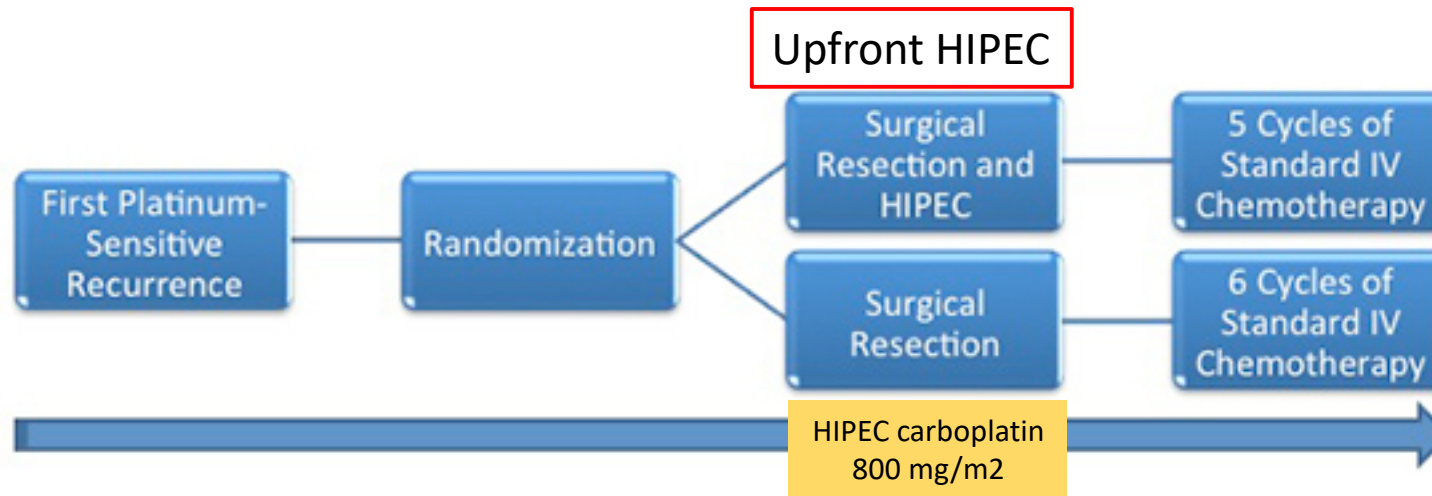
PFS	
HIPEC	No HIPEC
11.2 mo.	9.9 mo.
HR 0.72 (p=0.017)	



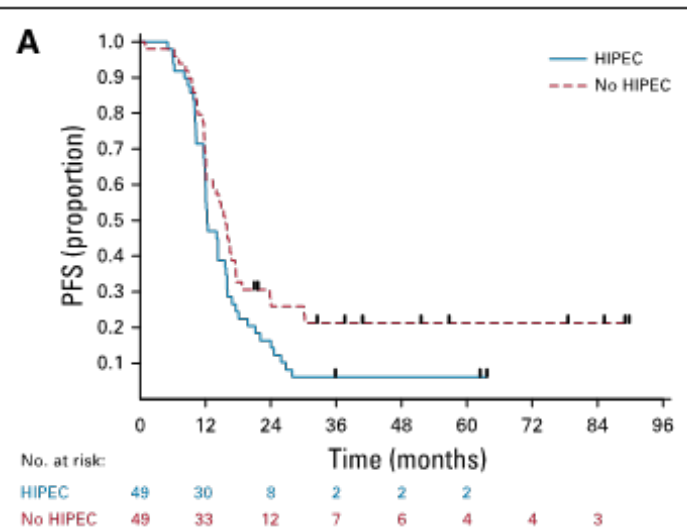
MSK study – No difference in PFS in recurrent carboplatin-sensitive ovarian cancer HIPEC

## Secondary Cytorreduction and Carboplatin Hyperthermic Intraperitoneal Chemotherapy for Platinum-Sensitive Recurrent Ovarian Cancer: An MSK Team Ovary Phase II Study

Oliver Zivanovic, MD<sup>1</sup>; Dennis S. Chi, MD<sup>1</sup>; Qin Zhou, MS<sup>1</sup>; Alexia Iasonos, PhD<sup>1</sup>; Jason A. Konner, MD<sup>1</sup>; Vicky Makker, MD<sup>1</sup>;

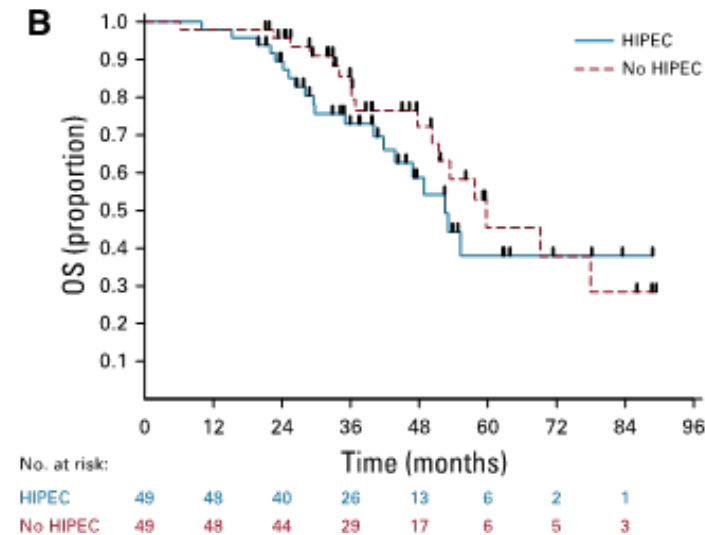


**Primary objective:** proportion of patients without evidence of disease progression at 24 months following secondary cytoreduction  
**Secondary end points:** OS, 30-day postoperative morbidity, ability to complete postoperative chemotherapy, pharmacokinetics



PFS	
HIPEC N=49	Control N=49
12.3 mo.	15.7 mo.
HR 1.54 (p=0.05)	

24-mo PFS %	
HIPEC	Control
16.3 %	28.3 %
Pts at 24 mo. who are NED	



OS	
HIPEC	Control
52.5 mo.	59.7 mo.
HR 1.39 (p=ns)	



# HIPEC upfront or after neoadjuvant chemo

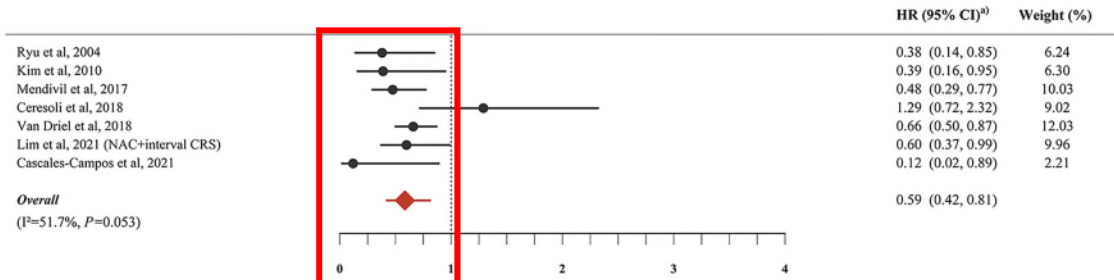
## Hyperthermic intraperitoneal chemotherapy for epithelial ovarian cancer: A meta-analysis

Se Ik Kim <sup>a,1</sup>, Ji Hyun Kim <sup>b,1</sup>, Sanghee Lee <sup>c</sup>, Hyunsoon Cho <sup>c</sup>, Willemien J. van Driel <sup>d</sup>, Gabe S. Sonke <sup>e</sup>, Robert E. Bristow <sup>f</sup>, Sang-Yoon Park <sup>b</sup>, Christina Fotopoulou <sup>g,2</sup>, Myong Cheol Lim <sup>b,h,i,j,2,\*</sup>

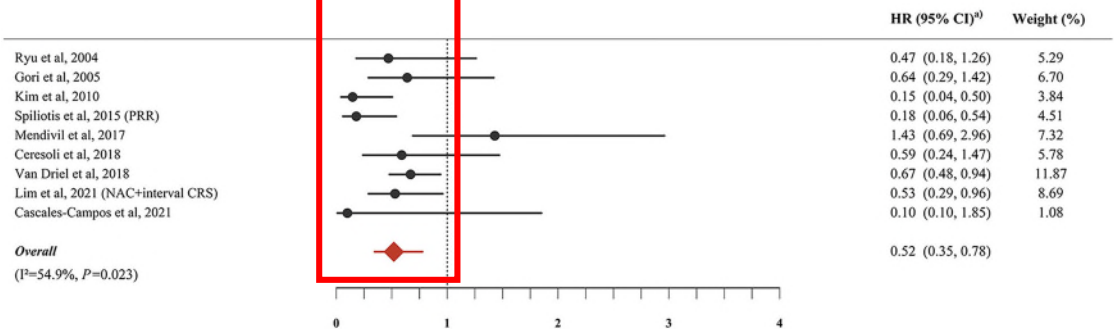
### Neoadjuvant chemo before HIPEC

Recent exposure to chemotherapy (+)

(A) Progression-free survival



(B) Overall survival



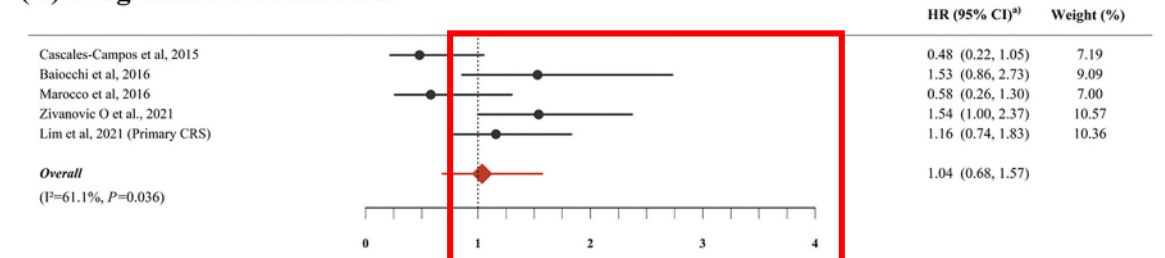
HIPEC better

HIPEC worse

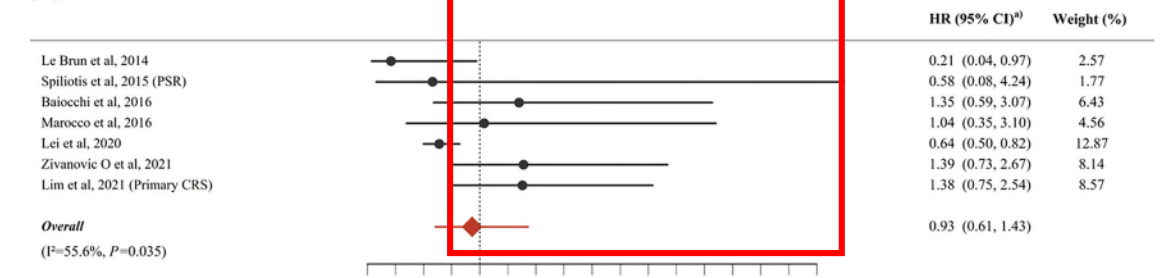
### No chemotherapy before HIPEC

Recent exposure to chemotherapy (-)

(A) Progression-free survival



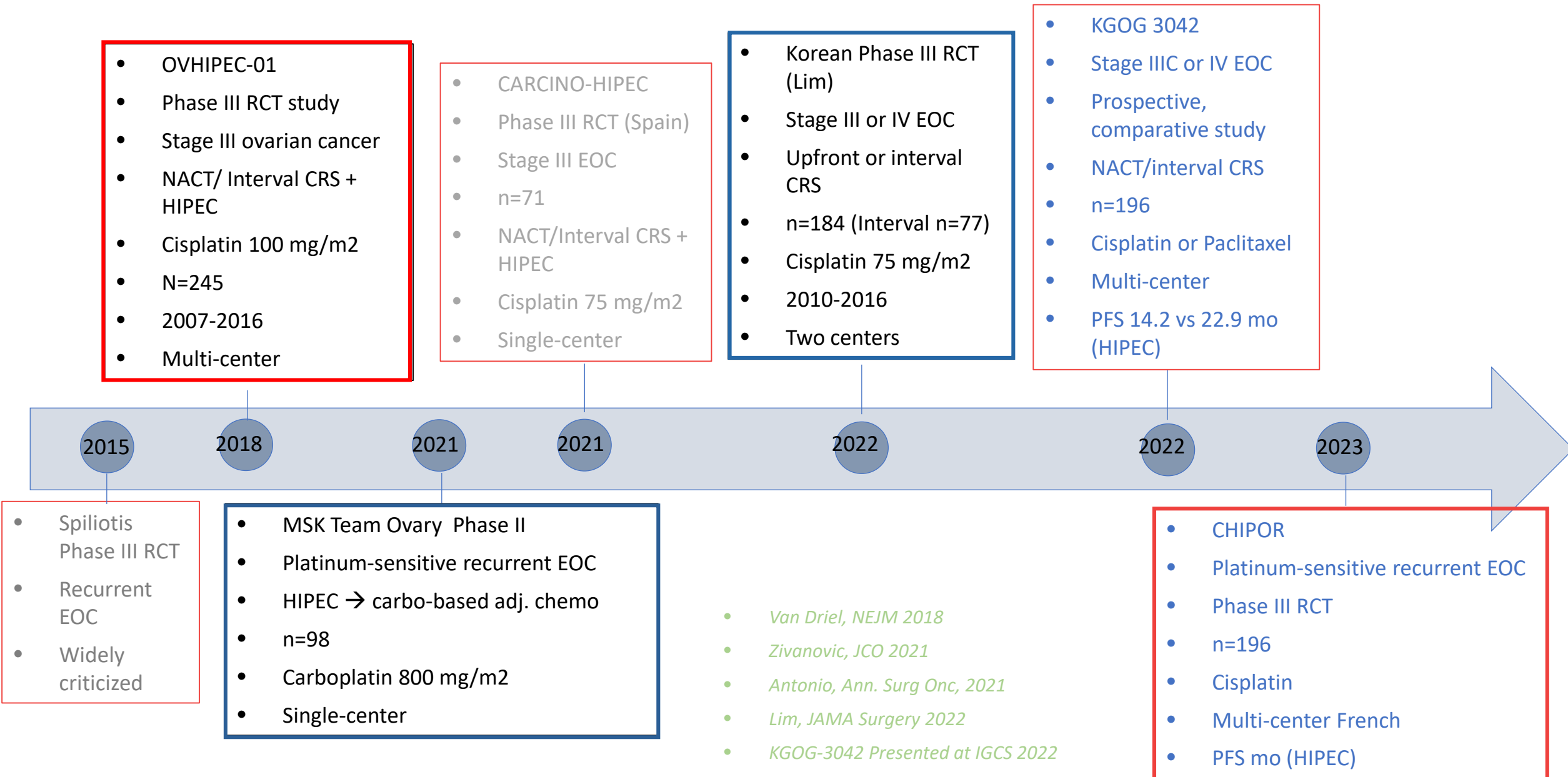
(B) Overall survival



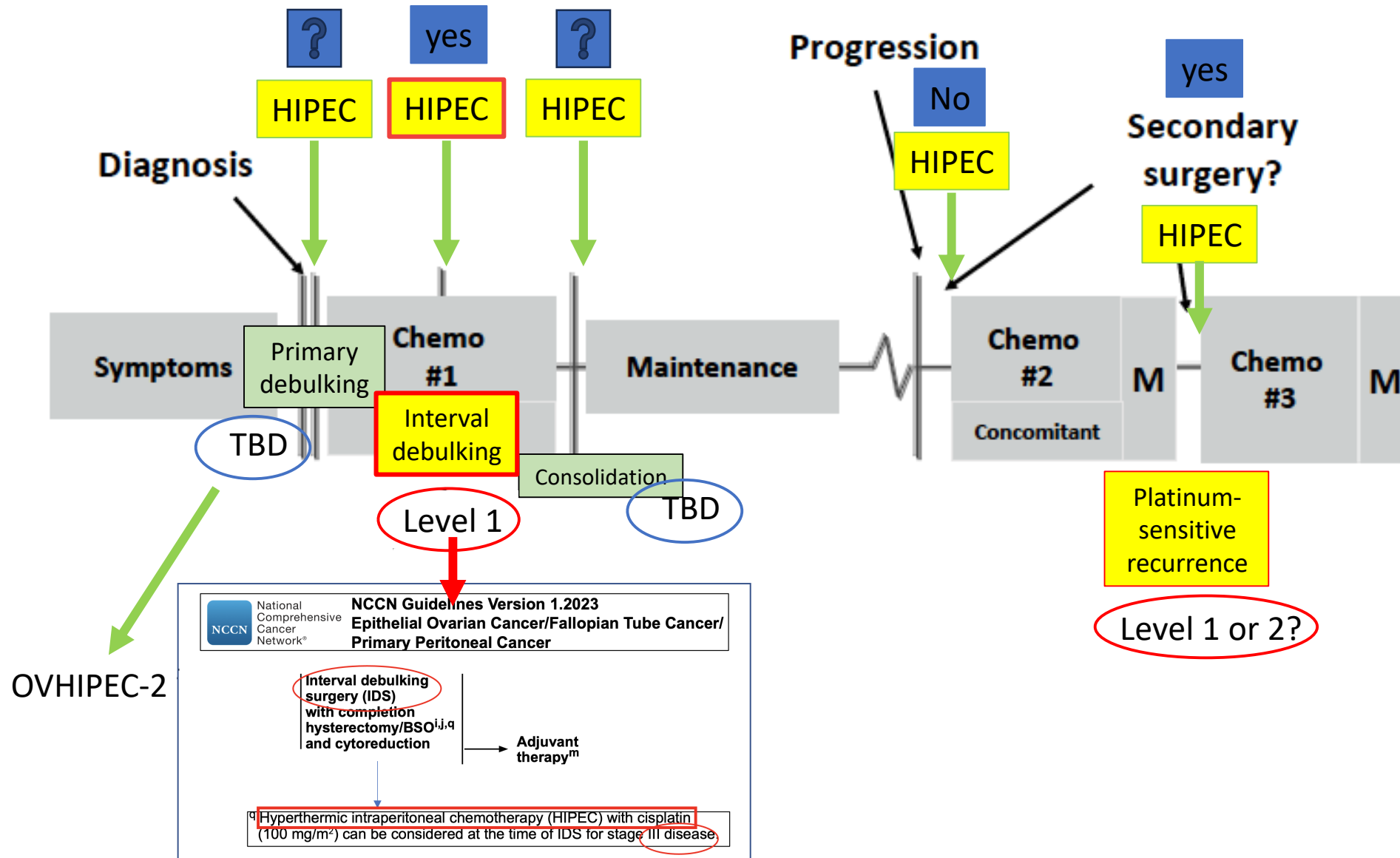
HIPEC better

HIPEC worse

# Completed randomized studies in HIPEC ovarian cancer



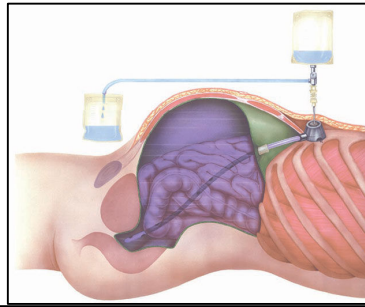
# Ovarian Cancer



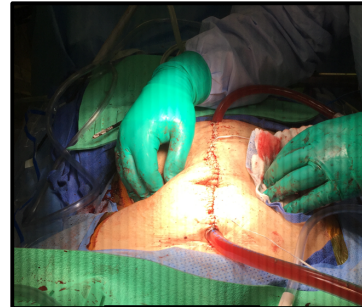
**Indications for HIPEC:**

- 1<sup>st</sup> line after NACT with Interval CRS
- 2<sup>nd</sup> line after NACT with 2ndary CRS

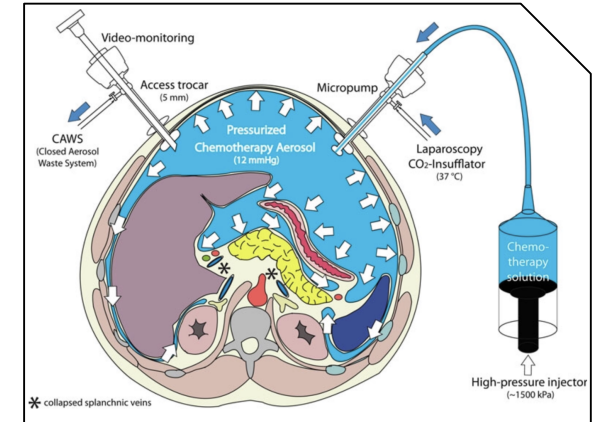
# Evolution of Intraperitoneal Chemotherapy in Ovarian Cancer



IP Chemotherapy

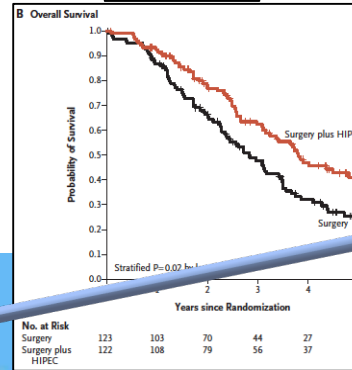
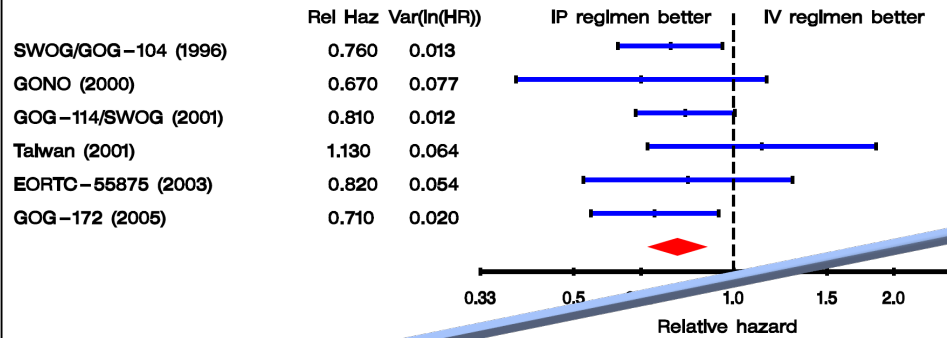


HIPEC



Does PIPAC have a role in ovarian cancer?

Treatment Hazard Ratios for Death Intraperitoneal vs Intravenous Therapy



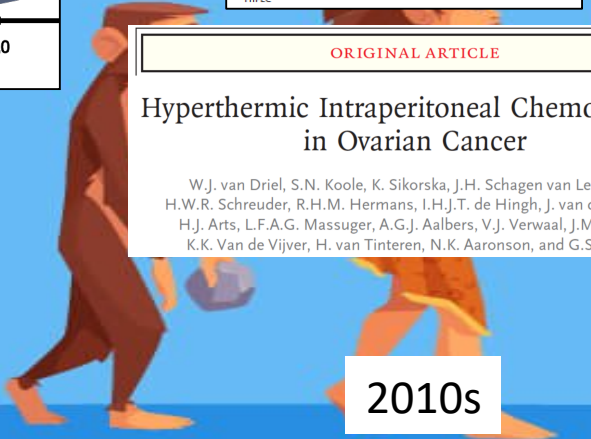
ORIGINAL ARTICLE

**Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer**

W.J. van Driel, S.N. Koole, K. Sikorska, J.H. Schagen van Leeuwen, H.W.R. Schreuder, R.H.M. Hermans, I.H.J.T. de Hingh, J. van der Velden, H.J. Arts, L.F.A.G. Massuger, A.G.J. Aalbers, V.J. Verwaal, J.M. Kieffer, K.K. Van de Vijver, H. van Tinteren, N.K. Aaronson, and G.S. Sonke



1990s-2000s



2010s



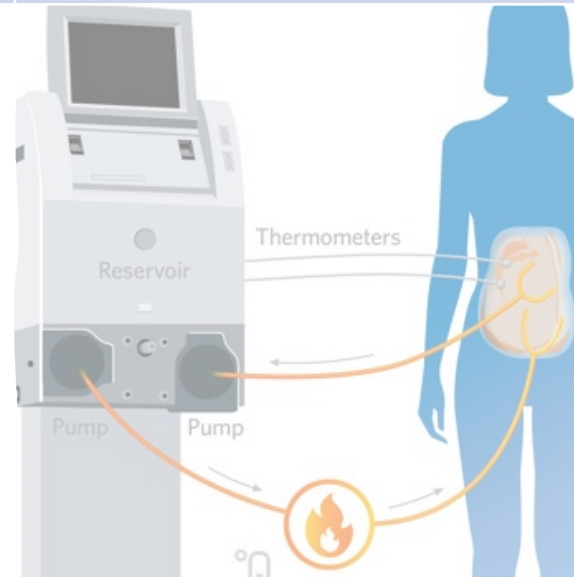
2020s



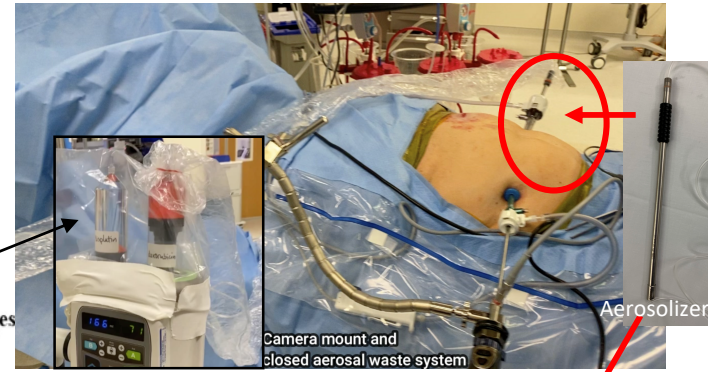
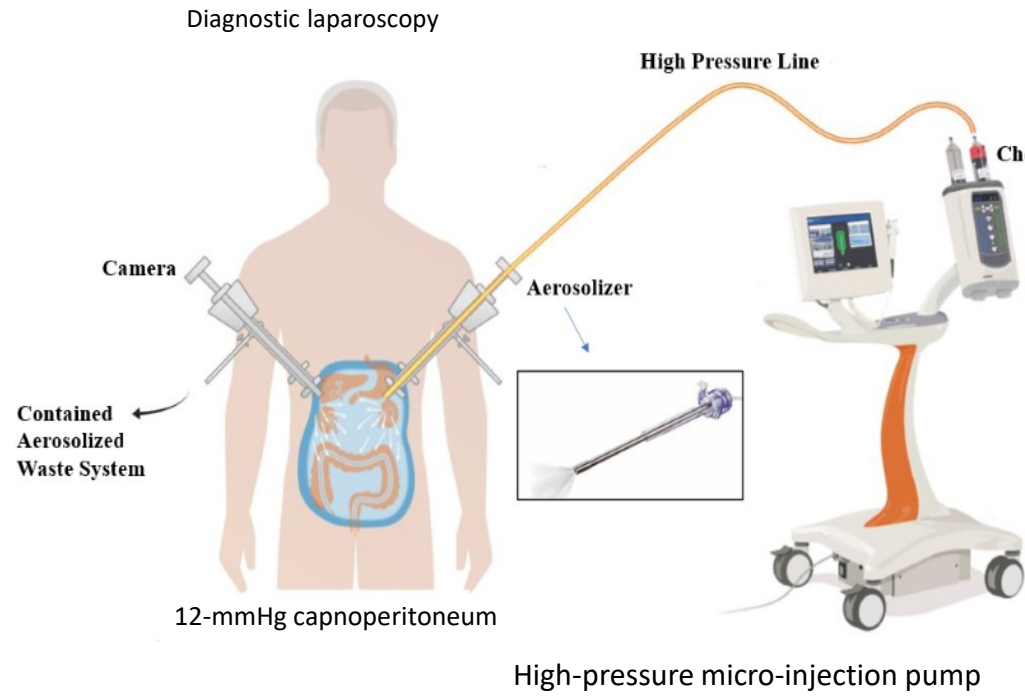
# Demystifying PIPACs and HIPECs

- PIPAC ≠ HIPEC
  - Intraperitoneal delivery of chemotherapy

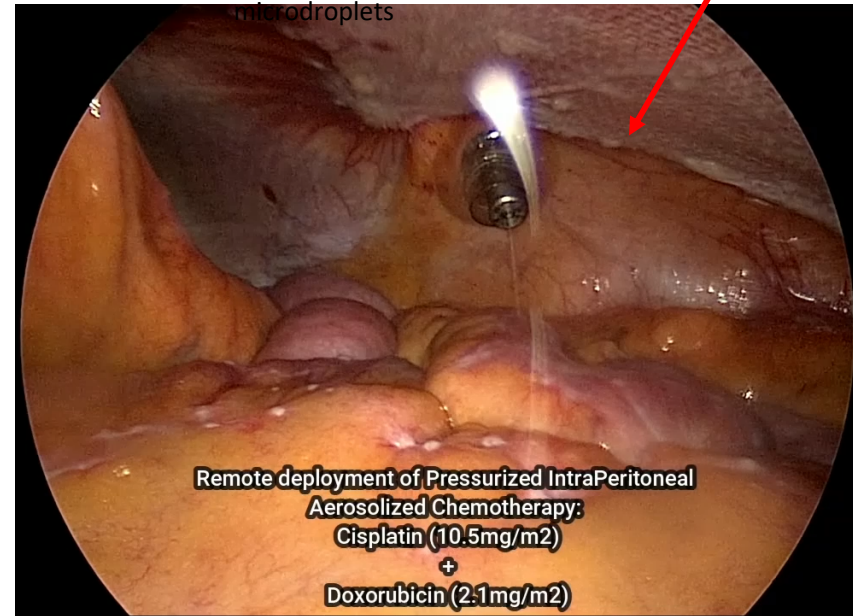
	HIPEC	PIPAC
Delivery method	Heat	Pressure
Therapeutic intent	Curative	Palliative
Surgical debulking	Yes	No!



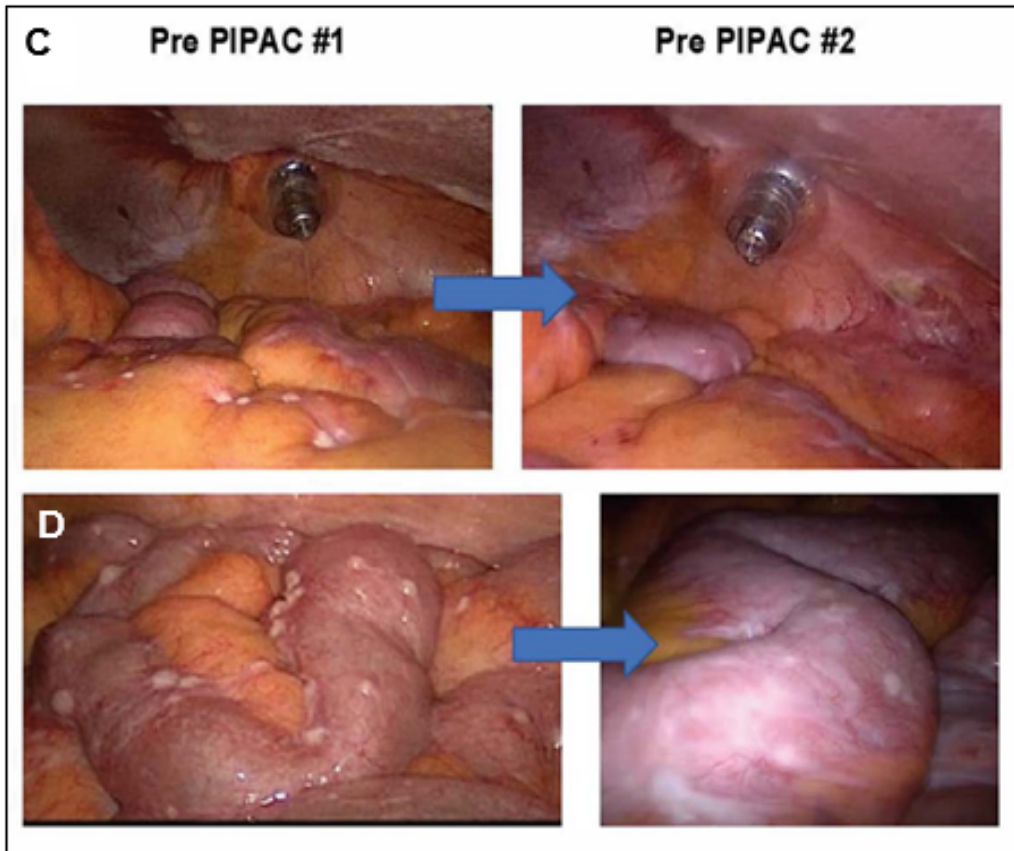
# PIPAC



Homogeneous, 'gas-like' drug distribution throughout the abdominal cavity, *via* formation of microdroplets

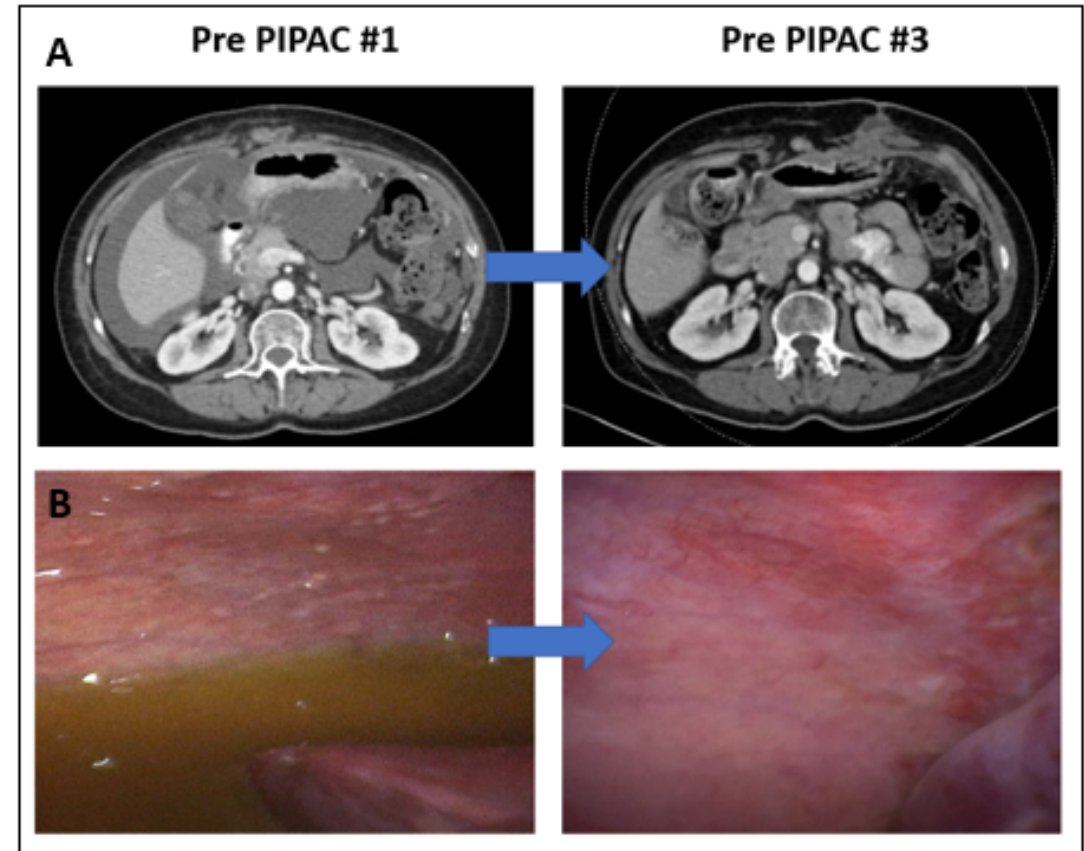


# PIPAC cisplatin/doxorubicin in Low Grade Serous (LGS) Ovarian cancer patients



68 yo F with Stage IV LGS metastatic to lung and liver, heavily pretreated with 10 prior lines

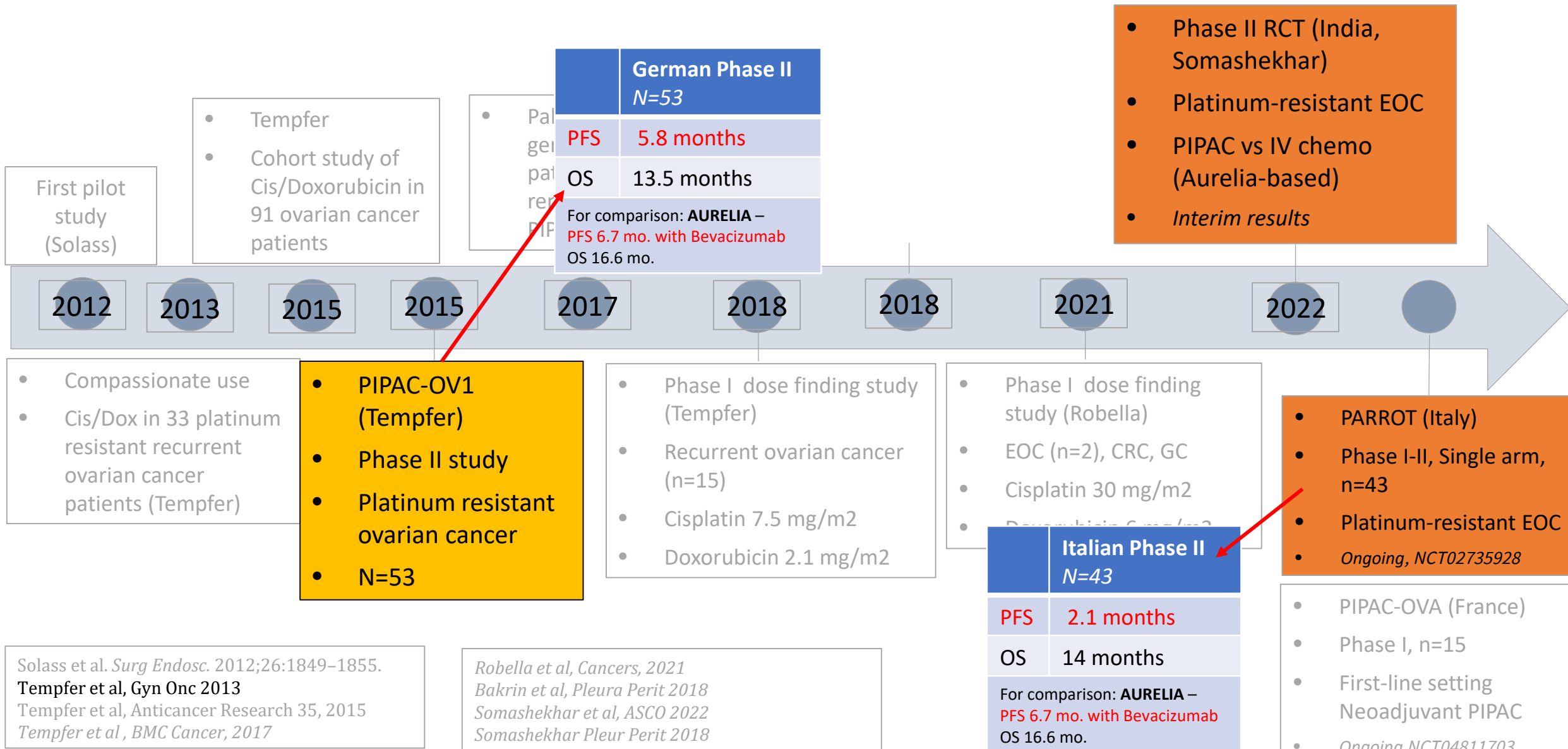
- Improved Peritoneal carcinomatosis index (PCI) 20 → PCI 14



59 yo F with Stage IIIC LGS, heavily pretreated with 5 prior lines.

- CA125 = 367 → 32
- Peritoneal tumor regression by RECIST
- Resolution of Ascites

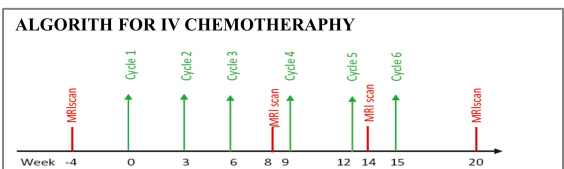
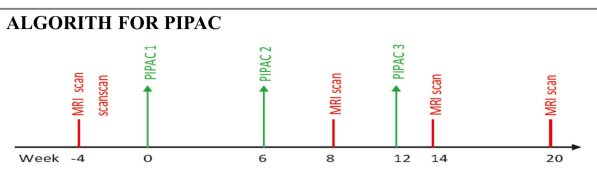
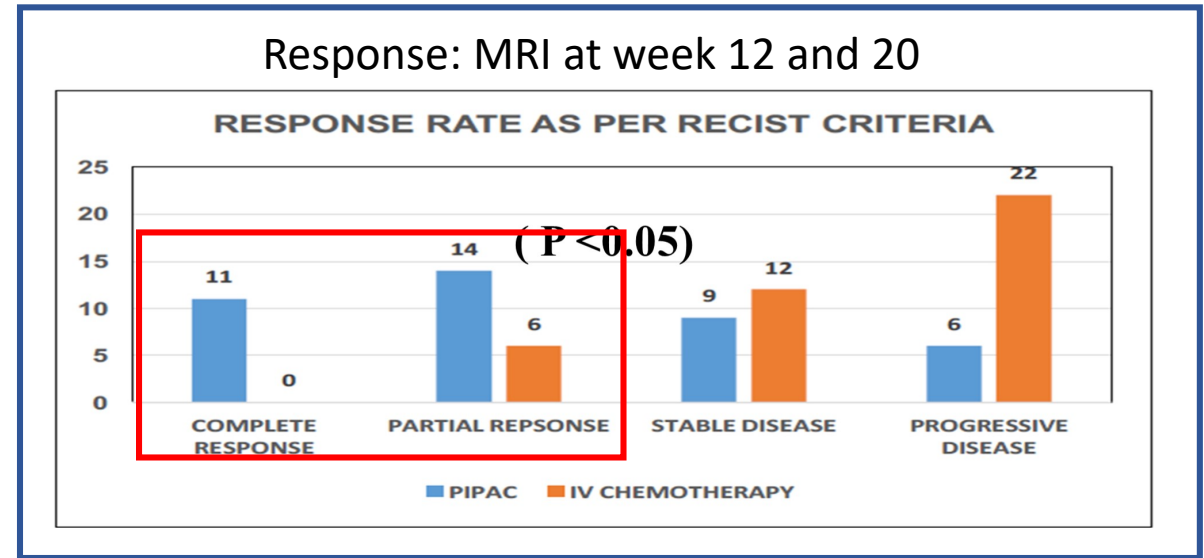
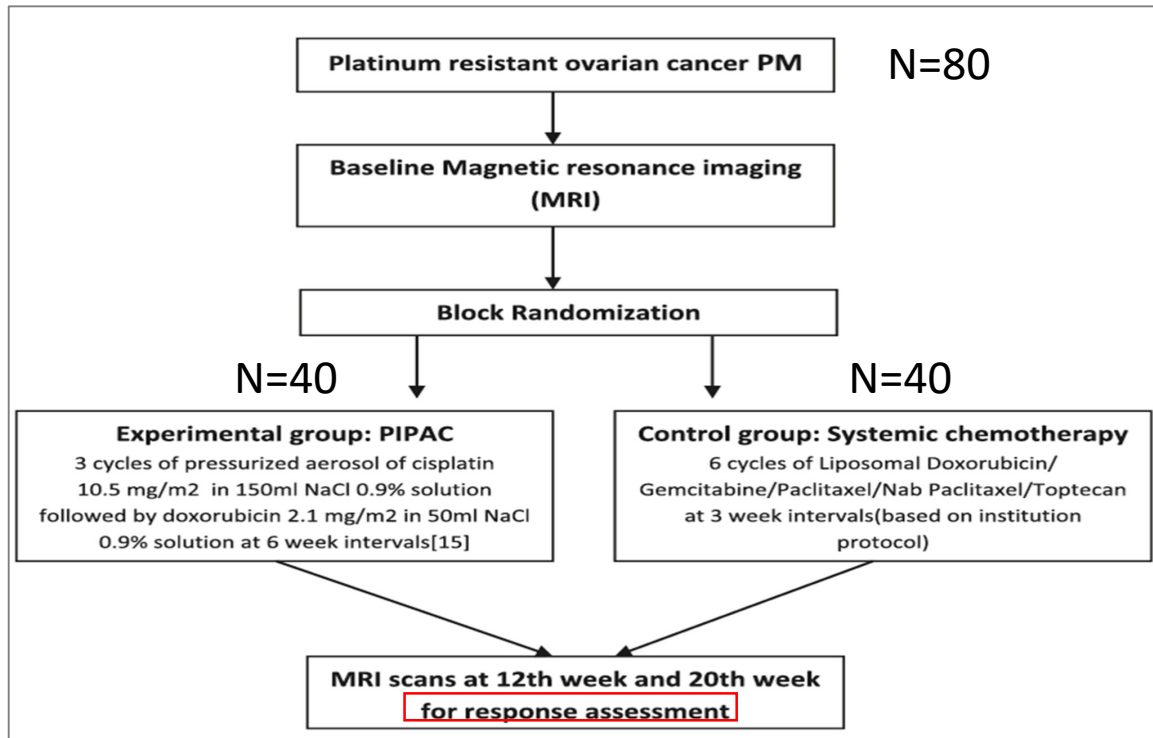
# PIPAC studies in ovarian cancer



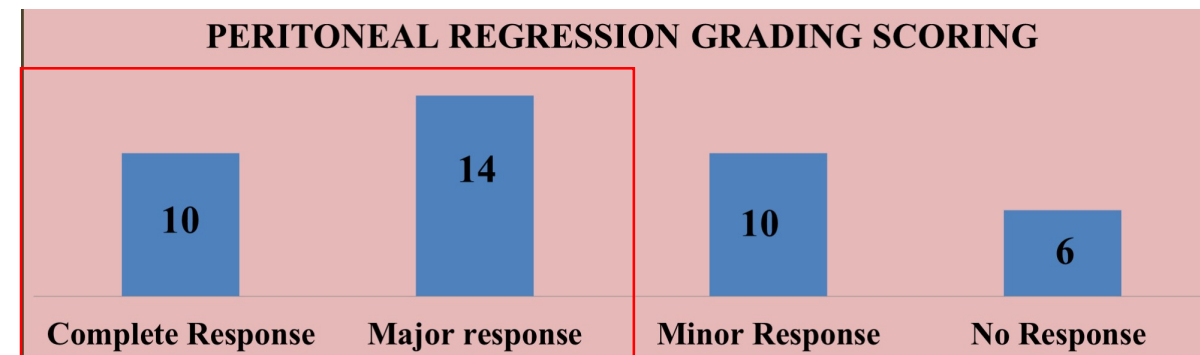


# First PIPAC randomized trial in platinum-resistant ovarian cancer - India

## PIPAC compared to AURELIA regimen



### Histologic response

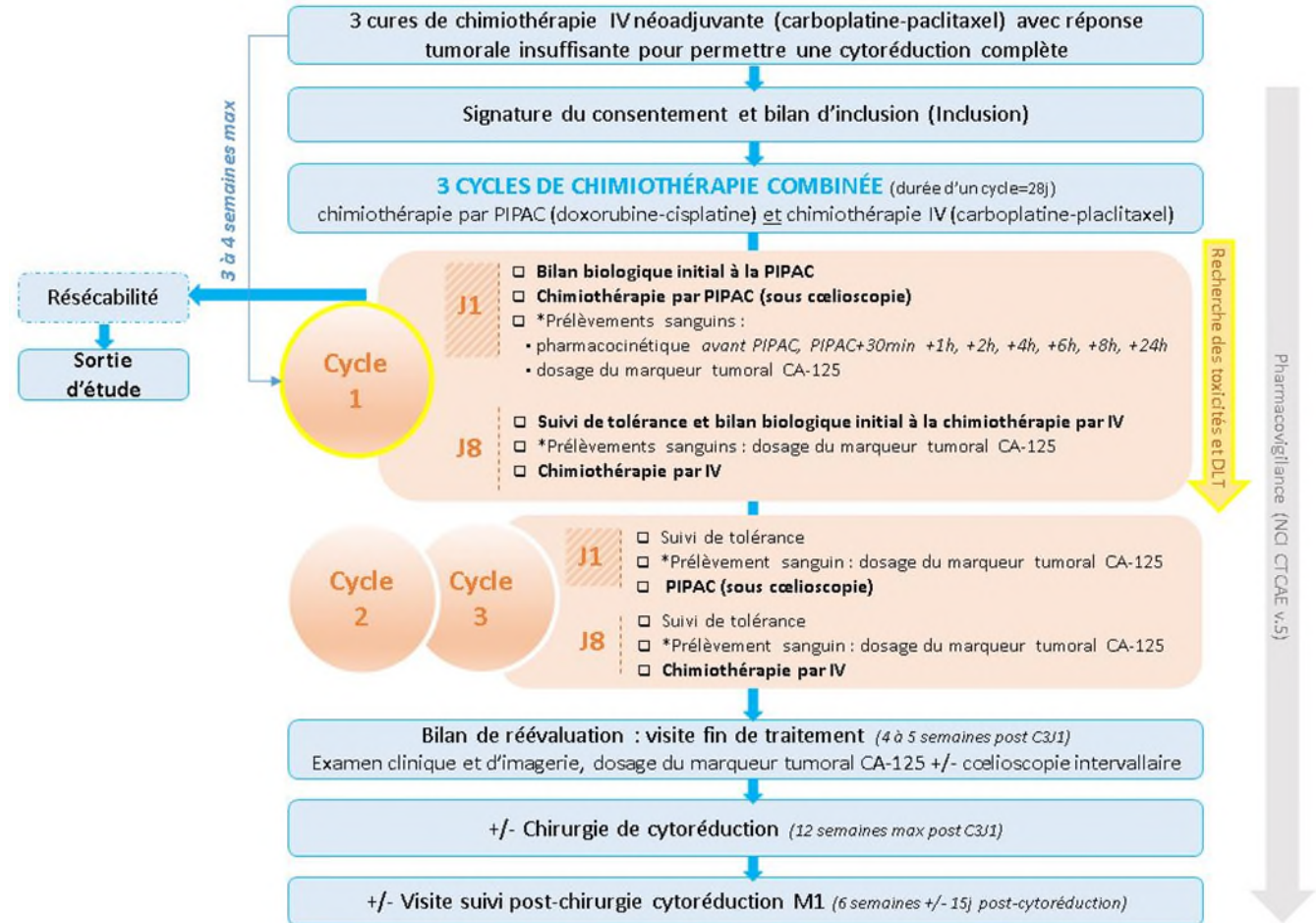


	PIPAC N=40	IV Chemo (N=40)	P-Value
Systemic Chemotherapy			
2 <sup>nd</sup> line	24	21	
>2 <sup>nd</sup> line	16	19	0.746

- Early in platinum-resistant recurrence course
- Over half of patients only had two prior lines

# Neoadjuvant PIPAC in combination with systemic chemotherapy in **first-line setting** - PIPACOVA

- **Phase I clinical trial in France**
- **Neoadjuvant** chemo x 3 cycles
- **Interval** Diagnostic laparoscopy
  - Surgically resectable → interval CRS
  - **Unresectable** → PIPAC
- dose escalation evaluating the **addition of PIPAC to neoadjuvant systemic chemotherapy**
- D1 = PIPAC (cisplatin/doxorubicin)
- D8 = IV carbo/taxol
- Dose escalation study
  - Cisplatin 10.5 → 31.5 mg/m<sup>2</sup>
  - Doxorubicin 2.1 → 6.3 mg/m<sup>2</sup>
- *Hospices Civils de Lyon | N=15 | Recruiting*
- *ClinicalTrials.gov Identifier: NCT04811703*

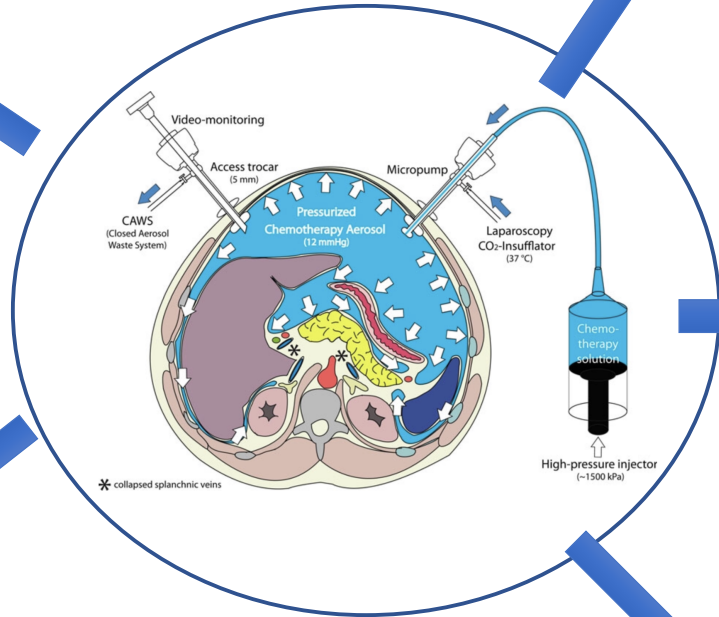


# Potential indications for PIPAC in ovarian cancer

1. Platinum-resistant ovarian cancer

2. Systemic chemotherapy intolerance

Geriatric patients ?



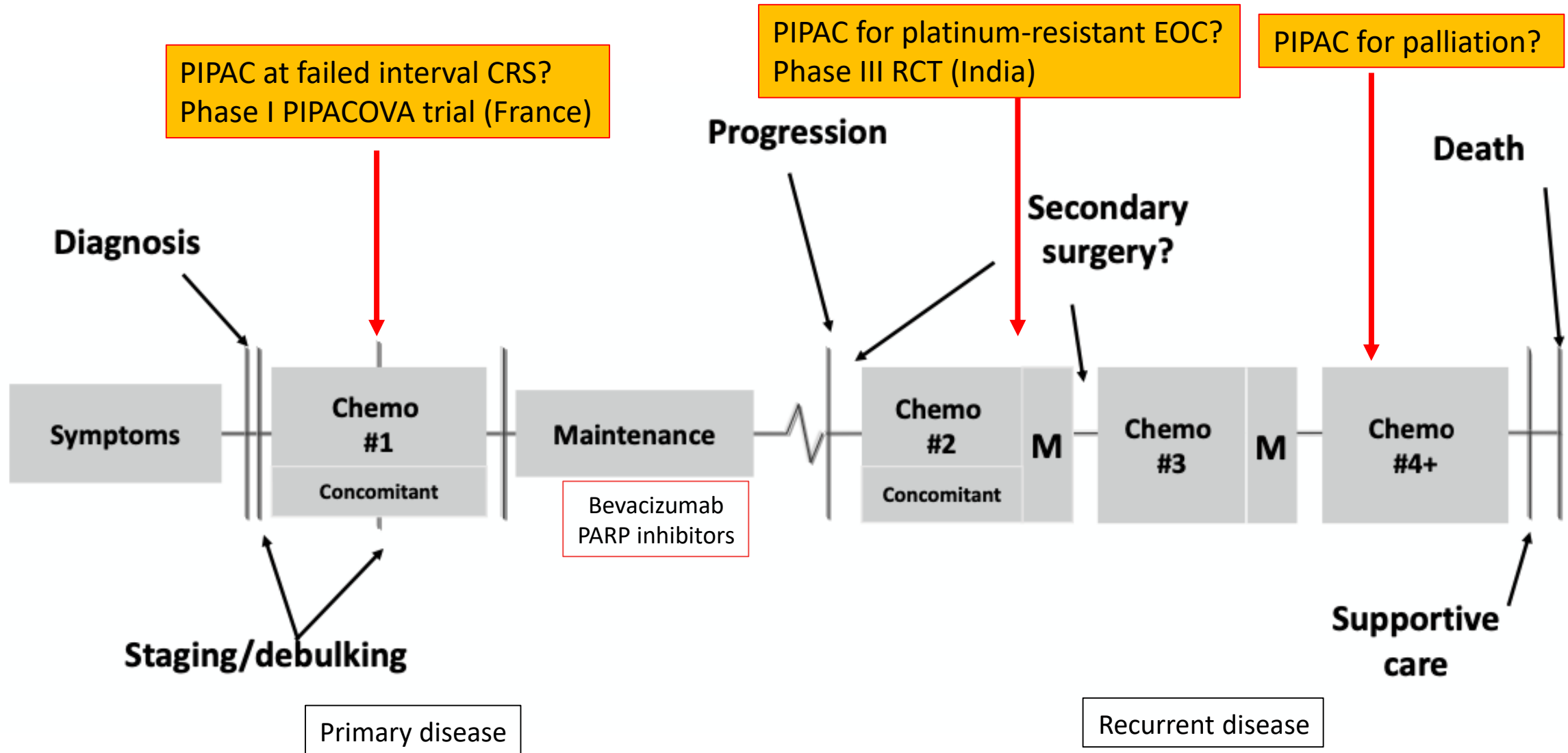
3. Low-grade serous ovarian cancer?

Cancers with relative chemoresistance?

4. *First-line setting:*  
Adjunct to neoadjuvant IV chemo to enable optimal interval CRS?

3. Adjunct to 2<sup>nd</sup> line chemotherapy with partial response, but residual peritoneal mets?

# Potential PIPAC indications in Treatment paradigm in ovarian cancer





# PIPAC in ovarian cancer

Experimental in the U.S.

- Clinical trial participation

Well tolerated with low toxicity profile

Recurrent ovarian cancer patients who seek less toxic alternatives to systemic chemotherapies

Quality of life

Establish indications

Establish optimal drug doses and combinations

Multimodal therapy

- IV chemo
- PARP inhibitors
- Bevacizumab
- Checkpoint inhibitors

Novel PIPAC drugs

- nab-paclitaxel
- Checkpoint inhibitors?

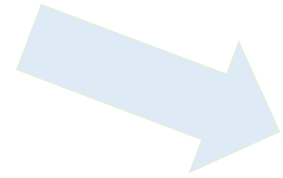
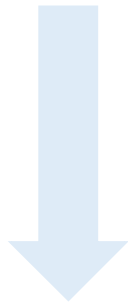
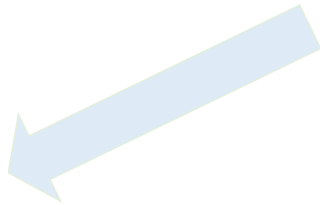


# Peritoneal surface malignancy Program

Ovarian cancer  
Uterine cancer

Colon cancer  
Appendiceal cancer

Gastric cancer



**HIPEC**

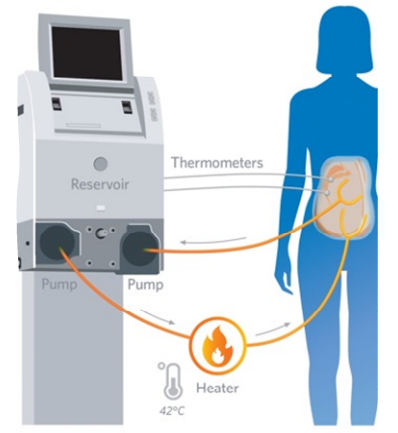
**OVHIPEC-2**

**GOG 3068**

**PIPAC**

PIPAC Phase I  
Clinical trial:  
*NCT04329494*

PIPAC Biliary  
Cancer Trial  
*NCT05285358*



Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

