

# **HIPEC in ovarian cancer**

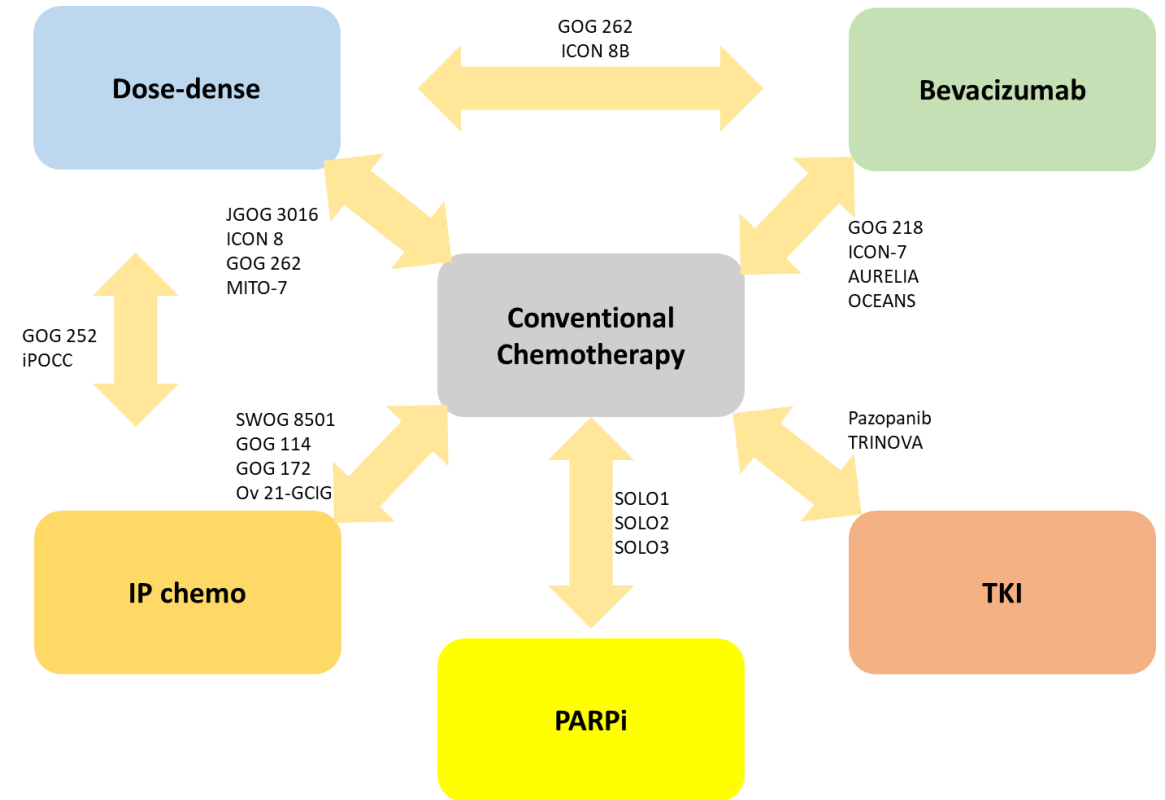
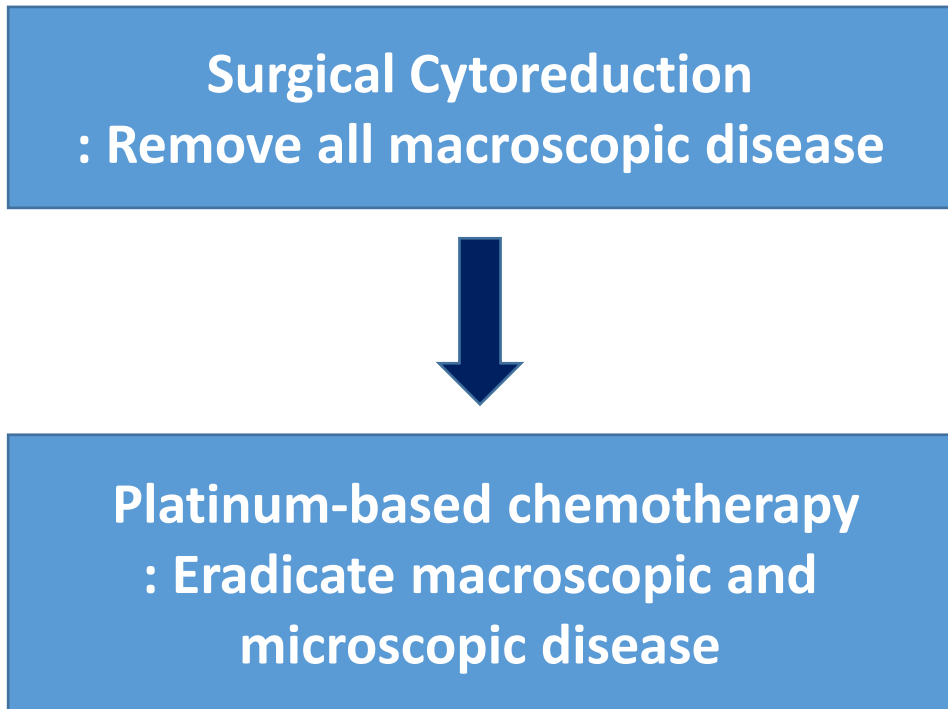
Yong Jae Lee

Department of Obstetrics and Gynecology  
Yonsei University College of Medicine, Seoul, Korea

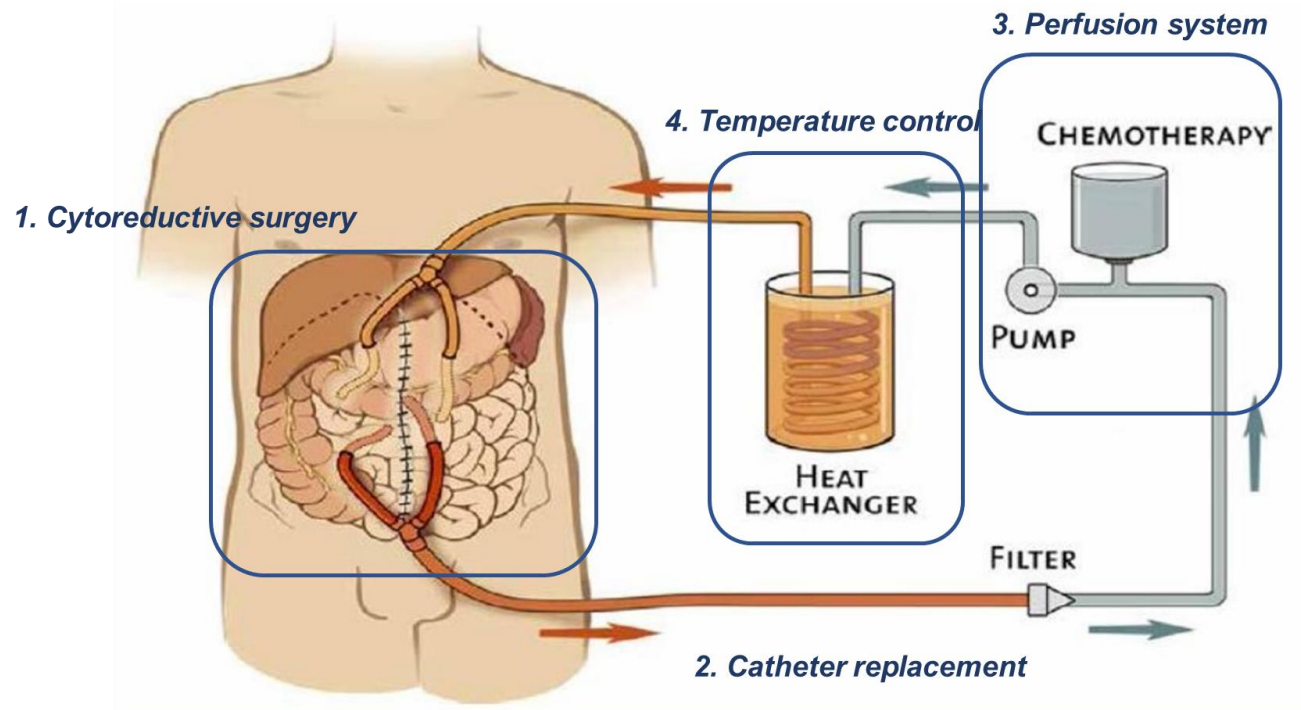
# Contents

- Rationale for HIPEC
- Implementation of HIPEC in ovarian cancer
- On-going trial
- Unanswered questions in HIPEC

# Treatment of advanced ovarian cancer



# Rationale for HIPEC



- **Intraperitoneal Chemotherapy**
  - Enhances drug delivery at the peritoneal surface
  - Eliminating residual microscopic peritoneal disease
- **Hyperthermia**
  - Increases the penetration of chemotherapy
  - Increases the sensitivity to chemotherapy
  - Direct cytotoxic effect by promoting the denaturation of protein

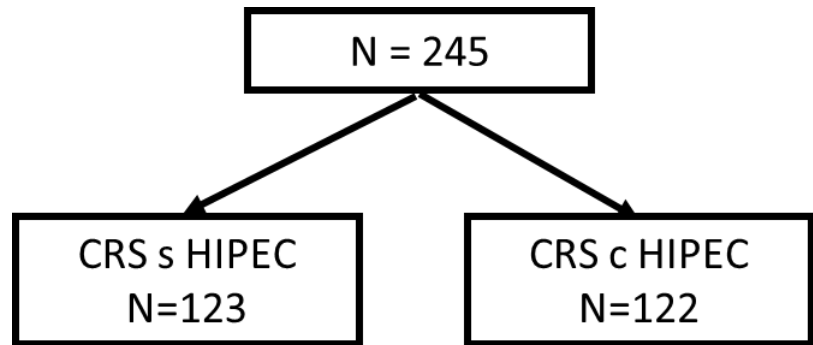
# Neoadjuvant setting

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

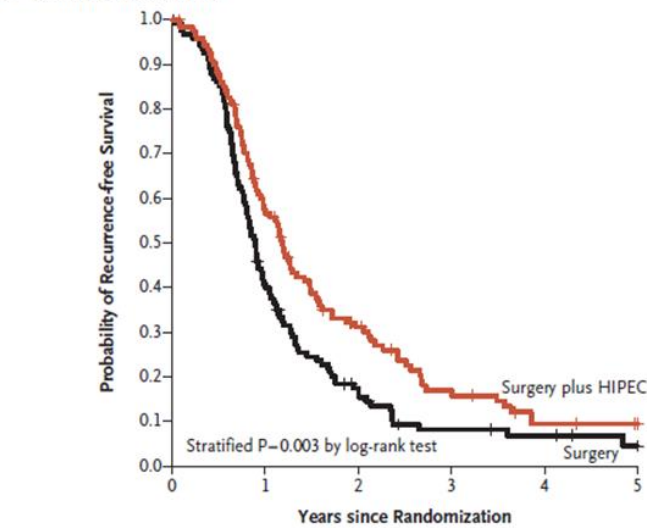
## Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

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



✓ Cisplatin 100mg/m<sup>2</sup>, N/S

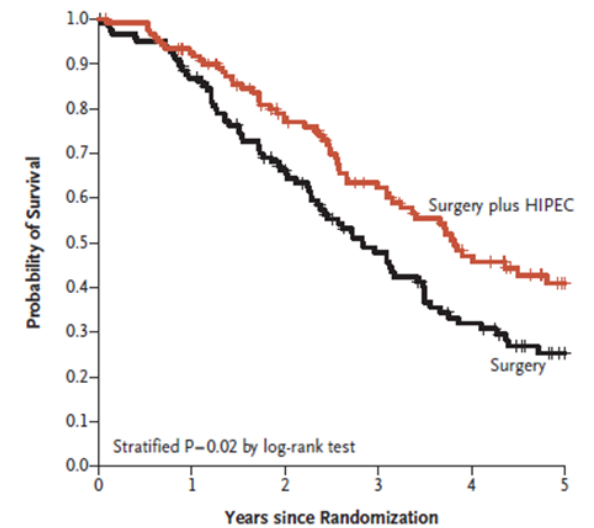
A Recurrence-free Survival



No. at Risk  
Surgery  
Surgery plus  
HIPEC

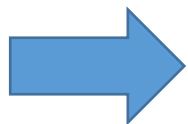
	0	1	2	3	4	5
Surgery	123	48	18	7	5	2
Surgery plus HIPEC	122	67	31	15	7	5

B Overall Survival



No. at Risk  
Surgery  
Surgery plus  
HIPEC

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



Survival benefits of HIPEC followed by interval cytoreductive surgery (ICS) in stage III ovarian cancer patients.

# Neoadjuvant setting

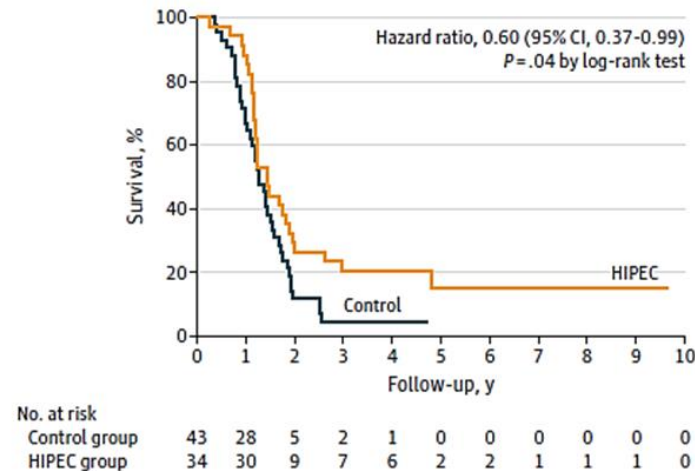
JAMA Surgery | Original Investigation

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

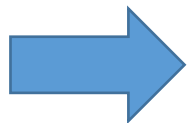
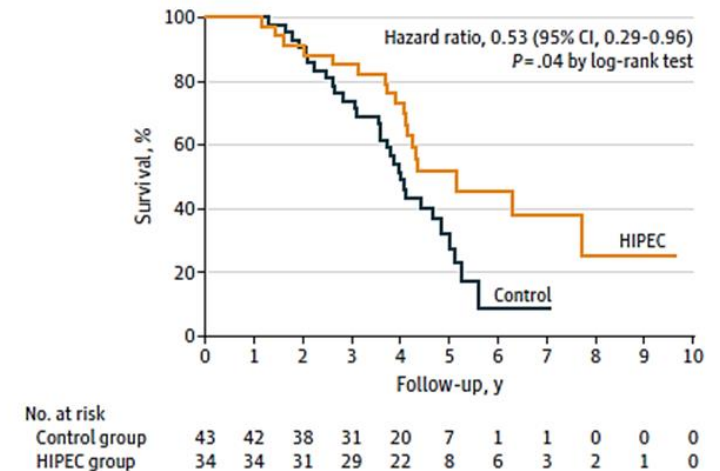
Myong Cheol Lim, MD, PhD; Suk-Joon Chang, MD, PhD; Boram Park, PhD; Heon Jong Yoo, MD, PhD; Chong Woo Yoo, MD, PhD; Byung Ho Nam, PhD; Sang-Yoon Park, MD, PhD; for the HIPEC for Ovarian Cancer Collaborators

✓ Subgroup analysis: ICS after NAC group  
ICS without HIPEC (N = 43)  
vs  
ICS with HIPEC (N = 34)  
✓ Cisplatin 75mg/m<sup>2</sup>, N/S

C Progression-free survival in patients undergoing interval cytoreductive surgery after neoadjuvant chemotherapy



D Overall survival in patients undergoing interval cytoreductive surgery after neoadjuvant chemotherapy



Survival benefits of HIPEC with ICS in subgroup analysis of patients who underwent neoadjuvant chemotherapy

# Primary ovarian cancer (Primary setting)

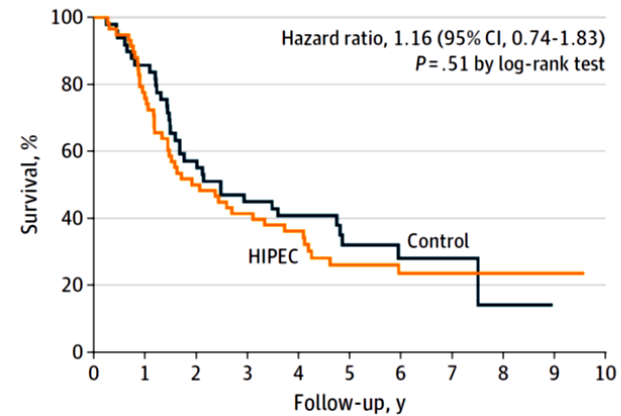
JAMA Surgery | Original Investigation

## 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; Byung Ho Nam, PhD; Sang-Yoon Park, MD, PhD; for the HIPEC for Ovarian Cancer Collaborators

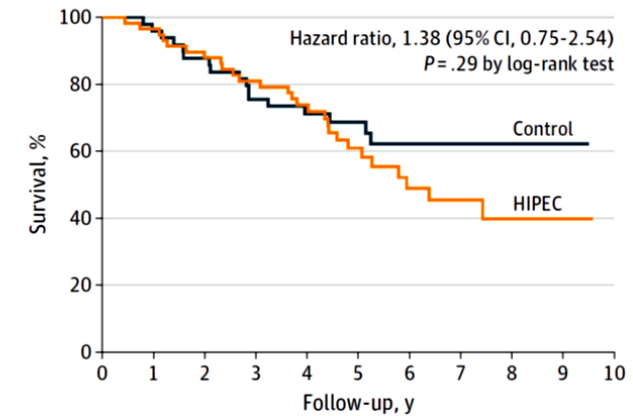
✓ Subgroup analysis : PCS  
PCS without HIPEC (N = 49)  
VS  
PCS with HIPEC (N = 58)  
✓ Cisplatin 75mg/m<sup>2</sup>, N/S

**A** Progression-free survival in patients undergoing primary cytoreductive surgery

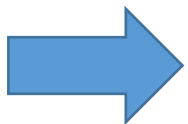


No. at risk	0	1	2	3	4	5	6	7	8	9	10
Control group	49	42	28	22	17	10	7	4	1	0	0
HIPEC group	58	44	29	24	18	10	8	6	3	1	0

**B** Overall survival in patients undergoing primary cytoreductive surgery



No. at risk	0	1	2	3	4	5	6	7	8	9	10
Control group	49	47	43	37	31	21	17	11	6	1	0
HIPEC group	58	56	51	46	38	23	14	10	4	2	0



No survival benefits of PCS with HIPEC in stage III or IV ovarian cancer patients.

# Primary ovarian cancer (Primary setting)



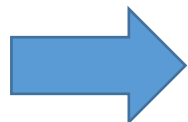
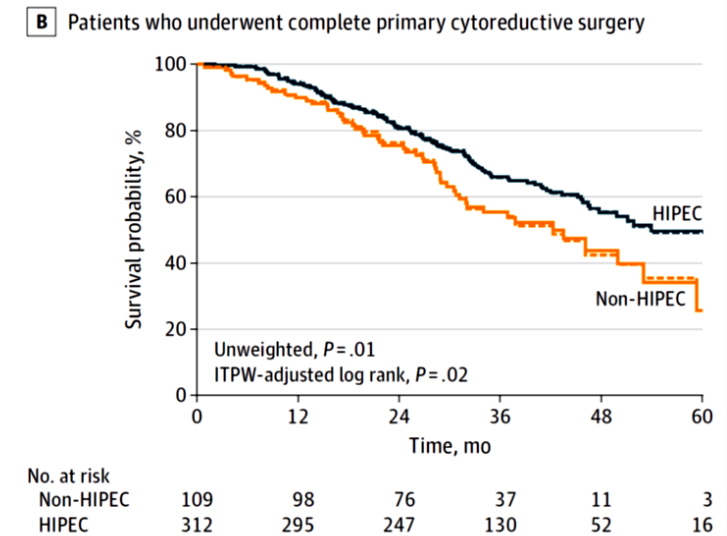
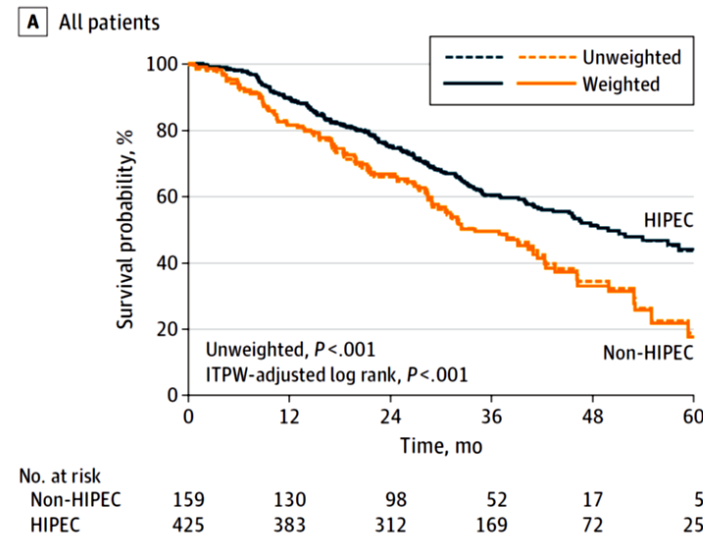
Original Investigation | Oncology

## Evaluation of Cytoreductive Surgery With or Without Hyperthermic Intraperitoneal Chemotherapy for Stage III Epithelial Ovarian Cancer

Ziying Lei, MD; Yue Wang, MD; Jiahong Wang, MD; Ke Wang, MD; Jun Tian, MD; Ying Zhao, MD; Lipai Chen, MD; Jin Wang, MD; Jiali Luo, PhD; Manman Jia, MD; Hongsheng Tang, MD; Qingjun He, MD; Quanxing Liao, MD; Xiansheng Yang, MD; Tianpei Guan, MD; Li Wang, MD; Shuzhong Cui, MD, PhD; for the Chinese Peritoneal Oncology Study Group (Gynecologic Oncology Study Group)

Median OS(months) : 49.8 vs 34.0  
 Median OS(months) in complete resection:  
 53.9 vs 42.3

✓ Multicenter, retrospective study  
 (N=584)  
 PCS without HIPEC (N = 159)  
 VS  
 PCS with HIPEC (N = 425)  
 ✓ Cisplatin 50mg/m<sup>2</sup>, N/S



Survival benefits of PCS with HIPEC in stage III ovarian cancer patients.



# Recurrent setting

## Cytoreductive Surgery and HIPEC in Recurrent Epithelial Ovarian Cancer: A Prospective Randomized Phase III Study

Annals of  
**SURGICAL ONCOLOGY**  
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

Recurrent (second line chemotherapy)

CRS without HIPEC (N = 60)

vs

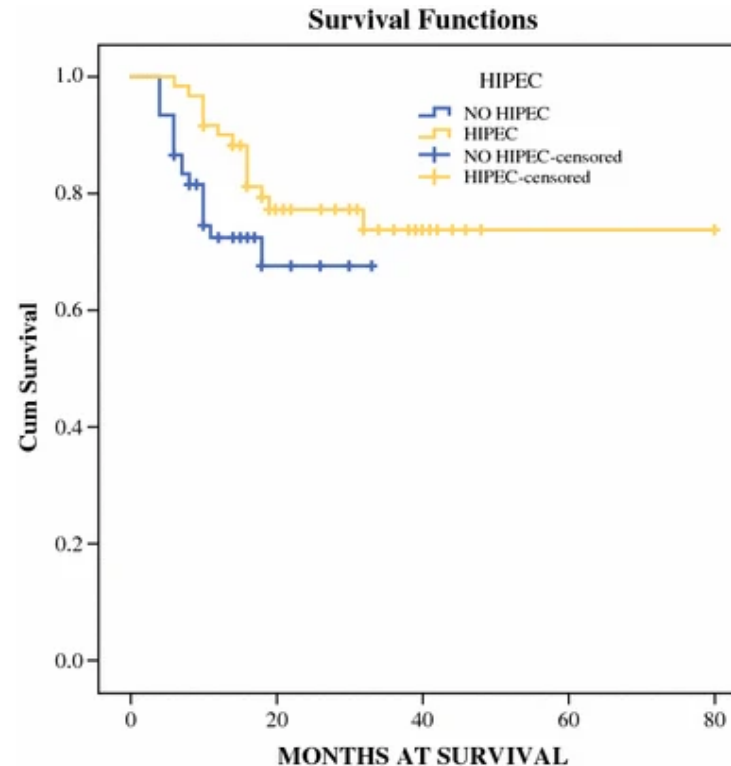
CRS with HIPEC (N = 60)

✓ Platinum-sensitive:

Cisplatin 100 mg/m<sup>2</sup> + paclitaxel 175 mg/m<sup>2</sup>

✓ Platinum-resistant

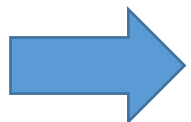
doxorubicin 35 mg/m<sup>2</sup> + mitomycin 15 mg/m<sup>2</sup>



Median OS(months) :

26.7 vs 13.4

P = 0.006

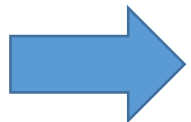
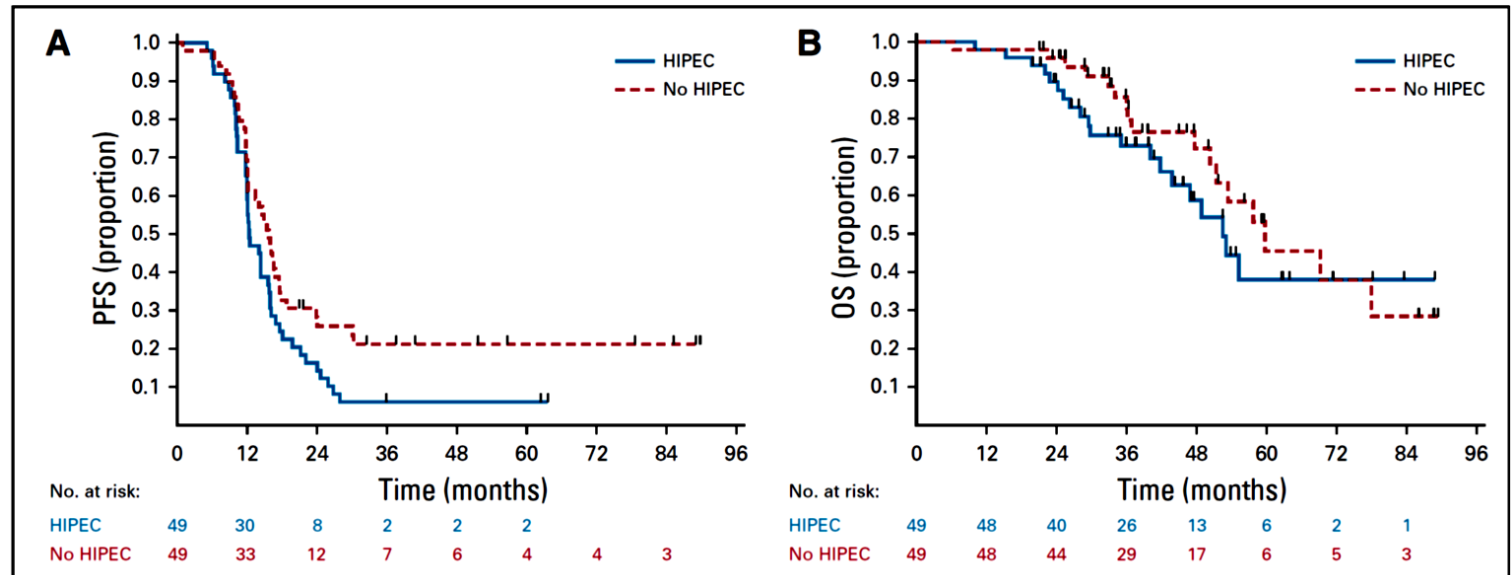


CRS and HIPEC offer a significant survival benefit to patients with recurrent EOC

# Recurrent setting

Secondary Cytoreduction and Carboplatin  
Hyperthermic Intraperitoneal Chemotherapy for  
Platinum-Sensitive Recurrent Ovarian Cancer: An  
MSK Team Ovary Phase II Study *Journal of Clinical Oncology*®

**Platinum-Sensitive Recurrent**  
secondary CRS without HIPEC (N = 49)  
VS  
secondary CRS with HIPEC (N = 49)  
✓ Carboplatin (800 mg/m<sup>2</sup>)



HIPEC with carboplatin was well tolerated but did not result in superior clinical outcomes

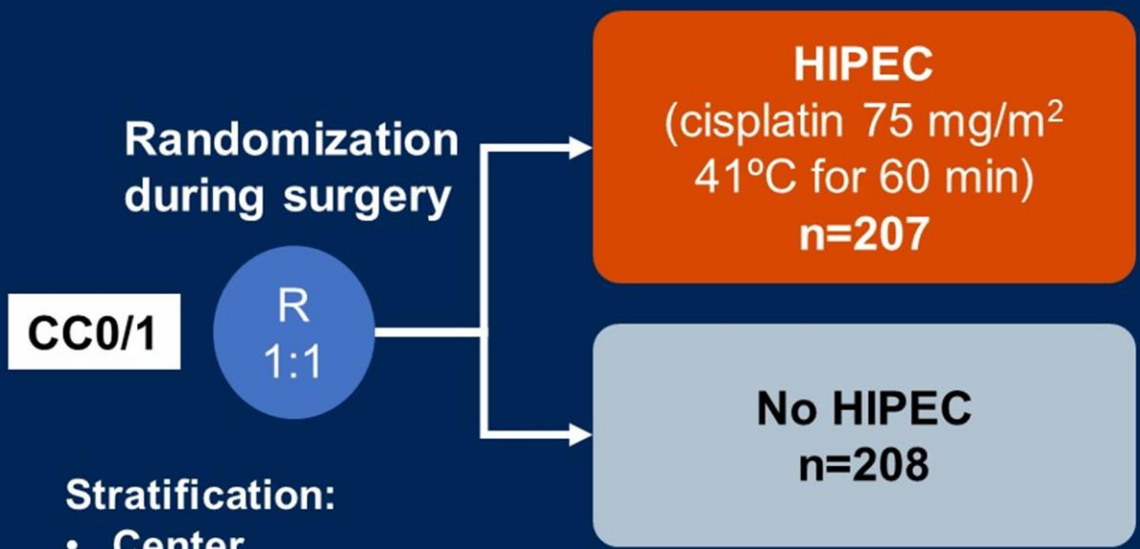
Ongoing trial

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

Median laparotomy  
Complete resection

- First relapse of epithelial ovarian cancer
  - PFI ≥6 months
  - Response to 6 cycles of platinum-based chemotherapy
  - Complete surgery achievable
- N=415

S  
U  
R  
G  
E  
R  
Y



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

# CHIPOR trial: Maintenance treatment after surgery

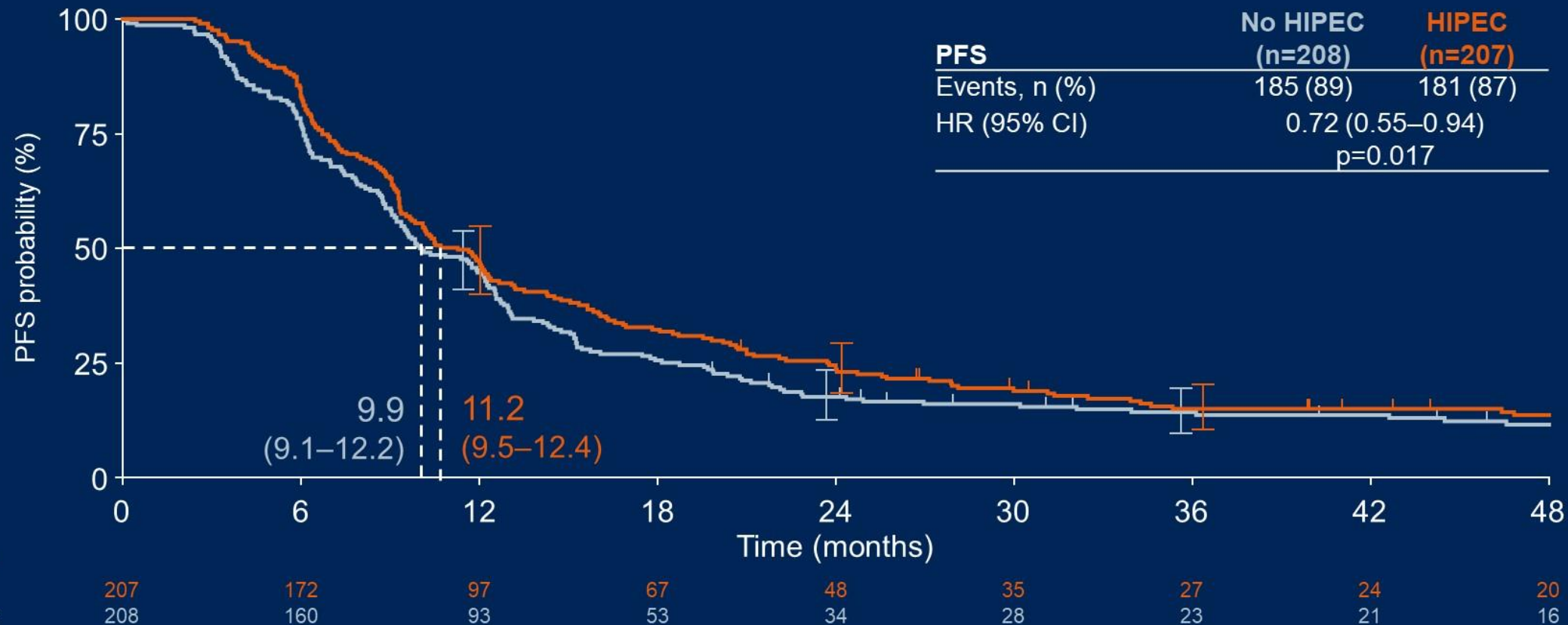
No. of patients (%)		No HIPEC (n=208)	HIPEC (n=207)
Maintenance bevacizumab		16 (8%)	7 (3%)
<i>BRCA</i> mutation status	Known	164 (79%)	167 (81%)
	Mutated	51/164 (31%)	48/167 (29%)
Maintenance PARP inhibitor *		46 (22%)	35 (17%)

\* Missing in 1 patient in the No HIPEC arm and 7 in the HIPEC arm

# CHIPOR trial: Primary endpoint (OS, ITT population)



# CHIPOR trial: PFS (secondary endpoint)



# Unanswered questions

- The impact of maintenance therapy after HIPEC
- Primary debulking surgery with HIPEC
- HIPEC agent dose, regimen, solution
- Platinum-Resistant recurrent ovarian cancer
- The benefit of HIPEC in patients with stage IV



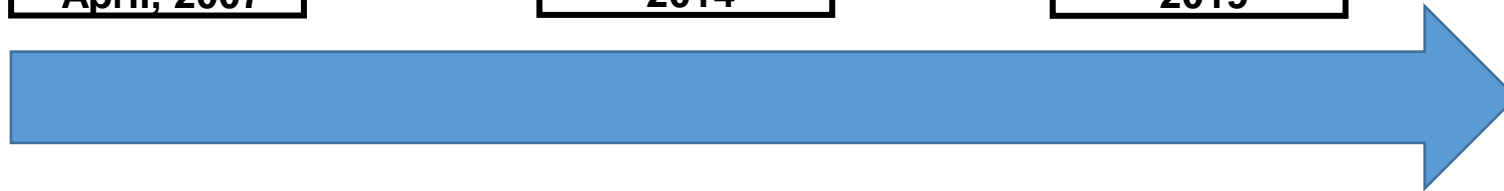
# Maintenance therapy after HIPEC

- Bevacizumab, PARPi
- No maintenance treatment in previous RCT

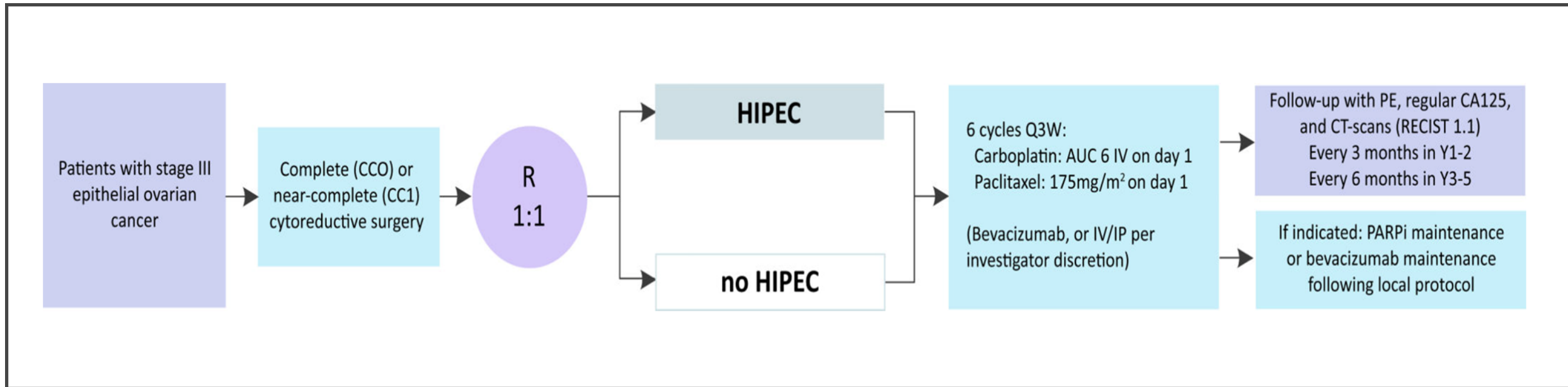
OVHIPEC-1  
initiated :  
April, 2007

Olaparib FDA  
approval:  
2014

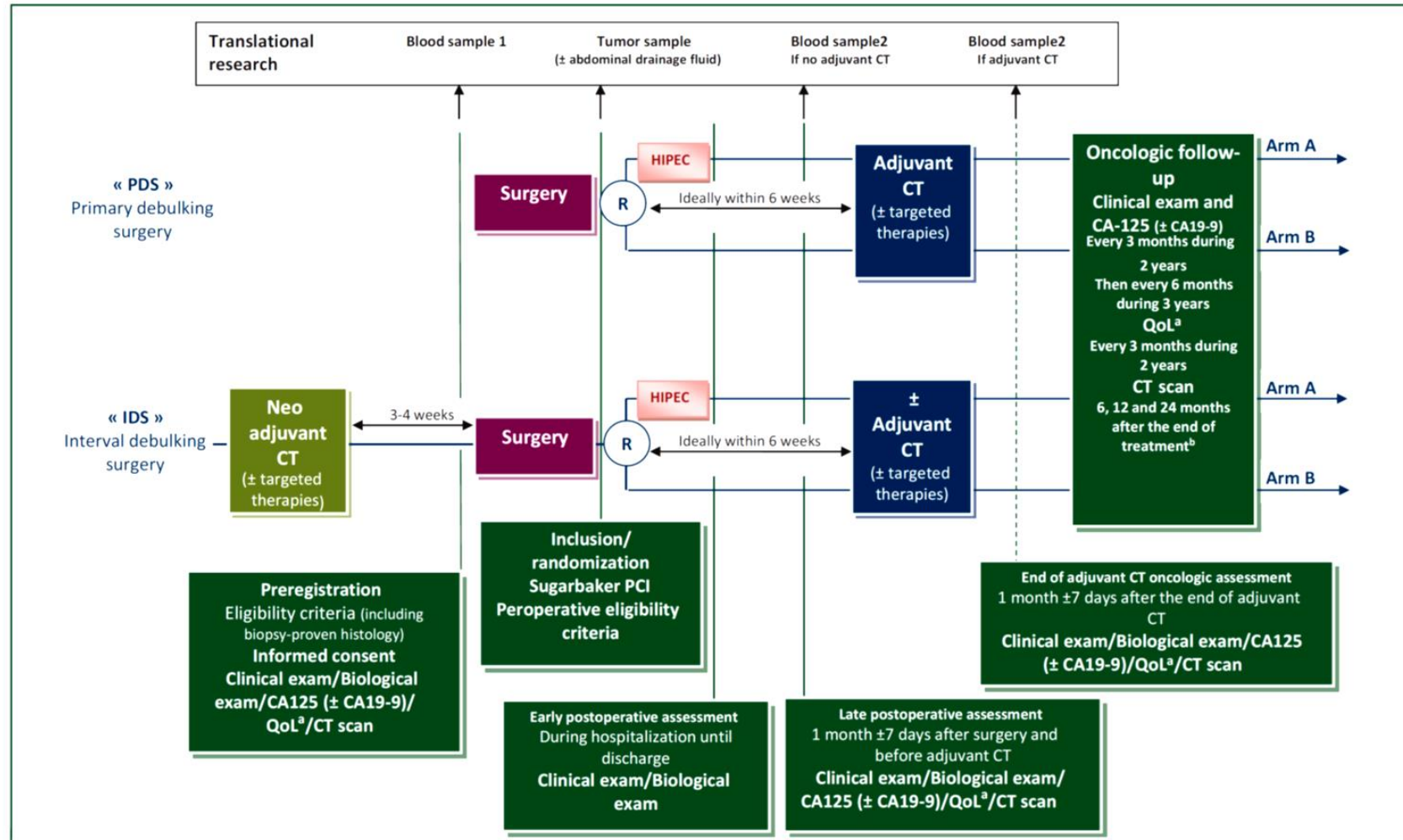
PAOLA-1  
published :  
2019



# OV-HIPEC2

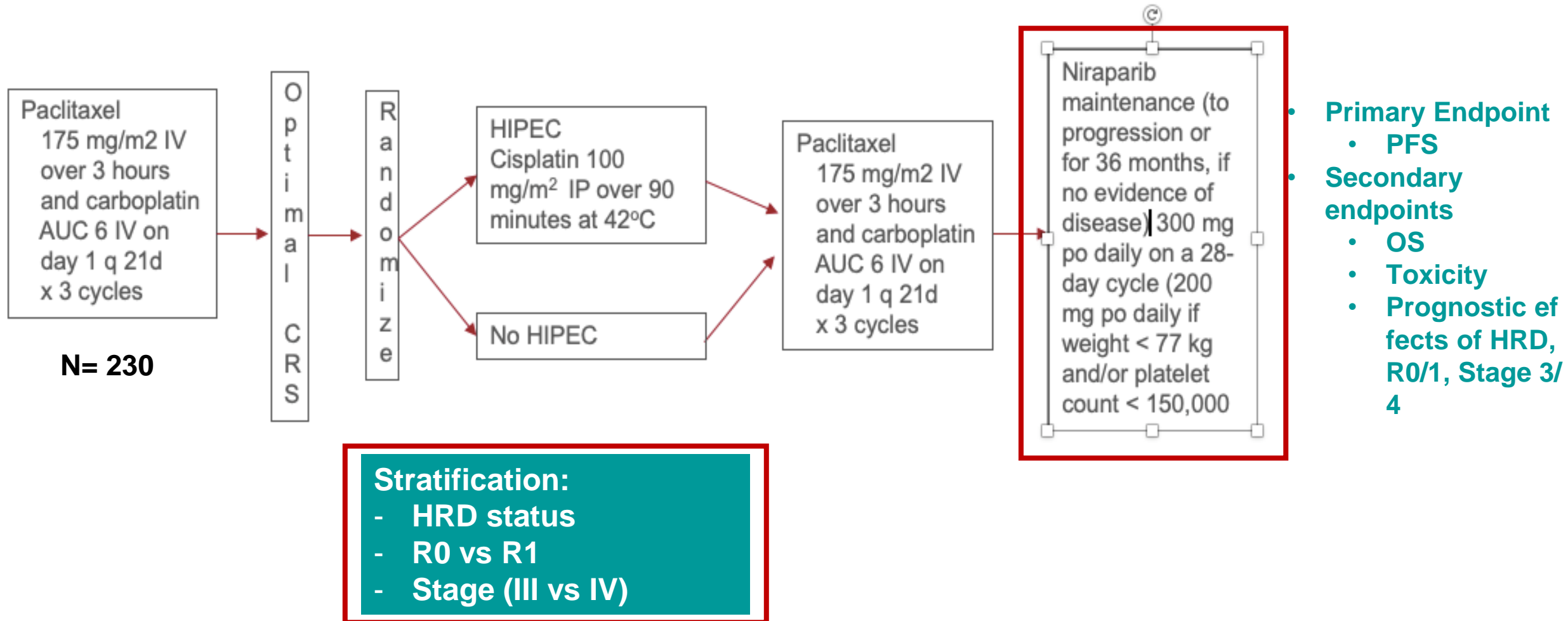


# a phase III randomized clinical trial evaluating hyperthermic intraperitoneal chemotherapy (HIPEC) for stage III ovarian cancer patients treated with primary or interval cytoreductive surgery (CHIPPI)



# GOG-3068/HIPEC in Ovarian Treatment Trial (HOTT)

Heated Intraperitoneal Chemotherapy Followed by Niraparib for Ovarian, Primary Peritoneal and Fallopian Tube Cancer (HOTT)



# HIPEC agent dose, regimen, solution

**Table 1. Characteristics of RCTs that used HIPEC in patients with ovarian cancer**

Author	Year of publication	Recruitment period	HIPEC group (n)	Control group (n)	Experimental arm	Duration (min)	Temp (°C)
<b>Primary ovarian cancer</b>							
Lim (NACT) <sup>22</sup>	2022	2010-2016	34	43	Cisplatin 75 mg/m <sup>2</sup>	90	41.5
Lim <sup>22</sup>	2022	2010-2016	58	49	Cisplatin 75 mg/m <sup>2</sup>	90	41.5
Campos <sup>23</sup>	2022	2012-2018	35	36	Cisplatin 75 mg/m <sup>2</sup>	60	42-43
Van Driel <sup>25</sup>	2018	2007-2016	122	123	Cisplatin 100 mg/m <sup>2</sup>	90	40
Diaz-Montes <sup>27</sup>	2018	2014-2018	10	9	Carboplatin 800 mg/m <sup>2</sup>	90	—
<b>Recurrent ovarian cancer</b>							
Zivanovic <sup>24</sup>	2021	2014-2019	49	49	Carboplatin 800 mg/m <sup>2</sup>	90	41-43
Spiliotis <sup>26</sup>	2014	2006-2013	60	60	Cisplatin 100 mg/m <sup>2</sup> and paclitaxel 175 mg/m <sup>2</sup> or doxorubicin 35 mg/m <sup>2</sup> and (paclitaxel 175 mg/m <sup>2</sup> or mitomycin 15 mg/m <sup>2</sup> )	60	42.5

- HIPEC drug
    - Cisplatin, carboplatin, paclitaxel, doxorubicin
  - Solution
    - 1.5% dextrose vs N/S
- >> HIPEC PK/PD in ovarian cancer**

# HIPEC in Platinum-Resistant recurrent ovarian cancer

## Randomized Phase III Trial of HIPEC in Platinum-Resistant Recurrent Ovarian Cancer (KOV-HIPEC-02)

ClinicalTrials.gov (NCT05316181)

Primary endpoint: Progression-free survival (PFS)



### Stratification factors

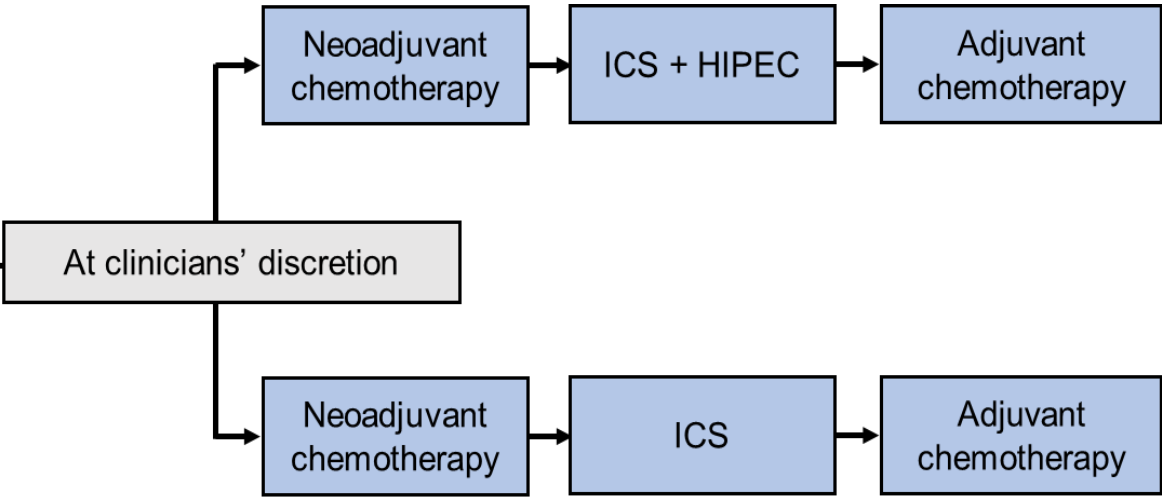
1. Histology (HGSOC vs non-HGSOC)
2. Number of prior lines of chemotherapy ( $\leq 1$  line vs  $\geq 2$  lines)

### HIPEC regimen

- Doxorubicin  $35\text{mg}/\text{m}^2$  + Mitomycin C  $15\text{mg}/\text{m}^2$
- 90 minutes,  $41.5^\circ\text{C}$  (range,  $41\text{-}42^\circ\text{C}$ )

# HIPEC After Interval Cytoreductive Surgery in Patients with Advanced-Stage Ovarian Cancer Undergoing Neoadjuvant Chemotherapy: A Multicenter Prospective Comparative Effectiveness Cohort Study (KGOG3042)

- Epithelial ovarian cancer
- FIGO stage III, IV
- High tumor burden
- Diagnostic laparoscopy: Fagotti score  $\geq 8$
- Pretreatment radiologic imaging



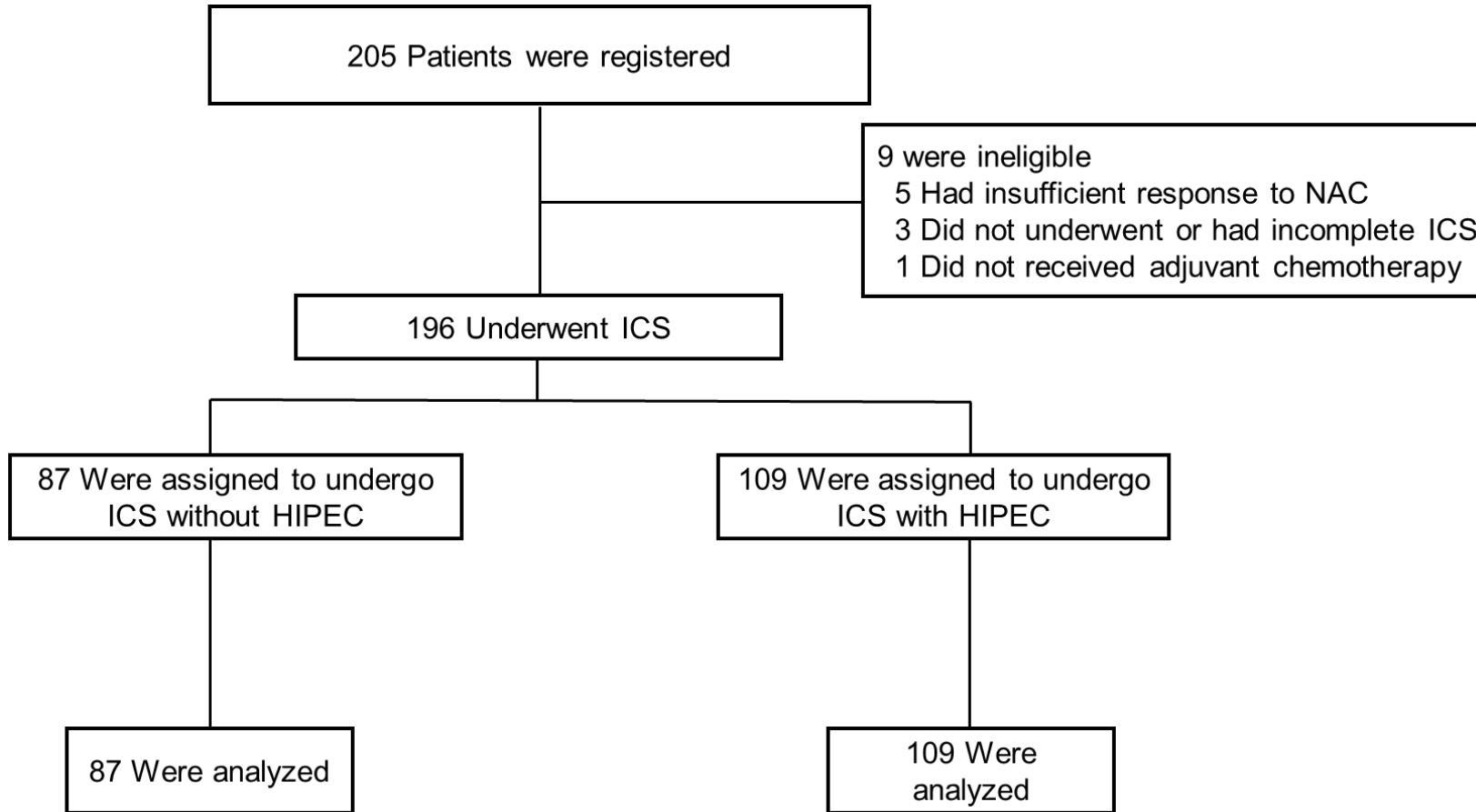
**Primary endpoint**

- Progression-free survival

**Secondary endpoints**

- Overall survival
- Safety

# Flowchart of enrollment



No.	Enrollment center
1	Yonsei University College of Medicine
2	Ajou University School of Medicine
3	CHA Bundang Medical Center
4	Seoul National University Bundang Hospital
5	Kyungpook National University Chilgok Hospital
6	Ewha Womans University College of Medicine
7	Korea University Medical Center

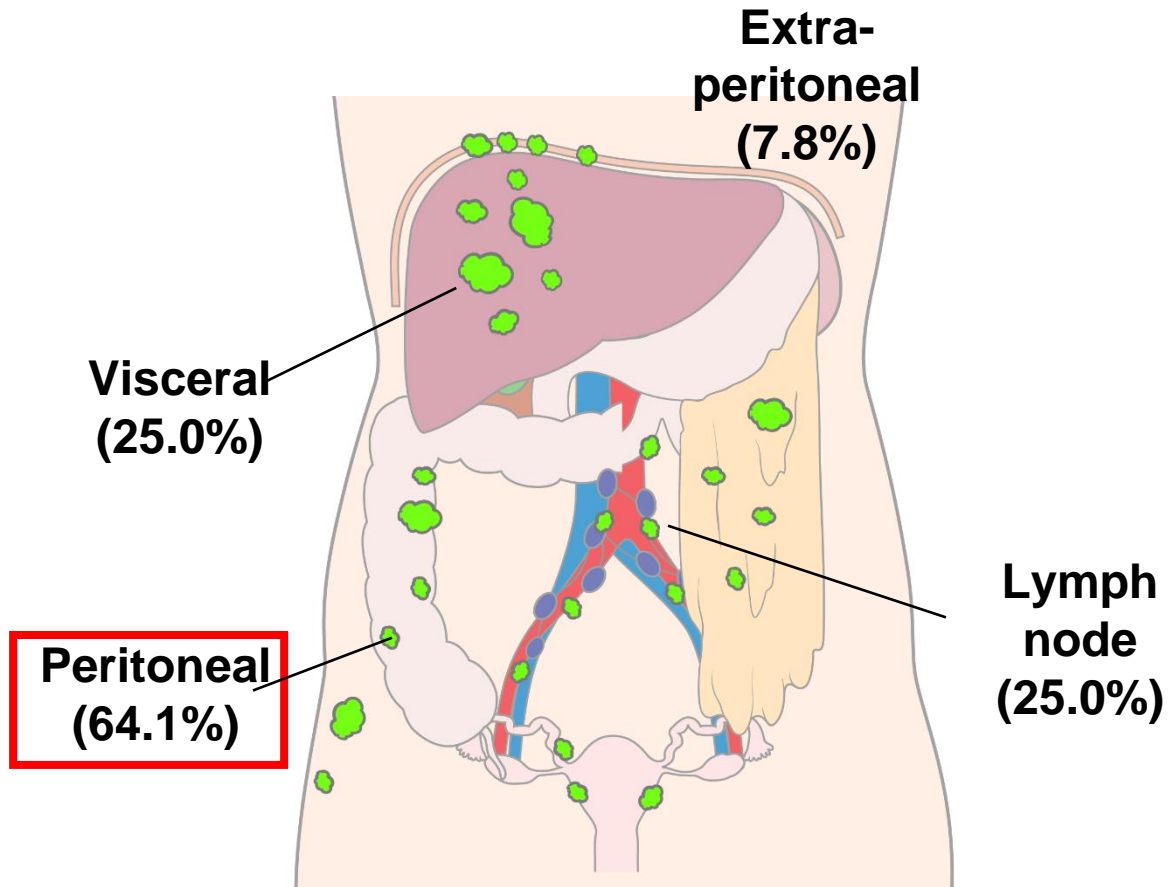


# HIPEC After Interval Cytoreductive Surgery in Patients with Advanced-Stage Ovarian Cancer Undergoing Neoadjuvant Chemotherapy: A Multicenter Prospective Comparative Effectiveness Cohort Study (KGOG3042)

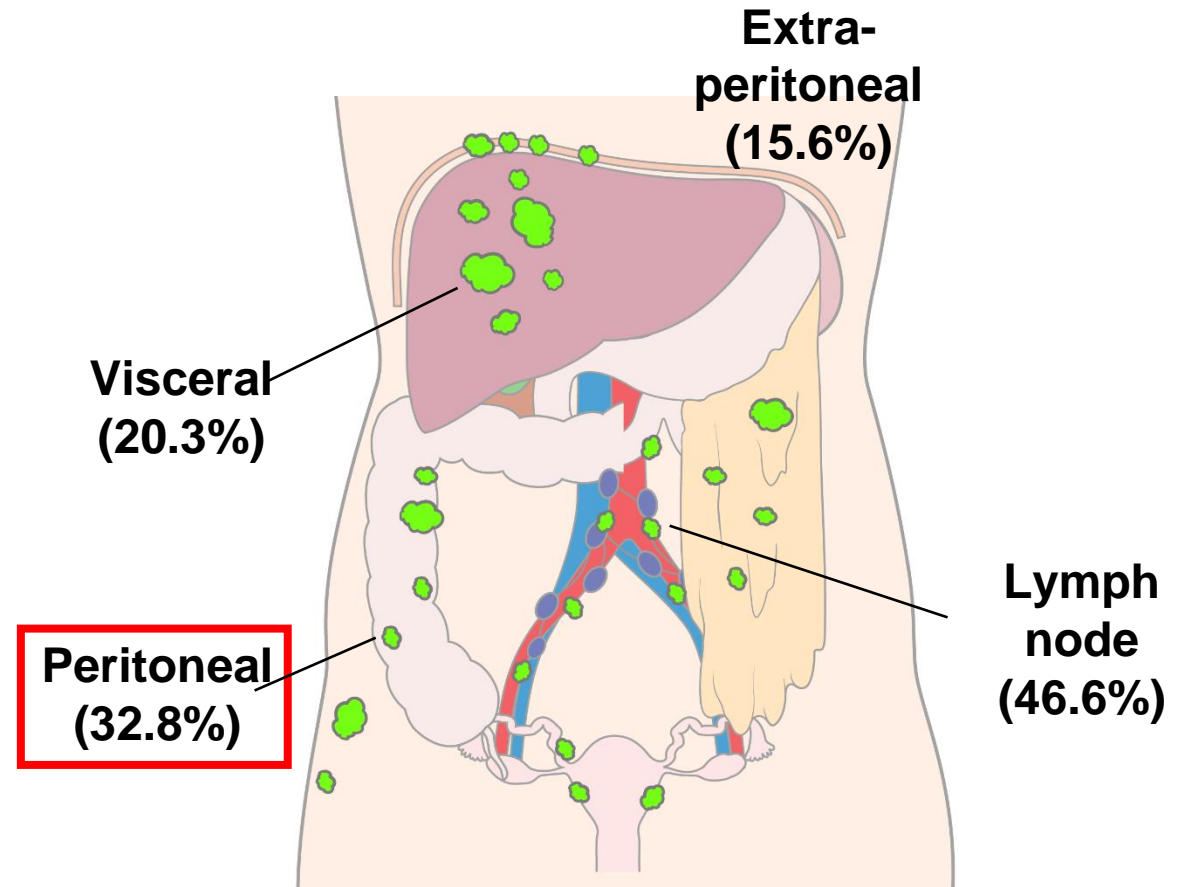
Variable	ICS (n = 87)	ICS + HIPEC (n = 109)	P
<b>BRCA status, n (%)</b>			
Wild-type	63 (72.4%)	80 (73.4%)	0.231
BRCA1/2 mutation	17 (19.5%)	26 (23.9%)	
Not applicable	7 (8.0%)	3 (2.8%)	
<b>Maintenance therapy, n (%)</b>			
No	66 (75.9%)	81 (74.3%)	0.198
Bevacizumab	12 (13.8%)	15 (13.8%)	
PARP inhibitors	9 (10.3%)	13 (11.9%)	

# Comparison of recurrence patterns

## ICS

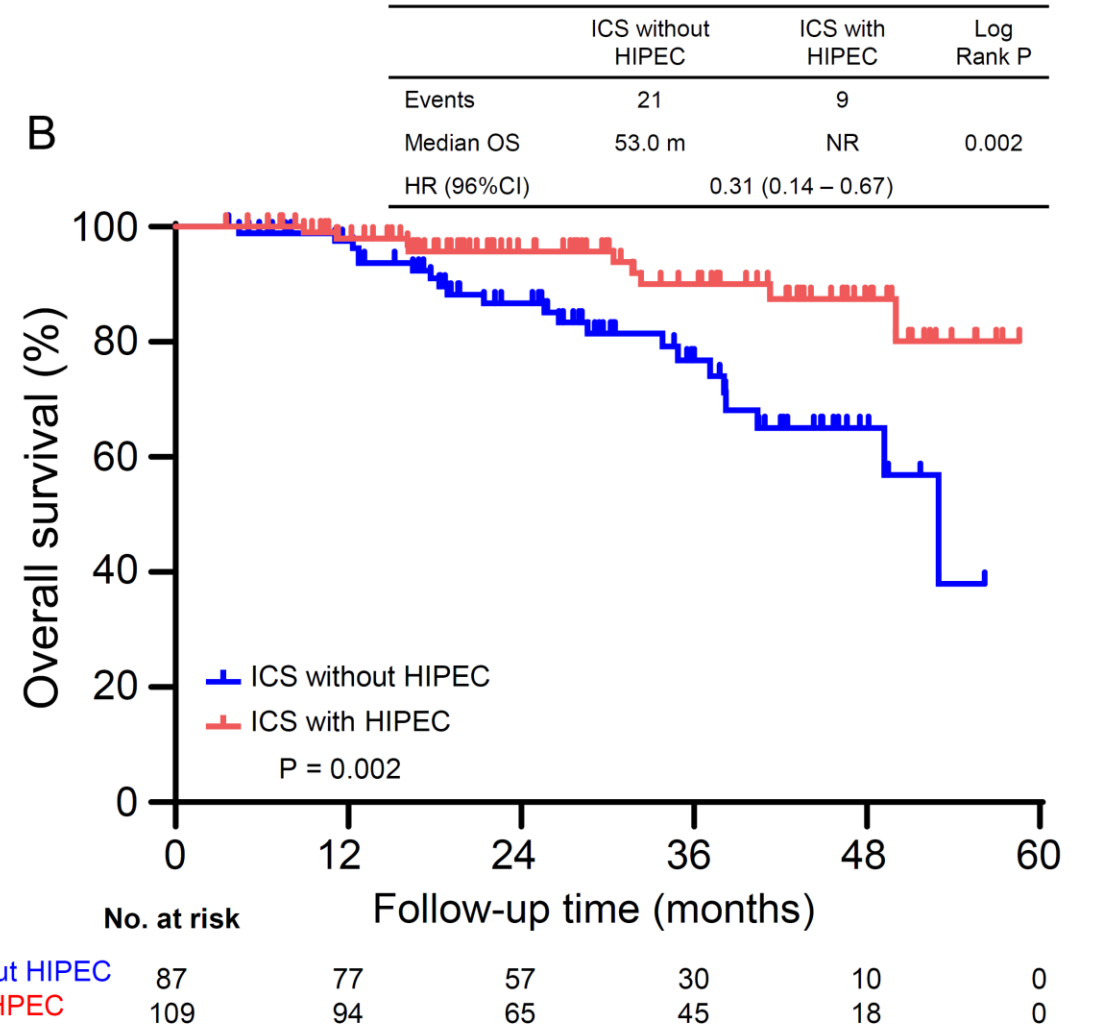
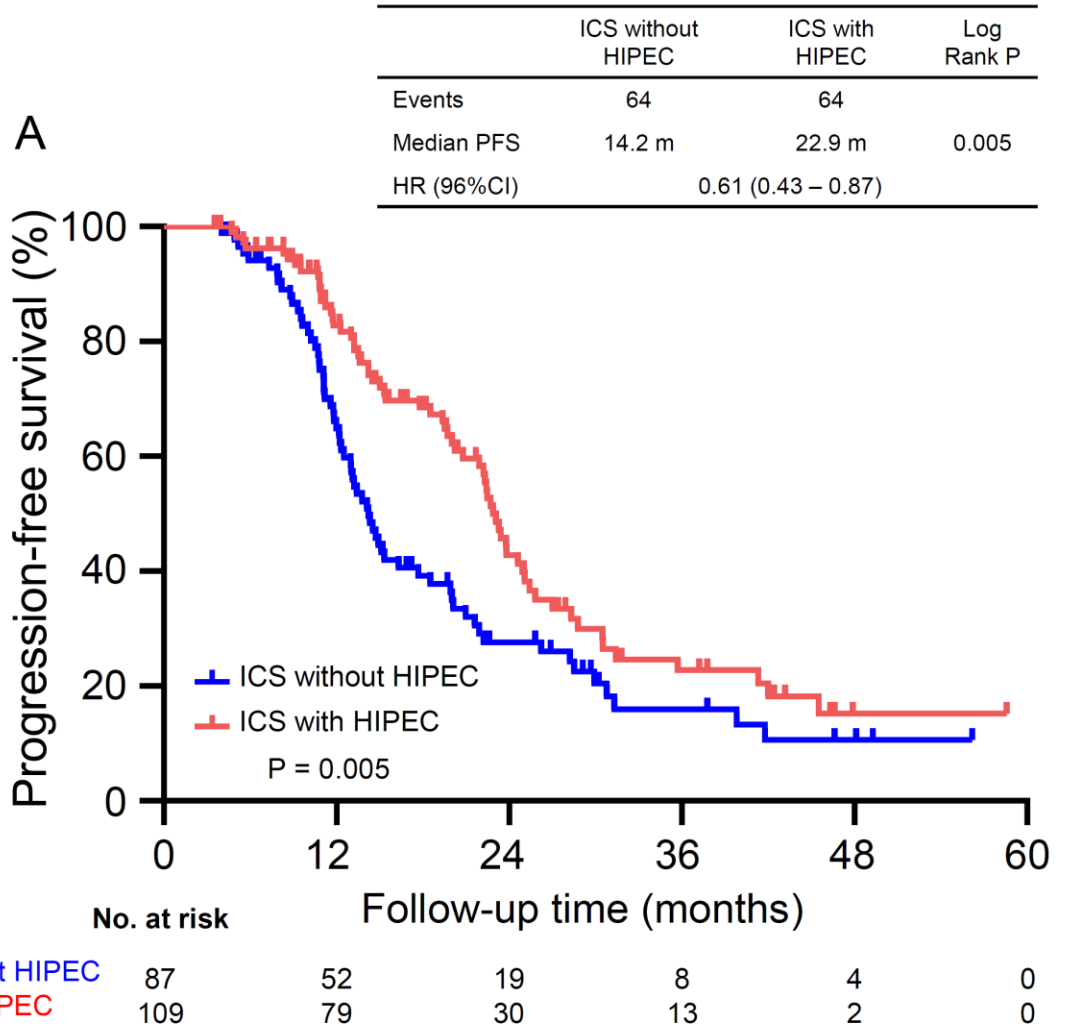


## ICS with HIPEC



# Comparison of recurrence patterns

	ICS (n = 87)	ICS + HIPEC (n = 109)	P
<b>Patients with recurrence, n (%)</b>	64 (73.6%)	64 (58.7%)	<0.001
<b>Recurrence site, n (%)</b>			
<b>Peritoneal</b>	41 (64.1%)	21 (32.8%)	0.001
<b>Extra-peritoneal</b>	5 (7.8%)	10 (15.6%)	
<b>Visceral metastasis</b>	6 (9.4%)	13 (20.3%)	
<b>Lymph node</b>	16 (25.0%)	30 (46.6%)	



Survival benefits of HIPEC with ICS in patients who underwent neoadjuvant chemotherapy

# Thank You!

## Yonsei Cancer Center

Inspires patients to live with and beyond cancer by offering total cancer care

### Integrated Cancer Treatment

- Multidisciplinary Clinic System & Total Care System
- The Best Cancer Specialist Team - 15 Cancer Centers
- Institute for Personalized Cancer Therapy (IPCT)
- Cancer Prevention Center
- Palliative Care Center
- Cancer Information Center
- Ambulatory Chemotherapy Center (100 beds)



Ambulatory Chemotherapy Center    Cancer Prevention Center    Cancer Information Center    Robotic Dept.

### Patient-oriented Care Process

- Fast Track System for Newly Diagnosed Cancer Patients

## Severance Hospital The First and the Best

### 5 Specialized Hospitals



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LARGEST NUMBER of International Patients in Korea

MECCA OF ROBOTIC SURGERY In Asia  
Performs over 12,000 cases as of April, 2014