City of Hope

THIRD ANNUAL

ISSPP Congress 2022

International Society for the Study of Pleura and Peritoneum

THE NEXT GREAT DEBATE

Is There a Role of Regional Therapies in Ovarian Cancer? (PRO)

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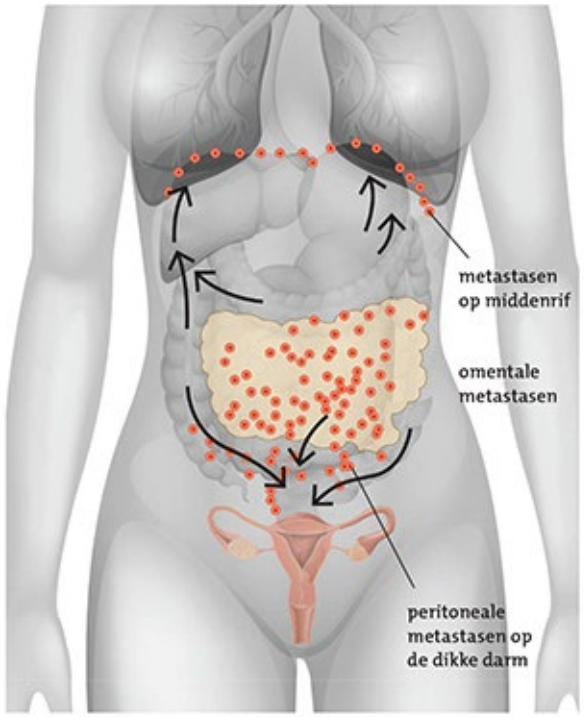
Disclosures

- 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.

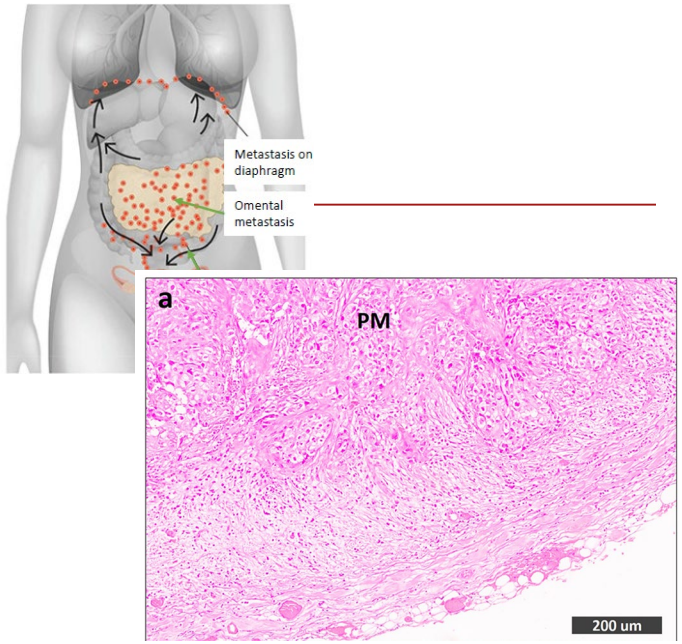
Defining the challenge

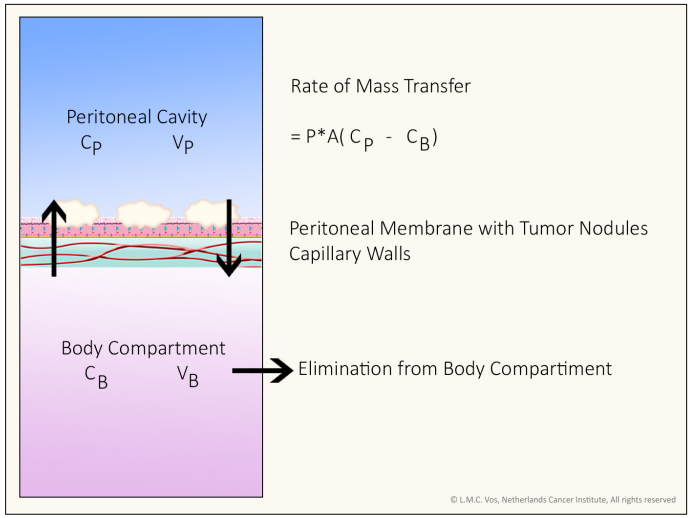


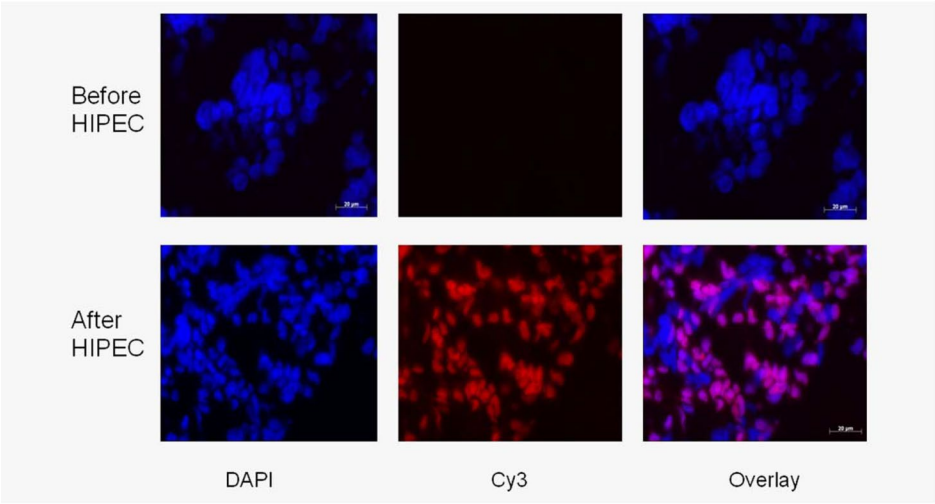
Ovarian cancer is spread to peritoneum in 70%

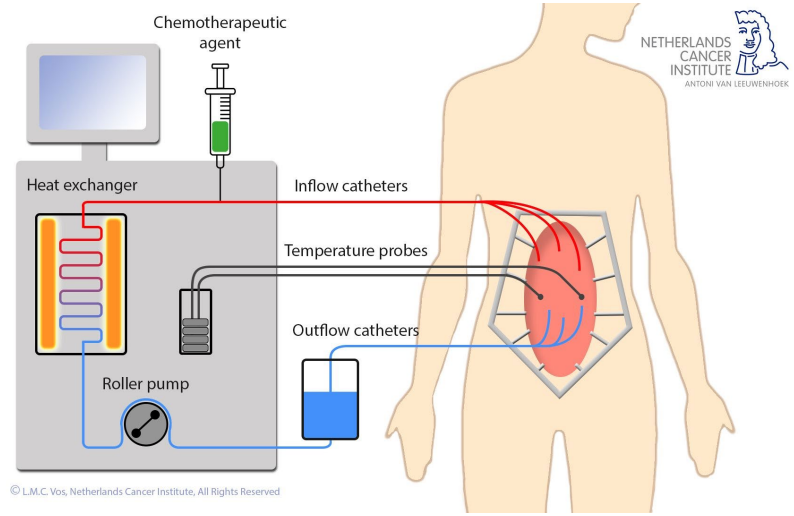
⟹ High recurrence rate

⟹ Low survival rates







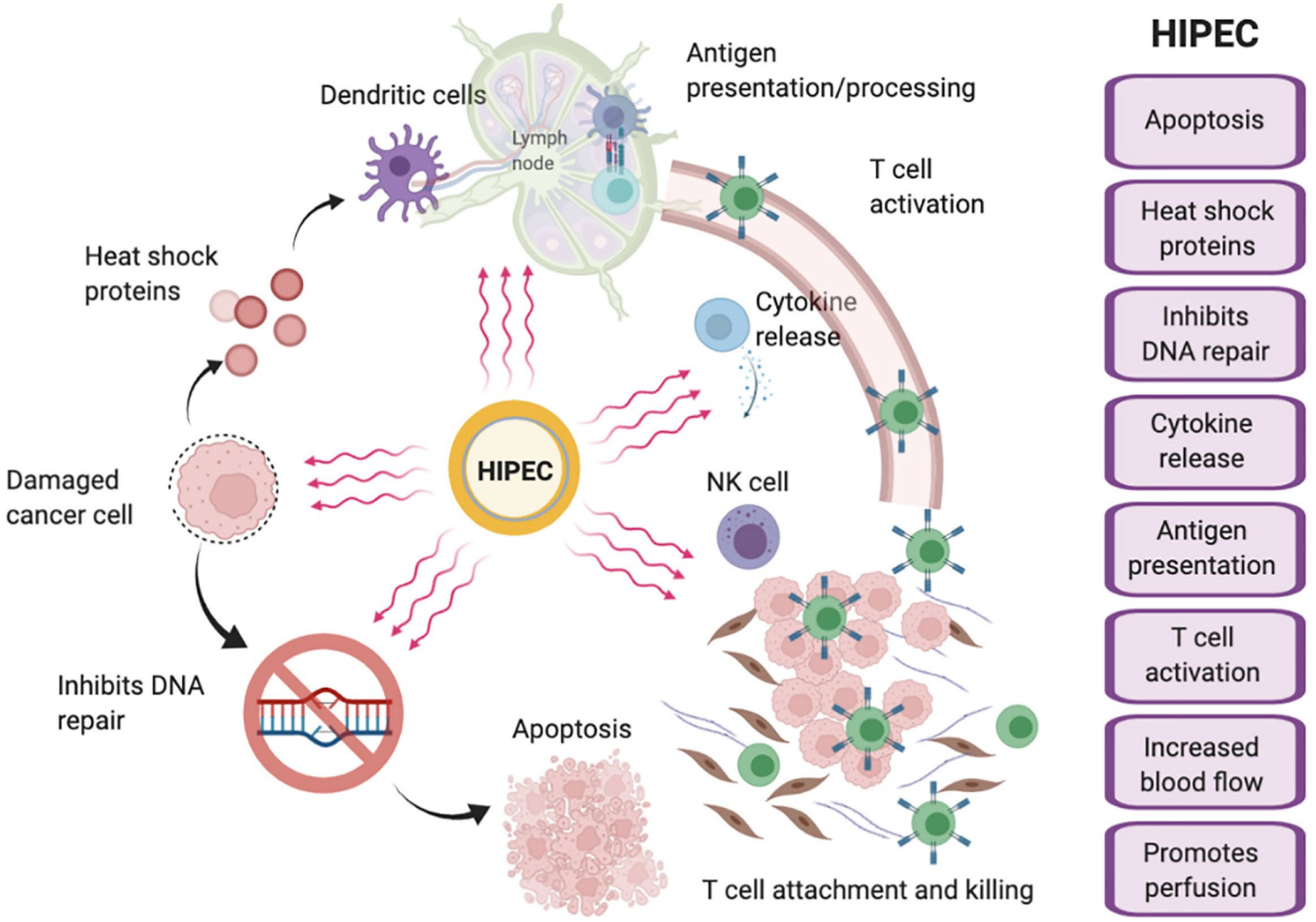


HIPEC

- Intraoperative procedure
- peritoneal disease is targeted
- High concentration of chemotherapy at site of disease
- Limiting systemic exposure and toxic effects

Zivanovic et al, Int J Cancer, 2014
Vos, Aronson et al, Best Prac & Res Obst and Gyn, 2021
Van Baal, Virchows archive, 2020

How does HIOPEC exerts its effect?



HIPEC

- Apoptosis
- Heat shock proteins
- Inhibits DNA repair
- Cytokine release
- Antigen presentation
- T cell activation
- Increased blood flow
- Promotes perfusion

Dellinger et al, gyn onc 2019

What?

Ideal candidate:

- Biological active
- Active stable form of drug
- Direct cytotoxic
- Cell cycle phase non-specific
- Minimal local and systemic toxicity
- Slow absorption from peritoneal cavity
- Synergistic effect with hyperthermia
- Adequate tissue penetration

Cisplatinum theoretically best candidate

Vos and Aronson et al; Best practice & research Clinical obstetrics & gynaecology, 2021

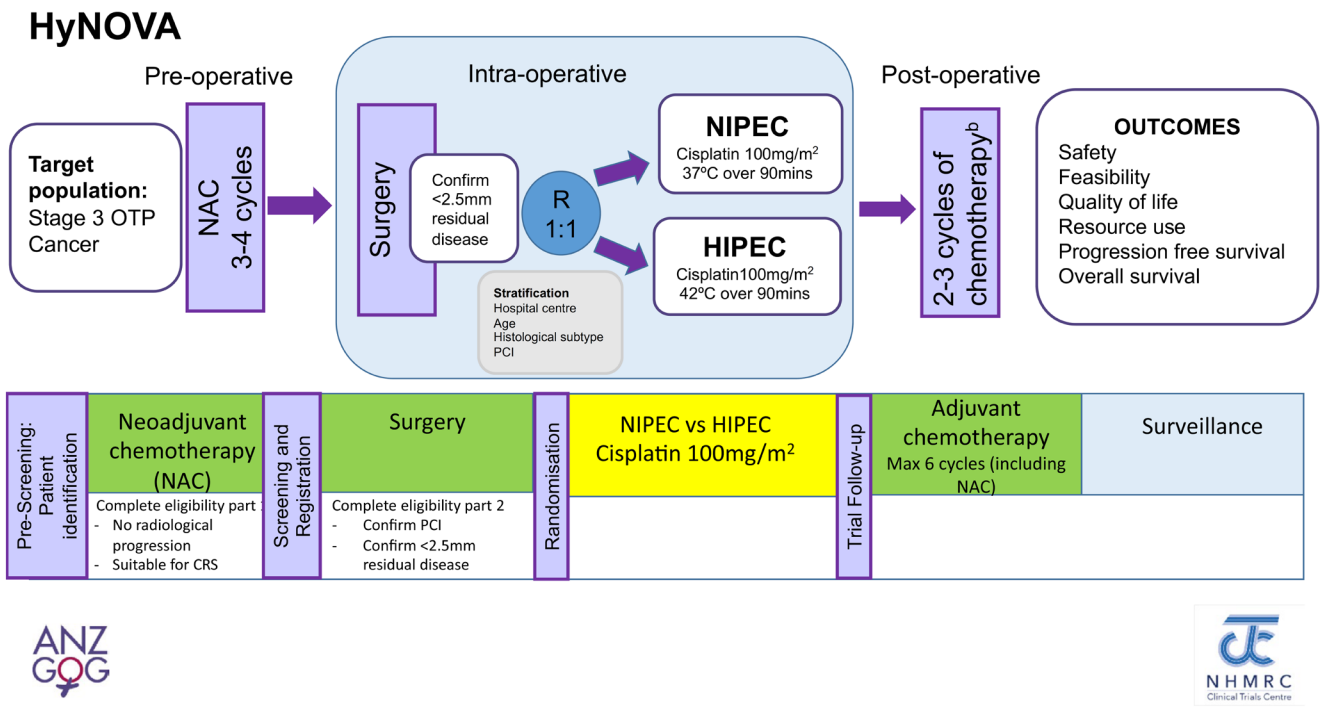
When?

Primary CRS

Interval CRS

Recurrent disease

Is hyperthermia necessary? – ANZGOG study



ANZ GOG

NHMRC Clinical Trials Centre

Sample size is calculated based on
- an estimated grade 3-5 rate of AE's at 90 days
- with HIPEC of 30% and NIPEC of 15%.
- N=80

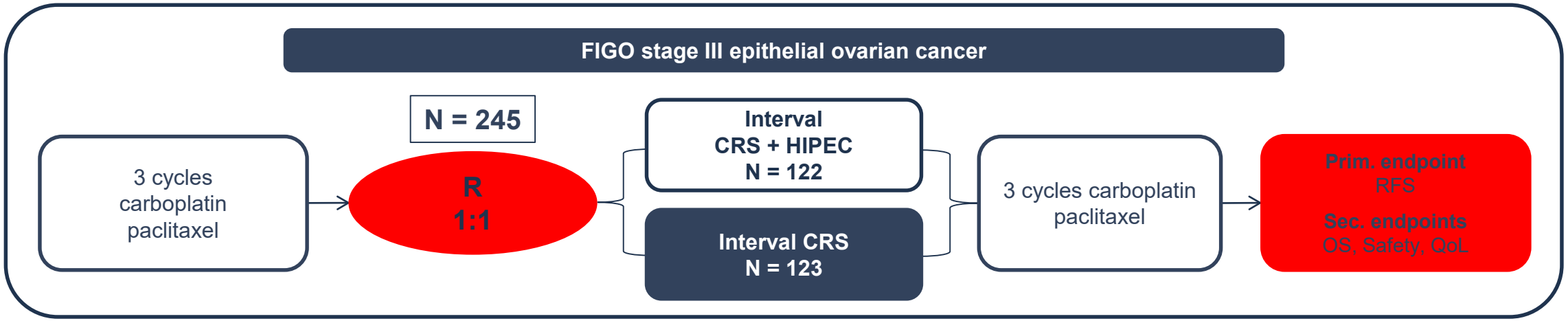
Primary endpoint:

- any adverse events ≥ grade 3 occurring within 90 days post-surgery

Secondary endpoints:

- Surgical morbidity
- Health related QOL
- Resource utilization
- Feasibility of NIPEC
- PFS
- OS

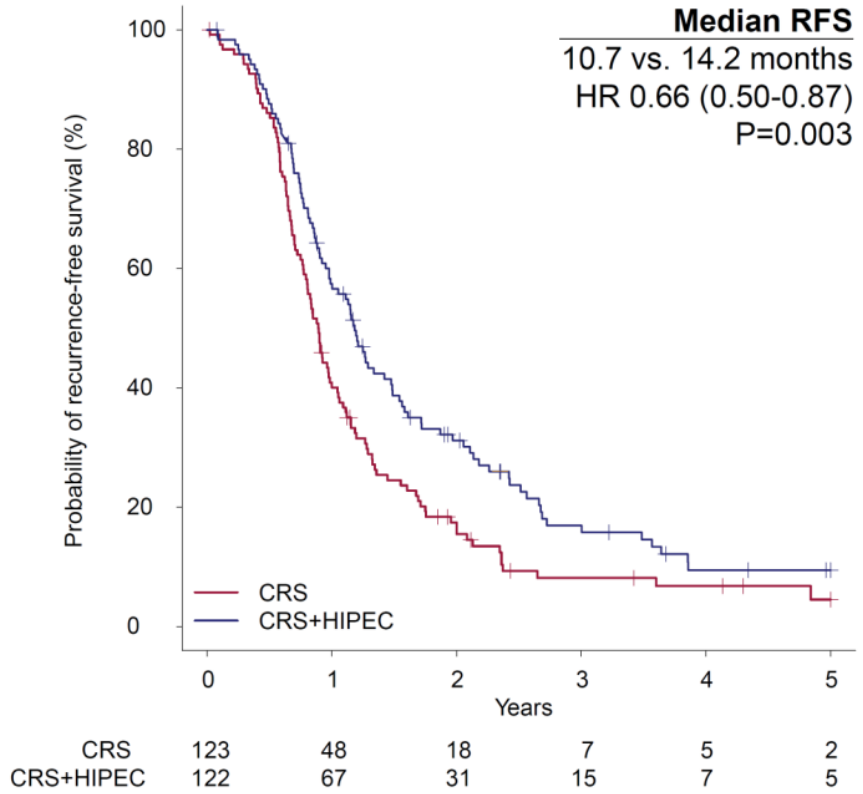
OVHIPEC-1 study

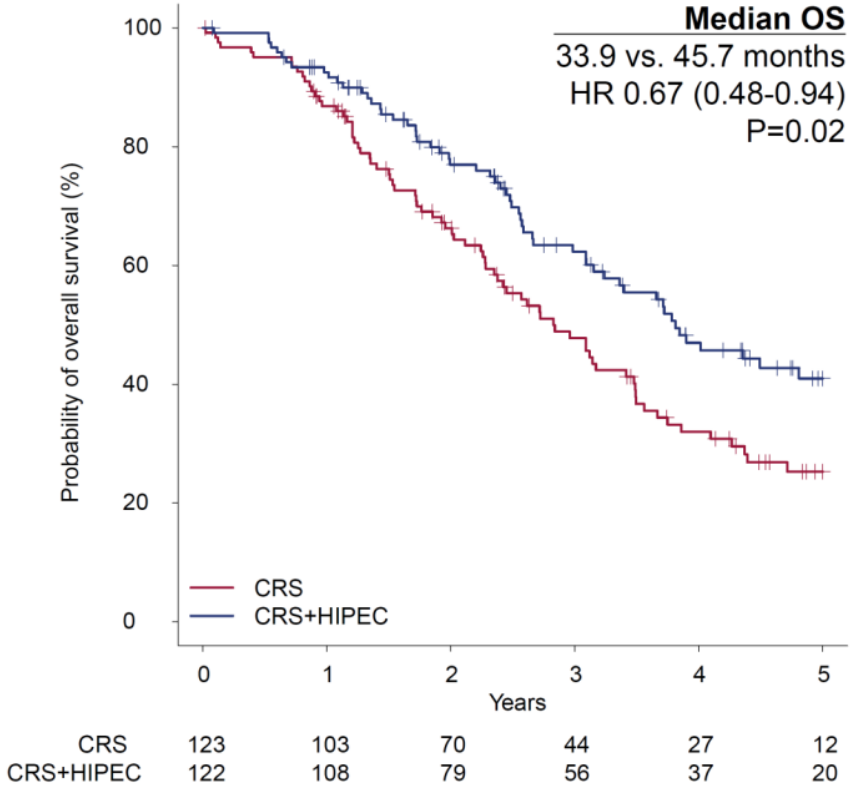


- Patients were ineligible for primary cytoreductive surgery (CRS) because of extent of disease
- Follow-up visits were performed every 3 months for the first 2 years, then every 6 months thereafter
- Tumor assessments with CT scans were performed 6, 12, and 24 months after the last chemotherapy
- The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 were used for grading toxicity

Interval CRS

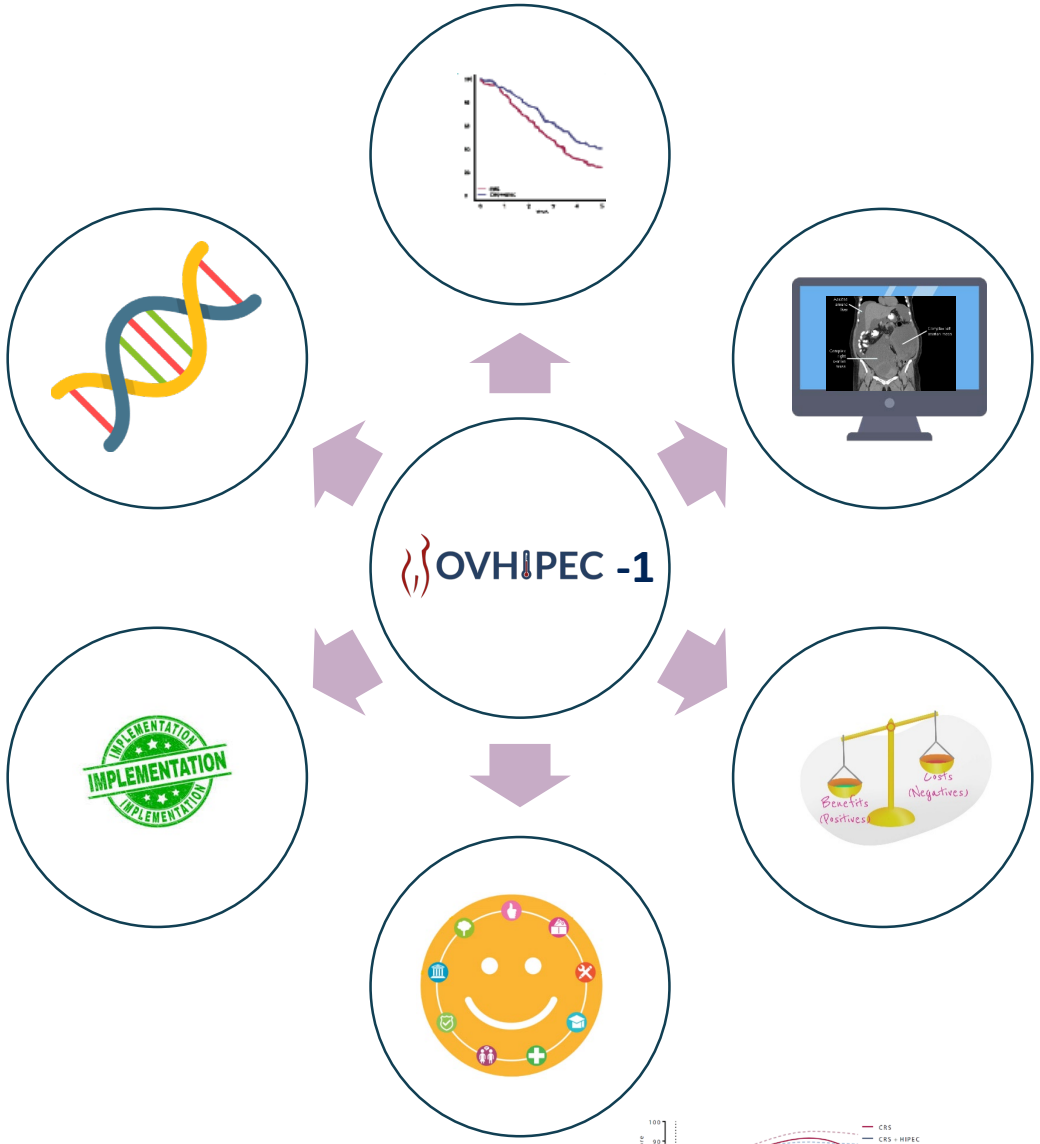
OVHIPEC-1 trial

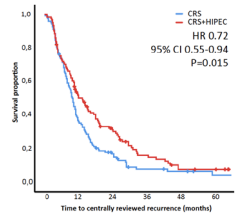


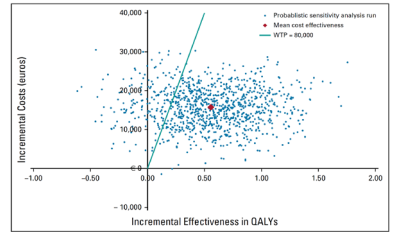


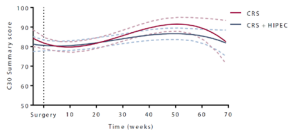
van Driel et al, NEJM, 2018

Following OVHIPEC-1









Can we select patients who benefit most from HIPEC?

	Interval CRS		Interval CRS + HIPEC		
BRCA mutation (%)	Nr	%	Nr	%	0.958
- gBRCA1†	7	(7%)	6	(6%)	
- tumor BRCA1	3	(3%)	4	(4%)	
- gBRCA2†	5	(5%)	5	(5%)	
- tumor BRCA2	3	(3%)	1	(1%)	
- BRCAwt	84	(77%)	75	(80%)	
- no panel mutation or germline information available	4	(4%)	3	(3%)	

Ovarian cancer-specific BRCA-like classifier

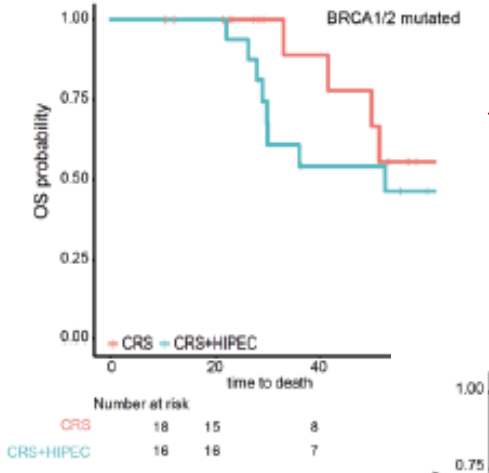
- Classifier based on DNA Copy-number profile
- Ovarian specific
- Developed on the Cancer Genome Atlas dataset
- Tested classifier on 300 ovarian cancer patient from AGO-TR1 cohort

- Identifies 95.6% of BRCA 1 mutations and promotor hypermethylation
- 50% on the non-BRCA-mutated ovarian cancer displayed a BRCA-like phenotype

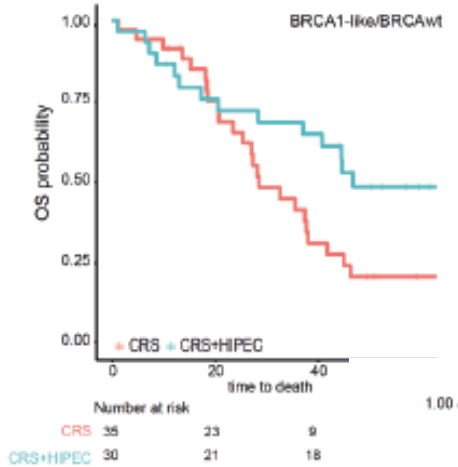
Schouten et al Clinical Cancer Research, 2021

Survival in relation HRD/BRCA status

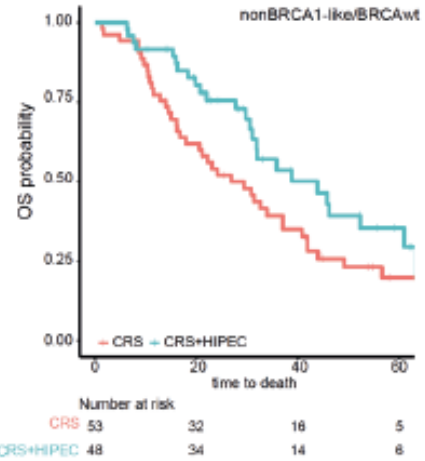
- *m*BRCA:



- BRCA-1 like/*wt*BRCA :



- Non-BRCA-1 like/*wt*BRCA:



Koole et al, Int J Cancer, 2022
Ghirardi et al, Can Tr Res Comm 2022

Pro-Con discussion

Cancer

Review Article
Free Access

Hyperthermic intraperitoneal chemotherapy for ovarian cancer: The heat is on

Simone N. Koole MD, Willemien J. van Driel MD, PhD, Gabe S. Sonke MD, PhD

First published: 03 December 2019

Cancer

Review Article
Free Access

Hyperthermic intraperitoneal chemotherapy does not improve survival in advanced ovarian cancer

Ignace Vergote MD, PhD, Philipp Harter MD, PhD, Luis Chiva MD, PhD

First published: 03 December 2019

Critical notes

Pointes raised	Counter argument
Primary endpoint not overall survival	PFS was preferred endpoint following OCCC 2004
Small study	Small study usually have problem to fail showing any difference; OVHIPEC-1 showed a difference in survival
Only 1 study	Smaller RCT's support result of OVHIPEC 1
Imbalance in non-high grade serous	Surgery group 15 non-HGSOC vs HIPEC group 9 non-HGSOC: imbalance of 3 – unlikely to influence outcome Not uncommon for surgical trials
Study took to long to accrue	No known relationship between length of accrual and quality of study

Vergote et al, Cancer 2019; Koole et al, Cancer 2019

Critical notes

Pointes raised	Counter argument
Sample size changed over time	Longer accrual time: participating patients contributed in longer follow-up time: fewer patients were needed to reach the same number of events
Underreported toxicity	**CTC-AE scale has shown to increase reported toxicity with 50% compared to Clavien-Dindo**
Open label design therefor bias	Not supported by outcome of result of CRS
Length of survival in control arm	Time of randomization during IDS: to compare it correctly add 12 weeks No difference to other studies in the same population
Study before Parp era	**Correct, but so are other recent surgical studies (Desktop, Lions): only reason to investigate relation HIPEC and parp inhibition further**
Unknown effect of bevacizumab	For this group of patients (complete CRS) beneficial effect of bevacizumab is clinical less relevant Vergote et al, Cancer 2019; Koole et al, Cancer 20

Interval CRS +/- HIPEC

Cascales et al - 2021

79 patients with FIGO stage 3B/C ovarian carcinoma following 3 cycles NACT

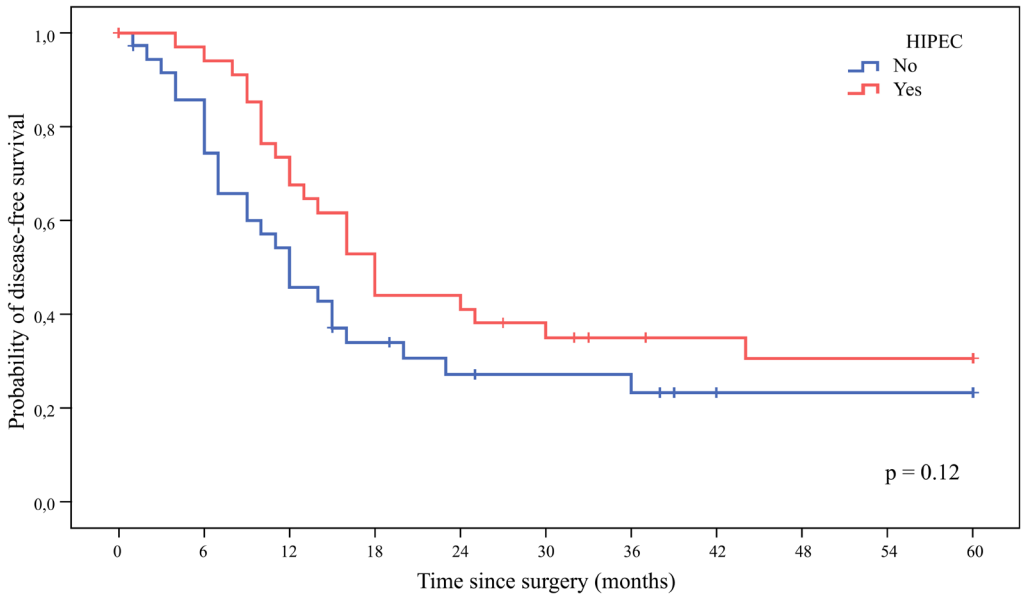
41 CRS
36 received assigned treatment → DFS: 12 months, OS: 45 months

38 CRS+HIPEC
35 received assigned treatment → DFS: 18 months, OS: 52 months

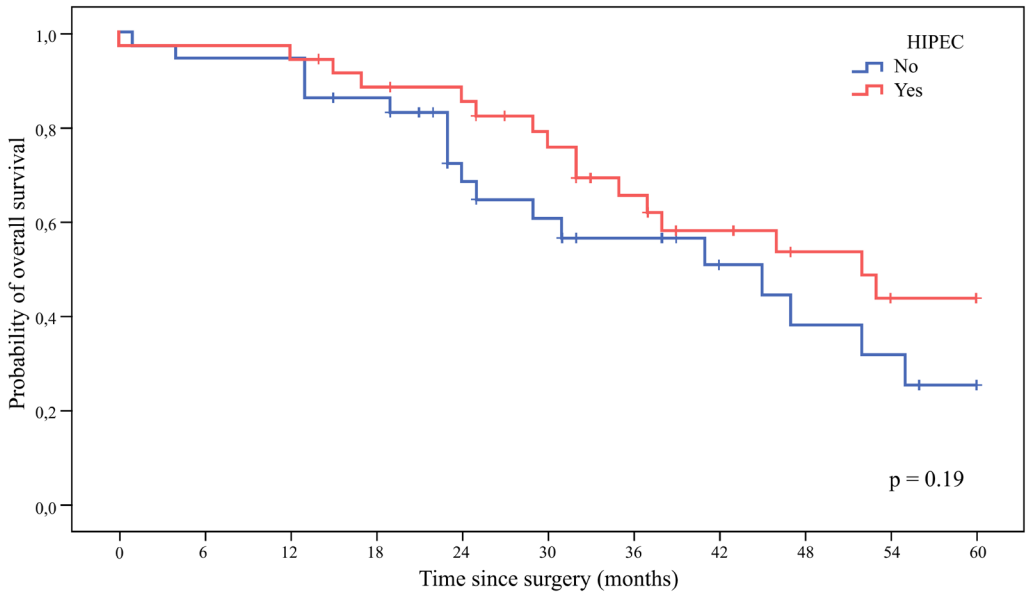
HIPEC 75 mg/m ^{2}
60 minutes
42^{o}C
Sodium thiosulphate

Cascales Campos, Annals of surgical oncology 2021

Disease Free Survival



Overall Survival

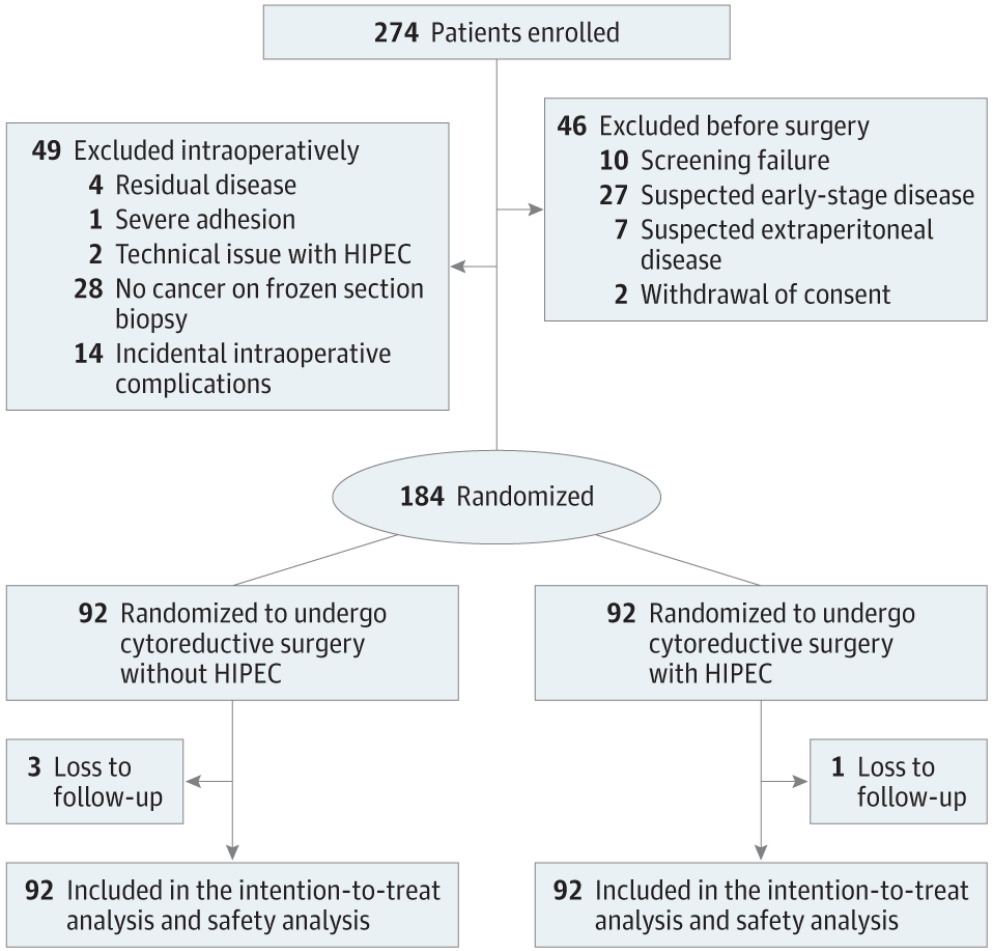


No differences in

- Postoperative morbidity
- Posto operative mortality
- Quality of live

Cascales Campos, Annals of surgical oncology 2021

Korean RCT – PDS/IDS +/- HIPEC



- 2010-2016
- Ovarian carcinoma FIGO III/IV
- < 75 years
- Primary CRS and interval CRS
- Per-operative randomization at the end CRS
- Cisplatinum 75 mg/m^2
- Closed technique

Lim et al, JAMA surgery, 2022

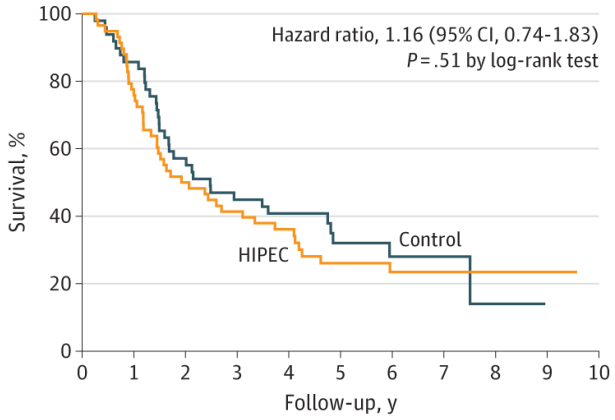
Baseline characteristics

- No differences in:
  - Clinical characteristics between HIPEC and control group
  - Similar operative procedures
  - Ileostomy formation in HIPEC (7.6%) and control (6.5%) group

Lim et al, JAMA surgery, 2022

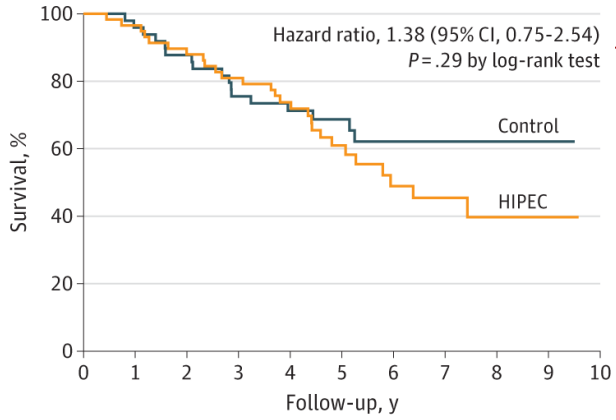
Survival curves

A Progression-free survival in patients undergoing primary cytoreductive surgery



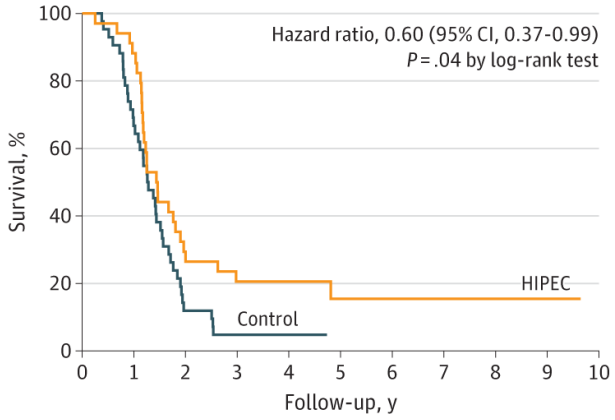
No. at risk											
Control group	49	42	28	22	17	10	7	4	1	0	0
HIPEC group	58	44	29	24	18	10	8	6	3	1	0

B Overall survival in patients undergoing primary cytoreductive surgery



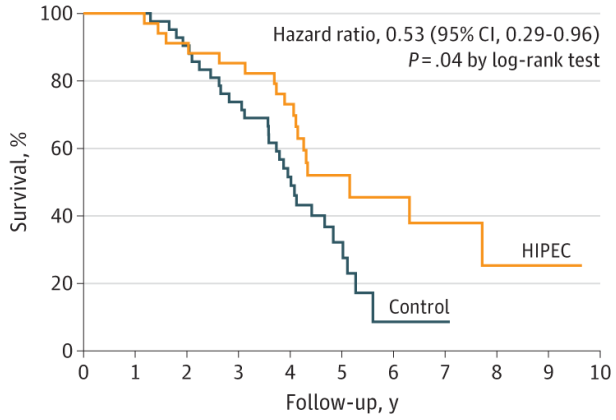
No. at risk											
Control group	49	47	43	37	31	21	17	11	6	1	0
HIPEC group	58	56	51	46	38	23	14	10	4	2	0

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



No. at risk											
Control group	43	28	5	2	1	0	0	0	0	0	0
HIPEC group	34	30	9	7	6	2	2	1	1	1	0

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



No. at risk											
Control group	43	42	38	31	20	7	1	1	0	0	0
HIPEC group	34	34	31	29	22	8	6	3	2	1	0

Lim et al, JAMA surgery, 2022

Discussion

- Rationale for applying HIPEC in extra-peritoneal disease/stage IV?
- Korean trial was not stratified for primary of interval CRS: imbalance in stage and initial treatment
- Small sample size

Comments and conclusion

HIPEC could be considered during interval CRS for patients with FIGO stage III ovarian carcinoma for whom primary CRS was not feasible due to extent of disease

Question remaining:
What is role of HIPEC in primary CRS and recurrent ovarian carcinoma
Is dose important?
Interaction with maintenance therapy

What happened after OVHIPEC-1 publication?

Netherlands

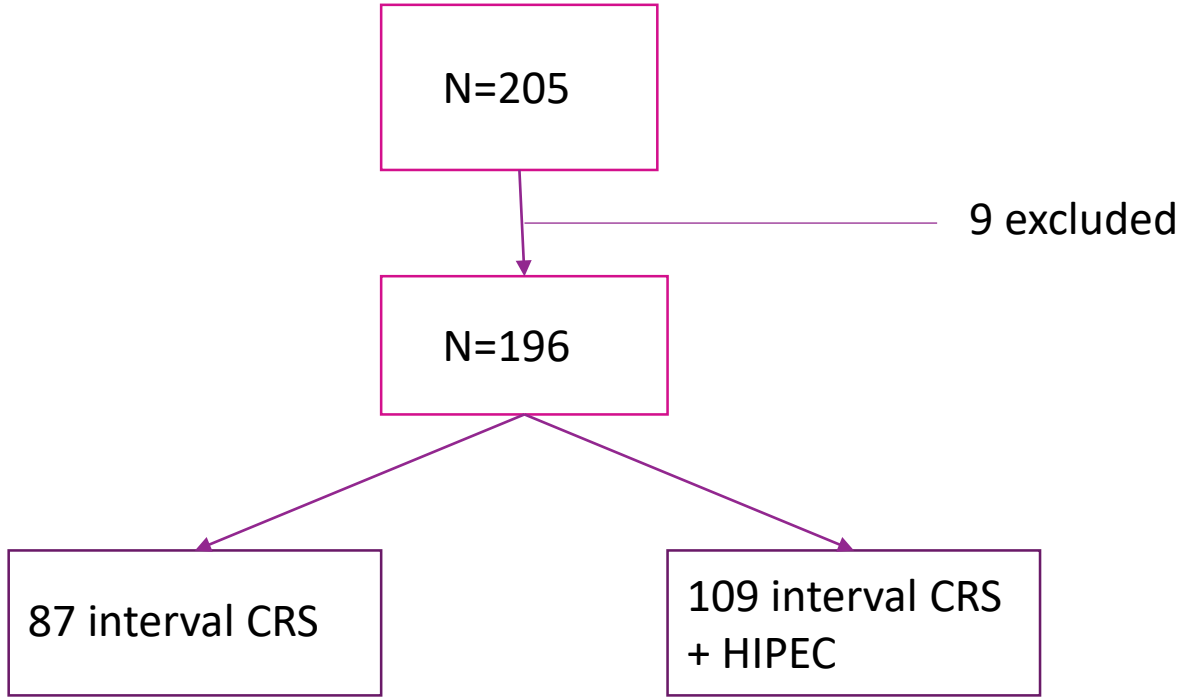
- 2018: financial reimbursement for OVHIPEC
- 2019: National guidelines approved
- Patients organizations involved
- Oncological care organized per geographic region
  - 8 regions: 1 or 2 hospitals resulting in 10 centers
- Implementation study
  - All centers are adequately trained
  - Evaluating results using nationwide clinical audit (DGOA)

Worldwide

- NCCN guidelines
- Ontaria guidelines
- Routine practice in countries worldwide
- ESMO/ESGO guidelines 2022: no consensus (2018: negative statement)

KGOG 3042: multicenter prospective cohort study

- 2017-2021; 7 institutions
- N=205
- Stage III and IV
- Neo-adjuvant chemotherapy, at least 3 cycles
- Prim endpoint: PFS
- Sec endpoint: OS and safety



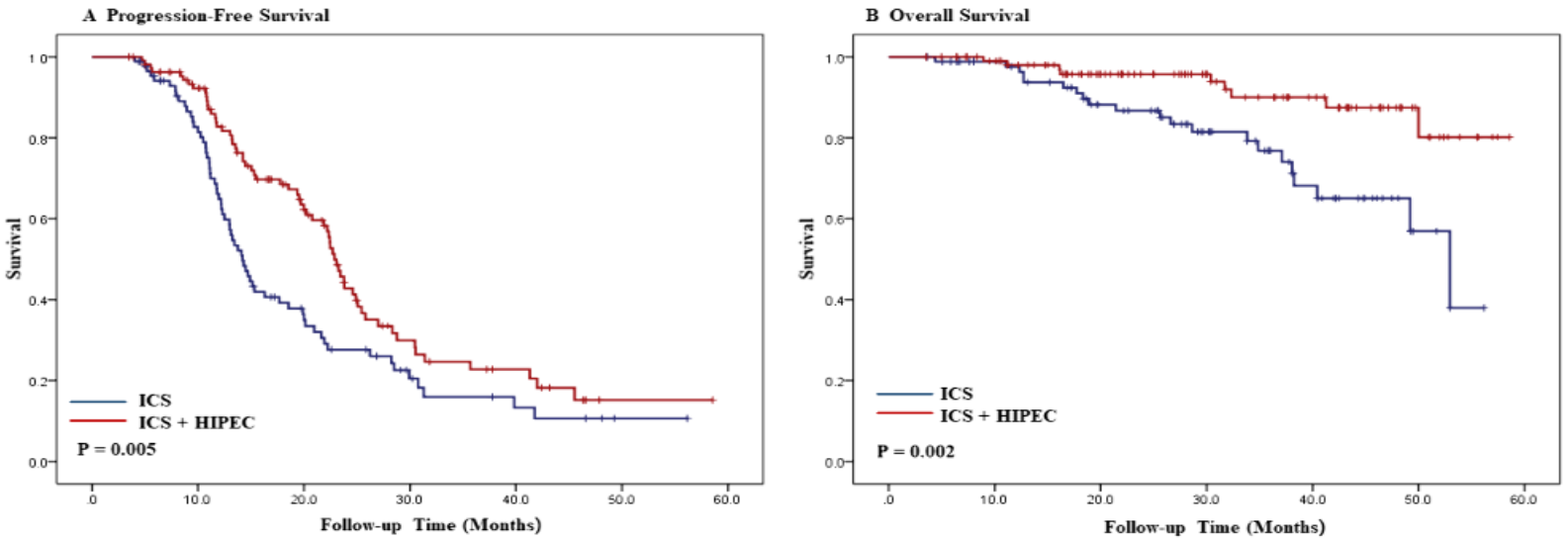
Results

Follow-up: 28.2 months

	Interval CRS	Interval CRS + HIPEC	P-value
PFS	14.2	22.9	0.005
OS	53.0	Not reached	0.002
Peritoneal recurrences	41/64 (64.1%)	21/64 (32.8%)	0.001

Lee et al, IGCS 2022

Figure. Kaplan-Meier curves of progression-free survival and overall survival according to HIPEC (A,B). ICS, interval cytoreductive surgery

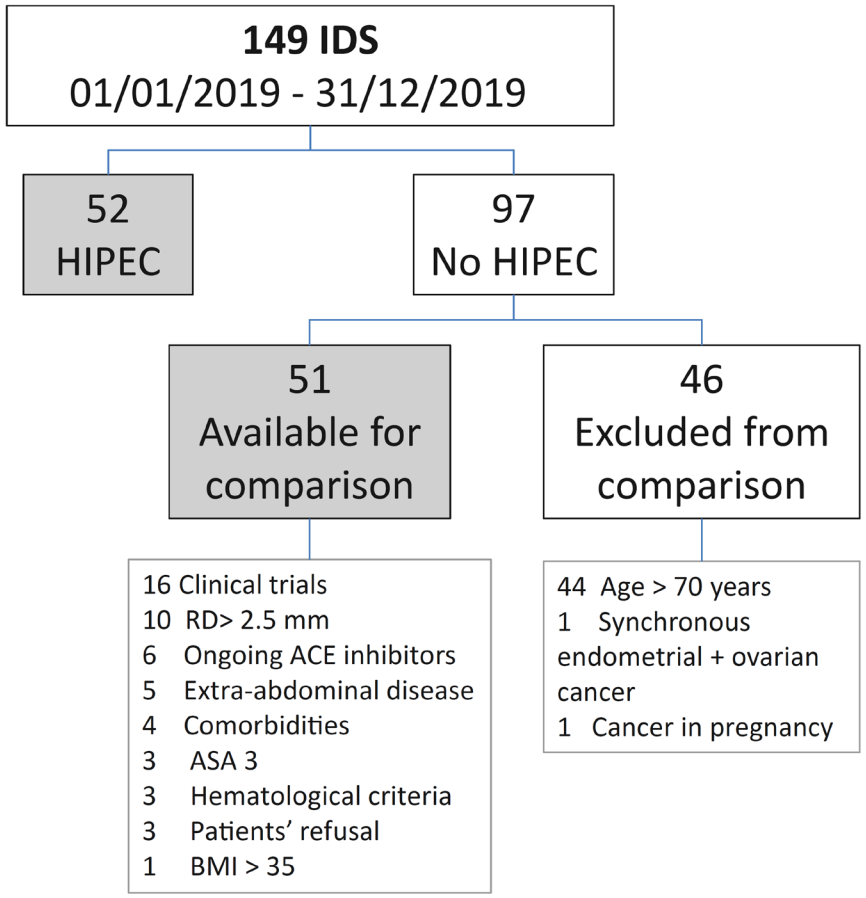


Lee et al, IGCS 2022

Discussion

- How were patients selected for interval CRS +/- HIPEC
- Rationale for including stage IV
- Different HIPEC regimes?
- Equal number of recurrences in both groups?

Real life experience – HIPEC and interval CRS



- Adding HIPEC to interval CRS is safe
- Does not result in more complications
- Does not increase time to start adjuvant chemotherapy
  - 39 and 36 days for HIPEC and CRS only
- Does not increase rate of stoma formation
  - 46.6% and 57.1% for HIPEC and CRS only group

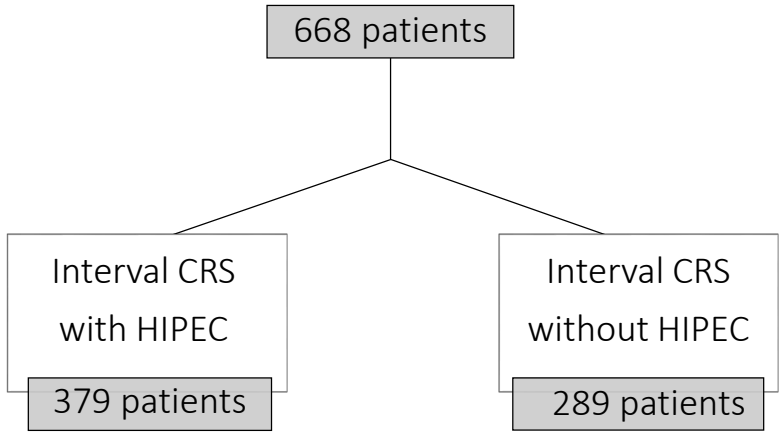
Ghirardi et al, Cancer 2020

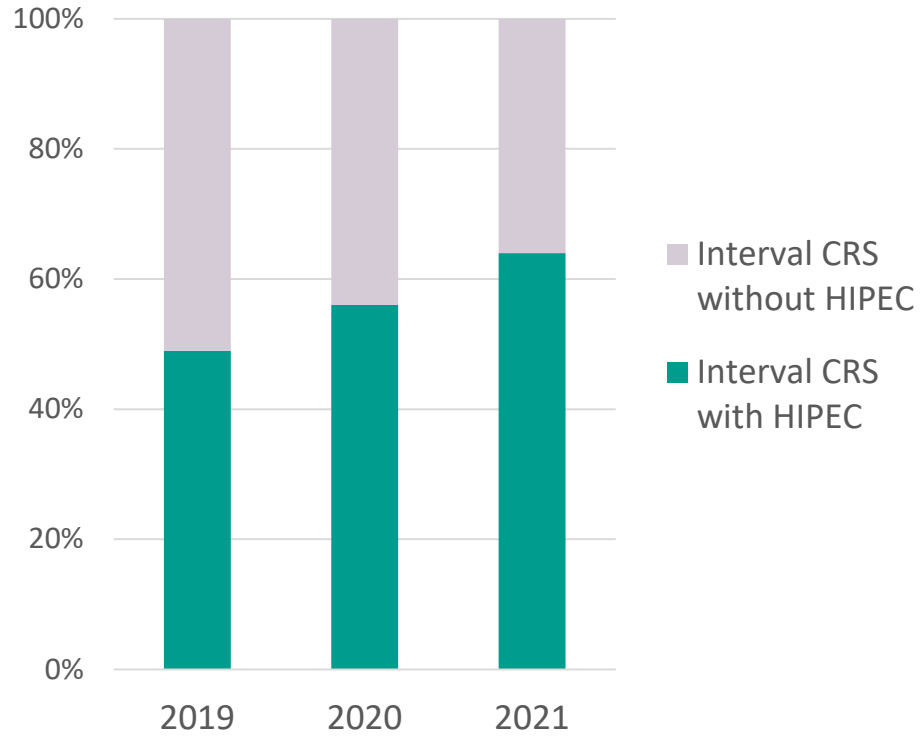
Real life experience in the Netherlands

Dutch Gynecological Oncology Audit

Selection criteria

- Primary EOC
- FIGO stage III
- <10 mm residual disease
- Interval CRS between Jan 1, 2019 and Dec 31, 2021 in the Netherlands





Van Stein et al, IGCS poster presentation, 2022

HIPEC use

Age	←
WHO performance score	←
Body Mass Index	
Charlson comorbidity index	
Previous abdominal surgery	
FIGO stage	
Residual disease	←

OVHIPEC-1 trial

	Interval CRS	Interval CRS with HIPEC
Bowel resection	24%	24%
with ileo- or colostomy	43%	72%

Clinical practice

	Interval CRS	Interval CRS with HIPEC
Bowel resection	29%	38%
with ileo- or colostomy	21%	30%

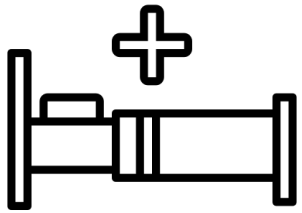
Van Stein et al, IGCS poster presentation, 2022

Postoperative outcomes

	Length of hospital stay ≥7d		Complications		Time to adjuvant chemotherapy ≥6w	
	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
HIPEC						
No	1		1		1	
Yes	4.1 (2.6-6.7)	<0.001	1.2 (0.8-1.9)	0.3	0.8 (0.4-1.4)	0.4

Clinical practice

6 vs. 8 days



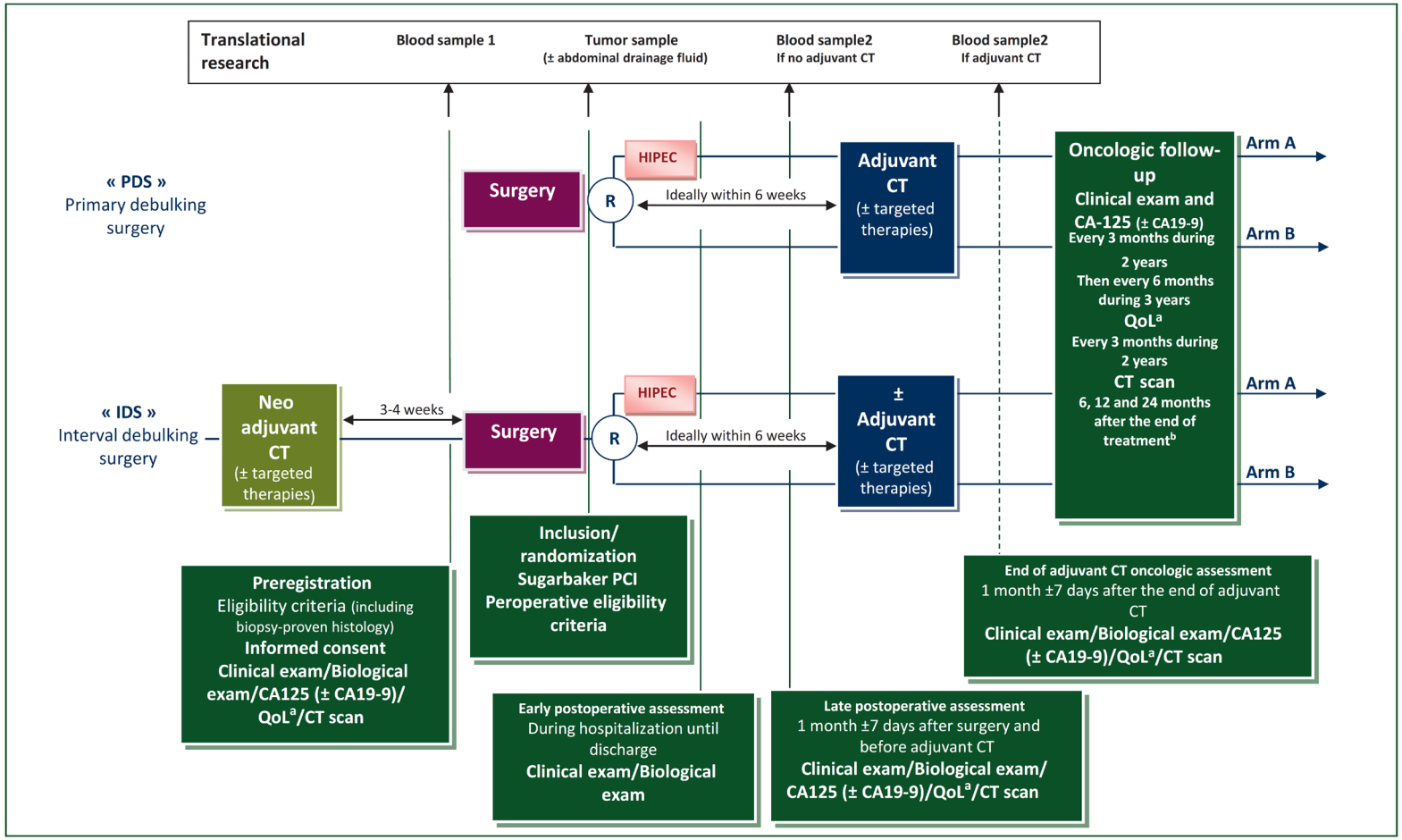
OVHIPEC-1 trial

8 vs. 10 days

Van Stein et al, IGCS poster presentation, 2022

Ongoing studies

CHIPPI study – design
N=432



HIPEC with cisplatinum 100 mg/m^2, with a maximum of 200 mg
90 minutes
Sodium thiosulphate
Randomization at the end of CRS

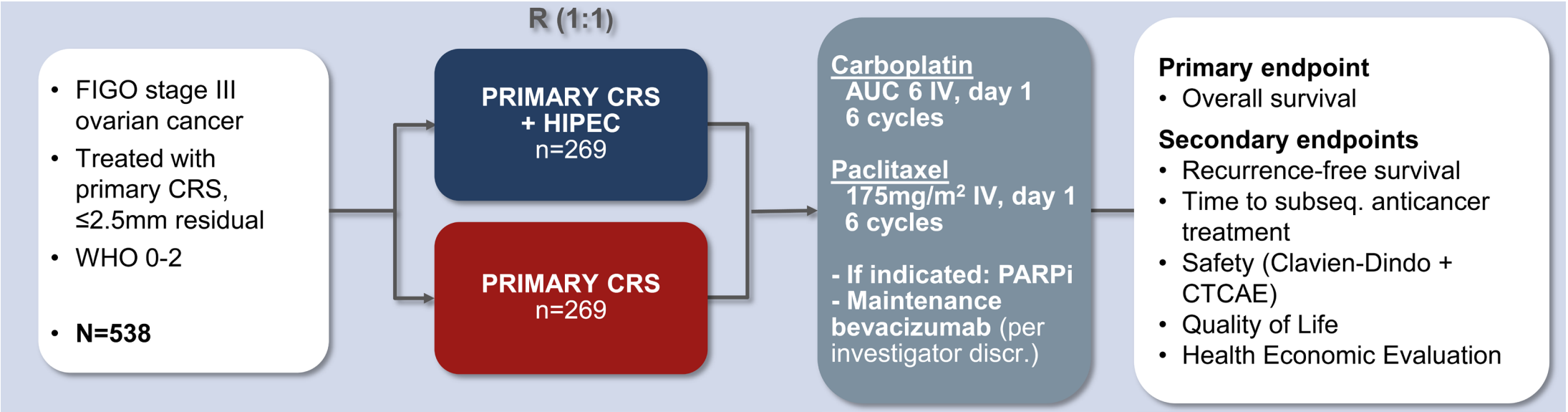
<u>Stratification:</u>
Disease burden/Postsurgery residue
Timing of surgery
Histological type

<u>Primary endpoint</u>
Disease free survival

<u>Secondary endpoint</u>
Overall survival
Safety/ QOL
Time to adjuvant treatment

El Hajj et al, ESMO open 2021

Study design OVHIPEC-2

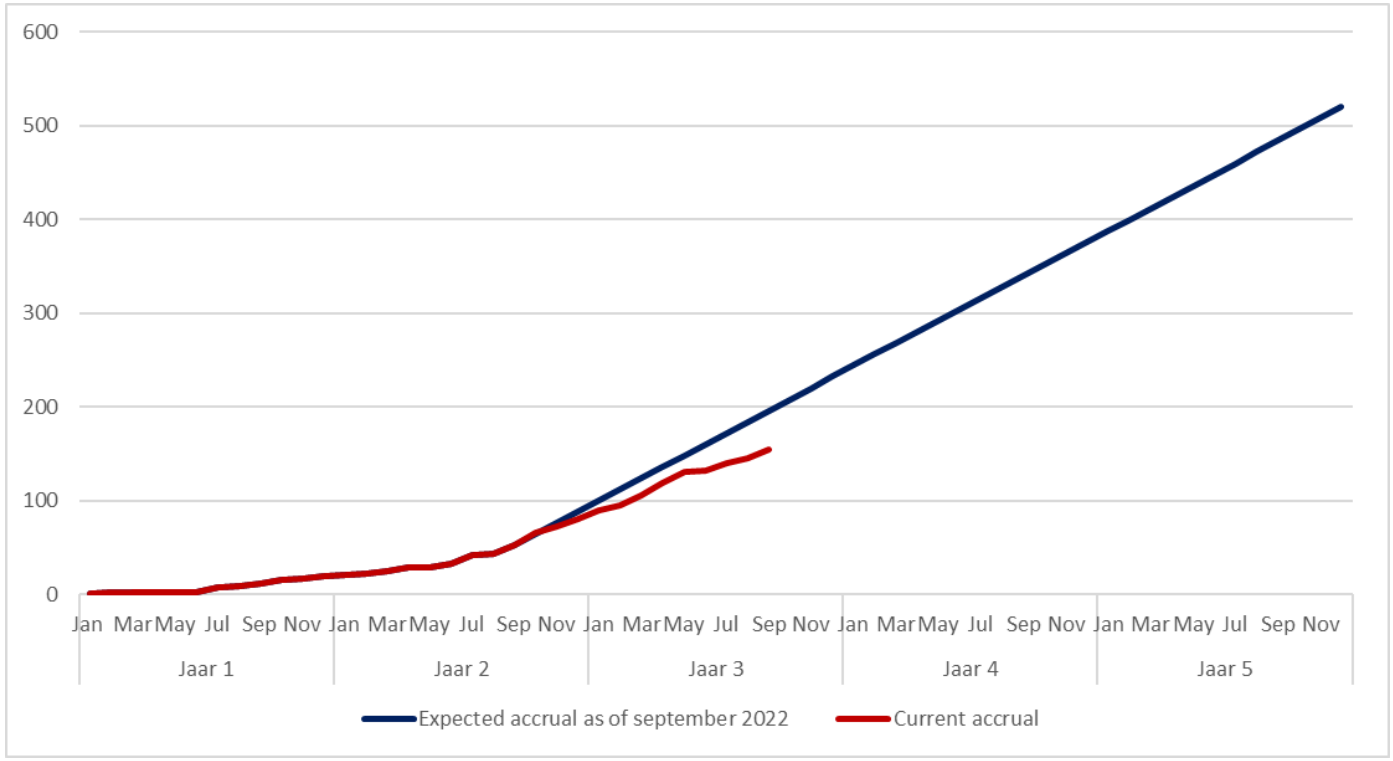


Koole et al, Int J Gynecol Cancer, 2020

Participating trial groups

Group	Approval	Start accrual
DGOG	Obtained	January 2020
Gineco	Obtained	November 2020
NSGO-CTU	Obtained	Q3 2021
MITO	Obtained	May 2021
USA: MSKCC 2 centers	Obtained In progress	Q1 2022
Cancer trials Ireland	Obtained	Q3 2022
NCRI-UK//India	Started funding application	
ANZGOG	Started funding application	
India	Started funding application	

Inclusion rate OV52-OVHIPEC 2

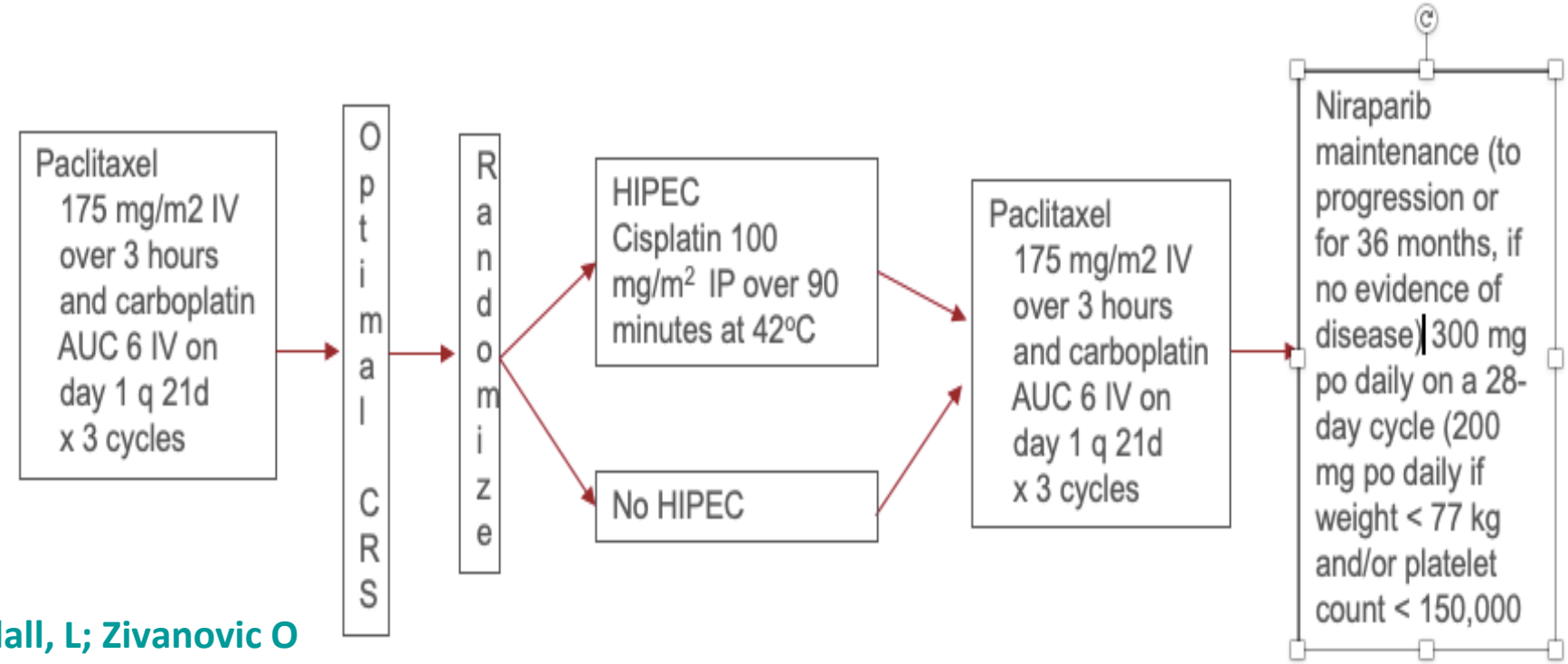


N=155/538

GOG-3068/HIPEC

A Phase III Randomized Trial of 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)**

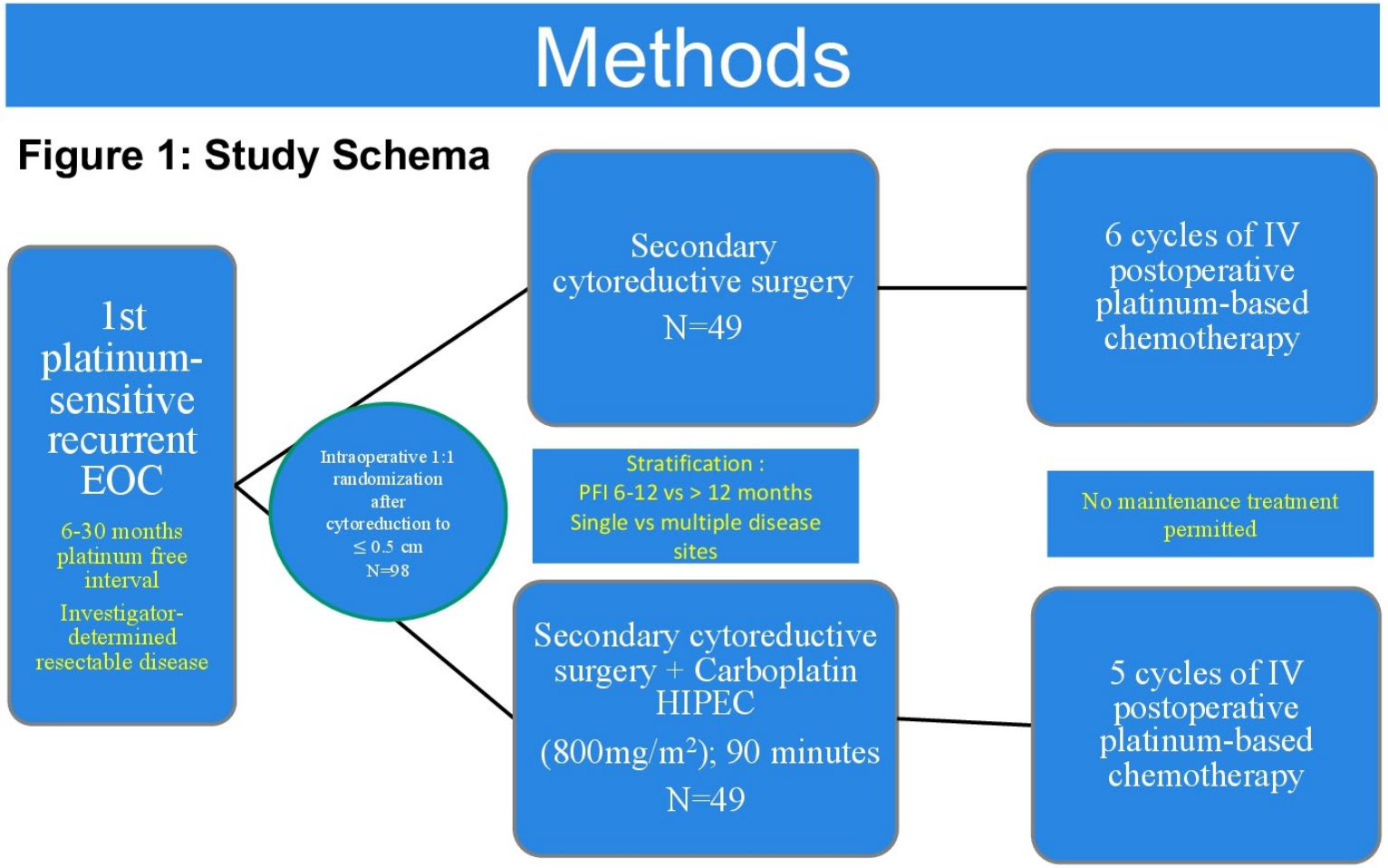


N= 230

Primary Endpoint = PFS

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

Recurrent ovarian carcinoma
Phase II study MSKCC



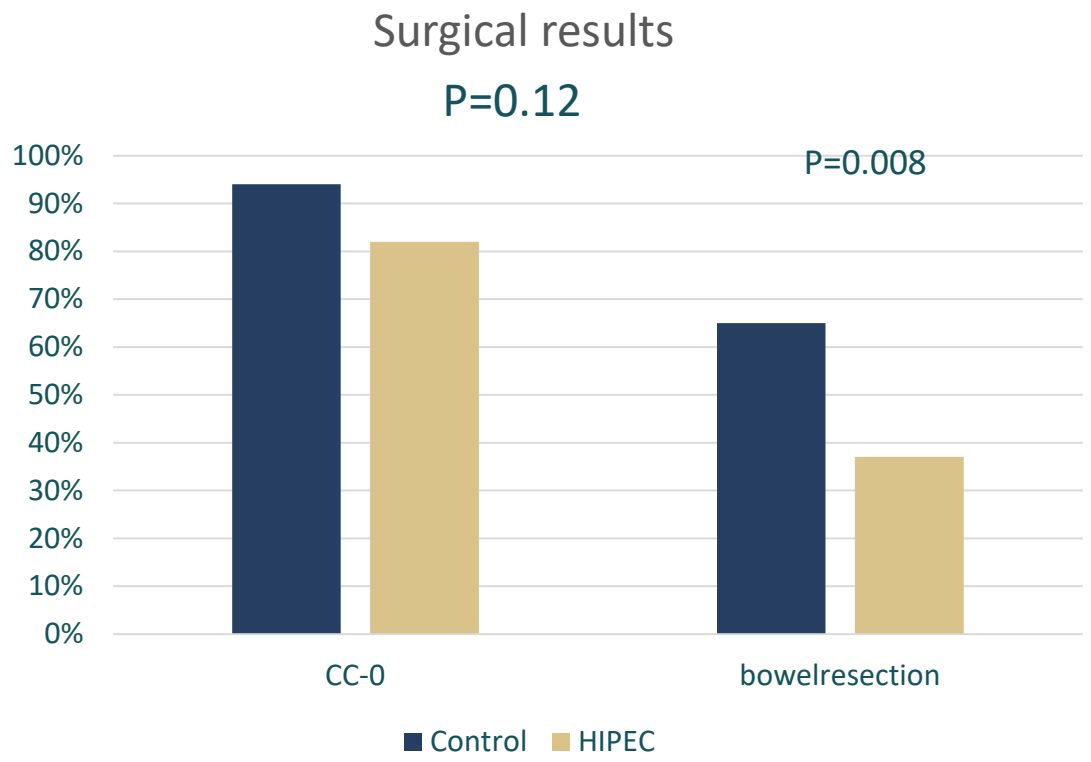
Zivanovic et al, J Clin Oncol 2021

HIPEC study MSKCC

Recurrent disease

Both groups were balanced for:

- Age
- Stage
- Histology
- BRCA mutation status
- Prior chemotherapy
- Disease free survival



Zivanovic et al, J Clin Oncol 2021

MSKCC: HIPEC with carboplatin for recurrent disease

Results

Figure 2: Progression Free Survival (PFS) for patients in the HIPEC (blue) and non-HIPEC (orange) arms

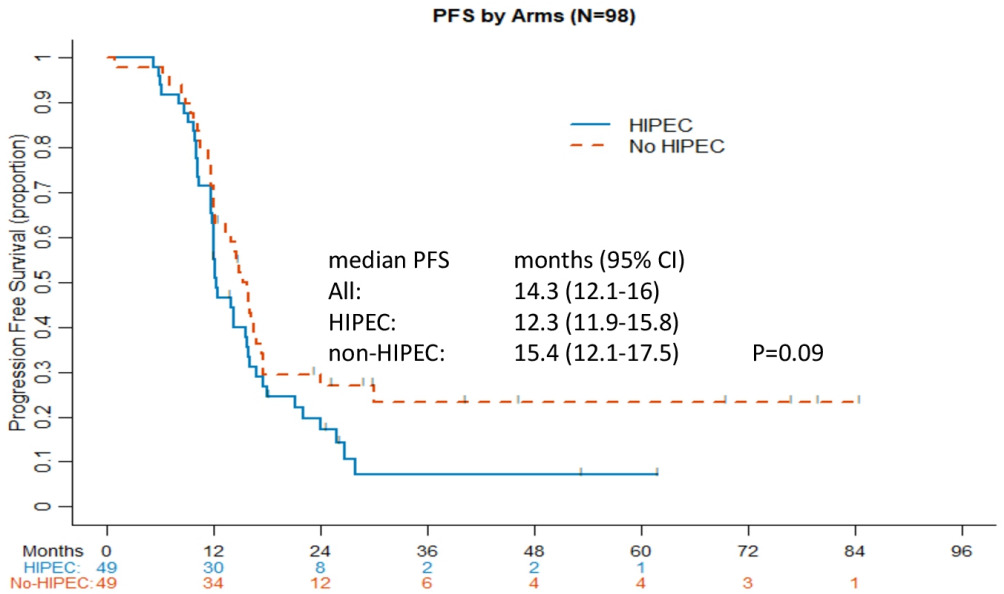
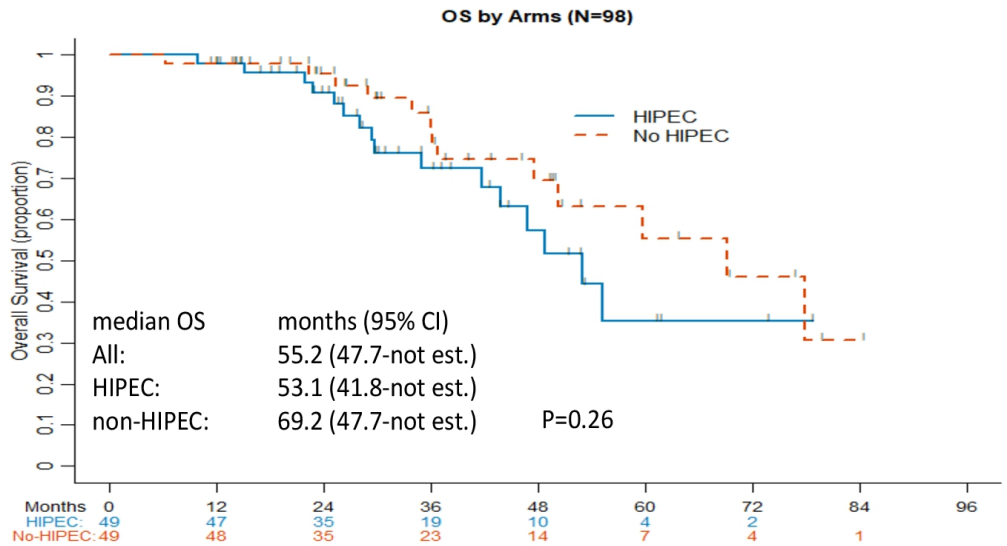
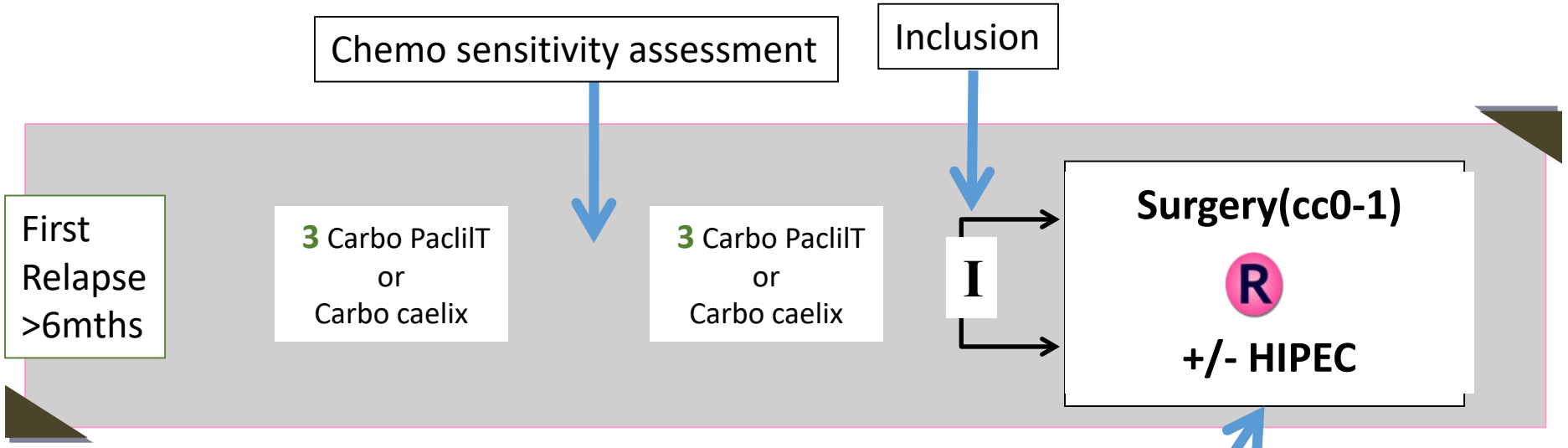


Figure 3: Overall survival (OS) for patients in the HIPEC (blue) and non-HIPEC (orange) arms



Zivanovic et al, J Clin Oncol 2021

Recurrent ovarian carcinoma
CHIPOR



Follow up 5 years

HIPEC:
CDDP: 75 mg /m²
41-42°C
60 mn
Open or closed

N=404/404

Prim endpoint: overall survival

JM Classe et al, France

Recurrent disease -
Horse – MITO 18 study

Recurrent ovarian carcinoma
- 6 months disease free
- Measurable disease
- Limited to abdominal cavity

N=158

Surgery CC-0 or CC-1

Surgery CC-0 or CC-1 + HIPEC

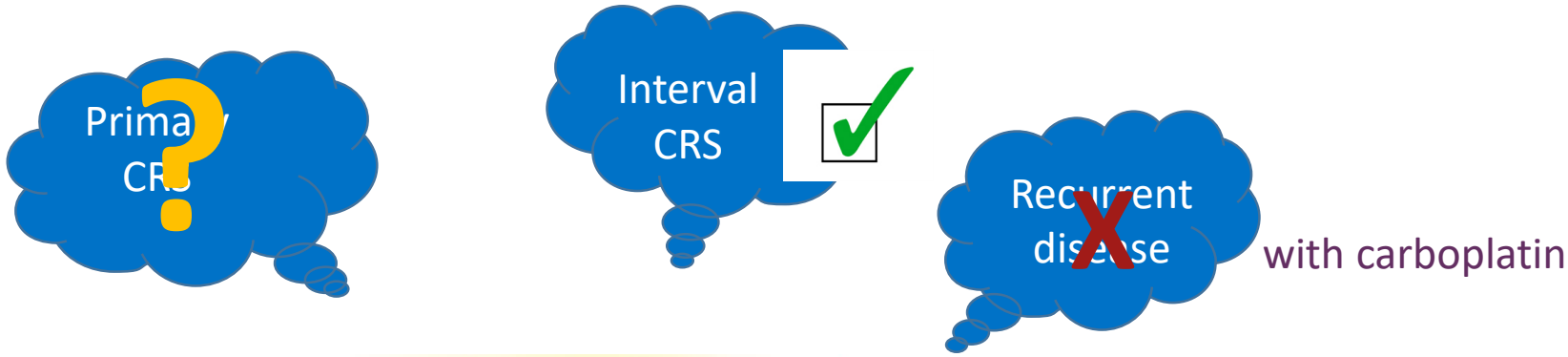
CDDP 75 mg/m^2 in 5L/m ^{2}
60 minutes
41.6 ^{o} C

Primary endpoint:
Disease free survival

Secondary endpoint:
Overall survival
Morbidity
Mortality
Patterns of recurrence
Quality of life

Fagotti et al

Take home message



Questions which remain to be solved:

- How to select patients who benefit most?
  - HRD status
  - Chemosensitivity score
  - Other factors
- Can we optimize dosing schedule?
- Can we sensitize tumor cells at time of HIPEC?

OVHIPEC-2

collaborations