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12th International Symposium
ADVANCED
OVARIAN
CANCER
Optimal Therapy. Update

PRO: HIPEC improves survival in AOC

Gabe Sonke, medical oncologist
Netherlands Cancer Institute

Disclosures

- Institutional research support from AstraZeneca, Merck, Novartis, and Roche


Friday 22nd February
12:35
Palau de la Música
Belgium
Netherlands
Does HIPEC improve survival in AOC?
12th International Symposium Advanced Ovarian Cancer


adidas
6
BELGIUM

Why consider HIPEC in ovarian cancer?

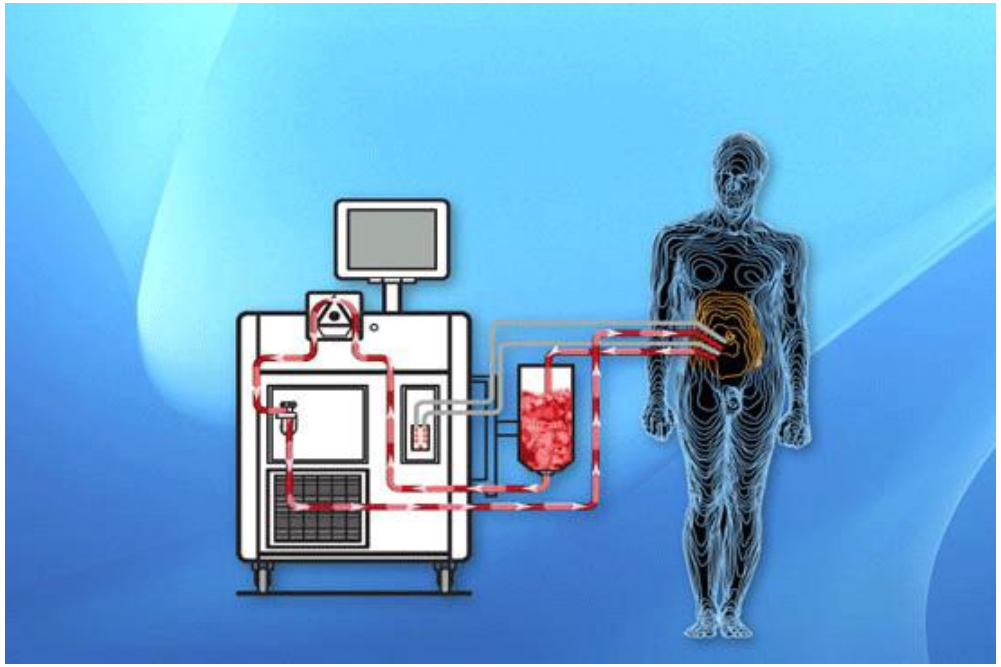
- Far too many women die from recurrent disease
- Peritoneal recurrences are common (even after complete resection)
- HIPEC increases peritoneal exposure to cisplatin
- Hyperthermia induces homologous recombination deficiency

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

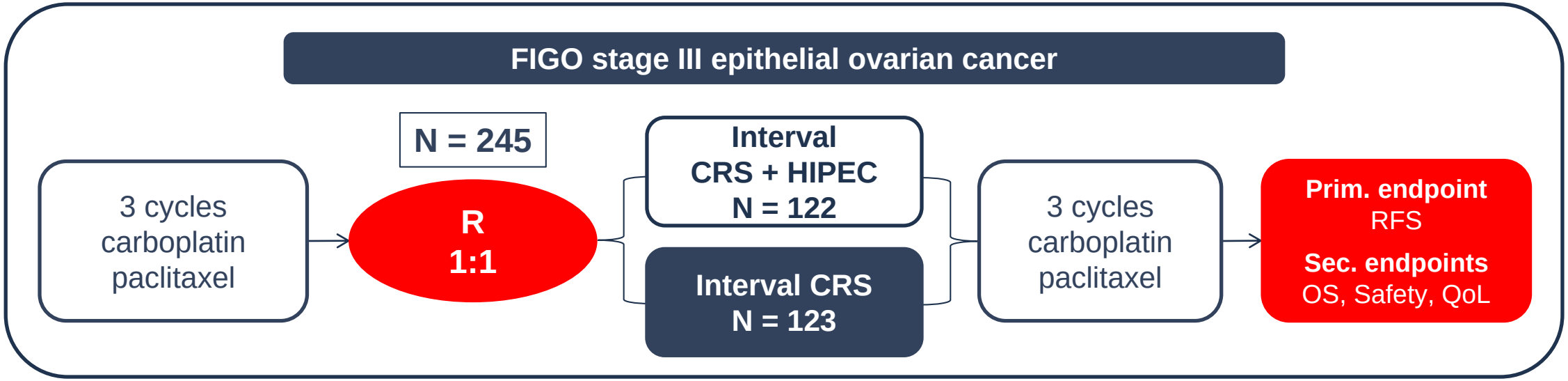
W.J. van Driel, S.N. Koole, K. Sikorska, J.H. Schagen van Leeuwen, H.W.R. Schreuder, R.H.M. Hermans, I.H.J.T. de Hingh, J. van der Velden, H.J. Arts, L.F.A.G. Massuger, A.G.J. Aalbers, V.J. Verwaal, J.M. Kieffer, K.K. Van de Vijver, H. van Tinteren, N.K. Aaronson, and G.S. Sonke



van Driel et al. NEJM 2018

OVHIPEC study

Design



- 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 was used for grading toxicity

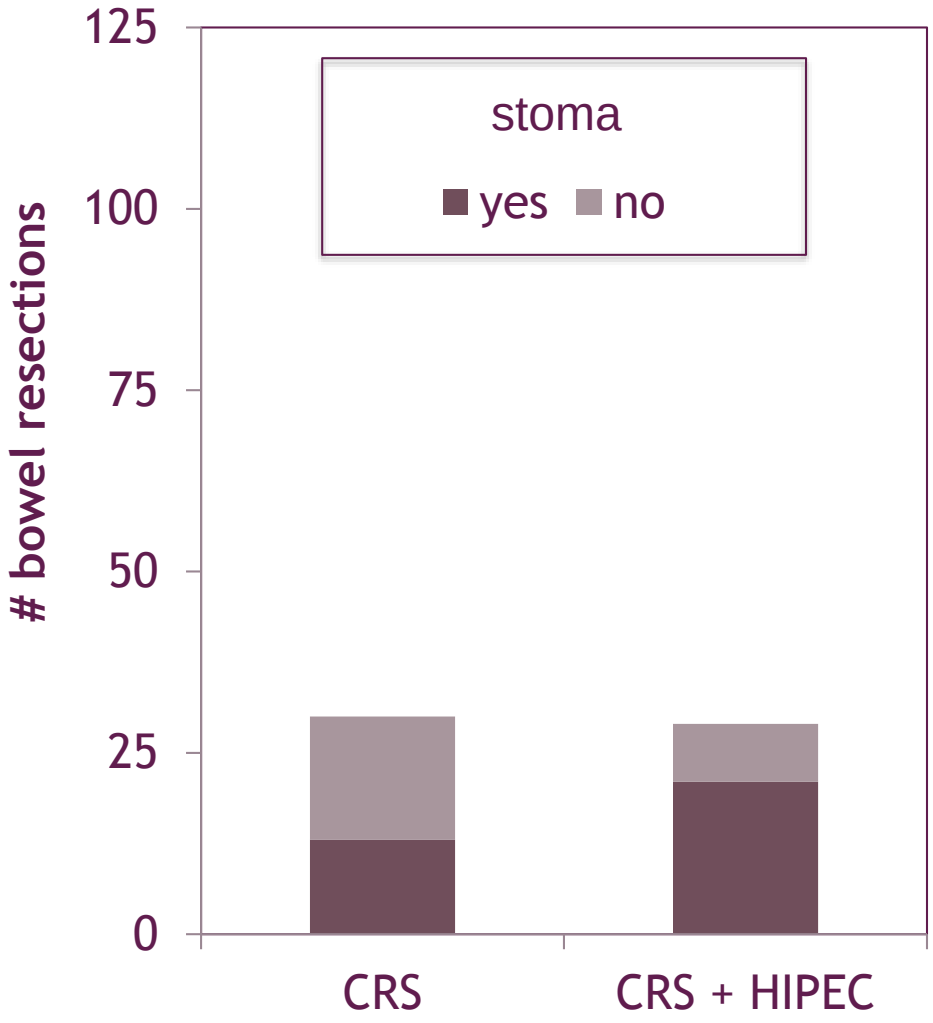
van Driel et al. NEJM 2018

OVHIPEC study

Surgical findings

- Differences
  - longer OR time (146 min, per protocol)
  - longer ICU stay (1 day, per protocol)

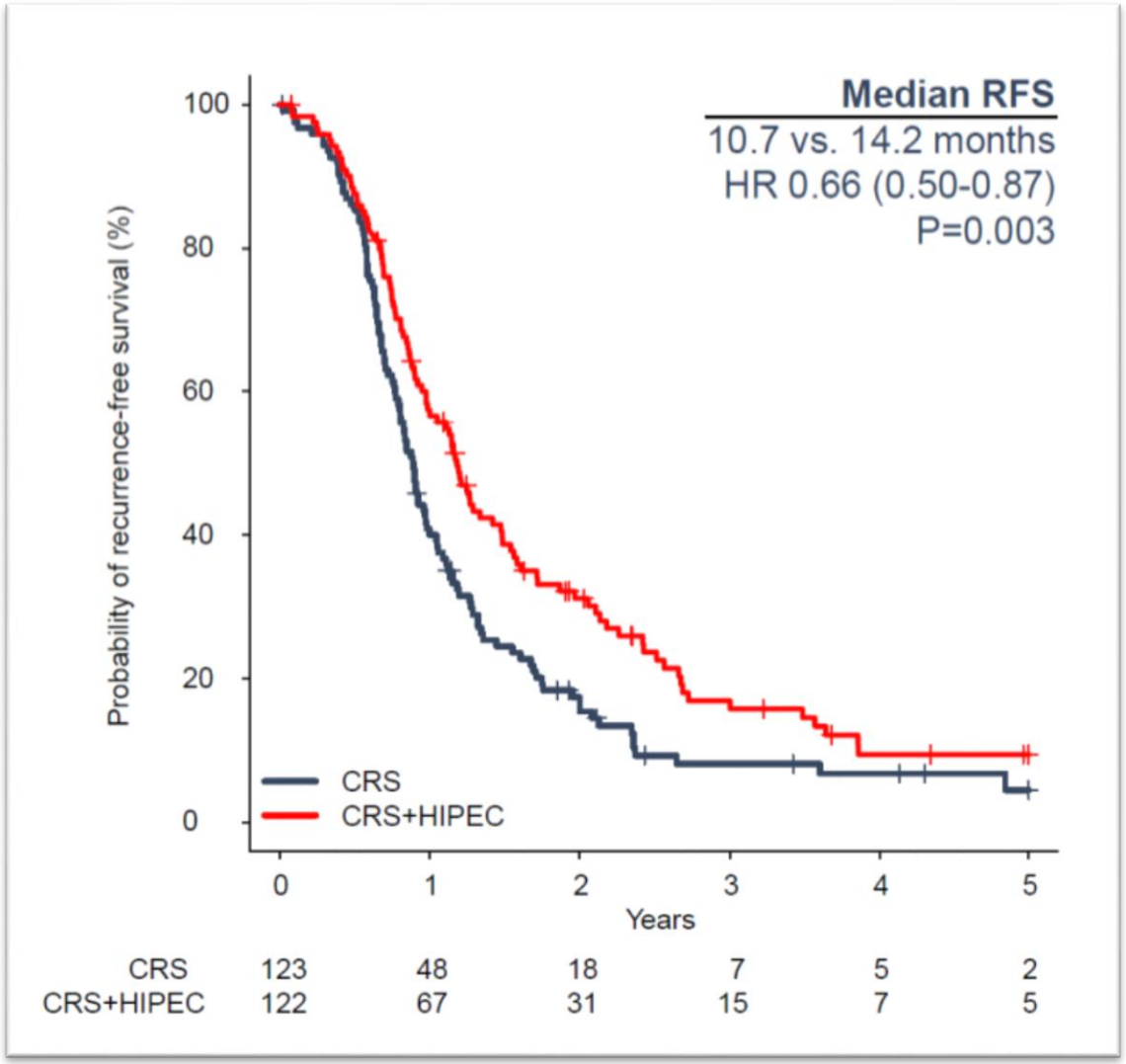
- No difference in
  - complete resections (68%)
  - optimal resections (30%)
  - bowel resections
  - quality of life
  - adverse events
  - days in hospital
  - time to restart chemotherapy
  - chemotherapy completion rate

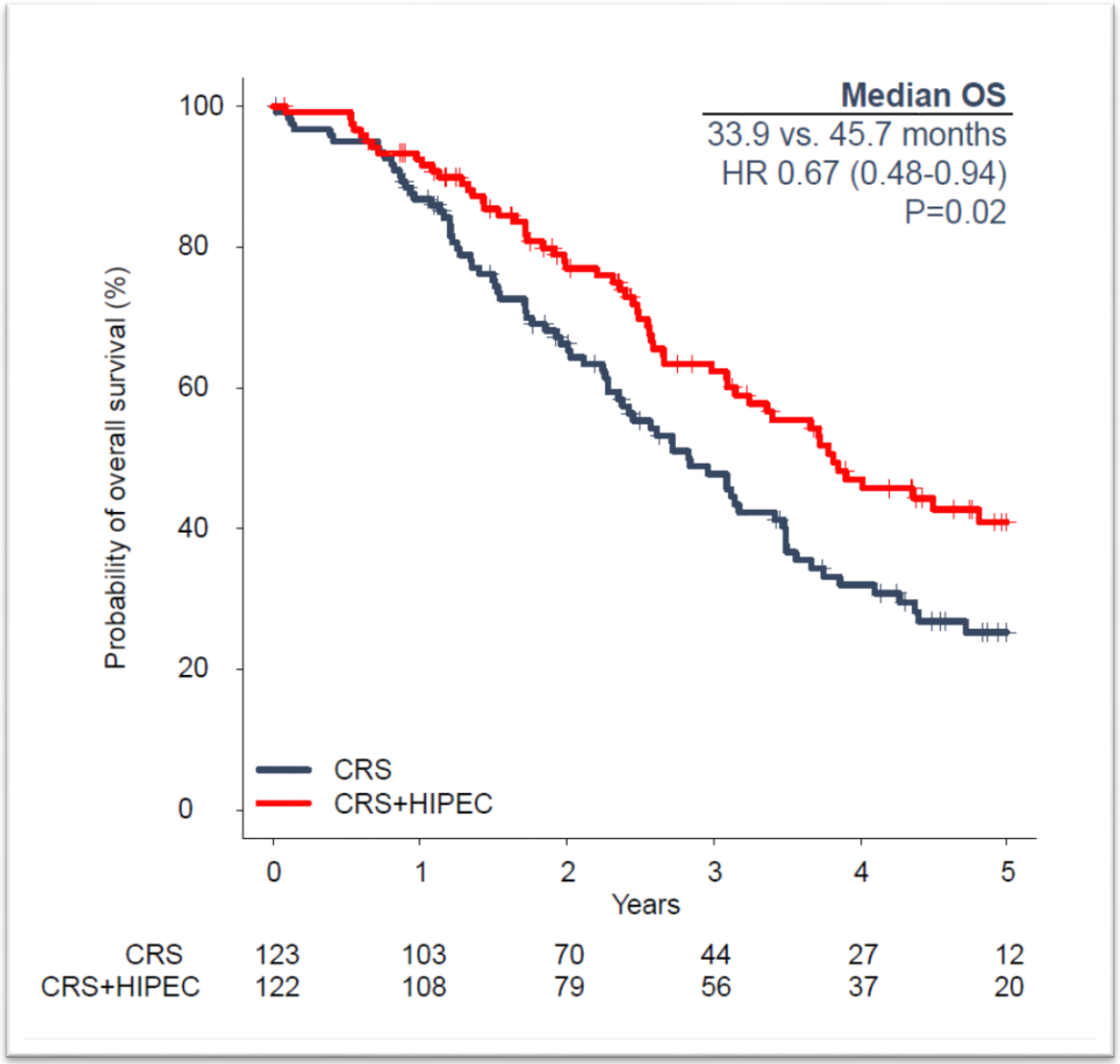


van Driel et al. NEJM 2018

OVHIPEC study

Results





van Driel et al. NEJM 2018

OVHIPEC study

Subgroups

Subgroup	Surgery	Surgery plus HIPEC	Hazard Ratio (99% CI)
	no. of events/total no.		
Age			
≥65 yr	43/45	34/43	0.63 (0.35–1.15)
<65 yr	67/78	65/79	0.72 (0.46–1.12)
Histologic type			
High-grade serous	96/107	91/112	0.69 (0.48–1.02)
Other	14/15	7/9	0.56 (0.17–1.86)
Previous surgery			
No	100/111	90/110	0.71 (0.49–1.03)
Yes	10/12	9/12	0.47 (0.14–1.61)
No. of involved regions			
0–5	73/83	62/83	0.64 (0.41–1.01)
6–8	37/40	37/39	0.66 (0.35–1.23)
Laparoscopy before surgery			
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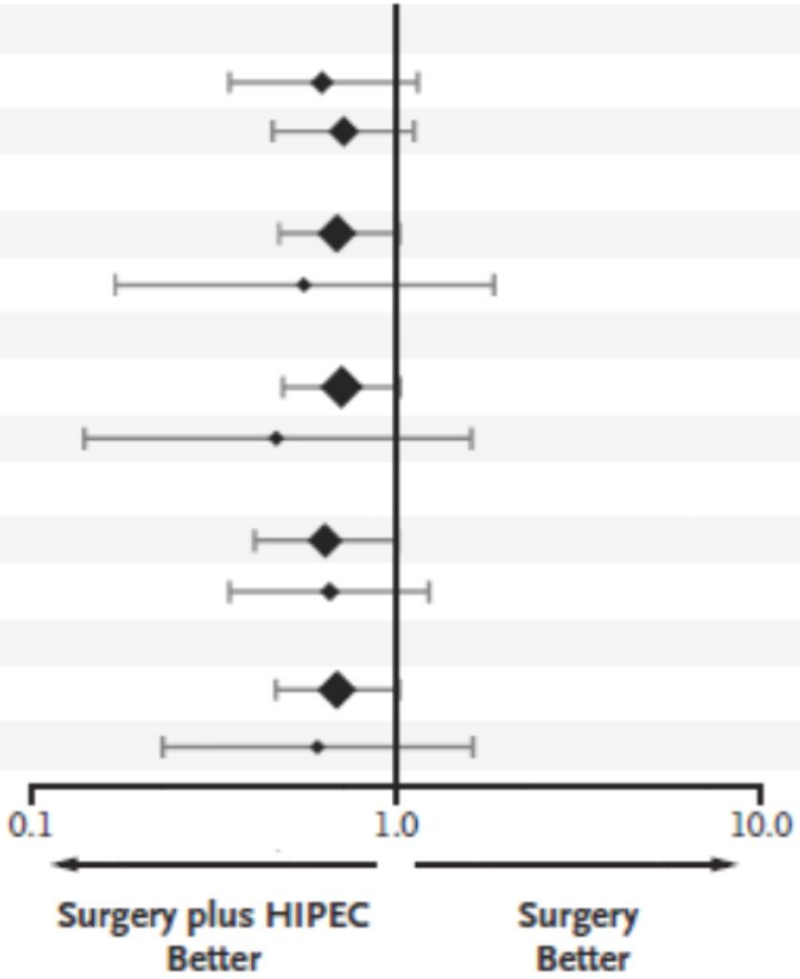

van Driel et al. NEJM 2018

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Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

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Archives of Gynecology and Obstetrics
https://doi.org/10.1007/s00404-018-4908-0

NEWS AND VIEWS

Is there a role for HIPEC in ovarian cancer?

Philipp Harter[1] · Andreas du Bois[1] · Jalid Sehouli[2] · Sven Mahner[3] · Ignace Vergote[4] · Luis Chiva[5] · Antonio Gonzalez-Martin[6] · Christina Fotopoulou[2,7]

ANNALS OF ONCOLOGY

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

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HIPEC: HOPE or HYPE in the fight against advanced ovarian cancer?

C. Fotopoulou[1,2,3,4*], J. Sehouli[2,3,4], S. Mahner[4,5], P. Harter[4,6], E. Van Nieuwenhuysen[7,8], A. Gonzalez-Martin[9,10], I. Vergote[7,8], L. Chiva[10,11] & A. Du Bois[4,6]

[1]Department of Surgery and Cancer, Gynecologic Oncology, Hammersmith Hospital Imperial College London, London, UK; [2]Department of Gynecology, Charité Medical University of Berlin, Berlin; [3]North-Eastern German Society of Gynaecologic Oncology (NOGGO) Ovarian Cancer Study Group, Taufkirchen; [4]Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) Study Group, Taufkirchen; [5]Department of Obstetrics and Gynecology, Ludwig-Maximilians-University Munich, München; [6]Department of Gynecology, Kliniken Essen Mitte, Essen, Germany; [7]University Hospitals Leuven, Leuven; [8]BGOG, Leuven, Belgium; [9]Department of Medical Oncology, Clínica Universidad de Navarra, Madrid; [10]GEICO Study Group, Madrid; [11]Department of Obstetrics and Gynecology, Clínica Universidad de Navarra, Madrid, Spain
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Issues raised by Vergote et al.

1. Study took long to accrue
2. Design of the study and endpoints
3. Study addresses only a small population of EOC patients
4. Heterogeneity of the results
5. Underreported toxicity
6. Korean study

Vergote et al. NEJM 2018; Fotopoulou et al. Ann Oncol 2018; Harter et al. Arch Gynecol Obstet 2018

Study took long to accrue

Only an average of 3.5 patients per year per center were recruited

Large difficulties […] in recruitment of the trial may be interpreted as surrogate marker for the quality of the study and the presence of strong selection bias.

- **Slow accrual due to limited funding (no pharmaceutical incentive)**
- **Individual hospitals had to pay for procedures**

- **I am not aware of any association between duration and quality**
- **I am not aware of any association between duration and strong selection bias**

Vergote et al. NEJM 2018; Fotopoulou et al. Ann Oncol 2018; Harter et al. Arch Gynecol Obstet 2018

Design: AGO DESKTOP III
(ENGOT-ov20; NCT01166737)

Sponsor: AGO
ENGOT Model A

Pts. with:
- 1st relapse
- PSROC
- AGO Score +ve

R
n = 408

Cytoreductive Surgery with max. effort for complete resection → **Platinum-based Combination therapy** *strongly recommended*

No OP → **Immediate Platinum-based Combination therapy** *strongly recommended* → *OP Allowed 3rd line*

- 80 centres in 12 countries
- Recruitment 9/2010 - 3/2015
- 407 of 409 pts evaluated
  (2 screening failures)

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Presented by: Andreas du Bois
AGO & KEM
Essen, Germany

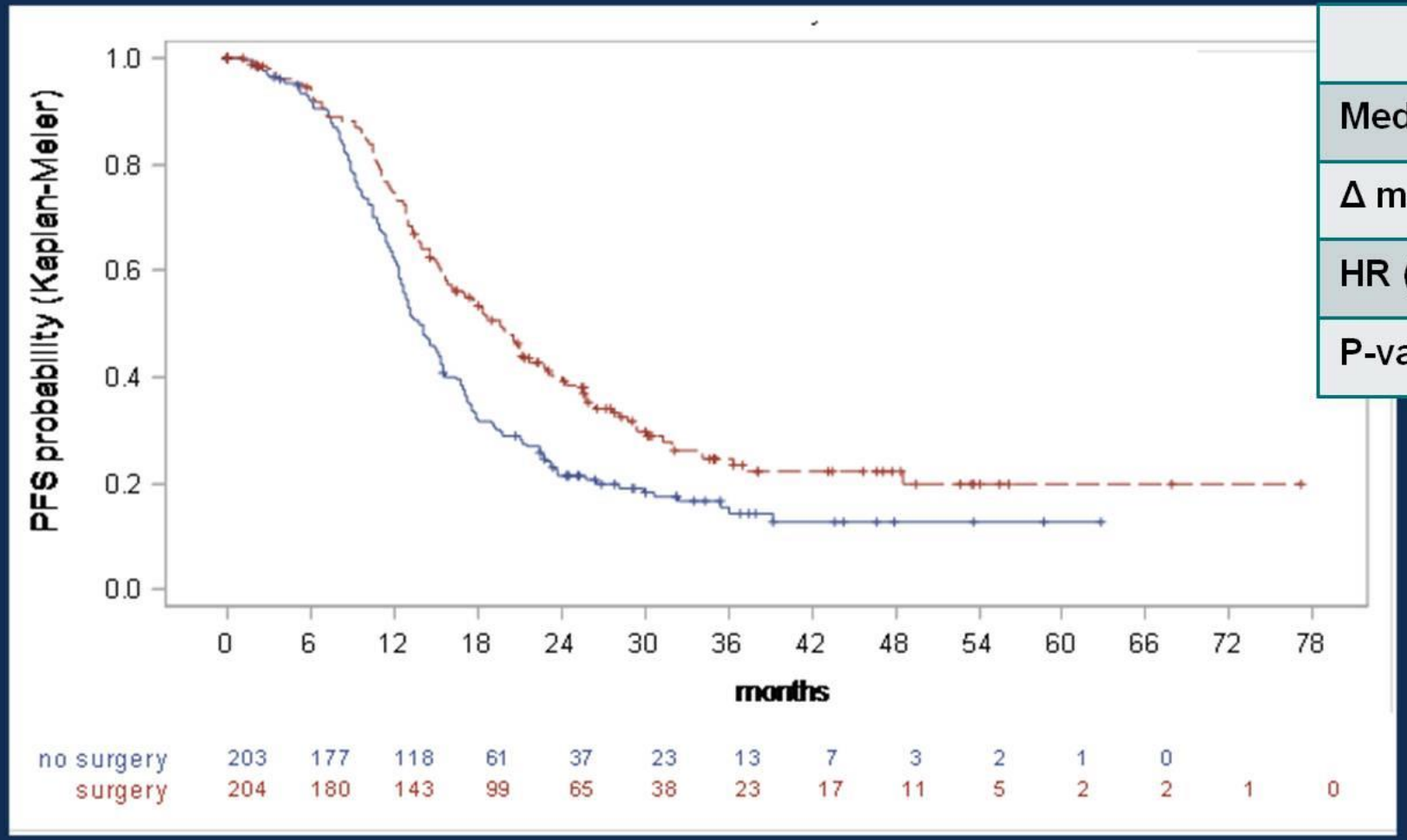
Design of the study and endpoints

The primary end point should have been overall survival, in which case the trial would have been larger and reliable enough to exclude significant bias

- **PFS advocated at the 3rd Ovarian Cancer Consensus Meeting**
- **a small study may lack the power to detect an OS difference**
- **however, since we observed a clear OS benefit, this arguments fails**

Vergote et al. NEJM 2018; Fotopoulou et al. Ann Oncol 2018; Harter et al. Arch Gynecol Obstet 2018; du Bois et al. 3rd ovarian cancer consensus meeting

AGO DESKTOP III: Outcome 2 (PFS, ITT population)
(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)



	Surgery	No surgery
Median PFS	19.6 mos	14.0 mos
Δ median PFS	5.6 mos	
HR (95% CI)	0.66 (0.52 – 0.83)	
P-value	< 0.001	

296 (73%) PFS events

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Statements 2nd cytoreductive surgery in ROC

1. Complete cytoreductive surgery followed by systemic treatment offers benefits regarding PFS and TFST in selected patients with first recurrent OC; an OS benefit has not been proven as data are not mature yet.

Patients eligible for cytoreductive surgery should be informed about this option.

Level 1 A

1.1 Patient selection may consider the following predictors for complete resection*

a. TFI platinum of 6+ months
b. The AGO Score (good performance status, complete resection at 1st surgery, absence of large volume ascites) (Level III A)
c. Imaging without signs of probably irresectable lesions
d. contraindications to surgery (e.g. co-morbidities, prior serious complications)

1.2 Centre selection may consider the following factors

a. available ressources and infrastructure
b. established multidisciplinary cooperation pre-, intra-, and post-operatively
c. Experience and volume of 2nd cytoreductive surgery with a track record of achieving a complete resection in the majority of these procedures

2. Cytoreductive surgery in second or later recurrence may provide benefit in highly selected patients and specialized centres.

Level V A

Study addresses only a small population of EOC patients

The 'super-selection' of patients in this trial […] affects a minority (<10%) of the entire patient population

Advanced ovarian cancer	*1000*
- stage IV	*300*
- frail / elderly	*100*
Leaves	*600*
- complete primary surgery possible (?)	*500*
Eligible for HIPEC	*100*

Even we only involve 10%, we normally embrace the improved outcome

Vergote et al. NEJM 2018; Fotopoulou et al. Ann Oncol 2018; Harter et al. Arch Gynecol Obstet 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

K. Moore, N. Colombo, G. Scambia, B.-G. Kim, A. Oaknin, M. Friedlander, A. Lisyanskaya, A. Floquet, A. Leary, G.S. Sonke, C. Gourley, S. Banerjee, A. Oza, A. González-Martín, C. Aghajanian, W. Bradley, C. Mathews, J. Liu, E.S. Lowe, R. Bloomfield, and P. DiSilvestro

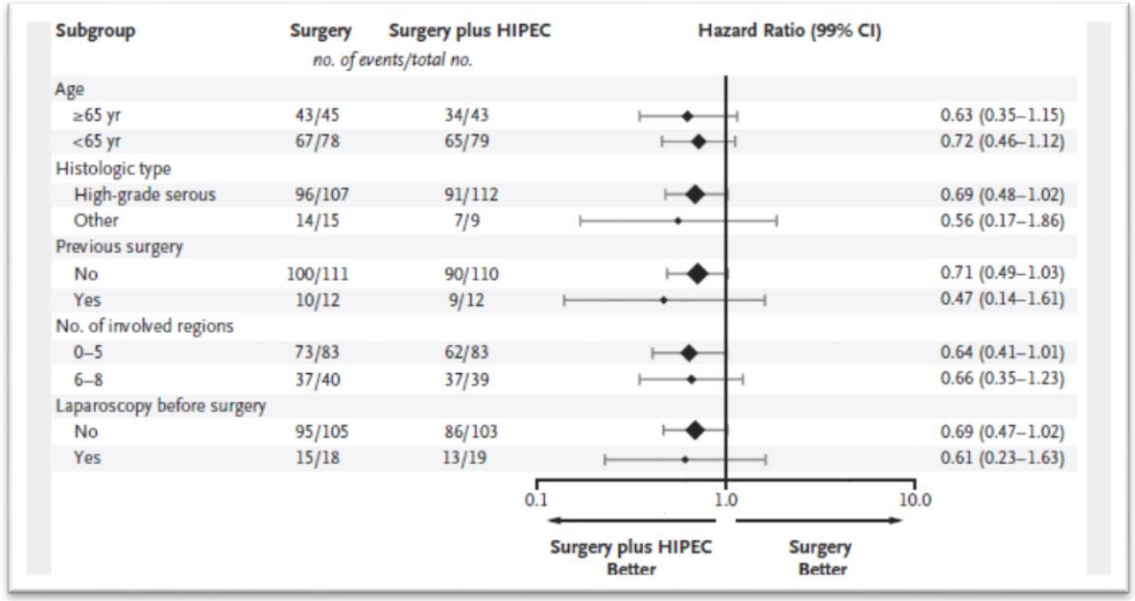
Let us be consistent in the use of scientific arguments!

Moore et al. N Engl J Med 2018; 379: 2495

Heterogeneity of the results

There is an imbalance of HGSOC and non-HGSOC in the two arms despite randomization

- **High-grade serous: 107 vs 112**
- **Randomization ensures equal prognosis of all factors combined**



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Vergote et al. NEJM 2018; Fotopoulou et al. Ann Oncol 2018; Harter et al. Arch Gynecol Obstet 2018

Heterogeneity of the results

A strong correlation between large centres showing the least effect and small centres driving the trial into positivity

- **Tests for interaction were all non-significant**

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SPECIAL REPORT

Statistics in Medicine — Reporting of Subgroup Analyses in Clinical Trials

Rui Wang, M.S., Stephen W. Lagakos, Ph.D., James H. Ware, Ph.D., David J. Hunter, M.B., B.S., and Jeffrey M. Drazen, M.D.

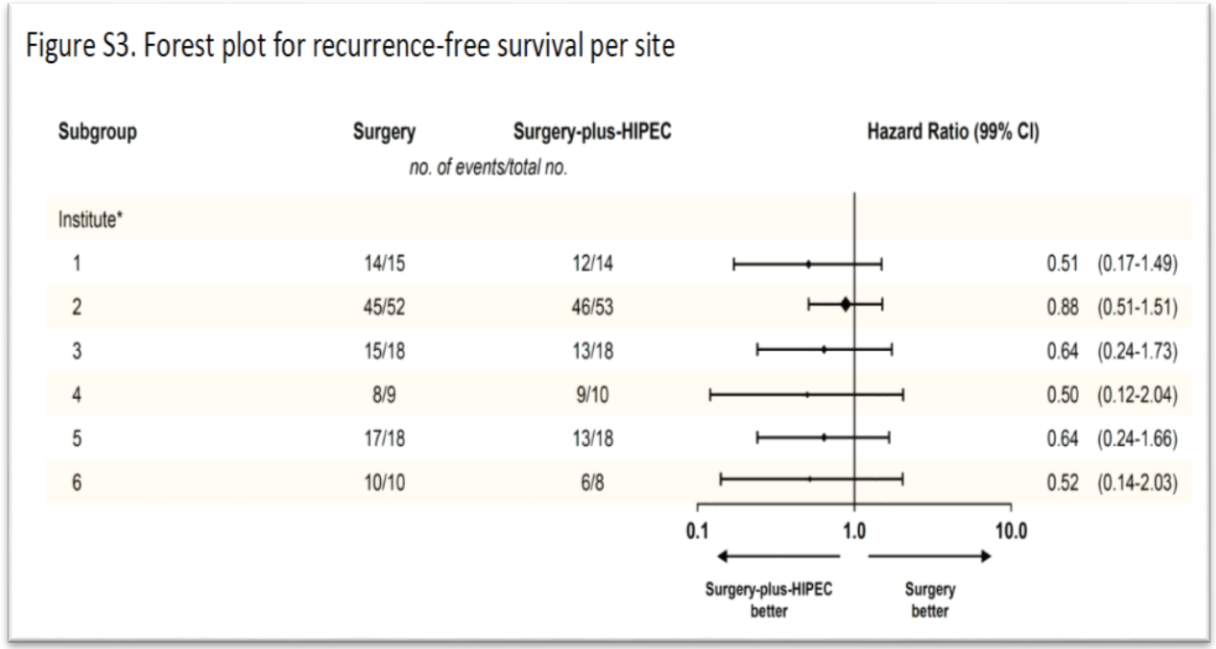


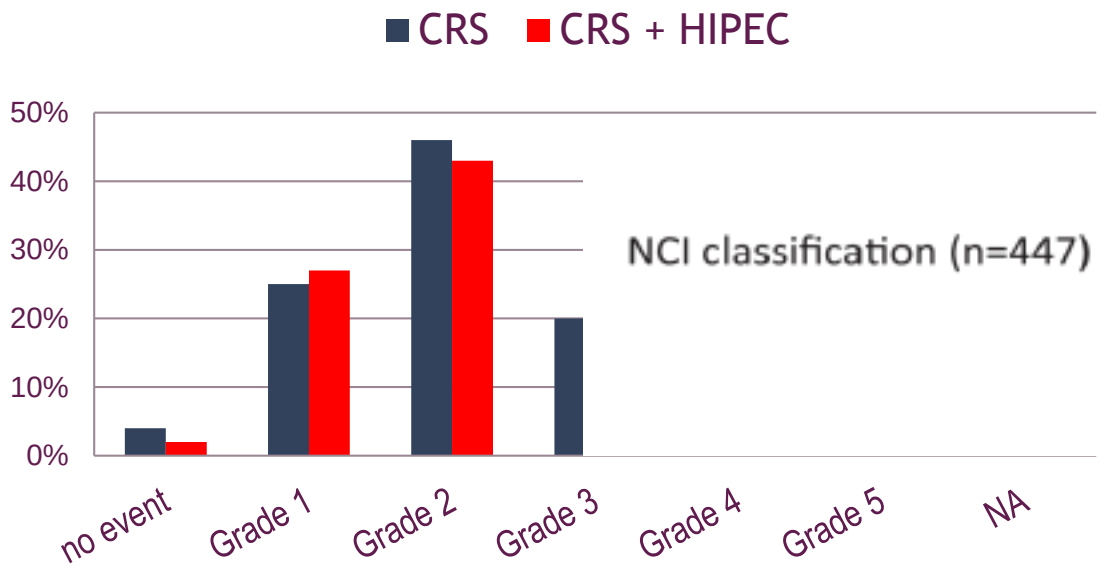
Figure S3. Forest plot for recurrence-free survival per site

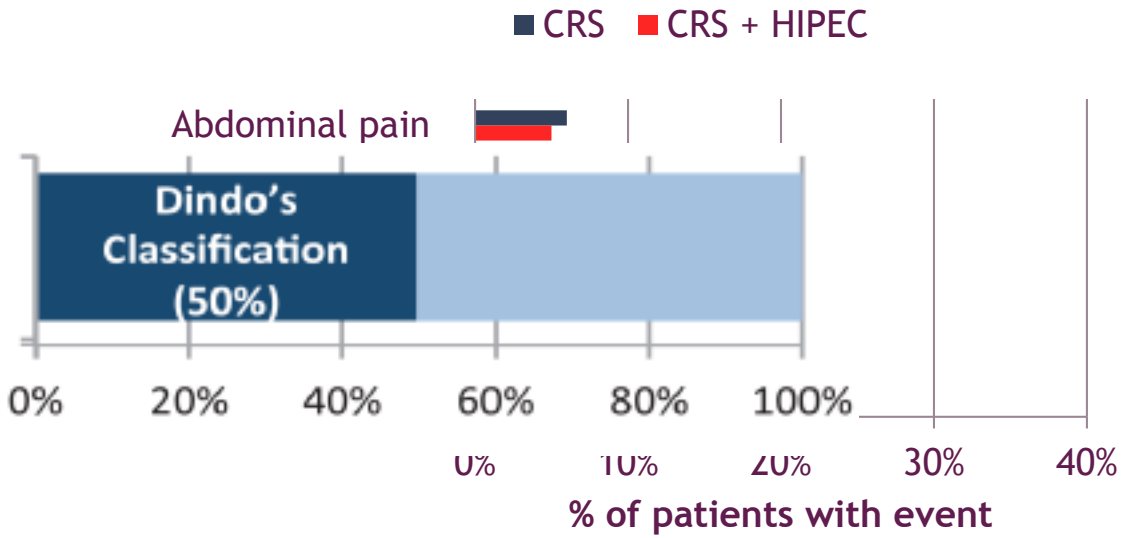
Subgroup	Surgery	Surgery-plus-HIPEC	Hazard Ratio (99% CI)
	no. of events/total no.		
Institute*			
1	14/15	12/14	0.51 (0.17-1.49)
2	45/52	46/53	0.88 (0.51-1.51)
3	15/18	13/18	0.64 (0.24-1.73)
4	8/9	9/10	0.50 (0.12-2.04)
5	17/18	13/18	0.64 (0.24-1.66)
6	10/10	6/8	0.52 (0.14-2.03)

Vergote et al. NEJM 2018; Fotopoulou et al. Ann Oncol 2018; Harter et al. Arch Gynecol Obstet 2018; Wang et al. NEJM 2007

Underreported toxicity

Significant underreported perioperative and long term toxicity, make the interpretation and broad acceptance of the trial even more challenging





van Driel et al. NEJM 2018; Alyami et al. Int J Hyperth 2017

ANTONI VAN LEEUWENHOEK
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Korean Study

No overall effect for HIPEC in interim analysis

	Van Driel et al.	Lim et al.
N	245	185
Stage	III	III and IV
Surgery	IDS	PDS and IDS
Population	European	Asian
Cisplatinum	100 mg/m2	75 mg/m2
Trial completed	Yes	no
Results published	Yes	Abstract only 2017
HR neo-adjuvant	0.66 (0.50 - 0.87)	0.29 (0.08 - 1.00)

Lim et al. ASCO 2017

What causes the reluctance to embrace HIPEC?

1. Study took long to accrue
2. Design of the study and endpoints
3. Study addresses a small population of EOC patients
4. Heterogeneity of the results
5. Underreported toxicity
6. Korean study

7. *We must question ourselves whether the resources […] are worth investing in broadly implementing HIPEC facilities […] or rather to perform maximal effort cytoreductive surgery and maintenance regimens*

HIPEC	€ 15.700
1 year bevacizumab	€ 66.300
1 year parp inhibition	€ 64.000

Vergote et al. NEJM 2018; Fotopoulou et al. Ann Oncol 2018; Harter et al. Arch Gynecol Obstet 2018

The Dutch view on OVHIPEC

Patients eligible for interval cytoreductive surgery should be offered this option

- Approval by health technology assessors (full reimbursement)
- Centralisation: 10 centers will perform OVHIPEC
- Results monitored in nationwide clinical audit

- New study in primary debulking setting

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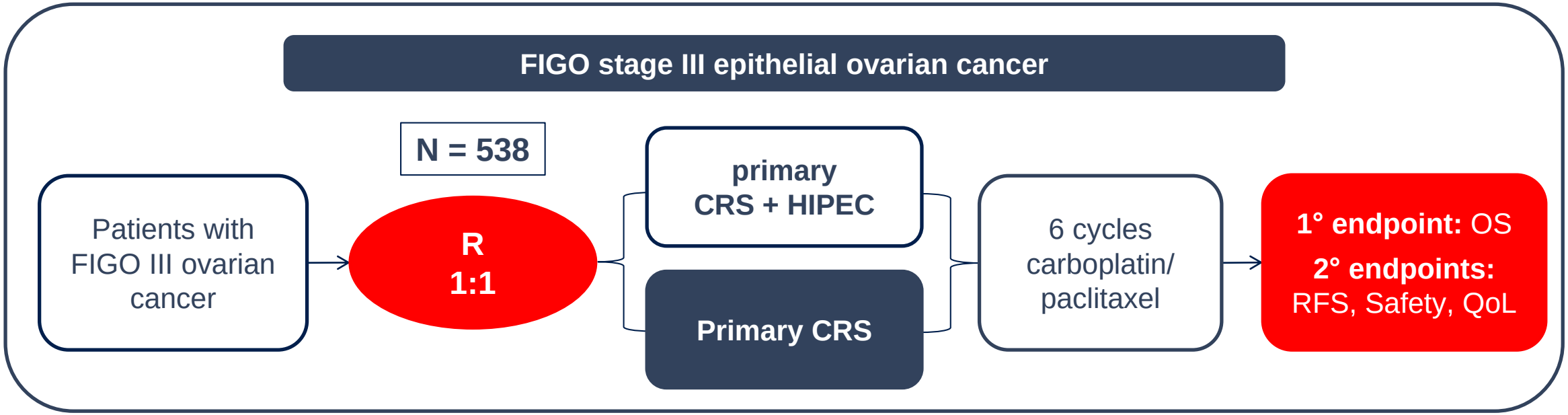
OVHIPEC-2 study

Design



- Patients eligible for primary cytoreductive surgery (CRS)
- ENGOT/GCIG study
- Trial groups from Ireland, Australia, NSGO, Netherlands, UK, France, Italy
- Funding from the Dutch Cancer Society and the Dutch government

Contact: Willemien van Driel (w.v.driel@nki.nl)

OVHIPEC-1

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OVHIPEC-2