# HIPEC in ovarian cancer

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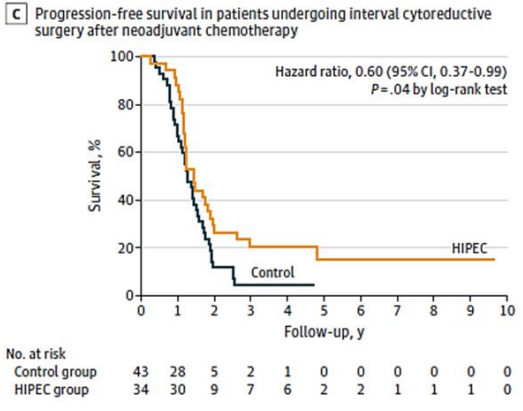
# Primary EOC – Neoadjuvant setting

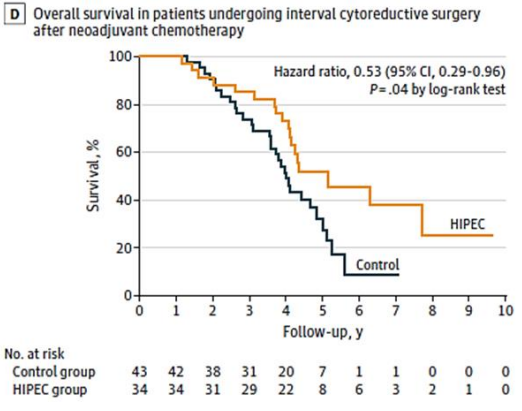
JAMA Surgery | Original Investigation

## 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$^2$, N/S




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

# Primary EOC – 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

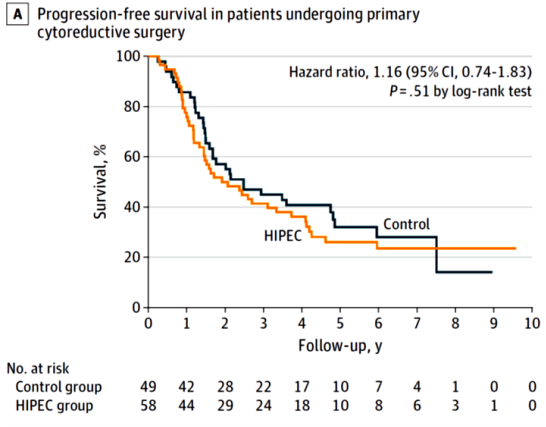
- ✓ Subgroup analysis : PCS

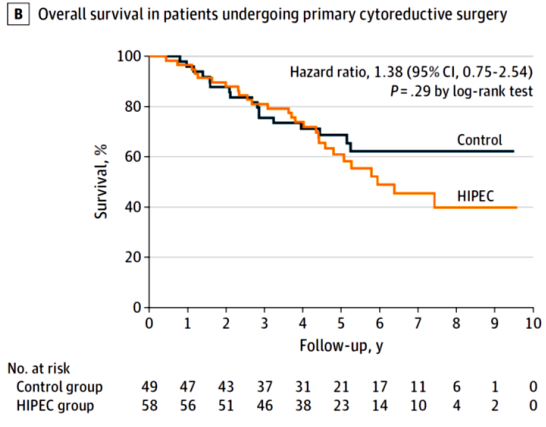
PCS without HIPEC (N = 49)

vs

PCS with HIPEC (N = 58)

- ✓ Cisplatin 75mg/m$^2$, N/S



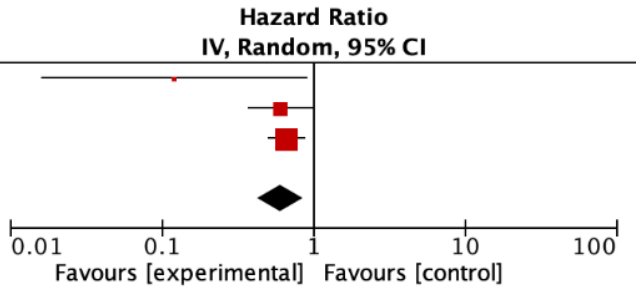

No survival benefits of PCS with HIPEC in stage III or IV ovarian cancer patients.

# Primary EOC - NACT and IDS (RCTs only)

PFS

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Cascales Campos A 2021 | −2.1203 | 1.0219 | 2.9% | 0.12 [0.02, 0.89] |
| Cheol Lim M 2022 | −0.5108 | 0.2467 | 34.4% | 0.60 [0.37, 0.97] |
| Van Driel W.J 2018 (1) | −0.4155 | 0.1417 | 62.7% | 0.66 [0.50, 0.87] |
| **Total (95% CI)** | | | **100.0%** | **0.61 [0.43, 0.86]** |

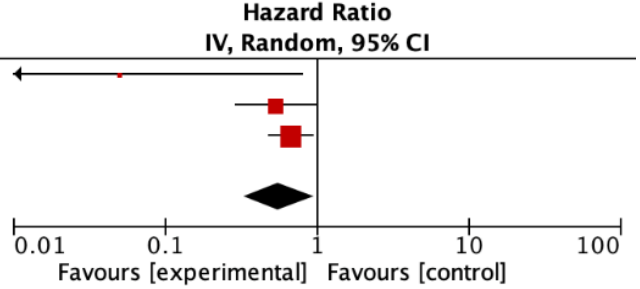
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 2.78$, df = 2 (P = 0.25); $I^2 = 28\%$
Test for overall effect: Z = 2.82 (P = 0.005)




OS

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Cascales Campos A 2021 | −2.9957 | 1.4146 | 3.5% | 0.05 [0.00, 0.80] |
| Cheol Lim M 2022 | −0.6349 | 0.3077 | 38.2% | 0.53 [0.29, 0.97] |
| Van Driel W.J 2018 | −0.4005 | 0.1702 | 58.3% | 0.67 [0.48, 0.94] |
| **Total (95% CI)** | | | **100.0%** | **0.56 [0.33, 0.95]** |

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 3.63$, df = 2 (P = 0.16); $I^2 = 45\%$
Test for overall effect: Z = 2.15 (P = 0.03)




Llueca M, et al. J Per Med 23

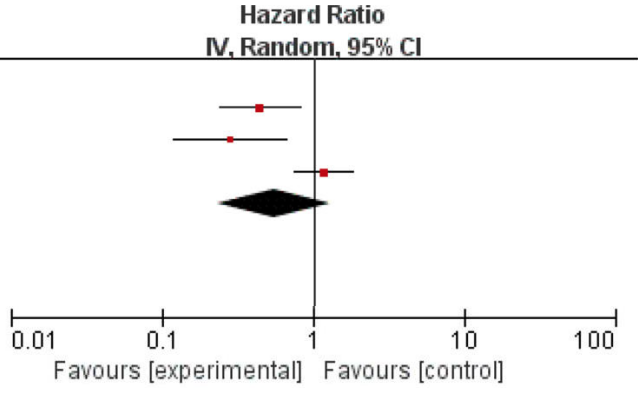
# Primary EOC – Primary cytoreduction (PDS)

PFS

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **1.6.1 PDS** | | | | |
| Bae, J carboplatin 2007 | -0.81419 | 0.308188 | 10.2% | 0.44 [0.24, 0.81] |
| Bae, J paclitaxel 2007 | -1.2694 | 0.438945 | 7.3% | 0.28 [0.12, 0.66] |
| Lim MC 2022 * | 0.14842 | 0.230975 | 12.3% | 1.16 [0.74, 1.82] |
| **Subtotal (95% CI)** | | | **29.8%** | **0.55 [0.24, 1.30]** |

Heterogeneity: Tau² = 0.46; Chi² = 11.31, df = 2 (P = 0.004); I² = 82%

Test for overall effect: Z = 1.36 (P = 0.17)

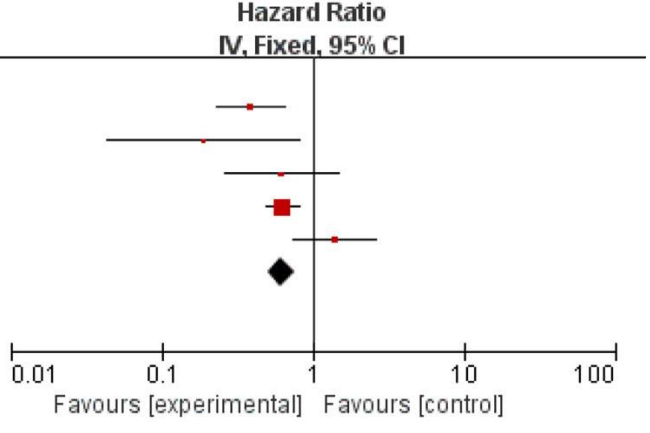



OS

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|
| **1.5.1 PDS** | | | | |
| Bae, J carboplatin 2007 | -0.92634 | 0.260196 | 8.6% | 0.40 [0.24, 0.66] |
| Bae, J paclitaxel 2007 | -1.62455 | 0.728754 | 1.1% | 0.20 [0.05, 0.82] |
| Gori 2005 | -0.46204 | 0.435742 | 3.1% | 0.63 [0.27, 1.48] |
| Lei, Z 2020 | -0.44629 | 0.126198 | 36.4% | 0.64 [0.50, 0.82] |
| Lim MC 2022 * | 0.322083 | 0.311185 | 6.0% | 1.38 [0.75, 2.54] |
| **Subtotal (95% CI)** | | | **55.1%** | **0.63 [0.52, 0.77]** |

Heterogeneity: Chi² = 12.09, df = 4 (P = 0.02); I² = 67%

Test for overall effect: Z = 4.50 (P < 0.00001)




Xia Y, et al. Int J Hyperthemia 23

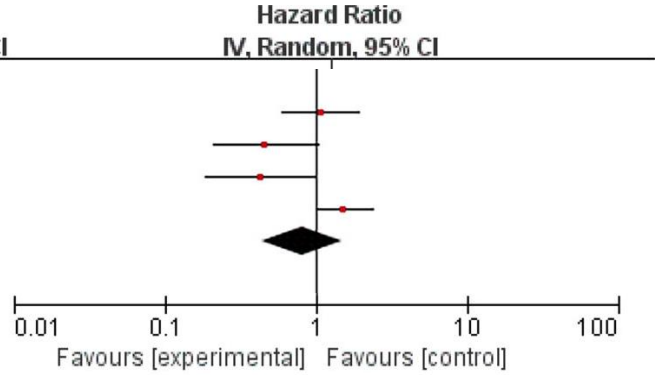
# Recurrent EOC

PFS

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **4.2.2 Recurrent EOC** | | | | |
| Baiocchi 2016 | 0.076961 | 0.296722 | 7.3% | 1.08 [0.60, 1.93] |
| Cascales-Campos 2015 | -0.76081 | 0.405175 | 5.9% | 0.47 [0.21, 1.03] |
| Fagotti 2012 | -0.84397 | 0.415886 | 5.8% | 0.43 [0.19, 0.97] |
| Zivanovic O 2021 * | 0.431782 | 0.220125 | 8.2% | 1.54 [1.00, 2.37] |
| **Subtotal (95% CI)** | | | **27.2%** | **0.82 [0.44, 1.52]** |

Heterogeneity: Tau² = 0.29; Chi² = 11.56, df = 3 (P = 0.009); I² = 74%

Test for overall effect: Z = 0.64 (P = 0.52)

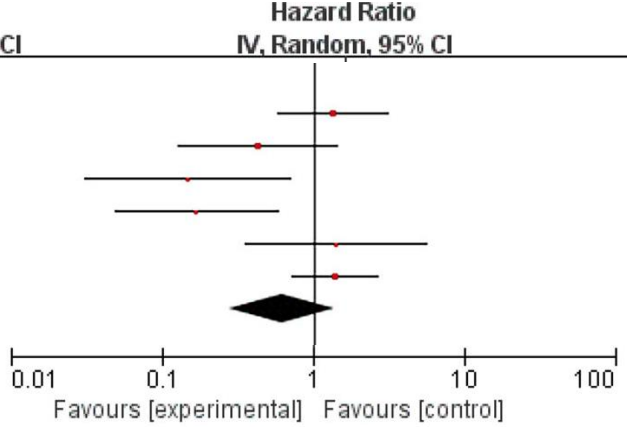



OS

| Study or Subgroup | log[Hazard Ratio] | SE | Weight | Hazard Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| **3.2.2 Recurrent EOC** | | | | |
| Baiocchi 2016 | 0.300105 | 0.420742 | 5.3% | 1.35 [0.59, 3.08] |
| Fagotti 2012 | -0.84397 | 0.604471 | 3.1% | 0.43 [0.13, 1.41] |
| Le Brun 2014 | -1.89712 | 0.788531 | 2.0% | 0.15 [0.03, 0.70] |
| Munoz 2009 | -1.77196 | 0.625256 | 3.0% | 0.17 [0.05, 0.58] |
| Spiliotis et al. 2015 * | 0.34359 | 0.695046 | 2.5% | 1.41 [0.36, 5.51] |
| Zivanovic O 2021 * | 0.329304 | 0.330814 | 7.1% | 1.39 [0.73, 2.66] |
| **Subtotal (95% CI)** | | | **23.0%** | **0.62 [0.28, 1.37]** |

Heterogeneity: Tau² = 0.65; Chi² = 16.67, df = 5 (P = 0.005); I² = 70%

Test for overall effect: Z = 1.18 (P = 0.24)




Xia Y, et al. Int J Hyperthemia 23

# 1st question

Why the survival benefits were mostly observed in primary setting?

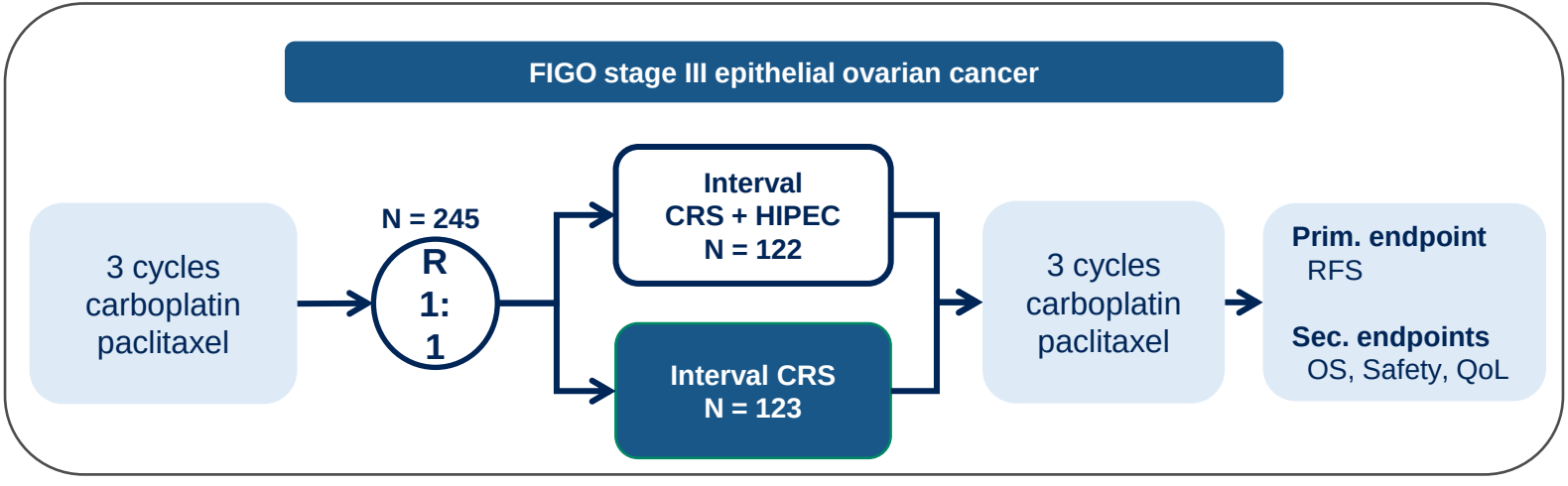
# OVHIPEC-1 Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

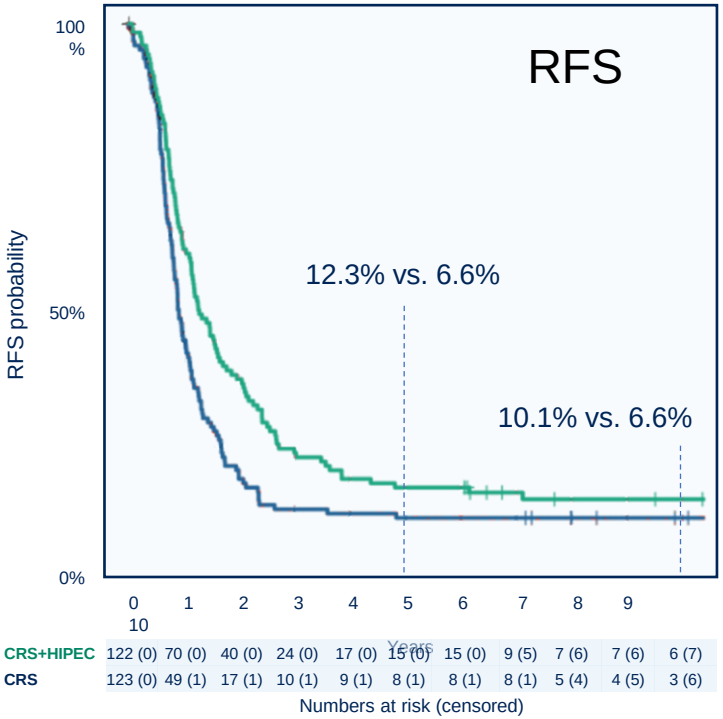
## Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

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

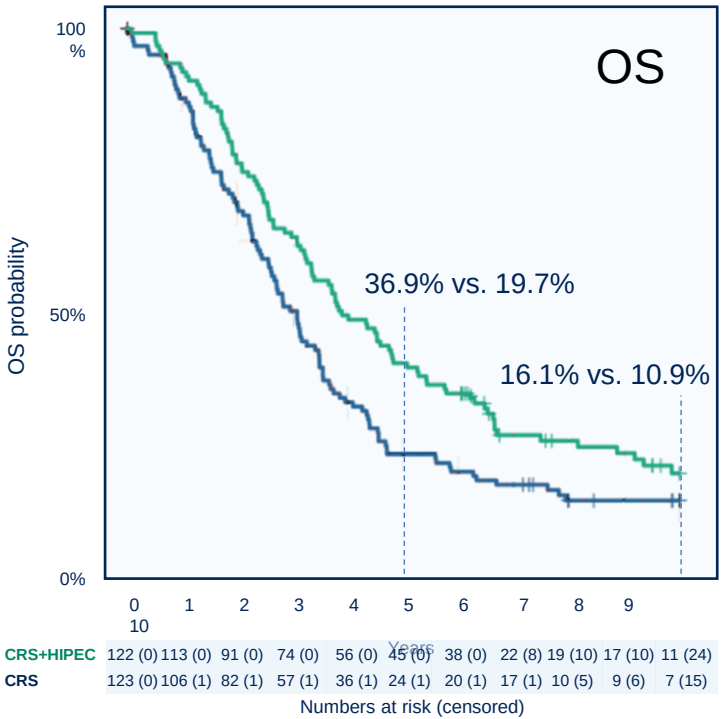



- Accrual between 2007-2016 in 8 centers in the Netherlands and Belgium
- Patients required neo-adjuvant chemotherapy due to extensive disease
- Follow-up visits every 3 months in year 1-2, every 6 months thereafter

Prof. Gabe S. Sonke – contact: ovhipec@nki.nl




| | CRS-HIPEC | CRS |
|---|---|---|
| Median RFS, mo | 14.3 | 10.7 |
| HR (95% CI) | **0.63 (0.48 – 0.83)** | |
| Stratified log-rank p | 0.0008 | |

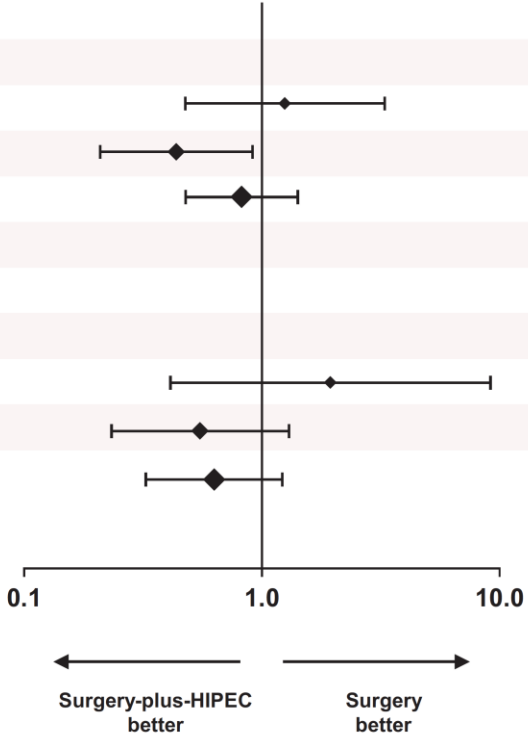



| | CRS-HIPEC | CRS |
|---|---|---|
| Median OS, mo | 44.9 | 33.3 |
| HR (95% CI) | **0.70 (0.53 – 0.92)** | |
| Stratified log-rank p | 0.0113 | |

Prof. Gabe S. Sonke – contact: ovhipec@nki.nl

# OVHIPEC - exploratory

| Subgroup | Surgery | Surgery-plus-HIPEC | Hazard ratio (99% CI) | |
|---|---|---|---|---|
| **RFS** | *No. of events/total no.* | | | |
| **HRD/HRP** | | | Interaction P = .024 | |
| gBRCA1/2 or sBRCA1/2 | 14/18 | 16/16 | 1.251 | (0.476-3.289) |
| BRCA1like/BRCAwt | 33/35 | 24/30 | 0.437 | (0.209-0.914) |
| Non-BRCA1like/BRCAwt | 50/53 | 41/48 | 0.822 | (0.477-1.415) |
| **OS** | | | | |
| **HRD/HRP** | | | Interaction P = .099 | |
| gBRCA1/2 or sBRCA1/2 | 4/18 | 9/16 | 1.941 | (0.412-9.155) |
| BRCA1like/BRCAwt | 24/35 | 15/30 | 0.550 | (0.233-1.299) |
| Non-BRCA1like/BRCAwt | 39/53 | 25/48 | 0.630 | (0.325-1.220) |




Koole SN, et al. Int J Cancer 22

# 2nd question

Why did survival benefits appear not very promising in patients with *BRCA* mutation?

| NCT number | Trial | Setting | Patients | No. | Arms | Primary endpoint |
|---|---|---|---|---|---|---|
| NCT03772028 | OVHIPEC-2: Primary Cytoreductive Surgery with or without Hyperthermic Intraperitoneal Chemotherapy | Primary CRS | Stage III EOC, up to 2.5 mm RD | 538 | 1. HIPEC with cDPP 100 mg/m$^2$ at 40–41 °C over 90 min (carbo/taxol +/- bev +/- PARPi)<br>2. Primary CRS without HIPEC (carbo/taxol +/- bev +/- PARPi) | OS |
| NCT03842982 | CHIPPI: Hyperthermic Intraperitoneal Chemotherapy In Ovarian Cancer | Primary or interval CRS | Stage III EOC, < 2.5 mm RD | 362 | 1. HIPEC with cDPP 100 mg/m2 at 40 °C for 90 min subsequent to (NACT) or followed by (primary CRS) 6 cycles of chemo, with additional chemo as per standard of care (+/- targeted) for the NACT group<br>2. Chemo regimens not specified; 6 cycles of NACT chemo to be given before interval CRS (+/- targeted) | PFS |
| NCT05659381 | HOTT: Heated Intraperitoneal Chemotherapy Followed by Niraparib for Ovarian, Primary Peritoneal and Fallopian Tube Cancer (GOG-3068) | Interval CRS | Stage III–IV HGSC or endometrioid ovarian cancer, up to 1 cm RD | 230 | 1. 3–4 cycles NACT with IV carbo AUC 6 and taxol 175 mg/m$^2$, HIPEC with cDPP 100 mg/m$^2$ at 42 °C for 90 min, followed by 2–3 cycles IV carbo AUC 6 and taxol 175 mg/m$^2$ for max 6 cycles<br>2. 3–4 cycles NACT with IV carbo AUC 6 and taxol 175 mg/m$^2$, interval CRS followed by 2–3 cycles IV carbo AUC 6 and taxol 175 mg/m$^2$ for max 6 cycles<br>*All patients to receive maintenance niraparib for 36 months or until progression | PFS |

# 3rd question

What is the best endpoint to evaluate the role of HIPEC alone (one-off event) with the use of PARPi +/- bev?