Intraperitoneal chemotherapy

Does it have a place in treatment?

ESMO Preceptorship, Prague, 21st April 2017

Iain McNeish
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Wolfson Wohl Cancer Research Centre
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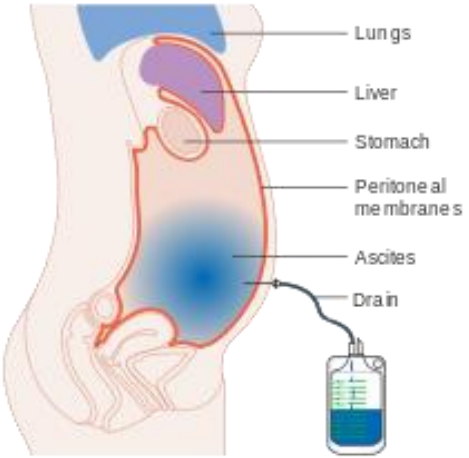
Intraperitoneal therapy – the theory

- Disease resides almost exclusively within the peritoneal cavity
- IP delivery ensures high local concentrations to tumour
- Drug also gets into systemic circulation for systemic action
- Ideal IP drug
    - Large M_R
    - Peritoneal clearance << plasma clearance
    - Highly active in chosen disease



Assumptions

- Steep dose response curve and dose intensity theory correct
- Chemotherapy acts identically in peritoneum to blood

    Presence of co-factors, hypoxia etc etc

Pharmacokinetics

Cisplatin (Howell et al Ann Intern Med. 1982 97: 845-51)

Peritoneal:plasma AUC 12:1

MTD **90 mg/m^2** single agent

Carboplatin (Elferink et al Cancer Chemother. Pharmacol. 1988 21:57-60)

Peritoneal:plasma AUC 10:1

MTD not defined (doses 200 – 500 mg/m^2)

Paclitaxel (Markman et al J Clin Oncol 1992 10:1485-1491)

Peritoneal:plasma AUC 1000:1

MTD 175 mg/m^2 (abdominal pain)

How to prove IP chemotherapy is superior to IV

- Large, adequately-powered phase III trial
- IV control arm accepted standard-of-care
- IP arm(s) – same dose/dose intensity as IV arm
- Improvement in PFS (+/- OS)

Three key trials

- GOG 172
- GOG 252
- OV21/PETROC

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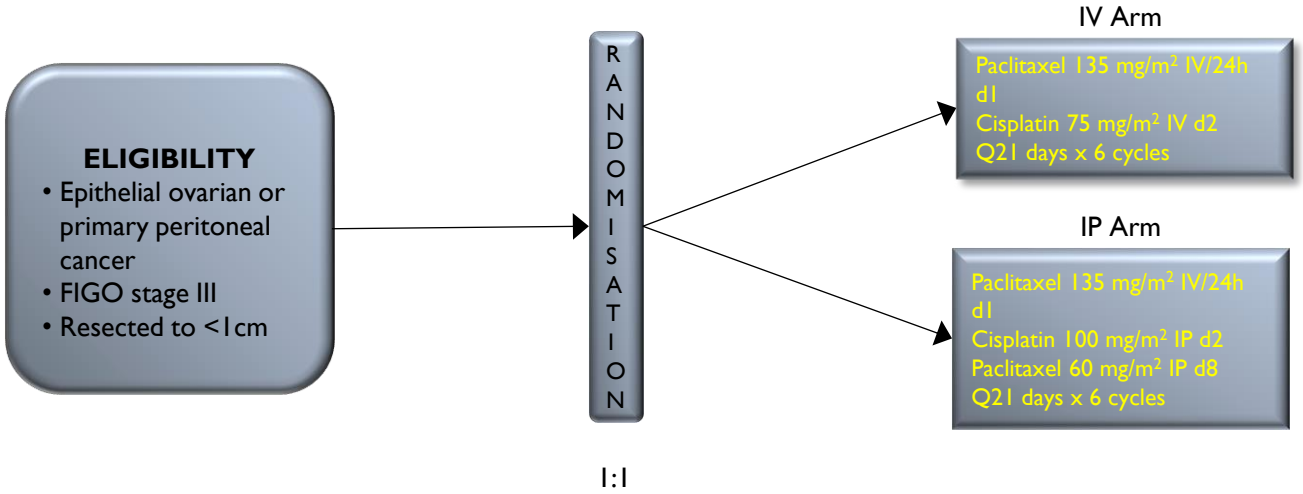
- OV21/PETROC

ORIGINAL ARTICLE

Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer

Deborah K. Armstrong, M.D., Brian Bundy, Ph.D., Lari Wenzel, Ph.D., Helen Q. Huang, M.S., Rebecca Baergen, M.D., Shashikant Lele, M.D., Larry J. Copeland, M.D., Joan L. Walker, M.D., and Robert A. Burger, M.D., for the Gynecologic Oncology Group*



ENDPOINTS

- PFS and OS
- Target HR = 0.66
- Target N = 384
- 90% one-sided
- $\alpha = 0.05$

- 429 enrolled
- 419 randomised
- 415 eligible

Armstrong et. al. N Engl J Med 2006;354:34-43

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IV Arm

210 Eligible Patients
Receipt of assigned intravenous therapy
174 Received 6 cycles = 82.9%
4 Received 5 cycles
2 Received 4 cycles
11 Received 3 cycles
9 Received 2 cycles
8 Received 1 cycles
2 Received 0 cycles
189 Received 6 cycles of therapy
174 Received all cycles of assigned intravenous treatment
15 Received intravenous carboplatin and paclitaxel for some cycles
21 Received <6 cycles of therapy
4 Died from treatment-related causes

IP Arm

205 Eligible Patients
Receipt of assigned intraperitoneal therapy
86 Received 6 cycles = 42.0%
11 Received 5 cycles
10 Received 4 cycles
14 Received 3 cycles
30 Received 2 cycles
38 Received 1 cycles
16 Received 0 cycles
170 Received 6 cycles of therapy
86 Received all cycles of assigned intraperitoneal treatment
84 Received intravenous treatment for some cycles
47 Intravenous cisplatin and paclitaxel
37 Intravenous carboplatin and paclitaxel
35 Received <6 cycles of therapy
5 Died from treatment-related causes

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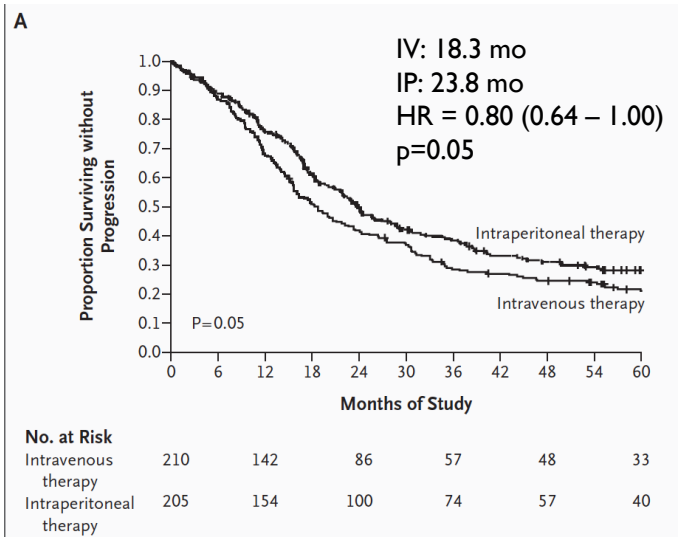
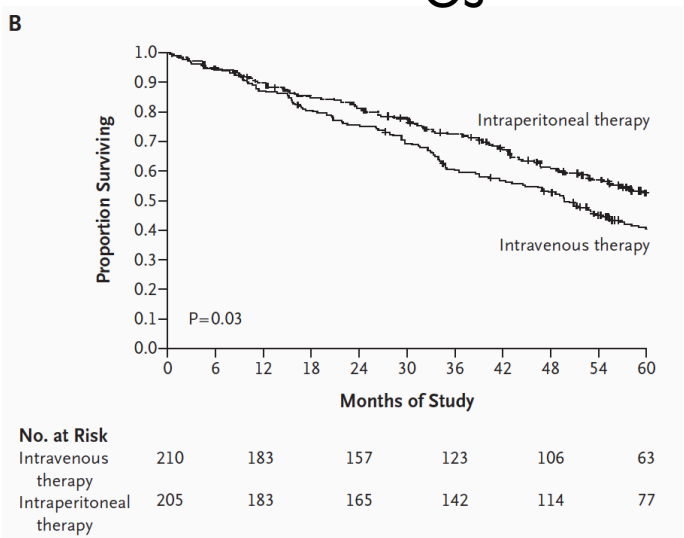
PFS



OS



IV: 49.7 mo
IP: 65.6 mo
HR = 0.75 (0.58 – 0.97)
p=0.03

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- Significant improvement in PFS/OS
- IP arm unacceptably toxic
- GOG 172 created huge publicity

Table 2. Frequency of Grade 3 or 4 Adverse Events.

Adverse Event	Intravenous-Therapy Group (N=210)	Intraperitoneal-Therapy Group (N=201)*	P Value†
	no. (%)		
Leukopenia‡	134 (64)	152 (76)	<0.001
Platelet count <25,000/mm³	8 (4)	24 (12)	0.002
Other hematologic event	190 (90)	188 (94)	0.87
Gastrointestinal event	51 (24)	92 (46)	<0.001
Renal or genitourinary event	5 (2)	14 (7)	0.03
Pulmonary event	5 (2)	7 (3)	0.50
Cardiovascular event	10 (5)	19 (9)	0.06
Neurologic event	18 (9)	39 (19)	0.001
Cutaneous change	2 (1)	2 (1)	0.96
Event involving lymphatic system	0	3 (1)	0.07
Fever	8 (4)	19 (9)	0.02
Infection	12 (6)	33 (16)	0.001
Fatigue	9 (4)	36 (18)	<0.001
Metabolic event	15 (7)	55 (27)	<0.001
Pain	3 (1)	23 (11)	<0.001
Hepatic event	1 (<1)	6 (3)	0.05
Other	1 (<1)	6 (3)	0.05

Armstrong et. al. N Engl J Med 2006;354:34-43

GOG-172

- Large, adequately-powered phase III trial – Yes-ish
- IV control arm accepted standard-of-care – Yes
- IP arm(s) – same dose/dose intensity as IV arm – No
- Improvement in PFS (+/- OS) - Yes

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JOURNAL OF CLINICAL ONCOLOGY | COMMENTS AND CONTROVERSIES

Intraperitoneal Chemotherapy in Ovarian Cancer Remains Experimental

Martin Gore, *Department of Medicine, Royal Marsden Hospital, London, United Kingdom*
Andreas du Bois, *Department of Gynecology and Gynecologic Oncology, Dr Horst-Schmidt-Klinik, Wiesbaden, Germany*
Ignace Vergote, *Division of Gynecologic Oncology, University Hospitals, Katholieke Universiteit Leuven, Leuven, Belgium*

Women should not be subjected to intraperitoneal chemotherapy outside the context of properly designed clinical trials. These trials must either assess IP therapy in comparison to standard treatment or address the issue of route of administration for equivalent doses and schedules of the same drugs, not a mosaic of these questions.

In the meantime, can someone come up with a sensible IP regimen?

Gore et. al. J Clin Oncol 2006;24:4528-30

Three key trials

- GOG 172
- GOG 252
- OV21/PETROC


ANNUAL MEETING ON WOMEN'S CANCER
SAN DIEGO
MARCH 19–22, 2016

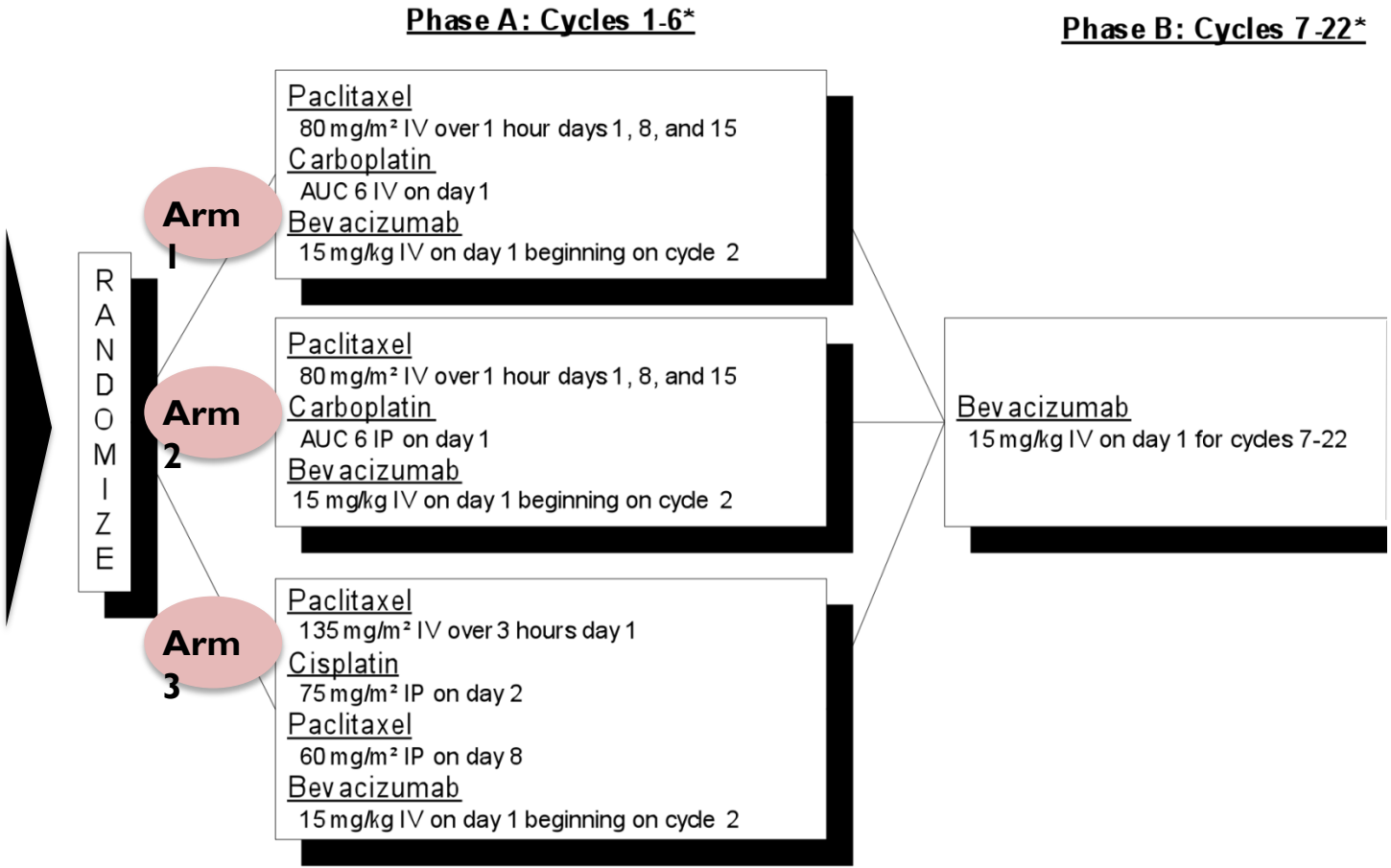
A PHASE III CLINICAL TRIAL OF BEVACIZUMAB WITH IV VERSUS IP CHEMOTHERAPY IN OVARIAN, FALLOPIAN TUBE AND PRIMARY PERITONEAL CARCINOMA NCI-SUPPLIED AGENT(S): BEVACIZUMAB (NSC #704865, IND #7921**)** **NCT01167712** a GOG/NRG Trial (GOG 252)

Joan L. Walker; Mark F Brady; Paul A DiSilvestro; Keiichi Fujiwara; David Alberts; Wenxin Zheng; Krishnansu Tewari; David E Cohn; Matthew Powell; Linda van Le; Stephen Rubin; Susan A Davidson; Heidi J Gray; Steven Waggoner; Tashanna Myers; Carol Aghajanian; Angeles Alvarez Secord; Robert S Mannel

GOG 252: Schema

Eligibility

- Stage II-III Epithelial Carcinoma: Ovary, Fallopian Tube, Peritoneal
- Resected to optimal: ≤1 cm visible tumour by surgeon report
- Exploratory: suboptimal (7%) and Stage IV (5%)



GOG 252 Arm 3 IP Cisplatin vs GOG 172

- Dose reduction cisplatin (100 down to 75 mg/m^2)
- Infusion time reduction 135 mg/m^2 paclitaxel (3hr instead of 24h)
- All outpatient therapy
- Bevacizumab 15 mg/kg for all arms on cycles 2-22
- Comparison arm dose dense paclitaxel with carbo IV AUC 6- GOG 262 (JGOG)
- Second experimental Arm IP carbo and dose dense paclitaxel

GOG 252 accrual and demographics

- 1560 participants from July 2009-Nov 2011
- Median age - 58 years
- White 90%; Black 3%; Hispanic 3%
- Stage III- 84%
- Stage II- 10%
- High grade serous – 72%
- No visible residual disease per surgeon – 57%
- Exploratory aim: suboptimal (7%) and Stage IV (5%)

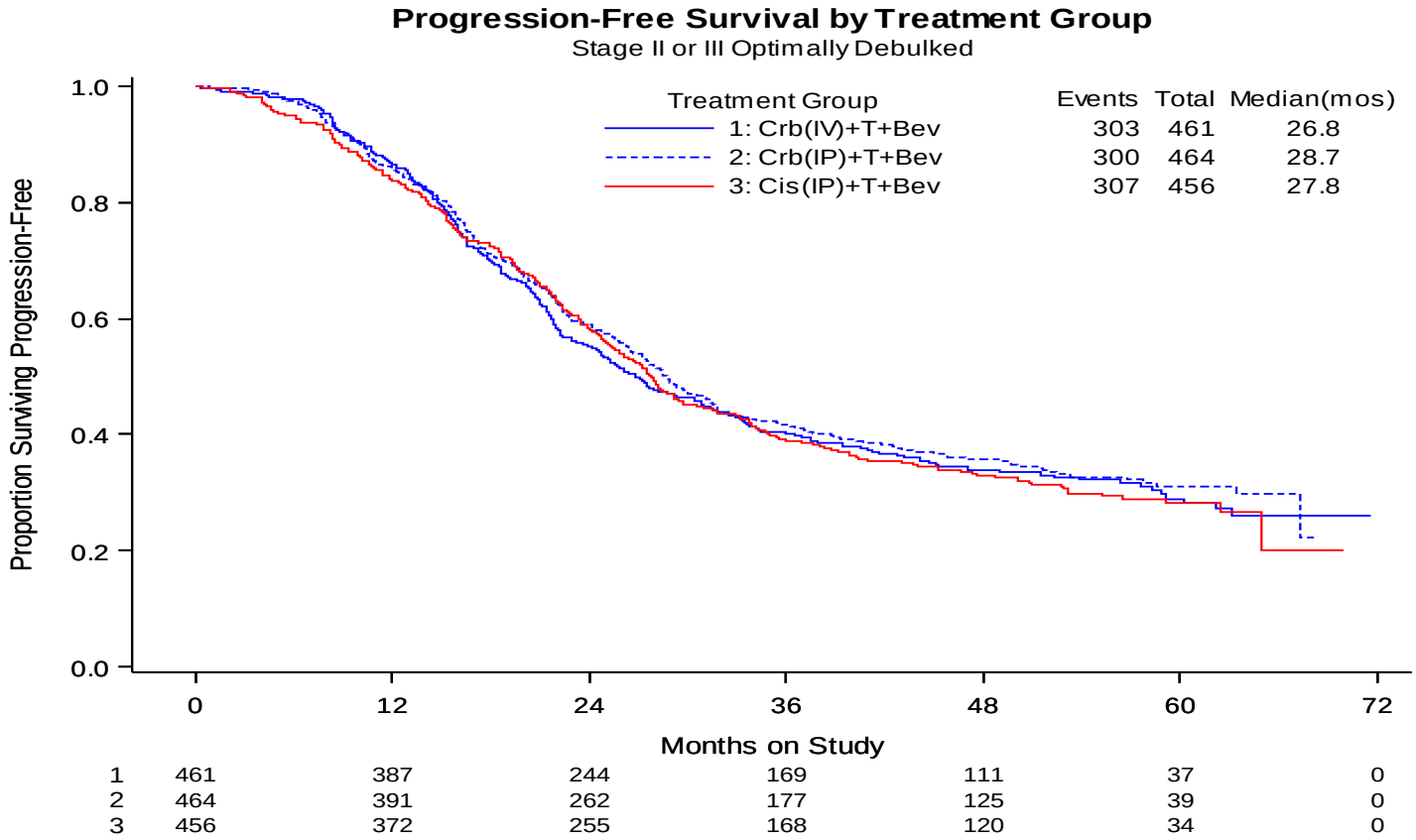
GOG 252 assigned treatment completion

Arm	At least 6 cycles of Platinum	At least 6 cycles of taxane	# Bev Cycles
Arm 1: IV Carbo	90%	87%	20
Arm 2: IP Carb	90%	88%	19
Arm 3: IP Cisp	84%	87%	17

GOG 252 Toxicity

Event	IV Carbo		IP Carbo		IP Cisp	
	G2	≥G3	G2	≥G3	G2	≥G3
Feb/neut		2.5%		2.6%		3.3%
Neut		71%		68%		64%
Platelets		17.6%		15.1%		6.1%
HTN		11.9%		13.8%		20.5%
Thromb		6.3%		8.4%		9.0%
N/V		5.1%		4.7%		11.2%
Fistula		5.3%		3.7%		4.3%
Urine Prot		2.7%		3.1%		1.6%
Sens Neur	24.1	5.7%	22.6	4.5%	21.3	5.5%

Progression Free Survival Optimal Stage II-III

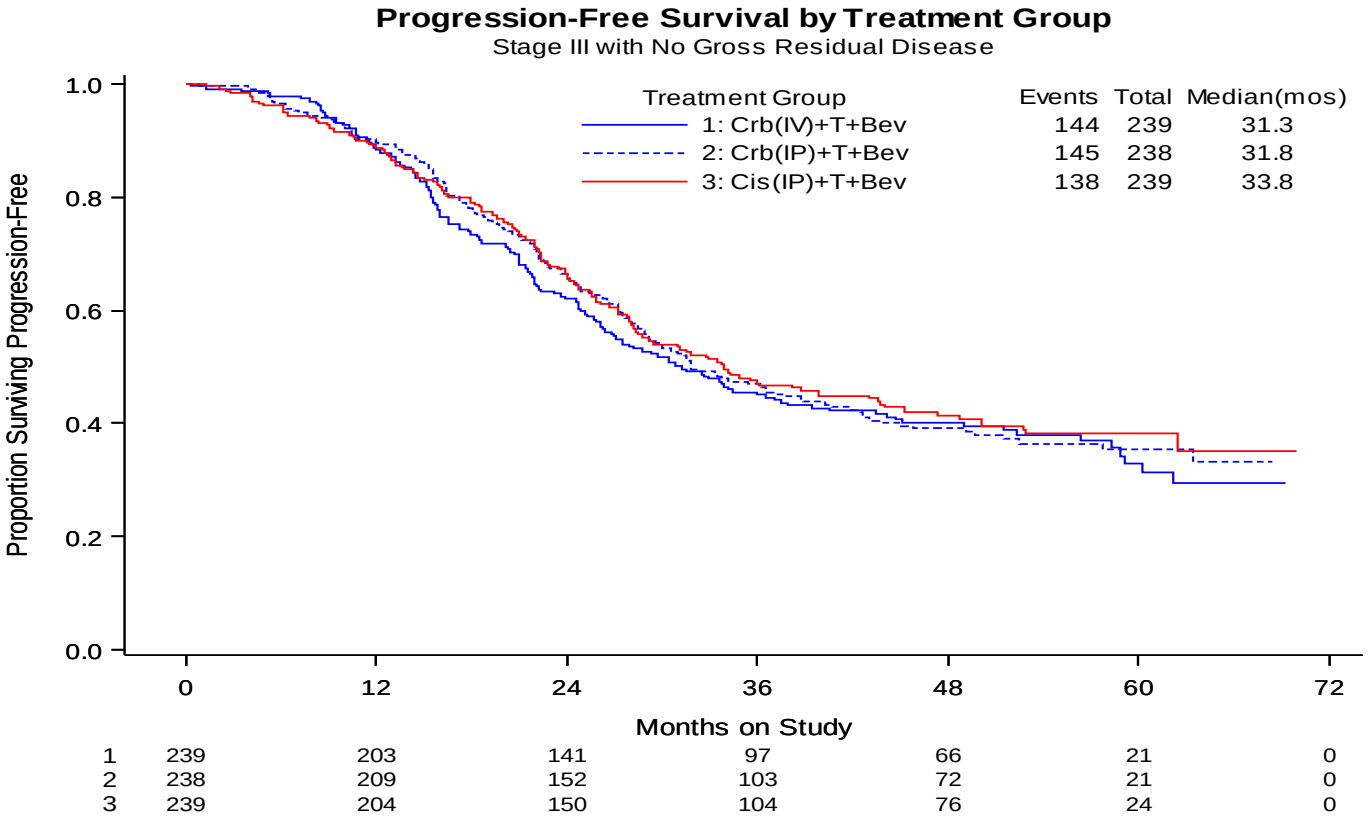


Progression Free Survival Optimal Stage II-III (10% stage II)

Arm	N	Events	Median PFS	HR [95% CI]	Logrank	Logrank
IV Carbo	461	303	26.8 months	Reference arm	P-value	Chi square
IP Carbo	464	300	28.7 months	0.947 [0.808-1.11]	0.416	0.661
IP Cisp	456	307	27.8 months	1.01 [0.858-1.18]	0.727	0.122

- CT required every 6 months for surveillance (not required in GOG172)

Progression Free Survival Optimal Stage III NGR



GOG-252

- Large, adequately-powered phase III trial – Yes
- Control arm agreed international standard-of-care – Sort of
- IP arm(s) – same dose/dose intensity as IV arm – Yes
- Improvement in PFS (+/- OS) – No

Conclusions

Women should not be subjected to intraperitoneal chemotherapy outside the context of properly designed clinical trials. These trials must either assess IP therapy in comparison to standard treatment or address the issue of route of administration for equivalent doses and schedules of the same drugs, not a mosaic of these questions.

In the meantime, can someone come up with a sensible IP regimen?

Three key trials

- GOG 172
- GOG 252
- OV21/PETROC

OV21/PETROC:
A randomized Gynecologic Cancer Intergroup (GCIG) phase II study of intraperitoneal (IP) versus intravenous (IV) chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer (EOC)

Helen J. Mackay, Christopher J. Gallagher, Wendy R Parulekar, Jonathan A. Ledermann, Deborah K. Armstrong, Charlie Gourley, Ignacia Romero, Amanda Feeney, Paul Bessette, Marcia Hall, Johanne I Weberpals, Geoff Hall, Susie K. Lau, Philippe Gauthier, Michael Fung-Kee-Fung, Elizabeth A. Eisenhauer, Chad Winch, Dongsheng Tu, Diane M. Provencher.

Canadian Cancer Trials Group | Groupe canadien des essais sur le cancer

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CANCER RESEARCH UK

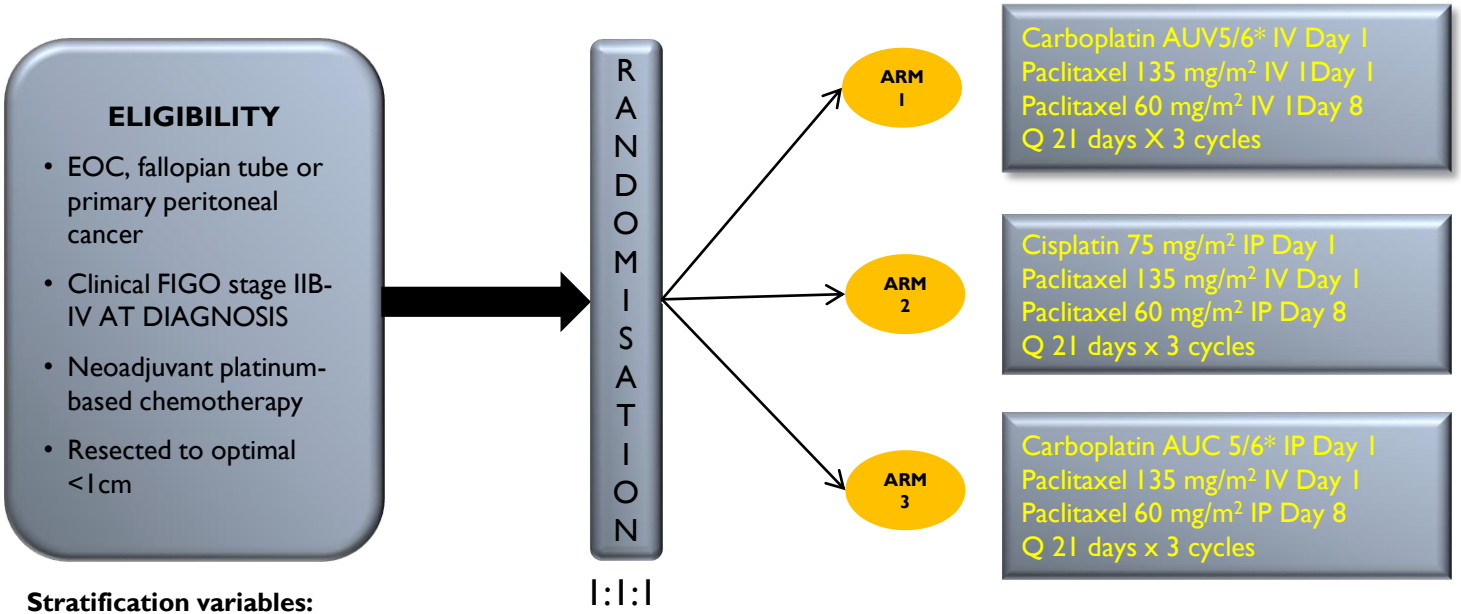
SWOG Leading cancer research. Together.
Grupo Español de Investigación en Cáncer de Ovario

NCI National Clinical Trials Network

OV21/PETROC: Key Eligibility Criteria

- Histologic diagnosis of EO, fallopian tube or serous type peritoneal cancer (mucinous excluded)
- Clinical/imaging stage IIB to III EOC at diagnosis (Stage IV allowed on basis of pleural effusion only)
- No primary cytoreductive surgery at diagnosis
- 3 or 4 cycles of platinum-based neoadjuvant chemotherapy
- Optimal (<1cm) cytoreductive surgery within 6 weeks of neoadjuvant chemotherapy
- Randomisation within 6 weeks of surgery
- ECOG 0-2

OV21/PETROC: Schema (2 stage study)



Stratification variables:

- Cooperative group
- Residual disease: macroscopic vs. microscopic
- Reason for NACT: non-resectable disease vs. other
- Timing of IP catheter insertion: intra-operative vs. postoperative

Presented by: Dr. Helen J MacKay

OV21/PETROC: Statistical Plan
First Stage: 3 Arm Phase II (N=50 each arm)

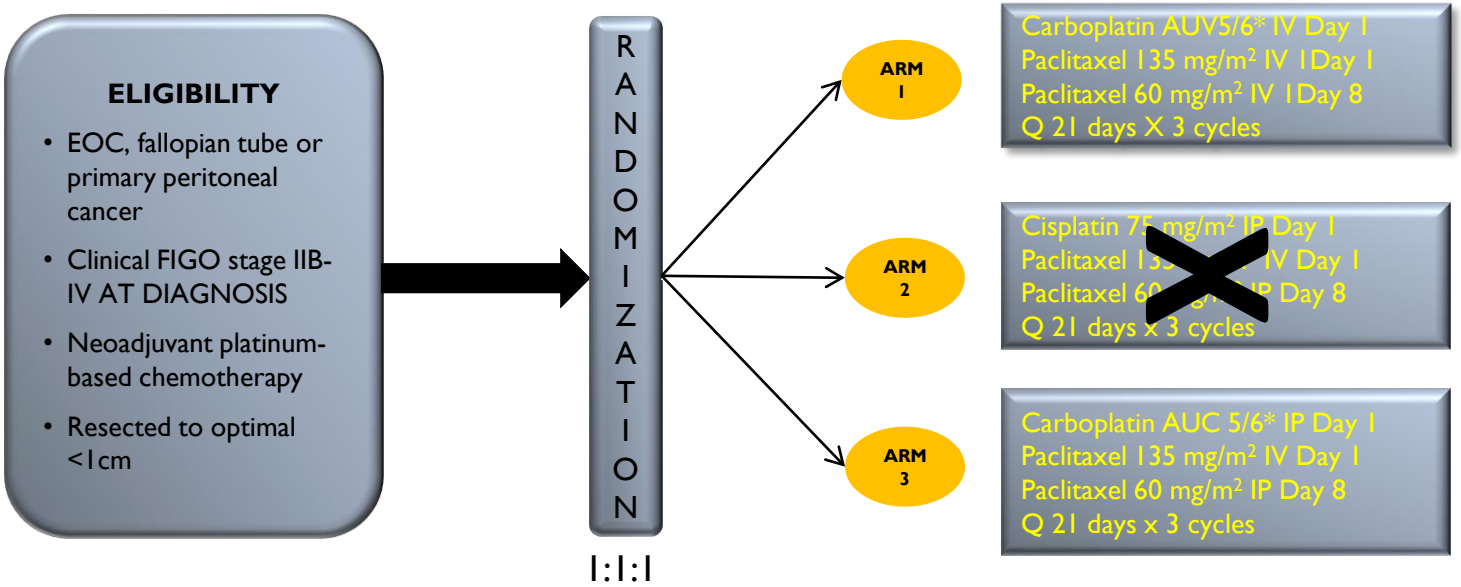
'Pick the IP winner' ('Drop the loser') design (DSMC recommendation)

- 9-month progression (PD) rate post randomization. Futility/superiority rule:

Assume 9-month PD rate in IV arm = 40%. Stop trial if neither IP arm is ≥ 5% better than IV. If both IP arms ≥ 5% better, IP arm with the lowest 9-month PD rate is selected

- Completion rate of treatment
- Toxic effects
- Feasibility

OV21/PETROC: Schema (2 stage study)



OV21/PETROC: Statistical Plan

Second Stage: Two Arm Expanded Randomized Phase II

- Planned as a phase III study. Trial design modified to phase II due to low accrual and funding issues
- **Primary endpoint** revised from PFS to **9 month PD rate post randomization** after consultation with DSMC
- **Revised sample size 200 patients total (arms 1 and 3).** 80% power to detect a 19% difference in progression rate at 9 months 2-sided, α=0.05
- **Secondary endpoints:** PFS, OS, toxicity, quality of life, correlative studies, outcomes related to variation in nursing-related practices

OV21/PETROC: Study Conduct

- Activated September 2009. Stage I accrual complete March 2013
- Analysis of stage I (n=150) January 2014
- Stage 2 activated February 2014. Arm 2 (IP cisplatin) closed to accrual
- Key protocol amendment October 2014 to randomized phase II study, change in primary endpoint
- Closed to accrual May 2015
- Data cut off, February 28th 2016. Data analysis March 4th 2016
- Median Follow up 33 months

PD Rate at 9 Months Following Randomization (Per-Protocol)

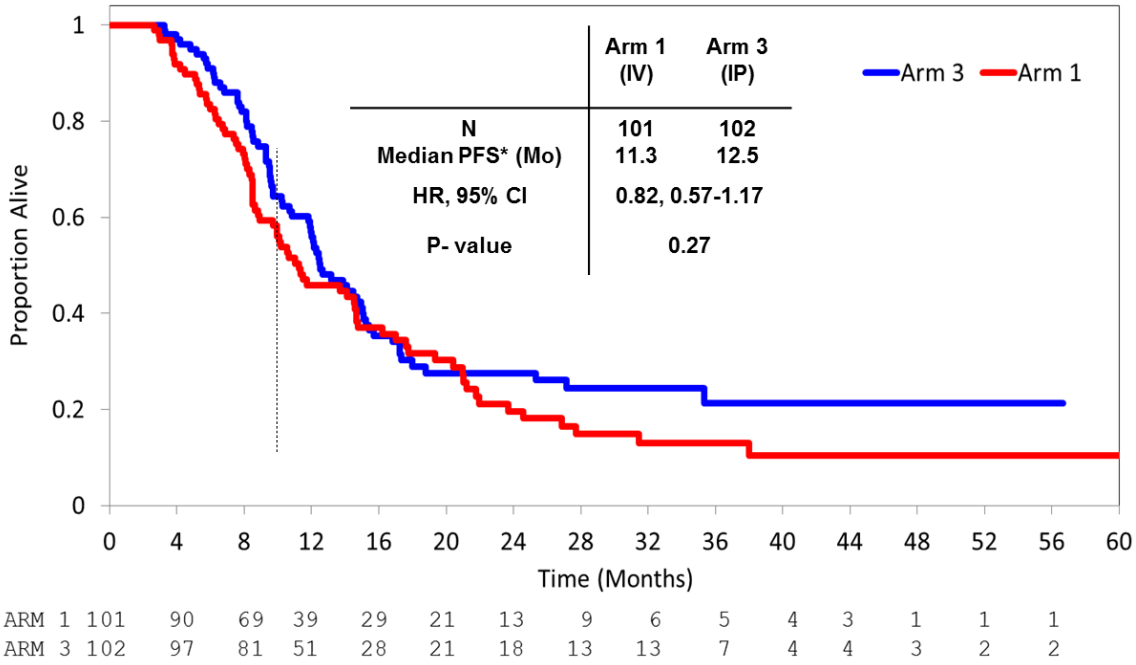
Arm	9-month PD rate	95% CI	P value Stratified	P Value Unstratified
1	42.2%	31.9% to 53.1%	0.03	0.01
3	23.3%	15.1% to 33.4%		

PD Rate at 9 Months Following Randomization (ITT)

Arm	9-month PD rate	95% CI	P value Stratified	P Value Unstratified
1	42.2%	29.1% to 48.8%	0.06	0.03
3	24.5%	16.6% to 34%		

Stratified: Cochrane-Mantel-Haenszel test
Unstratified: Fishers Exact test

OV21/PETROC: Progression-free Survival*



OV21/PETROC

- Large, adequately-powered phase III trial – No
- IV control arm accepted standard-of-care – Yes-ish
- IP arm(s) – same dose/dose intensity as IV arm – Yes
- Improvement in PFS (+/- OS) – Not really

The 'definitive' IP trial??

iPocc Trial

JGOG

Stage II to IV Ovarian, primary peritoneal, or fallopian tube cancer
Including Suboptimal/Exploratory Laparoscopy Cases
IDS Allowed

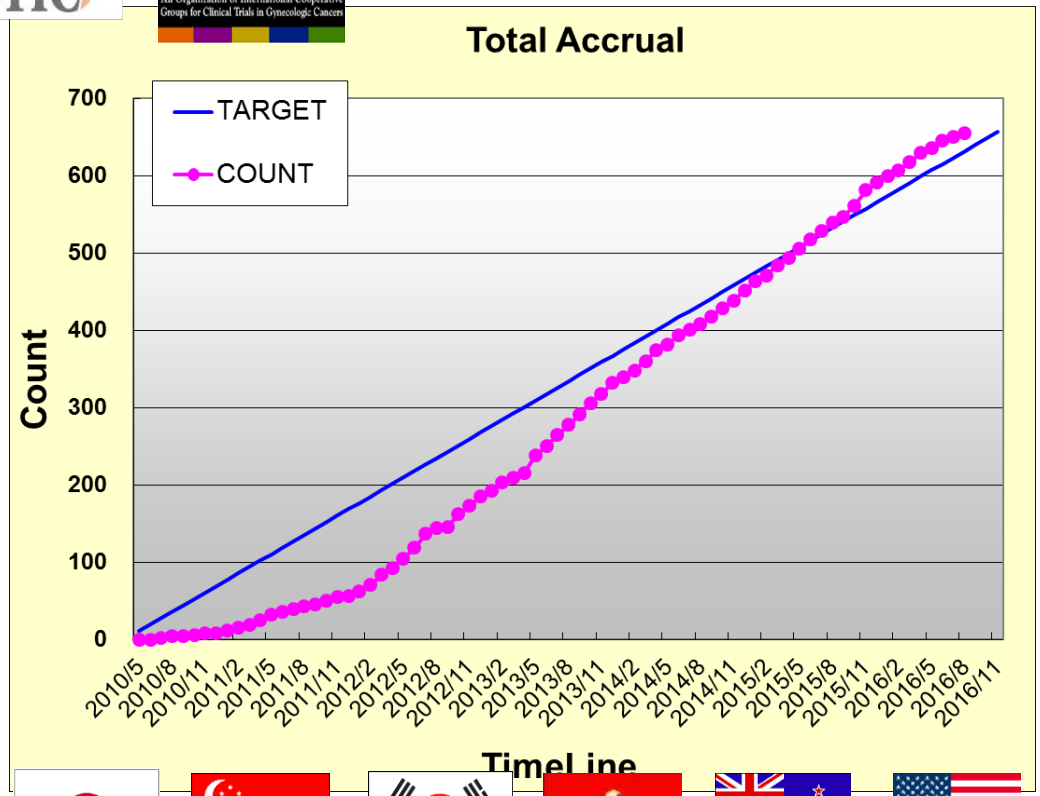
RANDOMIZE

Paclitaxel 80 mg/m^2/1h IV, weekly, Cycles 1-6
Carboplatin AUC 6 IV, Day 1, Cycles 1-6

Paclitaxel 80 mg/m^2/1h IV, weely, Cycles 1-6
Carboplatin AUC 6 IP, Day 1, Cycles 1-6

- **Accrual goal: 654 pts**
- **Primary Endpoint: PFS**
- **Secondary Endpoints: OS, Toxicity, QOL, Cost/Benefit**

iPocc Trial (GOTIC-001/JGOG3019)



Total 655: Singapore 32, KGOG 10, NZ 4, USA 4, Hong Kong 2

iPOCC

- Large, adequately-powered phase III trial – Yes
- IV control arm accepted standard-of-care – Yes
- IP arm(s) – same dose/dose intensity as IV arm – Yes
- Improvement in PFS (+/- OS) – ???

Overall conclusions and recommendations

- Multiple trials have suggested IP chemotherapy has PFS and OS advantages over IV
- The most positive trials are methodologically flawed
- The largest study (GOG 252) negative
- iPOCC study may offer final evidence but no IP paclitaxel

PERSONAL OPINION

- IP chemotherapy is not proven to be superior to IV