Randomized Phase III Trials of Intravenous vs. Intraperitoneal Therapy in Optimal Ovarian Cancer

Deborah K. Armstrong, M.D.

Associate Professor of Oncology,

Gynecology and Obstetrics

THE SIDNEY KIMMEL COMPREHENSIVE CANCER CENTER AT JOHNS HOPKINS

Development of Intraperitoneal Chemotherapy

- 1950's: First use of intraperitoneal chemotherapy for malignant ascites
- 1968: Long-term peritoneal access device
- 1978: Demonstration of slow peritoneal clearance of some drugs
- 1984: Feasibility of intermittent large volume intraperitoneal therapy
- 1996: First report of a survival benefit for IP vs. IV chemotherapy in advanced ovarian cancer

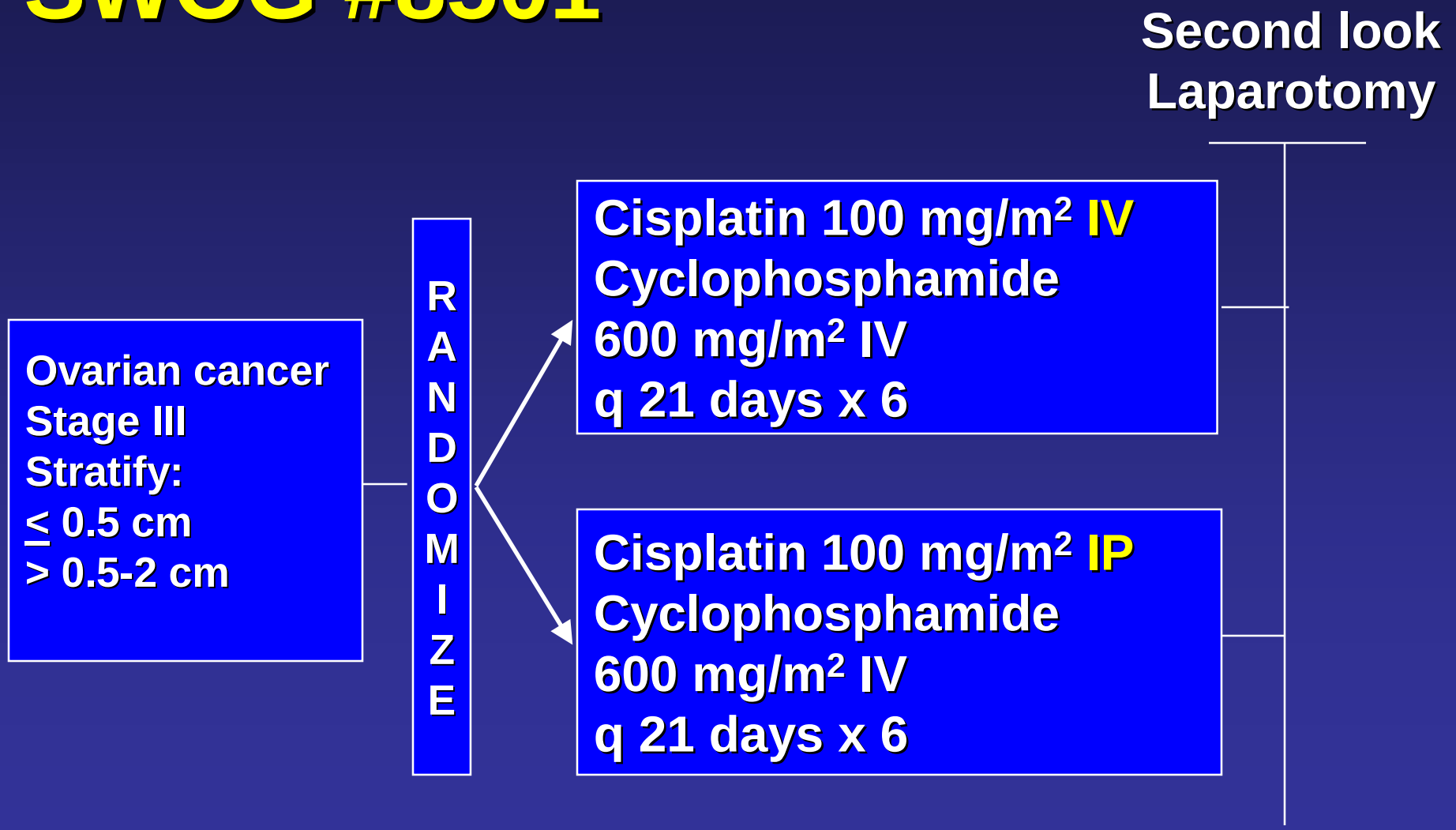
Peritoneal: Plasma Ratio

Drug	Peak	AUC
Cisplatin	20	12
Carboplatin	---	18
Melphalan	93	65
Adriamycin	474	---
5-FU	298	367
MTX	92	100
Paclitaxel	---	1,000

Intraperitoneal Therapy: Ovarian Cancer

- **Rationale:**
  - Major route of spread within the peritoneal cavity
  - Ability to reduce tumor volume with debulking
  - Residual peritoneal tumor exposed to increased concentration of drug for prolonged period of time
- **Limitations:**
  - Poor tumor penetration of bulk disease
  - Less exposure of extra-peritoneal disease to drug
- **Complications:**
  - Obstruction to flow or inadequate distribution
  - Infection: peritonitis, abdominal wall or catheter
  - Intestinal perforation

GOG #104
SWOG #8501



GOG #104

Alberts et.al. NEJM Dec 1996

	Cyclophosphamide and Cisplatin INTRAPERITONEAL	Cyclophosphamide and Cisplatin INTRAVENOUS	
Path CR	47%	36%	
Survival	49 mo	41 mo	p=.02

Consensus: GOG 104

The benefits of IP chemotherapy seen in GOG 104 are not greater than the benefits of the new agent, paclitaxel

GOG #114

Second look Laparotomy

Ovarian cancer
Stage III
≤ 1.0 cm

RANDOMIZE

Cisplatin 75 mg/m² IV
Cyclophosphamide 750mg/m² IV
q 21 days x 6

Cisplatin 75 mg/m² IV
Paclitaxel 135 mg/m² IV
q 21 days x 6

Carboplatin AUC=9 x 2 IV
then
Cisplatin 100 mg/m² IP
Paclitaxel 135 mg/m² IV
q 21 days x 6

GOG #114

Second look Laparotomy

Ovarian cancer
Stage III
≤ 1.0 cm

RANDOMIZE

Cisplatin 75 mg/m² IV
Cyclophosphamide 750mg/m² IV
q 21 days x 6

Cisplatin 75 mg/m² IV
Paclitaxel 135 mg/m² IV
q 21 days x 6

Carboplatin AUC=9 x 2 IV
then
Cisplatin 100 mg/m² IP
Paclitaxel 135 mg/m² IV
q 21 days x 6

GOG #114

Markman et.el. JCO Feb 2001

	IV Carbo IV Taxol IP Cisplatin	IV Taxol IV Cisplatin	
PFS	27.6 mos	22.5 mos	P=.01
Overall Survival	63.2 mos	52.5 mos	P=.05

Consensus: GOG 114

The benefits of IP in GOG 114 are likely explained by the use of eight cycles of chemotherapy, not the use if IP administration (see GOG 182)

GOG #172

Armstrong et.al. Abs #803, ASCO 2002

Second look Laparotomy (if chosen)

BRCA Analysis
DNA Banking

Ovarian cancer
Optimal (<1cm)
Stage III
Stratify:
Gross residual
Planned 2nd look

RANDOMIZE

Paclitaxel 135 mg/m²/24h
Cisplatin 75 mg/m²
q 21 days x 6

Paclitaxel 135 mg/m²/24h
Cisplatin 100 mg/m² IP D2
Paclitaxel 60 mg/m² IP D8
q 21 days x 6

Treatment Regimens
Every 21 days x 6

Regimen 1
Intravenous

D1 D2
IV IV

D1: IV Paclitaxel (135mg/m^2/24h)
D2: IV Cisplatin (75mg/m^2)

Regimen 2
Intraperitoneal

D1 D2 D8
IV IP IP

D1: IV Paclitaxel (135mg/m^2/24h)
D2: IP Cisplatin (100mg/m^2)
D8: IP Paclitaxel (60mg/m^2)

GOG #172: Non-hematologic toxicities

Armstrong et.al. Abs #803, ASCO 2002

	IV	IP
GI G3/4	24%	46%
Renal G3/4	1%	6%
Fatigue G3/4	5%	17%
Pain G3/4	1%	11%
Metabolic G3/4	7%	24%
Neuro G3/4	9%	19%

GOG #172: Hematologic Toxicities

Armstrong et.al. Abs #803, ASCO 2002

	IV	IP
Leukopenia G4	14%	31%
Infection G3/4	5%	16%
Plts G3/4	4%	12 %

Courses of Protocol Therapy by Regimen

# courses	Treatment Assignment					
	Intravenous			Intraperitoneal		
	Assigned Treatment (AT)		AT or Carboplatin*		Assigned Treatment (AT)		AT or Crossover to IV cisplatin		AT or Crossover to IV cisplatin or carboplatin*	
0	2	(1%)	0	(0%)	16	(8%)	5	(2%)	4	(2%)
1	8	(4%)	7	(3%)	38	(19%)	21	(10%)	10	(5%)
2	9	(4%)	4	(2%)	30	(15%)	20	(10%)	6	(3%)
3	11	(5%)	6	(3%)	14	(7%)	9	(4%)	4	(2%)
4	2	(1%)	0	(0%)	10	(5%)	5	(2%)	4	(2%)
5	4	(2%)	4	(2%)	11	(5%)	12	(6%)	7	(3%)
6	174	(83%)	189	(90%)	86	(42%)	133	(65%)	170	(83%)

* Carboplatin substituted for cisplatin

GOG #172:
Second Look Results

Second Look Finding	IV	IP
Negative 2nd look	35 (41%)	46 (57%)
Positive 2nd look	37 (44%)	23 (28%)
2nd look contraindicated	13 (15%)	12 (15%)
Total	85 (100%)	81 (100%)

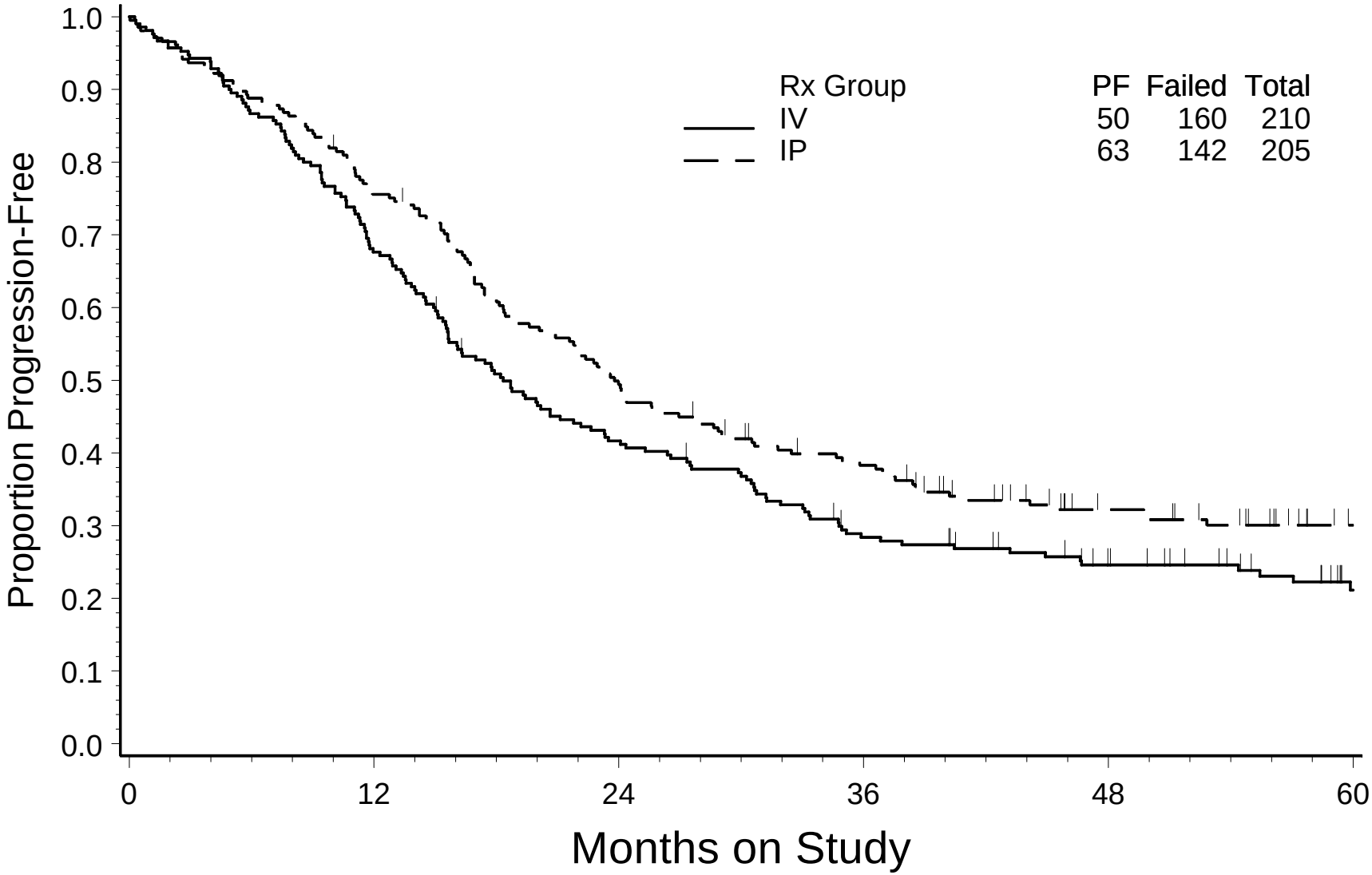
GOG #172: Survival

	Regimen 1 Intravenous	Regimen 2 Intraperitoneal
Progression-free	**18.3 mos**	**23.8 mos**
Overall Survival	**49.5 mos**	**66.9 mos**

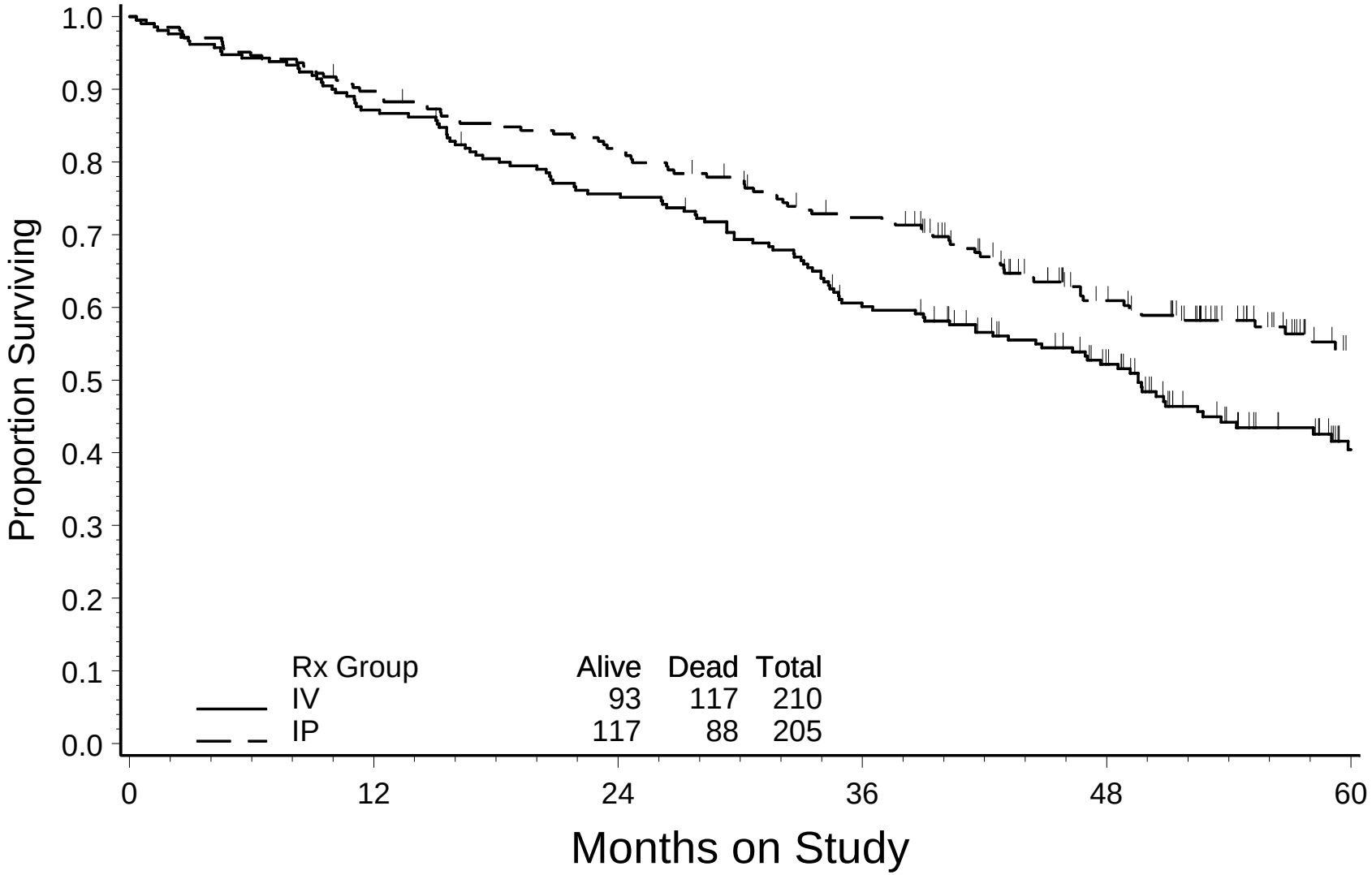
Relative Risk: IP vs. IV Therapy, GOG #172

	Relative Risk	95% CI	p-value
PFS	0.79	0.63-0.99	0.027
OS	0.71	0.54-0.94	0.0076

Progression – Free Survival
By Treatment Group



Survival
By Treatment Group



Modulating Toxicity of IP Therapy

- New approaches to improve toxicity profile
  - Type of catheter used
  - Timing of catheter placement
  - Timing of chemotherapy
    - relative to surgery
    - relative to catheter placement
  - Agents used
- Successful use of IP therapy requires:
  - Training
  - Skill
  - Experience
  - Dedication

Consensus: 2005

- The toxicities, inconvenience and cost of IP therapy are justified by the improved survival seen with this treatment
- New, targeted therapies are likely to be more effective in patients who have an excellent response to chemotherapy
- While we work to improve the tolerability and toxicities of IP therapy, it remains the most effective means of treating ovarian cancer today