Progress and Controversies in Gynecologic Oncology, Barcelona 2015

Interactive case discussion: Platinum-sensitive recurrent ovarian cancer

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Case Presentation

65-year-old patient with high-grade serous ovarian cancer stage FIGO IIIC, pT3c, pN0 (8/43 Ln), 1st diagnosis 12/2012

12/2012	Laparotomy with TAH + BSO + partial pelvic peritonectomy, infragastric omentectomy, debulking right diaphragm and lig. facliforme, debulking of enlarged pelvic + para-aortic lymph nodes. **residual tumor = 0.5 cm** (bowel serosa small and large intestine)
1-4/2013	6 x Carboplatin / Paclitaxel / Bevacizumab -> Bevacizumab single agent as maintenance therapy until 5/2014 (standard arm of AGO-OVAR 17; ENGOT-ov15; BOOST)
8/2014	16 months after last platinum and 3 months after last bevacizumab patient presented with some cough and she felt tired, gyn evaluation showed some ascites, but no pelvic tumor, CA 125 increased from normal to 185 U/ml
8/2014	Diagnostic work-up

BSO, bilateral salpingo-oophorectomy; LNE, lymphadenectomy; TAH, total abdominal hysterectomy

Image not available

What would you recommend?

1. Re-operation aiming at complete surgical debulking, followed by chemotherapy

2. Start with systemic therapy

What would you recommend?

1. Re-operation aiming at complete surgical debulking, followed by chemotherapy

14.7%

2. Start with systemic therapy

85.3%

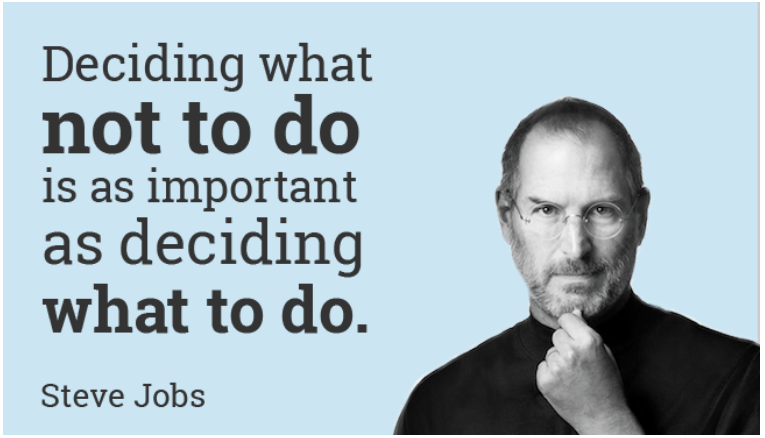
Image not available

1. Re-operation aiming at complete surgical debulking (eventually followed by chemotherapy)

..but would not suggest to do so,

Why?

Reasons not to operate:



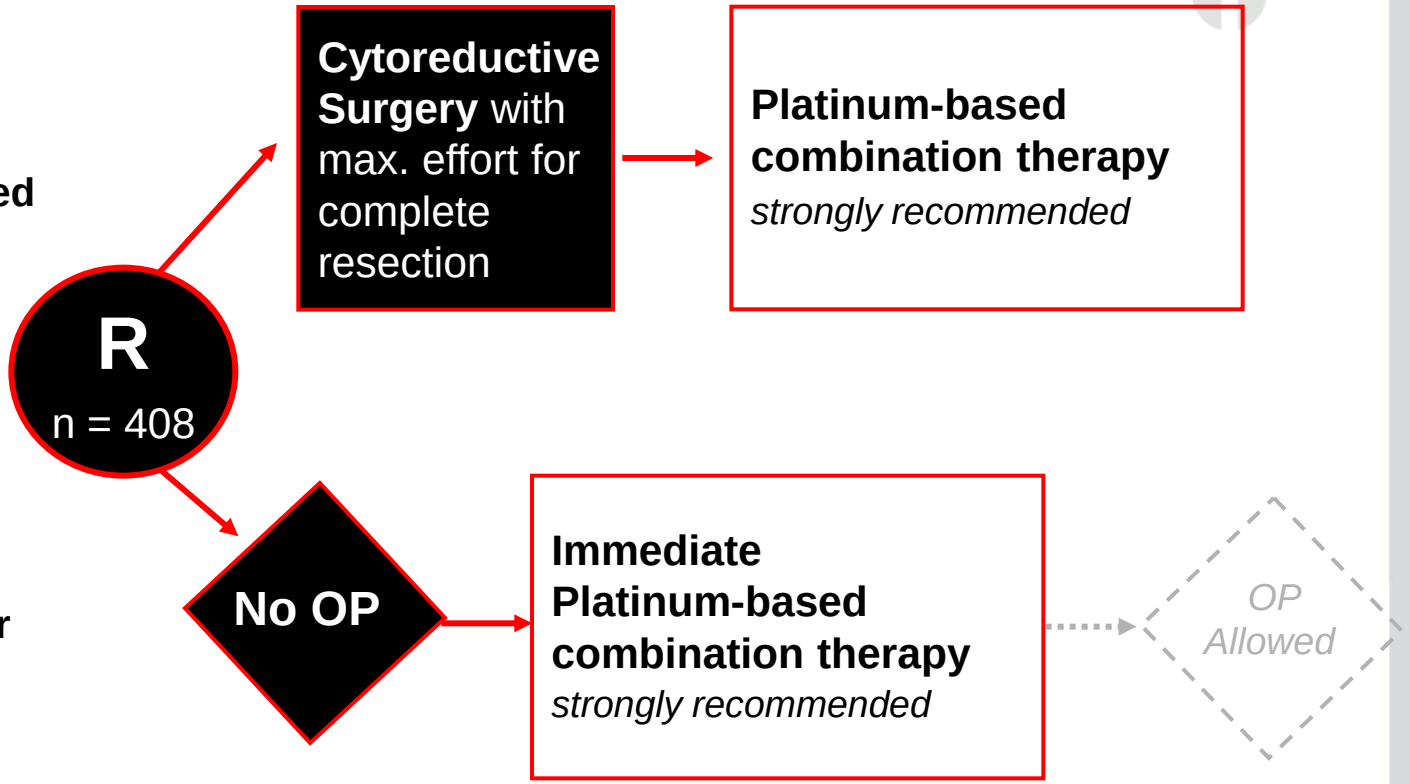
1. Initially incomplete resection due to peritoneal carcinomatosis

   -> Now, again signs for peritoneal carcinomatosis (ascites) reducing the probability of complete resection (and incomplete op without benefit)
2. Extraperitoneal spread (pleural effusion and mediastinal lymphnodes, and more?)
3. Symptoms rather associated with effusions than with resectable tumor

   -> early start of systemic treatment preferable?

DESKTOP III (AGO – OVAR OP.4; ENGOT-ov20)

- **Recurrent invasive ovarian, tubal, or peritoneal cancer**
- **Patient fit for extended abdominal surgery and for platinum-based combination**
- **1 prior chemothx until >6 months; max. 1 prior non-chemo maintenance therapy until >4 wks; no prior abdominal or pelvic radiotherapy**
- **Centre pre-defines chemotherapy regimen (for both arms)**



Endpoints: OS, PFS, Tox, QoL

Strata: centre, age (+/-65)

Recommended regimen: carbo-pegylated liposomal doxorubicin (PLD)
carbo-gemcitabine +/- bevacizumab
carbo-paclitaxel
any other platinum-containing regimen within studies

Centre		Randomized	DESKTOP III on 31. 12. 2014
Charite Berlin		42	
Leuven		25	
Toulouse		21	
KEM Essen / HSK Wiesbaden		16	
EvK Düsseldorf		15	
Napoli		14	
Odense		14	
Paris (Hopital Tenon; 908)		13	
Bordeaux (900)		12	
Clermont-Ferrand		11	
Paris (GPEH; 910)		9	
Shanghai (Fudan University, 802, 805)		9	
Stockholm		8	
Milan (Inst.tumori)		7	
Oslo		7	
Barcelona (Llobregat)		7	
St Herblain		6	
Hannover		6	
Kopenhagen		6	
Seoul		6	
Herlev		5	
Freiburg		5	
Aalborg		5	
Kiel UFK		4	
Badalona		4	
Nice		4	
Wien		4	
Valencia (La Fe; 657)		5	
Aviano		4	
London (UCL 784)		4	
Bad Homburg		3	
Wolverhampton		3	
London (Imperial 785)		3	
Guildford		3	
Valencia (Fudacion; 653)		3	
München Großhadern		3	
London (St Barth.783)		3	
Barcelona (656)		3	
Caen		3	
UFK Lübeck		3	
Diakonie Düsseldorf		2	
UFK Dresden		2	
Rouen (914)		2	
Suzhou		2	
Linköping		2	
Rennes		2	
Ravensburg		2	
Cambridge		2	
Barcelona (Sant Pau; 659)		2	
Birmingham		2	
London (Royal Marsden; 782)		2	
Manchester (834)		2	
Aarhus		2	
Sheffield		2	
Westerstede		2	
Rouen (915)		1	
Greifswald		1	
Kempten		1	
Hangzhou		1	
Fürth		1	
München 3. Orden		1	
Graz		1	
Paris (HPSJ; 927)		1	
Göttingen		1	
Schweinfurt		1	
Mainz		1	
Margate		1	
Pamplona		1	
Gateshead		1	
Palma de Mallorca		1	
Reims		1	
Mougins		1	
Wien (Wilhelminenspital; 717)		1	
Regensburg		1	
Poitiers		1	
London Mount Vernon (778)		1	
Innsbruck		1	
Girona		1	
Norwich		1	
Southampton		1	
Ulm		1	
Frankfurt UFK		1	
Nottingham		1	
Konstanz		1	
Sum		**387**	of 408 (95%)

The DESKTOP League

Country	Pts	centres
	116	24
	88	15
	32	16
	32	5
	27	9
	25	1
	25	3
	12	3
	10	2
	7	4
	6	1
	7	1

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2. Start with systemic therapy (with or w/o prior surgery)

… but which regimen?

Ferrari aka **Carbo-PLD**
(CALYPSO; AGO-OVAR 2.9)

Lamborghini aka **Carbo-Tax**
(ICON4; AGO-OVAR 2.2)

Porsche aka **Carbo-Gem**
(AGO-OVAR 2.5)

Porsche 911 Turbo S Cabriolet
aka **Carbo-Gem + Bev** (OCEANS)

Porsche plus Trailer
aka **Platinum -> Olaparib**

Which strategy would you recommend?
(either with or w/o prior surgery)

1. Platinum combination
    a. Re-induction with carboplatin + paclitaxel
    b. Platinum re-induction with another partner (PLD or Gem)
2. Platinum combination plus bevacizumab
3. Best platinum regimen followed by olaparib (PARPi)

Which strategy would you recommend?
(either with or w/o prior surgery)

1. Platinum combination
    a. Re-induction with carboplatin + paclitaxel
    b. Platinum re-induction with another partner (PLD or Gem)

2. Platinum combination plus bevacizumab

3. Best platinum regimen followed by olaparib (PARPi)

No. 1: Platinum combination

Paclitaxel plus platinum-based chemotherapy versus conventional platinum-based chemotherapy in women with relapsed ovarian cancer: the ICON4/AGO-OVAR-2.2 trial

Lancet 2003; 361: 2099–106

The ICON and AGO Collaborators

802 patients

- Relapsed OC >6 / >12 months after platinum
- 1 prior regimen with platinum (Italy)
  or
  platinum-paclitaxel (Germany)
  or
  at least 1 prior platinum regimen (UK)

RANDOMIZATION

Study arm

n = 392

Paclitaxel 175-185 mg/m² (3h)
+
Carboplatin AUC 5-6
or Cisplatin (10%)

Standard

n = 410

Platin without paclitaxel

- Carboplatin mono (71%)
- Cisplatin mono (2%)
- Other platin regimens (27%)

The ICON and AGO Collaborators.
Parmar MK, et al. *Lancet*. 2003;361(9375):2099-2106.

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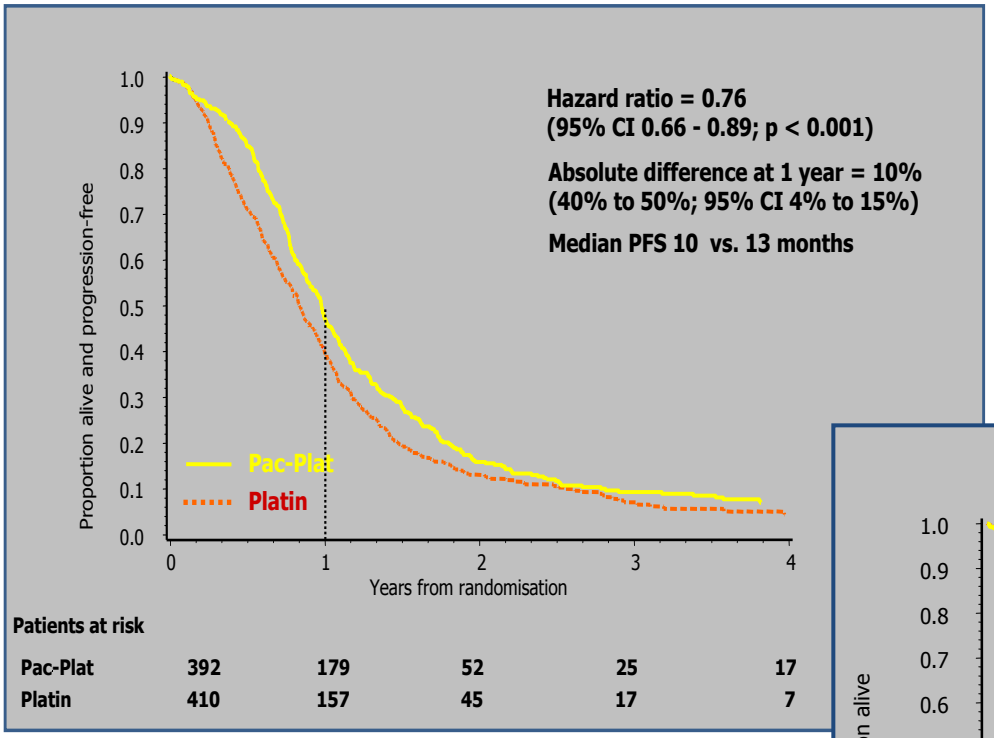
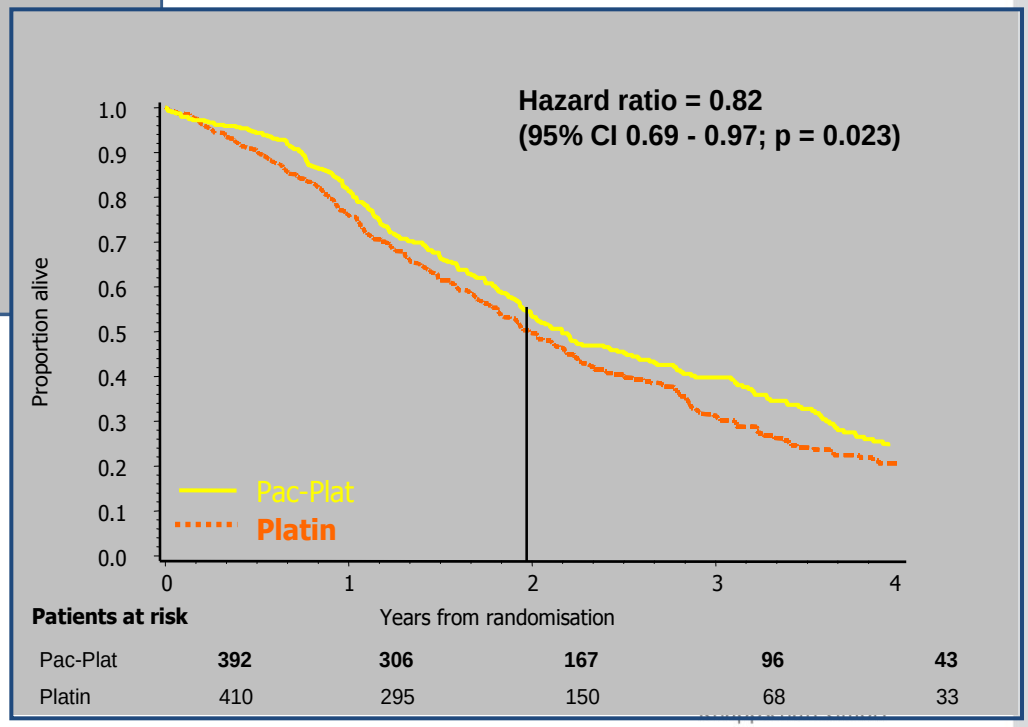
ICON4/AGO-OVAR 2.2
Progression-Free and Overall Survival





The ICON and AGO Collaborators.
Parmar MK, et al. *Lancet*. 2003;361(9375):2099-2106.

AGO-OVAR 2.5– NCIC CTG – EORTC GCG

- Recurrence >6 months after first-line therapy
- At least evaluable disease
- Strata:
  - Platinum-free interval (6-12 months, >12 months)
  - First-line therapy (platinum +/- paclitaxel)

    -> 71% had prior taxane (closer to SoA today)
  - Measurable vs evaluable disease

RANDOMIZATION

Gemcitabine 1000 mg/m² d 1+8

Carboplatin AUC 4 d 1

q 21 x 6 (-10)

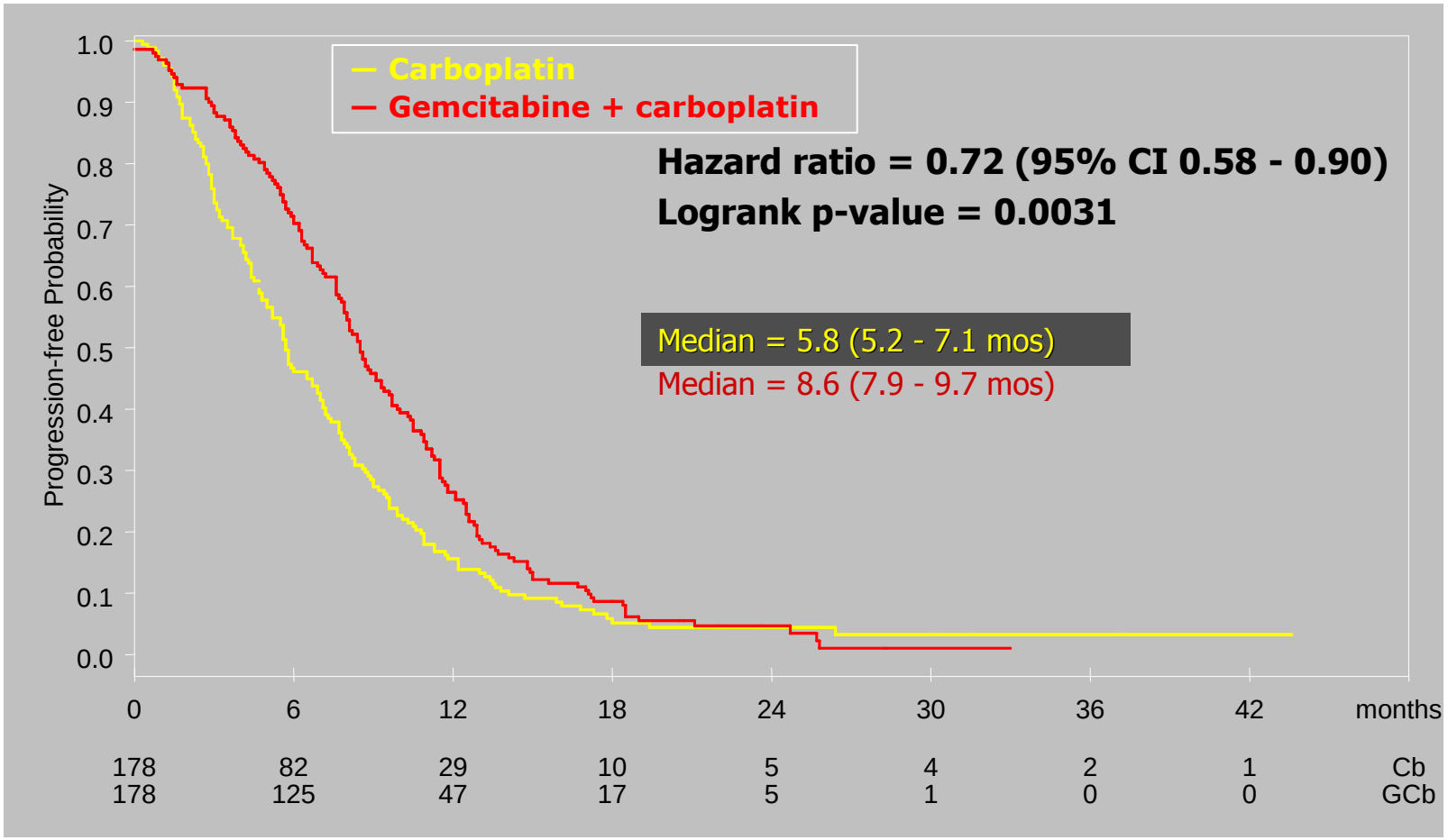
Carboplatin AUC 5 d 1

q 21 x 6 (-10)

SoA, state of the art

Pfisterer J, et al. *J Clin Oncol.* 2006;24(29):4699-4707.

AGO-OVAR 2.5:
Progression-Free Survival (Significant)



- Not powered for survival
- Explorative analysis: no difference, median 18 months vs 17.3 months, HR 0.96, *P* = .735

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Pfisterer J, et al. *J Clin Oncol.* 2006;24(29):4699-4707.

CALYPSO / AGO-OVAR 2.9

International, Intergroup, Open-Label, Randomized Phase III Study

Ovarian cancer in late relapse (>6 months) after first-line or second-line platinum and taxane therapy

(100% with prior taxane)

Strata:

- **Therapy-free interval (6-12 months vs >12 months)**
- **Measurable disease (yes vs no)**
- **Center**

RANDOMIZE

Experimental arm: CD

PLD 30 mg/m² IV d 1

Carboplatin AUC 5 d 1

Q 28 days x 6 courses*

Control arm: TC

Paclitaxel 175 mg/m² IV d 1

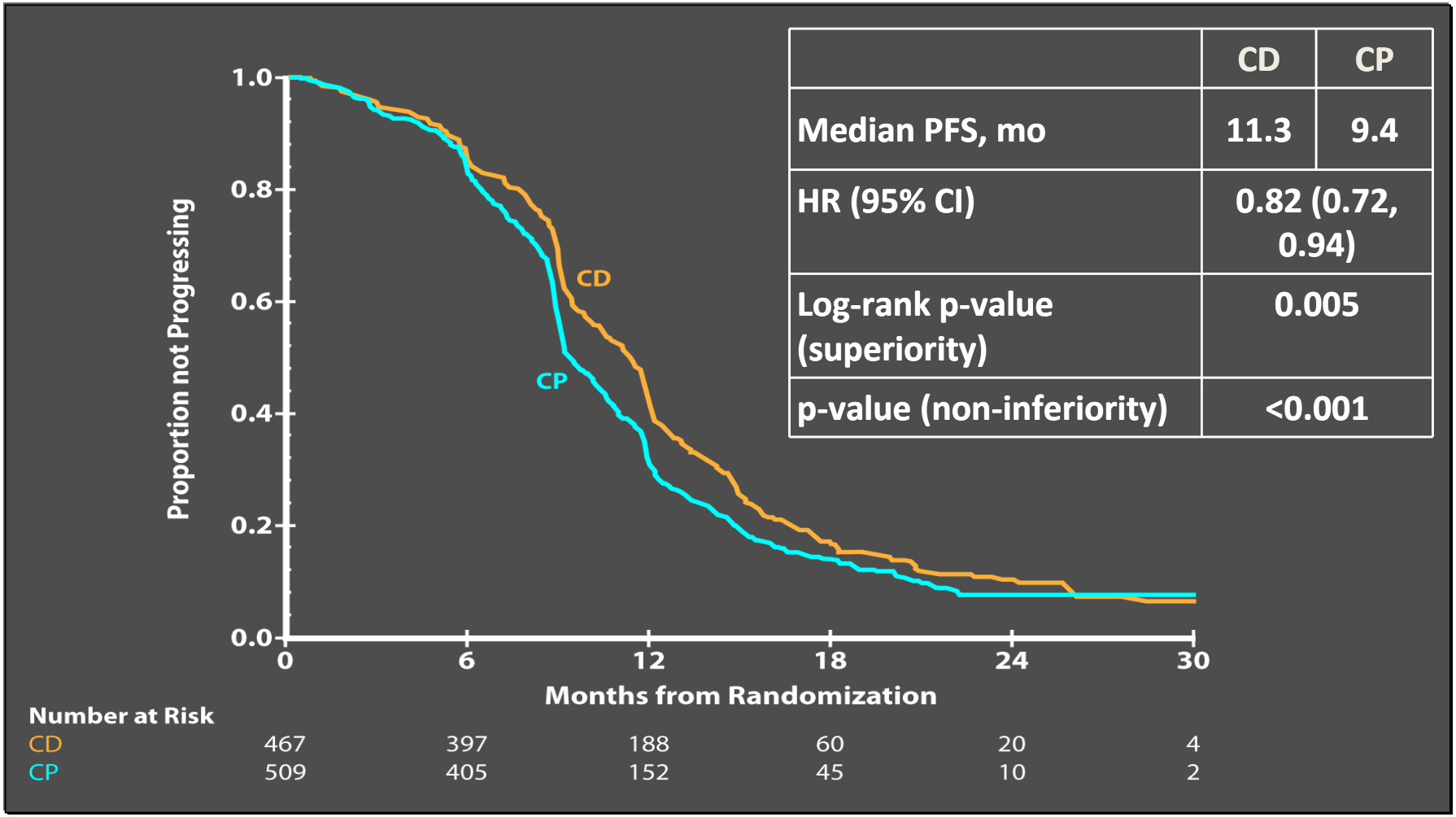
Carboplatin AUC 5 d 1

Q 21 days x 6 courses*

*Or progression in patients with SD or PR

Pujade-Lauraine E, et al. *J Clin Oncol.* 2010;28(20):3323-3329.

Progression-Free Survival (ITT)



	CD	CP
Median PFS, mo	11.3	9.4
HR (95% CI)	0.82 (0.72, 0.94)	
Log-rank p-value (superiority)	0.005	
p-value (non-inferiority)	<0.001	

- Survival not primary endpoint
- However, no difference, median 30.7 months vs 33 months, HR 0.99, *P* = .94

ITT, intent to treat

Pujade-Lauraine E, et al. *J Clin Oncol.* 2010;28(20):3323-3329.Wagner U, et al. *Br J Cancer.* 2012;107(4):588-591.

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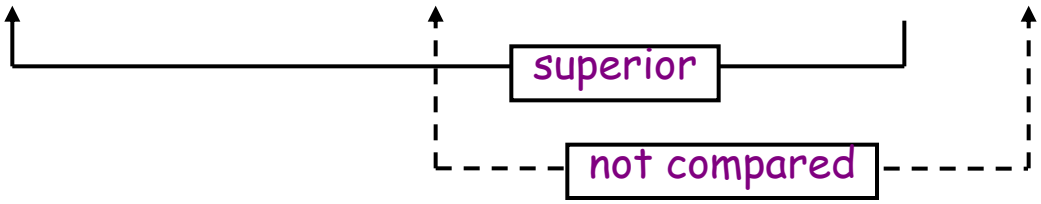
Platinum Combinations in PT-Sensitive ROC: How to Incorporate All the Available Data?

Paclitaxel + Carboplatin	Gemcitabine + Carboplatin	PLD + Carboplatin
▪ PFS TC > C ▪ OS TC > C	▪ PFS CG > C ▪ OS ?	▪ **PFS CC > TC** ▪ OS CC = TC
▪ Schedule: d1 q 3 w	▪ Schedule: d1+8 q 3 w	▪ Schedule: d1 q 4 w
▪ Neurotoxicity	▪ Hematotoxicity	▪ Skin/mucosa
▪ Alopecia 86%	▪ Alopecia 15%	▪ Alopecia 7%
▪ QoL identical	▪ QoL identical	▪ QoL identical



Answer to question No. 1: Platinum combinations

… and the golden apple goes to…

If I had to choose among the platinum combinations,

I would prefer carboplatin-PLD

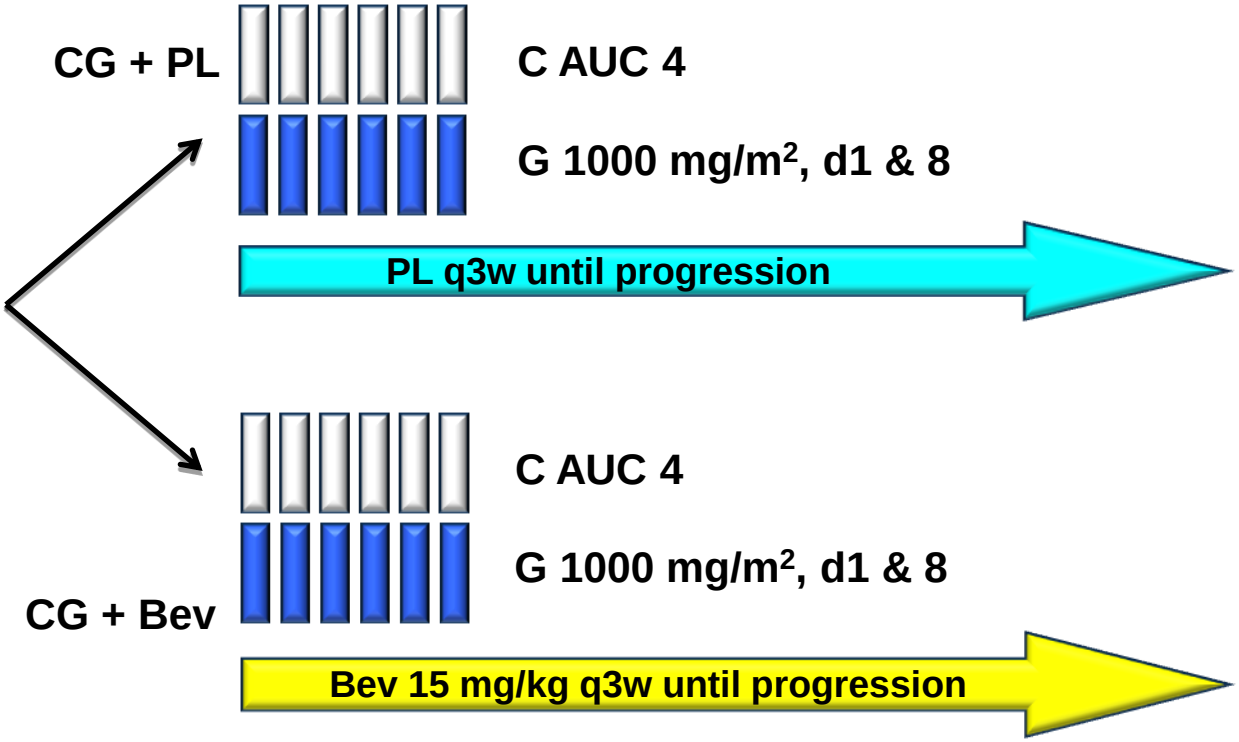
(if not contraindicated by co-morbidity ***and*** if available)

OCEANS: Study Schema

Platinum-sensitive recurrent OC

- **Measurable disease**
- **ECOG 0/1**
- **No prior chemo for recurrent OC**
- **No prior Bev**

(n = 484)



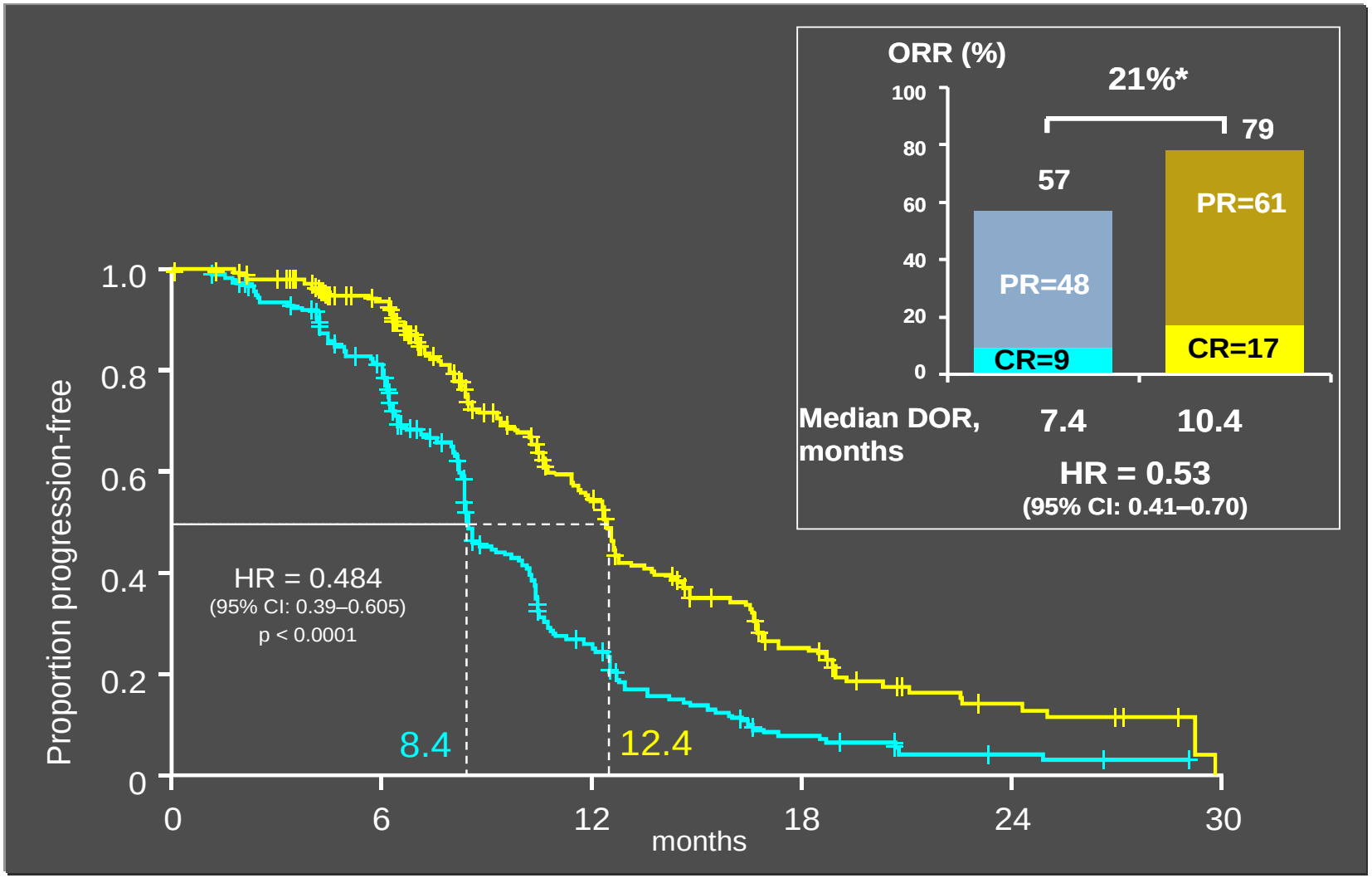
Strata:

- Platinum-free interval (6-12 months vs >12 months)
- **Unsuccessful** cytoreductive surgery for recurrent disease (yes vs no)

Bev, bevacizumab; PL, placebo; C, carboplatin; G, gemcitabine

Aghajanian C, et al. *J Clin Oncol.* 2012;30(17):2039-2045.

OCEANS: Efficacy PFS and OR



Aghajanian C, et al. *J Clin Oncol.* 2012;30(17):2039-2045.

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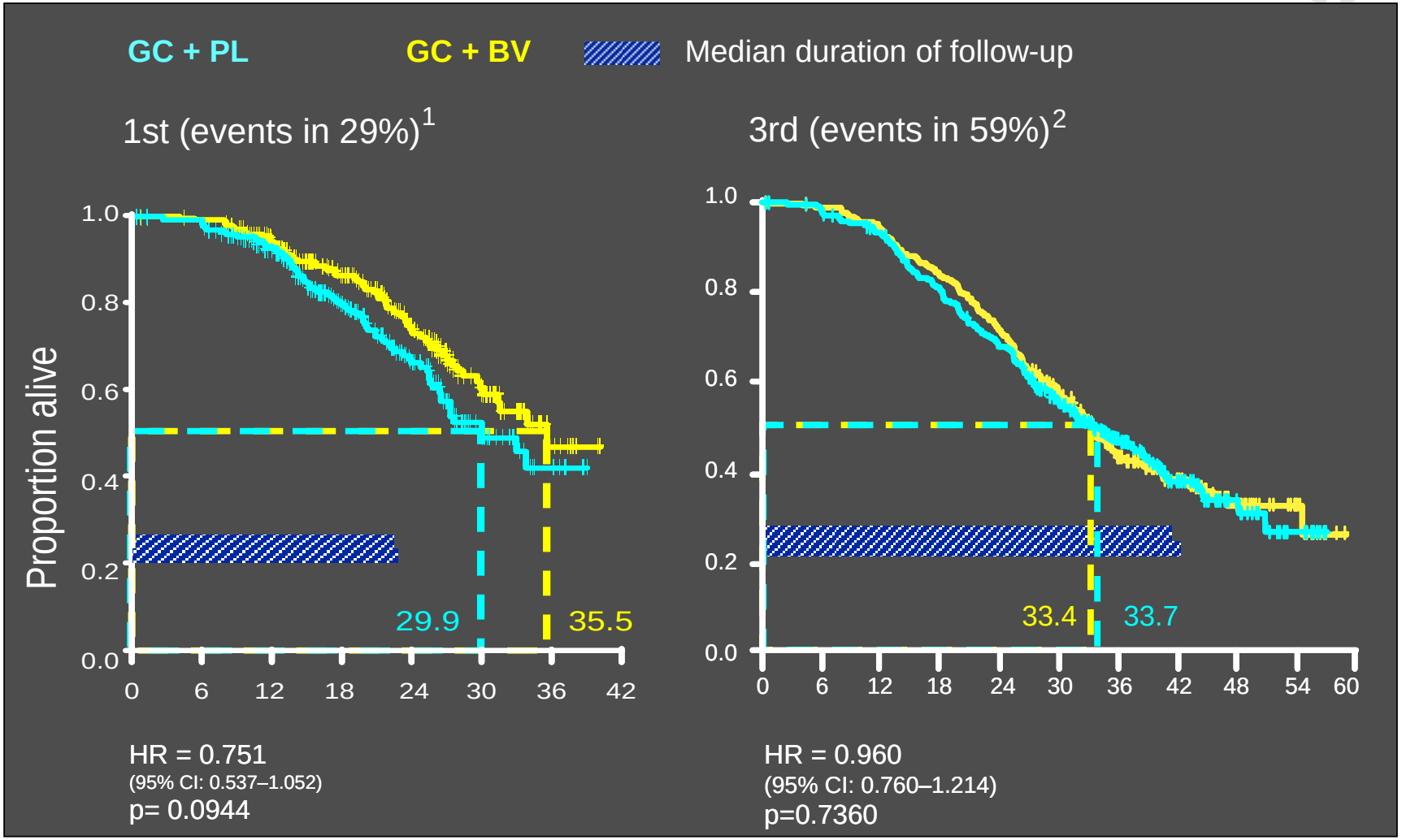
OCEANS: Survival Analyses



… again, neither survival benefit nor harm

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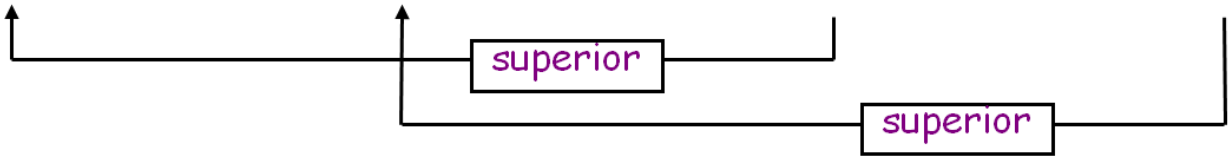
1. Aghajanian C, et al. *J Clin Oncol.* 2011;29(suppl): Abstract LBA5007; 2. Aghajanian C, et al. *Ann Oncol.* 2012:23(Suppl 9): Abstract 9670.

No. 1 and 2: Carbo-PLD or Carbo-Gem-Bev ?

Paclitaxel + Carboplatin	Gemcitabine + Carboplatin	PLD + Carboplatin	Gemcitabine + Carboplatin + Bevacizumab
▪ PFS TC > C ▪ OS TC > C	▪ PFS CG > C ▪ OS ?	▪ **PFS CC > TC** ▪ OS CC = TC	▪ **PFS CGB > CG** ▪ OS CGB = CG
▪ Schedule: d1 q 3 w	▪ Schedule: d1+8 q 3 w	▪ Schedule: d1 q 4 w	▪ Schedule: ▪ d1+8 q 3 w → d1 q3
▪ Neurotoxicity	▪ Hematotoxicity	▪ Skin/mucosa	▪ Hematotoxicity
▪ Alopecia 86%	▪ Alopecia 15%	▪ Alopecia 7%	▪ Hypertension 20%
▪ QoL identical	▪ QoL identical	▪ QoL identical	▪ QoL ?



Problem: Bevacizumab is only registered for one line – in Europe; either first-line or platinum-sensitive relapse or platinum-resistant relapse…. and this pat. had already received bev ?!

In problem? → **Call AGO & friends**

AGO-OVAR 2.21
ENGOT ov18

One possible solution (app. until summer 2015):

1:1

R

N = 870

Bevacizumab 15 mg/kg q3w until PD

Gemcitabine 1000 mg/m² d1 and 8

Carboplatin AUC 4 d1 q3w

Bevacizumab 10 mg/kg q2w

Bevacizumab 15 mg/kg q3w until PD

Pegylated Liposomal Doxorubicin 30 mg/m² d1

Carboplatin AUC 5 d1 q4w

OCEANS

vs

Calypso
+ Bev

Stratification Factor

- Platinum-free interval (6-12 months vs >12 months)
- In case of debulking surgery for recurrence: residual tumor (yes vs no)
  In case of no debulking surgery for recurrence: all pts categorized to residual tumor = yes
- **Prior anti-angiogenic treatment (yes vs no)**
- Study group

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I could offer study participation: ENGOT ov18 or … in some countries ENGOT-ov17

ENGOT Ov-17 Trial
MITO 16b; MANGO-OV2b
Study Design

- Ovarian Ca
- Platinum-sensitive
- Previous Bevacizumab
- ECOG 0-2
- Samples for transl. res.
- No Bev contraindications

R

CBDCA AUC5 + PAC 175 mg/m2 q3w
or
CBDCA AUC4, d1 + GEM 1000mg /m2, d1&8 q3w
or
CBDCA AUC5+PLD 30mg/m2 q4w

CBDCA AUC5 + PAC 175 mg/m2 q3w
Plus bevacizumab 15mg/kg q3w**
or
CBDCA AUC4, d1 + GEM 1000mg /m2, d1&8 q3w
Plus bevacizumab 15mg/kg q3w
or
CBDCA AUC5+PLD 30mg/m2 q4w
Plus bevacizumab 10mg/kg q2w

= Bevacizumab

No. 3: best platinum combination (Carbo-PLD) followed by Olaparib ?

No. 3: best platinum combination followed by Olaparib ?

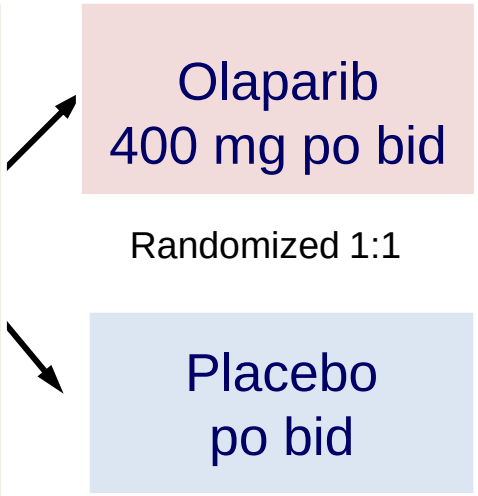
‘Study 19’
Randomized trial of maintenance olaparib in platinum-sensitive high-grade serous relapsed ovarian cancer

Study aim and design

265 patients

Patients:

- **Platinum-sensitive high-grade serous ovarian cancer**
- ≥2 previous platinum regimens
- Last chemotherapy was platinum-based, to which they had a maintained PR or CR prior to enrolment
- Stable CA-125



Ledermann J, Harter P, et al.
N Engl J Med. 2012;366(15):1382-1392.

Results: *BRCA* Testing

		tBRCA			
		Mutated	Wild type*	Not available	TOTAL
gBRCA	Mutated	71	3	22	96
	Wild type*	18	73	23	
	Not available	22	22	11	
					265

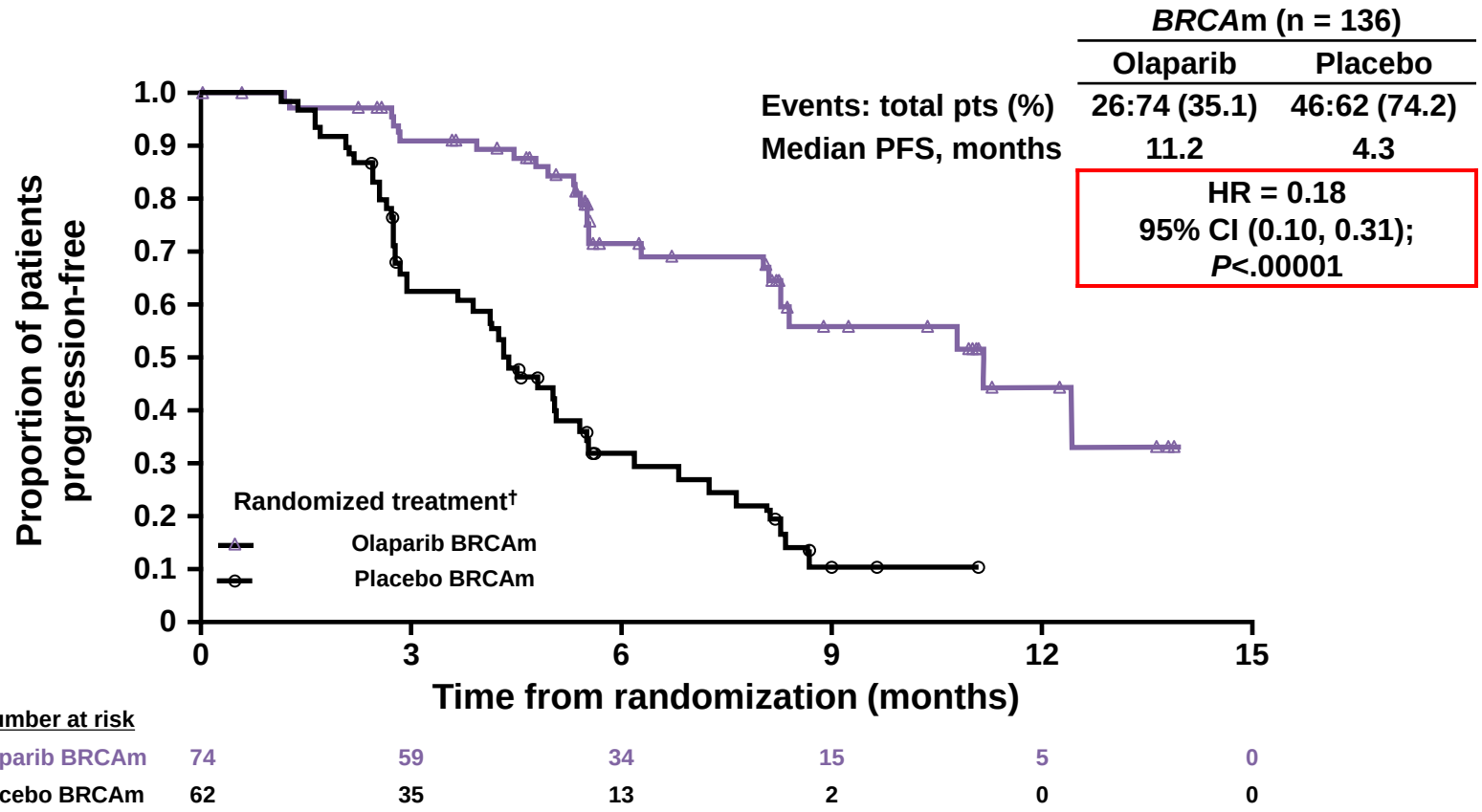
- **136 (51.3%) patients had a known deleterious *BRCA*m (*BRCA*m dataset)**
- 118 (44.5%) patients were defined as *BRCA1/2* wild type for this analysis
- 11 (4.2%) patients had neither a tumour nor a germline result available

➢ **The number of patients with a known *BRCA*m status increased from 97 (36.6%) to 254 (95.8%) out of 265**

Ledermann J, *et al. Lancet Oncol.* 2014;15(8):852–861.

PFS in Patients With a *BRCA1/2* Mutation*

- The greatest PFS benefit was observed in patients with a *BRCA1/2* mutation (*BRCA*m)

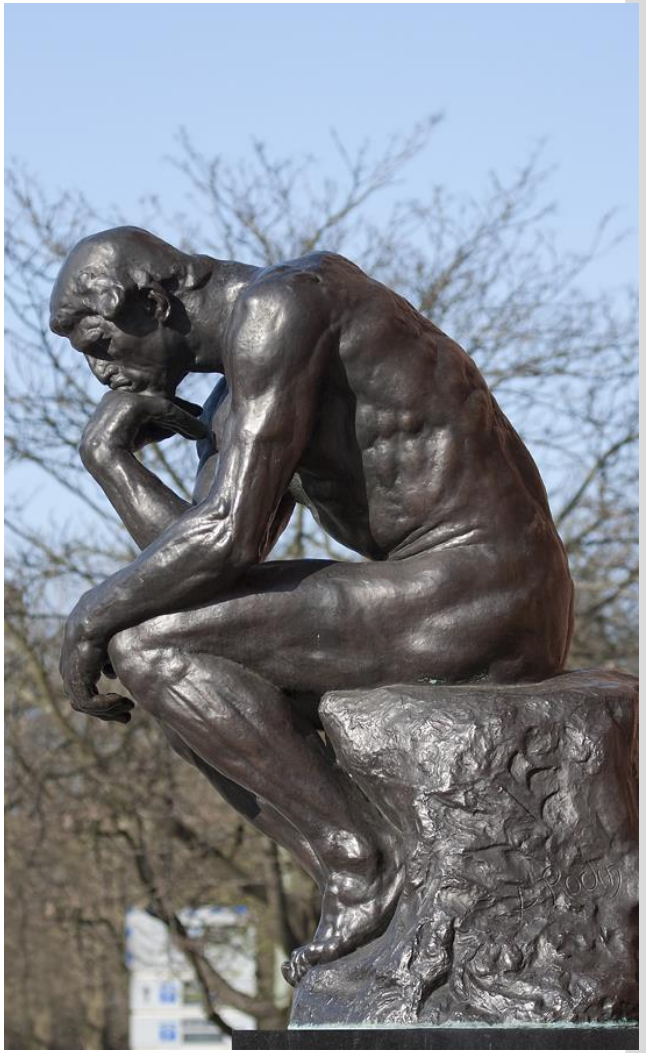


*Includes patients with germline and/or somatic mutations; †patients were treated until disease progression

Ledermann J, *et al. Lancet Oncol.* 2014;15(8):852–861.

Platinum-sensitive relapse
1st-line chemo + bevacizumab

- ***BRCA* testing**
  - **Negative**
    - **ENGOT study available?**
      - yes
        - **ENGOT ov18**
          - **Carbo-Gem-Bev -> Bev or Carbo-PLD-Bev -> Bev**
      - no
        - **Carbo-PLD**
  - **Positive**
    - **Carbo-PLD**
      - **Response**
        - no
          - *Plat-resistant relapse*
        - yes
          - **Olaparib**



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2015

Progress and Controversies in Gynecologic Oncology Conference