

Case Discussion: Platinum-Resistant Ovarian Cancer

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Patient Case (1)

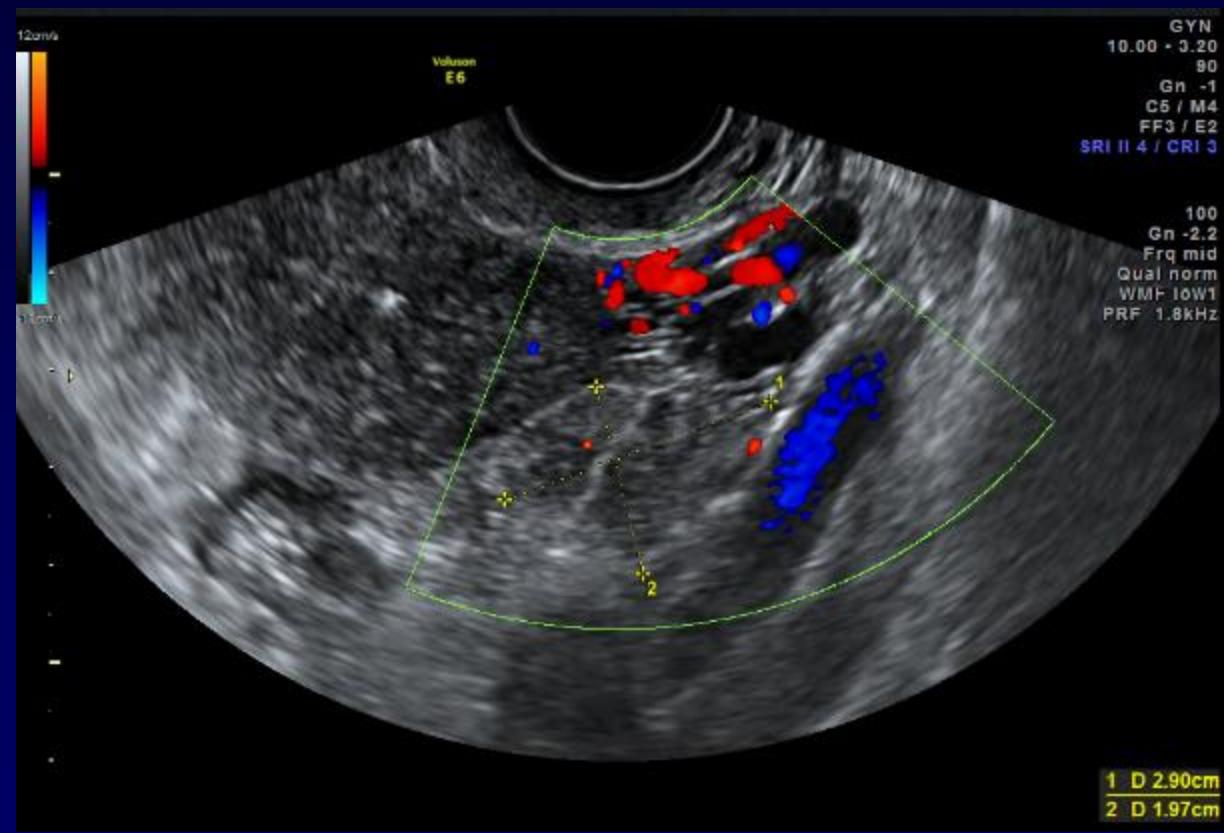
- ✓ Patient 67 years old, G4P3A1
- ✓ Medical history: negative except for mild hypertension
- ✓ Medication: lisinopril 2.5 mg/d
- ✓ Prior surgery: caesarean section (breech)
- ✓ Familial history: negative except for 2 nieces with breast cancer (out of 20 nieces).
- ✓ Regular PAP smears and mammography followed by her GP

Patient Case (2)

- ✓ The patient has had **pain** in the right iliac fossa for 3 months. No gastrointestinal or urinary complaints.
- ✓ Two months ago the GP ordered a **colonoscopy**, which was normal.
- ✓ Now the GP asks for a **sonography** of the abdomen, which is normal.
- ✓ Serum CA125: 125 KU/L (UNL 35)
- ✓ CEA: 1.3 µg/L (UNL: 3.8)
- ✓ The patient was referred to the gynecologist, who performed a **vaginal ultrasound**.

Patient Case (3)

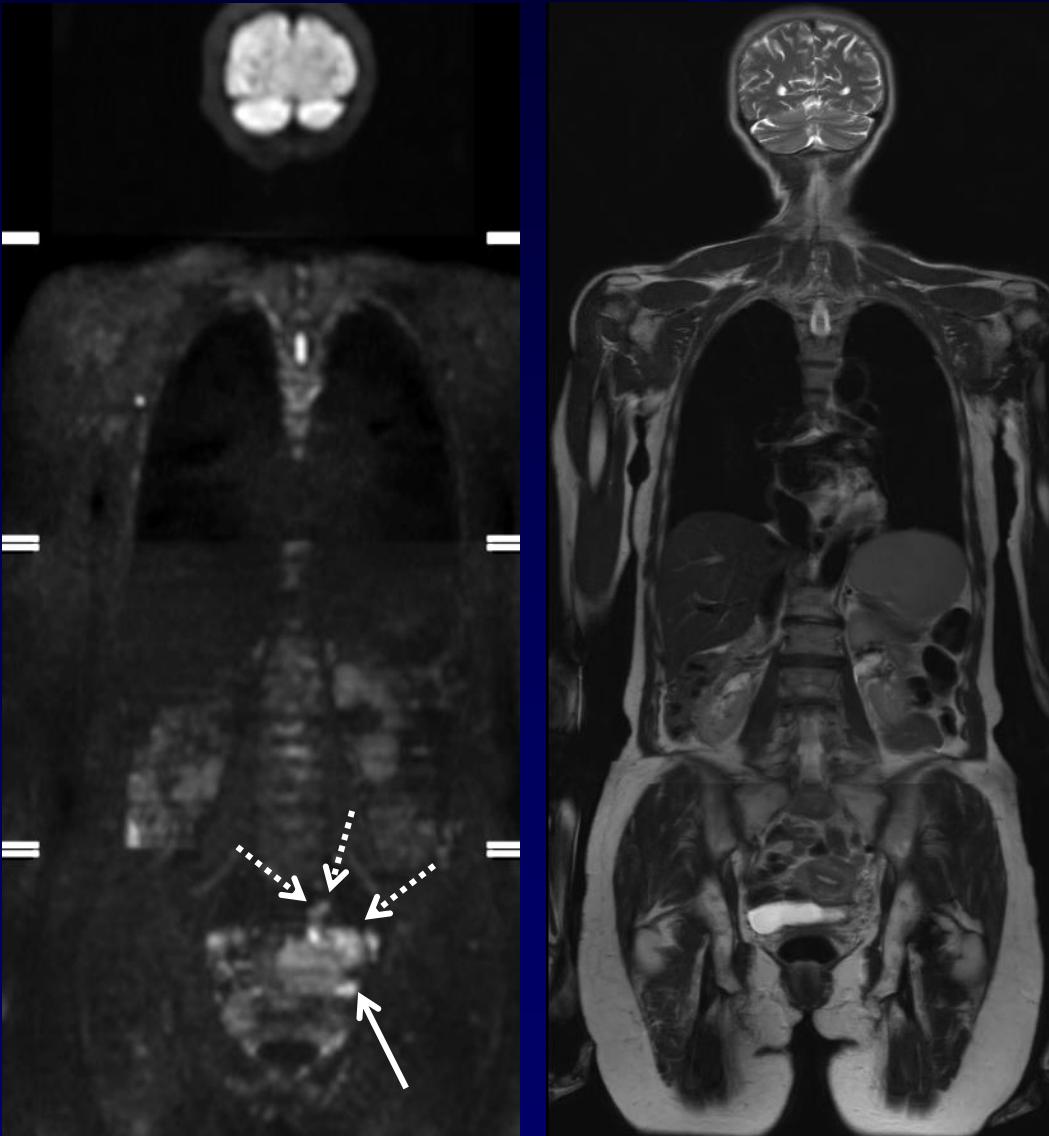
Vaginal Ultrasound



- ✓ Left ovary is composed of **2 solid areas** fixed between the uterus and sigmoid. Color score **2**.
- ✓ Right ovary, uterus, and upper abdomen are **normal**

Patient Case (4)

Diffusion-Weighted Whole-Body MRI

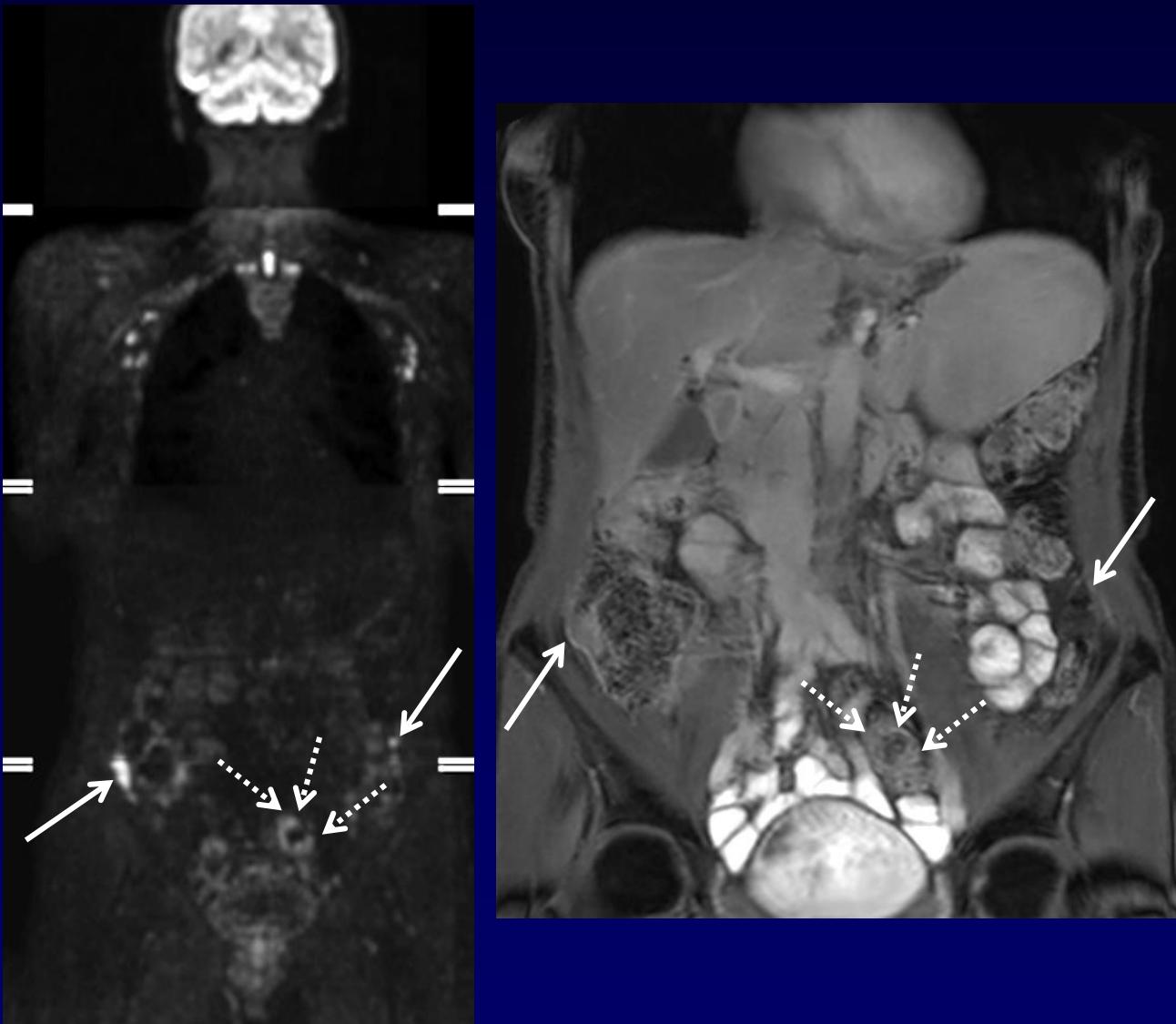


✓ **Left panel:**
diffusion MR
showing pathologic
uptake in left ovary
(arrow) and
infiltration sigmoid
(dash arrows)

✓ **Right panel:**
anatomical
correlative MR

Patient Case (5)

Diffusion-Weighted Whole-Body MRI



- ✓ **Left panel:** diffusion MR showing tumor in both paracolic gutters (arrows) and infiltration sigmoid (dashed arrows)
- ✓ **Right panel:** T2 Anatomical correlate at contrast MRI

Patient Case (6)

Diffusion-Weighted Whole-Body MRI

Further Findings:

- ✓ Peritoneal **carcinomatosis** in the pouch of Douglas and on the pelvic peritoneum, including bladder peritoneum
- ✓ Small (<1cm) metastases in the **omentum**
- ✓ Small nodules on the right **diaphragm**
- ✓ **No pathological lymph nodes**
- ✓ **No tumor in the thorax**

Question 1: What is your preferred management?

- 1. Primary debulking**
- 2. Neoadjuvant chemotherapy**



Question 1: What is your preferred management?

1. Primary debulking
 72.5%
2. Neoadjuvant chemotherapy
 27.5%



Patient Case (7)

Further Steps:

- ✓ The patient underwent a primary debulking with **extraperitoneal hysterectomy + BSO** with en bloc resection of **rectosigmoid** and side-to-end anastomosis, pelvic and paraaortic **lympadenectomy**, omentectomy, peritoneal stripping, **diaphragmatic resection**
- ✓ Macroscopic **no residual tumor**
- ✓ **High-grade serous ovarian carcinoma**

Patient Case (8)

Postoperative Management

- ✓ The patient received 6 courses of 3-weekly paclitaxel-carboplatin + weekly trebananib/placebo followed by maintenance trebananib/placebo in the **ENGOT-ov2/TRINOVA 3 study.**

Patient Case (9)

4 Months After the End of Paclitaxel-Carboplatin

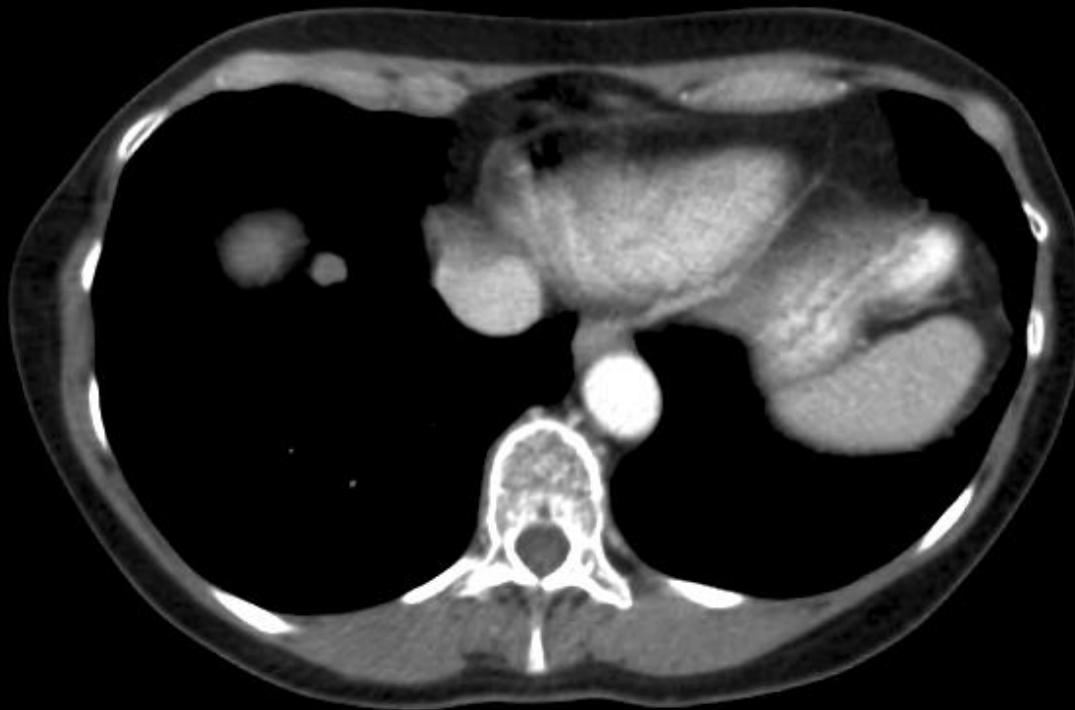
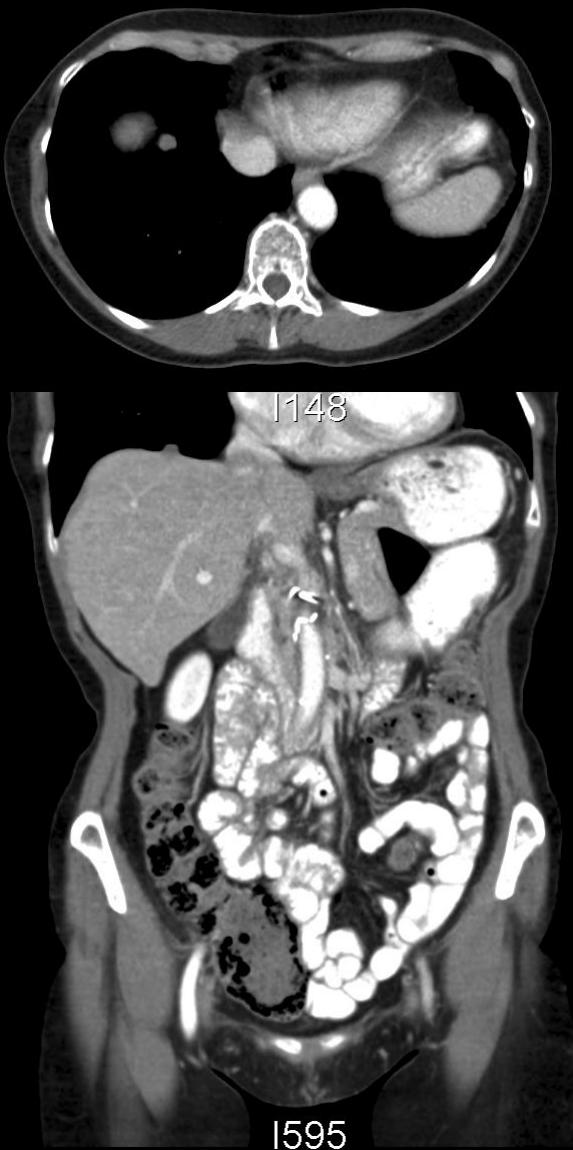
- ✓ The patient has an increasing pain on the right side of the abdomen and the right upper leg, with signs of subobstruction.
- ✓ CA125 increased from normal to 585 KU/L
- ✓ CT thorax-abdomen shows progressive disease intraabdominally

Lesion 1



- Retroperitoneal mass caudal from right kidney, with impression and probable invasion of r. psoas muscle.
- 62.5 mm diameter

Lesion 2



- Pleural implant, 10.9 mm diameter

Question 2: Platin-resistant ovarian cancer - What is your preferred treatment?

- 1. Supportive care**
- 2. Carboplatin weekly**
- 3. Paclitaxel w**
- 4. Paclitaxel w + bevacizumab**
- 5. Pegylated liposomal doxorubicin (PLD)**
- 6. PLD + Bev**
- 7. Topotecan**
- 8. Topotecan + Bev**
- 9. Studies**
- 10. Other**



Question 2: Platin-resistant ovarian cancer - What is your preferred treatment?

1. Supportive care

0.9%

2. Carboplatin weekly

0%

3. Paclitaxel w

2.7%

4. Paclitaxel w + bevacizumab

62.2%

5. Pegylated liposomal doxorubicin (PLD)

13.5%

6. PLD + Bev

10.8%

7. Topotecan

5.4%

8. Topotecan + Bev

0%

9. Studies

4.5%

10. Other

0%



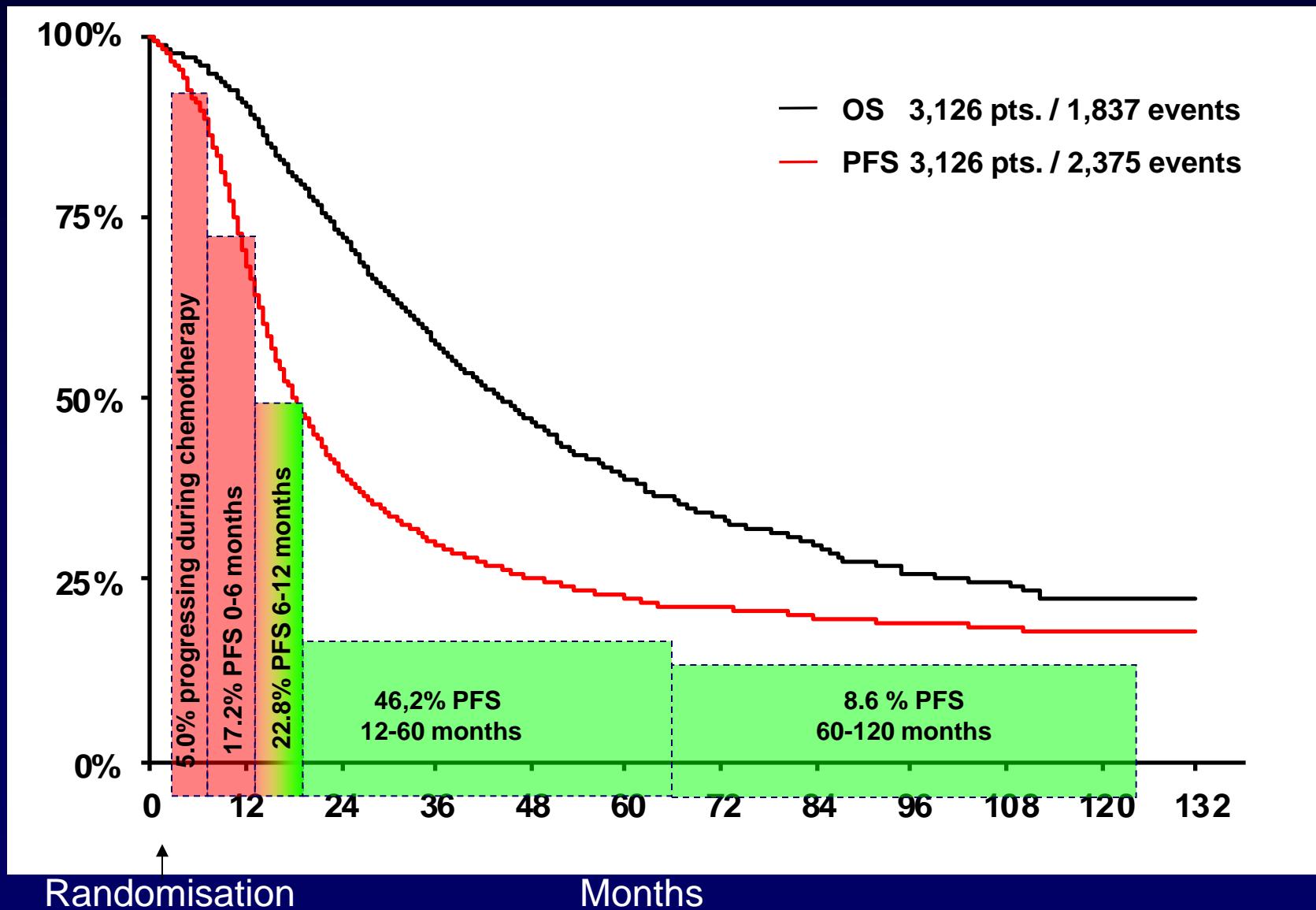
Recurrent Ovarian Cancer: GFIG Definition

**Treatment-Free
Interval (from last dose
of platin)**

Platinum sensitive	>12 mo
Platinum-partially sensitive	6-12 mo
Platinum-resistant	<6 mo
Platinum-refractory	<4 weeks

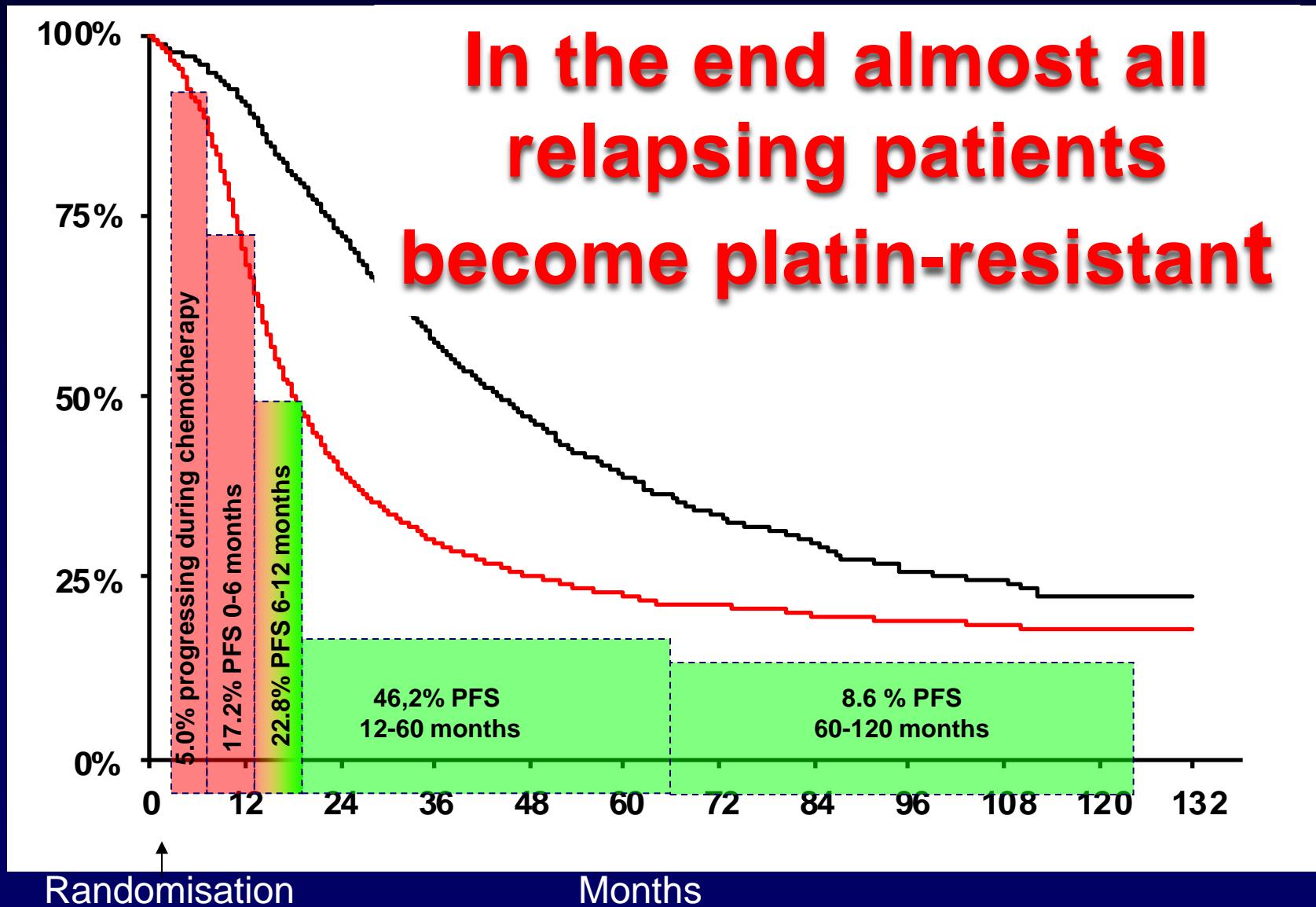
PFS and OS After Start of 1st-Line Chemotherapy

Results of the AGO-OVAR metadatabase (du Bois et al, *Cancer* 2009)



PFS and OS After Start of 1st-Line Chemotherapy

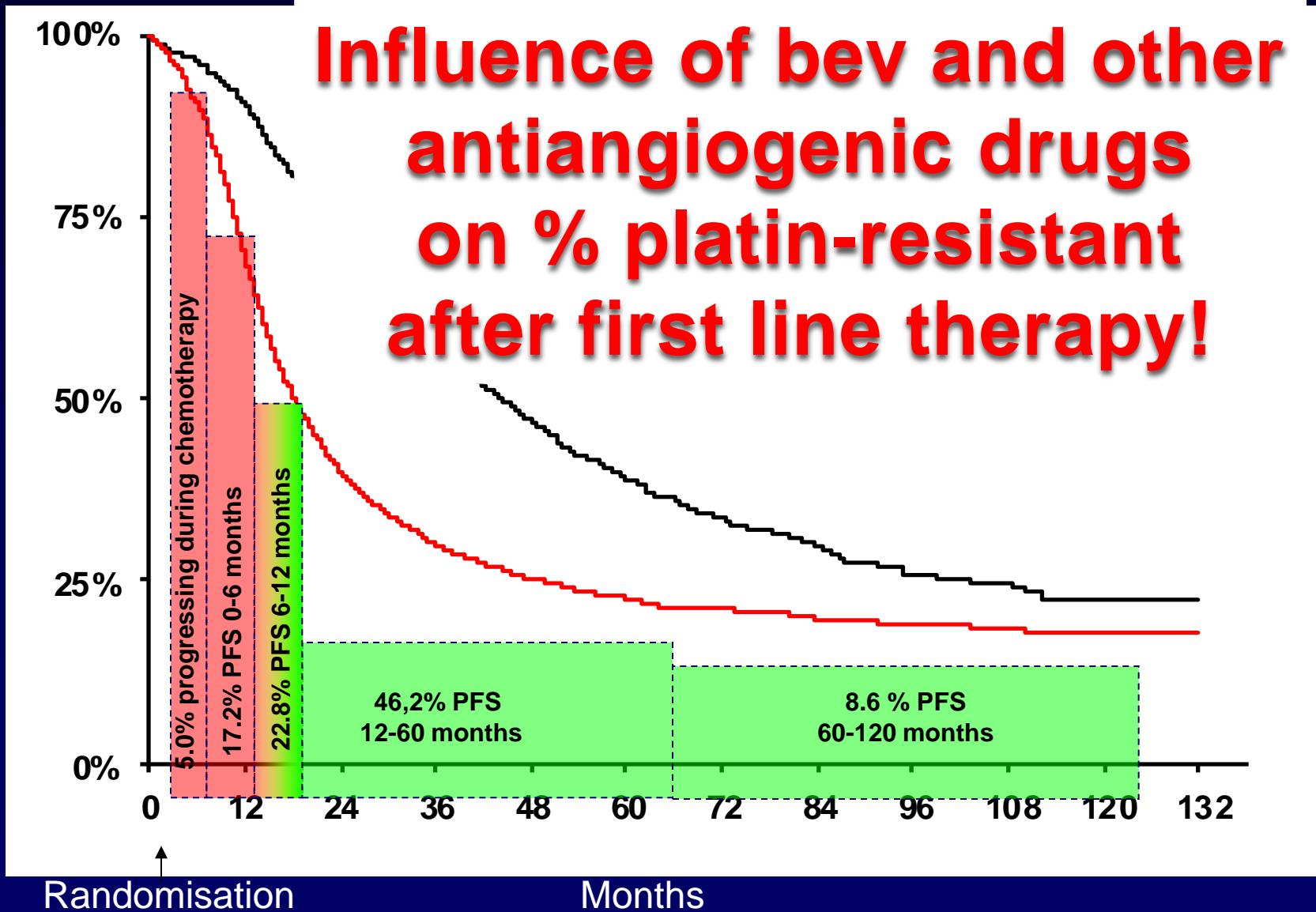
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PFS and OS After Start of 1st-Line Chemotherapy

Results of the AGO-OVAR metadatabase (du Bois et al, Cancer 2009)

Influence of bev and other
antiangiogenic drugs
on % platin-resistant
after first line therapy!



Question 2: Platin-resistant ovarian cancer - What is your preferred treatment?

1. Supportive care
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3. Paclitaxel w
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8. Topotecan + Bev
9. Studies
10. Other



Treatment of Patients With PFI <6 Months



- Expected median OS <12 months
- Main objective:
 - QoL (toxicity)
 - Control of symptoms

65 pts → Treosulfan 7 g/m² iv q21

63 pts → Topotecan 1.5 mg/m² d1-5 q21

R

232 pts → Canfosfamide 1g/m² iv d1 q21

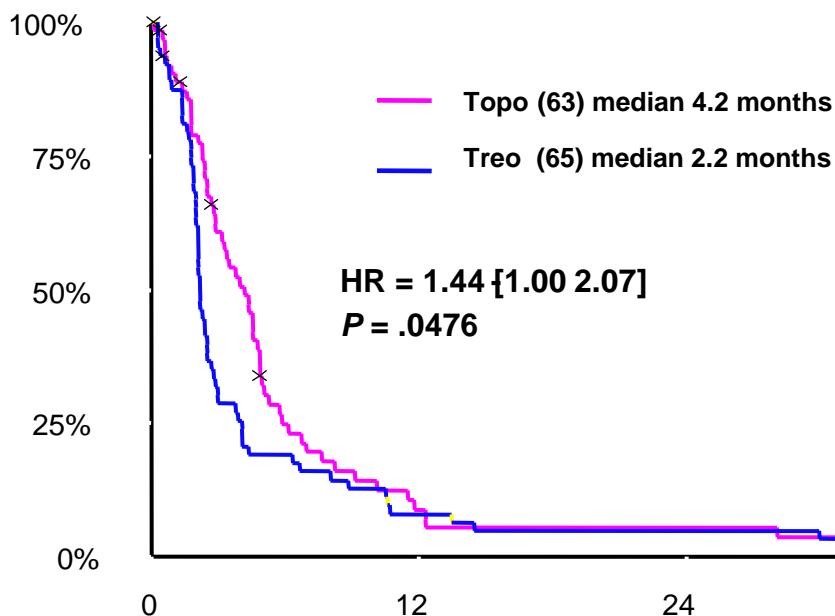
229 pts. → Pegylated liposomal doxorubicin 50 mg/m² iv q28 or Topotecan 1.5mg/m² iv d1-5 q21

R

AGO-OVAR 2.3

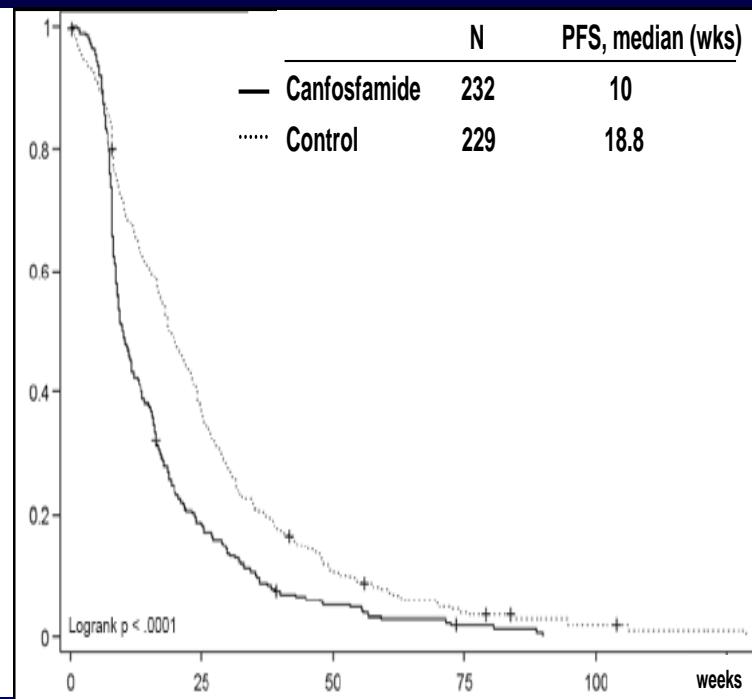
Meier W, et al. Proc Am Soc Clin Oncol. 2003;22: Abstract 1810.

Vergote I. Eur J Can. 2009;45(13):2324-2332.



HR = 1.44 [1.00 2.07]
P = .0476

OR 19.3% (topo) vs 7.0% (P =.0524)



Logrank p < .0001

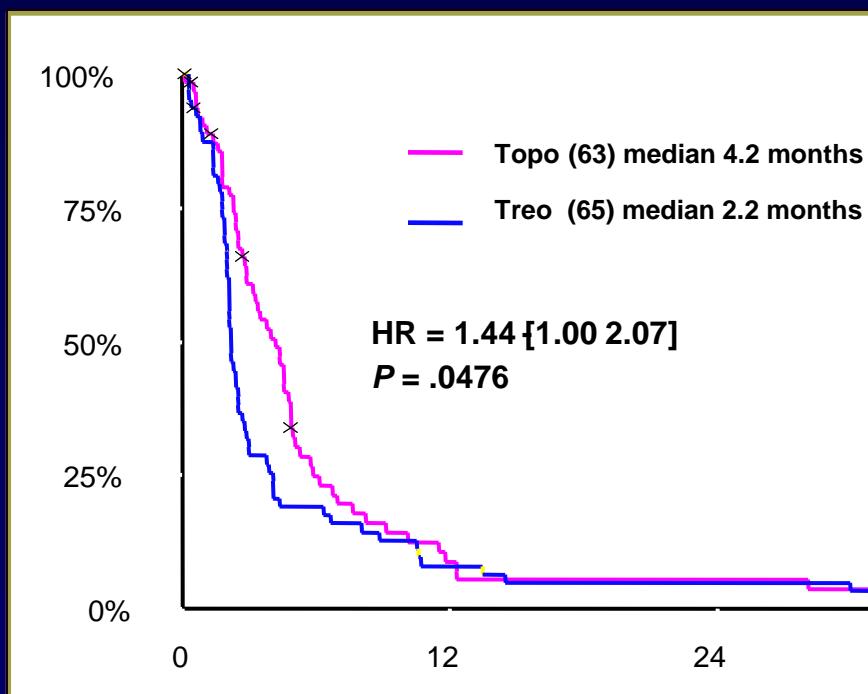


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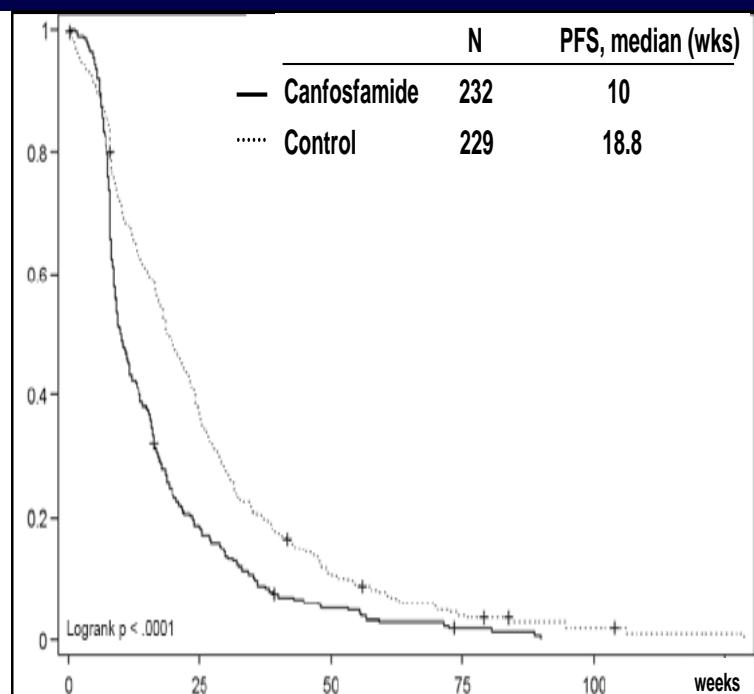
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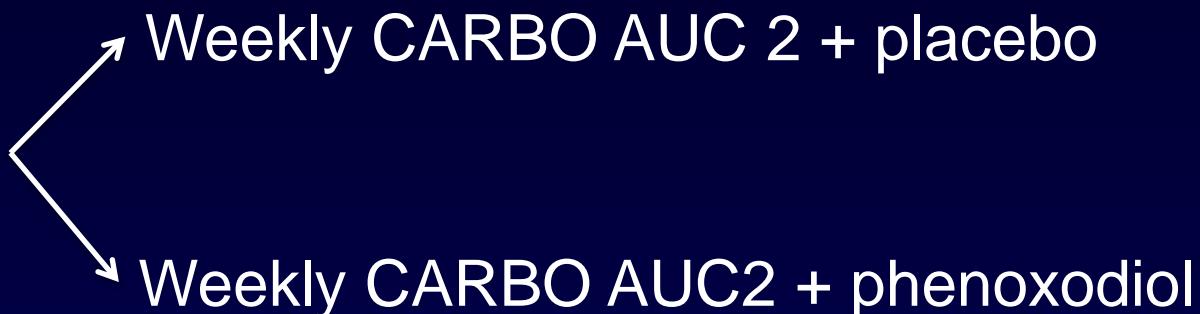
Carboplatin Weekly Monotherapy...

N = 142 PROC

2nd line ≈ 4%

3rd line ≈ 40%

>3rd line ≈ 55%



DRUG	ORR	PFS, weeks	OS, weeks
Weekly carbo AUC 2 + placebo	1%	15.4	38.3
Weekly carbo AUC2 + phenoxodiol	0%	20.1	45.7

Phenoxodiol: biomodulator shown to have chemoresistance-reversing potential

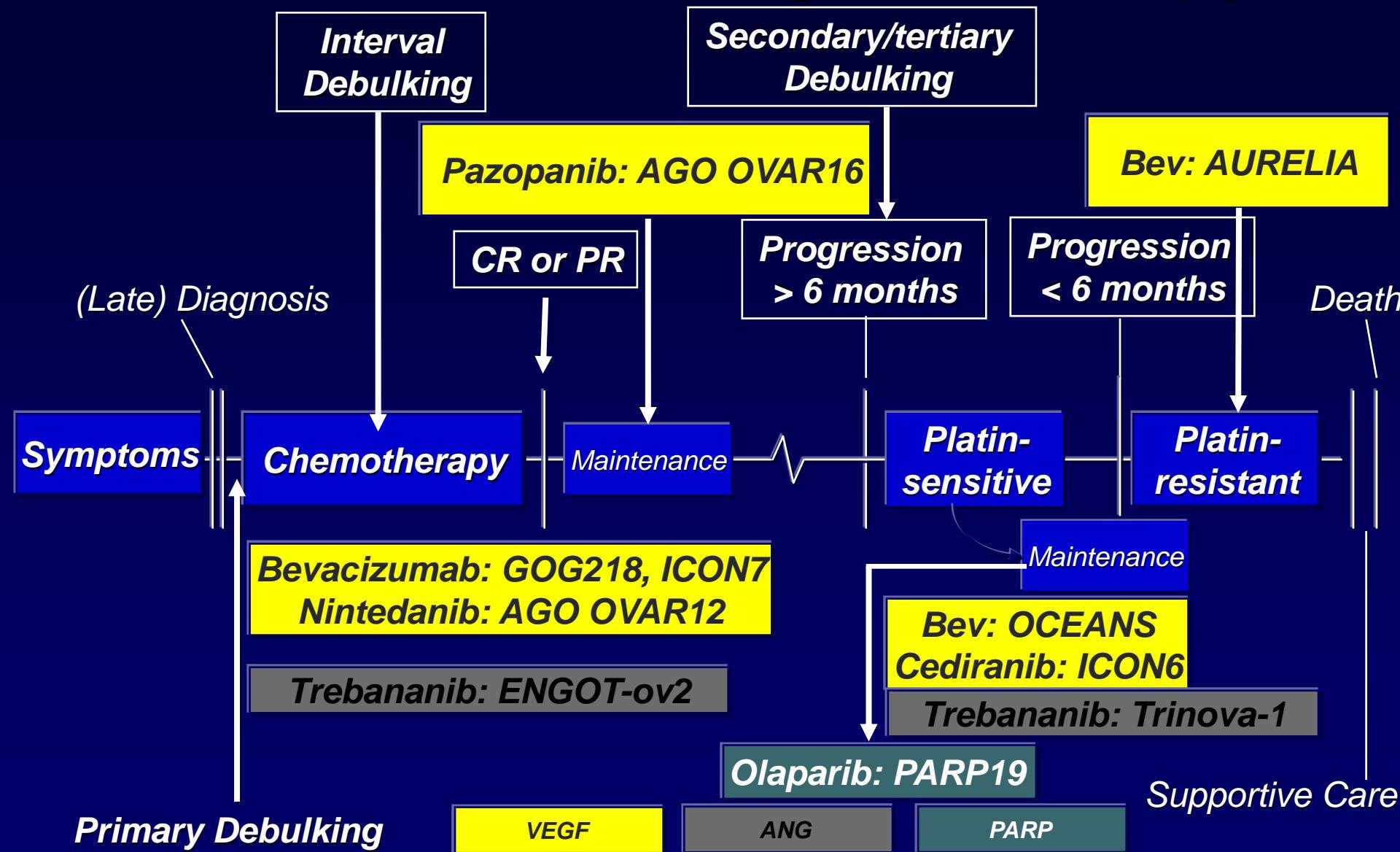
...is no longer active in PROC!!

PROC, platinum-resistant ovarian cancer

Targeted Therapy in OC

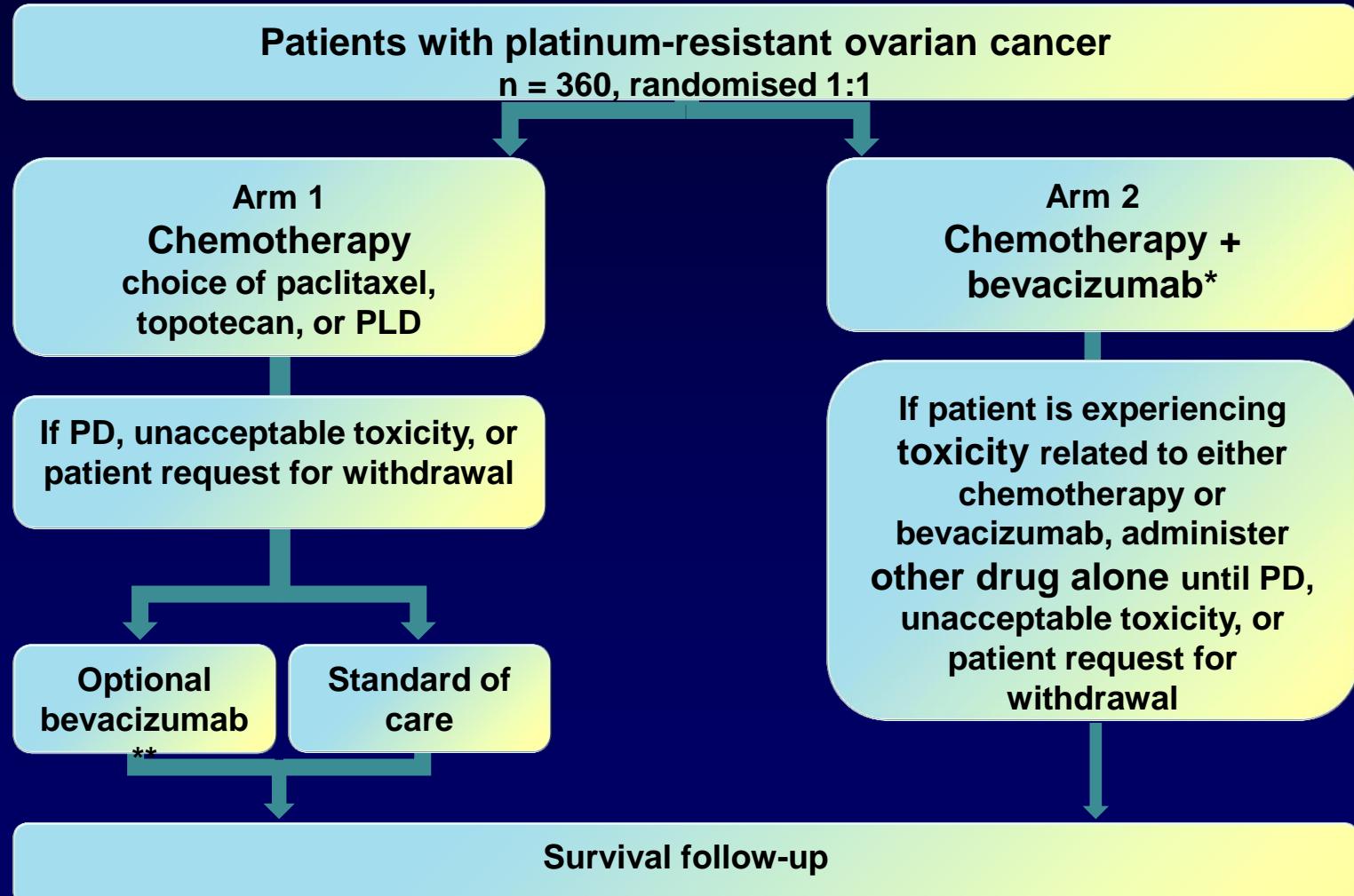
- ✓ Angiogenesis (no validated predictors)
- ✓ PARP inhibitors (high-grade serous – HRD)
- ✓ RAS-MEK pathway (low-grade serous)
- ✓ Folate receptor (all epithelial ov ca)
- ✓ EGFR (erlotinib negative in first line)
- ✓ ErbB3 (eg, pertuzumab...)
- ✓ PI3K/AKT/mTOR (PI3K: clear cell)
- ✓ Selective nuclear export inhibitors (SINE)
- ✓ p53, Aurora (eg, alisertib...)
- ✓ Immuno eg, anti PD-1/PD-L1)
- ✓ Targetting multiple pathways,
- ✓ ADC

Ovarian Carcinoma: Randomized Phase II-III Trials With Targeted Therapy



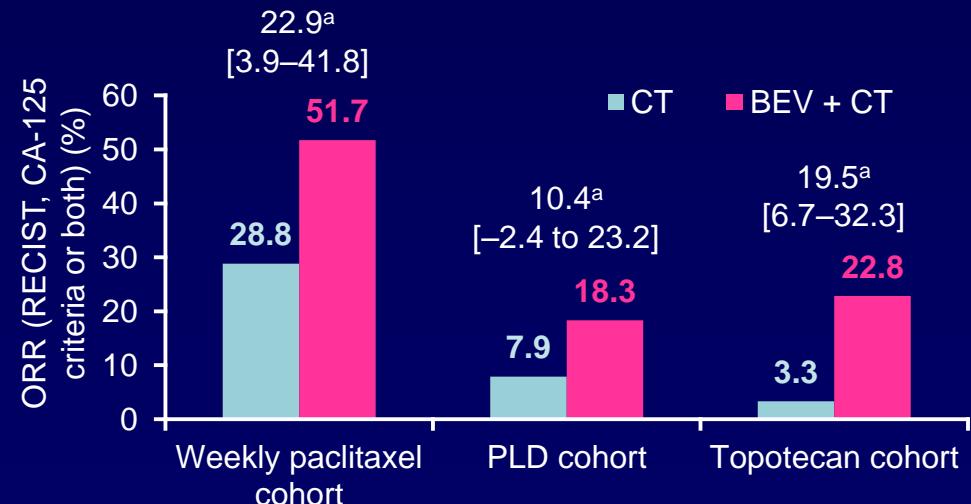
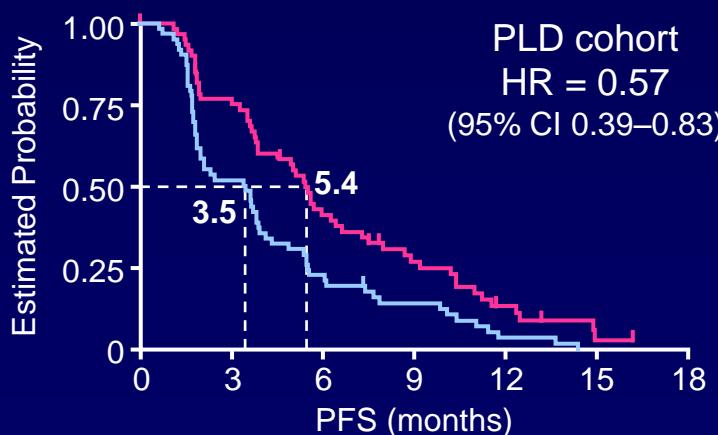
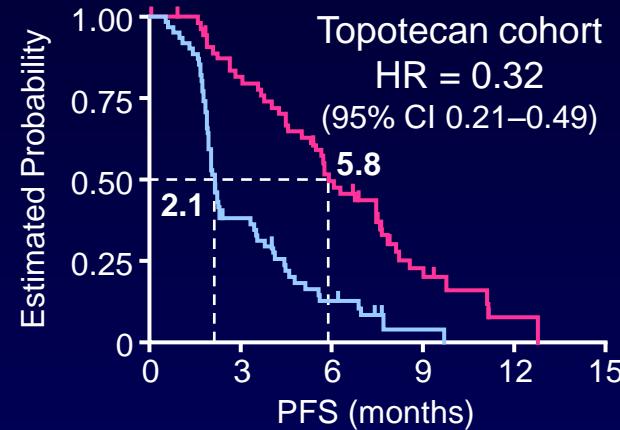
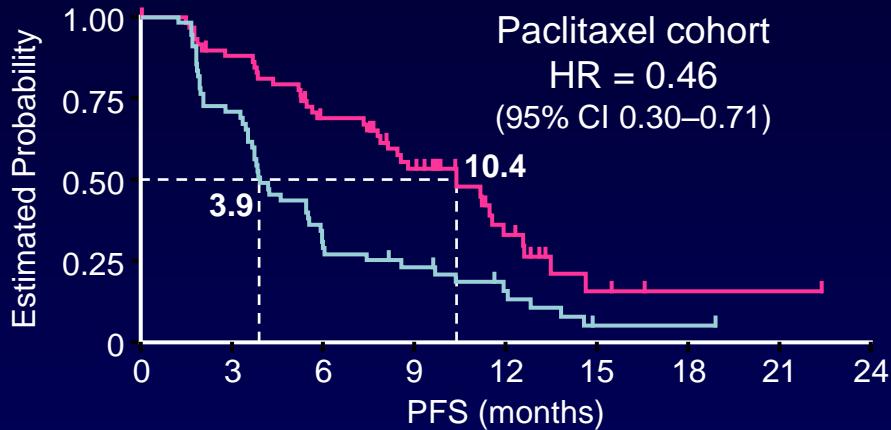


EN GOT-ov3: Gineco Aurelia Bevacuzimab AGO, BGOG, DGOG, MITO, MaNGO, NSGO, GEICO



*10 mg/kg iv q2w (15 mg/kg q3w will be used instead if topotecan is selected and administered at a dose of 1.25 mg/m² on a 1-5/q3w schedule); ** 15 mg/kg i.v. q3w; PLD, Pegylated liposomal doxorubicin; PD, progressive disease

ENGOT-ov3: AURELIA BEV in Relation to Treatment Cohort

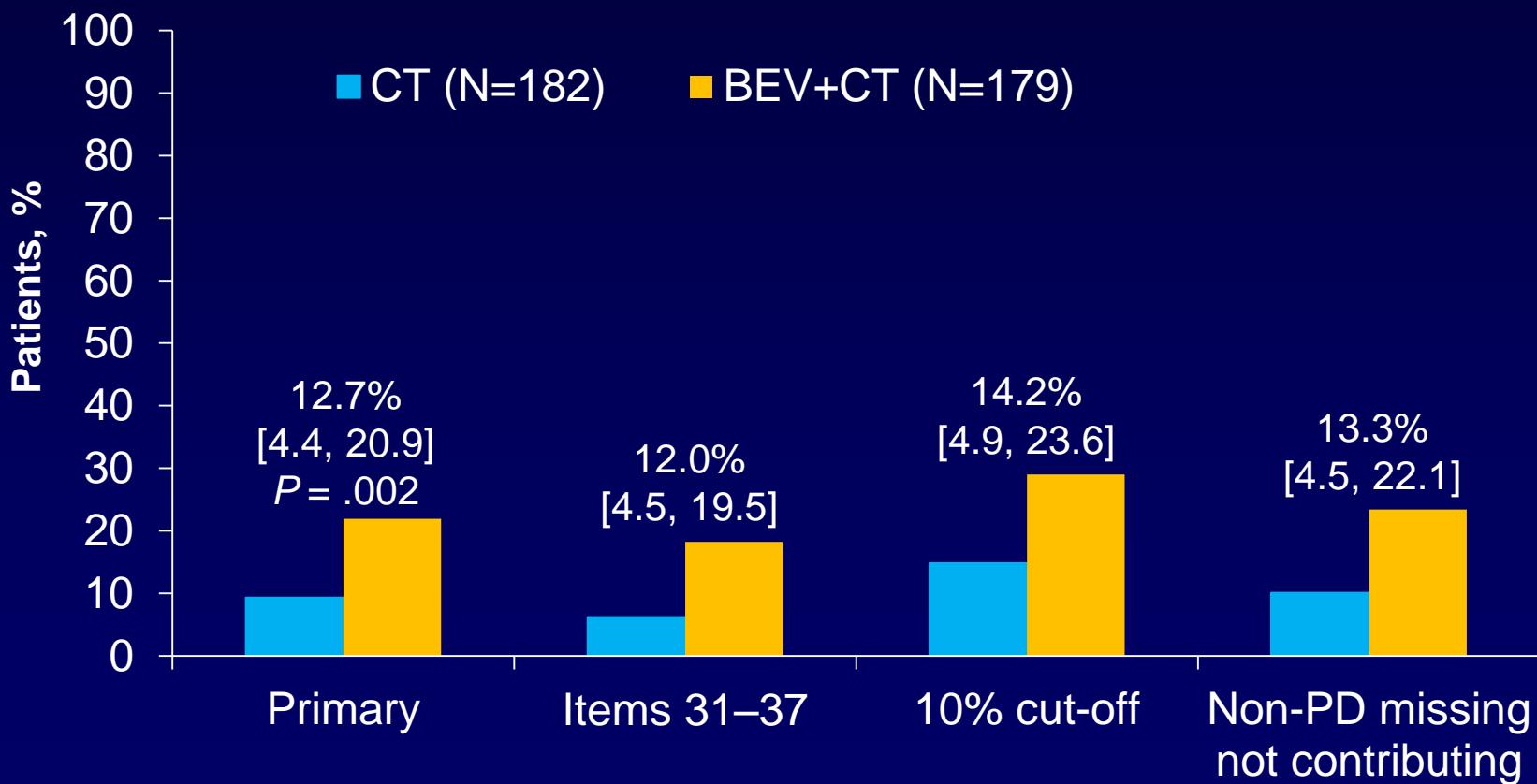


HR = hazard ratio

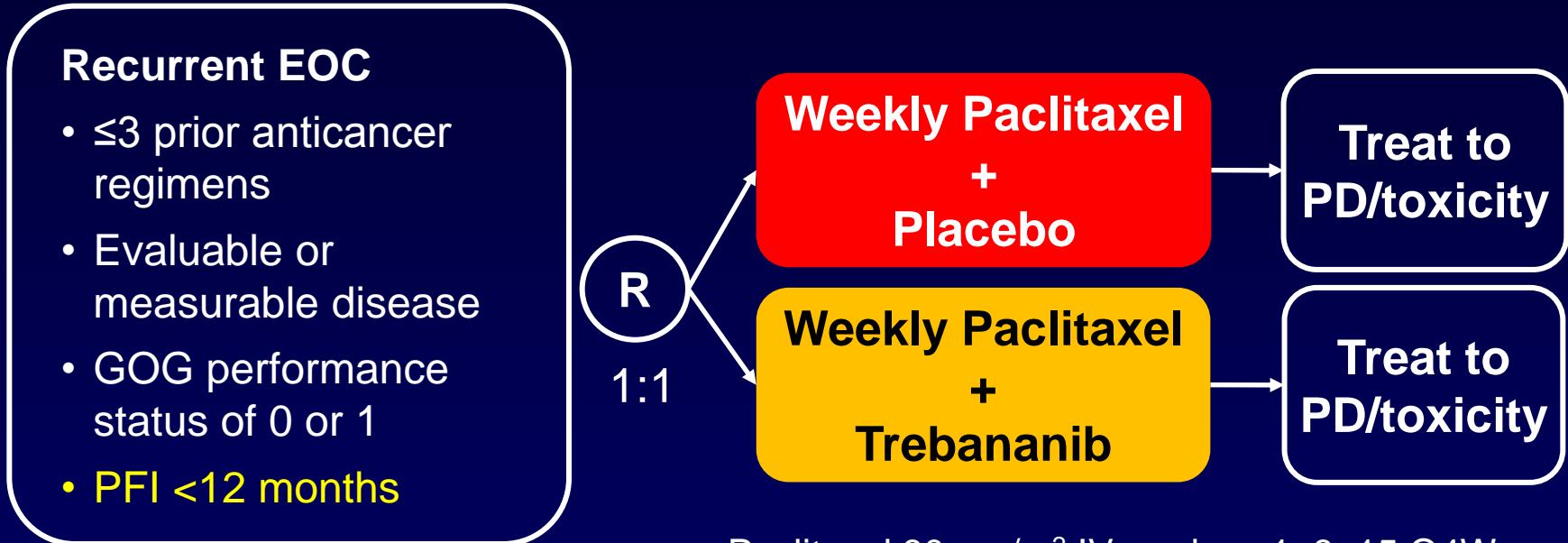
^aDifference in ORR; 95% CI with Hauck–Anderson continuity correction

AURELIA Patient-Reported Outcome Analysis

Primary and sensitivity analyses of the primary hypothesis (15% improvement abdominal/GI symptoms)



TRINOVA-1: Trebananib



Stratification Factors

- Platinum-free interval (PFI) (≤6 vs >6 months)
- Measurable disease (Yes/No)
- Region (North America, Western Europe/Australia, Rest of World)

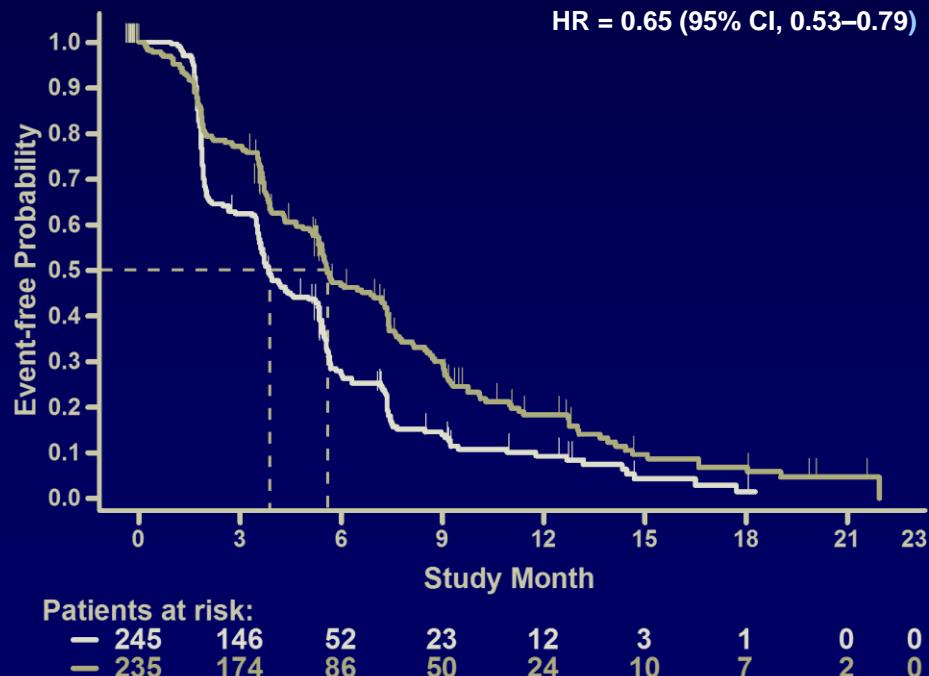
ClinicalTrials.gov Identifier: NCT01204749

EOC, epithelial ovarian cancer including primary peritoneal, or fallopian tube cancer; PD, progressive disease

TRINOVA-1: Progression-Free Survival Platinum-Free Interval (PFI)

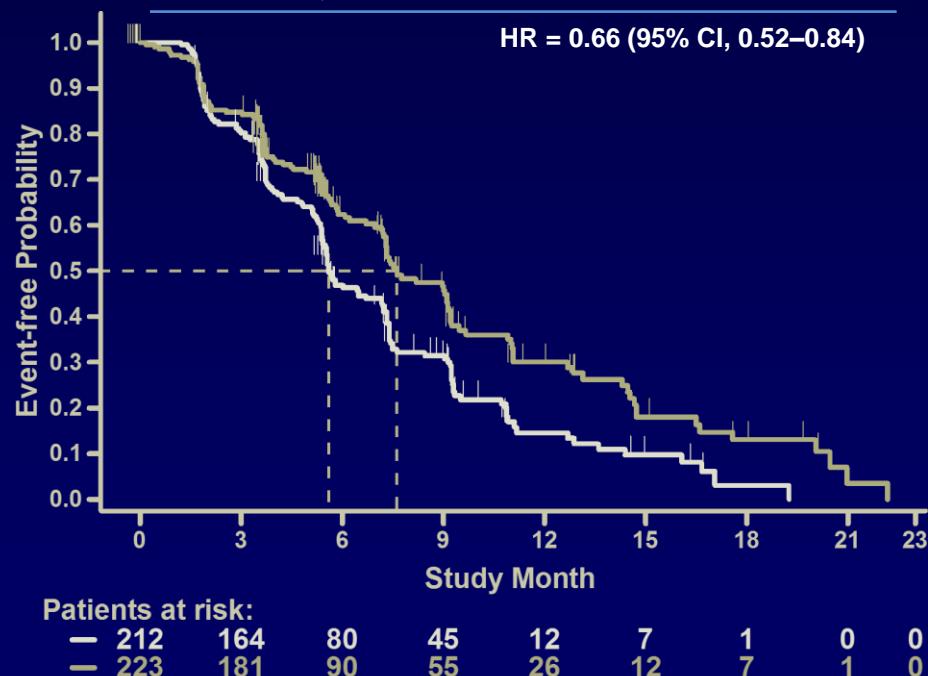
PFI ≤ 6 months	Pac + Placebo (n = 458)	Pac + Trebananib (n = 461)
Events/Patients (%)	203/245 (83)	178/235 (76)
Median PFS, mo	3.8	5.6

HR = 0.65 (95% CI, 0.53–0.79)

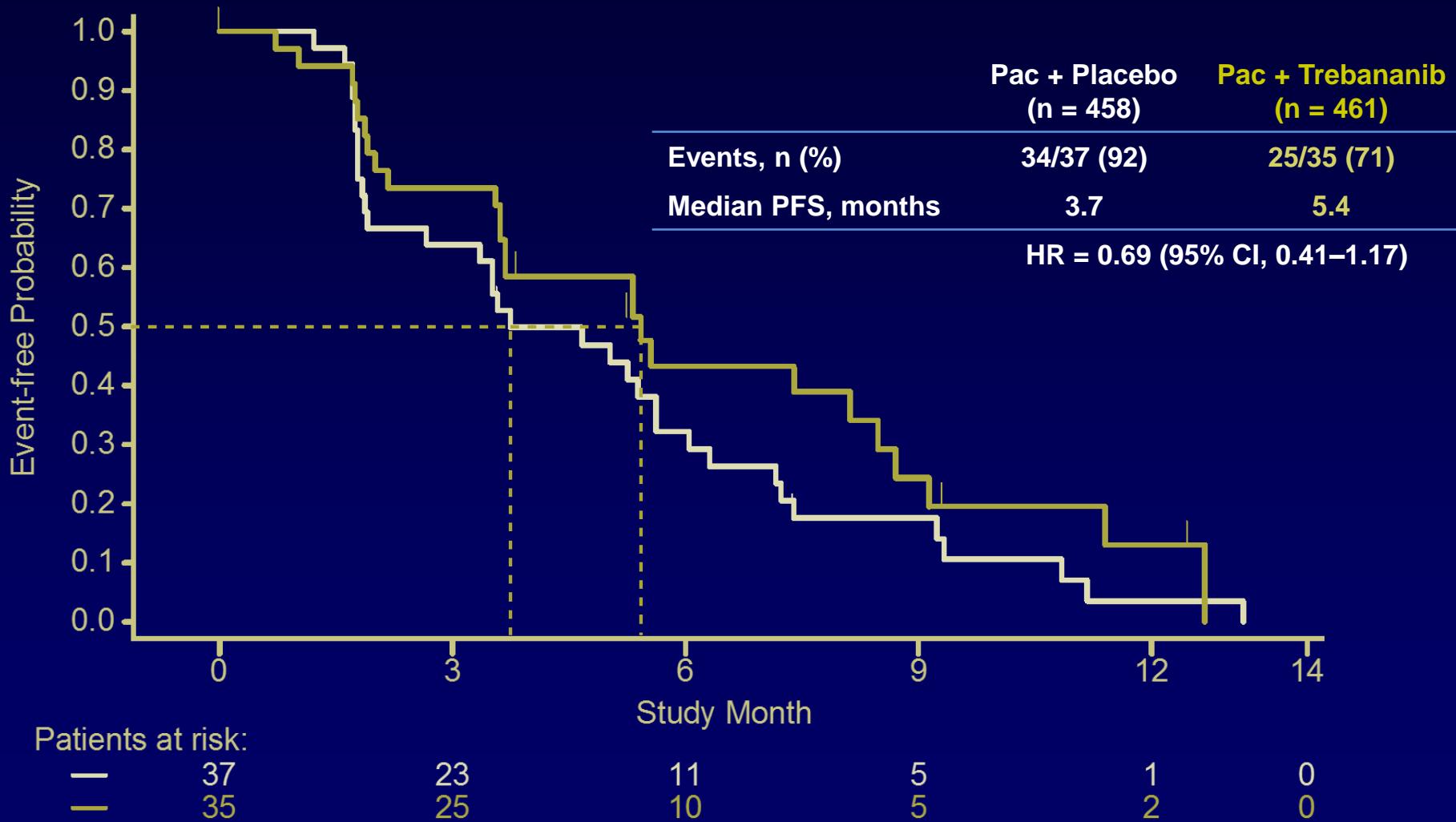


PFI > 6 months	Pac + Placebo (n = 458)	Pac + Trebananib (n = 461)
Events/Patients (%)	157/212 (74)	129/223 (58)
Median PFS, mo	5.6	7.6

HR = 0.66 (95% CI, 0.52–0.84)



TRINOVA-1: Progression-Free Survival Prior Antiangiogenic Therapy



Antiangiogenesis in Ovarian Cancer

What we know:

- **Antiangiogenetic** drugs, targeting VEGF or angiopoetin, are **active** in prolonging PFS and OS in some subgroups of ovarian cancer.

What we do not know:

- **When** should an angiogenesis inhibitor be given (first-line, platin-sensitive, platin-resistant)? Or in all lines? How **long**?
- **Which angiogenesis inhibitor** should be preferred in which group of ovarian cancer patients? And which are **active after progression** on another angiogenesis inhibitor?
- **Validated biomarkers** for efficacy of antiangiogenesis are still needed.
- What is the potential for **combination** of VEGF inhibitors with other classes of antiangiogenetic drugs (eg, ang inhibitors) or other targeted therapies such as PARP, MET,... inhibitors?

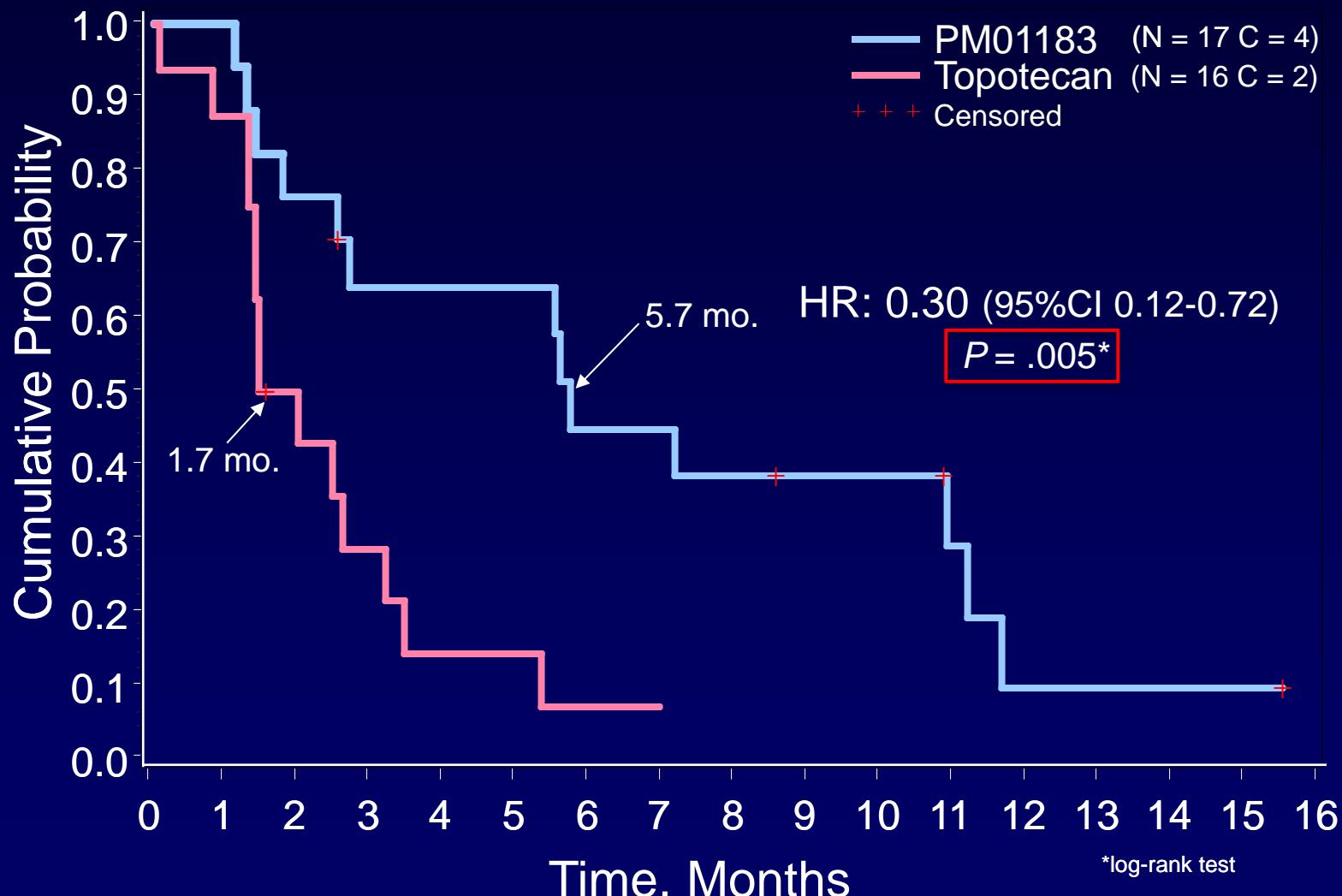
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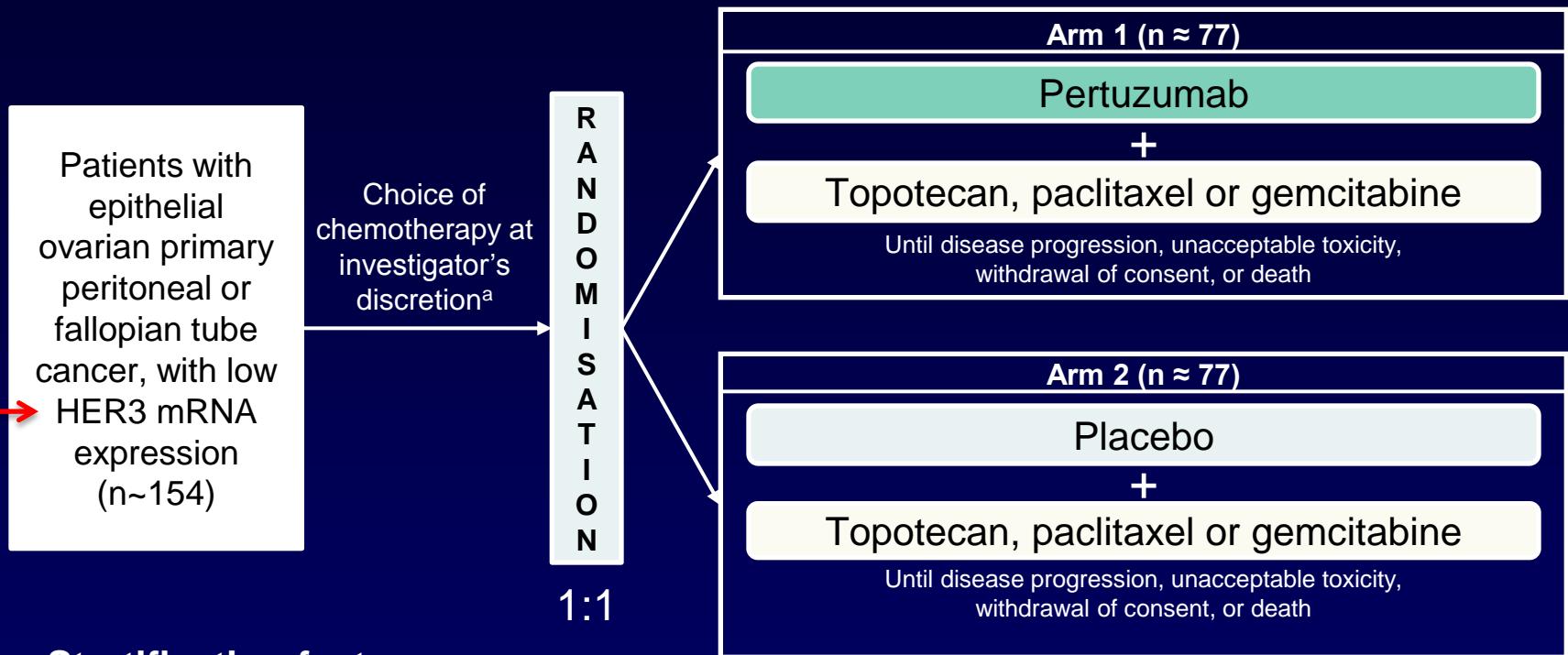


Progression-Free Survival – Lurbinecetin

Platinum Resistant



Pertuzumab: ENGOT-ov14/Penelope



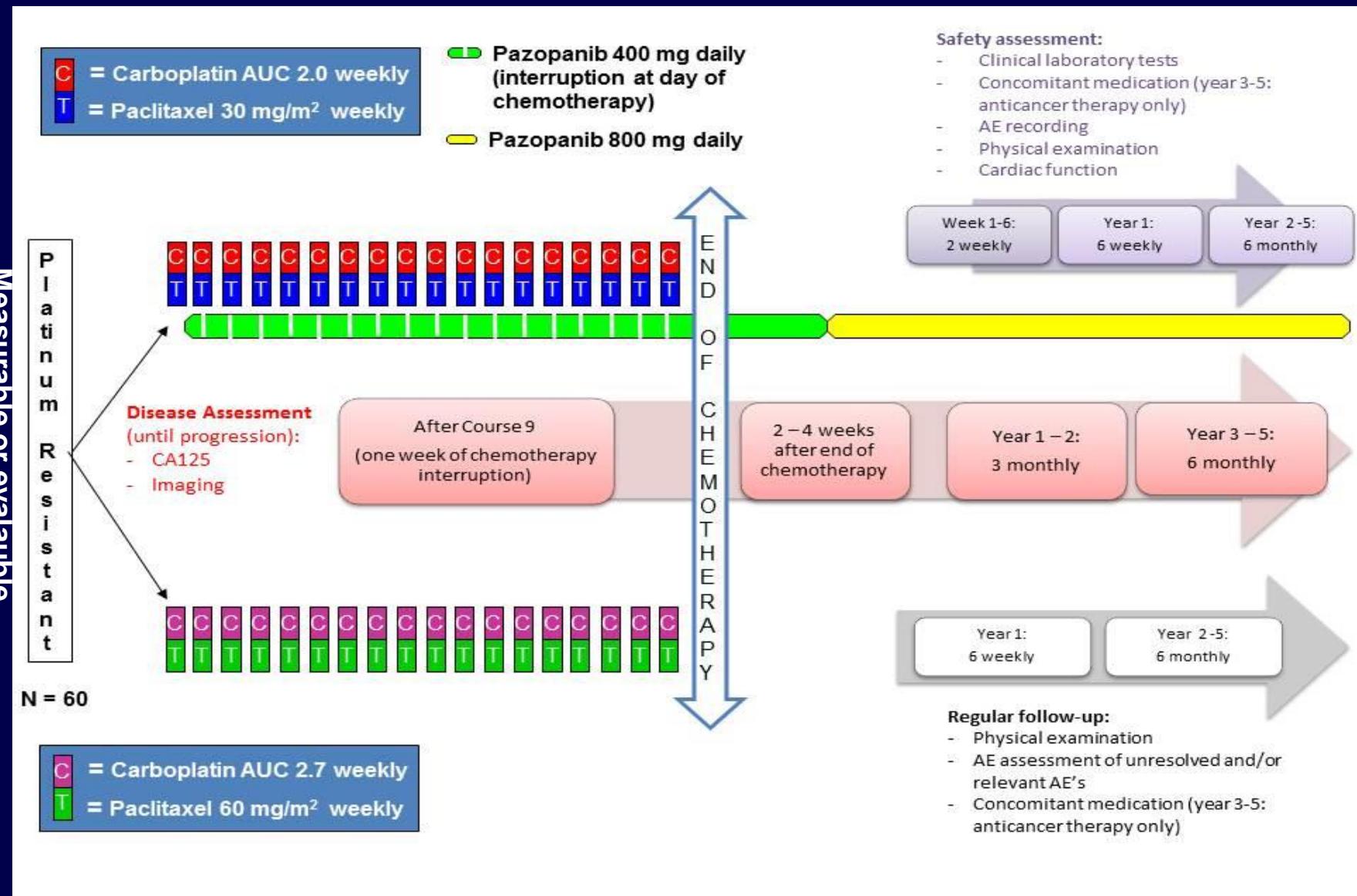
Stratification factors

- Selected chemotherapy cohort (topotecan vs paclitaxel vs gemcitabine)^b
- Previous antiangiogenic therapy (yes vs no)^c
- Treatment-free interval from last cycle of platinum to PD after platinum therapy (<3 vs 3–6 months)

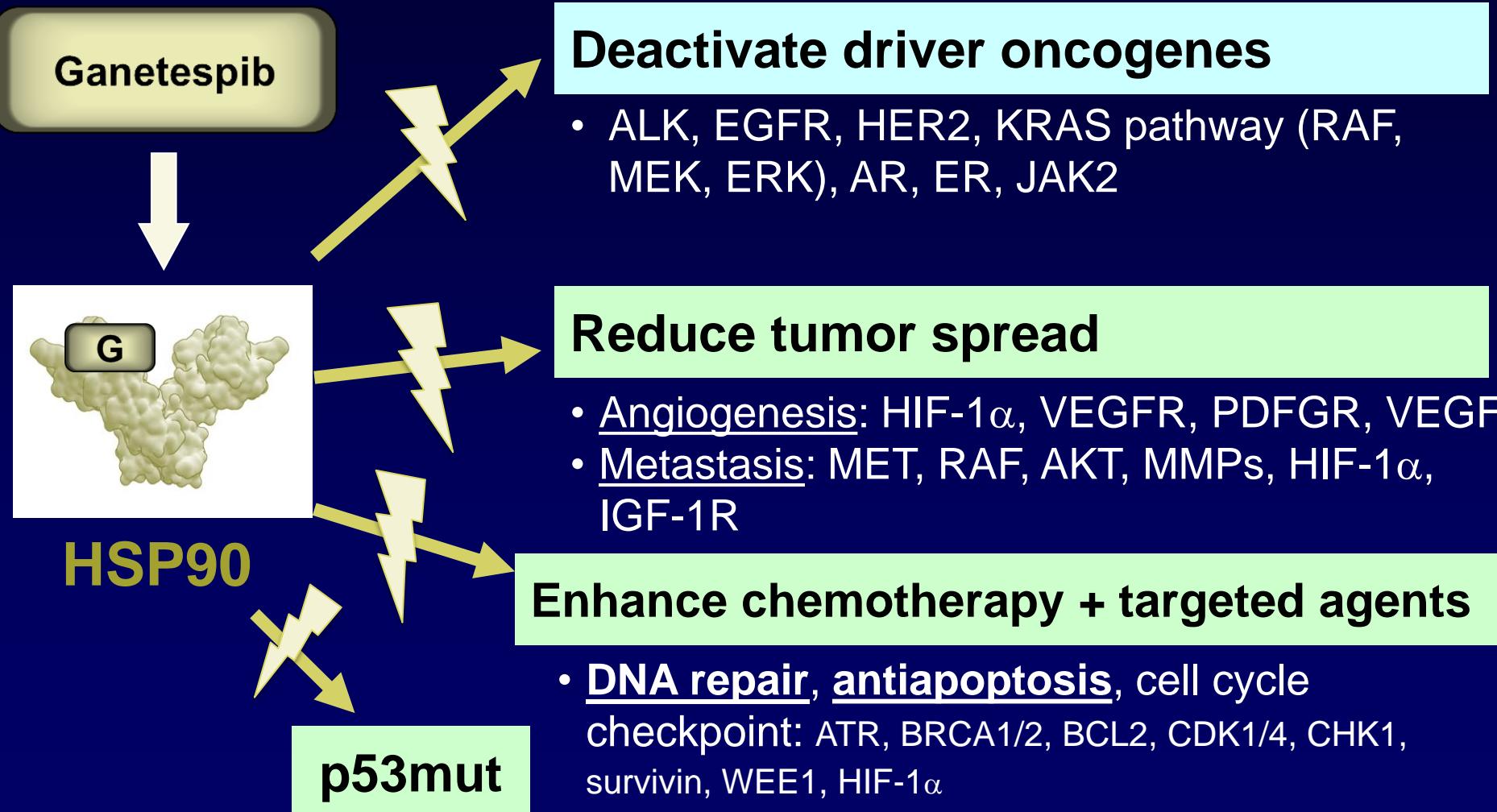
^aTopotecan, paclitaxel, or gemcitabine. ^bTo be amended if not all chemotherapy agents are used in Part 2.

^cIf a patient has previously participated in a blinded trial with an antiangiogenic agent, the patient will be enrolled in the same stratum as patients known to have previously received an antiangiogenic agent.

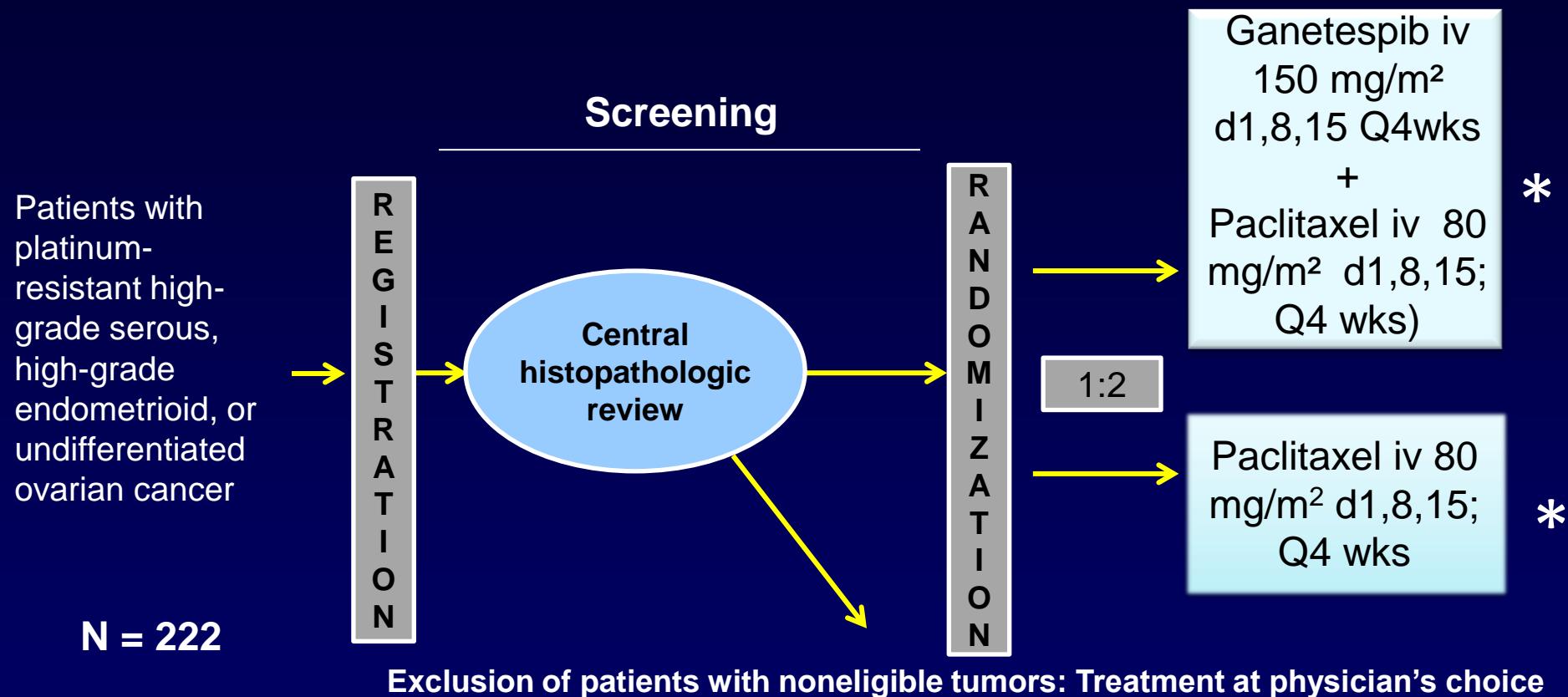
Randomized Phase II EORTC 55092 TC weekly with or without pazopanib in PROC



Single Target, Simultaneous Inhibition of Multiple Oncogenic Pathways : Hsp90 Clients



Randomised, Two-Arm Phase II Study

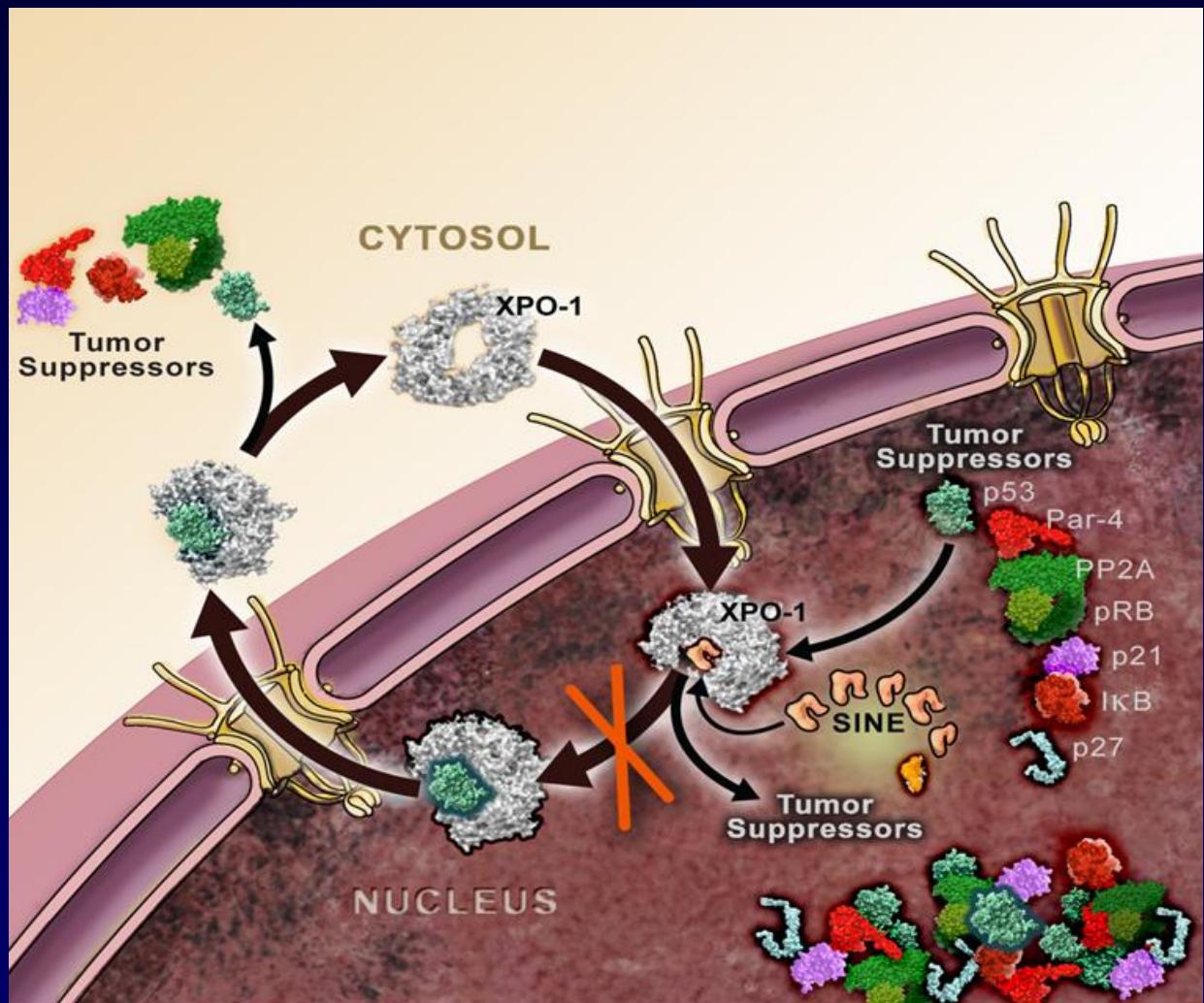


* Till progression. If paclitaxel no longer tolerated or after 6x Pw, maintenance G can be given.



Selective Inhibition of Nuclear Export (SINE): Agents Activating Multiple Tumor-Suppressor Proteins

- Cancer cells can inactivate their tumor-suppressor proteins (TSPs) via the nuclear export mechanism
- CRM1 (Exportin 1) is the nuclear exporter of most TSPs
- Blockade of CRM1 leads to nuclear retention and activation of multiple TSPs
- KPT-330 is an irreversible, oral selective inhibitor of nuclear export against CRM1



Randomized Phase II of DNIB0600A vs PLD in PROC

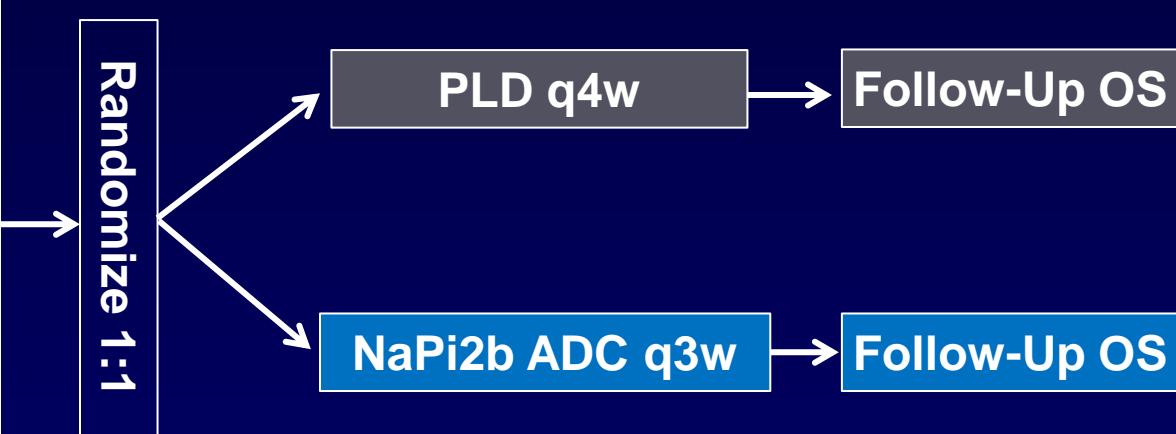
Overview of Trial Design

Enrollment:

- ~92 “all-comer” patients
- ~30 sites

Key eligibility:

- PROC with ≤ 1 cytotoxic therapy in the PROC setting
- Archival tissue confirmed at site



ADC, antibody-drug conjugate

Future Research on Targeted Therapy in Ovarian Cancer

1. Ovarian carcinoma comprises **different tumor types** and should be treated differently according to the **molecular profile**.
2. New trials are currently including only patients with
 1. A specific tumor **type** or
 2. With a **specific mutation or amplification** or
 3. An **ADC** with a target that is present in almost all ovarian cancer cells (**alpha folate receptor, NaPi2b, ...**) or
 4. Drugs attacking one target involved in **many pathways**.

Patient Case (10)

4 Months After the End of Paclitaxel-Carboplatin

- ✓ The patient has an increasing abdominal pain with signs of subobstruction.
- ✓ CA125 increased from normal to 585 KU/L
- ✓ CT thorax-abdomen shows progressive disease intraabdominally.

Patient Case (10)

4 Months After the End of Paclitaxel-Carboplatin

- ✓ The patient received weekly paclitaxel and bevacizumab.

2015

Progress and Controversies in Gynecologic Oncology Conference

