CURRENT STATUS OF TREATING ADVANCED OVARIAN CANCER IN 2017

Bradley J. Monk, MD, FACS, FACOG
Division of Gynecologic Oncology
Arizona Oncology (US Oncology Network)
University of Arizona College of Medicine
Creighton University School of Medicine
at St. Joseph's Hospital-Phoenix Arizona USA

bradley.monk@usoncology.com

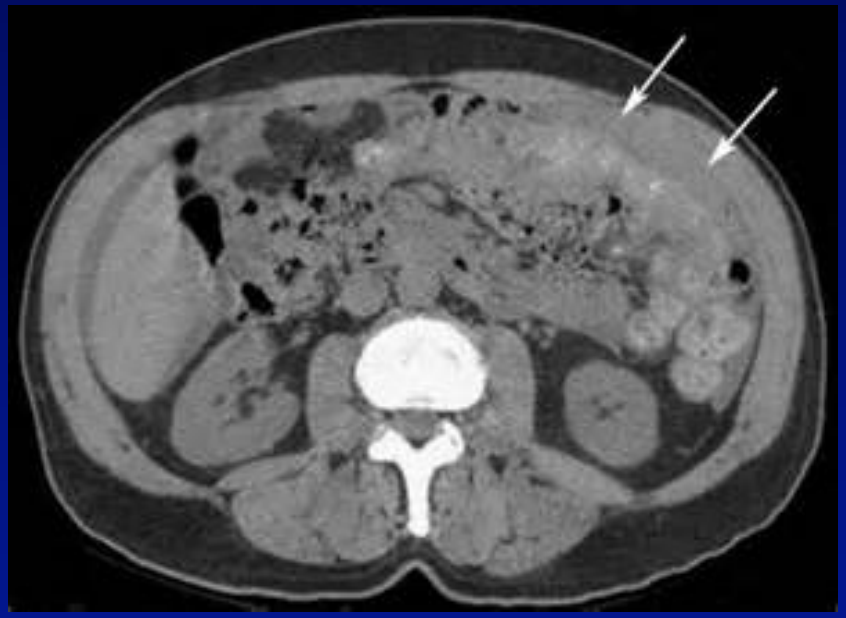
Newly Diagnosed Advanced Disease

- A 69-year-old woman presented to primary care physician with fatigue and persistent abdominal distension
- Medical history and preexisting conditions:
  - Controlled hypertension, BP 130/70 mm Hg with diuretic treatment
- Evaluation:
  - 4 x 5 x 7 cm right pelvic cystic pelvic mass
  - CA-125 1, 600 U/mL
  - Ascites with fluid wave on exam
  - ECOG PS 0
- Referred to gynecologic oncologist

BP=blood pressure.

Newly Diagnosed Advanced Disease

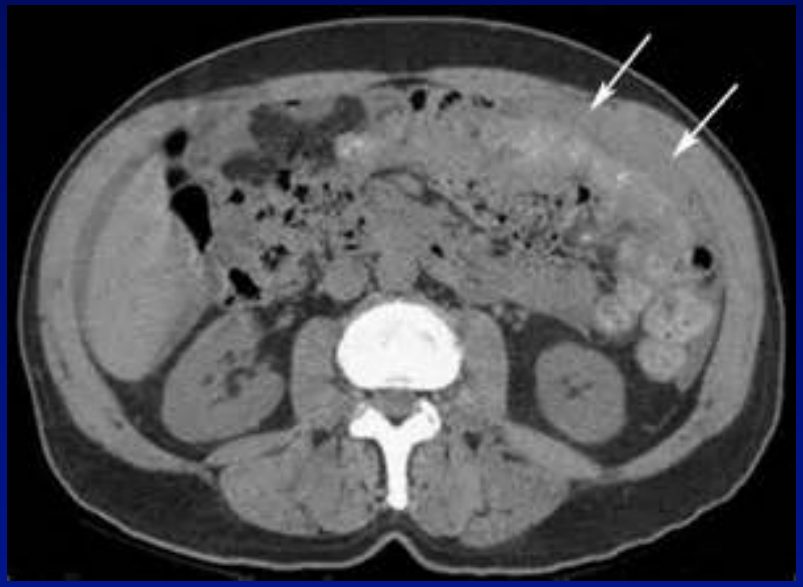
- PET/CT pelvis and abdomen showed right pelvic cystic pelvic mass, ascites, omental cake, but no other peritoneal lesions were seen
- CT assessment suggested she was a surgical candidate



CT=computed tomography; **PET=positron emission tomography.**

Newly Diagnosed Advanced Disease

- PET/CT pelvis and abdomen showed right pelvic cystic pelvic mass, ascites, omental cake, but no other peritoneal lesions were seen
- CT assessment suggested she was a surgical candidate



  - **At surgery, a complete resection was accomplished with no visible residual disease. Findings suggested stage IIIC disease**
  - **Treated with 6 cycles of IV carboplatin every 3 weeks (AUC of 6) and weekly paclitaxel 80 mg/m^2 (18 weeks)**
  - **Normalization of CA-125**

CT=computed tomography; **PET=positron emission tomography.**

Platinum Sensitive Relapse

- 22 months later, she noted persistent bloating and loss of appetite. Her CA-125 level had increased to 330 U/mL
- CT scan demonstrated peritoneal carcinomatosis
- ECOG PS=1; no residual toxicity from prior treatment
- Diagnosis: platinum-sensitive recurrent ovarian cancer

Platinum Sensitive Relapse

- The patient was treated with bevacizumab 15 mg/kg IV in combination with carboplatin AUC5 and paclitaxel 175 mg/m^2 every 3 weeks for 6 cycles
- After cycle 2, patient experienced increase in BP: 156/94 mm Hg (grade 2 hypertension)
- Continued diuretic and added ACE inhibitor
- At follow-up, BP was controlled (126/80 mm Hg)
- Patient continued bevacizumab + carboplatin + paclitaxel
- Continued antihypertensive therapy and BP monitoring

ACE=angiotensin-converting enzyme.

CURRENT STATUS OF TREATING ADVANCED OVARIAN CANCER IN 2017

Bradley J. Monk, MD, FACS, FACOG
Division of Gynecologic Oncology
Arizona Oncology (US Oncology Network)
University of Arizona College of Medicine
Creighton University School of Medicine
at St. Joseph's Hospital-Phoenix Arizona USA

bradley.monk@usoncology.com

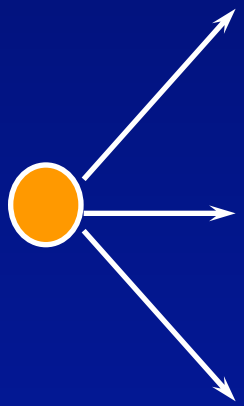
VERBAL DISCLOSURE

- My institution has received grants for me from Amgen, Genentech, Eli Lilly, Array, TESARO Inc., Morphotek, and Janssen/Johnson & Johnson.
- I have received honoraria for speakers' bureaus from Genentech, Roche, AstraZeneca, Myriad, and Janssen/Johnson & Johnson.
- I have received honoraria for my consulting with Merck, TESARO Inc., Gradalis, Advaxis, Amgen, Bayer, Insys, Clovis, Mateon (formally OxiGENE), Roche, Genentech, AstraZeneca, Pfizer, and PPD.
- I agree that the content of this presentation will be well balanced, unbiased, and evidence-based. Opinions that are not supported by evidence or are supported by limited or preliminary evidence will be so identified.

GOG-0252:

Stage II/III Disease: Small Volume Residual

- Epithelial Ovarian Cancer
- Optimal Stage III
- No prior therapy



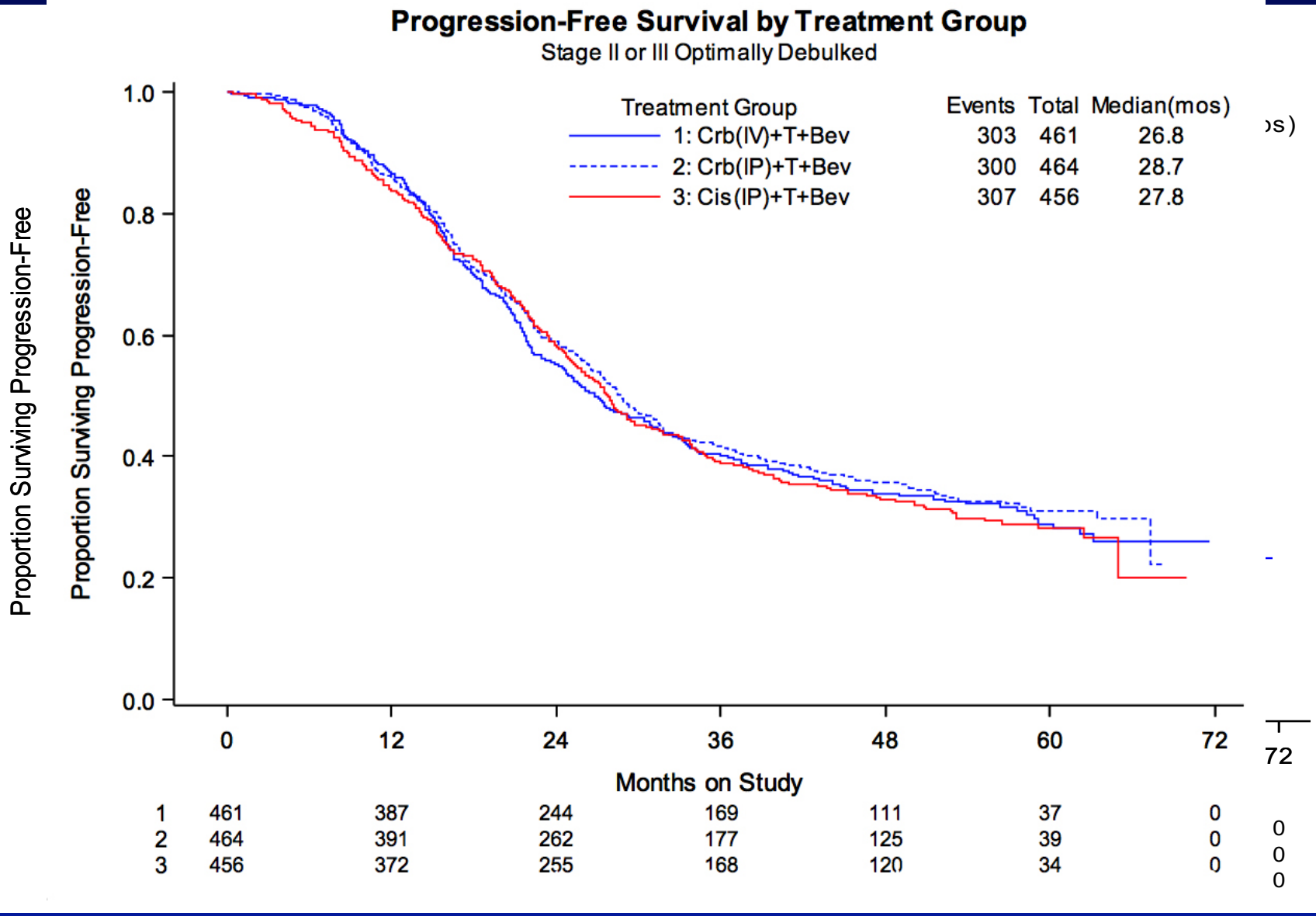
I	Carboplatin AUC=6 **(IV)** Paclitaxel 80 mg/m^2 (d1, 8, 15 3h) Bevacizumab (C2+C22) x 21 days
II	Carboplatin AUC=6 **(IP)** Paclitaxel 80 mg/m^2 (d1, 8, 15 3h) Bevacizumab (C2+C22) x 21 days
III	Cisplatin 75 mg/m^2 **(IP** d2**)** Paclitaxel 135 mg/m^2 (d1, 3h) Paclitaxel 60 mg/m^2 (d8, IP) Bevacizumab (C2+C22) x 21 days

- Phase III
- PFS primary endpoint

Open: 27 Jul 2009
Closed: 30 Nov 2011
Accrual: 1100
Study Chair: J Walker

ClinicalTrials.gov Identifier: NCT00951496

GOG-0252: PFS (< 1cm)



Walker J et al Society of Gynecologic Oncology, San Diego CA March 2016

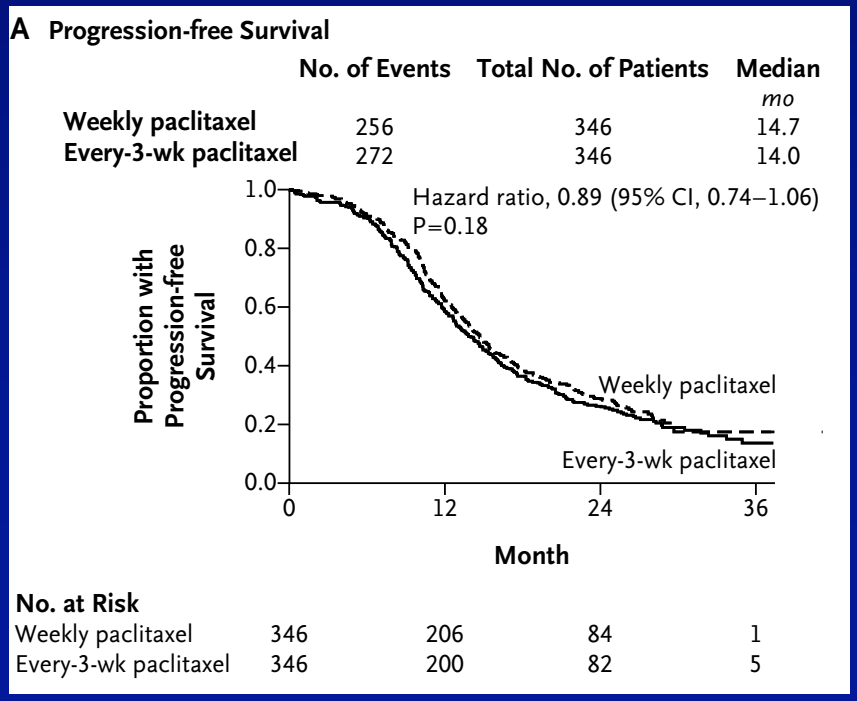
GOG Protocol 252: Toxicity

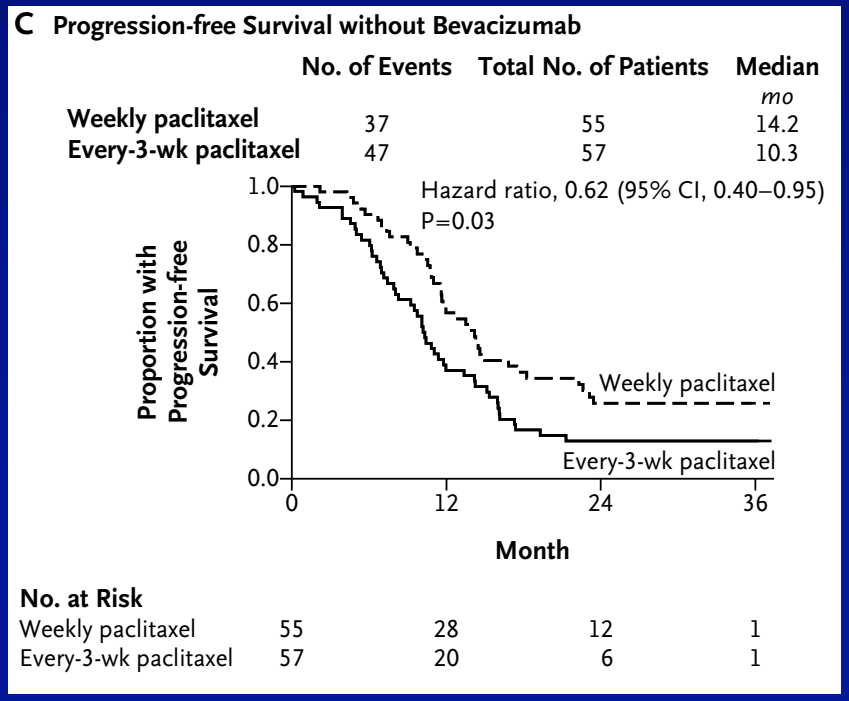
Event	IV Carbo		IP Carbo		IP Cisp	
	G2	≥G3	G2	≥G3	G2	≥G3
Feb/neut		2.5%		2.6%		3.3%
Neut		71%		68%		64%
Platelets		17.6%		15.1%		6.1%
HTN		11.9%		13.8%		20.5%
Thromb		6.3%		8.4%		9.0%
N/V		5.1%		4.7%		11.2%
Fistula		5.3%		3.7%		4.3%
Urine Prot		2.7%		3.1%		1.6%
Sens Neur	24.1	5.7%	22.6	4.5%	21.3	5.5%

Walker J et al Society of Gynecologic Oncology, San Diego CA March 2016

Did bevacizumab compromise GOG Protocol 252?

- Lessons learned from GOG Protocol 262
  - If yes? Integrate bevacizumab into every 3 week IV therapy!
  - If no? Use either every 3 week IV therapy with bevacizumab or dose dense weekly without!





Chan JK et al N Engl J Med. 2016 374:2603-4.

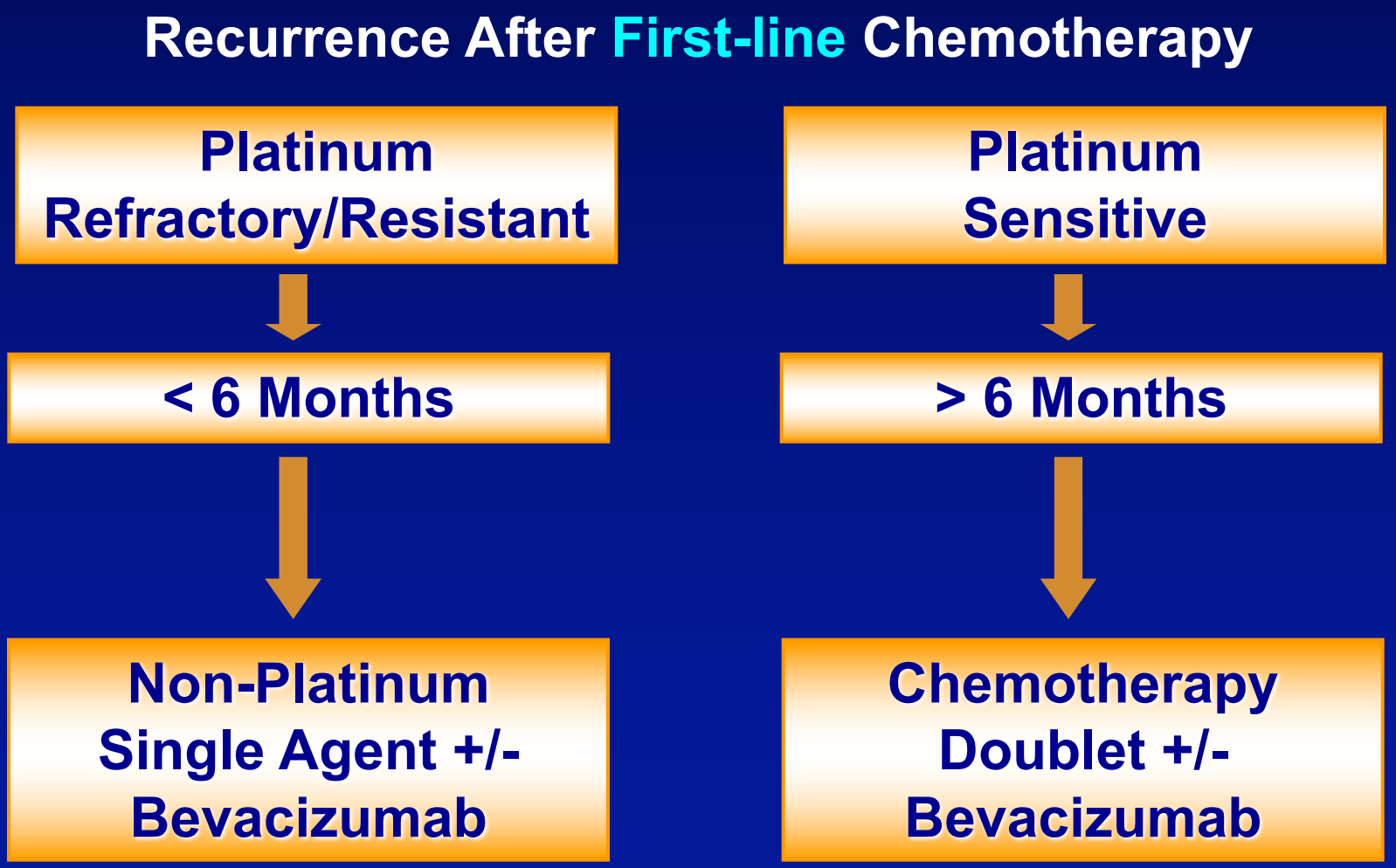
Recurrent Ovarian Cancer: Critical Issues

- What to treat with
  - Single-agent vs combination
  - Platinum vs nonplatinum
  - Conventional vs experimental therapy: Targeted agents
- Sequencing????

The ideal goal

Maximum time without symptoms and without treatment toxicity

The Traditional Treatment Paradigm

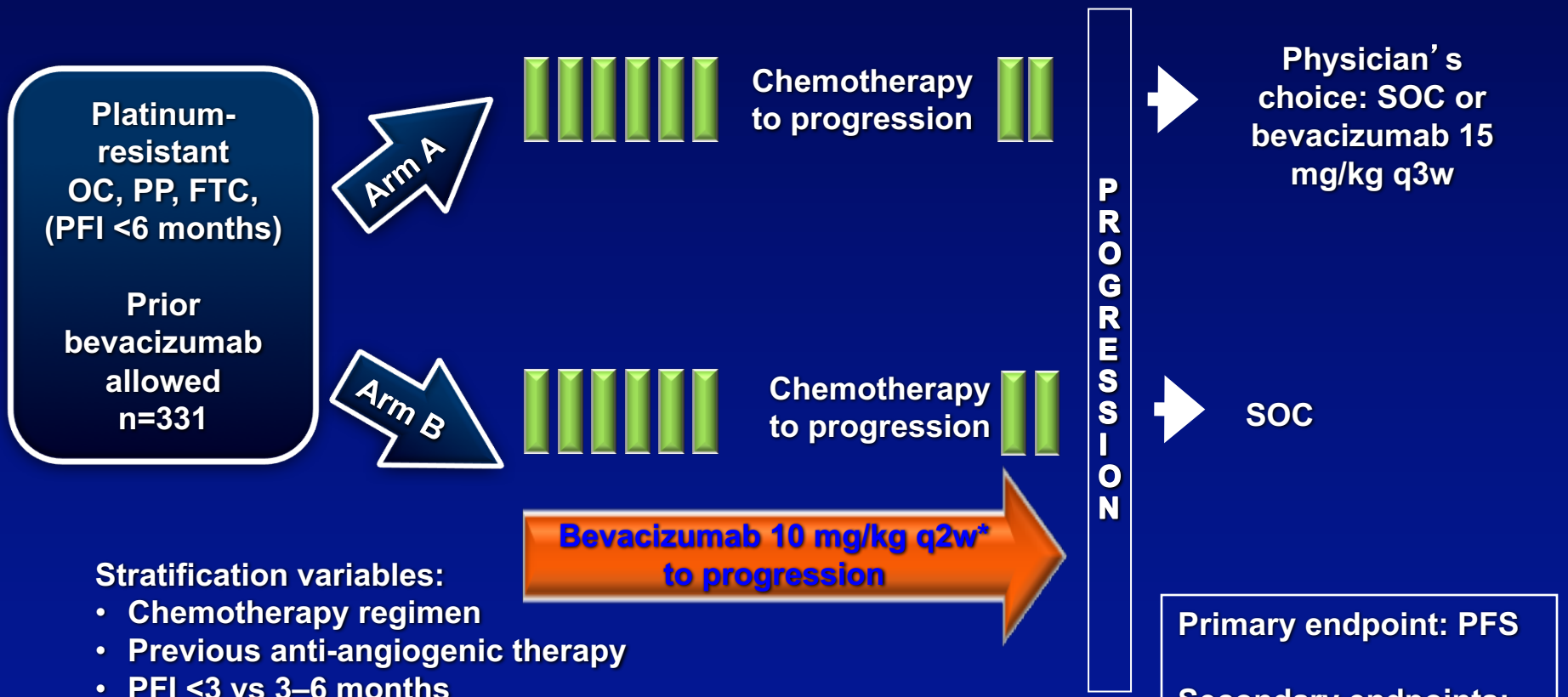


Proposed New Multiplex Classification System for Patients with Recurrent Ovarian Cancer

Characteristic	Subcategory
Histology (H)	1. HGSC/endometrioid
	2. Other, specify
Molecular signature (M)	1. BRCA mutation
	2. BRCA-like
	3. Other, specify
Treatment free interval (TFI)	1. <3 months
	2. 3–12 months
	3. >12 months
Number of prior chemotherapy regimens (N)	1. 3 or less
	2. >3

Alvarez RD, Matulonis UA, Herzog TJ, Coleman RL, Monk BJ, Markman M. Gynecol Oncol. 2016 Apr 8. pii: S0090-8258(16)30063-4.

AURELIA



Stratification variables:
- Chemotherapy regimen
- Previous anti-angiogenic therapy
- PFI <3 vs 3–6 months

Primary endpoint: PFS

Secondary endpoints: ORR, PFI_{bio}, OS, QoL, safety

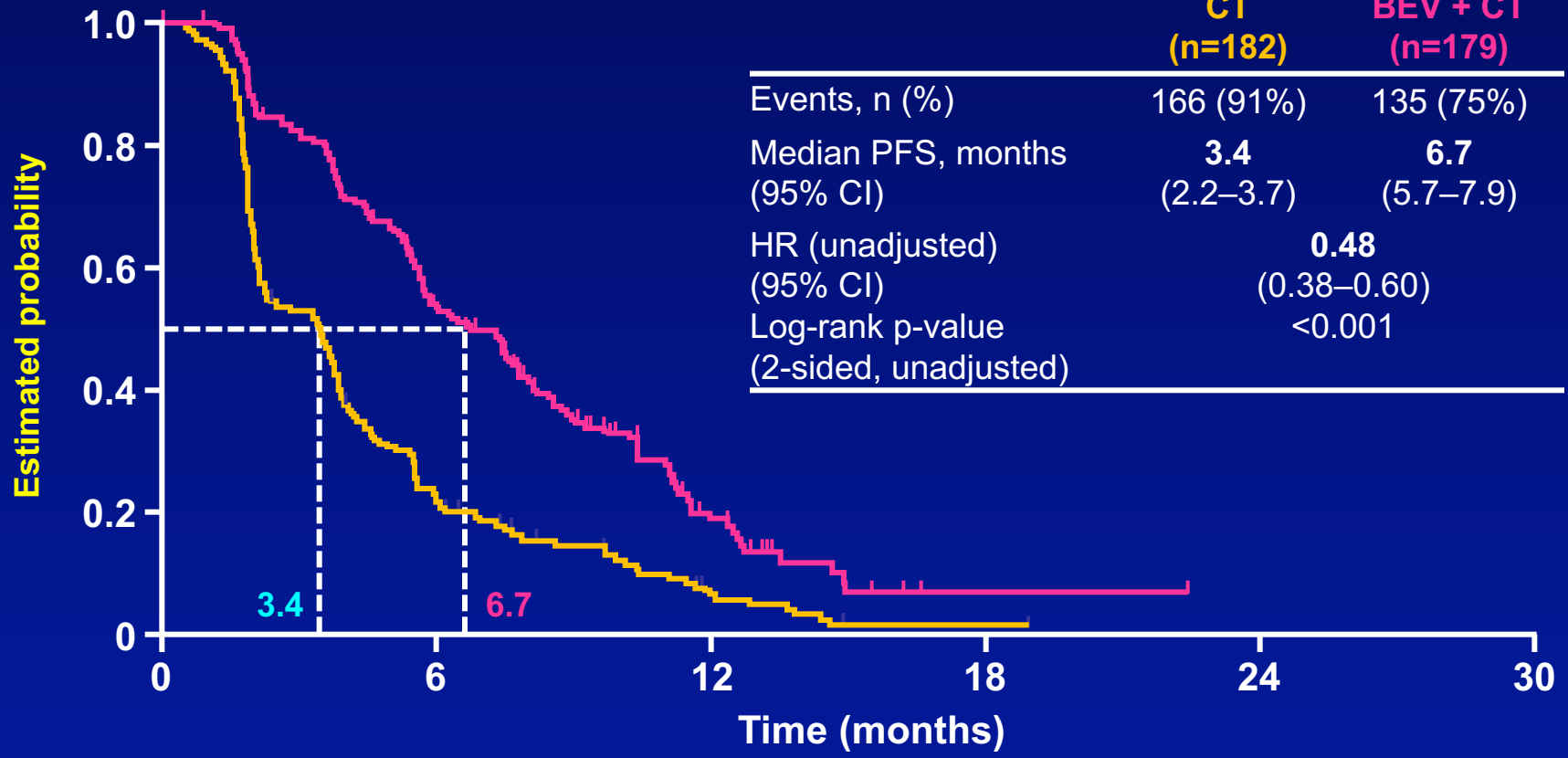
Chemotherapy options (physician's choice):
- Weekly paclitaxel 80 mg/m^2
- Topotecan (4 mg/m^2 d1, 8, 15 OR 1.25 mg/m^2 d1–5 q3w)
- Pegylated liposomal doxorubicin 40 mg/m^2 d1 q4w

*15 mg/kg q3w if combined with topotecan q3w

clinicaltrials.gov identifier: NCT00976911

Pujade-Laurain E et al J Clin Oncol 30, 2012 (suppl; abstr LBA5002^); J Clin Oncol. 2014 May 1;32(13):1302-8

AURELIA: Progression-free survival



	CT (n=182)	BEV + CT (n=179)
Events, n (%)	166 (91%)	135 (75%)
Median PFS, months (95% CI)	**3.4** (2.2–3.7)	**6.7** (5.7–7.9)
HR (unadjusted) (95% CI)	**0.48** (0.38–0.60)	
Log-rank p-value (2-sided, unadjusted)	<0.001	

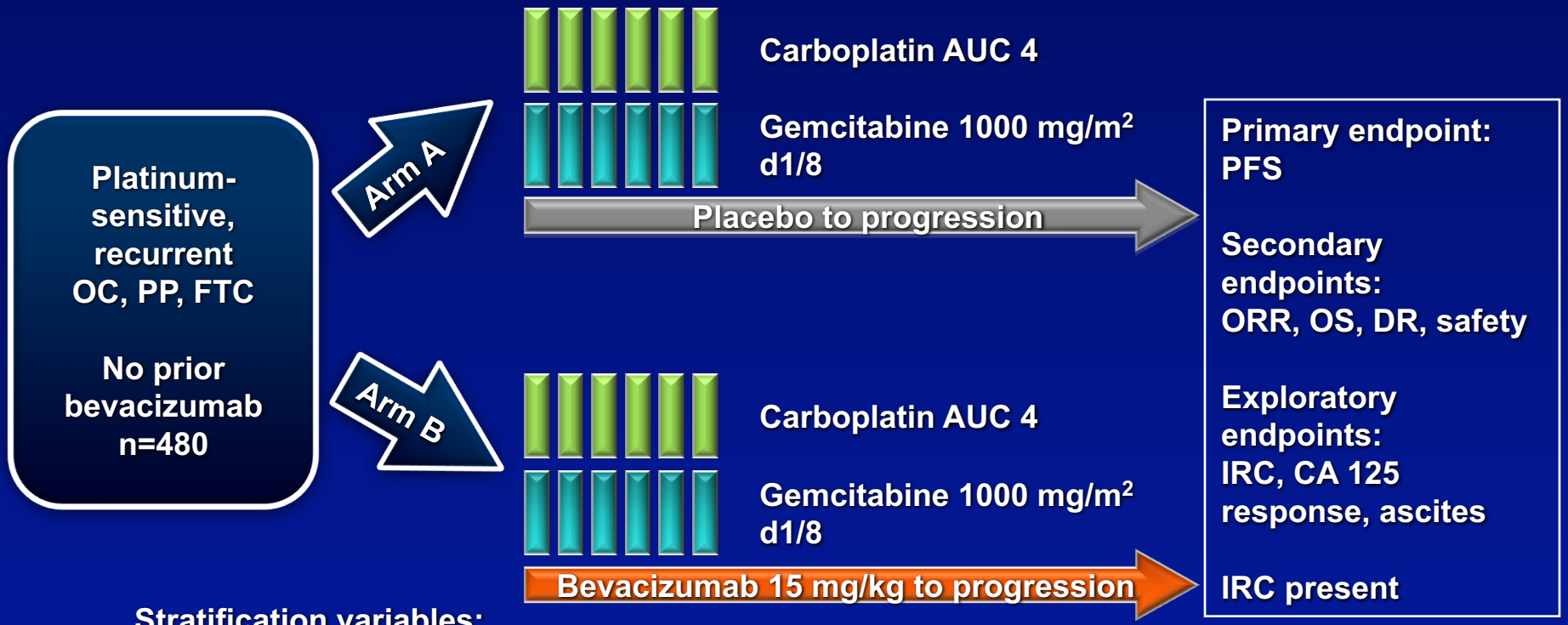
No. at risk:

CT	182	93	37	20	8	1	1	0	0
BEV + CT	179	140	88	49	18	4	1	1	0

Median duration of follow-up: 13.9 months (CT arm) vs 13.0 months (BEV + CT arm)

Pujade-Laurain E et al J Clin Oncol 30, 2012 (suppl; abstr LBA5002^); J Clin Oncol. 2014 May 1;32(13):1302-8

OCEANS



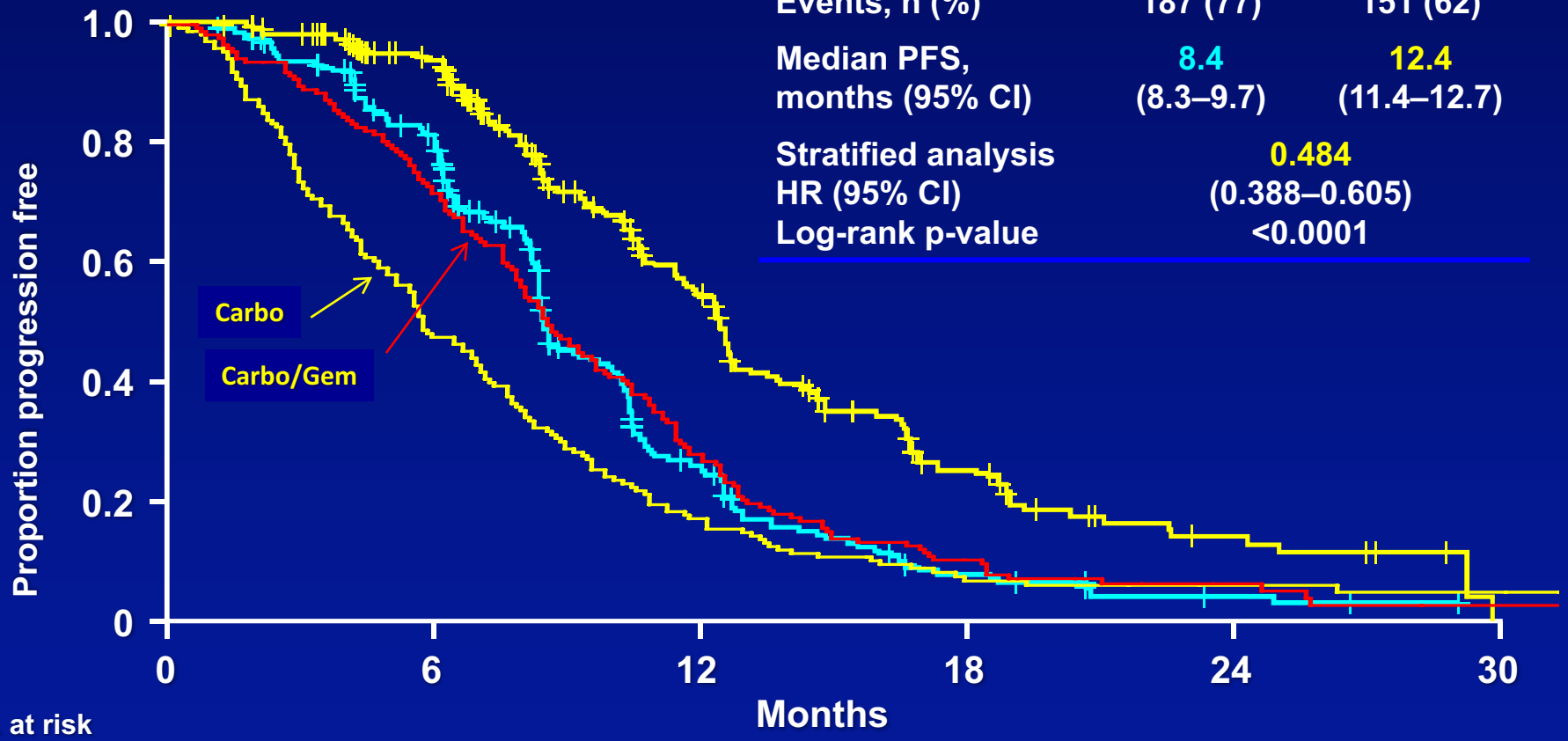
Stratification variables:
- Time to recurrence
- Cytoreductive surgery

ClinicalTrials.gov Identifier: NCT00434642

Aghajanian C et al J Clin Oncol 29: 2011 (suppl; abstr LBA5007) J Clin Oncol. 2012 Jun 10;30(17):2039-45.

OCEANS: Primary analysis of PFS

	CG + PL (n=242)	CG + BV (n=242)
Events, n (%)	187 (77)	151 (62)
Median PFS, months (95% CI)	8.4 (8.3–9.7)	12.4 (11.4–12.7)
Stratified analysis HR (95% CI)	0.484 (0.388–0.605)	
Log-rank p-value	<0.0001	

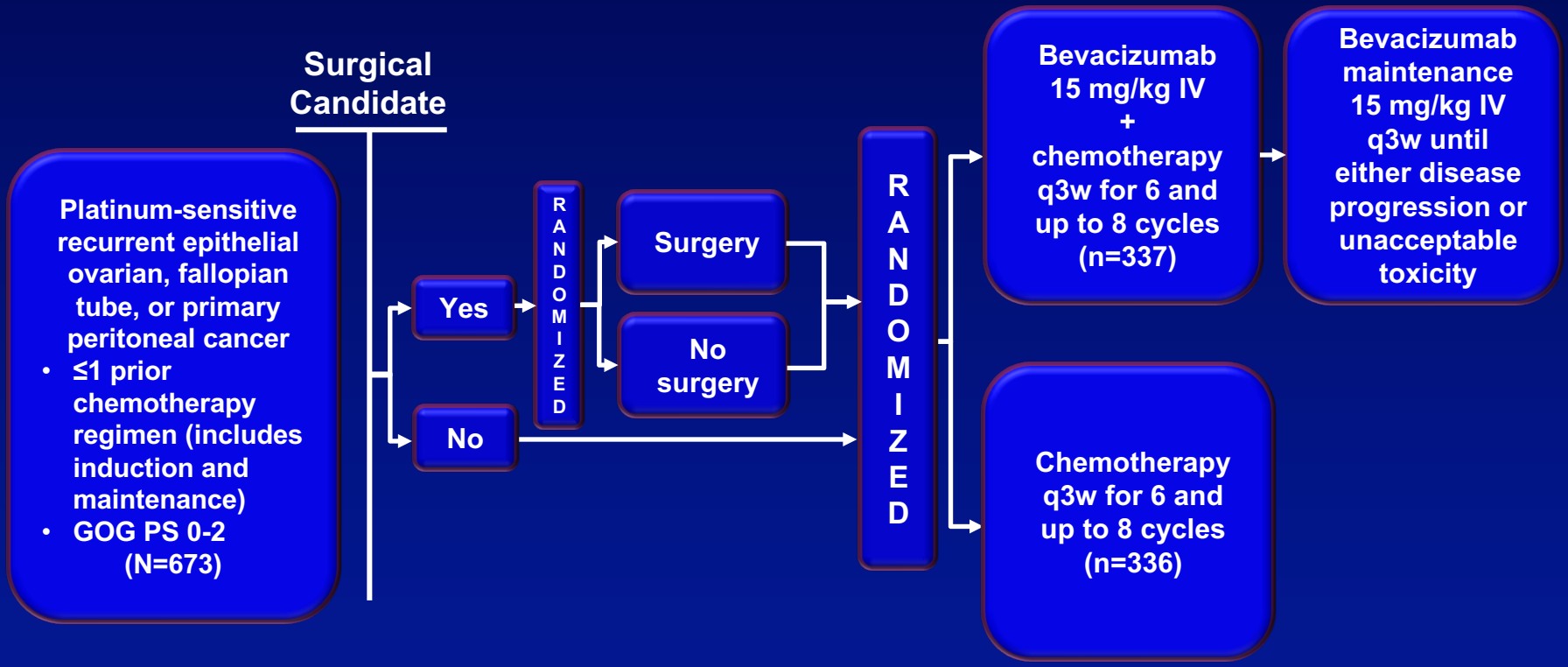


No. at risk						
CG + PL	242	177	45	11	3	0
CG + BV	242	203	92	33	11	0

Aghajanian C et al J Clin Oncol 29: 2011 (suppl; abstr LBA5007) J Clin Oncol. 2012 Jun 10;30(17):2039-45.

Pfisterer J et al. J Clin Oncol. 2006 Oct 10;24(29):4699-707.

GOG-0213 Trial Design: Bevacizumab Plus Chemotherapy in Platinum-Sensitive Ovarian Cancer



Main efficacy outcome measure: OS
Additional outcomes measures: PFS, ORR

Chemotherapy doses for both treatment arms: Carboplatin (AUC5) and paclitaxel (175 mg/m^2 over 3 hours) q3w

Stratification factors:

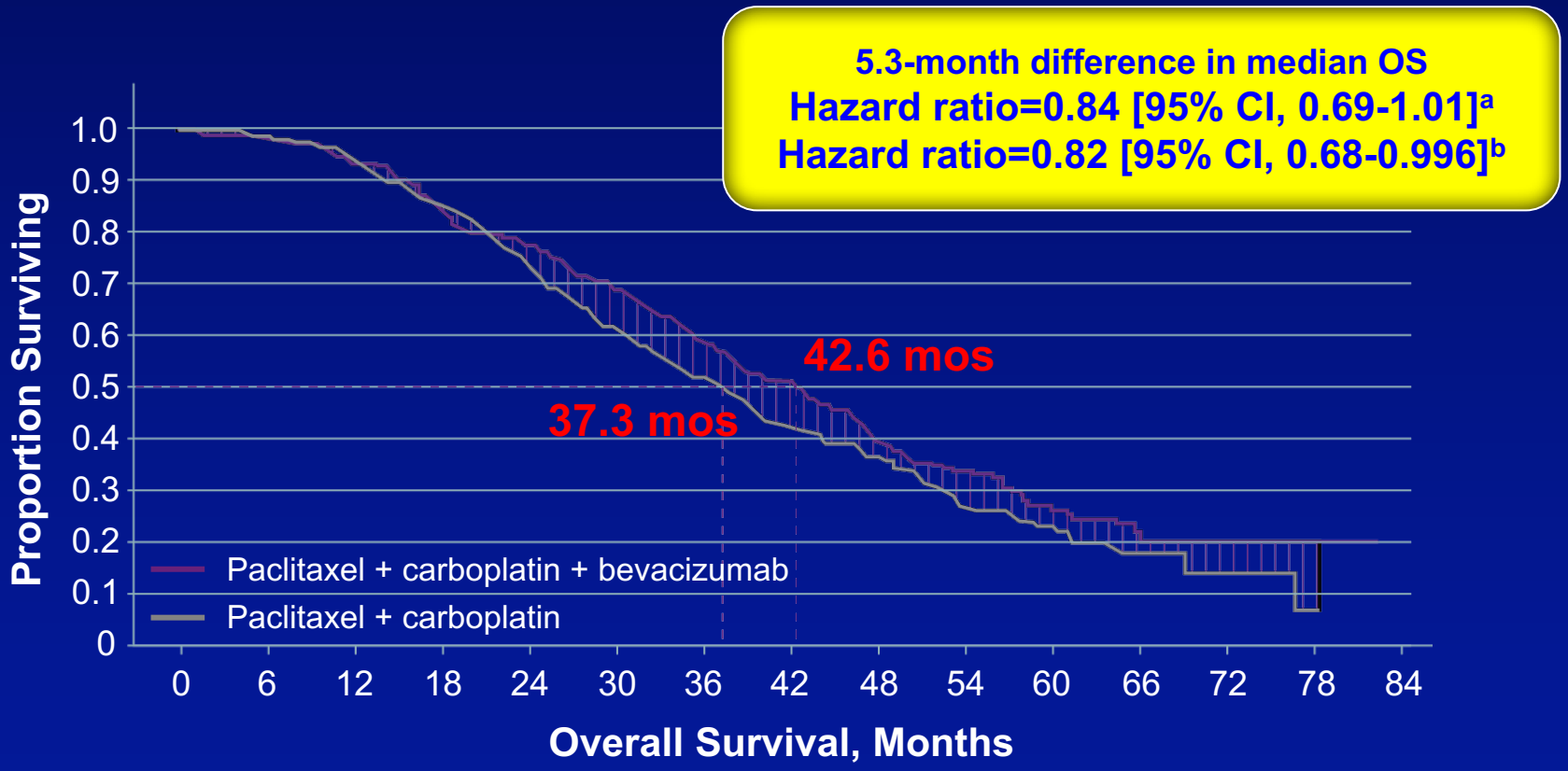
- **Participation in surgical randomization (yes or no)**
- **Platinum-free interval prior to study enrollment (6-12 months or ≥12 months)**

AUC=area under the curve; GOG=Gynecologic Oncology Group; ORR=objective response rate; OS=overall survival; **PFS=progression-free survival; PS=performance status.**

Coleman RL et al SGO 2015

GOG-0213 Trial: Overall Survival Results
Main Efficacy Outcome

Bevacizumab + Chemotherapy* vs Chemotherapy Alone



*Chemotherapy consisted of paclitaxel + carboplatin.

[a]Hazard ratio was estimated from Cox proportional hazards models stratified by the duration of treatment free-interval prior to enrolling onto this study per IVRS (interactive voice response system) and secondary surgical debulking status.

[b]Hazard ratio was estimated from Cox proportional hazards models stratified by the duration of platinum free-interval prior to enrolling onto this study per eCRF (electronic case report form) and secondary surgical debulking status.

Coleman RL et al SGO 2015

Discrepancy Between the EMA and FDA: Ovarian Cancer Indications for Bevacizumab

EMA

- ✓ Frontline + Maintenance
- ✓ Platinum resistant recurrent
- ✓ Platinum sensitive recurrent

FDA

- ❑ Frontline + Maintenance
- ✓ Platinum resistant recurrent
- ✓ Platinum sensitive recurrent

Conclusions

Front-line advanced

- Many would agree that in stage IV or large volume residual disease (suboptimal), every 3 week carboplatin and paclitaxel with bevacizumab is preferred
- The alternative is weekly chemotherapy
  - "Dose dense paclitaxel" in the fittest patients
  - "Fractionated" in the infirm and weak patients

Recurrent disease

Characteristic	Subcategory
Histology (H)	1. HGSC/endometrioid 2. Other, specify
Molecular signature (M)	1. BRCA mutation 2. BRCA-like 3. Other, specify
Treatment free interval (TFI)	1. <3 months 2. 3–12 months 3. >12 months
Number of prior chemotherapy regimens (N)	1. 3 or less 2. >3

Clinical Cases Study Ovarian Cancer