

Phase III Trial of Bevacizumab in the Primary Treatment of Advanced Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer: A Gynecologic Oncology Group (GOG) Study

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GOG-0218: Background and Rationale

- Ovarian cancer (epithelial ovarian [OV], primary peritoneal [PP], and fallopian tube [FT] cancers) remains a major public health problem¹
- Vascular endothelial growth factor (VEGF)–associated tumor angiogenesis in ovarian cancer is associated with malignant behavior^{2,3}
- Bevacizumab (BEV), monoclonal antibody to VEGF, inhibits tumor angiogenesis
 - Promising single-agent activity in phase II recurrent ovarian cancer studies^{4,5}
 - BEV combined with chemotherapy had been approved for the treatment of patients with metastatic colorectal and lung cancers
- GOG-0218 designed to study addition of BEV to standard chemotherapy in front-line treatment of ovarian cancer

1. Jemal A, et al. *CA Cancer J Clin.* 2009;59(4):225-249. 2. Hollingsworth HC, et al. *Am J Pathol.* 1995;147(1):33-41. 3. Burger RA. *J Clin Oncol.* 2007;25(20):2902-2908. 4. Burger RA, et al. *J Clin Oncol.* 2007;25(33):5165-5171. 5. Cannistra SA, et al. *J Clin Oncol.* 2007;25(33):5180-5186

GOG-0218: Schema

Front-Line:
Epithelial OV, PP,
or FT Cancer

- Stage III optimal (macroscopic)
- Stage III suboptimal
- Stage IV

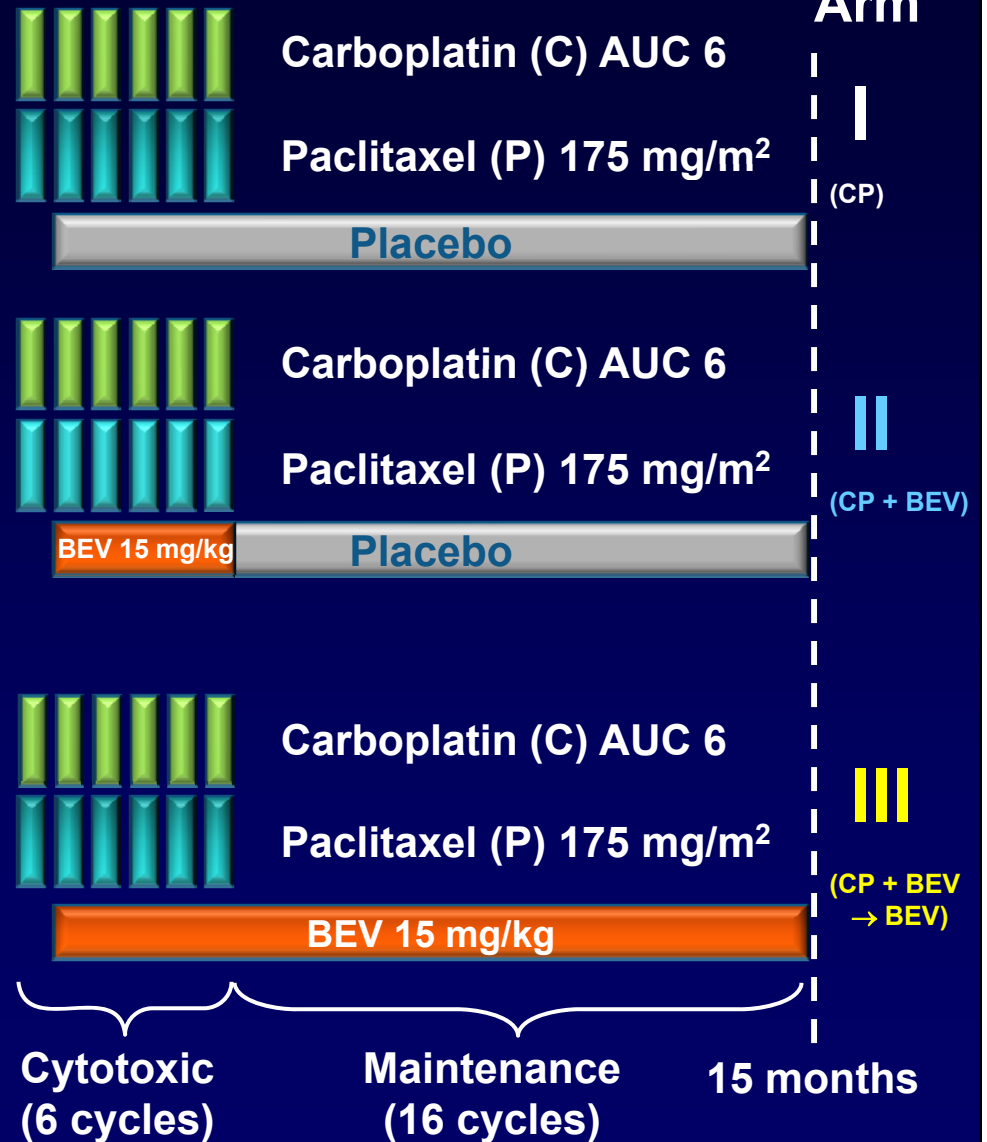
N = 1800 (planned)

Stratification variables:

- GOG performance status (PS)
- Stage/debulking status

R
A
N
D
O
M
I
Z
E

1:1:1



GOG-0218: Analysis Plan

- **Primary analysis**
 - Compare investigator-determined progression-free survival (PFS) for each BEV arm vs control
 - If both results positive, compare Arm III (CP + BEV → BEV) vs Arm II (CP + BEV)
 - Disease progression based on: RECIST, global clinical deterioration, or CA125¹
 - Planned sample size of 1800 based on:
 - 90% power to detect PFS hazard ratio (HR) ≤ 0.77
 - Median PFS shift: 14.0 months → 18.2 months
- **Secondary analyses: Overall survival (OS), safety, quality of life; correlative laboratory studies**

1. Gynecologic Cancer Intergroup Criteria - Rustin GJ, et al. *J Natl Cancer Inst.* 2004;96(6):487-488.

GOG-0218: Key Eligibility Criteria

- **Histologic diagnosis of epithelial OV, PP, or FT cancer**
- **Following maximal debulking surgery: stage III optimal (macroscopic residual disease ≤ 1 cm) or suboptimal (>1 cm), or stage IV**
- **No prior chemotherapy**
- **1–12 weeks after initial surgery**
- **GOG PS 0–2**
- **No history of significant vascular events**
- **No evidence of intestinal obstruction requiring parenteral support**
- **Written informed consent**

GOG-0218: Study Conduct

- **1873 patients from 336 sites (US, Canada, South Korea, Japan), October 2005–June 2009**
- **Key protocol amendments**
 - **Inclusion of optimally debulked (macroscopic residual disease) patients**
 - **Primary endpoint changed to PFS**
- **Final data analysis triggered by number of events in control arm**
- **Analyses**
 - **Efficacy population: n = 1873 (intent to treat)**
 - **Safety population: n = 1816 (intent to treat, as of cycle 2)**
- **Median follow-up: 17.4 months (range 0.0–50.7 months)**

GOG-0218: Baseline Clinical Characteristics

Characteristic	Arm I CP (n = 625)	Arm II CP + BEV (n = 625)	Arm III CP + BEV → BEV (n = 623)
Median age, years (range)	60 (25–86)	60 (24–88)	60 (22–89)
Race, n (%)			
Non-Hispanic white	526 (84)	519 (83)	521 (84)
Asian	41 (7)	37 (6)	39 (6)
Non-Hispanic black	25 (4)	28 (5)	27 (4)
Hispanic	21 (3)	28 (5)	25 (4)
Other, specified	8 (1)	5 (<1)	4 (<1)
GOG PS, n (%)			
0	311 (50)	315 (50)	305 (49)
1	272 (44)	270 (43)	267 (43)
2	42 (7)	40 (6)	51 (8)

Percentages may not total 100% due to rounding or categorization

GOG-0218: Baseline Surgical– Pathologic Characteristics

Characteristic, n (%)	Arm I CP (n = 625)	Arm II CP + BEV (n = 625)	Arm III CP + BEV → BEV (n = 623)
Stage/residual size			
III optimal (macroscopic)	218 (35)	205 (33)	216 (35)
III suboptimal	254 (41)	256 (41)	242 (39)
IV	153 (25)	164 (26)	165 (27)
Histology			
Serous	543 (87)	523 (84)	525 (84)
Endometrioid	20 (3)	15 (2)	25 (4)
Clear cell	11 (2)	23 (4)	18 (3)
Mucinous	8 (1)	5 (<1)	8 (1)
Tumor grade			
3 ^a	412 (66)	435 (70)	430 (69)
2	94 (15)	77 (12)	92 (15)
1	33 (5)	28 (4)	16 (3)
Not specified/pending	86 (14)	85 (14)	85 (14)

Percentages may not total 100% due to rounding or categorization

^aGrade 3 includes all clear cell tumors

GOG-0218: Patient Disposition

Characteristic	Arm I CP (n=625)	Arm II CP + BEV (n=625)	Arm III CP + BEV → BEV (n=623)
Median (range) number BEV/placebo cycles	11 (0–22 ^a)	12 (0–22 ^a)	14 (0–21)
On treatment at time of analysis, n (%)	86 (14)	82 (13)	117 (19)
Completed regimen, n (%)	100 (16)	104 (17)	148 (24)
Discontinued study treatment, n (%)			
Disease progression	299 (48)	264 (42)	164 (26)
Adverse events	69 (11)	86 (14)	94 (15)
Cycles 1–6	57 (9)	73 (12)	59 (9)
Cycle ≥7	12 (2)	13 (2)	35 (6)
Deaths	8 (1)	7 (1)	13 (2)
Patient refusal	44 (7)	55 (9)	50 (8)
Other	19 (3)	27 (4)	37 (6)

^aOne patient in each group received BEV/placebo in cycle 1
Percentages may not total 100% due to rounding or categorization

GOG-0218: Select Adverse Events

Onset Between cycle 2 and 30 Days After Date of Last Treatment

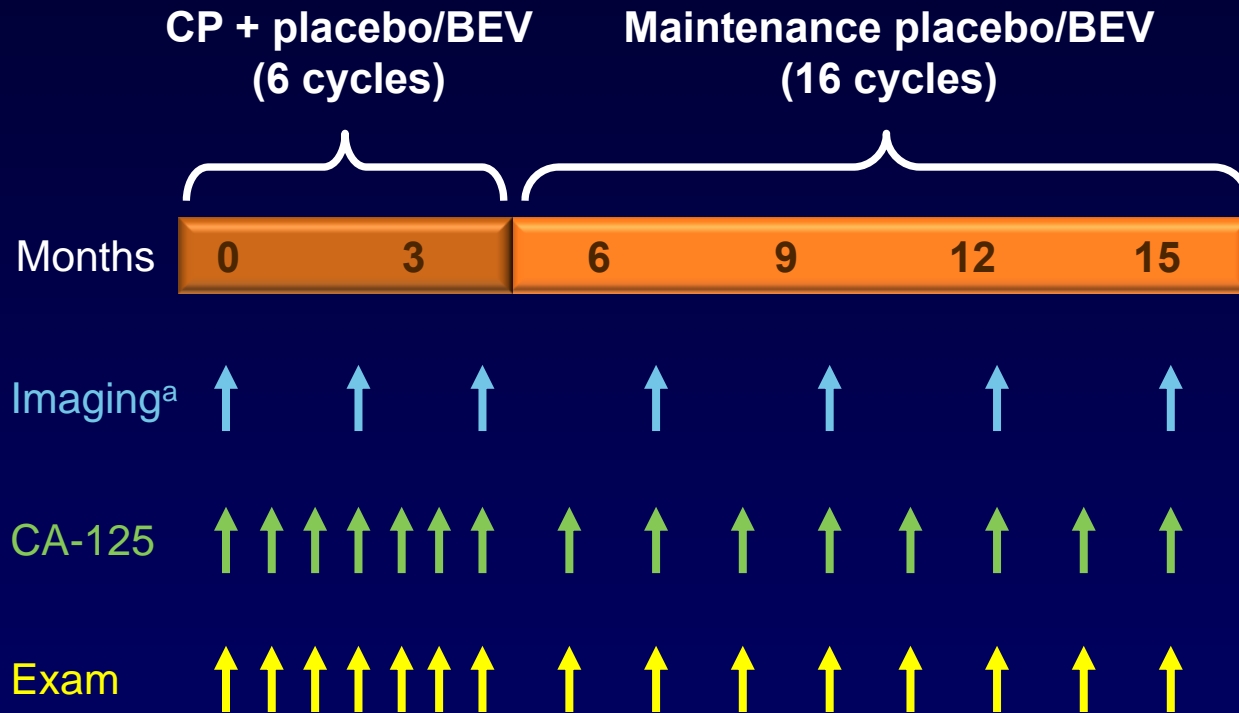
Adverse Event (Grade when Limited), n (%)	Arm I CP (n = 601)	Arm II CP + BEV (n = 607)	Arm III CP + BEV → BEV (n = 608)
GI events ^a (grade ≥2)	7 (1.2)	17 (2.8)	16 (2.6)
Hypertension (grade ≥2)	43 (7.2) ^b	100 (16.5) ^b	139 (22.9) ^b
Proteinuria (grade ≥3)	4 (0.7)	4 (0.7)	10 (1.6)
Pain (grade ≥2)	250 (41.7)	252 (41.5)	286 (47.1)
Neutropenia (grade ≥4)	347 (57.7)	384 (63.3)	385 (63.3)
Febrile neutropenia	21 (3.5)	30 (4.9)	26 (4.3)
Venous thromboembolic event	35 (5.8)	32 (5.3)	41 (6.7)
Arterial thromboembolic event	5 (0.8)	4 (0.7)	4 (0.7)
CNS bleeding	0	0	2 (0.3)
Non-CNS bleeding (grade ≥3)	5 (0.8)	8 (1.3)	13 (2.1)
RPLS	0	1 (0.2)	1 (0.2)

RPLS = reversible posterior leukoencephalopathy syndrome

^aPerforation/fistula/necrosis/leak

^b $P < .05$

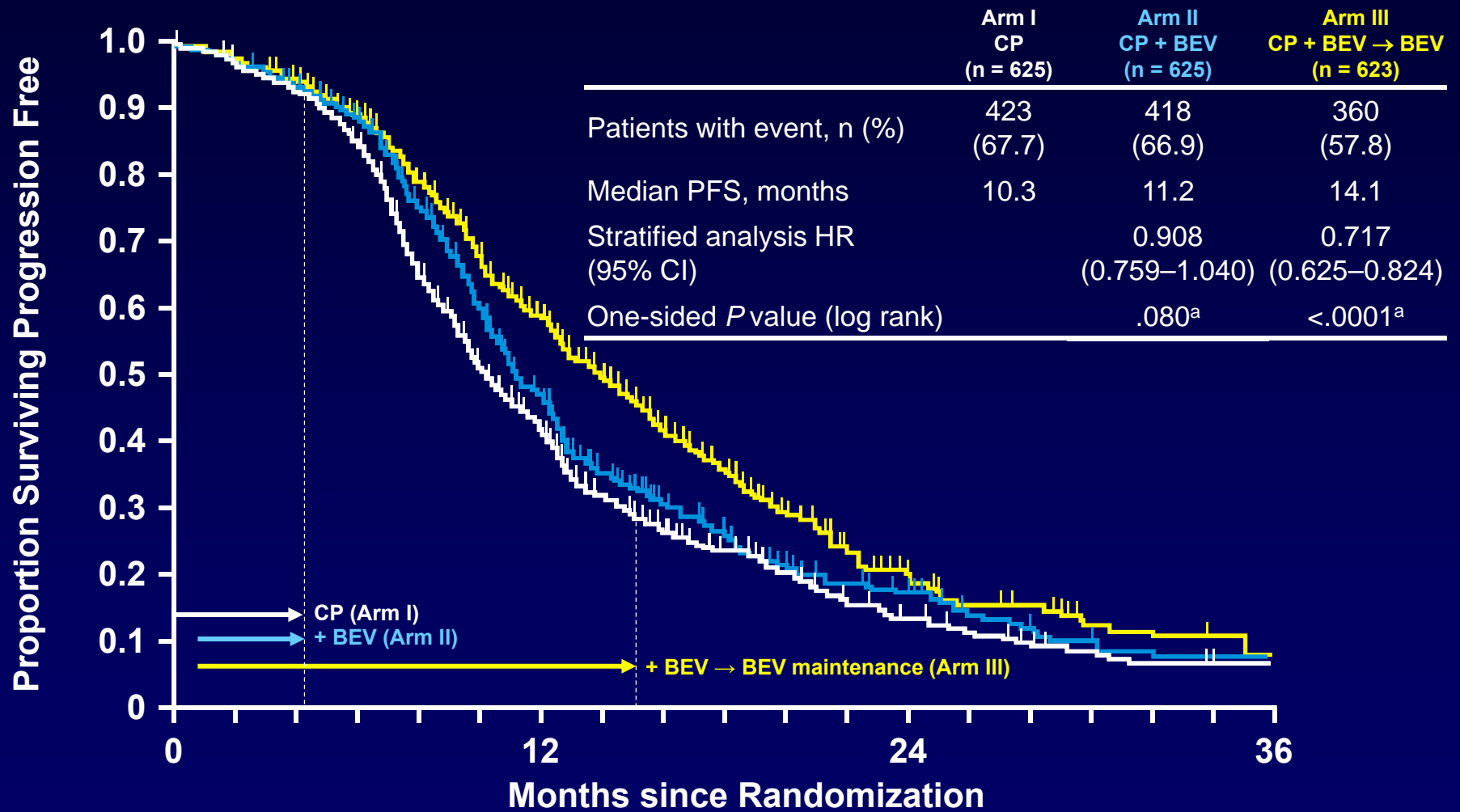
GOG-0218: Disease Assessment



Same intervals for all modalities:
Every 3 months for 2 years, then every 6 months for 3 years, then annually

^aConventional CT or MRI

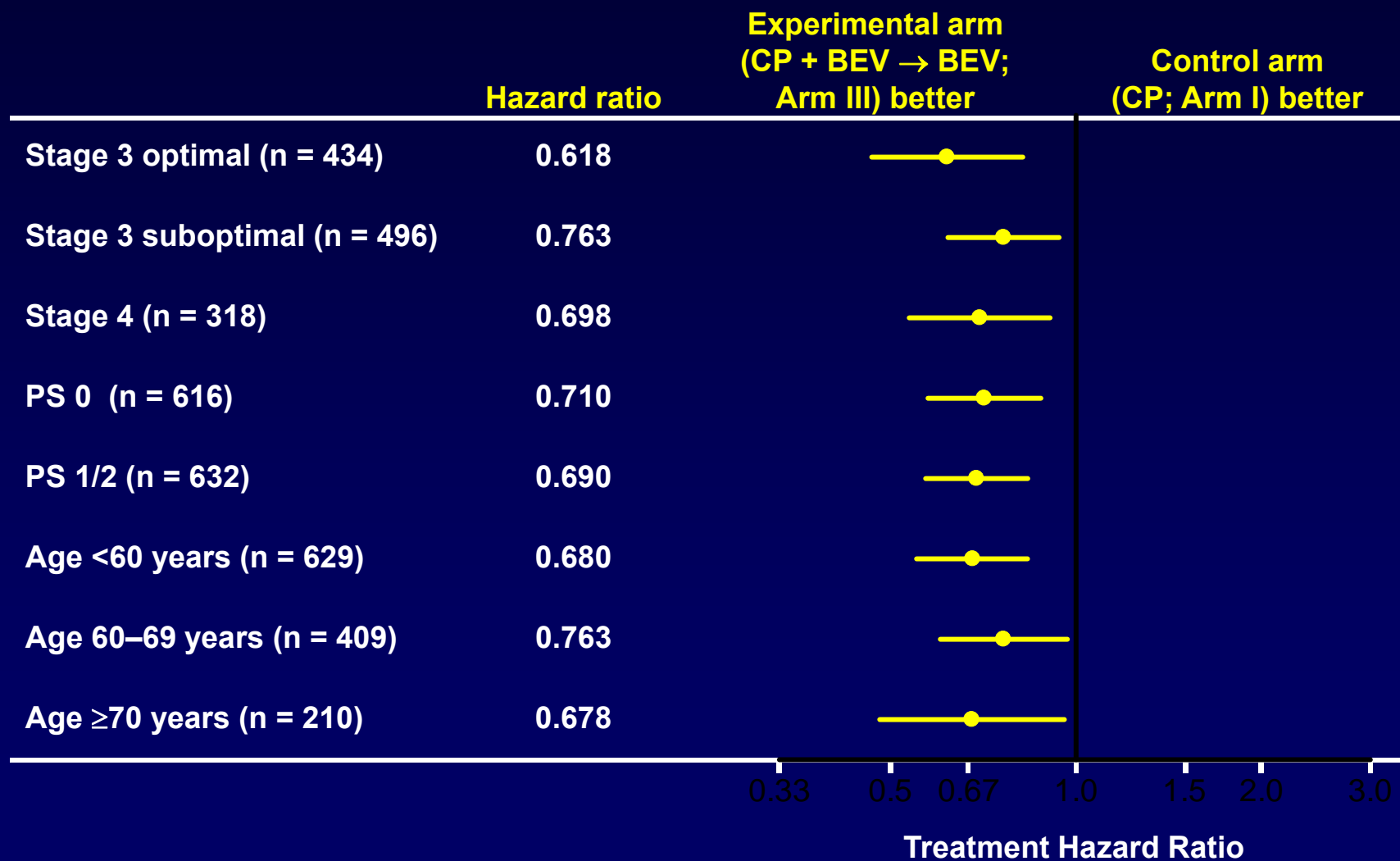
GOG-0218: Investigator-Assessed PFS



^a*P* value boundary = .0116

GOG-0218: Subgroup Analyses of PFS

CP + BEV → BEV (Arm III) vs CP (Arm I)

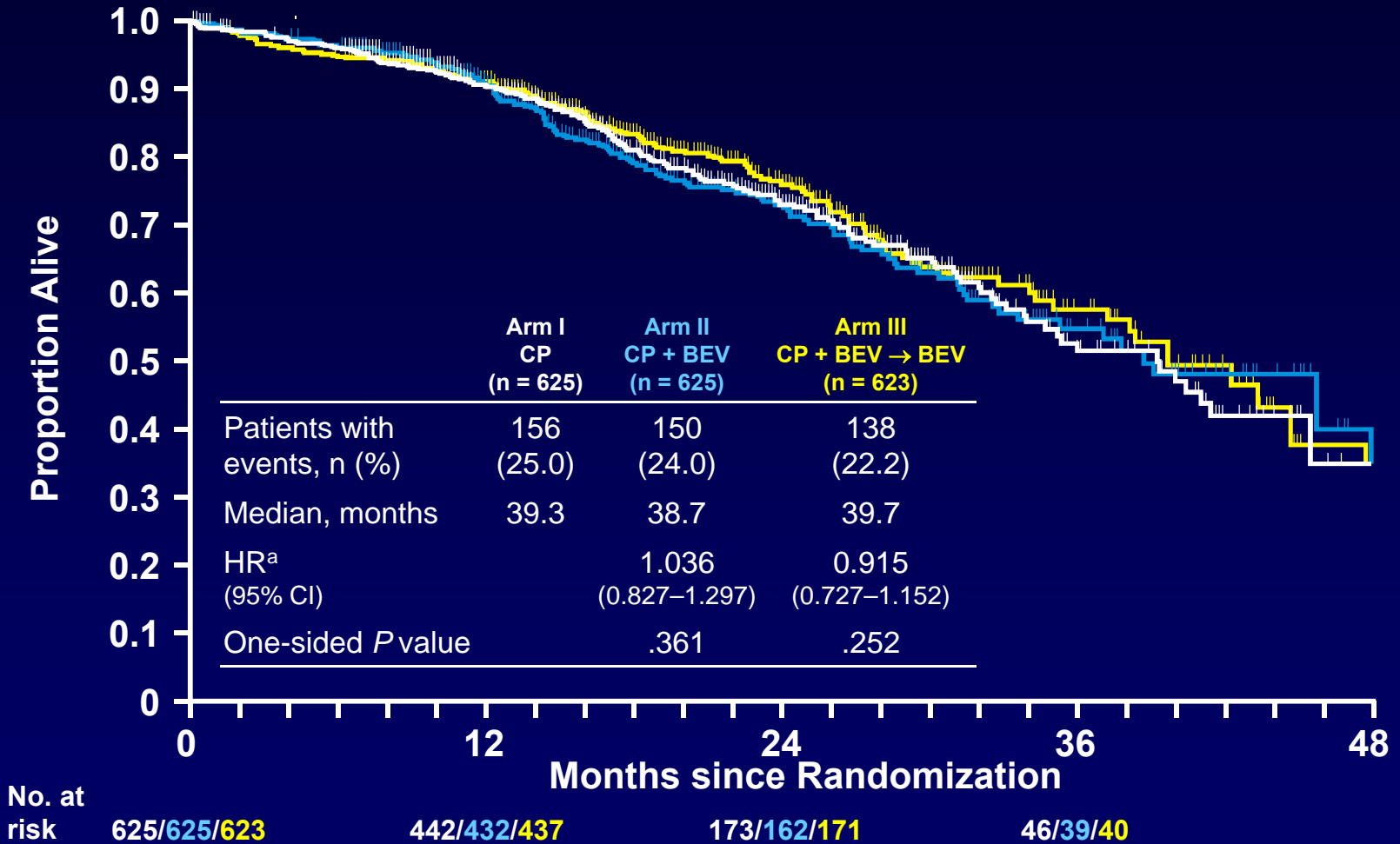


GOG-0218: Ramification of Using CA125 as Determinant of Progression

	Protocol-Defined PFS Analysis	CA125-Censored PFS Analysis
Median PFS, months		
CP (Arm I)	10.3	12.0
CP + BEV → BEV (Arm III)	14.1	18.0
Absolute difference in median PFS (months)	3.8	6.0
Hazard ratio	0.717	0.645
Censored for CA-125, %		
CP (Arm I)	0	20
CP + BEV → BEV (Arm III)	0	29

GOG-0218: Overall Survival Analysis

At Time of Final PFS Analysis



^aStratified analysis

GOG-0218: Overall Survival (OS)

Outcome	Arm I CP (n = 625)	Arm II CP + BEV (n = 625)	Arm III CP + BEV → BEV (n = 623)
Deaths, n (%)	156 (25.0)	150 (24.0)	138 (22.2)
1-year survival, %	90.6	90.4	91.3

- Events observed in 24% of patients at time of data lock
- After primary endpoint changed from OS to PFS
 - Unblinding to treatment assignment allowed at time of disease progression

GOG-0218: Conclusions

- **GOG-0218 met the primary objective in the front-line treatment of advanced ovarian (epithelial OV, PP, and FT) cancer; PFS with CP + BEV → BEV maintenance (Arm III) statistically superior to CP alone (Arm I)**
 - PFS with CP + BEV (Arm II) not statistically superior to CP (Arm I)
- **Interpretation of survival analysis limited**
- **Treatment regimen generally well tolerated; adverse events (including GI perforation) similar to previous BEV studies**
- **BEV – first molecular targeted and first anti-angiogenic agent to demonstrate benefit in this population**
- **CP + BEV → BEV maintenance should be considered one standard option**