Updated Overall Survival Analysis in OCEANS, a Randomized Phase 3 Trial of Gemcitabine + Carboplatin and Bevacizumab or Placebo Followed by Bevacizumab or Placebo in Platinum-Sensitive Recurrent Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

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Disclosures

- Drs. Aghajanian, Blank and Goff have no disclosures
- Dr. Nycum is a past member of a Roche/Genentech advisory board
- Drs. Husain and Nguyen are employees and stockholders of Roche/Genentech

BV in Recurrent OC

- BV: single-agent activity in single-arm studies[1,2]

Efficacy	GOG-170D[1] (n=62)	AVF2949g[2] (n=44)
Median PFS, months	4.7	4.4
6-month PFS rate, %	40.3	27.8
ORR, %	21	16
Median OS, months	16.9	10.7

Note: 41.9% of patients in GOG-170D had platinum-resistant disease, whereas 83.7% of patients in AVF2949g were primarily platinum-resistant.

BV, bevacizumab; GOG, Gynecology Oncology Group ; OC, ovarian cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival

[1]Burger et al. *J Clin Oncol*. 2007; [2]Cannistra et al. *J Clin Oncol.* 2007

GC in Recurrent OC

- GC: phase 3 AGO/NCIC/EORTC trial in platinum-sensitive recurrent OC[1]

Efficacy	C (n=178)	GC (n=178)
Median PFS, months	5.8	8.6
HR for PFS	0.72 (*P*=.0031)	
ORR, %	31	47
	P=.0016	
Median OS, months	17.3	18.0
HR for OS	0.96 (*P*=.7349)	

C, carboplatin; GC, gemcitabine + carboplatin; AGO, Arbeitsgemeinschaft für Gynäkologische Onkologie; NCIC, National Cancer Institute of Canada; EORTC, European Organization for Research and Treatment of Cancer

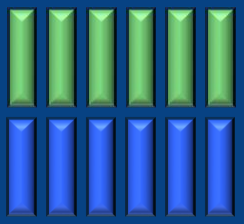
[1]Pfisterer et al. *J Clin Oncol.* 2006

OCEANS: Study Schema

Platinum-sensitive recurrent OC[a]
- Measurable disease
- ECOG PS 0/1
- No prior chemotherapy for recurrent OC
- No prior BV

N = 484
1:1

GC + PL

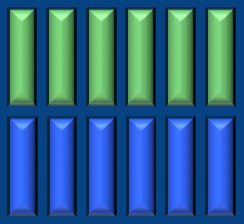


C AUC 4, q3w

G 1000 mg/m^2, days 1 and 8

PL q3w until progression

GC + BV



C AUC 4, q3w

G 1000 mg/m^2, days 1 and 8

BV 15 mg/kg q3w until progression

GC for 6 (up to 10) cycles

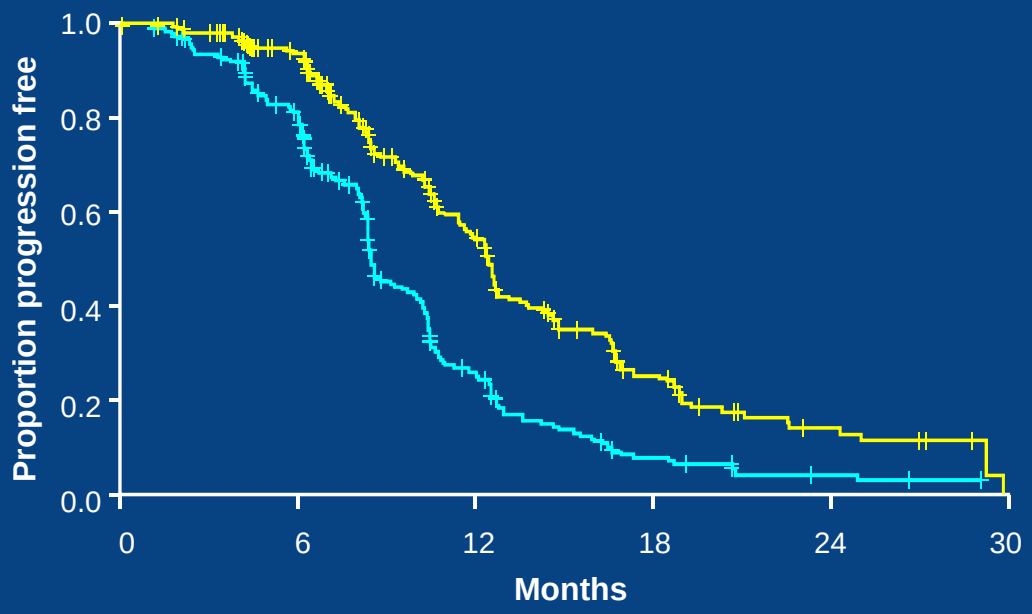
Stratification variables
- Platinum-free interval (6–12 vs >12 months)
- Cytoreductive surgery for recurrent disease (yes vs no)

- **Primary end point:** PFS by RECIST (investigator assessed)
- **Secondary end points:** ORR, DOR, OS, safety

AUC, area under the curve; BV, bevacizumab; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; GC, gemcitabine + carboplatin; OC, ovarian cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PL, placebo; PS, performance status; q3w, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors

[a]Epithelial ovarian, primary peritoneal, or fallopian tube cancer

OCEANS: Primary Analysis of PFS



	GC + PL (n=242)	GC + BV (n=242)
Median PFS (by INV), months	8.4	12.4
Stratified analysis		
HR	0.484	
Log-rank *P* value	<.0001	
Median PFS (by IRC), months	8.6	12.3
Stratified analysis		
HR	0.451	
Log-rank *P* value	<.0001	
ORR (by INV), %	57	79
Median DOR (by INV), months	7.4	10.4
HR	0.53	
ORR (by IRC), %	54	75
Median DOR (by IRC), months	6.0	8.3
HR	0.54	

Data cutoff date: September 17, 2010.

INV, investigator assessed; IRC, independent review committee assessed

PFS Post Last Dose of Carboplatin

	GC + PL (n=238)	GC + BV (n=241)
Events, n (%)	182 (76.5)	148 (61.4)
Median PFS, months	4.4	7.6
Stratified analysis HR (95% CI)	0.457 (0.365–0.573)	

Time from last dose of Carboplatin	GC + PL (n=242)		GC + BV (n=242)	
	Events, n (%)	Percent event free	Events, n (%)	Percent event free
6	131 (54.1)	**35.1**	69 (28.5%)	**64.5**
12	176 (72.7)	**8.7**	125 (51.7%)	**29.8**
24	182 (75.2)	**3.1**	146 (60.3%)	**9.9**

OCEANS: Overview of Adverse Events[a]

Patients, %	GC + PL (n=233)	GC + BV (n=247)
Any adverse event	100	100
Serious adverse event	25	35
Grade 3–5 adverse event	82	90
Grade 3–5 adverse event of special interest	62	74
Grade 5 adverse event	<1[b]	<1[c]

[a]Aghajanian et al. ASCO 2012 #5054

[b]Acute myocardial infarction in 1 patient; [c]Intracranial hemorrhage in 1 patient

OCEANS: Adverse Events of Special Interest[a]

Adverse events, n (%)	GC + PL (n=233)	GC + BV (n=247)
Arterial thromboembolic event (all grade)	2 (0.9)	7 (2.8)
Venous thromboembolic event (grade ≥3)	6 (2.6)	10 (4.0)
Bleeding (central nervous system) (all grade)	1 (0.4)	2 (0.8)
Bleeding (non-central nervous system) (grade ≥3)	2 (0.9)	14 (5.7)
Congestive heart failure (grade ≥3)	2 (0.9)	3 (1.2)
Febrile neutropenia (grade ≥3)	4 (1.7)	4 (1.6)
Neutropenia (grade ≥3)	130 (55.8)	144 (58.3)
Hypertension (grade ≥3)	1 (0.4)	44 (17.8)
Fistula/abscess (all grade)	1 (0.4)	4 (1.6)
Gastrointestinal perforation (all grade)[b]	0 (0)	0 (0)
Proteinuria (grade ≥3)	2 (0.9)	24 (9.7)
Reversible posterior leukoencephalopathy syndrome (all grade)	0 (0)	2 (0.8)
Wound-healing complication (grade ≥3)	0 (0)	2 (0.8)

[a]Aghajanian et al. ASCO 2012 #5054

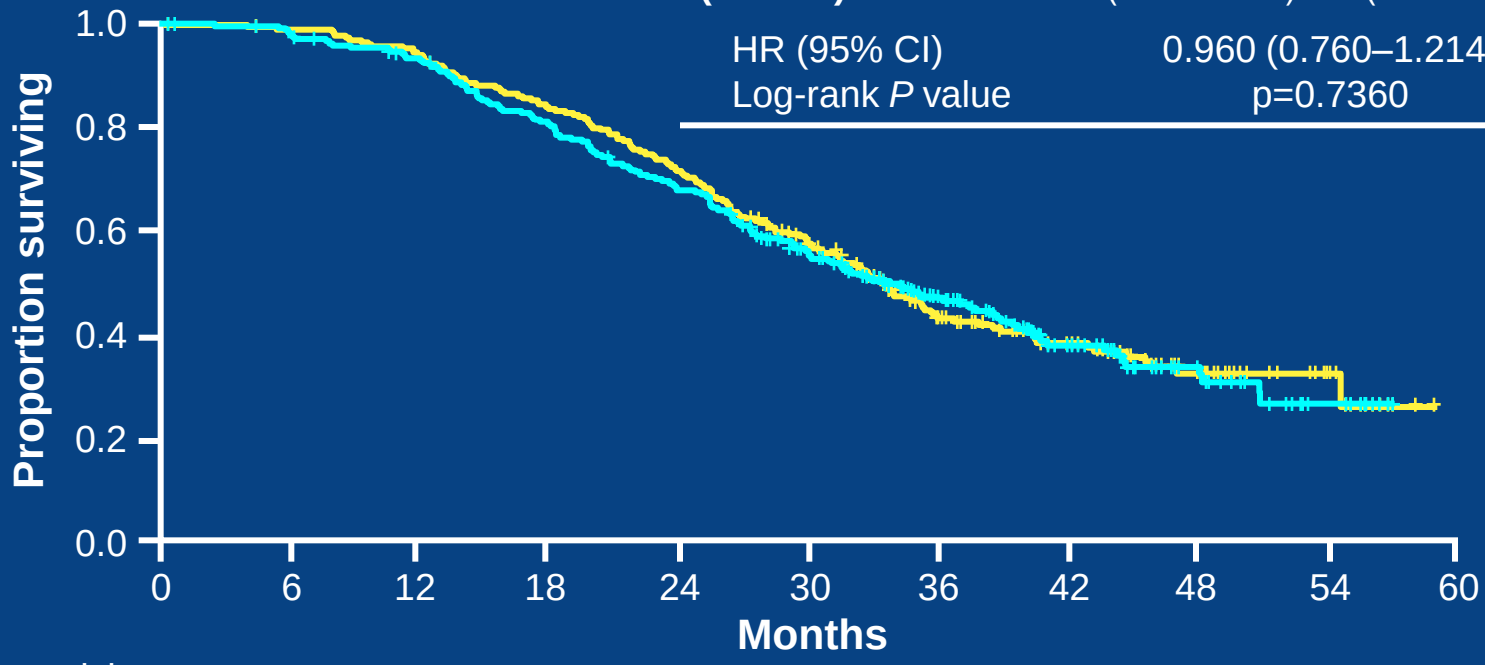
[b]Two gastrointestinal perforations occurred outside the 30-day safety reporting window

OCEANS: Need for Updated OS Analysis

- 1st interim OS analysis at time of PFS analysis
  - Events in only 29% (far fewer than anticipated)
  - High degree of censoring after 6 months
- 2nd interim OS analysis
  - Unstable data, events in <50% of patients
    - Considerable censoring after 18 months
    - Median OS at the median follow-up time
- 3rd interim OS analysis
  - Curves stable to 24 months due to minimal censoring
  - Median follow-up time longer than median OS

OCEANS: Third Interim OS Analysis[a]

	GC + PL (n=242)	GC + BV (n=242)
Events, n (%)	142 (58.7)	144 (59.5)
Median OS, months (95% CI)	33.7 (29.3–38.7)	33.4 (30.3–35.8)
HR (95% CI)	0.960 (0.760–1.214)	
Log-rank *P* value	p=0.7360	



Number at risk:

GC + PL	242	235	221	190	159	117	77	44	23	7	0
GC + BV	242	239	226	201	171	127	78	48	27	7	0

[a]Data cutoff date: March 30, 2012. Median follow-up 41.9 months in PL arm and 42.3 months in BV arm, with 286 deaths (59.1% of patients)

OCEANS: Causes of Death (Safety Population)

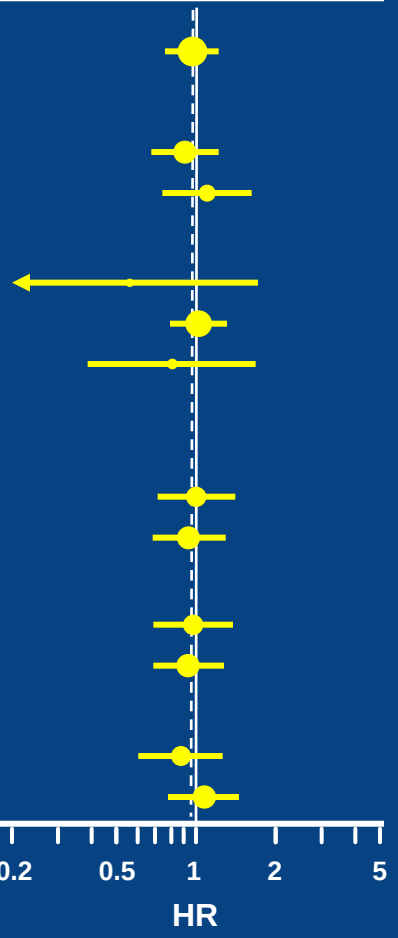
Cause of death, n (%)	GC + PL (n=233)	GC + BV (n=247)
Disease progression	137 (58.8)	141 (57.1)
Adverse event	1 (0.4)[a]	3 (1.2)[b]
Unknown	2 (0.9)	1 (0.4)
Total	140 (60.1)	145 (58.7)

[a]Acute myocardial infarction

[b]Intracranial hemorrhage in one patient; 2 patients died due to non-treatment emergent sepsis and respiratory failure that occurred 70 days and 302 days post last protocol treatment, respectively

OCEANS: Third Interim OS Subgroup Analyses

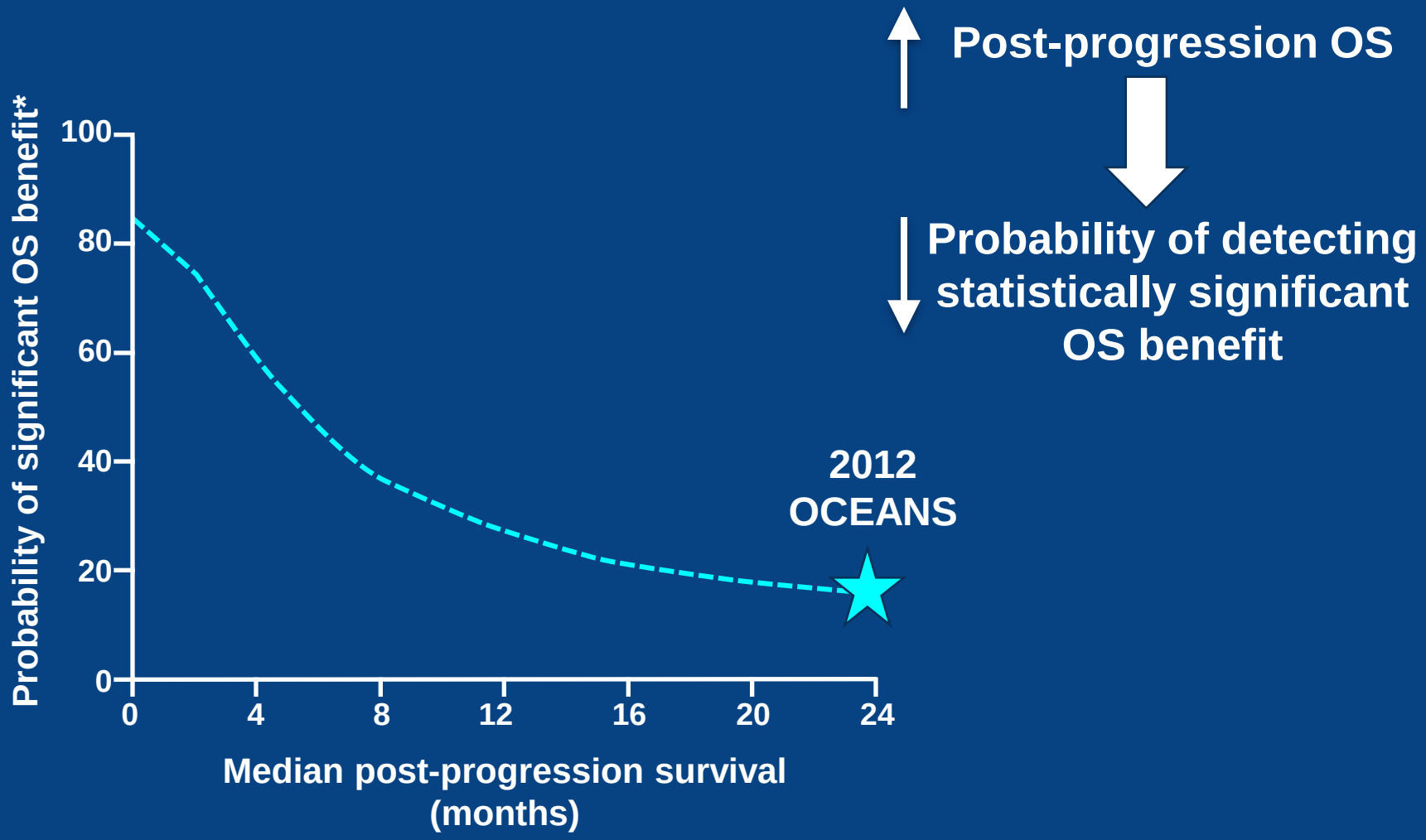
Baseline risk factor	No. of patients	Median OS (months) GC + PL (n=242)	Median OS (months) GC + BV (n=242)	HR (95% CI)
All patients	484	33.7	33.4	0.96 (0.76–1.22)
Age, years				
<65	306	32.9	33.7	0.91 (0.68–1.21)
≥65	178	35.2	31.3	1.10 (0.75–1.62)
Primary site				
Fallopian tube carcinoma	29	42.7	NE	0.56 (0.18–1.72)
Ovarian carcinoma	407	33.7	32.8	1.02 (0.79–1.31)
Primary peritoneal carcinoma	48	26.3	32.3	0.81 (0.39–1.69)
Recurrence since last platinum therapy				
6-12 months	202	29.9	28.1	1.00 (0.71–1.41)
>12 months	282	38.4	35.8	0.94 (0.69–1.29)
Baseline SLD of target lesions				
≤Median (59.0)	244	38.7	40.3	0.97 (0.68–1.37)
>Median	240	29.1	30.3	0.93 (0.68–1.27)
Baseline CA-125 (U/ml)				
≤Median (82.0)	232	40.1	42.8	0.87 (0.60–1.26)
>Median	226	29.1	26.3	1.06 (0.78–1.45)



CA-125, cancer antigen 125; NE; non-estimable; SLD, sum of longest diameters

PFS Benefit ≠ Gain in OS

Long post-progression survival decreases probability of discerning a gain in OS



*Trial with 80% power for PFS

Broglio & Berry. *J Natl Cancer Inst.* 2009

OCEANS: Subsequent Anticancer Therapy

Type of therapy, n (%)[a]	GC + PL (n=242)	GC + BV (n=242)
Any subsequent anticancer therapy	216 (89.3)	207 (85.5)
Subsequent BV	**85 (39.4)**	**46 (22.2)**
Subsequent chemotherapy[b]	213 (98.6)	203 (98.1)

[a]Percentage does not total 100% as patients may have received multiple therapies
[b]Percentages are based on patients who used NPT

OCEANS: Exposure to Anticancer Therapy

Total lines of anticancer therapy,[a] n (%)	GC + PL (n=242)	GC + BV (n=242)
3 or more	214 (88.4)	204 (84.3)
4 or more	168 (69.4)	164 (67.8)
5 or more	133 (55.0)	114 (47.1)
6 or more	87 (36.0)	64 (26.4)
7 or more	52 (21.5)	33 (13.6)
8 or more	27 (11.2)	22 (9.1)

[a]Includes frontline and OCEANS regimens

AGO/NCIC/EORTC and OCEANS

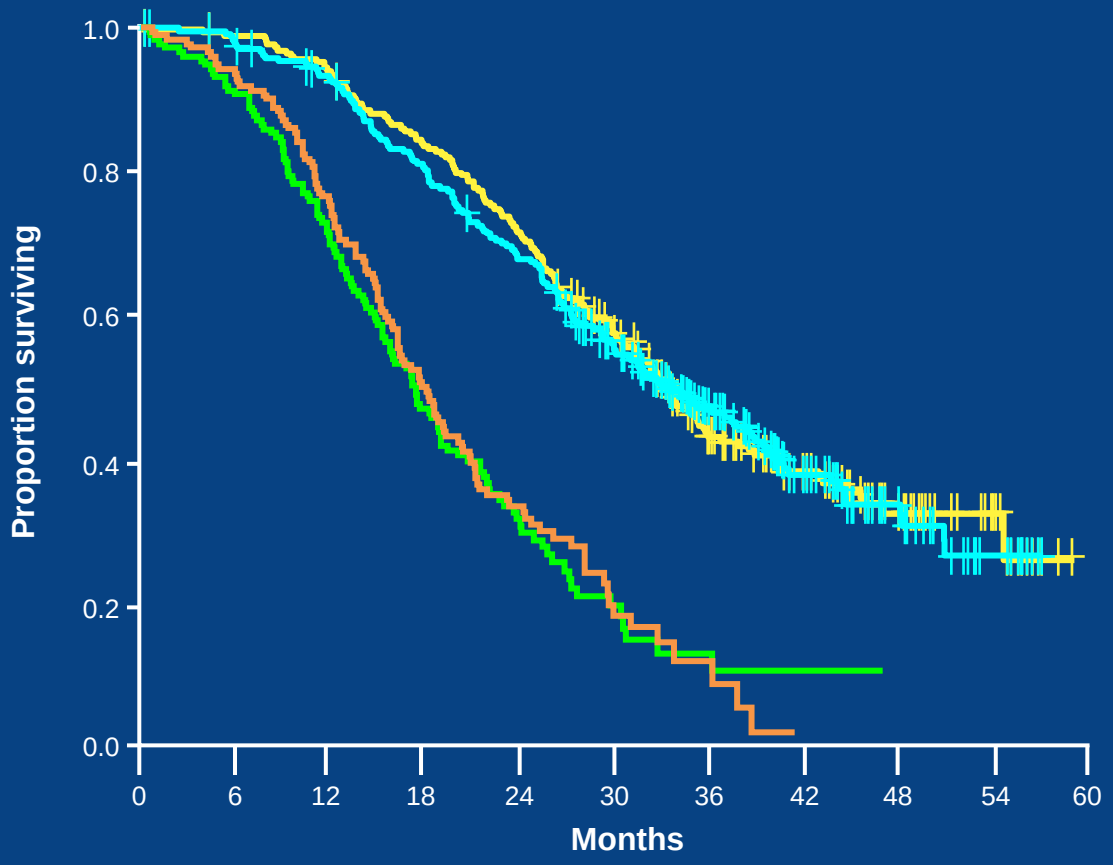
Overall survival and subsequent treatment

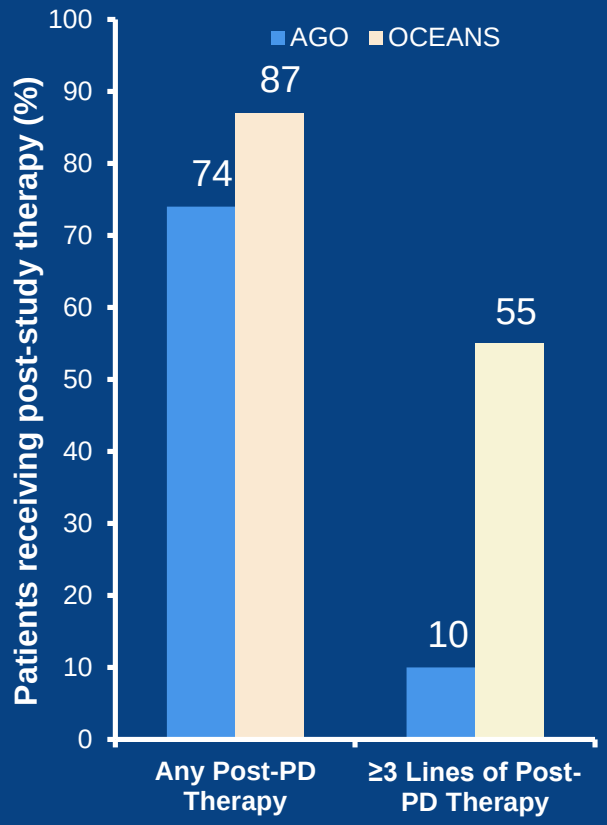
AGO/NCIC/EORTC: OS[1]

	C (n=178)	GC + PL (n=178)
Median OS, mo	17.3	18.0
HR (95% CI)	0.96 (0.75 – 1.23)	
Log-rank *P* value	.7349	

OCEANS: 3rd Interim OS Analysis

	GC + PL (n=242)	GC + BV (n=242)
Median OS, mo	33.7	33.4
HR (95% CI)	0.960 (0.760–1.214)	
Log-rank *P* value	.7360	





[1]Pfisterer et al. *J Clin Oncol.* 2006

OCEANS: Conclusions

- OCEANS met its primary objective of improving PFS
  - Robust HR supported by improved ORR, DOR and PFS by IRC
- Updated OS results show
  - No imbalance in deaths between the arms
  - Long post-progression survival (PPS)
  - Extensive therapy in PPS period, more BV in the control arm, potentially confounding OS
- An exploratory analysis of the platinum-free interval (PFI) demonstrates that BV extends the median PFI after the last dose of Carboplatin, with higher PFI rates through month 24
- These results continue to support a positive benefit:risk ratio for the GC + BV regimen in platinum-sensitive recurrent OC

Thank you

We gratefully acknowledge:

All the patients and their families who participated in the trial

All the investigators and staff who contributed their time and effort to make it a successful study