5 Minute JournalClub

SPECIAL EDITION
Issue 1, 2011

Bevacizumab (Bev) with Chemotherapy, Followed by Bev, in the Treatment of Newly Diagnosed and Platinum-Sensitive Recurrent Ovarian Cancer

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for diverse forms of cancer.

LEARNING OBJECTIVES

- Counsel patients about the risks and benefits of bevacizumab when added to carboplatin and gemcitabine for the treatment of platinum-sensitive recurrent ovarian cancer.
- Apply recent results of studies of the addition of bevacizumab to standard chemotherapy for high-risk ovarian cancer to the development of treatment algorithms for patients.

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This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located on our website at ResearchToPractice.com/5MJCASCO2011/Ovarian/CME.

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To go directly to the slides and investigator commentary for the featured abstracts, **click here**.

The electric pace of oncology in 2011 means that most busy practitioners barely have time to read abstracts, let alone dive into journal articles and watch or attend meeting presentations. Addressing that challenge, this latest experiment in cancer education attempts to provide our quickest take possible on the most memorable presentations from ASCO 2011. This first issue focuses on solid tumors (hematologic cancers will be coming next week), and for each of the presentations summarized below we have created a brief, clickable slide set reviewing the most essential findings and providing the perspectives of clinical investigators (presented on the last slide of each set). Here we go:

1. Vemurafenib and ipilimumab in melanoma

Two plenary papers on Phase III trials with these agents showed important survival benefits (**ab LBA4** and **LBA5**). The findings and recent FDA approval of both of these agents heighten the importance of BRAF V600E mutation testing and create a challenging choice between these two interesting novel compounds as first-line therapy for patients with tumors harboring these mutations.

2. GI cancers: Adjuvant imatinib in GIST; neoadjuvant treatment of rectal cancer

Another compelling plenary paper (**ab LBA1**) reported a trial in patients with high-risk GIST revealing that 3 years of adjuvant imatinib resulted in much better PFS and OS than 1 year. Importantly, in both groups relapses started occurring 6 months after the discontinuation of treatment, suggesting the need for longer-duration or perhaps indefinite imatinib.

Also in GI cancer, 2 trials (**ab 3503 and 3504**) addressed a couple of old, lingering questions in terms of the choice of chemotherapy to pair with radiation therapy in rectal cancer. Bottom line: There doesn't seem to be a current role for neoadjuvant oxaliplatin, and it's pretty challenging to think of a good reason to use 5-FU instead of capecitabine.

3. Important Phase I-II studies on novel agents
In our nominee for most exciting ASCO data set (**ab 4516**), the Met/VEGFR2 TKI cabozantinib (formerly XL 184) in prostate cancer produced some of the most stunning outcomes seen in this or any other solid tumor, including dramatic improvements evident on bone scans often associated with major symptom palliation.

A close second to the cabozantinib paper (**ab 7525**) and one that kept the faculty at our recent lung cancer Think Tank buzzing demonstrated that pan-EGFR blockade with the irreversible TKI afatinib combined with cetuximab resulted in significant responses in patients with advanced NSCLC resistant to an EGFR TKI, including those with T790M mutations.

Another encouraging NSCLC paper (**ab 7505**) evaluated the monoclonal antibody MetMAb and demonstrated improved PFS in the 52% of patients with Met overexpression.

4. Iniparib in triple-negative breast cancer
We all knew it was coming, but the biggest downer of the meeting (**ab 1007**) was the pretty much negative study — presented by the diminutive genius Joyce O'Shaughnessy — of iniparib plus chemo in advanced TNBC. These disappointing findings left many scratching their heads and have forced researchers back to the drawing board in an attempt to figure out why this putative PARP inhibitor worked in the Phase II but not the Phase III setting.

5. Reinforcement of the new lung adenocarcinoma advanced-disease paradigm
The PARAMOUNT trial (**ab CRA7510**) again supported the role of some type of maintenance strategy after first-line chemo with or without bev, this time the "continuation" of pemetrexed, and while we await Phase III data from the related PointBreak trial, pem/carbo with or without bev followed by pem and/or bev maintenance are commonly employed nonprotocol approaches.

In a similar vein, the EURTAC study (**ab 7503**) again demonstrated that for patients with EGFR mutation-positive advanced lung cancer, an EGFR TKI results in better short-term outcomes than chemo.

6. Bevacizumab with chemotherapy in breast and ovarian cancer
Two neoadjuvant breast trials (**ab LBA1005 and 1006**) demonstrated more path CRs with bev, and a reanalysis of the RIBBON 2 trial evaluating this anti-angiogenic agent in the second-line setting revealed a doubling of response rates for patients with triple-negative disease (**ab 1010**).

In recurrent ovarian cancer, chemo plus bev with bev maintenance until progression resulted in longer PFS (**ab LBA5007**), and more follow-up from the ICON7 "adjuvant" trial (**ab LBA5006**) continued to show a slowing of disease progression with chemo/bev followed by bev maintenance. However, as yet no impact on survival has been observed. What this means in both cancers outside a protocol setting and from a regulatory/reimbursement perspective continues to be vociferously debated.

Next up on our condensed ASCO highlights reel: Liquid tumor snippets.

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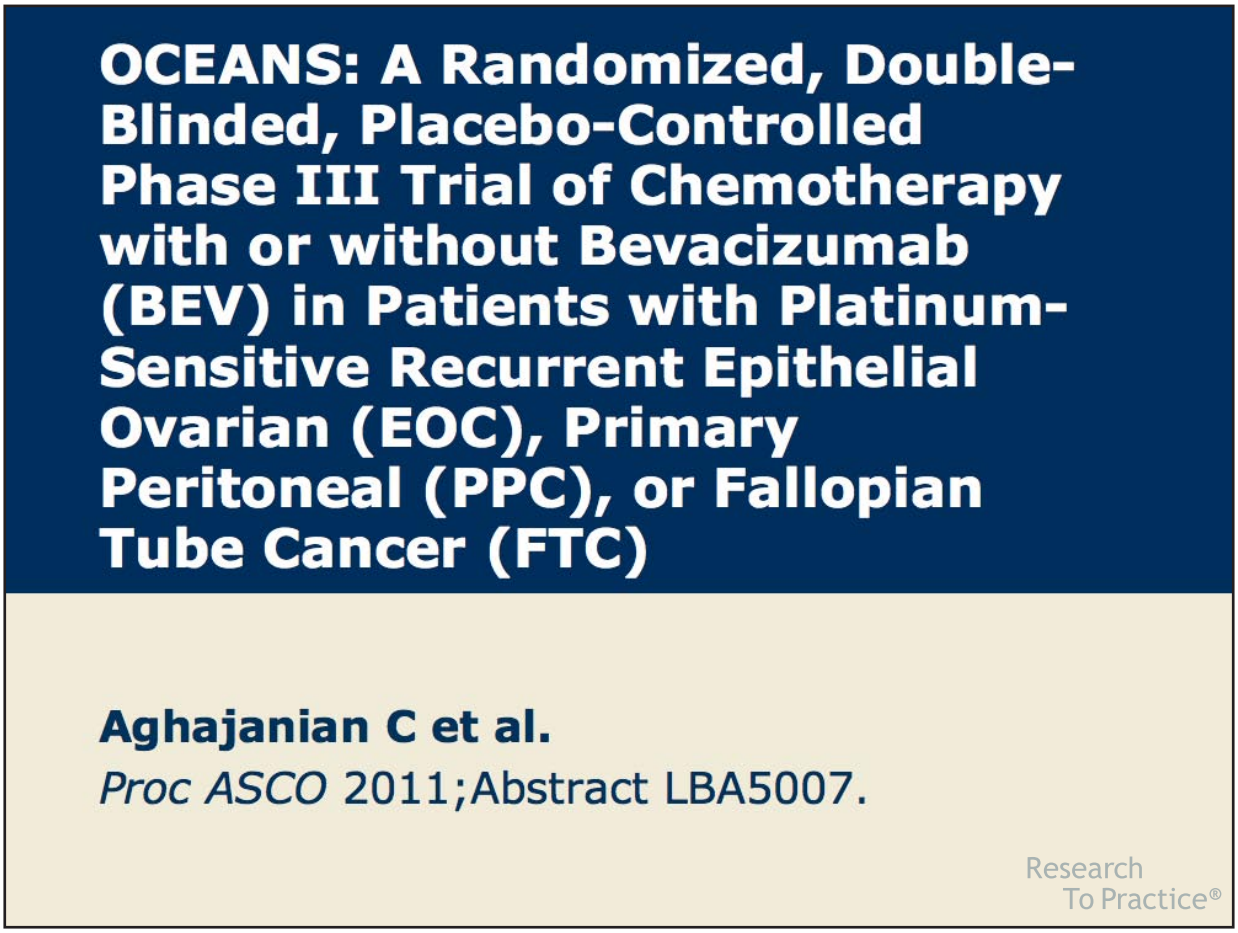
Bevacizumab (Bev) with Chemotherapy, Followed by Bev, in the Treatment of Newly Diagnosed and Platinum-Sensitive Recurrent Ovarian Cancer

Presentation discussed in this issue

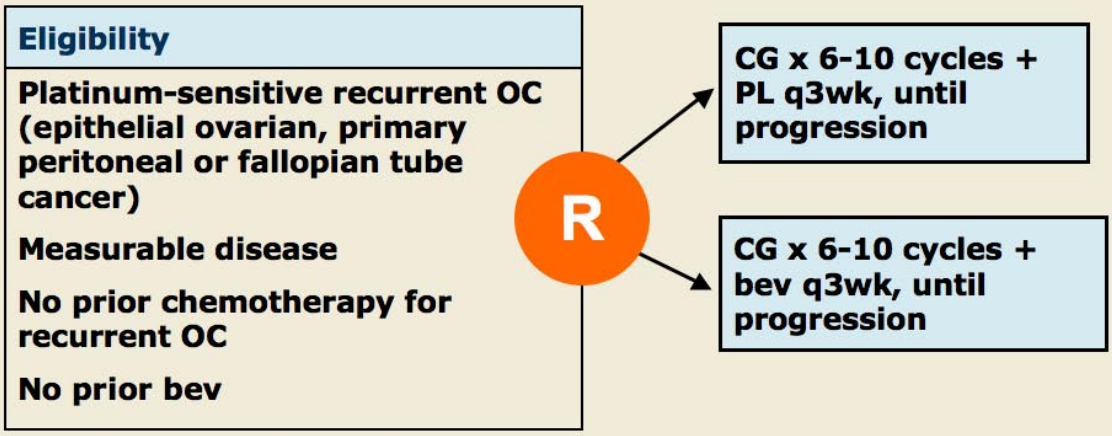
Aghajanian C et al. **OCEANS: A randomized, double-blinded, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab (BEV) in patients with platinum-sensitive recurrent epithelial ovarian (EOC), primary peritoneal (PPC), or fallopian tube cancer (FTC).** *Proc ASCO* 2011;**Abstract LBA5007**.

Slides from a presentation at ASCO 2011 and comments from Amit M Oza, MD and David R Spriggs, MD



Oceans Study Schema

Accrual: 484 (Closed)



C = carboplatin AUC4; G = gemcitabine 1,000 mg/m^2, d1 & 8;
PL = placebo; bev = bevacizumab

Aghajanian C et al. *Proc ASCO* 2011;Abstract LBA5007.

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OCEANS: Patient Characteristics

Characteristic	CG + PL (n = 242)	CG + bev (n = 242)
Median age, years	61	60
Age ≥ 65 years, %	38	35
Histologic subtype, % Serous Mucinous/clear cell Other	 84 3 14	 78 5 17
Platinum-free interval, % 6-12 months >12 months	 42 58	 41 59
Cytoreductive surgery for recurrent disease	10	12

Aghajanian C et al. *Proc ASCO* 2011;Abstract LBA5007.

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OCEANS: Response

Patients, %	CG + PL (n = 242)	CG + bev (n = 242)	Hazard ratio	*p*-value
Objective response	57%	78%	NR	<0.0001
Complete response	9%	17%		
Partial response	48%	61%		
Median duration of response (n = 139, 190)	7.4 mo	10.4 mo	0.534	<0.0001

Aghajanian C et al. *Proc ASCO* 2011;Abstract LBA5007.

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OCEANS: Progression-Free Survival

	CG + PL (n = 242)	CG + bev (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) Log-rank *p*-value	0.484 (0.388–0.605) <0.0001	

Aghajanian C et al. *Proc ASCO* 2011;Abstract LBA5007.

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OCEANS: Select Adverse Events

Patients, %	CG + PL (n = 233)	CG + bev (n = 247)
Neutropenia, Grade ≥3	56	58
Febrile neutropenia, Grade ≥3	2	2
Hypertension, Grade ≥3	<1	17
Fistula/abscess, all grades	<1	2
Proteinuria, Grade ≥3	1	9
GI perforations	0	0
Reversible leukoencephalopathy syndrome	0	1
Wound-healing complication, Grade ≥3	0	1

Aghajanian C et al. *Proc ASCO* 2011;Abstract LBA5007.

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Author Conclusions

- Bevacizumab/carboplatin/gemcitabine followed by bevacizumab until progression provides clinically meaningful benefit compared to chemotherapy alone in recurrent OC
  - Improved PFS: 12.4 months vs 8.4 months; HR = 0.484 ($p < 0.0001$)
  - Improved ORR: 78% vs 57% ($p < 0.0001$)
  - Improved DOR: 10.4 months vs 7.4 months
- Safety data are consistent with the profile for bevacizumab
- This regimen should be considered a new option for recurrent platinum-sensitive OC

Aghajanian C et al. *Proc ASCO* 2011;Abstract LBA5007.

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Investigator Commentary: Results from the OCEANS Phase III Trial

The OCEANS study built in concurrent chemotherapy with bevacizumab in a population that was platinum sensitive with recurrent disease. This study did provide bevacizumab until progression as maintenance and showed a significant separation of the curves from the beginning of therapy, which continued for a long time. The hazard ratio of about 0.48 was statistically significant, and I believe that continuing with bevacizumab until progression probably maintained disease control for a longer period. What seems to be emerging is that continuing with bevacizumab until progression would make sense in patients who are at high risk of having recurrent disease over a short period.

Amit M Oza, MD

The data in ovarian cancer have continued to accumulate in a positive way. The OCEANS study showed a substantial advantage in time to progression in the patients who had received bevacizumab with carboplatin and gemcitabine, as opposed to the carboplatin, gemcitabine and placebo group, and this seems to be a positive option.

David R Spriggs, MD

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