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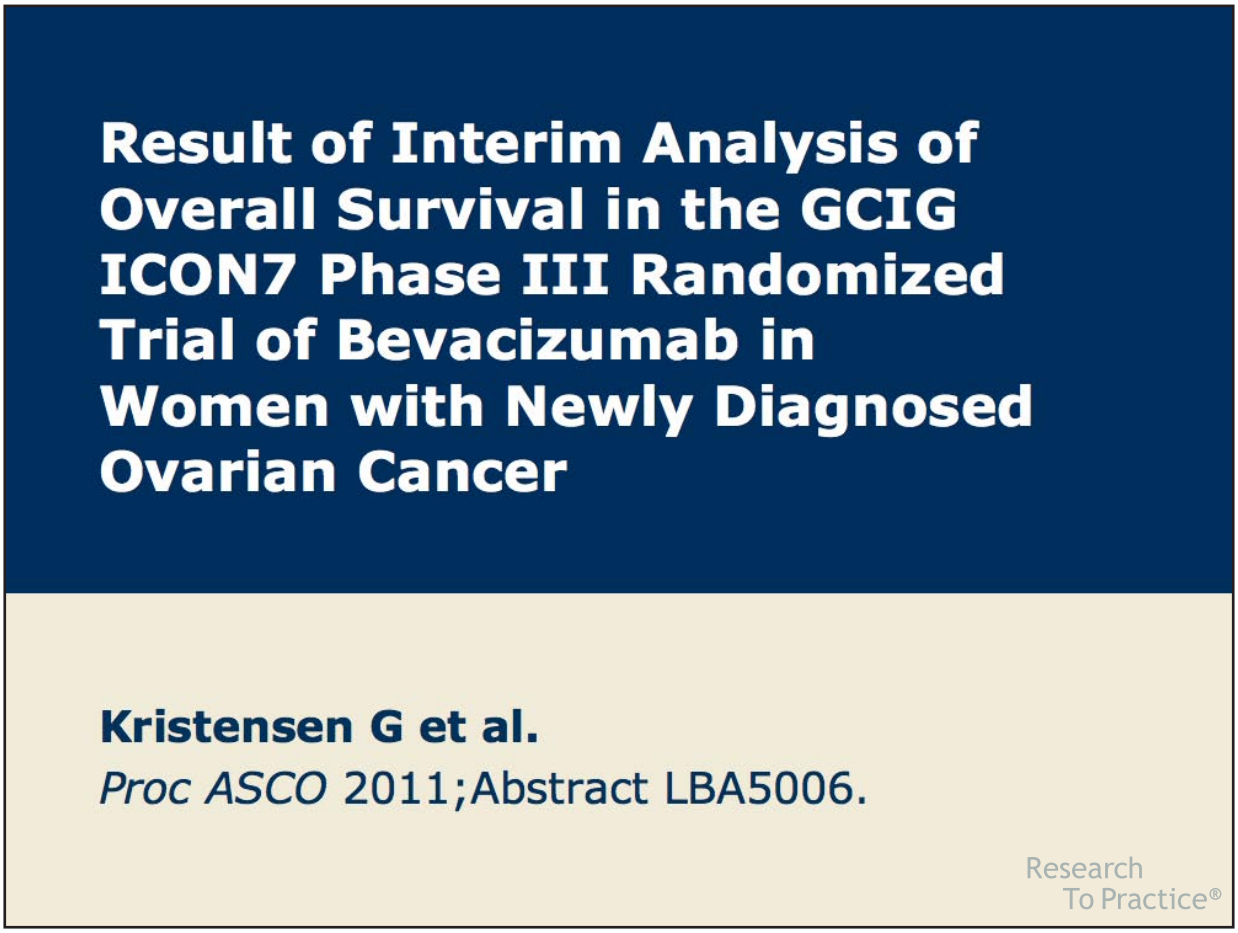
Bevacizumab (Bev) with Chemotherapy, Followed by Bev, in the Treatment of Newly Diagnosed and Platinum-Sensitive Recurrent Ovarian Cancer

Presentation discussed in this issue

Kristensen G et al. **Result of interim analysis of overall survival in the GCIG ICON7 phase III randomized trial of bevacizumab in women with newly diagnosed ovarian cancer.** *Proc ASCO* 2011;**Abstract LBA5006**.

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



Background

- Preliminary results of the ICON7 phase III trial of bevacizumab combined with carboplatin and paclitaxel followed by bevacizumab showed
  - Benefit in progression-free survival (PFS), with 15% improvement at 12 months, $p = 0.0041$
  - Suggestion of a trend in improved overall survival (OS), with early results, based on only 34% of the events required for final analysis (HR = 0.81, $p = 0.098$)
- Regulatory authorities requested an interim analysis with at least 51% of 715 required events to support filing for licensing.
  - Approved by independent data monitoring and steering committees
  - Exploratory subgroup analysis for poor prognosis patients was performed

Kristensen G et al. *Proc ASCO* 2011;Abstract LBA5006.

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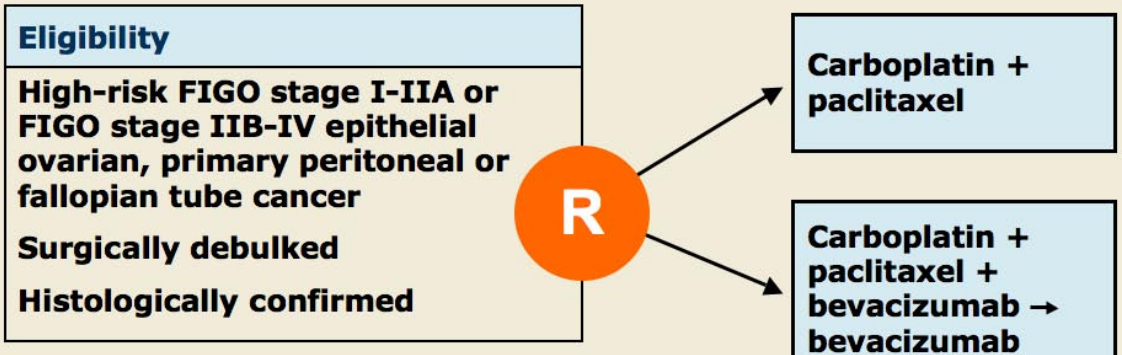
ICON7 Study Design

Accrual: 1,528 (Closed)



Stratification: Stage/extent of debulking; timing of intended treatment start; GCIG group

Carboplatin (C), AUC 5 or 6; Paclitaxel (P), 175 mg/m²; Bevacizumab (bev), 7.5 mg/kg q3w, 18 cycles (12 mo)

Kristensen G et al. *Proc ASCO* 2011;Abstract LBA5006.

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Updated Efficacy Results*

Efficacy parameter	C + P (n = 764)	C + P + bev (n = 764)	Hazard ratio	*p*-value
Median progression-free survival (PFS), months	17.4	19.8	0.87	0.039
Median overall survival (OS), months	Not reached	Not reached	0.85	0.11
1-year OS rate	92%	95%		
High-risk subgroup† (n = 234, 231)				
1-year OS	**86%**	**92%**	**0.64**	**0.002**
Median OS, months	**28.8**	**36.6**		

* Median follow-up = 28 months; † FIGO III >1 cm/FIGO IV debulking

Kristensen G et al. *Proc ASCO* 2011;Abstract LBA5006.

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Author Conclusions

- Bevacizumab combined with chemotherapy and continued alone versus chemotherapy demonstrates:
  - Continued improvement in PFS
  - Trend for improved OS continuing in the total population, at interim analysis
  - A greater treatment effect in patients at high risk of recurrence, which may be clinically relevant
- Final OS results are expected in 2013

Kristensen G et al. *Proc ASCO* 2011;Abstract LBA5006.

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Investigator Commentary: Interim Analysis of Overall Survival in the GCIG ICON7 Trial

What is emerging is the benefit to administering bevacizumab in conjunction with chemotherapy, then continuing into a maintenance setting with first-line therapy. Patients at higher risk, presenting with more disease or with suboptimally debulked or macroscopic residual disease, seem to be the ones who derive greater benefit from this regimen, certainly with respect to progression-free survival at this time. A trend in overall survival was reported but the data are maturing, and that endpoint will not be final until 2013.

The benefit observed in the suboptimal population in the ICON7 study with bevacizumab at the 7.5 mg/kg dose is similar to what was attained in the GOG-0218 study with bevacizumab administered at 15 mg/kg. If I could, I would administer bevacizumab at 7.5 mg/kg, and for longer than the 12 month duration specified in the study, because the benefit we saw in ICON7 peaked at 12 months, which was when bevacizumab was discontinued. The level of PFS benefit began to taper off after that time, and that does suggest that administering it for longer would perhaps be more advantageous.

Amit M Oza, MD