5 Minute JournalClub

Key ASCO Presentations
Issue 1, 2010

Bevacizumab in the Primary Treatment of Advanced Ovarian, Peritoneal or Fallopian Tube Carcinoma

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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 serial 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 patients with diverse forms of cancer.

LEARNING OBJECTIVE

- Describe the incremental benefit and risk of bevacizumab when incorporated into the front-line treatment of advanced ovarian, primary peritoneal or fallopian tube carcinoma.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Key ASCO Presentations
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To go directly to the slides, **click here**.

While cooperative research groups like the GOG have a notable heritage of executing important clinical trials in ovarian cancer, patients have been left with a number of challenging interventions such as surgical debulking and intraperitoneal chemotherapy that have not moved the survival bar as far forward as is needed.

In this first of eight email/web summaries of key ASCO data sets across all of cancer medicine, we focus on several ovarian cancer papers providing hope that the field may be moving in a very positive direction. Unlike last year's rare ovarian cancer ASCO plenary presentation on the role of CA125 testing, which was sort of the "same old, same old," the data this year were riveting as Bob Burger proudly presented the first results of GOG trial 218.

This landmark study evaluated carboplatin/paclitaxel alone or with concurrent bevacizumab or with concurrent bev followed by maintenance bev to a total of 15 months for patients with Stage III or Stage IV disease after surgery. The study reached its primary endpoint of improved PFS for patients receiving chemo/bev followed by bev maintenance (hazard ratio 0.717; PFS increase from 10.3 months to 14.1 months; no difference in survival). In his conclusion Dr Burger stated that this regimen should be considered "one standard option for these patients." However, other investigators have been more conservative in their responses (**click here** for five brief takes on this).

Dr Elizabeth Eisenhauer, in a fascinating discussion of these important findings, showed a number of theoretical models of what this might mean in terms of overall survival, and additional data from this and other maturing trials will clarify this controversial situation.

As is often the case at ASCO, a lot of the most interesting stuff wasn't at the plenary sessions or even at the organ-oriented oral sessions, and this year we were treated to a spectacular clinical science symposium focused on PARP inhibitors. The highlight of this session was a paradigm shaker — a **Phase II study of olaparib**, an orally administered PARP inhibitor with demonstrated monotherapy activity in BRCA-related breast and ovarian cancer. The big news was that partial tumor responses to this generally well-tolerated agent were observed in about a quarter of the 46 patients with high-grade serous ovarian carcinoma without BRCA mutations. The waterfall plot

showed additional patients with tumor regression. (Interestingly, no responses were seen in 15 patients with triple-negative breast cancer without BRCA mutations nor in eight patients with BRCA mutations and breast cancer.)

The presenter, Dr Karen Gelmon, discussed genetic explanations for these fascinating clinical observations, but while I could barely comprehend the DNA physiology, it was very easy to follow her comments about a patient with non-BRCA ovarian cancer who experienced a nine-month objective response after disease progression on several chemo regimens. Translational work is now attempting to define tumors more likely to respond to PARP inhibitors, including an interesting but complicated paper also presented at ASCO and just published in the *Journal of Clinical Oncology* attempting — as is being done in breast cancer — to define "BRCAness" in ovarian cancer with gene expression profiling.

The final data set profiled in this take on what was most newsworthy in ovarian cancer at ASCO relates to another biologic agent, AMG 386, which is an investigational peptide-Fc fusion protein that inhibits angiogenesis quite differently than does bevacizumab. For many this paper flew under the radar, but for Memorial's David Spriggs it was his favorite ASCO presentation on a new agent because unlike the many hard-to-interpret single-arm Phase II studies, this was a randomized Phase II trial yielding very encouraging results.

Next up on 5-Minute Journal Club: Another infrequent presence on the ASCO plenary stage — Metastatic melanoma.

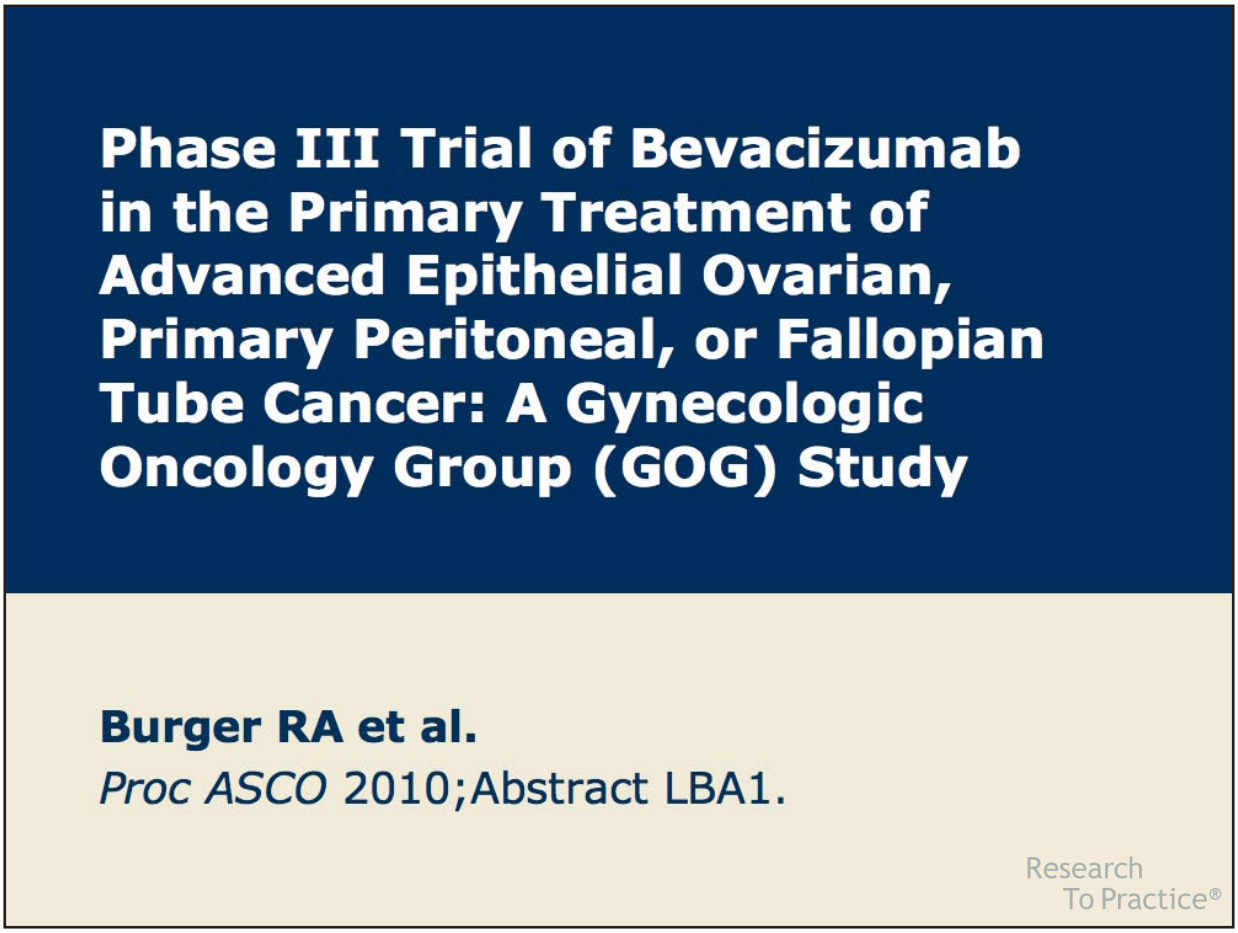
Neil Love, MD
Research To Practice
Miami, Florida

Bevacizumab in the Primary Treatment of Advanced Ovarian, Peritoneal or Fallopian Tube Carcinoma

Presentation discussed in this issue

Burger RA et al. **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.** *Proc ASCO* 2010;**Abstract LBA1**.

Slides from a presentation at ASCO 2010 and transcribed comments from recent interviews with Robert A Burger, MD (6/16/10), Robert L Coleman, MD (6/21/10), Thomas J Herzog, MD (6/21/10), Ursula A Matulonis, MD (6/16/10) and David R Spriggs, MD (6/23/10)



Introduction

- Bevacizumab (Bev) in combination with chemotherapy has been approved for the treatment of patients with metastatic colorectal and lung cancers.
- Single agent activity for Bev has been demonstrated in Phase II studies in recurrent ovarian cancer (*JCO* 2007;25:5165, *JCO* 2007;25:5180).
- **Current study objective:**
  - Assess the benefit in progression-free survival (PFS) when Bev is incorporated in the front-line treatment of patients with advanced ovarian, primary peritoneal or fallopian tube cancer.

Burger RA et al. *Proc ASCO* 2010;Abstract LBA1.

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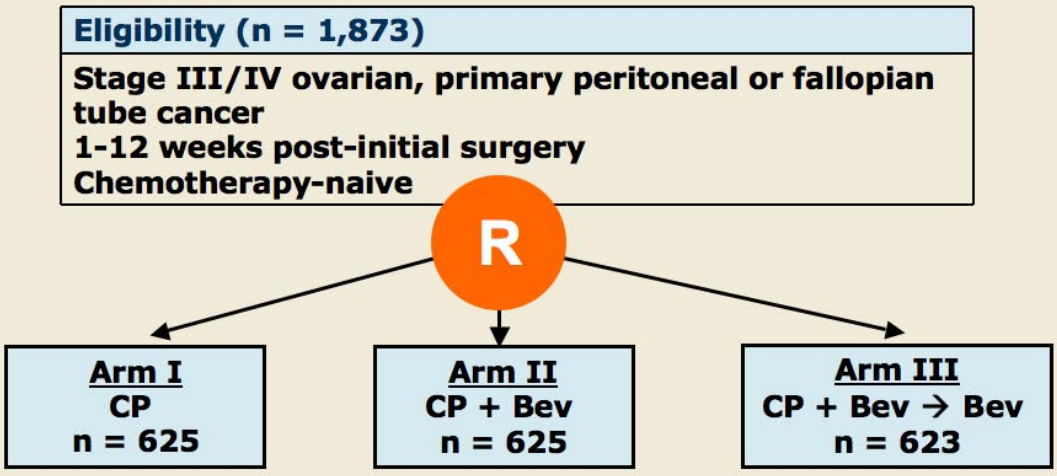
GOG-0218: Study Design



CP = Carboplatin AUC 6, Paclitaxel 175mg/m^2; Six 3-week cycles
CP + Bev = CP + Bev 15 mg/kg with each cycle of CP
CP + Bev → Bev = CP + Bev followed by sixteen 3-week cycles of Bev 15 mg/kg

Burger RA et al. *Proc ASCO* 2010;Abstract LBA1.

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Assessment of PFS

- GOG-0218 protocol-defined PFS was based on:
  - RECIST criteria
  - Global clinical deterioration
  - Serum CA-125 levels
- Serum CA-125 levels are used in clinical practice as a determinant of disease progression, though its incorporation in PFS has been questioned by regulatory agencies.
  - Therefore, sensitivity analysis of PFS with CA-125 censoring was done.

Burger RA et al. *Proc ASCO* 2010;Abstract LBA1.

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Study Participants

- GOG-0218 enrolled 1,873 patients from 336 sites (US, Canada, South Korea, Japan) from 2005 to 2009.
- Median age: 60

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)

Burger RA et al. *Proc ASCO* 2010;Abstract LBA1.

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Select Adverse Events

Adverse Event	Arm I CP (n = 601)	Arm II CP + Bev (n = 607)	Arm III CP + Bev → Bev (n = 608)
GI events (grade ≥2)*	**1.2%**	**2.8%**	**2.6%**
HTN (grade ≥2)	7.2%	16.5%	22.9%
Proteinuria	0.7%	0.7%	1.6%
Venous thromboembolic events	5.8%	5.3%	6.7%
Arteriovenous thrombotic events	0.8%	0.7%	0.7%
CNS bleeding	0%	0%	0.3%
Non-CNS bleeding	0.8%	1.3%	2.1%

*GI events include perforation, fistula, necrosis and leak.

Burger RA et al. *Proc* ASCO 2010;Abstract LBA1.

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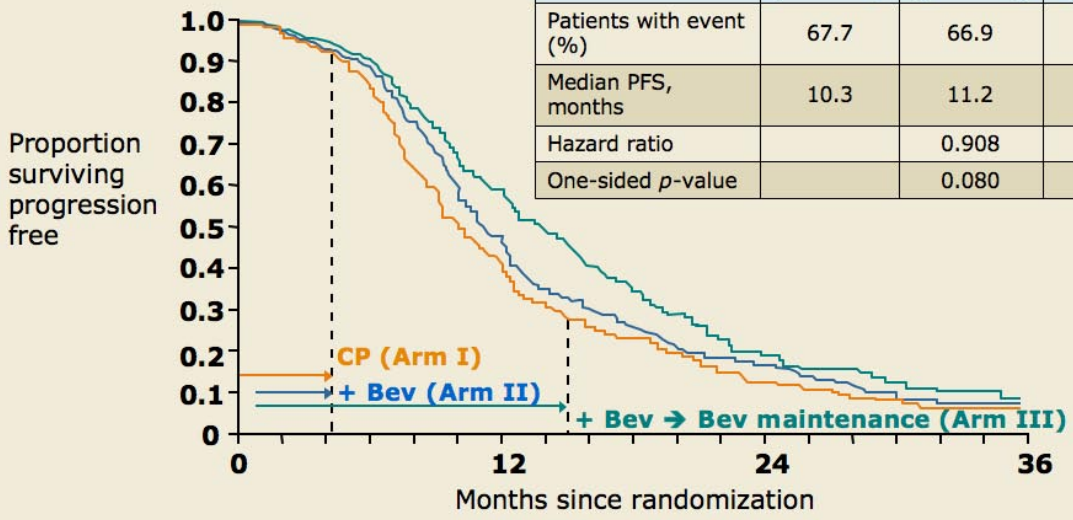
Primary Endpoint: PFS

	Arm I CP (n = 625)	Arm II CP + Bev (n = 625)	Arm III CP + Bev → Bev (n = 623)
Patients with event (%)	67.7	66.9	57.8
Median PFS, months	10.3	11.2	14.1
Hazard ratio		0.908	0.717
One-sided *p*-value		0.080	<0.0001



With permission from Burger RA et al. *Proc ASCO* 2010;Abstract LBA1.

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Sensitivity Analysis (CA-125 censored PFS analysis)

	Protocol Defined PFS	CA-125 Censored PFS
Arm I	10.3 months	12.0 months
Arm III	14.1 months	18.0 months
Absolute PFS improvement	3.8 months	6.0 months
Hazard ratio	0.717	0.645
p-value	< 0.0001	< 0.0001

Burger RA et al. *Proc ASCO* 2010;Abstract LBA1.

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Overall Survival

	Arm I CP (n = 625)	Arm II CP + Bev (n = 625)	Arm III CP + Bev → Bev (n = 623)
Deaths	156 (25.0%)	150 (24.0%)	138 (22.2%)
1-Year Survival	90.6%	90.4%	91.3%

Events were observed in ~ 24% of patients at the time of database lock.

Burger RA et al. *Proc ASCO* 2010;Abstract LBA1.

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Conclusions

- Significant improvement in PFS was observed with the addition of Bev to chemotherapy plus Bev maintenance as front-line treatment of advanced ovarian cancer.
- No significant PFS improvement was observed with the addition of Bev to chemotherapy without Bev maintenance.
- Interpretation of overall survival analysis is limited due to a smaller proportion of death events.
- Adverse events observed with Bev were similar to previous studies.
  - The rate of GI perforation and fistula was less than 3% in all study arms.
- Bev is the first targeted and first anti-angiogenic agent to demonstrate a benefit in this patient population.

Burger RA et al. *Proc ASCO* 2010;Abstract LBA1.

Practice Implications

- Use of Bev as a standard practice for the management of ovarian cancer remains uncertain.
  - PFS gain alone of 3.8 mos may not be meaningful to patients.
  - Mature OS and quality of life (QoL) data are needed.
  - Data from ongoing Phase III trial ICON7 examining standard chemotherapy ± Bev are needed.
- GOG-0218 trial results raise several questions:
  - Is maintenance therapy alone sufficient?
  - Is delayed progression associated with improved QoL?
  - Is CA125 progression definition simplifying or complicating clinical trial conduct?
  - Is there truly a nonlinear relationship between PFS and OS in trials of angiogenesis inhibitors?

Burger RA et al. *Proc ASCO* 2010;Abstract LBA1; Eisenhauer E. ASCO 2010;Discussion.

Investigator comments on GOG-0218

The benefit-to-risk ratio is favorable for most patients who meet the eligibility requirements for GOG-0218. I would be careful about adding bevacizumab for patients not meeting the eligibility criteria — for example, patients with active bowel obstruction or earlier-stage disease. The not-yet-reported ICON7 trial is enrolling patients with earlier-stage disease.

We also can't extrapolate from the GOG-0218 data to the patients who receive neoadjuvant chemotherapy before surgery. Patients in GOG-0218 underwent surgery before enrolling. We haven't established the safety and feasibility of this approach in the neoadjuvant setting. Also, for patients receiving intraperitoneal chemotherapy the safety and efficacy of adding bevacizumab have not been established, but this is being evaluated in a Phase III GOG trial.

Interview with Robert A Burger, MD, June 16, 2010

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Investigator comments on GOG-0218

We need to watch the data from this trial mature over time and see if the progression-free survival (PFS) changes or if a benefit in overall survival appears. Our group is discussing the results with patients who are newly diagnosed and also with those who are about to complete chemotherapy in terms of whether they should receive maintenance bevacizumab for a year. I caution patients with a bowel resection that they would probably assume a higher risk for developing a perforation at that site. It's a tricky situation.

Patients with high-grade serous cancer and remaining disease have approximately an 80 percent risk of the cancer recurring. So with those patients I'm definitely talking about bevacizumab during chemotherapy and as maintenance therapy, and then, of course, checking with their insurance company to find out whether their coverage includes this use of bevacizumab.

It will be interesting to see how future clinical trials are designed. For example, in the current up-front GOG study of intraperitoneal chemotherapy, patients on all three arms receive bevacizumab.

Interview with Ursula A Matulonis, MD, June 16, 2010

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Investigator comments on GOG-0218

I would not routinely offer bevacizumab to someone receiving intraperitoneal therapy, but much more problematic is the patient who meets the GOG-0218 study criteria. I don't know the right answer in that situation.

I don't believe it's ***the*** standard of care at this point, but is it ***a*** standard of care? Is it a reasonable option? I believe it is, based on the safety data that we've seen and the improvement in the primary endpoint of PFS. On the con side is the fact that the survival data are not yet available.

The other unavoidable issue is cost and how much you are gaining at that cost. Yet we are using more expensive therapies with arguably marginal gains. Before this becomes what people would consider ***the*** standard practice, we need to see mature survival data from GOG-0218 and also data from the ICON7 trial evaluating bevacizumab at a lower dose and a little less exposure time — 12 months.

Interview with Thomas J Herzog, MD, June 21, 2010

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Investigator comments on GOG-0218

It's a tough call. At my institution, we've taken the approach that at this point it is rational to administer bevacizumab up front with chemotherapy to women with ovarian cancer only in the context of a clinical trial.

We currently use bevacizumab for relapsed disease, and one of the possible interpretations of the lack of survival advantage in GOG-0218 is late crossover. Hopefully, by the end of 2010 we'll have data from two other trials, and we'll really begin to have a good sense of the effect of this agent in front-line treatment.

It could be that two years of bevacizumab is better than one year, but at some point, administering bevacizumab for an extended duration becomes unaffordable. Optimizing treatment duration and dose are two important avenues for trials to pursue as we try to figure out exactly how to best use a drug that is both potent and expensive.

Interview with David R Spriggs, MD, June 23, 2010

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Investigator comments on GOG-0218

A few surprises emerged with this trial — particularly the lack of benefit from adding bevacizumab to chemotherapy without maintenance — but overall, this is a welcome addition that may potentially change the standard front-line treatment of ovarian cancer.

I share many of the concerns raised by the ASCO discussant, Elizabeth Eisenhauer, not the least of which is cost, but a number of unanswered questions remain about this regimen, particularly related to overall survival.

Currently, we use bevacizumab predominantly in the recurrent setting, mainly as a single agent. A number of people have asked me, "If the mature data show no overall survival difference, can we just treat in later-line disease?" As the toxicity profiles become better understood in the recurrent setting, the answer to this question may not be yes. It may be that we need to use bevacizumab earlier because of the potential toxicity exacerbation in further-along therapy, but whether it's administered in the first line or in the second line in combination with chemotherapy remains to be seen.

Interview with Robert L Coleman, MD, June 21, 2010