5 Minute JournalClub

Key ASCO Presentations
Issue 1, 2010

AMG 386, an Angiogenesis Inhibitor, in the Treatment of Recurrent 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 efficacy and toxicity profile of AMG 386 combined with paclitaxel for patients with recurrent ovarian, 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:

Robert A Burger, MD
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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.

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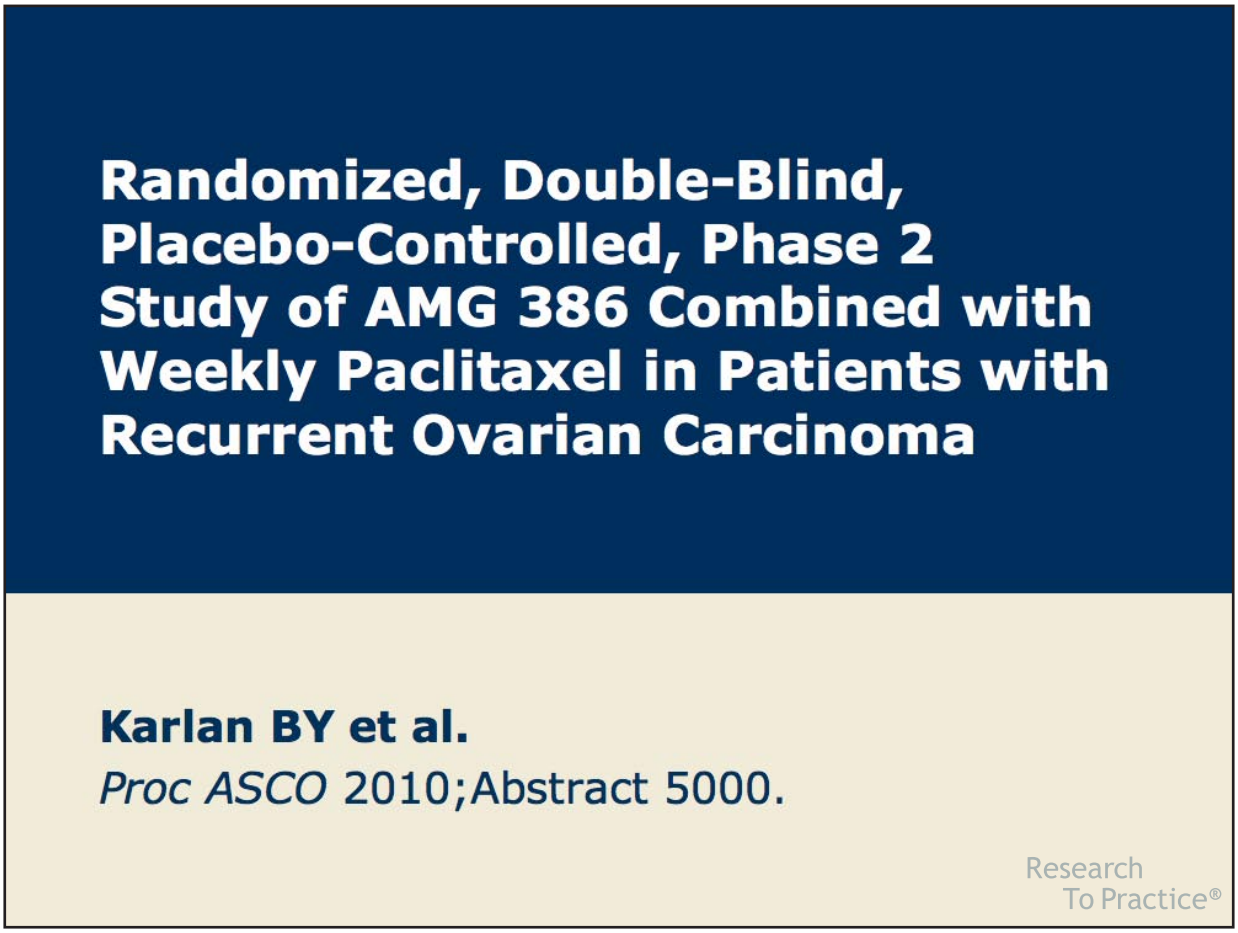
AMG 386, an Angiogenesis Inhibitor, in the Treatment of Recurrent Ovarian, Peritoneal or Fallopian Tube Carcinoma

Presentation discussed in this issue

Karlan BY et al. **Randomized, double-blind, placebo-controlled, Phase II study of AMG 386 combined with weekly paclitaxel in patients with recurrent ovarian cancer.** *Proc ASCO* 2010;**Abstract 5000**.

Slides from a presentation at ASCO 2010 and transcribed comments from a recent interview with Robert A Burger, MD (6/16/10)



Introduction

- Eighty percent of women with late stage ovarian cancer will experience recurrence and eventually die from the disease.
- Angiopoietins are pro-angiogenic factors involved in angiogenesis and vascularity in tumors (*Am J Pathol* 2000;176:2150).
- AMG 386 is a recombinant peptide-Fc fusion protein (peptibody) which binds and neutralizes angiopoietins.
- A patient with recurrent ovarian cancer had a durable PR when treated with AMG 386 in a first-in-human Phase I study (*JCO* 2009;27:3557).
- **Current study objective:**
  - Estimate the progression-free survival (PFS) in patients with recurrent ovarian cancer receiving weekly paclitaxel combined with either AMG 386 or placebo.

Karlan BY et al. *Proc ASCO* 2010;Abstract 5000.

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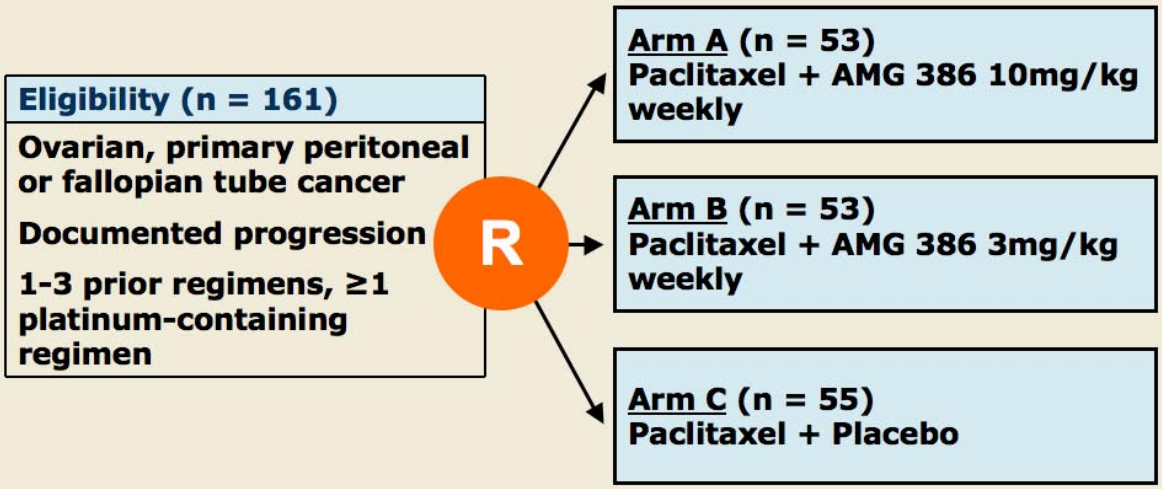
Randomized Phase II Study Design



Paclitaxel (Pac) given as 80 mg/m^2, 3 weeks on/1 week off in each arm

Karlan BY et al. *Proc ASCO* 2010;Abstract 5000.

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Primary Endpoint: PFS

	Arm A (n = 53) Pac + AMG 386 10 mg/kg	Arm B (n = 53) Pac + AMG 386 3 mg/kg	Arm C (n = 55) Pac + Placebo
Median PFS	7.2 months	5.7 months	4.6 months
	Hazard ratio	***p*-value**	**Trend test *p*-value**
Arms A+B vs placebo	0.76	0.17	0.037

Karlan BY et al. *Proc ASCO* 2010;Abstract 5000.

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Objective Response per RECIST

	Arm A Pac + AMG 386 10 mg/kg (n = 53)	Arm B Pac + AMG 386 3 mg/kg (n = 53)	Arm C Pac + Placebo (n = 55)
Patients with RECIST measurable disease at baseline	46 (87%)	47 (89%)	52 (95%)
Complete response (CR)	2 (4%)	1 (2%)	0
Partial response (PR)	15 (33%)	8 (17%)	14 (27%)
CR + PR	17 (37%)	9 (19%)	14 (27%)
Stable disease	20 (43%)	22 (47%)	18 (35%)

Karlan BY et al. *Proc ASCO* 2010;Abstract 5000.

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Adverse Events (AE) Where Percent Difference from Placebo Is ≥5%

	Arm A (n = 53) Pac + AMG 386 10 mg/kg ≥Grade 3 AE	Arm B (n = 52) Pac + AMG 386 3 mg/kg ≥Grade 3 AE	Arm C (n = 55) Pac + Placebo ≥Grade 3 AE
Hypokalemia	12%	11%	4%
Peripheral neuropathy	10%	2%	4%
Anorexia	2%	6%	0%
Neutropenia	8%	9%	4%
Dyspnea	2%	9%	4%

Karlan BY et al. *Proc ASCO* 2010;Abstract 5000.

Conclusion

- This study provides encouraging evidence of the antitumor activity of AMG 386 and paclitaxel in patients with advanced ovarian cancer.
- The primary endpoint of PFS improvement was met at AMG 386 dosage of 10 mg/kg.
- Exposure-response analysis suggests that investigation using higher doses of AMG 386 might be warranted.
- The adverse event profile was generally manageable and distinct from that of VEGF inhibitors.

Karlan BY et al. *Proc ASCO* 2010;Abstract 5000.

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Investigator comment on AMG 386

This is an exciting trial. The agent is an antibody that essentially blocks the interaction between angiopoietin and its receptor, which is commonly found in the endothelium.

The favorable effects on progression-free survival that were reported allow it to go to the next level in a Phase III trial and will also allow us to examine increased doses. In this study, they performed sophisticated pharmacokinetic analyses, calculating the AUC in patients receiving both dose levels, and patients with a higher effective concentration of the drug over time experienced an improvement in progression-free survival compared to others. Subsequent trials may evaluate the combination of a drug such as this with an anti-VEGF approach, either sequentially or in combination.

Some unique toxicities occurred, such as peripheral edema, which is usually mild and does not require therapeutic intervention. Hypokalemia is another interesting toxicity, but no other safety signal looks important for this agent.

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