5 Minute JournalClub

Key ASCO Presentations

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CME Information

LEARNING OBJECTIVES

- Describe the incremental benefit and risk of bevacizumab when incorporated into the front-line treatment of advanced ovarian, primary peritoneal or fallopian tube carcinoma.
- Describe the correlation between BRCA dysfunction and tumor responsiveness to the PARP inhibitor olaparib in patients with advanced serous ovarian cancer or TNBC.
- Describe the correlation of distinct gene expression profiles (BRCA-like and non-BRCA-like) with outcome and with responsiveness to platinum therapy and PARP inhibitors in sporadic ovarian tumors.
- Describe the efficacy and toxicity profile of AMG 386 combined with paclitaxel for patients with recurrent ovarian, peritoneal or fallopian tube carcinoma.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

FACULTY DISCLOSURES
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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CME Information (Continued)

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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

Burger RA et al.

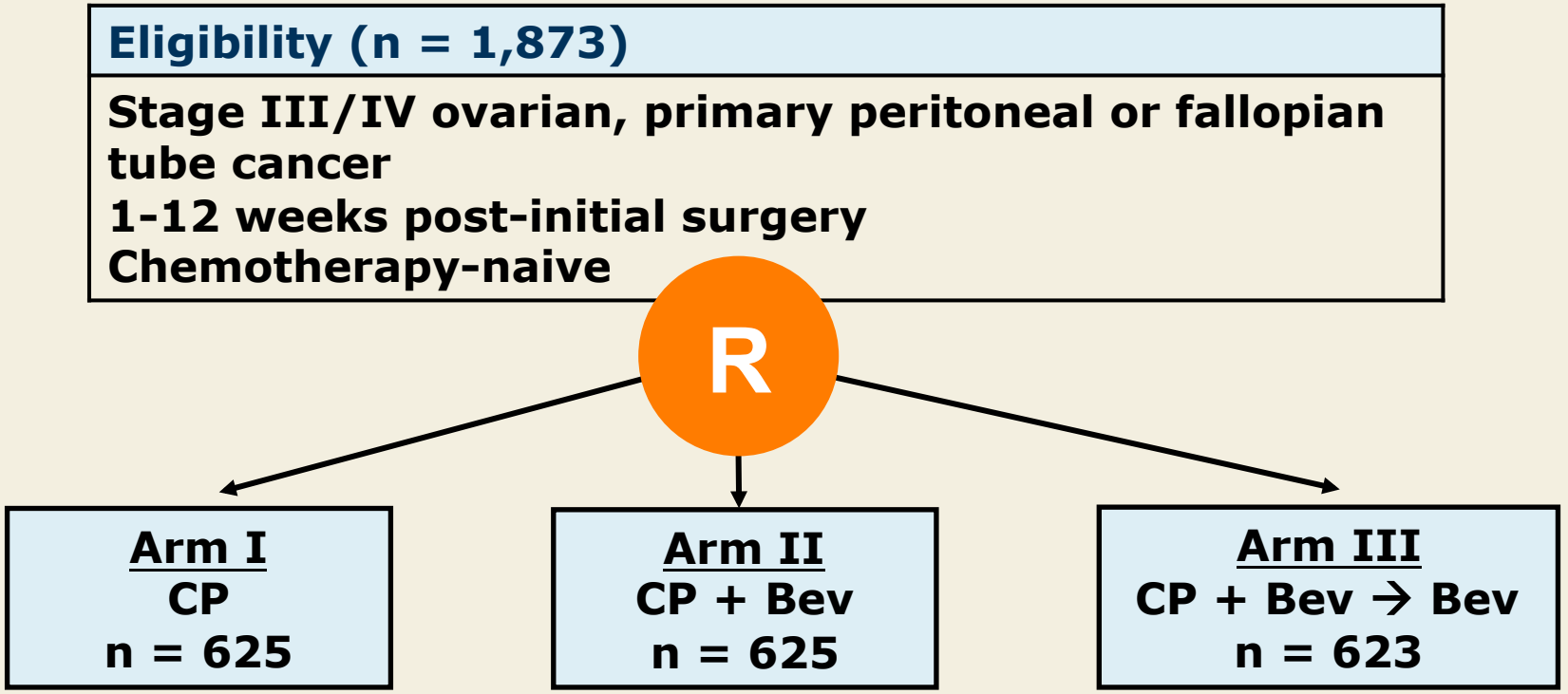
Proc ASCO 2010;Abstract LBA1.

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.

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.

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.

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.

Select Adverse Events

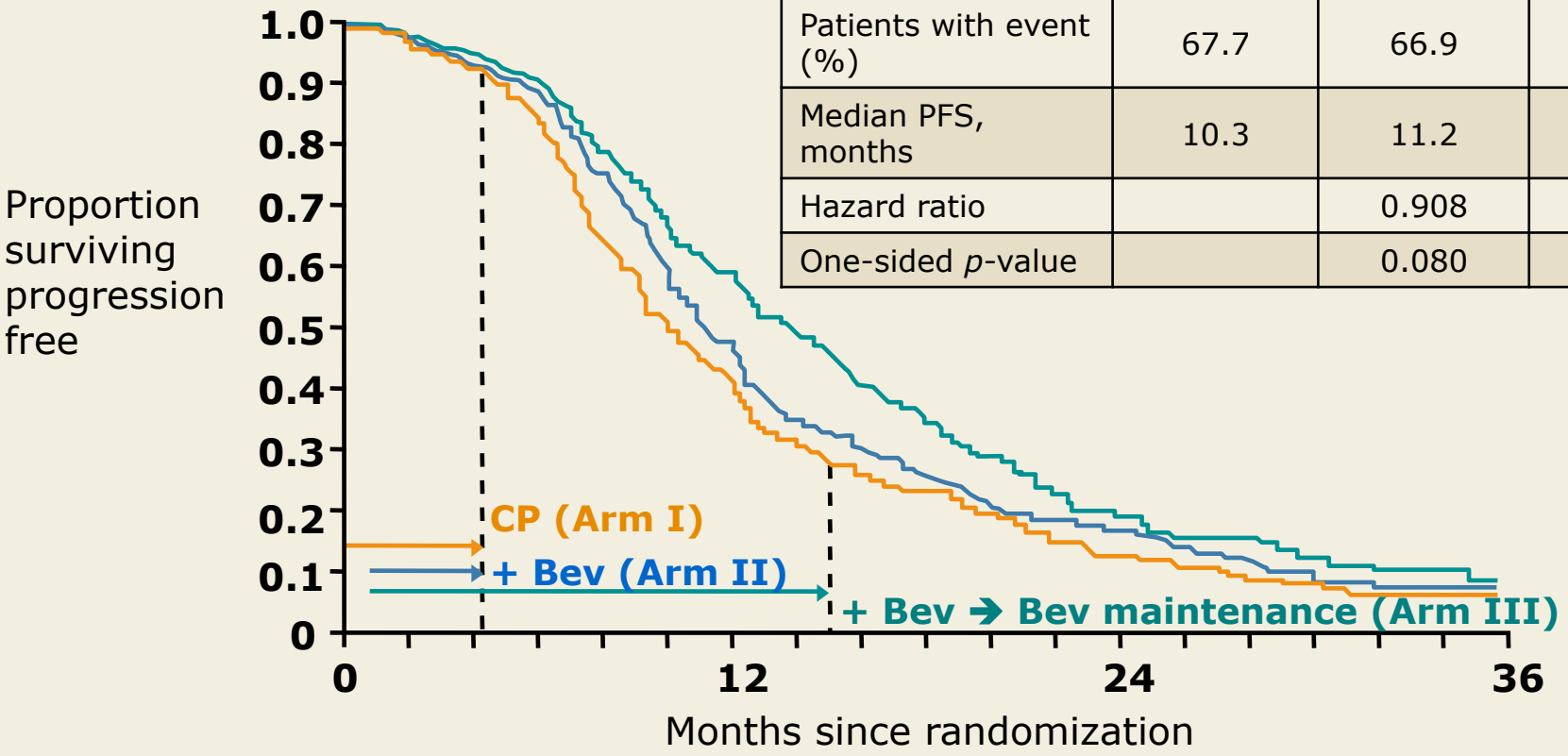
Adverse Event	Arm I CP (n = 601)	Arm II CP + Bev (n = 607)	Arm III CP + Bev → Bev (n = 608)
GI events (grade ≥2)*	**1.2%**	**2.8%**	**2.6%**
HTN (grade ≥2)	7.2%	16.5%	22.9%
Proteinuria	0.7%	0.7%	1.6%
Venous thromboembolic events	5.8%	5.3%	6.7%
Arteriovenous thrombotic events	0.8%	0.7%	0.7%
CNS bleeding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

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.

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.

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.

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

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

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

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

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

Can We Define Tumors That Will Respond to PARP Inhibitors? A Phase II Correlative Study of Olaparib in Advanced Serous Ovarian Cancer and Triple-Negative Breast Cancer

Gelmon KA et al.

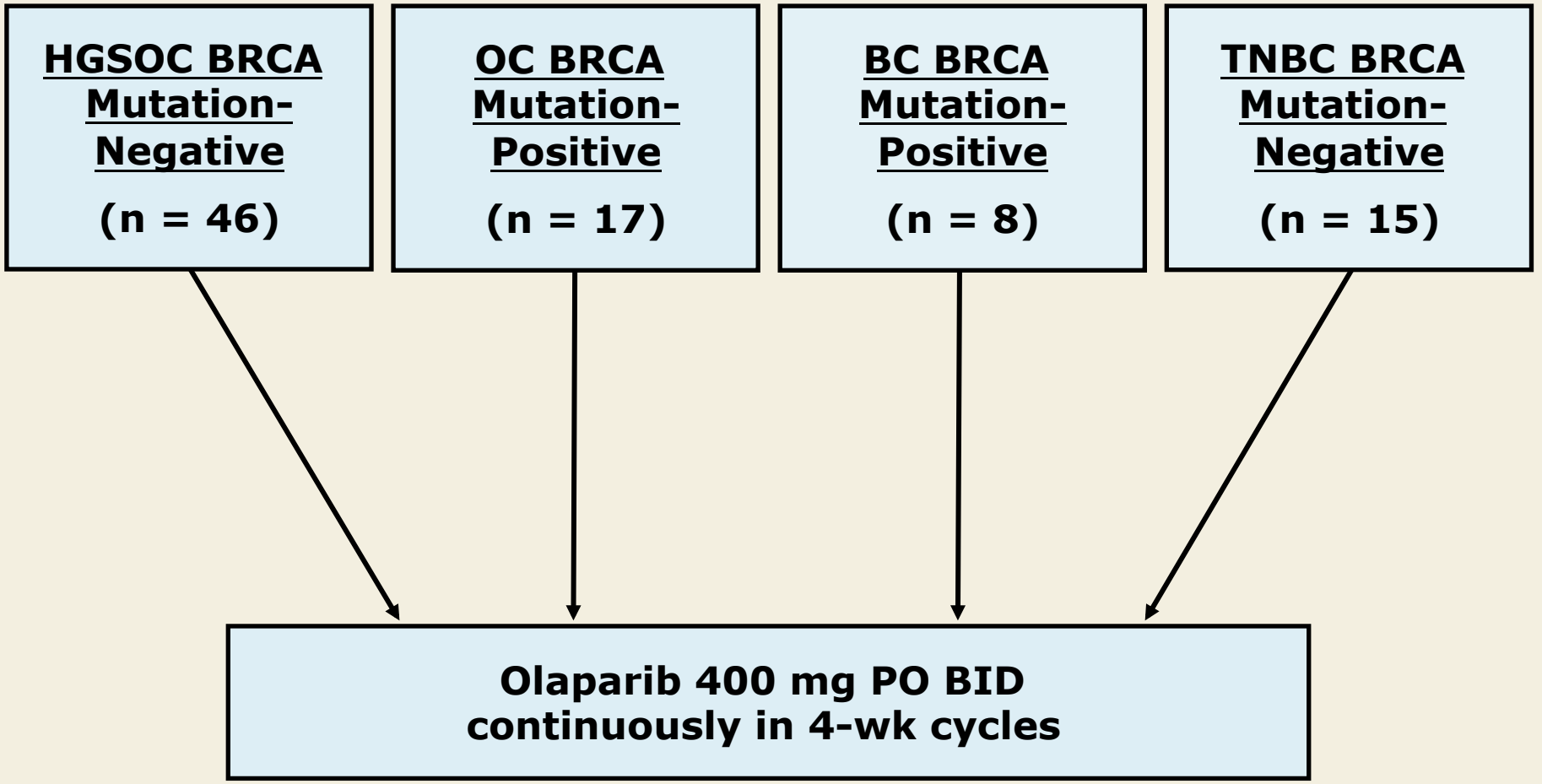
Proc ASCO 2010;Abstract 3002.

Introduction

- BRCA1/2-deficient cells are highly sensitive to inhibition of the enzyme PARP, a key regulator of the DNA damage repair process.
- A prospective study of 49 consecutive ovarian surface epithelial carcinomas showed that 21/38 (55%) of high-grade serous ovarian carcinomas (HGSOCs) had BRCA1 or BRCA2 mutations or functional loss of BRCA1 (*BMC Cancer* 2008;8:17).
- Olaparib, an orally active PARP inhibitor, was active and well tolerated in pretreated BRCA1/2 mutation carriers with advanced breast cancer[1,2] and ovarian cancer[1,3] ([1] *NEJM* 2009;361:123, [2] *Proc ASCO* 2009;Abstract CRA501, [3] *Proc ASCO* 2009;Abstract 5500).
- **Current study objective:**
  - Investigate BRCA dysfunction as a treatment target for patients with HGSOC or triple-negative breast cancer (TNBC) treated with olaparib.

Gelmon KA et al. *Proc ASCO* 2010;Abstract 3002.

Administration of Olaparib to Patients with Confirmed BRCA Mutation Status



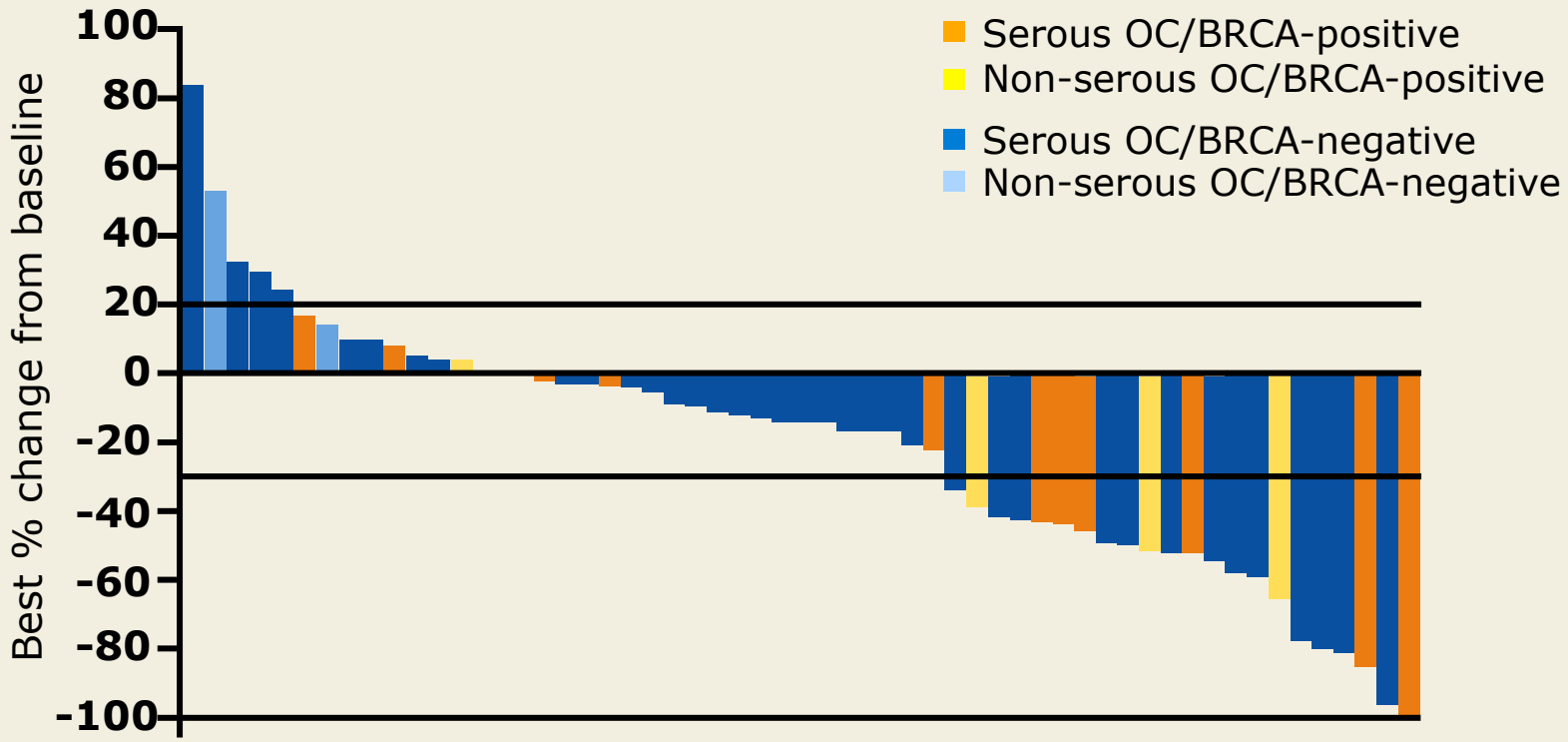
Gelmon KA et al. *Proc ASCO* 2010;Abstract 3002.

Objective Response Rate (by RECIST)

	BRCA Mutation-Positive	BRCA Mutation-Negative
Ovarian	7/17 (41.2%)	11/46 (23.9%)
Breast	0/8 (0)	0/15 (0)

Gelmon KA et al. *Proc ASCO* 2010;Abstract 3002.

Change in Target Lesion Size by OC Tumor Type and BRCA Mutation Status



The majority of patients with ovarian cancer had some tumor shrinking with olaparib irrespective of their BRCA mutation status.

With permission from Gelmon KA et al. *Proc ASCO* 2010;Abstract 3002.

Progression-Free Survival (PFS) (by RECIST)

	Ovarian (n = 64)	Breast (n = 26)
Total number of progression events	40	23
Median PFS	219 days	54 days
80% confidence interval for PFS	148-224	53-78
Number of patients remaining on treatment at end of study	14	0

Gelmon KA et al. *Proc ASCO* 2010;Abstract 3002.

Grade ≥3 Adverse Events

Adverse Event*	Ovarian (n = 64)	Breast (n = 26)
Any ≥Grade 3 adverse event	**35.9%**	**30.8%**
Fatigue	10.9%	0%
Anemia	7.8%	7.7%
Diarrhea	4.7%	0%
Abdominal pain	3.1%	0%
Dyspnea	1.6%	11.5%
Gamma-glutamyltransferase elevation	1.6%	7.7%

* Adverse events that occurred in >1 patient are listed.

Gelmon KA et al. *Proc ASCO* 2010;Abstract 3002.

Conclusions

- Olaparib monotherapy demonstrated encouraging activity in patients with BRCA mutation-negative HGSOC.
- The activity observed with this agent in BRCA germline mutation carriers and ovarian cancer confirms previous studies.
- Olaparib was well tolerated in both ovarian and breast cancer patient populations with a side-effect profile similar to those in previous trials.
- Preliminary serial biopsy sample analysis of a single patient indicates that overlapping and non-overlapping somatic mutations exist in primary tumors and in an ascitic recurrence (data not shown).

Gelmon KA et al. *Proc ASCO* 2010;Abstract 3002.

Investigator comment on Phase II study of olaparib

The response rates in high-grade serous ovarian cancer — which accounts for 75 to 80 percent of ovarian cancer cases — were similar to those seen in BRCA-associated ovarian cancer. What that says to me is that an abnormality in the homologous recombination pathway — similar to what happens when the BRCA gene is knocked out — is a characteristic of high-grade serous ovarian cancer.

Even if the BRCA gene is not knocked out, you can have lack of BRCA expression because of methylation changes that affect gene transcription, post-translational methylation changes that affect gene expression or post-translational modifications of the proteins that make them nonfunctional. It has been estimated that 35 to 40 percent of ovarian cancer cases may involve a BRCA-type phenotype, and these PARP data support that.

Studies of the long-term use of PARP inhibitors have been discussed, but continuously blocking DNA repair might have negative effects. We need DNA repair for recovery from sun exposure and from what we eat, drink and breathe. We have much to learn about how to use these agents, but at least we haven't seen a lot of extra toxicity so far.

Interview with Deborah K Armstong, MD, June 22, 2010

A Gene Expression Profile of BRCAness That Correlates with Outcome and with Responsiveness to Platinum and PARP Inhibitors in Epithelial Ovarian Cancer

Konstantinopoulos PA et al.
Proc ASCO 2010;Abstract 5004.

Konstantinopoulos PA et al.
J Clin Oncol 2010;[Epub ahead of print].

Study Methods

- A panel of 60 variably expressed genes that distinguished BRCA-like (BL) and non-BRCA-like (NBL) ovarian tumors was identified using gene expression data from 61 patients with pathologically confirmed epithelial ovarian cancer (*J Natl Cancer Inst* 2002;94:990).
- The ability of this gene expression profile (the BRCAness profile) to predict responsiveness to platinum therapy was assessed in 10 tumor biopsy samples from six patients previously treated with a platinum and with known BRCA1 or BRCA2 germline mutations.
  - Four patients had paired samples before and after the development of platinum resistance, and two had samples from the time of platinum-sensitive disease only.
- The ability of the BRCAness profile to predict responsiveness to PARP inhibitors was assessed in vitro using tumor cell lines with known BRCA mutations.

Konstantinopoulos PA et al. *Proc ASCO* 2010;Abstract 5004; Konstantinopoulos PA et al. *J Clin Oncol* 2010;[Epub ahead of print].

BCRAness Profile Correlates with Sensitivity to Platinum and PARP Inhibition of Tumor

- BRCAness profile distinguished between platinum-sensitive and platinum-resistant tumors, which in turn correlated with mutant or revertant BRCA status, respectively.
  - 5/6 tumors with BL profile were platinum sensitive
  - 3/4 tumors with NBL profile were platinum resistant
- BRCAness profile accurately distinguished between PARP inhibitor sensitivity and resistance in vitro.
  - BL signature was associated with two PARP inhibitor-sensitive clones tested
  - NBL signature was associated with two PARP inhibitor-resistant clones

Konstantinopoulos PA et al. *Proc ASCO* 2010;Abstract 5004; Konstantinopoulos PA et al. *J Clin Oncol* 2010;[Epub ahead of print].

Conclusions

- BL genomic profile correlates with:
  - Clinical responsiveness to platinum and in vitro responsiveness to PARP inhibitors
  - Improved disease-free survival (DFS) and overall survival (OS) in patients with advanced ovarian cancer (data not shown)
    - DFS: 34 mo vs 15 mo (BL vs NBL profile, $p = 0.013$)
    - OS: 72 mo vs 41 mo (BL vs NBL profile, $p = 0.006$)
- Selection of one discriminant set for validation in prospective randomized trials is needed to more accurately define BRCAness from the genomic standpoint.

Konstantinopoulos PA et al. *Proc ASCO* 2010;Abstract 5004; Konstantinopoulos PA et al. *J Clin Oncol* 2010;[Epub ahead of print]; Kohn EC. *Proc ASCO* 2010;Discussion.

Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of AMG 386 Combined with Weekly Paclitaxel in Patients with Recurrent Ovarian Carcinoma

Karlan BY et al.

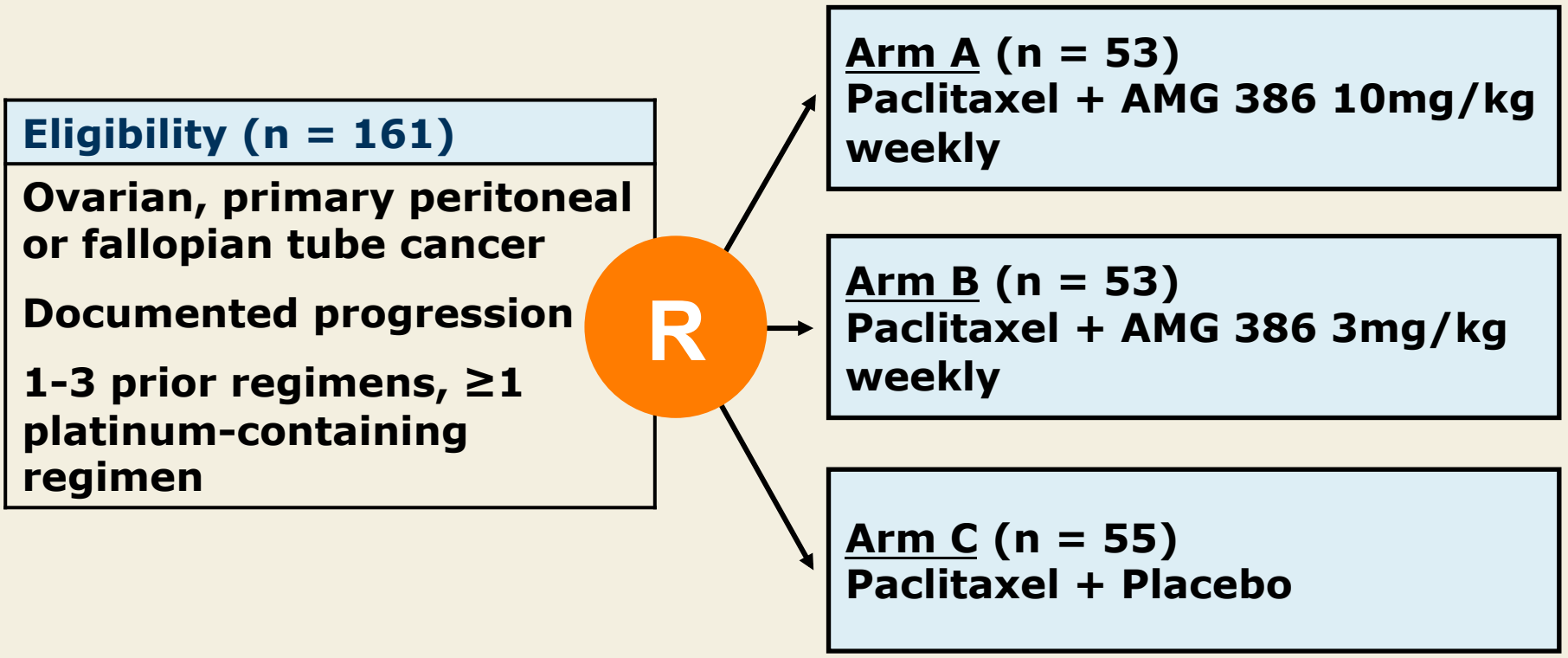
Proc ASCO 2010;Abstract 5000.

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.

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.

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.

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.

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.

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