5 Minute JournalClub

Key ASCO Presentations
Issue 1, 2010

Correlation of BRCA Mutation Status with Responses to Platinum Therapy and PARP Inhibitors in Patients with Ovarian Cancer and Triple-Negative Breast Cancer (TNBC)

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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 OBJECTIVES

- 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.

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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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Correlation of BRCA Mutation Status with Responses to Platinum Therapy and PARP Inhibitors in Patients with Ovarian Cancer and Triple-Negative Breast Cancer (TNBC)

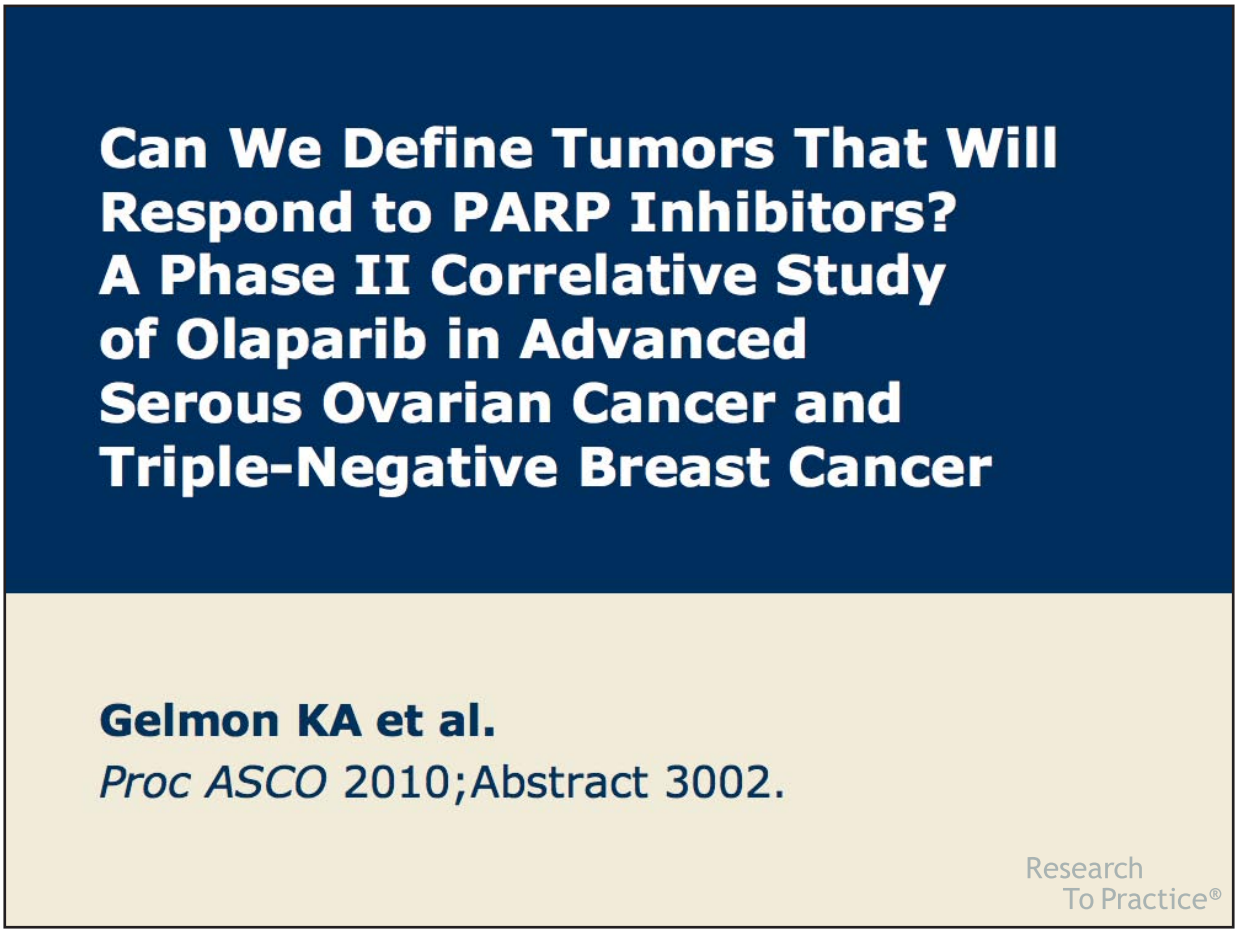
Presentations discussed in this issue

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

Konstantinopoulos PA et al. **A gene expression profile of BRCAness that correlates with responsiveness to platinum, PARP inhibitors and with outcome in epithelial ovarian cancer.** *Proc ASCO* 2010;**Abstract 5004**.

Konstantinopoulos PA et al. **Gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer.** *J Clin Oncol* 2010;[Epub ahead of print]. **Abstract**

Slides from presentations at ASCO 2010 and transcribed comments from a recent interview with Deborah K Armstong, MD (6/22/10)



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.

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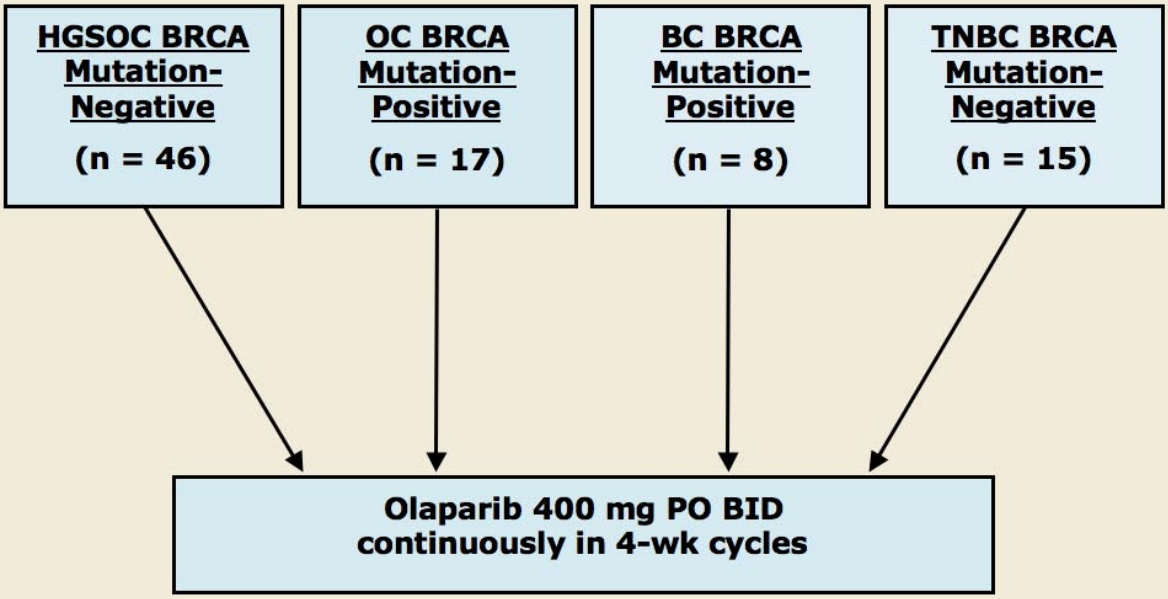
Administration of Olaparib to Patients with Confirmed BRCA Mutation Status



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

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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.

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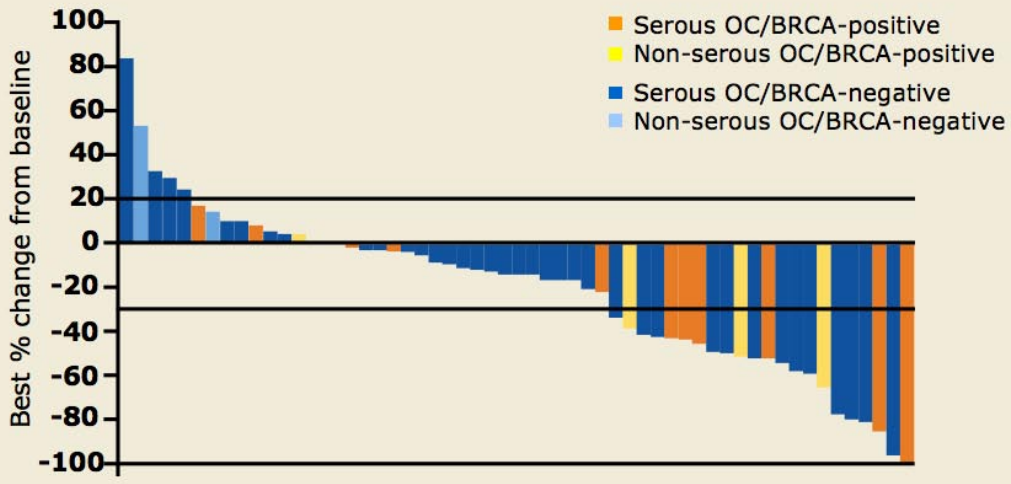
Change in Target Lesion Size by OC Tumor Type and BRCA Mutation Status



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.

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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.

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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.

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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.

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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

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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].

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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].

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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].

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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.

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