Bevacizumab Benefit in Large-Volume Ovarian Cancer

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August 01, 2019

Hopes that extended antiangiogenesis exposure with bevacizumab (multiple brands) might stave off tumor growth more effectively than a standard chemotherapy regimen plus or minus bevacizumab are still alive for a certain subset of ovarian cancer patients, say researchers.

This is despite the finding that there was no overall survival (OS) benefit with maintenance bevacizumab in the GOG-0218 trial, as reported when the final results were published online June 19 in the Journal of Clinical Oncology.

The final OS results from this innovative randomized trial will likely give rise to important discussions about the most appropriate treatment for patients with large-volume residual stage IV disease, for whom antiangiogenesis treatment is likely to be the most effective approach, said GOG-0218 senior author Bradley Monk, MD, professor of gynecologic oncology, University of Arizona College of Medicine, Phoenix.

On the other hand, for ovarian cancer tumors that are positive for several driver mutations, tumor mutational status may direct treatment more appropriately toward inhibition of the poly ADP ribose polymerase (PARP) enzyme with, for example, maintenance niraparib (Zejula, GlaxoSmithKline).

Niraparib maintenance therapy was put to the test in patients with first-line ovarian cancer following platinum-based chemotherapy in the large phase 3 PRIMA study. According to a recent press release, niraparib maintenance significantly improves progression-free survival (PFS) compared to platinum-based chemotherapy alone regardless of the patient's biomarker status.

More complete findings from PRIMA will be presented at the next major medical meeting in Europe. "Providers and patients will soon be likely to have to make a decision between bevacizumab and a PARP inhibitor," Monk commented in an interview with Medscape Medical News.

That discussion will come down to two key points:

- the stage of the cancer being treated — stage III or stage IV — and how much disease is left following resection of the primary tumor; and
- the molecular signature of the tumor — namely, BRCA or other defects in homologous recombination.

The stage and bulk of the residual tumor matter because larger tumors are more dependent on angiogenesis than smaller ones, Monk explained.

"The bigger the tumors are, the more blood supply they need," he said.

This is why the final report of the GOG-0218 trial showed that for patients with stage IV disease with larger-volume tumors, there was an OS advantage with maintenance bevacizumab, because it cut off new blood vessel growth for a much longer period than was possible with a concurrent regimen alone, he explained.

Indeed, this finding harmonizes with a relatively recent report from ICON7 trial investigators, who, when assessing their OS results in ovarian cancer patients, found that there was an OS benefit with maintenance bevacizumab for patients with poor-prognosis disease, even though there was no OS benefit for the study group as a whole.

"I think it's pretty clear that patients with large-volume residual stage IV disease should get bevacizumab, and this is consistent with the ESMO clinical practice guidelines," Monk reaffirmed.
"It's in the small-volume patients where the use of bevacizumab becomes more controversial," he added.

For patients with small-volume disease, providers will have to ask whether tumors are positive for either BRCA1/2 mutations or homologous recombinant repair (HRR) mutations. If so, patients should be preferentially treated with a PARP inhibitor, which inactivates both mutations.

HRR mutations are BCRA-like gene defects, Monk explained.

GOG-0218 Study Design

GOG-0218 enrolled 1873 women with incompletely resected stage III to IV ovarian, fallopian tube, or primary peritoneal cancer.

Women were randomly assigned to one of three treatment arms:

- standard chemotherapy with intravenous carboplatin and paclitaxel, followed by placebo (control arm);
- concurrent chemotherapy plus bevacizumab at a dose of 15 mg/kg, given from cycles two to six;
- chemotherapy plus concurrent bevacizumab followed by maintenance bevacizumab through cycle 22, both given at the a dose of 15 mg/kg.

For many of the patients (1195 of 1873, 64%), DNA was sequenced from blood, tumor samples, or both and were categorized as BRCA1/2 mutated, non-BRCA HRR mutated, or wild type (no mutations), lead author Krishnansu Tewari, MD, University of California, Irvine, Medical Center, in Orange, and colleagues write.

An earlier report of results from this study showed that at a median follow-up of 17.4 months, the risk for progression was reduced by approximately 28% among patients assigned to the maintenance bevacizumab arm relative to those who received chemotherapy alone, at a median PFS of 14.1 vs 10.3 months, respectively (P < .001).

This latest report shows that at a median follow-up of 102.9 months, median OS rates were very similar across the three treatment groups, and there were no significant differences in OS between those who received extended antiangiogenesis exposure and those who received the concurrent regimen.

Table. GOG-0218: Intent-to-Treatment Analysis of OS*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OS</th>
<th>Hazard Ratio</th>
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<tbody>
<tr>
<td>Control arm (chemotherapy alone)</td>
<td>41.1 months</td>
<td></td>
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<tr>
<td>Concurrent chemotherapy plus bevacizumab</td>
<td>40.8 months 1.06</td>
<td></td>
</tr>
<tr>
<td>Concurrent chemotherapy plus bevacizumab plus maintenance bevacizumab</td>
<td>43.4 months 0.96</td>
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*Median follow-up of 102.9 months

The authors note that none of the known clinical or pathologic prognostic markers correlated with OS in either of the bevacizumab-containing arms.

In contrast, relative to wild-type or no-mutation status, the hazard ratio for death when the BRCA1/2 mutation status was confirmed was 0.62, they report.

This was very similar to the hazard ratio for death as a result of having a non-BRCA1/2 HRR mutated tumor, at 0.65.

Although both BRCA1/2 mutations as well as HRR mutations were associated with improved prognosis in the study, mutational status did not predict bevacizumab activity in any patient group, the authors point out.
**Slow FDA Approval**

In the interview, Monk commented that the GOG-0218 investigators are often asked why it took the US Food and Drug Administration 7 years following the first publication of the PFS results in 2011 to approve bevacizumab for frontline and maintenance therapy for advanced ovarian cancer.

"The answer is simple — we had to come to an understanding that PFS is a valuable endpoint," Monk said.

Following a consensus article authored by Monk and colleagues, it was agreed that "it's not all about survival," as he noted — and PFS became an acceptable endpoint, provided the regimen proved reasonably tolerable.

It is noteworthy that there continued to be a PFS advantage in all relevant subgroups in GOG-0218 to study endpoint, but these rates were not presented in the final OS report, he added.

Monk also pointed out that they could not control for multiple subsequent treatments the patients invariably received during the long study follow-up, which "undoubtedly contaminated" the endpoint of OS.

Because of this, "OS is less relevant in GOG-0218, and PFS has clinically meaningful value," the investigators conclude.

*The study was supported by grants from the National Cancer Institute and the Department of Defense Ovarian Cancer Research Program and by the Ovarian Cancer Research Foundation Alliance Liz Tilberis Award. The authors' relevant financial relationships are listed in the original article.*

*J Clin Oncol.* Published online June 19, 2019. [Full text](https://www.medscape.com/viewarticle/916320_print)

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Cite this: Bevacizumab Benefit in Large-Volume Ovarian Cancer - Medscape - Aug 01, 2019.