Bradley Monk, MD, FACS, FACOG: Hello, and welcome to this educational activity entitled *Expert Answers to Common Questions for Optimizing First-Line Treatment Selection in Advanced Ovarian Cancer*.

My name is Brad Monk. I'm a gynecologic oncologist and professor here in Phoenix within the Division of Gynecologic Oncology both at the University of Arizona and Creighton University. I'm also a member of the US Oncology Network in practice here in Arizona Oncology.

This activity today will provide my expert perspective. I use that term loosely—as an expert, ha, ha. But I'm going to do my very best. And what I have done is I've acquired some participant questions from a recent series of AXIS-sponsored grand rounds that were focusing on newly diagnosed advanced ovarian cancer.

Here is a disclaimer and disclosure indicating that we may be discussing off-label uses of approved agents or agents that are in development.

And here is my financial disclosure information.

Here are the learning objectives for today's events. Upon completion of this activity, I hope that you will be better able to assess data about recent clinical trials and guideline recommendations incorporating anti-angiogenesis agents and novel therapies such as PARP into the first-line treatment of patients with advanced ovarian cancer. And I hope that you could apply these evidence-based clinical data and guidelines so that patients could benefit from these anti-angiogenesis agents, ideally in specific patient populations, to maximize therapeutic opportunities.

So these are the questions that were asked of the participants, and they were very interested in side effects and diagnoses, but there was a lot of what I call "other." And that included systemic therapy, although 12% wanted some general treatment, and 8% some surgical guidelines. I think I can put that together, that 20% right now, into a statement that about 50% of patients with newly diagnosed advanced ovarian cancer are treated with neoadjuvant chemotherapy, with the surgery integrated between the third and fourth cycles.

The decision to do that is very complicated. It's based on physical examination, the fitness of the patient, the radiologic findings, and sometimes even on laparoscopic assessment. But the rest of the questions were about systemic therapy, and that's what I'm going to focus on.

I want to focus on bevacizumab because bevacizumab was FDA approved for the first-line treatment of advanced ovarian cancer on December 13, 2018. I also want to focus on olaparib, because olaparib was FDA approved for *BRCA* mutation–positive disease on December 19, 2018. So, within 2018, we had 2 first-line FDA approvals—unprecedented; and, in fact, it's something new since the last approval of paclitaxel almost 2 decades ago. So, I'm very enthusiastic about this.

Then I'd like to discuss the upcoming trials, because this is a rapidly evolving field. There are 4 studies, one of which is VELIA, which is a GOG study 3005. We added veliparib to chemotherapy and then included it in maintenance. It's also a PARP inhibitor.

And then PRIMA, which is also first-line maintenance, but the idea is to expand it beyond BRCA, perhaps in a biomarker-identified patient such as homologous recombination deficiency patients, or maybe even all comers. And then the BOOST trial, which is increasing the duration of bevacizumab from the current FDA-approved indication of 15 months to 30 months.

And then, what really all of us are interested in, the combination. Maybe we should add a PARP inhibitor and bevacizumab together. So, PAOLA-1 takes the GOG-0218 indication, and then in the maintenance phase adds olaparib. This is a very interesting study because the first 2 PARP inhibitor trials, VELIA and PRIMA, are biomarker-driven—that is, the homologous recombination deficiency or loss of heterozygosity–high subgroup. BOOST is angiogenesis. We haven't really identified a biomarker. But PAOLA-1 tends more toward the angiogenesis side of things and is not a biomarker-driven primary endpoint.

So let's talk about newly diagnosed advanced ovarian cancer—who would be the best candidate for bevacizumab?

In this table, I outline the June 13, 2018 indication. And the label is: in combination with carboplatin/paclitaxel followed by bevacizumab as a single agent for stage III/IV epithelial ovarian cancer, as well as tubal and peritoneal after surgical resections. So it's a complex sentence, so the first is: stromal tumors, sex cord tumors. Germ cell tumors would not be eligible. Early stage disease would not be eligible. Histologic subtypes, certainly ovarian, fallopian tube, and peritoneal, but not sarcomas and following surgical resection.

This is according to our 2011 article published in *The New England Journal of Medicine*, and you can see that there are 2 endpoints: the 10.3 versus 14.1 endpoint in the article; and now 12.0 in the control arm placebo arm versus 18.2. And why is that? In the article, we used CA-125 as an endpoint, but for the label it's only radiologic RECIST. That's what the FDA wanted. That's what's in the label. The progression-free survival (PFS) got a little longer, because CA-125s go up earlier, 6.2 months improvement in PFS and a hazard ratio of 0.62.

And then on the right side of the table is the confirmatory trial, again, it was half the dose of bevacizumab, 12 months rather than 15 months. Earlier stage patients were included, but it's a confirmatory trial and published in the same edition of *The New England Journal of Medicine*. And the reference at the bottom of the slide, Oza, *Lancet Oncology*, is an update. Incidentally, the update on GOG-0218 is in press in the *Journal of Clinical Oncology* and look for it within the month.

So, other than what the label states—tubal, epithelial ovarian, and peritoneal III and IV after surgery—what else can be used to select the ideal patient? Well, I've already told you stage. We think that ascites basically is angiogenesis out of control. Those new blood vessels are fenestrated and leaky. As a new blood vessel forms, it's not completely tubularized. It leaks. Ascites is a biomarker in an initial subset analysis of 218 for the small benefit of PFS that was not in the upcoming overall survival update. Ascites is difficult to measure. Certainly in the AURELIA trial with weekly paclitaxel, again, platinum-resistant recurrent ovarian cancer, there's an improvement in patient-reported outcomes, presumably because there is a decrement in ascites.

Biomarkers, again, have been shown to not really pan out on antiangiogenic agents. Homologous recombination repair genetic signatures are prognostic, not predictive, meaning the patients who have *BRCA* mutations or *BRCA*-like mutations live longer. But that doesn't mean that they respond better to bevacizumab, but they do live longer because they respond better to DNA-damaging agents such as platinum.

Now, stage is appropriate for the label all stage III and IV, but here in this slide, again, in press in the *Journal of Clinical Oncology*, there was an overall survival advantage in stage IV disease. I really need you to have this as a take-home message. When bevacizumab is added to the regimen for patients with stage IV disease, they live 10 months longer compared to those who did not get bevacizumab. Said another way, if you add bevacizumab to the regimen for a patient with stage IV disease, she lives as long as a patient with stage III disease. You negate the negative impact of stage when bevacizumab is added.

This is supported by ICON7. So, I get it that it was an unplanned analysis, but because the identical observation is in ICON7, I think you can have some confidence in ICON7 in this, what they call the high-risk subset, which is a lot of stage IVs, but also large volume residual disease patients. If you look at what they call the restricted mean, there was a 5-month improvement in overall survival.

But if you look at the median here in the right-hand side of the slide, it's 9.4 months, which is pretty close to the 10-month GOG-0218 improvement in overall survival associated with stage IV disease. So I think, based on these 2 trials, although not prespecified, that we can be fairly confident that there's a 10-month improvement in overall survival in patients with stage IV disease.

I said that patients with ascites were good candidates, and the label is all stage III and IV after surgery, but restricted to epithelial ovarian, peritoneal, and fallopian tube cancer.

This is a meta-analysis of these factors. I talked about the PFS benefit and that all ages benefit. That grade, really there's no difference. Patients with a better performance status obviously do better, PS1 and 2 over 0.

So, as far as these mutations go, I showed you that when there's no *BRCA*-like or homologous recombination repair (HRR) deficiency genes on the left there's one outcome. And you can see on the right that the curves are shifted to the right. These patients who have HRR gene mutations have a better PFS, but you can see that both slides show a benefit from bevacizumab.

So that's what I mean when I say it's prognostic, meaning the HRR gene mutation groups do better, but it doesn't predict the increased efficacy of bevacizumab. And this is borne out also in the survival data that will come out in the *Journal of Clinical Oncology* any day.

So next, let's transition to talk about olaparib. The June 19, 2018 FDA approval, this was for maintenance. This was for patients with germline and somatic disease. Again, get treated with platinum/taxane generally, epithelial ovarian cancer, and if you respond, whether you got neoadjuvant primary debulking, even if you got bevacizumab, you can transition to maintenance olaparib. And it's both for germline and somatic disease, so you need to remember that it's not just testing the germline. You have to test the tumor. I would expect that the germline mutations would be somewhere around 17% or so.

That the somatics would be about 7% or so, which means that about one-fourth of patients can benefit from first-line-maintenance olaparib.

This was FDA approved based on this SOLO-1 study, which I'm going to show you. And it's already recommended by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®), and it's Category 1 for the germline mutations subgroup, but 2A for the somatic mutation subgroup, because there are only 2 somatic mutations, but the biology suggests that the outcomes are the same whether it's a germline *BRCA1* or *BRCA2* mutation, or whether it's a *BRCA1* or *BRAC2* somatic mutation.

And the NCCN Guidelines® have already been updated. They say you need to make sure of the *BRCA1* or *BRCA2* status after you complete treatment of ovarian tubal or fallopian tube cancer. So, don't delay the start of chemotherapy, because it takes time. But make sure you get it done before it's time after their 6 cycles, so that they cannot miss the opportunity for olaparib. This is the germline testing guideline, but we also recommend somatic testing.

And this is the trial of 291 patients randomized, if you respond, to olaparib versus a placebo. You've seen this published in *The New England Journal of Medicine*, presented last year at ESMO by our good friend and colleague, Katie Moore. This trial was also a GOG trial like GOG-0218.

And the endpoint is unprecedented: a hazard ratio of 0.30. An improvement of almost 3 years in PFS from about 14 months at the median to about 50 months at the median in the olaparib group. And you can see the decay—the progressions—in the patients who did not receive olaparib. You'd think that these patients would do very well. They don't. But with olaparib, there might even be more cures. And, in fact, at 3 years, there's a doubling of the PFS from 26.9% to 60.4%.

I don't know how you could deny a patient this opportunity. I talked to you about how to select bevacizumab for your patients, and we talked about some of the very important characteristics. I doubt that the patient would feel good if he/she had a *BRCA* mutation and didn't get maintenance olaparib. I think this is the standard of care.

This is the subgroup analyses, and you can see that there is an important improvement in PFS in all the relevant subsets. I point out the stage IIIs and IVs as well as the patients who have clinical partial or complete responses—this is unprecedented data.

I've shared these 4 studies. They differ in their populations. They differ in their designs, but they do not differ in the setting: newly diagnosed advanced ovarian cancer. They do not differ in their primary endpoints, PFS. And data for almost 3,000 patients will be reported within the next year, many of these probably at ESMO.

In 2018, we had 2 FDA approvals for maintenance therapy, one in a biomarker-negative group, bevacizumab, and the other in a biomarker-positive group, *BRCA1* and *BRCA2* germline and somatic mutations.

So, what are the key takeaways? The key takeaways are molecular testing, personalized treatments, and maintenance. I don't think it's credible any more to just do 6 doses of carboplatin and paclitaxel in newly diagnosed ovarian cancer and say, good luck. That's the best that we can do. It's not the best that we can do. We can add bevacizumab if you don't have a *BRCA* mutation, or we can add olaparib if you do. And this creates wonderful opportunities, and we're going to try to expand the duration of bevacizumab in the BOOST trial and try to expand the opportunity for PARP inhibitors in both HRR-deficient patients, but maybe even all-comers and maybe all-comers if you add both agents together.

So I want to thank AXIS. I want to thank you for participating in this activity. If you hear my enthusiasm, it's real. The thing that I did not discuss in the Cliff Notes summary are toxicities. Toxicities are important, I do not want you to forget to balance activity versus toxicity.

So, thank you very much. So long for now, and greetings from Phoenix, Arizona.

References

Armstrong DK, Alvarez RD, Bakkum-Gamez JN, et al. NCCN Clinical Practice Guidelines in Oncology. Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 1.2019. © 2019 National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf.

Burger RA, Brday MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med*. 2011;365:2473-2483.

Burger RA, Enserro D, Tewari KS, et al. Final overall survival (OS) analysis of an international randomized trial evaluating bevacizumab (BEV) in the primary treatment of advanced ovarian cancer: A NRG oncology/Gynecologic Oncology Group (GOG) study. *J Clin Oncol.* 2018;36: abstract 5517.

ClinicalTrials.gov. NCT02470585. Veliparib with carboplatin and paclitaxel and as continuation maintenance therapy in subjects with newly diagnosed stage III or IV, high-grade serous, epithelial ovarian, fallopian tube, or primary peritoneal cancer. https://clinicaltrials.gov/ct2/show/NCT02470585.

ClinicalTrials.gov. NCT02655016. A study of niraparib maintenance treatment in patients with advanced ovarian cancer following response on front-line platinum-based chemotherapy. https://clinicaltrials.gov/ct2/show/NCT02655016.

ClinicalTrials.gov. NCT01462890. Evaluation of optimal treatment duration of bevacizumab combination with standard chemotherapy in patients with ovarian cancer (BOOST). https://clinicaltrials.gov/ct2/show/NCT01462890.

ClinicalTrials.gov. NCT02477644. Platine, avastin and olaparib in 1st line (PAOLA-1). https://clinicaltrials.gov/ct2/show/NCT02477644.

FDA News Release. June 13, 2018. FDA approves bevacizumab in combination with chemotherapy for ovarian cancer. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm610664.htm.

FDA News Release. December 19, 2018. FDA approves olaparib for first-line maintenance of BRCA-mutated advanced ovarian cancer. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm628876.htm.

Moore KN, Colombo N, Scambia G, et al. Olaparib maintenance therapy following first-line platinum-based chemotherapy in patients with FIGO stage III–IV ovarian cancer (OC) with a BRCA1/2 mutation (BRCAm): phase III SOLO1 trial. *Ann Oncol*. 2018;29: abstract LBA7_PR.

Moore KN, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2018;379:2495-2505.

Norquist BM, Brady MF, Harrell MI, et al. Mutations in homologous recombination genes and outcomes in ovarian carcinoma patients in GOG 218: an NRG Oncology/Gynecologic Oncology Group study. *Clin Cancer Res*. 2018;24:777-783.

Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol*. 2015;16:928-936.

Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med*. 2011;365:2484-2496.

Pujade-Lauraine E, Oza AM, Perren TJ, et al. ICON7: Final overall survival results in the GCIG phase III randomised trial of bevacizumab in newly diagnosed ovarian cancer. *Int J Gynecologic Cancer* 2013;23(8).

Rossi L, Verrico M, Zaccarelli E, et al. Bevacizumab in ovarian cancer: a critical review of phase III studies. *Oncotarget* 2017;8:12389-12405.

Zhou M, Yu P, Qu X, Liu Y, Zhang J. Phase III trials of standard chemotherapy with or without bevacizumab for ovarian cancer: a meta-analysis. *PLoS One* 2013;8:e81858.