

OncLive®

State of the Science SUMMIT™

MEETING REPORTER

OVARIAN CANCER AND SOFT TISSUE SARCOMA | Washington University Siteman Cancer Center
June 20, 2019 | St. Louis, MO



Also in this issue...

Molecular Testing Continues to Evolve in Ovarian Cancer. **4**

Debate Persists Between Upfront Surgery and Neoadjuvant Chemo in Advanced Ovarian Cancer **5**

Evaluating Surgery and Angiogenesis Inhibition in Recurrent Ovarian Cancer. . . **6**

SOLO-1 Data Encourage Molecular Testing Immediately at Ovarian Cancer Diagnosis. . . **7**

JOIN US ON SOCIAL MEDIA

onclive.com/meetings/soss

Facebook [OncLive State of the Science Summit](#)

Twitter [@OncLiveSOSS](#)

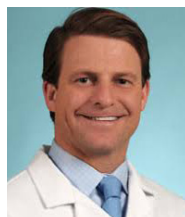
LinkedIn [OncLive](#)

YouTube [OncLiveTV](#)



Quest to Extend Reach of Immunotherapy, PARP Inhibitors Persists in Ovarian Cancer

By Caroline Seymour



Matthew Powell, MD

SINGLE-AGENT IMMUNOTHERAPY HAS ELICITED minimal responses in patients with ovarian cancer, but the preclinical rationale for combinations with chemotherapy, antivasular therapy, and PARP inhibitors is strong and worthy of further pursuit, said Matthew Powell, MD.

“There are now 4 large randomized trials that involve not only combinations of checkpoint inhibitors and chemotherapy, but also PARP inhibitors and/or antivasular agents,” said Powell. “The [rationale] has been demonstrated in preclinical and animal models. Now, we have real-life data showing that these combinations make sense.”

In addition, PARP inhibitors have demonstrated strong single-agent activity, both as later-line treatments and maintenance therapy—and frontline maintenance for

CONTINUED ON PAGE 2 ▶

Ongoing Research With Novel Approaches Continues in Uterine Sarcomas

By Kristi Rosa



Brian Van Tine, MD

DESPITE EXTENSIVE RESEARCH EFFORTS, clinical trials remain the standard of care for patients with uterine sarcomas, said Brian Van Tine, MD.

“This year, [the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting] was full of a lot of learning lessons about negative trials; we didn’t really have a lot of game-changers,” said Van Tine, an associate professor in the Department of Medicine and director of the Sarcoma Program, Division of Medical Oncology, Washington University School of Medicine in St. Louis.

However, promising agents are under clinical investigation for rare tumors, such as perivascular epithelioid cell tumors (PEComa) and uterine sarcoma, he added.

In an interview during the 2019 *OncLive*® State of the Science Summit™ on Ovarian

CONTINUED ON PAGE 3 ▶

► POWELL, CONTINUED FROM COVER

select agents—in patients with *BRCA1/2* mutations. The activity of these agents has also been noted in patients with homologous recombination deficiency (HRD) and wild-type tumors, added Powell.

In an interview during the 2019 *OncoLive*[®] State of the Science Summit™ on Ovarian Cancer and Soft Tissue Sarcoma, Powell, professor, Obstetrics and Gynecology, and chief, Division of Gynecologic Oncology, Washington University School of Medicine in St. Louis, discussed the trials that are generating excitement for combination immunotherapy as well as the impact of PARP inhibitors in the treatment of patients with ovarian cancer.

OncoLive[®]: Could you discuss the enthusiasm for immunotherapy in advanced ovarian cancer?

Powell: Initially, we had a lot of excitement for immunotherapy. Across oncology, checkpoint inhibitors were the latest and greatest thing. Unfortunately, in ovarian cancer, single-agent immunotherapy has been disappointing, with response rates around 9% to 10%. These responses have not been durable, either. Microsatellite instability–high status, which we know is a marker of response for patients receiving checkpoint inhibitors, is rare in ovarian cancer. We don't have a biomarker signal that's driving things yet.

However, we do know that combination therapy looks quite exciting. Combinations with PARP inhibitors and antiangiogenic agents seem to have a lot of promise. These combinations look good, and right now we're combining them with chemotherapy and moving them to the upfront setting.

Could you discuss the preclinical rationale for these combinations?

The NSGO-AVANOVA2/ENGOT-OV24 study, which was presented at the 2019 American Society of Clinical Oncology Annual Meeting and looked at niraparib (Zejula) versus niraparib plus bevacizumab (Avastin), showed an exciting doubling in progression-free survival (PFS). This is a nonchemotherapy regimen that was used in platinum-sensitive ovarian cancer. These data were quite impressive and almost unexpected.

We know PARP inhibitors can impede the cancer cell's ability to repair itself. When there's an inability to repair itself, more neoantigens are created. These neoantigens are, hopefully, what's allowing the immune system to interact with the cancer. When we use checkpoint inhibition, we're giving the immune system permission to attack the cancer and we can see increased benefit.

How else could we move away from chemotherapy?

To expand on the combinations between antivasular therapy and PARP inhibitors, we saw similar results from the initial study of olaparib (Lynparza) and cediranib in patients with germline mutations. The combination seemed to have much more of a benefit in patients who had wild-type tumors; these patients didn't have a *BRCA* mutation. That was really exciting to see. [These strategies] are designed with the hope of prolonging survival on maintenance strategies that have less toxicity and aren't leading

to damaged bone marrow, hair loss, and all the other adverse events (AEs) associated with standard chemotherapy.

What is the role of PARP inhibitors in the landscape?

We know that at least half of high-grade ovarian cancers have a deficiency in part of the repair process, which we call HRD. Capitalizing on that deficiency is where PARP inhibitors come in. It has been very exciting to move PARP inhibitors up from fourth- and fifth-line therapy to earlier on in the disease course. Now we have upfront data from the SOLO-1 study showing a striking benefit when olaparib is given as maintenance therapy after carboplatin and paclitaxel in patients with a germline or somatic *BRCA1/2* mutation. That has really enhanced our enthusiasm for using PARP inhibition in different [settings].

Data are also behind olaparib, rucaparib (Rubraca), and niraparib. The 2 olaparib trials, ARIEL3, and the NOVA studies all looked [at patients with platinum-sensitive recurrence] and showed very nice hazard ratios in the 0.2 to 0.3 range for patients with a germline or somatic mutation. There is a little less activity if patients do not have HRD, but it's still there—even if patients had wild-type cancers.

Regarding the AEs of these drugs, they are generally well tolerated. We have strategies for minimizing some of the AEs with dose holds and occasionally dose reductions to try to allow patients to be on these medications for a long time.

How do you differentiate among these agents?

It's really difficult; they are all about the same in terms of efficacy. There were differences in the trials, so it's hard to do cross-trial comparisons. We don't have any head-to-head trials. All of these trials were done with a placebo control. Therefore, we use their toxicity profiles to help guide us. Slight differences exist among the drugs as far as how they affect platelets and their dosing schedule. One PARP inhibitor is given once a day, whereas the other 2 are given twice a day. Some have a little bit more of an influence on elevating creatinine. These factors may drive our choices, but there's no clear and convincing winner. We individualize them to the patient.

What are the important data to be aware of regarding PARP inhibitors?

We looked at the differences in PFS [with these inhibitors]. The hazard ratio, in a patient with a *BRCA1/2* mutation, is around 0.3, which translates to a 70% reduction in the risk of recurrence. Patients with HRD have about a 60% reduction or 50% reduction in the risk of recurrence [with these agents]. *BRCA1/2* wild-type patients have a benefit, but it's a little more modest with a hazard ratio of around 0.6.

It's clear that we have a much better understanding of the biology of ovarian cancer. We also understand that biomarkers are important. Some of those biomarkers are the grade of the cancer and the molecular subtype, whether it's the gene mutation or the HRD signature. ■

► VAN TINE, CONTINUED FROM COVER

Cancer and Soft Tissue Sarcoma, Van Tine highlighted the latest developments in soft tissue sarcoma (STS), including uterine sarcoma, and data from key trials and further research being done in the rare tumor field.

OncLive®: What key advances have been made in STS?

Van Tine: At the State of the Science Summit™, we not only discussed all the advances made in ovarian cancer, but we also got a chance to talk about the recent data on sarcoma that were just released at the 2019 ASCO Annual Meeting.

A Twitter poll put out by OncLive® asked what agents [we] would use in a patient with leiomyosarcoma who had gemcitabine and docetaxel 2 years ago and 25% of the respondents actually recommended the doxorubicin plus olaratumab, which had just been shown to be an inactive agent in a randomized phase III trial. [This is why] the State of the Science Summit™ events are so important. So much knowledge needs to be disseminated.

Unfortunately, the olaratumab data were negative, and because of that, we got to focus on the GeDDiS trial and whether or not to use gemcitabine/docetaxel or doxorubicin as frontline [treatment]. We talked about [the article by] William D. Tap, MD, of Memorial Sloan Kettering Cancer Center, that was published in *Lancet Oncology*, in which the GeDDiS trial was published and [weighed the] pros and cons of both options. It comes down to the patient and the situation you're in since they do have the same overall survival and progression-free survival [benefits], although doxorubicin can be a little less toxic.

Then, finally, I reminded most of my gynecologic colleagues about trabectedin (Yondelis) and the work that is ongoing with gemcitabine transporters, which is kind of the new state of the science and where the field is headed.

What is the role of trabectedin in sarcoma?

It's important to remind everyone that trabectedin is there and it's a very active agent; it's very useful for uterine and nonuterine leiomyosarcoma and liposarcoma. Important factors

need to be remembered.

First, you can treat patients as outpatients; you don't have to admit them [to receive that treatment]. Second, I like to remind people about rhabdomyolysis, which is an adverse event that can be easily missed. When patients start complaining of dull aches and pains, sometimes it's very important to check for the liver toxicities and the various safety issues with trabectedin. However, it's a drug where [patients] don't really lose their hair; this is important because [we need] agents that are hair-preserving and that are very focused on quality of life.

Would you like to highlight any other key research presented at the 2019 ASCO Annual Meeting?

A few drugs for very rare diseases [are promising]. For example, a new mTOR inhibitor [ABI-009; nab-sirolimus] is given intravenously for patients with PEComa, and it looks like it's headed toward FDA approval. Also a drug called tazemetostat looks really, really promising for endothelial sarcoma, and it's moving forward in future clinical trials.

Could you speak to the importance of collaboration in this field?

I believe it's important to remember that the sarcoma field is a partner—especially with uterine leiomyosarcoma and endometrial stromal sarcoma. We work well together. We have many trial options and we would like to be able to reach out to them as we share patients. They are amazing surgeons and the surgical outcomes we get in our partnership are highly valued.

What is the key take-home message from your presentation?

Clinical trials are still the standard of care for sarcoma. Every patient should be given every opportunity, if they can get to a sarcoma center, to participate in hopefully what will be the future [standard of care]. If we don't put patients on trials, we're going to stay with the results we have for today, which really do need to be improved. ■



OncLive®

Sign up for our eNewsletter

Get the latest breaking news, specialty coverage, and conference coverage straight to your inbox at onclive.com.



facebook.com/onclive



twitter.com/onclive



youtube.com/user/onclivetv

Molecular Testing Continues to Evolve in Ovarian Cancer

By Ellie Leick



Jubilee
Brown, MD

AS PARP INHIBITORS HAVE showcased a survival benefit in select patients with ovarian cancer, Jubilee Brown, MD, explained that there must be a widespread approach to conduct molecular testing in all patients with the disease to provide them with a personalized treatment approach.

“Every single patient with ovarian cancer should be tested for germline and somatic mutations at diagnosis without exception,” said Brown, a professor of gynecologic oncology at Levine Cancer Institute, Atrium Health.

Promising data regarding PARP inhibition emerged from the SOLO-1 trial, in which there was a 70% reduction in the risk of disease progression or death with olaparib (Lynparza) compared with placebo in patients with *BRCA*-mutant ovarian cancer who were in complete or partial response to platinum-based chemotherapy (HR, 0.30; 95% CI, 0.23-0.41; $P < .0001$).

Moreover, Brown recommends looking for germline and somatic mutations when testing patients as a method to not only create a personalized treatment plan for patients with ovarian cancer, but also to prevent disease in those who may harbor genes that impact their risk.

In an interview during the 2019 *OncLive*[®] State of the Science Summit™ on Ovarian Cancer and Soft Tissue Sarcoma, Brown discussed the importance of molecular testing immediately after an ovarian cancer diagnosis and how this testing will shape the field.

***OncLive*[®]: Could you explain the significance of molecular testing for patients with ovarian cancer?**

Brown: So much has changed in the field in the last several years. We have the capacity now to test patients with ovarian cancer for both germline and somatic mutations. When we combine this information, it radically changes how we can treat patients. With the addition of the SOLO-1 trial, now we know that patients who both germline or somatic mutations in *BRCA* can really benefit from treatment with a PARP inhibitor; there’s a 70% reduction in the risk of recurrence in these patients with ovarian cancer. It’s really incumbent upon us to recommend treatment for our patients with either germline or somatic *BRCA*-mutant disease.

What factors do you take into consideration when you’re conducting molecular testing?

Now, based on these data, all patients with ovarian cancer need to have molecular profiling. Upfront, 7% of patients will

have *BRCA*-related mutations—that impacts how we treat these patients. They should all have maintenance therapy with a PARP inhibitor.

Additionally, even the National Comprehensive Cancer Network guidelines now tell us that patients with recurrent disease should be tested via molecular profiling to evaluate for somatic mutations. This often impacts what we can offer our patients, whether it’s a clinical trial that gives them options for treatment that they wouldn’t otherwise have, or an off-protocol option—commercially available agents, such as immunotherapy—that may be useful for these patients.

Could you expand on the benefits of germline testing?

When we talk about germline testing, we’re talking about [the search] for inherited mutations, like *BRCA1* or *BRCA2* mutations. There are also other less common germline mutations that confer risk for other cancers; therefore, surveillance for those cancers is really important. Additionally, testing the family members of patients with inherited mutations is important because we can prevent cancers in those people completely.

On the other hand, when we discuss somatic mutations, we’re looking for mutations that arise within the tumor itself; those things aren’t necessarily as common as germline mutations. They are a wider range of mutations. Even with rare ovarian cancers, we can find targets. These are called actionable mutations, meaning we can actually target the tumor with drugs that are more likely to work. This is cutting-edge science and we’re gathering a lot of information. Hopefully, in the next few years we’ll be able to target these tumor types with very specific drugs that will work.

How do you see the role of molecular testing evolving in the future?

It’s a huge, wide-open field. Over the next several years, we’re going to be able to refine who gets treated with what drug based on very smart technology and molecular profiling. We’ll be able to decide which drug is best for which patient—not just based on how something looks under the microscope, but based on personalized medicine. ■

REFERENCE

Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2018;379(26):2495-2505. doi: 10.1056/NEJMoa1810858.

FOLLOW US ON SOCIAL MEDIA
for more clinical practice resources



Debate Persists Between Upfront Surgery and Neoadjuvant Chemo in Advanced Ovarian Cancer

By Caroline Seymour



R. Wendel Naumann, MD

FOR PATIENTS WITH NEWLY diagnosed advanced ovarian cancer, but for those who are not candidates for who are not candidates for primary debulking surgery, neoadjuvant chemotherapy and interval debulking surgery may be used without sacrificing outcomes, said R. Wendel Naumann, MD.

“We know surgery is important in ovarian cancer, but there has been a paradigm

shift from only doing surgery in the upfront setting to using neoadjuvant chemotherapy and interval cytoreductive surgery,” said Naumann. “We know [neoadjuvant chemotherapy] decreases morbidity. Now, we have 4 randomized studies—3 noninferiority studies and 1 superiority study—that suggest that the oncologic outcomes regarding progression-free survival and overall survival are similar, and the morbidity from the surgery is much less.”

Although the decision of whether to pursue primary debulking surgery versus neoadjuvant chemotherapy should be done in a multidisciplinary setting, patients who are better suited for surgery are generally those who are symptomatic and require immediate treatment. Conversely, patients with advanced disease and large-volume ascites may benefit more from neoadjuvant chemotherapy, explained Naumann.

In an interview during the 2019 *OncLive*[®] State of the Science Summit™ on Ovarian Cancer and Soft Tissue Sarcoma, Naumann, director of Minimally Invasive Surgery in Gynecologic Oncology at Levine Cancer Institute, Atrium Health, discussed the patient criteria for primary debulking versus neoadjuvant chemotherapy and the settings in which such decisions should be reached.

***OncLive*[®]: Could you discuss the utility of neoadjuvant chemotherapy in a setting that has predominantly been led by surgery?**

Naumann: The thing that we forget is that much of the outcome is based on a patient’s disease burden as well as the surgical complexity. The benefit that we get from these very aggressive debulking procedures is probably less than we think.

Even if we get patients who have a high disease burden down to R0, they probably won’t have the outcome we think they will. A relatively high mortality is associated with aggressive upfront surgery that ranges from 5% to 8%. We have to make a decision in determining who is a good candidate for upfront surgery versus who is a good candidate for neoadjuvant chemotherapy. Importantly, we don’t lose anything by giving chemotherapy first and then operating later. That also opens up the possibility of more patients having a complete response (CR). In the initial study that

Ignace Vergote, MD, PhD, of Catholic University Leuven and of Cancer Institute at University Hospitals, and colleagues conducted in 2010, there was about a 5% CR rate. In patients who have *BRCA* mutations, the CR rate can be as high as 25%. To me, those patients can undergo minimally invasive surgery for debulking if they have a good response rate [to neoadjuvant chemotherapy].

What are some of the patient criteria for primary debulking surgery?

It’s a great question. Patients who are the best candidates for primary surgery are symptomatic, have very large masses, and may have a partial bowel obstruction; these patients require immediate attention. They can’t go through neoadjuvant chemotherapy and wait the 3 to 6 weeks for the chemotherapy to kick in. On the other hand of the spectrum, some patients have very advanced disease, stage IV disease, and upper abdominal disease with large-volume ascites; these patients are good candidates for neoadjuvant therapy. Once you’ve given the chemotherapy, you’ve reduced their surgical complexity and their need for ultraradical and upper abdominal procedures, which then reduces the morbidity of surgery.

What advice would you give your colleagues regarding this decision?

It is important that all patients are seen by a gynecologic oncologist upfront to help make this determination. This [process] could be done jointly because some patients do benefit from neoadjuvant chemotherapy or upfront surgery and that [decision] should be determined by a multidisciplinary team.

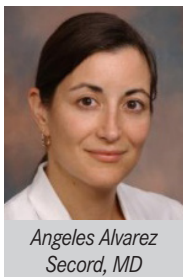
The main message is that if you do neoadjuvant chemotherapy, you do not compromise a patient’s oncologic outcomes. Furthermore, you can potentially make the surgery less morbid. However, the decision to do neoadjuvant chemotherapy versus primary surgery is a difficult decision that, again, needs to be made by a multidisciplinary team.

Where do you see the role of surgery headed in the future?

I hope we can get better upfront neoadjuvant chemotherapy that would allow for less aggressive surgery. It would be nice if we did not have to do super-radical surgery on patients with ovarian cancer. We have moved toward minimally invasive surgery in our institution and have shown that this is a reasonable strategy for many patients. More than 80% of patients can undergo minimally invasive surgery as opposed to open surgery; this allows them to not only have less morbidity, but the ability to get back on their chemotherapy sooner as well. ■

Evaluating Surgery and Angiogenesis Inhibition in Recurrent Ovarian Cancer

By Caroline Seymour



Angeles Alvarez Secord, MD

ALTHOUGH CHEMOTHERAPY REMAINS THE bedrock of treatment for patients with recurrent ovarian cancer, the field is moving beyond paradigms of platinum sensitivity and resistance and relying on a multiplex classification system to better design personalized treatment strategies.

In a presentation during the 2019 *OncLive*® State of the Science

Summit™ on Ovarian Cancer and Soft Tissue Sarcoma, Angeles Alvarez Secord, MD, a gynecologic cancers specialist at Duke Cancer Center and professor of obstetrics and gynecology at Duke University School of Medicine, discussed the available treatment modalities for patients with platinum-sensitive and -resistant recurrent ovarian cancer.

Chemotherapy and Surgery

There are mixed opinions on the value of surgery for advanced disease, explained Secord. Although the goal of surgery is optimal debulking, the likelihood of achieving a complete resection can be difficult to assess preoperatively. Therefore, investigators created the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) score to identify patients who could achieve a complete resection during secondary cytoreduction. Predictive characteristics included a good performance score, complete resection from frontline therapy, and ascites <500 mL.

Its predictive value was prospectively validated in patients with a platinum-free interval ≥6 months in the AGO DESKTOP II trial. In the phase III AGO DESKTOP III/ENGOT ov20 study,¹ patients were randomized to surgery and platinum chemotherapy or chemotherapy alone. Not only was the median progression-free survival (PFS) superior in the surgery arm compared with the control arm by 5.6 months (19.6 months vs 14.0 months, respectively), 72.5% of patients with a positive AGO score achieved a complete resection. However, patient selection is critical as investigators later determined that the benefit of surgery was limited to patients who had a complete resection prior to recurrence.

“If you [look] to see if someone is a candidate for secondary cytoreductive surgery, and they have peritoneal carcinomatosis, you should stop because you’re not going to help them,” cautioned Secord.

Although the AGO DESKTOP III trial demonstrated the safety and effectiveness of secondary cytoreductive surgery in select patients, the approach failed to result in improved overall survival (OS) in the phase III GOG-213 trial.² In 1 of the 2

objectives of this study, patients with investigator-determined resectable platinum-sensitive disease were randomized 1:1 to receive surgery followed by platinum-based chemotherapy or platinum-based chemotherapy alone.

At a median follow-up of 34.6 months, the hazard ratio was 1.28, which translated to a median OS of 53.6 months with secondary surgery versus 65.7 months in those who received chemotherapy alone. Although investigators concluded that secondary surgery can be safely performed in this population, it did not lead to an improved survival benefit.

Despite the fact that the study encouraged enrollment of only those deemed able to undergo a complete resection, the protocol was not enforced, which may have influenced the results, said Secord.

Until OS data mature from the AGO DESTOP III trial and the retrospective analysis of the GOG-213 patient population is published, Secord said that she will not offer secondary cytoreductive surgery in routine practice.

“Surgery is complicated,” said Secord. “We don’t know the answer yet, but the signs are not pointing positively to a role for cytoreductive surgery in the secondary setting.”

Chemotherapy and Bevacizumab

OCEANS

In the phase III OCEANS trial, patients with platinum-sensitive disease without prior exposure to bevacizumab (Avastin) were randomized to receive either concurrent carboplatin, gemcitabine, and bevacizumab followed by maintenance bevacizumab, or carboplatin and gemcitabine alone.

The addition of bevacizumab to chemotherapy resulted in a higher overall response rate and a complete response rate that was approximately double that of chemotherapy alone.³

Additionally, there was a 4-month extension in median PFS with the addition of bevacizumab at 12.4 months versus 8.4 months with chemotherapy alone (HR, 0.48; 95% CI, 0.390.61; $P < .0001$).

These findings, and those from the phase III GOG-0213 trial, the FDA approved the use of bevacizumab, either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine chemotherapy, followed by bevacizumab alone, for the treatment of patients with platinum-sensitive recurrent ovarian cancer.

GOG-213

The other objective of the GOG-213 trial evaluated the addition of bevacizumab to paclitaxel/carboplatin chemotherapy and as maintenance. For the bevacizumab component of the trial,

patients were randomized 1:1 to receive standard chemotherapy (n = 337) or standard chemotherapy plus bevacizumab (n = 377) every 3 weeks and continued as maintenance every 3 weeks until disease progression or toxicity.

At a median follow-up of 49.6 months, results showed a median OS of 42.2 months in the bevacizumab arm versus 37.3 months in the chemotherapy-alone arm.⁴

Response rates were expectedly higher with the bevacizumab arm at 79% versus 59% with chemotherapy, mirroring prior findings from the OCEANS trial.

Notably, bevacizumab's utility does not diminish if patients have been previously exposed to bevacizumab in the frontline setting, said Secord.

"The bottom line is that bevacizumab works pretty much everywhere," she added.

AURELIA

The benefit of bevacizumab has spanned to the platinum-resistant recurrent setting as well. In the AURELIA trial, women with platinum-resistant disease were randomized to receive standard chemotherapy plus bevacizumab or chemotherapy alone.

Investigators noted a striking benefit in PFS with the addition of bevacizumab of approximately 22 months versus 12 months with chemotherapy alone,⁵ said Secord. Notably, the benefit extended to all patients regardless of age, platinum-free interval, amount of measurable disease, or evidence of ascites.

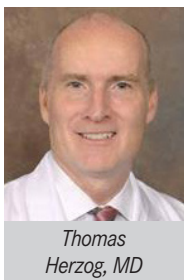
"Bevacizumab is a valuable maintenance agent in platinum-sensitive or platinum-resistant disease, and safety profiles indicate that it is feasible and tolerable," concluded Secord. ■

REFERENCES

1. Du Bois A, Vergote I, Ferron G, et al. Randomized controlled phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: AGO DESKTOP III/ENGOT ov20. *J Clin Oncol.* 2017;35(suppl 15); abstr 5501. doi: 10.1200/JCO.2017.35.15_suppl.5501.
2. Coleman RL, Enserro D, Spirtos N, et al. A phase III randomized controlled trial of secondary surgical cytoreduction (SSC) followed by platinum-based combination chemotherapy (PBC), with or without bevacizumab (B) in platinum-sensitive, recurrent ovarian cancer (PSOC): a NRG Oncology/Gynecologic Oncology Group (GOG) study. *J Clin Oncol.* 2018;36(suppl 15); abstr 5501. doi: 10.1200/JCO.2018.36.15_suppl.5501.
3. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol.* 2012;30(17):2039-2045. doi: 10.1200/JCO.2012.42.0505.
4. Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multi-centre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2017;18(6):779-791. doi: 10.1016/S1470-2045(17)30279-6.
5. Pujade-Lauraine E, Hilpert F, Weber B, et al; AURELIA Investigators. AURELIA: a randomized phase III trial evaluating bevacizumab (BEV) plus chemotherapy (CT) for platinum (PT)-resistant recurrent ovarian cancer (OC). *J Clin Oncol.* 2012;30(suppl 18); abstr LBA5002. doi: 10.1200/jco.2012.30.18_suppl.lba5002.

SOLO-1 Data Encourage Molecular Testing Immediately at Ovarian Cancer Diagnosis

By Ellie Leick



Thomas Herzog, MD

A KEY MESSAGE FROM the phase III SOLO-1 trial is that patients with ovarian cancer should be tested for *BRCA* mutations quickly after diagnosis to determine what treatment will be most effective, explained Thomas Herzog, MD.

Results of the study led to changes in practice and emphasized the importance of frontline therapy, according to Herzog.

In the study, treatment with olaparib led to a 70% reduction in the risk of disease progression or death compared with placebo in patients with *BRCA*-mutant advanced ovarian cancer who were in complete or partial response to platinum-based chemotherapy (HR, 0.30; 95% CI, 0.23-0.41; *P* < .0001).

Before SOLO-1, Herzog explained that *BRCA*-mutation testing should be conducted to see if patients were eligible for PARP-based therapy in the maintenance, third-, or fourth-line treatment. However, data demonstrate that *BRCA* status impacts frontline therapy decisions. Patients should be tested

for the *BRCA* mutation from the start in order to create an individualized treatment, according to Herzog.

"As we move forward, treatment is going to be more personalized medicine based on histology, molecular signature, and genomic sequencing," he said. "Using that, we will put together the best cocktail for the patient upfront and maybe eradicate all the cancer cells so we don't have the recurrence, because once we have the recurrence, the chances for cure are very minimal."

In an interview during the 2019 *OncLive*® State of the Science Summit™ on Ovarian Cancer and Soft Tissue Sarcoma, Herzog, a professor of obstetrics and gynecology and deputy director at University of Cincinnati Cancer Institute, discussed recent changes in the ovarian cancer landscape, specifically PARP inhibitors and the optimal use of bevacizumab (Avastin).

OncLive®: How has ovarian cancer treatment progressed in recent years?

Herzog: We have not made not a lot of progress in ovarian cancer treatment in the last 20 years from the standpoint ■

“As we move forward, treatment is going to be more personalized medicine based on histology, molecular signature, and genomic sequencing. Using that, we will put together the best cocktail for the patient upfront and maybe eradicate all the cancer cells so we don’t have the recurrence.”

– Thomas Herzog, MD

of changing standard of care for frontline disease. However, we have had tremendous impact in terms of looking at new approvals. Those approvals have largely been in maintenance for second-line therapies and beyond that. We also have had an approval for bevacizumab for frontline therapy. With PARP inhibitors and bevacizumab, many developments in the last few years have made a big difference in ovarian cancer treatment.

How have PARP inhibitors changed the ovarian cancer treatment?

In terms of looking at the 2 classes of agents that have had the greatest impact thus far, it’s really been antiangiogenic inhibitors, such as bevacizumab, and PARP inhibitors. We have 3 PARP inhibitors that have been approved by the FDA: olaparib, rucaparib (Rubraca), and niraparib (Zejula). Each of these agents have been able to show progression-free survival improvement over time. It’s important to understand that these agents, while they show PFS advantage, are only the beginning of our understanding of how these agents benefit the patients.

We have *BRCA* as a biomarker for PARP inhibitors. We also know that the biomarker extends into homologous combination deficiency. Yet, we see in platinum-sensitive disease, with maintenance therapy, that there is a benefit even in patients who do not exhibit either of those characteristics. With bevacizumab, among the big challenges is identifying the patients who will benefit the most. We have not been able to develop a biomarker successfully to date, but we still see that bevacizumab is helpful in platinum-resistant disease, platinum-sensitive disease, and frontline disease, all of which are approved.

What challenges still exist in ovarian cancer?

The biggest unmet need in ovarian cancer is a cure; that’s where the greatest challenge exists. If we look at patients today who have presented to us normally, 75% of those patients will present at an advanced stage of disease. If you look at that group of patients and try to predict recurrence, we know almost 75% of them will recur. How do we keep that from happening? We need to intervene at the earliest part of the disease process, which would be frontline treatment.

What considerations should be taken into account when deciding treatment for these patients?

The first question you need to ask is where the patient is positioned on the treatment timeline. For frontline disease, one thing that has become very clear in the last year is we need to know the *BRCA* status of the patient. Previously, we would say it’s not that important and that we’ll use it as a signature later on to determine if the patient is a candidate for platinum-sensitive maintenance or platinum-based therapy in the third- or fourth-line setting. Right now, since we have SOLO-1 data showing the amazing results in frontline therapy, we need to know *BRCA* status much sooner. Testing as soon as possible is really important, both for germline and somatic *BRCA* mutations.

What main points do you want to convey about ovarian cancer treatment?

We spent billions of dollars not making a lot of progress and just adding on to the chemotherapy backbone, until we hit upon bevacizumab and PARP inhibitors. Those therapies have made a difference in terms of improved PFS and hopefully overall survival. Looking at the SOLO-1 results, we hope that we may even be able to cure more women with ovarian cancer, but that remains to be seen. It’s a very optimistic view, but one that I hope occurs.

What is your take-home message to your colleagues regarding your presentation?

Testing for *BRCA* at an early enough stage or point in the timeline is important to make a difference for an individual patient. If we don’t know that upfront, we may miss that original opportunity for frontline maintenance, which could be the best chance for cure. We could miss even the chance for platinum-sensitive maintenance, which has shown a significant advantage in terms of PFS, and really improve the patient’s quality of life. The real message here is that we need to understand who to test—the earlier the better. We have changed the trajectory of ovarian cancer with the understanding of these biomarkers. ■

REFERENCE

Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2018;379(26):2495-2505. doi: 10.1056/NEJMoa1810858.