Gynecologic Cancers: 2021 ASCO Annual Meeting Highlights for the Advanced Practitioner

Laura Doherty, FNP-BC, AOCNP®, of Women & Infants Hospital of Rhode Island/Brown University, interprets data on adjuvant chemotherapy for locally advanced cervical cancer, bevacizumab for advanced ovarian cancer, a new treatment option for platinum-resistant ovarian cancer patients, and side effects that long-term ovarian cancer survivors experience. Reporting by *The ASCO Post*.

Abstract LBA3

OUTBACK: No Benefit for Adjuvant Chemotherapy in Cervical Cancer

By Caroline Helwick

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In women with locally advanced cervical cancer, adjuvant chemotherapy adds no benefit to standard cisplatin-based chemoradiation, results of the international phase III OUTBACK study have shown,[1] as reported at the 2021 ASCO Annual Meeting by Linda R. Mileshkin, MD, Professor of Medical Oncology at the Peter MacCallum Cancer Centre in Victoria, Australia.

"These findings do not support the use of adjuvant chemotherapy. Pelvic chemoradiation with concurrent weekly cisplatin continues to be the standard of care for the treatment of locally advanced cervical cancer," Dr. Mileshkin announced.

"This trial of 'OUTBACK' chemotherapy did not show any clinically meaningful benefit but did increase adverse reactions," said the study's senior investigator, Bradley Monk, MD, Professor of Gynecologic Oncology at the University of Arizona, Phoenix.

For locally advanced cervical cancer, concurrent cisplatin and radiation with brachytherapy has been the standard of care since 1999. Many patients relapse, however, and die of distant metastatic disease. A number of influential studies have suggested that more chemotherapy after chemoradiation might convey additional benefits. Despite flaws in these studies—including short follow-up and treatment intolerability—"the studies changed practice in some centers," Dr. Mileshkin said.

About OUTBACK

Based on the success with systemic therapy in both the chemoradiation setting and recurrent disease, the randomized OUTBACK trial tested the effect of four cycles of adjuvant chemotherapy after chemoradiation, the primary endpoint being overall survival at 5 years. The study enrolled 919 patients with cervical cancer suitable for chemoradiation with curative intent. Eligible women with locally advanced disease (FIGO 2008 stages IB1 and positive lymph nodes, IB2, II, IIIB, or IVA) were randomly assigned to con-

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current chemoradiation, or the same followed by adjuvant chemotherapy:

- Both arms: standard chemoradiation with 40 to 45 Gy of external-beam radiation in 20 to 25 fractions, including a nodal boost plus brachytherapy, plus cisplatin at 40 mg/m^2 weekly concurrently with radiation
- Adjuvant chemotherapy arm: carboplatin AUC 5 and paclitaxel at 155 mg/m^2 every 3 weeks for four cycles, following chemoradiation.

Primary Endpoint Not Met

After a median follow-up of 5 years, the 5-year overall survival rates were 71% with chemoradiation alone and 72% with the addition of adjuvant chemotherapy (hazard ratio [HR] = 0.90; *P* = .8). Progression-free survival was also similar between the arms: 61% and 63%, respectively (HR = 0.86; *P* = .6).

Moreover, patterns of relapse were similar, with 11% and 9%, respectively, experiencing distant relapse (with or without locoregional disease) and 7% and 10%, respectively, having locoregional recurrence alone. There was no evidence of benefit in subsets of women with higher-risk disease, Dr. Mileshkin reported.

Lack of Initiation in 22%

In both arms, 77% of the subjects completed chemoradiation, and the vast majority of patients received full doses of treatments. Of note, 22% of women in the experimental arm never started adjuvant chemotherapy—an observation that was most common among women aged ≥ 60, non-White women, and women who did not complete chemoradiation.

A sensitivity analysis according to completion, or not, of chemoradiation confirmed the lack of benefit based on interaction *P* values of .11 and .12 for overall survival and progression-free survival, respectively, she added.

In the panel discussion, Dr. Mileshkin said she was surprised that so many women failed to initiate adjuvant chemotherapy. "This was one reason we had to increase our sample size," she said. The ongoing phase III INTERLACE trial is evaluating additional induction chemotherapy prior to chemoradiation, which might have better adherence, she said.

The typical side effects of chemotherapy were significantly increased in the adjuvant chemotherapy arm. Grade 3 to 5 toxicities emerging within the first year of treatment occurred in 81% of the adjuvant chemotherapy arm and 62% of the chemoradiation arm. Quality of life was worse during adjuvant chemotherapy and for the following 3 to 6 months but was similar between the arms after 12 months.

Looking Ahead

"The use of the now widely used biologics, including bevacizumab, and checkpoint inhibitors, which are clearly active, was conspicuously untested," Dr. Monk added. Current clinical trials are now evaluating the addition of checkpoint inhibitors and targeted agents to chemoradiation and during maintenance, he said.

Encouraging data have clearly emerged for checkpoint inhibitors as a second-line treatment of recurrent disease. Most recently, as reported during a European Society for Medical Oncology (ESMO) Virtual Plenary in May 2021, the newer agent cemiplimab-rwlc showed a survival advantage over chemotherapy (HR = 0.73; *P* = .00306) in the GOG-Partners protocol 3016 Cervical Empower-1 trial.[2] Global regulatory filings are underway, said Dr. Monk, an investigator in that study.

References

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The Advanced Practitioner Perspective

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The results of the OUTBACK trial will not change our day-to-day practice, as we see that standard-of-care chemoradiation outcomes are not enhanced with adjuvant chemotherapy. Fortunately, there is continued effort to explore treatment regimens that will be less toxic to patients and result in better progression-free survival and overall survival. We see these efforts in Dr. Monk's discussion of the PD-1–blocking antibody cemiplimab-rwlc.

As advanced practitioners working with women who have undergone chemoradiation, we know the significant long-term side effects patients can experience. We follow with many women in clinic with long-standing and life-altering gastrointestinal and genitourinary side effects, fistula formation, chronic pain, and dyspareunia following standard-of-care chemoradiation. Even for women who do not have recurrence of disease, the long-term side effects are life altering and point to our need for improved treatment options. We look forward to continued research in this area.

Disclosure: Ms. Doherty has no conflicts of interest to disclose.

Abstract 5501

Bevacizumab in Advanced Ovarian Cancer: Phase III Trial Finds More Is Not Better

By Caroline Helwick

Visit https://meetinglibrary.asco.org/record/195539/abstract to read the full abstract and view author disclosures.

In advanced ovarian cancer, the duration of maintenance bevacizumab should remain 15 months, according to the European multicenter phase III ENGOT/GCIG trial. These results were presented during the 2021 ASCO Annual Meeting by Jacobus Pfisterer, MD, PhD, of the AGO Study Group and Gynecologic Oncology Center in Kiel, Germany.[1]

"Although median progression-free survival of about 2 years was longer than in the original trials [of maintenance bevacizumab], longer treatment with bevacizumab improved neither progression-free nor overall survival in patents with primary epithelial ovarian, follicular tube, or primary peritoneal cancer. The bevacizumab treatment duration of 15 months as part of the first-line treatment of advanced ovarian cancer remains the standard of care," Dr. Pfisterer said.

"This is a really important study that nicely answers the question about the optimal duration of bevacizumab in the upfront setting," said session co-moderator Rachel Grisham, MD, of Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York.

Background and Study Rationale

The GOG-2182 and ICON7/AGO-OVAR 113 trials revealed that the early and continuous addition of bevacizumab for 15 months and 12 months, respectively, to standard carboplatin/paclitaxel significantly improved progression-free survival. In both studies, the maximal benefit was observed at the time point of the highest cumulative bevacizumab exposure—immediately after the last bevacizumab cycle. However, the optimal bevacizumab duration was never clearly established, so the current randomized phase III ENGOT/GCIG trial examined whether prolonging bevacizumab for up to 30 months would improve its efficacy, explained Dr. Pfisterer.

About the ENGOT/GCIG Trial

The study enrolled 927 women from 161 centers with stage IIb to IV epithelial ovarian (84%), fallopian tube, or peritoneal cancer. Patients underwent primary cytoreductive surgery followed by six cycles of chemotherapy (paclitaxel at 175 mg/m^2 plus carboplatin AUC 5) and bevacizumab (15 mg/kg) every 3 weeks. After induction, they were randomly assigned to receive bevacizumab for either the standard 15 months or 30 months, which was the experimental arm.

The primary endpoint was investigator-assessed progression-free survival. The trial was

designed with 80.2% power to detect a hazard ratio of 0.66 favoring 30 months of maintenance bevacizumab, after 697 progression-free survival events.

Baseline characteristics were balanced between the arms; median age was 61 years, 96% had an Eastern Cooperative Oncology Group performance status of 0 or 1, 58% had no residual tumor, and 77% had high-grade serous histology.

Key Results and Toxicity

The study found no significant benefit to extending bevacizumab maintenance beyond 15 months to 30 months, as shown in Table 1.

Subgroup analyses examined outcomes in patients with FIGO (International Federation of Gynecology and Obstetrics) stage IIB to IIIC disease and no residual tumor as well as in patients with FIGO stage IIB to IIIC with residual tumor or FIGO stage IV disease. Median progression-free survival was approximately 38 months in the first group and approximately 19 months in the second group, with no significant differences between the treatment arms, Dr. Pfisterer reported.

"Due to evidence of a nonproportional distribution of events," he said the investigators performed restricted mean analyses of all those endpoints. They were all consistent with the initial results.

Grade 3 to 5 adverse events were observed in 63% of patients treated for 15 months and in 68% receiving 30 months of bevacizumab. Grade 5 events occurred in eight patients and two patients, respectively. Serious adverse events of special interest were seen in 32% and 38%, respectively, including grade ≥ 3 hypertension in 20% of the 15-month arm and 25% of the 30-month arm; other serious adverse events were rare, occurring in less than 5% per arm; they included thromboembolism, fistula, gastrointestinal perforation, proteinuria, hemorrhage, and myocardial infarction.

References

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TABLE 1: Outcomes With Bevacizumab Maintenance in ENGOT/GCIG Trial

Endpoint	BEV15 (n = 464)	BEV30 (n = 463)	Hazard Ratio/*P* Value
Progression-free survival	72%	73%	–
Median progression-free survival	24.2 months	26.0 months	HR = –0.99 *P* = .90
Overall survival	55%	59%	HR = 1.04
Median overall survival	54.3 months	60.0 months	*P* = .68

BEV15 = bevacizumab (15 mg/kg every 3 weeks) for 15 months; BEV30 = bevacizumab (15 mg/kg every 3 weeks) for 30 months.

The Advanced Practitioner Perspective

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Single-agent bevacizumab is a maintenance option for women who are *BRCA* wild type and homologous recombination proficient in the front-line setting. We understand from the GOG-0218 trial that bevacizumab maintenance can extend progression-free survival for a subset of high-risk women with advanced disease. GOG-0218 did not show a benefit in overall survival in the final survival analysis. With the data from the ENGOT/GCIG trial, we understand that longer treatment does not equal greater benefit and in fact leads to increased risk of adverse events.

In practice, we have had women on maintenance bevacizumab for extended periods of time on trial or at the oncologist's and patient's preference if the patient is tolerating it well. As advanced practitioners caring for women receiving bevacizumab, we see the myriad of side effects that our patients can experience with this VEGF inhibitor: hypertension, arthralgia, proteinuria, delayed wound healing, and the rare patient who develops posterior reversible encephalopathy syndrome or bowel perforation. As our goal of therapy is efficacy with the least amount of adverse events, we can now recommend bevacizumab for a shorter duration more confidently.

Disclosure: Ms. Doherty has no conflicts of interest to disclose.

Abstract 5504

Early-Phase Trial Finds Mirvetuximab Soravtansine Plus Bevacizumab Active in Recurrent Ovarian Cancer

By Caroline Helwick

Visit https://meetinglibrary.asco.org/record/195544/abstract to read the full abstract and view author disclosures.

In patients with recurrent ovarian cancer, the antibody-drug conjugate mirvetuximab soravtansine, given with bevacizumab, showed antitumor activity leading to durable responses in platinum-agnostic patients with strong expression of folate receptor alpha (FRα), researchers reported at the 2021 ASCO Annual Meeting.[1]

The combination led to a response rate of 64%, a median duration of response of 11.8 months, and a median progression-free survival of 10.6 months in patients with high FRα expression in the phase Ib FORWARD II trial, said David M. O'Malley, MD, Professor, Director of Gynecologic Oncology, and Co-Director of the Gynecologic Oncology Phase I Program of The Ohio State University Wexner Medical Center and James Cancer Hospital, Columbus.

"These data add to the previously reported findings[2] and support the use of mirvetuximab as the partner of choice for bevacizumab in patients with high FRα [expression] ovarian cancer following the use of platinum-based treatments," Dr. O'Malley said. "Further, development of mirvetuximab in combination with bevacizumab is warranted."

About Mirvetuximab Soravtansine

Mirvetuximab soravtansine is a first-in-class antibody-drug conjugate comprising an FRα-binding antibody, cleavable linker, and the maytansinoid DM4 (a potent tubulin-targeting agent). The combination of mirvetuximab soravtansine and bevacizumab was evaluated in patients with FRα-positive (medium/high expression; ≥ 50%/≥ 75% of cells with PS2+ staining intensity), platinum-agnostic ovarian cancer for whom a nonplatinum doublet would be appropriate. Patients with platinum-agnostic ovarian cancer were defined as having either platinum-resistant disease (recurrence within 6 months of last platinum dose) or platinum-sensitive disease (response to platinum and no disease progression within 6 months).

Mirvetuximab soravtansine at 6 mg/kg plus bevacizumab at 15 mg/kg was given on day 1 of a 21-day cycle to 60 patients, who had received a median of two prior lines of therapy and were followed for a median of 17.5 months. Many patients (68%) had epithelial ovarian cancer, whereas the rest had fallopian tube cancer (25%) and primary peritoneal cancer (7%). All patients had prior exposure to platinum-based compounds and tax-

anes, 40% had previously received bevacizumab, and 35% had exposure to poly (ADP-ribose) polymerase inhibitors.

By platinum sensitivity, there were 32 patients (53%) with platinum-resistant disease and 28 (47%) with platinum-sensitive disease. The primary endpoint of the trial was investigator-assessed response.

Response Rates Improved

In the overall patient population, high response rates and durability were observed, especially among patients with high FRα expression (Table 1). "These deep responses are rapid and durable... in patients with platinum-resistant and platinum-sensitive disease. Many of these durable responses continued beyond 6 to 12 months, with some patients' responses lasting more than 2 years," Dr. O'Malley said.

"Much like the data for the objective response rate and duration of response, the progression-free survival demonstrated that patients with high FRα [expression] benefit the most from the combination of mirvetuximab and bevacizumab," he said.

Median progression-free survival was 10.6 months in the subgroup with high FRα expression and 5.4 months in the subgroup with medium FRα expression. For high expressors, 80% had not experienced disease progression at 6 months, and 42% had no disease progression at 12 months.

Safety Profile

The adverse events observed with the doublet were manageable and consistent with the side-effect profiles of each agent, according to Dr. O'Malley. Treatment-related toxicities were generally low grade, with diarrhea (62%), blurred vision (60%), fatigue (60%), and nausea (57%) being the most common. The most common grade ≥ 3 events were hypertension (17%) and neutropenia (13%). In total, 30% of patients discontinued treatment with mirvetuximab soravtansine and bevacizumab due to treatment-related adverse events; the median time to treatment discontinuation was 13 cycles.

"The strength of these mature data warrant further development of this novel, targeted combination, and I look forward to evaluating this regimen in earlier lines of therapy," Dr. O'Malley concluded about the trial.

References

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TABLE 1: Outcomes With Mirvetuximab Soravtansine/Bevacizumab in Ovarian Cancer

Outcome	All Patients (n = 60)	High FRα Expression (n = 60)	High FRα Expression and Platinum Resistance (n = 17)	High FRα Expression and Platinum Sensitivity (n = 16)
ORR	50%	64%	59%	69%
mDOR	9.7 months	11.8 months	9.4 months	12.7 months
mPFS	8.3 months	10.6 months	9.7 months	13.3 months

FRα = folate receptor alpha; mDOR = median duration of response; mPFS = median progression-free survival; ORR = confirmed objective response rate.

The Advanced Practitioner Perspective

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It is always exciting to have a new treatment option on the horizon, especially for our platinum-resistant ovarian cancer patients. For a specific subset of women, the combination of mirvetuximab soravtansine and bevacizumab has the potential to be a meaningful treatment option, with close to half of the patients with high folate receptor alpha (FRα)-expressing tumors without progression of disease at 1 year in the FORWARD II trial.

The researchers report the treatment toxicities to be generally low grade; however, 30% of the women did stop treatment secondary to toxicity. We have cared for several patients in clinic who have received mirvetuximab soravtansine on protocol. Anecdotally, I can say that this has been a tolerable therapy, and these results seem to support that. We will be looking forward to phase II and III results to see if this changes our practice, especially in the setting of women with high FRα-expressing tumors.

Disclosure: Ms. Doherty has no conflicts of interest to disclose.

Abstract 12023

Analyzing Health Concerns in Long-Term Ovarian Cancer Survivors

By The ASCO Post Staff

Visit https://meetinglibrary.asco.org/record/200255/abstract to read the full abstract and view author disclosures.

Long-term survivors of ovarian cancer have a high frequency of health concerns, even 10 years after diagnosis and despite strong follow-up care, according to results of the "Carolin meets HANNA" study presented at the 2021 ASCO Annual Meeting. "Long-term survivors may be cured from cancer but still experience a wide range of long-term side effects," said study author Hannah Woopen, MD, MSc, Charité, of University Medicine of Berlin.

The study aimed to analyze the main concerns in long-term survival to improve follow-up care. From 2016 to 2021, 1,044 long-term (diagnosis more than 5 years ago) survivors with ovarian cancer were recruited. Median survival time at recruitment was 11 years. More than half of participants had been diagnosed with advanced stage ovarian cancer (58.6% FIGO III/IV). Almost half have developed recurrent disease (43.4%). 26.0% were under cancer treatment at recruitment.

52.0% of participants rated their health status as very good or good, while 20.3% reported a bad or very bad health status. Almost half (46.1%) of the long-term survivors reported experiencing current concerns or long-term side effects. The main concerns reported were fatigue (23.9%), pain (21.6%), polyneuropathy (16.9%), gastrointestinal symptoms (16.6%) and memory problems (15.5%). 42.8% still regard themselves as cancer patients.

Health status and distress did not differ between long-term survivors 5 to 10 years after diagnosis and more than 10 years after diagnosis ($p = 0.59$ and $p = 0.0843$, respectively). Patients with a history of recurrence and those under current treatment had a worse health status and more health concerns. Fatigue, polyneuropathy, nausea and concentration problems improved with the time of survival. However, fatigue is still present in 21.1% of patients after 10 years. There was no significant difference in pain between 5 to 10 (20.1%) and more than 10 years (22.0%) of survival time.

In this cohort, 94.2% receive regular follow-up care, including CA125 testing in 77.0%, clinical examination in 54.3%, transvaginal ultrasound in 55.1%, abdominal ultrasound in 43.9%, mammogram in 50.5% and further radiological examinations such as CT scans in 53.4%. "Specialized survivorship care should be offered beyond the typical five years of follow-up care with a focus on long-term side effects," Dr. Woopen commented.

The Advanced Practitioner Perspective

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The results of the Carolin meets HANNA study give us some much-needed insight as to the frequency and types of side effects long-term survivors of ovarian cancer experience. These side effects include fatigue, pain, polyneuropathy, gastrointestinal symptoms, and memory problems. To address these in a meaningful way, we need additional information: the extent to which the side effects are interfering with the patients' quality of life; which, if any, providers have been active in helping manage these symptoms; interventions they have tried; and barriers they have encountered.

A woman undergoing active treatment and followed by her oncology team should be queried at every treatment or maintenance clearance visit about her symptoms related to cancer and side effects related to treatment. A plan for addressing the concerns that are affecting her quality of life should be developed by the provider and patient at every visit.

In our practice, each patient has an end-of-treatment survivorship visit, at which time we perform detailed survivorship ROS and identify residual side effects that are affecting the patient's quality of life. Treatment plans to address the identified concerns are developed by the provider and patient, and we refer to appropriate resources as needed to help with management. We find this method to be effective in following and managing side effects. Of course, it is important to continue to check in with patients at their surveillance visits regarding any reported side effects following treatment.

Disclosure: Ms. Doherty has no conflicts of interest to disclose.