Gynecologic Cancer: 2022 ASCO Annual Meeting Highlights for the Advanced Practitioner

Laura Doherty, FNP-BC, AOCNP®, of Women & Infants Hospital/Brown University, interprets data presented at the 2022 ASCO Annual Meeting on rucaparib maintenance in advanced ovarian cancer, single-agent trabectedin in *BRCA*-positive ovarian cancer, tisotumab vedotin and pembrolizumab in cervical cancer, and patient selection for bevacizumab use in ovarian cancer.

Abstract LBA5500

Rucaparib Maintenance Improves Progression-Free Survival in Patients With Newly Diagnosed Advanced Ovarian Cancer Who Responded to Platinum-Based Therapy

By Alice Goodman

Visit https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.17_suppl.LBA5500 to read the full abstract and view author disclosures.

Maintenance therapy with the poly (ADP-ribose) polymerase (PARP) inhibitor rucaparib led to a significant improvement in progression-free survival compared with placebo in patients with newly diagnosed advanced ovarian cancer who responded to first-line platinum-based chemotherapy. The progression-free survival benefit of maintenance rucaparib was consistent in all patient subgroups in the final analysis of the phase III ATHENA-MONO trial, according to a presentation at the 2022 ASCO Annual Meeting.

"Despite the long history of PARP inhibitor use in ovarian cancer, the optimal first-line maintenance strategy for newly diagnosed, advanced ovarian cancer has not been elucidated. This study showed that patients with measurable disease at baseline have further tumor reduction with rucaparib. [Additionally], the rucaparib safety profile is consistent with prior studies," said lead author Bradley J. Monk, MD, Professor at the University of Arizona College of Medicine, and Director, Principal Investigator, Community Research Development, HonorHealth Research Institute.

Key Findings

Progression-free survival was extended with maintenance rucaparib vs placebo in both homologous recombination deficient (HRD)-positive and HRD-negative populations. However, the magnitude of benefit was greater for patients with HRD-positive disease. Median follow-up was 26.1 months.

The HRD cohort included pooled patients with *BRCA* mutation or wild-type *BRCA* and high loss of heterozygosity. In this group, median investigator-assessed progression-free survival was 28.7 months with rucaparib vs 11.3 months with placebo. On blinded independent central review, median progression-free survival was not reached vs 9.9 months, respectively.

J Adv Pract Oncol 2022;13(6):603-609
https://doi.org/10.6004/jadpro.2022.13.6.6 © 2022 Harborside™

In the intention-to-treat population, median progression-free survival was 20.2 months in the rucaparib arm vs 9.2 months in the placebo arm. The secondary endpoint of progression-free survival by blinded independent central radiology review showed a median progression-free survival of 25.9 months in the rucaparib arm vs 9.1 months in the placebo arm. In the HRD-negative population, median progression-free survival was 12.1 months with rucaparib vs 9.1 months with placebo.

"The magnitude of benefit based on molecular characteristics showed that rucaparib was of greater benefit in the HRD-positive patients than in the intent-to-treat analysis," he added.

Study Methodology

ATHENA was an international, randomized, double-blind, phase III trial in all comers evaluating maintenance rucaparib therapy in 1,000 patients, consisting of two independent comparisons: ATHENA-MONO and ATHENA-COMBO. Both parts of the study shared a rucaparib arm. In ATHENA-MONO, rucaparib was the experimental arm. Results of ATHENA-COMBO will be reported at a later date.

Dr. Monk presented mature results of ATHENA-MONO, which included 535 patients with newly diagnosed, stage III or IV high-grade primary peritoneal, fallopian tube, or epithelial ovarian cancer who were platinum-sensitive. Patients were randomly assigned to maintenance rucaparib or placebo and were stratified according to HRD status, disease status postchemotherapy, and timing of surgery. The study was conducted at 200 sites in 24 countries from 2018 to 2020.

In ATHENA-MONO, 425 women were randomly assigned to receive oral rucaparib at 600 mg twice daily plus intravenous placebo, and 110 women were randomly assigned to receive placebo. Treatment was continued for 2 years or until disease progression or unacceptable toxicity.

Baseline characteristics were mainly similar between the two treatment arms in both the HRD subset analysis and in the intention-to-treat analysis. The primary endpoint was investigator-assessed progression-free survival in the HRD subset, who all had loss-of-heterozygosity–high disease. If the analysis showed statistical significance for rucaparib vs placebo, then an intention-to-treat analysis of progression-free survival was performed.

"A blinded independent committee review analysis is a stand-alone secondary endpoint outside of the step-down analysis of progression-free survival," Dr. Monk explained.

Additional Results

In an investigator-assessed progression-free survival exploratory subgroup analysis, rucaparib continued to show increased benefit compared with placebo, regardless of the presence of a BRCA mutation, loss-of-heterozygosity–high disease, or HRD-negative disease.

"Everyone benefits in all subgroups. The greatest benefit was seen in the highest-risk patients—that is, those with residual disease after six cycles of a platinum doublet, stage IV disease, and persistently elevated CA-125 after six doses of chemotherapy," he told listeners. "Ten percent of patients had persistent disease and continued to respond to rucaparib, both in the HRD subset and the intention-to-treat analysis." Results were similar in the analysis by blinded independent central review.

Investigator-assessed objective response rate in the HRD population was 58.8% in the rucaparib arm vs 20.0% in the placebo arm and were mostly partial responses in both treatment arms. Median duration of response was 16.7 months with rucaparib vs 5.5 months with placebo.

In the intention-to-treat population, the objective response rate was 48.8% in the rucaparib arm vs 9.1% in the placebo arm. One complete response was observed in the rucaparib arm and none in the placebo arm. Median duration of response was 22.1 months and 5.5 months, respectively.

The median duration of treatment was 14.7 months in the rucaparib group and 9.9 months in the placebo arm. Median duration of follow-up was 26 months in both arms. The per-protocol 2-year treatment was completed by 23.7% of the rucaparib arm and 9% of the placebo arm.

Reasons for premature discontinuation of treatment included disease progression (41% vs 64.9%, respectively), adverse events (12.6% vs 5.4%), withdrawal of consent (4.9% vs 2.7%), or clinical disease progression (3.3% vs 5.4%).

"I think there is a therapeutic window for PARP inhibition. Dose intensity matters.

Throughout the study, 70% of patients on rucaparib were maintained on a dose of more than 500 mg through month 12." Dr. Monk commented on the "substantial dose flexibility of rucaparib, having four doses of 600, 500, 400, or 300 mg. There was no dose optimization needed in the study per se. We started every patient on 600 mg and did not reduce the dose based on age and/or body weight."

Safety Profile

Almost all patients—even those receiving placebo—had at least one treatment-emergent adverse event: 96.7% with rucaparib and 92.7% with placebo. Myelodysplastic syndrome or acute myeloid leukemia was observed in two patients in the rucaparib group and none in the placebo group.

At least one grade 3 or higher adverse effect was reported in 60.5% of patients in the rucaparib group vs 22.7% in the placebo group. Treatment interruptions or dose reductions due to treatment-emergent adverse events occurred in 63.8% and 21.8% of patients, respectively. The most common grade 3 or higher adverse events observed with rucaparib vs placebo were anemia or increased hemoglobin (28.7% vs 0%), neutropenia or neutrophil count decrease (14.6% vs 0.9%), and increased levels of alanine aminotransferase or aspartate aminotransferase (10.6% vs 0.9%).

No significant changes in bilirubin or increased levels of drug-induced liver toxicity were observed in the rucaparib-treated group. Additionally, 70% of patients continued to receive at least 500 mg of rucaparib twice daily through month 12, which was more than 80% of the starting dose.

Two deaths were reported in the rucaparib-treated group and none in the placebo arm.

"Quality of life matters. These patients were carefully monitored for quality of life, and quality of life was stable," said Dr. Monk.

The Advanced Practitioner Perspective

Laura Doherty, FNP-BC, AOCNP®
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We continue to see PARP inhibitors provide a significant benefit to patients with a known *BRCA* mutation or homologous recombination deficient (HRD) tumors. Our current clinical mainstay for front-line maintenance in this population after partial or complete response to platinum-based therapy is 2 years of olaparib (Lynparza). The data on rucaparib (Rubraca) continue to support PARP inhibitor use in this population.

It is important to tease out what the benefit was for the *BRCA*-negative, homologous recombination proficient population, as we still do not have a great maintenance option for this group. The overall progression-free survival (PFS) for patients with *BRCA*-negative, homologous recombination proficient tumors in ATHENA-MONO was 12.1 months for rucaparib vs. 9.1 for placebo. Progression-free survival for patients with *BRCA*-negative, homologous recombination proficient tumors in PRIMA was 8.1 months for niraparib (Zejula) and 5.4 months for placebo. The benefit was approximately 3 months of PFS on PARP inhibitor maintenance in patients with *BRCA*-negative, homologous recombination proficient tumors in both studies. The difference in patient selection and population may explain why the ATHENA-MONO patients had a 4-month longer PFS in both arms.

ATHENA-MONO reports on further improvement from baseline in patients with measurable disease while on rucaparib maintenance, which adds to the data to support PARP inhibitor usage in maintenance and as treatment. We may see rucaparib approval for front-line maintenance regardless of tumor *BRCA* or HRD status and can consider it along with niraparib for maintenance of the patient who is *BRCA* negative with a homologous recombination proficient tumor.

As always, advanced practitioners need to be cognizant of the quality of life of our patients receiving maintenance therapy. Three months of PFS may or may not be worth the side effect profile and burden of maintenance therapy. This decision will result from a balanced, individualized discussion between provider and patient.

Disclosure: Ms. Doherty has served on the speakers bureau for Merck.

Abstract LBA5504

New Findings on Trabectedin vs Clinician's Choice of Chemotherapy in *BRCA*-Positive Ovarian Cancer

By JADPRO Staff

Visit https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.17_suppl.LBA5504 to read the full abstract and view author disclosures.

Data were presented at the 2022 ASCO Annual Meeting from the phase III MITO23 trial on single-agent trabectedin vs clinician's choice of chemotherapy in patients with recurrent ovarian, primary peritoneal, or fallopian tube cancers of *BRCA*-mutated or BRCAness phenotype. Although trabectedin has demonstrated antitumor activity in relapsed platinum-sensitive disease, it does not appear to improve survival outcomes when compared with standard chemotherapy in the *BRCA*-mutated population.

MITO23

In this open-label, phase III, randomized trial, recurrent ovarian cancer patients harboring *BRCA* 1/2 mutations or with BRCAness phenotype (defined as patients who had received and responded to at least 2 previous platinum-based treatments) were assigned to receive trabectedin 1.3 mg/m^2 every 21 days or physician's choice of chemotherapy (among carboplatin, gemcitabine, weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan). The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS), overall response rate (ORR), and duration of response.

Study Findings

244 patients were randomized and analyzed based on the intent-to-treat principle. At a median follow up of 40 months, the median PFS was 4.4 and 4.9 months (hazard ratio [HR] = 1.03, p = .848), and median OS was 17.9 and 15.8 months (HR = 1.15 p = .304) in the control and experimental arm, respectively. Overall response rate was 20.2% in the group of patients receiving standard chemotherapies and 15.4% in the group of patients treated with trabectedin. No superior effect was reported for trabectedin in the prespecified subgroup analysis according to *BRCA* mutational status, type of chemotherapy, and platinum-free interval. No new signals of toxicity were reported for all the chemotherapies employed.

Conclusions

Trabectedin as a single agent does not improve survival outcomes when compared to standard chemotherapy in *BRCA*-mutant and BRCAness phenotype ovarian cancer patients.

The Advanced Practitioner Perspective

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The use of trabectedin (Yondelis) has been explored in ovarian cancer for some time. The OVA-301 trial showed the superiority of trabectedin plus pegylated liposomal doxorubicin (PLD) over single-agent PLD in 672 patients with relapsed ovarian cancer (35% risk reduction of disease progression or death). This superiority was suggested to be due to the differential impact of subsequent platinum therapy.

This was investigated further in the INOVATYON trial, which aimed to demonstrate an improvement in overall survival for the trabectedin/PLD regimen followed at relapse by platinum rechallenge over carboplatin/PLD. That study did not meet its primary endpoint of improving overall survival (OS) with the trabectedin/doxorubicin regimen followed by platinum over carboplatin/PLD regimen. It did reach similar OS.

These newest data on trabectedin as a single agent in *BRCA*-mutated and BRCAness phenotype ovarian cancer patients show that it does not meet the OS of standard of care, showing rather a 2-month shorter OS in the trabectedin population. We remain without any FDA-approved uses for trabectedin in ovarian cancer but may see the combination with doxorubicin used off label for patients with platinum-sensitive relapsed ovarian cancer.

Disclosure: Ms. Doherty has served on the speakers bureau for Merck.

Abstract 5507

Interim Results on Tisotumab Vedotin-tftv Plus Pembrolizumab in Cervical Cancer

By JADPRO Staff

Visit https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.5507 to read the full abstract and view author disclosures.

Interim safety and efficacy results from a third dose-expansion cohort evaluating first-line tisotumab vedotin-tftv (TV) plus pembrolizumab in patients with recurrent or metastatic cervical cancer were presented at the 2022 ASCO Annual Meeting. Data on the combination showed durable antitumor activity with a manageable safety profile.

Background

Tisotumab vedotin-tftv monotherapy has received US accelerated approval for previously treated recurrent or metastatic cervical cancer with disease progression on or after chemotherapy based on clinically meaningful tumor response rate and duration of response (DOR) reported from the GOG-3023/ENGOT-cx6/innovaTV 204 study. Recently, the recommended phase 2 dose (RP2D) and feasibility of TV + pembrolizumab, TV + carboplatin, and TV + bevacizumab in recurrent or metastatic cervical cancer (r/mCC) were reported from the dose-escalation phase; interim safety and efficacy data from two dose-expansion cohorts, first-line TV + carboplatin and second-line/third-line TV + pembrolizumab from the ENGOT-cx8/GOG-3024/innovaTV 205 study, were also reported. This study reported interim safety and efficacy results from a third dose-expansion cohort evaluating first-line TV + pembrolizumab in patients with r/mCC.

"These data showed encouraging and durable antitumor activity and provide rationale for the continued development of tisotumab vedotin in front-line recurrent or metastatic cervical cancer, including its potential use as part of triplet or quadruplet combination therapy," said Domenica Lorusso, MD, PhD, a gynecologic oncologist working at the Gynaecology Oncology Unit of Policlinico Gemelli IRCCS of Rome and an investigator of the innovaTV 205 clinical trial. "These early results from multiple expansion cohorts of innovaTV 205 support our continued efforts to investigate TV as part of combination therapy to further improve treatment response and durability for this group of patients with high unmet need."

Study Design

Patients with r/mCC who had not received prior systemic therapy (excluding chemoradiation) for r/mCC were treated with the RP2D of TV 2.0 mg/kg + pembrolizumab 200 mg intravenously every 3 weeks. The primary endpoint was objective response rate (ORR) per RECIST v1.1; secondary endpoints included DOR, progression-free survival (PFS), overall survival (OS), and safety.

Study Results

33 patients were treated with first-line TV + pembrolizumab (median 6 cycles). At data cutoff, the median duration of exposure to TV + pembrolizumab was 5.1 months and median follow-up was 12.2 months. Confirmed ORR among 32 evaluable patients was 41%, with 3 (9%) complete responses and 10 (31%) partial responses. Median time to response was 1.4 months; median DOR was not reached, with response ongoing in 7/13 patients. Median PFS was 5.3 months, and median OS was not reached.

Treatment-Emergent Adverse Events

The most common treatment-emergent adverse events (TEAEs) were alopecia (61%), diarrhea (55%), epistaxis (49%), conjunctivitis (46%), and nausea (46%). Grade ≥ 3 TEAEs occurred in 67% of patients, the most common being anemia (12%); asthenia (9%); hypokalemia (9%); and increased alanine aminotransferase, decreased white blood cell count, dyspnea, and acute kidney injury (6% each). Three grade 5 TEAEs were reported of which one, disseminated intravascular coagulation, was considered treatment-related. Prespecified AEs of interest (grade 1–2/grade ≥ 3) with TV included ocular (58%/9%), peripheral neuropathy (45%/3%), and bleeding (61%/6%).

The Advanced Practitioner Perspective

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This small study of patients receiving first-line tisotumab vedotin (TV) and pembrolizumab (Keytruda) showed a good response rate and durable response in a patient population that traditionally does not have a lot of great options. The biomarker analysis of these patients' tumors will be revealing, with special attention to PD-L1 status and the combined positive score (CPS) of this trial population. That information is needed to better understand who is most likely to respond to this combination.

We know from KEYNOTE-826 that pembrolizumab can be added to platinum-based combination therapy for patients with recurrent or metastatic disease and a PD-L1 CPS greater than or equal to 1. KEYNOTE-826 showed a progression-free survival (PFS) of 10.4 months in the pembrolizumab arm vs. 8.2 in placebo. Platinum-based combination therapy with pembrolizumab is the current standard practice for any patient with recurrent or metastatic cervical cancer and positive PD-L1 scores. Experimental arm H of GOG-3024 is looking at TV + pembrolizumab + carboplatin +/- bevacizumab, and the results of this will be interesting to compare to that of KEYNOTE-826 as we strive to understand the best first-line treatment option in this patient population.

At our clinic, we care for a patient who received TV + pembrolizumab as a third-line therapy and remained on trial for 27 cycles, eventually discontinuing the TV due to neuropathy and continuing single-agent pembrolizumab for about a year. She has had no treatment for the past 6 months and remains with no evidence of disease. She was PD-L1 positive and had a CPS of 100%. Her neuropathy has almost completely resolved, and she is spending this summer pursuing her favorite pastime, gardening.

I remain excited to see the biomarker analysis of the study population, so we can continue to individualize treatments to the patient and get them back to doing the things they love.

Disclosure: Ms. Doherty has served on the speakers bureau for Merck.

Abstract 5553

Ovarian Cancer: Who Benefits From Bevacizumab in the First-Line Setting?

By JADPRO Staff

Visit https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.5553 to read the full abstract and view author disclosures.

Benoit You, MD, PhD, of Lyon University Hospital (HCL, France) and GINECO group (France), discussed findings from the GOG-0218 trial of patients with ovarian cancer, which appears to confirm earlier data on the link between poor tumor chemosensitivity and benefit from concurrent plus maintenance bevacizumab at the 2022 ASCO Annual Meeting. In Dr. You's validation study, patients who derived the most progression-free and overall survival benefit from bevacizumab were those with high-risk disease (stage IV or incompletely resected stage III) associated with an unfavorable KELIM score (CA-125 kinetic elimination rate constant, calculable online).

Background

In patients with high-grade ovarian cancer in the first-line setting, predictive factors of bevacizumab efficacy are needed for selecting patients. In the ICON-7 trial, a poor tumor intrinsic chemosensitivity (defined by unfavorable modeled CA-125 kinetic ELIMination rate constant K; KELIM) was a predictive biomarker. Among patients with high-risk diseases, only those with unfavorable KELIM had survival benefit from bevacizumab (median overall survival: 29.7 vs. 20.6 months, hazard ratio [HR = 0.78]). The objective was to perform an external validation in the GOG-0218 trial.

Methods

In GOG-0218, 1,873 patients were treated with carboplatin-paclitaxel +/- concurrent bevacizumab/placebo followed by a 15-month maintenance. Patient KELIM values were estimated with longitudinal CA-125 kinetics during the first 100 chemother-

apy days. The association between KELIM score (categorized as favorable ≥ 1, or unfavorable < 1) and efficacy of bevacizumab (bevacizumab-concurrent + maintenance, vs. placebo) for progression-free survival (PFS) and overall survival (OS) was assessed using univariate/multivariate analyses, in a Training set with 2/3 patients managed by the investigators, and then a Validation set with all patients.

Results

KELIM was assessable in 1,662 patients with ≥ 3 CA-125 available values. In both sets, the patients with unfavorable KELIM derived benefit from bevacizumab compared with placebo (Training: PFS, HR = 0.65; OS, HR = 0.80; Validation: PFS, HR = 0.69; OS, HR = 0.87), while those with favorable KELIM had no benefit from bevacizumab (Training: PFS, HR = 0.96; OS, HR = 1.05; Validation, PFS, HR = 0.96; OS HR = 1.11). The highest benefit was observed in patients with high-risk diseases (stage IV or suboptimally resected stage III) characterized by unfavorable KELIM for PFS (Learning [n = 276]: mPFS: 9.0 vs. 5.2 months, HR = 0.61; Validation [n = 433]: mPFS: 9.1 vs. 5.6 months, HR = 0.64), and for OS (Learning [n = 278]: mOS: 38.9 vs. 27.9 months, HR = 0.72, Validation set [n = 438]: mOS: 35.1 vs. 29.1 months, HR = 0.79).

Conclusions

This validation analysis of GOG-0218 trial confirms the outcomes of the ICON-7 trial about the association between poor tumor chemosensitivity and benefit from concurrent + maintenance bevacizumab, suggesting that bevacizumab is mainly effective in patients with poorly chemosensitive diseases. No benefit was found in patients with favorable KELIM. The patients who derived the highest benefit from bevacizumab in PFS and OS (OS absolute benefit of about 6 to 9 months) were those with high-risk diseases (stage IV, or incompletely resected stage III) associated with an unfavorable KELIM score (calculator on https://www.biomarker-kinetics.org/CA-125).

The Advanced Practitioner Perspective

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Those of us treating patients with gynecologic cancers are familiar with bevacizumab (Avastin) and the myriad of toxicities that can result from its use. We never want to overtreat and certainly do not want to expose patients to extra toxicity or additional financial burden. We understand that appropriate patient selection for use of bevacizumab is important. The CA-125 ELIMination Rate Constant K (KELIM) score is an accessible tool that can help us with this selection process.

The initial survival analysis of GOG-0218 showed no benefit in overall survival (OS) for patients treated with bevacizumab. When looking at these patients through a new lens, the authors show us that there is an OS absolute benefit of 6 to 9 months in the patients who have high-risk diseases (stage IV or incompletely resected stage III) and are associated with an unfavorable KELIM score, who were treated with bevacizumab.

The presence of high-risk disease and the KELIM score is easy to assess after just a couple of cycles of treatment or at time of interval debulking. For the patient with high-risk disease and unfavorable KELIM score, we can more confidently recommend bevacizumab following this validation analysis.

Disclosure: Ms. Doherty has served on the speakers bureau for Merck.