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Evidence indicates that we are beginning to hit the target in ovarian cancer, with recent advances in the treatment of platinum-resistant ovarian cancer and low-grade serous carcinoma, while the utility of PARP inhibitors continues to evolve

In 2022, the most significant advances in the treatment of gynecologic cancers were achieved for patients with ovarian cancer. While ovarian cancer continues to carry the worst prognosis of all gynecologic cancers, 5-year relative survival has gradually increased, from 34.4% in 1975 to 52.4% in 2014.<sup>1</sup>

In this Update, we highlight the recent advances in our understanding of targeted therapy in ovarian cancer. We review SORAYA, a trial that demonstrated that mirvetuximab

soravtansine, an antibody-drug conjugate, has promising efficacy in platinum-resistant ovarian cancers that overexpress folate receptor  $\alpha$ . We also spotlight progress in the treatment of low-grade serous ovarian cancer, another notoriously chemotherapy-resistant disease, in GOG 281/LOGS, a phase 2 study of the MEK inhibitor trametinib. Finally, we discuss emerging long-term follow-up data on poly(ADP-ribose) polymerase (PARP) inhibitors, which are helping to refine the role of these groundbreaking drugs.

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## New drug approved for platinum-resistant epithelial ovarian cancer—the first since 2014



Matulonis UA, Lorusso D, Oaknin A, et al. Efficacy and safety of mirvetuximab soravtansine in patients with platinum-resistant ovarian cancer with high folate receptor alpha expression: results from the SORAYA study. *J Clin Oncol.* 2023;41:2436-2445. doi:10.1200/JCO.22.01900.

While most patients diagnosed with advanced ovarian cancer will respond to platinum-based chemotherapy, those whose disease recurs eventually develop resistance to platinum agents. Treatment options for platinum-resistant

**WHAT THIS EVIDENCE MEANS FOR PRACTICE**

The FDA has granted accelerated approval to mirvetuximab soravtansine-gynx for women with platinum-resistant ovarian cancer with high folate receptor  $\alpha$  expression who have received 1 to 3 prior systemic treatment regimens.

ovarian cancer are limited and prognosis is poor. Most regimens have a response rate of only 10%. Since the approval of bevacizumab combined with chemotherapy in 2014, no new agents have been approved by the US Food and Drug Administration (FDA) for use in platinum-resistant ovarian cancer.

**Efficacy shown with mirvetuximab**

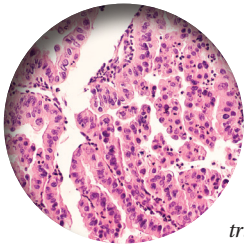
Recently, Matulonis and colleagues published results of the SORAYA study, a single-arm, phase 2 trial, that examined the efficacy and

safety of mirvetuximab soravtansine-gynx among women with platinum-resistant ovarian cancer.<sup>2</sup> Mirvetuximab is an antibody-drug conjugate composed of an antibody directed at the folate receptor  $\alpha$  attached to a cytotoxic microtubule inhibitor.

The study included 106 patients with platinum-resistant ovarian cancer whose tumors expressed folate receptor  $\alpha$  at a high level—a feature of approximately 50% of patients screened for the study. Twenty-nine patients experienced a partial response and 5 had a complete response, corresponding to a remarkable objective response rate of 32.4%. The median progression-free survival was 4.3 months.

Like other antibody-drug conjugates, ocular toxicities, including blurred vision (41%) and keratopathy (29%), were common. However, toxicity was manageable and rarely led to drug discontinuation.

## A novel agent for recurrent low-grade serous ovarian carcinoma



*Gershenson DM, Miller A, Brady WE, et al. Trametinib versus standard of care in patients with recurrent low-grade serous ovarian cancer (GOG 281/LOGS): an international, randomised, open-label, multicentre, phase 2/3 trial. Lancet. 2022;399:541-553. doi:10.1016/S0140-6736(21)02175-9.*

Low-grade serous carcinoma is a histologic subtype that makes up approximately 5% of all epithelial ovarian cancers.<sup>3</sup> Patients with low-grade serous carcinoma are often younger and, because of the indolent nature of the histology, generally have a longer overall survival compared with patients with high-grade serous carcinoma. Unlike high-grade disease, however, low-grade serous carcinoma usually is resistant to chemotherapy, making treatment options limited for patients with advanced and recurrent disease.

**Trametinib: A potential option**

In an international, randomized, open-label trial (GOG 281/LOGS), Gershenson and colleagues investigated the efficacy of trametinib compared with standard-of-care chemotherapy in patients with recurrent low-grade serous ovarian cancer.<sup>4</sup> Trametinib, a mitogen-activated protein kinase MEK inhibitor, is a targeted agent that is FDA approved for treatment in *BRAF*-mutated melanoma, lung, and thyroid cancers.

Patients with recurrent low-grade serous ovarian cancer were randomly assigned to trametinib (n = 130) or 1 of 5 standard-of-care treatment options (n = 130), including both chemotherapy and hormonal treatments. Those assigned to trametinib were significantly less likely to have disease progression (78% vs 89%), with a median progression-free survival of 13 months, compared with 7.2 months in controls (hazard ratio [HR],

0.48; 95% confidence interval [CI], 0.36–0.64). Additionally, patients who had a radiographic response to trametinib experienced a longer duration of response compared with those who responded to standard-of-care treatment (13.6 months vs 5.9 months).

While there was no statistically significant difference in overall survival (HR, 0.76; 95% CI, 0.51–1.12), crossover to trametinib from the standard-of-care group was allowed and occurred among 68% of patients, which limits the study's ability to measure differences in overall survival.

Trametinib was well tolerated by patients, but skin rash and anemia followed by hypertension were the most common adverse effects. In the standard-of-care

### WHAT THIS EVIDENCE MEANS FOR PRACTICE

Although trametinib is not yet FDA approved for the treatment of ovarian cancer, the National Comprehensive Cancer Network has added trametinib as a treatment option for recurrent low-grade serous ovarian carcinoma, given the significant improvement in progression-free survival compared with standard-of-care treatment.

group, the most common toxicities were abdominal pain, nausea, and anemia. A slightly higher proportion of patients in the trametinib group discontinued the drug due to toxicity compared with the standard-of-care group (36% vs 30%), but there was no difference between the 2 groups in scores on quality-of-life assessments.

## PARP inhibitors benefit many women with ovarian cancer, but they may hurt others

*Monk BJ, Parkinson C, Lim MC, et al. A randomized, phase III trial to evaluate rucaparib monotherapy as maintenance treatment in patients with newly diagnosed ovarian cancer (ATHENA-MONO/GOG-3020/ENGOT-ov45). J Clin Oncol. 2022;40:3952-3964. doi:10.1200/JCO.22.01003.*

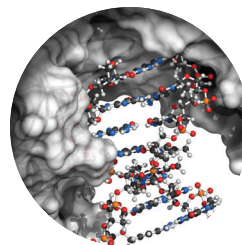
**P**oly(ADP-ribose) polymerase (PARP) inhibitors are a class of oral anticancer agents that target DNA repair. Since the initial FDA approval in 2014 of olaparib for the treatment of patients with recurrent *BRCA*-mutated ovarian cancer, PARP inhibitors have been approved for maintenance in both the frontline setting and after platinum-sensitive recurrence, and as single-agent treatment for ovarian cancer with *BRCA* mutations or evidence of homologous recombination deficiency (HRD), a *BRCA*-like molecular phenotype.<sup>5</sup> The expanding role for PARP inhibitors in ovarian cancer seemed inexorable.

### Restricted prescribing advised

In 2022, we learned that in certain settings, PARP inhibitors may be the wrong choice. Several “Dear Health Care Provider” letters were issued by AstraZeneca, Clovis, and GSK to advise physicians to restrict the prescribing of olaparib, rucaparib, and niraparib.<sup>6,7</sup>

AstraZeneca and Clovis issued letters spurred by the final analysis of ARIEL4 and SOLO3 studies, 2 randomized trials that investigated, respectively, rucaparib and olaparib monotherapy compared with chemotherapy in recurrent ovarian cancer.<sup>8,9</sup> In both cases patients randomized to PARP inhibitors may have experienced an overall survival decrement compared with those who received chemotherapy.

At the FDA's request, Clovis has withdrawn rucaparib as a treatment for patients with recurrent *BRCA*-mutant ovarian cancer who had received 2 or more lines of



## WHAT THIS EVIDENCE MEANS FOR PRACTICE

PARP inhibitor maintenance therapy after upfront chemotherapy in women with *BRCA*-mutant and HRD epithelial ovarian cancer has been game changing in ovarian cancer. However, PARP inhibitors have a more limited role than previously thought for patients with recurrent ovarian cancer.

chemotherapy, and AstraZeneca withdrew olaparib monotherapy in germline *BRCA*-mutant patients with recurrent ovarian cancer. Shortly after these withdrawals, GSK also withdrew its indication for niraparib as a treatment for women with HRD, platinum-sensitive ovarian cancer who have received 3 or more prior chemotherapies. Furthermore, based on the final overall survival analysis of the NOVA study, GSK also restricted its indication for niraparib maintenance for recurrent ovarian cancer to patients with germline *BRCA* mutations, due to evidence of an overall survival detriment in this setting.<sup>10</sup>

## Positive study results

Fortunately, 2022 was not all bad news for PARP inhibitors in ovarian cancer. In June 2022, the ATHENA-MONO trial, a phase 3 double-blind randomized controlled trial, demonstrated that rucaparib maintenance in patients with newly diagnosed epithelial ovarian cancer was associated with a significantly longer progression-free survival compared with placebo.<sup>11</sup> The effect was most pronounced in the *BRCA*-mutant/HRD population, with a median progression-free survival of 28.7 months in the rucaparib group compared with 11.3 months in the placebo group (HR, 0.47; 95% CI, 0.31–0.72). Thus, rucaparib was added to the list of PARP inhibitors approved for upfront maintenance therapy in epithelial ovarian cancer.

Similarly, the long-term overall survival analysis from the upfront trials SOLO-1 and PAOLA-1 showed an overall survival advantage of PARP inhibitor, compared with placebo, maintenance in patients with *BRCA* mutations or HRD tumors.<sup>12,13</sup> ●

## FAST TRACK

*The long-term overall survival analysis from the upfront trials SOLO-1 and PAOLA-1 showed an overall survival advantage of PARP inhibitor, compared with placebo, maintenance in patients with BRCA mutations or HRD tumors*

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