

Dear SGO Members,

The landscape of PARP inhibitor indications in ovarian cancer has recently evolved as new overall survival data have emerged1. This can create confusion in clinical practice. Updated survival data have prompted recent revisions to the FDA approvals for PARP inhibitors for individuals with ovarian cancer and the issuance of “Dear Healthcare Provider” letters2-10. A “Dear Healthcare Provider” letter is a communication sent by a drug manufacturer who has been made aware of a serious problem with its product or similar products or when the manufacturer needs to provide updated information on the use of the product. The SGO recognizes the importance of clear communication and guidance for its membership.

Below is a brief summary of the newly updated **FDA approved** indications for PARP inhibitors in the management of epithelial ovarian cancer.

* **Indications for Maintenance Therapy**
	+ **1st line** *maintenance* following response to platinum-based chemotherapy for newly diagnosed, advanced stage, high-grade ovarian cancer patients
		- Olaparib
			* Germline or somatic deleterious *BRCA* alteration
		- Olaparib with bevacizumab
			* Germline or somatic deleterious *BRCA* alteration and/or homologous recombination deficient (HRD) positive tumors
		- Niraparib
			* All (Any *BRCA* or HRD status)
	+ **2nd or greater line** *maintenance* following response to platinum-based chemotherapy for patients with recurrent platinum-sensitive ovarian cancer
		- Niraparib
			* Germline or suspected germline *BRCA* deleterious alteration *4,*7
		- Olaparib
			* All (any *BRCA* or HRD status)\*\*
		- Rucaparib
			* *Planned revision:* Germline or somatic deleterious *BRCA* alteration \*\* 8

Below is a brief summary of the newly **withdrawn** **FDA approvals** for PARP inhibitors in the management of epithelial ovarian cancer.

* **Withdrawn Indications for Maintenance Therapy**
	+ **2nd or greater line** *maintenance* following response to platinum-based chemotherapy for recurrent platinum-sensitive ovarian cancer
		- Niraparib
			* *Non-*germline *BRCA 4,*7 *no longer FDA approved* in this setting
* ***Anticipated Withdrawal* of Indication for Maintenance Therapy**
	+ **2nd or greater line** *maintenance* following response to platinum-based chemotherapy for recurrent platinum-sensitive ovarian cancer **\*\***
		- Rucaparib
			* *Non-BRCA*8 *will no longer be FDA approved* in this setting
* **Withdrawn Indications for Single-agent Treatment**
	+ Olaparib 3,6, rucaparib 2,5 and niraparib 9,10 *no longer FDA approved* in this setting

**Considerations:**

* **\*\*Further revisions** **are anticipated** to the approval for rucaparib and possibly olaparib in the 2nd or greater line *maintenance* therapy setting.
* The continuation of PARP inhibitors in patients who are deriving clinical benefit from a PARP inhibitor in a setting that is no longer FDA approved should be done after a thorough discussion with the patient.
* The Oncology Drugs Advisory Committee (ODAC) will continue to review the role of PARP inhibitors as new data emerges.
* The “Dear Healthcare Provider letters” provided preliminary overall survival results in subgroups of patients. Hazard ratios were used to estimate the overall survival in the various groups. The 95% confidence intervals for the overall survival hazard ratios crossed 1. Once published the corresponding peer-reviewed manuscripts for overall survival may provide additional insight into the survival outcomes for these subgroups.

Below is a brief summary of the **“Dear Healthcare Provider”** letters issued in conjunction with the aforementioned FDA withdrawals for previously approved indications.

* **Maintenance Therapy Setting**

NOVA study: New overall survival data prompted an initial “Dear Healthcare Provider” letter to be issued May 2022 4 and a second letter on November 2022 7 to announce the voluntary withdrawal of the FDA approval of niraparib as maintenance therapy for patients with recurrent platinum-sensitive ovarian cancer that is not germline *BRCA* associated.

* + Overall survival data from NOVA study: Reduced overall survival with niraparib in subgroup of patients with non-germline *BRCA* ovarian cancer compared to placebo.
	+ Led to withdrawal of FDA approval of niraparib as maintenance for patients with platinum-sensitive, non-germline *BRCA* ovarian cancer following response to platinum-based chemotherapy

ARIEL3 study: Although a “Dear Healthcare Provider” letter has not yet been issued, the plan to voluntarily withdraw the FDA approval of rucaparib as maintenance therapy for patients with recurrent platinum-sensitive ovarian cancer that is not germline or somatic *BRCA* associated was announced on December 1st 2022.8

* + This will lead to withdrawal of FDA approval of rucaparib as maintenance for patients with platinum-sensitive, non *BRCA* associated ovarian cancer following response to platinum-based chemotherapy
* **Single-agent Treatment Setting**

ARIEL4, SOLO3 and QUADRA Studies: New overall survival data prompted the following “Dear Healthcare Provider” letters to be issued for rucaparib in June 2022, for olaparib in August 2022 and for niraparib in September 2022. These letters were followed by withdrawal of the FDA approval of PARP inhibitors as a single-agent treatment for recurrent ovarian cancer.

* + - Overall survival data from ARIEL4 study: Reduced overall survival in subgroup of patients with platinum-resistant disease treated with rucaparib compared to the chemotherapy arm 5
		- Led to withdrawal of FDA approval of rucaparib as treatment for germline or somatic *BRCA*-associated ovarian cancer patients with 2+ prior lines of therapy
		- Overall survival data from SOLO3: Reduced overall survival in subgroup of patients who had 3+prior lines and received treatment with olaparib 6
		- Led to withdrawal of FDA approval for patients with germline *BRCA* associated ovarian cancer with 3+ prior lines of therapy
		- Quadra: A single arm study of niraparib in patients who had received 3+ prior lines of chemotherapy 9,10 The letter referred to the overall survival data for the randomized controlled trials of the other PARP inhibitors in this setting (ARIEL4 and SOLO3) that had suggested possible detrimental overall survival in certain subgroups when compared to chemotherapy.
		- Led to withdrawal of FDA approval for patients with recurrent platinum-sensitive, HRD positive with 3+ prior lines of therapy.

References:

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2. Kristeleit R, Lisyanskaya A, Fedenko A, et al. Rucaparib versus standard-of-care chemotherapy in patients with relapsed ovarian cancer and a deleterious BRCA1 or BRCA2 mutation (ARIEL4): an international, open-label, randomised, phase 3 trial. [Lancet Oncol](https://doi.org/10.1016/s1470-2045%2822%2900122-x). 2022;23(4):465-478.
3. Penson RT, Valencia RV, Colombo N, et al. Final overall survival results from SOLO3: phase III trial assessing olaparib monotherapy versus non-platinum chemotherapy in heavily pre-treated patients with germline BRCA1- and/or BRCA2-mutated platinum-sensitive relapsed ovarian cancer. Presented at: 2022 SGO Annual Meeting on Women’s Cancer. March 18-21, 2022. Phoenix, Arizona.
4. GlaxoSmithKline: [Dear Healthcare Provider Letter, May 2022](https://www.zejulahcp.com/content/dam/cf-pharma/hcp-zejulahcp-v2/en_US/pdf/ZEJULA%20%28niraparib%29%20Dear%20HCP%20Letter.pdf). Published May 2022. Accessed November 15, 2022.
5. Clovis Oncology, Inc: [Dear Healthcare Professional Letter, June 2022](https://clovisoncology.com/pdfs/US_DHCPL_final_signed.pdf). Published June 2022. Accessed November 15, 2022.
6. AstraZeneca: [Dear Healthcare Professional Letter](https://www.accc-cancer.org/docs/ossn-network/industry-news-announcements/solo3-dhcp.pdf). Published August 2022. Accessed November 15, 2022.
7. GlaxoSmithKline: [Dear Health Care Provider Letter (Niraparib)](https://www.zejulahcp.com/content/dam/cf-pharma/hcp-zejulahcp-v2/en_US/pdf/ZEJULA%20%28niraparib%29%20Dear%20HCP%20Letter%20November%202022.pdf). GSK plc. Published November 2022. Accessed November 15, 2022.
8. Clovis Oncology, Inc: [United States Securities and Exchange Commission Form 8-K](https://d18rn0p25nwr6d.cloudfront.net/CIK-0001466301/c27075d6-6d64-42e0-af52-a7b855dc2748.pdf). Published December 2022. Accessed December 5, 2022.
9. GlaxoSmithKline: [Dear Health Care Provider Letter (Niraparib)](https://medinfo.gsk.com/5f95dbd7-245e-4e65-9f36-1a99e28e5bba/57e2a3fa-7b9b-432f-a220-5976a509b534/57e2a3fa-7b9b-432f-a220-5976a509b534_viewable_rendition__v.pdf). Published September 2022. Accessed November 15, 2022.
10. Moore K, Alvarez Secord A, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. [*Lancet Oncol*](https://doi.org/10.1016/S1470-2045%2819%2930029-4)*.* 2019;20(5):636-648.

We hope that this interim guidance will aid our SGO membership. For questions or further guidance, please email sgo@sgo.org.



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\**These recommendations are not meant to be a substitute for clinical judgement at the individual patient level, nor should they supersede other policies at the institutional level. All decisions should be made in the context of the unique circumstances where members practice, including other local resource considerations. We encourage members to work closely with their institutions to ensure that patients’ needs are being met.*