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NCCN Guidelines Panel: Ovarian Cancer

On behalf of Clovis Oncology, Inc., I respectfully request that the NCCN Ovarian Cancer Panel review the enclosed information and consider updating the recommendations on OV-7 "Therapy for Persistent Disease or Recurrence" to recommend oral PARP inhibitor (niraparib, olaparib, or rucaparib) maintenance treatment over observation following a complete or partial response to platinum-based chemotherapy in light of the COVID-19 pandemic and associated challenges for patients with cancer and their healthcare teams.

Specific Changes: We recommend that "Observe" on page OV-7 be downgraded from category 2A to 2B or 3 and that "Observe" should only be considered for patients who cannot be treated with PARP inhibitors. We also request that the NCCN Panel consider updating the PARP inhibitor class from category 2A to category 1 in recurrent ovarian cancer given the consistent data across three randomized controlled phase 3 trials in the setting of recurrent ovarian cancer.

FDA Approvals of PARP Inhibitors in Ovarian Cancer:

Lynparza® (olaparib) is indicated: [1]

- For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated (g*BRCA*m or s*BRCA*m) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.
- In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:
    - a deleterious or suspected deleterious *BRCA* mutation, and/or
    - genomic instability.

  Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza
- For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.
- For the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated (g*BRCA*m) advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

Rubraca® (rucaparib) is indicated:[2]

- For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.
- For the treatment of adult patients with deleterious *BRCA* mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more

chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for RUBRACA.

Zejula® (niraparib) is indicated:[3]

- For the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based Chemotherapy.
- For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.
- For the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:
    - a deleterious or suspected deleterious *BRCA* mutation
    - genomic instability and who have progressed more than six months after response to the last platinum-based chemotherapy.
- Select patients for therapy based on an FDA-approved companion diagnostic for ZEJULA.

Rationale: On March 11, 2020, the World Health Organization (WHO) declared the outbreak of the novel coronavirus SARS-CoV-2 and its associated disease COVID-19 a pandemic [4]. There is a critical need to contain and mitigate transmission of SARS-CoV-2 to prevent surges of ill patients that may overwhelm healthcare systems and resources. In addition, healthcare resources—including the types of therapies that are given—are being managed closely by healthcare systems to ensure there are adequate resources to treat patients. For example, use of therapies that require intravenous administration place increased burden on healthcare systems by requiring patients to visit an infusion center. Intravenous therapies also require that healthcare providers use personal protective equipment (PPE), infusion kits, and other resources that are not required with use of oral therapies. Clinic visits may also increase nosocomial outbreaks of SARS-CoV-2, including among healthcare professionals, caregivers, and patients. At least two prospective, non-interventional observational hospital-based studies are currently evaluating the nosocomial spread of SARS-CoV-2 (NCT04330638 and NCT04339881)

In March 2020, the American Society of Clinical Oncology (ASCO) created a COVID-19 resource center to help ensure individuals with cancer receive high quality care during the pandemic. Specifically, ASCO provides helpful guidance for managing immunosuppressive therapy during the COVID-19 crisis and suggests that some patients may be able to switch chemotherapy from IV to oral therapies, which would decrease the frequency of clinic visits but would require greater vigilance by health care teams to ensure patients are taking medicines correctly [5].

In April 2020, the European Society of Medical Oncology (ESMO) also developed management and treatment-adapted recommendations for patients with cancer in the COVID-19 era, including patients with epithelial ovarian cancer. These recommendations prioritize certain routine practices as high, medium, or low priority based on the ESMO committee's assessment of need for urgent follow-up during the COVID-19 pandemic. For outpatients, follow-up visits on PARP inhibitor maintenance are considered low priority because most visits can be managed through telemedicine with scheduled blood tests and imaging done close to patients' homes. For patients with advanced disease, continuation of post-operative chemotherapy for high-grade serous/endometrioid tumors is a high priority. The importance of *BRCA* testing continues as these patients are eligible for treatment with PARP inhibitors and should be considered for shortened chemotherapy cycles. A reduced number of cycles (4-5) should be considered in responding patients before adding a PARP inhibitor. The recommendations also emphasize caution with bevacizumab due to associated hypertension which may worsen COVID-19 outcomes. PARP inhibitor maintenance is recommended in high-grade serous/endometrioid cancers with a *BRCA* mutation responding to platinum-based therapy. In patients with a *BRCA* mutation who are PARP inhibitor naïve, ESMO

recommends the consideration of rucaparib monotherapy in situations where platinum therapy cannot be given [6].

We agree with many of ASCO's and ESMO's COVID-19 resources and recommendations, including reducing visits to the clinic when possible and potential reduction in the number of chemotherapy cycles. With this goal in mind, we kindly request a revision to the NCCN Ovarian Cancer Guidelines to recommend the use of PARP inhibitor maintenance therapy over observation to treat individuals with recurrent ovarian cancer, allowing patients to receive active therapy while at home, which potentially reduces their risk of contracting SARS-CoV-2 in a healthcare setting while keeping patients out of the clinic for routine care during the COVID-19 pandemic.

In the setting of recurrent ovarian cancer, observation without treatment can lead to rapid disease recurrence [7-10]; this may have the unintended consequence of placing more demands on the healthcare system during the COVID-19 pandemic. Three large, phase 3, placebo-controlled, double-blind studies (SOLO-2, ARIEL3 and NOVA) [7, 9,10] and a randomized, double-blind, phase 2 study (Study 19) [8] were conducted to evaluate PARP inhibitor maintenance therapy versus placebo among patients with recurrent ovarian cancer. All studies showed similar outcomes with significantly prolonged progression-free survival (PFS) with PARP inhibitor maintenance compared to placebo (analogous to observation). Among the intent-to-treat (ITT) population, the median PFS ranged from 8.4 to 10.8 months with PARP inhibitors and 4.8 to 5.4 months with placebo. Among patients with *BRCA* mutations, the median PFS ranged from 11.2 to 21.0 months with PARP inhibitors and 4.3 to 5.5 months with placebo [7-10].

In addition to consistent PFS benefit versus placebo, PARP inhibitors have also demonstrated significantly longer time to start of first subsequent therapy (TFST) versus placebo in the aforementioned trials [7, 11-13]. TFST was significantly prolonged with olaparib versus placebo among patients with recurrent ovarian cancer as demonstrated in the phase 3 SOLO-2 study and the phase 2 Study 19. In SOLO-2, TFST was significantly prolonged with olaparib maintenance (n=196) compared to placebo (n=99). The median TFST was 27.9 months for olaparib and 7.1 months for placebo (hazard ratio [HR], 0.28; 95% CI: 0.21-0.38; P<0.0001) among study patients, 97% of whom had a germline *BRCA1/2* mutation [7]. In Study 19, among all patients, the median TFST for olaparib (n=136) was 13.4 months versus 6.7 months for placebo (n=128) (HR, 0.39; 95% CI: 0.29-0.51; P<0.0001). The median TFST among patients with *BRCA* mutations was 15.6 months for olaparib (n=74) and 6.2 months for placebo (n=62) (HR, 0.32; 95% CI: 0.22-0.48; P<0.0001).[11]

In the phase 3 ARIEL3 study, TFST was also significantly longer with rucaparib maintenance versus placebo for all three molecularly defined cohorts. Among patients with *BRCA* mutations, the median TFST was 18.9 months for rucaparib (n=130) and 7.2 months for placebo (n=66) (HR, 0.28; 95% CI: 0.20-0.41; P<0.0001). Among the cohort of patients with *BRCA* mutation or *BRCA* wild type/high loss of heterozygosity (HRD+), the median TFST was 16.4 months for rucaparib (n=236) versus 7.4 months for placebo (n=118) (HR, 0.39; 95% CI: 0.30-0.51; P<0.0001) Finally, among the ITT population, the median TFST was 12.4 months for rucaparib (n=375) versus 7.2 months for placebo (n=189) (HR, 0.43; 95% CI: 0.35-0.52; P<0.0001) [12].

TFST was also prolonged with niraparib versus placebo across all three molecularly defined cohorts in the phase 3 NOVA study. Among the germline *BRCA* mutated cohort, the median TFST was 21.0 months for niraparib (n=138) versus 8.4 months for placebo (n=65) (HR, 0.31; 95% CI: 0.21, 0.48). In the subgroup of patients in the non-germline *BRCA* mutated cohort who were HRD+, the TFST was 15.9 months for niraparib (n=106) versus 6.0 months for placebo (n=56) (HR, 0.36; 95% CI: 0.23, 0.57). Finally, among the entire non-germline *BRCA* mutated cohort, the median TFST was 11.8 months for niraparib (n=234) versus 7.2 months for placebo (HR, 0.55; 95% CI: 0.41, 0.72) [13].

The most common adverse reactions (≥10%) for olaparib in clinical trials as a single agent were nausea, fatigue (including asthenia), vomiting, abdominal pain, anemia, diarrhea, dizziness, neutropenia, leukopenia, nasopharyngitis/upper respiratory tract infection/influenza, respiratory tract infection, arthralgia/myalgia, dysgeusia, headache, dyspepsia,

decreased appetite, constipation, stomatitis, dyspnea, and thrombocytopenia [1].

For rucaparib, the most common adverse reactions (≥20%) were nausea, fatigue (including asthenia), vomiting, anemia, dysgeusia, AST/ALT elevation, constipation, decreased appetite, diarrhea, thrombocytopenia, neutropenia, stomatitis, nasopharyngitis/URI, rash, abdominal pain/distention, and dyspnea [2].

The most common adverse reactions (incidence ≥10%) of patients who received niraparib were nausea, thrombocytopenia, anemia, fatigue, constipation, musculoskeletal pain, abdominal pain, vomiting, neutropenia, decreased appetite, leukopenia, insomnia, headache, dyspnea, rash, diarrhea, hypertension, cough, dizziness, acute kidney injury, urinary tract infection, and hypomagnesemia [3].

In summary, PARP inhibitors help delay recurrence vs. active surveillance or watchful waiting in recurrent ovarian cancer, which may have the unintended consequence of placing more demands on healthcare systems during the COVID-19 pandemic, especially if intravenous infusion is required following recurrence. In addition, use of non-oral therapies may increase the frequency of visits to the clinic, which may have the unintended consequence of aiding community spread of SARS-CoV-2 amongst healthcare workers, patients, and caregivers during this pandemic [14]. Additionally, the safety profile of PARP inhibitors is considered manageable and follow-up visits are considered low priority by ESMO as the majority can be managed through telemedicine and scheduled blood tests and imaging performed close to home. Caution should be used with bevacizumab due to associated hypertension which may worsen COVID-19 outcomes and use of resources with maintenance therapy [6].

The following articles and presentations are submitted in support of this proposed change.

1. Lynparza. Prescribing Information. AstraZeneca Pharmaceuticals LP; 2020. https://www.azpicentral.com/lynparza_tb/lynparza_tb.pdf#page=1. Accessed May 15, 2020.
2. Rubraca. Prescribing Information. Clovis Oncology, Inc.; 2020. https://clovisoncology.com/pdfs/RubracaUSPI.pdf. Accessed May 15, 2020.
3. Zejula. Prescribing information. Tesaro, Inc.; 2020. https://www.zejula.com/application/files/6915/8818/8598/Zejula_USPI_PRIMA_to_FDA_29_April_2020_Clean.pdf Accessed May7, 2020.
4. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. World Health Organization website. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed May 7, 2020.
5. COVID-19 Patient Care Information. American Society for Clinical Oncology website. https://www.asco.org/asco-coronavirus-information/care-individuals-cancer-during-covid-19. Accessed May 7, 2020.
6. ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: Epithelial Ovarian Cancer. European Medical Society of Medical Oncology website. https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic/gynaecological-malignancies-epithelial-ovarian-cancer-in-the-covid-19-era. Accessed May 7, 2020.
7. Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2017 Sep;18(9):1274-1284.
8. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol*. 2014 Jul;15(8):852-61.
9. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017 Oct 28;390(10106):1949-1961.

10. Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med* 2016 Dec 1;375(22):2154-2164.
11. Ledermann JA, Harter P, Gourley C, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Oncol.* 2016 Nov;17(11):1579-1589.
12. Ledermann JA, Oza AM, Lorusso D, et al. Rucaparib for patients with platinum-sensitive, recurrent ovarian carcinoma (ARIEL3): post-progression outcomes and updated safety results from a randomised, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2020 May;21:710-22.
13. Niraparib multidisciplinary review. Center for Drug Evaluation and Research. United States Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208447Orig1s000MultidisciplineR.pdf. Accessed May 7, 2020.
14. Walsh CS. Latest clinical evidence of maintenance therapy in ovarian cancer. *Curr Opin Obstet Gynecol*. 2020 Feb;32(1):15-21.

We sincerely appreciate the opportunity to provide this information for consideration by the NCCN Ovarian Cancer Panel.

Sincerely,

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