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Date of Request: June 3, 2019
NCCN Guidelines Panel: Ovarian Cancer

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Ovarian Cancer to consider updating the guidelines based on the enclosed SOLO-3 data for LYNPARZA® (olaparib) which was presented at the 2019 American Society of Clinical Oncology (ASCO) meeting in Chicago, IL on June 3, 2019.

Specific Changes:
We respectfully request your consideration of the following changes:

- Page OV-C, 6 of 9, Under "Targeted Therapy (single agents)," add a footnote next to olaparib stating, "For patients with deleterious germline *BRCA*-mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy."
- Page MS-23, consider adding brief SOLO-3 study summary under "Olaparib" section.

FDA Status:[1] The use of olaparib for the *treatment* of women with platinum-sensitive relapsed g*BRCA*m advanced ovarian cancer who had two or more prior lines of chemotherapy is not currently FDA-approved.

Rationale:

This request is based on the results of the SOLO-3 study, a Phase III randomized, open-label, controlled, multicenter trial evaluating the efficacy and safety of olaparib tablets versus physician's choice of non-platinum chemotherapy in women with platinum-sensitive relapsed g*BRCA*m high-grade serous or endometrioid ovarian, primary peritoneal, and/or fallopian tube cancer who had received two or more prior lines of platinum-based chemotherapy.[2] The trial randomized 266 patients with a deleterious or suspected deleterious germline *BRCA1* and/or *BRCA2* mutation who had progressed at least 6 months after their last platinum-based chemotherapy regimen. Eligible patients were randomized (2:1) to receive olaparib 300 mg tablets twice daily (n=178) or physician's choice single-agent chemotherapy (n=88; pegylated liposomal doxorubicin [n=47], paclitaxel [n=20], gemcitabine [n=13], or topotecan [n=8]). Patients were stratified according to physician's choice of chemotherapy, number of prior lines of chemotherapy, and time to progression after previous platinum-based chemotherapy. The primary endpoint was objective response rate (ORR) by blinded independent central review and key secondary endpoints included progression-free survival (PFS), time to first subsequent therapy (TFST), time to second disease progression or death (PFS2), and overall survival (OS).

Efficacy Results:

Efficacy results reported in the SOLO-3 study are summarized in the following tables.

TABLE I: Efficacy Results - Response Rates.

Endpoints	Olaparib (n=178)	Chemotherapy (n=88)	OR (95% CI), p-value
All patients,* n (%)	151 (85)	72 (82)	
ORR, (%)	72	51	2.53; 1.40-4.58; p=0.002
CR, (%)	9	3	
PR, (%)	63	49	
Patients with 2 prior lines of chemotherapy,* n (%)	78 (44)	39 (44)	
ORR, (%)	85	62	3.44; 1.42-8.54
CR, (%)	12	5	
PR, (%)	73	56	
Patients with ≥3 prior lines of chemotherapy,* n (%)	73 (41)	33 (38)	
ORR, (%)	59	39	2.21; 0.96-5.20
CR, (%)	7	0	
PR, (%)	52	39	

CI = confidence interval; CR = complete response; OR = odds ratio; ORR = objective response rate; PR = partial response.
*Patients with measurable disease at baseline

TABLE II: Efficacy Results – Secondary Endpoints.

Endpoints	Olaparib (n=178)	Chemotherapy (n=88)	HR (95% CI), p-value
Median PFS, months (BICR)	13.4	9.2	0.62; 0.43-0.91; p=0.013
Median PFS, months (IA)	13.2	8.5	0.49; 0.35-0.70; p<0.001
Median TFST, months	15.1	10.2	0.48; 0.33-0.71; p<0.001
Median PFS2, months	23.6	19.6	0.81; 0.52-1.26; p=0.35

BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; IA = investigator-assessed; PFS = progression-free survival; PFS2 = second disease progression or death; TFST = time to first subsequent therapy.

Safety Results:

- The median total treatment duration for the olaparib arm was 11.3 months (0.1-39.5). Median total treatment durations within the chemotherapy arms were 6.0 months for pegylated liposomal doxorubicin (0.9-15.4), 5.1 months for paclitaxel (1.8-18.2), 3.3 months for gemcitabine (0.7-14.3), and 6.2 months for topotecan (2.3-9.7).
- Safety results reported in the SOLO-3 study are summarized in the following tables.

TABLE III: Safety Results – Safety Overview.

Endpoints	Olaparib (n=178)	Chemotherapy (n=76)
All grade AEs, n (%)	174 (98)	73 (96)
Grade ≥3 AEs, n (%)	89 (50)	36 (47)
Serious AEs, n (%)*	42 (24)	14 (18)
AEs leading to dose interruption, n (%)	85 (48)	32 (42)
AEs leading to dose reduction, n (%)	48 (27)	25 (33)
AEs leading to treatment discontinuation, n (%)†	13 (7)	15 (20)

AE = adverse event
*Most common serious AE in the olaparib arm was anemia (3%) and in the chemotherapy arm was vomiting (4%)
†Most common AEs leading to treatment discontinuation in the olaparib arm were vomiting, anemia, and thrombocytopenia (all 1%), and in the chemotherapy arm were palmar-plantar erythrodysesthesia (9%), mucosal inflammation, peripheral neuropathy, and neutropenia (all 3%)

TABLE IV: Safety Results – Summary of Adverse Events*.

Event, (%)	Olaparib (n=178)		Chemotherapy (n=76)	
	All grades	Grade ≥3	All grades	Grade ≥3
Nausea	64.6	1.1	34.2	1.3
Fatigue/asthenia	52.2	4.5	42.1	1.3
Anemia†	51.1	21.3	25.0	0.0
Vomiting	38.2	1.1	22.4	2.6
Diarrhea	28.1	0.0	17.1	0.0
Neutropenia†	23.0	9.6	42.1	15.8
Abdominal Pain	21.3	1.1	14.5	0.0
Thrombocytopenia†	11.8	3.9	10.5	2.6
Constipation	12.4	0.0	22.4	0.0
Alopecia	6.2	0.0	15.8	1.3
Peripheral Neuropathy	2.8	0.0	10.5	2.6
PPE	0.6	0.0	35.5	11.8

PPE = palmar-plantar erythrodysesthesia.
*All grades, frequency ≥20%; grade ≥3, frequency ≥5%
†Grouped terms

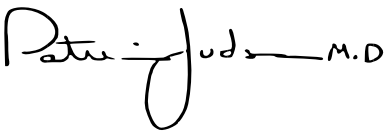
- Myelodysplastic syndrome or acute myeloid leukemia: occurred in 4 of 178 patients (2%) in the olaparib arm and 3 of 76 patients (4%) in the chemotherapy arm.
- Three new primary malignancies occurred in the olaparib arm (lung cancer [g*BRCA2*m], gastric cancer [g*BRCA1*m], and breast cancer [g*BRCA*1m]).

Health-Related Quality of Life:
The adjusted mean change from baseline in the Mean Trial Outcome Index (TOI) score was -2.3 points in the olaparib arm (n=167), compared with -4.8 points in the physician's choice chemotherapy arm (n=62). The estimated between group difference was 2.5 points (95% CI, -0.5 to 5.5); the difference was not considered to be clinically or statistically significant.

References submitted in support of this proposal:

1. LYNPARZA Prescribing Information.
2. Penson RT, Valencia RV, Cibula D, et al. Olaparib monotherapy versus chemotherapy for germline BRCA-mutated platinum-sensitive relapsed ovarian cancer patients: Phase III SOLO3 trial [oral presentation]. Presented at: American Society of Clinical Oncology (ASCO); June 3, 2019; Chicago, IL. Abstract 5506.

Sincerely,



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