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NCCN Guidelines Panel: Pancreatic Adenocarcinoma

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Pancreatic Adenocarcinoma to review the enclosed data for inclusion in the guidelines of LYNPARZA® (olaparib) as a monotherapy option for the maintenance treatment of adult patients with *BRCA*-mutated metastatic adenocarcinoma of the pancreas. This request is based on the POLO data that was presented at the 2019 American Society of Clinical Oncology (ASCO) meeting in Chicago, IL, June 2, 2019, as well as published online in the *New England Journal of Medicine* on June 2, 2019. Additionally, pertinent efficacy and safety results from Study 42 (Kaufman B et al 2014) are included in this submission.

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

- Page PANC-8, add olaparib as maintenance treatment for known *BRCA*1/2 mutations following no disease progression after first line chemotherapy
- Page PNC-F 4 of 7, add olaparib as a preferred regimen only for known *BRCA*1/2 mutations as a maintenance treatment following no disease progression after first line chemotherapy

FDA Status: The use of olaparib for the maintenance treatment of patients who have a *BRCA*1 or *BRCA*2 mutation and metastatic pancreatic cancer is not currently FDA-approved.

Rationale:
This request is chiefly based on the results of the POLO trial (Golan T et al).[1] POLO is a randomized, double-blind, placebo-controlled, phase 3 multicenter international trial evaluating the efficacy of olaparib maintenance monotherapy in patients who were diagnosed with a germline *BRCA*1 or *BRCA*2 mutation and metastatic pancreatic cancer and disease that had not progressed during first-line platinum-based chemotherapy.

Following completion of at least 16 weeks of continuous platinum-based chemotherapy, patients were randomized in a 3:2 ratio to receive maintenance olaparib tablets 300 mg twice daily or matching placebo. The intervention was initiated 4 to 8 weeks after the last dose of first-line chemotherapy.

The primary endpoint was progression-free survival (PFS) defined as the time from randomization until objective radiological disease progression, as assessed by blinded independent central review (BICR) according to modified Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 criteria. Prespecified sensitivity analyses of PFS were performed.

Secondary end points included the following:

- Overall survival (OS)
- Time from randomization to a second progression event or death (second progression-free Survival [PFS2]; defined as investigator-assessed objective radiologic or symptomatic progression)
- Objective response rate (ORR), assessed by BICR according to modified RECIST, version 1.1
- Change in scores for global health-related quality of life (measured as the adjusted mean change from baseline)

In total, 154 patients were randomized; 90 of 92 patients were assigned to the olaparib group (one patient withdrew before receiving any study treatment and one did not meet eligibility criteria) and 61 of 62 patients

were assigned to the placebo group (one patient did not receive placebo because he/she did not meet eligibility criteria). All patients had a germline *BRCA* mutation.

TABLE I. Efficacy Results (Primary endpoint)[1]

	Olaparib (n=92)	**Placebo (n=62)**
Progression-Free Survival		
Number of events (%)	60 (65%)	44 (71%)
Median, months	7.4	3.8
Hazard ratio (95% CI)	0.53 (0.35-0.82)	
p-value	0.004	

TABLE II. Efficacy Results (Secondary endpoints)[1]

	Olaparib (n=92)	**Placebo (n=62)**
PFS2 (46% maturity)		
Median, months	13.2	9.2
Hazard ratio (95% CI)	0.76 (0.46-1.23)	
Overall Survival (46% maturity)		
Median, months	18.9	18.1
Hazard ratio (95% CI)	0.91 (0.56-1.46)	
p-value	0.68	
Objective Response Rate		
Patients with measurable disease at baseline, n (%)	78	52
ORR, n (%)	18 (23)	6 (12)
Odds ratio (95% CI)	2.3 (0.89-6.76)	

The median duration of response was 24.9 months (95% CI, 14.8 to could not be calculated) and 3.7 months (95% CI, 2.1 to could not be calculated) and the median time to response was 5.4 months and 3.6 months in the olaparib and placebo groups, respectively.[1]

TABLE III. Safety Results [Summary of Adverse Events (AEs)][1]

AE, n (%)	**Olaparib (n=91)**		**Placebo (n=60)**	
CTCAE Grade	Any	Grade ≥3	Any	Grade ≥3
Any	87 (96)	36 (40)	56 (93)	14 (23)
Fatigue or asthenia	55 (60)	5 (6)	21 (35)	1 (2)
Nausea	41 (45)	0	14 (23)	1 (2)
Anemia[a]	25 (28)	10 (11)	10 (17)	2 (3)
Abdominal Pain	26 (29)	2 (2)	15 (25)	1 (2)
Diarrhea	26 (29)	0	9 (15)	0
Decreased appetite	23 (25)	3 (3)	4 (7)	0
Constipation	21 (23)	0	6 (10)	0
Vomiting	18 (20)	1 (1)	9 (15)	1 (2)
Back pain	17 (19)	0	10 (17)	1 (2)
Arthralgia	14 (15)	1 (1)	6 (10)	0
AEs leading to dose interruption	32 (35)	NA	3 (5)	NA
AEs leading to dose reduction	15 (16)	NA	2 (3)	NA
AEs leading to treatment discontinuation	5 (5)	NA	1 (2)	NA

[a]The anemia category includes anemia, hemoglobin decreased, red blood cell count decreased, hematocrit decreased, erythropenia, anemia macrocytic, normochromic anemia, normochromic normocytic anemia, or normocytic anemia.
CTCAE = Common Terminology Criteria for Adverse Events

Serious adverse events (grade ≥3) occurred in 24% of the patients who received olaparib and in 15% of the patients who received placebo.[1] No adverse events that occurred during the trial intervention resulted in death. No cases of myelodysplastic syndrome or acute myeloid leukemia were reported in either group.

Health Related Quality of Life[1]
No clinically meaningful change from baseline was noted in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) global health-related quality-of-life score in either group, and there was no difference in the overall change from baseline between the groups. The adjusted mean (±SE) change from baseline across all time points was −1.20±1.42 (95% CI, −4.01 to 1.62) in 84 patients in the olaparib group and 1.27±1.95 (95% CI, −2.58 to 5.12) in 54 patients in the placebo group. The corresponding estimated between-group difference of −2.47 points (95% CI, −7.27 to 2.33) on a 100-point scale was not clinically meaningful.

Study 42[2]
Study 42 was a multicenter phase 2 study that enrolled patients (n=298) with a germline *BRCA1/2* mutation and recurrent cancer. Eligibility criteria for patients with pancreatic cancer included ≥ one measurable or evaluable lesion according to RECIST (version 1.1), Eastern Cooperative Oncology Group performance status of 0 to 2, life expectancy ≥ 16 weeks and disease progression during gemcitabine treatment in the advanced setting (or felt to be unsuitable for gemcitabine). The primary efficacy endpoint was tumor response rate (in all patients) according to RECIST. Secondary endpoints included objective response rate (in those with measurable disease at baseline) PFS and duration of response. In the cohort of 23 patients with advanced g*BRCA*m pancreatic cancer in the treatment setting, 17 (74%) had a *BRCA*2 mutation, 5 (22%) had a *BRCA*1 mutation and 1 (4%) had a mutation in both *BRCA*1 and *BRCA*2. The mean number of prior therapies was two (SD, 1.6; range, one to eight); all but one had received gemcitabine, and 65% had received prior platinum. Patients received Lynparza 400 mg capsules twice daily.

Efficacy results: The tumor response rate in the pancreatic cancer cohort was 21.7% (95% CI, 7.5-43.7); median PFS was 4.6 months; objective response rate was 34.8% (n= 8; 95% CI, 16.4-57.3); and median duration of response was 4.4 months. There was no apparent difference in response rates in those with (20%; 95% CI, 4.3 to 48.1) or without (25%; 95% CI, 3.2 to 65.1) prior platinum for pancreatic cancer.

Table IV. Safety Results: Any-Grade AEs Reported in >15% of Patients Overall or Grade ≥3 AEs Reported in >5% of Patients Overall[2]

Pancreas (n=23)		
AE, n (%)	**Any Grade**	**Grade ≥3**
Fatigue	17 (73.9)	3 (13.0)
Nausea	11 (47.8)	0 (0)
Vomiting	9 (39.1)	1 (4.3)
Anemia	9 (39.1)	4 (17.4)
Diarrhea	7 (30.4)	0 (0)
Abdominal pain	7 (30.4)	1 (4.3)
Decreased appetite	4 17.4)	0 (0)
Dyspepsia	2 (8.7)	0 (0)
Headache	1 (4.3)	0 (0)
Dysgeusia	1 (4.3)	0 (0)

Serious AEs were seen in 30.4% of the patients in the pancreatic cancer group; 17.4% experienced serious AEs considered causally related to olaparib. Among the overall study population, 9 patients died as a result of AEs, including sepsis (n=2), leukemia (n=2), chronic obstructive pulmonary disease (n=1), pulmonary embolism (n=1), myelodysplastic syndrome (MDS; n=1; reported during post–follow-up period), wound dehiscence (n=1), and cerebrovascular accident (n=1). Two events (sepsis and MDS) were considered causally related to olaparib.

References submitted in support of this proposal:

1. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer [published online June 2, 2019]. *N Engl J Med*. doi:
2. Kaufman B, et al. Olaparib Monotherapy in Patients with Advanced Cancer and a Germline *BRCA*1/2 Mutation. *J Clin Oncol*. 2015; 33(3):244-50.

Sincerely,

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