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Date of Request: October 7, 2019
NCCN Guidelines Panel: Genetic/Familial High-Risk Assessment: Breast and Ovarian

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 review the enclosed data for inclusion in the guidelines of LYNPARZA® (olaparib) as a combination therapy option for the first-line maintenance treatment of women with advanced ovarian cancer. This request is based on the PAOLA-1 data that was presented at the 2019 European Society for Medical Oncology (ESMO) meeting in Barcelona, Spain, on September 28, 2019.

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

- Page BRCA-1 the Title: "NCCN Guidelines Version 3.2019 BRCA-Related Breast and/or Ovarian Cancer Syndrome". Change to: "**BRCA-Related Cancer Syndrome**"
- Page BRCA-2 (now GENE-1) under GENETIC TESTING:
  - "Consider multi-gene testing, if appropriate". Change to "Consider HRD genomic scar testing or multi-gene testing, if appropriate".
- Page BRCA-2, (now GENE-1) add an asterisk and footnote: *HRD genomic scar testing measures genomic instability associated with homologous recombination deficiency, and typically assesses Loss of Heterozygosity (LOH), Tellomeric Allelic Imbalance (TAI), and Large-Scale Transitions (LST)
- Page GENE-1 (now EVAL-A 3 of 6): Add a segment on HRD genomic scar testing

FDA Status: The use of olaparib in combination with bevacizumab for the maintenance treatment of women with advanced ovarian cancer is not currently FDA-approved.

Rationale:
This request is based on the results of the PAOLA-1 trial, a randomized, double-blind Phase III study evaluating the efficacy and safety of olaparib added to bevacizumab vs. placebo plus bevacizumab alone in women with or without *BRCA* gene mutations, in the 1st-line maintenance setting for advanced ovarian cancer.

Eligible patients were women with newly-diagnosed advanced FIGO Stage III-IV high grade serous or endometrioid ovarian, fallopian tube, or peritoneal cancer (collectively referred to as OC) or non-mucinous OC with a *BRCA* mutation who had a complete or partial response to 1st-line treatment with platinum-based chemotherapy and bevacizumab, and for whom bevacizumab maintenance therapy was planned. All patients were tumor *BRCA* tested prior to randomization.

In total, 806 patients were randomized 2:1 to olaparib 300 mg twice daily for up to 24 months plus bevacizumab 15 mg/kg vs placebo for 24 months and bevacizumab 15 mg/kg. All patients received standard maintenance care of bevacizumab (15 mg/kg every three weeks) for up to 15 months.

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

Secondary end points included:

- Time from randomization to a second progression event or death (second progression-free survival; PFS2)
- Overall survival (OS)
- Time to first subsequent therapy (TFST) and time to second subsequent therapy (TSST)
- Health-related Quality of Life (HRQoL)

Exploratory endpoints included PFS in predefined centrally tested subgroups including t*BRCA*m, homologous recombination repair (HRR) status and homologous recombination repair deficiency (HRD) score.

TABLE I. Efficacy Results[1]

	Median in months		**Hazard Ratio (95% CI)**
	Olaparib + bevacizumab	**Placebo + bevacizumab**	
PFS in overall ITT (primary endpoint) (n=537 and 269; 806 total)	22.1	16.6	0.59 (0.49-0.72) p<0.0001
PFS by t*BRCA*m status			
t*BRCA*m (n=157 and 80; 237 total)	37.2	21.7	0.31 (0.20-0.47)
Non-t*BRCA*m (n=376 and 189; 565 total)	18.9	16.0	0.71 (0.58-0.88)
PFS by HRD status			
HRD-positive (n=387)	37.2	17.7	0.33 (0.25-0.45)
HRD-positive, non-t*BRCA* (n=152)	28.1	16.6	0.43 (0.28-0.66)
HRD-negative/unknown (n=419)	16.9	16.0	0.92 (0.72-1.17)

ITT, intention to treat; t*BRCA*m, tumor *BRCA* mutation

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

	Olaparib + bevacizumab	**Placebo + bevacizumab**
PFS by BICR		
Median, months	26.1	18.3
Hazard ratio (95% CI)	0.63 (0.51-0.77, p<0.0001)	
TFST		
Median, months	24.8	18.5
Hazard ratio (95% CI)	0.59 (0.49-0.71, p<0.0001	
Interim PFS2 (39% maturity)		
Median, months	32.3	30.1
Hazard ratio (95% CI)	0.86 (0.69-1.09)	
Overall Survival (26%) maturity)		
Median, months	OS data immature	
Hazard ratio (95% CI)		

TABLE III. Safety Results (Summary of AEs and AEs of Special Interest)[1]

AE, n (%)	Olaparib + bevacizumab (n=535)	Placebo + bevacizumab (n=267)
All grade TEAEs	531 (99)	256 (96)
Grade ≥3 TEAEs	303 (57)	136 (51)
Serious TEAEs	167 (31)	83 (31)
Deaths	1 (<1)	4 (1)
MDS/AML/AA	6 (1)	1 (<1)
New primary malignancies	7 (1)	3 (1)
Pneumonitis/ILD	6 (1)	0
AEs leading to dose interruption	291 (54)	65 (24)
AEs leading to dose reduction	220 (41)	20 (7)
AEs leading to treatment discontinuation	109 (20)	15 (6)

AA, aplastic anemia; AEs, adverse events; AML, acute myeloid leukemia; ILD, interstitial lung disease; MDS, myelodysplastic syndrome

TABLE IV. Safety Results (Most Common AEs)[1]

AE, n (%)	Olaparib (n=535)		Placebo (n=267)	
CTCAE Grade	All Grades (≥15%)	Grade ≥3	All Grades (≥15%)	Grade ≥3
Fatigue/asthenia*	53	5	32	1
Nausea	53	2	22	1
Hypertension	46	19	60	30
Anemia*	41	17	10	<1
Lymphopenia	24	7	9	1
Arthralgia	22	1	24	1
Vomiting	22	1	11	2
Abdominal Pain	19	1	20	2
Diarrhea	18	2	17	2
Neutropenia*	18	6	16	3
Leukopenia*	18	2	10	1
Urinary tract infection	15	<1	10	1

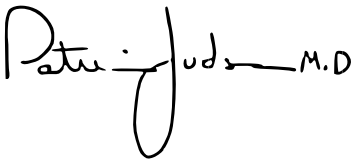
CTCAE = Common Terminology Criteria for Adverse Events

*Grouped terms. All grade thrombocytopenia (grouped term) occurred in 8% of patients in the olaparib group, and 3% of patients in the placebo group, grade ≥3 thrombocytopenia occurred in 2% of patients in the olaparib group and <1% of patients in the placebo group

Reference submitted in support of this proposal:

Ray-Coquard I, Pautier P, Pignata S, et al. Phase III PAOLA-1/ENGOT-ov25: maintenance olaparib with bevacizumab in patients with newly diagnosed, advanced ovarian cancer treated with platinum-based chemotherapy and bevacizumab as standard of care [oral presentation]. Presented at: European Society for Medical Oncology (ESMO); September 30, 2019; Barcelona, Spain.

Sincerely,



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