Submitted by: Susan L. Pajak, PharmD
Company/Organization: AstraZeneca/US Medical Affairs
Address: One MedImmune Way, Gaithersburg, MD 20878
Phone: 301-398-0360
E-mail: Susan.Pajak@AstraZeneca.com
Date of Request: October 1, 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 review the enclosed data for inclusion in the guidelines of LYNPARZA® (olaparib) as a combination therapy option with bevacizumab 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 OV-1: Under genetic risk evaluation, change "should have genetic risk evaluation and BRCA 1/2 testing (if not previously done)" to "should have genetic risk evaluation, BRCA 1/2 testing **and HRD genomic scar test** (if not previously done)"
- Page OV-2: Under genetic risk evaluation, change "should have genetic risk evaluation and BRCA 1/2 testing (if not previously done)" to "should have genetic risk evaluation, BRCA 1/2 testing **and HRD genomic scar test** (if not previously done)"
- Page OV-5: Under Maintenance Therapy for partial or complete remission when bevacizumab is used as part of primary therapy, revise "Postremission bevacizumab or olaparib…" to "Postremission bevacizumab **and** olaparib"
- Page OV-5: remove footnote 's'
- Page OV-5: add an asterisk and footnote: *HRD genomic scar testing measures genomic instability associated with homologous recombination deficiency, and assesses: Loss of Heterozygosity (LOH), Telomeric allelic imbalance (TAI), and Large-scale state transitions (LST)
- Page OV-B 1 of 3: Under Tumor molecular analysis as clinically indicated: add **"HRD genomic scar test"**
- Page OV-C 3 of 9: Paclitaxel 175 mg/m2 IV over 3 hours followed by carboplatin AUC 5-6 over 1-hour day 1. Repeat every 3 weeks x 6 cycles**, then olaparib 300mg twice daily maintenance therapy for two years in women with a BRCA 1/2 mutation**
- Page OV-C 3 of 9: Paclitaxel 175 mg/m2 IV over 3 hours followed by carboplatin AUC 6 over 1-hour Day 1. Repeat every 3 weeks x 6 cycles. Starting day 1 of cycle 2 give bevacizumab 15 mg/kg IV over 30-90 minutes every 3 weeks **with induction chemotherapy followed by maintenance for up to 15 months. Once chemotherapy is complete add olaparib 300mg twice daily maintenance therapy for two years.**
- Page MS-16: In the section including bevacizumab (3rd paragraph), add "Bevacizumab may be continued, **with the addition of olaparib**, after primary systemic therapy if an upfront chemotherapy/bevacizumab regimen was used."
- Page MS-17: Under 'Recommendations After Primary Treatment'. Change to "After initial treatment (eg, surgery followed by chemotherapy), patients should undergo **maintenance therapy with bevacizumab or bevacizumab plus olaparib (if bevacizumab was used with chemotherapy) or olaparib alone.**

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, including t*BRCA*m (n=387)	37.2	17.7	0.33 (0.25-0.45)
HRD-positive, excluding t*BRCA*m (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

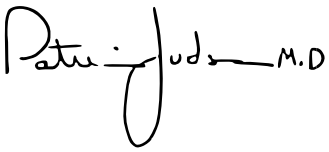
CTCAE = Common Terminology Criteria for Adverse Events

*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

References submitted in support of this proposal:

1. 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,



Patricia L. Judson, MD
Gynecologic Oncologist
US Medical Head, Gynecologic Oncology
AstraZeneca Pharmaceuticals, LP
Patricia.Judson@AstraZeneca.com