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Date of Request: May 15, 2020
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 updated request is based on the PAOLA-1 data that led to the FDA-approval of a new indication in advanced ovarian cancer and was published in the *New England Journal of Medicine* on December 19, 2019.[1,2]

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

- Page OV-1: Following PRIMARY TREATMENT section, revise recommendation to, "Patients with…**should receive genetic risk evaluation, germline and somatic *BRCA*1/2 mutation testing and/or tumor homologous recombination deficiency (HRD) testing (if not previously done)"**
- Page OV-1: Within footnote 'e', revise statement to "Germline and/or somatic *BRCA*1/2 and/or tumor HRD genomic instability status informs maintenance therapy"
- Page OV-2: Within PRIMARY TREATMENT section, revise recommendation to, "Neoadjuvant therapy… genetic risk evaluation, germline and somatic *BRCA*1/2 mutation testing and or tumor homologous recombination deficiency (HRD) testing (if not previously done)"
- Page OV-5: Under POST-PRIMARY TREATMENT, switch second column (bevacizumab therapy) and third column (testing). Rationale: based on the FDA approval, the tumor mutation profile guides treatment decision rather than bevacizumab use
- Page OV-5: Under POST-PRIMARY TREATMENT, within existing third column (after 'Bevacizumab used as part of primary therapy' section), revise '*BRCA*1/2 wild-type or unknown' to "**HRD positive and non-*BRCA* 1/2 mutation**"
    - Within 'Bevacizumab + olaparib' under 'Maintenance Therapy', include new footnote: "**Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza"**
    - Insert a third arrow in this section and add "**HRD negative and non-*BRCA* 1/2 mutation**."

- Page OV-5: Under POST-PRIMARY TREATMENT, within existing third column, after **'**No Bevacizumab used as part of primary therapy' section, revise *BRCA*1/2 wild-type or unknown' to "**HRD positive and non-*BRCA* 1/2 mutation**" and add olaparib + bevacizumab under maintenance therapy (based on our indication)
    - Within 'Bevacizumab + olaparib' under 'Maintenance Therapy', include new footnote: "**Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza**"
    - Insert a third arrow in this section and add "**HRD negative and non-*BRCA*1/2 mutation**."
- Page OV-B 1 of 3: Under "Tumor molecular analysis as clinically indicated:", revise third bullet to, **Test for homologous recombination deficiency by evaluating for genomic instability**.
- Page OV-B 1 of 3: Under "Tumor molecular analysis as clinically indicated:" insert in fourth bullet, "can be considered at the **treating physician's or pathologist's** discretion"
- Page MS-15: Revise 3rd paragraph to, "Bevacizumab **with or without olaparib** may be continued…"

FDA Status: On May 8, 2020, olaparib was approved for use 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[1,3]

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 maintenance olaparib added to bevacizumab vs. placebo/bevacizumab in women who were in complete or partial response following first-line platinum-based chemotherapy plus bevacizumab.[1,2]

Eligible patients included women with newly-diagnosed advanced FIGO Stage III-IV high grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal cancer (collectively referred to as OC), or nonmucinous OC with a germline *BRCA* 1/2 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 plus bevacizumab 15 mg/kg (n=537) vs placebo and bevacizumab 15 mg/kg (n=269). Patients continued bevacizumab in the maintenance setting and started treatment with olaparib after a minimum of 3 weeks and up to a maximum of 9 weeks after their last dose of chemotherapy. Olaparib treatment was continued for up to 24 months or until progression of the underlying disease or unacceptable toxicity. Patients could be treated beyond 24 months, if in the opinion of the treating physician, they could derive further benefit. All patients received bevacizumab (15 mg/kg every three weeks) for up to 15 months, including period given with chemotherapy and as maintenance

The primary endpoint was investigator-assessed progression-free survival (PFS) defined as the time from randomization until objective radiological disease progression or death 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 or death (TFST) and time to second subsequent therapy or death (TSST)
- Health-related Quality of Life (HRQoL)

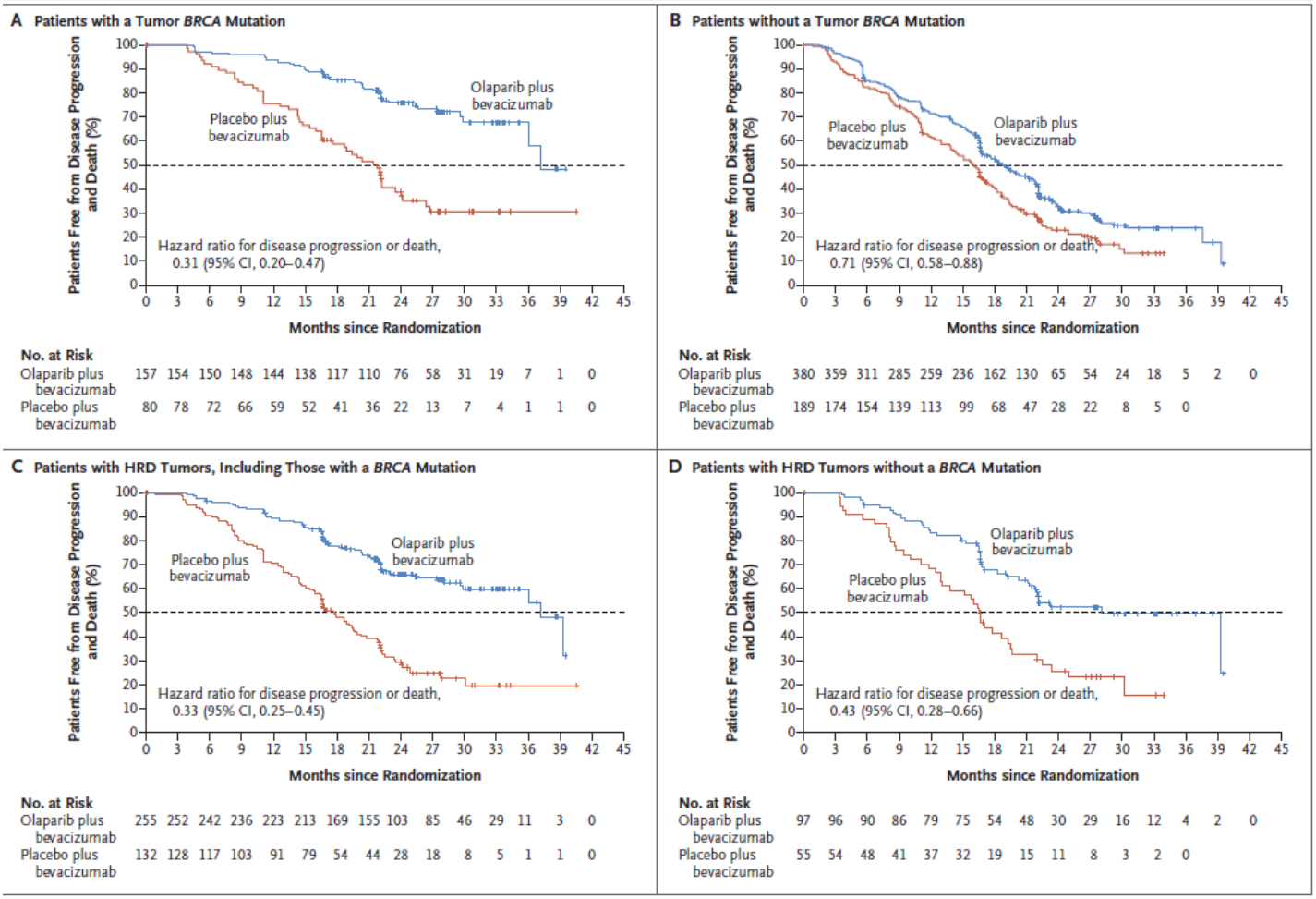
Prospectively defined exploratory endpoints included PFS in predefined centrally tested subgroups including t*BRCA*m, and homologous recombination repair deficiency (HRD) score.

TABLE I. Efficacy Results[1,2]

	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<0.001
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=380 and 189; 569 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)

*HRD-positive was defined as tumor score ≥42 on the myChoice HRD Plus assay or tumor BRCA mutation
CI Confidence interval

FIGURE 1.
Kaplan–Meier Estimates of Investigator-Assessed Progression-free Survival, According to Tumor BRCA Mutation Status and Homologous-Recombination Deficiency (HRD) Status.[2]



Among the patients with a tumor BRCA mutation (prespecified subgroup analysis):
(**Panel A**), the Kaplan–Meier estimate of the percentage of patients who were free from disease progression and death at 24 months was 76% in the olaparib-plus-bevacizumab group and 39% in the placebo-plus-bevacizumab group.

Among the patients without a tumor BRCA mutation (prespecified subgroup analysis):
(**Panel B**), the Kaplan–Meier estimate of the percentage of patients who were free from disease progression and death at 24 months was 33% in the olaparib-plus-bevacizumab group and 23% in the placebo-plus-bevacizumab group.

Among the patients with HRD-positive tumors, as defined by a tumor HRD score of 42 or higher or a tumor BRCA mutation (prespecified subgroup analysis):
(**Panel C**), the Kaplan–Meier estimate of the percentage of patients who were free from disease progression and death at 24 months was 66% in the olaparib-plus-bevacizumab group and 29% in the placebo-plus-bevacizumab group.

Among the patients with HRD-positive tumors without a BRCA mutation (prespecified subgroup analysis):
(**Panel D**), the Kaplan–Meier estimate of the percentage of patients who were free from disease progression and death at 24 months was 52% in the olaparib-plus bevacizumab group and 26% in the placebo-plus-bevacizumab group. Tumor HRD status was determined for 82% of the tumor samples.

TABLE II. Efficacy Results (Select Secondary endpoints in ITT population)[2]

	Olaparib + Bevacizumab (n= 537)	Placebo + bevacizumab (n= 269)
PFS by BICR		
Median, months	26.1	18.3
Hazard ratio (95% CI)	0.63 (0.51-0.77)	
TFST		
Median, months	24.8	18.5
Hazard ratio (95% CI)	0.59 (0.49-0.71)	
Overall Survival		
Median, months	OS data immature	
Hazard ratio (95% CI)		

TABLE III. Adverse Reactions* Occurring in ≥10% of Patients Treated with Lynparza/bevacizumab in PAOLA-1 and at ≥5% Frequency Compared to the Placebo/bevacizumab Arm[1]

Adverse Reactions	Olaparib + bevacizumab (n=535)		Placebo + bevacizumab (n=267)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)†	53	5	32	1.5
Gastrointestinal Disorders				
Nausea	53	2.4	22	0.7
Vomiting	22	1.7	11	1.9
Blood and Lymphatic Disorders				
Anemia‡	41	17	10	0.4
Lymphopenia§	24	7	9	1.1
Leukopenia‖	18	1.9	10	1.5

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

† Includes asthenia, and fatigue.

‡ Includes anemia, anemia macrocytic, erythropenia, hematocrit decreased, hemoglobin decreased, normochromic anemia, normochromic normocytic anemia, normocytic anemia, and red blood cell count decreased. Includes B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia, and T-lymphocyte count decreased.

§ Includes B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia, and T-lymphocyte count decreased.

‖ Includes leukopenia, and white blood cell count decreased.

Fatal adverse reactions occurred in 1 patient due to concurrent pneumonia and aplastic anemia. Serious adverse reactions occurred in 31% of patients who received Lynparza/bevacizumab. Serious adverse reactions in >5% of patients included hypertension (19%) and anemia (17%).[1]

In addition, venous thromboembolic events occurred more commonly in patients receiving Lynparza/bevacizumab (5%) than in those receiving placebo/bevacizumab (1.9%).[1]

TABLE IV. Laboratory Abnormalities Reported in ≥25% of Patients in PAOLA-1[*1]

Laboratory Parameter[†]	Olaparib + bevacizumab (n[†]= 535)		Placebo + bevacizumab (n[‡]= 267)	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	79	13	55	0.4
Decrease in lymphocytes	63	10	42	3.0
Increase in serum creatinine	61	0.4	36	0.4
Decrease in leukocytes	59	3.4	45	2.2
Decrease in absolute neutrophil count	35	7	30	3.7
Decrease in platelets	35	2.4	28	0.4

* Reported within 30 days of the last dose.
† Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
‡ This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

References submitted in support of this proposal:

1. LYNPARZA Prescribing Information
2. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *N Engl J Med*. 2019;381:2416-28.
3. Myriad Genetics, Inc. News Release; Myriad Receives FDA Approval of myChoice CDx® as Companion Diagnostic for Lynparza™ (olaparib) In Patients with Advanced Ovarian Cancer. May 11, 2020.

Sincerely,

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