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NCCN Guidelines Panel: Prostate Cancer

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Prostate Cancer to review the enclosed data for inclusion of LYNPARZA® (olaparib) in the guidelines as a monotherapy option for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) who have a homologous recombination repair mutation (HRRm) and have progressed on prior treatment with enzalutamide and/or abiraterone. This request is based on the PROfound study data that was presented at the 2019 European Society for Medical Oncology (ESMO) meeting in Barcelona, Spain on September 30, 2019. Additionally, data from central prospective HRRm tissue testing from patients screened for the PROfound study are included in this submission.

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

- Page PROS-9, under "Molecular and biomarker analysis of tumor" for Metastatic Risk group, consider changing to, "Recommend tumor testing for homologous recombination gene mutations and consider tumor testing for MSI or dMMR."
- Pages PROS-9, PROS-14, and PROS-16, consider changing footnote ee to "Recommend evaluating tumor for alterations in homologous recombination DNA repair such as *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, and *CDK12*. At present, this information may be used for genetic counseling, early use of platinum chemotherapy, olaparib, and/or eligibility for clinical trials (eg, PARP inhibitors)."
- Pages PROS-17 and PROS-18, under "Second-Line Treatment" following "Prior therapy enzalutamide/abiraterone," consider adding olaparib for patients with an HRRm.
- Pages PROS-17 and PROS-18, under "Second-Line Treatment" following "Prior therapy docetaxel," consider adding olaparib for patients with an HRRm.
- Page PROS-G, under "Systemic Therapy for M1 CRPC," consider inclusion of olaparib in men who have an HRRm and have progressed on prior treatment with enzalutamide and/or abiraterone, regardless of prior docetaxel therapy.
- Page MS-3, under "Homologous DNA Repair Genes," consider adding prevalence of HRR single and co-occurring gene alterations in tumor tissue from patients screened for PROfound
- Page MS-5, under "Somatic Tumor Testing Based on Risk Groups," consider changing the first recommendation to, "Tumor testing for somatic homologous recombination gene mutations (eg, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*) is recommended in patients with regional or metastatic prostate cancer."
- Page MS-46, consider adding brief PROfound study summary and adding olaparib as a therapeutic option for men with prostate cancer and DNA repair gene mutations under "Treatment Implications for Patients with DNA Repair Gene Mutations" section.
- Page MS-57, under "Metastatic CRPC," consider changing to, "These patients should be recommended for germline and tumor testing to check for mutations in homologous recombination genes (ie, *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *FANCA*, *RAD51D*, *CHEK2*, and

CDK12). This information may be "used for genetic counseling, early use of platinum chemotherapy, olaparib, or eligibility for clinical trials (eg, PARP inhibitors)."
- Page MS-59, under "Progression After Enzalutamide or Abiraterone," consider adding olaparib as an option for patients with an HRRm.

FDA Status:[1] The use of olaparib for the treatment of men with mCRPC who have an HRRm and have progressed on prior treatment with enzalutamide and/or abiraterone is not currently FDA-approved.

Rationale: This request is based on the results of the PROfound study, a Phase III randomized, open-label, multicenter trial evaluating the efficacy and safety of olaparib versus enzalutamide or abiraterone in men with mCRPC who have failed prior treatment with enzalutamide and/or abiraterone and have a qualifying tumor mutation in one of 15 genes involved in the homologous recombination repair (HRR) pathway.[2]

The trial randomized 387 patients with mCRPC who had disease progression on prior abiraterone and/or enzalutamide and who had mutations in at least 1 of any pre-specified qualifying genes with a direct or indirect role in HRR (*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* or *RAD54L*). Eligible patients were divided into two cohorts, Cohort A (*BRCA1, BRCA2,* or *ATM* [n=245]) and Cohort B (other alterations [n=142]).

Patients in each cohort were randomized (2:1) to receive olaparib 300 mg twice daily or physician's choice of enzalutamide 160 mg once daily or abiraterone 1000 mg once daily plus prednisone 5 mg twice daily. Randomization was stratified by previous taxane therapy and measurable disease at baseline. The primary endpoint was radiographic progression-free survival (rPFS) in Cohort A (RECIST 1.1 and PCWG3 by blinded independent central review [BICR]). Upon BICR progression, patients in the physician's choice arm were eligible to crossover to the olaparib arm. Key secondary endpoints included rPFS in Cohorts A+B, confirmed radiographic objective response rate (ORR) in Cohort A, time to pain progression (TTPP) in Cohort A, and overall survival (OS) in Cohort A.

HRRm in tumor tissue from >4000 men with mCRPC screened for PROfound study:[3]

- An investigational next-generation sequencing assay (Foundation Medicine, Inc. [Cambridge, MA]) intended to be developed as a companion diagnostic was used to prospectively screen patients with mCRPC for a qualifying HRRm in their tumor tissue to determine eligibility for the PROfound study. A panel of 15 genes involved directly or indirectly in HRR was pre-specified.
- Of the 4425 patients screened, 4047 had samples tested, of which 2792 (69%) were successfully sequenced and had a biomarker status reported.
- A qualifying HRRm was observed in 27.9% of patients with mCRPC with a successful tumor test result.
- More than half of the detected HRR gene mutations were in the Cohort A group of genes. Alterations in *BRCA2* were the most prevalent and were detected in 8.7% of screened patients, making up 31.1% of detected alterations.
- A co-occurring qualifying HRRm in ≥1 gene was detected in 59 (7.6%) patients, most commonly with *BRCA2* (n=30), *CDK12* (n=24) and *ATM* (n=13).
- The distribution of mutations in HRR genes within the randomized population reflected that observed in the screened population.

Efficacy Results:[2]

TABLE I: Primary Endpoint - rPFS by BICR in Cohort A

	Olaparib (n=162)	Physician's Choice (n=83)
Radiographic Progression-Free Survival		
Number of events (%)	106 (65.4)	68 (81.9)
Median, months	7.39	3.55
Hazard ratio (95% CI)	0.34; 0.25-0.47	
p-value	<0.0001	

TABLE II. Secondary Endpoints (Cohort A)

	Olaparib (n=162)	Physician's Choice (n=83)
Confirmed Objective Response Rate		
Patients with measurable disease at baseline, n (%)	84 (51.9)	43 (51.8)
ORR, %	33.3	2.3
Odds ratio (95% CI)	20.86 (4.18-379.18)	
p-value	<0.0001	
Time to Pain Progression		
Number of events (%)	21 (13.0)	14 (16.9)
Median, months	NR	9.92
Hazard ratio (95% CI)	0.44; 0.22-0.91	
p-value	0.0192	
Overall Survival (38% maturity)		
Median, months	18.50	15.11
Hazard ratio (95% CI)	0.64; 0.43-0.97	
p-value	0.0173[a]	

[a]Alpha spend at interim was 0.01; statistical significance not reached

TABLE IV. Secondary Endpoints in the Overall Population (Cohorts A+B)

	Olaparib (n=256)	Physician's Choice (n=131)
Radiographic Progression-Free Survival		
Number of events (%)	180 (70.3)	99 (75.6)
Median, months	5.82	3.52
Hazard ratio (95% CI)	0.49; 0.38-0.63	
p-value	<0.0001	
Overall Survival (41% maturity)		
Median, months	17.51	14.26
Hazard ratio (95% CI)	0.67; 0.49-0.93	
p-value	0.0063 (nominal)	

Of the physician's choice arm patients who were eligible following BICR progression, 80.6% in Cohort A and 84.6% in Cohort B crossed over to olaparib.

Safety Results:[2]

TABLE V. Safety Summary in the Overall Population (Cohorts A+B)[1]

Adverse Event (AE), n (%)	Olaparib (n=256)		Physician's Choice (n=130)	
CTCAE Grade	Any	Grade ≥3	Any	Grade ≥3
Any AE	244 (95.3)	-	114 (87.7)	-
Any AE Grade ≥3	-	130 (50.8)	-	49 (37.7)
AEs leading to dose reduction	57 (22.3)	-	5 (3.8)	-
AEs leading to discontinuation	42 (16.4)	-	11 (8.5)	-
Death due to AE	10 (3.9)	-	5 (3.8)	-
Related to study treatment	1 (0.4)	-	1 (0.8)	-

CTCAE = Common Terminology Criteria for Adverse Events

TABLE VI. Most Common AEs (>10% of Patients in Either Arm) in Overall Population (Cohorts A+B)

Adverse Event (AE), %	Olaparib (n=256)		Physician's Choice (n=130)	
CTCAE Grade	Any	Grade ≥3	Any	Grade ≥3
Anemia	46.5	21.5	15.4	5.4
Nausea	41.4	1.2	19.2	0
Fatigue and asthenia	41.0	2.7	32.3	5.4
Decreased appetite	30.1	1.2	17.7	0.8
Diarrhea	21.1	0.8	6.9	0
Vomiting	18.4	2.3	12.3	0.8
Constipation	17.6	0	14.6	0
Back pain	13.7	0.8	11.5	1.5
Peripheral edema	12.5	0	7.7	0
Cough	10.9	0	2.3	0
Dyspnea	10.2	2.3	3.1	0
Arthralgia	9.4	0.4	10.8	0
Urinary tract infection	7.0	1.6	11.5	3.8

CTCAE = Common Terminology Criteria for Adverse Events

- Median treatment duration in the overall treatment population was 7.4 months and 3.9 months for the olaparib arm and physician's choice arm, respectively.
- The safety profile of olaparib was generally consistent with that seen in other cancers, with the exception of pulmonary embolism which was reported in 4.3% of patients in the olaparib arm and 0.8% of patients in the physician's choice arm. None of these events were fatal and further assessments are being made. There were no reports of myelodysplastic syndromes or acute myeloid leukemia.

References in support of this proposal:

1. LYNPARZA Prescribing Information.
2. Hussain M, Mateo J, Fizazi K, et al. Phase III study of olaparib versus enzalutamide or abiraterone for metastatic castration-resistant prostate cancer with homologous recombination repair gene alterations[oral presentation]. Presented at: European Society for Medical Oncology (ESMO); September 30, 2019; Barcelona, Spain. Abstract LBA12_PR.

3. de Bono J, Fizazi K, Saad F, et al. Central, prospective detection of homologous recombination repair gene alterations in tumour tissue from >4000 men with metastatic castration-resistant prostate cancer screened for the PROfound study [poster]. Presented at European Society for Medical Oncology (ESMO); September 29, 2019; Barcelona, Spain. Abstract 847PD.

Sincerely,

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