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Date of Request: June 9, 2021
NCCN Guideline Panel: Breast Cancer

Dear Sir or Madam:

On behalf of AstraZeneca, this letter is a formal request to the National Comprehensive Cancer Network (NCCN) Panel for Breast Cancer to review the enclosed data for the inclusion of LYNPARZA® (olaparib) in the guidelines as a monotherapy option for the adjuvant treatment of patients with gBRCAm, HER2-negative early breast cancer at high risk of recurrence who have previously been treated with neoadjuvant or adjuvant chemotherapy. This request is based on the OlympiA study that was presented at the 2021 American Society of Clinical Oncology (ASCO) meeting and published online in the *New England Journal of Medicine* on June 3, 2021.

Specific Changes:

We respectfully request the following changes:

Page Number NCCN BC V 4. 2021	**Changes requested**
BINV-6	For HR-positive, HER2-negative breast cancer with pN2/pN3 (≥4 ipsilateral metastases >2 mm) tumors, adjuvant chemotherapy followed by endocrine therapy and **1 year of olaparib for patients with *BRCA* mutations**
BINV-8	For HR-positive, HER2-negative breast cancer with pN2/pN3 (≥4 ipsilateral metastases >2 mm) tumors, adjuvant chemotherapy followed by endocrine therapy and **1 year of olaparib for patients with *BRCA* mutations**
BINV-10	For HR-negative, HER2-negative disease with tumor 0.6-1.0cm, or tumor >1cm, or pN+(1≥ ipsilateral metastases>2mm) tumor, adjuvant chemotherapy followed by **1 year of olaparib for patients with *BRCA* mutations**
BINV-12	Add a new footnote: Provide genetic counseling if patient is at risk for hereditary breast cancer
BINV-16	For HR-positive/HER2-negative breast cancer with ypT1-4, N0 or ypN≥1 tumors after preoperative therapy, adjuvant endocrine therapy and **1 year of olaparib for patients with *BRCA* mutations**
BINV-16	For HR-negative/HER2-negative breast cancer with ypT1-4, N0, or ypN≥1 tumors after preoperative therapy, consider capecitabine or **1 year of olaparib for patients with *BRCA* mutations**
BINV-K	Add a new footnote: 1 year of olaparib as adjuvant treatment to be used with endocrine therapy in patients with *BRCA* mutations

BINV-L 1 of 7	Under Preferred Regimens: If triple negative breast cancer (TNBC) and residual disease after preoperative therapy with taxane-, alkylator- and anthracycline-based chemotherapy: capecitabine or **1 year of olaparib for patients with *BRCA* mutations**
BINV-L 1 of 7	Add a new footnote: Olaparib PO 300 mg twice daily for 1 year.
MS	Please include a summary of OlympiA study in appropriate section

FDA Status:[1]

The use of olaparib for the treatment of early breast cancer in adjuvant setting is not currently FDA-approved.

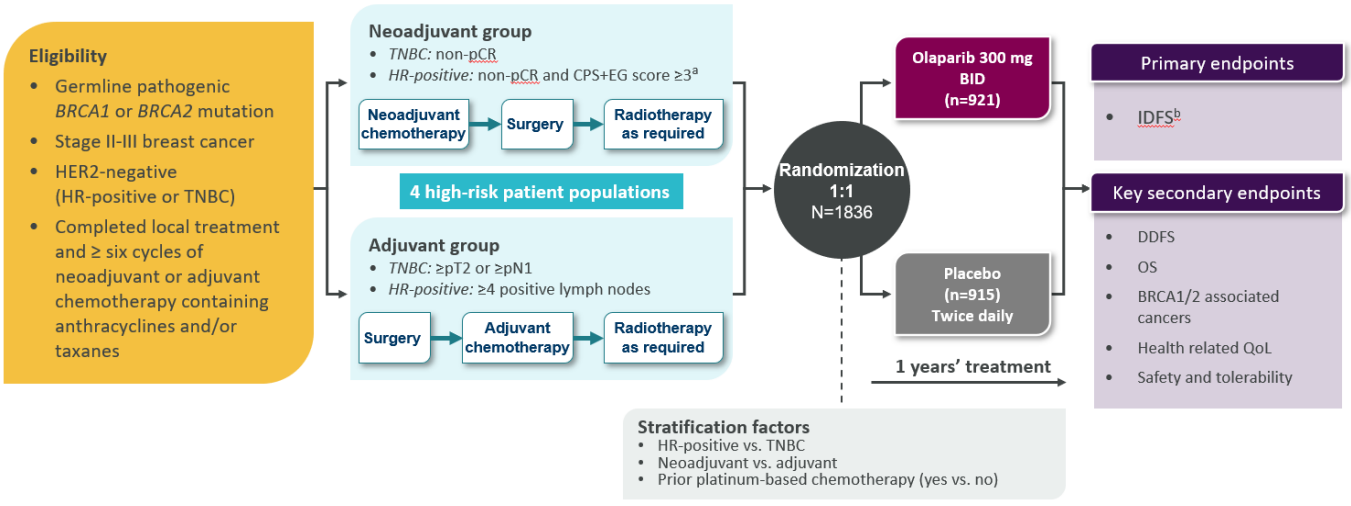
Olaparib is approved for the treatment of adult patients with deleterious or suspected deleterious g*BRCA*m, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza.

Rationale:

OlympiA[2]

OlympiA is a Phase III, randomized, double-blind, placebo-controlled trial evaluating efficacy and safety of olaparib versus placebo as adjuvant therapy in patients with high-risk, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer and with germline BRCA1 and/or BRCA2 mutations who have completed local surgery and neoadjuvant or adjuvant chemotherapy. Patients received treatments for 52 weeks (1 year).

Figure 1. OlympiA study design[2]



[a]CPS+EG score incorporates pretreatment clinical stage, estrogen receptor status, nuclear grade and pathological stage after neoadjuvant chemotherapy; [b] by standardized definitions for efficacy end points (STEEP) system.
BID = twice daily; CPS+EG = pretreatment clinical stage / post-treatment pathologic stage + estrogen receptor status

/ tumor grade; DDFS = distant disease-free survival; *gBRCA* = germline breast cancer gene; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; HRQoL = health-related quality of life; IDFS = invasive disease-free survival; OS = overall survival; pCR = pathologic complete response; QoL = quality of life; TNBC = triple negative breast cancer

Table 1. Select Patient Baseline Characteristics[2]

Characteristics	Olaparib (N=921)	Placebo (N=915)
Median age, years (interquartile range)	42 (36-49)	43 (36–50)
Hormone Receptor status, n (%)		
Hormone receptor positive/HER2-negative	168 (18.2%)	157 (17.2%)
Triple-negative breast cancer[a]	751 (81.5%)	758 (82.8%)
Prior chemotherapy, n (%)		
Neoadjuvant	460 (49.9%)	460 (50.3%)
Adjuvant	461 (50.1%)	455 (49.7%)
Platinum-based neoadjuvant or adjuvant therapy	247 (26.8%)	239 (26.1%)
Germline BRCA mutation type, n (%)		
BRCA1	657 (71.3%)	670 (73.2%)
BRCA2	261 (28.3%)	239 (26.1%)
Both	2 (0.2%)	5 (0.5%)

[a]Two patients (both in the olaparib group) were excluded from the summary of the triple–negative breast cancer subset because they do not have confirmed HER2–negative status.

Efficacy Results

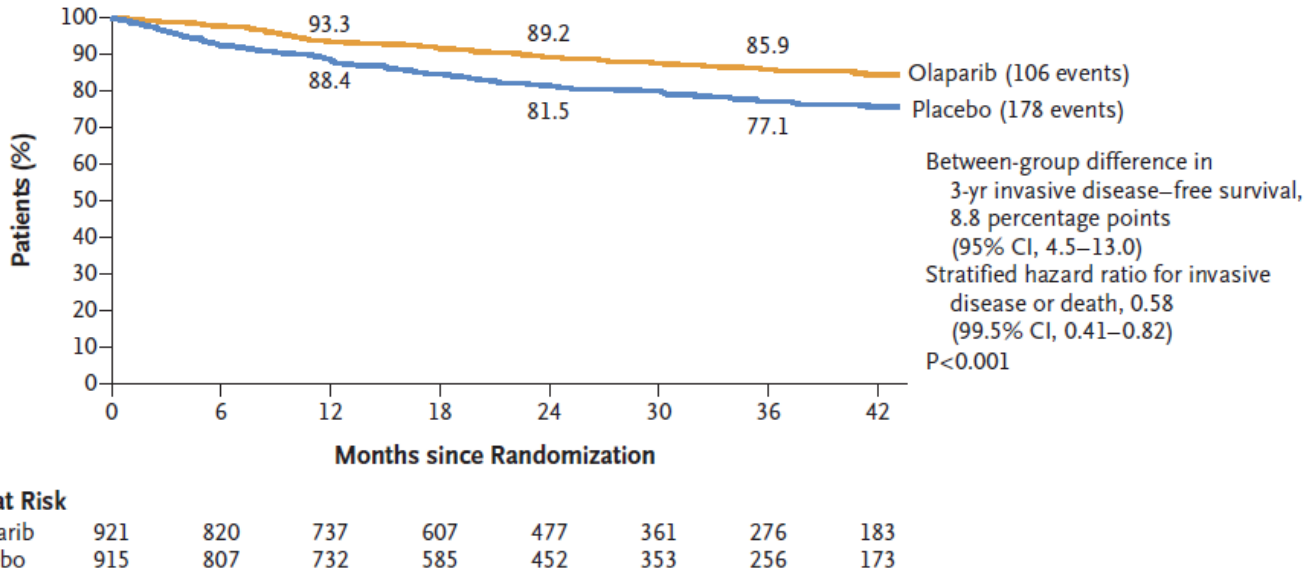
Table 2. Summary of Efficacy Results[2,3]

Endpoints	Olaparib (N=921)	Placebo (N=915)
IDFS		
HR (99.5% CI)	0.58 (0.41-0.82)	
p value	p<0.0001	
3-year IDFS rate (ITT)	85.9%	77.1%
Difference (95% CI)	8.8% (4.5-13.0)	
3-year DDFS rate	87.5%	80.4%
HR (99.5% CI)	0.57 (0.39-0.83)	
p value	p<0.0001	
3-year OS rate	92.0%	88.3%
HR (99% CI)	0.68 (0.44-1.05)	
p value	p=0.024	

DDFS = distant disease-free survival; HR = hazard ratio; IDFS = Invasive disease-free survival; OS = Overall Survival

- The IDFS benefit of adjuvant olaparib vs. placebo was observed irrespective of the germline *BRCA* mutation (BRCA1 vs. BRCA2), the hormone-receptor status, or the timing of previous chemotherapy (neoadjuvant vs. adjuvant), with confidence intervals that crossed the point estimate of the hazard ratio in the overall population.
- Fewer deaths were reported in the olaparib arm (n=59) compared to placebo arm (n=86) (HR=0.68, 99% CI, 0.44 to 1.05, p=0.024), although the difference was not statistically significant at an interim-analysis boundary of p<0.01.

Figure 2. Kaplan-Meier Curve for Invasive Disease-Free Survival.[2]

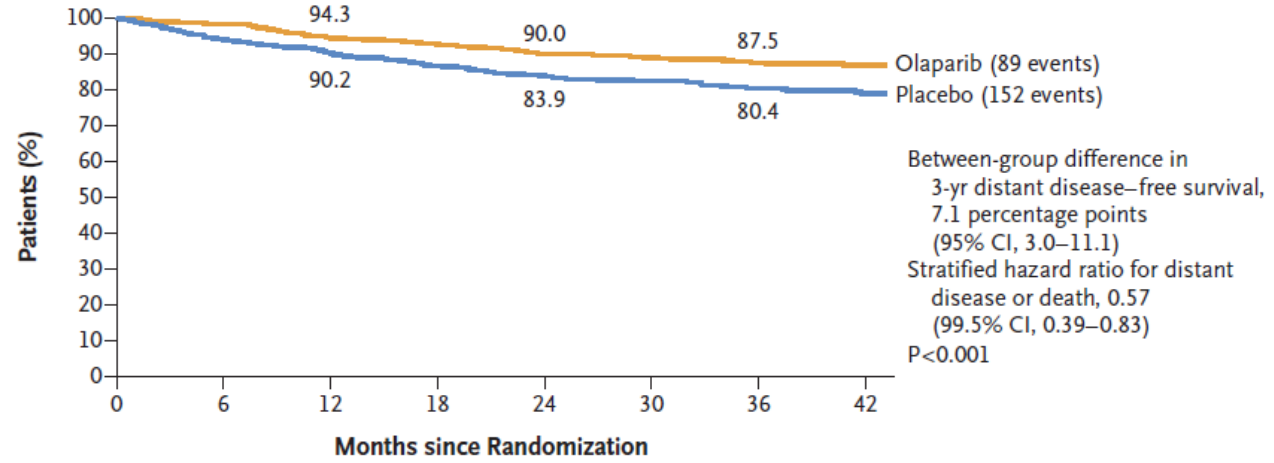


No. at Risk

Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173

Kaplan-Meier plot for IDFS in the ITT population. IDFS was defined as the time from randomization until the date of one of the following events: ipsilateral invasive breast tumor; locoregional invasive disease; distant recurrence; contralateral invasive breast cancer; second primary invasive cancer; or death from any cause.

Figure 3. Kaplan-Meier Curve for Distant Disease-Free Survival.[2]

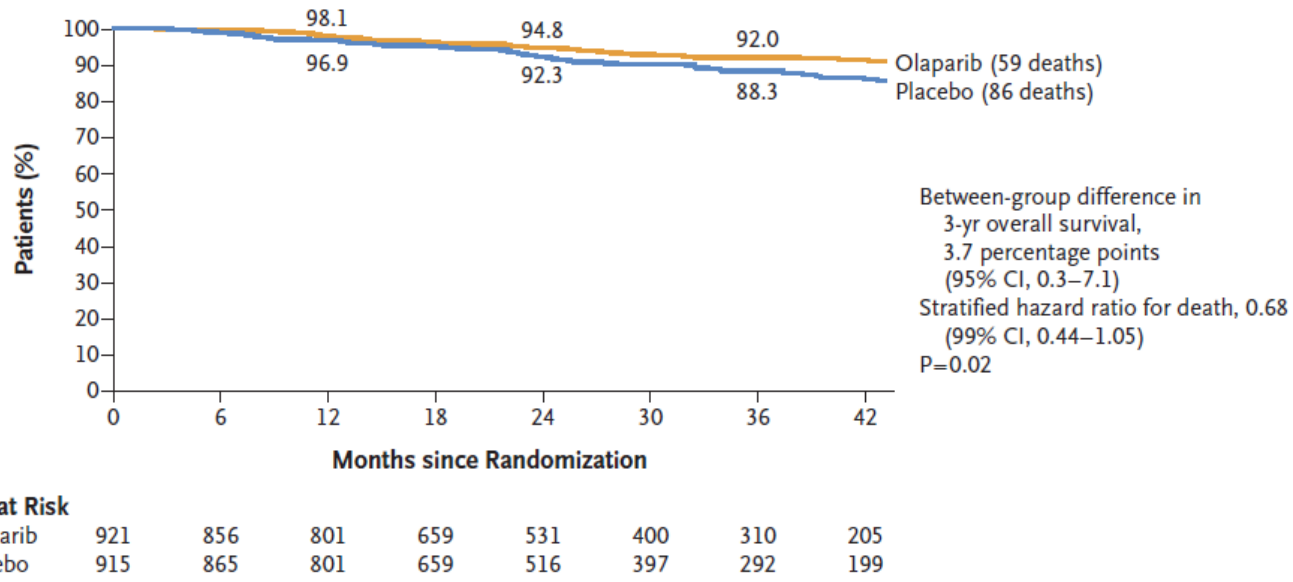


No. at Risk

Olaparib	921	823	744	612	479	364	279	187
Placebo	915	817	742	594	461	359	263	179

Kaplan-Meier plot for DDFS in the ITT population. DDFS was defined as the time from randomization until documented evidence of first distant recurrence of breast cancer or death. Distant recurrence includes the following events: distant recurrence (metastatic disease-breast cancer that has either been biopsy confirmed or radiologically diagnosed as recurrent invasive breast cancer); death attributable to any cause, including breast cancer, non-breast cancer, or unknown cause; second primary non-breast invasive cancer.

Figure 4. Kaplan-Meier Curve for Overall Survival.[2]



Kaplan-Meier plot for OS in the ITT population. OS was defined as the time from the date of randomization until death due to any cause.

Safety Results[2]

- Median duration of treatment was 338 days for the olaparib group and 358 day for the placebo group.
- Safety data were consistent with known safety profile of olaparib, with no significant increase in serious adverse reaction or adverse reactions of special interest by olaparib.

Table 3. Adverse Reactions Reported in ≥10% of Patients in Either Treatment Arm[a,2,3]

	Olaparib (N=911)		Placebo (N=904)	
Event, n (%)	**All grades**	**Grade ≥3[b]**	**All grades**	**Grade ≥3[b]**
Nausea	518 (56.9)	7 (0.8)	211 (23.3)	0 (0.0)
Fatigue	365 (40.1)	16 (1.8)	245 (27.1)	4 (0.4)
Anemia	214 (23.5)	79 (8.7)	35 (3.9)	3 (0.3)
Vomiting	206 (22.6)	6 (0.7)	74 (8.2)	0 (0.0)
Headache	180 (19.8)	2 (0.2)	152 (16.8)	1 (0.1)
Diarrhea	160 (17.6)	3 (0.3)	124 (13.7)	3 (0.3)
Neutrophil count decreased	146 (16.0)	44 (4.8)	59 (6.5)	7 (0.8)
White blood cell count decreased	143 (15.7)	27 (3.0)	52 (5.8)	3 (0.3)
Decreased appetite	119 (13.1)	2 (0.2)	53 (5.9)	0 (0.0)
Dysgeusia	107 (11.7)	0 (0.0)	38 (4.2)	0 (0.0)
Dizziness	104 (11.4)	1 (0.1)	67 (7.4)	1 (0.1)
Arthralgia	84 (9.2)	2 (0.2)	107 (11.8)	2 (0.2)

[a]The table includes ARs of any grade with an incidence of at least 10% in either treatment arm in the safety analysis set. [b]All listed adverse events are grade 3 except for 10 grade 4 events in the olaparib arm: (neutrophil count decreased, n=5; anemia, n=4; fatigue, n=1).

Table 4. Summary of Adverse Reactions[2]

	Olaparib (N=911)	Placebo (N=904)
Any adverse reaction, n (%)	835 (91.7%)	753 (83.3%)
Serious adverse reaction, n (%)	79 (8.7%)	76 (8.4%)
Adverse reaction of special interest, n (%) MDS/AML Pneumonitis New primary malignancy	30 (3.3%) 2 (0.2%) 9 (1.0%) 20 (2.1%)	46 (5.1%) 3 (0.3%) 11 (1.2%) 32 (3.5%)
Grade ≥3 adverse reaction, n (%)	221 (24.3%)	102 (11.3%)
Grade 4 adverse reaction, n (%)	17 (1.9%)	4 (0.4%)
Adverse reaction leading to permanent discontinuation of treatment, n (%)[a]	90 (9.9%)	38 (4.2%)
Adverse reaction leading to death, n (%)[b]	1 (0.1%)	2 (0.2%)

AML = acute myeloid leukemia; MDS = myelodysplastic syndrome. Includes adverse events with an onset date on or after the first dose date and up to and including 30 days following date of last dose of study medication [a]Adverse events leading to permanent discontinuation of treatment in the olaparib group that occurring in > 1% were; nausea, anemia and fatigue; [b]In the olaparib group, cardiac arrest led to death in one patient. In the placebo group, AML and ovarian cancer led to death in one patient each.

References submitted in support of this proposal:

1. LYNPARZA Prescribing Information.
2. Tutt ANJ, Garber JE, Kaufman B et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. *N Eng J Med*. 2021. DOI: 10.1056/NEJMoa2105215. Accessed June 4, 2021.
3. Tutt A. A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline BRCA1/2 mutations and high-risk HER2-negative early breast cancer [presentation]. Presented at: the American Society of Clinical Oncology (ASCO) Annual Meeting (Virtual); June 4-8, 2021.

Sincerely,
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