נובמבר 2019

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

Lynparza 100 mg film-coated tablets: פרסום עדכון בעלון התכשיר
Lynparza 150 mg film-coated tablets

הרכב:

Each film-coated tablet contains 100 mg olaparib.
Each film-coated tablet contains 150 mg olaparib.
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התוויה:

Ovarian cancer
Lynparza is indicated as monotherapy for the:

- maintenance treatment of adult patients with advanced (FIGO stages III and IV) *BRCA1/2*- mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.
- Maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

Germline BRCA-mutated HER2-negative Metastatic Breast Cancer
Lynparza is indicated in patients with deleterious or suspected deleterious *gBRCAm*, 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.

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון עלון בהתאם להוראות משרד הבריאות בתאריך **ספטמבר 2019.**

העדכון העיקרי בעלון לרופא הוא:

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Ovarian cancer
Lynparza is indicated as monotherapy for the:

- maintenance treatment of adult patients with advanced (FIGO stages III and IV) *BRCA1/2*-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

~~Maintenance Treatment of Recurrent Ovarian Cancer:~~

- ~~Lynparza is indicated as monotherapy for the m~~Maintenance treatment of adult patients with platinum-sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy.

4.2 Posology and method of administration
Detection of BRCA1/2 mutations
Before Lynparza treatment is initiated for first-line maintenance treatment of high-grade epithelial ovarian cancer (EOC), fallopian tube cancer (FTC) or primary peritoneal cancer (PPC), patients must

have confirmation of deleterious or suspected deleterious germline and/or somatic mutations in the breast cancer susceptibility genes (BRCA) 1 or 2 using a validated test.
There is no requirement for BRCA1/2 testing prior to using Lynparza for the maintenance treatment of relapsed EOC, FTC or PPC who are in a complete or partial response to platinum-based therapy.
For germline breast cancer susceptibility genes (gBRCA1/2) mutated human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer, patients must have confirmation of a deleterious or suspected deleterious gBRCA1/2 mutation before Lynparza treatment is initiated. gBRCA1/2 mutation status should be determined by an experienced laboratory using a validated test method. Data demonstrating clinical validation of tumour BRCA1/2 tests in breast cancer are not currently available.
Genetic counselling for patients tested for mutations in BRCA1/2 genes should be performed according to local regulations

Posology
~~***Ovarian cancer***~~
~~Patients should start treatment with Lynparza no later than 8 weeks after completion of their final dose of the platinum-containing regimen.~~
Patients with platinum-sensitive relapsed (PSR) high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy should start treatment with Lynparza no later than 8 weeks after completion of their final dose of the platinum-containing regimen.~~It is recommended that treatment be continued until progression of the underlying disease. There are no data on retreatment with Lynparza following subsequent relapse (see section 5.1).~~

Duration of treatment
First-line maintenance treatment of BRCA-mutated advanced ovarian cancer:
Patients can continue treatment until radiological disease progression, unacceptable toxicity or for up to 2 years if there is no radiological evidence of disease after 2 years of treatment. Patients with evidence of disease at 2 years, who in the opinion of the treating physician can derive further benefit from continuous treatment, can be treated beyond 2 years.

Maintenance treatment of platinum sensitive relapsed ovarian cancer:
For patients with platinum sensitive relapsed high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer, it is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.

gBRCA1/2-mutated HER2-negative metastatic breast cancer:
It is recommended that treatment be continued until progression of the underlying disease or unacceptable toxicity.
There are no efficacy or safety data on maintenance retreatment with Lynparza following first or subsequent relapse in ovarian cancer patients or on retreatment of breast cancer patients (see section 5.1).

4.4 Special warnings and precautions for use

Myelodysplastic syndrome/Acute myeloid leukaemia
..The incidence of MDS/AML cases was similar among gBRCA1m and gBRCA2m patients (1.7% and 1.4%, respectively). Some of the patients had a history of previous cancer or of bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with Lynparza, it is recommended that Lynparza should be discontinued and the patient be treated appropriately.

Embryofoetal toxicity
~~Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza~~

Pregnancy/contraception
Lynparza should not be used during pregnancy ~~and in women~~. Women of childbearing potential must use two forms of~~not using~~ reliable contraception before starting Lynparza treatment, during therapy and for 1 month after receiving the last dose of Lynparza. Two highly effective and complementary forms of

contraception are recommended. Male patients and their female partners of childbearing potential should use reliable contraception during therapy and for 3 months after receiving the last dose of Lynparza (see section 4.6).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females

Women of childbearing potential should not become pregnant while on Lynparza and not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment and considered regularly throughout treatment.

Women of childbearing potential must use two forms of reliable ~~effective~~ contraception before starting Lynparza therapy, during therapy and for 1 month after receiving the last dose of Lynparza, unless abstinence is the chosen method of contraception (see section 4.4). Two highly effective and complementary forms of contraception are recommended.

Since it cannot be excluded that olaparib may reduce exposure to substrates of CYP2C9 through enzyme induction, the efficacy of some hormonal contraceptives may be reduced if co-administered with olaparib. Therefore, an additional non-hormonal contraceptive method should be considered during treatment (see section 4.5). For women with hormone dependent cancer, two non-hormonal contraceptive methods should be considered.

~~and regular pregnancy tests should be considered during treatment (see section 4.5).~~

Contraception in males

It is not known whether olaparib or its metabolites are found in seminal fluid. Male patients must use a condom during therapy and for 3 months after receiving the last dose of Lynparza when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients must also use highly effective contraception if they are of childbearing potential (see section 4.4). Male patients should not donate sperm during therapy and for 3 months after receiving the last dose of Lynparza

~~*Males*~~

~~Based on findings in genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Lynparza~~

4.8 Undesirable effects

~~**Ovarian Cancer**~~

Summary of the safety profile

Lynparza monotherapy has been associated with adverse reactions generally of mild or moderate severity (CTCAE grade 1 or 2) and generally not requiring treatment discontinuation. The most frequently observed adverse reactions across clinical trials in patients receiving Lynparza monotherapy (≥ 10%) were nausea, vomiting, diarrhoea, dyspepsia, fatigue, headache, dysgeusia, decreased appetite, dizziness, upper abdominal pain, cough, dyspnoea, anaemia, neutropenia, thrombocytopenia and leukopenia~~and anaemia.~~

The Grade ≥ 3 adverse reactions occurring in > 2% of patients were anaemia (16%), neutropenia (6%), fatigue/asthenia (6%), leukopenia (3%), thrombocytopenia (2%) and vomiting (2%).

Adverse reactions that most commonly led to dose interruptions and/ or reductions were anaemia (13.9%), vomiting (7.1%), nausea (6.6%), fatigue/asthenia (6.1%) and neutropenia (5.8%). Adverse

reactions that most commonly led to permanent discontinuation were anaemia (1.3%), nausea (0.8%) and thrombocytopenia (0.5%).

Tabulated list of adverse reactions

The safety profile is based on pooled data from 1,~~248~~ 826 patients with solid tumours treated with…

Table 1 Tabulated list of adverse reactions:

	Adverse reactions	
MedDRA System Organ Class	**Frequency of All CTCAE grades**	**Frequency of CTCAE grade 3 and above**
Blood and lymphatic system disorders	**Very common** Anaemia[a] ~~**Common**~~ Neutropenia[a], Thrombocytopenia[a], Leukopenia[a] **Common**~~**Uncommon**~~ Lymphopenia	**Very common** Anaemia[a] **Common** Neutropenia[a], Thrombocytopenia[a], Leukopenia[a] **Uncommon** Lymphopenia
Respiratory, thoracic and mediastinal disorders	**Very common** Cough[a], Dyspnoea[a]	**Common** Dyspnoeaa **Uncommon** Cough[a]
Gastrointestinal disorders	**Very common** Vomiting, Diarrhoea, Nausea, Dyspepsia, Upper abdominal pain **Common** Stomatitis, ~~Upper abdominal pain~~	**Common** Vomiting, Diarrhoea, Nausea **Uncommon** Stomatitis[a], Upper abdominal pain

[a] Anaemia includes preferred terms (PTs) of anaemia, anaemia macrocytic, erythropenia, haematocrit decreased, haemoglobin decreased, normochromic anaemia, normochromic normocytic anaemia, normocytic anaemia and red blood cell count decreased, ~~erythropenia and haematocrit decreased~~; Neutropenia includes PTs of agranulocytosis, febrile neutropenia, ~~granulocytopenia~~, granulocyte count decreased, granulocytopenia, idiopathic neutropenia, neutropenia, neutropenic infection, neutropenic sepsis and neutrophil count decreased, ~~febrile neutropenia, neutropenic infection and neutropenic~~ ~~sepsis~~; Thrombocytopenia includes PTs of ~~thrombocytopenia~~, platelet count decreased, platelet production decreased, ~~and~~
plateletcrit decreased and thrombocytopenia; Leukopenia includes PTs of leukopenia and white blood cell count decreased; Lymphopenia includes PTs of B-lymphocyte count decreased, lymphocyte count decreased, lymphopenia and T-lymphocyte count decreased; Cough includes PTs of cough and productive cough; Rash includes PTs of rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, exfoliative rash and generalised erythema; Hypersensitivity includes
PTs of hypersensitivity and drug hypersensitivity; Dermatitis includes PTs of dermatitis, dermatitis allergic and dermatitis exfoliative. Dyspnoea includes PTs of dyspnoea and dyspnoea exertional; Stomatitis includes PTs of aphthous ulcer, mouth ulceration and stomatitis.
~~[b] Represents the incidence of laboratory findings of elevations in mean corpuscular volume from baseline to above the upper limit of normal (ULN), not of reported adverse reactions.~~

Description of selected adverse reactions

Haematological toxicity

.. In clinical studies with the tablet ~~formulation~~SOLO2~~,~~ the incidence of anaemia adverse reactions was ~~43.6~~38.8% (CTCAE grade ≥3 ~~19.5~~17.4%) and the incidences of dose interruptions, reductions and discontinuations for anaemia were ~~16.9~~15.7%, ~~8.2~~10.8 % and ~~3.1~~1.9%, respectively; ~~17.9~~20.9% of patients treated with olaparib needed one or more blood transfusions. An exposure-response relationship between olaparib and decreases in haemoglobin has been demonstrated. In clinical studies with

Lynparza the incidence of CTCAE grade ≥ 2 shifts (decreases) from baseline in haemoglobin was 20%, absolute neutrophils ~~15~~20%, platelets 5%, lymphocytes 30% and leucocytes 20% (all % approximate).

Other laboratory findings
In clinical studies with Lynparza the incidence of CTCAE grade ≥ 2 shifts (elevations) from baseline in blood creatinine was approximately ~~15~~10%...

~~**Treatment of *gBRCAm* HER2-negative Metastatic Breast Cancer**~~
~~*OlympiAD*~~
~~The safety of Lynparza tablets as monotherapy was also evaluated in *gBRCAm* patients with HER2-negative metastatic breast cancer who had previously received up to two lines of chemotherapy for the treatment of metastatic disease in OlympiAD. This study was a randomized, open-label, multi-center study in which 296 patients received either Lynparza 300 mg twice daily (n=205) or a chemotherapy(capecitabine, eribulin, or vinorelbine) of the healthcare provider's choice (n=91) until disease progression or unacceptable toxicity. The median duration of study treatment was 8.2 months in patients who received Lynparza and 3.4 months in patients who received chemotherapy. Dose interruptions due to an adverse reaction of any grade occurred in 35% of patients receiving Lynparza and 28% of those receiving chemotherapy; dose reductions due to an adverse reaction occurred in 25% of Lynparza patients and 31% of chemotherapy patients. Discontinuation occurred in 5% of Lynparza patients and 8% in chemotherapy patients.~~
~~Table 2 summarizes the adverse reactions that occurred in at least 20% of patients who received Lynparza in OlympiAD. Table 3 presents the laboratory abnormalities that occurred in at least 25% of patients who received Lynparza in OlympiAD.~~

~~**Table 2 Adverse Reactions[a] in OlympiAD (≥20% of Patients Who Received Lynparza)**~~

~~**Adverse Reactions**~~	~~**Lynparza tablets n=205**~~		~~**Chemotherapy n=91**~~	
	~~**Grades 1-4 %**~~	~~**Grades 3-4 %**~~	~~**Grades 1-4 %**~~	~~**Grades 3-4 %**~~
				~~**Blood and lymphatic disorders**~~
~~Anemia[b]~~	~~40~~	~~16~~	~~26~~	~~4~~
~~Leukopenia[c]~~	~~25~~	~~5~~	~~31~~	~~13~~
~~Neutropenia[d]~~	~~27~~	~~9~~	~~50~~	~~26~~
				~~**Gastrointestinal disorders**~~
~~Nausea~~	~~58~~	~~0~~	~~35~~	~~1~~
~~Vomiting~~	~~30~~	~~0~~	~~15~~	~~1~~
~~Diarrhea~~	~~21~~	~~1~~	~~22~~	~~0~~
				~~**Infections and infestations**~~
~~Respiratory tract infection[e]~~	~~27~~	~~1~~	~~22~~	~~0~~
				~~**General disorders and administration site conditions**~~
~~Fatigue (including asthenia)~~	~~37~~	~~4~~	~~36~~	~~1~~
				~~**Nervous system disorders**~~
~~Headache~~	~~20~~	~~1~~	~~15~~	~~2~~

~~a. Graded according to NCI CTCAE 4.0.~~
~~b. Represents grouped terms consisting of anemia (anemia erythropenia, hematocrit decreased, hemoglobin decreased and red blood cell count decreased).~~
~~c. Represents grouped terms consisting of leukopenia (leukopenia and white blood cell count decreased).~~
~~d. Represents grouped terms consisting of neutropenia (febrile neutropenia, granulocyte count decreased, granulocytopenia, neutropenia, neutropenic infection, neutropenic sepsis, neutrophil count decreased).~~
~~e. Represents grouped terms consisting of bronchitis, influenza, lower respiratory tract infection, nasopharyngitis, pharyngitis, respiratory tract infection, rhinitis, sinusitis, upper respiratory tract infection, upper respiratory tract infection bacterial.~~

~~In addition, adverse reactions in OlympiAD that occurred in <20% of patients receiving Lynparza were cough, decreased appetite, thrombocytopenia, dysgeusia, lymphopenia, dizziness, dyspepsia, stomatitis, upper abdominal pain, rash, increase in serum creatinine and dermatitis.~~

~~**Table 3 Laboratory Abnormalities Reported ≥25% of Patients in OlympiAD**~~

Laboratory Parameter[a]	Lynparza tablets n[b]= 205		Chemotherapy n[b]= 91	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Increase in mean corpuscular volume[c]	71	-	33	-
Decrease in hemoglobin	82	17	66	3
Decrease in leukocytes	71	8	70	23
Decrease in lymphocytes	73	21	63	3
Decrease in absolute neutrophil count	46	11	65	38
Decrease in platelets	33	3	28	0

a. Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
b. 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.
c. Represents the proportion of subjects whose mean corpuscular volume was > ULN.

In first-line ovarian cancer maintenance treatment, patients experienced nausea events (77% on olaparib, 38% on placebo), vomiting (40% on olaparib, 15% on placebo), diarrhoea (34% on olaparib, 25% on placebo) and dyspepsia (17% on olaparib, 12% on placebo). Nausea events led to discontinuation in 2.3% of olaparib-treated patients (CTCAE Grade 2) and 0.8% of placebo-treated patients (CTCAE Grade 1); 0.8% and 0.4% of olaparib-treated patients discontinued treatment due to low grade (CTCAE Grade 2) vomiting and dyspepsia, respectively. No olaparib or placebo-treated patients discontinued due to diarrhoea. No placebo-treated patients discontinued due to vomiting or dyspepsia. Nausea events led to dose interruption and dose reductions in 14% and 4%, respectively, of olaparib-treated patients. Vomiting events led to interruption in 10% of olaparib-treated patients; no olaparib-treated patients experienced a vomiting event leading to dose reduction.

Paediatric population
No studies have been conducted in paediatric patients.

5. PHARMACOLOGICAL PROPERTIES

Detection of *BRCA1/2* mutations
Local or central testing of blood and/or tumour samples for ~~If~~ *BRCA1/2* mutations have been used in different studies. Depending on the test used and the international classification consensus, the BRCA1/2 mutations have been classified as deleterious/suspected deleterious or pathogenic/likely pathogenic. Genetic testing ~~mutation status is determined, it~~ should be conducted by an experienced laboratory using a validated test ~~method~~.

~~Genetic counselling for patients tested for mutations in breast cancer susceptibility genes 1/2 (BRCA1/2) should be performed according to local regulations.~~

Clinical efficacy and safety
First-line maintenance treatment of BRCA-mutated advanced ovarian cancer: SOLO1 Study
~~*SOLO2 study (D0816C00002)*~~
The safety and efficacy of olaparib as maintenance therapy were studied in patients with newly diagnosed advanced (FIGO Stage III-IV) high-grade serous or endometrioid BRCA1/2 mutated (BRCA1/2m) ovarian cancer following completion of first-line platinum-based chemotherapy in a Phase III randomised, double-blind, placebo-controlled, multicentre trial ~~in patients with~~ In this study 391 patients were randomised 2:1 to receive either Lynparza (300 mg [2 x 150 mg tablets] twice daily) or placebo. Patients were stratified by response to first-line platinum chemotherapy; complete response (CR) or partial response (PR). Treatment was continued until radiological progression of the underlying disease, unacceptable toxicity or for up to 2 years. For patients who remained in complete clinical response (i.e. no radiological evidence of disease), the maximum duration of treatment was 2 years; however, patients who had evidence of disease that remained stable (i.e. no evidence of disease progression) could continue to receive Lynparza beyond 2 years.
Patients with germline *or somatic BRCA1/2 mutations were identified prospectively either from germline testing in blood via a local test (n=208) or central test (n=181) or from testing a tumour sample using a*

local test (n=2). By central germline testing, deleterious or suspected deleterious mutations were identified in 95.3% (365/383) and 4.7% (18/383) of patients, respectively. Large rearrangements in the BRCA1/2 genes were detected in 5.5% (21/383) of the randomised patients. The gBRCAm status of patients enrolled via local testing was confirmed retrospectively by central testing. Retrospective testing of patients with available tumour samples was performed using central testing and generated successful results in 341 patients, of which 95% had an eligible mutation (known [n=47] or likely pathogenic [n=277]) and 2 gBRCAwt patients were confirmed to have sBRCAm only. There were 389 patients who were germline BRCA1/2m and 2 who were somatic BRCA1/2m in SOLO1.
~~*BRCA1/2 mutated*~~
Demographic and baseline characteristics were generally well balanced between the olaparib and placebo treatment arms. Median age was 53 years in both arms. Ovarian cancer was the primary tumour in 85% of the patients. The most common histological type was serous (96%), endometrioid histology was reported in 2% of the patients. Most patients were ECOG performance status 0 (78%), there are no data in patients with performance status 2 to 4. Sixty-three percent (63%) of the patients had upfront debulking surgery and of these the majority (75%) had no macroscopic residual disease. Interval debulking surgery was performed in 35% of the patients and of these 82% had no macroscopic residual disease reported. Seven patients, all stage IV, had no cytoreductive surgery. All patients had received first-line platinum-based therapy. There was no evidence of disease at study entry (CR), defined by the investigator as no radiological evidence of disease and cancer antigen 125 (CA-125) within normal range, in 73% and 77% of patients in the olaparib and placebo arms, respectively. PR, defined as the presence of any measurable or non-measurable lesions at baseline or elevated CA-125, was reported in 27% and 23% of patients in the olaparib and placebo arms, respectively. Ninety three percent (93%) of patients were randomised within 8 weeks of their last dose of platinum-based chemotherapy. Patients who had been treated with bevacizumab were excluded from the study, therefore there are no safety and efficacy data on olaparib patients who had previously received bevacizumab. There are very limited data in patients with a somatic *BRCA* mutation.
The primary endpoint was progression-free survival (PFS) defined as time from randomisation to progression determined by investigator assessment using modified Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, or death. Secondary efficacy endpoints included time from randomisation to second progression or death (PFS2), overall survival (OS), time from randomisation to discontinuation of treatment or death (TDT), time from randomisation to first subsequent anti- cancer therapy or death (TFST) and health related quality of life (HRQoL). Patients had tumour assessments at baseline and every 12 weeks for 3 years, and then every 24 weeks relative to date of randomisation, until objective radiological disease progression.
The study demonstrated a clinically relevant and statistically significant improvement in investigator assessed PFS for olaparib compared to placebo. The investigator assessment of PFS was supported with a blinded independent central radiological (BICR) review of PFS. At the time of PFS analysis, interim OS data were immature (21%), with HR 0.95 (95% CI 0.60, 1.53; p-value=0.9). Efficacy results are presented in Table 2 and Figures 1 and 2.

Table 2 Efficacy results for newly diagnosed patients with *BRCA1/2m* advanced ovarian cancer in SOLO1

	Olaparib 300 mg bd	**Placebo[c]**
PFS (51% maturity)[a]		

Number of events: Total number of patients (%)	102:260 (39)	96:131 (73)
Median time (months)	NR	13.8
HR (95% CI)[b]	0.30 (0.23-0.41)	
P value (2-sided)	p<0.0001	
PFS2 (31% maturity)		
Number of events: Total number of patients (%)	69:260 (27)	52:131 (40)
Median time (months)	NR	41.9
HR (95% CI) [c]	0.50 (0.35-0.72) P	
value (2-sided)	p=0.0002	
TFST (49% maturity)		
Number of events: Total number of patients (%)	99:260 (38)	94:131 (72)
Median time (months)	51.8	15.1
HR (95% CI) [c]	0.30 (0.22-0.40) P	
value* (2-sided)	p<0.0001	

[a] Based on Kaplan-Meier estimates, the proportion of patients that were progression free at 24 and 36 months were 74% and 60% for olaparib versus 35% and 27% for placebo; the median follow-up time was 41 months for both the olaparib and placebo arms.

[b] A value <1 favours olaparib. The analysis was performed using a Cox proportional hazards model including response to previous platinum chemotherapy (CR or PR) as a covariate.

[c] Of the 94 patients on the placebo arm who received subsequent therapy, 49 (52%) received a PARP inhibitor.

* Not controlled for multiplicity.

bd Twice daily; NR Not reached; CI Confidence interval; PFS Progression-free survival; PFS2 Time to second progression or death; OS Overall survival; TFST Time from randomisation to first subsequent anti-cancer therapy or death.

Figure 1 SOLO1: Kaplan-Meier plot of PFS in newly diagnosed patients with *BRCA1/2m* advanced ovarian cancer (51% maturity - investigator assessment)

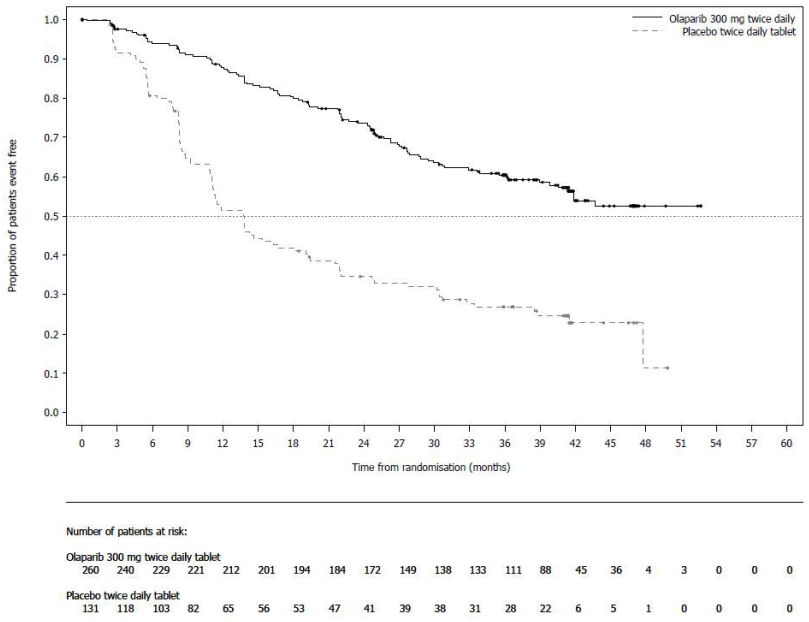
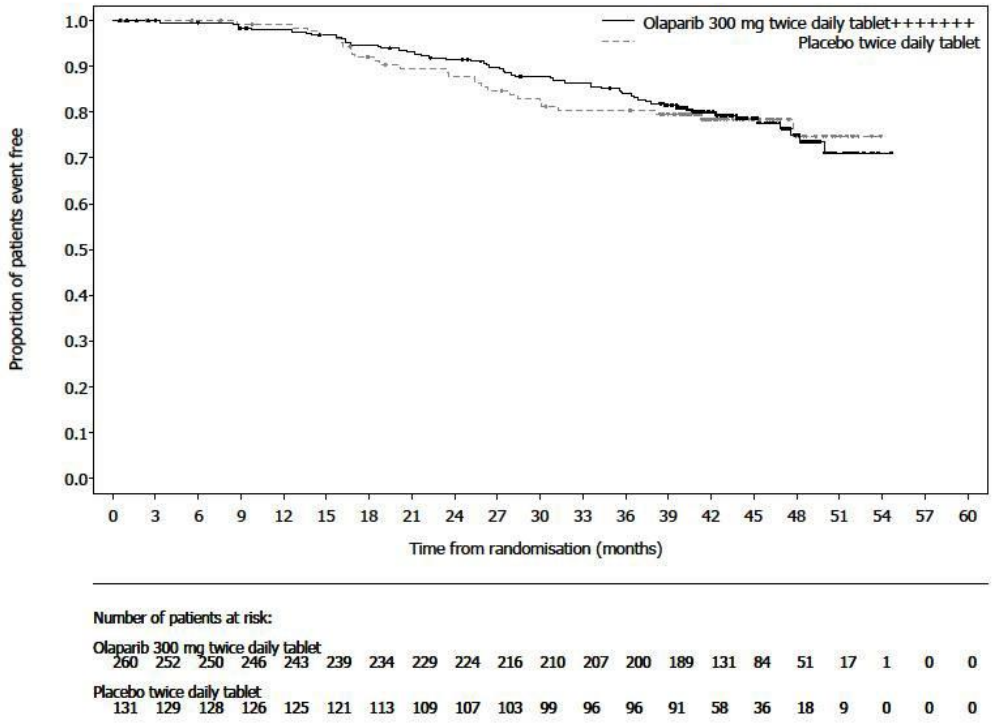


Figure 2 SOLO1: Kaplan-Meier plot of OS in newly diagnosed patients with *BRCA1/2m* advanced ovarian cancer (21% maturity)



Consistent results were observed in the subgroups of patients by evidence of the disease at study entry. Patients with CR defined by the investigator had HR 0.34 (95% CI 0.24–0.47); median PFS not reached on olaparib vs 15.3 months on placebo. At 24 and 36 months, respectively, 68% and 45% patients remained in CR in the olaparib arm, and 34% and 22% of patients in the placebo arm. Patients with PR at study entry had PFS HR 0.31 (95% CI 0.18, 0.52; median PFS 30.9 months on olaparib vs 8.4 months on placebo). Patients with PR at study entry either achieved CR (15% in olaparib arm and 4% in the placebo arm at 24 months, remained in CR at 36 months) or had further PR/stable disease (43% in olaparib arm and 15% in the placebo arm at 24 months; 17% in olaparib arm and 15% in placebo arm at 36 months). The proportion of patients who progressed within 6 months of the last dose of platinum-based chemotherapy was 3.5% for olaparib and 8.4% for placebo.

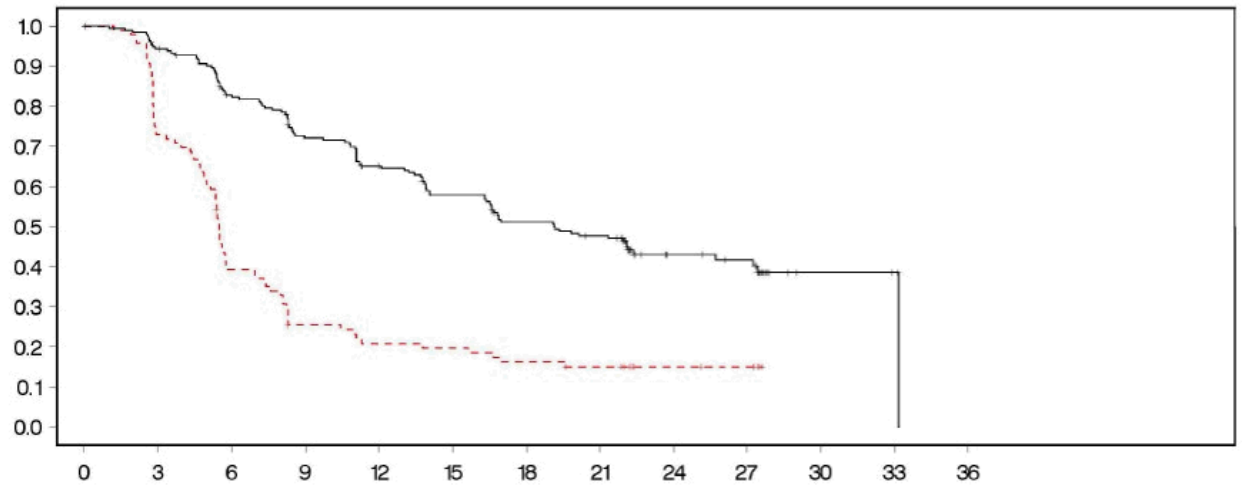
Maintenance treatment of platinum-sensitive relapsed (PSR) ovarian cancer

SOLO2 Study

The safety and efficacy of olaparib as maintenance therapy were studied in a Phase III randomised, double-blind, placebo-controlled trial in patients with germline *BRCA1/2*-mutated PSR ovarian,, fallopian tube or primary peritoneal cancer. The study compared the efficacy of Lynparza maintenance treatment (300 mg [2 x 150 mg tablets] twice daily) taken until progression with placebo treatment in 295 patients with high-grade

serous or endometrioid PSR ovarian cancer (2:1 randomisation: 196 olaparib and 99 placebo) who were in response (CR or PR) following completion of platinum-containing chemotherapy.

Figure 3 SOLO2: Kaplan-Meier plot of PFS in patients with g*BRCA1/2m* PSR ovarian cancer (63% maturity - investigator assessment)



Time from randomisation (months)

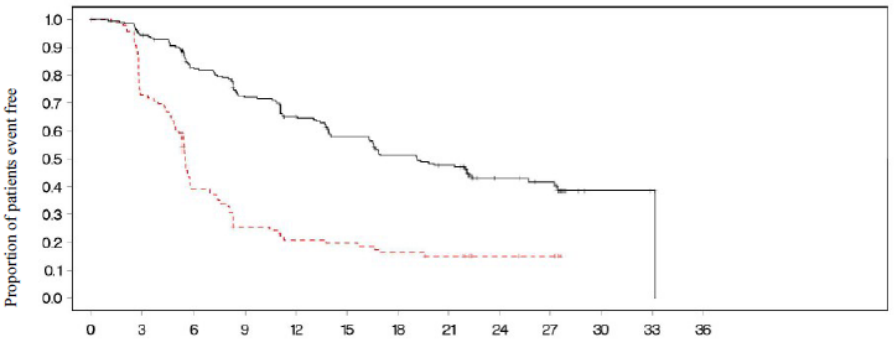
- - - - - - - - - Placebo bd ----------Olaparib 300 mg bd

Number of patients at risk:

196	182	156	134	118	104	89	82	32	29	3	2	0	Olaparib 300 mg bd
99	70	37	22	18	17	14	12	7	6	0	0	0	Placebo bd

bd Twice daily; PFS Progression free survival

Figure 1 SOLO2: Kaplan-Meier plot of PFS in patients with g*BRCA1/2m* PSR ovarian cancer (63% maturity - investigator assessment)



Time from randomisation (months)

- - - - - - - - - Placebo bd ----------Olaparib 300 mg bd

Number of patients at risk:

196	182	156	134	118	104	89	82	32	29	3	2	0	Olaparib 300 mg bd
99	70	37	22	18	17	14	12	7	6	0	0	0	Placebo bd

bd Twice daily; PFS Progression free survival

~~Treatment of~~ *gBRCA1/2-mutated* HER2-negative Metastatic Breast Cancer

OlympiAD *(Study D0819C00003)*

The safety and efficacy of olaparib in patients with *gBRCA1/2*-mutations who had HER2-negative metastatic breast cancer were studied in a Phase III randomised, open-label, controlled trial (OlympiAD). In this study 302 patients with a documented deleterious or suspected deleterious g*BRCA* mutation were randomised 2:1 to receive either Lynparza (300 mg [2 x 150 mg tablets] twice daily) or physician's choice of chemotherapy (capecitabine 42%, eribulin 35%, or vinorelbine 17%) until progression or unacceptable toxicity. Patients with *BRCA1/2* mutations were identified from germline testing in blood via a local test or by central testing at Myriad. Patients were stratified based on: receipt of prior chemotherapy regimens for metastatic breast cancer (yes/no), hormone receptor (HR) positive vs triple negative (TNBC), prior platinum treatment for breast cancer (yes/no). The primary endpoint was PFS assessed by blinded independent central review (BICR) using RECIST 1.1. Secondary endpoints included PFS2, OS, objective response rate (ORR) and HRQoL.

Patients must have received treatment with an anthracycline unless contraindicated and a taxane in either a (neo)adjuvant or metastatic setting. Patients with HR+ (ER and/or PgR positive) tumours must have received and progressed on at least one endocrine therapy (adjuvant or metastatic) or had disease that the treating physician believed to be inappropriate for endocrine therapy. Prior therapy with platinum was allowed in the metastatic setting provided there had been no evidence of disease progression during platinum treatment and in the (neo)adjuvant setting provided the last dose was received at least 12 months prior to randomisation. No previous treatment with a PARP inhibitor, including olaparib, was permitted.

Demographic and baseline characteristics were generally well balanced between the olaparib and comparator arms (see Table 7).

Table 7 Patient demographic and baseline characteristics in OlympiAD ~~OlympiAD (NCT02000622) was an open-label study in which patients (n=302) with *gBRCAm* HER2- negative metastatic breast cancer were randomized 2:1 to receive Lynparza 300 mg tablets or healthcare provider's choice of chemotherapy (capecitabine, eribulin, or vinorelbine, at standard doses) until progression or unacceptable toxicity. Randomization was stratified by prior use of chemotherapy for metastatic disease (yes vs no), hormone receptor status (hormone receptor positive vs triple negative), and previous use of platinum-based chemotherapy (yes vs no). Patients were required to have received treatment with an anthracycline (unless contraindicated) and a taxane, in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor-positive disease must have progressed on at least 1 endocrine therapy (adjuvant or metastatic), or have disease that the treating healthcare provider believed to be inappropriate for endocrine therapy. Patients with prior platinum therapy were required to have no evidence of disease progress during platinum treatment. No prior treatment with a PARP inhibitor was permitted. Of the 302 patients randomized onto OlympiAD, 299 were tested with the BRACAnalysis CDx® and 297 were confirmed to have deleterious or suspected deleterious *gBRCAm* status; 202 were randomized to the Lynparza arm and 95 to the healthcare provider's choice of chemotherapy arm.~~

~~Among the 205 patients treated with Lynparza, the median age was 44 years (range: 22 to 76), 65% were White, 4% were males and all the patients had an ECOG PS of 0 or 1. Approximately 50% of patients had triple-negative tumors and 50% had estrogen receptor and/or progesterone receptor positive tumors and the proportions were balanced across treatment arms. Patients in each treatment arm had received a median of 1 prior chemotherapy regimen for metastatic disease; approximately 30% had not received a prior chemotherapy regimen for metastatic breast cancer. Twenty-one percent of patients in the Lynparza arm and 14% in the chemotherapy arm had received platinum therapy for metastatic disease. Seven percent of patients in each treatment arm had received platinum therapy for localized disease.~~

~~The major efficacy outcome measure was PFS assessed by blinded independent central review (BICR) using RECIST version 1.1. A statistically significant improvement in PFS was demonstrated for the Lynparza arm compared to the chemotherapy arm. Efficacy data for OlympiAD are displayed in Table 4 and Figure 4. Consistent results were observed across patient subgroups defined by study stratification factors. An exploratory analysis of investigator-assessed PFS was consistent with the BICR-assessed PFS results.~~

	Olaparib 300 mg bd n=205	**Chemotherapy n=97**
Age - year (median)	44	45
Gender (%)		
Female	200 (98)	95 (98)
Male	5 (2)	2 (2)
Race (%)		
White	134 (65)	63 (65)
Asian	66 (33)	28 (29)
Other	5 (2)	6 (6)
ECOG performance status (%)		
0	148 (72)	62 (64)
1	57 (28)	35 (36)
Overall disease classification		
Metastatic	205 (100)	97 (100)
Locally advanced	0	0
New metastatic breast cancer (%)	26 (13)	12 (12)
Hormone receptor status (%)		
HR+	103 (50)	49 (51)
TNBC	102 (50)	48 (49)
g*BRCA* mutation type (%)		
g*BRCA1*	117 (57)	51 (53)
g*BRCA2*	84 (41)	46 (47)
g*BRCA1* and g*BRCA2*	4 (2)	0
≥2 Metastatic sites (%)	159 (78)	72 (74)
Location of the metastasis (%)		
Bone only	16 (8)	6 (6)
Other	189 (92)	91 (94)
Measurable disease (%)	167 (82)	66 (68)
Progressive disease at time of randomization (%)	159 (78)	73 (75)
Tumour grade at diagnosis		

Well differentiated (G1)	5 (2)	2 (2) Moderately
differentiated (G2)	52 (25)	23 (24) Poorly
differentiated (G3)	108 (53)	55 (57)
Undifferentiated (G4)	4 (2)	0
Unassessable (GX)	27 (13)	15 (16)
Missing	9 (4)	2 (2)
Number of prior lines of chemotherapy for metastatic breast cancer (%)		
0	68 (33)	31 (32)
1	80 (39)	42 (43)
2	57 (28)	24 (25)
Previous platinum-based therapy (%)	60 (29)	26 (27)
in (neo)adjuvant setting	15 (7)	7 (7)
metastatic setting	43 (21)	14 (14)
in (neo)adjuvant and metastatic setting	3 (1)	1 (1)
Previous anthracycline treatment		
in (neo) adjuvant setting	169 (82)	76 (78)
metastatic setting	41 (20)	16 (17)
Previous taxane treatment		
in (neo)adjuvant setting	146 (71)	66 (68)
metastatic setting	107 (52)	41 (42)
Previous anthracycline and taxane treatment	204 (99.5)	96 (99)

As subsequent therapy, 0.5% and 8% of patients received a PARP inhibitor in the treatment and comparator arms, respectively; 29% and 42% of patients, respectively, received subsequent platinum therapy.

A statistically significant improvement in PFS, the primary efficacy outcome, was demonstrated for olaparib-treated patients compared with those in the comparator arm (see Table 8 and Figure 6).

Table 8 Summary of key efficacy findings for patients with *gBRCA1/2*-mutated HER2- negative metastaticbreastcancerinOlympiAD

	Olaparib 300 mg bd	**Chemotherapy**
PFS (77% maturity) – DCO 09 December 2016		
Number of events: Total number of patients (%)	163:205 (80)	71:97 (73)
Median time (months) (95% CI)	7.0 (5.7-8.3)	4.2 (2.8-4.3)
HR (95% CI)	0.58 (0.43-0.80)	
P value (2-sided)[a]	p=0.0009	
PFS2 (65% maturity) - DCO 25 September 2017[b]		
Number of events: Total number of patients (%)	130:205 (63)	65:97 (67)
Median time (months) (95% CI)	12.8 (10.9-14.3)	9.4 (7.4-10.3)
HR (95% CI)	0.55 (0.39-0.77)	
P value (2-sided)[a]	p=0.0005	
OS (64% maturity) – DCO 25 September 2017		
Number of events: Total number of patients (%)	130:205 (63)	62:97 (64)
Median time (months) (95% CI)	19.3 (17.2-21.6)[c]	17.1 (13.9-21.9)
HR (95% CI)	0.90 (0.66-1.23)	
P value (2-sided)[a]	p=0.5131	
Confirmed ORR – DCO 09 December 2016		
Number of objective responders: Total number of patients with measurable disease (%)	87: 167 (52)[d]	15:66 (23)

95% CI	44.2-59.9	13.3-34.7
DOR – DCO 09 December 2016		
Median, months (95% CI)	6.9 (4.2, 10.2)	7.9 (4.5, 12.2)

[a] Based on stratified log-rank test.
[b] Post-hoc analysis.
[c] The median follow-up time in censored patients was 25.3 months for olaparib versus 26.3 months for comparator.
[d] Confirmed responses (by BICR) were defined as a recorded response of either CR/PR, confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed. In the olaparib arm 8% with measurable disease had a complete response versus 1.5% of patients in the comparator arm; 74/167 (44%) of patients in the olaparib arm had a partial response versus 14/66 (21%) of patients in the chemotherapy arm. In the TNBC patient subgroup the confirmed ORR was 48% (41/86) in the olaparib arm and 12% (4/33) in the comparator arm. In the HR+ patient subgroup the confirmed ORR was 57% (46/81) in the olaparib arm and 33% (11/33) in the comparator arm.
bd Twice daily; CI Confidence interval; DOR Duration of response; DCO Data cut off; HR Hazard ratio; HR+ Hormone receptor positive, ORR Objective response rate; OS overall survival; PFS progression-free survival; PFS2 Time to second progression or death, TNBC triple negative breast cancer.

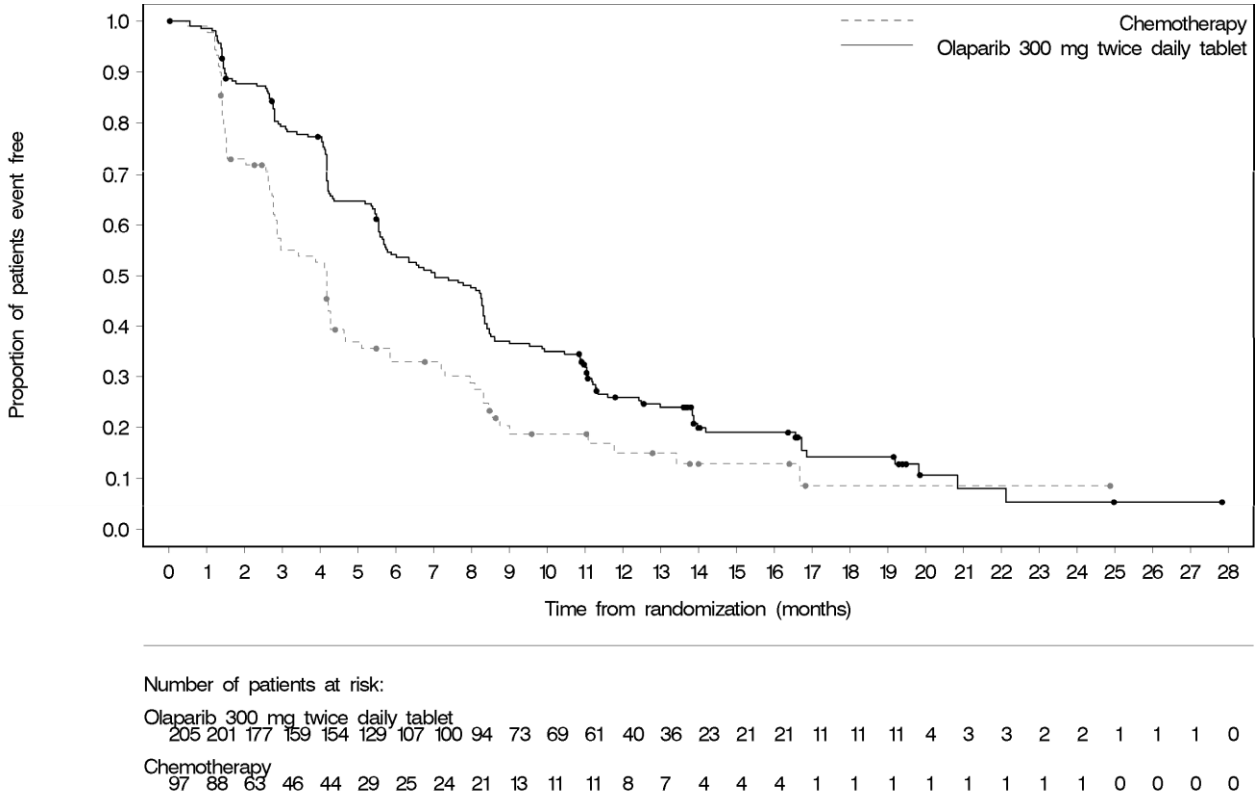
Figure 6 OlympiAD: Kaplan-Meier plot of BICR PFS in patients with *gBRCA1/2*-mutated HER2-negative metastatic breast cancer (77% maturity) DCO 09 December 2016

~~**Table 4 Efficacy Results - OlympiAD (BICR-assessed)**~~

	~~**Lynparza tablets (n=205)**~~	~~**Chemotherapy (n=97)**~~
~~**Progression-Free Survival**~~		
~~Number of events (%)~~	~~163 (80%)~~	~~71 (73%)~~
~~Median, months~~	~~7.0~~	~~4.2~~
~~Hazard ratio (95% CI)[a]~~	~~0.58 (0.43, 0.80)~~	
~~p-value[b]~~	~~0.0009~~	
~~**Patients with Measurable Disease**~~	~~n=167~~	~~n=66~~
~~Objective Response Rate (95% CI)[c]~~	~~52% (44, 60)~~	~~23% (13, 35)~~
~~**Overall Survival**~~		
~~Number of events (%)~~	~~130 (63%)~~	~~62 (64%)~~
~~Median, months~~	~~19.3~~	~~17.1~~
~~Hazard ratio (95% CI)[a]~~	~~0.90 (0.66, 1.23)~~	

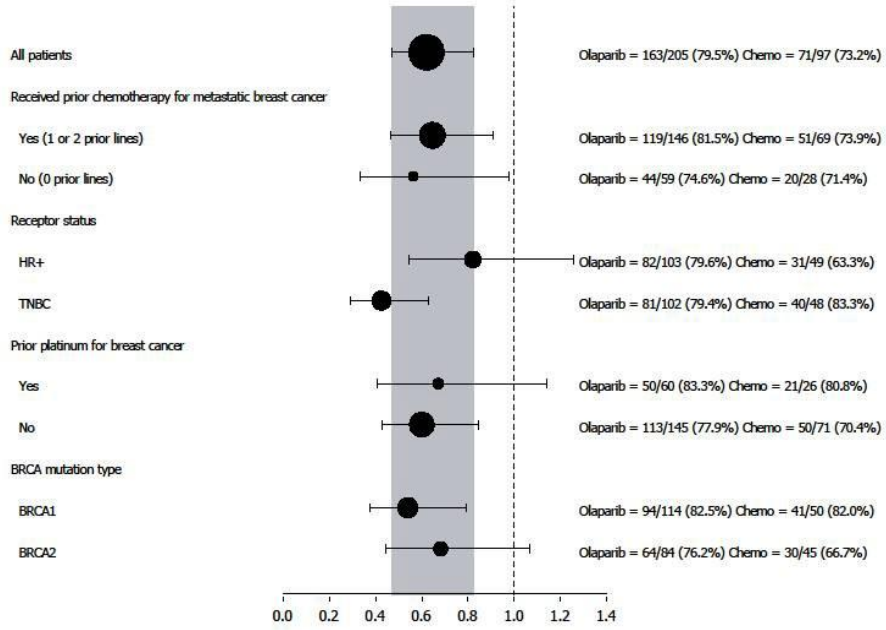
~~[a] Hazard ratio is derived from a stratified log-rank test, stratified by ER, PgR negative versus ER and/or PgR positive and prior chemotherapy (yes versus no).~~
~~[b] For PFS, p-value (2-sided) was compared to 0.05.~~
~~[c] Response based on confirmed responses. The confirmed complete response rate was 7.8% for Lynparza compared to 1.5% for chemotherapy arm.~~

~~**Figure 4: Kaplan-Meier Curves of Progression-Free Survival - OlympiAD**~~



Consistent results were observed in all predefined patient subgroups (see Figure 7). Subgroup analysis indicated PFS benefit of olaparib versus comparator in TNBC (HR 0.43; 95% CI: 0.29-0.63, n=152) and HR+ (HR 0.82; 95% CI: 0.55-1.26, n=150) patient subgroups.

Figure 7 PFS (BICR), Forest plot, by prespecified subgroup

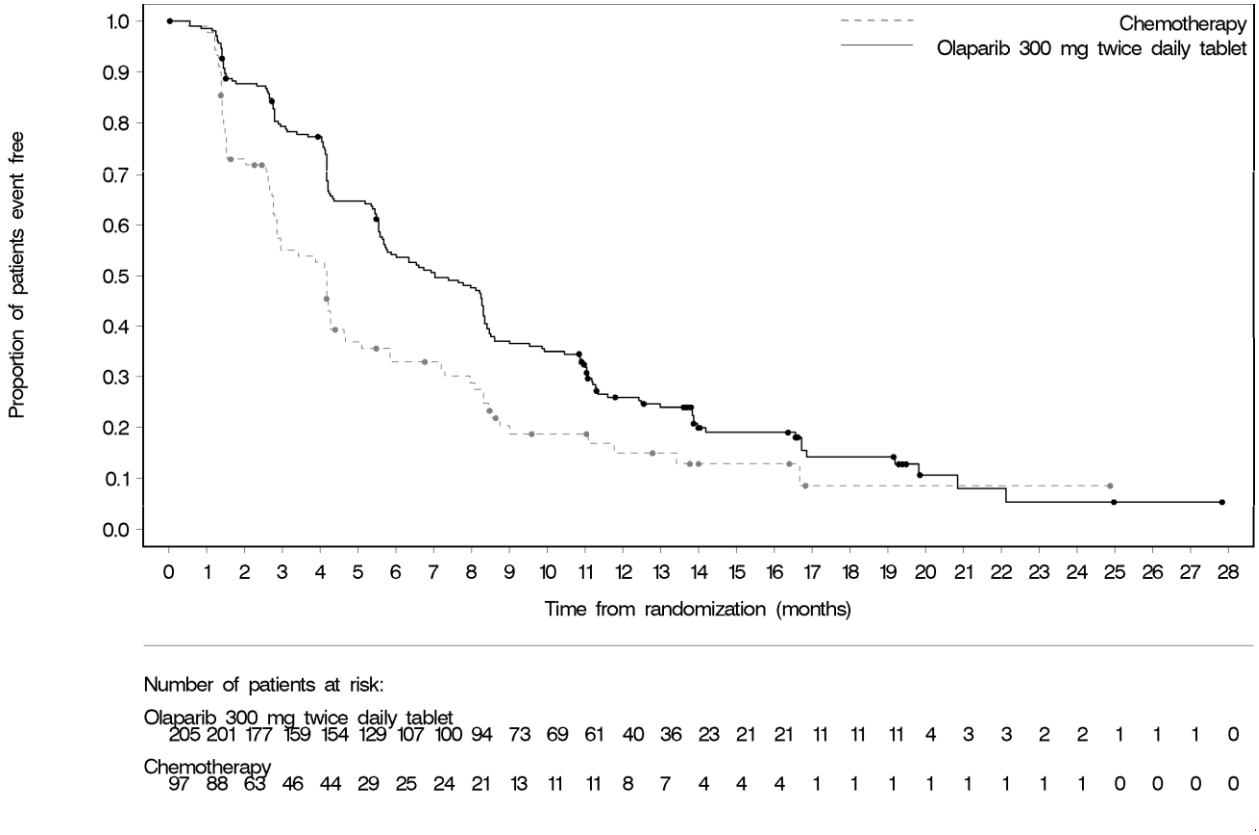


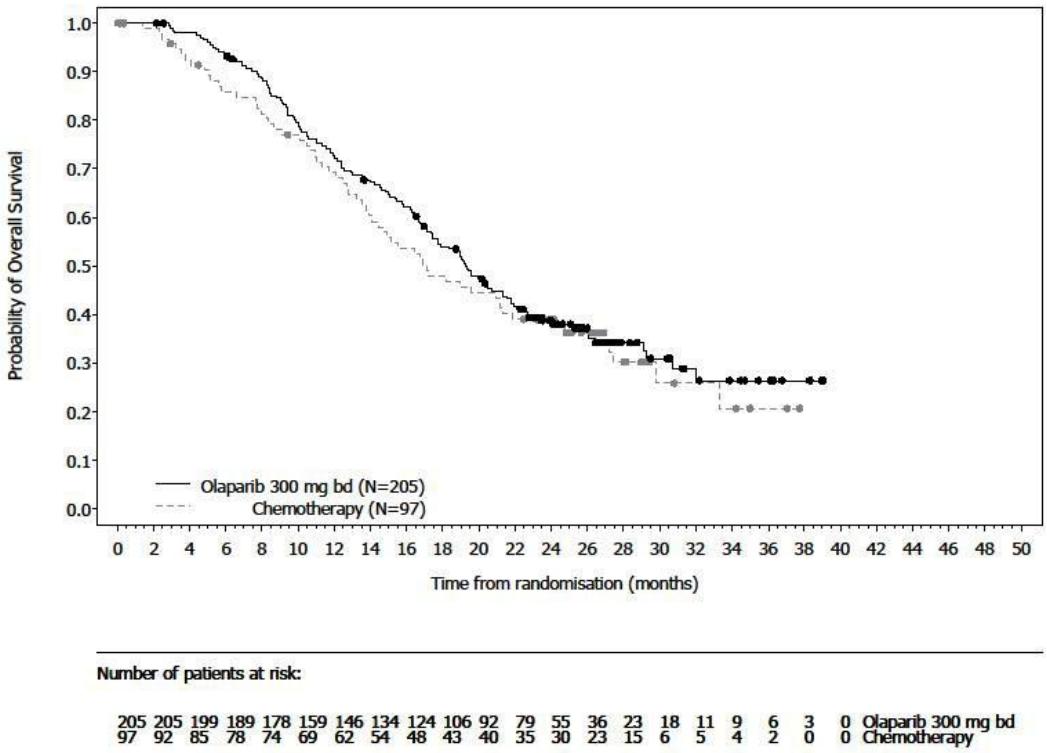
In a post-hoc analysis of the subgroup of patients that had not progressed on chemotherapy other than platinum, the median PFS in the olaparib arm (n=22) was 8.3 months (95% CI 3.1-16.7) and 2.8 months (95% CI 1.4-4.2) in the chemotherapy arm (n=16) with a HR of 0.54 (95% CI 0.24-1.23).

However, the number of patients is too limited to make meaningful conclusions on the efficacy in this subgroup.

Seven male patients were randomised (5 olaparib and 2 comparator). At the time of the PFS analysis, 1 patient had a confirmed partial response with a duration of response of 9.7 months in the olaparib arm. There were no confirmed responses in the comparator arm.

Figure 8 OlympiAD: Kaplan-Meier plot of OS in patients with g*BRCA1/2*-mutated HER2-negative metastatic breast cancer (64% maturity) DCO 25 September 2017





OS analysis in patients with no prior chemotherapy for metastatic breast cancer indicated benefit in these patients with a HR of 0.45 (95% CI 0.27-0.77), while for further lines of therapy HR exceeded 1.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Lynparza in all subsets of the paediatric population, in ovarian carcinoma (excluding rhabdomyosarcoma and germ cell tumours) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties
In vitro, olaparib produced little/no inhibition of UGT1A4, UGT1A9, UGT2B7…

העדכון העיקרי בעלון לצרכן הוא:

1. למה מיועדת התרופה?

לינפארזה מיועדת:

- טיפול אחזקתי, יחידני, בסרטן שחלה מתקדם (או חצוצרות, או סרטן ראשוני של הצפק) מסוג high-grade epithelial בנשים בוגרות אשר להן מוטציה (מולדת או נרכשת) ב-BRCA1/2 ושהגיבו (תגובה מלאה או חלקית) לטיפול כימותרפי מבוסס פלטינום בקו הראשון. ~~קיימת בדיקה מאבחנת המבררת האם יש לך סרטן שחלה עם מוטציית BRCA.~~
- לטיפול אחזקתי בסרטן שחלה חוזר (או חצוצרות, או סרטן ראשוני של הצפק) מסוג high grade epithelial בחולות רגישות לפלטינה ~~הנושאות מוטציית BRCA~~ אשר הגיבו (תגובה מלאה או חלקית) לטיפול כימותרפי מבוסס פלטינום בקו הראשון~~לטיפול כמותרפיה קודם מבוסס פלטינום. יש לבצע בדיקה כדי לקבוע שהסרטן שלך הינו עם מוטציית BRCA~~.
- לטיפול בסרטן שד גרורתי במטופלים הנושאים מוטציית BRCA ו-HER2 שלילי, שטופלו בכימותרפיה לפני או אחרי השלב הגרורתי.

אם הגידול מאופיין בקולטנים הורמונליים חיוביים ,(HR)-positive disease, ההמלצות הן מתן טיפול אנדוקריני. הרופא צריך לערוך בדיקה על מנת לוודא שלינפארזה אכן מתאים לך.

לינפארזה מכילה את החומר הפעיל אולפריב. אולפריב הוא סוג של תרופה לסרטן הנקרא מעכב PARP.

מעכבי PARP יכולים לגרום להרג תאי הסרטן על ידי חסימת האנזים שמסייע לתיקון הדנ"א.

הריון, הנקה ופוריות

גברים:

- יש להשתמש בקונדום בעת קיום יחסי מין עם בת הזוג, גם אם בת זוגך בהריון, במהלך הטיפול בלינפארזה ובמשך ~~3~~ חודשים לאחר נטילת המנה האחרונה של לינפארזה. לא ידוע האם לינפארזה מועברת בזרע.
- בת הזוג חייבת גם היא להשתמש באמצעי מניעה יעיל.
- ~~על גברים שבת זוגם בהריון או יכולה להיכנס להריון להשתמש באמצעי מניעה יעילים במהלך הטיפול ובמשך 3 חודשים אחרי המנה האחרונה של לינפארזה.~~ אין לתרום זרע במהלך הטיפול ובמשך 3 חודשים לאחר נטילת המנה האחרונה.

4. תופעות לוואי

תופעות לוואי אחרות:

תופעות לוואי שכיחות מאוד (משפיעות על יותר מ- 1 מתוך 10 מטופלים):

- כאב באזור הבטן מתחת לצלעות (כאב בבטן העליונה)
- קוצר נשימה

תופעות לוואי שכיחות מאוד העלולות להראות בבדיקות דם:

- ירידה במספר הטסיות בדם (תרומבוציטופניה) – ייתכן ותחוש בסימפטומים הבאים:
  - הופעת חבורות או דימום ממושך יותר מהרגיל בעת פציעה
- ספירה נמוכה של תאי דם לבנים (לויקופניה, נוטרופניה) אשר עלולה להוריד את יכולתך להילחם בזיהומים ועלולה להיות קשורה לחום.

תופעות לוואי שכיחות (שמופיעות ב 1-10 משתמשים מתוך 100):

- ~~כאב באזור הבטן מתחת לצלעות (כאב בבטן העליונה)~~

תופעות לוואי שכיחות ועלולות להראות בבדיקות דם:

- ~~ירידה במספר הטסיות בדם (תרומבוציטופניה) – ייתכן ותחוש בסימפטומים הבאים:~~
  - ~~הופעת חבורות או דימום ממושך יותר מהרגיל בעת פציעה~~
- ספירה נמוכה של תאי דם לבנים (~~לויקופניה, נוטרופניה או~~ לימפופניה) אשר עלולה להוריד את יכולתך להילחם בזיהומים ועלולה להיות קשורה לחום.

העלונים מפורסמים במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום.

בכבוד רב,

אורה סטוליק
רוקחת ממונה
אסטרהזניקה (ישראל) בע"מ

אסטרהזניקה (ישראל) בע"מ, ת.ד 1455, הוד השרון 4524075
טלפון 09-7406528 פקס 09-7406527