Recommendation No. 5/2021

of 26 January 2021

of the President of the Agency for Health Technology Assessment and Tariff System

on the assessment of the drug Zejula (niraparib) under the drug program, for the indication: "Treatment of patients with ovarian cancer, fallopian tube cancer or peritoneal cancer (ICD-10 C56, C57, C48)"

The President of the Agency does not recommend the inclusion of the following medicinal product in the reimbursement scheme:

- Zejula (niraparyb), hard capsules, 100 mg, 56, capsules, EAN code: 05909991425487,
- Zejula (niraparyb), hard capsules, 100 mg, 84, capsules, EAN code: 05909991425494,

for the indication: under the drug programme "Treatment of patients with ovarian cancer, fallopian tube cancer or peritoneal cancer (ICD-10 C56, C57, C48)" within the new limit group and dispense it free of charge.

Explanation for recommendation

The President of the Agency, taking into account the position of the Transparency Council, available scientific evidence, clinical guidelines and reimbursement recommendations, considers the public financing of the technology named in the application to be unjustified under the current conditions.

The efficacy assessment of the technology indicated in the application is based primarily on the results of an RCT with the acronym NOVA directly comparing the effects of niraparib (NIR) versus placebo (PLC) for supportive treatment in adult patients with platinum-sensitive recurrent high-grade serous ovarian, fallopian tube, or peritoneal cancer in whom partial or complete response to platinum-based chemotherapy was achieved (for patients without BRCA1/2 gene mutations). For the population of patients with BRCA1/2 gene mutations, the RCT STUDY 19 (directly comparing OLP versus PLC) was included in the analysis for indirect comparison (niraparib vs olaparib, OLP).

Consistent with the results of the NOVA trial in the BRCA mutation-free population, the median time to progression (PFS) (independent assessment was 9.3 months in the niraparib arm and 3.9 months in the placebo arm. In the population with a germinal or somatic BRCA mutation, the median PFS was 20.9 months in the niraparib arm and 5.7 months in the placebo group.

It is important to note that the overall survival (OS) data published to date in the NOVA study are immature (no median OS was reached in either arm of the study for the cut-off date of 30 May 2016). The above issue is a limitation and affects the reliability of inference in assessing the clinical efficacy of drug use. Thus, there is no evidence to suggest that differences in favour of NIR vs PLC in terms of time to progression will translate into corresponding results in terms of overall survival.

No statistically significant differences were found in the non-gBRCAmut and gBRCAmut populations in terms of quality of life scores (EQ-5D-5L) or in terms of disease symptom scores according to the FOSI.

An indirect analysis for the comparison of niraparib vs olaparib used as supportive monotherapy in patients with platinum-sensitive recurrent low-grade serous carcinoma of the ovary, fallopian tube, or peritoneum with BRCA1 and/or BRCA2 gene mutations showed no statistically significant differences between the compared groups in terms of progression-free survival, overall survival, and time to first subsequent therapy.

According to the results of the economic analysis, the use of niraparib in place of no supportive treatment (in the population without BRCA1 and/or BRCA2 mutations) (trade secret) ICUR from the perspective of the NHF is (trade secret). For the population with BRCA1 and/or BRCA2 mutations (trade secret).

On the other hand, the budget impact analysis concerning the public payer from the perspective of the National Health Fund showed (trade secret)

Reimbursement recommendations issued in other countries are not unequivocal and some emphasise the lack of cost-effectiveness of the technology named in the application.

Considering the above limitations of the assessment of clinical efficacy and the results of the analysis (trade secret)

Subject of the application

The order of the Minister of Health concerns the assessment of the validity of public financing of medicinal products:

- Zejula (niraparib), hard capsules, 100 mg, 56, capsules, EAN code: 05909991425487, proposed net sales price is (trade secret)
- Zejula (niraparib), hard capsules, 100 mg, 84, capsules, EAN code: 05909991425494, proposed net sales price is (trade secret)

for the indication: under the drug programme "Treatment of patients with ovarian cancer, fallopian tube cancer or peritoneal cancer (ICD-10 C56, C57, C48)".

Proposed payment and dispensing category: free of charge, the drug is to be used under a drug programme as part of a new limit group. (trade secret)

Health problem

Ovarian cancer

Ovarian cancer is a heterogeneous group of pathologies that are classified based on histologic type and degree of differentiation.

The current histopathologic classification distinguishes more than 70 types of tumours that can develop in the ovary. They can be divided into two large groups: epithelial and nonepithelial cancers. The most commonly diagnosed category are epithelial neoplasms (more than 95% of ovarian malignancies) which include tumours originating from the ovarian epithelium and the stroma of the ovary. The following epithelial neoplasms are distinguished: serous, mucinous, endometrioid, clear-cell, transitional-cell, mixed, undifferentiated and unclassified neoplasms. Non-epithelial neoplasms include tumours originating from the primordial germ cell, gonad-specific, mixed, and non-epithelial metastatic tumours. These neoplasms are much less common than epithelial neoplasms.

In most, ca. 90-95%, of hereditary ovarian cancer cases, mutations in the BRCA1 or BRCA2 genes are present – which also predispose to breast cancer. The presence of a mutation in the BRCA1 gene increases a woman's lifetime risk of developing ovarian cancer to about 16-60%, and mutation in the BRCA2 gene - up to ca. 11-27% - compared to a risk of 1.6% in the absence of this mutation. However, due to the limitations of current mutation detection tests, failure to find a mutation in the BRCA gene does not rule out a genetic basis for ovarian cancer.

In addition to hereditary forms of cancer in which germinal BRCA mutations (gBRCAm) are inherited, ovarian cancer with BRCA mutations also includes cases of sporadic mutations in BRCA genes in tumour cells (somatic BRCA mutation - sBRCAm).

There are no pathognomonic symptoms in ovarian cancer, but most patients have nonspecific dyspeptic symptoms more than a year before the diagnosis of cancer.

Major risk factors for ovarian cancer include:

- carrying BRCA1 and BRCA2 gene mutations (applies to up to 13% of all ovarian cancer cases);
- hereditary breast and ovarian cancer syndromes;
- a family history of hereditary non-polyposis colorectal cancer (Lynch syndrome — non-polyposis colorectal cancer, endometrial cancer, upper gastrointestinal cancer, urothelial carcinoma of the ureter);
- childlessness, prolonged ovulation stimulation, unsuccessful IVF attempts.

In 2017 in Poland ovarian cancers were on the sixth position in terms of incidence (ca. 3,700 cases per year) and were the 4th most common cause of death (ca. 2,700 deaths per year) in women. The incidence of ovarian malignancies in 2015 was 11.2/million inhabitants.

Ovarian cancer is the worst-prognosis gynecologic malignancy with the lowest survival rate, which is primarily due to the difficulty in early diagnosis and unfavourable anatomic location. Overall, it is estimated that about 40% of patients survive 5 years after the diagnosis of ovarian cancer.

Fallopian tube cancer

Primary fallopian tube carcinoma is a rare neoplasm, with an incompletely known aetiology, histologically and clinically similar to ovarian cancer.

The early stages of the disease are poorly symptomatic or asymptomatic. The most common clinical manifestations in higher grades include abnormal genital tract bleeding, watery discharge, colicky abdominal pain accompanying bleeding and discharge, tumour in the lesser pelvis, ascites, and organ-specific symptoms for metastases.

Genetic, hormonal, and reproductive factors similar to those in ovarian cancer are thought to influence the development of fallopian tube cancer. Germinal BRCA1 and BRCA2 mutations are a documented factor associated with the aetiology of fallopian tube cancer. Among patients with the above mutations, fallopian tube cancer is 120 times more common than in the rest of the population with an onset 10 years earlier than sporadic fallopian tube cancer.

The incidence of primary fallopian tube cancer is 0.14-1.8% of all malignant tumours of the female reproductive organs, and the incidence is approx. 3.6/million women. It is most often diagnosed in 4th to 6th decade of life - the average age of onset is 55 years of age (17-88 years).

Because fallopian tube cancer is classified under the ICD-10 diagnosis code C57 Malignant neoplasm of other and unspecified female genital organs, it is not possible to provide reliable data on its epidemiology based on Polish National Cancer Registry (KRN) data.

If diagnosed early, when the cancer is still only in the mucosa of the fallopian tube, the 5-year survival rate is 95%. If the cancer has spread to the walls of the fallopian tube, the 5-year survival rate is 45%. Overall, the 5-year survival of patients is approx. 44%-59%.

Primary peritoneal carcinoma

Primary serous peritoneal carcinoma (synonyms: serous surface papillary carcinoma, extraovarian primary peritoneal carcinoma) is a neoplasm with a tumour structure identical to invasive epithelial ovarian cancer.

Typically, primary peritoneal carcinoma is classified as a malignancy of the retroperitoneal space and peritoneum (C48 according to the ICD-10 International Classification of Diseases).

Patients present with clinical symptoms similar to those of advanced ovarian cancer. These include abdominal swelling (ascites), constipation, gastrointestinal upset, nausea, vomiting, anorexia and weight loss.

Women with BRCA1 mutations have an increased risk of developing PPC.

In 2017, 101 women were diagnosed with this type of cancer and 114 deaths were reported. A difficulty in determining the incidence of primary peritoneal carcinoma is the fact that other cancers also belong to group C48 and that primary peritoneal carcinoma is sometimes included in other diagnosis-related groups. In addition, Polish data differ from global reports which estimate that peritoneal cancer occurs with a frequency of at least

one-tenth that of ovarian cancer. In Poland, 3,775 cases of ovarian cancer were reported in 2017, so by analogy with global data, peritoneal cancer should have been diagnosed in at least 378 women during the same time period.

The prognosis of peritoneal carcinoma is not fully clarified. Some studies show that the disease course is very similar to advanced ovarian cancer, while others report poorer treatment outcomes and shorter patient survival. Among men diagnosed with cancer between 2003 and 2005, the 1-year survival rate was 70.3%, while it was 70.7% among women. Five-year survival among patients with soft tissue cancer during the first decade of the 21st century increased: in men from 41.9% to 46.0%, in women from 43.8% to 50.5%.

Alternative health technology

The most recent European guidelines found in the assessed indication recommend olaparib or rucaparib in addition to the niraparib named in the application, regardless of BRCA status.

According to one of the clinical experts interviewed by the Agency, in the case of ovarian cancer patients without BRACA-1/2 mutation, after successful treatment of relapse with platinum derivatives, currently, there is no option of supportive treatment with PARP inhibitors in Poland, with the only remaining option of observation until the next relapse.

In accordance with the notice of the Minister of Health of 21 December 2020 for the indication: supportive treatment of patients with advanced recurrent platinum-sensitive ovarian cancer, fallopian tube cancer or primary peritoneal cancer (ICD-10 C56, C57, C48), Lynparza (olaparib) is the medicinal product reimbursed under Drug Programme B.80. "Supportive treatment of patients with advanced recurrent platinum-sensitive ovarian cancer, fallopian tube cancer or primary peritoneal cancer (ICD-10 C56, C57, C48). Olaparib is funded in the population of patients with a known mutation in the BRCA1/2 gene.

The applicant, based on the clinical guidelines found and the opinions of clinical experts, identified the following comparators:

- in the non-gBRCAmut population, observation ("watch and wait" or "routine surveillance" strategy, i.e. observation of patients without active supportive treatment; in clinical trials, patients may also receive placebo in addition to observation);
- in the population of patients with a known mutation in the BRCA1/2 gene (gBRCAmut) - olaparib (capsules).

In view of the above, the Applicant's choice of comparators was considered reasonable.

Description of the benefit named in the application

The medicinal product Zejula contains niraparib which is an inhibitor of poly(ADP-ribose) polymerases (PARPs), PARP 1 and PARP 2, which play a role in DNA repair processes.

According to the Summary of Product Characteristics (SmPC) of Zejula, the drug is registered for use:

- as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.
- as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

The indication named in the application covers supportive treatment in adult patients with platinum-sensitive relapsed low-differentiated serous ovarian, fallopian tube or primary peritoneal cancer, after at least two prior lines of treatment with platinum derivative-containing chemotherapy regimens, with an objective response after the last treatment regimen, and is therefore consistent with the registration indication for Zejula.

Evaluation of efficacy (clinical and practical) and safety

This evaluation consists of collecting data on the health consequences (efficacy and safety) of a new therapy for a given health problem and other therapies that are currently publicly funded and represent alternative treatments available for the particular health problem. Subsequently, this evaluation involves determining the reliability of the collected data and comparing the efficacy and safety results of the new therapy against therapies that are already available for the treatment of the health problem in question.

Based on the above, the assessment of efficacy and safety provides an answer to the question of the measure of health outcome (in terms of both efficacy and safety) to be expected for the new therapy compared to other therapeutic options considered.

As part of the systematic review, the applicant included 1 RCT directly comparing the treatment effects of niraparaib (NIR) with placebo (PLC)

- NOVA (Mirza 2016, Oza 2018, Matulonis 2019, Del Campo 2019, Fabbro 2019, study protocol, EMA report, Matulonis 2017, Juden 2019, Mirza 2019, Mirza 2020) - A randomised multicentre phase III double-blind two-arm clinical trial. Hypothesis type: superiority. Number of patients: Population with inherited BRCA gene mutation (gBRCAmut): NIR: 138, PLC: 65. Population without an inherited mutation in the BRCA gene (non-gBRCAmut): NIR: 234, PLC: 116. Study period: Until disease progression (median follow-up: 16.9 months for the general population, in the gBRCAmut population: 16.4 months; in the non-gBRCAmut population: 17.5 months). The Cochrane risk of bias of the NOVA study was assessed as low in all analysed domains.

For indirect comparison of niraparib vs olaparib (OLA) for the subgroup of patients with BRCA1/2 gene mutations, the following study was included in the analysis:

- STUDY 19: A randomised phase II parallel-group double-masked multicentre clinical trial of olaparib capsules in patients with recurrent disease. Hypothesis type: superiority. Median duration of OLP treatment: 206.5 days (range: 3; 469), PLC: 141 days (range: 34; 413). Median follow-up: 78 months. Total number of patients: OLP 136, PLC 129, including *BRCAmut* OLP population: 74, PL: 62, *gBRCAmut* population OLP: 53, PL: 43. Cochrane risk of bias for STUDY 19 was assessed as low.

Additionally, 15 systematic reviews were included (Kerliu 2020, Haddad 2020, Gu 2020, Cook 2019, Jiang 2019, Yi 2019, Chen 2018, Liu 2018, Mittica 2018, Strapoli 2018, Taylor 2018, Walsh 2018, Heo 2018, Sisay 2017, Zhou 2017), with this recommendation refraining from presenting the results of the above-mentioned secondary research studies.

The applicant's analysis also included a publication by Gallagher (2019) on the practical effectiveness of niraparib in the population named in the application. Results of the publication are presented in this recommendation.

In addition, this assessment considered the results of the full-text publication by Mirza (2020), which presents a long-term safety analysis.

The remaining publications found are systematic reviews/meta-analyses: Ruscito 2020, Stemmer 2020, Jiang 2020, Gong 2020 and a publication on RWE - Eakin 2020. The authors' key findings and conclusions are summarised in this recommendation.

The following parameters, among others, were used to show effectiveness:

- HR – *hazard ratio*,
- OR – *Odds ratio*

Efficacy

<u>NIR vs PLC – direct comparison</u>

In the NOVA study, efficacy was assessed for the population according to the planned treatment (the intention-to-treat analysis, ITT), except for patient-centred health outcome (PRO) assessment.

For direct NIR vs PLC comparison, results are presented for the population without a known BRCA1/2 gene mutation and for patients with a BRCA1/2 gene mutation.

The following endpoints were assessed in efficacy analysis:

- Progression-free survival (PFS)

  In the non-gBRCAmut patient population, the median study time was 17.5 months. In the gBRCAmut patient population, the median study time was 16.4 months.

  In the non-gBRCAmut population, the median PFS (as assessed by the Independent Review Committee, IRC) among patients using NIR was more than 2 times longer than the median in patients using PLC - an increase of 5.4 months in median time to progression. The use of NIR in this population resulted in a statistically

significant 55% reduction in the risk of progression or death from ovarian cancer compared with the PLC-treated group - HR=0.45 (95% CI: 0.34; 0.61).

The use of NIR in the subgroup of patients with BRCAwt also resulted in a statistically significant 62% reduction in the risk of progression or death from ovarian cancer compared with PLC - HR=0.38 (95% CI: 0.23; 0.63).

In the gBRCAmut+sBRCAmut population, the use of NIR compared to PLC contributed to a statistically significant prolongation of PFS as assessed by IRC (p-value, p=0.0003). The median PFS among patients using NIR was almost 4 times longer than the median in patients using PLC. The use of NIR instead of PLC for supportive treatment in gBRCAmut+sBRCAmut patients resulted in a statistically significant 74% reduction in the risk of progression or death from ovarian cancer.

The duration of PFS in the gBRCAmut patient population was statistically significantly longer in the group of patients treated with NIR vs PLC in both IRC (p<0.0001) and investigator's (p<0.0001) assessment.

In the non-gBRCAmut population, the median study period was 17.5 months (cut-off point 30 May 2016); no data were available for the BRCAwt population.

The median PFS (IRC assessment) was 9.3 months in the NIR arm and 3.9 months in the PLC arm (HR = 0.45 (95% CI: 0.34; 0.61)). For the BRCAwt population, the median PFS in the NIR arm was 9.3 months and in the PLC arm was 3.7 months (HR = 0.38 (95% CI: 0.23; 0.63)).

In the gBRCAmut population, the median study period was 16.4 months (cut-off point 30 May 2016); no data were available for the total gBRCAmut+sBRCAmut population. In the gBRCAmut+sBRCAmut population, the median PFS (IRC assessment) was 20.9 months, while in the PLC group it was 5.7 months (HR = 0.26 (95% CI: 0.18; 0.39)). In the gBRCAmut population, the median PFS was 21.0 months, whereas in the PLC group it was 5.5 months (HR = 0.27 (95% CI: 0.17; 0.41)).

- Overall survival (OS)

  In the non-gBRCAmut population, 44 patients (19%) died in the NIR-treated group, while 27 deaths (23%) occurred in the PLC group. In contrast, in the gBRCAmut population, 16 (12%) died in the NIR group, while 8 deaths (12%) occurred in the PLC group. No data are available for the BRCAwt population and the combined gBRCAmut+sBRCAmut group.

- Chemotherapy-free interval and time to first subsequent therapy (CFI, TFST)

  The median CFI in the non-gBRCAmut population treated with NIR was 12.7 months, while in the PLC group it was 8.6 months (deferring anticancer therapy by an average of 4.1 months). The HR value was 0.50 (95% CI: 0.37; 0.67).

  The use of NIR instead of PLC in the non-gBRCAmut population resulted in a statistically significant 45% reduction in the risk of needing first subsequent line of ovarian cancer therapy.

  In contrast, the median CFI in the gBRCAmut group treated with NIR was 22.8 months and in the PLC group was 9.4 months (delaying the anticancer therapy by 13.4 months on average). The HR value was 0.26 (95% CI: 0.17; 0.41).

  The use of NIR instead of PLC in the gBRCAmut population resulted in a statistically significant 69% reduction in the risk of needing first subsequent line of ovarian cancer therapy.

  The odds ratio of using subsequent anticancer therapy in the gBRCAmut population is 0.35 (95% CI: 0.19; 0.65).

- The progression-free survival after first subsequent therapy (PFS2)

  The use of NIR instead of PLC for maintenance therapy in the non-gBRCAmut population resulted in a statistically significant reduction in the risk of disease progression or death from ovarian cancer after first subsequent therapy by 31% (3-month increase in median time to progression (MTTP) after first subsequent therapy), and in the gBRCAmut population by 52% (6.3-month increase in MTTP).

Patient-reported outcomes (PROs) assessment.

- NCCN-FACT Ovarian Symptom Index (NFOSI).

The NFOSI value was calculated as the sum of the scores obtained in response to questions concerning the following 8 symptoms: lack of energy, vomiting, pain, nausea, swelling in the stomach area, concern about deterioration of health status, satisfaction with current quality of life, cramps in the stomach area. The dimensions are rated using a 5-point Likert scale. A positive change from baseline indicates improvement (higher score means fewer symptoms).

The initial NFOSI value in the non-gBRCAmut population was 25.4 (SD=3.92) in the NIR group and 25.0 (SD=4.07) in the PLC group; during screening, the NFOSI value was 25.0 in the NIR group and 24.9 in the PLC group.

The initial NFOSI value in the gBRCAmut population was 25.1 (SD=4.18) in the NIR group and 25.6 (SD=3.84) in the PLC group; during screening, the NFOSI value was 24.8 in the NIR group and 24.9 in the PLC group.

During the NOVA study, there were no statistically significant differences between patients treated with NIR or PLC in the non-gBRCAmut and gBRCAmut populations.

- Quality of life assessment according to EQ-5D-5L

  The EQ-5D-5L questionnaire includes 5 dimensions of quality of life: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The dimensions are rated using a 5-point Likert scale. A positive change from baseline indicates improvement.

  The initial value for EQ-5D-5L in the non-gBRCAmut population was 0.837 (SD=0.12) in the NIR group and 0.824 (SD=0.14) in the PLC group; during screening, the EQ-5D-5L score was 0.839 in the NIR group and 0.836 in the PLC group.

  The initial value for EQ-5D-5L in the gBRCAmut population was 0.850 (SD=0.12) in the NIR group and 0.847 (SD=0.13) in the PLC group; during screening, the EQ-5D-5L score was 0.851 in the NIR group and 0.849 in the PLC group.

  PROs indicate that patients in the NIR-treated group reported no significant differences with respect to individual parameters compared to the PLC-treated group in both populations.

Indirect comparison between NIR and OLP

An indirect comparison in terms of clinical efficacy was performed in the gBRCAmut (NOVA study, NIR)/BRCAmut (STUDY 19 study, OLP) population. In the case of the analysis of the endpoint: progression-free survival; the NOVA study also identified data for the gBRCAmut + sBRCAmut population. In addition, STUDY 19 identified an assessment of the endpoint of progression-free survival for the gBRCAmut population, which was also included in the indirect comparison.

The indirect analysis for the comparison between NIR and OLP, which are used in maintenance monotherapy in patients with platinum-sensitive recurrent high-grade serous ovarian, fallopian tube, or peritoneal cancer with BRCA1 and/or BRCA2 gene mutations showed no statistically significant differences between the compared groups in terms of progression-free survival (PFS) in each of the analysed populations, overall survival (OS) and time to first subsequent therapy (TFST).

Safety

In the NOVA study, the safety assessment was conducted primarily in the general population. The following endpoints were analysed:

- Treatment discontinuation (total, due to AEs, due to disease progression)

  The analysis of the non-gBRCAmut population revealed that patients receiving NIR were statistically significantly less likely to discontinue treatment in total compared to patients receiving PLC (by 53%, OR=0.47 [95%CI: 0.24; 0.93]). Treatment discontinuation due to disease progression occurred significantly more frequently in patients receiving PLC compared to patients receiving NIR (by 79%, OR=0.21 [95% CI: 0.11; 0.37]). In contrast, treatment discontinuation due to AEs occurred significantly more frequently in the group of patients receiving NIR (by 9.33 times, OR=9.33 [95%CI: 2.20; 39.63]).

  The analysis of the gBRCAmut population revealed that patients receiving NIR were statistically significantly less likely to discontinue treatment in total compared to patients receiving PLC (by 88%, OR=0.12 [95%CI: 0.04; 0.36]). Treatment discontinuation due to disease progression occurred significantly more frequently in patients receiving PLC compared to patients receiving NIR (by 72%,

OR=0.28 [95% CI: 0.15; 0.54]). In contrast, treatment discontinuation due to AEs occurred significantly more frequently in the group of patients receiving NIR (by 9.14 times, OR=9.14 [95%CI: 1.19; 70.28]).

The analysis of the overall population also revealed that patients receiving NIR were statistically significantly (p<0.001) less likely to discontinue treatment in total compared to patients receiving PLC (OR=0.29 [95%CI: 0.16; 0.51]). Treatment discontinuation due to disease progression occurred significantly more frequently in patients receiving PLC compared to patients receiving NIR (by 76%, OR=0.24 [95% CI: 0.15; 0.37]). In contrast, treatment discontinuation due to AEs occurred significantly more frequently in the group of patients receiving NIR (by 9.25 times, OR=9.25 [95%CI: 2.84; 30.10]).

- Overall treatment-emergent adverse events (overall TEAEs) and treatment-related TEAEs

  In the general patient population, overall TEAEs, treatment-related TEAEs, TEAEs ≥3 grade according to CTCAE, treatment-related TEAEs ≥3 grade according to CTCAE, severe overall TEAEs, severe treatment-related TEAEs, TEAE leading to temporary discontinuation of treatment, TEAEs leading to dose reduction and TEAE leading to discontinuation of treatment were observed significantly more frequently in the NIR-treated group.

  No deaths occurred during the treatment in either the niraparib-treated or placebo-treated groups. During the follow-up period, 3 patients died (1 patient in the NIR group, 2 patients in the PLC group) due to myelodysplastic syndrome or acute myeloid leukemia. Two (2) deaths (1 in the NIR group, 1 in the PLC group) were considered by the researcher as related to the treatment.

- Individual adverse events in grade 1-4 of severity, ≥3 severity, and ≥2 severity

  The data concerning adverse events reported at any grade of severity in at least 10% of patients in the general population and at grade ≥3, which corresponded with adverse events of any grade of severity.

  In the general patient population, nausea (grade 1-4), anaemia (1-4 grade, ≥3 grade), thrombocytopenia (1-4 grade, ≥3 grade), fatigue (1-4 grade, ≥3 grade), constipation (1-4 grade), emesis (1-4 grade), headache (1-4 grade), decreased appetite (1-4 grade), insomnia (1-4 grade) were reported significantly more frequently in the NIR-treated group, as well as decreased platelet count (1-4 grade, ≥3 grade), dyspnoea (1-4 grade), hypertension (1-4 grade, ≥3 grade), neutropenia (1-4 grade, ≥3 grade), dizziness (1-4 grade), asthenia (1-4 grade), cough (1-4 grade), decreased neutrophil count (1-4 grade, ≥3 grade), palpitations (1-4 grade) and dysgeusia (1-4 grade).

Long-term safety assessment

The applicant has identified three conference reports: a poster by Juden (2019), an abstract by Juden (2019), and by Mirza (2019). As part of a search update by the Agency, the full-text publication by Mirza (2020) was found.

Mirza 2020, Cut off date: September 2017.

The authors of this publication analysed the incidence of TEAEs in patients receiving niraparaib >2 years.

According to recent data, approximately 20% of patients received maintenance therapy with niraparaib for at least two years:

- for the gBRCAmut population: 47 patients in the NIR group vs. 4 patients in the PLC group;
- for the non-gBRCAmut population: 46 patients in the NIR group vs. 12 patients in the PLC group.

In the Mirza's 2020 publication, safety results were presented for the general population of the study.

- Hematologic TEAEs

  In the final exposure period of 3-4 years (37-42 and 43-48 weeks of therapy), no hematologic TEAEs ≥3 grade were reported in either the niraparib-treated or placebo-treated groups.

  Symptomatic TEAEs (diarrhoea, nausea, emesis, fatigue, hypertension and insomnia)

  The authors of this study emphasise that among patients receiving niraparaib, the incidence of symptomatic TEAEs of ≥3 grade was low (<5%) for all follow-up periods analysed. In contrast, the incidence of symptomatic TEAEs of any degree of toxicity began to remain low (<5%) beginning at month 6 of niraparib treatment (at which level it remained until discontinuation of the treatment).

The mean (median) duration of fatigue was 533 days (330 days) in the niraparib-treated group and 600 days (767 days) in the placebo group. Patients who received niraparib for more than one year suffered from TEAEs: fatigue, hypertension, nausea, emesis and diarrhoea.

- Hepatic and renal toxicity

  The incidence of liver toxicity (liver enzyme levels with 3 times the upper limit of normal level (3xULN) and ≥3 grade toxicity defined as 5xULN) and renal toxicity (creatinine levels 1.5xULN and ≥3 grade toxicity defined as 3xULN) is low in both the NIR-treated (1-6%) and PLC-treated (1-3%) groups. The results of the statistical analysis indicate that the chance for an elevated total creatinine level in the NIR-treated group is 3.56 times higher than the corresponding chance in the placebo-treated group. For the other endpoints, there were no statistically significant differences between the groups compared.

  The long-term use of niraparib (a 4-year follow-up period) is associated with good tolerability in terms of hepatic and renal toxicity assessed.

  The results presented in the Mirza's 2020 publication confirm that the long-term use of niraparib is a safe and well-tolerated therapy. The incidence of anemia, neutropenia, thrombocytopenia, nausea and emesis was highest during the first month of the NOVA study. Therapy interruption or dose reduction are effective in reducing the incidence of these AEs.

Indirect comparison between NIR and OLP

An indirect safety comparison was conducted in the general population. In the NOVA study, the safety analysis was performed for the general population and thus for STUDY 19, the data related to the general population were also included.

- The indirect comparison yielded no statistically significant differences between the comparison groups in terms of safety profile assessment (SPA), except for the endpoints such as treatment-related AEs, which occurred statistically significantly more frequently in the NIR-treated group compared to OLP group (OR = 5.37 [95% CI: 1.99; 14.44]), and grade 1-4 neutropenia, which also occurred statistically significantly more frequently in the NIR-treated group compared to OLP group (OR=4.74 [1.11; 20.25]).

Additional efficacy and safety analysis

Real-world evidence (RWE)

Primary studies

As a result of the search, the applicant found a retrospective observational study that presents the results of maintenance treatment with niraparib in adult patients with platinum-sensitive, recurrent high-grade serous ovarian, fallopian tube or primary peritoneal cancer in terms of safety in RWE – Gallagher 2019.

According to the study results, a total of 57 patients (37%) who started treatment with niraparaib 200 mg/day experienced at least one of the three most common AEs (nausea, thrombocytopenia, fatigue) within the first 3 months. No deaths were reported.

In Gallagher's 2019 study (RWE terms and conditions), when niraparaib 200 mg/day was used, fatigue occurred in 37 patients (24%), nausea in 24 patients (16%) and thrombocytopenia in 21 patients (14%). Grade 3-4 thrombocytopenia was reported in 4 patients (3%).

The authors of Gallagher's 2019 study compared the obtained safety outcomes with those of the NOVA study. In the NOVA study, grade 3-4 thrombocytopenia was reported in 124 patients (34%) receiving niraparib at a dose of 300 mg/day. In the case of 153 patients analysed in the RWE setting, grade 1-3 thrombocytopenia was diagnosed in 17 patients (11%) during a prior treatment regimen before the initiation of niraparib, of which only 4 patients developed thrombocytopenia (grade 1 in 3 patients, grade 2 in 1 patient) after the initiation of maintenance treatment with niraparib. In 1 patient diagnosed with thrombocytopenia during a prior treatment regimen, a platelet transfusion was performed before the initiation of niraparib. It should be noted that no AEs were reported in that patient during niraparaib treatment.

The AEs related to discontinuation of therapy, dose reduction and treatment interruption included thrombocytopenia (n=14), fatigue (n=12), nausea (n=8), diarrhoea (n=5) and emesis (n=4). However, physicians were not asked which specific AEs led to the change in niraparib dosage. Anemia and neutropenia did not contribute to treatment discontinuation.

The authors conclude that the incidence of AEs was lower among patients initiating treatment with niraparaib 200 mg/day in RWE compared to patients initiating treatment with niraparaib 300 mg/day in the NOVA study.

Through their own searches, the Agency analysts additionally found a publication concerning the RWE data – Eakin 2020.

Eakin 2020

The purpose of this study was to describe the real-world experience, including clinical and financial burden, of PARP (poly-ADP-ribose polymerase) inhibitors in a large population undergoing oncological treament.

The retrospective review identified a total of 47 patients and 506 cycles of PARP (122 olaparib - 24%; 89 rucaparib - 18%; 294 niraparib - 58%). The incidence of grade ≥ 3 AEs was similar to those previously reported. Toxicity resulted in drug interruption, reduction or discontinuation in 69%, 63%, and 29% of patients, respectively. Dose interruptions occurred most frequently in the case of niraparib, however, they resulted in fewer cases of treatment discontinuations (p=0.01). The mean duration of drug use was 7.46 cycles (olaparib 10.52, rucaparib 4.68, niraparib 7.34). The average cost of PARP inhibitor therapy was $ 8,018 per cycle.

The authors conclude that the toxicity profile of PARP inhibitors was similar to results of randomised clinical trials (olaparib – SOLO1, SOLO2, STUDY19; rucaparib – Ariel; niraparib – NOVA), however, RWE revealed more dose modifications and treatment discontinuations due to toxicity.

Secondary research studies

In addition to the studies identified and completed by the Applicant, the Agency's own searches found systematic reviews such as Ruscito 2020, Stemmer 2020, Jiang 2020, Gong 2020. The main conclusions of the authors of these systematic reviews are presented below.

Stemmer 2020

The purpose of this review was comparing PARP inhibitors as maintenance therapy in platinum-sensitive ovarian cancer.

The authors conclude that there was no statistically significant difference between the three PARP inhibitors with respect to PFS or OS. However, there is a statistical difference in terms of toxicity, as niraparaib is associated with a higher risk of thrombocytopenia and neutropenia.

Jiang 2020

The purpose of this review was updating the evaluation of the efficacy and safety of PARP inhibitors in advanced stage of epithelial ovarian cancer.

According to the authors' conclusions, PARP inhibitors are an effective and well-tolerated treatment for patients with advanced epithelial ovarian cancer.

Gong 2020

The purpose of this review was evaluating PARP inhibitor treatment regimens in BRCA-mutated ovarian cancer in patients responding to the first-line platinum treatment (bevacizumab and olaparib, veliparib and chemotherapy, olaparib) or in patients with recurrence (olaparib, rucaparib, niraparib) in phase III controlled and randomised trials.

The authors conclude that the choice of PARP regimens for both initial and recurrent treatment should consider not only efficacy and toxicity, but also costs in patients with BRCA mutations. PARP regimens for initial treatment are less toxic than those used for relapse.

Ruscito 2020

The purpose of this review is analysing the available results obtained from the use of PARP regarding efficacy and safety in the treatment of recurrent or primary advanced ovarian cancer.

In their conclusions, the authors indicated that PARP inhibitors are an effective option for the treatment of patients with both primary and recurrent ovarian cancer and with a relatively low incidence of severe AEs.

According to Zejula's SmPC, the most common AEs in all degrees of severity, according to the CTCAE scale, include:

- Very common AEs (≥ 1/10): urinary tract infection, thrombocytopenia, anemia, neutropenia, leukopenia, decreased appetite, insomnia, headache, dizziness, palpitations, hypertension, dyspnoea, cough, rhinopharyngitis, nausea, constipation, emesis, abdominal pain, diarrhoea, indigestion, back pain, joint pain, fatigue, weakness.
- Common AEs (≥1/100 to <1/10): bronchitis, conjunctivitis, hypersensitivity, hypokalemia, anxiety, depression, dysgeusia, tachycardia, epistaxis, dry mouth, flatulence, mucositis, oral cavity inflammation, photosensitivity, rash, myalgia, peripheral oedema, elevated gamma-glutamyl transpeptidase activity, elevated AspAT levels, elevated blood levels of creatinine, elevated AlAT activity, elevated blood activity of alkaline phosphatase, decreased body weight.
- Not very common AEs (≥ 1/1,000 to < 1/100): pancytopenia, neutropenic fever, confusional state, pneumonia.
- Rare AEs (≥ 1/10,000 to < 1/1,000): posterior reversible encephalopathy syndrome (PRES), hypertensive crisis.

On the websites of institutions monitoring the safety of medicinal products (Office for Registration of Medicinal Products, Medical Devices and Biocidal Products [Pol. URPL]; European Medicines Agency [EMA] and the United States Food and Drug Administration [FDA]), the following notices or information relating to the technology named in the application were found.

- There was a document on EMA's website, which incorporates the findings of the PSUR report for the period from 25 Mar 2018 to 25 Sep. 2018. Conclusions regarding the assessment of the link between the used intervention (niraparaib) and the incidence of neutropenic fever are included in the current Zejula drug's SmPC. The PRAC committee concluded that they should be added in section 4.8 of the SmPC as a new, "not very common" AE of the drug.
- No niraparib safety alerts or notices were found on the URPL or FDA websites.

Limitations

The reliability of the results presented is mainly affected by the following:

- There are no head-to-head studies that directly compare the efficacy and safety of Zejula with a selected comparator (olaparib) in a population of adult patients with platinum-sensitive recurrent high-grade serous ovarian, fallopian tube or primary peritoneal cancer; with BRCA1 and/or BRCA2 gene mutations (inherited and/or somatic); after at least two prior lines of treatment with platinum-based chemotherapy regimens, and who achieved an objective response to treatment (complete or partial response according to RECIST 1.1 criteria) after the last platinum-based regimen. Therefore, an indirect comparison with limitations was conducted to asses the treatment effects of niraparib compared to olaprib (STUDY 19).
- In STUDY 19, the population of patients with BRCA1 and/or BRCA2 gene mutations is broader than in the NOVA study because it includes both patients with germline/inherited and somatic BRCA1 and/or BRCA2 gene mutations. In the NOVA study, eligible patients were assigned to one of two cohorts based on their BRCA germline mutation test result: a group with a BRCA germline mutation and a group without a BRCA germline mutation. In contrast, in STUDY 19, patients were not stratified by BRCA mutation status at the time of randomisation. In STUDY 19, the subgroup of patients with a mutation in the BRCA genes (BRCAmut subpopulation) included patients who had a pathogenic or likely pathogenic, germline or somatic mutation in the BRCA genes. This implies a retrospective nature of the analysis of outcomes in the subpopulation of patients according to the BRCA gene status. The above-mentioned issues affect the reliability of inference based on the indirect comparison.
- The OS data from the NOVA study are immature (the OS median was not achievable for either arm of the study) for a cut-off date of 30 May 2016. Data from a longer follow-up period are not available.
- In the NOVA study, the survival analysis was performed using non-randomised data. The data maturity level was 75%. Therefore, the inference should be confirmed after data maturity. The EMA document indicates that patients will continue to be followed-up for assessment of overall survival (OS), and updated information will be provided in the final CSR (Clinical Study Report).

- In the NOVA study included on the side of the evaluated intervention, the safety assessment was performed for the general population (no data were available for the gBRCAmut patient population). Therefore, for STUDY 19, safety data related to the general female patient population were included in the analysis. Hence, the indirect safety comparison was conducted in the general population.
- The NOVA study did not report safety data according to the BRCA gene status. Therefore, it was not possible to perform the indirect comparison with olaparib in a population consistent with the STUDY 19 study, i.e., with a BRCA gene mutation. Only an indirect safety comparison was performed for the general population.
- The systematic reviews also included studies for first-line treatment, including niraparib.
- Only patients with a BRCA mutation were included in the Gong's 2020 systematic review.

(trade secret)

Economic evaluation, including estimates of cost to health outcomes achieved

Economic evaluation involves estimating and comparing the costs and health outcomes that may be associated with using the new therapy for an individual patient in place of already reimbursed therapies.

The costs of therapy are estimated in the currency of our country, and health outcomes are usually expressed in life-years gained (LYG) or quality-adjusted life years (QALY) as a result of the therapy.

By comparing the cost and outcome values of the new therapy to the costs and outcomes of already reimbursed therapies, one can answer the question of whether the health outcome achieved for an individual patient with the new therapy is associated with a higher cost compared to already reimbursed therapies.

The obtained results of the cost to health outcome ratio are compared with the use of the so-called break-even point, i.e. a result that indicates that given the wealth of our country (expressed in GDP), the maximum cost of the new therapy that is expected to produce a unit of health outcome (1 LYG or 1 QALY) compared to already available therapies should not exceed three times the GDP per capita.

Currently, the break-even point is PLN 155,514 (3 x PLN 51,838).

The cost to health outcome ratio does not estimate or determine the value of life, it only enables its assessment and, among others, on this basis, choose the therapy related to potentially the best outcome.

A cost-effectiveness analysis of Zejula (niraparib) for the treatment of adult patients with platinum-sensitive recurrent high-grade serous ovarian, fallopian tube or primary peritoneal cancer, after at least two prior lines of treatment with platinum derivative-containing chemotherapy regimens, with an objective response after the last treatment regimen in the case of patients with BRCA1 and/or BRCA2 gene mutations, a *cost-minimisation analysis* (CMA) was applied for the comparison between niraparib and olaparib. In contrast, for patients without BRCA1 and/or BRCA2 mutations, a *cost utility analysis* (CUA) was performed for the comparison between niraparib and no maintenance treatment.

Analysis assumptions:

- the public payer's (NHF) perspective (the analysis was not performed from the shared (NHF+patient) perspective, as estimates with the NHF perspective are identical),
- lifetime time horizon (40 years),
- included costs of active ingredients such as niraparib and olaparib, as well as substances used in chemotherapy (after disease progression); costs of outpatient consultation related to drug administration (niraparib, olaparib); costs of monitoring therapy and diagnostic testing within the drug programme; costs of treatment of adverse events; costs of monitoring patients remaining without maintenance treatment; costs of administering chemotherapy after relapse; costs of monitoring chemotherapy; cost of palliative care.

<u>Niraparib vs. olaparib (CMA) – population with BRCA1 and/or BRCA2 mutations</u>

According to the Applicant's estimates, the average costs of treating one patient with niraparib (trade secret)

The Zejula's net selling price estimated by the Applicant, at which the cost of its use is the same as the cost of olaparib therapy in the assumed time horizon, is (trade secret) for a package of 56 capsules a 100 mg and (trade secret) for a package of 84 capsules a 100 mg .

Niraparib vs. no maintenance treatment – population without BRCA1 and/or BRCA2 mutations

(trade secret)

At the current break-even point (PLN 155,514), the break-even price estimated based on the pharmaco-economic model provided by the Applicant is (trade secret) for a package of 56 capsules a 100 mg and (trade secret) for a package of 84 capsules a 100 mg .

The sensitivity analysis included deterministic and probabilistic analyses.

According to the sensitivity analysis' results relating to the comparison between niraparaib and no maintenance treatment (CUA) (trade secret)

Limitations

A key uncertainty in the results of the analysis stems from the lack of data concerning OS, particularly for the comparison between niraparib and no maintenance treatment. It should also be noted that according to the results of the clinical analysis (Oza's 2018 publication), there is no significant differences between niraparib and no maintenance treatment in terms of quality of life (EQ-5D-5L) of the non-GBRCAmut population. Therefore, inclusion of the difference in terms of this domain raises Agency's concerns and it has the potential to underestimate ICUR values.

When compared with olaparib, this should not affect the inference due to the assumption of no difference in terms of clinical efficacy. Nonetheless, it should be noted that the assumption of no difference in terms of clinical efficacy is based on the indirect comparison, hence there is no direct evidence to meet the said assumption. Moreover, treatment-related AEs showed statistically significant differences in favour of olaparib.

The lack of patient survival data from the NOVA study adds significant uncertainty to the inference, especially in light of the fact that the most recent data are from the cut-off point on 30 May 2016. The Applicant should have much more mature data that should be used for reducing uncertainty in the inference from the economic analysis.

Indication whether the circumstances referred to in Art. 13 sec. of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices (Journal of Laws of 2020, item 357, as amended).

If the applicant's clinical analysis does not include randomised clinical trials proving the superiority of the drug over health technologies already reimbursed in a particular indication, the official sales price of the drug must be calculated in such a way that the cost of use of the drug whose reimbursement is applied for is not higher than the cost of health technology with the most favourable ratio of obtained health outcome to the cost of obtaining them.

According to the Agency, due to the failure to present randomised clinical trials in the clinical analysis that would prove the superiority of niraparaib over olaparib, the circumstances of Art. 13 of the Reimbursement Act apply.

According to the Agency, due to the presentation of randomised clinical trials in the clinical analysis that would prove the superiority of niraparaib over no maintenance treatment, the circumstances of Art. 13 of the Reimbursement Act apply.

Assessment of the impact on the healthcare system, including the impact on the budget of the public payer

The health system impact assessment has two major parts.

First, a payer budget impact analysis allows estimating the potential expenses associated with public funding of the new therapy.

Estimates of expenses associated with the new therapy (the "tomorrow" scenario) are compared to how much is currently spent on treating a health problem (the "today" scenario). On this basis, it is possible to assess whether a new therapy will require more resources to treat a given health problem or is associated with savings in the payer's budget.

A budget impact assessment determines whether a payer has adequate resources to fund a particular technology.

The assessment of health system impact in the second part answers the question of how the decision to fund the new therapy may affect the organisation of service delivery (particularly in the context of adjusting to the requirements of delivering the new therapy) and the availability of other healthcare services.

The budget impact analysis should be performed for the decision to reimburse Zejula (niraparib) for the treatment of adult patients with platinum-sensitive recurrent high-grade serous ovarian, fallopian tube or primary peritoneal cancer, after at least two prior lines of treatment with platinum derivative-containing chemotherapy regimens and achieving an objective response (complete response or partial response according to RECIST 1.1 criteria) after the last treatment regimen containing platinum compounds, within the applied drug programme "Niraparib maintenance treatment in patients with recurrent platinum-sensitive advanced ovarian, fallopian tube or primary peritoneal cancer (ICD-10 C56, C57, C48)", was conducted from the perspective of the public payer (NHF) in a three-year time horizon (for the period 2021-2023). This perspective is the same as the shared (public payer+patient) perspective. Costs were assumed as in the economic analysis. The combined size of the target population (gBRCAmut and non-gBRCAmut) was estimated to be (trade secret) patients in Year I, (trade secret) patients in Year II, and (trade secret) patients in Year III of the analysis.

(trade secret)

The applicant has conducted a unidirectional sensitivity analysis:

(trade secret)

Limitations

The uncertainty in the estimates of the above-mentioned analysis is mainly influenced by the Applicant's assumptions concerning the assumed costs of the compared interventions, the size of the target population and the prevalence of the therapy.

(trade secret) reflects the coverage of maintenance treatment for the population in which the follow-up period is currently used. The results of the budget impact analysis for the non-gBRCAmut population have greater uncertainty compared to the results for the gBRCAmut population.

The Applicant determined the size of the population that is eligible for treatment within the drug programme based on the results of a survey conducted among Polish clinical experts. Given that the non-gBRCAmut population do receive treatment at this moment in time, there are no precise NHF data concerning the size of this population. Hence, the estimates of the non-gBRCAmut population size have greater uncertainty compared to estimates of the gBRCAmut population size.

When it comes to the prevalence of therapy, the Applicant's analysis assumed that NIR would acquire in the new scenario (trade secret) OLP shares in subsequent years of the analysis in patients starting treatment (gBRCAmut population). On the other hand, in the population of patients without the presence of a BRCA mutation, (trade secret) was assumed. In contrast, the opinions of clinical experts surveyed by the Agency indicated that the percentage of patients using OLP, if NIR was reimbursed, could be halved. In relation to the prevalence of therapy among patients in the non-gBRCAmut population, it was indicated that there would be a 70 p.p. reduction in the percentage of patients under observation (trade secret)

Given the above-mentioned limitations related to the estimation of the non-gBRCAmut population, the prevalence of the therapy and the fact that after the inclusion of Zejula (niraparib) in the reimbursement programme it will be the only therapeutic option reimbursed under the programme in this group of patients, the actual expenses related to niraparib reimbursement may increase in relation to the Applicant's estimates.

(trade secret)

Comments on the drug programme

Clinical experts did not comment on the drug programme in their opinions submitted to the Agency.

However, it should be emphasised that the agreed drug programme assumes the possibility of treating patients with an overall ECOG performance status of 0-2 with niraparaib. In contrast, patients with ECOG performance status 0-1 were eligible for the NOVA study. Moreover, according to Zejula's SmPC, there are no clinical data available for patients with an ECOG score of 2-4. Therefore, it is proposed to narrow the aforementioned

inclusion criterion in terms of the overall ECOG performance status of 0-1, which is in line with the inclusion criteria of the NOVA study.

Discussion of the solutions proposed in the rationalisation analysis

The rationalisation analysis aims to identify a mechanism whose introduction will result in the release of public funds in an amount corresponding to at least the increase in costs resulting from a positive decision on reimbursement of the health technology named in the application.

A rationalisation analysis is submitted if the budget impact analysis for the entity responsible for funding shows an increase in reimbursement costs.

As part of the rationalisation analysis, solutions were proposed to release public funds in excess of the payer's estimated (trade secret) expenses related to the reimbursement of Zejula (niraparib) under the agreed drug programme.

Discussion of recommendations in relation to the evaluated technology

The following clinical recommendations related to the indication named in the application were found:

- European Society for Medical Oncology, ESMO 2020 (European);
- National Comprehensive Cancer Network, NCCN 2020 (American);
- International Federation of Gynecology and Obstetrics, FIGO 2018 (international)
- Polish Society of Gynecologists and Obstetricians, PTG 2016 (Polish)
- Polish Society of Gynecologic Oncology, PTGO 2017 (Polish)
- Polish Society of Clinical Oncology, PTOK 2013 (Polish);

In conclusion, the most current European ESMO 2020 guidelines for the evaluated indication (maintenance treatment of patients with recurrent ovarian, fallopian tube or primary peritoneal cancer who responded after treatment with platinum derivatives) recommend the use of olaparib, niraparib or rucaparib, regardless of BRCA status.

The American NCCN 2020 guidelines, in the case when bevacizumab has not been previously used, recommend nirapargib or a follow-up period in the absence of a BRCA mutation, or additionally olaparib in the event of a germline or somatic BRCA1/2 mutation. However, if bevacizumab has been used as part of the primary therapy in the absence of a BRCA mutation, bevacizumab with olaparib or bevacizumab in monotherapy are recommended. In the case of patients with a BRCA1/2 mutation, either bevacizumab with olaparib or olaparib, or niraparib are recommended.

According to the 2018 FIGO guidelines, there is good evidence supporting the use of PARP inhibitors as maintenance therapy after the response to chemotherapy is achieved in platinum-sensitive patients with recurrent ovarian cancer, as well as monotherapy in selected patients with recurrent ovarian cancer.

According to the 2017 PTGO guidelines, PARP inhibitors are recommended for the treatment of patients with a low-maturity subtype of serous ovarian cancer with a BRCA1/2 gene mutation (germline and/or somatic) after treatment of platinum-sensitive relapse with platinum derivatives when the objective response is achieved.

It should be noted that the most recent Polish recommendations were published before the date of the first marketing authorisation of Zejula (niraparib) by the EMA, i.e. before 16 November 2017.

The search also yielded 7 reimbursement recommendations relating to the financing of the technology named in the application, including:

- 1 favourable one:
    - ✓ Haute Autorité de Santé HAS 2018 (France), according to which the actual benefit of Zejula is high, while also noting that Zejula provides little clinical added value compared to placebo in the registration indication.
- 3 conditionally favourable ones:

- ✓ Canadian Agency for Drugs and Technologies in Health CADTH 2020 (Canada), which recommends the use of niraparib provided that the cost-effectiveness ratio improves to an acceptable level.
- ✓ National Institute for Health and Care Excellence NICE 2018 (UK), which requires Cancer Drugs Fund funding (niraparib cannot be recommended for routine use as part of the NHS) due to the uncertainty of the clinical evidence and the resulting highly uncertain cost-effectiveness estimates.
- ✓ Scottish Medicines Consortium SMC 2018 (Scotland), according to which niraparib should only be used in patients who do not have germline BRCA gene mutations.

- 1 unfavourable one:
  - ✓ National Centre for Pharmacoeconomics NCPE 2019 (Ireland), which recommends that niraparib not be considered for reimbursement until cost-effectiveness is improved over existing therapies

In addition, the IQWIG 2020 recommendation (January) was found, according to which there was no proven additional benefit of niraparib compared to olaparib.

In contrast, according to the IQWIG 2020a recommendation (March), there is an hint of lesser benefit compared to the use of selected comparators.

According to the information provided by the Applicant (trade secret)

Basis for the recommendation

The recommendation was prepared under an order of 3 November 2020 of the Minister of Health (letter code: PLR.4500.293.2020.16.MO, PLR.4500.292.2020.14.MO) on preparation of the President's recommendation on evaluation of the Zejula drug (niraparib), hard capsules, 100 mg, 56, capsules, EAN code: 05909991425487; Zejula (niraparib), hard capsules, 100 mg, 84 capsules, EAN code: 05909991425494; as part of the drug programme "Treatment of patients with ovarian, fallopian tube or peritoneal cancer (ICD-10 C56, C57, C48)", based on Art. 35 sec. 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices (Journal of Laws of 2020, item 357, as amended), having received the Position of the Transparency Board No. 5/2021 of 25 January 2021 on the evaluation of the Zejula drug (niraparib) as part of the drug programme "Treatment of patients with ovarian, fallopian tube or peritoneal cancer (ICD-10 C56, C57, C48)".

PRESIDENT

dr n. med. Roman Topór-Mądry

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References

1. Position of the Transparency Board No. 5/2021 of 25 January 2021 on the evaluation of the Zejula drug (niraparib) as part of the drug programme "Treatment of patients with ovarian, fallopian tube or peritoneal cancer (ICD-10 C56, C57, C48)".
2. Report No. OT.4331.45.2020 "Application for inclusion in the reimbursement and setting the official trading price of the medicinal product Zejula (niraparib) as part of the drug programme: "Treatment of patients with ovarian, fallopian tube or peritoneal cancer (ICD-10 C56, C57, C48)". Verification analysis. Completion date: 14 January 2021