Niraparib (Zejula®) in patients with newly diagnosed advanced ovarian cancer

General information

Drug description [1]	Indication [2]
Niraparib is an inhibitor of poly(adenosine diphosphate–ribose) polymerase (PARP).	Niraparib is indicated 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.

Current treatment [3]

NICE recommends olaparib for maintenance treatment of BRCA-mutated ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy.

Regulatory status

EMA [3]

Approval status for this indication: On 17 September 2020, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Zejula®. The CHMP adopted an extension to the existing indication as follows:

- ❖ Niraparib is indicated 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.

Other indications:

- ❖ Niraparib is indicated 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.

- ✓ **Orphan status**
- ✓ **Medicine under additional monitoring**

FDA

Approval status for this indication: On 29 April 2020, the FDA approved Zejula® for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy [4].

Other indications: Niraparib is indicated:

- ❖ for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy
- ❖ for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:
  - a deleterious or suspected deleterious BRCA mutation, or
  - genomic instability and who have progressed more than six months after response to the last platinum-based chemotherapy [5].

Costs

84 Zejula® hard capsules 100 mg = € 7,665.74 [6]

Assuming a daily dose of 300 mg niraparib, costs for 1 cycle (28 days) of treatment = € 7,665.74.

Posology [7]

Patients should be encouraged to take their dose at approximately the same time each day. Bedtime administration may be a potential method for managing nausea.

Special warnings and precautions for use [7]

- ❖ **Haematologic adverse reactions**
  - Haematologic adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with niraparib. Patients with lower body weight or lower baseline platelet count may be at increased risk of Grade 3+ thrombocytopenia. Testing complete blood counts weekly for the first month, followed by monthly monitoring for the next 10 months of treatment and periodically after this time is recommended to monitor for clinically significant changes in any haematologic parameter during treatment. If a patient develops severe persistent haematologic toxicity including pancytopenia that does not resolve within 28 days following interruption, niraparib should be discontinued. Due to the risk of thrombocytopenia, anticoagulants and medicinal products known to reduce the thrombocyte count should be used with caution.
- ❖ **Myelodysplastic syndrome/acute myeloid leukaemia**
  - Cases of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) have been observed in patients treated with niraparib monotherapy or combination therapy in clinical trials and postmarketing. The duration of niraparib treatment in patients prior to developing MDS/AML varied from 0.5 months to > 4.9 years. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had received multiple platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow dysplasia. If MDS and/or AML are confirmed while on treatment with niraparib, treatment should be discontinued and the patient treated appropriately.

- **Hypertension, including hypertensive crisis**
  - Hypertension, including hypertensive crisis, has been reported with the use of niraparib. Pre-existing hypertension should be adequately controlled before starting niraparib treatment. Blood pressure should be monitored at least weekly for two months, monitored monthly afterwards for the first year and periodically thereafter during treatment with niraparib. Home blood pressure monitoring may be considered for appropriate patients with instruction to contact their health care provider in case of rise in blood pressure. Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the niraparib dose, if necessary. In the clinical programme, blood pressure measurements were obtained on Day 1 of each 28-day cycle while the patient remained on niraparib. In most cases, hypertension was controlled adequately using standard antihypertensive treatment with or without niraparib dose adjustment. Niraparib should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.
- **Posterior Reversible Encephalopathy Syndrome (PRES)**
  - There have been reports of PRES in patients receiving niraparib. PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging. In case of PRES, it is recommended to discontinue niraparib and to treat specific symptoms including hypertension. The safety of reinitiating niraparib therapy in patients previously experiencing PRES is not known.
- **Pregnancy/contraception**
  - Niraparib should not be used during pregnancy or in women of childbearing potential not willing to use reliable contraception during therapy and for 1 month after receiving the last dose of niraparib. A pregnancy test should be performed on all women of childbearing potential prior to treatment.
- **Lactose**
  - Niraparib hard capsules contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
- **Tartrazine (E 102)**
  - This medicinal product contains tartrazine (E 102), which may cause allergic reactions.

Study characteristics [1, 8]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
PRIMA/ENGOT-OV26/GOG-3012 NCT02655016	733	Oral niraparib 300 mg **OR** 200 mg[1] once daily in 28-day cycles for 36 m or until disease progression	Placebo	PFS	randomized, double-blind, placebo-controlled, phase 3 trial	-	GlaxoSmithKline	Link

Efficacy (I vs. C)

Median PFS (HRD population): 21.9 vs. 10.4 months (HR for disease progression or death 0.43; 95% CI 0.31-0.59; p<0.001)
Median PFS (overall population): 13.8 vs. 8.2 months (HR 0.62; 95% CI, 0.50-0.76; p<0.001)
OS rate (overall population; at the 24-month interim analysis): 84% vs. 77% (HR 0.70; 95% CI, 0.44-1.11), **median OS:** NA
Estimated probability of 24-month survival (HRD population): 91% vs. 85% (HR 0.61; 95% CI, 0.27-1.39)
PFS 2[2]: HR 0.84 (0.49-1.45) in the HRD population; HR 0.81 (0.58-1.14) in the overall population
QoL: The analysis of patient-reported outcomes did not indicate a between-group difference in health-related QoL scores.

Safety (I vs. C)

Overall population: niraparib group (n=484) vs. placebo group (n=244)
Grade ≥3 AEs: n=341/484 (70.5%) vs. n=46/244 (18.9%)
Treatment-related grade ≥3 AEs: 316/484 (65.3%) vs. n=16/244 (6.6%)
Serious treatment-related AEs: n=118/484 (24.4%) vs. n=6/244 (2.5%)
Death[3]: n=2/484 (0.4%) vs. n=1/244 (0.4%)
Discontinuation[4]: n=58/484 (12.0%) vs. n=6/244 (2.5%)

ESMO-MCBS version 1.1 (overall population)

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM

[1] In the initial protocol, all the patients started at a fixed dose of 300 mg once daily. The trial was amended on 27 November 2017, to incorporate an individualized starting dose of 200 mg once daily for patients with a baseline body weight of less than 77 kg, a platelet count of less than 150,000 per cubic millimeter, or both.
[2] PFS 2 = defined as time from randomization to progression while the patient was receiving a subsequent anticancer therapy
[3] death due to AE(s)
[4] discontinuation due to AE(s)

Original	NC	2b	>6 m	PFS: +5.6 m	0.62 (0.50-0.76)	HR ≤0.65 AND Gain ≥3 m	3	-	ND	-	3
Adapted	NC	2b	>6 m	PFS: +5.6 m	0.62 (0.50-0.76)	HR ≤0.65 AND Gain ≥3 m	3	+51.6% grade ≥3 AEs, +21.9 SAEs, +9.5% discontinuation	ND	-1	2

Risk of bias (study level)				
Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	unclear	yes	unclear[5]	yes[6]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, AML=acute myeloid leukaemia, BRCA=breast cancer gene, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, DNA=deoxyribonucleic acid,EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FIGO= International Federation of Gynecology and Obstetrics, FM=final magnitude of clinical benefit grade, HRD= homologous recombination deficiency, HR=hazard ratio, I=intervention, Int.=intention, MDS=myelodysplastic syndrome, n=number, NA=not available, NICE=National Institute for Health and Care Excellence, m=months, MG=median gain, n=number of patients, ND=no difference, NE=not estimable, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PRES=posterior reversible encephalopathy syndrome, QoL=quality of life, SAE=serious adverse event, ST=standard treatment

References:

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8. Supplement to: González-Martín A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2019;381:2391-402.

[5] Interim analysis data; the trial is ongoing until March 2024.
[6] The trial was designed by the sponsor, in collaboration with the European Network for Gynecological Oncological Trial (ENGOT) groups and the cooperative group leadership of GOG Partners. The sponsor was responsible for overseeing the collection, analysis, and interpretation of the data. The authors wrote the manuscript, with medical writing assistance funded by the sponsor.