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ADISINSIGHT REPORT

Niraparib: First Global Approval

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Abstract Oral niraparib, a highly-selective, potent poly (ADP-ribose) polymerase (PARP)-1 and PARP-2 inhibitor, is approved in the USA 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. It is also under regulatory review in the EU for use in maintenance treatment in patients with platinum-sensitive, recurrent epithelial ovarian cancer who are in response to platinum-based chemotherapy. In the multinational, phase 3 NOVA trial in adult patients with platinum-sensitive, recurrent ovarian cancer, niraparib significantly prolonged median progression-free survival, irrespective of the presence or absence of a germline *BRCA* (*gBRCA*) mutation and irrespective of the presence or absence of homologous recombinant deficiency. Niraparib is also in development for use in other solid tumours, including breast and prostate cancer. This article summarizes the milestones in the development of niraparib leading to its first global approval for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer.

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch and beyond.

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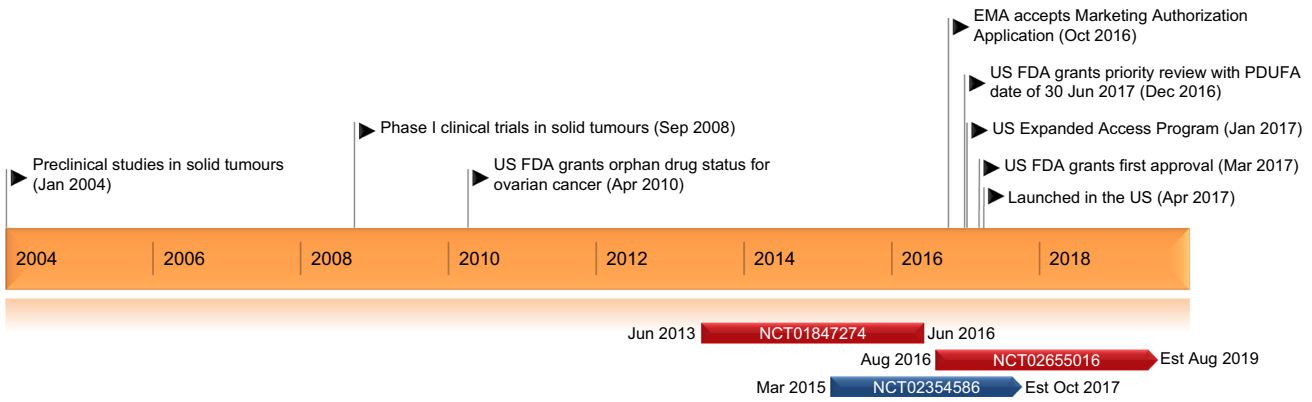
1 Introduction

Niraparib (Zejula™) is an oral, small molecule inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, including PARP-1 and PARP-2 [1, 2]. The drug is being developed by Tesaro Inc. for use in the treatment of various solid tumours [3]. The PARP family of enzymes (≥17 enzymes) are primarily involved in detecting single-stranded DNA breaks and triggering a cascade of events leading to the recruitment of DNA repair factors [1, 2]. Inhibition of PARPs is an effective strategy for treating cancers involving defects in DNA repair mechanisms that are caused by specific aberrations in DNA repair genes such as *BRCA1* and *BRCA2*, mutations that predispose individuals to hereditary breast and ovarian cancer. In preclinical studies, PARP inhibition of tumour cells deficient in *BRCA1* or *BRCA2* (i.e. *BRCA−/BRCA−* cancer cells) resulted in accumulation of DNA damage and consequent cell death, with cell death requiring both processes (i.e. inhibition of base excision repair mediated by PARP inhibition and defects in DNA double-strand break repair mediated by the loss of *BRCA1* and *BRCA2*) [1, 2].

Oral niraparib has been approved and launched in the USA for 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 [4]. Niraparib is also under regulatory review in the EU for use in maintenance treatment in patients with platinum-sensitive, recurrent epithelial ovarian cancer who are in response to platinum-based chemotherapy [5, 6]. Niraparib is also in development for use in other solid tumours, including breast and prostate cancer.

In the USA, the recommended regimen of niraparib is 300 mg once daily, with treatment continuing until disease progression or unacceptable adverse reaction [4].



Key milestones in the development of oral niraparib for the treatment of ovarian, fallopian tube or primary peritoneal cancer. *Est* estimated completion date

To manage adverse reactions, consider interruption of treatment, dose reductions or treatment discontinuation [4].

2 Scientific Summary

2.1 Pharmacodynamics

Niraparib is a potent, highly-selective PARP-1 and PARP-2 inhibitor (50% inhibitory concentrations of 3.8 and 2.1 nmol/L), with a 100-fold higher selectivity for these than for other PARP-family members (PARP-3, v-PARP and TANK-1) [7]. In cultured *BRCA1* and *BRCA2* deficient cancer cell lines, niraparib selectively inhibited cancer cell proliferation but not normal cell line proliferation, with niraparib-induced cytotoxicity in *BRCA*-deficient cells resulting from cell cycle arrest at the G2/M phase leading to apoptosis and mitotic catastrophe [1].

Preclinical studies [8–10] suggest that niraparib enhances the effects of radiation therapy in a p53-independent manner, based on in vitro studies [8–10] and murine xenograft models [9, 10]. In vitro, niraparib radiosensitized human breast, lung and/or prostate tumour cell lines, but not normal tissue-derived cell lines, in a p53-independent manner; an effect that appears to involve conversion of radiation-induced sublethal single stranded breaks into lethal double strand breaks [8–10]. In lung and breast cancer xenografts, including in a triple negative breast cancer xenograft model, niraparib enhanced the response to radiation therapy in a p53-independent manner using clinically relevant radiation-dose fractionation schedules [10]. Similarly, in a murine xenograft model of metastatic neuroblastoma, combining niraparib treatment with radiation therapy prolonged survival compared with either treatment alone, with mechanisms involved including augmentation of DNA repair, apoptotic cell death and, in mice treated with niraparib, down regulation of poly-ADP-ribose levels [9].

At recommended doses, niraparib has the potential to effect pulse rate and BP, which may be related to the pharmacological inhibition of the dopamine transporter, norepinephrine transporter and serotonin transporter [4]. In the NOVA trial in adult patients with platinum-sensitive, recurrent ovarian cancer (Sect. 2.3), mean greatest increases from baseline in pulse rate in the niraparib and placebo groups were 24.1 and 15.8 beats/min, with respective mean greatest increases in systolic BP of 24.5 and 18.3 mmHg and in diastolic BP of 16.5 and 11.6 mmHg. There were no large (>20 ms) changes in the mean corrected QT interval in patients treated with niraparib 300 mg once daily in a randomized, placebo-controlled trial in cancer patients ($n = 546$) [4].

2.2 Pharmacokinetics

Oral niraparib exhibits dose-proportional pharmacokinetics across the dose range of 30–400 mg [4]. Niraparib is rapidly absorbed with maximum plasma concentrations attained within 3 h. The mean absolute bioavailability of niraparib is ≈73%, with 83% of the drug bound to human plasma proteins. The average apparent volume of distribution (Vd) was 1220 (±1114) L; based on population pharmacokinetic analysis, the Vd of niraparib in cancer patients was 1074 L. Concomitant administration of niraparib with a high-fat meal had no clinically relevant effect on the pharmacokinetics of niraparib [4].

Niraparib is primarily metabolized by carboxylesterases (CEs) to form a major inactive metabolite (M1), which subsequently undergoes glucuronidation [4]. The mean elimination half-life of niraparib is 36 h following multiple daily 300 mg doses [4]. After a single radiolabeled 300 mg dose of niraparib, 47.5 and 38.8% of the administered dose

Features and properties of niraparib

Alternative names	MK-4827
Class	Antineoplastics, Benzamides, Indazoles, Piperidines, Small molecules
Mechanism of action	Poly(ADP-ribose) polymerase (PARP)inhibitor
Route of administration	Oral
Pharmacodynamics	Highly-selective, potent inhibitor of PARP-1 and -2, with antitumour activity in cells with mutations in the *BRCA1*/2 genes
Pharmacokinetics	Dose-proportional pharmacokinetics; rapidly absorbed, with a mean half-life of 36 h
Adverse events	
Most frequent (incidence ≥10%)	Haematological abnormalities, palpitations, gastrointestinal events, mucositis/stomatitis, dry mouth, fatigue/asthenia, urinary tract infection, aminotransferase enzyme elevations, myalgia, back pain, arthralgia, headache, dizziness, dysgeusia, insomnia, anxiety, nasopharyngitis, dyspnoea, cough, rash, hypertension
Occasional (incidence <1%)	Myelodysplastic syndrome/acute myeloid leukaemia
ATC codes	
WHO ATC code	LO1
EphMRA ATC code	L1
Chemical name	2-[4-(Piperidin-3-yl)phenyl]-2*H*-indazole-7-carboxamide 4-methylbenzenesulfonate hydrate

was recovered within 21 days in the urine and faeces, respectively; of which, unchanged drug accounted for 11 and 19% of the administered dose [11].

There was no clinically relevant effect on the pharmacokinetics of niraparib based on age (aged 18–65 years), race or mild to moderate renal impairment [4]. The effect of severe renal impairment or end-stage renal disease undergoing haemodialysis on the pharmacokinetics of niraparib is unknown, as is the effect of moderate or severe hepatic impairment [4].

No formal drug interaction studies have been conducted with niraparib [4]. In vitro, niraparib and the M1 metabolite do not inhibit CYPA2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 enzymes or induce CYP3A4; niraparib weakly induces CYP1A2. In vivo, niraparib is a substrate for CEs and UGTs. Niraparib, but not M1, is a weak inhibitor of BCRP, with neither niraparib nor M1 inhibiting p-glycoprotein (P-gp), bile salt export pump (BSEP), OATP1B1, OATP1B3, OCT1, OAT1, OAT3 or OCT2. Niraparib is a substrate for P-gp and BCRP, but not BSEP, with M1 not a substrate for any of these. Niraparib and M1 are not a substrate of OATP1B1, OATP1B3, OCT1, OAT1, OAT3 or OCT2 [4].

2.3 Therapeutic Trials

The efficacy of oral niraparib in adult patients with platinum-sensitive, recurrent, histologically-confirmed ovarian cancer was established in the pivotal, randomized, double-blind, multinational, phase 3 NOVA trial (NCT01847274) [12]. The trial enrolled two independent cohorts on the basis of the presence ($n = 203$) or absence ($n = 350$) of a germline *BRCA* mutation (the *gBRCA* and non-*gBRCA* cohorts). Patients received niraparib 300 mg or placebo once daily in 28-day cycles until disease progression, unacceptable toxicity, death, withdrawal of consent or loss to follow-up, whichever came first. Treatment could be interrupted for up to 28 days because of haematological toxicity, with dose reductions mandated for thrombocytopaenia (recurrence of grade 1 or occurrence of grade 2 or above). Across treatment groups, the median age of patients ranged from 57 to 63 years, approximately two-thirds of patients had an ECOG performance status of 0 and one-third an ECOG performance status of 1, and ≈50 and 33% of patients in the *gBRCA* and non-*gBRCA* cohorts had received ≥3 lines of chemotherapy. The primary endpoint was the duration of progression-free survival (PFS) in intent-to-treat analyses of the three predefined primary efficacy populations [the *gBRCA* cohort ($n = 138$ and 65 in the niraparib and placebo groups), a subgroup of patients with homologous recombinant deficiency (HRD) in the non-*gBRCA* cohort ($n = 106$ and 56), and the overall non-*gBRCA* cohort ($n = 234$ and 116)], using a predefined hierarchical testing procedure; if the primary endpoint was significant in the subgroup of patients with HRD tumours, then the overall non-*gBRCA* efficacy population was tested [12].

At a median follow-up of 16.9 months, median PFS was significantly ($p < 0.001$) prolonged in the niraparib groups compared with the placebo groups in the three predefined primary efficacy populations [12]. The risk of disease progression in niraparib recipients was reduced by 73% in the *gBRCA* cohort [median PFS 21.0 vs. 5.5 months in the placebo group; hazard ratio (HR) 0.27; 95% CI 0.17–0.41;

$p < 0.001$], by 62% in the subgroup of patients in the non-*gBRCA* cohort with HRD-positivity (median PFS 12.9 vs. 3.8 months; HR 0.38; 95% CI 0.24–0.59; $p < 0.001$) and by 55% in the overall non-gBRCA cohort (median PFS 9.3 vs. 3.9 months; HR 0.45; 95% CI 0.34–0.61; $p < 0.001$). For all three primary efficacy populations, with the exception of patients who were non-white or of unknown race (potentially reflecting low patient numbers in this subgroup), niraparib significantly (i.e. the 95% CIs for the HR did not cross 1) prolonged median PFS compared with placebo in all prespecified subgroup analyses, including based on age, geographic region, time to disease progression prior to study enrolment, bevacizumab use, best overall response to platinum therapy, platinum in the last and penultimate therapies, total number of previous platinum regimens and the cumulative number of previous chemotherapy regimens [12].

Secondary endpoints also favoured niraparib treatment over placebo at this timepoint in the *gBRCA* and overall non-*gBRCA* cohorts [12]. Median chemotherapy-free intervals in the niraparib and placebo group in the *gBRCA* cohort were 22.8 and 9.4 months (HR 0.26; 95% CI 0.17–0.41; $p < 0.001$) and in the overall non-*gBRCA* cohort were 12.7 and 8.6 months (HR 0.50; 95% CI 0.37–0.67; $p < 0.001$). The median time to first subsequent treatment was also significantly delayed in the niraparib groups in the *gBRCA* cohort (median 21.0 vs. 8.4 months in the placebo group; HR 0.31; 95% CI 0.21–0.48; $p < 0.001$) and the overall non-*gBRCA* cohort (median 11.8 vs. 7.2 months; HR 0.55; 95% CI 0.41–0.72; $p < 0.001$). Data relating to the time from randomization until progression during receipt of the next anticancer therapy after termination of study treatment (i.e. PFS2) were not mature at the time of the database unlock; preliminary data indicate that PFS2 was prolonged in the *gBRCA* ($p = 0.006$ vs. placebo) and non-*gBRCA* cohorts ($p = 0.03$) [12].

Prespecified exploratory analyses in the HRD-positive non-*gBRCA* subgroup indicated that niraparib significantly ($p \leq 0.02$ vs. placebo) prolonged median PFS in patients with wild-type *BRCA* and in those with a *BRCA* somatic mutation [12]. Niraparib treatment also prolonged PFS in patients with HRD-negative tumours in the non-*gBRCA* cohort ($p = 0.02$ vs. placebo) [12].

Niraparib treatment did not adversely impact health-related quality of life, with similar results for patient-reported outcomes in the niraparib and placebo groups [12].

2.4 Adverse Events

Oral once-daily niraparib had a manageable safety profile in adults with platinum-sensitive, recurrent ovarian cancer in the pivotal NOVA trial [12]. Although at least 95% of patients experienced at least one treatment-emergent adverse event (TEAE; 100% in the niraparib group and 95.5% in the placebo group; $n = 367$ and 179), relatively few patients discontinued treatment because of these events

Key clinical trials of niraparib

Drug(s)	Cancer indication	Phase	Status	Location(s)	Identifiers	Sponsors
Niraparib vs. placebo	Ovarian	3	Completed	Multinational	NCT01847274 (NOVA); PR-30-5011-C	Tesaro Inc.
Niraparib vs. placebo	Ovarian	3	Recruiting	Multinational	NCT02655016 (PRIMA); PR-30-5017-C	Tesaro Inc.
Niraparib	Ovarian	2	Recruiting	Canada/USA	NCT02354586 (QUADRA); PR-30-5020-C	Tesaro Inc.
Niraparib ± bevacizumab vs. bevacizumab	Ovarian	1/2	Recruiting	Denmark	NCT02354131 (AVANOVA); ENGOT-OV24-NSGO/AVANOVA	Nordic Society for Gynaecologic Oncology
Niraparib + pembrolizumab	Breast or ovarian	1/2	Recruiting	USA	NCT02657889 (TOPACIO); 3000-PN162-01-001	Tesaro Inc.
Niraparib vs. physician's choice	Breast	3	Recruiting	Multinational	NCT01905592 (BRAVO); PR-30-5010-C	Tesaro Inc
Niraparib	Breast	2	Not yet open for recruiting	Netherlands	NCT02826512; M14ABC	Netherlands Cancer Institute
Niraparib	Prostate	2	Recruiting	Multinational	NCT02854436 (Galahad); CR108208; 64091724PCR2001; 2016-002057-38	Janssen Research and Development, LLC
Niraparib	Endometrial	2	Not yet open for recruiting	Canada	NCT03016338; NEC	University Health Network, Toronto

(14.7 vs. 2.2%). In the niraparib group, TEAEs lead to treatment interruption in 68.9% of patients (vs. 5.0% in the placebo group) and dosage reductions in 66.5% (vs. 14.5%). The incidence of TEAES of at least grade 3 in the niraparib and placebo groups was 74.1 and 22.9%, most of which were haematological abnormalities. No patients died during the treatment period, with three deaths from myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) occurring during the follow-up period; two of which were considered by investigators to be treatment-related (one in each group) [12].

TEAEs of any grade occurring in at least 15% of patients in the niraparib group were nausea (73.6 vs. 35.2% in the placebo group), thrombocytopaenia (61.3 vs. 5.6%), fatigue (59.4 vs. 41.3%), anaemia (50.1 vs. 6.7%), constipation (39.8 vs. 20.1%), vomiting (34.3 vs. 16.2%), neutropaenia (30.2 vs. 6.1%), headache (25.9 vs. 9.5%), decreased appetite (25.3 vs. 14.5%), insomnia (24.3 vs. 7.3%), abdominal pain (22.6 vs. 29.6%), dyspnoea (19.3 vs. 8.4%), hypertension (19.3 vs. 4.5%), diarrhoea (19.1 vs. 20.7%), dizziness (16.6 vs. 7.3%) and cough (15.0 vs. 4.5%) [12].

The most common (incidence $\geq$10% in either group) treatment-emergent haematological adverse events occurring in the niraparib and placebo groups were thrombocytopenia (61.3 vs. 5.6%), anaemia (50.1 vs. 6.7%) and neutropaenia (30.2 vs. 6.1%) [12]. Most of these events occurred within the first three treatment cycles and very few patients discontinued treatment because of these events ($\leq$3.3% in the niraparib group and $\leq$0.06% in the placebo group). Most haematological adverse events were manageable with dose modifications and/or interruptions. In the niraparib group, common grade 3 or 4 haematological adverse events were thrombocytopaenia (33.8% of patients), anaemia (25.3%0 and neutropaenia (19.6%) [12]. In clinical studies, MDS/AML was reported in 0.9% of 751 niraparib-treated patients after up to 2 years' treatment [4].

In the NOVA trial, grade 3 or 4 hypertension occurred in 9% of patients in the niraparib group and 2% of patients in the placebo group, with <1% of patients discontinuing treatment because of these events [4].

2.5 Ongoing Clinical Trials

A phase 3 trial is currently recruiting patients with advanced ovarian cancer following response to front-line platinum-based chemotherapy to evaluate niraparib maintenance therapy (NCT02655016; PRIMA) [13]. A phase 2 trial will evaluate niraparib treatment in patients with ovarian cancer who have received three or four previous chemotherapy regimens (NCT02354586; QUADRA; recruiting) [14]. The phase 3 BRAVO trial will evaluate niraparib treatment in HER2-negative, germline *BRCA* mutation-positive breast cancer (NCT01905592; recruiting) [15]; a phase 2 trial will evaluate niraparib in patients with advanced, *BRCA1*-like, HER2-negative breast cancer (NCT02826512; not yet open for recruiting). Niraparib treatment will also be investigated in phase 2 trials in patients with recurrent endometrial cancer (NCT03016338; not yet open for recruiting) and in men with metastatic castration-resistant prostate cancer (NCT 02854436; Galahad; recruiting).

Several planned or ongoing trials will evaluate niraparib combination therapy. A phase 1/2 trial will evaluate niraparib plus bevacizumab combination therapy in patients with HRD platinum-sensitive ovarian cancer (NCT02354131; AVANOVA; recruiting) [16, 17]. A phase 1/2 trial will evaluate niraparib in combination with pembrolizumab in patients with triple-negative breast cancer or ovarian cancer (NCT02657889; TOPACIO; recruiting) [18]. Phase 1 trials will evaluate niraparib in combination with enzalutamide in patients with metastatic, castrate-resistant prostate cancer (NCT02500901; ongoing trial) [19] and in combination with radium Ra 223 dichloride in patients with hormone-resistant prostate cancer (NCT03076203; not yet open for recruiting). Niraparib is also being investigated in a phase 1 trial in combination with temozolomide or irinotecan in patients with previously-treated, incurable Ewing's sarcoma (NCT02044120; recruiting).

3 Current Status

Niraparib received its first global approval on the 27th of March 2017 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 in the USA.

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