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ADISINSIGHT REPORT

Rucaparib: First Global Approval

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Abstract Rucaparib (Rubraca™) is an oral, small molecule, poly (ADP-ribose) polymerase inhibitor being developed by Clovis Oncology, Inc. (Boulder, CO, USA) for the treatment of solid tumours. It has been approved in the USA as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. A marketing authorization application for rucaparib for the same indication has been submitted to the European Medicines Agency. Rucaparib is also under phase II or III investigation in ovarian, breast and prostate cancer. This article summarizes the milestones in the development of rucaparib leading to this first approval for ovarian cancer.

1 Introduction

Rucaparib (Rubraca™) is an oral, small molecule inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP-1, -2 and -3 [1, 2]. It is being developed by Clovis Oncology, Inc. (Boulder, CO, USA) for the treatment of solid tumours. PARP enzymes play a key role in DNA repair and inhibition of these enzymes forms toxic PARP-DNA complexes in cells, resulting in DNA damage, ultimately leading to cell death [1, 2]. PARP inhibition is synthetically lethal in cells with homologous recombination deficiency (HRD), such as those with mutation in the *BRCA1* and/or *BRCA2* genes or high genomic loss of heterozygosity (LOH) [2, 3].

Oral rucaparib has been approved in the USA as monotherapy for the treatment of patients with deleterious *BRCA* mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies [1]. Patients are selected for rucaparib treatment based on a US FDA-approved companion diagnostic (Sect. 2.5). Rucaparib received accelerated approval based on objective response rate (ORR) and duration of response seen in phase II trials (Sect. 2.3.1). Continued approval of rucaparib in this indication may be contingent upon verification and description of clinical benefit in confirmatory trials [1]. A marketing authorization application for rucaparib in ovarian cancer has been submitted to the European Medicines Agency.

Rucaparib is also under phase II or III investigation in ovarian, breast and prostate cancer. Use of an intravenous formulation of rucaparib for the treatment of malignant melanoma was explored early in the development, prior to the acquisition of rucaparib by Clovis Oncology [4], and has since been discontinued.

1.1 Company Agreements

Rucaparib was originated by Cancer Research Technology owned by Cancer Research UK and was licensed to Agouron Pharmaceuticals (later Pfizer). In June 2011,

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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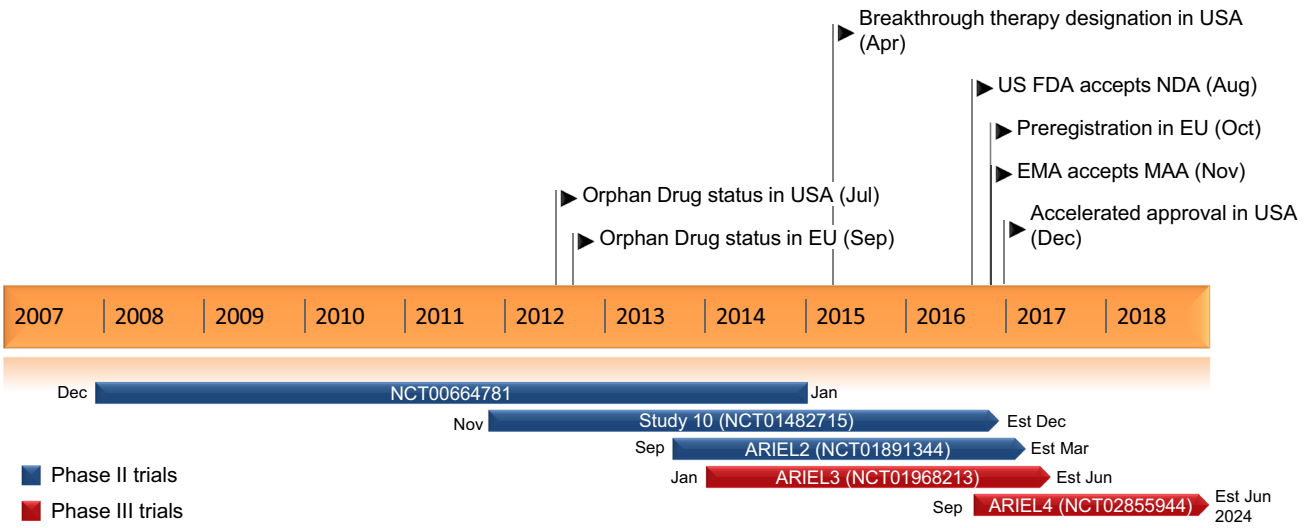


Key milestones in the development of oral rucaparib monotherapy for the treatment of ovarian cancer. *Est* estimated completion date, *MAA* marketing authorization application, *NDA* new drug application

Clovis Oncology entered into a license agreement with Pfizer under which Clovis Oncology gained rights for global development and commercialisation of rucaparib [5]. Pfizer has received an upfront fee and is eligible for milestone and royalty payments from Clovis Oncology [5]. Pfizer is not involved in the development of rucaparib any longer, but the agreement will remain effective until expiration of the royalty and sublicense revenue obligations of Clovis Oncology to Pfizer.

In April 2012, Clovis Oncology gained from AstraZeneca exclusive rights to patents and patent applications for PARP inhibitors (including rucaparib) in certain indications. AstraZeneca has received an upfront fee and is eligible for milestone and royalty payments from Clovis Oncology [6]. Clovis Oncology signed a long-term manufacturing agreement for rucaparib with Lonza in October 2016 [7].

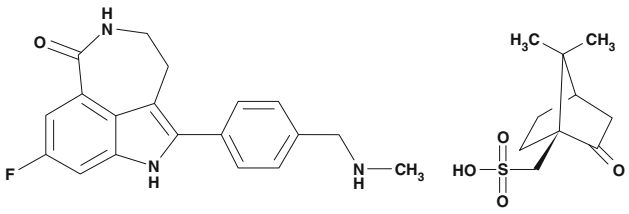
2 Scientific Summary

2.1 Pharmacodynamics

Rucaparib is a potent PARP inhibitor at nanomolar concentrations [8], with potentially greater PARP inhibitory activity than olaparib or niraparib [9]. Following a single oral or intraperitoneal dose of rucaparib in tumour-bearing mice, the drug accumulated and was retained in tumours, and inhibited PARP enzymes for 7 days [10]. Intravenous [11] or oral [12] rucaparib inhibited PARP-1 enzyme activity in peripheral blood lymphocytes from patients with metastatic melanoma [11], or advanced ovarian or breast cancer [12]. A single oral dose of 92 mg inhibited the enzyme activity by a mean ≥90% from pretreatment levels at 24 h post-dose; however, a continuous dosing schedule was necessary to maintain the inhibition [12].

Rucaparib showed PARP-dependent and -independent cytotoxic mechanisms in cancer cells [8, 13]. In vitro, rucaparib was more cytotoxic than olaparib [14]. The cytotoxicity of rucaparib is increased in cancer cells with mutations in the *BRCA1/2* genes and other DNA repair genes [13, 15, 16]. Rucaparib reduced tumour growth in mouse xenograft models of human cancer with [10, 15, 16] or without [1] *BRCA* mutations. An HRD signature (Sect. 2.3.1) and a two-gene (*CYB5R2*, *GSTT1*) signature [17] have been shown to predict response to rucaparib.

Rucaparib showed synergistic or additive interactions with commonly used chemotherapeutic agents, in vitro and in vivo [13, 18–21]. It sensitized cancer cells to platinum therapy [16, 22], chemoradiotherapy [23], irradiation [24, 25] and radiopharmaceuticals [25, 26]. Rucaparib is known to induce vasodilation, which may increase accumulation of cytotoxic drugs in cancer cells by increasing tumour perfusion [27–29].



Chemical structure of rucaparib

Mechanisms of resistance to rucaparib therapy include recovery of HRD [30] and defects in non-homologous end joining [31]. Rucaparib is efficiently transported by multidrug efflux transporters, such as BRCP and P-glycoprotein, and therefore, they can restrict oral bioavailability and brain penetration of rucaparib [32, 33]. Rucaparib may partially offset its efficacy by activating the phosphatidylinositol 3-kinase (PI3K)/AKT signalling pathway; overexpression of the *INPP4B* gene, which negatively regulates this pathway, enhanced the antitumor activity of rucaparib in cancer cells [34].

2.2 Pharmacokinetics

All rucaparib pharmacokinetic data discussed herein are from patients with cancer. Rucaparib showed linear, dose-proportional and time-independent pharmacokinetics over a dose range of 240–840 mg twice daily [1]. Following the recommended 600 mg twice daily dosage, the median T_{max} [time to maximal plasma concentration (C_{max})] was 1.9 h. When taken with a high-fat meal, C_{max} and the area under the plasma concentration-time curve from time 0 to 24 h ($AUC_{0–24}$) were increased by 20 and 38%, respectively, and T_{max} was delayed by 2.5 h relative to dosing under fasted condition; however, the effect is not considered clinically significant and rucaparib can be taken with or without food. Rucaparib immediate-release tablet has a mean absolute bioavailability of 36% [1]. Following administration of 600 mg twice daily in a 28-day cycle, rucaparib steady state was observed on day 15 of cycle 1 [3]. At steady state, accumulation of rucaparib was 3.5 to 6.2 fold at tested dose levels [1].

Rucaparib had a volume of distribution of 113–262 L following a single intravenous dose of 12–40 mg [1]. At therapeutic concentrations, in vitro plasma protein binding of rucaparib was 70% in human plasma, and the drug preferentially distributed into red blood cells (blood to plasma concentration ratio 1.83). In vitro, rucaparib was metabolized primarily by cytochrome P450 (CYP) enzyme CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4. Rucaparib steady-state concentrations did not differ markedly across CYP2D6 or CYP1A2 genotype subgroups [1].

Oral rucaparib had a mean terminal half-life of 17–19 h after a single 600 mg dose and an apparent clearance of 15.3–79.2 L/h after multiple doses of 600 mg twice daily [1]. After a single intravenous dose of rucaparib, 11% of the dose was recovered in the urine over 24 h, indicating that this is not the major excretion route of the drug [11].

Mild or moderate renal impairment increased rucaparib exposure by 15 and 32%, respectively, versus normal renal function; mild hepatic impairment did not markedly affect the pharmacokinetics of rucaparib [1]. Starting dosage adjustment is not recommended in these patients. The pharmacokinetics of rucaparib in patients with severe renal impairment (creatinine clearance <30 mL/min) and in those with moderate to severe hepatic impairment (total bilirubin >1.5 times the upper limit of normal) are unknown, and therefore, starting dosage recommendation is not available for these patients [1].

Interactions of rucaparib with enzymes and transporters were evaluated in vitro. Rucaparib is a substrate and inhibitor of BCRP and P-glycoprotein [1]. It inhibits (CYP1A2, CYP2C19, CYP2C9, CYP3A, and CYP2C8, CYP2D6, UGT1A1 to a lesser extent), induces (CYP1A2) or down-regulates (CYP2B6, CYP3A4) several CYP enzymes. Rucaparib inhibits several transporter proteins potently (MATE1 and MATE2-K), moderately (OCT1) or

Features and properties of rucaparib

Alternative names	AG 014699; AG-14699; CO-338; PF-01367338; PF-1367338; RUBRACA; Rucaparib camsylate
Class	3-Ring heterocyclic compounds, antineoplastics, azepines, indoles, small molecules
Mechanism of action	Poly(ADP-ribose) polymerase inhibitors
Route of administration	Oral
Pharmacodynamics	Shows antitumour activity in cells with mutations in the *BRCA1/2* and other DNA repair genes
Pharmacokinetics	Displays linear, dose-proportional, time-independent pharmacokinetics; T_{max} 1.9 h
Most frequent adverse events	Nausea, fatigue (including asthenia), vomiting, anaemia, abdominal pain, dysgeusia, constipation, decreased appetite, diarrhoea, thrombocytopenia, dyspnoea, increase in creatinine, ALT, AST and cholesterol, and decrease in haemoglobin, lymphocytes, platelets and neutrophils
WHO ATC code	L01X-X55 (Rucaparib)
EphMRA ATC code	L1 (Antineoplastics)
Chemical name	8-fluoro-2-{4-[(methylamino)methyl]phenyl}-1,3,4,5-tetrahydro-6H-azepino[5,4,3-cd]indol-6-one ((1S,4R)-7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)methanesulfonic acid salt

weakly (MRP4, OATP1B1, OATP1B3, OAT1 and OAT3). The clinical relevance of these interactions is not clear. Concomitant administration of rucaparib with proton pump inhibitors has no clinically meaningful change in rucaparib steady-state exposure [1].

2.3 Therapeutic Trials

2.3.1 Ovarian Cancer

Rucaparib efficacy data are available from fully published articles [3, 12], US prescribing information [1], a conference presentation [35], posters [36, 37] and an abstract [38].

In a pooled analysis of ARIEL2 (NCT01891344) and Study 10 (NCT01482715), rucaparib treatment produced an ORR [assessed by the investigator using Response Evaluation Criteria In Solid Tumours (RECIST) 1.1] of 54% (95% CI 44–64) in 106 evaluable patients with high-grade ovarian cancer who had progressed on ≥2 prior platinum-based chemotherapies [1, 35]. Complete and partial responses were seen in 9 and 45% of patients, respectively [1, 35]. The median duration of response was 9.2 months (95% CI 6.6–11.6) [1, 35]. The median progression-free survival (PFS) was 10.0 months (95% CI 7.3–12.5) and 41% of patients were progression-free at 12 months [35]. ARIEL2 was a two-part, single-group, open-label, multinational, phase II trial [3] and Study 10 was a phase I/II trial [36]. Women with recurrent ovarian cancer with a deleterious *BRCA1/2* mutation (germline or somatic [3] or germline [36]) were among those included in these trials. All patients received rucaparib 600 mg twice daily as monotherapy until disease progression or unacceptable toxicity [1]. This was the recommended phase II/III dose identified in the phase I portion of the Study 10 in patients with ovarian or other solid tumours ($n = 56$) [38].

In pooled subgroup analyses of ARIEL2 and Study 10, ORRs did not differ (95% CI overlapped) between germline and somatic mutations (53.4 and 46.2%), *BRCA1* and *BRCA2* mutations (53.7 and 53.8%), 2 and ≥2 prior chemotherapy (68.3 and 53.8%) or 2 and ≥2 prior platinum-based regimen (65.0 and 53.8%) subgroups [35]. In platinum-refractory, -resistant and -sensitive subgroups, the ORR (95% CI) was 0% (0.0–41.0), 25.0% (8.7–49.1) and 65.8% (54.3–76.1), respectively. In patients with a progression-free interval (after the latest platinum therapy) of <6, ≥6 to 12, and >12 months, the ORR (95% CI) was 18.5% (6.3–38.1), 62.5% (48.6–75.1) and 73.9% (51.6–89.8), respectively [35].

ARIEL2 (part 1) results suggest that an HRD signature can be a predictive biomarker of response to rucaparib in women with ovarian cancer [3]. Patients were classified into three predefined subgroups: deleterious *BRCA1/2* germline or somatic mutation (*BRCA*-mutant; $n = 40$); *BRCA* wild-type with high or low LOH [high and low LOH, respectively; $n = 82$ and 70]. The median duration of rucaparib treatment was 5.7 months. The median PFS (95% CI) was 12.8 months (9.0–14.7) in the *BRCA*-mutant, 5.7 months (5.3–7.6) in the high LOH and 5.2 months (3.6–5.5) in the low LOH subgroups. The median PFS was significantly longer in the *BRCA* mutant [hazard ratio (HR) 0.27; 95% CI 0.16–0.44; $p < 0.0001$)] and high LOH (0.62; 0.42–0.90; $p = 0.011$) subgroups, compared with the low LOH subgroup. The proportion of patients with PFS (95% CI) at 12 months in these subgroups was 50% (33–65), 28% (18–39), and 10% (4–19), respectively [3].

In ARIEL2 (part 1), consistent with PFS, confirmed ORRs (by RECIST 1.1) were significantly higher in the *BRCA*-mutant (80%; $p < 0.0001$) and high LOH (29%; $p = 0.0033$) subgroups than in the low LOH subgroup (10%) [3]. A similar trend in ORRs were seen when RECIST 1.1 plus cancer antigen (CA)-125 criteria were applied. The median duration of response was also significantly ($p < 0.05$) longer in the *BRCA*-mutant (9.2 months) and high LOH (10.8 months) subgroups than in the low LOH subgroup (5.6 months). ORRs were generally similar irrespective of whether the *BRCA* mutation was germline or somatic, or *BRCA1* or *BRCA2*. Among patients with *BRCA* wild-type tumours, genomic LOH predicted response to rucaparib with a significantly greater sensitivity (78%) than a mutation in non-*BRCA* homologous recombination genes (11%; $p < 0.0001$) or methylation of *BRCA1* or *RAD51C* (48%; $p < 0.021$) [3]. The HRD signature identified in part 1 will be further refined (using a higher LOH cut-off) and prospectively applied to ARIEL2 (part 2) and ARIEL3 (Sect. 2.6) [3, 37].

In the phase II portion of the Study 10, rucaparib produced an ORR of 67 and 77% by RECIST 1.1 and RECIST 1.1 plus CA-125 criteria, respectively, in patients with ovarian cancer ($n = 39$ evaluable) [36]. In subgroup analyses, the ORR (by RECIST 1.1) was 67 and 73% in patients with *BRCA1* ($n = 27$) or *BRCA2* ($n = 11$) mutation, 64 and 82% in patients with a progression-free interval (after the latest platinum therapy) of 6–12 ($n = 25$) and >12 ($n = 11$) months, and 69% in those who had received ≥3 prior chemotherapy regimens ($n = 13$). The disease control rate (complete or partial response plus stable disease for >24 weeks) was 87% [36].

In an investigator-initiated trial (NCT00664781), a continuous dosing schedule of oral rucaparib (92–480 mg once daily or 240–600 twice daily within a 21-day cycle) was associated with disease control (complete or partial response plus stable disease for ≥12 weeks) in 12 of 13 patients with ovarian cancer [12]. This was an open-label, phase II trial in which 78 women with advanced breast or ovarian cancer harbouring proven germline *BRCA1/2*

mutations were treated with intermittent or continuous schedules of intravenous or oral rucaparib [12].

2.3.2 Other Malignancies

In an investigator-initiated phase II trial (NCT01074970), rucaparib (intravenous and then oral) plus cisplatin given after preoperative neoadjuvant therapy did not improve 2-year disease-free survival in patients with triple negative breast cancer [$n = 128$] (abstract presentation [39]). The dosage of rucaparib administered in this study was substantially lower than the recommended phase II/III dose of oral rucaparib 600 mg twice daily (Sect. 2.3.1) [39].

In the RUCAPANC trial (NCT02042378), oral rucaparib was associated with clinical benefit in some patients with relapsed pancreatic cancer and a known deleterious germline or somatic *BRCA* mutation [$n = 19$] (poster presentation [40]). The investigator-assessed ORR (by RECIST 1.1) was 15.8% (95% CI 3.4–39.6) and the disease control rate (complete or partial response plus stable disease for ≥12 weeks) was 31.6% (95% CI 12.6–56.6). RUCAPANC was an open-label, phase II trial in which patients received rucaparib 600 mg twice daily in 28-day cycles until disease progression [40].

In a phase II study sponsored by Pfizer, an intravenous formulation of rucaparib in combination with temozolomide was associated with confirmed partial response (17.4% of patients; 95% CI 7.9–31.6) and stable disease for ≥24 weeks (17.4%; 7.9–31.6) in some patients with metastatic melanoma ($n = 46$) [4]. The median PFS and overall survival was 3.5 (95% CI 2.0–6.2) and 9.9 (6.2–14.7) months, respectively. The 1-year survival rate was 40%. Rucaparib was administered at 12 mg/m^2 1 h before temozolomide 200 mg/m^2 (starting dosages) on days 1–5 in a 28-day cycle [4].

2.4 Adverse Events

Monotherapy with oral rucaparib 600 mg twice daily had a manageable tolerability profile in women with high-grade ovarian cancer who had progressed on ≥2 prior platinum-based chemotherapies in the pooled analysis of ARIEL2 and Study 10 ($n = 377$) [1, 35]. The median duration of treatment was 5.5 months [1] and the median dose intensity

Key clinical trials of rucaparib

Drug(s)	Indication	Phase	Status	Location	Trial identifier	Sponsors
Rucaparib, chemotherapy	Ovarian cancer	III	Recruiting	Multinational	NCT02855944 (ARIEL4)	Clovis Oncology
Rucaparib, placebo	Ovarian cancer	III	Ongoing	Multinational	NCT01968213 (ARIEL3)	Clovis Oncology
Rucaparib	Ovarian cancer	II	Ongoing	Multinational	NCT01891344 (ARIEL2)	Clovis Oncology
Rucaparib	Ovarian cancer, solid tumours	I/II	Ongoing	Multinational	NCT01482715 (Study 10)	Clovis Oncology
Rucaparib	Ovarian or breast cancer	II	Completed	UK	NCT00664781	Cancer Research UK
Rucaparib + bevacizumab	Ovarian cancer	II	Planned	NA	NA	NA
Rucaparib + atezolizumab	Ovarian cancer	Ib	Planned	NA	NA	Clovis Oncology, Genentech
Rucaparib, abiraterone acetate, enzalutamide, docetaxel	Prostate cancer	III	Recruiting	Multinational	NCT02975934 (TRITON3)	Clovis Oncology
Rucaparib	Prostate cancer	II	Recruiting	Multinational	NCT02952534 (TRITON2)	Clovis Oncology
Rucaparib	Breast cancer	II	Ongoing	UK	EudraCT2014-003319-12 (RIO)	The Royal Marsden NHS Foundation Trust, The Institute of Cancer Research
Rucaparib	Breast cancer	II	Recruiting	France	NCT02505048 (RUBY)	UNICANCER
Rucaparib + cisplatin, cisplatin	Breast cancer	II	Ongoing	USA	NCT01074970	Hoosier Cancer Research Network
Rucaparib	Pancreatic cancer	II	Completed	Multinational	NCT02042378 (RUCAPANC)	Clovis Oncology
Rucaparib	Solid tumours	I	Recruiting	Hungary	NCT02986100 (AME)	Clovis Oncology
Rucaparib + carboplatin	Solid tumours	I	Completed	UK	NCT01009190	Clovis Oncology

NA not available

was 0.92 [35]. Treatment-related all-grade and grade ≥3 adverse events were reported in 96 and 47% of patients, respectively [35]. Adverse events led to dose interruption or reduction in 62% of patients, most commonly because of anaemia (27%) and fatigue/asthenia (22%) [1]. Adverse events led to treatment discontinuation in 10% of patients, most commonly because of fatigue/asthenia (2%) [1]. Eight patients (2%) died because of progression of malignancy and one patient because of sepsis, which was assessed by the investigator as not related to rucaparib [35].

In the pooled analysis, the most common (incidence ≥20% for all grade) treatment-emergent adverse events (all grade; grade 3–4) were: nausea (77%; 5%), asthenia/fatigue (77%; 11%), vomiting (46%; 4%), anaemia (44%; 25%), constipation (40%; 2%), decreased appetite (39%; 3%), dysgeusia (39%; 0.3%), diarrhoea (34%; 2%), abdominal pain (32%; 3%), dyspnoea (21%; 0.5%) and thrombocytopenia (21%; 5%) [35]. Laboratory abnormalities reported in ≥35% of patients included (any worsening grade; shift to grade 3–4): an increase in creatinine (92%; 1%), ALT (74%; 13%), AST (73%; 5%) or cholesterol (40%; 2%), and a decrease in haemoglobin (67%; 23%), lymphocytes (45%; 7%), platelets (39%; 6%) or neutrophils (35%; 10%) [1]. AST and ALT levels normalised over time with continued treatment [35].

In the pooled analysis, myelodysplastic syndrome/acute myeloid leukaemia were reported in <1% of patients [35]. Therefore, patients should be monitored for haematological toxicity at baseline and monthly thereafter [1]. Based on its mechanism of action and data from animal studies, rucaparib can cause embryo-foetal toxicity when administered to pregnant women [1]. Hence, contraception is advised in women of reproductive potential during and 6 months after rucaparib treatment [1].

At steady state, rucaparib 600 mg twice daily increased Fridericia's formula-corrected QT interval from baseline by a mean 14.9 ms in patients with solid tumours [1].

2.5 Companion Diagnostic

Foundation Medicine has developed a companion diagnostic (FoundationFocus™ CDx$_{BRCA}$) for rucaparib [41]. It is a next-generation sequencing-based in vitro device for the qualitative detection of *BRCA1/2* sequence alteration in ovarian tumour tissue [41]. The test is approved by the US FDA for selecting patients for the treatment of ovarian cancer with rucaparib [1, 41].

2.6 Ongoing Clinical Trials

The pivotal programme for rucaparib in ovarian cancer is ongoing and includes two phase III trials, ARIEL3 (NCT01968213) [3] and ARIEL4 (NCT02855944) [35]. These trials are evaluating rucaparib in maintenance (ARIEL3) or treatment (ARIEL4) settings. ARIEL4 will compare rucaparib with standard chemotherapy. ARIEL2 and Study 10 are also still ongoing. An investigator-initiated phase II trial is planned to evaluate rucaparib in combination with bevacizumab (as a first-line maintenance therapy) and a phase Ib trial is planned in collaboration with Genentech to investigate the combination of rucaparib with atezolizumab in women with advanced ovarian cancer [42].

With regard to other indications, phase II (TRITON2; NCT02952534) and phase III (TRITON3; NCT02975934) trials are investigating rucaparib in metastatic castration-resistant prostate cancer. In addition to NCT01074970, two other investigator-initiated phase II trials are evaluating rucaparib in breast cancer [RIO (EudraCT2014-003319-12); RUBY (NCT02505048)]. The RIO trial is investigating the activity of rucaparib using Ki67 as a surrogate marker in patients with primary, sporadic, triple-negative or *BRCA1/2*-positive breast cancer [43]. A phase I trial is investigating the absorption, metabolism and excretion of rucaparib following a single oral dose in patients with advanced solid tumours (NCT02986100). An additional phase I trial is investigating drug interactions of rucaparib with caffeine, digoxin, omeprazole, vitamin K or warfarin in patients with solid tumours (NCT02740712).

3 Current Status

Rucaparib received its first global approval on the 19th of December 2016 for ovarian cancer in the USA.

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