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ADISINSIGHT REPORT

Fuzuloparib: First Approval

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Abstract
Fuzuloparib (AiRuiYi®, 艾瑞颐; formerly fluzoparib) is a small molecule, orally active PARP inhibitor being developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd. (formerly Jiangsu Hengrui Medicine Co., Ltd.) for the treatment of solid cancers. Fuzuloparib has been approved in China for the treatment of ovarian cancer (including fallopian tube cancer or primary peritoneal cancer), and phase II and III trials are investigating fuzuloparib for the treatment of other solid cancers, including cancers of the pancreas, breast, prostate and lungs. This article summarizes the milestones in the development of fuzuloparib leading to this first approval for the treatment of platinum-sensitive recurrent ovarian cancer, fallopian tube cancer or primary peritoneal cancer in patients with germline *BRCA* mutation who have undergone second-line or above chemotherapy.

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Fuzuloparib (AiRuiYi®, 艾瑞颐): Key points

A small molecule PARP inhibitor is being developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd. (formerly Jiangsu Hengrui Medicine Co., Ltd.) for the treatment of ovarian cancer and other solid cancers

Received its first approval on 11 Dec 2020 in China

Approved for use in platinum-sensitive recurrent ovarian cancer, fallopian tube cancer or primary peritoneal cancer in patients with germline *BRCA* mutation who have undergone second-line or above chemotherapy

1 Introduction

Fuzuloparib (AiRuiYi®, 艾瑞颐; formerly fluzoparib) is a PARP inhibitor being developed by Jiangsu Hengrui Pharmaceuticals Co., Ltd. (formerly Jiangsu Hengrui Medicine Co., Ltd.) for the treatment of recurrent ovarian cancer (including fallopian tube cancer or primary peritoneal cancer) and other solid cancers. Fuzuloparib is the first original PARP inhibitor to be developed in China and it expands the number of PARP inhibitors available for the treatment of cancer [1]. Fuzuloparib received its first approval on 11 Dec 2020 in China for the treatment of platinum-sensitive recurrent ovarian cancer, fallopian tube cancer or primary peritoneal cancer (hereafter referred to as ovarian cancer) in patients with germline *BRCA* mutation (*gBRCAm*) who have undergone second-line or above chemotherapy [1–3]. Fuzuloparib is not yet indicated for maintenance therapy of ovarian cancer [3], however, development in this indication is ongoing.

The recommended dosage of fuzuloparib is 150 mg taken orally twice daily. Detection of a harmful or suspected harmful *gBRCA1/2* mutation using a method approved by the National Medical Products Administration is required in China prior to starting treatment with fuzuloparib. Reducing the dose to 50 mg is recommended with the concurrent administration of a moderate CYP3A4 inhibitor; concurrent administration with a strong CYP3A4 inhibitor or inducer is not recommended. Dose reduction or interruption may also be required to manage adverse events (AEs). The use fuzuloparib is contraindicated during breastfeeding; do not breastfeed during treatment and for one month after the last dose of fuzuloparib [3].

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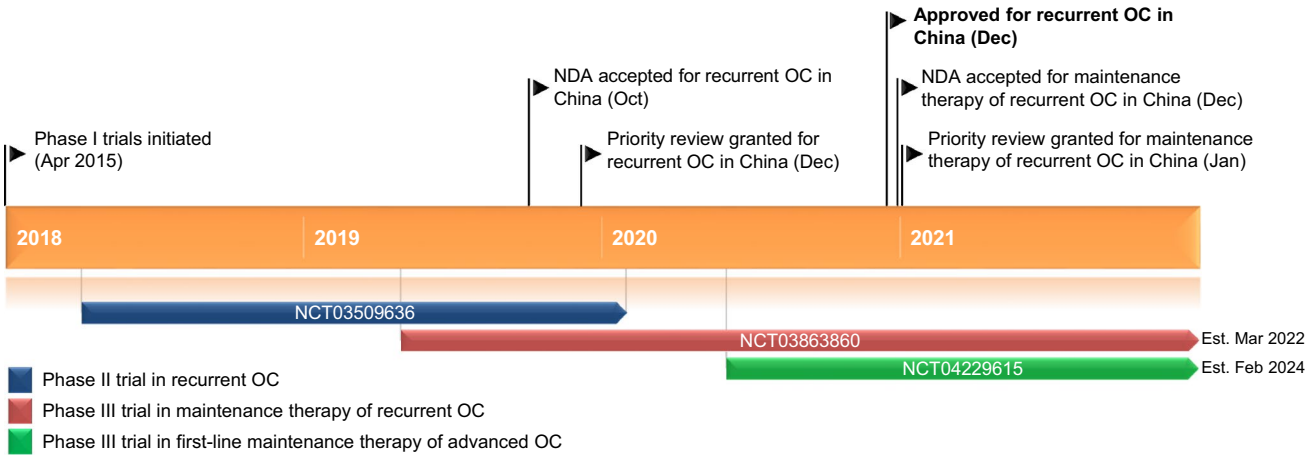


Key milestones in the development of fuzuloparib for the treatment of OC. *NDA* New drug application, *OC* ovarian cancer

2 Scientific Summary

2.1 Pharmacodynamics

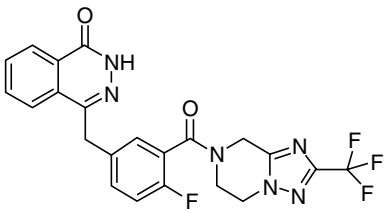
Inhibition of the PARP1 enzyme with fuzuloparib was comparable with olaparib (PARP1 IC_{50} 1.46 nM with fuzuloparib and 1.34 nM with olaparib) when measured using ELISA [4]. Both fuzuloparib and olaparib inhibited *BRCA1* or *BRCA2*-deficient lung fibroblast, ovarian cancer and breast cancer cell lines in cell culture experiments (IC_{50} 0.053–1.57 μM with fuzuloparib and 0.035–2.16 μM with olaparib); though no relevant inhibition of *BRCA1* or *BRCA2*-positive cell lines were observed with both inhibitors ($IC_{50} > 10$ μM with both inhibitors). In animal studies, fuzuloparib 30 mg/kg and olaparib 30 mg/kg inhibited the growth of *BRCA1*-negative breast cancer in mice (day 21 inhibition rate 59% with fuzuloparib and 44% with olaparib). Neither PARP inhibitor was associated with significant differences in body weight compared with placebo treated mice [4].

PARP inhibition is known to induce embryo-foetal toxicity in animal studies, and fuzuloparib may cause foetal harm in pregnant women. Contraception is recommended in women of childbearing age during treatment and for 6 months after the last dose of fuzuloparib [3].

2.2 Pharmacokinetics

A dose-proportional increase in the AUC_{0-t} and C_{max} of fuzuloparib occurs across a dose range of 10–150 mg when administered as a single dose. The accumulation ratio (in AUC_{0-t}) after 13 days is 1.86 in patients receiving fuzuloparib 150 mg twice daily. The administration of fuzuloparib after a high-fat meal does not have a significant effect on the AUC, though the t_{max} is delayed from 3 h to 6 h. The apparent volume of distribution of fuzuloparib is 34.6 L. Plasma binding of fuzuloparib is 74.3–81.6% over a concentration range of 20–2000 ng/mL. The terminal half-life of fuzuloparib is 9.14 h in patients administered multiple doses of fuzuloparib 150 mg twice daily. Fuzuloparib is predominantly metabolised by CYP3A4, with the most common metabolites being mono-oxidation and subsequently hydrogenated products; each metabolite contributes < 10% of the total plasma radioactivity. 44.2% and 59.1% of the radioactivity from the original dose is excreted into the faeces and urine. 15.8–16.8% of the original dose is excreted as unchanged fuzuloparib in urine [3].

Concomitant administration of itraconazole (strong CYP3A4 inhibitor) increases the C_{max}, AUC_{0-t} and AUC_{∞} of fuzuloparib by 51.0%, 325% and 381%, respectively; increases of 32.4%, 104.5% and 109.6%, respectively, are observed with fluconazole (moderate CYP3A4 inhibitor). Induction of CYP3A4 by rifampicin decreases the C_{max}, AUC_{0-t} and AUC_{∞} of fuzuloparib to 32.0%, 10.4%, and 10.4%, respectively. Inhibition of the CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 enzymes by fuzuloparib poses a low risk for drug–drug interactions, and no drug–drug inhibition studies are required according to relevant guidelines. Fuzuloparib may induce CYP1A2, CYP2B6 and CYP3A4 at a concentration of 5 μM, based on data from in vitro studies. Clinical



Chemical structure of fuzuloparib

studies to investigate the induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 by fuzuloparib are ongoing. Fuzuloparib is not recommended in patients with moderate or severe hepatic impairment or renal impairment as data are not yet available in these patient populations. Mild hepatic impairment and mild renal impairment does not cause relevant changes in clearance of fuzuloparib [3].

2.3 Therapeutic Trials

2.3.1 Ovarian Cancer

The first approval of fuzuloparib in the treatment of recurrent ovarian cancer was granted following the results from a phase II, open-label trial (NCT03509636). This trial enrolled patients with platinum-sensitive, recurrent, *BRCA1/2*-mutant, high-grade serous or endometrioid ovarian cancer who had previously received 2–4 lines of platinum-based chemotherapy. 113 patients were treated with fuzuloparib 150 mg twice daily in 28-day cycles. Fuzuloparib achieved an independent review committee (IRC)-assessed objective response rate (ORR) of 69.9% (primary endpoint); with 4.4% of patients achieving a complete response (CR) and 65.5% with a partial response (PR). The median follow-up duration was 15.9 months as of the latest data cut-off (21 Mar 2020) [5].

Fuzuloparib was investigated as a maintenance therapy for recurrent ovarian cancer in a randomised phase III trial (NCT03863860) in patients with platinum-sensitive, recurrent, high-grade serous or endometrioid ovarian cancer who received at least two previous lines of platinum-based chemotherapy and achieved either CR or PR to their most recent regimen. 167 patients were randomised to receive fuzuloparib 150 mg twice daily in 28-day cycles, and 85 patients were assigned to receive placebo. Fuzuloparib significantly ($p < 0.0001$) prolonged blinded independent review committee (BIRC)-assessed progression-free survival (PFS) versus placebo in the overall trial population. The median BIRC-assessed PFS was 12.9 and 5.5 months in the fuzuloparib and placebo treatment groups [hazard ratio (HR) 0.25; 95% confidence interval (CI) 0.17–0.36], though the median PFS for fuzuloparib was an estimate as data are not yet mature. Furthermore, fuzuloparib was superior to placebo in extending BIRC-assessed PFS in a subgroup of patients with *gBRCAm* [HR 0.14; 95% CI 0.07–0.28] (co-primary endpoints). As of the latest data cut-off date (1 Jul 2020), 67% of planned PFS events occurred in the overall population and the median follow-up duration was 8.5 months [6].

2.3.2 Other Solid Cancers

Fuzuloparib as a monotherapy in advanced solid tumours was examined in a phase I study (NCT02575651). 79 patients who had advanced solid tumours (including ovarian, breast and colorectal cancers) which were refractory to standard treatment or cancers which did not have a standard treatment were enrolled in this study. Patients were treated with fuzuloparib

Features and properties of fuzuloparib

Alternative names	Fluzoparib, AiRuiYi®, 艾瑞颐, 氟唑帕利胶囊, HS10160, SHR3162
Class	2-ring heterocyclic compounds, antineoplastics, fluorobenzenes, phthalazines, pyrazines, small molecules, triazoles
Mechanism of action	Small molecule PARP inhibitor; inhibition of DNA repair pathways leads to cell cycle arrest and prevents the proliferation of tumour cells
Route of administration	Oral
Pharmacodynamics	PARP1 IC_{50} 1.46 nM; IC_{50} 1.57 μM in *BRCA1*-negative MDA-MB-436 cells and 0.053 μM in *BRCA2*-negative V-C8 cells; no relevant inhibition of *BRCA1* or *2*-positive cell lines; day 21 inhibition rate 59% in ovarian MDA-MB-436 tumours in mice
Pharmacokinetics	Proportional increases in AUC_{0-t} and C_{max} with single fuzuloparib doses between 10–150 mg; accumulation ratio of 1.86 after 13 days of receiving fuzuloparib 150 mg twice daily; V_d 34.6 L; 74.3%–81.6% human plasma protein binding; mainly metabolised by CYP3A4; most common metabolites were mono-oxidation and subsequently hydrogenated products (< 10% each in plasma); $t_{½}$ 9.14 h; ~ 60% of the dose is excreted in urine and ~ 40% in faeces; ~ 16% of the dose is excreted in urine as unchanged drug
Most frequent adverse events	
All-grade events (incidence ≥ 40%)	Anaemia, nausea, leukopenia, fatigue and thrombocytopenia
Most frequent grade ≥ 3 events (incidence ≥ 2%)	Anaemia, thrombocytopenia, neutropenia, leukopenia and lymphopenia
ATC codes	
WHO ATC code	L01X-X
EphMRA ATC code	L1X9
Chemical name	4-[[4-fluoro-3-[2-(trifluoromethyl)-6,8-dihydro-5H-[1,2,4]triazolo[1,5-a]pyrazine-7-carbonyl]phenyl]methyl]-2H-phthalazin-1-one

dosages ranging from 10 mg once daily to 200 mg twice daily. An ORR of 6.2% (all PR) and a disease control rate of 30.8% at 24 weeks was reported in 65 evaluable patients [7].

In a dose-escalation phase I study (NCT03026881), 39 patients with advanced gastric or gastroesophageal junction cancer who did not respond to platinum-based chemotherapy were treated with a combination of fuzuloparib, apatinib and paclitaxel. 12 of 36 evaluable patients achieved a confirmed PR and 13 patients had stable disease following combination treatment [8].

2.4 Adverse Events

Safety data on monotherapy with fuzuloparib 150 mg twice daily were collected from three studies that enrolled a total of 294 patients with ovarian cancer [3]. All-grade AEs were reported in 94.9% of patients, with the most common AEs with an incidence ≥ 40% being anaemia (58.5% of patients), nausea (57.1%), leukopenia (54.4%), fatigue (43.5%) and thrombocytopenia (41.5%). The most common grade ≥ 3 AEs with an incidence ≥ 2% were haematological AEs; anaemia (25.5%), thrombocytopenia (13.3%), neutropenia (10.5%), leukopenia (9.9%) and lymphocytopenia (5.1%). The overall incidence of grade ≥ 3 haematological AEs was 40.5%. Dose interruption or reduction were required in some patients due to anaemia (dose interruption in 23.1% of patients and dose reduction in 9.2% of patients), thrombocytopenia (13.9% and 6.5%), neutropenia (8.8% and 2.0%), leukopenia (9.5% and 3.4%) and lymphocytopenia (2.0% and 0.7%). Monitor complete blood count at baseline then every fortnight for three months after initiating treatment and regularly afterwards. Consult local prescribing information for recommendations on dose reduction or interruption. Cases of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) have been reported during clinical trials in other PARP inhibitors used for the treatment of cancer. If signs and symptoms of MDS or AML are observed, discontinue fuzuloparib treatment and administer appropriate therapy [3].

Gastrointestinal AEs have been reported with fuzuloparib, with an overall all-grade incidence of 72.8% (2.4% for grade ≥ 3). The incidence of all-grade nausea was 57.1% (0.3% for grade ≥ 3) and 26.2% (1.4% for grade ≥ 3) for vomiting. Grade ≥ 2 nausea and vomiting may be managed with dose interruption, dose reduction and/or antiemetic medications [3].

2.5 Ongoing Clinical Trials

Fuzuloparib is being investigated in phase II and III trials in various solid cancers. There are four trials of fuzuloparib in ovarian cancer, NCT03863860 for maintenance therapy in patients with recurrent platinum-sensitive ovarian cancer who received at least two previous lines of platinum-based chemotherapy and achieved either CR or PR to their most recent regimen (phase III; fuzuloparib vs placebo); NCT04229615 for maintenance treatment in patients with advanced ovarian cancer following response on first-line platinum-based chemotherapy (phase III; fuzuloparib with/without apatinib vs placebo); NCT04517357 in patients with high-grade serous or endometrioid ovarian cancer who completed two or more platinum-containing regimens (phase II; fuzuloparib monotherapy vs fuzuloparib plus apatinib) and NCT03509636 in patients with platinum-sensitive *BRCA1/2*-mutant disease who received 2–4 chemotherapy regimens (phase II; fuzuloparib arm only).

Two trials are assessing fuzuloparib in pancreatic cancer, NCT04300114 for maintenance therapy in patients with *gBRCA/PALB2*-mutatant metastatic pancreatic cancer whose disease has not progressed following first-line platinum-based chemotherapy (phase III; fuzuloparib vs placebo) and NCT04228601 for combination therapy and subsequent maintenance therapy in advanced pancreatic cancer (phase I/II; fuzuloparib plus mFOLFIRINOX followed by fuzuloparib maintenance therapy vs placebo plus mFOLFIRINOX followed by placebo maintenance therapy).

Three trials are evaluating fuzuloparib in metastatic castration-resistant prostate cancer, NCT04691804 for combination therapy as a first-line treatment (phase III; fuzuloparib plus abiraterone acetate and prednisone vs placebo plus abiraterone acetate and prednisone), NCT04869488 for combination therapy or monotherapy in patients who failed prior treatment with abiraterone/enzalutamine and with or without homologous recombination repair gene mutations (phase II; fuzuloparib with/without apatinib vs abiraterone/enzalutamine plus prednisone) and NCT04102124 for combination therapy in patients who did not respond to abiraterone and docetaxel treatment (phase II; fuzuloparib plus rezvilutamide vs rezvilutamide plus placebo vs placebo).

Other trials of fuzuloparib includes NCT04296370 in patients with *HER2*-negative metastatic breast cancer with *gBRCAm* who received no more than two lines of chemotherapy, received prior therapy with an anthracycline and a taxane and did not respond to one endocrine therapy or are not candidates for endocrine therapy (phase III; fuzuloparib with/without apatinib vs chemotherapy) and NCT04400188 combination therapy in patients with relapsed small cell lung cancer who failed at least one line of platinum-based chemotherapy (phase I/II; fuzuloparib plus temozolomide with/without adebrelimab).

3 Current Status

Fuzuloparib received its first approval on 11 Dec 2020 for treatment of platinum-sensitive recurrent ovarian cancer, fallopian tube cancer or primary peritoneal cancer in patients with *gBRCAm* who have undergone second-line or above chemotherapy in China [1–3].

Key Phase II and III clinical trials of fuzuloparib in China (sponsored by Jiangsu Hengrui Pharmaceuticals Co., Ltd.)

Drug(s)	Indication	Phase	Status	Identifier
Ovarian cancers				
Fuzuloparib, placebo	Maintenance therapy in platinum-sensitive recurrent ovarian cancer after at least two previous lines of platinum-based chemotherapy and achieved either CR or PR to their most recent regimen	III	Active	NCT03863860
Fuzuloparib, apatinib, placebo	Maintenance therapy in advanced ovarian cancer following response on first-line platinum-based chemotherapy	III	Recruiting	NCT04229615
Fuzuloparib, apatinib	Advanced ovarian cancer following 2 or more platinum-containing regimens	II	Recruiting	NCT04517357
Fuzuloparib	Platinum-sensitive, *BRCA1/2*-mutant recurrent ovarian cancer following 2 or more chemotherapy regimens	II	Active	NCT03509636
Pancreatic cancers				
Fuzuloparib, placebo	Maintenance therapy in patients with *gBRCA/PALB2*-mutant metastatic pancreatic cancer whose disease has not progressed following first-line platinum-based chemotherapy	III	Recruiting	NCT04300114
Fuzuloparib, placebo, mFOLFIRINOX	Combination therapy and subsequent maintenance therapy in advanced pancreatic cancer	I/II	Recruiting	NCT04228601
Prostate cancers				
Fuzuloparib, placebo, abiraterone acetate and prednisone	First-line treatment in metastatic castration-resistant prostate cancer	III	Not yet recruiting	NCT04691804
Fuzuloparib, abiraterone, apatinib, enzalutamine, prednisone	Metastatic castration-resistant prostate cancer in patients who failed prior treatment with abiraterone/enzalutamine and with or without homologous recombination repair gene mutations	II	Not yet recruiting	NCT04869488
Fuzuloparib, rezvilutamide, placebo	Metastatic castration-resistant prostate cancer patients who did not respond to abiraterone and docetaxel treatment	II	Active	NCT04102124
Breast cancers				
Fuzuloparib, apatinib, chemotherapy	*HER2*-negative metastatic breast cancer with germline *BRCA* mutation in patients who received no more than two lines of chemotherapy, received prior therapy with an anthracycline and a taxane and did not respond to one endocrine therapy or are not candidates for endocrine therapy	III	Recruiting	NCT04296370
Lung cancers				
Fuzuloparib, adebrelimab, temozolomide	Relapsed small cell lung cancer in patients who failed one line of platinum-based chemotherapy	I/II	Recruiting	NCT04400188

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Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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