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ADISINSIGHT REPORT

Rezvilutamide: First Approval

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Abstract
Rezvilutamide (艾瑞恩®) is an oral, second-generation androgen receptor antagonist being developed by Jiangsu Hengrui Medicine Co., Ltd for the treatment of prostate cancer. In June 2022, rezvilutamide was approved in China for the treatment of patients with metastatic hormone-sensitive prostate cancer (mHSPC) with high tumour burden. This article summarizes the milestones in the development of rezvilutamide leading to this first approval for patients with prostate cancer.

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Rezvilutamide (艾瑞恩®): Key points

A second-generation androgen receptor antagonist being developed by Jiangsu Hengrui Medicine Co., Ltd for the treatment of prostate cancer

Received its first approval on 28 June 2022 in China

Approved for use in patients with mHSPC with high tumour burden

1 Introduction

The onset and progression of prostate cancer, an androgen-dependent malignancy, is associated with androgen receptor (AR) activity. Therefore, androgen deprivation therapy (ADT) is a cornerstone in the treatment of prostate cancer, especially high-risk cancers [1–3]. Metastatic hormone-sensitive prostate cancer (mHSPC) with a high tumour burden (≥ 4 bone metastases and/or visceral metastasis) has a poor prognosis [4], and often progresses rapidly to metastatic castration-resistant prostate cancer (mCRPC) [5]. A combination of ADT, chemotherapy (e.g., docetaxel) and novel hormonal therapy (e.g., abiraterone, enzalutamide, apalutamide) is a treatment option for mHSPC [6]. ADT plus novel hormonal therapy is also a treatment option for mCRPC [1].

Rezvilutamide, an oral second-generation AR antagonist, is being developed by Jiangsu Hengrui Medicine Co. Ltd for the treatment of prostate cancer. Rezvilutamide was approved in June 2022 in China for the treatment of patients aged ≥ 18 years with mHSPC, with a high tumour burden. The recommended dosage is 240 mg once daily, with or without food. Patients should also be receiving concomitant ADT [i.e., concomitant gonadotropin-releasing hormone agonist therapy] or have undergone bilateral orchiectomy. Treatment should be withheld if the patient develops ≥ grade 3 toxicity or intolerable adverse reactions; when symptoms improve to ≤ grade 1 or the original grade, rezvilutamide can be restarted at the same or a lower daily dose (160 or 80 mg). Dosage adjustments are not required in patients with mild hepatic or kidney impairment; rezvilutamide is not recommended in patients with moderate or severe hepatic or kidney impairment as there are no data on the use of rezvilutamide in these patients [7].

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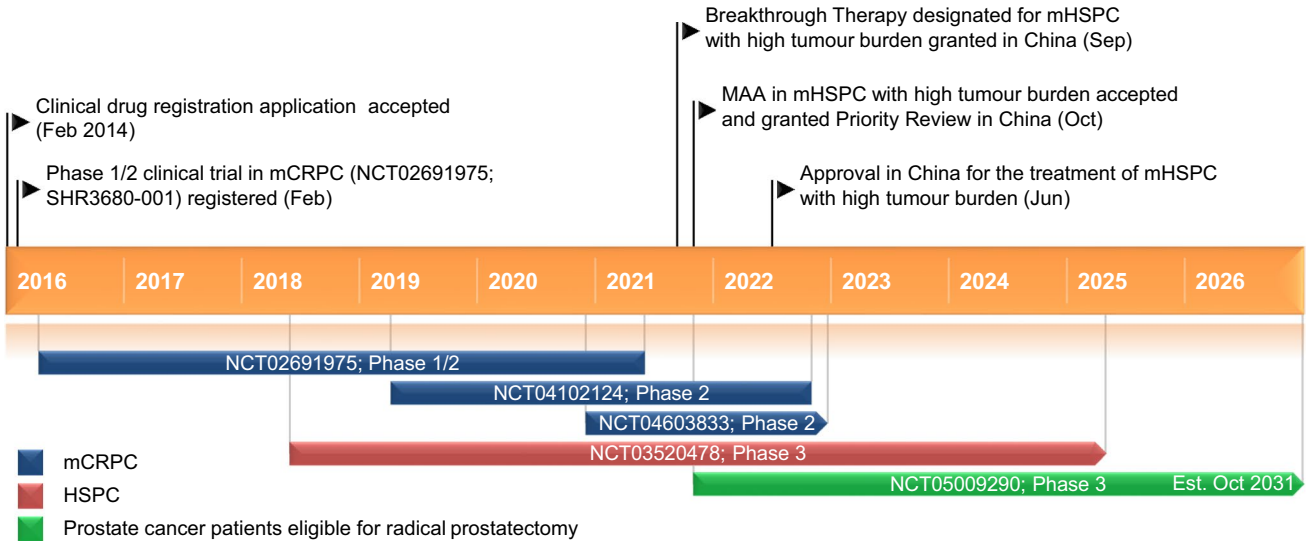


Key milestones in the development of rezvilutamide in the treatment of prostate cancer. *mCRPC* metastatic castration-resistant prostate cancer, *mHSPC* metastatic hormone-sensitive prostate cancer, *MAA* marketing authorization application

2 Scientific Summary

2.1 Pharmacodynamics

Rezvilutamide binds to the ligand binding domain of the AR and competitively inhibits androgen binding to the AR, preventing androgen-induced AR activation and inhibiting AR nuclear translocation. By binding to DNA, rezvilutamide reduces AR-mediated gene transcription and inhibits expression of genes that regulate prostate cancer cell proliferation [3, 7, 8].

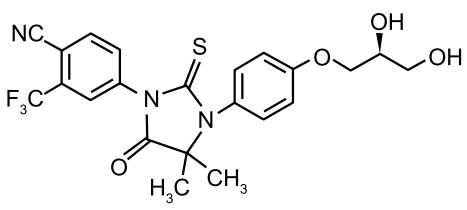
In a mouse model of epilepsy, rezvilutamide had a lower distribution to the brain than enzalutamide, based on the brain : plasma concentration ratio. Rezvilutamide was also associated with a decreased risk of seizure induction than enzalutamide, showing a longer latency to seizure duration and Straub's tail response, and a significant ($p < 0.001$) reduction in the number of myoclonic seizures [9].

2.2 Pharmacokinetics

Rezvilutamide was rapidly absorbed after oral administration in a phase 1/2 trial (NCT02691975) in patients with mCRPC [7, 9]. The mean C_{max} of 7.62 μg/mL after a single 240 mg dose was achieved in a median 7 h (T_{max}). Steady state was achieved after 15 days' administration of rezvilutamide 240 mg once daily; at steady state, mean C_{max} was 32.5 μg/mL, median T_{max} was 2 h, mean C_{trough} was 23.1 μg/mL and mean AUC_{24} was 649.0 μg/mL [7, 9]. After 28 days' administration, the accumulation ratio was ≈4.1. Rezvilutamide is highly protein bound (97.2–100.0%) and the mean apparent volume of distribution after a single 240 mg dose in patients with mCRPC was 32.5 L. Food had no effect on the pharmacokinetics of rezvilutamide in healthy subjects [7].

Rezvilutamide is extensively metabolized by oxidative decarboxylation (main metabolic pathway; metabolites account for 40.2% of a dose), glucuronic acid conjugation, O-dealkylation and further glucuronic acid conjugation. After a single oral 240 mg dose of $^{[14C]}$rezvilutamide in healthy subjects, the unchanged drug accounted for 8.78% and 10.8% of radioactivity excreted in urine and faeces, respectively [7]. The mean apparent clearance in patients with mCRPC was 0.251 L/h and the mean $t_{1/2}$ was 89.6 h (single 240 mg dose) and 74.9 h (at steady state after 240 mg/day) [7, 9]. The total recovery rate of radioactive substances in urine and faeces over 28 days was 89.8% of a dose, mainly in urine (64.3%) [7].

Phase 1 pharmacokinetic drug interaction studies (NCT04664725 and NCT04676035) indicate that rezvilutamide is a potent inducer of CYP3A4 and CYP2C19, and



Chemical structure of rezvilutamide

Features and properties of rezvilutamide	
Alternative names	瑞维鲁胺; 艾瑞恩®; SHR-3680
Class	Alcohols, Antineoplastics, Fluorinated hydrocarbons, Imidazolidines, Ketones, Nitriles, Organic sulfur compounds, Phenyl ethers, Small molecules
Mechanism of action	Androgen receptor (AR) antagonists
Route of administration	Oral
Pharmacodynamics	Competitively inhibits androgen binding to the AR, preventing androgen-induced AR activation and inhibiting AR nuclear translocation ↓distribution to the brain and ↓ risk of seizure induction vs enzalutamide in a mouse model of epilepsy Significantly reduced PSA levels from baseline in clinical trials in prostate cancer
Pharmacokinetics (mean values at steady state)	C_{max} 32.5 μg/mL, C_{trough} 23.1 μg/mL, AUC_{24} 649.0 μg/mL, $t_{1/2}$ 74.9 h; accumulation ratio 4.1, 97.2–100.0% protein bound
Adverse events	
Most frequent (any grade, incidence ≥ 20%)	Weight gain, musculoskeletal pain, ↑triglycerides, anaemia, joint pain, hypertension, ↑cholesterol, URTI, ↑AST, ↑ALT, hyperglycaemia, back pain, non-musculoskeletal pain
Chemical name	4-(3-(4-((S)-2,3-Dihydroxypropoxy)phenyl)-4,4-dimethyl-5-oxo-2-thioxoimidazolidin-1-yl)-2-(trifluoromethyl)benzonitrile

↑ increases, ↓ decreased

a moderate inducer of CYP2B6, CYP2C8 and CYP2C9 [7, 8]. Coadministration of rezvilutamide with drugs that are primarily metabolized by these CYP isoenzymes may reduce exposure to these drugs, and should be avoided, where possible. If rezvilutamide is coadministered with an anticoagulant metabolized by CYP2C9 (e.g. warfarin), additional INR monitoring is required [7]. In vitro data indicate that rezvilutamide is a substrate of the transporter P-gp, and has the potential to inhibit the P-gp and other transporters (BCRP, OATP1B1, OATP1B3, MATE1 and MATE2-K); coadministration of rezvilutamide and drugs that are P-gp, BCRP, OATP1B1, OATP1B3 and MATE1/MATE2-K substrates may increase their exposure. A phase 1 drug interaction study in patients with mCRPC or mHSPC (NCT04621669) is ongoing [7].

2.3 Therapeutic Trials

2.3.1 Metastatic Hormone-Sensitive Prostate Cancer

Rezvilutamide plus ADT significantly improved radiographic progression-free survival (PFS) and overall survival (OS) compared with bicalutamide plus ADT in patients with high-volume mHSPC in the phase 3 CHART trial (NCT03520478) [2]. The CHART trial enrolled men aged ≥ 18 years from China and Eastern Europe (Poland, Czech Republic and Bulgaria) with histologically or cytologically confirmed prostate adenocarcinoma, without neuroendocrine differentiation or small-cell histology. Patients were required to have high volume disease [defined as either ≥ 4 bone lesions on [^{99}TC] bone scan with ≥ 1 lesion beyond the pelvis or vertebral column or evidence of visceral metastasis

Key clinical trials of rezvilutamide (Jiangsu HengRui Medicine Co., Ltd.)					
Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Rezvilutamide; placebo	Localized/locally advanced prostate cancer	3	Recruiting	China	NCT05009290; SHR3680-III-302
Rezvilutamide; bicalutamide	HSPC	3	Ongoing	China, Bulgaria, Poland, Czech Republic	NCT03520478; SHR-3680-III-HSPC
Rezvilutamide; docetaxel	mCRPC	2	Ongoing	China	NCT04603833; SHR3680-II-203
Rezvilutamide, fuzuloparib, placebo	mCRPC	2	Terminated	China	NCT04102124; SHR3680-SHR3162-II-CRPC
Rezvilutamide	mCRPC	1/2	Completed	China	NCT02691975; SHR3680-001

HSPC hormone-sensitive prostate cancer, *mCRPC* metastatic castration-resistant prostate cancer

(excluding lymph node metastasis) by CT or MRI] and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients who had a history of or predisposition to seizures, or who had received previous chemotherapy or other localised prostate cancer treatment or treatment with second-generation AR inhibitors or other androgen synthesis inhibitors were ineligible. At baseline, median age was 69 years, 90% of patients were from China, > 80% had a Gleason score ≥ 8 and all had metastases at initial diagnosis. Eligible patients were randomized to receive once daily oral rezvilutamide 240 mg plus ADT ($n = 326$) or once daily oral bicalutamide 50 mg plus ADT ($n = 328$) in 28-day cycles until disease progression, unacceptable toxicity, withdrawal of consent, or investigator's decision [2].

In CHART, at the preplanned interim analysis for radiographic PFS (median follow-up 21.2 months), median radiographic PFS assessed by a blinded independent review committee (co-primary endpoint) had not been reached in the rezvilutamide arm, but was 25.1 months in the bicalutamide arm [HR 0.44 (95% CI 0.33–0.58); $p < 0.0001$]. 2-year radiographic PFS was 72.3% in rezvilutamide recipients and 50.0% in bicalutamide recipients [2]. At the preplanned interim analysis for OS (median follow-up 29.3 months) [co-primary endpoint], 25% of patients in the rezvilutamide arm had died, compared with 38% in the bicalutamide arm; while OS was significantly longer with rezvilutamide compared with bicalutamide [HR 0.58 (95% CI 0.44–0.77); $p = 0.0001$], median OS had not been reached in either treatment arm. The 2-year OS rate was 81.6% in the rezvilutamide arm and 70.3% in the bicalutamide arm [2].

Prostate-specific antigen (PSA) level was 79 ng/mL in the rezvilutamide arm and 51 ng/mL in the bicalutamide arm at baseline in CHART [2]. At week 12, the PSA response rates (% of patients with a ≥ 90% decrease from baseline at the beginning of cycle 4 among those who were ADT-naïve before randomization) were 94.4% in rezvilutamide plus ADT recipients (135/143 evaluable) and 78.9% in bicalutamide plus ADT recipients (112/142). In the overall population, undetectable PSA rates (% of patients with the lowest value ≤ 0.2 ng/mL after randomization) were 68.7% (224/326 patients) and 33.5% (110/328), respectively [2].

In CHART, time to pain progression (assessed by the patient-reported Brief Pain Inventory-Short Form) did not differ significantly between the rezvilutamide and bicalutamide arms [2]. However, in a prespecified sensitivity analysis that included unconfirmed pain progression at the last assessment as an event, 24-month pain progression-free rate estimate was 64.3% in the rezvilutamide group and 55.5% in the bicalutamide group [HR 0.75 (95% CI 0.58–0.9)]. Furthermore, health-related quality of life (assessed by the patient-reported Functional Assessment of Cancer Therapy-Prostate questionnaire; version 4) tended to be better in the rezvilutamide arm than in the bicalutamide arm [2].

2.3.2 Metastatic Castration-Resistant Prostate Cancer

Rezvilutamide showed promising antitumour activity across all doses tested (40–480 mg once daily) in patients with mCRPC in a phase 1/2 trial (NCT02691975; $n = 197$), with 240 mg once daily identified as the recommended phase 3 dosage [9]. Eligible patients were men aged 18–80 years with a histological diagnosis of prostatic adenocarcinoma who had progressed on (or were intolerant to or unwilling to receive) previous docetaxel-containing chemotherapy, had a castrate level of testosterone ≤ 50 ng/dL or 1.73 nmol/L, had an ECOG status of 0 or 1 and a life expectancy of ≥ 6 months. Patients who had a history of or predisposition to seizures, or who had received previous treatment with second-generation AR inhibitors or other androgen synthesis inhibitors, were ineligible [9].

In NCT02691975, a ≥ 50% decrease in the PSA level at week 12 (PSA response; primary endpoint) was seen in 68.0% of patients [9]. Throughout the course of treatment, a maximum PSA decrease from baseline of ≥ 50% and ≥ 90% was seen in 78.2% and 43.7% of patients, respectively; PSA response was not dose dependent. A confirmed radiological objective response was seen in 27.3%, 31.6% and 38.5% of patients receiving rezvilutamide 80 mg ($n = 11$ radiologically evaluable patients), 160 mg ($n = 19$) and 240 mg ($n = 26$) in the dose expansion portion. Disease control was seen in 63.6%, 100% and 84.6% of these patients, respectively. Stable disease in bone at week 12 was seen in 89.7% ($n = 39$), 90.4% ($n = 73$) and 84.2% ($n = 76$) of patients in the 80, 160 and 240 mg arms, respectively [9].

2.4 Adverse Events

In the phase 3 CHART trial in patients with mHSPC, the most common adverse reactions and laboratory abnormalities (any grade; incidence ≥ 20% in the rezvilutamide group) in the rezvilutamide ($n = 323$) and bicalutamide ($n = 324$) groups (median exposure 21.1 months and 12.8 months, respectively) were weight gain (56.3% vs 52.5%), musculoskeletal pain (39.6% vs 35.5%), elevated triglycerides (36.5% vs 25.6%), anaemia (34.1% vs 34.0%), joint pain (29.4% vs 22.8%), hypertension (27.2% vs 21.0%), elevated cholesterol (25.4% vs 22.2%), upper respiratory tract infection (25.1% vs 21.9%), elevated AST (22.9% vs 14.8%), elevated ALT (22.9% vs 13.0%), hyperglycaemia (22.0% vs 18.8%), back pain (21.7% vs 20.1%) and non-musculoskeletal pain (21.1% vs 19.8%) [7].

Adverse events ≥ grade 3 were reported in 47.4% of patients in the rezvilutamide group and 40.4% in the bicalutamide group; the most frequent were hypertension (9.0% vs 9.3%), elevated triglycerides (7.1% vs 2.2%), weight gain (6.2% vs 3.4%) and anaemia (3.7% vs 4.6%). Serious adverse events were reported in 24.5% and 20.1%

of patients in the rezvilutamide and bicalutamide groups, respectively [7].

In the rezvilutamide group, 1.2% of patients discontinued treatment because of adverse events [increased ALT (0.6%) and increased AST (0.6%)]; 11.1% of rezvilutamide recipients required dose suspension or dose reduction because of adverse events, the most frequent of which were increased ALT (1.9%) and increased AST (1.2%) [7].

In the CHART safety population, grade 1–2 QT prolongation was reported in 8.4% (27/323) of patients in the rezvilutamide arm and 5.6% (18/324) of those in the bicalutamide arm [7]. Grade 3 QT prolongation occurred in 2 rezvilutamide recipients and 1 bicalutamide recipient. No grade 4 QT prolongation was reported [2, 7]. Two patients (0.6%) in the rezvilutamide arm and none in the bicalutamide arm required dose interruption due to ECG QT prolongation; no patients discontinued treatment because of ECG QT prolongation or dose reduction [2, 7]. A clinical pharmacology study of QT/QTc interval prolongation with rezvilutamide in patients with mCRPC is underway (NCT05607693; SHR3680-I-QTc).

2.5 Ongoing Clinical Trials

In addition to the phase 3 CHART trial in patients with high-volume mHSPC (NCT03520478), a phase 2 trial comparing rezvilutamide plus docetaxel with either agent alone in patients with mCRPC who had been previously treated with abiraterone (NCT04603833) is ongoing. A phase 3 trial of rezvilutamide in patients with high-risk localized or locally advanced prostate cancer who are candidates for radical prostatectomy (NCT05009290) is currently recruiting.

3 Current Status

Rezvilutamide received its first approval on 28 June 2022 for the treatment of mHSPC with high tumour burden in China [7, 10, 11].

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-022-01831-y.

Declarations

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

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