Rezvilutamide for metastatic castration-sensitive prostate cancer: CHART trial

Kirti Singh*

Department of Urology, AIIMS, Bhubaneswar, Odisha, India
*E-mail: kirtisingh2604@gmail.com

SUMMARY

The CHART trial[1] was a phase 3, active-controlled, open-label, multinational, *randomized controlled trial* (RCT) conducted at 72 hospitals. It recruited 654 men from four countries with high-volume metastatic hormone-sensitive prostate cancer/*metastatic* castration-*sensitive prostate cancer* (mHSPC/mCSPC) with an Eastern Cooperative Oncology Group (ECOG) performance level <2. Patients who had received previous chemotherapy or any localized treatment were not eligible. Patients were randomly allocated in a 1:1 ratio to receive androgen deprivation therapy (ADT) with rezvilutamide (240 mg) or bicalutamide (50 mg). The coprimary endpoints were the independent review committees (IRC)-assessed radiographic progression-free survival (RPFS) and overall survival (OS).

Notable findings of CHART trail were that rezvilutamide significantly improved IRC-assessed median RPFS compared with bicalutamide (hazard ratio [HR] 0·44), and treatment effect of rezvilutamide on RPFS was seen in all subgroups except in patients with visceral metastases and patients outside China. On interim analysis, the median follow-up duration for RPFS and OS was 21.2 and 29.3 months, respectively, and most secondary and exploratory endpoints favored rezvilutamide over bicalutamide, except for time to pain progression, which did not differ significantly between the two treatment groups. OS was significantly longer in the rezvilutamide group (HR 0·58); median RPFS and median OS were not reached in either group at the time of interim analysis.

Frequencies of adverse events in any grade were similar between treatment groups. The most common Grade 3 adverse events were hypertension, hypertriglyceridemia, increased weight, anemia, and hypokalemia. Serious adverse events were reported in 28% of the rezvilutamide group and 21% of the bicalutamide group. No treatment-related deaths occurred due to rezvilutamide.

This RCT concluded that rezvilutamide plus ADT significantly improved RPFS (HR = 0·44) and OS (HR = 0·58) compared with bicalutamide plus ADT in patients with high volume, mHSPC with a tolerable safety profile.

COMMENTS

With the multitude of drugs being added for treating mHSPC, management has shifted to the use of combination therapy. All the latest guidelines acknowledge that combination therapy with ADT is better than ADT alone in improving the OS. Based on the EAU guidelines,[2] the current standard of care (SOC) for mHSPC is ADT with the addition of docetaxel or androgen antagonists (abiraterone, enzalutamide, or apalutamide).

Rezvilutamide (SHR 3680) is an orally bioavailable novel androgen receptor antagonist (ARA) with potential antineoplastic activity. Its low penetrance of the blood–brain barrier translates clinically to a reduced incidence of central nervous system adverse effects, such as fatigue and seizures, making it a less toxic option than its counterparts enzalutamide and apalutamide. Based on this context, a first-in-human phase 1/2 study[3] in patients with metastatic castrate-resistant prostate cancer was done, and it showed that rezvilutamide is well tolerated and safe in them; so CHART trial was done to see its efficacy in mCSPC also.The authors[1] highlighted the benefit of adding a novel ARA to ADT for the treatment of mHSPC.

Previous studies[4] have found that prostate cancer in Asian men differs from that in White patients both epidemiologically and genomically, raising the question as to whether there might be a differential response to antiandrogen therapies, so it is interesting and reassuring to note that Asian patients (mainly from China) fared well in terms of RPFS and OS in the CHART trial.

CHART trial was well structured, but only recruited patients with high-volume disease and did not detail whether patients had *de novo* or metachronous metastatic disease, whereas similar studies (e.g. ARCHES and TITAN trials) have shown a survival benefit,[2] for patients with low-volume disease, leaving open the question of whether rezvilutamide is a

viable option for these patients also. CHART also excluded patients who had previously received docetaxel, not so in ARCHES and TITAN trials,[2] leaving the potential benefit of docetaxel with rezvilutamide yet to be established. Furthermore, this trial did not include patients with poor performance status (ECOG ≥2), which form a significant portion of mHSPC patients, so the effect remains unknown in this group.

In contrast to this trial design, in current clinical practice, patients are frequently restaged with the more sensitive prostate-specific membrane antigen positron emission tomography–computed tomography. Rezvilutamide could have been compared with the SOC or placebo and not with bicalutamide, which is not used in clinical practice. The comparison could have been done with apalutamide or enzalutamide as they are readily available, and the data would have been more robust. It may have made the RPFS and OS curves lesser effective hypothetically but perhaps practically important.

With more evidence, increased accessibility, and affordability of the treatment, rezvilutamide could be added to first line treatment. At present, it will be prohibitively expensive and may not be readily available, and it may not be considered the SOC in developing countries like India.

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Received: 29.09.2022, **Revised:** 16.12.2022,

Accepted: 09.03.2023, **Published:** 31.03.2023

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/iju.iju_336_22

How to cite this article: Singh K. Rezvilutamide for metastatic castration-sensitive prostate cancer: CHART trial. Indian J Urol 2023;39:171-2.