Editorial Commentary

Rezvilutamide: yet another androgen receptor pathway inhibitor for metastatic hormone-sensitive prostate cancer?

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The treatment of metastatic hormone-sensitive prostate cancer (mHSPC) has evolved rapidly in the last few decades especially with the advent of the novel androgen-signaling agents. The current standard of care involves use of androgen deprivation therapy (ADT) as the backbone with additional androgen signaling agents with abiraterone or apalutamide or enzalutamide or chemotherapy with docetaxel. In the past year, additional triplet therapy with ADT and docetaxel as the backbone with added additional androgen receptor pathway inhibitors (ARPI) abiraterone or darolutamide showed improvement in overall survival (OS) in the PEACE-1 and ARASENS trials, respectively. These trials established either doublet therapy or triplet therapy as the mainstay of treatment for all patients presenting with mHSPC. Rezvilutamide, formerly known as SHR3680, is a novel androgen signaling inhibitor which was developed by Jiangsu Hengrui Medicine Co., Ltd., and initially studied in a phase I/II trial initially for metastatic castrate-resistant prostate cancer (mCRPC) (1). The primary endpoint for the phase I trial was safety while measures of efficacy especially prostate specific antigen (PSA) response was evaluated in the phase II portion of the trial. A 12-week PSA response was achieved in 68% of patients with radiographic bone disease stabilization seen in 88.3% of patients at week 12, and soft tissue response in 34.4% of patients. The drug was well-tolerated with treatment-related adverse events (TRAEs) occurring in 58.9% patients, with proteinuria being the most common at 13.7%. The promising results of this trial led to subsequent phase III CHART trial.

CHART was a phase III trial that studied rezvilutamide and enrolled patients predominantly in China (*Table 1*), with additional 63 patients accrued from a few other countries in Poland, Czech Republic and Bulgaria (2). The trial screened 792 patients and randomized 654 patients to either ADT with rezvilutamide (n=326) or ADT with bicalutamide (n=328) at standard dosing. The trial enrolled a predominantly Asian population of patients (90%) with the trial being conducted in China (90%) with accrual in other regions at 10%. Patient eligibility included high-volume disease per the CHAARTED criteria including presence of either four or more bone lesions at least one of which is beyond the axial and pelvic skeleton or presence of visceral metastasis by conventional imaging with computed tomography (CT) and bone scan. Routine eligibility criteria included good performance status of either Eastern Cooperative Oncology Group (ECOG) 0 or 1 (with majority having ECOG performance status of 1 at 74%), adequate organ function, and while prior ADT is allowed, it could not have been more than 3 months before and no disease progression in the immediate time prior to study initiation. Patients could not have received prior chemotherapy and while most had *de novo* metastatic

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Table 1 Characteristics of CHART

Characteristics	Comments
Clinical trial name	CHART
No. of patients	n=654
Experimental arm *vs.* SOC arm	ADT + rezvilutamide *vs.* ADT + bicalutamide
Primary endpoint	IRC rPFS and OS
mOS (ADT + experimental arm)	NR; 2-year OS: 81.6%
mOS (ADT alone or as SOC)	NR; 2-year OS: 70.3%
HR	HR: 0.58; 95% CI: 0.44–0.77; P=0.0001
Secondary endpoints (experimental *vs.* SOC arms)	PSA response: 94.4% *vs.* 78.9%; PSA undetectable: 68.7% *vs.* 33.5%; ORR by IRC: 81% *vs.* 67.9%
mPFS	rPFS = NR *vs.* 25.1 months ADT + bicalutamide
	HR: 0.44; 95% CI: 0.33–0.58); P<0.0001
Discontinuation due to toxicity	2% (*vs.* 2% ADT + bicalutamide)
Metastatic burden percentage	100%
References	Gu *et al.*, *Lancet Oncol* 2022

SOC, standard of care; IRC, independent-review committee; rPFS, radiographic progression-free survival; OS, overall survival; mOS, median overall survival; ADT, androgen deprivation therapy; NR, not reached; HR, hazard ratio; CI, confidence interval; PSA, prostate specific antigen; ORR, objective response rate.

prostate cancer, about 10% had prior surgery. Most patients had no pain (62%) and most had high-risk prostate cancer with Gleason 8 or more (85% in the rezvilutamide arm and 78% in the bicalutamide arm), with very few patients who have undergone prior radiotherapy (1%) previously and about 9% to 10% underwent prior surgery.

The study design involved a 1:1 randomization to either ADT with rezvilutamide or with bicalutamide and additional stratification included presence of visceral metastases and ECOG performance status. Investigators and patients were not masked to study assignment and the rezvilutamide group were given 240 mg tablets while bicalutamide was the 50 mg dose tablets. The study had co-primary endpoints which included an Investigator-assessed and independent-review committee (IRC) assessed radiographic progression-free survival (rPFS) and OS in the intention-to-treat (ITT) population, that would provide 95% power with two-sided significance and type I error of 0.05 to detect 282 radiographic progression or death events for an hazard ratio (HR) of 0.65. OS events needed to detect an HR of 0.7 would incur 325 events with a power of 89% and corresponding two-sided significance of 0.05. There was a planned interim analysis for OS after 195 events were reported but given changes in the standard of care with additional androgen signaling agents, a protocol amendment allowed for another interim analysis for rPFS after 170 events with either radiographic progression or death occurred, using Lan-DeMets O'Brien Fleming for the interim and final analyses. Additional efficacy analyses was analyzed with the ITT population, the Kaplan-Meier method was used to estimate the primary endpoints and corresponding 95% confidence interval (CI) were calculated using the Brookmeyer-Crowley method with HRs and 95% CI calculated using a stratified Cox proportional hazards model. Other secondary endpoints including objective response rate, PSA response rate, undetectable PSA rates were calculated for 95% CI via the Clopper-Pearson method. Further subgroup analyses were also evaluated using unstratified Cox proportional hazards model. Patient-reported outcomes using questions with The Functional Assessment of Cancer Therapy-Prostate (FACT-P) were obtained. Conventional re-staging scans with CT and bone scan was obtained at certain timelines including at baseline, at cycle 5 and every 4 cycles thereafter.

At the time of data cut-off on February 28, 2022, the independent data monitoring committee deemed that rPFS crossed the pre-specified boundary of 0.018 and therefore the study continued as planned to the second

interim analysis for OS analyses. At a median follow-up of 29.3 months, 25% of patients in the rezvilutamide group has died compared to 38% in the bicalutamide group, OS was longer for the rezvilutamide group at an HR of 0.58 (95% CI: 0.44–0.77), P=0.0001 with a 2-year OS that was 81.6% in the rezviltuamide group compared to 70.3% in the bicalutamide arm. Median rPFS was also better with rezvilutamide which was not reached in the rezvilutamide group compared to bicalutamide at 23.5 months (HR of 0.46; 95% CI: 0.36–0.6) similar to the investigator-assessed rPFS which was not reached compared to bicalutamide at 18.5 months (14.8–25.7 months; HR: 0.39, 95% CI: 0.3–0.5). In addition, rPFS was better for the rezvilutamide arm across all subgroups except for those with visceral metastases and those not from China, although these numbers were relatively small. Several other secondary endpoints including median time to PSA progression and time to next skeletal-related event were both in favor of the ADT with rezvilutamide arm which was not reached for both parameters compared to the ADT with bicalutamide group which was 11 and 38.7 months, with HR of 0.21 (95% CI: 0.16–0.27) and HR of 0.65 (95% CI: 0.5–0.84), respectively. Treatment exposure was twice as long for the rezvilutamide group at 28.9 months compared to the bicalutamide group at 12.9 months, with the most common reason for treatment discontinuation being radiographic progression that occurred in 52% of the rezvilutamide group compared to 44% of those in the bicalutamide arm. The most common treatment side-effect was hypertension that occurred in 8% in the rezvilutamide and 7% in the bicalutamide, hypertriglyceridemia in 7% compared to 2%, weight gain in 6% of rezvilutamide and 4% in bicalutamide, hyperkalemia in 3% in rezvilutamide and 1% in bicalutamide and anemia in 4% in rezvilutamide and 5% in bicalutamide arm. Serious adverse events occurred in 28% of patients who received rezviltuamide and 21% of those who got bicalutamide with transaminitis being the most common at 1% in the rezvilutamide arm. Dose interruption of rezvilutamide occurred in 12% compared to bicalutamide in 5% of patients.

The use of rezvilutamide in this patient population is promising. Multiple other ARPI have been combined with ADT and has changed the landscape of treatment and has become the standard of care for metastatic castration-sensitive prostate cancer (mCSPC) or mHSPC. However, it is increasingly clear that not all patients who are deemed eligible for treatment intensification actually receive it. For instance, one real-world database study looking at trends of ADT and intensification use spanning across January 2014 to July 2019 from two large United States database system (one from commercial and Medicare Advantage programs and the other from Centers for Medicare & Medicaid Services-sourced Medicare Fee-for-Service/FFS plans) concluded that about 45% of patients eligible for systemic intensification received ADT monotherapy only and only about 13% received abiraterone and 1% received docetaxel (3). Similarly, a Veterans Health administration claims database spanning 2013 to 2018 showed majority of men (67%) with mHSPC received ADT monotherapy, and about 24% received ADT with a novel ARPI but only 8% received ADT with docetaxel with 5% who received ADT and abiraterone (4). While the rationale is poorly understood, it is conceivable that toxicity is factored in these decisions rather than lack of awareness of study results especially when treatment intensification entails use of drug therapies that need to be undertaken for a prolonged period of time.

The eligibility population for CHART closely mimicked that of LATITUDE (5), which enrolled a narrow population of patients with predominantly high-risk group though the high-risk definition in LATITUDE included at least two of the three following high-risk factors: a Gleason score of ≥8, at least three bone lesions, and the presence of measurable visceral metastasis. On the other hand, CHART's eligibility definition was limited to high-volume disease per the CHAARTED (6) criteria which included presence of either four or more bone lesions at least one of which is beyond the axial and pelvic skeleton or presence of visceral metastasis by conventional imaging with CT and bone scan. This sets it apart from most other ADT with ARPI trials including the abiraterone trials in all-comers of *de novo* metastatic HSPC in STAMPEDE (7), enzalutamide for ARCHES (8) and ENZAMET (9) and apalutamide for TITAN (10), since the aforementioned trials included all patients regardless of volume status. In addition, the comparator arm for CHART was ADT with bicalutamide rather than ADT alone. Regardless, the potential benefits over bicalutamide warrants further analyses.

However, the ultimate question is how different (or similar) is rezvilutamide compared to currently existing and available ARPIs. While cross-comparison amongst different trials should not be made, the HRs for mOS and mOS rates appear to be comparable to most studies with ADT with ARPI (11). No patients in CHART received prior docetaxel so this was a rather homogeneous population of patients. While drug interaction was not well reported in this trial, cytochrome P450 enzyme inducer or inhibitor interactions

will be reported separately, as per the authors. In addition, given potentially less blood-brain-barrier penetration and off-target effects and inhibition of γ-aminobutyric acid (GABAa) receptor, there may be less central nervous effects as compared to other ARPIs like enzalutamide (1), though how similar this would be to darolutamide which does not cross the blood-brain-barrier well (12), is unknown. In terms of molecular structure, there are similarities though differences amongst different anti-androgens as well (13). Taken together, these datasets suggest a good rationale for adding rezvilutamide to the armamentarium of ARPIs. The ultimate question and limitation remains to be the accessibility and marketing opportunities for wider availability of this new drug across the globe, even as the market is dominated by currently existing ARPIs, some of which are cost-prohibitive and ultimately affects compliance and poses significant financial burdens (14).

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Qin X, Ji D, Gu W, et al. Activity and safety of SHR3680, a novel antiandrogen, in patients with metastatic castration-resistant prostate cancer: a phase I/II trial. BMC Med 2022;20:84.
2. Gu W, Han W, Luo H, et al. Rezvilutamide versus bicalutamide in combination with androgen-deprivation therapy in patients with high-volume, metastatic, hormone-sensitive prostate cancer (CHART): a randomised, open-label, phase 3 trial. Lancet Oncol 2022;23:1249-60.
3. Ryan CJ, Ke X, Lafeuille MH, et al. Management of Patients with Metastatic Castration-Sensitive Prostate Cancer in the Real-World Setting in the United States. J Urol 2021;206:1420-9.
4. Freedland SJ, Sandin R, Sah J, et al. Treatment patterns and survival in metastatic castration-sensitive prostate cancer in the US Veterans Health Administration. Cancer Med 2021;10:8570-80.
5. Fizazi K, Tran N, Fein L, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med 2017;377:352-60.
6. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med 2015;373:737-46.
7. James ND, de Bono JS, Spears MR, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med 2017;377:338-51.
8. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol 2019;37:2974-86.
9. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N Engl J Med 2019;381:121-31.
10. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med 2019;381:13-24.
11. Aragon-Ching JB. ARASENS: making sense out of

first-line metastatic hormone-sensitive prostate cancer treatment. Asian J Androl 2023;25:1-4.
12. Abbasi A, Movahedpour A, Amiri A, et al. Darolutamide as a Second-Generation Androgen Receptor Inhibitor in the Treatment of Prostate Cancer. Curr Mol Med 2021;21:332-46.
13. MedChemExpress (MCE) Chemical Structure: rezvilutamide, nilutamide, flutamide, bicalutamide, enzalutamide, darolutamide, apalutamide 2023. Available online: https://www.medchemexpress.com/rezvilutamide.html
14. Cortese BD, Chang SS, Talwar R. Urological Drug Price Stewardship: Potential Cost Savings Based on the Mark Cuban Cost Plus Drug Company Model. J Urol 2023;209:309-11.

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