

Polypharmacy and potential drug–drug interactions with novel androgen receptor signaling inhibitors (ARSIs) in patients (pts) with high-risk non-metastatic castration-resistant prostate cancer (nmCRPC) in a real-world setting.

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Background: Patients (pts) with nmCRPC are typically elderly, with comorbidities often leading to polypharmacy and a higher risk of drug–drug interactions (DDIs). Efficacy and safety of ARPIs may be compromised by DDIs. We aimed to evaluate the prevalence and relevance of polypharmacy and potential DDIs involving ARPIs in a real-world setting. **Methods:** We conducted a retrospective cohort (March 2009 to July 2023) at a tertiary cancer center. Patients with high-risk nmCRPC were defined by ≥ 3 consecutive PSA rises and a PSA doubling time (PSADT) < 10 months, with no metastasis on conventional imaging (CT and bone scans), as per criteria from pivotal trials (SPARTAN, PROSPER, ARAMIS). DDIs were assessed using Drugs.com and Lexicomp. Polypharmacy was defined as > 4 concomitant drugs. Overall survival (OS), prostate cancer–specific survival (PCSS), and metastasis-free survival (MFS) were estimated from nmCRPC diagnosis by the Kaplan–Meier method and analyzed with univariate Cox models. **Results:** A total of 1,234 pts with prostate cancer (ICD-10 C61) were screened, and 96 had high-risk nmCRPC. Median age was 73 years (IQR 69–80), PSA 3.0 ng/mL (IQR 1.1–8.5), PSADT 3.3 months (IQR 1.8–5.6), and Charlson Comorbidity Index 5 (IQR 5–7). Most patients (97%) used at least 1 concomitant medication, with a median of 4 (IQR 3–6). Polypharmacy occurred in 43% and was associated with a trend to shorter OS (3.6 vs 4.5 y; HR 1.53, 95% CI 0.93–2.47, $p = 0.08$) and PCSS (3.6 vs 5.1 y; HR 1.52, 95% CI 0.95–2.47, $p = 0.09$), but not MFS (2.1 vs 2.9 y, $p = 0.64$). Potential DDIs were more frequent with enzalutamide and apalutamide (Table). Amlodipine (18%) was the most common major interaction in the Drugs.com database; omeprazole (18%) was most associated with prohibitive interactions (risk rating X) in Lexicomp. Cross-database inconsistencies were identified: 1 major and 15 moderate interactions reported only in Drugs.com, and 6 Lexicomp category C interactions not listed in Drugs.com. **Conclusions:** Polypharmacy and potential DDIs with ARPIs are common in nmCRPC. Although darolutamide was associated with fewer interactions, some major or X-rated DDIs were observed, reinforcing the need for individualized management and database cross-checking. Research Sponsor: None.

Potential DDIs with ARPIs in different databases.			
Drugs.com – n (%)			
	Minor	Moderate	Major
Enzalutamide	1 (1%)	83 (86.4%)	28 (29.1%)
Apalutamide	1 (1%)	82 (85.4%)	28 (29.1%)
Darolutamide	27 (28.1%)	20 (20.1%)	2 (2.1%)
Lexicomp – n (%)			
	C	D	X
Enzalutamide	60 (62.5%)	9 (9.37%)	1 (1%)
Apalutamide	49 (51%)	7 (7.3%)	20 (20.8%)
Darolutamide	40 (41.6%)	1 (1%)	1 (1%)