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Review

Androgen receptor pathway inhibitors, prostate cancer, and older adults: a global Young International Society of Geriatric Oncology drug review

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***Abstract*:** Prostate cancer is a disease of older adults that has undergone a significant therapeutic paradigm shift in the last decade with the emergence of novel androgen receptor pathway inhibitors (ARPis). One of the more commonly used ARPis is enzalutamide. This drug, along with darolutamide and apalutamide, initially received approvals in the metastatic castrate-resistant prostate cancer setting but is now utilized frequently in the metastatic castrate-sensitive and non-metastatic castration-resistant settings. Landmark phase III data illustrating ARPi efficacy in older adults are limited to those with excellent performance status. However, its role in unfit older prostate cancer patients remains to be explored in the context of a narrative review. This first-of-its-kind drug review aims to shed light on the most up-to-date evidence behind the unique toxicity profile of ARPis in the context of geriatric vulnerabilities such as cognitive and functional impairment, along with potential solutions and supporting evidence that exists to circumvent these issues in the vulnerable older adult.

Keywords: hormone therapy, palliative treatment, prostate cancer, targeted therapy, toxicity management

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Introduction

Prostate cancer is a disease in older men. Seventy-five percent of prostate cancer incidence and >90% of prostate cancer mortality occur in men over 65 years.[1] Older men are also more likely to have other concomitant comorbidities. It has been reported that more than 50% of men with prostate cancer over 75 years have at least one severe comorbidity.[2] In addition to comorbidities, they may also have decreased functional reserves due to normal aging.[3] Thus, these factors must be considered in treating older prostate cancer patients.

The treatment of metastatic prostate cancer has changed significantly over the past decade. In the past, surgical or chemical castration *via* androgen deprivation therapy (ADT) was the mainstay of treatment upon diagnosis of metastatic castrate-sensitive prostate cancer (mCSPC). Treatment with cytotoxic chemotherapy regimens was typically recommended upon progression to metastatic castrate-resistant prostate cancer (mCRPC).[4] More recently, several pivotal randomized controlled trials (RCTs) have established the role of androgen receptor pathway inhibitors (ARPis) in different stages of the disease course. Initially, the use of ARPis was evaluated in the post-docetaxel mCRPC setting, which showed an absolute improvement in median overall survival (OS) of approximately 4 months.[5,6] When the use of ARPis in the upfront mCSPC setting was evaluated, the improvement in OS was significantly larger.[4,7–9] These drugs have also found their place in improving outcomes of nonmetastatic castrate-resistant prostate cancer (nmCRPC).[10,11] No phase III trials specifically investigated the role of ARPis in older adults, they still constitute a large proportion of enrolled patients in these pivotal studies.

The Young International Society of Geriatric Oncology (SIOG) interest group comprises junior SIOG members within 10 years of exit from a formal training program who share a common interest in advancing the care of older adults with cancer. Our narrative review provides a focused study of randomized and observational data that define the successes and limitations of ARPis in the vulnerable patient population of older adults with prostate cancer. We will use elements of the geriatric assessment (GA) to inform discussions about what is known about this drug's off-target effects on objective measures of frailty and health status in line with the recently published SIOG guidelines.[12]

Post-hoc analyses of RCTs involving ARPis

Several post-hoc subgroup analyses on pivotal trials of ARPis have been conducted to review its role in older adults, as shown in Table 1. AFFIRM and PREVAIL were phase III trials investigating the role of enzalutamide in the post-docetaxel and docetaxel-naïve mCRPC settings, respectively.[5] In the AFFIRM trial, enzalutamide was compared to placebo, and it showed a significantly prolonged median OS of 18.4 *versus* 13.6 months, hazard ratio (HR) 0.63 [95% confidence interval (CI): 0.53–0.75; $p < 0.001$]. A post-hoc analysis of the AFFIRM trial was conducted to review the safety and efficacy of enzalutamide in the older adult population as defined by age ⩾75 years. In patients ⩾75 years, median OS was 18.2 *versus* 13.3 months; HR 0.61 (95% CI 0.43–0.86); $p = 0.004$. Adverse events (AEs) were similar between ⩾75 and <75 age groups, the exceptions being an increase in the rates of all grade peripheral edema (22.1% *versus* 12.5%), fatigue (39.7% *versus* 31.6%), and diarrhea (26.6% *versus* 19.6%), which were higher in the ⩾75 age group. The study concluded that although the post-hoc analysis showed a clinical benefit in older adults regardless of age, most of the patients (91.5%) in the trial were Eastern Cooperative Oncology Group (ECOG) 0-1 despite having had 1 or 2 rounds of cytotoxic chemotherapy.[5,13] These results emphasize the importance of assessing physiological age rather than chronological age as an indicator of fitness for treatment.

The PREVAIL trial compared enzalutamide to a placebo in the docetaxel naïve mCRPC setting. This trial showed a prespecified subgroup analysis of men ⩾75 years and <75 for co-primary endpoints and AEs. In all, 609 men were aged ⩾75 years, of which 317 patients received enzalutamide and 292 received a placebo. A comparison between the subgroups of men ⩾75 years and <75 showed a higher proportion of younger patients with a better ECOG performance score of 1 at 45% *versus* 24.7% compared to the older-aged subgroup. In the older patient subgroup, the median OS was 32.4 *versus* 25.1 months; HR = 0.61; 95% CI: 0.47–0.79; $p = 0.0001$, suggesting the benefit of enzalutamide in the elder with mCRPC.[14] In terms of AEs, the age ⩾75 years subgroup had a higher incidence of any grade AEs, falls (any grade, 19.2% *versus* 7.2%; grade ⩾3, 2.2% *versus* 0.9%), fractures (15.8% *versus* 9.9%), decreased appetite (22.1% *versus* 15.9%), and asthenia (17.0% *versus* 10.6%), compared to the aged <75 years subgroup. The analysis concluded that enzalutamide was associated with improved OS in patients ⩾75 years old, although the drug led to an increased risk of falls among the elderly.[14]

Besides the pivotal phase III trials, randomized phase II studies on enzalutamide in the mCRPC setting have also been conducted. TERRAIN is a phase II trial that randomized patients to either enzalutamide or bicalutamide. A post-hoc analysis of older (⩾75 years of age) and younger (<75 years of age) patient subgroups was conducted to evaluate the efficacy and safety of enzalutamide compared with bicalutamide. Results of the trial showed that enzalutamide significantly reduced the risk of disease progression compared to bicalutamide in both subgroups (HR: 0.59; 95% CI: 0.37–0.92; $p = 0.018$ in the older subgroup). AEs between both subgroups were similar, although there was a higher incidence of specific grade 3 AEs with enzalutamide in the age <75 subgroups compared to the ⩾75 subgroups. These included cardiac events (2.4% *versus* 12.1%), urinary tract infections (2.4% *versus* 20.7%), falls (4.0% *versus* 12.1%), and decreased appetite (6.4% *versus* 15.5%).[15]

Two pivotal phase III trials published in 2019, ENZAMET and ARCHES, investigated the role of enzalutamide in the mCSPC setting. The ENZAMET trial randomized 1125 mCSPC men receiving ADT to either enzalutamide or a non-steroidal anti-androgen, for which docetaxel was allowed in the trial based on physician choice. ENZAMET was the first enzalutamide trial to report a significant improvement in OS (HR: 0.67, 95% CI: 0.52–0.86) in mCSPC patients. In this trial, 514 (45%) patients were aged ⩾70 years, with results of the subgroup analysis showing an

Table 1. Summary of age-stratified post-hoc analysis of RCTs with ARPis.

	Demographics	OS	PFS	AEs
AFFIRM[5]	⩾75 years: $n=199$; <75 years: $n=601$	⩾75 years: median (18.2 *versus* 13.3); HR: 0.61 (95% CI: 0.43–0.86); $p=0.004$	⩾75 years: rPFS HR: 0.27 (95% CI: 0.20–0.37); $p<0.001$	All grade peripheral edema (22.1% *versus* 12.5%), fatigue (39.7% *versus* 31.6%), and diarrhea (26.6% *versus* 19.6%) between ⩾75 and <75 years
PREVAIL[14]	⩾75 years: $n=609$; <75 years: $n=1108$	⩾75 years: median (32.4 *versus* 25.1) HR: 0.61 (95% CI: 0.47–0.79); $p=0.0001$	⩾75 years: rPFS (NR *versus* 3.7 months) HR: 0.17 (95% CI: 0.12–0.24); $p<0.0001$	Any grade ⩾3 AEs (48.9% *versus* 39.5%), falls (any grade, 19.2% *versus* 7.2%; grade ⩾3, 2.2% *versus* 0.9%), fractures (15.8% *versus* 9.9%), decreased appetite (22.1% *versus* 15.9%), and asthenia (17.0% *versus* 10.6%) between ⩾75 and <75 years
TERRAIN[15]	⩾75 years: $n=130$; <75 years: $n=245$	Not available	⩾75 years: HR: 0.59 (95% CI: 0.37–0.92); $p=0.018$	Grade 3 AEs (50% *versus* 32%), grade ⩾3 cardiac (12.1% *versus* 2.4%), urinary tract infections (20.7% *versus* 2.4%), falls (12.1% *versus* 4.0%), and decreased appetite (15.5% *versus* 6.4%) between ⩾75 and <75 years
ENZAMET[8]	⩾70 years: $n=257$; <70 years: $n=306$	⩾70 years: HR: 0.56 (0.39–0.81)	⩾70 years: HR: 0.33 (0.25–0.44)	No subgroup analysis by age
ARCHES[16,17]	⩾75 years: $n=339$; <75 years: $n=811$	⩾75 years: median (NR *versus* 49.7 months); HR: 0.76; CI: 0.54–1.09	⩾75 years, rPFS (48.6 *versus* 43.1 months); HR: 0.72 (CI: 0.52–1.02)	Any grade 3 AEs (55.9% *versus* 39.6%), any grade cardiac (11.4% *versus* 7.9%), falls (17.3% *versus* 7.2%), fracture (14.3% *versus* 13.1%), cognitive impairment (8.3% *versus* 5.9%), loss of consciousness (6.0% *versus* 1.2%) between ⩾75 and <75 years
SPARTAN[18]	⩾80 years: $n=317$; 65–79 years: $n=741$; <65 years: $n=149$	⩾80 years: HR: 0.81; CI: 0.58–1.15; 65–79 years: HR: 0.89; CI (0.69–1.16).	⩾80 years: HR: 0.43; CI (0.28–0.65); 65–79 years: MFS HR: 0.29; CI (0.23–0.37)	AEs leading to treatment discontinuation, falls, and ischemic heart disease were increased with age regardless of treatment. Rates of skin rash were increased with age in the apalutamide groups
TITAN[18]	⩾80 years: $n=93$; 65–79 years: $n=628$; <65 years: $n=331$;	⩾80 years: HR: 0.74; CI: 0.40–1.39; 65–79 years: HR: 0.70; CI: 0.54–0.91	⩾80 years: rPFS HR: 0.55; CI (0.25–1.21); 65–79 years: rPFS HR: 0.51; CI (0.39–0.68)	
ARAMIS[11]	⩾85: $n=130$; 75–84 years: $n=593$; 65–74: n=589; <65 years: $n=197$	⩾85 years: HR 0.51; CI: 0.27–0.96; 75–84 years: HR: 0.43; CI: 0.31–0.60; 65-74 years: HR 0.35 (0.26–47); ⩾65 HR 0.59 (0.37–0.95).	No subgroup analysis by age	No subgroup analysis by age

AEs, adverse events; ARPis, androgen receptor pathway inhibitors; CI, confidence interval; HR, hazard ratio; MFS, metastasis-free survival; RCTs, randomized controlled trials; rPFS, radiographic progression-free survival.

improvement in OS and PFS with HR = 0.56 (0.39–0.81) and HR = 0.33 (0.25–0.44), respectively, in this group.[8] Unfortunately, there has been no analysis of the adverse effects based on age.

On the other hand, the ARCHES trial randomized 1150 men with mCSPC to receive ADT with either enzalutamide or placebo. The primary endpoint was radiographic progression-free survival (rPFS). In this trial, 73% of the men were

aged ⩾65 years, with 29% aged ⩾75. The addition of enzalutamide to ADT significantly reduced the risk of radiographic progression (HR: 0.39, 95% CI: 0.30–0.50). Across patients ⩾65 years, there was a consistent benefit of rPFS at HR = 0.44 (0.33–0.58). Grade 3 or higher AEs leading to discontinuation were similar in both groups.[9] A recent report out of final OS data of ARCHES at ESMO 2021 revealed extended survival *versus* placebo at HR = 0.66 (0.53–0.81) with similar results in most prespecified subgroups, including age.[16] A follow-up post-hoc age-stratified (<75 and ⩾75 years) analysis of enzalutamide's efficacy from ARCHES recently presented at ASCO's May 2022 annual scientific meeting by Szmulewitz *et al.* revealed improved OS (not reached *versus* 49.7 months) and rPFS (48.6 *versus* 43.1 months) compared to placebo in the ⩾75 years group. Although the HR CIs for both outcomes crossed 1.0, OS benefit was observed when adjusted for a crossover done by about 30% of the placebo cohort. Furthermore, a higher incidence of falls, cognitive impairment, cardiovascular events, and loss of consciousness was reported among this population compared to their younger counterparts (see Table 1).[17]

After its success in the mCSPC[19] and nmCRPC[10] settings, apalutamide has had one combined post-hoc age-stratified analysis of its efficacy and safety of TITAN and SPARTAN cohorts.[18] By dividing patients into <65 and 65–79 and ⩾80 age groups, Shen *et al.* found that while older adults received acceptable PSA response, quality of life (QoL), and PFS benefit, those over 80 did not receive a net survival benefit. Furthermore, an examination of exposure-adjusted rates of AEs leading to treatment discontinuation falls, and ischemic heart disease from both trial cohorts revealed increased incidence with age regardless of treatment group, associated with an immediate 50% reduction in median treatment duration in those over 80.[18] Skin rash seen with apalutamide was also more common with age in the apalutamide groups.[18]

ARAMIS was the first trial to demonstrate darolutamide safety and efficacy in nmCRPC.[11] The trial randomized 1509 nmCRPC patients receiving ADT to either darolutamide or placebo. ARAMIS reported improvements in metastasis-free survival (MFS) (HR: 0.41, 95% CI: 0.34–0.50) and OS (NR *versus* 78 months, HR: 0.71, 95% CI: 0.50–0.99). In this trial, 723 (48%) patients were aged ⩾75 years, with results of the subgroup analysis revealing an improvement in MFS in both 75–84 years (HR: 0.43, 95% CI: 0.31–0.60) and ⩾85 years (HR: 0.51, CI: 0.27–0.96). There has been no analysis of the adverse effects based on age.[11]

Geriatric assessment and ARPis

Current 2019 recommendations put forth by the International SIOG stipulate that men over the age of 70 years with prostate cancer should be managed according to their health status rather than their chronological age[12] SIOG recommends that, at a minimum, the G8 and Mini-Cog screen for cognitive impairment should be performed as part of a GA of health, comorbidities, and nutritional status impairment. Patients with a score of <3/5 on the Mini COG must be referred for evaluation of dementia and decision-making capacity,[20] and <14/17 on the G8 was considered abnormal[21] and should be followed by a GA. Guidelines suggest that patients be divided into groups, like 'healthy or fit', 'vulnerable', or 'frail' (see Figure 1). Fit individuals were defined as those who scored >14/17 on Geriatric 8 (G8) screening and were, therefore, appropriate for standard treatment. Frail patients were noted as those with significant comorbidities or who cannot independently carry out many Activities of Daily Living (ADLs). Frail patients are unlikely to benefit from standard treatment and should receive adapted or palliative treatment instead. Vulnerable patients lie between the two groups and have impairment in some ADLs or moderate malnutrition or comorbidities. With geriatric interventions implemented based on GA findings, vulnerable patients can become fit enough to be eligible for standard treatment.

The GA is a comprehensive tool that assesses a gamut of domains, including but not limited to functional status, psychiatric disease, fatigue, comorbidity, nutrition, and cognitive decline (see Figure 2).[22] The GA has proven to help predict survival and expected toxicity from chemotherapies in older cancer patients.[23] Backed by randomized data,[24,25] the GA also guides geriatric interventions that could later improve oncologic outcomes and treatment tolerability. Various studies have shown that information obtained from a GA leads to modification of the initial treatment proposed by the oncologist in up to 50% of cases depending on the series.[26–31] Another advantage of the GA is that it detects problems that would have otherwise been missed if only functional status assessment (e.g. ECOG) was done.[32]

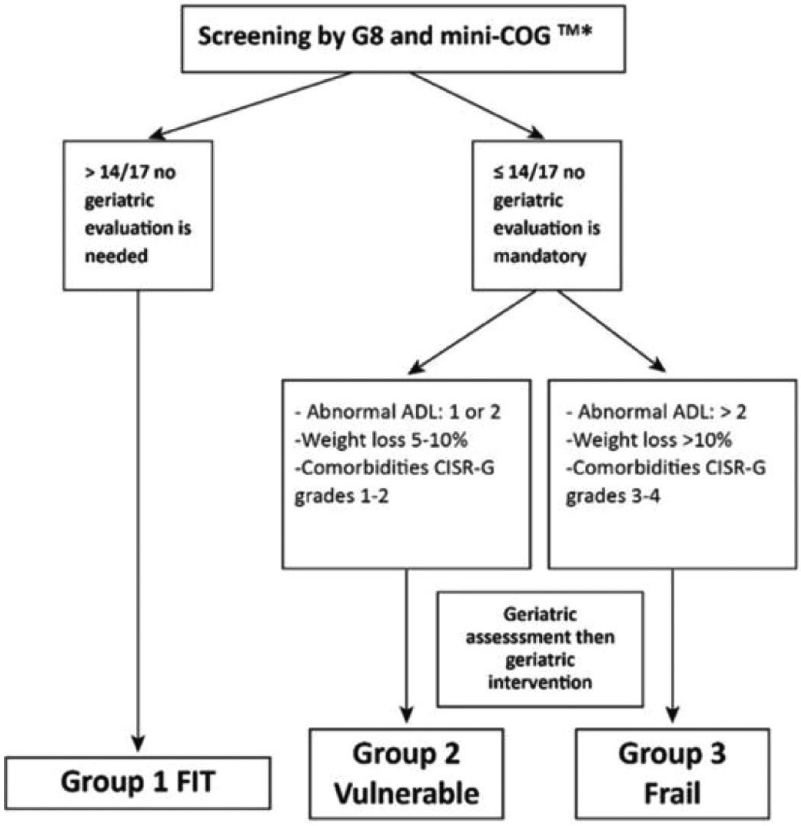

Figure 1. Adapted SIOG decision tree to evaluate health status in the geriatric patient with cancer.[12]
SIOG, International Society of Geriatric Oncology.

Given the success of the GA when considering older patients for chemotherapy, its role in predicting the benefit and toxicities of ARPis has yet to be elucidated. While there is evidence to suggest that patients over the age of 75 benefit from the use of ARPis like enzalutamide, geriatric testing has the potential also to identify older (>75 years) prostate cancer patients who might derive the most survival benefit with acceptable levels of toxicity. As ARPis are associated with fatigue, falls, but are even approved in the non-metastatic setting,[34] a detailed look at recent evidence linking geriatric syndromes to ARPi exposure is warranted and summarized in Table 2. It is worth noting that most studies in this space rarely explore ARPis like enzalutamide in isolation. Most often compare ARPis toxicity to other novel androgen synthesis inhibitors like abiraterone or report it in the context of castrate-resistant disease. Results are also derived from observational and retrospective research or systematic reviews confounded by significant heterogeneity.

Functional capacity and sarcopenia

Objective changes in physical function and body composition occur as the prostate cancer stage advances.[35] These changes may be key to understanding enzalutamide's objective and physical consequences.

A cross-sectional analysis of previously published data on four cohorts of non-cancer controls, mCSPC, and mCRPC by Hanson *et al.* has recently demonstrated that body composition and physical function change along the continuum of cancer, castrate sensitivity, and novel ARPi exposure.[35] Whole body dual-energy X-ray absorptiometry measured absolute and relative total fat and lean muscle mass. Physical function was evaluated using 6-meter rapid walk, five chair stands, stair climbing, and timed up and go tests. Healthy men had lower absolute fat mass, higher lean mass, and higher physical function compared to men with mCSPC, who had evidence of a higher fat to lean muscle ratio. Men who had

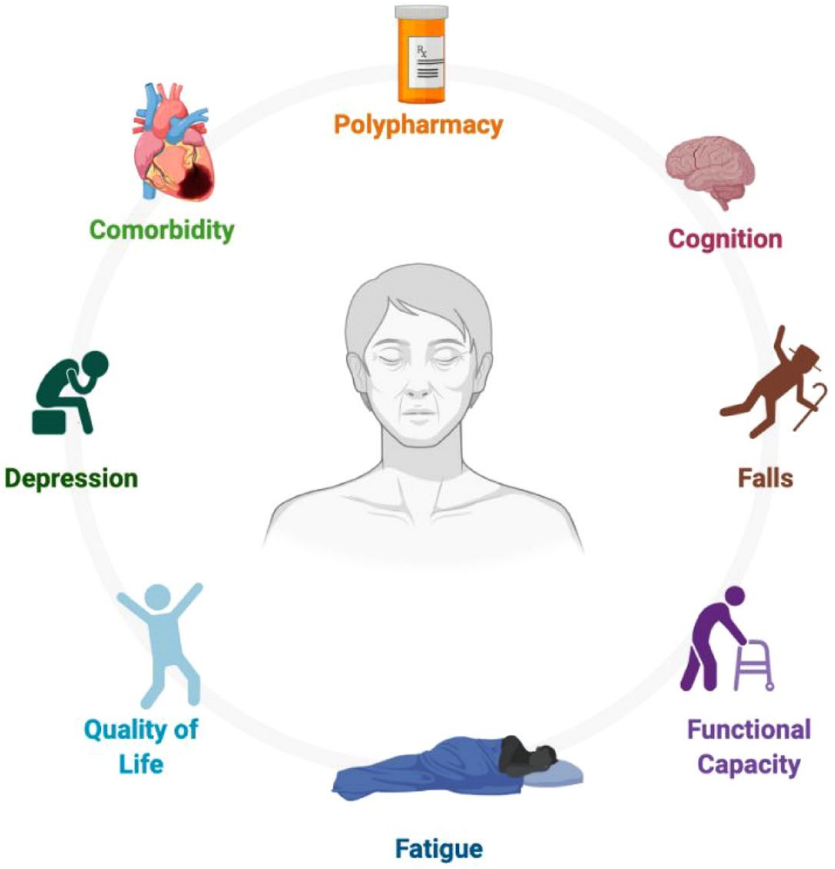

Figure 2. Core components of the CGA.
Source: Adapted from 'why we need to increase diversity in the immunology research community', by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates.
CGA, comprehensive geriatric assessment.

progressed to castrate resistance and required ARPis like enzalutamide had further deterioration in body composition, significantly lower physical function, and lower QoL compared to the other two cohorts.

Furthermore, men with mCRPC who were started on ARPis, as opposed to mCSPC patients on ADT alone, were noted to have the *lowest* functional performance in tasks against gravity, such as the timed up and go and stair climbing.[35] Hanson *et al.* also noted that ADT duration was similar between mCSPC and mCRPC groups, which suggests that the addition of an ARPis contributes, in part, to further worsening of body composition and decline in physical function. Even so, changes in physical performance with ARPis like enzalutamide are not always negative and do not only impact tests against gravity. A recent publication from the University of Toronto examined similar measures of physical performance at baseline, 3 months, and 6 months in patients with mCRPC. They found no significant change in outcomes such as the short physical performance battery (SPPB), which also involves chair stands (i.e. tests against gravity)[36] even when stratifying for treatment type (enzalutamide *versus* other ARPis).[37] Interestingly, frail men in this cohort had significantly poorer baseline SPPB scores ($p < 0.0001$) and grip strength ($p < 0.0001$) but had the most remarkable improvement in SPPB and physical well-being over time with enzalutamide therapy while losing the points in grip strength.

While differences between mCSPC and mCRPC patients are apparent, it is clear that changes in physical performance measures are not only related to castration status. Baseline composition likely also plays a role; those with leaner body composition profiles (lower fat % and higher lean mass %) in the Hanson *et al.* study were more likely to have

Table 2. Summary of GA-relevant outcomes with ARPis exposure described in the literature.

GA outcomes	Conclusions on ARPis
Functional capacity and sarcopenia	Enzalutamide mixed impact on elder-relevant physical function outcomes[35–37] [Level: 3] Consistent declines in muscle mass with enzalutamide [ref][35,38–40] [Level: 2]
Fatigue	Significant self-reported fatigue noted with enzalutamide is likely more prevalent in those with a higher burden of disease or pre-treated patients regardless of age but potentially more intense in mCSPC patients.[41] Self-reported fatigue with apalutamide compared to baseline is likely not different than placebo in mCSPC.[42] [Level: 2] Enzalutamide is associated with a higher risk of any grade fatigue but not a statistically significant difference in high-grade fatigue compared to abiraterone in mCRPC[43] [Level: 1-] No significant difference in fatigue in high-risk nmCRPC patients with apalutamide, enzalutamide *versus* darolutamide[44] [Level: 1-]
Quality of Life	No statistically or clinically significant quality of life changes are seen with enzalutamide or apalutamide in mCSPC[45] [Level :2] Enzalutamide seems to be associated with poorer short-term health-related quality of life than abiraterone in men treated for mCRPC. This difference was not apparent at longer follow-up.[46] [Level: 1-] No significant difference in quality of life in nmCRPC patients with apalutamide, enzalutamide *versus* darolutamide.[47] [Level: 1-]
Falls and fracture	Increase in falls and fractures as a class effect regardless of age in metastatic prostate cancer but darolutamide is likely the lowest risk offender[48] especially in nmCRPC.[44] [Level: 1-]
Cognition and depression	ARis, most notably enzalutamide, are associated with a higher incidence of neurocognitive symptoms in patients with mCRPC.[49–51] [Level: 1-]
Comorbidity and polypharmacy	Enzalutamide has a significant positive relationship with ischemic heart disease[52,53], and risk of major drug–drug interactions[54,55] [Level 4] Darolutamide displays safety and efficacy even in nmCRPC patients with multiple comorbidities or concomitant medications[56] [Level: 2]

*Categories and grades of evidence from the 2011 Oxford Center for evidence-based medicine levels of evidence, http://www.cebm.net.
'-' represents significant or unknown heterogeneity in systematic review.
ARPis, androgen receptor pathway inhibitors; GA, geriatric assessment; mCRPC, metastatic castrate-resistant prostate cancer; mCSPC, metastatic castrate-sensitive prostate cancer; nmCRPC, nonmetastatic castrate-resistant prostate cancer.

higher functional capacity. Duration of ARPis exposure is also impactful. Patients in the mCRPC cohort who had lost lean mass in Hanson *et al.*'s study were on therapy for 6 months (std dev ± 5 months).[35] A separate Toronto cohort of mCRPC patients who had been on enzalutamide ($n = 29$) for 24 months had evidence of an increase in the rate of loss of muscle mass/sarcopenia after 1 year of therapy by CT-derived Psoas Muscle Index (defined as the total contour area of the left

and right psoas muscle at the inferior endplate of L3 divided by patients' height in meters).[38] Unfortunately, how a longer duration of treatments like enzalutamide and castration status interacts with measures of body composition and physical performance remains to be determined. These changes in muscle mass may also not be unique to enzalutamide as described in both cohorts[35,38] and previous studies using patients from the French AFFIRM cohort, which found similar changes in body composition with enzalutamide as compared to that by other therapies like abiraterone.[39] The HEAT RCT compared both drugs head to head in the mCRPC population and found a small but consistent negative impact weight, body mass index, lean body mass, and visceral adiposity in enzalutamide users.[40] Such *objective* measures of function and body composition are also not standard in prostate cancer trials that use enzalutamide in adults aged 70 or above. Understanding these changes bears importance when assessing the ability of the older adult to function, live independently, and determine their risk of falls.

Falls, Fatigue, and Quality of Life

Subjective measures are more commonly used as part of routine AE reporting for ARPi clinical trials due to their ease of measurement. These include patient-reported outcome (PRO) measures of fatigue, functional QoL, and the incidence of reported falls and fractures while on therapy. These measures are all components of the GA and are functional endpoints to assess in older adults on treated with ARPi therapy.

Fatigue is a common complaint among community-dwelling older adults.[57] Patients with prostate cancer also experience this, and its intensity increases with disease progression and the use of enzalutamide.[41] Using the single-item fatigue score Functional Assessment of Cancer Therapy–Prostate questionnaire (FACT-P) item GP1 'I have a lack of energy', Tombal *et al.* compared patient-reported fatigue over time in the four pivotal placebo-controlled trials of Enzalutamide: ARCHES,[9] PROSPER,[34] PREVAIL,[13] and AFFIRM.[39,41] More than 50% of patients on enzalutamide experienced fatigue despite castration status. The highest *prevalence* of fatigue was seen in patients with a high metastatic burden and heavily pretreated castrate-resistant disease. In contrast, the *fatigue intensity* with enzalutamide displays an interesting pattern of presentation. The *early* presentation of worsening fatigue was notable across all studies but more pronounced, compared to placebo, in the mCRPC setting (AFFIRM and PREVAIL). Worsening grades of fatigue (by $\geqslant$13 units of intensity in item GP1) were seen in all cohorts with more mCSPC patients (ARCHES) reporting higher intensity of fatigue (by $\geqslant$3 units) by the end of assessment. Nevertheless, the overall difference in intensity was low between cohorts and the level of fatigue remained grossly stable between Weeks 13/17 until the end of assessment across all cohorts. Furthermore, in the mCRPC setting, age over 75 does not seem to modulate the prevalence or intensity of fatigue either, as reported in the recent post-hoc analysis of the PREVAIL compared to those younger than 75 (37.5% *versus* 34.5%).[14]

Chungh *et al.* analysis of self-reported fatigue at baseline and averaged over 7 first consecutive days each cycle (D-6 to D + 1) from the TITAN study found that mCSPC patients on apalutamide reported no additional fatigue from baseline compared to placebo when scored using the Brief Fatigue Inventory. Data from all time points, including baseline PRO score and stratification factors were included in the analysis.[42] A literature-based meta-analysis of fatigue of ARPi use in mCRPC setting found enzalutamide to show a statically significant increase in any-grade fatigue with a low heterogeneity (relative risk RR = 1.34, 95% CI: 1.21–1.48; $p < 0.05$) while abiraterone had a lower RR of grade 3–4 fatigue; high-grade fatigue with abiraterone was not significantly different than enzalutamide.[43]

Falls are another AE that appears to be a class effect among ARPis as reported in a systematic review of 11 clinically heterogeneous randomized clinical trials using novel ARPis (enzalutamide, apalutamide, or darolutamide). All-grade falls and fractures with enzalutamide were 8% (6.78–8.39%) and 1.8% (95% CI, 1.4–2.2%), respectively; this was second to ARPis like apalutamide but better than darolutamide.[48] Age may also modulate this effect where patients >75 in the PREVAIL study had a higher reported incidence of falls (19.2% *versus* 7.2%) and fracture (15.8% *versus* 9.9%) compared to the <75 cohort.[14] Similar age-stratified findings were reported in the TERRAIN trial of enzalutamide *versus* bicalutamide in mCRPC, where a post-hoc analysis concluded that those treated with enzalutamide suffered increased falls of all grades of, particularly in the older >75 age group (12.1% *versus* 4.0%) (see Table 1).[15] A systematic review and network meta-analysis focusing on AEs in high-risk

nmCRPC of apalutamide *versus* enzalutamide *versus* darolutamide found no statistically significant difference in grade 3–4 fatigue or falls but consistently found darolutamide to be the lowest risk offender by network meta-analysis-derived ranking.[44]

Finally, QoL is commonly measured in ARPi clinical trials, but there is limited evidence isolated to vulnerable older adults. A systematic review and network meta-analysis by Menges *et al.* found substantial between-study variation in reported instruments and analyses of HRQoL-related outcomes, precluding the conduct of meta-analyses but comparison within drugs, enzalutamide and apalutamide, did not find a statistical or clinically significant reduction in QoL.[45] A systematic literature review of PROs by Ternov *et al.* found that mCRPC enzalutamide users reported no change or minor reductions in long-term QoL but relatively lower short-term QoL than abiraterone users of all ages, including those aged >75.[46] A recent phase IV RCT by Ternov *et al.* studying fatigue and health-related QoL in the same mCRPC population found that after 12 weeks, abiraterone users had overall less fatigue and a statistically positive trend to favorable QoL but suffered a higher incidence of new-onset diabetes compared to enzalutamide users.[40] A meta-analysis comparing apalutamide, enzalutamide, and darolutamide in phase III clinical trials (SPARTAN, TITAN, PROSPER) involving patients with nonmetastatic castration-resistant prostate cancer QoL found all three drugs generally well tolerated.[47]

Cognition and Depression

Cognitive decline occurs with advancing age and may be worsened by exposure to ADT and treatment with enzalutamide.[58] Cognitive dysfunction markedly affects patients' QoL,[59] reduces decision-making capacity with autonomy,[60] and may even contribute to cancer-related mortality,[61] making cognition a central component of the GA. A recent review by Morgans *et al.*[58] summarized factors contributing to cognitive decline in patients requiring androgen deprivation for their prostate cancer. Such factors include the following:

- Genetic susceptibilities to dementia
- Occurrence of stroke or propensity for other neurocognitive disorders
- Use of concomitant medications like opioids

Compared to darolutamide and apalutamide, enzalutamide is reported to cross the blood–brain barrier at a significantly higher rate,[62] makes understanding its cognitive toxicities crucial to guide prescribing. Darolutamide, on the other hand, has shown limited CNS penetration in human studies.[63]

REAAcT, a real-world study of nearly 100 mCRPC patients receiving enzalutamide or abiraterone, found that patients consuming enzalutamide reported more frequent and unique cognitive symptoms, including confusion and amnesia, memory impairment, and other non-specific cognitive symptoms (52% *versus* 36%). Also, more frequent dose reductions (16% *versus* 6%) than those receiving abiraterone acetate.[49] However, the mean changes from baseline for the Cogstate tests (a computer program that objectively measures four cognitive domains, including simple reaction time, choice reaction time, visual episodic memory, and working memory) and the subjective FACT-Cog assessment were similar. Caregiver survey responses noted more fatigue with enzalutamide and more moodiness with abiraterone than patient responses.[50] These results are further supported by Briggs *et al.*'s disproportionality analysis of all hormone therapies within VigiBase, the World Health Organization's international pharmacovigilance database. The authors found higher odds of neurocognitive and dementia-related AEs with ARPis, driven mostly by enzalutamide rather than apalutamide and abiraterone, over traditional ADT.[51]

Similar results were reported in the prospective 12-month multisite phase IV AQUARiUS 2019 study. Patients with mCRPC receiving enzalutamide reported significantly higher fatigue, perceived cognitive impairment, and cognitive decline than those receiving abiraterone acetate.[64] Some of the earliest (within 30 days), largest, and most significant differences in cognition PROs were reported in 'perceived cognitive impairment' by FACT-Cog, which prevailed even within 300 days of exposure. Even more extensive and earlier retrospective studies support this difference; Pilon *et al.* compared enzalutamide (N= 592) to other hormonal (abiraterone (N= 1067) or chemotherapy agents (N= 256) used in mCRPC.[65] Patients starting treatment with enzalutamide were more likely to have CNS events at

12 months than abiraterone (46.0% *versus* 39.5%, $p = 0.0036$) and chemotherapy (51.1% *versus* 39.5% $p = 0.0277$). Given this, compliance to enzalutamide has proven challenging; adherence data presented by Rescigno *et al*. at 2022 ASCO GU found that enzalutamide users ($n = 148$) out of 234 mCRPC patients over age 70 started on either abiraterone or enzalutamide experience more nonadherence (5.2 *versus* 4.2 missed/prescribed pills, $p < 0.001$) most commonly due to forgetfulness (42% *versus* 17%, $p < 0.001$). Abiraterone users in this cohort were found to have a longer PFS [28.4 (24.2–32.5) *versus* 23.1 (18.2–28.1) months, $p = 0.041$].[66]

Depression is another crucial component of the GA. A systematic review of 15 heterogeneous studies amounting to nearly 9000 patients found ARPis as class improve PRO emotional well-being measures compared to placebo or prednisone alone but not compared to bicalutamide; enzalutamide, however, delayed short-term emotional functioning and was likely more cognitively harmful compared to abiraterone.[67] Psychiatric concerns appear to translate to the real-world setting. The European Union EudraVigilance database and meta-analysis of registrational phase III studies found that, compared to placebo, enzalutamide showed an increased RR of psychiatric disorders ($R = 2.41$; 95% CI: 1.54–3.77) and nervous system events across all age groups.[68]

Comorbidity and polypharmacy

Estimating comorbidity and a comprehensive medication review is central to the GA and may inform the use of enzalutamide in older individuals with metastatic prostate cancer. Cardiovascular disease is more prevalent in older adults[69] and thus is a known factor when selecting therapeutics for prostate cancer. Large retrospective studies of the Veterans Health Administration show that veterans prescribed enzalutamide tend to be older (74.2 *versus* 73.7 years, $p = 0.032$), have higher Elixhauser comorbidity scores (7.1 *versus* 6.7, $p = 0.002$), and remain on treatment longer (10.5 months *versus* 9.0 months, $p < 0.001$) than those who were prescribed abiraterone.[70] A more focused assessment of veterans with chemotherapy naïve mCRPC found that even with adjusting for baseline comorbidity, enzalutamide-treated patients had a 16% reduced risk of death (HR: 0.84; 95% CI: 0.76–0.94; $p = 0.0012$) compared to those treated with abiraterone. These differences could be due to the well-established cardiovascular toxicities of abiraterone.[71,72] However, data isolated from a combined analysis of enzalutamide's placebo-controlled RCTs suggest a significant risk of ischemic heart disease with this agent[52] and a recent Surveillance, Epidemiology, and End Results-Medicare–linked (SEER-Medicare) retrospective study of showed a higher 6-month mortality rate in both groups with pre-existing CVD conditions independent of the drug used.[53] These results support using a standard comorbidity assessment as recommended by SIOG but warrant further prospective studies when evaluating those with cardiovascular comorbidities.[12] In contrast, darolutamide has demonstrated safety in the nmCRPC ARAMIS patients with multiple comorbidities (including cardiovascular disease) or multiple concomitant medications where the reported incidence of AEs and AEs leading to treatment discontinuation were comparable to placebo.[73]

Another factor worth considering that is also central to the GA is polypharmacy. Drug–drug interactions (DDIs) are a recognized phenomenon with enzalutamide. A retrospective review of pharmacy records of men on enzalutamide for mCRPC by Benoist *et al.* showed that 85% of patients were at risk for *major* DDIs requiring therapy modification, 45% were at risk of cognitive dysfunction due to concurrent use of a CNS depressant, and 31% were taking medications with potential pharmacokinetic interactions with enzalutamide.[54] Similar results have been reported in French mCSPC and mCRPC cohorts with enzalutamide and apalutamide having frequent DDIs.[55] Enzalutamide is also a potent CYP enzyme inducer and could reduce the potency of commonly metabolized drugs like proton pump inhibitors, steroids, and opioids like oxycodone. Enhanced opioid metabolism could explain some of the difficulties in pain management reported in this population.[74] On the other hand, Shore *et al.* examined comorbidities and comedication use in the nmCRPC ARAMIS participants treated with darolutamide 600 mg twice daily or placebo and found no significant effect of such GA deficits on darolutamide pharmacokinetics or AEs.[56]

Future directions and considerations

Treatment decision-making in prostate cancer is significantly impacted by deficits abstracted from

a comprehensive GA. There is strong evidence to support the impact of ARPis on several GA domains, including falls, fractures, neurocognitive impairment, and fatigue; darolutamide appears to be a better-tolerated option in this vulnerable population.[75] More evidence is needed for treatment stratification and alternative dosing/formulation strategies. Further prospective evaluation of these drugs in the context of toxicity is also being performed. Figure 3 summarizes the proposed paradigms that aim to optimize ARPi efficacy and safety in a vulnerable population. We summarize these paradigms below using available examples from the literature studying enzalutamide.

Un-fit: Risk prediction and clinical benefit

The survival benefit and tolerability of upfront combination androgen deprivation remains unknown in the unfit patient, and identifying high-risk groups remains crucial. Scores such as the Cancer and Aging Research Group (CARG) tool have successfully predicted the risk of severe chemotherapy-related toxicities with docetaxel. It may have a discriminatory ability to predict grade 3 or higher toxicities of novel androgen inhibitors like enzalutamide and abiraterone compared to low-risk groups (intermediate OR: 2.72; CI: 1.10–6.68; $p=0.030$; high OR: 15.2 CI: 1.66–139.4; $p=0.016$).[76] However, the same study's significant results require cautious interpretation given the wide CIs. The study was also not powered to discern bothersome QoL-impacting Grade 2 toxicities and toxicities specific to enzalutamide. Another high-risk group of ARPi-naive mCRPC patients outlined by Annala *et al.*, defined as 'poor prognosis', included patients with visceral metastasis, early castrate resistance, or abnormal performance status and laboratories including albumin, alkaline phosphatase, and lactate dehydrogenase were evaluated prospectively in a randomized phase II of cabazitaxel *versus* ARPi found that fewer patients on ARPi achieved the primary endpoint of clinical benefit (62% *versus* 90%, $p=0.039$) with a trend to a difference in survival favoring cabazitaxel (15.5 *versus* 37.0 months, HR = 0.58, $p=0.073$).[77] Thus, enzalutamide use could likely be restricted in those with mCRPC and low CARG scores or no 'poor prognosis' features; however, the use of the CARG requires further investigation in a prospective context for it to support clinical decision-making with regards to the ARPi use in older prostate cancer patients.

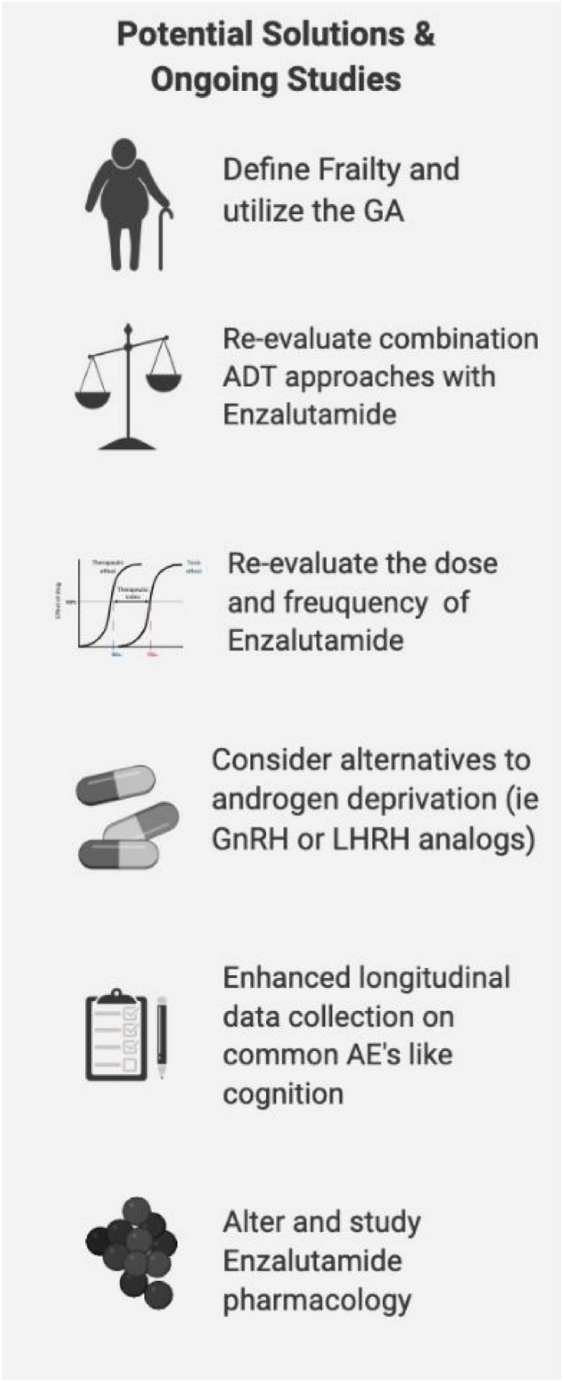

Figure 3. Current paradigms in research to optimize enzalutamide's safety & efficacy.
Source: Adapted from 'why we need to increase diversity in the immunology research community', by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates.

Enzalutamide Dosimetry

Reductions in enzalutamide dose are commonplace, mainly when used to manage treatment-induced

fatigue; such practices in mCRPC are prevalent among prostate specialists compared to community practitioners (89% *versus* 53%) in a 2021 survey of over 400 oncologists from the Canadian Genitourinary Research Consortium.[78] Furthermore, despite having similar benefits in OS and PFS, men over 75 years old with mCSPC in the ARCHES study also experience more dose interruptions and reductions than <75-year-olds (32.1% *versus* 18.1%).[17] The efficacy of this practice in octogenarians has been reported in several case reports [79–81] and real-world data suggest mCRPC patients who are older, with poor ECOG status and more cardiovascular issues, are more likely to get dose reductions of enzalutamide to 80 mg from the standard 160 mg and still, have comparable disease control and progression-free survival.[82] A follow-up retrospective by the same authors revealed that starting with a ⩽50% dose of enzalutamide (⩽80 mg/day) *versus* standard dose (160 mg/day) may also improve longevity (measured by restrict-mean survival time) while lowering AEs and not compromising efficacy; this effect was seen regardless of age.[83] A dose reduction strategy does have pharmacologic grounding. Data from pharmacodynamic /pharmacokinetic studies of enzalutamide show that antitumor effect is seen at *all* doses,[84] and no single plasma trough level quartile was associated with a significantly better response.[85]

Significant increments in QoL with preserved PSA response may also be achievable with enzalutamide dose modifications and reductions in response to toxicity, as reported in a smaller retrospective study of 66 men with mCRPC.[86] Another strategy involving *Treatment Breaks (TB)*, defined as an interruption of 4 weeks or more, was associated with improved OS (HR = 2.39, 1.53–3.76, $p = 0.002$), total treatment time (median 15 *versus* 8 months; $p = 0.0001$), time to treatment failure (median: 11 *versus* 6 months; $p = 0.008$), and dose reductions (41% *versus* 9%) in a retrospective analysis of 129 mCRPC patients [median age in TB group 78 years (63–88)] who already achieved a PSA response >50% with enzalutamide.[87] Similar results were also reported in a retrospective study of octogenarians with mCRPC ($n = 153$) who required more enzalutamide dose reductions ($n = 125$) than abiraterone (44.8% *versus* 22.9%; $p > 0.001$) without any significant differences in outcomes, including time to progression or OS.[88]

A dose-escalation strategy (starting at 80 mg followed by escalation) was explored in a retrospective safety evaluation of 107 patients with mCRPC compared to standard enzalutamide dosing (160 mg daily); AEs were lower (63.3% *versus* 88.2%, $p = 0.02$) as were Grade ⩾3 (6.7% *versus* 23.5%; $p = 0.02$). Median time to treatment failure was longer in the dose-escalation group [18.0 months (11.5–22.8); $p = 0.19$ *versus* 10.4 months (2.6–31.3)].[89] However, an *upfront* dose reduction strategy may not always translate to benefits as a recent Japanese study of 124 mCRPC showed worse PSA response (66.3% *versus* 87.4%, $p = 0.02$) with no difference in AEs between the two groups (22.6 *versus* 34.4, $p = 0.24$)].[90] Firm conclusions from these studies are limited by their small sample size and unbalanced treatment arms, thus begging the need for larger and more prospective evaluations of these strategies, especially in vulnerable older adults who remain a challenge to oncologic decision-making.

Prospective Studies

Phase I evaluations of particular interest include HC-1119; a deuterated form of enzalutamide with a slow metabolism and a lower exposure to the brain in animal models.[91] At steady state, with 80 mg of HC-119, this drug achieves a biologically active drug plasma concentration similar to that of the clinical dosing of 160 mg enzalutamide with the potential for a favorable safety profile.[91] Phase II studies of enzalutamide combinations with ADT alternatives like dutasteride or finasteride in patients with mCSPC ⩾65 years at high risk for AEs from ADT showed 90% response at a median of 7 weeks (7–20) with minimal impact on GA variables other than iADL.[92] Exercise is a known means of improving physical function, sarcopenia and EXTEND is the first RCT to demonstrate support for the role of exercise in improving cardiorespiratory fitness and mitigating deficits in fatigue and functional capacity in patients on enzalutamide,[93] but more evidence is needed to determine if exercise can relieve enzalutamide's cognitive deficits.

Remote daily symptom monitoring has shown to be an effective strategy for promoting treatment modifications in patients with metastatic prostate cancer.[94] Real-world data have also help shed light on the impacts of ARPis; mCRPC patients appear to suffer worse QoL and high pain scores compared to mCSPC patients[95] though an early peek of the behemoth global registry of advanced prostate cancer, IRONMAN, does not support this conclusion.[96] Nevertheless, both diseases

require a significant caregiver burden of up to 30 h per week[95] – a poorly studied impact of prostate cancer care that warrants more exploration.

While there are no pending or active studies reporting objective physical and functional consequences of ARPis in isolation, DaroACT is the first prospective trial to compare the effects of Daro to those of Enza on physical and neurocognitive function, and daily physical activity, in men with both mCRPC and nmCRPC.[97] The authors aim to use objective measures such as the Timed Up and Go, SPPB and measurements of daily activity with an accelerometer at designated time points, and neurocognitive tests.[97] Fatigue is measured using the self-report, and recruitment should be complete by the end of 2022.[97] Finally, we await the results of the 2017 Cog-Pro study, a multicenter longitudinal study including CRPC patients ⩾70 years old treated with novel ARPIs, looking at outcomes such as cognitive, geriatric, and QoL assessment and biological tests.[98]

Conclusion

Prostate cancer is a disease of older adults, and recent data suggest a net clinical benefit in using enzalutamide to improve overall and progression-free survival. Nonetheless, like all drugs that interfere with testosterone activity, there is a risk of off-target AEs such as fatigue, cognitive impairment, and functional decline that result in an elevated risk of falls, functional decline, and poor QoL. Given that ARPis like enzalutamide is dosed daily, needed for months, and possesses a wide therapeutic window, more prospective data on enzalutamide's unique AE profile in the context of the GA is required to evaluate this drug's safety in a growing older and more vulnerable population of older adults with prostate cancer. Novel dosing/scheduling, combinations, pharmacologic modifications, and exercise-based interventions are needed to improve the ARPi safety profile for vulnerable older adults with prostate cancer.

Declarations

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Consent for publication

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Author contribution(s)

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