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Conceptual Paper

The Paradigm Shift of Second Generation Anti-Androgen Therapy from Metastatic to Non-Metastatic Castrate Resistant Prostate Cancer

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Prostate cancer is the second most prevalent cancer in men and is the sixth most common cause of cancer-related death for men worldwide [1]. Metastatic castrate resistant prostate cancer (CRPC) is a lethal disease, with a median overall survival of approximately three years since diagnosis. Therefore prevention of metastasis and delaying disease progression is an initial goal [2]. CRPC is an advanced stage of the disease that stopped responding to initial androgen deprivation therapy (ADT). It is associated with rapid metastasis development, shortened survival and death [3]. Non metastatic CRPC is defined by a rising PSA level while on ADT, testosterone level less than 50 ng/dl with no evidence of metastasis on radiological and nuclear imaging.

According to the National Comprehensive Cancer Network (NCCN) guidelines for prostate cancer, patients with non-metastatic CRPC having a PSA doubling time (PSADT) of > 10 months should be observed, and those with a PSADT < 10 months are candidate to receive additional lines of hormonal therapies [4].

Multiple drugs were evaluated in men with non-metastatic CRPC who were at high risk for developing metastasis. Enzalutamide, Apalutamide, and Darolutamide are orally administered drugs that act at multiple sites in the androgen receptor signaling pathway, including blocking the binding of androgen to the androgen receptor (AR), inhibition of nuclear translocation of the AR, and inhibition of binding the AR with nuclear DNA.

Spartan trial is a phase III randomized study that evaluated Apalutamide versus placebo in non-metastatic CRPC and PSA doubling time ≤ 10 months: 1207 participants were stratified according to PSADT (> 6 months v/s ≤ 6 months), use of bone-sparing agents, and the presence of metastatic pelvic lymph nodes < 2 cm below iliac bifurcation (N0 v/s N1). After a median follow-up of 20.3 months, Apalutamide at 240 mg/d with ADT improved the primary endpoint of metastasis-free survival over placebo with ADT (40.5 months vs. 16.2 months; HR for metastasis or death, 0.28; 95% CI, 0.23 - 0.35; P < 0.001). Apalutamide showed an improvement across all end points including: time to metastasis, progression-free survival, time to symptomatic progression, time to PSA progression and PSA decline [3]. Although overall survival (OS) data were not mature at the time of final analysis for metastasis-free survival, there was no significant difference seen in OS. In the Apalutamide group, 52.5% of patients progressed to metastatic CRPC and received subsequent treatment (75.8% received Abiraterone acetate plus prednisone), thus leading to a second progression free survival (PFS) data. The exploratory end point in the Apalutamide group showed a significant 51% risk reduction in PFS2. Consequently, the patients will benefit from an additional line of treatment, and SPARTAN trial confirmed the absence of cross-resistance between Apalutamide and Abiraterone, in difference with Enzalutamide. The most common adverse events (AEs) included rash (24% v/s 5.5%), fracture (11% v/s 6.5%), and hypothyroidism (8% v/s 2%). Overall grade 3 and 4 AEs were 45% in Apalutamide group compared with 34% in placebo.

Prosper trial is another phase III double-blind, randomized study, that evaluated the use of Enzalutamide v/s placebo in 1401 men with non-metastatic CRPC with PSADT ≤ 10 months and a PSA level more than 2 ng/ml. Men were stratified according to PSADT (< 6 months v/s ≥ 6 months) and use of osteoclast-targeted agents. Enzalutamide improved the primary endpoint of metastasis-free survival over placebo (36.6 months vs. 14.7 months; HR for metastasis or death, 0.29; 95% CI, 0.24 - 0.35; P < 0.0001). No significant difference was seen in OS, although OS data were not mature at the time of final analysis for metastasis-free survival [2]. The most common reported adverse events were fatigue (33% v/s 14%), hypertension (12% v/s 5%), major adverse cardiovascular events (5% v/s 3%), and mental impairment disorders (5% v/s 2%). Patient reported outcomes from this trial showed that Enzalutamide delays pain progression, symptom worsening and decrease in functional status, compared with placebo.

Aramis is a third phase III double-blind, placebo-controlled trial that randomized 1509 patients with M0 CRPC and PSADT ≤ 10 months, 2:1 to Darolutamide (600 mg twice daily) or placebo. Participants were stratified according to PSADT (> 6 months v/s ≤ 6 months) and the use of bone-sparing agents. After a median follow-up of 17.9 months, Darolutamide improved the primary endpoint of metastasis-free survival compared with placebo (40.4 months v/s 18.4 months; HR for metastasis or death, 0.41; 95% CI, 0.34 - 0.50; P < 0.001) [5]. Remarkably, at the first interim analysis, data showed an improvement in overall survival (HR for death, 0.71; 95% CI, 0.50-0.99; P = 0.045) in difference to the previously listed trials: SPARTAN and PROSPER. However, these data could be immature and must be interpreted cautiously knowing that median survival was not reached in either arm. Adverse events that occurred more frequently with Daralutamide included fatigue (12.1% v/s 8.7%), pain in an extremity (5.8% v/s 3.2%) and rash (2.9% v/s 0.9%). The incidence of fractures was similar between the two groups (4.2% v/s 3.6%) in contrary to SPARTAN trial where Apalutamide was associated with a higher risk of falls and fractures (Any grade: 16% falls and 12% fractures).

Consequently, Apalutamide, Enzalutamide and Darolutamide are currently approved as category 1 for the treatment of non-metastatic CRPC. Given similar efficacy and risk profile (Table 1), decision should be made according to other factors such as cost, cardiovascular risk, fracture risk, falls risk, seizure/central nervous system toxicity and availability (Figure 1).

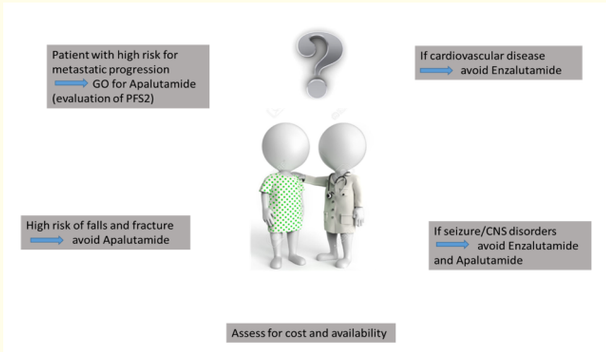

Figure 1: Factors that could influence the drug choice when the three therapeutic options are available (Apalutamide, Enzalutamide and Darolutamide) in the era of financial toxicity. CNS: central nervous system.

Trials	SPARTAN	PROSPER	ARAMIS
Study drug	Apalutamide	Enzalutamide	Darolutamide
Primary endpoint: Metastasis Free survival	40.5 months	36.6 months	40.4 months
Overall Survival (OS)	No significant difference in OS	No significant difference in OS	Promising improvement in OS (data still immature)
Progression Free Survival – 2 (PFS2)	51% risk reduction in PFS2	Not Evaluated	Not Evaluated
Most common adverse events	Rash, fracture, hypothyroidism	Major cardiovascular events, seizures	Lesser side effects

Table 1: A comparative table showing the efficacy and risk profile between the three available second generation anti-androgen therapies: Apalutamide, Enzalutamide and Darolutamide across the three pivotal trials: SPARTAN, PROSPER and ARAMIS respectively.

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