REVIEW ARTICLE

Clinical Research

Second generation anti-androgens and androgen deprivation therapy with radiation therapy in the definitive management of high-risk prostate cancer

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BACKGROUND: Evolving data suggest that men with high-risk localized prostate cancer may benefit from more potent androgen receptor inhibition in the context of curative intent radiotherapy. Recently updated American Society for Clinical Oncology (ASCO) evidence-based guidelines and the National Comprehensive Cancer Network (NCCN) Guidelines have updated recommendations for the consideration of adding second generation anti-androgens to androgen deprivation therapy (ADT) in men receiving radiation therapy (RT) for noncastrate locally advanced high and very high risk nonmetastatic or node positive prostate cancer.
METHODS AND RESULTS: We conducted a comprehensive review of existing published and abstract presented evidence behind RT with ADT for the definitive management of high-risk prostate cancer, particularly focused on the current phase II and III trial evidence for the addition of second generation anti-androgens to ADT in definitive RT treatment of high-risk prostate cancer and specifically focused on the recent STAMPEDE trial results with abiraterone acetate. We review the biological mechanisms in which second generation anti-androgens may help mitigate ADT resistance and provide radiosensitization through inhibition of DNA repair. Finally, we discuss ongoing clinical trials of potent androgen receptor (AR) inhibitors with ADT in this non-metastatic high-risk radiotherapy setting that may inform on future treatment guidelines.
CONCLUSIONS: Recent data suggest an overall survival benefit as well as increased probabilities of disease free and metastasis free survival in men with high and very high-risk localized, node positive, and oligometastatic hormone sensitive prostate cancer with abiraterone acetate and prednisone and support the use of potent AR inhibitors in this setting after informed decision making.

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INTRODUCTION

Radiation therapy (RT) with androgen deprivation therapy (ADT) is a standard of care treatment option in high-risk prostate cancer.

RT has been used in the definitive treatment of high-risk prostate cancer and includes various external beam radiation therapy (EBRT) techniques with or without brachytherapy. EBRT techniques include 3D conformal radiation therapy, intensity-modulated radiation therapy, and proton beam radiation therapy. EBRT can be delivered by conventional fractionation (CF; 1.8–2 Gy per fraction over 8–9 weeks), moderate hypofractionation (MHF; 2.4–3 Gy per fraction over 4–6 weeks), and extreme-hypofractionation (6.7–10 Gy per fraction over 1–2 weeks; also known as stereotactic body radiotherapy (SBRT)).

Brachytherapy as a boost improves biochemical progression-free survival (bPFS) in men with intermediate and high-risk prostate cancer, but no difference in freedom from metastasis, prostate cancer specific mortality (PCSM) or overall survival (OS) has been observed [1]. In an analysis of treatment-related morbidity, at a median follow-up of 6 years, increased GU morbidity was seen with prostate brachytherapy boost compared to EBRT with no differences in the frequency of erectile dysfunction [2]. On patient-reported health-related quality of life (HRQOL) outcomes, a statistically significant decline in physical function and urinary function was noted in patients who received prostate brachytherapy arm compared with those who received EBRT [3].

The utilization of SBRT is increasing for localized prostate cancer [4]. A recent randomized phase 3 trial, HYPO-RT-PC, have shown that ultra-hypofractionation (42.7 Gy in 7 fractions, 3 days per week for 2.5 weeks), is non-inferior to conventional fractionated RT (78.0 Gy in 39 fractions, 5 days per week for 8 weeks) for tumor control (estimated failure free survival at 5 years was 84% in both treatment groups) and late toxicity [5]. There was more early grade 2 or worse urinary toxicity in the ultra-hypofractionation group (28% patients vs 23% patients; $p = 0.057$) [5]. Most men in this trial had intermediate risk prostate cancer (89%) and only 11% had high-risk prostate cancer. This trial did not permit ADT, which is standard of care in the United States for unfavorable intermediate and high-risk men with prostate cancer.

ADT is used as a neoadjuvant, concurrent, and/or adjuvant to RT in patients with high-risk prostate cancer. In this setting, ADT is

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delivered using an LHRH agonist with or without a first-generation antiandrogen or delivered using an LHRH antagonist. In high-risk prostate cancer, the addition of EBRT to ADT improves bPFS, cancer specific survival, and OS compared with ADT alone [6]. This OS benefit has been found in multiple trials [6, 7]. Specifically, in the trial SPCG-7/SFU0-3, patients treated with ADT + RT had a 10-year OS of 70% compared to 61% in the ADT alone arm [6]. In the trial NCIC CTG PR.3/MRC UK PR 07, OS was also significantly improved in patients who received ADT and RT compared to ADT alone (HR 0.70; 95% CI: 0.57–0.85) with a modest, non-significant negative impact on HRQOL outcomes [7–9].

Furthermore, multiple trials for patients with high-risk or locally advanced prostate cancer have shown that the addition of ADT to EBRT improves OS compared with EBRT alone [10–12]. In RTOG 8531, 10-year OS was significantly greater for those who received EBRT with adjuvant ADT than men who received EBRT alone: 49% vs. 39%, respectively. The 10-year rates for distant metastases and PCSM was also significant at 24% vs. 39% and 16% vs. 22%, respectively, both in favor of the EBRT with adjuvant RT arm. In EORTC 22863, 10-year OS was 39.8% in patients receiving RT alone and 58.1% in those receiving ADT + EBRT (HR 0.60, 95% CI: 0.45–0.80) and 10-year PCSM was 30.4% and 10.3%. respectively (HR 0.38, 95% CI: 0.24–0.60) [12]. In RTOG 8610, the addition of 4 months of neoadjuvant and concurrent ADT improved DFS, PCSM, but had no OS survival benefit [11]. Of note, the duration of ADT used in the trial is less than what would be used in the modern era for high-risk prostate cancer. As a result of these trials, ADT with RT is an established standard of care treatment for men with high-risk prostate cancer. Many recent studies have investigated the duration of ADT in high-risk prostate cancer (Table 1). For example, in RTOG 9202, which has a long-term follow-up of 19.6 years, long term ADT (4 months of flutamide and goserelin with definitive RT plus an additional 24 months goserelin) significantly improved DFS (29% relative reduction in failure rate), local progression (46% relative reduction), distant metastases (36% relative reduction), disease-specific survival (30% relative reduction) and OS (12% relative reduction) compared to short term ADT (4 months of flutamide and goserelin) [13, 14]. As a result of these studies (Table 1), 1.5–3 years of ADT is generally added to EBRT for initial therapy of high-risk prostate cancer and this is a category 1 recommendation in the 2022 National Comprehensive Cancer Network (NCCN) guidelines [15]. In patients with high-risk prostate cancer who receive EBRT with brachytherapy boost and ADT, it is a NCCN category 1 recommendation for ADT and duration of ADT is recommended for 1–3 years.

All studies investigating duration of ADT in high-risk prostate cancer have been in men who received neoadjuvant, concurrent, and/or adjuvant ADT and RT. The effect of ADT in the setting of moderate hypofractionation and SBRT is unknown. Some currently open randomized trials allow for various fractionation schedules (NRG-GU009, NRG-GU010) but others are testing ADT in the setting of SBRT (ex. NTC03056638, NCT01517451, NCT02296229).

Until there is level one evidence in this area, it remains standard that men with high-risk prostate cancer who receive EBRT have at least 18 months of ADT unless medically contraindicated.

ANDROGEN DEPRIVATION THERAPY AND SECOND GENERATION ANTIANDROGENS

In the metastatic hormone-sensitive prostate cancer (mHSPC) and castration-resistant prostate cancer (mCRPC) settings, there has been a significant expansion of treatment options; in recent years, second generation anti-androgens have shown to have efficacy when combined with ADT and have changed the practice in metastatic prostate cancer [16–22]. These anti-androgens have included abiraterone, apalutamide, darolutamide, and enzalutamide. Abiraterone acts as an androgen synthesis inhibitor in the testes, adrenal glands, and prostate cancer tissue (Fig. 1a, b). Apalutamide, darolutamide, and enzalutamide function as second generation androgen receptor (AR) inhibitors by binding to the androgen binding site in the androgen receptor (Fig. 1c). They inhibit AR nuclear translocation, DNA binding, and mobilization of coactivators, which ultimately leads to prostate cell apoptosis.

To date, most clinical studies involving second generation anti-androgens have been in patients with mHSPC. Second generation anti-androgens have been shown to increase OS in men with mHSPC in several randomized phase III trials that have supported the addition of abiraterone, apalutamide, enzalutamide, and darolutamide to ADT in this setting (Table 2) [18–21, 23–26]. Briefly, in LATITUDE, the final OS analysis revealed that the addition of abiraterone to ADT led to improved OS than the placebo group (53.3 months versus 36.5 months; HR 0.66, 95% CI 0.56–0.78) [19]. In STAMPEDE, patients with M1 disease received abiraterone and prednisone until progression while patients with node positive or localized high-risk M0 disease received 2 years of abiraterone plus prednisolone with definitive EBRT. Abiraterone added to ADT led to significant improvement in PFS (HR 0.40; 95% CI 0.34–0.47) and OS (HR 0.63; 95% CI 0.52–0.76). In ENZAMET, enzalutamide added to ADT was associated with significantly longer PFS (HR 0.40; 95% CI, 0.33–0.49) and OS (HR for death, 0.67; 95% CI, 0.52–0.86) and the effect was seen in low volume disease [20]. In ARCHES, the final OS analysis revealed that enzalutamide added to ADT significantly extended OS versus ADT (HR 0.66; 95% CI 0.53–0.81) [23]. In TITAN, the final analysis results showed that apalutamide plus ADT improved OS with a 35% reduction in risk of death, which increased to 48% reduction after adjusting for patients who crossed over from ADT to apalutamide plus ADT [24]. In ARASENS, the addition of darolutamide was found to significantly improve OS (HR 0.68; 95% CI 0.57–0.80) [26].

The efficacy of second generation anti-androgens in mHSPC and the synergy of combined ADT and second generation anti-androgens in the mHSPC setting have led to some of these anti-androgens being investigated in the non-metastatic and node positive prostate cancer setting. Thus far, two arms of the STAMPEDE trial has provided evidence regarding the addition of anti-androgens to ADT with RT in patients with non-metastatic prostate cancer [27]. These arms included evaluating the efficacy of adding abiraterone with prednisolone as discussed previously and the efficacy of adding enzalutamide and abiraterone with prednisolone. Patients in this trial were recommended to receive treatment with 3 years of ADT that started no longer than 12 weeks before randomization. RT as per local guidelines was delivered in 74 Gy in 37 fractions to the prostate and seminal vesicles or equivalent using hypofractionated schedules. The patients on that study were mandated to have RT if they had newly diagnosed, node-negative, nonmetastatic disease and strongly encouraged in patients with newly diagnosed node positive nonmetastatic disease. The STAMPEDE trial results that failure free survival was significantly improved for patients with nonmetastatic disease treated with ADT and abiraterone with prednisolone compared with those treated with ADT alone along with the results of aforementioned trials have led to the American Society of Clinical Oncology Guidelines to consider ADT plus abiraterone and prednisolone for men with non-castrate locally advanced nonmetastatic prostate cancer rather than castration monotherapy [28].

A pooled analysis of the two phase III trials conducted in the STAMPEDE protocol further analyzed the efficacy of adding abiraterone and prednisolone alone to ADT or abiraterone and prednisolone with enzalutamide to ADT in men with high-risk non-metastatic prostate cancer [29]. Metastasis-free survival (MFS) was significantly longer in the combination therapy groups (median not reached) than in the control groups with 6-year MFS improved from 69% in the control groups to 82% in the combination therapy groups. OS was significantly longer in the

Table 1. There have been multiple randomized trials on radiation therapy and duration of androgen deprivation therapy in men with locally advanced higher risk prostate cancer.

Clinical trial	Study cohort	Trial arms	Median follow-up	Outcomes
RTOG 9202 [21, 22]	Clinical T2c -T4, N0-NX, M0 prostate adenocarcinoma, retreatment PSA < 150 ng/mL, KPS > 70	Short term ADT (STAD: 4 months of flutamide 250 mg three times per day and goserelin 3.6 mg per month) and definitive RT versus long term ADT (LTAD: STAD with definitive RT plus 24 months of monthly goserelin)	19.6 years	LTAD improved DFS (29% relative reduction in failure rate, $p < 0.0001$), local progression (46% relative reduction, $p = 0.02$), distant metastases (36% relative reduction, $p < 0.0001$), disease specific survival (30% relative reduction, $p = 0.003$), and overall survival (12% relative reduction, $p = 0.03$)
RTOG 8531 [17, 23]	Clinical T3 or prostate cancer with regional lymphatic involvement	RT and adjuvant goserelin (drug started during the last week of RT and was to be continued indefinitely or until signs of progression) versus RT alone followed by observation and application of goserelin at relapse	7.6 years	10-year OS was significantly greater for the adjuvant arm than for the control arm: 49% vs. 39%, respectively ($p = 0.002$). The 10-year LF rate for the adjuvant arm was 23% vs. 38% for the control arm ($p < 0.0001$). 10-year rates of distant metastases and disease-specific mortality was 24% vs. 39% ($p < 0.001$) and 16% vs. 22% ($p = 0.0052$), respectively, both in favor of the adjuvant arm
EORTC 22961 [16]	Pathological T1c-T2a-b, N1 or N2, M0 or clinical T2c-T4, N0-N2, M0 prostate adenocarcinoma, pretreatment PSA of up to 40x upper limit of normal, WHO PS 0-2	EBRT plus 6 months of ADT followed by no further treatment versus receive 2.5 years of further treatment with a LHRH agonist	6.4 years	5-year overall mortality for STAD and LTAD was 19.0% and 15.2%, respectively; the observed hazard ratio was 1.42 (upper 95.71% confidence limit, 1.79; $P = 0.65$ for noninferiority)
DART01/05 GICOR trial [24]	Clinical T1c–T3b N0, M0 prostate adenocarcinoma with intermediate-risk and high-risk factors according to 2005 NCCN criteria	3D CRT with 4 months of neoadjuvant and concomitant ADT (goserelin with flutamide or bicalutamide) or the same treatment followed by 24 months of ADT	5.3 years	5-year bDFS was significantly better among patients receiving LTAD than among those receiving STAD (90% [95% CI 87–92] *vs* 81% [78–85], HR 1.88 [95% CI 1.12–3.15]; $p = 0{\cdot}01$). 5-year OS (95% [95% CI 93–97] vs 86% [83–89]; HR 2.48 [95% CI 1·31–4·68]; $p = 0{\cdot}009$) and 5-year MFS (94% [95% CI 92–96] *vs* 83% [80–86]; HR 2·31 [95% CI 1.23–3.85]; $p = 0{\cdot}01$) were significantly better in the LTAD than in the STAD
TROG 03.04 RADAR [25]	Clinical T2b-4, N0 M0 or T2a, N0 M0 prostate cancer with Gleason score ≥7 and pretreatment PSA ≥ 10 μg/L	2 × 2 factorial trial, patients in the control group received 6 mo of neoadjuvant ADT with leuprorelin and RT alone (STAD), this treatment was either followed by 12 mo of ADT with leuprorelin, intermediate-term ADT, or accompanied by 18 mo of zoledronic acid starting at randomization (STAD plus zoledronic acid), or both (ITAS plus zoledronic acid).	10.4. years	Total number of deaths was 375 (200 men receiving 6 ADT + RT and 175 men receiving 18 ADT + RT), of which 143 (38%) were attributable to prostate cancer (81 men receiving 6 ADT + RT and 62 men receiving 18 ADT + RT). When analyzed by ADT duration, the adjusted cumulative incidence of PCSM was 13.3% (95% CI 10.3–16.0) for 6 ADT + RT versus 9·7% (7.3–12.0) for 18 ADT + RT, representing an absolute difference of 3.7% (95% CI 0·3–7·1; [sHR 0.70 [95% CI 0.50–0.98], adjusted $p = 0{\cdot}035$).
PCS IV [20]	Clinical T3–T4 N0M0 or a PSA > 20 ng/ml or a Gleason score >7 prostate cancer Zubrod ≤1, age ≤80 years	Standard arm of RT and 36 mo of ADT (goserelin and bicalutamide) (LTAD) and the experimental arm of RT and 18 mo of the same ADT (STAD)	9.4 years	5-yr OS rates (95% confidence interval) were 91% for long arm (88–95%) and 86% for short arm (83–90%), $p = 0.07$. QoL analysis showed a significant difference ($p < 0.001$) in six scales and 13 items favoring 18 mo ADT.

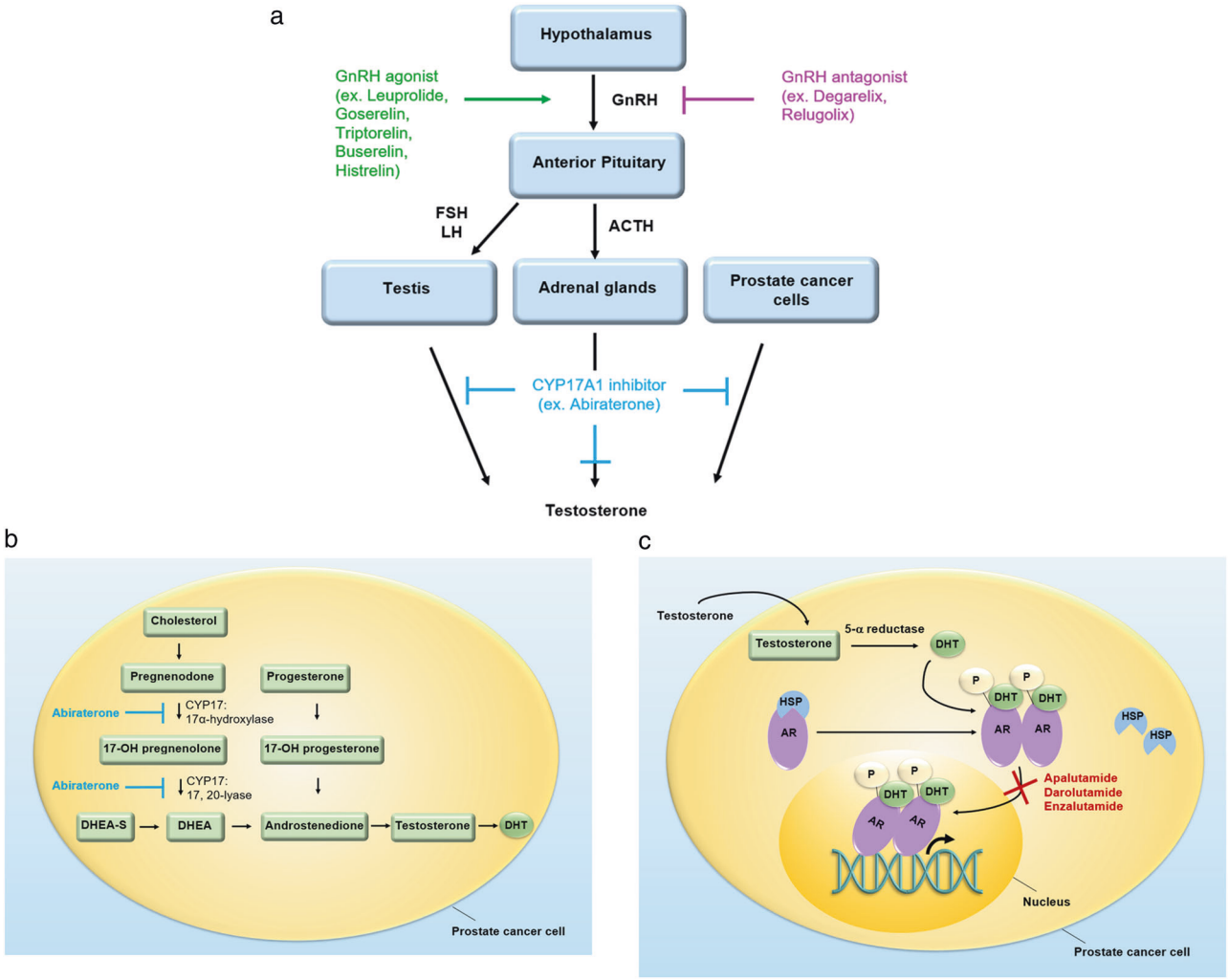

Fig. 1 Mechanisms of action of second generation androgen receptor (AR) inhibitors. a Gonadotropin-releasing hormone (GnRH) agonists function by producing an initial increase in follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which leads to an increase in testosterone and dihydrotestosterone production. Continuous GnRH then leads to downregulation of GnRH receptors and subsequent decline in anterior pituitary production of LH and FSH. The fall in LH leads to a decrease in serum testosterone. GnRH antagonists function by binding to the GnRH receptors on the gonadotropin-producing cells and suppressing subsequent testosterone production without stimulating an initial release of LH or FSH. Abiraterone inhibits CYP17, which is an enzyme that converts steroid precursors to androgenic steroids. **b** Abiraterone blocks intracrine androgen signaling within the prostate cancer cell. **c** Testosterone is converted to dihydrotestosterone (DHT) by 5-α reductase. DHT binds to the AR dissociating heat shock proteins (HSP), which act as chaperone proteins. The AR molecules homodimerize and translocate to the nucleus where it binds to a specific sequence of DNA known as the hormone response element, acting as transcription factors to signal downstream targets. Apalutamide, darolutamide, and enzalutamide are AR ligand binding domain inhibitors. They inhibit AR nuclear translocation, DNA binding, and mobilization of coactivators, which ultimately leads to prostate cell apoptosis. Abbreviations: GnRH: Gonadotropin-releasing hormone, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, ACTH: Adrenocorticotropic hormone DHT: Dihydrotestosterone, AR: Androgen receptor, XRT: Radiation therapy, HSP: Heat shock protein.

combination therapy groups (median not reached) than in the control groups (median not reached) with 6-year survival improved from 77% in the control groups to 86% in the combination therapy groups. There was no evidence of difference in MFS when enzalutamide and abiraterone were administered concurrently compared with abiraterone alone (HR 1.02, 95% CI, 0.70–1.50, $p = 0.91$). Furthermore, the combination of enzalutamide and abiraterone was associated with more frequent adverse events grade 3 or higher during the first 24 months compared with abiraterone alone. The study concluded that the addition of enzalutamide to abiraterone leads to no evidence of a difference in treatment effect and comes with additional toxicity.

There has been increasing interest in adding second generation anti-androgens to earlier curative intent setting with ADT and definitive RT. Although there are currently few studies with results in this setting, prospective single arm phase 2 trials have been performed to study the efficacy and safety of second generation anti-androgens in combination with current standard of care treatments for patients with high-risk prostate cancer [30–32].

A prospective single-arm phase II trial was conducted in men with localized prostate cancer ($n = 3$ intermediate risk and $n = 19$ high risk) who received 6 months of neoadjuvant and concurrent abiraterone with a LHRH agonist and RT [30]. RT target volume was the whole pelvis with a cone down boost field to the prostate and proximal seminal vesicles. All men who were compliant with therapy (95%) had a nadir ≤0.3 ng/mL. At a median follow-up of 21 months, only one patient (who had discontinued abiraterone at 3 months) had biochemical recurrence (BCR). The rate of grade 3 toxicities was 27% and were known adverse events related to abiraterone or androgen deprivation. Overall, the authors concluded that the addition of abiraterone to LHRH agonists with RT is safe and achieves effective prostatic androgen suppression.

Table 2. Randomized phase III trials of second generation anti-androgens in men with metastatic hormone sensitive prostate cancer (mHSPC).

Clinical trial	Study arms	Median follow-up	Overall survival (OS)	Reference
LATITUDE	Abiraterone with prednisone or placebos	51.8 months	OS at 41.8 months were 54% in the abiraterone with prednisone group vs 43% in the placebo group (HR 0.66, 95% CI 0.56–0.78) with 12% crossover	Fizazi et al. [18, 19]
STAMPEDE	Abiraterone with prednisolone or placebos	40 months	OS at 3 years were 83% in the abiraterone with prednisolone vs 76% in the placebo group (HR 0.63; 95% CI 0.52–0.76) In the metastatic group, OS 3 years were 70% in the abiraterone with prednisone group vs 57% in the placebo group (HR 0.61; 95% CI 0.49–0.75)	James et al. [25]
ENZAMET	Enzalutamide or placebo	34 months	OS at 3 years were 80% in the enzalutamide group vs 72% in the placebo group (HR 0.67; 95% CI, 0.52–0.86)	Davis et al. [20]
ARCHES	Enzalutamide or placebo	44.6 months	OS at 4 years were 71% in the enzalutamide group vs 57% in the placebo group (HR 0.66; 95% CI 0.53–0.81) with 31.3% crossover	Armstrong et al. [21, 23]
TITAN	Apalutamide or placebo	44 months	OS at 4 years were 65% in the apalutamide group vs 52% in the placebo group (HR 0.65, 95% CI 0.53–0.79, $p < 0.001$) with 39.5% crossover	Chi et al. [22, 24]
ARASENS	Darolutamide or placebo and 6 cycles of docetaxel	43.7 months in the darolutamide group and 42.4 months in the placebo group	OS at 4 years were 62.7% (95% CI, 58.7–66.7) in the darolutamide group vs 50.4% (95% CI, 46.3–54.6) in the placebo group	Smith et al. [26]

A phase II study, the STREAM trial, investigated the addition of enzalutamide to ADT for 6 months with salvage RT and was the first study to describe the efficacy and safety of enzalutamide with radiation therapy in the early curative intent setting [33]. Specifically, the primary endpoint of 2-yr PFS was 65% versus 51% in a trial of men with similar eligibility treated with salvage RT and adjuvant docetaxel. In the study, 29% men experienced grade 3 toxicities. Recently, a single arm, single site, phase II trial studied the addition of enzalutamide to ADT and RT in patients with high-risk localized or regional, nonmetastatic patients with prostate cancer [31]. The patients in this trial were treated with 24 months of enzalutamide and leuprolide and 5 weeks of conventionally fractionated RT to the whole pelvis followed by a brachytherapy boost to the prostate. All men had a nadir ≤0.3 ng/mL at completion of RT. At 36 months of follow-up, one of nine patients had BCR, with a time to BCR of 21.8 months. The authors noted the patient with the BCR had not completed the full 24 months of enzalutamide and leuprolide due to adverse events. The rate of grade 3 adverse events was 36%. Overall, the study suggested that enzalutamide in combination with ADT and RT was effective and well-tolerated.

The 5-year results of AbiRT were presented at American Society of Radiation Oncology 2021 [34]. In this prospective multi-center single arm trial, patients with unfavorable intermediate risk or low volume high risk prostate cancer were treated with 6 months of abiraterone, prednisone, and depot GnRH agonist initiated 8 weeks prior to conventionally fractionated RT to prostate/seminal vesicles ± pelvis. The 5-year bPFS was 92% (95% CI: 72–98%) in the entire cohort. Median time to testosterone recovery was 9.2 months and in those men with testosterone recovery, the 5-year bPFS was also 92% (95% CI: 71–98%). Hormonal/sexual function declined at six months but improved by 24 months and remained stable. This study suggested that a short course of complete androgen blockade (abiraterone with prednisone and GnRH agonist) and definitive RT may be beneficial without long-term toxicity as compared to 2–3 years of abiraterone and ADT.

In the very high-risk prostate cancer group, the NCCN guidelines recommends the option of EBRT with ADT (2 years) with docetaxel for 6 cycles or EBRT with ADT (2 years) with abiraterone [15]. Most common (>20%) side effects of abiraterone/prednisone include fatigue, back or joint comfort, peripheral edema, diarrhea, nausea, or constipation, hypokalemia, hypophosphatemia, hot flushes, and hypertension [15]. Abiraterone has a better side effect profile than docetaxel and is easier to administer logistically, but treatment duration is longer, there may be some long-term effects of glucocorticoid use, and cost is a consideration [25]. The randomized phase III RTOG 0521 study evaluated the addition of docetaxel to ADT + RT in high-risk nonmetastatic prostate cancer [35]. In an update of this trial at the 2020 Genitourinary Cancer Symposium, the 10-yr OS rates were 64% (95% CI: 58–70%) for ADT + RT and 69% (95% CI: 63–75%) for ADT + RT + docetaxel (HR 0.89, 90% CI: 0.70–1.13, 1-sided $p = 0.22$) [36]. There was evidence of non-proportional hazards. The trial suggested a very modest benefit of docetaxel consistent with other randomized controlled trials, which have suggested that men with unfavorable-risk M0 prostate cancer do not experience prolonged OS with ADT + RT + docetaxel compared with ADT + RT alone [37]. In the STAMPEDE trial, the addition of docetaxel to ADT ± RT improved FFS in the non-metastatic prostate cancer group (HR 0.60, 95% CI: 0.45–0.80) with no significant difference in prostate cancer specific survival (subHR 0.82, 95% CI: 0.48–1.40, $p = 0.48$), but this subset analysis was limited in power [38]. In a phase III randomized controlled trial by D'Amico and colleagues, it was found that in a subgroup of men with PSA < 4 ng/mL unfavorable risk M0 prostate cancer, the addition of docetaxel to ADT + RT may reduce PCSM (0.00% vs. 28.57%) potentially supporting a distinct biology that may benefit from docetaxel [37]. Significantly fewer RT-induced cancers were observed in the docetaxel arm [37].

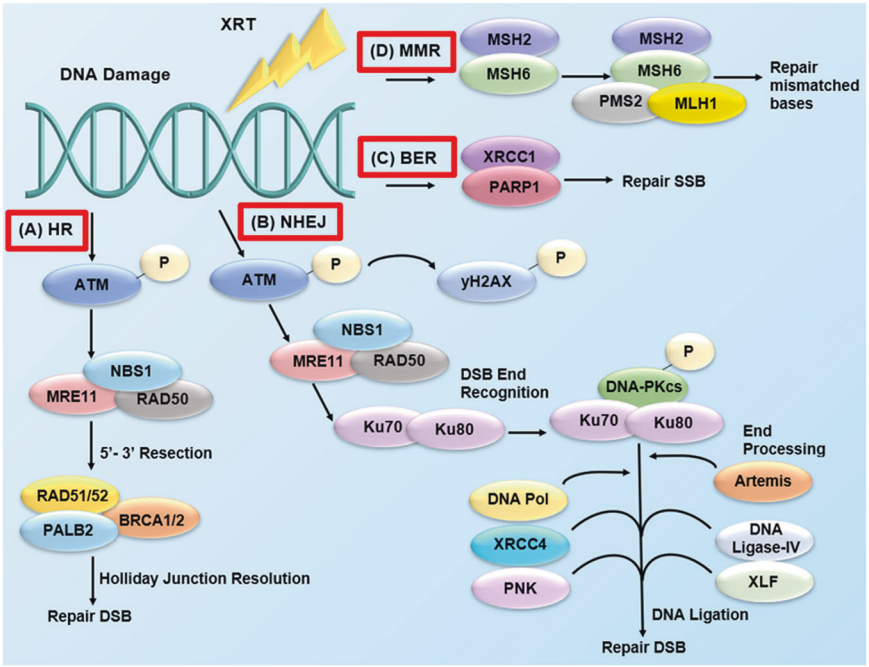

Fig. 2 DNA is the principal target for the biologic effects of radiation therapy. Radiation therapy can induce base damage, single-strand breaks (SSB), double-strand breaks (DSB), and DNA protein crosslinks. There are many DNA repair pathways that help normally with repair including, but not limited to mismatch repair (MMR), base excision repair (BER), non-homologous end joining (NHEJ), and homologous recombination (HR). The two predominant pathways for repair of DNA DSB are the HR and NHEJ. This illustration depicts some major mechanisms in some of the most prominent DNA repair pathways. Defective DNA repair pathways can lead to increased radiation therapy sensitivity. Abbreviations: XRT: Radiation therapy, HR: Homologous recombination, NHEJ: Non-homologous end joining, BER: Base excision repair, MMR: Mismatch repair, SSB: Single-strand break, DSB: Double-strand break.

Since there are no comparative data between the additions of abiraterone versus docetaxel to ADT and RT, the choice of approach is often chosen based on a discussion with the patient regarding the advantages and disadvantages of each option.

RATIONALE OF SYNERGY BETWEEN RADIATION THERAPY WITH ANDROGEN DEPRIVATION THERAPY AND SECOND GENERATION ANTI-ANDROGEN

The biological underpinnings of RT and ADT have been well studied. DNA is the principal target for the biologic effects of RT. RT can induce base damage, single-strand breaks, double-strand breaks (DSB), and DNA protein crosslinks. DNA DSBs induced by ionizing RT are repaired through nonhomologous end joining (NHEJ) or homologous recombination (HR) (Fig. 2). Dysregulation of these processes can reduce cellular viability or alternatively, promotes pro-tumorigenic DNA alternations. Heightened DNA damage repair (DDR) can drive cancer progression and promote therapeutic resistance. Clinical observations suggest that steroid hormones might modulate the response to DNA damage in hormone-responsive cancers like prostate cancer.

Prostate adenocarcinoma is dependent on androgen receptor (AR) activity for growth and survival. Upon binding of androgens, AR is activated, released from inhibitory heat-shock proteins, homodimerizes, and translocate to the nucleus where it binds to androgen response elements on DNA and induces gene expression for prostatic adenocarcinoma maintenance (Fig. 1c). When AR signaling is blocked by ADT, prostate cancer cells cannot efficiently activate DDR. Studies have demonstrated that prostate cancer cells treated with ionizing radiation plus androgen demonstrate enhanced DNA repair and decreased DNA damage and furthermore that anti-androgen treatment causes increased DNA damage and decreased clonogenic survival [39]. Anti-androgen treatment also results in decreased classical NHEJ. Thus, the combination of ADT and radiotherapy enhances DNA damage and lethality of RT.

While ADT is efficacious, resistance can occur. In men with prostate cancer that progress on ADT, a subset appears to have resistance to AR inhibitors. Resistance of prostate cancer to ADT can be mediated by many mechanisms including alterations involving the AR gene such as AR amplification, the development of mutations in the receptor in response to anti-androgen treatment, and androgen receptor splice variants (ARV) [40]. In addition, other methods of resistance include AR indifference and oncogenic bypass pathways independent of AR [41].

Androgen indifference is a state in which tumors have AR proteins but are less dependent on androgen signaling leading to tumors that potentially have a less durable and less robust response to ADT. Briefly, AR indifference has been associated with double-negative prostate cancer and classically with variant prostate cancer histology such as small cell prostate cancer (SCPC) or neuroendocrine prostate cancer (NEPC) [41, 42]. Hormonal therapy-associated SCPC/NEPC in patients with metastatic CRPC is more common than a primary diagnosis of SCPC [43, 44]. The molecular background of NEPC is distinct from prostate adenocarcinoma with many signaling pathways that have been shown to play a role in the development of NEPC. Preclinical studies with RNA sequencing have found that the over-expression and gene amplification of both Aurora kinase A and of the oncogenic transcription factor N-myc (MYCN) contributes to the development of SCPC/NEPC [45, 46]. In a molecular analysis by The Cancer Genome Atlas Research Network, genomic aberrations in the phosphatidylinositol-3-kinase (PI3K)/AKT pathway were seen in approximately 17% of primary prostate cancer and 50% of metastatic CRPC [47]. PI3K/AKT pathway downregulation resulting from phosphatase and tensin homolog (PTEN) loss has been associated with resistance to androgen sensitivity and development of CRPC through suppressing AR transcription output

[48, 49]. On the other hand, PTEN loss or inhibition can further activate PI3K/AKT pathway through downregulation of the AR-regulated FKBP5 scaffold protein-PHLPP phosphatase negative feedback loop to AKT activation, enhancing AKT activation and subsequent AR-independent cell proliferation [48]. Studies have also shown that there are multiple DNA and mRNA changes in SCPC/NEPC compared to prostate adenocarcinoma including retinoblastoma susceptibility gene (RB1) loss and mutation or deletion of tumor protein p53 (TP53) [50]. The loss in RB1 and mutation or deletion of TP53 has been linked to prostate cancer lineage plasticity and AR indifference [51]. The loss of RB1 is common in SCPC and promotes small cell carcinoma pathogenesis when concurrent with TP53 mutation [52]. Additionally, AR indifference with the loss of RB1 alone and decrease in AR transcriptional output is associated with poor survival [53].

Of note, intensive AR inhibition with abiraterone in addition to ADT in prostate cancer can lead to a reduced, but persistent AR activity in residual tumors with no increase in neuroendocrine differentiation [54]. A study showed cell proliferation correlated negatively with AR activity, but positively with decreased RB1 expression [54]. Whole-exome sequencing showed enrichment for RB1 genomic loss and confirmed a common clonal origin in residual tumor foci with multiple oncologic alterations that have been selected for by the intensive AR inhibition. Subclonal RB1 loss may be an early event in intermediate- to high-risk primary prostate cancer independent of neuroendocrine differentiation, in the development of mCRPC.

Low AR activity tumors can also be identified in hormone-naïve primary prostate cancers [55]. In a study using genome-wide expression profiles of prostate adenocarcinoma from radical prostatectomy or biopsy samples of patients with primary prostate cancer, a low AR-active subclass was found to comprise 9–11% of the cohort and was characterized by increased immune signaling, higher neuroendocrine marker expression, and decreased DNA repair pathway expression including individual genes of mismatch repair (PMS2 and MLH1) as well as mismatch repair pathway gene sets [55]. In addition, low AR-active primary prostate cancer had higher expression of alternative nuclear hormone receptors (e.g., PGR, NR3C1, and ESR1) that are found in association with metastatic CRPC [55] Lower AR-active patients were significantly more likely to have higher Decipher scores, suggesting a more aggressive biologic phenotype with increased metastatic potential. In a clinical validation of three independent cohorts in the study, lower AR-active tumors were associated with worse metastatic outcome. Clinically, patients who had the low AR-active localized tumors were also found to be less sensitive to ADT and more likely to develop CRPC [55].

There are ongoing clinical trials in progress to further elucidate which patients derive the greatest benefit from AR inhibition using genomic tests. Specifically, NRG GU009 (PREDICT-RT, NCT04513717) is a phase III randomized trial currently open to accrual for high-risk prostate cancer to determine which patients may benefit from higher intensity treatment with AR inhibition versus a lower intensity treatment. This trial is discussed in more detail further in this article. Additionally, NRG GU010 (GUIDANCE, NCT05050084) will soon open with a similar parallel studies design with a de-intensification study and an intensification study for patients with intermediate risk prostate cancer based on genomic risk score. In the deintensification study, patients considered to be of low genomic risk for distant-metastasis rates, based on Decipher score, will be randomized to RT with or without ADT.

Evidence suggests that AR activity is induced by DNA damage, activated AR promotes expression and activity of key factors involved in the DNA damage response (DDR), activated AR promotes resolution of double-strand breaks, and resistance to DNA damage [56]. Specifically, findings from a study suggest a model where androgen-induced DNA-dependent protein kinase, catalytic subunit (DNA-PKcs) expression and activity enhances AR activity, creating a positive circuit through which androgens promote DNA repair and tumor resistance to DNA damage-inducing therapeutics (Fig. 3) [56]. In addition, ARVs can mediate DDR in response to RT in an ADT-independent manner [57]. ARVs lack the AR ligand-binding domain (AR-LBD) and are not responsive to therapies targeting the AR-LBD. In one study using prostate cancer cells that express ARVs, the combination of RT and ADT was found to not be more effective than RT alone in blocking the DNA damage response [57]. RT was found to induce the interaction between ARVs and DNA-PKc. DNA-PKC inhibition blocked its interaction with ARVs and resulted in persistence of DNA damage and RT-mediated tumor cell kill. The study suggested a potential clinical trial rationale for combining drugs targeting AR and DNA-PKc in combination with RT for patients with localized prostate cancer.

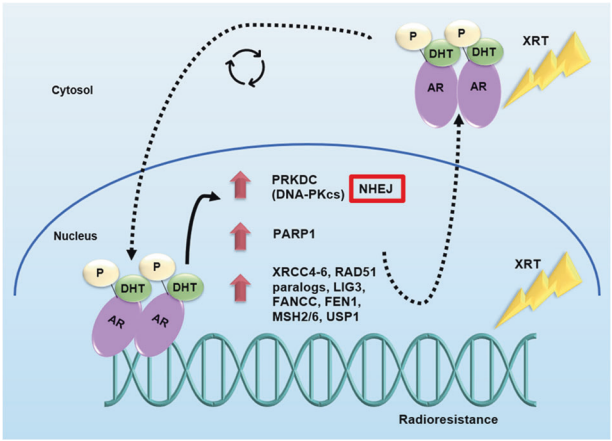

Fig. 3 Activation of androgen receptors (AR) can lead to increased DNA repair and radioresistance in prostate cancer. One mechanism by which this may occur is illustrated in this schematic. Upon exposure to radiation therapy, ARs dimerize and relocate to promoters of DNA repair genes and activate their transcription. Enhanced expression of DNA repair factors including DNA-Kcs and PARP1 can lead to more efficient repair of radiation therapy induced DNA lesions and lead to an increase in the prostate cancer cell's radioresistance. This illustration is adapted from Bartek, et al. Cancer Discovery 2013. Abbreviations: DHT: Dihydrotestosterone, AR: Androgen receptor, XRT: Radiation therapy.

In addition to DNA-Pcs, enhanced expression of other DNA repair factors such as poly(ADP-ribose) polymerase 1 can lead to more efficient repair of RT induced DNA lesions and lead to an increase in the prostate cancer cell's radio-resistance. Targeting the AR-DDR crosstalk is dependent on the ability to decrease AR activity and disrupt DDR by targeting factors critical for damage repair, though targeting the diminishing AR activity in CRPC has proven challenging. One potential implication is that more potent AR inhibition using second generation anti-androgens might prevent or mitigate the negative consequences of AR upregulation after RT [40].

A complete survey of mechanisms of ADT resistance [58, 59] is beyond the scope of this review, but these aforementioned studies serve to support that there are multiple mechanisms of resistance to ADT. The addition of second generation anti-androgens may help in mitigating some of these mechanisms of resistance.

Ongoing trials of second generation anti-androgens with radiation therapy in high-risk prostate cancer

Due to significant interest in second generation anti-androgens in the primary, non-metastatic high risk prostate cancer setting, there have been multiple ongoing randomized controlled trials that are testing androgen receptor inhibition in patients with high-risk prostate cancer receiving primary RT (Table 3). In the high-risk prostate cancer primary setting, current ongoing

Table 3. Ongoing randomized phase III trials testing androgen receptor inhibition with second generation anti-androgens in patients with high-risk prostate cancer receiving primary radiation therapy.

Clinical trial	Official Title	NCT Identifier	Arms	Primary Endpoint
STAMPEDE	STAMPEDE: Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy: A Multi-Stage Multi-Arm Randomized Controlled Trial	NCT00268476	Active Comparator: Standard of Care: ADT (plus RT for newly-diagnosed non-metastatic disease, plus or minus docetaxel, plus or minus abiraterone) (control) Experimental arms: ADT + zoledronic acid ADT + docetaxel+prednisolone ADT + celecoxib ADT + zoledronic acid+docetaxel+prednisolone ADT + zoledronic acid+celecoxib ADT + abiraterone acetate+prednisolone ADT + radiotherapy to the prostate (M1 RT) ADT + abiraterone+enzalutamide+prednisolone ADT + metformin Transdermal oestradiol	Overall survival
PREDICT-RT (NRG GU009)	Parallel Phase III Randomized Trials for High Risk Prostate Cancer Evaluating De-Intensification for Lower Genomic Risk and Intensification of Concurrent Therapy for Higher Genomic Risk With Radiation (PREDICT-RT*)	NCT04513717	Active Comparator: RT + ADT for 24 months (De-intensification) Experimental arm: RT + ADT for 12 months (De-intensification) Active Comparator: RT + ADT for 24 months (Intensification) Experimental arm: RT + ADT + Apalutamide (Intensification)	Metastasis-free survival
ENZARAD (ANZUP 1303, TROG 14.01)	Randomized Phase 3 Trial of Enzalutamide in Androgen Deprivation Therapy With Radiation Therapy for High Risk, Clinically Localized, Prostate Cancer: ENZARAD	NCT02446444	Active Comparator: RT + conventional non-steroidal anti-androgen for 6 months + ADT for 24 months Experimental arm: RT + Enzalutamide + ADT for 24 months	Metastasis-free survival
ATLAS	ATLAS: A Randomized, Double-blind, Placebo-controlled Phase 3 Study of JNJ-56021927 in Subjects With High-risk, Localized or Locally Advanced Prostate Cancer Receiving Treatment With Primary Radiation Therapy	NCT02531516	Active comparator: RT + apalutamide placebo for 30 months + GnRH agonist for 30 months + bicalutamide for 4 months Experimental arm: RT + apalutamide for 30 months + GnRH agonist for 30 months + bicalutamide placebo for 4 months	Metastasis-free survival
DASL-HiCaP	DASL-HiCaP: Darolutamide Augments Standard Therapy for Localized Very High-Risk Cancer of the Prostate (ANZUP1801): A Randomized Phase 3 Double-blind, Placebo-controlled Trial of Adding Darolutamide to Androgen Deprivation Therapy and Definitive or Salvage Radiation in Very High Risk, Clinically Localized Prostate Cancer	NCT04136353	Placebo Comparator: RT + ADT for 96 weeks + placebo for 96 weeks Experimental arm: RT + ADT for 96 weeks + darolutamide for 96 weeks	Metastasis-free survival

randomized controlled trials include STAMPEDE, PREDICT-RT (NRG GU009), ENZARD (ANZUP1303, TROG 14.01), ATLAS, and DASL-HiCaP (ANZUP1801).

In most of these trials, the primary endpoint is MFS apart from STAMPEDE, in which the primary endpoint is OS. In recent years, MFS has been used more often as a primary end point in trials since adjuvant clinical trials in prostate cancer can take more than a decade to reach the endpoint of OS; MFS as a surrogate can potentially accelerate the evaluation of new (neo)adjuvant therapies. In a study by the ICECaP Working Group, MFS has been found to be a strong surrogate for OS in clinically localized prostate cancer in a patient population with an ~15% chance of dying of prostate cancer over 10 years despite potentially curative local therapy [60]. In another study by the same group, event-free survival was determined to be a weak surrogate for OS and was not suitable for use as an intermediate clinical endpoint to substitute for OS to accelerate phase III (neo)adjuvant trials of prostate cancer therapies for primary RT.

The large multi-stage multi-arm randomized controlled trial STAMPEDE has been open since 2005 and has one control arm and several comparator arms to assess inclusion of therapies beyond standard ADT alone. Part of the patient population included in these arms include men with high-risk, non-metastatic, node negative disease as well as men with node-positive disease. Some of the results of this trial are already known as discussed previously in this article including the addition of abiraterone to ADT and RT [61].

Genomic testing to stratify patients into cohorts of higher and lower risk of metastases is a promising way to improve risk stratification to personalize therapy for men with high-risk prostate cancer by de-intensification versus intensification of therapy. Decipher 22-gene genomic classifier (GC) is one such test to help inform treatment decisions for men with localized prostate cancer and after radical prostatectomy. Recently, preliminary results were presented from a study validating the performance of the Decipher 22-gene GC in pretreatment biopsy samples of highest-grade tumors from participants in three randomized phase III high-risk definitive RT trials: NRG/RTOG 9202, 9413, and 9902 [62]. GC scores were obtained on 385 samples of which 69% passed microarray quality control; mean follow-up was 11 years. The GC score was found to be prognostic for distant metastases (HR 1.24, 95% CI 1.11–1.39), prostate cancer specific mortality (HR 1.27, 95% CI 1.13–1.43), OS (HR 1.12, 95% CI 1.05–1.20) on multivariate analysis after adjusting for age, PSA, GS, clinical tumor stage, trial, and randomized treatment arm [62]. The rate of distant metastasis at 10 years was 29% for those with a GC ≥ 0.45 (representing the intermediate and high GC) compared to 13% for low GC. To assess whether the Decipher score could not only be prognostic, but also predictive in men with high-risk prostate cancer, the randomized trial PREDICT-RT (NRG GU009, NCT04513717) is currently underway. In this trial, men with high-risk prostate cancer and a Decipher score in the bottom two thirds (GC ≤ 0.85) are eligible for the de-intensification study while men with high-risk prostate cancer and a Decipher score in the upper one third (GC ≥ 0.85) or node positive are eligible for the intensification study. Patients in the de-intensification study are randomized to 12 months of ADT + RT or 24 months of ADT + RT. The primary objective is to determine if men the lower Decipher score range can be treated with less ADT and achieve similar MFS. Patients in the intensification study are randomized to 24 months of ADT with RT or 24 months of ADT with RT with 24 months of apalutamide. The primary objective of the intensification study is to determine if the addition of apalutamide can improve MFS for men in the higher Decipher score range.

CONCLUSION

The use of second generation anti-androgens for consideration with RT and ADT in the definitive management of high-risk prostate cancer is a promising treatment option for some men. Currently, the NCCN guidelines endorses the use of abiraterone along with EBRT and ADT for 2 years in men with very high-risk prostate cancer only. Second generation anti-androgens are an exciting addition to the standard of care treatment options available for men with high-risk prostate cancer. Biologically, it works complementarily with RT and ADT. It may also help mitigate resistance to ADT, especially in localized prostate cancers without AR amplifications or mutations. Ongoing randomized controlled trials on the use of second generation anti-androgens in high-risk prostate cancer will further help elucidate the patient populations who may most benefit from the addition of second generation anti-androgens as well as provide further information on novel effective therapy combinations to improve patient outcomes.

DATA AVAILABILITY

The authors confirm that the data supporting the findings of this study are available within the article.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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