

# Combining prostate cancer radiotherapy with therapies targeting the androgen receptor axis

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## ABSTRACT

**Background** Prostate cancer (pca) is the most common non-dermatologic cancer and the 3rd leading cause of male cancer mortality in Canada. In patients with high-risk localized or recurrent pca, management typically includes the combination of long-term androgen deprivation therapy (ADT) and radiotherapy (RT). New androgen-receptor-axis targeted therapies (ARATs), which await validation, offer an option to intensify therapy.

**Methods** In this narrative review, we report the relevant history that has supported combining ADT with RT. The literature in PubMed was searched for studies involving pca and novel ARATs (abiraterone acetate, enzalutamide, apalutamide, darolutamide) published between 1995 and 2019. Literature discussing clinical trials in which those modalities were combined was extracted and synthesized into a combined molecular and clinical discussion. Potential treatment intensification mechanisms and rationales are explored.

**Results** Early results from three phase I/II trials demonstrated that concurrent abiraterone acetate, ADT, and RT is safe, improves the extent of chemical castration, and is associated with limited treatment failures. A single *in vitro* study implies synergy for radiosensitization beyond that facilitated by conventional ADT. Studies investigating the combination of other ARATs with RT are under way, including multiple phase III trials, but short-term results are not yet available.

**Key Words** Androgen deprivation therapy, abiraterone acetate, apalutamide, darolutamide, enzalutamide, prostate cancer, radiation therapy, treatment intensification

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## INTRODUCTION

Prostate cancer (pca) is the most common non-dermatologic malignancy affecting men in both Europe and North America<sup>1</sup>. Given the broad range of prognoses for patients with localized pca, stratification into low-, moderate-, and high-risk groups is usually performed (Table 1). In high-risk pca, a common treatment approach is to combine radiotherapy (RT) with androgen deprivation therapy (ADT). Extensive evidence from randomized controlled trials and meta-analyses has demonstrated that ADT with RT—generally external-beam RT (EBRT)—provides benefit for the full spectrum of pertinent oncologic outcomes in localized pca: overall survival (OS), metastasis-free

survival, biochemical progression-free survival, and local failure<sup>2-10</sup>.

Even though multiple relevant endpoints have been observed to be improved with dose-escalated EBRT (DE-EBRT), patients in the highest-risk pca groups are still being considered for treatment intensification. Without such intensification, treatment with DE-EBRT and long-term ADT (LT-ADT) will have failed for almost 50% of those patients by 6 years<sup>11</sup>. To refine the ability to design trials that further intensify therapy, a better understanding is required of ADT's mechanisms for sensitizing pca to RT. In the present review, we walk through the relevant history of that therapeutic combination, we explore the potential mechanisms for its synergy, and we consider strategies for improved therapeutic combinations.

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**TABLE I** Risk group according to the National Comprehensive Cancer Network<sup>1</sup> and D'Amico *et al.*, 2004<sup>2</sup>

Variable	Risk group		
	Low	Intermediate	High
National Comprehensive Cancer Network	All of:	Any of:	Any of:
Tumour stage	cT1c–2a	cT2b–c	cT3
Serum PSA	<10.0 ng/mL	>0.0 ng/mL to 20.0 ng/mL	>20.0 ng/mL
Gleason score	<7	7	8–10
D'Amico	All of:	Any of:	Any of:
Tumour stage	cT1c–2a	cT2b	cT2c–3
Serum PSA	<10.0 ng/mL	>10.0 ng/mL to 20.0 ng/mL	>20.0 ng/mL
Gleason score	<7	7	8–10

PSA = prostate-specific antigen.

### Evidence Supporting Neoadjuvant and Adjuvant ADT with EBRT

Several phase III randomized trials have proved the benefit of combining neoadjuvant and adjuvant ADT with EBRT for patients with high-risk pCa<sup>2–6</sup> (Table II). Although a meta-analysis showed that the addition of ADT significantly lowered the risk of biochemical failure, local failure, distant metastases, disease-specific survival, and OS, the studies used in the analysis were conducted in the era of conventional EBRT dosing ( $\leq 70$  Gy)<sup>12</sup>.

Once DE-EBRT ( $\geq 74$  Gy), relative to conventional doses, was noted to improve biochemical outcomes<sup>13</sup>, a demonstration that ADT still improved outcomes was necessary to justify the associated toxicity<sup>14</sup>. Two trials in combined populations of high- and intermediate-risk patients—the European Organisation for Research and Treatment of Cancer 22991 trial and the U.K. Medical Research Council RT01 trial—produced long-term results demonstrating that, compared with DE-EBRT alone, adding short-term ADT (ST-ADT) resulted in improved 5-year and 10-year biochemical progression-free survival (mature survival data are awaited)<sup>7,8</sup>. Preliminary results from phase III DE-EBRT trials (PCS III, GETUG 14) imply that adding ST-ADT to DE-EBRT produces only a biochemical progression-free survival benefit for patients with intermediate-risk pCa<sup>9,10</sup>.

### Optimal Duration of ADT in Combination with EBRT

In four randomized trials, it was observed that at least 4–6 months of ADT were required for clinical benefit (Table III). In those heterogeneous trials involving intermediate- and high-risk patients, biochemical control rates with ST-ADT and with EBRT alone were compared. The Trans-Tasman Radiation Oncology Group 96.01 trial demonstrated that 3 months and 6 months of ADT were both superior to no ADT<sup>18</sup>. Quebec L-101 and L-200 compared 3–5 or 10 months of ADT, reporting improved biochemical control with both regimes<sup>15</sup>. However, only the Radiation Therapy Oncology Group 9910 trial performed inter-comparisons of ST-ADT durations. Extending ST-ADT to 9 months from 4 months was not found to further improve any biochemical or survival outcomes<sup>19</sup>.

The extension of ADT to its present standard of 24–36 months in high-risk pCa was largely based on the European Organisation for Research and Treatment of Cancer 22961 trial and the Radiation Therapy Oncology Group 9202 trial<sup>16,17,22</sup>. Those trials compared ST-ADT and LT-ADT with conventional-dose EBRT in patients with predominantly high-risk pCa. Both studies showed improved disease-specific survival and OS with LT-ADT (28–36 months) as opposed to ST-ADT (4–6 months).

Two trials evaluated whether that length of ADT was still necessary for patients with high-risk pCa in the era of DE-EBRT. The DART 01/05 trial found that extending ADT to 28 months from 4 months improved biochemical control, metastasis-free survival, and OS<sup>20</sup>. The PCS IV trial was designed to show—and in fact showed—that intermediate-term ADT (18 months) was not inferior to LT-ADT (36 months) with respect to OS<sup>21</sup>. Given the gains in quality of life with a shorter course of ADT, those results have prompted consideration of intermediate-term ADT as a new standard of care for selected patients with high-risk pCa treated with DE-EBRT.

### ADT Plus RT: Intracellular Mechanisms for Interaction

Numerous preclinical studies, *in vitro* and *in vivo*, have evaluated the interactions between ADT and RT. Based on patient specimens, ADT has been observed to induce apoptosis in epithelial cells and to inhibit proliferation<sup>23</sup>. *In vitro* studies of LNCaP cells [an androgen receptor (AR)-positive hormone-sensitive human pCa cell line] showed that more apoptosis was produced during treatment with ADT and RT than with either monotherapy<sup>24</sup>. Combination treatment with goserelin and RT using cultures of both LNCaP and PC3 (an AR-negative hormone-insensitive human pCa cell line) inhibited cell proliferation by inhibition of the epidermal growth factor receptor<sup>25</sup>. However, neither study demonstrated the statistically significant reduction in survival required to demonstrate radiosensitivity.

Zietman *et al.*<sup>26</sup> were the first to show that ADT lowers the TCD50 (the dose of RT necessary to control 50% of cultured tumour). They hypothesized two nonexclusive molecular mechanisms for that radiosensitization: suppression of

**TABLE II** Phase III trials comparing androgen deprivation therapy (ADT) plus radiotherapy (RT) with RT alone in prostate cancer

RT type and reference (study name)	Population risk level	Study arms	Outcomes	
			5-Year	10-Year
<i>Conventional-dose RT</i>				
Pilepich <i>et al.</i> , 1997 <sup>3</sup> (RTOG 85-31)	High	(A) RT (B) RT plus indefinite ADT	bRFS: 21/55 DM: 29/15 OS: 71/76	DM: 39/24 OS: 39/49 bPFS: 9/31 LF: 38/23 DSS: 78/84
Jones <i>et al.</i> , 2001 <sup>6</sup> (RTOG 9408)	Low, intermediate, and high	(A) RT (B) RT plus 4 months of ADT	LF: 39/21 (2 years)	bRFS: 59/47 OS: 57/62 DM: 8/6
Pilepich <i>et al.</i> , 2001 <sup>5</sup> (RTOG 8610)	High	(A) RT (B) RT plus 4 months of ADT	bRFS: 10/28 DM: 39/29 OS: 68/72 <sup>a</sup>	OS: 34/43 <sup>a</sup> bRFS: 80/65 DM: 27/35 DSS: 23/36
Bolla <i>et al.</i> , 2002 <sup>4</sup> (EORTC 22863)	High	(A) RT (B) RT plus 3 years of ADT	bPFS: 45/76 DM: 29/10 OS: 62/78 LF: 1/7	DFS: 23/48 OS: 40/58 DSS: 10/30
D'Amico <i>et al.</i> , 2004 <sup>2</sup>	Intermediate and high	(A) RT (B) RT plus 6 months of ADT	OS: 77/88 bPFS: 55/79	OS: 61/74 (8 years) DSS: 84/78 (8 years) OS: 28/35 <sup>a</sup> (15 years)
<i>Dose-escalated RT</i>				
Dearnaley <i>et al.</i> , 2014 <sup>8</sup> (MRC RT01)	Low, intermediate, and high	(A) RT (64 Gy) plus 3–6 months of ADT (B) RT (74 Gy) plus 3–6 months of ADT	—	bPFS: 43/55 OS: 71/71
Nabid <i>et al.</i> , 2015 <sup>9</sup> (PCS III)	Intermediate	(A) RT (70 Gy) plus 6 months of ADT (B) RT (76 Gy) plus 6 months of ADT (C) RT (76 Gy)	BF: 7/2/14 <sup>b</sup> DFS: 93/97/86 <sup>b</sup> OS: 90/94/91 <sup>a</sup>	BF: 22/22/33 <sup>b</sup> DFS: 78/78/67 <sup>b</sup> OS: 63/72/75 <sup>a</sup>
Bolla <i>et al.</i> , 2016 <sup>7</sup> (EORTC 22991)	Intermediate and high	(A) RT (70 Gy, 74 Gy, 78 Gy) (B) RT (70 Gy, 74 Gy, 78 Gy) plus 6 months of ADT	bRFS: 70/83 DM: 4/8 <sup>a</sup> OS: 88/91 <sup>a</sup>	Not reported
Dubray <i>et al.</i> , 2016 <sup>10</sup> (GETUG 14/EU20503/ NCT00104741)	Intermediate	(A) RT (80 Gy) (B) RT (80 Gy) plus 4 months of ADT	bRFS: 76/84 OS: 94/93 <sup>a</sup>	Not reported

<sup>a</sup> Nonsignificant.<sup>b</sup> Nonsignificant between arms A and B.

RTOG = Radiation Therapy Oncology Group; bRFS = biochemical relapse-free survival; DM = distant metastases; OS = overall survival; bPFS = biochemical progression-free survival; LF = local failure; DSS = disease-specific survival; EORTC = European Organisation for Research and Treatment of Cancer; DFS = disease-free survival; MRC = U.K. Medical Research Council; BF = biochemical failure; GETUG = Unicancer Genitourinary Group.

tumour neovascularization improves blood flow through the more competent vasculature, and apoptosis-induced cyto-reduction facilitates vascular access to hypoxic tissues.

Tumour hypoxia has since been associated with impaired outcomes in *pca*<sup>27</sup>. Mechanistically, hypoxia stimulates angiogenic factors (for example, vascular endothelial growth factor), impairing tumour oxygenation secondary to the formation of incompetent vasculature<sup>28</sup>. As ADT suppresses hypoxia-induced AR activity, the subsequent

inhibition of hypoxia-inducible factor 1 $\alpha$  transcription reduces the expression of vascular endothelial growth factor and limits neovascularization of hormone-sensitive *pca* cells, providing *in vitro* support for the latter hypothesis<sup>29,30</sup>.

It is important to appreciate that RT initially upregulates AR expression, with preclinical studies showing that RT induces the expression of AR-regulated proteins<sup>31</sup>. Work by Goodwin *et al.*<sup>32</sup> outlines how the addition of castration-resistant *pca* to AR influences DNA repair—and

**TABLE III** Clinical trials comparing various durations of androgen deprivation therapy (ADT), with conventional or dose-escalated radiotherapy (RT)

RT type and reference (study name)	Population risk level	Study arms	Outcome	
			5-Year	10-Year
<i>Conventional-dose RT</i>				
Laverdiere <i>et al.</i> , 2004 <sup>15</sup> (Quebec L-101)	Intermediate and high-risk	(A) RT alone (B) RT plus 3 months of ADT (C) RT plus 10 months of ADT	bRFS: 42/66/69 <sup>b</sup> (7 years)	Not reported
(Quebec L-200)	Low, intermediate and high-risk	(A) RT plus 5 months of ADT (B) RT plus 10 months of ADT	bRFS: 70/70 <sup>b</sup> (4 years)	Not reported
Horwitz <i>et al.</i> , 2008 <sup>16</sup> (RTOG 9202)	High or locally advanced	(A) RT plus 4 months of ADT (B) RT plus 28 months of ADT	bRFS: 44/72 DM: 17/12 OS: 79/80 <sup>b</sup>	bRFS: 32/48 DM: 23/15 OS: 51/54 <sup>b</sup> LF: 22/12 DSS: 84/89
Bolla <i>et al.</i> , 2009 <sup>17</sup> (EORTC 22961)	High or locally advanced	(A) RT plus 6 months of ADT (B) RT plus 36 months of ADT	OS: 81/85 DSS: 95/97 DM: 6/14	Not reported
Denham <i>et al.</i> , 2011 <sup>18</sup> (TROG 96.01)	Intermediate	(A) RT (B) RT plus 3 months of ADT (C) RT plus 6 months of ADT	bRFS: 32/49/52 DM: 19/22/13 <sup>a</sup> LF: 28/17/12	bRFS: 70/60/53 OS: 57/63/71 <sup>a</sup>
Pisansky <i>et al.</i> , 2015 <sup>19</sup> (RTOG 9910)	Intermediate	RT plus 9 months of ADT RT plus 4 months of ADT	Not reported	bRFS: 73/73 <sup>b</sup> DM: 6/6 <sup>b</sup> OS: 67/66 <sup>b</sup>
<i>Dose-escalated RT</i>				
Zapatero <i>et al.</i> , 2011 <sup>20</sup> (DART01/05)	Intermediate or high-risk	(A) RT (70 Gy, 74 Gy, 78 Gy) plus 4 months of ADT (B) RT (70 Gy, 74 Gy, 78 Gy) plus 28 months of ADT	bRFS: 81/90 DMFS: 83/94 OS: 86/95	Not reported
Nabid <i>et al.</i> , 2013 <sup>21</sup> (PCS IV)	High	(A) RT plus 36 months of ADT RT plus 18 months of ADT	OS: 91/86 <sup>b</sup>	OS: 62/59 <sup>b</sup>

<sup>a</sup> Nonsignificant between arms 1 and 2.

<sup>b</sup> Nonsignificant.

bRFS = biochemical relapse-free survival; RTOG = Radiation Therapy Oncology Group; DM = distant metastases; OS = overall survival; LF = local failure; DSS = disease-specific survival; EORTC = European Organisation for Research and Treatment of Cancer; TROG = Trans-Tasman Radiation Oncology Group; DMFS = distant metastasis-free survival.

thus, radioresistance. After RT, DNA double-strand breaks activate the AR to enhance expression of numerous DNA repair genes (*PRKDC*, *KU70*, *PARP1*) and DNA repair protein RAD51. More than 32 DNA repair genes contain AR binding sites in their enhancer sequences<sup>33</sup>. Induction of those proteins can induce a positive feedback loop that causes radioresistance<sup>32</sup>. Initially, RT recruits DNA protein kinase catalytic subunit (PKCs) to a double-strand break. Subsequent activation of DNA PKCs also increases transcription of the AR. The AR then induces the expression and activity of additional DNA PKCs through AR-mediated DNA repair. Ultimately, the DNA PKCs and AR upregulate each other in a process that expedites repair of the RT-caused double-strand breaks. Importantly, intervention can interrupt the process. After castration, the decreased expression of *KU70* in prostate tissue implies increased radiosensitivity of tumour<sup>32</sup>.

### Strategies for Improving Therapeutic Combinations of ADT and EBRT

Relative to older anti-androgens, which were efficacious despite achieving only partial antagonism of the AR<sup>34,35</sup>, modern AR antagonists (for example, apalutamide, enzalutamide) have significantly improved binding affinity, can penetrate the cell for intracytosolic binding, and inhibit nuclear translocation of the AR<sup>36,37</sup>. Preclinically, our group demonstrated that a modern AR antagonist induced radiosensitization beyond that seen with ADT alone<sup>38</sup>. Enzalutamide alone potentiated the response to radiation in LNCaP cells and, in combination with ADT, in C4-2 hormone-resistant human pCa cells. Dose-enhancement factors were 1.75 and 1.30 respectively. Maximal radiosensitization was achieved when enzalutamide was given concurrently with—as opposed to before or after—RT, and increased expression of phospho-H2AX was consistent with enhanced DNA damage.

The other new agents in this class of modern ARATs are abiraterone and darolutamide. Darolutamide is also an AR antagonist, but maintains efficacy against the AR F876L, AR W741L, and AR T877A resistance mutations that limit the efficacy of apalutamide and enzalutamide<sup>39</sup>. Also, limited access by darolutamide to the cerebral circulation has produced a modest neurocognitive adverse effects profile<sup>40</sup>. Abiraterone differs significantly in its mechanism. Despite the achievement of castrate levels of serum testosterone by ADT in most patients, production of intraprostatic or adrenal androgens (dehydroepiandrosterone and androstenedione) are sufficient to maintain expression of androgen-responsive genes<sup>41,42</sup>. Abiraterone selectively and irreversibly reduces both of those androgen biosynthesis pathways by potent inhibition of CYP17A1, suppressing the predominant remaining pathway for androgen biosynthesis<sup>43</sup>. Theoretically, that suppression could better potentiate the synergistic benefits seen with less-complete suppression of the androgen axis<sup>26</sup>.

The most recent clinical trial investigating DE-EBRT and LT-ADT in a high-risk population in need of further intensification showed worrisome rates of relapse approaching 50% at 6 years after treatment<sup>11</sup>. Although treatment intensification with chemotherapy can improve survival, the benefit came at the cost of increased toxicity, including treatment-related deaths. Implementing next-generation ARATs offers a more tolerable route to treatment intensification in the localized setting, preserving docetaxel as an effective choice for metastatic PCA<sup>44-46</sup>. Because the ARATs have demonstrated clinical efficacy in more advanced clinical settings<sup>47-51</sup> and because there is preclinical evidence that these agents are radiosensitizers<sup>38</sup>, their combination with RT is the next logical step for treatment intensification in patients with high-risk PCA.

**METHODS**

Relevant articles resulting from a literature search of PubMed for 1995–2019 were reviewed. These search terms and phrases were used individually and in combination: “localized prostate cancer,” “androgen deprivation therapy,” “radiation therapy,” “randomized trial,” “review,” “high-risk prostate cancer,” “intensification,” “enzalutamide,” “abiraterone acetate,” “apalutamide,” “darolutamide,” and “clinical trials.” All published, presented, or registered trials addressing the concurrent use of novel ARATs with RT were extracted for further review. For extracted works that combined RT with a novel ARAT, populations, interventions, and outcomes were extracted and summarized.

**RESULTS**

**Clinical Trials Combining Abiraterone Acetate with RT**  
 Three trials of abiraterone combined with RT were found (Table IV). A single phase I study investigated the safety of combining abiraterone with salvage RT<sup>54</sup> and two phase II trials evaluated efficacy based on the extent of castration as assessed by testosterone level<sup>52,53</sup>. The two phase II trials varied in their populations and ADT durations. At a median follow-up of 21 and 23 months, a single treatment failure

**TABLE IV** Summary of completed clinical trials combining abiraterone acetate (AA) with radiotherapy (RT) for prostate cancer (PCa)

ClinicalTrials.gov ID (study name)	Phase	Eligibility	Pts (n)	Study arms	Status	Primary endpoint	Results
NCT01023061, Cho et al., 2015 <sup>52</sup> (RAD1)	II	Intermediate-risk or high-risk PCa	24	(A) AA, prednisolone, ADT, and RT	Completed	Toxicity evaluation	No treatment stopped prematurely by protocol Grade 3 toxicities: lymphopenia, 64%; hypertension, 9%; elevated liver function tests, 9%; fatigue, 5%; and hypokalemia, 5% Grade 4 toxicity: none Single incidence of biochemical failure (1/22) Median follow-up: 21 months
NCT01717053, Koontz et al., 2018 <sup>53</sup>	II	High-risk PCa	37	(A) AA, prednisolone, ADT, and RT	Completed	PSA <0.1 ng/mL at 1 year	Median follow-up: 23 months PSA <0.1 ng/mL: 52% PSA <0.5 ng/mL: 95% To date, no failures by Phoenix definition Grade 3 toxicities: 32% Grade 4+ toxicity: none Testosterone recovery at 12 months: 62%
NCT01780220, Supiot et al., 2018 <sup>54</sup> (CARLHA)	I, II	Biochemical recurrence after partial response	43	(A) AA, prednisolone, ADT, and RT (B) AA, prednisolone, and RT	Completed	Determine MTD	MTD: 750 mg daily with RT Complete castration: (A) 100%; (B) 78%

Pts = patients; ADT = androgen deprivation therapy; MTD = maximal tolerated dose; PSA = prostate-specific antigen.

had occurred in the phase II studies. Notably, in the one 2-arm study, which compared abiraterone monotherapy with combined therapy using ADT, castration levels of testosterone were achieved in only 78% of men receiving monotherapy compared with 100% of those receiving combination therapy. Toxicity data showed a 64% cumulative incidence of grade 3 lymphopenia during DE-EBRT<sup>52</sup>.

### Clinical Trials Combining Enzalutamide with RT

Eight ongoing clinical trials assessing the combination of enzalutamide with RT were found (Table v), seven of which are phase II studies. The patient populations being evaluated have predominantly intermediate- and high-risk pCa, and in one trial (NCT02057939), patients are receiving salvage radiotherapy. The primary endpoints in most of the phase II trials are acute and late toxicities and biochemical endpoints.

Two studies are randomized controlled trials: ENZARAD (NCT02446444,  $n=802$ , accrual complete) and NCT02203695 (target accrual  $n=122$ ). NCT02203695, a multicentre trial in patients who are receiving salvage RT and ST-ADT is randomizing participants to either enzalutamide or placebo and has a primary endpoint of biochemical control. The fully accrued phase III ENZARAD trial is randomizing patients with high-risk pCa to receive either enzalutamide or placebo for 24 months in addition to DE-EBRT and LT-ADT. Its primary outcome is OS, and based on the timing of its accrual, it is expected to be the first phase III trial to provide insight into whether an ARAT can safely and effectively intensify DE-EBRT and ADT.

### Clinical Trials Combining Apalutamide with RT

Seven ongoing trials, all either phase II or III, are evaluating the combination of apalutamide with RT (Table vi). Three of the seven trials are combining apalutamide with DE-EBRT. Another two are the only trials identified in our search to be combining stereotactic body RT with a novel ARAT (NCT02772588, NCT03503344), and two trials are combining salvage radiotherapy with an ARAT (NCT03311555, NCT03141671). Notably, two phase III randomized controlled trials are including patients with high-risk pCa.

The fully accrued ATLAS trial has a primary outcome of metastasis-free survival, an established surrogate for OS<sup>56</sup>. In ATLAS, the accepted standard of DE-EBRT and LT-ADT has been intensified, randomizing participants to either apalutamide or placebo bicalutamide. In contrast, the European Organisation for Research and Treatment of Cancer's upcoming phase III randomized controlled trial limits ADT to the neoadjuvant and concurrent period, with a primary outcome of disease-free survival, but will *not* consider biochemical failure to be disease progression. Patients with intermediate- and high-risk pCa will receive ADT and DE-EBRT and will be randomized to receive either apalutamide or placebo while on ADT.

### Clinical Trials Combining Darolutamide with RT

Our search methods did not identify any clinical trials combining darolutamide with RT directly. Outside our established search, abstracts made reference to the upcoming Darolutamide Augments Standard Therapy for Localized High-Risk Cancer of the Prostate, a randomized

phase III trial in patients with high-risk pCa receiving RT. Participants will be randomized to receive concurrent darolutamide or placebo with RT and LT-ADT [Canadian Cancer Trials Group (CCTG). Darolutamide augments standard therapy for localized high-risk cancer of the prostate (DASL-HiCaP). Kingston, ON: CCTG; 2019].

## DISCUSSION

This review of the clinical and preclinical evidence highlights the influence of RT on AR-mediated protein expression and the AR's role in enhancing DNA repair and radioresistance<sup>31,32</sup>. Such data outline how the combination of ADT and RT can disrupt those interactions to facilitate the survival benefits seen in patients with pCa<sup>33</sup>. Despite combination therapy, key trials still show that an unacceptable proportion of men with high-risk pCa will not achieve long-term disease control<sup>11,16,57</sup>.

Preclinical work has provided a limited demonstration that an ARAT can provide further synergy beyond ADT's known potentiation of RT-mediated DNA damage. Combined with the known clinical efficacy of those agents, the rationale to combine them with RT to facilitate treatment intensification is strong. The review of the literature in the Results section demonstrate that a multitude of studies exploring this concept are under way. Although studies combining RT with abiraterone have been completed and have not been followed with phase III trials, randomized phase III trials are evaluating RT combined with apalutamide [ATLAS (NCT03488810)], darolutamide [Canadian Cancer Trials Group (CCTG). Darolutamide augments standard therapy for localized high-risk cancer of the prostate (DASL-HiCaP). Kingston, ON: CCTG; 2019], and enzalutamide [ENZARAD (NCT02446444)]. Of those trials, ATLAS and ENZARAD have both fully accrued, but even early results are still awaited. Another incidental observation is that upcoming assessments in oligometastatic pCa might also produce clinical data about subgroups that received an ARAT in combination with RT (NCT03784755). A notable absence is any phase III trial that is accruing patients exclusively in the salvage setting, although four randomized phase II trials are exploring that setting (NCT02057939, NCT02203695, NCT03311555, and NCT03141671).

Reflecting on past preclinical data can direct the field's next steps to intelligently fill this rapidly crowding clinical trials space. In consideration of ARAT and RT scheduling, the timing of bicalutamide treatment relative to RT affects the radiosensitivity of hormone-sensitive cell lines<sup>34</sup>. Furthermore, our group's preclinical work demonstrated that concurrent enzalutamide—compared with neoadjuvant enzalutamide, adjuvant enzalutamide, or ADT—provides the most potent radiosensitization<sup>38</sup>.

Such observations direct the field to a few key areas that should be considered for preclinical investigation before clinical trials:

- Establishing the most effective radiosensitizers of the novel ARATS
- Scheduling of the agents to optimize radiosensitization

With those studies completed, the duration and timing of a novel ARAT could be optimized and then compared

**TABLE V** Ongoing trials of enzalutamide combined with radiotherapy (RT) in prostate cancer (PCa)

ClinicalTrials.gov ID (study name)	Phase	Eligibility	Pts (n)	Study arms	Status	Endpoints	
						Primary	Secondary
NCT02023463	I	Intermediate-risk or high-risk PCa	25	Enzalutamide, ADT, and RT	Active, not recruiting	Acute toxicities	Serum PSA and quality of life
NCT02028988	II	Intermediate-risk PCa	64	Enzalutamide and RT	Active, not recruiting	Serum PSA after 6 months of enzalutamide therapy	Quality of life, hormone levels, and body fat
NCT02057939 (STREAM)	II	Biochemical relapse after partial response	38	Enzalutamide, ADT, and salvage RT	Active, not recruiting	Progression-free survival	Biochemical progression-free survival, progression-free survival, PSA <0.1 ng/mL, PSA nadir, and time to testosterone recovery
NCT02064582	II	High-risk PCa	9	Enzalutamide, ADT, and RT	Active, not recruiting	Assess the safety and tolerability of combining enzalutamide, ADT, and RT	Assessing intratumoural androgen-regulated gene expression before and after combination therapy
NCT02203695	II	Biochemical relapse after partial response	122	(A) Salvage RT and placebo (B) Salvage RT and enzalutamide	Recruiting	Freedom from PSA progression	Metastasis-free survival rate and local recurrence
NCT02446444 (ENZARAD) (ANZUP 1303)	III	High-risk PCa	802	(A) Enzalutamide, ADT, and RT (B) Nonsteroidal anti-androgen, ADT, and RT	Active, not recruiting	Overall survival	Biochemical progression-free survival, progression-free survival, and metastasis-free survival
NCT02508636	II	High-risk PCa	11	Enzalutamide, ADT, and RT	Active, not recruiting	Rate of acute toxicity Rate of late toxicity PSA complete response rate	Biochemical progression-free survival, disease-free survival, time to clinical progression, and quality of life
NCT03196388 (ENZART)	II	Intermediate-risk PCa	70	Enzalutamide and RT	Recruiting	80% Reduction from baseline PSA	

Pts = patients; PSA = prostate-specific antigen; ADT = androgen deprivation therapy.

**TABLE VI** Ongoing trials of apalutamide combined with radiotherapy (RT) in prostate cancer (PCa)

ClinicalTrials.gov ID (study name)	Phase	Eligibility	Pts (n)	Study arms	Status	Endpoints	
						Primary	Secondary
NCT02531516 (ATLAS) <sup>55</sup>	III	High-risk and locally advanced PCa	1500	(A) Placebo, bicalutamide, ADT, and RT (B) Apalutamide, bicalutamide, ADT, and RT	Active, not recruiting	Metastasis-free survival	Time to locoregional recurrence, time to castration-resistant disease, time to distant metastasis, and overall survival
NCT02772588 (AASUR)	II	Very-high-risk PCa	58	(A) Apalutamide, AA, prednisone, ADT, and stereotactic body RT	Recruiting	Proportion of patients with biochemical failure	
NCT03141671 (FORMULA-509)	II	Biochemical complete response after radical prostatectomy	190	(A) ADT, bicalutamide, and salvage RT (B) ADT, AA, apalutamide, prednisone, and salvage RT	Recruiting	Progression-free survival	PSA progression-free survival, metastasis-free survival, overall survival, time to testosterone recovery, grades 1–5 toxicity, time to re-initiation of ADT, quality of life, and cardiovascular events consisting of myocardial infarction
NCT03311555 (STARTAR)	II	Biochemical complete response after radical prostatectomy	42	Apalutamide, ADT, docetaxel, and salvage RT	Recruiting	Progression-free survival	Proportion of participants with serum PSA < 0.1 ng/mL and testosterone recovery, time to testosterone recovery, biochemical progression-free survival, and median PSA nadir value
NCT03371719	II	Locally advanced PCa	324	(A) Placebo and RT (B) Apalutamide and RT	Recruiting	Biochemical progression-free survival	Distant metastasis, metastasis-free survival, disease-free survival, and cancer-specific mortality
NCT03488810	III	Intermediate-risk and high-risk PCa	990	(A) ADT and RT (B) Apalutamide, ADT, and RT	Not yet recruiting	Disease-free survival	Progression-free survival, distant metastasis-free survival, overall survival, serum PSA, and prostate cancer-specific survival
NCT03503344 (PILLAR)	II	Castration-resistant PCa	60	(A) Stereotactic body RT (B) Apalutamide and stereotactic body RT	Not yet recruiting	Proportion of patients with undetectable serum PSA	Time to PSA progression, progression-free survival, and incidence of adverse events

Pts = patients; ADT = androgen deprivation therapy.



with the various available agents. It would be reasonable to expect that maximally suppressing the androgen axis with the combination of abiraterone and a modern AR antagonist could further potentiate radiosensitization. Such preclinical studies could have a signal adequate to support a clinical trial.

The ongoing clinical work and the opportunities for preclinical studies hold great promise to direct and establish novel strategies that will enhance outcomes for patients with high-risk pCa.

## CONCLUSIONS

Suppressing the function of the AR (historically with the use of ADT) remains an essential component in treating advanced pCa. Although ADT works synergistically with RT to provide further benefit, whether the use of novel ARATs could further potentiate that interaction is unknown. Early preclinical experiments and phase I/II studies have implied that such combinations might be efficacious. Multiple phase III trials in patients with high-risk pCa are ongoing and will more firmly address those hypotheses.

## CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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