THEMATIC REVIEW

Androgen receptor signaling inhibitors: post-chemotherapy, pre-chemotherapy and now in castration-sensitive prostate cancer

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Abstract

Based on pioneering work by Huggins, Hodges and others, hormonal therapies have been established as an effective approach for advanced prostate cancer (PC) for the past eight decades. However, it quickly became evident that androgen deprivation therapy (ADT) via surgical or medical castration accomplishes inadequate inhibition of the androgen receptor (AR) axis, with clinical resistance inevitably emerging due to adrenal and intratumoral sources of androgens and other mechanisms. Early efforts to augment ADT by adding adrenal-targeting agents (aminoglutethimide, ketoconazole) or AR antagonists (flutamide, bicalutamide, nilutamide, cyproterone) failed to achieve overall survival (OS) benefits, although they did exhibit some evidence of limited clinical activity. More recently, four new androgen receptor signaling inhibitors (ARSIs) successfully entered clinical practice. Specifically, the CYP17 inhibitor abiraterone acetate and the second generation AR antagonists (enzalutamide, apalutamide and darolutamide) achieved OS benefits for PC patients, confirmed the importance of reactivated AR signaling in castration-resistant PC and validated important concepts that had been proposed in the field several decades ago but had remained so far unproven, including adrenal-targeted therapy and combined androgen blockade. The past decade has seen steady advances toward more comprehensive AR axis targeting. Now the question is raised whether we have accomplished the maximum AR axis inhibition possible or there is still room for improvement. This review, marking the 80-year anniversary of ADT and 10-year anniversary of successful ARSIs, examines their current clinical use and discusses future directions, in particular combination regimens, to maximize their efficacy, delay emergence of resistance and improve patient outcomes.

Key Words

- ▶ prostate cancer
- ▶ androgen deprivation therapy
- ▶ androgen receptor (AR)
- ▶ abiraterone
- ▶ enzalutamide apalutamide
- ▶ darolutamide

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Introductory concepts and historical perspective

The pioneering work of Huggins & Hodges (1941), that we are celebrating in this issue of ERC (Zoubeydi & Ghosh 2021), not only set the framework for the hormonal

treatment of advanced prostate cancer (PC), but also was one of the first successful ‘targeted’ therapies for cancer in general. While most patients with advanced PC benefited

from castration (androgen deprivation therapy (ADT)), resistance emerged quickly in most cases (within 1–3 years, in general). This led to a series of important questions:

- What are the mechanisms of resistance to first-line ADT?
- Can a more comprehensive approach targeting all sources of androgenic stimulation delay emergence of resistance to ADT?
- What is the best timing of the treatment intensification? Is earlier use of intensified ADT more effective? How early is early enough?
- If deeper AR axis inhibition can accomplish better clinical outcomes, then how deep AR inhibition is enough to maximize the clinical benefit?
- What are the mechanisms of resistance to the newer androgen receptor signaling inhibitors (ARSIs) and what is the next step in their use for improving outcomes for our patients?

Historically, the term ADT has been and still is used to refer only to suppression of production of testosterone by the testicular Leydig cells via surgical castration (bilateral orchiectomy) or medical castration (targeting the hypothalamic-testicular axis with GnRH analogs) (Mitsiades *et al.* 2011, Mitsiades 2013, Relugolix FDA Package Insert 2020). For the purposes of this article, we will refer to this regimen as ‘standard ADT’ (sADT). In PC patients receiving sADT, a circulating (peripheral) testosterone (circT) level of <50 ng/dL has been and still is considered adequate testosterone suppression (Mitsiades *et al.* 2011, Relugolix FDA Package Insert 2020). When clinical progression would, inevitably, occur while maintaining circT <50 ng/dL, it would be and still is defined as castration-resistant PC (CRPC).

However, several studies have reported that accomplishing stricter (lower) circT thresholds (<30 ng/dL, <25 ng/dL, or even <20 ng/dL) was associated with even better clinical outcomes (Bertaglia *et al.* 2013, Wang *et al.* 2017, Ozyigit *et al.* 2019). The same was shown when circT was analyzed as a continuous variable (Perachino *et al.* 2010). Collectively, these results suggest that our ideal therapeutic goal should be to lower androgenic stimulation to as low as safely achievable. In further support, several mechanisms of PC cell resistance to ADT involve hypersensitization of the PC cells to (low levels of residual) androgens, for example, due to overexpression of AR mRNA and protein, frequently due to amplification at the AR gene locus (Visakorpi *et al.* 1995, Mitsiades *et al.* 2011, 2012, Mitsiades 2013, Quigley *et al.* 2018, Takeda *et al.* 2018, Viswanathan *et al.* 2018). Therefore, it is important

to simultaneously suppress testosterone levels to the lowest level achievable and that goal requires comprehensive targeting of all sources of androgenic stimulation: gonadal, adrenal and intratumoral steroidogenesis (Mitsiades 2013).

In healthy adult men, >95% of circT is of gonadal origin. The rest is synthesized either in the adrenals or in other, peripheral tissues (including the prostate gland and PC tissues). In situ (‘intracrine’) steroidogenesis can be de novo (with all enzymatic steps from cholesterol to testosterone and DHT happening in some PC tissues) or by conversion of weaker androgen precursors of adrenal origin: DHEA and androstenedione. DHEA, in the form of DHEA-sulfate, is the steroid with the highest circulating concentration in humans and thus, is an abundantly available precursor. Upon initiation of ADT, these extra-gonadal sources of androgens become very important for residual AR activation that allows for the survival of the PC cells, until other mechanisms of resistance make the cells completely resistant.

The importance of intratumoral steroid metabolism is highlighted by strong evidence that even well suppressed circT levels do not guarantee complete depletion of intratumoral androgens (Montgomery *et al.* 2008). In fact, intratumoral androgens and AR-dependent gene expression drop by a much lower degree compared to the degree of suppression of serum androgens after ADT (Mostaghel *et al.* 2007). Several steroidogenic enzymes are expressed in the prostate gland and in PC tissue (Montgomery *et al.* 2008) and can even be upregulated by androgen withdrawal (Mitsiades *et al.* 2012). For example, the mRNA levels of AKR1C3, an enzyme that can convert androstenedione to testosterone, are upregulated in PC cells within a few hours of androgen withdrawal (Mitsiades *et al.* 2012). Therefore, androgen deprivation triggers an acute adaptation feedback loop that enhances the ability of the PC cell to metabolize adrenal precursors into testosterone and DHT, thus sustaining tissue androgen levels and AR stimulation.

In essence, the term ADT has been used historically to describe, under the form of sADT, a now outdated hormonal therapy regimen that was inadequate androgen deprivation at the cellular level within the PC microenvironment, as intratumoral androgens actually persisted under these conditions (Montgomery *et al.* 2008). The PC field has since moved significantly forward with the addition of ARSIs to the ADT backbone. For the purposes of this review, we will focus our discussion on the newer, more effective ARSIs: specifically, the CYP17 inhibitor abiraterone and the second generation AR ligand-binding domain (LBD) antagonists (antiandrogens) enzalutamide, apalutamide

and darolutamide, as these are the agents that have entered the market in recent years. Several names have been used to describe these regimens such as 'Intense Androgen Deprivation', 'intensified ADT', 'Comprehensive AR axis Targeting', 'augmented ADT', etc. The clinical successes of these combination regimens have led to substantial clinical benefits for PC patients, while validating the old hypotheses in the field about concurrently targeting all sources of androgenic stimulation, and redefining the use of ADT.

Can a more comprehensive approach targeting all sources of androgenic stimulation delay emergence of resistance to ADT?

Historical review of older efforts

Earlier efforts to target the androgenic contribution of extra-gonadal sources in CRPC go back several decades, with some clinical successes (some well-documented response rates and PFS benefits), but never established a definitive prolongation of overall survival (OS) via Phase III randomized controlled trials (RCTs) in the pre-abiraterone/enzalutamide era. As a result, while intriguing and sometimes widely used, these early approaches failed to gain level 1 evidence in their support.

Earlier adrenal-targeted approaches

Suppression of adrenal steroid production via surgical adrenalectomy or use of exogenous glucocorticoids in the past yielded some clinical successes (Storlie *et al.* 1995, Sartor *et al.* 1998, Kantoff *et al.* 1999, Nishimura *et al.* 2000, Fossa *et al.* 2001, Koutsilieris *et al.* 2001, Saika *et al.* 2001, Berry *et al.* 2002, Morioka *et al.* 2002, Tannock *et al.* 2004, Mitsiades *et al.* 2011) that have historical significance as proof-of-principle for the role of adrenal steroids in CRPC. Similarly, chemical adrenalectomy via the anticonvulsant aminoglutethimide or the antifungal ketoconazole (both are also non-specific inhibitors of several cytochrome P450 enzymes, including those involved in steroidogenesis) accomplished PSA responses in some patients (Small *et al.* 1997, Kruit *et al.* 2004, Peer *et al.* 2014) but the lack of an OS benefit in Phase III RCTs together with their significant toxicity (nausea, fatigue, edema, hepatotoxicity, neurotoxicity, rash, anorexia) and multiple interactions with other P450 substrate drugs prevented their formal FDA approval for this indication (Abratt *et al.* 2004, Small *et al.* 2004, Mitsiades *et al.* 2011).

However ketoconazole was widely used (off label) in CRPC and did serve as a forerunner of CYP17 inhibitors such as abiraterone.

Earlier anti-androgens and 'combined androgen blockade'

Another approach to target residual AR activation in ADT-treated patients is to directly displace the androgenic ligand from the AR, via a competitive ligand-binding domain (LBD) inhibitor (also called an anti-androgen). The first generation of such agents included flutamide, bicalutamide, nilutamide and cyproterone acetate (Chen *et al.* 2009, Mitsiades *et al.* 2011), which achieved PSA responses in some CRPC patients and gained popularity in this setting, but never definitively established an OS benefit for CRPC patients (Mitsiades *et al.* 2011). Moreover, they were extensively tested in the metastatic castration-sensitive PC (mCSPC) setting in combination with sADT under the concept of 'maximal' or 'combined androgen blockade' (Labrie *et al.* 1985), with a miniscule, at best, survival benefit (Klotz 2008, Mitsiades *et al.* 2011). One possible explanation for that overall failure was that these agents were not adequately potent AR antagonists, but rather partial agonists, and also prone to 'antagonist-to-agonist' conversion (Culig *et al.* 1999), an intellectually interesting (yet clinically detrimental) clinical phenomenon where the very hormonal treatment used was actually fueling the growth of the PC cells. This was first noticed due to clinical responses encountered in a subset of anti-androgen-treated CRPC patients (15–30%) after withdrawal of the anti-androgen (Kelly & Scher 1993, Leone *et al.* 2018) and was attributed to dysregulation of the AR complex via various types of somatically-acquired events, including:

- AR LBD gain-of-function mutations such as T878A, W742C/L, H875Y and L702H (originally reported as T877A, W741C/L, H874Y and L701H, respectively) and others (Taplin *et al.* 1995, Marcelli *et al.* 2000, Hara *et al.* 2003, Yoshida *et al.* 2005, Chen *et al.* 2009, Gottlieb *et al.* 2012, Leone *et al.* 2018). (Note: A change in the current reference sequence of the androgen receptor cDNA (Gottlieb *et al.* 2012, McEwan & Brinkmann 2016) led to a +2 shift in amino acid numbering between residues 78 and 449 and to a +1 shift between residues 472 and 919 compared with the previously used, original reference sequence (M20132.1)).
- AR mRNA and protein overexpression, attributed to numerous mechanisms such as copy number gains

of the AR coding sequence and/or of an upstream enhancer, as well as changes in epigenetic and microRNA regulatory loops (Visakorpi *et al.* 1995, Chen *et al.* 2004, Mitsiades *et al.* 2012, Mitsiades 2013, He *et al.* 2014, Coarfa *et al.* 2016, Quigley *et al.* 2018, Takeda *et al.* 2018, Viswanathan *et al.* 2018).

- Altered expression and recruitment of AR coactivators. for example, the p160 steroid receptor coactivators (SRCs) SRC-1, SRC-2 and SRC-3, also known as Nuclear Coactivators NCoA1, NCoA2 and NCoA3, are found to be overexpressed in advanced PC and, in particular, CRPC (Gregory *et al.* 2001, Agoulunik *et al.* 2005, 2006, Zhou *et al.* 2005, Taylor *et al.* 2010).

Overall, the first generation anti-androgens had suboptimal clinical performance with inadequate AR inhibitory activity and, while FDA-approved for use in PC, never achieved documented OS benefits in CRPC or as 'combined androgen blockade' in CSPC.

Better drugs validate old concepts

So were the concepts of adrenal-targeted therapy, anti-androgen use and combined androgen blockade flawed? No – they were just impeded by the availability of only suboptimal first generation agents with clear PD deficiencies. The field has significantly advanced due to emergence of:

- (a) More selective enzymatic inhibitors of androgen synthesis that are better-tolerated and more effective. Specifically, the CYP17 inhibitor abiraterone (CB7598) is a potent inhibitor of androgen biosynthesis. CYP17 (steroid 17- α -hydroxylase/17,20 lyase; gene name CYP17A1) has two enzymatic activities: 17-hydroxylase (necessary for the synthesis of both androgens and glucocorticoids) and 17,20 lyase (necessary for the synthesis of androgens only). Abiraterone inhibits both activities. Consequently, in the absence of glucocorticoid supplementation, abiraterone raises serum ACTH levels and increases adrenal conversion of cholesterol to pregnenolone, progesterone and mineralocorticoids (which do not require CYP17). The mineralocorticoid excess can cause fluid retention, edema, hypertension and hypokalemia, while progesterone can function as a non-canonical AR agonist (especially in the case of LBD-mutant AR) and as a canonical PR agonist, both of which can drive resistance to abiraterone (Cai *et al.* 2011, Chen *et al.* 2015a). For that reason, abiraterone-treated patients are also given replacement doses of

prednisone or prednisolone (P), in order to decrease the risk of mineralocorticoid side-effects and to enhance anticancer activity (Danila *et al.* 2010, Bedoya & Mitsiades 2013).

Because abiraterone has poor oral absorption and is susceptible to hydrolysis by esterases, abiraterone acetate (AA, CB7630) was developed as an orally bioavailable, esterase-resistant prodrug (Ryan & Cheng 2013). Abiraterone is at least 10-times more potent as an inhibitor of CYP17 than ketoconazole (Haidar *et al.* 2003) and more selective, hence better tolerated. Not surprisingly, several studies have shown that AA+P is more effective than ketoconazole (Peer *et al.* 2014) and still somewhat effective even in ketoconazole-resistant CRPC (Danila *et al.* 2010, Kim *et al.* 2014). It deserves to be noted that there are additional proposed mechanisms of action for the anticancer activity of abiraterone, including direct antagonism of AR (Richards *et al.* 2012, Norris *et al.* 2017).

- (b) Second generation orally bioavailable anti-androgens (enzalutamide, apalutamide and darolutamide) with improved PD properties: As mentioned above, flutamide, bicalutamide, nilutamide and cyproterone are prone to 'antagonist-to-agonist' conversion in PC cells due to overexpression of AR or its coactivators, somatic AR mutations, or other mechanisms (Mitsiades *et al.* 2011). For that reason, a library of nonsteroidal anti-androgens were rationally optimized for inhibition of AR transcriptional activity based on the AR crystal structure and were screened to select for lack of agonistic activity (Tran *et al.* 2009). The lead compound MDV3100 (enzalutamide) and the related ARN-509 (apalutamide) were reported to bind AR with higher affinity than bicalutamide, prevent its nuclear translocation and DNA binding, and have anticancer activity in preclinical *in vitro* and *in vivo* models without incurring agonistic activity (Tran *et al.* 2009, Scher *et al.* 2010, Clegg *et al.* 2012, Rathkopf & Scher 2013). The phase 1–2 study of enzalutamide documented antitumor effects at all doses used (Scher *et al.* 2010) and set the stage for its rapid entry into Phase III testing and FDA approval. In agreement with its higher inhibitory activity and lower propensity for 'antagonist-to-agonist' conversion, anti-androgen withdrawal responses after discontinuing enzalutamide, although possible, are significantly less common and less durable than what was encountered with first generation anti-androgens (Phillips 2014, Schrader *et al.* 2014, von Klot *et al.* 2014a, von Klot *et al.* 2014b, Rodriguez-Vida *et al.* 2015,

Poole *et al.* 2017, Leone *et al.* 2018). Still, the AR F877L (previously F876L) mutation has been reported to confer an antagonist-to-agonist switch to enzalutamide and apalutamide that drives resistance (Balbas *et al.* 2013, Joseph *et al.* 2013, Korpál *et al.* 2013).

More recently, darolutamide (ODM-201, BAY-1841788), an AR antagonist with a distinct chemical structure, was introduced to the clinic and approved for the treatment of patients with non-metastatic castration-resistant PC (nmCRPC) (Fizazi *et al.* 2019, 2020). Some preclinical experiments indicate that darolutamide is active against LBD-mutant ARs that confer resistance to enzalutamide and apalutamide such as AR F877L (previously F876L) and W742C/L (previously W741C/L), but that remains to be confirmed in the clinic (Sugawara *et al.* 2019). Darolutamide is reported to exhibit negligible blood-brain barrier (BRB) penetration, which may explain why, contrary to enzalutamide, its trials show that it does not significantly increase the risk of seizures, falls, or fractures (Moilanen *et al.* 2015, Shore 2017, Sugawara *et al.* 2019).

Novel ARSIs find their place in PC treatment

Early phase II studies of abiraterone (Danila *et al.* 2010, Reid *et al.* 2010) and enzalutamide (Scher *et al.* 2010) provided proof of principle that these are active agents in CRPC and established that the term ‘androgen-independent’ PC, in the way that it had been used until those studies, was actually a misnomer. The same Phase II studies provided evidence that abiraterone and enzalutamide are active even in CRPC patients previously treated with older agents such as ketoconazole or bicalutamide, although in some cases with somewhat lower response rate (Danila *et al.* 2010). As a result, subsequent studies generally excluded patients with prior exposure to any ARSI of any generation in order to avoid cross-resistance. In these Phase III studies, both abiraterone and enzalutamide had substantial OS benefits and PSA response rates in mCRPC patients, both in the post-chemotherapy and pre-chemotherapy settings (Table 1), and that led to their approval, first for chemotherapy-refractory mCRPC and, soon afterwards, for chemotherapy-naïve mCRPC. Subsequent results from Phase III studies established the efficacy of abiraterone and enzalutamide in earlier disease states, namely non-metastatic (M0) CRPC and mCSPC. Apalutamide and darolutamide, which entered clinical development a few years after abiraterone and enzalutamide, were examined directly in these earlier disease states, as their administration to CRPC patients who had already received enzalutamide (or even abiraterone)

would likely mask their clinical efficacy. Based on these clinical trials (timeline presented in Table 1), the current status of regulatory approval at the time of this writing (February 2021) is:

- AA+P is approved for the treatment of patients with metastatic castration-resistant PC (mCRPC) and metastatic high-risk castration-sensitive PC (CSPC).
- Enzalutamide is approved for the treatment of patients with CRPC (irrespective of metastatic or not status) and metastatic CSPC (mCSPC), irrespective of risk stratification.
- Apalutamide is approved for the treatment of patients with mCSPC, irrespective of risk stratification, and non-metastatic CRPC (nmCRPC).
- Darolutamide is approved for the treatment of patients with nmCRPC.
- Ongoing clinical trials are examining the role of ARSIs in earlier disease states such as enhancing neoadjuvant sADT prior to prostatectomy (e.g. <https://clinicaltrials.gov/ct2/show/NCT03080116>, <https://clinicaltrials.gov/ct2/show/NCT03767244>).

Conclusions from the ARSI clinical trials and thoughts on augmenting frontline ADT

- Deeper AR axis inhibition accomplished better outcomes: It is clear that the concepts of adrenal-targeted therapy, anti-androgen use, and combined androgen blockade were correct but were previously impeded by the lack of good pharmacological agents. These newer ARSIs have validated the old concepts because they have superior PD and PK properties. In addition to the overall success of the newer ARSIs (which far eclipses any efficacy the older agents such as first generation anti-androgens and ketoconazole had ever shown), head-to-head comparison trials (TERRAIN (Shore *et al.* 2016), STRIVE (Penson *et al.* 2016)) have also confirmed that enzalutamide is clearly superior to bicalutamide and, consequently, has almost completely replaced it in the clinic (although still included as an option in the National Comprehensive Cancer Network guidelines). Similarly, the use of ketoconazole in PC has essentially been completely replaced by AA+P (although still included as an option in the National Comprehensive Cancer Network guidelines).
- Direct comparison of the absolute clinical benefit between these studies is hindered by the differences

Table 1 Timeline of major clinical trials that have led to the approval of ARSIs.

Arsi	Metastatic CRPC (chemotherapy-refractory)	Metastatic CRPC (chemotherapy-naïve)	Non-metastatic (M0) CRPC	Metastatic CSCP	N1M0 and High-risk NOM0 CSCP
Abiraterone	COU-AA-301 (de Bono et al. 2011) OS benefit 3.9 months over the control arm. PSA RR 29%.	COU-AA-302 (Ryan et al. 2013, 2015) OS benefit 4.4 months over the control arm. PSA RR 62%.	No Phase III trial data reported yet and no FDA approval in this clinical space, but a phase II single-arm trial showed ≥50% PSA reduction in 86.9% of patients and a ≥90% PSA reduction in 59.8% of patients (Ryan et al. 2018).	- LATITUDE ^a (Fizazi et al. 2017, 2019) OS benefit was 16.8 months over the control arm. 3-year OS was 66% (vs 49% in the control arm). HR for death was 0.66. - STAMPEDE (arm G) ^b (James et al. 2017, Hoyle et al. 2019). Low-risk group: 3-year OS was 83% vs 78% in the control arm. High-risk group: 3-year OS was 65% (vs 45% in the control arm). HR for death was 0.66 for low-risk and 0.54 for high-risk patients. - ENZAMET (Davis et al. 2019) 3-year OS 80% (vs 72% in the control arm) HR for death was 0.67. PSA progression- free survival HR was 0.39. - ARCHES (Armstrong et al. 2019) HR for radiographic progression or death was 0.39 with enzalutamide plus ADT vs placebo plus ADT. TITAN (Chi et al. 2019) 2-year OS 82.4% (vs 73.5% in the control arm). HR for death was 0.67 In the final analysis, presented at the 2021 Genitourinary Cancers Symposium, HR for death was 0.52. The median OS was not reached in the apalutamide arm and was 52.2 months in the placebo arm (HR 0.65). The 48-mo survival rates were 65% (apalutamide) vs 52% (placebo) (Chi et al. 2021).	STAMPEDE (arm G) ^b (James et al. 2017)
Enzalutamide	AFFIRM (Scher et al. 2012) OS benefit 4.8 months over the control arm. HR for death was 0.63. PSA RR 54%.	PREVAIL (Beer et al. 2014) OS benefit 2.2 months over the control arm. HR for death was 0.71. PSA RR 78%.	PROSPER (Hussain et al. 2018, Sternberg et al. 2020) Median OS 67.0 months (vs 56.3 months in the placebo arm). HR for death was 0.73		
Apalutamide			SPARTAN (Smith et al. 2018b, 2021, Small et al. 2019) 4-year OS 72% (vs 65% in the placebo arm, or 61% if adjusted for crossover). Median OS 73.9 months (vs 59.9 months in the placebo arm) despite 19% crossover (placebo to apalutamide) HR for death was 0.78		
Darolutamide			ARAMIS (Fizazi et al. 2019, 2020) 3-year OS 83% (vs 77% in the placebo arm). HR for death was 0.69.		

^aLATITUDE enrolled metastatic high-risk CSCP patients; defined as having at least two of three high-risk factors: Gleason ≥8, at least three bone lesions, or visceral metastasis. ^bSTAMPEDE (arm G) enrolled a heterogeneous population of patients: patients had M1 disease (52%), N1 (or indeterminate) M0 disease (20%), and NOM0 disease (28%). XRT was mandatory for NOM0 and encouraged for abiraterone. The current (February 2021) FDA approval for abiraterone use in metastatic CSCP is for high-risk M1 patients (as defined by LATITUDE ([Fizazi et al. 2017](#))). Technically, the use of abiraterone in the low-risk M1, N1M0 or NOM0 CSCP settings is still off-label, but can be justified as an extrapolation based on the STAMPEDE data ([James et al. 2017, Hoyle et al. 2019](#)). HR, hazard ratio; OS, overall survival; RR, response rate.

between study populations and trial designs, and can only be considered hypothesis-generating. With those caveats in mind, one could notice that *all four ARSIs are biologically active* and no particular pattern of superiority emerges from the results of the studies in [Table 1](#). PSA response rates tend to be slightly numerically higher with enzalutamide than with AA+P, but this does not appear to translate into longer survival benefits. As of February 2021, enzalutamide has the broadest approval for use in all states of CRPC (irrespective of metastatic status and prior chemotherapy use) and metastatic CSPC. The current approval for AA+P covers only metastatic CRPC and metastatic high-risk (as defined by the LATITUDE criteria ([Fizazi et al. 2017](#))) CSPC. However, arm G of the STAMPEDE trial (AA+P) also enrolled patients with low-risk metastatic CSPC or lymph-node positive PC or non-metastatic PC receiving ADT. From this heterogeneous study arm, in our clinical practice (NM) we frequently extrapolate and extend, off label, the use of AA+P to intensify ADT used in the low-risk M1 or N1M0 or N0M0 CSPS settings.

More significantly, it is our opinion that the differences in the approved indications between the four ARSIs in [Table 1](#) simply reflect strategic decisions of the respective manufacturers to prioritize positioning of each drug in certain clinical spaces, rather than actual differences in clinical activity. The approved indications for all ARSIs are very likely to continue expanding in the near future, based on emerging data from ongoing and future clinical trials. For example, AA+P does not (yet) have FDA approval for use in non-metastatic (M0) CRPC, but this is only due to lack of reported Phase III clinical trial data, and it has actually shown promising Phase II data ([Ryan et al. 2018](#)). Similarly, apalutamide and darolutamide would be expected to be active in an ARSI-naïve, chemotherapy-refractory metastatic CRPC patient, but such patients should be uncommon now that four ARSIs carry approved indications for much earlier disease states and, therefore, such a clinical trial would be both very difficult to accrue and practically irrelevant for real-world clinical care. Thus, lack of data supporting activity in that clinical space does not mean lack of activity in that space.

Timing of the intensification

The use of ARSIs in pre-chemotherapy mCRPC is not substantially more effective than their use in post-chemotherapy mCRPC (the PSA response rates are

numerically higher in the pre-chemotherapy setting, but the OS benefits are not). However, the use of ARSIs in mCSPC or nmCRPC is substantially more effective than use in the mCRPC state. For example, the improvement in median OS upon addition of AA+P to sADT in mCRPC patients is about 4 months (irrespective of prior chemotherapy use), but four times as much in mCSPC patients. Similarly, the improvement in median OS with the addition of enzalutamide to sADT is far more substantial in nmCRPC than in mCRPC patients. That suggests that initiating an ARSI earlier (before establishment of metastatic CRPC or before emergence of clinical metastasis) is associated with substantially better clinical outcomes. Data from the addition of an ARSI to sADT in the nmCSPC state is not yet available, but it would be very interesting to know if the clinical benefits will be even higher in that even earlier disease state.

Why does the combination of an(y) ARSI with sADT work better if started earlier? One possible explanation is that, because several mechanisms of resistance overlap between sADT and ARSIs, implementing more comprehensive AR axis inhibition earlier prevents the emergence of resistant clones ([Mitsiades 2013](#)). Several studies examining the significance of the PSA nadir on ADT support this hypothesis. The SWOG Trial 9346 (INT-0162) showed that the absolute PSA value after ADT is a strong independent predictor of survival in mPC ([Hussain et al. 2006](#)). Specifically, median survival was 13 months for patients with a PSA of more than 4 ng/mL after 7 months of ADT, 44 months for patients with PSA of more than 0.2–4 ng/mL after seven months of ADT, and 75 months for patients with PSA of 0.2 ng/mL or less after seven months of ADT. In a subsequent SWOG study, metastatic PC patients with a suboptimal response to ADT (PSA > 4.0 ng/mL after 6–12 months of ADT) had their hormonal regimen augmented with AA+P. However, only five of 40 participants (13%) patients achieved a PSA level of ≤0.2 ng/mL, while 13 (33%) additional patients achieved a reduction in the PSA level to <4.0 ng/mL but >0.2 ng/mL ([Flaig et al. 2017](#)). A cumulative PSA response rate of 45% in this small study may not be statistically different from what was seen in COU-AA-302 ([Ryan et al. 2013, 2015](#)), but overall, this study failed to reach its predefined endpoint, and was considered as evidence that ADT intensification after castration-resistance has emerged in metastatic PC may be too late for optimal efficacy.

Optimal ARSI sequencing and cross-resistance

All major clinical trials that led to the clinical development, registration, and FDA approval of each ARSI ([Table 1](#))

excluded patients who had been significantly exposed to any other ARSI (including older generation agents such as ketoconazole, aminoglutethimide, etc.) in order to avoid contamination by cross-resistance. As a result, all ARSIs entered the market based only on data from ‘ideal cases’ of patients who were naïve to all other ARSIs and without any studies directly comparing (‘head-to-head’) the activity of different ARSIs or examining cross-resistance between them. As pointed out in the previous section, the informal numerical comparison of the response rates and OS benefits seen in these registration trials (interpreted with caution, as the use of different study populations and trial designs prohibits a formal comparison), do not highlight any particular ARSI as substantially superior to the others (enzalutamide tends to give numerically higher PSA response rates than abiraterone, but this does not appear to translate into longer survival benefits). Moreover, a prospective study that randomized mCRPC patients to first-line abiraterone (+P) or enzalutamide for a head-to-head comparison found no significant difference between the two ARSIs in time to PSA progression, even though PSA responses were more common in the enzalutamide cohort (Khalaf *et al.* 2019).

After FDA approval of these agents and general use in real-world practice, it became a common experience that the clinical responses to either abiraterone (+P) or enzalutamide as second-line ARSIs after progression on the other agent are, at best, modest (PSA response rates in the range of 2–36%) and not durable (Loriot *et al.* 2013, Noonan *et al.* 2013, Bianchini *et al.* 2014, Azad *et al.* 2015a, Attard *et al.* 2018, de Bono *et al.* 2018, Khalaf *et al.* 2019). This cross-resistance between these two classes of ARSIs is not surprising, as several mechanisms can provide resistance to both CYP17 inhibitors and 2nd generation anti-androgens. Such mechanisms include constitutively active AR variants (including ARv7), and treatment-associated NEPC transdifferentiation (see section on ‘Mechanisms of resistance to ARSIs’). Nevertheless, crossover from one ARSI to another is used frequently in the clinic, especially as it is more appealing to use another hormonal agent instead of cytotoxic chemotherapy.

In that scenario, the question arises regarding the optimal sequencing of the ARSIs: The same study of mCRPC patients by Khalaf *et al.* found that the abiraterone (+P) → enzalutamide sequence may be associated with longer time to second PSA progression and higher PSA response rates on second-line ARSI therapy compared to the inverse sequence (Khalaf *et al.* 2019). A systematic review and meta-analysis of 10 crossover studies confirmed that the abiraterone (+P) →

enzalutamide sequence was significantly associated with better PFS than with the opposite treatment sequence, but the OS barely missed statistical significance (pooled HR: 0.77, 95% CI: 0.59–1.01, $P=0.055$) (Mori *et al.* 2020). Thus, it is possible that using abiraterone acetate followed by enzalutamide may provide the maximum possible benefit, at least as far as PFS. Other factors that may affect clinical decision making in selecting which ARSI to use first are the adverse event profile of each agent (Table 2) and cost (abiraterone is already generic in the US, while the three second generation anti-androgens are not). The use of biomarkers in this setting remains to be explored. For example, it is plausible but remains to be established whether ARv7-negative status after progression to the first ARSI agent would accurately predict sensitivity to a second ARSI agent.

Again, it should be noted that irrespective of the sequencing of these ARSIs, the response to whichever agent is used as a second-line ARSI is short-lived. In our own clinical practice (N M), after progression on an ARSI, we stratify patients based on severity of symptoms and urgency of the need for a clinical response at that point. We offer the option of a second ARSI agent in sequence after progression on the first ARSI agent only for those CRPC patients who are generally asymptomatic and are not at imminent risk of harm from delaying active therapy. In metastatic CRPC patients who, after progression on the first ARSI agent, are symptomatic or at high risk for a skeletal event, visceral crisis or other major complication, we strongly recommend cytotoxic chemotherapy (taxane). This is supported by the results of the CARD trial, where patients who had progressed on abiraterone or enzalutamide received the other ARSI or cabazitaxel, with cabazitaxel showing superior progression-free survival and overall survival (de Wit *et al.* 2019).

Depth of AR axis inhibition: how much is optimal?

With the (long overdue) success of combining two hormonal agents (sADT+ one ARSI), have we reached the maximum potential benefit or is there room for further improvement in our hormonal regimens for PC? If the addition of an ARSI to sADT improves clinical outcomes (two hormonal agents in combination work better than one), then one could hypothesize that the combination of three hormonal agents (sADT to suppress testicular androgen production+CYP17 inhibitor to suppress

adrenal steroidogenesis+anti-androgen to block binding of any escaping/residual androgen to the AR) might target that AR axis more comprehensively, overcoming more putative mechanisms of resistance and might yield even better clinical results. Unfortunately, this has not been the case so far:

- (1) *Adding the second ARSI after progression to the first ARSI in CRPC patients:* The randomized PLATO study examined whether, in the setting of enzalutamide resistance in mCRPC, the addition of AA+P to continuous enzalutamide use would be superior to switching to AA+P (plus placebo). Unfortunately, there was no difference in PFS between the groups, and the PSA response rates were very low (1% for the combination group that received the two ARSIs concurrently and 2% for the sequential treatment group that switched from enzalutamide to AA+P (Attard *et al.* 2018)).
- (2) *Combining two ARSIs with ADT in ARSI-naïve CRPC:* The phase III trial Alliance A031201 (NCT01949337) examined whether the addition of AA+P to enzalutamide would be superior to enzalutamide monotherapy in men with ARSI-naïve mCRPC. Unfortunately, the study showed no advantage for the combination of the 2 ARSIs over enzalutamide alone. Grade 3–5 adverse events occurred in 55.6% and 68.8% of patients taking enzalutamide and enzalutamide/abiraterone/prednisone, respectively. Treatment discontinuation (12% vs 5%) and patient withdrawal rates (13% vs 5%) were higher in the combination group due to adverse events. Another trial (ACIS) examined a similar concept, using apalutamide instead of enzalutamide. Again, the combination of apalutamide+abiraterone/prednisone did not improve OS compared to abiraterone/prednisone in mCRPC (Rathkopf *et al.* 2021). The combination of enzalutamide with abiraterone and sADT has also been undergoing testing since July 2014 as arm J of the STAMPEDE trial (NCT00268476) (Attard *et al.* 2014).
- (3) *Using two ARSIs+ADT in the neoadjuvant setting:* The neoadjuvant setting allows to rapidly assess the anticancer activity of a systemic therapy, examine possible biomarkers of response, and dissect mechanistic hypotheses. Neoadjuvant systemic therapy is now commonly used in early breast cancer and the achievement of pathologic complete response (pCR) has been proposed as a surrogate endpoint for OS. On the contrary, despite significant efforts, neoadjuvant systemic therapy (including hormonal

therapy) is still not considered a standard-of-care approach for localized/locally advanced PCs prior to prostatectomy and was never able to improve disease-free survival (DFS) and overall survival (OS). It is possible that sADT cannot adequately suppress the AR axis inside the PC cells in order to achieve pCR. Indeed, in a randomized phase II trial, the addition of AA+P to ADT resulted in more effective suppression of intraprostatic androgens than ADT alone (Taplin *et al.* 2014). Still, in the same study, even after 24 weeks of neoadjuvant hormonal therapy with ADT+AA+P, the pCR rate was only 10%. For that reason, a follow-up study examined whether the combination of neoadjuvant ADT+enzalutamide+AA+P would be more effective than ADT+enzalutamide for 6 months before radical prostatectomy in men with locally advanced PC (McKay *et al.* 2019). Unfortunately, the pCR rate was only 10 and 8% in the two groups, respectively. In addition, more intense hormonal therapy was not associated with better outcomes as far as surgical margin positivity, extracapsular extension, or seminal vesicle invasion, although it showed a non-statistically significant trend for more minimal residual disease (less than 5 mm). In agreement, in another phase II neoadjuvant study of six months ADT+apalutamide with or without abiraterone in localized high-risk PC, dual ARSI treatment did not result in better outcomes at the time of prostatectomy (Efstathiou *et al.* 2020).

In summary, so far the clinical evidence suggests that combining more than one ARSI with ADT is not beneficial. This may sound counterintuitive at first, and a mechanism to explain it has not been established. It is possible that the combination of ADT with one ARSI (either AA+P or second generation anti-androgen) may have already brought AR axis activation to its nadir, and there is no more additional benefit from the third agent. Another point to consider is that AA must be administered together with glucocorticoids (albeit at replacement doses) and glucocorticoids are known to drive resistance to second generation anti-androgens via GR (see section on 'Mechanisms of resistance to ARSIs'); therefore, perhaps this combination is flawed at its inception. Finally, a more complex hypothesis comes from an interesting study that suggests that, while originally considered a pure AR antagonist, enzalutamide may function as a partial agonist that reprograms AR binding from canonical AREs to a distinct DNA motif and to a different set of genes that promote CRPC growth (Chen *et al.* 2015b). The pioneer transcription factor GATA2 may play a role in this switch (Yuan *et al.* 2019) and

Table 2 Reported Adverse Events of ARSIs, from Abiraterone FDA Package Insert (2020), Apalutamide FDA Package Insert (2020), Enzalutamide FDA Package Insert (2020), Darolutamide FDA Package Insert (2021).

Abiraterone	Enzalutamide	Apalutamide	Darolutamide
Hypertension, hypokalemia, edema, due to mineralocorticoid excess.	Risk of seizure (0.5% across all patients and 2.2% in those with predisposing factors).	Risk of seizure (0.4% across all patients).	Reportedly not crossing the blood-brain barrier, so it does not significantly increase risk of seizures or falls.
Liver toxicity, fatigue. Need for glucocorticoid replacement (concern for diabetics, etc.).	Posterior reversible encephalopathy syndrome (PRES) Asthenia, musculoskeletal pain and arthralgias. Falls and fractures. No need for glucocorticoid replacement (actually, discouraged as it may drive resistance).	Musculoskeletal pain and arthralgias, decreased neutrophil count. Falls and fractures. Hyperglycemia and hypertriglyceridemia. No need for glucocorticoid replacement (actually, discouraged as it may drive resistance).	Fatigue, decreased neutrophil count, transaminitis, hyperbilirubinemia. No need for glucocorticoid replacement (actually, discouraged as it may drive resistance).

both androgen deprivation and enzalutamide are known to increase the levels of GATA2 in PC cells (He *et al.* 2014). Thus, one can propose that in patients treated with ADT alone (testicular androgen suppression only), adrenal and intratumoral steroidogenesis results in substantial tissue DHT levels that drive AR signaling and can be antagonized by enzalutamide (hence explaining the significant clinical benefit of adding enzalutamide to sADT in CSPC and CRPC), while in patients receiving ADT+AA+P the intratumoral androgen levels have already been suppressed so low that now the dominant effect of enzalutamide is its GATA2-mediated agonistic effect on AR. Certainly, this hypothesis remains to be proven in the clinic, and the development of a GATA2 inhibitory approach would be one way to examine whether it can overcome the agonistic activity of enzalutamide (as a quadruple therapy of ADT+2 ARSIs+GATA2 inhibitor).

Mechanisms of resistance to ARSIs

Several mechanisms of resistance to ARSIs have been proposed (Vlachostergios *et al.* 2017), including:

- (a) Reactivation of the AR transcriptional program via alterations in AR itself such as
 - AR mRNA and protein overexpression. AR represses its own mRNA expression, and profound AR inhibition leads to adaptive derepression of its expression. Additionally, amplification events in the AR gene locus (involving the gene body and/or upstream enhancer sequences) are common in CRPC, in particular ARSI-resistant CRPC (Visakorpi *et al.* 1995, Waltering *et al.* 2009, Grasso *et al.* 2012, Mitsiades *et al.* 2012, He *et al.*

2014, Azad *et al.* 2015b, Romanel *et al.* 2015, Foley & Mitsiades 2016, Quigley *et al.* 2018, Takeda *et al.* 2018, Viswanathan *et al.* 2018).

- AR LBD mutations that restore AR activity in the presence of ARSI (Balk 2002, Steinkamp *et al.* 2009, Gottlieb *et al.* 2012, Azad *et al.* 2015b, Wyatt *et al.* 2016, Steinestel *et al.* 2019). The AR F877L (previously F876L) mutation has been reported to confer an antagonist-to-agonist switch to enzalutamide and apalutamide that drives resistance (Balbas *et al.* 2013, Joseph *et al.* 2013, Korpai *et al.* 2013). It needs to be examined clinically whether darolutamide can overcome that resistance, as has been proposed based on *in vitro* studies (Sugawara *et al.* 2019).
- Constitutively active, truncated AR splice variants that lack part of or the entire LBD and function in a ligand-independent manner (Hu *et al.* 2009, Dehm & Tindall 2011, Hornberg *et al.* 2011, Lu & Luo 2013, Antonarakis *et al.* 2014, Djusberg *et al.* 2017, Jernberg *et al.* 2017, Prekovic *et al.* 2018).
- (b) Reactivation of the AR transcriptional program via an alternate steroid receptor. Four steroid receptors (AR, progesterone receptor (PR), glucocorticoid receptor (GR) and mineralocorticoid receptor (MR)) can recognize and bind to the same DNA motif, allowing for overlap in their transcriptional output and functional compensation (Isikbay *et al.* 2014). Active AR suppresses not only its own expression, but also the expression of GR. Consequently, inhibition of the AR axis results in derepressed expression of both AR and GR, and GR activity can bypass the AR blockade from ARSIs (Arora *et al.* 2013, Xie *et al.* 2015, Puhr *et al.* 2018).
- (c) AR-program-independent mechanisms of resistance such as:

- Increased activation of kinase pathways, for example, PI3K/AKT (Carver *et al.* 2011, Liu & Dong 2014, Adelaiye-Ogala *et al.* 2020) and receptor tyrosine kinases (RTKs) (Drake *et al.* 2012, 2013, 2014, 2016, Faltermeier *et al.* 2016, VanDeusen *et al.* 2020).
- Cell lineage plasticity and transdifferentiation from a luminal epithelial phenotype to other AR-indifferent phenotypes, including neuroendocrine (NEPC), small cell, as well as the double-negative PC (DNPC) that is both AR-negative and neuroendocrine-negative and is driven by the FGF and MAPK pathways (Bluemn *et al.* 2017, Abida *et al.* 2019, Handle *et al.* 2019, Yamada & Beltran 2021). An aberrant CRPC type with a gastrointestinal-lineage transcriptome has also been described (Shukla *et al.* 2017). Such transdifferentiation is frequently driven by transcription factors (ONECUT2, HNF4G, HNF1A, SOX2, ASCL1, BRN2, MYCN), epigenetic changes in DNA methylation, histone modifications, chromatin integrity and accessibility, and EZH2 activity (Beltran *et al.* 2011, Shukla *et al.* 2017, Abida *et al.* 2019, Yamada & Beltran 2021). Ku *et al.* reported that EZH2 inhibition is able to reverse the lineage switch and restore the sensitivity to AR-targeted therapy (Ku *et al.* 2017). Interestingly, several of the transcription factors driving this transdifferentiation are suppressed by AR under hormone-replete conditions; thus deep AR axis inhibition results in their derepressed expression. In other words, the emergence of these NEPC and other AR-indifferent CRPC phenotypes is not via random, stochastic events, but is based on pre-determined transcriptional programs that were repressed by androgen, and thus represent an inescapable consequence of deep AR inhibition (Kaochar & Mitsiades 2019). In agreement, these AR-indifferent PC phenotypes are very rarely seen *de novo* in hormone-naïve PC patients, become more frequent in CRPC after sADT, and even more common after the use of ARSIs for deeper AR inhibition. In parallel, the related process of epithelial-mesenchymal transition (EMT) (Dicken *et al.* 2019), which is involved in cancer cell invasion and metastasis (Kahn *et al.* 2014), has been shown to be regulated by the androgen-AR signaling axis. Complex and frequently opposing effects of AR signaling on EMT have been reported (Zhu & Kyprianou 2010, Matuszak & Kyprianou 2011, Jacob *et al.* 2014, Nakazawa & Kyprianou 2017, Lin *et al.* 2018).

Future directions

This year marks not only the 80-year anniversary of ADT, but also the 10-year anniversary of the introduction of the first successful ARSI to the market (abiraterone 2011). In the past decade, ARSIs have prolonged survival and improved quality of life for many PC patients, but resistance eventually emerges in the clinic and requires innovative approaches to address it.

In the case of ARSI-resistance driven by full-length AR, there is room for additional inhibition, for example, via degradation by proteolysis targeting chimeras (PROTACs) (Han *et al.* 2019, Neklesa *et al.* 2019, Kregel *et al.* 2020, Petrylak *et al.* 2020), an approach that can target both ligand-dependent and ligand-independent functions of full-length AR. A PROTAC consists of a protein-ligand domain (that recruits the target protein), a linker region, and a ligase ligand domain (that binds a specific E3 ubiquitin ligase, which will ubiquitinate the protein of interest and promote its degradation). One advantage of PROTACs is their activity at very low concentrations, because they promote the degradation of their target proteins, essentially functioning in a catalytic manner and not as competitive antagonists. The protein-ligand domain is obviously critical in determining which forms of the target protein will be degraded. The presence of a LBD on full-length AR makes it an obvious choice for PROTAC design but also limits PROTAC activity accordingly. For example, ARCC-4, a prototypic PROTAC that was designed by linking enzalutamide to a VHL E3 ligase ligand, promotes the degradation of full-length AR, including of the F877L mutant that is functionally activated by the parent LBD ligand (enzalutamide). Thus, the switch from a competitive antagonism mechanism to a degradation-promoting mechanism of action can broaden the spectrum of activity of a LBD ligand. However, as expected, ARCC-4 cannot promote degradation of the LBD-lacking ARv7 (Salami *et al.* 2018). Similarly, ARV-110, a related PROTAC that is already in clinical trials, targets for degradation WT full-length AR and many of its variants (T878A, H875Y, F877L, M895V), but not L702H or ARv7 (Neklesa 2019, Petrylak 2020).

As a result, for ARSI-resistant CRPCs driven by AR variants that lack the LBD, a different approach is needed. The N-terminal domain (NTD) of AR (which is present in all AR variants, including LBD-mutants and LBD-lacking splice variants), has been proposed as druggable, and clinical results from this promising approach are eagerly awaited (Andersen *et al.* 2010, Myung *et al.* 2013, Banuelos *et al.* 2016, Sadar 2020).

Our prediction is that further targeting of AR, either at the LBD or at the NTD, may benefit select patients with specific mechanisms of resistance such as ligand-dependent (e.g. LBD-mutant AR) and ligand-independent (e.g. LBD-lacking splice variants) CRPC, thus having a clinical value in a biomarker-driven manner. However, at the same time, they would be expected to drive even more CRPCs, as an adaptive pre-determined mechanism, toward AR-indifferent biology and, in particular, treatment-associated NEPC and related phenotypes. This will further increase the urgent need for developing targeted therapies to address this lethal transition (Beltran & Demichelis 2021).

Another direction is to combine ARSIs with other pathway inhibitors in a biomarker-guided approach. For example, the addition of the Akt inhibitor ipatasertib to the CYP17 inhibitor abiraterone in patients with mCRPC showed superior antitumor activity to abiraterone alone in a phase Ib/II study, especially in patients with PTEN loss (de Bono *et al.* 2019). In the subsequent phase III, randomized, double-blind IPATential150 study, adding ipatasertib to abiraterone in asymptomatic or mildly symptomatic patients previously untreated for mCRPC, improved PFS in patients who had PTEN loss (de Bono *et al.* 2020). Other combinations of ARSIs with PARP inhibitors (Rao *et al.* 2021) or chemotherapy (Smith *et al.* 2018a) are currently being investigated as well.

However, combination regimens need to be approached carefully and in a manner driven by rationale, mechanism and evidence. Not all combinations benefit patients, as described above regarding combinations involving AA+P plus a second generation anti-androgen. Furthermore, in ERA-223, a randomized, double-blind, placebo-controlled, phase 3 trial in chemotherapy-naïve CRPC with bone metastases, the addition of radium-223 to AA+P did not improve symptomatic skeletal event-free survival, and was associated with an increased frequency of bone fractures compared with placebo. In fact, the study was unblinded prematurely, after more fractures and deaths were noted in the radium-223 group than in the placebo group (Smith *et al.* 2019). Similarly, the addition of enzalutamide to radium-223 did not improve OS (Ahmed *et al.* 2021). Consequently, these combinations are not recommended at this point.

General thoughts/reflections on the state of the field

The last decade has seen dramatic progress in the treatment of advanced PC. The four approved ARSIs have improved outcomes for patients and also have validated older

concepts about hormonal treatment, thus cementing our understanding of PC biology. Reflecting on these advances, we would like to give some personal opinions:

- (a) Is there still a role/indication for using standard ADT as monotherapy without ARSI (thus targeting testicular androgen production only) in any setting in PC?

Technically, in the case of men with high-risk N0M0 or N1M0 (regional lymphadenopathy) CSPC who initiate treatment with ADT±radiation, there is no FDA approval for adding an ARSI to the ADT. As mentioned above, in our clinical practice (N M), we frequently extrapolate based on the STAMPEDE data (James *et al.* 2017, Hoyle *et al.* 2019) and add AA+P, off-label, to the ADT regimen in such patients. Strictly speaking, though, as of February 2021, AA+P is not FDA-approved even for metastatic CSPC that falls in the low-risk M1 stratification (as defined by LATITUDE (Fizazi *et al.* 2017)), a clinical state for which enzalutamide and apalutamide are approved. Again, our clinical practice (N M) is to consider AA+P, enzalutamide and apalutamide as equally acceptable options for all metastatic CSPC patients who start ADT, irrespective of risk stratification. Finally, for patients who initiate ADT for biochemical recurrence (non-metastatic or M0 disease) after prior prostatectomy or prostate irradiation, there is again no FDA approval for adding any ARSI.

Our personal opinion is that these subtleties (as well as those detailed in Table 1) most likely represent the way clinical trials for each ARSI were designed and prioritized, and do not suggest any actual differences in clinical activity. We anticipate that future evidence will expand the upfront incorporation of ARSIs across the entire space of ADT use. Hence we propose that if a patient is to initiate ADT, he should be offered the best AR axis suppression possible (which, as of February 2021, is ADT+ any one of the four ARSIs that are on the market), unless comorbidities, life expectancy, adverse effects and patient preference would favor otherwise. We believe that failure to add an ARSI allows residual adrenal and intratumoral androgens to persistently activate the AR axis, which increases the opportunities for PC cells to survive, adapt and evolve into CRPC.

- (b) How to deal with outdated (and incorrect) terminology?

The term ‘androgen deprivation therapy’, as used historically (without ARSI), is a misnomer, because intratumoral androgens actually persist (Montgomery *et al.* 2008). Similarly, the term ‘hormone-independent’ PC was a misnomer at the time before ARSIs.

Nowadays, however, ARSIs are approaching the goal of achieving true 'androgen deprivation therapy' at the cellular level, and the resistant PC cells are frequently truly 'hormone-independent' PC at the cellular level (although not always). For example, NEPC could be called a truly hormone-independent PC. So could the term 'androgen-independent' PC make a clinical comeback, this time to describe post-ARSI CRPC that is driven by ligand-independent mechanisms?

Technically, this time the term may be correct at a cellular level for many ARSI-refractory CRPCs and it could be used accurately in select cases after molecular studies have carefully dissected and confirmed such mechanisms of resistance on an individual level, but it would probably be too confusing to bring it back in the clinic to describe ARSI-refractory CRPC. To avoid confusion, use of a different term such as 'androgen-indifferent' or similar term, is preferred.

For the same reason, while the current use of second generation anti-androgens together with frontline ADT in metastatic CSPC is essentially a combined androgen blockade (CAB), that term is (unfortunately) linked to the previously tried use of first generation anti-androgens in that setting, so perhaps it would be best to leave that term in the past as well, to avoid confusion.

- (c) Better (deeper, earlier, more comprehensive) AR axis targeting will benefit patients, but will also make 'androgen-indifferent' variants more common in an inevitable, deterministic way that is driven by our own hormonal therapies. Metastatic prostate adenocarcinoma patients will receive endocrine therapies for significant periods of time, but the disease phenotype that will be most lethal in the future will resemble small cell cancer of the lung (and perhaps will be treated borrowing principles and advances from that field).
- (d) Despite the widespread use of AR targeting as first-line choice for treating advanced PC, it is remarkable that the decision to start hormonal therapy and the choice of the specific hormonal regimen has essentially never been driven by a genetic/genomic biomarker. At a time in Precision Oncology where targeted therapies are chosen for each patient based on matching to activating mutations in their targets, the use of hormonal therapies in advanced PC remains remarkably not biomarker-driven. Review of any genomic dataset from treatment-naïve PC reveals little (if any) evidence to nominate AR as a major therapeutic target. In fact, AR overexpression,

gene amplification, mutations, expression of splice variants, etc., happen in meaningful frequencies only after the hormonal equilibrium of the PC cell has been perturbed by ADT, when depressed feedback loops and escape mechanisms try to re-equilibrate the cell's intracellular signaling balance. In the clinic, we utilize ADT as first-line therapy irrespective of the patient's baseline serum testosterone levels, AR mutation status, or even whether the tumor expresses AR or not. In fact, we do not even test for AR expression in regular clinical practice, although one could point out that the production of PSA by the tumor is evidence of AR activity (but also greatly affected by tumor burden and thus not a quantitatively accurate measure of AR activity). In other words, the clinical algorithm for making decisions regarding when to start hormonal therapy and which agents to use does not incorporate any assessment of the specific degree of AR dependence or any predictive biomarker of responsiveness of each patient's PC to hormonal therapy.

An explanation for this paradox is that ADT does not treat only PC – it treats the entire prostate epithelial lineage as a whole, and we (the physicians) have accepted that normal prostate function will be sacrificed in the process, just as we (the physicians) consider hot flashes, erectile dysfunction, loss of bone density, etc., as unavoidable consequences of ADT. But all these adverse effects add significant morbidity for our patients, which is also becoming more prolonged as their life expectancy increases due to more active therapy. More emphasis on survivorship for ADT-treated patients is needed, and we need clinical trials that will try to mitigate these adverse events such as via intermittent use of ADT±ARSI or more refined patient selection. This may at first sound contrary to the point we made above in (a) ('if you initiate ADT, offer the best AR axis suppression possible by adding an ARSI'), but it is actually not. Standard ADT is an incomplete therapy that practically guarantees emergence of CRPC, while the patients still have to suffer the adverse events of androgen deprivation. As an alternative approach, more comprehensive AR axis targeting with ADT+ARSI for shorter periods of time may allow for more definitive control of the cancer that then can be followed by careful withdrawal of hormonal therapy in select cases and under close monitoring. This is similar to the concept of 'intermittent ADT', which in recent years has been less popular, after [Hussain *et al.* \(2013\)](#) gave us reasons for concern that intermittent ADT may not be adequate therapy. It is possible, though, that,

just like the ARSIs validated several other old concepts in the last decade, they could also resurrect the concept of cycling between periods of intense therapy and de-intensification. Again, the theme is to look back at older paradigms that possibly had value but previously failed in the clinic due to lack of appropriate pharmacological agents, and examine them again in well-designed, biomarker-driven clinical trials that incorporate ARSIs.

- (e) And finally, we close our article honoring the pioneering work of [Huggins & Hodges \(1941\)](#) by mentioning the Holy Grail of AR targeting in PC: to separate the growth-promoting effects of AR signaling on PC cells from the normal functions of androgens and AR in the rest of the body, so that we can, someday, selectively target PC cells while sparing healthy cells in the body, thus minimizing the adverse events of ADT for our patients. The work continues!

Declaration of interest

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