AR-Signaling in Human Malignancies: Prostate Cancer and Beyond

Michael T. Schweizer 1,2,* and Evan Y. Yu 1,2

1 Division of Oncology, Department of Medicine, University of Washington, Seattle, WA 98109, USA; evanyu@u.washington.edu
2 Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA

* Correspondence: schweize@u.washington.edu

Academic Editor: Emmanuel S. Antonarakis

Received: 29 November 2016; Accepted: 5 January 2017; Published: 11 January 2017

Abstract: In the 1940s Charles Huggins reported remarkable palliative benefits following surgical castration in men with advanced prostate cancer, and since then the androgen receptor (AR) has remained the main therapeutic target in this disease. Over the past couple of decades, our understanding of AR-signaling biology has dramatically improved, and it has become apparent that the AR can modulate a number of other well-described oncogenic signaling pathways. Not surprisingly, mounting preclinical and epidemiologic data now supports a role for AR-signaling in promoting the growth and progression of several cancers other than prostate, and early phase clinical trials have documented preliminary signs of efficacy when AR-signaling inhibitors are used in several of these malignancies. In this article, we provide an overview of the evidence supporting the use of AR-directed therapies in prostate as well as other cancers, with an emphasis on the rationale for targeting AR-signaling across tumor types.

Keywords: prostate cancer; breast cancer; bladder cancer; renal cell carcinoma; pancreatic cancer; ovarian cancer; hepatocellular cancer; ovarian cancer; endometrial cancer; androgen receptor

1. Androgen Receptor Biology

Androgens, or male sex hormones, have a wide range of functions, including promoting the development of male secondary sexual characteristics, stimulating erythropoiesis, increasing metabolic rate, increasing bone density and stimulating libido [1]. In men, androgens are produced predominately by the testes, while the sole source of androgens in women are the adrenal glands. Consequently, women have considerably lower androgen levels compared to men. The normal physiologic function of androgens is a result of stimulating the androgen receptor (AR).

The AR is a member of the nuclear hormone receptor family of transcription factors, which also includes the estrogen receptor (ER), glucocorticoid receptor (GR), progesterone receptor (PR) and others [2,3]. Like the other nuclear hormone receptors, transcription of AR target genes is induced by the receptor binding androgenic ligands. Canonical AR-signaling involves a well-described series of events, including: (1) AR binding to androgens; (2) dissociating from heat-shock proteins; (3) translocating to the nucleus and the formation of AR homodimers; (4) binding to androgen response elements (AREs) within the promoter region of AR target genes; (5) recruitment of coactivators; and (6) transcription of target genes [4].

In addition to its normal physiologic role, prostatic adenocarcinomas remain dependent on AR-signaling even at later stages. Supporting the importance of AR to prostate cancer biology is the observation that AR target genes (e.g., PSA) are usually expressed even in men progressing on androgen deprivation therapy (ADT), with AR pathway alterations commonly observed in late stage...
disease [5]. This has served as the basis for ADT through medical and surgical castration, as well as the development of next generation AR-directed therapies like abiraterone and enzalutamide.

As our understanding of AR biology has improved, it has become apparent that the AR-signaling pathway can interact with a number of additional oncogenic signaling pathways, including those involved in promoting growth and resistance across a variety of tumor types (e.g., AKT/mTOR/PI3K, EGFR, HER2/Neu, Wnt) [5–12]. Interestingly, in spite of differences in consensus DNA binding motifs, AR is able to bind estrogen response elements and activate a transcriptional program similar to the ER—indicating that AR may be an important mediator of breast cancer cell survival as well as other ER-dependent tumors [13,14]. The pleiotropic effects of AR-signaling raise the specter that targeting this pathway may have beneficial effects in a number of different cancers. In this review, we will outline the current evidence for testing AR-directed therapies in prostate, breast and other “non-hormonally” driven cancer like bladder, renal cell and pancreatic cancer, to name a few.

2. AR Targeting in Prostate Cancer

In 1941, Charles Huggins published his seminal paper describing the remarkable palliative effects of surgical castration in men with advanced prostate cancer [15]. We now understand that the beneficial effects of castrating therapy are a direct result of inhibiting AR-signaling, and as such targeting the AR has remained the backbone of prostate cancer therapy since the 1940s. As it stands, ADT is most often achieved through the use of luteinizing hormone releasing hormone (LHRH) agonists/antagonists as opposed to surgical castration; however, both achieve the same effect of lowering testosterone levels to the castrate range (i.e., <20–50 ng/dL) [16]. While ADT is initially highly effective, it does not represent a cure, and the vast majority of men with advanced prostate cancer will progress on ADT, developing castration-resistant prostate cancer (CRPC) [17,18].

Work over the last decade has shown that the AR remains a viable therapeutic target even in the castration-resistant setting. This was born out of the observation that AR target genes (e.g., PSA) are often expressed at high levels in patients with CRPC, and that expression of AR will go up in response to ADT [19,20]. It has also come to light that alternative sources of androgens, including those generated intratumorally, may also drive tumor growth in this setting [21,22]. As such, a number of next-generation AR-directed therapies have been developed to further inhibit AR-signaling, with abiraterone and enzalutamide both approved on the basis of Phase III data demonstrating improved overall survival compared to controls [23–27]. Abiraterone is a CYP17 inhibitor that targets extragonadal androgen biosynthesis in the tumor microenvironment and adrenal glands. Enzalutamide is an AR antagonist that is more effective than the first generation non-steroidal antiandrogens (e.g., bicalutamide, nilutamide). Because both of these agents target the ligand-AR interaction—abiraterone through ligand depletion and enzalutamide through antagonizing the AR-ligand binding domain—it is not surprising that numerous groups have documented evidence of cross-resistance between these drugs [28–35].

More recently, a number of studies have described mechanisms whereby AR-signaling is able to reemerge in spite of treatment with next generation AR-signaling inhibitors. Examples of these mechanisms include: AR amplification/overexpression, intratumoral androgen production, activation via feedback pathways (e.g., AKT/mTOR/PI3K, HER2/Neu), activating AR ligand binding domain mutation, emergence of constitutively active AR splice variants and activation through other nuclear hormone transcription factors (e.g., GR) [6,7,19,21,36–48]. Several in depth reviews of these mechanisms have been published, and a detailed overview of their role in promoting resistance to AR-directed therapies is beyond the scope of this paper [3,20,49]. Suffice it to say, many ongoing drug development efforts are focused on developing more effective AR-directed therapies (e.g., drugs not targeting the ligand-AR interaction like EPI-506) or drugs to target key feedback pathways in selected populations (e.g., Akt inhibitors in patients with PTEN loss) [50–52].
3. Breast Cancer

3.1. AR in Breast Cancer

Like prostate cancer, breast cancer is a hormonally regulated malignancy. Indeed, shortly following the discovery that surgical castration was effective in men with advanced prostate cancer, Charles Huggins began exploring oophorectomy and adrenalectomy (with hormone replacement) as treatments for advanced breast cancer [53]. It is worth noting, however, that the German surgeon Albert Schinzinger was first credited with proposing oophorectomy as a treatment for breast cancer in the late 19th century [54]. While most hormonal-based therapies for breast cancer involve inhibiting estrogen receptor (ER)-signaling in hormone receptor positive subtypes, it has recently come to light that AR-signaling is likely an important modulator of breast cancer cell survival and may also be a viable target [55,56].

Several lines of clinical data support the biologic importance of AR-signaling in breast cancer, although AR positivity has been found to have variable prognostic impact across studies. V era-Badillo, et al. conducted a systemic review of 19 studies that assessed AR immunohistochemistry (IHC) in 7693 patients with early stage breast cancer and found AR staining present in 60.5% of patients; interestingly, AR positivity was associated with improved overall survival (OS) [57]. The authors also found that AR positivity was more common in ER positive compared to ER negative tumors (74.8% vs. 31.8%, \( p < 0.001 \)). However, it should be noted that AR antibodies used across studies was not consistent, nor was the cutoff defining “positivity”, making it difficult to draw firm conclusion regarding the overall prevalence of AR positivity across breast cancer subtypes.

Another study analyzing AR expression from tissue microarrays (TMAs) of 931 patients reported that 58.1% stained positive for AR, and that the association of AR with improved OS was only true for patients with ER positive tumors [58]. Apocrine tumors (ER negative, AR positive) with HER2 positivity associated with poorer survival, while AR did not appear to impact OS in triple negative breast cancer (TNBC) cases. A study by Choi and colleagues focused specifically on TNBCs (\( n = 559 \)), found that AR was expressed in 17.7% of these cases, and that AR positivity was a negative prognostic feature. Two subsequent meta-analyses found that AR expression associated with better outcomes across tumor subtypes, however (i.e., ER positive, ER negative, and TNBC) [59,60].

3.2. Targeting AR in Breast Cancer

As mentioned, AR and ER are both nuclear hormone transcription factors and share a number of similar biologic features [55]. Upon binding their respective ligands, they undergo conformational changes, dissociate from heat shock proteins, dimerize and bind to DNA response elements where they promote transcription of target genes [3,61]. A number of studies have documented mechanisms whereby crosstalk between AR and ER exists, with most evidence supporting a model in which AR inhibits ER signaling through a variety of mechanisms—providing a biological basis for why AR positivity may associate with improved outcomes in ER positive breast cancers. AR is able to compete with ER for bindings at ER response elements (EREs), and transfection of MDA-MB-231 breast cancer cells with the AR DNA binding domain has been shown to inhibit ER activity [13]. Because the transcriptional machinery of both ER and AR involves a number of shared coactivator proteins, AR also likely inhibits ER activity through competing for binding of these cofactors [62,63]. Interestingly, there is also evidence that AR and ER can directly interact, with the AR N-terminal domain binding to the ERx ligand binding domain leading to decreased ERx transactivation [64].

The biologic action of AR in ER-negative breast cancers may differ significantly. AR is expressed in 12% to 36% of TNBCs, and in contrast to ER-positive breast cancers, data suggests that AR may be able to drive progression in some ER-negative cell lines [65–71]. Supporting the biologic importance of AR, and its viability as a therapeutic target, preclinical data has shown that AR antagonists (e.g., bicalutamide, enzalutamide) exert an anti-tumor effect in a number of ER-negative breast cancer models [65,67,72].
AR positive TNBCs are generally referred to as molecular apocrine tumors; however, more recent work has defined TNBCs on the basis of their molecular phenotype [73,74]. Work by Lehmann and colleagues have defined six subtypes of TNBC on the basis of their gene expression profiles: basal-like 1 and 2, immunomodulatory, mesenchymal, mesenchymal stem-like, and luminal androgen receptor (LAR) [74]. Interestingly, in spite of being ER-negative, the LAR subtype shares a gene expression signature similar to the luminal, ER-positive breast cancers. Chromatin immunoprecipitation (ChIP)-sequencing studies demonstrate that AR-binding events are similar to those of ERα in ER-positive breast cancer cell lines, indicating that AR may be able to substitute for ER in this context [14].

It should be noted that in addition to LAR tumors, other ER-negative, AR-positive breast cancer subtypes are sensitive to the effects of androgens [65,67]. Ni and colleagues have shown that in HER2-positive, ER-negative cell lines, AR mediates activation of Wnt and HER2 signaling in a ligand-dependent manner [67]. Further speaking to the importance of AR across breast cancer subtypes, Barton and colleagues reported that the next-generation AR antagonist enzalutamide is effective in several non-LAR TNBC subtypes. Interestingly, it has been shown that constitutively active AR splice variants (AR-Vs)—a well-described resistance mechanism in prostate cancer—are present in a large subset of breast cancer tumors, and that treatment of MDA-MB-453 cells (ER/PR-negative, HER2-negative, AR-positive) with enzalutamide can lead to the induction of AR-Vs [75]. The fact that a well-known resistance mechanism to AR-directed therapy appears relevant to breast cancer provides further support for the importance of AR-signaling in breast cancer.

3.3. Clinical Trials Targeting AR-Signaling in Breast Cancer

Early clinical data reported by Gucalp and colleagues supported AR as a therapeutic target in AR-positive, ER-negative/PR-negative breast cancers [76]. They conducted a single-arm, Phase II study testing bicalutamide 150 mg daily in patients with >10% nuclear AR staining. The primary endpoint was clinical benefit rate (CBR) defined as complete response (CR), partial response (PR) or stable disease >6 months. Overall, 51 of 424 (12%) screened patients were AR-positive as defined by the study. Twenty-eight patients were treated per protocol, with only 26 being evaluable for the primary endpoint. The study reported a clinical benefit in five patients (all with stable disease), which exceeded the predefined threshold (CBR = 4/28 patients) needed to justify further study.

A single-arm Phase II study testing enzalutamide in AR-positive TNBCs was more recently reported [77]. The primary endpoint was the CBR in “evaluable” patients which were defined as those with ≥10% AR staining and a response assessment. After testing 404 patient samples, 55% were found to have AR staining in ≥10% of cells. 118 patients were treated with enzalutamide, and 75 were “evaluable”. Of the evaluable patients, the CBR at 16 and 24 weeks was 35% and 29% respectively. The median progression free survival (PFS) in this group was 14 weeks. In patients with an AR gene signature (n = 56), clinical outcomes were numerically improved compared to the overall “evaluable” group and those lacking the gene signature (N = 62)—suggesting that further refinement of predictive biomarkers beyond AR IHC is necessary.
Table 1. Ongoing studies testing AR-directed therapies in breast cancer. Abi, abiraterone; Enza, enzalutamide; AR, androgen receptor; AE, adverse event; MTD, maximum tolerated dose; CR, complete response; PR, partial response; and SD, stable disease.

| Indication                              | Therapeutic Agent(s)                                      | Disease State       | Study Phase | Sample Size | Primary Endpoint                                      | NCT Number       |
|-----------------------------------------|----------------------------------------------------------|---------------------|-------------|-------------|------------------------------------------------------|-----------------|
| Breast cancer                           | Enza, enza + anastrozole, enza + exemestane, enza + fulvestrant | Advanced            | Phase I     | 101         | Safety                                               | NCT01597193     |
| Breast cancer                           | Enza + exemestane                                         | Advanced            | Phase II    | 247         | Progression free survival                           | NCT02007512     |
| Triple-negative breast cancer           | Enza + paclitaxel vs. placebo + paclitaxel                | Advanced            | Phase III   | 780         | Progression free survival                           | NCT02929576     |
| AR positive, triple-negative breast cancer | Enza + taselisib                                          | Advanced            | Phase I/II  | 73          | MTD                                                  | NCT02457910     |
| AR positive, triple-negative breast cancer | Enza + paclitaxel                                        | Localized           | Phase II    | 37          | Pathologic complete response and minimal residual disease | NCT02689427     |
| HER2 positive and AR positive breast cancer | Enza + trastuzumab                                       | Advanced            | Phase II    | 80          | Clinical benefit rate: combined CR, PR and SD       | NCT02091960     |
| AR positive, triple-negative breast cancer | Enza                                                     | Localized           | Phase II    | 200         | Treatment discontinuation rate                      | NCT02750358     |
| AR positive, triple-negative breast cancer | Enza                                                     | Advanced            | Phase II    | 118         | Clinical benefit rate: combined CR, PR and SD       | NCT01889238     |
| Breast cancer                           | VT-464                                                   | Advanced            | Phase I/II  | 110         | MTD                                                  | NCT02580448     |
| Breast cancer                           | Abi                                                      | Advanced            | Phase I/II  | 74          | MTD, causality of AEs, and clinical benefit rate: combined CR, PR and SD | NCT00755885     |
| ER positive HER2 negative breast cancer  | Abi                                                      | Advanced            | Phase II    | 299         | Progression free survival                           | NCT01381874     |
| HER2 negative breast cancer             | Abi                                                      | Advanced            | Phase II    | 31          | Clinical benefit rate: combined CR, PR and SD       | NCT01842321     |
| ER positive HER2 negative breast cancer  | Abi vs. anastrozole                                      | Localized           | Phase II    | -           | Gene expression differences                        | NCT01814865     |
| AR positive breast cancer               | Orteronel                                                | Advanced            | Phase II    | 86          | Response rate: complete and partial responses        | NCT01990209     |
| Breast cancer                           | Orteronel                                                | Advanced            | Phase I     | 8           | Safety, recommended Phase II dose, and decrease in estradiol levels | NCT01808040     |
Abiraterone, an inhibitor of extragonadal androgen biosynthesis, has also been tested in breast cancer [78]. In a randomized Phase II trial, abiraterone was compared to the aromatase inhibitor exemestane or the combination. In contrast to the aforementioned studies, this study focused on ER-positive patients and did not require positive AR staining in order to enroll. The authors cited two reasons for not mandating AR-positivity: (1) upwards of 80% of ER-positive breast cancers are also positive for AR; and (2) inhibition of CYP17 will also decrease estrogen levels. The primary endpoint was PFS. A total of 297 patients were randomized between treatment arms, with 102 receiving exemestane, 106 receiving exemestane plus abiraterone and 89 receiving abiraterone. Of note, enrollment to the abiraterone monotherapy arm was discontinued early after a pre-specified analysis determined that futility conditions had been met. After a median follow up of 11.4 months, there was no difference in median PFS between when abiraterone was compared to exemestane (3.7 vs. 3.7 months, \( p = 0.437 \)), or when abiraterone plus exemestane was compared to exemestane (4.5 vs. 3.7 months, \( p = 0.794 \)). Of note, there was also no difference in PFS in the subset of patients with AR-positive disease.

Given that some studies have shown signs of activity for AR-signaling inhibitors, a number of additional trials are either planned or underway testing AR-directed therapies in breast cancer patients (Table 1). However, it seems likely that these agents will only be effective in a subset of patients, and as such, the development of predictive biomarkers will be critical. Whether the AR will prove to be a clinically important target in breast cancer remains to be seen, but evidence to date does support further testing of drugs designed to inhibit this oncogenic pathway.

4. Other Tumor Types

In addition to prostate and breast cancer, there are a number of other malignancies in which AR-signaling appears to play a role in driving tumor growth. As such, there are several ongoing clinical trials testing AR-directed therapies across an array of cancer types (Table 2). A brief overview of the rationale for targeting AR in these malignancies is provided below.

4.1. Bladder Cancer

In 2016, it is estimated that 58,950 American men will be diagnosed with bladder cancer compared to only 18,010 women [79]. Even after controlling for environmental risk factors (e.g., tobacco exposure) men still have a 3–4-fold increased risk of developing bladder cancer [80–82]. The observed epidemiologic differences in bladder cancer risk between the sexes points to the potential for sex steroid pathways to play a role in the pathogenesis of this disease [83]. Women have also been found to have a worse prognosis compared to men after adjusting for stage at presentation, further bolstering the case that underlying biologic differences between the sexes influencing outcomes [84].

Androgen receptor has been found to be variably expressed in urothelial carcinoma specimens, with AR staining present in 12% to 77% of patients [85–89]. In general, AR expression appears comparable in men and women [85,86]. There is no clear relationship between AR expression and clinical outcomes, and gene expression profiling studies do not demonstrate a clear relationship between AR expression levels and The Cancer Genome Atlas (TCGA) subtype [86,90,91].

Preclinical studies evaluating the effect of androgens and AR-signaling on urothelial carcinoma tumorigenesis have found that AR-signaling may promote tumor formation. In vitro siRNA studies have found that AR knockdown can lead to decreased tumor cell proliferation and increased apoptosis, possibly mediated through AR’s effect on cyclin D1, Bcl-x(L) and MMP-9 gene expression [92]. In a separate set of experiments, mice engineered to not express AR in urothelial cells were found to have a lower incidence of bladder cancer following exposure to the carcinogen BBN [N-butyl-N-(4-hydroxybutyl)-nitrosamine] [93]. In vitro experiments found that this effect may be due to modulation of p53 and DNA damage repair. Studies have also implicated AR in modulating various other oncogenic signaling pathways (e.g., EGFR, ERBB2, β-catenin), offering more evidence for the importance of AR-signaling as it pertains to bladder cancer biology [94,95].
### Table 2. Ongoing studies testing AR-directed therapies in cancers other than breast or prostate cancer. Enza, enzalutamide; AR, androgen receptor; and MTD, maximum tolerated dose.

| Indication                          | Therapeutic Agent(s)                  | Disease State          | Study Phase | Sample Size | Primary Endpoint                          | NCT Number       |
|-------------------------------------|---------------------------------------|------------------------|-------------|-------------|--------------------------------------------|------------------|
| Endometrial cancer                  | Enza + carboplatin + paclitaxel       | Advanced               | Phase II    | 69          | Safety/objective tumor response             | NCT02684227      |
| Hepatocellular carcinoma            | Enza vs. placebo                      | Advanced               | Phase II    | 144         | Overall survival                           | NCT02528643      |
| Hepatocellular carcinoma            | Enza vs. Enza + sorafenib             | Advanced               | Phase I/II  | 73          | Safety                                     | NCT02642913      |
| Non-muscle invasive bladder cancer  | Enza                                  | Localized (chemoprevention) | Phase II    | 50          | Recurrence rate                            | NCT02605863      |
| Bladder cancer                      | Enza + cisplatin + gemcitabine        | Advanced               | Phase I     | 24          | MTD                                        | NCT02300610      |
| AR positive ovarian cancer          | Enza                                  | Advanced               | Phase II    | 58          | Response rate: complete and partial responses | NCT01974765      |
| Pancreatic cancer                   | Enza + gemcitabine + nab-paclitaxel   | Advanced               | Phase I     | 38          | MTD                                        | NCT02138383      |
| Renal cell carcinoma                | Enza                                  | Localized (neoadjuvant)| Pilot/Phase 0| 20          | Cell proliferation and tumor apoptosis     | NCT02885649      |
| Mantle cell lymphoma                | Enza                                  | Advanced               | Pilot/Phase 0| 20          | Response rate: complete and partial responses | NCT02489123      |
| AR positive salivary cancer         | Enza                                  | Advanced               | Phase II    | 45          | Response rate: complete and partial responses | NCT02749903      |
Kawahara and colleagues recently published a paper describing a series of in vitro and in vivo experiments in AR-positive and AR-null bladder cancer models [96]. They found that DHT increased AR-positive bladder cancer cell line viability and migration in culture, while AR antagonists (i.e., hydroxyflutamide, bicalutamide and enzalutamide) inhibited viability and migration. Similarly, apoptosis was decreased following exposure to DHT, and anti-androgens had the opposite effect. Importantly, enzalutamide was found to inhibit AR-positive bladder cancer xenograft growth in vivo. On the basis of these findings, two clinical trials have opened to test enzalutamide in patients with bladder cancer. One is testing enzalutamide monotherapy as a chemoprevention strategy in patients with non-muscle invasive bladder cancer [clinicaltrials.gov: NCT02605863], and the other is testing it in patients with advanced bladder cancer in combination with gemcitabine plus cisplatin [clinicaltrials.gov: NCT02300610].

4.2. Renal Cell Carcinoma

Androgen receptor is expressed in the distal and proximal tubules of normal kidneys and is expressed in approximately 15% to 42% of renal cell carcinomas (RCC) [97–99]. IHC studies correlating AR expression with clinical outcomes have not been consistent, with some reporting an association with decreased survival, while others have found that AR expression was correlated with a favorable pathologic stage and an overall favorable prognosis [97,100,101].

In a study evaluating AR transcript levels using real-time PCR, it was found that AR mRNA expression levels correlated with pathologic T stage and cancer specific survival. Multivariate regression analysis found AR transcript levels were independently associated with cancer specific survival. Of note, AR mRNA levels did not differ between sexes.

A more recent analysis of the TCGA data revealed that high AR protein and transcript levels was associated with improved overall survival in patients with clear cell RCC (the most common pathologic subtype), but not other histologic subtypes of RCC (i.e., papillary or chromophobe) [102]. Interestingly, in clear cell RCC cases they found that AR mRNA expression did not differ between men and women, but that AR protein expression was significantly higher in men. The authors concluded that AR might function as a tumor suppressor in this context.

In vitro experiments have reported that exposure to DHT causes proliferation in AR-positive RCC cells, while enzalutamide can reduce cell viability [103]. Other groups have found that AR may mediate tumor growth through activating HIF-2α/VEGF-signaling [104]. Preclinical studies have shown that enzalutamide can inhibit RCC cell migration and invasion by modulating HIF-2α/VEGF expression at the mRNA and protein levels. A neoadjuvant Pilot study testing enzalutamide in RCC patients is currently underway, with the primary goal to determine the effects of enzalutamide on RCC apoptosis and cellular proliferation [clinicaltrials.gov: NCT02885649].

4.3. Pancreatic Cancer

Although the incidence of AR expression is not well defined in pancreatic cancer, AR does appear to be expressed [105]. A number of in vitro/in vivo studies have tested the effects of antiandrogens and/or androgen deprivation in pancreatic cancer models, and have, for the most part, shown that inhibiting AR-signaling exerts anti-tumor effect [106–113]. Preclinical work has demonstrated that this effect may be mediated through IL-6, with a model whereby IL-6 activates AR-signaling via STAT3 and MAPK. Importantly, IL-6 has been shown to enhance pancreatic cell migration, an effect that is blocked through AR knockdown with an AR siRNA [114].

Greenway reported the results of a randomized trial comparing flutamide (a non-steroidal antiandrogen) vs. placebo (n = 49) in patients with both localized and metastatic pancreatic cancer [115]. It should be noted that histologic confirmation of pancreatic cancer was not required, and 32 included subjects were diagnosed on the basis of clinical presentation/imaging studies. This trial reported a median survival of 226 vs. 120 days in the flutamide and placebo groups, respectively (p = 0.079,
Wilcoxon; \( p = 0.01 \), log-rank). Several other studies in patients with pancreatic cancer have not shown hormonal therapies to be beneficial, however [116–121]. Preliminary results from an ongoing Phase I study testing enzalutamide in combination with gemcitabine and nab-paclitaxel in patients with metastatic pancreatic cancer have recently been reported [122]. They have treated 19 patients, and report that 37% had tumor tissue positive for AR. Among 15 evaluable patients, two had a partial response and 13 had stable disease. Pharmacokinetic (PK) analyses did not find any evidence that enzalutamide altered the PK of either chemotherapeutic agent. Whether enzalutamide will prove to be an effective treatment for pancreatic cancer remains to be seen.

4.4. Hepatocellular Carcinoma

Androgen receptor appears to be expressed in subset of hepatocellular carcinomas (HCC), although, like pancreatic cancer, the incidence has not been well defined [123–126]. The majority of studies show that AR-positivity is associated with worse outcomes, including decreased progression free and overall survival as well as increased tumor size [126–129]. Studies have also linked AR-signaling with increased risk of developing hepatitis B and C related HCC [130–133]. AR has been found to promote HCC growth, migration and invasion in several preclinical studies, possibly through increasing oxidative stress and DNA damage, as well as suppressing p53 [134–136]. In vitro and in vivo studies targeting AR with either AR-siRNA or ASC-J9 (an AR protein degrader) resulted in decreased tumor growth [134]. A randomized Phase II study testing enzalutamide vs. placebo in HCC is currently underway [clinicaltrials.gov: NCT02528643].

4.5. Ovarian Cancer

In 1998, Risch hypothesized that epithelial ovarian cancers may develop as a result of androgens stimulating epithelial cell proliferation, and as it stands, a number of lines of evidence support the role for AR-signaling in the pathogenesis of the disease [137,138]. AR is highly expressed in ovarian cancers, with approximately 44% to 82% of tumors staining positive for AR [139–141]. Polycystic ovarian syndrome (PCOS), and its resultant hyperandrogenic state, are associated with hyperplastic and metaplastic changes in the surface epithelium of the ovaries, and women with ovarian cancer are more likely to have a history of PCOS compared to control cases [142,143]. The use of exogenous androgens (i.e., danazol, testosterone) has been associated with a >3-fold increased risk of developing ovarian cancer [144]. Preclinical models also support the hypothesis that androgens play a role in the development of epithelial ovarian cancers, with a number of oncogenic signaling pathways implicated in this process (e.g., TGF-\( \beta \), IL-6/IL-8, EGFR) [138,145–147]. However, as it stand, the prognostic impact of AR expression in epithelial ovarian cancers is not clear [138].

A handful of clinical trials testing AR-signaling inhibitors in women with ovarian cancer have been completed, with no clear signs of activity. A single-arm Phase II study testing flutamide in ovarian cancer patients progressing on platinum chemotherapy has previously been reported [148]. Out of 68 women enrolled, only two objective responses (one complete and one partial response) were observed. In a second single-arm Phase II study, flutamide was given to 24 ovarian cancer patients who failed chemotherapy and only one partial response was observed [149]. Finally, in a single-arm Phase II study, Levine and colleagues treated 35 women with ovarian cancer who were in second or greater complete remission with bicalutamide and goserelin (LHRH agonist) [150]. This trial failed to meet the pre-specified metric to justify further studies testing this regimen, which was arbitrarily set at median PFS >13.5 months. More recent preclinical work has shown that enzalutamide is able to significantly inhibit the growth of ovarian cancer xenografts [151]. On this basis, a Phase II study has been launched to test enzalutamide in women with AR-positive, advanced ovarian cancer [clinicaltrials.gov: NCT01974765].
4.6. Endometrial Cancer

Similar to prostate and breast cancer, endometrial cancers are hormonally dependent, and hormonal agents targeting ER-/PR-signaling are options for select patients [152]. Given the similarities to breast and prostate cancer, Tangen and colleagues sought to explore the potential for targeting AR-signaling in advanced endometrial cancer [153]. They found that the majority of hyperplastic endometrial specimens evaluated (93%) had evidence of AR expression. This number decreased in primary tumors, and high-grade tumors (i.e., grade 3) were found to express less AR than low-grade tumors (i.e., grade 1) (53% vs. 74%). Metastatic specimens from 142 patients revealed AR expression in 48% of samples. On multivariate analyses, AR status did not provide additional prognostic value, however. Short-term cell culture experiments demonstrated that cell proliferation was inhibited by enzalutamide, and stimulated by the synthetic androgen R1881, providing justification for a Phase II study testing enzalutamide in combination with carboplatin and paclitaxel [clinicaltrials.gov: NCT02684227].

4.7. Mantle Cell Lymphoma

Mantle cell lymphoma shows a male predominance, and interestingly, male sex appears to associate with higher mortality based on a retrospective SEER analysis [154]. While it is not clear what underlies the poor outcomes in men with mantle cell lymphoma, AR is expressed across an array of hematopoietic cells, and may account for gender differences in the function of platelets and the immune system [155–157]. Furthermore, in contrast to other lymphomas, AR appears to be hypomethylated in mantle cell lymphoma—indicating that epigenetic silencing of AR gene expression may not be present in mantle cell lymphoma [158,159]. To our knowledge, large studies examining AR protein expression in mantle cell lymphoma samples have not been conducted. On the basis of these observations a pilot study was recently launched to assess the clinical effects of enzalutamide in patients with mantle cell lymphoma [clinicaltrials.gov: NCT02489123].

4.8. Salivary Gland Cancer

AR is expressed in the majority of lacrimal gland ductal carcinomas, and as a result AR staining is often used as part of the workup to confirm the diagnosis [160–166]. To date, there have been a handful of case reports/series documenting favorable outcomes in patients with salivary gland cancers treated with AR-directed therapies. A small case series (n = 10) reported a clinical benefit when ADT—most often single agent bicalutamide—was given to patients with salivary ductal carcinoma, with 50% of patients experiencing clinical benefit (i.e., stable disease, n = 3; partial response, n = 2) [167]. A case report has also reported favorable outcomes when ADT was combined with radiation therapy in a patient with AR-positive salivary gland cancer [168]. A single arm Phase II study testing enzalutamide in AR-positive salivary gland cancers is ongoing [clinicaltrials.gov: NCT02749903].

5. Conclusions

AR signaling is involved in a number of normal physiologic processes, and there is varying levels of evidence for its role in promoting cancer growth and progression across an array of malignancies. To date, prostate cancer remains the only malignancy with Level 1 evidence supporting the use of AR-directed therapies as an integral part of its treatment paradigm. However, mounting preclinical, epidemiologic and early phase clinical trial data support the further exploration of these drugs in diseases as varied as breast and salivary gland cancers, and it is likely that in the ensuing decade next generation AR-directed drugs will extend their reach beyond prostate cancer.

Acknowledgments: M.T.S. has received funding through a Prostate Cancer Foundation Young Investigator Award and DOD award W81XWH-16-1-0484.

Conflicts of Interest: The authors declare no conflict of interest.
References

1. Heemers, H.V.; Tindall, D.J. Androgen receptor (AR) coregulators: A diversity of functions converging on and regulating the ar transcriptional complex. Endocr. Rev. 2007, 28, 778–808. [CrossRef] [PubMed]
2. Robinson-Rechavi, M.; Escriva Garcia, H.; Laudet, V. The nuclear receptor superfamily. J. Cell Sci. 2003, 116, 585–586. [CrossRef] [PubMed]
3. Schweizer, M.T.; Yu, E.Y. Persistent androgen receptor addiction in castration-resistant prostate cancer. J. Hematol. Oncol. 2015, 8, 128. [CrossRef] [PubMed]
4. Koryakina, Y.; Ta, H.Q.; Gioeli, D. Androgen receptor phosphorylation: Biological context and functional consequences. Endocr. Relat. Cancer 2014, 21, T131–T145. [CrossRef] [PubMed]
5. Robinson, D.; van Allen, E.M.; Wu, Y.M.; Schultz, N.; Lonigro, R.J.; Mosquera, J.M.; Montgomery, B.; Taplin, M.E.; Pritchard, C.C.; Attard, G.; et al. Integrative clinical genomics of advanced prostate cancer. Cell 2015, 161, 1215–1228. [CrossRef] [PubMed]
6. Yeh, S.; Lin, H.K.; Kang, H.Y.; Thin, T.H.; Lin, M.F.; Chang, C. From HER2/Neu signal cascade to androgen receptor and its coactivators: A novel pathway by induction of androgen target genes through map kinase in prostate cancer cells. Proc. Natl. Acad. Sci. USA 1999, 96, 5458–5463. [CrossRef] [PubMed]
7. Drake, J.M.; Graham, N.A.; Lee, J.K.; Stoyanova, T.; Faltermeier, C.M.; Sud, S.; Titz, B.; Huang, J.; Pienta, K.J.; Graeber, T.G.; et al. Metastatic castration-resistant prostate cancer reveals intrapatient similarity and interpatient heterogeneity of therapeutic kinase targets. Proc. Natl. Acad. Sci. USA 2013, 110, E4762–E4769. [CrossRef] [PubMed]
8. Hsieh, A.C.; Liu, Y.; Edlind, M.P.; Ingolia, N.T.; Janes, M.R.; Sher, A.; Shi, E.Y.; Stumpf, C.R.; Christensen, C.; Bonham, M.J.; et al. The translational landscape of mtor signalling steers cancer initiation and metastasis. Nature 2012, 485, 55–61. [CrossRef] [PubMed]
9. Mulholland, D.J.; Cheng, H.; Reid, K.; Rennie, P.S.; Nelson, C.C. The androgen receptor can promote beta-catenin nuclear translocation independently of adenomatous polyposis coli. J. Biol. Chem. 2002, 277, 17933–17943. [CrossRef] [PubMed]
10. Chesire, D.R.; Isaacs, W.B. Beta-catenin signaling in prostate cancer: An early perspective. Endocr. Relat. Cancer 2003, 10, 537–560. [CrossRef] [PubMed]
11. Yang, F.; Li, X.; Sharma, M.; Sasaki, C.Y.; Longo, D.L.; Lim, B.; Sun, Z. Linking beta-catenin to androgen-signaling pathway. J. Biol. Chem. 2002, 277, 11336–11344. [CrossRef] [PubMed]
12. Traish, A.M.; Morgentaler, A. Epidermal growth factor receptor expression escapes androgen regulation in prostate cancer: A potential molecular switch for tumour growth. Br. J. Cancer 2009, 101, 1949–1956. [CrossRef] [PubMed]
13. Peters, A.A.; Buchanan, G.; Ricciardelli, C.; Bianco-Miotto, T.; Centenera, M.M.; Harris, J.M.; Jingal, S.; Segara, D.; Jia, L.; Moore, N.L.; et al. Androgen receptor inhibits estrogen receptor-alpha activity and is prognostic in breast cancer. Cancer Res. 2009, 69, 6131–6140. [CrossRef]
14. Robinson, J.L.; Macarthur, S.; Ross-Innes, C.S.; Tilley, W.D.; Neal, D.E.; Mills, I.G.; Carroll, J.S. Androgen receptor driven transcription in molecular apocrine breast cancer is mediated by foxa1. EMBO J. 2011, 30, 3019–3027. [CrossRef] [PubMed]
15. Huggins, C.; Hodges, C.V. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. J. Urol. 2002, 168, 948–952. [CrossRef]
16. Nishiyama, T. Serum testosterone levels after medical or surgical androgen deprivation: A comprehensive review of the literature. Urol. Oncol. 2014, 32, 38.e17–38.e28. [CrossRef]
17. Scher, H.I.; Halabi, S.; Tannock, I.; Morris, M.; Sternberg, C.N.; Carducci, M.A.; Eisenberger, M.A.; Higano, C.; Bubley, G.J.; Dreicer, R.; et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: Recommendations of the prostate cancer clinical trials working group. J. Clin. Oncol. 2008, 26, 1148–1159. [CrossRef] [PubMed]
18. Scher, H.I.; Morris, M.J.; Stadler, W.M.; Higano, C.S.; Halabi, S.; Smith, M.R.; Basch, E.M.; Fizazi, K.; Ryan, C.J.; Antonarakis, E.S.; et al. The prostate cancer working group 3 (PCWG3) consensus for trials in castration-resistant prostate cancer (CRPC). In Proceedings of the American Society of Clinical Oncology Annual Meeting, Chicago, IL, USA, 29 May–2 June 2015.
19. Chen, C.D.; Welsbie, D.S.; Tran, C.; Baek, S.H.; Chen, R.; Vessella, R.; Rosenfeld, M.G.; Sawyers, C.L. Molecular determinants of resistance to antiandrogen therapy. *Nat. Med.* 2004, 10, 33–39. [CrossRef] [PubMed]

20. Scher, H.J.; Sawyers, C.L. Biology of progressive, castration-resistant prostate cancer. Directed therapies targeting the androgen-receptor signaling axis. *J. Clin. Oncol.* 2005, 23, 8253–8261. [CrossRef] [PubMed]

21. Montgomery, R.B.; Mostaghel, E.A.; Vessella, R.; Hess, D.L.; Kalhorn, T.F.; Higano, C.S.; True, L.D.; Nelson, P.S. Maintenance of intratumoral androgens in metastatic prostate cancer: A mechanism for castration-resistant tumor growth. *Cancer Res.* 2008, 68, 4447–4454. [CrossRef] [PubMed]

22. Mohler, J.L.; Titus, M.A.; Bai, S.; Kermerley, B.J.; Lih, F.B.; Tomer, K.B.; Wilson, E.M. Activation of the androgen receptor by intratumoral bioconversion of androstenediol to dihydrotestosterone in prostate cancer. *Cancer Res.* 2011, 71, 1486–1496. [CrossRef] [PubMed]

23. Scher, H.J.; Fizazi, K.; Saad, F.; Taplin, M.E.; Sternberg, C.N.; Miller, K.; de Wit, R.; Mulders, P.; Chi, K.N.; Shore, N.D.; et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N. Engl. J. Med.* 2012, 367, 1187–1197. [PubMed]

24. Ryan, C.J.; Armstrong, A.J.; Rathkopf, D.E.; Loriot, Y.; Sternberg, C.N.; Higano, C.S.; Iversen, P.; Bhattacharya, S.; Carles, J.; Chowdhury, S.; et al. Enzalutamide in metastatic castration-resistant prostate cancer before chemotherapy. *N. Engl. J. Med.* 2014, 371, 424–433. [CrossRef] [PubMed]

25. De Bono, J.S.; Logothetis, C.J.; Molina, A.; Fizazi, K.; North, S.; Chu, L.; Chi, K.N.; Jones, R.J.; Goodman, O.B., Jr.; Saad, F.; et al. Abiraterone and increased survival in metastatic prostate cancer. *N. Engl. J. Med.* 2011, 364, 1995–2005. [CrossRef]

26. Ryan, C.J.; Smith, M.R.; de Bono, J.S.; Molina, A.; Logothetis, C.J.; de Souza, P.; Fizazi, K.; Mainwaring, P.; Piulats, J.M.; Ng, S.; et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N. Engl. J. Med.* 2013, 368, 138–148. [PubMed]

27. Ryan, C.J.; Smith, M.R.; Fizazi, K.; Saad, F.; Mulders, P.F.; Sternberg, C.N.; Miller, K.; Logothetis, C.J.; Shore, N.D.; Small, E.J.; et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (coub-aa-302): Final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol.* 2015, 16, 152–160. [CrossRef]

28. Loriot, Y.; Bianchini, D.; Ileana, E.; Sandhu, S.; Patrikiodou, A.; Pezaro, C.; Albiges, L.; Attard, G.; Fizazi, K.; de Bono, J.S.; et al. Antitumour activity of abiraterone acetate against metastatic castration-resistant prostate cancer progressing after docetaxel and enzalutamide (MDV3100). *Ann. Oncol.* 2013, 24, 1807–1812. [CrossRef] [PubMed]

29. Noonan, K.L.; North, S.; Bitting, R.L.; Armstrong, A.J.; Ellard, S.L.; Chi, K.N. Clinical activity of abiraterone acetate in patients with metastatic castration-resistant prostate cancer progressing after enzalutamide. *Ann. Oncol.* 2013, 24, 1802–1807. [CrossRef] [PubMed]

30. Schrader, A.J.; Boegemann, M.; Ohlmann, C.H.; Schnoeller, T.J.; Krabbe, L.M.; Hajili, T.; Jentzmik, F.; Stoeckle, M.; Schrader, M.; Herrmann, E.; et al. Enzalutamide in castration-resistant prostate cancer patients progressing after docetaxel and abiraterone. *Eur. Urol.* 2014, 65, 30–36. [CrossRef] [PubMed]

31. Bianchini, D.; Lorente, D.; Rodriguez-Vida, A.; Omlin, A.; Pezaro, C.; Ferraldeschi, R.; Zivi, A.; Attard, G.; Chowdhury, S.; de Bono, J.S. Antitumour activity of enzalutamide (MDV3100) in patients with metastatic castration-resistant prostate cancer (CRPC) pre-treated with docetaxel and abiraterone. *Eur. J. Cancer* 2014, 50, 78–84. [CrossRef] [PubMed]

32. Suzman, D.L.; Luber, B.; Schweizer, M.T.; Nadal, R.; Antonarakis, E.S. Clinical activity of enzalutamide versus docetaxel in men with castration-resistant prostate cancer progressing after abiraterone. *Prostate* 2014, 74, 1278–1285. [CrossRef] [PubMed]

33. Badrising, S.; van der Noort, V.; van Oort, I.M.; van den Berg, H.P.; Los, M.; Hamberg, P.; Coenen, J.L.; van den Eertwegh, A.J.; de Jong, I.J.; Kerver, E.D.; et al. Clinical activity and tolerability of enzalutamide (MDV3100) in patients with metastatic, castration-resistant prostate cancer who progress after docetaxel and abiraterone treatment. *Cancer* 2014, 120, 968–975. [CrossRef] [PubMed]

34. Cheng, H.H.; Gulati, R.; Azad, A.; Nadal, R.; Twardowski, P.; Vaishampayan, U.N.; Agarwal, N.; Heath, E.L.; Pal, S.K.; Rehman, H.T.; et al. Activity of enzalutamide in men with metastatic castration-resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel. *Prostate Cancer Prostatic Dis.* 2015, 18, 122–127. [CrossRef]
35. Azad, A.A.; Eigl, B.J.; Murray, R.N.; Kollmannsberger, C.; Chi, K.N. Efficacy of enzalutamide following abiraterone acetate in chemotherapy-naive metastatic castration-resistant prostate cancer patients. *Eur. Urol.* **2015**, *67*, 23–29. [CrossRef]

36. Antonarakis, E.S.; Lu, C.; Wang, H.; Luber, B.; Nakazawa, M.; Roesser, J.C.; Chen, Y.; Mohammad, T.A.; Chen, Y.; Fedor, H.L.; et al. Ar-v7 and resistance to enzalutamide and abiraterone in prostate cancer. *N. Engl. J. Med.* **2014**, *371*, 1028–1038. [CrossRef] [PubMed]

37. Asangani, I.A.; Dommeti, V.L.; Wang, X.; Malik, R.; Cieslik, M.; Yang, R.; Escara-Wilke, J.; Wilder-Romans, K.; Dhanireddy, S.; Engelke, C.; et al. Therapeutic targeting of bet bromodomain proteins in castration-resistant prostate cancer. *Nature* **2014**, *510*, 278–282. [CrossRef] [PubMed]

38. Carreira, S.; Romanel, A.; Goodall, J.; Grist, E.; Ferraldeschi, R.; Miranda, S.; Prandi, D.; Lorente, D.; Frenel, J.S.; Pezaro, C.; et al. Tumor clone dynamics in lethal prostate cancer. *Science Transl. Med.* **2014**, *6*, 254ra125. [CrossRef]

39. Chang, K.H.; Li, R.; Kuri, B.; Lotan, Y.; Roehrborn, C.G.; Liu, J.; Vessella, R.; Nelson, P.S.; Kapur, P.; Guo, X.; et al. A gain-of-function mutation in dht synthesis in castration-resistant prostate cancer. *Cell* **2013**, *154*, 1074–1084. [CrossRef] [PubMed]

40. Cho, E.; Montgomery, R.B.; Mostaghel, E.A. Mini review: Slco and abc transporters: A role for steroid transport in prostate cancer progression. *Endocrinology* **2014**, *155*, 4124–4132. [CrossRef] [PubMed]

41. Evaul, K.; Li, R.; Papari-Zareei, M.; Auchus, R.J.; Sharifi, N. 3beta-hydroxysteroid dehydrogenase is a possible pharmacological target in the treatment of castration-resistant prostate cancer. *Endocrinology* **2010**, *151*, 3514–3520. [CrossRef] [PubMed]

42. Li, Z.; Bishop, A.C.; Alyamani, M.; Garcia, J.A.; Dreicer, R.; Bunch, D.; Liu, J.; Upadhyay, S.K.; Auchus, R.J.; Sharifi, N. Conversion of abiraterone to d4a drives anti-tumour activity in prostate cancer. *Nature* **2015**, *523*, 347–351. [CrossRef] [PubMed]

43. Malik, R.; Khan, A.P.; Asangani, I.A.; Cieslik, M.; Prensner, J.R.; Wang, X.; Iyer, M.K.; Jiang, X.; Borkin, D.; Escara-Wilke, J.; et al. Targeting the mll complex in castration-resistant prostate cancer. *Nat. Med.* **2015**, *21*, 344–352. [CrossRef] [PubMed]

44. Mostaghel, E.A.; Marck, B.T.; Plymate, S.R.; Vessella, R.L.; Balk, S.; Matsumoto, A.M.; Nelson, P.S.; Montgomery, R.B. Resistance to CYP17A1 inhibition with abiraterone in castration-resistant prostate cancer: Induction of steroidogenesis and androgen receptor splice variants. *Clin. Cancer Res.* **2011**, *17*, 5913–5925. [CrossRef]

45. Mostaghel, E.A.; Solomon, K.R.; Pelton, K.; Freeman, M.R.; Montgomery, R.B. Impact of circulating cholesterol levels on growth and intratumoral androgen concentration of prostate tumors. *PLoS ONE* **2012**, *7*, e30062. [CrossRef] [PubMed]

46. Wright, J.L.; Kwon, E.M.; Ostrander, E.A.; Montgomery, R.B.; Lin, D.W.; Vessella, R.; Stanford, J.L.; Mostaghel, E.A. Expression of slco transport genes in castration-resistant prostate cancer and impact of genetic variation in SLCO1B3 and SLCO2B1 on prostate cancer outcomes. *Cancer Epidemiol. Biomark. Prev.* **2011**, *20*, 619–627. [CrossRef] [PubMed]

47. Yang, M.; Xie, W.; Mostaghel, E.; Nakabayashi, M.; Werner, L.; Sun, T.; Pomerantz, M.; Freedman, M.; Ross, R.; Regan, M.; et al. SLCO2B1 and SLCO1B3 may determine time to progression for patients receiving androgen deprivation therapy for prostate cancer. *J. Clin. Oncol.* **2011**, *29*, 2565–2573. [CrossRef] [PubMed]

48. Yu, Z.; Chen, S.; Sowalsky, A.G.; Voznesensky, O.S.; Mostaghel, E.A.; Nelson, P.S.; Cai, C.; Balk, S.P. Rapid induction of androgen receptor splice variants by androgen deprivation in prostate cancer. *Clin. Cancer Res.* **2014**, *20*, 1590–1590. [CrossRef] [PubMed]

49. Boudadi, K.; Antonarakis, E.S. Resistance to novel antiandrogen therapies in metastatic castration-resistant prostate cancer. *Clin. Med. Insights Oncol.* **2016**, *10*, 1–9. [PubMed]

50. De Bono, J.; De Giorgi, U.; Massard, C.; Bracarda, S.; Rodrigues, D.; Kocak, I.; Font, A.; Arija, J.; Shih, K.; Radavoi, G.; et al. Pten loss as a predictive biomarker for the akt inhibitor ipatasertib combined with abiraterone acetate in patients with metastatic castration-resistant prostate cancer (MCRPC). *Ann. Oncol.* **2016**, *27*, vi243–vi265.

51. Montgomery, R.B.; Antonarakis, E.S.; Hussain, M.; Fizazi, K.; Joshua, A.M.; Attard, G.; Sadar, M.; Perabo, F.; Chi, K.N. A phase 1/2 open-label study of safety and antitumor activity of epi-506, a novel ar n-terminal domain inhibitor, in men with metastatic castration-resistant prostate cancer (MCRPC) with progression after enzalutamide or abiraterone. In *Proceedings of the American Society of Clinical Oncology Annual Meeting*, Chicago, IL, USA, 29 May–2 June 2015.
52. Dehm, S.M.; Tindall, D.J. Androgen receptor structural and functional elements: Role and regulation in prostate cancer. *Mol. Endocrinol.* 2007, 21, 2855–2863. [CrossRef] [PubMed]

53. Huggins, C.; Dao, T.L. Adrenalectomy and oophorectomy in treatment of advanced carcinoma of the breast. *J. Am. Med. Assoc.* 1953, 151, 1388–1394. [PubMed]

54. Love, R.R.; Phillips, J. Oophorectomy for breast cancer: History revisited. *J. Natl. Cancer Inst.* 2002, 94, 1433–1434. [CrossRef] [PubMed]

55. Fioletti, F.M.; Sita-Lumsden, A.; Bevan, C.L.; Brooke, G.N. Revising the role of the androgen receptor in breast cancer. *J. Mol. Endocrinol.* 2014, 52, R257–R265. [CrossRef] [PubMed]

56. Pietri, E.; Conteduca, V.; Andreis, D.; Massa, I.; Melegari, E.; Sarti, S.; Cecconetto, L.; Schirone, A.; Bravaccini, S.; Serra, P.; et al. Androgen receptor signaling pathways as a target for breast cancer treatment. *Endocr. Relat. Cancer* 2016, 23, R485–R498. [CrossRef] [PubMed]

57. Vera-Badillo, F.E.; Templeton, A.J.; de Gouveia, P.; Diaz-Padilla, I.; Bedard, P.L.; Al-Mubarak, M.; Seruga, B.; Tannock, I.F.; Ocana, A.; Amir, E. Androgen receptor expression and outcomes in early breast cancer: A systematic review and meta-analysis. *J. Natl. Cancer Inst.* 2014, 106, djt319. [CrossRef] [PubMed]

58. Kim, Y.; Jae, E.; Yoon, M. Influence of androgen receptor expression on the survival outcomes in breast cancer: A meta-analysis. *J. Breast Cancer* 2015, 18, 134–142. [CrossRef] [PubMed]

59. Le Romancer, M.; Poulard, C.; Cohen, P.; Sentis, S.; Renoir, J.M.; Corbo, L. Cracking the estrogen receptor’s posttranslational code in breast tumors. *Endocr. Rev.* 2011, 32, 597–622. [CrossRef] [PubMed]

60. Risbridger, G.P.; Davis, I.D.; Birrell, S.N.; Tilley, W.D. Breast and prostate cancer: More similar than different. *Nat. Rev. Cancer* 2010, 10, 205–212. [CrossRef] [PubMed]

61. Lanzino, M.; De Amicis, F.; McPhaul, M.J.; Marsico, S.; Panno, M.L.; Ando, S. Endogenous coactivator ara70 interacts with estrogen receptor alpha (eralpha) and modulates the functional eralpha/androgen receptor interplay in MCF-7 cells. *J. Biol. Chem.* 2005, 280, 20421–20430. [CrossRef] [PubMed]

62. Panet-Raymond, V.; Gottlieb, B.; Beitel, L.K.; Brooke, G.N. Revising the role of the androgen receptor in breast cancer and preclinical analysis of enzalutamide. *Breast Cancer Res.* 2016, 18, 352–360. [CrossRef] [PubMed]

63. Lanzino, M.; De Amicis, F.; McPhaul, M.J.; Marsico, S.; Panno, M.L.; Ando, S. Endogenous coactivator ara70 interacts with estrogen receptor alpha (eralpha) and modulates the functional eralpha/androgen receptor interplay in MCF-7 cells. *J. Biol. Chem.* 2005, 280, 20421–20430. [CrossRef] [PubMed]

64. Bianchini, G.; Balco, J.M.; Mayer, I.A.; Sanders, M.E.; Gianni, L. Triple-negative breast cancer: Challenges and opportunities of a heterogeneous disease. *Nature Rev. Clin. Oncol.* 2016, 13, 674–690. [CrossRef] [PubMed]

65. Ni, M.; Chen, Y.; Lim, E.; Wimberly, H.; Bailey, S.T.; Imai, Y.; Rimm, D.L.; Liu, X.S.; Brown, M. Targeting androgen receptor in estrogen receptor-negative breast cancer. *Cancer Cell* 2011, 20, 119–131. [CrossRef] [PubMed]

66. Barton, V.N.; D’Amato, N.C.; Gordon, M.A.; Lind, H.T.; Spoelstra, N.S.; Babbs, B.L.; Heinz, R.E.; Elias, A.; Jedlicka, P.; Jacobsen, B.M.; et al. Multiple molecular subtypes of triple-negative breast cancer critically rely on androgen receptor and respond to enzalutamide in vivo. *Mol. Cancer Ther.* 2015, 14, 769–778. [CrossRef] [PubMed]

67. Collins, L.C.; Cole, K.S.; Marotti, J.D.; Hu, R.; Schnitt, S.J.; Tamimi, R.M. Androgen receptor expression in breast cancer in relation to molecular phenotype: Results from the nurses’ health study. *Mod. Pathol.* 2011, 24, 924–931. [CrossRef] [PubMed]

68. Mrklic, I.; Pogorelic, Z.; Capkun, V.; Tomic, S. Expression of androgen receptors in triple negative breast carcinomas. *Acta Histochem.* 2013, 115, 344–348. [CrossRef] [PubMed]

69. Thike, A.A.; Yong-Zheng Chong, L.; Cheok, P.Y.; Li, H.H.; Wai-Cheong Yip, G.; Huat Bay, B.; Tse, G.M.; Iqbal, J.; Tan, P.H. Loss of androgen receptor expression predicts early recurrence in triple-negative and basal-like breast cancer. *Mod. Pathol.* 2014, 27, 352–360. [CrossRef] [PubMed]

70. Safarpour, D.; Pakneshan, S.; Tavassoli, F.A. Androgen receptor (AR) expression in 400 breast carcinomas: Is routine ar assessment justified? *Am. J. Cancer Res.* 2014, 4, 353–368. [PubMed]

71. Cochrane, D.R.; Bernales, S.; Jacobsen, B.M.; Cittelly, D.M.; Howe, E.N.; D’Amato, N.C.; Spoelstra, N.S.; Edgerton, S.M.; Jean, A.; Guerrero, J.; et al. Role of the androgen receptor in breast cancer and preclinical analysis of enzalutamide. *Breast Cancer Res.* 2014, 16, R7. [CrossRef] [PubMed]
73. Farmer, P.; Bonnefoi, H.; Becette, V.; Tubiana-Hulin, M.; Fumoleau, P.; Larsimont, D.; Macgregor, G.; Bergh, J.; Cameron, D.; Goldstein, D.; et al. Identification of molecular apocrine breast tumours by microarray analysis. Oncogene 2005, 24, 4660–4671. [CrossRef] [PubMed]

74. Lehmann, B.D.; Bauer, J.A.; Chen, X.; Sanders, M.E.; Chakravarthy, A.B.; Shyr, Y.; Pietenpol, J.A. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. J. Clin. Investig. 2011, 121, 2750–2767. [CrossRef] [PubMed]

75. Hickey, T.E.; Irvine, C.M.; Dvinge, H.; Tarulli, G.A.; Hanson, A.R.; Ryan, N.K.; Pickering, M.A.; Birrell, S.N.; Hu, D.G.; Mackenzie, P.I.; et al. Expression of androgen receptor splice variants in clinical breast cancers. Oncotarget 2015, 6, 44728–44744. [PubMed]

76. Gucalp, A.; Tolaney, S.; Isakoff, S.J.; Ingle, J.N.; Liu, M.C.; Carey, L.A.; Blackwell, K.; Rugo, H.; Nabhell, L.; Forero, A.; et al. Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic breast cancer. Clin. Cancer Res. 2013, 19, 5505–5512. [CrossRef] [PubMed]

77. Traina, T.; Miller, K.; Yardley, D.; O’Shaughnessy, J.; Cortes, J.; Awada, A.; Kelly, C.; Trudeau, M.; Schmid, P.; Gianni, L.; et al. Results from a phase 2 study of enzalutamide (ENZA), an androgen receptor (AR) inhibitor, in advanced AR+ triple-negative breast cancer (TNBC). In Proceedings of the ASCO Annual Meeting, Chicago, IL, USA, 29 May–2 June 2015.

78. O’Shaughnessy, J.; Campone, M.; Brain, E.; Neven, P.; Hayes, D.; Bondarenko, I.; Griffin, T.W.; Martin, J.; De Porge, P.; Kheoh, T.; et al. Abiraterone acetate, exemestane or the combination in postmenopausal patients with estrogen receptor-positive metastatic breast cancer. Ann. Oncol. 2016, 27, 106–113. [CrossRef] [PubMed]

79. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2016. CA Cancer J. Clin. 2016, 66, 7–30. [CrossRef] [PubMed]

80. Scosyrev, E.; Noyes, K.; Feng, C.; Messing, E. Sex and racial differences in bladder cancer presentation and mortality in the us. Cancer 2009, 115, 68–74. [CrossRef] [PubMed]

81. Castelo, J.E.; Yuan, J.M.; Skipper, P.L.; Tannenbaum, S.R.; Gago-Dominguez, M.;Crowder, J.S.; Ross, R.K.; Yu, M.C. Gender- and smoking-related bladder cancer risk. J. Natl. Cancer Inst. 2001, 93, 538–545. [CrossRef] [PubMed]

82. Hartge, P.; Harvey, E.B.;Linehan, W.;Silverman, D.T.;Sullivan, J.W.;Hoover, R.N.;Fraumeni, J.F., Jr. Unexplained excess risk of bladder cancer in men. J. Natl. Cancer Inst. 1990, 82, 1636–1640. [CrossRef] [PubMed]

83. Godoy, G.; Gakis, G.; Smith, C.L.; Fahmy, O. Effects of androgen and estrogen receptor signaling pathways on bladder cancer initiation and progression. Bladder Cancer 2016, 2, 127–137. [CrossRef] [PubMed]

84. Mungan, N.A.; Aben, K.K.; Schoenberg, M.P.; Visser, O.; Coebergh, J.W.; Witjes, J.A.; Kiemeney, L.A. Gender differences in stage-adjusted bladder cancer survival. Urology 2000, 55, 876–880. [CrossRef] [PubMed]

85. Boorjian, S.; Ugras, S.; Mongan, N.P.; Gudas, L.J.; You, X.; Tickoo, S.K.; Scherr, D.S. Androgen receptor expression is inversely correlated with pathologic tumor stage in bladder cancer. Urology 2004, 64, 383–388. [CrossRef] [PubMed]

86. Mir, C.; Shariat, S.F.; van der Kwast, T.H.; Ashfaq, R.; Lotan, Y.; Evans, A.; Skeldon, S.; Hanna, S.; Vajpeyi, R.; Kuk, C.; et al. Loss of androgen receptor expression is not associated with pathological stage, grade, gender or outcome in bladder cancer: A large multi-institutional study. BJU Int. 2011, 108, 24–30. [CrossRef] [PubMed]

87. Nam, J.K.; Park, S.W.; Lee, S.D.; Chung, M.K. Prognostic value of sex-hormone receptor expression in non-muscle-invasive bladder cancer. Yonsei Med. J. 2014, 55, 1214–1221. [CrossRef] [PubMed]

88. Williams, E.M.; Higgins, J.P.; Sangoi, A.R.; McKenney, J.K.; Troxell, M.L. Androgen receptor immunohistochemistry in genitourinary neoplasms. Int. Urol. Nephrol. 2015, 47, 81–85. [CrossRef]

89. Zhuang, Y.H.; Blauer, M.; Tammela, T.; Tuohimaa, P. Immunodetection of androgen receptor in human urinary bladder cancer. Histopathology 1997, 30, 556–562. [CrossRef] [PubMed]

90. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 2014, 507, 315–322.

91. Choi, W.; Porten, S.; Kim, S.; Willis, D.; Plimack, E.R.; Hoffman-Censits, J.; Roth, B.; Cheng, T.; Tran, M.; Lee, I.L.; et al. Identification of distinct basal and luminal subtypes of muscle-invasive bladder cancer with different sensitivities to frontline chemotherapy. Cancer Cell 2014, 25, 152–165. [CrossRef] [PubMed]

92. Wu, J.T.; Han, B.M.; Yu, S.Q.; Wang, H.P.; Xia, S.J. Androgen receptor is a potential therapeutic target for bladder cancer. Urology 2010, 75, 820–827. [CrossRef] [PubMed]
93. Hsu, J.W.; Hsu, I.; Xu, D.; Miyamoto, H.; Liang, L.; Wu, X.R.; Shyr, C.R.; Chang, C. Decreased tumorigenesis and mortality from bladder cancer in mice lacking urothelial androgen receptor. *Am. J. Pathol. 2013*, 182, 1811–1820. [CrossRef] [PubMed]

94. Li, Y.; Zheng, Y.; Izumi, K.; Ishiguro, H.; Ye, B.; Li, F.; Miyamoto, H. Androgen activates beta-catenin signaling in bladder cancer cells. *Endocr. Relat. Cancer 2013*, 20, 293–304. [CrossRef] [PubMed]

95. Zheng, Y.; Izumi, K.; Yao, J.L.; Miyamoto, H. Dihydrotestosterone upregulates the expression of epidermal growth factor receptor and erbB2 in androgen receptor-positive bladder cancer cells. *Endocr. Relat. Cancer 2011*, 18, 451–464. [CrossRef]

96. Kawahara, T.; Ide, H.; Kashiwagi, E.; El-Shishtawy, K.A.; Li, Y.; Reis, L.O.; Zheng, Y.; Miyamoto, H. Enzalutamide inhibits androgen receptor-positive bladder cancer cell growth. *Urol. Oncol. 2016*, 34, 432.e15–432.e23. [CrossRef] [PubMed]

97. Langner, C.; Ratschek, M.; Rehak, P.; Schips, L.; Zigeuner, R. Steroid hormone receptor expression in renal cell carcinoma: An immunohistochemical analysis of 182 tumors. *J. Urol. 2004*, 171, 611–614. [CrossRef] [PubMed]

98. Brown, D.F.; Dababo, M.A.; Hladik, C.L.; Eagan, K.P.; White, C.L., 3rd; Rushing, E.J. Hormone receptor immunoreactivity in hemangioblastomas and clear cell renal cell carcinomas. *Mod. Pathol. 1998*, 11, 55–59. [PubMed]

99. Quinkler, M.; Bujalska, I.J.; Kaur, K.; Onyimba, C.U.; Buhner, S.; Alloio, B.; Hughes, S.V.; Hewison, M.; Stewart, P.M. Androgen receptor-mediated regulation of the alpha-subunit of the epithelial sodium channel in human kidney. *Hypertension 2005*, 46, 787–798. [CrossRef] [PubMed]

100. Noh, S.J.; Kang, M.J.; Kim, K.M.; Bae, J.S.; Park, H.S.; Moon, W.S.; Chung, M.J.; Lee, H.; Lee, D.G.; Jang, K.Y. Acetylation status of p53 and the expression of DBC1, SIRT1, and androgen receptor are associated with survival in clear cell renal cell carcinoma patients. *Pathology 2013*, 45, 574–580. [CrossRef] [PubMed]

101. Zhu, G.; Liang, L.; Li, L.; Dang, Q.; Song, W.; Yeh, S.; He, D.; Chang, C. The expression and evaluation of androgen receptor in human renal cell carcinoma. *Urology 2014*, 83, 510.e519–510.e524. [CrossRef] [PubMed]

102. Zhao, H.; Leppert, J.T.; Peehl, D.M. A protective role for androgen receptor in clear cell renal cell carcinoma based on mining tcga data. *PLoS ONE 2016*, 11, e0146505. [CrossRef]

103. Ha, Y.S.; Lee, G.T.; Modi, P.; Kwon, Y.S.; Ahn, H.; Kim, W.J.; Kim, I.Y. Increased expression of androgen receptor mrna in human renal cell carcinoma cells is associated with poor prognosis in patients with localized renal cell carcinoma. *J. Urol. 2015*, 194, 1441–1448. [CrossRef] [PubMed]

104. He, D.; Li, L.; Zhu, G.; Liang, L.; Guan, Z.; Chang, L.; Chen, Y.; Yeh, S.; Chang, C. Asc-γ9 suppresses renal cell carcinoma progression by targeting an androgen receptor-dependent HIF2ALPHA/vegf signaling pathway. *Cancer Res. 2014*, 74, 4420–4430. [CrossRef] [PubMed]

105. Corbishley, T.P.; Iqbal, M.J.; Wilkinson, M.L.; Williams, R. Androgen receptor in human normal and malignant pancreatic tissue and cell lines. *Cancer 1986*, 57, 1992–1995. [CrossRef]

106. Konduri, S.; Schwarz, M.A.; Cafasso, D.; Schwarz, R.E. Androgen receptor blockade in experimental combination therapy of pancreatic cancer. *J. Surg. Res. 2007*, 142, 378–386. [CrossRef] [PubMed]

107. Sumi, C.; Brinck-Johnsen, T.; Longnecker, D.S. Inhibition of a transplantable pancreatic carcinoma by castration and estradiol administration in rats. *Cancer Res. 1989*, 49, 6687–6692. [PubMed]

108. Lhoste, E.F.; Roebuck, B.D.; Stern, J.E.; Longnecker, D.S. Effect of orchectomy and testosterone on the early stages of azaserine-induced pancreatic carcinogenesis in the rat. *Pancreas 1987*, 2, 38–43. [CrossRef] [PubMed]

109. Sumi, C.; Longnecker, D.S.; Roebuck, B.D.; Brinck-Johnsen, T. Inhibitory effects of estrogen and castration on the early stage of pancreatic carcinogenesis in fischer rats treated with azaserine. *Cancer Res. 1989*, 49, 2332–2336. [PubMed]

110. Lhoste, E.F.; Roebuck, B.D.; Brinck-Johnsen, T.; Longnecker, D.S. Effect of castration and hormone replacement on azaserine-induced pancreatic carcinogenesis in male and female fischer rats. *Carcinogenesis 1987*, 8, 699–703. [CrossRef] [PubMed]

111. Meijers, M.; Visser, C.J.; Klijn, J.G.; Lamberts, S.W.; van Garderen-Hoetmer, A.; de Jong, F.H.; Foekens, J.A.; Woutersen, R.A. Effects of orchectomy, alone or in combination with testosterone, and cyproterone acetate on exocrine pancreatic carcinogenesis in rats and hamsters. *Int. J. Pancreatol. 1992*, 11, 137–146. [CrossRef] [PubMed]

112. Siu, T.O.; Kwan, W.B. Hormones in chemotherapy for pancreatic cancer, chemoagents or carriers? *In Vivo 1989*, 3, 255–258. [PubMed]
Cancers 2017, 9, 7

113. Selvan, R.S.; Metzgar, R.S.; Petrov, V. Growth modulatory effects of some 6-methylenic steroids on human and hamster pancreatic adenocarcinoma cells in vitro. Drug Des. Discov. 1992, 9, 119–133. [PubMed]

114. Okitsu, K.; Kanda, T.; Imazeki, F.; Yonemitsu, Y.; Ray, R.B.; Chang, C.; Yokosuka, O. Involvement of interleukin-6 and androgen receptor signaling in pancreatic cancer. Genes Cancer 2010, 1, 859–867. [CrossRef] [PubMed]

115. Greenway, B.A. Effect of flutamide on survival in patients with pancreatic cancer: Results of a prospective, randomised, double blind, placebo controlled trial. BMJ 1998, 316, 1935–1938. [CrossRef] [PubMed]

116. Sharma, J.; Razvillas, B.; Stephens, C.D.; Hilsenbeck, S.G.; Sharma, A.; Rothenberg, M.L. Phase II study of flutamide as second line chemotherapy in patients with advanced pancreatic cancer. Investig. New Drugs 1997, 15, 361–364. [CrossRef]

117. Negi, S.S.; Agarwal, A.; Chaudhary, A. Flutamide in unresectable pancreatic adenocarcinoma: A randomized, double-blind, placebo-controlled trial. Investig. New Drugs 2006, 24, 189–194. [CrossRef] [PubMed]

118. Corrie, P.; Mayer, A.; Shaw, J.; D’Ath, S.; Blagden, S.; Blesing, C.; Price, P.; Warner, N. Phase II study to evaluate combining gemcitabine with flutamide in advanced pancreatic cancer patients. Br. J. Cancer 2002, 87, 716–719. [CrossRef] [PubMed]

119. Keating, J.J.; Johnson, P.; Cochrane, A.M.; Gazzard, B.G.; Krasner, N.; Smith, P.M.; Trewby, P.N.; Wheeler, P.; Wilkinson, S.P.; Williams, R. A prospective randomised controlled trial of tamoxifen and cyproterone acetate in pancreatic cancer. Br. J. Cancer 1989, 60, 789–792. [CrossRef] [PubMed]

120. Philip, P.A.; Carmichael, J.; Tonkin, K.; Buamah, P.K.; Britton, J.; Dowsett, M.; Harris, A.L. Hormonal treatment of pancreatic carcinoma: A phase II study of lhrh agonist goserelin plus hydrocortisone. Br. J. Cancer 1993, 67, 379–382. [CrossRef] [PubMed]

121. Swarovsky, B.; Wolf, M.; Havemann, K.; Arnold, R. Tamoxifen or cyproterone acetate in combination with buserelin are ineffective in patients with pancreatic adenocarcinoma. Oncology 1993, 50, 226–229. [CrossRef] [PubMed]

122. Mahipal, A.; Springett, G.; Burke, N.; Neuger, A.; Copolla, D.; Kim, R. Phase I trial of gemcitabine with flutamide in advanced pancreatic cancer patients. Br. J. Cancer 2002, 87, 716–719. [CrossRef] [PubMed]

123. Vizoso, F.J.; Rodriguez, M.; Altadill, A.; Gonzalez-Dieuguez, M.L.; Linares, A.; Gonzalez, L.O.; Junquera, S.; Fresno-Forcelledo, F.; Corte, M.D.; Rodrigo, L. Liver expression of steroid hormones and apolipoprotein d receptors in hepatocellular carcinoma. World J. Gastroenterol. 2007, 13, 3221–3227. [CrossRef]

124. Nagasue, N.; Ito, A.; Yukaya, H.; Ogawa, Y. Androgen receptors in hepatocellular carcinoma and surrounding parenchyma. Gastroenterology 1985, 89, 643–647. [CrossRef]

125. Negro, F.; Papotti, M.; Pacchioni, D.; Galimi, F.; Bonino, F.; Bussolati, G. Detection of human androgen receptor mrna in hepatocellular carcinoma by in situ hybridisation. Liver 1994, 14, 213–219. [CrossRef] [PubMed]

126. Kalra, M.; Mayes, J.; Assefa, S.; Kaul, A.K.; Kaul, R. Role of sex steroid receptors in pathobiology of hepatocellular carcinoma. World J. Gastroenterol. 2008, 14, 5945–5961. [CrossRef] [PubMed]

127. Nagasue, N.; Yu, L.; Yukaya, H.; Kohno, H.; Nakamura, T. Androgen and oestrogen receptors in hepatocellular carcinoma and surrounding liver parenchyma: Impact on intrahepatic recurrence after hepatic resection. Br. J. Surg. 1995, 82, 542–547. [CrossRef]

128. Boix, L.; Castells, A.; Bruix, J.; Sole, M.; Bru, C.; Fuster, J.; Rivera, E.; Rodes, J. Androgen receptors in hepatocellular carcinoma and surrounding liver: Relationship with tumor size and recurrence rate after surgical resection. J. Hepatol. 1995, 22, 616–622. [CrossRef]

129. Zhang, X.; He, L.; Lu, Y.; Liu, M.; Huang, X. Androgen receptor in primary hepatocellular carcinoma and its clinical significance. Chin. Med. J. 1998, 111, 1083–1086. [PubMed]

130. Yu, M.W.; Yang, Y.C.; Yang, S.Y.; Cheng, S.W.; Liaw, Y.F.; Lin, S.M.; Chen, C.J. Hormonal markers and hepatitis b virus-related hepatocellular carcinoma risk: A nested case-control study among men. J. Natl. Cancer Inst. 2001, 93, 1644–1651. [CrossRef] [PubMed]

131. Kanda, T.; Steele, R.; Ray, R.; Ray, R.B. Hepatitis c virus core protein augments androgen receptor-mediated signaling. J. Virol. 2008, 82, 11066–11072. [CrossRef] [PubMed]

132. White, D.L.; Tavakoli-Tabasi, S.; Kuzniarek, J.; Pascua, R.; Ramsey, D.J.; El-Serag, H.B. Higher serum testosterone is associated with increased risk of advanced hepatitis c-related liver disease in males. Hepatology 2012, 55, 759–768. [CrossRef] [PubMed]
133. Kanda, T.; Jiang, X.; Yokosuka, O. Androgen receptor signaling in hepatocellular carcinoma and pancreatic cancers. World J. Gastroenterol. 2014, 20, 9229–9236. [PubMed]
134. Ma, W.L.; Hsu, C.L.; Wu, M.H.; Wu, C.T.; Wu, C.C.; Lai, I.J.; Jou, Y.S.; Chen, C.W.; Yeh, S.; Chang, C. Androgen receptor is a new potential therapeutic target for the treatment of hepatocellular carcinoma. Gastroenterology 2008, 135, 947–955.e5. [CrossRef] [PubMed]
135. Ma, W.L.; Hsu, C.L.; Yeh, C.C.; Wu, M.H.; Huang, C.K.; Jeng, L.B.; Hung, Y.C.; Lin, T.Y.; Yeh, S.; Chang, C. Hepatic androgen receptor suppresses hepatocellular carcinoma metastasis through modulation of cell migration and anoikis. Hepatology 2012, 56, 176–185. [CrossRef]
136. Ao, J.; Meng, J.; Zhu, L.; Nie, H.; Yang, C.; Li, J.; Gu, J.; Lin, Q.; Long, W.; Dong, X.; et al. Activation of androgen receptor induces id1 and promotes hepatocellular carcinoma cell migration and invasion. Mol. Oncol. 2012, 6, 507–515. [CrossRef] [PubMed]
137. Risch, H.A. Hormonal etiology of epithelial ovarian cancer, with a hypothesis concerning the role of androgens and progesterone. J. Natl. Cancer Inst. 1998, 90, 1774–1786. [CrossRef] [PubMed]
138. Zhu, H.; Zhu, X.; Zheng, L.; Hu, X.; Sun, L.; Zhu, X. The role of the androgen receptor in ovarian cancer carcinogenesis and its clinical implications. Oncotarget 2016. [CrossRef]
139. Lee, P.; Rosen, D.G.; Zhu, C.; Silva, E.G.; Liu, J. Expression of progesterone receptor is a favorable prognostic marker in ovarian cancer. Gynecol. Oncol. 2005, 96, 671–677. [CrossRef] [PubMed]
140. Cardillo, M.R.; Petrangeli, E.; Aliotta, N.; Salvatori, L.; Ravenna, L.; Chang, C.; Castagna, G. Androgen receptors in ovarian tumors: Correlation with oestrogen and progesterone receptors in an immunohistochemical and semiquantitative image analysis study. J. Exp. Clin. Cancer Res. CR 1998, 17, 231–237. [PubMed]
141. Chadha, S.; Rao, B.R.; Slotman, B.J.; van Vroonhoven, C.C.; van der Kwast, T.H. An immunohistochemical evaluation of androgen and progesterone receptors in ovarian tumors. Hum. Pathol. 1993, 24, 90–95. [CrossRef]
142. Schildkraut, J.M.; Schwingl, P.J.; Bastos, E.; Evanoff, A.; Hughes, C. Epithelial ovarian cancer risk among women with polycystic ovary syndrome. Obstet. Gynecol. 1996, 88, 554–559. [CrossRef]
143. Resta, L.; Russo, S.; Colucci, G.A.; Prat, J. Morphologic precursors of ovarian epithelial tumors. Obstet. Gynecol. 1993, 82, 181–186. [PubMed]
144. Cottreau, C.M.; Ness, R.B.; Modugno, F.; Allen, G.O.; Goodman, M.T. Endometriosis and its treatment with danazol or lupron in relation to ovarian cancer. Clin. Cancer Res. 2003, 9, 5142–5144. [PubMed]
145. Edmondson, R.J.; Monaghan, J.M.; Davies, B.R. The human ovarian surface epithelium is an androgen responsive tissue. Br. J. Cancer 2002, 86, 879–885. [CrossRef] [PubMed]
146. Elattar, A.; Warburton, K.G.; Mukhopadhyay, A.; Freer, R.M.; Shaheen, F.; Cross, P.; Plummer, E.R.; Robson, C.N.; Edmondson, R.J. Androgen receptor expression is a biological marker for androgen sensitivity in high grade serous epithelial ovarian cancer. Gynecol. Oncol. 2012, 124, 142–147. [CrossRef] [PubMed]
147. Gruessner, C.; Gruessner, A.; Glaser, K.; AbuShahin, N.; Zhou, Y.; Laughren, C.; Wright, H.; Pinkerton, S.; Yi, X.; Stoffler, J.; et al. Flutamide and biomarkers in women at high risk for ovarian cancer: Preclinical and clinical evidence. Cancer Prev. Res. 2014, 7, 896–905. [CrossRef] [PubMed]
148. Levine, D.; Park, K.; Juretzka, M.; Esch, J.; Hensley, M.; Aghajanian, C.; Levin, S.; Konner, J.; Derosa, F.; Spriggs, D.; et al. A phase II evaluation of goserelin and bicalutamide in patients with ovarian cancer in second or higher complete clinical disease remission. Cancer 2007, 110, 2448–2456. [CrossRef] [PubMed]
149. Park, B.Y.; Grisham, R.N.; den Hollander, B.; Thapi, D.; Berman, T.; de Stanchina, E.; Zhou, Q.; Iyer, G.; Aghajanian, C.; Spriggs, D.R. Tumor inhibition by enzalutamide in a xenograft model of ovarian cancer. J. Exp. Clin. Cancer Res. CR 2016, 35, 94289–49298. [CrossRef] [PubMed]
154. Chandran, R.; Gardiner, S.K.; Simon, M.; Spurgeon, S.E. Survival trends in mantle cell lymphoma in the united states over 16 years 1992–2007. *Leuk. Lymphoma* **2012**, *53*, 1488–1493. [CrossRef] [PubMed]

155. Danel, L.; Menouni, M.; Cohen, J.H.; Magaud, J.P.; Lenoir, G.; Revillard, J.P.; Saez, S. Distribution of androgen and estrogen receptors among lymphoid and haemopoietic cell lines. *Leuk. Res.* **1985**, *9*, 1373–1378. [CrossRef]

156. Khetawat, G.; Faraday, N.; Nealen, M.L.; Vijayan, K.V.; Bolton, E.; Noga, S.J.; Bray, P.F. Human megakaryocytes and platelets contain the estrogen receptor beta and androgen receptor (AR): Testosterone regulates ar expression. *Blood* **2000**, *95*, 2289–2296. [PubMed]

157. Klein, S.L. Immune cells have sex and so should journal articles. *Endocrinology* **2012**, *153*, 2544–2550. [CrossRef] [PubMed]

158. Yang, H.; Chen, C.M.; Yan, P.; Huang, T.H.; Shi, H.; Burger, M.; Nimmrich, I.; Maier, S.; Berlin, K.; Caldwell, C.W. The androgen receptor gene is preferentially hypermethylated in follicular non-hodgkin’s lymphomas. *Clin. Cancer Res.* **2003**, *9*, 4034–4042.

159. Shi, H.; Maier, S.; Nimmrich, I.; Yan, P.S.; Caldwell, C.W.; Olek, A.; Huang, T.H. Oligonucleotide-based microarray for DNA methylation analysis: Principles and applications. *J. Cell. Biochem.* **2003**, *88*, 138–143. [CrossRef] [PubMed]

160. Andreasen, S.; Grauslund, M.; Heegaard, S. Lacrimal gland ductal carcinomas: Clinical, morphological and genetic characterization and implications for targeted treatment. *Acta Ophthalmol.* **2016**. [CrossRef] [PubMed]

161. Rahimi, S.; Lambiase, A.; Brennan, P.A.; Abdolrahimzadeh, S. An androgen receptor-positive carcinoma of the lacrimal drainage system resembling salivary duct carcinoma: Case report and review of the literature. *Appl. Immunohistochem. Mol. Morphol.* **2016**, *24*, e69–e71. [CrossRef] [PubMed]

162. Simpson, R.H. Salivary duct carcinoma: New developments–morphological variants including pure in situ high grade lesions; proposed molecular classification. *Head Neck Pathol.* **2013**, *7*, S48–S58. [CrossRef] [PubMed]

163. Kapadia, S.B.; Barnes, L. Expression of androgen receptor, gross cystic disease fluid protein, and CD44 in salivary duct carcinoma. *Mod. Pathol.* **1998**, *11*, 1033–1038. [PubMed]

164. Di Palma, S.; Simpson, R.H.; Marchio, C.; Skalova, A.; Ungari, M.; Sandison, A.; Whitaker, S.; Parry, S.; Reis-Filho, J.S. Salivary duct carcinomas can be classified into luminal androgen receptor-positive, her2 and basal-like phenotypes. *Histopathology* **2012**, *61*, 629–643. [CrossRef] [PubMed]

165. Williams, M.D.; Roberts, D.; Blumenschein, G.R., Jr; Temam, S.; Kies, M.S.; Rosenthal, D.I.; Weber, R.S.; El-Naggar, A.K. Differential expression of hormonal and growth factor receptors in salivary duct carcinomas: Biologic significance and potential role in therapeutic stratification of patients. *Am. J. Surg. Pathol.* **2007**, *31*, 1645–1652. [CrossRef] [PubMed]

166. Fan, C.Y.; Wang, J.; Barnes, E.L. Expression of androgen receptor and prostatic specific markers in salivary duct carcinoma: An immunohistochemical analysis of 13 cases and review of the literature. *Am. J. Surg. Pathol.* **2000**, *24*, 579–586. [CrossRef] [PubMed]

167. Jaspers, H.C.; Verbist, B.M.; Schoffelen, R.; Mattijssen, V.; Slootweg, P.J.; van der Graaf, W.T.; van Herpen, C.M. Androgen receptor-positive salivary duct carcinoma: A disease entity with promising new treatment options. *J. Clin. Oncol.* **2011**, *29*, e473–e476. [CrossRef] [PubMed]

168. Soper, M.S.; Iganej, S.; Thompson, L.D. Definitive treatment of androgen receptor-positive salivary duct carcinoma with androgen deprivation therapy and external beam radiotherapy. *Head Neck* **2014**, *36*, E4–E7. [CrossRef]