Oncology Oral, Prostate Cancer Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
abiraterone acetate (Zytiga®)[1]	generic, Janssen	▪ In combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) or metastatic high-risk castration-sensitive prostate cancer (mCSPC)
abiraterone acetate (Yonsa®)[2]	Sun	▪ In combination with methylprednisolone for the treatment of patients with mCRPC
apalutamide (Erleada®)[3]	Janssen	▪ Treatment of patients with non-metastatic castration-resistant prostate cancer (NM-CRPC) ▪ Treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC)
bicalutamide (Casodex®)[4]	generic, Ani	▪ In combination therapy with a luteinizing hormone-releasing hormone (LHRH) analog for the treatment of stage D_2 metastatic carcinoma of the prostate*
darolutamide (Nubeqa®)[5]	Bayer	▪ Treatment of non-metastatic castration resistant prostate cancer (NM-CRPC)
enzalutamide (Xtandi®)[6]	Astellas	▪ Treatment of patients with CRPC ▪ Treatment of patients with mCSPC
estramustine (Emcyt®)[7]	Pfizer	▪ Palliative treatment of metastatic and/or progressive carcinoma of the prostate
flutamide[8]	generic	▪ In combination with LHRH agonists for the management of locally confined stage B_2-C and stage D_2 metastatic carcinoma of the prostate
nilutamide (Nilandron®)[9]	generic, Concordia	▪ In combination with surgical castration for the treatment of metastatic prostate cancer (stage D_2)†

* Bicalutamide is not approved for use alone or with treatments other than LHRH analogs.
† For maximum benefit, treatment with nilutamide tablets must begin on the same day as or on the day after surgical castration.

OVERVIEW

In the United States (US), prostate cancer is the most commonly diagnosed cancer in men (excluding non-melanoma skin cancers), with an estimated 191,930 cases projected to be diagnosed in 2020.[10] While prostate cancer accounts for the largest percentage of diagnosed cases in US males (20%), it only accounts for about 10% of all cancer deaths in this population, far behind the leading cause of cancer death, which is lung cancer, accounting for 24% of US male cancer deaths.[11,12] There has been a decreasing incidence of prostate cancer diagnoses since the early 1990s, and from 2011 to 2015, the incidence of prostate cancer declined approximately 7% per year. This decreased incidence in the diagnosis of prostate cancer was likely secondary to a change in practice during that time which saw a decreased rate of routine prostate-specific antigen (PSA) screening. This decrease in routine PSA screening was based on prior recommendations against routine PSA screening from the US Preventive Services Task Force (USPSTF). These recommendations were subsequently revised in early 2018 when the USPSTF recommended that the decision of whether or not to perform PSA testing should be individualized for men ages 55 to 69 years of age based on a discussion with a clinician regarding the potential benefits and harms associated with screening (Grade C recommendation).[13] The benefits include a small chance of reducing the odds of dying of prostate cancer, while the potential harms include possible false-positive results requiring additional testing and possible unnecessary prostate

biopsy. Other potential harms include over-diagnosis and over-treatment with potential treatment complications, such as incontinence and impotence. The 2018 USPSTF statement also recommends against PSA-based screening for men ages 70 years or older (Grade D). The National Comprehensive Cancer Network (NCCN) guideline for Prostate Cancer Early Detection supports the continued discussion and use of baseline PSA testing in informed, healthy men ages 45 to 75 years.[14] The NCCN guidelines also note that due to a higher incidence of prostate cancer and increased prostate cancer mortality seen in African American men, shared decision making about PSA screening may be considered earlier, beginning at age 40, for this population. Likewise, men with known germline BRCA1/2 mutations may consider shared decision making about PSA screening beginning at age 40 years and both groups may consider screening at annual intervals rather than every other year.[15] Similarly, the American Cancer Society (ACS) recommends men should receive information about the uncertainties, risks, and potential benefits of prostate cancer screening prior to making an informed choice and that screening should not be conducted unless men have received this information. The age at which to begin these discussions varies depending on the individual risk level based on race and family history.[16] The 2013 American Urological Association (AUA) guideline for the early detection of prostate cancer was reviewed and validity confirmed by the AUA in 2018; it recommends average risk men ages 55 to 69 years participate in a shared decision making process with their provider to determine their desire for PSA screening (Evidence Strength Grade B).[17] According to a 2012 American Society of Clinical Oncology (ASCO) Provisional Clinical Opinion, the role of PSA testing should be discussed with all men with a life expectancy of > 10 years. ASCO notes that although PSA testing is a useful marker for detecting prostate cancer at early stages, it may also be associated with complications resulting from potentially unnecessary biopsy, surgery, or radiation treatment.[18]

Prostate cancer is rare in men under the age of 40 years, but the risk increases with each subsequent decade of life. Overall, 1 in 9 US men will develop prostate cancer during their lifetime.[19] Aside from age, the risk factors most strongly associated with development of prostate cancer include race/ethnicity and family history. Prostate cancer mortality in non-Hispanic African Americans is more than twice that seen in the US Caucasian population.[20]

Androgens (specifically testosterone) are a known growth signal for prostate cancer, and the majority of prostate cancers are hormonally dependent. Due to the hormone responsiveness of the tumor, androgen deprivation therapy (ADT) is a cornerstone of prostate cancer treatment. ADT is utilized as the backbone of therapy in advanced or metastatic disease as well as in combination with radiation therapy for locally-advanced prostate cancer. ADT can be accomplished by utilizing either a surgical approach (bilateral orchiectomy) or a medical approach with the administration of a luteinizing hormone-releasing hormone (LHRH) agonist or a LHRH antagonist, to suppress serum testosterone concentrations to castrate levels (< 50 ng/dL).

The prognosis of patients diagnosed with prostate cancer is determined by several factors, including the tumor size, histologic grade (reported as a Gleason score), PSA level, and disease stage. While early stage disease is highly curable, advanced, metastatic disease is currently considered incurable.

In addition to the treatment approaches discussed in this review, other pharmaceutical treatment modalities exist. Intravenous chemotherapy options, such as docetaxel and cabazitaxel (Jevtana®), as well as immunotherapy options for certain patients, including sipuleucel-T (Provenge®) or pembrolizumab (Keytruda®), and a radiopharmaceutical option, radium-223 (Xofigo®), may also be utilized in the treatment of metastatic prostate cancer. The use of docetaxel, cabazitaxel, sipuleucel-T,

pembrolizumab and radium-223 for the management of metastatic prostate cancer is beyond the scope of this review.

Localized (non-metastatic) Prostate Cancer

According to the 4.2019 NCCN guidelines, optimal treatment for men with localized, non-metastatic prostate cancer is determined by both their life expectancy and their stratification into risk groups (very-low, low, intermediate, high, and very high risk).[21] Risk groups are defined by assessing the tumor TNM classification, Gleason score, and PSA value, at a minimum. Likewise, the 2017 American Urological Association (AUA)/American Society of Radiation Oncology (ASTRO)/Society of Urologic Oncology (SUO) joint guidelines recommend a shared decision making approach to disease management of localized prostate cancer by counseling the patient regarding their risk category, in addition to consideration of patient values and preferences, life expectancy, and other individualized considerations (Strong Recommendation; Evidence Level: Grade A).[22] In 2018, ASCO endorsed the AUA/ASTRO/SUO guidelines for clinically localized prostate cancer noting 2 exceptions which cited the lack of evidence to support the use of cryotherapy in this setting.[23] In 2019, ASCO published a guideline regarding the use of screening for molecular biomarkers in patients with localized prostate cancer. ASCO notes that although molecular biomarkers may improve risk stratification when added to other standard measures, these assays are not recommended for routine use due to lack of prospective data and lack of information regarding improvements in long-term outcomes, such as quality of life, need for treatment or overall survival.[24]

Due to the increased risk of adverse effects associated with treatment and the lack of definitive evidence for benefit, the 4.2019 NCCN guideline recommends active surveillance for certain men depending on their risk group and estimated life expectancy. ASCO also supports active surveillance for patients with low-risk (Gleason score ≤ 6) localized prostate cancer.[25] The AUA/ASTRO/SUO guideline recommends active surveillance as the best available care option for very-low risk localized disease (Strong Recommendation; Evidence Level A), and this approach is also recommended as the preferable care option for most low-risk localized prostate cancer patients (Moderate Recommendation; Evidence Level: Grade B).[26] Patients undergoing active surveillance should be monitored for evidence of disease progression with the expectation to start therapy with curative intent if the cancer progresses. Studies have demonstrated that approximately two-thirds of men eligible for active surveillance successfully avoided treatment at 5 years and 55% of the active surveillance population remain untreated at 15 years.[27,28] Furthermore, other studies have demonstrated that in the proportion of men who do eventually require treatment, the delay in treatment does not seem to impact cure rate.[29]

Men with localized disease who are stratified as high or very high risk and who have a prolonged life expectancy may be treated with either surgery (radical prostatectomy) or radiation therapy with the addition of ADT therapy for 1 to 3 years (category 1) according to the NCCN guidelines.[30] The AUA/ASTRO/USO guidelines also recommend radical prostatectomy or radiotherapy plus ADT for both patients with intermediate-risk (Strong Recommendation; Evidence Level: Grade A) as well as patients with high-risk disease (Strong Recommendation; Evidence Level: Grade A).[31]

Biochemical failure, as determined by either PSA persistence or a subsequently rising PSA after treatment with either surgery or radiation, is an indication for ADT in most patients. To minimize adverse effects, intermittent ADT may be considered in men with biochemical failure but who do not have evidence of metastases. In this setting, intermittent ADT therapy has been shown to be non-inferior to continuous ADT with respect to survival and is associated with a better quality of life.[32]

Patients who experience disease progression (either radiographically or biochemically) while receiving ADT that is successfully suppressing serum testosterone to castrate levels, are described as having castration-recurrent (or resistant) prostate cancer (CRPC). CRPC may occur in either the nonmetastatic setting (NM-CRPC) which is usually diagnosed as a result of a rising PSA (biochemical disease progression) or in cases where distant metastases have occurred (metastatic castration-resistant prostate cancer [mCRPC]). For both NM-CRPC and mCRPC, continued ADT with maintenance of castrate serum levels of testosterone is recommended by all guidelines.[33,34,35] For patients with NM-CRPC who have a PSA doubling time (PSADT) of ≤ 10 months, NCCN guidelines recommend apalutamide, darolutamide, or enzalutamide (all category 1) or other secondary hormone therapy (category 2A).[36] The AUA guideline regarding CRPC was updated in 2018 to state that the addition of apalutamide or enzalutamide to ADT should be the standard treatment for NM-CRPC patients who are at high risk for developing metastatic disease (Standard; Evidence Level Grade A [apalutamide]/B [enzalutamide]).[37] The AUA guidelines have not been updated to include darolutamide at this time. An ASCO provisional clinical opinion (PCO) published in April 2017 states antiandrogens or CYP17 inhibitors (e.g., abiraterone, ketoconazole) may be considered for patients with NM-CRPC who are at high risk for metastatic disease (rapid PSADT or velocity) but, otherwise, secondary hormonal therapy is not suggested. This ASCO PCO, while still listed as current was published prior to the FDA approvals for apalutamide, darolutamide, and enzalutamide in this setting.[38]

The Institute for Clinical and Economic Review (ICER) published a final evidence report of the effectiveness and value of antiandrogen therapies for NM-CRPC.[39] For the use of either apalutamide or enzalutamide plus ADT in men with NM-CRPC who have a rapid PSADT (≤ 10 months), ICER states there is a substantial net health benefit for either agent when compared to ADT alone (both A rating). The ICER evaluation was conducted prior to the approval of darolutamide.

Advanced or Metastatic Prostate Cancer

Metastatic prostate cancer may be either metastatic castration-sensitive prostate cancer (mCSPC) or metastatic CRPC (mCRPC). ADT is the backbone of all regimens for the treatment of metastatic prostate cancer.[40] According to the NCCN principles of ADT for metastatic prostate cancer, the addition of a first-generation antiandrogen (bicalutamide, flutamide, or nilutamide) to LHRH agonist therapy may be utilized.[41] These agents should precede or coincide treatment with LHRH agonist therapy for a minimum of 7 days in patients with overt metastases as they may decrease the risk of tumor flare upon initiation of therapy with a LHRH agonist related to the initial surge in release of androgens. The peripheral androgen receptor blockade helps to mitigate the short-term painful symptoms of tumor flare. An LHRH agonist, LHRH antagonist, or orchiectomy also may be combined with abiraterone, enzalutamide, or apalutamide. The NCCN principles of ADT section now includes information regarding alternative dosing administration of abiraterone.[42] The labeled dose of abiraterone for metastatic prostate cancer is 1,000 mg orally once daily. According to the NCCN revised principles of ADT, abiraterone with prednisone can be administered at a dose of 250 mg/day following a low-fat breakfast or at a dose of 1,000 mg/day after an overnight fast.[43]

In April 2018, ASCO published a clinical practice guideline regarding the optimal therapy for mCSPC.[44] This guideline recommends the addition of either docetaxel or abiraterone to ADT in newly diagnosed patients with mCSPC because these regimens have shown a survival benefit compared to the previous standard of care in this setting, ADT therapy alone. Likewise, the NCCN guidelines for mCSPC now give category 1 recommendations to the addition of docetaxel, abiraterone plus prednisone, apalutamide,

or enzalutamide to ADT in this setting.[45] Abiraterone with methylprednisolone is a NCCN category 2B recommendation.

For the treatment of mCRPC, the NCCN guidelines stratify treatment recommendations based on the presence or absence of visceral metastases.[46] For mCRPC patients who have no visceral metastases, first-line therapeutic options include abiraterone acetate given in combination with either prednisone 5 mg once daily or methylprednisolone 4 mg orally twice daily (depending on the formulation of abiraterone utilized), enzalutamide, or docetaxel (all category 1 except abiraterone with methylprednisolone which is a category 2A recommendation). For mCRPC patients with visceral metastases, first-line therapy options include docetaxel (category 1), enzalutamide (category 1), or abiraterone with either prednisone or methylprednisolone (both category 2A). Abiraterone and enzalutamide have been shown to extend survival in patients who have progressed on docetaxel. Estramustine (Emcyt) increases toxicities without enhancing efficacy when added to docetaxel and, therefore, is not recommended per the NCCN guidelines.

An ASCO provisional clinical opinion (PCO) regarding second-line hormonal therapy for chemotherapy-naive mCRPC recommends continuation of ADT and the addition of either abiraterone acetate plus prednisone or enzalutamide) for patients who have radiographic evidence of metastases and minimal symptoms. These agents have been shown to significantly increase radiographic progression-free survival (PFS) and OS. (PCO type: evidence based; Strength of PCO: strong).[47]

ASCO's clinical practice guideline regarding systemic therapy of mCRPC cites a survival benefit and improved quality of life (QOL) with a favorable benefit-to-harm ratio for adding abiraterone acetate plus prednisone or enzalutamide to ADT.[48] Improved survival and QOL also occurs with docetaxel plus prednisone but this regimen is also associated with a moderate toxicity risk. The ASCO guidelines do not recommend estramustine due to lack of benefit and excess toxicity.

The AUA guidelines addressing CRPC recommend abiraterone acetate plus prednisone or enzalutamide or docetaxel for either asymptomatic or symptomatic mCRPC patients with a good performance status who have not previously been treated with docetaxel (Standard; Evidence Level Grade A [abiraterone plus prednisone and enzalutamide]/ Evidence Level Grade B for [docetaxel]).[49] Alternatively, first-generation antiandrogen therapy (flutamide, bicalutamide, or nilutamide) may be offered to patients who do not wish to receive or cannot receive standard therapy. These guidelines also endorse the use of abiraterone acetate plus prednisone or enzalutamide for patients with a poor performance status who have not received prior docetaxel therapy (Option; Evidence Level Grade C). Finally, the AUA guidelines recommend abiraterone plus prednisone (unless previously given), enzalutamide, or cabazitaxel for mCRPC patients with good performance status who have received prior docetaxel therapy. The AUA guidelines, like the ASCO and NCCN guidelines, do not recommend the use of estramustine.

With regard to sequencing of abiraterone acetate and enzalutamide for mCRPC, most of the published guidelines do not offer recommendations. Studies have demonstrated that abiraterone and enzalutamide are effective in both the pre-docetaxel and the post-docetaxel setting of mCRPC. Some of the guidelines favor the use of docetaxel upfront in patients who have more symptomatic, higher volume disease and a good performance status. One consideration with regard to sequencing these agents is that cross-resistance does occur between androgen-receptor targeting agents. While the response rate to enzalutamide after abiraterone appears to be about 15% to 30%, the response rate for abiraterone therapy after treatment with enzalutamide is likely < 10%.[50] The decision regarding

sequencing of docetaxel, abiraterone, and enzalutamide for mCRPC may also consider patient preference with respect to duration of therapy and cost issues.

PHARMACOLOGY[51,52,53,54,55,56,57,58,59,60]

Antiandrogen Therapies

Bicalutamide (Casodex), flutamide, and nilutamide (Nilandron) are all considered first-generation antiandrogen therapies while enzalutamide (Xtandi), darolutamide (Nubeqa), and apalutamide (Erleada) are considered second-generation antiandrogens.

Bicalutamide is a non-steroidal androgen receptor inhibitor. Bicalutamide competitively binds to cytosol androgen receptors to block the action of androgens on the target tissue.

Flutamide exerts its antiandrogenic action by inhibiting androgen uptake and/or by inhibiting binding of androgen in the target tissue.

Nilutamide has been shown *in vitro* to block the effects of testosterone at the androgen receptor level. *In vivo,* nilutamide interacts with the androgen receptor and prevents the normal androgenic response.

Enzalutamide is an androgen receptor antagonist. It competitively inhibits androgen binding to androgen receptors and inhibits androgen receptor nuclear translocation and interaction with deoxyribonucleic acid (DNA). The androgen-androgen receptor signaling pathway is important in CRPC. Enzalutamide is a pure androgen receptor antagonist that inhibits the androgen-androgen receptor pathway at the receptor and post-receptor ligand binding level.[61]

Apalutamide (Erleada) is an androgen receptor inhibitor that blocks translocation, transcription, and DNA binding of the androgen receptor. A metabolite, N-desmethyl apalutamide, also inhibits the androgen receptor, and accounts for an observed one-third of in vitro activity of apalutamide.

Similarly, darolutamide competitively inhibits androgen binding, translocation, and transcription. Its unique structure results in low penetration of the blood brain barrier and low affinity for gamma-aminobutyric acid type A ($GABA_A$) receptors, which is thought to impact its adverse effect profile.[62]

Androgen biosynthesis inhibitors

Abiraterone acetate (Zytiga, Yonsa), an androgen biosynthesis inhibitor, is converted to abiraterone which inhibits 17 α-hydroxylase/C17, 20-lyase (CYP17). CYP17 is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. While treatment with traditional ADT (LHRH agonists or bilateral orchiectomy) decreases androgen production in the testes, these therapies do not affect non-gonadal androgen production by the adrenals or in the tumor microenvironment and, therefore, abiraterone acetate provides an additional source of androgen depletion.

Other

Estramustine (Emcyt) is classified as a nitrogen mustard alkylating agent but has antimicrotubular activity resulting in the disassembly and arrest of cell division in the G_2/M phase of the cell cycle.[63] Estramustine also combines the nornitrogen mustard moiety with estradiol via a carbamate link. Prolonged treatment with estramustine produces elevated total plasma concentrations of estradiol that fall within ranges similar to the elevated estradiol levels found in prostate cancer patients given

conventional estradiol therapy and the hormonal effects are similar in these patients whether they are treated with estramustine or conventional estradiol.

PHARMACOKINETICS[64,65,66,67,68,69,70,71]

Drug	Half-Life (hr)	Tmax (hr)	Excretion (%)
abiraterone acetate (Zytiga, Yonsa*)	12	2	Feces: 88 Urine: 5
apalutamide (Erleada)	3 days	2	Feces: 24 Urine: 65
bicalutamide (Casodex)	5.8 days	31.3	--
darolutamide (Nubeqa)	20	4	Feces: 32.4 Urine: 63.4
enzalutamide (Xtandi)	5.8 (range, 2.8 to 10.2)	1 (range, 0.5 to 3)	Feces: 14 Urine:71
estramustine (Emcyt)	20–24	2–3	Predominantly non-renal
flutamide	6	2	Feces: 4 Urine: 96
nilutamide (Nilandron)	41–49	--	Feces: 1.4–7 Urine: 62

hr = hours; Tmax = time to maximum concentration

*Abiraterone acetate marketed under the trade name Yonsa is a micronized formulation that contains a smaller overall particle size when compared to abiraterone acetate marketed as the Zytiga formulation. Systemic exposure of abiraterone when given with food may differ between the 2 branded formulations. For the Zytiga formulation, abiraterone area under the curve was 5 to 10 fold higher when Zytiga is administered with a low-fat or high fat meal, respectively, compared to fasting. The abiraterone area under the curve was 4.4 fold higher when Yonsa was administered with a high-fat meal compared to fasting.

CONTRAINDICATIONS/WARNINGS[72,73,74,75,76,77,78,79,80]

Contraindications

The agents in this review are not indicated for use in women. Abiraterone acetate (Yonsa), and bicalutamide (Casodex) are contraindicated in women who are or may become pregnant. While no longer listed as a contraindication, abiraterone acetate (Zytiga) and enzalutamide (Xtandi) also should not be used in women who are or may become pregnant. Likewise, darolutamide (Nubeqa) and apalutamide (Erleada) have no contraindications but should not be used by women. These agents may cause fetal harm and potential loss of pregnancy.

Bicalutamide, flutamide, estramustine (Emcyt), and nilutamide (Nilandron) are contraindicated in patients with hypersensitivity to the active drug or any of the components. Allergic reactions and angioedema, at times involving the airway, have been reported with estramustine.

Flutamide and nilutamide are contraindicated in patients with severe hepatic impairment.

Nilutamide is contraindicated in patients with severe respiratory insufficiency.

Estramustine is contraindicated in patients with active thrombophlebitis or thromboembolic disorders, except in those cases where the actual tumor mass is the cause of the thromboembolic phenomenon and the physician feels the benefits of therapy may outweigh the risks.

Warnings

abiraterone acetate (Zytiga, Yonsa)

Abiraterone acetate may cause hypertension, hypokalemia, and fluid retention resulting from increased mineralocorticoid levels as a result of CYP17 inhibition. Hypertension should be controlled and hypokalemia corrected before treatment. Safety has not been established in patients with left ventricular ejection fraction (LVEF) < 50% or New York Heart Association (NYHA) Class III or Class IV heart failure due to clinical trial exclusion. Cases of QT prolongation and torsades de pointes have occurred in patients who develop hypokalemia while taking abiraterone acetate. Monitor blood pressure, serum potassium, serum phosphate levels, and symptoms of fluid retention at least monthly. Mineralocorticoid excess may also mask signs and symptoms of adrenocortical insufficiency that may result when abiraterone acetate is given in conjunction with prednisone. Increased dosage of corticosteroids may be indicated before, during, or after stressful situations in patients receiving a combination of abiraterone acetate and prednisone.

In postmarketing experience, cases of fulminant hepatitis and acute liver failure as well as death have been reported with abiraterone acetate. Patients with baseline moderate hepatic impairment receiving abiraterone acetate were more likely to experience elevated liver function tests (LFTs) than patients with baseline LFTs in the normal range, usually within the first 3 months. All patients should have their serum transaminases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), as well as bilirubin levels, measured prior to starting treatment. If baseline values are normal, monitoring should continue every 2 weeks for 3 months, and monthly thereafter. If baseline values are elevated, monitoring should occur every week for the first month, every 2 weeks for the following 2 months, and once a month thereafter. Treatment with abiraterone acetate should be interrupted if AST or ALT rise above 5 times the upper limit of normal (ULN) or bilirubin rises above 3 times the ULN. Treatment with abiraterone acetate should be permanently discontinued in patients who develop a concurrent elevation of ALT > 3 times the ULN and a total bilirubin > 2 times the ULN.

An increased rate of fractures and mortality was seen with abiraterone acetate (Zytiga) when used in combination with prednisone/prednisolone and radium 223 dichloride during a clinical trial; its use is not recommended in this combination outside of a clinical trial.

apalutamide (Erleada)

Falls and fractures have been reported in patients taking apalutamide. The median time to fracture in the randomized SPARTAN study was 314 days, with falls and fractures occurring in 16% and 12%, respectively, of patients receiving apalutamide versus 9% and 7%, respectively, of patients taking placebo; grade 3 and 4 fractures occurred in 3% of patients receiving apalutamide compared to 1% treated with placebo. The median time to fracture in the randomized TITAN study was 56 days, with fractures occurring in 9% of patients receiving apalutamide compared to 6% of placebo patients; grade 3 and 4 fractures occurred in 2% of apalutamide and placebo patients. Patients taking apalutamide should be monitored for fall and fracture risk and managed appropriately.

Seizures have also been observed in patients taking apalutamide. In the SPARTAN and TITAN studies, seizures occurred in 5 patients (0.4%) receiving apalutamide versus 1 patient (0.1%) taking placebo. If a patient develops a seizure during treatment, apalutamide should be permanently discontinued.

Ischemic cardiovascular events, including fatal events, have been reported in patients taking apalutamide. In the SPARTAN and TITAN studies, ischemic cardiovascular events occurred in 4% of

apalutamide-treated patients compared to 3% (SPARTAN) and 2% (TITAN) of patients given placebo. A total of 6 patients (0.5%) who received apalutamide died from an event compared with 2 patients (0.2%) who received placebo. Patients should be monitored for ischemic heart disease and discontinuation of apalutamide considered for grade 3 or 4 events.

Based on its mechanism of action, apalutamide can cause fetal harm when administered to a pregnant women.

bicalutamide (Casodex)

Serum transaminase levels should be monitored prior to starting treatment with bicalutamide and at regular intervals for the first 4 months of treatment and periodically thereafter. Severe hepatic injury and hepatic failure fatalities have been observed with bicalutamide.

Serious bleeding complications have occurred in patients taking a stable dose of a coumarin anticoagulant after days to weeks following introduction of bicalutamide. For patients receiving a coumarin anticoagulant, and after beginning bicalutamide, the prothrombin time (PT)/ international normalized ratio (INR) should be closely monitored and the anticoagulant dose adjusted accordingly.

Blood glucose monitoring should be considered in patients receiving bicalutamide in combination with a LHRH agonist. Diabetic patients should also be carefully monitored while receiving estramustine (Emcyt) because glucose tolerance may be decreased in these patients.

Gynecomastia and breast pain have been reported during treatment with bicalutamide (Casodex) as a single agent, as well as with flutamide given in conjunction with a LHRH agonist. Gynecomastia and impotence are known estrogenic effects and therefore may occur with the use of estramustine (Emcyt).

Antiandrogen therapy may cause morphological changes in spermatozoa. Although the effects of bicalutamide on sperm morphology has not been evaluated and no such changes have been reported, patients receiving bicalutamide and/or their partners should follow adequate contraception during and for 130 days after bicalutamide therapy.

darolutamide (Nubeqa)

Based on its mechanism of action, darolutamide can cause fetal harm when administered to a pregnant women.

enzalutamide (Xtandi)

Seizures occurred in 0.5% of patients receiving enzalutamide in clinical trials, which excluded most patients with predisposing risk factors for seizure. These seizures occurred from 13 to 1,776 days after initiation of enzalutamide and resolved after discontinuation of therapy. A single-arm trial was conducted to determine seizure risk in patients with one or more pre-disposing factors who take enzalutamide. This study revealed that 2.2% of patients (n=366) experienced a seizure while taking the medication. Patients should be advised of the risk of seizures and the resulting risk of sudden loss of consciousness. Enzalutamide should be permanently discontinued in patients who develop a seizure during treatment.

Reports of posterior reversible encephalopathy syndrome (PRES) have occurred in patients receiving enzalutamide. PRES is a neurological disorder which can present with rapidly evolving symptoms, including seizure, headache, lethargy, confusion, blindness, and other visual and neurological

disturbances, with or without associated hypertension. Discontinue enzalutamide in patients who develop PRES as confirmed by brain imaging.

Hypersensitivity reactions, including pharyngeal, lingual, labial, and facial edema, have occurred with enzalutamide; it should be permanently discontinued if a serious hypersensitivity reaction occurs.

In clinical trials, ischemic heart disease occurred more often in patients treated with enzalutamide compared to placebo (2.9% versus 1.3%, respectively) with 1.4% of enzalutamide patients experiencing grade 3 or 4 events as compared to 0.7% of placebo patients. These events were fatal in 0.4% of enzalutamide-treated patients as compared to 0.1% of placebo patients. Monitor for signs and symptoms and manage risk factors as appropriate; enzalutamide should be discontinued for grade 3 or 4 ischemic heart disease.

Falls and fractures have been reported with enzalutamide; evaluate patients for fracture and fall risk and manage risks according to guidelines. Falls were reported in 11% of enzalutamide-treated patients compared to 4% of placebo patients, and fractures occurred in 10% and 4% of patients, respectively, with grade 3 or 4 fractures observed in 3% of enzalutamide patients compared to 2% of placebo patients.

Based on its mechanism of action, enzalutamide can cause fetal harm when administered to a pregnant women.

estramustine (Emcyt)

Hypertension may occur with estramustine treatment and blood pressure should be monitored periodically.

There is an increased risk of thrombosis, including fatal and nonfatal myocardial infarction, in men receiving estrogens for prostate cancer and, therefore, estramustine should be used with caution in patients with a history of thrombophlebitis, thrombosis, thromboembolic disorders, cerebral vascular disease, or coronary artery disease.

Estramustine may cause fluid retention and, thus, an exacerbation of preexisting peripheral edema or congestive heart disease. Other conditions that may be impacted by fluid retention including epilepsy, migraine, or renal dysfunction should be monitored closely in patients receiving estramustine.

Estramustine should be administered with caution to patients with impaired liver function. Estramustine should be used with caution in patients with metabolic bone diseases associated with hypercalcemia or with renal insufficiency due to estramustine's influence on the metabolism of calcium and phosphorus. Prostate cancer patients with osteoblastic metastases are at risk for hypocalcemia and should have calcium levels closely monitored. Estramustine may cause mutagenic effects and patients should be advised to use contraceptive measures.

flutamide

Flutamide has a boxed warning regarding hepatoxicity; post-marketing reports of hospitalization, and, rarely, death due to liver failure have been reported with flutamide. The hepatic injury was reversible after discontinuation of therapy in some patients. Flutamide is not recommended in patients whose ALT values exceed 2 times the ULN. Liver function tests should be measured prior to starting treatment and monthly for the first 4 months and then periodically, as well as at the first signs and symptoms suggestive of liver dysfunction (nausea, vomiting, abdominal pain, fatigue, anorexia, flu-like symptoms,

hyperbilirubinuria, jaundice, or right upper quadrant tenderness). If the patient develops jaundice or has an ALT rise above 2 times the ULN, flutamide should be immediately discontinued and the patient should receive close follow-up until liver function test abnormalities have resolved.

Monitoring of methemoglobin levels should be considered in patients receiving flutamide who are susceptible to aniline toxicity, such as patients with glucose-6-phosphate dehydrogenase deficiency, hemoglobin M disease, or smokers. These patients may be at increased risk of methemoglobinemia, hemolytic anemia, and cholestatic jaundice due to potential toxicity from the 4-nitro-3-fluoro-methylaniline metabolite of flutamide.

nilutamide (Nilandron)

Nilutamide (Nilandron) has a boxed warning regarding the risk of interstitial pneumonitis. In controlled clinical trials, a 2% incidence was reported, but a small study in Japanese subjects showed that 8 out of 47 patients (17%) developed interstitial pneumonitis. Symptoms including exertional dyspnea, cough, chest pain, and fever, along with chest X-rays showing interstitial changes, have been reported. Most cases occurred within the first 3 months of treatment and most were reversed with discontinuation of therapy. A chest X-ray should be performed prior to initiating therapy with nilutamide and consideration should be given to performing baseline pulmonary function tests. Any patient developing new or worsening shortness of breath should report these symptoms promptly and nilutamide should be immediately discontinued until it can be determined if the symptoms are related to nilutamide administration.

Hepatotoxicity has occurred with nilutamide and generally occurs within the first 3 to 4 months of treatment. Serum transaminase levels should be measured prior to beginning treatment with nilutamide, at regular intervals for the first 4 months of treatment, and periodically thereafter. Liver function tests (LFTs) should also be drawn if the patient develops signs or symptoms of liver dysfunction such as nausea, vomiting, abdominal pain, fatigue, anorexia, dark urine, jaundice, “flu-like” symptoms, or right upper quadrant tenderness. If the patient has jaundice or their ALT increases to above 2 times the ULN, nilutamide should be immediately discontinued until liver function test abnormalities have resolved.

Isolated cases of aplastic anemia have been reported in which a causal relationship with nilutamide could not be ascertained during post-marketing surveillance.

DRUG INTERACTIONS[81,82,83,84,85,86,87,88,89]

Substrates of CYP3A4

The R-stereoisomer of bicalutamide (Casodex) is an inhibitor of CYP3A4 and caution should be used when bicalutamide is co-administered with CYP3A4 substrates. Enzalutamide (Xtandi) is a strong CYP3A4 inducer. Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus) should be avoided as enzalutamide may decrease their exposure. Apalutamide (Erleada) is a strong CYP3A4 inducer. Medications metabolized largely by CYP3A4 can have lower exposure if co-administered with apalutamide, and substitutions for these medications are recommended if possible.

Co-administration of CYP3A4 Inducers

Administration of abiraterone acetate (Zytiga, Yonsa) and enzalutamide with potent inducers of CYP3A4 (e.g., phenytoin, phenobarbital, carbamazepine, rifampin, rifabutin) may result in decreases in plasma concentrations of abiraterone acetate and enzalutamide. Concurrent administration of abiraterone acetate and enzalutamide with strong inducers of CYP3A4 should be avoided or used with caution. If abiraterone acetate must be co-administered with one of these agents, its dosing frequency should be increased to twice daily during coadministration. Concomitant use of darolutamide (Nubeqa) with a combined P-glycoprotein (P-gp) and strong or moderate CYP3A4 inducer decreases plasma concentrations of darolutamide and should be avoided. Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin, St. John's wort) may also reduce the plasma expose of enzalutamide and should be avoided, if possible.

Co-administration of CYP3A4 Inhibitors

Co-administration of a strong CYP3A4 inhibitor (itraconazole) increased the composite area under the curve (AUC) of enzalutamide by 1.3 fold in healthy volunteers. Co-administration of a strong inhibitor of CYP3A4 may increase exposure to apalutamide. The dose of apalutamide should be reduced based on tolerability, but no initial dose adjustment is recommended. Concomitant use of darolutamide with a combined P-gp and strong CYP3A4 inhibitor increases plasma concentrations of darolutamide. Monitor patients more frequently for adverse effects and adjust dosage as needed.

CYP2B6 and CYP2C8 Enzyme Inhibitors or Substrates

Abiraterone acetate is an inhibitor of CYP2D6 and CYP2C8. The use of abiraterone acetate with substrates of CYP2D6 that have a narrow therapeutic index (e.g., thioridazine) should be avoided. If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug. In a drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (a CYP2C8 substrate) was increased by 46% when given with a single dose of abiraterone acetate. Patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

CYP2B6 and CYP2C8 Inhibitors

Co-administration of a strong CYP2C8 inhibitor, such as gemfibrozil, with enzalutamide should be avoided, if possible. When the co-administration of a strong CYP2C8 inhibitor with enzalutamide cannot be avoided, reduce the dose of enzalutamide. Co-administration of a strong inhibitor of CYP2C8 may increase exposure to apalutamide. The dose of apalutamide should be reduced based on tolerability, but no initial dose adjustment is recommended.

CYP2B6, CYP2C8, CYP2C9, and CYP2C19

The effects of CYP2C8 inducers (e.g., rifampin) on the pharmacokinetics of enzalutamide have not been evaluated *in vivo.* However, co-administration of enzalutamide with strong or moderate CYP2C8 inducers may alter the serum concentrations of enzalutamide and should be avoided, if possible. Selection of a concomitant medication with no or minimal CYP2C8 induction potential is recommended.

Enzalutamide is a moderate CYP2C9 and CYP2C19 inducer in humans. Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP2C9 (e.g., phenytoin,

warfarin) or CYP2C19 (e.g., S-mephenytoin) should be avoided as enzalutamide may decrease their exposure.

Apalutamide is a strong inducer of CYP2C19 and a weak inducer of CYP2C9. Medications metabolized by these pathways may result in lower exposure if co-administered with apalutamide. Substitutions for these medications are recommended if possible.

Warfarin

Prothrombin times should be closely monitored in patients receiving coumarin anticoagulants in conjunction with apalutamide, bicalutamide, enzalutamide, flutamide, or nilutamide (Nilandron). Increases in prothrombin time have been noted in patients receiving long-term warfarin therapy after flutamide or bicalutamide was initiated. If enzalutamide, flutamide, bicalutamide, or nilutamide must be administered with warfarin, conduct additional INR monitoring and adjust the anticoagulant dose, as necessary.

Other

Nilutamide inhibits CYP-450 isoenzymes and, therefore, drugs with a narrow therapeutic window, such as phenytoin and theophylline, could have delayed elimination and increases in their serum half-life leading to a toxic level. The dosage of these drugs or others with a similar metabolism may need to be modified if they are administered concomitantly with nilutamide.

Milk, milk products and calcium-rich foods or drugs may impair the absorption of estramustine (Emcyt).

Darolutamide inhibits Breast Cancer Resistance Protein (BCRP) transporter, which may increase the risk of BCRP substrate-related toxicities; avoid concomitant use or decrease substrate dose if concomitant use cannot be avoided.

ADVERSE EFFECTS[90,91,92,93,94,95,96,97,98]

Drug	Fluid Retention/ Edema	Hypertension	Increased LFTs	Hot Flush	Diarrhea	Anemia	Hematuria	Dyspnea	Nausea
abiraterone acetate (Zytiga) + prednisone (n=791) placebo + prednisone (n=394) post docetaxel	26.7 (18.3)	8.5 (6.9)	11.1-30.6 (10.4-36.3)	19 (16.8)	17.6 (13.5)	nr	nr	nr	nr
abiraterone acetate (Zytiga) + prednisone (n=542) placebo + prednisone (n=540) chemotherapy-naïve	25.1 (20.7)	21.6 (17.8)	41.9/37.3 (29.1/28.47)	22.3 (18.1)	21.6 (17.8)	nr	10.3 (5.6)	11.8 (9.6)	nr
apalutamide (Erleada) + GnRH analog or bilateral orchiectomy (n=803) placebo + GnRH analog or bilateral orchiectomy (n=398) nonmetastatic CRPC	11 (9)	25 (20)	nr	14 (9)	20 (15)	70 (64)	nr	nr	18 (16)
apalutamide (Erleada) + GnRH analog or bilateral orchiectomy or placebo (n=524) + GnRH analog or bilateral orchiectomy (n=527) metastatic CSPC	nr	18 (16)	nr	23 (16)	9 (6)	nr	nr	nr	nr
bicalutamide (plus LHRH analog; n=401)	13	8	7	53	12	11	12	13	15
darolutamide (Nubeqa) (n=954) placebo (n=554) nonmetastatic CRPC	nr	reported	16-23 (7-13)	nr	reported	nr	≥ 1	nr	reported
enzalutamide (Xtandi) (n=800) placebo (n=399) mCRPC post docetaxel	15.4 (13.3)	6.4 (2.8)	10 (18)	20.3 (10.3)	21.8 (17.5)	nr	6.6 (4.5)	nr	nr

Adverse Effects (continued)

Drug	Fluid Retention/ Edema	Hypertension	Increased LFTs	Hot Flush	Diarrhea	Anemia	Hematuria	Dyspnea	Nausea
enzalutamide (Xtandi) (n=871) placebo (n=844) mCRPC chemotherapy-naïve	11.5 (8.2)	14.2 (4.1)	10 (16)	18 (7.8)	16.8 (14.3)	nr	8.8 (5.8)	11 (8.5)	nr
enzalutamide (Xtandi) (n=930) placebo (n=465) nonmetastatic CRPC	nr	12 (5.2)	nr	13 (7.7)	nr	nr	nr	nr	11 (8.6)
enzalutamide (Xtandi) (n=572) placebo (n=574) metastatic CSPC	nr	8 (5.6)	reported	27 (22)	reported	nr	nr	nr	nr
estramustine (Emcyt) (n=93) diethylstilbestrol (DES) (n=93)	19 (17)	nr	31 (28)	0 (1)	12 (11)	nr	nr	11 (3)	15 (8)
flutamide +LHRH analog (n=294) placebo + LHRH analog (n=285)	4	1	nr	61 (57)	12 (4)	6	nr	nr	11 (10)
nilutamide +leuprolide (n=209) placebo + leuprolide (n=202)	12.4 (17.3)	9.1 (9.9)	9.1-12.9 (8.9-13.9)	66.5 (59.4)	2	7.2 (6.4)	8.1 (7.9)	10.5 (7.4)	23.9 (8.4)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for placebo group are reported in parentheses. nr = not reported.

There was a higher frequency of visual disturbances (e.g., impaired adaptation to darkness, abnormal vision, and colored vision) which resulted in therapy discontinuation of nilutamide in 1% to 2% of patients. Interstitial pneumonitis has also been experienced by a small proportion of patients (2%) treated with nilutamide.

In the pooled clinical trial data for abiraterone acetate (mCRPC) following chemotherapy [Study 1] and mCRPC prior to chemotherapy [Study 2]), cardiac failure occurred more often in patients treated with abiraterone acetate compared to patients given placebo (2.1% versus 0.7%). Grade 3 to 4 cardiac failure occurred in 1.6% of patients taking abiraterone acetate and led to 5 treatment discontinuations and 2 deaths. Grade 3 to 4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and 1 death due to cardiac failure in the placebo group.

Data from 4 pooled, placebo-controlled trials evaluating enzalutamide in the following patient populations: metastatic CRPC following chemotherapy, chemotherapy-naïve metastatic CRPC, non-metastatic CRPC, and metastatic CSPC. In these studies, laboratory abnormalities occurring in ≥ 5% of patients and in > 2% of enzalutamide-treated patients compared to placebo, respectively, were neutrophil count decreased (20% versus 17%), white blood cell decreased (17% versus 9.8%), hyperglycemia (83% versus 75%), hypermagnesemia (16% versus 13%), hyponatremia (13% versus 8.6%), and hypercalcemia (6.8% versus 4.5%). The TERRAIN clinical study compared enzalutamide to bicalutamide in chemotherapy-naïve metastatic CRPC. In this study, common adverse reactions occurring in ≥ 10% of enzalutamide patients compared to bicalutamide, respectively, were asthenic conditions (32% versus 23%), back pain (19% versus 18%), musculoskeletal pain (16% versus 14%), hot flush (15% versus 11%), hypertension (14% versus 7.4%), nausea (14% versus 18%), constipation (13% for both), diarrhea (12% versus 9%), upper respiratory tract infection (12% versus 6.3%), and weight loss (11% versus 7.9%).

In the SPARTAN trial conducted in patients with nonmetastatic CRPC, apalutamide was associated with increased risk of rash, occurring in 24% of patients treated with apalutamide versus 6% treated with placebo. The rash resolved in 81% of patients and recurred in about half of patients when rechallenged. Hypothyroidism occurred in 8% of patients treated with apalutamide in the SPARTAN trial compared to 2% of patients treated with placebo. Thyroid replacement therapy should be initiated when clinically indicated. In the TITAN trial conducted in patients with metastatic CSPC, 2% of patients discontinued treatment due to rash which occurred in 28% of apalutamide-treated patients compared to 9% of placebo patients. Pruritus also occurred in more apalutamide patients (11%) than placebo patients (5%). Hypothyroidism occurred in 4% of apalutamide patients compared to 1% of placebo patients. White blood cell counts were decreased in more apalutamide-treated patients (27% versus 19% placebo), and hypertriglyceridemia occurred in more apalutamide patients as well (17% versus 12% placebo).

A randomized clinical trial of abiraterone plus prednisone/prednisolone in combination with radium Ra 223 dichloride found an increased incidence of fractures (28.6% versus 11.4%) and deaths (38.5% versus 35.5%) in patients who received that combination compared to patients who received placebo, respectively, in combination with abiraterone plus prednisone/prednisolone. Abiraterone plus prednisone/prednisolone in combination with radium Ra 223 dichloride is not recommended.

Neutrophil count decrease occurred in more often with darolutamide compared to placebo (20% versus 9%, all grades, respectively). Other clinically important adverse events occurring in ≥ 2% of darolutamide-treated patients compared to placebo, respectively, were ischemic heart disease (4%

versus 3.4%) and heart failure (2.1% versus 0.9%). Laboratory abnormalities occurring more often in darolutamide patients than placebo patients, respectively, were neutrophil count decreased (20% versus 9%), AST increased (23% versus 14%), and bilirubin increased (16% versus 7%).

SPECIAL POPULATIONS[99,100,101,102,103,104,105,106,107,108]

Pediatrics

The safety and effectiveness of abiraterone acetate (Zytiga, Yonsa), apalutamide (Erleada), bicalutamide (Casodex), darolutamide (Nubeqa), enzalutamide (Xtandi), flutamide, estramustine (Emcyt), and nilutamide (Nilandron) have not been established in pediatric patients.

Pregnancy

The agents in this review are not intended for use in women.

In compliance with the Pregnancy and Lactation Labeling Rule (PLLR), the Pregnancy Category X designation for abiraterone acetate, bicalutamide and enzalutamide have been replaced with descriptive information. Apalutamide and darolutamide also have descriptive information regarding pregnancy risk. The use of bicalutamide is contraindicated in pregnant women due to the risk of fetal harm. Use of apalutamide, darolutamide, or enzalutamide in pregnant women can cause fetal harm and loss of pregnancy. Therapy with antiandrogens such as bicalutamide may cause morphological changes in spermatozoa. Males with female partners of reproductive potential should use effective contraception during treatment with abiraterone acetate and for 3 weeks following the last dose. Males with partners of reproductive potential should be advised to use effective contraception during treatment and for 130 days after the final dose of bicalutamide. Males with female partners of reproductive potential should use effective contraception during treatment with darolutamide and for 1 week following the last dose. Males with female partners of reproductive potential who are receiving apalutamide or enzalutamide should use effective contraception during treatment and for 3 months after the final dose.

Nilutamide is Pregnancy Category C. Animal reproduction studies have not been conducted with nilutamide.

Both estradiol and nitrogen mustard are known to be mutagenic; some patients who had been impotent while on estrogen therapy regained potency with estramustine. Since estramustine may cause male-mediated teratogenicity, males receiving estramustine and their female partners of reproductive age should be advised to use contraceptive measures.

Apalutamide and flutamide have not been studied in women.

Geriatrics

No clinical differences in responses between elderly and younger patients have been reported with abiraterone acetate or darolutamide, but greater sensitivity of some older individuals cannot be ruled out.

No significant relationship between age and serum levels of total bicalutamide or the active R-enantiomer has been demonstrated.

Adverse events were similar between patients less than 75 years old and those greater than 75 years old in clinical trials with enzalutamide.

There were no differences in overall effectiveness between patients 75 years and over, patients 65 years and over, and younger patients treated with apalutamide during the SPARTAN and TITAN trials. The incidence of adverse effects were modestly higher in patients 75 years and over versus patients 65 years and over. The proportion of patients experiencing falls also increased with increasing age.

Renal Impairment

No dosage adjustments are necessary for abiraterone acetate, flutamide, or bicalutamide for renal insufficiency.

No dose reduction of darolutamide is necessary for patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73 m^2). A dose reduction (300 mg twice daily) is recommended for patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) not on dialysis. The use of darolutamide in patients with end stage renal disease has not been studied.

No initial dosage adjustment of enzalutamide is necessary for patients with mild to moderate renal impairment (CrCl, 30 to ≤ 89 mL/min). Patients with severe renal impairment (CrCl < 30 mL/min) and end stage renal disease have not been studied.

No dose adjustment of apalutamide is recommended for patients with mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 89 mL/min/1.73m^2). Patients with severe renal impairment or end stage renal disease (eGFR ≤ 29 mL/min/1.73m^2) have not been studied.

Hepatic Impairment

No dosage adjustment of abiraterone acetate is necessary for patients with baseline mild hepatic impairment. Patients with baseline moderate hepatic impairment (Child-Pugh Class B) should have their dose of abiraterone acetate reduced to 250 mg once daily. Abiraterone acetate should not be used in patients with baseline severe hepatic impairment (Child-Pugh Class C). Abiraterone acetate should be permanently discontinued in patients who develop a concurrent elevation of ALT > 5 times the ULN and total bilirubin > 3 times the ULN.

Bicalutamide should be used with caution in patients with moderate to severe hepatic impairment. Limited data in subjects with severe hepatic impairment suggest that excretion of bicalutamide may be delayed.

No dosage adjustment of darolutamide is required for patients with mild hepatic impairment (Child-Pugh Class A). A dose reduction (300 mg twice daily) is recommended in patients with moderate hepatic impairment (Child-Pugh Class B). There are no data on the use of darolutamide in patients with severe hepatic impairment (Child-Pugh Class C).

No initial dosage adjustment of enzalutamide is necessary for patients with baseline mild or moderate hepatic impairment (Child-Pugh Class A or B). There are no data on the use of enzalutamide in patients with severe baseline hepatic impairment (Child-Pugh Class C).

No dose adjustment of apalutamide is recommended for patients with mild or moderate (Child-Pugh A or B) hepatic impairment. Patients with severe hepatic impairment (Child-Pugh C) have not been studied.

There is no information on the pharmacokinetics of flutamide in the setting of hepatic impairment.

Nilutamide is contraindicated with severe hepatic impairment.

DOSAGES[109,110,111,112,113,114,115,116,117]

Drug	Dose	Administration Notes	Available Strengths
abiraterone acetate (Zytiga)	▪ mCRPC: 1,000 mg (two 500 mg tablets or four 250 mg tablets) once daily along with prednisone 5 mg twice daily ▪ Metastatic high-risk CSPC: 1,000 mg (two 500 mg tablets or four 250 mg tablets) once daily along with prednisone 5 mg once daily	Take on an empty stomach 1 hour before or 2 hours after meals Swallow tablets whole; do not crush or chew tablets	250 mg tablet (uncoated), 500 mg tablet (film-coated)
abiraterone acetate (Yonsa)	▪ mCRPC: 500 mg (four 125 mg tablets) once daily in combination with methylprednisolone 4 mg administered orally twice daily	May be taken with or without food; tablets should be swallowed whole with water; do not crush or chew tablets	125 mg tablet
apalutamide (Erleada)	▪ 240 mg (four 60 mg tablets) once daily	Take with or without food at the same time each day, and swallow the tablets whole	60 mg tablet
bicalutamide (Casodex)	▪ 50 mg once daily ▪ Treatment should be started at the same time as treatment with an LHRH agonist	Take with or without food at the same time each day (morning or evening)	50 mg tablet
darolutamide (Nubeqa)	▪ 600 mg (two 300 mg tablets) twice daily	Administer with food; swallow whole	300 mg tablet
enzalutamide (Xtandi)	▪ 160 mg (four 40 mg capsules) once daily	Take with or without food Swallow capsules whole; do not chew, dissolve or open the capsules	40 mg capsule
estramustine (Emcyt)	▪ 14 mg/kg/day divided into 3 to 4 oral daily doses; (doses often range from 10 mg/kg/day to 16 mg/kg/day)	Store in the refrigerator; Take 1 hour before or 2 hours after meals with water; Milk, milk products and calcium-rich foods or drugs must not be taken simultaneously	140 mg capsule
flutamide	▪ 250 mg (two 125 mg capsules) every 8 hours for a total daily dose of 750 mg	Stage D2 metastatic carcinoma: treatment should be started at the same time as treatment with an LHRH agonist Stage B_2-C prostatic carcinoma: treatment should be started with goserelin acetate implant 8 weeks prior initiating radiation and continue during radiation therapy	125 mg capsule
nilutamide (Nilandron)	▪ 300 mg once a day for 30 days, followed thereafter by 150 mg once a day	Take with or without food	150 mg tablet

See individual product labeling for dose adjustment details.

Patients taking abiraterone acetate (Zytiga, Yonsa), darolutamide (Nubeqa), enzalutamide (Xtandi), or apalutamide (Erleada) should also receive a co-administered GnRH analog or have had a bilateral orchiectomy.

To avoid medication errors and overdose, awareness of the different formulations of abiraterone acetate is required. Different formulations of abiraterone acetate have different dosing regimens and may also have different food effects that may impact systemic exposure to abiraterone acetate.

Patients with baseline moderate hepatic impairment (Child-Pugh Class B) should have their dose of abiraterone acetate reduced to 250 mg once daily for the Zytiga formulation and to 125 mg once daily for the Yonsa formulation. If elevations in AST and/or ALT > 5x ULN or total bilirubin> 3x ULN occur in patients with baseline moderate hepatic impairment, discontinue abiraterone acetate and do not re-treat patients with abiraterone acetate.

For patients who develop hepatotoxicity during treatment (ALT and/or AST ≥ 5x ULN or total bilirubin ≥ 3x ULN), interrupt treatment with abiraterone acetate. Re-treatment with abiraterone acetate at a reduced dose of Zytiga 750 mg once daily or Yonsa 375 mg once daily may occur only after LFTs have returned to the patient's baseline or AST/ALT ≤ 2.5x ULN and total bilirubin is ≤ 1.5x ULN. If these reduced doses result in a recurrence of hepatotoxicity, treatment should be interrupted again and may be restarted at further reduced doses of Zytiga 500 once daily or Yonsa 250 mg once daily if LFTS return to the patient's baseline or meet the parameters described above. If hepatotoxicity recurs at the reduced doses of Zytiga 500 once daily or Yonsa 250 mg once daily, discontinue treatment with abiraterone acetate. Permanently discontinue abiraterone acetate for patients who develop a concurrent elevation of ALT > 3x ULN and total bilirubin >2x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed using the term “prostate cancer” and drugs in this class, and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of ≥ 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

abiraterone acetate (Zytiga)/prednisone versus placebo/prednisone – pre- or post-chemotherapy

COU-AA-301: A randomized, placebo-controlled, multicenter, phase 3 trial enrolled 1,195 patients with metastatic castration-resistant prostate cancer who had received prior therapy with docetaxel to

receive either abiraterone acetate (Zytiga) 1,000 mg orally daily with prednisone 5 mg orally twice daily (n=797) or placebo once daily with prednisone 5 mg orally twice daily (n=398).[118,119] Treatment was continued until disease progression (defined as a 25% increase in PSA over the patient's baseline/nadir together with protocol-defined radiographic progression and symptomatic or clinical progression), initiation of new treatment, unacceptable toxicity, or withdrawal. The study was unblinded after a pre-specified interim analysis displayed a statistically significant improvement in overall survival (OS) for the abiraterone acetate (Zytiga) arm. Patients treated with abiraterone acetate (Zytiga) showed an improved OS rate (mean of 14.8 months) compared to patients in the placebo arm (mean 10.9 months) (p<0.0001). An updated OS analysis showed a survival of 15.8 months versus 11.2 months for abiraterone acetate (Zytiga) versus placebo (hazard ratio [HR], 0.74; 95% CI, 0.64 to 0.86; p<0.0001).[120,121] The most common adverse events (each in < 1% of abiraterone acetate patients) leading to discontinuation of the drug were increased AST and/or ALT, urosepsis, or cardiac failure. Significant improvements in health-related quality of life (HRQoL) scores, as measured by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire, were seen in 48% of the patients receiving abiraterone acetate (Zytiga) compared with 32% of patients receiving only prednisone (p<0.001). Also, the median time to deterioration of the FACT-P score was significantly longer (p<0.001) in patients receiving abiraterone acetate (Zytiga) compared to prednisone alone (59.9 weeks versus 36.1 weeks).[122]

COU-AA-302: Abiraterone acetate (Zytiga) was evaluated in patients with metastatic castration-resistant prostate cancer who had not received prior chemotherapy.[123] In a double-blind study, 1,088 patients were randomized to receive abiraterone acetate (Zytiga) 1,000 mg plus prednisone (5 mg twice daily) or placebo plus prednisone. The co-primary endpoints were radiographic progression-free survival (PFS) and overall survival (OS). Median time to radiographic progression was 16.5 months in the abiraterone-prednisone group and 8.3 months in the prednisone-alone group (HR, 0.53; 95% CI, 0.45 to 0.62; p<0.001). Patients receiving abiraterone acetate (Zytiga) also had an extended time until the initiation of opiate analgesia or treatment with cytotoxic chemotherapy, as well as delays in onset of pain and decline in health-related quality of life. At a median follow up of 49.2 months, median OS was significantly longer in the abiraterone acetate (Zytiga) group than in the placebo group (34.7 months versus 30.3 months (HR, 0.81; 95% CI, 0.7 to 0.93; p=0.0033]). This improved OS for the abiraterone acetate group occurred despite the fact that 44% of patients initially randomized to prednisone alone eventually crossed over to receive abiraterone acetate plus prednisone.[124] Fatigue, arthralgia, and peripheral edema were more commonly reported in the abiraterone-prednisone group. Grade 3 to 4 adverse events included cardiac disorders (8% versus 4%), increased ALT (6% versus < 1%), and hypertension (5% versus 3%) in the abiraterone acetate (Zytiga) groups versus the prednisone alone arms, respectively. Subsequent analyses have demonstrated patients randomized to the abiraterone acetate (Zytiga) arm also reported superior HRQoL scores including decreased pain.[125]

abiraterone acetate (Zytiga) plus prednisone plus androgen-deprivation therapy (ADT) versus placebo plus ADT – metastatic, castration-sensitive prostate cancer (mCSPC)

LATITUDE: A phase 3, multinational, randomized placebo-controlled trial evaluated abiraterone acetate and prednisone added to ADT compared to placebo added to ADT in patients with high-risk, newly diagnosed, mCSPC.[126] A total of 1,199 patients diagnosed with mCSPC in the preceding 3 months were randomized in a 1:1 ratio to receive abiraterone acetate plus prednisone plus ADT (n=597) or placebo plus ADT (n=602). The 2 primary efficacy endpoints were radiographic PFS and OS. The results were based on the first interim analysis of OS at a median follow-up of 30.4 months. There were 593

radiographic progressions or deaths at the time of the interim analysis. Due to a recommendation from the independent safety committee in response to the interim analysis, the trial was unblinded and patients in the placebo group began to receive abiraterone acetate. OS was significantly higher in the abiraterone acetate group, with a relative risk of death 38% lower than placebo (hazard ratio [HR], 0.62; 95% confidence interval [CI], 0.51 to 0.76; p<0.001). Radiographic PFS in the abiraterone acetate group was 33 months and 14.8 months in the placebo group (HR, 0.47; 95% CI, 0.39 to 0.55; p<0.001). Secondary and exploratory endpoints included patients with a PSA response and median time to pain progression, PSA progression, next symptomatic skeletal event, time to receipt of chemotherapy, and subsequent prostate cancer therapy. For all secondary and exploratory endpoints, abiraterone acetate was significantly superior to placebo.

abiraterone acetate fine particle formulation (Yonsa) plus prednisolone versus abiraterone acetate originator product (Zytiga) plus prednisone – metastatic castration-resistant prostate cancer (mCRPC)

STAAR was a multicenter, randomized, open-label study designed to assess the therapeutic equivalence, steady-state pharmacokinetics and safety of abiraterone acetate fine particle formulation (AAFP) 500 mg plus methylprednisolone compared to the originator abiraterone acetate (OAA) 1,000 mg plus prednisone in men with mCRPC.[127] Patients were randomized 1:1 to either AAFP 500 mg daily plus 4 mg methylprednisolone orally twice daily (n=24) or OAA 1,000 mg daily plus prednisone 5 mg twice daily (n=29) for 84 days. Assessment endpoints included serum testosterone, serum PSA, trough steady-state abiraterone levels, and safety. The averaged absolute testosterone levels ≤ 1 ng/dL were achieved in 25% of AAFP-treated patients and 17% of OAA-treated patients. Both agents led to similar PSA-50 response rates as well as similar abiraterone trough levels. No new safety concerns were detected.

apalutamide (Erleada) plus ADT versus placebo plus ADT – non-metastatic CRPC (NM-CRPC)

SPARTAN: A phase 3, multicenter, double-blind, placebo-controlled clinical trial evaluated the effectiveness of apalutamide in patients with NM-CRPC.[128] A total of 1,207 patients with non-metastatic disease confirmed by blinded independent central review (BICR) and who had a prostate specific antigen doubling time (PSADT) ≤ 10 months, were randomized to receive 240 mg of apalutamide (n=806) once daily or placebo (n=401). All patients in the trial received concomitant GnRH analog or had a bilateral orchiectomy. At baseline, the median age was 74 years (range, 48 to 97 years), with 26% of patients ≥ 80 years of age. The primary endpoint for the study was metastasis-free survival (MFS), calculated as the time from randomization to the time of first evidence of distant metastasis or death due to any cause. Additional secondary endpoints used were time to metastasis (TTM), PFS, time to symptomatic progression, time to the initiation of chemotherapy, and OS. Improvement of MFS was observed in the apalutamide treated group with a median MFS of 40.5 months versus 16.2 months in the placebo group, (HR, 0.28; 95% CI, 0.23 to 0.35; p<0.0001). Statistically significant improvements in TTM of 40.5 months for apalutamide treated patients versus 16.6 months for placebo (HR, 0.27; 95% CI, 0.22 to 0.34; p<0.0001) and median PFS of 40.5 versus 14.7 months (HR, 0.29; 95% CI, 0.24 to 0.36; p<0.0001) were also observed. Median time to symptomatic progression and median time to initiation of chemotherapy had not been reached while median OS in the placebo arm was 39 months and had not yet been reached in the apalutamide arm.

apalutamide (Erleada) plus ADT versus placebo plus ADT – metastatic CSPC (mCSPC)

TITAN: A phase 3, multinational, double-blind, placebo-controlled clinical trial evaluated the effectiveness of apalutamide in patients with mCSPC.[129] A total of 1,052 patients with adenocarcinoma of the prostate and distant metastatic disease based on ≥ 1 lesion visible on bone scanning who had castration-sensitive disease (patients had not progressed while receiving ADT) were randomized to receive 240 mg of apalutamide (n=525) once daily or placebo (n=527). All patients received continuous ADT. At baseline, the median age was 68 years (range, 43 to 94 years) with the majority of patients having an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 and most patients having newly diagnosed metastatic disease rather than relapsed metastatic disease following an initial diagnosis of localized disease. The primary endpoints were radiographic PFS (time from randomization to first imaging-based documentation of progression or death, whichever occurred first) and OS (time from randomization to death from any cause). Secondary endpoints included time to cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, and time to skeletal-related event. At 24 months, radiographic PFS was 68.2% in the apalutamide-treated patients compared with 47.5% with placebo patients (HR, 0.48; 95% CI, 0.39 to 0.6; p<0.001) demonstrating a 52% reduction in the risk for disease progression or death with apalutamide compared to placebo. OS was also significantly improved with apalutamide at 24 months with 82.4% of apalutamide-treated patients still alive compared to 73.5% of placebo patients (HR, 0.67; 95% CI, 0.51 to 0.89; p=0.005) corresponding with a 33% reduced risk of death in the apalutamide-treated patients. Although the time to cytotoxic chemotherapy was significantly improved with apalutamide compared to placebo, the time to pain progression did not demonstrate a statistically significant difference between study arms. As a result, no further statistical analysis of secondary endpoints was conducted on the basis of the prespecified hierarchical testing sequence.

bicalutamide (Casodex) + LHRH analog versus flutamide + LHRH analog – advanced prostate cancer

A multicenter, double-blind, controlled clinical trial with 813 patients with previously untreated advanced prostate cancer were randomized to receive bicalutamide (Casodex) 50 mg once daily or flutamide 250 mg three times daily, each in combination with an LHRH analog (either goserelin acetate implant or leuprolide acetate depot).[130] After a median follow-up of 160 weeks, 213 (52.7%) patients treated with bicalutamide (Casodex)-LHRH analog therapy and 235 (57.5%) patients treated with flutamide-LHRH analog therapy had died. There was no significant difference in survival or any other clinical measure of efficacy between the 2 groups. Quality of life questionnaires did not indicate consistently significant differences between the 2 treatment groups.

darolutamide (Nubeqa) plus ADT versus placebo plus ADT – non-metastatic CRPC (NM-CRPC)

ARAMIS: A phase 3, multicenter, double-blind trial randomized 1,509 patients with NM-CRPC and a PSA doubling time of ≤ 10 months to either darolutamide (n=955) 600 mg twice daily or placebo (n=554), while both arms continued to receive standard ADT.[131] The primary endpoint was metastasis-free survival (MFS), defined as time to radiographic progression or death, whichever occurred first. Secondary endpoints included OS, time to first cytotoxic chemotherapy, and a variety of endpoints related to pain and subsequent need for pain management interventions. The median MFS was 40.4 months in the darolutamide arm and 18.4 months in the placebo arm (HR, 0.41; 95% CI, 0.34 to 0.5;

p<0.001). Darolutamide was statistically superior to placebo in all of the defined secondary endpoints, although the median OS had not been reached in either arm at the time of the reported data analysis. Grade 3 or higher adverse effects occurred in 24.7% of patients receiving darolutamide and 19.5% of those receiving placebo. The percentage of patients who discontinued the medication due to adverse effects was similar in both arms (8.9% of darolutamide plus ADT patients compared to 8.7% of patients receiving placebo plus ADT). Fatigue, reported in 12.1% of darolutamide-treated patients, was the only reported adverse event that occurred in more than 10% of patients in either arm of the trial. The rates of falls and nonpathologic fractures, seizures, and CNS adverse effects in patients receiving darolutamide were similar to those seen in the placebo group.

enzalutamide (Xtandi) plus ADT versus placebo plus ADT – non-metastatic CRPC (NM-CRPC)

PROSPER: A phase 3, double-blind trial randomized 1,401 patients with NM-CRPC and a PSA doubling time of ≤ 10 months in a 2:1 fashion to either receive ADT plus enzalutamide 160 mg daily or ADT plus placebo.[132] The median PSA doubling time of the enrolled study population was 3.7 months. The primary endpoint was MFS which was defined as the time to radiographic progression or death, whichever occurred first. Secondary endpoints included time to PSA progression, PSA response rate, time to first use of a subsequent antineoplastic therapy, QOL assessments, OS and safety. The median MFS was 36.6 months in the enzalutamide group compared to 14.7 months in the placebo group (HR, 0.29; 95% CI, 0.24 to 0.35; p<0.001). Time to PSA progression (37.2 months versus 3.9 months, respectively; p<0.001) and time to first use of a subsequent antineoplastic (39.6 months versus 17.7 months, respectively; p<0.001) for enzalutamide versus placebo, respectively, were statistically significant. At the time of data reporting, median OS had not been reached in either group. Grade 3 or higher adverse events as well as drug discontinuation for adverse events occurred more frequently in the enzalutamide group compared to the placebo group. The most common adverse effect in the patients receiving enzalutamide was fatigue. Adverse events of special interest that occurred more frequently in patients receiving enzalutamide included hypertension (12% versus 5%, respectively), major cardiovascular events which included myocardial infarction, hemorrhagic or ischemic cerebrovascular conditions and heart failure (5% versus 3%, respectively) and mental impairment disorders including memory impairment, disturbance in attention, cognitive disorders, amnesia and various forms of dementia (5% versus 2%, respectively). Falls and non-pathologic fractures were also more common in patients receiving enzalutamide compared to patients who received placebo. There were nine (1%) patient deaths due to cardiac events in the enzalutamide group and 2 cardiac related deaths in the placebo group (< 1%).

enzalutamide (Xtandi) versus placebo – mCRPC pre- or post-chemotherapy

AFFIRM: The safety and effectiveness of enzalutamide (Xtandi) (160 mg once daily) were evaluated in a randomized, placebo-controlled, multicenter phase 3 study of 1,199 (enzalutamide [Xtandi], n=800; placebo, n=399) patients with metastatic castration-resistant prostate cancer (CRPC) who had received prior treatment with docetaxel.[133] All patients continued androgen deprivation therapy. Patients were allowed, but not required to, continue or initiate glucocorticoids. During the trial, 48% of enzalutamide (Xtandi) patients and 46% of placebo patients received glucocorticoids. Median overall survival (primary endpoint) for patients receiving enzalutamide (Xtandi) was significantly higher at 18.4 months versus 13.6 months for patients who received placebo (HR, 0.63; 95% CI, 0.53 to 0.75; p<0.0001). Secondary endpoints were time to first skeletal-related adverse event; change in pain severity from

baseline, pain palliation, and progression at week 13; overall improvement in HRQoL; and time to HRQoL deterioration. Enzalutamide was statistically significantly superior to placebo in all of these secondary endpoints.[134] Of the 1,199 patients in the AFFIRM trial, a total of 938 patients (674 enzalutamide, 264 placebo) were evaluable for changes in the Functional Assessment of Cancer Therapy-Prostate (FACT-P) as measured at baseline and at least 1 post-baseline evaluation during treatment. After 25 weeks, the mean FACT-P score decreased by 1.52 points with enzalutamide (Xtandi) compared with a decrease of 13.73 points with placebo (p<0.001).[135]

PREVAIL was a randomized, double-blind, placebo-controlled, multinational, phase 3 trial comparing enzalutamide (Xtandi) 160 mg daily to placebo in 1,717 men with mCRPC who were chemotherapy-naïve.[136] Co-primary endpoints were radiographic PFS and OS. Secondary endpoints included the time until initiation of cytotoxic chemotherapy and the time until first skeletal-related event. At 12 months of follow-up, the rate of radiographic PFS was 65% versus 14% in the enzalutamide (Xtandi) versus placebo groups, respectively (HR, 0.19; 95% CI, 0.15 to 0.23; p<0.001). At the planned interim analysis with 22 months of follow up, treatment with enzalutamide (Xtandi) resulted in a 29% decrease in the risk of death (HR, 0.71; 95% CI, 0.6 to 0.84; p<0.001). An updated analysis of OS after an additional 116 deaths had occurred determined that the estimated median survival was 31 months in the placebo group and had not yet been reached in the enzalutamide (Xtandi) group. The median time to initiation of cytotoxic chemotherapy was 28 months in the enzalutamide (Xtandi) group compared with 10.8 months in the placebo group (HR, 0.35; p<0.001). At a median of 31 months, 32% of patients in the enzalutamide (Xtandi) group compared to 37% of patients in the placebo group had experienced a skeletal-related event (HR, 0.72; p<0.001). Patients in the enzalutamide (Xtandi) arm had higher rates of fatigue, back pain, constipation, hot flush, hypertension, falls, and arthralgia compared to patients in the placebo arm. The most common grade 3 or higher adverse event in the enzalutamide group was hypertension. Health-related quality of life (HRQoL) during the PREVAIL trial was assessed at baseline and during treatment using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaires. Median time to deterioration in FACT-P score was 11.3 months (95% CI, 11.1 to 13.9) in the enzalutamide (Xtandi) group and 5.6 months (95% CI, 5.5 to 5.6) in the placebo group (HR, 0.62; 95% CI, 0.54 to 0.72; p<0.0001). A significantly greater proportion of patients in the enzalutamide (Xtandi) group (40%) than in the placebo group (23%) reported clinically meaningful improvements in FACT-P total score.[137]

enzalutamide (Xtandi) versus bicalutamide – mCRPC

TERRAIN: A double-blind, phase 2 study randomized 184 patients to enzalutamide 160 mg/day and 191 patients to bicalutamide 50 mg/day in addition to ADT.[138] All men had mCRPC. ADT was accomplished either by bilateral orchiectomy or administration of a LHRH agonist or antagonist which was started before or after the diagnosis of metastases. The primary endpoint was PFS. Median follow up time was 20 months for the enzalutamide group and 16.7 months for the bicalutamide group. Patients in the enzalutamide group had significantly improved median PFS compared to the bicalutamide group (15.7 months versus 5.8 months; HR, 0.44; 95% CI, 0.34 to 0.57; p<0.0001). Adverse events that occurred more commonly in the enzalutamide arm were fatigue, back pain and hot flush while adverse events that occurred more frequently in the bicalutamide arm included nausea, constipation and arthralgia. Serious adverse events were reported by 31% of enzalutamide-treated patients and 23% of bicalutamide-treated patients. There is an open-label portion of this trial that is still ongoing which allows patients at the end of the double-blind period to receive open-label enzalutamide at the discretion of the patient and study investigator.

enzalutamide (Xtandi) versus bicalutamide – NM-CRPC and mCRPC

STRIVE: A double blind, phase 2 trial randomized men with nonmetastatic CRPC (n=139) as well as men with mCRPC (n=257) to either enzalutamide 160 mg/day or bicalutamide 50 mg/day; ADT was continued in both arms.[139] The primary endpoint was PFS. The patients randomized to enzalutamide had a median PFS of 19.4 months compared with a median PFS of 5.7 months for the patients receiving bicalutamide (HR, 0.24; 95% CI, 0.18 to 0.31; p<0.001). Enzalutamide was superior in all measured secondary endpoints as well including time to PSA progression, proportion of patients with a ≥ 50% PSA response and radiographic PFS in patients with metastatic disease. The favorable treatment effect of enzalutamide compared to bicalutamide was consistent across both the patients with non-metastatic CRPC and the patients with mCRPC. The observed adverse effect profile was consistent with that from phase 3 enzalutamide trials.

enzalutamide (Xtandi) versus placebo – mCSPC

ARCHES: A double-blind, multinational, phase 3 trial randomized 1,150 men with metastatic hormone-sensitive prostate cancer (mHSPC) 1:1 to either enzalutamide 160 mg/day or placebo; ADT was continued in both arms.[140] Adult males with pathologically confirmed prostate adenocarcinoma, without neuroendocrine differentiation, signet-cell, or small-cell features that had hormone-sensitive metastatic disease were eligible for enrollment. The 2 treatment groups were similar at baseline in terms of patient age (median, 70 years), Caucasian race (~80%), confirmed metastases at screening (> 92% for both groups), and majority of patients having not received prior docetaxel chemotherapy (~82% of patients). More than two-thirds of patients had received ≤ 3 months of ADT and 17.9% of patients had received prior docetaxel chemotherapy. The primary endpoint was radiographic PFS as assessed by independent central review or death from any cause, whichever occurred first. PFS was defined as time from randomization to first objective evidence of disease progression. Secondary endpoints included time to PSA progression, time to initiation of new antineoplastic therapy, PSA undetectable rate, objective response rate (ORR), time to deterioration of urinary symptoms, and OS. A significant reduction in the risk for radiographic disease progression or death was seen with enzalutamide compared to placebo (15.9% versus 34.9%, respectively; HR, 0.39 [95% CI, 0.3 to 0.5; p<0.001]). At the time of data analysis, the median radiographic PFS had not been reached in the enzalutamide arm compared to 19 months (95% CI, 16.6 to 22.2 months) for placebo patients. Enzalutamide was demonstrated to be superior to placebo for the secondary endpoints of time to PSA progression, time to initiation of new antineoplastic therapy, PSA undetectable rate, and ORR. Data for the OS endpoint was immature at the time of analysis, and enzalutamide was not found to significantly improve the time to deterioration of urinary symptoms compared to placebo.

enzalutamide (Xtandi) versus bicalutamide (Casodex), nilutamide (Nilandron), or flutamide – mCSPC

ENZAMET: An open-label, multinational, phase 3 trial randomized 1,125 men with metastatic, hormone-sensitive prostate cancer (mHSPC) 1:1 to either enzalutamide 160 mg/day or to bicalutamide, nilutamide, or flutamide (standard-care group); testosterone suppression therapy was continued in both arms and was started up to 12 weeks before randomization.[141] Based on patient and physician discretion, early administration of docetaxel with testosterone suppression was allowed following an update to the protocol and was used in determining stratification prior to randomization. Therapy was continued until disease progression or unacceptable toxicity. Patients were required to have prostatic

adenocarcinoma with metastases visible on a CT or bone scan with technetium-99 or both. The primary endpoint was OS based on time from randomization to death from any cause or the date at which the patient was last known to be alive. Secondary endpoints evaluated PSA PFS and clinical PFS. Patients enrolled were an average of 68 years old with the majority of patients (> 50%) having high volume disease with an average of 3 months since diagnosis of metastasis. The most common prior therapies were LHRH analogs (> 70% of patients) or anti-androgen therapy (> 50% of patients) started within the 12 weeks prior to randomization. At the time of analysis, there were significantly fewer deaths in the enzalutamide group compared to the standard-care group (102 deaths versus 143 deaths; HR, 0.67 [95% CI, 0.52 to 0.86; p=0.002]) with Kaplan-Meier estimates of OS at 3 years of 80% for enzalutamide-treated patients and 72% for standard-care patients. PSA PFS was also significantly improved with enzalutamide compared to standard-care group (174 events versus 333 events, respectively; HR, 0.39 [95% CI, 0.33 to 0.47; p<0.001]). Clinical PFS was also significantly improved with enzalutamide compared to standard-care (167 events versus 320 events, respectively; HR, 0.4 [95% CI, 0.33 to 0.49; p<0.001]). Overall, enzalutamide therapy demonstrated longer OS and PFS compared to standard-care with bicalutamide, nilutamide, or flutamide in men with mHSPC.

estramustine (Emcyt) versus diethylstilbestrol (DES)

A double blind, randomized crossover trial included 236 patients with stage D prostate cancer who received either estramustine or diethylstilbestrol.[142] The majority of patients (n=170) had not undergone surgical castration. Patients received their assigned drug until time of disease progression at which time they crossed over to the other treatment. The primary endpoint was time between start of therapy and objective progression of disease. Uncastrated patients randomized to receive estramustine first-line had significantly longer duration without progression than those treated with DES as first-line therapy (p<0.01). Estramustine was also superior to DES in all pain subgroups (little or no pain, moderate to severe pain) as well as whether or not the patient had a history of cardiovascular disease. Estramustine was superior in both patients < 70 years of age and those > 70 years. The secondary therapy received at time of crossover was less effective than the first assigned therapy in both groups: 46% of patients receiving estramustine and 40% of patients receiving DES had no progression at 6 months on second-line therapy. Adverse events were similar for both drugs with the exception of more gastrointestinal toxicity associated with estramustine.

nilutamide (Nilandron) versus placebo – post-orchiectomy

A double-blind, randomized, multicenter trial compared 225 patients treated with orchiectomy and nilutamide (Nilandron) and 232 patients treated with orchiectomy and placebo. The progression-free survival (PFS) was 14.9 months in the placebo group and 21.1 months in the nilutamide (Nilandron) group, while median survival was 23.6 months in the placebo group and 27.3 months in the nilutamide (Nilandron) group.[143]

SUMMARY

Prostate cancer is the most commonly diagnosed malignancy (excluding non-melanoma skin cancers) for men in the United States (US). However, it only accounts for 10% of all cancer deaths in this population. Prostate-specific antigen (PSA) screening is a controversial early detection strategy. Many cases of prostate cancer detected through PSA screening may be an indolent form of the cancer that is unlikely to cause morbidity or mortality. Most guidelines now recommend a shared decision making

approach, based on a patient discussion with a clinician regarding the potential benefits and harms associated with PSA screening.

For men diagnosed with early stage prostate cancer who lack negative prognostic indicators, active surveillance is a reasonable treatment option due to the harms associated with treatment and the potential lack of benefit for treatment of these men. Patients undergoing active surveillance should be monitored for evidence of disease progression with the expectation to start therapy with curative intent if the cancer progresses.

Due to the hormone responsiveness of most prostate cancers, androgen deprivation therapy (ADT) is a cornerstone of prostate cancer treatment. ADT can be accomplished by utilizing either a surgical approach (bilateral orchiectomy) or a medical approach with the administration of a luteinizing hormone-releasing hormone (LHRH) agonist, or antagonist, to suppress serum testosterone concentrations to castrate levels (< 50 ng/dL). ADT is utilized both in the adjuvant setting of localized disease for patients with a high risk of disease recurrence and in the setting of advanced or metastatic prostate cancer as primary systemic therapy.

When employing medical castration with LHRH agonists, an initial surge in androgen production occurs prior to leading to hypogonadism. Bicalutamide (Casodex) and flutamide act as androgen receptor antagonists to diminish the side effects associated with this initial androgen surge known as tumor flare. The current role of bicalutamide and flutamide in therapy is primarily in this setting of prophylaxis of tumor flare upon initiation of an LHRH agonist. Nilutamide (Nilandron), also an antiandrogen, is indicated for use in combination with surgical castration for the treatment of metastatic prostate cancer.

The standard of care for the treatment of metastatic castration-sensitive prostate cancer (mCSPC) has recently changed. Historically, ADT alone had been considered the standard first-line treatment of patients with mCSPC; however, recent trials have established that combination therapy with either docetaxel or abiraterone acetate or antiandrogens in addition to ADT represents the new standard of care based on significant improvements in overall survival with combination therapy. In February 2018, the FDA approved abiraterone acetate (Zytiga) in combination with prednisone for metastatic high-risk castration-sensitive prostate cancer, and in 2019, the FDA expanded the indication for the androgen receptor inhibitors apalutamide (Erleada) and enzalutamide (Xtandi) to include mCSPC.

In most cases of advanced prostate cancer, the disease will eventually stop responding to traditional ADT and become categorized as castration-recurrent (or resistant) prostate cancer (CRPC). CRPC may be seen in the setting of non-metastatic disease (NM-CRPC) or with metastatic disease (mCRPC). For patients without radiographic proven metastatic disease, castration resistance typically manifests as biochemical failure signaled by a rising PSA. For both NM-CRPC and mCRPC, continued ADT with maintenance of castrate serum levels of testosterone is universally recommended by all guidelines. For patients with NM-CRPC who have a PSA doubling time (PSADT) of ≤ 10 months, the National Comprehensive Cancer Network (NCCN) recommends apalutamide, enzalutamide, or darolutamide (Nubeqa) (all category 1). In addition, all 3 agents are now are FDA-approved for use in NM-CRPC as they have been shown to improve metastasis-free survival compared to ADT therapy alone in this setting.

For mCRPC, combination therapy with ADT and either docetaxel, abiraterone acetate, or enzalutamide is now considered the standard of care due to demonstration of improved overall survival with combination therapy. Both abiraterone acetate and enzalutamide have efficacy in both the pre-

docetaxel and the post-docetaxel setting. Appropriate sequencing of these agents in the setting of mCRPC is still under investigation.

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