

Prostate Cancer Subclass I/II Drugs Oral Oncology

Executive Summary

- Clinical symptoms, prostate pathology, metastatic state, and castration sensitivity are main features that determine prostate cancer clinical states and appropriate treatment. Drug selection is also dependent on prior treatment history.
- Many patients currently progress from the older to newer agents given the natural course of the disease.
- Patients and providers may choose to cycle through older and newer agents if they were previously successful.
- All oral agents are more efficacious than placebo. There are no head-to-head trials of the newer oral agents.
- Among the older agents, bicalutamide (Casodex) is preferred over others due to ease of dosing and a favorable side effect profile. Bicalutamide has been shown to be as effective as flutamide, which is dosed three times daily. Nilutamide (Nilandron) and flutamide (Eulexin) are used sequentially and are often considered second-line agents.
- In addition to a unique mechanism of action, the requirement for concomitant steroids when prescribing abiraterone acetate (Zytiga) differentiates it from enzalutamide (Xtandi). Adverse effects with Zytiga result from its mechanism of action and require close patient monitoring for hypertension, electrolytes, and edema due to mineralocorticoid excess.
- Both Zytiga and Xtandi have been shown to extend survival in the post-chemotherapeutic patient as well as those that are chemotherapy-naïve.

Background

- No oncology drug class review, to include prostate cancer, has been previously completed. As a result, none of the products that are part of this review have been previously designated nonformulary.
- There were an estimated 233,000 new cases of prostate cancer in 2014 and an estimated 29,480 will die from the disease.
- The number of newly diagnosed prostate cancer cases has increased significantly in the last several decades with the advent of prostate specific antigen (PSA) screening that detects many early-stage prostate cancers. As a result of PSA screening, more patients are diagnosed with asymptomatic localized prostate cancer.
- MHS expenditures and utilization of all oral oncology products, including prostate specific agents, are increasing.
- Initially approved in the late 1980s and mid-1990s, the older agents have been a mainstay in treatment of prostate cancer.
- The older agents are all indicated for use in conjunction with LHRH analogues.
- Prior authorizations are currently in place reflecting FDA indications of the newer agents. Zytiga and Xtandi are indicated in the treatment of metastatic castration-resistant prostate cancer.
- Since 2011, 2 oral agents, Zytiga and Xtandi entered the market. Zytiga was initially approved for use post chemotherapy in April 2011. Zytiga proceeded to gain approval for use in the chemotherapy-naïve patient in December 2012. Xtandi was initially approved for post chemotherapy in August 2012, and then for chemotherapy-naïve patients in September 2014.
- See Table 1 for the drugs in the two subclasses.

Table 1: Drugs in the Class

Prostate Cancer Oral Agents			
Subclass I Anti-Androgens (Older Agents)			
Generic	bicalutamide	nilutamide	flutamide
Brand	Casodex	Nilandron	Eulexin
Manufacturer	AstraZeneca	Covis	Schering
Approval Yr	1989	1995	1996
Dose	50 mg	150 mg	125 mg
Frequency	Daily	2 tabs daily x 1 month, then once daily	Three times daily
Indication	In combination with LHRH analogue for treatment of metastatic prostate cancer	In combination with surgical castration for metastatic prostate cancer	In combination with LHRH agonists for metastatic prostate cancer
Subclass II Survival Prolonging (Newer Agents)			
Generic	abiraterone acetate	enzalutamide	
Brand	Zytiga	Xtandi	
Manufacturer	Janssen/JNJ	Astellas/Medivation	
Approval Yr	2011, 2012	2012, 2014	
Dose	1000 mg	160 mg	
Frequency	Daily, with prednisone twice daily	Daily	
Indication	mCRPC	mCRPC	

- The older agents are all generically available. There are no generic formulations approved by the FDA for the newer agents.
 - FDA considers overall survival and progression-free survival key endpoints in the treatment of prostate cancer. Unblinding of studies limits the statistical validity of results as findings become a combination of those who had received placebo and can prevent agents from showing statistical significance for endpoints determined at the start of the study. Unblinding occurs when there is a significant enough trend towards improvement in overall survival that warrants allowing patients on placebo the ethical option of treatment with the active agent.
- Agents not reviewed but used in treatment of prostate cancer: docetaxel (Taxotere), cabazitaxel (Jevtana), radium 223 (Xofigo), sipuleucel-T (Provenge), LHRH agonists/antagonists, ketoconazole, steroids.

Summary of the Evidence

Subclass I Anti-Androgens (Older Agents)

- Efficacy: The literature provides limited data regarding the clinical benefits of older anti-androgens.
 - American Society of Clinical Oncology and Cancer Care Ontario guidelines (ASCO/CCO 2014) found older agents to be less efficacious than more recently developed drugs. The older agents are more accessible for some patients in low resource contexts. They can be considered particularly for patients with lower disease burden or limited other options. The use of older anti-androgens should be accompanied by discussion of unknown survival and quality of life benefits.
 - The National Comprehensive Cancer Network guidelines (NCCN 2015) recommend considering addition of or switching to older agents in patients who are chemotherapy-naïve or with minimal symptoms.
- There has been one head-to-head trial of bicalutamide and flutamide (Schellhammer 1999). The clinical outcomes evaluated included time to progression and time to death. There was a trend favoring bicalutamide for both primary endpoints but they were not statistically significant.
- The Prostate Cancer Trialists Collaborative Group completed a meta-analysis comprised of 20 trials evaluating the benefit of addition of anti-androgens (nilutamide and flutamide) in 6500 men to androgen suppression via medical or surgical intervention:
 - The combined results showed questionable clinical significance for the combined treatment. There was no difference in 2-year survival and a 2.9% difference (95% CI 0.4–5.4%) in 5-year survival. Quality of life in the setting of combined androgen blockade was worse in the first few months of therapy.
- Safety: In regards to safety, the older agents each have unique safety issues. Flutamide is known to cause a greater number of gastrointestinal side effects. Nilutamide causes patients to have difficulties with light to dark adaptation, alcohol intolerance, and pulmonary toxicity, which limit its use. All the older agents have issues with gynecomastia, hot flashes, and hepatic toxicity.
- Anti-androgen therapy, when used, should be in combination with LHRH agonists. Anti-androgen monotherapy appears to be less effective and is not recommended by guidelines (NCCN, ASCO/CCO) but is often used due to preservation of sexual function and libido.

Subclass II Survival Prolonging (Newer agents)

- Efficacy: Both Zytiga and Xtandi have independently demonstrated clinical benefit and thus represent a new standard of care in metastatic castrate-resistant prostate cancer, irrespective of chemotherapy status.
 - NCCN 2015 recommends that choice of agent in this clinical state should be based on clinical considerations, patient preferences, prior treatment, presence or absence of visceral disease, symptoms, and potential side effects.
 - ASCO/CCO 2014 found that Zytiga and Xtandi were both therapies that demonstrated survival and quality of life benefits and should be offered to patients as options for treatment.
- Zytiga had a 3.6 and 5.2 month overall survival difference in treated patients in pivotal studies (COU-301, COU-302) that lead to FDA approval. In COU-301, unblinding occurred at a preplanned interim analysis since results exceeded pre-planned criteria for study termination. In COU-302, the data monitoring committee recommended unblinding data and allowing for crossover of patients from placebo to treatment after second interim analysis, again limiting statistical validity.
- As compared with placebo, treatment with Zytiga:
 - Decreased the risk of death by 35% (55% of expected events in placebo arm versus 42% of expected events in treatment arm) in post-chemotherapy setting and 25% reduction (34% of expected events in placebo arm versus 27% of expected events) in the chemotherapy-naïve setting.
- Xtandi had a 4.8 and 2.2 month overall survival difference in treated patients in pivotal studies (AFFIRM, PREVAIL) that led to FDA approval. In the AFFIRM trial, the data monitoring committee recommended halting and unblinding at first interim analysis as there was a statistically significant and clinically meaningful benefit observed. In PREVAIL, the

committee recommended halting and unblinding after the first interim analysis showed statistically significant benefits in overall survival and radiographic progression free survival.

- As compared with placebo, treatment with Xtandi:
 - Decreased the risk of death by 37% (50% of expected events in placebo arm versus 41% expected events in treatment arm) in post-chemotherapy setting and 29% (82% of expected events in placebo arm versus 73% expected events in treatment arm) in the chemotherapy-naïve setting.
- There are currently no head-to-head trials, predictive models, or biomarkers to identify those who are likely to benefit from either option. There are preliminary findings based on case series to suggest some resistance to later therapies that result from utilizing either agent first.
- There are studies underway evaluating simultaneous use of the agents to take advantage of the different mechanisms of action.
- In regards to safety, the products have distinct adverse reaction profiles.
 - Zytiga causes CYP17 inhibition, which produces mineralocorticoid excess resulting in adrenocortical insufficiency, hypertension, hypokalemia, and fluid retention. Prednisone coadministration helps to mitigate the severity of side effects but does not eliminate them. Liver function abnormalities, electrolytes, and blood pressure need to be monitored. Caution is recommended in patients with history of cardiovascular disease and severe liver dysfunction.
 - Xtandi is well tolerated but was associated with seizure concerns in earlier Phase I and II studies. In the initial Phase III post-chemotherapy trial (AFFIRM), patients at risk of seizure were ineligible for enrollment. In the chemotherapy-naïve trial (PREVAIL) no seizure limitations were placed on enrollees and 0.9% had a seizure as an adverse effect. Xtandi also had higher percentage (7.2%) of patients that had hypertension as an adverse event.

References

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Abbreviations

The following abbreviations are used in this review:

AE	– adverse event(s)
ASCO/CCO	– American Society of Clinical Oncology/Cancer Care Ontario
CaP	– prostate cancer
LHRH	– luteinizing hormone-releasing hormone
mCRPC	– metastatic castration-resistant prostate cancer
NCCN	– National Comprehensive Cancer Network