Practical guide to the use of enzalutamide

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Introduction: *We summarize the development, definitive trials, and practical use of enzalutamide for practicing urologists and medical oncologists.*
The care paradigm for patients with metastatic castration resistant prostate cancer (mCRPC) is a changing landscape, with the ongoing discovery of drivers of cancer progression yielding actionable targets for drug development. Since 2010, sipuleucel-T, cabazitaxel, abiraterone with prednisone, radium 223 and enzalutamide have been Food and Drug Administration approved based upon improvement in overall survival in men with mCRPC.
Materials and methods: *A MEDLINE search for "enzalutamide or MDV3100" yielded 258 results. Prospective trials were reviewed. Abstracts from ASCO (American Society of Clinical Oncology) meetings and press release information were included where applicable.*
Results: *Enzalutamide, an oral inhibitor of the androgen receptor pathway, was approved in 2012 based upon improvement in overall survival of 4.8 months in men with mCRPC following docetaxel versus placebo. Measures of prostate-specific antigen (PSA) and radiographic response, and clinically significant endpoints such as quality of life improvement and toxicity parameters favored enzalutamide. Toxicity is modest with asthenia and fatigue being most common, with a 1% incidence of seizure reported, though patients can be selected to decrease this risk.*
Conclusion: *Enzalutamide is an effective oral therapy for mCRPC, with an overall survival benefit before and following chemotherapy. Toxicity is mild, and seizure risk can be mitigated by careful patient selection. Ongoing studies will help determine the best sequence of novel agents for prostate cancer, along with safe and effective combinations of therapies. Better understanding of tumor characteristics, particularly reliance on the androgen receptor pathway, will lead to personalized approaches to prostate cancer therapy.*

Key Words: enzalutamide, androgen receptor, metastatic prostate cancer, castration resistant, docetaxel refractory

Introduction

Enzalutamide is an oral potent inhibitor of the androgen receptor (AR) signaling pathway, with actions including inhibition of ligand/receptor binding, nuclear translocation of activated androgen receptor, and inhibition of AR regulated nuclear transcription.[1] This inhibition of the AR signaling pathway by enzalutamide is dramatically more potent than bicalutamide, and is without potential agonist properties that are sometimes acquired with bicalutamide treatment. In the phase I/II trial, the enzalutamide (formerly MDV3100) dose range was 30 mg to 600 mg daily, with ketoconazole and docetaxel naïve men experiencing the most robust responses.[2] Seizures were confirmed or suspected in one patient each at 600 mg, 480 mg, and 360 mg cohorts, suggesting dose dependency of this toxicity.

Phase III AFFIRM study: efficacy and toxicity

Based upon data from the phase I/II trial, 160 mg daily was the dose selected for the pivotal phase III AFFIRM trial, in which men with metastatic castration resistant prostate cancer (mCRPC) and disease progression following docetaxel were randomized to receive enzalutamide versus placebo.[3] Enzalutamide treatment led to a median overall survival of 18.4 months (95% CI, 17.3 months to not yet reached)

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compared to 13.6 months (95% CI, 11.3 months to 15.8 months) in the placebo cohort. This improvement in median survival by 4.8 months, corresponding to a 37% reduction in the risk of death compared with placebo, was determined when the study was stopped early at a planned interim analysis (HR for death in enzalutamide group 0.63, $p < 0.001$). Enzalutamide treatment led to superior outcomes in prostate-specific antigen (PSA) reduction > 50%, radiographic response rate, time to progression and time to first skeletal related event over placebo.

Toxicity rates between the two groups were similar, despite a significantly longer on treatment time for men in the enzalutamide cohort. More men in the enzalutamide arm experienced fatigue, diarrhea, hot flashes, musculoskeletal pain, headache and hypertension. Of note, five patients in the enzalutamide cohort experienced seizure activity, with possible predisposing comorbid brain metastasis, organic brain disease, and adverse drug interaction cited as possible contributing factors. In this and in ongoing trials, patients with history of brain metastasis, seizure, head trauma with loss of consciousness, transient ischemic attack in the last 12 months, stroke, brain arteriovenous malformation, or use of concomitant medications which could lower the seizure threshold were excluded, and thus the safety of enzalutamide in these populations is not known, see Table 1.

Which subsets of patients benefit from enzalutamide?

The cohorts in the AFFIRM study were well matched for all factors at baseline, including by Gleason grade, with median Gleason grade of 8 in each group, and Gleason grade > 7 in 50.4% and 52.4% in the enzalutamide and placebo cohorts respectively. The benefit of enzalutamide was seen across all pre-specified subgroups, including those < 65 versus 65 and older, by geographic treatment location, baseline pain score and type of disease progression at study entry (PSA or radiographic). Post-hoc subgroup analyses demonstrated similar benefit of enzalutamide in men < 75 versus 75 and older, as well as benefit in those with liver and lung metastasis when compared to placebo.[4,5] Clinical benefit, assessed by health related quality of life scores, was significantly better for men treated on enzalutamide, with improvements in physical, social, emotional and functional well-being compared to those treated with placebo.[6] Evaluation of patients who were found to be long term responders, on study agent for > 12 or > 18 months, were noted to have less baseline disease burden, longer time from cancer diagnosis to study enrollment, and improved rates of biochemical and radiographic response to enzalutamide compared to those on study < 12 months.[7] Multivariate analysis of hazard ratio for death demonstrated survival advantage for those with ECOG performance status 0 or 1 compared to 2, lower baseline pain score, PSA as compared to radiographic progression, no visceral disease, lower values of LDH and higher values of hemoglobin at study entry.[3] Gleason grade at diagnosis was not included in this multivariate analysis due to substantial missing data, thus the effect of Gleason grade upon efficacy of enzalutamide post docetaxel is not known.

Should steroids be prescribed concomitantly with enzalutamide?

Many men treated post docetaxel are on long term steroid therapy, and may represent a fundamentally different population than men not on, or who have not progressed on steroids. The authors sought to understand differences between patients with disease progression on steroids at enrollment (approximately 30% in each cohort), compared to those who were not on steroids upon outcomes in the AFFIRM study in post-hoc analyses.[8] A multivariate analysis showed median overall survival was 11 months versus median survival not met in men with baseline corticosteroid use compared to those not on baseline steroids, despite study treatment group. By study group, patients in the enzalutamide cohort on corticosteroids had a median overall survival of 12.3 months compared to 9.3 months on placebo, and this difference remained statistically significant.

Following trial enrollment, men not on steroids at baseline were also permitted to initiate corticosteroid therapy at investigator discretion, and thus the effect of all on study use of corticosteroids was also evaluated.[9] The combined baseline and on study initiation of steroids was 48% in the ezalutamide and 45% in the placebo group. The median survival in all patients treated with on study corticosteroids was 11.5 months, and not met in those not on corticosteroids. Statistically significant benefit of enzalutamide over placebo in all outcome measures was retained despite steroid use. Notably, grade 3 and 4 adverse event rates were higher in all patients on corticosteroids. Though baseline prognostic factors were reported to be slightly better in patients not on corticosteroids, the authors contend that steroid use may be associated with unmeasured or unidentified disease factors or other properties of steroid use. These may include promotion of tumor growth via aberrant mutant AR activation.[10]

TABLE 1. **Administration and strategies to manage side effects of therapy**

Toxicity (AFFIRM enzalutamide incidence)	**Strategy to manage toxicity** **Dose de-escalation/discontinuation as clinically indicated**
Seizure (0.9%)	Avoidance in patients meeting trial exclusion criteria, safety not determined: • History of seizure including febrile • Loss of consciousness or transient ischemic attack < 12 months • Conditions which may predispose to seizure –stroke, brain AV malformation, head trauma with loss of consciousness. • Brain metastasis. • Patients who experienced seizure on study were withdrawn from study. Avoidance/caution with use of concomitant medications which can lower seizure threshold (list not comprehensive): • Bronchial agents: aminophylline, theophylline • Antidepressants: tricyclics, buproprion (Wellbutrin, Aplenzin), doxepin (Silenor) • Antipsychotics: chlorpromazine, haloperidol (Haldol), perphenazine, prochlorperazine (Compazine), thioridazine, trifluoperazine (Terfluzine) • Analgesics: fentanyl, meperidine, propoxyphene, tramadol • Antibiotics: ampicillin, carbenicillin, cephalosporins, imipenem, isoniazid, lindane, metronidazole, oxacillin, penicillin, ticarcillin, pyrimethamine
Hypertension (6.4%)	Optimization of blood pressure before administration. Periodic ECG monitoring, significant increases in QT interval were not observed. Overall incidence of cardiac disorders was not different between the two treatment groups.
Fatigue and asthenia (50.6%)	High incidence in both groups, including grade 3-4 fatigue/asthenia. • Consider starting treatment at lower dose and quickly titrate to full dose as patient tolerates. 4.6% of enzalutamide and 1.3% of placebo treated patients experienced falls on study. Observe caution in this older population at risk, those with prior neuropathy, and at risk for fracture. Consideration of exercise, physical therapy and other falls prevention strategies.
Mental impairment (4.3%)	1.6% incidence of hallucinations in AFFIRM, the majority whom were on concomitant opioids. Judicious review of concomitant medications. These symptoms can improve over time.
Infections (19.4%)	Neutropenia reported in 15% of enzalutamide and 6% of placebo treated patients, death from infection in 1% and 0.3% respectively. Consideration for routine evaluation of blood counts.
Diarrhea (21.8%)	Hydration and use of anti-diarrheal as supportive measure as indicated. Consideration of volume status as contribution to symptoms of fatigue and adverse outcomes such as falls.
Drug interactions	Strong CYP2C8 inhibitors can increase plasma exposure, consider dose reduction of enzalutamide. • Strong CYP2C8 inhibitors: abiraterone, gemfibrozil (increases enzalutamide AUC by over 2x), ritonavir, sorafenib. • Moderate CYP2C8 inhibitors: celecoxib, deferasirox, felodipine, irbesartan, lapatinib, nilotinib, pioglitazone, quinine, rabeprazole, rosiglitazone, tamoxifen, teriflunomide, trimethoprim. Concomitant use of CYP3A4 or CYP2C8 inducers may decrease plasma concentration of enzalutamide. Conduct additional INR monitoring on warfarin.
Enzalutamide administration	• Recommended dose: 160 mg (in 40 mg capsules) oral once daily. • Food effect: none, take with or without food. • Renal impairment: no significant differences seen between men with normal or abnormal renal function, effect in severe renal impairment (CrCl<30 mL/min) or end stage renal disease is not known. • Hepatic impairment: effect in severe hepatic impairment (Child-Pugh Class C) is not known • Pharmacokinetics: median peak plasma concentration, 1 hour, steady state at 28 days following daily administration, metabolized predominantly by liver, half-life 5.8 days.

Does the advantage of enzalutamide oral therapy justify its use before docetaxel?

In an open label single arm phase II study of enzalutamide 160 mg daily in 67 hormone naïve non-castrate men with prostate cancer at any stage, 39% of whom had radiographic metastasis, PSA response rate of > 80% was 93% at week 25.[11] The median decrease in PSA level was -99%, with maintenance or increase in levels of testosterone. Gynecomastia, fatigue and hot flushes were the most common toxicities. These data are promising, but activity and toxicity profile of enzalutamide in large studies of docetaxel naïve men are not completely reported, and thus use prior to docetaxel is not currently endorsed. Completed and maturing, as well as ongoing studies will provide these answers.

Preliminary results from the PREVAIL study, a phase 3 trial in 1700 chemotherapy naïve men with mCRPC administered enzalutamide 160 mg daily compared to placebo have recently been completed and results updated (NCT01212991). An independent data safety monitoring board recommended the current protocol be stopped to allow all patients on the placebo arm to be treated with enzalutamide since the interim analysis showed a 30% reduction in risk of death and an 81% reduction in risk of radiographic progression or death in favor of the enzalutamide arm.[12] Abiraterone and prednisone, studied in the same mCRPC chemotherapy naïve population, was FDA endorsed based upon significant improvement in radiographic PFS and trend toward overall survival (overall survival abiraterone-prednisone not reached versus 27.2 months for prednisone alone, HR 0.75; 95% CI 0.61 to 0.93, p = 0.01). The survival benefit of enzalutamide compared to placebo is more robust, despite a smaller absolute difference in overall survival in the enzalutamide group (overall survival: enzalutamide arm: 32.4 months [range 31.5 months to limit NR] versus placebo arm: 30.2 months [range 28 months to limit NR]). The trend toward longer median survival even in the comparator arms (30.2 months for placebo on enzalutamide study versus 27.2 months for prednisone as abiraterone comparitor) is possibly explained by the increasing array of agents available for mCRPC which continue to improve upon overall survival in the post docetaxel setting. Full report of the data from PREVAIL as well as an FDA endorsement for use of enzalutamide prior to docetaxel is expected in 2014. Decisions regarding best sequence of abiraterone and enzalutamide in the pre and post docetaxel setting will require further study.

Ongoing studies are underway to assess toxicity of abiraterone and enzalutamide when combined. Phase II studies of enzalutamide compared to bicalutamide, the US STRIVE study which is enrolling men with mCRPC with biochemical as well as those with radiographic progression, and the European TERRAIN trial, enrolling mCRPC patients only, are ongoing (NCT01664923). Enzalutamide is being evaluated in smaller studies in the post-prostatectomy setting for men with high risk features, in the pre-prostatectomy space, in the localized hormone naïve space, as well as in novel combinations. A phase I combination of docetaxel every 21 days with enzalutamide 160 mg daily appeared well tolerated without demonstrable effect upon docetaxel pharmacokinetics.[13] Ongoing and planned studies of enzalutamide combinations and sequences include studies with PSA-Tricom, abiraterone acetate with prednisone (AAP), tivozanib, and sipuleucel-T.

How should enzalutamide be sequenced with other agents?

Enzalutamide following abiraterone acetate with prednisone

Though studies are ongoing, we know little about the toxicity and efficacy of novel prostate cancer agents given in sequences not previously studied. Reports from compassionate use programs for enzalutamide and abiraterone provide some insight. In Germany, 35 patients with mCRPC and progression following docetaxel and AAP received enzalutamide.[14] Rate of PSA response to enzalutamide > 50% was 28%, less than the 54% in the AFFIRM study. Those who initially responded to AAP had higher PSA response rate to enzalutamide (43% abiraterone responders versus 15% non-responders), though the numbers were small. In Britain 46 patients with mCRPC with progression following docetaxel and AAP had mean time to PSA progression on enzalutamide of 15 weeks, less than the 8.3 months in the AFFIRM study.[15] Caution should be taken for any comparison to AFFIRM however, given early reporting and small numbers, with 30 patients still on ezalutamide at the time of database publication. Rates of toxicity were similar to those reported in AFFIRM, though the authors cited an increased rate of psychiatric side effects than previously reported.

Abiraterone acetate with prednisone following enzalutamide

Thirty-eight patients from two European sites with mCRPC with disease progression on enzalutamide following AFFIRM unblinding were prospectively followed and subsequently treated with AAP.[16] Of these men, 45% did not demonstrate a PSA response of > 50% during enzalutamide treatment. On AAP, PSA response

> 50% was seen in 8% of patients, with one patient responding to AAP who had not previously responded to enzalutamide. One patient had a radiographic response. Median overall survival on AAP in this group following enzalutamide therapy on AFFIRM was 7.2 months. Toxicity of AAP following enzalutamide was consistent with previous AAP studies.

In a similar report, twenty-seven evaluable men from four centers with disease progression following enzalutamide on AFFIRM received AAP.[17] In this group where 60% experienced a 50% decline in PSA on enzalutamide, only 3% had a > 50% PSA response to AAP. There were no radiographic responses and the median overall survival was 50.2 weeks. Toxicity was not reported, though no patient discontinued study drug due to toxicity.

Conclusion

Enzalutamide is another agent in the expanding therapeutic field for men with mCRPC. Current labeling supports use following docetaxel, though soon data should be available from the PREVAIL study regarding clinical benefit and safety in men with mCRPC prior to docetaxel. The lure of an oral agent like enzalutamide for convenience and possible toxicity benefit over cytotoxic chemotherapy may not reflect actual outcomes, particularly for those at risk for toxicities unique to enzalutamide. Findings in the small study of hormone naïve patients indicate that monotherapy in non-castrate individuals may lead to short term response without suppressing testosterone levels, but the long term rates of control, toxicity and survival will need to be determined. The survival benefit of enzalutamide for men following docetaxel is clear, but whether this benefit will be potentiated for docetaxel naïve men with mCRPC, and if enzalutamide will lead to response improvement relative to bicalutamide in docetaxel naïve men, is yet to be determined. Steroids are required for the safe administration of abiraterone acetate, are routinely used with docetaxel, and are frequently used as a comparator in randomized trials thus better understanding the effects of corticosteroids in men with mCRPC is warranted. Small series of patients that have been treated with enzalutamide on the AFFIRM study and those patients followed in the compassionate use programs for enzalutamide, have reported a decrease in the overall response to subsequent treatment with abiraterone acetate with prednisone. This preliminary data indicate that a cross resistance mechanisms does exist to enzalutamide and abiraterone, highlighting another area of future research to improve the care of men with mCRPC.

Disclosure

Dr. Jean Hoffman-Censits has no potential conflict of interest.
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