Delfini

Evidence Review

Critical Appraisal with Evidence Advisements: Scher 12 AFFIRM Trial: Enzalutamide vs Placebo

Scher HI, Fizazi K, Saad F, Taplin ME, Sternberg CN, Miller K, de Wit R, Mulders P, Chi KN, Shore ND, Armstrong AJ, Flaig TW, Fléchon A, Mainwaring P, Fleming M, Hainsworth JD, Hirmand M, Selby B, Seely L, de Bono JS; AFFIRM Investigators. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012 Sep 27;367(13):1187-97. Epub 2012 Aug 15. PubMed PMID: 22894553.

Reviewers: Michael E. Stuart MD & Sheri Ann Strite
February 2013

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B. FUNDING, INVOLVEMENT & INDEPENDENCE

Delfini performed an unfunded preliminary evaluation of this study and found that it passed a validity and clinical relevance appraisal. Funding for this more detailed review was provided by Astellas Scientific and Medical Affairs, Inc. (ASMA). As reviewers, we had complete control over the entire review. Our focus is on reliability of evidence and clinical usefulness of outcomes from a patient perspective. When we receive industry support, we may ask a funder to provide additional details of studies and analyses, with our complete discretion as to interpretation and inclusion in this report. Where we receive such information, we make note of that in the document. We also may invite further information from a funder when it might help provide clarity about the trials especially as editors of publications may have excised or disallowed needed details of studies, details in additional resources such as protocols may be needed to be confirm or clarify information in the published report or the funder may have access to other useful information. We also may give a funder an opportunity to review and comment. However, we may make modifications if we feel they are appropriate for the review, and we retain full control over all decisions for the final report.

Evidence Review: Critical Appraisal with Evidence Advisements
Scher 12 AFFIRM TRIAL: Enzalutamide vs Placebo—February 2013

C. PUBLISHED STUDY ABSTRACT

Background

Enzalutamide (formerly called MDV3100) targets multiple steps in the androgenreceptor–signaling pathway, the major driver of prostate-cancer growth. We aimed to evaluate whether enzalutamide prolongs survival in men with castration-resistant prostate cancer after chemotherapy.

Methods

In our phase 3, double-blind, placebo-controlled trial, we stratified 1199 men with castration-resistant prostate cancer after chemotherapy according to the Eastern Cooperative Oncology Group performance-status score and pain intensity. We randomly assigned them, in a 2:1 ratio, to receive oral enzalutamide at a dose of 160 mg per day (800 patients) or placebo (399 patients). The primary end point was overall survival.

Results

The study was stopped after a planned interim analysis at the time of 520 deaths. The median overall survival was 18.4 months (95% confidence interval [CI], 17.3 to not yet reached) in the enzalutamide group versus 13.6 months (95% CI, 11.3 to 15.8) in the placebo group (hazard ratio for death in the enzalutamide group, 0.63; 95% CI, 0.53 to 0.75; P<0.001). The superiority of enzalutamide over placebo was shown with respect to all secondary end points: the proportion of patients with a reduction in the prostate-specific antigen (PSA) level by 50% or more (54% vs. 2%, P<0.001), the soft-tissue response rate (29% vs. 4%, P<0.001), the quality-of-life response rate (43% vs. 18%, P<0.001), the time to PSA progression (8.3 vs. 3.0 months; hazard ratio, 0.25; P<0.001), radiographic progression-free survival (8.3 vs. 2.9 months; hazard ratio, 0.40; P<0.001), and the time to the first skeletal-related event (16.7 vs. 13.3 months; hazard ratio, 0.69; P<0.001). Rates of fatigue, diarrhea, and hot flashes were higher in the enzalutamide group. Seizures were reported in five patients (0.6%) receiving enzalutamide.

Conclusions

Enzalutamide significantly prolonged the survival of men with metastatic castration resistant prostate cancer after chemotherapy. (Funded by Medivation and Astellas) Pharma Global Development; AFFIRM ClinicalTrials.gov number, NCT00974311.)

D. EXECUTIVE SUMMARY

Conclusions for Outcomes of Interest	Strength of Evidence (SOE) & Key Comments
Efficacy: Sufficient Evidence For Efficacy	**High-to-Moderate Quality Evidence at Low Risk of Bias and Low Risk of Chance Effects** Evidence is sufficient to conclude that enzalutamide compared to placebo improves overall survival in men with metastatic castration resistant prostate cancer after chemotherapy. Superiority was shown for all primary and secondary endpoints in a well-designed, reported and conducted double-blinded randomized controlled trial.
Clinical meaningfulness: Sufficient Evidence for Clinical Meaningfulness	Increased overall survival of 18.4 months (95% confidence interval [CI], 17.3 to not yet reached) in the enzalutamide group versus 13.6 months (95% CI, 11.3 to 15.8) in the placebo group (hazard ratio for death in the enzalutamide group, 0.63; 95% CI, 0.53 to 0.75; P<0.001) is a clinically meaningful difference between groups.

Safety: Borderline Evidence For Safety and Inconclusive Evidence for Safety; Standard Cautions apply **Note** Delfini takes a conservative patient-centered approach. Because safety is difficult to assess and may never be fully understood even over time, our SOE conclusions for safety are almost always Borderline or Insufficient. We may conclude Sufficient Evidence for a specific safety outcome in an instance in which there is definitive causal information about the occurrence of a harm**. Standard Cautions** almost always apply.	Rates of adverse outcomes were similar in the enzalutamide and placebo groups. The most common adverse events that were reported more frequently in the enzalutamide group compared to placebo included fatigue (34% vs 29%), diarrhea (21% vs 18%), hot flashes (20% vs 10%), musculoskeletal pain (14% vs 10%), headache (12% vs 6%), and seizures which were reported in five patients (0.6%) receiving enzalutamide, but in zero patients on placebo. **Standard Cautions** Safety is often difficult to assess. Safety can only potentially be established with long-term follow-up. Patients should be informed about known safety issues and the quality of the safety evidence even when the evidence is weak. Patients should also be informed that there may be unknown risks of adverse events from healthcare interventions. Reports of no differences between groups should be viewed with caution because the population studied may have been too small for a true difference to be revealed. However, reports of adverse events might not, in fact, be due to the intervention.

Other Considerations & Comments	Scher 12 is a very well designed, reported and executed study. The following strongly supports the conclusion that enzalutamide compared to placebo improves overall survival in men with metastatic castration resistant prostate cancer after chemotherapy:
	• Low risk of bias overall including—
	  ○ Likely balanced groups
	  ○ Likely successful blinding, including concealed allocation
	  ○ Likely no different treatment experiences for patients while on study treatment
	  ○ Appropriate use of censoring in the time-to-event analyses
	• Other supportive evidence including several sensitivity analyses all favoring enzalutamide
	• Consistency in patterns including this supportive evidence plus superiority was shown for all primary and secondary endpoints
	
	While the discontinuation rates are (understandably) high and many patients who discontinued received other oncology agents, we believe that it is **improbable that the superior outcomes in the enzalutamide group can be due to other treatments experienced by patients**. Large and statistically significant differences*

	against placebo were observed in patients who discontinued their study agent, who discontinued due to disease progression and who were taking at least one post-study drug—all of which, in a balanced and successfully blinded clinical trial—as this one appears to be—is a strong indication of patients experiencing benefit from enzalutamide (*Delfini computations—see **Other Supportive Evidence** at end of report). If enzalutamide **does not work**, certain requirements would have to be fulfilled—they **do not appear to be fulfilled** as outlined in the table below: **Requirements Necessary if Enzalutamide Does Not, in Fact, Result in Improved Efficacy Outcomes for Patients**. We found no other potentially perceived threats to validity worth discussing in this **Executive Summary**. Details of our critical appraisal and analysis are provided below in **Bias And Clinical Usefulness Assessment.**

Requirements Necessary if Enzalutamide Does Not, In Fact, Result in Improved Efficacy Outcomes for Patients

Requirement	Outcome	Actual Finding
Faulty randomization	Rejected	Groups appear to be balanced
Unsuccessful blinding	Rejected	Blinding appears to be successful
Differences in treatment experiences such that the enzalutamide group received other treatment that was successful while placebo patients received other treatment that was not effective or no other treatment	Rejected	Balance in groups and successful blinding would make it very unlikely that the groups were treated differently in any way. Review of Supplementary Appendix data (Table 3S) shows that the treatment choices were comparable for patients who discontinued but received at least one oncology agent after discontinuing study treatment and any differences are small.
The analysis omitted patients from the analysis that should	Rejected	The study reports that all patients were included in the analysis, and

have been included (this would logically have to be biased omissions unfavorable to enzalutamide and favorable to placebo in sufficient numbers to overcome enzalutamide being reported as superior).		censoring appears to be reasonable and would not appear to favor one group over another.
Fraudulent data reporting	Cannot be Known	No reason to suspect fraud

E. METHODS

This review was carried out by two evidologists—Michael E. Stuart MD and Sheri A. Strite—for threats to validity and for clinical usefulness. Key validity domains were evaluated, using an approach similar to that used by the Cochrane Collaboration (Higgins 11) including evaluation for selection bias, performance bias, data collection/attrition bias, assessment bias and other threats to validity.

Our approach is always conservative which we consider to be in the best interest of the patient, for credibility and to adjust for distorting effects of bias that otherwise cannot be gleaned from reading the report of the research.

The evidence advisements are prepared based on professional experience working with many payers. Payers range widely in their knowledge about critical appraisal. Misconceptions are common. The advisements are an attempt to help address these issues.

F. BIAS AND CLINICAL USEFULNESS ASSESSMENT

Area of Considerations	Quality Indicator	Critical Appraisal Findings	Comments
Selection Bias			
1. **Number of participants**	Good	• 1199 randomized patients = large population	**Key Points About Study Size** • Small studies are 100 or less and more prone to chance effects and lack of generalizability. **Payer Notes** • Some payers are confused about power and

Area of Considerations	Quality Indicator	Critical Appraisal Findings	Comments
			may look at the power calculation and believe that "power was not reached" if fewer patients completed the study than estimated for the power calculation. These payers should be advised that the purpose of a power calculation is to guestimate the number of patients that need to be enrolled in a study. The answer as to whether a study was sufficiently powered lies in the results. Power means that a sufficient number of patients were studied to find a statistically significant outcome if one exists. In this case, statistical significant outcomes occurred—therefore, these outcomes were sufficiently powered.
2. **Patient population**	Appropriate population	• Patients with progressive castration-resistant prostate cancer who have been previously treated with docetaxel-based chemotherapy. The study was conducted at 156 sites in 15 countries. Patients were eligible for enrollment if they had a histologically or cytologically confirmed diagnosis of prostate cancer, castrate levels of testosterone (<50 ng per deciliter [1.7 nmol per liter]), previous treatment with docetaxel, and progressive disease defined according to PCWG2 criteria (see the Study End Points section below), including three increasing values for prostate specific	**Payer Notes** • Payers may have some external validity issues due to inclusion and exclusion criteria. Does not represent a major threat to external validity.

Area of Considerations	Quality Indicator	Critical Appraisal Findings	Comments
		antigen (PSA) or radiographically confirmed progression with or without a rise in the PSA level. • The protocol provides highly detailed inclusion and exclusion criteria.	
3. **Random** allocation of study subjects to their groups	Probably good	• Recommend supplying details of generation of the randomization sequence: it is not directly stated that a computer-generated randomization scheme was used, but it is reasonable to assume so given the wording (stratified/permuted block) and study of this size funded by industry. • Plus, while no guarantee, the review of baseline characteristics is suggestive of successful randomization.	**Payer Notes** • Assuming that we are correct about methods used to generate the sequence, payers who understand the importance of this issue should be reassured by this method. • Some payers may question whether a 2:1, as compared to a 1:1, study allocation ratio is problematic. We see no reason why this should distort study results. Payers should be reassured that this is not thought to be a threat to validity by us or by many other reviewers.
4. Adequate methods for blinding the allocation of subjects to their groups (aka "**concealment of allocation**")	Good	• Patients were assigned to study treatment centrally by means of an interactive voice-response system (IVRS).	**Key Points About Concealment of Allocation** • Concealment of allocation is a process used in a randomized controlled trial to hide the assignment to a study group. The purpose is to ensure that no one can influence or control which study subject gets assigned to which group. • Concealed allocation is important as a starting point for blinding overall. **Effective Concealed Allocation Is A Key Strength For This Study** • Good method for concealment of allocation to

Area of Considerations	Quality Indicator	Critical Appraisal Findings	Comments
			study arm. **Payer Notes** • Payers who understand the importance of this issue should be reassured by this method. • Most payers are unlikely to be aware of this potential threat to validity, so frequently this will be a non-issue. • Some payers will be aware of this potential threat to validity, but will not understand that IVRS is an acceptable method to conceal allocation to treatment assignment. • Some payers confuse "concealment of allocation" with blinding. To answer them effectively, they will benefit from being educated on what concealment of allocation is and its import, and they will need this detangled from the concept of "blinding" which occurs after allocation to treatment groups.

Area of Considerations	Quality Indicator	Critical Appraisal Findings	Comments
5. **Balanced distribution of prognostic variables** as assessed through review of baseline characteristics	Good	• Extensive baseline characteristics look very similar for cancer burden and other clinical characteristics; nothing to suggest placebo group was sicker.	**Payer Notes** • Payers who understand the importance of this issue should be reassured by this finding. • Most payers have at least a modest to a reasonable understanding that you need similarity in study groups. What they may be less aware of is that you need everything in a study to be the same between groups, except what is being studied. • Payers will often look at this information to assess generalizability to their populations (external validity).
Performance Bias			
6. **Comparisons** are reasonable	Good	• Comparison to placebo	**Payer Note** • Some payers will not place as high a value on placebo comparisons as comparisons to active agents. However, comparison to placebo is very important. Example: in the VIGOR study, rofecoxib was compared to an active agent, which created the potential for uncertainty in safety because there was no placebo comparison which would have clearly revealed that the safety problems were due to rofecoxib and not some protective effect of the comparator.
7. **Blinding** of subjects and all working with subjects and their data was performed and success was likely	Good	• Study drugs were identical in appearance • Protocol states that all subjects, investigators, and the sponsor's staff involved in the conduct of the study	**Supporting Evidence for Effects of Active Agents Unlikely to Unmask Treatment Arm** • We observed no major and observable difference in an effect of an active agent that would be likely to unmask this study.

Area of Considerations	Quality Indicator	Critical Appraisal Findings	Comments
		will be blinded to treatment assignment • See **Supporting Evidence for Effects of Active Agents Unlikely to Unmask Treatment Arm ➔** • These factors, in conjunction with effective concealment of allocation, mean that there is a high likelihood that this study was effectively blinded.	(Example: comparison of an oncology agent with severe side effects compared to placebo in which patients in the oncology arm experience alopecia.) • With the exception of seizure (5 patients in the enzalutamide arm), each of the reported side effects had patients in each arm experiencing that side effect. Therefore, with the possible exception of patients experiencing seizure, it is unlikely that the study agent would be revealed in a single patient because of experiencing a side effect considered to be unique to one agent, and the overall number of patients experiencing seizure was small (5 out 800 patients).
8. Everything is the **same between the groups** except for the subject of interest (e.g., groups are **concurrent** and **balanced**, use of **co-interventions** is the same, same **care experiences**, **adherence** is balanced, **protocol deviations** are balanced, etc.) and no bias is present affecting the groups as a whole (e.g., measurement problems, changes due to time, etc.)	Probably good See **Reviewer Notes ➔**	• Due to likely effective randomization, concealment of allocation, and blinding—including the likelihood of the blind being maintained— there is no reason to believe that there would be a group effect of patients being treated differently while on their study medications. • Because of likely effective randomization and blinding, the major differences between groups that occurred lend support to the effectiveness of enzalutamide over placebo.	**Reviewer Notes** • If groups are balanced at the start of the trial and blinding is effective it would be expected that any use of co-interventions, adherence issues, protocol deviations, etc., would be balanced between groups unless something about an effect from the agents under study caused some readily observable difference—which we believe was unlikely to happen. • Delfini performed several sensitivity analyses constructed from various data sets*. The following **statistically significant** differences between groups*—which we believe are unlikely to have occurred as a result of treating the

Area of Considerations	Quality Indicator	Critical Appraisal Findings	Comments
			groups differently due to systematic bias and which all favor enzalutamide—are as follows: ○ Overall mortality (analyzed as an ITT analysis with no imputation). ○ Completers compared to discontinueds ○ Discontinueds due to disease progression as compared to not discontinued due to disease progression ○ On at least one post-study drug as compared to not *See details below in **Other Supportive Evidence**.
9. **Adherence** was achieved	Unknown, however, no reason to believe a likely distortion of the direction of the results ➔	• No information	• Recommend obtaining adherence information if possible; however, due to effective randomization, successful blinding and low agent toxicity, we believe it is unlikely that there was an imbalance between groups while on their study drugs.
10. **Duration** of treatment and follow-up is reasonable	Good	• Investigators specified that a single interim analysis would be performed after 520 (a large number) deaths (80% of the 650 total events) had occurred. The median survival of castration-resistant disease is currently approximately 12 months. Median duration of follow-up to ascertain survival status was 14.4 months in the trial.	• Number of deaths is an appropriate method of determining the duration of an oncology trial in advanced prostate cancer. With more than 500 events [Guyatt 12] and without obvious biases favoring the drug, the trial is at low risk for a chance effect as the explanation for survival differences in the two groups (see results).
Data Collection/Attrition Bias			
11. Are **measurement methods**	Good	• See study protocol for detailed	• Methods are appropriate.

Area of Considerations	Quality Indicator	Critical Appraisal Findings	Comments
valid and the same between groups? "Validated" may not really be valid. Consider duration of follow-up.		description of measurement methods for primary and secondary endpoints.	
12. Are **missing data** likely to distort results? Could high **discontinuation rates** distort the outcomes resulting in under reporting of safety problems or otherwise create a distortion due to such issues as subjects using other interventions?	See **Discontinuation Rates** & **Reviewer Notes** ➔	**Discontinuation Rates** While rates are high, due to likely effective randomization and blinding, patients were likely to be treated the same while on their study medications. This strongly suggests that the statistically significant difference* in discontinueds between the groups is related to an effect of a study agent. We believe that this is highly suggestive that enzalutamide is more effective than placebo in treating this population. *Delfini computation—see details below in **Other Supportive Evidence.**	**Reviewer Notes** • The number of patients who were randomized as compared to the number of patients who were not able to complete the study is high. • The fact that this is a typical reality for advanced cancer populations does not address whether this could distort study results and so this is an area that is worth looking at closely. **1. Is it possible that new treatments taken by patients who discontinued have affected the results?** ▪ **Yes, in favor of placebo. There was a statistically significant* difference in the number of patients who discontinued and in the number of patients who received at least one post-study drug, strongly suggesting efficacy in favor of enzalutamide.** *Delfini computation—see details below in **Other Supportive Evidence.** **Payer Notes**

Area of Considerations	Quality Indicator	Critical Appraisal Findings	Comments
			• Payer reaction to this area is likely to vary widely. Understanding the critical thinking behind the issues in this area and how study strengths and supportive evidence may mitigate potential threats to validity in this area are important.
Assessment Bias			
13. Was **assessment blind**?	Good	• Protocol states that all subjects, investigators, and the sponsor's staff involved in the conduct of the study will be blinded to treatment assignment.	No comments
14. Were **analysis methods appropriate** including predefined groups for analysis?	Good	• For efficacy, patients were analyzed as randomized which is appropriate. • For the primary endpoint a two-sided test at the 0.05 level of significance was used. • The protocol specified that the interim analysis would be prepared by an independent statistical vendor and presented only to the independent data monitoring committee who would make recommendations about the ongoing conduct of the study.	Requires statistical knowledge to fully assess; however we saw nothing irregular in analysis methods and prespecification was done and exploratory endpoints defined as such.
15. Were assumptions used for **modeling** reasonable?	Appears reasonable, plus there is supportive evidence for the direction of	• A Kaplan-Meier model was used for assessment of primary outcome measures. • Censoring rules are reported in the protocol and appear reasonable including the outcome of survival (i.e.,	**Reviewer Notes on ITT Terminology** • Many authors use intent-to-treat terminology (ITT) when doing time-to-event analyses (TTE). This may be an area of controversy, but we do not believe that this term is appropriately applied in cases of TTE analyses because data is

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	effect. See **Other Supportive Evidence** below this table.	that patients who do not reach the endpoint will be censored at the date last known to be alive).	censored. So we believe that this section does not apply, but there may be confusion for some readers because of the use of the term, yet the circumstances do not fit. • However, analyzing patients in the groups to which they were randomized is appropriate. **Payer Notes on ITT** Most payers are not likely to be familiar with issues surrounding ITT analysis. **Reviewer Notes on Right Censoring Terminology** • We prefer a definition of "right censoring" as follows: study has been terminated and late enrollees have not experienced the endpoint. In this study the term "right censoring" is used, but is defined differently. However, upon review of the censoring rules, we consider them to be appropriate. **Payer Notes** • Most payers are not likely to be familiar with issues surrounding censoring in time-to-event analysis.
16. Was reporting likely to have been **selective**?	Appropriate	• Reporting of outcomes followed the protocol.	• Selective reporting in clinical trials occurs when outcome data are collected but not reported, and when investigators do many analyses but report only the most favorable. We see no such issues with this study.

Area of Considerations	Quality Indicator	Critical Appraisal Findings	Comments
17. Was **safety assessed** and reported?	Appropriate	• The rates of adverse events in the two groups were similar. Safety analyses were assessed for all randomized patients who received any study drug. Adverse event reporting period defined as the time from the first dose of study drug until 30 days after the last dose of study drug or the initiation of subsequent antineoplastic therapy, whichever occurred. The period of observation for the enzalutamide group was more than twice that for the placebo group, the rates of adverse events were similar in the two groups. • The most common adverse events that were reported more frequently in the enzalutamide group compared to placebo included fatigue (34% vs 29%), diarrhea (21% vs 18%), hot flashes (20% vs 10%), musculoskeletal pain (14% vs 10%), headache (12% vs 6%), and seizures which were reported in five patients (0.6%) receiving enzalutamide, but in zero patients on placebo.	**Payer Notes** • Some payers may not be aware that only persons receiving the drug is the appropriate population when assessing safety. An ITT approach would not be an appropriate method for safety as it would diminish safety findings per agent.
18. Have results been **confirmed** in other valid studies?	Good	• See comments ➔	**Reviewer Notes** • Further support for the benefit for the efficacy of enzalutamide is provided by the impressive, consistent differences between the groups in

Area of Considerations	Quality Indicator	Critical Appraisal Findings	Comments
			secondary outcomes in the present study. • In a previous phase 1-2 study of a different population, **which we did not critically appraise,** (patients with progressive metastatic CRPC treated at Memorial Sloan-Kettering Cancer Center (MSKCC), Oregon Health and Science University Knight Cancer Institute, the University of Washington, Dana-Farber Cancer Institute, and M.D. Anderson Cancer Center investigators reported encouraging antitumor activity on all outcomes assessed: declines in serum PSA of 50% or more in 56% of patients, responses in soft tissue, stabilized bone disease, and conversion from unfavourable to favourable circulating tumour cell counts [Scher 10]. • We also conducted sensitivity analysis with which supports the results— see **Other Supportive Evidence** below this table.
Chance Assessment			
19. **Early stopping**	Good	• The study was stopped early after a planned interim analysis at the time of 520 deaths—this is reasonable because over 500 events was reached [Guyatt 12].	**Key Points About Early Stopping** • Early stopping of a clinical trial for benefit increases the likelihood of chance findings at the point of interim analysis. This study was designed to allow an independent statistical vendor to advise regarding stopping at the time of 520 deaths. The results were presented only to the independent data monitoring committee who made recommendations about the ongoing conduct of the study.

Area of Considerations	Quality Indicator	Critical Appraisal Findings	Comments
			Payer Notes • Payers may need to be advised that the risk of bias is low if studies are stopped when more than 500 events have occurred. Payers who understand the importance of this issue should be reassured by this finding. However, we believe that most payers are not going to be familiar with this area.
20. **Statistical significance testing**	Good	No comments	No comments
Conclusions			
21. **Efficacy**	Sufficient Evidence For Efficacy	Evidence is sufficient to conclude that enzalutamide compared to placebo improves overall survival in men with metastatic castration resistant prostate cancer after chemotherapy. Superiority was shown for all primary and secondary endpoints.	Acceptable risk of bias to accept efficacy results.
22. **Clinical meaningfulness**	Sufficient Evidence for Clinical Meaningfulness	Increased overall survival of 18.4 months (95% confidence interval [CI], 17.3 to not yet reached) in the enzalutamide group versus 13.6 months (95% CI, 11.3 to 15.8) in the placebo group (hazard ratio for death in the enzalutamide group, 0.63; 95% CI, 0.53 to 0.75; P<0.001) is a clinically meaningful difference between groups.	Overall survival is a meaningful outcome.

Area of Considerations	Quality Indicator	Critical Appraisal Findings	Comments
23. **Safety**	Borderline and Inconclusive Evidence For Safety See notes at top of this document in **Executive Summary** ↑	Rates of adverse outcomes were similar in the enzalutamide and placebo groups. The most common adverse events that were reported more frequently in the enzalutamide group included diarrhea (21% vs 18%) , fatigue (34% vs 29%), and hot flashes (20% vs 10%).	Additional safety evidence is needed. Safety can only be established with long-term follow-up.

G. OTHER SUPPORTIVE EVIDENCE OF THE LIKELY EFFICACY OF ENZALUTAMIDE OVER PLACEBO

Delfini performed several sensitivity analyses utilizing 2 x2 tables constructed from various data sets which—in the absence of systematic bias, as discussed above—appear to lend strong support to the efficacy of enzalutamide over placebo. While these are post-hoc analyses, the large effect sizes in these new analyses along with consistency in patterns including with those in reported findings of superiority in all primary and secondary endpoints, as reported in Scher 12, are strongly suggestive that these are not chance effects, due to other treatments, due to systematic bias or due to other confounding, but are due to the effects of the study agents.

Data is all from Scher 12:

Mortality

- Page 6. Col 1. Para 1. Line 1: "In the intention-to-treat population, 308 of 800 patients (39%) died in the enzalutamide group and 212 of 399 patients (53%) died in the placebo group."
    - ARR 14.63%, P = < 0.0001, 95% CI (8.69% to 20.58%)

Completers

- Page 6. Col 1. Para 1. Line 2: "When the study was unblinded, 231 patients (29%) in the enzalutamide group were receiving the study drug, as compared with only 19 patients (5%) in the placebo group."
    - ARR 24.11%, P = < 0.0001, 95% CI (20.34% to 27.89%)

Discontinued due to disease progression compared to did not discontinue due to disease progression

- From the Supplementary Appendix, Figure 1S CONSORT Diagram on page 6 of 16:
  - ARR 19.06%, P = < 0.0001, 95% CI (13.55% to 24.57%)

Patients taking At Least One Post-Study Drug

- From Supplementary Appendix, page 16 (possible discrepancy adjusted to favor placebo)
  - ARR 19.4%%, P = < 0.0001, 95% CI (13.53% to 25.28%)

- Further support for the benefit for the efficacy of enzalutamide is provided by the impressive, consistent differences between the groups in secondary outcomes reported by Scher 10 (which we did not critically appraise): In a phase 1-2 study conducted in a different population (patients with progressive metastatic CRPC treated at Memorial Sloan-Kettering Cancer Center (MSKCC), Oregon Health and Science University Knight Cancer Institute, the University of Washington, Dana-Farber Cancer Institute, and M.D. Anderson Cancer Center investigators reported encouraging antitumor activity on all outcomes assessed:
  - Declines in serum PSA of 50% or more in 56% of patients,
  - Responses in soft tissue,
  - Stabilized bone disease, and conversion from unfavourable to favourable circulating tumour cell counts [Scher 10].

H. REFERENCES

#	Short Reference	Citation
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#	Short Reference	Citation
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