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Comparison of Out-of-Pocket Costs and Adherence Between the Two Arms of the Prospective, Randomized Abiraterone Food Effect Trial

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Abstract

PURPOSE: Abiraterone acetate, prescribed for metastatic prostate cancer, has enhanced absorption with food. This effect was exploited in a randomized trial which showed noninferiority of PSA decline for 250 mg abiraterone with a low-fat meal (LOW) compared to 1,000 mg abiraterone fasting (STD). Drug was obtained via patient insurance. Patient out-of-pocket costs and adherence were surveyed.

METHODS: Trial participants were randomized to STD or LOW, and surveys of adherence and out-of-pocket costs were administered at baseline and just before coming off study (follow-up).

RESULTS: Out-of-pocket costs were available from 20 of 36 STD and 21 of 36 LOW patients. Median out-of-pocket costs for a month of drug were $0 (LOW) and $5 (STD); mean costs were $43.61 (LOW) and $393.83 (STD). The two groups did not differ significantly (p = 0.421). Maximum out-of-pocket cost was $1,000 (LOW) and $4,000 (STD). Monthly out-of-pocket costs >$500 were found in 1 LOW and 5 STD patients. For adherence, only 11 STD and 19 LOW patients had questionnaires completed at both baseline and follow-up. STD adherence was 98.18% at baseline and 91.69% at follow-up, differing significantly (p = 0.0078). LOW adherence was 96.52% at baseline and 97.86% at follow-up, not differing significantly (p = 0.3511). Adherence

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CODE AVAILABILITY: RStudio. No custom code was used.

ETHICS APPROVAL: The trial (ClinicalTrials.gov NCT01543776; registered March 5, 2012) was approved by the University of Chicago Institutional Review Board (IRB). The trial was performed in accordance with the Declaration of Helsinki.

CONSENT TO PARTICIPATE: Informed consent was obtained from all individual participants in the study.

CONSENT FOR PUBLICATION: All subjects enrolled in the trial consented for their results to be published.

did not correlate with demographics. At follow-up, increasing adherence correlated significantly with decreasing dose ($p = 0.013$; rho = −0.458).

CONCLUSIONS: Out-of-pocket costs did not differ significantly in this limited analysis. Adherence was significantly different in STD as the trial progressed, which was not found in LOW.

ClinicalTrials.gov NCT01543776; registered March 5, 2012.

Keywords

Prostate cancer; abiraterone; food effect; adherence; costs

INTRODUCTION

Abiraterone acetate is a selective inhibitor of CYP17, the enzyme complex responsible for the synthesis of testosterone, and is one of the most widely prescribed agents for metastatic prostate cancer [1–3]. The drug was first approved by the Food and Drug Administration (FDA) in 2012 for treatment of metastatic castration-resistant prostate cancer (CRPC) and the label was subsequently expanded to include non-metastatic and metastatic high-risk castration-sensitive prostate cancer [4].

Because evidence from early clinical studies demonstrated abiraterone serum drug levels were significantly increased by food, registration studies were designed with abiraterone being dosed while fasting to avoid potentially variable food-effect drug levels [5,6]. As a result, the FDA label for abiraterone dosing is 1,000 mg per day taken in a fasting state, either one hour before or two hours after a meal [4]. This approach left open an opportunity to use the food effect to increase serum drug concentration to efficacious levels with a lower dose, thus decreasing the cost of this extremely expensive medication. The strategy of exploiting pharmacologic properties of a drug to reduce costs while maintaining equivalent efficacy has come to be the essence of a new discipline, interventional pharmacoeconomics [7].

To test whether a lower dose of abiraterone (one 250 mg tablet) taken with food was comparable to the FDA labeled dose of 1,000 mg while fasting, an international randomized phase II study in CRPC was conducted. The trial demonstrated noninferiority based on predefined criteria of prostate serum antigen (PSA) decline as well as PSA progression-free survival [8]. Pharmacokinetic parameters were also similar and in contrast to prior hypotheses were less variable in the fasting arm. The trial’s findings have led the National Comprehensive Cancer Network (NCCN) to include low-dose abiraterone with food as an alternative to standard dosing in a fasting state in its guidelines [9].

Despite the overwhelming preference of oncology patients for oral drugs over intravenous drugs, adherence issues are commonplace [10]. It was thought that patients with cancer would have much higher rates of adherence to their oral medications because the consequences of being nonadherent are potentially more dire than for other chronic conditions [11,12]. The reality is contrary to this belief as many of these patients have varying adherence to oral oncology therapies [13]. Research in the area of oral oncology

medication nonadherence has mostly focused on breast cancer adjuvant treatment and chronic myelogenous leukemia (CML). A large study of adjuvant breast cancer oral hormonal therapy adherence showed only 49% of patients actually took the therapy for the full duration at the optimal schedule, and nonadherence to therapy was associated with increased mortality [14,15]. Nonadherence in CML was observed in greater than 30% and resulted in adversely affected event-free survival [16,17]. In agreement with these findings, a recent meta-analysis of 51 papers on adherence to oral antineoplastic therapy showed that a substantial proportion of patients struggle with drug adherence [18]. The reasons for nonadherence are complex with multiple influences from provider interactions to health delivery systems to side effects of medications to patient perceptions and beliefs about medications and disease [19,20,13].

A major driver of adherence is individual financial toxicity. The cost of one month's supply of Zytiga, the branded abiraterone, is greater than $11,000. Even the recently approved generic version costs more than $3,000 per month. Despite the obvious higher cost of the higher dose regimen, individual out-of-pocket cost and financial toxicity can vary widely due to complex insurance, copay, and patient support mechanisms. Besides out-of-pocket costs, nonadherence to oncology drugs has been associated with higher doses comprised of multiple tablets or capsules [17]. It is thus plausible that there could be a difference in adherence to one tablet vs four tablets of abiraterone.

As such, the aforementioned randomized trial of low versus standard-dose abiraterone also conducted patient surveys assessing adherence to abiraterone and prostate cancer and collected out-of-pocket expense data to attempt to determine if there was a difference between the two abiraterone dosing strategies. Presented here is the analysis of that data.

SUBJECTS AND METHODS

Patient Selection:

Eligible patients had a diagnosis of metastatic CRPC without prior use of abiraterone, enzalutamide, or other potent androgen pathway-targeted therapy. CRPC was defined as disease progression despite a testosterone level < 50 ng/dL or surgical castration. Disease progression was defined radiographically as either two or more new lesions on bone scan or soft tissue progression on CT or MRI per Response to Evaluation Criteria in Solid Tumors 1.1 [21]. Prior use of chemotherapy and/or high-dose ketoconazole was allowed. Other exclusions included hormonal therapies aside from LHRH agonists/antagonists, any herbal products known to decrease PSA levels, and any other systemic corticosteroid besides prednisone ≤ 10 mg daily. Eligibility also included an Eastern Cooperative Oncology Group performance status ≤ 2, acceptable liver function, renal function, electrolytes, and baseline blood pressure.

Study Design:

The trial design was reported previously [8]. The trial (ClinicalTrials.gov NCT01543776) was IRB approved and performed in accordance with the Declaration of Helsinki. Briefly, the trial was a multinational randomized open-label study conducted at six sites in the

United States and Singapore. Participants who enrolled were randomized (1:1) to 1,000 mg abiraterone fasting (STD) or 250 mg abiraterone with a low-fat meal (LOW) (see Figure 1). Abiraterone was not provided by the study but was procured by patients through their pharmacy. All patients received 5 mg of prednisone orally twice daily while taking abiraterone.

Patients were given surveys to complete regarding abiraterone adherence and out-of-pocket costs of abiraterone after having been on the trial for 60 days ("baseline") and just before coming off study ("follow-up"). Out-of-pocket costs were compared using a Wilcoxon rank-sum test. Adherence questions were derived from previously validated instruments of adherence in various other medical settings with an addition of several new questions (ASK-12 [22], BMQ-Specific [23], Basel Assessment of Adherence Scale [24,25], and Morisky Adherence Scale [26]). Baseline to follow-up adherence for each group was compared using the Wilcoxon signed-rank test. Associations between adherence and variables such as socioeconomic status were determined by Spearman correlation. The analysis was done using RStudio software.

RESULTS

Surveys were completed and available for analysis of out-of-pocket costs from 20 of 36 patients on the STD arm and 21 of 36 from the LOW arm (see Figure 1). Due to the differences in health systems, the few patients from Singapore were excluded from the cost analysis so that all remaining patients were from the United States. Patients from Singapore were included in the adherence analysis. Only 11 patients from the STD arm and 19 patients from the LOW arm had questionnaires completed at both baseline and follow-up timepoints (see Figure 1). Of these patients with questionnaires at both timepoints, patients were from the U.S. except for 1 patient from Singapore in the STD arm and 3 patients from Singapore in the LOW arm.

The patients from each arm, STD and LOW, were roughly comparable in terms of demographics (see Table 1). The median out-of-pocket cost for a month of drug (see Table 2) was $0 on the LOW abiraterone arm and $5 on the STD abiraterone arm. The average out-of-pocket cost for a month of abiraterone was $43.61 on the LOW arm and $393.83 for the STD arm. Using a Wilcoxon rank-sum test to compare the two groups, there was no significant difference with the p-value = 0.421. The maximum out-of-pocket cost for standard dose abiraterone was $4,000 while the maximum for low-dose abiraterone was $1,000. One patient in the LOW arm and 5 patients in the STD arm had monthly out-of-pocket costs of >$500.

Patients on the trial were asked questions assessing adherence to abiraterone therapy (see Table 3). The results were used to determine a composite index of adherence for each patient. The average of the composite index percentages for adherence for the STD group (n = 11 patients) at baseline was 98.18% and follow-up was 91.69%. The two timepoints in the STD group were significantly different (p = 0.0078). The average of the composite index percentages for adherence for the LOW (n = 19 patients) group at baseline was 96.52% and

follow-up was 97.86%. The LOW group's two timepoints did not differ significantly (p = 0.3511).

The correlation of the composite index of adherence from the follow-up timepoint from both groups (n = 30) with demographics and dose was assessed. The only significant correlation was between increasing adherence and decreasing dose with a p-value of 0.013 and a rho of −0.458, signifying a moderate correlation (see Table 4).

DISCUSSION

There was no significant difference in out-of-pocket costs between the LOW compared to STD doses, largely because the vast majority of patients had minimal to no out-of-pocket costs. It is interesting to note that despite the 4-fold cost impact of the STD dose, the complex health system in the U.S. shields many patients from these issues. In spite of this, out-of-pocket costs, even with good health insurance, can be substantial for certain patients. In this study, the maximum out-of-pocket costs per month in this study were $4,000 on the STD arm compared to $1,000 on the LOW arm. It is more probable that the patients who have more cost passed on to them by payers are more likely to be taking abiraterone 1 000 mg with fasting daily. In this study, 5 patients in the STD group had out-of-pocket costs >$500 monthly compared to 1 patient in the LOW group. It has been previously shown that medications with an out-of-pocket cost of $500 per month are four times more likely to be abandoned than drugs with a cost of $100 or less [27]. Therefore, a patient with financially toxic higher out-of-pocket costs has a much higher likelihood of abandoning his abiraterone and being nonadherent to treatment. This, in turn, could lead to worsening of his cancer to the point he requires hospitalization and/or more expensive interventions, clearly leading to greater costs to the patient and payers.

In this analysis, adherence is significantly reduced between the two timepoints in the STD arm, providing evidence that taking one tablet (250 mg) of abiraterone every day is easier than four tablets (1,000 mg). It is not clear whether the high cost or the inconvenience of drug administration contributed to the STD group's significant adherence decline over time in comparison to the LOW group. Given the limited number of patients impacted by financial toxicity, we presume that the LOW group's one tablet with food is easier to adhere to than four tablets while fasting. Admittedly, the conclusions are limited by the small overall sample size of the trial and low response rates to the questionnaires. This trial was small and only 30 total patients, 11 in the STD group and 19 in the LOW group, completed surveys at the two different timepoints needed to compare adherence. These patients who filled out both surveys may have been more conscientious and could reasonably be expected to have a higher degree of adherence.

The hypothesis of higher adherence with one tablet with food compared to four tablets while fasting will need to be tested in a larger trial to provide a more definitive answer. Complicating the matter further are other studies showing that adherence to abiraterone is fairly high already when compared to other medications.[28,29] Still, despite a relatively high baseline adherence, there is still potential room for improvement, as the STD arm still had a significant decrease in adherence while the LOW group did not. Furthermore, the

patients at the follow-up timepoint had a significant correlation between dose and adherence with the lower dose correlating with higher adherence.

Even if the direct patient impact of the LOW strategy of dosing is limited to a small subset of U.S. patients, the impact on health systems could be tremendous. For example, a recent cost-effectiveness analysis estimated that the yearly cost savings to the Indian health care system would be approximately $182 million (U.S. dollars) if all Indian patients prescribed abiraterone used the low dose with food strategy.[30] The cost savings for the U.S. would be substantially greater considering the higher prices Americans pay for drugs [31]. For example, one analysis found that low-dose abiraterone could potentially lead to an annual savings of around $700 million for Medicare alone [32]. Potential savings overall are even higher if commercial insurers were to adopt low-dose abiraterone along with Medicare.

Considering the enormous potential benefits in terms of improved adherence and cost reduction from a low-dose abiraterone with food strategy, a larger prospective study or a real-world retrospective study is needed to more firmly establish these differences in adherence, out-of-pocket savings to patients, and decreases in costs for payers between the two dosing strategies.

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CONFLICTS OF INTEREST/COMPETING INTERESTS:

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AVAILABILITY OF DATA AND MATERIAL:

The dataset generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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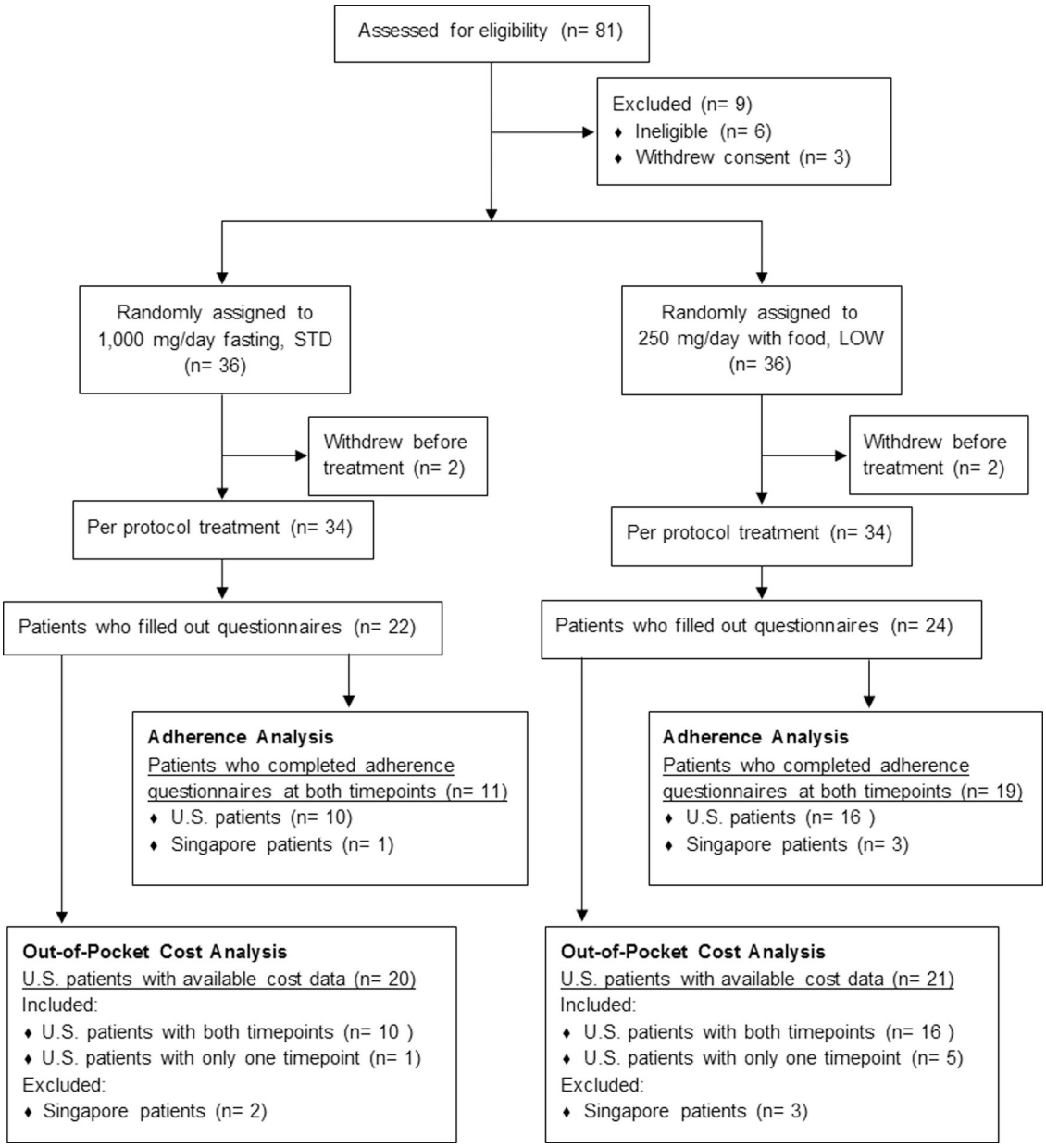

Figure 1:
Trial Diagram

Table 1:

Patients Demographics for Cost and Adherence Analysis.

	STD (1 000 mg with fasting)		LOW (250 mg with food)	
	Cost Analysis	Adherence Analysis	Cost Analysis	Adherence Analysis
	N = 20	N = 11	N = 21	N = 19
Age (median in years):	73.1	69.6	72.6	73.2
Ethnicity:				
Asian or pacific islander	5% (1/20)	9% (1/11)	5% (1/21)	11% (2/19)
Black of African American	10% (2/20)	18% (2/11)	33% (7/21)	32% (6/19)
Latino, Hispanic or of Spanish origin or descent	0% (0/20)	0% (0/11)	0% (0/21)	0% (0/19)
Native American	0% (0/20)	0% (0/11)	0% (0/21)	0% (0/19)
White	85% (17/20)	73% (8/11)	62% (13/21)	58% (11/19)
Some other race	0% (0/20)	0% (0/11)	0% (0/21)	0% (0/19)
Education:				
Some high school	10% (2/20)	9% (1/11)	14% (3/21)	16% (3/19)
High school	15% (3/20)	27% (3/11)	19% (4/21)	11% (2/19)
Some college	25% (5/20)	45% (5/11)	29% (6/21)	37% (7/19)
College graduate	30% (6/20)	18% (2/11)	24% (5/21)	26% (5/19)
Some postgraduate	0% (0/20)	0% (0/11)	0% (0/21)	0% (0/19)
Postgraduate or professional degree	15% (3/20)	0% (0/11)	14% (3/21)	11% (2/19)
Other	5% (1/20)	0% (0/11)	0% (0/21)	0% (0/19)
Employment Prior to Cancer Diagnosis:				
Full-time	35% (7/20)	45% (5/11)	57% (12/21)	58% (11/19)
Part-time	0% (0/20)	0% (0/11)	0% (0/21)	0% (0/19)
Retired	65% (13/20)	55% (6/11)	43% (9/21)	42% (8/19)
Not Employed	0% (0/20)	0% (0/11)	0% (0/21)	0% (0/19)
Current Employment:				
Full-Time	15% (3/20)	27% (3/11)	19% (4/21)	11% (2/19)
Part-Time	20% (4/20)	18% (2/11)	14% (3/21)	11% (2/19)
Not Working/Retired	65% (13/20)	55% (6/11)	62% (13/21)	74% (14/19)
Not Answered	0% (0/20)	0% (0/11)	5% (1/21)	5% (1/19)
Income:				
Less than $5 000	0% (0/20)	9% (1/11)	0% (0/21)	0% (0/19)
$5 001 to $19 999	5% (1/20)	9% (1/11)	14% (3/21)	5% (1/19)
$20 000 to $39 999	15% (3/20)	27% (3/11)	19% (4/21)	16% (3/19)
$40 000 to $59 999	25% (5/20)	36% (4/11)	48% (10/21)	47% (9/19)
$60 000 to $79 999	5% (1/20)	0% (0/11)	5% (1/21)	5% (1/19)
≥ $80 000	35% (7/20)	9% (1/11)	14% (3/21)	16% (3/19)
Don’t know	0% (0/20)	0% (0/11)	0% (0/21)	11% (2/19)

	STD (1 000 mg with fasting)		LOW (250 mg with food)	
	Cost Analysis	**Adherence Analysis**	**Cost Analysis**	**Adherence Analysis**
	N = 20	**N = 11**	**N = 21**	**N = 19**
Refused	15% (3/20)	9% (1/11)	0% (0/21)	0% (0/19)
Marital Status:				
Married	75% (15/20)	55% (6/11)	71% (15/21)	84% (16/19)
Divorced/Separated	5% (1/20)	9% (1/11)	10% (2/21)	5% (1/19)
Widowed	15% (3/20)	27% (3/11)	14% (3/21)	5% (1/19)
Single	5% (1/20)	9% (1/11)	5% (1/21)	5% (1/19)
Health Status:				
Excellent	10% (2/20)	9% (1/11)	0% (0/21)	0% (0/19)
Very Good	20% (4/20)	18% (2/11)	14% (3/21)	16% (3/19)
Good	40% (8/20)	27% (3/11)	52% (11/21)	58% (11/19)
Fair	25% (5/20)	45% (5/11)	29% (6/21)	26% (5/19)
Poor	5% (1/20)	0% (0/11)	5% (1/21)	0% (0/19)

Note: Percentages rounded to the nearest whole number.

Table 2:

Patient Out-of-Pocket Costs from STD and Low Groups.

	STD (1,000 mg with fasting)	**LOW (250 mg with food)**
	U.S. Patients (N = 20)	**U.S. Patients (N = 21)**
Median	$5	$0
Average	$393.83	$43.61
Maximum	$4,000	$1,000
Difference between the two groups	p = 0.421	

Note: Due to the difference in health systems, patients from Singapore were excluded from the cost analysis.

Table 3:

Adherence Results from the STD and Low Groups.

Adherence Statement or Question	Responses	STD (1,000 mg with fasting)		LOW (250 mg with food)	
		Adherence Analysis (N = 11)		Adherence Analysis (N = 19)	
		Baseline	Follow-Up	Baseline	Follow-Up
Do you ever forget to take your abiraterone?	Yes:	1	2	2	3
	No:	10	9	17	16
Have you skipped several doses in a row of your abiraterone?	Yes:	1	1	0	0
	No:	10	10	19	19
Have you lowered or raised the prescribed amount of your abiraterone on your own?	Yes:	0	1	0	0
	No:	11	10	19	19
Do you recall taking your abiraterone more than 2 hours earlier or later than the prescribed dosing time?	Yes:	0	1	2	5
	No:	11	10	17	13*
When you feel better do you sometimes stop taking your abiraterone?	Yes:	0	0	0	0
	No:	11	11	19	18*
I run out of my abiraterone because I don't get refills on time.	Strongly Agree:	0	1	2	0
	Agree:	0	1	0	0
	Neither agree nor disagree:	2	1	4	1
	Disagree:	1	4	2	2
	Strongly disagree:	8	3*	9**	16
Have you skipped or stopped abiraterone because you didn't think it was working?	In the last week:	0	1	0	0
	In the last two weeks:	0	0	0	0
	In the last month:	0	1	0	0
	In the last 3 months:	0	0	0	0
	Never:	11	9	19	19
Have you skipped or stopped taking abiraterone because it made you feel bad?	In the last week:	0	0	0	0
	In the last two weeks:	0	1	0	0
	In the last month:	0	1	0	0
	In the last 3 months:	0	0	1	0
	Never:	11	9	18	18*
Have you skipped, stopped, not refilled, or taken less abiraterone because of cost?	In the last week:	0	0	0	0
	In the last two weeks:	0	1	0	0
	In the last month:	0	0	0	0
	In the last 3 months:	0	0	0	0
	Never:	11	10	19	19

Have you not had abiraterone with you when it was time to take it?	In the last week:	0	0	0	0
	In the last two weeks:	0	0	0	0
	In the last month:	0	0	0	1
	In the last 3 months:	0	0	0	0
	Never:	10 *	11	19	18
Adherence Composite Index Comparison		**STD (1,000 mg with fasting)**		**LOW (250 mg with food)**	
		Baseline	**Follow-Up**	**Baseline**	**Follow-Up**
Average of Adherence Composite Index Percentages:		98.18%	91.69%	96.52%	97.86%
Value for Comparison of Baseline to Follow-Up		p = 0.0078		p = 0.3511	

*one patient failed to answer the question;

**two patients failed to answer the question

Table 4:
Spearman Correlation of Adherence with Demographics.

Patient composite adherence scores at follow-up were correlated to demographic factors and patient perceived health status.

Adherence	Age p-value (rho)	Ethnicity p-value (rho)	Education p-value (rho)	Employment Before Illness p-value (rho)	Employment Currently p-value (rho)	Income p-value (rho)	Marital Status p-value (rho)	Health Status p-value (rho)	Dose P-value (rho)
Patients at "Follow-Up" Timepoint	0.960 (0.009)	0.750 (0.059)	0.437 (0.144)	0.618 (0.092)	0.682 (0.076)	0.805 (−0.045)	0.671 (−0.080)	0.108) (−0.298)	0.013 (−0.458)