Original Study

Safety and Efficacy of Maintenance Therapy With a Nonspecific Cytochrome P17 Inhibitor (CYP17i) After Response/Stabilization to Docetaxel in Metastatic Castration-Resistant Prostate Cancer

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Abstract

Ketoconazole blocks adrenal androgen synthesis, acting as an effective therapy against metastatic castration-resistant prostate cancer (mCRPC) before and after progression to docetaxel. Its role in the maintenance setting after response/stabilization to docetaxel has been unexplored. For the first time to our knowledge, this study shows superior progression-free survival (PFS) in patients receiving ketoconazole-based maintenance therapy after response/stabilization to docetaxel, with a favorable toxicity profile.

Background: Frontline treatment of metastatic castration-resistant prostate cancer (mCRPC) consists of docetaxel-based chemotherapy. The median time to progression (TTP) from chemotherapy initiation is 6 to 8 months. Ketoconazole, a nonspecific cytochrome P17 inhibitor (CYP17i), blocks adrenal androgen synthesis. Low-dose ketoconazole (LDK), (200 mg three times daily [t.d.s]) has shown activity in mCRPC after progression to androgen deprivation. The role of a CYP17i after docetaxel treatment in the maintenance setting has been unexplored. **Methods:** We identified 38 patients with mCRPC who showed progression to luteinizing hormone releasing–hormone agonists (LHRHa) and who were treated with a median of 7 cycles of frontline three-weekly docetaxel (75 mg/m^2) plus prednisone (10 mg/d) and LHRHa. Medical charts of 20 patients who showed no progression to docetaxel were reviewed. After the last docetaxel cycle, 10 patients received LDK maintenance treatment plus prednisone (10 mg/d) and LHRHa, whereas 10 patients received LHRHa alone. TTP was the primary endpoint. **Results:** After a follow-up of 27 months, disease in all patients receiving LHRHa alone progressed, whereas 8/10 patients progressed to maintenance therapy. Median TTP from docetaxel initiation was 11.5 months (95% confidence interval [CI], 6.3-16.6) for maintenance therapy and 9.2 months (95% CI, 8.5-9.9) for LHRHa alone (P = .047). The maintenance treatment was well tolerated. Only 1 patient experienced a grade 4 adverse event due to a nonsymptomatic pulmonary embolism. **Conclusion:** This is the first study evaluating a CYP17i for maintenance therapy after docetaxel therapy. We showed a 2-month significant benefit in TTP for patients with mCRPC treated with LDK maintenance therapy after docetaxel, with a favorable toxicity profile. A large prospective randomized study using a CYP17i is warranted.

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Keywords: Cytochrome P17 inhibitor (CYP17i), Docetaxel, Maintenance therapy, mCRPC, Time to progression

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Introduction

The prevalence of prostate cancer is one of the highest among patients with cancer because of its high incidence and its relatively low death rate. Thus this tumor represents a major clinical issue in public health. Nevertheless, metastatic castration-resistant prostate cancer (mCRPC) causes around 30,000 deaths/year in the United States.[1]

In 2004, for the first time two different clinical trials demonstrated a significant survival advantage in patients with mCRPC receiving first-line docetaxel-based chemotherapy compared with mitoxantrone-based treatment.[2,3] Since then, the frontline treatment of mCRPC consists of docetaxel-based chemotherapy. At least 50% of the patients showed a 50% prostate-specific antigen (PSA) reduction during docetaxel treatment. However most of these patients presented with disease progression after a median of 6 to 8 months.[2,3]

Androgen receptor (AR) signaling has a key role in the pathogenesis of prostate cancer. AR gene amplification, AR overexpression, and activating mutations in the AR occur more frequently as mCRPC evolves, with intratumoral androgen levels remaining sufficient for AR activation despite castration.[4] The source of these androgens might be either adrenal or intratumoral. AR signaling therefore remains a valid treatment target for patients with mCRPC.

Cytochrome P17 (CYP17) is a crucial enzyme for androgen synthesis.[5] In 1984, a small pilot study in 13 patients with advanced prostate cancer who were treated with the imidazole antifungal agent ketoconazole, a nonspecific CYP17 inhibitor (CYP17i), for the first time showed an ability to effectively block adrenal androgen synthesis.[6] In the past two decades, ketoconazole combined with a luteinizing hormone-releasing-hormone agonist (LHRHa) has constituted a frequent, active, and safe secondary hormone manipulation in patients with prostate cancer after progression to androgen deprivation therapy (ADT).[7] However ketoconazole remains unlicensed for this indication.

Although ketoconazole has been tested in several studies using a high-dose approach (400 mg, t.d.s), a dose-escalation study by Nakabayashi et al showed a clinical benefit of low-dose ketoconazole (LDK) 200 mg t.d.s in terms of PSA response, comparable to high-dose ketoconazole as secondary hormone therapy in patients with CRPC but with significantly less toxicity.[8]

LDK has recently shown a 21% biochemical response rate and a 35% stable disease (SD) rate in mCRPC after progression to ADT, before or after first-line docetaxel-based chemotherapy.[9] However analysis of retrospective series showed short progression-free survival (PFS) when challenging patients with mCRPC who were previously treated with taxane-based chemotherapy with ketoconazole as a secondary hormone treatment.[10]

Interestingly, abiraterone acetate, a selective and irreversible CYP17i, has recently demonstrated increased survival compared with placebo and with a favorable toxicity profile in patients with mCRPC after progression to a docetaxel-based frontline regimen.[11] Thus the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have already granted approval for this indication.

In other advanced types of cancer exhibiting a relatively short time to progression (TTP) after a frontline chemotherapy regimen, a so-called maintenance therapy approach has gained strong support in recent years among patients, clinicians, and regulatory agencies.[12-15] The maintenance therapy would consist of a drug (or drug combination) given to patients showing response or SD right after a determined number of cycles (generally 4) of a first chemotherapy line. This drug can be part of the first chemotherapy regimen (the so-called true or continuation maintenance) or a third compound not previously included in the frontline treatment (also called switch maintenance). Most of the maintenance approaches to date have tested drugs with a favorable toxicity profile that can be administered over prolonged periods to ensure treatment compliance and continuation until disease progression.

In patients with CRPC, the only widely used maintenance approach after first-line docetaxel-based chemotherapy is the continuous administration of LHRHa.[16] More recently, the preliminary data from 2 different phase II trials in the maintenance setting for patients with mCRPC have been reported. In one of them, the antiangiogenic multitarget drug sunitinib was administered to 13 patients who showed evidence of response or SD at completion of docetaxel-based treatment in a phase II multicenter trial.[17] The other multicenter study evaluated the safety and efficacy of the mammalian target of rapamycin inhibitor temsirolimus in 10 patients with documented treatment response by PSA levels or Response Evaluation Criteria in Solid Tumors (RECIST) after docetaxel-based first-line chemotherapy.[18]

To our knowledge, the role of a CYP17i in the maintenance setting of patients with mCRPC after response/stabilization to docetaxel has never been studied. Thus in the present study we aimed to evaluate the impact of the CYP17i ketoconazole on the TTP in this type of patients showing response or stabilization to docetaxel-based first-line chemotherapy according to our single center's experience.

Patients and Methods

From 2007 to 2010, 38 patients with mCRPC were treated at the Department of Oncology of the Clínica Universidad de Navarra, with frontline chemotherapy consisting of three-weekly docetaxel (75 mg/m^2) plus 10 mg of daily prednisone after progression to ADT, as an induction therapy. All patients additionally continued to receive LHRHa as part of the treatment regimen.

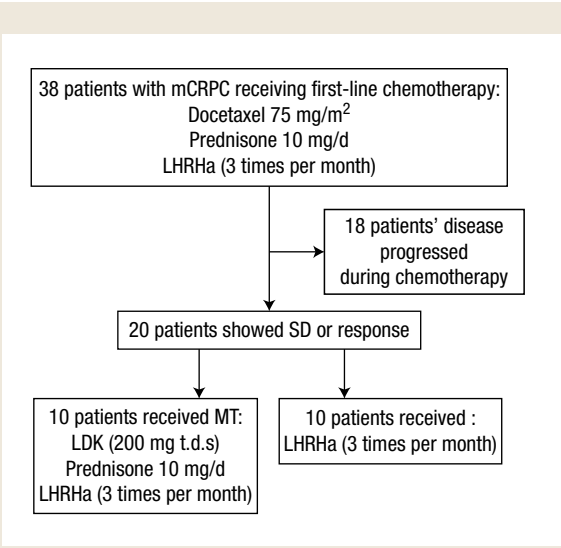
The PSA serum levels were determined at treatment initiation and monitored every 3 weeks during chemotherapy per protocol. Routine bone scans and computed tomography (CT) were performed every 6 weeks during chemotherapy treatment according to each patient's baseline documented disease.

Treatment

After a median administration of 7 cycles (range, 3-12 cycles) of induction chemotherapy, 20 of the 38 patients had a biochemical response or stabilization to docetaxel in the absence of radiologic or bone scan progression, whereas the 18 remaining patients showed either biochemical and/or radiologic/bone scan progression.

In 10 of the 20 patients who showed no progression to docetaxel, LDK (200 mg t.d.s) plus prednisone (10 mg daily) was started 1 month after the last chemotherapy cycle as maintenance therapy. In addition, continuation of LHRHa was prescribed. In the remaining 10 patients, only the LHRHa was continued and these patients were

Figure 1 Patient Flow Chart



Abbreviations: LHRHa = luteinizing hormone–releasing hormone agonists; LDK = low-dose ketoconazole; MT = maintenance therapy; SD = stable disease.

Table 1 Characteristics of Patients in Both Groups

Variable	Maintenance (n = 10)	No Maintenance (n = 10)
Median Age (range)	64 (49-83)	64.5 (53-82)
Median ECOG PS (range)	1 (0-2)	1 (0-2)
Median Gleason Score (range)	8 (7-9)	8 (7-10)
Median Stage at Onset (T, N, M)	3, 0, 0	2, 0, 0
Median Previous CT Cycles (range)	6 (5-8)	8 (3-12)
Median PSA Response After CT (%)	78.56 (5-98.59)	71.77 (6.38-98.31)
Median Number of MTS Sites (range)	2 (1-3)	2 (1-2)

Abbreviations: CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; MTS = metastasis; PSA = prostate-specific antigen.

used as the control arm. The patient flow chart is summarized in Figure 1.

Clinical and Imaging Follow-up

After completion of chemotherapy, all patients were followed every month with a complete physical examination and a general blood test, including liver enzyme and PSA serum levels. In addition, patients were interviewed regarding symptoms of clinical progression and treatment toxicity. Bone and computed tomographic scans were performed every 2 months per standard clinical practice in our center. Toxicity was defined according to the National Cancer Institute Common Toxicity Criteria, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

Study Endpoints

TTP was the primary endpoint of the study. TTP was defined as the time from the first dose of chemotherapy until evidence of biochemical or clinical disease progression. Biochemical progression was defined as an increase in the PSA level by >25% and >2 ng/mL from the baseline or nadir as defined by the Prostate Cancer Clinical Trials Working Group (PCWG) criteria. Clinical progression was defined as new findings on physical examination or scans (measurable disease response and progression were evaluated according to RECIST, version 1.1). Bone scan progression was defined as 2 or more new lesions seen on bone scan.

Statistical Analysis

To study the potential differences in TTP between both treatment groups, Kaplan-Meier survival curves and the log-rank significance test were calculated using SPSS software, version 15 (SPSS Inc, Chicago, IL).

Regulatory Considerations

This research was approved by the Clinical Research Ethics Committee of Navarra.

Results

Patient Characteristics

The characteristics of the patients who showed no progression to induction docetaxel-based chemotherapy and who were treated with maintenance therapy or LHRHa alone are summarized in Tables 1 and 2. Overall, both groups were well balanced and no relevant differences were observed between them.

Briefly, in both groups patients were relatively young (median age, 64 years), had an Eastern Cooperative Oncology Group good performance status (PS) (median PS, 1), had tumors with a median Gleason score of 8, showed a major PSA response after first-line docetaxel-based chemotherapy (median PSA reduction >70% in both groups), and the median number of metastatic sites at the time of chemotherapy initiation (including bone, lymph nodes, and local recurrences) was 2 in both groups (Table 1). In addition, although patients receiving LHRHa after docetaxel-based chemotherapy seemed to have a higher baseline PSA level, the PSA reduction rate (Table 1) and the postchemotherapy PSA level (Table 2) were similar in both groups. Finally, a similar proportion of patients with SD and patients with partial response (PR) according to RECIST criteria was observed in both groups (Table 2).

According to institutional guidelines, every patient starting first-line docetaxel-based chemotherapy is intended to receive a minimum of 6 cycles and a maximum of 12 cycles of that regimen. However because of poor tolerance, 1 patient in the group receiving LHRHa alone and another patient among those treated with maintenance therapy received only 3 and 5 cycles, respectively, before observation or maintenance treatment was initiated.

Therefore patients treated with LHRHa alone received a median of 8 cycles (range, 3-12 cycles) of docetaxel-based chemotherapy compared with those treated with maintenance therapy, who received a median of 6 cycles (range, 5-8 cycles) and seemed to have less bulky tumors at onset compared with patients receiving maintenance therapy (median stage T2 in patients who received LHRHa vs. median stage T3 in patients treated with maintenance).

Table 2 Prostate-Specific Antigen Levels Before and After First-Line Docetaxel-Based Chemotherapy and Radiographic Response Achieved During Chemotherapy for Every Patient in Both Groups

Variable	PSA (ng/mL) Before Docetaxel-Based First-Line Chemotherapy	PSA (ng/mL) After Docetaxel-Based First-Line Chemotherapy	Radiographic Response According to RECIST v1.1
No Maintenance (Patient No.)			
1	94	88.0	SD
2	8.7	0.3	PR
3	19.5	16.5	PR
4	112.9	104.9	PR
5	4.8	1.7	SD
6	91.3	19.2	NA
7	16.5	6.0	NA
8	282.3	4.75	PR
9	108.3	13.9	NA
10	146.0	11.1	PR
Maintenance (Patient No.)			
1	164.0	2.3	NA
2	5.8	4.7	PR
3	28.4	13.1	SD
4	74.8	8.6	PR
5	10.9	1.9	PR
6	24.1	2.7	SD
7	13.3	10.0	NA
8	25.4	9.5	SD
9	5.1	1.6	PR
10	18.7	2.1	PR

Patients with exclusive bone metastases that were not evaluable by radiographic assessment are marked as NA (not applicable).
Abbreviations: PR = partial response; SD = stable disease.

Treatment Administered

Patients who received maintenance therapy (LDK, prednisone, and LHRHa) were treated for a median of 8 months (range, 1.93-35 months). No dose reduction or discontinuation was required during maintenance treatment. Patients were treated until progression as previously defined.

Clinical Outcome

After a median follow-up of 27 months, all patients in the control arm had disease progression after docetaxel treatment, whereas 80% of the patients in the other group progressed to maintenance therapy. As shown in Figure 2, TTP from docetaxel initiation was 11.5 months (95% confidence interval [CI], 6.3-16.6) for maintenance therapy and 9.2 months (95% CI, 8.5-9.9 months) for patients treated with LHRHa alone ($P = .047$).

One patient in the maintenance therapy group remained progression free for 35 months (Figure 3).

Toxicity Profile

Overall, patients receiving LDK, prednisone, and LHRHa showed a good tolerance to the maintenance therapy. No grade 5 adverse events were recorded and no patient required treatment discontinuation.

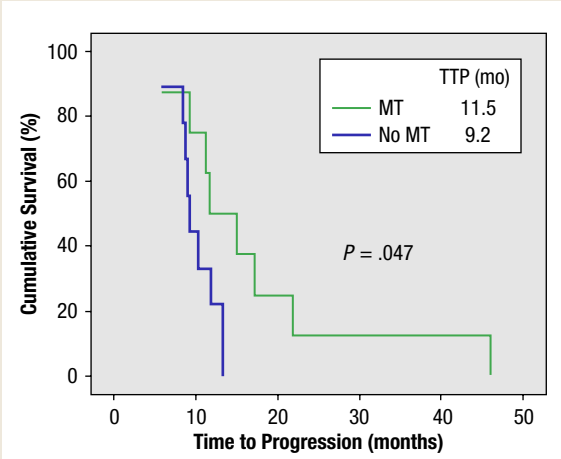
As shown in Table 3, the most common adverse events observed were asthenia (grade 1 in 3 patients and grade 2 in 2 patients), hot flashes worsening (grade 1 in 1 patient and grade 2 in 4 patients), and fluid retention in 3 patients (grade 1 in 1 patient and grade 2 in 2 patients). Other grade 1 and 2 toxicities recorded were hepatotoxicity (2 patients, both due to an exclusive and transient elevation of γ-glutamyltransferase in the absence of alcohol consumption), diarrhea (2 patients), grade 2 hyporexia in 1 patient, and grade 1 cephalgia in 1 patient.

In 1 patient, a nonsymptomatic pulmonary embolism (adverse event grade 4) was diagnosed incidentally in a routine chest computed tomographic scan during follow-up after 8 weeks of maintenance therapy (Table 3).

Discussion

In this retrospective study, we show for the first time to our knowledge that maintenance therapy with a CYP17i after response or stabilization to docetaxel-based first-line chemotherapy can signifi-

Figure 2 Kaplan-Meier Time to Progression (TTP) Curve and Log-Rank Test



Abbreviation: MT = maintenance therapy.

cantly prolong the TTP of patients with mCRPC, with a remarkably favorable toxicity profile.

The ultimate reason for the recent success of different maintenance strategies in the clinical management of patients with cancer relies on the short median TTP times after frontline systemic therapy that most of the patients with different types of malignancies experience and the limited number of regimens or compounds we count on.[19-21]

In 2008, the PCWG published new recommendations for eligibility and outcome measures in trials that evaluate systemic treatment for patients with progressive prostate cancer and castrate levels of testosterone. Regarding the clinical outcomes for phase II studies, they stated that a reliably determined, clinically relevant improvement in TTP can provide the most useful way to assess whether to proceed from a phase II to a phase III trial and may, if reproduced in a randomized controlled trial, be evidence of clinical benefit from a regulatory perspective.[22]

Thus in accordance with that recommendation and other studies in different tumor types in the maintenance setting,[12,23] in the present study TTP was also the primary endpoint because the most clinically meaningful aim in this setting is to prolong the time the patient is free of progression after completion of a first-line chemotherapy regimen. Conversely, the overall survival (OS) time may be partially influenced by the second-line regimens the patient receives and therefore is not a pure reflection of the benefit provided by the maintenance strategy itself. The OS results of our study, currently unavailable, are being analyzed considering second-line treatments received by the patients after progression to LDK maintenance therapy or observation, depending on the patient.

At the time we conceived this analysis, no second-line drugs or regimens had demonstrated a survival advantage for patients with mCRPC after a docetaxel-based first-line regimen, so the need for a strategy to keep those patients free of disease progression for a longer time was the major aim of this study.

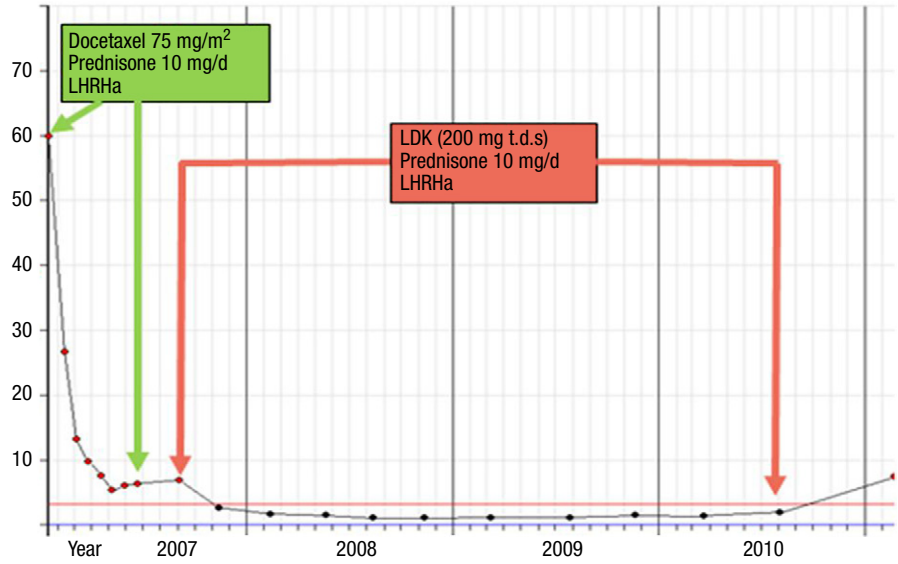
Most patients receiving first-line systemic treatment with docetaxel-based chemotherapy at the castration-resistant stage show progression after a median time of 6 to 8 months.[2,3] For example, in the experience of Zhang et al, patients showing PSA response or SD after first-line docetaxel-prednisone combination therapy had a mean TTP of 25.3 weeks (range, 8-61 weeks; 6.3 months).[24] Oudard et al reported a PSA TTP of 8.8 months when estramustine was added to the frontline docetaxel-prednisone regimen.[25] Accordingly, we observed a median TTP of 9.2 months in our cohort of patients who showed a PSA response or SD after docetaxel-prednisone first-line therapy and were treated with LHRHa alone after completion of chemotherapy. In contrast, those patients receiving LDK maintenance therapy experienced a significantly superior median TTP of 11.5 months (2.3-month advantage for the maintenance group).

No previous studies evaluating the impact of such a maintenance approach on the TTP of patients with CRPC after docetaxel therapy have been reported. However a similar maintenance strategy using hormonal therapy after a first-line chemotherapy regimen has been tested in other hormone-dependent tumors, such as breast cancer, and showed encouraging results.

The only prospective randomized study available in that setting was published by Kloke et al in 1999.[26] In this phase III trial, 90 patients with metastatic breast cancer whose disease was well controlled after 6 cycles of an anthracycline- and ifosfamide-containing regimen were randomized to either receive maintenance therapy with medroxyprogesterone acetate or not. A longer median TTP was reported among patients who were treated with maintenance hormone therapy (4.9 vs. 3.7 months; $P = .02$). Other authors have reported positive results in retrospective studies supporting the routine clinical use of hormone maintenance treatment after a first-line chemotherapy regimen in the absence of disease progression in patients whose tumors express hormone receptors. In a trial by Bertelli et al, 58 postmenopausal patients with metastatic breast cancer who had responded or showed SD with first-line chemotherapy were sequentially treated with maintenance letrozole 2.5 mg/d starting within 8 weeks of the last cycle of chemotherapy.[27] Most of the patients' tumors were hormone receptor–positive (81%) or the receptor status was unknown (19%). Although no control group was used for comparison, a TTP of 18.5 months was observed. In contrast with our study, the TTP was measured from the time of hormone treatment initiation and not from the first chemotherapy cycle. No OS data were reported. The treatment was well tolerated.

In a more recent retrospective analysis by Dufresne et al, a total of 560 patients with hormone receptor–positive metastatic breast cancer were studied to detect predictive factors for the duration of PFS after first-line chemotherapy, and the impact of hormone treatment given as maintenance therapy was analyzed as 1 of those factors.[28] In accordance with our study, the duration of PFS in this analysis was defined as the time from the beginning of first-line chemotherapy to the date of progressive disease or death. The median PFS for patients receiving hormone maintenance therapy with tamoxifen, aromatase inhibitors, fulvestrant, or megestrol acetate after response/stabilization to anthracycline or taxane-based chemotherapy was 16.3 months compared with 7.77 months in patients not receiving hor-

Figure 3 Prostate-Specific Antigen Curve During Maintenance Therapy in a Patient Showing Time to Progression of 35 Months



Abbreviation: LHRHa = luteinizing hormone–releasing hormone agonists.

Table 3 Adverse Events Recorded in Patients Assigned to Maintenance Therapy with Low-Dose Ketoconazole, Prednisone, and LHRHa

Toxicity	Grade (n)				
	1	2	3	4	5
Asthenia	3	2	—	—	—
Diarrhea	1	1	—	—	—
Hepatotoxicity	1	1	—	—	—
Hyporexia	—	1	—	—	—
Cephalgia	1	—	—	—	—
Hot Flashes	1	4	—	—	—
Fluid Retention	1	2	—	—	—
Pulmonary Embolism	—	—	—	1	—

Abbreviation: LHRHa = luteinizing hormone–releasing hormone agonists.

mone maintenance treatment ($P < .0001$). In that trial, the PFS advantage was translated into a statistically significant OS benefit of 18.05 months (48.08 vs. 30.03 months).[28]

With regard to the clinical significance of the magnitude of the differences in outcome we observed, they have to be assessed in the context of other solid tumors in which maintenance therapy has gained regulatory approval. For example, in the non–small-cell lung cancer (NSCLC) setting, 2 different drugs (erlotinib and pemetrexed) have already been approved by the FDA for the maintenance treatment of patients with NSCLC after response or stabilization to a first-line platinum-based regimen.

In the case of erlotinib,[29] patients assigned to switch maintenance therapy with this epidermal growth factor receptor tyrosine kinase inhibitor, showed a PFS of 2.8 months compared with 2.6 months in the placebo arm. Although the difference was statistically significant, its magnitude does not seem to be clinically relevant. However the OS in the same study also favored the maintenance arm with erlotinib (12 vs. 11 months; $P = .009$).

Pemetrexed has been tested in both continuation and switch maintenance settings in patients with NSCLC. The first to gain FDA approval was switch maintenance therapy with pemetrexed in patients with metastatic NSCLC whose disease showed no progression after 4 cycles of a cisplatin-based first-line regimen that did not contain pemetrexed.[30] However, also in the case of pemetrexed as a switch maintenance therapy, the statistically significant benefit of the intervention arm in terms of PFS was 2 months (2 vs. 4 months). Nevertheless this small clinical benefit in PFS translated into an OS benefit for those patients with NSCLC assigned to maintenance therapy with pemetrexed (13.4 vs. 10.6 months, respectively; $P = .012$). Thus in both cases, small PFS advantages have been shown to have an impact in a more clinically relevant outcome benefit in terms of OS, and regulatory approval has been gained.

More recently, the preliminary results of the PARAMOUNT study, which tested the efficacy in terms of PFS advantage (primary endpoint) in patients receiving pemetrexed continuation maintenance therapy after 4 cycles of cisplatin-pemetrexed, were revealed.[15] Patients assigned to the maintenance arm showed a median PFS of 4.1 months compared with the 2.8 months PFS in patients given placebo. Interestingly, although the positive OS data from the PARAMOUNT trial were disclosed in June 2012, in 2011 the EMA approved pemetrexed for continuation maintenance therapy after

cisplatin-pemetrexed doublet treatment based on the aforementioned PFS advantage of 1.3 months for the maintenance arm.

The efficacy and safety of low-dose ketoconazole treatment in the present study is similar to the described in previous trials[7,10] and similar to current compounds with analogous mechanisms of action.[11] The incidence and severity of adverse drug-related reactions were very low and reversible and indicate that long-term treatment is feasible.

Although both treatment groups were in general well balanced, the main caveat of our retrospective study was that the choice of patient/tumor characteristics determining who would or would not receive the maintenance hormone therapy was not random or controlled in any way, so a potential selection bias cannot be ruled out.

Nevertheless the clinical impact obtained by maintenance CYP17i after first-line docetaxel-based chemotherapy in this study might indicate that this strategy should be prospectively tested in a larger randomized study. However for this purpose we would recommend using a more potent selective irreversible CYP17i such as abiraterone acetate, which is already approved after progression to a docetaxel-based first-line regimen but has never been tested in the maintenance setting.

Clinical Practice Points

- Ketoconazole, a nonspecific CYP17i, blocks adrenal androgen synthesis.
- LDK (200 mg t.d.s) has shown activity in mCRPC after progression to androgen deprivation.
- The role of a CYP17i after docetaxel treatment in the maintenance setting has been unexplored.
- This study shows, for the first time to our knowledge, superior PFS in patients receiving ketoconazole-based maintenance therapy after response/stabilization to docetaxel, with a favorable toxicity profile.
- Further studies testing the potential efficacy of more specific and potent CYP17 inhibitors, such as abiraterone acetate, in this novel maintenance setting are warranted.

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Disclosure

The authors have stated that they have no conflicts of interest.

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