Cancer Therapy: Clinical

Phase I Safety and Pharmacodynamic of Inecalcitol, a Novel VDR Agonist with Docetaxel in Metastatic Castration-Resistant Prostate Cancer Patients

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Abstract

Purpose: We conducted a phase I multicenter trial in naïve metastatic castrate-resistant prostate cancer patients with escalating inecalcitol dosages, combined with docetaxel-based chemotherapy. Inecalcitol is a novel vitamin D receptor agonist with higher antiproliferative effects and a 100-fold lower hypercalcemic activity than calcitriol.

Experimental Design: Safety and efficacy were evaluated in groups of three to six patients receiving inecalcitol during a 21-day cycle in combination with docetaxel (75 mg/m² every 3 weeks) and oral prednisone (5 mg twice a day) up to six cycles. Primary endpoint was dose-limiting toxicity (DLT) defined as grade 3 hypercalcemia within the first cycle. Efficacy endpoint was ≥30% PSA decline within 3 months.

Results: Eight dose levels (40–8,000 µg) were evaluated in 54 patients. DLT occurred in two of four patients receiving 8,000 µg/day after one and two weeks of inecalcitol. Calcemia normalized a few days after interruption of inecalcitol. Two other patients reached grade 2, and the dose level was reduced to 4,000 µg. After dose reduction, calcemia remained within normal range and grade 1 hypercalcemia. The maximum tolerated dose was 4,000 µg daily. Respectively, 85% and 76% of the patients had ≥30% PSA decline within 3 months and ≥50% PSA decline at any time during the study. Median time to PSA progression was 169 days.

Conclusion: High antiproliferative daily inecalcitol dose has been safely used in combination with docetaxel and shows encouraging PSA response (≥30% PSA response: 85%; ≥50% PSA response: 76%). A randomized phase II study is planned.

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Introduction

Prostate cancer is the most common cancer in men and the second leading cause of cancer-related male deaths. Patients with symptomatic metastatic castrate-resistant disease have an overall survival (OS) of approximately 24 months with new chemotherapeutic options (docetaxel and cabazitaxel) and novel hormonal therapies such as abiraterone acetate and enzalutamide. Alpharadin, a bone-targeted isotopic drug, has also been associated with an OS increase in this disease. Metastatic castrate-resistant prostate cancer (mCRPC) continues to remain a medical challenge and alternative therapeutic approaches are required (1).

Vitamin D analogues (VDA) have been demonstrated to exert anticancer activity (2–6) via genomic pathways (7). Genomic activity is mediated through the vitamin D receptor (VDR). VDRs are expressed in many types of cancer cells. VDA bind to VDRs, promoting the formation of a heterodimer complex with the retinoid X receptor. These complexes can interact with vitamin D response elements in DNA and recruit coactivators, which regulate target gene transcription.

Antineoplastic properties of VDA include inhibition of cell proliferation, reduction in cellular invasiveness, angiogenesis, and induction of apoptosis. Synergistic antitumor effects have been observed with chemotherapeutic agents (8–10). Glucocorticoids, which are typically combined with...
Clinical Cancer Research

Translational Relevance

Metastatic castrate-resistant prostate cancer (mCRPC) remains a medical challenge, and alternative therapeutic approaches are needed. Hypercalcemia is a common toxicity of calcitriol, the active metabolite of natural vitamin D, prompting a search for a less calcemic analogue for treatment of mCRPC. Herein we report the results of a phase I study investigating the use of inecalcitol, a new synthetic vitamin D analogue, in combination with docetaxel, for this disease. Inecalcitol showed a favorable toxicity profile, with hypercalcemia only observed at a very high dose. Preliminary efficacy results for this combination are promising. This article presents bone metabolism data and includes a comprehensive review of findings from earlier failed phase III studies based on several other combinations with docetaxel. Future development of inecalcitol will be based upon molecular profiles to avoid late failures in the drug development process.

Docetaxel in mCRPC therapeutic regimens, potentiate the antitumor effect of VDA and decrease their hypercalcemic effects (11, 12).

Calcitriol, the active metabolite of natural vitamin D, has been extensively explored as a treatment for prostate cancer (13–15). However, hypercalcemia has precluded its use at an antiproliferative dose, prompting the search for less calcemic analogues. Inecalcitol is a novel oral synthetic VDA with higher antiproliferative activity and differentiation effects as well as considerably less hypercalcemic effects compared with calcitriol (14, 16–18).

This reduction of hypercalcemic effects might be due to the proprietary chemical structure of inecalcitol, a unique conformation of the carbon atom in position 14. In consequence, inecalcitol binds to the VDR but in a different conformation than calcitriol (17). The inecalcitol/VDR/RXR complex binds with different affinities than calcitriol to VDR response element (19), and the genes upregulated or downregulated following inecalcitol binding are different.

The aim of this study was to evaluate an escalating dose of inecalcitol in combination with docetaxel according to the Federal Drug Administration–approved regimen in patients with mCRPC. Safety and efficacy of this association are also presented.

Materials and Methods

Study design

This was an open-label multicenter, nonrandomized dose-escalation study. Eight dose levels and three schedules were evaluated in sequential cohorts of 3 to 6 patients. Inecalcitol doses were escalated in the absence of dose-limiting toxicity (DLT) during the 3 weeks following the initial administration. If DLT occurred in one patient, an additional 3 patients were then treated. The dose was only escalated if no further patients had DLT and was stopped if at least two patients had DLT. The recommended dose was the dose at which no more than one patient out of six experienced DLT. DLT was defined as grade ≥3 common toxicity criteria V3.0 hypercalcemia or persistent treatment-related grade ≥3 toxicities that were considered treatment related. The local Institutional Ethics Review Board granted permission for this study. All patients gave their informed written consent to be included in the study.

Drug administration

Inecalcitol (Hybrigenics S.A) was supplied as soft gel capsules administered once daily (qd), every other day (qod), or twice a day (bid), in combination with a 1-hour intravenous infusion of 75 mg/m² docetaxel once every 3 weeks and 5 mg oral prednisone bid. Patients received up to six 21-day treatment cycles. The maximum number of cycles of docetaxel in combination with inecalcitol was 6. No maintenance therapy with inecalcitol was allowed. Luteinizing hormone–releasing hormone agonist therapy was maintained throughout the study. Antiandrogen therapy was discontinued before enrolment.

Bisphosphonates could be administered after the first cycle. During the study, calcium intake was not restricted, but calcium supplementation was not permitted. Hematologic growth factor (G-CSF and erythropoietin) was not allowed during the first cycles, and was only authorized later.

Outcome measures

For patients with PSA ≥2 ng/mL, response was assessed according to PSA decline ≥30% and ≥50% from baseline within 3 months of treatment initiation (20, 21).

For patients achieving a 30% or 50% PSA decline, the median time to decline was determined between treatment initiation and first occurrence based on the Kaplan–Meier method.

Time to PSA progression was defined as the time between treatment start and PSA progression. Progression was defined as a PSA increase of ≥25% and ≥2 ng/mL above the nadir in case of a decrease from baseline level at study entry confirmed at least 3 weeks later or after 3 months (4 cycles) of treatment if there was no decrease from baseline level at study entry (22).

Phosphorus/calcium balance parameters

Phosphorus/calcium balance parameters (calcium, ionized calcium, phosphorus, creatinine clearance, parathyroid hormone [PTh], 1,25(OH)2/25(OH) Vitamin D3, osteocalcin and C-Telopeptide) were serially monitored along time in each included patient. Data were reported using mean values and NCI-CTC grades.

Statistical analysis

Because of the sequential design of this study, it was not possible to determine in advance the exact number of patients to be enrolled. For qualitative variables, numbers and percentages are provided. For quantitative variables, means with SD, minimum and maximum, are provided. Kaplan–Meier curves were used to obtain time to PSA progression.
Phase I of Inecalcitol with Docetaxel in mCRPC Patients

Results

Patient characteristics

A total of 56 patients were enrolled between November 2007 and September 2010 at six French centers, 54 of whom had at least one inecalcitol intake. Patient characteristics at study entry are summarized in Table 1.

Dose escalation and DLT

Fourteen dose administration schedules covering eight dose levels [40 μg qd (N = 3), 80 μg qod (N = 3) and qd (N = 3), 160 μg qod (N = 3) and qd (N = 6), 300 μg qod (N = 3), and qd (N = 4), 600 μg qod (N = 3) and qd (N = 6), 1,000 μg qod (N = 3), and qd (N = 5), 2,000 μg qd (N = 5), and 4,000 μg qd (N = 3) or bid (N = 4)] were evaluated in 54 patients, 77.8% of whom completed six treatment cycles. Following DLT of grade 3 hypercalcemia evaluated in 54 patients, 77.8% of whom completed six dose levels [40 μg qd and bid]. Grade 2 events did not require inecalcitol interruption and normalized rapidly without corrective treatment. In cases of grade 3, return to normal values was observed 2 days after inecalcitol interruption. During the study, only 6 patients were treated with zoledronic acid.

Safety

Overall, the combination regimen was well tolerated at all dose levels, other than the highest dose (4,000 μg bid). Toxicity was generally manageable; the 11.1% rate of patient withdrawals due to treatment-related toxicity (3.7% due to inecalcitol) was acceptable, whereas at the recommended dose, a 99% rate of delivery of the planned inecalcitol dose and 100% for docetaxel were reported. The inecalcitol safety profile at all doses evaluated was characterized by non-severe transient hypercalcemia, the majority of events being grade 1. A total of 17 patients (31.5%) reported at least one case of grade 1 hypercalcemia (worse grade) at most dose levels, the majority of which were just above the upper limit of normal and of short duration (1–2 days). In grades 2 and 3, hypercalcemia occurred in 3 patients (5.6%) and were only reported at the two highest dose levels, 4,000 μg qd and bid. Grade 2 events did not require inecalcitol interruption and normalized rapidly without corrective treatment. In cases of grade 3, return to normal values was observed 2 days after inecalcitol interruption.

Although a higher-than-expected frequency of neutropenia was reported compared with the frequency in the docetaxel prednisone combination, docetaxel dose intensity was maintained, with only one episode of febrile neutropenia (1.9%). Grade 3 to 4 events are presented in Table 2.

Mean PTH levels slightly decreased during the course of the study in the overall population. At recommended dose, PTH levels were below the lower limit of normal throughout treatment with a similar evolution of 1,25 OH2 vitamin D3 levels. No effect was observed on 25 OH vitamin D3 and phosphorous levels. Mean osteocalcin values decreased over time and mean cross-linked C-telopeptide of type I collagen values decreased in the overall population.

Table 1. Patient characteristics at study entry (N = 54)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Median (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.0 (49–87)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>53 (98.1%)</td>
</tr>
<tr>
<td>2</td>
<td>1 (1.9%)</td>
</tr>
<tr>
<td>PSA, ng/mL</td>
<td>28.5 (0.8–962)</td>
</tr>
<tr>
<td>NSE, ng/mL</td>
<td>9.8 (2.7–547)</td>
</tr>
<tr>
<td>Chromogranin A, ng/mL</td>
<td>62.5 (30–604)</td>
</tr>
<tr>
<td>Gleason score</td>
<td>7 (6–10)</td>
</tr>
<tr>
<td>Gleason score &gt;7</td>
<td>46%</td>
</tr>
<tr>
<td>Prior treatment</td>
<td></td>
</tr>
<tr>
<td>Prostatectomy</td>
<td>26 (48.1%)</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>28 (51.9%)</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>8 (14.8%)</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>54 (100%)</td>
</tr>
<tr>
<td>Duration of hormone therapy (mo), median (range)</td>
<td>38.7 (26–170.4)</td>
</tr>
<tr>
<td>Time from diagnosis to first hormone therapy (mo), median (range)</td>
<td>18.89 (0–163.9)</td>
</tr>
<tr>
<td>Metastases</td>
<td></td>
</tr>
<tr>
<td>Bone only</td>
<td>20 (37.0%)</td>
</tr>
<tr>
<td>Lymph nodes and/or soft tissues only</td>
<td>7 (13.0%)</td>
</tr>
<tr>
<td>Bone, lymph nodes, and/or soft tissue</td>
<td>26 (48.1%)</td>
</tr>
<tr>
<td>Anemia grade 1</td>
<td>37.0%</td>
</tr>
<tr>
<td>25(OH) vitamin D &lt;LLN</td>
<td>65.4%</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; LLN, lower limit of normal; NSE, neuron-specific enolase.

Table 2. Grade 3 to 4 adverse events, NCI-CTCAE (N = 54)

<table>
<thead>
<tr>
<th>Category</th>
<th>G3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>80%</td>
</tr>
<tr>
<td>General physical health deterioration</td>
<td>6%</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>6%</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>6%</td>
</tr>
<tr>
<td>Anemia</td>
<td>4%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4%</td>
</tr>
<tr>
<td>Dehydration</td>
<td>4%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4%</td>
</tr>
<tr>
<td>Syncope</td>
<td>4%</td>
</tr>
<tr>
<td>Pain</td>
<td>4%</td>
</tr>
</tbody>
</table>
Efficacy

PSA response was evaluated using serum levels over time and the percentage change relative to the first day of treatment. Percentage change was analyzed using the thresholds of ≥30% and ≥50% change during the first 3 months and at any time during treatment.

Out of the 54 patients treated, 4 were not assessable for PSA response with PSA level <2 ng/mL at baseline and over the study. Out of the 50 patients assessable for PSA response, 3 did not receive a complete cycle of treatment. PSA decline ≥30% within 3 months of initiation of treatment was observed in 80% (40/50) and 85% (40/47) depending on if they received less or more than one cycle of treatment. Sixty-four percent (64%) of patients were still responding after six treatment cycles.

Evaluation of PSA decline ≥30%, ≥50%, and ≥90% within 3 months and at any time during the study is summarized in Table 3.

A per patient description of best PSA response at 3 months is shown in Fig. 1.

Kaplan–Meier analyses in the 40 patients with a ≥30% decline within the first 3 months showed a median time of 40 days [95% confidence interval (CI), 22–42, range 16–83+ days] between treatment initiation and first occurrence of a ≥30% decline. For the 36 patients with a ≥50% decline at any time during the study, median time to first occurrence of a ≥50% decline was 48 days (95% CI, 41–62, range 16–133+ days).

Efficacy was also evaluated using median time to PSA progression, which was 169 days.

Phosphorus/calcium balance parameters

The large majority of patients had calcium and phosphorus parameters within normal ranges throughout the study. Mean values for each parameter were similar between cohorts (data not shown).

Median PTH levels slightly decreased during the course of the study in the overall population. At recommended dose, PTH levels were below the lower limit of normal throughout treatment with a similar evolution of 1,25 OH2 vitamin D3 levels. No effect was observed on 25 OH vitamin D3 and phosphorous levels. Mean osteocalcin values decreased over time and mean cross-linked C-telopeptide of type I collagen values decreased in the overall population. These results are summarized in Table 4.

Discussion

The study was designed to initially determine the maximum tolerated dose of inecalcitol in combination with docetaxel standard-of-care in patients with mCRPC. Hypercalcemia is the only limiting toxicity reported with VDA. Although calcitriol shows promising activity against cancer cells in vitro, no significant clinical activity was observed in several clinical trials in patients with various cancer types (13, 14). Antiproliferative effects have been observed in vitro

Table 3. PSA response in patients with baseline PSA ≥2 ng/mL receiving at least one treatment cycle

<table>
<thead>
<tr>
<th>PSA decline relative to baseline</th>
<th>Within 3 mo (N = 50)</th>
<th>Any time during the study (N = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30%</td>
<td>40 (80%)/40 (85.1%)</td>
<td>40 (85.1%)</td>
</tr>
<tr>
<td>≥50%</td>
<td>33 (66%)/33 (70.2%)</td>
<td>36 (76.6%)</td>
</tr>
<tr>
<td>≥90%</td>
<td>11 (23.4%)</td>
<td>17 (36.2%)</td>
</tr>
</tbody>
</table>

*All treated pts with PSA > 2 ng/mL at baseline and over the study.

*All pts treated ≥1 month, with PSA > 2 ng/mL at baseline and during the study.
at doses that can cause hypercalcemia and thus prevented dose escalation of daily calcitriol above the range required for antitumor effects (23, 24). Intermittent dosing decreases risk of hypercalcemia, and various administration schedules (qd, qod, bid) have permitted a small dose increase, but only for a short duration (25–27). A new high-dose formulation of calcitriol was evaluated during a weekly administration in 38 patients, with 18 patients who received 45 μg once weekly for a median of 11 weeks with no DLT (14, 23).

In our study, calcium levels were monitored every 2 days during the first cycle and weekly thereafter. We were able to demonstrate that inecalcitol could be adminis-
istered at a much higher dose than calcitriol, and on a daily basis, without an increase in side effects. Toxic daily dose was 8,000 μg with an expected therapeutic daily dose of 4,000 μg, approximately 100-fold more than the weekly 45 μg of calcitriol evaluated in phase II with docetaxel (14). The minimal toxicity profile observed with inecalcitol is due to its proprietary chemical structure characterized by a unique conformation of the carbon atom in position 14, termed 14-epimerization formulation (18, 19). Furthermore, no unexpected toxicities were observed. The main severe toxicity was neutropenia (80% of patients), which was higher than that in the TAX327 and SWOG99-16 trials. The reason for this higher rate of neutropenia is unclear, as the PK of inecalcitol is due to its proprietary chemical structure.

Phase I of Inecalcitol with Docetaxel in mCRPC Patients

Table 4. Modifications of median phosphorus/calcium balance parameters between baseline and the end of the study

<table>
<thead>
<tr>
<th>Time points of dosage</th>
<th>PTH</th>
<th>Corrected calcium</th>
<th>Phosphorus</th>
<th>25(OH)D3</th>
<th>C-telopeptide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole population (n = 54)</td>
<td>Baseline</td>
<td>41.5</td>
<td>2.35</td>
<td>1.16</td>
<td>14.5</td>
</tr>
<tr>
<td></td>
<td>End of study</td>
<td>39</td>
<td>2.37</td>
<td>1.12</td>
<td>15.2</td>
</tr>
<tr>
<td>At the recommended dose (n = 3)</td>
<td>Baseline</td>
<td>29</td>
<td>2.3</td>
<td>1.16</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>End of study</td>
<td>17.2</td>
<td>2.4</td>
<td>1.04</td>
<td>15</td>
</tr>
</tbody>
</table>

This is the first study, testing inecalcitol in combination with docetaxel in mCRPC. It was hypothesized that sustained VDR binding to inecalcitol following daily administration would improve the efficacy of docetaxel. Here, we report a ≥30% PSA decline in 85% of patients within 3 months of treatment initiation, which was maintained after 4.5 months in 64% of patients, and a ≥50% PSA decline in 76% of patients throughout the entire study. The small size of the cohorts (3–6 patients) and the fact that each patient received docetaxel did not permit to show any significant change of PSA between dose levels. This high global PSA decline rate observed could be possibly related to the low proportion of patients (13%) with visceral metastasis and to the quite low median PSA (28.5 ng/mL).

Other published studies with standard docetaxel/prednisone combined with new drugs targeting angiogenesis have not improved PSA response. Thalidomide, achieved a 53% PSA response rate in combination with weekly docetaxel (29). On the basis of a bevacizumab, docetaxel, and estramustine combination in a phase II study, Petrylak and colleagues (30) showed a PSA response of ≥50% in 79% of patients. In the VENICE study, a double-blind, randomized phase III study, aflibercept in combination with docetaxel did not improve OS. PSA response was reported in 68.6% of patients treated with aflibercept versus 63.5% with docetaxel alone (P = 0.075; 31).

Finally, calcitriol did not demonstrate a higher PSA decline than docetaxel alone in the phase II trial, ASCENT1, as 58% of calcitriol regimen patients experienced a ≥30% decline versus 49% of patients on docetaxel alone (32). However, docetaxel was given as a weekly schedule, which produces lower PSA response rates than with the 3-weekly schedule. In the phase III study, ASCENT2, Scher and colleagues compared a 3-weekly schedule of docetaxel with a 3 out of 4 weeks of weekly docetaxel in combination with calcitriol. At interim analysis, the study was interrupted because of shorter OS (17.8 months compared with 20.2 months, P = 0.002), in the experimental arm. This difference might be due not only to the weekly schedule of docetaxel, which has shown a trend toward inferior efficacy. There was also in the experimental arm a comparatively higher number of dose modifications due to docetaxel...
toxicity, although no significant increase of severe calcitriol related adverse events were observed (33).

The data of the current study suggest a short time to achieve a PSA response. Median time between treatment start and first occurrence of a ≥30% and ≥50% decline was 40 days and 48 days (1.4 months), respectively. Docetaxel alone required 5.3 months to achieve a 50% decline in PSA for half of the patients and 2.9 months in combination with calcitriol in the ASCENT1 trial (32).

These results illustrate the difficulties associated with identifying the activity of novel agents in mCRPC. Most patients have disease limited to the bone, which is notoriously difficult to assess for response. PSA measurement is much simpler to obtain and approximately 95% of patients with metastatic prostate cancer have elevated PSA (20). Changes in PSA will often precede changes on bone scans, and its use could theoretically permit new agents to be screened more rapidly for activity. Armstrong and colleagues (21) identified PSA decline ≥30% within 3 months as a reliable prognostic surrogate marker for OS in patients with mCRPC treated with docetaxel/prednisone in the large randomized phase III study (TAX327; ref. 26), as was previously demonstrated with docetaxel/estramustine (22).

During the last 6 years, nearly 10,000 patients were included in eight randomized phase III studies evaluating targeted therapies in combination with docetaxel. Despite promising results observed in phase I to II studies, none of these phase III studies showed OS improvement. The decision-making processes to proceed from phase II to phase III need to be revised (34).

Recent discoveries of inherited and acquired genetic markers associated with prostate cancer initiation and progression provide an opportunity to apply such findings to guide decision-making and better define populations to include in future phase III studies (35). In the case of the inerocalcitol activity pathway, biologic studies on the VDR in prostate cancer have shown that cancer cells display de novo and acquired mechanisms of resistance to VDA. Data suggest that VDR activity in advanced solid tumors is retained, but was skewed by epigenetic mechanisms selectively suppressing antiproliferative target gene promoter responses (36). Ting and colleagues showed a downregulation of VDR expression, a reduced VDR-mediated transcriptional activity, and an attenuated antiproliferative response to vitamin D in aggressive androgen-independent prostate cancer cells (37). Khamin and Banwell have reported an elevated level expression of coexpressor proteins of VDR, Ncor, and SMRT in prostate and breast cancer cell lines (38, 39). Abedin and colleagues showed that antiproliferative effect of VDA could be restored in prostate cancer cell lines with HDAC inhibitor (36).

These findings suggest that the integrity of the vitamin D signaling pathway is crucial in predicting vitamin D responsiveness and thus provide a rationale to select patients on molecular profiles and improve efficacy of VDA with innovative combination regimens.

In mCRPC, the TAX327 study shows a survival improvement with docetaxel. However, in this rapidly changing landscape, phase III clinical trials combining docetaxel with new different agents have not yet demonstrated any survival advantages despite encouraging results observed in phase II studies. Several questions arise from these results, such as: “What would be the most predictive endpoint to use in phase II studies?” and “How can the population for phase III studies be narrowed?” The improvement in PSA outcome observed in this dose-escalation study with inerocalcitol, a new VDA, is encouraging. However, these preliminary results based on PSA response must be confirmed in a randomized study in the light of the molecular tumor profile based on VDR and coregulators expression level as well as protein expression level regulated by vitamin D. Translational research, which will aim to characterize responders on genomics, epigenomics, and proteomics, is scheduled to be performed in future phase II studies with inerocalcitol.

Disclosure of Potential Conflicts of Interest
S. Renaux and J.F. Dufour-Lamartinie are employees of Hybrigenics. S.M. Oudard reports receiving speakers bureau honoraria from Astellas, Bayer, Hybrigenics, Janssen, Sanofi, and Tadeka. S. Mackenzie reports receiving commercial research support from Hybrigenics. No potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Medioni, G. Deplanque, J.-F. Dufour-Lamartinie, S.M. Oudard
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J. Medioni, G. Deplanque, S. Mackenzie, S.M. Oudard
Writing, review, and/or revision of the manuscript: J. Medioni, G. Deplanque, J.-F. Ferrero, E. Raymond, J. Allyon, G. Matsui, P. Houllier
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J. Allyon, S. Mackenzie, C. Le Rest, S.M. Oudard
Study supervision: J. Medioni, J. Allyon, S. Renaux, R. Elaidi, S.M. Oudard

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