Phase I Safety and Pharmacodynamic of inecalcitol, a novel VDR agonist with docetaxel in metastatic castration-resistant prostate cancer patients

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TRANSLATIONNAL RELEVANCE.

In this paper we report results of a Phase I study regarding a new synthetic vitamin D analogue in combination with docetaxel for metastatic prostate cancer. This Cancer Therapy study should be considered for publication for several reasons: Inecalcitol has a favorable profile of toxicity and only hypercalcemia at a very high dose has been reported. Preliminary efficacy results are promising. The study was performed in association with physiologists, and data of bone metabolism are presented.

A comprehensive discussion is presented, with a review of the previously failed phase III studies based on a combination of several anti-cancer agents with docetaxel. Future development of inecalcitol will be based upon molecular profiles, to avoid late failures in the drug development process.

Our results were partially presented at ASCO Meeting in 2009 and ASCO Genitourinary Cancer Symposium in 2011.
ABSTRACT

Purpose

We conducted a Phase I multicenter trial in naïve metastatic CRPC patients with escalating inecalcitol dosages, combined to 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 3-6 patients receiving inecalcitol during a 21-day cycle in combination with docetaxel (75mg/m2 every 3 weeks) and oral prednisone (5mg 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 to 8000 µg) were evaluated in 54 patients. DLT occurred in 2/4 patients receiving 8000 µg/day after 1 and 2 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 4000 µg. After dose reduction, calcemia remained within normal range and grade 1 hypercalcemia. The maximum tolerated dose was 4000 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 2 study is planned.
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 anti-cancer activity (2,3,4,5,6) via genomic pathways (7). Genomic activity is mediated through the vitamin D receptor (VDR). VDRs are expressed in many types of cancer cells. Vitamin D analogues bind to VDRs, promoting the formation a heterodimer complex with the retinoid X receptor. These complexes can interact with vitamin D response elements in DNA and recruit co-activators, 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 (8,9,10). Glucocorticoids, which are typically combined with 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 (13,14,15). 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 anti-proliferative activity and differentiation effects as well as considerably less hypercalcemic effects compared to calcitriol (16,17,18,14).
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 up- or down-regulated following inecalcitol binding are different.

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

Materials and methods

Study design

This was an open-label multicenter, non-randomized dose-escalation study. Eight dose levels and three schedules were evaluated in sequential cohorts of three to six 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 three 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 (RD) 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. Paris, France) 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. Anti-androgen 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. Hematological Growth factor (G-CSF and erythropoietin) were not allowed during the first cycles, and only authorized later.

**Outcome measures**

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

For patients achieving a 30 or 50% PSA decline, 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 $\geq$ 25% and $\geq$ 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, 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 section**

Due to 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, mean with standard deviation, minimum and maximum will be provided.

Kaplan-Meier curves were used to obtain time to PSA progression.

**Results**

**Patient characteristics**

Fifty-six 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), 1000 µg qod (N=3) and qd (N=5), 2000 µg qd (N=5), and
4000 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 (albumin-corrected calcium) during the first treatment cycle in two of the four patients treated at 4000 µg bid (after 8 and 17 days treatment), the RD for inecalcitol in combination with docetaxel 75 mg/m² and 5 mg prednisone bid was defined as the next lowest dose level, 4000 µg qd. Three patients were treated at the RD. The dose was reduced to 4000 µg qd from cycle 2 onwards in two patients.

**Safety**

Overall, the combination regimen was well tolerated at all dose levels, other than the highest dose (4000 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 RD 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 to 2 days). In grades 2 and 3 hypercalcemia occurred in three patients (5.6%) and were only reported at the two highest dose levels, 4000 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.

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

**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, four (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, three (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 Figure 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% 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 $\geq 50\%$ 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 parathyroid hormone (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.

INSERT TABLE 4

**Discussion**

The study was designed to initially determine the maximum tolerated dose of inecalcitol in combination with docetaxel the standard of care in mCRPC patients. 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). Anti-proliferative effects have been
observed in vivo 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 (25,26,27). 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 (25,14).

In our study calcium levels were monitored every two days during the first cycle and weekly thereafter. We were able to demonstrate that inecalcitol could be administered at a much higher dose than calcitriol, and on a daily basis, without an increase in side-effects. Toxic daily dose was 8000 µg with an expected therapeutic daily dose of 4000 µg, approximately 100-fold greater than the weekly 45 µg of calcitriol evaluated in phase 2 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 in the TAX327 and SWOG99-16 trials. The reason for this higher rate of neutropenia is unclear, as the PK of docetaxel remained unchanged with inecalcitol. Non-hematologic toxicities were primarily grade 2, the most frequent being asthenia (46%) and alopecia (22%), with incidences similar to those in TAX327 and SWOG99-16 trials (28,22).

For mCRPC, docetaxel-based chemotherapy remains the standard of care offering a survival advantage. Progress in the understanding of the molecular biology of prostate cancer has led to targeted therapies being administered in combination with docetaxel. Numerous classes of agents have been combined with docetaxel in phase 2 studies in mCRPC, including tyrosine kinase inhibitors, antiangiogenic agents, bone-targeted agents, BCL-2 inhibitors, chemotherapies, immunologic agents, calcitriol and and first generation vitamin D analogues.
(VDA). In several cases, promising rates of PSA response, tumor response, and survival trends have been reported. However to date, no drug has demonstrated a survival improvement when combined with docetaxel, while some combinations have caused increased toxicity.

This is the first study, testing inecalcitol in combination with docetaxel in mCRPC. It was hypothesized that sustained vitamin D receptor 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 to 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 (28.5ng/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). Based on a bevacizumab, docetaxel and estramustine combination in a phase 2 study, Petrylak et al. (30) showed a PSA response of ≥50% in 79% of patients. In the VENICE study, a double-blind, randomized phase 3 study, aflibercept in combination with docetaxel did not improve OS. PSA response was reported in 68.6% of patients treated with aflibercept vs. 63.5% with docetaxel alone (p=0.075) (31).

Finally, calcitriol did not demonstrate a higher PSA decline than docetaxel alone in the phase 2 trial, ASCENT1, as 58% of calcitriol regimen patients experienced a ≥30% decline vs. 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 3 study, ASCENT2, Scher et al. compared a 3 weekly schedule of docetaxel to a 3 out of 4 weeks of weekly docetaxel in combination with calcitriol. At interim analysis, the study was interrupted because of shorter overall survival (17.8 months compared to 20.2 months, P=.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, but also to in the experimental arm to 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 et al. (21) identified PSA decline ≥30% within 3 months as a reliable prognostic surrogate marker for OS in mCRPC patients treated with docetaxel/prednisone in the large randomized phase 3 study (TAX327) (26), as was previously demonstrated with docetaxel/estramustine (22).
During the last 6 years nearly 10,000 patients were included in eight randomized phase 3 studies evaluating targeted therapies in combination with docetaxel. Despite promising results observed in phase 1-2 studies, none of these phase 3 studies showed OS improvement. The decision-making processes to proceed from phase 2 to phase 3 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 3 studies (35). In the case of the inecalcitol activity pathway, biological studies on the VDR in prostate cancer have shown that cancer cells display de novo and acquired mechanisms of resistance to vitamin D analogues. 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 et al. 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). Khanin and Banwell have reported an elevated level expression of corepressor proteins of VDR, Ncor and SMRT in prostate and breast cancer cell lines (38,39). Abedin et al. 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 signalling 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 regimen.

**Conclusion**

In mCRPC, the TAX327 study, which shows a survival improvement with docetaxel. However, in this rapidly changing landscape, phase 3 clinical trials combining docetaxel with new different agents have not yet demonstrated any survival advantages despite encouraging
results observed in phase 2 studies. Several questions arise from these results, such as: “What would be the most predictive end point to use in phase 2 studies?” and “How can the population for phase 3 studies be narrowed?” The improvement in PSA outcome observed in this dose escalation study with inecalcitol, a new vitamin D analogue, 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 2 studies with inecalcitol.
REFERENCES


9 Moffatt KA, Johannes WU, Miller GJ. 1Alpha,25dihydroxyvitamin D3 and


Scher HI, Jia X, Chi K, de Wit R, Berry WR, Albers P, et al. Randomized, Open-Label Phase III Trial of Docetaxel Plus High-Dose Calcitriol Versus Docetaxel Plus Prednisone for Patients With Castration-Resistant Prostate...


<table>
<thead>
<tr>
<th></th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Table 1: Patient characteristics at study entry (N=54)</strong></td>
<td></td>
</tr>
<tr>
<td>Age median (range), years</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 median (range), ng/mL</td>
<td>28.5 (0.8-962)</td>
</tr>
<tr>
<td>NSE median (range), ng/mL</td>
<td>9.8 (2.7-547)</td>
</tr>
<tr>
<td>Chromogranin A, median (range), ng/mL</td>
<td>62.5 (30-604)</td>
</tr>
<tr>
<td>Gleason score, median (range)</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 (months), median (range)</td>
<td>38.7 (2.6-170.4)</td>
</tr>
<tr>
<td>Time from diagnosis to first hormone therapy (months), 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>

ECOG PS: Eastern Cooperative Oncology Group Performance Status; LLN: lower limit of normal; PSA: prostate-specific antigen; NSE: neuron specific enolase
Table 2: Grade 3-4 adverse events, NCI-CTCAE (N=54)

<table>
<thead>
<tr>
<th>Condition</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>
Table 3: PSA response in patients with baseline PSA \( \geq 2 \) ng/mL receiving at least one treatment cycle

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

* all treated pts with PSA > 2ng/mL at baseline and over the study  
** all pts treated \( \geq 1 \) month, with PSA > 2ng/mL at baseline and during the study
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></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>41.5</td>
<td>2.35</td>
<td>1.16</td>
<td>14.5</td>
<td>0.53</td>
</tr>
<tr>
<td>End of study</td>
<td>39</td>
<td>2.37</td>
<td>1.12</td>
<td>15.2</td>
<td>0.35</td>
</tr>
<tr>
<td>At the recommended dose (n=3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>29</td>
<td>2.3</td>
<td>1.16</td>
<td>19</td>
<td>0.24</td>
</tr>
<tr>
<td>End of study</td>
<td>17.2</td>
<td>2.4</td>
<td>1.04</td>
<td>15</td>
<td>0.25</td>
</tr>
</tbody>
</table>

PTH: parathyroid hormone
Legend for figure

Figure 1: Best PSA response within 3 months, per patient (N=47)
Figure 1
Phase I Safety and Pharmacodynamic of inecalcitol, a novel VDR agonist with docetaxel in metastatic castration-resistant prostate cancer patients

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