A Phase I Study to Determine the Maximum Tolerated Dose and Safety of Oral LR-103 (1α,24(S)Dihydroxyvitamin D_2) in Patients with Advanced Cancer

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Abstract

Background—The objective of this study was to determine the maximum tolerated dose (MTD) and safety of LR-103, a Vitamin D analogue, in patients with advanced cancer.

Methods—In Step A, patients received once daily oral LR-103 in 14-day cycles with intra-patient dose escalation per accelerated dose escalation design. Dose limiting toxicity (DLT) for Step A was defined as ≥ grade (gr.) 2 hypercalcemia and/or > gr. 2 other toxicities. Starting dose was 5μg/day. Step B used a 3+3 design starting at Step A MTD with 28-day cycles. DLT was defined as ≥ gr. 3 hypercalcemia or any gr. 3 or 4 non-hematologic toxicity, except hypercalciuria.

Results—21 patients were enrolled; 8 were treated in Step A. At dose level 3 (15 μg/day), 2patientsshad DLT. One had gr. 4 hyperuricemia. The other had gr. 4 GGT plus gr. 3 alkaline phosphatase, fatigue and UTI. Dose level 2 (10 μg/day) was the MTD for Step A and was starting dose for Step B. The dose was escalated to dose level 5 (30 μg/day) with 1 patient experiencing gr 3 DLT of hypercalcemia. The study was discontinued before reaching the MTD due to sponsor decision. Modest increases in serum osteocalcin and calcium and decrease in parathyroid hormone were noted. Best response was stable disease; 4 patients were on therapy for ≥ 6 months.

Conclusion—Step A DLTs limited accelerated dose escalation. The MTD of LR-103 was not reached prior to study termination and this agent is no longer being developed.

Keywords

Vitamin D; phase I; cancer

Introduction

The Dvitamins are steroid molecules which interact with the Vitamin D receptor and are important in calcium homeostasis. Calcitriol (1α,25Dihydroxyvitamin D) is the endogenous active form of vitamin D. Epidemiologic studies suggest a link between low levels of Vitamin D and the risk of developing cancer[1–7].The vitamin D receptor is expressed in a variety of human tumors and *in vitro* and *in vivo* preclinical studies demonstrate that calcitriol and other vitamin D compounds inhibit the growth of cancer cell lines and xenografts through a number of mechanisms including inhibition of cycle regulation, induction of differentiation, modulation of growth factors and hormones, the induction of apoptosis and the inhibition of angiogenesis[8–15]. These results suggest vitamin D compounds may have a role in the treatment of cancer. However, early phase clinical trials of calcitriol and other vitamin D compounds have been limited by hypercalcemia and hypercalciuria,[16, 17] which have led to adaptations in dosing schedules to allow for safer delivery[18–22].

LR-103 (1α,24(S)Dihydroxyvitamin D_2; 1α,24(S)$(OH)_2D_2$) is an investigational vitamin D compound. It is a naturally occurring metabolite of vitamin D2 (ergocalciferol) which has been identified in several species[23], including humans[24]. LR-103 has approximately the same binding affinity for the vitamin D receptor as calcitriol, but about one tenth of the affinity for the vitamin D binding protein which transports vitamin D in the circulation[23, 25].

Vitamin D compounds with lower affinities for the DBP may be more available to the vitamin D receptor.

In vitro studies have demonstrated that LR-103 is equipotent with calcitriol in the growth inhibition of primary keratinocytes[26] and osteosarcoma, breast, prostate, colon and leukemia cancer cell lines[27, 28]. *In vitro* experiments with the LNCaP prostate cancer cell line and MCF-7 breast cancer cell line demonstrated additive or synergistic anti-proliferative effects when LR-103 was used in combination with other anti-cancer agents[29]. In a xenograft model of MCF-7 breast cancer cells implanted into nude mice, administration of LR-103 significantly decreased the rate of tumor growth and tumor volume, with no significant changes in serum calcium levels, as compared to controls[30]. The results of *in vivo* studies in rats[31] indicate that LR-103 is significantly less calcemic than calcitriol, with 10–40 fold difference depending on the experimental model. In a repeated dose, 90-day subchronic toxicity study in rats and a repeated dose, 28-day subchronic toxicity study in cynomolgus monkeys, LR-103 was very well tolerated. The findings from these studies were consistent with the pharmacology and toxicity expected with a vitamin D compound. Increases in urine and serum calcium with tissue mineralization at higher doses were observed.

In summary, LR-103 is a novel vitamin D compound, which in pre-clinical studies has equivalent anti-cancer activity as compared to calcitriol, but without significant hypercalcemia and hypercalciuria. The objectives of this phase I study of single agent LR-103 were to define the maximum tolerated dose, safety, pharmacokinetics and preliminary anti-tumor activity of this agent in patients with advanced malignancies.

Patients and Methods

Patient selection

Men and women age 18 or older with a National Cancer Institute (Zubrod) performance status of 0,1 or 2, predicted life expectancy ≥12 weeks, and histologically or cytologically verified solid or hematologic malignancy were eligible for study enrollment. Patients must have been ≥ 2 weeks from most recent radiation or biologic response modifiers (such as interferon or hormonal therapy) and ≥ 4 weeks from most recent chemotherapy (except nitrosoure as and mitomycin C which required a minimum of 6 weeks). Patients with prostate cancer on hormonal therapy for medical castration were allowed to continue this therapy. Patients must have had adequate organ function, defined as absolute neutrophil count ≥ 1,500/μl, platelet count ≥ 100,000/μl, bilirubin ≤1.5× institutional upper limit of normal (ULN), AST and ALT ≤ 1.5× ULN, calcium and creatinine ≤ ULN. No concurrent calcium or vitamin D therapy was allowed. Baseline vitamin D levels were not used as an inclusion criteria. Exclusion criteria included pregnant or lactating women, use of thiazide diuretics or digoxin within 2 weeks of study enrollment, or co-morbid conditions including nephrolithiasis, uncontrolled hypercalcemia, cardiovascular disease, HIV or history of brain metastases. All patients signed an informed consent document prior to study participation. This protocol was approved by the University of Wisconsin Institutional Review Board.

Study design and treatment

This was a single institution, open-label, phase I dose escalation study using a novel accelerated dose escalation design.[32] The starting dose level for LR-103 was based on the FDA guidance, "Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Health Volunteers".[33] These guidelines were applied to this Phase I clinical trial as it fit well with the approach of initiating the Phase I trial with a conservative dose and then rapidly escalating. The maximum recommended starting dose determined from these guidelines was 5 μg/day. Patients were instructed to take LR-103 at the same time each morning after fasting from midnight without pre-medications. LR-103 was provided in capsule form by Genzyme Corporation.

A total of 8 weeks of LR-103 treatment was planned, although patients could continue on treatment if clinical benefit was noted. Patients were treated until development of progressive disease, unacceptable adverse event possibly related to study drug, lack of compliance with study requirements, inter current illness requiring medications not allowed by protocol, or withdrawal of consent.

This novel study design incorporated two steps of dose escalation. Step A used an accelerated dose escalation design. This was followed by Step B which used a standard 3+3 design. Step A was designed to efficiently eliminate doses well below the maximum tolerated dose (MTD) and step B was designed to determine the MTD. Step A had independent criteria for intra-patient dose escalation and dose limiting toxicity (DLT). Dose escalation was only allowed in patients with minimal to no toxicity. For patients with grade 1 hypercalcemia or grade 2 other toxicities, the dose was not escalated. The definition of dose-limiting toxicity (DLT) for Step A included ≥ grade 2 hypercalcemia and/or > grade 2 other toxicities. This design was supported by preclinical modeling which predicted LR-103 was 10–20 fold less hypercalcemic than comparative products and prior reports that hypercalciuria would be an early sign of risk of further development of hypercalcemia. Thus, it was expected that very low doses of LR-103 would be unlikely to cause clinically significant hypercalcemia and an accelerated dose-escalation design would be appropriate.

In Step A, LR-103 was administered to the patient once each morning continuously in 14 day cycles. The first patient was treated at 5 μg/day. If during the first cycle the patient experienced no or minimal toxicity (defined as grade 0 hypercalcemia and/or ≤ grade 1 other toxicities), an intra-patient dose-escalation to the next dose level was planned. If the patient experienced no or minimal toxicity again, a second intra-patient dose-escalation was planned (Table 1). If moderate toxicity (grade 1 hypercalcemia and/or grade 2 other toxicities) or a severe toxicity (also a Step A DLT) occurred, no intra-patient dose-escalation was performed. Patients continued on Step A for up to 8 weeks with 2 dose-escalations allowed per patient. Any adverse event occurring during the first 2 cycles (4 weeks) at a dose level was considered for DLT criteria for Step A. The starting dose for subsequent patients enrolled in Step A was the highest dose at which the previous patients had not experienced a moderate toxicity or DLT. Enrollment into Step A continued until two DLTs were noted at the same dose level. The Step AMTD was the highest evaluable dose level that the observed severe toxicity incidence rate was ≤ 1/3.

Step B was a standard 3+3 dose escalation design starting at the MTD determined in Step A. LR-103 was administered once daily consecutively for a 28-day cycle. No intra-patient dose escalations were allowed. Dose escalation continued until ≥ 2 DLTs were observed in a cohort of patients. DLT was defined as ≥ grade 3 hypercalcemia or any grade 3 or 4 non-hematologic toxicity, except hypercalciuria. The MTD for Step B was defined as the dose level at which 0–1 of 6 patients experiences a DLT with the next higher dose level having at least 2 patients with a DLT. Patients unable to complete at least 14 days of treatment in Step A or 28 days in Step B for reasons other than toxicity were not considered evaluable for determination of the MTD and were replaced. Once the Step B MTD was established, a dose expansion cohort of up to 10 further patients for pharmacokinetic and safety analysis was planned. Change in baseline laboratory parameters were analyzed by Wilcoxon signed-rank test.

Assessments

Pre-trial eligibility screening and baseline imaging was performed within 14 days of initial treatment. During treatment, patients were evaluated on days 1, 8, 15, 22 of each 28 day cycle. CBC with differential, calcium, phosphorus and other electrolytes, creatinine, liver function tests, and uric acid were collected weekly. Parathyroid hormone (PTH) and PTH-related protein levels were collected on cycle 1, days 1, 8 and 15 and cycle 2, days 1, 15 and 28. Twenty-four hour urine collections for calcium, phosphorus and creatinine and serum markers of bone turnover (N-telopeptide, osteocalcin and bone-specific alkaline phosphatase) were also collected serially. Physical exam was performed at screening, week 4 and at the end of cycle 2. Radiographic assessment for tumor response was performed every 8 weeks with CT imaging. RECIST version 1.0 was used to classify response to therapy for solid tumor cases.[34]Adverse events (AE) were graded using NCI CTCAE, version 2.0. No attribution to study drug were required for DLT definitions. Patients experiencing grade 2 or higher hypercalcemia were instructed to discontinue LR-103 and calcium supplements and initiate a low calcium diet until the hypercalcemia resolved. For calcium >12 mg/dL or for severe symptoms, intravenous fluids, bisphosphonates and/or calciton in were recommended. If hypercalcemia resolved within 7 days, treatment with LR-103 could be resumed at 1 dose level lower.

Samples were also collected for pharmacokinetic (PK) and pharmacodynamics analysis. On cycle 1, day 1 samples were drawn pre-dose and at 0.5, 1, 2, 4, 6, 7, 10, 12, 16 and 24 hours post-dose. Subsequent trough samples were collected weekly to determine levels of vitamin D metabolites and LR-103. PTH, PTHrP and bone turnover markers (osteocalcin, N-telopeptide, bone specific alkaline phosphatase) were measured at baseline and end of week 8. Descriptive statistics were used for baseline characteristics and Wilcoxon signed-rank test for laboratory tests.

Results

Patient Characteristics

Between May 2004 and March 2006, a total of 21 patients were enrolled and treated on the study: 8 in Step A and 13 in Step B. Baseline patient characteristics are described in Table 2.

The median age was 63 years (range 45–86). Twelve patients (57.1%) were female. The most common tumor types were ovarian (19%), uterine (19%) and prostate cancer (14.3%). Other tumor types included cervical, colon, esophageal, Ewing's Sarcoma, cholangiocarcinoma, melanoma, non-Hodgkin lymphoma, pancreatic, and thyroid cancers. The majority of patients had a baseline Zubrod performance score of 0–1 (95.2%). All patients had metastatic disease. The majority had prior systemic therapy (90.5%)and about half of the patients hadradiation therapy (47.6%) for treatment of metastatic disease. At baseline, 47.6% of patients were taking a general multivitamin. There was no recorded increased use of calcium, vitamin D or general multivitamins during this study. No change in medications that can alter calcium metabolism were noted in patients on study (e.g. bisphosphonates). Furthermore, no intravenous bisphosphonates were administered to any patient on trial.

Treatment Summary

The results from the accelerated dose escalation cohort (Step A) are described in Table 3a. A total of twenty-nine 14-day cycles (range 1–11) were administered. Per protocol intra-patient dose escalation was performed in 3 of 8 patients. The maximum dose administered in Step A was 20 μg/day after dose-escalation in one of those patients. At dose level 3 (15 μg/day), two patients experienced dose-limiting toxicities meeting protocol criteria for Step A. One patient experienced grade 4 hyperuricemia on cycle 1, day 8leading to dose reduction. The other experienced grade 4 GGT (gamma-glutamyl transpeptidase) and grade 3 alkaline phosphatase elevation, fatigue and urinary tract infection at the end of week 4. This patient also developed grade 1 hypercalcemia and grade 2 hypercalciuria. Dose level 2 (10 μg/day) was the maximum tolerated dose for Step A.

Thirteen patients were enrolled on Step B (Table 3b). The first cohort was started at dose level 2 (10 μg/day), the maximum-tolerated dose reached in Step A. A total of 47.5,28-day cycles (range 1–14) were administered. The dose was escalated to a maximum dose of 30ug/day. One patient at 30 μg/day experienced a DLT of grade 3 hypercalcemia. Another patient treated at 15 μg/day developed grade 4 hypercalcemia, leading to study drug discontinuation after more than 1 year on therapy. Part B was discontinued before reaching the maximum tolerated dose due to the slow dose escalation and adverse events noted. Subsequently, the drug supply ceased and the industry sponsor had a change in drug development priority.

Alterations in Laboratory Parameters with LR-103

Table 4 demonstrates that treatment with LR-103 resulted in a statistically significant increase from baseline in osteocalcin (+ 12.2ng/ml; $p < 0.001$), serum calcium (+0.6mg/dL; $p < 0.001$) and 24 hour urine calcium excretion (+184mg/24hours; $p < 0.001$), as well as a decrease in parathyroid hormone levels (−28.6 pg/ml, $p < 0.001$). Although the bone specific alkaline phosphatase, phosphorus, albumin, creatinine and uric acid levels did increase from baseline, the changes were not statistically significant. The changes are expected based on the vitamin D receptor agonist mechanism of LR-103.

Adverse Events

Adverse events that were definitely, probably, or possibly related to the study treatment and affecting two or more patients are listed in Table 5. The most common non-hematologic toxicities irrespective of severity were diarrhea (19.0%), fatigue (23.8%), hypercalcemia (38.1%), hyperuricemia (19%), and hypercalciuria (38.1%). Related or unrelated grade 3 or 4 events on study included increased alkaline phosphatase, GGT, hypercalcemia, hyperuricemia, and hypercalciuria, acute renal failure, fatigue, pneumonia, urinary tract infection, and ureteric obstruction. Related grade 3/4 events included one patient with grade 3 alkaline phosphatase and two patients with grade 3 fatigue at dose level 2, one patient with grade 4 hypercalcemia at dose level 3, one patient with grade 4 alkaline phosphatase at dose level 4 and at dose level 5, there was one patient with grade 3 hypercalcemia. As expected, no grade 3 or 4 hematologic events occurred during the study.

Clinical activity and Pharmacokinetics

No RECIST partial or complete responses were noted in any patients. Four patients had prolonged stable disease: 3 remained on study for more than 6 months and 1 patient had stable disease for more than 12 months. The first patient with thyroid cancer was treated in Step A and remained at dose level 3 (15 μg/day) for 6 months before disease progression. Another patient with endometrial cancer was treated at dose level 2 (10 μg/day) in Step B and remained on trial for 11 months before progressive disease. A patient with ovarian cancer was treated at dose level 4 (20 μg/day) in Step B and had stable disease for 6 months prior to electing to coming off study. A patient with cholangiocarcinoma was treated at dose level 3 (15 μg/day) in Step B with disease control for 14 months. Pharmacokinetic samples were not processed secondary to lack of development of assays to detect the compound or its metabolites in plasma.

Discussion

This phase I first-in-human study of the investigational vitamin D compound,LR-103, was initiated based on preclinical evidence of anti-cancer efficacy with less toxicity compared to other vitamin D therapies, including calcitriol. Although the study was not completed and did not define the MTD of this agent, this phase I study used a novel study design that could be considered for future phase I studies. The study design incorporated two steps: Step A used an accelerated dose escalation design and Step B a standard 3+3 design. This design allowed for intra-patient dose escalations in order to achieve a more rapid dose-escalation and limit patients treated at doses well below the maximum tolerated dose. This methodology was selected since preclinical data with LR-103 suggested toxicity was unexpected at lower doses of this agent. Safety was maintained by using a stricter definition for dose-limiting toxicities in the Step A population.

Unexpectedly in this study, DLTs were noted early in Step A (at dose level 3; 15μg/day) with grade 4 hyperuricemia and elevated GGT and grade 3 elevated alkaline phosphatase, fatigue, and urinary tract infection. These adverse events may have been unrelated to the LR-103 therapy but attribution was not required per the study protocol. Future studies incorporating this accelerated intra-patient dose escalation design may benefit from limiting

DLT to those toxicities attributed to the agent. Per protocol, the 3+3 dose escalation (Step B) was initiated at 10μg/day. The dose of LR-103 was able to be successfully escalated to 30μg/day in this cohort of patients with one patient experiencing a DLT (grade 3 hypercalcemia). The study was terminated prior to determination of the Step B MTD.

The anti-tumor preclinical data with LR-103 was promising in several cancer subtypes. In this study, 4 patients experienced prolonged stable disease greater than 6 months per RECIST 1.0 criteria and one patient was on trial for more than 12 months. These patients had advanced cholangiocarcinoma, ovarian, thyroid, and endometrial cancers. No clinical complete or partial responses were noted. Although prolonged stable disease may represent the natural history of disease for these patients, the duration of control is encouraging and this finding may represent an anti-tumor benefit of LR-103.

Despite the preclinical data suggesting LR-103 had limited calcemic effects and that low doses of LR-103 were administered in this phase I study, it is interesting that modest laboratory changes consistent with vitamin D pathway activation were detected. The main role of the vitamin D system is to mediate calcium homeostasis, which is critical for normal cellular function and skeletal stability[35]. This involves interactions among the kidneys, bones, parathyroid glands, and intestines. Excess vitamin D receptor activation is expected to lead to hypercalcemia and hyperphosphatemia, increased osteocalcin and lower parathyroid hormone levels. The laboratory changes noted during LR-103 treatment in this study were consistent with the expected effect from a vitamin D analog. Other than hypercalcemia, these laboratory changes were not clinically significant toxicities. Although hypercalcemia limited the initial development of vitamin D analogues as a treatment for malignancy,[20, 22, 36] subsequent studies have demonstrated that agents in this class can be safely delivery[18–22]. However, phase III studies have yet to demonstrate improved cancer outcomes from a vitamin D analogue[37]. This suggests that optimal dosing may not yet be established or that vitamin D analogs may be more effective in chemoprevention as lower drug levels for a prolonged period of time may be a viable strategy. Epidemiologic data also supports investigating Vitamin D analogs further for chemoprevention[1–7]. In either case, vitamin D analogs may not be safe to use in patients with baseline hypercalcemia, active nephrolithiasis, primary hyperparathyroidism or in patients with evidence of vitamin D toxicity.

The major limitation of this study is the lack of completion of Step B due to the decision by the industry sponsor to discontinue drug development. Therefore, it is unclear if further dose escalation of LR-103 with management of hypercalcemia would have been feasible. Another limitation of this study is the lack of pharmacokinetic data for LR-103. This analysis was not done as an assay was never developed for detection of LR-103 or its metabolites. However, despite the administration of low doses of LR-103, the statistically significant changes in expected laboratory parameters suggest that the doses were adequate to activate the vitamin D receptor. Additionally, baseline Vitamin D levels were not recorded and information on exogenous vitamin D and calcium use was limited. These could impact the anti-tumor activity and adverse event profile of a novel vitamin D analog.

Many ongoing studies are evaluating the role of vitamin D and cancer. [45] Although LR-103 is no longer in clinical development, targeting the vitamin D pathway remains a promising approach for future anti-cancer therapies, in particular for chemoprevention. Future studies of vitamin D analogs need to consider the dose and schedule of these agents, with the goal of limiting or optimally managing the expected adverse events of hypercalcemia and hypercalciuria while maintaining the anti-tumor effect.

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Table 1

Dose Escalation Scheme

Dose Level	LR-103 (μg/day)
1	5
2	10
3	15
4	20
5	30
6	40
7	60
8	80
9	110
10	150
11	200

Table 2

Patient Characteristics

Patient Characteristics			
	Total (N=21)	**Step A (N=8)**	**Step B (N=13)**
Median Age (range)	63 (45–86)	64 (49–86)	63 (45–78)
Gender			
Male	9 (42.9%)	3 (37.5%)	6 (46.2%)
Female	12 (57.1%)	5 (62.5%)	7 (53.8%)
Zubrod Performance Status			
0	3 (14.3%)	2 (25%)	1 (7.7%)
1	17 (81.0%)	5 (62.5%)	12 (92.3%)
2	1 (4.8%)	1 (12.5%)	0
Tumor Type			
Cervical	1 (4.8%)	1 (12.5%)	
Colon	1 (4.8%)		1 (7.7%)
Esophageal	1 (4.8%)		1 (7.7%)
Ewing's Sarcoma	1 (4.8%)		1 (7.7%)
Cholangiocarcinoma	1 (4.8%)		1 (7.7%)
Melanoma	1 (4.8%)		1 (7.7%)
Non-Hodgkin's Lymphoma	1 (4.8%)	1 (12.5%)	
Ovarian	4 (19.0%)		4 (30.8%)
Pancreatic	1 (4.8%)	1 (12.5%)	
Prostate	3 (14.3%)	2 (25.0%)	1 (7.7%)
Thyroid	1 (4.8%)	1 (12.5%)	
Uterine	4 (19.0%)	1 (12.5%)	3 (23.1%)
Other	1 (4.8%)	1 (12.5%)	
Prior Cancer Treatment			
Systemic therapy			
Yes	19 (90.5%)	7 (87.5%)	12 (92.3%)
No	2 (9.5%)	1 (12.5%)	1 (7.7%)
Radiation therapy			
Yes	10 (47.6%)	4 (50.0%)	6 (46.2%)
No	11 (52.4%)	4 (50.0%)	7 (53.8%)

Table 3a

Treatment Summary Step A

Patient No.	Starting dose (level/dose)	Intra-patient dose escalation (level/dose)	No. of Cycles Administered (14 day)	Dose-Limiting Toxicity[+] (DLT)	Reason for study discontinuation
1	1 (5 μg/day)	No	<1	None	Clinical deterioration
2	1 (5 μg/day)	Yes to level 3 (15μg/day)	3	None	Physician discretion
3	1 (5 μg/day)	Yes to level 2 (10 μg/day) *No further escalation due to Gr 2 PTT*	3	None	Clinical deterioration
4	3 (15 μg/day)	Yes, to level 4 (20 μg/day) *No further escalation due to Gr 2 Hypercalciuria*	4	None	Progressive disease
5	3 (15 μg/day)	No *No further escalation due to Gr 2 Hgb and Gr 1 Hypercalcemia*	4	None	Progressive disease
6	3 (15 μg/day)[$]	No	1.5	Gr 4 Hyperuricemia	MD discretion
7	3 (15 μg/day)	No	2	Gr 4 GGT, Gr 3 Alk Phos, Fatigue and UTI.	Progressive disease
8	3 (15 μg/day)	No *No further escalation due to Gr 1 Hypercalcemia*	11	None	Progressive disease

Table 3b. Treatment Summary Step B

Dose Level (dose)	No. Patients	No. of Patients with DLT	Mean No. Cycles Administered (28 day)	Best response
2 (10 μg/day)	4[+]	0	4	Stable disease 11 mo
3 (15 μg/day)	3	0	5.5	Stable disease 14 mo
4 (20 μg/day)	4[+]	0	3	Stable disease 6 mo[$]
5 (30 μg/day)	2	1 (gr 3 hypercalcemia)	1.5	Progressive disease

[+]For Step A defined as ≥ grade 2 hypercalcemia and/or > grade 2 other toxicities

[$]Dose was reduced to 10 μg/day after 7 days due to development of grade 4 hyperuricemia.

Abbreviations: Gr (Grade); PTT (Partial thromboplastin time); Hgb (Hemoglobin); GGT (Gamma-glutamyl transpeptidase); Alk Phos (Alkaline Phosphatase); UTI (Urinary tract infection)

[+]1 patient in each cohort was unevaluable per protocol (one for progression of disease after only 7 days of drug therapy and other for missed protocol-specific laboratory collections).

[$]Patient preference to discontinue

Table 4

Alterations in Laboratory Parameters with LR-103

Laboratory Parameter	Mean Baseline Level (range)	Mean Level at Week 8/Last visit (range)	Mean Change from Baseline (Wilcoxon signed-rank p-value)[$]
Parathyroid Hormone/PTH (pg/ml)	66.5 (16.9–168.7)	36.3 (3.8–152.8)	−28.6 ($p < 0.001$)
Bone Specific Alkaline Phosphatase (U/L)	54.1 (19–218.5)	67.0 (15.6–457.0)	17.2 ($p = 0.932$)
Osteocalcin (ng/ml)	15.6 (4.4–37.2)	29.1 (5.4–94.5)	12.2 ($p < 0.001$)
Calcium (mg/dL)	9.3 (8.4–10.3)	9.9 (8.7–11.4)	0.6 ($p < 0.001$)
Phosphorus (mg/dL)	3.6 (2.4–4.8)	4.0 (2.8–7.4)	0.2 ($p = 0.232$)
Albumin (g/dL)	3.9 (3.2–4.7)	4.0 (2.7–4.7)	0.1 ($p = 0.360$)
Creatinine (mg/dL)	1.0 (0.6–1.3)	1.4 (0.6–6.5)	0.1 ($p = 0.005$)
24 hour urinary calcium (mg/24h)	130.9 (23–267.8)	283 (4–508)	184 ($p < 0.001$)
Uric Acid (mg/dL)	5.8 (2.4–9.8)	6.8 (2.6–10.8)	0.7 ($p = 0.037$)

[$]Only patients with baseline and Week 8/last visit results were included in this analysis.

Table 5

Treatment Emergent Adverse Events[$].

	Total	Step B	Step B			
Toxicity	**(n=21)**	**(n=8)**	**10 μg (n=4)**	**15 μg (n=3)**	**20 μg (n=4)**	**30 μg (n=2)**
Diarrhea	4	0	1	1	1	1
Fatigue	5	2	0	1	0	2
ALT[+] increase	3	1	0	1	1	0
AST[+] increase	2	1	0	0	1	0
Hypercalcemia	8	4	1	1	1	1
Hyperuricemia	4	2	1	0	0	1
Creatinine increase	3	0	0	1	1	1
Hypercalciuria	8	5	2	0	1	0
Decreased appetite	2	0	0	2	0	0

[$] Adverse event (AE) of any grade occurring in at least 2 patients (27 independent AEs were reported in total). Events considered unlikely to be related to treatment were excluded.

[+] ALT (SGPT, Alanine transaminase); AST (SGOT, aspartate transaminase)