A Phase I Study of LGD1069 in Adults with Advanced Cancer


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ABSTRACT

LGD1069 [Targretin; 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphtalenyl) propenyl] benzoic acid] is a novel synthetic retinoid X receptor-selective retinoid that has been recently identified. The goals of this study were to determine the safety, toxicity, pharmacokinetics (PKs), and metabolic profile of LGD1069 in advanced cancer patients. Sixty patients received oral LGD1069 at doses ranging from 5–1000 mg/m²/day with PK sampling performed on days 1 and 15. No dose-limiting toxicities (DLTs) were observed up to the 500 mg/m²/day dose level. DLT observed at and above 650 mg/m²/day included skin desquamation, hyperbilirubinemia, transaminase elevation, leukopenia, and diarrhea. Asymptomatic, dose-related alterations in lipid and thyroid metabolism were also observed. DLTs frequently observed with retinoic acid receptor-selective retinoids and pan agonists, including headache, mucocutaneous toxicity, and hypercalcemia, were not dose-limiting with LGD1069. Day 1 LGD1069 Cmax and area under the curve values increased dose-proportionately up to 800 mg/m²/day. Repeat-dose (day 15) area under the curve values varied between 25 and 105% of day 1 values. Although no objective tumor responses were observed, tumor progression may have been substantially arrested or delayed in non-small cell lung cancer (5 of 16) and in head and neck cancer (1 of 5), as well as other tumor types. At the higher dose levels, the molar concentration of LGD1069 was up to 10-fold higher than observed with other retinoids, yet toxicity was minimal. LGD1069 is a retinoid X receptor-selective retinoid agonist with a more favorable PK and toxicity profile than previously studied retinoids and merits further investigation as a chemopreventive and anticancer agent. On the basis of this Phase I trial, the recommended Phase II dose is 500 mg/m²/day.

INTRODUCTION

Retinoids, including vitamin A and its analogues, regulate the morphogenesis, development, growth, and differentiation of cells (1). Retinoids and their precursors suppress carcinogenesis in experimental animals (2) and have shown promise as chemopreventative agents in epithelial tumors (3, 4) and as therapeutic agents in acute promyelocytic leukemia (5). Retinoids modulate normal, premalignant, and malignant cell phenotypes by changes in gene expression that are mediated through binding to two classes of nuclear hormone receptors, the RARs² and the RXRs (6). There are six known retinoid IR subtypes, RAR (α, β, γ) and RXR (α, β, γ), which are members of the steroid receptor superfamily. These retinoid IRs form heterodimers that bind to specific DNA RA response elements and act as ligand-dependent transcriptional regulators for RA-responsive genes. The cytoplasmic RA binding proteins CRABPI and CRABPII exhibit specific patterns of expression and correspond to a second level of complexity in the retinoid signaling pathway (1). The RARs and RXRs coexist in most cells, and the effects of RA on cellular differentiation and death may reflect selective activation of RARs and/or RXRs (7, 8). RAR, vitamin D receptor, TR, PPAR, and LXRα (liver X receptors) preferentially bind to their hormone response elements in vitro as heterodimers complexed with RXR (9–11). Thus, RXRs seem to be essential pleiotropic regulators of several signaling pathways.

Naturally occurring and synthetic ligands have been described that have distinctive binding properties and transactivation effects on the various RAR and RXR subtypes, thereby allowing differential modulation of retinoid receptor gene expression. ATRA binds RAR with high affinity, but does not bind to RXR, whereas 9-cis-RA transactivates both RARs and RXRs (12). Using a series of RXR- and RAR-selective ligands, it has been shown that, in leukemic cells, activation of RAR pathways regulates cell proliferation and differentiation, whereas activation of RXR pathways leads to the induction of apoptosis (13). LGD1069 (Targetretin) has been identified as an RXR-selective ligand that does not have significant RAR binding and transactivation of RAR-responsive genes (14). LGD1069 has been shown to have antiproliferative activity in preclinical in vitro and in vivo models, including human tumor xenografts of head
and neck carcinomas. LGD1069 can reduce, in a dose-dependent manner, the volume of skin papillomas in the 7,12-dimethylbenz(a)anthracene-induced SENCAR mouse two-stage skin papilloma model. In the N-nitrosos-N-methylurea-induced rat mammary tumor model, LGD1069 showed a 90% reduction in tumor burden and tumor incidence compared with vehicle-treated rats (15); in this model, LGD1069 was very well tolerated without the classic signs of traditional retinoid toxicities. On the basis of these preclinical observations, this Phase I clinical trial of LGD1069 was conducted as a dose-finding study to determine the safety, toxicity, PKs, and metabolic profile of this agent in advanced cancer patients.

PATIENTS AND METHODS

Patient Selection. Patients were entered into the study after approval of the clinical protocol by the Georgetown University Institutional Review Board. Inclusion criteria included: (a) histologically confirmed advanced cancer having failed standard therapy; (b) 18 years of age or older; (c) Eastern Cooperative Oncology Group performance status of 0–2; (d) adequate hematological, hepatic, and renal function; and (e) negative pregnancy test and effective means of contraception. Exclusion criteria included: (a) surgery, chemotherapy, radiotherapy or investigational therapy within 21 days of the study; (b) brain metastases; and (c) concurrent vitamin A (or other retinoid) use. All patients provided signed informed consent.

Treatment Plan. This study was an open-label, multiple-dose, dose escalation, safety evaluation study of oral LGD1069 in patients with advanced cancer. The drug was supplied by Ligand Pharmaceuticals, Inc. as 10-mg and 25-mg soft gelatin capsules, and doses were rounded to the nearest 5 mg. During the course of the study, a new micronized formulation that increased the surface area of LGD1069 from 0.37 m²/g to 5.3 m²/g became available and was introduced with an anticipated 6.8-fold enhancement of oral bioavailability based on evaluation of repeat-dose AUC 0–6 divided by day 1 AUC 0–6 were determined as the slope of the terminal log-linear portion of the plasma concentration-time profile, and terminal elimination half-life (t₁/₂) values were determined as 0.693/z parameter. AUC from time zero to infinite time (AUC 0–∞) was determined by summing AUC 0–t, and C(last)/z parameter values. Because (AUC 0–∞) values were not determinable for all patients, AUC 0–6 values were used for comparisons. Ratios of repeat-dose AUC 0–6 divided by day 1 AUC 0–6 were determined as an indicator of autoinduction of clearance.

RESULTS

Patient Characteristics. A total of 60 patients were treated with LGD1069 at 16 dose levels. Patient characteristics are shown in Table 1. One patient in this study had non-Hodgkin’s lymphoma, and the remainder of the patients had a solid tumor, as described in Table 1.

| Table 1 Characteristics of patients treated with LGD1069 |
|----------------|----------------|
| Number     | Percentage    |
| Patients treated | 60            |
| Age (yrs)  |                |
| Median     | 63             |
| Range      | 27–80          |
| ECOG performance status |          |
| 0          | 21             |
|            | 35.0           |
| 1          | 32             |
|            | 53.3           |
| 2          | 7              |
|            | 11.7           |
| Sex        |                |
| Male       | 31             |
|            | 51.7           |
| Female     | 29             |
|            | 48.3           |
| Malignancy |                |
| Lung       | 16             |
|            | 26.7           |
| Colon      | 7              |
|            | 12.8           |
| Head and neck | 5             |
|            | 8.3            |
| Melanoma   | 6              |
|            | 10             |
| Other      | 26             |
|            | 43.3           |

ECOG, Eastern Cooperative Oncology Group.

PK Studies. Patients underwent PK studies on days 1 and 15. After an overnight fast, LGD1069 was taken after ingestion of a liquid formula of defined lipid content (Ensure; 250 ml; Abbott Laboratories, Columbus, OH). Heparinized whole-blood samples were collected before dosing and at 0.5-, 1-, 2-, 4-, and 6-h time points. Plasma samples were obtained after centrifugation and stored at -20°C.

Analytical Methods. Plasma samples were analyzed to determine LGD1069 drug substance concentrations using a validated gas chromatography-mass spectroscopy assay. In brief, internal standard (3H1-13C-LGD1069) was added to plasma, and samples were extracted with 1-chlorobutane. The upper organic layer was evaporated to dryness, and derivatization solution (5% acetyl chloride in methanol) was added. The residue was taken up in 25 μl of chloroform, and 3-μl aliquots were injected into the gas chromatography. Detection was by mass spectroscopy in the single ion mode. PK parameters were determined by non-compartmental methods using the PK analysis program Topfit, version 2.0 (16). Peak plasma LGD1069 concentrations (C max ), trough concentrations (C min ), and time to peak plasma concentration (t max ) values were recorded as observed. When determinable, apparent terminal elimination rate constants (z) were determined as the slope of the terminal log-linear portion of the plasma concentration-time profile, and terminal elimination half-life (t₁/₂) values were determined as 0.693/z parameter. AUC from time zero to 6 h (AUC 0–6) was determined by linear trapezoidal approximation. AUC from time zero to infinite time (AUC 0–∞) was determined by summing AUC 0–t, and C(last)/z parameter values. Because (AUC 0–∞) values were not determinable for all patients, AUC 0–6 values were used for comparisons. Ratios of repeat-dose AUC 0–6 divided by day 1 AUC 0–6 were determined as an indicator of autoinduction of clearance.
Adverse Events. Of the 18 patients treated from 5–75 mg/m²/day of the nonmicronized formulation, only 3 experienced mild (grade I) headache, flushing, and skin reaction (data not shown). Eighteen patients were treated from 21–380 mg/m²/day of the micronized formulation, of which 6 patients experienced grade I headache, 5 patients experienced grade I skin toxicity, 1 patient experienced grade II leukopenia, and 1 patient experienced grade III PT elevation at day 99 that was reversed with drug discontinuation. Adverse events in the remaining 21 patients treated at doses >380 mg/m²/day are listed in Table 2.

Headache was observed in 13 of 60 patients, but was only mild (grade I/II) and not dose-limiting. Flushing, similarly, was mild (grade I) and occurred in six patients. Dose-dependent skin toxicity was observed in 22 of 60 patients and was the most common toxicity. Most frequently, only mild skin dryness was observed, which was controlled with emollients. Only one patient experienced skin dryness and peeling that was dose-limiting, and this occurred at the 650 mg/m²/day dose level; this patient was successfully rechallenged with study drug at 500 mg/m²/day.

Leukopenia occurred in 10 patients in this study, although it was mild (grade I/II) in 8 patients. Two patients experienced dose-limiting grade III leukopenia, and these cases occurred at 800 mg/m²/day. No infection-related complications resulted from LGD1069-related leukopenia.

Five of 60 patients experienced transaminitis with LGD1069 treatment, and none occurred below 650 mg/m²/day. Only one of five patients experienced grade III dose-limiting transaminitis, and this occurred at 1000 mg/m²/day. One patient experienced grade II hyperbilirubinemia at 800 mg/m²/day, and one patient experienced dose-limiting grade III hyperbilirubinemia at 1000 mg/m²/day. One patient experienced dose-limiting grade IV hyperbilirubinemia at 650 mg/m²/day, which occurred at day 71 of therapy.

Four patients experienced grade I PT prolongation at the 650–1000 mg/m²/day dose levels. One patient at 230 mg/m²/day developed a PT prolongation that rose to 40.1 by day 99 of therapy and was dose-limiting, but not considered a DLT because it occurred beyond the initial 4-week study period. It was not associated with clinical bleeding, and a coagulation evaluation including factors V, VII, VIII, and thrombin time was normal.

Asymptomatic metabolic alterations occurred in a dose-dependent manner with LGD1069 therapy. Hypertriglyceridemia was observed, to some degree, in the majority of patients treated with LGD1069. Hypertriglyceridemia typically occurred within 1 week of starting treatment and persisted while on LGD1069 therapy. The hypertriglyceridemia was most marked at the higher dose levels as is shown in Fig. 1. Also observed was hypercholesterolemia with concomitant modest reductions in high-density lipoprotein and elevation in low-density protein levels (data not shown). No clinical sequelae were observed with these alterations in lipid profile. Treatment with a lipid-lowering agent (gemfibrozil) was attempted in two patients and was not found to be effective; however, hyperlipidemia was found to be reversible on discontinuation of treatment with LGD1069.

Thyroid function (free and total T4 and TSH) was evaluated on days 1 and 29, and TSH and free T4 values are shown in Figs. 2 and 3. At higher dose levels, both TSH and free T4 levels decreased with continuous LGD1069 dosing and corrected to baseline values when LGD1069 was discontinued. This decline was not associated with clinical hypothyroidism. Patients did not have clinical evidence of fatigue, cold intolerance, or other clinical sequelae observed with hypothyroidism.

### Table 2

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Headache</th>
<th>Flushing</th>
<th>Skin</th>
<th>Diarrhea</th>
<th>Bilirubin</th>
<th>Transaminase</th>
<th>Leukocytes</th>
<th>Prothrombin time</th>
<th>Creatinine</th>
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<tr>
<td>500 mg/m²</td>
<td>I 2</td>
<td>II 1</td>
<td>III 2</td>
<td>IV 1</td>
<td></td>
<td></td>
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<tr>
<td>650 mg/m²</td>
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<td>II 1</td>
<td>III 1</td>
<td>IV 2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>800 mg/m²</td>
<td>I 2</td>
<td>II 2</td>
<td>III 4</td>
<td>IV 3</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000 mg/m²</td>
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<td>II 3</td>
<td>III 5</td>
<td>IV 4</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

* Day 71.

Fig. 1 LGD1069 dose-relationship to mean peak serum triglyceride levels. The mean peak serum triglyceride level was measured after LGD1069 treatment following treatment with 21–1000 mg/m²/day of the micronized formulation.
Some patients at the higher dose levels of LGD1069 had subjective complaints of fatigue, however, it did not impair function and was not considered a toxicity by the National Cancer Institute Toxicity Criteria.

Responses. No objective tumor regression was observed; however, LGD1069 may have resulted in disease stabilization in 5 of 16 patients with NSCLC and 1 of 5 patients with head and neck cancer. NSCLC represented the most frequent tumor type in this study. Of the 16 NSCLC patients treated, disease stabilization for more than 3 months was observed in 5 patients. One of five patients with squamous cell carcinoma of the head and neck had persistent disease after surgery, radiation therapy, and chemotherapy. After starting LGD1069 at the 75 mg/m²/day (nonmicronized) dose level, the patient had resolution of pain, improvement in swallowing, softening of his neck mass, and remains clinically and radiologically without evidence of disease for more than 4.5 years on treatment. This patient remains without evidence of disease and on active treatment. Two other patients that had also received at least one prior chemotherapy regimen with rectal and esophageal cancer also have stable disease and are on active treatment at over 3.5 years and 3 years, respectively.

PKs. After the initial daily dose of the micronized LGD1069 formulation, the mean LGD1069 C max values increased from 183 (± 91) ng/ml to 6110 (± 1940) ng/ml as the dose increased from 21 mg/m²/day to 800 mg/m²/day. The mean day 1 C max value for the 1000 mg/m²/day dose group (2680 ± 1240 ng/ml) did not increase dose-proportionally, suggesting there may have been saturation of absorption mechanisms. The mean day 1 t max values for the micronized formulation ranged from 1.4 –3.6 h. Mean plasma AUC 0–6 values increased from 491 (± 256) ng·h/ml to 23900 (± 8880) ng·h/ml as the dose increased from 21 mg/m²/day to 800 mg/m²/day (Fig. 4). As observed for C max, day 1 AUC 0–6 for the 1000 mg/m²/day dose level (10300 ± 5260 ng·h/ml) was not significantly different from the 800 mg/m²/day dose group. For dose groups up to 500 mg/m²/day, terminal elimination half-live values generally ranged from 1–2 h and were independent of dose and study day. At the higher doses levels, apparent t½ values were longer, possibly due to prolonged or delayed absorption of the large doses. In many patients, particularly at the higher dose levels, the shape of the concentration-time profile suggested that absorption was still continuing at the time of the last sampling point (6 h). For this reason, it is likely that a large fraction of the AUC was not captured at the time of the last sample point, and, therefore, reported AUC values for the higher doses may be underestimates of the true AUC parameters (data not shown).

Up to the 140 mg/m²/day dose level, repeat-dose AUC values were similar to day 1 values. Above 140 mg/m²/day, repeat-dose AUC values varied between 25 and 105% of day 1 values (Fig. 5). The inconsistency of repeat-dose AUC values may be due to intraindividual variability in LGD1069 PKs or interindividual patient differences in the effect of repeat-dose administration on LGD1069 PKs.

Mean dose-normalized day 1 AUC 0–6 values for the micronized and nonmicronized formulations were 1.4 (ng·h/ml)/(mg/m²) and 19.8 (ng·h/ml)/(mg/m²), respectively, suggesting there was an approximate 14-fold enhancement of LGD1069 absorption after micronization of drug substance.

DISCUSSION
A major limitation with the clinical application of retinoids has been their toxicity (17). Thus, the ratio of efficacy to toxicity, termed the “therapeutic index,” has become an important consideration in assessing the potential clinical use of different retinoids (18). LGD1069 has demonstrated to have the potential for a favorable therapeutic index with little clinical toxicity up to the 650 mg/m²/day dose level.

Skin reactions (cheilitis, xeroderma, skin peeling) occurred in up to 90% of patients treated with ATRA and 13-cis-RA, but were relatively infrequent and milder with LGD1069 (19, 20). Ocular toxicity (eye dryness, conjunctivitis) were seen in 25–40% of patients treated with ATRA or 13-cis-RA, but were relatively infrequent and milder with LGD1069 in this study.
These mucocutaneous toxicities are a frequent complication of RAR-selective retinoids and pan-agonists, but were minimal with LGD1069 and observed only at the higher dose levels. This supports the theory that mucocutaneous toxicity is mediated by the RAR. Although LGD1069 is an RXR-selective ligand, weak RAR binding and transactivation does occur, particularly at higher doses, and may explain the mild cutaneous toxicity we observed. Similarly, headache was mild and infrequent in this study, and hypercalcemia was not observed; both have been frequently dose-limiting with RAR-selective and retinoid pan agonist.

In a Phase I study with LGD1069 conducted by Miller et al. (21), patients were escalated to 500 mg/m²/day, with transaminitis being the most common DLT. Two of six patients experienced dose-limiting leukopenia and transaminitis at 400 mg/m²/day, such that the recommended Phase II dose in the study by Miller et al. (21) was 300 mg/m²/day. In a Phase I study (in progress) evaluating LGD1069 in combination with chemotherapy in the treatment of NSCLC, LGD1069 had been safely given in with vinorelbine and cisplatin at doses up to 400 mg/m²/day, and enrollment is continuing at the 600 mg/m²/day (22). In this study, two of six patients experienced DLT at the 650 mg/m²/day dose level, however, one of the two patients did not experience a DLT until he had been on study for 71 days, such that dose escalation had already continued to 800 and 1000 mg/m²/day. Although this second DLT at 650 mg/m²/day occurred beyond the initial 4-week study period, this toxicity needs to be considered when defining a recommended phase II dose. Clearly, the toxicities overall increased considerably with the 500–650 mg/m²/day dose escalation, and our recommended phase II dose (RP2D) in this study is 500 mg/m²/day.
hormone-response elements present within the TRH promoter. It has been shown that the specific negative thyroid hormone-response present within the human TRH promoter interact with TRs and the RXR (26); therefore, LGD1069 treatment may lead to central inhibition of thyroid function, although this explanation is not entirely satisfactory because RXR is a silent partner to TR, and this heterodimer is T3-responsive. However, RXRγ has also been identified in the anterior pituitary gland and found to be restricted to thyrotrope cells within the pituitary. There is data to suggest that retinoids can independently mediate suppression of TSHβ promoter activity in TtT-97 thyrotropes and that the promoter region responsible for retinoid effect is distinct from the T3-responsive region (27). Further study of the effects of LGD1069 is required to increase our understanding of the complex interactions of hormones on regulation of gene expression.

Five of 60 patients experienced PT prolongation with LGD1069 therapy, however, the mechanism whereby PT prolongation occurs with LGD1069 therapy has not been defined. A recent study showed that in the hepatoma cell line HepG2, a ligand-dependent enhancement of the antithrombin gene expression is regulated by RXR, as well as TRβ (28). Antithrombin is a single chain 58.2-kDa glycoprotein that is a member of the serine protein inhibitor (serpin) superfamily that inhibits thrombin and several other activated coagulation factors (29). It is unclear whether there is a relationship between antithrombin and PT elevation with LGD1069 therapy though, as the one patient with a grade IV elevation had a normal coagulation profile otherwise including a normal thrombin time.

ATRA has been shown to induce remission in patients with acute promyelocytic leukemia, but as a single agent did not maintain patients in remission (30). Recent PK studies have demonstrated after 28 days of chronic oral dosing of ATRA, the AUC is up to 80% lower by day 28 than on day 1 of therapy (31, 32). At the molecular level, ATRA can increase CRABPII and cytochrome P450 gene transcription. This results in an increase of proteins that induce ATRA catabolism, which is proposed to lead to the reduced plasma levels observed during ATRA therapy (33). LGD1069 catabolism may have occurred to a lesser degree in this Phase I study with LGD1069 AUC values decreasing an average of 44% of day 1 values by day 15. Similarly, in the study by Miller et al. (21), at 400 mg/m²/day, LGD1069 AUC values decreased an average of 29% of day 1 values by day 28. In our study, the reductions on day 15 were inconsistent, possibly reflecting intraindividual variability in LGD1069 PKs or interindividual patient differences in the effect of repeat-dose administration on LGD1069 PKs. Despite the reduction in LGD1069 levels by catabolism, LGD1069 levels continue to be maintained in the range considered active in preclinical studies. In preclinical studies, induction of apoptosis with LGD1069 was studied in HL-60 cells; transglutaminase activity was measured as an indicator of apoptosis, and the EC₅₀ value was 6 μM. The ability of LGD1069 to alter growth was also examined in cell lines, including a human head and neck squamous cell carcinoma cell line (1483) and a breast carcinoma cell line (MCF7). In all of these cell lines, LGD1069 inhibited cell growth with an IC₅₀ value of 1–5 μM. This is consistent with values achieved clinically. In this study, the day 1 μM concentrations ranged from 0.9–17.5 μM, and the day 15 μM concentrations ranged from 0.54–5.9 μM, which remains in the active range based on preclinical studies.

Although no objective tumor responses were observed in this study, disease stabilization may have occurred with patients with a variety of tumor types remaining on study with stable disease for extended periods of time. The most impressive observations included: (a) one patient with a head and neck cancer who had persistent disease after surgery, radiation, and chemotherapy, who had resolution of clinical symptoms and remains without evidence of disease for more than 4.5 years on study; (b) five of 16 patients with NSCLC had stable disease on LGD1069 therapy for up to 394 days (mean, 132), however, 3 of 5 of these patients had not received prior chemotherapy, and this observation may reflect a more indolent group of patients with NSCLC. No patients with cutaneous T-cell lymphoma were treated in this study, however, in the study by Miller et al. (21), two patients with cutaneous T-cell lymphoma had major
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responses. Also in the study by Miller et al., seven patients with advanced NSCLC remained on study for 3 months or more including one patient who remained on study for 8 months.

LGD1069 represents a novel RXR-selective retinoid with the potential for a more favorable therapeutic index than previous retinoids. The clinical observation that this agent can result in plasma concentrations up to 10-fold higher than previous retinoids without significant clinical toxicity is encouraging for its development as an anticancer and chemopreventive agent. Most of our present knowledge is derived from experiments performed in vitro or in transiently transfected cultured cells that overexpress receptors and recombinant reporter genes that are not in a natural chromatin environment. We do not know if interactions between receptors, ligands, regulatory proteins, and DNA observed under these conditions are also taking place in vivo. This Phase I study of LGD1069 gives a preliminary understanding of the clinical effects of an RXR-selective ligand. The biological activity of RXR ligands is so different from RAR ligands that it has been suggested that RXR activators should be considered a distinct class of pharmacological agents and referred to as “rexinoids," to distinguish their activity from “retinoids" (34). This Phase I study of LGD1069 supports the uniqueness of this agent and further study of this agent and its biological effects is merited in the development of this rexinoid as an effective anticancer or chemopreventive agent.

REFERENCES

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