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CLINICAL TRIAL REPORT

# The effect of bexarotene on atorvastatin pharmacokinetics: results from a phase I trial of bexarotene plus chemotherapy in patients with advanced non-small cell lung cancer

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**Abstract**
*Purpose* Bexarotene (Targretin® capsules) is a retinoid-X-receptor agonist and an inducer of CYP3A4-mediated metabolism. This phase I trial evaluated the pharmacokinetic (PK) and drug–drug interactions of bexarotene with chemotherapy and a lipid-lowering agent (atorvastatin or fenofibrate). This trial was run in parallel with phase III trials of the combinations to determine whether repeated doses of bexarotene capsules affect the pharmacokinetics (PK) of the chemotherapeutic or the lipid-lowering agents.
*Methods* Patients ($n = 48$) with advanced non-small cell lung cancer were treated with repetitive cycles of either paclitaxel/carboplatin or cisplatin/vinorelbine chemotherapy, bexarotene (400 mg/m$^2$/day) administered continuously starting on day 4 of chemotherapy, and a lipid-lowering drug,

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either atorvastatin or fenofibrate, starting at least 5 days before chemotherapy due to hypertriglyceridemia induced by bexarotene. Extensive plasma sampling to characterize the PK profiles of the lipid-lowering drugs, relevant chemotherapy agents was performed on day 1 (without bexarotene) and during chemotherapy cycles 2 or 3 (with bexarotene).

*Results* Here, we report the drug–drug interactions between the lipid-lowering agents and bexarotene. Mean atorvastatin clearance and dose-corrected AUC values were reduced by nearly 50% with the addition of concomitant bexarotene. As fenofibrate was less effective at controlling hypertriglyceridemia, too few patients received this agent to make any meaningful conclusions about drug–drug interactions.

*Conclusions* A drug–drug interaction was seen in this trial with bexarotene co-administration leading to a significant reduction in the AUC of atorvastatin. The likely mechanism for this interaction is through induction of CYP3A4 by bexarotene given the role of this enzyme in the metabolism of atorvastatin. Knowledge of this interaction is important for optimizing lipid management with atorvastatin for patients receiving bexarotene.

**Keywords** Bexarotene · Atorvastatin · Pharmacokinetics · Non-small cell lung cancer

## Introduction

Bexarotene is a synthetic retinoid analog that preferentially binds the retinoid-X (RXR) and is approved for the treatment of refractory cutaneous T-cell lymphomas (CTCL) [5, 8]. It works by altering gene expression mediated through RXRs thus modifying many aspects of cellular function including differentiation, reproduction, and immune function [7, 12, 20].

Bexarotene's tolerability as a single agent was demonstrated in phase I studies with maximum tolerated doses (MTDs) ranging from 300 to 500 mg/m$^2$/day and toxicities including transiently elevated liver function tests (LFTs), leukopenia, hypothyroidism, headache, hypercholesterolemia, hypertriglyceridemia (rarely leading to pancreatitis), and hypercalcemia and at higher doses, desquamation, hyperbilirubinemia, diarrhea, and elevated prothrombin time [14, 17]. Daily dosing of bexarotene is adequate to provide continuous exposure according to pharmacokinetic data from the phase I studies with an estimated elimination half-life of the parent compound of 7–9 h.

In humans, bexarotene is metabolized to oxidative metabolites via the cytochrome P450 enzyme CYP3A4 and additionally acts as a modest inducer of this enzyme [10, 19]. Because of CYP3A4 induction, some decrease in maximum concentration ($C_{max}$) and area under the curve (AUC) is seen with repeat dosing of bexarotene, but not to a clinically relevant degree [10, 19]. Bexarotene excretion is almost entirely hepatobiliary with a very minor renal component [14, 17].

Through induction of CYP3A4 metabolism, bexarotene capsules could affect the pharmacokinetics and decrease the plasma concentrations of atorvastatin and other agents primarily metabolized by CYP3A4. Fenofibric acid, the active moiety of fenofibrate, is primarily eliminated by glucuronidation and should not be affected by bexarotene. Because of the significant hypertriglyceridemia seen with bexarotene, co-administration of a lipid-lowering agent is imperative with the drug, making these potential interactions of clinical significance. Concomitant administration of bexarotene capsules and gemfibrozil resulted in substantial increases in plasma concentrations of bexarotene [12]. This combination also leads to increased triglyceride levels and increased risk of pancreatitis [21]. Co-administration of bexarotene and gemfibrozil is therefore not recommended. Under similar conditions, bexarotene concentrations were not affected by concomitant atorvastatin administration, but detailed evaluations of PK interactions between these drugs have not previously been published.

In a study of patients taking single agent bexarotene for the treatment of CTCL, response rates were higher for patients taking both atorvastatin and fenofibrate, perhaps due to maximal lipid control allowing for higher doses of bexarotene, but this combination can potentially lead to myopathy and rhabdomyolysis [21]. This combination of lipid-lowering agents was not explored in the current study.

Two phase I studies of bexarotene with chemotherapy combinations (carboplatin/paclitaxel or cisplatin/vinorelbine) were conducted to look for interactions between bexarotene, the chemotherapeutic agents and lipid-lowering agents including atorvastatin or fenofibrate. These phase I trials were done in parallel with phase III trials of the combinations in advanced-stage non-small cell lung cancer (NSCLC). The chemotherapy and bexarotene PK data and toxicity data from the phase I trials will be published separately [18, 23]. This paper focuses on the PK interactions between bexarotene and atorvastatin, which has implications in other combination regimens and in the treatment of other malignancies, such as cutaneous T-cell lymphoma where bexarotene is approved.

## Patients and methods

### Study design

This was a multicenter, open-label, phase 1 study of patients diagnosed with non-small cell lung cancer (NSCLC) assessing the safety, tolerability and pharmacokinetics of

bexarotene in combination with platinum-containing doublet chemotherapy and aggressive lipid-lowering therapy. The study was designed to evaluate two chemotherapy treatments: paclitaxel and carboplatin (Arm A); and vinorelbine and cisplatin (Arm B). Up to 60 patients were to be enrolled in the study to provide for at least 30 evaluable patients (15 in each arm). Patients were categorized as evaluable if they received bexarotene capsules during at least two cycles of the specified combination chemotherapy and blood collections for pharmacokinetic profiling were obtained. Each patient not meeting the inclusion criteria was replaced. Patients in both treatment arms also received either atorvastatin or fenofibrate. Eligible patients had confirmed advanced-stage NSCLC, no active brain metastasis, ECOG performance status 0 or 1, adequate organ system function (transaminases and bilirubin less than 3 times upper limits of normal (ULN), adequate hematologic parameters (hemoglobin >8 g/dl, absolute neutrophil count >1,000/mm$^3$ and platelets >50,000/mm$^3$)), fasting serum triglycerides within the normal range (baseline lipid-lowering therapy was allowed), no risk factors for pancreatitis, no prior investigational agent for at least 30 days, no prior systemic anticancer therapy for at least 14 days, no use of vitamin A in excess of 15,000 IU/day within 14 days. Women of childbearing potential were required to have negative serum pregnancy test results (beta–human chorionic gonadotropin) 7 days before initiation of treatment and monthly, while on therapy and both men and women were required to use effective means of contraception for at least 4 weeks before and continuing for at least 1 month after completion of bexarotene therapy. Use of any gemfibrozil or any retinoid class drugs, beta-carotene compounds or vitamin A doses beyond 15,000 IU per day was strictly prohibited and caution was advised with hypoglycemic agents and all drugs (including grapefruit) with known interaction with cytochrome P450 3A4.

All treatment doses of the chemotherapeutics, lipid-lowering agents and bexarotene in this phase I study were identical to parallel phase III trials evaluating the efficacy of these two regimens (SPIRIT I [16] and SPIRIT II) [4]. All patients signed a written informed consent document approved by the local institutional investigational review board (IRB).

## Procedures

Chemotherapy in Arm A consisted of intravenous carboplatin with a dose calculated by the Calvert formula [6] to an area under the curve (AUC) of 6 over 30 min and paclitaxel at 200 mg/m$^2$ over 3 h intravenously each cycle repeated every 3 weeks. In Arm B, vinorelbine was infused intravenously for 15 min at a dose of 25 mg/m$^2$ once weekly starting on day 1, and cisplatin (100 mg/m$^2$) was infused intravenously over 60 min every 4 weeks following the vinorelbine. Chemotherapy started on Day 1 and bexarotene treatment started on Day 4 in both arms. Chemotherapy for both arms was obtained commercially and dose reductions due to toxicity were allowable and were made according to product labeling and current standards of care. Patients took once-daily oral bexarotene capsules 400 mg/m$^2$ with food beginning on day 4. The actual dose of bexarotene was rounded to within 37.5 mg or less of the calculated dose using the available capsule strength of 75 mg. Treatment continued as long as the patient was potentially benefiting and no unacceptable toxicity was occurring. In the event of a bexarotene capsule-related toxicity, the dose of bexarotene capsules for an individual patient were reduced from 400, to 300, to 200, and then to 100 mg/m$^2$/day. Bexarotene capsules could be suspended at any time, as necessary. Every patient was seen weekly with regular adverse event, physical examination, clinical laboratory, and pharmacokinetic data collected.

Treatment with a lipid-lowering agent was initiated at least 5 days prior to the start of the first cycle of chemotherapy with patients assigned to either atorvastatin or fenofibrate. The lipid-lowering agent selected was administered according to approved prescribing information and patients were started on no less than the highest initial dose allowed by the package insert (atorvastatin 20 mg, or fenofibrate 67 mg). For patients requiring a greater degree of lipid control, the dose of the lipid-lowering agent was increased, as permitted by the package insert and as tolerated by the patient.

Close monitoring to maintain serum triglyceride levels below 400 mg/dl was done with increases in lipid-lowering therapy as needed and bexarotene dose reductions (for triglyceride levels over 800 mg/dl). If serum triglyceride levels were over 1,200 mg/dl and were not brought down with dose modifications, then patients were withdrawn from the study.

Blood samples for lipid-lowering drug concentrations were drawn predose, and at 1, 2, 3, 4, 6, 9, 12, and 24 h post-dose on cycle 1 day 1 (without bexarotene) and on cycle 2 or 3 day 1 (with bexarotene). Bexarotene levels were drawn predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 h post-dose on day 1 and day 1 of cycle 2 or 3 (i.e., at steady state with and without chemotherapy). The blood samples were stored in a refrigerator or ice bath and centrifuged within 30 min of collection. Following centrifugation of blood samples, plasma was removed and stored at −20°C or lower until assayed for bexarotene, lipid-lowering, and/or chemotherapeutic agents.

### *Analytical methods*

Bexarotene, and atorvastatin, concentrations in heparinized human plasma were determined using validated high-performance liquid chromatography/tandem mass

spectroscopy methods (LC/MS/MS). The validated assay method for bexarotene concentrations in heparinized human plasma was previously reported [22]. The assay performance for atorvastatin, and fenofibric analytical methods had appropriate selectivity, reproducibility and accuracy.

The beraxotene assay was linear over the range of 3.00 ng/ml, the lower limit of quantification, to 1,500 ng/ml. For the QC samples in the low, medium, and high pools, interday coefficient of variation (CV) values were 2.8–4.3%, and the intraday CV values were 2.4–5.7%. The intraday CV value for the very high QC pool was 5.1%.

Atorvastatin is extensively metabolized by CYP3A4 but significant amount of parent drug remains in the systemic circulation. Plasma samples were processed by LC/MS/MS for atorvastatin. Atorvastatin assay had a linear calibration range of 0.200–60.0 ng/ml with a lower limit of quantitation of 0.200 ng/ml. For the QC samples, interday coefficient of variation (CV) values for the low, medium, and high pools were 4.7–7.8%. The intraday CV values for the low, medium, high, and very high QC pools were 2.4–5.5%.

Following oral administration, fenofibrate is rapidly hydrolyzed by esterases to the active metabolite fenofibric acid, which is the main circulating entity. Thus, plasma samples were processed by LC/MS/MS for fenofibric acid. Fenofibric acid calibration range was from 100 to 20,000 ng/ml with a limit of quantitation of 100 ng/ml. For the EDTA plasma validation, the QC samples in the low, medium, and high pools, interday coefficient of variation (CV) values were 1.9–3.9%, and the intraday CV values were 1.9–2.2%. The interday CV value for the very high QC pool was 11.3%.

*Analysis of data* Non-compartmental methods were used to determine multiple-dose (steady state) pharmacokinetics of bexarotene and lipid-lowering (atorvastatin or fenofibric acid). Pharmacokinetic parameters were determined for bexarotene including area under the concentration–time curve for the 24 h dosing interval ($AUC_{0-24}$), maximum plasma concentration ($C_{max}$), time to $C_{max}$ ($T_{max}$), and half-life ($T_{1/2}$) values. Similar PK parameters were obtained for atorvastatin and fenofibric acid. For bexarotene, oral clearance (CL/F) and oral volume of distribution for the terminal elimination phase ($V_z$/F) estimates were also determined.

Assessment of pharmacokinetic drug–drug interactions employed linear mixed-effects models using WinNonlin Professional (Version 4.0.1) Bioequivalence Wizard. Statistical assessments for the pharmacokinetic evaluation included descriptive statistics of pharmacokinetic parameters, and, for select parameters, mixed-effect models to contrast mean pharmacokinetic parameter estimates across treatment periods (after natural log transformation). Values of pharmacokinetic parameters were natural log transformed prior to analysis and dose-dependent parameters (AUC and $C_{max}$) were dose-normalized. Dose-normalization was necessary to compare pharmacokinetic parameters between treatment periods for those subjects who required protocol-allowable dose-adjustments between pharmacokinetic sampling periods. The models used period (e.g., without or with bexarotene capsules) as the fixed effect and subject as a random effect. The analyses implemented restricted maximum likelihood estimation and the Satterwaite approximation for degrees of freedom. Differences with $P$ values of $<0.05$ were considered statistically significant.

## Results

### Study design

This was a multicenter, open-label, phase 1 study of patients diagnosed with NSCLC assessing the safety, tolerability and pharmacokinetics of daily oral bexarotene in combination with a platinum-containing doublet chemotherapy and aggressive lipid-lowering therapy (daily oral atorvastatin or fenofibrate). A total of 22 patients were enrolled in Arm A (every 3 weekly intravenous carboplatin and paclitaxel) and 16 completed the PK analysis. In Arm B (every 4 weekly intravenous cisplatin and weekly intravenous vinorelbine), 26 patients were enrolled and 18 completed the pharmacokinetic sampling. All patients enrolled and exposed to at least one dose of bexarotene capsules were evaluated for safety and toxicity. Of the 48 total patients, 33 were men and 15 were women, with a median age of 61 years (range 35–77) and the majority (>75%) was non-Hispanic White. All patients had NSCLC except for two patients initially believed to have NSCLC, who were subsequently determined to have another malignancy (one mesothelioma, one breast cancer).

### Pharmacokinetics

#### *Bexarotene*

To evaluate the effect of concomitant lipid-lowering therapy on the pharmacokinetics of bexarotene, $AUC_{0-24}$ values in the absence of chemotherapy for patients receiving steady state atorvastatin were contrasted to those receiving steady state fenofibrate. The range of individual values and the mean bexarotene AUC values were similar in patients treated with atorvastatin or fenofibrate suggesting that the lipid-lowering agents did not affect the pharmacokinetics of bexarotene.

**Table 1** Atorvastatin pharmacokinetic parameters with and without concomitant bexarotene capsules (Arm A carboplatin/paclitaxel and Arm B cisplatin/vinorelbine)

| | No bexarotene | | | With bexarotene | | |
|---|---|---|---|---|---|---|
| | Mean | SD | *N* | Mean | SD | *N* |
| Arm A | | | | | | |
| Dose (mg) | 34.4 | 28.3 | 9 | 61.8 | 31.2 | 11 |
| $T_{1/2}$ (hour) | 8.3 | 6.8 | 7 | 6.9 | 4.5 | 8 |
| $T_{max}$ (hour) | 3.3 | 1.1 | 9 | 3.1 | 1.6 | 11 |
| Arm B | | | | | | |
| Dose (mg) | 34.2 | 28.7 | 12 | 51.9 | 27.1 | 16 |
| $T_{1/2}$ (hour) | 12.2 | 20.7 | 12 | 11.0 | 13.6 | 16 |
| $T_{max}$ (hour) | 3.45 | 1.51 | 12 | 3.23 | 1.28 | 16 |
| Arm A: dose adjusted[a] to 10 mg | | | | | | |
| $C_{max}$ (ng/ml) | 67.6 | 50.1 | 9 | 57.5 | 63.9 | 11 |
| $AUC_{0-24}$ (ng h/ml) | 339.8 | 167.4 | 9 | 208.9 | 114.2 | 11 |
| Arm B: dose adjusted[a] to 10 mg | | | | | | |
| $C_{max}$ (ng/ml) | 22.6 | 26.9 | 12 | 9.40 | 8.10 | 16 |
| $AUC_{0-24}$ (ng h/ml) | 120.2 | 57.7 | 12 | 65.8 | 60.4 | 16 |

All patients on Arm A also received intravenous paclitaxel and carboplatin and all patients on Arm B also received intravenous vinorelbine and cisplatin

*AUC*$_{0-24}$ area under the plasma concentration–time curve over the interval of time zero to 24 h, $C_{max}$ maximum observed plasma concentration, $t_{1/2}$ terminal elimination half-life, $T_{max}$ time to $C_{max}$

[a] Atorvastatin was administered orally once-daily to steady state at doses from 10 mg to 80 mg

*Atorvastatin Arm A (carboplatin/paclitaxel)* A total of 9 patients received atorvastatin on both pharmacokinetic sampling days (i.e., with and without bexarotene). Atorvastatin dosing ranged from 10 to 100 mg and dosing on pharmacokinetic collections days was identical on day 1 (without bexarotene) and during cycle 2 or 3 (with bexarotene) for all but 3 patients. These 3 patients developed hypertriglyceridemia and required dose increases of atorvastatin between the two collection periods. Individual and descriptive statistics of atorvastatin pharmacokinetics with and without bexarotene capsules are summarized in Table 1. Atorvastatin $C_{max}$ and AUC were 30 and 50% lower, respectively, with concomitant bexarotene capsules than respective values without concomitant bexarotene capsules (Table 2). The difference was statistically significant for AUC ($P = 0.04$), but not for $C_{max}$ ($P = 0.45$).

Individual changes in AUC generally (in 7 of 9 patients) showed decreases in plasma atorvastatin exposure with concomitant administration of bexarotene capsules (Fig. 1a). The mean plasma atorvastatin concentration versus time profiles are presented in Fig. 2a. The mean atorvastatin concentrations were lower with bexarotene at all time points (Fig. 2a).

*Atorvastatin Arm B (cisplatin/vinorelbine)* Twelve patients provided plasma samples to generate atorvastatin concentration–time data both with and without concomitant bexarotene capsules. Once-daily atorvastatin doses ranged from 10 to 80 mg. Atorvastatin dosing ranged from 10 to 80 mg once-daily and dosing on pharmacokinetic collection days was identical on day 1 (without bexarotene) and during cycle 2 or 3 (with bexarotene) for all but 4 patients. These 4 patients developed hypertriglyceridemia and required dose increases of atorvastatin between the two collection periods. Individual patient atorvastatin pharmacokinetic parameter values with and without bexarotene capsules and associated descriptive statistics are summarized in Table 1. Consistent with the results in Arm A, atorvastatin $C_{max}$ and AUC values were approximately

**Table 2** Comparison of dose-normalized (to 10 mg) steady state atorvastatin

| | Parameter | Treatment | GeoLSM | % Ratio of GeoLSM | 90% CI | *P* value[a] |
|---|---|---|---|---|---|---|
| Arm A | $C_{max}$ (ng/ml) | −Bexarotene | 60.26 | 70.15 | 31.42–156.64 | 0.4498 |
| | | +Bexarotene | 42.27 | | | |
| Arm B | $C_{max}$ (ng/ml) | −Bexarotene | 16.29 | 44.49 | 27.93–70.86 | 0.0064 |
| | | +Bexarotene | 7.25 | | | |
| Arm A | $AUC_{0-24}$ (ng h/ml) | −Bexarotene | 346.80 | 52.70 | 31.96–86.90 | 0.0406 |
| | | +Bexarotene | 182.78 | | | |
| Arm B | $AUC_{0-24}$ (ng h/ml) | −Bexarotene | 106 | 47.76 | 31.39–72.69 | 0.0059 |
| | | +Bexarotene | 50.6 | | | |

Pharmacokinetic parameters with and without bexarotene capsules in patients with NSCLC (Arm A)

All patients on Arm A ($n = 8$) also received intravenous paclitaxel and carboplatin

All patients on Arm B ($n = 12$) also received intravenous vinorelbine and cisplatin

*AUC*$_{0-24}$ Area under the plasma concentration–time curve over the interval of time zero to 24 h, $C_{max}$ Maximum observed plasma concentration, *GeoLSM* Geometric least squares mean, *90% CI* 90% confidence interval

[a] For differences between GeoLSM

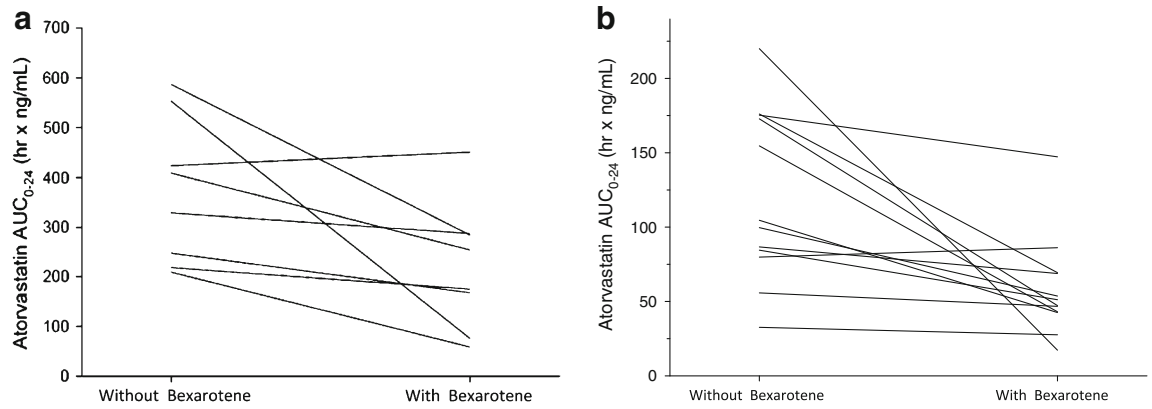


**Fig. 1** **a** Individual dose-adjusted (to 10 mg) atorvastatin area under the concentration–time curve from time 0 to 24 h ($AUC_{0-24}$) with and without concomitant bexarotene capsules in patients with NSCLC (Arm A). **b** individual patient dose-adjusted (to 10 mg) atorvastatin area under the concentration–time curve values from time 0 to 24 h ($AUC_{0-24}$) with and without concomitant bexarotene capsules in patients with NSCLC (Arm B)

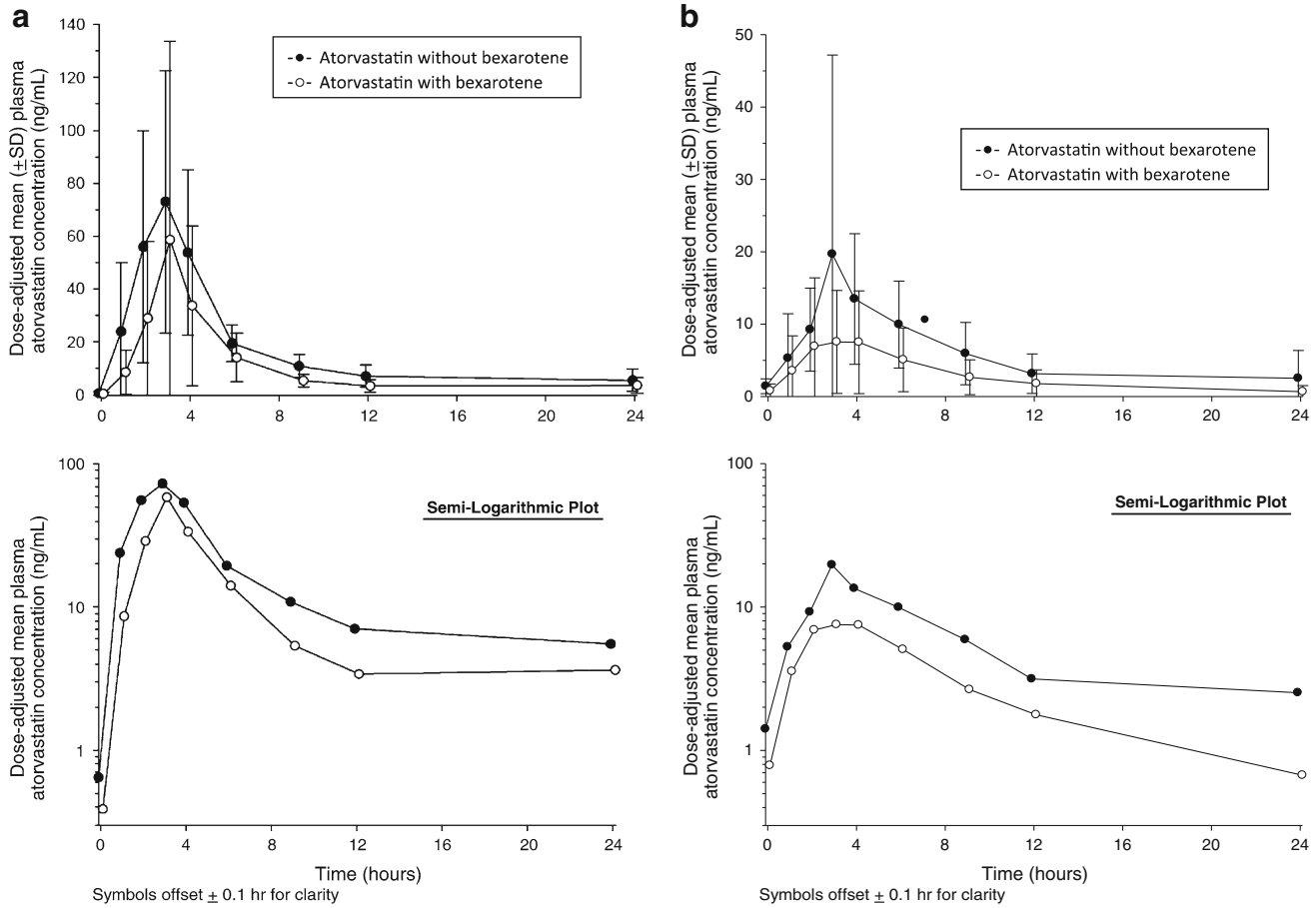


**Fig. 2** **a** Mean dose-adjusted (to 10 mg) plasma atorvastatin concentrations with and without concomitant bexarotene capsules in patients ($N = 8$) receiving carboplatin/paclitaxel chemotherapy (Arm A). **b** mean dose-adjusted (to 10 mg) plasma atorvastatin concentrations with ($N = 16$) and without ($N = 12$) concomitant bexarotene capsules in patients receiving cisplatin/vinorelbine (Arm B)

45% lower with concomitant bexarotene capsules than respective values without concomitant bexarotene capsules (Table 2). These differences in AUC and $C_{max}$ were statistically significant ($P < 0.05$).

Individual patient changes in AUC generally showed slight to marked decreases in plasma atorvastatin exposure with concomitant administration of bexarotene capsules (Fig. 1b). The mean dose-adjusted plasma atorvastatin

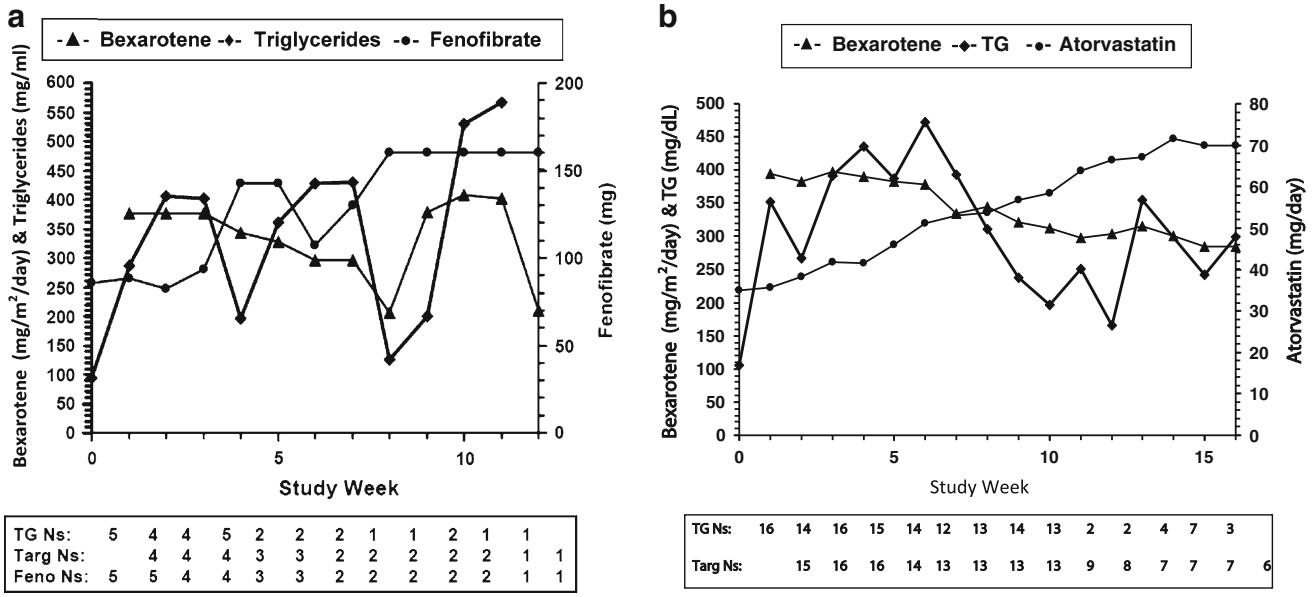


**Fig. 3** **a** Mean actual bexarotene dose, mean triglycerides and mean actual atorvastatin dose by study week for patients who received atorvastatin only in study Arm A ($N = 11$). **b** mean actual bexarotene dose, mean triglycerides and mean actual atorvastatin dose by study week for patients who received atorvastatin only in study Arm B. Number of subjects per week are given below

concentration versus time profiles are presented in Fig. 2b. Mean dose-adjusted atorvastatin concentrations were lower with bexarotene capsules at all time points.

Fenofibric Acid (Arms A and B): Only 2 patients from Arm A and 1 from Arm B completed PK analysis both with and without bexarotene for fenofibric acid so no statistical analysis of the effect of bexarotene on fenofibric acid pharmacokinetics data was conducted. Individual patient in AUC values in plasma fenofibric acid exposure was similar with and without concomitant administration of bexarotene capsules, and the mean dose-adjusted plasma fenofibric acid concentration versus time profiles was similar (data not shown).

## Safety evaluation

As previously reported, there was no enhanced toxicity with this combination regimen [11] and toxicities were as would be expected from the chemotherapeutic agents or bexarotene alone. Toxicities at least possibly related to bexarotene include hypertriglyeridemia, hypothyroidism, hypercholesterolemia, folliculitis, headache, transaminase elevations, and various rashes (including exfoliative dermatitis that required dose suspension in 1 patient).

Of the 48 total patients, 11 had serious adverse events (SAEs) of which 4 were fatal, but none were related to bexarotene. Focused toxicity data for this report include a total of 4 patients who withdrew from the trial due to hypertriglyceridemia that was related to bexarotene. Hypertriglyceridemia reached grade 3 in 12 patients and grade 4 in 3 patients. Hypercholesterolemia reached grade 3 in 4 patients and grade 4 in 1 patient. Three patients had some elevation in transaminases, and 1 reached grade 3 levels. Pancreatitis was not reported.

### *Lipids Arm A (carboplatin/paclitaxel)*

Mean triglyceride levels rose rapidly from a baseline level of 80–714 mg/dl within the first 2 weeks and then tended to remain within a range of 287–570 mg/dl during weeks 3 through 12. Patients on atorvastatin had less of an increase (max 435 mg/dl), but those on fenofibrate had poorer control of hypertriglyceridemia. Ten patients had significant hypertriglyceridemia on trial. Six patients required dose reductions of bexarotene due to hypertriglyceridemia (1 by 25%, 4 by 50%, and 1 by 75%). Four patients (13.6%) discontinued treatment due to this toxicity. The overall average dose of bexarotene was 324 mg/m$^2$/day for all patients on the trial, but was higher (327–396 mg/m$^2$/day) through week 12 for those on atorvastatin, implying a decreased requirement for dose reductions. More patients who started on fenofibrate ($n = 5$) had to switch to atorvastatin, than vice versa ($n = 1$). Figure 3a compares the mean bexarotene dose, mean triglyceride levels and mean atorvastatin doses during the study. Mean atorvastatin dose ranged from 30 to 69 mg/day during the first 12 weeks.

Median total cholesterol increased after the start of bexarotene therapy, but the relative increase was less pronounced than the change in triglycerides. The median

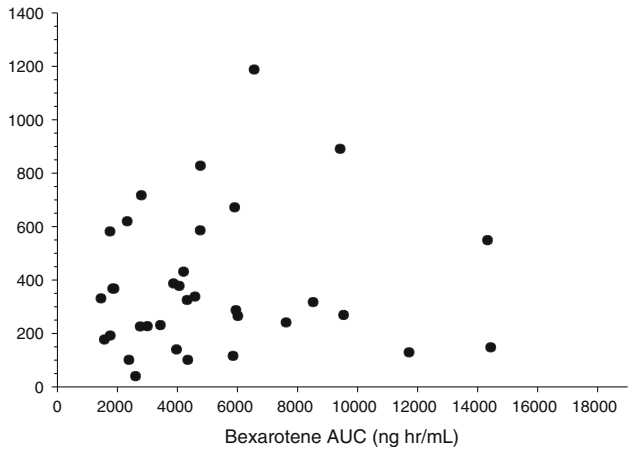


**Fig. 4** Individual patient bexarotene exposure (AUC) and serum triglyceride values during or immediately prior to pharmacokinetic sampling in patients receiving bexarotene in combination with chemotherapy and lipid-lowering agents (Arms A + B, $n = 33$)

total cholesterol was 158 mg/dl at baseline and was highest (276 mg/dl) at Week 3. The median high-density lipoprotein (HDL) cholesterol fell from 44 mg/dl at baseline to a nadir of 15 mg/dl by Week 11. The median low-density lipoprotein (LDL) cholesterol was 94 mg/dl at baseline and 124 mg/dl by Week 3 with a median of 154 mg/dl at Week 7.

*Lipids Arm B* Mean triglyceride levels rose rapidly from a mean baseline level of 97–456 mg/dl within the first six weeks and remained within a range of 197 to 456 mg/dl during weeks 3–12. Eight patients required dose reductions of bexarotene due to hypertriglyceridemia (2 by 25% (300 mg/m$^2$), 4 by 50% (200 mg/m$^2$), and 2 by 75% (100 mg/m$^2$)). Three additional patients required temporary suspension of therapy. Only 1 patient withdrew from the trial due to hypertriglyceridemia. Figure 3b compares the mean actual bexarotene dose, mean triglyceride levels, and mean actual atorvastatin doses during the study. Mean atorvastatin dose ranged from 35 to 66 mg/day during the first 12 weeks of the study.

Median total cholesterol increased after the start of bexarotene therapy, but the relative increase was less pronounced than the change in triglycerides. The median total cholesterol was 152 mg/dl at week 0 and was highest (240 mg/dl) at week 10. The median high-density lipoprotein (HDL) cholesterol fell from 46 mg/dl to a nadir of 28 mg/dl in the first 3 weeks. The median low-density lipoprotein (LDL) cholesterol was 96 mg/dl at week 0 and 102 mg/dl at week 2 and peaked at 161 mg/dl at week 10.

There was no clear correlation between the individual patient bexarotene exposure (AUC) and serum triglyceride levels, and the relationship is presented in Fig. 4.

## Discussion

Bexarotene has proven clinical activity in cutaneous T-cell lymphomas (CTCLs) at a dose of 300 mg/m$^2$/day with a reported 45% response rate in refractory advanced-stage CTCL patients [8]. One of the major toxicities of the drug is hypertriglyceridemia, which if left untreated can lead to pancreatitis. In this study, atorvastatin controlled hypertriglyceridemia in patients treated with bexarotene more effectively than fenofibrate, although patient numbers are low. Gemfibrozil has previously been shown to cause a harmful drug–drug interaction with bexarotene and should not be used with bexarotene [1]. This combination leads to markedly elevated levels of bexarotene as well as increased hypertriglyceridemia and toxicity [12, 21]. Although there are no formal interaction studies, the mechanism is thought to be due to inhibition of CYP3A4 metabolism by gemfibrozil. Other lipid-lowering agents are therefore mandatory and the statin agent atorvastatin is the most commonly utilized and the most effective.

Not surprisingly, given that bexarotene has been shown to induce cytochrome P450 3A4 enzymes [12], and atorvastatin is mainly metabolized by the CYP3A4 system [3, 15], this study demonstrated that bexarotene capsule co-administration resulted in decreased atorvastatin peak concentrations and AUC values. Other inducers of CYP3A4 have previously been shown to decrease the efficacy of atorvastatin, likely through this mechanism [1]. Rifampin, a known strong inducer of cytochrome P450, reduced the total area under the plasma concentration–time curve (AUC) of unchanged atorvastatin (acid) by 80% by rifampin, reflecting induction of the first-pass metabolism of atorvastatin [2]. Thus, the induction effect of bexarotene may be considered moderate compared to that of rifampin. Potentially, bexarotene may induce the metabolism of other drugs metabolized by CYP3A4.

In our analysis, despite small numbers, this reduction, on the order of 50% for the AUC of atorvastatin, was statistically significant ($P < 0.05$). It is therefore necessary to increase atorvastatin doses more aggressively than one might consider in a patient not taking bexarotene. The reduction in atorvastatin concentrations with concomitant administration of bexarotene capsules should be considered when selecting initial atorvastatin doses and for atorvastatin dose-escalation as required for management of hypertriglyceridemia. In extremely difficult to control cases, the combination of atorvastatin and fenofibrate can even be considered [21]. Theoretically, this could lead to increased risk of myopathy and rhabdomyolysis, though at least one detailed pharmacokinetic analysis found no significant interactions between the agents [9]. The use of bexarotene in CTCL is well established, and this analysis

will provide insight into optimal lipid management for patients on the agent.

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**Conflict of interest** Dr. Arturo Lopez-Anaya was an employee of Eisai Pharmaceuticals at the time of his work on this manuscript. All other authors have no conflict of interest with regard to financial or personal relationships with other people or organizations that could inappropriately influence this work.

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