A Phase I and Pharmacokinetic Study of Lapatinib in Combination with Letrozole in Patients with Advanced Cancer

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Abstract

Purpose: The main objectives of this phase I and pharmacokinetic, open-label study were to determine the optimally tolerated regimen (OTR), safety, pharmacokinetics, and clinical activity of lapatinib in combination with letrozole in patients with advanced solid malignancies.

Experimental Design: Patients with advanced breast cancer with immunohistochemically detectable estrogen or progesterone receptors or other cancers were eligible. Doses of lapatinib were escalated in cohorts of three subjects from 1,250 mg/d to a maximum of 1,500 mg/d based on dose-limiting toxicities in the first treatment cycle. The letrozole dose was fixed at 2.5 mg/d. Additional patients were enrolled at the OTR dose level to further evaluate safety and for pharmacokinetic analyses.

Results: Thirty-nine patients were enrolled in the study: 12 in the dose-escalation group, 7 in the OTR safety group, and 20 in the pharmacokinetic group. The OTR dose level was identified as 1,500 mg/d lapatinib and 2.5 mg/d letrozole. The most common (>25% of patients) drug-related adverse events were diarrhea (77%), rash (62%), nausea (46%), and fatigue (26%). No significant differences were observed in the pharmacokinetic variables (Cmax and AUC) of lapatinib and letrozole when coadministered compared with single-agent administration. One patient with endometrial cancer had a confirmed partial response.

Conclusions: Clinically relevant doses of lapatinib in combination with letrozole were well tolerated and did not result in a pharmacokinetic interaction, and clinical antitumor activity was observed.
Patients and Methods

Eligibility criteria. Male and female cancer patients ages ≥18 years with advanced histologically/cytologically confirmed, breast cancer with immunohistochemically detectable ER or progesterone receptor (PgR) or other tumors (e.g., ovarian and endometrial) that were likely to potentially benefit from a lapatinib/letrozole combination regimen were eligible to participate. Patient’s tumors were not required to be ErbB2+. Female eligibility criteria also included postmenopausal status were eligible to participate. Patient’s tumors were not required to be with immunohistochemically detectable ER or progesterone receptor (letrozole and lapatinib may be a rational approach for improving response and delaying or bypassing endocrine-resistant tumor progression (1, 27, 31).

The purpose of the current study was to determine the safety, optimally tolerated regimen (OTR), pharmacokinetics, and clinical activity of lapatinib in combination with letrozole in patients with advanced breast cancer and other solid malignancies.

target tissues (28). Differences in their pharmacologic mechanism may account for differences in clinical activity between tamoxifen and the aromatase inhibitors. Clinical studies have reported that the aromatase inhibitor letrozole (Femara; Novartis Pharmaceuticals) is superior to tamoxifen in postmenopausal women in the neoadjuvant, adjuvant, and advanced breast cancer settings (28–30).

Cross-talk between growth factors and the ER occurs at multiple levels and seems to play a crucial role in breast cancer etiology and progression (27). Recent data also suggest that endocrine resistance is linked to certain cellular kinase and growth factor pathways (27). Given the existence of cross-talk between the ER and ErbB pathways, combination therapy with letrozole and lapatinib may be a rational approach for improving response and delaying or bypassing endocrine-resistant tumor progression (1, 27, 31).

After determination of the OTR, up to 15 patients were to be enrolled in the OTR expansion group to further evaluate the safety of lapatinib and letrozole at the OTR dose, and (c) a pharmacokinetic group to determine the pharmacokinetic variables of each agent alone and in combination. With the exception of the pharmacokinetic group (discussed below), patients received oral daily lapatinib and oral daily letrozole beginning on the first day of treatment period 1 (treatment period = 1 month) continuing for the duration of the study. Lapatinib could be taken with a light, low-fat breakfast. On pharmacokinetic sampling days only, patients in the pharmacokinetic group were required to fast 4 h before lapatinib dosing and 2 h afterwards on pharmacokinetic sampling days. All patients continued on study until disease progression, unacceptable toxicity, or withdrawal of consent.

Study drug dose modification and dose intensity analysis. Lapatinib was reduced by 250 and 500 mg for grade 3 and 4 diarrhea, respectively. For other toxicities and their causality with lapatinib, dose modification was made following discussions among the study investigators. Percent of prescribed dose intensity was calculated by dividing the administered dose intensity/prescribed dose intensity and multiplying by 100%. Administered dose intensity calculations included dose reductions, treatment interruptions, and compliance as assessed by the study investigators.

Dose-escalation and OTR expansion group. At least 3 patients were initially enrolled in the first dosing cohort [lapatinib, 1,250 mg/d once daily continuous; letrozole, 2.5 mg/d once daily continuous (dose level 0)] and monitored for toxicity for one treatment period. The starting dose of lapatinib represented a lower dose than the highest doses administered in phase I studies of monotherapy lapatinib (1,600–1,800 mg/d; refs. 32, 33) or the typical monotherapy dose used in phase II trials (1,500 mg/d; ref. 23). The starting dose of letrozole was 2.5 mg/d, the Food and Drug Administration–approved monotherapy dose, and remained fixed during the study. If no dose-limiting toxicity (DLT) was observed, 3 additional patients were entered at the next higher dose level [lapatinib, 1,500 mg/d; letrozole, 2.5 mg/d (dose level +1)] and evaluated for DLT in the first treatment period or the maximum lapatinib dose of 1,500 mg/d was reached in the absence of DLT. If 1 of 3 patients experienced a DLT at a given dose, 3 additional patients were entered at that dose level; however, if ≥2 patients at any given dose level involving 2 to 6 total patients experienced DLT, a lower dose was explored to more precisely determine the OTR.

DLT was defined as evidence of at least grade 3 toxicity with “suspected” or “probable” relationship to investigational product during the first treatment period. Additionally, any grade 2 nonhematologic toxicity persisting beyond treatment period 1 was considered a DLT if deemed dose limiting in the judgment of the study investigators. The OTR was defined as the dose level of lapatinib and letrozole at which no more than 1 of 6 patients experienced a DLT in the first treatment cycle. After determination of the OTR, up to 15 patients were to be enrolled in the OTR expansion group to evaluate the safety and efficacy of lapatinib at the dose level identified as the OTR.
**Pharmacokinetic group.** Additional patients were enrolled at OTR dose level and randomly assigned to one of four treatment sequences in a randomized crossover to determine the potential for drug-drug interaction affecting either letrozole or lapatinib at steady state. In sequence 1, lapatinib was dosed on days 1 to 8, letrozole was dosed on day 8, and blood was sampled for letrozole analysis on days 7 and 8. In sequence 2, lapatinib was dosed on days 1 to 23, letrozole was dosed on day 8, and blood was sampled for lapatinib assay on days 8 and 23. In sequence 3, letrozole was dosed on days 1 to 28, lapatinib was dosed on day 28 and blood was sampled for letrozole analysis on days 21 and 28. In sequence 4, letrozole was dosed on days 1 to 28, lapatinib was dosed on day 21, and blood was sampled for letrozole analysis on day 21 and 28. Blood samples (2 or 4 mL) were collected before dosing and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 h after dosing. Samples were centrifuged at 1,000 × g for 15 min, and the plasma was separated and stored at -80°C until assayed.

**Sample and pharmacokinetic analyses.** Plasma concentrations of lapatinib were measured by an online extraction, liquid chromatography/tandem mass spectroscopy method described previously (34). The limit of quantitation was 5 ng/mL. Plasma concentrations of letrozole were measured by liquid chromatography/tandem mass spectroscopy after solid-phase extraction using an electrospray interface with multiple reaction monitoring in the positive ion mode. The limit of quantification was 0.5 ng/mL. Precision and accuracy for both methods were within 15%.

Plasma concentration data were analyzed by standard noncompartmental methods using WinNonlin Professional software version 4.1 (Pharsight). Area under the plasma drug concentration-time curve within a steady-state dosing interval (AUC<sub>ss</sub>), maximum observed plasma drug concentration (C<sub>max</sub>), time to maximum observed plasma drug concentration (t<sub>max</sub>), and plasma concentration at the end of a dosing interval (C<sub>r</sub>) were calculated for lapatinib and letrozole for each patient in each treatment period in the pharmacokinetic phase of the study. AUC<sub>ss</sub>, C<sub>max</sub>, and C<sub>r</sub> were analyzed by ANOVA; t<sub>max</sub> and t<sub>lag</sub> were analyzed using nonparametric statistical methods. ANOVA of both AUC<sub>ss</sub> and C<sub>max</sub> were done using a mixed model to estimate a point and a 90% confidence interval estimate of the true difference in least squares means between the test and reference treatments. Nonparametric methods were used to evaluate paired differences between treatments for t<sub>max</sub>.

**Safety assessments.** Safety assessments were done at all clinic visits throughout the study. Measurements used to assess safety included vital signs, clinical laboratory tests (hematology and chemistry), 12-lead electrocardiogram, Karnofsky performance status, and multiple gated acquisition scan or echocardiogram. Adverse events/serious adverse events were monitored at each visit, each scheduled assessment, and at 28-day poststudy follow-up.

Adverse events and toxicities were graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 (35). Patients who presented with decreased LVEF were referred to their referring cardiologist before participation, and patients with LVEF <60% from baseline were excluded from this study. Treatment was held if LVEF <50% from baseline. All patients had an LVEF test performed within 15%.

**Assessment of clinical activity.** Antitumor response and disease status were determined using the Response Evaluation Criteria in Solid Tumors guidelines (37). The number of patients with complete response, partial response, stable disease, and progressive disease was determined.

## Results

**Patient characteristics and disposition.** Thirty-nine patients, whose pertinent demographic characteristics are listed in Table 1, were enrolled in the study. The most common tumor types were breast (46%) and ovarian cancer (41%; Table 1). The majority of patients were heavily pretreated with previous cytotoxic and hormonal therapy (Table 1). Five patients had received prior trastuzumab and 4 patients had received prior letrozole. Twelve patients were enrolled in the dose-escalation phase, 7 patients were enrolled in the OTR expansion phase, and 20 patients were enrolled in the pharmacokinetic phase. Estrogen, progesterone, and ErbB2 status are provided in Table 1. Four patients received starting doses of lapatinib of 1,250 mg and letrozole of 2.5 mg. Thirty-four patients received starting doses of lapatinib of 1,500 mg and letrozole of 2.5 mg. An additional patient in the pharmacokinetic cohort was assigned to receive a starting dose of lapatinib of 1,500 mg and letrozole of 2.5 mg, received letrozole, but discontinued before receiving lapatinib due to deterioration in performance status.

**Determination of the OTR.** Four patients were enrolled at dose level 0 (1,250 mg lapatinib and 2.5 mg letrozole) and no DLT were reported in the first treatment cycle and the next dose level (dose level 1) was opened for enrollment. The third patient at dose level 1 (1,500 mg lapatinib + 2.5 mg letrozole) had a DLT of grade 2 diarrhea that was considered dose-limiting by the investigator. The diarrhea developed 2 days following the start of lapatinib therapy and resolved 4 days later. Lapatinib was temporarily interrupted and restarted at a reduced dose on resolution of the diarrhea. Five additional subjects were enrolled (8 total subjects at dose level 1) and there were no other DLT in the first treatment cycle. The OTR was defined as 1,500 mg/d lapatinib and 2.5 mg/d letrozole.

![Table 1. Patient characteristics](https://www.aacrjournals.org/doi/fig/10.1158/1078-0432.CCR-07-2443.s1-1)

<table>
<thead>
<tr>
<th>Assessment variable</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. subjects</td>
<td>39 (100)</td>
</tr>
<tr>
<td>Age (y), median (range)</td>
<td>57 (31-73)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>38 (97)</td>
</tr>
<tr>
<td>Male</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>34 (87)</td>
</tr>
<tr>
<td>American Hispanic</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>African American</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Karnofsky performance status, median (range)</td>
<td>90 (70-100)</td>
</tr>
<tr>
<td>Prior therapy</td>
<td></td>
</tr>
<tr>
<td>Hormonal therapy, median (range)</td>
<td>1 (0-5)</td>
</tr>
<tr>
<td>Cytotoxic therapy, median (range)</td>
<td>3.5 (0-12)</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>18 (46)</td>
</tr>
<tr>
<td>Ovary</td>
<td>16 (41)</td>
</tr>
<tr>
<td>Endometrium</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Bladder</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Cervix</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Fallopian tube</td>
<td>1 (3)</td>
</tr>
<tr>
<td>ER/PgR status</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
</tr>
<tr>
<td>ER+</td>
<td>23 (100)*</td>
</tr>
<tr>
<td>PgR+</td>
<td>15 (79)*</td>
</tr>
<tr>
<td>Breast cancer patients</td>
<td>18 (100)</td>
</tr>
<tr>
<td>ER+</td>
<td>12 (75)*</td>
</tr>
<tr>
<td>PgR+</td>
<td></td>
</tr>
<tr>
<td>HER-2 status (breast cancer patients)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>IHC3* and/or FISH+</td>
<td></td>
</tr>
</tbody>
</table>

*ER status was unknown in 16 patients.  
1PgR status was unknown in 20 patients.  
2PgR status was unknown in 2 breast cancer patients.  
3ErbB2 status was unknown in 3 breast cancer patients.
Dose administration and modification. The median percent of prescribed dose intensity was 100% (range, 63.6-100%) for lapatinib and 100% (range, 54-100%) for letrozole. Four patients required lapatinib dose reductions: 3 patients with grade 3 diarrhea and 1 patient with grade 2 diarrhea. Letrozole was not dose reduced during the study.

Safety. The safety population consisted of all 39 study participants: 4 patients received 1,250 mg lapatinib plus 2.5 mg letrozole and 35 patients received 1,500 mg lapatinib plus 2.5 mg letrozole. One patient in the pharmacokinetic group assigned to receive 1,500 mg lapatinib plus 2.5 mg letrozole only received 2.5 mg letrozole before discontinuing therapy due to clinical deterioration due to disease progression. Lapatinib was generally well tolerated in combination with 2.5 mg letrozole at doses up to 1,500 mg. The most frequently (≥10%) reported drug-related adverse events were diarrhea (77%), rash (62%), nausea (46%), fatigue (26%), vomiting (23%), anorexia (23%), and mucositis (13%; Fig. 1). No grade 3 or 4 drug-related adverse events were reported in the 1,250 mg lapatinib plus 2.5 mg letrozole group. Nine patients receiving 1,500 mg lapatinib plus 2.5 mg letrozole experienced a drug-related grade 3 adverse events [diarrhea (n = 6), rash (n = 1), anemia (n = 1), and clostridium colitis (n = 1)], but no drug-related grade 4 adverse events were reported in this group.

Two patients in the 1,500 mg lapatinib plus 2.5 mg letrozole group discontinued study drug due to adverse events. One patient discontinued treatment because of drug-related grade 3 rash, and the other patient discontinued treatment because of non-drug-related grade 4 respiratory failure. The latter patient died, but the investigator did not attribute the toxicity to drug treatment.

Four patients (3 in the 1,500 mg lapatinib + 2.5 mg letrozole group and 1 in the 1,250 mg lapatinib + 2.5 mg letrozole group) had ≥20% decrease in LVEF relative to their pretreatment values. In only one of these patients did the post-treatment ejection fraction decline to a value of <50%. In this patient, the baseline LVEF value of 70% decreased to a 48% value after 2 months of therapy (31% decline relative to their pretreatment value). The patient remained on study drug until disease progression and had a LVEF measurement of 64% (9% decline relative to their pretreatment value) at their post-study assessment.

Antitumor activity. Thirty-four patients (4 receiving 1,250 mg lapatinib + 2.5 mg letrozole and 30 receiving 1,500 mg lapatinib + 2.5 mg letrozole) had at least one available disease assessment after baseline evaluation and were analyzed for clinical activity. Five patients were removed from the study before their initial disease assessment for the following reasons: (a) ulcerative colitis, (b) drug-related grade 3 rash, (c) decreased performance status, (d) non-drug-related pneumothorax, and (e) noncompliance.

Two patients, one with endometrial cancer and the other with breast cancer, experienced partial response. The endometrial cancer patient (ER/PgR status unknown) who responded
had stable disease until a partial response was noted after 225 days of therapy. The partial response, confirmed by repeat radiologic assessments, lasted for 161 days. This patient had not received prior hormonal therapy or chemotherapy. The responding patient with breast cancer (ER+/PgR+, ErbB2+), an unconfirmed partial response, achieved partial response at initial disease assessment (day 53) but had progressive disease at the next assessment (day 106). This patient had received prior adjuvant chemotherapy and tamoxifen and three cytotoxic chemotherapy and two hormonal regimens for metastatic disease. Twenty patients had stable disease as their best response (range, 32-289 days); of the patients with stable disease, 2 patients with breast cancer (both patients were ER+/PgR+ and ErbB2+) experienced stable disease lasting 247 and 289 days. One of the patients had received prior adjuvant tamoxifen therapy and five cytotoxic and two hormonal regimens for metastatic disease and the second patient had received prior adjuvant chemotherapy and hormonal therapy and two cytotoxic and two hormonal regimens for metastatic disease.

Pharmacokinetics. The pharmacokinetic phase of the study involved 20 patients. Letrozole pharmacokinetic data were obtained from 8 patients that completed their assigned treatment sequence. Lapatinib pharmacokinetic data were obtained from 9 patients that completed their assigned treatment sequence. Plasma concentration versus time profiles obtained from 9 patients that completed their assigned treatment sequence. Lapatinib pharmacokinetic data were obtained from 8 patients that completed their assigned treatment sequence. Letrozole pharmacokinetic data were obtained from 10 patients. Combined lapatinib + letrozole pharmacokinetic data were obtained from 8 patients. The pharmacokinetic phase of the study was conducted in neoadjuvant and advanced breast cancer settings, and phase III trials using these treatment approaches are now under way (39, 40, 45, 46).

In the current study, coadministration of lapatinib and letrozole in patients with advanced breast cancer or other solid tumors was generally well tolerated. The most frequently reported drug-related adverse events were diarrhea, rash, nausea, fatigue, vomiting, anorexia, and mucositis with few drug-related grade 3 adverse events and no drug-related grade 4 adverse events. The OTR was defined as 1,500 mg/d lapatinib in combination with 2.5 mg/d letrozole, which represent the typical monotherapy doses of lapatinib and letrozole, respectively.

The toxicities of the drugs in combination were similar to that reported previously for each drug individually although diarrhea and rash were more frequent (33, 47). Drug-related diarrhea in the current study (77%; grade 3, 15%) was more frequent than in phase II studies of monotherapy 1,500 mg/d lapatinib (36-54%; grade 3, 3%; ref. 23). Diarrhea was typically managed with dose delays, antidiarrheal medications, and occasionally dose reductions. Likewise, rash was more frequent (62%; grade 3, 3%) in the current study than reported previously with 1,500 mg/d lapatinib (27-30%; grade 3, 1%; ref. 23), although this increase was primarily due to an increase

### Table 2. Pharmacokinetic variables for lapatinib and letrozole

<table>
<thead>
<tr>
<th>Variables</th>
<th>Lapatinib alone (n = 9)*</th>
<th>Lapatinib + letrozole (n = 10)*</th>
<th>Comparison †</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;t&lt;/sub&gt; (h μg/mL)</td>
<td>31.9 (17.2-59.2)</td>
<td>27.0 (13.3-54.8)</td>
<td>0.84 (0.62-1.13)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (μg/mL)</td>
<td>2.47 (1.47-4.13)</td>
<td>1.94 (1.13-3.34)</td>
<td>0.78 (0.57-1.06)</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>3.00 (0.00-12.2)</td>
<td>3.00 (2.50-12.0)</td>
<td>0.02 (-0.37-1.75)</td>
</tr>
<tr>
<td>C&lt;sub&gt;r&lt;/sub&gt; (μg/mL)</td>
<td>0.78 (0.37-1.66)</td>
<td>0.72 (0.30-1.73)</td>
<td>0.90 (0.63-1.28)</td>
</tr>
<tr>
<td>Variables</td>
<td>Letrozole alone (n = 8)*</td>
<td>Letrozole + lapatinib (n = 8)*</td>
<td>Comparison †</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------------</td>
<td>---------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;t&lt;/sub&gt; (h μg/mL)</td>
<td>2.23 (1.34-3.71)</td>
<td>2.09 (1.30-3.34)</td>
<td>0.94 (0.79-1.11)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (μg/mL)</td>
<td>0.14 (0.08-0.22)</td>
<td>0.12 (0.08-0.19)</td>
<td>0.90 (0.79-1.02)</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>1.75 (1.50-24.0)</td>
<td>1.25 (0.00-6.00)</td>
<td>-1.75 (-12.0-1.00)</td>
</tr>
<tr>
<td>C&lt;sub&gt;r&lt;/sub&gt; (μg/mL)</td>
<td>0.09 (0.05-0.17)</td>
<td>0.08 (0.05-0.13)</td>
<td>0.86 (0.71-1.05)</td>
</tr>
</tbody>
</table>

*Geometric mean (95% confidence interval), except median (range) for t<sub>max</sub>.
† Geometric least-squares mean ratio (90% confidence interval), except median difference and 90% confidence interval for t<sub>max</sub>.
in grade 1 rash. It is unclear why diarrhea and rash were increased. No pharmacokinetic interaction was observed (as noted below). Whether this increase is evidence of a pharmacodynamic interaction or due to the small sample size is unclear. No increase in adverse events was reported in a recent combination trial of gefitinib and anastrozole in breast cancer patients (46).

No clinically significant cardiotoxicity was observed in the current study. In a recent analysis of 3,127 cancer patients receiving lapatinib, a 1.3% incidence of decreased LVEF was reported (National Cancer Institute Common Toxicity Criteria grade 3 or 4 or asymptomatic LVEF decline of ≥20% relative to baseline and below the institutions lower limit of normal). Only 0.1% of patients had symptomatic LVEF dysfunction and this was generally reversible or nonprogressive (48).

The potential for a metabolic drug-drug interaction between these agents was considered because letrozole is a substrate of CYP3A4 (49) and lapatinib has been shown to inhibit this enzyme in vitro (50). The results of this study suggest that coadministration of these agents is unlikely to produce a clinically significant alteration in the pharmacokinetics of either drug.

The results of this study indicate that the combination of lapatinib and letrozole is safe, does not have a pharmacokinetic interaction, and has clinical activity. A current phase III trial of lapatinib plus letrozole versus letrozole plus placebo (EGF30008) in previously untreated, postmenopausal patients with ER/PrR* breast cancer is ongoing. This study will provide important answers about the clinical feasibility of inhibiting membrane growth factor pathways and ER cross-talk.

Disclosure of Potential Conflicts of Interest

Q.S.C. Chu has a commercial research grant from GlaxoSmithKline. M.E. Cianfrocca has a commercial research grant from GlaxoSmithKline and has received honoraria from GlaxoSmithKline and Novartis. E. Paul, L. Pandite, K.M. Koch, R.A. Fleming, and J. Lofftiss are employed by GlaxoSmithKline. E.K. Rowinsky is employed by and has an ownership interest in ImClone Systems. L.J. Goldstein has received honoraria from GlaxoSmithKline.

References


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