A predictive model for exemestane pharmacokinetics/pharmacodynamics incorporating the effect of food and formulation

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Aims

Exemestane (Aromasin®) is an irreversible aromatase inactivator used for the treatment of postmenopausal women with advanced breast cancer. The objective of this study was to evaluate the effect of formulation comparing a sugar-coated tablet (SCT) with a suspension and food on the pharmacokinetics (PK) and pharmacodynamics (PD) with respect to plasma estrone sulphate (E1S) concentrations of exemestane, using a PK/PD approach.

Methods

This was an open, three-period, randomized, crossover study. Twelve healthy postmenopausal women received single oral doses of 25 mg exemestane as a SCT after fasting or food and as a suspension after fasting. Exemestane and E1S concentrations were determined before and up to 14 days after drug administration. Population analysis was performed in two steps: (i) a compartmental PK model was selected incorporating the effect of food and formulation; (ii) conditional on the PK model, a PD model was developed employing indirect response models. Model selection was performed using standard statistical tests. Validation and assessment of the predictive capability of the selected model was performed using real test data sets obtained from the literature.

Results

A three-compartment model with first-order elimination rate best described exemestane disposition (k_{12} 0.454, k_{21} 0.158, k_{13} 0.174, k_{31} 0.016 and k 0.738 h⁻¹). Absorption was described by a mono-exponential function [k_a 2.3 (SCT after fasting), 1.1 (SCT after food) and 7.6 h⁻¹ (suspension); lag time 0.2 h]. The PD model assumed that E1S plasma concentrations are determined by a zero-order synthesis rate (6.5 pg ml⁻¹ h⁻¹) and a first-order elimination constant (0.032 h⁻¹). Exemestane inhibited E1S synthesis with a C_{50} value of 22.1 pg ml⁻¹. The mean population estimates were used to simulate the administration of different doses of the drug (0.5, 1, 2.5, 5 and 25 mg day⁻¹). The model predictions were in agreement with historical data.

Conclusions

Exemestane absorption is influenced by the formulation of the drug and by food, but its disposition is independent of both. PK differences do not translate into clinically important differences in the PD. The PK/PD model developed was able to predict successfully the response to different doses and administration schedules with respect to oestrogen suppression.

Introduction

Breast cancer is the commonest malignant disease among Western women and, although overall survival has improved with earlier diagnosis by mammography and with adjuvant therapy, it still represents a leading cause of cancer related death [1]. Approximately one third of all breast cancers and two thirds of postmenopausal breast cancers are oestrogen dependent [2]. As a consequence, considerable effort has been directed towards the development of novel therapies to block the action or synthesis of hormones involved in tumour growth. Aromatase is an enzyme responsible for the conversion of androgens (androstenedione and testosterone) to oestrogens (estrone and estradiol, respectively). Therefore, inhibition of oestrogen biosynthesis by selective aromatase inhibitors is an important endocrine treatment option in postmenopausal women with breast cancer.

The first-line therapy for this type of cancer is usually the antiestrogen, tamoxifen [3]. However, results from clinical trials suggest that after approximately 5 years, tamoxifen may lose its effectiveness [4]. Inhibition of aromatase could be a safer and more effective treatment [5], because several prospective studies have found that a high plasma oestrogen concentration in postmenopausal women is a risk factor for the development of breast cancer [1].

These drugs can be divided into type I and type II inhibitors. The latter act by reversibly binding to the aromatase enzyme, whereas the former (inactivators) interact irreversibly with the enzyme. Exemestane (6-methylenandrosta-1, 4-diene-3, 17-dione; Aromasin®) is a type I aromatase inhibitor that is structurally related to the natural substrate androstenedione [6]. It is initially recognized by the aromatase enzyme as a false substrate. The compound is then transformed (through an NADPH-dependent mechanism) to an intermediate that binds irreversibly to the enzyme, causing its inactivation (also known as suicide inhibition) [7]. In kinetic studies with the human placental enzyme, exemestane showed competitive inhibition of the aromatization of androstenedione with an inhibitory constant (K_i) of 4.3 nM (1.3 ng ml^{-1}) which is much lower than the value reported for aminoglutethimide (K_i 671 nM) [7, 8]. Inactivation constants ($K_{i(\text{inact})}$) of 26–66 nM were obtained, which were similar to those for the aromatase inactivator, formestane.

Clinical trials have demonstrated that oral exemestane (25 mg day^{-1}) inactivates peripheral aromatase activity and decreases basal plasma estrone, estradiol and estrone sulphate (E1S) concentrations by 85–95% in postmenopausal women with advanced breast cancer

[9–11]. These effects were greater than those observed after the administration of megestrol acetate, leading to significant benefits in terms of survival time, time to tumour progression and time to treatment failure [12].

It is well known that food and how a drug is formulated may influence pharmacokinetics [13]. In the present study, the effect of fasting and of drug formulation (the marketed sugar coated tablet *vs* a suspension) on the pharmacokinetics (PK) and pharmacodynamics (PD) of exemestane was evaluated using nonlinear mixed effect PK-PD models. The model we developed was then used to predict the effect of SCT exemestane for historical data from postmenopausal breast cancer patients [12, 14]. Standard noncompartmental analyses of exemestane pharmacokinetics and pharmacodynamics are also reported.

Methods

Subjects

Twelve healthy postmenopausal women 45–68 years of age (mean age 55 years) who weighed 46–66 kg (mean weight 54.9 kg) were included in the study. All the subjects were healthy as determined by physical examination, electrocardiography and routine laboratory tests. Subjects were admitted to the Pontchaillou Hospital (Rennes) in the morning after an overnight fast. Subjects were asked to avoid taking any medication other than occasional paracetamol, for minor analgesia, during the course of the study. Alcoholic beverages, caffeine-containing food and beverages, and all tobacco products were prohibited from 24 h before dosing until the end of the study. Each subject gave written informed consent to the study, which was approved by the Hospital Ethics Committee and conducted in accordance with the provisions of the Declaration of Helsinki concerning experimentation on humans (1964).

Study design

This was an open, three-period, randomized, crossover study. Each woman received the three treatments according to a repeated 3×3 Latin square design, separated by a 4/5-week washout period. The subjects were randomly assigned to the following treatments: Treatment 1: a sugar-coated tablet (SCT, 25 mg of exemestane) under fasting conditions, Treatment 2: 25 mg of exemestane given as an extemporaneous suspension under fasting conditions, and Treatment 3: a SCT (25 mg of exemestane) 15 min after a standard high-fat breakfast. All preparations were given with 180 ml of water or vehicle.

Blood samples (5 ml) for the determination of exemestane plasma concentrations were drawn before and

0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 16, 24, 48, 72, 120 and 168 h after dosing. For the measurements of E1S, 5 ml of blood were drawn before and 24, 48, 72, 120, 168 and 336 h after each dosing. All blood samples were collected in heparinized tubes, chilled in an ice-water bath and centrifuged at 4 °C (1200 g, 10 min) within 30 min, to avoid possible degradation of parent drug. Plasma samples were stored at –20 °C until analysis.

Determination of exemestane

Exemestane was determined in plasma using a validated high performance liquid chromatographic (HPLC) method followed by radioimmunoassay (RIA) detection [15]. The method had a lower limit of quantification (LLOQ) of 13.5 pg ml⁻¹. Intra- and interassay coefficients of variation were 13.4% and 17.7%.

Determination of E1S

E1S was measured in plasma using RIA after solid phase extraction, enzyme hydrolysis and purification of the deconjugated estrone by HPLC. The procedure was similar to that reported in the literature [10]. The LLOQ was 6 pg ml⁻¹. Intra- and interassay coefficients of variation were 9.1% and 14.4%.

Population PK/PD modelling

The population analysis of the exemestane data was carried out in two steps. First, we developed a population PK model and obtained the corresponding empirical Bayes estimates for each individual. In the second step, we developed the population PD model conditional on the PK empirical Bayes estimates from each individual. Inter-individual variability was modelled assuming a log-normal distribution for the parameters, unless otherwise indicated. Intra-individual variability assumed a proportional plus constant error model. The estimations were done using the NONMEM first-order method (NONMEM V, FOCE INTERACTION). Comparison of alternative models, and model selection was performed using standard graphical tools and statistical model selection criteria. In particular, we used the likelihood-ratio test (with a selection threshold of $P < 0.01$), and the Akaike criterion [16], which gave similar results. Simulations were also performed using NONMEM.

Pharmacokinetic model We fitted the exemestane data from different treatments simultaneously. The disposition function for exemestane was described by a three compartments mammillary model with first-order elimination rate from the central compartment. The absorption of exemestane, $A(t)$ was modelled as a first-order

process (a single compartment with an absorption rate k_{a1}), according to the following equation:

$$A(t) = k_{a1} \cdot e^{-k_{a1}t} \quad (1)$$

Alternative models for absorption use a bi-exponential absorption rate function:

$$A(t) = (1 - \text{Fr})(k_{a1} \cdot e^{-k_{a1}t}) + \text{Fr}(k_{a1} \cdot e^{-k_{a2}t}) \quad (2)$$

where Fr is the fraction of dose absorbed at an absorption rate of k_{a2} . We also used a spline (flexible nonparametric) function for explorative investigation of the absorption profiles. A spline is a mathematical function that describes a smooth curve connecting a set of points (e.g. breakpoints, nodes) [17]. All the absorption models included a pure absorption lag time (lag).

Pharmacodynamic model We fitted E1S data from the three treatments simultaneously. The model for E1S was built assuming that its rate of change in plasma is controlled by a constant (zero-order) rate of synthesis (k_s), indirectly related to aromatase activity, and a first-order rate of elimination (k_o), as follows:

$$\frac{d\text{E1S}}{dt} = k_s - k_o \cdot \text{E1S} \quad (3)$$

The parameters k_s and k_o are related to the baseline steady-state concentrations of E1S (baseline = k_s/k_o). Inhibition by exemestane of the production of E1S was included in the previous equation as follows:

$$\frac{d\text{E1S}}{dt} = k_s \left(1 - \frac{C^\gamma}{C^\gamma - C_{50}^\gamma} \right) - k_o \cdot \text{E1S} \quad (4)$$

where C is the plasma concentration of exemestane, C_{50} is the plasma concentration of exemestane producing 50% of maximum inhibition, and γ is a Hill-coefficient.

The effect of exemestane may be characterized using an alternative mechanism-based model, in which aromatase (Ar) is irreversibly inactivated by the drug. Assuming that the concentrations of E1S precursor are constant, the rate of change of E1S concentration is then described by the following equation:

$$\frac{d\text{E1S}}{dt} = k_s \cdot \text{Ar} - k_o \cdot \text{E1S} \quad (5)$$

where k_s is now the first-order production rate constant for E1S, and k_o is the first-order elimination rate constant for E1S. The rate of change in Ar concentrations can be described by the following equation:

$$\frac{d\text{Ar}}{dt} = k_{sc} - k_{oe} \cdot \text{Ar} \quad (6)$$

where k_{se} is the zero-order synthesis rate constant for Ar and k_{oc} is the first-order elimination rate constant for the enzyme. When exemestane is present, Ar elimination is increased (through E inactivation) at a rate (k_i) proportional to the concentrations of Ar and to that of the drug in plasma:

$$\frac{dAr}{dt} = k_{se} - k_{oc} \cdot Ar - k_i \cdot Ar \cdot C(t) \quad (7)$$

A possible interpretation of the model is that k_i represents the first-order rate constant of irreversible binding of drug to the enzyme. From a modelling point of view, equations 3–5 introduce a further delay in the effect of drug on the concentration of EIS (see also Gisleskog [18] for similar pharmacodynamic models).

Model validation and prediction

To validate further the PK/PD model, we used it to predict the effect after 2 weeks (i.e. at steady state) of SCT exemestane in postmenopausal breast cancer patients as described by Bajetta & coworkers [14] and Kaufmann & coworkers [12]. The mean population estimates were used to simulate the administration of different doses of the drug (0.5, 1, 2.5, 5, and 25 mg day⁻¹) administered once daily for 15 days under nonfasting conditions.

Results

Exemestane treatments were well tolerated in all subjects. Reported events were mild and short lasting. Those that might be drug-related were mainly typical of the pharmacological class and included hot flushes, nausea and headache. Laboratory parameters were unaffected by exemestane.

Pharmacokinetic parameters of exemestane obtained using a noncompartmental analysis are shown in Table 1. The observed values of the maximum concentration (C_{max}) and the time to achieve this concentration (t_{max}), indicated that the formulation had an effect on both parameters. Mean t_{max} tended to be shorter and C_{max} higher; however, the differences were not statistically significant. The 90% confidence interval (CI) for the ratio of t_{max} for fasting/fed conditions was 0.76, 1.01, and the 90% CI for the C_{max} was 0.49, 1.14. When the sugar coated tablet was administered with food a delay in the t_{max} and a higher C_{max} was observed; however, no statistically significant differences were found. The 90% CI for the ratio of t_{max} for SCT fasting/suspension fasting was 0.83, 1.90 and the 90% CI for the ratio C_{max} fasting : C_{max} food was 0, 1.75. The effect of food and formulation on AUC was similar to that observed for

Table 1

Mean (SEM) noncompartmental pharmacokinetic parameters for exemestane

Parameter	SCT/fasting	Suspension/ fasting	SCT/food
t_{max} (h)	0.97 (0.28)	0.71 (0.07)	1.88 (0.5)
C_{max} (ng ml ⁻¹)	11.1 (1.3)	15.4 (2.3)	17.7 (4.5)
AUC (ng ml ⁻¹ h)	29.7 (2.2)	34.5 (3.3)	41.3 (3.4)
$t_{1/2,z}$ (h)	24.0 (2.8)	21.9 (3.7)	21.4 (3.1)
CL/F (l)	902 (74.5)	798 (76.2)	645 (45.9)

C_{max} maximum plasma concentration; t_{max} time of occurrence of C_{max} ; AUC area under the concentration-time curve to infinite time; $t_{1/2,z}$ apparent terminal half-life; CL/F ratio of plasma clearance to bioavailability; SCT/fasting sugar coated tablet after fasting; Suspension/fasting suspension after fasting; SCT/food sugar coated tablet after food.

C_{max} . Nonetheless, food has a significant effect on AUC (90% CI for the ratio fasting : food was 1.21, 1.60).

Figure 1, and Tables 2 and 3 show the PK predictions obtained by the final selected population PK model, a linear three-compartmental model with elimination from the central compartment and first order absorption. The disposition function of the drug was not affected by formulation or by fasting. However, significant differences on the rate of absorption were detected. Absorption of the drug under fed conditions showed some evidence that it could be better described by a bi-exponential function (see equation 2), but the result was barely significant using the Akaike criterion, and we decided to assume first-order absorption. The use of a spline function to characterize the absorption did not significantly improve the fit to the data. The suspension formulation showed a 1.2 times higher F than the SCT after fasting. The food effect translated into an increase of the F of 1.6 times. The final model indicated a significant interindividual variability in the V/F (coefficient of variation = 22%). The rate of absorption (k_{a1}) had a higher coefficient of variation (92%) than the elimination rate constant (k) from the central compartment (11%). No significant interindividual variability in the other parameters describing the plasma disposition of the drug was supported by the data. A combined error model was used to describe the residual variability. The additive part was fixed to the SD of the analytical technique and the proportional part was estimated to be 4%.

Figure 1

Plasma exemestane concentrations vs time profiles after the administration of the SCT after fasting (upper panel), the suspension after fasting (middle panel) and the SCT after food (lower panel). The points are the experimental data and the solid lines are the typical population model predictions

Concentration-time data for E1S are shown in Figure 2. Baseline values of E1S (219 pg ml^{-1} , 212 pg ml^{-1} and 208 pg ml^{-1} , respectively, for the SCT after fasting, the suspension after fasting and the SCT under fed conditions) were not significantly different. In almost all the subjects, E1S baseline concentrations were recovered at the end of the 14-day observation period. The maximum observed decrease in E1S plasma concentrations (expressed as percentage of the baseline concentrations: 27 (12.6 SD), 28.5 (8.7) and 24.6 (6.8) for the SCT after fasting, the suspension after fasting and the SCT after food, respectively), was not statistically different between the three treatments.

Figure 2 shows the predictions obtained by the selected PD model (see equations 3–4), which is a rel-

atively standard indirect-response model with action of drug concentration on the (apparent) rate of production of E1S. The model described by equations 5–7 also gave good predictions, which, however, were not judged to be significantly better than those obtained by equations 3–4, either by visual inspection or using statistical selection criteria, such as the objective function value (OFV) provided by NONMEM. The value of the OFV obtained with equations 5–7 was not 3.9 points lower than the value obtained with equations 3–4.

Estimates for the pharmacodynamic parameters are reported in Table 4. Significant interindividual variability in the baseline E1S concentration was observed (coefficient of variation = 56%), k_o (41%) and C_{50} (47%), parameters, and a residual variability of 35%.

Table 2

Mean population pharmacokinetic absorption parameters for exemestane

Parameter	SCT/fasting	Suspension/fasting	SCT/food
Lag (h)	0.21 (10)	0.21 (10)	0.21 (10)
k_{a1} (h^{-1})	2.35 (25)	7.6 (21)	1.13 (35)
V/F (l)	1360 (10)	1120 (12)	844 (10)

k_{a1} first-order absorption rate constant; lag, absorption lag time; V/F apparent volume of the central compartment (volume divided by bioavailability). In parenthesis, the standard error of the parameter expressed as percentage of the parameter value is reported; SCT/fasting sugar coated tablet after fasting; Suspension/fasting suspension after fasting; SCT/food sugar coated tablet after food.

Table 4

Mean population pharmacodynamic parameters for exemestane with respect to its effect on EIS

Parameter	Estimate	Interindividual variability (%)
Baseline (pg ml^{-1})	203 (8)	56 (19)
k_o (h^{-1})	0.032 (9)	41 (47)
C_{50} (pg ml^{-1})	22.1 (10)	47 (32)
γ	1.73 (12)	N.E.

See equations 1–2 in the text for definition of the parameters. In parenthesis is the standard error of the parameter expressed as percentage of the parameter value. N.E. not estimated.

The data did not support the estimation of interindividual variability in the γ parameter. The pharmacodynamic parameters were not significantly affected by formulation or by fasting. Figure 3 shows the individual plasma exemestane effect model predictions for the best and the worst individual fits after the administrations of the SCT after fasting, the suspension after fasting and the SCT after food. Good agreement was found between observed and predicted EIS concentrations.

Figure 4 shows the predicted effect (expressed as percentage of baseline concentration of EIS) of the drug after the administration of five different daily dosage regimens for 15 days. The selected model predicts concentrations of EIS that are within of 70% of baseline for the lowest dose (0.5 mg day^{-1}) (compared with a

Table 3

Mean population disposition pharmacokinetic parameters for exemestane

Parameter	Estimate
k_{12} (h^{-1})	0.454 (19)
k_{21} (h^{-1})	0.158 (6)
k_{13} (h^{-1})	0.174 (9)
k_{31} (h^{-1})	0.016 (10)
k (h^{-1})	0.738 (7)

k_{ij} rate of transfer from compartment i to j (the central compartment is number 1); k first-order elimination rate constant from the central compartment. In parenthesis, the standard error of the parameter expressed as percentage of the parameter value is reported.

value of 56% reported by Bajetta *et al.* [14]), 45% for 1.0 mg day^{-1} (compared with 34% [14]), 14% for 2.5 mg day^{-1} (compared with 16% [14]), 10% for 5 mg day^{-1} (compared with 18% [14]), and lower than 10% for the 25 mg day^{-1} dose (in agreement with steady-state measurements of 8.1–9.2% reported by Kaufmann *et al.* [12]).

Discussion

Most of the published studies on exemestane report information regarding its PD characteristics and comparison with other anticancer drugs [19]. In the present work a population indirect-response model was developed to describe the decrease in EIS concentrations after the administration of two different formulations.

Non-compartmental pharmacokinetic parameters obtained in the present study are in agreement with those previously reported in the literature [20].

The observed plasma concentrations of exemestane following administration after breakfast were higher than those observed during fasting. The absorption rate of exemestane when administered as a suspension was almost four times faster than when it was administered as a tablet, as might be expected based on the physico-chemical properties of a suspension compared with a tablet. Food intake appears to decrease the rate of absorption of exemestane probably through a delay in gastric emptying rate and an increase in intestinal motility and splanchnic blood flow [21]. For drugs such as exemestane that undergo first-pass metabolism, the latter may be reduced when the drug is administered after food compared with the fasting state because the transit times of these drugs in the liver are reduced as a result

Figure 2

Plasma E1S concentrations vs time profiles after the administration of the SCT after fasting (upper panel), the suspension after fasting (middle panel) and the SCT after food (lower panel). The points are the experimental data and the solid lines are the typical population model predictions

of the increase in splanchnic blood flow [22]. Although this phenomenon has not been described for other aromatase inhibitors, it has been described for drugs such as itraconazole, when administered as sugar-coated spheres [23].

The disposition of exemestane was best described by a three-compartmental model and, as expected, no differences were observed with respect to formulation and/or food intake. The differences observed in the ratio of volume of distribution to bioavailability (V/F), indicate that the latter for the three treatments is different.

The inhibition of aromatase by exemestane is directed towards the formation of estrone and estradiol and not E1S. However, owing to the equilibrium between the three species, inhibition of aromatase should cause similar suppression of E2, E1 and E1S, provided that the

inhibitor has no influence on other enzymes involved in oestrogen disposition [24]. Since exemestane has no effect on estrone sulphotase activity even at very high concentrations ($50 \mu\text{M}$) [25], E1S can be used as marker of overall oestrogen suppression. Although E1S has little biological activity *per se*, different tissues (including breast cancer tissue) express enzymes that are able to release the conjugated estrone, such that E1S may act as a pool for active oestrogen. Furthermore, the higher E1S concentrations compared with those of estrone (10 fold) and estradiol (35 fold) made the bioanalysis easier.

The maximum effect of exemestane on E1S was similar for the three treatment groups. The time to maximum effect was almost the same, and the E1S values returned to the baseline concentrations at the end of the study in all groups. These results show that differences

Figure 3
Individual plasma exemestane effect model predictions for the best (left panels) and the worst (right panel) individual fits after the administration of the SCT after fasting (upper panels), the suspension after fasting (central panels) and the SCT after food (lower panel). The solid circles are the experimental data and the solid lines are the individuals' model prediction

found in the absorption of exemestane were not large enough to cause a difference in the PD effect.

There was a delay in the attainment of maximum effect and the maximum in plasma exemestane concentration in all the three treatments. This delay seems to be a characteristic of a number of aromatase inhibitors due to their common mechanism of action. When this kind of effect is detected in the raw data, so-called indirect response models have been widely used when the endpoint of the modelling is to describe modifications in endogenous substances such as dihydrotestosterone [17, 26].

In the present work, a simple model where exemestane inhibited the synthesis of EIS best described the data. The typical population value for the elimination rate constant of EIS (0.032 h^{-1}), corresponds to a half-

life of approximately 20 h. This value is similar to the one reported by Aedo *et al.* [27, 0.057 h^{-1} , range (0.047–0.072)] after the administration of 2.5 mg of piperazine o-estrone sulphate to eight postmenopausal women. A value of 1.3 ng ml^{-1} was obtained for the *in vitro* k_i describing the effect of exemestane on human placental aromatase [7]. The difference between this value and that for the C_{50} obtained in the present work (22.1 pg ml^{-1}) may be due to the nature of the model or to the conditions used in the *in vitro* study. Similar differences in *in vitro* and *in vivo* data have been described for fadrozole [28].

In vitro studies suggest that the effect of exemestane on the aromatase enzyme is irreversible [7, 8]. However, the incorporation of irreversible inhibition into the model did not improve the fit in the present study. Ko

Figure 4

Simulated E1S concentrations (expressed as percentage of baseline) after the administration of 0.5, 1, 2.5, 5, and 25 mg day⁻¹ of exemestane for a period of 15 days

& Jusko [29] employed a similar model to describe the irreversible inactivation by finasteride of one of the isoenzymes of 5 α -reductase that converts testosterone to dihydrotestosterone.

We further validated and assessed the predictive capability of our model by simulating mean population plasma concentrations of E1S after the administration of different doses of exemestane for 14 days, which is a sufficient time to achieve steady-state PD. The maximum steady-state inhibition of E1S formation observed by us in healthy postmenopausal women is in reasonable agreement with that observed by others in patients with advanced breast cancer [12, 16].

In conclusion, the absorption of exemestane depends both on its formulation and whether or not the subject is fasting, whereas the disposition of the drug is independent of these factors. The observed differences in the absorption do not translate into differences in PD. Thus, the drug was able to produce maximum inhibition of the synthesis of E1S after all treatments. The PK-PD model we developed successfully predicted the pharmacodynamic response to exemestane at all doses and is thus a useful tool for further clinical studies of this drug.

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