Breast Cancer Res Treat (2010) 123:453–461
DOI 10.1007/s10549-010-1022-9

CLINICAL TRIAL

Results of a phase II study comparing three dosing regimens of fulvestrant in postmenopausal women with advanced breast cancer (FINDER2)

Kathleen I. Pritchard · Janusz Rolski · Zsuzsanna Papai · Louis Mauriac · Fatima Cardoso · Jose Chang · Lawrence Panasci · Carmen Ianuli · Zsuzsanna Kahan · Kenjiro Fukase · Justin P. O. Lindemann · Merran P. Macpherson · Patrick Neven

Received: 23 June 2010 / Accepted: 25 June 2010 / Published online: 15 July 2010

Abstract The **F**aslodex **In**vestigation of **D**ose evaluation in **E**strogen **R**eceptor-positive advanced breast cancer (FINDER)2 study evaluated the efficacy, safety, and pharmacokinetics (PK) of three fulvestrant dosing regimens. FINDER2 enrolled Western postmenopausal women recurring or progressing after prior endocrine therapy. Primary endpoint: objective response rate (ORR); secondary endpoints: time to progression (TTP), clinical benefit rate (CBR), tolerability, and PK parameters. Patients were randomized to receive fulvestrant: 250 mg/month (approved dose [AD]); 250 mg plus loading dose (loading dose [LD]; 500 mg on day 0, 250 mg on days 14, 28, and monthly thereafter); or 500 mg (high dose [HD]; 500 mg/month plus 500 mg on day 14 of Month 1). Treatment continued until disease progression or discontinuation. 144 patients were randomized: fulvestrant AD ($n = 47$); LD ($n = 51$); HD ($n = 46$). ORRs were: 8.5% (95% confidence interval [CI]: 2.4, 20.4%), 5.9% (1.2, 16.2%), and 15.2% (6.3, 28.9%) in the AD, LD, and HD arms, respectively. CBRs were: 31.9% (95% CI: 19.1, 47.1%), 47.1% (32.9, 61.5%), and 47.8% (32.9, 63.1%) for the AD, LD, and HD arms, respectively. Median TTP (months) was numerically longer for HD (6.0) and LD (6.1) versus AD (3.1). Tolerability was similar across dosing regimens. Steady-state plasma fulvestrant concentrations were predictable and achieved earlier with LD and HD. While there appeared to be a trend toward improved efficacy with HD and LD versus AD, no significant differences could be shown. A parallel study (FINDER1) has reported similar findings in Japanese patients.

Keywords Fulvestrant · Advanced breast cancer · Faslodex · High dose · Loading dose · Endocrine

K. I. Pritchard (✉)
Sunnybrook Odette Cancer Centre
and the University of Toronto, 2075 Bayview Avenue,
M4N 3M5 Toronto, ON, Canada
e-mail: kathy.pritchard@sunnybrook.ca

J. Rolski
Oncological Institute, Krakow, Poland

Z. Papai
State Health Centre, Budapest, Hungary

L. Mauriac
Institut Bergonié, Bordeaux, France

F. Cardoso
Jules Bordet Institute, Brussels, Belgium

J. Chang
RS McLaughlin Durham Regional Cancer Centre,
Oshawa, ON, Canada

L. Panasci
Jewish General Hospital, Montreal, QC, Canada

C. Ianuli
Ianuli Med Consult, Bucharest, Romania

Z. Kahan
Department of Oncotherapy, University of Szeged,
Szeged, Hungary

K. Fukase
AstraZeneca KK, Osaka, Japan

J. P. O. Lindemann · M. P. Macpherson
AstraZeneca Pharmaceuticals, Macclesfield, UK

P. Neven
Multidisciplinary Breast Centre, UZ-KU Leuven, Belgium

Introduction

Fulvestrant is an estrogen receptor (ER) antagonist without known agonist activity that is able to reduce cellular levels of estrogen and progesterone receptors. Fulvestrant has a distinct mechanism of action, compared with other endocrine (anti-estrogen) therapies, thereby lacking cross-resistance with other anti-cancer agents such as tamoxifen [1, 2].

On the basis of data from two large, worldwide Phase III clinical trials [3, 4], fulvestrant is licensed at a dose of 250 mg/month (approved dose; AD) for the treatment of postmenopausal women with advanced breast cancer following progression or recurrence after prior endocrine therapy. Although fulvestrant AD has established efficacy in this setting, it has been hypothesized that alternative dosing regimens may improve efficacy even further [5].

To address this question, the **F**aslodex **In**vestigation of **D**ose evaluation in **E**strogen **R**eceptor-positive (ER+) advanced breast cancer (FINDER) 1 and 2 studies have evaluated the efficacy, tolerability, and pharmacokinetic (PK) profiles of three different fulvestrant dose regimens in postmenopausal women with advanced breast cancer, as follows:

1. AD (250 mg/month)
2. 250 mg loading dose (LD) regimen (500 mg on day 0 and 250 mg on days 14 and 28 of Month 1, and 250 mg every 28 days thereafter)
3. High-dose (HD) regimen (500 mg/month plus 500 mg on day 14 of Month 1).

Here, we describe the results from FINDER2, which has been performed in a predominantly Western (i.e., non-Japanese) patient population.

Methods

Study design and treatment

FINDER2 (9238IL/0068; NCT00313170) was a randomized, double-blind, parallel-group, international, Phase II study conducted across 34 centers in eight countries: Belgium, Canada, Czech Republic, France, Hungary, Poland, Romania, and Turkey.

Patients were randomized 1:1:1 to one of the three fulvestrant dosing regimens (AD, LD, or HD). Treatment continued until patients experienced disease progression, or until any other criterion for discontinuation was met: voluntary discontinuation, safety concerns (according to the investigators' judgment), non-compliance, or lost to follow-up.

Patients

FINDER2 enrolled postmenopausal women, all with measurable disease and documented ER+ (≥10% positive staining by immunohistochemistry), locally advanced/metastatic breast cancer. Eligible patients had: relapsed during or within 12 months of completion of adjuvant endocrine therapy; progressed after endocrine therapy started ≥12 months after the completion of adjuvant endocrine treatment; or progressed after first-line endocrine therapy for patients with de novo advanced breast cancer.

Patients were excluded if they had: life-threatening visceral metastases; received more than one previous regimen of systemic anti-cancer therapy (other than one regimen of endocrine treatment for advanced disease); extensive radiation therapy or systemic anti-cancer therapy within 4 weeks prior to randomization; abnormal laboratory values or a severe concomitant condition.

All patients provided written informed consent and the study was performed in accordance with the Declaration of Helsinki and was consistent with International Conference on Harmonization Good Clinical Practice.

Efficacy assessments

The primary study endpoint was the objective response rate (ORR) of patients treated with fulvestrant AD, LD, or HD, evaluated according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria [6]. The best overall response for each patient was categorized as a response (complete response or partial response) or a non-response (stable disease, progressive disease, or not evaluable).

Secondary endpoints included time to progression (TTP), clinical benefit rate (CBR), and duration of response (DoR). All endpoints were evaluated according to RECIST criteria [6].

Pharmacokinetic parameters

Plasma samples for PK analysis were collected from patients who consented to PK measurement. Blood samples (4 ml) were drawn at baseline and prior to injection on days 14, 28, 56, and 84. Two additional samples were collected between days 5 and 10 and days 33 and 38. Drug concentration–time data were analyzed with NONMEM V5.0, using a non-linear mixed-effects model approach. The primary PK parameters were fulvestrant clearance and volume of distribution at steady state, and secondary parameters of maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), minimum plasma concentration (C_{min}), area under plasma concentration time curve from zero to the end of the dosing interval ($AUC_{0-\tau}$), and half life ($t_{½}$) were derived.

Safety assessments

The safety and tolerability of the three fulvestrant dosing regimens were assessed by continuous evaluation of adverse events (AEs), clinical laboratory tests, vital signs, electrocardiogram (ECG), and physical examinations. Safety assessments were performed at baseline, throughout the study period, and up to 8 weeks after the last injection of study medication.

Statistical analysis

Overall, 43 patients per group were required for 90% probability that the best dose regimen by response rate be correctly selected, assuming that the lowest response rate was 19.2% (based on results for AD in previous studies) and that the difference in response rate between the best and next-best dose regimen was 15%. To allow for drop-out, a total of 135 patients were to be recruited to this study (45 patients per group). No formal hypothesis tests were planned for the efficacy endpoints.

Results

Patients

Overall, 144 patients were randomized to treatment (intent-to-treat population); fulvestrant AD ($n = 47$), LD ($n = 51$), and HD ($n = 46$). One patient in the LD group did not receive treatment and was excluded from the safety population. Patient disposition throughout the study is shown in Fig. 1.

Baseline characteristics, including treatment history, were generally well balanced across the treatment groups, with no major discrepancies between arms. The majority of

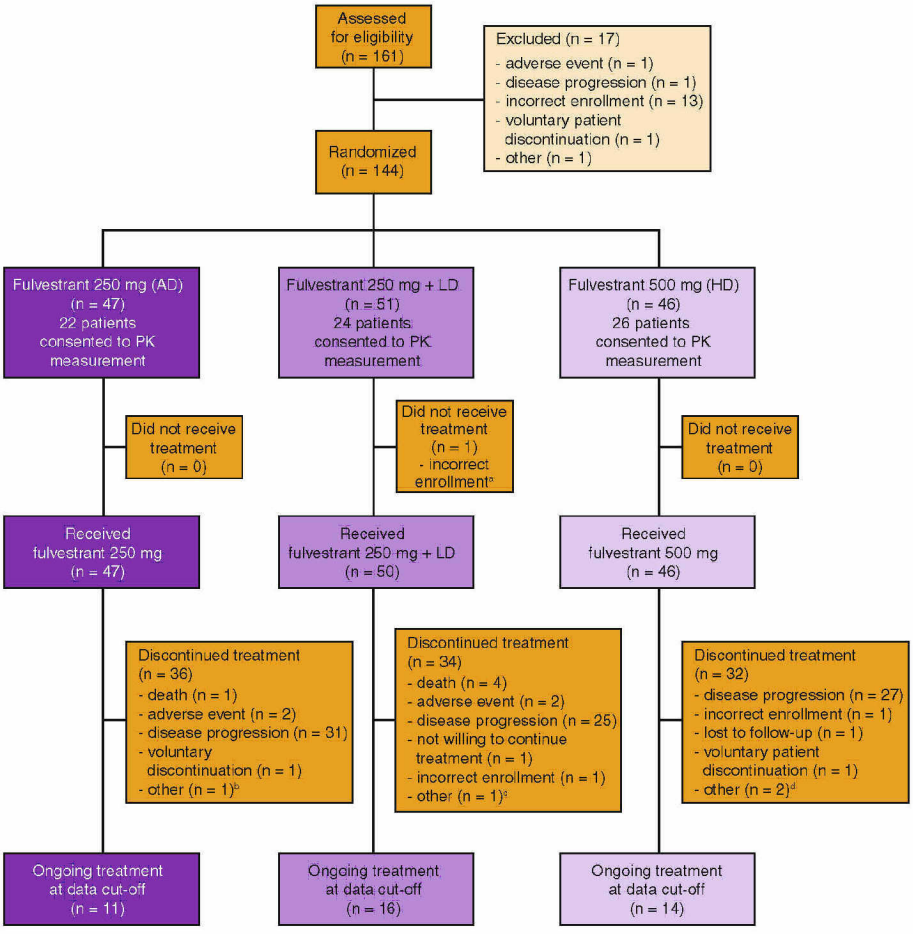

Fig. 1 Patient disposition during FINDER2 (CONSORT diagram)

[a]Failed inclusion criterion
[b]Disease progression
[c]Disease progression listed under 'Other' on the CRF
[d]Dosing error (n = 1); brain metastases (n = 1)
AD, approved dose; HD, high dose; LD, loading dose; PK, pharmacokinetic

Table 1 Baseline demographics and disease characteristics

	Fulvestrant regimen		
	AD ($n = 47$)	LD ($n = 51$)	HD ($n = 46$)
Median age, years (range)	63 (42–88)	69 (38–85)	67 (49–85)
Race Caucasian, *n* (%)	45 (95.7)	51 (100)	46 (100)
WHO performance status, *n* (%)[a]			
0	26 (55.3)	31 (60.8)	31 (67.4)
1	20 (42.6)	16 (31.4)	14 (30.4)
2	0	4 (7.8)	1 (2.2)
ER status, *n* (%)	47 (100)	51 (100)	46 (100)
PgR status, *n* (%)			
PgR+	30 (63.8)	32 (62.7)	32 (69.6)
PgR–	16 (34.0)	18 (35.3)	14 (30.4)
Unknown	1 (2.1)	1 (2.0)	0
HER2 status, *n* (%)			
Positive	2 (4.3)	1 (2.0)	3 (6.5)
Negative	37 (78.7)	37 (72.5)	32 (69.6)
Unknown	8 (17.0)	13 (25.5)	11 (23.9)
Disease stage, *n* (%)			
Locally advanced only	1 (2.1)	3 (5.9)	2 (4.3)
Metastatic	46 (97.9)	48 (94.1)	44 (95.7)
Visceral involvement, *n* (%)	34 (72.3)	41 (80.4)	37 (80.4)
Tumor histology, *n* (%)			
Infiltrating ductal carcinoma	36 (76.6)	39 (76.5)	33 (71.7)
Infiltrating lobular carcinoma	8 (17.0)	4 (7.8)	6 (13.0)
Other/missing	3 (6.4)	8 (15.7)	7 (15.2)
Tumor grade, *n* (%)			
1	7 (14.9)	8 (15.7)	5 (10.9)
2	15 (31.9)	22 (43.1)	23 (50.0)
3	16 (34.0)	11 (21.6)	10 (21.7)
Unavailable/unknown	9 (19.1)	10 (19.6)	8 (17.4)
Prior therapy, *n* (%)			
Radiotherapy	25 (53.2)	29 (56.9)	25 (54.3)
Chemotherapy	28 (59.6)	25 (49.0)	26 (56.5)
Endocrine therapy[b]			
Anastrozole	18 (38.3)	15 (29.4)	17 (37.0)
Tamoxifen	28 (59.6)	36 (70.6)	27 (58.7)
Exemestane	11 (23.4)	12 (23.5)	16 (34.8)
Relapse categories, *n* (%)			
During adjuvant endocrine therapy	24 (51.1)[c]	18 (35.3)[d]	15 (32.6)
Within 12 months after completion of adjuvant endocrine therapy	2 (4.3)	3 (5.9)	1 (2.2)[e]
>12 months after completion of adjuvant endocrine therapy	5 (10.6)	12 (23.5)[f]	9 (19.6)[g]
Progressed on an endocrine therapy given as first-line treatment for de novo advanced breast cancer	16 (34.0)	18 (35.3)	20 (43.5)
Other[h]	0	0	1 (2.2)

AD approved dose, *ER* estrogen receptor, *HD* high dose, *HER2* human epidermal growth factor receptor 2, *LD* loading dose, *PgR* progesterone receptor, *WHO* World Health Organization

[a] WHO performance status was missing for one patient in the AD and HD groups

[b] Use of more than one endocrine agent in the adjuvant setting was acceptable. Endocrine therapies with a total incidence ≥10% are shown

[c] Two patients failed inclusion criterion as they had <12-month gap between adjuvant tamoxifen therapy and starting aromatase inhibitor treatment for advanced disease

[d] One patient failed inclusion criterion: patient was third line

[e] One patient failed inclusion criterion: patient was first line

[f] One patient failed inclusion criterion: patient was third line

[g] One patient failed inclusion criterion: patient relapsed >12 months after completion of 5 years' adjuvant hormonal therapy, but did not receive treatment in the advanced setting

[h] Patient failed inclusion criteria

patients were Caucasian (98.6%) and median age across the groups was 67 (range 38–88) years (Table 1). All patients enrolled were ER+; approximately two-thirds of patients (65.3%) were progesterone receptor-positive as well as ER+. Despite all tumors being confirmed as ER+, some appeared to have the clinical behavior of a relatively

endocrine-resistant tumor, with many patients relapsing either during adjuvant endocrine therapy (39.6%) or while receiving first-line endocrine treatment for de novo advanced breast cancer (37.5%) (Table 1). Only 18.1% of all tumors showed a late recurrence (i.e., >12 months after completion of adjuvant endocrine treatment).

Efficacy

Comparison of data across the three treatment arms shows that fulvestrant AD, LD, and HD had similar efficacy (Table 2). Although ORR was numerically lower with the fulvestrant AD (8.5%) and LD (5.9%) regimens compared with HD (15.2%), the 95% confidence intervals (CIs) for all three treatment arms were overlapping. Similarly, for the CBRs observed with fulvestrant AD (31.9%), LD (47.1%), and HD (47.8%) the 95% CIs for all three treatment arms also overlapped (Table 2).

While the estimated median TTP was numerically shorter with fulvestrant AD (3.1 months; Fig. 2), compared with the LD and HD arms (6.1 and 6.0 months, respectively), the incidence of progression events was similar between groups (AD: 35; LD: 31, and HD: 34 events, respectively).

The low number of responders in all treatment arms prevented meaningful assessment of DoR.

Pharmacokinetics

In this study, a two-compartment model with first-order absorption and first-order elimination was fitted to the concentration–time data from the 72 patients who consented to PK measurements. Plots of the observed versus population-predicted fulvestrant concentrations demonstrated a reasonable overall fit of the model to the PK data (Fig. 3).

The mean apparent clearance of fulvestrant was 31.0 l/h; inter-individual variability (IIV) was 39%. The mean apparent volume of distribution at steady state was 56300 l (IIV 40%), which was similar to values determined previously with fulvestrant AD [7]. Residual variability was estimated at 22%.

In the fulvestrant AD arm, steady-state concentrations were approached during the third month of dosing (Table 3; Fig. 3). The inclusion of an additional dose of fulvestrant at day 14 in the LD and HD regimens led to the achievement of steady-state fulvestrant concentrations in the first month of dosing. A higher C_{min} for the LD regimen and a similar C_{min} for the HD regimen demonstrate this in the first versus the third month of dosing for both the LD and HD regimens (Table 3; Fig. 3).

At month 3, C_{min} and the AUC were similar for the AD and LD regimens, whereas these parameters were approximately doubled with the HD regimen. This indicates that the PK of fulvestrant is linear and predictable in this study (Table 3).

Safety

All three fulvestrant dose regimens were well tolerated, with no differences observed between the safety profiles. The incidence of AEs was generally similar across the three treatment regimens: 76.6, 72.0, and 69.6% in the AD, LD, and HD groups, respectively, and there was no evidence of a dose response for any of the AE categories.

Few patients experienced serious AEs (SAEs) with a non-fatal outcome (4, 9, and 4 patients in the AD, LD, and HD arms, respectively), with no clustering of event types. Of these, only pleural effusion and pulmonary embolism

Table 2 Summary of efficacy results for each treatment arm (intent-to-treat population)

	Fulvestrant regimen		
	AD ($n = 47$)	LD ($n = 51$)	HD ($n = 46$)
ORR, *n* (%) [95% CI]	4 (8.5) [2.4, 20.4]	3 (5.9) [1.2, 16.2]	7 (15.2) [6.3, 28.9]
CR, *n* (%)	0	0	0
PR, *n* (%)	4 (8.5)	3 (5.9)	7 (15.2)
SD ≥24 weeks, *n* (%)	11 (23.4)	21 (41.2)	15 (32.6)
CBR, *n* (%) [95% CI]	15 (31.9) [19.1, 47.1]	24 (47.1) [32.9, 61.5]	22 (47.8) [32.9, 63.1]
PD, *n* (%)	24 (51.1)	20 (39.2)	19 (41.3)
TTP[a]			
Events, *n* (%)	35 (74.5)	34 (66.7)	31 (67.4)
Median, months	3.1	6.1	6.0

AD approved dose, *CBR* clinical benefit rate, *CI* confidence interval, *CR* complete response, *HD* high dose, *LD* loading dose, *ORR* objective response rate, *PD* progressive disease, *PR* partial response, *SD* stable disease, *TTP* time to progression

[a] TTP was estimated using the Kaplan–Meier method

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.