

Three dose regimens of fulvestrant in postmenopausal Japanese women with advanced breast cancer: results from a double-blind, phase II comparative study (FINDER1)

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Background: FINDER1 compared efficacy, tolerability and pharmacokinetics (PK) of three fulvestrant dose regimens in postmenopausal Japanese women with estrogen receptor (ER)-positive locally advanced/metastatic breast cancer recurring or progressing after prior endocrine therapy.

Patients and methods: The primary end point of this randomised, multicentre, phase II study was objective response rate (ORR) and the secondary end points included time to progression (TTP), clinical benefit rate (CBR), PK profiles and tolerability. Postmenopausal women with ER-positive advanced breast cancer were randomised to 28-day cycles of fulvestrant approved dose (AD), loading dose (LD) or high dose (HD) until disease progression.

Results: Hundred and forty-three patients (median age 61 years) received fulvestrant AD ($n = 45$), LD ($n = 51$) or HD ($n = 47$). ORR was similar across dose regimens: 11.1%, 17.6% and 10.6% for AD, LD and HD, respectively, with overlapping confidence intervals. TTP and CBR were also similar between groups (median TTP: 6.0, 7.5 and 6.0 months, respectively; CBR: 42.2%, 54.9% and 46.8% for AD, LD and HD, respectively). C_{max} and area under the plasma concentration-time curve were dose proportional and PK steady state was reached earlier with LD and HD than with AD. All three doses were well tolerated, with a similar adverse-event profile and no emerging safety concerns.

Conclusion: Fulvestrant AD, LD and HD had similar efficacy and tolerability profiles in postmenopausal Japanese women with ER-positive advanced breast cancer.

Key words: advanced breast cancer, endocrine, Faslodex, fulvestrant, high dose, loading dose

introduction

Fulvestrant (FaslodexTM) is an estrogen receptor (ER) antagonist that is devoid of agonist activity [1]. The mechanism of action of fulvestrant differs from that of other endocrine therapies; on binding to the ER, fulvestrant induces a rapid degradation and loss of the ER and the progesterone receptor (PgR) [2–4]. Fulvestrant has demonstrated efficacy in several phase III clinical trials in postmenopausal women with advanced breast cancer [5–8]. Notably, the different mechanism of action of fulvestrant compared with other endocrine therapies affords a lack of cross-resistance with other

endocrine therapies, and, consequently, fulvestrant has demonstrated efficacy in patients with recurrent disease following prior tamoxifen [6, 8] and nonsteroidal aromatase inhibitor (AI) therapy [5].

Fulvestrant is currently licensed in Europe and the United States for the treatment of postmenopausal women with advanced breast cancer who have progressed or recurred after previous endocrine (antiestrogen) treatment [9]. The efficacy of fulvestrant at the approved dose (AD, 250 mg/month) is well established [7, 8], but there is evidence to indicate that the efficacy of fulvestrant could be further improved by increasing the dose [3, 6, 10]. It has been hypothesised that greater efficacy may be achieved by using a loading dose (LD) to achieve steady state more quickly or by using a high-dose (HD) fulvestrant regimen to achieve higher mean plasma fulvestrant levels,

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without affecting tolerability [11]. Two recent studies have confirmed the feasibility of this approach. A small, pilot study in Japanese women ($n = 20$) showed fulvestrant HD to have good clinical activity and a favourable tolerability profile in the treatment of advanced or recurrent breast cancer [12].

Furthermore, pharmacokinetic (PK) analysis demonstrated that fulvestrant HD achieved plasma levels approximately double those seen with fulvestrant AD. Pharmacodynamic evaluation in a neoadjuvant study comparing fulvestrant AD and HD regimens ($n = 211$) reported significantly greater Ki67 and ER down-regulation with fulvestrant HD than AD and that both doses were similarly well tolerated [13].

The FINDER1 (Faslodex INvestigation of Dose evaluation in Estrogen Receptor-positive advanced breast cancer) study evaluates the efficacy, tolerability and PK profile of three different fulvestrant dose regimens (AD, LD and HD) in postmenopausal Japanese women with ER-positive advanced breast cancer recurring or progressing after previous endocrine therapy.

patients and methods

FINDER1 (9238IL/0066; NCT00305448) is a randomised, double-blind, parallel-group, multicentre, phase II study conducted in Japan. The primary objective of the study was to evaluate the objective response rate (ORR) of patients treated with fulvestrant AD, LD or HD, and secondary end points included determination of time to progression (TTP), clinical benefit rate (CBR), PK profiles and tolerability.

patients

Eligible patients were postmenopausal women with locally advanced/metastatic breast cancer who had demonstrated a positive ER status of primary or metastatic tumour tissue ($\geq 10\%$ positive staining by immunohistochemistry by local laboratory testing). Patients were required to have relapsed during, or ≤ 12 months after completion of, adjuvant endocrine therapy; be progressing on an endocrine therapy which was started ≥ 12 months after prior adjuvant endocrine therapy or be progressing on an endocrine therapy administered for *de novo* advanced disease. In addition, patients had to have measurable disease as per modified RECIST.

All patients provided written informed consent and the study was carried out in accordance with the Helsinki Declaration and was consistent with International Conference on Harmonisation Good Clinical Practice. The study protocol was approved by the review boards of participating institutions.

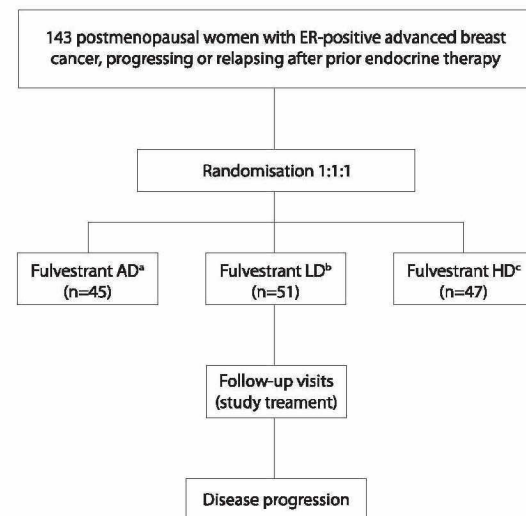
study treatment

Patients were randomised 1 : 1 : 1 to fulvestrant AD (250 mg fulvestrant on days 0 and 28 and every 28 days thereafter, with two placebo injections given on day 14), fulvestrant LD (after an initial dose of 500 mg at day 0 and 250 mg fulvestrant on day 14 and 28 and every 28 days thereafter) or fulvestrant HD (500 mg fulvestrant on days 0, 14 and 28 and every 28 days thereafter) (Figure 1). Treatment with fulvestrant was continued until disease progression or until any other discontinuation criterion was met.

study assessments

Efficacy was assessed by ORR, TTP and CBR (complete response, partial response or stable disease lasting ≥ 24 weeks, according to RECIST). All patients were followed up every 12 weeks for progression.

PK samples were collected from a cohort of 70 patients in total, with sample collection at baseline and just before injection on days 14, 28, 56 and



*AD (approved dose) = 250 mg (1 fulvestrant injection and 1 placebo injection) on Days 0, 28 (± 3) and every 28 (± 3) days thereafter, and 2 additional placebo injections on Day 14 (± 3).

*LD (loading dose) = after an initial dose of 500 mg at Day 0 (2 fulvestrant injections), 250 mg fulvestrant (1 fulvestrant injection and 1 placebo injection) on Days 14 (± 3), 28 (± 3) and every 28 (± 3) days thereafter.

*HD (high dose) = 500 mg fulvestrant (2 fulvestrant injections) on Days 0, 14 (± 3), 28 (± 3) and every 28 (± 3) days thereafter.
ER, oestrogen receptor.

Figure 1. FINDER1 study design.

84. Two additional PK samples were collected between days 5 and 10 and between days 33 and 38.

Tolerability was evaluated by assessment of adverse events (AEs) classified according to the National Cancer Institute—Common Toxicity Criteria for AEs (version 3.0) at baseline and at 4-weekly intervals thereafter. The primary analysis was carried out when all ongoing patients had been followed up for at least 24 weeks.

statistical analysis

As the aim of the study was selection of a dose regimen, sample size was calculated based on selection formulation [14], instead of hypothesis testing formulation. Overall, 43 patients per group were required for 90% probability that the best dose regimen by response rate be correctly selected [assuming that the smallest response rate was 19.2% (based on the result of AD in previous studies) and the difference in response rate between the best and next best dose regimen was 15%]. To allow for dropout, a total of 135 patients were to be recruited to this study (45 patients per group). The point estimate and the corresponding two-sided 95% confidence interval (CI) were calculated for ORR and CBR for each treatment group. Kaplan–Meier plots were produced for TTP for each treatment group and subgroup. Drug concentration–time data were analysed with NONMEM v5.0 using a nonlinear mixed-effects model approach, and the PK parameters [clearance (CL/F) and volume of distribution at steady state (V_{dss}/F), C_{max} , T_{max} , C_{min}], area under the plasma concentration–time curve from time 0 to the last measurable concentration ($AUC_{0-\tau}$) and $f_{1/2}$] were determined.

results

In total, 143 patients were recruited from 40 centres in Japan and randomised to receive fulvestrant AD ($n = 45$), fulvestrant LD ($n = 51$) or fulvestrant HD ($n = 47$). All randomised patients were included in the main analysis (full analysis set population), but one patient received no randomised treatment and was excluded from the safety population. Overall, 70 patients were

included in the PK analysis set (25, 21 and 24 patients in the AD, LD and HD treatment arms, respectively).

Baseline characteristics were generally well balanced across the treatment groups (Table 1). Median age was 61 years. All patients were ER positive and approximately two-thirds of patients (68.5%) were PgR positive as well as ER positive. The majority of patients (97.9%) had metastatic disease and more than half (56.6%) had visceral involvement. In total, 33.6% and 66.4% of patients had received prior radiotherapy and/or chemotherapy, respectively, as well as prior endocrine therapy. The majority of patients (72.8%) had progressed during adjuvant endocrine therapy (44.1%) or endocrine therapy for *de novo* metastatic disease (28.7%). Patients received fulvestrant therapy for a median of 197, 225 and 213 days in the AD, LD and HD groups, respectively.

primary end point

The ORRs with the different fulvestrant dose regimens were similar: 11.1% (95% CI 3.7–24.1), 17.6% (95% CI 8.4–30.9) and 10.6% (95% CI 3.5–23.1) for fulvestrant AD, LD and HD, respectively (Table 2). The ORR was numerically higher in the fulvestrant LD regimen, but the CIs of all three treatment arms overlapped. The limited numbers of responders in each of the predefined subgroups meant that further subgroup analyses for efficacy parameters were not useful.

secondary end points

Median TTP was similar across the dose regimens: 6.0, 7.5 and 6.0 months for fulvestrant AD, LD and HD, respectively, with a similar number of events observed between groups: 30, 31 and 31 events, respectively (Figure 2). CBRs were similar across the dose regimens: 42.2% (95% CI 27.7–57.8), 54.9% (95% CI 40.3–68.9) and 46.8% (95% CI 32.1–61.9) for fulvestrant AD, LD and HD, respectively (Table 2).

PK parameters

A two-compartment model, with first-order absorption and first-order elimination, was fitted to the fulvestrant concentration–time data. CL/F was estimated at a mean of 35.4 l/h and varied between individuals by ~31%, and the mean estimate of V_{dss}/F ($=V_{d1}/F + V_{d2}/F$) was 35300 l, with variation of V_{d1}/F among individuals by ~42%. Residual variability was proportional in nature [coefficient of variation (CV): 25%] and parameters were generally well estimated. The secondary parameters derived from the model are shown in Table 3. In the fulvestrant AD regimen, C_{min} , C_{max} and $AUC_{0-\tau}$ values were higher in month 3 compared with month 1, but the values for fulvestrant LD and HD were similar or decreased in month 3 compared with month 1. These data indicate that steady-state exposures were reached in the first month of dosing with the LD and HD regimens and this was the result of an additional dose of fulvestrant given around day 14. Mean $t_{1/2}$ was similar among the treatment regimens at ~29 days, indicating that 90% of steady-state exposure should be achieved in ~3 months with the AD regimen. The estimates of exposure at month 3 with the AD regimen were similar to that with the LD regimen and were close to half of that with HD, indicating linear PK. The secondary PK parameters obtained in this study were similar to those previously reported [15–17].

Table 1. Patient baseline demographics and disease characteristics

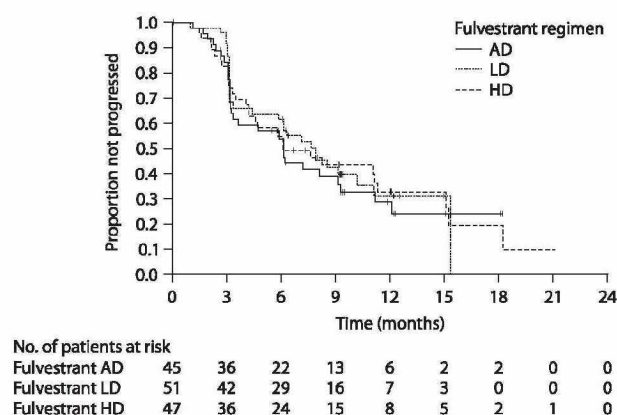
	Fulvestrant regimen		
	AD (n = 45)	LD (n = 51)	HD (n = 47)
Median age, years (range)	61 (50–77)	62 (43–86)	61 (45–83)
WHO performance status, n (%)			
0	39 (86.7)	44 (86.3)	40 (85.1)
1	6 (13.3)	6 (11.8)	7 (14.9)
2	0	1 (2.0)	0
HR status			
ER positive, PgR positive, n (%)	32 (71.7)	36 (70.6)	30 (63.8)
ER positive, PgR negative, n (%)	13 (28.9)	15 (29.4)	17 (36.2)
HER2 status, n (%)			
Positive	6 (13.3)	1 (2.0)	7 (14.9)
Negative	36 (80.0)	50 (90.8)	40 (85.1)
Unknown	3 (6.7)	0	0
Disease stage, n (%)			
Locally advanced only	1 (2.2)	2 (3.9)	0
Metastatic	44 (97.8)	49 (96.1)	47 (100.0)
Visceral involvement, n (%)	26 (57.8)	28 (54.9)	27 (57.4)
Tumour histology, n (%)			
Infiltrating ductal carcinoma	41 (91.1)	50 (98.0)	44 (93.6)
Infiltrating lobular carcinoma	1 (2.2)	1 (2.0)	2 (4.3)
Other	3 (6.7)	0	1 (2.1)
Tumour grade, n (%)			
1	6 (13.3)	5 (9.8)	3 (6.4)
2	20 (44.4)	19 (37.3)	18 (38.3)
3	7 (15.6)	12 (23.5)	13 (27.7)
Unevaluable/unknown	12 (26.7)	15 (29.4)	13 (27.7)
Prior therapy, n (%)			
Radiotherapy	15 (33.3)	12 (23.5)	21 (44.7)
Chemotherapy	25 (55.6)	37 (72.5)	33 (70.2)
Endocrine therapy ^a	45 (100)	51 (100)	47 (100)
Anastrozole	26 (57.8)	28 (54.9)	27 (57.4)
Tamoxifen	19 (42.2)	19 (37.3)	23 (48.9)
Exemestane	9 (20.0)	10 (19.6)	8 (17.0)
Time of relapse in relation to endocrine therapy			
During adjuvant therapy	18 (40.0)	17 (33.3)	28 (59.6)
0–12 months after completion of adjuvant therapy	5 (11.1)	2 (3.9)	0
>12 months after completion of adjuvant therapy	10 (22.2)	15 (29.4)	6 (12.8)
During therapy for <i>de novo</i> advanced disease	12 (26.7)	17 (33.3)	12 (25.5)
Other	0	0	1 (2.1)

^aUse of more than one endocrine agent in the adjuvant setting was acceptable. Endocrine therapies with $\geq 10\%$ incidence in total are given in the table. AD, approved dose; ER, estrogen receptor; HD, high dose; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LD, loading dose; PgR, progesterone receptor; WHO, World Health Organization.

Table 2. Summary of best objective response

	Fulvestrant regimen		
	AD (<i>n</i> = 45)	LD (<i>n</i> = 51)	HD (<i>n</i> = 47)
Complete response, <i>n</i> (%)	2 (4.4)	0	0
Partial response, <i>n</i> (%)	3 (6.7)	9 (17.6)	5 (10.6)
Stable disease ≥24 weeks, <i>n</i> (%)	14 (31.1)	19 (37.3)	17 (36.2)
Stable disease <24 weeks	9 (20.0)	5 (9.8)	10 (21.3)
Progression, <i>n</i> (%)	17 (37.8)	17 (33.3)	14 (29.8)
Not assessable, <i>n</i> (%)	0	1 (2.0)	1 (2.1)
Objective response rate, <i>n</i> (%) [95% CI]	5 (11.1) [3.7–24.1]	9 (17.6) [8.4–30.9]	5 (10.6) [3.5–23.1]
Clinical benefit rate, <i>n</i> (%) [95% CI]	19 (42.2) [27.7–57.8]	28 (54.9) [40.3–68.9]	22 (46.8) [32.1–61.9]

AD, approved dose; CI, confidence interval; HD, high dose; LD, loading dose.



AD, approved dose; HD, high dose; LD, loading dose.
Tick marks indicate censored observations.

Figure 2. Kaplan–Meier plot of time to progression.

tolerability

A total of 765 AEs were reported by 137 (96.5%) of the 142 patients, including 8 patients (5.6%) who experienced a serious adverse event (SAE). The incidence of AEs was similar among the three treatment arms. There were few SAEs and no clinically important differences in SAE profiles among the three treatment arms. The majority of AEs were of mild or moderate intensity, with only 16.2% of patients experiencing AEs ≥grade 3. AEs required treatment discontinuation in three patients overall (2.1%); one patient discontinued from each treatment group. There were no deaths attributable to AEs. AEs observed in ≥10% of patients were nasopharyngitis (33.8%), injection-site pain (27.5%), hot flushes (18.3%), nausea (18.3%), injection-site induration (17.6%), fatigue (14.8%), constipation (11.3%) and headache (10.6%) (Table 4). Notably, all injection-site AEs were ≤grade 2 intensity, with the majority grade 1, and there were no dose-dependent differences in frequency or intensity between the treatment arms. There were notable changes in neither haematology and clinical chemistry nor vital signs and electrocardiogram.

discussion

The phase II FINDER1 study evaluated the relative efficacy and tolerability of three different fulvestrant dose regimens in

Table 3. Secondary pharmacokinetic parameters for months 1 and 3

	Fulvestrant regimen		
	AD	LD	HD
Number of patients	25	21	24
Mean $t_{1/2}$, days (SD)	30.5 (3.4)	28.4 (2.1)	29.2 (2.3)
Month 1 (visit 4)			
Number of patients	25	20	24
Mean C_{max} , ng/ml (CV)	11.1 (35.9)	17.0 (29.6)	28.7 (27.0)
Median T_{max} , days (minimum–maximum)	4.5 (3.8–5.2)	3.5 (3.2–3.8)	3.9 (3.6–4.4)
Mean C_{min} , ng/ml (CV)	3.02 (16.4)	10.7 (22.2)	17.8 (19.2)
Mean AUC_{0-24} , ng h/ml (CV)	4370 (27.7)	9260 (29.4)	13000 (25.9)
Month 3 (visit 7)			
Number of patients	20	20	20
Mean C_{max} , ng/ml (CV)	15.5 (30.3)	14.1 (30.0)	29.4 (23.8)
Median T_{max} , days (minimum–maximum)	4.2 (3.7–4.6)	4.2 (3.9–4.4)	4.2 (3.9–4.5)
Mean C_{min} , ng/ml (CV)	5.39 (20.1)	5.87 (23.9)	11.4 (18.2)
Mean AUC_{0-24} , ng h/ml (CV)	6630 (24.7)	6600 (26.6)	13300 (20.6)

AD, approved dose; CV, coefficient of variation; HD, high dose; LD, loading dose, SD, standard deviation.

postmenopausal Japanese women with ER-positive advanced breast cancer. The study was initiated because previous clinical and biological studies had indicated that there was a dose–response to fulvestrant and that the efficacy of 250 mg might be improved by increasing the dose [3, 6, 10]. In a presurgical trial in which postmenopausal women received a single injection of fulvestrant, dose-dependent reductions in Ki67, ER and PgR were observed, with no evidence of a plateau effect up to the maximum dose tested (250 mg/month) [3]. Clinical evidence supporting further dose increases emerged from a combined interim analysis of two phase III studies (trials 0020 and 0021) comparing two doses of fulvestrant (125 and 250 mg/month)

Table 4. Most commonly reported adverse events ($\geq 5\%$ in total)

Adverse event, <i>n</i> (%)	Fulvestrant regimen		
	AD (<i>n</i> = 45)	LD (<i>n</i> = 51)	HD (<i>n</i> = 46)
Nasopharyngitis	17 (37.8)	15 (29.4)	16 (34.8)
Injection-site pain	14 (31.1)	11 (21.6)	14 (30.4)
Nausea	11 (24.4)	9 (17.6)	6 (13.0)
Hot flush	8 (17.8)	11 (21.6)	7 (15.2)
Injection-site induration	9 (20.0)	6 (11.8)	10 (21.7)
Fatigue	7 (15.6)	7 (13.7)	7 (15.2)
Constipation	4 (8.9)	7 (13.7)	5 (10.9)
Headache	3 (6.7)	8 (15.7)	4 (8.7)
Back pain	3 (6.7)	6 (11.8)	3 (6.5)
Arthralgia	2 (4.4)	7 (13.7)	2 (4.3)
Pyrexia	2 (4.4)	4 (7.8)	5 (10.9)
Injection-site pruritis	4 (8.9)	2 (3.9)	4 (8.7)
Stomatitis	2 (4.4)	3 (5.9)	5 (10.9)
Anorexia	2 (4.4)	4 (7.8)	3 (6.5)
Pruritis	2 (4.4)	3 (5.9)	4 (8.7)
Insomnia	4 (8.9)	3 (5.9)	1 (2.2)

AD, approved dose; HD, high dose; LD, loading dose.

with anastrozole (1 mg/day) in postmenopausal women with advanced breast cancer [6, 10]. This analysis demonstrated insufficient clinical activity with fulvestrant 125 mg/month compared with the 250 mg/month arm or the comparator, anastrozole, which prompted closure of this treatment arm.

In the current study, two fulvestrant dose regimen modifications were employed that differed from the approved fulvestrant regimen. The total doses administered in the first month were 500, 1000 and 1500 mg for AD, LD and HD, respectively.

Although the ORR and CBR were numerically higher for the fulvestrant LD compared with AD and HD regimen, the 95% CIs overlapped substantially among all three treatment regimens. Furthermore, the Kaplan–Meier plots were similar between the three treatment regimens, although the median TTP was numerically higher for the fulvestrant LD compared with AD and HD regimens. Some potential difference in efficacy may have been missed due to the relatively small size of the present dose selection phase II study and thus any definitive conclusions could not be drawn regarding the recommended fulvestrant dose regimen in this population. A far greater sample size would be required to achieve statistical significance for each of the study end points.

Phase III data were recently reported for fulvestrant LD in postmenopausal women with ER-positive advanced breast cancer progressing or recurring after nonsteroidal AI therapy [5]. In this setting, fulvestrant LD and exemestane were equally efficacious and well tolerated.

The phase II NEWEST (Neoadjuvant Endocrine Therapy for Women with Estrogen-Sensitive Tumors) study was the first study designed to evaluate fulvestrant HD and fulvestrant AD as neoadjuvant endocrine therapy in postmenopausal women with locally advanced breast cancer [13]. In NEWEST, fulvestrant HD reduced the mean Ki67 labelling index to

a significantly greater extent than AD at week 4, and this corresponded to a significantly greater reduction in ER expression at week 4 for HD versus AD. Furthermore, recent findings from the phase II FIRST (Fulvestrant fIRST-line Study comparing endocrine Treatments) study demonstrated that fulvestrant HD was at least as effective as anastrozole in terms of CBR and ORR and was associated with significantly longer TTP in the first-line advanced breast cancer setting [18]. Fulvestrant HD has also been further investigated in the advanced disease setting. The CONFIRM (COMparisoN of Fulvestrant In Recurrent or Metastatic breast cancer) study was a large, randomised, double-blind phase III study designed to elucidate fully any benefit of fulvestrant HD versus AD in postmenopausal women with metastatic disease. The primary study end point of TTP was significantly longer for fulvestrant HD compared with fulvestrant AD (6.5 versus 5.5 months; hazard ratio 0.80; 95% CI 0.68–0.94; $P = 0.006$), a difference that corresponds to a 20% reduction in the risk of progression. Numerical advantages were also observed in CBR (45.6% versus 39.6%), duration of clinical benefit (16.6 versus 13.9 months) and overall survival (25.1 versus 22.8 months) for patients treated with HD versus AD. Together with a favourable tolerability profile and no evidence of dose-related AEs, this equated to an improved benefit–risk profile for HD compared with AD [19].

The mean population clearance seen in this study (35.4 ± 4.9 l/h, CV 31%) was similar to that determined for Japanese patients in a phase I study (28.4 ± 5.4 l/h) [12] and for western patients in phase III studies (33.2 ± 1.1 l/h) [17], and the phase II NEWEST study (34.5 l/h, CV 30%) [15]. The estimate of V_{dss}/F (35300 l, CV 42% for V_{d1}/F) was also similar between this study and the phase II NEWEST study (34400 l, CV up to 72%). As expected, PK steady state was achieved earlier with fulvestrant HD and LD than with fulvestrant AD. Furthermore, the steady-state levels achieved were higher with fulvestrant HD than with fulvestrant AD and LD. The current results for fulvestrant LD are also consistent with the recently reported Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) PK data [16].

In line with the findings of other fulvestrant studies in the advanced and early breast cancer settings [5, 13, 18], all three fulvestrant dose regimens (AD, LD and HD) were well tolerated, with no emerging safety concerns, and no differences were observed between the regimens. As expected, the most frequently reported treatment-related AEs were injection-site reactions, but all injection-site AEs were of \leq grade 2 intensity, with the majority being grade 1. None of the AEs at the injection site led to discontinuation of study treatment.

A parallel study is being undertaken in Caucasian patients (FINDER2) and it is anticipated that evaluation of data from both these studies will help to determine any ethnic differences in the efficacy, tolerability and PK profiles of fulvestrant in ER-positive postmenopausal women with advanced breast cancer.

conclusion

While the current data alone do not allow determination of the optimum fulvestrant dose regimen, they confirm the clinical feasibility of the fulvestrant HD and LD regimens and add to

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