

Fulvestrant for the treatment of advanced breast cancer

Abstract

Introduction: The current issues with endocrine therapy for treatment of advanced breast cancer include balance of efficacy of therapy versus tolerability as well as hormone resistance. The efficacy of fulvestrant, a selective oestrogen receptor degrader (SERD), has been demonstrated in hormone receptor positive patients previously untreated or treated with hormonal therapy.

Areas covered: In this review we discuss the journey of fulvestrant licensing, its efficacy in combination with other endocrine therapies and the future role it may have within breast cancer treatment.

Expert Opinion:

Within phase III trials, fulvestrant has demonstrated equivalent or improved clinical efficacy when compared with established endocrine agents. In the recent decade, fulvestrant has achieved licensing as a second line agent in non-operative advanced breast cancer at initially 250mg, increasing to 500mg. Presently, fulvestrant is licensed globally as first line endocrine management for advanced breast cancer in post-menopausal women. Early combination trials of fulvestrant and cyclin dependent kinase 4/6 inhibitors have demonstrated good clinical efficacy with improved progression free survival when compared to fulvestrant alone.

Keywords: fulvestrant, advanced breast cancer, endocrine therapy, pure anti-oestrogen

1.0 Introduction

Breast cancer is the most common cancer in women worldwide. Two thirds of breast cancers are oestrogen receptor (ER) positive and the frequency of ER positive tumours is highest amongst older women [1,2]. In advanced breast cancer, maximising the quality of life (QOL) is an important goal of treatment [3,4]. Endocrine therapy is the recommended first line treatment of choice for ER positive advanced breast cancer, except for patients with life-threatening and/or rapidly progressing symptomatic disease due to extensive metastases [3-5]. One of the concerns with present endocrine agents are the adverse effects caused by oestrogen like effects throughout the body, excluding the breast tissue[6]. The novel endocrine agent fulvestrant, is a pure antioestrogen, which down-regulates the ER by inhibiting receptor dimerization and exerts no oestrogen agonistic effects [7]. In this review we will outline its use as both a monotherapy and in combination with other agents, in first and second line treatment of advanced breast cancer and discuss current licensing as well as future studies and uses of the drug.

1.1 Overview of the market

Within endocrine therapy for breast cancer in postmenopausal women, three key drug classes are present; aromatase inhibitors (AIs), selective oestrogen receptor modulators (SERMs) and selective oestrogen receptor degraders (SERDs). The first, AIs, exert their action via oestrogen deprivation, resulting in reduced tumour growth but also systemic side effects affecting QOL, including osteoporosis, joint pains and hot flushes [8]. The second drug class SERMs, are anti-oestrogens where the key prototype is tamoxifen. Tamoxifen binds to the ER, instigating conformational change in the receptor and halting tumour growth [9]. However, the oestrogen like nature of tamoxifen results in an increase in thromboembolic events and endometrial proliferation while offering some protective effect to bone mineral density [10]. Inclusive within the third class of drugs, SERDS, is fulvestrant. Fulvestrant has a unique method of action in that it is a highly specific agent which inhibits oestrogen receptors within the mammary gland and down regulates the ER via inhibition and degradation [11]. It exerts no oestrogen agonistic effects systematically therefore its side effect profile appears more favourable when compared with AIs and tamoxifen [11].

Although modern endocrine therapies are extremely effective, the majority of ER-positive patients will develop hormone resistance [12]. Hormone resistance presents in two forms; de novo (primary) and acquired (secondary) resistance [12]. De novo resistance occurs when patients do not respond to first line treatment with endocrine therapy, whereas, acquired resistance develops after an initial response to treatment has occurred [12]. This is often multifactorial in nature and includes cell survival pathways progressing independently of oestrogen [13]. Response to a new endocrine therapy after progression on another is a well recognized phenomenon [13]. Tumours within these patients remain oestrogen dependent but have become resistant to ER targeted therapy. Although no clear cause of this phenomenon is known, subsequent responses to endocrine therapies are often shorter and ER levels decline suggesting the development of an alternative escape pathway within tumours [13]. In the case of fulvestrant, one proposed possibility of resistance development is the over-expression of microRNAs mi-R221/222 [14]. This over expression seen within ER positive cells was shown to oppose the effects of oestradiol depletion or fulvestrant induced cell death, signifying hormone independent cell growth and resistance to fulvestrant. Cyclin dependent kinase 4/6 inhibitors are a class of drug that bypass hormone resistance by targeting cell proliferation directly and do not rely on oestrogen receptor status. Used in addition to endocrine therapy, CDK 4/6 inhibitors may prove to be the future for tackling hormone resistance [15]. Therefore, the three important issues challenging the optimal use of endocrine therapy in the setting of advanced breast cancer are improving efficacy, minimising additional side effects, and tackling hormone resistance.

2.0 Introduction to the drug

Fulvestrant (ICI182,780) is a steroidal 7 α - alkylamide analogue of oestradiol; it is a pure anti-oestrogen which exerts no partial agonist effects [7]. The clinical potential of fulvestrant was identified in the early 1990s where ICI182,780 demonstrated competitive inhibition of the ER within the rat uterus [7]. It was these preliminary findings that led to the selection of fulvestrant for further pre-clinical and clinical trials.

2.1 Pharmacodynamics:

Fulvestrant competitively inhibits the binding of oestradiol to the ER and once bound, defunctions activating functions 1 and 2 (AF1, AF2), reducing translocation of the receptor to the nucleus thereby leading to increased degradation of the ER [11]. This in turn inhibits cell growth and blocks cell division within the G1 phase of the cell cycle thereby giving fulvestrant its pure antioestrogen quality [7,16]. Once bound, the fulvestrant-ER complex itself is unstable and accelerated degradation of the ER protein occurs when compared with oestradiol or tamoxifen bound ER [17]. The combination of competitive ER inhibition and ER degradation illustrates how fulvestrant is an effective endocrine therapy in ER positive breast cancer.

2.2 Pharmacokinetics:

In order for effective oestrogen inhibition to be achieved, down regulation of the ER via dimerization, must be sustained over time. Similarly to many steroidal compounds, oral bioavailability of fulvestrant is poor as the drug is rapidly excreted due to rapid first pass metabolism in the liver[18]. Intravenous (IV) administration of fulvestrant demonstrates a steady state peak one hour post infusion however plasma concentrations decline rapidly within 30 minutes due to extensive and rapid plasma distribution [18]. Initial intramuscular (IM) administration studies showed that maximum plasma concentration (C_{max}) was achieved 12-24 hours post injection with what is now considered low doses of fulvestrant (2, 6, 18, and 36 mg) [18,19]. This is a slower absorption rate compared with IV administration. With an increase of fulvestrant to 250 mg IM, C_{max} was reached within a 2-19 day window. Following administration, plasma concentrations of fulvestrant declined slowly and plasma profiles were detectable over at least 28 days; a half-life of 40 days was demonstrated [19].

Conversely, other studies have shown that with 250 mg/month drug administration, steady state is reached within approximately 3-6months [20]. However, with administration of fulvestrant 500 mg on day 0, 250 mg on days 14 and 28 and 250 mg/month thereafter, a steady state was achieved within one month and maintained throughout the monthly regimen [21]. Following this, dosing was revised and loading regimens trialed. A second study demonstrated that a similar C_{max} level was achieved when a loading dose (LD) of 500mg was administered on days 0,14 and 28 of the first month compared with the C_{max} at month three, when once monthly dosing was

administered (C_{max} 25.1 LD vs 28 at month 3) [22]. This evidence has supported the use of higher and loading dose regimes of fulvestrant used within clinical trials.

3.0 Clinical efficacy

Fulvestrant has undergone three key milestones in its development thanks to pivotal trials. Initial approval as second line endocrine therapy at a dose of 250mg was gained following the results of two combined analysis studies which compared fulvestrant and anastrozole treatment in post menopausal women with advanced breast cancer who had previously undergone endocrine therapy; primary end point was time to progression (TTP) [23-25]. Following this, licensing at an increased dose of 500 mg was agreed, the basis of which was founded on the results of the CONFIRM trial (Comparison of Faslodex in Recurrent or Metastatic Breast Cancer) [26] whereby progression free survival (PFS) was assessed in postmenopausal women receiving either a 250mg or 500mg fulvestrant dosing regimen, who had previously received endocrine therapies. Subsequent to that, fulvestrant has achieved approval as first line endocrine therapy in advanced breast cancer throughout the world following results of the FALCON (Fulvestrant and Anastrozole Compared in Hormonal Therapy Naïve Advanced Breast Cancer) trial [27] whereby PFS was assessed in endocrine naïve postmenopausal women receiving either fulvestrant or anastrozole therapy. The results of these trials and importance of their findings will be discussed below.

3.1 Early trials

Early trials into fulvestrant compared its efficacy with that of tamoxifen, the gold standard endocrine treatment for advanced breast cancer at the time. One such pre-clinical trial [28] compared the effects of tamoxifen and fulvestrant on the growth of human MCF-7 tumours injected into mice. Fulvestrant suppressed tumour growth for twice as long, down regulated oestrogen-related genes more effectively and delayed tumourigenesis to a greater extent when compared with tamoxifen [28]. These early results were highly promising, albeit ultimately cell resistance to fulvestrant was demonstrated.

Following pre-clinical trials, the biological effects of fulvestrant and tamoxifen were compared in patients prior to tumour resection surgery [29]. This partially blind, randomised, multicentre study compared the effects of single doses of fulvestrant with tamoxifen or placebo on ER, progesterone receptor (PR) and Ki67 (proliferation

associated antigen labeling index) expression and apoptotic index levels within the breast tumours of previously untreated patients (stages T1-T3; ER positive or unknown). Patients were randomised and fulvestrant at various once only doses (50mg, 125mg or 250mg), oral tamoxifen 20mg or placebo were administered for 14 to 21 days prior to surgery. Results illustrated statistically significant reductions in ER expression at all doses of fulvestrant versus placebo and fulvestrant 250mg versus tamoxifen. Fulvestrant also demonstrated dose dependent ER down regulation (Table 1). PR values were significantly lower in fulvestrant doses versus tamoxifen and Ki67 values were significantly reduced when compared to placebo. Apoptotic index did not change. These findings support the pharmacodynamics qualities of fulvestrant seen in the pre-clinical settings and support the use of higher dose fulvestrant (250mg). The beneficial effects of using second line fulvestrant following tamoxifen resistance have been illustrated in a small cohort of patients in a phase II trial [30]. All patients were post-menopausal and received 250mg once monthly IM fulvestrant (four patients received a single 100mg dose then subsequent 250mg doses). Multiple dosing demonstrated drug accumulation (increase of Cmax from 10.5ng/ml-1 month 1 to 12.6ng/ml-1 in the sixth month) but no increase in side effect profile was observed. Endometrial proliferation ceased but no regression of endometrial tissue was seen. Luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels rose but plateaued within three months and no significant change in sex hormone-binding globulin (SHBG) and prolactin levels was observed, suggesting that fulvestrant has no effect on the pituitary-hypothalamic axis. The study showed that thirteen (69%) patients responded to fulvestrant for a median duration of 25 months, supporting the use of fulvestrant in tamoxifen resistant breast cancers. Following these findings, fulvestrant usage in tamoxifen resistant breast cancer was compared with alternative endocrine treatment, in order to assess the relative value of the drug. One small, non-randomised study [31] supported the use of fulvestrant as a second line treatment compared with megestrol acetate, as the duration of remission following treatment was significantly longer; 26 months versus 14months respectively (P=0.04). Before phase III and larger trials involving fulvestrant treatment commenced, the effects of subsequent endocrine therapies after fulvestrant use was assessed. A phase II study [32] examined fulvestrant use as first to ninth line treatment in postmenopausal women with advanced breast cancer whereby the effects of further endocrine treatment after disease progression were assessed. Within a cohort of

predominantly ER positive women (5 had unknown ER status), fulvestrant 250mg IM was administered to 54 patients, of which 83% received fulvestrant as first or second line therapy. Clinical benefit following fulvestrant treatment was observed in half of patients (52%) and median TTP was 9.3 months (range 1-75 months) for all subjects. Subsequent to disease progression, all patients received one of the following endocrine therapies; anastrozole, tamoxifen, megestrol acetate, exemestane, ethinyloestradiol or withdrawal therapy. With subsequent therapy, partial response or stable disease was demonstrated with tamoxifen, anastrozole and megestrol acetate administration in patients who had derived clinical benefit from fulvestrant. Within the cohort of 26 patients who had not derived clinical benefit, only 3 patients demonstrated a response with subsequent therapy. These results demonstrated that further endocrine response can be induced after fulvestrant failure.

3.2 Dosing

Early clinical trials demonstrated the effectiveness of fulvestrant in both laboratory and clinical settings. The next step was to establish the clinically effective dose. The biological effects of differing fulvestrant doses were assessed in a neoadjuvant study, NEWEST (Neoadjuvant Endocrine Therapy for Women with Estrogen-Sensitive Tumors) [33]. This compared 500mg vs 250mg fulvestrant dosing in postmenopausal women prior to surgery and assessed biomarker changes. A greater reduction in Ki67 and ER expression with 500mg dosing over 250mg fulvestrant dosing was seen (-78.8% vs -47.4% $p < 0.0001$ for Ki67 expression respectively, -25% vs -13.5% $p < 0.0002$ respectively) illustrating the superior biological activity fulvestrant 500mg has over the lower dose. These results concur with the phase I/II trial [29] which also demonstrated a dose-dependent reduction in ER expression with varying fulvestrant doses.

Clinical benefit of varying doses of fulvestrant was examined with a Japanese study (FINDER1: Faslodex INvestigation of Dose evaluation in Estrogen Receptor-positive advanced breast cancer 1) which compared the efficacy of three fulvestrant dosing regimens in 143 postmenopausal Japanese women with ER- positive breast cancer [34]. These regimens consisted of the approved (at the time) dose (AD) of 250mg/month, a loading dose (LD) of 500mg day 0, 250mg days 14 and 28 and once monthly thereafter, and a high dose (HD) of 500mg day 0,14,28 and monthly thereafter. The primary endpoint of objective response rates (ORR) was similar

across all regimens (11.1%, 17.6% and 10.6% for AD, LD and HD respectively) as were median TTP (AD 6.0 months, LD 7.5 months and HD 6.0 months) and clinical benefit rate (CBR) (AD42.2%, LD54.9% and HD46.8%). No significant difference in side effects was demonstrated between the three groups. Although these findings did not determine the optimum fulvestrant regimen, they confirmed the feasibility of the LD and HD regimens in clinical practice. A similar study, namely FINDER2, evaluated the efficacy of multiple fulvestrant dosing levels in 144 Western postmenopausal women [35]. Dosing regimens were identical to that of FINDER1, and no significant difference was seen between dosing groups in the outcomes analyzed. ORRs within the cohorts were 8.5% AD, 5.9% in LD and 15.2% in HD. Median TTP was 3.1 months, 6.0 months and 6.1 months respectively for AD, HD and LD and CBRs were 31.9%, 47.1% and 47.8% respectively. Although no significant benefit with higher dosing of fulvestrant was seen in CBRs, ORRs or TTP within these two trials, the results are not unfavorable to the higher dosing. The pivotal trial prompting a change in license from 250mg to 500mg fulvestrant dosing was the CONFIRM trial [26]. Fulvestrant 500mg was administered IM on days 0, 14, 28 and monthly thereafter versus fulvestrant 250mg once monthly. A statically significant increase in PFS, the primary endpoint, was demonstrated with higher dose fulvestrant 500mg when compared with the lower dose of 250mg (Table 2). This was observed when 85.8% of 250mg treatment group developed progression events, compared to 82% of those receiving 500mg. The median PFS was significantly longer within the 500mg than 250mg cohort (hazard ratio (HR)= 0.8, P=.006) and median overall survival (OS) was longer within the 500mg group versus 250mg; 25.1months and 22.8 months respectively, although no significant difference was demonstrated (HR=0.84, P=0.91). The final OS analysis data, published 3 years subsequent to the original study publication, demonstrated a median OS of 26.4month vs 22.3months within the fulvestrant 500mg and 250mg respectively (HR 0.81, nominal p=0.02) [36]. The higher dosage of fulvestrant was well tolerated, no dose-dependent adverse events occurred and no significant difference in regards to QOL was reported between the two cohorts (Table 3). The significant improvement in PFS demonstrated in this trial, led the way to 500mg licensing of fulvestrant.

3.3 Second and third line therapy

During the progression of fulvestrant use to phase III trials, there was a parallel

development within endocrine agent licensing. AIs moved from second to first line treatment for advanced inoperable breast cancer in post-menopausal women [3,4,37]. Therefore fulvestrant was no longer compared with tamoxifen but with AIs. Here we review some of the key comparison trials.

Two phase III randomised, multi-centre, parallel-group trials were conducted in Europe/rest of the world (Trial 0020) [23] and North America (Trial 0021) [25] which compared fulvestrant 250mg/month with the standard second line endocrine therapy at the time, anastrozole, in postmenopausal women with advanced breast cancer [23-25]. In this planned prospective combined analysis of the two trials, 80% of the patient cohorts were ER positive and the majority of patients who received endocrine treatment first line, received tamoxifen. Trial 0020 was open label whereas Trial 0021 was double blind and patients received either placebo tablets or injections as indicated. Median TTP was the primary end point of the study with results of 5.5 months versus 4.1 months between fulvestrant and anastrozole respectively (HR 0.95, $p=0.48$). CBR was demonstrated in 43.5% of fulvestrant cohort compared with 40.9% of anastrozole treated patients but duration of clinical benefit CB was similar in both groups (11.8 months vs 11.2 months respectively). Adverse effects were similar in both study arms (Table 3). In OS analysis data, gathered from extended follow up at 27months, 319 (74.5%) of the fulvestrant cohort and 322 (76.1%) of the anastrozole cohort had died [38]. 10-20% of the patients treated in the study were alive >5years. Although no superiority of fulvestrant over anastrozole was demonstrated within this trial, results show fulvestrant to have equal efficacy and clinical benefit to anastrozole. This combined analysis trial was proven to be pivotal in the licensing of fulvestrant 250mg as second line endocrine treatment.

A second trial that compared AIs with fulvestrant was the EFECT trial (Evaluation of Faslodex versus Exemestane Clinical Trial) [39]. The efficacy of exemestane in women with advanced ER positive breast cancer, who had previous exposure to at endocrine therapy, was compared with that of fulvestrant; LD regime applied. All patients were postmenopausal women whose disease had relapsed on either adjuvant treatment or during first-line treatment with an AI. The primary endpoint of median TTP was 3.7months in both groups. The CBR was similar between fulvestrant and exemestane (32.3% vs 31.5% respectively). Duration of clinical benefit was 9.3 months and 8.3 months between fulvestrant and exemestane cohorts respectively, which is encouraging, as all patients had previously relapsed with non-steroidal AI

treatment. By 6 months however, 70% of participants had undergone disease progression which may have been due to previous endocrine exposure triggering hormone resistance or due to inadequate treatment with fulvestrant and exemestane. Both the EFACT trial [39] and combined analysis of the two second line trials [23-25] demonstrated equivalent efficacy of fulvestrant to AIs when used second line. The latter led to the licensing of fulvestrant 250mg as second line endocrine therapy.

3.4 First line licensing

Once second line licensing of fulvestrant was achieved, a push to first line was instigated and comparative trials were performed.

The phase II FIRST (Fulvestrant First-Line Study Comparing Endocrine Treatments) study, compared anastrozole with high dose fulvestrant as first line endocrine treatment in breast cancer [40]. The high dose regime of 500mg day 0,14,28 and monthly thereafter was administered to patients (100 per arm), the majority of whom had no previous exposure to endocrine therapy. The primary end point was CBR which was shown to be similar and not significant between cohorts (72.5% fulvestrant and 67% anastrozole). A similar ORR (36% fulvestrant and 35.5% anastrozole) was also seen. In regards to median TTP, anastrozole demonstrated a median duration of 12.5 months but the median TTP was not reached on initial data analysis (time of 21 months given). Further follow up analysis of FIRST, performed when 79.5% of participants had discontinued treatment, identified a significant difference in median TTP of 23.4 months versus 13.1 months in fulvestrant and anastrozole treated cohorts respectively (HR 0.66, $p=0.01$) [41]. Additionally on extended follow up, OS analysis was performed. As this was not a primary endpoint initially, several limitations of OS assessment were present, including reduced patient participation. Despite this, the OS results strongly suggested that fulvestrant improves OS compared with anastrozole; 61.8% (n=63) of fulvestrant and 71.8% (n=74) of anastrozole group had died (HR=0.7, $p=0.04$) [42]. Both cohorts at initial data analysis and follow up assessments demonstrated good drug tolerability.

In light of the promising results of the FIRST study, the phase III study FALCON was initiated [27]. Unlike the previous study, all patients were endocrine therapy naïve. Study findings demonstrated significantly longer PFS in the fulvestrant treatment cohort versus anastrozole (16.6 months versus 13.8 months respectively, HR 0.797, $p=0.0486$). ORR was similar within the two groups (fulvestrant 46% versus

anastrozole 45%) but median duration of response (DOR) was longer in fulvestrant (20.0 months) than anastrozole (13.2 months) although not significantly different. Subgroup analysis indicated that the benefit in terms of PFS and fulvestrant over anastrozole, was more markedly seen amongst patients with non-visceral disease when compared to those with visceral disease. Serious adverse events were reported in 13% of both cohorts and key adverse events are demonstrated in table 3. The findings in the FALCON study have led to emerging approvals for fulvestrant being licensed as first line endocrine therapy in all major territories including the US FDA, Europe and Japan [62,63].

3.5 Maximal endocrine treatment

Comparison trials demonstrate that fulvestrant has superior efficacy to anastrozole treatment (FALCON) [27]. There is however some pre-clinical evidence which suggests that ‘maximal’ endocrine therapy, whereby there is ER inhibition on a background of oestrogen deprivation, may provide better clinical efficacy than single endocrine treatment alone [43,44]. Hence trials into combination therapy of AIs and fulvestrant were undertaken.

The FACT trial (Fulvestrant and Anastrozole Combination Therapy) [45], compared fulvestrant 250mg loading dose regimen in combination with anastrozole in post-menopausal or pre-menopausal women receiving a gonadotropin-releasing hormone agonist in ER positive breast cancer. Adjuvant antioestrogen therapy had been given to two thirds (348) of participants prior to the trial. Results showed a median TTP of 10.8 months in the combination arm and 10.2 months with anastrozole alone.

Duration of CBR was 18.5 months in combination versus 18.1 months with anastrozole alone and median OS was 37.8 months in combination versus 38.2 months with anastrozole alone group. No clinical advantage was illustrated with the combination group over anastrozole monotherapy however no decrease in efficacy was observed either.

A second fulvestrant combination trial is the SoFEA trial (Study of Faslodex with or without concomitant Arimidex vs Exemestane following progression on non-steroidal Aromatase inhibitors) [46]. Three treatment arms were present within this study; fulvestrant 250 mg + anastrozole 1mg, fulvestrant 250 mg + placebo and oral exemestane 25mg. Median PFS demonstrated no significant difference between all three groups; fulvestrant plus anastrozole 4.4 months, fulvestrant plus placebo 4.8

months and exemestane 3.4 months and median OS was also similar; fulvestrant plus anastrozole 20.2 months, fulvestrant plus placebo 19.4 months and exemestane 21.6 months. Additionally, no significant difference in treatment efficacy (CBR) was demonstrated between the three groups. These results suggest administration of endocrine treatment following non-steroidal AIs resistance has very little efficacy and clinical benefit for patients.

Conversely, when combination treatment was used in endocrine naïve patients as demonstrated in the SWOG 0226 trial, clinical benefit was seen [47]. Fulvestrant, in combination with anastrozole, was administered to patients, of which 60% were anti-oestrogen treatment naïve. Results of the primary endpoint, PFS, demonstrated a difference, although not significant, between tamoxifen naïve and previously treated patients: tamoxifen naïve patients, anastrozole versus the combination group demonstrated a median PFS of 12.6 months versus 17 months respectively (HR=0.74, p=0.006). In tamoxifen treated women, median PFS was 14.1 months versus 13.5 months respectively (HR=0.89, p=0.37). The superiority of combination therapy over monotherapy, in regards to PFS, was seen to improve with time; rates at 1 year 57% versus 56% respectively but at 3 years rates of 25% versus 16%

Additionally, within the SWOG 0226 trial, pharmacokinetic analysis of possible drug interactions within the combined treatment arm was performed [48]. The concentration of anastrozole within the differing cohorts was assessed four times prior to patients receiving their next treatment dose (at 2,4,6 and 8 months). Lower concentrations of anastrozole were seen when combination therapy with fulvestrant was administered, proving to be significant (p<0.001). The mechanism behind these results is not yet known and verification of the effect of the combined treatment efficacy is still required however, these results may indicate why expected efficacy with combined endocrine treatments was not seen in some studies, namely FACT and SoFEA trials.

Table 4 illustrates the hazard ratios for either TTP or PFS for each trial and the percentage of patients previously undergoing endocrine therapy. SWOG0226 has the largest cohort of endocrine naïve patients and demonstrates a statistically improved TTP/PFS over the other trials. This demonstrates that the chance of inducing clinical benefit with fulvestrant increases with earlier exposure to fulvestrant, supporting its use as a first line therapy.

3.6 Hormone resistance and CDK 4/6 inhibitors

CDK4/6 inhibitors are a relatively new class of cancer treatments that address the dysregulation aspect of tumour cell growth. Inhibitors target proteins controlling mitochondrial function, cell growth, adhesion and motility [49]. In vitro studies have demonstrated that activation genes, required for oestrogen independent cell growth, undergo activation by CDK4, therefore inhibition of this protein can halt cell proliferation even in oestrogen resistant breast cancer [50]. Palbociclib is one such CDK 4/6 inhibitor which induces G1 arrest in the cell cycle and therapeutic doses have demonstrated elimination of the proliferative marker Ki-67 and down regulation of the E2F activation gene [15]. The use of CDK 4/6 inhibitors in addition to endocrine therapy therefore has the therapeutic potential to either delay hormone resistance or bypass the effect of it altogether.

Phase II and III trials that administer CDK4/6 inhibitors in conjunction with AIs, have demonstrated promising results with significantly increased PFS when treatment was used in combination [51-53]. The PALOMA1 and 2 (Palbociclib – Ongoing Trials in the Management of Breast Cancer) trials led to full approval of palbociclib in combination with any AI. This was secondary to the results of the trial demonstrating improved PFS when palbociclib was used in combination with letrozole, although no significant improvement in OS was seen (37.5 months versus 34.5 months with palbociclib in combination with letrozole and letrozole alone respectively; $p=0.28$) [52,54,55]. The results of first and second line studies using fulvestrant and CDK 4/6 inhibitors in combination, have been promising thus far. The PALOMA-3 trial assessed the use of palbociclib and fulvestrant compared to fulvestrant alone in advanced breast cancer in patients who had received prior endocrine treatment [56]. Results between the combination and fulvestrant alone groups demonstrated a significant primary end point of median PFS to be 9.5 months versus 4.6 months respectively (HR=0.46, $p < 0.0001$). Neutropenia was the most common grade 3 or 4 adverse event to occur, predominantly in the palbociclib group (81%) compared to the control group (3%) along with anaemia (3% versus 2%) and leucopenia (28% versus 1%). This study ended prematurely as its primary endpoint was met early and significantly improved PFS was demonstrated when palbociclib was used in combination with fulvestrant. This trial led to the approval of palbociclib and fulvestrant use in combination in receptor positive or metastatic breast cancer following disease progression with prior endocrine therapy.

MONARCH 2 (A study of abemaciclib combined with fulvestrant in women with hormone receptor positive HER2 negative breast cancer) is a second study which has trialed a CKD4/6 inhibitor, in this case abemaciclib, with fulvestrant [57]. The majority of patients had prior endocrine therapy exposure and the results of this patient cohort demonstrate combination treatment of abemaciclib plus fulvestrant significantly extended PFS when compared to fulvestrant treatment alone (16.4 months versus 9.3 months respectively, HR=0.553, P<0.001). Early results of the small subset of endocrine naïve patients who received the above treatment demonstrated a comparable increase in PFS with combination therapy over single therapy although the significance of these results is not yet available as median PFS has yet to be reached [58]. Again neutropenia was a common adverse event (46% versus 4% combination versus fulvestrant respectively). It was the results from this study that led to FDA approval of combination fulvestrant and abemaciclib use in the treatment of receptor positive breast cancer following disease progression from previous endocrine therapy use.

Following results from the MONALEESA-2 (Study of Efficacy and Safety of LEE011 in Postmenopausal Women with Advanced Breast Cancer) phase 3 trial [53], the CDK4/6 inhibitor ribociclib in combination with an AI, has recently received approval from the US FDA for the initial treatment of postmenopausal women with HR+ advanced or metastatic breast cancer. Ribociclib combined with letrozole was compared to placebo plus letrozole and the duration of PFS at 24months was longer in the ribociclib group, compared to placebo (54.7% versus 35.9%).

These phase III trials [53, 56,57] demonstrate a significantly improved PFS when fulvestrant is used in combination with CDK 4/6 inhibitors as a second line therapy and initial results of first line combination use are promising [58].

4.0 Post-marketing surveillance

4.1 Safety and tolerability of fulvestrant

In addition to clinical efficacy, tolerability is an essential part of drug administration. The novel treatment mechanism of fulvestrant means that side effects are limited. The lack of oestrogen agonist activity causes no increase in thromboembolic events and endometrial proliferation when compared to tamoxifen [59].

Fulvestrant, unlike AIs, lacks oestrogen deprivation, and similar or lower rates of musculoskeletal side effects have been demonstrated [23-27]. Furthermore, no known

detrimental effects on bone mineral density have been demonstrated [60]. One potential concern with fulvestrant however, is its parenteral nature of administration. In a review of the key trials, injection site pain is an uncommon adverse effect and no patients have withdrawn from studies secondary to drug administration [23-27]. Additionally, no significant increase in injection site discomfort was observed between different fulvestrant doses and no change in QOL was reported between dosing groups [26]. Conversely, regular injections ensure frequent contact with health care professionals and allows for close monitoring of drug compliance. Administration can also occur even when oral intake is restricted or not possible, for example in patients with bowel obstruction [61].

4.2 Regulatory affairs

Fulvestrant 500mg is currently licensed for hormone receptor positive postmenopausal advanced breast cancer following prior anti-oestrogen therapy, worldwide. Approvals for first line use have recently been obtained in Europe, Russia, Japan and the USA [62,63]. Approval has also been gained for palbociclib use in combination with fulvestrant in advanced hormone-receptor positive, HER2-negative tumours after disease progression on endocrine therapy, following results of the PALOMA-3 trial [64] and combination use of fulvestrant and abemaciclib has been approved by US FDA as second line therapy, following the results of the MONARCH-2 study [65].

5.0 Conclusion

Fulvestrant demonstrates good efficacy in phase III trials when used both as monotherapy and in combination with targeted or biological therapies for the treatment of advanced breast cancer. Optimum dosing of fulvestrant has been established with 500mg administration on day 0, 14 and 28 followed by monthly injections thereafter. Comparison trials have demonstrated equal if not superior efficacy of fulvestrant when compare with AIs. Maximal endocrine therapy using a combination of fulvestrant (250mg + loading dose) and AI has not been shown to be superior to single therapy except in the case of SWOG 0226 trial where a significant proportion of patients recruited were endocrine therapy naïve. Early trials assessing fulvestrant and CDK4/6 inhibitors are promising. Thus far, an improvement in clinical efficacy has been demonstrated when the two therapies are used in combination

compared to monotherapy. Ongoing trials will help define the precise role of combination therapies in the treatment of advanced breast cancer.

5.1 Expert commentary and five-year view

The recent approval of global first line fulvestrant use is a breakthrough in licensing. Many comparison and combination trials remain ongoing including those looking at long term adverse effects of fulvestrant [66]. In particular, the early trials into fulvestrant use in combination with CDK 4/6 inhibitors are proving promising. This combination of treatment may help to delay the development of hormone resistance and subsequently increase survival rates. To investigate this further, there are a multitude of active studies; PARSIFAL trial (Phase II Trial to Evaluate the Efficacy and Safety of Palbociclib in Combination With Fulvestrant or Letrozole) [67] is comparing palbociclib and fulvestrant with palbociclib and letrozole as first line treatment in advanced breast cancer. The FLIPPER study (compare the efficacy and tolerability of Fulvestrant 500mg with Placebo and fulvestrant 500mg in combination with Palbociclib as first line treatment for postmenopausal women with hormone Receptor positive metastatic breast cancer) [68] is similar to that of the PALOMA-3 trial, and is comparing fulvestrant 500 mg and palbociclib with fulvestrant and placebo in patients previously exposed to endocrine treatment. MONALEESA-3 (study of ribociclib in combination with fulvestrant for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer) [69] is comparing the use of other CDK4/6 inhibitors with fulvestrant versus fulvestrant alone. The primary end point of these three trials will be PFS at one year. The results will help determine the precise role of combination CKD 4/6 inhibitor therapy in advanced breast cancer.

An aspect of treatment not thoroughly addressed as yet, is the use of fulvestrant within pre-menopausal women. Fulvestrant has been studied little in pre-menopausal patients although pre-menopausal patients within PALOMA 3 and MONARCH-2 studies did not exhibit any concerns regarding efficacy or tolerability [56,57].

Although not inclusive of fulvestrant, the ongoing MONALEESA-7 trial administered tamoxifen or an AI with ribociclib and ovarian suppression to pre or peri-menopausal women [70]. The primary end point, PFS, was significantly improved with treatment compared to placebo. The final results of this study will help to inform on future endocrine therapies for pre-menopausal women. In regards to fulvestrant use, one

study saw favorable biological effects when a single fulvestrant 750mg dose was given to premenopausal women prior to surgery [71]. A significant decrease in ER and Ki67 expression within tumour cells was seen when compared to tamoxifen administration, illustrating that fulvestrant is effective at reducing the effects of oestrogen within pre-menopausal women. Additionally, the FLAG (Fulvestrant (F)/Goserelin (G) vs Anastrozole (A)/G vs G for premenopausal women) trial, is currently comparing the efficacy of fulvestrant versus anastrozole within premenopausal women [72]. Outcomes such as TTP, along with toxicity are being assessed. Evidence from this and future studies involving pre-menopausal women, will provide verification of fulvestrant efficacy within this patient cohort and lead the way to future fulvestrant licensing.

Although first line licensing of fulvestrant has been achieved globally, ongoing trials will help personalize the optimal use of endocrine therapy, alone or in combination with a biological agent, in the treatment of advanced breast cancer.

Given the wide use of adjuvant endocrine therapy, the currently available trial results on fulvestrant with or without a biological agent, especially those in the first line (hormone therapy naïve) setting, may not provide the evidence base for routine clinical practice but the results of the ongoing trials discussed may do just that. The future use of optimal endocrine therapy will become more complex but should demonstrate improved survival rates. The choice of endocrine therapy remains to be determined by efficacy, toxicity, cost effectiveness and disease burden.

Key comments

- Fulvestrant is a pure anti-oestrogen that down regulates ER expression through receptor dimerization and reduces cell turnover. It exerts no agonist effects and is well tolerated with minimal systemic side effects.
- Fulvestrant 500mg is licensed globally for first line use in hormone receptor positive post-menopausal advanced breast cancer
- Approval has been granted for palbociclib and abemaciclib (cyclin dependent kinase 4/6 inhibitors) use in combination with fulvestrant or an aromatase inhibitor in advanced hormone-receptor positive, HER2-negative tumours

- Ongoing research into fulvestrant use in premenopausal women will help establish the drug's efficacy within this patient cohort and may lead to treatment approval.
- The potential use of maximal endocrine therapy (fulvestrant and anastrozole) should be investigated in the adjuvant setting
- Given the wide use of adjuvant endocrine therapy, and the currently available trial results on fulvestrant with or without a biological agent, the future use of optimal endocrine therapy will become more complex. Efficacy, toxicity, cost effectiveness and disease burden should be taken into account.

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