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REVIEW ARTICLE **CME**

Expanding Treatment Arsenal for Oestrogen Receptor–Positive Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer

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ABSTRACT

Hormonal therapy is an established treatment for oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer. It is the preferred treatment due to its high efficacy and good tolerability, provided there is no immediately life-threatening visceral involvement. Aromatase inhibitors (AI) have been the standard first-line therapy for postmenopausal patients because of its superiority to older generation hormone therapies such as tamoxifen and megestrol acetate. Fulvestrant, a selective ER down regulator, has been evaluated in different dosages and combinations with other agents. Recent data suggest a greater benefit when it is used early in the disease course. A better understanding of resistance to endocrine therapy has been achieved over the past decades and new drugs have been developed to tackle alternative signalling pathways. Among them, mammalian target of rapamycin (mTOR) and cyclin-dependent kinase (CDK) 4/6 inhibitors have achieved great success in improving treatment outcome. Everolimus, an mTOR inhibitor, in combination with exemestane is effective for patients whose disease has progressed on a non-steroidal AI. CDK 4/6 inhibitors including palbociclib, ribociclib and abemaciclib have shown unique clinical efficacy and are in different phases of drug development. Their emergence has redefined the treatment strategy in both the first- and second-line settings. Today, the treatment paradigm is moving away from AI monotherapy towards hormone-targeted therapy. Research is now focused on the optimal drug combination and sequencing as well as a personalised treatment approach.

Key Words: *Breast neoplasms; Receptor, ErbB-2; Treatment outcome*

中文摘要

雌激素受體陽性人類表皮生長因子受體2陰性轉移性乳腺癌的擴大療法

施俊健

激素療法是雌激素受體（ER）陽性人類表皮生長因子受體2（HER2）陰性轉移性乳腺癌的既定治療方法。因為它具有高效和良好耐受性，在沒有立即危及生命的內臟病灶時是優選的治療方法。芳香

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環酶抑製劑（AI）是停經後患者的標準一線療法，其治療效果較老一代激素療法如他莫昔芬和醋酸甲地孕酮優勝。有研究將氟維司群（一種選擇性ER下調調節劑）以不同劑量和與其他藥物組合進行評估。近來數據也表明在病程早期使用會有更佳效果。過去不少研究也對內分泌治療抗拒作出更深入的瞭解，並開發新藥作為信號傳導途徑的替代方案。其中，哺乳動物雷帕黴素靶蛋白（mTOR）和週期蛋白依賴性激酶（CDK）4/6抑製劑在改善治療效果方面取得了巨大成功。依維莫司是一種mTOR抑製劑，與依西美坦聯合使用對非甾體AI疾病進展的患者有效。包括帕博西尼、瑞博西尼和玻瑪西尼在內的CDK 4/6抑製劑已顯示獨特的臨床功效，且處於藥物開發的不同階段。他們的出現為一線和二線治療策略重新定義。今天，治療範式正從AI單一療法轉向激素靶向療法。目前的研究重點是最佳藥物組合和測序以及個性化治療方法。

INTRODUCTION

Oestrogen receptor (ER)–positive, human epidermal growth factor receptor 2 (HER2)–negative breast cancer accounts for about 70% of all breast cancers and is the most common type of breast cancer for both early and metastatic diseases. For over a century, hormone therapy has been the cornerstone of treatment for endocrine-responsive breast cancer.[1] Despite effective adjuvant treatment with hormone therapy, with or without chemotherapy, many patients still have relapse and metastases. Endocrine therapy is often initially successful in the treatment of metastatic breast cancer but resistance inevitably develops. Over the past two decades, advances in basic research have enabled a better understanding of the mechanisms of resistance and identification of alternative cellular signalling pathways. New therapeutic agents have been developed with very encouraging results from clinical trials. These have led to significant improvements in treatment outcome and the treatment paradigm is evolving continuously. This article summarises the current treatment concepts and options for patients with ER-positive HER2-negative advanced breast cancer.

TREATMENT APPROACH

The goals of treatment for metastatic disease are to prolong survival and maintain quality of life. Hormone therapy is the preferred option for ER-positive HER2-negative metastatic breast cancer because of its high efficacy and mild toxicity. Delaying chemotherapy in this situation becomes a clear advantage. International guidelines consistently recommend the use of hormone therapy as the upfront treatment, even in the presence of visceral metastases. Sequential lines of hormone therapy should be considered except in cases of rapid disease progression with organ dysfunction.[2-5] Postmenopausal patients have a wider range of more effective agents available to them, but ovarian ablation or suppression should be considered for premenopausal patients.

Historical literature demonstrates that neither survival nor quality of life is improved by treating patients with initial chemotherapy compared with hormone therapy although a higher tumour response rate could probably be achieved by chemotherapy.[6] Chemotherapy is thus preferred only in situations where a fast response is necessary. "Visceral crisis" has been used to describe a clinical condition where there is organ dysfunction due to cancer involvement as assessed by signs and symptoms and laboratory studies. It implies an immediately life-threatening condition due to visceral compromise and chemotherapy is indicated because of its more rapid effect.

Chemotherapy or endocrine therapy in combination with other agents should also be considered when there is concern about endocrine resistance. Attempts have been made to define hormone sensitivity. In the international consensus guideline for Advanced Breast Cancer (ABC 2), primary endocrine resistance is defined as relapse during the first 2 years of adjuvant endocrine therapy, or progressive disease within the first 6 months of first-line endocrine therapy for metastatic breast cancer.[3] Secondary or acquired endocrine resistance is defined as relapse while on adjuvant endocrine therapy but after the first 2 years, relapse within 12 months of completing adjuvant endocrine therapy, or progressive disease ≥6 months after initiating endocrine therapy for metastatic breast cancer. It is worth noting that endocrine resistance is a continuum and these definitions are useful mainly for clinical trials and not necessarily for routine clinical practice. Clinical judgement and consideration of other factors including tumour extent, disease tempo, response to previous treatment, performance status,

co-morbidities, and patient preference are important in decision making.

TAMOXIFEN, MEGESTROL ACETATE, AND OESTROGEN

Tamoxifen is a selective ER modulator with mixed agonistic and antagonistic effects on ER, depending on the target tissue. It was initially developed as an anti-fertility agent in Great Britain and its use for disseminated breast cancer was first reported by Cole et al[7] at Christ Hospital in 1971. Tamoxifen has been compared with other older-generation hormone therapies such as diethylstilboestrol, ethinyloestradiol, and progestins for advanced breast cancer.[8-10] Similar rates of response and overall survival were observed, but tamoxifen was associated with a much more favourable toxicity profile. Today, tamoxifen at doses of 20 to 40 mg daily is still commonly used in the setting of metastatic breast cancer.

Megestrol acetate (MA) is a semisynthetic progestin with physiologic effects similar to natural progesterone. It has a long-standing history in the treatment of metastatic breast cancer and has demonstrated similar efficacy to tamoxifen.[11,12] However, MA at the standard dose of 160 mg daily is associated with side-effects such as weight gain and thromboembolism. With the advent of newer hormone agents including aromatase inhibitors (AIs), which have been shown to be superior to MA in terms of time to progression (TTP) and survival, MA has fallen out of favour.[13,14] However, its efficacy and safety have been demonstrated in hormone-responsive disease progressing on a non-steroidal AI. MA therefore remains a reasonable option particularly when novel agents are not readily available or are limited by cost constraints.[15]

Oestrogen stimulates the progression of ER-positive breast cancer in normal circumstances. Paradoxically, oestrogen might suppress breast cancer growth particularly after long-term oestrogen depletion by mechanisms that are still not fully understood. Recent phase II studies suggested the potential benefit of low-dose oestradiol (2-6 mg daily) after failure of an AI with enhanced tolerability over higher-dose oestradiol. The observation of re-sensitisation to AI after an extended period of oestradiol therapy by re-treatment with an AI at oestradiol progression is interesting and warrants further exploration.[16,17]

AROMATASE INHIBITORS

About 90% of the total body oestrogen in postmenopausal women is synthesised by aromatisation of androstenedione and testosterone to estrone and oestradiol, respectively, by the aromatase enzyme that can be detected in and around breast tumours and is expressed in the ovaries and peripheral adipose tissues. Inhibition of aromatase by AIs can result in a low oestrogen environment and lead to antitumor effects. Aminoglutethimide was one of the first-generation AIs to achieve a tumour response comparable with tamoxifen but was associated with significant side-effects including inhibition of cortisol production, lethargy, and dermatitis.[18] Second-generation and third-generation AIs have since been developed.

Third-generation AIs including anastrozole, letrozole, and exemestane have improved clinical efficacy and tolerability. They were first assessed as a second-line therapy and demonstrated superiority to MA.[13,14] Based on these positive results, they were then evaluated in the first-line setting versus tamoxifen (Table 1).[19-27] Overall, AIs demonstrated superior efficacy: the objective response rates were modestly improved from 17% to 33% for tamoxifen to 21% to 46% for AIs and the TTP or progression-free survival (PFS) was extended from 5.6 to 8.3 months for tamoxifen to 8.2 to 11.1 months for AIs. These data established the role of AIs as the first-line treatment of ER-positive metastatic breast cancer in postmenopausal women. It is noteworthy that these trials were conducted in an early era with less stringent patient selection and those with unknown ER status were included. This may explain the less favourable treatment outcomes compared with more contemporary series.

AI can be divided into two classes, steroidal and non-steroidal, based on their structure and mechanism of action. Non-steroidal AIs, letrozole and anastrozole, bind non-covalently and reversibly to the active site of the aromatase enzyme. For the steroidal AI, exemestane, binding to the active site is covalent and irreversible. The clinical relevance of such differences is unclear. One Japanese phase 3 trial that compared exemestane with anastrozole in the first-line setting among 298 patients showed no statistically significant difference in the response rates or TTP.[25] Another Spanish phase 2 study that compared these two drugs also showed similar clinical activity.[26] Comparison of the two non-steroidal AIs, letrozole and anastrozole, has been reported by a phase IIIb / IV trial in 713 patients with progressive disease on first-line anti-oestrogen or who were clinically resistant to adjuvant tamoxifen. The TTP was 5.7 months in both arms but the response rate was higher in the letrozole group (19.1% vs. 12.3%; $p = 0.013$).[27]

Table 1. Aromatase inhibitors in first- and second-line treatment of hormone receptor–positive metastatic breast cancer.

Trial	Phase	Treatment	No. of patients	Unknown ER status	Prior adjuvant hormonal therapy	ORR (%)	CBR (%)	TTP / PFS (months)	OS (months)
First-line AI vs. tamoxifen									
Nabholtz et al[19,20]	III	Anastrozole	171	11	21	21	59	11.1	39.2
		Tamoxifen	182	11	18	17	46 (p = 0.0098)	5.6 (p = 0.005)	40.1
Bonneterre et al[21]	III	Anastrozole	340	54	12	33	56	8.2	NR
		Tamoxifen	328	56	11	33 (p = 0.787)	56	8.3 (p = 0.941)	NR
Mouridsen et al[22,23]	III	Letrozole	453	34	19	30	49	9.4	34
		Tamoxifen	454	33	18	20 (p = 0.0006)	38 (p = 0.001)	6.0 (p = 0.0001)	30 (p = 0.53)
Paridaens et al[24]	II / III	Exemestane	182	8	21	46	NR	9.9	37.2
		Tamoxifen	189	7	21	31 (p = 0.005)	NR	5.8 (p = 0.121)	43.3 (p = 0.821)
First-line SAI vs. NSAI									
Iwata et al[25]	III	Exemestane	149	0	17	44	75	13.8	Not reached
		Anastrozole	149	0	17	39	77	11.1	60.1
Llombart-Cussac et al[26]	II	Exemestane	51	0	51	36	60	6.1	19.9
		Anastrozole	52	4	50	46	68	12.1 (p = 0.558)	48.3 (p = 0.296)
Second-line (after anti-oestrogen) NSAI vs. NSAI									
Rose et al[27]	IIIb / IV	Letrozole	356	51	NR	19	27	5.7	22.0
		Anastrozole	357	53	NR	12 (p = 0.013)	23 (p = 0.216)	5.7 (p = 0.92)	20.3 (p = 0.624)

Abbreviations: AI = aromatase inhibitor; CBR = clinical benefit rate; ER = oestrogen receptor; NR = not reported; NSAI = non-steroidal aromatase inhibitor; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SAI = steroidal aromatase inhibitor; TTP = time to progression.

In the second-line setting after progressive disease on an initial AI, clinical activity has been observed with use of a steroidal AI after failure to initial non-steroidal AI or vice versa.[28,29] Table 1 summarises the clinical trials investigating the efficacy of AI in metastatic breast cancer. Additional trials using AI as control arms can be found in Tables 2 to 4.

FULVESTRANT

Fulvestrant is a selective ER downregulator that binds, blocks, and causes irreversible degradation of ER with consequent inhibition of subsequent downstream oestrogen signalling. It has a potent ER antagonistic property with no known agonist effects. Multiple randomised controlled trials have been conducted since the 1990s with fulvestrant to evaluate its efficacy in the treatment of advanced breast cancer, on its own or in combination with an aromatase inhibitor. Some of these early trials showed inconsistent results due to heterogenous study design and dosage of fulvestrant. Recent data have revealed supportive evidence for fulvestrant as one of the standard options for patients with metastatic breast cancer.

Second-line Setting

Two similar randomised phase III studies, Trial 0020 conducted in Europe, Australia and South Africa and Trial 0021 in North America, evaluated fulvestrant 250 mg/month versus anastrozole in postmenopausal women with locally advanced or metastatic breast cancer whose disease had progressed during adjuvant endocrine therapy or first-line endocrine therapy for advanced disease.[30,31] The majority of patients had prior exposure to tamoxifen. Both studies disappointingly showed no significant difference in the clinical activity of fulvestrant and anastrozole. In a combined analysis of these two trials, similar median TTP (5.5 months vs. 4.1 months; p = 0.48) and objective response rates (19.2% vs. 16.5%; p = 0.31) were observed for fulvestrant and anastrozole, respectively. Joint disorders were less frequent in the fulvestrant group.[32] The action of fulvestrant after failure to an initial non-steroidal AI has also been studied. The Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) compared fulvestrant (fulvestrant 500 mg on day 0, 250 mg on days 14, 28 and 250 mg monthly thereafter) with exemestane in 693 postmenopausal patients with advanced hormone

Table 2. Fulvestrant for hormone receptor-positive metastatic breast cancer.

Trial	Phase	Treatment	No. of patients	Visceral metastases	ORR (%)	CBR (%)	TTP / PFS (months)	OS (months)
First-line								
Trial 0025[37]	III	Fulvestrant 250 mg	313	34	32	54	6.8	36.9
		Tamoxifen	274	34	34	62	8.3	38.7
					(p = 0.45)		(p = 0.088)	HR = 1.29 (p = 0.04)
FIRST[38-40]	II	Fulvestrant 500 mg	102	47	36	73	23.4	54.1
		Anastrozole	103	56	36	67	13.1	48.4
					(p = 0.947)	(p = 0.386)	HR = 0.66 (p = 0.01)	HR = 0.70 (p = 0.04)
FALCON[41]	III	Fulvestrant 500 mg	230	59	46	78	16.6	NR
		Anastrozole	232	51	45	74	13.8	NR
					(p = 0.729)	(p = 0.3045)	HR = 0.797 (p = 0.0486)	
SWOG[43]	III	Fulvestrant 250 mg + anastrozole	349	52	27	73	15.0	47.7
		Anastrozole	345	48	22	70	13.5	41.3
					(p = 0.26)	(p = 0.39)	HR = 0.80 (p = 0.007)	HR = 0.81 (p = 0.05)
FACT[44]	III	Fulvestrant 250 mg + anastrozole	258	52	32	55	10.8	37.8
		Anastrozole	256	48	34	55	10.2	38.2
					(p = 0.76)	(p = 0.99)	(p = 0.91)	(p = 1.00)
Second-line								
Trial 0020[30]	III	Fulvestrant 250 mg	222	47	21	45	5.5	NR
		Anastrozole	229	51	16	45	5.1	NR
					(p = 0.20)	(p = 0.85)	(p = 0.84)	
Trial 0021[31]	III	Fulvestrant 250 mg	206	53	18	42	5.4	NR
		Anastrozole	194	54	18	36	3.4	NR
					(p = 0.96)	(p = 0.26)	(p = 0.43)	
EFECT[33]	III	Fulvestrant 250 mg	351	56	7	32	3.7	NR
		Exemestane	342	58	7	32	3.7	NR
					(p = 0.736)	(p = 0.853)	(p = 0.6531)	
CONFIRM[35,36]	III	Fulvestrant 500 mg	362	66	9	46	6.5	26.4
		Fulvestrant 250 mg	374	62	10	40	5.5	22.3
					(p = 0.795)	(p = 0.100)	(p = 0.006)	(p = 0.02)
SoFEA[42]	III	Fulvestrant 250 mg + anastrozole	243	57	7	34	4.4	20.2
		Fulvestrant 250 mg	231	62	7	32	4.8	19.4
		Exemestane	249	58	4	27	3.4	21.6
					NS	NS	NS	NS

Abbreviations: CBR = clinical benefit rate; HR = hazard ratio; NR = not reported; NS = not statistically significant; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; TTP = time to progression.

responsive breast cancer who had progressive disease after treatment with a non-steroidal AI. Median TTP was the same for both the fulvestrant and exemestane groups (3.7 months), and the overall response rates (7.4% vs. 6.7%; p = 0.736) as well as clinical benefit rates (32.2% vs. 31.5%; p = 0.853) were similar for fulvestrant and exemestane, respectively.[33] Fulvestrant at such a dosage seemed not so impressive compared with existing standards of care.

Early clinical data suggested a dose-response effect for fulvestrant and trials then evaluated its use at a higher dose.[34] The phase III COmparisoN of Faslodex In Recurrent or Metastatic breast cancer (CONFIRM) trial compared fulvestrant 500 mg (500 mg on day 0, then 500 mg on days 14 and 28 and monthly thereafter) or 250 mg monthly in 736 patients with hormone receptor–positive metastatic breast cancer who had progressed on prior endocrine therapy. Fulvestrant 500 mg was associated with significantly longer PFS than fulvestrant 250 mg (6.5 vs. 5.5 months, respectively; p = 0.006). Objective response and clinical benefit rates were similar. Importantly, fulvestrant 500 mg was well tolerated with no dose-dependent adverse events and quality of life

Table 3. Hormone-targeted therapy for ER-positive HER2-negative metastatic breast cancer in a first-line setting.

Trial	Phase	Treatment	No. of patients	Visceral metastases (%)	No. of disease sites ≥ 3 (%)	Disease-free interval (%)*		ORR (%)	CBR (%)	PFS (months)
						Newly metastatic disease (de novo)	>12 months			
HORIZON[48]	III	Temsirolimus + letrozole	556	NR	NR	NR	NR	27	NR	8.9
		Letrozole	556	NR	NR	NR	NR	27	NR	9.0 (p = 0.25)
PALOMA-1[57]	II	Palbociclib + letrozole	84	44	NR	52	30	43	87	20.2
		Letrozole	81	53	NR	46	37	33	70	10.2 HR = 0.49 (p = 0.0004)
PALOMA-2[58]	III	Palbociclib + letrozole	444	48	43	38	40	42	85	24.8
		Letrozole	222	50	47	37	42	35	70	14.5 HR = 0.58 (p < 0.001)
MONALEESA-2[59]	III	Ribociclib + letrozole	334	59	34	34	65	41	80	Not reached
		Letrozole	334	59	34	34	63	28	73	14.7 HR = 0.56 ($p = 3.29 \times 10^{-6}$)

Abbreviations: CBR = clinical benefit rate; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; NR = not reported; ORR = objective response rate; PFS = progression-free survival.
* Disease-free interval refers to the time from diagnosis of primary breast cancer to first relapse in patients who received adjuvant therapy.

was similar for both arms.[35] In the final overall survival analysis, fulvestrant 500 mg demonstrated a longer median overall survival compared with fulvestrant 250 mg (26.4 vs. 22.3 months, respectively; p = 0.02).[36] As a result, fulvestrant 500 mg is a viable treatment option for some patients following failure of treatment with prior endocrine therapy.

First-line Setting

Pushing fulvestrant to the first-line setting in the management of advanced breast cancer had a complicated start, again because of the low-dose regimen as in other early studies. In Trial 0025 that compared fulvestrant 250 mg monthly with tamoxifen, there was no statistically significant difference in median TTP (6.8 vs. 8.3 months, respectively; p = 0.088). Objective response rates were also similar in both treatment groups. In the overall population, between-group differences in efficacy end-points favoured tamoxifen although statistical non-inferiority of fulvestrant was not demonstrated.[37]

The Fulvestrant First-Line Study Comparing Endocrine Treatments (FIRST) trial was a phase II trial to compare fulvestrant 500 mg (500 mg/month plus 500 mg on day 14 of month 1) with anastrozole as first-line treatment for postmenopausal patients with advanced hormone-sensitive breast cancer. Response rates were comparable in the treatment arms while a remarkable improvement in TTP, a secondary end point, was observed for fulvestrant versus anastrozole (23.4 vs. 13.1 months, respectively; p = 0.01).[38-40] The FALCON (Fulvestrant and AnastrozoLe Compared in hormonal therapy-Naïve advanced breast cancer) trial was a phase III randomised multicentre trial to confirm the efficacy of fulvestrant 500 mg compared with an AI in patients with advanced breast cancer and no prior endocrine therapy. The median PFS was significantly longer in the fulvestrant group (16.6 vs. 13.8 months; p = 0.0486). In the subgroup analysis, an even greater impact on PFS was observed in patients without visceral metastases (22.3 vs. 13.8 months; hazard ratio [HR] = 0.59, 95% confidence interval [CI] = 0.42-0.84). On the contrary, for patients with visceral disease, fulvestrant was not so effective in prolonging the PFS (13.8 vs. 15.9 months for fulvestrant and anastrozole, respectively; HR = 0.99, 95% CI = 0.74-1.33)[41] It provides strong data to

Table 4. Hormone-targeted therapy for ER-positive HER2-negative metastatic breast cancer in a second-line setting.

Trial	Phase	Treatment	No. of patients	Visceral metastases	No. of disease sites ≥ 3	Disease-free interval* >24 months (%)	Previous sensitivity to endocrine therapy (%)†	ORR (%)	CBR (%)	PFS (months)
TAMRAD[49]	II	Everolimus + tamoxifen	54	57	NR	NR	50	14	61	8.6
		Tamoxifen	57	49	NR	NR	51	13	42 (p = 0.045)	4.5 HR = 0.54 (p = 0.002)
BOLERO-2[50-52]	III	Everolimus + exemestane	485	56	36	56	84	12.6	51.3	7.8
		Exemestane	239	56	37	54	84	1.7 (p < 0.0001)	26.4 (p < 0.0001)	3.2 HR = 0.45 (p < 0.0001)
PALOMA-3[55,56]	III	Palbociclib + fulvestrant	347	59	39	79	79	19	67	9.5
		Fulvestrant	174	60	36	77	78	9 (p = 0.0019)	40 (p < 0.0001)	4.6 HR = 0.46 (p < 0.0001)
MONARCH 1 (after chemotherapy)[60]	II	Abemaciclib	132	90	51	NR	NR	19.7	42.4	6.0

Abbreviations: CBR = clinical benefit rate; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; HR = hazard ratio; NR = not reported; ORR = objective response rate; PFS = progression-free survival.

* Disease-free interval refers to the time from diagnosis of primary breast cancer to first relapse in patients who received adjuvant therapy.

† Sensitivity to prior endocrine therapy: at least 24 months of endocrine therapy before recurrence in the adjuvant setting or a response or stabilisation for at least 24 weeks of endocrine therapy for advanced disease.

support the use of fulvestrant monotherapy as one of the preferred options in the first-line treatment of ER-positive advanced breast cancer, especially for those without visceral metastases.

Combination with an Aromatase Inhibitor

Preclinical studies have described marked beneficial effect of a combination of fulvestrant and an AI. The Study of Faslodex with or without concomitant Arimidex vs Exemestane following progression on non-steroidal Aromatase inhibitors (SoFEA) trial compared fulvestrant 250 mg plus anastrozole or placebo with exemestane monotherapy in patients with relapsed disease or who had progressed with locally advanced or metastatic disease on a non-steroidal AI. Results were disappointing as no statistically significant differences in outcome were found: the median PFS was 4.4, 4.8 and 3.4 months for the fulvestrant plus anastrozole, fulvestrant and exemestane groups, respectively.[42]

In the first-line setting, this strategy has been tested in two phase III randomised trials with intriguing findings. In the Southwest Oncology Group (SWOG) Cooperative Group S0226 trial, 694 postmenopausal women with previously untreated metastatic disease were randomly assigned to receive either anastrozole or anastrozole plus fulvestrant (fulvestrant 500 mg on day 1 and 250 mg on days 14 and 28 and monthly thereafter). The combination therapy was shown to improve the median PFS (15.0 vs. 13.5 months; p = 0.007) and increase overall survival by more than 6 months, despite the fact that 41% of patients crossed over to fulvestrant after progression.[43] In contrast, the Fulvestrant and Anastrozole Combination Therapy (FACT) trial with an identical study design compared anastrozole with or without fulvestrant and demonstrated no sign of improvement in treatment outcome by the combination approach.[44] These contradictory findings have led to much scepticism about the benefit of combining fulvestrant with an AI as first-line therapy. One possible reason for the discordant results is that a higher percentage of patients had received prior hormone therapy in the FACT trial (almost 70% in FACT vs. 40% in SWOG) and in the SWOG study, almost 40% of the patients presented with *de novo* metastatic disease. In some way, these findings may be consistent with what we have learnt from previous studies: the effect of

fulvestrant may be greatest for treatment-naïve patients as in the FIRST and FALCON studies, and in studies of a second-line setting where the effect of fulvestrant was not so dramatic if patients had previous exposure to hormone therapy. An on-going phase III neoadjuvant trial testing the use of fulvestrant 500 mg in combination with anastrozole may provide further insight into the role of this combination regimen.[45] Table 2 summarises the randomised trials of fulvestrant in ER-positive metastatic breast cancer.

MECHANISMS OF ENDOCRINE RESISTANCE

Metastatic breast cancer resembles a Darwinian evolutionary system and can develop clones that are resistant to hormone therapy by several molecular mechanisms. Mutations in ER, including certain *ESR1* mutations, are constitutively active in the absence of oestrogen and more difficult to suppress with conventional endocrine treatment such as AI.[46] The upregulation of alternative oncogenic signalling pathways has also been identified as a contributing factor in the development of endocrine resistance, including the insulin-like growth factor, fibroblast growth factor, hepatocyte growth factor and phosphatidylinositol 3-kinase (PI3K), AKT, and mammalian target of rapamycin (mTOR) signalling pathways.[47] Amplification or overexpression of genes that encode oncogenic proteins and transcription factors, thus promoting cancer cell proliferation, invasiveness and metastasis, is another important mechanism that underlies treatment resistance. The identification of such genetic aberrations has led to the clinical development of new targeted therapies for metastatic breast cancer.

MAMMALIAN TARGET OF RAPAMYCIN INHIBITORS

Activation of the PI3K pathway confers endocrine resistance by ligand-independent ER activation through mTOR, a major component of the PI3K machinery. In a randomised phase III trial (HORIZON), the efficacy of temsirolimus, an mTOR inhibitor, was evaluated as a first-line therapy in combination with letrozole versus letrozole alone in 1112 patients with AI-naïve, hormone receptor–positive advanced breast cancer. HER2 was positive or unknown in 59% and 53% of the patients in the temsirolimus plus letrozole and letrozole groups, respectively. Despite appealing preclinical evidence, no improvement in PFS was observed by the addition of temsirolimus to letrozole in this study (HR = 0.90, 95% CI = 0.76-1.07; p = 0.25).[48] Several hypotheses have been suggested to explain this absence of benefit, including a suggestion that the dose and schedule of temsirolimus was suboptimal.

The use of mTOR inhibitors in the second-line setting after initial exposure to an AI has been a great success. In the phase II TAMRAD (Tamoxifen Plus Everolimus) trial, 111 postmenopausal patients with hormone receptor–positive, HER2-negative, AI-resistant metastatic breast cancer were randomly assigned to tamoxifen plus everolimus 10 mg daily or tamoxifen alone. The median TTP significantly increased from 4.5 months with tamoxifen alone to 8.6 months with tamoxifen plus everolimus. One interesting exploratory subgroup analysis showed that the everolimus benefit was mostly for patients with secondary hormone resistance, while patients with primary resistance benefited to a lesser degree.[49] Finally, a phase 3 registration trial (BOLERO-2) successfully confirmed the efficacy of everolimus in combination with exemestane in 724 postmenopausal patients with advanced breast cancer and progression on a non-steroidal AI. It showed significant improvement in median PFS from 3.2 months with exemestane alone to 7.8 months with everolimus plus exemestane (HR = 0.45, 95% CI = 0.38-0.54; $p < 0.0001$).[50,51] Overall survival was not significantly improved by everolimus (30 months vs. 26 months for everolimus-exemestane vs. exemestane alone; p = 0.14) but it should be noted that BOLERO-2 was not powered to detect difference in overall survival.[52] The 4-month advantage obtained in PFS seemed to be maintained and carried over to the final overall survival. Side-effect management is an important issue with everolimus. More than half of the patients could experience some degree of mucositis and grade 3 mucositis was observed in 8% of the patients, usually occurring within the first 2 months of therapy. It has been proposed that steroid-based mouthwash may alleviate the incidence of mucositis.[53] Non-infectious pneumonitis and hyperglycaemia are less frequent but clinically important complications that require a high level of clinical vigilance and prompt management. Overall, everolimus is an active agent in combination with exemestane after failure to a non-steroidal AI. The combination of everolimus with another hormone agent may also be a reasonable option for patients who have previous exposure to exemestane.

CYCLIN-DEPENDENT KINASE 4/6 INHIBITORS

Cyclin-dependent kinase 4/6 inhibitors are activated in the cell cycle by cyclin D1 (CCND1) and other D-type cyclins to promote cell cycle entry by phosphorylating

retinoblastoma protein to initiate transition from the G1 phase to the S phase and facilitate cell cycle progression. Overexpression of CCND1 and activation of CDK 4/6 have been identified as key drivers of proliferation and resistance to endocrine therapy in ER-positive breast cancer.[54] Inhibition of CDK 4/6 has strong activity against ER-positive breast cancer and recent clinical trials have shown unique clinical efficacy of CDK 4/6 inhibitors.

Palbociclib

The phase 3 PALOMA-3 trial investigated the efficacy of palbociclib in patients with advanced ER-positive HER2-negative breast cancer that had relapsed or progressed during endocrine therapy. Both postmenopausal and premenopausal women were eligible. Pre- or peri-menopausal women also received goserelin. A total of 521 patients were randomly assigned to receive palbociclib with fulvestrant or placebo with fulvestrant. The median PFS was significantly prolonged by fulvestrant plus palbociclib (9.5 vs. 4.6 months; HR = 0.46, 95% CI = 0.36-0.59; $p < 0.0001$). A beneficial effect was seen in the pre- and post-menopausal women, as well as visceral and non-visceral disease subgroups. The most common grade 3 or 4 adverse events for the fulvestrant plus palbociclib group were neutropenia (65%) and leukopenia (28%). Despite such a high rate of neutropenia, the risk of febrile neutropenia was extremely low (1%). Other side-effects were relatively uncommon.[55,56]

The use of palbociclib in the first-line setting for endocrine-sensitive advanced breast cancer has also achieved impressive results in randomised studies. The PALOMA-1 trial was a phase 2 trial in first-line advanced ER-positive HER2-negative breast cancer in which patients were randomised to receive palbociclib plus letrozole or letrozole alone. It included a pre-specified cohort of patients whose tumours harboured CCND1 amplification, loss of p16, or both. A remarkable improvement in PFS by 10 months with the combination regimen was achieved. Neither CCND1 amplification nor p16 loss was associated with efficacy.[57] These results were confirmed in the phase 3 PALOMA-2 trial that also showed a 10-month improvement in the median PFS: 24.8 vs. 14.5 months for patients receiving palbociclib plus letrozole and letrozole plus placebo, respectively. The benefit of palbociclib-letrozole was homogenously observed in all subgroups. The objective response rate reached 55% for patients who received palbociclib-letrozole and had measurable disease. Consistent with previous studies, the most common grade 3 or 4 adverse events associated with palbociclib-letrozole were neutropenia (66%) and leukopenia (25%) while the rate of febrile neutropenia was exceedingly low (1.8%).[58] The PALOMA-2 and PALOMA-3 studies are expected to lead to regulatory approval of palbociclib in many countries.

Ribociclib

The Mammary Oncology Assessment of LEE011's (Ribociclib's) Efficacy and Safety (MONALEESA-2) trial is a phase 3 study to compare the safety and efficacy of ribociclib in combination with letrozole compared with letrozole alone in postmenopausal women with ER-positive HER2-negative advanced breast cancer and no prior therapy (the same population as used in the PALOMA-2 trial). In May 2016, the Independent Data Monitoring Committee recommended stopping the trial early as it met the primary endpoint, significantly extending PFS compared with letrozole alone, at the pre-planned interim analysis. A total of 668 patients were recruited in the study. The duration of PFS was significantly longer in the ribociclib group than in the placebo group (HR = 0.56, 95% CI = 0.43-0.72; $p = 3.29 \times 10^{-6}$). The median PFS was not reached in the ribociclib group and was 14.7 months in the placebo group. In patients with measurable disease at baseline, the overall response rate was 53% and 37%, respectively ($p < 0.001$). Similar to the PALOMA studies, the most common grade 3 or 4 adverse events were neutropenia (59%) and leukopenia (21%), while the rate of febrile neutropenia was again very low (1.5%). An increase of >60 ms in the QTcF interval occurred in 2.7%; most were able to continue ribociclib without interruption.[59]

Abemaciclib

Abemaciclib is also a highly specific small molecule CDK 4/6 inhibitor that is in the later stages of clinical development. A phase II trial (MONARCH 1) tested the efficacy of abemaciclib monotherapy in the treatment of patients with ER-positive HER2-negative metastatic breast cancer who had received at least two prior lines of chemotherapy. Abemaciclib demonstrated single-agent activity in this group of heavily pre-treated patients with 90% having visceral involvement and half at least three sites of metastases. An objective response rate of 19.7% was achieved. The median duration of response was 8.6 months; median PFS was 6.0 months and the median overall survival was 17.7 months. Concerning grade 3 to 4 adverse events, abemaciclib showed a different profile to the other two CDK 4/6 inhibitors and was more often

associated with diarrhoea (20%) and fatigue (13%) while the risk of neutropenia appeared to be lower (27%).[60] Further randomised studies will confirm its clinical role and benefit.

CONCLUSION AND FUTURE SCOPE

Hormone therapy has been the major treatment of ER-positive HER2-negative metastatic breast cancer and in recent years we have witnessed an expansion of the treatment arsenal with a plethora of new drugs demonstrating enhanced activity against the hormone pathway and targeted actions towards other cellular signalling pathways. Tables 3 and 4 summarises the results of recent clinical trials of hormone-targeted therapy in the first- and second-line setting, respectively. Given the evolving therapeutic options, there is a clear emerging need for identification of biomarkers of resistance and response. To date, no reliable biomarkers can accurately predict responsiveness to endocrine or targeted therapies and clinical judgement is still necessary in treatment decision making. In the first-line setting, it is unclear if all patients need hormone therapy in combination with a CDK 4/6 inhibitor or if there is a selected subgroup of patients for whom hormone therapy alone should be sufficient. The optimal sequence of endocrine agents and combinations with targeted therapies is currently unknown and is a research priority. Clinical data beyond progression from clinical trials are important to better understand the efficacy of each class of agent when given after the other. Comprehensive molecular profiling of the primary and metastatic tumours combined with longitudinal monitoring with liquid biopsies using cell-free DNA or circulating tumour cells are also under intense study in order to provide information about the dynamic genetic changes to tumour cells in response to treatment. New drugs that act on other alternative signalling pathways are being developed and treatment is moving towards a more personalised approach. With the remarkable progress that has been achieved in the past century, especially over the last two decades, it is hopeful that hormone-targeted therapy will enter a new era and the prospect of patients living longer and better will be very promising.

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