RESEARCH

Optimising endocrine therapy in postmenopausal women with advanced breast cancer

Thomas Ho Lai Yau and Kwok-Leung Cheung

School of Medicine, University of Nottingham, Derby, UK

Correspondence should be addressed to K-L Cheung: kl.cheung@nottingham.ac.uk

Abstract

Hormone receptor-positive breast cancer is commonly treated with endocrine therapy (ET); however, over time, cancer cells can develop endocrine resistance. This review aims to document combination therapy and sequential therapy in the use of endocrine agents and targeted agents, by conducting two systematic searches using four databases: Cochrane Library, MEDLINE, EMBASE and Web of Science. A total of 26 studies that covered combination therapy were obtained and included for the review. Fourteen were phase III documenting combinations of mechanistic target of rapamycin (mTOR), phosphoinositide-3-kinase (PI3K), vascular endothelial growth factor receptor, human epidermal growth factor receptor 2 and cyclin-dependent kinase 4/6 (CDK4/6) inhibitors. The remaining studies were of phase II nature that reported combinations involving inhibitors in mTOR, endothelial growth factor receptor, CDK4/6 and TKI. Interesting findings in inhibitor combinations involving CDK4/6, mTOR and PI3K suggest clinical activity that can overcome endocrine resistance. On the other hand, there were 0 studies that covered sequential therapy. Overall findings showed that combination therapy improved treatment efficacy over monotherapy in postmenopausal patients with hormone receptor-positive advanced breast cancer. Inevitably, the benefits are accompanied with increased toxicity. To optimise ET, further research into combinations and effective patient selection will need to be defined. Additionally, this review warrants future studies to explore sequential therapy.

Key Words

- ▶ breast cancer
- ▶ hormone receptor positive
- ▶ advanced
- ▶ postmenopausal
- ▶ endocrine therapy
- ▶ combination
- ▶ sequential

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Introduction

Endocrine therapy (ET) is often used as first-line treatment in patients with hormone receptor-positive (HR+) breast cancer and preferred to chemotherapy when there are no signs of visceral crisis (Reinert & Barrios 2015). In terms of efficacy, ET improves progression-free survival (PFS), time to progression (TTP), objective response rate (ORR) and clinical benefit response (CBR), while possessing a favourable toxicity profile when compared

to chemotherapy. Although the therapeutic action of ET is slower than chemotherapy, the duration of response in ET is more sustainable with longer-term survival benefits (Cheung 2007). Recent data from the FALCON trial observed significant improvements in not just PFS and TTP but also overall survival (OS) for postmenopausal patients with endocrine-naïve, HR+ locally advanced/metastatic breast cancer (LABC/MBC) when treated

with fulvestrant 500mg, as opposed to anastrozole 1 mg (Robertson *et al.* 2016). All HR+ breast cancers can be represented with the presence of oestrogen receptor (ER) and/or progesterone receptor (PR) (Cheung 2007). The American Society of Clinical Oncology/College of American Pathologists recommended HR+ tumours be defined as having at least 1% of tumour nuclei stained positively for either ER or PR on immunohistochemistry (Hammond *et al.* 2010). Unfortunately, patients with ER+ breast cancer are susceptible to risks of progressive disease (PD) or develop endocrine resistance (Dixon 2014). As a result, investigations in modalities of ET agents have been thorough and produced a wide range of ET options for patients to use.

A greater understanding in cancer biology has shown that ESR1 mutation is associated with mechanisms of endocrine resistance, especially to tamoxifen and fulvestrant (Jeselsohn *et al.* 2015). About 15–20% of ER+ LABC/MBC were shown to have ESR1 mutation, with increased frequencies detected in patients with multiple ET exposure. Research into biochemical pathways associated with proliferation has identified that cross-talk between signalling pathways can activate ERs, despite conventional ER pathways being blocked or inactivated (Pietras 2006, Dixon 2014). For instance, cross-talk between ER and specific pathways such as the phosphoinositide 3-kinase/v-akt murine thymoma viral oncogene/mammalian target of rapamycin (PI3K/AKT/mTOR) can result in continued proliferation of the cancer cells and hence develop resistance to ET (Dixon 2014). Targeted therapy agents (TAs) are designed to interfere with specific targets that are involved with growth. Often TAs act on specific molecular targets to achieve blockade of cell proliferation and potential cross-talks between the ER-mediated pathway and other signalling pathways. Most TAs are categorised by their molecular target (Table 1). Accordingly, the concomitant use of TA with other cancer therapeutics can potentially further increase treatment efficacy and overcome endocrine resistance

(Pietras 2006). However, combination therapy is prone to a greater toxicity profile when compared to monotherapy. Hence, an alternative would be the sequential application of ET and TA, which is expected to lessen the toxicity profile of these regimens. In sequential therapy, the patient will be exposed to only one toxicity profile at once rather than two during combination therapy. From Fig. 1, it was of interest if sequential application of an ET agent and TA will produce similar efficacy when compared to combination therapy. Another interesting comparison of these treatments would be to compare the results of different sequencing pattern in sequential ET (in this case treatment B and C). Henceforth, this was the definition of combination therapy and sequential therapy in this review.

An ever-growing arsenal of anticancer agents requires knowledge in optimal application for clinicians and patients to make informed decisions regarding therapeutic strategies. The aim was to assimilate methodologies and conclusions of randomised control trials (RCTs) investigating the benefits/limitations of combination and sequential therapy of ET/TA.

Methods

This systematic review was conducted by electronic searches to include relevant phase II/III RCTs that have reviewed the application of ET and TA in combination therapy or sequential therapy. Relevant literatures were screened for their title, followed by evaluation of abstracts befitting the selection criteria. Lastly, availability of full articles and abstracts in eligible literature were reviewed. Two separate searches were performed in parallel to accommodate the aims of the review.

A comprehensive search was performed with multiple databases: Medline, EMBASE, Cochrane Library and Web of Science. Both searches included 'endocrine therapy', 'hormone', 'advanced breast cancer', 'metastatic' and 'postmenopausal'. Additional search terms: 'combination',

Table 1 Some targeted therapy agents that have been used in treating breast cancer in combination with other forms of cancer treatment.

Molecular target	Action	Example(s)
Human epidermal growth factor receptor 2 (HER2)	Inhibit	Trastuzumab, lapatinib
Mechanistic target of rapamycin (mTOR)	Inhibit	Everolimus, temsirolimus
Vascular endothelial growth factors receptors (VEGFR)	Inhibit	Bevacizumab
Phosphoinositide 3-kinase (PI3K)	Inhibit	Buparlisib
Endothelial growth factor receptor (EGFR)	Inhibit	Gefitinib, sapatinib
Cyclin dependent kinase 4/6 (CDK4/6)	Inhibit	Palbociclib, ribociclib
Tyrosine kinase inhibitor (TKI)	Inhibit	Dovitinib

Combination therapy vs Sequential therapy **Figure 1**

A hypothetical comparison of combination therapy (treatment A) and sequential therapy (treatment B and C). ET, endocrine therapy agent; TA, targeted agent; ET/TA, combination of endocrine therapy agent and targeted agent; Blocked arrow, duration of effective treatment from ET/TA; Dashed arrow, duration of effective treatment from ET; Straight arrow, duration of effective treatment from TA.

'plus', 'add' and 'together' were incorporated into the search for combination therapy. Whereas, search terms: 'sequential', 'switch', 'concurrent', and 'concomitant' were included for the sequential therapy search. Cross-referencing of relevant literature was also conducted to expand the literature search. Conference abstracts were also considered for screening, to include on-going studies for review. The search was limited to English language and RCTs that investigated combinations or sequential applications of ET and TA in postmenopausal patients with HR+ advanced/MBC in phase II/III. The search was carried out from 1998 onwards, because trastuzumab was approved by the Food and Drug Administration on this year (Roche & Ingle 1999). The Critical Appraisal Skill Programme (CASP) RCT checklist was used for critical appraisal of founded studies.

Inclusion criteria

- ET combination with TA
- Sequential use of ET with TA
- Primary interest of ET agents includes:
 - Selective oestrogen receptor modulators (SERMs): tamoxifen

- Steroidal third-generation aromatase inhibitors (AIs): exemestane
- Non-steroidal third-generation AIs: anastrozole or letrozole
- Selective oestrogen receptor downregulators (SERDs): fulvestrant
- Study title must be a RCT that report any of the following molecular TA with ET:
 - HER2 inhibitors
 - mTOR inhibitors
 - CDK4/6 inhibitors
 - VEGFR inhibitors
 - EGFR inhibitors
 - PI3K inhibitors
 - TKIs
- Study must offer full text or abstract that provide details in:
 - Background/Introduction
 - Methods
 - Results
 - Discussion/Conclusion
- HR+ breast cancer may include:
 - ER+, PR+, HER2+
 - ER+, PR+, HER2–
 - ER+, PR–, HER2–
 - ER+, PR–, HER2+
 - ER–, PR+, HER2+
 - ER–, PR+, HER2–
- Study must recruit postmenopausal patients or in addition to premenopausal patients
- Prior chemotherapy was acceptable in abstract screening of RCTs

Exclusion criteria

- Keywords 'chemotherapy' or 'radiotherapy' stated in title or in combination with ET
- Combination of ET agents (SERDs, AIs, SERMs)
- 'Premenopausal' or 'early breast cancer' stated in title
- Study solely on premenopausal patients
- Non-human studies
- Neo-adjuvant studies

Primary outcome

The primary objective was to evaluate the effectiveness of combination therapy and sequential therapy in optimising ET. The optimisation of ET will be measured by observed improvements in PFS, ORR, TTP, CBR and OS. Remarks of overcoming endocrine resistant will also be considered.

Secondary outcome

The benefits and limitations of combination therapy and sequential therapy were evaluated. Parameters included quality of life (QoL), toxicity and cost-effectiveness will also be considered.

It was hypothesised that combination therapy was a more suitable option to optimising ET when compared to sequential therapy in terms of improving treatment efficacy and overcoming endocrine resistance.

Results

Combination therapy search

From Fig. 2, an initial detection of 2866 articles from the 4 databases. A final total of 26 studies were achieved, after removal of duplicates, title and abstract screening

according to the inclusion and exclusion criteria stated in methods.

From Table 2, there are 9 studies addressing ET/mTOR, 3 ET and CDK4/6, 1 study addressing ET/PI3K, 3 studies addressing ET/HER2, 2 studies addressing ET/VEGFR, 5 studies addressing ET/EGFR and 3 studies addressing ET/TKI combinations. 2 studies had CBR as their primary endpoint and the rest of the studies had PFS.

ET combinations with mTOR inhibitors (phase III/II)

The combination of exemestane and everolimus was well documented in the international, phase 3, multicentre, randomised, double-blind, placebo-controlled trial: BOLERO-2 (Baselga *et al.* 2012, Piccart *et al.* 2012, Burris *et al.* 2013a,b, Yardley *et al.* 2013). The targeted population consisted of postmenopausal women with

Studies addressing combination ET with TA

Figure 2

A flow diagram displaying the study selection process that addressed for combinations of ET with targeted agents. Adapted, under the terms of the Creative Commons Attribution License, from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine* 6(7): e1000097.

Table 2 Summary of included phase II/III studies that address combination of ET and TA (mTOR inhibitors; CDK4/6 inhibitors; PI3K inhibitor; HER2 inhibitors; VEGFR inhibitor; EGFR inhibitor and TKI).

Authors	Combination of ET and TA	Target	Phase	Number of studies	Number of patients	Primary endpoint	Abstract or Full text
Bachelot <i>et al.</i> (2012)	Tamoxifen + everolimus	mTOR	2	1	111	CBR	Full text
Baselga <i>et al.</i> (2012), Piccart <i>et al.</i> (2012), Burris <i>et al.</i> (2013a,b), Yardley <i>et al.</i> (2013)	Exemestane + everolimus	mTOR	3	5	722	PFS	Full text, Full text, Abstract, Abstract, Full text
Carpenter <i>et al.</i> (2005), Wolff <i>et al.</i> (2013)	Letrozole + temsirolimus	mTOR	3, 2	2	1110	PFS	Full text, Abstract
Kornblum <i>et al.</i> (2017)	Fulvestrant + everolimus	mTOR	2	1	130	PFS	Abstract
Baselga <i>et al.</i> (2016)	Fulvestrant + buparlisib	PI3K	3	1	1141	PFS	Abstract
Burstein <i>et al.</i> (2014)	Fulvestrant + lapatinib	HER2	3	1	291	PFS	Full text
Johnston <i>et al.</i> (2009)	Letrozole + lapatinib	HER2	3	1	1171	PFS	Full text
Kaufmann <i>et al.</i> (2009)	Anastrozole + trastuzumab	HER2	3	1	207	PFS	Full text
Cristofanilli <i>et al.</i> (2016)	Fulvestrant + palbociclib	CDK4/6	3	1	521	PFS	Full text
Finn <i>et al.</i> (2016a,b)	Letrozole + palbociclib	CDK4/6	3, 2	2	666, 165	PFS	Abstract, Full text
Martin <i>et al.</i> (2015), Dickler <i>et al.</i> (2016)	Letrozole + bevacizumab	VEGFR	3	2	343, *374	PFS	Full text, Full text
Martin <i>et al.</i> (2015)	Fulvestrant + bevacizumab	VEGFR	3	1	*374	PFS	Full text
Osborne <i>et al.</i> (2011)	Tamoxifen + gefitinib	EGFR	2	1	289	PFS	Full text
Valero <i>et al.</i> (2009)	Anastrozole + gefitinib	EGFR	2	4	93, **141	PFS, CBR	Full text, Full text, Full text, Abstract
Cristofanilli <i>et al.</i> (2010), Carlson <i>et al.</i> (2012), Tryfonidis <i>et al.</i> (2016)							
Carlson <i>et al.</i> (2012)	Fulvestrant + gefitinib	EGFR	2	1	**141	CBR	Full text
Wright <i>et al.</i> (2011)	Fulvestrant + dasatinib	TKI	2	1	99	PFS	Abstract
Musolino <i>et al.</i> (2017)	Fulvestrant + dovitinib	TKI	2	1	97, 71	PFS	Full text
Johnston <i>et al.</i> (2016)	Anastrozole + AZD8931	TKI	2	1	359	PFS	Full text

Data with * and ** represent data from the same study.

HR+, HER2– locally ABC or MBC whom experienced PD from letrozole or anastrozole. Eligible patients were randomised in a blind manner at a 2:1 ratio for the experimental arm (25 mg/day exemestane and 10 mg/day oral everolimus) or matching placebo. The investigation in BOLERO-2 showed significant improvements in PFS and other efficacy parameters (Table 3). These improvements in efficacy were also maintained in patients with visceral disease, elderly and of Asian ethnicity. Thus, the everolimus/exemestane combination represents an improvement in managing a wider population of postmenopausal women with HR+, HER2-ABC. Furthermore, BOLERO-2 is the only study that reported QoL. Burris *et al.* reported similar baseline global health status score in treatment and placebo regimen (64.7 vs 65.3) (Burris *et al.* 2013b). The similar outcome of QoL further supports the use of everolimus with ET.

Despite BOLERO-2 advocated the benefits of using mTOR inhibitor, contrasting finding in PFS was observed in the HORIZON study (Wolff *et al.* 2013). This study investigated the use of letrozole in combination with oral mTOR inhibitor temsirolimus in the phase III setting, following positive findings of improvement

in PFS and CBR from previous phase II trial (Carpenter *et al.* 2005). This combination failed to improve PFS (8.9 vs 9.0 months), ORR (27% vs 27%) and OS. Moreover, a raised toxicity profile in the combination arm resulted in more grade 3/4 adverse events (AEs) (37% vs 24%). However, it was speculated that the contrasting findings in both trials were due to key differences in eligible patient characteristics (Wolff *et al.* 2013). For instance, HORIZON excluded patients with prior AI exposure within 12 months, whereas eligible patients in BOLERO-2 required progression from a non-steroidal AI during or within 12 months. This speculation highlights the significance of patient selection to determining the success of the treatment regimen. Interestingly, it was noted in the HORIZON study observed an improved PFS (9.0 vs 5.6 months) limited to patients aged ≤65 years treated with the combination letrozole/temsirolimus rather than in patients aged ≥65 (8.5 vs 10.1 months). This finding suggests that temsirolimus activity may favour the younger population over the older population (Wolff *et al.* 2013). Again, this proposal accentuates the importance of patient selection for treatment success.

Table 3 Summarised findings of different parameters from each phase III studies.

Experimental arm vs comparative arm	PFS (months)	ORR (%)	TTP (months)	CBR (%)	OS (months)*	QoL	Toxicity	Cost-effectiveness
Parameters investigated in phase III studies addressing combinations of ET with targeted agents								
Exemestane + everolimus vs exemestane + placebo (Baselga et al. 2012)	6.9 vs 2.8 (Hr=0.43, $P<0.001$)	9.5 vs 0.4 ($P<0.001$)	–	–	Immature interim analysis, with a total of 83 deaths	–	<ul style="list-style-type: none"> Stomatitis (8% vs 1%) Anaemia (6% vs <1%) Hyperglycaemia (4% vs <1%) Pneumonitis (3% vs 0%) 	–
Fulvestrant + buparlisib vs fulvestrant + placebo (Baselga et al. 2016)	6.9 vs 5.0 PIK3CA mutant ctDNA (7.0 vs 3.2)	12 vs 8 PIK3CA mutant ctDNA (18 vs 4)	–	44 vs 42 PIK3CA mutant ctDNA (47 vs 32)	–	–	<ul style="list-style-type: none"> Elevated alanine aminotransferase/aspartate vs 1%/3%) Hyperglycaemia (15% vs 0.2%) Rash (8% vs 0%) Common grade 3 or 4 AEs: Stomatitis Hyperglycaemia Fatigue 	–
Exemestane + everolimus vs exemestane + placebo (Burriss et al. 2013a,b)	10.5 vs 6.9	12.6 vs 1.7 ($P<0.0001$)	–	–	–	Baseline global health status scores=64.7 vs 65.3 health-related QoL was not worse with everolimus/exemestane	<ul style="list-style-type: none"> Common grade 3 or 4 AEs: Stomatitis Hyperglycaemia Fatigue 	–
Fulvestrant + lapatinib vs fulvestrant + placebo (Burstein et al. 2014)	4.7 vs 3.8 (Hr=1.04, $P=0.37$), HER2+: 5.9 vs 3.3 (Hr=1.23), HER2–: 4.1 vs 3.8 (Hr=1.00)	20 vs 9 ($P=0.048$), HER2+ tumour (38 vs 7), HER2– tumour (13 vs 23)	–	–	30 vs 26.4 (Hr=0.91, $P=0.25$)	–	<ul style="list-style-type: none"> Grade 3 AEs (19% vs 6%): Rash/acne (3% vs 0%) Diarrhoea (8% vs 0%) Fatigue (3% vs 1%) 	–
Fulvestrant + palbociclib vs fulvestrant + placebo (Cristofanilli et al. 2016)	9.5 vs 4.6 (Hr=0.46, $P<0.0001$)	66 vs 15 (OR=2.69, $P=0.0012$)	–	67 vs 40 PIK3CA+ (60 vs 36) PIK3CA– (72 vs 40)	–	–	Grade 1–2 AEs: <ul style="list-style-type: none"> Anaemia (25% vs 9%) Thrombocytopenia (19% vs 0%) Infection (40% vs 27%) Grade 3 AEs: <ul style="list-style-type: none"> Neutropenia (55% vs 0%) Leukopenia (27% vs 1%) Hypertension (24% vs 2%) Proteinuria (11% vs 0%) 	–
Letrozole + bevacizumab vs letrozole + placebo (Dickler et al. 2016)	20.2 vs 15.6 (Hr=0.75, $P=0.016$)	69 vs 49 ($P=0.004$)	–	80 vs 62 ($P<0.001$)	47.2 vs 43.9 (Hr=0.87, $P=0.188$), Deaths=81 vs 90	–	<ul style="list-style-type: none"> Neutropenia (55% vs 0%) Leukopenia (27% vs 1%) Hypertension (24% vs 2%) Proteinuria (11% vs 0%) 	–
Letrozole + palbociclib vs letrozole + placebo (Finn et al. 2016a,b)	24.8 vs 14.5 (Hr=0.58, $P<0.000001$)	42.1 vs 34.7 ($P=0.031$)	–	84.9 vs 70.3 ($P<0.0001$)	Immature data	–	<ul style="list-style-type: none"> Neutropenia (79.5% vs 6.3%) Nausea (35.1% vs 26.1%) Arthralgia (33.3% vs 33.8%) Alopecia (32.9% vs 15.8%) 	–

Letrozole + lapatinib vs letrozole + placebo (<i>Johnston et al. 2009</i>)	8.2 vs 3.0 (Hr=0.71, P=0.019)	28 vs 15 (OR=0.4, P=0.021)	48 vs 29 (OR=0.4, P=0.003)	33.3 vs 32.3 (Hr=0.74, P=0.113)	–	<ul style="list-style-type: none"> • Grade 1/2 AEs:Diarrhoea (32%/22% vs 15%/4%) • Rash (28%/15% vs 11%/2%) • Nausea (22%/8% vs 14%/6%) • Arthralgia (12%/6% vs 16%/6%) 	–
Anastrozole + trastuzumab vs anastrozole alone (<i>Kaufman et al. 2009</i>)	4.8 vs 2.4 (Hr=0.63, P=0.016)	Partial response (20.3 vs 6.8, P=0.018)	5.6 vs 3.9 (P=0.0007)	28.5 vs 23.9 (P=0.451)	–	<ul style="list-style-type: none"> • Grade 3/4 AEs (23%/5% vs 15%/1%) • Diarrhoea (20.4% vs 7.7%) • Arthralgia (14.6% vs 9.6%) • Dyspnoea (12.6% vs 8.7%) 	–
Letrozole/ fulvestrant + bevacizumab vs letrozole/fulvestrant alone (<i>Martin et al. 2015</i>)	19.3 vs 14.4 (Hr=0.83, P=0.126)	41 vs 22 (P<0.001)	77 vs 66 (P=0.041)	52.1 vs 51.8 (Hr=0.87, P=0.518)	–	<ul style="list-style-type: none"> • 14 vs 2 • Grade 3/4 AEs:Hypertension (15.0% vs 3.0%) • Aminotransferase elevation (3.7% vs 1.0%) • Proteinuria (7.0% vs 0.0%) 	–
Exemestane + everolimus vs exemestane + placebo (<i>Piccart et al. 2012</i>)	7.8 vs 3.2 (Hr=0.45, P<0.0001)	–	–	Death rate: 25.4% vs 32.2%	–	–	–
Letrozole + temsirolimus vs letrozole + placebo (<i>Wolff et al. 2013</i>)	8.9 vs 9 (Hr=0.90, p=0.25), Pts aged ≤65: 9.0 vs 5.6 (Hr=0.75, P=0.009), Pts aged >65: 8.5 vs 10.1 (Hr=1.21, P=0.17)	27 vs 27	–	Not estimable	–	<ul style="list-style-type: none"> • Grade 3/4 AEs (37% v 24)Hy-perglycaemia (4% vs 1%) • Diarrhoea (2% vs 1%) • Mucositis/stomatitis (up to 2% vs <1%) • Hyperlipidaemia (2% vs <1%) 	–
Exemestane + everolimus vs exemestane + placebo (<i>Yardley et al. 2013</i>)	7.8 vs 3.2 (Hr=0.45, P<0.0001)	12.6 vs 1.7 (P<0.0001)	51.3 vs 26.4 (P<0.0001)	Prolong OS	–	<ul style="list-style-type: none"> • Grade 3/4 AEs:Diarrhoea (10% vs 1%) • Rash (1% vs 0%) 	–

The table is formatted as followed: (experimental arm vs comparative arm). Regarding toxicities column, selected toxicity was chosen by availability from study and prevalence.

*The changing of unit will be stated in the cell

ctDNA, circulating tumour DNA; Hr, hazard ratio; OR, odd ratio; P, P value.

From the open-labelled RCT (TAMRAD) that investigated the tamoxifen/everolimus combination. An interesting finding in CBR suggested possible reversal of ET resistance and subsequent improvements. Overall, CBR at 6 months was 61% vs 42%. Moreover, improvements in CBR were consistent in patients with secondary resistance (74% vs 48%) and in patients with primary resistance (46% vs 38%). Similar findings in TTP (14.8 vs 5.5 months) was more prominent in patients with secondary resistance as opposed to those with primary resistance (5.4 vs 3.8 months) (Bachelot *et al.* 2012). Therefore, this combination may benefit patients with AI-resistant MBC. However, this trial was relatively small with a total of 111 patients and may be prone to bias. Small imbalances between groups' performance status were notable (Bachelot *et al.* 2012). Hence, this study was confirmed only for hypothesis generating and warrant further study into this area (Bachelot *et al.* 2012). An alternate combination of fulvestrant and everolimus has shown positive improvements in PFS (10.4 vs 5.1 months) against AI-resistant MBC in the phase II settings (Kornblum *et al.* 2017). Once again, this highlights the potential of combination therapy in overcoming resistance.

ET combinations with CDK4/6 inhibitor (phase III/II)

Positive results were observed when novel CDK4/6 inhibitor palbociclib was added to ET. From Table 3, PALOMA-2 (letrozole/palbociclib) and PALOMA-3 (fulvestrant/palbociclib) have shown improvements in efficacy parameters. In both PALOMA-2 and PALOMA-3, significant improvements in PFS, ORR and CBR were reported. In terms of toxicity, neutropenia (79.5% vs 6.3%) was evident when palbociclib was added. Nonetheless, PALOMA-2 confirmed the significant clinical benefits and safety of using palbociclib/letrozole to treat postmenopausal patients whom had no prior systemic therapy for their ER+, HER2– ABC (Finn *et al.* 2016a,b).

From PALOMA-3, patients with HR+, HER2– MBC were randomised in a double-blind manner to fulvestrant (500mg, intramuscular injections on days 1 and 15 of cycle one and then on day 1 of each 28-day cycle) and palbociclib or placebo (125mg/day oral for 3 weeks, followed by 1 week off in a 28-day cycle). Although this trial recruited both premenopausal and postmenopausal women, premenopausal women were treated with goserelin (LHRH agonist) to induce postmenopausal status.

Significant improvements in PFS (9.5 vs 4.6 months), ORR (66% vs 15%) and CBR (67% vs 40%) were observed. The benefits of palbociclib/fulvestrant in PFS compared to fulvestrant/placebo were consistent irrespective of the degree of HR expression, PIK3CA mutation, ET resistance and ethnicity. These findings propose the possibility of re-sensitising endocrine sensitivity in ET-resistant tumours by targeting of CDK4/6. Common toxicities include: neutropenia, leukopenia, fatigue and anaemia were observed in ET/palbociclib arms. These haematological changes should be considered during patient selection for this therapeutic strategy. Endocrine monotherapy had limited efficacy in patients with PD from prior ET, proposing a need for further investigations into the effective use of combination regimens to overcome this problem (Cristofanilli *et al.* 2016).

ET combinations with PI3K inhibitors (phase III)

BELLE-2 was a randomised, double-blinded, placebo-controlled phase III trial that investigated the addition of buparlisib to fulvestrant. Overall, promising results were observed; with PFS, ORR and CBR all being improved in the experimental arm. The toxicity profile of the addition of buparlisib seems to be associated with liver function, with increase in alanine aminotransferase (26% vs 1% and aspartate aminotransferase (18% vs 3%)). Hence, the use of buparlisib in patients with poor liver function should be cautioned. Interestingly, Baselga *et al.* reported that buparlisib significantly improved median PFS, ORR and CBR in patients with PIK3CA-mutant ctDNA, but the same activity was not observed in patients without the mutation. Furthermore, patients characterised with PIK3-mutated tumours are associated with endocrine-resistant HR+, HER2– ABC (Baselga *et al.* 2016). This proposes the possibility that the targeting of PI3K pathway may be an area to explore for overcoming endocrine resistance.

ET combinations with HER2 inhibitors (phase III)

Positive results of adding HER2 inhibitor to ET was shown in the TAnDEM study (anastrozole/trastuzumab) and in a phase III study that investigated letrozole in combination with lapatinib (Johnston *et al.* 2009, Kaufman *et al.* 2009, Burstein *et al.* 2014). PFS and CBR were greatly enhanced, with a doubling of PFS was seen in both studies (Table 3). However, the increase in PFS did not correlate with OS. More AEs were reported in the combination arm in both studies. Moreover, an increase in cardiac events

(14 vs 2) was observed in anastrozole/trastuzumab when compared to anastrozole alone. Johnston *et al.* also discussed the problem of ET resistance in HR+, HER2+ breast cancer and concluded that the addition of lapatinib did not delay disease progression with letrozole in endocrine-sensitive tumours. In general, the studies concur that addition of HER2 inhibitors to ET in HR+, HER2+ breast cancer can prolong chemoprevention and increase ET efficacy.

CALGB 40302 was a randomised, double-blinded, placebo-controlled phase III study that investigated the fulvestrant/lapatinib combination. Conversely, there was a lack of improvement in clinical outcomes. Though, it was noted that PFS was improved in patients with HER2+ tumours (5.9 vs 3.3 months) as opposed to HER2– tumours (4.1 vs 3.8 months) when lapatinib was added. However, this study had a small number of HER2+ cases (18%) with the majority being HER2– tumours (81%). Hence, this could be a limitation of the study that patient recruitment could have been amended to include more HER2+ cases to maximise activity of the HER2 inhibitor. Although the experimental regimen was generally tolerable, there were more AEs and treatment discontinuation caused from the raised toxicity. Overall, CALGB 40302 concluded that lapatinib did not significantly improve clinical benefits when added to fulvestrant (Burstein *et al.* 2014).

ET combinations with VEGFR inhibitor (phase III)

From Table 3, the CALGB 40503 (letrozole with bevacizumab) and LEA study (letrozole/fulvestrant with bevacizumab), reported of contrasting findings in PFS. According to the CALGB 40503 study, the addition of bevacizumab to letrozole improved PFS (20.2 vs 15.6 months) when compared to the placebo arm. Moreover, ORR (69% vs 49%) and CBR (80% vs 62%) exhibited similar improvements from the addition of bevacizumab. However, the significant improvement in PFS, ORR and CBR did not correlate with OS (47.2 vs 43.9 months) (Dickler *et al.* 2016). Similar improvements in PFS (19.3 vs 14.4 months), ORR (41% vs 22%) and CBR (77% vs 66%) were observed in the LEA study. However, the difference in PFS was not statistically significant: the hazard ratio of the combination arm vs ET alone was 0.83 ($P=0.126$) (Martin *et al.* 2015). Unsurprisingly, bevacizumab combinations were associated with increased AEs; mainly hypertension and proteinuria. The LEA study reported of deaths in the bevacizumab arm that seem to be associated with conditions that may have been

worsened from the hypertensive side effects (Martin *et al.* 2015). As a result, patients with hypertensive conditions should avoid the use of bevacizumab.

One of the limitations of the LEA study was the lack of comparison of letrozole and fulvestrant when in combination with bevacizumab. All the data assimilated were grouped together either as ET/bevacizumab and ET alone. Further sub-groups within ET/bevacizumab to compare letrozole/bevacizumab and fulvestrant/bevacizumab would have provided more information on optimal application of bevacizumab to ET.

ET combinations with EGFR inhibitor (phase II)

Marked advantage in PFS was reported when gefitinib was added to anastrozole in comparison to placebo (Table 4) (Valero *et al.* 2009, Cristofanilli *et al.* 2010). Improvement in PFS was also observed in the study of tamoxifen in combination with gefitinib. For this trial, patients were split into two groups: stratum 1 (PD after tamoxifen) and 2 (PD during/after AI). PFS was only improved in stratum 1 (10.9 vs 8.8 months), but not in stratum 2 (5.7 vs 7.0 months). The significant improvement of PFS in stratum 1 suggests possible endocrine re-sensitisation when gefitinib was added to an ET (tamoxifen, in this case) that was previously used (Osborne *et al.* 2011). A sub-analysis of PFS in patients with prior ET therapies (11.2 vs 7.1 months) and ET naïve (20.2 vs 8.4 months) was observed using gefitinib/anastrozole vs placebo arm (Cristofanilli *et al.* 2010). These findings suggest a potential role of overcoming ET resistance from using gefitinib. On the other hand, Tryfonidis *et al.* argued that the toxicity profile (mainly skin and gastrointestinal related) of gefitinib resulted in premature therapy interruption in 33% of patients. Additionally, the PFS rate at 1 year was only 35% for combination arm and 32% for placebo arm (Tryfonidis *et al.* 2016). Hence, the use of gefitinib was not supported in a risk/benefit point of view. Carlson *et al.* echoed similar opinion in further trials of combinations of gefitinib with anastrozole/fulvestrant, despite modest findings in anti-tumour activities (Carlson *et al.* 2012). Overall, PFS comparison seemed similar (5.3 vs 5.2 months in anastrozole and fulvestrant arms respectively) but in patients who had prior chemotherapy, a significant deterioration in PFS was seen in the fulvestrant/gefitinib arm (2.6 months) (Tryfonidis *et al.* 2016). Although it was unexplained why these changes were observed, it can be inferred that prior treatment can have an impact on future treatments.

ET combinations with TKI (phase II)

The general consensus toward TKI/ET combinations seems negative. Johnston *et al.* reported a 3 arms trial of anastrozole (1mg/day) in combination with AZD8931 at 20mg (twice daily), 40mg (twice daily) or placebo. Although PFS (13.8 vs 14.9 vs 10.9 months) was increased, it was statistically insignificant (Table 4) (Johnston *et al.* 2016). This therapeutic strategy does not seem to enhance ET responsiveness and was generally associated with a greater toxicity profile when compared to ET alone. Wright *et al.* reported that the addition of dasatinib to fulvestrant did not improve PFS (6.0 months vs 5.3 months), CBR and OS. In fact, CBR (28.0% vs 32.7%) and OS (17.0 vs 21.7 months) seemed to worsen with dasatinib/fulvestrant when compared to placebo (Wright *et al.* 2011). This may suggest that a worse safety profile and patient tolerability could potentially influence the patient's QoL and ultimately OS. Finally, in the fulvestrant/dovitinib study, an improvement in PFS (10.9 vs 5.5 months) was observed, although this was only limited to patients with FGF pathway-amplified breast cancer in fulvestrant/dovitinib vs placebo arm respectively. Contrastingly, patients without FGF pathway amplification gained no effect from the addition of dovitinib (5.5 vs 5.5 months), other than the increased toxicity associated in combination therapy (Musolino *et al.* 2017). This discovery highlights the importance of patient selection by identifying cancer biology to maximise treatment prognosis.

Sequential therapy search

From Fig. 3, an initial detection of 901 articles. A final total of 0 studies were identified, after removal of duplicates, title and abstract screening according to the inclusion and exclusion criteria stated in methods. Therefore, the search for relevant literature in the sequential application of ET and TA was unsuccessful.

Discussion

This review aimed to explore options for the optimisation of ET with TA by methods of combination therapy or sequential therapy. From assimilating relevant studies, it was clear that combination therapy is investigated more thoroughly than sequential therapy. The identification of benefits and limitations in both combination and sequential therapy was not met due to the absence of literature available in sequential therapy. The result of

0 articles warrants the need of future investigation in this area.

It was hypothesised that combination therapy would be the better option in optimising ET. Most combinations of ET and TA have yielded extremely promising results, notably in enhancing treatment efficacy (PFS, ORR and CBR). The classes of TA reviewed in this systematic review included: mTOR inhibitors, EGFR inhibitors, TKI, CDK4/6 inhibitors, VEGFR inhibitors, PI3K inhibitor and HER2 inhibitors. Most treatment combinations were effective in treating patients with HR+, HER2– ABC/MBC. Evidently, the best combination arms included CDK4/6 inhibitor, PI3K inhibitor and mTOR inhibitors in treating this population. These combinations seem to optimise ET by producing significant improvements in PFS, CBR and ORR, regardless of patients' treatment history and overcoming endocrine resistant. The additional benefits from combination therapy were associated with an increase in toxicity. This was a common trend in all included studies. Consequently, combination therapy may prove difficult in patients whom do not tolerate these regimens, for instance, in the elderly population.

All studies documented the toxicity profile of the combination against the comparison arm. However, it was unknown how these toxicities may have impacted the patient being treated. Most studies had stated that one of the main reasons for patient discontinuation was related to treatment toxicity. Data in these areas should identify treatment tolerability, patients' QoL and financial feasibility for sustainable treatment. Therefore, clinicians will be provided with a better understanding on the ideal application of ET and TA.

Throughout the review, it was evident that some combinations (TKI, EGFR and VEGFR) failed to produce any benefits over ET alone. Differences in study design seemed to be the most likely explanation for contrasting findings in RCTs with similar experimental arms. Most RCTs used methods such as: double-blinding, placebo-controlled and 2-arm trial. Although some RCTs deviated from this and employed an open-label approach and the absent of placebo. Hence, those RCTs may be of lower power than those that used the double-blinding and placebo-control methods to minimise chances of bias.

Patient selection

It was implied that the importance of patient selection seemed to influence treatment prognosis. From assimilating relevant study findings, this review suggests

Table 4 Summarised findings in different parameters from each phase II studies.

Experimental arm vs comparative arm	PFS (months)*	ORR (%)	TTP (month)	CBR (%)	OS (months)	QoL	Toxicity/adverse events (AEs)	Cost-effectiveness
Parameters investigated in phase II studies addressing combinations of ET with TA								
Tamoxifen+everolimus vs tamoxifen alone (Bachelot <i>et al.</i> 2012)	–	14 vs 13	8.6 vs 4.5 (Hr=0.54, P=0.002), 2° resistance (14.8 vs 5.5), 1° resistance (5.4 vs 3.8)	61 vs 42 (P=0.045), 2° resistance (74 vs 48), 1° resistance (46 vs 36)	Median OS not reached with tamoxifen+everolimus; tamoxifen alone (32.9)=55% reduction in the risk of death associated with combination therapy (Hr=0.45, P=0.007)	–	<ul style="list-style-type: none"> Fatigue (72% vs 53%) Stomatitis (56% vs 7%) Rash (44% vs 7%) Anorexia (43% vs 18%) Diarrhoea (39% vs 11%) 	–
Anastrozole/fulvestrant+gefitinib vs anastrozole/fulvestrant+gefitinib (Carlson <i>et al.</i> 2012)	5.3 (anastrozole+gefitinib) vs 5.2 (fulvestrant+gefitinib), prior chemotherapy: 6.4 (anastrozole+gefitinib) vs 2.6 (fulvestrant+gefitinib)	–	–	43.5 (anastrozole and gefitinib) vs 40.9 (fulvestrant and gefitinib)	Median survival=30.3 months (anastrozole and gefitinib) vs 23.9 months (fulvestrant and gefitinib)	–	Mostly Grade 1/2 toxicity: <ul style="list-style-type: none"> Fatigue (41% vs 32%) Nausea (27% vs 18%) Dehydration (38% vs 41%) Grade 3/4 toxicity: 	–
Letrozole+temsirolimus vs letrozole alone (Carpenter <i>et al.</i> 2005)	PFS rate 1 year: 10 mg daily (69%), 30 mg intermittent (62%), letrozole alone (48%)	10 mg daily (9 pr), 30 mg intermittent (1 cr, 8 pr), letrozole alone (2 cr, 10 pr)	–	10 mg daily (82%), 30 mg intermittent (83%), letrozole alone (79%)	–	–	<ul style="list-style-type: none"> 36% (anastrozole and gefitinib) 35% (fulvestrant and gefitinib) Grade 3/4 AEs: 10 mg daily: hyperglycaemia (9%) 30 mg intermittent: hyperglycaemia (17%), asthenia (7%), hypertension (7%), hypokalaemia (7%) 	–
Anastrozole+gefitinib vs anastrozole+placebo (Cristofanilli <i>et al.</i> 2010)	14.7 vs 8.4 (Hr=0.55), Prior ET: 11.2 vs 7.1 (Hr=0.65), ET naïve: 20.2 vs 8.4 (Hr=0.39)	2 vs 12	–	49 vs 34	Number of deaths before data cut-off (anastrozole plus gefitinib=6; anastrozole plus placebo=7)	–	<ul style="list-style-type: none"> Diarrhoea (63% vs 18%) Fatigue (40% vs 26%) Rash (37% vs 10%) Pruritus (26% vs 10%) Dry skin (14% vs 2%) Acne (12% vs 0%) Grade 3/4 AEs: 	–
Letrozole+palbociclib vs letrozole alone (Finn <i>et al.</i> 2016a,b)	Median: 20.2 vs 10.2 (Hr=0.488, P=0.0004), Cohort 1: 26.1 vs 5.7 (Hr=0.299, P<0.0001), Cohort 2: 18.1 vs 11.1 (Hr=0.508, P=0.0046)	43 vs 33 (P=0.13)	–	81 vs 58 (P=0.0009)	37.5 vs 33.3 (Hr=0.813, P=0.42)	–	<ul style="list-style-type: none"> Neutropenia (54% vs 1%) Leukopenia (19% vs 0%) Fatigue (4% vs 1%) Serious AEs: 	–
							<ul style="list-style-type: none"> Pulmonary embolism (4%) Back pain (2%) Diarrhoea (2%) 	

(Continued)

Table 4 Continued.

Experimental arm vs comparative arm	PFS (months)*	ORR (%)	TTP (month)	CBR (%)	OS (months)	QoL	Toxicity/adverse events (AEs)	Cost-effectiveness
Anastrozole + AZD8931 vs anastrozole alone (Johnston <i>et al.</i> 2016)	AZD8931 20mg: 10.9 (Hr=1.37, P=0.135), AZD8931 40 mg: 13.8 (Hr=1.16, P=0.485), Placebo: 14.0	AZD8931 20mg: (31.2), AZD8931 40 mg: (34.6), Placebo: (28.8)	–	0	AZD8931 20mg: (16 deaths), AZD8931 40 mg: (20 deaths), Placebo: (12 deaths)	–	Incident of AEs: <ul style="list-style-type: none"> AZD8931 20mg (95%) AZD8931 40mg (97%) Placebo (84%)Common AEs of AZD8931: <ul style="list-style-type: none"> Diarrhoea Skin related AEs Grade 3/4 AEs (53%/3% vs 23%/3%):Hyperglycaemia (16%/0% vs 0%) Stomatitis (11%/0% vs 0%) Hypertriglyceridemia (9%/2% vs 0%) Lymphopenia (9%/0% vs. 0%) Pneumonitis (6%/2% vs 0%) 	–
Fulvestrant + everolimus vs fulvestrant + placebo (Kornblum <i>et al.</i> 2017)	10.4 vs 5.1 (Hr=0.61, P=0.02)	–	–	–	–	–	–	–
Fulvestrant + dovitinib vs fulvestrant + placebo (Musolino <i>et al.</i> 2017)	5.5 vs 5.5 (Hr=0.68), FGF pathway–amplified: 10.9 vs 5.5 (Hr=0.64), FGF pathway–nonamplified: 5.5 vs 5.5 (Hr=0.69)	27.7 vs 10.0, FGF pathway–amplified: 20.0 vs 12.5, FGF pathway–nonamplified: 31.3 vs 8.8	–	–	OS was not reached (18.6 – not estimable) in the dovitinib arm and was 25.9 (18.4– not estimable) in the placebo arm	–	Grade 3 AEs:Diarrhoea (6.4% vs 0%) Alanine aminotransferase/Aspartate aminotransferase (4.3% vs 2.0%) Rash (4.3% vs 0%) Grade 3/4 toxicity (41% vs 15%) Incidence of serious AE (26.1% vs 15.4%)	–
Tamoxifen + gefitinib vs tamoxifen + placebo (Osborne <i>et al.</i> 2011)	Stratum 1: 10.9 vs 8.8 (Hr=0.84, P=0.314), Stratum 2: 5.7 vs 7.0 (Hr=1.16, P=0.577)	Stratum 1: 12.4 vs 14.9 (Hr=0.76, P=0.518), Stratum 2: 0 vs 0	–	Stratum 1: 50.5 vs 45.5 (OR=1.10, P=0.748), Stratum 2: 29.2 vs 31.4 (OR=0.72, P=0.517)	–	–	–	–
Anastrozole + gefitinib vs anastrozole + placebo (Tryfonidis <i>et al.</i> 2016)	PFS rate 1 year (35.3% vs 32.4%)	22.2% vs 28.1%	–	–	–	–	–	–
Anastrozole + gefitinib vs anastrozole + placebo (Valero <i>et al.</i> 2009)	14.5 vs 8.2 (Hr=0.55)	2 vs 12	–	49 vs 34	–	–	–	–
Fulvestrant + dasatinib vs fulvestrant alone (Wright <i>et al.</i> 2011)	6.0 vs 5.3	–	–	28.0 vs 32.7	17.0 vs 21.7	–	–	–
						–	Grade 1/2 AEs:Pleural effusion (24% vs 8%) Diarrhoea (34% vs 10%) Nausea (40% vs 6%) Fatigue (30% vs 18%)	–

The table is formatted as followed: (experimental arm vs comparative arm). Regarding toxicities column, selected toxicity was chosen by availability from study and prevalence.

*Change of unit will be stated in the cell.
cr, complete response; Hr, hazard ratio; OR, odds ratio; P, P value; pr, partial response.

that patient selection can be categorised into three main areas: patient characteristics, cancer biology and pharmacology.

Patient characteristics

Patient characteristics such as age have shown to influence drug efficacy. In the HORIZON study, temsirolimus produced PFS benefits in younger patients as opposed to older patients (Wolff *et al.* 2013). Thus, the use of SERMs and SERDs in combination to temsirolimus may exhibit greater benefit in selected younger patients than using AIs, which are restricted to the postmenopausal population. However, it should be reminded that not all postmenopausal patients are of the older population. Younger patients can obtain the postmenopausal status

via oophorectomy or the use of a luteinising hormone-releasing hormone agonist. Another aspect to consider in older patients would be treatment tolerability. From the LEA study, details of patients' deaths were reported in the bevacizumab arm ($n=8$) (Martin *et al.* 2015). Some deaths were associated with conditions that may have been exacerbated from the hypertensive side effects. Further inspection, revealed that the patient age ranged from 53 to 82 years and 5 out of 8 patients had hypertension as baseline co-morbidity (Martin *et al.* 2015). Therefore, specific co-morbidities in individual patients should be considered when selecting regimens. As evidently different classes of TA are associated with specific toxicities: palbociclib (neutropenia), bevacizumab (hypertension), trastuzumab (cardiac events) and EGFR inhibitors (skin and gastrointestinal).

Studies addressing sequential ET with TA

Figure 3

A flow diagram displaying the study selection process that addressed for sequential use of ET with targeted agents. Adapted, under the terms of the Creative Commons Attribution License, from Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Medicine* 6(7): e1000097.

Cancer biology

The identification of specific targets can broaden the options for therapeutic strategies. For instance, the use of dovitinib (TKI that inhibits FGF pathways) in combination with fulvestrant was shown to significantly improve PFS in patients with FGF pathway-amplified breast cancer (10.9 vs 5.5 months) when compared to the placebo arm. However, patients without FGF pathway amplification did not benefit from the dovitinib/fulvestrant combination (5.5 vs 5.5 months) (Musolino *et al.* 2017). Burstein *et al.* also reported greater improvement in PFS and ORR, when the HER2 inhibitor lapatinib was added to fulvestrant in patients with HER2+ status than in those with HER2- (Burstein *et al.* 2014). These findings support the importance of patient selection, by identifying cancer biology to maximise treatment success.

Pharmacology

Pharmacology was another factor that should be considered during patient selection for suitable therapeutic strategy. It was clear from the findings in this systematic review, that prior therapy can influence treatment prognosis. This was evident in studies of ET/EGFR combinations, whereby prior ET or chemotherapy had caused dramatic changes in treatment outcome. In the phase II study that investigated the anastrozole/gefitinib combination, Cristofanilli *et al.* reported an exploratory *post hoc* subset analysis of patients with endocrine naïve and prior ET. An all-round improvement in PFS was observed in both subsets. But, the data seem to suggest superior benefits in PFS for patients with endocrine naïve (20.2 months) in contrast to patients who had prior ET (11.2 months) (Cristofanilli *et al.* 2016). From these findings, it was confirmed that endocrine monotherapy had limited efficacy in patients with PD from prior ET, proposing a need for further investigations into the effective selection of combination regimens to overcome this problem. Furthermore, this proposes that the use of combination therapy in a first-line setting may benefit those with naïve treatment. Although some combinations (CDK4/6, PI3K, EGFR and mTOR) have shown activity to overcome ET resistance in patients with prior ET exposure. Yet, it was unspecified if the number of prior therapies may further diminish the outcome in combination therapy. Hence, this may be another area to be for future investigations.

Overcoming resistance

One of the criteria for optimising ET in this review was to overcome ET resistance. This question was met in findings from phase III PALOMA-3 and BELLE-2 studies suggesting that targeting CDK4/6 and PI3K hold the most promise. This was supported by *in vitro* evidence suggesting cancer cells that have developed ET resistance remain dependent on cyclin D1 and CDK4 for proliferation. Similarly, pre-clinical evidence has identified a potential cause of endocrine resistance via cross-talk between ER and PI3K pathways (Milani *et al.* 2014). Additional findings from phase II ET combinations with gefitinib and everolimus suggested signs of delaying ET resistance or re-sensitising tumours with ET resistance promise (Bachelot *et al.* 2012, Tryfonidis *et al.* 2016). This prompts further research into overcoming ET resistance by targeting these pathways.

Sequential application

There was evidently a lack of knowledge about the sequential application of ET and TA. This review has identified areas that combination therapy has failed to impress, and a new approach in optimal application of specific target agents was needed. For instance, the activity of gefitinib with ET has suggested effects of delaying ET resistance. But in a combination setting, the regimen seemed to only increase toxicity while retaining similar efficacy seen in endocrine monotherapy (Tryfonidis *et al.* 2016). Hence, the sequential application of these agents could be a feasible alternative. A predicted decrease in toxicity would provide a more tolerable profile for patients. This will be important for management of the elderly population where tolerability may be an issue. Classes of TA such as TKIs, VEGFR inhibitors and HER2 inhibitors when in combination created unfavourable tolerability in patients. Therefore, those classes of agents may benefit from this sequential approach.

Limitations

The term 'targeted agents' was narrowly defined to fit the feasibility of generating this systematic review. Several agents were excluded from this review included: proteasome inhibitors and farnesyltransferase inhibitors. Moreover, combination therapy was strictly defined to only include 2 agent combinations and excluding studies that have explored the feasibility of more than

2 agent combinations such as triple combinations. Thus, this review does not reflect the true potential depth of combination therapy and diversity of TA available for optimising ET.

The method in selecting papers was rigorously determined by the presence of specific keywords. Studies that were excluded solely based on title alone, may have contained relevant information in the abstract or within the full text. Thus, there was the possibility that relevant studies were missed.

Furthermore, many trial status were 'on-going' or 'results pending', this resulted in a narrow range of agents being incorporated into this review. This was especially evident in the attempt of including novel agents that targeted the PI3K pathway. Consequently, the protocol was amended to allow inclusion of abstracts to generate a wider pool of agents and subsequent findings. However, limited information was provided in the abstracts when compared to full text. This was evident during analysis of study design and results.

Conclusion

Combination of ET and TA has proven to be effective at improving treatment efficacy over monotherapy in postmenopausal patients with HR+ ABC/MBC. However, not all combinations are adding benefit to ET and some are only increasing the toxicity profile. Indisputably, tolerability of toxicity in combination therapy of the elderly population possesses an issue in patient management. As a result, this may be an opportunity for sequential therapy of ET and TA to be explored in this specific population.

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