Critical Reviews in Oncology/Hematology 100 (2016) 57–68

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Endocrine therapy in post-menopausal women with metastatic breast cancer: From literature and guidelines to clinical practice

Valentina Sini[a,b], Saverio Cinieri[c], Pierfranco Conte[d,e], Michelino De Laurentiis[f], Angelo Di Leo[g], Carlo Tondini[h], Paolo Marchetti[i,j,*]

[a] Surgical and Medical Department of Clinical Sciences, Biomedical Technologies and Translational Medicine, "Sapienza" University of Rome, Italy
[b] Oncology Department, Santo Spirito Hospital, Rome, Italy
[c] Medical Oncology Department & Breast Unit—Hospital of Brindisi and Medical Oncology Department—European Institute of Oncology, Milan, Italy
[d] Medical Oncology 2, Venetian Oncological Institute, Padova, Italy
[e] Department of Surgical, Oncological and Gastroenterological Sciences, University of Padova, Padova, Italy
[f] Department of Breast Oncology, National Cancer Institute "Fondazione Pascale", Naples, Italy
[g] Medical Oncology Department, "Sandro Pitigliani" Hospital of Prato, Istituto Toscano Tumori, Prato, Italy
[h] USC Oncologia Medica, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy
[i] Department of Clinical and Molecular Medicine, Medical Oncology Division, Sant'Andrea Hospital, "Sapienza" University of Rome, Rome, Italy
[j] IDI-IRCCS, Rome, Italy

Contents

ARTICLE INFO

Article history:
Received 17 November 2015
Accepted 15 February 2016

ABSTRACT

Current international guidelines recommend endocrine therapy as the initial treatment of choice in hormone receptor positive advanced breast cancer. Endocrine therapy has been a mainstay of hormone responsive breast cancer treatment for more than a century. To date it is based on different

* Corresponding author at: Medical Oncology, "Sapienza" University of Rome, Via di Grottarossa, 1035-39, 00189 Rome, Italy.
E-mail address: paolo.marchetti@ospedalesantandrea.it (P. Marchetti).

http://dx.doi.org/10.1016/j.critrevonc.2016.02.008

Keywords:
Advanced breastcancer
Endocrine therapy
Hormone receptor positive
Postmenopausal
Treatment
Maintenance
Endocrine resistance

approaches,such as blocking the estrogen receptor through selective receptor estrogen modulators, depleting extragonadal peripheral estrogen synthesis by aromatase inhibitors or inducing estrogen receptor degradation using selective down-regulators. Despite estrogen and/or progesterone receptor positive status, up to a quarter of patients could be either primarily resistant to hormone therapies or will develop hormone resistance during the course of their disease. Different mechanisms, either intrinsic or acquired, could be implicated in endocrine resistance.
In the present work available endocrine therapies and their appropriate sequences have been reviewed, and the most promising strategies to overcome endocrine resistance have been highlighted.

1. Introduction

About 70% of breast cancers express the hormone receptor (HR). Hormonal manipulation has been a mainstay of hormone responsive breast cancer treatment for more than a century, and often represents the first of several lines of treatment in the metastatic setting.

To date endocrine therapy is based on different approaches, such as blocking the estrogen receptor (ER) through selective ER modulators (SERMs), reducing estrogen levels by depleting extragonadal peripheral estrogen synthesis by aromatase inhibitors (AIs) or inducing ER degradation using selective ER down-regulators (SERDs).

A substantial proportion of patients, up to one-quarter, despite ER and/or progesterone receptor (PgR) positive status, could be either primarily resistant to hormone therapies or will develop hormone resistance during the course of their disease.

ER maintains active in tumor with acquired resistance to endocrine therapy, and continued endocrine therapy in combination with other agents are effective in such patients.

Other available therapies, such chemotherapy or combinations of endocrine and target therapies, as PI3K-mTOR inhibitors, could have a key role in primary or secondary resistant HR+ metastatic breast cancer.

Also, a proper view of available endocrine therapies, related studies, their appropriate sequences and relative strategies to overcome endocrine resistance, could help our daily clinical practice.

2. Certainties and new approaches in the treatment of estrogen receptor positive metastatic breast cancer

Sites and extent of disease, related symptoms, ER levels and human epidermal growth factor-2 (HER2) status, disease-free and treatment-free intervals, and performance status are key factors in the choice of treatment in metastatic HR+ breast cancer.

While hormone-unresponsive or life-threatening disease requires chemotherapy, HR+ metastatic breast cancer patients are usually candidate to endocrine therapy. Indeed while initial treatment with chemotherapy rather than endocrine therapy may be associated with a higher response rate, the two initial treatments had a similar effect on overall survival(OS) (Wilcken et al., 2003). No studies directly compared endocrine and chemotherapy in this setting.

Main international guidelines recommend endocrine therapy as the treatment of choice in HR+ advancedbreast cancer:

- NCCN Guidelines: Many women with hormone-responsive breast cancer benefit from sequential use of endocrine therapy at disease progression. Therefore, women with breast cancer who respond to endocrine therapy with either tumor shrinkage or long-term disease stabilization should receive additional endocrine therapy at disease progression (NCCN, 2015).

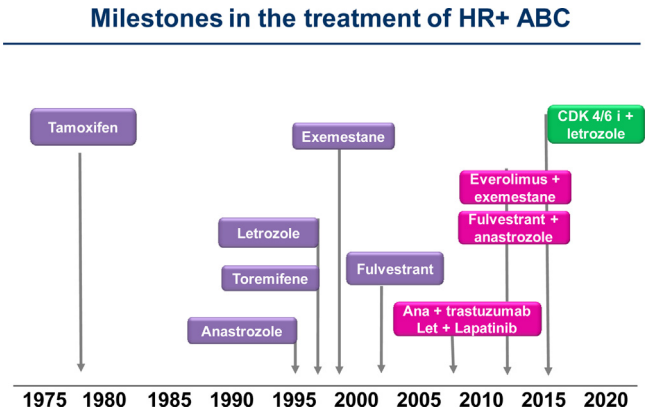

Fig. 1. Endocrine therapy involves many agents.

- ABC1 Guidelines: Endocrine therapy is the preferred option for HR + disease, even in the presence of visceral disease, unless there is concern or proof of endocrine resistance or there is disease needing a fast response (Cardoso et al., 2012a).
- ESMO Guidelines: Endocrine therapy is the preferred option except if clinically aggressive disease mandates a quicker response or if there are doubts regarding endocrine responsiveness of the tumor (Cardoso et al., 2012b).

To date endocrine therapy involves many agents (Fig. 1). For many years tamoxifen, a selective ER modulator (SERM) which antagonises estrogen signaling in HR+ breast cancer,has been the mainstay in the treatment of HR+ breast cancer. Tamoxifen became the standard therapy for advanced breast cancer after having demonstrated first-line efficacy and more favorable toxicity profile when compared with a range of other endocrine agents in this setting (Fossati et al., 1998). A systematic review, on 35 randomized controlled trials (RCTs), comparing tamoxifen witha range of other endocrine therapies, including ovarectomy, megestrol acetate, aromatase inhibitors (AIs), medroxyprogesterone acetate, SERMs, goserelin and fluoxymesterone, reported an overall response rate (ORR) of 30% withtamoxifen versus 29% with the other agents and an OS hazard ratio of 1.02 [confidence interval (CI) 0.94–1.10], without gross statistical heterogeneity between trials ($p = 0.48$) or differences hormonal categories ($p = 0.60$) (Fossati et al., 1998).

2.1. Tamoxifen versus megestrol acetate

In at least five RCTs (Allegra et al., 1985; Gill et al., 1993; Ingle et al., 1982; Morgan, 1985; Muss et al., 1988; Paterson et al., 1990) tamoxifen demonstrated to have comparable efficacy with megestrol acetate, that acts by inhibiting pituitary function and thus suppressing luteinizing hormone and the subsequent production of estrogen, in terms of ORR and OS, with a better side-effect profile.

2.2. Tamoxifen versus other SERMs

Tamoxifen has also been tested against several other SERMs, and, overall, it was therefore deemed to be as good as, or better than, all alternative SERMs. In particular tamoxifen resulted comparable to toremifene (n = 1421) (Pyrhonen et al., 1999) or idoxifene (n = 220) (Johnston, 2001) and was superior to droloxifene [ORR (P = 0.02) and time to progression (TTP) (P < 0.001)] (Buzdar et al., 2002) and to arzoxifene [progression-free survival (PFS; P = 0.01)] (Deshmane et al., 2007).

The study of approaches for patients with tumors resistant to tamoxifen led to the development of new strategies:

2.3. Tamoxifen versus first- and second-generation AIs

The first generation AI aminoglutethimide was shown to be comparable with tamoxifen alone (Lipton et al., 1982; Smith et al., 1981) or with aminoglutethimide plus tamoxifen (Ingle et al., 1986; Rose et al., 1986). AIs work by inhibiting aromatase signaling, which ultimately blocks the estrogen receptor. But first generation compounds were unspecific with subsequent toxicity and need of adrenal hormonal supplementation.

2.4. Third-generation AIs: anastrozole andletrozole (competitive, non-steroidal) and exemestane (non-competitive, steroidal) versus megestrol acetate in advanced pretreated breast cancer

With third generation AIs, letrozole, anatrozole and exemestane, problems about adrenal toxicity of previous compounds were overcome. They were evaluated in comparison with hormonal agents used in "tamoxifen-resistant" disease, of which megestrol acetate was the drug of choice before the coming of AIs and fulvestrant.

Anastrozole showed no significant difference in TTP from megestrol acetate on an initial analysis (Buzdar et al., 1997; Jonat et al., 1996). However, a planned subsequent analysis found anastrozole 1 mg to be associated with significantly increased OS versus megestrol acetate (median 26.7 versus 22.5 months, respectively; P < 0.025) (Buzdar et al., 1998). Two studies of letrozole 2.5 mg versus megestrol acetate showed no significant difference in TTP or OS (Buzdar et al., 2001; Dombernowsky et al., 1998). Exemestane resulted in an increased TTP (4.7 versus 3.8 months; P = 0.037) and a significantly longer OS (median OS not reached for exemestane at time of publication versus 28.5 months for megestrol acetate;P = 0.039) compared with megestrol acetate (Kaufmann et al., 2000). AIs were initially introduced based on better side-effect profile but similar TTP versus megestrol acetate. Subsequently, this decision was supported by the OS data with anastrozole and the increased efficacy seen with exemestane.

2.5. Third-generation AIS: anastrozole andletrozole (competitive, non-steroidal) and exemestane (non-competitive, steroidal) versus tamoxifen as first-lineendocrine therapy

Similarly to the adjuvant setting, where third-generation AIs resulted superior to tamoxifen in large trials (Forbes et al., 2008; Jonat et al., 2006; Coates et al., 2007; van de Velde et al., 2011; Coombes et al., 2004), in the advanced disease, overall, the third-generation AIs were deemed more effective in terms of disease control than tamoxifen, in potentially "tamoxifen-sensitive" disease. They were well tolerated. Therefore they became the preferred first-line endocrine therapy.

In particular, anastrozole was shown to be superior to tamoxifen in terms ofTTP in a North American-based trial (Nabholtz et al., 2000). On the other hand no significant difference in TTP was reported in the TARGET trial (Bonneterre et al., 2000).

However, only 45% of patients in the TARGET trial were known to have an HR+ tumor; while almost 90% of patients in the North American-based trial were known to be HR+, and in a pooled retrospective analysis of the two trials including patients with known HR+ tumors, anastrozole resulted superior to tamoxifen in terms of TTP, without differences in OS (Nabholtz et al., 2003).

Letrozole significantly prolonged TTP compared with tamoxifen without a significant difference in OS (Mouridsen et al., 2003). Also exemestane showed longer PFS (assessed using the Wilcoxon test) than tamoxifen (Paridaens et al., 2008).

2.6. Fulvestrant

Fulvestrant is a selective estrogen receptor down regulator (SERD). Unlike the selective ER modulator tamoxifen, fulvestrant is devoid of any known agonist activity. Fulvestrant has a steroidal structure that competitively binds to the ER with an affinity much greater than that of tamoxifen. Fulvestrant, binding to the ER, down-regulates, blocks, and causes degradation of the ER, culminating in complete abrogation of estrogen-sensitive gene transcription (Wakeling, 2000). Preclinical studies confirmed the potential of fulvestrant to inhibit the growth of tamoxifen-resistant, as well as tamoxifen-sensitive, human breast cancer cell lines (Wakeling et al., 1991; Hu et al., 1993; Lykkesfeldt et al., 1994). This unique mechanism of action may result in a lack of cross-resistance with other endocrine agents.

After studies had showed that it was as effective as anastrozole 1 mg/day in the treatment of HR+ advanced breast cancer in the second-line setting pre-treated with tamoxifen (Robertson et al., 2003, 2004), it was initially approved at a dose of 250 mg/month.

Preclinical models and pharmacokinetic studies suggested the possibility to obtain, through a loading dose, plasma concentrations of fulvestrant twice higher than those obtained with the conventional monthly administration. Besides, higher doses of fulvestrant (500 mg) allowed to obtain the steady state in few weeks from the beginning of treatment (Robertson et al., 2007).

Based on these information, randomized studies evaluated efficacy of a schedule with loading dose, followed by standard dose of fulvestrant (250 mg) (Chia et al., 2008) or the use of high dose fulvestrant (500 mg) (Wakeling et al., 1991).

Fulvestrant 500 mg was compared to fulvestrant 250 mg in a phase III randomized controlled trial in women with advanced breast cancer (CONFIRM trial) (Di Leo et al., 2010, 2012) and to anastrozole 1 mg/die in first line setting (FIRST trial) (Robertson et al., 2009, 2010; Robertson, 2014) and, as herein after more extensively reported, Fulvestrant 500 resulted superior both to Fulvestrant 250 and to anastrozole.

Furthermore, this finding is fully consistent with the previous reported increased biological effects seen with the 500 mg dose compared with 250 mg (Kuter et al., 2007).

In summary, fulvestrant 500 mg has a biologically greater effect and provides a clinically meaningful benefit over fulvestrant 250 mg. The standard dosing schedule of fulvestrant should be5 00 mg and, based on its increased efficacy, should be considered early in the treatment of advanced disease (Cardoso et al., 2012b).

3. First line endocrine therapy: which studies?

3.1. Main contemporary studies in first line setting for HR + Her2− metastatic breast cancer patients

- *FIRST trial* is a randomized phase II randomized, open-label, multicenter study on 205 patients randomized to receive fulvestrant high-dose (HD) regimen (500 mg/month plus 500 mg on day 14 of month 1) versus anastrozole (1 mg/d) in the

first-line setting. All patients enrolled in this trial were post-menopausal women with ER+ and/or PgR+ locally advanced or metastatic breast cancer never treated with endocrine therapy for advanced disease, but could have received adjuvant endocrine therapy for early disease, provided it was completed more than 12 months before random assignment. This study showed a significant advantage for fulvestrant 500 mg in terms of TTP (hazard ratio = 0.626; P = 0.0496) (Robertson et al., 2009). The significant difference in TTP persisted with longer follow-up (23.4 months with fulvestrant versus 13.1 months with anastrozole; hazard ratio = 0.66; P = 0.01) (Robertson et al., 2010). Moreover, as reported at *San Antonio Breast Cancer Symposium* 2014, Fulvestrant showed a benefit in OS versus anastrozole: 54.1 months for fulvestrant versus 48.4 months for those who received anastrozole (Robertson, 2014). Adverse events were comparable between the two treatment arms (Robertson et al., 2009).

- *CONFIRM trial* is a double-blind, parallel-group, multicenter, phase III study. Patients were randomly assigned to fulvestrant 500 mg (500 mg intramuscularly on day 1, then 500 mg on days 14 and 28 and every 28 days thereafter, n = 362 patients) or 250 mg every 28 days (n = 374). Primary end point was PFS. Secondary end points included objective response rate (ORR), clinical benefit rate (CBR), duration of clinical benefit (DoCB), OS, and quality of life (QOL). PFS was significantly longer for fulvestrant 500 mg than 250 mg (hazard ratio = 0.80; 95% CI, 0.68–0.94; P = .006). ORR was similar in both arms (9.1% v 10.2%, respectively). CBR was 45.6% for fulvestrant 500 mg and 39.6% for fulvestrant 250 mg. DoCB and OS were 16.6 and 25.1 months, respectively, for the 500-mg group, whereas DoCB and OS were 13.9 and 22.8 months, respectively, in the 250-mg group. Fulvestrant 500 mg was well tolerated with no dose-dependent adverse events. QOL was similar for both arms (Di Leo et al., 2010). The final OS analysis at 75% maturity, presented at San Antonio Breast Cancer Symposium 2012, showed that fulvestrant 500 mg is associated with 4.1-month increase in median OS and a 19% reduction in the risk of death compared with fulvestrant 250 mg (Di Leo et al., 2012). The study included both first and subsequent lines patients. It is worth noting that the most represented subgroups were patients who experienced relapse on adjuvant endocrine therapy (48.3% in fulvestrant 500 mg arm and 45.2% in fulvestrant 250 mg arm) and patients who presented with de novo advanced disease and experienced progression on first-line endocrine therapy (35.9% and 33.4% respectively). Overall, the last endocrine therapy before fulvestrant was an aromatase inhibitor for 42.5% of patients and an antiestrogen for the remaining 57.5% of patients
- *SWOG 0226 study* evaluated combined endocrine therapy agents with the anti estrogen fulvestrant plus the AIanastrozole, aimed at seeking to leverage ER degradation by fulvestrant in endocrine-resistant disease. This study included a population of 694 post-menopausal patients, randomized to receive anastrozole 1 mg daily (n = 345 patients) or the combination of anastrozole and fulvestrant 500 mg loading dose followed by a monthly injection of fulvestrant 250 mg (n = 349). All patients were previously untreated for metastatic disease, Prior adjuvant tamoxifen was allowed, and 40% of patients received this adjuvant endocrine therapy. The study demonstrated a 6-month improvement in OS for the combination fulvestrant plus anastrozole (median OS 47.7 versus 41.3 months, hazard ratio = 0.81; p = 0.049). This benefit likewise appeared to be mainly restricted to those who were entirely endocrine therapy-naive, even in the adjuvant setting (47.7 versus 39.7 months, hazard ratio = 0.74) (Mehta et al., 2012).
- *FACT study* is a phase III randomized trial that randomly assigned 514 patients to receive fulvestrant plus anastrazole (experimental arm; n = 258 patients) or anastrozole (standard arm; n = 256), at the same schedule of SWOG 0226 trial. They were post-menopausal or pre-menopausal women receiving Gn-RH, previously untreated for metastatic disease. This trial allowed the enrollment of patients who received adjuvant endocrine therapy, and also AI, if completed >12 months before the enrolment. Endocrine-pretreated patients showed no benefit from the combination (Bergh et al., 2012). Median TTP was 10.8 and 10.2 months in experimental versus standard arm, respectively (hazard ratio 0.99; 95% CI 0.81–1.20, p = 0.91). Median OS resulted 37.8 and 38.2 months for experimental and standard arm, respectively (hazard ratio 1.0; 95% CI 0.76–1.32, p = 1.00) (Bergh et al., 2012).
- *HORIZON* trial is a large multicenter international randomized placebo-controlled phase III trial that tested the efficacy and safety of first-line oral letrozole 2.5 mg daily/temsirolimus 30 mg daily (5 days every 2 weeks) versus letrozole/placebo in 1112 patients with AI-naive, HR+ advanced disease. Patients had to be never treated for metastatic disease. 40% had received adjuvant endocrine therapy. The study did not show overall improvement in the primary end point PFS (median PFS = 9 months; hazard ratio = 0.90; 95% CI, 0.76–1.07; P = .25) nor in the 40% patient subset with prior adjuvant endocrine therapy. Those on letrozole/temsirolimus experienced more grade 3–4 events (37% v 24%) than letrozole alone. Adding temsirolimus to letrozole did not improve PFS as first-line therapy in patients with AI-naive advanced breast cancer. Indeed, the trial was stopped for futility by the independent data monitoring committee. ORR and OS were also similar between groups. The patient population in the HORIZON study was largely AI-naive and temsirolimus/letrozole was the first endocrine treatment for metastatic disease (Wolff et al., 2013).
- The Breast Cancer Trials of Oral Everolimus-2 (*BOLERO-2*) is a randomized phase III study in 724 patients with HR+ advanced breast cancer who had recurrence or progression while receiving previous therapy with a nonsteroidal aromatase inhibitor in the adjuvant setting or to treat advanced disease (or both), that compared everolimus and exemestane versus exemestane and placebo (randomly assigned in a 2:1 ratio). The primary end point was PFS. Secondary end points included OS, ORR, and safety. Combination therapy with exemestane and the mTOR inhibitor everolimus resulted in a significantly longer PFS (6.9 months with everolimus plus exemestane and 2.8 months with placebo plus exemestane, according to assessments by local investigators (hazard ratio = 0.43; 95% CI 0.35–0.54; P < 0.001). Median PFS was 10.6 months and 4.1 months, respectively, according to central assessment (hazard ratio, 0.36; 95% CI, 0.27–0.47; P < 0.001) and higher response rate than the single agent exemestane. The most common grade 3 or 4 adverse events were stomatitis (8% in the everolimus-plus-exemestane group versus 1% in the placebo-plus-exemestane group), anemia (6% versus <1%), dyspnea (4% versus 1%), hyperglycemia (4% versus <1%), fatigue (4% versus 1%), and pneumonitis (3% versus 0%). Everolimus combined with an AI improved PFS in patients with HR+ advanced breast cancer previously treated with nonsteroidal aromatase inhibitors. This trial only included pretreated population. Previous therapy included letrozole or anastrozole (100%), tamoxifen (48%), fulvestrant (16%), and chemotherapy (68%) (Baselga et al., 2012; Piccart-Gebhart et al., 2012).
- In the Tamoxifen and RAD001 (*TAMRAD*) study, a smaller randomized phase II trial in a similar patient population, patients receiving the combination of tamoxifen and everolimus had higher clinical benefit rate (61%) and longer TTP (8.6 months) than the group receiving tamoxifen alone (42% and 4.5 months). In that study, patients with secondary resistance to AI seemed to benefit more from the combination than patients with primary resistance, supporting the concept that cross-talk between pathways and the sequential upregulation of the PI3 K/mTOR signaling is a mechanism of resistance (Bachelot et al., 2012).

- It is worth of note that these benefits were not without toxicity. In this study, as the previous (Bolero-2) (Baselga et al., 2012; Piccart-Gebhart et al., 2012)combined everolimus/endocrine therapy had substantially higher stomatitis, rash, fatigue, diarrhea, and anorexia than single-agent endocrine therapy.
- *In the San Antonio Breast Cancer Symposium 2012* results froma randomized phase II study comparing letrozole alone (L) to letrozole plus PD 0332991 (L + P) were presented. PD 0332991 is a selective inhibitor of CDK 4/6 that prevents cellular DNA synthesis by blocking cell cycle progression. Preclinical studies in breast cancer cell line panel identified in the luminal ER subtype, elevated expression of cyclin D1 and Rb protein, and reduced p16 expression as being associated with sensitivity to PD 0332991 (Finn et al., 2009). It was designed as a two-part study, in which part 1 enrolled post- menopausal women with ER+/HER2–advanced BC; part 2 in addition to ER+/HER2–as eligibility criteria, screened for CCND1 amplification and/or loss of p16, evaluated by FISH. The primary endpoint was PFS; secondary endpoints include ORR, OS, safety, and correlative biomarker studies. In both parts, post-menopausal women with ER+/HER2–advanced BC were randomized 1:1 to receive letrozole either with or without PD0332991. 66 pts were randomized in Part 1 and 99 pts in Part 2. Preliminary results from Part 1 of this study have been previously reported (Finn, 2012) demonstrating a significant improvement in median PFS in the L + P versus L arm (HR = 0.35; 95% CI, 0.17–0.72; p = 0.006). With the additional 99 pts randomized in Part 2 (N = 165), the statistically significant improvement in median PFS (26.2 versus 7.5 months, respectively) continues to be observed (hazard ratio = 0.32; 95% CI, 0.19–0.56; p <0.001). The ORR for the L + P arm (n = 84) was 31% versus 26% for the L arm (n = 81) and the clinical benefit rate was 68% versus 44%, respectively. The most commonly reported treatment-related adverse events in the combination arm were neutropenia, leukopenia, anemia, and fatigue. The combination of PD 0332991 and letrozole is well tolerated and shows encouraging clinical benefit, confirming the sensitivity of ER+ breastcancerto PD 0332991 observed in preclinical models (Finn et al., 2012). A phase 3 trial in this setting is now on going.
- Very recently, during the last *ASCO Meeting*, results from PALOMA 3 (Nicholas et al., 2015) study were presented. It assessed the efficacy of palbociclib and fulvestrant in endocrine-resistant advanced breast cancer. Palbociclib combined with fulvestrant improved progression free survival in HR advanced breast cancer that had progressed on prior endocrine therapy. Median PFS was 9.2 months for Palbociclib + Fulvestrant and 3.8 months for Placebo + Fulvetratnt (HR 0.422, 95% CI 0.318–0.560, P < 0.000001) and it resulted well tolerated.

4. Resistance to endocrine therapy: new approaches

Unfortunatelyboth de novo and acquired resistance to endocrine therapy are important clinical problems. Different mechanisms have been implicated in endocrineresistance, either intrinsic, occurring de novo at theinitial exposure to endocrine therapies or acquired, occurringafter an initial response to therapy (Bedard et al., 2008; Dawood and Cristofanilli, 2007), and recent efforts have centeredaround strategies to combat this resistance (Moy and Goss, 2006).

ERexpression is currently the main biomarker ofresponse to endocrine therapy and the lack of ER has to beconsidered the principal mechanism of primary endocrineresistance (Zilli et al., 2009; Musgrove and Sutherland, 2009). Loss of ERalfa or ER beta mutations are widely acceptedas potential mechanisms of acquired resistance. Ofnote is that loss of ER occurs in 15–20% of endocrine resistantbreast cancers and less than 1% of HR+ tumorshave ER mutations (Gutierrez et al., 2005; Herynk and Fuqua, 2004).

Furthermore ER activity is a part of a more complexsystem of intracellular signaling pathway, and the bidirectional crosstalk between ER and growth factors signaling is implicated in both de novo andacquired resistance. Preclinical studiesimplicate cross-talk between ER and critical signaling pathways,such as the epidermal growth factor receptor/human epidermal-growth factor receptor-2 (EGFR/HER2) and IGFR or activation of their downstream signaling pathway through extracellular signal-regulating kinase1/2/mitogen activated protein kinase cascade and the phosphoinositide3-kinase (PI3 K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway, as key mediators of endocrine resistance (Johnston et al., 2005; Johnston, 2010).

4.1. Enhancing benefit of endocrine therapy by targeting growth factor receptors

Targeting EGFR"up-front", as shown in xenograft models,might delay resistance to tamoxifen (Thoennissen et al., 2010). For HER2+ tumors, combined targeted therapy at the onset of "acquired endocrine resistance" is better than delaying resistance up-front (Wang et al., 2005).

A number of clinical trials have been designedin order to determine whether the addiction of signaltransduction inhibitors to endocrine therapy may overcomeendocrine resistance, including combinations of endocrinetherapies with anti-HER targeted drugs, complete blockade of ER signaling and combinations with drugs that target the downstream signaling pathways.

To date, several trials have explored the efficacy of endocrinetherapy in combination with anti-HER2 monoclonal antibody trastuzumab or with EGFR/HER2 tyrosine kinase inhibitors as lapatinib, erlotinib and gefitinib (Johnston, 2009a).

Cristofanilli et al., 2010 reported prolonged PFS with anastrozole plus gefitinib (n = 43 patients) versus anastrozole plus placebo (n = 50;hazard ratio = 0.55; 95% CI 0.32–0.94) in postmenopausal women with HR+ metastatic breast cancer. These results, however, did not agree with those coming from the neoadjuvant randomized controlled trial of anastrozole versus anastrozole plus gefitinib (Smith et al., 2007). Moreover the combination oftamoxifen with or without gefitinib did not result in a PFS benefit with the addition of gefitinib to tamoxifen (Osborne et al., 2007).

Rationale for clinical trials exploring the combination of hormonal therapies and antiHer2 agents in metastatic breast cancer came from preclinical studies which demonstrated that the addition of trastuzumab to tamoxifen results in a strong growth inhibitionthrougha cell cycle arrest in G0-G1 (Thoennissen et al., 2010).

TAnDEM was the first randomized phase III study to combine a hormonal agent and trastuzumab as treatment for HER2+ and HR+ metastatic breast cancer. That trial (on 207 patients) randomly assigned to receive anastrozole (n = 104 patients) or anastrozole plus trastuzumab (n = 103) and demonstrated that the addition of trastuzumab to anastrozole significantly improves PFS, TTP, and OS compared with anastrozole alone (Kaufman et al., 2009).

The efficacy of the addition of lapatinib, a dual tyrosine kinase inhibitor, to letrozole has been investigated as first line treatment in 1286 women with hormone receptor positive (HER2+/−) metastatic breast cancer. The association of lapatinib and letrozole significantly improved PFS compared to letrozole alone in HER2+ population, with a 29% reduction in the risk of disease progression (Johnston et al., 2009). No benefit in the whole population in which the combination lapatinibandletrozole did not result better than letrozole (median PFS 14.7 versus 15 months) (Kaufman et al., 2009).

In bothstudies, the addition of the growth factor inhibitor improvedclinical benefit rate (CBR) and PFS but there was no significantdifference in OS (P = 0.325 for trastuzumab (Osborne et al., 2007);not reported for lapatinib) (Kaufman et al., 2009).

A third trial on HR+/Her2+ metastatic breast cancer, the eLEcTRA trial, compared efficacy and safety of letrozole combined with trastuzumab to letrozole alone. The study only included patients with HER2 and HR+ metastatic breast cancer, that were randomized to either letrozole alone (arm A, n = 31 patients) or letrozole plus trastuzumab (arm B, n = 26) as first-line treatment. Additional 35 patients with HER2- and HR+ tumors received letrozole alone (arm C). Median TTP in arm A was 3.3 months compared to 14.1 months in arm B (hazard ratio 0.67; p = 0.23) and 15.2 months in arm C (hazard ratio 0.71; p = 0.03). Clinical benefit rate was 39% for arm A compared to 65% in arm B (odds ratio 2.99, 95% CI 1.01–8.84) and 77% in arm C (odds ratio 5.34, 95% CI 1.83–15.58). This trial confirmed that the combination of endocrine and antiHer2-therapy is an effective treatment option for patients with HER2 and HR + metastatic breast cancer (Huober et al., 2012).

A phase III study evaluated Fulvestrant with or without lapatinib in patients with HR+ advanced breast cancer.In this trial both patients HER2+/− were included. At a third interim analysis, no improvements were observedin PFS or OS with the addition of lapatinib to fulvestrant. However, in patients with HER2+ tumors, a trend towardsimproved PFS was observed (5.9 versus 2.8 months forfulvestrant + lapatinib versus fulvestrant alone; P = 0.29). Treatment was generally well tolerated (Burstein et al., 2010).

So, “up-front” co-targeting of HER2 and HR can improve resistanceto AIs, and benefit from this strategy is restricted to known ER+ HER2+ metastatic breast cancer patients.

4.2. Targeting angiogenesis and endocrine resistance in HR+ metastatic BC

Preclinical (la Haba de et al., 2011) and retrospective clinical (Linderholm et al., 2011; Manders et al., 2003; Rydén et al., 2005) data suggest that high vascular endothelial growth factor (VEGF) levels in tumor tissue from breast cancerare associated with a decreased response to endocrine therapy.

The combination of endocrine therapy and bevacizumab has shown to be safe and active in phase II clinical trials (Traina et al., 2010; Forero-Torres et al., 2010).

The LEA trial, a phase III study presented in the San Antonio Breast Cancer Symposim 2012, addressed the hypothesis that anti-VEGF treatmentmight delay resistance to endocrine therapy in patients with HR+ advanced breast cancer. It was a binational, multicentric, randomized, open label phase III study in which 380 patients with unresectable locally advanced or metastatic HR+/HER2- breast cancer patients were randomized to receive endocrine therapy (Letrozole 2.5 mg d or Fulvestrant 250 mg 1 q 28) or the same endocrine therapy with Bevacizumab 15 mg/kg q3 weeks. The addition of Bevacizumab resulted in a better PFS (18.4 versus 13.8 months), hazard ratio 0.83 (CI 0.65–1.06, p = 0.1391) (Martin et al., 2012).

4.3. Combinations of different endocrine agents in HR+ metastatic BC

Similarly, studies evaluated combined endocrinetherapy agents. Rationale for these studies, that evalutated the combination of the pure antiestrogen fulvestrant plus an AI, came from the possibility of seeking toleverage ER degradation by fulvestrant in endocrine-resistant disease.

A recent study, the *SWOG 0226 trial,*(described in more detail below) demonstrated a 6-month improvement in OS for the combination fulvestrant plus anastrozole versus anastrozole alone. This study included a population of primarily endocrine therapy–naive patients treated in the first line setting, and the population benefiting from the combination appeared to be mainly those who were entirely endocrine therapy-naive, even in the adjuvant setting (Mehta et al., 2012).

By contrast, the FACT study, another randomized trial of anastrazole with or without fulvestrant that enrolled endocrine-pretreated patients, showed no benefit from the combination (Bergh et al., 2012).

4.4. Combinations of mTOR inhibitors in ER+ metastatic breast cancer

The mammalian target of rapamycin (mTOR) is a signaling kinase of the phosphatidylinositol 3-kinase/protein kinase B (also known as Akt) signaling pathway that mediates cell growth and metabolism.It has two main downstream messengers: the ribosomalp70 S6 kinase (S6K1) and the eukaryotic translation initiationfactor 4E-binding protein (4E-BP1) (Margariti et al., 2011). Both proteins aretranslational activators critical for ribosome biogenesis and translation, including the synthesis of proteins necessary forcell cycle progression. In addition to its effect on proteintranslation mediated by S6K1 and 4E-BP1, mTORactivation-leads to the phosphorylation of several downstream effectorsand transcription factors.Dysregulation of the mTOR pathway creates a favorable environment for the development and progression of many cancers, including breast cancer, and is associated with the development of resistance to endocrine therapy and to the anti-HER2 monoclonal antibody trastuzumab.Interest on the PI3 K/AKT/mTOR pathway has recently intensified, not only because PI3K-activating mutations are found in 36% of human breast cancers (CGA Network, 2012), but also based on data coming from preclinical studies. They demonstrated the association between activation of the PI3 K/AKT/mTOR pathway and endocrine resistance (Clark et al., 2002; Miller et al., 2009), but sensitivity may be restored by treatment with mTOR inhibitors (deGraffenried et al., 2004).

In addition, estrogen deprivation increases apoptosis following PI3 K inhibitor treatment, providing a rationale for combined therapy in HR+ disease (Sanchez et al., 2011).

Moreover, in models of estrogen-responsive BC, subnanomolar everolimus concentrations reduced the growth of BC cells *in vitro*, and enhanced antitumor activities were observed in combination with the AI, letrozole (Boulay et al., 2005).

Clinical statement to the value of co-targeting ERand the PI3 K/AKT/mTOR pathway comes from several key trials.

In the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2), a randomizedphase III study of 724 postmenopausal women with HR+, HER2-negative metastatic breast cancer, progressed on therapy with a nonsteroidal AI, combination therapy with exemestane and the mTOR inhibitor everolimus resulted in a significantly longer PFS (7.8 versus 3.2 months) and higher response rate than the single agent exemestane (Baselga et al., 2012; Piccart-Gebhart et al., 2012).

In the Tamoxifen and RAD001 (TAMRAD) study, a smaller randomized phase II trial in a similar patient population, patients receiving the combination of tamoxifen and everolimus had higher clinical benefit rate (61%) and longer TTP (8.6 months) than the group receiving tamoxifen alone (42% and 4.5months). In that study, patients with secondary resistance to AIseemed to benefit more from the combination than patients withprimary resistance, supporting the concept that cross-talk betweenpathways and the sequential upregulation of the PI3 K/mTOR signaling is a mechanism of resistance (Bachelot et al., 2012).

It is worth of note that these benefits were not without toxicity. In both studies combined everolimus/endocrine therapy had

substantially higher stomatitis (56%), rash (36% to 44%), fatigue (33% to 72%), diarrhea (30% to 39%), and anorexia (29% to43%) than single-agent endocrine therapy.

The third study evaluating the combination, the HORIZON trial,found no benefit in PFS associated with the addition of the mTORinhibitor (temsirolimus) to AI therapy (letrozole). Indeed, the trial was stopped for futility by the independentdata monitoring committee. Response rate and OS were also similar between groups (Wolff et al., 2013).

One key difference between these studies is that the patient population in the HORIZON study was largely AI-naive and temsirolimus/letrozole was the first endocrine treatment for metastatic disease. By contrast, patients in both BOLERO-2 and TAMRAD had AI-resistant disease. In BOLERO-2, 84% of patients had initially endocrine-sensitive disease and then progressed on an AI, so this population was essentially characterized by the same secondary resistance population that showed the greatest benefit in TAMRAD.

Based on these differences, it seems that the mTOR inhibitor benefit may be restricted to those with acquired AI resistance.

However, it is worth of note that the combination therapy has also marginallyoutperformed single-agent AI in the previously untreated neoadjuvant setting (Baselga et al., 2009).

In this phase II randomized trial of 270postmenopausal women, those that who received 4 months of preoperative therapy with letrozole and everolimus had a clinical response rate of 68% compared with 59% in those receiving letrozole alone, suggesting that cotargeting both ER and mTOR circumvents de novo endocrine resistance,or at least increases effectiveness of initial ER-targeting, in some untreated tumors.

Tumor biologic differences could also play a role in the differentialbenefit seen in these trials. In this neoadjuvant trial of everolimus plus AI, Boulay et al., 2005 found that patients whose tumors had activating mutations in exon 9 of PIK3CA showed strong anti proliferative response (Ki67) to mTOR/AI combination therapy but poor responseto AI alone.

There is a substantial variability in PIK3CA mutation rates across molecularsubtypes, with 45% in the luminal A compared with only 29% in theluminal B subsets (Margariti et al., 2011). Neither BOLERO-2 nor the HORIZON trial included intrinsic subtyping or other correlative biomarker data, and, in the absence of biomarker data, there could be unknown cross-trial differences in the proportion of tumors with PTEN loss, PI3 K activating mutation, or other pathway aberrancy. Retrospective analysis results presented by Gabriel N. Hortobagyi in the 2013 ASCO Meeting suggest no predictive marker of everolimus efficacy. Everolimus benefit maintained in patients regardless of gene alterations in PI3KCA and PI3 K pathway genes (Hortobagyi et al., 2013). This analysis suggests that PI3 K pathway itself or PI3KCA status alone is not a biomarker of the efficacy of everolimus. This benefit was slightly less pronounced in patients with FGFR1/2 alterations. These observations suggest that a large subgroup of patients (76%), defined by minimal genetic variations in the PI3 K or FGFR pathways, or CCND1, derives the most benefit from everolimus therapy (HR = 0.27 versus 0.40 for the full next-generation sequencing population).

These observations appear inconclusive and predictive biomarkers for targeting the PI3 K/mTOR pathway are still a work in progress (Juric and Baselga, 2012).

It is unlikely that we will find a single approach that incontrovertibly reverses endocrine resistance across all populations, and different strategies to combat endocrine therapy resistance have failed to yield consistent results. For example, among several trials of epidermal growth factor receptor inhibition combined with endocrine therapy, some have demonstrated PFS benefit from the combinationin patients who had not received prior endocrine therapy (Johnston, 2009b) while trials in more heavily pretreated patients have not confirmed this benefit (Osborne and Schiff, 2011).

So, the addition of mTOR inhibitors resulted positive in pretreated HR+ metastatic breast cancer, but no gain with the combination in the first line treatment.

Above all "acquired resistant" population has the most to gain, as current PFS with further endocrine therapies after first line setting range from 3–4 months, and, properly in this setting, combinations with agents that overcome resistance can improve the outcomes of patients (Baselga et al., 2012; Piccart-Gebhart et al., 2012).

5. Algorithm for management of post-menopausal HR+ metastatic breast cancer

While hormone-unresponsive or life-threatening disease requires chemotherapy, no life-threatening disease HR + metastatic BC patients are candidate to first line endocrine therapy.

Sites and extent of disease, related symptoms, ER levels and HER2 status, disease-free and treatment-free intervals, performance status and patient wishes are key factors in first line treatment choice (Fig. 2).

To date, a non-steroidal AI is the standard choice for first-line treatment in de novo metastatic HR+ breast cancer, in patients who did not receive prior adjuvant hormonal therapy, in whom that progressed on adjuvant tamoxifen or >1 disease-free interval post-adjuvant tamoxifen. Selected previously untreated metastatic breast cancer patients could benefit from a combined endocrine therapy with fulvestrant plus AI, above all if entirely endocrine therapy-naive, even in the adjuvant setting (Mehta et al., 2012).

It worth of note that primarily endocrine therapy-naive metastatic BC patients are not a typical contemporary metastatic population. Actually, the great majority of patients with HR+ metastatic BC received endocrine therapy in the adjuvant setting. Tamoxifen is the mainstay in the treatment of premenopausal women. On the other hand in post-menopausal women third-generation AIs resulted superior to tamoxifen in large adjuvant trials. Main studies evaluated 5 years of AI versus tamoxifen for 5 years (up-front strategy) or 2–3 year of AIs after 3–2 years of tamoxifen (early switch) (Forbes et al., 2008; Jonat et al., 2006; Coates et al., 2007; van de Velde et al., 2011; Coombes et al., 2004).

Being non-steroidal AIs widely used in the adjuvant setting, the choice of different endocrine agents for first-line advanced disease has to be considered (Table 1).

Since the results at a long-term follow-up, fulvestrant has to be considered a valid therapeutic option in first line setting.

The FIRST trialdemonstrated a reduction in the risk of progression and death with fulvestrant 500 mg versus anastrozole 1 mg (hazard ratio = 0.626; P = 0.0496) (Robertson et al., 2010; Robertson, 2014). Again, in the CONFIRM trial fulvestrant 500 mg was demonstrated to be superior to fulvestrant 250 mg in terms of TTP and OS (Di Leo et al., 2010, 2012). It is worth of note that all patients had received a previous endocrine therapy and the study included patients relapsing during adjuvant treatment,with a < or >12 month disease free interval post-adjuvant AI therapy, or progressing after first line endocrine therapy for "de novo" advanced disease. Approximately half of the patients had received prior AI and half prior tamoxifen. Therefore fulvestrant 500 mg would appear to have convincing data in the post-adjuvant AI setting and it could be recommended in first line setting for patients that relapse on adjuvant endocrine AI either after a disease-free interval post-adjuvant AI. CONFIRM trial also supports the use of fulvestrant as second line treatment for metastatic HR+ patients who progress during first line AI therapy.

The use of mTOR inhibitors associated with endocrine therapy could be a valid option but studies that evaluated these combinations reported conflicting data (Wolff et al., 2013; Baselga et al., 2012; Piccart-Gebhart et al., 2012; Bachelot et al., 2012).These

	In favour of chemotherapy	*Uncertain*	*In favour of endocrine therapy*
Disease-free interval	On treatment or <1yr	1-2 yrs	>2 yrs
Visceral Metastases	Massive burden (visceral crisis)	Moderate burden	Minimal burden
Symptoms	Heavy	Moderate	Minimal or absent

Fig. 2. Current Criteria used to support First Line treatment choices in HR+ Metastatic Breast Cancer.

Table 1
Treatment algorithm of endocrine therapy in metastatic breast cancer based on phase III data, phase II data or *treatment option but not supported by randomized, controlled, data.*

Prior treatment	First line	Second line	Third line
De novo/no prior adjuvant endocrine therapy	AI (anastrozole or letrozole)(Nabholtz et al., 2000, 2003; Bonneterre et al., 2000; Mouridsen et al., 2003) or Anastrozole + fulvestrant[a] (Mehta et al., 2012)	Fulvestrant 500 MG (Di Leo et al., 2010, 2012; Robertson et al., 2009, 2010; Robertson, 2014) or exemestane + everolimus (Baselga et al., 2012; Piccart-Gebhart et al., 2012) or AI (anastrozole or letrozole)(Buzdar et al., 1997, 1998, 2001; Jonat et al., 1996; Dombernowsky et al., 1998)	Exemestane + everolimus (Baselga et al., 2012; Piccart-Gebhart et al., 2012) or AI (Anastrozole or Letrozole) (Buzdar et al., 1997, 1998, 2001; Jonat et al., 1996; Dombernowsky et al., 1998) or Fulvestrant 500 mg (Robertson et al., 2003, 2004)
Recurrence on adjuvant tamoxifen or >1 disease-free interval post-adjuvant tamoxifen	AI (anastrozole or letrozole)(Nabholtz et al., 2000, 2003; Bonneterre et al., 2000; Mouridsen et al., 2003) or Fulvestrant 500 MG (Di Leo et al., 2010, 2012)	Fulvestrant 500 MG (Di Leo et al., 2010, 2012) or exemestane + everolimus (Baselga et al., 2012) or AI (anastrozole or letrozole) (Buzdar et al., 1997, 1998, 2001; Jonat et al., 1996; Dombernowsky et al., 1998)	AI (Anastrozole or Letrozole or Exemestane) (Buzdar et al., 1997, 1998, 2001; Jonat et al., 1996; Dombernowsky et al., 1998; Kaufmann et al., 2000) or Fulvestrant 500 mg (Robertson et al., 2003, 2004)
Prior non-steroidal AI therapy with >1 year disease-free interval post-adjuvant AI	Fulvestrant 500 MG (Di Leo et al., 2010, 2012; Robertson et al., 2010) or Exemestane + everolimus (Baselga et al., 2012; Piccart-Gebhart et al., 2012)	Exemestane + everolimus (Baselga et al., 2012) or Fulvestrant (Robertson et al., 2003; Di Leo et al., 2010, 2012)	Tamoxifen or Different AI
Recurrence on adjuvant AI	Exemestane + everolimus (Baselga et al., 2012; Piccart-Gebhart et al., 2012) or Fulvestrant 500 MG (Di Leo et al., 2010, 2012)	Fulvestrant 500 MG (Robertson et al., 2003; Di Leo et al., 2010, 2012) or Exemestane + everolimus (Baselga et al., 2012; Piccart-Gebhart et al., 2012)	Tamoxifen or Different AI

Abbreviations: AI, aromatase inhibitor, CT: chemotherapy

[a] It may be that patients unexposed to prior endocrine therapy with highly endocrine-sensitive tumors could derive the largest benefit from the combination of an AI + Fulvestrant. However considering the contradictory results of the SWOG[50] and the FACT[51] trials, it seems appropriate to wait for further evidence before considering this combination as "a standard of care".

studies, as previously reported, evaluated patients in different treatment settings, and one key difference is that the patient population in the HORIZON study was largely AI-naive and the addition of the mTOR inhibitor (temsirolimus) to AI therapy (letrozole), as first line endocrine treatment for metastatic disease, determined no benefit in PFS.Indeed, the trial was stopped for futility by the independent data monitoring committee. By contrast, patients in both BOLERO-2 and TAMRAD presented AI-resistant disease. In BOLERO-2, 84% of patients had initially endocrine-sensitive disease and then progressed on an AI, so this population was essentially characterized by the same secondary resistance population that showed the greatest benefit in TAMRAD. Above all, in the BOLERO-2 trial 16% of patients in both arms had received fulvestrant before exemestane ± everolimus and these patients benefitted from the combination. On the other hand no data support the reverse sequence.

Based on these differences, it seems that the benefit from the addition of mTOR inhibitor may be restricted to patients with

acquired AI resistance. Moreover these benefits were not without toxicity. In both studies combined everolimus/endocrine therapy had substantially higher stomatitis (56%), rash (36% to 44%), fatigue (33% to 72%), diarrhea (30% to 39%), and anorexia (29% to 43%) than single-agent endocrine therapy.

Interesting data in first line setting derive from the combination of letrozole plus PD 0332991 (Finn et al., 2012) (see par.1.2), but these data need to be confirmed by the ongoing phase III trial.

To date, during first several lines of treatment in the metastatic setting patients could develop acquired resistance to endocrine therapy, and it constitutes an important clinical problem. In this context, different strategies could overcome the acquired resistance.

It is unlikely that a single approach could incontrovertibly reverse endocrine resistance across all population. So, properly planning an algorithm that includes all the available approaches allows the most useful long-term strategy.

6. Maintenance endocrine therapy: which evidence?

The use of endocrine therapy is well established inpatients with hormone-dependent metastatic breast cancer. The role of maintenance endocrine therapy in controlling the regrowth of hormone-dependent clones after maximum cytoreduction with chemotherapy is an interesting issue, even though, in literature, data focused on this strategy are rare. Only one prospective randomized study published by Kloke et al. in 1999 is available. In this phase-III trial, 90 patients with a disease controlled after 6 cycles of anthracyclin- and ifosfamide-containing regimen were randomized to receive or not maintenance therapy by medroxyprogesterone acetate. A longer median TTP was reported among patients who were treated by maintenance hormone therapy (4.9 versus 3.7 months; $p = 0.02$). However the small sample size, the inclusion of receptor-negative patients, and the use of an older generation endocrine compound limit the interpretation of this trial.

Two retrospective studies found hormonal maintenance therapy as a significant factor among several prognostic factors for PFS and OS after first line chemotherapy. In 1997, Berruti et al., analysed factors influencing ORR and OS among 207 patients treated by epirubicin, followed or not by maintenance hormone therapy. Patients who received maintenance endocrine therapy survived significantly longer than those submitted to observation, in both uni- and multivariate analysis. The author concluded that "the positive impact of maintenance hormonal therapy is impressive and deserves confirmation in randomized studies".

Montemurro et al., 2002 studied 109 consecutive patients with ER and/or PgR-positive metastatic breast cancer, receiving high-dose chemotherapy with hematopoietic progenitor cell transplant (HDCT), who were progression free for at least 4 months after HDCT with cyclophosphamide, carmustine and thiotepa, and analysed the factors which improve its efficacy. Of these, 55 were non-randomly submitted to maintenance endocrine therapy. This maintenance hormonal therapy appeared to be a significant factor in multivariate analysis, since that treatment improved the PFS from 19.2 to 31.1 months ($p = 0.022$). Maintenance endocrine therapy retained independent prognostic value in the multivariate model considering other important prognostic factors, like complete response (CR) to HDCT, disease extent and pattern of metastatic disease.

The largest retrospective study on this subject included 934 patients treated for metastatic breast cancer in 4 French cancer centres (Dufresne and Pivot et al., 2008). Hormonal treatment administered after response or stabilization with first-line chemotherapy seemed related to a better outcome with 7.8–16.3 months for the duration of PFS ($p < 0.0001$) and from 30 to 48.1 months for the overall duration of metastatic survival ($p < 0.0001$). Maintenance hormonal therapy was given alone after chemotherapy in 308 patients. Hormonal treatments included tamoxifen(94), aromatase inhibitors (153), fulvestrant (47) and megesterol acetate (14). The median duration of first line chemotherapy was 4.4 months (ranges: 3–9.7). Even the influence of the type of response achieved by first line chemotherapy is well established (Greenberg et al., 1996), strikingly, this study demonstrated that this benefit was observed independently of the type of response achieved by first line chemotherapy. The choice of patient/tumor characteristics for who would or would not receive the maintenance hormonal therapy was not random, or controlled in any way, and this may have led to a selection of better prognosis patients.

Nevertheless the major impact obtained by maintenance hormonal treatment after the first line chemotherapy might indicate that this strategy should be recommended in patients with an ER or PgR positive tumors.

Based on the amplitude of the benefit observed, it may be ethically debatable to conduct a prospective randomized study. Moreover, randomized trials which assess the benefit of a new chemotherapy regimen should allow the possibility to give maintenance hormonal treatment.

In conclusion no compelling evidence exists for maintenance endocrine therapy. However, given its low toxicity, maintenance endocrine therapy appears a reasonable option in endocrine responsive tumors responding to chemotherapy.

7. Conclusions

To date, endocrine therapy is the mainstay of hormone responsive breast cancer treatment. It is based on different approaches and it does not appear the sequence of hormonal agents used alters overall survival. Also its widely recognized role in controlling the regrowth of hormone-sensitive clones after maximum cytoreduction with chemotherapy is an interesting issue, even though, in literature, data focused on this strategy are rare. It is worth of note that some patients, despite HR+ status, could be either primarily resistant to hormone therapies or will develop hormone resistance during the course of their disease. The recent availability of the combination of everolimus and exemestane is a significant and important advance in patients with acquired endocrine resistance but we need to better predict and manage toxicities.

Authors' disclosures of potential conflicts of interest

The following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Employment or Leadership Position: None. SaverioCinieri: partecipation in speakers' bureau yes. Angelo Di Leo: Grant Support from AstraZeneca, Pfizer; Honoraria from AstraZeneca, Novartis, Roche, Pfizer, Eisai, Genomic Health; Advisory boards AstraZeneca, Novartis, Roche, Pfizer, Bayer, Lilly. Michelino De Laurentiis: Honoraria from AstraZeneca, Novartis, TakedaIpsen. Paolo Marchetti: Grant Support from AstraZeneca, Novartis, Roche, Bristol Myers Squibb, GlaxoSmithKline. Other Remuneration: None.

Other authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Author contributions

Manuscript writing: All authors.
Final approval of manuscript: All authors.

Funding

No funds were requested from any pharmaceutical firms or other industries/institutions. Valentina Sini was financed through the PhD University Grant program "Clinical and Experimental Research Methodologies in Oncology" provided by the Faculty of Medicine and Psychology, "Sapienza" University of Rome.

Acknowledgement

Valentina Sini was financed through the PhD University Grant program "Clinical and Experimental Research Methodologies in Oncology" provided by the Faculty of Medicine and Psychology, "Sapienza" University of Rome.

References

Allegra, J.C., Bertino, J., Bonomi, P., et al., 1985. Metastatic breast cancer: preliminary results with oral hormonal therapy. Semin. Oncol. 12, 61–64.

Bachelot, T., Bourgier, C., Cropet, C., et al., 2012. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptorpositive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. J. Clin. Oncol. 30, 2718–2724.

Baselga, J., Semiglazov, V., van Dam, P., et al., 2009. Phase II randomized study of neoadjuvanteverolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. J. Clin. Oncol. 27, 2630–2637.

Baselga, J., Campone, M., Piccart, M., et al., 2012. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N. Engl. J. Med. 366, 520–529.

Bedard, P.L., Freedman, O.C., Howell, A., Clemons, M., 2008. Overcoming endocrine resistance in breast cancer—are signal transduction inhibitors the answer. Breast Cancer Res. Treat. 108, 307–317.

Bergh, J., Jonsson, P.E., Lidbrink, E.K., et al., 2012. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. J. Clin. Oncol. 30, 1919–1925.

Berruti, A., Zola, P., Buniva, T., et al., 1997. Prognostic factors in metastatic breast cancer patients obtaining objective response or disease stabilization after first-line chemotherapy with epirubicin. Evidence for a positive effect of maintenance hormonal therapy on overall survival. Anticancer Res. 17 (4A), 2763–2768.

Bonneterre, J., Thurlimann, B., Robertson, J.F., et al., 2000. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J. Clin. Oncol. 18, 3748–3757.

Boulay, A., Rudloff, J., Ye, J., et al., 2005. Dual inhibition of mTOR and estrogen receptor signaling in vitro induces cell death in models of breast cancer. Clin. Cancer Res. 11, 5319–5328.

Burstein, H.J., Barry, W.T., Cirrincione, C., et al., 2010. Fulvestrant with or without lapatinib as therapy for hormone receptor positive advanced breast cancer: a double-blinded, placebo-controlled, randomized phase III study. Cancer Res. 70 (24 Suppl) (Abstract PD05-01).

Buzdar, A.U., Jones, S.E., Vogel, C.L., et al., 1997. A phase III trial comparing anastrozole (1 and 10 milligrams), a potent and selective aromatase inhibitor, with megestrolacetate in postmenopausal women with advanced breast carcinoma. Arimidex Study Group. Cancer 79, 730–739.

Buzdar, A.U., Jonat, W., Howell, A., et al., 1998. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on a combined analysis of data from two mature phase III trials. Arimidex Study Group. Cancer 83, 1142–1152.

Buzdar, A., Douma, J., Davidson, N., et al., 2001. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. J. Clin. Oncol. 19, 3357–3366.

Buzdar, A., Hayes, D., El-Khoudary, A., et al., 2002. Phase III randomized trial of droloxifeneandtamoxifen as first-line endocrine treatment of ER/PgR-positive advanced breast cancer. Breast Cancer Res. Treat. 73, 161–175.

CGA Network, 2012. Comprehensive molecular portraits of human breast tumours. Nature 490, 61–70.

Cardoso, F., Costa, A., Norton, L., et al., 2012a. 1st International consensus guidelines for advanced breast cancer (ABC 1). Breast 21 (June (3)), 242–252.

Cardoso, F., Harbeck, N., Fallowfield, L., Kyriakides, S., Senkus, E., ESMO Guidelines Working Group, 2012b. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 23 (Suppl. 7), 11–19.

Chia, S., Gradishar, W., Mauriac, L., et al., 2008. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior non steroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J. Clin. Oncol. 26, 1664–1670.

Clark, A.S., West, K., Streicher, S., et al., 2002. Constitutive and inducible Akt activity promotes resistance to chemotherapy, trastuzumab, or tamoxifen in breast cancer cells. Mol. Cancer Ther. 1, 707–717.

Coates, A.S., Keshaviah, A., Thurlimann, B., et al., 2007. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J. Clin. Oncol 25, 486–492.

Coombes, R.C., Hall, E., Gibson, L.J., et al., 2004. Intergroup Exemestane Study: a randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N. Engl. J. Med. 350 (11), 1081–1092.

Cristofanilli, M., Valero, V., Mangalik, A., et al., 2010. Phase II, randomized trial to compare anastrozole combined with gefitinib or placebo in postmenopausal women with hormone receptor-positive metastatic breast cancer. Clin. Cancer Res. 16, 1904–1914.

Dawood, S., Cristofanilli, M., 2007. Endocrine resistance in breast cancer: what really matters. Ann. Oncol. 18, 1289–1291.

deGraffenried, L.A., Friedrichs, W.E., Russell, D.H., et al., 2004. Inhibition of mTOR activity restores tamoxifen response in breast cancer cells with aberrant Akt activity. Clin. Cancer Res. (10:8059-8067).

Deshmane, V., Krishnamurthy, S., Melemed, A.S., et al., 2007. Phase III double-blind trial of arzoxifene compared with tamoxifen for locally advanced or metastatic breast cancer. J. Clin. Oncol. 25, 4967–4973.

Di Leo, A., Jerusalem, G., Petruzelka, L., et al., 2010. Results of the CONFIRM phase III trial comparing fulvestrant 250mg with fulvestrant 500mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. J. Clin. Oncol. 28, 4594–4600.

Di Leo, A., Jerusalem, G., Petruzelka, L., et al., 2012. Final analysis of overall survival for the Phase III confirm trial: fulvestrant 500 mg versus 250 mg. San Antonio Breast Cancer Symposium, S1–S4.

Dombernowsky, P., Smith, I., Falkson, G., et al., 1998. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrolacetate. J. Clin. Oncol. 16, 453–461.

Dufresne, A., Pivot, X., et al., 2008. Maintenance hormonal treatment improves progression free survival after a first line chemotherapy in patients withMetastatic breast cancer. Int. J. Med. Sci. 5, 100–105.

Finn, R., et al., 2009. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Cancer Res. 11, 1–13.

Finn, R.S., Crown, J.P., Lang, I., et al., 2012. Results of a randomized phase 2 study of PD 0332991, a cyclin-dependent kinase (CDK) 4/6 inhibitor, in combination with letrozole vs letrozole alone for first-line treatment of ER+/HE?advanced breast cancer (BC). Cancer Res. 72 (December (24)), Supplement 3; SABCS12-S1-6.

Finn, R.S. Results of a randomized phase 2 study of PD 0332991, a cyclin-dependent kinase (CDK) 4/6 inhibitor, in combination with letrozole vsletrozole alone for first-line treatment of ER+, HER2- advanced breast cancer (TRIO-18) Presenter. 4th IMPAKT Breast Cancer Conference. May 3–5, 2012.

Forbes, J.F., Cuzick, J., Buzdar, A., et al., 2008. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol. 9, 45–53.

Forero-Torres, A., Saleh, M.N., Galleshaw, J.A., et al., 2010. Pilot trial of preoperative (neoadjuvant) letrozole in combination with bevacizumab in postmenopausal women with newly diagnosed estrogen receptor- or progesterone receptor-positive breast cancer. Clin. Breast Cancer 10 (4), 275–280.

Fossati, R., Confalonieri, C., Torri, V., et al., 1998. Cytotoxic and hormonal treatment formetastatic breast cancer: a systematic review of published randomized trials involving 31,510 women. J. Clin. Oncol. 16, 3439–3460.

Gill, P.G., Gebski, V., Snyder, R., et al., 1993. Randomized comparison of the effects of tamoxifen, megestrol acetate, or tamoxifenplusmegestrol acetate on treatment response and survival in patients with metastatic breast cancer. Ann. Oncol. 4, 741–744.

Greenberg, P.A., Hortobagyi, G.N., Smith, T.L., et al., 1996. Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. J. Clin. Oncol. 14 (8), 2197–2205.

Gutierrez, M.C., Detre, S., Johnston, S., Mohsin, S.K., Shou, J., Allred, D.C., Schiff, R., Osborne, C.K., Dowsett, M., 2005. Molecular changes in tamoxifenresistant breast cancer: relationship between estrogen receptor, HER-2, and p38 mitogen-activated protein kinase. J. Clin. Oncol. 23, 2469–2476.

Herynk, M.H., Fuqua, S.A., 2004. Estrogen receptor mutations in human disease. Endocr. Rev. 25, 869–898.

Hortobagyi, Gabriel N., Piccart-Gebhart Martine, J., RugoHope, S., et al., 2013. Correlation of molecular alterations with efficacy of everolimus in hormone receptor–positive, HER2-negative advanced breast cancer: results from BOLERO-2. J. Clin. Oncol. 31 (suppl; abstr LBA509).

Hu, X.F., Veroni, M., De Luise, M., Wakeling, A., Sutherland, R., Watts, C.K., Zalcberg, J.R., 1993. Circumvention of tamoxifen resistance by the pure anti-estrogen ICI 182. Int. J. Cancer 55, 873–876.

Huober, J., Fasching, P.A., Barsoum, M., et al., 2012. Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer – results of the eLEcTRA trial. Breast 21, 27–33.

Ingle, J.N., Ahmann, D.L., Green, S.J., et al., 1982. Randomized clinical trial of megestrolacetate versus tamoxifen in paramenopausal or castrated women with advanced breast cancer. Am. J. Clin. Oncol. 5, 155–160.

Ingle, J.N., Green, S.J., Ahmann, D.L., et al., 1986. Randomized trial of tamoxifen alone or combined with aminoglutethimide and hydrocortisone in women with metastatic breast cancer. J. Clin. Oncol. 4, 958–964.
Johnston, S.R., Martin, L.A., Head, J., et al., 2005. Aromatase inhibitors: Combinations with fulvestrant or signal transduction inhibitors as a strategy to overcome endocrine resistance. J. Steroid Biochem. Mol. Biol. 95, 173–181.
Johnston, S., Pippen Jr., J., Pivot, X., Lichinitser, M., Sadeghi, S., Dieras, V., Gomez, H.L., Romieu, G., Manikhas, A., Kennedy, M.J., Press, M.F., Maltzman, J., Florance, A., O'Rourke, L., Oliva, C., Stein, S., Pegram, M., 2009. Lapatinib Combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. J. Clin. Oncol. 27, 5538–5546.
Johnston, S.R., 2001. Endocrine manipulation in advanced breast cancer: recent advances with SERM therapies. Clin. Cancer Res. 7, 4376–4387.
Johnston, S.R., 2009a. Enhancing the efficacy of hormonal agents with selected targeted agents. Clin. Breast Cancer 9, S28–S36.
Johnston, S.R., 2009b. Enhancing the efficacy of hormonal agents with selected targeted agents. Clin. Breast Cancer 9 (Suppl. 1), S28–S36.
Johnston, S.R.D., 2010. New strategies in estrogen receptor–positive breast cancer. Clin. Cancer Res. 16, 1979–1987.
Jonat, W., Howell, A., Blomqvist, C., et al., 1996. A randomised trial comparing two doses of the new selective aromatase inhibitor anastrozole (Arimidex) withmegestrolacetate in postmenopausal patients with advanced breast cancer. Eur. J. Cancer 32A, 404–412.
Jonat, W., Gnant, M., Boccardo, F., et al., 2006. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. Lancet Oncol. 7, 991–996.
Juric, D., Baselga, J., 2012. Tumor genetic testing for patient selection in phase I clinical trials: the case of PI3K inhibitors. J. Clin. Oncol. 30, 765–766.
Kaufman, B., Mackey, J.R., Clemens, M.R., Bapsy, P.P., Vaid, A., Wardley, A., Tjulandin, S., Jahn, M., Lehle, M., Feyereislova, A., Révil, C., Jones, A., 2009. Trastuzumab plus anastrozole versus anastrozolealone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor- positive metastatic breast cancer: results from the randomized phase III TAnDEM study. J. Clin. Oncol. 27, 5529–5537.
Kaufmann, M., Bajetta, E., Dirix, L.Y., et al., 2000. Exemestane is superior to megestrolacetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. The Exemestane Study Group. J. Clin. Oncol. 18, 1399–1411.
Kloke, O., Klaassen, U., Oberhoff, C., et al., 1999. Maintenance treatment with medroxyprogesterone acetate in patients with advanced breast cancer responding to chemotherapy: results of a randomized trial. Essen Breast Cancer Study Group. Breast Cancer Res. Treat. 55, 51–59.
Kuter, I., Hegg, R., Singer, C.F., et al., 2007. Fulvestrant 500mg vs 250mg: first results from NEWEST, a randomized, phase II neoadjuvant trial in postmenopausal women with locally advanced, estrogen receptor-positive breast cancer. Breast Cancer Res. Treat. 106, 23.
la Haba de, J., Berciano, M., Cañabate, M., et al., 2011. Combined antiangiogenic and anti-estrogen therapy in breast cancer. Molecular mechanisms involved. Cancer Res. 71 (24 Suppl) (Abstract nr P2-05-07).
Linderholm, B.K., Hellborg, H., Johansson, U., et al., 2011. Vascular endothelial growth factor receptor 2 and downstream p38 mitogen-activated protein kinase are possible candidate markers of intrinsic resistance to adjuvant endocrine treatment in steroid receptor positive breast cancer. Breast Cancer Res. Treat. 125, 457–465.
Lipton, A., Harvey, H.A., Santen, R.J., et al., 1982. A randomized trial of aminoglutethimideversustamoxifen in metastatic breast cancer. Cancer 50, 2265–2268.
Lykkesfeldt, A.E., Madsen, M.W., Briand, P., 1994. Altered expression of estrogen-regulated genes in a tamoxifen-resistant and ICI 164,384 and ICI 182,780 sensitive human breast cancer cell line, MCF-7/TAMR-1. Cancer Res. 54, 1587–1595.
Manders, P., Beex, L.V., Tjan-Heijnen, V.C., et al., 2003. Vascular endothelial growth factor is associated with the efficacy of endocrine therapy in patients with advanced breast carcinoma. Cancer 98 (10), 2125–2132.
Margariti, N., Fox, S.B., Bottini, A., Generali, D., 2011. Overcoming breast cancer drug resistance with mTOR inhibitors. Could it be a myth or a real possibility in the short-term future? Breast Cancer Res. Treat. 128, 599–606.
Martin, M., et al., 2012. Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer—first efficacy results from the LEA study. SABCS (Abstract S1-7).
Mehta, R.S., Barlow, W.E., Albain, K.S., et al., 2012. Combination anastrozole and fulvestrant in metastatic breast cancer. N. Engl. J. Med. 367, 435–444.
Miller, T., Fox, E., Gonzalez-Angulo, A., et al., 2009. Resistance to endocrine therapy in estrogen receptor-positive (ER+) breast cancer is dependent upon phosphatidylinositol-3 kinase (PI3K) signaling. Cancer Res. 69 (24 Suppl).
Montemurro, F., Rondoín, G., Ueno, N.T., et al., 2002. Factors affecting progression-free survival in hormone-dependent metastatic breast cancer patients receiving high-dose chemotherapy and hematopoietic progenitor cell transplantation: role of maintenance endocrine therapy. Bone Marrow Transplant. 29, 861–866.
Morgan, L.R., 1985. Megestrol acetate v tamoxifen in advanced breast cancer in postmenopausal patients. Semin. Oncol. 12, 43–47.
Mouridsen, H., Gershanovich, M., Sun, Y., et al., 2003. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J. Clin. Oncol. 21, 2101–2109.
Moy, B., Goss, P.E., 2006. Estrogen receptor pathway: resistance to endocrine therapy and new therapeutic approaches. Clin. Cancer Res. 12, 4790–4793.
Musgrove, E.A., Sutherland, R.L., 2009. Biological determinants of endocrine resistance in breast cancer. Nat. Rev. Cancer 9, 631–643.
Muss, H.B., Wells, H.B., Paschold, E.H., et al., 1988. Megestrol acetate versus tamoxifen in advanced breast cancer: 5-year analysis—a phase III trial of the Piedmont Oncology Association. J. Clin. Oncol. 6, 1098–1106.
NCCN, 2015. Clinical Practice Guidelines in Oncology version 1.
Nabholtz, J.M., Buzdar, A., Pollak, M., et al., 2000. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. J. Clin. Oncol. 18, 3758–3767.
Nabholtz, J.M., Bonneterre, J., Buzdar, A., et al., 2003. Anastrozole (Arimidex) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results. Eur. J. Cancer 39, 1684–1689.
Turner, Nicholas C., Ro, Jungsil, Andre, Fabrice, et al., 2015. PALOMA3: a double-blind, phase III trial of fulvestrant with or without palbociclib in pre- and post-menopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer that progressed on prior endocrine therapy. J. Clin. Oncol. 33 (suppl; abstr LBA502).
Osborne, C.K., Schiff, R., 2011. Mechanisms of endocrine resistance in breast cancer. Annu. Rev. Med. 62, 233–247.
Osborne, K., Neven, P., Dirix, L., et al., Randomized Phase II study of gefitinib (IRESSA) or placebo in combination with tamoxifen in patients with hormone receptor positive metastatic breast cancer. CTRC-AACR 2007. San Antonio Breast Cancer Symposium, 13–16 December 2007, Poster 2067.
Paridaens, R.J., Dirix, L.Y., Beex, L.V., et al., 2008. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. J. Clin. Oncol. 26, 4883–4890.
Paterson, A.H., Hanson, J., Pritchard, K.I., et al., 1990. Comparison of antiestrogen and progestogen therapy for initial treatment and consequences of their combination for second-line treatment of recurrent breast cancer. Semin. Oncol. 17, 52–62.
Piccart-Gebhart, M.J., Noguchi, S., Pritchard, K.I., et al., 2012. Everolimus for postmenopausal women with advanced breast cancer: updated results of Bolero-2 phase III trial. J. Clin. Oncol. 30 (21s) (suppl; abstr 559).
Pyrhonen, S., Ellmen, J., Vuorinen, J., et al., 1999. Meta-analysis of trials comparing toremifene with tamoxifen and factors predicting outcome of antiestrogentherapy in postmenopausal women with breast cancer. Breast Cancer Res. Treat. 56, 133–143.
Robertson, J.F., Osborne, C.K., Howell, A., et al., 2003. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials. Cancer 98, 229–238.
Robertson, J.F., Erikstein, B., Osborne, K.C., et al., 2004. Pharmacokinetic profile of intramuscular fulvestrant in advanced breast cancer. Clin. Pharmacokinet. 43, 529–538.
Robertson, J.F., Semiglazov, V., Nemsadze, G., et al., 2007. Effects of fulvestrant 250mg in premenopausal women with oestrogenreceptor-positive primary breast cancer. Eur. J. Cancer 43, 64–70.
Robertson, J.F., Llombart-Cussac, A., Rolski, J., et al., 2009. Activity of fulvestrant 500mg versus anastrozole 1mg as first-line treatment for advanced breast cancer: results from the FIRST study. J. Clin. Oncol. 27, 4530–4535.
Robertson, J.F.R., Lindemann, J.P.O., Llombart-Cussac, A., et al., 2010. A comparison of fulvestrant 500mg with anastrozole as first-line treatment for advanced breast cancer: follow-up analysis from the FIRST study. Cancer Res. 70 (24 Suppl), 76s.
Robertson, 2014. Fulvestrant improves survival over anastrozole for patients with advanced breast cancer. San Antonio Breast Cancer Symposium (Abstract S6-04).
Rose, C., Kamby, C., Mouridsen, H.T., et al., 1986. Combined endocrine treatment of postmenopausal patients with advanced breast cancer. A randomized trial of tamoxifen vs. tamoxifen plus aminoglutethimide and hydrocortisone. Breast Cancer Res. Treat., S45–S50.
Rydén, Lisa, Jirström, Karin, Bendahl, Pär-Ola, et al., 2005. Tumor-specific expression of vascular endothelial growth factor receptor 2 but not vascular endothelial growth factor or human epidermal growth factor receptor 2 is associated with impaired response to adjuvant tamoxifen in premenopausal breast cancer. J. Clin. Oncol. 23, 4695–4704.
Sanchez, C.G., Ma, C.X., Crowder, R.J., et al., 2011. Preclinical modeling of combined phosphatidylinositol-3-kinase inhibition with endocrine therapy for estrogen receptor-positive breast cancer. Breast Cancer Res. 13, R21.
Smith, I.E., Harris, A.L., Morgan, M., et al., 1981. Tamoxifen versus aminoglutethimide in advanced breast carcinoma: a randomized cross-over trial. Br. Med. J. (Clin. Res. Ed.) 283, 1432–1434.
Smith, I.E., Walsh, G., Skene, A., et al., 2007. A phase II placebo-controlled trial of neoadjuvantanastrozole alone or with gefitinib in early breast cancer. J. Clin. Oncol. 25, 3816–3822.
Thoennissen, N.H., O'Kelly, J., Lu, D., et al., 2010. Capsaicin causes cell-cycle arrest and apoptosis in ER-positive and -negative breast cancer cells by modulating the EGFR/HER-2 pathway. Oncogene 29 (2), 285–296.

Traina, T.A., Rugo, H.S., Caravelli, J.F., et al., 2010. Feasibility trial of letrozole in combination with bevacizumab in patients with metastatic breast cancer. J. Clin. Oncol. 28, 628–633.
Wakeling, A.E., Dukes, M., Bowler, J., 1991. A potent specific pure antiestrogen with clinical potential. Cancer Res. 51, 3867–3873.
Wakeling, A.E., 2000. Similarities and distinctions in the mode of action of different classes of antioestrogens. Endocr. Relat. Cancer 7, 17–28.
Wang, C.X., Koay, D.C., Edwards, A., Lu, Z., Mor, G., Ocal, I.T., Digiovanna, M.P., 2005. In vitro and in vivo effects of combination of Trastuzumab (Herceptin) and Tamoxifen in breast cancer. Breast Cancer Res. Treat. 92, 251–263.
Wilcken, N., Hornbuckle, J., Ghersi, D., 2003. Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database Syst. Rev., Art. No.: CD002747. 10.1002/14651858. CD002747.
Wolff, A.C., Lazar, A.A., Bondarenko, I., et al., 2013. Randomized phase III placebo controlled trial of letrozole plus oral temsirolimus as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer. J. Clin. Oncol. 31, 195–202.
Zilli, M., Grassadonia, A., Tinari, N., Di Giacobbe, A., Gildetti, S., Giampietro, J., Natoli, C., Iacobelli, S., 2009. Molecular mechanisms of endocrine resistance and their implication in the therapy of breast cancer. Biochim. Biophys. Acta 1795, 62–81.
van de Velde, C.J., Rea, D., Seynaeve, C., et al., 2011. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. Lancet 377 (9762), 321–331.

Biographies

Valentina Sini (MD, PhDs) She received her Medical Degree in 2006 from Tor Vergata University of Rome, Italy. In 2011 she received her postgraduate diploma in Oncology from Tor Vergata University of Rome. Since 2011 she is PhDs in PhD University Grant program 'Clinical and Experimental Research Methodologies in Oncology', provided by the Faculty of Medicine and Psychology, Sapienza University of Rome. She is currently an assistant at the Onco-Haematology Unit, Oncology Department, ASLRME-Santo Spirito Hospital. She is a member of the American Society of Clinical Oncology, the European Society of Medical Oncology and Associazione Italiana di OncologiaMedica (AIOM). She is a member of steering committee 'ProgettoSpeciale AIOM Follow-up, fertilità e riabilitazione' and 'Cardio-Oncologia'. She authored/coauthored more than 10 papers published in peer-reviewed international journals and has lectured at national meetings. Current areas of research include new treatments of breast cancer, cardiac and endocrine-related toxicity of targeted and cytotoxicagents, optimization of endocrine therapy in breast cancer.

Saverio Cinieri (MD) He is currently Head of the Medical Oncology, UnitSan Antonio Perrino Hospital Brindisi and Director of Breast Unit ASL Brindisi, a position which he took up in 2007. After graduating in medicine and surgery at the University of Perugia in 1991, he received his postgraduate diploma in medical oncology from the University of Perugia in 1995.From 1997–2007, he worked at European Institute of Oncology, Milan. Dr Cinieri's main research interests focus on the diagnosis and treatment of solid tumors and hematological diseases. He is involved in ongoing clinical trials in solid tumors (particularly breast cancer), myelomas and lymphomas. DrCinieri is the author of many peer-reviewed articles and is journal reviewer for Annals of Oncology, British Journal of Cancer, American Journal of Clinical Oncology and Oncology, The Breast.

PierFranco Conte (MD, PhD) Chair of the Medical Oncology IstitutoOncologico Veneto IRCCS PadovaItaly, a position which he took up in February 2013. He is Director of Breast Unit and Oncology Department of Azienda Ospedaliera Padova - Istituto Oncologico Veneto IRCCS Padova. He graduated in medicine and surgery at the University of Torino in 1974, he received his postgraduate diploma in medical oncology from the University of Torino in 1977, postgraduate diploma in immunology in 1980 from the University of Milan and in hematology in 1984 from the University of Genoa and in 1978 received his PhD. He is the author of 320 peer-reviewed articles and has lectured extensively at national and international meetings. He is a member of the Associazione Italiana di Oncologia Medica, European Society of Medical Oncology, American Society of Clinical Oncology, Società Italiana di Cancerologia, Italian Society Basic & Applied Cell Kinetics, The Cell Kinetics Society, International Gynecologic Cancer Society, The New York Academy of Sciences, New England Cancer Society (Honorary Member).

Michelino De Laurentis (MD, PhD) He is currently Director of Breast Oncology Division National Cancer Institute Naples, Italy, a position which he took up in October 2010. After graduating in medicine and surgery at the University of Naples in 1989, he received his postgraduate diploma in medical oncology from the University of Naples in 1993, and his PhD Degree in Oncology in 2000 from the University Ğ. D'AnnunzioČhieti. He trained at the Ďederico IIÜniversity of Naples and in 2005 he became Assistant Professor, Dipartimento di Endocrinologia ed OncologiaMolecolare e Clinica at the same University. Dr De Laurentisis the author of many peer-reviewed articles.

Angelo Di Leo (MD, PhD) He is currently Head of the Sandro Pitigliani Medical Oncology Unit, and Chair of the Oncology Department, at the Hospital of Prato, Istituto ToscanoTumori, Italy, a position which he took up in September 2003. After graduating in medicine and surgery at the University of Palermo in 1988, he received his postgraduate diploma in medical oncology from the University of Pavia in 1992, and in 1996, received his European certification in medical oncology. Dr Di Leo trained at the National Cancer Institute in Milan, where he worked for 7 years until 1996. From 1996–2003, he worked at the Chemotherapy Unit of the Jules Bordet Institute in Brussels, where in 1997 he was appointed senior staff member and Medical Director of the Breast European Adjuvant Studies Team. Dr Di Leo's main research interest is breast cancer and he has coordinated a number of international, pivotal Phase III trials in new adjuvant therapies. He is also heavily involved in the evaluation of molecular markers with potential predictive value to treat breast cancer patients. Dr Di Leo is the author of many peer-reviewed articles and has lectured extensively at national and international meetings. He is a member of the Early Breast Cancer Trialists' Cooperative Group steering committee, a member of the Scientific Advisory Council of the Susan G. Komen for the Cure® and a member of the Breast International Group Executive Board. He has also served as a member of the American Society of Clinical Oncology grants selection committee (2006–2009) and of the ASCO Education Committee (2012–2014).

Carlo Tondini (MD) He is currently Chair of the Oncology Unit, Papa Giovanni XXIII Hospital of Bergamo, a position which he took up in June 2008. After graduating in medicine and surgery at the University of Milan in 1982, he received his postgraduate diploma in medical oncology (1985) and hematology (1996) from the University of Milan. Dr Tondini trained at the National Cancer Institute in Milan, where he worked until 1986. Obtained the certification of recognition of Degree in Medicine and Surgery in the United States, from 1986 to 1989, he worked at the Dana-Farber Cancer Institute, Harvard Medical School Boston (USA). From 1989–1999, he worked at the National Cancer Institute in Milan. From 1999–2008, Director of Ospedali Riuniti di Bergamo (today Ospedale Papa Giovanni XXIII) Breast Oncology and Prevention Division. Dr Tondini's main research interest is breast cancer and he has been involved in many international, pivotal Phase III trials. Dr Tondiniis the author of many peer-reviewed papers.

Paolo Marchetti (MD, PhD) He is currently Full Professor of Medical Oncology, Chief of Medical Oncology, Sant'Andrea Hospital, Rome, Director of Postgraduate Course in Oncology, Director of II Level Master in Psycho-oncology and Relationship with the Patient. Medical Consultant: IDI - IRCCS (recognized by the Italian Ministry of Health as a Scientific Institute carrying out biomedical research and clinical activities of relevant national interest), Rome, Italy. Prof. Marchetti is author of Principal areas of research: Alterations of hormone receptor status in hormone related tumors and their clinical implications on prognosis and therapy; chemoprevention of breast cancer; familial/hereditary breast cancer and BRCA1/2 mutations; clinical implications of the inactivation of tumor suppressor genes in solid tumors; innovative molecular scanning techniques for the detection of gene mutations; treatment of breast cancer, melanoma, lung, colorectal and gynacological cancers; palliative care in cancer patients. Professor Marchetti is the author of many peer-reviewed articles and has lectured extensively at national and international meetings.