Targeted Therapies Overcoming Endocrine Resistance in Hormone Receptor-Positive Breast Cancer

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Introduction

Breast cancer is a heterogeneous disease and the different treatment strategies depend primarily on the molecular subtype [1]. Approximately 70% of breast cancers express oestrogen receptor (ER) α and are endocrine responsive. However, the possibility of altered tumour characteristics with a switch of hormone receptor (HR) expression has to be considered [2]. Due to its high efficacy and favourable tolerability, endocrine therapy is the treatment of choice for patients with an advanced hormone receptor-positive tumour with the only exception of acute life threatening disease [3–5]. Over time, a large proportion of patients develop a primary/de novo resistance or secondary/acquired resistance. It is, therefore, important to understand the pathways and cross-talk involved to determine a way to overcome the resistance mechanisms. A large number of publications deal with the cross-talk between steroid receptors (ER and progesterone receptor (PR)) and growth factor receptors (e.g. epidermal growth factor receptor (EGFR)/human epidermal growth factor receptor (HER) [6], insulin-like growth factor receptor (IGFR) [7], and fibroblast growth factor receptor (FGFR) [8]) as well as the intracellular pathways (e.g. phosphatidylinositol 4,5-bisphosphate-3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signalling).

This review focuses on the intracellular PI3K/AKT/mTOR signalling pathway and cyclin-dependant kinases (CDKs) in oestrogen receptor (ER)-positive breast cancer. Study results clearly show that both inhibition of the PI3K/AKT/mTOR pathway and CDK4/6 are promising ways to improve the efficacy of endocrine treatment in ER-positive breast cancer patients with comparably few side effects. Further clinical trials are needed to identify the patient population who would benefit most from a dual inhibition.

HER2/EGFR

Patients with HER2-overexpressing breast cancer are less responsive to endocrine therapy. It was hypothesized that endocrine resistance is due to a cross-talk between HER and HR pathways. Therefore, HER signalling was one of the first pathways analysed, also in
HER-negative breast cancer. The HER family includes four tyrosine kinase receptors, HER1 (EGFR, ErbB1), HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4). The formation of homo- and heterodimers results in an activation of several downstream pathways such as the PI3K- or the mitogen-activated protein kinase (MAPK) pathway [9]. This dual blockade was examined in several clinical trials. The largest trial until now, a phase III study with 1,286 patients, compared daily letrozole (2.5 mg orally) plus lapatinib (1,500 mg orally) versus letrozole alone in patients with ER-positive metastatic breast cancer [10]. This trial showed a significantly enhanced progression-free survival (PFS; primary endpoint, 8.2 vs. 3.0 months, hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.53–0.96; p = 0.019) and response rate for patients with HER2-positive breast cancer. There was no benefit in PFS for HER2-negative tumours. The results of the TAnDEM-trail also demonstrated an advantage for co-targeting HER2 in endocrine-resistant breast cancer (median PFS 4.8 vs. 2.4 months, HR 0.63, 95% CI 0.47–0.84; p = 0.0016; centrally confirmed HR-positive tumours 5.6 vs. 3.8 months, p = 0.006) [11]. In this phase III study, 207 patients with HER2- and HR-positive metastatic breast cancer were randomised to anastrozole (1 mg/day orally) with or without trastuzumab (4 mg/kg intravenous infusion on day 1, then 2 mg/kg every week). However, in the CALGB 40302-study, no significant improvement for a dual inhibition was seen [12]. In this phase III study 295 patients with HR-positive advanced breast cancer, regardless of HER2 status, were randomised to fulvestrant (500 mg on day 1 followed by 250 mg on days 15 and 28 and then every 4 weeks) and either daily lapatinib (1,500 mg) or placebo (median PFS 4.7 vs. 3.8 months, HR 1.04, 95% CI 0.82–1.33, p = 0.37. Taken together, these results indicate that dual blockade of ER and HER2 has the potential to improve outcome in patients with advanced ER- and HER2-positive but not HER2-negative breast cancer patients.

**mTOR**

PI3K mutations are the most common alterations in ER-positive breast cancer cells [13] and an up-regulation of this pathway is frequently seen in long-term oestrogen-deprived breast cancer cells [14]. The PI3K/AKT/mTOR pathway has been well analysed in several cellular processes, including proliferation, apoptosis, angiogenesis and survival. The PI3K heterodimer, comprising a regulatory (p85) and a catalytic (p110) subunit, is regulated by different growth factor receptors, e.g. EGFR/HER, IGFR, FGFR (fig. 1). PIP2 (phosphatidylinositol 4,5-bisphosphate) is the catalytic product of the p110, which leads to a stimulation of the mTOR via phosphorylation/activation of protein kinase B/AKT (a serine/threonine kinase). mTOR is always present as a protein complex [15]. The mTORC 1 complex (fig. 1) is the target of rapamycin and rapamycin analogues, such as everolimus (inhibitor of the mTOR) or temsirolimus. In July 2012, the US Food and Drug Administration (FDA) [16] and the European Commission (EMA) approved everolimus for treating postmenopausal women with hormone receptor-positive/HER2-negative advanced breast cancer. The study that led to the approval was the BOLERO-2-trial, a phase III study that included 724 patients and compared everolimus (10 mg/day) plus exemestane (25 mg/day) to exemestane alone in postmenopausal women with advanced hormone receptor-positive breast cancer, whose cancer had either failed treatment with non-steroidal aromatase inhibitors in the metastatic disease or recurred in the adjuvant setting [17]. The results for the primary endpoint after a median follow-up of 18 months indicated that a co-inhibition of the compensatory pathway via everolimus led to a doubling of PFS (local assessment: 7.8 vs. 3.2 months, HR 0.45, 95% CI 0.38–0.54, p < 0.0001; central assessment: 11.0 vs. 4.1 months, HR 0.38, 95% CI 0.31 to 0.48, p <
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case, buparlisib (BKM120), a pan-class-PI3K-inhibitor, is cur-
rently being analysed in the study designs of the BELLE (Buparlisib
Breast Cancer Clinical Evaluation) trials. The BELLE-2-trial, a
phase III study, examined the addition of fulvestrant plus buparlisib to tamoxifen (20 mg/day) in postmenopausal women with advanced hor-
mone receptor-positive breast cancer showing primary or sec-
ondary resistance to aromatase inhibitors [21]. The study results
suggested an increased clinical benefit (primary endpoint, clinical
benefit rate (CBR) 61% vs. 42%; 95% CI, 47–74 vs. 29–56,
p = 0.045), longer time to progression (8.6 vs. 4.5 months, 95%
CI, 5.9–13.9 vs. 3.6–8.7; p = 0.002) and reduced risk of death
(55%, HR 0.45; 95% CI, 0.24–0.81; p = 0.007). In particular, pa-
tients with a secondary endocrine resistance, defined as 6 months
after stopping endocrine therapy in the adjuvant setting or at least
6 months after initiating endocrine treatment for metastatic breast cancer, achieved benefit from an additional inhibition with
everolimus. A different approach was assessed in the Horizon
study in which a mTOR inhibitor was used in the first-line setting to try to avoid endocrine resistance. This phase III study
(n = 1,112) evaluated the addition of temsirolimus (20 mg/day for 5
days every 2 weeks) to letrozole in the first-line setting in pa-
tients with hormone receptor-positive advanced breast cancer
[22]. Most of the patients were endocrine therapy naive. How-
evertheless, the study was terminated at an early point by the data-mon
itoring committee because of a lack of efficacy in the interim anal
ysis (PFS 9 vs. 8.9 months, HR 0.9, 95 % CI 0.76–1.07, p = 0.25; 
overall response rate in both arms 27%).

PI3K/AKT

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mone receptor-positive, HER2-negative advanced breast cancer that was refractory to the treatment with arom-
atase inhibitors [23] and the phase III BELLE-3 study investi-
gated whether fulvestrant plus buparlisib was able to restore the endocrine sensitivity after the treatment with an mTOR inhibitor
[24]. Final study results are still pending.
gether 450 genes were differentially expressed between sensitive and resistant tumours. As expected, Rb and cyclin D1 were elevated and p16 was decreased in the most sensitive lines. These in vitro results represented a strong rationale for the treatment of ER-positive breast cancer patients.

To proceed with the clinical development of this drug, a phase I trial investigated dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) of the first-in-class oral CDK4/6 inhibitor PD-0332991 administered once daily for 21 of 28 days in patients with Rb-positive advanced solid tumours. This phase I study led to the conclusion that PD-0332991 warranted phase II testing at 125 mg once daily, a dose at which neutropenia was the sole significant toxicity [29]. As a next step, 37 patients with advanced breast cancer positive for Rb were enrolled in a single-arm phase II trial. The majority of the patients (84%) were HR positive and HER2 negative. Patients had received a median of 2 prior cytotoxic therapies. Palbociclib showed clinical activity in this heavily pretreated cohort of breast cancer patients with a clinical benefit rate of 19% overall. Median PFS overall was 3.7 months, but significantly longer for those with HR-positive versus HR-negative disease \((p = 0.03)\) and those who had previously progressed through endocrine therapy for advanced disease \((p = 0.02)\). The major toxicity was neutropenia \((51\% \text{ grade III/IV})\), which could be easily managed with dose reduction. However, neither analysis of p16 nor cyclin D1 identified a sensitive population [30].

Building on the encouraging results of palbociclib in HR-positive breast cancer, an open-label randomized phase II trial enrolled 165 postmenopausal ER-positive and HER2-negative breast cancer patients who had not received any systemic therapy for advanced disease [31]. Patients were randomized either to letrozole alone or to letrozole + palbociclib \((125 \text{ mg, given once daily for 3 weeks followed by 1 week off over 28-day cycles})\). Patients were enrolled sequentially in 2 separate cohorts: in cohort 1, patients were enrolled on the basis of their ER-positive and HER2-negative biomarker status alone, whereas in cohort 2 they were also required to have amplification of cyclin D1 or loss of p16\(^{INK4A}\). Median PFS was 10.2 months for the letrozole group and 20.2 months for the palbociclib plus letrozole group \((HR 0.488, 95\% \text{ CI } 0.319–0.748; p = 0.0004)\). Grade III/IV neutropenia was reported in 54\% in the palbociclib plus letrozole group versus 1\% in the letrozole group. However, no cases of febrile neutropenia were reported. Building on this substantial improvement of PFS with the addition of palbociclib to letrozole, the FDA granted accelerated approval to palbociclib (IBRANCE, Pfizer Inc.) for use in combination with letrozole for the treatment of postmenopausal women with ER-positive HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease.

**New Therapeutic Options, New Challenges**

To ensure adequate safety in the use of these innovative and promising therapeutic options, it is important to pay attention to the new range of side effects of these small molecules. Possible specific side effects of mTOR inhibitors are stomatitis, diarrhoea, dyspnoea, non-infectious/interstitial pneumonitis, hyperglycaemia, fatigue and rash [32]. The number of adverse-event-related on-treatment deaths is particularly evident in patients above 65 years [20], therefore the FDA recommends strict indications especially for elderly patients. Moreover, for PI3K inhibitors mood changes have been described as a further serious side effect, which can be connected to a possible crossing of the blood-brain barrier [33–35]. The major toxicity of palbociclib is neutropenia [31]. A further challenge is selecting the ideal patient population. More recently, the questions of which biomarkers would be useful predictive factors and in which clinical situation dual inhibition would be most effective have been controversially discussed [36, 37].

**Conclusion**

The results clearly show that inhibition of the PI3K/AKT/mTOR pathway and CDK4/6 are promising ways to improve the efficacy of endocrine treatment in ER-positive breast cancer patients with comparably few side effects. Further studies have to deal with advanced strategies to overcome endocrine resistance. Due to the heterogeneity of breast cancer, translational approaches are necessary in order to define suitable patient cohorts and predictive biomarkers for a personalised therapy with a high therapeutic index.

**Disclosure Statement**

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