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Review

New agents for endocrine resistance in breast cancer

Christian Maurer [a, b], Samuel Martel [a, c], Dimitrios Zardavas [d], Michail Ignatiadis [a, *]

[a] Clinique d'Oncologie Médicale, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium
[b] Department I of Internal Medicine and Center of Integrated Oncology Cologne Bonn, University of Cologne, Cologne, Germany
[c] Département d'hémato-oncologie, CISSS Montérégie centre/Hôpital Charles Lemoyne, centre affilié de l'Université de Sherbrooke, Greenfield Park, QC, Canada
[d] Breast International Group (BIG), Brussels, Belgium

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ABSTRACT

Estrogen receptor positive (ER+) and HER2-negative (HER2-) breast cancer (BC) is the most common BC subtype, defined by expression of the ER and absence of HER2 amplification. Endocrine treatment (ET), aiming at therapeutic blockade of ER signaling, represents the therapeutic mainstay for patients with both early and advanced disease. Despite its wide therapeutic efficacy, ET fails for a proportion of ER+, HER2- BC patients with early disease who develop endocrine resistance, resulting in disease recurrence. Endocrine resistance occurs almost invariably in patients with metastatic disease. Recently, increasing understanding of the molecular mediators of endocrine resistance has been achieved. This review focuses on the molecular mechanisms mediating endocrine resistance, on molecularly targeted agents to overcome or delay it, and potential predictive biomarkers for accurate patient stratification.

1. Introduction

Approximately 70% of all breast cancer (BC) primary tumors express estrogen and/or progesterone receptor (ERs and PgR, respectively) [1]. Endocrine treatment (ET) represents the cornerstone of systemic treatment for patients with hormone receptor positive (HR+) disease, in both adjuvant and metastatic setting; however, a considerable number of patients show either primary (de novo) or secondary (acquired) endocrine resistance (Fig. 1), [2,3]. Neoadjuvant ET leads to a limited clinical response rate between 35 and 70% and a pathological complete response (pCR) rate of less than 10% [2,4–6] and despite adjuvant ET a substantial proportion of patients (as high as 40–50%) still relapse and die from this disease [7]. Furthermore endocrine resistance inevitably develops in the metastatic setting with the majority of the patients progressing within 2–3 years after the start of ET [2].

There has been significant progress in deciphering mechanisms of estrogen-independent growth of HR + BC. In this review, we will focus on the evidence supporting the involvement of several aberrations and/or signaling pathways as mediators of endocrine resistance: i) the cyclin-dependent kinase (CDK)-4/6-retinoblastoma (pRb) axis, ii) the phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR (mammalian target of rapamycin) pathway, iii) the ER-alpha (*ESR1*) gene mutations, iv) the cross talk between ER and growth factor receptor signaling, and v) epigenetic modifications (Fig. 2), [8–12]. Furthermore, we will present clinical data from completed and ongoing clinical trials assessing targeted agents to overcome or delay endocrine resistance, as well as data concerning potential predictive biomarkers for accurate patient stratification. Discussing immune response modulation which might as well be linked to endocrine resistance is beyond the scope of this article.

1.1. Mechanisms of endocrine resistance and new drugs

Several potential mechanisms of endocrine resistance have been identified (Fig. 2). Table 1 summarizes the characteristics of the most important new drugs, whereas Table 2 provides an overview of selected ongoing trials addressing endocrine resistance. BC is an extremely heterogeneous disease with high plasticity and different resistance mechanisms may play a role in different stages of the disease.

* Corresponding author. Department of Medical Oncology, Institut Jules Bordet, Université Libre de Bruxelles, Rue Héger-Bordet 1, 1000 Brussels, Belgium.
E-mail address: michail.ignatiadis@bordet.be (M. Ignatiadis).

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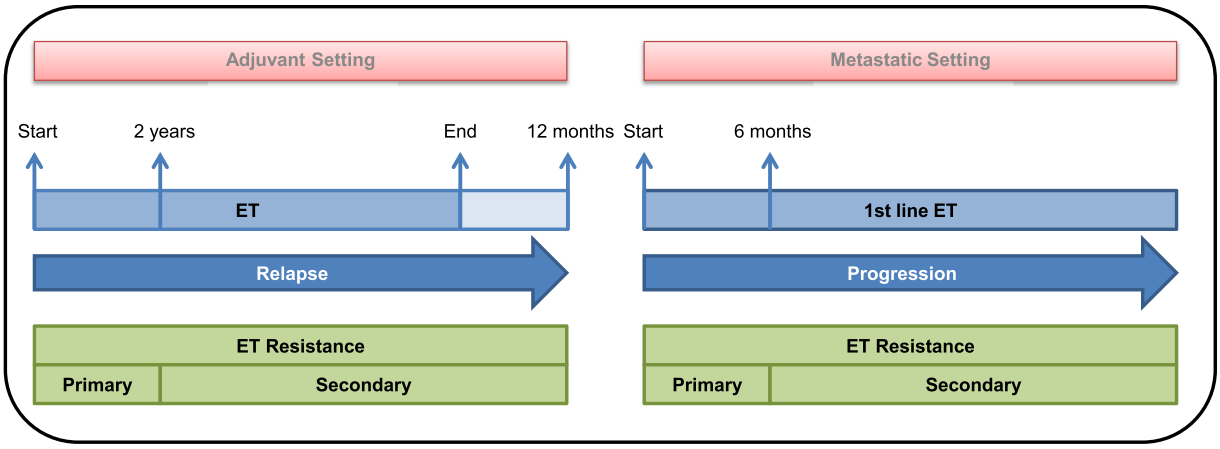

Fig. 1. Definitions of Endocrine Resistance. The concept of endocrine resistance was refined at the ESO-ESMO 3rd international consensus guidelines for advanced breast cancer (ABC2). Based on expert opinion, a distinction between primary and secondary resistance was established. A) in the adjuvant setting, primary resistance to ET corresponds to a relapse that occurs during the first two years of treatment and secondary resistance corresponds to a relapse that occurs while on ET but after the first 2 years of ET or within a year after the completion of adjuvant treatment. B) in the metastatic setting, primary resistance to ET corresponds to a disease progression that occurs within the first six months of ET and secondary resistance corresponds to a disease progression that occurs ≥6 months after initiating ET while on treatment [3].

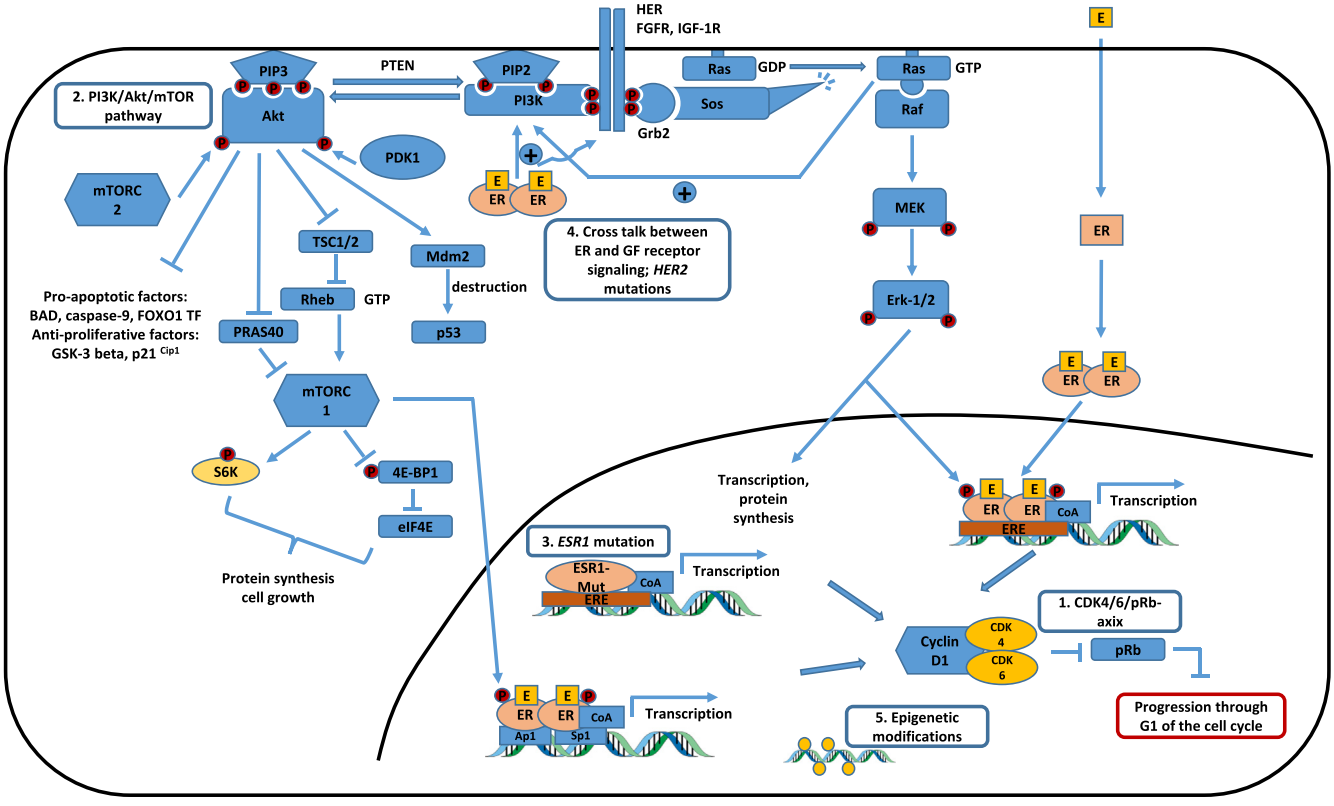

Fig. 2. Biology of ER and Molecular Pathways of Endocrine Resistance. Upon estrogen binding, the cytosolic ER migrates into the nucleus, forms dimers and binds to specific sequences of DNA known as estrogen response elements (ERE) which are present in the promotor of estrogen-responsive genes. Many of the genes that are regulated by ER are important for cell proliferation, stimulation of invasion and metastasis, inhibition of apoptosis and promotion of angiogenesis. Furthermore ER itself can function as a coactivator protein at alternative DNA sequences (AP-1/SP-1) and thus regulate the expression of IGF1R and cyclin D1 [8]. Besides influencing the transcription, ERs show as well a non-genomic activity. ERs implicated in this process are located in the plasma membrane and cytoplasm and form complexes with G proteins, receptor tyrosine kinases (EGFR, IGF1R) and non-receptor tyrosine kinases (PI3K, Src) [8–12]. Via mTORC1 and Erk-1/2 ligand independent activation of the ER is possible. So far several mechanisms leading to endocrine resistance have been described (1.-5.). Of special interest is the cyclin D-CDK4/6 axis that plays an important role in the tumorigenesis of luminal, ER + BC, the PI3K/Akt/mTOR pathway, ESR1 mutation and the cross talk between ER and GF receptor signaling. AbbreviationsER, estrogen receptor; IGF1R, insulin-like growth factor 1 receptor; PI3K, phosphatidylinositol-3-kinase; PIP3, phosphatidylinositol-3,4,5-triphospahte; mTORC1/2, mammalian target of rapamycin complex 1/2; Erk-1/1, extracellular signal-regulated kinases-1/2; CDK4/6, cyclin-dependent kinase 4/6; BC, breast cancer; GF, growth factor.