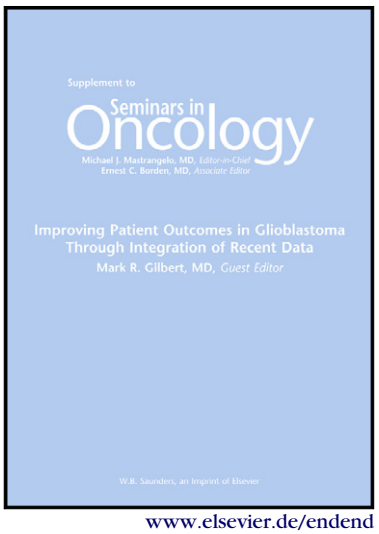

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BETTER TOGETHER: TARGETED COMBINATION THERAPIES IN BREAST CANCER

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Abstract

Recent discoveries both in cell proliferation and survival mechanisms and new

antineoplastic agents have led to deep change in the breast cancer treatment paradigm. Nonetheless, all of the progress in knowledge and strategy has not been enough to overcome mechanisms of escape and resistance put in place by the tumor cells. New targeted agents mean new possibilities for combinations, a viable option to try to stop compensatory pathways of tumor growth activated in response to therapeutics. The main challenges in designing a combined therapy come from the variety of subtypes of breast cancer (Luminal A, Luminal B, Her2-enriched and Basal-like) and from the multitude of pathways each subtype can exploit. Recent research has focused on dual blockade of HER2 (trastuzumab-lapatinib; trastuzumab-pertuzumab) and concomitant blockade of the endocrine driver and other pathways such as the PI3K/AKT/mTOR pathway (everolimus-exemestane), HER2 (trastuzumab/lapatinib-endocrine therapy) and the cell cycle through cyclin-dependent kinase inhibition (letrozole-palbociclib). This combined and personalized approach to treatment needs a profound knowledge of the mechanisms leading to proliferation in each tumor subtype. Deepening our understanding of tumor growth is mandatory to keep improving the efficacy of combination therapy.

Introduction

Medical treatment in oncology has dramatically changed over the last few decades. This was related both to the improvement in understanding the process of

oncogenesis and the biological characteristics of different cancers and to the introduction of new drugs in clinical practice.

In particular, regarding the management of breast cancer, we can classify this heterogeneous disease in different subtypes: luminal, Human Epidermal Growth Factor-2 (HER-2) enriched, and basal-like tumors.[1] Luminal tumors are characterized by the expression of hormonal receptors (HR), defined as estrogen receptors (ER) and progesterone receptors (PR); and are further subdivided in luminal A with ER positive (ER+), HER2-negative, low Ki-67 expression (<14%) or intermediate Ki-67 expression (14% to 19%) and high PR levels (≥20%),[2] and luminal B (HER2-negative) tumors with ER+, HER2-negative, intermediate Ki-67 expression (14% to 19%) and low PR levels (<20%), or high Ki-67 expression (≥20%).[3] HER2 enriched are characterized by the over-expression of HER2 protein. Basal-like tumors are defined by the lack of estrogen, progesterone and HER2 receptors. The definition of these different subtypes has permitted identification of customized treatment for each group. In fact luminal tumors, because of HR expression, present a characteristic sensitivity to hormonal therapy that is therefore recognized as a milestone in the treatment of this type of tumors.

Over the years different types of hormonal treatments were introduced, including selective estrogen receptor modulators (SERMs) such as tamoxifen, and the aromatase inhibitors (AI) (letrozole, anastrozole, exemestane). These two categories of drugs are currently used in metastatic and adjuvant setting, where tamoxifen is

indicated in premenopausal and AI in postmenopausal patients. In the complex and ever evolving world of premenopausal breast cancer therapy even the centerpiece of treatment, Tamoxifen, has been recently put into question. TEXT and SOFT trials have reported the results of comparison between exemestane with ovarian suppression, obtained by the association with LHRH analogs, and tamoxifen either alone or in association with LHRH analogs, in premenopausal women, to identify if there is a benefit with AI also in premenopausal patients. The results are in favor of the combination of exemestane + ovarian suppression compared to tamoxifen or tamoxifen + LHRH analogs in terms of rate of freedom from breast cancer at 5 years, especially in young (<35 years) and high risk patients.[4,5] It was 67.7% (95% confidence interval [CI], 57.3 to 76.0) for patients assigned to tamoxifen alone, 78.9% (95% CI, 69.8 to 85.5) for those treated with tamoxifen plus ovarian suppression, and 83.4% (95% CI, 74.9 to 89.3) for those assigned to exemestane plus ovarian suppression. This is an example indicating that treatment strategy becomes more and more complex, according to the improvements in our knowledge.

Trastuzumab (Herceptin®, Roche), a humanized monoclonal antibody targeting HER-2 extracellular domain, has dramatically changed the prognosis of patients with HER2-positive breast cancers both in metastatic and adjuvant setting. Several clinical trials have shown that trastuzumab improves overall survival (OS) in metastatic breast cancer (MBC),[6,7] increases pathological complete response (pCR) in the neoadiuvant setting[8] and improves disease free survival (DFS) and OS in the adjuvant setting.[9,10]

Basal-like tumors, also defined as triple negative breast cancers (TNBC), include different histological subtypes and molecular profiles. They are generally more aggressive than luminal tumors, with higher rates of relapse in the early stages and poor prognosis in the metastatic setting.[11,12] Specific molecular targets for this subtype of breast cancers have not been defined yet, so chemotherapy remain the mainstay of treatment, particularly anthracycline- and taxane-based regimens.

Despite the important results achieved in all these categories, MBC remains an incurable disease. The principal reason is the ability of tumor cells to develop different mechanisms of resistance that allow progression of tumor cells during treatment.

Mechanisms of resistance

Luminal tumors

Several mechanisms have been described regarding resistance to endocrine treatments and ER represents a key point in this setting. There are two forms of ER: α and β. The most studied and well known is the ERα, that accounts for approximately 70% of all breast cancer cases.[13] Loss of ERα expression is one of the major mechanism that confers resistance to endocrine treatment: it represents the expression of an *innate resistance* to endocrine therapy in ER negative tumors, and a mechanism of *acquired resistance* in patients treated with tamoxifen or AI.[14] Another mechanism of acquired resistance is the appearance of mutations of ER genes that may lead to an altered function of ER; for example the substitution of

lysine 303 with arginine produces a hypersensitive receptor able to activate cell growth also in case of low estrogen levels.[15] Activity of ER is mediated by co-regulatory proteins, activators and repressors, therefore alterations of these co-regulators may contribute to endocrine resistance.

Over the last few years several studies demonstrated that there are multiple interactions between ER, growth factors and different kinase signaling pathways, as Epidermal Growth Factor Receptor (EGFR)/HER2 family,[16] Insulin-like growth factor receptor (IGFR) family,[17] mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase (ERK) pathway,[18] and the phosphatidyl-inositol-3-OH kinase (PI3K) pathway. Despite the down regulation of the ER pathway during endocrine treatment, activation of different pathways leads to cell proliferation with endocrine resistance.

The PI3K pathway is one of the most studied signaling pathways. When activated by tyrosine kinase receptors, PI3K catalyzes the production of phosphatidylinositol 3,4,5 trisphosphate (PIP3) and subsequent activation of the serine/threonine protein kinase AKT: this activation promotes cellular proliferation and anti-apoptotic responses.[19] A major downstream effector of AKT activation is mammalian Target of Rapamycin (mTOR) protein, that acts as signaling integration node receiving inputs also from various cellular signaling pathways, such as MAPK pathway. There are evidences of reciprocal interaction between the PI3K cell survival pathway and ER mediated signaling; therefore activation of the PI3K/AKT/mTOR pathway

phosphorylates the ER resulting in hormone-independent activation.[20] For these reasons, many clinical trials have evaluated association between hormonal treatment with mTOR-inhibitors, such as everolimus and temsirolimus, to overcome endocrine resistance and restore hormone-sensitivity. These trials have led to the introduction of the association between exemestane (a steroidal AI) and everolimus as a new combination treatment in postmenopausal women with luminal MBC, as we will discuss in the next paragraph.

HER2-enriched tumors

HER2 is a transmembrane tyrosine kinase receptor expressed in about 15-25% of breast cancer and involved in proliferation and survival of epithelial cells. Trastuzumab has dramatically changed natural history of this type of tumors with poor prognosis. Its antitumor activity is related to two different mechanisms of action: downregulation of the intracellular PI3K and MAPK signaling pathways, and activation of the immune response via antibody dependent cell-mediated cytotoxicity (ADCC) and adaptive immune response.[21-23]

Nevertheless, patients treated with trastuzumab in adjuvant or metastatic settings, relapse or progress. This could be explained with the appearance of molecular mechanisms of trastuzumab resistance, such as involvement of other HER receptors (HER3 or EGFR),[24] activation of PI3K/AKT/mTOR,[25] overexpression of c-MET,[26] increased vascular endothelial growth factor (VEGF) expression.[27] Therefore,

concomitant inhibition of two or more of these pathways could overcome trastuzumab resistance. To date, successful strategies in overcoming trastuzumab resistance have been the association between trastuzumab and lapatinib(Tykerb/Tyverb®, GlaxoSmithKline), or trastuzumab with pertuzumab (Perjeta®, Genentech).

Lapatinib is a small molecule, potent and reversible inhibitor of the ATP-binding site at the tyrosine kinase (TK) domains of EGFR and HER2.[28] With the combined blockade of two receptors involved in tumor proliferation Lapatinib results in a synergistic inhibition of tumor cell growth, and in linking the intracellular domain of HER2, lapatinib is able to overcome trastuzumab resistance due to truncated HER2 receptors. These preclinical evidences were confirmed in clinical trials in the metastatic and neoadjuvant setting that showed the superiority of combination lapatinib plus trastuzumab over Ttrastuzumab alone in terms of OS and pCR, respectively.[29,30]

Pertuzumab is a monoclonal antibody that inhibits HER2/HER3 dimerization, thus it can prevent this mechanism of resistance to trastuzumab.[31] The association between these two monoclonal antibodies provides a more complete blockade of HER signaling pathway, which has shown enhanced activity in preclinical studies with reduction in the levels of HER proteins. Subsequent clinical trials investigated this combination in different settings of breast cancer, demonstrating the benefit in addiction of pertuzumab to trastuzumab. As we will further explain, this

combination is now the new standard of care for first line therapy of women with metastatic disease.

Basal-like tumors

If luminal and HER2-enriched breast cancers treatment profoundly changed in the last few years following knowledge of different mechanisms of resistance to traditional treatments, in TNBC we have not obtained the same results. In fact the signaling pathways responsible for cell growth and proliferation of this subtype of breast cancer are not as well understood as the others. The expression of EGFR and androgen receptors, as well as the mutation of BRCA1/BRCA2 genes, are under investigation as possible targets in basal-like tumors.[32,33] In fact approximately 20% of TNBC are carriers of BRCA1 or BRCA2 gene mutation; these genes play an important role in DNA double-strand break repair, contributing to the maintenance of DNA stability.[34] Poly Adenosine Diphosphate-ribose polymerase (PARP) enzymes are critical in processing and repair of DNA breaks. PARP inhibitors showed activity against tumor cell lines lacking functional BRCA1 or BRCA2,[35] so promising results are expected from the association of these molecules with chemotherapy, but to date no clinical trials demonstrated a significant efficacy in this subtype of breast cancer. Further studies are warranted to improve treatment strategies for TNBC.

Combination therapy

Exemestane and everolimus

As previously described, PI3K/AKT/mTOR pathway represents one of the most important mechanisms of escape during endocrine therapy for tumor cells expressing ER. For this reason inhibitors of this pathway have been studied in association with hormonal treatments to overcome endocrine resistance. In particular, everolimus (Afinitor®, Novartis) is an orally mTOR inhibitor that binds with high affinity to the intracellular receptor FKBP12 creating the everolimus-FKBP12 complex that interacts with mTOR to inhibit downstream signaling events.[36]

The TAMRAD study[37] is a randomized phase II trial evaluating the combination between tamoxifen and everolimus in postmenopausal patients with MBC previously exposed to AI. The primary end point of the study was the clinical benefit rate (CBR). The association between tamoxifen and everolimus led to a 6 months CBR of 61% vs 42% in patients treated with tamoxifen alone. Time to progression (TTP) was 8.6 months in the combination arm and 4.5 months in patients treated with Tamoxifen alone, corresponding to a 46% reduction in risk of progression with the combination. Also OS was increased in combination arm, with a 55% reduction in the risk of death with everolimus plus tamoxifen in comparison to tamoxifen alone [hazard ratio (HR) 0.45; 95% CI, 0.24 to 0.81].

Another phase II study conducted between March 2008 and October 2012 enrolled 33 patients with MBC ER+ pretreated with AI, to receive fulvestrant 250 mg every 28

days, after a first loading dose (fulvestrant 500 mg day 1 and fulvestrant 250 mg day 14) in combination with everolimus.[38] CBR was 49%, indicating promising activity of this type of combination regimen. Nevertheless one-third of patients exhibited de novo resistance to treatment. Furthermore the fulvestrant schedule used in the trial appears to be inadequate in consideration of the results of the CONFIRM trial published by Di Leo and colleagues.[39] Even so, the combination between fulvestrant and everolimus evaluated in this phase II trial confirmed the potential efficacy of combination between mTOR inhibitors and endocrine therapy in MBC ER + patients.

The BOLERO-2 trial definitively demonstrated the efficacy of mTOR inhibitor everolimus combined with endocrine therapy in restoring sensitivity to hormonal treatment.[40] In this phase III trial, 724 patients with advanced breast cancer ER+ who had recurrence or progression while receiving previous therapy with a non-steroidal AI, were randomized to receive everolimus plus exemestane versus exemestane plus placebo. Primary end point of the study was Progression Free Survivall (PFS) that was significantly improved in combination arm. In fact the median PFS on the basis of radiographic studies assessed by the local investigators, was 6.9 months for everolimus plus exemestane versus 2.8 months for placebo plus exemestane (HR for progression or death = 0.43; 95% CI, 0.35 to 0.54; p<0.001), and the median PFS on the basis of central assessment were 10.6 months and 4.1 months, respectively (HR=0.36; 95% CI, 0.27 to 0.47; P<0.001). The safety analysis showed that serious adverse events (SAE) were reported in 23% of patients in combination arm and in 12% of patients in exemestane alone group. The most

common grade 3 or 4 adverse events were stomatitis, anemia, dyspnea, hyperglycemia, fatigue, and pneumonitis. The data published by Piccart et al. about OS showed a trend in advantage for combination treatment versus exemestane monotherapy, with 31.0 months versus 26.6 months, without reaching statistical significance (HR=0.89; 95% CI 0.73-1.10; log-rank P = 0.14).[41] The results obtained in PFS led to the Food and Drugs Administration (FDA) and European Medicines Agency (EMA) approvals for the combination of Everolimus and Exemestane in HR positives MBC previously treated with non steroidal AIs.

Therefore everolimus plus exemestane represents the first combination between endocrine treatment and mTOR inhibitors approved in HR-positive MBC. This treatment is not free from side effects but a careful clinical evaluation makes it possible to define who are the candidates for this combination therapy.

Letrozole and Palbociclib

Recently FDA granted accelerated approval of palbociclib (Ibrance®, Pfizer) in combination with letrozole for treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer as first line endocrine therapy in metastatic disease. Palbociclib is an inhibitor of cyclin-dependent kinase (CDK) 4 and 6, proteins responsible of cell cycle progression from phase G1 into S.[42] This accelerated approval is based on a randomized, multicenter, open-label trial in postmenopausal women with ER+, HER2-negative MBC who had not received previous systemic treatment for advanced disease, in which the combination of

palbociclib and letrozole demonstrated an improvement in PFS versus letrozole alone. In fact PFS was 20.2 months (95% CI 13.8- 27.5) in the palbociclib plus letrozole arm and 10.2 months (95% CI 5.7- 12.6) in the letrozole alone arm (HR= 0.488 (95% CI 0.319- 0.748)).[43] This approval permits the introduction of a new category of drugs in the oncology setting and confirms the importance of combining treatments with different mechanisms of action to overcome drug resistance.

Trastuzumab and lapatinib

The phase III study EGF104900 investigated the dual HER2 blockade with trastuzumab and lapatinib in HER2-positive MBC who progressed during trastuzumab treatment. Patients were randomly assigned to receive lapatinib in monotherapy or lapatinib in association with trastuzumab. The combination arm was associated with a significant improvement in PFS (HR=0.74; 95% CI 0.58 to 0.94; p = 0.011) and OS (HR=0.74; 95% CI 0.57 to 0.97; p = 0.026).[29]

The synergism between lapatinib and trastuzumab was also observed in the NeoALTTO study: patients in neo-adjuvant setting were randomly assigned to lapatinib, trastuzumab, or lapatinib plus trastuzumab, all in combination with paclitaxel after six weeks of targeted therapy alone. The pCR rate was significantly higher in the group treated with dual HER2 blockade (51.3%) as compared to trastuzumab alone (29.5%) (a 21.1% difference; 95% CI 9.1 to 34.2; p = 0.0001). There was no significant difference in pCR between the lapatinib and the trastuzumab group.[30] Unfortunately, the NeoALTTO trial was not powered to detect

significant differences in survival so it was not possible to verify if the combination resulted in an improvement in OS.[44]

Another study that evaluated the combination between lapatinib and trastuzumab in neoadjuvant setting is the NSABP B-41. In this phase III trial 529 patients were randomly assigned to receive weekly paclitaxel with lapatinib daily, or with trastuzumab weekly, or with the trastuzumab plus lapatinib association, before surgery. In the arms with lapatinib or trastuzumab as single agents there was a similar percentage of pCR (53.2% with lapatinib and 52.5% with trastuzumab, p=0.98). The dual HER2 blockade was associated with a higher pCR rate (62%; 95%CI 54.3 to 68.8) as compared with single agent HER2 blockade, but the difference in this trial was not statistically significant (p=0.095).[45]

The association lapatinib plus trastuzumab was evaluated also in the adjuvant setting. The ALLTO study is a phase III trial where patients were randomly assigned after surgery to the concurrent use of trastuzumab and lapatinib, to the sequential use of trastuzumab followed by lapatinib, or to trastuzumab alone for one year. The majority received the anti-HER2 agents after completing chemotherapy, otherwise a taxane was administered concomitantly after antracyclines. A total of 8381 women were involved in this trial. At a median follow-up of 4.5 years, dual targeting was associated with a slight reduction in disease recurrences, but the difference versus Trastuzumab alone was not statistically significant. Disease-free survival (DFS) rates at 4 years were 86% with trastuzumab, 88% with concurrent HER2-directed

treatment, and 87% in the sequential arm. Median OS rates were 94%, 95%, and 95%, respectively. HR ranged from 0.80 to 1.00, not statistically significant.[46] In consideration of these results the combination of lapatinib and trastuzumab is currently indicated only in the metastatic setting as an alternative regimen in patients with HER2-enriched tumors.

Trastuzumab and Pertuzumab

The dual HER2 blockade was also evaluated with the combination of two mAbs: trastuzumab and pertuzumab. In the CLEOPATRA trial, patients with MBC were randomized to receive docetaxel plus trastuzumab plus pertuzumab versus docetaxel plus trastuzumab plus placebo as first line treatment. First results, showing a PFS improvement superior by 6 months with the combination for HER2 blockade,[47] have led to FDA and successive EMA approvals for the use of pertuzumab in association with trastuzumab as first line treatment in MBC HER2+. Final results of this trial were presented at the European Society for Medical Oncology (ESMO) Congress in Madrid at the end of September 2014 and showed an unprecedented increase in OS: 56.5 months in the combination group and 40.8 months in the placebo group, with a statistically significant difference of 15.7 months between the two arms.[48]

The combination of chemotherapy with pertuzumab and trastuzumab has also shown important results in the neoadjuvant setting. The Neosphere phase II trial evaluated the efficacy of dual HER2 blockade with trastuzumab and pertuzumab in

combination or without docetaxel. Patients given pertuzumab and trastuzumab plus docetaxel had a significantly improved pCR rate (45.8% [95% CI 36.1 to 55.7]) compared with those given trastuzumab plus docetaxel (29.0%; p=0.0141). Moreover 24.0% of women given pertuzumab plus docetaxel had a pCR, as did 16.8% given pertuzumab and trastuzumab without chemotherapy.[49]

This significant improvement in pCR rate obtained with the combination of pertuzumab and trastuzumab plus chemotherapy is confirmed in an another neoadjuvant phase II study, the TRYPHAENA trial.[50] These important results have led to FDA approval for the combination of pertuzumab and trastuzumab also in neoadjuvant setting; we are waiting for the results of the APHINITY trial to see if this combination is effective also in the adjuvant setting.[51]

Trastuzumab/lapatinib plus hormonal therapy

Another example of combination treatment is the association between endocrine treatment and anti-HER2 target therapies. This strategy is feasible for treatment of hormonal receptors positive tumors overexpressing also HER2 (luminal B HER2-enriched). Up-regulation and autocrine activation of this protein conveys increased resistance to hormonal treatment and chemotherapy, so the concomitant suppression of endocrine and HER2 pathways is studied to improve the results obtained with monotherapy. Three randomized trials have examined the effectiveness of combined AI and HER2-targeted therapy: the eLEcTRA trial (Study of the Efficacy and Safety of Letrozole Combined with Trastuzumab in Patients with

MBC),[52] the TAnDEM trial (Trastuzumab in Dual HER2 ER-Positive MBC),[53] and the EGF30008 trial.[54] All these trials provided evidence of the clinical benefit of adding HER2-targeted therapy to an AI, so the combination between lapatinib or trastuzumab and AI is an alternative regimen in postmenopausal patients with HR+ and HER2+ MBC.

Considering that one of the mechanisms of endocrine treatment seems to be over-expression of the HER2 receptor, combination of hormonal therapy and HER2 target treatment was evaluated also in patients with MBC HR+, regardless of HER2 expression. In the CALGB 40302 study patients with ER+ and/or PR+ tumors previously treated with AI, received fulvestrant 500 mg intramuscularly on day 1, followed by 250 mg on days 15 and 28 and every 4 weeks thereafter, and either lapatinib 1,500 mg or placebo daily. At the final analysis, there was no difference in PFS (median PFS was 4.7 months for fulvestrant plus lapatinib versus 3.8 months for fulvestrant plus placebo), neither in OS (HR, 0.91; 95% CI, 0.68 to 1.21; p = 0.25).[55] These results show that combination between hormonal and HER2 treatments is specific only for HR+ and HER2 positive MBC.

PARP-inhibitors plus chemotherapy

Iniparib, a PARP1 inhibitor, showed anticancer activity in preclinical models. In particular, in in vitro models of TNBC, it was able to enhance antiproliferative and cytotoxic effects of a platin and gemcitabine[56]; for this reason combination between chemotherapy and iniparib was evaluated in a phase II trial.[57] In this study 123

patients with metastatic TNBC were randomly assigned to receive gemcitabine plus carboplatin alone or in combination with iniparib. The rate of clinical benefit (primary end point of the study) was 56% (34 of 61 patients) in the iniparib group and 34% (21 of 62 patients) in the chemotherapy group (p=0.01). Combination treatment showed no significant increase in toxicity as compared with chemotherapy alone. In particular the rate of serious adverse events was similar in the groups (29% in the chemotherapy-alone group and 28% in the iniparib group). The encouraging results of this study led to a phase III trial the data of which are expected to see if the combination of chemotherapy plus iniparib could become a new standard of care in metastatic TNBC (ClinicalTrials.gov number, NCT00938652).

The association between PARP inhibitors and chemotherapy was evaluated also in the multidrug I-SPY 2 trial.[58] Using advanced statistical techniques, this study identifies and graduates regimens that have an 85% Bayesian predictive probability of success in a 300 patient biomarker-linked phase III neoadjuvant trial. In this study the combination between velaparib and carboplatin has graduated for patients with TNBC signature, so further studies evaluating this combination plus standard chemotherapy are warranted to confirm these results.

Conclusions

Over the last years the introduction of new agents improved treatment of breast cancer in every setting. These results were obtained especially with the combination

of different molecules that act at various levels in the signaling pathways responsible of tumor cell proliferation (Figure 1). New treatments targeting PI3K/AKT/mTOR, FGFR, IGFR, HER2 pathways are under investigation and could change our clinical practice in the next years. Association between these new agents and standard treatments currently in use seems to be the winning strategy (Table 1). A better knowledge of resistance mechanisms responsible of cell proliferation and the identification of further predictive factors will certainly be critical to the recognition of future customized combinations.

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Tables and Figures

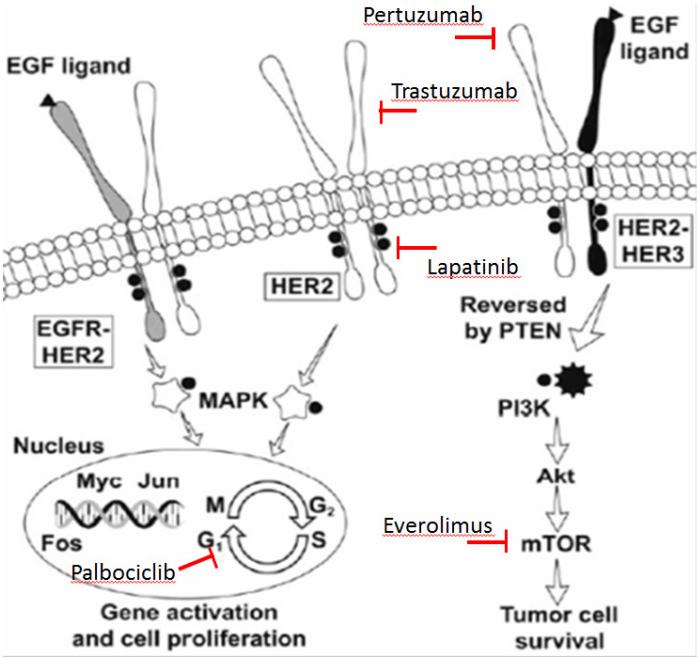
Table 1

Milestone treatments and new combinations in breast cancer subtypes.

Figure 1

Target treatments of HER2 pathway, mTOR and cell-cycle proteins. Pertuzumab, Trastuzumab and Lapatinib block HER2 pathway at different levels; Everolimus inhibits mTOR signalling, and Palbociclib blocks cell cycle progression from phase G1 into S.

(Adapted from Esteva FJ, Pusztai L. Optimizing outcomes in HER2-positive breast cancer: the molecular rationale. Oncology (Williston Park). 2005 Nov;19(13 Suppl 5):5-16.)



BREAST CANCER SUBTYPES	SETTING	MAINSTAY TREATMENT	COMBINATION THERAPY
Luminal	Adjuvant	Tamoxifen Aromatase Inhibitors	Tamoxifen + LHRHa [4,5] Exemestane + LHRHa [4,5]
	Metastatic	Hormonal therapy (Tamoxifen, Aromatase Inhibitors, Fulvestrant)	Tamoxifen + everolimus [37] Fulvestrant + everolimus [38] Exemestane + everolimus [40] Letrozolo + palbociclib [43]
HER2-positive	Neoadjuvant	Trastuzumab	Trastuzumab + Lapatinib [30,45] Trastuzumab + Pertuzumab [49,50]
	Adjuvant	Trastuzumab	Trastuzumab + Lapatinib [46]
	Metastatic	Trastuzumab	Trastuzumab+Pertuzumab [47] Trastuzumab + Lapatinib [44]
TNBC	Neoadjuvant	Chemotherapy	Velaparib + Chemotherapy [58]
	Metastatic	Chemotherapy	Iniparib + Chemotherapy [57]