ORIGINAL ARTICLE

Targeted Therapies in Breast Cancer

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■ **Abstract:** Targeted therapeutic agents in breast cancer are representing a larger proportion of new drugs entering clinical testing. Carcinogenesis is a multistep process characterized by genetic alterations that influence key cellular pathways involved in growth and development. Therefore, there are numerous opportunities for pharmacologic targeting. Hormonal therapy is the prototype of a treatment targeting hormone receptors, and this class of drugs still provides the greatest overall impact on outcome. Even though chemotherapy is considered a cytotoxic and nonspecific therapy, it does modulate many key cellular pathways and therefore shares characteristics of biologic drugs. It is clear that targeted therapies are going to play a greater role in improving survival and quality of life in advanced breast cancer, with trastuzumab (Herceptin) serving as a successful model that is a relatively nontoxic agent associated with survival benefits. However, several challenges to the successful identification and application of therapeutic targets remain. These include the dissection of complicated and interacting biologic pathways and the limitations of preclinical models that will allow for a better prioritization of which drugs and combinations will succeed best in the clinic. Better methods for selecting ideal candidates for therapy need to be based on known modes of action. Mechanisms of intrinsic and acquired resistance need further exploration in order to refine drug design. Toxicities that might result from modulation of the targeted pathway must be expected and fully characterized. Some biologic strategies may need to be tested in less refractory cases, or even in early stages, even though this may be more costly and could raise safety concerns. Fortunately progress in all of these areas is expected with the availability of new technologies and a growing infrastructure for preclinical and clinical testing. ■

Key Words: biological therapy, breast cancer, review, targeted therapy

The great promise and enthusiasm surrounding targeted therapeutics in breast cancer have been somewhat muted by the slow progress in the clinic and ongoing challenges, including limited efficacy in humans despite robust activity in preclinical models, emergence of resistance, and unexpected toxicities. The "Targeted Therapeutics in Breast Cancer" workshop highlighted several critical areas using examples from the laboratory and from clinical trials:

- How specific is a given target, and how pivotal to cell growth (or death) is the target?
- Why do preclinical models overestimate benefit seen in human trials?
- What are mechanisms of intrinsic and acquired resistance to targeted therapies?
- How can synergy with other drugs be detected and tested clinically?
- What is the best initial design for testing targeted therapies?
- What is the best method for determining the optimal candidate for a given targeted therapy?
- How can one predict and mitigate the toxicities of targeted therapies?

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IDENTIFYING SPECIFIC AND CRITICAL TARGETS

Hormonal therapy represents the earliest targeted treatment used in breast cancer, even though its early use antedated our understanding of hormone receptor biology (1). The intricacies of hormone receptor signaling are still not fully understood, yet substantial advances in hormonal therapy have been made, even very recently, with the demonstration of an adjuvant benefit from aromatase inhibitors (2–4). Despite the notion that hormonal therapy is a "static" drug and induces slow responses in advanced disease, this class of drugs still accounts for the largest impact of all systemic therapies for breast cancer and yields greater relative reductions in recurrence for early stage disease than chemotherapy (5). Chemotherapy also represents a form of targeted therapy in that the disruption of DNA replication and cell division preferentially affects tumor cells. Furthermore, chemotherapy activates many other cellular pathways, such as apoptosis and inhibition of cell cycle. As such, chemotherapy still accounts for the largest number of cures by systemic treatment across all cancer types.

Several biologic pathways have emerged over the last few decades that appear to be critical to carcinogenesis and can be exploited for prognostic and therapeutic purposes (6). Newer technologies that allow for the dissection of the individual components of cancer-related pathways and cell growth have identified many new targets for

Table 1. Pathway Targets and Targeting Agents

Pathways	
	Growth factor receptors
	Signal transduction
	Angiogenesis, proteolysis
	Cell motility, metastases
	Immune responses
	Apoptosis
	Cell cycle control
	Mitochondria/energy production
	Gene expression reprogramming
Targeting agents	
	Antibodies
	Peptides/immunoconjugates
	Cytokines
	Small molecules
	Gene therapy
	Gene knockdown (ribozymes, small interfering RNAs)

cancer drug development. These pathways and prototypical pharmacologic approaches are summarized in Table 1 and Fig. 1. Some hematologic malignancies that have limited genetic anomalies, such as chronic myelogenous leukemia (CML) in its early phases, are more amenable to drugs such as imatinib (Gleevec) that target the single chromosomal alteration that results in the *bcr-abl* fusion gene (7). However, as more genetic aberrations arise, as is the case with imatinib-refractory CML or CML in transformation, single drugs or even combinations are not as effective. Solid tumors exhibit much more complex genetic changes and heterogeneity compared to hematologic malignancies. Therefore any breast cancer therapy that targets a single genetic or biochemical lesion will only be effective in a limited proportion of patients. In addition, many potential mechanisms for the development of resistance are likely to evolve over time, resulting in transient responses (to be discussed in more detail later). Finding a truly breast cancer–specific target and one that is sufficiently pivotal to malignancy is a true challenge and one that is not likely to be met with any one given agent alone.

EXAGGERATED EFFECTS FROM PRECLINICAL MODELS

All drug development strategies rely on testing in a model system. The vast majority of models utilize human cancer cell lines that have typically been established from a metastatic site (particularly effusions) and propagated in cell culture over a long time. Most cells derived from a primary tumor do not grow well in culture and require stromal host cells and matrix. Hence there is a selection bias in established cell lines toward more aggressive features (8). Also, additional genetic alterations such as gene loss, amplification, translocation, and point mutations tend to occur in culture. For example, HER-2 gene amplification and expression in many HER-2-positive cell lines is much greater than in most HER-2-positive human cancers. These exaggerations result in much greater growth inhibition using in vitro and in vivo models compared to what one might see in human disease. Furthermore, the doubling times of most cell lines is much shorter than human cancer, and this also enhances the cell kill seen with any drug.

This phenomenon can lead to "false positive" results in the testing of novel targeted drugs and can also create misleading conclusions about synergistic interactions with other agents. More accurate models are being explored. Primary human tumor cells grown directly in the mammary fat pads or subrenal capsular spaces of mice may maintain their original genotype and phenotype and also reflect normal tumor-stromal interactions (9). Transgenic mice can be created to contain one or more genetic lesions, and several of these models demonstrate evolutionary changes at both the histologic and genomic levels (10). Even human models can be used using surrogate markers and short-term exposures to new agents with serial biopsies in patients being treated for locally advanced tumors prior to definitive surgery. These models may more accurately predict agents and combinations that are more likely to produce stepwise improvements in outcome in the clinic.

MECHANISMS OF INTRINSIC AND ACQUIRED RESISTANCE

Even a successful targeted drug like trastuzumab (Herceptin) is not effective as a single agent in all patients who express the HER-2 target (11–13). Initial resistance is usually attributed to cellular mechanisms, which might include signaling pathways that bypass the target or altogether different pathways unrelated to HER-2. More specific cellular mechanisms of resistance may include abnormalities in apoptosis pathways, cell cycle checkpoint function, and consequences of tumor hypoxia (Table 2). Small studies assessing numerous gene and protein markers in human tumors have been unable to reproducibly define protein or gene markers that predict responses to targeted drugs like trastuzumab or gefitinib (Iressa), although the general phenotype of increased apoptosis did predict a clinical response to trastuzumab in one study (14,15). In addition to cellular mechanisms, kinetic resistance (regrowth between cycles) or problems with drug delivery due to vascular penetration or molecular size may also be factors (16). Drug penetration may be a limiting step with large molecules such as antibodies and may also

Table 2. Mechanisms of Resistance to Targeted Therapies

Intrinsic	Acquired
Bypassing pathways	Membrane transporter
Incomplete target blockade	Enhanced drug metabolism
Hypoxia	Modulation or loss of target
Attenuated apoptosis	Immunosuppressive effects
Poor drug penetration	
Kinetic resistance	

be affected by tumor vasculature, cellular architecture, and extracellular matrix.

Acquired resistance invariably develops in any cancer system where genetic evolution and selective advantage occurs. This is typical of solid tumors where genomic instability is high and multiple genetic changes develop early in tumorigenesis. Mechanisms of acquired resistance may be similar to what has been described for chemotherapy, including changes in drug metabolism enzymes and the expression of membrane transporters (increased drug efflux) (17). In the case of targeted therapies, alterations in upstream or downstream components, as well as changes in the target itself, are currently being explored, but at this time there are no accepted assays other than the target itself for either hormonal or HER-2-directed therapy. Moreover, mechanisms of resistance to combination therapies may be more complicated and difficult to observe. This has created a clinical dilemma of continuing the targeted component of therapy when progression is seen with trastuzumab plus chemotherapy. While responses are seen in this setting based on uncontrolled observational studies, randomized studies have been difficult to complete and the independent contribution of trastuzumab is unknown (18).

SYNERGY AND COMBINATORIAL THERAPEUTICS

There are three principle reasons to believe that combinations of targeted therapies rather than single agents may yield the most favorable effects. The first is a generic reason: drugs that do not overlap with toxicities or resistance mechanisms may yield additive effects and quantum leaps in benefits. This has certainly been observed with chemotherapy in hematologic malignancies, and to a lesser extent with breast cancer (19,20). Second, mathematical synergy using in vitro or in vivo models can be shown by combining targeted agents with chemotherapy or other biologic drugs (21). Such models for chemotherapy-trastuzumab synergy have been used to justify these combinations in the design of clinical trials (22). The third reason is independent of synergy, but is due to the fact that solid tumors exhibit multiple genetic abnormalities and significant heterogeneity. It is unlikely that a single targeted drug would be successful in a majority of cases. Also, enough cell kill to make a clinical impact is more likely to be achieved with combination therapy. Furthermore, insufficient cell kill provides ample opportunity for the emergence of resistance.

The challenge of testing combinatorial therapy is the number of permutations of two- and three-drug combinations, with an ever-increasing number of pipeline drugs now entering clinical testing. Clinical trials are being designed empirically using chemotherapy agents approved for a given indication. In other cases, a small amount of cell line data are generated to support a particular combination. It is becoming clear that large clinical trials will not be feasible to test every combination. This underscores the earlier point of developing more reliable preclinical models and surrogate endpoints that can be tested in smaller patient cohorts with short-term follow-up.

OPTIMAL TRIAL DESIGN FOR TARGETED DRUGS

Most conventional and new drugs work best in the early stages of breast cancer and in patients who have received less prior therapy. Additional characteristics of targeted therapies such as limited penetration and slow onset of action may also bias against activity in more advanced disease. One example is the use of a vaccine against the sialyl Tn antigen (Theratope) in patients with advanced breast cancer after achieving a response or stability from chemotherapy. This placebo-controlled randomized study showed no improvement in the primary endpoint of time to disease progression with the use of the vaccine (Table 3) (23). However, the median time to the development of an

Table 3. Results of a Randomized Placebo-Controlled Trial of Theratope Vaccine Based on Hormonal Therapy Use

	Theratope	Control	*p*-value
Number of patients (*N*)	523	505	
Median TTP (months)	3.4	3.0	0.35
Median OS (months)	23.1	22.3	0.92
Number of patients receiving hormone therapy	168	161	
Hormone therapy TTP[a]	8.2	5.7	0.48
Hormone therapy OS[a]	34.9	30.7	0.22
Number of patients receiving no hormone therapy	355	344	
No hormone therapy TTP	2.8	2.8	0.52
No hormone therapy OS	19.1	20.4	0.42

[a]Subgroup that received hormonal therapy.
OS, overall survival; TTP, time to disease progression.

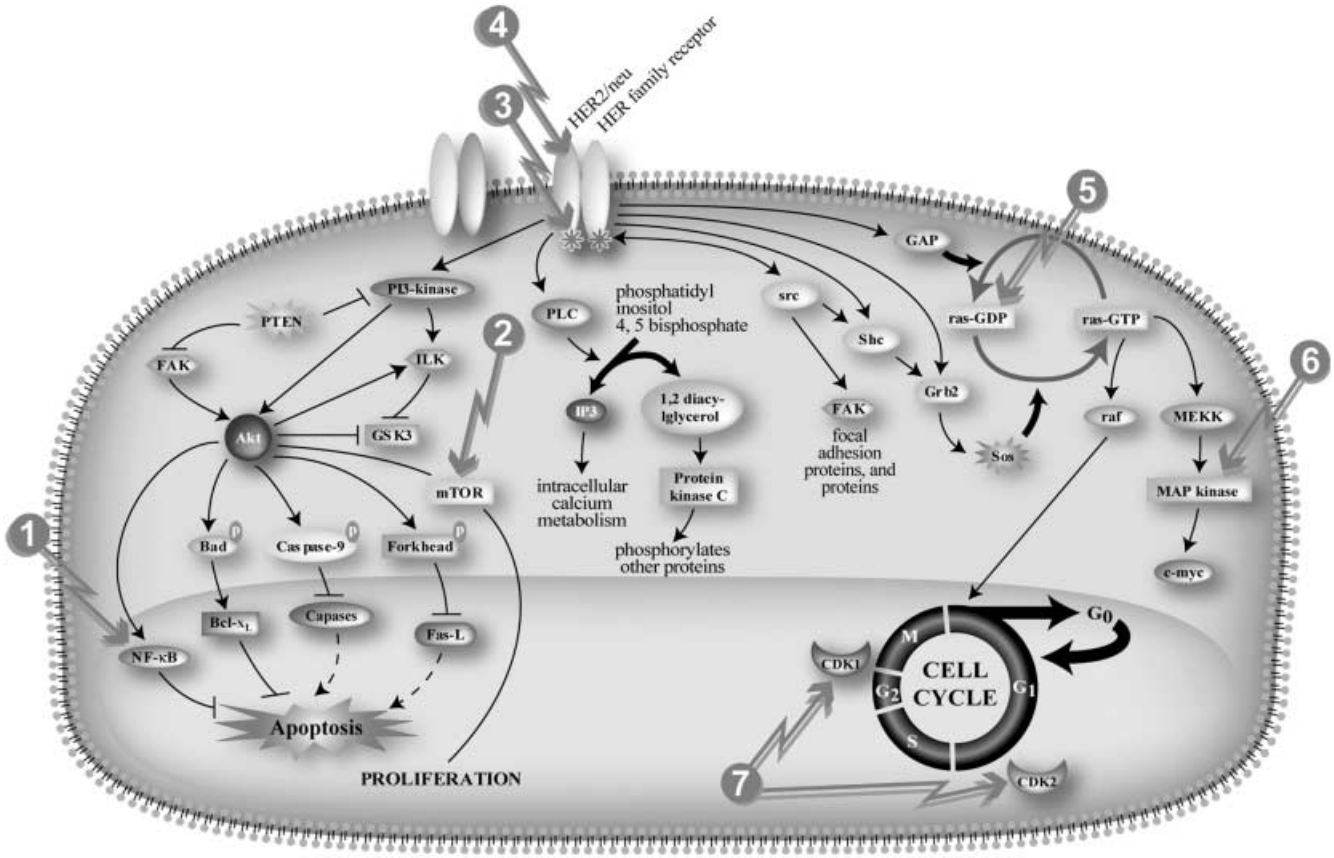

Figure 1. Multiple signaling pathways involved in cancer and the action of targeted therapeutics. 1, proteasome inhibitors (among other targets, NF-κB inhibitor IKB); 2, mTOR inhibitors; 3, receptor tyrosine kinase inhibitors; 4, growth factor receptor antibodies; 5, farnesyl transferase inhibitors; 6, MEK inhibitors; 7, cell cycle (CDK) inhibitors.

immune response to the vaccine was more than 4 months. The median time to disease progression was around 3 months; therefore most patients were progressing before an expected vaccine immune reaction was possible. In the subgroup that received hormonal therapy [mostly estrogen receptor (ER)-positive patients], median time to progression was 5.7 months in the placebo arm and 8.2 months in the vaccine arm, a nonsignificant trend ($p = 0.48$) that might reflect some degree of activity in more indolent disease. An exploratory analysis with longer follow-up showed a stronger trend, although still not achieving statistical significance.

These results illustrate the need to match the patient population to the proposed mechanism of action. Furthermore, reagents to test for the antigenic epitope showed expression in only 30% of cases. This suggests that the optimal population for testing might be patients with indolent or early stage breast cancer, perhaps focusing on higher-risk patients so the number of subjects would be as small as possible. The strategy of testing agents at early stages of disease requires large patient numbers and longer follow-up. When one takes into account the poor predictive nature of preclinical models, it is easy to understand why pharmaceutical companies cannot afford to test new agents in early stage disease. A compromise approach might be testing of a new agent in the neo-adjuvant setting for both clinical and biomarker responses, as well as long-term outcomes of disease-free and overall survival. Many trials are now using this design, and much more refinement in the interpretation of intermediate endpoints will be needed.

IDENTIFYING OPTIMAL CANDIDATES FOR TARGETED THERAPIES

With certain biologic agents, the therapeutic target is clearly defined. In the case of trastuzumab, only HER-2-positive patients were enrolled in the early pivotal trials, but it later became clear that the initial assay for HER-2 determination was not specific enough (24). Superior response rates were seen with either very strong

immunoreactivity or with HER-2 gene amplification, but still many patients, even by those criteria, did not respond. In the case of epidermal growth factor receptor (EGFR)-targeted therapy, EGFR expression does not seem as critical (25). So far, the status of downstream signaling proteins has not yielded a consistent pattern that predicts response. However, there is now evidence that mutations in the adenosine triphosphate (ATP) binding domain of EGFR predicts response to gefitinib in lung cancer, and this has led to several ongoing studies to sequence target genes and downstream mediators for other growth factor receptor-based drugs (26,27). More comprehensive analysis of tumors at the gene expression or protein level may generate profiles of responsiveness to targeted therapies in a similar fashion as is emerging for chemotherapy (28).

There may be a limit to the predictive power of either individual markers or large-scale protein or gene profiles. Cellular pathways are highly interconnected. However, as gene array and proteomic technologies for multiparametric analysis become more standardized and available, they will undoubtedly enter the clinical arena for standard therapies and will be integrated into studies testing novel targeted therapies and combinations.

PREDICTING TOXICITIES FROM TARGETED THERAPY

The perfect "magic bullet" that affects only cancer cells while sparing normal cells is not fully possible since cancer cells bear more similarities than differences to normal cells. Cardiac toxicity from trastuzumab was not expected since HER-2 was initially felt to be fairly tumor specific. However, HER-2 is expressed at low levels on other epithelial cells, possibly explaining the mild pharyngitis and diarrhea seen when it is used as a single agent (12,13). More importantly, low levels of HER-2 are expressed on myocytes. In embryogenesis, HER-2 expression appears to be critical to the development of the cardiac and neural systems (29). In the adult heart, HER-2 may still be important in cardiac remodeling under stress and could explain why trastuzumab-related cardiomyopathy is more common in patients with anthracycline exposure, increased age, and a history of hypertension (30,31). While the benefit from trastuzumab outweighs the toxicities (including cardiotoxicity) in the advanced setting, it is not clear that this will be the case in the adjuvant setting, where short-term clinical cardiotoxicity rates of 4% have been seen, while the long-term sequelae are unknown (32,33).

Similarly other receptor targets such as EGFR may have even more side effects, as this receptor is more ubiquitously expressed on epithelial cells. EGFR-targeting antibodies and small molecules cause very predictable skin and gastrointestinal toxicities (34). Angiogenesis targeting also can affect normal microvessels, causing hypertension, thrombosis, and proteinuria (35). Antibodies tend to be more specific to the target compared to small molecule inhibitors. However, even good specificity can lead to direct and indirect consequences through complex and interacting pathways. Genetic variability can also account for differences in side effect profiles for both conventional and biologic drugs, and the field of pharmacogenomics will play an increasingly important role in predicting and managing drug toxicities (36).

In summary, targeted therapies to an expanding list of cellular pathways are becoming more widely tested in the clinic, and a growing number of antibodies, small molecules, cytokines, and gene-based therapies are in preclinical testing. While individual drugs are not likely to profoundly impact the outcome of a majority of patients, combinations and better patient selection will maximize their effect. More sophisticated and individualized analysis of tumor and host characteristics will also better predict individual toxicities for targeted therapy. Newer large-scale gene and protein-based analytical methods are leading to biologically driven tumor classifications. These tools will allow for a more rational selection of patients suitable for specific types of targeted drugs. Ultimately these methods can also identify and validate surrogate markers of clinical benefit, which in turn will provide more rapid and accurate readouts of the potential success of novel agents and combinations.

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