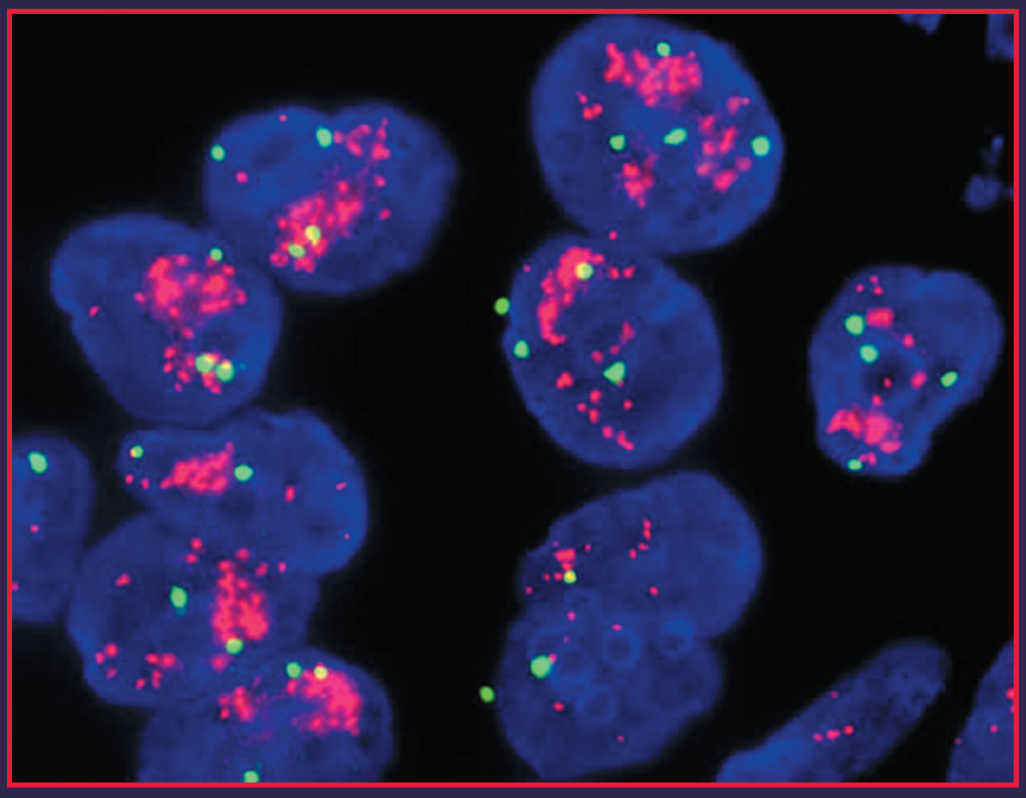
Therapeutic Strategies

TARGETED THERAPIES IN BREAST CANCER

G. W. Sledge, Jr. · J. Baselga



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Edited by

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Acronyms and abbreviations

17-AAG	17-allylamino-17-demethoxy-geldanamycin
4HPR	N-4-hydroxyphenyl
5-FU	fluorouracil
5′-DFUR	5′-deoxy-5-fluorouridine
ACOSOG	American College of Surgeons Oncology Group
ADC	antibody-drug conjugate
ADCC	antibody-dependent cell-mediated cytotoxicity
ADH	atypical ductal hyperplasia
AI	aromatase inhibitor
AJCC	American Joint Committee on Cancer
ALDH1	aldehyde dehydrogenase 1
ALH	atypical lobular hyperplasia
ALK	anaplastic lymphoma kinase
ALTTO	Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation
AMP	adenosine monophosphate
APHINITY	Adjuvant Pertuzumab and Herceptin IN Initial TherapY of Breast Cancer
ASCO	American Society of Clinical Oncology
ATP	adenosine triphosphate
AVADO	Avastin And Docetaxel
AVEREL	AVastin in combination with hERceptin/docetaxEL in HER2-positive metastatic breast cancer
BMD	bone mineral density
BOLERO	Breast cancer trials of OraL EveROlimus
CAP	College of American Pathologists
CES-D	Center for Epidemiologic Studies Depression Scale
CHD	coronary heart disease
CI	confidence interval
CLEOPATRA	CLinical Evaluation Of Pertuzumab And TRAstuzumab
CLSI	Clinical and Laboratory Standard Institute
CNA	copy number alterations
CNS	central nervous system
COE	Center of Excellence
CORE	Continuing Outcomes Relevant to Evista
COX	cyclooxygenase
CTL	cytotoxic T lymphocyte
DAB	3,3'-diaminobenzidine
DCIS	ductal carcinoma in situ
dCK	deoxycytidine kinase
dFdCMP	fluourodeoxycytidine monophosphate
dFdCTP	2′-2′-difluourodeoxycytidine triphosphate
DFS	disease-free survival

DHFR	dihydrolate reductase
DPYD	dihydropyrimidine dehydrogenase
DVT	deep vein thrombosis
EGFR	epidermal growth factor receptor
EMILIA	An Open-Label Study of Trastuzumab Emtansine (T-DM1) vs Capecitabine+Lapatinib in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer
EMT	epithelial-mesenchymal transition
ER	estrogen receptor
ERK1/2	extracellular signal regulated kinase
FDA	Food and Drug Administration
FDR	false discovery rate
FdUMP	fluorodeoxyuridine monophosphate
FFPE	formalin-fixed paraffin embedded
FISH	fluorescent in situ hybridization
FUTP	fluorouridine triphosphate
GM-CSF	granulocyte macrophage colony-stimulating factor
GO	gene ontology
GSEA	gene set enrichment analysis
GST	glutathione S-transferase
GWAS	genome-wide association study
hCNT	human concentrative transporter
hENT	human equilibrative transporter
HER	human epidermal growth factor receptor
hNT	human nucleotide transporter
HOT	HRT Opposed to low-dose Tamoxifen
HR	hazard ratio
Hsp90	heat shock protein 90
IBIS	International Breast Cancer Intervention Study
IGF-1	insulin-like growth factor 1
IgG	immunoglobulin G
IHC	immunohistochemical
LCIS	lobular carcinoma in situ
LDL	low-density lipoprotein
mAb	monoclonal antibody
MARIANNE	A Study of Trastuzumab Emtansine (T-DM1) Plus Pertuzumab/ Pertuzumab Placebo Versus Trastuzumab [Herceptin] Plus a Taxane in Patients With Metastatic Breast Cancer
MEK1/2	mitogen-activated extracellular-signal regulated kinase
MINDACT	Microarray In Node-negative and 1-3 node positive Disease may Avoid ChemoTherapy
MORE	Multiple Outcomes of Raloxifene Evaluation
MOS	Medical Outcomes Study
NCI	National Cancer Institute
NCIC-CTG	National Cancer Institute of Canada Clinical Trials Group
NeoALTTO	Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation
NSABP	National Surgical Adjuvant Breast and Bowel Project
OR	odds ratio
OS	overall survival
PAM	prediction analysis of microarrays
pCR	pathologic complete response

PCR	polymerase chain reaction
PDGF	platelet-derived growth factor
PDK1	phosphoinositide-dependent kinase 1
PE	pulmonary embolism
PEARL	Postmenopausal Evaluation and Risk-reduction with Lasofoxifene
PEPI	preoperative endocrine prognostic index
PET	positron emission tomography
PFS	progression-free survival
PIP2	phosphatidylinositol 4,5-diphosphate
PIP3	phosphatidylinositol 3,4,5-triphosphate
pNR	pathologic no response
pPR	pathologic partial response
PR	progesterone receptor
PTEN	phosphatase and tensin homolog
QA	quality assurance
QOL	quality of life
qRT-PCR	quantitative reverse transcriptase polymerase chain reaction
RCB	residual cancer burden
ROR	risk of recurrence
RR	relative risk
RUTH	Raloxifene Use for the Heart
SAM	significance analysis of microarrays
SERM	selective estrogen receptor modulator
SF-36	Short Form Health Survey
SNP	single nucleotide polymorphism
STAR	Study of Tamoxifen and Raloxifene
TAILOR x	Trial Assigning IndividuaLized Options for Treatment (Rx)
T-DM1	trastuzumab-DM1
TEACH	Tykerb Evaluation After Chemotherapy
TIA	transient ischemic attack
TNBC	triple-negative breast cancer
TOP2A	topoisomerase II alpha
TRYPHAENA	Trastuzumab plus Pertuzumab in Neoadjuvant HER2-Positive Breast Cancer
TTP	time to progression
TYMP	thymidine phosphorylase
TYMS	thymidylate synthase
VEGF	vascular endothelial growth factor
WG-DASL	Whole Genome cDNA-mediated Annealing, Selection extension and Ligation

1

The new biology of breast cancer and its therapeutic implications

G. W. Sledge Jr.

INTRODUCTION

Breast cancer therapy has undergone a series of evolutionary (and sometimes revolutionary) steps, a process that has accelerated in the past two decades as our understanding of breast cancer biology has steadily improved. This chapter, and indeed this book, outline some of these changes and attempt to place them in the context of breast cancer biology.

It is important to recognize that breast cancer therapy, from its earliest days in the modern scientific period of medicine, has always had both a strong theoretical as well as a pragmatic and empirical basis. If one begins with the last years of the nineteenth century, two theories of breast cancer biology were already being examined for their therapeutic benefit.

First, and the dominant strand for over half a century, was the work of Halsted and colleagues, who posited that breast cancer was a disease with a logical basis of metastasis via direct extension from the breast to the regional lymph nodes to distant sites via the lymphatic system. This theoretical conception of breast cancer biology implied the necessity for complete removal of all local–regional disease, and served as the basis for both breast cancer surgery and radiation therapy as potentially curative modalities.

The second strand, and ultimately the most important one for our purposes, was the recognition by Sir George Beatson that many breast cancers, though not all, were under the control of the ovaries in premenopausal women, and that breast cancers (both in the breast and at distant sites) could regress if the ovaries were resected [1]. This deep insight was ignored and forgotten for many years, but eventually served as the basis for our modern understanding of breast cancer biology.

BREAST CANCER AS A FAMILY OF DISEASES

The modern synthesis of breast cancer biology began with the discovery of the estrogen receptor (ER) in the 1960s, and the recognition by the mid-1970s that the ER could be measured in human breast cancers and predicted therapeutic response to manipulations of the internal hormonal milieu [2]. The recognition that the ER played a key role in many breast cancers also led to the development of numerous agents targeting either the ER or its ligand, estrogen.

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These agents included, famously, the selective ER modulator tamoxifen, an agent which perhaps represented the first real molecularly-targeted therapy in all of oncology, and to this day the agent that has arguably saved more lives than any other in all of oncology.

Tamoxifen was followed by numerous other agents (e.g. aromatase inhibitors, LHRH agonists, fulvestrant; and steroidal agents in the progesterone, androgen, and estrogen families), but serves as an excellent example of targeted therapy. First, measure the target (in this case, the ER, though the progesterone receptor was soon added as a measure of an intact ER pathway); then use the target to determine which patients were likely to benefit from an endocrine manipulation; and then, finally, apply agents that specifically interfere with either estrogen production or the ER itself.

Though initially limited to the treatment of metastatic breast cancer, tamoxifen and its therapeutic relatives were eventually drafted for other therapeutic purposes. These have included, first and most importantly, the treatment of micrometastatic disease in the adjuvant setting, but have also included use as chemoprevention and as neoadjuvant (preoperative) therapy. Large randomized controlled trials have repeatedly demonstrated the benefits for these agents in every setting.

In both the early and advanced stages of ER-positive breast cancer, drug resistance remains a major issue. Numerous potential causes of resistance to ER-targeted therapy have been evaluated in the laboratory, as described in this volume. Few therapeutic approaches have emerged from these analyses for clinical use. An exception has been the description of the molecular target of rapamycin (mTOR) as a final common nodal point for several growth factor receptors implicated in resistance to endocrine therapy. Recently this has led to the development and evaluation of the mTOR inhibitor everolimus in combination with second-line aromatase inhibitor therapy using exemestane. The combination of these two agents is superior to exemestane alone with regard to progression-free survival in metastatic ER-positive breast cancer [3].

By the 1980s several facts became evident. While ER positivity was common in breast cancer, it was not ubiquitous. Many breast cancers clearly lacked an ER, and among those that had it, not all responded to endocrine manipulation. The search therefore began for other stimulants of breast cancer growth, and for mechanisms of resistance to ER-targeted therapy. This search led to the discovery of the second great driver of breast cancer growth, the human epidermal growth factor receptor type 2, or HER2 as it is more commonly known.

HER2 over-expression, in contrast to ER positivity, was primarily a matter of amplification of the portion of the long arm of chromosome 17 that carries the *HER2* gene. The end result of this amplification was the increased expression of HER2 on the cell membrane. This trans-membrane receptor kinase, when activated via dimerization with either other HER2 molecules or with other members of the epidermal growth factor receptor family, affected numerous intracellular functions, but particularly two major signal pathways: mitogen-activated protein (MAP) kinase and phosphoinositide 3-kinase (PI3K). Inhibition of MAP kinase and PI3K resulted in cell growth arrest and apoptosis, respectively.

HER2 amplification was initially demonstrated to be associated with impaired outcome for patients with early stage breast cancer in 1987 [4]. By the mid 1990s this observation had been amply confirmed in numerous pathological studies. It only awaited the development of a therapeutic agent to exploit this for clinical intent. The first agent to be developed in this regard was the humanized monoclonal antibody trastuzumab, which binds to the external membrane domain of the HER2 molecule.

The development of trastuzumab paralleled the earlier course pioneered by ER-based therapeutics. First, measure the receptor in human breast cancers. In the case of the ER, measurement eventually fixed on immunohistochemical analysis of the nuclear receptor. HER2, in contrast, could be measured either at the protein level (by immunohistochemical staining of the cell surface membrane receptor), or at the DNA level via fluorescence *in situ* hybridization (know as FISH; commonly expressed as a ratio of *HER2* to chromosome 17).

Measurement of HER2 was, and remains, a controversial subject, though standardization of HER2 testing (via the American Society of Clinical Oncology/College of American Pathologists guidelines) has improved HER2 testing significantly in recent years.

Next, following measurement of the HER2 molecule, treat the patients with an agent specific to HER2. Though trastuzumab was the initial HER2-targeting therapy, and remains the most commonly used agent for HER2 [5], other agents have followed. These have included, though certainly are not limited to, the small molecule receptor kinase inhibitor lapatinib [6], the monoclonal antibody pertuzumab (which interferes with HER2 dimerization with other members of the HER family) [7], and the trastuzumab-maytansanoid conjugate T-DM1 (essentially using trastuzumab to deliver a cytotoxic agent to HER2-positive breast cancer) [8].

HER2-based therapeutics followed the path trod by ER-based therapeutics in another important way. After initial positive trial results in the metastatic disease setting, trastuzumab was rapidly moved to the micrometastatic disease setting in a set of parallel trials [9, 10]. All of these trials were strikingly positive, with results suggesting that appropriate therapeutic targeting in a well-defined breast cancer subset could offer important advantages for the conduct of clinical trials. In contrast to older trials in unselected patient populations, HER2 adjuvant trials were virtually all over-powered from a statistical standpoint; such was the potency of the intervention.

The first generation of adjuvant trials also explored important questions regarding HER2 therapeutics. What represents the appropriate duration of therapy? What represents the optimal chemotherapeutic combination? Should that combination include an anthracycline, perhaps improving efficacy, but definitely increasing cardiac toxicity and with long-term effects yet to be well defined? These questions remain problematic and controversial, though answers to some important questions (particularly duration of therapy) are now beginning to emerge.

The development of later generations of HER2-targeted drugs, and in parallel an improved understanding of HER2 biology, has opened up both new questions and novel therapeutic opportunities. Partial or complete resistance to trastuzumab is ultimately quite common in metastatic disease, and remains an important cause of death in the micrometastatic disease setting. Should we, in addition to targeting the extracellular membrane receptor, also block either the downstream receptor kinase domain, or alternatively interfere with dimerization with other members of the HER family? Preclinical studies have suggested that both approaches might help prevent the development of resistance to trastuzumab.

This increased understanding of resistance mechanisms, as well as the availability of new agents developed in the metastatic disease setting, has led to the creation of several adjuvant trials examining the benefits of combined blockade of the HER2 pathway. Both health care professionals and their patients anxiously await the results of these trials. Are we close to closing the door on HER2-positive disease as a major cause of breast cancer mortality? If so, therapeutic targeting of HER2 will have been a signal success in the human cancer story.

A curious thing happened in the past decade. Oncologists had long been aware of the fact that many human breast cancers lacked either estrogen-driven or HER2-driven cancer biology. Yet these cancers had never been explored to any significant extent, either as a biological mechanism or specific clinical subset worthy of focused investigation. The demonstration of HER2- and ER-driven breast cancers (and, indeed, by cancers driven by both) ultimately focused the attention of cancer researchers on patients incapable of benefiting from either therapeutic approach.

In recent years these cancers have been colloquially known as ‘triple negative breast cancer’ (interestingly, the term did not enter the medical literature until the past decade). Such cancers had several defining characteristics. They tended to be poorly differentiated tumors

characterized by high proliferative capacity and an increased likelihood of early distant metastasis. Though these were often sensitive to adjuvant systemic chemotherapy (the only therapy available in routine practice), in the overt metastatic setting chemotherapy proved a progressively weaker asset, with rapidly diminishing returns and the emergence of multidrug resistance.

Most troubling, both to patients and physicians, is the fact that chemotherapeutic agents are notoriously unselective in their effects. We cannot, in simple terms, define a population that will routinely benefit from, say, paclitaxel as opposed to doxorubicin. We therefore treat patients with agents that will not work for the majority of patients in hope that some will benefit, exposing all to the very real toxic effects. In this regard, triple negative breast cancer therefore represents an area of biologic uncertainty, ethical complexity and therapeutic uncertainty.

THE GENOMIC ERA IN BREAST CANCER THERAPEUTICS

Curiously, while relatively little progress has been made regarding the targeting of specific chemotherapy agents, significant progress has occurred in predicting general chemotherapy benefit, particularly in patients with ER-positive early stage breast cancer. This progress has come about largely through the application of novel genomic technology to the breast cancer problem.

If, by the turn of the millennium, breast cancer had resolved itself into a family of diseases, characterized by distinct biologies requiring separate therapeutic approaches, what was the ultimate basis for these differences? Genomic studies using early RNA microarray technology suggested an underlying biological basis for the divisions seen in breast cancer [11]. Initial studies suggested that breast cancer could be divided into four (or perhaps five) families: Luminal A and B, basal (or basaloid), HER2, and (perhaps) normal.

In particular, Luminal A and B appeared to describe populations of ER-positive breast cancer patients with either relative lesser (Luminal A) or greater (Luminal B) proliferative capacity. Several multigene assays were developed during the past decade, and used to examine therapeutic benefit as well as evaluate overall prognosis. As a meta-analysis of these assays has shown, a proliferative gene cassette appears to be a common element predicting outcome.

One such assay, the 21-gene OncotypeDX assay, may serve as an exemplar for this approach. Analysis of early adjuvant chemotherapy trials in ER-positive lymph node-negative patients (NSABP B-14 and B-20) allowed one to determine whether a patient was at greater or lesser risk for early recurrence, and (perhaps more importantly) which patients appeared to derive benefit from the administration of adjuvant chemotherapy [12, 13]. As the hazard ratio for chemotherapy benefit in a high recurrence score subset was equivalent or superior to the hazard ratio for benefit seen with trastuzumab in HER2-positive breast cancer, adjuvant chemotherapy suddenly became a form of targeted therapy for such patients. This has fundamentally changed our approach to treatment in ER-positive, lymph node-negative patients, a population where the previous standard of care had been the application of chemotherapy to all patients with primary cancers >1 cm. The best way to avoid unnecessary toxicity is to omit treatment for patients who will not benefit from therapy.

Similar genomic analyses have been applied to earlier stage breast cancer. Evaluation of ECOG E5194 ductal carcinoma *in situ* tumor samples has suggested that a gene signature that emphasizes a proliferation cassette of genes predicts patients at increased risk for local recurrence following lumpectomy alone, and may describe a population of patients who can be spared post-lumpectomy radiation.

Subsequent genomic studies have used so-called 'deep sequencing' to evaluate early stage breast cancer, with the recent production of a veritable cornucopia of data, as organiza-

tions such as The Cancer Genome Atlas consortium (TCGA) and the International Cancer Genome Consortium (ICGC) have evaluated literally thousands of breast cancers. In general, these studies have confirmed the broad outlines of previous first-generation mRNA-based studies, suggesting that the so-called 'intrinsic subtypes' had a real genetic basis. But they have also suggested a deeper level of complexity that was previously only suspected.

The hope underlying deep sequencing of the cancer genome was that, similar to *BCR-ABL* in chronic myelogenous leukemia, we might be able to identify actionable driver mutations. But while several novel driver mutations have been identified by recent studies (in genes such as *AKT2*, *ARID1B*, *CASP8*, *CDKN1B*, *MAP3K1*, *MAP3K13*, *NCOR1*, *SMARCD1* and *TBX3*), there is no dominant driver mutation that suggests a panacea for any breast cancer subtype. Instead, it is the sheer complexity of the mutational landscape that impresses: looking at 100 cancers, one such study found driver mutations in at least 40 cancer genes and 73 different combinations of mutated cancer genes. The authors went on to note that, "Thus, most breast cancers differed from all others." [14] There were numerous differences seen amongst these 100, with 28 cases having only a single identifiable driver, but some having as many as six. Modern medicine has never intentionally targeted six different mutational drivers at one time, suggesting the difficulty of the task ahead of us.

Serena Nik-Zainal of the International Cancer Genome Consortium recently published a paper entitled *The Life History of 21 Breast Cancers*, analyzing breast cancers as living, evolving, dynamic cell populations [15]. Their modeling suggests that each individual breast cancer has a "most recent common ancestor" (a term derived from evolutionary biology) that occurred early in the molecular history of the cancer, and that most of the cancer's history is spent "driving subclonal diversification and evolution among the nascent cancer cells". These subclones persist until the evolutionary pressures occurring in a cancer result in one subclone eventually becoming dominant. Many mutations may occur before this dominant subclone emerges: in one case described by Nik-Zainal *et al*, the dominant subclone (65% of the cancer) had ~15,600 mutations present. The paper concludes "... we glimpse a model of long-lived, but sparse, lineages of cells passively accumulating mutations until provoked into a major quest for tumor dominance. It is only when this subclone has grown sufficiently populous that the tumor mass becomes clinically detectable."

Unsurprisingly, genomic alterations may affect therapeutic outcome. Ellis and colleagues obtained breast cancer tissue from patients treated with preoperative letrozole, then performing deep genomic sequencing to discern patterns of response and resistance. [16] Their first finding was that resistance is a *quantitative* as well as a *qualitative* problem: resistant tumors had twice as many mutations as sensitive tumors. The second finding is a daunting one: many separate mutational events were associated with resistance to hormonal therapy.

The availability of genomic analysis is rapidly increasing, a function of the plummeting cost of DNA sequencing. We are only a few years away from a time when every patient's cancer will provide informative data on the specific genetic basis for that cancer's biology. How such genomic analyses will be applied in real-life clinical scenarios represents a major challenge for the next decade.

PHARMACOGENOMICS: THE HOST GENOME AND THERAPEUTIC RESPONSE

The host genome represents a novel area of exploration for cancer researchers. Clinicians have known for decades that human variability affects patient response to systemic therapy, but it has only been in recent years that our improving technology has allowed us to study the effects of host genomic variability on therapeutic outcome (pharmacogenomics) through examination of single nucleotide polymorphisms (SNPs). In theory, genomic variability could affect both toxicity due to inborn differences in drug metabolism, and efficacy (to the extent that host variability affects drug concentration).

Numerous such SNP analyses have been performed in recent years. Perhaps the greatest effort to date has been expended on the effect of host variability in the cytochrome p450 enzyme, cyp2D6, on tamoxifen metabolism. While this literature has been both confusing and contentious, current data do not suggest that cyp2D6 SNP measurements are ready for routine clinical use.

As with tumor genomics, measurements of the host genome have become significantly less expensive in recent years, leading to an explosion of clinical study analyses. Many of these are ongoing, and evaluating large clinical trials, so it is reasonable to expect that progress will be rapid in coming years.

However, the story revealed by host genomics is likely to be a complicated one, with few simple answers. The 1000 Genomes Project recently examined the genomes of 1092 people from 14 populations around the globe. [17] The investigators discovered some 38 million SNPs (twice the previous known number), many of them quite rare, as well as 1.4 million short insertions and deletions, and some 14,000 larger deletions and rearrangements. The average person carries 76–190 rare deleterious variants expected to affect protein function, plus 20 more loss of function and disease-associated SNPs. Both the high frequency of rare variants, and the large number of deleterious variants seen, suggest that host variability will be a difficult and complicated story, and one that will require extensive study if we are to avoid misapplication of this promising technology.

ANTIANGIOGENIC THERAPY: A BLIND ALLEY?

One area that seemed immensely promising only a few years ago now seems much less so. We have know for many years that angiogenesis, or new blood vessel formation, is one of the central hallmarks of cancer biology, and that measures of angiogenesis were associated with impaired outcome. A large body of research evaluated the biology of angiogenesis, and implicated the vascular endothelial growth factor receptors (VEGFR) and their ligands as principle players in tumor angiogenesis [18].

These discoveries led, in the late 1990s, to the development of numerous agents targeting the VEGF/VEGFR complex. The first agent to see widespread experimental and clinical use was the humanized monoclonal antibody, bevacizumab. After an initial phase II experience suggested therapeutic activity, a large phase III trial was performed in front-line metastatic breast cancer combining bevacizumab and paclitaxel. The E2100 trial demonstrated a striking doubling in median progression-free survival for patients with metastatic breast cancer, and formed the basis for the subsequent approval of bevacizumab by regulatory agencies [19].

The story of anti-VEGF therapy in breast cancer, regrettably, did not end there. The E2100 study, while it demonstrated an improvement in progression-free survival, was not associated with an improvement in overall survival. Subsequent phase III trials with bevacizumab, while positive for progression-free survival, were less impressive than E2100 for this endpoint, and like E2100 failed to demonstrate an overall survival advantage. Taking these results and the known toxicities of bevacizumab into account, the Food and Drug Administration removed bevacizumab's breast cancer indication.

Adjuvant trials of bevacizumab are continuing, and may still reveal a role for this agent in breast cancer. Nevertheless, what has become clear in studies of bevacizumab and other anti-VEGF therapies in breast cancer is that they are not targeted therapies in any meaningful sense: we are currently unable to demonstrate a specific population of patients who benefit from this approach, despite the widespread appreciation that some patients benefit. Turning anti-VEGF therapy into targeted therapy remains an important part of the scientific agenda in breast cancer.

CONCLUSION: OUR PROMISING FUTURE

This volume represents an early, rather than a final, examination of targeted therapy in breast cancer. Early, because it is clear that our understanding of breast cancer biology is in a state of rapid evolution. We do not yet understand the proper application of either host or tumor genomics, as described above.

Similarly, other technologies are likely to alter our approach to the breast cancer patient in coming years. Combinatorial chemistry continues to produce a profusion of new agents for application in the clinic, their use to be described by our understanding of individual patient tumor and host biology. The related technologies of epigenomics and proteomics have barely been evaluated in breast cancer, and virtually never in the ultimate laboratory of large clinical trial sets. Finally, molecular imaging of breast cancer, a promising approach with obvious potential application for targeted therapy, is barely in its infancy.

What is clear is that the next few years will be an exciting period in the history of breast cancer biology, and that this new biology will have numerous therapeutic applications. This can only benefit our patients.

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