**Abstract**

Human epidermal growth factor receptor (EGFR), HER, targeting has formed the basis of extensive and growing drug development programs in various companies. However, receptor biology is often poorly explained and confusing. The HER family of four naturally occurring receptors and one tumor-specific mutant can activate signaling via a complex and sophisticated range of mechanisms, which we are only beginning to understand. HER1/EGFR downstream signaling can lead to tumor growth and development via a host of processes, including enhanced cellular proliferation, survival, and metastasis. A range of potential therapeutic targets exists within the HER signaling system, both inside and outside the cell. Monoclonal antibodies and tyrosine kinase inhibitors, acting extracellularly and intracellularly, respectively, comprise two classes of agents most advanced in clinical development or already available for use. Despite promising single-agent activity in chemotherapy-resistant patients with non-small cell lung cancer (NSCLC), disappointing results from two phase III trials of the tyrosine kinase inhibitor gefitinib in NSCLC have been of concern to some. However, many factors may have contributed to this outcome, and it is not necessarily predictive of the future usefulness of these agents. Patient characteristics, lack of patient selection, dosing schedule, and trial design may all have played roles. It is important to remember that intracellular targeting of HER is a relatively novel approach, and our knowledge of how best to optimize such treatment is still unfolding. More clinical experience is needed. *The Oncologist* 2004;9:58-67

**Introduction**

A new understanding of tumor biology and genetics has enabled the development of novel approaches for the targeted treatment of cancer. These innovative avenues heralded a promising era of hope for oncologists and their patients, particularly in the treatment of solid tumors, cancers traditionally refractory to conventional chemotherapy and with poor prognoses. While expectations are, understandably, high, some confusion exists about the basis for such therapy. Clinicians are keen to use any therapeutic tool that

**Key Words.** Cancer · HER · Targeted therapy · Tyrosine kinase inhibitors · Erlotinib · Gefitinib
may work in this poorly served patient group. However, the underlying science of tumor targeting is complex and remains to be clarified. In addition, given the vast and growing published work on this subject, clinicians sometimes find it difficult to translate early clinical data into its potential value in clinical practice. This is especially true when trial results are not as positive as expected. This paper sets out first to demystify the science underlying the mechanisms of action of the main cancer therapies targeting the human epidermal growth factor receptor (EGFR), HER, family and second to put early clinical trial data in perspective with regard to differentiating these agents and predicting their potential benefits in widespread clinical use.

**HER Biology**

The HER family of receptor proteins plays a key role in tumorigenesis and disease progression. The HER molecules are cell membrane-bound proteins comprising four distinct receptors: HER1/EGFR, HER2, HER3, and HER4 [1, 2]. Three mutant HER1/EGFR receptors have been defined, with EGFRvIII (variant III) the most commonly detected in human solid tumors [3]. Receptor nomenclature varies across the literature (Table 1), though the HER terminology used in this paper reflects a species-specific precision (in this case, human) that is both simple to remember and scientifically correct.

Nonmutant HERs are each divided into three regions: an extracellular ligand binding region, an intracellular region with tyrosine kinase activity and regulatory functions, and a region that spans the cell membrane and anchors the receptor to the cell [2]. In the inactive state, each HER exists as a monomer. Ligand binding promotes either homodimerization (between monomers of the same receptor, e.g., HER1 HER1) or heterodimerization between the bound receptor and other members of the HER family (e.g., HER1/HER2), activating the receptor tyrosine kinase (Fig. 1). This biochemical trigger starts a cascade of complex cell biochemistry called downstream signaling that regulates various aspects of cell function [2], namely, cell proliferation, programmed cell death (apoptosis), angiogenesis, adhesion, and motility [4]. In abnormal cells, these pathways become dysregulated, leading to cell hyperproliferation and migration or metastasis.

The HER-family cell signaling process utilizes at least 11 EGF-like ligands [5]. HER1/EGFR is known to bind with a high affinity to several ligands, including EGF and transforming growth factor-α [6]. HER2 is structurally almost identical to HER1/EGFR, but no HER2 ligand has, as yet, been identified [7, 8]. However, despite this, HER2 tyrosine kinase is frequently activated, because this receptor is the most common heterodimerization partner for the HER family [9, 10]. HER3 and HER4 also structurally resemble HER1/EGFR, though HER3 has no intrinsic tyrosine kinase activity [11] and must associate with another HER-family receptor, usually HER2, to trigger signaling [10, 12].

The various signaling cascades activated through homo- or heterodimerization result in different cellular effects. Two major signal-transduction pathways are involved in HER1/EGFR signaling: the mitogen-activated protein kinase (MAPK) pathway, important in regulating cell growth, and the Akt pathway, predominantly involved in apoptosis and cell survival. Interestingly, recent studies suggest that these pathways may also regulate chemoresistance [13, 14]. However, further work is needed to fully understand the complex downstream signaling mechanisms that promote tumorigenesis and disease progression.

EGFRvIII, a mutant receptor, has a modified binding region and, consequently, cannot bind to a ligand [15]; it also does not dimerize [16]. However, it does have an intact tyrosine kinase domain that is constitutively activated and can initiate downstream signaling [3]. This mutant receptor is not found in normal cells, but is present in a wide range of solid tumors. Its constitutively activated state and association with

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**Table 1. Synonyms for members of the HER family**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Synonyms</th>
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<tbody>
<tr>
<td>HER1</td>
<td>erbB-1, EGFR</td>
</tr>
<tr>
<td>HER2</td>
<td>erbB-2, neu</td>
</tr>
<tr>
<td>HER3</td>
<td>erbB-3</td>
</tr>
<tr>
<td>HER4</td>
<td>erbB-4</td>
</tr>
</tbody>
</table>

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**Figure 1. Overview of the HER signaling system.**

A) HER2 homodimerization occurs without ligand (L) involvement (constitutive activation) and is enhanced when there is receptor overexpression. B) Ligand binding to HER1/EGFR facilitates heterodimerization with HER2, the most common coreceptor. C) Although HER3 has no active tyrosine kinase (K), ligand binding initiates signaling via heterodimerization with HER2. D) The mutant EGFRvIII lacks an extracellular ligand-binding domain and does not dimerize, but can still initiate signaling via constitutive activation.
The most promising and advanced therapeutic strategies are:

- Interruption of tumorigenic cellular mechanisms have emerged. Several possible points for therapeutic inhibition.

- HER1/EGFR and HER2 are the most widely studied HERs. HER1/EGFR is involved in normal cell growth, differentiation, and repair [2]. In many cancers, HER1/EGFR expression is abnormal or upregulated, indicative of a possible role in tumorigenesis [5, 18] (Table 2) [19-28]. Evidence suggests that HER1/EGFR overexpression or dysregulation correlates with disease progression, survival, stage, and response to therapy [18, 29, 30], indicating it may be a good target for therapeutic inhibition.

Although the complexities of HER-driven cell signaling have not yet been fully elucidated, several possible points for interruption of tumorigenic cellular mechanisms have emerged. The most promising and advanced therapeutic strategies are:

- **Small-molecule tyrosine kinase inhibitors (TKIs):** These are given orally and comprise, arguably, the most promising class of targeted agents currently in development. They work by inhibiting the intracellular portion of the target HER, thus blocking downstream signaling. TKIs can be reversible or irreversible and can have single, dual, or pan HER specificity. Examples include erlotinib (Tarceva™; Genentech Inc.; South San Francisco, CA; OSI Pharmaceuticals, Inc.; Melville, NY; and F. Hoffmann-La Roche Ltd.; Basel, Switzerland) and gefitinib (Iressa™; AstraZeneca; Wilmington, DE), which are both HER1/EGFR-targeted reversible TKIs currently being evaluated in late phase clinical development.

- **Monoclonal antibodies (mAbs):** These are injected and were the earliest approach to targeting HERs. They bind to the extracellular portion of the target HER, preventing activation. Examples are HER2-specific trastuzumab (Herceptin®; Genentech Inc.; South San Francisco, CA), already established in clinical practice, and cetuximab (Erbitux®; ImClone Systems, Inc; New York, NY), a HER1/EGFR-targeted mAb now in advanced clinical development.

As space in this paper is limited, it is impossible to do justice to the entire field of HER-targeted therapies. Recent news of disappointing results from two phase III trials evaluating the TKI gefitinib in non-small cell lung cancer (NSCLC) has focused attention on this class of compound. Therefore, it seems appropriate at this time to reexamine these data and attempt to put them in perspective in the context of HER targeting as a therapeutic approach, with regard to TKIs in particular.

### Table 2. HER1/EGFR overexpression in human solid tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>HER1/EGFR expression rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>14%-91%</td>
<td>[19-21]</td>
</tr>
<tr>
<td>Colon</td>
<td>25%-77%</td>
<td>[18, 22]</td>
</tr>
<tr>
<td>NSCLC</td>
<td>40%-80%</td>
<td>[18, 23-25]</td>
</tr>
<tr>
<td>Ovarian</td>
<td>35%-70%</td>
<td>[18, 26, 27]</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>30%-50%</td>
<td>[18, 28]</td>
</tr>
</tbody>
</table>

An invasive tumor phenotype [17] may reflect an important role in cancer pathogenesis.

Although the complexities of HER-driven cell signaling have not yet been fully elucidated, several possible points for interruption of tumorigenic cellular mechanisms have emerged. The most promising and advanced therapeutic strategies are:

- **Small-molecule tyrosine kinase inhibitors (TKIs):** These are given orally and comprise, arguably, the most promising class of targeted agents currently in development. They work by inhibiting the intracellular portion of the target HER, thus blocking downstream signaling. TKIs can be reversible or irreversible and can have single, dual, or pan HER specificity. Examples include erlotinib (Tarceva™; Genentech Inc.; South San Francisco, CA; OSI Pharmaceuticals, Inc.; Melville, NY; and F. Hoffmann-La Roche Ltd.; Basel, Switzerland) and gefitinib (Iressa™; AstraZeneca; Wilmington, DE), which are both HER1/EGFR-targeted reversible TKIs currently being evaluated in late phase clinical development.

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As space in this paper is limited, it is impossible to do justice to the entire field of HER-targeted therapies. Recent

### Making Sense of the Evidence

Two phase III trials (Iressa NSCLC Trial Assessing Combination Treatment [INTACT] 1 and INTACT 2), involving a total of 2,130 patients with untreated, advanced NSCLC, evaluating gefitinib in combination with one of two standard chemotherapeutic regimens (carboplatin and paclitaxel or gemcitabine and cisplatin), found no significantly greater overall survival, progression-free survival, or time to worsening symptoms associated with the addition of this TKI to chemotherapy, compared with chemotherapy plus placebo (Table 3) [31-37]. In the Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) 1 and IDEAL 2 phase II trials, gefitinib monotherapy showed promising results in NSCLC. Overall response rates at 250 and 500 mg/day were 18.4% and 19%, respectively, in IDEAL 1 [33], and 11.8% and 8.8%, respectively, in IDEAL 2 [34] (Table 3). While patients enrolled in the IDEAL 1 and IDEAL 2 trials had received at least one, and sometimes several, prior chemotherapy regimens, those enrolled in the INTACT 1 and INTACT 2 trials were chemotherapy naïve. The lack of additional benefit from combining gefitinib with chemotherapy as first-line therapy is entirely consistent with observations that, with conventional chemotherapy, triplet regimens are not superior to doublets in NSCLC [38]. Responses in the IDEAL 1 and IDEAL 2 trials were seen in a patient population already heavily pretreated with, and refractory to, chemotherapy, and may reflect a greater dependence of these tumors on HER1/EGFR pathways for growth and survival after chemotherapy-induced stress. Interestingly, the poor first-line combination data with gefitinib were in marked contrast to data obtained from preclinical studies in murine models [39]. The reason for this lack of concordance is unclear, but it could be a result of the different drug administration schedules used in the clinical and preclinical settings. Studies to examine the effect of scheduling on the efficacy of chemotherapeutic and targeted combinations are in progress.

Evidence, although unconfirmed, suggests that cancers can become dependent on one or more specific elements of the cell signaling circuit, requiring their continued presence in order to remain malignant [40]. Thus, if a cancer becomes dependent on the HER1/EGFR pathway, or some element of it, response to inhibition of this pathway may be greater in tumors that depend on the pathway, which offers another
Table 3. A selection of trials for tyrosine kinase inhibitors now in late-phase clinical development

A) Phase III trials

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial name</td>
<td>PA. 3</td>
<td>INTACT I (European Union/Japan)</td>
<td>INTACT 2 (U.S.)</td>
<td>TALENT (European Union)</td>
<td>TRIBUTE (U.S.)</td>
<td>BR.21 (ex-U.S.)</td>
</tr>
<tr>
<td>Date of completion</td>
<td>2004</td>
<td>mid-2002</td>
<td>mid-2002</td>
<td>Late 2003</td>
<td>Late 2003</td>
<td>Early 2004</td>
</tr>
<tr>
<td>Design</td>
<td>Randomized, double-blind, placebo-controlled, multicenter</td>
<td>Randomized, double-blind, placebo-controlled, multicenter</td>
<td>Randomized, double-blind, placebo-controlled, parallel-group, multicenter</td>
<td>Randomized, double-blind, placebo-controlled, parallel-group, multicenter</td>
<td>Randomized, double-blind, placebo-controlled, multicenter</td>
<td></td>
</tr>
<tr>
<td>Protocol</td>
<td>Combination with gemcitabine</td>
<td>Combination with gemcitabine and cisplatin</td>
<td>Combination with gemcitabine and paclitaxel</td>
<td>Combination with gemcitabine and cisplatin</td>
<td>Combination with paclitaxel and carboplatin</td>
<td>Monotherapy</td>
</tr>
<tr>
<td>Cancer</td>
<td>Pancreatic cancer (carcinoma)</td>
<td>Advanced NSCLC (carcinoma); chemotherapy-naïve stage III/IV (ECOG PS 0-2)</td>
<td>Advanced NSCLC (carcinoma); chemotherapy-naïve stage IIb/IV (ECOG PS 0 or 1)</td>
<td>NSCLC (carcinoma); chemotherapy-naïve stage IIIb/IV (ECOG PS 0 or 1)</td>
<td>NSCLC (carcinoma); chemotherapy-naïve stage IIIb/IV (ECOG PS 0 or 1)</td>
<td>NSCLC (carcinoma); chemotherapy-naïve stage IIIb/IV (ECOG PS 0 or 1)</td>
</tr>
<tr>
<td>Dose/Regimen</td>
<td>100 mg/day (150 mg/day after safety phase)</td>
<td>Standard chemotherapy + 250 or 500 mg/day</td>
<td>Standard chemotherapy + 250 or 500 mg/day</td>
<td>150 mg/day</td>
<td>150 mg/day</td>
<td>150 mg/day</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>No results yet</td>
<td>Diarrhea, rash</td>
<td>Diarrhea, rash</td>
<td>No results yet</td>
<td>No results yet</td>
<td>No results yet</td>
</tr>
<tr>
<td>Activity</td>
<td>No results yet</td>
<td>No difference in overall survival, progression-free survival, or time to worsening symptoms</td>
<td>No difference in overall survival, progression-free survival, or time to worsening symptoms</td>
<td>No results yet</td>
<td>No results yet</td>
<td>No results yet</td>
</tr>
</tbody>
</table>

B) Phase II trials

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial name</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A (U.S.)</td>
<td>IDEAL 1 (European Union/Japan)</td>
<td>IDEAL 2 (U.S.)</td>
</tr>
<tr>
<td>Design</td>
<td>Open-label</td>
<td>Open-label</td>
<td>Open-label</td>
<td>Randomized, double-blind, parallel group, multicenter</td>
<td>Randomized, double-blind, parallel group, multicenter</td>
</tr>
<tr>
<td>Protocol</td>
<td>Monotherapy</td>
<td>Monotherapy</td>
<td>Monotherapy</td>
<td>Monotherapy</td>
<td>Monotherapy</td>
</tr>
<tr>
<td>n of patients</td>
<td>124</td>
<td>34</td>
<td>57</td>
<td>209</td>
<td>216</td>
</tr>
<tr>
<td>Cancer</td>
<td>HNSCC refractory to chemo-/radiotherapy</td>
<td>Advanced ovarian cancer refractory to taxane and/or platinum</td>
<td>Advanced NSCLC (carcinoma) refractory to platinum-based chemotherapy</td>
<td>Advanced NSCLC (carcinoma); 1-2 prior chemotherapy cycles</td>
<td>Advanced NSCLC (carcinoma) ≥2 prior chemotherapy cycles</td>
</tr>
<tr>
<td>Dose/regimen</td>
<td>150 mg/day</td>
<td>150 mg/day</td>
<td>150 mg/day</td>
<td>250 or 150 mg/day</td>
<td>250 or 500 mg/day</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Rash, diarrhea</td>
<td>Rash, diarrhea</td>
<td>Rash, diarrhea</td>
<td>Rash, gastrointestinal</td>
<td>Rash, gastrointestinal</td>
</tr>
<tr>
<td>Activity</td>
<td>PR 6%; PR/SD 46%</td>
<td>PR 6%, PR/SD 51%</td>
<td>CR/PR 12%; CR/PR/SD 51%; OS 8.4 months</td>
<td>CR/PR 18% and 19%; CR/PR/SD 54% and 51%; OS 7.6 and 7.9 months at 250 and 500 mg/day</td>
<td>CR/PR 12% and 9%; CR/PR/SD 42% and 36%; OS 6.5 and 5.9 months at 250 and 500 mg/day</td>
</tr>
</tbody>
</table>

Abbreviations: CR = complete response; ECOG PS = Eastern Cooperative Oncology Group performance status; HNSCC = head and neck squamous cell carcinoma; OS = overall survival; PR = partial response; SD = stable disease
cetuximab in combination with chemotherapy showed all responses occur, therapy is effectively incomplete, leaving behind a residual subpopulation of more aggressive, resistant tumor cells. This would explain the responses seen in the IDEAL 1 and IDEAL 2 trials, versus the absence of any survival benefit in the INTACT 1 and INTACT 2 trials. More work is needed to establish whether such treatment actually directly kills tumor cells and, if not or if killing is incomplete, what consequences may result for subsequent tumor development. This will require the detailed study of tumor biopsies before, during, and after treatment, but will give a better understanding and so enable future treatment optimization.

Preselecting potentially responsive patients prior to therapy may increase the chances of achieving a positive outcome with new agents. Experience with trastuzumab has taught us that screening for a marker, HER2, prior to therapy with this agent is critical. If patients had not been selected for phase III trastuzumab trials based on HER2 expression, the objective response rate would have been so low that the trial would have resulted in a negative outcome and a potentially beneficial new therapy may have been overlooked [41]. The predictive marker for trastuzumab was easily identified as HER2, the target receptor; however, no reliable marker predictive of response has yet been identified for therapy with HER1/EGFR-targeted agents. HER1/EGFR, the most obvious choice, is overexpressed or dysregulated in many types of cancers [42], but several recent experimental studies suggest no correlation exists between HER1/EGFR overexpression and response to HER1/EGFR therapy [43, 44]. Although some studies have shown that the level of HER1/EGFR expression correlates with poor disease prognosis and lower survival, the data are inconclusive [18]. Indeed, HER1/EGFR expression has been used to preselect patients for therapy with some agents, but trials enrolling only HER1/EGFR-positive patients showed little better numbers of responsive patients [36, 37, 45]. This outcome may have resulted from the difficulties in quantifying HER1/EGFR expression [41] or the unrecognized molecular heterogeneity of tumors [46]. Interestingly, findings from a recent study examining cetuximab in combination with chemotherapy showed all responders had a +3-HER1/EGFR status [47]. However, the number of patients enrolled in that trial was relatively low (n = 30) and, therefore, further data are required to confirm these findings.

In a highly complex system such as the HER1/EGFR signaling network, the entire receptor family needs to be considered, its ligands, the role of gene mutations, and crosstalk with other signaling pathways. Studies have shown that overexpression of HER2 enhances the efficacy of TKIs and downregulates HER1/EGFR downstream pathways [48, 49]. In an attempt to identify pretreatment characteristics associated with response, a recent study analyzing 140 patients with NSCLC treated with gefitinib monotherapy showed that bronchioalveolar features and a history of not smoking were the only predictors of response to gefitinib [50]. These data are supported by recent findings with erlotinib, which show that nonsmoking patients are potential responders to therapy [51]. These studies suggest that NSCLC may have a different biology in patients who have never smoked and may help unravel the mechanism of action of these agents. In summary, a deeper understanding of tumor biology and continued examination of tumor samples from clinical trials is required to identify markers that may predict response, hopefully, allowing the realization of the full potential of these agents.

As erlotinib progresses through two similar phase III trials, there may be some understandable apprehension among the clinical community regarding outcomes. As with the INTACT 1 and INTACT 2 trials, the erlotinib trials (Tarceva Lung Cancer Investigation [TALENT] and Tarceva Responses in Conjunction with Paclitaxel and Carboplatin [TRIBUTE]) are important steps on the road to optimizing the application and use of this novel class of targeted agents. However, as these agents are still being used in an untargeted manner, the results may be difficult to interpret. However, some differences do exist between these agents that may, at least in part, account for the observed lack of response to gefitinib in the INTACT trials and may provide some reason not to presume a similar outcome for erlotinib.

Tumors are likely to express variable but excessive numbers of HER1/EGFRs [18]. Unless all receptors are effectively inhibited from initiating signaling, there is likely to be sufficient residual tumorigenic activity to maintain disease. If a tumor cell has, say, 500,000 HER1/EGFRs, and a therapeutic agent inhibits only 90%, that leaves 50,000 HER1/EGFR signaling receptors remaining; even if 99% inhibition was achieved, 5,000 HER1/EGFR signaling receptors per cell would still remain. In addition, studies have shown that the concentration of TKI required to
inhibit receptor-mediated downstream signaling is much higher than that required to inhibit receptor autophosphorylation [49]. This suggests that, to achieve 100% receptor inhibition and completely block downstream signaling in as many tumors as possible, the therapeutic goal may require the administration of TKIs at as high a dose as can be tolerated without dose-limiting toxicities, that is, at the MTD. Erlotinib shows high plasma exposure for a relatively modest administered dose. Phase I data show maximum plasma levels (C_{\text{max}}) of 1,737 µg/ml of erlotinib at its MTD of 150 mg/day compared with a C_{\text{max}} of 307 µg/ml and a C_{\text{max}} of 903 µg/ml for gefitinib attained at daily doses of 225 mg and 525 mg, respectively [52, 53], close to recommended doses, but significantly below the MTD of 700 mg/day to >1,000 mg/day [53-55]. Although used at a much higher plasma concentration than gefitinib, erlotinib has a good safety profile [35-37, 52].

As with any pharmacotherapeutic intervention, ultimately, patient tolerability determines the therapeutic regimen. If sufficient tumor concentration of drug cannot be achieved before toxicity becomes dose limiting, therapeutic efficacy is compromised. As one approaches the MTD, toxic effects increasingly manifest. For example, rash, the most common class-related toxicity for TKIs, appears to depend on dose level [52-55]. However, the appearance of a rash may act as a marker of TKI therapeutic efficacy, a hypothesis that is borne out by analysis of data from a phase II trial of erlotinib in 57 patients with advanced NSCLC in whom the occurrence of a rash was associated with clinical benefit. All patients who showed complete or partial responses, and 95% of those who had stable disease also had rashes. Conversely, of those patients who had disease progression, only 54% had rashes. Rash was also significantly correlated with greater survival, both in terms of occurrence and grade of severity.

The hypothesis that the occurrence of a rash correlates with survival is also supported by data for cetuximab. Findings from four recent trials examining cetuximab as monotherapy or in combination with chemotherapy in patients with colorectal, head and neck, and pancreatic cancers show a strong correlation between cetuximab-related rash and survival [56]. In the largest trial of cetuximab given in combination with irinotecan to 120 patients with colorectal cancer, the median survival times for patients with no rash, grade 1 rash, grade 2 rash, and grade 3 rash were 4.1, 6.2, 10.5, and 14.9 months, respectively (\(p = 0.0001\)). Similarly, in a phase II trial of patients with HNSCC administered the higher recommended dose of gefitinib (500 mg/day), results show a strong correlation between skin toxicity and response (\(p = 0.004\), progression-free survival (\(p = 0.0002\), and overall survival (\(p = 0.001\)) [57]. Findings from phase I studies with various TKIs also suggest that rash is related to dose and support a correlation between rash and response/survival. Thus, we can hypothesize that dosing to increase rash may improve outcome [53-55]. Perhaps the recommended (tolerated) therapeutic dose for gefitinib is by necessity suboptimal in some patients. At this stage of our understanding of the biology of cancer and how TKIs affect it, we may be wiser to consider these agents as functional narrow-sparing chemotherapy, and administer them at or near the MTD, rather than following the concept of an optimal biological dose, which is very difficult to define. Based on this premise, a phase II multicenter trial is in progress examining whether dose escalation of erlotinib in patients with less severe skin toxicity may increase rash and therefore improve outcome.

HER1/EGFR and HER2 both play key roles in the tumorigenic process. Since HER2 is the preferential coreceptor for the HER family, inhibition of HER1/EGFR alone will not prevent signaling via, for example, HER2/HER3 heterodimerization. Multiple pathway activation probably functions as a key feature of aggressive and refractory cancers, such as NSCLC. An agent that can knock out not only the preferred aberrant signaling route of the tumor, but also a subordinate one, may have added clinical benefits. Studies show that erlotinib inhibited not only isolated HER2 tyrosine kinase, but also blocked HER2/HER3-mediated activation of downstream signaling in a receptor-rich model in vitro [49, 58], both at concentrations that could possibly be attained by this compound in a clinical setting. This agent has also shown dose-dependent inhibition of tumor growth that was cytotoxic at higher doses and did not plateau [59]. This suggests that the ability to give erlotinib at the higher end of the dosing spectrum could have the added advantage of multiple dimer blockade and/or cytotoxic activity.

Patients enrolled in initial clinical trial programs for any new treatment in oncology are likely to comprise cases of advanced, refractory, and conventionally untreatable cancers. As such, new strategies are being evaluated in the sickest, most previously overmedicated, and least responsive individuals. There is little time, therefore, within any given study for perfecting an optimal regimen or accurately predicting efficacy in widespread clinical practice. Clinical trial design is an imprecise art at the best of times; in this patient population, it poses a real challenge. Constraints of time, ethical considerations, small patient numbers in early studies, and the fact that one is trying to treat late-stage terminal illness in which secondary physiological effects have taken hold all conspire

\[ p = 0.0001 \]
to make both implementation of the trial and interpretation of the resulting data a medical minefield. Subtle differences among studies, such as patient population demographics in terms of disease stage, can lead to very different conclusions about efficacy and may or may not accurately predict the true place of an agent in the oncologist’s armamentarium. Phase II trials are designed to establish at least putative efficacy, which ideally means incorporation of a placebo control arm. However, in oncology, this can be ethically challenging, though not impossible, to achieve. Without this check, it cannot be assumed with 100% certainty that a clinical response is due to the treatment, even though in terminally ill patients a placebo effect of any magnitude is unlikely. Phase II trials evaluating gefitinib monotherapy in advanced NSCLC, the IDEAL 1 and IDEAL 2 trials, showed promising responses, but did not include a placebo arm, thus making definitive interpretation difficult. An ongoing phase III trial (BR.21) in a similar patient group addresses this question by comparing erlotinib monotherapy with placebo (Table 3).

A clinical trial is a licensing necessity, but it is also not always an exact science. Many factors can affect clinical trial outcomes, including trial design, dosing regimen, protocol, and patient selection criteria. For example, splitting a relatively small patient population into several even smaller groups to evaluate more than one dosing schedule can serve to hide modest survival benefits and make subsequent analyses less meaningful. The INTACT 1 and INTACT 2 trials had three arms, to take into account the two different doses of gefitinib used plus the control group [31, 32]. This may have contributed to a statistical dilution effect. The TALENT and TRIBUTE trials have two arms only, one to evaluate a single dose of erlotinib and one acting as the placebo control. From a statistical analysis perspective, this design effectively doubles the patient population on active medication and should help to reveal any effect on survival.

Other considerations to bear in mind when trying to interpret trial results include:

- **Protocol**: For targeted agents, the timing of administration within a combination therapy or overall clinical case management framework may be crucial in determining response. For example, TKIs may be optimally effective either after a course of conventional chemotherapy (to prevent tumor cell repair/recovery and facilitate apoptosis) or as pretreatment sensitizers for radiotherapy [60, 61].

- **Disease stage**: Preliminary trials are usually conducted in patients with advanced, near-terminal cancers, most of whom already have metastatic disease and associated physiological disturbances. By this time, cancer behaves like a ‘runaway train,’ generating its own momentum and biochemistry. Targeted agents offer an elegant solution for controlling cell aberrations, not a ‘chemical sledgehammer,’ and thus are probably being evaluated in a setting not best suited to their use, greatly underestimating their potential value. There is considerable strength in the argument that TKIs will work best when started in early-stage disease, that is, in an adjuvant or neoadjuvant context.

**Conclusion**

The mysteries of the complex mechanisms driving tumorigenesis, and of the HER pivotal role in this process, are only beginning to be unraveled. In some respects, novel targeted therapies are being fast-tracked to market because of an unmet medical need, leaving a knowledge gap in their wake regarding how best they should be used. Rather than balking at the challenges this presents, or arriving at conclusions too soon, we must share the responsibility for finding ways to ensure optimal utilization of these agents. This will likely involve identifying molecular markers that predict for response, thereby allowing the selection of the correct agent, or therapeutic “cocktail,” for the right patient, cancer, and clinical need. A veritable tidal wave of new diagnostic and therapeutic developments gives good reason for optimism about the future (Fig. 2).

Few, if any, preliminary studies, particularly those involving a novel class of compound, have gotten it right the first time. Rather than basing definitive prediction, good or bad, prima facie on such trials alone, it is important to constructively critique and to intelligently question all aspects of their rationale. Only then can such trials have meaningful value, not merely as predictors of clinical efficacy but, as importantly, as components of a process of learning and refinement leading to this goal. The experience of the INTACT trials with gefitinib should be put in perspective and considered in the context of the many other trials evaluating TKI therapy, both completed and ongoing, many of which have already shown encouraging results and only a few of which are shown in Table 3. One dictionary definition of trial states it to be a “preliminary contest.” No single clinical trial is an adequate substitute for consistent ongoing evaluation in clinical practice. As oncologists, we need to show a willingness to persevere with novel approaches, particularly when so much is at stake for us and our most vulnerable patients.
Figure 2. Selected HER-targeted cancer therapeutics in development.

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