



Donna Morrison. *Old Boca Grande*. Watercolor on Yupo, 32" × 38".

For a specialized patient population, the use of EGFR inhibitors appears to offer some benefits in non-small cell lung cancer.

Epidermal Growth Factor Receptor-Targeted Agents for Lung Cancer

Petra Martin, MB, BCh, BAO, MRCP, Catherine M. A. Kelly, MB, BCh, BAO, MRCP, and Desmond Carney, MD, PhD, FRCP

Background: *Approximately 150,000 people were diagnosed with non-small cell lung cancer (NSCLC) in the United States in 2005. Most presented with inoperable advanced-stage disease. Although combination chemotherapy remains the standard treatment, median survival with these regimens is only 8 to 10 months. Recent advances in our understanding of lung cancer on a molecular level have led to the introduction of targeted therapies.*

Methods: *We reviewed the mechanism of action of gefitinib and erlotinib as well as the results of phase I, II, and III trials with these drugs.*

Results: *No survival advantage was seen with the addition of gefitinib or erlotinib to combination chemotherapy in first-line treatment of advanced NSCLC. Erlotinib has shown a survival advantage over placebo in patients with NSCLC after first- or second-line chemotherapy. Recently, mutations in the epidermal growth factor receptor-tyrosine kinase domain have been identified. Patients who express these mutations have shown a higher probability of response to gefitinib.*

Conclusions: *Combination chemotherapy remains the first-line treatment of advanced NSCLC. The benefit of alternating drug schedules and combinations has been small. Targeted therapies such as gefitinib and erlotinib, although to date have shown no survival advantage when combined with chemotherapy in the first-line setting, remain promising. Ongoing studies of patient characteristics of responding patients and molecular studies of tumors may help to identify patients most likely to respond to these therapies.*

From the Oncology Registrar at the Mater Misericordiae University Hospital, Dublin, Ireland.

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Address correspondence to Prof Desmond Carney, Mater Private Hospital, Eccles Street, Dublin 7, Ireland. E-mail: dcarney@materprivate.ie

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Abbreviations used in this paper: NSCLC = non-small cell lung cancer, EGFR-TK = epidermal growth factor receptor-tyrosine kinase, ATP = adenosine triphosphate.

Introduction

Approximately 150,000 individuals were diagnosed with non-small cell lung cancer (NSCLC) in the United States in 2005. While public awareness of this cancer and its associated early warning signs has improved along with increasing use of screening techniques, the majority of patients will have advanced-stage inoperable disease at the time of presentation.

Treatment options for patients with early-stage disease include surgery or radiation therapy alone or in combination with systemic chemotherapy, which can improve symptom control, increase overall survival, and lead to cure in a small proportion of patients. For patients with advanced-stage metastatic NSCLC, the goals of treatment are to improve survival, improve quality of life with good symptom control, and minimize side effects of treatment. For patients with stage IV metastatic disease, current combination chemotherapy remains the standard treatment option for those fit enough. However, many patients are often not candidates for combination chemotherapy because of poor performance status or comorbid medical conditions frequently associated with a long history of tobacco smoking.

In the mid 1990s, it was demonstrated that for suitable patients, cisplatin-based chemotherapy was associated with a small survival advantage over best supportive care. The development in the past decade of newer cytotoxic agents with activity in the management of NSCLC, including docetaxel, paclitaxel, vinorelbine, and gemcitabine, led to the development of a large number of clinical trials evaluating these agents either alone or in combination with cisplatin or carboplatin. The results of four large, multicenter, open randomized clinical trials evaluating these agents in combination with either cisplatin or carboplatin have been reported over the past 2 years and have yielded similar results.¹⁻⁴ It is clear from these studies that no single regimen demonstrated a significant superiority over any other combination. In these studies in which most patients had an excellent performance status (Eastern Cooperative Oncology Group [ECOG] PS 0-1), the objective overall response rate ranged from 17% to 32%. The 1-year survival rate was 31% to 46%, and the median overall survival was approximately 8 months. Patients with a poor PS were poorly tolerant of combination chemotherapy, and those with an ECOG PS ≥ 2 were frequently excluded from trials.

For the minority of patients who failed or progressed after initial combination chemotherapy but remained well enough for further systemic chemotherapy, the overall response rates were lower and median survival time to second- and rarely third-line chemotherapy was of a shorter duration.^{5,6}

The ECOG trial E4599 recently reported a phase II/III randomized trial of paclitaxel plus carboplatin with or without bevacizumab, an antivascular endothelial growth factor monoclonal antibody in patients with advanced NSCLC who had received no prior chemotherapy. The trial reported a median survival of 10.2 months vs 12.5 months ($P = .0075$) in favor of the bevacizumab arm. If these results are confirmed, then this regimen might become a new treatment choice for patients with NSCLC.⁷

While the majority of cases of lung cancer can be prevented by smoking cessation, a large number of patients will continue to develop this tumor in the foreseeable future. Newer cytotoxic agents developed over the past decade have had some effect on overall response rate, survival, and quality of life, but the majority of patients will die of their disease. Thus, there is an urgent need for the development of new therapeutic approaches in the treatment and control of this tumor.

Advances in our understanding of the molecular pathogenesis of lung cancer have allowed the identification of specific targets for therapeutic approaches. This article discusses our current understanding and results of agents specifically directed at the HER2 family of growth factors and receptors in the treatment of NSCLC.

Epidermal Growth Factor Receptor

Function

The epidermal growth factor receptor (EGFR) is a member of the HER family of cell surface receptors that are important mediators of cell growth, differentiation, and survival. EGFR has been selected as a target in NSCLC because (1) EGFR plays a key role in cell signal transduction, (2) it is an oncogene causing cancer through overexpression of EGFR ligands, amplification of EGFR, and the prolonged activation in mutated EGFR-TK, and (3) EGFR activity can be inhibited by monoclonal antibodies directed against it.⁸

Activation

The EGFR is activated by binding of an appropriate ligand such as EGF or transforming growth factor alpha (TGF- α). Once bound, the EGFR binds to another EGFR or another member of the HER growth factor receptor family to form a homodimer or heterodimer, respectively. Formation of the dimer activates the intracellular tyrosine kinase (TK) domain. This triggers autophosphorylation of various tyrosine residues in the catalytic C-terminal domain of the TK. These phosphorylated tyrosine residues bind recruitment proteins that serve as substrates for EGFR-mediated phosphorylation or adaptor proteins. These link the receptor to various downstream effector pathways

such as the ras-raf-MAP-*fos* pathway, which is linked to proliferation of the cell or the PI3-Akt pathway associated with anti-apoptosis (Fig 1).^{9,10}

Gene Structure

The EGFR gene sequence is highly conserved and varies little across species. The human EGFR gene is located on chromosome 7 at position 7p11.2 and spans approximately 200 kb of genomic DNA.¹¹ It consists of 28 exons and encodes a 170 kDa glycoprotein that comprises three domains: an extracellular domain (exons 1–16), an intracellular domain (exons 18–28), and the membrane spanning region (exon 17). The

extracellular domain has four subdomains (I–IV). The intracellular domain has a C-terminal regulatory domain and TK (Fig 2).¹²

EGFR-TK Domain

The EGFR-TK domain is composed of two lobes — the N lobe and the C lobe. Adenosine triphosphate (ATP) binds in the cleft between the two lobes, and the substrate binds at the entrance of the cleft closely aligned by the γ -phosphate of ATP.¹³ The phosphate loop and the activation loop are two regions that are highly conserved across TKs. Both regions play an essential part in the catalytic process. The phosphate loop interacts

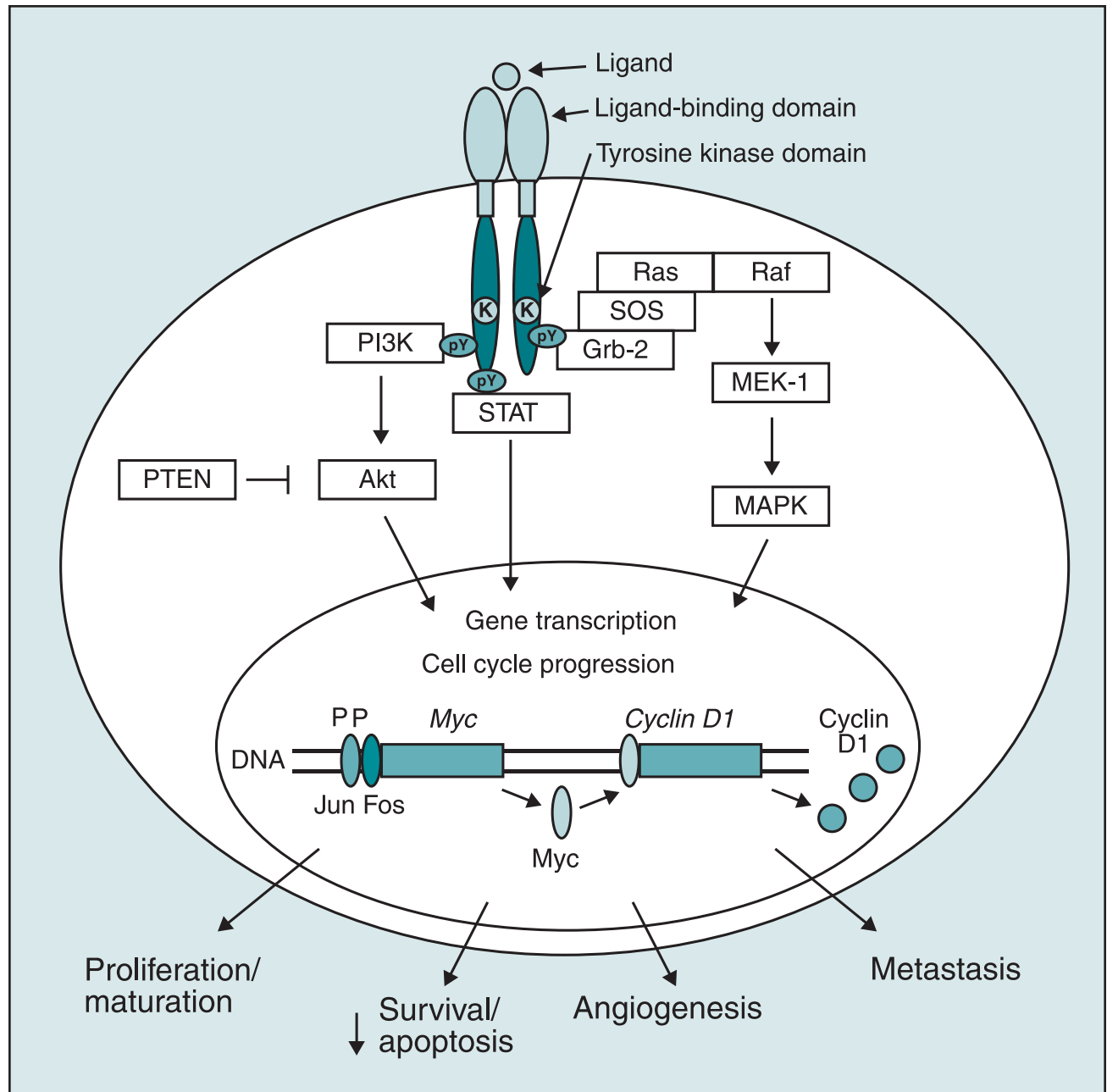


Fig 1. — EGFR growth factor signaling. From Baselga J. New technologies in EGFR-targeted cancer therapy. *Signal*. 2000;1:12-21. Reprinted with permission from Adis International, Wolters Kluwer Health.

directly with ATP, and the activation loop is located at the entrance to the cleft between the N lobe and C lobe proximal to the protein substrate and ATP molecule.¹⁴

Tyrosine Kinase Inhibitors

Small Molecule Inhibitors (Gefitinib)

The human vulvar squamous carcinoma cell line A431 provided the initial substrate for testing the first EGFR-TK inhibitors. This cell line expresses EGFR in high numbers, and it demonstrates both amplification and mutated forms of EGFR. The initial TK inhibitor had activity against A431 human tumor in xenografts in nude mice *in vivo* but was rapidly metabolized. Further modifications aimed at increasing stability and half-life led to the development of gefitinib (Iressa, ZD1839).¹⁵ Gefitinib is a low-molecular-weight, synthetic anilinoquinazoline. It is a competitive inhibitor of EGFR-TK. It

acts at the cytosolic ATP binding domain and inhibits autophosphorylation. These small molecule TK inhibitors are not specific for EGFR, and some degree of cross-reactivity occurs within the ATP binding domain of other members of the HER family.¹⁶ TK inhibitors may also mediate modification of the physiological receptor internalization-degradation pathway as occurs with CI-1033, an irreversible HER2 TK inhibitor.^{17,18}

Clinical Experience With Gefitinib

Gefitinib was the first EGFR-TK inhibitor approved by the US Food and Drug Administration in April 2003 for clinical use in advanced NSCLC. It is now licensed in more than 30 countries worldwide.

Four phase I studies found good tolerability and activity of ZD1839 in a range of tumors including NSCLC.¹⁹⁻²² Two large phase II studies have been reported: IDEAL 1 and 2 (Iressa Dose Evaluation in Advanced Lung Cancer).^{23,24}

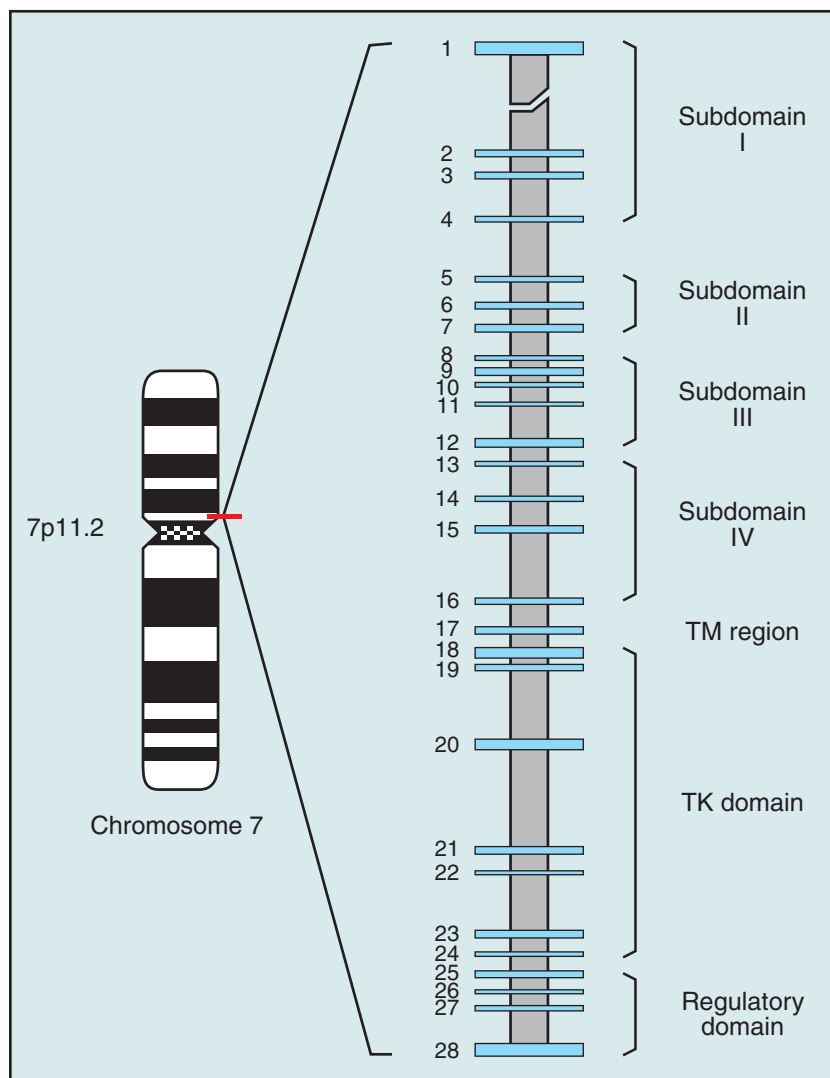


Fig 2. — Chromosomal location of the EGFR gene, its exon structure, and EGFR protein domains. Modified from Salomon DS. Exon structure of the EGFR gene. *Signal*. 2004;5:30-31. Reprinted with permission from Adis International, Wolters Kluwer Health.

IDEAL 1 and IDEAL 2 Studies

The objective of IDEAL 1 was to evaluate the efficacy and tolerability of two doses of gefitinib in patients with advanced NSCLC who were previously treated with one or two chemotherapy regimens (at least one containing a platinum). A total of 210 patients were randomized to receive either 250 mg or 500 mg oral doses of gefitinib once daily. IDEAL 2 was a double-blind randomized trial designed to assess differences in symptomatic and radiographic responses among patients with NSCLC receiving 250 mg or 500 mg doses of gefitinib once daily. The trial randomized 221 patients with either stage IIIB or IV NSCLC who had received at least two chemotherapy regimens. The patient characteristics are summarized in Table 1.

IDEAL 1 randomized patients who had received at least one or two previous chemotherapy regimens. IDEAL 2 required that patients received at least two prior chemotherapy regimens that included platinum and docetaxel administered either concurrently or as separate regimens. In the IDEAL 2 study, 60% of patients had received three or more prior chemotherapy regimens. All patients in the IDEAL 2 trial were symptomatic at entry, compared with only 65% of patients in the IDEAL 1 study treated at 250 mg/day. There were no Japanese patients in IDEAL 1.

The highest fraction of EGFR mutations that correlated to response to gefitinib was observed in Japanese women with adenocarcinoma (8 of 14 women, 57%). The significance of EGFR mutations is discussed later. Trials using cytotoxic agents have shown that response rates and survival generally decrease with subsequent chemotherapy regimens; Massarelli et al²⁵ reported a response rate of 20.9% for first-line treatment, 16.3% for second-line treatment, and 2.3% for third-line treatment.

Interestingly, the IDEAL trials showed the response rate for gefitinib at a dose of 250 mg/day was 12% to 18%, depending on the number of prior chemotherapy regimens and performance status (Table 2).

Response was rapid in these trials. Greater than 70% of patients had a response within 4 to 5 weeks. The median duration of response was 13 months (range, 2.0–19.8+) in the IDEAL 1 study and 7 months (range, 3.4–18.6+) in the IDEAL 2 study; some patients are still in remission. Disease control was achieved in 42% to 54% of patients, and 30% to 36% of patients had stable disease. Symptom control was achieved in 40.3% and 43.1% of patients in IDEAL 1 and 2, respectively. Improvements in disease-related symptoms occurred within 8 to 10 days. A positive correlation between symptom improvement and radiological response was observed. In IDEAL 2, 100% patients who had an objective response reported symptom improvement.

Gefitinib was well tolerated by patients in both trials. The most common drug-related adverse effects

Table 2. — Disease Control Rates of Patients in IDEAL 1 and 2 Trials Treated With Gefitinib 250 mg/day

	IDEAL 1 N = 103	IDEAL 2 N = 102
Objective response rate	18.4%	11.8%
Median duration of response	13 months	7 months
Stable disease rate	35.9%	30.4%
Disease control rate	54.4%	42.2%
Median duration of disease control	3.2 months	4.1 months

were rash and diarrhea. It was initially suggested that the rash could serve as a prognostic marker for tumor response to gefitinib. However, in IDEAL 2, among those who received gefitinib at 250 mg/day, 67% of patients who ultimately responded did not have a rash on day 14, and 25% who ultimately responded did not have a rash at day 28. In both IDEAL 1 and 2 trials, 29% of responders did not develop skin toxicity. It was therefore concluded that symptom improvement after initiation of gefitinib was a better correlate of response.²⁶

The phase II studies showed that gefitinib was well tolerated. Response to gefitinib was not dependent on the number of prior chemotherapy regimens and performance status. The level of expression of EGFR did not correlate to clinical response to gefitinib. Tumor EGFR expression was analyzed in 157 patients enrolled in the IDEAL trials, and no correlation between levels of expression and radiographic or symptomatic improvement was noted.²⁷ Both IDEAL 1 and 2 revealed that certain subgroups — female gender and adenocarcinoma subtype — had a higher probability of response to gefitinib. IDEAL 1 also added Japanese race, and subsequently, a multivariable analysis of 140 patients treated with gefitinib showed that nonsmokers and those with bronchoalveolar histologic features in their tumor specimens were also more likely to respond.²⁸

Phase III INTACT 1 and 2 Studies

Preclinical work on human tumor xenografts demonstrated synergy between gefitinib and cytotoxic agents when coadministered.^{29,30} This provided the rationale for two phase III trials, INTACT 1 and 2 (Iressa NSCLC Trial Assessing Combination Treatment) designed to evaluate gefitinib combined with 6 cycles of chemotherapy. Patients in the INTACT 1 study were randomized to receive 6 cycles of gemcitabine/cisplatin with either gefitinib 250 mg/day, gefitinib 500 mg/day, or placebo. Patients in the INTACT 2 study received 6 cycles of paclitaxel and carboplatin with gefitinib 250 mg/day, gefitinib 500 mg/day, or placebo. No survival advantage was seen with the addition of gefitinib to chemotherapy in either trial. There were no differences in the secondary or tertiary end points including response rate and time to progression. These results were disappointing, with the two large phase II IDEAL

Table 1. — Characteristics of Patients in the IDEAL 1 and 2 Trials Treated With Gefitinib 250 mg/day

	IDEAL 1 N = 103	IDEAL 2 N = 102
Median age	61.0 yrs (range 28–85)	61.0 yrs (range 34–84)
Gender		
Men	78 (76%)	60 (59%)
Women	25 (24%)	42 (41%)
Race		
Caucasian	48 (47%)	93 (91%)
Japanese	51 (49%)	0
Other	4 (4%)	9 (9%)
Tumour histology		
Adenocarcinoma	63 (61%)	70 (68%)
Squamous cell carcinoma	25 (24%)	14 (14%)
Large-cell carcinoma	9 (9%)	2 (2%)
Other	6 (6%)	16 (16%)
Performance status		
0	18 (17%)	18 (17%)
1	72 (70%)	64 (63%)
2	13 (13%)	19 (19%)
Not recorded	0	1 (1%)
Stage of disease		
IIIA	4 (4%)	0
IIIB	19 (18%)	15 (15%)
IV	80 (78%)	87 (85%)
Symptomatic at entry	67 (65%)	102 (100%)

studies reporting response rates of 11.8% and 18.4% and symptom improvement of 40%.

EGFR Mutations

IDEAL I and II identified certain patient subgroups with a higher probability of response to gefitinib. A significant step toward elucidating the mechanism responsible for response in these subgroups was made this year. Two separate groups identified mutations in the EGFR-TK domain that predicted for response to gefitinib.^{31,32} A total of 18 different mutations were identified involving exons 18–21, which code for the TK domain (Fig 2). The mutations were present in the subgroups previously identified as having a higher probability of response to gefitinib (Table 3).¹⁴

The most frequently identified mutations were in-frame deletions or substitutions. The 2155G → T-gene substitution gives the G719 mutation in EGFR protein that falls within the highly conserved phosphate loop, and the 2573 T → G substitution results in the L858R EGFR protein mutation that is located in the activation loop, again another region highly conserved across TKs.

How do these mutations predict for increased response to gefitinib? Lynch et al³¹ demonstrated prolonged activation of the mutant EGFR-TK when compared to the wild-type EGFR-TK. It appears that the presence of these mutations in EGFR-TK stabilizes the enzyme-substrate interaction, resulting in prolonged activation. This may be due to conformational changes within the active site affecting substrate binding to the mutant ATP pocket. The pattern of autophosphorylation

is also important in predicting the kind of response that the tumor cell will have to gefitinib. Sordella et al³³ generated cell lines expressing wild-type EGFR or mutant EGFR. They analyzed EGF-mediated autophosphorylation of multiple tyrosine residues linked to activation of distinct downstream effectors. Different patterns of phosphorylation were observed between the wild-type EGFR and the mutant EGFR. At the C-terminal sites, phosphorylation at Y992 and Y1068 was increased in the mutant EGFR-TK and not in the wild-type EGFR. This suggests that gefitinib-sensitive mutant EGFRs have a potential to transduce signals that are qualitatively distinct from those transduced by the wild-type EGFR. The authors hypothesized that the efficacy of gefitinib on mutant EGFRs may reflect its inhibition of critical anti-apoptotic pathways on which these lung cancer cells have become dependent. Mutant EGFRs demonstrate increased sensitivity to gefitinib (>100 times more sensitive to inhibition by gefitinib than wild-type). As noted earlier, this most likely reflects the altered drug binding to the ATP domain. However, it would appear that some of the rapidly responding tumor cells may have become dependent on specific anti-apoptotic pathways for increased survival. This in turn is dependent on autophosphorylation of specific tyrosine residues within the active site of the TK, which are specific for distinct EGFR mutations. To test this hypothesis, they compared the phosphorylation status of several downstream targets of EGFR, ERK 1, ERK 2, ras, Akt, STAT3, STAT5, and JAK2. The phosphorylation status of Akt, STAT5, and STAT3 was increased in both EGFR mutants expressing the L858R and the delE746-A750 mutations. Activation of Akt and STAT has been linked to anti-apoptosis.³³

Table 3. — Mutations Identified in the EGFR-TK Domain in Patients Who Had Dramatic Response

	Exon	Mutation in the EGFR Gene*	Consequent Mutation in the EGFR Protein**
Lynch et al ³¹	18	2155 G → T	G719C
	19	Δ2235-2249	ΔE746-A750
	19	Δ2240-2251	ΔL747-A752, P753S
	19	Δ2240-2257	L858R
	21	2573 T → G	L861Q
	21	2582 T → A	L861Q
Paez et al ³²	19	Δ2239-2247, 2248 G → C	ΔL747-E749, A750P
	19	Δ2240-2257	ΔL747-S752, P753S
	19	Δ2238-2255, 2237 A → T	ΔL747-S752, E746V
	21	2573T → G	L858R

* ΔX–Y = deletion of nucleotides X–Y (inclusive); X A → B = substitution of nucleotide A with nucleotide B at position X. Numbering is according to the Genbank entry for the coding region of the human EGFR gene (Accession number NM 005228). Available at: www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=41327737&itemID=1&view=gbwithparts.

** Standard one-letter code is used for amino acid residues. ΔX–Y = deletion of amino acid residues at positions X–Y (inclusive); X123Z = substitution of amino acid residue X at position 123 with amino acid residue Z. Numbering is according to the Genbank entry for the human EGFR protein (accession number NP 005219). Available at: www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NP_005219.2.

From Baselga J. The science of EGFR inhibition: a roadmap to improved clinical outcomes? *Signal*. 2004;5:4-8. Reproduced with permission from Adis International, Wolters Kluwer Health.

Future Directions

We know from the IDEAL trials that 12% to 18% of patients have a rapid response to gefitinib. Subgroups of patients who have a higher probability of responding to gefitinib can be identified on a clinical, histologic, and molecular level. Determining a patient's gender, race, smoking history, and histologic subgroup is routine; however, identifying the presence of an EGFR mutation in a patient is complex, and a standardized method to do so is not widely available. Therefore, it is not yet possible to determine who will respond and who will not. Many clinicians would agree that until we have a standardized and validated method of identifying patients likely to respond, all patients deserve a trial of gefitinib. The IDEAL trials reported good tolerability and minimal toxicities, and when patients did have a response it was early on in their treatment, so this approach is not an unreasonable one. A number of ongoing trials should further advance our knowledge regarding the appropriate use of gefitinib (Table 4). These trials are comparing gefitinib as monotherapy to best supportive care in the adjuvant setting; they also are studying the use of gefitinib with chemotherapy and following chemotherapy. Additional research is needed to identify further mutations that predict response, to determine the downstream effectors responsible for tumor growth and survival that may also serve as future targets, and to discover other cell membrane receptors that may also act as targets (eg, endothelin receptors and the vascular endothelial growth factor receptor).

Clinical Experience With Erlotinib (OSI-774)

Erlotinib (Tarceva, OSI-774), a quinazoline-based agent, is an orally administered reversible HER1/EGFR inhibitor.³⁴ It acts at an intracellular level competing with ATP for binding in the receptor's TK domain. By inhibiting the TK activity, downstream signal transduction is blocked. Akita et al³⁵ report that erlotinib can also inhibit HER2 phosphorylation and downstream signal transduction in HER2/HER3 overexpressing cells.

Phase I Trials

Phase I studies were undertaken to determine the maximum tolerated dose of erlotinib, its main toxicities, and its pharmacokinetic behavior in order to recommend a dose for subsequent studies. Results of these investigations showed that erlotinib had dose-independent pharmacokinetics and that daily dosing did not result in drug accumulation.³⁶ Erlotinib at 150 mg/day was determined to be the maximum tolerated dose and at which biologically relevant plasma levels were achieved. The most common toxicities associated with erlotinib in phase I trials were a dose-dependent acneiform rash and diarrhea. A similar rash has been observed with other TK inhibitors. Diarrhea is also a common side effect seen with other TK inhibitors, leading to the speculation that these symptoms are a result of inhibition of the EGFR. The histologic characteristics of this rash differ from that seen in typical acne. The pathologic finding showed a neutrophilic infiltrate in a perifollicular distri-

Table 4. — Ongoing Trials With Gefitinib 250 mg/day

Trial	Objectives	Projected Accrual (No.)
Adjuvant:		
NCIC BR.19	Gefitinib vs placebo in stage IB II, and IIIA completely resected NSCLC	1,242
First-line:		
INSTEP	Gefitinib + best supportive care vs placebo + best supportive care in chemotherapy-naive patients with advanced (stage IIIB or IV) NSCLC and poor performance status	200
INVITE	Gefitinib vs vinorelbine in chemotherapy-naive patients with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC	186
Second-line:		
INTEREST	Gefitinib vs docetaxel in patients with locally advanced or metastatic recurrent NSCLC who have previously received a platinum-based chemotherapy	1,440
ISEL	Gefitinib + best supportive care vs best supportive care in patients with advanced NSCLC who have received one or two prior chemotherapy regimens and are refractory or intolerant to their most recent regimen	1,692
Maintenance:		
EORTC 08021/LCP	Gefitinib vs placebo following chemotherapy	736
SWOG 0023	Cisplatin/etoposide/radiotherapy with consolidation docetaxel followed by maintenance gefitinib or placebo in inoperable, advanced stage III NSCLC	840
IMAC	Gefitinib vs placebo following chemotherapy	750

bution. This cutaneous manifestation was most commonly observed during the second week of treatment and then gradually resolved despite continuing with erlotinib. Other less common adverse reactions were mucositis, nausea, vomiting and headache.³⁶

The maximum tolerated dose of 150 mg/day was recommended for phase II trials. However, it remains unclear what dosage of the drug will cause complete receptor inhibition.

Phase II Trials

A phase II trial was conducted to evaluate erlotinib in advanced refractory NSCLC. This trial evaluated the effect of erlotinib at 150 mg/day on tumor response, survival, quality of life, and safety of patients with stage IIIB/4 HER1/EGFR-positive NSCLC, ECOG 0-2 who had failed prior platinum-based chemotherapy.³⁷ Fifty-seven patients were enrolled and the median age was 62 years (range, 31-83 years). All patients received erlotinib, and the median duration of treatment was 9 weeks (range, 2-131 weeks). EGFR positivity was defined as at least 10% of the malignant cells being positive for EGFR as determined by immunohistochemistry. The median time from initial diagnosis to study entry was 17.7 months (range, 4-137 months), and 82% of patients had received two or more chemotherapy regimens. Results of this phase II trial reported complete responses in 2 patients (4%), partial responses lasting between 12 and 56 weeks in 5 patients (9%), and prolonged stable disease in 22 patients (39%). Median survival was 8.4 months (95% confidence interval [CI], 4.8-13.9 months), the 1-year survival rate was 40%, and median progression-free survival was 9 weeks (95% CI, 8-15 weeks). The most common side effects were rash (67%) and diarrhea (56%). Patients who developed a rash survived longer (1.5 months) than those who did not have a rash, and the median survival duration was longer for those with grade 2/3 rash (19.6 months) compared with grade 1 rash (8.5 months).³⁷ This positive correlation suggests that rash may be a marker of HER1/EGFR kinase inhibition with the use of erlotinib. Lung cancer symptoms (fatigue, dyspnea, cough) improved with erlotinib use. Pretreatment characteristics that predicted for response or overall survival included time since initial diagnosis, time since last chemotherapy, and ECOG performance status. The extent of prior chemotherapy and EGFR levels did not predict for response or overall survival. In conclusion, phase II investigation showed that erlotinib was well tolerated and had improved survival compared with phase II trials of docetaxel monotherapy (8.4 months compared with 7.2 months, respectively).³⁸ Overall survival data were favorable for patients on erlotinib treatment compared with survival data from IDEAL 1 gefitinib trials (gefitinib 250 mg = 7.6 months; gefitinib 500 mg = 8.1 months) and IDEAL 2 (gefitinib 250 mg = 6.5 months; gefitinib 500 mg = 5.9 months).

Phase II trials evaluating erlotinib as first-line treatment in advanced NSCLC were presented at the 2005 annual meeting of the American Society of Clinical Oncology. In the first study, Giaccone et al³⁹ enrolled 54 chemotherapy-naive patients with stage IIIB/IV NSCLC and an ECOG PS of 0-2 to receive erlotinib 150 mg/day until disease progression or withdrawal. The non-progression rate was 55%, with responses seen in both genders. However, responses were more common in women (9 partial responses) than in men (1 complete response, 3 partial responses) and mostly in those with adenocarcinoma (7 patients) or bronchioloalveolar carcinoma (4 patients), and in nonsmokers or former smokers (12 patients). Five patients were reported to have a grade 3 adverse event. In a similar phase II study⁴⁰ evaluating erlotinib as first-line monotherapy in patients >70 years of age, chemotherapy-naive patients with stage III/IV disease and an ECOG PS of 0-2 were treated with erlotinib at 150 mg/day. At 13 months, 53 patients were evaluable for response. Eighteen patients experienced a grade 3 adverse event, most commonly rash (5 patients) and interstitial pneumonitis (3 patients). No patients achieved a complete response, but partial responses occurred in 6 patients (10.9%), stable disease in 30 (54.5%), and progressive disease in 19 (34.5%). Median survival for all patients was 10.5 months.

These early studies are encouraging as they show activity for erlotinib as first-line monotherapy and are also well tolerated.

Phase III Trials

Following these findings, a phase III randomized, double-blind, placebo-controlled trial was initiated by the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG-BR.21) to determine overall survival and symptom improvement with erlotinib compared with best supportive care in NSCLC patients after first- or second-line chemotherapy.⁴¹

Eligible patients included those with stage III or IV NSCLC and an ECOG PS of 0-3 who had received one or two prior chemotherapy regimens. A total of 731 patients were randomized in a 2:1 ratio to either receive erlotinib at 150 mg/day or placebo. Patients were stratified according to center, ECOG performance status, response to prior therapy, number of prior regimens, and previous platinum exposure. Median age at randomization was 61.4 years. Almost half (49%) had received two prior chemotherapy regimens and 93% had received platinum-based chemotherapy.

The response rate was 8.9% in the erlotinib arm and less than 1% in the placebo group ($P < .001$). The median duration of response was 7.9 months and 3.7 months, respectively. Overall survival was 6.7 months for those in the erlotinib regimen compared with 4.7 months in the placebo arm ($P < .001$; hazard ratio [HR] = 0.7). Progression-free survival was 2.2 months with

erlotinib and 1.8 months with placebo ($P < .001$; HR = 0.70). Five percent of patients discontinued erlotinib due to toxicity. This study showed that erlotinib significantly prolonged survival and improved symptoms. Analysis of quality of life showed that patients in the erlotinib group had statistically significant time to deterioration of tumor-related symptoms. In addition, there was a general trend toward improvement in symptoms (except diarrhea) and quality of life domains in the erlotinib group and deterioration in the placebo group.

Tumor samples of patients in this NCIC CTG study were used to assess whether the response to erlotinib and its impact on survival were associated with EGFR expression, gene amplification, or mutations.⁴² In phase II studies, responsiveness to erlotinib and gefitinib have been associated with female gender, Asian ethnicity, adenocarcinoma histology, and patients who have never smoked. These associations were confirmed in this study. In this study of 731 patients, 325 specimens were analyzed: 197 for EGFR gene mutations and 221 for the number of EGFR genes. Among those whose tumors were tested, 57% expressed EGFR.

On multivariate analysis, the response rate was higher for patients with EGFR-positive tumors than for those with EGFR-negative tumors — 11% vs 4%, respectively. In addition, patients who had polysomy or amplification of EGFR had a higher response rate (20%) than those without this feature (2%). However, the number of copies of EGFR was not a significant prognostic factor in multivariate analysis. Mutations were found in

23% of analyzed samples. Previous studies have found that mutations in the EGFR-TK domain (exons 18–21) increase the sensitivity of tumor cells to erlotinib and gefitinib. The most commonly identified mutations reported are in-frame deletions, with or without insertions in exon 19, and missense point mutations in exon 21. In this study by Tsao et al,⁴² 45 mutations were identified in 23% of the samples. Twenty-one mutations were either deletions in exon 19 or the exon 21 L858R mutation, and 24 were novel mutations. Although patients who had a mutation achieved a higher response rate, this was not significant and there was no significant difference in survival benefit seen in the erlotinib group compared with the placebo group in patients with exon 19 deletion or exon 21 L858R mutation ($P = .39$; HR for death = .65) or in patients with novel mutations ($P = .41$; HR = .67). Therefore, multivariate analysis confirmed that expression and an increased copy number of EGFRs but not mutations were associated with response to erlotinib but not with increased survival.

Two phase III randomized, double-blind, placebo-controlled trials assessed erlotinib with combination chemotherapy in the first-line setting — the TRIBUTE trial (erlotinib with paclitaxel and carboplatin) and the TALENT trial (erlotinib with cisplatin and gemcitabine).

The US-based TRIBUTE trial compared overall survival of patients with NSCLC receiving either erlotinib in combination with paclitaxel and carboplatin or paclitaxel plus carboplatin alone.⁴³ This prospective, placebo-controlled trial randomized patients with previously

Table 5. — Phase III Trials With Erlotinib 150 mg/day

Trial Design	Previous Treatment	Overall Survival (months)	Progression-Free Survival (months)	1-Year Survival (%)	Toxicity	Comment
Erlotinib vs placebo (NCIC CTG-BR.21 Trial ³³)	2nd- or 3rd-line	6.7 vs 4.7	2.23 vs 1.84	31 vs 22	Rash and diarrhea were the most frequent symptoms; 5% discontinued erlotinib due to toxicity compared to 2% taking placebo	Statistically significant overall and progression-free survival; first trial to show prolonged survival after 1st- or 2nd-line chemotherapy for NSCLC with HER1/EGFR inhibitor
Erlotinib plus carboplatin/paclitaxel × 6 followed by monotherapy vs carboplatin/paclitaxel alone × 6 (TRIBUTE Trial ³⁴)	1st-line	10.8 vs 10.6	5.1 vs 4.8	47 vs 43	Increased incidence of rash and diarrhea in erlotinib arm (47.7% vs 43.2%)	No difference in overall survival or in median time to progression for patients treated with erlotinib and carboplatin/paclitaxel over carboplatin/paclitaxel alone
Erlotinib plus cisplatin/gemcitabine × 6 followed by monotherapy vs cisplatin/gemcitabine alone × 6 (TALENT Trial ³⁶)	1st-line	9.9 vs 10.2	5.5 vs 5.7	41 vs 42	Toxicity profile not significantly different, but increased incidence of diarrhea with erlotinib (6%) vs placebo (<1%) and rash erlotinib (10%) vs placebo (<1%)	No statistically significant differences in overall survival, time to progression, or quality of life

untreated advanced NSCLC (stage IIIB/4) to receive erlotinib at a dose of 150 mg/day or placebo with 6 cycles of carboplatin plus paclitaxel followed by maintenance monotherapy. The primary end point was overall survival, and secondary end points included time to progression, objective response, duration of response, and time to symptomatic progression. A total of 1,059 patients were randomized: 526 received erlotinib and 533 received placebo). There was no difference found in patients treated with erlotinib and carboplatin/paclitaxel in comparison to those treated with carboplatin/paclitaxel alone: overall survival was 10.8 months with erlotinib vs 10.6 months with placebo ($P = .95$; HR 0.99), objective response was 5.5 months with erlotinib vs 5.0 months with placebo ($P = .32$; HR 0.85), and median time to progression was 5.1 months with erlotinib vs 4.9 months with placebo ($P = .36$; HR 0.94) (Table 5). Adverse reactions were similar in both groups, but rash and diarrhea were more common in the erlotinib group (47.7% with erlotinib vs 43.2% with placebo). This study concluded that erlotinib combined with carboplatin/paclitaxel chemotherapy did not confer a survival advantage over carboplatin/paclitaxel alone in previously untreated advanced NSCLC.

A subgroup analysis of the TRIBUTE trial assessed overall survival in patients who never smoked and were treated with erlotinib. This analysis showed that the addition of erlotinib to carboplatin/paclitaxel prolonged survival in these patients (median survival 23 vs 10 months; HR 0.49; 95% CI, 0.28–0.85).⁴⁴ This finding will require confirmation in a randomized trial.

The design and end points examined in the TALENT trial were similar to those in the TRIBUTE trial. However, the chemotherapy regimen was 6 cycles of gemcitabine/cisplatin with erlotinib at 150 mg/day or with placebo.⁴⁵ In comparing those treated with erlotinib

and those given placebo, there was no statistically significant difference in overall survival (301 days vs 309 days, respectively), time to progression (167 days vs 170 days, respectively), and quality of life (Table 5). This lack of survival benefit when an EGFR inhibitor is added to chemotherapy in the first-line setting in advanced NSCLC has also been reported in the INTACT trials with gefitinib (Fig 3).

Further Research

Additional investigation is needed to assess for reasons for failure of combination chemotherapy with erlotinib. It may be that patient selection is critical in determining those who respond to erlotinib, and although EGFR expression, gene copies, and EGFR mutations are associated with a response, response was also seen in patients without these features. Additionally, mutations and markers that correlate with response or additional signaling pathways have yet to be identified. Therefore, further research investigating additional EGFR-related pathways may provide information on the mechanism of action of this drug. Also, by identifying the molecular characteristics of a tumor, we may be able to predict who would be most likely to respond to therapy.

Other Small Molecules

CI-1033 is an irreversible “pan-erb” TK inhibitor, ie, it inhibits all four members of the EGFR class. Several phase I trials involving various solid tumors, including NSCLC, have been reported. The most common dose-limiting toxicities included diarrhea, rash, and anorexia, as seen with other small molecules.⁴⁶ In addition, grade 3 thrombocytopenia has also been reported.⁴⁷ In a

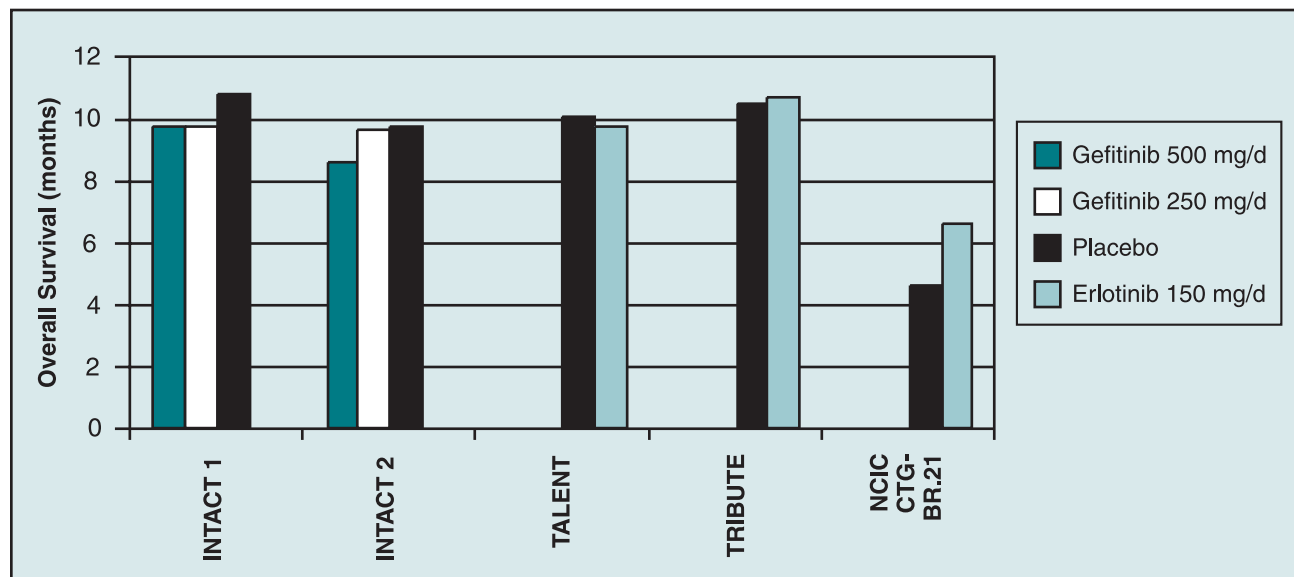


Fig 3. — Comparison of median overall survival among the INTACT 1, INTACT 2, TALENT, TRIBUTE and NCIC CTG-BR.21 trials.

phase I trial by Nemunaitis et al,⁴⁶ stable disease was seen in 10 of 32 individuals enrolled; however, no partial or complete responses were observed. This drug is currently in phase II trials.

GW572016 is a small molecule with dual inhibition of EGFR/Erb-2 kinase. In phase I trials, the most common adverse events included skin rash, diarrhea, and headache.⁴⁸ In one phase I trial, 2 patients with NSCLC who were resistant to gefitinib achieved minor responses. Therefore, the dual specificity of GW572016 may be more effective than more specific agents in some individuals.⁴⁹ However, this will require further investigation. Phase II trials are currently ongoing.

Monoclonal Antibodies

The anti-HER2 recombinant humanized monoclonal antibody 2C4 binds to a different part of the receptors domain than seen with trastuzumab (Herceptin). It inhibits the receptor from interacting with other HER family members. This prevents ligand-dependent HER2 signaling in HER2-positive and -negative cell lines. Phase I trials of 2C4 have shown no unexpected toxicity at highest doses.⁵⁰ Phase II trials will assess 2C4 in NSCLC.

Conclusions

Advanced inoperable metastatic NSCLC remains a major therapeutic dilemma, with the benefits from current chemotherapeutic regimens having reached a plateau at this time. Modest gains may be achieved with either alternating the schedule of the agents used (ie, weekly vs 3 weekly) or changing the doublets used; however, these gains are small. In recent years the molecular approach to the treatment of lung cancer has been developed. While initial responses may appear at first glance to be disappointing, this approach represents a major new direction in the treatment of solid tumors. The use of EGFR inhibitors appears to offer some benefits, if only in a specific patient population. Perhaps only a small minority of patients will benefit from these therapeutic approaches and thus patient selection may be vital in improving response rate. Detailed studies of the characteristics of responding patients (eg, gender, race, smoking history) are ongoing. In addition to pathologic and molecular studies of tumors, including the use of fluorescence in situ hybridization analysis to specific gene amplification, additional investigations of gene mutations and the use of gene arrays for genetic profiles and proteomics for protein profiles may ultimately define the characteristics of patient tumors most likely to benefit from such molecular-targeted therapies.

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