Lung cancer remains the number one cause of cancer-related mortality in the world. Despite advances in diagnosis, imaging, staging, and treatment, five-year survival in this disease is less than 20%. In the US, approximately 175,000 new cases are expected to be diagnosed in 2006 with nearly 162,500 deaths from this disease.¹ The majority of patients present with advanced disease, thus limiting the role of potentially curative surgery. Chemotherapy remains the mainstay for treating metastatic non-small cell lung cancer (NSCLC) with proven benefit in improvement of symptoms and quality of life, along with prolongation of survival. To date, no specific regimen of chemotherapy has clearly established superiority over another,² and the choice is largely governed by the patient’s performance status, comorbid conditions and the treating physician’s preference. Toxicity and relative non-specificity remain major drawbacks of chemotherapy in NSCLC. A better understanding of the molecular signaling pathways in lung carcinogenesis has led to the exploration of rationally developed novel therapeutic agents. This brief review will outline some of these agents under investigation in lung cancer.

The process of cellular differentiation, proliferation, and apoptosis is a tightly regulated one with multiple interactions within the cell and the surrounding extracellular matrix. A simplistic schema of intracellular signaling is shown in Figure 1. Disruption of one or more components in these pathways is often specific to the malignant phenotype, occurs commonly in NSCLC, and can serve as potential targets for intervention toward reversal.³

**Epidermal Growth Factor Receptor**

The epidermal growth factor receptor (EGFR) belongs to a family of receptor tyrosine kinases (TK) that includes ErbB (HER2/neu), ErbB3, and ErbB4. Activation of EGFR by ligand binding or by mutational conformation leads to TK activity, autophosphorylation, and activation of a cascade of cytoplasmic and nuclear signaling eventually culminating in cell proliferation and survival. EGFR is often over-expressed in NSCLC and portends a poorer prognosis.⁴ ⁵ Inhibition of EGFR activity can be achieved using monoclonal antibodies against the receptor, small molecule TK inhibitors, and antisense oligonucleotides.

**Anti-EGFR Monoclonal Antibodies**

Cetuximab (C-225) is a chimeric human–murine monoclonal antibody (MoAb) that competitively binds to the extracellular ligand domain of the EGFR with subsequent inhibition of phosphorylation and downstream signaling. In the US, it is currently approved in the treatment of refractory colorectal cancer (either singly or in combination with irinotecan) and squamous cell carcinoma of the head and neck (in combination with radiation or after failure of platinum-based chemotherapy). Studies in NSCLC are currently on-going, with early data suggesting a modest response rate of 4.5% when used after failure of standard therapy. Interestingly, disease stabilization was seen in nearly one-third of patients in this small trial.⁶ Cetuximab has also been used in combination with chemotherapy in the phase II setting with response rates approaching 30%.⁷ Results from the Southwest Oncology Group (SWOG)-0342 trial were recently reported in 225 patients using cetuximab in combination with carboplatin and paclitaxel, either concurrently or sequentially (as maintenance therapy).⁴ Response rates were higher with concurrent therapy (37% versus 25%) and median overall survival was prolonged (10.5 months versus 8.7 months). These results suggest that further study of cetuximab in NSCLC is of merit and a phase III trial is on-going.

Panitumumab is a recombinant human immunoglobulin (Ig)G2 kappa MoAb that binds specifically to the EGFR. It was recently approved in the US for EGFR-expressing chemotherapy-refractory colorectal cancer. This drug is being evaluated in combination with chemotherapy and other multi-kinase inhibitors in advanced NSCLC. Results should be forthcoming in the near future. Another selective anti-EGFR MoAb, matuzumab (EMD 72000), abrogates ligand-mediated activation and was shown to be well tolerated in combination with paclitaxel in
a phase I trial of advanced NSCLC. Four of 18 patients in this trial demonstrated a response, including one complete response.

**Small Molecule Receptor Tyrosine Kinase Inhibitors**

Erlotinib and gefitinib are two reversible receptor tyrosine kinase inhibitors (RTKIs) that are currently approved for the treatment of advanced NSCLC. These agents prevent binding of adenosine triphosphate to the intracellular tyrosine kinase region and, hence, can abolish downstream signaling even in conditions of ligand binding or mutational activation of the EGFR.

The enthusiasm for the use of gefitinib after its accelerated approval in 2003 has been tempered by the lack of demonstrable improvement in survival in the Iressa Survival Evaluation in Lung Cancer (ISEL) trial. This drug is no longer recommended unless patients are experiencing benefit from on-going use or when utilized under the aegis of a clinical trial. Erlotinib, an oral EGFR-specific anilinoquinazoline, was evaluated in BR.21, conducted by the National Cancer Institute of Canada Clinical Trials Group. In a 2:1 randomized placebo controlled design, 731 NSCLC patients were enrolled after failure of standard chemotherapy. The response rate and overall survival favored the erlotinib group (8.9% and 6.7 months) compared with placebo (1% and 4.7 months), both statistically significant results. Further evaluation of trials using these agents has demonstrated that response appears to be associated with certain phenotypes (East Asian descent, never-smokers, women, and patients with adenocarcinoma) and genotypes (EGFR activating mutations and EGFR copy number). Another reversible EGFR inhibitor, GW572016 (lapatinib), has been evaluated in advanced NSCLC. The drug was well-tolerated, with diarrhea, rash, and nausea being the most commonly reported adverse effects. Efficacy results are awaited. On-going elucidation of these translational paradigms in cancer biology may assist in the rationale selection of therapy for patients.

Despite exhibiting initial sensitivity to gefitinib or erlotinib, most tumors eventually become resistant to treatment. The development of secondary mutations in the tumor has been recently recognized as a potential mechanism of acquired resistance. In several tumor specimens examined, a new mutation in exon 20 leading to substitution of methionine for threonine at position 790 (T790M) was identified. This mutation has also been identified in tumors from therapy-naïve patients. This hinders drug binding to the adenosine triphosphate (ATP)-binding pocket within the tyrosine kinase domain. Some of the newer irreversible EGFR inhibitors have been shown to circumvent this resistance. EKB-569 is an irreversible EGFR tyrosine kinase inhibitor with demonstrated activity in vitro in gefitinib-resistant NSCLC cell lines. In a phase I study in patients with advanced solid cancers, the dose-limiting toxicity was diarrhea at the maximum tolerated dose (MTD) of 75 mg. One patient with NSCLC had stable disease (SD) for 33 weeks. Another structurally related novel dual-specific inhibitor, HKI272, that targets ErB2 and EGFR, has been shown to be similarly effective in gefitinib-resistant cell lines and is currently undergoing phase I testing in human trials. In the US, two industry-sponsored trials evaluating canertinib (CI1033), a pan-ErB inhibitor, in NSCLC have completed accrual and results should be available shortly. For a detailed description of EGFR inhibitors in development, the interested reader is referred to excellent reviews on this subject.

**Vascular Endothelial Growth Factor**

The importance of angiogenesis in the process of tumor growth and metastasis has been well recognized for over two decades. However, its utility as a target for therapeutic intervention has only recently been exploited. The vascular endothelial growth factor (VEGF) and its isoforms are the most commonly upregulated angiogenic factors in cancer and their over-expression has generally been linked to a poorer prognosis in lung cancer, among other tumors.

Bevacizumab is a recombinant, humanized monoclonal antibody that binds VEGF and prevents its interaction with VEGF receptors Flt-1 (VEGFR-1), KDR (VEGFR-2), and Flt-4 (VEGFR-3), thereby
inhibiting endothelial cell proliferation and reducing microvessel density. Following encouraging results seen with the addition of bevacizumab to conventional chemotherapy (carboplatin and paclitaxel) in a randomized phase II setting,25 ECOCG launched a randomized placebo-controlled phase III trial (ECOG 4599), results of which were presented at the 2005 annual meeting of the American Society of Clinical Oncology (ASCO).24 Patients receiving the combination of bevacizumab, paclitaxel, and carboplatin had a significantly improved response rate (27% versus 10%), overall survival (12.5 months versus 10.2 months) and one-year and two-year survival rates (52% versus 44% and 22% versus 17%) compared with those receiving chemotherapy only. Of note, this trial excluded patients with tumors of squamous cell histology, those with hemoptysis, and those with brain metastases given apparent risk factors identified in the preceding study. As expected, significant toxicities included hemorrhagic adverse events (4.5%) and hypertension (6%) in the experimental arm. Based on these results, bevacizumab in combination with paclitaxel and carboplatin has received regulatory approval for the therapy of advanced and metastatic non-squamous NSCLC in the US.

VEGF Trap is partially comprised of the extracellular domains of VEGFR-1 and -2 fused to the Fc portion of human IgG. This drug binds to circulating and tissue-bound VEGF thereby decreasing its availability to bind to its naturally occurring receptors. AVE0005 is currently being examined in NSCLC to determine its safety and efficacy. It has been used in advanced solid tumors in combination with oxaliplatin- and irinotecan-based chemotherapy regimens.

Another strategy within this pathway involves inhibition of VEGF receptor tyrosine kinase activity. A number of these agents inhibit the kinase activity of multiple receptors. Selected agents are shown in Table 1. Vatalanib (PTK787/ZK222584) is one such oral small molecule TK inhibitor with multi-targeted activity against VEGFR-2, c-kit, platelet derived growth factor receptor (PDGFR), and Flt-3. In a phase II trial in the second-line setting in advanced NSCLC using a dose of 1,250mg/d, a disease stabilization rate of 33% was obtained (one partial response, 17 SD) at week 12 and median survival was 7.2 months.25 Common adverse reactions included nausea, vomiting, and dizziness.

Sunitinib is another small molecule multi-RTKI that targets VEGFR, stem-cell factor receptor (KIT), platelet derived growth factor receptors (α and β), RET, and FLT3. Socinski et al. reported a 9.5% response rate (and 43% SD rate) to this agent after failure of platinum-based chemotherapy in patients with stage IIIB or stage IV NSCLC.26 Median overall survival was 24 weeks. There were three hemorrhage-related deaths believed to be secondary to treatment. Given this promising activity in a largely treatment-refractory population, additional trials of sunitinib in combination with other agents, including targeted therapy are on-going.

Dual VEGFR/EGFR Inhibitors

ZD6474 (vandetanib) is an oral small molecule inhibitor of VEGFR, EGFR, and RET tyrosine kinase activity. Theoretically, abrogating more than one pathway of carcinogenesis may lead to greater anti-tumor activity, a concept that may be important in a

![Figure 1: Simplified Scheme of Intracellular Signal Transduction Pathways](image)
molecularly heterogeneous tumor. In phase I studies, a dose of 300mg/day was established as the maximum tolerated dose with diarrhea, rash, and asymptomatic QTc prolongation being the most common side effects of ZD6474. Two phase II studies of ZD6474 (alone or in combination with chemotherapy) in nearly 300 patients with refractory NSCLC have demonstrated an improvement in progression-free survival compared with gefitinib or docetaxel.2,2 Randomized trials in the therapy-naive as well as refractory NSCLC population are currently on-going. Other agents in this class include AEE788 and XL647.29

The Ras-Raf-mitogen Activated Protein Kinase Pathway as a Target

The Ras-Raf-mitogen activated protein kinase (MAPK) pathway has been implicated in lung carcinogenesis and, potentially, the maintenance of the malignant phenotype in these tumors. As a result, numerous approaches to inhibiting this pathway in lung cancer have been explored in the last decade. Inhibition of raf kinase and MEK is currently under investigation.

Raf Kinase Inhibitors

The Raf family consists of serine/threonine kinases downstream of Ras, which play an important role in proliferative signal transduction from the extracellular stroma to the cell nucleus. Sorafenib is a novel bi-aryl urea that was initially developed as a specific inhibitor of the RAF/MEK/ERK pathway. Subsequent studies have shown this compound to also inhibit several other TKs involved in tumor progression, including VEGFRs, PDGFR, Flt-3, and c-kit.30 Gatzeimeier et al. reported a 59% SD rate with single-agent sorafenib (400mg orally twice daily) in advanced refractory NSCLC, although there were no partial responses.31 Patients with SD had a progression-free survival of 23.7 weeks versus 11.9 weeks for all evaluable subjects. Diarrhea, hand–foot syndrome and fatigue were the most commonly reported side effects of this drug, which is currently approved in the US for metastatic renal cell carcinoma. There was no adverse impact of sorafenib on patient-reported outcomes in function and symptom response. At least two phase III studies of this compound either singly or in combination with chemotherapy in lung cancer are currently on-going in Europe and North America.

MEK Inhibitors

The only known substrate for MEK (or mitogen-activated protein kinase kinase) is MAP kinase. Sequential activation of MEK and MAPK (also known as extracellular-related kinase or ERK) classically occurs downstream of, but can be independent of, Ras and Raf. Inappropriate oncogenic activation of this pathway is a feature of many neoplasms. CI-1040 is an orally active difluorobenzamide that exhibited highly selective, nanomolar inhibition of MEK in pre-clinical studies. This was the first MEK inhibitor to undergo clinical testing. Based on promising findings in phase I studies, a broad phase II study was performed in patients with breast, pancreatic, colorectal, and NSCLC. Eighteen patients with NSCLC previously treated with one systemic chemotherapy regimen were enrolled. No objective responses were documented in these 18 patients. Three patients maintained disease stability for three, three, and 10 months, respectively. The median TTP was 4.2 months, and median survival was 5.2 months. Interestingly, 70% of NSCLC tumor samples overexpressed p-ERK at baseline, indicating that the MEK pathway is activated in these tumors. Poor pharmacokinetics were felt to have contributed in large part to the lack of efficacy of CI-1040 in phase II studies.32

### Table 1: Selected Multiple Receptor Tyrosine Kinase Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Doses studied</th>
<th>Clinical toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vandetanib (ZD6474)</td>
<td>EGFR and VEGFR-2 TK</td>
<td>Up to 900–1,800mg/2d</td>
<td>Diarrhea</td>
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<td></td>
<td></td>
<td></td>
<td>Nausea/vomiting</td>
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<td></td>
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<td></td>
<td>Constipation</td>
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<td></td>
<td></td>
<td></td>
<td>Headache</td>
</tr>
<tr>
<td>Sorafenib (BAY 439006)</td>
<td>Raf and VEGFR kinase</td>
<td>200–800mg/1–2d</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Skin rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td>Sunitinib (SU11248)</td>
<td>PDGFR,VEGFR, KIT, FLT-3</td>
<td>50mg daily</td>
<td>Fatigue/asthenia</td>
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<tr>
<td></td>
<td></td>
<td>four weeks on,</td>
<td>Nausea/vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>two weeks off</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Vatalanib (PTK787)</td>
<td>VEGFR-1, KDR, VEGFR-2 PDGFR-β, c-kit</td>
<td>1,000mg/1–2d</td>
<td>Nausea/vomiting</td>
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<tr>
<td></td>
<td></td>
<td>14 days or 150–750mg</td>
<td>Hypertension</td>
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<tr>
<td></td>
<td></td>
<td>alternate days</td>
<td>Headache</td>
</tr>
<tr>
<td>AEE788 (AG-013736)</td>
<td>VEGFR,EGFR, HER-2/neu</td>
<td>Up to 100mg daily</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Skin rash</td>
</tr>
<tr>
<td>Axitinib (GW786034)</td>
<td>VEGFR-1, KDR, VEGFR-2 PDGFR-β, c-kit</td>
<td>800mg half daily</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25mg half daily</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Pazopanib (GW786034)</td>
<td>VEGFR-1, KDR, VEGFR-2 PDGFR-β, c-kit</td>
<td>50mg 3 times daily</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fatigue</td>
</tr>
<tr>
<td>AMG 706</td>
<td>VEGFR-1, KDR, VEGFR-2 PDGFR-β, c-kit</td>
<td>25mg half daily</td>
<td>Diarrhea</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Fatigue</td>
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</tbody>
</table>
Based on the above, and because of the documented activation of the MEK pathway in NSCLC, MEK is still felt to be a valid target for lung cancer therapy. Phase I studies of two second-generation MEK inhibitors, PD0325901 and ARRY-142886/AZD6244 are on-going.\(^3\)

**mTOR Inhibitors**

The mammalian target of rapamycin (mTOR) is a member of the family of phosphatidylinositol kinases and plays an important role in the regulation of translation initiation. Rapamycin, temsirolimus, everolimus, and AP23573 are inhibitors of mTOR currently under investigation. In a recently reported phase I study of temsirolimus, asthenia, nausea, cutaneous toxicity, and mucositis were the commonly reported drug adversities.\(^3\) A confirmed partial response lasting over 12 months was observed in a patient with NSCLC. Results from trials of other mTOR inhibitors in lung cancer are eagerly awaited.

**Conclusions**

In a disease where pharmacologic progress has been generally stunted with a plateau in chemotherapy options, the availability of rationally developed targeted drugs is indeed encouraging. In the investigation of these newer biologic agents we may need to incorporate novel surrogate end-points of activity and/or efficacy, thus changing paradigms in the treatment of lung cancer. Future trials need to focus on the optimal method to incorporate these agents into clinical practice.

**References**

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