Recent progress in molecular biology has shown that cancer cells acquire common phenotypes such as self-sufficiency of growth signals, resistance to anti-proliferative and apoptotic signals through the accumulation of genetic and epigenetic changes. Recently developed anticancer drugs target these molecular mechanisms and good results have been reported for various cancer types. In lung cancer, tyrosine kinase inhibitors specific for the epidermal growth factor receptor such as gefitinib and erlotinib have changed clinical practice dramatically. About half of the Japanese patients with lung cancers harbor an activating mutation of the epidermal growth factor receptor gene and they are very sensitive to epidermal growth factor receptor tyrosine kinase inhibitors. Progression-free survival of such patients is \( \frac{10}{24} \) months when treated with gefitinib, whereas the survival for those treated with platinum doublet therapy is \( \frac{6}{24} \) months.

Target therapies against echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase fusion protein or a mutated ERBB2 (v-ERB-B avian erythroblastic leukemia viral oncogene homologue 2) present in \( \frac{5}{24} \) and \( \frac{3}{24} \) of the Japanese patients with adenocarcinomas, respectively, are currently under development. Addition of an anti-epidermal growth factor receptor antibody, cetuximab, or anti-vascular endothelial growth factor antibody, bevacizumab, to platinum doublet therapy significantly but modestly prolonged the survival in recent clinical trials. However, clinical development of small molecule multi-kinase inhibitors including those targeting vascular endothelial growth factor receptors, such as vandetanib, sunitinib and sorafenib, has not been very successful. Through these collaborations among clinicians, basic researchers and pharmaceutical companies, it should be possible to individualize lung cancer treatment to turn this fatal disease into a chronic disorder and, eventually, to cure it.

**Key words:** EGFR – tyrosine kinase inhibitor – antibody therapy – oncogene addiction – angiogenesis inhibitors

**INTRODUCTION**

Lung cancer is a major cause of cancer-related mortality worldwide. Although various chemotherapeutic agents were developed in the late 1980s and 1990s, platinum doublet therapy seems to have reached a therapeutic plateau with an objective response rate of 30–40% and a median survival time (MST) of about 1 year for patients with Stage IIIIB or IV disease (1,2). To circumvent this situation, a new class of drugs that specifically targets certain molecular pathways leading to cancer phenotypes is being developed. Table 1 is a partial list of such target drugs that are in clinical use or are being tested. This review describes recent advances of target therapy of lung cancer with an emphasis on molecular markers.

**EPIDERMAL GROWTH FACTOR RECEPTOR TYROSINE KINASE INHIBITORS**

Small molecules that specifically inhibit the tyrosine kinase activity of the epidermal growth factor receptor (EGFR), such as gefitinib and erlotinib, were the first drugs to become clinically available in the treatment of non-small cell lung cancer (NSCLC). Gefitinib was approved in Japan...
in 2002 for the first time in the world. Asian women with adenocarcinomas and no history of smoking were found remarkably sensitive to EGFR-tyrosine kinase inhibitors (EGFR-TKIs) during the early clinical development of these drugs (3,4). In 2004, the reason for this high response rate was shown to be a somatic mutation of the \textit{EGFR} gene in this subgroup (5,6). About 90\% of these \textit{EGFR} mutations are either short in-frame deletions in exon 19 (usually five amino acids) or point mutations that result in a substitution of arginine for leucine at amino acid 858 (\textit{L858R})(7).

Subsequent retrospective and prospective studies showed that the response rate to EGFR-TKIs of patients with \textit{EGFR} mutations was 70–80\% (7). Furthermore, patients with \textit{EGFR} mutations showed a significantly longer survival than those with wild-type \textit{EGFR} when treated with gefitinib (8–10). However, data on the predictors for survival were initially controversial. Some investigators claimed that \textit{EGFR} mutations were prognostic rather than predictive and that the \textit{EGFR} gene copy number was more important (11), until the results of the IPASS study was reported (12). This was a Phase III trial that compared gefitinib with standard chemotherapy as a first-line treatment for Asian patients with lung adenocarcinomas, with no smoking history or only a light usage (12). Progression-free survival (PFS) of patients treated with gefitinib was significantly superior. However, the Kaplan–Meier survival curves crossed at 6 months (initially chemotherapy was better but later the gefitinib therapy was better). Molecular subset analysis for about one-third of the patients showed that the benefit was limited to patients with an \textit{EGFR} mutation and that gefitinib treatment was detrimental for those without mutations (12). Furthermore, two recent Japanese trials (NEJ002 and WJTOG3405) selected patients according to the presence of an \textit{EGFR} mutation. These trials confirmed that the determinant of clinical efficacy is the presence of an \textit{EGFR} mutation and not the clinical background of the patient (13,14). The PFS of patients with \textit{EGFR} mutation treated with gefitinib was around 10 months, whereas the PFS for those treated with platinum doublet chemotherapy was around 6 months. These figures are highly reproducible (Table 2).

It is almost inevitable for patients to show progression in the disease after presenting with an initial good response. A secondary mutation resulting in a change from threonine to methionine at codon 790 (\textit{T790M}) is responsible for this acquired resistance in at least half of the patients (15,16). Substitution of the threonine at codon 790 with methionine restores the affinity of the EGFR protein to ATP to be higher than the affinity of EGFR to EGFR-TKI, resulting in resistance to EGFR-TKI (17). In about 20\% of the patients with acquired resistance, \textit{MET} gene amplification is found. The \textit{MET} protein activates ERBB3 and subsequently AKT, resulting in evasion of apoptosis (18,19). To circumvent this acquired resistance, irreversible EGFR-TKIs such as PF002998904 (20) and BIBW2992 (21) are currently in clinical trials for patients with \textit{T790M}. Patients with \textit{MET} amplification could be treated with an EGFR-TKI plus an \textit{MET} inhibitor (19).

**EGFR Antibody**

Antibodies directed against the extracellular domain of EGFR (such as cetuximab, matuzumab and panitumumab) are also in development for treating patients with lung cancers. There have been several randomized trials

Table 1. Target drugs for lung cancer that are currently in clinical use or in development

<table>
<thead>
<tr>
<th>Target</th>
<th>Mechanism</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>TK inhibition</td>
<td>Gefitinib (Iressa), erlotinib (Tarceva)</td>
</tr>
<tr>
<td></td>
<td>Antibody</td>
<td>Cetuximab (Erbitux), panitumumab, matuzumab</td>
</tr>
<tr>
<td>EGFR + ERBB2</td>
<td>TK inhibition</td>
<td>BIBW2992, PF00299804</td>
</tr>
<tr>
<td>ERBB2</td>
<td>Antibody</td>
<td>Trastuzumab (Herceptin)</td>
</tr>
<tr>
<td>ALK</td>
<td>TK inhibitor</td>
<td>PF02341066</td>
</tr>
<tr>
<td>VEGFR</td>
<td>Antibody</td>
<td>Bevacizumab (Avastin)</td>
</tr>
<tr>
<td>VEGFR + EGFR</td>
<td>TK inhibition</td>
<td>Vandetanib (Zactima)</td>
</tr>
<tr>
<td>VEGFR + KIT + RAF</td>
<td>TK inhibition</td>
<td>Sorafenib (Nexabar)</td>
</tr>
<tr>
<td>VEGFR + KIT + PDGFR</td>
<td>TK inhibition</td>
<td>Sunitinib (Sutent), axitinib, AZD2171 (cediranib)</td>
</tr>
<tr>
<td>IGF1R</td>
<td>Antibody</td>
<td>CP751, 871</td>
</tr>
<tr>
<td>MET</td>
<td>TK inhibition</td>
<td>ARQ197, XL184</td>
</tr>
<tr>
<td>mTOR</td>
<td></td>
<td>CCI-779, RAD009</td>
</tr>
<tr>
<td>HSP90</td>
<td></td>
<td>17-AAG, 17-DMAG, CNF1010</td>
</tr>
<tr>
<td>Vascular disrupting agent</td>
<td></td>
<td>ASA-404 (DMXAA)</td>
</tr>
</tbody>
</table>

As of October 2009, only gefitinib and erlotinib are approved for treating patients with lung cancer in Japan. EGFR, epidermal growth factor receptor; TK, tyrosine kinase; ALK, anaplastic lymphoma kinase; VEGF, vascular endothelial cell growth factor; IGF1R, insulin like growth factor 1 receptor; mTOR, mammalian target of rapamycin; HSP90, heat shock protein 90.
comparing chemotherapy with chemotherapy plus cetuximab. The FLEX study was the first to show significant survival advantage by the addition of cetuximab to cisplatin plus vinorelbine, although the difference in MST was not great [i.e. 11.3 vs. 10.1 months; hazard ratio, 0.871; $P = 0.044$] (22). In addition, exploratory subset analysis for Asian patients ($n = 121$) revealed that prolongation of overall survival was not seen in this group (i.e. 17.6 months for the cetuximab group vs. 20.4 months for the control group) (22). However, small sample size (10% of total) and differences in histology and post-study EGFR-TKI treatments do not allow us to draw definite conclusions at present.

In patients with colorectal cancer, it is now established that a KRAS mutation is a negative predictive marker for any benefit of cetuximab treatment (23,24). However, this negative impact of KRAS mutations was not observed in the FLEX study (25).

**SEARCH FOR ANOTHER ACHILLES’ HEEL OF NSCLC**

In addition to EGFR, investigators have found molecular abnormalities in the oncopgenes that occur in mutually exclusionary fashion each other, suggesting complementary roles of these mutations in lung carcinogenesis. These genes include ERBB2, KRAS, BRAF, and MET and translocation in anaplastic lymphoma kinase (ALK). Figure 1 shows the approximate incidence of these genetic disorders in Japanese patients with adenocarcinoma of the lung; more than three-quarters have at least one such mutation. It is anticipated that cancer cells usually contain multiple genetic and epigenetic abnormalities in each type of adenocarcinoma. For example, about 40% of adenocarcinoma harboring EGFR mutation also has TP53 mutation (26). Despite this complexity, their growth and survival can often be impaired by the inactivation of a single oncogene, the phenomenon known as ‘oncogene addiction’ (27). A typical example is EGFR-TKI as described. Therefore, it is expected that other genes listed here can be promising target for therapy of lung cancer.

The ERBB2 gene is mutated in a subset of patients with lung adenocarcinomas, although the frequency is low (28,29). These mutations are usually small in-frame insertions or duplications in exon 20 (28,29). Cells harboring the G776insV_G/C mutation in the HER2-encoded tyrosine kinase are shown to be sensitive to HKI-272, an irreversible dual-specific kinase inhibitor targeting both EGFR and ERBB2 (30). Similarly, lung cancers arising in female, non-smoking patients with an HER2 mutation have been treated successfully using a combination of trastuzumab (anti-HER2 antibody) plus paclitaxel (31).

In 2007, Soda et al. identified the gene resulting from the fusion of that for echinoderm microtubule-associated protein-like 4 (EML4) and the gene for ALK as a transforming activity in mouse 3T3 fibroblasts from DNA of lung cancer in a Japanese man with a smoking history (32). This EML4–ALK fusion gene results from a small inversion within chromosome 2p. By fusing the coiled-coil domain of EML4 with the kinase domain of ALK, the ALK protein dimerizes without ligand binding, leading to oncogenic activation (32). A recent larger study has shown that an ALK translocation is

**Table 2. Summary of results of the recent clinical trials evaluating EGFR mutations as a predictive factor of the efficacy of gefitinib compared with chemotherapy in a first-line setting**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient selection</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-CAMP (42) ($n = 148$)</td>
<td>Pooled analysis of seven prospective non-randomized studies for patients with EGFR mutations</td>
<td>10.7, HR $= 0.35$ (0.23–0.52)</td>
<td>6.0</td>
</tr>
<tr>
<td>IPASS (12) ($n = 261$)</td>
<td>Subset of patients with EGFR mutations in a Phase III randomized study</td>
<td>9.5, HR $= 0.48$ (0.36–0.64)</td>
<td>6.3</td>
</tr>
<tr>
<td>NEJ002 (13) ($n = 194$)</td>
<td>Phase III randomized study for patients with EGFR mutations</td>
<td>10.4, HR $= 0.357$ (0.252–0.507)</td>
<td>5.5 28.0 23.6</td>
</tr>
<tr>
<td>WJTOG3405 (14) ($n = 172$)</td>
<td>Phase III randomized study for patients with EGFR mutations</td>
<td>9.2, HR $= 0.489$ (0.336–0.710)</td>
<td>6.3 N/A N/A</td>
</tr>
</tbody>
</table>

PFS, progression-free survival; OS, overall survival; G, gefitinib; CTx, chemotherapy; HR, hazard ratio. Numbers in parentheses are 95% confidence intervals.

![Figure 1. Molecular classification of lung adenocarcinomas according to the ‘addicted oncogene’. EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.](https://academic.oup.com/jjco/article-abstract/40/2/101/1005421)
Associated with patients without a smoking history, of younger age and acinar type adenocarcinomas (33). PF-02341066 is an orally available, potent and selective ATP competitive inhibitor of MET and ALK kinases and its clinical activity observed in a Phase I dose escalation trial for patients carrying activating ALK gene fusion was reported in ASCO 2009 (34). The results were certainly promising. The overall response rate was 53% (10/19 patients) and disease control rate at 8 weeks was 79% (15/19 patients), while four patients had progression at first evaluation (34).

**Anti-angiogenesis Therapy**

It is believed that tumor cells have to attract new blood vessels to bring nutrients and oxygen for them to grow over a certain size. Bevacizumab is a humanized antibody that targets vascular endothelial cell growth factor (VEGF), which is thought to play a pivotal role in tumor angiogenesis. In a Phase II trial, there was an increased risk of hemorrhage in patients with squamous cell carcinomas, especially those with a central location (35). Therefore, these patients were not eligible for subsequent clinical trials. There have been two randomized Phase III trials and one randomized Phase II trial conducted in Japan. The first Phase III trial, E4599, showed significant survival prolongation (MST: 10.2 vs. 12.5 months) by the addition of bevacizumab (15 mg/kg) to carboplatin/paclitaxel (36). However, the similarly designed AVAIL study, in which addition of 7.5 or 15 mg/kg bevacizumab; C/T, carboplatin plus paclitaxel; RR, response rate. *P < 0.05.

**Table 3. Results of three randomized trials that evaluated the effects of addition of bevacizumab to platinum double chemotherapy**

<table>
<thead>
<tr>
<th></th>
<th>AVAIL</th>
<th>E4599</th>
<th>JO19907</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>347 345 351</td>
<td>433 417 59</td>
<td>121</td>
</tr>
<tr>
<td>RR 20% 34%* 30%* 15% 35%* 31% 61%*</td>
<td>6.1 6.7* 6.5* 4.5 6.2* 5.9 6.9*</td>
<td>13.1 13.6 13.4 10.3 12.3* N/A N/A</td>
<td></td>
</tr>
<tr>
<td>PFS 6.1 6.7* 6.5* 4.5 6.2* 5.9 6.9*</td>
<td>13.1 13.6 13.4 10.3 12.3* N/A N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS 10.6 months</td>
<td>10.2 vs. 12.5 months</td>
<td>10.2 vs. 12.5 months</td>
<td></td>
</tr>
</tbody>
</table>

AVAil and E4599 are Phase III studies, whereas JO19907 is a Phase II study. G/P, gemcitabine plus cisplatin; 7.5, 7.5 mg/kg bevacizumab; 15, 15 mg/kg bevacizumab; C/T, carboplatin plus paclitaxel; RR, response rate. *P < 0.05.

Various small molecule VEGFR TKIs have been tested for their activity against NSCLCs. Most of them also inhibit other tyrosine kinases than VEGFR. For example, Vandetanib is known to inhibit EGFR and RET in addition to VEGFR. In 2009, results of two large Phase III trials comparing chemotherapy plus Vandetanib with chemotherapy were presented: ZODIAC comparing docetaxel plus Vandetanib with Docetaxel (39) and ZEAL comparing pemetrexed plus Vandetanib with pemetrexed. Addition of Vandetanib generated significantly better response in both trials; however, prolongation of PFS was significant only in the ZODIAC trial (39,40). Overall survival was not significant in either trial (39,40).

Sorafenib is a multiple kinase inhibitor that inhibits VEGFR, PDGFR and RAF. However, the ESCAPE study examined the effect of addition of sorafenib to standard carboplatin plus paclitaxel in a first-line setting. The result was negative with an MST for the sorafenib group of 10.7 vs. 10.6 months for controls. Addition of sorafenib was even detrimental for patients with squamous cell histology (41).

**Conclusion**

Here, I have reviewed recent progress in target drug therapy for patients with lung cancers. Identification of new molecular targets of the Achilles’ heel type and development of their inhibitors as well as efficient patient screening by biomarkers will be the keys to novel cancer therapeutics in the twenty-first century.

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