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New targets and new treatments in non-small cell lung cancer

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Abstract

New agents directed against molecular targets have now been tested in large prospectively randomized clinical trials for patients with untreated advanced non-small cell lung cancer (NSCLC). The trials have included small molecule inhibitors of receptor tyrosine kinases (gefitinib and erlontinib), monoclonal antibodies directed against either the ligands (bevicizumab against vascular endothelial growth factor) or their receptors (trastuzumab against ErbB2) and antisense nucleotides directed against mRNA coding for molecular targets (ISIS 3521 against protein kinase C alpha). The largest mature trials have included agents directed against ErbB1 (epidermal growth factor receptor). Two different small molecule inhibitors of erbB1 (gefitinib and erlontinib) and have been tested in 4 large international randomized trials. Two trials treated patients with advanced NSCLC with either gemcitabine and cisplatin or the same chemotherapy drugs combined with two different doses of gefitinib or one dose of erlontinib (INTACT 1 and TALENT). The other two trials treated patients with advanced NSCLC with either paclitaxel and carboplatin or the same chemotherapy drugs combined with either one of two doses of gefitinib or a single dose of erlontinib (INTACT 2 or TRIBUTE respectively). The results of INTACT 1 and INTACT2 showed no significant difference in survival between those treated with conventional combination chemotherapy and those treated with the same chemotherapy plus gefitinib. The results of the TRIBUTE and TALENT studies showed their primary endpoints of improving overall survival were not met. The monoclonal antibody, bevacizumab, is being tested in an ongoing clinical trial. The trial will compare the outcome of patients with untreated advanced adenocarcinoma of the lung treated with paclitaxel plus carboplatin to those treated with the same chemotherapy drugs plus bevacizumab. The results are scheduled to be available in 2005–2006. Although the initial trials adding newly developed molecular targeted agents have not shown initial success when added to conventional combination chemotherapy, further clinical trials are needed to ultimately define their role in the treatment of non-small cell lung cancer.
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1. Introduction

Patients with metastatic non-small cell lung cancer benefit from treatment with chemotherapy by living longer and having an improved quality of life compared to patients treated with supportive care alone [1,2]. It appears the treatment of patients with advanced non-small cell with different combinations of chemotherapy has reached a therapeutic plateau. Patients treated with platinum-containing chemotherapy achieve a median survival of 8–10 months and only 2% of these patients are alive 5 years after the start of therapy [3–5]. The median survival of patients treated for advanced non-small cell lung cancer has increased by only two weeks in the past 20 years and the 5-year survival remains less than 2% [3]. Therefore, additional therapies are needed to improve the outcome of these patients.

Research to identify potential targets for therapeutic intervention in lung cancer has been ongoing for more than 2 decades. These findings are now being applied in large randomized phase III studies for patients with advanced non-small cell lung cancer. In this article we report on the molecular target, the patient population, the status of the trial, and the outcome of the trial if already know. Although there are many agents which inhibit different molecular targets in single agent and combination phase I and II trials, this article will focus on those that have been tested in patients with non-

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small cell lung cancer in either mature large phase II or phase III randomized trials.

2. Methods

The trials reviewed for this article include the molecularly targeted agents for patients with advanced non-small cell lung cancer that were reported at two recent meetings. The meetings were entitled Targeted Therapies for Treatment of Lung Cancer in Aspen, CO, USA in January 2003 and the joint International Association for the Study of Lung Cancer and American Society of Clinical Oncology International Conference, Molecular Targeted Therapies in Lung Cancer in Marabella Spain in January 2003. These two meetings included broad representation from the pharmaceutical industry and academic institutions with participants from 22 countries. The randomized trials which employed molecularly targeted agents for patients with advanced non-small cell lung cancer reported at the American Society of Clinical Oncology and European Society of Medical Oncology between 2000 and 2003 were also identified. These lung cancer trials were also confirmed by contact with the leaders of the lung cancer committees of the cooperative groups in Europe, North America, and Japan. The trials on listed on the web sites www.nci.nih.gov/clinicaltrials and www.eortc.be/ were also reviewed.

Information about each trial was obtained including the number of patients enrolled on study, the gender of the patients, chemotherapy regimens used, the targeted agent, the median and 1-year survival, and differences in overall survival between the treatment groups.

3. Results

3.1. ErbB family inhibitors

There have been extensive efforts to develop agents which can inhibit the 4 member family of ErbB receptors with most of the current emphasis on ErbB1 [6]. The agents that have been tested most extensively in non-small lung cancer are the small molecular inhibitors of the epidermal growth factor receptor, ErbB1, gefitinib and erlontinib.

Gefitinib and erlontinib have undergone phase I testing and phase II doses have been selected [7,8]. Gefitinib and erlontinib have undergone phase II testing as single agents in approximately 500 previously treated patients with advanced non-small cell lung cancer [9–11]. The patients treated with erlontinib needed to have documentation of ErbB1 on 10% or more of their non-small cell lung cancer cells while the trials using gefitinib did not need to document the presence of ErbB1. The trials using gefitinib and erlontinib had single agent response rates of 10–20% and have been associated with symptomatic responses in approximately 40% of the patients treated.

These two trials have also identified subsets of patients with non-small cell lung cancer who are more likely to respond to gefitinib [9,10]. The 155 women treated in the two trials of 426 patients were approximately 3-fold more likely to have a partial response to gefitinib than the men. The 281 patients with adenocarcinoma were approximately 4-fold more likely to have a partial response to gefitinib than patients with other non-small cell lung cancer histologies.

Gefitinib was tested in two different randomized studies of more than 2000 patients. Patients with stage IIIB or IV non-small cell lung cancer were treated with either gemcitabine and cisplatin (Europe and Japan) in a trial designated INTACT-1 or paclitaxel and carboplatin (United States) in a trial designated INTACT-2 (Table 1) [12,13]. The patients underwent a 3-way randomization to the chemotherapy plus placebo, chemotherapy plus 250 mg of gefitinib or chemotherapy plus 500 mg of gefitinib daily. The results of the two trials were presented in the fall of 2002 and showed no difference in median survival, 1-year survival, or time to progression.

The phase II studies, phase III studies, expanded access program making gefitinib available to patients prior to regulatory approval, and post approval use in the United States and Japan have identified patients with interstitial lung disease. The package insert states that interstitial lung disease has been observed in about 1% of patients treated with gefitinib which is fatal in 1/3 or 0.3% of the patients treated (www.astrazeneca.com). This includes patients previously treated with chest radiotherapy, chemotherapy, and patients who have not received any prior treatment. Patients who develop symptoms, signs, and radiographic evidence of interstitial lung disease should have gefitinib discontinued.

Erlontinib has been tested in two large randomized studies of more than 1000 patients each. Patients with stage IIIB or IV non-small cell lung cancer were treated with either paclitaxel carboplatin plus placebo or the

Table 1
ErbB family inhibitors in lung cancer trials

Molecule	Company	Target	Phase investigation
Small molecules			
Gefitinib	Astra Zeneca	ErbB1	Finished Phase III
Erlontinib	Genentech	ErbB1	Finished Phase III
CI-1033	Pfizer	ErbB1-4	Phase II
Antibodies			
IMC-C225	Imclone/BMS	ErbB1	Phase II
ABX-EGF	Abgenics	ErbB1	Phase II
Trastuzumab	Genentech	ErbB2	Randomized Phase II

same chemotherapy plus 150 mg of erlontinib in a trial performed in the United States designated TRIBUTE. In the other trial, patients with stage IIIB or IV non-small cell lung cancer were treated with either gemcitabine cisplatin plus placebo or the same chemotherapy plus 150 mg of erlontinib in a trial performed outside the United States designated TALENT. The outcome of the studies has been reported in part to state they were not successful in meeting their primary endpoints of improving overall survival (www.gene.com).

Trials with other agents are planned for patients with non-small cell lung cancer including CI-1033 which irreversibly inhibits ErbB1-4 [14] and two antibodies that are directed against ErbB1, ABX-EGF and IMC-C225. CI-1033 is being tested as monotherapy for patients with previously treated non-small cell lung cancer. ABX-EGF and IMC-C225 are being tested in combination with paclitaxel plus carboplatin in previously untreated patients with non-small cell lung cancer. Trastuzumab is an antibody directed against the ErbB2 receptor and is approved by the Food and Drug Administration in the United States for use in patients with breast cancer and the ErbB2 receptor. The randomized phase II studying the outcome of patients with non-small cell lung cancer and ErbB2 on their lung cancer cells treated with trastuzumab combined with chemotherapy to patients treated with chemotherapy alone have not yet shown evidence of antitumour activity [15]. The information generated by these trials will be used to help define the potential role of the agents targeted against the family of ErbB receptors.

3.2. Antiangiogenic agents

The formation and expansion of blood vessels is essential for the growth and propagation of lung cancer [16]. Agents directed against potential therapeutic targets of the angiogenic pathway are being studied in patients with lung cancer. These include monoclonal antibodies directed against agonist proteins; monoclonal antibodies directed against receptors involved in angiogenic pathways, and small molecule inhibitors of the tyrosine kinase domain of the receptors involved in the angiogenic pathway [16]. The agent that is the most advanced in clinical development for patients with lung cancer is the recombinant humanized monoclonal antibody directed against vascular endothelial growth factor, bevacizumab. A randomized phase II trial was performed for 99 patients with stage IIIB and IV non-small cell lung cancer [17,18]. Patients were treated with paclitaxel plus carboplatin or the same two chemotherapeutic agents plus one of two different doses of bevacizumab. The 78 patients with adenocarcinoma treated with chemotherapy plus the higher dose of bevacizumab (15 mg/kg) had a median survival of 18 months compared to 12 months for the patients treated with the lower dose of bevacizumab (7.5 mg/kg) and 15 months for the control group treated with chemotherapy alone. However, 6 patients of the 99 patients had life threatening hemoptysis and 4 of these patients died. Four of the 6 patients with life-threatening hemoptysis had squamous cell histology and central tumours.

Based on these findings, a trial has been designed to exclude patients with hemoptysis and those with squamous cell carcinomas. The trial is being led by the Eastern Cooperative Oncology Group which compares the outcome of patients with advanced adenocarcinoma of the lung treated with paclitaxel plus carboplatin to those treated with the same chemotherapy drugs plus bevacizumab given at a dose 15 mg per kilogram (Table 2). The trial is enrolling patients and the results are scheduled to be available in 2005–2006.

There are other agents that have not shown evidence of antitumour activity against non-small cell lung cancer in phase II trials that are subjects of further study. This includes a randomized trial in which AE-941 or Neovastat, a shark cartilage preparation, is combined with a platinum containing chemotherapy regimen and chest radiotherapy (combined modality therapy) for patients with stage III non-small cell. The outcome of the patients treated with this combined modality therapy plus AE-941 will be compared to patients treated with the same chemotherapy plus chest radiotherapy. Thalidomide is also being tested in a similar randomized trial design. Thalidomide is combined with paclitaxel and carboplatin plus chest radiotherapy for patients with stage III non-small cell. The outcome of the patients treated with combined modality therapy plus thalidomide will be compared to patients randomized to the same chemotherapy plus chest radiotherapy without thalidomide. The small molecule inhibitor of vascular endothelial growth factor receptor 2 tyrosine kinase, ZD6474, has just entered a randomized phase II trial with docetaxel in patients with relapsed non-small cell lung cancer [19].

3.3. Antisense nucleotides

Novel targeted therapies include antisense nucleotides directed against mRNA of genes that are associated with more rapid growth of lung cancer. The agents work by using an antisense nucleotide to bind to its complimentary mRNA to prevent the translation from mRNA to protein [20]. An antisense phosphorothioate DNA oligonucleotide, ISIS 3521, has been developed against protein kinase C alpha [21]. ISIS 3521 has been combined with paclitaxel and carboplatin in a phase II trial. Fifty-three patients with previously untreated stage IIIB and IV non-small cell lung cancer were treated with paclitaxel plus carboplatin plus a 14-day infusion of ISIS 3521 [22]. The patients treated with

chemotherapy plus ISIS 3521 had a median survival of 16 months. This encouraging data has prompted a large randomized phase III trial. Six hundred sixteen patients have been entered on a randomized trial where half are treated with paclitaxel plus carboplatin while the other half are treated with these two drugs plus ISIS 3521 [23]. The trial showed the median survival in the paclitaxel carboplatin arm was 9.7 months compared to 10 months for the patients treated with paclitaxel carboplatin plus ISIS 3521 ($P=0.81$). Another antisense nucleotide, Oblimersen or G3139, directed against Bcl-2 is being tested in a randomized trial. Bcl-2 is a protein that inhibits apoptosis so prevention of its protein translation aids in killing the cancer cells. Oblimersen is being tested in combination with docetaxel in previously treated non-small cell lung cancer.

3.4. Matrix metalloproteinase inhibitors

The last class of molecularly targeted agents that have been tested in large phase III clinical trials include matrix metalloproteinase inhibitors. This class of agents inhibits the family of enzymes which break down intercellular matrix needed for cancer cell to extravasate, migrate, and implant to form metastases [24,25]. One of these classes of drugs, which inhibit the matrix metalloproteinases, includes prinomostat or AG 3340. This agent has been combined with gemcitabine and cisplatin tested in a phase III trials for patients with advanced non-small cell lung cancer. Three hundred sixty-two patients with previously untreated stage IIIB or IV non-small cell lung cancer were treated with either gemcitabine cisplatin or the same combination plus prinomostat. Prinomostat could be continued after the chemotherapy was finished [26]. The median survival of the patients treated with gemcitabine plus cisplatin was 11.5 months versus 10.8 months for the patients treated with gemcitabine, cisplatin, and prinomostat ($P=0.82$). The one-year survival was 43% for the patients treated with chemotherapy plus prinomostat compared to 38% for the patients treated with chemotherapy alone.

There is another ongoing pharmaceutical industry-sponsored randomized phase III trial of a matrix metalloproteinase inhibitor. Patients with previously untreated stage IIIB or IV non-small cell lung cancer are treated with either paclitaxel and carboplatin alone or the same drugs plus a matrix metalloproteinase inhibitor, BMS-275291. The study opened in 2000 and planned accrual for 776 patients has been completed. We await presentation of the outcome of the trial results.

Another matrix metalloproteinase drug, BAY 12-9566 been tested in patients with non-small cell lung cancer. The trials included patients with both non-small cell and small cell lung cancer. The trial was stopped early when an interim analysis showed the patients with small cell lung cancer in a companion trial had shortened survival when treated with chemotherapy and BAY 12-9566 compared to the patients treated with chemotherapy alone. The outcome of the patients with non-small cell lung cancer participating in the trial has yet to be reported. There is a single published randomized phase III study of a matrix metalloproteinase inhibitor [27]. This trial compared the outcome of patients with small cell lung cancer with a partial or complete response to conventional treatment treated with marimastat to those given a placebo. Marimastat did not prolong the survival of the patients participating in that trial and caused significant musculoskeletal side effects.

4. Discussion

The clinical research to identify new targets and develop new treatments in non-small cell lung cancer has been ongoing for about 20 years. The small molecule tyrosine kinase inhibitors, gefitinib and erlontinib, were discovered to have anticancer activity in patients with relapsed lung cancer in phase I trials. This prompted an extensive clinical research program initiated and supported by the pharmaceutical industry and now joined by cooperative groups in the North America, Europe and Japan. The phase II trials in previously treated patients with non-small cell lung cancer demonstrated both symptomatic and radiographic tumour responses. This has led to the approval of gefitinib in Japan in 2002. The Food and Drug Administration in the United States has licensed gefitinib as monotherapy for treatment of locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based and docetaxel chemotherapies.

The initial trials to combine gefitinib and erlontinib with conventional chemotherapy for patients with non-small cell lung cancer have been disappointing. There was no evidence of additional anticancer activity when two different doses of gefitinib doses and erlontinib were combined with either paclitaxel and carboplatin or gemcitabine plus cisplatin. Further trials are now planned or ongoing to examine the efficacy of these two agents using single agent therapy in patients with recurrent disease or a maintenance design. Phase II and III trials are being performed to determine the anticancer activity of gefitinib and erlontinib in special populations including untreated patients older than 70 years, untreated patients with bronchioloalveolar carcinoma, and patients with non-small cell lung cancer that have been previously treated with a chemotherapy combination. The other clinical setting where the drugs are being studied include gefitinib or erlontinib given to patients after the completion of conventional treatment for patients with stage II, III or IV non-small cell lung cancer.

Table 2
Antiangiogenic agents in lung cancer trials

Molecule	Company	Target	Phase Investigation
Antibodies			
Bevacizumab	Genentech	VEGF	Phase III
IMC-1C11	Imclone	VEGFR2	
Small molecules			
ZD6474	Astra Zeneca	VEGFR2 and ErbB1	Phase II
AE-941	Aeterna Labs	Angiogenesis	Phase III
Thalidomide	Celgene	Angiogenesis	Phase III

The other approach to improve the therapeutic efficacy is to identify the subsets of patients with non-small cell lung cancer who are more likely to respond to the small molecule inhibitors of the receptor tyrosine kinases. Clinical research is ongoing to determine if gender and histology can help predict who is likely to respond to treatment with EGFR inhibitors. Laboratory research is also ongoing to identify molecular determinants of response to potentially enrich populations of patients with non-small cell lung cancer more likely to benefit from these small molecules. This could add new entry criteria for a more focused clinical trial where the agents may be able to add to the efficacy of conventional chemotherapeutic agents.

The targeted antiangiongenic agent, bevacizumab, had important clinical and treatment data generated in the preceding randomized phase II trial[17, 18]. It provided a dose of 15 mg/kg and identified a patient subset who is more at risk for bleeding complications. Therefore, patients with squamous cell carcinomas and a history of hemoptysis are now excluded from patient entry in the randomized phase III trial. This potentially eliminates some of the patient risk from participating in the trial. One problem with this approach of eliminating patients with squamous cell carcinoma from this trial to reduce the risk of bleeding is the potential difficulty distinguishing between adenocarcinoma and squamous cell carcinoma in some of the diagnostic pathology specimens, particularly cytology specimens.

The lessons learned from these trials will be important as some of the newer molecules entered clinical trials. Small molecule inhibitors of the vascular endothelial growth factor receptor 2 including ZD6474, PTK 787, SU5416, SU11248, and the antibody directed against the same receptor, IMC-1C11, may be able to be employed more safely in patients with non-small cell lung cancer from the results of previous trials.

Despite the encouraging survival information obtained in a single arm phase II trial of ISIS 3521 combined with paclitaxel plus carboplatin, the phase III study did not show a difference in outcome [23]. The patients treated with paclitaxel plus carboplatin plus ISIS 3521 did not live longer than patients treated with the chemotherapy alone. We await the outcome of ongoing studies to provide potential evidence of anticancer activity of the antisense nucleotide directed against Bcl-2, Oblimersen, combined with docetaxel.

There has thus far been no evidence of antitumour activity of the class of matrix metalloproteinase inhibitors for patients with non-small cell lung cancer. There have been trials for patients with small cell lung cancer with marimastat given in the maintenance situation [27] and prinomostat given concurrently with combination chemotherapy for patients with non-small cell lung cancer [26]. Neither trial shows evidence of antitumour activity with the matrix metalloproteinase inhibitors. These agents are inhibitors of a molecular pathway active in the development of metastases. It is questionable whether small cell lung cancer or advanced non-small cell lung cancer is the right setting for investigating these agents when the cancer is already disseminated and metalloproteinase inhibitors may need to be studied in patients with earlier stage disease. If the trials with BAY 12-9566 and BMS-275291 show no evidence of antitumour activity, careful preclinical work will be needed to help find an appropriate clinical setting for further testing of this class of compounds.

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