# Targeted therapy for lung cancer

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The identification of new molecular targets and the development of treatment specific to these targets have been areas of intense basic and clinical research in the last decade. Several targeted therapies have been investigated or are being investigated in both small cell (SCLC) and non-small cell lung cancer (NSCLC).

One of the first targeted therapies to be evaluated in lung cancer was the family of matrix metalloproteinase inhibitors (MMPIs), and many lessons were learned from these trials. Metalloproteinases (MMPs) form a family of proteolytic enzymes capable of degrading the extracellular matrix and basement membrane. Tumour growth and metastasis have been shown to be associated with excessive expression and activation of MMPs, and in SCLC, high levels of MMPs were shown to be independent negative prognostic factors, thus suggesting that inhibition of MMPs might improve outcome. Despite this fairly strong preclinical work suggesting a role for MMPIs, all trials in both SCLC and NSCLC were negative. Furthermore, all trials reported significant toxicity in the MMPI arm that had a negative impact on quality of life. This was true, even in the trial of BMS 27529, a broad-spectrum MMPI that was expected to have less musculoskeletal toxicity than marimastat or prinomastat. One of the problems of the MMPI trials was the lack of a target that could be easily measured to assess "target effect" in Phase I or II studies. However, despite this drawback, the results of these trials could perhaps have been predicted, and large trials by performing smaller randomised Phase II trials with appropriate control arms.

Other negative trials of targeted agents include two trials of chemotherapy plus or minus aprinocarsen, a protein kinase C-alpha inhibitor; one large study of SCH-66336, a farnesyl transferase inhibitor; and two trials of targeting a retinoic acid receptor inhibitor to name but a few.

Growth factors and their receptors play important roles in the pathogenesis of several human cancers including lung cancer. The epidermal growth factor receptor (EGFR) family (including HER2 and EGFR) has been a target of intense research activity in NSCLC. In a randomised Phase II trial, patients with advanced NSCLC who had 2+ or 3+ HER2 protein expression (by IHC) were randomised to receive treatment with gemcitabine/cisplatin ± trastuzamab, a monoclonal antibody against HER2. Only 13% of screened patients had high expression by IHC (1% 3+, 12% 2+), and only 2% demonstrated gene amplification by FISH. The latter may explain the poor results achieved; response was seen in 32% of trastuzumab patients and 41% of control. Progression free survival was 6.1 months for trastuzumab and 7 months for control. However, 5/7 seven FISH positive patients responded to treatment.

EGFR inhibitors that have been studied most extensively include the tyrosine kinase inhibitors erlotinib and gefitinib. In randomised Phase II trials (IDEAL 1 and 2) of gefitinib 250 mg or 500 mg/daily, 10%–20% of patients previously treated with platinum-based regimens achieved response, and approximately forty percent of patients had symptom improvement. Toxicity consisting mainly of diarrhea and rash was higher with the 500 mg dose, but treatment was seldom stopped for toxicity at either dose. In a single-arm Phase II trial of erlotinib in previously treated NSCLC patients whose tumours showed >10% EGFR expression, the response rate was 12.3%. These results led to randomised trials of both of these agents in both chemotherapy naïve and previously treated patients.

Two studies of gefitinib 250 mg/day or 500 mg/day or placebo combined with first-line systemic chemotherapy (paclitaxel/carboplatin or gemcitabine/cisplatin) have also been completed in advanced NSCLC. Similar trials with these combinations were also performed with erlotinib, although only one dose of erlotinib, 150 mg/day was compared to placebo. These four trials that included more than 4000 patients were all negative showing no benefit with the addition of an EGFR inhibitor to chemotherapy (Table 1).

There have been two large placebo-controlled trials of single agent erlotinib (BR.21) and gefitinib (ISEL) in patients previously treated with one or two lines of chemotherapy. In the BR.21 trial, patients treated with erlotinib had significantly longer progression-free

Table 1
Randomized phase III trials of gefitinib or erlotinib in NSCLC[a]

| Trial | Number of patients | Treatment | Response rate (CR + PR) | Median survival (months) | 1 Year survival |
|---|---|---|---|---|---|
| INTACT 1[b] | 363 | gemcitabine/cisplatin + placebo | 47.2% | 10.9 | 44% |
| | 365 | gemcitabine/cisplatin + gefitinib 250 mg | 51.2% | 9.9 | 41% |
| | 365 | gemcitabine/cisplatin + gefitinib 500 mg | 50.3% | 9.9 | 43% |
| | | | P = NS | P = 0.456 | |
| INTACT 2[b] | 345 | paclitaxel/carboplatin + placebo | 28.7% | 9.9 | 42% |
| | 345 | paclitaxel/carboplatin + gefitinib 250 mg | 30.4% | 9.8 | 41% |
| | 347 | paclitaxel/carboplatin + gefitinib 500 mg | 30.0% | 8.7 | 37% |
| | | | P = NS | P = 0.6385 | |
| TALENT[b] | 1172 | gemcitabine/cisplatin + placebo | 29.9% | 10.2 | 41% |
| | total | gemcitabine/cisplatin + erlotinib 150 mg | 31.5% | 9.9 | 42% |
| | | | P = NS | P = NS | |
| TRIBUTE[b] | 540 | paclitaxel/carboplatin + placebo | 19.3% | 10.5 | 43.8% |
| | 539 | paclitaxel/carboplatin + erlotinib 150 mg | 21.5% | 10.6 | 46.9% |
| | | | P = 0.36 | P = 0.95 | |
| NCIC-CTG | 243 | Placebo | – | 4.7 | 22% |
| BR21[c] | 488 | Erlotinib 150 mg | 9% | 6.7 | 31% |
| | | | P<0.0001 | | |
| ISEL | 563 | Placebo | – | 5.1 | 22% |
| | 1129 | Gefitinib 250 mg | 8.2% | 5.9 | 27% |
| | | | | P = 0.11 | |

[a] CR: complete response; PR: partial response.
[b] The INTACT 1 and 2, TRIBUTE and TALENT trials included only chemotherapy-naïve patients
[c] The NCIC-CTG BR.21 and ISEL studies included previously treated patients who had received first-line and second-line chemotherapy. NCIC-CTG: National Cancer Institute of Canada – Clinical Trials Group.

(2.2–*vs* 1.8 months; HR 0.61, P < 0.001) and overall survival (6.7 vs 4.7 months; HR 0.71; P < 0.001) in favor of the erlotinib arm. Furthermore, treatment was accompanied by improvements in cough, pain and shortness of breath as well as overall quality of life and physical function. In th ISEL trial, there was a trend towards improvement in overall survival with gefitinib, but the difference was not significant.

Tumour angiogenesis is essential for tumour growth. One of the most well characterised angiogenic factors is vascular endothelial growth factor (VEGF). A monoclonal antibody directed against VEGF (bevacisumab) has been evaluated in advanced NSCLC in combination with T/C at doses of 7.5 mg/kg and 15 mg/kg q 3 weeks in a 100 patient randomised Phase II trial. The highest response rate was seen at the 15 mg/kg rHuMAb VEGF dose, and this was also associated with the longest time to progression and survival. These results led to a large randomised Phase III ECOG trial of chemotherapy ± bevacisumab in advanced NSCLC. This trial that was limited to patients with adenocarcinoma without brain metastases or a history of hemoptysis showed a significant survival advantage for patients treated with bevacisumab (10.2 vs 12.5 months, P = 0.0075) and higher response rate (10% vs 27%, p <0.0001).

It is also possible to target VEGF through its receptors. The most important receptor for VEGF is thought to be FLK-1 (KDR), and several small-molecule receptor tyrosine kinase inhibitors of FLK-1 are under development. ZD6474, an oral FLK-1 inhibitor that also has EGFR tyrosine kinase activity, has been evaluated in the second line setting of NSCLC. In a randomised Phase II trial that compared docetaxel alone to docetaxel with ZD6474 100 or 300 mg daily, response rates and progression free survival both favoured the ZD6474 arms. NCI-Canada

is also conducting a trial of adjuvant ZD6474 versus placebo in responding patients with SCLC.

These novel targeted agents differ considerably from classical cytotoxic chemotherapy. We are still learning how best to evaluate these treatments in cancer patients, how to assess their efficacy in Phase I/II trials, how to combine them with standard therapy, and at what stage of the disease they might be most effective. Initially it was though that because these targeted drugs might be cytostatic rather than tumouricidal, Phase II testing looking for response might not be necessary or even applicable. This thinking resulted in the initiation of many of the large clinical studies discussed above, based only on laboratory models and Phase I toxicity testing. Sadly, many initially promising treatments fell by the wayside as they failed to improve outcome when tested in large randomised trials. The unprecedented number of negative trials comprising thousands of patients world-wide has led to a re-evaluation of drug development strategy for these molecularly targeted agents. Clearly, Phase II testing is still necessary, and in fact, randomised Phase II trials with an appropriate control arm should probably be conducted before large Phase III studies are initiated. Phase III trials should be considered only if an adequate "signal" is seen in Phase II. The importance of this strategy is most clearly demonstrated in the development of bevacisumab in lung cancer where a small Phase II trial gave a strong "signal" that clarified the dose of bevacisumab to be studied, identified important and unexpected toxicities and ultimately led to the design of the strongly positive Phase III trial.

Recent experience with targeted agents has also shown us that our standard approach of treating all patients with chemotherapy, yet knowing that the majority would not respond, is likely not appropriate for molecularly target agents. Experience with the small molecule tyrosine kinase inhibitors of EGFR has clearly taught us that both the clinical characteristics of patients and the molecular characteristics of their lung cancers may have a significant effect on response and survival. It can not be overemphasized how critical it will be to establish tumour banks for all future trials of targeted therapy in order to identify the appropriate patients to treat. These banks must also include samples from untreated control patients in order to clarify the prognostic impact of molecular changes as well as to determine whether a differential treatment effect is seen in patients who express or over-express the target of interest.