suggesting a similar overall survival benefit for the two drugs. Furthermore survival subset analyses in BR21 were consistent with ISEL, with the largest survival benefits for erlotinib also seen in the never-smoking and Asian subgroups. The objective response rates were comparable for gefitinib and erlotinib in these two studies (8% vs. 9%, respectively).[1,2]

As the ISEL result was surprising, a number of comparisons have been made.[3]

In ISEL 45% of patients had progressed and only 18% responded on the most recent chemotherapy, whereas for BR21 28% progressed and 38% had responded, the more refractory patients may have had less chance of benefiting. Erlotinib has a greater affinity for the receptor and was used at the MTD (150 mg) the similar dose for gefitinib would be 700 mg not the 250 mg used in ISEL. Further work investigating patient characteristics e.g. smoking status, identification of more sensitive populations and molecular markers will be important.

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S54. PROTEIN LYSATE ARRAY ASSESSMENT OF THERAPEUTIC TARGETS IN SARCOMA

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Small molecule inhibitors have brought new hope for cancers with dire prognoses. These molecular medicines turn off specific signaling intermediaries within cells, leaving others unaffected. Their efficacy has been demonstrated clinically with medicines such as imatinib for CML and GI stromal tumor and erlotinib for EGFR-dependent head and neck, lung and breast cancer. More small molecules are being developed. To rationally apply this development to more diseases, a rapid screening tool is required to identify expression and activity of protein targets in an individual patient's tumor. The technical challenges for this tool are significant: assessing dozens, if not hundreds, of potential targets accurately using the small amount of tissue available through core needle biopsies. We have begun applying a novel technology – protein lysate array analysis – to address this problem in sarcoma. Tumor lysates are arrayed on nitrocellulose matrix using a modified DNA arrayer, creating 100+ duplicate slides using as little as one microgram total protein. Individual slides are assayed with monospecific antibodies and comparisons made between phospho- and total protein levels, identifying the activation state of dozens of potential therapeutic targets. We have used this technique preclinically to test the downstream effects of erlotinib in osteosarcoma and Ewing sarcoma, identifying changes in MAPK, mTOR, AKT and JNK pathway signaling. We will use it in a clinical trial of an anti-ERBB medicine to assess the correlation between disease response and changes in signaling, using paired samples of pre- and post-treatment tissue. We envision prospective testing of tumor tissue, allowing the clinician to choose those small molecule(s) able to inhibit the specific pathway(s) active in an individual's tumor.

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S55. MOLECULAR STAGING OF NSCLC: 2006

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The treatment of lung cancer has undergone a remarkable transformation over the past five years. Previously histology and anatomic stage were the primary determinants of treatment. While these still have an important role, the future of treating this disease will be based on molecular staging strategies. This will allow us to select more effective and less toxic treatments in the initial treatment of metastatic disease. It will also permit informed selection of patients for adjuvant treatment. Finally aggressive molecular staging will hopefully uncover new targets that will result in new drugs that may one day transform lung cancer into a chronic disease with long-term survival the rule and not the exception.

Agents that target the epidermal growth factor receptor (EGFR) tyrosine kinase are among the most important new drugs in use to treat non-small cell lung cancer. Both gefitinib and erlotinib are capable of producing remarkable tumor responses as single agents that are durable. These dramatic responses are often associated with mutations in the EGFR tyrosine kinase domain. In addition when used in second and third line treatment of lung cancer erlotinib has been shown to prolong survival in this setting. This clinical benefit is best predicted by increased EGFR gene copy number as measured by FISH.

The use of EGFR-TKI provides an exceptional opportunity for molecular staging. EGFR mutation testing is being used to select patients for first line treatment with both gefitinib and erlotinib. Trials in the United States, Japan and Europe are employing this strategy and early results should be reported by the end of 2006. The potential to identify a population of patients who might be able to be treated with EGFR-TKI monotherapy as first line would potentially deliver equivalent anti-tumor activity with fewer side effects than combination chemotherapy.

Measurement of gene copy number by FISH is being used to select patients for treatment with EGFR-TKI treatment in several clinical scenarios. Patients who are FISH positive are being entered onto trials of erlotinib plus chemotherapy as first line treatment. Adjuvant studies of chemotherapy plus erlotinib given as sequential therapy are under review. Finally there is some controversy as to the relative value of EGFR protein expression as measured by immunoperoxidase staining. Some thoughtful investigators feel that the best way to select adjuvant and first line metastatic patients for TKI treatment is by using a combination of FISH and immunoperoxidase staining.

While FISH and immunoperoxidase may be important modalities in the molecular staging of lung cancer, mutation testing offers a potential benefit not available with those methods. Patients who are resistant to EGFR-TKI treatment have been found