research effort accompanying the randomized clinical trial EORTC26981/NCIC CE.3 indeed showed that the benefit from TMZ was mainly confined to patients whose tumors carried an epigenetically inactivated MGMT gene. At 2 years, 46% of the patients treated with TMZ/radiotherapy and whose tumors had a methylated MGMT promoter survived, compared with only 14% for the patients with an unmethylated MGMT status (overall log-rank P = 0.0001). Prospective validation of this factor for prediction of benefit from TMZ is ongoing.

However, even in the cohort of patients with a methylated MGMT overall survival remains unsatisfactory and extremely variable, indicating additional mechanisms of treatment resistance. A first step is the identification of relevant molecular mechanisms driving the aggressive biological behavior of glioblastoma. We investigated glioblastoma gene expression profiles and identified new independent mechanisms of resistance to this treatment that may be targeted as part of an improved trial design.

Conclusions: To date, the test for the MGMT-methylation status is the only tool available that may direct the choice for alkylating agents in glioblastoma patients, but many others may hopefully become part of an arsenal to stratify patients to respective targeted therapies within the next years.

S22

Biomarkers of brain tumors to EGFR-TKI

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Glioblastoma is one of the most aggressive human cancers with a median survival of about 15 months despite optimal therapy with surgery, radiation, and chemotherapy. Reasons for this dismal track record of current therapeutics are unknown and are likely to include disease-specific genetic abnormalities, limited penetration of therapeutics across the blood-brain barrier, and the difficulty to obtain serial tissue samples for the monitoring of tumor cell response to therapy. Since about 40% of primary glioblastomas harbor amplification of the EGFR gene locus and often express a mutant EGF receptor with constitutively activity due to an in-frame truncation within the ligand-binding domain (EGFRvIII), inhibition of EGFR signaling presents a molecularly compelling strategy for the treatment of glioblastoma. We and others have observed clear antitumor activity of small molecule EGFR tyrosine kinase inhibitors (EGFR TKIs) in 10−20% of glioblastoma patients. Clinical response was highly correlated with coexpression in tumor cells of the tumor suppressor PTEN and EGFRvIII. We have also identified missense mutations in the extracellular domain of EGFR as novel mechanisms for oncogenic EGFR conversion in glioblastoma. These observations raise a number of questions for the clinical evaluation and optimal deployment of EGFR kinase inhibitors in glioblastoma which will be discussed in this presentation.

S23

Biomarkers of lung cancer response to EGFR-TKI

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Introduction: More than three years have passed since mutations of the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) were discovered in patients with lung cancer who had dramatic clinical responses to treatment with gefitinib. The other common genomic changes that arise in lung cancer that have an impact on EGFR-TKI sensitivity include KRAS mutations, secondary T790M mutations in EGFR, and MET amplification. The retrospective studies have shown that EGFR mutations are closely associated with response while EGFR copy number and EGFR detection by immunohistochemistry are most closely associated with a prolongation in time to progression and survival in randomized studies of EGFR-TKI versus placebo. These retrospective studies have now led to prospective studies incorporating these different biomarkers of response and outcome into trials using EGFR-TKIs as therapeutic agents.

Main Message: Prospective studies of lung cancer patients with EGFR mutations treated with gefitinib and erlotinib have reported a response rate of approximately 80%, a median time to progression in excess of approximately one year, and a median survival in excess of two years. This has led to ongoing trials in Japan comparing patients with EGFR mutations being treated with either chemotherapy or gefitinib and the development of commercial tests to determine if the DNA from tumors retrieved from patients with adenocarcinoma have a mutation of the EGFR. The EGFR copy number assessments by FISH have been prospectively incorporated into trials that have been recently reported. One trial called INVITE compared 196 patients older than 70 years of age with non-small cell lung cancer who were randomly assigned to either treatment with gefitinib or vinorelbine. A lung cancer specimen was required for entry onto the study to determine biomarkers and EGFR copy number could be assessed in 158 of the 196 patients' tumors. Increased EGFR copy number was not associated with increased response or survival benefit in patients given gefitinib compared to those given vinorelbine. A second trial called INTEREST studied patients with non-small cell lung cancer previously treated with one or two chemotherapy regimens. 1466 patients were randomized to treatment with either gefitinib or docetaxel given every 3 weeks. Lung cancer specimens were not required for entry onto the study to determine biomarker status. Once again, there was no difference in outcome between the two arms and no relationship between EGFR copy number determined by FISH and response rate, time to progression, or survival on either arm.

The genomic change associated with resistance to treatment with gefinib and erlotinib is a DNA mutation which changes the threonine to methionine at the 790th amino acid of EGFR known as the (T790M) mutation as well as amplification of the MET oncogene. The T790M mutation in EGFR is responsible for approximately half