new brain lesions on study, none during treatment. No treatment discontinuations occurred due to AEs.

Conclusion: The current analyses indicate that atezolizumab has an acceptable safety profile in patients with NSCLC who have asymptomatic or previously treated stable brain metastases. Further investigation is needed to fully assess the efficacy of atezolizumab in this patient population.

Keywords: Immunotherapy, atezolizumab, brain metastases, NSCLC

P2.03b-015
Efficacy of the Irreversible ErbB Family Blocker Afatinib in Treatment of an Intracerebral Non-Small Cell Lung Cancer in Mice

Topic: Brain Meta

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Background: The prognosis of brain metastases (BM) from lung cancer is extremely poor. Some studies showed patients with BM responded well to afatinib, while little was known on detail mechanism. This study aimed to evaluate the efficacy of afatinib for BM and address whether it could actively penetrate brain-blood barrier (BBB) and hit its target.

Methods: Tumor burden was evaluated weekly after administration of afatinib and vehicle, and pharmacokinetic and pharmacodynamics characteristics were measured in both normal mice and BM model mice.

Results: Administration of 15mg/kg afatinib inhibited in vivo PC-9 tumor growth in brain with tumor growth inhibitory rate (TGI) of 79.8% and 90.2% on day 7 and 14, respectively. 30mg/kg afatinib exhibited the tumor regression on day 7 and 14 with TGI of 124.7% and 105%. The plasma concentration was 91.4±31.2 nM/L at 0.5h after afatinib administration, reached the peak (417.1±119.9 nM/L) at 1h, and still be detected at 24h. The CSF concentrations followed a similar pattern. A good correlation (R^2=0.732) between plasma and CSF concentrations was demonstrated. Immunohistochemistry showed the signal of pEGFR was reduce by 90% at 1 hour after administration of 30mg/kg afatinib. A positive correlation between afatinib concentrations in CSF and pEGFR modulation was observed.

Conclusion: Afatinib could penetrate into BBB contributing to brain tumor response. The exposure in CSF correlated with that in plasma, which was correlated with modulations of pEGFR in the tumor tissues. Our findings provide implication of potential application of afatinib in NSCLC patients with brain metastases.

Keywords: Brain metastasis, afatinib, non-small cell lung cancer, tyrosine kinase inhibitor

P2.03b-016
Tesevatinib in NSCLC Patients with EGFR Activating Mutations and Brain Metastases (BM) or Leptomeningeal Metastases (LM)

Topic: Brain Meta

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Background: Tesevatinib is a potent reversible EGFR inhibitor with strong preclinical evidence of brain penetration: brain:plasma ratios of 1-4 and brain:meninges ratios of 10-15 in rodents (AACR 2015 Abstract 2590). Tesevatinib was previously shown to have significant clinical activity in patients presenting with EGFR mutant NSCLC, but not in patients with T790M mutation. Approximately 25% of patients with EGFR activating mutations progress in the CNS, and metastases there have a low rate (10%) of T790M mutations.

Methods: Patients with NSCLC driven by activating EGFR mutations who had BM or LM occurring or progressing while receiving erlotinib, gefitinib, or afatinib were treated with 300 mg of tesevatinib daily. Patients with BM had RECIST 1.1 measurable disease in the brain, and RECIST 1.1 evaluated response. Patients with symptomatic LM were diagnosed by either CSF cytology or MRI findings. Response was measured by improvement in symptoms, CSF cytology, and MRI. Patients with both BM and symptomatic LM were enrolled in the LM cohort. Target accrual is 20 patients in each cohort.

Results: To date, 7 patients have been enrolled [2M:5F; median age 61 (36-66); 1 Asian], all with CNS symptoms. Four were in the BM cohort and 3 in the LM cohort. All had prior CNS radiotherapy, either WBRT or SRS or both. All had prior systemic therapy (median 3; range 1-6). Three patients had EGFR del 19, 3 had L858R, and 1 had L861Q. Gr $\geq$ 3 adverse events, regardless of relationship to study drug, have included Gr 3 prolonged QTc, Grade 3 hypokalemia, Gr 3 dehydration, Gr 3 UTI, and Gr 3 ALT elevation. Three patients had dose reductions due to asymptomatic QTc interval prolongation. Six out of the 7 patients had CNS symptom improvement, often occurring within 14 days of tesevatinib initiation. Two patients decreased steroids. One BM patient had marked improvement in right leg strength and a 19% reduction in the target BM on Study Day 23. One patient with BM and LM had resolution of LM symptoms, a 57% reduction in BM target lesion, and clearance of LM enhancement on MRI at Study Day 41.

Conclusion: Early data from the first 7 patents in this ongoing clinical trial indicate that tesevatinib has clinical activity in the CNS in EGFR mutant disease manifesting as BM or LM in patients previously treated with erlotinib, gefitinib, or afatinib. An additional cohort of 20 treatment-naïve patients who have initial presentation with brain metastases is being added.

Keywords: EGFR Inhibitor, Brain Metastases, Leptomeningeal Metastases

P2.03b-017
Differences of Central Nerve System Metastasis during Gefitinib or Erlotinib Therapy in Patients with EGFR-Mutated Lung Adenocarcinoma

Topic: Brain Meta

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Background: A few reports have suggested a difference in the incidences of new metastasis to the central nerve system (CNS) during gefitinib and erlotinib therapy. However, a direct comparison of these two therapies has not yet been reported. We planned a retrospective study to investigate the incidences of CNS metastasis progression (new CNS metastasis or progression of existing CNS metastasis) during gefitinib and erlotinib therapy in patients with non-small cell lung cancer (NSCLC) harboring EGFR mutation.

Methods: We retrospectively analyzed the incidences of CNS metastasis progression and the outcomes of NSCLC patients harboring EGFR mutation who received gefitinib or erlotinib as a first-line EGFR-TKI treatment at the National Cancer Center Hospital between 2008 and 2014.

Results: A total of 175 patients were analyzed; 148 patients had received gefitinib, and 27 had received erlotinib. The median (range) ages were 64.5 (32-81) years and 62.0 (27-68) years, respectively; exon 19 deletion/L858R point mutations were present in 84/64 (56.7%/43.3%) and 17/10 (63.0%/37.0%) cases, respectively. The status of CNS metastasis before EGFR-TKI therapy was negative/positive in 105/43 (71.0%/29.0%) cases in the gefitinib group and 21/6 (77.8%/22.2%) cases in the erlotinib group, respectively. The incidence of CNS metastasis progression in the gefitinib group tended to be higher than that in the erlotinib group (29.0% vs. 11.1%; $P = 0.051$). In patients without CNS metastasis before EGFR-TKI therapy, the incidence of new CNS metastasis during EGFR-TKI treatment was significantly higher in the gefitinib group than in the erlotinib group (24.7% vs. 4.8%, $P = 0.04$). The progression-free survival (PFS) and overall survival (OS) periods of the patients who presented with CNS progression were shorter than those of the patients who presented without CNS progression (median PFS, 9.5 vs. 12.6 months, $P = 0.034$; median OS, 23.8 vs. 34.1 months, $P = 0.002$). Fifty-six patients underwent re-biopsy after the failure of EGFR-TKI therapy, but no difference in the incidences of *EGFR* T790M mutation was seen between patients with and those without CNS metastasis progression (40.0% for patients without CNS progression vs. 63.6% for patients with CNS metastasis progression, $P = 0.19$).

Conclusion: The incidence of the progression of CNS metastasis during gefitinib therapy was higher than that during erlotinib therapy. In addition, the difference in this incidence was more remarkable among patients who had not developed CNS metastasis prior to the start of EGFR-TKI therapy.

Keywords: EGFR-mutated NSCLC, Erlotinib, CNS Metastasis, gefitinib