TPS2090 **Poster Session**

Delayed or upfront brain radiotherapy in treatment-naïve lung cancer patients with asymptomatic or minimally symptomatic brain metastases and ALK rearrangements (DURABLE).

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Background: Patients with non-small cell lung cancer (NSCLC) with ALK rearrangements have a high frequency of brain metastases. Alectinib was shown to be superior to crizotinib in the first-line treatment of patients with ALK-positive NSCLC in the ALEX trial, and the intracranial response rate (CNS ORR) was 85.7% with alectinib versus 71.4% with crizotinib in patients who received prior radiotherapy and 78.6% versus 40.0%, respectively, in those who had not. Alectinib has also shown benefit in earlier stages of NSCLC. Given the high intracranial efficacy rate demonstrated by alectinib, as well as the known toxicities of cranial irradiation, the role of early irradiation of CNS disease vs delaying radiation in favor of treatment with alectinib needs to be defined to inform clinical practice. **Methods:** NCT05987644 is a multi-center, multi-cohort study consisting of a Phase 1b and Phase 2 portion. The Phase 1b portion of the study is a single-arm, open label study of alectinib in patients with CNS disease. Twelve subjects will be enrolled in the Phase 1b portion of the study and treated with alectinib alone; patients with PD will come off study treatment and move on to standard of care treatment per national guidelines. The phase 2 portion will be a randomized, non-blinded, open-label study. Forty-four subjects will be enrolled and randomized 1:1 to either alectinib upfront (Arm A) or alectinib + SRS (arm B). A group sequential design will be implemented with one interim analysis for futility and, and one final analysis using the composite outcome. The primary objective of phase 1b is to determine the safety and feasibility of delayed brain radiation in patients with ALK fusion positive NSCLC and CNS metastases. The primary objective of the phase 2 study is to determine whether treatment with alectinib results in preserved neurological status and control of CNS disease at 12 months compared to alectinib plus SRS. Secondary endpoint will be intracranial progression free survival at 12 months (icPFS12), response rate and icPFS, OS, and safety and tolerability. The study is open and accruing at 4 sites. Clinical trial information: NCT05987644. Research Sponsor: Genentech.