PRECLINICAL EVIDENCE AND CLINICAL CASES OF AZD9291 ACTIVITY IN EGFR-MUTANT NON-SMALL CELL LUNG CANCER (NSCLC) BRAIN METASTASES (BM)


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Aim: AZD9291 is a potent, selective, oral irreversible EGFR-TKI effective against the EGFR-TKI-sensitising (EGFRm+) and resistance T790M mutations. We researched the potential efficacy of AZD9291 against EGFRm+ NSCLC BM.

Methods: Preclinical brain exposure of AZD9291 and an active circulating metabolite (AZ5104) were evaluated in mouse models. In vivo efficacy of AZD9291 was assessed in a mouse EGFRm+ (exon 19 deletion) BM xenograft (PC9) model. Human doses that could potentially deliver BM efficacy were predicted using a preclinical pharmacokinetic/pharmacodynamic (PK/PD) mathematical model, adapted to account for the differential exposure and binding of AZD9291 and AZ5104 in brain compared with plasma. Selected case reports of clinical activity in EGFRm+ NSCLC BM were available from a Phase I, open-label, dose-escalation study of AZD9291 (AURA; NCT01802632). Collection of cerebrospinal fluid and plasma PK samples are ongoing.

Results: In preclinical studies, AZD9291 showed significant exposure in the brain. Concentrations in mouse brain tissue compared with plasma were 5–25-fold higher for AZD9291 and approximately equivalent for AZ5104. At clinically relevant doses, AZD9291 distribution to the brain is ~10-fold higher than gefitinib. In the PC9 BM model, AZD9291 5 mg/kg/day showed tumour growth inhibition of BM. Using an adapted preclinical PK/PD model, simulations with clinical AZD9291/AZ5104 PK data predicted that a human dose of 80 mg would be sufficient to target EGFRm+ BM. In AURA, extracranial objective responses according to RECIST were observed at all dose levels (20–240 mg) and for some patients shrinkage in BM was reported. Clinical cases will be presented.

Conclusions: Preclinical studies indicate AZD9291 has significant exposure in the brain and activity against EGFRm+ BM. In light of early clinical evidence of AZD9291 activity in patients with EGFRm+ NSCLC BM, further investigation into the potential benefit of AZD9291 in patients with EGFRm+ NSCLC and BM is warranted.