Aim: AZD9291 is in clinical development to address T790M-mediated drug resistance associated with treatment of EGFR-mutant NSCLC. Genotyping of circulating plasma DNA may provide an option to identify patients (pts) unable to provide tissue biopsies. We aimed to study plasma levels of EGFR T790M in relation to AZD9291 drug activity.

Methods: 101 pts with advanced NSCLC consented to plasma analysis as part of the Phase I study of AZD9291 (NCT01802632). Central tumour genotyping was performed when feasible using the cobas™ assay. After pre-amplification of plasma DNA, levels of pre-dose T790M, L858R and exon 19 del variants were quantified using an emulsion PCR assay (cobas™). Cases with no detectable plasma-sensitising mutation were omitted from T790M analysis. Response rate (RR) as of 16 Jan 2014 was calculated as the proportion of pts with ≥1 follow-up tumour measurement having a diameter decrease ≥30%.

Results: Plasma assays for L858R and 19 del were studied in 44 pts with 19 del and 28 pts with L858R centrally confirmed in their tumour. A threshold of 0.05% mutant had 0% false positive rate (FPR) and 83% sensitivity for these mutations. In 64 pts with central T790M results, the same threshold applied to plasma T790M had 50% FPR, 89% sensitivity. Notably, of 6 cases falsely T790M+ in plasma, 5 were also T790M+ using a second plasma assay (cobas™). RR was 61% (25/41) and 24% (5/21) in 62 pts with central T790M+ and T790M- tumour genotyping (p = 0.008). Similarly, RR was 65% (33/51) and 38% (8/21) in 72 pts with T790M+ and T790M- plasma genotyping (p < 0.001). No responses were seen in 6 pts T790M- in both tumour and plasma. In 34 pts without tissue for central genotyping, RR was 87% (13/15) and 36% (4/11) for T790M+ and T790M- in plasma (p = 0.01). Updated data will be presented.

Conclusions: Plasma levels of EGFR-TKI-sensitising mutations correlate more closely with tumour genotype than T790M, likely due to the greater genomic heterogeneity of resistance. RR is higher in T790M+ pts than in T790M- pts, either using tumour or plasma genotyping. Plasma T790M genotyping using emulsion PCR may be an attractive alternative to rebiopsy for tumour genotyping of NSCLC pts with acquired EGFR resistance.