Background: The uncommon *EGFR* exon 19 deletion (del19) L747\_A750delinsP is less sensitive to inhibition by 1st and 3rd generation EGFR tyrosine kinase inhibitors (TKI) than the common del19 E746\_A750del owing to a higher ATP binding affinity associated with L747\_A750delinsP. Accordingly, EGFR L747\_A750delinsP is associated with worse outcomes with erlotinib and osimertinib treatment compared to E746\_A750del. In preclinical studies, L747\_A750delinsP and the common del19 E746\_A750del do not differ in sensitivity to afatinib, a 2nd generation TKI, which may be more effective for targeting L747\_A750delinsP.

Methods: To evaluate outcomes in patients with advanced NSCLC harboring a L747\_A750delinsP mutation treated with afatinib, we analyzed data pooled from 4 clinical trials (LUX-Lung 2, LUX-Lung 3, LUX-LUNG 7, SWOG S1403) of afatinib for patients with *EGFR* mutant (*EGFR*+) non-small cell lung cancer (NSCLC). We investigated objective response rate (ORR), progression free survival (PFS), and overall survival (OS) for patients with tumors with E746\_A750del vs. L747\_A750delinsP. Median PFS and OS were estimated using Kaplan-Meier method.

Results: Eighty-seven patients with advanced *EGFR*+ NSCLC treated with afatinib monotherapy were evaluated, 78 harboring E746\_A750del and 9 with L747\_A750delinsP. Sex, race, and ECOG performance status were similar, but L747\_A750delinsP was associated with older age (median 60 vs. 69 years). ORR to afatinib was 76% for E746\_A750del vs. 87.5% for L747\_A750delinsP (ORR Odds Ratio 0.85 [80% CI, 0.18-2.97]). Median PFS was 10.1 months for E746\_A750del vs. 10.1 months for L747\_A750delinsP (Figure 1) with PFS Hazard Ratio (HR) 1.68 [80% CI, 0.90-3.11], and median OS was 25.3 months for E746\_A750del vs. 29.0 months for L747\_A750delinsP (Figure 2) with OS HR 1.79 [0.97-3.28].

Conclusion: These data support a potential role for afatinib as the preferred TKI for patients with EGFR+ NSCLC harboring L747\_A750delinsP, corroborating prior preclinical and clinical findings. Prospective data comparing afatinib to osimertinib for patients with tumors harboring EGFR L747\_A750delinsP is needed.

