Within a previously negatively reported NSCLC cohort, using hybrid capture assays we identified additional 12 (6.6%) patients with NEOliquid and 5 (16.5%) patients with NEOplus with druggable alterations.

**Conclusions**

- **HC-NGS can detect less prevalent, novel or complex and even druggable alterations that would not be detectable with commonly used routine diagnostic methods.**
- **Due to the broad landscape of driver events in NSCLC, basic routine screening methods often fail to detect actionable and druggable alterations, such as BRAF, RET, MET or NTRK.**
- **The detection of actionable EGFR mutations in a pre-screened, potential EGFR-negative cohort might be explained by the lower sensitivity or lack of testing in routine assays, especially with respect to non-classical EGFR mutations such as p.(I744_E746delinsMK) or p.(G719C), p.(S768I).**

**Results**

- We analysed 213 samples that were previously documented to be, based on previous routine screening (i.e. IHC, PCR), negative for EGFR and negative or untested for ALK, BRAF, EGFR, ERBB2, KRAS, MET, RET, ROS1, NTRK2.
- NEOliquid v1 (FDNA) identified driver events in ALK (6), BRAF (10), EGFR (6), RET (2), ROS1 (1), ERBB2 (4), KRAS (32), MET (12) in 56 out of the 183 blood samples.
- NEOplus v1 (FFPE) identified driver events in NTRK2 (1), ALK (1), EGFR (1), KRAS (6), MET (1), RET (1), ROS1 (1), in 12 out of the 30 tumor samples.
- Out of these, druggable alterations were identified in 12 patients analysed with NEOliquid (6.6%), and in further 5 patients with NEOplus (16.5%).