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Hybrid Capture-Based Assays in Primary Diagnostics of NSCLC Patients – Results from the NEOlung Study

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Background
Routine molecular screening of non-small cell lung cancer (NSCLC) patients for actionable mutations is often challenging due to limited tumor material and assay sensitivity. NEOlung, a multi-centric exploratory study evaluated the usefulness of non-invasive liquid biopsy and FFPE-based hybrid capture-based next generation sequencing (NGS) assays in the primary diagnostic setting.

Methods
We evaluated 201 blood (cfDNA) samples and tissue isolated DNA from 35 FFPE samples, previously tested negative for EGFR and negative or not at all for KRAS mutations. With the two hybrid-capture-based gene panels NEOplus v1 and NEOliquid v1 in combination with a proprietary bioinformatics, we performed NGS to detect point mutations, small InDels, copy number alterations and selected gene fusions in up to 39 (NEOliquid v1) and 94 (NEOplus v1) genes respectively.

Results
Of the 236 total samples, 23 carried a rare driver event, such as ERBB2 or BRAF activating mutations or ALK- or ROS1-fusion based on pre-screening, while 213 samples (183 blood and 30 FFPE) were previously documented to be negative or untested for ALK, BRAF, EGFR, ERBB2, KRAS, MET, RET, ROS1, NTRK1.

In the 213 presumably pan-negative samples, NEOliquid v1 identified driver events in ALK (1), BRAF (10), EGFR (6), RET (2), ROS1 (1), ERBB2 (4), KRAS (31), MET (1) in 56 out of the 183 blood samples. NEOplus v1 identified driver events in NTRK1 (1), ALK (1), EGFR (1), KRAS (6), MET (1), RET (1), ROS1 (1) in 12 out of the 30 FFPE samples.

Conclusion
Of the identified mutations, non-invasive NEOliquid v1 identified 12 (6.6%) samples, while FFPE sample-based NEOplus v1 identified 5 (16.7%) samples with known drug approvals. Furthermore, 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.

In conclusion, we identified an additional 6.6% of patients with druggable alterations using NEOliquid v1 and 16.5% using NEOplus v1 within a presumably negative cohort, which shows the added value of hybrid capture-based NGS assays to identify clinically targetable genomic alterations.

Clinical trial identification
Study Number 2016/01