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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