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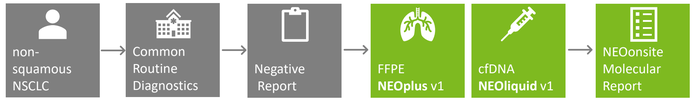
Hybrid Capture-Based Assays in Primary Diagnostics of NSCLC Patients
Results from the NEOlung Study

Balazs Jori[1], Oliver Gautschi[2], Martin Kimmich[3], Sophie Beaucaire Danel[4], Niels Reinmuth[5], Pilar Garrido[6], Federico Cappuzzo[7], Martin Forster[8], Krishna Patel[8], Christian Grohé[9], Annette Müller[10], Claas Wesseler[11], Roopika Menon[1], Judith Müller[1], Erika Mariotti[1], Julia Brinkmann[12], Lukas Heukamp[13], Frank Griesinger[14]

[1] NEO New Oncology, Cologne, Germany, [2] University of Berne and Cantonal Hospital of Lucerne, Switzerland, [3] Department of Pneumology, Clinic Schillerhoehe, Gerlingen, Germany, [4] Institut du Thorax Curie-Montsouris, Institut Curie, Paris, France, [5] Asklepios Lung Clinic, Munich-Gauting, Germany, [6] Medical Oncology Department, Hospital Ramón y Cajal, Madrid, Spain, [7] Department of Oncology & Hematology, AUSL Romagna, Ravenna, Italy, [8] Cancer Clinical Trials Unit, University College Hospitals, London, United Kingdom, [9] Evangelische Lungenklinik Berlin, Berlin, Germany, [10] Department of Hematology and Oncology, University Hospital of Mannheim, Mannheim, Germany, [11] Thoraxonkologie, Asklepios Klinikum, Hamburg, Germany, [12] Oncology, Pfizer Pharma GmbH, Berlin, Germany, [13] Lung Cancer Network, NOWEL, Oldenburg, Germany, [14] Hematology and Oncology, Pius Hospital, University of Oldenburg, Oldenburg, Germany

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 hybrid capture-based next generation sequencing (HC-NGS) assays NEOliquid v1 and NEOplus v1 in the primary diagnostic setting. Our aim was to evaluate the added value of both assays in a presumed negative, untreated NSCLC patient population.



NSCLC Samples

- 183 blood and 30 FFPE samples
- Prior, common routine diagnostics resulted:
  - negative for *EGFR*
  - negative or untested for *KRAS, ALK, MET, ERBB2, RET, ROS1, BRAF, NTRK1*

Methods

- DNA-based HC-NGS
- NEOliquid v1 for cfDNA
- NEOplus v1 for FFPE
- NEO proprietary bioinformatic pipeline

Alterations detected

- Point mutations
- Small InDels
- Copy Number Variations
- Gene Fusions

Genes in NEOliquid v1

ALK	ARAF	ATM	ATR	*BRAF*	BRCA1	BRCA2	CDK4	CDKN2A	CDKN2B	CTNNB1	DDR2
EGFR	**ERBB2**	*FGFR1*	*FGFR2*	*FGFR3*	HRAS	IDH1	IDH2	KEAP1	KIT	KRAS	MAP2K1
MDM2	**MET**	MTOR	NFE2L2	NRAS	PDGFRA	PIK3CA	PTEN	RB1	*RET*	*ROS1*	STK11
TP53	TSC1	TSC2									

In addition to SNVs and small InDels, the test covers genes applicable for CNV (bold) and for fusion detection (italic).

Genes in NEOplus v1

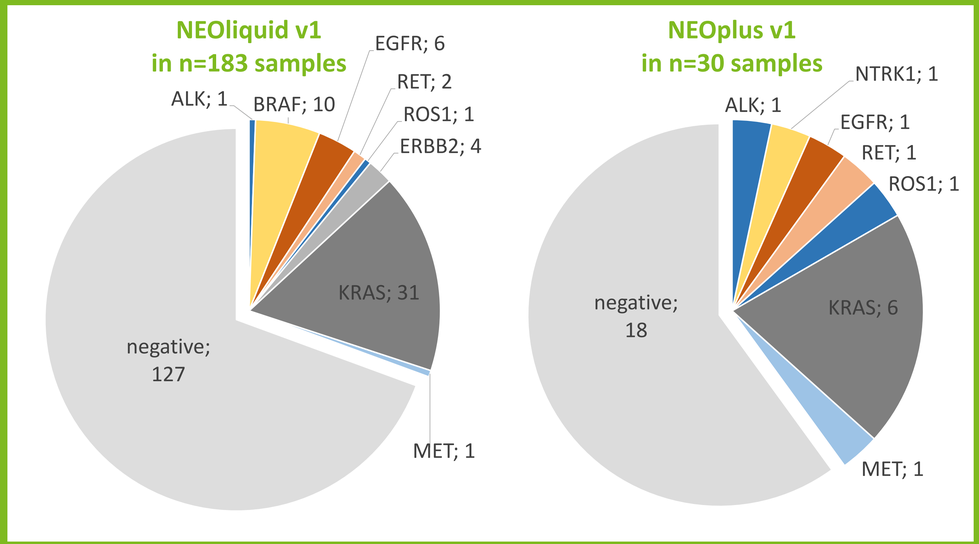
ABL1	AKT1	*ALK*	APC	AR	ARAF	ARID1A	ARID1B	ATM	ATR	B2M	BCL6
BRAF	BRCA1	BRCA2	*BRD4*	BRIP1	CCND1	CCNE1	CD274	*CD74*	CDH1	CDK4	CDK6
CDKN2A	CDKN2B	CHEK1	CHEK2	CTNNB1	DDR2	*EGFR*	*EML4*	ERBB2	ERBB3	ESR1	FBXW7
FGFR1	*FGFR2*	*FGFR3*	FGFR4	GNA11	GNA13	GNAI2	GNAQ	GNAS	GNAT2	HRAS	IDH1
IDH2	JAK2	KDR	KEAP1	*KIF5B*	KIT	KRAS	MAP2K1	MAP2K2	MDM2	*MET*	MTOR
MYC	MYCL1	MYCN	NF1	NFE2L2	NRAS	*NRG1*	*NTRK1*	PALB2	*PDGFRA*	*PDGFRB*	PIK3CA
PIK3R1	POLD1	POLE	PRKDC	PTCH1	PTEN	RAD50	RAD51	*RAF1*	RB1	*RET*	RICTOR
	ROS1	RPTOR	SMO	STK11	TERT	TP53	TP53BP1	TSC1	TSC2	VHL	

In addition to SNVs, small InDels and CNV, the test covers genes applicable for fusion detection (italic).

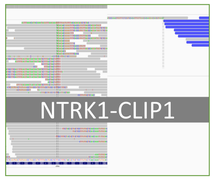
Within a **previously negatively reported NSCLC** cohort, using hybrid capture assays we identified

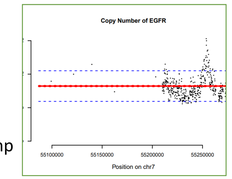
additional
12 (6.6%) patients with NEOliquid and
5 (16.5%) patients with NEOplus

with **druggable alterations**.



Distribution of driver alterations detected with NEOliquid v1 and NEOplus v1 in NSCLC samples that were *previously reported as negative* in routine molecular analysis.





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, NTRK1.*
- NEOliquid v1 (cfDNA) 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 (FFPE) identified driver events in *NTRK1* (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%).

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).

Conflict of interest
B. Jori, R. Menon, E. Mariotti, J. Müller are employed by NEO New Oncology GmbH. *J. Brinkmann* is employed by Pfizer Pharma GmbH. *P. Garrido* declares conflict of interest as of Roche, Speaker, Advisory Role, AstraZeneca, Speaker, Advisory Role, Bristol (BMS), Speaker, Advisory Role, Guardant Health, Advisory Role, MSD, Speaker, Advisory Role, Pfizer, Speaker, Advisory Role, Janssen, Advisory role, Boehringer Ingelheim, Speaker, Advisory Role, Novartis, Speaker, Advisory Role, Gilead, Speaker, Rovi, Speaker, Abbvie, Advisory Role Lilly, Advisory Role, Takeda, Advisory Role, Speaker, Sysmex, Speaker Blueprint Medicines, Advisory Role, Bayer, Advisory Role. *M. Forster* has research grants from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, MSD & Merck and honoraria for advisory and consultancy work from Achilles, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Guardant Health, Merck, MSD, Nanobiotix, Novartis, Oxford VacMedix, Pfizer, PharmaMar, Roche & Takeda.

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Contact
NEO New Oncology GmbH, Gottfried-Hagen-Str. 20, 51105 Köln, Germany www.newoncology.de, email jori@newoncology.de