DAkkS Deutsche Akkreditierungsstelle D-ML-13403-01-00 D-PL-13403-01-00

Überörtliche Berufsausübungsgemeinschaft
MVZ · Dr. Eberhard & Partner Dortmund

Laboratoriumsmedizin Dortmund

LabmedLetter

MVZ Dr. Eberhard & Partner Dortmund
Postfach 10 10 40
44010 Dortmund
Brauhausstraße 4
44137 Dortmund
www.labmed.de
info@labmed.de
mikro@labmed.de
Labor:
Tel.: 0231 · 95 72 - 0
Fax: 0231 · 57 98 34
Mikrobiologie:
Tel.: 0231 · 95 72 - 5100
Fax: 0231 · 55 34 62

Laboratory information 7/2017

Non-Small Cell Lung Cancer (NSCLC)

Medical background

Cancer mutations in the kinase domain are designated as "activating mutations" because they lead to a ligand-independent activation of kinase activity. EGFR with these somatic mutations has been shown to be associated with a better prognosis than wild-type EGFR. In non-small cell lung cancer (NSCLC) patients who are treated with EGFR tyrosine kinase inhibitors (TKIs), these somatic mutations are additionally associated with clinical response and even more prolonged survival. The activating mutations in the adenosine triphosphate (ATP)-binding pocket in the receptor TK-domain, encoded in exons 18 to 21 in the EGFR gene, are the most important predictors of overall survival (OS) and response to EGFR-TKIs. Approximately 90% of alterations affect hotspots within that TK domain, where TKIs like erlotinib or gefitinib can bind. In-frame deletions (codons 746-750) in exon 19 and arginine at EGFR position 858 (p.L858R) in exon 21 are most frequently found. The remaining mutations are insertions in exon 20 (5%) and rare substitutions spanning exons 18-21. These activating mutations render tumors susceptible to the drugs gefitinib and erlotinib and are more common in women, never smokers and patients with adenocarcinoma history. The median OS of patients treated with e.g. gefitinib as first-line therapy was 28.5 months in contrast to the median OS of patients only treated with platinum-based chemotherapy (8-10 months).
Some of the mutations mainly in Exon 20 have shown to be associated with TKI resistance. First of all the c.2369C>T (T790M) mutation has been found to arise in NSCLC cells during TKI therapy and most recently may be treated with osimertinib.

In smokers *KRAS* mutations have been described to be the predominant mutations of NSCLC. *KRAS* mutations in codon 12, 13, 61 and 146, which are also EGFR-TKI resistant, have been treated using selumitinib.

Furthermore, BRAF and PIK3CA mutations are also important indicators for EGFR-TKI therapy decisions. In about 3% of NSCLC BRAF, a serine/threonine kinase, is activated by the somatic point mutations in codon 600 (50%), codon 594 (11%) (in exon 15) or G469A (39%) in exon 11. In those cases with BRAF mutations, a combination of dabrafenib and trametinib showed a better response. In vast majority of cases, BRAF mutations are not overlapping with other mutations found in NSCLC. PIK3CA mutations are detected more frequently in squamous than in nonsquamous NSCLCs and show also EGFR-TKI resistance but have been treated using buparlisib and docetaxel in combination.

Analyses and therapeutics of NSCLC
(mutations present in less than 20% of cells cannot be detected by Sanger sequencing!)

EGFR mutated (Exons 18-21): gefitinib, erlotinib
EGFR mutated T790M (Exon 20): osimertinib
KRAS mutated (Codons 12, 13, 61, 117, 146): selumetinib
BRAF mutated (Codon 469, 594, 600): dabrafenib and trametinib
PIK3CA mutated (Exons 11, 22): buparlisip and docetaxel

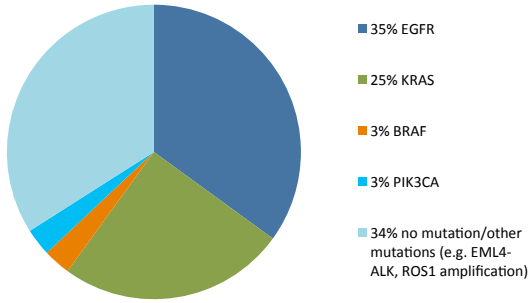

Figure : Frequency of mutations in NSCL

Methods

Mutations present in less than 20% of cells might not be detected by Sanger sequencing!
A highly sensitive method analyzes the known loci seen above. Using NGS (next generation sequencing method) the cancer hotspot panel can detect 2800 cosmic mutations in further 46 different genes.

Material and pre-analysis

Tumor sections in 1.5 ml Eppendorf-Tubes (3 slices of FFPE tumor tissue minimum 10 µm thick)

Turnaround time and reporting

Turnaround time approx. 14 days.
For each medical report, we supply an individual interpretation along with further diagnostic recommendation.

Contact

Dr. rer. nat. A. Beckmann: abeckmann@labmed.de

Literature

1. Gazdar, Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. Oncogene, 2009, 28:S24–S31
2. Inoue et al., Characteristics and overall survival of EGFR mutation-positive non-small cell lung cancer treated with EGFR tyrosine kinase Inhibitors: a retrospective analysis for 1600 Japanese patients. Jpn J Clin Oncol., 2016, 46:462-7
3. Lee et al., Somatic Mutations in Epidermal Growth Factor Receptor Signaling Pathway Genes in Non-small Cell Lung Cancers. J Thorac Oncol, 2010, 5: 1734-40
4. Li et al., Coexistence of EGFR with KRAS, or BRAF, or PIK3CA somatic mutations in lung cancer: a comprehensive mutation profiling from 5125 Chinese cohorts. 2014 110: 2812–2820
5. Sequist et al., Response to Treatment and Survival of Patients with Non-Small Cell Lung Cancer Undergoing Somatic EGFR Mutation Testing. Oncologist, 2007, 12:90-8
6. Siegelin and Borczuk, Epidermal growth factor receptor mutations in lung adenocarcinoma. Lab Invest, 2014, 94 129–137
7. Massacesi et al., PI3K inhibitors as new cancer therapeutics: implications for clinical trial design. Onco Targets Ther, 2016; 9:203-10
8. Ku et al., AZD9291 overcomes T790M mediated resistance through degradation of EGFR (L858R/T790M) in non-small cell lung cancer cells. Invest New Drugs, 2016, 34:407-15
9. Planchard, et al., Dabrafenib plus trametinib in patients with previously treated BRAF V600E mutant nmetastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. Lancet Oncol, 2016, 17, 984–993
10. My Cancer Genome: lung cancer: https://www.mycancergenome.org/content/disease/lung-cancer/

FÄ für Laboratoriumsmedizin: Dipl.-Chem. Dr. med. Arnold Eberhard · Dr. med. Petra Kappelhoff · Dr. med. Bettina Eberhard · Dr. medic. (RO) Csilla Rompf · Dr. med. Karim Gorschlüter; **FÄ für Mikrobiologie und Infektionsepidemiologie:** Felix Pranada · Dr. med. Arthur Pranada · Dr. med. Anja Sägers; **FÄ für Humangenetik:** Dr. med. Annemarie Schwan · Dr. med. Stefanie Vogt · Dr. med. Stefan Wieczorek · Dr. med. Judith Kötting