ADVANCED NON-SMALL-CELL LUNG CANCER. THE SIGNIFICANCE OF PERSONALIZED THERAPY

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Abstract. For several entities of advanced non-small-cell lung cancer (NSCLC), tyrosine kinase and immune checkpoint inhibitors are the basis for the so-called personalized or precision therapy and have become the standard of care in the first- and second-line setting. In previously untreated NSCLC patients with activating EGFR-mutation, ALK or ROS1 translocation status, tyrosine kinase inhibitors (TKIs) replace the chemotherapy and are the new standard of care. In previously untreated patients with a high level of programmed cell death ligand 1 (PD-L1), pembrolizumab leads to significantly longer PFS, longer OS, and fewer adverse events than platinum-based chemotherapy regardless the histologic subtype. In previously treated patients with squamous carcinoma, nivolumab is the new standard of care, independent of PD-L1 expression. In the future, combination therapies have to be proved, whether they are more effective than monotherapy.

Key words: NSCLC, personalized therapy, combination therapies, stratified treatment, monotherapy, efficiency of therapy, molecular markers.


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Personalization is one of the most important subjects and challenges of actual medicine generally and of cancer medicine, particularly. The prediction of diseases as well as a targeted therapy are not new, but recent developments and findings in molecular biology have changed the research as well as healthcare fundamentally. Due to more thorough knowledge about biological features, completely new perspectives are nowadays opened – for clinicians, for investigators, and, eventually, for the patients.

Solid tumours are initiated by specific genomic alterations, each with unique features, driver mutations, but also with starting points for a targeted, personalized therapy. Lung cancer, until recently classified only into two substantial types, the small-cell and the non-small-cell lung cancer, is now divided into at least two dozen generally different entities, which can and should be treated differentially.

Even in patients with advanced stages of the non-small-cell lung cancer (NSCLC) with multiple metastases, longer progression-free (PFS) and overall survival (OS) rates as well as a reduction of adverse events can be obtained by the treatment with new drugs following molecular genetic diagnostics. Under the actual development, molecular genetic diagnostics is an attempt for a causal therapy. The treatment of patients with advanced NSCLC, however, still remains a palliative one.

Lung cancer patients have a poor prognosis. According to the most recent publication on "Cancer in Germany 2016", edited by the Robert-Koch Institute and the Society of Epidemiological Cancer Registers in Germany in November 2016, lung cancer is the most frequent cancer-induced cause of death in males, the third frequent in females [1].

From the about 53,500 patients, diseased in Germany in 2013, about 34,500 are males; about 44,800 died, 29,700 males and 15,100 females. The relative 5-year-survival rate, thus, is only 16 % for males, 21 % for females. In males as well as in females, the proportion of adenocarcinomas appears to be increasing, when the subtypes are differentiated.

NSCLC is the most prevalent type of lung cancer and accounts for around 85 % of the patients. About 60% are diagnosed in stage IV [2]. Beyond other factors, like general condition, comorbidity, and patient preferences, the selection of the drugs to be administered is determined by the histological classification of the tumour, immunophenotyping, molecular pathologic alterations, and the degree of PD-L1 expression of the tumour cells. For the palliative treatment of NSCLC, a platinum-based chemotherapy was the former standard in first-line treatment, mostly in combination with one of the following drugs: Pemetrexed, Vinorelbine, Paclitaxel, Nab-Paclitaxel, Docetaxel, Gemcitabine, Etoposide.

Even by these highly effective, empirically selected cytotoxic chemotherapy regimens, the life expectancy of most NSCLC patients is unsatisfying. In recent years, two classes of drugs were developed, the TKIs effective in distinct mutations by interrupting the signal ways of the cancer cells, and the immune checkpoint inhibitors, which are able to summon the endogenous immune system in the fight against the cancer.

Although driver mutations are known in the majority of patients with NSCLC, only a small proportion of patients have mutations, which can be treated with tailored TKIs. Of the NSCLC, about 10-15 % are EGFR positive, about
2.5 % show the ALK-translocation and 1-2 % ROS1-rearrangement. In Asian populations, however, up to 55 % of the NSCLC are EGFR-positive. Patients with these genetic aberrations show a better prognosis than patients without when treated with targeted drugs. The median prognosis can be improved from 8-10 months to up to >30 months. The efficacy of the treatment can be predicted by molecular pathologic tests. For this personalized therapy, the most relevant biomarkers should be screened for each patient with non-squamous NSCLC and non-smokers with squamous carcinoma prior to the start of first-line treatment (table 1).

### Predictive molecular markers for a stratified NSCLC treatment

<table>
<thead>
<tr>
<th>Molecular Marker</th>
<th>Description</th>
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<tbody>
<tr>
<td>EGFR-Mutation</td>
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<tr>
<td>EGFR: epidermal growth factor receptor</td>
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<tr>
<td>EML4-ALK-Translocation</td>
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<tr>
<td>EML4: echinoderm microtubule-associated protein-like 4</td>
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<td>ALK: anaplastic lymphoma kinase</td>
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<td>ROS1: c-ros oncogene 1 receptor tyrosine kinase</td>
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<tr>
<td>KIF5B: kinesin family member 5B gene</td>
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The knowledge of the therapeutic options enables an optimal patient management. In Germany, the treatment to be applied, is individually discussed in a local Tumour Board either in an academic center or in the community for every patient according to the actual guidelines and the patients’ personal data.

Sex appears to be an independent prognostic factor, whereas smoking status, age, and histology appear to have no influence.

#### EGFR-Mutations

In patients with activating EGFR-mutations (membrane- standing receptor protein kinase), the TKI erlotinib, gefitinib or afatinib show remission rates of 50-75 %, PFS of 9-13 months, and a median OS of 30-36 months (in comparison to 10 months under chemotherapy) [3]. Afatinib is a second-generation TKI, which irreversibly inhibits signalling of EGFR, HER2 and HER4, whereas the first-generation TKI erlotinib and gefitinib reversibly inhibit EGFR. Under afatinib, patients with del19 show a significantly better OS and 27 % less progress in comparison to gefitinib. Even after two years, 18% are progression free (in the gefitinibarm only 8 %) [4].Dacomitinib, a further powerful second-generation EGFR-inhibitor, is still an investigational agent, not approved by any regulatory agency at this time. Dacomitinib seems to be a more effective new option in the treatment of EGFR-positive NSCLC, but at a cost of greater toxicity [5].

Specific resistance mutations may occur, especially the T790M-mutation. If this mutation is proved by biopsy, a treatment with the third-generation inhibitor osimertinib is recommended: the remission rate of TKI-pretreated patients amounts to 65-70 %, the PFS to 9-11 months [6]. Due to its potential for blood-brain barrier penetration, osimertinib is also highly effective in relapsed patients with CNS metastases developing in up to 40 % of patients, with a response rate of 70 % [7].

In patients with this mutation and progressive disease after prior TKI, rociletinib appears also to be effective with ORR of 60 % and median PFS of 8-10.3 months [8].

#### ALK- or ROS1 Translocations

NSCLC patients with activating ALK-translocation or ROS1-rearrangement show remission rates of 60-80 %, a PFS of 9-11 months (18 months in ROS1+) and OS of 30-36 months when treated with the TKI crizotinib. Together with an improvement of the quality of life and less side effects, however, these results are significantly better than chemotherapy with platinum and pemetrexed. Various treatment-related adverse events may occur. Thus, crizotinib has hitherto been regarded as the treatment of choice in first-line therapy [9]. In the second-line treatment of ALK-positive patients, ceritinib and alectinib show response rates of 44-65 %, PFS of 6-15 months, and intracranial activity against CNS metastases [10]. In a recently reported trial comparing alectinib with crizotinib in first-line treatment of ALK-positive NSCLC, alectinib showed highly significant longer PFS (25.7 months) and delay of CNS progression. Alectinib, thus, appears to be the new standard of care, although OS and the handling of relapses still is open [11]. A pemetrexed-containing chemotherapy is recommended in patients after failure of an ALK-inhibitor or ROS1-positive patients after failure of crizotinib.

#### Immunotherapy by Immune Checkpoint Inhibitors

The immune checkpoint inhibitors are a new class of substances utilizing the natural ability of the patient’s own immune system for the fight against cancer.

The principle of the checkpoint inhibitors is [12, 13, 14, 15]: Inhibitory molecules are blocked by monoclonal antibodies. The body’s own immune system is able to block the overreaction of activated T cells. This occurs by activation of the programmed cell death (PD-1) receptor. This natural blockade inhibits an effective reaction of the immune system against malignant cells. Nivolumab and pembrolizumab are monoclonal anti-PD-1 antibodies directed against PD-1. They bind to the PD-1 receptor, found on T cells, block the interaction with the PD-1 ligands PD-L1 and PD-L2, reactivate the activity of the T cells, and intensify the body’s own immune reaction. They show anti-tumour activity in melanoma [16, 17, 18, 19, 20], NSCLC [22, 23, 24, 25], renal cell [27, 28, 29], head and neck [30], and bladder cancers [31, 32, 33, 34], as well as in Hodgkin lymphoma [35, 36], among others. In tumours with high mutational load, expressing programmed death ligand 1 (PD-L1), nivolumab and pembrolizumab show increased activity [24, 25, 37]. Beyond the CTLA-4...
The immune checkpoint inhibitors have changed the therapeutic action in at least a fraction of patients. About 25-30% of the patients show a high level of programmed cell death ligand 1 (PD-L1) expression defined as membraneous deathligand 1 (PD-L1). Most immune-mediated events were of grade 1 or 2, but up to 10% of grade 3 or 4 [23]. Even lethal events due to toxicity were reported [22].

**Non-squamous Carcinomas without Activating EGFR-, ALK- or ROS1-Aberrations**

The immune checkpoint inhibitors have changed the therapeutic action in at least a fraction of patients. About 25-30% of the patients show a high level of programmed cell death ligand 1 (PD-L1) expression defined as membraneous PD-L1 expression on at least 50% of tumour cells [23]. In previously untreated patients without activating EGFR, ALK- or ROS1-aberrations, pembrolizumab lead to a significantly longer PFS (+6 months), longer OS and fewer adverse events than platinum-containing chemotherapy [23]. For those patients, for whom pembrolizumab is not as effective as cytotoxic chemotherapy, combinations with chemotherapy or other immunotherapies might be needed [22]. Whether previously untreated patients with a tumour proportion score between 1 and 50% will also have benefit of pembrolizumab over chemotherapy, is examined in ongoing phase 3 studies.

Platinum-based chemotherapy is still the standard of care for all other patients. The selection of the drugs is mainly determined by their toxicity profile and by the patients’ preferences. The combination with the angiogenesis inhibitor bevacizumab, a recombinant humanized monoclonal antibody inhibiting vascular growth factor A (VEGF-A), proceeds with an enhancement of the remission rate and a prolongation of PFS [39, 40, 41].

After progress, the combination of docetaxel with the TKI and angiokinase inhibitor nintedanib or with the monoclonal antibodyramucirumab improves OS.

In comparison with docetaxel monotherapy, nivolumab and pembrolizumab lead to an improvement of survival and a higher remission rate in immune checkpoint inhibitor-naive patients with a PD-L1 expression of ≥1% [22, 24].

**Squamous Carcinomas without Activating EGFR-, ALK- or ROS1-Aberrations**

For untreated patients with squamous carcinoma and without activating EGFR-, ALK- or ROS1-aberrations, platinum-based chemotherapy is indicated. Patients with a tumour proportion score of at least 50% may benefit from pembrolizumab [23]. Bevacizumab and pemetrexed are not approved and not indicated in squamous carcinoma.

In previously treated recurrent patients with squamous carcinoma, nivolumab is the standard of care. In contrast to non-squamous carcinomas, PD-L1 expression in tumour tissue is not a predictive marker. Nivolumab leads to a significantly better PFS, OS, remission rate and tolerability than docetaxel monotherapy [25]. In PD-L1 expression tumours, pembrolizumab is also effective [22].

Atezolizumab, the humanized monoclonal antibody of IgG1 isotype against the protein programmed cell death-ligand1 (PD-L1), is approved only in USA by the Food and Drug Administration for previously treated NSCLC, regardless of their PD-L1 status and histology. In a phase III trial, a prolongation of OS of 4.2 months was shown for previously treated squamous or non-squamous NSCLC patients versus docetaxel regardless of PD-L1 expression [26].

The drugs approved in Germany for the first-line treatment of advanced NSCLC are summarized in an algorithm published in onkopedia-guidelines, edited by the German Society of Haematology and Medical Oncology on April 11, 2017 [42]. Most recently, an update of the 2015 ASCO guideline on systemic therapy for patients with advanced NSCLC has been published [43].

**Combination Therapies**

Due to the huge growth in knowledge at present, it does not take much of an imagination to realize that seemingly innumerable biomarker therapy combinations lay ahead in the near future. At the ASCO Annual Meeting 2017,
for example, more than 250 contributions involving checkpoint inhibitors, were presented, more than 1,000 studies are underway [44]. Combination trials and optimal sequencing are a challenge for optimizing the use of TKIs and checkpoint inhibitors. In a Japanese trial, for instance, the combination of the TKI erlotinib with the monoclonal VEGF-antibody bevacizumab extends median PFS 6 months (16.0 months versus 9.7 months) with comparable quality of life in EGFR-mutation-positive patients with advanced non-squamous NSCLC [45]. It has now to be proved, whether rational combinations of TKIs or immune checkpoint inhibitors with cytotoxic therapies or with angiogenesis inhibitors are superior to monotherapies with regard to the antitumor immune response, but also to the side effects and the tolerability.

In order not to financially overtax the health system, the financial viability of these medically necessary, cost-intensive drugs appears only to be possible by cooperation and concerted actions. Networking of all involved groups, healthcare providers and payers, is, for instance, proposed by the German Cancer Society in the complex recently published position paper «Knowledge Generating Oncological Care» [46].

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ВЗАИМОДЕЙСТВИЯ: ВЛИЯНИЕ МИНОРНЫХ КОМПОНЕНТОВ МЕТАБОЛИЗМА
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Резюме. Научный обзор посвящен вопросу изучения влияния минорных компонентов на белок-лигандные взаимодействия. Практически в любом биологическом процессе, происходящем в клетке, участвуют белки, показывая неисчерпаемое разнообразие функций: регуляторная, каталитическая, транспортная, защитная и многие другие. Полифункциональность белков обусловлена их возможностью изменять конформацию молекулы при взаимодействии с лигандами. Белки могут взаимодействовать практически со всеми типами молекул – от небольших органических соединений: металлов, сахаров, жирных кислот, фосфолипидов клеточных мембран до высокомолекулярных белков и нуклеиновых кислот. В статье изложены актуальные аспекты взаимодействия в системе белок-белкового, белок-лигандного, фермент-субстратного взаимодействия, приведены примеры влияния малых молекул на белковые структуры клетки.

Ключевые слова: белок-белковые взаимодействия, белок-лигандные взаимодействия, белок-ферментные взаимодействия, минорные компоненты метаболизма, малые молекулы, лиганды, метаболом.


PROTEIN-LIGAND INTERACTIONS: THE INFLUENCE OF MINOR COMPONENTS OF METABOLISM
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Abstract. The scientific review is devoted to the study of the influence of minor components to protein-ligand interactions. Practically in any biological process occurring in the cell, proteins are involved, showing an inexhaustible variety of functions: regulatory, catalytic, transport, protective and many others. Polymorphism of proteins is due to their ability to change the conformation of the molecule when interacting with ligands. Proteins can interact with almost all types of molecules – from small organic compounds: metals, sugars, fatty acids, phospholipids of cell membranes to high molecular proteins and nucleic acids. The article contains the topical aspects of interaction in the system of protein-protein, protein-ligand, enzyme-substrate interaction, examples of the effect of small molecules on the protein structure of the cell are given.

Key words: protein-protein interactions, protein-ligand interactions, protein-enzyme interactions, minor metabolism components, small molecules, ligands, metabolite.

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Метаболические пути, в которых осуществляются взаимопревращения основных метаболитов, чрезвычайно похожи у всех живых организмов и носят название центральных [1]. Многообразие метаболических путей нашло отражение в метаболических картах, в которых собрана информация об образующихся в