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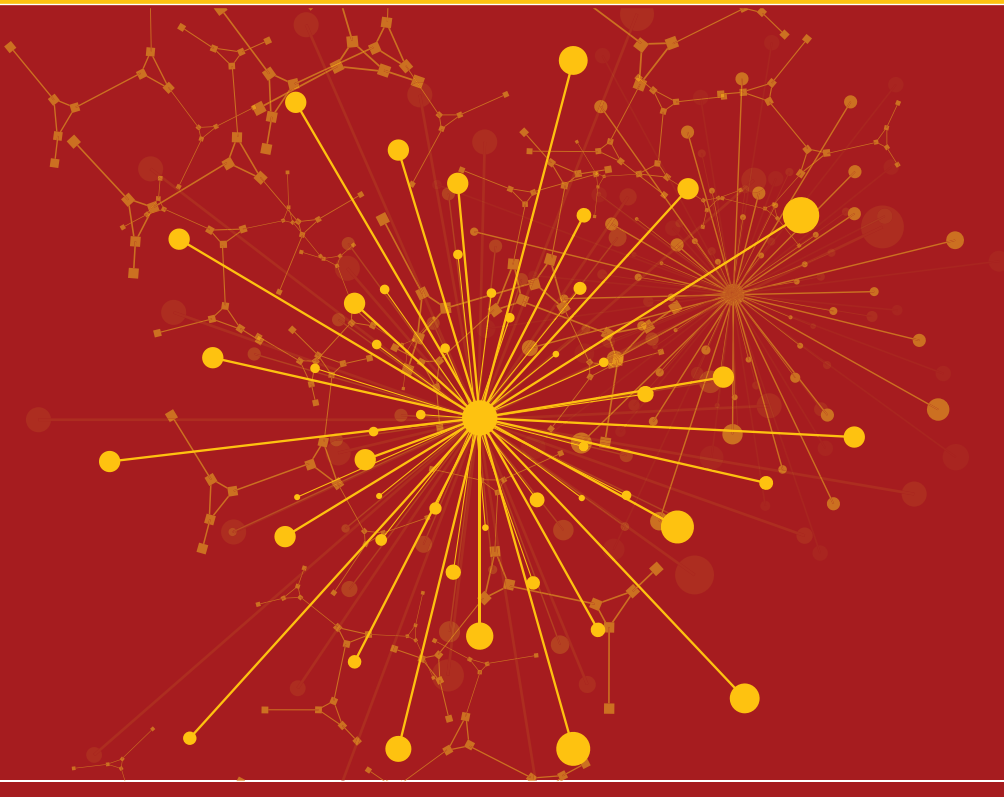
Preceptorship Cologne 2018



LUNG CANCER INTERNATIONAL PRECEPTORSHIP

Cologne, February 1–2, 2018

IMPRESSUM/PUBLISHER

Media owner and publisher: Springer-Verlag GmbH, Professional Media, Prinz-Eugen-Straße 8–10, 1040 Vienna, Austria, **Tel.:** +43(0)1/330 24 15-0, **Fax:** +43(0)1/330 24 26-260, **Internet:** www.springernature.com, www.SpringerMedizin.at. **Copyright:** © 2018 Springer-Verlag GmbH Austria. Springer Medizin is a Part of Springer Nature. **Managing Directors:** Joachim Krieger, Dr. Alois Sillaber, Dr. Heinrich Weinheimer. **Medical Writer:** Josef Gulden. **Proof Reading:** Stefanie Wurm. **Corporate Publishing:** Elise Haidenthaller. **Layout:** Katharina Bruckner. **Published and produced in:** Vienna. **Printer:** digitale druckwerkstatt, 1160 Vienna;
The editors of "memo, magazine of european medical oncology" assume no responsibility for this supplement.

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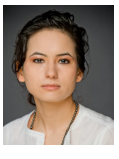

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Preface

Dear Colleagues,

This report summarizes presentations that were given during the Lung Cancer International Preceptorship Conference that took place in Cologne, Germany, on February 1 and 2, 2018. The University Hospital of Cologne and the Center for Integrated Oncology Köln-Bonn jointly organized this conference, which was addressed to medical oncologists involved in the care of patients with lung cancer. This was not just an interdisciplinary exchange of experience of specialists from different Departments of the University Hospital and the Lung Cancer Group of Cologne through lectures and discussions on scientific and clinical topics, as the participants also had the opportunity to gain some practical insight during guided tours through the Molecular Pathology Unit, the Cyberknife Department and the Interdisciplinary Outpatient Clinic. In addition, in parallel, workshop participants could learn how to design trials on topics like EGFR TKI resistance, immunotherapy, brain metastases, and neoadjuvant therapy.

The lectures were organized in different sections with a strong focus on diagnostics and treatment of the different stages of non–small-cell lung cancer (NSCLC). Molecular pathology was a particularly important topic across almost all aspects of the program. In recent years, a multitude of studies has provided us with a range of innovative therapies, the application of which demands algorithms that support physicians in the shaping of their treatment decisions. Molecular pathology therefore has developed into a kind of gatekeeper in this process of designing therapeutic strategies for these patients. We hope that this summary of the Preceptorship will provide physicians with better understanding of the challenges linked to the care of patients with lung cancer.

Jürgen Wolf, MD,
University Hospital of Cologne

Challenges and State of the Art: The early stage patient

Surgery: How aggressive should it be?

Surgical treatment of patients with early lung cancer is often a challenging task that requires robust preoperative risk assessment as a first step. Wherever possible, pneumonectomy should be avoided, in an attempt to maximally preserve functional capacity, as Khosro Hekmat, MD, Department of Cardiothoracic Surgery, University Hospital of Cologne, emphasized. To decide whether surgery is possible at all, and how radical it might need to be, not only the tumor stage needs to be considered, but also the preoperative risk assessment, which includes clinical factors, spirometry, gas exchange parameters, exercise testing, and radionuclide studies to differentially examine each lung. For many stage IIIA cancers and nearly all stage IIIB cancers, the tumor might be difficult, and sometimes impossible, to remove. In such cases, the thoracic surgeon can recommend chemotherapy combined with radiotherapy prior to further considering surgery.

The complex anatomy of the bronchial tree and its intimate connection with neighboring tissues, and especially the pulmonary vessels, require the use of intricate surgical resection techniques, which include bronchial sleeve resections and vascular sleeve resections. Bronchial sleeve resection includes resection of infested bronchial sections, together with the contaminated parts of the parenchyma, and the subsequent anastomosis of the remaining bronchial segments [1]. Where large pulmonary vessels are also affected, a more complicated procedure can be applied, known as vascular sleeve resection. Here, small affected parts of the vascular wall are removed and grafted with patches of tissue. Where large areas are affected, the respective part of the artery can be removed, and the remaining ends rejoined surgically, or the gap can be replaced using an extravascular graft [2].

Oligometastatic lung cancer is defined as the synchronous presentation of a primary lung tumor and a distant site of extrapulmonary metastasis. This represents stage IV according to the International Union for Cancer Control (UICC) classification, but in selected cases, it can be amenable to surgical treatment with curative intention. According to the TNM staging system, UICC stage IV is subdivided as follows: Stage M1a is defined by – in addition to

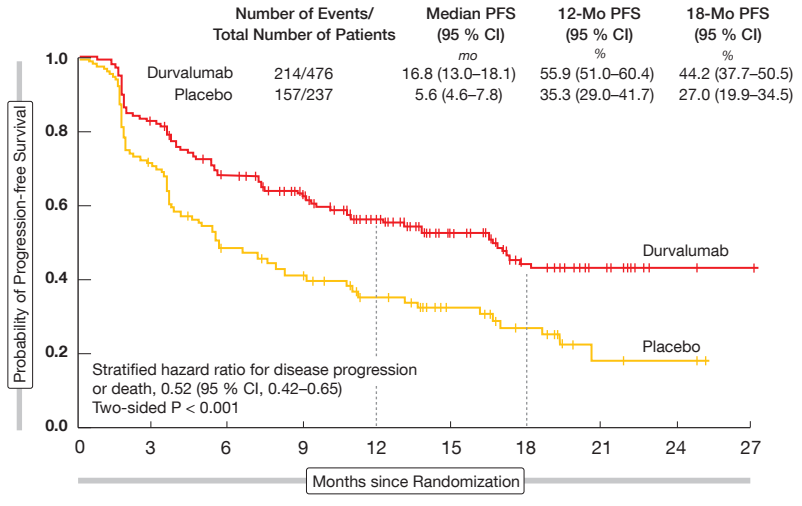

Figure 1: The PACIFIC trial. There was a tripling of progression-free survival by durvalumab *versus* placebo in patients with stage III NSCLC. Modified from [6].

the primary tumor – the presence of a separate tumor in a contralateral lobe, or pleural or pericardial nodules, or malignant pleural or pericardial effusion. In stage M1b, a single extrathoracic metastasis is present, and in stage M1c, the patient has multiple extrathoracic metastases in one or more organs. About one third of oligometastases are located in the brain or lungs. Prognosis is strongly dependent on intrathoracic *versus* extrathoracic localization of the oligometastases. In a literature review, patients with intrathoracic disease (stage IVA) showed median survival of 11.5 months, and 2-year and 5-year survival rates of 23 % and 10 %, respectively, whereas for patients with extrathoracic disease (stage IVB) these were 6.0 months, 10 %, and 0 %, respectively [3].

Adjuvant chemotherapy: how to balance benefit and toxicity

In patients with solid tumors, surgical removal of the primary malignancy is essential, although this might not be sufficient for cure. A malignant tumor has to contain about 10^8 cancer cells to be detectable by computed tomography (CT), and 10^9 cells to be clinically palpable; therefore, even the most radical operation does not guarantee freedom from small (micro-)metastases, especially in locally advanced stages. Real-world data suggest that even in stage I NSCLC, 5-year survival rates are only about 35 %, and for all patients with NSCLC together, this becomes only about 10 %.

Therefore, there clearly is a rationale for adjuvant treatment of patients with lung cancer after surgical resection, and several trials have been conducted to this end. Ten years ago, a meta-analysis of five large trials with more than 4,500 patients with stage I–III NSCLC already showed significant improvement in overall survival (OS) with postoperative cisplatin-based chemotherapy, as Matthias Scheffler, MD, Department of Internal Medicine I, University Hospital of Cologne, stated [4]. After a median follow-up of 5.2 years, the hazard ratio (HR) for death was 0.89 in favor of adjuvant chemotherapy, with a 5-year absolute survival benefit of 5.4 %. This benefit was independent of type of chemotherapy (which always included cisplatin), although it appeared not to apply to patients with stage IA disease and those with an Eastern Cooperative Oncology Group (ECOG) performance status of 2. Otherwise, parameters like sex, age, histology, type of surgery, planned radiotherapy, and planned total dose of cisplatin did not influence the results. Postoperative cisplatin-based chemotherapy therefore significantly improves survival in patients with NSCLC.

A more recent Cochrane meta-analysis of 47 trials with more than 11,000 patients also demonstrated clear benefit of adjuvant chemotherapy for these patients, irrespective of whether chemotherapy was given in addition to surgery alone (HR, 0.86; 95 % confidence interval [CI], 0.81–0.92; $p < 0.0001$) or to surgery plus radiotherapy (HR, 0.88; 95 % CI, 0.81–0.97; $p = 0.009$) [5]. For both situations (i.e., adjuvant chemotherapy after surgery alone or after surgery plus radiotherapy), there were similar benefits for recurrence outcomes, and the benefits were largely independent of the type of chemotherapy or other characteristics. The effects of adjuvant chemotherapy on quality of life and adverse events were not investigated in this meta-analysis, because quality of life information had not routinely been collected during all of the trials included. As far as toxicity was assessed and mentioned in these publications, it was thought to be manageable.

Novel combinations with chemotherapy

The future of chemotherapy of early stage NSCLC, as Scheffler mentioned, will be mainly characterized by the use of more individualized approaches. A glimpse of this future can already be gained from the results of the phase III PACIFIC trial, in which treatment of patients with stage III disease with the anti-PD-L1 antibody durvalumab for 2 years after chemoradiotherapy achieved a tripling of median progression-free survival (PFS), from 5.6 to 16.8 months (HR, 0.52; 95 % CI, 0.42–0.65; $p < 0.001$) (**Fig. 1**; [6]). This effect was similar for all of the subgroups investigated. ■

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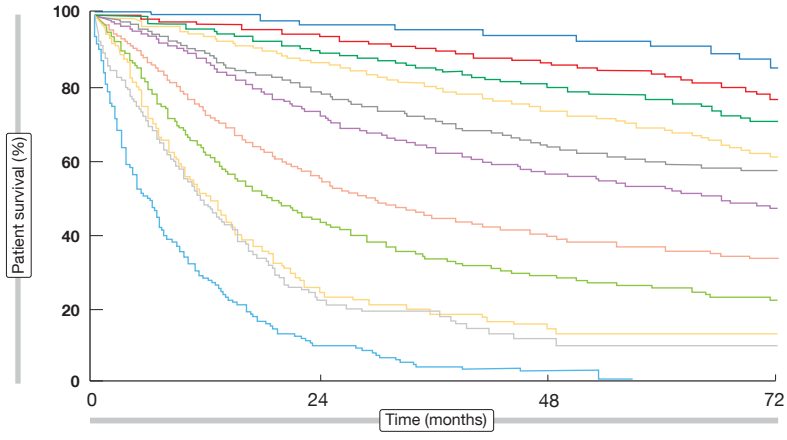
Challenges and State of the Art: The intermediate stage patient

Staging: How to precisely determine mediastinal lymph node involvement

A key determinant for which type of treatment can be offered to patients with NSCLC is their intrathoracic (mediastinal) nodal status. If the disease has not spread to the ipsilateral mediastinal nodes, subcarinal (N2) nodes, or both, and the patient is otherwise considered fit for surgery (i.e., 'functional resectability'), resection is often the treatment of choice. The planning of treatment therefore critically depends on accurate staging of the disease. Positron-emission tomography–computed tomography (PET-CT) is increasingly available and used by lung cancer multidisciplinary teams for staging the mediastinum. The non-invasive nature of PET-CT defines one of its major advantages; however, it might be suboptimal for the detection of malignancy in normal-sized lymph nodes, as well as to rule out malignancy in patients with coexisting inflammatory or infectious diseases.

The definition of stage III disease changed with the introduction of the 8th TNM classification. For example, further subdivision of stages III and IV has resulted in two stages (i.e., IIIC, IVA), as Markus Dietlein, MD, Department of Nuclear Medicine, University Hospital of Cologne, pointed out: Stage IIIC includes patients with T3 or T4 tumors and N3 nodal status, but M0, whereas in stage IVA, patients with M1a and M1b are grouped, irrespective of their T and N stages. Survival curves of patients with stages IIIC and IVA overlap, while the prognosis for patients with stages IIIA and IIIB is significantly better (**Fig. 2**; [1]). Determination of the nodal status (N0–3) is therefore of the utmost importance regarding the prognosis of a patient, as survival differs significantly between all neighboring categories (**Fig. 3**; [2]).

Detection of mediastinal lymph-node metastasis is a prerequisite for accurate staging of stage III NSCLC, which is in turn required for individualized, stage-adapted therapy. There is currently no single modality for accurate



Proposed classification	Events recorded (n/N)	MST (months)	Overall survival (%) 24 months	60 months
IA1	68/781	NR	97	92
IA2	505/3105	NR	94	83
IA3	546/2417	NR	90	77
IB	560/1928	NR	87	68
IIA	215/585	NR	79	60
IIB	605/1453	66.0	72	53
IIIA	2052/3200	29.3	55	36
IIIB	1551/2140	19.0	44	26
IIIC	831/986	12.0	24	13
IVA	336/484	11.5	23	10
IVB	328/398	6.0	10	0

Figure 2: Overall survival of patients with NSCLC by clinical stage according to the 8th edition of the TNM classification. Mod. according to [1]. MST, median survival time in months. Survival is weighted by type of database submission: registry versus other.

characterization of enlarged mediastinal lymph nodes as benign or malignant. In addition to ^{18}F-fluorodeoxyglucose (^{18}F-FDG), the radioactively labeled nucleoside ^{18}F-fluorothymidine (^{18}F-FLT) has recently been introduced as a tracer in PET, as it represents a proliferation marker in contrast to the metabolic nature of ^{18}F-FDG. In a prospective study, both techniques were investigated in parallel in 70 consecutive patients with mediastinal lymphadenopathy detected on CT or chest radiographs [3]. Nodal uptake of the respective tracers was determined by calculation of the maximum standardized uptake (SUV_{max}) with each of the tracers. The results of PET-CT were compared with histopathology of the lymph nodes.

In nine patients with NSCLC, the ^{18}F-FDG SUV_{max} and ^{18}F-FLT SUV_{max} of the lymph nodes with pathologically detected tumor infiltrations were 6.7 and 3.9, respectively, while in those without nodal infiltration, these were 6.4 and 3.7, respectively. Either of the tracers alone did not therefore characterize the nodal status as malignant or benign ($p > 0.05$), but the ^{18}F-FDG tracer appeared to be taken up more avidly by suspicious lesions. These results suggest that reliable determination of the state of the mediastinal nodes is not possible based on SUV_{max} values alone.

In a retrospective series that compared PET-CT and pathological results at surgery for 200 N2 lymph nodes in 64 patients with NSCLC, logistic regression demonstrated significant linear association between PET-CT sensitivity and time from scanning to surgery ($p = 0.031$), but not for the specificity. In

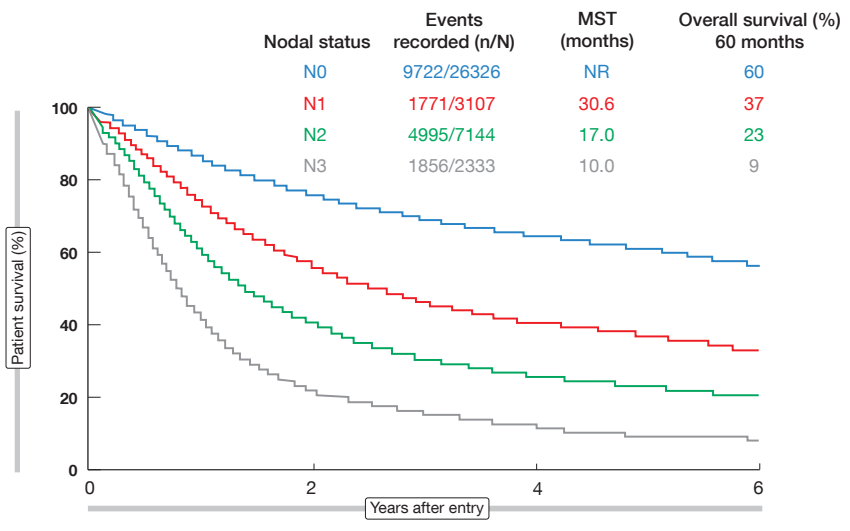


Figure 3: Overall survival of patients with NSCLC by nodal status according to the 8th edition of the TNM classification. Modified from [2]. MST, median survival time in months.

patients scanned < 9 weeks prior to pathological sampling, PET was significantly more sensitive (64 % at < 9 weeks, 0 % at ≥ 9 weeks, p = 0.013) and more accurate (94 % at < 9 weeks, 81 % at ≥ 9 weeks, p = 0.007). No differences in specificity were seen. Thus, the authors recommended that if a PET-CT scan was taken more than 9 weeks previously, and the detection of N2 nodes would alter management decisions, re-staging of the mediastinum is advisable [4].

In a cohort study that included 938 patients with NSCLC staged as T1/T2 by CT and N0/N1 by PET, a model was developed to predict the risk of N2 lymph nodes. Among six risk variables, only N1 stage detected by PET was significantly associated with higher probability of pathological N2 stage (p < 0.001) in the multivariate analysis. While the potential impact of prediction models like this one on outcome remains unclear, further development and validation of similar models might enable physicians to reduce the frequency of invasive staging procedures, and thereby the associated risk and cost for lung cancer patients with low probability of pN2 disease [5].

To test the suggestion that endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is not necessary when mediastinal lymph nodes are PET-CT negative, an analysis was performed on 167 patients with N0 (n = 115) and N1 (n = 52) lung cancer and no involvement of the mediastinum at PET-CT. The probability of clinically relevant up-staging by EBUS-TBNA in patients judged as N0 and N1 according to PET-CT was 6.0 % overall; however, this was only 0.9 % in patients originally classified as N0 by PET-CT, but 17.3 % in patients originally classified as N1 by PET-CT. The risk of overlooking N2 or N3 disease after both PET-CT and EBUS-TBNA was 10.4 % [6].

To explore predictors for false-negative N2 diagnosis in PET-CT, the data of clinically (PET-CT) N0 patients who had subsequently been operated on were analyzed retrospectively. In a training set of 284 patients, the false-negative rate was 8.5 %, with these tumors appearing predominantly in subcarinal and right lower paratracheal lymph nodes. A higher SUV_{max} of the primary tumor was a unique independent risk factor for occult N2 NSCLC (odds ratio, 0.88; 95 % CI, 0.81–0.96; p = 0.003). A cut-off threshold of 2.6 for SUV_{max} discriminated patients into low risk and high risk for occult N2 nodes (1.0 % vs. 12.5 %; p = 0.001). This correlation was confirmed in a test set of 151 patients (9.3 % with N2 overall, 4 % with low, and 11.9 % with high SUV_{max}). Thus, in patients with SUV_{max} of the primary tumor ≥ 2.6, there is a level of risk of N2 disease that should not be ignored. These patients might be candidates for mediastinoscopy [7].

A multicenter study investigated ^{18}F-FDG-PET predictors of mediastinal malignancy that could minimize inter-center variability and improve the selection of the subsequent staging procedures. Here, 121 NSCLC patients were staged by ^{18}F-FDG-PET and EBUS-NA, and they subsequently underwent therapeutic surgery with systematic nodal dissection as the gold standard. Ninety-four (72 %) of these patients had ≥1 hypermetabolic spots in the mediastinum. The variability between hospitals of ^{18}F-FDG-PET measures in terms of the mean SUV_{max} of the primary tumor and the median SUV_{max} of the highest hypermetabolic spots in the mediastinum was statistically significant (p = 0.016, p < 0.001, respectively), although significance was lost when the ratio or the difference between the SUV_{max} in the mediastinum and the primary tumor were chosen as the parameters. The SUV_{max} mediastinum/tumor ratio showed high accuracy under ROC analysis (AUC, 0.77; 95 % CI, 0.68–0.85; p < 0.001), and high predictive power for mediastinal malignancy with a ratio of 0.4 as cut-off (OR, 6.62; 95 % CI, 2.98–14.69). The sensitivities and negative predictive powers obtained by clinical staging using EBUS-NA ranged between 57 % and 92 % after ^{18}F-FDG-PET, and increased with tumors > 3 cm in diameter and/or SUV_{max} mediastinum/tumor ratio > 0.4 [8].

In an approach to create a reliable method for interpretation of visible mediastinal lymph nodes from visual assessment of PET images, a standardized windowing (threshold: 2 × liver SUV_{mean}) was introduced to assess the lymph node uptake using a four-step score (1: LN uptake ≤ mediastinal blood pool structures [MBPS]; 2: MBPS < LN < liver; 3: liver ≤ LN < 'black'; 4: LN appears 'black'). When used by three independent readers with varying levels of experience, this score was reliable for identification of 54 of 278 lymph nodes as malignant when using an optimal cut-off of > 3 for defining malignancy. All three readers achieved comparable levels of accuracy with no differences between subgroups of patients (e.g., hilar vs. mediastinal lymph nodes, adenocarcinoma vs. squamous cell carcinoma, grading G1/2 vs. G3/4). Thus, by applying unified windowing, highly accurate and robust lymph node assessment is achievable through introduction of this score [9].

In a Cochrane analysis of 45 trials that assessed the diagnostic accuracy of integrated PET-CT for diagnosing N2 disease in patients with suspected resectable NSCLC and used pathology as

the reference standard, the authors come to the conclusion that the accuracy of PET-CT is not sufficient as the sole source of guidance for management of these patients. They recommended adherence to National Institute for Health and Care Excellence (NICE) guidance on this topic, where PET-CT is used to guide clinicians to the next step, as either a biopsy, or where nodes are negative and small, directly to surgery. An apparent difference in PET-CT accuracy estimates between scanner types, NSCLC subtypes, ^{18}F-FDG dose, and country of origin of study, along with the general variability of the results, suggested that large centers should actively monitor their accuracy [10].

In another meta-analysis that included eight studies with 654 patients, the diagnostic performance of dual-time-point PET-CT was compared with single-time-point imaging for the detection of mediastinal nodal metastases in patients with NSCLC. Dual-time-point PET-CT performed a little better than single-time-point imaging. Due to the small sample size and large heterogeneity, however, current evidence does not justify implementation of dual-time-point imaging in routine PET protocols for mediastinal lymph node staging of NSCLC [11].

Many patients with NSCLC have positive mediastinal lymph nodes on preoperative PET, but do not have mediastinal involvement after surgery. The prognostic significance of this discordance was assessed in a study of 547 patients, of whom 105 (19 %) were PET positive in the mediastinum prior to surgery. There were no significant differences between PET-positive and PET-negative patients in terms of 5-year risk of local recurrence, patterns of local failure, risk for distant metastases, and OS. Also in multivariate analysis, a false-positive PET was not significant for local recurrence (HR, 1.00; p = 1.00), distant metastases (HR, 0.82; p = 0.42), or OS (HR, 1.08; p = 0.62). Thus, pathologic staging remains the standard to determine the N2 status of patients with NSCLC [12].

In summary, Dietlein stated that interpretation of mediastinal PET-CT cannot be improved by building the ratio of $SUV_{mediastinum}$:$SUV_{tumor,}$ by scoring of mediastinal uptake, and by dual-time-point PET acquisition. Clearly, a time from PET-CT scan to surgery of more than 9 weeks decreases the sensitivity to detect N2 stage by PET-CT.

How to integrate chemotherapy, radiotherapy and surgery

Stage III NSCLC includes a very heterogeneous group of patients with differences in localization and extent of disease. Many aspects of their treatment remain controversial, as Karolina Jablonska, MD, Department of Radiooncology, University Hospital of Cologne, pointed out – the more so, because the definition of stage III disease has changed with the introduction of the new TNM classification. For example, differences in terms of survival between the newly defined stages IIIC and IVA are becoming blurred (see **Fig. 2**). Clinical trials that investigate treatments in specific patient populations can often be limited by recruitment of heterogeneous patient populations, inadequate power to detect small differences in therapeutic outcome, missing randomization, or limited duration of follow-up. Up-front consultation as a multidisciplinary tumor board and determination of resectability is therefore mandatory in every case.

Treatment options for stage III NSCLC following, for instance, the European Society for Medical Oncology and the National Comprehensive Cancer Network guidelines [13, 14] usually consist of multimodal therapies that combine surgery, chemotherapy, and radiotherapy, including:

- Disease with limited extent is usually resected and treated by adjuvant chemotherapy or radiochemotherapy. For adjuvant chemotherapy, an OS benefit of 4 % to 5 % after 5 years has been shown for patients with N1 or N2 stage, as well as for those with N0 and tumor size > 4 cm [15].
- Patients with initial stage I or II and up-staged pathologically to N2 after surgery can also receive postoperative chemotherapy and radiotherapy.
- The same applies to patients where the resection cannot be performed with maximal radicality (R1/2).
- Patients with extensive disease can receive neoadjuvant radiochemotherapy followed by surgery or preoperative chemotherapy and postoperative radiotherapy. The optimal timing of these interventions has not been established and remains controversial. Although one meta-analysis showed that preoperative chemotherapy can improve outcomes in patients with stage IB–IIIA NSCLC [16], differences between preoperative and postoperative chemotherapy were confirmed in a large meta-analysis with data from more than 10,000 patients [17].
- Patients with unresectable disease (T4, N2 or N3) and who are sufficiently fit are treated with definitive concurrent chemoradiation as the preferred option. In the latter situation, based on the recently published data of the PACIFIC trial, a consolidation treatment with the PD-L1 antibody durvalumab can be recommended as soon as it is approved for this indication [18].
- A further meta-analysis investigated trials in which definitive radiochemotherapy was compared with surgery in patients with mainly stage IIIA N2 disease. In the patients treated with induction chemotherapy, there was no difference in terms of OS between surgical resection and definitive radiochemotherapy (HR, 0.92; [19]). However, in the surgical arms, there was a trend towards excess early mortality (within the first 6 months of follow-up) and an advantage in comparison to definitive radiochemotherapy thereafter (HR, 0.78; 95 % CI, 0.63–0.98). With respect to PFS, no significant differences were found, although in the largest of the trials analyzed, there was an advantage for the surgical arm (HR, 0.77; 95 % CI, 0.62–0.96). The authors of the meta-analysis concluded by saying: "Currently, based on the finding of a comparable outcome in survival in the randomized trials, the safer approach of radiochemotherapy remains the preferred approach in many institutions. Surgery may represent a good treatment choice within a multimodality treatment program for patients in good condition and up-front potentially resectable tumors provided that patients will be treated by an expert team incorporating all disciplines of thoracic oncology, en-

suring a high level of expertise."

- Finally, frail patients who are not resectable and who cannot tolerate aggressive definitive treatment can receive sequential chemotherapy and radiotherapy, or radiotherapy alone. ■

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Challenges and State of the Art: The advanced stage patient

With 2-year OS of < 15 %, the prognosis of patients with advanced lung cancer has been invariably poor for decades, irrespective of the chemotherapy that was combined with platinum compounds, as Jürgen Wolf, MD, Department of Internal Medicine I, University Hospital of Cologne, remarked (e. g. [1]). Consequently, as Scheffler pointed out, in recent years there has been a dramatic decline in published trials using chemotherapy alone, and in contrast, a steep rise in the numbers of trials with targeted and immune therapies. This is also reflected in the current recommendations proposed by Wolf for systemic therapy of patients in advanced stages of NSCLC (**Fig. 4**).

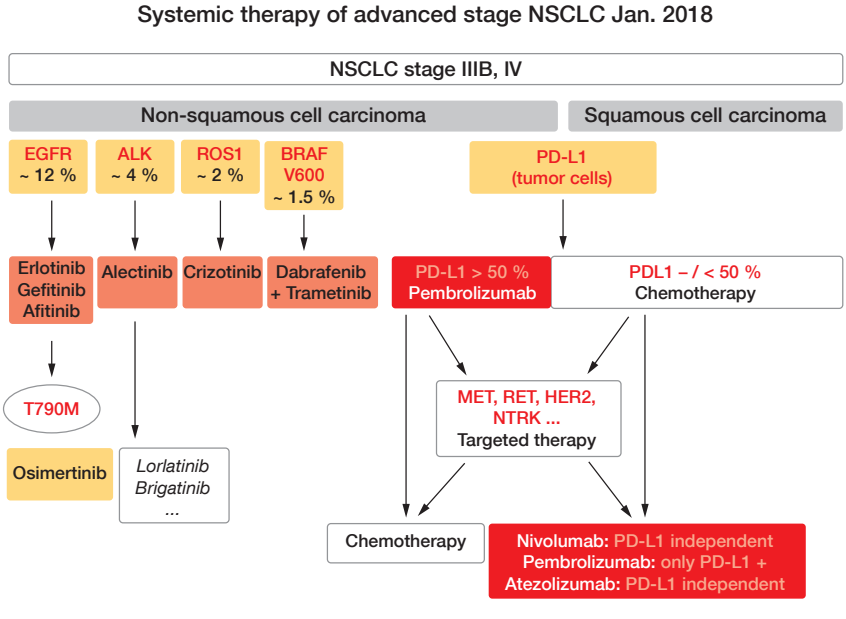

Figure 4: Systemic therapy of advanced stage NSCLC as of January 2018. Courtesy of J. Wolf.

Targeted therapies: Tyrosine kinase inhibitors

When targeted therapies were first tried for NSCLC they showed only marginal activities in unselected patients and for advanced stages. The first real breakthrough in systemic therapy was promoted by the identification of driver mutations in certain genes; e. g. the

genes for epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), *ROS1*, and *BRAF*, among others. The detection of these mutations allowed the selection of patients whose tumors were sensitive to the specific tyrosine kinase inhibitors (TKIs) of the mutated proteins. With this type of directed, or personalized, therapy, rapid progress has been made possible over the last few years [2].

At present, three EGFR TKIs are approved in the European Union for first-line therapy of *EGFR*-mutant NSCLC: gefitinib, erlotinib, and the second-generation afatinib. These have all proven to be superior to chemotherapy in terms of responses and PFS. However, as Richard Riedel, MD, Department of Internal Medicine I, University Hospital of Cologne, pointed out, development of resistance to these drugs is almost inevitable. While in cases of limited progression (e. g., in the CNS, or in single extra-CNS sites) continuation of the first-line drug might be an option, probably in conjunction with local therapeutic approaches, systemic progression in multiple sites invariably calls for a change in systemic therapy. To decide on the follow-up therapy, investigation of the mechanism of resistance is obligatory.

In more than half of the cases, resistance against first-line *EGFR* inhibitors is caused by the T790M mutation of the *EGFR* gene. Tumors with this mutation can be successfully treated with the third-generation TKI osimertinib: in the phase III AURA 3 trial, osimertinib more than doubled PFS in these patients, compared to platinum-pemetrexed chemotherapy (median PFS, 10.2 vs. 4.4 months; HR, 0.30; $p < 0.001$; [3]). Furthermore, in the first-line phase III FLAURA trial, osimertinib was superior to standard of care in unselected patients with newly diagnosed, advanced, *EGFR*-mutated NSCLC (median PFS, 18.9 vs. 10.2 months; HR, 0.46; $p < 0.0001$; [4]). Approval of osimertinib for this indication is currently pending.

In about 10 % of cases, resistance against first- or second-generation TKIs is associated with c*MET* amplification. In these patients, combinations of first- or third-generation TKIs with new agents, like savolitinib, appear to be beneficial in terms of responses [5, 6]; however, at the moment, none of these new agents have been approved.

For patients with NSCLC and *ALK* translocations, the second-generation *ALK* inhibitor alectinib has been approved for first-line therapy on the basis of phase III data that showed its superiority over crizotinib, with PFS of about 26 months. When progressing, these tumors must be re-biopsied to identify the mechanism of resistance, which determines the further lines of treatment.

Immunotherapy

A second paradigm shift in the treatment of advanced NSCLC was made possible some years ago by the deepening of our understanding of how immune tolerance of T-lymphocytes against cancer cells is mediated. Immune checkpoint inhibitors such as anti-PD/PD-L1 or anti-CTLA-4 monoclonal antibodies can unleash an antitumor immune response by interfering in the T-cell priming and effector phases. By introducing this new type of immunotherapy, a new avenue of cancer therapy has been opened up for a wide variety of cancers, including lung cancer, as Diana S.Y. Abdulla, MD, Department of Internal Medicine I, University Hospital of Cologne, explained.

At present, there are data from a series of phase III trials that show superior OS with PD-1/PD-L1 immune checkpoint inhibition *versus* chemotherapy in patients with pretreated NSCLC, irrespective of the histological subtype (i.e., squamous or non-squamous NSCLC). The corresponding studies are CheckMate-017/-057 (nivolumab; [7]), KEYNOTE-010 (pembrolizumab; [8]) and the OAK trial (atezolizumab; [9]).

For first-line therapy, only one checkpoint inhibitor is available at present: pembrolizumab has been approved for patients with newly diagnosed stage IV NSCLC with PD-L1 expression of ≥ 50 % (given as the tumor proportion score), which was on the basis of the results of the KEYNOTE-024 trial [10]. In this phase III trial, pembrolizumab resulted in significant pro-

Management of immune-related adverse events

The advent of checkpoint inhibitor therapy in oncology has been accompanied by the occurrence of new types of adverse events that are triggered specifically by this type of drug, as Abdulla mentioned. Immune-related adverse events following treatments with checkpoint inhibitors can affect virtually any organ system, including the endocrine organs, gastrointestinal tract, lungs, nervous system, eyes, heart, skin, liver, and kidneys. In addition, generalized symptoms like fatigue, anorexia, or nausea have been observed. However, overall, in the randomized trials that have compared checkpoint inhibitors with chemotherapy, treatment-related adverse events and discontinuation rates have been lower with immunotherapy.

The time to onset of immune-related side effects generally depends on the organ involved, as was shown in an analysis of the CheckMate-017/-057 trial [7]. While, for example, skin or gastrointestinal symptoms occur at a median of 5 to 6 months from the onset of therapy, the median for endocrine events is around 9 months, and pulmonary side effects are generally seen later on in the treatment (median, 30 months). An analysis of the KEYNOTE-024 trial with pembrolizumab indicated that 29 % of patients have immune-related adverse events of any grade, while in 10 %, they are grade 3 or 4; grade 5 events were not seen [14].

It is of paramount importance, as Abdulla stated, that physicians who treat patients with checkpoint inhibitors are familiar with these toxicities. General treatment recommendations are available [15]. The main pillars of successful toxicity management are early recognition, careful consideration of possible differential diagnoses, close monitoring, and treatment according to severity and dynamics of the immune-related adverse events. In severe cases, multidisciplinary management with the consultation of organ-specific specialists is recommended. By far the most of immune-related adverse events are resolved, especially when patients are treated with immune-modulating drugs, as was shown in an analysis of CheckMate-017/-057 [7]. According to Abdulla, patient education is an important issue when aiming at early recognition of immune-related side effects. The identification of predictive biomarkers and the underlying predisposing factors for this type of toxicity are of current research interest, to help identify patients at risk of these side effects.

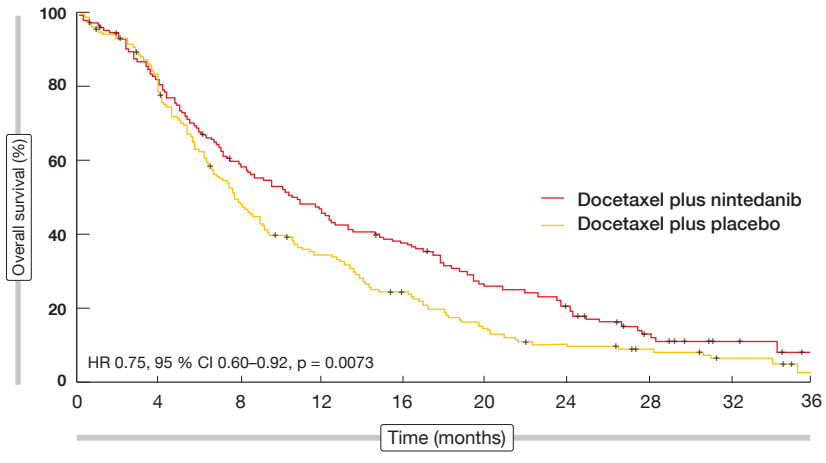

Figure 5: The LUME-Lung 1 trial. Overall survival of patients with adenocarcinoma histology and time since start of first-line therapy of less than 9 months, as docetaxel plus nintedanib *versus* docetaxel plus placebo. Modified from [10].

longation of PFS compared to platinum-based chemotherapy (median PFS, 10.3 vs. 6.0 months; HR 0.50; p < 0.001), as well as improved OS (median OS, 30.0 vs. 14.2 months; HR 0.63; p = 0.002) [11].

Thus, within a little over a decade, the therapeutic landscape of advanced NSCLC has changed dramatically by the introduction of various new drugs with distinct mechanisms of action. In 2018, targeted therapy has been approved for four driver mutations in advanced NSCLC in the first-line setting. To enable these patients to benefit from such treatments, it is indispensable for all patients with a first diagnosis of an adenocarcinoma to be tested for mutations in their *EGFR*, *ALK*, *ROS1* and *BRAF* genes. Immune checkpoint inhibitors that target PD-1 are indicated for first-line treatment when EGFR and ALK are wild-type and ≥ 50 % of the carcinoma cells express the PD-L1 protein in the histology-based test, defining their 'PD-L1 immunohistochemistry' (IHC). Thus, both sequencing and IHC are necessary to guide treatment decisions here. In the second-line setting, checkpoint inhibitors can be used independent of the PD-L1 and mutational status.

In cases of relapse after TKI therapy, identification of the resistance mutations is essential to define the treatment with the next generation inhibitors, to overcome the mechanism(s) of resistance.

Angiogenesis

Among the 'hallmarks of cancer' postulated by Hanahan and Weinberg in 2000 [12], the induction of angiogenesis is among those that can already be approached therapeutically. Attempts to interfere with tumor-induced neo-angiogenesis (e. g., by blocking the VEGF, FGF or PDGF pathways) have met with some, although heretofore limited, success. For example, nintedanib is a triple angiokinase inhibitor as it can block all three of the above-mentioned mechanisms, and in the phase III LUME-Lung 1 trial it led to prolongation of OS in patients with adenocarcinoma histology, from a median of 10.3 to 12.6 months (HR, 0.83; p = 0.0359). When the analysis was restricted to the predefined population of patients with adenocarcinoma who had progressed within 9 months of the start of first-line therapy, OS was also significantly longer in the docetaxel plus nintedanib group compared to the docetaxel plus placebo group (median OS, 10.9 vs. 7.9 months; HR, 0.75; p = 0.0073; **Figs. 4, 5**; [13]). To improve upon results like these, biomarkers for selection of patients would be helpful, but these are currently lacking for anti-angiogenic therapies. Another promising approach might be a combination of strategies, as Scheffler stated; for instance, by normalizing tumor vasculature up-front with the aid of angiogenesis inhibitors, and subsequently adding other therapies with different modes of action. ■

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Focus Molecular Diagnostics

Molecular diagnostics: which markers, which methods?

All existing guidelines call for timely determination of molecular parameters relevant for approved targeted and immune treatments of unresectable NSCLC, as Reinhard Büttner, MD, Department of Pathology, University Hospital of Cologne, emphasized. *EGFR* mutations, *ALK* and *ROS* rearrangements, *BRAF* mutations, PD-L1 expression and – hopefully soon – amplifications, mutations or rearrangements of *MET* have been connected with effective new therapeutics, and have therefore to be identified as soon as possible in the course of disease (**Fig. 6**). This is not only true for first-line therapy, but also in the resistant situation where molecular pathology is also involved in decision making; e. g., when detection of a T790M-mutation in the *EGFR* gene opens the way to treatment with the third-generation inhibitor osimertinib, or when resistance mutations in the *ALK*-fusion gene dictate the choice of ALK inhibitors. So, there are roughly 27 genes and a series of immunohistochemically determined parameters that have to be analyzed for the first-line and second-line situations, to ascertain that the patients are treated with the extremely successful therapies that target the respective alterations.

Another strategy, which in recent years has been employed very successfully for treatment of many tumors including NSCLC, is the blockade of immune checkpoint molecules like PD-1. The immune checkpoint mechanisms that have developed in the mammalian immune system have the task of protecting tissues from autoimmune attacks by T-cells – in utero as well as in a variety of immune-privileged spaces in the adult organism. Checkpoint molecules like PD-1 on T-cells recognize specific ligands like PD-L1 on tissue cells, and as a consequence of this interaction the cytotoxic activity of the immune cells is being blocked. Cancer cells utilize this mechanism by expressing proteins like PD-L1 themselves and thereby

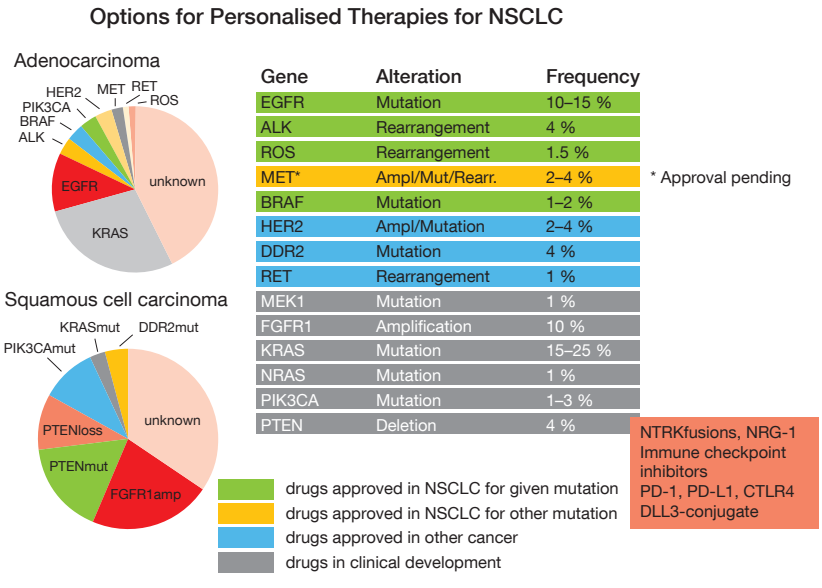

Figure 6: Options for personalized therapies for NSCLC. Courtesy of R. Büttner.

preventing their own lysis by T-cells. In the KEYNOTE-024 trial first-line therapy with the PD-1 antibody pembrolizumab could prolong PFS as well as OS of patients with NSCLC expressing PD-L1 on at least 50 % of their cells as determined by IHCs [1].

Determination of PD-L1 expression is therefore of paramount importance when considering checkpoint inhibitor therapies for patients with NSCLC. At the moment, PD-L1 expression is the only approved biomarker for immunotherapy, and for first-line treatment with pembrolizumab, it is mandatory to score the proportion of tumor cells that express PD-L1; in addition, it is optional to determine the proportion of PD-L1–positive immune cells. Andreas Scheel, MD, Department of Pathology, University Hospital of Cologne, led the pivotal German harmonization trial for standardizing PD-L1 IHC [2–4]. This IHC technique is a fast and relatively cheap method, and it requires little tissue. It can be standardized to a high degree, although appropriate validation and quality control are essential. Furthermore, each of the five PD-1/PD-L1 inhibitors has been validated clinically with different IHC assays, which are not interchangeable. Biomarker testing will certainly develop further, Scheel stated, because more clinical trials with different PD-L1 IHC tests and cut-offs are ongoing, and more methods are being evaluated, including RNA expression analysis and comprehensive DNA sequencing, to define the so-called 'tumor mutational burden.'

Traditionally molecular genetics testing has been performed using multiplex PCR, with specific panels for each type of tumor, thereby restricting the region of DNA investigated to a few thousand base pairs. This is currently not enough for assumptions to be made concerning the total mutational burden (e.g., microsatellite instability, BRCA mutation, UV or smoking signature). So, more recently in Cologne, larger hybrid capture panels were developed that allow determination of mutations, fusions and amplifications, and also patterns of mutational load that include copy-number variations [5].

Indeed, this type of assay might explain the contradictory results from some checkpoint inhibitor trials, where some of the patients with high PD-L1 expression did not respond. In the CheckMate-026 trial, for example, patients with PD-L1 expression > 50 % but with low or medium tumor mutational

burden had shorter PFS with nivolumab than with chemotherapy, while for those with PD-L1 > 50 % and high tumor mutational burden, the median PFS was not reached after 18 months. Measurement of tumor mutational burden therefore is a very promising biomarker candidate, provided there is an assay that can be used readily in clinical practice. Usually, the tumor mutational burden has been determined using whole exome sequencing, which, however, requires at least 200 ng DNA from formalin-fixed, paraffin-embedded tissues. For example, in the CheckMate-026 trial, sufficient samples could not be obtained from 42 % of the patients. Therefore, there are efforts underway, as Sabine Merkelbach-Bruse, MD, Department of Pathology, University Hospital of Cologne, stated, to develop panel sequencing techniques for tumor mutational burden analysis.

In addition, the nature of the immune infiltrate of a tumor might be relevant for patient prognosis, such as whether a tumor consists predominantly of T-cells or of more immunosuppressive myeloid cells. The aim, as Büttner put it, is the creation of an "integrated immune score", as some cancer immunologists called it a couple of years ago [6].

Implementation: Network Genomics Medicine

When talking about the Network of Genomics Medicine (NGM) that was founded at the University of Cologne in 2010, Anna Kron, University Hospital of Cologne, mentioned its association with the Lung Cancer Group Cologne (LCGC) to achieve a number of challenging goals:

- establish a comprehensive clinical trials program (with a focus on early proof-of-concept trials);
- participate in (or better, lead) practice-changing pharmaceutical trials;
- translate discoveries from the academic setting into clinical practice ('from bench to bedside');
- initiate investigator-initiated trials within LCGC, and expand them to multicenter trials;
- start an immunotherapy trial program, and try to integrate this with genomics (BIOLUMA).

The first evaluation of the NGM in 2013 already showed clear superiority over standard chemotherapy of personalized treatments with *EGFR* and *ALK* inhibitors after molecular testing, with these data in line with those from the respective controlled trials [7]. At present, the NGM provides genotyping of lung cancers for about 10 % of all patients in Germany, with the ultimate goal being to increase this to 100 %. Reimbursement of next-generation sequencing is now possible for around one third of all lung cancer patients in Germany, with the final goal being uniform cost coverage for all in-patients and out-patients. Having repeatedly shown survival benefits through molecular testing and participation in clinical trials, the NGM is striving to achieve nationwide documentation and evaluation of treatments and outcomes in patients with lung cancer. Nationwide molecular screening is another goal, with one purpose (among others) being the organization of clinical trials for rare subgroups of patients. Finally, Merkelbach-Bruse mentioned the harmonization of quality standards for diagnostics and treatment as the overarching aim of all of these efforts, one prominent example being the German harmonization study for PD-L1 testing.

To achieve all of this at a national level, the National NGM was founded in September 2017, and funding from German Cancer Aid started on April 1, 2018. In this context, lung cancer serves as a model for other solid tumors.

The main reason for implementation of molecular diagnostics as a tool in daily practice lies in the need to better differentiate groups of patients with a diagnosis of lung cancer. The organizational investments are huge, but they are justified by the ever-growing complexity of the individual therapies that are mainly determined by patient characteristics, molecular markers, and new substances, and the success that can be achieved by this approach that has been shown in clinical trials. ■

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The preceptorship was sponsored by an unrestricted educational grant from Boehringer Ingelheim International GmbH