Editorial

Abstracts from the European Respiratory Society Annual Conference 2018 on Thoracic Oncology

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Lung cancer is the number one cause of death due to cancer worldwide. According to WHO, it accounts for 1.69 million new cases in 2015 (1), whereas in Europe 20.8% of all deaths due to cancer (over 266,000 cases) were attributable to lung cancer in 2011 (2). For patients with advanced non-small cell lung cancer (NSCLC), platinum based chemotherapy (CT) has been the standard-of-care in the first line setting and docetaxel has remained a cornerstone of second-line treatment for more than 20 years. Recently, novel therapeutic agents have emerged, targeting the multiple ways in which lung cancer cells evade the immune system. Nivolumab, a programmed death-1 (PD-1) immune-checkpoint—inhibitor antibody, resulted in two phase III trials, in significantly longer overall survival than docetaxel among patients with advanced or metastatic NSCLC and disease progression during or after platinum-based CT (3,4).

Costantini *et al.* investigated the clinical benefit of blood biomarkers in patients with advanced NSCLC under immunotherapy (IMT). In a prospective design, 43 consecutive patients were enrolled and plasma samples taken at three time points (T1: at time of diagnosis, T2: at initiation of nivolumab, and T3: 2 months after initiation of nivolumab). Tumor response was assessed according to iRECIST. The serum levels of interleukine-2 (Il-2), interferon-gamma (IFN-γ), soluble PD-L1 (sPD-L1), soluble PD-L2 (sPD-L2), and granzyme B (GranB) were measured by an enzyme-linked immunosorbent assay. Additionally, before nivolumab initiation, patient plasma was screened for micro RNA (miRNA) as well as immunohistochemical PD-L1-staining tumor specimen for PD-L1 expression was performed using the E13LN-antibody.

Regarding efficacy of nivolumab, elevated sPD-L1- and decreased GranB-levels at the beginning and during therapy correlated with diminished tumor response, overall survival and progression-free survival, whereas down-expression of miRNA-320b and -375 indicated long-term clinical benefit. Likewise, in this study, worse tolerability of nivolumab (based on grade 3 or 4 toxicities) could be estimated by decreased serum levels of sPD-L2 and Il-2 or an increase of IFN-γ.

Thus, the authors concluded an added benefit of using these liquid biomarkers in the control of nivolumab therapy.

Continuing their previous work (5), Raniszewska *et al.* explored the presence and predictive value of lung cancer stem cells (LCSCs) with regard to locoregional lymph node (LN) metastases in lung cancer. LN stations 7, 10 and 11 were examined and aspirates obtained by endobronchial ultrasound (EBUS). The stem cell markers CD133 and EpCAM were utilized to detect LCSCs in the EBUS samples with flow cytometry. PD-L1 expression on LCSC was tested with an anti-PD-L1 antibody.

In their cohort of 21 lung cancer patients, 11 patients proved to have LN metastases. PD-L1 positivity could be demonstrated in CD133+/EpCAM–, CD133–/EpCAM+ and CD133+/EpCAM+ LCSCs with pulmonary adenocarcinoma metastases exhibiting the highest amounts of PD-L1+ LCSCs. The proportion of CD133+/EpCAM+/PD-L1+ LCSCs in metastatic locoregional LNs exceeded

benign ones with median values of 4.23% and 0.02%, respectively.

As a résumé, the researchers highlighted the possible diagnostic potential of LCSCs for lung cancer immunoscoring while routine locoregional lymph node sampling.

In a prospective investigational study in 15 patients with stage IIIB/IV NSCLC as well as healthy individuals, Ferreira Rodrigues Figueiredo *et al.* characterized and compared immunological status patterns based on flow cytometry analyses of peripheral blood samples. Lung cancer patients scheduled for checkpoint-inhibitor therapy were grouped according to their treatment status: (I) at time of diagnosis (DX), (II) at initiation of IMT subsequent to CT, and (III) during IMT. Blood donors served as healthy controls (CTRLs).

All three NSCLC groups were distinguished from CTRLs by a considerable higher rate of myeloid-derived suppressor cells (MDSCs), in particular in the form of monocytic MDSCs (defined as Lin-HLA-DR-CD33+CD11b+CD14+CD15–). In addition, IMT-group patients showed a distinct elevation of myeloid dendritic cells (mDC2; defined as Lin-HLA-DR+CD11c+CD123+) as well as of certain subsets of T cells (T CD8, activated HLA-DR+CD38+ T CD8, memory CCR7-CD45RA+ T CD8 and Tregs), B cells (transitional CD24highCD38high), NK cells (CD56bright) and NKT-like cells (CD3+CD56+). Despite the augmentation of all these named white blood cell types, a significant decrease in the ratio of effector to suppressor cells was noticed (with CD8 T cells and NK cells considered as effector cells, and MDSCs and Tregs cells as suppressor cells). During immunotherapy, the PD-1 positive cell proportion and PD-1 density alike revealed a marked drop in T CD4 (including Th1) cells and T CD8 (including Tc1) cells as well as in Treg cells, monocytes, and dendritic cells.

Even though further research is needed, the authors' conclusion anticipates a predictive role of these white blood cell subsets in future routine immunotherapy management.

Over the past decade, advanced understanding of molecular pathways that drive oncogenesis in NSCLC has improved and eventually led to the development of agents targeting specific molecular pathways. Currently, therapeutic approach to NSCLC is based on classification of NSCLC into molecular subsets based on their distinct oncogene driver, which can be treated with targeted agents directed against the specific oncogenes. The epidermal growth factor receptor (EGFR) represents one of the distinct molecular targets which bears certain activating mutations or is amplified in many NSCLC patients. Patients with these alterations initially respond well to EGFR-targeted therapies, however, all will subsequently relapse due to emerging drug resistance. The underlying mechanisms of resistance to targeted therapies are still not fully understood (6-11).

In two basic science studies, Hwang *et al.* focused on the role of mitochondrial TNF receptor-associated protein 1 (TRAP1) on gefitinib-resistance in NSCLC which is explained by the already proven upregulation of TRAP1 in various tumor types preventing cancer cells from drug-induced apoptosis and oxidative stress. In both of their *in vitro* models, the study group applied a variant of the human pulmonary adenocarcinoma cell line HCC827 (originally bearing an activating EGFR mutation) with an acquired resistance to gefitinib (HCC827 GR).

The first study design explored the effects of the TRAP1 inhibitor gamitrinib-triphenylphosphonium (G-TPP) on mitochondrial reactive oxygen species (ROS) and its mediation of mitochondrial dysfunction and apoptosis. Annexin V binding and MitiSoX assays as well as immunoblot analysis were utilized as detection methods.

Small interfering RNA (siRNA)- as well as G-TPP-related downregulation of TRAP1 led to augmented apoptosis through ROS in HCC827 GR while the opposite effect was observed when inducing TRAP1 overexpression. The antioxidants NAC and DPI blocked apoptosis in HCC827 GR when gefitinib and G-TPP was given. Interestingly, levels of manganese-dependent superoxide dismutase (MnSOD), an enzyme antagonizing ROS, were diminished under gefitinib and G-TPP. The combination of both plus MnSOD siRNA (limiting gene translation into effective MnSOD enzyme) resulted in enhanced apoptosis, whereas MnSOD gene overexpression reversed the promotion of apoptosis by gefitinib and G-TPP.

The second experimental design investigated the impact of TRAP1 in HCC827 GR on epithelial-mesenchymal transition (EMT) which is an essential developmental step of local cancer progression towards metastatic spread.

Through western blotting and confocal microscopy, the researchers demonstrated that siRNA- or G-TPP-induced TRAP1 downregulation attenuated TGF-β1- and hypoxia-dependent EMT in HCC827 GR. The reduction of EMT was indirectly recognized by an up-regulation of E-cadherin and downregulation of mesenchymal markers and transcriptional factors as well as directly observed by an impaired migration and invasion of HCC827GR cells.

In summary, both studies could demonstrate that

downregulation of TRAP1 may be a key target in overcoming gefitinib resistance through restoring the altered ROS-mediated apoptotic pathway as well as withholding EMT in NSCLC with an activating EGFR mutation.

Malignant pleural mesothelioma (MPM) is a highly aggressive mesenchymal tumor commonly associated with asbestos exposure. Therapeutic options are limited and management for most patients is largely palliative and based on combined cisplatin and pemetrexed chemotherapy. Many traditional, soluble (glycol-) protein biomarkers have been evaluated in mesothelioma over time, mostly in case-control settings, likewise diagnostic or screening markers (12).

Tsim *et al.* reported initial results from the DIAPHRAGM study which aims to evaluate diagnostic and prognostic biomarkers in the rational assessment of MPM. One key focus of this prospective multicentric investigational study in 22 Irish and UK centres was the diagnostic potential of the two blood biomarkers fibulin-3 (F3) and SOMAscan® (SS) to distinguish dignity in suspected pleural malignancy (SPM) in comparison to the established marker mesothelin. Between December 2013 and December 2016, 639 patients with SPM (defined as unilateral pleural effusion or mass) and fitness for diagnostic sampling were included into DIAPHRAGM according to the study protocol accomplishing the pre-calculated target sample size for robust statistical power. Approximately one quarter of the study population was diagnosed with MPM (156 patients, 24.4), one third with secondary pleural malignancy (213 patients, 33.3%). The final results of DIAPHRAGM are eagerly awaited as they will help to clarify the individual values of F3, SS and Mesothelin in MPM diagnosis. In addition, the stored biomaterials of this well-defined patient population will set the basis for subsequent biomarker-driven studies.

Endobronchial cryobiopsy has been shown to be a safe technique with a higher diagnostic yield in benign and malignant pulmonary lesions compared to standard forceps biopsy, extending the available tools for obtaining sufficient endobronchial and pulmonary tissue for a definitive diagnosis (13,14).

Nishida *et al.* compared the validity of cryobiopsy and standard sampling knife in surgical specimen from 43 resected lung cancer patients. Cryobiopsy probes were artificially extracted from the surgical specimen and paired with a corresponding standard pathological biopsy obtained by sampling knife. Immunohistochemistry was performed on the pairs of formalin-fixed and paraffin-embedded biopsies staining thyroid transcription factor-1 (TTF-1), p40, Ki67, and programmed death-ligand 1 (PD-L1; antibody: 22C3). Two or more observers assessed H-scores for TTF-1 and p40 (cut-off value of 50) as well as proportion scores for Ki67 and PD-L1. Results were confirmed by a pathologist.

Statistical analysis revealed strong correlations between cryoprobe and sampling knife specimens for TTF-1, p40, Ki67, and PD-L1 with Pearson's correlation coefficients R2 of 0.977, 0.996, 0.896, and 0.851 respectively. Notably, intra-tumoral heterogeneity led to different categorization of PD-L1 assessment in 4 out 43 patients (9%) while matching smaller cryobiopsies with larger sampling knife samples of tumor tissue.

In their conclusion, the authors pointed out the good concordance of both sampling techniques related to standard IHC testing.

Patients with chronic obstructive pulmonary disease (COPD) bear a significantly increased risk of developing lung cancer compared to healthy individuals. Newer studies revealed multiple mechanisms which may contribute to this association (15). Electronic nose technology (eNose) may become a future tool for early detection of lung cancer through molecular profiling of exhaled air and detection of potential lung cancer disease in COPD patient populations. De Vries *et al.* reported on their ongoing multicentric observational study BreathCloud in patients with an established diagnosis of asthma, COPD or lung cancer. The study group demonstrated already the feasibility of eNose breath analysis with the SpiroNose® tool in phenotyping clinical and inflammatory patterns in chronic airway diseases (16). As part of BreathCloud, COPD patients underwent exhaled breath analysis and were then prospectively followed for at least 1-year for the occurrence of lung cancer.

Thirty-five out of the tested 639 COPD patients (5.5%) were diagnosed with lung cancer within the 1-year observational period. The authors described one volatile component reliably differentiating COPD patients with or without lung cancer manifestation.

Based on their findings, de Vries *et al.* derived the feasibility of eNose assessment for early lung cancer detection in COPD patients and anticipate a potential application of this technique in lung cancer screening in this specific patient cohort.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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