Navigating the advanced NSCLC patient pathway: new markers and targets

An independent satellite symposium held at the 6th European Lung Cancer Conference (ELCC)

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Chaired by Martin Reck

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Dear Colleagues

Thank you for attending the satellite symposium entitled ‘Navigating the advanced NSCLC patient pathway: new markers and targets’ at the European Lung Cancer Conference, which we hope you found engaging and informative.

Geneva again provided an excellent host city for this conference, bringing together a unique community of medical professionals to facilitate a personalised approach to the management of lung and other thoracic cancers, and the implementation of new discoveries, into clinical practice.

The symposium addressed the challenges of treating advanced NSCLC patients in an increasingly complex therapy landscape.

The therapy landscape and, accordingly, the patient pathway through it, has greatly increased in complexity in recent years. During the session, the expert Faculty guided us through this complexity by placing the latest developments in advanced NSCLC into the context of treatment. They provided their insights into how we can use our biological knowledge not only to improve treatment pathways, but also to maximise treatment outcomes by understanding approaches.

We hope that you found this symposium educational, and that it helped further your understanding of this evolving field by providing advice to facilitate decision making in your clinical practice.

Yours faithfully,

Martin Reck

Chair
Faculty biographies

Professor Martin Reck
(Symposium Chair)
Grosshansdorf, Germany

Professor Reck undertook his medical training at The University of Hamburg, Germany, from 1986 to 1993. He completed his doctorate at the General Hospital Wandsbek, Hamburg, in 1995 and received post-graduate training at the Hospital Grosshansdorf, Germany. In 2001 he was appointed as a specialist in internal medicine and in 2002 he was also appointed as a specialist in pulmonology. In 2008 he was awarded a post-doctoral lecturing qualification by the University of Schleswig-Holstein, Germany.

Professor Reck has been a Principal Investigator (PI) or Co-PI in various clinical trials since 1993. His main interests are targeted therapies in non-small-cell lung cancer, new approaches in small-cell lung cancer and modern therapies in malignant pleural mesothelioma, as well as translational research related to predictive markers. He has been involved in several key trials investigating new treatment approaches in the treatment of advanced stage of disease such as, maintenance treatment or treatment with targeted therapies, as well as key biomarker trials.

He is Head of the Department of Thoracic Oncology as well as Head of the Clinical Trial Department in the Department of Thoracic Oncology at the Lung Clinic Grosshansdorf. Furthermore, he is PI in the German centre for lung research (DZL) in the area of lung cancer.

Martin Reck is a member of: the German Working Group for Lung Cancer, the German Cancer Society, the German Society of Pulmonology, the International Association for the Study of Lung Cancer (IASLC), the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO).
Johan Vansteenkiste
Leuven, Belgium

Professor Vansteenkiste is Professor of Internal Medicine in the Faculty of Medicine at the Catholic University of Leuven, Belgium, and Head of Clinic in the Respiratory Oncology Unit and its Clinical Trial Unit at the Leuven University Hospital.

He studied medicine at the University of Leuven before becoming a Board Certified Pulmonologist-Oncologist. He had additional training in respiratory oncology at the European School of Oncology in Milan, Italy, and in respiratory endoscopy at the Laser Centre in Marseille, France, before gaining his PhD at the University of Leuven in 1996.

Professor Vansteenkiste is an active member of different international societies such as ESMO, IASLC, ASCO, and others. He was Secretary of the Thoracic Oncology Assembly of the ERS and a member of the ERS School Board in 2009-2012. He was a member of the Board of Directors of IASLC in 2009-2013. He is a member of the ESMO Lung Educational Group and Guidelines Group, and chaired the European Lung Cancer Conference in April 2015.

He is the principal investigator or co-investigator in several clinical trials in the area of lung cancer. He is Associate Editor at the Annals of Oncology, a member of the editorial board of several other journals, and author or co-author of more than 250 peer-reviewed papers and book chapters.

Keith Kerr
Aberdeen, UK

Professor Kerr completed his BSc with first class honours in Pathology in 1978, followed by MB ChB in 1981 and post-graduate training in Pathology at Edinburgh University Medical School and the Royal Infirmary of Edinburgh. He obtained a MRCPath in 1988, FRCPath in 1998 and was elected Honorary FRCP(Ed) in 2006. He has been a Consultant Pathologist in Aberdeen since 1989.

Professor Kerr has been a member of the IASLC for 16 years. He was elected to the IASLC Board of Directors for four years, 2013-2017, and is also Associate Editor for the Journal of Thoracic Oncology. Professor Kerr is also a member of the International Mesothelioma Panel, and served as Pathology Chair for the European Organisation for Research and Treatment of Cancer (EORTC) lung cancer group from 2006-2014. He is Pathology Chair for the ETOP Lungscape group and was a member of the panel for the 2004 and 2015 WHO lung cancer classifications. He serves on the International Pulmonary Pathology Society council and is a British Thoracic Society member.

He is currently involved in the revision of the BTS Mesothelioma guidelines and is a panel member for the revision of the College of American Pathologists (CAP), the International Association for the Study of Lung Cancer (IASLC), and the Association for Molecular Pathology (AMP) guidelines for molecular pathology testing in lung cancer. He is a lead author of the ESMO Consensus Guidelines on pathology and molecular biomarkers for non-small-cell lung cancer.

Throughout his career, he has worked in diagnostic histopathology with a special interest in thoracic pathology. He has had a career-long interest in lung cancer and has research interests in pulmonary pre-neoplasia and carcinogenesis, lung tumour diagnosis and classification, and in the identification of predictors of therapy response.
Introduction

The symposium Chair Professor Martin Reck, from Lung Clinic Grosshansdorf in Germany, opened the independent satellite symposium with an overview of squamous non-small-cell lung cancer (NSCLC).

Eight-five percent of all lung cancer cases are non-small-cell in nature, he said, and of these, 20–30% have squamous histology1 (Figure 1).

Squamous NSCLC is a “distinct disease”, said Reck, both morphologically and also in terms of clinical presentation, with centrally located tumours that are found more commonly in men, smokers and older patients2–6.

The prognosis of patients with squamous histology is poor, and research into treatment options for these patients has proved “extremely challenging”. The Chair observed that trials of new agents and combinations have mostly been negative with no overall survival (OS) improvements for patients, while certain drugs have induced a “severe safety risk” in patients with advanced squamous disease7–15.

Figure 1: Epidemiology of NSCLC1
Noting that improving the outcomes of squamous NSCLC patients is an unmet need, Martin Reck said that this symposium will focus on diagnostic and therapeutic approaches in this population and provide practical insights for clinicians.

References

5. Rosado-de-Christenson ML et al. Radiographics 1994; 14: 429–446
Professor Keith Kerr explained that squamous cell carcinoma (SCC) is a malignant epithelial bronchogenic tumour of the lung and reiterated that it is a “different disease” from adenocarcinoma. SCC is primarily defined by morphological characteristics – the creation of keratin by tumour cells and the presence of intercellular bridges. But, according to the most recent World Health Organization classification, immunohistochemistry (IHC) markers, such as p40, p63 and CK5/6, are also considered defining features for the diagnosis of SCC, especially when morphological features cannot be assessed as a result of, for instance, sampling errors.

The emphasis on the molecular definition serves to remind us that SCCs mainly arise from the central bronchial epithelium, the basal cells of which express p40, p63 and CK5/6, whereas adenocarcinomas develop from the peripheral pulmonary epithelium, which is characterised by TTF1 expression (Figure 2). 

So many mutations, so few actionable targets

A wide variety of molecular changes, including genetic and epigenetic abnormalities, contribute to the development of lung carcinoma. But SCC, primarily a tobacco-driven tumour, results from the downregulation of tumour suppressor genes, which has “enormous therapeutic implications” as the “knockdown of tumour suppressor genes as an oncogenic event is not a very fruitful target for intervention”, said Kerr.

And although SCC is the “most mutated” of solid cancers, as shown by the analysis of The Cancer Genome Atlas data and a Korean study conducted in East Asian patients, there are few, if any, actionable targets among the most frequently altered genes.

The presenter drew attention to the fact that although the same tyrosine kinase signalling pathways are deregulated in both adenocarcinomas and SCC, it is the nature of deregulation that differs. Specifically, adenocarcinomas are driven by mutations and translocations in genes involved in the pathways whereas in SCC the alterations tend to involve up- or down-regulation of wild-type genes. Thus, instead of additive oncogenes as in adenocarcinomas, “a number of molecular abnormalities together contribute to the oncogenic drive of SCC”, said Kerr, which is not fertile territory for intervention.

EGFR: to test or not to test

Kerr outlined the three types of dysregulation that EGFR can undergo in lung cancer, namely mutation, gene amplification and protein overexpression, where the latter can be associated with amplification but not necessarily so.

Mutations in EGFR are rare in patients with squamous histology, restricted largely to never smokers or long time ex-smokers, a fact that is reflected in testing guidelines that recommend EGFR analysis only in the context of a never smoking history. And although EGFR gene amplifications are known to occur in adenocarcinomas, the relationship with SCC is less well elucidated. By contrast, the EGFR protein is commonly overexpressed in SCC and may contribute to the oncogenic drive, but not as the sole driver.

Keith Kerr noted that from a practical point of view, the EGFR test will depend on the therapy a clinician wants to pursue – for example, if the clinician wants to go down the tyrosine kinase inhibitor route, then they will need to test for activating or sensitising mutations in...
the gene. But if they want to prescribe the anti-EGFR monoclonal antibody necitumumab, then testing for wild-type protein upregulation by IHC or fluorescent in situ hybridisation is appropriate.

**Immunotherapy and beyond**

The presenter believes that immunotherapy targeting the checkpoint proteins is definitely an option for patients with SCC, but he emphasized the need for biomarker testing for many, if not all, available immunotherapies. For now, he said, we can conduct PD-L1 IHC in our patients until something better comes along.

**References**

1. Travis WD et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon, International Agency for Research on Cancer; 2015
Navigating the advanced NSCLC pathway: a case study

Professor Johan Vansteenkiste opened his presentation on treatment approaches in SCC patients by highlighting that the difference between SCC and adenocarcinoma is “much more than a histology difference”. Not only do their characteristics differ – patients with SCC tend to be older, heavy smokers and often have major comorbidities – but there are also dissimilarities in treatment options. Unlike patients with adenocarcinoma, those with SCC cannot be treated with either pemetrexed or bevacizumab, nor are there any druggable targets at present. 

So what are the available options for this patient population?

First-line pathway of the SCC patient

Vansteenkiste used the case study of a 71-year-old man diagnosed with SCC in June 2013 to illustrate the treatment options available for this patient population. 

The patient was an ex-smoker with chronic obstructive pulmonary disease, diabetes and associated grade I neuropathy, and a chest x-ray showed the presence of a left hilar mass. Bronchoscopy revealed the presence of a tumour in the left upper lobe, and IHC results were negative for TTF1 and positive for p63, thus favouring squamous histology. The patient had liver and adrenal gland metastases, but no brain metastases.

When asked to vote on how they would have treated this patient at diagnosis, the majority (59.1%) of the audience opted for cisplatin-based doublet chemotherapy, but nearly a third (33.7%) chose carboplatin-based double chemotherapy, with only a very small proportion choosing single-agent chemotherapy, best supportive care alongside local radiotherapy and triplet chemotherapy.

The split in the audience highlights the “old dilemma” between cisplatin and carboplatin, said Vansteenkiste. The main difference between the agents lies in the toxicity profile, with cisplatin associated with more nonhaematological side effects and carboplatin with more haematological toxicities, and thus there is no dilemma as such, just a matter of considering what is best for your patient, he added.

The other issue to consider is the number of drugs – research has shown that OS is significantly better with doublet versus single-agent therapy, but the former is not always feasible. Based on the experience at their institution, Vansteenkiste said that they strongly advocate starting with the doublet, and going down to monotherapy if need be.

Discussing the options in more detail, Vansteenkiste cautioned against using molecularly targeted agents in patients with SCC, at least in the first-line setting given the “disappointing” results thus far.

As for nab-paclitaxel, the speaker explained that it is considered less toxic than the solvent-bound version. However, in a phase III trial in which patients with
advanced NSCLC were randomly assigned to receive carboplatin either with nab- (n=521) or solvent-bound paclitaxel (n=531), the significant improvement in objective response rate (33 vs 25%) did not translate into an improvement in either progression-free survival (PFS) or OS. Admittedly neurotoxicity was less with nab-paclitaxel, but Vansteenkiste commented that “the best way to avoid neurotoxicity is to not use paclitaxel at all”.

The anti-EGFR monoclonal antibody cetuximab was not approved by the European Medicines Agency (EMA) despite the positive results of the randomised FLEX trial, which compared cisplatin plus vinorelbine either given alone or together with cetuximab. The risk–benefit profile was not considered favourable, with a higher than 20% incidence of febrile neutropenia in the cetuximab arm. But Vansteenkiste pointed out that febrile neutropenia also occurred at a high rate in the control arm, so perhaps the choice of doublet “could have been better”.

By contrast, necitumumab, also an anti-EGFR antibody, was approved by the EMA in February 2016 for patients with advanced EGFR-positive squamous NSCLC. The approval was based on the results of the phase III SQUIRE trial which showed a significant OS and PFS benefit for the 545 squamous NSCLC patients randomly assigned to receive necitumumab in addition to cisplatin and gemcitabine relative to the 548 who received just chemotherapy. Importantly, the incidence of grade 3 or worse febrile neutropenia was low (<1%) in both arms.

**Figure 3: Progression-free and overall survival in the TAILOR trial**

**Relapse pathway of the SCC patient**

Going back to the case study, Vansteenkiste told the audience that the patient was treated with four cycles of carboplatin plus gemcitabine, which led to a decrease in tumour volume and a partial RECIST response. His general condition improved and he tolerated the treatment well. But after 10 months, the constitutional symptoms reappeared and his disease progressed, although again without brain metastases.

On being asked the next step in treatment – in April 2014 – over a third of the audience each picked second-line docetaxel (38%) and “a desperate attempt to get immunotherapy” (34.8%). A small proportion of the audience chose second-line erlotinib (15.5%) and clinical trial with a molecular targeted therapy (9.1%), with very few choosing best supportive care as the next viable step.

The phase III TAILOR trial was a head-to-head comparison of docetaxel and erlotinib in previously treated SCC patients with tumours wild-type for EGFR. Docetaxel treatment significantly prolonged OS compared with erlotinib, at a median of 8.2 versus 5.4 months (Figure 3). “The message is clear for patients who can tolerate docetaxel”, said Vansteenkiste, but it is not possible for all patients.

He then asked the audience what they would have done in the same relapse scenario if they were treating the patient at the present time. Two-thirds (65.5%) of the responders opted for second-line immunotherapy while...
a quarter (25.8%) chose second-line docetaxel plus ramucirumab, with a very small proportion choosing second-line docetaxel, clinical trial with a molecularly targeted therapy or best supportive care.

The anti-PD-1 agent nivolumab was compared with docetaxel in the second-line setting in the phase III CheckMate 017 trial\textsuperscript{10}. The findings were “quite convincing”, the speaker observed, with a doubling of the 1-year OS rate among the 135 nivolumab-treated SCC participants versus the 137 given docetaxel. But Vansteenkiste pointed out that although the long-term results are exciting, nevertheless half the patients experience early progression regardless of treatment, making it important to ensure that alternatives are available for these patients.

In the phase III REVEL trial\textsuperscript{11}, treatment with the VEGFR2 blocker ramucirumab plus docetaxel led to a significant boost in OS and PFS for the 628 advanced NSCLC patients given this combination compared with the 625 treated with placebo plus docetaxel. More importantly, adverse events of grade 3 or 4 were generally low in the ramucirumab arm and not too different from the placebo group – a finding that Vansteenkiste described as “remarkable” given the problems previously encountered with angiogenesis inhibitors in this patient population.

Based on these findings, both nivolumab and ramucirumab have been approved by EMA, the former only for patients with squamous NSCLC and the latter for all NSCLC patients\textsuperscript{12,13}.

**Concluding remarks**

Vansteenkiste said that although NSCLC patients with squamous histology have historically not seen the same improvements as their nonsquamous counterparts, new options have become available for them in the past few years.

“We need careful clinical judgement and appropriate use of these new agents to improve the prospects of patients with squamous NSCLC”, he concluded.

**References**

Panel discussion

What do you consider to be the greatest challenge in first-line treatment for squamous NSCLC?

The panel opened the discussion with a question to the audience – what, in their opinion, is the biggest challenge in the first-line treatment of patients with squamous NSCLC?

The audience was largely split between limited improvement in efficacy of systemic treatment over time (32.8%), lack of treatable oncogenic alterations (26.1%) and comorbidities of the patient (21.8%), with a smaller proportion considering the lack of efficacious maintenance strategies (11.8%) and the management of treatment-related toxicity (7.6%) as the greatest challenge.

In response to a question from the Chair regarding his personal experience with squamous NSCLC patients, Vansteenkiste commented that he considers the lack of treatable oncogenic aberrations as the greatest challenge as most of the progress in the treatment of nonsquamous disease has been due to the presence of druggable targets. However, recently there has been progress in the treatment of squamous NSCLC, and we can do a bit more for these patients, he observed.

Reck asked Kerr whether there was the likelihood of discovering an equivalent of the EGFR mutation – that is, an addictive oncogene – for squamous NSCLC?

Kerr replied that he “hated to be negative”, but the biology of most SCCs and the context in which they arise is not conducive to the generation of a tumour driven by a pure oncogenic target – “we are unlikely to see an EGFR mutation or an ALK alteration”. What this means, he added, is that we need alternative strategies, be it immunotherapy or other legitimate targets that may not be addictive oncogenes, but can be utilised in combination with something else. The Chair added that combining different treatment modalities, like radiotherapy and systemic therapy, could be one such alternative.

In your daily practice, do you conduct EGFR IHC expression testing for squamous patients?

The majority (61.5%) of the audience voted no, as you don't see the benefit to the patient.

Asked to comment on the difficulty and cost of such testing, Kerr said that it's a relatively easy test to conduct and to interpret, and good interobserver consistency can be obtained with training. It's also not expensive, relatively speaking, and results can be obtained as early as the next day. Additionally, Vansteenkiste pointed out that IHC testing for EGFR protein does not cost a lot of tissue, you can run it in the initial immunohistochemistry assessment with TTF-1 and p63.

In your opinion, what would be a clinical meaningful improvement in first-line chemotherapy of squamous cell NSCLC?

Reck noted that the opinion of the audience was very clear, with the overwhelming majority wanting to see a significant OS improvement (with a hazard ratio ≤0.85 or ≤0.80). But the Chair wondered how realistic such a goal is in squamous cell lung cancer?
Vansteenkiste responded that such improvements have been seen in the second-line setting with nivolumab and in the first-line setting with necitumumab, but only in the subgroup of patients with high EGFR expression. However, he believes that outside of the immuno-oncology context, achieving this goal is not very likely.

The Chair asked the panel whether they consider improvements only in PFS, but not in OS, an acceptable outcome? Vansteenkiste said, and Reck agreed, that PFS can be important, but there needs to be an important difference numerically (of several months) and the improvement needs to be accompanied with patient benefits, such as improved symptom control and quality of life.

Conclusions and future directions

The symposium provided a comprehensive overview of molecular biomarkers and treatment approaches in patients with squamous NSCLC.

The speakers highlighted that although historically the options for this patient population have been limited, progress has been made in the past few years. Immunotherapeutic agents, such as nivolumab, and targeted drugs, such as necitumumab, have improved outcomes, and have been approved by US and European regulatory agencies.

However, challenges remain – for instance, despite being a heavily mutated tumour, there is a lack of targetable oncogenic aberrations and the biology of the disease makes the identification of an addictive oncogene in the future unlikely. Therefore, alternative approaches – perhaps combining different treatment modalities – are needed.

Additionally, clinicians need guidance on how best to utilise the currently available therapeutic options in order to provide the best individualised care for their patients. What order should the agents be given in, should they be given alone or alongside other drugs, what markers should we test for – these are just some of the questions that need to be addressed to improve the prospects of patients with squamous NSCLC.
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